Department of Chemistry

Faculty of Mathematics, Informatics and Natural Sciences

Syntheses of potent and selective MMP-13 inhibitors with increased metabolic stability

Dissertation

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By

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LIST OF ABBREVIATIONS

δ	Chemical shift
µg	Microgram
µL	Microliter
µM	Micromolar
ṽ	Wavenumber
$[\alpha]_D^{20}$	Specific rotation
®	Registered trademark
Ø	diameter of the column
2D-NMR	Two-dimensional nuclear magnetic resonance
A. aeolicus	*Aquifex aeolicus*
A. baumanni	*Acinetobacter baumannii*
AaLpxC	*Aquifex aeolicus* LpxC
ACE	Angiotensin-converting enzyme
ACP	Acyl-carrier protein
AEX	Ion exchange
Ala	Alanine
Arg	Arginine
Asp	Aspartate
Boc	tert-Butyloxycarbonyl
Bu	Butyl
c	Concentration
CD-14	Cluster of differentiation-14
$CDCl_3$	Deuterated chloroform
cfu	Colony-forming units
CMP-Kdo	Cytidine 5'-monophospho-3-deoxy-D-manno-2-octulosonic acid
DABCO	1,4-Diazabicyclo(2.2.2)octane
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE	Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DMA	Dimethylacetamide
DMAP	Dimethylamino pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Deuterated dimethylsulfoxide
DPA	Dipicolinic acid
E. coli	*Escherichia coli*
EcLpxC	*Escherichia coli* LpxC
EDTA	Ethylenediaminetetraacetic acid
ESBL	Extended-spectrum-β-lactamase-producing
ESI	Electrospray ionization
ESI-TOF	Electrospray Ionisation Time-of-Flight
ESKAPE	*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species
Et_3N	Triethylamine
EU ml^{-1}	Endotoxin Units per milliliter
EXFS	Extended X-ray absorption fine structure studies
FBS	Fragment-based screening
FLAP	Fingerprints for ligands and proteins
Fmoc	Fluorenylmethyloxycarbonyl
FRET	Fluorescence resonance energy transfer
FT	Fourier transform
GABC	General acid-base pair
gCOSY	Gradient-selected correlation spectroscopy
gHMBC	Gradient-selected heteronuclear multiple bond correlation
gHSQC	Gradient-selected heteronuclear single quantum coherence
Glu	Glutamate

Gly	Glycine
h	Height of the stationary phase
h	Hour
HDACs	Histone deacetylases
His	Histidine
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HTTP	High-throughput screening
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration
ICP	Inductively coupled plasma emission spectroscopy
IL	Interleukin
IPTG	Isopropyl β-D-1-thiogalactopyranoside
IR	Infrared
ISP	Isopropanol
J	Coupling constant
Kd	Dissociation constant
kDa	Kilodalton
Kdo	3-deoxy-D-manno-octulosonic acid
kg	Kilogram
K_i	Enzyme-inhibitor dissociation constant
K_M	Michaelis-Menten constant
kV	Kilovolt
L	Liter
l	pathlength
LB	Lysogeny broth
LBP	Lipopolysaccharide-binding protein
LC	Liquid chromatography
LC-MS	Liquid chromatography mass spectrometry
Leu	Leucine

LPS	Lipopolysaccharide
Cy	cyclohexane
DIP	Direct insertion probe
GC-MS	Gas chromatography mass spectrometry
LpxC	UDP-(3-*O*-(*R*-3-hydroxymyristoyl))-*N*-acetylglucosamine deacetylase
Lys	Lysine
M	Molar
m.p.	Melting point
m/z	Mass-to-charge ratio
MD-2	Myeloid differentiation factor-2
MeCN	Acetonitrile
MeOD-d_4	Deuterated methanol
MeOH	Methanol
MIC	Minimum inhibitory concentration
min	Minute
mL	Milliliter
MMP	Matrix metalloproteinase
MMPIs	Inhibitors of matrix metalloproteinases
MRM	Multiple reaction monitoring
MS	Mass spectrometry
MT-MMP	Membrane-type matrix metalloproteinase
MWCO	Molecular weight cut-off
nM	Nanomolar
NMR	Nuclear magnetic resonance
NPDF	Natural-products-derived fragments
OA	Osteoarthritis
p	para
P. aeruginosa	*Pseudomonas aeruginosa*
PaLpxC	*Pseudomonas aeruginosa* LpxC
Pd/C	Palladium on carbon

PDB	Protein data bank
PET	Positron emission tomography
PG	Protecting group
Phe	Phenylalanine
pM	Picomolar
PMSF	Phenylmethylsulfonyl chloride
ppm	Parts per million
Pro	Proline
RA	Rheumatoid arthritis
R_f	Retention factor
rt	Room temperature
SD	Standard deviation
SDSPAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SEC	Size exclusion
t	Tertiary
$t_{1/2}$	Half-life
TBAB	Tetra-n-butyl ammonium bromide
TBAF	Tetra-n-butyl ammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thr	Threonine
TIMPs	Tissue inhibitors of metalloproteinases
TLC	Thin layer chromatography
TLR4	Toll-like receptor-4
TMS	Trimethylsilyl
TPP	Triphenylphosphine
UDP-diacyl-GlcN	Uridine diphosphate-2,3-bis-(3R-hydroxy-tetradecanoyl)-alphaD-glucosamine
UDP-GlcNAc	Uridine diphosphate N-acetylglucosamine
UHPLC	Ultra-high performance liquid chromatography
UV	Ultraviolet

V	Fraction size
V/V	volume/volume
WHO	World Health Organization

ZUSAMMENFASSUNG

MMP-13-Inhibitoren

Da eine Dysregulation der Matrix-Metalloprotease (MMP)-13 mit pathophysiologischen Zuständen wie menschlichen Karzinomen, rheumatoider Arthritis und Osteoarthritis in Zusammenhang gebracht wurde, stellt MMP-13 eine geeignete Zielstruktur für die Arzneistoffentwicklung dar. Weil die Familie der Matrix-Metalloproteasen im Menschen mehr als 23 Mitglieder umfasst, sollte ein potentieller Arzneistoff MMP-13 selektiv und potent hemmen, um Nebenwirkungen zu vermeiden, die aus einem Mangel an Selektivität resultieren. Zusätzlich sollte ein potentieller Arzneistoffkandidat ein günstiges pharmakokinetisches Profil aufweisen.

Um das Ziel zu erreichen, potente und selektive MMP-13-Inhibitoren mit erhöhter metabolischer Stabilität zu entwickeln, wurde die chemische Struktur von Leitverbindung **41**, einem potenten und selektiven picomolaren Inhibitor von MMP-13 aus einer vorangegangenen Arbeit von KALININ *et al*., ausgiebig variiert, um strukturell unterschiedliche Inhibitoren zu erhalten (Abbildung I).

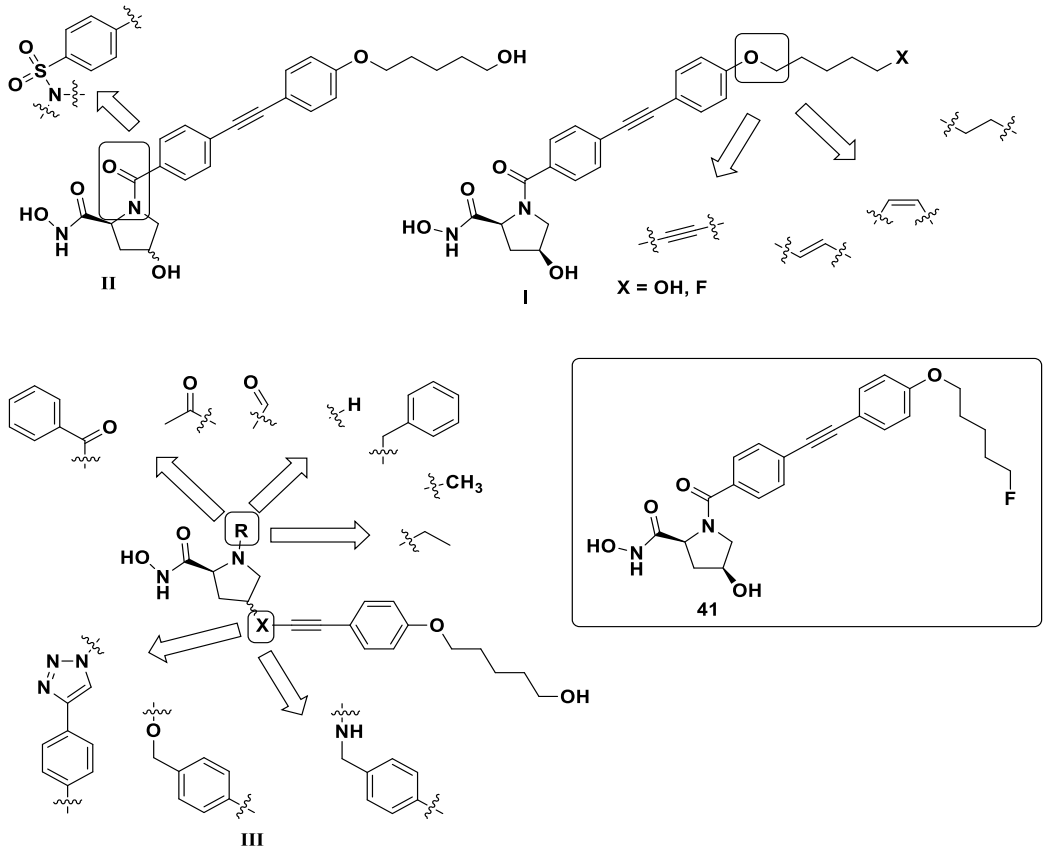


Abbildung I: Durchgeführte Modifikationen von Leitstruktur **41**, um neuartige MMP-13-Inhibitoren zu erhalten.

Zunächst wurde die Oxymethylen-Gruppe der lipophilen Seitenkette von **41** durch Ethylen-, Vinylen- und Acetylen-Einheiten ersetzt, um eine mögliche *O*-Desalkylierung zu verhindern (Abb. I). Diese veränderten lipophilen Seitenketten wurden aus Ausgangsstoffen wie 1,4-Diiodbenzen (**43**), 1-Brom-4-iodbenzen (**80**) sowie 4-Iodanilin (**49**) und durch chemische Reaktionen wie C-C-Kupplungsreaktionen, katalytische Hydrierungen, die Semi-Reduktion von Alkinen, Diazotierungen und Desilylierungen hergestellt. Die entsprechenden fluorierten Derivate wurden durch Umsetzung der hydroxylierten Seitenketten mit DAST erhalten. Ausgehend von Hydroxyprolin-Derivat **57** wurde Amid **59**, welches den zentralen Baustein der Synthesen darstellt, durch Benzoylierungs-, MITSUNOBU- und Verseifungsreaktionen hergestellt. Schließlich konnten die Hydroxamsäuren **I** durch SONOGASHIRA-Kupplungsreaktionen der verschiedenen Seitenketten mit Aryliodid **59** sowie Aminolysen mit Hydroxylamin erhalten werden.

Um die Carbonylfunktion von **41** durch eine hydrolysestabilere Sulfonylgruppe zu ersetzen, wurde Prolin-Derivat **57** in die diastereomeren Sulfonamide **II** durch Sulfonylierungs-, MITSUNOBU- und Verseifungsreaktionen überführt. Durch C-C-Kupplungsreaktionen mit dem

Ether-basierten terminalen Alkin **71** und Aminolysen konnten schließlich die Sulfonamid-basierten Hydroxamsäuren **72** und **73** erhalten werden.

Um die Struktur-Wirkungsbeziehungen zu erweitern, wurde die lipophile Seitenkette von **41** aus der Position 1 des Pyrrolidinrings in die Position 4 verschoben, wo sie über Benzyloxy-, Benzylamino- und Phenyltriazolyl-Gruppen mit dem Heterocyclus verknüpft wurde. Gleichzeitig sollte das Pyrrolidinstickstoffatom verschiedene Substituenten wie Methyl-, Benzyl-, Ethyl-, Benzoyl-, Acetyl- und Formyl-Reste tragen. Zusätzlich wurden *N*-unsubstituierte Prolinderivate synthetisiert (Abb. I). Hydroxamsäuren **III**, die all diese Modifikationen aufweisen, wurden in chiral-pool-Synthesen ausgehend von Methyl-(2*S*,4*R*)-4-hydroxypyrrolidin-2-carboxylathydrochlorid (**57**) durch Reaktionen wie Acylierungen, Alkylierungen, Boc-Schützung, WILLIAMSON-Ethersynthesen, Kupfer-katalysierte Azid-Alkin-Cycloadditionen, reduktive Aminierungen, Aza-WITTIG-Reaktionen, Hydrierungen, C-C-Kupplungsreaktionen und Aminolysen hergestellt.

Die neu hergestellten Inhibitoren **I** mit veränderten Seitenketten erwiesen sich als weniger potente und selektive MMP-13-Inhibitoren als Leitverbindung **41** (IC_{50} = 0.07 nM), wenngleich sie das Enzym im einstellig nanomolaren Bereich hemmten. Der potenteste Vertreter dieser Serie von Verbindungen war Hydroxamsäure **66** (IC_{50} = 1.7 nM), die eine *trans*-Alkenyl-Seitenkette aufweist. Die Fluorierung der Seitenkette hatte keinen signifikanten Einfluss auf die inhibitorische Aktivität gegenüber MMP-13 und zeigte uneinheitliche Effekte auf Potenz und Selektivität. Die Sulfonamide **II** wiesen moderate inhibitorische Aktivität gegenüber MMP-13 auf, waren der Leitverbindung **41** jedoch in Hinblick auf Potenz und Selektivität unterlegen. Das (4*S*)-konfigurierte Sulfonamid **73** war potenter als sein (4*R*)-konfiguriertes Diastereomer **72**. Die Triazol-, Ether- und 4-Aminoprolin-basierten Hydroxamsäuren **III** zeigten keine inhibitorische Aktivität gegenüber MMP-13.

Diese Befunde legen nahe, dass (*S*)-Konfiguration in Position 4 des Pyrrolidinrings, die Oxymethylen-Einheit von **41** und die Verknüpfung der lipophilen Seitenkette über das Pyrrolidinstickstoffatom entscheidend für die Aktivität der Verbindungen sind.

LpxC-Inhibitoren

Durch multiresistente Keime ausgelöste bakterielle Infektionen verursachen jedes Jahr Tausende von Todesfällen. Obwohl Fortschritte bei der Behandlung von Infektionen durch multiresistente grampositive Bakterien gemacht wurden, ist die Behandlung von Infektionen durch multiresistente gramnegative Organismen aufgrund von Resistenzentwicklungen schwerlich möglich. Um diese Herausforderung zu überwinden, besteht die Notwendigkeit,

neue Antibiotika zu entwickeln, die in Stoffwechselwege eingreifen, die in der Therapie bisher noch nicht ausgenutzt wurden.

Gramnegative Bakterien besitzen eine charakteristische äußere Membran, die Lipid A als essentiellen Bestandteil aufweist. Lipid A stellt den hydrophoben Membrananker der Lipopolysaccharide dar und ist wichtig für Wachstum und Überleben der Bakterien. Folglich ist die Inhibition von Enzymen, die an der Lipid A-Biosynthese beteiligt sind, eine attraktive Strategie für die Entwicklung von neuen Antibiotika. Von den neun Enzymen, die an der Lipid A-Biosynthese beteiligt sind, ist die UDP-3-*O*-((*R*)-3-hydroxymyristoyl)-*N*-acetylglucosamindeacetylase (LpxC), die den insgesamt zweiten aber ersten irreversiblen Schritt dieser Biosyntheseroute katalysiert, ein vielversprechendes Target für die Antibiotika-Entwicklung.

Daher wurden als Teil dieses Projekts LpxC-Inhibitoren hergestellt, indem ausgewählte Zwischenstufen aus den Synthesen der zuvor beschriebenen MMP-13-Inhibitoren verwendet wurden. So wurden die Sulfonamid-basierten Hydroxamsäuren **IV** sowie die Ether-, Triazol- und 4-Aminoprolin-basierten Hydroxamsäuren **V** synthetisiert, indem dieselben Reaktionen und Reaktionsbedingungen verwendet wurden, die auch zur Herstellung der MMP-13-Inhibitoren eingesetzt wurden, mit Ausnahme der SONOGASHIRA-Kupplungsreaktionen zum Aufbau der lipophilen Seitenketten, bei denen das Morpholin-basierte terminale Alkin **103** verwendet wurde (Abbildung II).

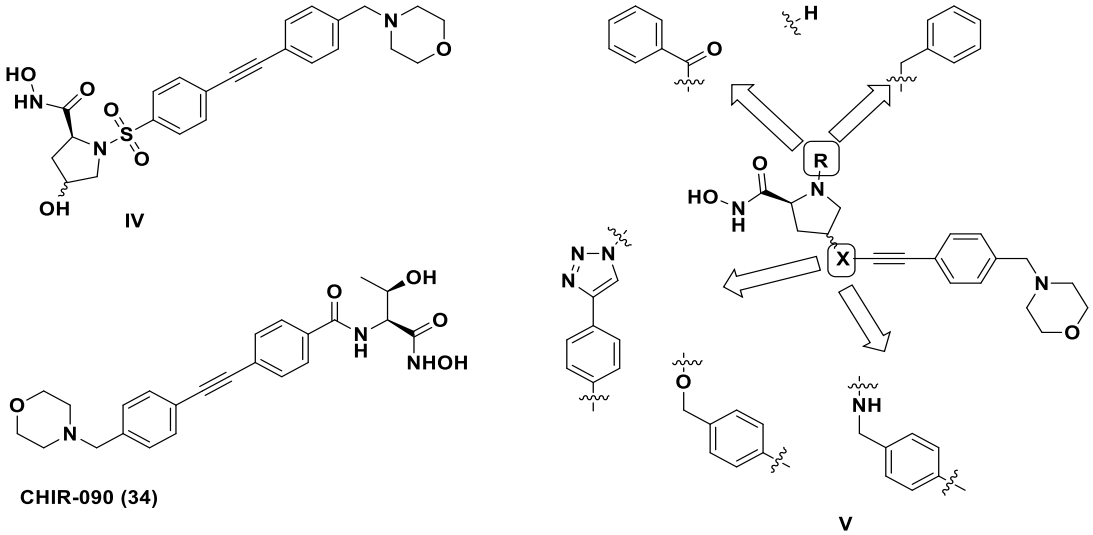


Abbildung II. Hergestellte LpxC-Inhibitoren.

Die antibakteriellen und LpxC-inhibitorischen Aktivitäten der neu hergestellten Verbindungen wurden untersucht. Alle neu hergestellten LpxC-Inhibitoren erwiesen sich als weniger potent als die Leitverbindung CHIR-090 (**34**) (K_i = 0.008 µM), eine Threonin-basierte Hydroxamsäure. Die Sulfonamid-basierten Hydroxamsäuren **IV** (K_i = 1.4 µM bzw. 0.72 µM) waren potente LpxC-Inhibitoren, wobei das (4*S*)-konfigurierte Derivat einen besseren antibakteriellen Wirkstoff und LpxC-Inhibitor darstellte als sein (4*R*)-konfiguriertes Diastereomer **78**. Die (4*S*)-konfigurierten Ether waren bessere LpxC-Inhibitoren als ihre entsprechenden (4*R*)-konfigurierten Diastereomere. Hier wurde ein übereinstimmender Trend in Hinblick auf die antibakterielle Aktivität der Ether gegenüber *E. coli* D22 beobachtet. Eine Ausnahme stellten die am Pyrrolidinstickstoff unsubstituierten Derivate dar, die ähnliche Aktivität aufwiesen. Unter den Ethern stellte das (4*S*)-konfigurierte *N*-Benzyl-substituierte Derivat **141** den potentesten LpxC-Inhibitor (K_i = 0.582 µM) und antibakteriellen Wirkstoff dar. Alle Ether-basierten Hydroxamsäuren waren gegen *E. coli* BL21 (DE3) inaktiv. Die Triazole zeigten schwache antibakterielle Aktivität. Trotzdem wiesen sie vielversprechende inhibitorische Aktivität gegenüber LpxC auf, wobei die Benzamid-basierten Triazole bessere LpxC-Inhibitoren waren als die *N*-Benzyl-substituierten Triazole. Unter den 4-Aminoprolin-Derivaten erwies sich das Benzamid-basierte Derivat **217** als potenter LpxC-Inhibitor, während das *N*-Benzyl-substituierte Derivat **227** wenig bis keine Aktivität zeigte. Der umgekehrte Trend wurde bei den 4-Aminoprolin-Derivaten hinsichtlich der Empfindlichkeit von *E. coli* D22 gegenüber den Verbindungen beobachtet. Wie die Ether und Traizole wiesen die 4-Aminoprolin-Derivate **217** und **227** (MICs >64) keine Aktivität gegen *E. coli* BL21 auf.

ABSTRACT

MMP-13 inhibitors

A dysregulation of matrix metalloproteinase (MMP)-13 has been correlated with pathophysiological conditions like human carcinomas, rheumatoid arthritis, and osteoarthritis. This makes MMP-13 a suitable target for drug development. Since the family of MMPs comprises more than 23 different members in humans, a potential drug candidate should selectively and potently inhibit MMP-13 in order to avoid side effects resulting from a lack of selectivity. Additionally, the desired drug candidate should have a suitable pharmacokinetic profile.

To realize the aim of developing potent and selective inhibitors of MMP-13 that are metabolically more stable, the chemical structure of lead compound **41**, a potent and selective picomolar inhibitor of MMP-13 from an earlier work of KALININ *et al*., was extensively varied to access structurally diverse inhibitors (Figure I).

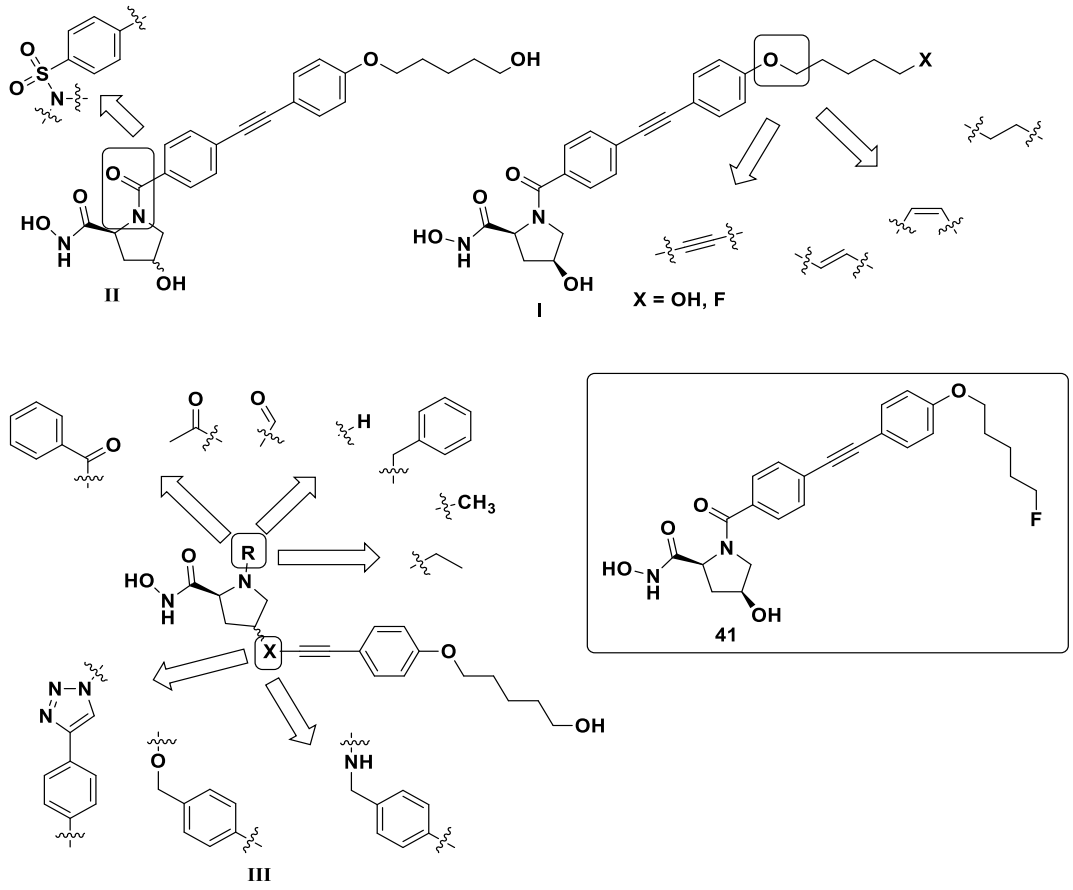


Figure III: Modifications made to lead compound **41** to afford novel MMP-13 inhibitors.

First, to avoid a possible *O*-dealkylation, the oxymethylene moiety of the lipophilic side chain of **41** was replaced with ethylene, vinylene, and acetylene moieties (Figure I). These varied lipophilic side chains were accessed from starting materials like 1,4-diiodobenzene (**43**), 1-bromo-4-iodobenzene (**80**), and 4-iodoaniline (**49**) by employing reactions like C-C couplings, catalytic hydrogenation, semi-reduction of alkynes, diazotization, and desilylation. The respective fluorinated derivatives were obtained by reacting the various hydroxylated side chains with DAST. Starting from hydroxyproline derivative **57**, amide **59**, the central building block of the synthesis, was obtained by benzoylation, MITSUNOBU, and saponification reactions. Thus, hydroxamic acids **I** were obtained after SONOGASHIRA coupling reactions of the various side chains with aryl iodide **59** and aminolyses with hydroxylamine.

In order to replace the carbonyl function of **41** with a sulfonyl moiety, which is more stable to hydrolysis, proline derivative **57** was transformed into diastereomeric sulfonamides **II** via sulfonylation, MITSUNOBU, and saponification reactions. Hence, sulfonamide-based hydroxamic acids **72** and **73** were afforded by C-C couplings with ether-based terminal alkyne **71** and aminolyses.

To further broaden structure-activity relationships, the lipophilic chain of **41** was moved from position 1 to position 4 of the pyrrolidine ring where it was anchored via benzyloxy, benzylamino, and phenyltriazolyl moieties. At the same time, different residues like methyl, benzyl, ethyl, benzoyl, acetyl, and formyl were substituted onto the pyrrolidine nitrogen. Additionally, *N*-unsubstituted proline derivatives were synthesized (Figure I). Hydroxamic acids **III** with all these modifications were accessed in chiral pool syntheses starting from methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**57**) and using reactions like acylation, alkylation, Boc protection, WILLIAMSON ether syntheses, copper-catalyzed azide-alkyne cycloadditions, reductive aminations, aza-WITTIG reactions, hydrogenation, C-C couplings, and aminolyses.

The newly synthesized inhibitors **I** with varied side chains were revealed to be less potent and less selective MMP-13 inhibitors than lead compound **41** (IC_{50} = 0.07 nM), though they were single-digit nanomolar inhibitors. The most potent in the series was hydroxamic acid **66** (IC_{50} = 1.7 nM) possessing a *trans*-alkenyl side chain. Fluorination was found to not significantly affect MMP-13 inhibitory activity, thus, producing inconsistent outcomes for both potency and selectivity. The sulfonamides **II** exhibited moderate MMP-13 inhibitory activity, being inferior to lead compound **41** in potency and selectivity. The (4*S*)-configured sulfonamide **73** was more

potent than its (4*R*)-configured diastereomer **72**. The triazole-based, ether-based, and 4-aminoproline based hydroxamic acids **III** exhibited no MMP-13 inhibitory activity.

These findings suggested that (4*S*)-configuration in position 4 of the pyrrolidine ring, the oxymethylene moiety of **41**, and the pyrrolidine nitrogen as anchoring point for the lipophilic side chains are pivotal for activity.

LpxC inhibitors

Bacterial infections caused by multi-drug resistant bacteria cause thousands of deaths every year. Though much progress has been made in the treatment of infections caused by multi-drug resistant Gram-positive organisms, the treatment of infections caused by multi-drug resistant Gram-negative organism is elusive due to the development of resistance. To overcome this challenge, there is a need to develop new antibacterial agents that target enzymatic pathways that have not been exploited before.

Gram-negative bacteria possess a unique outer membrane of which lipid A is an essential component. Lipid A, the hydrophobic membrane anchor of the lipopolysaccharides, is very important for bacterial viability and survival, hence, targeting the enzymes involved in lipid A biosynthesis provides an attractive strategy for the development of new antibacterial agents. Of the nine enzymes being involved in lipid A biosynthesis, the UDP-3-*O*-((*R*)-3-hydroxymyristoyl)-*N*-acetylglucosamine deacetylase (LpxC), catalyzing the second overall and first irreversible step of this biosynthetic route, is a promising target for antibacterial drug development.

Hence, as part of this project, LpxC inhibitors were developed using selected intermediates of the elaborated syntheses of the previously described MMP-13 inhibitors. As such, sulfonamide-based hydroxamic acids **IV** as well as ether-based, triazole-based, and 4-aminoproline-based hydroxamic acids **V** were synthesized (Figure II) by using the same reactions and conditions used for accessing the MMP-13 inhibitors, except that the morpholine-based terminal alkyne **103** was used in the SONOGASHIRA coupling reactions to build up the lipophilic side chain (Figure II).

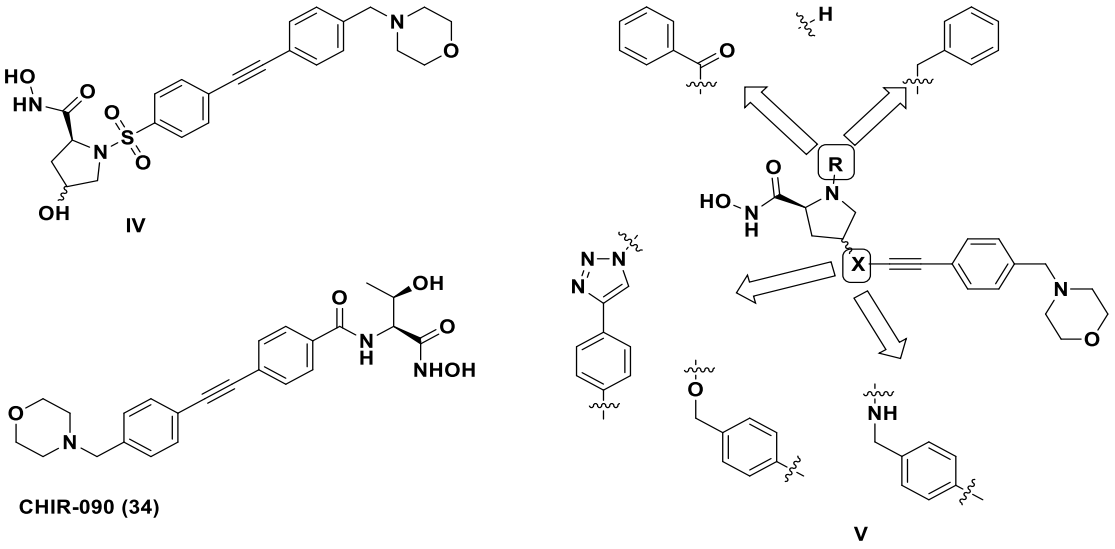


Figure IV. LpxC inhibitors synthesized.

The antibacterial and LpxC inhibitory activities of the newly synthesized compounds were evaluated. All the newly synthesized LpxC inhibitors were found to be less potent than lead compound CHIR-090 (**34**) (K_i = 0.008 μM), a threonine-based hydroxamic acid. The sulfonamide-based hydroxamic acids **IV** (K_i = 1.4 μM and 0.72 μM) were potent LpxC inhibitors with the (4*S*)-configured derivative **79** being a better LpxC inhibitor and antibacterial agent than its diastereomer **78**. The (4*S*)-configured ethers were better LpxC inhibitors than their respective (4*R*)-configured diastereomers. A concurrent trend was observed for antibacterial activity of the ethers against *E. coli* D22 except for the *N*-unsubstituted derivatives that exhibited similar activity. Among the series of ethers, the (4*S*)-configured *N*-benzyl-substituted derivative **141** was the most potent LpxC inhibitor (K_i = 0.582 μM) and antibacterial agent. All the ether-based hydroxamic acids were inactive against *E. coli* BL21 (DE3). The triazoles had weak antibacterial activity. In spite of this, they displayed promising LpxC inhibitory activity with the benzamide-based triazoles being better LpxC inhibitors than the *N*-benzyl-substituted triazoles. Regarding the 4-aminoprolines, the benzamide-based derivative **217** was a strong LpxC inhibitor while the *N*-benzyl-substituted derivative **227** had very little to no activity. A reversed trend was observed for the 4-aminoprolines with regard to the susceptibility of *E. coli* D22. Like the ethers and triazoles, the 4-aminoproline derivatives **217** and **227** (MICs >64) had no activity against *E. coli* BL21

1.0 INTRODUCTION

1.1 Zinc and Zn^{2+}-dependent metalloenzymes

The chemical element zinc is very important for all forms of life, including plants, microorganisms, and animals.[1,2] It is estimated to form about 0.004% of the crust of the earth, hence, making it one of the most abundant elements. It is thought to be indispensable to life because of its ready reactivity with negatively charged groups in biological material that contains greater amounts of zinc than other elements that are more abundant in the environment.[3,4] In 1969, RAULIN proved zinc to be necessary for the survival of living organisms by showing experimentally that it was indispensable for the growth of the filamentous fungus *Aspergillus niger*.[4] However, it was not until mid-1930s that conclusive evidence for the relevance of zinc for the normal growth and development of animals was adduced.

In 1940, KEILIN and MANN isolated carbonic anhydrase, an enzyme that maintains acid-base homeostatic balance by reversibly catalyzing the dehydration of carbonic acid, a process which is critical to the elimination of carbon dioxide. Zinc (Zn^{2+}) was found to be a catalytic cofactor of carbonic anhydrase, playing a role in its mechanism of action.[3,5] This finding propelled a lot of research in this area, establishing Zn^{2+} to be very important for physiological processes and pathological states. As the second most abundant trace element in the human body, it is responsible for the structure and catalytic activity of more than 300 enzymes.[6]

After carbonic anhydrase, bovine pancreatic carboxypeptidase was the next enzyme whose function was found to be Zn^{2+}-dependent. Over time, the list of Zn^{2+}-dependent enzymes grew. The term zinc (Zn^{2+}) metalloenzymes refers to a group of enzymes whose structure and activity are regulated by zinc. These enzymes are involved in very important physiological processes in animals such as the regulation of antioxidant activity (superoxide dismutase)[2,7-9], inflammation (neutrophils)[10,11], immune responses (protein kinase C)[12-14], apoptosis (caspase)[15], and several other processes. In Gram-negative bacteria, the Zn^{2+}-dependent deacetylase LpxC plays a very crucial role in the synthesis of constituents of the outer membrane, thus, being required for bacterial survival and viability.[16,17]

In spite of the many functions played by Zn^{2+}-dependent metalloenzymes, their malfunction or dysregulation can led to certain disease conditions like cardiovascular diseases (superoxide dismutase)[18], vascular diseases (matrix metalloproteinases)[19-21], immune diseases (protein kinase C)[22-25], asthma (caspase)[26,27], hypogeusia (carbonic anhydrase)[28-30], bone disorders (alanine phosphatase)[31-34], cancers (matrix metalloproteinases)[35], and so on. This makes Zn^{2+}-

dependent enzymes attractive targets for drug discovery and Zn^{2+}-binding agents promising candidates for drug development.

Though scientists have successfully developed inhibitors for some Zn^{2+}-dependent enzymes, such as carbonic anhydrase, angiotensin-converting enzyme (ACE), and human histone deacetylases (HDACs), which are used clinically for managing hypertension (Lisinopril Captopril etc.)[36], glaucoma (Acetazolamide, Dorzolamide etc.)[37], and cancer (Vorinostat, Panobinostat etc.)[38], respectively, the development of selective and potent inhibitors for clinically important Zn^{2+}-dependent enzymes like the matrix metalloproteinases (MMP) and the bacterial deacetylase LpxC is somewhat elusive. The development of suitable MMP inhibitors has been plagued with a lack of selectivity and the associated off-target effects, which are usually musculoskeletal in origin, a lack of efficacy, a poor pharmacokinetic profile, and other problems.[39] In case of the LpxC inhibitors, in spite of efforts and huge financial investments, none has been approved for therapeutic use, with only one reaching human trials thus far.[17]

Therefore, this project is aimed at the synthesis and biological evaluation of selective and potent MMP-13 inhibitors with increased metabolic stability, building on an earlier work by KALININ *et al.* (2016).[19] As part of the project, there will also be the synthesis and biological evaluation of inhibitors of the bacterial deacetylase LpxC.

1.2 Targeting matrix metalloproteinase-13 (MMP-13)

Matrix metalloproteinases, also known as matrixins, are a family of Zn^{2+}- and Ca^{2+}-dependent endopeptidases that are responsible for degrading various components of the extracellular matrix like gelatin, elastin, casein, and collagen.[40] These enzymes play important roles in wound healing, tissue remodeling, angiogenesis, and so on in normal healthy individuals. However, when MMP activity is dysregulated such that their activities become excessive, they can contribute to the progression of diseases like rheumatoid arthritis, periodontal disease, and cancer.[41]

1.2.1 Classification of MMPs

Based on the following characteristics, the MMPs have been defined functionally:

- They are endopeptidases that are capable of degrading at least one of the components of the extracellular matrix.
- They are normally secreted in their latent forms as proenzymes or zymogens (with the membrane-associated MMPs being the only exceptions), requiring activation for the

exertion of their proteolytic activity. This way, MMPs are prevented from cleaving essential cell components.

- Tissue inhibitors of metalloproteinases (TIMPS) are their main physiologic inhibitors.
- They are homologous enzymes that share common amino acid sequences.[41,42]

With few exceptions (MMP-11 and MMP-23), MMPs have broad substrate specificity and as a result are capable of degrading major and minor components of the extracellular matrix. In addition to degrading extracellular matrix components, they can act as activators of biologically important molecules. Based on their substrate specificity and the pre-synthetic region on chromosomes[40], MMPs are classified into at least four groups: Collagenases (MMPs-1, -8, and -13), gelatinases (MMPs-2 and -9), stromelysins (stromelysin 1 or MMP-3, stromelysin 2 or MMP-10, MMP-11), membrane-type (MT) MMPs (MT2-MMP, MT3-MMP, and MT4-MMP), macrophage elastase (MMP-12), and other MMPs (MMPs-19, -20, -23, -26, -27, -28).[19,35,40-45]

1.2.2 Matrix metalloproteinase 13

The human MMP-13 was first identified and cloned in 1994 from a breast tumor. It showed the structural characteristics of a collagenase and was designated collagenase 3 or MMP-13. Notwithstanding its detection in breast tumor cells, it was absent in normal liver, prostate, parotid gland, ovary, or breast tissue.[46,47] Soon afterwards, it was reported that chondrocytes in the human cartilage produce MMP-13 and that it was overexpressed in osteoarthritis (OA). Just about the same time, MMP-13 was found to be expressed in the synovial membranes of rheumatoid arthritis (RA) patients, but not detectable in the brain, heart, kidney, lungs, liver, and pancreas.[48,49] Based on sequence homology studies, the human MMP-13 gene was surprisingly found to be up to 84% homologous rather to MMP-1 and not to MMP-13 of mice and rats.[50]

1.2.2.1 Structure and function of MMP-13

Structure of MMP-13: MMP-13 is a 53 kDa protein composed of a sequence of 471 amino acids and made up of four distinct domains; the highly conserved N-terminal signal sequence or signal peptide, the pro-domain, the catalytic domain and the C-hemopexin-like domain (Figure 1, top panel). The C-terminal hemopexin-like domain is connected to the catalytic domain by a flexible proline-rich hinge region. Directed by the signal peptide, newly synthesized MMP-13 enzymes are secreted into the endoplasmic reticulum.[51] The pro-domain contains a thiol group which interacts with the catalytic zinc, and needs to be cleaved proteolytically to render the enzyme active.[46,52-54] The catalytic domain comprises three α-

helixes and five β-sheets that are connected by eight loops. The highly conserved catalytic domain also contains a catalytic Zn^{2+} ion to which three histidine residues bind, a structural Zn^{2+} ion, and three Ca^{2+} ions that stabilize the enzyme (Figure 1, bottom panel). Whereas the substrate residues N-terminal to the scissile peptide bond are denoted as P1, P2, P3, etc., the corresponding binding pockets for these substrate substituents are denoted S1, S2, S3, etc., respectively. Accordingly, the substrate residues C-terminal to the scissile peptide bond are designated P1′, P2′, P3′, etc. and the respective binding pockets in the catalytic site of the enzyme are called S1′, S2′, S3′, etc. The S1′ pocket is the most important pocket in determining MMP substrate specificity, because it is the most variable in depth and amino acid constitution. Some MMPs have large S1′ pockets (MMPs-3, -11, -12, -13, and -14), while others have intermediate (MMPs-2, -8, and -9) or shallow (MMPs-1 and-7) pockets.[55,56]

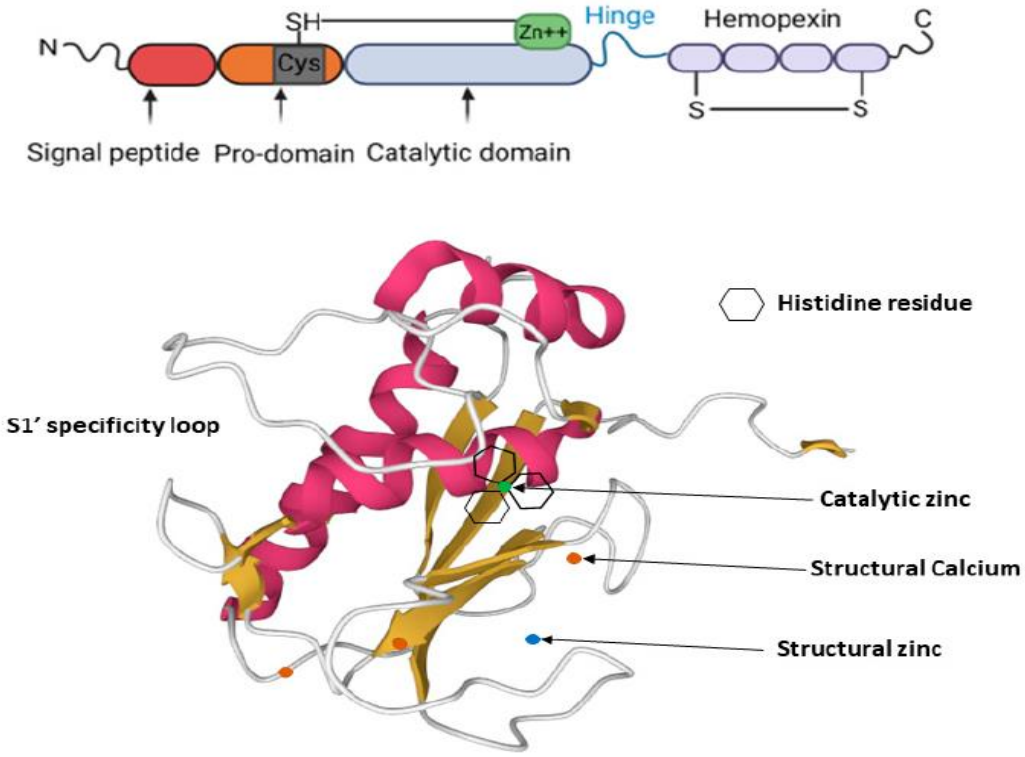


Figure 5: MMP-13 structure: MMP-13 has a highly conserved signal peptide, a pro-domain, a catalytic domain, a proline-rich hinge region, and a C-terminal hemopexin-like domain (top panel). The thiol group (SH) of the cysteine residue (in grey) of the pro-domain interacts with the Zn^{2+} in the catalytic domain of the proMMP-13 enzyme. The MMP-13 catalytic domain is shown in the bottom panel (PDB2OW9). The structural zinc is in blue, the catalytic zinc is in green, and the three calcium ions are shown in orange. The three histidine residues shown as hexagons bind to the catalytic zinc ion.[54]

Activation: As with other MMPs, MMP-13 is secreted as an inactive proenzyme (proMMP-13), and this inactive state is maintained by a cysteine switch motif, the cysteine residue of which interacts with Zn^{2+} in the catalytic domain. proMMP-13 is activated extracellularly by a proteolytic cleavage at the N-terminus. proMMP-13 is cleaved *in vivo* by MMP-14 (MT1-MMP) and MMP-2 (gelatinase A) to give the active form, MMP-13.[57] Trypsin-2 and MMP-3 (stromylesin-1) are also known to activate MMP-13.[58]

Inhibition: Tissue inhibitors of metalloproteinases (TIMPs) are the physiologic or endogenous inhibitors of MMPs. The TIMPs are low molecular weight proteins that specifically bind to activated forms of MMPs in a 1:1 ratio to form tight binary complexes with a high dissociation constant (K_d) (10^{-10}–10^{-9}).[40] Active MMP-13 is inhibited by TIMPs-1, -2, and -3 in a stoichiometric ratio of 1:1. Even though TIMPs are effective MMP inhibitors, they are not specific inhibitors of MMP-13.[50] Apart from the TIMPs, α_2-macroglobulins, which are large molecular weight proteins (~750kDa) produced by the liver and can be detected in normal serum, act as non-specific inhibitors of MMPs. After they are cleaved by a proteinase, α_2-macroglobulins trap the enzymes and deny them access to protein substrates.[59]

Substrates of MMP-13: Type II collagen, the major collagen type in cartilage, is preferentially hydrolyzed by MMP-13.[48] Other substrates like collagen types IV, IX, X, and XIV, gelatin, fibronectin, and aggrecan are also susceptible to hydrolysis by MMP-13.[46,60] The spectrum of substrates, according to emerging reports, has been broadened to include fibrinogen and connective tissue growth factor and the cleavage of these promotes arthritis and interrupts blood clot formation, respectively.[61]

Hence, to find new inhibitors of MMP-13, this project was focused on the synthesis of inhibitors that mimic certain structural features of collagen, a major MMP-13 substrate. Collagen displays a triple helix with a repeating XaaYaaGly sequence, where Xaa is (2*S*)-proline and Yaa is usually (2*S*,4*R*)-4-hydroxyproline.[62,63] As such, the envisaged MMP-13 inhibitors will be based on (2*S*,4*R*)-4-hydroxyproline and (2*S*,4*S*)-4-hydroxyproline.

1.2.2.2 MMP-13 associated pathologies

In fetal development, MMP-13 is expressed in osteoblasts and hypertrophic chondrocytes. In normal adult tissues, there is usually very little or no expression of MMP-13. It is however, overexpressed in conditions that require tissue repair and remodeling. This limited distribution of MMP-13 plus its ability to degrade the various substrates, make it a suitable target in arthritis.[50]

In osteoarthritis (OA), MMP-13 has been established to play a role in disease progression. In animal models, MMP-13 administered via the intraarticular route into the knee joint degraded articular collagen, yielding collagen fragments.[64] In a similar study involving transgenic mice, MMP-13 expressed in hyaline cartilages led to a degradation of collagen, proteoglycan loss, and synovial hyperplasia, in a fashion similar to what is observed in human OA.[65] Also, chondrocytes proximal to OA lesions expressed more MMP-13 than the distal ones.[66] Many more studies have implicated MMP-13 in the progression of OA.

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by cartilage destruction. In the synovial membranes of RA patients, MMP-13 was found to be overexpressed, and its presence positively correlates with disease progression, along with other inflammatory markers like C-reactive proteins.[67]

Apart from breast carcinomas, from which it was originally cloned and identified, MMP-13 is dysregulated and overexpressed in various human cancers like gastric cancer, colorectal cancer, non-small cell lung cancers, esophageal cancers, multiple myeloma, and others.[54]

1.2.2.3 Inhibitors of MMP-13

The catalytic Zn^{2+} ion in the active site of MMPs is surrounded by six other subsites designated S1, S1′, S2, S2′, S3, and S3′, as revealed by detailed enzymatic studies. Among the MMPs, the specificity loop of S1′ differs most in length and amino acid sequence in relation to the other subsites.[68] Of note is the fact that the S1′ specificity loop of MMP-13 is long and can be addressed by large P′ groups.[69] Also, the side pocket (S′*) of MMP-13, situated beneath the S1′ specificity loop, differs from those of other MMPs. These two unique structural features are exploited by researchers in the development of selective inhibitors for MMP-13.[70] The discovery of MMP-13 inhibitors in recent years has gathered a lot of pace, owing to the use of advanced approaches like high-throughput screening (HTS), natural-products-derived fragments (NPDF), fingerprints for ligands and proteins (FLAP), just to mention a few. Inhibitors of MMP-13 can broadly be classified as Zn^{2+}-binding and non-Zn^{2+}-binding.[71]

1.2.2.3.1 Zn^{2+}-binding MMP-13 inhibitors

Hydroxamic Acids: The hydroxamic acid moiety binds the Zn^{2+} ion at the catalytic site of the enzyme and prevents the enzyme from degrading the substrate. To address the long S1′ specificity loop and the side pocket of MMP-13, the aryl sulfonyl chain of lead compound **1** was elongated to give **2** (Figure 2). This increased the MMP-13 inhibitory activity (IC_{50} = 3.0 nM) by 15-fold.[72] Compound **3**, bearing a 2-naphthylsulfonamide moiety (Figure 2), showed a

far superior selectivity for MMP-13 (IC_{50} = 3.0 nM) over MMP-2 (IC_{50} = 384 nM).[73] Comparing the α-sulfone hydroxamate derivatives **4** and **5**, **4** (IC_{50} = 4.4 nM) was a more potent inhibitor of MMP-13 than **5** (IC_{50} = 9.0 nM) and also displayed a much better selectivity of about 1659-fold for MMP-13 over MMP-2.[74]

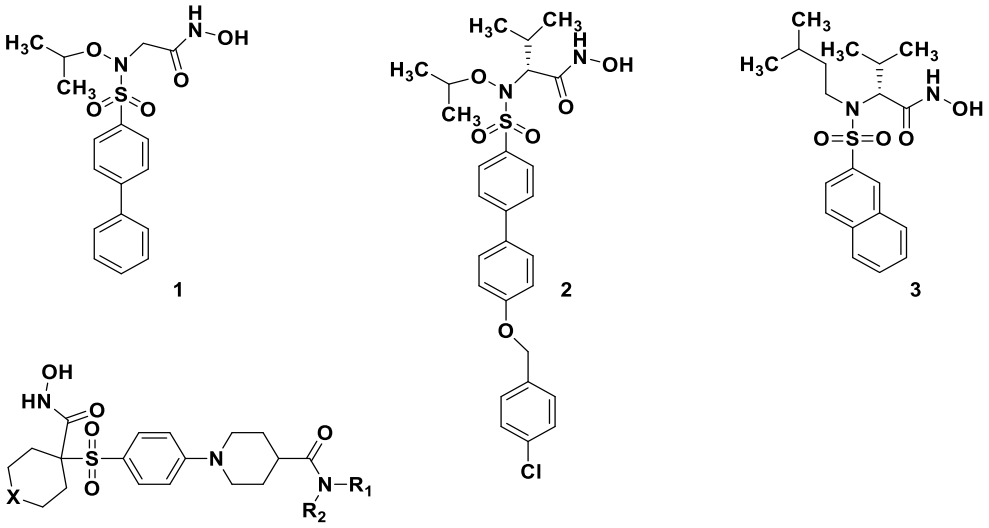


Figure 6: Hydroxamic acid-based MMP-13 inhibitors **1-5.**[72-74]

Carboxylic acids: The carboxylic acids are weaker Zn^{2+}-binders than the hydroxamic acids. The presence of the large S′ specificity loop in MMP-13 allows large P′ groups to be tolerated. A number of carboxylic acid-based benzofuran derivatives have demonstrated high MMP-13 inhibitory activity and selectivity over other MMPs. The MMP-13 inhibitory activity of **6** (IC_{50} = 4.4 nM) was due to the large P′ group, a 3,4-disubstituted benzofuran (Figure 3). Compound **6** also showed an over 200-fold selectivity over MMPs-1, -2, -9, and -14.[75] The optimization of orally active compound **7** (IC_{50} = 0.3 nM) afforded compound **8** (IC_{50} = 0.5 nM) with comparable MMP-13 inhibitory potency, but being devoid of any MMP-1 inhibitory activity. Also, **8** caused a dose-dependent inhibition of MMP-13-induced cartilage degradation in a rat model.[76]

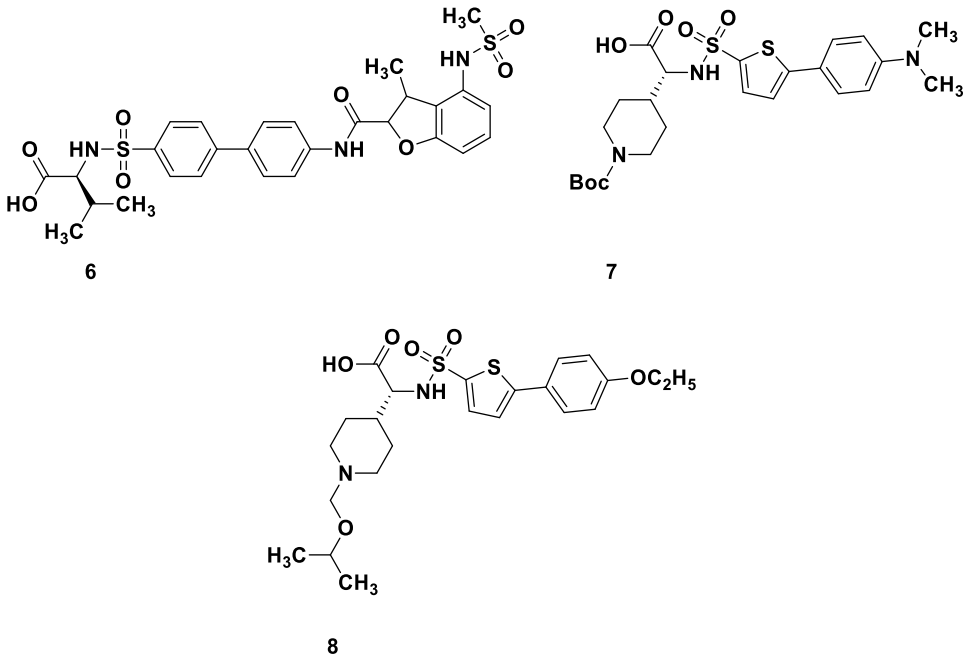


Figure 7. Carboxylic acid-based MMP-13 inhibitors **6-8**.[75,76]

Pyrimidinetriones: Based on theoretical considerations that the carbonyl oxygen, the ring nitrogen, or both atoms can bind Zn^{2+} ions, a number of pyrimidinetrione-based MMP-13 inhibitors have been developed. Compound **9** has been identified as a modest inhibitor of MMP-13 (IC_{50} = 390 nM) (Figure 4).[77] To increase potency and MMP-13 selectivity, the C-4 position of the aromatic ring was modified using different substituents to afford **10**, being a more potent MMP-13 inhibitor (IC_{50} = 1 nM) and also showing high selectivities over MMP-14 (220-fold) and MMP-1 (1300-fold). Additionally, **10** showed a good pharmacokinetic profile; excellent oral absorption, moderate half-life ($t_{1/2}$ = 4 h), a low volume of distribution (0.20 L/kg), and a low clearance (0.63 mL/min/kg). Further modifications yielded **11** (Figure 4) with a long side chain for a deep insertion into the S1′ subsite. Compound **11** proved to be a very potent MMP-13 inhibitor, had a very high selectivity for MMP-13 over MMPs-1, -3, -9, and -14. It also had an excellent pharmacokinetic profile.[78] Further work on the pyrimidinetriones led to **12**, a spiropyrrolidine derivative (Figure 4), which strongly inhibited MMP-13 (IC_{50} = 0.12 nM), was very selective over MMP-12 (1198-fold), and had good pharmacokinetic properties.[79]

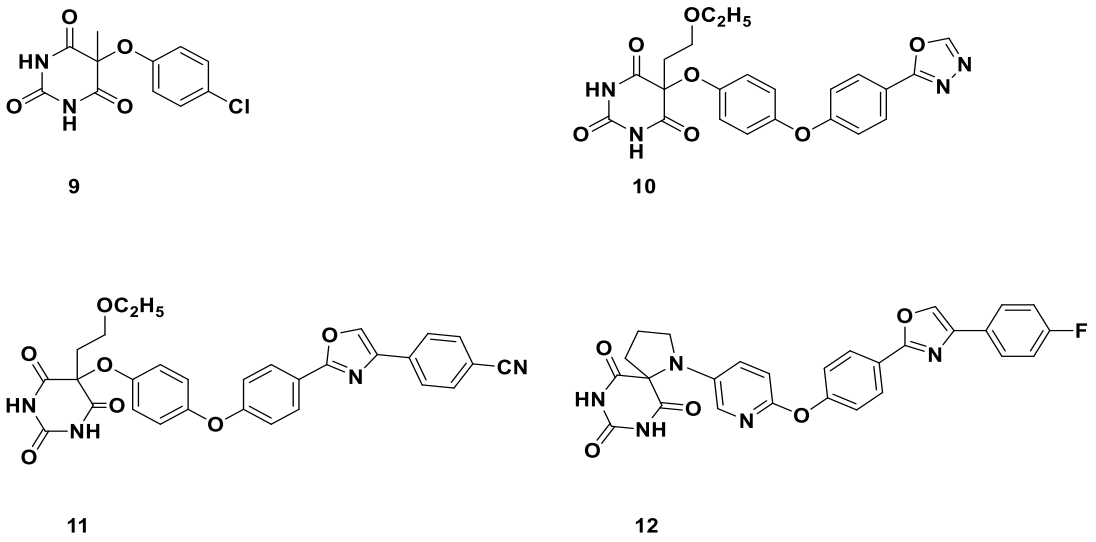


Figure 8. Pyrimidinetrione-based MMP-13 inhibitors **9-12**.[77-79]

Triazolone and Triazoles: Triazolone derivative **13** showed good MMP-13 inhibitory potential and high selectivity over other MMPs (Figure 5). In studies using rats, the oral bioavailability of **13** was found to be rather poor, probably because it was poorly soluble and permeable.[80] Among a series of synthesized triazoles, **14** demonstrated the highest MMP-13 inhibitory potency (IC_{50} = 0.036 nM) and high selectivities (>1200-fold) over MMPs-1, -2, -3, -7, -8, -9, -10, and -14. (Figure 5) Also, it displayed a high oral bioavailability in mice and rats, among other desirable pharmacokinetic parameters. It was therefore considered as a possible candidate for further development.[81]

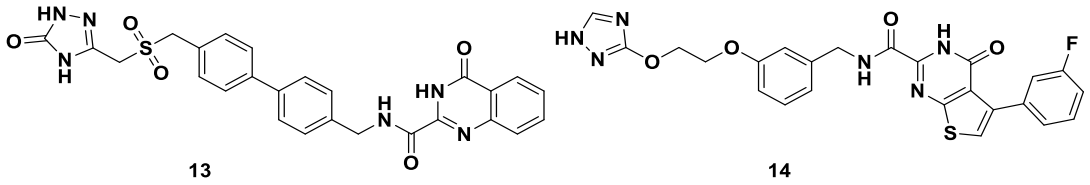


Figure 9. Triazolones and triazole-based MMP-13 inhibitors **13** and **14**.[80,81]

1.2.2.3.2 Non-Zn^{2+}-binding MMP-13 inhibitors

Generally, most MMPIs exert their MMP-13 inhibitory activities by binding the Zn^{2+} ion in the catalytic site and addressing the S1′ pocket using hydrophobic moieties.[82-84] The most potent and selective MMP-13 inhibitors known so far address both the S1′ and S1′* pockets.[85-88]

Hence, the potency and selectivity elicited by these molecules by means of addressing these pockets reduce the need for a Zn^{2+}-binding group. As such, a number of molecules lacking a Zn^{2+}-binding group have been developed. Besides addressing the S1′ and S1′* pockets, they also have atoms or moieties that undergo certain interactions (hydrogen bonding, hydrophobic interactions, etc.) with the enzyme's active site to increase their potency.

Furans: Furan derivative **15** was found to inhibit MMP-13 (IC_{50} = 430 nM) and to display some level of selectivity over MMP-14. Though it did not bind Zn^{2+}, its activity was mediated through interactions with the histidine residues in the active site via hydrogen bonding and л-л stacking interactions. Since **15** did not fully address the S1′ pocket, modifications were made to afford more potent compounds with long tails that fully addressed the S1′ pocket. One of these compounds was **16** (Figure 6), which was a very potent MMP-13 inhibitor (IC_{50} = 4 nM) and was selective (>200-fold) over MMPs-2, -8, -9, and -12. Its selectivities over MMPs-3 and -10 were modest and it was also not metabolically stable.[89] Further modifications of **15** gave **17** (Figure 6), which was less potent than **16** but had a similar selectivity profile to **16**.[90]

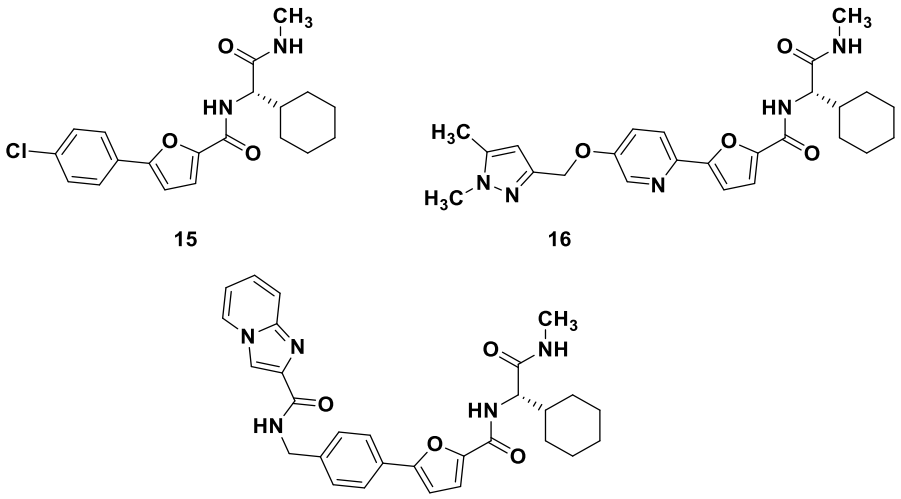


Figure 10. Furan-based MMP-13 inhibitors **15-17**.[89,90]

Indoles: With the aid of fragment-based screening (FBS), indole derivative **18** was found to have a moderate MMP-13 inhibitory potential. Structural modifications at positions 2 and 5 of the indole ring afforded **19** (Figure 7), which exhibited an exponential increase of about 39000-fold in MMP-13 inhibition.[91]

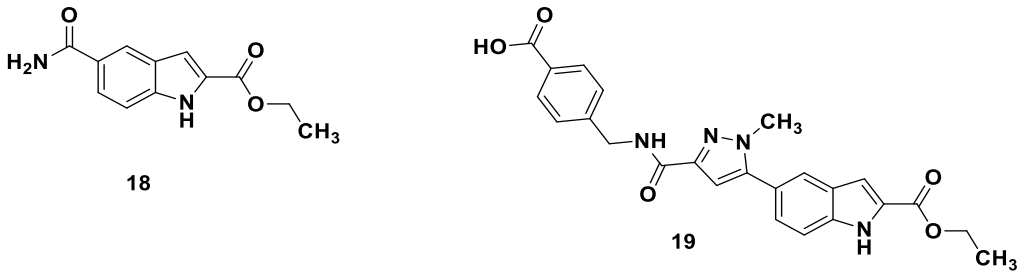


Figure 11. Indole-based MMP-13 inhibitors **18** and **19**.[91]

Pyrimidines: The pyrimidine-based MMP-13 inhibitors were very selective. Derivative **20** strongly inhibited MMP-13 (IC_{50} = 8 nM) and was highly selective (>10000-fold) over other MMPs. Crystallographic studies revealed that, though it did not chelate the Zn^{2+} ion in the catalytic site, **20** addressed the S1′* side pocket of MMP-13 and its two carbonyl groups interacted via hydrogen bonding with some threonine residues. Removal of the fluoro groups of **20** yielded **21** (Figure 8), which produced a marked reduction in MMP-13 inhibitory potential (IC_{50} = 72 nM) due to the loss of hydrophobic interactions with some amino acid residues.[92] Compound **22** has been reported to be an excellent MMP-13 inhibitor (K_i = 1.5 nM) and was also found to be highly selective over 14 isoenzymes. Additionally, **22** showed good oral bioavailability and low clearance rates according to pharmacokinetic data.[69]

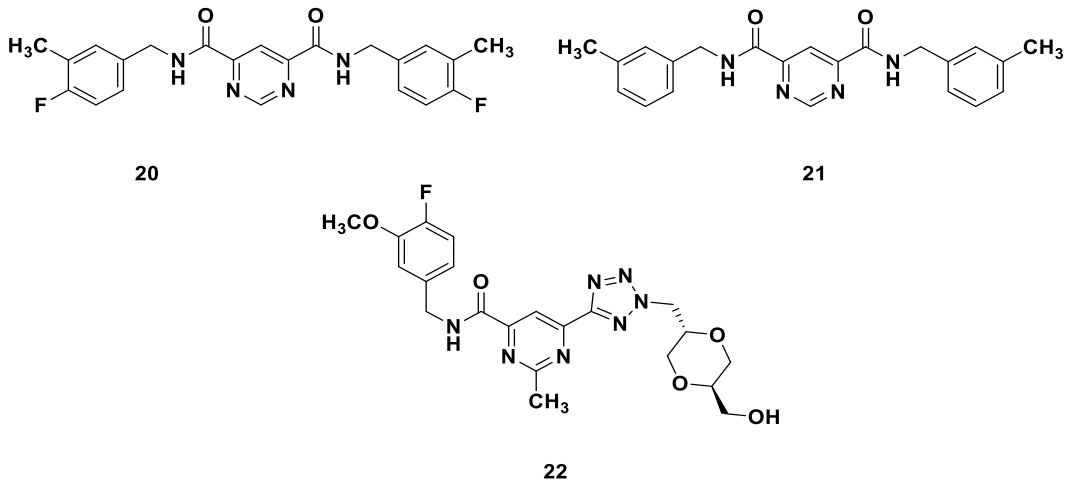


Figure 12. Pyrimidine-based MMP-13 inhibitors **20-22**.[69,92]

Fused-pyrimidines: Derivative **23** was found to effectively inhibit MMP-13 in the low nanomolar range (IC_{50} = 1.3 nM) and also demonstrated high selectivities (>5000-fold) over MMPs-1, -2, -3, -7, -8, -9, -12, and -14.[93,94] Modifications were made to **23** to give **24** (Figure 9), which exhibited a far superior inhibitory activity (IC_{50} = 0.03 nM) and selectivity (>20000-fold) over MMPs-1, -2, -3, -7, -8, -9, -12, and -14. High concentrations of **24** were seen in the cartilage of rats even 8 weeks after intra-articular injection and it retained its inhibitory activity for 3 weeks in the joint. Also, in acute and chronic toxicity studies using mice and rats, **24** was not observed to produce any unwanted adverse effects. These impressive data make **24** a promising agent for further advancement as a potential drug for osteoarthritis.[95] Quinazoline-2-carboxamide derivative **25** (Figure 9) strongly inhibited MMP-13 (IC_{50} = 3.9 pM), and was very selective over MMPs-1, -2, -3, -7, -8, -9, -10, and -14 (>41000-fold). Though according to crystallographic studies, **25** did not chelate the catalytic Zn^{2+} ion, the quinazoline ring was inserted and anchored in the S1′ pocket of MMP-13 via hydrogen bonding interactions with threonine residues (Thr 245 and Thr 247). Its high potency and selectivity were attributed to these β-sheet interactions. The phenethyloxy group of **25** addressed the S1′* side pocket of MMP-13, which is unique to MMP-13. The monosodium salt of **25**, since the free compound is poorly water-soluble, gave good pharmacokinetic and toxicity profiles in guinea pigs, rats, rabbits, and other animals.[96] It is therefore being considered for further development and evaluation.[71] Compound **26**, a thienopyrimidin-4-one, was a potent MMP-13 inhibitor and a very selective agent. The activity of **26** was due to β-sheet interactions between positions 3 and 4 of the pyrimidine ring and the threonine residues in the S1′ pocket and S1′* side pocket of MMP-13.[97]

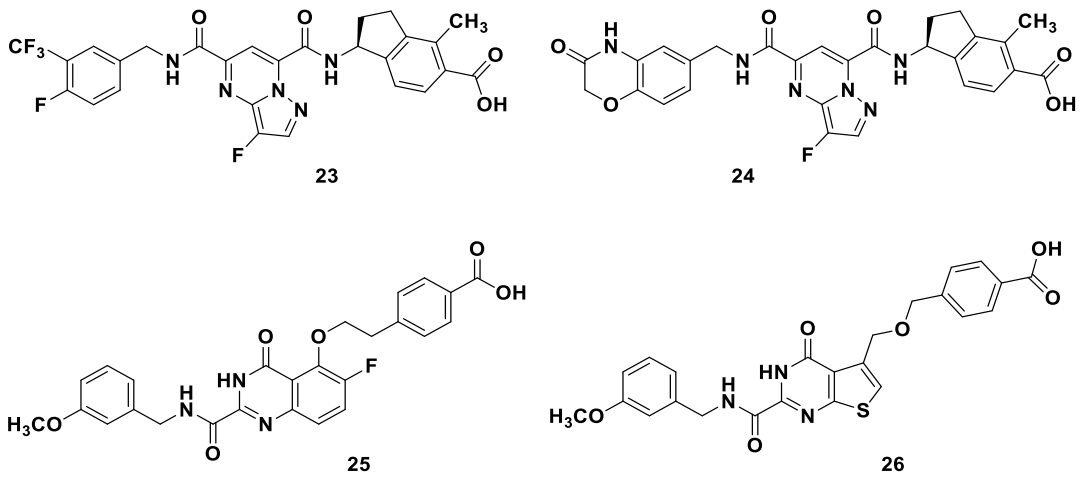


Figure 13. Fused pyrimidine-based MMP-13 inhibitors **23**-**26**.[93-97]

Because of side effects like the musculoskeletal syndrome owing to a lack of selectivity for MMP-13 and a lack of efficacy associated with the use of broad spectrum MMPIs, most inhibitors have been withdrawn from clinical studies.[98,99] A careful look at the potential inhibitors discussed above show that an ideal MMP-13 inhibitor should possess the following features:

- A Zn^{2+}-binding group of which the hydroxamate moiety should be favored because it is the strongest binder of Zn^{2+} ions among the examples mentioned.
- A long lipophilic tail or side chain that fully addresses the S1′ pocket of MMP-13. To further enhance MMP-13 selectivity, the inhibitor should possess large groups (P′) that additionally address the S1′* side pocket that is unique to MMP-13.
- Groups or moieties that undergo useful interactions such as hydrogen bonding and hydrophobic interactions with residues within the active site to increase potency and selectivity.
- Desirable pharmacokinetic profiles. A potential drug candidate should be retained in biological systems long enough to elicit the desired responses.

Hence, this project focuses on the development of inhibitors that attempt to combine all the above-mentioned points to yield potent, selective, and metabolically stable MMP-13 inhibitors.

1.3 Targeting the bacterial LpxC Enzyme

1.3.1 Bacterial antibiotic resistance

Multi-drug resistant bacterial infections are a major public health concern. According to a 2012 study by the World Health Organization (WHO), multi-drug resistant bacteria annually cause 400,000 morbidities, out of which 25,000 lead to fatalities in Europe alone.[100] For example, carbapenem-resistant *Enterobacteriaceae*, multidrug resistant *Pseudomonas aeruginosa*, and extended-spectrum-β-lactamase-producing (ESBL) *Enterobacteriaceae* pose very serious health threats to human lives.

Several other bacterial pathogens have also developed various resistance mechanisms to existing antibiotics, thus, prompting researchers both in academia and the pharmaceutical industry to make frenetic efforts in the discovery of new antibacterial compounds. To bypass the resistance mechanisms of bacteria to existing antibacterial agents, new molecules are being designed to target enzymatic pathways that have not been exploited before.[100,101]

A number of nosocomial infections, in both the developed and developing world, are caused by multi-drug resistant bacteria like *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species, the so-called ESKAPE bugs.[100,102] While significant gains have been made in the treatment of infections caused by multi-drug resistant Gram-positive organisms, same cannot be said of the multi-drug resistant Gram-negative bacteria.[103]

Though both Gram-positive and Gram-negative bacteria exhibit a peptidoglycan layer and a cytoplasmic inner membrane, Gram-negative bacteria additionally possess an outer membrane that contains lipopolysaccharides (LPS), which in turn can be subdivided into the O-antigen domain, a core oligosaccharide, and lipid A as distinct units.[100] Lipid A is essential for bacterial growth and viability. This suggests that, targeting the enzymes of lipid A biosynthesis, which have no human analogs, provides an attractive strategy for the development of new antibiotics with no off-target effects.

The biosynthesis of lipid A is catalyzed by nine enzymes. The second overall and the first irreversible step is catalyzed by the UDP-3-*O*-((*R*)-3-hydroxymyristoyl)-*N*-acetylglucosamine deacetylase, simply known as LpxC (Figure 10).

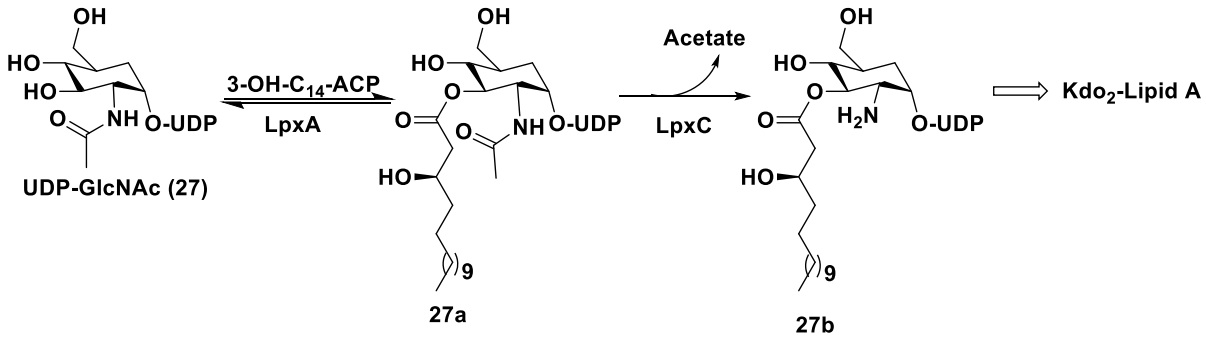


Figure 14. Lipid A biosynthesis depicting the step catalyzed by LpxC.[17]

LpxC has become an attractive target for the development of novel agents to curb the menace of multi-drug resistant Gram-negative bacteria.[104] Thus, as part of this project, novel LpxC inhibitors should be developed.

1.3.2 Lipid A and Lipopolysaccharide (LPS)

Gram-negative bacteria possess two distinct membranes, namely, an outer membrane and an inner membrane. The lipopolysaccharides (LPS) are a major constituent of the outer leaflet of the outer membrane. LPS can be subdivided into three well defined regions: an O-specific antigen, which can also be referred to as O-antigen or somatic antigen, which is a long chain polysaccharide made of identical units containing one to seven monosaccharide units; the core oligosaccharide, which is made up of approximately 10 monosaccharides; and lipid A, a β-(1→6)-linked disaccharide of glucosamine with ester, amide, and diester-linked fatty acids, and also with 4-amino-arabinose, phosphate, or both substituents on the sugars. Lipid A is released from LPS by a mild acid hydrolysis.[105] Some of the toxic effects of bacterial infections are caused by lipid A. Different bacteria have varied LPS, which may account for differences in their virulence.

Immune cells such as dendritic cells, monocytes, macrophages, and neutrophils of the host immune systems are equipped with toll-like receptors 4 (TLR4) to identify and recognize the lipid A anchor of LPS using MD-2, which is a small protein.[106] The presentation of LPS to MD-2 is also facilitated by proteins such as LBP and CD-14.[107,108] Adapter molecules such as MyD88, Mal, Tram, and Trif are then recruited by TLR4 upon activation for the propagation of a signal. Protein kinases are in turn turned on by these adapter molecules to augment the signal, thus, leading to an immune response.

High levels of LPS have been known to cause fever, increased heart rate, septic shock, and ultimately, death due to lung and kidney failure. At low concentrations, however, LPS triggers a general immune response against bacteria and viruses, thus, acting as an immunomodulator.[109-111]

1.3.2.1 Biosynthesis of LPS

The LPS are crucial for the survival of bacteria. The biosynthesis of LPS has been studied extensively to help discover ways to control Gram-negative bacteria. Although LPS is found on the cell surface, it is synthesized in the cytoplasm and transported to the cell surface of the bacteria. This process has been studied very extensively in *E. coli*. The biosynthesis starts from UDP-*N*-acetylglucosamine (UDP-GlcNAc), which is transformed by several enzymes through several steps to give LPS. Among the three major components of the LPS, lipid A is the most widely conserved.[109]

Biosynthesis of Lipid A: The first steps in the biosynthetic pathway comprise the synthesis of Kdo_2-Lipid A. This occurs on the inner surface of the inner membrane and in the cytoplasm and involves 9 enzymes. The first three reactions which are catalyzed by LpxA, LpxC, and LpxD, achieve the transformation of the starting material, UDP-GlcNAc (**27**), to UDP-diacyl-GlcN (**28**) (Figure 11). The first step, which is catalyzed by LpxA, is reversible.[112-114] The first irreversible step of the three reactions is the second one, which is catalyzed by LpxC (Figure 10). Next, UDP-diacyl-GlcN (**28**) is hydrolyzed by LpxH to give Lipid X (**29**), which is condensed with its precursor, UDP-diacyl-GlcN (**28**), by LpxB to give disaccharide 1-P (**30**).[115-117] Both LpxH and LpxB are peripheral membrane proteins, while LpxK, KdtA, LpxL, and LpxM, that catalyze the ensuing reactions of the biosynthetic pathway, are integral proteins of the inner membrane. Disaccharide 1-P (**30**) is phosphorylated at position 4′ by LpxK, a kinase, to afford lipid IV_A.[118] Using the sugar nucleotide CMP-Kdo as donor, two 3-deoxy-D-manno-octulosonic acid (Kdo) residues are incorporated by the enzyme KdtA at position 6′ of lipid IV_A.[119] The resulting product, Kdo_2-lipid IV_A, is subjected to further transformations catalyzed by LpxL and LpxM to form Kdo_2-lipid A (**31**). First, LpxL adds a secondary lauroyl residue, followed by the addition of a myristoyl residue to the distal glucosamine moiety by LpxM (Figure 11).[120]These final acylations are independent of Kdo *in vivo*.[121]

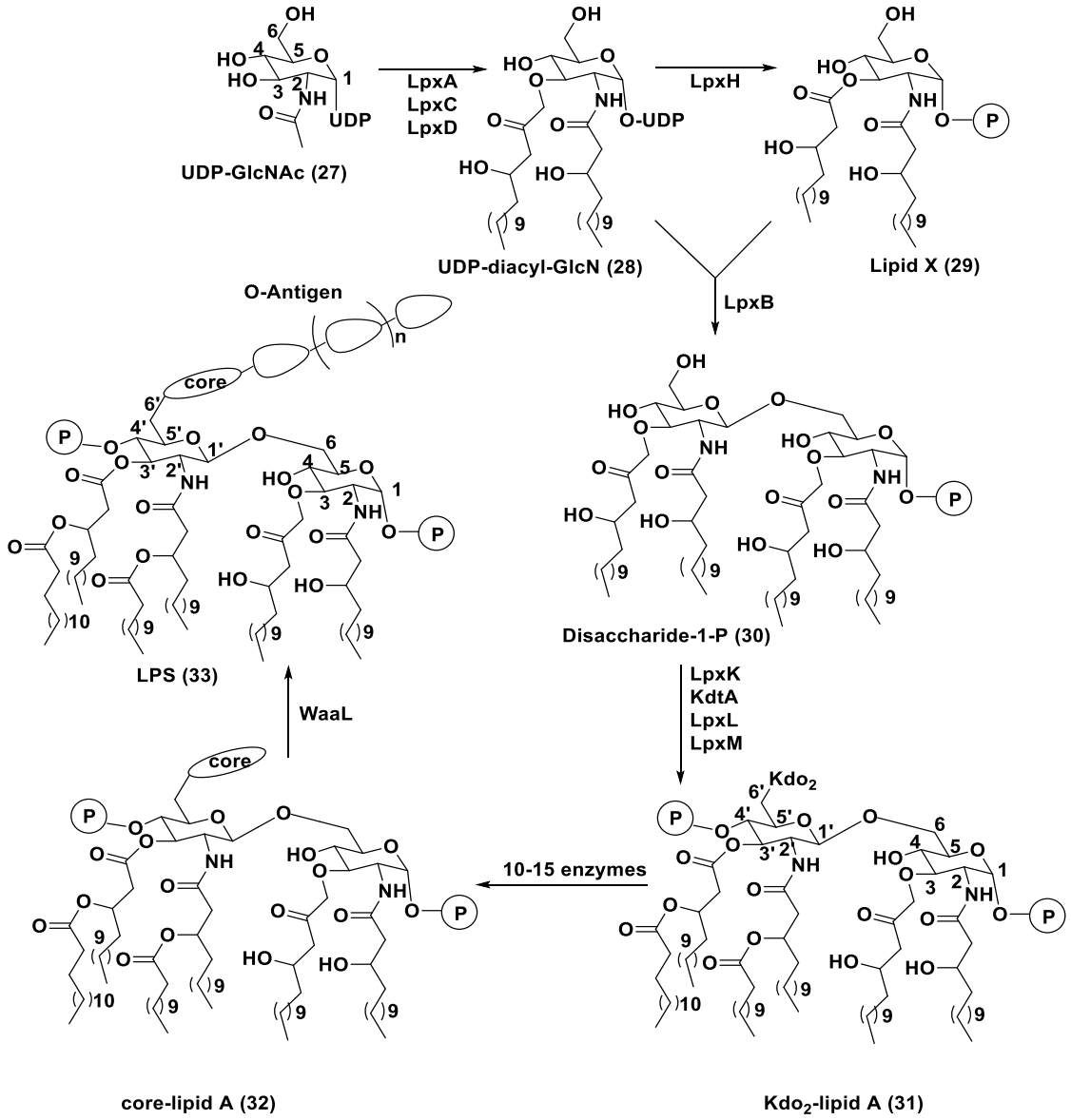


Figure 15. Structure and biosynthesis of LPS (**33**) in *E. coli*. The enzymes that catalyze the various steps are given. The names and structures of the substrates are also given, but the structures of the core oligosaccharide and O-antigen are denoted by symbols since these two regions show many variations.[109]

All nine enzymes involved in the biosynthesis of lipid A are substrate specific. Though these enzymes are generally present in Gram-negative bacteria, LpxA and LpxC are the most highly conserved.[122]

In *E. coli* and other bacterial species, the enzymes LpxD, FabZ, LpxB, and LpxA are encoded by the lpxD-fabZ-lpxA-lpxB gene cluster.[123,124] The initial steps of the lipid A biosynthetic pathway, in which (3*R*)-hydroxyacyl-ACP is used as a donor, are catalyzed by LpxA and LpxD. The dehydration of (3*R*)-hydroxyacyl-ACP to 2-*trans*-enoyl ACP, which is required for fatty acid synthesis and consequently for the synthesis of phospholipids, is catalyzed by FabZ.[125]

Therefore, this cluster of genes (lpxD-fabZ-lpxA-lpxB) plays a role in balancing the amounts of phospholipids and LPS (**33**) in bacterial membranes. Many Gram-negative bacteria have the msbA-lpxK cluster of genes: while lpxK encodes LpxK, a kinase, that phosphorylates lipid A at position 4′, msbA encodes MsbA which mainly transports LPS (**33**).[118,126]

Connection of the core oligosaccharide: Unlike the structure of lipid A that is highly conserved, the sugar moieties of the core oligosaccharide vary. The sequential assembly of the core oligosaccharide on lipid A involves membrane-bound glycosyltransferases that use nucleotide sugars as donors. This rapid and efficient assembly on lipid A happens at the cytoplasmic surface of the inner membrane. The core oligosaccharide can be subdivided into the inner core and the outer core. The inner core is connected to lipid A whereas the outer core is connected to the O-antigen. The inner core is well conserved within a genus or family and typically contains Kdo and L-glycero-D-manno-heptose (Hep).

Three operons of genes, *gmhD*, *waaQ*, and *kdtA*, code for the enzymes that are involved in the biosynthesis of the core oligosaccharide in *E. coli* and *Salmonella*.[127] For example, the two residues of Kdo are incorporated in lipid IV_A by the enzyme KdtA.[119] The biosynthesis of the inner core of *E. coli* K-12 requires the *gmhD* operon that contains g*mhD-waaf-waac-waal*.[128] The enzymes responsible for the biosynthesis and transfer of Hep are encoded by the *gmhD*, *waaF*, and *waaC* genes, while the *waaL* gene encodes the ligase enzyme that attaches O-antigen to core-lipid A.[129] Comparatively, there is more structural diversity within the outer core. The enzymes involved in the biosynthesis and modification of the outer core polysaccharide are encoded by genes contained in the *waaQ* operon.

O-antigen addition to form LPS (33): The O-antigen repeat is also synthesized on the cytoplasmic surface of the inner membrane. Membrane-associated glycosyltransferases assemble the O-antigen units using sugar nucleotides as donors. In *E. coli* and *Salmonella enterica*, the enzymes that synthesize the unique O-antigen sugar nucleotide precursors, glycosyltransferases and polymerases that assemble O-antigen and the components that traffic O-antigen polymers across the inner membrane, are encoded by the *rfb* cluster of genes.[130] The O-antigen of the LPS (**33**) may be homopolymeric or heteropolymeric, and the connected O-antigen units may be straight or branched. Additionally, the monomeric units as well as the stereochemistry and position of the *O*-glycosidic linkages may vary. Thus, the O-antigens of the LPS (**33**) are not conserved. For example, in *S. enterica* and *E coli*, though there are 60 and 164 O-antigen groups, respectively, only three structures are overlapping in both bacteria.[109]

After their synthesis on the inner face of the inner membrane, core-lipid A and the O-antigen repeat are trafficked to the periplasmic face of the inner membrane for further transformation.

To afford LPS (**33**), the O-antigen repeats are polymerized by the polymerase Wzy and the co-polymerase Wzz and joined to core-lipid A by the ligase Waal.[131]

1.3.3 Structure, function, and mechanism of LpxC

The first committed step in the biosynthetic pathway of lipid A in Gram-negative bacteria is catalyzed by the Zn^{2+}-dependent enzyme LpxC, which catalyzes the irreversible deacetylation of UDP-3-*O*-((*R*)-3-hydroxymyristoyl)-*N*-acetylglucosamine (**27a**) to yield UDP-3-*O*-((*R*)-hydroxymyristoyl)-glucosamine and acetate (**27b**). As such, the inhibition of LpxC blocks this very crucial step, preventing the synthesis of lipid A, which is essential for bacterial viability and survival.[132]

Though LpxC is a Zn^{2+}-dependent enzyme, other divalent cations such as Co^{2+}, Ni^{2+}, Fe^{2+}, and Mn^{2+} also support enzymatic activity.[132,133] The fact that LpxC activity is completely lost when the enzyme is incubated with metal chelators like ethylenediaminetetraacetic acid (EDTA) and dipicolinic acid (DPA) shows that one or more Zn^{2+} ions are required for catalytic activity. The loss of LpxC activity following incubation with these chelators can be reversed by the addition of Zn^{2+} ions. Purified samples of *E. coli* LpxC contained Zn^{2+} according to inductively coupled plasma emission spectroscopy (ICP). In spite of this, the enzyme is inhibited when more than one equivalent of Zn^{2+} is added. The inhibitory Zn^{2+} engages in coordination with groups that are pivotal for catalysis like a carboxylate side chain that acts a general acid-base catalyst.[101,132,134]

The LpxC enzyme has two main domains, domain I and domain II, exhibiting similar folds. Each domain has a double layer of secondary structural elements, with a primary β-sheet having a layer of two α-helices packed against it (Figure 12).[113,135,136] Besides these structural motifs, each domain contains a unique insert region. While a small antiparallel β-sheet composed of three strands is formed by the insert region of domain I, the one of domain II displays a β-α-α_L-β motif and forms a hydrophobic tunnel. The main β-sheets and the two insert regions are somewhat perpendicular to each other. The packing of the two domains is such that the α-helices are sandwiched between the β-sheets (Figure 12). The α1 of domain I and the α1′ of domain II intersect each other, forming an angle of approximately 70°. The two insert regions that make up the active site of the enzyme are found on the same side of the enzyme.[101,135]

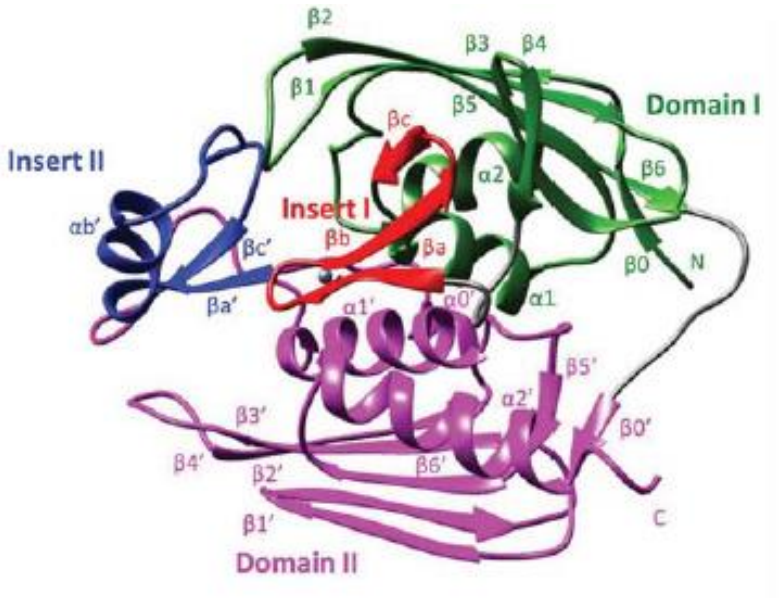


Figure 16. Structure of the LpxC from *Aquifex aeolicus* (PDB 1XXE). Domain I is given in green, Domain II is in magenta, Insert I in red and Insert II in blue. The Zn^{2+} is depicted as a gray sphere.[122]

Originally, it was assumed that in analogy to other metalloamidases, the catalytic Zn^{2+} in LpxC is coordinated by four ligands in a tetrahedral geometry. Site-directed mutagenesis of 10 conserved His, Asp, and Glu residues revealed two histidine residues (His74 and His226 of *Aquifex aeolicus* LpxC) as ligands. Either His253 or Asp234 was suggested to be the third ligand and the fourth ligand was assumed to be a water molecule. In the crystal structure of the *Aquifex aeolicus* LpxC-TU-514 complex, His74 and His226 were positioned side by side as a result of the packing of α1 in domain I and α1′ in domain II. The hydroxamate moiety of the inhibitor (TIU-514) was positioned nearby, hence, allowing a good geometry for coordination of the Zn^{2+} (Figure 13a). Since His253 and Asp 234 were positioned at distances of 4.5 Å and 8.5 Å, respectively, they were not able to coordinate Zn^{2+}. Within the LpxC enzymes, Asp230 is highly conserved and well positioned to coordinate Zn^{2+} and thus, acts as the third ligand. A mutation of Asp230 to Ala led to more than 1000-fold loss of enzyme activity, thus, confirming it as the third ligand (Figures 13a and 13b). The oxygen of the hydroxamate moiety is bound to the catalytic Zn^{2+} as the fourth ligand, which is presumably replaced by a water molecule when the native substrate is bound to the enzyme (Figures 13a and 13b).[132,135] Thus, the Zn^{2+}-binding motif of the LpxC metalloamidases is characterized by three non-water zinc ligands, namely two histidines and one aspartate.[113]

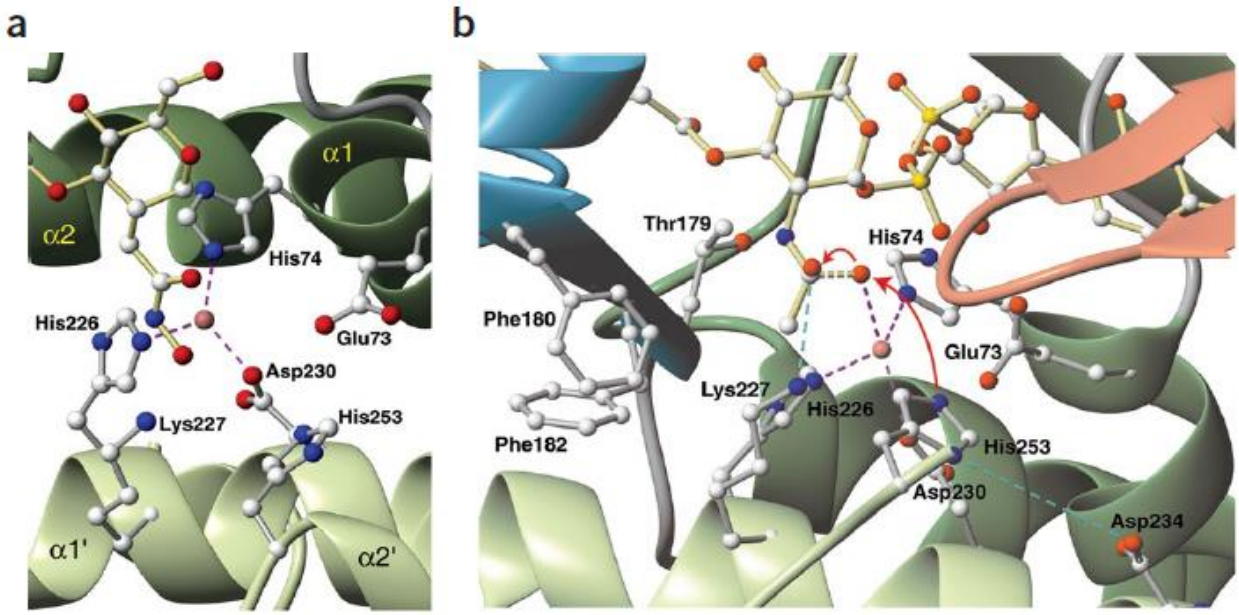


Figure 17. Structure of the active site and proposed catalytic mechanism. (a) Active site of LpxC with TU-514 bound. (b) Proposed mechanism of the LpxC enzyme displaying the model of the reaction transition state. Activation of water by His 253 and the nucleophilic attack by the activated water molecule on the carbonyl carbon are shown with orange arrows. Dashed lines show partial bonding between water and substrate (yellow), coordination of water to zinc (magenta), and salt bridges between oxyanion and Lys227, and between His253 and Asp234 (blue). The dark green ribbons represent Domain I and the light green ribbons, Domain II.[135]

The mechanism of the AalpxC-catalyzed reaction is similar to the one of other metalloamidases involving a general catalytic base and a general catalytic acid.[101] Two possible reaction mechanisms were suggested for LpxC based on structural and kinetic studies (Figure 14).[132] In the first mechanism, glutamate (Glu78) acts as base to activate the Zn^{2+}-water complex by abstracting a proton. Then, the formed hydroxide ion attacks the carbonyl carbon of the substrate. The Zn^{2+} interacts with the carbonyl oxygen which leads to the polarization of the ground state and the stabilization of the tetrahedral intermediate. Additionally, a positively charged histidine (His265) stabilizes the tetrahedral intermediate. Finally, protonation of the amine leaving group by the protonated glutamate (Glu78), acting as the general acid catalyst, collapses the tetrahedral intermediate. In the mechanism just described, glutamate (Glu78) plays a bi-functional role of a general acid-base catalyst (GABC) (Figure 14A). In an alternative mechanism, histidine (His265) and glutamate (Glu78) act as a GABC pair. The Zn^{2+}-water complex acts as nucleophile, and the Zn^{2+} polarizes the carbonyl oxygen by interacting with it. Here, coordination with Zn^{2+} and hydrogen bonding with a threonine residue (Thr191) stabilize

the tetrahedral intermediate. Finally, the tetrahedral intermediate collapses when being protonated by histidine (His265) (Figure 14B).[101,132,133]

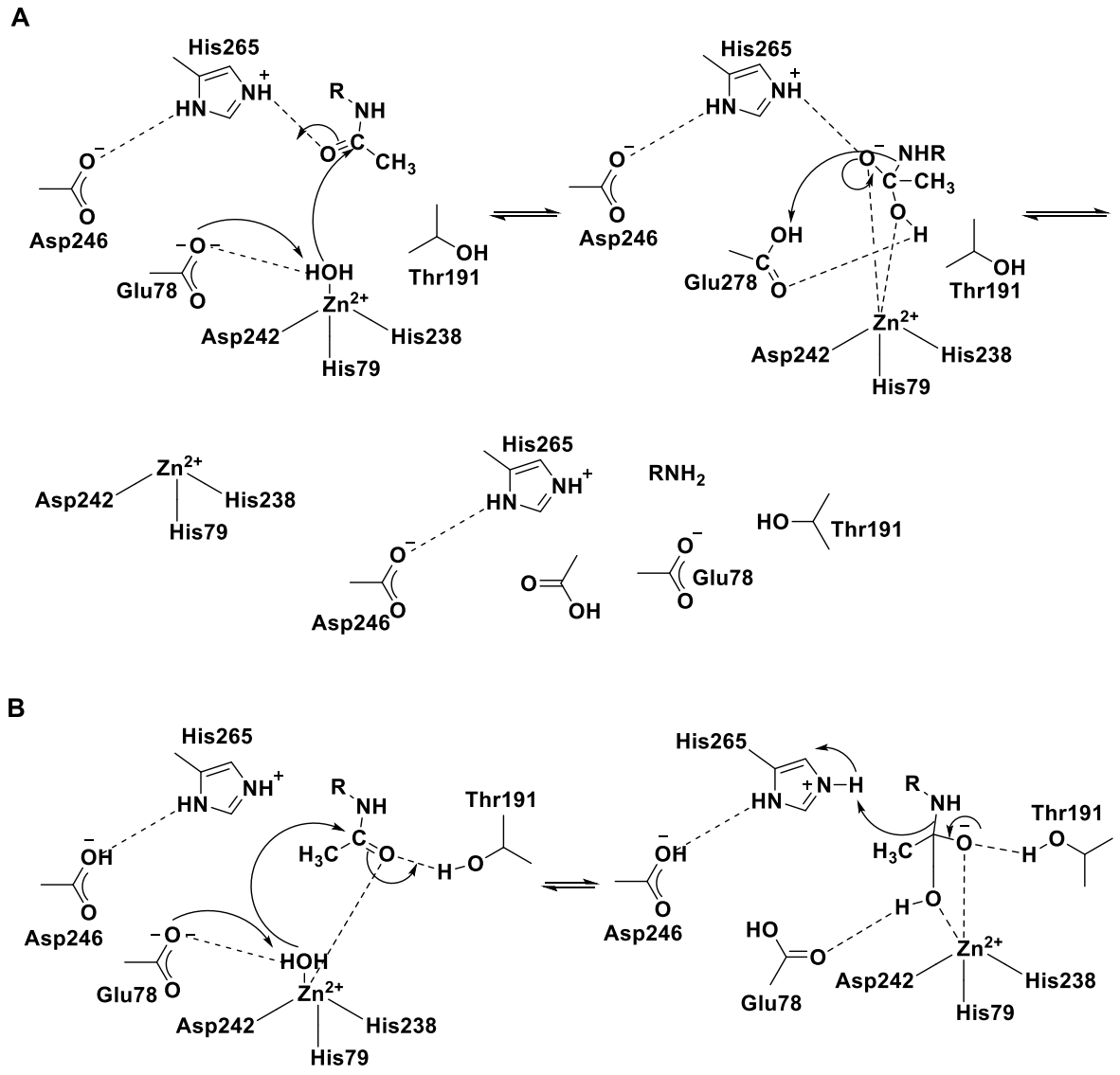


Figure 18. Proposed LpxC mechanisms using a bi-functional GABC (Panel A) or a GABC pair (Panel B).[101,132]

As mutations of glutamate in the active site of LpxC had no effect on enzymatic activity, it was unlikely to be the catalytic general base. In contrast, mutations of histidine, lysine, and aspartate led to an inactivation of the LpxC enzyme. These observations emphasized the importance of lysine, histidine, and aspartate to LpxC catalysis. The glutamate is orientated such that it forms a hydrogen bond with the histidine, thereby functioning as an outer coordination shell. It may also help to stabilize the histidine or position the catalytic water molecule.

Studies on the *A. aeolicus* LpxC enzyme show that it is able to bind a second inhibitory Zn^{2+} located in the active site.[137] The inhibitory Zn^{2+} forms a bridged structure with the catalytic water by binding well-positioned histidine and glutamate residues. The fourth group that binds the inhibitory Zn^{2+} is not yet known. In case of *E. coli*, this fourth group that binds the inhibitory Zn^{2+} is assumed to be a cysteine residue.[122]

1.3.4 Inhibitors of LpxC

Most LpxC inhibitors described in the literature are small molecules that have certain structural similarities. They contain a Zn^{2+}-binding group (for example, a hydroxamic acid) and a lipophilic tail which mimics the 3-hydroxyacyl moiety found in the natural substrate of LpxC. The lipophilic tail addresses the hydrophobic tunnel of the enzyme and interacts with the enzyme via van der Waals interactions.[138]

Literature is replete with compounds based on very different chemical scaffolds that target and inhibit LpxC to varying degrees. A potent inhibitor is the threonyl hydroxamate compound CHIR-090 (**34**) (Figure 15). It is bactericidal against *E. coli* and *P. aeruginosa in vitro*. However, in comparison to *E. coli*, it is 600-fold less active against orthologs from the Rhizobiaceae family. While this raised concerns of a possible antibiotic resistance to CHIR-090 (**34**), structural and biochemical studies of the LpxC/CHIR-090 complex have revealed that the reduced activity against members of the Rhizobiaceae family is due to van der Waals clashes between the distal phenyl ring of the diphenylacetylene tail of CHIR-090 (**34**) and residues located within the hydrophobic tunnel.[139]

To avoid the unwanted van der Waals clashes that diminish antibacterial activity, newer molecules were based on chemical scaffolds with smaller radii. For instance, 1,4-diphenyl-1,3-butadiyne (diphenyldiacetylene)-based LPC-009 (**35**) (Figure 15) demonstrated better activity (more than 2-4-fold) against *E. coli* (0.05 μg/mL) and *P. aeruginosa* (0.74 μg/mL) than CHIR-090 (**34**). Also, LpxC enzymes of bacteria from the Rhizobium family were more susceptible to LPC-009 (**35**) because of a reduction (~20-fold) in resistance as compared to CHIR-090 (**34**).[139,140]

Extensive efforts by Achaogen Inc to find agents against multi-drug resistant *P. aeruginosa* led to the development of the LpxC inhibitor ACHN-975 (**36**), a butadiyne derivative (Figure 15).[141] Till date, it is the first and only LpxC inhibitor to enter phase I human clinical trials, but had to be withdrawn due to cardiovascular toxicity. It showed pronounced activity against multi-drug resistant *P. aeruginosa*, including wild-type strains (MICs ≤1 μg/mL), and several

other Gram-negative bacteria such as *E. coli* (MIC = 0.125 μg/mL), *K. pneumoniae* ATCC43816 (MIC = 0.5 μg/mL), *Yersinia enterocolitica* (MIC = 2 μg/mL), just to mention a few. In spite of this impressive spectrum of activity against Gram-negative bacteria, ACHN-975 (**36**) showed almost no activity against *A. baumannii*, possibly because of its ability to cope with the loss of LPS (**33**).[140,142]

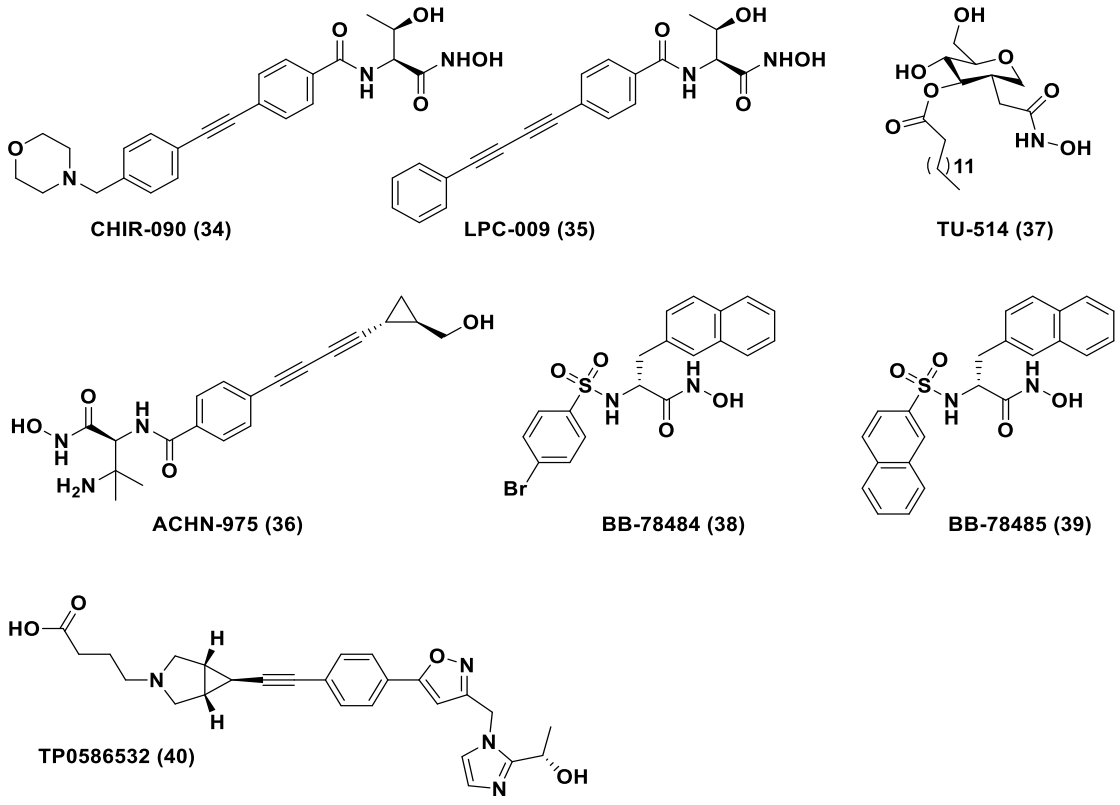


Figure 19. Structures of some LpxC inhibitors from the literature.[101,139,140,143]

To discover broad spectrum LpxC inhibitors, JACKMAN and coworkers led an effort to synthesize a new series of substrate analogs that mimic the hexose and acyl chain moieties but had a hydroxamate group in place of the acetate. Among this series, TU-514 (**37**) (Figure 15) was one of the most potent molecules and also demonstrated the broadest range of LpxC inhibition. For AaLpxC, the K_i values were 1 nM and 650 nM at pH of 7.4 and 5.5, respectively, while for EcLpxC, the K_i value was 650 nM at both pH 7.4 and 5.5. Even though most LpxC orthologs, including PaLpxC, were inhibited by TU-514 (**37**) with a similar potency, it had no antimicrobial activity. This could be due to the long hydrophobic acyl chain preventing the penetration of the cell wall by TU-514 (**37**).[101,144]

In 2002, two branched sulfonamide-based compounds, BB-78484 (**38**) and BB-78485 (**39**), were reported (Figure 15).[145] These two unique compounds have a hydroxamate core with two hydrophobic moieties around it. For EcLpxC, the estimated dissociation constants for BB-78484 (**38**) and BB-78485 (**39**) were 50 nM and 20 nM, respectively. Thus, BB-78485 (**39**) was the most potent LpxC inhibitor at the time.[146] Both compounds were very active against a number of Gram-negative organisms, including *Serratia*, *Burkholderia*, and *Klebsiella*. However, *P. aeruginosa* was found to be resistant to both compounds.[101]

Bacterial LPS is implicated in the pathophysiology of sepsis and septic shock in patients. High levels of LPS trigger the release of pro-inflammatory cytokines like interleukin (IL)-6, which can lead to septic shock and possibly to death.[147,148] Conventional antibiotics like the beta-lactams, which are usually first-line antibiotics, are able to induce LPS release both *in vitro* and *in vivo*, and can cause adverse effects in patients suffering from sepsis.[149] To reduce LPS production by bacteria, a non-hydroxamate LpxC inhibitor, TP0586532 (**40**), was developed (Figure 15). It exerted a better inhibitory effect on LPS production (58-225 EU mL^{-1}) in *Klebsiella pneumonia* than ciprofloxacin (1770-13106 EU mL^{-1}), ceftazidime (4809–5321 EU mL^{-1}), and meropenem (2837-10937 EU mL^{-1}) *in vitro*. Furthermore, though TP0586532 (**40**), ciprofloxacin, and meropenem/ cilastatin showed equivalent efficacy in reducing the viable cell count of *K. pneumonia* in the lungs of mice, the TP0586532 (**40**)-treated mice had the lowest levels of IL-6 in the lungs.[143]

2.0 AIM OF THE PROJECT

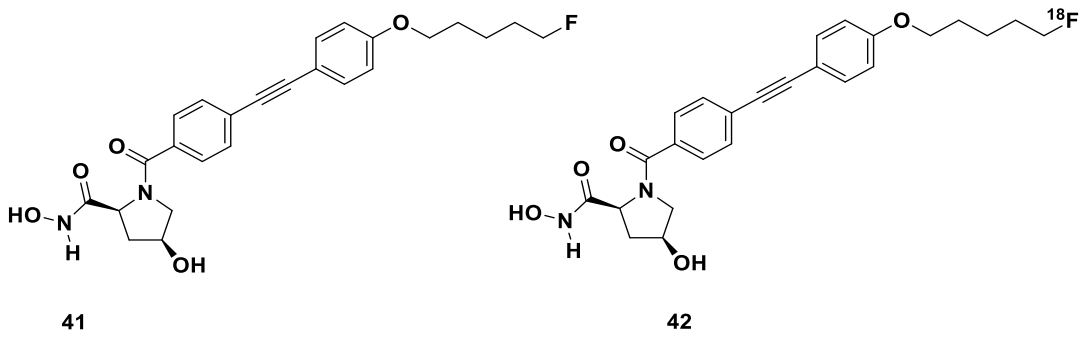
The aim of this project was the development of potent and selective inhibitors of the Zn^{2+}-dependent enzymes MMP-13 and LpxC based on proline-derived scaffolds. To realize this goal, the following objectives were set:

1. Propose structural modifications to lead compound **41** (Figure 16), which from a previous work selectively and potently inhibited MMP-13;
2. To devise and implement synthetic strategies for affording the envisaged compounds;
3. Using selected intermediates of MMP-13 target compounds as scaffolds for synthesizing LpxC inhibitors;
4. To evaluate the biological activities of the synthesized compounds in appropriate assays;
5. To elaborate structure-activity relationship studies for synthesized compounds.

2.1 Targeting MMP-13: Lead compounds and envisaged modifications

HOLL and co-workers synthesized the (2*S*,4*S*)-configured 4-hydroxyproline derivative **41** (Figure 16), which selectively inhibited MMP-13 in the picomolar range (IC_{50} (MMP-13) = 0.7 nM) with selectivities over MMPs-2, -8, and -9 ranging from 71 to 1543. The respective [^{18}F]-labeled compound **42** (Figure 16) was used as PET-tracer. Although the compound was found to be stable in human and mouse serums, an *in vivo* biodistribution study in mice showed that it was rapidly washed out from blood, revealing a hepatobiliary excretion pathway (Figure 16).[19] This indicated poor pharmacokinetic properties of the compound, which might result from metabolic instability.

A



B

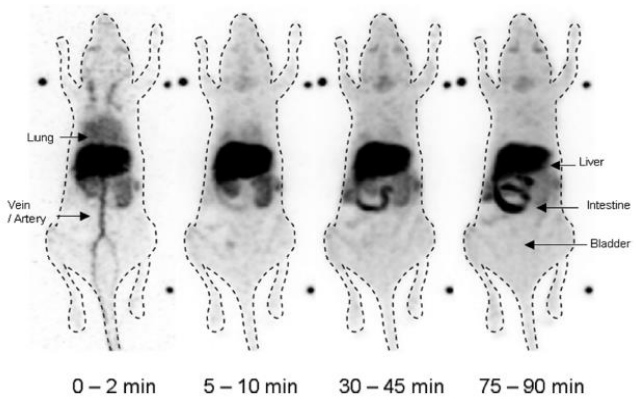


Figure 20. (A) Structures of hydroxyproline derivative **41** and the radiolabeled compound **42**. (B) The *in vivo* biodistribution of **42** in mice.[19]

Structural considerations suggest that, the main routes of metabolism of compound **41** might be hydrolysis or glucuronidation of the hydroxamate moiety, oxidation of the secondary alcohol, amide cleavage, and *O*-dealkylation of the 5-fluoropentyl moiety. Therefore, these functional groups should be bioisosterically replaced by metabolically more stable groups.

Thus, the aim of this project was the development of a compound that is still a very potent and selective MMP-13 inhibitor, but exhibits improved pharmacokinetic properties, thus, being excreted from systemic circulation less rapidly.

The synthetic plan to optimize the (2*S*,4*S*)-configured 4-hydroxyproline derivative in that way was divided into two main parts:

2.1.1 Variation of the lipophilic side chain

The lipophilic side chain addresses the S1′ pocket of the enzymes which varies in length and amino acid residues among the MMP isoforms. The S1′ pocket of MMP-13 is long and together with its unique S1′* side pocket, MMP-13 can accommodate ligands with long lipophilic chains. Therefore, the long lipophilic side chain employed should enhance MMP-13 selectivity.

In order to prevent *O*-dealkylation of the 5-fluoropentyl moiety, the oxymethylene moiety of **41** should be replaced with ethylene, vinylene, and acetylene moieties (Figure 17). The hydroxylated and fluorinated derivatives of the envisaged hydroxamic acids should be synthesized.

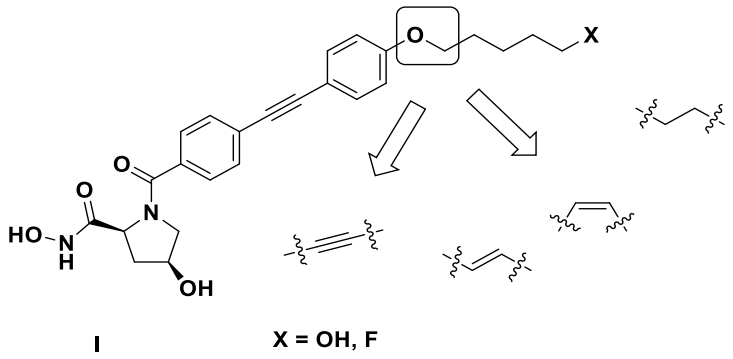


Figure 21. Compound **I** depicting functions that will replace the oxymethylene moiety of compound **41**.

2.1.2 Variations at the core structure

The amide moiety linking the lipophilic side chain with the pyrrolidine core structure will be replaced by a sulfonamide, which is more resistant to hydrolysis[150] (Figure 18A). The configuration of the carbon atom in position 4 of the pyrrolidine ring will be inverted via a MITSUNOBU reaction to afford a diastereomeric pair of sulfonamide-based hydroxamic acids. Additionally, to broaden structure-activity relationships, the lipophilic side chain should be moved from position 1 to position 4 of the pyrrolidine ring, where it should be anchored via benzyloxy, *N*-benzyl amine, and phenyltriazolyl moieties. Simultaneously, various substituents should be introduced at the pyrrolidine nitrogen, for example, methyl, ethyl, benzyl, formyl, acetyl, and benzoyl groups, or the nitrogen should remain unsubstituted (Figure 18B). As envisaged for the sulfonamide-based compounds, both (4*R*)- and (4*S*)-configured hydroxamic acids should be accessed in chiral pool syntheses. The retention of the very long lipophilic side

chain in the envisaged compounds, particularly in the triazole-based hydroxamic acids, is to enhance MMP-13 selectivity, since the enzyme has a deep S1′ pocket.

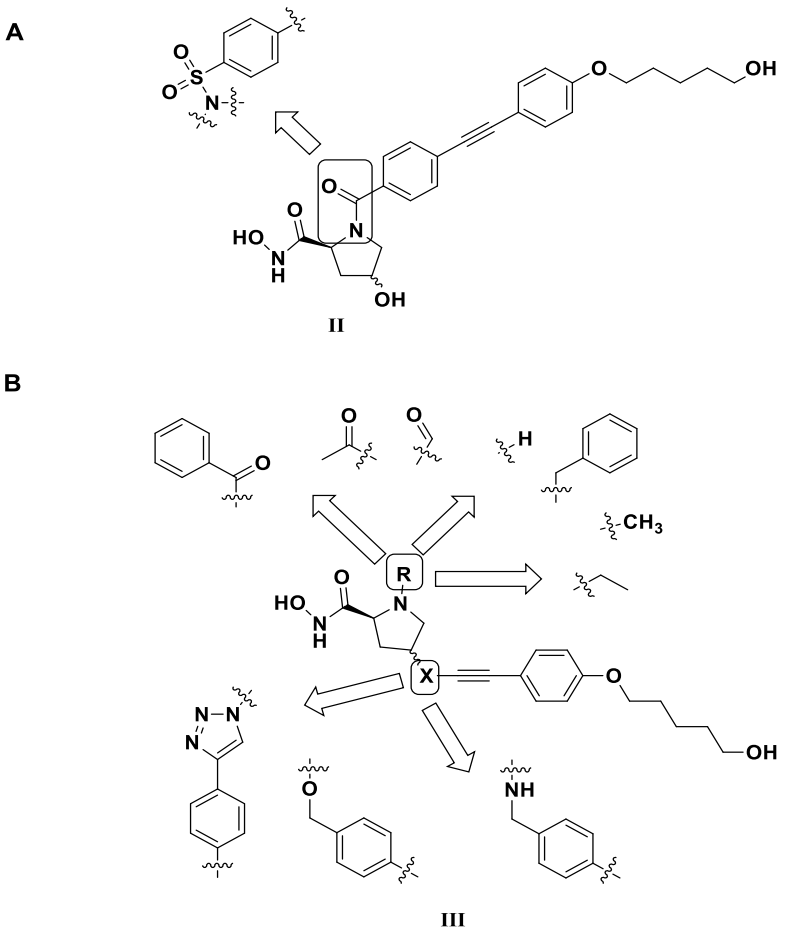


Figure 22. Variations at the core structure of compound **41**. (A) Compound **II** depicting a replacement of the amide moiety by linking the lipophilic side chain via a sulfonamide. (B) Compound **III** shows the introduction of the lipophilic side chain in position 4 of the pyrrolidine ring while varying the residue on the nitrogen.

2.2 Targeting LpxC: Envisaged inhibitors with proline-based scaffolds

One of the most potent LpxC inhibitors developed to date is CHIR-090 (**34**), which is based on threonine (Figure 19).[139]

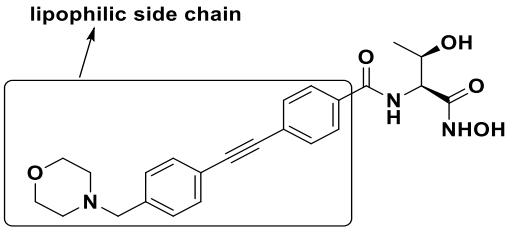


Figure 23. Structure of CHIR-090 (**34**) highlighting the lipophilic side chain that should be used.

In order to reduce the conformational flexibility of CHIR-090 (**34**), the threonine moiety should be replaced by a proline-based scaffold. This approach seemed to be feasible as threonine and the envisaged proline-based scaffolds have common atoms or pharmacophoric elements that may be needed for beneficial interactions with residues in the LpxC active site being responsible for the antibacterial activity of CHIR-090 (**34**).

Thus, selected intermediates of the syntheses of the envisaged MMP-13 inhibitors should be used as starting materials for the syntheses of LpxC inhibitors. Particularly, the compounds should exhibit the morpholinomethyl-substituted diphenylacetylene side chain of CHIR-090, which addresses the hydrophobic tunnel of LpxC. Thus, besides sulfonamide-based LpxC inhibitors **IV**, *N*-benzoyl-, *N*-benzyl-, and *N*-unsubstituted benzylamine-, ether-, and triazole-based proline derivatives **V** bearing the lipophilic side chain of CHIR-090 should be synthesized (Figure 20). All envisaged LpxC inhibitors should bear a diphenylacetylene and a hydroxamate moiety very much like CHIR-090.

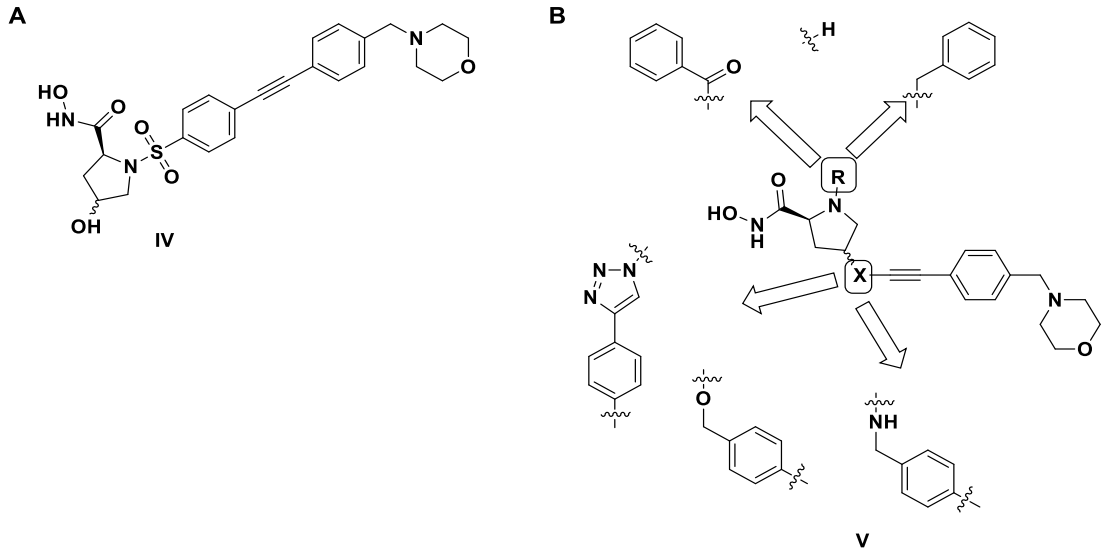


Figure 24. Envisaged LpxC inhibitors. (A) Sulfonamide-based LpxC inhibitors **IV**. (B) Other LpxC inhibitors **V** with benzyloxy, phenyltriazolyl, and benzylamine linkers in position 4 of the pyrrolidine ring and varying residues on the nitrogen.

2.3 Synthesis plan

2.3.1 MMP-13 inhibitors

2.3.1.1 Variation of the lipophilic side chain

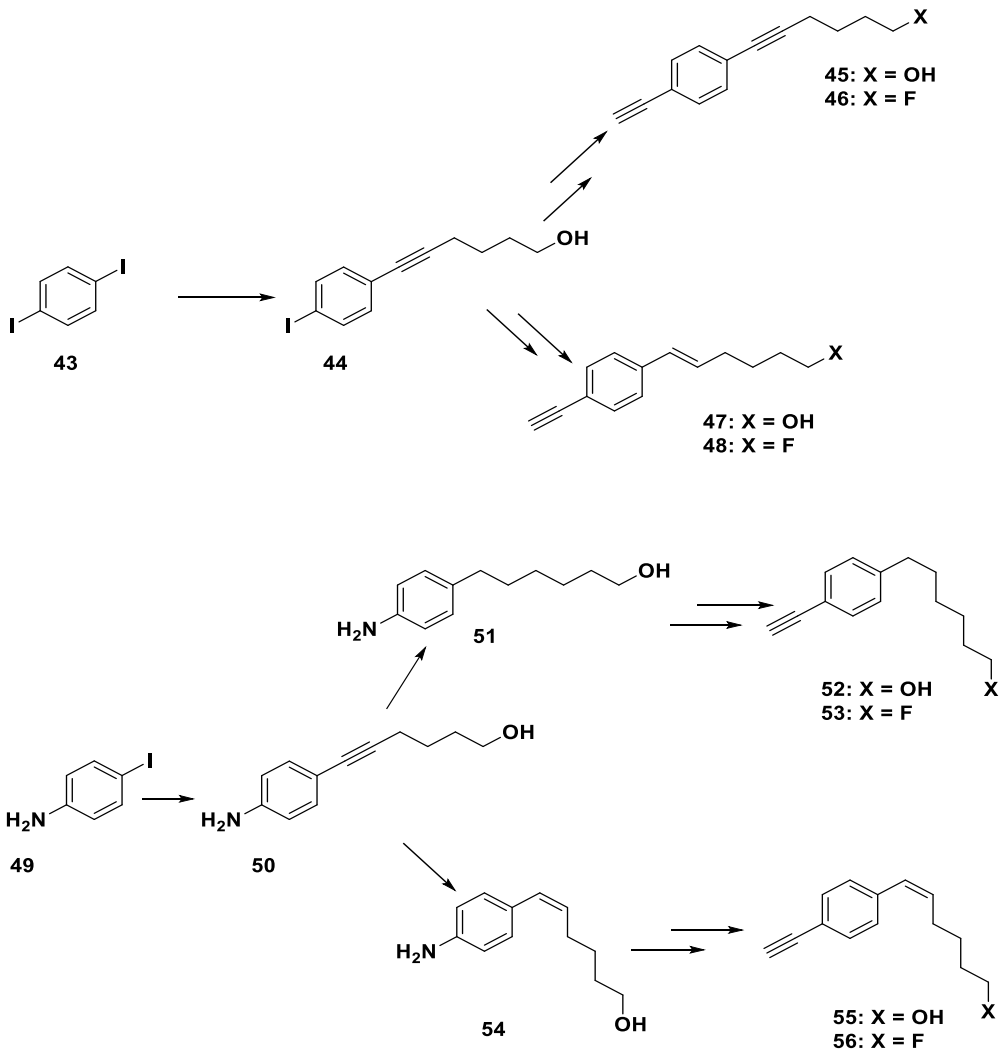
To address the metabolic instability of **41** while retaining MMP-13 selectivity and potency, the oxymethylene moiety of the lipophilic side chain ought to be replaced with alkyne, alkene (*cis* and *trans*), and alkane moieties to prevent *O*-dealkylation.

Thus, to obtain alkynyl side chains **45** and **46**, 1,4-diiodobenzene (**43**) should be subjected to a SONOGASHIRA coupling with hex-5-yn-1-ol to yield compound **44**. Subsequently, the aryl iodide should be coupled with trimethylsilylacetylene and the resulting product should be desilylated to give alcohol **45**. The fluorination of alcohol **45** with DAST should lead to fluorinated derivative **46** (Scheme 1).

To obtain *trans*-alkenes **47** and **48**, alkyne **44** should be partially reduced. Another SONOGASHIRA coupling of the *trans*-alkene intermediate with trimethylsilylacetylene should give the protected terminal alkyne, which when treated like described for the alkynyl side chains should yield hydroxylated and fluorinated derivatives **47** and **48**, respectively (Scheme 1).

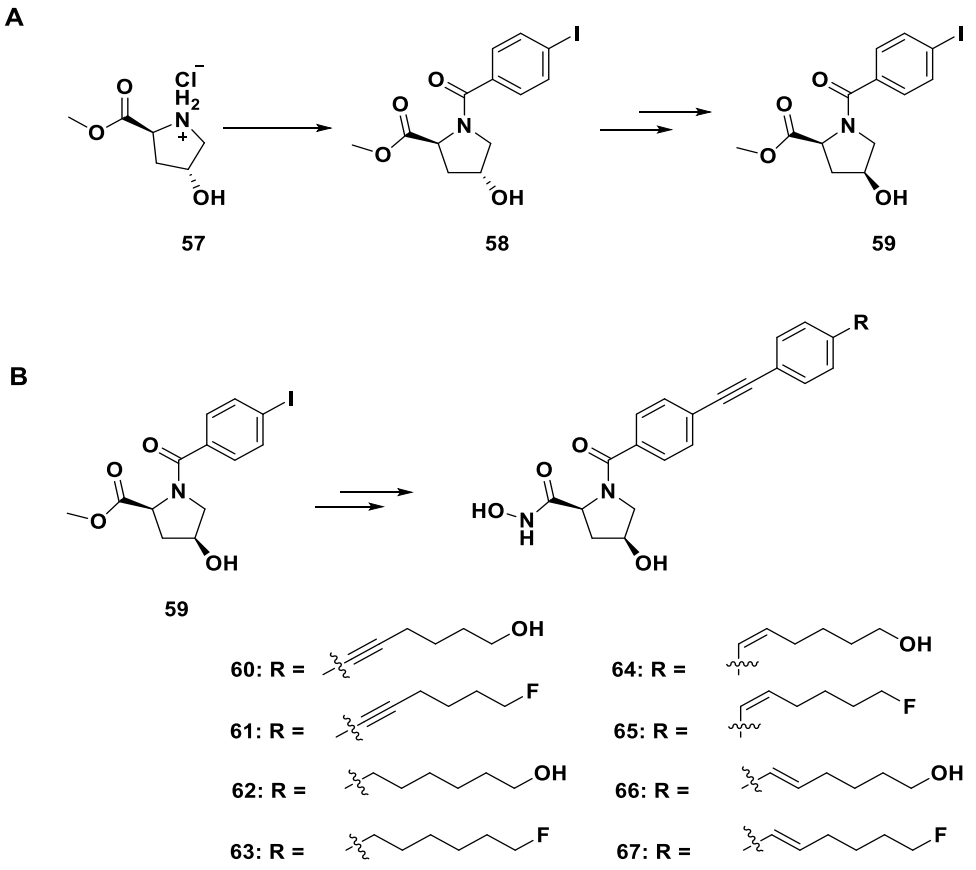
To replace the oxymethylene moiety with ethylene, 4-iodoaniline (**49**) should undergo a SONOGASHIRA coupling with hex-5-yn-1-ol and the resulting alkyne **50** should be reduced fully to give **51**. To enable coupling with the proline scaffold **59**, the primary aromatic amine **51** should be transformed into a terminal alkyne. Hence, **51** should be subjected to diazotization and a C-C coupling reaction with trimethylsilylacetylene and the resulting product, as before, should be desilylated and fluorinated to access hydroxylated and fluorinated derivatives **52** and **53**, respectively (Scheme 1).

In order to afford the respective *cis*-alkenes, alkyne **50** should be partially reduced under a hydrogen atmosphere using a LINDLAR catalyst to yield *cis*-alkene **54**. To obtain hydroxylated and fluorinated derivatives **55** and **56**, **54** should be transformed like **51** (Scheme 1).



Scheme 1. Synthetic strategy to access the lipophilic side chains.

In order to anchor the lipophilic side chain to the proline scaffold, (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**57**) should be acylated to give amide **58**. The desired (4*S*)-configured proline scaffold (**59**) should be obtained by inverting the configuration in position 4 of the pyrrolidine ring of **58** via a MITSUNOBU reaction (Scheme 2). To afford the envisaged hydroxamic acids, the various lipophilic side chains should then be coupled with aryl iodide **59** and the resulting diphenylacetylene derivatives subjected to aminolyses with hydroxylamine (Scheme 2).

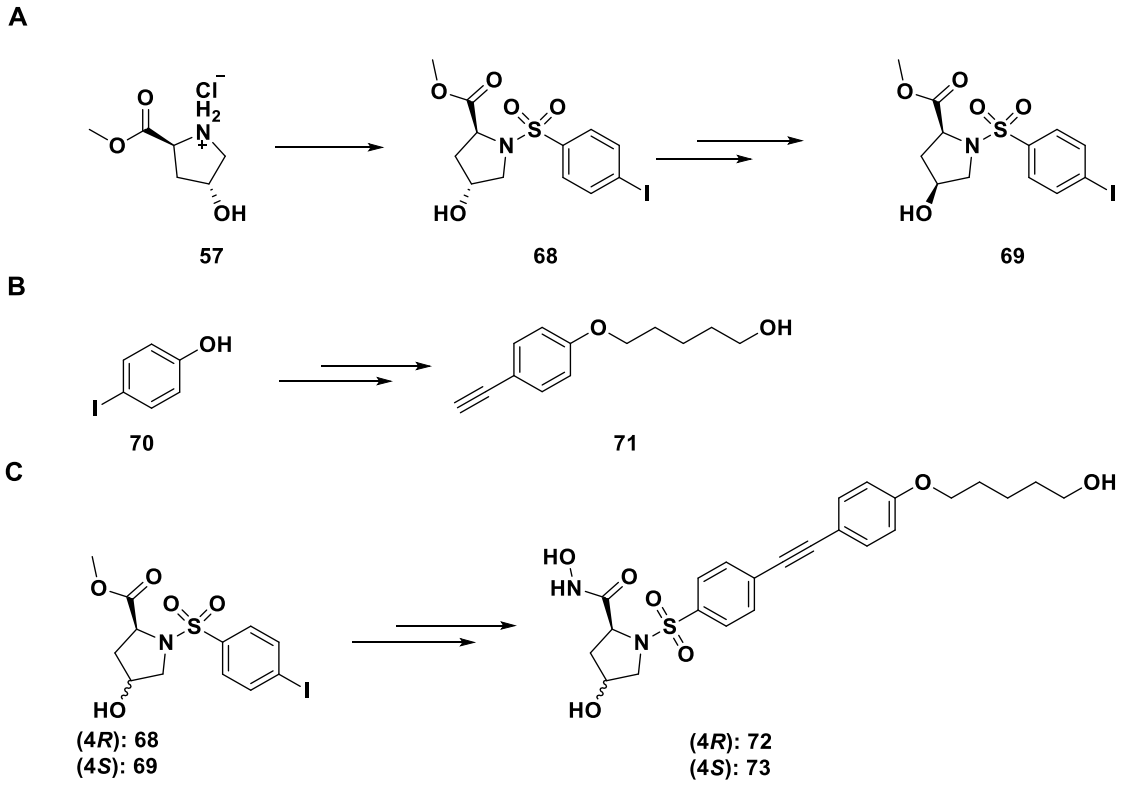


Scheme 2. (A) Strategy for synthesizing proline scaffold **59**. (B) Synthetic plan for envisaged hydroxamic acids **60**-**67** with different lipophilic side chains.

2.3.1.2 Variations at the core structure

To avoid hydrolysis of the amide moiety of **41**, it should be replaced by a sulfonamide, which is more stable to hydrolysis. Thus, proline derivative **57** should be subjected to sulfonylation to give sulfonamide **68**. The diastereomer of **68**, which is **69**, should be obtained via a MITSUNOBU reaction (Scheme 3A). To afford terminal alkyne **71**, 4-iodophenol (**70**) should be sequentially

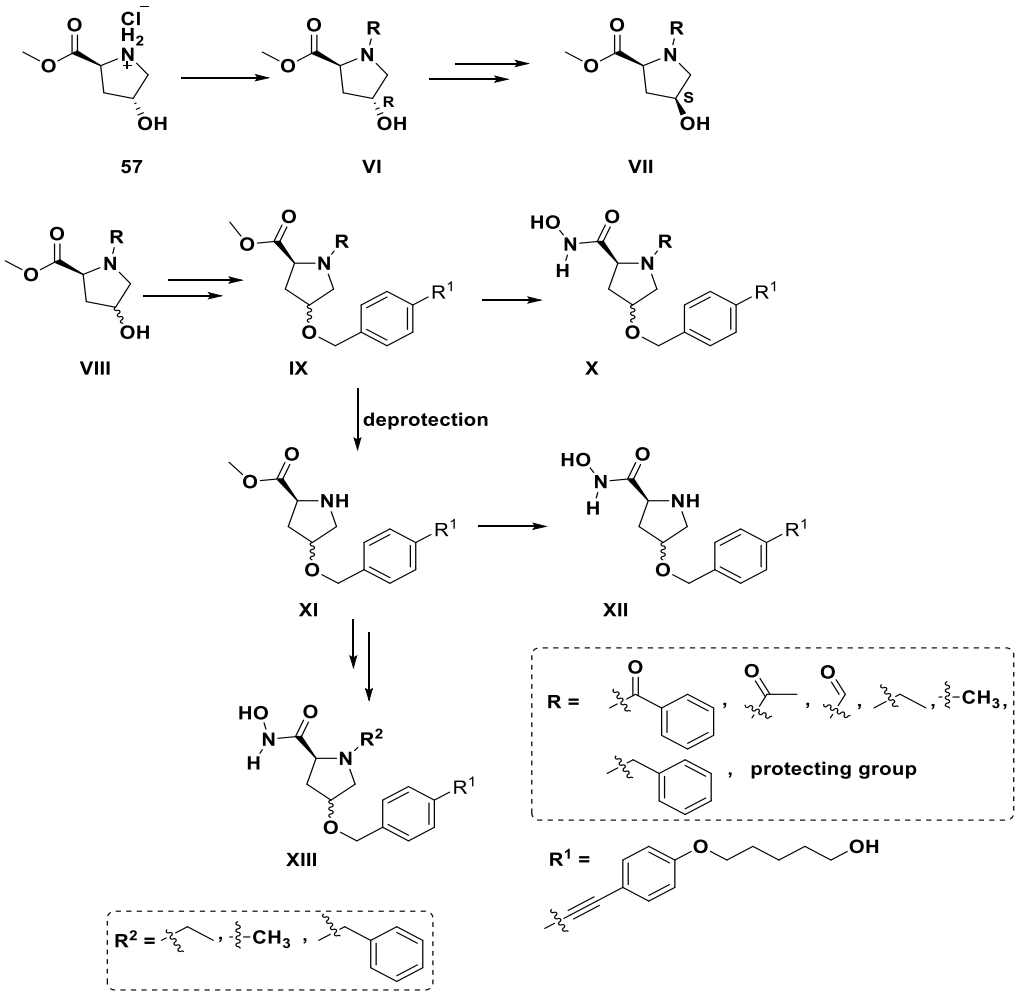
transformed via *O*-alkylation, C-C coupling with trimethylsilylacetylene, and desilylation. After the Sonogashira couplings of **71** with **68** and **69**, the obtained esters should be finally subjected to aminolyses to give hydroxamic acids **72** and **73** (Schemes 3B and 3C).



Scheme 3. (A) Syntheses plan for diastereomeric sulfonamides **68** and **69**. (B) Synthesis plan for the terminal alkyne **71**. (C) Syntheses plan for the envisaged diastereomeric sulfonamide-based hydroxamic acids **72** and **73**.

To move the lipophilic side chain to position 4 of the pyrrolidine ring and thus broaden structure-activity relationships, the hydroxy group of 4-hydroxyproline derivative **57** should be transformed into benzyloxy, *N*-benzylamine, and triazolyl moieties, acting as anchoring points for the side chain. Additionally, the replacement of the hydroxy group should prevent its oxidation and glucuronidation. After the translocation of the lipophilic side chain, the nitrogen atom of the pyrrolidine ring should remain unsubstituted. Furthermore, an additional substituent should be introduced at this position via acylations with benzoyl, acetyl, and formyl groups, as well as via alkylations with benzyl, methyl, and ethyl groups. Last but not least, the diastereomers of all envisaged hydroxamic acids should be accessed.

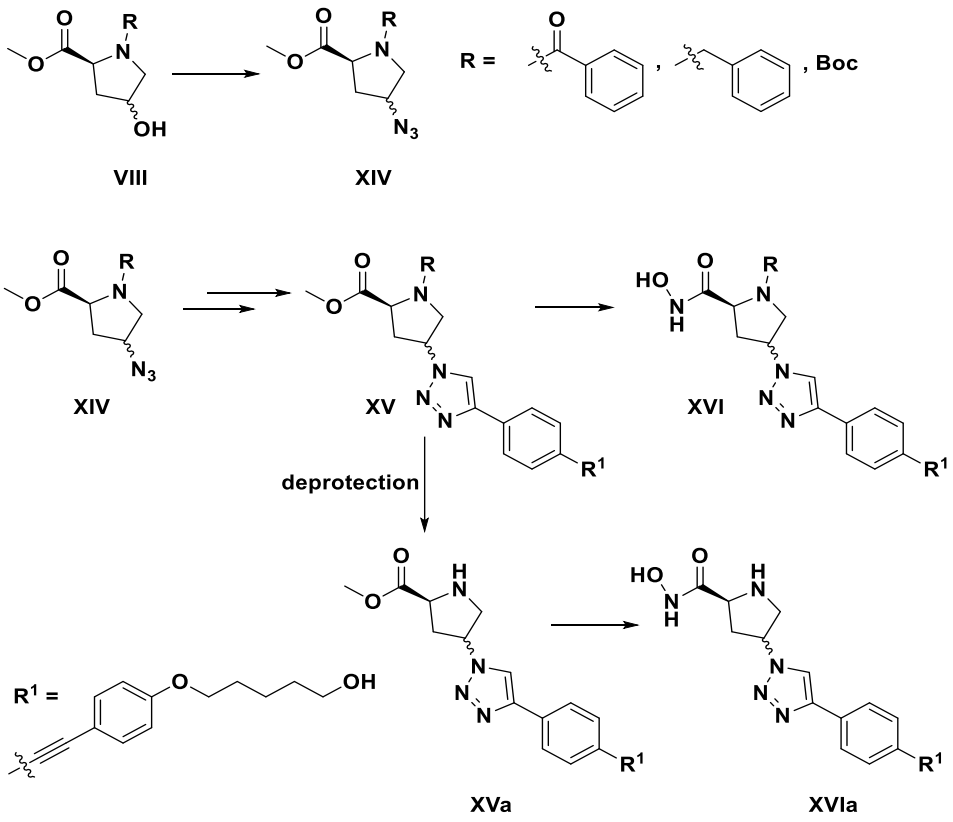
Thus, to afford the ether-based hydroxamic acids **X** in which the pyrrolidine nitrogen is acylated, proline ester **57** should be benzoylated, formylated, and acetylated to yield acylated compounds of general formula **VIII** (Scheme 4). Alternatively, the nitrogen should be protected with an appropriate protecting group or alkylated with an alkyl halide. Then, or after an inversion of configuration in position 4 via a MITSUNOBU reaction, the obtained N-substituted compounds should be etherified with 4-iodobenzyl bromide and subsequently coupled with terminal alkyne **71** to give esters possessing general formula **IX**. In case of the compounds already bearing the desired substituent at the pyrrolidine nitrogen, the respective esters should be subjected to aminolyses to generate hydroxamic acids of general formula **X** (Scheme 4). To afford hydroxamic acids bearing no substituent at the pyrrolidine nitrogen, the protecting group should be removed after the Sonogashira coupling and the obtained secondary amines **XI** should be reacted with hydroxylamine to afford the envisaged hydroxamic acids **XII** (Scheme 4).



Scheme 4. Synthetic strategy for ether-based hydroxamic acids **X, XII** and **XIII.**

Alternatively, the *N*-alkylated compounds could be accessed from secondary amines **XI** via direct alkylations using the respective alkyl halides or via reductive aminations employing the respective aldehydes in the presence of reducing agents like sodium triacetoxyborohydride. The resulting tertiary amines should then be subjected to aminolyses with hydroxylamine to give the envisaged hydroxamic acids **XIII** (Scheme 4).

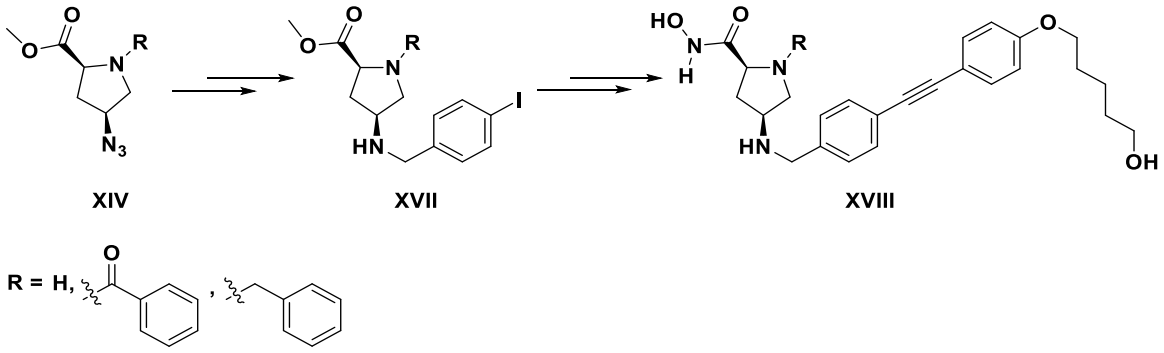
In order to transform the hydroxy group in position 4 of the pyrrolidine ring into a triazole moiety, the diastereomeric *N*-substituted alcohols **VIII** should be transformed into azides **XIV** via a MITSUNOBU reaction, proceeding under inversion of configuration in position 4 (Scheme 5). The azides **XIV** should be reacted with 1-ethynyl-4-iodobenzene via copper-catalyzed azide-alkyne cycloadditions to yield aryl iodides, that should be coupled with terminal alkyne **71** to give triazoles **XV**. To afford (4*R*)- and (4*S*)-configured triazole-based hydroxamic acids with benzoyl and benzyl substituents at the pyrrolidine nitrogen, the respective C-C coupled products **XV** should be subjected to aminolyses with hydroxylamine to afford the envisaged target compounds of general formula **XVI** (Scheme 5).



Scheme 5. Syntheses plan for triazole-based hydroxamic acids **XVI** and **XVIa**.

The *N*-protected diphenylacetylene derivatives **XV** should be deprotected prior to aminolyses to give the desired diastereomeric unsubstituted triazole-based hydroxamic acids **XVIa** (Scheme 5).

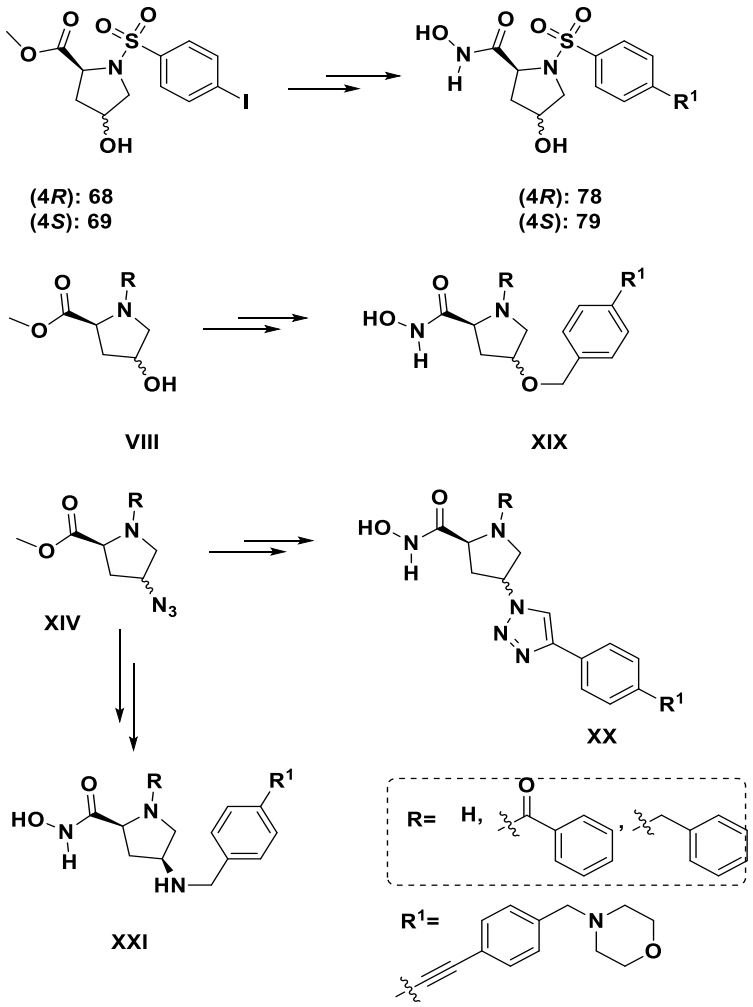
The (4*S*)-configured benzylamine-based hydroxamic acids **XVIII** should be accessed by transforming azides **XIV** into the respective primary amines by reduction under a hydrogen atmosphere or via the STAUDINGER reduction and a subsequent *N*-alkylation or a reductive amination with a suitable reducing agent like sodium triacetoxyborohydride to yield secondary amines **XVII**. Alternatively, a one-pot aza-WITTIG reaction followed by reduction could be employed to directly obtain the desired secondary amines **XVII**.[151] At this point, the secondary amines should be coupled with terminal alkyne **71**. The resulting diphenylacetylene derivatives should be subjected to aminolyses with hydroxylamine directly or after the removal of the protecting group at the pyrrolidine nitrogen to give the desired (4*S*)-configured hydroxamic acids **XVIII** (Scheme 6).



Scheme 6. Syntheses plan for *N*-benzyl amine-based hydroxamic acids **XVIII**.

2.3.2 LpxC inhibitors

Generally, to access proline-based LpxC inhibitors exhibiting the diphenylacetylene side chain of CHIR-090 (**34**), the envisaged hydroxamic acids should be synthesized from selected intermediates of the syntheses of the aforementioned MMP-13 inhibitors. These intermediates should be transformed into LpxC inhibitors via the same reaction steps as proposed for the MMP-13 inhibitors, except that in place of alkyne **71**, the appropriate terminal alkyne, 4-(4-ethynylbenzyl)morpholine, should be installed via the C-C coupling reactions (Scheme 7).

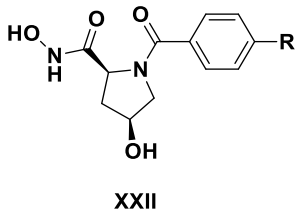


Scheme 7. Syntheses plan for the envisaged LpxC inhibitors.

3.0 SYNTHESES

3.1 Syntheses of hydroxamic acids with varied lipophilic side chains

In this chapter, the syntheses of proline-based MMP-13 inhibitors with varied lipophilic side chains are described.

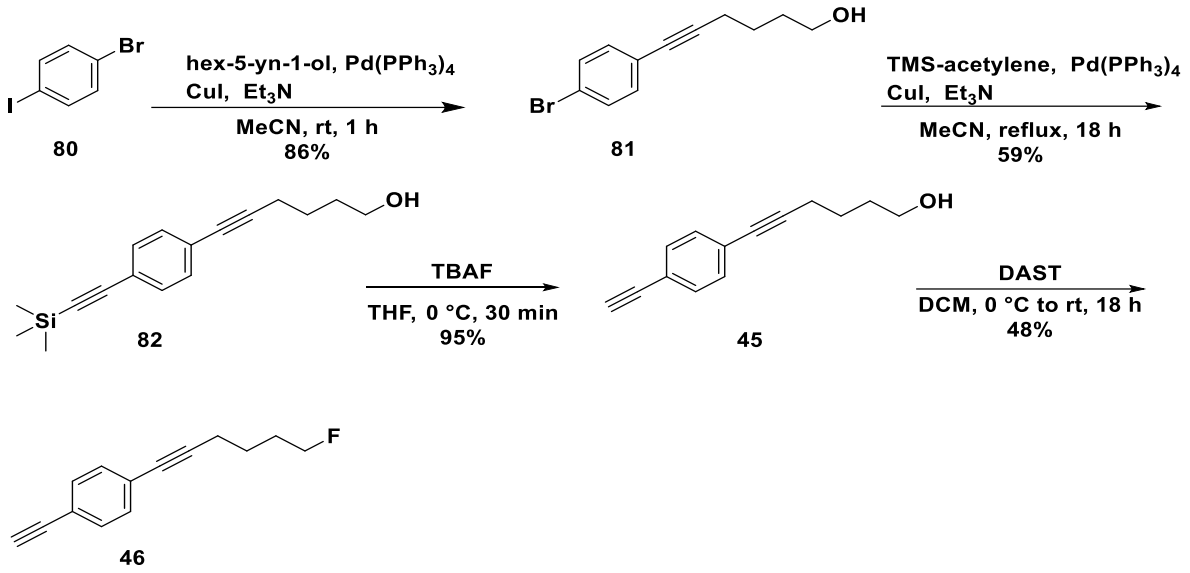


XXII

R= lipophilic side chain

Figure 25. General structure of (2*S*,4*S*)-4-hydroxyproline-based hydroxamic acids **XXII** with varied lipophilic side chains.

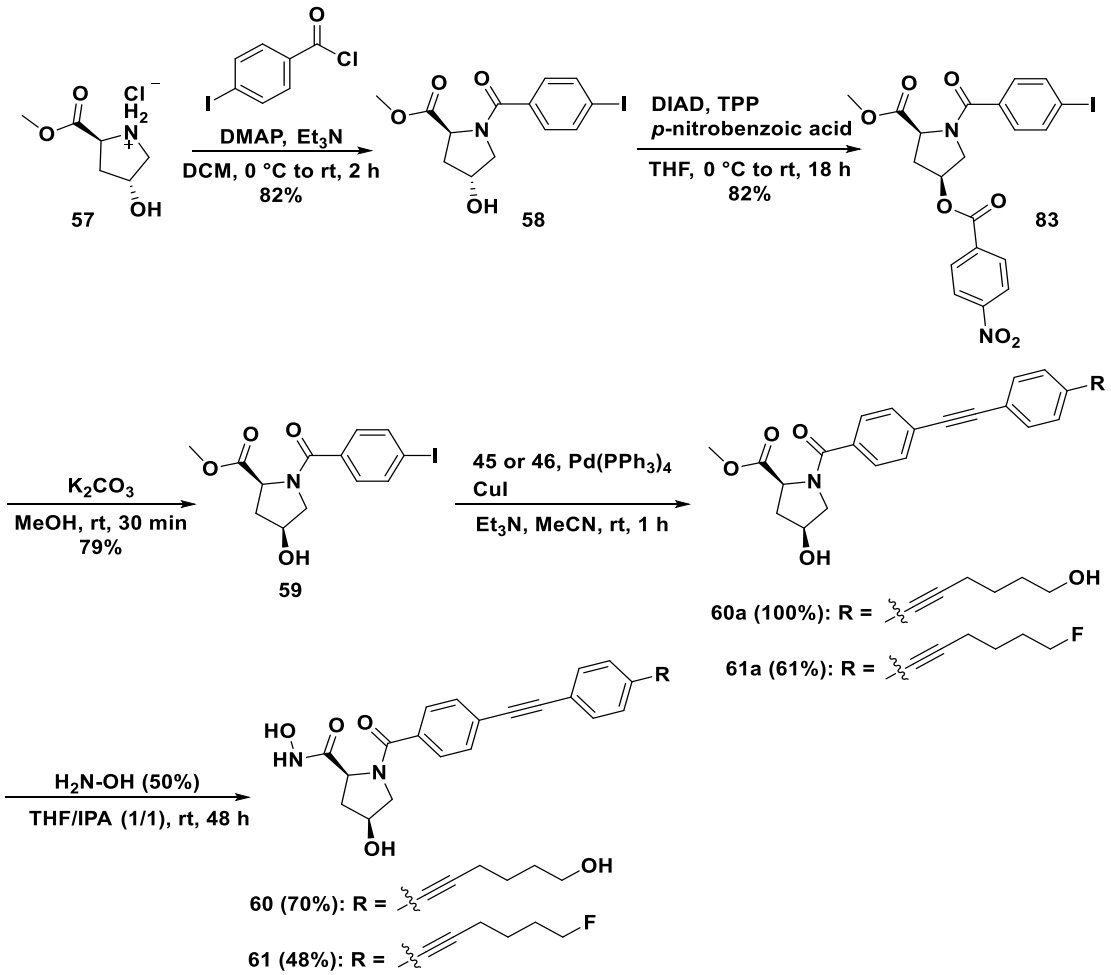
First, *p*-bromoiodobenzene (**80**) was subjected to two consecutive SONOGASHIRA coupling reactions. The coupling of **80** with hex-5-yn-1-ol gave alkyne **81**, which was coupled with trimethylsilylacetylene to give dialkyne **82**. The yield of **81** (86%) was higher than the one of **82** (59%) as a result of the higher reactivity of iodide than bromide. Subsequently, silyl ether **82** was treated with TBAF to afford terminal alkyne **45**, which was reacted with DAST in DCM to give the fluorinated derivative **46** (Scheme 8). The observation of a doublet of triplets at 4.51 ppm for the -C*H*$_2$F protons of **46** in its ^{1}H NMR spectrum and a large coupling constant of 154.7 Hz for the fluorinated carbon in the ^{13}C NMR spectrum confirmed the successful fluorination.



Scheme 8. Syntheses of terminal alkynes **45** and **46**.

To afford the (4*S*)-configured proline derivative **59** that should be coupled with the various lipophilic side chains, 4-hydroxyproline derivative **57** was acylated with 4-iodobenzoyl iodide to yield amide **58**. To invert the configuration in position 4 of the pyrrolidine ring of **58** from (*R*) to (*S*), alcohol **58** was subjected to a MITSUNOBU reaction and the resulting ester **83** was saponified with excess potassium carbonate in methanol to afford alcohol **59**, the (4*S*)-configured diastereomer of **58** (Scheme 9). Rotamers due to the amide bond were seen in the ^{1}H NMR spectra of **58**, **59**, and **83**. While rotamers in ratios of 89/11 and 65/35 were observed for **58** and **83**, respectively, several rotamers were seen for **59**.

Then, terminal alkynes **45** and **46** were each coupled with aryl iodide **59** via SONOGASHIRA coupling reactions to give diphenylacetylene derivatives **60a** and **61a** in respective yields of 100% and 61%. Esters **60a** and **61a** were reacted with hydroxylamine to afford hydroxamic acids **60** and **61**, respectively (Scheme 9). The structures of **60** and **61** were confirmed with NMR spectroscopy and MS. The disappearance of the singlet for the methyl protons of the ester group, occurring at 3.66 ppm and 3.67 ppm in the ^{1}H NMR spectra of **60a** and **61a**, respectively, in the spectra of the corresponding hydroxamic acids **60** and **61** confirmed the successful aminolyses. Furthermore, high-resolution mass spectrometry was used to confirm the successful synthesis of hydroxamic acids **60** and **61**.

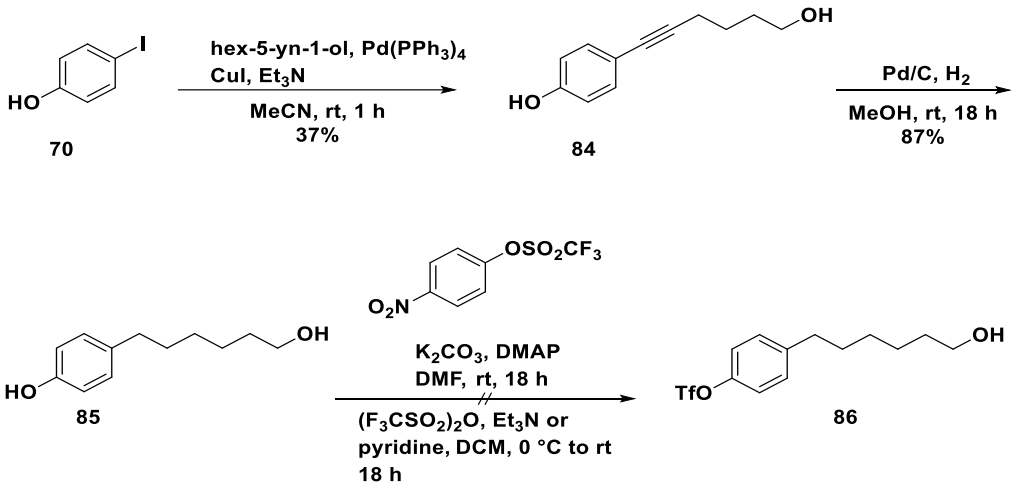


Scheme 9. Syntheses of hydroxamic acids **60** and **61**.

To afford the envisaged saturated lipophilic side chains, at first, *p*-iodophenol (**70**) was coupled with hex-5-yn-1-ol via a SONOGASHIRA coupling reaction. Then, the resulting alkyne **84** was hydrogenated in the presence of a palladium catalyst to give diol **85**. The triflation of phenol derivative **85** to give pseudohalide **86** amenable to C-C couplings was unsuccessful. At first, this was attempted with triflic anhydride using pyridine or triethylamine as base in methylene chloride at 0 °C.[152,153] Then, 4-nitrophenyl trifluoromethanesulfonate (4-nitrophenyltriflate) in DMF was used in the presence of potassium carbonate with and without DMAP as catalyst (Table 1 and Scheme 10).[154]

Table 1. Conditions assayed for the triflation of **85**

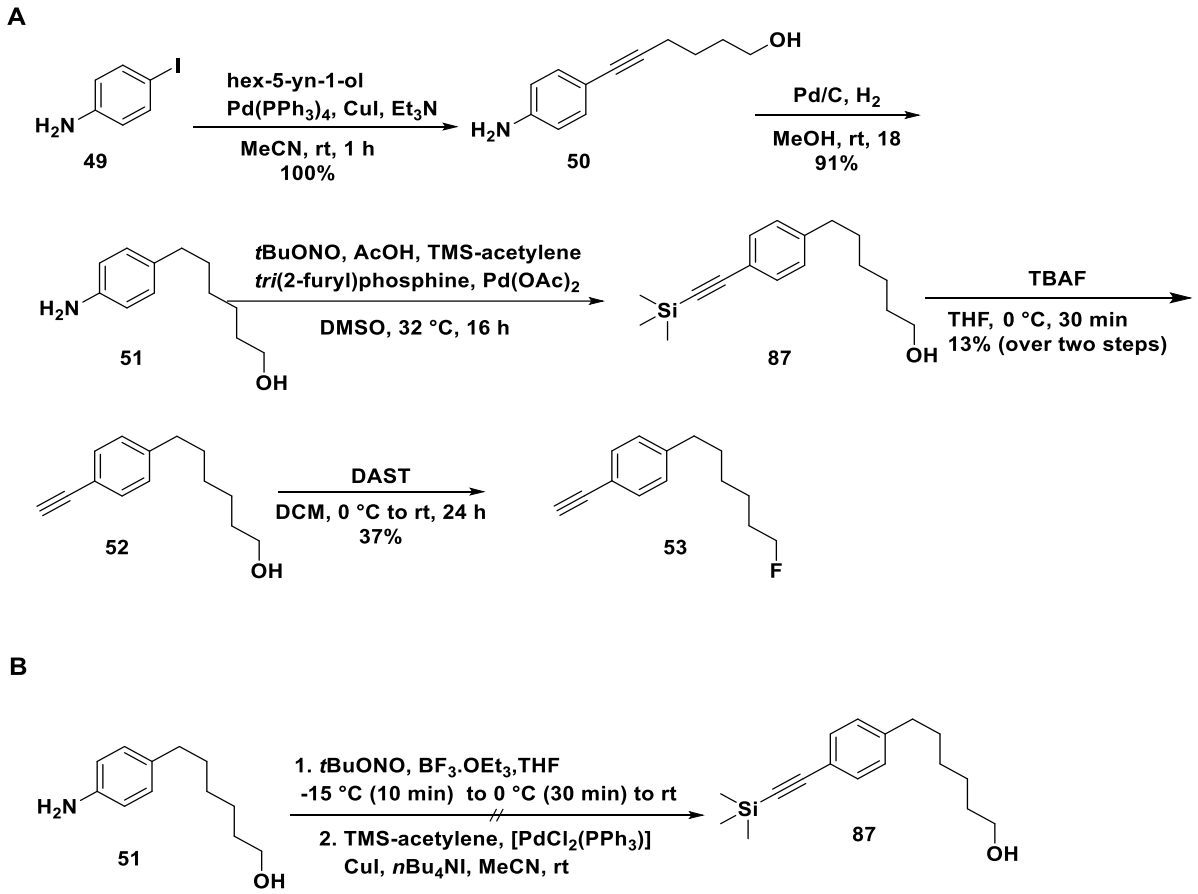
Nr.	Reagents/ Chemicals	Reaction conditions			Yield [%]
		Solvent	Temperature [°C]	Time [h]	
1	Triflic anhydride, pyridine	DCM	0 to rt	18	-
2	Triflic anhydride, triethylamine	DCM	0 to rt	18	-
3	4-nitrophenyl triflate, K_2CO_3	DMF	rt	24	-
4	4-nitrophenyl triflate, K_2CO_3, DMAP	DMF	rt	24	-



Scheme 10. Unsuccessful triflation of **85**.

To circumvent this obstacle, 4-iodoaniline (**49**) was coupled with hex-5-yn-1-ol and the resulting alkyne **50** was fully reduced in a hydrogen atmosphere using a palladium catalyst to give **51**. In the ^{13}C NMR spectrum of **51**, the disappearance of the alkyne signals observed at 81.7 ppm and 86.7 ppm in the spectrum of compound **50** confirmed the successful reduction. Then, the primary aromatic amine of **51** was diazotized with *tert*-butyl nitrite and glacial acetic acid in DMSO and the resulting diazonium salt was coupled with trimethylsilylacetylene to give alkyne **87** (Scheme 11).[155] The observation of a very tall singlet signal for the protons of the trimethylsilyl group in the very high field close to 0 ppm in the ^1H NMR spectrum of **87**,

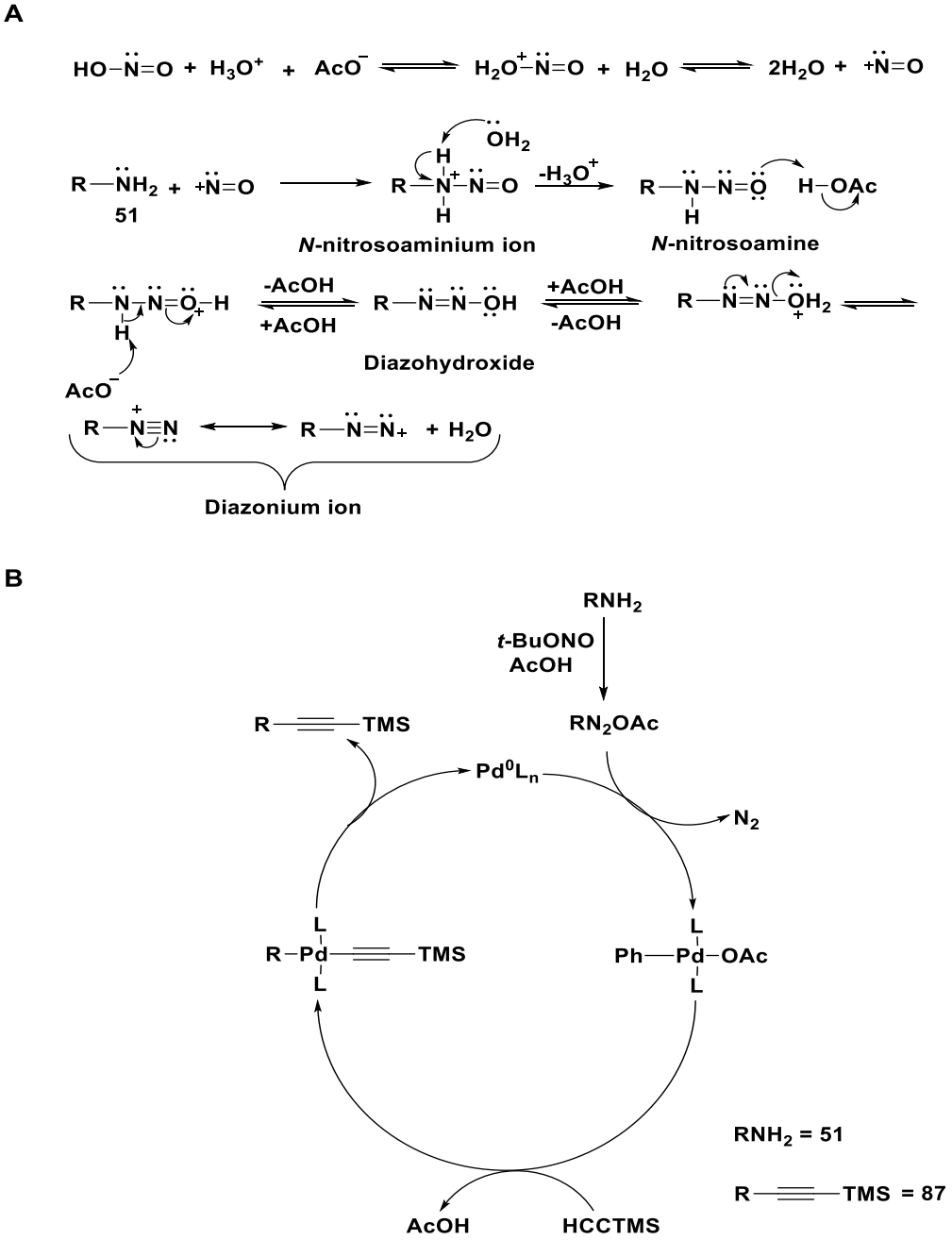
which integrated as approximately nine protons, and the appearance of two signals between 80 and 90 ppm for the alkyne carbons in the ^{13}C NMR spectrum confirmed the success of the reaction.



Scheme 11. (A) Syntheses of terminal alkynes **52** and **53**. (B) Unsuccessful one-pot diazotization and C-C coupling of **51**.

Tert-butyl nitrite and glacial acetic acid were used to generate nitrous acid, which further dissociated in the presence of the acid to yield nitronium ions. The nitronium ions reacted with the nitrogen of the aromatic amine to give an unstable *N*-nitrosoaminium ion as an intermediate. This intermediate lost a proton to form a *N*-nitrosoamine, which tautomerized to give a diazohydroxide. In the presence of the acid, the diazohydroxide lost water to give the diazonium ion *in situ* (Scheme 12A). Since diazonium groups are good leaving groups, which are expelled as nitrogen gas, it was possible to perform a coupling with TMS-acetylene to afford **87** as shown in Scheme 11A. Thus, there was oxidative addition of the *in situ* produced diazonium salt to the Pd(0)-phosphine complex which was produced from palladium acetate to give an arylpalladium(II) intermediate. Then, a subsequent acetate-assisted deprotonation of

trimethylsilylacetylene generated the corresponding aryl(alkynyl)palladium(II) species which finally afforded **87** via reductive elimination and regenerated the active Pd(0) species for the next catalytic cycle (Scheme 12B).[155] Prior to this, a similar one-pot domino approach described by FABRIZI *et al.* in 2010 [156] was attempted employing the conditions given in scheme 11B without success.

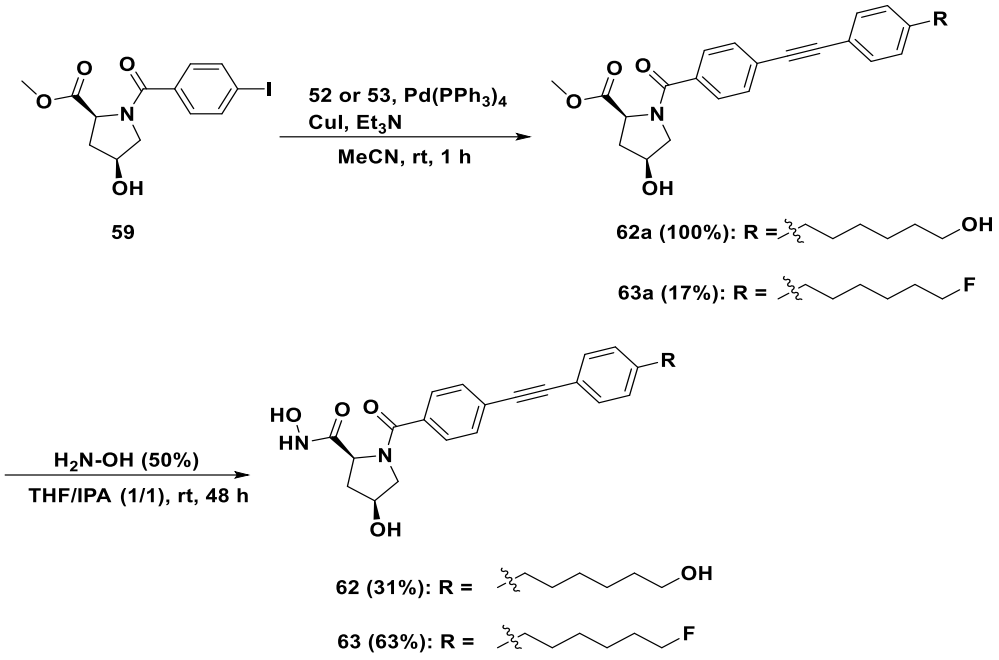


Scheme 12. (A) Generation of the diazonium salt from **51** *in situ*. (B) Proposed mechanism for converting **51** to **87**.[155]

The reaction to afford **87** gave a lot of side products and even after two purification steps using flash column chromatography, it could not be rendered sufficiently pure. To save time and

minimize losses, crude **87** was desilylated to afford the more polar terminal alkyne **52**, which made it easier to get rid of the side products. This laborious pretreatment of **87** followed by the desilylation process afforded **52** in a low yield of 13% over the two reaction steps and with a purity of only 63% according to HPLC. To afford **53**, the fluorinated derivative of **52**, the latter was treated with DAST in DCM (Scheme 11).

Finally, terminal alkynes **52** and **53** were coupled with proline derivative **59** and the obtained diphenylacetylene derivatives **62a** and **63a** were reacted with hydroxylamine to obtain hydroxamic acids **62** and **63**, respectively (Scheme 13).



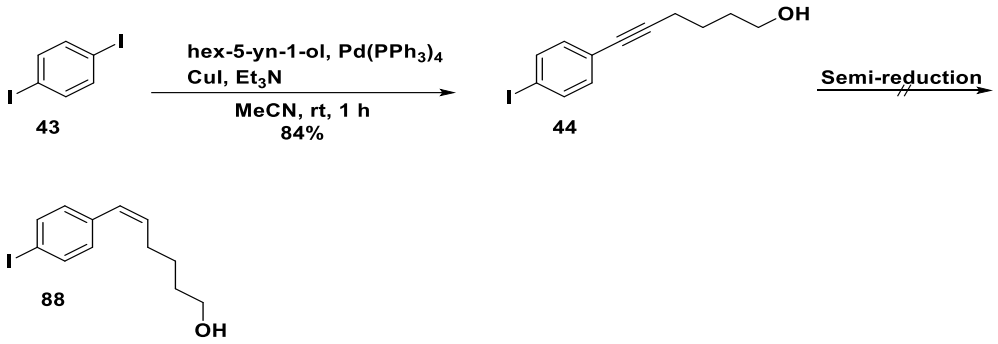
Scheme 13. Syntheses of hydroxamic acids **62** and **63**.

To afford the envisaged *cis*-alkenes, at first, 1,4-diiodobenzene (**43**) was subjected to a C-C coupling reaction with hex-5-yn-1-ol to give alkyne **44**. The decision to use 1,4-diiodobenzene (**43**) this time instead of *p*-bromoiodobenzene (**80**) was to avoid the heating and long reaction times that would be required for the second C-C coupling reaction involving the bromide. Also, C-C coupling reactions with iodides gave higher yields than with bromides (Scheme 8). Then, unsuccessful initial attempts to semi-reduce alkyne **44** were made. Alkyne **44** was heated in DMF with palladium acetate as catalyst and potassium hydroxide (1.5 eq). According to reports by Li *et al.* in 2010, DMF hydrolyses at high temperatures in the presence of hydrated potassium hydroxide to produce formic acid *in situ*, which serves as a hydrogen source in the proper concentration range to semi-reduce the alkyne via transfer hydrogenation. Additionally, in the

first of two attempts carried out in dioxane, **44** was heated with palladium chloride as catalyst, potassium carbonate and formic acid. In the other attempt, **44** was heated with formic acid, 1,4-bis(diphenylphosphino)butane, tris(dibenzylideneacetone)dipalladium(0) as catalyst, and potassium hydroxide (Scheme 14 and Table 2).[157-159] It is worth noting that in all the cases, alkyne **44** was reisolated.

Table 2. Conditions of failed attempts to semi-reduce **44** to the *cis*-alkene **88**.

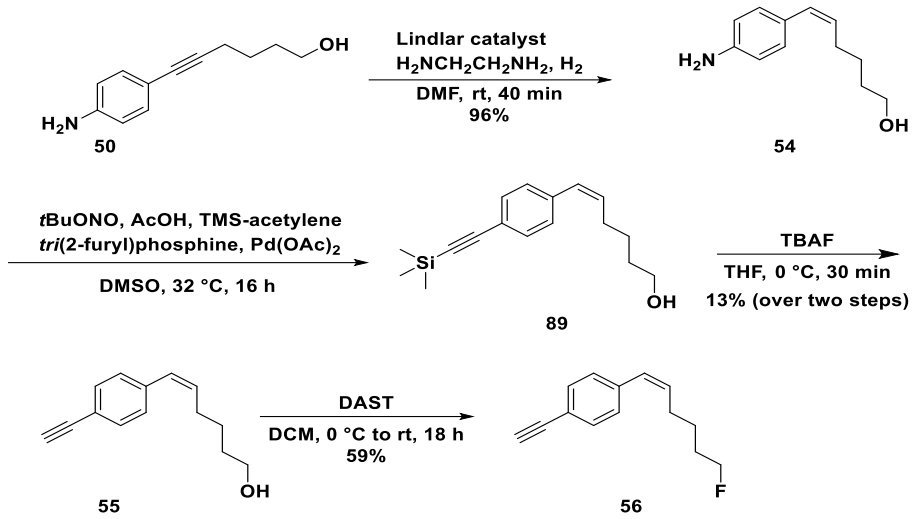
Nr.	Reagents/ Chemicals	Reaction conditions			Yield [%]
		Solvent	Temperature [°C]	Time [h]	-
1	$Pd(OAc)_2$, KOH	DMF	145	6-9	-
2	$PdCl_2$, K_2CO_3, HCOOH	Dioxane	80	36	-
3	$Pd_2(dba)_3$, dppb, HCOOH	Dioxane	80	15	-



Scheme 14. Unsuccessful semi-reduction of **44** to the *cis*-alkene **88**.

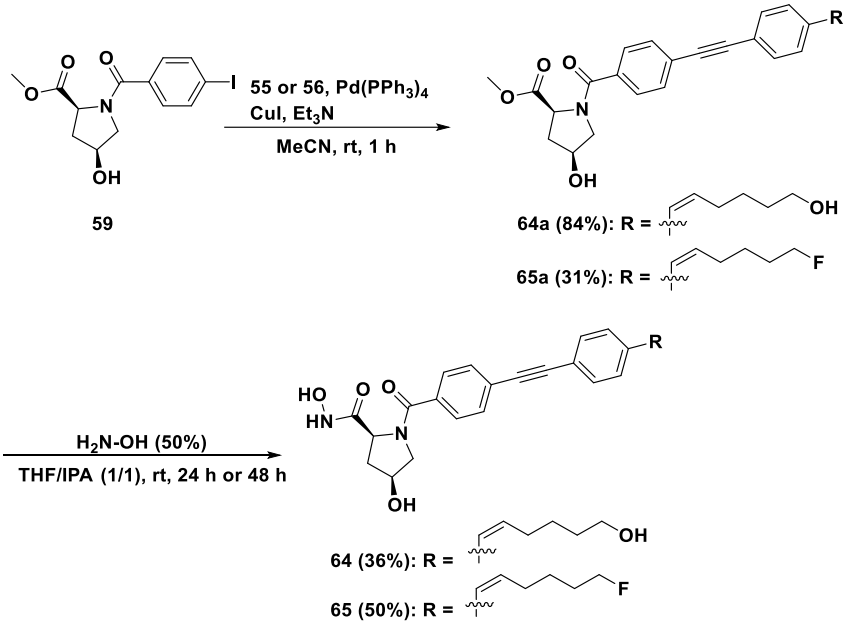
Then, alkyne **50** was reduced using the LINDLAR catalyst poisoned with ethylene diamine under a hydrogen atmosphere using DMF as solvent.[160] The progress of the reaction was monitored at predetermined time intervals by TLC to avoid the complete reduction to the respective alkane **51**. Thus, *cis*-alkene **54** could be obtained after 40 min in 96% yield. The observation of multiplets for each of the two alkene protons at low field in the ^{1}H NMR spectrum of **54**, one at 5.38 ppm and the other at 6.18 ppm, confirmed the structure of the obtained *cis*-alkene. Also, in the ^{13}C NMR spectrum, the disapperance of the signals for the alkyne carbons of **50** at 81.7 ppm and 86.7 ppm and the appearance of signals at 128.1 ppm and 128.9 ppm for the alkene carbons of **54** showed the presence of the *cis*-alkene. Having synthesized *cis*-alkene **54**, the

compound was subjected to the same reactions as **51** to access the hydroxylated and fluorinated *cis*-alkenes **55** and **56**, respectively (Scheme 15).



Scheme 15. Syntheses of **55** and **56**.

To afford hydroxamic acids **64** and **65**, terminal alkynes **55** and **56** were coupled with aryl iodide **59** via Sonogashira reactions and the resulting diphenylacetylene derivatives **64a** and **65a** were subjected to aminolyses with hydroxylamine (Scheme 16).



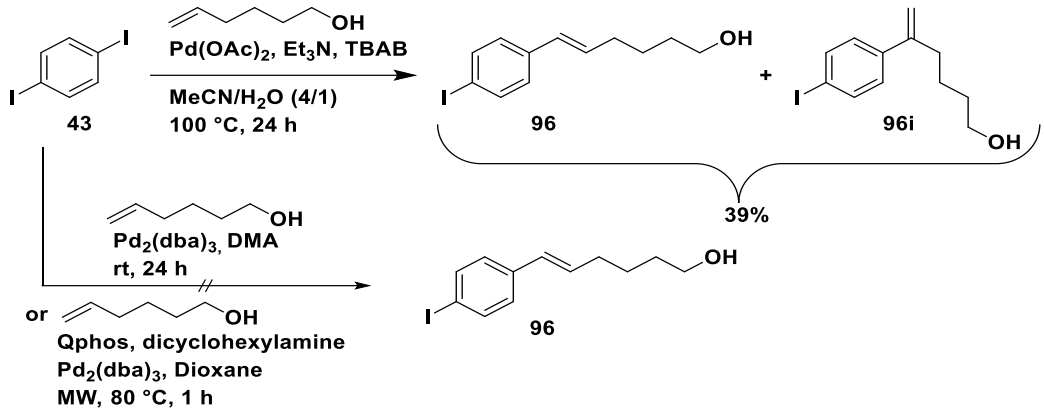
Scheme 16. Syntheses of hydroxamic acids **64** and **65**.

Diphenylacetylene derivative **65a** was found to be spoiled with triphenylphosphine oxide according to HPLC, MS, and NMR spectroscopy. To get rid of this impurity, which was difficult to remove via normal phase flash column chromatography, the product was purified twice on a reversed phase column to afford a clean product for aminolysis. A such, **65a** was obtained in a yield of only 31%.

Next, the HECK reaction should be used to access the *trans*-alkenes. However, all attempts were not successful. When 1,4-iodobenzene (**43**) was heated with hex-5-en-1-ol, palladium acetate, triethylamine, and tetra-*n*-butylammonium bromide in acetonitrile/water (4/1) (Table 3, number 1) at 100 °C for 24 h, the desired product **96** and its isomer **96i** were obtained as an inseparable mixture in approximately equal amounts (Scheme 17). Other reported procedures for HECK reaction in the literature failed to produce the desired alkene **96**. At first, a microwave-assisted heating of **43** with hex-5-en-1-ol, tris(dibenzylideneacetone)dipalladium(0) as catalyst, Qphos, and dicylohexylamine in dioxane for 1 h was performed. Secondly, **43** was stirred with hex-5-en-1-ol and tris(dibenzylideneacetone)dipalladium(0) in DMA for 24 h at ambient temperature (Table 3 and Scheme 17).[161,162]

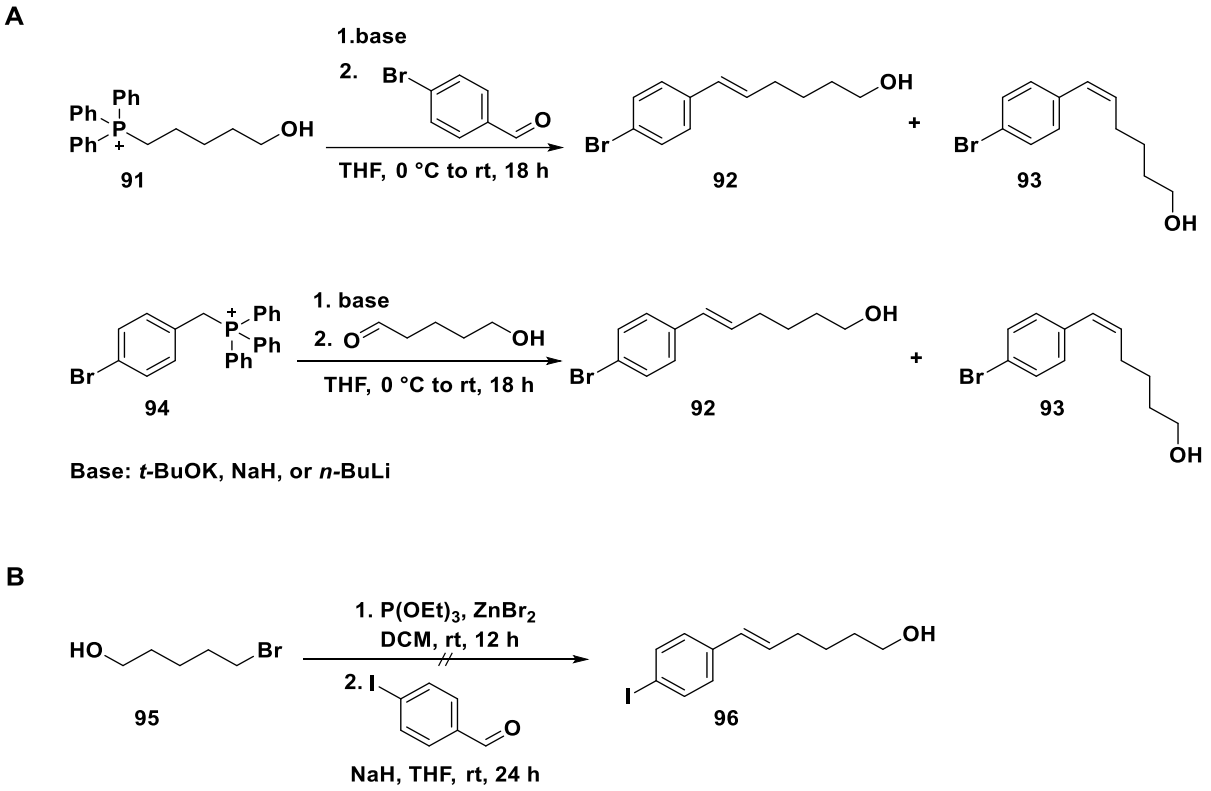
Table 3. Conditions used in the HECK reaction to afford **96**.

Nr.	**Reagents/ Chemicals**	**Reaction conditions**			**Yield [%]**
		Solvent	**Temperature [°C]**	**Time [h]**	
1	$Pd(OAc)_2$, Et_3N, TBAB	MeCN/ H_2O (4.1)	145	24	39 (~1:1 of 96 and 96i)
2	$Pd_2(dba)_3$, Qphos, dicyclohexylamine	Dioxane	80 (Microwave-assisted)	1	-
3	$Pd_2(dba)_3$	DMA	rt	24	-



Scheme 17. Synthesis of **96** via HECK reaction.

The WITTIG method for synthesizing alkenes was also investigated. At first, 5-hydroxypentyltriphenylphosphonium bromide (**91**) was deprotonated using different bases like potassium *tert*-butoxide, sodium hydride, and *n*-butyllithium and reacted with *p*-bromobenzaldehyde. While the reactions with potassium *tert*-butoxide gave quite low yields (~30%) of *cis*- and *trans*-isomers, higher yields (>60%) of the mixtures were obtained with the other two bases. Furthermore, when the phosphonium salt was changed to (4-bromobenzyl)triphenylphosphonium bromide (**94**) and the aldeyde to 5-hydroxypentanal under the same reaction conditions given above, a similar observation was made as before; inseparable mixtures of the *trans*- and *cis*-isomers were obtained (Scheme 18). In both cases, when *n*-butyllithium was used as a base, the ratio of the *trans*- (**92**) to the *cis*-isomer (**93**) was 1/2, whereas the use of sodium hydride as base yielded a 1/3 ratio of *trans*- and *cis*-isomer.



Scheme 18. (A)WITTIG synthesis of **92**. (B) ARBUZOV and HORNER-WARDSWORTH-EMMONS synthesis of **96**.

Also, the HORNER-WARDSWORTH-EMMONS olefination, a modification of the WITTIG reaction for synthesizing *trans*-alkenes, failed to yield the desired product. The first stage of the reaction was the ARBUZOV reaction to generate phopshonate ester from trimethylphosphite and 5-bromopentanol and a catalytic amount of zinc bromide in DCM for 12 h.[163] Then, after removing the DCM *in vacuo*, the residue was taken up in THF and reacted with 4-iodobenzaldehyde in the presence of sodium hydride at ambient temperature. However, after 24 h, TLC control did not show the formation of the desired alkene **96** (Scheme 18).

Finally, to obtain the desired *trans*-alkene **96**, alkyne **44** was semi-reduced via an *in-situ* two-step process. In the course of this reaction, a ruthenium-catalyzed addition of triethoxysilane across the triple bond occurred, followed by the removal of the silane group using TBAF and cuprous iodide (Scheme 19).[164] The structure of *trans*-alkene **96** was confirmed by ^{1}H NMR spectroscopy. The signals for the two alkene protons (H_x and H_y) could be observed at 6.31 ppm and 6.23 ppm. In case of *trans*-alkene **96** the alkene protons couple with each other with a coupling constant of about 15.9 Hz, whereas the respective protons of *cis*-alkene **54** exhibited a coupling constant of about 11.7 Hz (Figure 22).

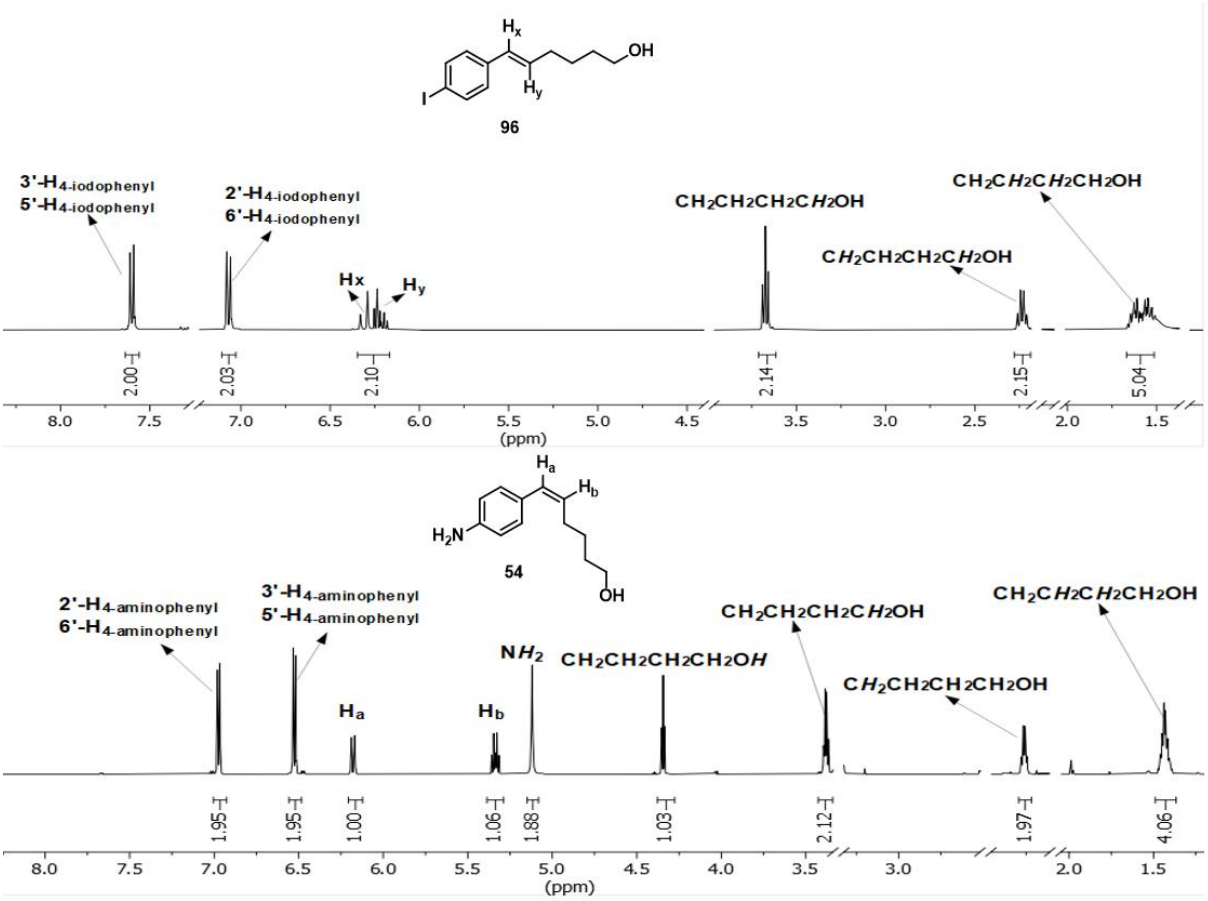
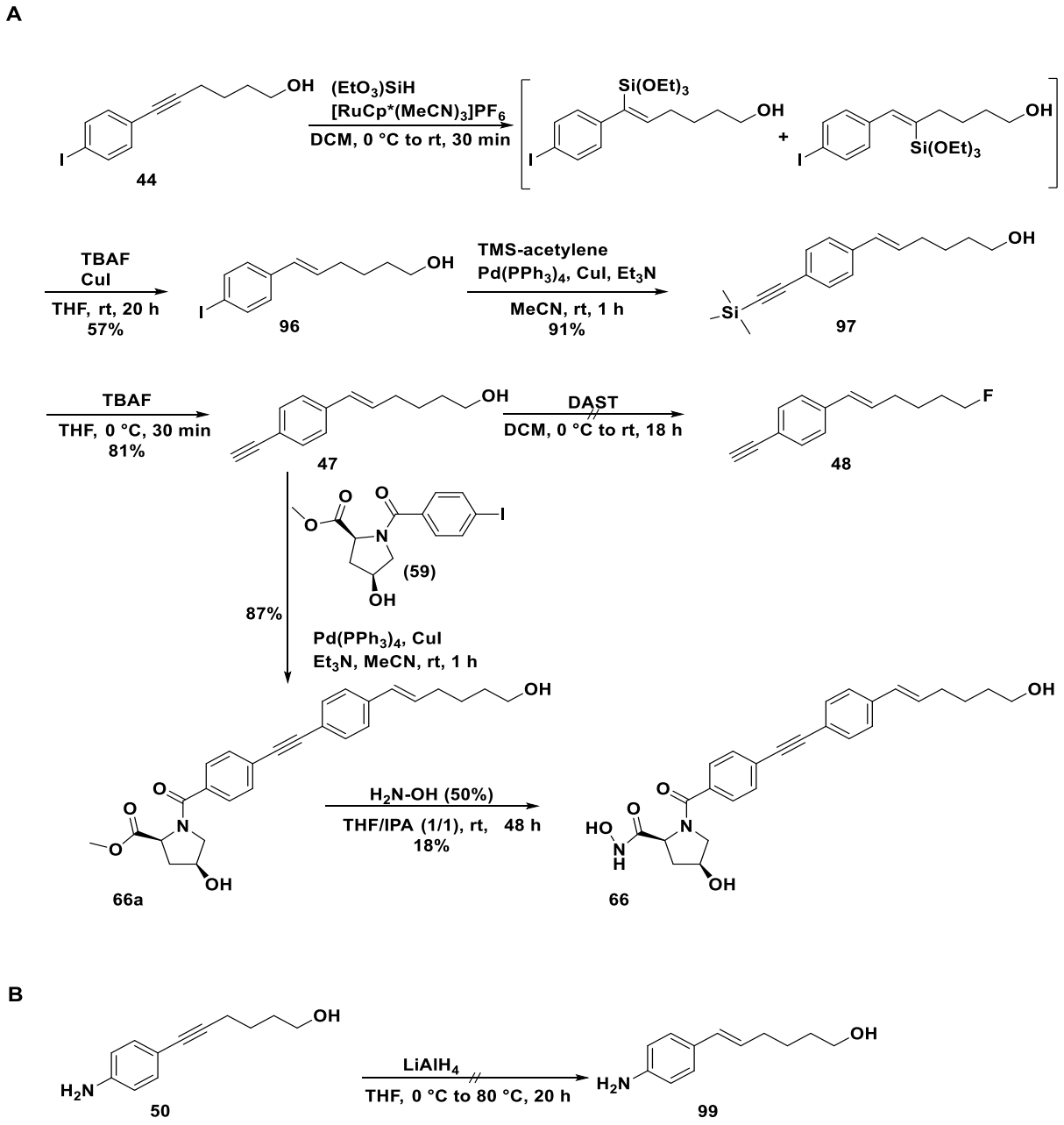


Figure 26. Comparison of the ^{1}H NMR spectra of **54** (DMSO-d_6) and **96** ($CDCl_3$) showing the differences in the distribution of the signals of the *cis*- and *trans*-alkene protons.

Then, aryl iodide **96** was coupled with TMS-acetylene to give alkyne **97**, which was subsequently desilylated to afford terminal alkyne **47** in a yield of 81%. However, the envisaged fluorination of alcohol **47** with DAST to obtain **48** was unsuccessful. Subsequently, all attempts to repeat the synthesis of **47** were unsuccessful, even with new reagents and catalysts (Scheme 19A).

Even though the stability of the amino group of **50** to displacement by the reducing agent made it a more suitable starting material than **44**, *trans*-alkene **99** could not be afforded when **50** was added to a solution of $LiALH_4$ in THF at 0 °C and gently warmed to reflux for 20 h (Scheme 19B).[165]

To access hydroxamic acid **66**, alkyne **47** was coupled with aryl iodide **59** via a SONOGASHIRA coupling and the resulting product **66a** was subjected to an aminolysis with hydroxylamine (Scheme 19A).



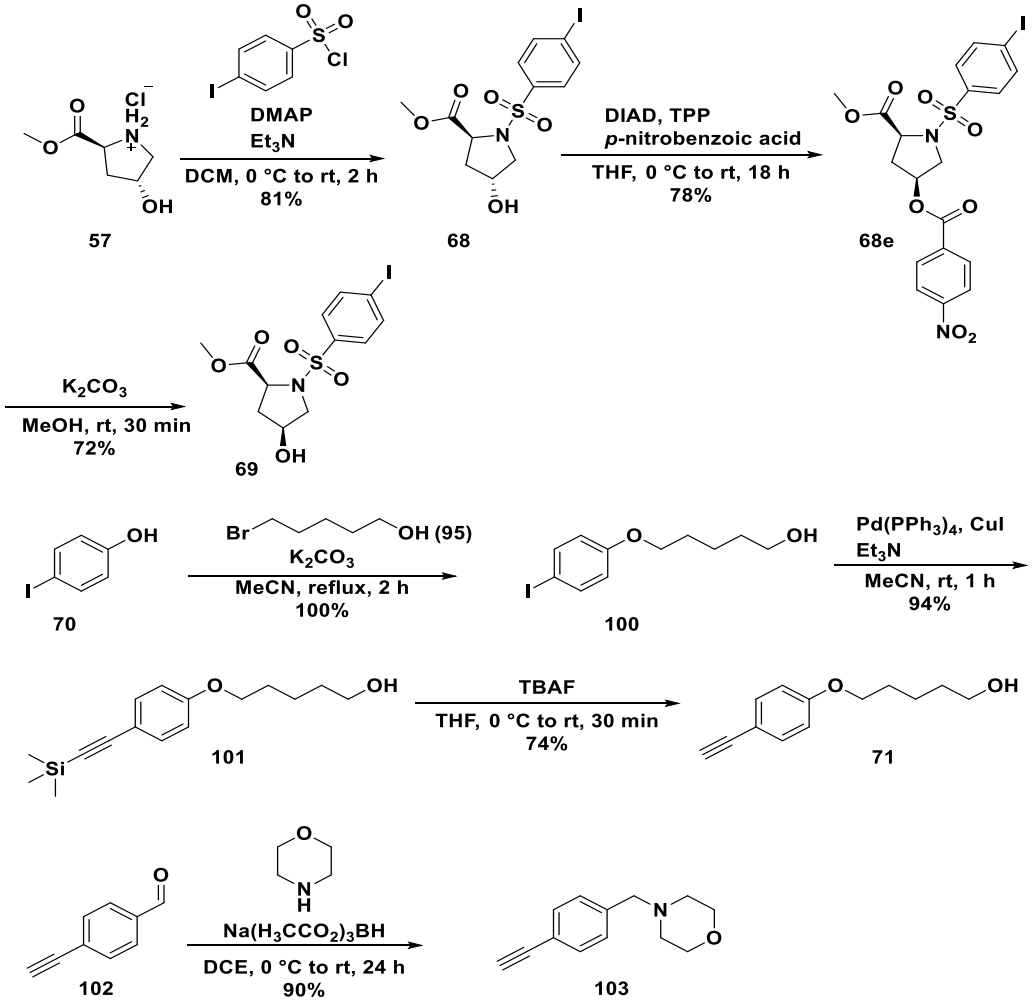
Scheme 19. (A) Syntheses of alkyne **31** and hydroxamic acid **33** and unsuccessful fluorination of **47**. (B) Unsuccessful semi-reduction of **50**.

3.2 Syntheses of hydroxamic acids with a varied core

3.2.1 Syntheses of diastereomeric sulfonamide-based hydroxamic acids

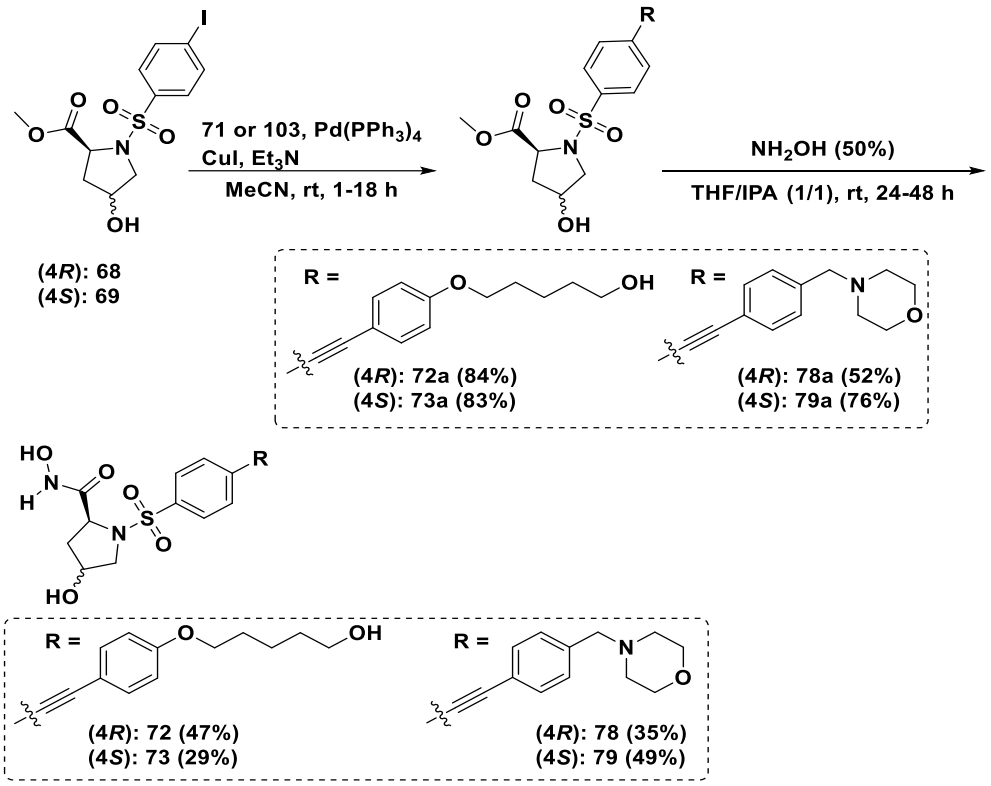
Sulfonamide **68** was synthesized from hydroxyproline derivative **57** employing the same conditions which were used in the synthesis of amide **58**, however, using 4-iodosulfonyl chloride in place of 4-iodobenzoyl chloride. To obtain hydroxyproline derivative **69**, the (4*S*)-configured diastereomer of **68**, the latter was transformed via a MITSUNOBU reaction and a

subsequent saponification (Scheme 20). To obtain terminal alkyne **71**, at first, 4-iodophenol (**70**) was refluxed with 5-bromopentan-1-ol (**95**) using potassium carbonate as base in MeCN to give ether **100** in quantitative yield. Then, to introduce the acetylene moiety for future coupling reactions with all scaffolds, aryl iodide **100** was coupled with TMS-acetylene via a Sonogashira coupling to yield silyl ether **101**, which was finally desilylated to give terminal alkyne **71**. Morpholinomethyl-substituted phenylacetylene **103** was afforded by reductively aminating 4-ethynylbenzaldehyde (**102**) with morpholine (Scheme 20) in about 90% yield.



Scheme 20. Syntheses of **68**, **69**, **71**, and **103**.

The desired hydroxamic acids were obtained by coupling aryl iodides **68** and **69** with terminal alkynes **71** and **103** via SONOGASHIRA coupling reactions. The obtained products **72a**, **73a**, **78a**, and **79a** were subsequently reacted with hydroxylamine to yield hydroxamic acids **72**, **73**, **78** and **79** (Scheme 21).

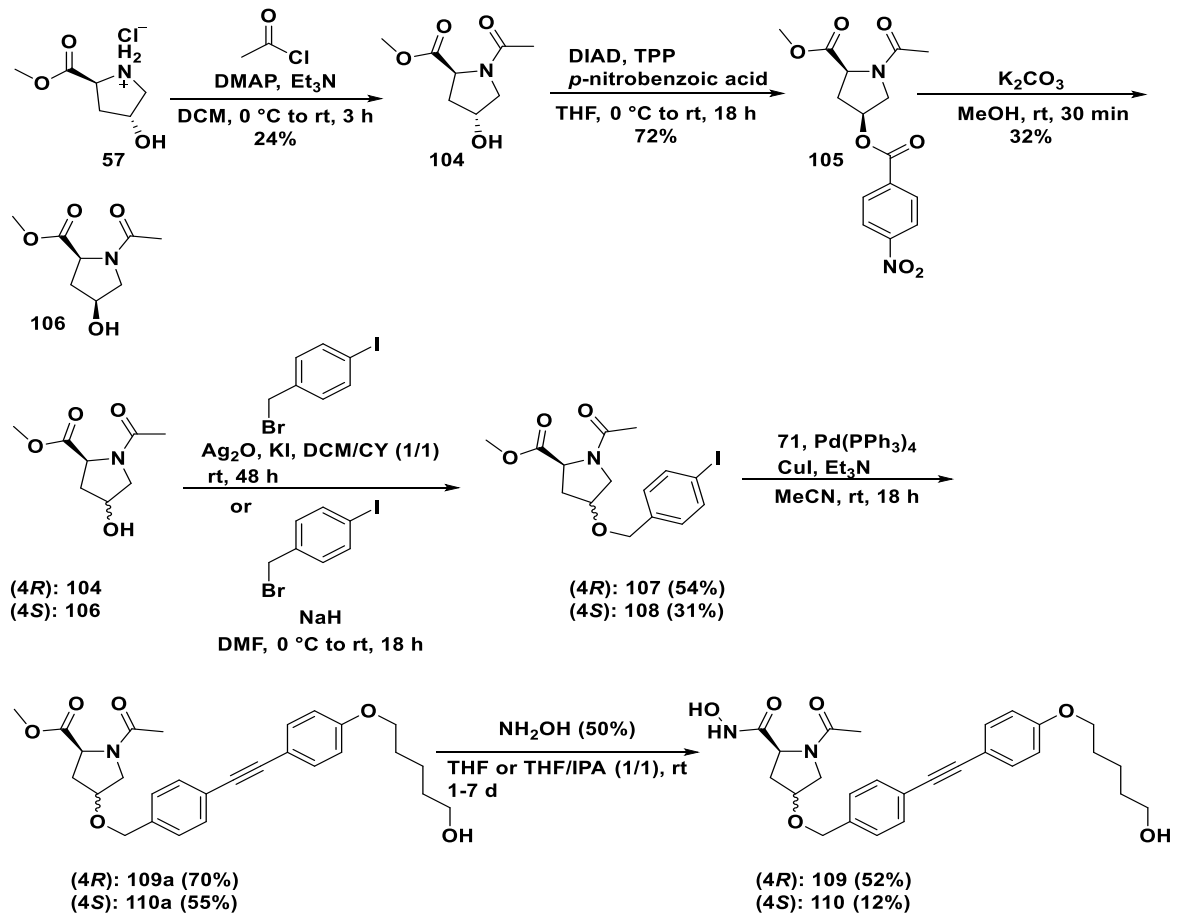


Scheme 21. Syntheses of diastereomeric sulfonamide-based hydroxamic acids **72**, **73**, **78**, and **79**.

3.2.2 Syntheses of diastereomeric ether-based hydroxamic acids

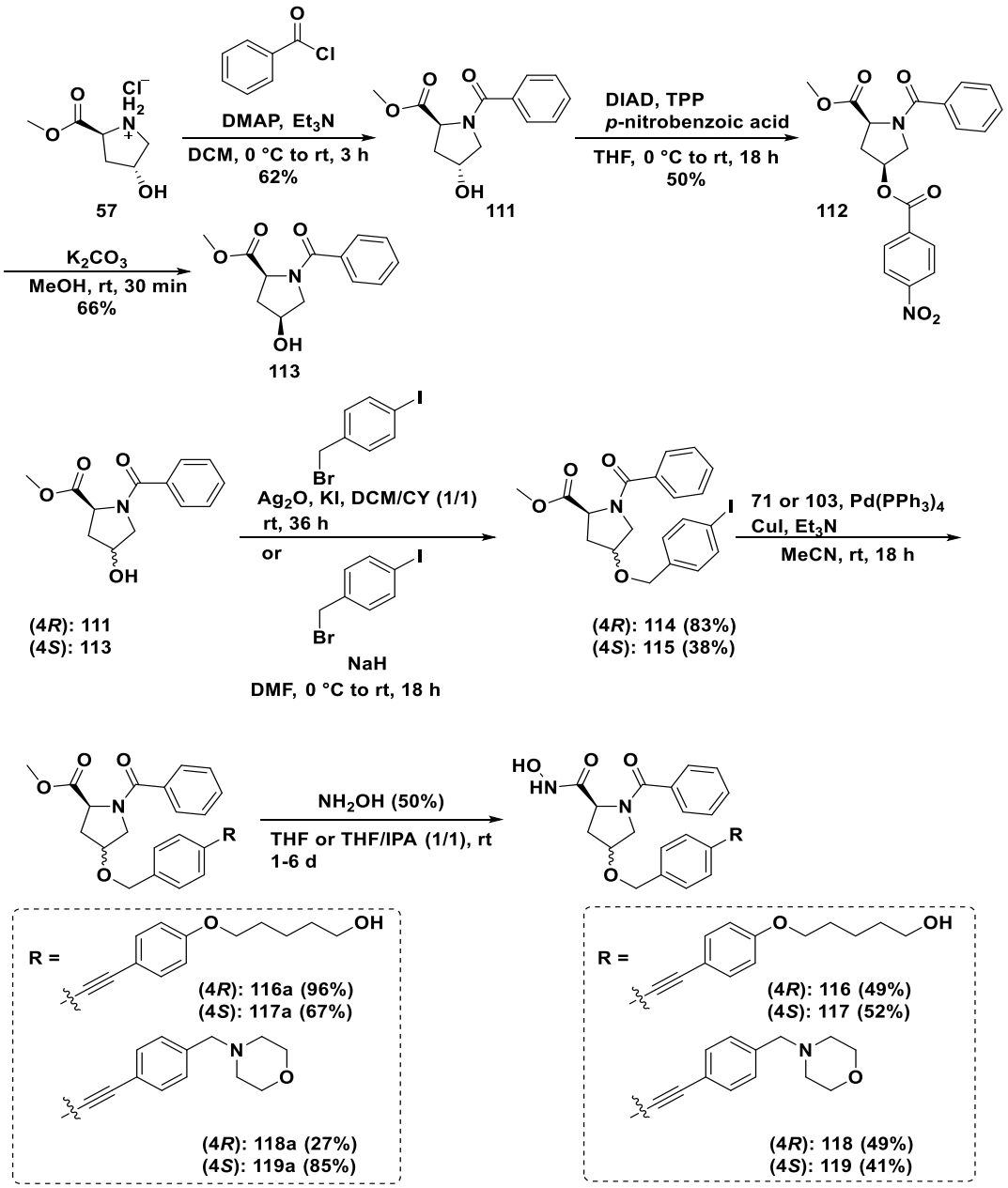
When synthesizing the envisaged ether-based hydroxamic acids, at first, compounds bearing an acetyl group at the pyrrolidine nitrogen should be prepared. Thus, to obtain these compounds, 4-hydroxyproline derivative **57** was acetylated with acetyl chloride in DCM using triethylamine as base and DMAP as catalyst to give acetamide **104**. The (4*S*)-configured diastereomer of **104**, which is **106**, was obtained via a MITSUNOBU reaction and a subsequent saponification. Rotamers in the ratio of 1/5 were observed in the ^{1}H NMR spectra of both **104** and **106** as a result of the amide bond. Also, in their ^{1}H NMR spectra, the signals for the methine protons at positions 2 and 4 of the pyrrolidine ring of **104** were seen at 4.25 ppm and 4.33 ppm, respectively while those of **106** were observed at 4.51 ppm and 4.43 ppm, respectively. Since the signal for the methine proton at position 2 of the pyrrolidine ring was observed upfield of the signal for methine proton at position 4 of **104** and vice versa for **106**, just like observed in the ^{1}H NMR spectra for the diastereomers **58** and **59**, both compounds were confirmed to be diastereomers.

To afford benzyl ether **107**, 4-iodobenzyl bromide was reacted with alcohol **104** using silver(I) oxide as base in the presence of catalytic amounts of potassium iodide in DCM/cyclohexane (1/1) to give ether **107** in a yield of 54%. This method of etherification did not work for the (4*S*)-configured diastereomer. Hence, to obtain ether **108**, the diastereomer of **107**, the etherification of alcohol **106** was carried out using sodium hydride as base in DMF to give a 31% yield of ether **108**. The disappearance of the broad absorption bands between 3200 and 3400 cm^{-1}, which were seen in the IR spectra of alcohols **104** and **106** due to the O-H stretch, in the spectra of compounds **107** and **108** confirmed the successful ether formation. Furthermore, the observation of two sets of multiplets in the low field, which are typical for *para*-substituted aromatic systems, and the appearance of the signals for the benzylic protons between 4 and 5 ppm in the ^1H NMR spectra of the ethers confirmed the success of the reactions. To afford the target hydroxamic acids **109** and **110**, aryl iodides **107** and **108** were coupled with alkyne **71**, and the resulting diphenylacetylene derivatives **109a** and **110a** subjected to aminolyses with hydroxylamine (Scheme 22).



Scheme 22. Syntheses of acetamide-based hydroxamic acids **109** and **110**.

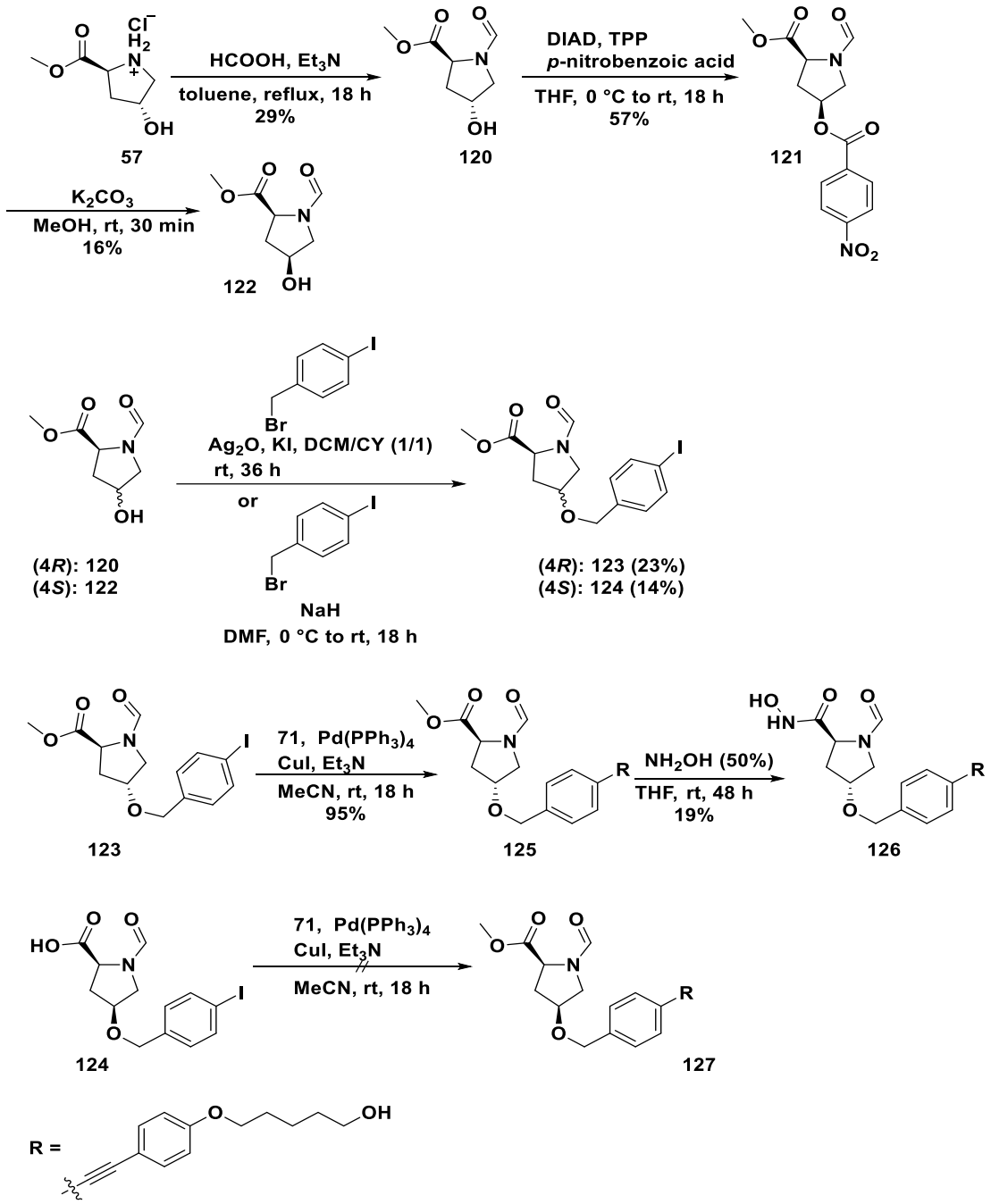
The benzamide-based compounds were obtained by reacting proline derivative **57** with benzoyl chloride in DCM using triethylamine as base and DMAP as catalyst to give amide **111** in a yield of 62%. Inversion of the configuration in position 4 of hydroxyproline derivative **111** could be achieved via a Mitsunobu reaction yielding 4-nitrobenzoic acid ester **112**, which was saponified to afford the (4*S*)-configured pyrrolidine derivative **113**. As described for the acetamide-based compounds, alcohols **111** and **113** were etherified with 4-iodobenzyl bromide to give ethers **114** and **115** using silver(I) oxide, catalytic amounts of potassium iodide in DCM/cyclohexane (1/1), and sodium hydride in DMF, respectively. Each of the two diastereomeric aryl iodides **114** and **115** was coupled with ether-based terminal alkyne **71** as well as morpholine-based alkyne **103** in Sonogashira coupling reactions to give diphenylacetylene derivatives **116a**, **117a**, **118a**, and **119a**. Finally, hydroxamic acids **116**, **117**, **118**, and **119** were obtained from the respective esters by reacting these compounds with hydroxylamine (Scheme 23).



Scheme 23. Syntheses of benzamide-based hydroxamic acids **116**, **117**, **118**, and **119**.

To obtain the respective formamide derivatives, first, hydroxyproline ester **57** should be formylated with formic acid. Thus, secondary amine **57** was refluxed with formic acid in toluene in the presence of triethylamine to give amide **120** in a yield of 29%. The formylation gave a lot of side products, which together with the absence of a chromophore in **120** made purification difficult. The observation of the signal for the proton of the formyl group of **120** at 8.23 ppm in the ^{1}H NMR spectrum confirmed the success of the formylation. Although rotamers were observed, it is difficult to give their ratio due to the crude nature of **120** used for obtaining the ^{1}H NMR spectrum. Furthermore, high-resolution mass spectrometry was used to confirm

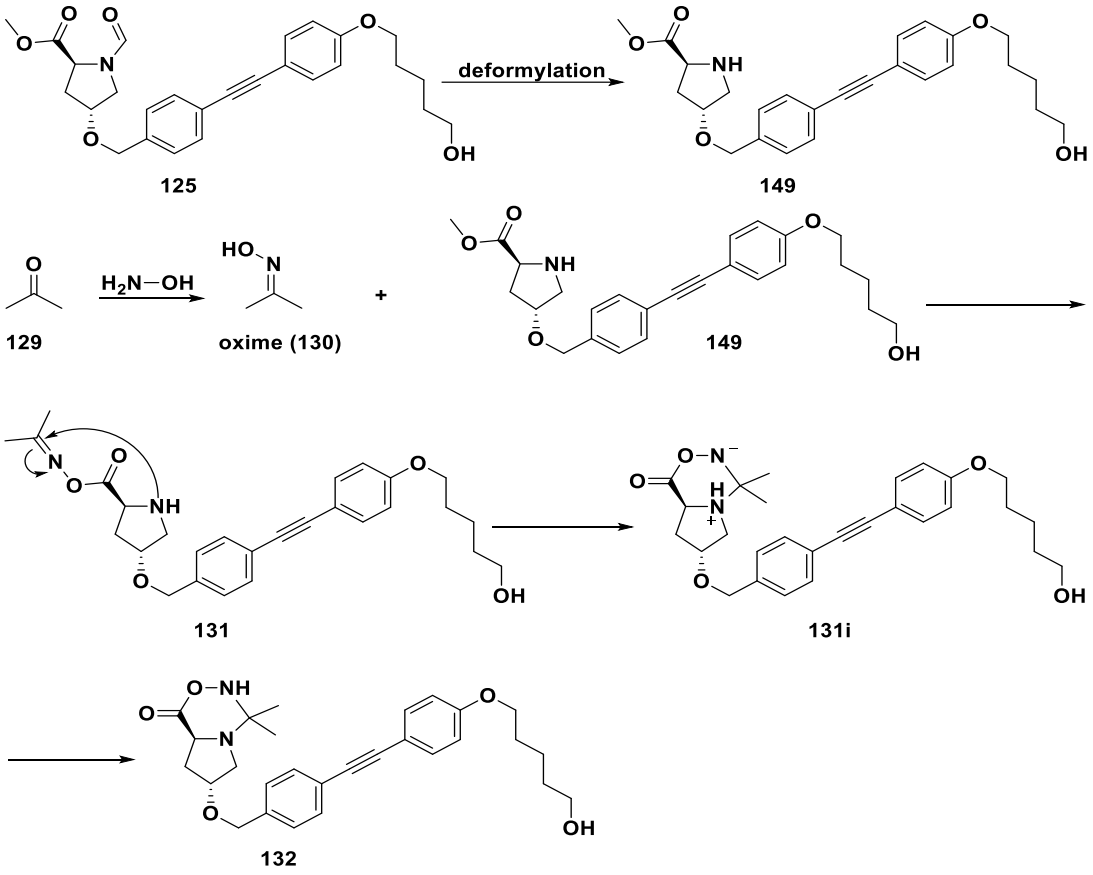
the successful synthesis of formamide **120**. The (4*S*)-configured diastereomer of **120**, which is **122**, was obtained as described for the acetamide-based compounds (Scheme 22). Unlike **120**, **122** was obtained in a purer state than **120** since the purifications after MITSUNOBU reaction and saponification eliminated most of the impurities. Thus, clean NMR spectra were obtained for **122**. As such, to confirm the structure of **122**, the formyl proton of **122** was seen as several signals at low field between 8.20-8.30 ppm in the ^{1}H NMR spectrum due to the occurrence of rotamers. Then, **120** and **122** were etherified with 4-iodobenzyl bromide with silver(I) oxide, catalytic amounts of potassium iodide in DCM/cyclohexane (1/1), and sodium hydride in DMF to give ethers **123** and **124**, respectively, which were subsequently coupled with alkyne **71** via SONOGASHIRA coupling reactions. While aryl iodide **123** gave the desired diphenylacetylene derivative **125**, the coupling between compounds **124** and **71** did not give the desired product **127**. Though some coupling occurred between **124** and **71**, the ^{1}H NMR showed that the unidentified coupled product obtained was not **127**. Four distinct signals were observed for the aromatic protons of this unknown compound at 6.83 ppm, 7.04 ppm, 7.47 ppm, and 7.68 ppm with each signal integrating as two protons. The distribution of the aromatic signals was completely at variance with those of **125** when the two ^{1}H NMR spectra were compared. Hence, the signals for the aromatic protons of **125** were observed at 6.86 ppm, 7.26 ppm, and 7.46 ppm that were respectively integrated as two, two, and four protons. Additionally, whereas the successful synthesis of diphenylacetylene derivative **125** was confirmed by high-resolution mass spectrometry, the spectrum of the unidentified compound did not show the calculated *m*/*z* for the desired product **127**. To obtain hydroxamic acid **126**, ester **125** was reacted with hydroxylamine (Scheme 24).



Scheme 24 Synthesis of formamide-based hydroxamic acid **126**.

In a first attempt, the conditions generally used for aminolyses were employed. Thus, ester **125** was reacted with hydroxylamine in THF/IPA (1/1). However, the desired product was not obtained. A very close look at the ^{1}H, ^{13}C, and 2D NMR spectra of the isolated compound suggested that *O*-acylhydroxylamine derivative **132** was formed. The proposed structure of the side product fits well with the data from the ^{1}H NMR and HRMS ESI spectra (Figure 23). Apparently, under the reaction conditions, several unexpected and undesired reactions had

occurred. It was speculated that on the one hand, deformylation of **125** occurred to give **149**. On the other hand, isopropanol was either oxidized to acetone (**129**) or was spoiled with traces of acetone (**129**), which formed oxime **130**. The latter (**130**) underwent a transesterification with the ester moiety of compound **149** yielding *O*-acylhydroxylamine derivative **131**. The nucleophilic attack of the pyrrolidine nitrogen on the imine carbon of the oxime moiety of intermediate **131** led to the formation of an aminal and thus to the closure of the oxadiazinane ring of **132** (Scheme 25). It is not very clear why similar observations were not made in case of other aminolyses.



Scheme 25. Proposed structure of side product **132** using isopropanol as cosolvent for **126** synthesis.

Therefore, in a subsequent attempt to synthesize hydroxamic acid **126**, isopropanol was excluded and THF was used as the only solvent. In this way, compound **126** could be obtained in 19% yield.

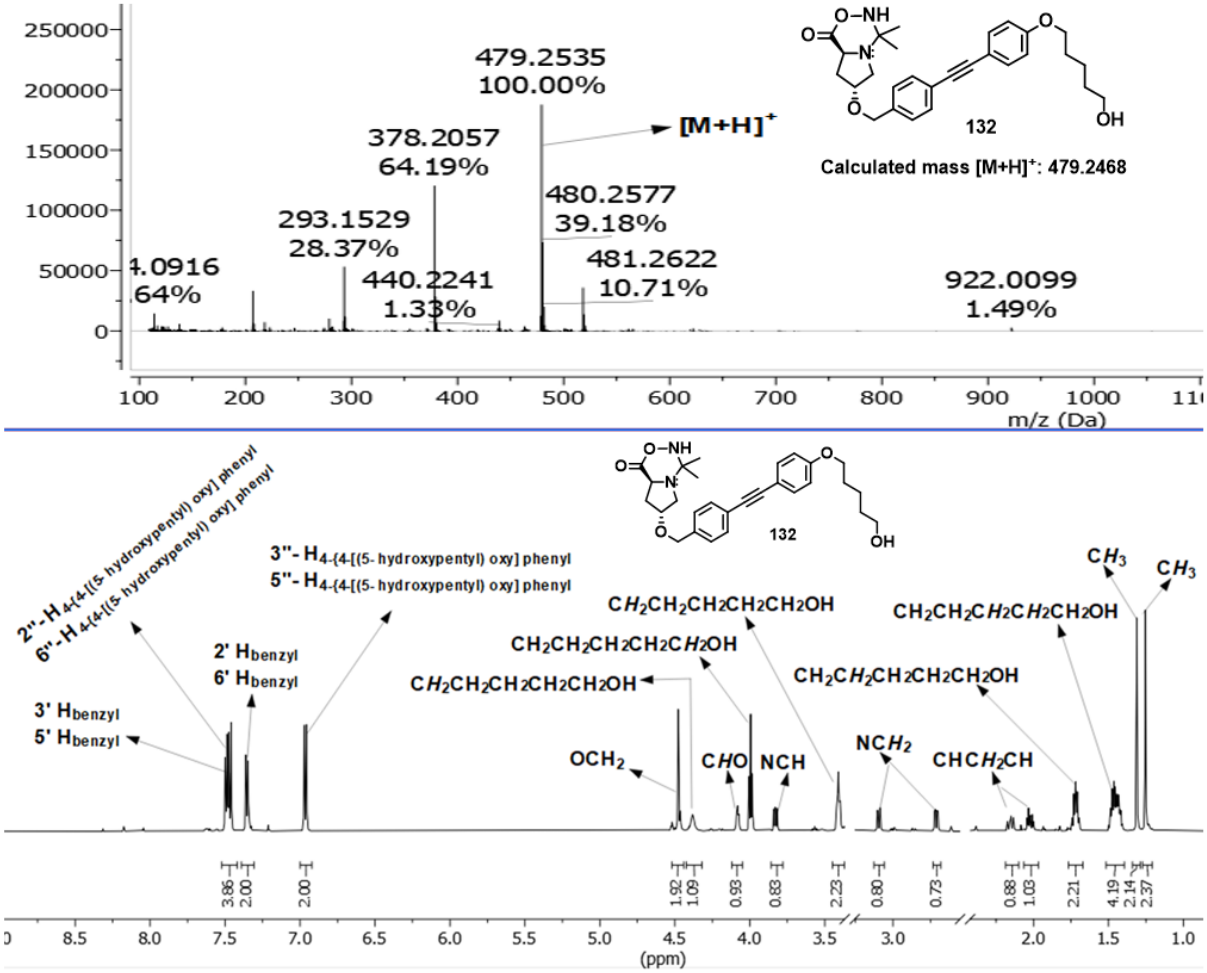
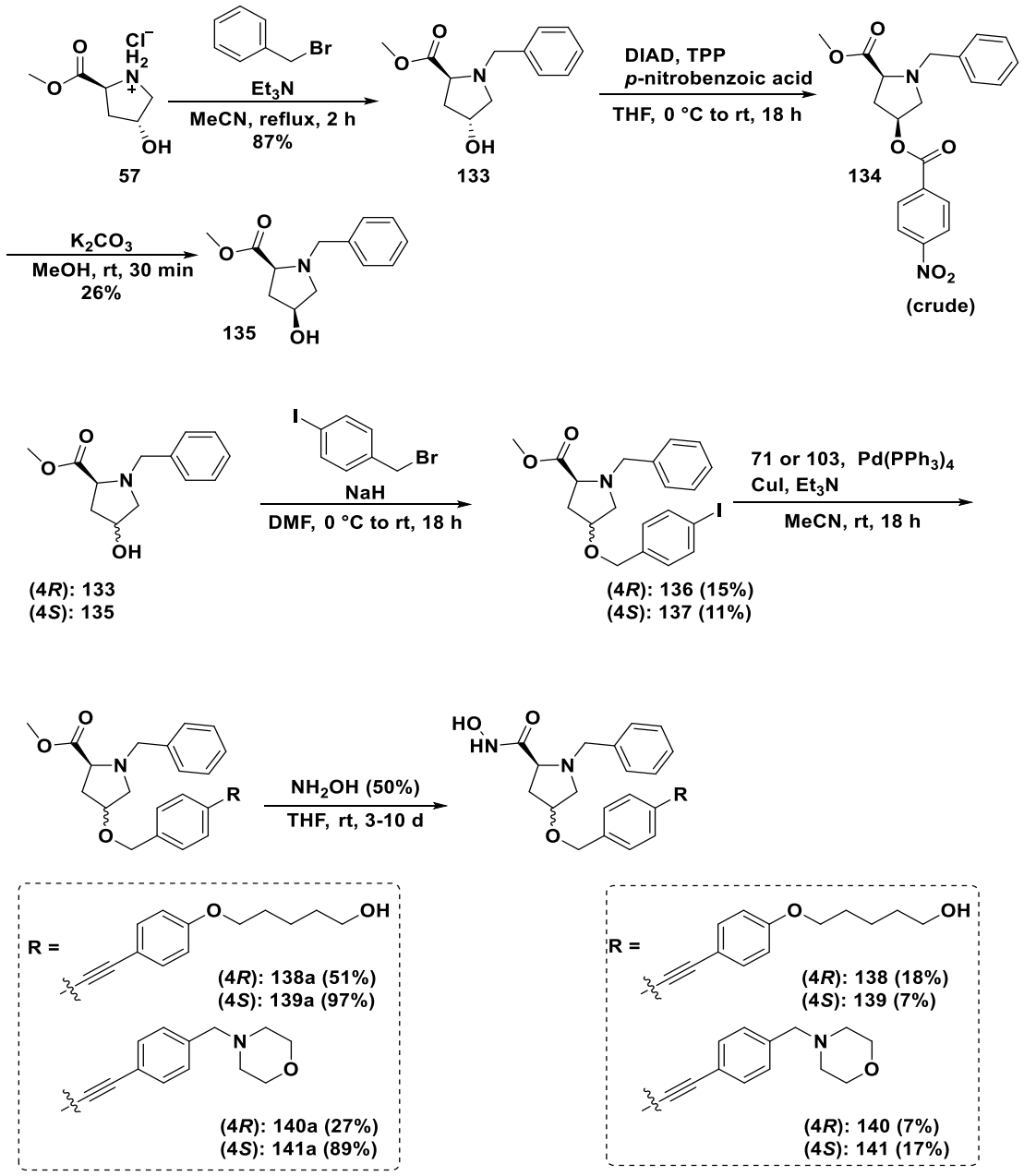


Figure 27. ^{1}H NMR (DMSO-d_6) and HRMS ESI spectra of side product **132**.

To access the *N*-alkylated proline derivatives, at first, hydroxyproline ester **57** was benzylated with benzyl bromide in refluxing acetonitrile using triethylamine as base to give tertiary amine **133** in a yield of 87%. In the ^{1}H NMR of **133**, signals characteristic for the protons of a monosubstituted benzene ring that integrated as five protons were observed at 7.28 ppm. Furthermore, two signals that integrated as one proton each for the benzylic protons were seen at 3.51 ppm and 3.85 ppm, thereby confirming a successful benzylation. A MITSUNOBU reaction of alcohol **133** and saponification of the resulting ester **134**, which was obtained as a crude product, gave the (4*S*)-configured pyrrolidine derivative **135** in a yield of 26% and had a purity of 100% according to HPLC. Both diastereomeric alcohols, **133** and **135**, were etherified using sodium hydride as base and 4-iodobenzyl bromide as alkylating agent in DMF to give ethers **136** and **137**. The etherification reactions produced many side products. As such, **136** and **137** were obtained in low yields of 15% and 11%, respectively. Both aryl iodides **136** and **137** were

coupled with alkynes **71** and **103** to give diphenylacetylene derivatives **138a**, **139a**, **140a**, and **141a** that were reacted with hydroxylamine to give hydroxamic acids **138**, **139**, **140**, and **141a**, respectively (Scheme 26).



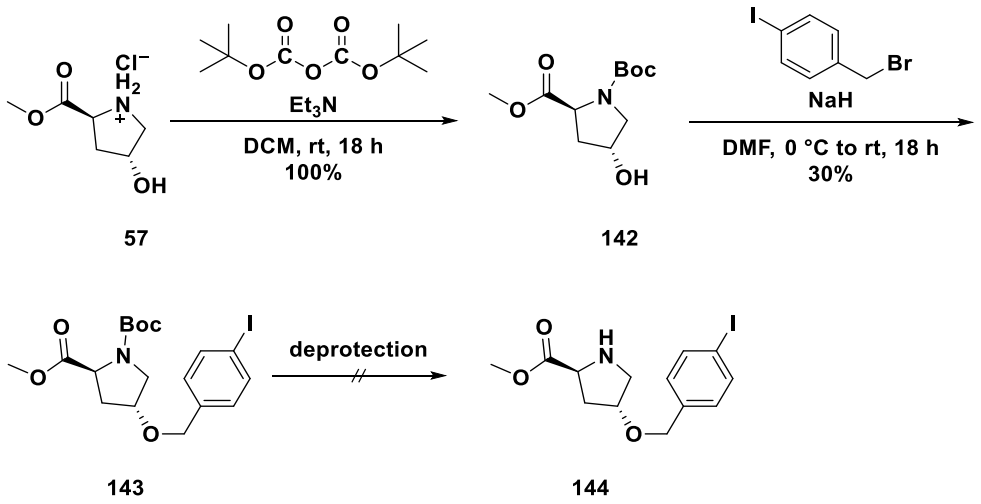
Scheme 26:Syntheses of benzyl-substituted hydroxamic acids **138**, **139**, **140**, and **141**.

In an attempt to achieve hydroxamic acids with an unsubstituted pyrrolidine nitrogen, the secondary amine of hydroxyproline ester **57** was Boc-protected in a reaction with di-*tert*-butyl dicarbonate in DCM employing triethylamine as base to afford carbamate **142** in a yield of

100%. The successful installation of the protecting group was confirmed by the observation of a signal at 1.40 ppm that integrated as nine protons for the three methyl groups of the Boc group of **142** in the ^{1}H NMR spectrum. Also, several rotamers were observed in the ^{1}H NMR spectrum. The protection of the pyrrolidine nitrogen was to avoid its benzylation in the subsequent etherification step (Scheme 27). The protected proline ester **142** was then subjected to a WILLIAMSON ether synthesis using sodium hydride as base and 4-iodobenzyl bromide as alkylating agent to give ether **143** in a yield of 30%. To access secondary amine **144**, the pyrrolidine nitrogen of ether **143** should be deprotected. Several conditions were assayed without success (Table 4).

Table 4. Conditions investigated for the envisaged Boc deprotection of **143**.[166-171]

Nr.	Reagents / Chemicals	Reaction conditions			Yield [%]
		Solvent	Temperature [°C]	Time [h]	
1	TFA	DCM	rt	0.5	-
2	$BF_3{\cdot}O(CH_2CH_3)_2$	DCM	rt	20	-
3	*p*-TsOH	DCM	80	24	-
4	4 N HCl	dioxane	rt	24	-
5	Oxalyl chloride	MeOH	rt	0.5	-
6	HCl saturated MeOH	MeOH	rt	18	-

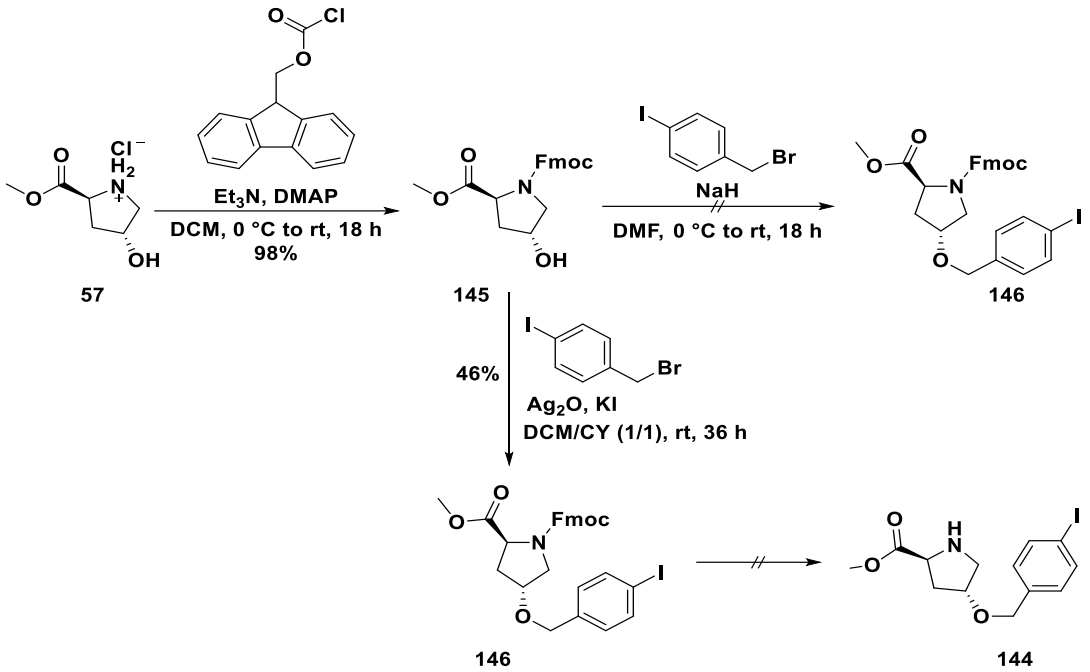


Scheme 27. Synthesis of ether **143** and unsuccessful Boc deprotection.

The unsuccessful attempts to remove the Boc group required a change of the protecting group. Thus, the Fmoc group was installed by reacting **57** with fluorenylmethyloxycarbonyl chloride using triethylamine as base in DCM to afford **145** in yield of 98% (Scheme 28), which could not be etherified with 4-iodobenzyl bromide using sodium hydride as a base. As such, silver(I) oxide was used as base in the etherification process using 4-iodobenzyl bromide with a catalytic amount of KI in DCM/cyclohexane (1/1) to give benzyl ether **146** in a yield of 46%. Again, the removal of the protecting group of **146** to give secondary amine **144** was unsuccessful using various basic conditions (Table 5 and Scheme 28).[172,173]

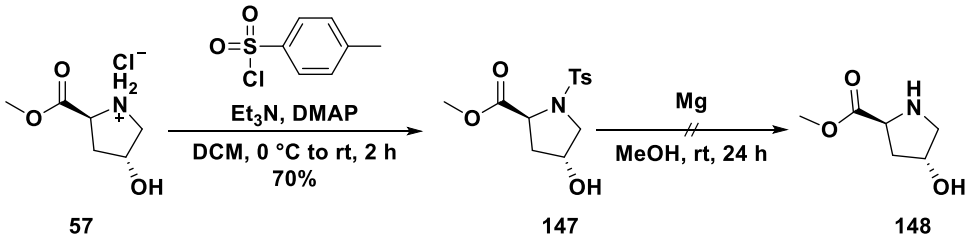
Table 5. Conditions investigated for the envisaged Boc deprotection of **146**

Nr	**Base**	**Reaction conditions**			**Yield [%]**
		Solvent	**Temperature [°C]**	**Time [h]**	
1	25% piperidine	DMF	rt	24	-
2	DBU	DCM	rt	24	-
3	DABCO	DCM	rt	24	-
4	NaN_3	DMF	rt	24	-
5	Triethylamine	Triethylamine	rt	72	-



Scheme 28. Synthesis of ether **146** and unsuccessful Fmoc deprotection.

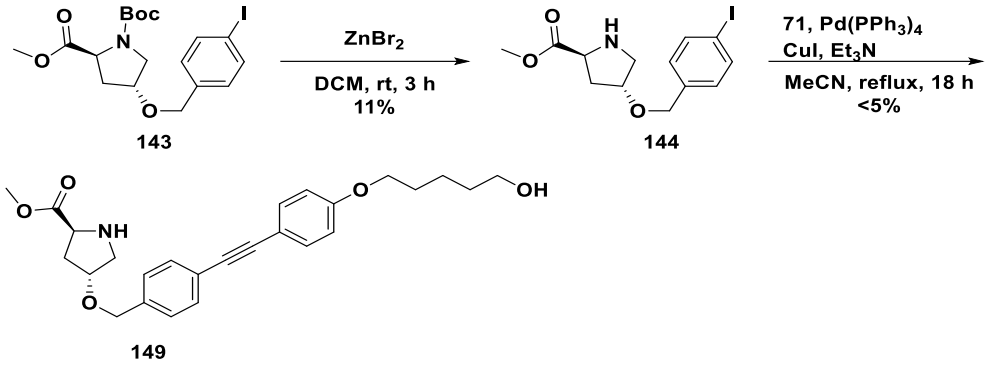
Alternatively, the pyrrolidine nitrogen of **57** was tosylated with tosyl chloride in DCM using triethylamine as base and DMAP as catalyst to give sulfonamide **147** in 70% yield (Scheme 29). Unfortunately, Mg in methanol, which has been reported to cleave arenesulfonamides, failed to deprotect **147** to give amine **148**.[174,175]



Scheme 29. Synthesis of sulfonamide **147** and unsuccessful detosylation.

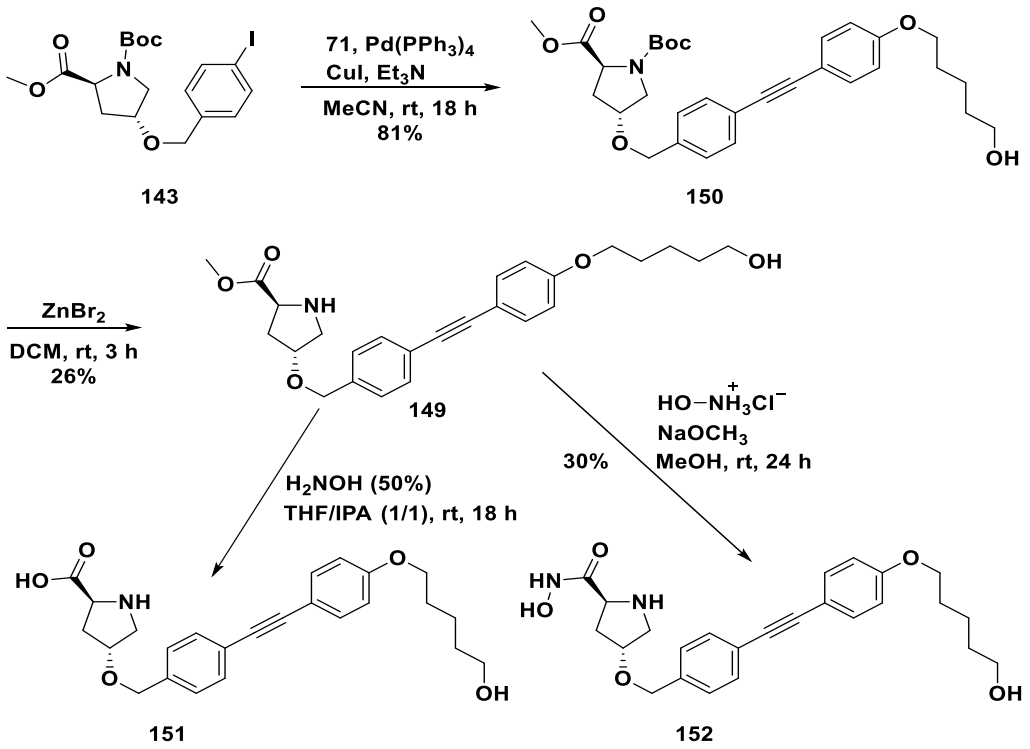
A further review of literature methods for Boc deprotection led to the use of zinc bromide in DCM for the removal of the protecting group. Thus, proline derivative **143** was treated with zinc bromide in DCM for 3 h at ambient temperature to afford secondary amine **144** in 11% yield.[176] The loss of the signals for the nine protons at 1.34 ppm for the Boc group of **143** in the ^{1}H NMR spectrum of **144** confirmed a successful removal of the protecting group. Then, aryl

iodide **144** was coupled with alkyne **71** via a C-C coupling reaction in refluxing acetonitrile since **144** was poorly soluble at room temperature. The reaction gave diphenylacetylene derivative **149** in a yield of less than 5% (Scheme 30). Of note is the fact that the coupling reaction failed in DMF (at room temperature and under reflux) as well as in refluxing DMSO. Obviously, **144** coupled very poorly with **71** under the conditions assayed.



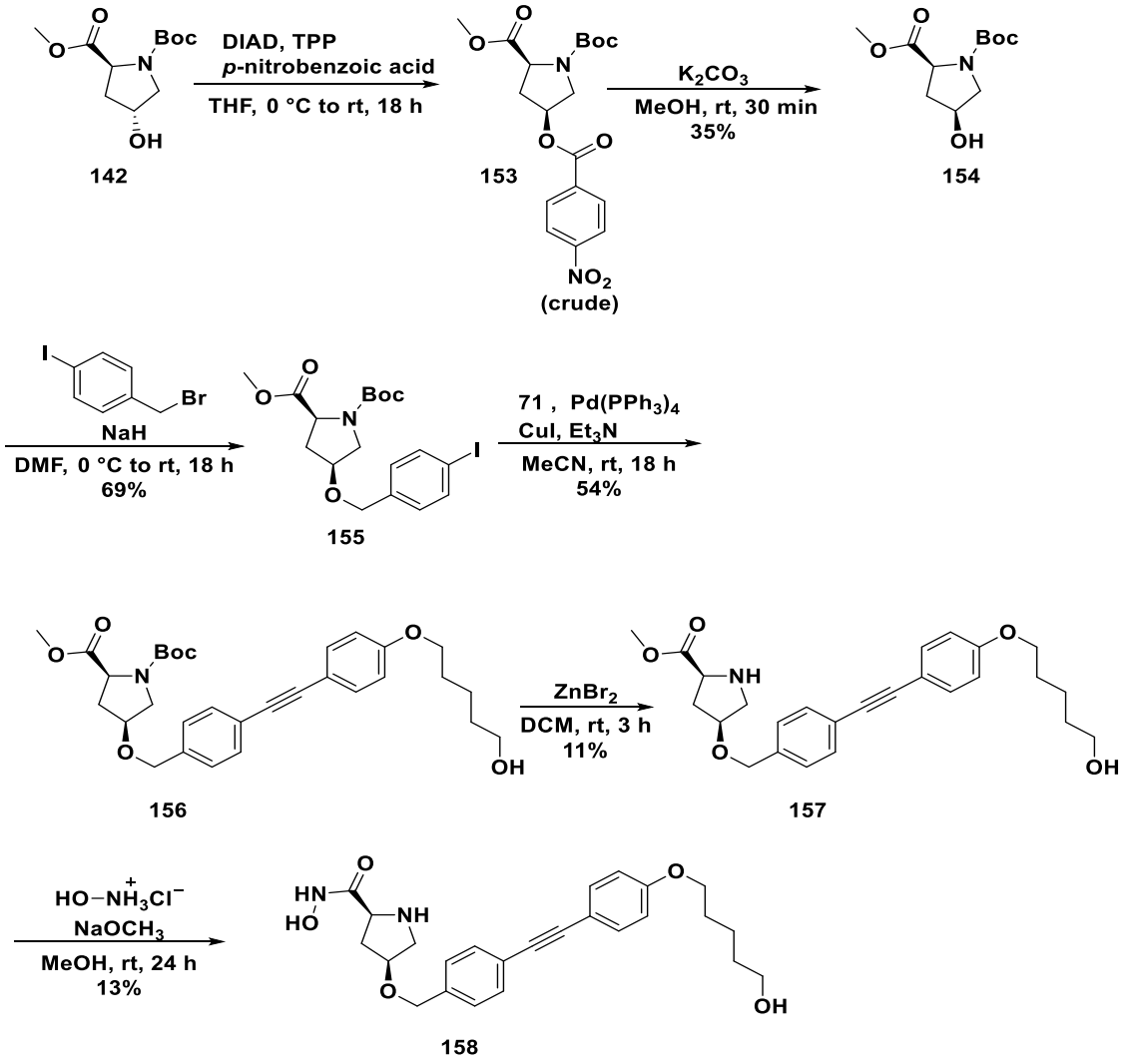
Scheme 30. Successful deprotection of **143** and synthesis of diphenylacetylene **149**.

To optimize the overall yield of diphenylacetylene derivative **149**, the synthetic route was slightly changed. Thus, at first, aryl iodide **143** was coupled with alkyne **71** to give Boc-protected diphenylacetylene derivative **150** in 80% yield. Then, the Boc group was removed with zinc bromide in DCM to give secondary amine **149** obtainable in yields of up to about 50%. An initial aminolysis of ester **149** with a 50% aqueous solution of hydroxylamine afforded the respective carboxylic acid **151** rather than the desired hydroxamic acid **152**. To avert this, the aminolysis was conducted in dry methanol with hydroxylamine hydrochloride using sodium methoxide in methanol as base. This gave the desired hydroxamic acid **152** in 30% yield (Scheme 31). The success of the aminolysis was confirmed by high-resolution mass spectrometry and LC-MS.



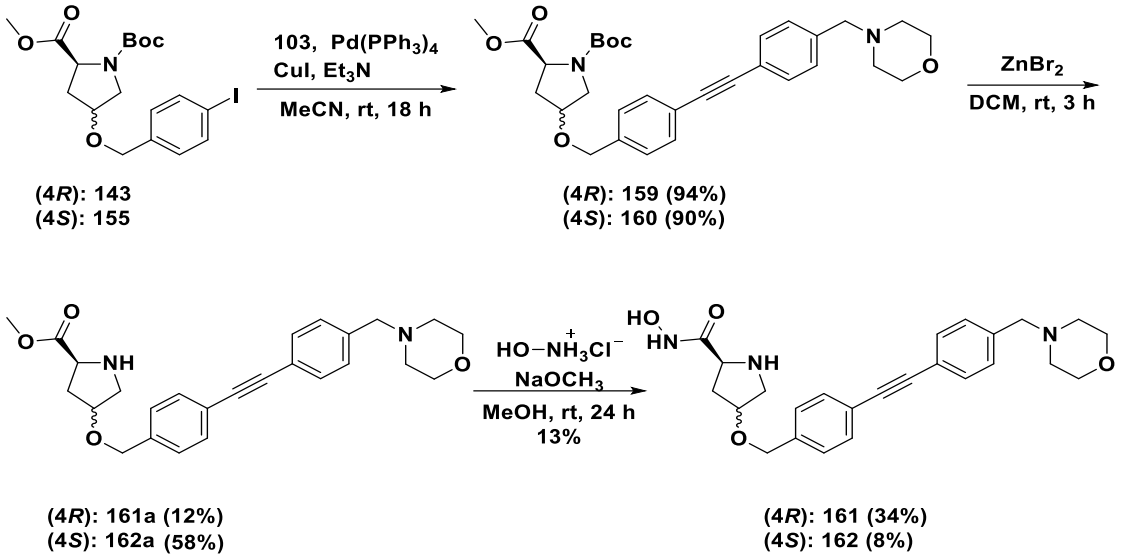
Scheme 31. Synthesis of hydroxamic acid **152**.

The (4*S*)-configured hydroxamic acid **158** was also obtained from Boc-protected 4-hydroxyproline derivative **142**. At first compound **142** was subjected to a MITSUNOBU reaction to yield benzoate ester **153**. Subsequently, saponification of **153** yielded the (4*S*)-configured alcohol **154**. Then, alcohol **154** was transformed into hydroxamic acid **158** employing the same reaction pathways as described for the synthesis of hydroxamic acid **152** from alcohol **142** (Scheme 32).



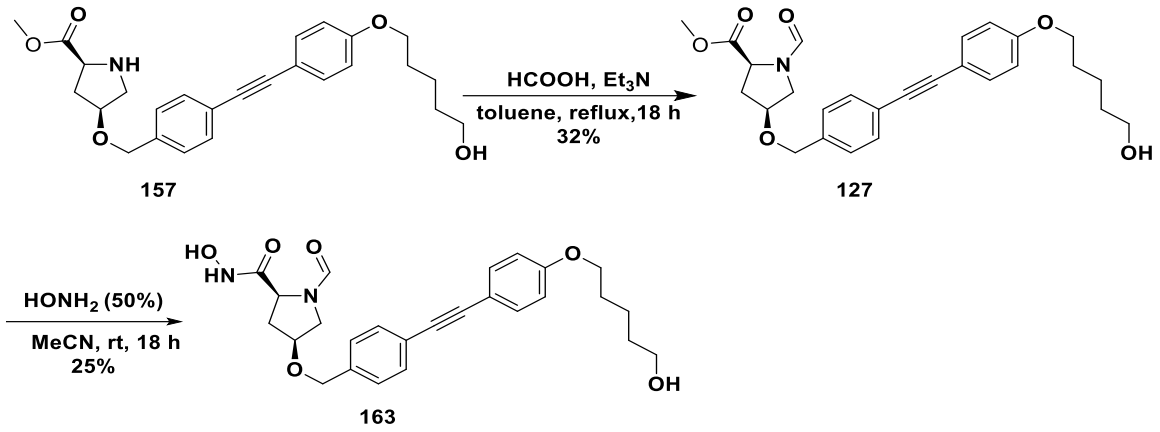
Scheme 32. Synthesis of hydroxamic acid **158**.

In order to obtain the *N*-unsubstituted proline derivatives **159** and **160**, bearing the same lipophilic side chain as LpxC inhibitor CHIR-090, aryl iodides **143** and **155** were coupled with morpholine-based alkyne **103** in SONOGASHIRA coupling reactions to yield 94% and 90% of diphenylacetylene derivatives **159** and **160**, respectively. The esters were subsequently transformed into the corresponding hydroxamic acids **161** and **162** in 34% and 8% yields, employing the same reaction steps used to access hydroxamic acids **152** and **158** from esters **149** and **157**, respectively (Scheme 33).



Scheme 33. Syntheses of hydroxamic acids **161** and **162**.

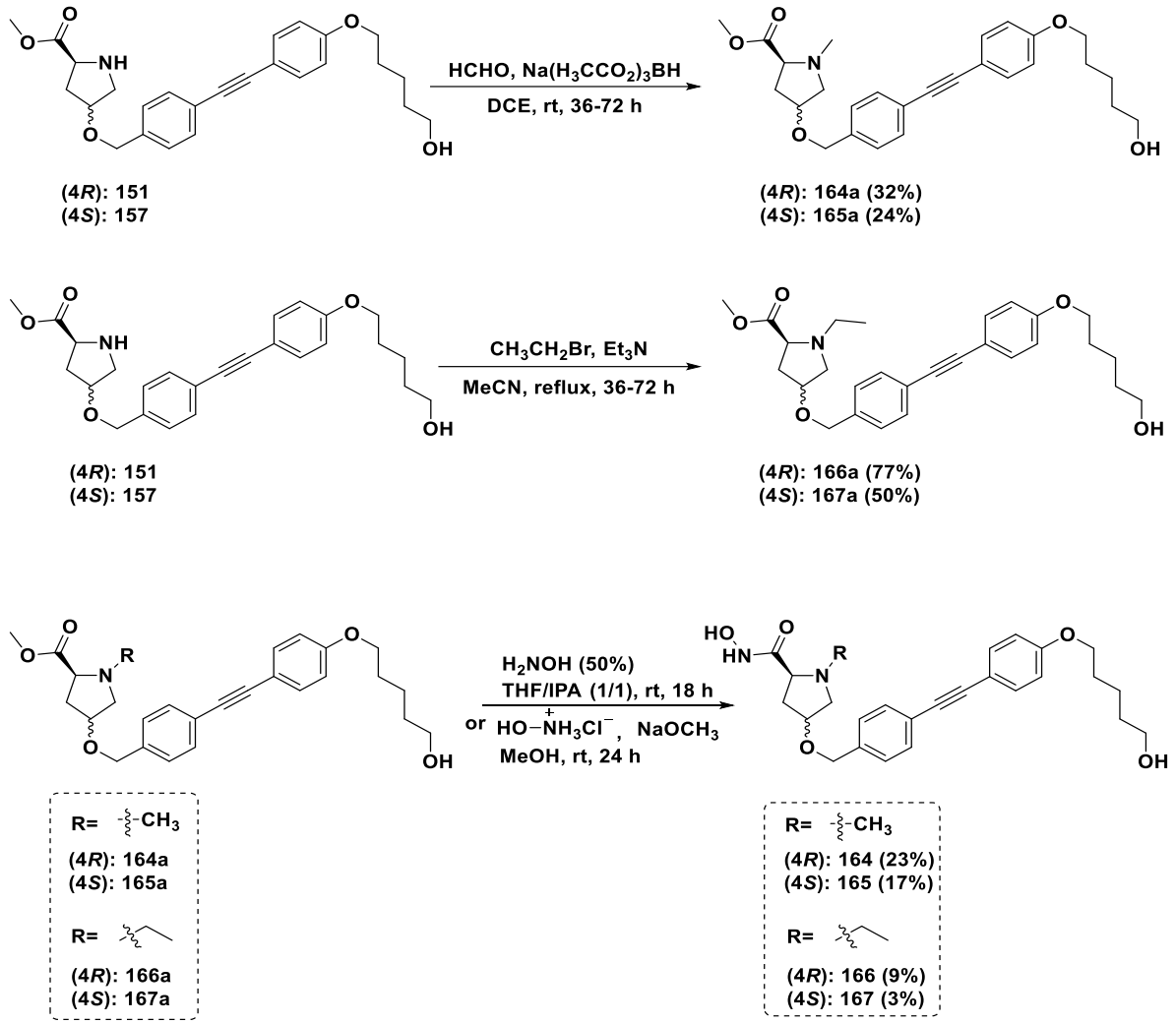
The successful Boc deprotection after the establishment of the lipophilic side chain offered an alternative route to access some target compounds. For instance, the (4*S*)-configured formamide-based hydroxamic acid **163**, which could not be obtained in previous attempts (Scheme 24), could be successfully synthesized via this route. Thus, secondary amine **157** was formylated by refluxing the compound with formic acid and trimethylamine in toluene. The obtained formamide **127**, which was accessed in a yield of 32%, was reacted with hydroxylamine in acetonitrile to afford the corresponding hydroxamic acid **163** in a yield of 25% (Scheme 34). Unlike the previously obtained product, the distribution of the aromatic signals of **127** was consistent with that of its diastereomer **125**. As such, in the ^{1}H NMR spectrum, the aromatic signals were observed at 6.86 ppm, 7.23 ppm, and 7.45 ppm and integrated respectively as 2 protons, 2 protons, and 4 protons. Also, the signal for the formyl proton of **127** was seen at 8.27 ppm, thus, confirming the success of the formylation. Acetonitrile was chosen as solvent for the subsequent aminolysis because the reaction in THF proceeded very slowly with much of the starting material not converted after 5 d. Also, unlike isopropanol in the case of **126** (Scheme 25), acetonitrile did not participate in the reaction.



Scheme 34. Synthesis of formamide **163**.

The *N*-methylated proline derivatives were also accessed from secondary amines **151** and **157**, which were reductively alkylated with formaldehyde using sodium triacetoxyborohydride as reducing agent in DCE to yield 32% and 24% of tertiary amines **164a** and **165a**, respectively. In their ^{1}H NMR spectra, signals were observed at 2.47 ppm and 2.52 ppm for the methyl protons of **164a** and **165a**, respectively. Hence, the *N*-methylation was ascertained to be successful. Then, **164a** and **165a** were reacted with hydroxylamine to obtain hydroxamic acids **164** and **165** in yields of 23% and 17%, respectively.

Refluxing amines **151** and **157** with ethyl bromide and triethylamine in acetonitrile gave ethyl-substituted tertiary amines **166a** and **167a**, which were reacted with hydroxylamine to give hydroxamic acids **166** and **167** in 9% and 3% yields, respectively. (Scheme 35). High-resolution mass spectrometry was used to confirm the successful synthesis of the hydroxamic acids.

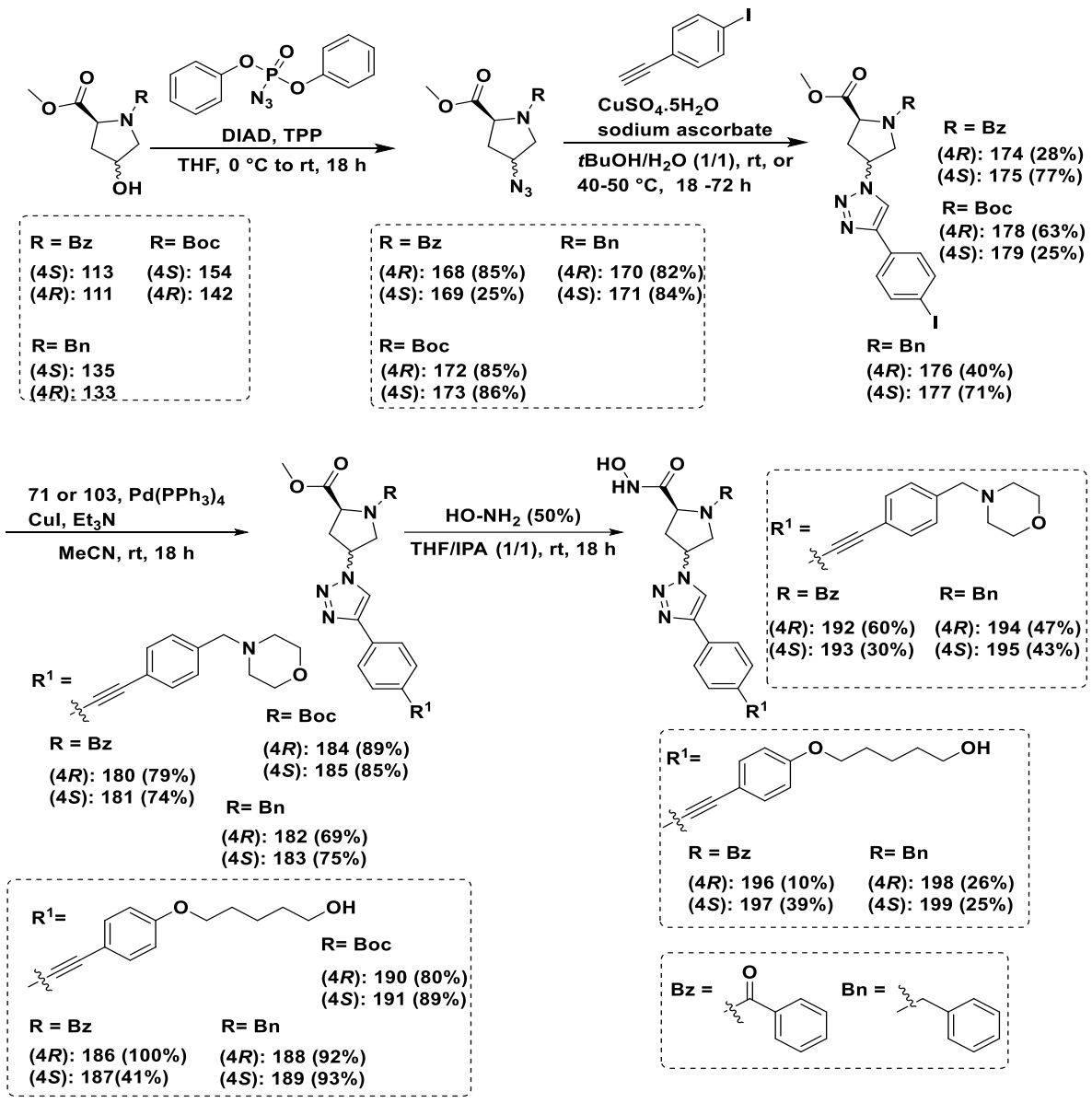


Scheme 35. Syntheses of hydroxamic acids **164**, **165**, **166**, and **167**.

3.2.3 Syntheses of triazole-based hydroxamic acids

Azides undergo copper-catalyzed cycloadditions with alkynes to form 1,2,3-triazoles. To obtain azides for this purpose, selected 4-hydroxyproline derivatives were converted to the respective azides via MITSUNOBU reactions (Schemes 36). Thus, diastereomeric benzamide-based (**111** and **113**), *N*-benzyl-substituted (**133** and **135**), and *N*-Boc-protected (**142** and **154**) 4-hydroxyproline derivatives were chosen as starting points for the syntheses of the envisaged triazole-based hydroxamic acids. The conditions of the MITSUNOBU reactions were the same as described earlier. However, diphenylphosphoryl azide was used instead of *p*-nitrobenzoic acid as nucleophile in the reaction to afford benzamide-based azides **168** and **169** in respective yields of 85% and 25%; *N*-benzyl-substituted azides **170** and **171** in respective yields of 82% and 84%; and Boc-protected azides **172** and **173** in corresponding yields of 85% and 86%. The disappearance of the signals due to the O-H stretch in the IR spectra of the alcohols between

3300 and 3500 cm^{-1} and the appearance of strong signals around 2100 cm^{-1} in the IR spectra of the azides confirmed the success of the MITSUNOBU reaction. Having synthesized the azides, the compounds were reacted with 1-ethynyl-4-iodobenzene using copper(II) sulfate pentahydrate as catalyst and sodium ascorbate as reducing agent in *tert*-butanol/water (1/1) to afford the respective triazoles. The low yields obtained for **174**, **176**, and **179** were due to incomplete conversion of the azides to the corresponding triazoles. Hence, in some cases, refluxing at 40-50 °C was done to yield enough of the triazoles for further reactions. The success of the click reactions was confirmed by the appearance of a singlet for the proton in 5-position of the triazole ring and two sets of multiplets for the protons of the *para*-substituted aromatic ring in the aromatic region of the ^{1}H NMR spectra of the obtained compounds. Furthermore, in the ^{13}C NMR spectra, the presence of iodide in position 4 of the benzene ring was noticed by the lower chemical shift of the carbon atom (around 93-95 ppm) to which it was bound compared to the chemical shifts of the other aromatic carbon atoms. Then, the triazoles were coupled with alkynes **71** and **103** to yield diphenylacetylene derivatives **180** to **185**. Finally, the *N*-benzyl-substituted and benzamide-based diphenylacetylene derivatives **180** to **183** and **186** to **189** were reacted with hydroxylamine to give the desired hydroxamic acids **192** to **195** and **196** to **199** (Scheme 36).



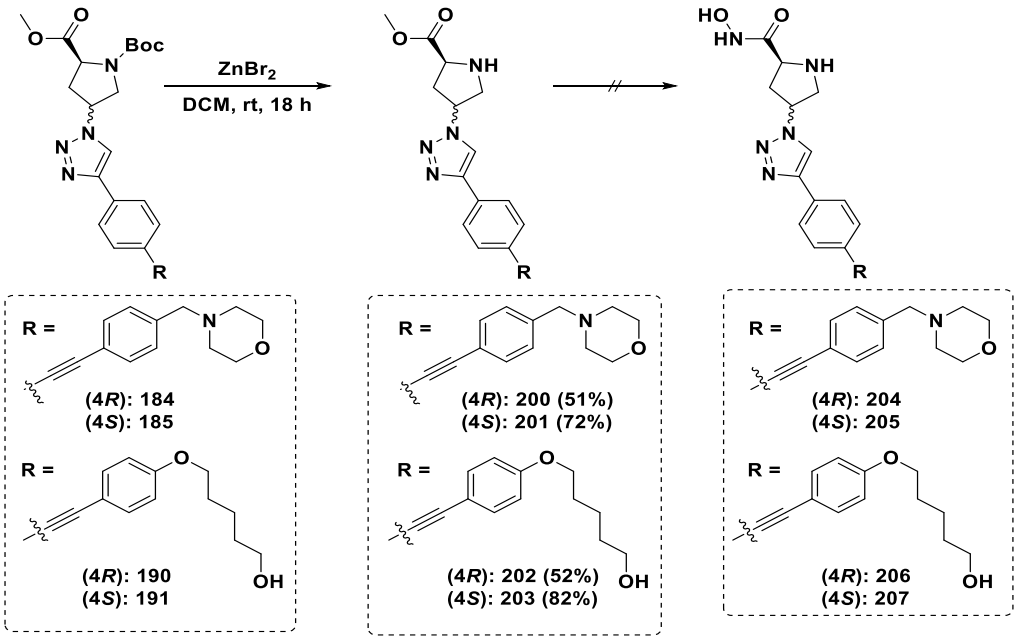
Scheme 36. Syntheses of hydroxamic acids **192-195** and **196-199**.

To access the *N*-unsubstituted proline derivatives, the Boc-protected diphenylacetylene derivatives **184**, **185**, **190**, and **191** were deprotected with zinc bromide in DCM to respectively afford secondary amines **200**, **201**, **202**, and **203** in 51%, 72%, 52%, and 82% yields. The esters were subjected to aminolyses with hydroxylamine, which did not yield the desired hydroxamic acids (Scheme 37). Anhydrous conditions like using hydroxylamine hydrochloride with sodium methoxide in dry methanol that worked well for the *N*-unsubstituted ethers did not work for the *N*-unsubstituted triazoles. Different other bases like triethylamine and potassium hydroxide with hydroxylamine hydrochloride were tried in different solvents like acetonitrile,

dichloromethane, and a THF-isopropanol mixture without success (Table 6 and Scheme 37).[177-179]

Table 6. Conditions assayed for aminolyses of **200**-**203**.

Nr.	Reagents/ Chemicals	Reaction conditions			Yield [°C]
		Solvent	Temperature [°C]	Time [h]	
1	NH_2OH (50%)	THF/ISP (1:1)	rt	18	-
2	$NH_3^+OHCl^-$, CH_3ONa/ MeOH	MeOH	rt	24	-
3	$NH_3^+OHCl^-$, KOH	MeOH	rt	24	-
4	NH_3^+OHCl, Et_3N	DCM	rt	120	-
5	NH_3^+OHCl, Et_3N	MeCN	80	24	-



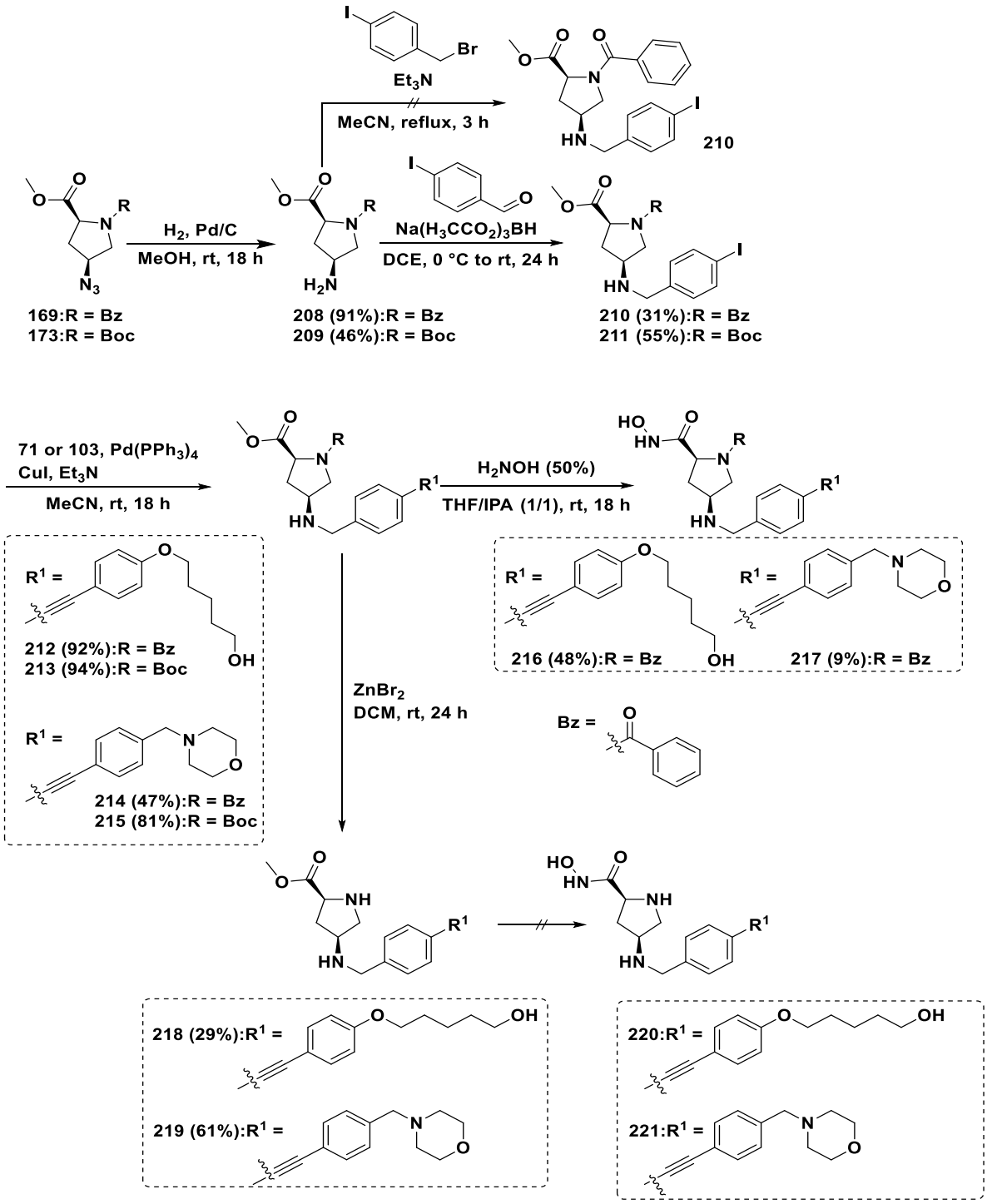
Scheme 37. Syntheses of *N*-unsubstituted proline derivatives.

3.2.4 Syntheses of 4-aminoproline-based hydroxamic acids

In order to access 4-aminoproline-based hydroxamic acids, *N*-benzoyl substituted and *N*-Boc-protected 4-azidoproline derivatives **169** and **173** were reduced under a hydrogen atmosphere in the presence of a palladium catalyst to afford the respective primary amines **208** and **209**.

Next, primary amines **208** and **209** should be transformed into secondary amines **210** and **211**, bearing a 4-iodobenzyl substituent. The direct *N*-alkylation of **208** with 4-iodobenzyl bromide using triethylamine as base in refluxing acetonitrile failed, producing several spots whose R_f values as revealed by TLC control indicated an unsuccessful *N*-alkylation. However, the reductive alkylation of primary amines **208** and **209** using 4-iodobenzaldehyde with sodium triacetoxyborohydride as reducing agent in DCE gave the desired secondary amines **210** and **211** in yields of 31% and 55%, respectively. This time, TLC control revealed two spots, with the less polar compound identified as the product of double alkylation (tertiary amine) and the more polar one being the desired secondary amine. Confirming the *N*-alkylation, benzylic proton signals of **210** and **211** were observed at 3.60 ppm and 3.75 ppm and signals for *para*-substituted aromatic systems were also seen in their ^{1}H NMR spectra. Thus, **210** and **211** were coupled with alkynes **71** and **103** to give diphenylacetylene derivatives **212** to **215** (Scheme 38). In the case of the benzamide-based derivatives, the reactions of diphenylacetylene derivatives **212** and **214** with hydroxylamine gave hydroxamic acids **216** and **217** in yields of 48% and 9%, respectively. The low yield of **217** was due to the formation of the respective carboxylic acid in high amount.

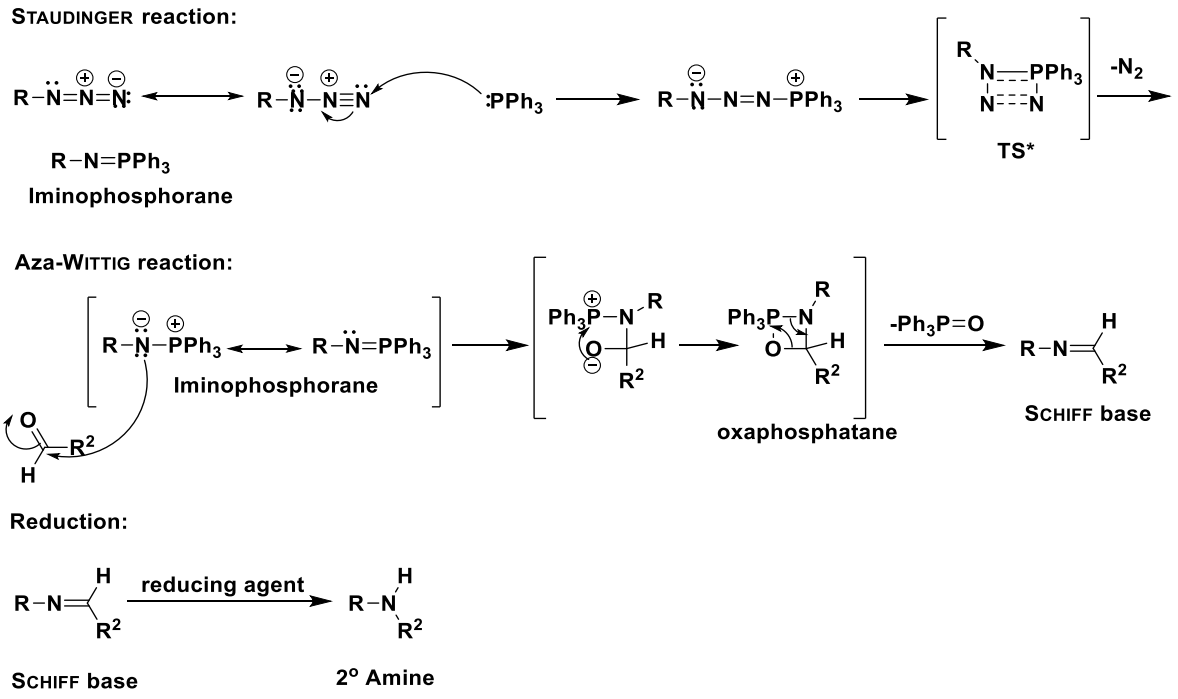
The *N*-Boc-protected proline derivatives **213** and **215** were first deprotected using zinc bromide in DCM to afford secondary amines **218** and **219** in yields of 29% and 61%, respectively. The subsequent aminolyses afforded very low yields of the crude hydroxamic acids. Even though the hydroxamic acids were detected in the crude product using MS, they could not be rendered pure enough (<20% purity) for biological activity testing (Scheme 38).



Scheme 38. Syntheses of hydroxamic acids **216** and **217** and of *N*-unsubstituted proline derivatives.

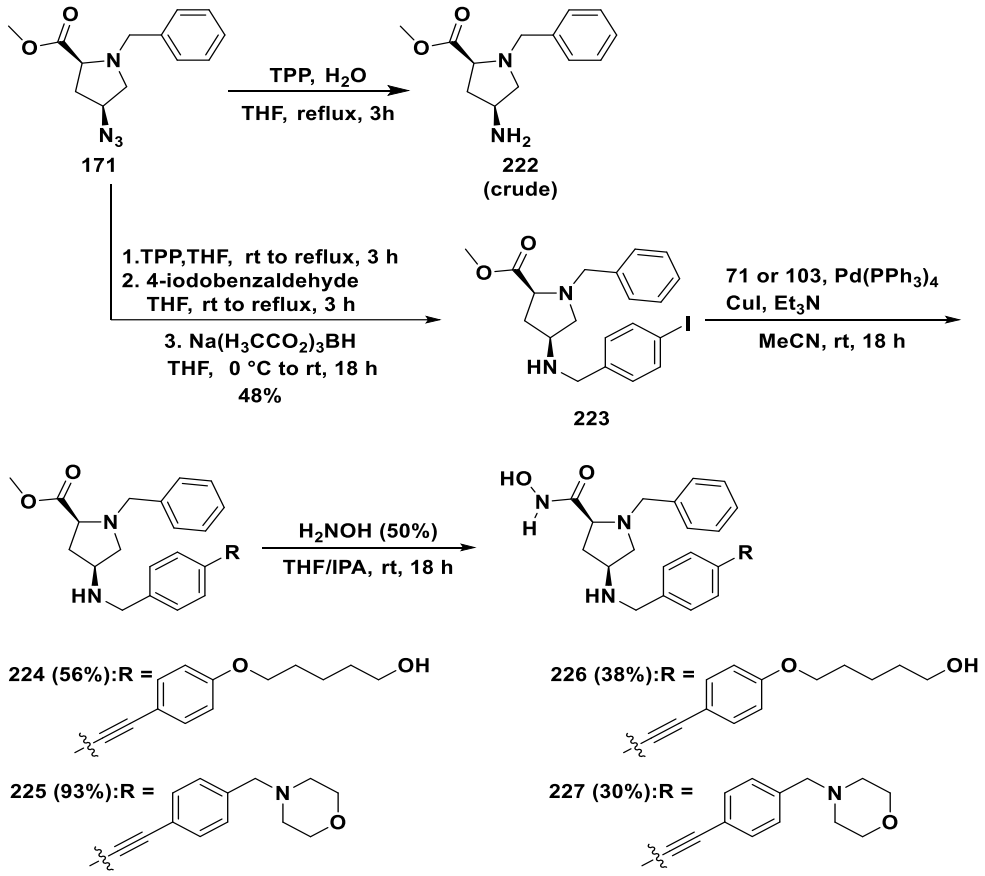
In case of the *N*-benzyl-substituted 4-azidoproline derivative **171**, the previously applied method to reduce the azide group did not yield the desired primary amine. Based on TLC control and using benzamide **208** as a reference compound, several spots with R_f values lower than the one of primary amine **208** were observed. Thus, the reduction was ascertained to be unsuccessful Therefore, the STAUDINGER reaction was used to afford primary amine **222** (Schemes 39 and 40). Unfortunately, primary amine **222** could not be rendered sufficiently pure

for the subsequent reductive amination. Using an impure or crude product, in which the exact amount of the amine is not accurately known, could result in very low yields and many side products, notably, a product with a doubly alkylated nitrogen if the aldehyde was in excess. Thus, to avoid this, the aza-WITTIG reaction together with a reducing agent was used in a one-pot procedure to generate the desired secondary amine **223**.[151] In this reaction sequence, at first, triphenylphosphine reacts with the azide to give an iminophosphorane with the loss of nitrogen (Scheme 39, STAUDINGER reaction). Then, the iminophosphorane reacts with the aldehyde to give an oxaphosphatane, a four-membered intermediate, from which a SCHIFF base and triphenylphosphine oxide are released (Scheme 39, Aza-WITTIG). Finally, the SCHIFF base is reduced to afford the secondary amine (Scheme 39, Reduction). In this way, secondary amine **223** could be obtained from azide **171** in a yield of 48% and a purity of about 86% according to HPLC.



Scheme 39. Reaction mechanism for the synthesis of secondary amines from alkyl azides.

The coupling between aryl iodide **223** and alkynes **71** and **103** gave diphenylacetylene derivatives **224** and **225** in 56% and 93% yields, respectively. Finally, esters **224** and **225** were reacted with hydroxylamine to give the desired hydroxamic acids **226** and **227** in respective yields of 38% and 30% (Scheme 40).



Scheme 40. Syntheses of hydroxamic acids **226** and **227**.

4.0 BIOLOGICAL EVALUATION RESULTS AND DISCUSSION

4.1 MMP-13 inhibitors

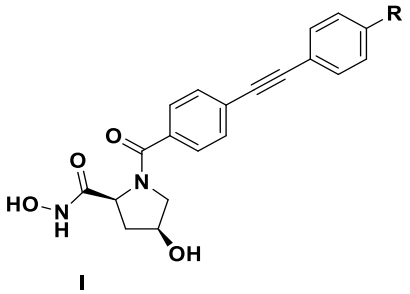
Since an overexpression of MMP-13 activity is correlated with disease conditions like human carcinomas, rheumatoid arthritis, and osteoarthritis, MMP-13 is a suitable target for the development of diagnostic and therapeutic tools. Most agents intended for clinical use had to be withdrawn as a result of a lack of efficacy and selectivity that lead to undesirable side effects like musculoskeletal syndrome.[180-183]

To develop potent and selective agents against MMP-13, structural features of the enzyme that differentiate it from other isoforms were exploited. The MMP-13 enzyme has a deep S1′ pocket which varies in length and amino acid sequence.[81] Additionally, it has a unique S′* side pocket that differentiates it from other MMPs. As such, all the synthesized hydroxamic acids possess a long lipophilic side chain that should fully address the S1′ pocket. In order to evaluate the inhibitory properties of the synthesized compounds, the proline derivatives were assayed *in vitro* against MMP-13. To properly evaluate the MMP-13 selectivity profile of all test compounds, other MMPs with intermediate S1′ pockets like MMPs-2, -8, and -9 were included in the testing protocol. This implies that MMP-1 and -7 with shallow S1′ pockets did not have to be considered since their inhibition requires agents with shorter lipophilic side chains.[55,184]

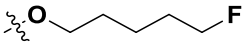
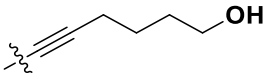
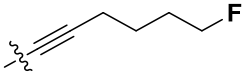
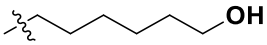
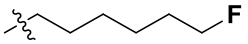
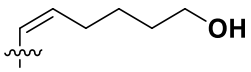
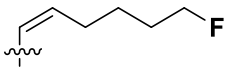
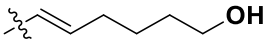
4.1.1 Variation of the lipophilic side chains

First, the hydroxamic acids **I** with varied lipophilic side chains were tested *in vitro* for their ability to inhibit activated collagenases MMP-8 and MMP-13 as well as gelatinases MMP-2 and MMP-9. The IC_{50}-values obtained in the assays are summarized in Table 7.

Table 7: MMP inhibitory activity of the synthesized hydroxamic acids **I** with varied lipophilic side chains.



I

Compound	R	IC_{50} ± SD [nM]			
		MMP-2	**MMP-8**	**MMP-9**	**MMP-13**
41		5 ± 1	21 ± 8	108 ± 11	0.07 ± 0.02
60		39.2 ± 1.9	17.5 ± 1.8	51.3 ± 4.5	2.5 ± 0.3
61		9.7 ± 5.7	2.1 ± 0.4	2.9 ± 1.3	1.8 ± 0.6
62		2.6 ± 1.4	56 ± 10	26 ± 3	2.9 ± 0.9
63		19 ± 9	42 ± 15	32 ± 14	3.3 ± 1.0
64		20 ± 4	8.7 ± 0.3	6.8 ± 2.6	4.6 ± 1.7
65		29 ± 8	19 ± 14	2.6 ± 0.2	3.6 ± 2.2
66		34 ± 25	70 ± 14	82 ± 52	1.7 ± 0.2

Generally, all newly synthesized proline derivatives with varied lipophilic side chains were found to be potent inhibitors of MMP-13 with IC_{50}-values in the single-digit nanomolar range, but less potent than lead compound **41** (IC_{50} = 0.07 nM), a picomolar MMP-13 inhibitor with 70- to 1500-fold selectivities over MMPs-2, -8, and -9.[19] Also, the selectivities of **41** for MMP-13 over the other investigated MMPs were superior to those of the newly developed hydroxamic acids. Apparently, the replacement of the oxymethylene group by the investigated groups led to a reduction in MMP-13 potency and selectivity.

Among the hydroxamic acids with the varied side chains, *trans*-alkene **66** was the most potent inhibitor of MMP-13 (IC_{50} = 1.7 nM), while *cis*-alkenes **64** and **65** were the least potent MMP-13 inhibitors with IC_{50}-values of 4.6 nM and 3.6 nM, respectively. Alkynes **60** (IC_{50} = 2.5 nM) and **61** (IC_{50} = 1.8 nM) were found to be more potent MMP-13 inhibitors than proline

derivatives **62** (IC_{50} = 2.9 nM) and **63** (IC_{50} = 3.3 nM) possessing saturated lipophilic side chains. Fluorination produced ambiguous results with respect to MMP-13 inhibition. When comparing alcohols **60** and **64** with their respective fluorinated derivatives **61** and **65**, it was observed that fluorination did not significantly enhance MMP-13 inhibitory potency, with the fluorinated derivatives being slightly more potent than their respective hydroxylated derivatives. However, in the case of proline derivatives **62** and **63** bearing a saturated side chain, the former was marginally more potent. Thus, fluorination did not significantly improve or affect the MMP-13 inhibitory potency of these compounds.

Next, the selectivities of the compounds for MMP-13 were investigated. Alkyne **60**, exhibited MMP-13 selectivities ranging from 7-20 over MMPs-2, -8, and -9. The fluorinated derivative of alcohol **60**, which is **61**, was found to be a more potent MMP-13 inhibitor than **60**, however the compound exhibited lower selectivity toward MMP-13 with selectivities over MMPs-2, -8, and -9 ranging from 1-5.

Hydroxamic acids **62** (IC_{50} = 2.9 nM) and **63** (IC_{50} = 3.3 nM) possessing saturated side chains showed a comparable MMP-13 inhibitory potency. While the affinities of alcohol **62** for both MMPs-2 and-13 were approximately the same (~1-fold), it showed about a 10- and 20-fold selectivities over MMPs-9 and -8, respectively. The fluorinated compound **63**, unlike alcohol **62**, had a 6-13-fold selectivity for MMP-13 over all other tested MMPs, including MMP-2.

cis-Alkene **64** was found to be a potent MMP-13 inhibitor (IC_{50} = 4.6 nM) with low selectivities of 1.5-4-fold over MMPs-2, -8, and -9. Its fluorinated analog **65** was more potent (IC_{50} =3.6 nM) than **64** but exhibited no significant difference (~1-fold) in its affinities toward MMP-13 and MMP-9. It was however about 5-fold and 8-fold selective over MMPs-2 and -8, respectively.

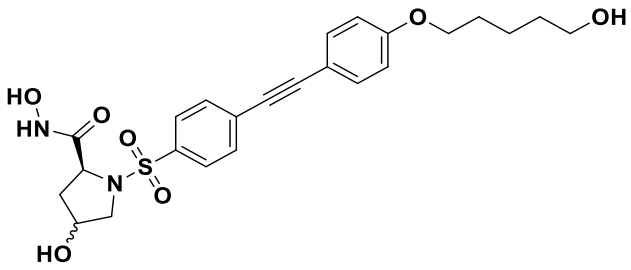
Finally, *trans*-alkene **66** was revealed to be the most potent (IC_{50} = 1.7 nM) and most MMP-13 selective inhibitor among the synthesized proline derivatives with varied lipophilic side chains, but inferior to lead compound **41** in both potency (IC_{50} = 0.07 nM) and selectivity (70-1500). The *trans*-alkene exhibited MMP-13 selectivities of about 20-, 40-, and 50-fold over MMPs-2, -8, and -9, respectively.

4.1.2 Variations at the core of the structure

4.1.2.1 Sulfonamide-based hydroxamic acids

The diastereomeric 4-hydroxyproline derivatives of general formula **II**, possessing a sulfonyl moiety in place of the carbonyl group of lead compound **41**, were assayed *in vitro* against MMPs-2, -8, -9, and -13. However, due to the very high intrinsic fluorescence of the (4*R*)-configured diastereomer **72**, it was not possible to evaluate the inhibitory potency of the compound against MMPs-8 and -9. The determined IC_{50}-values are summarized in Table 8.

Table 8: MMP inhibitory activity of sulfonamide-based hydroxamic acids **II**.



II

Compound	Stereoisomer	IC_{50} ± SD [nM]			
		MMP-2	**MMP-8**	**MMP-9**	**MMP-13**
72	(2*S*,4*R*)	96 ± 11	n.d.	n.d.	125 ± 23
73	(2*S*,4*S*)	82 ± 40	160 ± 24	405 ± 164	74 ± 8

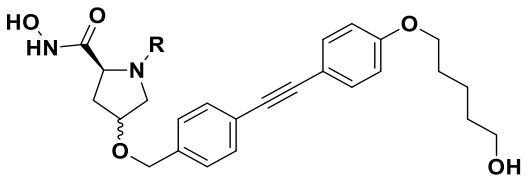
n.d.: not determinable

The sulfonamide-based hydroxamic acids **72** and **73** were moderate MMP-13 inhibitors, with both compounds exhibiting their inhibitory potential in the nanomolar region. Obviously, in comparison to lead compound **41** (IC_{50} = 0.07 nM), **72** and **73** were more than three orders of magnitude inferior MMP-13 inhibitors with a poorer selectivity profile. The (4*R*)-configured hydroxamic acid **72** (IC_{50} = 125 nM) was a less potent MMP-13 inhibitor than its (4*S*)-configured diastereomer **73** (IC_{50} = 74 nM). Though both MMP-13 inhibitors exhibited no selectivity over MMP-2, sulfonamide-based hydroxamic acid **73** showed selectivities of 2-fold and 5-fold over MMPs-8 and -9, respectively.

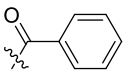
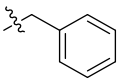
4.1.2.2 Ether-based hydroxamic acids

The ether-based compounds **XXIII** were all inactive against MMP-13 as well as MMPs-2, -8, and -9, even at the highest concentrations tested. A summary of the results is given in Table 9.

Table 9. MMP-inhibitory activity of ether-based hydroxamic acids **XXIII**.



XXIII

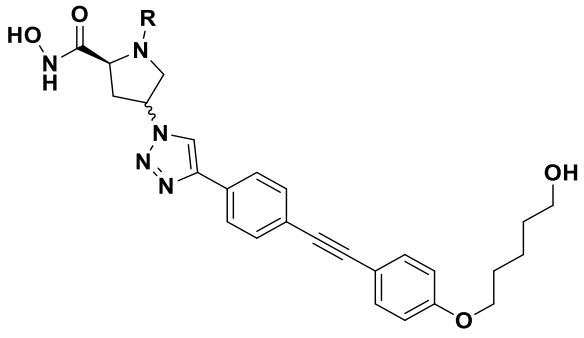
Compound	R	Stereoisomer	IC_{50} ± SD [nM]			
			MMP-2	MMP-8	MMP-9	MMP-13
109		(2*S*,4*R*)	n.a	n.a	n.a	n.a.
110		(2*S*,4*S*)				
116		(2*S*,4*R*)	n.a	n.a	n.a	n.a.
117		(2*S*,4*S*)				
126		(2*S*,4*R*)	n.a	n.a	n.a	n.a.
163		(2*S*,4*S*)				
138		(2*S*,4*R*)	n.a	n.a	n.a	n.a.
139		(2*S*,4*S*)				
152	H	(2*S*,4*R*)	n.a	n.a	n.a	n.a.
158		(2*S*,4*S*)				
164		(2*S*,4*R*)	n.a	n.a	n.a	n.a.
165		(2*S*,4*S*)				
166		(2*S*,4*R*)	n.a	n.a	n.a	n.a.
167		(2*S*,4*S*)				

n.a.: not active

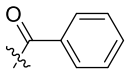
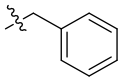
4.1.2.3 Triazole-based hydroxamic acids

The triazole-based test compounds **XXIV** were all inactive against MMP-13 as well as MMPs-2, -8, and -9, even at the highest concentrations tested. A summary of the results is given in Table 10.

Table 10. MMP-inhibitory activity of triazole-based hydroxamic acids **XXIV**.



XXIV

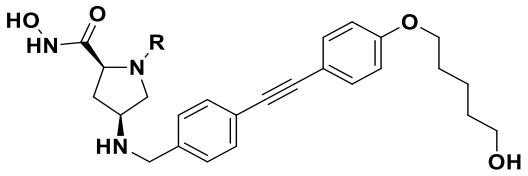
Compound	R	Stereoisomer	IC_{50} ± SD [nM]			
			MMP-2	MMP-8	MMP-9	MMP-13
196		(2*S*,4*R*)	n.a.	n.a.	n.a.	n.a.
197		(2*S*,4*S*)				
198		(2*S*,4*R*)	n.a.	n.a.	n.a.	n.a.
199		(2*S*,4*S*)				

n.a.: not active

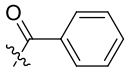
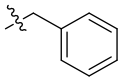
4.1.2.4 4-Aminoproline-based hydroxamic acids

The 4-aminoproline-based hydroxamic acids were all inactive against MMP-13 as well as MMPs-2, -8, and -9, even at the highest concentrations tested. A summary of the results is given in Table 11.

Table 11. MMP-inhibitory activity of 4-aminoproline-based hydroxamic acids **216** and **226**.



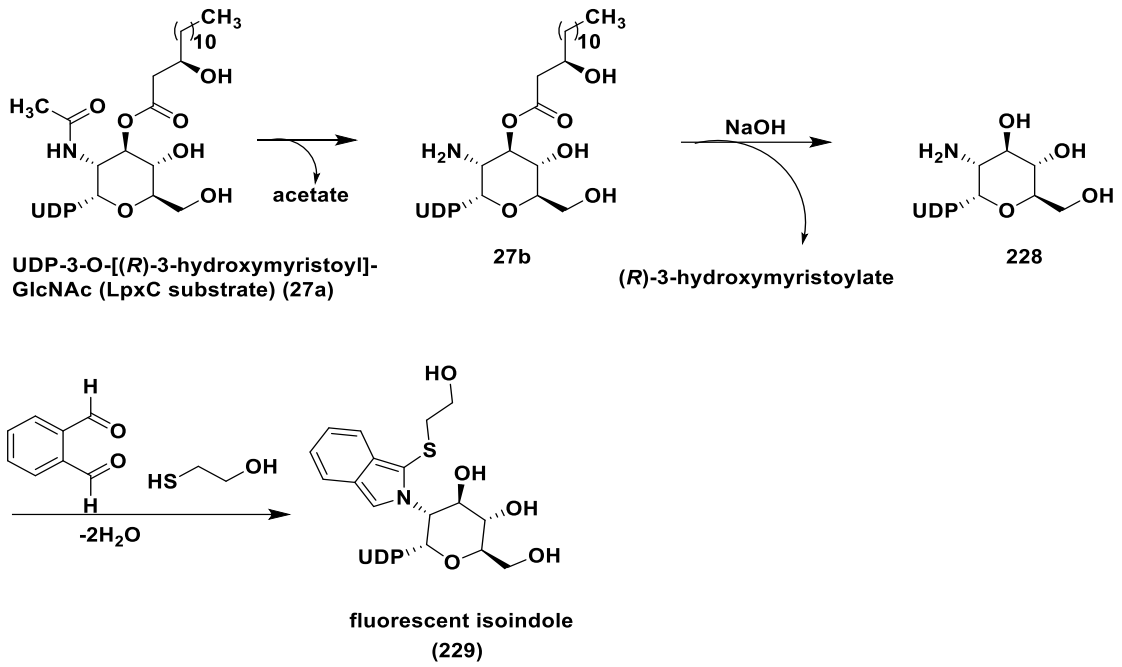
216, 226

Compound	R	IC_{50} ± SD [nM]			
		MMP-2	**MMP-8**	**MMP-9**	**MMP-13**
216		n.a.	n.a.	n.a.	n.a.
226		n.a.	n.a.	n.a.	n.a.

n.a.: not active

4.2 LpxC inhibitors

To explore the antibacterial and LpxC inhibitory properties of the synthesized LpxC inhibitors, several assays were performed. On the one hand, the antibacterial activities of the various hydroxamic acids were determined using cells of *E. coli* BL21 (DE3) and the defective *E. coli* D22 strain, exhibiting an *lpxC* mutant that shows a reduced LpxC activity. The antibacterial activities were determined as minimal inhibitory concentrations (MIC) in a broth dilution test and as inhibition zone diameters in a disc diffusion assay. On the other hand, *in vitro* enzyme assays were performed to ascertain that the synthesized compounds exerted their antibacterial activities via the inhibition of the bacterial deacetylase LpxC. In these assays, *E. coli* LpxCC63A, which has a lower susceptibility to high Zn^{2+} concentrations compared to the wild-type enzyme, was employed.[137,145,185] Generally, the inhibitory potencies of the synthesized LpxC inhibitors were studied using a fluorescence-based enzyme assay. The method is based on the ability of an inhibitor to prevent the LpxC-catalyzed deacetylation of the enzyme's natural substrate **27a** (Scheme 41). As such, the amount of the deacetylated product **27b**, which is formed in the presence of a certain concentration of the inhibitor, is determined by derivatizing it to the fluorescent isoindole **229**.



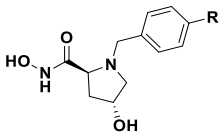
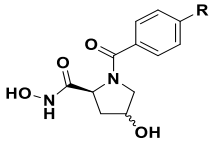
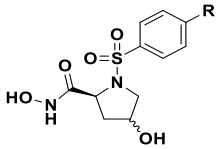
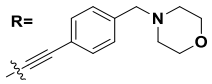
Scheme 41. LpxC-catalyzed deacetylation of UDP-3-O-[(*R*)-3-hydroxymyristoyl]-GlcNAc (**27a**) and formation of fluorescent isoindole **229**.

As some compounds, like the triazole-based and 4-aminoproline-based compounds, were excessively fluorescent, the fluorescence-based assay could not be performed for these compounds. Their LpxC inhibitory activities were therefore evaluated by employing an LC-MS/MS-based assay.

The antibacterial and LpxC inhibitory activities of the synthesized hydroxamic acids were compared with those of reference compounds obtained from the master's thesis of PATRICK MYSLINSKI (**235** and **236**) and the doctoral thesis of DMITRII KALININ (**230** to **234**).

4.2.1 Sulfonamide-based LpxC inhibitors

Table 12. LpxC inhibitory activity and antibacterial properties of the synthesized sulfonamide-based hydroxamic acids **78** and **79**.

Compound			Zone of inhibition [mm]		MIC [μg mL^{-1}]		K_i [μM]
			E. coli BL21 (DE3)	*E. coli* D22	*E. coli* BL21 (DE3)	*E. coli* D22	*E. coli* LpxC C63A
230		(4*R*)	12.3 ± 0.6	21.0 ± 1.0	>64	4	9.13 ± 2.06
231		(4*R*)	7.5 ± 0.7	20.7 ± 1.5	>64	8	7.04 ± 2.74
232		(4*S*)	11.3 ± 0.6	19.5 ± 0.6	>64	8	4.34 ± 2.31
78		(4*R*)	14.7 ± 0.6	23.2 ± 2.1	64	4	1.35 ± 0.0653
79		(4*S*)	11.3 ± 1.5	24.7 ± 2.1	16	0.5	0.719 ± 0.115
							

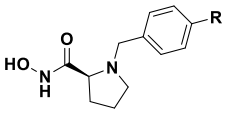
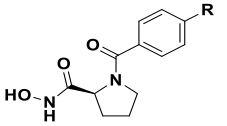
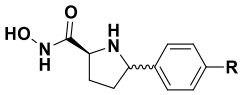
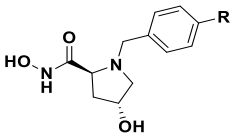
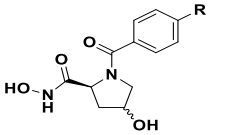
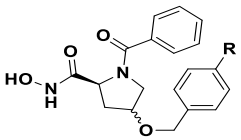
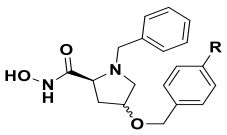
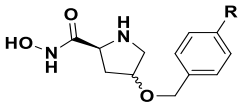
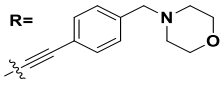
The benzenesulfonamide-based hydroxamic acids **78** and **79** were found to be potent LpxC inhibitors with K_i-values of 1.4 μM and 0.72 μM, respectively. The (4*S*)-configured sulfonamide-based hydroxamic acid **79** generally displayed better LpxC inhibitory and antibacterial activities than its (4*R*)-configured diastereomer **78**. An exception was the disc diffusion assay against *E. coli* BL21 (DE3) where **78** gave a larger zone of inhibition than **79**. This might have resulted from different solubilities and diffusion rates in the agar medium.

With respect to benzamide-based reference compounds **231** and **232**, the replacement of the carbonyl function with a sulfonyl group generally enhanced both antibacterial activity and LpxC inhibitory potency.

The replacement of the methylene moiety of benzylamine **230** with a sulfonyl group, leading to sulfonamide **78**, caused only a slight increase in antibacterial activity against *E. coli* BL21 (DE3) and a similar activity against *E. coli* D22, even though LpxC inhibition increased significantly (~7-fold).

4.2.2 Ether-based LpxC inhibitors

Table 13. LpxC inhibitory activity and antibacterial properties of the synthesized ether-based hydroxamic acids **118**, **119**, **140**, **141**, and **142**.

Compound			**Zone of inhibition [mm]**		**MIC [μg mL^{-1}]**		**K_i [μM]**
			***E. coli* BL21 (DE3)**	***E. coli* D22**	***E. coli* BL21 (DE3)**	***E. coli* D22**	***E. coli* LpxC C63A**
233		-	15.0 ± 1.7	25.0 ± 3.0	64	2	1.54 ± 0.750
234		-	13.2 ± 0.3	20.0 ± 1.0	32	8	6.71 ± 2.10
235		(5*R*)	14.0 ± 2.4	22.0 ± 1.0	16	0.5	1.51 ± 0.0521
236		(5*S*)	10.0 ± 2.2	19.0 ± 1.0	>64	4	8.44 ± 1.87
230		(4*R*)	12.3 ± 0.6	21.0 ± 1.0	>64	4	9.13 ± 2.06
231		(4*R*)	7.5 ± 0.7	20.7 ± 1.5	>64	8	7.04 ± 2.74
232		(4*S*)	11.3 ± 0.6	19.5 ± 0.6	>64	8	4.34 ± 2.31
118		(4*R*)	≤6	12.3 ± 0.6	>64	8	3.74 ± 0.175
119		(4*S*)	6.7 ± 0.6	15.3 ± 1.2	>64	4	1.56 ± 0.331
140		(4*R*)	≤6	9.0 ± 1.0	>64	2	5.28 ± 3.30
141		(4*S*)	≤6	11.7 ± 1.2	>64	1	0.582 ± 0.119
161		(4*R*)	8.7 ± 1.5	19.7 ± 1.5	>64	2	4.19 ± 1.28
162		(4*S*)	9.0 ± 1.0	18.7 ± 0.6	>64	2	1.78 ± 0.326
R= 							

From the results of the biological evaluation of the ether-based inhibitors, it became obvious that the (4*S*)-configured compounds demonstrated better LpxC inhibitory activities than their corresponding (4*R*)-configured diastereomers. With the exception of the *N*-unsubstituted compounds **161** and **162** that showed similar antibacterial activities, the (4*S*)-configured ethers generally showed better antibacterial properties, especially against *E. coli* D22, than the (4*R*)-configured ones. All of the ethers exhibited little activity against *E. coli* BL21 (DE3). Hence, among the ethers, (4*S*)-configuration was important for LpxC inhibitory activity and antibacterial activity against *E. coli* D22. Among the synthesized ether-based compounds tested, the (*4S*)-configured *N*-benzyl-substituted ether **141** was the most potent antibacterial agent and LpxC inhibitor. Interestingly, ether **140**, the diastereomer of **141**, was the least potent LpxC inhibitor in the series. In agreement with its low K_i-value, ether **141** exhibited the lowest MIC against *E. coli* D22. Whereas the *N*-unsubstituted compounds **161** and **162** were found to be weaker LpxC inhibitors than *N*-benzyl-substituted ether **141**, their K_i-values were in the same range as the ones of the respective benzamide-based ethers **118** and **119**. However, the *N*-unsubstituted ethers **161** and **162** gave better results in terms of activity against *E. coli* D22 than the benzamide-based ethers **118** and **119**, which among the ethers exhibited the weakest antibacterial activities against *E. coli* D22 in the MIC assays.

To elucidate the effect of the translocation of the lipophilic side chain from position 1 of the pyrrolidine ring via position 5 to position 4, at first, compounds with a basic pyrrolidine nitrogen were compared. In case of tertiary amines **233** and **230**, bearing the lipophilic side chain in position 1, the 4-unsubstituted proline derivative **233** demonstrated better LpxC inhibitory potential (K_i = 1.54 μM) as well as antibacterial activity than the (4*R*)-configured 4-hydroxyproline derivative **230**. The translocation of the lipophilic side of tertiary amine **233** to position 5 of the pyrrolidine ring led to secondary amines **235** and **236**, of which the (5*S*)-configured diastereomer **236** was found to be the less potent LpxC inhibitor. The (5*R*)-configured secondary amine **235**, however, was shown to inhibit LpxC as potently as tertiary amine **233**, being two serial dilution steps more active against *E. coli* BL21 and *E. coli* D22 than the latter compound. Finally, the shift of the side chain to position 4 led to *N*-unsubstituted ethers **161** and **162**, of which the (4*S*)-configured diastereomer exhibited similar LpxC inhibitory activity as amines **233** and **235** but showed reduced antibacterial activity against the two investigated *E. coli* strains compared to these two compounds. Finally, *N*-benzylation transformed secondary amine **162** into tertiary amine **141**, which was the most potent LpxC inhibitor of the investigated series of compounds (K_i = 0.582 μM) but exhibited weaker antibacterial activity than secondary amine **235**.

Additionally, the *N*-acylated compounds were compared. Among the proline derivatives bearing the lipophilic side chain in position 1 of the pyrrolidine ring, the 4-hydroxyproline derivatives **231** and **232** exhibited slightly lower and slightly higher LpxC inhibitory activities than the 4-unsubstituted compound **234**, which showed the highest antibacterial activity of the three compounds, particularly against *E. coli* BL21. Translocating the lipophilic side chain to position 4 while keeping a benzoyl group at the pyrrolidine nitrogen yielded ethers **118** and **119**, which displayed higher LpxC inhibitory activities than alcohols **231** and **232**. In all cases, the (4*S*)-configured compounds exhibited lower K_i-values than the respective (4*R*)-configured diastereomers.

4.2.3 Triazole- and 4-aminoproline-based LpxC inhibitors

Table 14. LpxC inhibitory activity and antibacterial properties of the synthesized triazole- and 4-aminoproline-based hydroxamic acids **192** to **195**, **217**, and **227**.

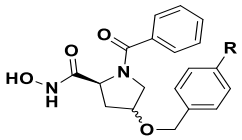
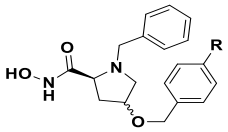
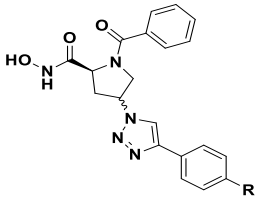
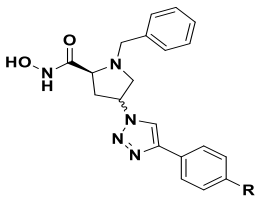
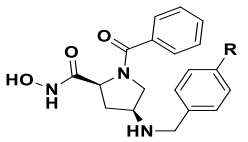
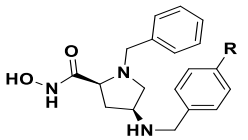
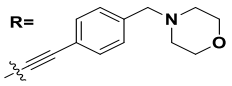
Compound			**Zone of inhibition [mm]**		**MIC [µg mL^{-1}]**		**K_i [µM]**
			***E. coli* BL21 (DE3)**	***E. coli* D22**	***E. coli* BL21 (DE3)**	***E. coli* D22**	***E. coli* LpxC C63A**
118		(4*R*)	≤6	12.3 ± 0.6	>64	8	3.74 ± 0.175
119		(4*S*)	6.7 ± 0.6	15.3 ± 1.2	>64	4	1.56 ± 0.331
140		(4*R*)	≤6	9.0 ± 1.0	>64	2	5.28 ± 3.30
141		(4*S*)	≤6	11.7 ± 1.2	>64	1	0.582 ± 0.119
192		(4*R*)	≤6	8.3 ± 0.6	>64	32	1.87 ± 0.296
193		(4*S*)	≤6	≤6	>64	>64	1.50 ± 0.208
194		(4*R*)	≤6	≤6	>64	>64	3.38 ± 0.275
195		(4*S*)	≤6	≤6	>64	16	>31.6

Table 14 (continued):

Compound			Zone of inhibition [mm]		MIC [µg mL^{-1}]		K_i [µM]
			***E. coli* BL21 (DE3)**	***E. coli* D22**	***E. coli* BL21 (DE3)**	***E. coli* D22**	***E. coli* LpxC C63A**
217		(4*S*)	≤6	11.3 ± 1.2	>64	64	1.64 ± 0.446
227	 	(4*S*)	≤6	12.3 ± 1.5	>64	16	>31.6

The triazole-based hydroxamic acids generally showed weak antibacterial activity. In contrast to their antibacterial activity, they showed good LpxC inhibitory potential, with the benzamide-based compounds being more potent than benzyl-substituted proline derivatives. Whereas the diastereomeric benzamide-based triazoles **192** and **193** exhibited similar K_i-values toward LpxC, in case of the *N*-benzyl-substituted compounds **194** and **195**, the (4*R*)-configured proline derivative **194** was found to be a considerably more potent LpxC inhibitor than its (4*S*)-configured diastereomer **195**. This is in contrast to the ether-based compounds, among which the (4*S*)-configured *N*-benzyl derivative **141** displayed the highest LpxC inhibitory activity. The comparison of the benzamide-based triazoles **192** and **193** with the respective ethers **118** and **119** revealed that the replacement of the ether moiety by a triazole ring led to a slight increase in LpxC inhibitory activity but a considerable loss in antibacterial properties. In case of the *N*-benzyl-substituted compounds, inconsistent effects were observed. In case of the (4*R*)-configured proline derivatives **140** and **194**, also a slight increase in LpxC inhibitory activity and a loss in antibacterial properties were observed when the ether group was replaced by a triazole ring. However, in case of the respective (4*S*)-configured stereoisomers, the same exchange transformed the potent LpxC inhibitor **141** into the inactive compound **195**.

Finally, the biological activities of 4-aminoproline-based LpxC inhibitors **217** and **227** were investigated. Similar trends as in case of the (4*S*)-configured triazole derivatives were observed.

In case of the benzamide-based compounds, the replacement of the ether oxygen by an amino group did not considerably change LpxC inhibitory activity, however a loss of antibacterial was observed. In case of the benzyl-substituted proline derivatives **141** and **227**, no LpxC inhibitory activity was observed after the transformation of ether **141** into secondary amine **227**.

5.0 CONCLUSION AND SUMMARY

5.1 MMP-13 inhibitors

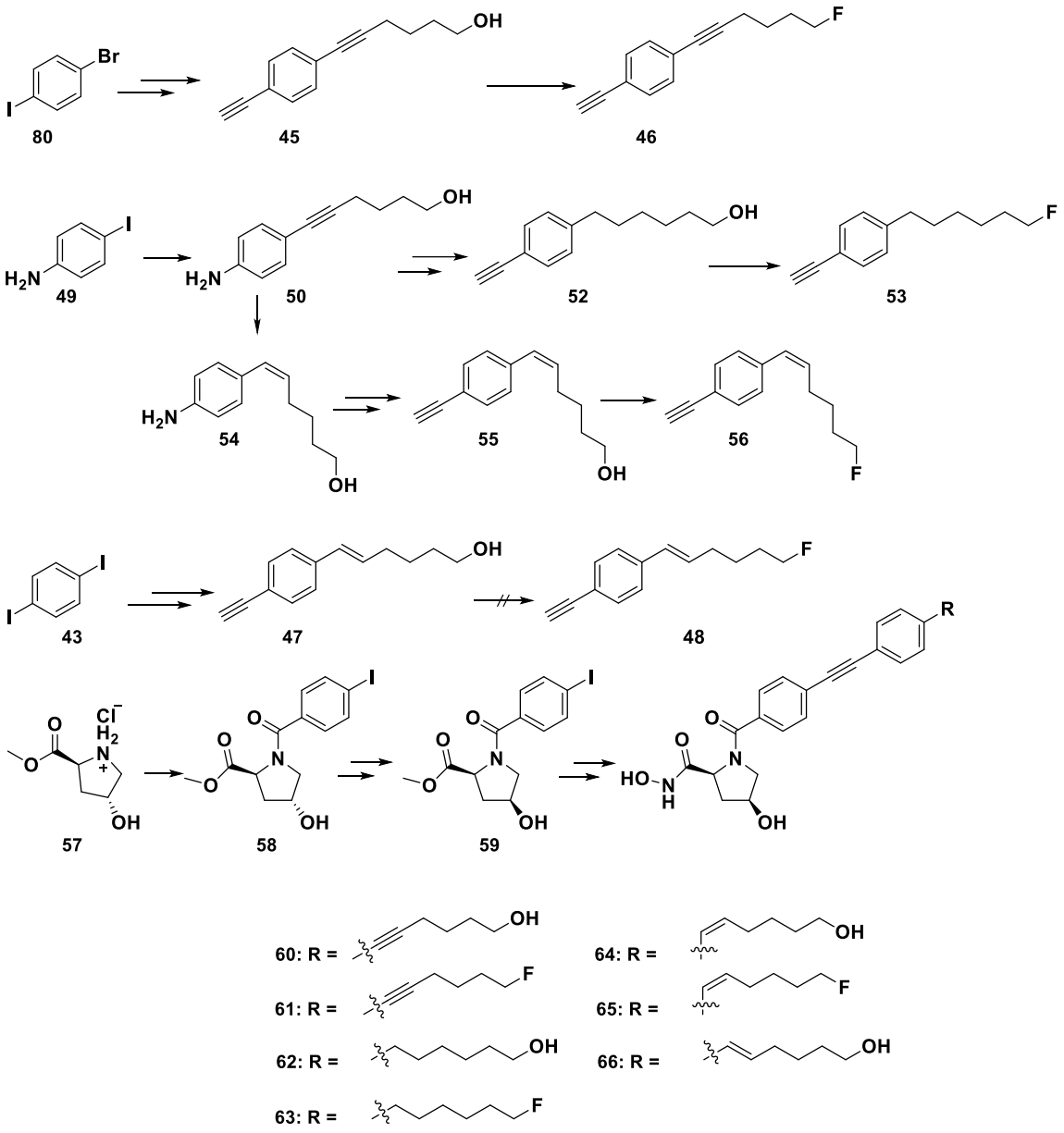
As a result of modifications to lead compound **41**, various MMP-13 inhibitors were accessed in chiral pool syntheses starting from methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**57**).

5.1.1. Variation of the lipophilic side chain

In order to elaborate structure activity relationships, the oxymethylene group of the lipophilic side chain of **41** was replaced with ethylene, vinylene (*trans* and *cis*), and acetylene moieties. Additionally, besides the hydroxylated compounds, the respective fluorinated derivatives of these hydroxamic acids were accessed (Scheme 42).

To afford the lipophilic side chains with an internal acetylene moiety, 4-bromoiodobenzene (**80**) was subjected to two successive SONOGASHIRA coupling reactions with hex-5-yn-1-ol and trimethylsilylacetylene as well as a desilylation to give alcohol **45**. To obtain the fluorinated derivative **46**, **45** was treated with DAST. To access the saturated lipophilic side chains **52** and **53**, at first, 4-iodoaniline (**49**) was coupled with hex-5-yn-1-ol to give internal alkyne **50**. Then, alkyne **50** was fully reduced in a hydrogen atmosphere to the respective alkane, which was diazotized and coupled with trimethylsilylacetylene in a one-pot procedure. The resulting protected alkyne was desilylated to give alcohol **52** that was further fluorinated to access the fluorinated derivative **53**. In order to obtain *cis*-alkenes **55** and **56**, alkyne **50** was first partially reduced in the presence of a LINDLAR catalyst to give *cis*-alkene 54, which was then transformed via the processes of one-pot diazotization and coupling, desilylation, and fluorination, employing the same conditions used for accessing the aforementioned saturated lipophilic side chains. The *trans*-alkene **47** was obtained from 1,4-diiodobenzene (**43**) by employing reactions like SONOGASHIRA couplings, a ruthenium-catalyzed partial reduction of an internal alkyne, and a desilylation. However, the fluorinated derivative of **47**, which is **48**, could not be obtained.

The proline scaffold **59** was obtained by benzoylating proline derivative **57** and transforming the obtained amide **58** into its diastereomer **59** by using MITSUNOBU and saponification reactions. The various hydroxamic acids with varied lipophilic side chains (**60** to **66**) were obtained after coupling all the synthesized terminal alkynes with the (4*S*)-configured proline derivative **59** and reacting the diphenylacetylene derivatives with hydroxylamine (Scheme 42)



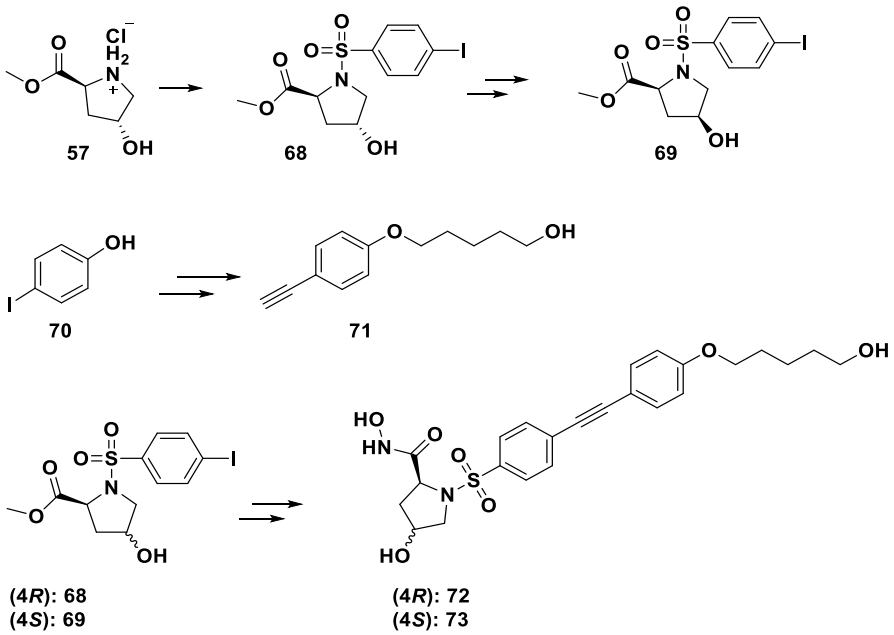
Scheme 42. Summary of syntheses of hydroxamic acids **60** to **66** with varied lipophilic side chains.

Though the hydroxamic acids possessing these varied lipophilic side chains were potent nanomolar inhibitors of MMP-13, they were less potent than lead compound **41** that inhibited MMP-13 in the picomolar range. Apparently, the replacement of the oxymethylene moiety with the different groups led to the loss of useful interactions with certain groups in the enzyme's S1′ pocket, leading to the observed loss in MMP-13 potency. Also, MMP-13 selectivities were significantly lost or reduced when compared with lead compound **41** that exhibited selectivities for MMP-13 over MMPs-2, -8, and -9 ranging from 70-1500. It was also noted that, among the hydroxamic acids with the varied lipophilic chains, fluorination generally did not significantly enhance MMP-13 inhibitory potency, though the results were ambiguous.

5.1.2 Variation at the core structure

5.1.2.1 Sulfonamide-based hydroxamic acids

Replacement of the carbonyl moiety of lead compound **41** by a sulfonyl group afforded sulfonamide **73**, being only a moderate MMP-13 inhibitor with no selectivity over MMP-2 but displaying MMP-13 selectivities of 2-5-fold over MMPs-8 and -9. To obtain the sulfonamide-based hydroxamic acids **72** and **73**, firstly, the diastereomeric sulfonamides **68** and **69** were obtained by sulfonylation, MITSUNOBU, and saponification reactions. Thus, to obtain ether-based terminal alkyne **71** which was coupled with **68** and **69** as well as other scaffolds, 4-iodophenol (**70**) was etherified with 5-bromopentan-1-ol (**95**) and the ether obtained was subjected to SONOGASHIRA coupling and desilylation reactions, consecutively. Finally, to obtain hydroxamic acids **72** and **73**, sulfonamides **68** and **69** were converted via SONOGASHIRA reactions and aminolyses (Scheme 43).



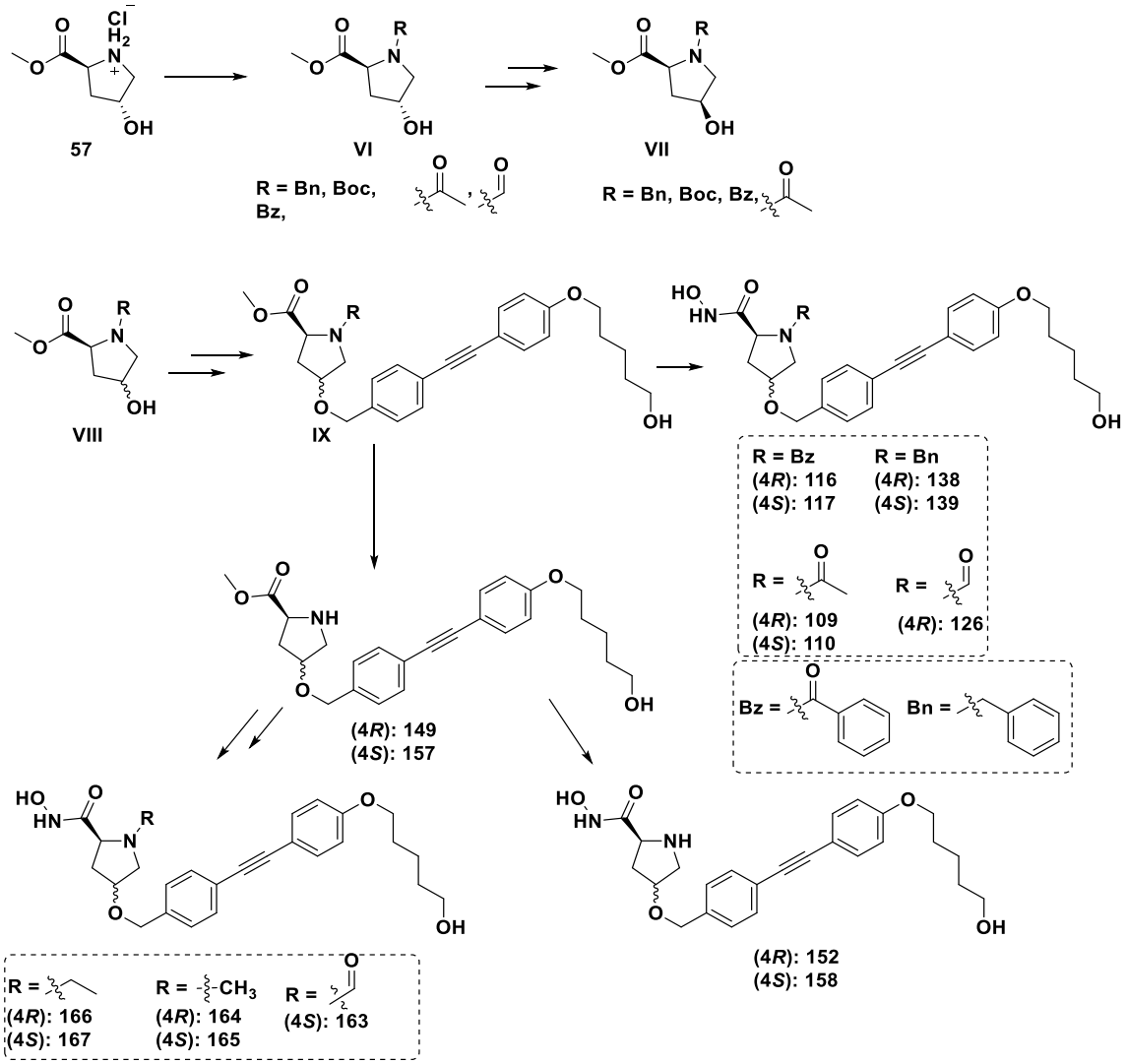
Scheme 43. Summary of syntheses of sulfonamides **72** and **73**.

Though the diastereomeric sulfonamides **72** and **73** were moderate MMP-13 inhibitors, exhibiting IC_{50}-values in the nanomolar range, **73** was about nearly twice as potent as **72**. This implies that (4*S*)-configuration at the carbon atom bearing the hydroxy group is crucial for MMP-13 inhibitory activity.

5.1.2.2 Ether-based, triazole-based, and 4-aminoproline-based hydroxamic acids

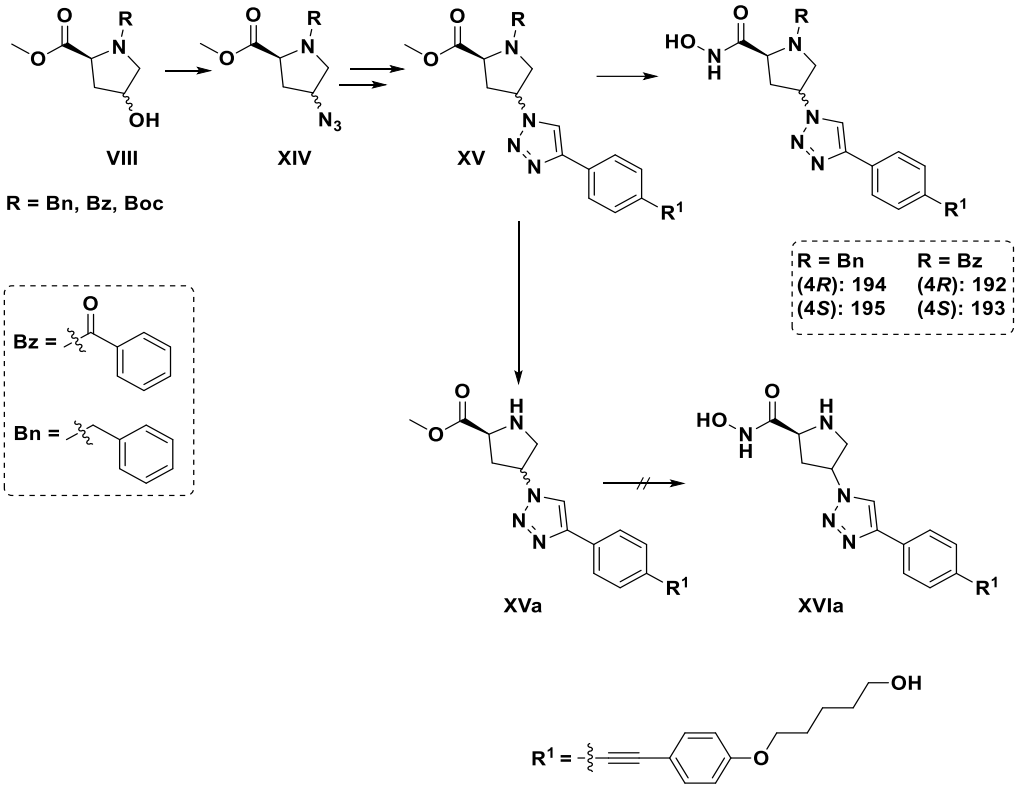
Moving the lipophilic side chain to position 4 of the pyrrolidine ring while varying the residue on the pyrrolidine nitrogen gave ether-, triazole-, and 4-aminoproline-based compounds. In the cases of the ether- and triazole-based compounds, the (4*R*)-configured diastereomers were also synthesized.

To obtain the ether-based hydroxamic acids, proline derivative **57** was first acylated, benzylated, or Boc protected to give derivatives **VI** whose configurations were inverted via MITSUNOBU reactions to afford the (4*S*)-configured derivatives of general formula **VII**. Then, diastereomeric alcohols **VIII** were sequentially transformed via WILLIAMSON etherification with 4-iodobenylbromide, SONOGASHIRA coupling reactions, and aminolyses to afford the benzamide-based (**116** and **117**), acetamide-based (**109** and **110**), (4*R*)-configured formamide-based (**126**), and benzyl-substituted (**138** and **139**) hydroxamic acids. In case of the Boc protected derivatives, deprotection preceded the aminolyses to yield *N*-unsubstituted hydroxamic acids **152** and **158**. The secondary amines **149** and **157** afforded following the removal of the Boc group was successfully alkylated using direct alkylation and reductive amination as well as formylated to give ethyl- (**166** and **167**) and methyl-substituted (**164** and **165**) as well as formamide-based (**163**) hydroxamic acids, respectively (Scheme 44).



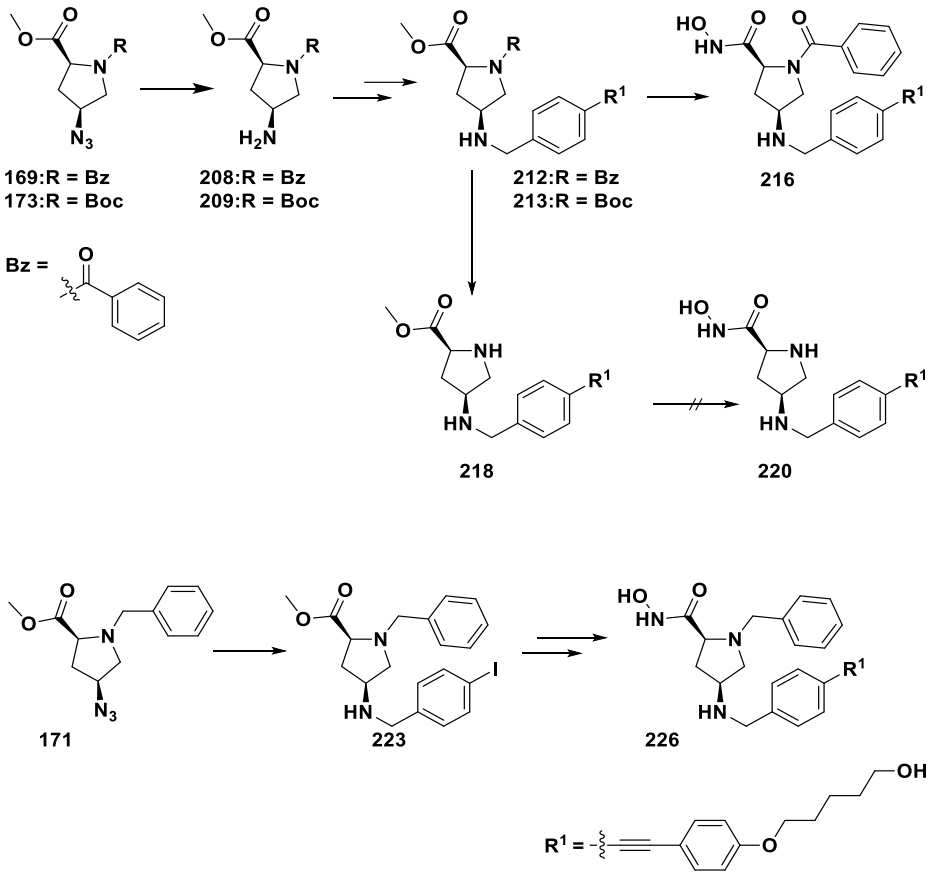
Scheme 44. Summary of the syntheses of ether-based hydroxamic acids.

The triazole-based inhibitors **192** to **195** were obtained by converting the hydroxy groups of alcohols **VIII** to azides **XIV** via MITSUNOBU reactions, proceeding under an inversion of configuration in position 4. Then, the diastereomeric azides **XIV** were modified into triazoles by copper-catalyzed azide-alkyne cycloadditions to give triazoles that were converted into hydroxamic acids **192** to **195** following SONOGASHIRA reactions and aminolyses. The *N*-unsubstituted triazole-based hydroxamic acids **XVIa** could not be obtained (Scheme 45).



Scheme 45. Summary of the syntheses of triazole-based hydroxamic acids.

The benzamide-based 4-aminoproline **216** was afforded by the transformation of azide **169** by employing a hydrogenation, a reductive amination with 4-iodobenzaldehyde, a SONOGASHIRA reaction, and an aminolysis, consecutively. The *N*-unsubstituted hydroxamic acid **220** could not be obtained due to unsuccessful aminolysis of the secondary amine precursor **218** with hydroxylamine. In case of the benzyl-substituted hydroxamic acid **226**, azide **171** was transformed into aryl iodide **223** via an aza-WITTIG reaction, which was further subjected to a C-C coupling reaction and aminolysis (Scheme 46).



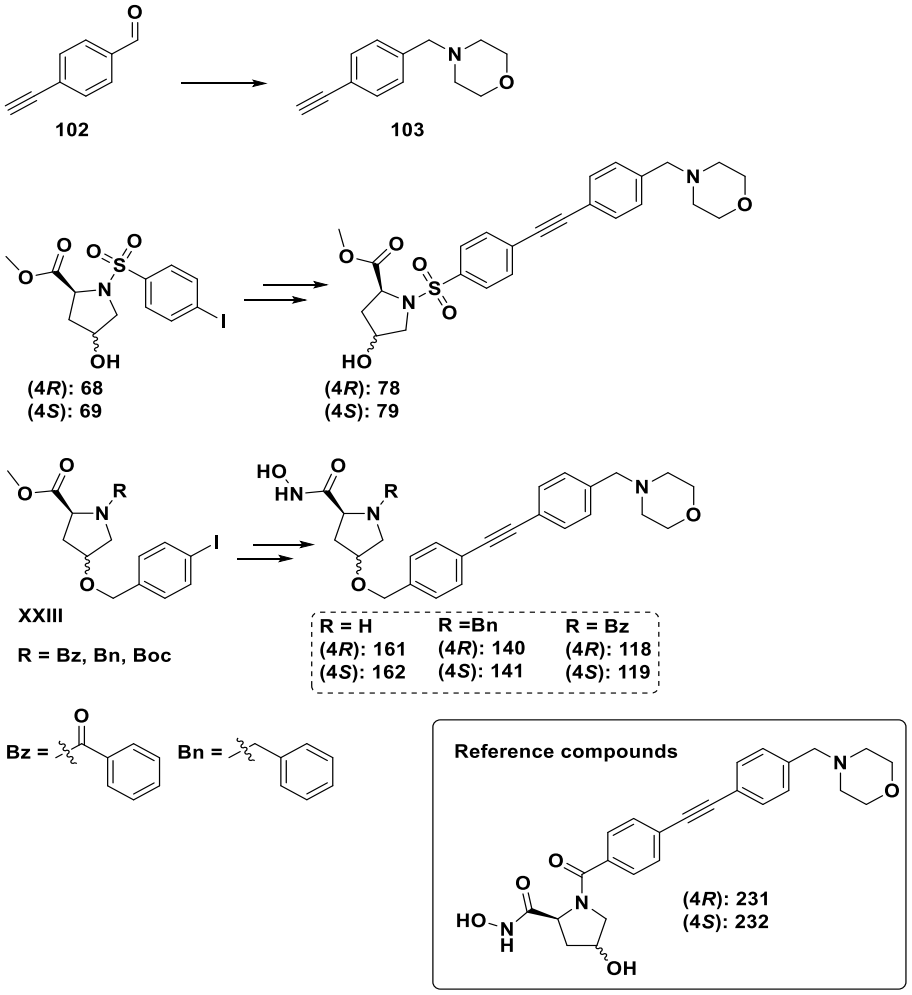
Scheme 46. Summary of syntheses of 4-aminoproline hydroxamic acids **216** and **226**.

All the hydroxamic acids afforded by modifying the hydroxy group this way exhibited no MMP-13 activity. Though it was envisaged that a long lipophilic side chain especially in the case of the triazoles, should enhance potency and selectivity by fully addressing the deep S1′ pocket of MMP-13, the assay results highlighted the importance of the location of the lipophilic side chain at the pyrrolidine nitrogen as well as the presence of the hydroxy group at the proline scaffold for activity.

5.2 LpxC inhibitors

A series of conformationally constrained proline-based LpxC inhibitors was synthesized, employing selected intermediates previously used to access sulfonamide-based, ether-based, triazole-based, and 4-aminoproline-based MMP-13 inhibitors (Schemes 47 to 49). Using the morpholine-based terminal alkyne **103**, obtained by reductively alkylating 4-ethynylbenzaldehyde (**102**), the selected intermediates were transformed into the respective target compounds employing the same reaction conditions and pathways used for accessing the

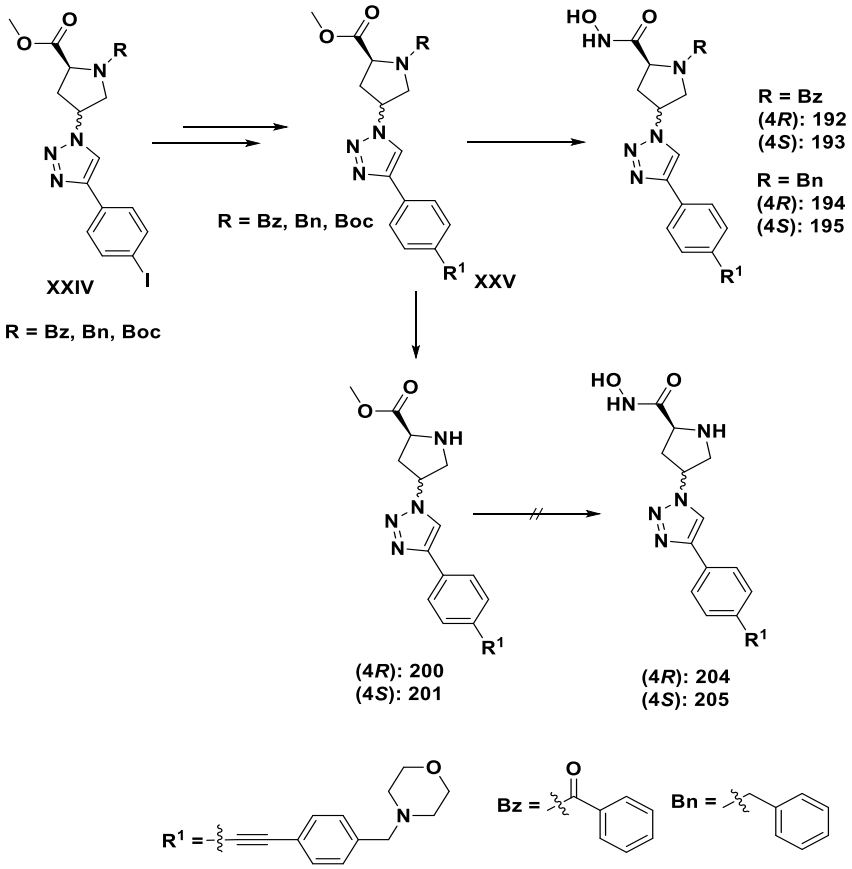
corresponding MMP inhibitors. Similarly, the *N*-unsubstituted triazole- and 4-aminoproline-based LpxC inhibitors could not be obtained. All the synthesized hydroxamic acids were less potent LpxC inhibitors than the threonine-based LpxC-inhibitor CHIR-090 (**34**) (K_i = 0.008 μM).[186] The rigid nature of the proline scaffold may have affected or limited certain useful interactions with residues in the LpxC active site, leading to a reduced inhibitory activity.



Scheme 47. Summary of syntheses of sulfonamide-based and ether-based hydroxamic acids.

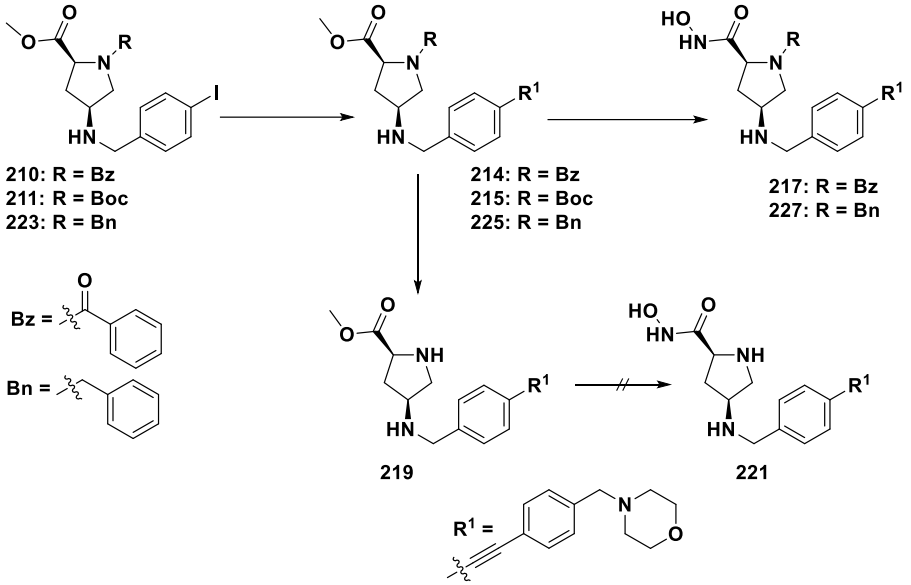
The sulfonamide-based inhibitors **78** and **79** (Scheme 47) were potent LpxC inhibitors with the (4*S*)-configured sulfonamide **79** being about twice as potent as its diastereomer, **78**. Also, sulfonamide **79** had better antibacterial activity than stereoisomer **78**. Comparing the antibacterial and LpxC inhibitory activities of the sulfonamides with the previously described benzamides **231** and **232** used as reference compounds, it was inferred that (*S*)-configuration at position 4 and the sulfonyl moiety were important for enhanced antibacterial and LpxC inhibitory activities.

Among the ether-based LpxC inhibitors (Scheme 47), the (4*S*)-configured compounds were better inhibitors of LpxC than the respective (4*R*)-configured diastereomers. The *N*-benzyl-substituted ether **141** was found to be the most potent LpxC inhibitor, exhibiting a lower K_i-value than the sulfonamides and all the reference compounds. While *E. coli* D22 showed high susceptibility to **141**, *E. coli* BL21 (DE3) was not susceptible. A concurrent trend was noted for all the newly synthesized ethers, which showed antibacterial bacterial activity against *E. coli* D22, but had no effect on *E. coli* BL21 (DE3).



Scheme 48. Summary of syntheses of triazole-based hydroxamic acids.

The triazole-based compounds (Scheme 48) displayed a high LpxC inhibitory potential. However, the compounds were weaker LpxC inhibitors than the sulfonamides and ether **141**. The (4*S*)-configured benzamide-based triazole **193** exhibited the highest LpxC inhibition among the triazoles. Conversely, the compound had little to no antibacterial activity, a trend observed generally for the triazoles. Thus, (4*S*)-configuration, a triazole ring in position 4 bearing the lipophilic side chain, and a benzoyl moiety on the pyrrolidine nitrogen had two effects: an increase in LpxC inhibition and a loss of antibacterial activity against *E. coli* D22.



Scheme 49. Summary of the syntheses of the 4-aminoproline-based hydroxamic acids.

Amine **217** was the more potent LpxC inhibitor of the two 4-aminoproline derivatives (Scheme 49) and equally as active as ether **119** and triazole **193**. The nature of the residue on the pyrrolidine nitrogen of the 4-aminoprolines had contrasting effects on antibacterial activity against *E. coli* D22 and LpxC inhibitory activity, whereas no effect on the activity against *E. coli* BL21 (DE3) was observed.

6.0 EXPERIMENTAL SECTION

6.1 General procedures and materials

6.1.1 General remarks

Moisture and oxygen sensitive reactions were carried out under nitrogen, dried with molecular sieves (3 Å, 8 to 12 mesh, Acros Organics), in dry glassware (Schlenk flasks, sealed with rubber septa). Reaction mixtures were stirred with magnetic stirrer RCT basic (IKA).
Reaction temperatures were controlled with:

- Cryostat (Julabo FT902),
- Ice/water (0 °C),
- Magnetic stirrer MR 3001 K (Heidolph), together with temperature controller EKT HeiCON (Heidolph) and paraffin oil bath.

6.1.2 Solvents

Anhydrous solvents were purchased from Acros Organics (extra dried over molecular sieves). Solvents for flash column chromatography were of technical grade but distilled prior to use. Bi-distilled water for automatic reversed-phase column chromatography and HPLC was obtained by using a Sartorius arium® pro system (Sartopore 0.2 μm, UV). Acetonitrile for automatic reversed-phase column chromatography and HPLC was purchased from VWR (HPLC grade).

6.1.3 Thin layer chromatography (TLC)

Thin-layer chromatography was performed with Macherey Nagel pre-coated TLC sheets (ALUGRAM® Xtra SIL G/UV254) as stationary phase and conducted in a saturated chamber at ambient temperature. Spot visualization was done with UV light (254 nm) and with reagents like iodine (vapor), vanillin dipping bath [vanillin (15 g), C_2H_5OH (250 mL), conc. H_2SO_4 (2.5 mL)], ninhydrin dipping bath [ninhydrin (1.5 g), *n*-$CH_3(CH_2)_3OH$ (100 mL), CH_3COOH (3.0 mL)], and cerium molybdate dipping bath [Ce $(SO_4)_2$ (1.8 g), $(NH_4)_6Mo_7O_{24} \times 4\ H_2O$ (45 g), conc. H_2SO_4 (45 g), H_2O (900 mL)] with additional heating using a heat gun. The compositions of the mobile phases and the retention factors (R_f) of the compounds are given in the descriptions of the synthetic procedures. Since the R_f-values strongly depend on the exact ratio of the components of the mobile phase and some of these are highly volatile, the given R_f-values are just approximate values.

6.1.4 Flash column chromatography

For flash column chromatography, Macherey Nagel silica gel 60 M (40-63 µm) was used as stationary phase. Pressure was applied with compressed air. In the descriptions of the synthetic procedures, the diameter of the column (Ø), height of the stationary phase (h), fraction size (V), the eluent, and R_f-values are given in brackets.

6.1.5 Automatic flash column chromatography and lyophilization

The samples were chromatographed using the chromatography systems Isolera™ One (Biotage®) or Interchim puriFlash® XS 420. In the description of the synthetic procedures, the system employed, the used cartridge-type, and the eluent are given in brackets. In case of the Interchim puriFlash® XS 420 system, which was used for normal-phase chromatography, the fractions containing the desired product were combined and concentrated *in vacuo* to remove organic solvent. In case of the Isolera™ One (Biotage®) system, which was used for reversed-phase chromatography, fractions containing the desired product were combined, frozen with liquid nitrogen, and subjected to lyophilization using an ALPHA 2-4 LDplus (Christ) freeze-dryer with a RZ5 (Vacuubrand) rotary vane pump.

6.1.6 Melting points

Melting points were determined with a Büchi Melting Point M-565. The values are uncorrected.

6.1.7 Polarimetry

Optical rotation α [deg] was determined with a P8000 polarimeter (A. Krüss Optronic GmbH). The linearly polarized light (589 nm, sodium D-line) was passed through a sample with a path length (l) of 1 dm at +20 °C.

The specific rotation was calculated using the formula $[\alpha]_D^{20} = \frac{\alpha}{c \times l}$

Its unit [deg mL dm^{-1} g^{-1}] is omitted. The concentration of the sample c [mg mL^{-1}] and the solvent used are given in brackets.

6.1.8 High performance liquid chromatography (HPLC)

All HPLC methods were carried out at ambient temperature.

6.1.8.1 HPLC method 1

- VWR Hitachi equipment: pump: 5160; autosampler: 5260; column oven: 5310; UV/Vis detector: 5420; Interface: Organizer; Data Acquisition and evaluation: Chromaster software.
- Column: LiChrospher® 60 RP-select B (5 µm), LiChroCART® 250-4 mm cartridge

- Guard column: LiChrospher® 60 RP-select B (5 μm), LiChroCART® 4-4 mm cartridge
- Solvents: A: water with 0.05 % (V/V) trifluoroacetic acid; B: acetonitrile with 0.05 % (V/V) trifluoroacetic acid.
- Gradient:

Time [min]	Solvent A [%]	Solvent B [%]
0.0	90.0	10.0
4.0	90.0	10.0
29.0	0.0	100.0
31.0	0.0	100.0
31.5	90.0	10.0
40.0	90.0	10.0

- Flow rate: 1.0 mL/min
- Injection volume: 5.0 μL, method: cut
- Detection wavelength: 210 nm
- Stop time: 30.0 min
- Calculation:
    - Integration: Manual
    - Calculation method: Area%
    - Use of blank subtraction from the same series

6.1.8.2 HPLC method 2

- VWR Hitachi equipment: pump: 5160; autosampler: 5260; column oven: 5310; UV/ Vis detector: 5420; Interface: Organizer; Data Acquisition and evaluation: Chromaster software.
- Column: phenomenex Gemini® 5 μm C6-Phenyl 110 Å, LC Column 250 × 4.6 mm
- Solvents:
    - A: acetonitrile: 10mM ammonium formate =10 : 90 with 0.1% formic acid;
    - B: acetonitrile: 10 mM ammonium formate = 90 : 10 with 0.1% formic acid

- Gradient

Time [min]	Solvent A [%]	Solvent B [%]
0.0	100.0	0.0
5.0	100.0	0.0
12.0	0.0	100.0
20.0	0.0	100.0
22.0	100.0	0.0
30.0	100.0	0.0

- Flow rate: 1.0 mL/min
- Injection volume: 5.0 µL, method: cut
- Detection wavelength: 254 nm
- Stop time: 20.0 min
- Calculation:
    - Integration: Manual
    - Calculation method: Area%
    - Use of blank subtraction from the same series

6.1.9 Mass spectrometry (MS)

6.1.9.1 High resolution mass spectrometry (HRMS)-Electrospray ionization (ESI)

The electrospray ionization (ESI) mass spectra were recorded in the positive ion mode with a 6224 ESI-TOF spectrometer (Agilent) with a scan range of 110-3200 *m/z*. Data were analyzed with MestReNova x64 software (version 14.1.0-24037, © 2019 by Mestrelab Research S.L.).

6.1.9.2 Liquid chromatography mass spectrometry (LC-MS)

The analytical mass spectrometry-coupled liquid chromatography (LC-MS) spectra were obtained with an Agilent 1200 system with coupled 6224 ESI-TOF using a C18 column (Agilent, ZORBAX RRHD Extend-C18, 80Å, 2.1 × 50 mm, 1.8 µm). The electrospray ion source was operated in the positive ionization mode with a scan range of 110 – 3200 *m/z*.
Solvents:

- A: 0.1% formic acid in acetonitrile
- B: 0.1% formic acid in ultrapure water

The gradient employed was the same as that given for HPLC method 2 above at a detection wavelength of 254 nm.
Data were analyzed with MestReNova x64 software (version 14.1.0-24037, © 2019 by Mestrelab Research S.L.).

6.1.9.3 Direct insertion probe (DIP)

The electron ionization (EI) spectra were recorded with a Thermo ISQ LT EI coupled toThermo Trace 1300 with a scan range of 40-800 *m/z*. Data were analyzed with MestReNova x64 software (version 14.1.0-24037, © 2019 by Mestrelab Research S.L.).

6.1.9.4 Gas chromatography mass spectrometry (GC-MS)

The GC-MS spectra were recorded with Agilent 5975C VL MSD coupled to Agilent GC 7890A with a scan range of 40-800 *m/z*. Data were analyzed with MestReNova x64 software (version 14.1.0-24037, © 2019 by Mestrelab Research S.L.).

6.1.10 Nuclear magnetic resonance (NMR) spectroscopy

NMR spectra were recorded at room temperature on Bruker Fourier 300 MHz, Bruker Avance III HD 400 MHz (AVIII400), Bruker Avance I 500 MHz (AV500), and Avance III HD 600 MHz (AVIII600) spectrometers. The NMR spectra were analyzed with MestReNova x64 software (version 14.1.0-24037, © 2019 by Mestrelab Research S.L.). Solvents (DMSO-d_6, MeOD-d_4, and $CDCl_3$) for NMR measurements were purchased from Eurisotop.

6.1.10.1 ^{1}H NMR spectroscopy

- NMR frequency: 300, 400, 500, and 600 MHz

Chemical shifts (δ) are reported in parts per million [ppm] and are referenced to the solvent signal.[187]

- Abbreviations for the multiplicities of the signals: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, etc.

6.1.10.2 ^{13}C NMR Spectroscopy

- NMR frequency: 76, 101, 126, and 151 MHz

Chemical shifts (δ) are reported in parts per million [ppm] and are referenced to the solvent signal.[187]

6.1.10.3 Two-dimensional (2D) NMR spectroscopy

Where necessary, ^{1}H and ^{13}C NMR assignments were supported by the following two-dimensional (2D) NMR spectroscopic techniques:

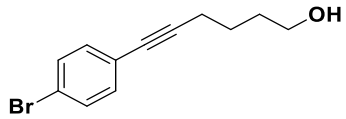
- gCOSY (^{1}H, ^{1}H-correlation spectroscopy)
- gHSQC (gradient heteronuclear single quantum coherence)
- gHMBC (gradient heteronuclear multiple bond correlation)

6.1.11 Infrared (IR) spectroscopy

IR spectra were recorded with a Bruker Alpha-P spectrometer and data were analyzed with OPUS 7.5 software. All samples were applied to the device without solvent and were directly measured. Absorption bands are characterized by their wavenumbers ($\tilde{\nu}$).

6.2 Synthetic procedures and analytical data

6-(4-Bromophenyl)hex-5-yn-1-ol (81)



$C_{12}H_{13}BrO$

$M_r = 253.1$

Under N_2 atmosphere, copper(I) iodide (69 mg, 0.36 mmol), tetrakis(triphenylphosphine)palladium(0) (210 mg, 0.18 mmol), triethylamine (4.0 mL, 2.9 g, 29 mmol), and hex-5-yn-1-ol (0.40 mL, 360 mg, 3.6 mmol) were added to a solution of 1-bromo-4-iodobenzene (**80**) (1.0 g, 3.6 mmol) in acetonitrile (80 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol = 1/0 → 98/2) to give **81** (790 mg, 3.1 mmol, 86%) as yellow oil.

TLC: R_f = 0.28 (dichloromethane/methanol = 98/2);

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 1.52 – 1.61 (m, 4H, $CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 2.37 – 2.47 (m, 2H, $C\mathit{H}_2CH_2CH_2CH_2OH$), 3.38 – 3.47 (m, 2H, $CH_2CH_2CH_2C\mathit{H}_2OH$), 7.29 – 7.36 (m, 2H, 2'-$H_{4\text{-bromophenyl}}$, 6'-$H_{4\text{-bromophenyl}}$), 7.50 – 7.57 (m, 2H, 3'-$H_{4\text{-bromophenyl}}$, 5'-$H_{4\text{-bromophenyl}}$);

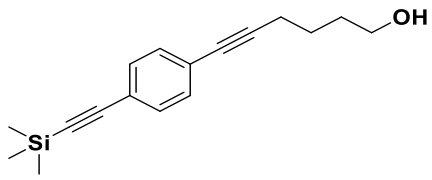
^{13}C NMR (101 MHz, DMSO-d_6): δ [ppm] = 18.5 (1C, $CH_2CH_2CH_2CH_2OH$), 24.7 (1C, $CH_2CH_2CH_2CH_2OH$), 31.7 (1C, $CH_2CH_2CH_2CH_2OH$), 60.2 (1C, $CH_2CH_2CH_2CH_2OH$), 79.5 (1C, C≡CAr), 92.2 (1C, C≡CAr), 121.1 (1C, C-4'$_{4\text{-bromophenyl}}$), 122.5 (1C, C-1'$_{4\text{-bromophenyl}}$), 131.6 (2C, C-2'$_{4\text{-bromophenyl}}$, C-6'$_{4\text{-bromophenyl}}$), 133.2 (2C, C-3'$_{4\text{-bromophenyl}}$, C-5'$_{4\text{-bromophenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3419, 2944, 2924, 2895, 1485, 1344, 1071, 1058, 1037, 1011, 988, 824, 814, 595, 563, 541, 516, 403;

MS (EI): *m*/*z* [%] = 252 (M, 5);

HPLC (method 1): t_R = 22.8 min, purity 94.5%.

6-{4-[(Trimethylsilyl)ethynyl]phenyl}hex-5-yn-1-ol (82)



$C_{17}H_{22}OSi$

M_r = 270.4

Under N_2 atmosphere, copper(I) iodide (50 mg, 0.26 mmol), tetrakis(triphenylphosphine)palladium(0) (150 mg, 0.13 mmol), triethylamine (3.0 mL, 2.1 g, 21 mmol), and trimethylsilylacetylene (0.38 mL, 260 mg, 2.7 mmol) were added to a solution of **81** (790 mg, 3.1 mmol) in acetonitrile (40 mL). After heating the reaction mixture to reflux for 18 h, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/0 → 3/2) to give **82** (440 mg, 1.6 mmol, 59%) as yellow oil.

TLC: R_f = 0.48 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 0.22 (s, 9H, Si(CH_3)$_3$), 1.51 – 1.62 (m, 4H, $CH_2CH_2CH_2CH_2OH$), 2.39 – 2.47 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 3.38 – 3.47 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 4.42 (t, *J* = 5.2 Hz, 1H, O*H*), 7.32 – 7.38 36 (m, 2H, 2'-H$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$, 6'-H$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$), 7.38 – 7.43 (m, 2H, 3'-H$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$, 5'-H$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$);

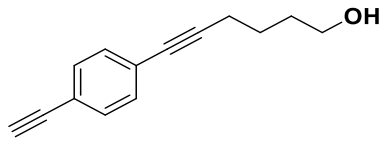
^{13}C NMR (101 MHz, DMSO-d_6): δ [ppm] = -0.2 (3C, Si(CH$_3$)$_3$), 18.5 (1C, CH$_2$CH$_2$CH$_2$CH$_2$OH), 24.8 (1C, CH$_2$$CH_2CH_2CH_2$OH), 31.7 (1C, CH$_2CH_2$$CH_2CH_2$OH), 60.2 (1C, CH$_2CH_2CH_2$$CH_2$OH), 80.1 (1C, Ar$C$≡CCH$_2$), 93.3 (1C, ArC≡$CCH_2$), 95.9 (1C, Si$C$≡CAr), 104.7 (1C, SiC≡$C$Ar), 121.4 (1C, C-4'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$), 123.8 (1C, C-1'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$), 131.4 (2C, C-2'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$, C-6'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$), 131.8 (2C, C-3'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$, C-5'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3332, 2938, 2899, 2862, 2154, 1503, 1492, 1369, 1332, 1247, 1219, 1062, 1038, 843, 829, 756, 697, 679, 625, 547;

MS (EI): *m*/*z* [%] = 270 (M, 29), 211 (M – CH$_2$CH$_2$CH$_2$OH, 62);

HPLC (method 1): t_R = 26.8 min, purity 93.6%.

6-(4-Ethynylphenyl)hex-5-yn-1-ol (45)



C$_{14}$H$_{14}$O

M$_r$ = 198.3

Tetrabutylammonium fluoride trihydrate (1.0 g, 3.2 mmol) was added to an ice-cooled solution of **82** (430 mg, 1.6 mmol) in dry THF (40 mL) and the mixture was stirred at 0 °C for 30 min. Then, a saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 3/1 → 3/2) to give **45** (300 mg, 1.5 mmol, 95%) as yellow oil.

TLC: R_f = 0.43 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 1.52 – 1.61 (m, 4H, CH$_2$CH_2CH_2CH$_2$OH), 2.40 – 2.48 (m, 2H, CH_2CH$_2$CH$_2$CH$_2$OH), 3.40 – 3.46 (m, 2H, CH$_2$CH$_2$CH$_2$CH_2OH), 4.30 (s, 1H, HC≡CAr), 4.41 (t, J = 5.2 Hz, 1H, OH), 7.35 – 7.40 (m, 2H, 2'-H$_{4\text{-ethynylphenyl}}$, 6'-H$_{4\text{-ethynylphenyl}}$), 7.41 – 7.46 (m, 2H, 3'-H$_{4\text{-ethynylphenyl}}$, 5'-H$_{4\text{-ethynylphenyl}}$);

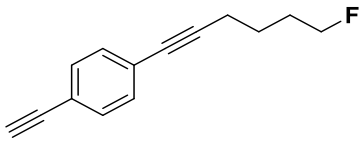
^{13}C NMR (126 MHz, DMSO-d_6): δ [ppm] = 18.5 (1C, *C*H_2CH$_2$CH$_2$CH$_2$OH), 24.8 (1C, CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 31.7 (1C, CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 60.2 (1C, CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 80.1 (1C, Ar*C*≡CCH$_2$), 82.4 (1C, H*C*≡CAr), 83.0 (1C, HC≡*C*Ar), 93.1 (1C, ArC≡*C*CH$_2$), 121.0 (1C, C-4'$_{4\text{-ethynylphenyl}}$), 123.8 (1C, C-1'$_{4\text{-ethynylphenyl}}$), 131.4 (2C, C-2'$_{4\text{-ethynylphenyl}}$, C-6'$_{4\text{-ethynylphenyl}}$), 131.8 (2C, C-3'$_{4\text{-ethynylphenyl}}$, C-5'$_{4\text{-ethynylphenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3287, 2936, 2230, 1603, 1505, 1497, 1455, 1430, 1403, 1366, 1331, 1058, 991, 836, 645, 617, 546, 485;

MS (EI): *m*/*z* [%] = 198 (M, 22), 139 (M – CH$_2$CH$_2$CH$_2$OH, 100);

HPLC (method 1): t_R = 21.9 min, purity 91.3%.

1-Ethynyl-4-(6-fluorohex-1-yn-1-yl)benzene (46)



$C_{14}H_{13}F$

M_r = 200.3

Diethylaminosulfur trifluoride (2.7 mL, 3.3 g, 20 mmol) was added to an ice-cooled solution of **45** (200 mg, 1.0 mmol) in dry dichloromethane (20 mL) and the reaction mixture was slowly warmed to ambient temperature. After stirring the mixture at ambient temperature for 24 h, a saturated aqueous solution of $NaHCO_3$ was carefully added and the mixture was extracted with dichloromethane (3×). The combined organic layers were washed with 0.5 N hydrochloric acid, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/methanol = 1/0 → 9/1) to give **46** (97 mg, 0.48 mmol, 48%) as yellow oil.

TLC: R_f = 0.83 (petroleum ether/methanol = 9/1);

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.67 – 1.98 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_2$F), 2.49 (t, *J* = 6.8 Hz, 2H, C*H*$_2$CH$_2$CH$_2$CH$_2$F), 3.14 (s, 1H, *H*C≡CAr), 4.51 (dt, *J* = 47.2/5.9 Hz, 2H, CH$_2$CH$_2$CH$_2$C*H*$_2$F), 7.30 – 7.36 (m, 2H, 3'-H$_{benzene}$, 5'-H$_{benzene}$), 7.37 – 7.44 (m, 2H, 2'-H$_{benzene}$, 6'-H$_{benzene}$);

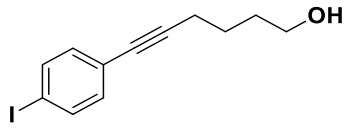
^{13}C NMR (126 MHz, $CDCl_3$): δ [ppm] = 19.3 (1C, *C*$H_2CH_2CH_2CH_2F$), 24.6 (d, *J* = 5.0 Hz, 1C, CH_2*C*$H_2CH_2CH_2F$), 29.7 (d, *J* = 19.8 Hz, 1C, CH_2CH_2*C*H_2CH_2F), 78.6 (1C, H*C*≡CAr), 80.9 (1C, Ar*C*≡CCH_2), 83.5 (1C, HC≡*C*Ar), 83.8 (d, *J* = 164.7 Hz, 1C, $CH_2CH_2CH_2$*C*H_2F), 91.8 (1C, ArC≡*C*CH_2), 121.4 (1C, C-1'$_{benzene}$), 124.5 (1C, C-4'$_{benzene}$), 131.6 (2C, C-3'$_{benzene}$, C-5'$_{benzene}$), 132.1 (2C, C-2'$_{benzene}$, C-6'$_{benzene}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3289, 2961, 2904, 2233, 1603, 1497, 1454, 1260, 1102, 1042, 1017, 987, 959, 930, 884, 836, 620, 546, 485;

MS (EI): *m*/*z* [%] = 200 (M, 46), 139 (M – $CH_2CH_2CH_2F$, 100);

HPLC (method 1): t_R = 25.5 min, purity 95.2%.

6-(4-Iodophenyl)hex-5-yn-1-ol (44)



$C_{12}H_{13}IO$

M_r = 300.1

Under N_2 atmosphere, copper(I) iodide (120 mg, 0.61 mmol), tetrakis(triphenylphosphine)palladium(0) (240 mg, 0.20 mmol), triethylamine (23 mL, 16 g, 160 mmol), and hex-5-yn-1-ol (2.3 mL, 2.0 g, 20 mmol) were added to a solution of 1,4-diiodobenzene (**43**) (8.1 g, 24 mmol) in dry acetonitrile (50 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/1) to give **44** (5.2 g, 17 mmol, 84%) as black oil.

TLC: R_f = 0.38 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.64 – 1.79 (m, 4H, CH_2C*H*$_2$C*H*$_2CH_2OH$), 2.40 – 2.48 (m, 2H, C*H*$_2CH_2CH_2CH_2OH$), 3.68 – 3.74 (m, 2H, $CH_2CH_2CH_2$C*H*$_2$OH), 7.07 – 7.15 (m, 2H, 2'-H$_{4\text{-iodophenyl}}$, 6'-H$_{4\text{-iodophenyl}}$), 7.57 – 7.64 (m, 2H, 3'-H$_{4\text{-iodophenyl}}$, 5'-H$_{4\text{-iodophenyl}}$);

^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 19.4 (1C, *C*$H_2CH_2CH_2CH_2OH$), 25.0 (1C, CH_2*C*$H_2CH_2CH_2OH$), 32.0 (1C, CH_2CH_2*C*H_2CH_2OH), 62.6 (1C, $CH_2CH_2CH_2$*C*H_2OH),

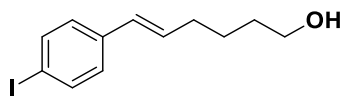
80.2 (1C, C≡*C*Ar), 91.6 (1C, *C*≡CAr), 93.3 (1C, C-4'$_{4\text{-iodophenyl}}$), 123.6 (1C, C-1'$_{4\text{-iodophenyl}}$), 133.3 (2C, C-2'$_{4\text{-iodophenyl}}$, C-6'$_{4\text{-iodophenyl}}$), 137.5 (2C, C-3'$_{4\text{-iodophenyl}}$, C-5'$_{4\text{-iodophenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3340, 2933, 2863, 2231, 1735, 1481, 1389, 1254, 1058, 1005, 817, 510;

MS (EI): *m*/*z* [%] = 300 (M, 14), 241 (M – $CH_2CH_2CH_2OH$, 29);

HPLC (method 1): t_R = 23.4 min, purity 96.9%.

(*E*)-6-(4-Iodophenyl)hex-5-en-1-ol (96)



$C_{12}H_{15}IO$

M_r = 302.2

Under N_2 atmosphere, triethoxysilane (2.1 mL, 1.8 g, 11 mmol) was added to solution of **44** (2.3 g, 7.7 mmol) in dry dichloromethane (30 mL). After cooling the mixture to 0 °C, tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) hexafluorophosphate (46 mg, 0.091 mmol) was added and the mixture was allowed to warm to ambient temperature. After stirring for 30 min at ambient temperature, the mixture was diluted with diethyl ether (30 mL), filtered and the filtration residue was washed with additional diethyl ether. The filtrate was concentrated *in vacuo* and the residue was taken up in THF (30 mL) under N_2 atmosphere. At ambient temperature, copper(I) iodide (170 mg, 0.91 mmol) was added to the resulting mixture followed by the dropwise addition of a solution of tetrabutylammonium fluoride trihydrate (5.7 g, 18 mmol) in THF (30 mL). After stirring the reaction mixture for 20 h at ambient temperature, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/1) to give **96** (1.3 g, 4.4 mmol, 57%) as orange oil, which solidified upon standing at ambient temperature.

TLC: R_f = 0.40 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 1.50 – 1.67 (m, 4H, $CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 2.20 – 2.27 (m, 2H, $C\mathit{H}_2CH_2CH_2CH_2OH$), 3.67 – 3.70 (m, 2H, $CH_2CH_2CH_2C\mathit{H}_2OH$),

6.18 – 6.26 (m, 1H, ArCH=C*H*CH_2), 6.27 – 6.34 (m, 1H, ArC*H*=$CHCH_2$), 7.04 – 7.09 (m, 2H, 2'-$H_{4\text{-iodophenyl}}$, 6'-$H_{4\text{-iodophenyl}}$), 7.57 – 7.63 (m, 2H, 3'-$H_{4\text{-iodophenyl}}$, 5'-$H_{4\text{-iodophenyl}}$);

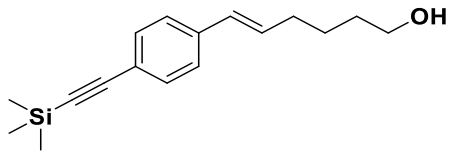
^{13}C NMR (101 MHz, $CDCl_3$): δ [ppm] = 25.5 (1C, CH_2*C*$H_2CH_2CH_2OH$), 32.4 (1C, CH_2CH_2*C*H_2CH_2OH), 32.8 (1C, *C*$H_2CH_2CH_2CH_2OH$), 62.9 (1C, $CH_2CH_2CH_2$*C*H_2OH), 92.0 (1C, C-4'$_{4\text{-iodophenyl}}$), 127.9 (2C, C-2'$_{4\text{-iodophenyl}}$, C-6'$_{4\text{-iodophenyl}}$), 129.3 (1C, Ar*C*H=$CHCH_2$), 131.8 (1C, ArCH=*C*HCH_2), 137.4 (1C, C-1'$_{4\text{-iodophenyl}}$), 137.7 (2C, C-3'$_{4\text{-iodophenyl}}$, C-5'$_{4\text{-iodophenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3300, 2927, 2855, 1646, 1582, 1481, 1396, 1056, 1029, 1017, 1001, 971, 846, 800, 725, 499;

MS (EI): *m*/*z* [%] = 302 (M, 32);

HPLC (method 1): t_R = 24.0 min, purity 94.8%.

(*E*)-6-{4-[(Trimethylsilyl)ethynyl]phenyl}hex-5-en-1-ol (97)



$C_{17}H_{24}OSi$

M_r = 272.5

Under N_2 atmosphere, copper(I) iodide (25 mg, 0.13 mmol), tetrakis(triphenylphosphine)palladium(0) (51 mg, 0.044 mmol), triethylamine (1.8 mL, 1.3 g, 13 mmol), and trimethylsilylacetylene (1.0 mL, 690 mg, 7.0 mmol) were added to a solution of **96** (1.3 g, 4.4 mmol) in dry acetonitrile (20 mL). After stirring the reaction mixture at ambient temperature for 1 h, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/1) to give **97** (1.1 g, 4.0 mmol, 91%) as dark brown oil.

TLC: R_f = 0.43 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 0.24 (s, 9H, Si(CH_3)$_3$), 1.52 – 1.59 (m, 2H, CH_2C*H*$_2CH_2CH_2OH$), 1.60 – 1.66 (m, 2H, CH_2CH_2C*H*$_2CH_2OH$), 2.23 – 2.28 (m, 2H, C*H*$_2CH_2CH_2CH_2OH$), 3.68 (t, *J* = 6.5 Hz, 2H, $CH_2CH_2CH_2$C*H*$_2OH$), 6.24 (dt, *J* = 15.8/6.9 Hz, 1H, ArCH=C*H*CH_2), 6.33 – 6.39 (m, 1H, ArC*H*=$CHCH_2$),

7.24 – 7.27 (m, 2H, 2'-$H_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$, 6'-$H_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$), 7.37 – 7.40 (m, 2H, 3'-$H_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$, 5'-$H_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$);

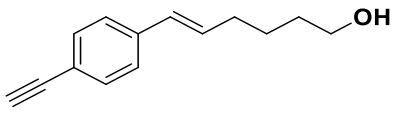
^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 0.1 (3C, Si(*C*H_3)$_3$), 25.5 (1C, CH_2*C*$H_2CH_2CH_2OH$), 32.4 (1C, CH_2CH_2*C*H_2CH_2OH), 32.9 (1C, *C*$H_2CH_2CH_2CH_2OH$), 63.0 (1C, $CH_2CH_2CH_2$*C*H_2OH), 94.5 (1C, Si*C*≡CAr), 105.5 (1C, SiC≡*C*Ar), 121.5 (1C, C-4'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$), 125.8 (2C, C-2'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$, C-6'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$), 129.8 (1C, Ar*C*H=CHCH$_2$), 131.9 (1C, ArCH=*C*HCH$_2$), 132.3 (2C, C-3'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$, C-5'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$), 138.1 (1C, C-1'$_{4\text{-[(trimethylsilyl)ethynyl]phenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3333, 2932, 2859, 2154, 1777, 1506, 1249, 1061, 966, 861, 838, 758, 696, 640, 542;

MS (EI): *m*/*z* [%] = 272 (M, 39);

HPLC (method 1): t_R = 27.2 min, purity 93.8%.

(*E*)-6-(4-Ethynylphenyl)hex-5-en-1-ol (47)



$C_{14}H_{16}O$

M_r = 200.3

Tetrabutylammonium fluoride trihydrate (2.5 g, 8.0 mmol) was added to an ice-cooled solution of **97** (1.1 g, 4.0 mmol) in THF (50 mL) and the mixture was stirred at 0 °C for 30 min. Then, a saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 3/2) to give **47** (650 mg, 3.2 mmol, 81%) as red oil.

TLC: R_f = 0.40 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.52 – 1.59 (m, 2H, CH_2C*H*$_2CH_2CH_2OH$), 1.59 – 1.66 (m, 2H, CH_2CH_2C*H*$_2CH_2OH$), 2.23 – 2.28 (m, 2H, C*H*$_2CH_2CH_2CH_2OH$), 3.08 (s, 1H, *H*C≡CAr), 3.67 (t, *J* = 6.5 Hz, 2H, $CH_2CH_2CH_2C$*H*$_2$OH),

6.25 (dt, *J* = 15.8/6.9 Hz, 1H, ArCH=C*H*CH_2), 6.34 – 6.39 (m, 1H, ArC*H*=$CHCH_2$), 7.26 – 7.30 (m, 2H, 2'-$H_{4\text{-ethynylphenyl}}$, 6'-$H_{4\text{-ethynylphenyl}}$), 7.39 – 7.43 (m, 2H, 3'-$H_{4\text{-ethynylphenyl}}$, 5'-$H_{4\text{-ethynylphenyl}}$);

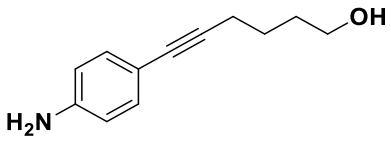
^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 25.5 (1C, $CH_2CH_2CH_2CH_2OH$), 32.4 (1C, $CH_2CH_2CH_2CH_2OH$), 32.9 (1C, $CH_2CH_2CH_2CH_2OH$), 62.9 (1C, $CH_2CH_2CH_2CH_2OH$), 77.5 (1C, HC≡CAr), 84.0 (1C, HC≡CAr), 120.4 (1C, C-4'$_{4\text{-ethynylphenyl}}$), 125.9 (2C, C-2'$_{4\text{-ethynylphenyl}}$, C-6'$_{4\text{-ethynylphenyl}}$), 129.7 (1C, Ar*C*H=$CHCH_2$), 132.2 (1C, ArCH=*C*$HCH_2$), 132.4 (2C, C-3'$_{4\text{-ethynylphenyl}}$, C-5'$_{4\text{-ethynylphenyl}}$), 138.4 (1C, C-1'$_{4\text{-ethynylphenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3290, 2933, 2861, 2105, 1735, 1505, 1373, 1241, 1044, 967, 855, 810, 641, 608, 539;

MS (EI): *m*/*z* [%] = 200 (M, 18), 141 (M – $CH_2CH_2CH_2OH$, 48);

HPLC (method 1): t_R = 22.4 min, purity 97.4%.

6-(4-Aminophenyl)hex-5-yn-1-ol (50)



$C_{12}H_{15}NO$

M_r = 189.3

Under N_2 atmosphere, copper(I) iodide (100 mg, 0.55 mmol), tetrakis(triphenylphosphine)palladium(0) (210 mg, 0.18 mmol), triethylamine (7.6 mL, 5.5 g, 55 mmol), and hex-5-yn-1-ol (2.0 mL, 1.8 g, 18 mmol) were added to a solution of 4-iodoaniline (**49**) (4.0 g, 18 mmol) in dry acetonitrile (80 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **50** (3.4 g, 18 mmol, 100%) as red oil.

TLC: R_f = 0.25 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 1.46 – 1.60 (m, 4H, $CH_2CH_2CH_2CH_2OH$), 2.29 – 2.39 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 3.35 – 3.49 (m, 2H, $CH_2CH_2CH_2CH_2OH$),

4.31 – 4.46 (m, 1H, O*H*), 5.34 (s br, 2H, NH_2), 6.43 – 6.51 (m, 2H, 3'-$H_{4\text{-aminophenyl}}$, 5'-$H_{4\text{-aminophenyl}}$), 6.97 – 7.06 (m, 2H, 2'-$H_{4\text{-aminophenyl}}$, 6'-$H_{4\text{-aminophenyl}}$);

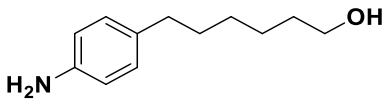
^{13}C NMR (76 MHz, DMSO-d_6): δ [ppm] = 18.6 (1C, *C*H_2CH$_2$CH$_2$CH$_2$OH), 25.2 (1C, CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 31.7 (1C, CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 60.3 (1C, CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 81.7 (1C, Ar*C*≡CCH$_2$), 86.7 (1C, ArC≡*C*CH$_2$), 109.6 (1C, C-1'$_{4\text{-aminophenyl}}$), 113.6 (2C, C-3'$_{4\text{-aminophenyl}}$, C-5'$_{4\text{-aminophenyl}}$), 132.2 (2C, C-2'$_{4\text{-aminophenyl}}$, C-6'$_{4\text{-aminophenyl}}$), 148.5 (1C, C-4'$_{4\text{-aminophenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3348, 3221, 2936, 2862, 1621, 1606, 1595, 1511, 1274, 1175, 1054, 1043, 827, 636, 525;

MS (EI): *m*/*z* [%] = 189 (M, 32), 144 (M – CH$_2$CH$_2$OH, 33), 130 (M – CH$_2$CH$_2$CH$_2$OH, 100);

HPLC (method 1): t_R = 12.7 min, purity 92.4%.

6-(4-Aminophenyl)hexan-1-ol (51)



C$_{12}$H$_{19}$NO

M$_r$ = 193.3

Under N_2 atmosphere, palladium on activated charcoal (10%, 180 mg) was added to a solution of **50** (650 mg, 3.4 mmol) in methanol (40 mL). The reaction mixture was stirred under hydrogen atmosphere (balloon) at ambient temperature for 18 h. Then, the mixture was filtered through Celite® and the filtrate was concentrated *in vacuo* to give **51** (600 mg, 3.1 mmol, 91%) as pale red oil.

TLC: R_f = 0.25 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (300 MHz, DMSO-d_6): δ [ppm] = 1.15 – 1.54 (m, 8H, CH$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$CH$_2$OH), 2.33 – 2.41 (m, 2H, C*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 3.30 – 3.41 (m, 2H, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$OH), 4.31 (t, *J* = 5.2 Hz, 1H, O*H*), 4.79 (s br, 2H, NH_2), 6.42 – 6.52 (m, 2H, 3'-$H_{4\text{-aminophenyl}}$, 5'-$H_{4\text{-aminophenyl}}$), 6.76 – 6.87 (m, 2H, 2'-$H_{4\text{-aminophenyl}}$, 6'-$H_{4\text{-aminophenyl}}$);

^{13}C NMR (76 MHz, DMSO-d_6): δ [ppm] = 25.4 (1C, CH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 28.5 (1C, CH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 31.5 (1C, CH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH),

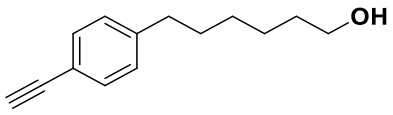
32.5 (1C, $CH_2CH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 34.4 (1C, $\mathit{C}H_2CH_2CH_2CH_2CH_2CH_2OH$), 60.7 (1C, $CH_2CH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 114.0 (2C, C-3'$_{4\text{-aminophenyl}}$, C-5'$_{4\text{-aminophenyl}}$), 128.6 (2C, C-2'$_{4\text{-aminophenyl}}$, C-6'$_{4\text{-aminophenyl}}$), 129.3 (1C, C-1'$_{4\text{-aminophenyl}}$), 146.2 (1C, C-4'$_{4\text{-aminophenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3345, 2921, 2849, 1617, 1515, 1461, 1351, 1253, 1059,1040, 992, 896, 818, 761, 723, 545, 500;

MS (EI): *m*/*z* [%] = 193 (M, 21), 106(M – $CH_2CH_2CH_2CH_2CH_2OH$, 100);

HPLC (method 1): t_R = 13.2 min, purity 90.0%.

6-(4-Ethynylphenyl)hexan-1-ol (52)



$C_{14}H_{18}O$

M_r = 202.3

Under N_2 atmosphere, *tert*-butyl nitrite (90%, 0.9 mL, 790 mg, 6.9 mmol), glacial acetic acid (0.4 mL, 410 mg, 6.9 mmol), palladium(II) acetate (31 mg, 0.14 mmol), *tri*-(2-furyl)phosphine (96 mg, 0.41 mmol), and trimethylsilylacetylene (0.8 mL, 540 mg, 5.5 mmol) were added to solution of **51** (1.3 g, 6.9 mmol) in DMSO (30 mL). After heating the reaction mixture to 32 °C for 16 h, brine was added and the mixture was extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/1). Fractions containing the desired product (**87**) were combined and evaporated *in vacuo.*

A share (280 mg, 83%) of the obtained residue **87** (340 mg) was dissolved in THF (20 mL) and tetrabutylammonium fluoride trihydrate (640 mg, 2.0 mmol) was added at 0 °C. After stirring the mixture at 0 °C for 30 min, a saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/0 → 3/2) to give **52** (140 mg, 0.70 mmol, 13%) as yellow oil.

TLC: R_f = 0.53 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 1.22 – 1.34 (m, 4H, $CH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2CH_2OH$), 1.35 – 1.44 (m, 2H, $CH_2CH_2CH_2CH_2C\mathit{H}_2CH_2OH$), 1.51 – 1.59 (m, 2H, $CH_2C\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 2.54 – 2.60 (m, 2H, $C\mathit{H}_2CH_2CH_2CH_2CH_2CH_2OH$), 3.33 – 3.39 (m, 2H, $CH_2CH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 4.08 (s, 1H, C≡C*H*), 4.30 (t, *J* = 5.0 Hz, 1H, O*H*), 7.17 – 7.22 (m, 2H, 2'-$H_{4\text{-ethynylphenyl}}$, 6'-$H_{4\text{-ethynylphenyl}}$), 7.35 – 7.40 (m, 2H, 3'-$H_{4\text{-ethynylphenyl}}$, 5'-$H_{4\text{-ethynylphenyl}}$);

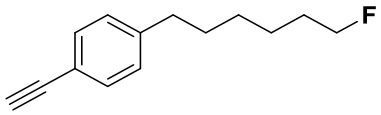
^{13}C NMR (126 MHz, DMSO-d_6): δ [ppm] = 25.3 (1C, $CH_2CH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 28.4 (1C, $CH_2CH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 30.7 (1C, $CH_2\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 32.4 (1C, $CH_2CH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 34.9 (1C, $\mathit{C}H_2CH_2CH_2CH_2CH_2CH_2OH$), 60.6 (1C, $CH_2CH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 80.0 (1C, C≡*C*H), 83.6 (1C, *C*≡CH), 118.9 (1C, C-4'$_{4\text{-ethynylphenyl}}$), 128.6 (2C, C-2'$_{4\text{-ethynylphenyl}}$, C-6'$_{4\text{-ethynylphenyl}}$), 131.6 (2C, C-3'$_{4\text{-ethynylphenyl}}$, C-5'$_{4\text{-ethynylphenyl}}$), 143.5 (1C, C-1'$_{4\text{-ethynylphenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3291, 2929, 2856, 1606, 1507, 1454, 1053, 1029, 840, 821, 699, 642, 608, 554;

MS (EI): *m*/*z* [%] = 202 (M, 10), 115 (M – $CH_2CH_2CH_2CH_2CH_2OH$, 100);

HPLC (method 1): t_R = 22.9 min, purity 63.1%.

1-Ethynyl-4-(6-fluorohexyl)benzene (53)



$C_{14}H_{17}F$

M_r = 204.3

Diethylaminosulfur trifluoride (2.1 mL, 2.6 g, 16 mmol) was added to an ice-cooled solution of **52** (160 mg, 0.79 mmol) in dry dichloromethane (20 mL) and the reaction mixture was slowly warmed to ambient temperature. After stirring the mixture at ambient temperature for 24 h, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were washed with 0.5 N hydrochloric acid, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether) to give **53** (60 mg, 0.29 mmol, 37%) as yellow oil.

TLC: R_f = 0.13 (petroleum ether);

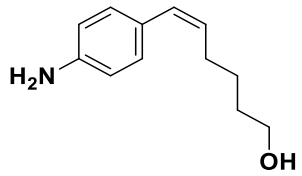
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.30 – 1.50 (m, 4H, $CH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2CH_2F$), 1.56 – 1.78 (m, 4H, $CH_2C\mathit{H}_2CH_2CH_2C\mathit{H}_2CH_2F$), 2.57 – 2.65 (m, 2H, $C\mathit{H}_2CH_2CH_2CH_2CH_2CH_2F$), 3.03 (s, 1H, C≡C*H*), 4.32 – 4.54 (m, 2H, $CH_2CH_2CH_2CH_2CH_2C\mathit{H}_2F$), 7.10 – 7.16 (m, 2H, 3'-$H_{1\text{-ethynylbenzene}}$, 5'-$H_{1\text{-ethynylbenzene}}$), 7.38 – 7.43 (m, 2H, 2'-$H_{1\text{-ethynylbenzene}}$, 6'-$H_{1\text{-ethynylbenzene}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3294, 2930, 2857, 2108, 1606, 1507, 1455, 1390, 1046, 1020, 992, 841, 822, 747, 699, 642, 554;

MS (EI): *m*/*z* [%] = 204 (M, 23), 115 (M – $CH_2CH_2CH_2CH_2CH_2F$, 100);

HPLC (method 1): t_R = 26.4 min, purity 69.5%.

(*Z*)-6-(4-Aminophenyl)hex-5-en-1-ol (54)



$C_{12}H_{17}NO$

M_r = 191.3

Under N_2 atmosphere, ethylenediamine (2.3 mL, 2.1 g, 35 mmol) and LINDLAR Catalyst (5% Pd, 1.5 g) were added to a solution of **50** (3.3 g, 17 mmol) in DMF (60 mL). After stirring the reaction mixture under hydrogen atmosphere (balloon) at ambient temperature for 40 min, the mixture was filtered through Celite®. A saturated aqueous solution of ammonium chloride was added to the filtrate and the mixture was extracted with ethyl acetate (3×). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, ethyl acetate) to give **54** (3.2 g, 17 mmol, 96%) as yellow oil.

TLC: R_f = 0.56 (ethyl acetate);

^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 1.38 – 1.48 (m, 4H, $CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 2.23 – 2.29 (m, 2H, $C\mathit{H}_2CH_2CH_2CH_2OH$), 3.36 – 3.40 (m, 2H, $CH_2CH_2CH_2C\mathit{H}_2OH$), 4.34 (t, *J* = 5.2 Hz, 1H, O*H*), 5.12 (s br, 2H, $N\mathit{H}_2$), 5.34 (dt, *J* = 11.6/7.1 Hz, 1H, ArCH=C*H*CH_2),

6.16 – 6.20 (m, 1H, ArC*H*=CHCH$_2$), 6.51 – 6.55 (m, 2H, 3'-H$_{4\text{-aminophenyl}}$, 5'-H$_{4\text{-aminophenyl}}$), 6.95 – 7.00 (m, 2H, 2'-H$_{4\text{-aminophenyl}}$, 6'-H$_{4\text{-aminophenyl}}$);

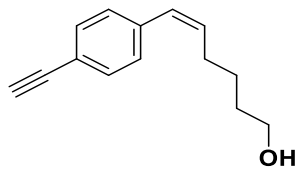
^{13}C NMR (151 MHz, DMSO-d_6): δ [ppm] = 26.1 (1C, CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 28.1 (1C, *C*H$_2$CH$_2$CH$_2$CH$_2$OH), 32.2 (1C, CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 60.5 (1C, CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 113.5 (2C, C-3'$_{4\text{-aminophenyl}}$, C-5'$_{4\text{-aminophenyl}}$), 125.0 (1C, C-1'$_{4\text{-aminophenyl}}$), 128.1 (1C, ArCH=*C*HCH$_2$), 129.0 (1C, Ar*C*H=CHCH$_2$), 129.5 (2C, C-2'$_{4\text{-aminophenyl}}$, C-6'$_{4\text{-aminophenyl}}$), 147.4 (1C, C-4'$_{4\text{-aminophenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3315, 2930, 2859, 1486, 1404, 1069, 1008, 836, 792, 698, 627, 518, 502;

MS (EI): *m*/*z* [%] = 191 (M, 38), 132 (M – CH$_2$CH$_2$OH, 100);

HPLC (method 1): t_R = 13.0 min, purity 96.3%.

(*Z*)-6-(4-Ethynylphenyl)hex-5-en-1-ol (55)



C$_{14}$H$_{16}$O

M$_r$ = 200.3

Under N$_2$ atmosphere, *tert*-butyl nitrite (90%, 2.7 mL, 2.3 g, 20 mmol), glacial acetic acid (1.2 mL, 1.2 g, 20 mmol), palladium(II) acetate (75 mg, 0.33 mmol), *tri*-(2-furyl)phosphine (230 mg, 1.0 mmol), and trimethylsilylacetylene (3.6 mL, 2.5 g, 25 mmol) added to solution of **54** (3.2 g, 17 mmol) in DMSO (30 mL). After heating the reaction mixture to 32 °C for 16 h, brine was added and the mixture was extracted with ethyl acetate (3×). The combined organic phases were dried (Na$_2$SO$_4$), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl

acetate = 1/0 → 3/2). Fractions containing the desired product **89** were combined and evaporated *in vacuo.*

The obtained residue (2.2 g) was dissolved in THF (100 mL) and tetrabutylammonium fluoride trihydrate (5.1 g, 16 mmol) was added at 0 °C. After stirring the mixture at 0 °C for 30 min, a saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ethyl acetate (3×). The combined organic phases were dried (Na$_2$SO$_4$), filtered, and the

solvent was removed *in vacuo*. The residue was purified by flash column chromatography (*Ø* = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 3/2) to give **55** (450 mg, 2.2 mmol, 13%) as yellow oil.

TLC: R_f = 0.53 (petroleum ether/ethyl acetate = 3/2);

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.50 – 1.56 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 1.56 – 1.63 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 2.35 (qd, *J* = 7.3/1.8 Hz, 2H, $CH_2CH_2CH_2CH_2OH$), 3.08 (s, 1H, C≡C*H*), 3.64 (t, *J* = 6.4 Hz, 2H, $CH_2CH_2CH_2CH_2OH$), 5.69 (dt, *J* = 11.7/7.3 Hz, 1H, ArCH=C*H*CH_2), 6.37 – 6.42 (m, 1H, ArC*H*=$CHCH_2$), 7.20 – 7.23 (m, 2H, 2'-$H_{4\text{-ethynylphenyl}}$, 6'-$H_{4\text{-ethynylphenyl}}$), 7.43 – 7.46 (m, 2H, 3'-$H_{4\text{-ethynylphenyl}}$, 5'-$H_{4\text{-ethynylphenyl}}$);

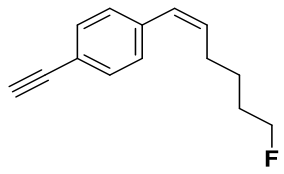
^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 26.1 (1C, $CH_2CH_2CH_2CH_2OH$), 28.5 (1C, $CH_2CH_2CH_2CH_2OH$), 32.4 (1C, $CH_2CH_2CH_2CH_2OH$), 62.9 (1C, $CH_2CH_2CH_2CH_2OH$), 77.4 (1C, C≡CH), 83.9 (1C, C≡CH), 120.2 (1C, C-4'$_{4\text{-ethynylphenyl}}$), 128.6 (1C, ArCH=$CHCH_2$), 128.8 (2C, C-2'$_{4\text{-ethynylphenyl}}$, C-6'$_{4\text{-ethynylphenyl}}$), 132.1 (2C, C-3'$_{4\text{-ethynylphenyl}}$, C-5'$_{4\text{-ethynylphenyl}}$), 133.9 (1C, ArCH=$CHCH_2$), 138.4 (1C, C-1'$_{4\text{-ethynylphenyl}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3288, 2932, 2861, 1708, 1504, 1370, 1248, 1062, 850, 607, 545, 514;

MS (EI): *m*/*z* [%] = 200 (M, 11), 141 (M – $CH_2CH_2CH_2OH$, 44);

HPLC (method 1): t_R = 22.2 min, purity 77.2%.

(*Z*)-1-Ethynyl-4-(6-fluorohex-1-en-1-yl)benzene (56)



$C_{14}H_{15}F$

M_r = 202.3

Diethylaminosulfur trifluoride (5.9 mL, 7.8 g, 48.2 mmol) was slowly added to an ice-cooled solution of **55** (450 mg, 2.2 mmol) in dry dichloromethane (30 mL) and the reaction mixture was slowly warmed to ambient temperature. After stirring the mixture at ambient temperature for 18 h, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with dichloromethane (3×). The combined organic layers were washed with 0.5 N hydrochloric

acid, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether) to give **56** (270 mg, 1.3 mmol, 59%) as yellow oil.

TLC: R_f = 0.12 (petroleum ether);

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 1.44 – 1.55 (m, 2H, $CH_2CH_2CH_2CH_2F$), 1.59 – 1.74 (m, 2H, $CH_2CH_2CH_2CH_2F$), 2.29 – 2.37 (m, 2H, $CH_2CH_2CH_2CH_2F$), 4.20 (s, 1H, C≡C*H*), 4.42 (dt, *J* = 47.5/6.0 Hz, 2H, $CH_2CH_2CH_2CH_2F$), 5.71 (dt, *J* = 11.8/7.2 Hz, 1H, $ArCH=CHCH_2$), 6.40 – 6.46 (m, 1H, $ArCH=CHCH_2$), 7.28 – 7.32 (m, 2H, 3'-$H_{benzene}$, 5'-$H_{benzene}$), 7.43 – 7.48 (m, 2H, 2'-$H_{benzene}$, 6'-$H_{benzene}$);

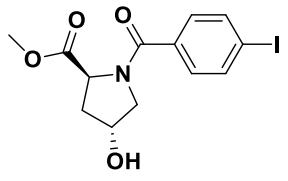
^{13}C NMR (101 MHz, DMSO-d_6): δ [ppm] = 24.9 (d, *J* = 5.3 Hz, 1C, $CH_2CH_2CH_2CH_2F$), 27.7 (1C, $CH_2CH_2CH_2CH_2F$), 29.4 (d, *J* = 19.2 Hz, 1C, $CH_2CH_2CH_2CH_2F$), 81.0 (1C, C≡CH), 83.4 (1C, C≡CH), 83.6 (d, *J* = 161.9 Hz, 1C, $CH_2CH_2CH_2CH_2F$), 119.8 (1C, C-1'$_{benzene}$), 128.2 (1C, $ArCH=CHCH_2$), 128.7 (2C, C-3'$_{benzene}$, C-5'$_{benzene}$), 131.6 (2C, C-2'$_{benzene}$, C-6'$_{benzene}$), 133.6 (1C, $ArCH=CHCH_2$), 137.6 (1C, C-4'$_{benzene}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3292, 2960, 2936, 1504, 1456, 1390, 1057, 1029, 986, 932, 851, 700, 642, 616, 546, 513;

MS (EI): *m*/*z* [%] = 202 (M, 34), 141 (M – $CH_2CH_2CH_2F$, 100);

HPLC (method 1): t_R = 25.8 min, purity 70.0%.

Methyl (2*S*,4*R*)-4-hydroxy-1-(4-iodobenzoyl)pyrrolidine-2-carboxylate (58)



$C_{13}H_{14}INO_4$

M_r = 375.2

Triethylamine (3.7 mL, 2.7 g, 27 mmol) was added to an ice-cooled solution of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**57**) (2.0 g, 11 mmol) in dichloromethane (100 mL) and the mixture was stirred for 15 min at 0 °C. Then, 4-dimethylaminopyridine (140 mg, 1.1 mmol) and 4-iodobenzoyl chloride (2.9 g, 11 mmol) were added and the mixture

was stirred for 2 h at ambient temperature. Afterwards, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with dichloromethane (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, ethyl acetate) to give **58** (3.4 g, 9.0 mmol, 82%) as colorless solid.

m.p. = 146-147 °C;

TLC: R_f = 0.38 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -92.0 (2.3, methanol);

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 1.96 (ddd, J = 13.0/9.3/4.3 Hz, 1H, CHCH_2CH), 2.16 – 2.24 (m, 1H, CHCH_2CH), 3.26 – 3.31 (m, 1H, NCH_2), 3.66 (s, 3H, CO_2CH_3), 3.72 (dd, J = 11.0/3.7 Hz, 1H, NCH_2), 4.25 – 4.31 (m, 1H, C*H*OH), 4.52 – 4.57 (m, 1H, NC*H*), 5.11 (d, J = 3.0 Hz, 1H, CHO*H*), 7.30 – 7.35 (m, 2H, 2'-$H_{4\text{-iodobenzoyl}}$, 6'-$H_{4\text{-iodobenzoyl}}$), 7.82 – 7.87 (m, 2H, 3'-$H_{4\text{-iodobenzoyl}}$, 5'-$H_{4\text{-iodobenzoyl}}$), two rotamers exist in the ratio 89/11, the signals of the major rotamer are given;

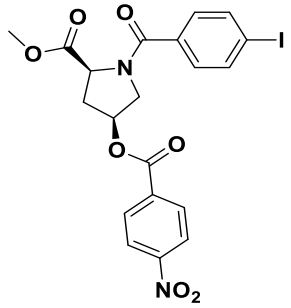
^{13}C NMR (126 MHz, DMSO-d_6): δ [ppm] = 37.1 (1C, CH*C*H_2CH), 51.9 (1C, $CO_2C$$H_3$), 57.7 (1C, N*C*H), 57.8 (1C, N*C*H_2), 68.9 (1C, *C*HOH), 97.6 (1C, C-4'$_{4\text{-iodobenzoyl}}$), 129.4 (2C, C-2'$_{4\text{-iodobenzoyl}}$, C-6'$_{4\text{-iodobenzoyl}}$), 135.0 (1C, C-1'$_{4\text{-iodobenzoyl}}$), 137.2 (2C, C-3'$_{4\text{-iodobenzoyl}}$, C-5'$_{4\text{-iodobenzoyl}}$), 168.0 (1C, Ar*C*ON), 172.3 (1C, *C*O_2CH_3), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3408, 2946, 2918, 1741, 1583, 1552, 1438, 1356, 1273, 1200, 1165, 1150, 1090, 1009, 831, 755, 500;

HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{15}INO_4$: 376.0040, found: 376.0029;

HPLC (method 1): t_R = 16.5 min, purity 100%.

Methyl (2*S*,4*S*)-1-(4-iodobenzoyl)-4-[(4-nitrobenzoyl)oxy]pyrrolidine-2-carboxylate (83)



$C_{20}H_{17}IN_2O_7$

M_r = 524.3

Under N_2 atmosphere, DIAD (2.3 mL, 2.4 g, 12 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (3.1 g, 12 mmol) in dry THF (60 mL) and the mixture was stirred for 5 min at 0 °C. Then, a solution of *p*-nitrobenzoic acid (1.8 g, 11 mmol) and **58** (2.0 g, 5.3 mmol) in dry THF (20 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 3/2 → 1/2) to give **83** (2.3 g, 4.4 mmol, 82%) as colorless solid.

m.p. = 119-120 °C;

TLC: R_f = 0.60 (petroleum ether/ethyl acetate = 1/2);

Specific rotation: $[\alpha]_D^{20}$ = +39.0 (1.0, methanol);

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 2.29 – 2.36 (m, 1H, CHC*H*$_2$CH), 2.66 – 2.79 (m, 1H, CHC*H*$_2$CH), 3.67 (s, 3H, CO_2CH_3), 3.69 – 3.75 (m, 1H, NC*H*$_2$), 3.95 (dd, *J* = 11.9/5.2 Hz, 1H, NC*H*$_2$), 4.86 (dd, *J* = 9.5/2.3 Hz, 1H, NC*H*), 5.49 – 5.55 (m, 1H, C*H*O), 7.30 – 7.39 (m, 2H, 2'-H$_{4\text{-iodobenzoyl}}$, 6'-H$_{4\text{-iodobenzoyl}}$), 7.82 – 7.89 (m, 2H, 3'-H$_{4\text{-iodobenzoyl}}$, 5'-H$_{4\text{-iodobenzoyl}}$), 8.08 – 8.14 (m, 2H, 2''-H$_{4\text{-nitrobenzoyl}}$, 6''-H$_{4\text{-nitrobenzoyl}}$), 8.35 – 8.40 (m, 2H, 3''-H$_{4\text{-nitrobenzoyl}}$, 5''-H$_{4\text{-nitrobenzoyl}}$), two rotamers exist in the ratio 65/35, the signals of the major rotamer are given;

^{13}C NMR (126 MHz, DMSO-d_6): δ [ppm] = 34.1 (1C, CH*C*H$_2$CH), 52.2 (1C, CO_2CH$_3$), 54.1 (1C, N*C*H$_2$), 57.4 (1C, N*C*H), 74.4 (1C, *C*HO), 97.3 (1C, C-4'$_{4\text{-iodobenzoyl}}$), 123.9 (2C, C-3''$_{4\text{-nitrobenzoyl}}$, 5''$_{4\text{-nitrobenzoyl}}$), 129.0 (2C, C-2'$_{4\text{-iodobenzoyl}}$, C-6'$_{4\text{-iodobenzoyl}}$), 130.6 (2C, C-2''$_{4\text{-nitrobenzoyl}}$, C-6''$_{4\text{-nitrobenzoyl}}$), 134.7 (1C, C-1''$_{4\text{-nitrobenzoyl}}$), 135.2 (1C, C-1'$_{4\text{-iodobenzoyl}}$),

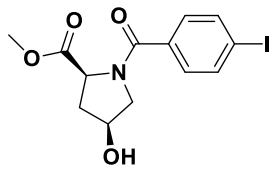
137.3 (2C, C-3'$_{4\text{-iodobenzoyl}}$, C-5'$_{4\text{-iodobenzoyl}}$), 150.4 (1C, C-4"$_{4\text{-nitrobenzoyl}}$), 163.5 (1C, Ar*C*O_2), 167.8 (1C, Ar*C*ON), 171.2 (1C, *C*O_2CH_3), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3114, 3081, 3056, 2944, 1743, 1718, 1637, 1526, 1391, 1345, 1275, 1198, 1169, 1106, 1054, 1008, 831, 749, 719, 500;

HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{18}IN_2O_7$: 525.0153, found: 525.0116;

HPLC (method 1): t_R = 23.5 min, purity 97.2%.

Methyl (2*S*,4*S*)-4-hydroxy-1-(4-iodobenzoyl)pyrrolidine-2-carboxylate (59)



$C_{13}H_{14}INO_4$

M_r = 375.2

At ambient temperature, potassium carbonate (3.3 g, 24 mmol) was added to a solution of **83** (1.1 g, 2.1 mmol) in dry methanol (60 mL). After stirring the reaction mixture for 30 min, the mixture was filtered and the filtrate was acidified by adding 0.5 N HCl. Then, a saturated aqueous solution of $NaHCO_3$ was added in excess to render the mixture alkaline and the mixture was extracted with dichloromethane (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **59** (0.62 g, 1.7 mmol, 79%) as colorless solid.

m.p. = 141-143 °C;

TLC: R_f = 0.28 (petroleum ether/ethyl acetate = 1/4);

Specific rotation: $[\alpha]_D^{20}$ = -50.3 (2.0, methanol);

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 1.82 (dt, *J* = 12.5/6.5 Hz, 1H, CHC*H*$_2$CH), 2.41 (ddd, *J* = 12.5/8.6/5.7 Hz, 1H, CHC*H*$_2$CH), 3.26 – 3.42 (m, 1H, NC*H*$_2$), 3.56 (dd, *J* = 10.2/5.9 Hz, 1H, NC*H*$_2$), 3.65 (s, 3H, CO_2C*H*$_3$), 4.18 – 4.27 (m, 1H, C*H*OH), 4.55 (dd, *J* = 8.5/6.8 Hz, 1H, NC*H*), 5.15 – 5.23 (m, 1H, CHO*H*), 7.27 – 7.36 (m, 2H, 2'-H$_{4\text{-iodobenzoyl}}$, 6'-H$_{4\text{-iodobenzoyl}}$),

7.81 – 7.88 (m, 2H, 3'-$H_{4\text{-iodobenzoyl}}$, 5'-$H_{4\text{-iodobenzoyl}}$), several rotamers exist, the signals of the major rotamer are given;

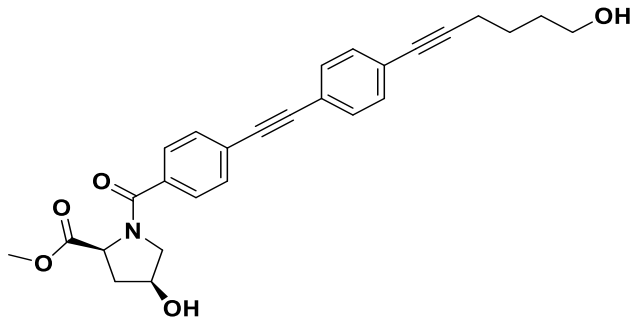
^{13}C NMR (101 MHz, DMSO-d_6): δ [ppm] = 36.8 (1C, CH*C*H_2CH), 51.9 (1C, CO_2*C*H_3), 56.2 (1C, N*C*H_2), 57.2 (1C, N*C*H), 68.5 (1C, *C*HOH), 97.3 (1C, C-4'$_{4\text{-iodobenzoyl}}$), 129.2 (2C, C-2'$_{4\text{-iodobenzoyl}}$, C-6'$_{4\text{-iodobenzoyl}}$), 135.4 (1C, C-1'$_{4\text{-iodobenzoyl}}$), 137.2 (2C, C-3'$_{4\text{-iodobenzoyl}}$, C-5'$_{4\text{-iodobenzoyl}}$), 167.7 (1C, Ar*C*ON), 171.7 (1C, *C*$O_2$$CH_3$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3273, 2947, 2918, 1739, 1600, 1588, 1431, 1329, 1207, 1170, 1081, 1009, 967, 815, 747, 709, 502;

HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{15}INO_4$: 376.0040, found: 376.0008;

HPLC (method 1): t_R = 16.5 min, purity 99.5%.

Methyl (2*S*,4*S*)-4-hydroxy-1-(4-{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl}benzoyl)pyrrolidine-2-carboxylate (60a)



$C_{27}H_{27}NO_5$

M_r = 445.5

Under N_2 atmosphere, copper(I) iodide (8 mg, 0.042 mmol), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.020 mmol), triethylamine (0.50 mL, 360 mg, 3.6 mmol), and **45** (95 mg, 0.48 mmol) were added to a solution of **59** (150 mg, 0.40 mmol) in dry acetonitrile (40 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 2 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate = 3/2 → 0/1) to give **60a** (180 mg, 0.40 mmol, 100%) as brown solid.

m.p. = 110-112 °C;

TLC: R_f = 0.23 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -16.2 (1.1, methanol);

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm] = 1.49 – 1.64 (m, 4H, $CH_2CH_2CH_2CH_2OH$), 1.79 – 1.89 (m, 1H, $CHCH_2CH$), 2.34 – 2.49 (m, 3H, $CHCH_2CH$ (1H), $CH_2CH_2CH_2CH_2OH$), 3.40 – 3.46 (m, 3H, NCH_2 (1H), $CH_2CH_2CH_2CH_2OH$), 3.59 (dd, J = 10.2/5.8 Hz, 1H, NCH_2), 3.66 (s, 3H, CO_2CH_3), 4.20 – 4.30 (m, 1H, $CHOH$), 4.58 (dd, J = 8.4/6.8 Hz, 1H, NCH), 7.39 – 7.47 (m, 2H, 3''-$H_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$, 5''-$H_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$), 7.50 – 7.60 (m, 4H, 2''-$H_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$, 6''-$H_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$, 2'-$H_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-$H_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 7.61 – 7.67 (m, 2H, 3'-$H_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 5'-$H_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), the signals of the major rotamer are given;

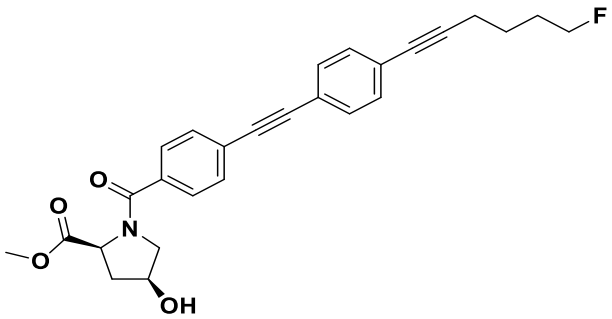
^{13}C NMR (101 MHz, DMSO-d_6): δ [ppm] = 18.6 (1C, $CH_2CH_2CH_2CH_2OH$), 24.8 (1C, $CH_2CH_2CH_2CH_2OH$), 31.7 (1C, $CH_2CH_2CH_2CH_2OH$), 36.8 (1C, $CHCH_2CH$), 52.0 (1C, CO_2CH_3), 56.3 (1C, NCH_2), 57.3 (1C, NCH), 60.2 (1C, $CH_2CH_2CH_2CH_2OH$), 68.5 (1C, $CHOH$), 80.3 (1C, $ArC{\equiv}CCH_2$), 90.2 (1C, $ArC{\equiv}CAr$), 90.4 (1C, $ArC{\equiv}CAr$), 93.4 (1C, $ArC{\equiv}CCH_2$), 121.3 (1C, C-1''$_{\text{4-(6-hydroxyhex-1-yn-1-yl)phenyl}}$), 123.9 (2C, C-4''$_{\text{4-(6-hydroxyhex-1-yn-1-yl)phenyl}}$, C-4'$_{\text{4-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 127.6 (2C, C-2'$_{\text{4-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{\text{4-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 131.4 (2C, C-3'$_{\text{4-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, C-5'$_{\text{4-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 131.6 (2C, $C_{arom.}$), 131.7 (2C, $C_{arom.}$), 136.0 (1C, C-1'$_{\text{4-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 167.7 (1C, $ArCON$), 171.8 (1C, CO_2CH_3), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3402, 2927, 1743, 1592, 1428, 1345, 1213, 1176, 1085, 873, 834, 760, 617, 545, 528;

MS (EI): m/z [%] = 445 (M, 13), 301 ($HOCH_2CH_2CH_2CH_2C{\equiv}CPhC{\equiv}CPhCO$, 100);

HPLC (method 1): t_R = 20.3 min, purity 93.4%.

Methyl (2*S*,4*S*)-1-(4-{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl}benzoyl)-4-hydroxypyrrolidine-2-carboxylate (61a)



$C_{27}H_{26}FNO_4$

M_r = 447.5

Under N_2 atmosphere, copper(I) iodide (7 mg, 0.037 mmol), tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.019 mmol), triethylamine (0.50 mL, 360 mg, 3.6 mmol), and **46** (93 mg, 0.46 mmol) were added to a solution of **59** (150 mg, 0.39 mmol) in dry acetonitrile (30 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 10 g). Fractions containing the desired product were combined and subjected to lyophilization to give **61a** (110 mg, 0.24 mmol, 61%) as colorless solid.

m.p. = 105-107 °C;

TLC: R_f = 0.30 (dichloromethane/methanol = 98/2);

Specific rotation: $[\alpha]_D^{20}$ = -26.5 (1.3, methanol);

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 1.60 – 1.68 (m, 2H, $CH_2CH_2CH_2CH_2F$), 1.73 – 1.87 (m, 3H, $CH_2CH_2CH_2CH_2F$, $CHCH_2CH$ (1H)), 2.35 – 2.57 (m, 2H, $CH_2CH_2CH_2CH_2F$, $CHCH_2CH$ (1H)), 3.36 (dd, J = 10.3/5.7 Hz, 1H, NCH_2), 3.59 (dd, J = 10.3/5.9 Hz, 1H, NCH_2), 3.67 (s, 3H, CO_2CH_3), 4.21 – 4.29 (m, 1H, CHOH), 4.50 (dt, J = 47.4/6.0 Hz, 2H, $CH_2CH_2CH_2CH_2F$), 4.58 (dd, J = 8.5/6.8 Hz, 1H, NCH), 5.19 (s br, 1H, OH), 7.41 – 7.47 (m, 2H, 3''-H$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$, 5''-H$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$), 7.51 – 7.60 (m, 4H, 2'-H$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-H$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 2''-H$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$, 6''-H$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$),

7.62 – 7.67 (m, 2H, 3'-H$_{4\text{-}\{[4\text{-}(6\text{-fluorohex-1-yn-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$, 5'-H$_{4\text{-}\{[4\text{-}(6\text{-fluorohex-1-yn-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), the signals of the major rotamer are given;

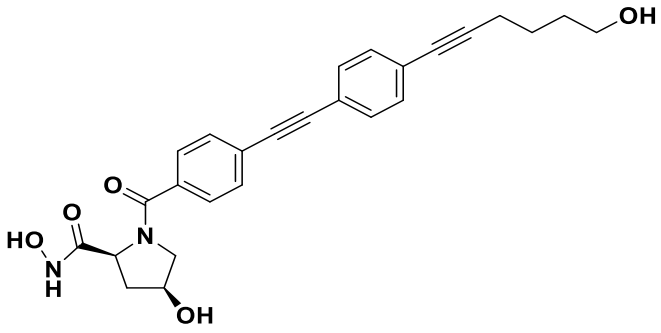
^{13}C NMR (126 MHz, DMSO-d_6): δ [ppm] = 18.3 (1C, *C*H$_2$CH$_2$CH$_2$CH$_2$F), 24.0 (d, *J* = 5.2 Hz, 1C, CH$_2$*C*H$_2$CH$_2$CH$_2$F), 29.1 (d, *J* = 19.4 Hz, 1C, CH$_2$CH$_2$*C*H$_2$CH$_2$F), 36.8 (1C, CH*C*H$_2$CH), 51.9 (1C, CO$_2$*C*H$_3$), 56.2 (1C, N*C*H$_2$), 57.2 (1C, N*C*H), 68.5 (1C, *C*HOH), 80.4 (1C, Ar*C*≡CCH$_2$), 83.4 (d, *J* = 161.8 Hz, 1C, CH$_2$CH$_2$CH$_2$*C*H$_2$F), 90.2 (1C, Ar*C*≡CAr), 90.4 (1C, ArC≡*C*Ar), 92.8 (1C, ArC≡*C*CH$_2$), 121.3 (1C, C-1"$_{4\text{-}(6\text{-fluorohex-1-yn-1-yl})\text{phenyl}}$), 123.7 (1C, C$_{arom.}$), 123.8 (1C, C$_{arom.}$), 127.6 (2C, C-2'$_{4\text{-}\{[4\text{-}(6\text{-fluorohex-1-yn-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$, C-6'$_{4\text{-}\{[4\text{-}(6\text{-fluorohex-1-yn-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), 131.3 (2C, C-3'$_{4\text{-}\{[4\text{-}(6\text{-fluorohex-1-yn-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$, C-5'$_{4\text{-}\{[4\text{-}(6\text{-fluorohex-1-yn-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), 131.60 (2C, C$_{arom.}$), 131.65 (2C, C$_{arom.}$), 136.0 (1C, C-1'$_{4\text{-}\{[4\text{-}(6\text{-fluorohex-1-yn-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), 167.6 (1C, Ar*C*ON), 171.7 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3484, 3413, 2959, 1743, 1705, 1612, 1593, 1425, 1204, 1175, 1089, 836, 763, 544, 523;

HRMS (*m*/*z*): [M+H]$^+$ calcd for C$_{27}$H$_{27}$FNO$_4$: 448.1919, found: 448.1892;

HPLC (method 1): t_R = 23.4 min, purity 90.1%.

(2*S*,4*S*)-*N*,4-Dihydroxy-1-(4-{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl}benzoyl)pyrrolidine-2-carboxamide (60)



C$_{26}$H$_{26}$N$_2$O$_5$

M$_r$ = 446.5

An aqueous solution of hydroxylamine (50 wt%, 7.0 mL) was added to a solution of **60a** (120 mg, 0.26 mmol) in a mixture of THF (6 mL) and isopropanol (6 mL). After stirring the reaction mixture for 48 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na$_2$SO$_4$), filtered,

and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using an Interchim puriFlash® XS 420 system (dichloromethane/methanol = 1/0 → 4/1, Biotage® SNAP Ultra HP-Sphere™ 10 g) to give **60** (83 mg, 0.19 mmol, 70%) as colorless solid.

m.p. = 178-180 °C (decomposition);

TLC: R_f = 0.15 (dichloromethane/methanol = 9/1);

Specific rotation: $[\alpha]_D^{20}$ = +45.0 (0.6, methanol);

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.64 – 1.75 (m, 4H, $CH_2CH_2CH_2CH_2OH$), 1.99 – 2.04 (m, 1H, $CHCH_2CH$), 2.45 – 2.53 (m, 3H, $CHCH_2CH$ (1H), $CH_2CH_2CH_2CH_2OH$), 3.54 (dd, *J* = 10.7/4.7 Hz, 1H, NCH_2), 3.62 (t, *J* = 6.2 Hz, 2H, $CH_2CH_2CH_2CH_2OH$), 3.71 (dd, *J* = 10.7/5.4 Hz, 1H, NCH_2), 4.27 – 4.34 (m, 1H, $CHOH$), 4.52 (dd, *J* = 8.7/5.7 Hz, 1H, NCH), 7.35 – 7.40 (m, 2H, 3''-H$_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$, 5''-H$_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$), 7.43 – 7.49 (m, 2H, 2''-H$_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$, 6''-H$_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$), 7.56 – 7.64 (m, 4H, 2'-H$_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 3'-H$_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 5'-H$_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-H$_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), the signals of the major rotamer are given;

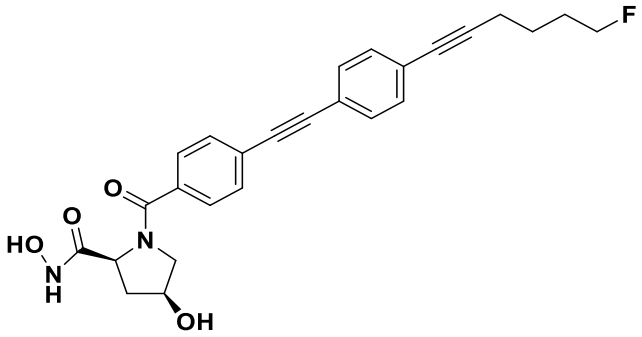
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 19.9 (1C, $CH_2CH_2CH_2CH_2OH$), 26.2 (1C, $CH_2CH_2CH_2CH_2OH$), 32.8 (1C, $CH_2CH_2CH_2CH_2OH$), 38.2 (1C, $CHCH_2CH$), 58.7 (1C, NCH), 58.8 (1C, NCH_2), 62.4 (1C, $CH_2CH_2CH_2CH_2OH$), 70.9 (1C, $CHOH$), 81.4 (1C, $ArC{\equiv}CCH_2$), 90.6 (1C, $ArC{\equiv}CAr$), 91.7 (1C, $ArC{\equiv}CAr$), 93.2 (1C, $ArC{\equiv}CCH_2$), 123.2 (1C, C-1''$_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$), 125.9 (1C, C-4''$_{4\text{-(6-hydroxyhex-1-yn-1-yl)phenyl}}$), 126.8 (1C, C-4'$_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 128.7 (2C, C-2'$_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 132.54 (2C, $C_{arom.}$), 132.57 (2C, $C_{arom.}$), 132.61 (2C, $C_{arom.}$), 136.7 (1C, C-1'$_{4\text{-\{[4-(6-hydroxyhex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 171.6 (2C, $ArCON$, $CONHOH$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3186, 2922, 2866, 2212, 1656, 1629, 1598, 1422, 1088, 1068, 1048, 1026, 834, 765, 640, 613, 532;

HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{26}N_2NaO_5$: 469.1734, found: 469.1691;

HPLC (method 2): t_R = 14.4 min, purity 99.3%.

(2*S*,4*S*)-1-(4-{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl}benzoyl)-*N*,4-dihydroxypyrrolidine-2-carboxamide (61)



$C_{26}H_{25}FN_2O_4$

M_r = 448.5

An aqueous solution of hydroxylamine (50 wt%, 5.0 mL) was added to a solution of **61a** (84 mg, 0.19 mmol) in a mixture of THF (15mL) and isopropanol (15 mL). After stirring the reaction mixture for 24 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using an Interchim puriFlash® XS 420 system (dichloromethane/methanol = 1/0 → 4/1, Biotage® SNAP Ultra HP-Sphere™ 10 g) to give **61** (40 mg, 0.089 mmol, 48%) as colorless solid.

m.p. = 142-143 °C (decomposition);

TLC: R_f = 0.10 (dichloromethane/methanol = 98/2);

Specific rotation: $[\alpha]_D^{20}$ = +30.0 (1.2, methanol);

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.69 – 1.76 (m, 2H, $CH_2CH_2CH_2CH_2F$), 1.80 – 1.91 (m, 2H, $CH_2CH_2CH_2CH_2F$), 1.98 – 2.06 (m, 1H, $CHCH_2CH$), 2.44 – 2.53 (m, 3H, $CH_2CH_2CH_2CH_2F$, $CHCH_2CH$ (1H)), 3.54 (dd, *J* = 10.7/4.6 Hz, 1H, NCH_2), 3.71 (dd, *J* = 10.7/5.4 Hz, 1H, NCH_2), 4.27 – 4.34 (m, 1H, CHOH), 4.49 (dt, *J* = 47.5/5.9 Hz, 2H, $CH_2CH_2CH_2CH_2F$), 4.50 – 4.55 (m, 1H, NCH), 7.35 – 7.40 (m, 2H, 3''-H$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$, 5''-H$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$), 7.44 – 7.50 (m, 2H, 2''-H$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$, 6''-H$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$), 7.55 – 7.64 (m, 4H, 2'-H$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 3'-H$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 5'-H$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-H$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), the signals of the major rotamer are given;

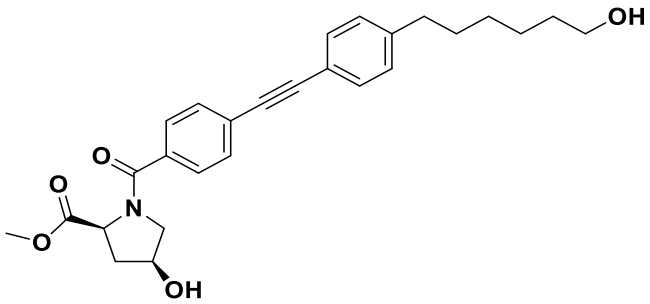
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 19.7 (1C, *C*$H_2CH_2CH_2CH_2F$), 25.7 (d, *J* = 5.0 Hz, 1C, CH_2*C*$H_2CH_2CH_2F$), 30.8 (d, *J* = 19.8 Hz, 1C, CH_2CH_2*C*H_2CH_2F), 38.2 (1C, CH*C*H_2CH), 58.7 (1C, N*C*H), 58.8 (1C, N*C*H_2), 70.9 (1C, *C*HOH), 81.5 (1C, Ar*C*≡CCH$_2$), 84.5 (d, *J* = 163.8 Hz, 1C, $CH_2CH_2CH_2$*C*H_2F), 90.7 (1C, Ar*C*≡CAr), 91.7 (1C, ArC≡*C*Ar), 92.9 (1C, ArC≡*C*CH$_2$), 123.2 (1C, C-1"$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$), 125.8 (1C, C-4"$_{4\text{-(6-fluorohex-1-yn-1-yl)phenyl}}$), 126.8 (1C, C-4'$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 128.7 (2C, C-2'$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 132.55 (2C, C$_{arom.}$), 132.60 (2C, C$_{arom.}$), 132.63 (2C, C$_{arom.}$), 136.7 (1C, C-1'$_{4\text{-\{[4-(6-fluorohex-1-yn-1-yl)phenyl]ethynyl\}benzoyl}}$), 171.6 (2C, Ar*C*ON, *C*ONHOH), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3180, 3073, 2919, 2867, 1652, 1634, 1598, 1422, 1222, 1088, 1069, 1049, 837, 764, 699, 624, 532;

HRMS (*m*/*z*): [M+Na]$^+$ calcd for $C_{26}H_{25}FN_2NaO_4$: 471.1691, found: 471.1747;

HPLC (method 2): t_R = 16.2 min, purity 92.9%.

Methyl (2*S*,4*S*)-4-hydroxy-1-(4-{[4-(6-hydroxyhexyl)phenyl]ethynyl}benzoyl)pyrrolidine-2-carboxylate (62a)



$C_{27}H_{31}NO_5$

M_r = 449.5

Under N_2 atmosphere, copper(I) iodide (2 mg, 0.010 mmol), tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.004 mmol), triethylamine (0.20 mL, 150 mg, 1.4 mmol), and **52** (97 mg, 0.48 mmol) were added to a solution of **59** (150 mg, 0.40 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate = 3/2 → 0/1) to give **62a** (180 mg, 0.40 mmol, 100%) as brown solid.

m.p. = 99-101 °C;

TLC: R_f = 0.30 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -17.9 (2.2, methanol);

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 1.22 – 1.35 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 1.36 – 1.45 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 1.52 – 1.62 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 1.80 – 1.88 (m, 1H, $NCHCH_2CH$), 2.38 – 2.47 (m, 1H, $NCHCH_2CH$), 2.56 – 2.65 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 3.32 – 3.43 (m, 3H, $CH_2CH_2CH_2CH_2CH_2CH_2OH$, NCH_2 (1H)), 3.60 (dd, J = 10.2/5.9 Hz, 1H, NCH_2), 3.66 (s, 3H, CO_2CH_3), 4.21 – 4.29 (m, 1H, $CHOH$), 4.32 (s br, 1H, CH_2OH), 4.58 (dd, J = 8.4/6.8 Hz, 1H, NCH), 5.15 – 5.21 (m, 1H, $CHOH$), 7.24 – 7.28 (m, 2H, 3''-$H_{4\text{-(6-hydroxyhexyl)phenyl}}$, 5''-$H_{4\text{-(6-hydroxyhexyl)phenyl}}$), 7.47 – 7.51 (m, 2H, 2''-$H_{4\text{-(6-hydroxyhexyl)phenyl}}$, 6''-$H_{4\text{-(6-hydroxyhexyl)phenyl}}$), 7.54 – 7.58 (m, 2H, 2'-$H_{4\text{-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$, 6'-$H_{4\text{-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$), 7.60 – 7.64 (m, 2H, 3'-$H_{4\text{-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$, 5'-$H_{4\text{-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$), two rotamers exist in the ratio 3/1, the signals of the major rotamer are given;

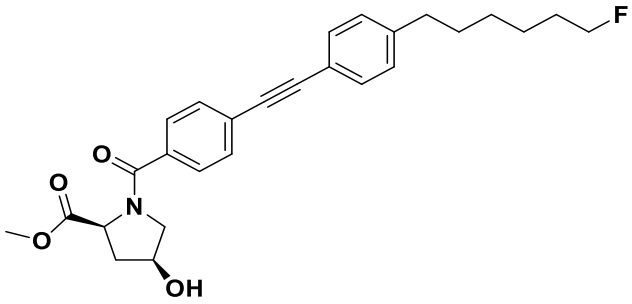
^{13}C NMR (126 MHz, DMSO-d_6): δ [ppm] = 25.2 (1C, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 28.5 (1C, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 30.6 (1C, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 32.4 (1C, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 34.9 (1C, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 36.8 (1C, $NCHCH_2CH$), 51.9 (1C, CO_2CH_3), 56.2 (1C, NCH_2), 57.2 (1C, NCH), 60.6 (1C, $CH_2CH_2CH_2CH_2CH_2CH_2OH$), 68.5 (1C, $CHOH$), 88.1 (1C, ArC≡CAr), 91.0 (1C, ArC≡CAr), 119.1 (1C, C-1''$_{\text{4-(6-hydroxyhexyl)phenyl}}$), 124.2 (1C, C-4'$_{\text{4-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$), 127.5 (2C, C-2'$_{\text{4-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{\text{4-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$), 128.7 (2C, C-3''$_{\text{4-(6-hydroxyhexyl)phenyl}}$, C-5''$_{\text{4-(6-hydroxyhexyl)phenyl}}$), 131.2 (2C, C-3'$_{\text{4-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$, C-5'$_{\text{4-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$), 131.4 (2C, C-2''$_{\text{4-(6-hydroxyhexyl)phenyl}}$, C-6''$_{\text{4-(6-hydroxyhexyl)phenyl}}$), 135.6 (1C, C-1'$_{\text{4-\{[4-(6-hydroxyhexyl)phenyl]ethynyl\}benzoyl}}$), 143.7 (1C, C-4''$_{\text{4-(6-hydroxyhexyl)phenyl}}$), 167.7 (1C, Ar$C$ON), 171.7 (1C, CO_2CH_3), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3385, 2925, 2853, 1750, 1594, 1435, 1348, 1211, 1178, 1088, 1052, 1018, 844, 820, 760, 520;

HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{32}NO_5$: 450.2275, found: 450.2289;

HPLC (method 1): t_R = 21.2 min, purity 84.2%.

Methyl (2*S*,4*S*)-1-(4-{[4-(6-fluorohexyl)phenyl]ethynyl}benzoyl)-4-hydroxypyrrolidine-2-carboxylate (63a)



$C_{27}H_{30}FNO_4$

M_r = 451.5

Under N_2 atmosphere, copper(I) iodide (2 mg, 0.010 mmol), tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.004 mmol), triethylamine (0.20 mL, 150 mg, 1.4 mmol), and **53** (160 mg, 0.79 mmol) were added to a solution of **59** (150 mg, 0.40 mmol) in dry acetonitrile (20 mL). After stirring the mixture for 1 h at ambient temperature, the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, dichloromethane/methanol = 1/0 → 9/1) and by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 10 g). Fractions containing the desired product were combined and subjected to lyophilization to give **63a** (30 mg, 0.066 mmol, 17%) as brown oil.

TLC: R_f = 0.48 (dichloromethane/methanol = 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -3.9 (2.5, methanol);

^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 1.28 – 1.41 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CH_2F$), 1.56 – 1.68 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CH_2F$), 1.81 – 1.86 (m, 1H, NCHC*H*$_2$CH), 2.43 (ddd, *J* = 12.5/8.6/5.8 Hz, 1H, NCHC*H*$_2$CH), 2.59 – 2.64 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2F$), 3.36 (dd, *J* = 10.3/5.7 Hz, 1H, NC*H*$_2$), 3.60 (dd, *J* = 10.3/5.9 Hz, 1H, NC*H*$_2$), 3.66 (s, 3H, CO_2CH_3), 4.21 – 4.28 (m, 1H, C*H*OH), 4.42 (dt, *J* = 47.6/6.1 Hz, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2F$), 4.58 (dd, *J* = 8.5/6.9 Hz, 1H, NC*H*), 5.19 (d, *J* = 4.2 Hz, 1H, CHO*H*), 7.25 – 7.29 (m, 2H, 3''-H$_{4\text{-(6-fluorohexyl)phenyl}}$, 5''-H$_{4\text{-(6-fluorohexyl)phenyl}}$), 7.47 – 7.51 (m, 2H, 2''-H$_{4\text{-(6-fluorohexyl)phenyl}}$, 6''-H$_{4\text{-(6-fluorohexyl)phenyl}}$), 7.54 – 7.58 (m, 2H, 2'-H$_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$),

6'-$H_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$), 7.60 – 7.64 (m, 2H, 3'-$H_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$, 5'-$H_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$), the signals of the major rotamer are given;

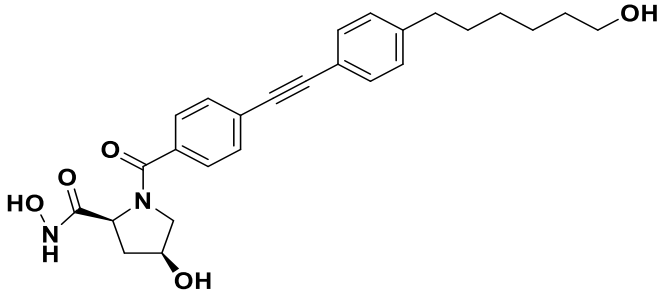
^{13}C NMR (151 MHz, DMSO-d_6): δ [ppm] = 24.5 (d, J = 5.3 Hz, 1C, $CH_2CH_2CH_2\mathit{C}H_2CH_2CH_2F$), 28.2 (1C, $CH_2CH_2\mathit{C}H_2CH_2CH_2CH_2F$), 29.7 (d, J = 19.1 Hz, 1C, $CH_2CH_2CH_2CH_2\mathit{C}H_2CH_2F$), 30.5 (1C, $CH_2\mathit{C}H_2CH_2CH_2CH_2CH_2F$), 34.9 (1C, $\mathit{C}H_2CH_2CH_2CH_2CH_2CH_2F$), 36.8 (1C, NCH$\mathit{C}H_2$CH), 51.9 (1C, $CO_2\mathit{C}H_3$), 56.2 (1C, N$\mathit{C}H_2$), 57.3 (1C, NCH), 68.5 (1C, CHOH), 83.8 (d, J = 161.6 Hz, 1C, $CH_2CH_2CH_2CH_2CH_2\mathit{C}H_2F$), 88.1 (1C, Ar$\mathit{C}$≡CAr), 91.1 (1C, ArC≡$\mathit{C}$Ar), 119.2 (1C, C-1''$_{4\text{-}(6\text{-fluorohexyl})phenyl}$), 124.2 (1C, C-4'$_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$), 127.6 (2C, C-2'$_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$, C-6'$_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$), 128.8 (2C, C-3''$_{4\text{-}(6\text{-fluorohexyl})phenyl}$, C-5''$_{4\text{-}(6\text{-fluorohexyl})phenyl}$), 131.2 (2C, C-3'$_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$, C-5'$_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$), 131.4 (2C, C-2''$_{4\text{-}(6\text{-fluorohexyl})phenyl}$, C-6''$_{4\text{-}(6\text{-fluorohexyl})phenyl}$), 135.6 (1C, C-1'$_{4\text{-}\{[4\text{-}(6\text{-fluorohexyl})phenyl]ethynyl\}benzoyl}$), 143.7 (1C, C-4''$_{4\text{-}(6\text{-fluorohexyl})phenyl}$), 167.7 (1C, Ar$\mathit{C}$ON), 171.8 (1C, $\mathit{C}O_2CH_3$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3385, 2931, 2856, 1744, 1621, 1419, 1204, 1177, 1089, 1048, 1024, 1004, 824, 763, 540;

HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{31}FNO_4$: 452.2232, found: 452.2241;

HPLC (method 1): t_R = 24.2 min, purity 83.4%.

(2*S*,4*S*)-*N*,4-Dihydroxy-1-(4-{[4-(6-hydroxyhexyl)phenyl]ethynyl}benzoyl)pyrrolidine-2-carboxamide (62)



$C_{26}H_{30}N_2O_5$

M_r = 450.5

An aqueous solution of hydroxylamine (50 wt%, 7.6 mL) was added to a solution of **62a** (130 mg, 0.29 mmol) in a mixture of THF (6 mL) and isopropanol (6 mL). After stirring the reaction mixture for 24 h at ambient temperature, brine was added and the mixture was

extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 10 g). Fractions containing the desired product were combined and subjected to lyophilization to give **62** (40 mg, 0.089 mmol, 31%) as colorless solid.

m.p. = 149-151 °C (decomposition);

TLC: R_f = 0.10 (dichloromethane/methanol = 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +16.7 (0.75, methanol);

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.34 – 1.44 (m, 4H, $CH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2CH_2OH$), 1.50 – 1.57 (m, 2H, $CH_2CH_2CH_2CH_2C\mathit{H}_2CH_2OH$), 1.62 – 1.69 (m, 2H, $CH_2C\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 1.98 – 2.05 (m, 1H, $NCHC\mathit{H}_2CH$), 2.50 (ddd, *J* = 13.1/8.8/5.7 Hz, $NCHC\mathit{H}_2CH$), 2.65 (t, *J* = 7.7 Hz, 2H, $C\mathit{H}_2CH_2CH_2CH_2CH_2CH_2OH$), 3.51 – 3.57 (m, 3H, $CH_2CH_2CH_2CH_2CH_2C\mathit{H}_2OH$, $NC\mathit{H}_2$ (1H)), 3.72 (dd, *J* = 10.7/5.4 Hz, 1H, $NC\mathit{H}_2$), 4.28 – 4.33 (m, 1H, C*H*OH), 4.52 (dd, *J* = 8.7/5.7 Hz, 1H, NC*H*), 7.19 – 7.25 (m, 2H, 3"-$H_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$, 5"-$H_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$), 7.40 – 7.47 (m, 2H, 2"-$H_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$, 6"-$H_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$), 7.52 – 7.64 (m, 4H, 2'-$H_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$, 3'-$H_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$, 5'-$H_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$, 6'-$H_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$);

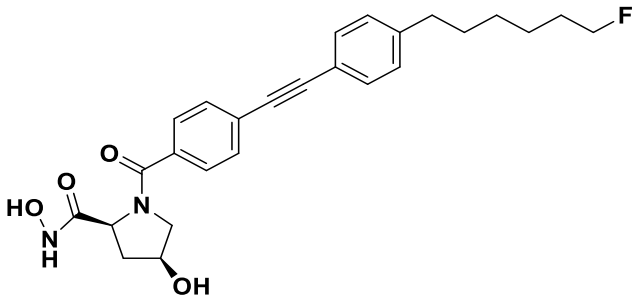
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 26.8 (1C, $CH_2CH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 30.1 (1C, $CH_2CH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.4 (1C, $CH_2\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 33.6 (1C, $CH_2CH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 36.8 (1C, $\mathit{C}H_2CH_2CH_2CH_2CH_2CH_2OH$), 38.2 (1C, $NCH\mathit{C}H_2CH$), 58.7 (1C, N*C*), 58.8 (1C, N*C*), 62.9 (1C, $CH_2CH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 70.9 (1C, *C*HOH), 88.7 (1C, Ar*C*≡CAr), 92.4 (1C, ArC≡*C*Ar), 121.3 (1C, C-1"$_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$), 127.2 (1C, C-4'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$), 128.6 (2C, C-2'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$, C-6'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$), 129.7 (2C, C-3"$_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$, C-5"$_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$), 132.4 (2C, C-3'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$, C-5'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$), 132.6 (2C, C-2"$_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$, C-6"$_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$), 136.4 (1C, C-1'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhexyl})phenyl]ethynyl\}benzoyl}$), 145.2 (1C, C-4"$_{4\text{-}(6\text{-hydroxyhexyl})phenyl}$), 171.6 (1C, *C*=O), 171.7 (1C, *C*=O);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3430, 3179, 3075, 2925, 2852, 1680, 1651, 1630, 1595, 1423, 1090, 1069, 1051, 850, 764, 688, 620, 522;

HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{26}H_{31}N_2O_5$: 451.2227, found: 451.2270;

HPLC (method 2): t_R = 14.8 min, purity 99.0%.

(2*S*,4*S*)-1-(4-{[4-(6-Fluorohexyl)phenyl]ethynyl}benzoyl)-*N*,4-dihydroxypyrrolidine-2-carboxamide (63)



$C_{26}H_{29}FN_2O_4$

M_r = 452.5

An aqueous solution of hydroxylamine (50 wt%, 3.8 mL) was added to a solution of **63a** (64 mg, 0.14 mmol) in a mixture of THF (15 mL) and isopropanol (15 mL). After stirring the reaction mixture for 48 h at ambient temperature, brine was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 10 g). Fractions containing the desired product were combined and subjected to lyophilization to give **63** (40 mg, 0.088 mmol, 63%) as colorless solid.

m.p. = 140-142 °C (decomposition);

TLC: R_f = 0.10 (dichloromethane/methanol = 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +46.8 (1.6, methanol);

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.36 – 1.48 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CH_2F$), 1.62 – 1.72 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CH_2F$), 1.98 – 2.06 (m, 1H, NCHCH_2CH), 2.50 (ddd, *J* = 13.1/8.8/5.7 Hz, 1H, NCHCH_2CH), 2.63 – 2.67 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2F$), 3.55 (dd, *J* = 10.7/4.7 Hz, 1H, NCH_2), 3.72 (dd, *J* = 10.7/5.4 Hz, 1H, NCH_2), 4.28 – 4.33 (m, 1H, C*H*OH), 4.40 (dt, *J* = 47.6/6.1 Hz, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2F$),

4.53 (dd, *J* = 8.7/5.7 Hz, 1H, NC*H*), 7.20 – 7.24 (m, 2H, 3''-$H_{4\text{-(6-fluorohexyl)phenyl}}$, 5''-$H_{4\text{-(6-fluorohexyl)phenyl}}$), 7.42 – 7.46 (m, 2H, 2''-$H_{4\text{-(6-fluorohexyl)phenyl}}$, 6''-$H_{4\text{-(6-fluorohexyl)phenyl}}$), 7.56 – 7.63 (m, 4H, 2'-$H_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$, 3'-$H_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$, 5'-$H_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$, 6'-$H_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$);

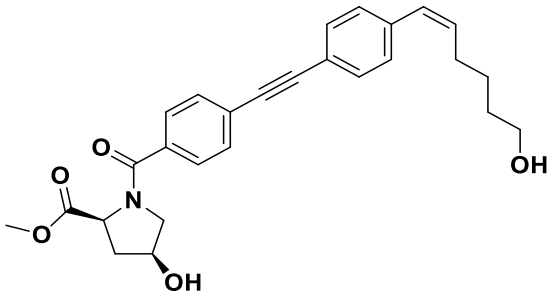
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 26.2 (d, *J* = 5.3 Hz, 1C, $CH_2CH_2CH_2\mathit{C}H_2CH_2CH_2F$), 29.9 (1C, $CH_2CH_2\mathit{C}H_2CH_2CH_2CH_2F$), 31.5 (d, *J* = 19.6 Hz, 1C, $CH_2CH_2CH_2CH_2\mathit{C}H_2CH_2F$), 32.3 (1C, $CH_2\mathit{C}H_2CH_2CH_2CH_2CH_2F$), 36.7 (1C, $\mathit{C}H_2CH_2CH_2CH_2CH_2CH_2F$), 38.2 (1C, NCH$\mathit{C}H_2$CH), 58.7 (1C, N*C*), 58.8 (1C, N*C*), 70.9 (1C, *C*HOH), 84.8 (d, *J* = 163.6 Hz, 1C, $CH_2CH_2CH_2CH_2CH_2\mathit{C}H_2F$), 88.7 (1C, Ar*C*≡CAr), 92.4 (1C, ArC≡*C*Ar), 121.3 (1C, C-1''$_{4\text{-(6-fluorohexyl)phenyl}}$), 127.2 (1C, C-4'$_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$), 128.6 (2C, C-2'$_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$), 129.7 (2C, C-3''$_{4\text{-(6-fluorohexyl)phenyl}}$, C-5''$_{4\text{-(6-fluorohexyl)phenyl}}$), 132.4 (2C, C-3'$_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$, C-5'$_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$), 132.7 (2C, C-2''$_{4\text{-(6-fluorohexyl)phenyl}}$, C-6''$_{4\text{-(6-fluorohexyl)phenyl}}$), 136.4 (1C, C-1'$_{4\text{-\{[4-(6-fluorohexyl)phenyl]ethynyl\}benzoyl}}$), 145.2 (1C, C-4''$_{4\text{-(6-fluorohexyl)phenyl}}$), 171.6 (1C, *C*=O), 171.7 (1C, *C*=O);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3182, 2924, 2853, 1635, 1600, 1421, 1088, 1069, 1050, 1017, 974, 850, 764, 722, 694, 616, 540;

HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{29}FN_2NaO_4$: 475.2004, found: 475.2020;

HPLC (method 2): t_R = 16.7 min, purity 96.5%.

Methyl (2*S*,4*S*)-4-hydroxy-1-(4-{[4-((*Z*)-6-hydroxyhex-1-en-1-yl)phenyl]ethynyl}benzoyl)pyrrolidine-2-carboxylate (64a)



$C_{27}H_{29}NO_5$

M_r = 447.5

Under N_2 atmosphere, copper(I) iodide (1 mg, 0.005 mmol), tetrakis(triphenylphosphine)palladium(0) (2 mg, 0.002 mmol), triethylamine (0.09 mL, 65 mg, 0.64 mmol), and **55** (52 mg, 0.26 mmol) were added to a solution of **59** (80 mg, 0.21 mmol) in dry acetonitrile (25 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate = 1/0 → 3/2) to give **64a** (80 mg, 0.18 mmol, 84%) as yellow oil.

TLC: R_f = 0.30 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = +7.7 (1.1, methanol);

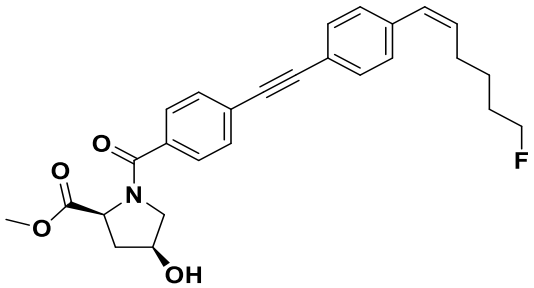
^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ [ppm] = 1.42 – 1.50 (m, 4H, $CH_2CH_2CH_2CH_2OH$), 1.80 – 1.87 (m, 1H, $CHCH_2CH$), 2.28 – 2.36 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 2.43 (ddd, *J* = 12.5/8.5/5.8 Hz, 1H, $CHCH_2CH$), 3.34 – 3.43 (m, 3H, $CH_2CH_2CH_2CH_2OH$, NCH_2 (1H)), 3.60 (dd, *J* = 10.2/5.9 Hz, 1H, NCH_2), 3.67 (s, 3H, CO_2CH_3), 4.21 – 4.30 (m, 1H, CHOH), 4.56 – 4.61 (m, 1H, NCH), 5.70 – 5.77 (m, 1H, $ArCH=CHCH_2$), 6.40 – 6.47 (m, 1H, $ArCH=CHCH_2$), 7.33 – 7.39 (m, 2H, 3''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 5''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 7.53 – 7.59 (m, 4H, 2''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 6''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 2'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 7.61 – 7.66 (m, 2H, 3'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 5'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3377, 2932, 2860, 1732, 1606, 1428, 1212, 1176, 1085, 1044, 846, 763, 540;

HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{30}NO_5$: 448.2118, found: 448.2145;

HPLC (method 1): t_R = 20.6 min, purity 79.4%.

Methyl (2*S*,4*S*)-1-(4-{[4-((*Z*)-6-fluorohex-1-en-1-yl)phenyl]ethynyl}benzoyl)-4-hydroxypyrrolidine-2-carboxylate (65a)



$C_{27}H_{28}FNO_4$

M_r = 449.5

Under N_2 atmosphere, copper(I) iodide (5 mg, 0.026 mmol), tetrakis(triphenylphosphine)palladium(0) (11 mg, 0.010 mmol), and triethylamine (0.40 mL, 290 mg, 2.8 mmol) were added to a solution of **59** (350 mg, 0.93 mmol) in dry acetonitrile (25 mL). Then, a solution of **56** (280 mg, 1.4 mmol) in dry acetonitrile (2 mL) was added dropwise. After stirring the reaction mixture for 1 h at ambient temperature, the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, dichloromethane/methanol = 1/0 → 95/5) and by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 10 g). Fractions containing the desired product were combined and subjected to lyophilization to give **65a** (130 mg, 0.29 mmol, 31%) as yellowish-brown oil.

TLC: R_f = 0.60 (dichloromethane/methanol = 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -29.6 (1.4, methanol);

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.55 – 1.62 (m, 2H, $CH_2CH_2CH_2CH_2F$), 1.66 – 1.76 (m, 2H, $CH_2CH_2CH_2CH_2F$), 2.07 (dt, *J* = 13.1/5.5 Hz, 1H, NCHCH_2CH), 2.37 – 2.43 (m, 2H, $CH_2CH_2CH_2CH_2F$), 2.52 (ddd, *J* = 13.1/8.9/5.4 Hz, 1H, NCHCH_2CH),

3.52 (dd, *J* = 10.8/4.6 Hz, 1H, NC*H*$_2$), 3.70 (dd, *J* = 10.8/5.5 Hz, 1H, NC*H*$_2$), 3.78 (s, 3H, CO_2C*H*$_3$), 4.35 – 4.46 (m, 3H, $CH_2CH_2CH_2C$*H*$_2$F, C*H*OH), 4.73 (dd, *J* = 8.9/5.6 Hz, 1H, NC*H*), 5.71 – 5.77 (m, 1H, ArCH=C*H*CH$_2$), 6.43 – 6.48 (m, 1H, ArC*H*=CHCH$_2$), 7.29 – 7.33 (m, 2H, 3''-H$_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$, 5''-H$_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$), 7.49 – 7.53 (m, 2H, 2''-H$_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$, 6''-H$_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$), 7.57 – 7.64 (m, 4H, 2'-H$_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$,

3'-H$_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 5'-H$_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-H$_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), the signals of the major rotamer are given;

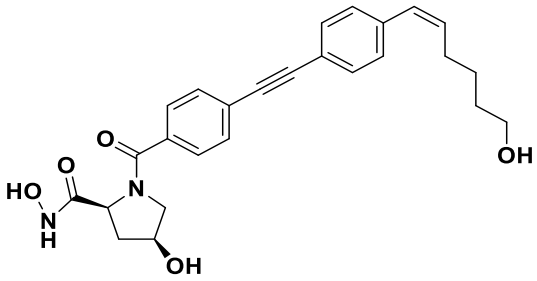
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 26.6 (d, *J* = 5.1 Hz, 1C, CH_2*C*$H_2CH_2CH_2$F), 29.3 (1C, *C*$H_2CH_2CH_2CH_2$F), 31.1 (d, *J* = 19.7 Hz, 1C, CH_2CH_2*C*H_2CH_2F), 38.1 (1C, NCH*C*H_2CH), 52.9 (1C, CO_2*C*H_3), 57.9 (1C, N*C*H_2), 59.2 (1C, N*C*H), 70.6 (1C, *C*HOH), 84.6 (d, *J* = 163.9 Hz, 1C, $CH_2CH_2CH_2$*C*H_2F), 89.5 (1C, Ar*C*≡CAr), 92.2 (1C, ArC≡*C*Ar), 122.2 (1C, C-1''$_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$), 127.0 (1C, C-4'$_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 128.5 (2C, C-2'$_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 129.8 (1C, Ar*C*H=CHCH$_2$), 130.0 (2C, C-3''$_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$, C-5''$_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$), 132.5 (2C, $C_{arom.}$), 132.6 (2C, $C_{arom.}$), 134.6 (1C, ArCH=*C*HCH$_2$), 136.6 (1C, C-1'$_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 139.6 (1C, C-4''$_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$), 171.4 (1C, Ar*C*ON), 173.7 (1C, *C*O_2CH_3);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3401, 2951, 2869, 2215, 1735, 1606, 1417, 1204, 1176, 1086, 1046, 1017, 969, 928, 846, 763, 541;

HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{27}H_{29}FNO_4$: 450.2075, found: 450.2041;

HPLC (method 1): t_R = 23.7 min, purity 80.1%.

2*S*,4*S*)-*N*,4-Dihydroxy-1-(4-{[4-((*Z*)-6-hydroxyhex-1-en-1-yl)phenyl]ethynyl}benzoyl)pyrrolidine-2-carboxamide (64)



$C_{26}H_{28}N_2O_5$

M_r = 448.5

An aqueous solution of hydroxylamine (50 wt%, 4.1 mL) was added to a solution of **64a** (70 mg, 0.16 mmol) in a mixture of THF (10 mL) and isopropanol (10 mL). After stirring the reaction mixture for 24 h at ambient temperature, brine was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 10 g). Fractions containing the desired product were combined and subjected to lyophilization to give **64** (25 mg, 0.056 mmol, 36%) as colorless solid.

m.p. = 127-129 °C (decomposition);

TLC: R_f = 0.20 (dichloromethane/methanol = 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +18.8 (1.7, methanol);

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.51 – 1.61 (m, 4H, $CH_2CH_2CH_2CH_2OH$), 1.98 – 2.05 (m, 1H, $CHCH_2CH$), 2.35 – 2.42 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 2.50 (ddd, *J* = 13.1/8.7/5.7 Hz, 1H, $CHCH_2CH$), 3.51 – 3.58 (m, 3H, $CH_2CH_2CH_2CH_2OH$, NCH_2 (1H)), 3.72 (dd, *J* = 10.7/5.4 Hz, 1H, NCH_2), 4.27 – 4.34 (m, 1H, CHOH), 4.53 (dd, *J* = 8.7/5.7 Hz, 1H, NCH), 5.75 (dt, *J* = 11.7/7.3 Hz, 1H, $ArCH=CHCH_2$), 6.42 – 6.46 (m, 1H, $ArCH=CHCH_2$), 7.29 – 7.34 (m, 2H, 3''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 5''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 7.47 – 7.53 (m, 2H, 2''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 6''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 7.53 – 7.64 (m, 4H, 2'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 3'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 5'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), the signals of the major rotamer are given;

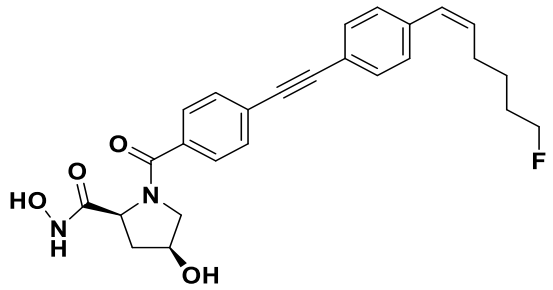
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 27.2 (1C, $CH_2CH_2CH_2CH_2OH$), 29.5 (1C, $CH_2CH_2CH_2CH_2OH$), 33.2 (1C, $CH_2CH_2CH_2CH_2OH$), 38.2 (1C, NCHCH$_2$CH), 58.7 (1C, NC), 58.8 (1C, NC), 62.7 (1C, $CH_2CH_2CH_2CH_2OH$), 70.9 (1C, CHOH), 89.5 (1C, ArC≡CAr), 92.2 (1C, ArC≡CAr), 122.1 (1C, C-1"$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 127.0 (1C, C-4'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 128.7 (2C, C-2'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 129.5 (1C, ArCH=CHCH$_2$), 130.0 (2C, C-3"$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, C-5"$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 132.5 (4C, C-3'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-5'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-2"$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, C-6"$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 135.0 (1C, ArCH=CHCH$_2$), 136.6 (1C, C-1'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 139.7 (1C, C-4"$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 171.6 (2C, C=O);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3189, 2931, 2865, 1680, 1652, 1631, 1594, 1421, 1088, 1071, 1050, 846, 764, 530;

HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{28}N_2NaO_5$: 471.1890, found: 471.1884;

HPLC (method 2): t_R = 14.7 min, purity 97.9%.

(2*S*,4*S*)-1-(4-{[4-((*Z*)-6-Fluorohex-1-en-1-yl)phenyl]ethynyl}benzoyl)-*N*,4-dihydroxypyrrolidine-2-carboxamide (65)



$C_{26}H_{27}FN_2O_4$

M_r = 450.5

An aqueous solution of hydroxylamine (50 wt%, 3.5 mL) was added to a solution of **65a** (60 mg, 0.13 mmol) in a mixture of THF (10 mL) and isopropanol (10 mL). After stirring the reaction mixture for 48 h at ambient temperature, brine was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage®

SNAP KP-C18-HS 10 g). Fractions containing the desired product were combined and subjected to lyophilization to give **65** (30 mg, 0.067 mmol, 50%) as colorless solid.

m.p. = 143-145 °C (decomposition);

TLC: R_f = 0.18 (dichloromethane/methanol = 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +24.3 (1.1, methanol);

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.55 – 1.62 (m, 2H, $CH_2CH_2CH_2CH_2F$), 1.67 – 1.77 (m, 2H, $CH_2CH_2CH_2CH_2F$), 1.99 – 2.05 (m, 1H, $NCHCH_2CH$), 2.37 – 2.43 (m, 2H, $CH_2CH_2CH_2CH_2F$), 2.50 (ddd, *J* = 13.1/8.8/5.6 Hz, 1H, $NCHCH_2CH$), 3.55 (dd, *J* = 10.7/4.7 Hz, 1H, NCH_2), 3.72 (dd, *J* = 10.7/5.4 Hz, 1H, NCH_2), 4.28 – 4.33 (m, 1H, CHOH), 4.41 (dt, *J* = 47.5/6.0 Hz, 2H, $CH_2CH_2CH_2CH_2F$), 4.53 (dd, *J* = 8.7/5.6 Hz, 1H, NCH), 5.74 (dt, *J* = 11.7/7.3 Hz, 1H, $ArCH=CHCH_2$), 6.44 – 6.49 (m, 1H, $ArCH=CHCH_2$), 7.28 – 7.35 (m, 2H, 3''-$H_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$, 5''-$H_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$),

7.47 – 7.53 (m, 2H, 2''-$H_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$, 6''-$H_{4\text{-(6-fluorohex-1-en-1-yl)phenyl}}$), 7.56 – 7.66 (m, 4H, 2'-$H_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 3'-$H_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 5'-$H_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-$H_{4\text{-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), the signals of the major rotamer are given;

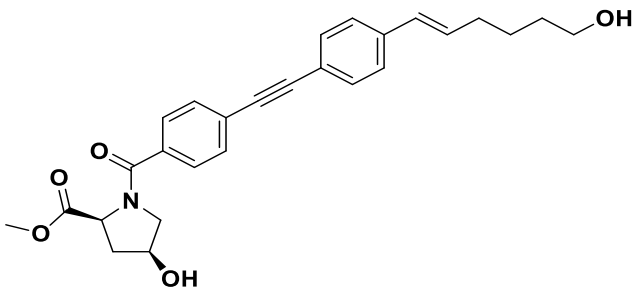
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 26.6 (d, *J* = 5.0 Hz, 1C, $CH_2CH_2CH_2CH_2F$), 29.3 (1C, $CH_2CH_2CH_2CH_2F$), 31.2 (d, *J* = 19.6 Hz, 1C, $CH_2CH_2CH_2CH_2F$), 38.2 (1C, $NCHCH_2CH$), 58.7 (1C, NC), 58.8 (1C, NC), 70.9 (1C, CHOH), 84.6 (d, *J* = 163.9 Hz, 1C, $CH_2CH_2CH_2CH_2F$), 89.5 (1C, ArC≡CAr), 92.2 (1C, ArC≡CAr), 122.2 (1C, C-1''$_{\text{4-(6-fluorohex-1-en-1-yl)phenyl}}$), 127.0 (1C, C-4'$_{\text{4-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 128.7 (2C, C-2'$_{\text{4-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{\text{4-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 129.8 (1C, $ArCH=CHCH_2$), 130.0 (2C, C-3''$_{\text{4-(6-fluorohex-1-en-1-yl)phenyl}}$, C-5''$_{\text{4-(6-fluorohex-1-en-1-yl)phenyl}}$), 132.5 (4C, C-3'$_{\text{4-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-5'$_{\text{4-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-2''$_{\text{4-(6-fluorohex-1-en-1-yl)phenyl}}$, C-6''$_{\text{4-(6-fluorohex-1-en-1-yl)phenyl}}$), 134.6 (1C, $ArCH=CHCH_2$), 139.6 (1C, C-4''$_{\text{4-(6-fluorohex-1-en-1-yl)phenyl}}$), 171.6 (2C, C=O), the signal for C-1'$_{\text{4-\{[4-(6-fluorohex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$ cannot be observed in the spectrum;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3187, 3054, 2903, 2220, 1634, 1604, 1435, 1422, 1176, 1118, 1088, 846, 763, 720, 693, 538;

HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{27}FN_2NaO_4$: 473.1847, found: 473.1870;

HPLC (method 2): t_R = 16.5 min, purity 98.8%.

Methyl (2*S*,4*S*)-4-hydroxy-1-(4-{[4-((*E*)-6-hydroxyhex-1-en-1-yl)phenyl]ethynyl}benzoyl)pyrrolidine-2-carboxylate (66a)



$C_{27}H_{29}NO_5$

M_r = 447.5

Under N_2 atmosphere, copper(I) iodide (3 mg, 0.016 mmol), tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol), triethylamine (0.20 mL, 150 mg, 1.4 mmol), and **47** (120 mg, 0.58 mmol) were added to a solution of **59** (180 mg, 0.48 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **66a** (190 mg, 0.42 mmol, 87%) as yellowish-brown solid.

m.p. = 125-127 °C;

TLC: R_f = 0.20 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -1.8 (0.85, methanol);

^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 1.44 – 1.51 (m, 4H, $CH_2CH_2CH_2CH_2OH$), 1.81 – 1.86 (m, 1H, $NCHCH_2CH$), 2.17 – 2.25 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 2.40 – 2.46 (m, 1H, $NCHCH_2CH$), 3.36 (dd, *J* = 10.3/5.7 Hz, 1H, NCH_2), 3.39 – 3.45 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 3.60 (dd, *J* = 10.2/5.9 Hz, 1H, NCH_2), 3.66 (s, 3H, CO_2CH_3), 4.22 – 4.29 (m, 1H, $CHOH$), 4.58 (dd, *J* = 8.5/6.8 Hz, 1H, NC*H*), 6.37 – 6.46 (m, 2H, $ArCH=CHCH_2$), 7.44 – 7.47 (m, 2H, 3''-$H_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 5''-$H_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 7.49 – 7.53 (m, 2H, 2''-$H_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 6''-$H_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 7.54 – 7.58 (m, 2H, 2'-$H_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-$H_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$),

7.61 – 7.64 (m, 2H, 3'-H$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$, 5'-H$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), the signals of the major rotamer are given;

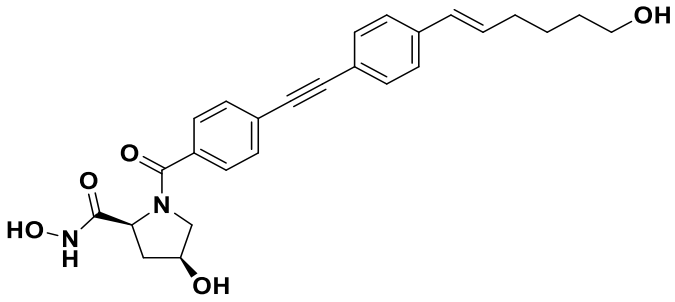
^{13}C NMR (151 MHz, DMSO-d_6): δ [ppm] = 25.2 (1C, $CH_2CH_2CH_2CH_2OH$), 32.1 (1C, $CH_2CH_2CH_2CH_2OH$), 32.3 (1C, $CH_2CH_2CH_2CH_2OH$), 36.8 (1C, $NCHCH_2CH$), 51.9 (1C, CO_2CH_3), 56.2 (1C, NCH_2), 57.2 (1C, NCH), 60.5 (1C, $CH_2CH_2CH_2CH_2OH$), 68.5 (1C, CHOH), 89.1 (1C, ArC≡CAr), 120.0 (1C, C-1"$_{4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}}$), 124.1 (1C, C-4'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), 126.1 (2C, C-3"$_{4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}}$, C-5"$_{4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}}$), 127.6 (2C, C-2'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$, C-6'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), 128.9 (1C, ArCH=$CHCH_2$), 131.2 (2C, C-3'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$, C-5'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), 131.7 (2C, C-2"$_{4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}}$, C-6"$_{4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}}$), 132.8 (1C, ArCH=$CHCH_2$), 135.7 (1C, C-1'$_{4\text{-}\{[4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}]\text{ethynyl}\}\text{benzoyl}}$), 138.1 (1C, C-4"$_{4\text{-}(6\text{-hydroxyhex-1-en-1-yl})\text{phenyl}}$), 167.7 (1C, ArCON), 171.7 (1C, CO_2CH_3), the signal for ArC≡CAr cannot be observed in the spectrum;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3385, 2927, 2854, 1749, 1594, 1434, 1345, 1213, 1177, 1087, 1052, 966, 843, 810, 760, 617, 525;

HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{30}NO_5$: 448.2118, found: 448.2093;

HPLC (method 1): t_R = 20.6 min, purity 98.3%.

(2*S*,4*S*)-*N*,4-Dihydroxy-1-(4-{[4-((*E*)-6-hydroxyhex-1-en-1-yl)phenyl]ethynyl}benzoyl)pyrrolidine-2-carboxamide (66)



$C_{26}H_{28}N_2O_5$

M_r = 448.5

An aqueous solution of hydroxylamine (50 wt%, 8.3 mL) was added to a solution of **66a** (140 mg, 0.31 mmol) in a mixture of THF (10 mL) and isopropanol (10 mL). After stirring the reaction mixture for 48 h at ambient temperature, brine was added and the mixture was

extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 10 g). Fractions containing the desired product were combined and subjected to lyophilization to give **66** (25 mg, 0.056 mmol, 18%) as colorless solid.

m.p. = 148-150 °C (decomposition);

TLC: R_f = 0.18 (dichloromethane/methanol = 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +13.8 (1.1, methanol);

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 1.52 – 1.65 (m, 4H, $CH_2CH_2CH_2CH_2OH$), 1.99 – 2.05 (m, 1H, $NCHCH_2CH$), 2.25 – 2.30 (m, 2H, $CH_2CH_2CH_2CH_2OH$), 2.50 (ddd, *J* = 13.1/8.8/5.7 Hz, 1H, $NCHCH_2CH$), 3.52 – 3.57 (m, 1H, NCH_2), 3.59 (t, *J* = 6.3 Hz, 2H, $CH_2CH_2CH_2CH_2OH$), 3.72 (dd, *J* = 10.8/5.5 Hz, 1H, NCH_2), 4.28 – 4.33 (m, 1H, $CHOH$), 4.52 (dd, *J* = 8.7/5.7 Hz, 1H, NCH), 6.33 – 6.39 (m, 1H, $ArCH=CHCH_2$), 6.41 – 6.46 (m, 1H, $ArCH=CHCH_2$), 7.36 – 7.41 (m, 2H, 3''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 5''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 7.42 – 7.48 (m, 2H, 2''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, 6''-H$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 7.56 – 7.63 (m, 4H, 2'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 3'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 5'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, 6'-H$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), the signals of the major rotamer are given;

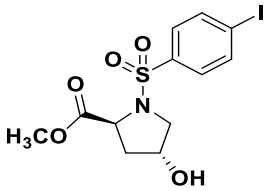
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 26.7 (1C, $CH_2CH_2CH_2CH_2OH$), 33.2 (1C, $CH_2CH_2CH_2CH_2OH$), 33.9 (1C, $CH_2CH_2CH_2CH_2OH$), 38.2 (1C, $NCHCH_2CH$), 58.7 (1C, NC), 58.8 (1C, NC), 62.8 (1C, $CH_2CH_2CH_2CH_2OH$), 70.9 (1C, $CHOH$), 89.6 (1C, ArC≡CAr), 92.3 (1C, ArC≡CAr), 122.3 (1C, C-1''$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 127.1 (3C, C-4'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-3''$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, C-5''$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 128.7 (2C, C-2'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-6'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 130.7 (1C, $ArCH=CHCH_2$), 132.5 (2C, C-3'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$, C-5'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 132.9 (2C, C-2''$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$, C-6''$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 133.4 (1C, $ArCH=CHCH_2$), 136.5 (1C, C-1'$_{4\text{-\{[4-(6-hydroxyhex-1-en-1-yl)phenyl]ethynyl\}benzoyl}}$), 139.9 (1C, C-4''$_{4\text{-(6-hydroxyhex-1-en-1-yl)phenyl}}$), 171.6 (2C, C=O);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3191, 2927, 2858, 1599, 1419, 1088, 1069, 1051, 1015, 969, 851, 806, 764, 695, 619, 541, 527;

HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{28}N_2NaO_5$: 471.1890, found: 471.1903;

HPLC (method 2): t_R = 14.6 min, purity 96.0%.

Methyl (2*S*,4*R*)-4-hydroxy-1-[(4-iodophenyl)sulfonyl]pyrrolidine-2-carboxylate (68)



$C_{12}H_{14}INO_5S$

M_r = 411.2

Triethylamine (2.5 mL, 1857 mg, 15 mmol) was added to an ice-cooled solution of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**57**) (1380 g, 7.6 mmol) in dichloromethane (20 mL) and the mixture was stirred for 15 min at 0 °C. Then, 4-dimethylaminopyridine (93 mg, 0.76 mmol) and 4- benzenesulfonyl chloride (2.3 g, 7.60 mmol) were added and the mixture was stirred for 2 h at ambient temperature. Afterwards, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with dichloromethane (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, ethyl acetate) to give **68** (2.5 g, 9.0 mmol, 81%) as colorless oil.

TLC: R_f = 0.48 (petroleum ether/ethyl acetate, 1/2);

Specific rotation: $[\alpha]_D^{20}$ = -78.6 (1.4, methanol);

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ [ppm]= 1.89 – 2.06 (m, 2H, CHC*H*$_2$CH), 3.14 (m, *J* = 10.9/1.8 Hz, 1H, NC*H*$_2$), 3.47 (dd, *J* = 10.8/3.9 Hz, 1H, NC*H*$_2$), 3.66 (s, 3H, CO_2CH_3), 4.15 (m, *J* = 8.5/7.5 Hz, 1H, NC*H*), 4.18 – 4.24 (m, 1H, C*H*OH*)*, 4.87 (d, *J* = 3.1 Hz, 1H, CHO*H)*, 7.51 – 7.57 (m, 2H, 2′-H$_{(4\text{-iodophenyl)sulfonyl}}$, 6′-H$_{(4\text{-iodophenyl)sulfonyl}}$), 7.96 – 8.02 (m, 2H, 3′-H$_{(4\text{-iodophenyl)sulfonyl}}$, 5′-H$_{(4\text{-iodophenyl)sulfonyl}}$);

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ [ppm]= 38.9 (1C, CH*C*H$_2$CH), 52.3 (1C, CO_2CH_3), 56.4 (1C, N*C*H$_2$), 59.5 (1C, N*C*H), 68.4 (1C, *C*HOH), 101.5 (1C, C-4′$_{(4\text{-iodophenyl)sulfonyl}}$),

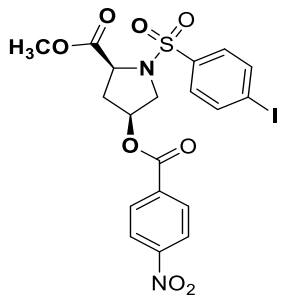
129.0 (2C, C-2′$_{(4\text{-iodophenyl})\text{sulfonyl}}$, C-6′$_{(4\text{-iodophenyl})\text{sulfonyl}}$), 136.7 (1C, C-1′$_{(4\text{-iodophenyl})\text{sulfonyl}}$), 138.0 (2C, C-3′$_{(4\text{-iodophenyl})\text{sulfonyl}}$, C-5′$_{(4\text{-iodophenyl})\text{sulfonyl}}$), 172.1 (1C, CO_2CH_3);

IR (neat): ṽ [cm^{-1}] = 3515, 2951, 1733, 1569, 1437, 1373, 1333, 1199, 1154, 1082, 1001, 811, 729, 608, 575;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{14}INO_5S$: 411.9637, found: 411.972;

HPLC (method 1): t_R =19.0 min, purity 98.9%.

Methyl (2S,4*S*)-1-({4-iodophenyl)sulfonyl]-4-[(4-nitrobenzoyl}oxy)pyrrolidine-2-carboxylate (68e)



$C_{19}H_{17}IN_2O_8S$

M_r = 560.3

Under N_2 atmosphere, DIAD (2.5 mL, 2550 mg, 12.61 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (3308 mg, 12.61 mmol) in dry THF (40 mL) and the mixture was stirred for 5 min at 0 °C. Then, a solution of *p*- nitrobenzoic acid (1916 mg, 11.46 mmol) and **68** (2357 mg, 5.73 mmol) in dry THF (20 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/1 → 0/1) to give **68e** (1800 mg, 3.21 mmol, 78%) as yellow oil.

TLC: R_f = 0.48 (petroleum ether/ethyl acetate, 1/2);

Specific rotation: $[\alpha]_D^{20}$ = +42.9 (0.7, chloroform);

^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm]= 2.29 – 2.40 (m, 2H, CHCH_2CH), 3.51 (dd, J = 11.5/4.6 Hz, 1H, NCH_2), 3.57 (m, J = 11.5/1.2 Hz, 1H, NCH_2), 3.62 (s, 3H, CO_2CH_3), 4.66 (dd, J = 8.7/2.9 Hz, 1H, NCH), 5.43 – 5.49 (m, 1H, CHO), 7.63 – 7.69 (m, 2H, 2′-$H_{(4\text{-iodophenyl)sulfonyl}}$, 6′-$H_{(4\text{-iodophenyl)sulfonyl}}$), 7.99 – 8.05 (m, 2H, 3′-$H_{(4\text{-iodophenyl)sulfonyl}}$, 5′-$H_{(4\text{-iodophenyl)sulfonyl}}$), 8.05 – 8.10 (m, 2H, 2″-$H_{4\text{-nitrobenzoyl}}$, 6″-$H_{4\text{-nitrobenzoyl}}$), 8.36 – 8.41 (m, 2H, 3″-$H_{4\text{-nitrobenzoyl}}$, 5″-$H_{4\text{-nitrobenzoyl}}$);

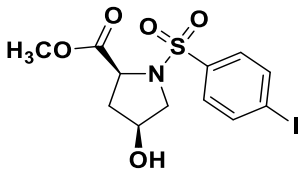
^{13}C NMR (126 MHz, DMSO-d_6) δ [ppm] = 35.6 (1C, CHCH$_2$CH), 52.4 (1C, CO_2CH_3), 53.4 (1C, NCH$_2$), 59.3 (1C, NCH), 74.4(1C, CHO), 101.8 (1C, C-4′$_{(4\text{-iodophenyl)sulfonyl}}$), 123.9 (2C, C-3″$_{4\text{-nitrobenzoyl,}}$ C-5″$_{\text{nitrobenzoyl}}$), 129.0 (2C, C-2′$_{(4\text{-iodophenyl)sulfonyl}}$, 6′$_{(4\text{-iodophenyl)sulfonyl}}$) , 130.6 (2C, C-2″$_{4\text{- nitrobenzoyl,}}$ C-6″ $_{\text{nitrobenzoyl}}$), 134.6 (1C, C-1″$_{4\text{- nitrobenzoyl}}$), 136.7 (1C, C-1′$_{(4\text{-iodophenyl)sulfonyl}}$), 138.3 (2C, C-3′$_{(4\text{-iodophenyl)sulfonyl}}$, C-5$_{(4\text{-iodophenyl)sulfonyl}}$) 150.4 (1C, C-4″$_{4\text{-nitrobenzoyl}}$), 163.5 (1C, Ar$CO_{2\text{-nitrobenzoyl}}$), 171.4 (1C, CO$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 2950, 1751, 1720, 1531, 1344, 1273, 1193, 1159, 1105, 1040, 875, 735, 620, 576, 492;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{19}H_{17}IN_2O_8S$: 560.9750, found: 560.982;

HPLC (method 1): t_R = 24.7 min, purity 99.7%.

Methyl (2*S*,4*S*)-4-hydroxy-1-[(4-iodophenyl)sulfonyl]pyrrolidine-2-carboxylate (69)



$C_{12}H_{14}INO_5S$

M_r = 411.2

At ambient temperature, potassium carbonate (2836 mg, 20.52 mmol) was added to a solution of **68e** (1000 mg, 1.78 mmol) in dry methanol (40 ml). After stirring the mixture for 30 min, the mixture was filtered and the filtrate was acidified by adding 0.5N HCl. Then, a saturated aqueous solution of $NaHCO_3$ was added in excess to render the mixture alkaline and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column

chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/1 → 1/0) to give **69** (530 mg, 1.29 mmol, 72%) as colorless oil.

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = +123.0 (2.7, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.12 (m, *J* = 14.1/1.7 Hz, 1H, CHC*H*$_2$CH), 2.21 (m, *J* = 14.3/9.8/4.6 Hz, 1H, CHC*H*$_2$CH), 3.38 (dd, *J* = 10.3/4.2 Hz, 1H, NC*H*$_2$), 3.50 (m, *J* = 10.4/1.4 Hz, 1H, NC*H*$_2$), 3.76 (s, 3H, CO_2C*H*$_3$), 4.33 – 4.40 (m, 1H, NC*H*), 4.33 - 4.40 (m, 1H, C*H*OH), 7.51 – 7.62 (m, 2H, 2′- H$_{(4\text{-iodophenyl)sulfonyl}}$, 6′-H$_{(4\text{-iodophenyl)sulfonyl}}$), 7.87 – 7.92 (m, 2H, 3′-H$_{(4\text{-iodophenyl)sulfonyl}}$, 5′-H$_{(4\text{-iodophenyl)sulfonyl}}$);

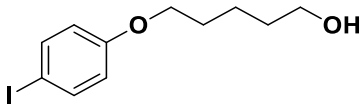
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 38.9 (1C, CH*C*H$_2$CH), 53.2 (1C, CO_2*C*H$_3$), 57.1 (1C, N*C*H$_2$), 59.3 (1C, N*C*H), 71.4 (1C, *C*HOH), 100.9 (1C, C-4′$_{(4\text{-iodophenyl)sulfonyl}}$), 129.0 (2C, C-2′$_{(4\text{-iodophenyl)sulfonyl}}$, C-6′$_{(4\text{-iodophenyl)sulfonyl}}$), 137.9 (1C, C-1′$_{(4\text{-iodophenyl)sulfonyl}}$), 138.6 (2C, C-3′$_{(4\text{-iodophenyl)sulfonyl}}$, C-5′$_{(4\text{-iodophenyl)sulfonyl}}$), 174.2 (1C, *C*O$_2CH_3$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3489, 2950, 1736, 1568, 1350, 1210, 1099, 1088, 1033, 1003, 842, 822, 730, 616, 577, 510, 491;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}INO_5S$: 433.9637, found: 433.953;

HPLC (method 1): t_R = 19.0 min, purity 95.9%.

5-(4-iodophenoxy)pentan-1-ol (100)



$C_{11}H_{15}IO_2$

M_r = 306.1

Potassium carbonate (12.6 g, 90.90 mmol) and 5-bromopentan-1-ol (1.5 mL, 1822 mg, 10.91 mmol) were added to 4-iodophenol (**70**) (2 g, 9.09 mmol) in acetonitrile (50 mL). After refluxing the mixture for 2 h, the mixture was filtered, and the solvent was removed *in vacuo*.

The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/0 → 1/2) to give **100** (2.8 g, 9.13 mmol, 100%) as colorless oil.

TLC: R_f = 0.38 (petroleum ether/ethyl acetate, 3/2);

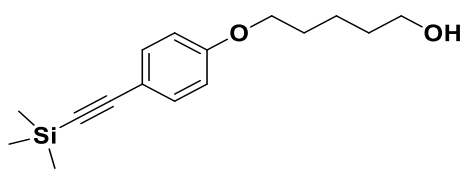
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.47 – 1.58 (m, 2H, $OCH_2CH_2C\mathit{H}_2CH_2CH_2OH$), 1.64 (m, *J* = 8.8/6.4 Hz, 2H, $OCH_2CH_2CH_2C\mathit{H}_2CH_2OH$), 1.80 (m, *J* = 14.3/6.6 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 3.67 (t, *J* = 6.5 Hz, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.92 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 6.56 – 6.74 (m, 2H, 2′-$H_{4\text{-iodophenoxy}}$, 6′-$H_{4\text{-iodophenoxy}}$), 7.46 – 7.61 (m, 2H, 3′-$H_{4\text{-iodophenoxy}}$, 5′-$H_{4\text{-iodophenoxy}}$);
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 29.1 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 62.9 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 68.1 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 82.7 (1C, C-4′$_{4\text{-iodophenoxy}}$), 117.1 (2C, C-2′$_{4\text{-iodophenoxy}}$, C-6′$_{4\text{-iodophenoxy}}$), 138.3 (2C, C-3′$_{4\text{-iodophenoxy}}$, C-5′$_{4\text{-iodophenoxy}}$), 159.1 (1C, C-1′$_{4\text{-iodophenoxy}}$);

IR (neat): ṽ [cm^{-1}] = 3336, 2935, 2864, 1585, 1485, 1470, 1282, 1238, 1173, 1057, 1028, 997, 817, 631, 505;

MS (EI): *m*/*z* [%] = 306 (M, 17.7);

HPLC (method 1): t_R = 22.7 min, purity 97.4%.

5-{4-[(trimethylsilyl)ethynyl]phenoxy}pentan-1-ol (101)



$C_{16}H_{24}O_2Si$

M_r = 276.5

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (95 mg, 0.08 mmol), copper(I) iodide (47 mg, 0,25 mmol), triethylamine (3.41 mL, 2490 mg, 24.61 mmol), and trimethylsilyl acetylene (1.81 ml, 1283 mg, 13.0 mmol) were added to a solution of **100** (2511 mg, 8.20 mmol) in acetonitrile (50 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the

solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/0 → 1/1) to give **101** (2132 mg, 7.71 mmol, 94.0%) as brown oil.

TLC: R_f = 0.45 (petroleum ether/ethyl acetate, 3/2);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 0.23 (s, 9H, Si(CH_3)$_3$), 1.49 – 1.67 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.81 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.68 (t, *J* = 6.5 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.96 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 6.76 – 6.85 (m, 2H, 2′-$H_{4\text{–[(trimethylsilyl)ethynyl]}}$, 6′-$H_{4\text{–[(trimethylsilyl)ethynyl]}}$), 7.35 – 7.42 (m, 2H, 3′-$H_{4\text{–[(trimethylsilyl)ethynyl]}}$, 5′-$H_{4\text{–[(trimethylsilyl)ethynyl]}}$);

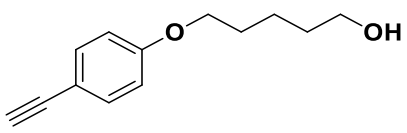
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 0.3 (3C, Si(*C*H_3)$_3$), 22.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 29.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 63.0 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 68.0 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 92.5 (1C, Si*C*≡CAr), 105.5 (1C, SiC≡*C*Ar), 114.5 (2C, C-2′$_{4\text{–[(trimethylsilyl)ethynyl]}}$, C-6′$_{4\text{–[(trimethylsilyl)ethynyl]}}$), 115.3 (1C, C-4′$_{4\text{-[(trimethylsilyl)ethynyl)}}$), 133.6 (2C, C-3′$_{4\text{–[(trimethylsilyl)ethynyl]}}$, C-5′$_{4\text{–[(trimethylsilyl)ethynyl]}}$), 159.4 (1C, C-1′$_{4\text{-[(trimethylsilyl)ethynyl]}}$);

IR (neat): ṽ [cm^{-1}] = 3332, 2940, 2868, 2154, 1604, 1505, 1245, 1170, 1056, 1028, 862, 830, 758, 540;

MS (EI): *m*/*z* [%] = 276 (M, 15);

HPLC (method 1): t_R = 26.0 min, purity 86.1%.

5-(4-ethynylphenoxy)pentan-1-ol (71)



$C_{13}H_{16}O_2$

M_r= 204.3

Tetrabutylammonium fluoride trihydrate (4479 mg, 14.2 mmol) was added to an ice-cooled solution of **101** (1934 mg, 7.1 mmol) in dry THF (100 mL) and the mixture was stirred at 0 °C for 30 min. Then, a saturated aqueous solution of ammonium chloride was added and the

mixture was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/2 → 1/1) to give **71** (1.1 g, 5.6 mmol, 74%) as yellow oil.

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 3/2);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.51 – 1.60 (m, 2H, $OCH_2CH_2C\mathit{H}_2CH_2CH_2OH$), 1.61-1.69 (m, 2H, $OCH_2CH_2CH_2C\mathit{H}_2CH_2OH$), 1.82 (m, *J* = 7.8/6.4 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 2.99 (s, 1H, $\mathit{H}C{\equiv}CAr$), 3.68 (t, *J* = 6.5 Hz, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.97 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 6.74 – 6.90 (m, 2H, 2′-$H_{4\text{-ethynylphenoxy}}$, 6′-$H_{4\text{-ethynylphenoxy}}$), 7.38 – 7.44 (m, 2H, 3′-$H_{4\text{-ethynylphenoxy}}$, 5′-$H_{4\text{-ethynylphenoxy}}$);

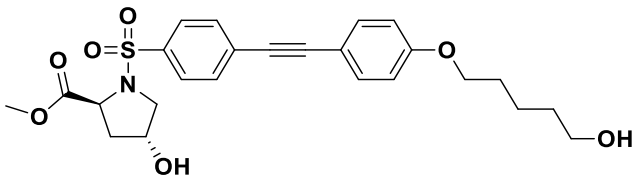
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm] = 22.5 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 29.1 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 62.9 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 68.0 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 75.9 (1C, $H\mathit{C}{\equiv}CAr$), 83.9 (1C, $HC{\equiv}\mathit{C}Ar$), 114.2 (1C, C-4′$_{4\text{-ethynylphenoxy}}$), 114.6 (2C, C-2′$_{4\text{-ethynylphenoxy}}$, C-6′$_{4\text{-ethynylphenoxy}}$), 133.8 (2C, C-3′$_{4\text{-ethynylphenoxy}}$, C-5′$_{4\text{-ethynylphenoxy}}$), 159.6 (1C, C-1′$_{4\text{-ethynylphenoxy}}$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3253, 2943, 2869, 1607, 1506, 1471, 1289, 1245, 1171, 1036, 989, 833, 733, 689, 640, 537;

MS (EI): *m*/*z* [%] = 204 (M + CH_4, 100);

HPLC (method 1): t_R = 21.0 min, purity 94.8%.

Methyl (2*S*,4*R*)-4-hydroxy-1-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]sulfonyl}pyrrolidine-2-carboxylate (72a)



$C_{25}H_{29}NO_7S$

M_r = 487.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.01mmol), copper(I) iodide (3 mg, 0.02 mmol), triethylamine (0.2 mL, 148 mg, 1.46 mmol), and **71** (149 mg, 0.73 mmol) were added to a solution of **68** (200 mg, 0.49 mmol) in acetonitrile (50 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V.= 20 mL, petroleum ether/ethyl acetate, 1/0 → 1/1) to give **72a** (201 mg, 0.41 mmol, 84%) as yellow oil.

TLC: R_f = 0.28 (petroleum ether/ethyl acetate, 1/5);

Specific rotation: $[\alpha]_D^{20}$ = -108.6 (3.3, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.52 – 1.67 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.78 – 1.87 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.08 (m, *J* = 13.1/8.6/4.4 Hz, 1H $CHCH_2CH$), 2.15 (m, *J* = 13.1/7.5/3.0/1.7 Hz, 1H, $CHCH_2CH$), 3.34 (m, 1H, NCH_2), 3.58 - 3.63 (m, 1H, NCH_2), 3.58 – 3.63 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.76 (s, 3H, CO_2CH_3), 4.04 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.30 – 4.33 (m, 1H, NC*H*), 4.35 (m, *J* = 4.1/2.6 Hz, 1H, C*H*OH), 6.90 – 6.99 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 7.46 – 7.49 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 7.65 – 7.701 (m, 2H, 3′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, 5′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 7.83 – 7.88 (m, 2H, 2′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate,}$ 6′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$);

^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.4 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 40.3 (1C, $CHCH_2CH$), 53.1 (1C, CO_2CH_3), 57.9 (1C, NCH_2), 61.5 (1C, NCH), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$),

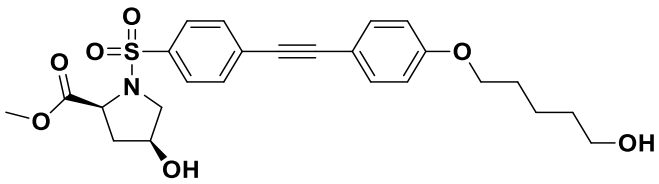
69.2 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 70.6 (1C, C*H*OH), 87.6 (1C, Ar*C*≡CAr), 94.2 (1C, ArC≡*C*Ar), 115.6 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})\text{oxy}]\text{phenyl}\}\text{ethynyl})\text{phenyl}]}$), 115.9 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})\text{oxy}]\text{phenyl}\}\text{ethynyl})\text{phenyl}]}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})\text{oxy}]\text{phenyl}\}\text{ethynyl})\text{phenyl}]}$), 129.1 (2C, C-2′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$, C-6′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$), 130.1 (1C, C-4′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$), 132.8 (2C, C-3′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$, C-5′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$), 134.5 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})\text{oxy}]\text{phenyl}\}\text{ethynyl})\text{phenyl}]}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})\text{oxy}]\text{phenyl}\}\text{ethynyl})\text{phenyl}]}$), 137.9 (1C, C-1′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$), 161.4 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})\text{oxy}]\text{phenyl}\}\text{ethynyl})\text{phenyl}]}$), 174.6 (*C*O$_2CH_3$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3373, 2941, 2869, 2213, 1736, 1604, 1589, 1511, 1334, 1244, 1157, 1135, 1087, 1021, 831, 813, 714, 623, 590, 539;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{25}H_{29}NO_7S$: 488.1665, found: 488.173;

HPLC (method 1): t_R = 21.3 min, purity 87.6%.

Methyl (2*S*,4*S*)-4-hydroxy-1-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]sulfonyl}pyrrolidine-2-carboxylate (73a)



$C_{25}H_{29}NO_7S$

M_r = 487.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.004mmol), copper(I) iodide (3 mg, 0.01 mmol), triethylamine (0.18 mL, 133 mg, 1.31 mmol), and **71** (116 mg, 0.57 mmol) were added to a solution of **69** (180 mg, 0.44 mmol) in acetonitrile (50 mL) and the mixture was stirred for 1 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 2cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate, 3/1 → 0/1) to give **73a** (177 mg, 0.36 mmol, 83%) as yellow oil.

TLC: R_f = 0.28 (petroleum ether/ethyl acetate, 1/5);

Specific rotation: $[\alpha]_D^{20}$ = -16.8 (1.1, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 1.50 – 1.71 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.83 (m, *J*= 6.5 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 2.02 - 2.29 (m, 2H, $CHC\mathit{H}_2CH$), 3.41 (m, *J* = 10.3/9.5/3.0 Hz, 1H, $NC\mathit{H}_2$), 3.56 (m, *J* = 10.3/1.4 Hz, 1H, $NC\mathit{H}_2$), 3.69 (td, *J* = 6.4/3.3 Hz, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.78 (s, 3H, $CO_2C\mathit{H}_3$), 3.97 - 4.02 (t, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.34 - 4.47(m, 1H, $NC\mathit{H}$), 4.34 - 4.47 (m, 1H, $C\mathit{H}OH$), 6.85 – 6.96 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 7.31 – 7.51 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 7.57 – 7.69 (m, 2H, 3′-$H_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, 5′-$H_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 7.78 – 7.89 (m, 2H, 2′-$H_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate,}$ 6′-$H_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$);

^{13}C NMR (101.MHz, $CDCl_3$) δ [ppm] = 22.5 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 29.1 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 38.9 (1C, $CH\mathit{C}H_2CH$), 53.3 ($CO_2\mathit{C}H_3$), 57.3 (1C, $N\mathit{C}H_2$), 59.2 (1C, $N\mathit{C}H$), 63.0 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 68.1 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 71.3 (1C, $C\mathit{H}OH$), 86.8 (1C, Ar*C*≡CAr),

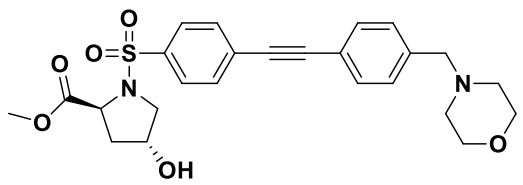
93.9 (1C, ArC≡*C*Ar), 114.4 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 114.9 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 127.7 (2C, C-2′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, C-6′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 129.2 (1C, C-4′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 132.1 (2C, C-3′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, C-5′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 133.5 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 136.5 (1C, C-1′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 160.0 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 174.4 (1C, $\mathit{C}O_2CH_3$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3359, 2939, 2868, 2213, 1734, 1568, 1511, 1342, 1284, 1245, 1158, 1135, 1088, 1028, 831, 808, 723, 627, 591, 539;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{29}NO_7S$: 488.1665, found: 488.175;

HPLC (method 1): t_R = 21.4 min, purity 85.4%.

Methyl (2*S*,4*R*)-4-hydroxy-1-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)sulfonyl]pyrrolidine-2-carboxylate (78a)



$C_{25}H_{28}N_2O_6S$

M_r = 484.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (9 mg, 0.01mmol), copper(I) iodide (5 mg, 0.02 mmol), triethylamine (0.33 mL, 244 mg, 2.41 mmol), and **103** (242 mg, 1.20 mmol) were added to a solution of **68** (330 mg, 0.80 mmol) in acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **78a** (201 mg, 0.41 mmol, 52%) as very sticky brown oil.

TLC: R_f = 0.23 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -110.5 (1.0, methanol);

^{1}H NMR (500 MHz, MeOD-d_4) δ [ppm]= 2.09 (m, *J* = 13.0/8.6/4.4 Hz, 1H, CHCH_2CH), 2.16 (m, *J* = 12.1/7.5/3.0/1.6 Hz, 1H, CHCH_2CH), 2.49 (t, 4H, NCH_2CH$_2$O), 3.36 (m, 1H, NCH_2), 3.57 (s, 2H ArCH_2), 3.61 (dd, *J* = 11.1/3.9 Hz, 1H, NCH_2), 3.69 – 3.74 (t, 4H, NCH$_2$CH_2O), 3.77 (s, 3H, CO$_2$CH_3), 4.30 – 4.39 (m, 1H, C*H*OH), 4.30- 4.39 (m, 1H, NC*H*), 7.42 (m, *J* = 8.1 Hz, 2H, 3″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.51 – 7.57 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.69 – 7.75 (m, 2H, 3′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, 5′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 7.85 – 7.91 (m, 2H, 2′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, 6′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$);

^{13}C NMR (126 MHz, MeOD-d_4) δ [ppm]= 40.3 (1C, CHCH_2CH), 53.1 (1C, *C*O$_2$CH$_3$), 54.8 (2C, NCH_2CH$_2$O), 57.9 (1C, NCH_2), 61.3 (1C, NC*H*), 64.0 (1C, ArCH_2), 67.9 (2C, NCH$_2$CH_2O), 70.6 (1C, C*H*OH), 88.8 (1C, ArC≡CAr), 93.6 (1C, ArC≡CAr), 122.8 (1C, C-1″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 129.1 (2C, C-2′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, C-6′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 129.6 (1C, C-4′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate)}$, 130.9 (2C, C-3″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$,

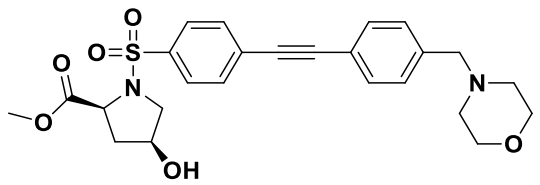
C-5″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.8 (2C, C-2″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 133.1 (2C, C-3′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, C-5′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 138.4 (1C, C-1′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 140.1 (1C, C-4″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 174.6 (1C, CO_2CH_3);

IR (neat): ṽ [cm^{-1}] = 3391, 2951, 2812, 1739, 1591, 1438, 1347, 1200, 1157, 1135, 1112,1005, 864, 837, 710, 625, 591, 561, 539, 523;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{28}N_2O_6S$: 485.1668, found: 485.173;

HPLC (method 1): t_R = 16.3, purity 96.7%.

Methyl (2*S*,4S)-4-hydroxy-1-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)sulfonyl]pyrrolidine-2-carboxylate (79a)



$C_{25}H_{28}N_2O_6S$

M_r = 484.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.01mmol), copper(I) iodide (3 mg, 0.02 mmol), triethylamine (0.21 mL, 155 mg, 1.53 mmol), and **103** (154 mg, 0.77 mmol) were added to a solution of **69** (210 mg, 0.51 mmol) in acetonitrile (10 mL) and stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **79a** (188 mg, 0.39 mmol, 76%) as brown oil.

TLC: R_f = 0.30 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -37.3 (1.3, methanol);

^{1}H NMR (600 MHz, MeOD-d_4) δ [ppm]= 2.11 (m, *J* = 13.3/3.5/1.0 Hz, 1H, CHCH_2CH), 2.17 (m, *J* = 13.7/9.1/4.8 Hz, 1H, CHCH_2CH), 2.48 (t, *J* = 4.6 Hz, 4H, NCH_2CH_2O), 3.30 – 3.34 (m, 1H, NCH_2), 3.47 (dd, *J* = 10.6/5.1 Hz, 1H, NCH_2), 3.57 (s, 2H, ArCH_2), 3.71 (t, *J* = 4.7 Hz, 4H,

NCH_2CH_2O), 3.73 (s, 3H, CO_2CH_3), 4.24 (m, *J* = 5.0/3.1 Hz, 1H, C*H*OH), 4.47 (m, *J* = 9.1/3.6 Hz, 1H, NC*H*), 7.39 – 7.44 (m, 2H, 3″-$H_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, 5″-$H_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 7.51 – 7.57 (m, 2H, 2″-$H_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, 6″-$H_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 7.69 – 7.76 (m, 2H, 3′-$H_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$, 5′-$H_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$), 7.89 – 7.92 (m, 2H, 2′-$H_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$, 6′-$H_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$);

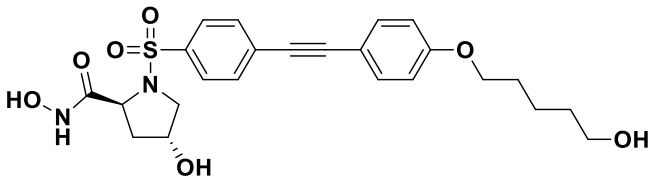
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 39.9 (1C, $CHCH_2CH$), 53.1 (1C, CO_2CH_3), 54.8 (2C, NCH_2CH_2O), 56.9 (1C, NCH_2), 61.1 (1C, NCH), 64.0 (1C, $ArCH_2$), 67.9 (2C, NCH_2CH_2O), 70.9 (1C, CHOH), 88.7 (1C, ArC≡CAr), 93.7 (1C, ArC≡CAr), 122.8 (1C, C1″-$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 129.0 (2C, C-2′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$, C-6′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$), 129.6 (1C, C-4′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate)}}$, 130.9 (2C, C-3″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-5″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 132.9 (2C, C-2″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-6″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 133.3 (2C, C-3′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$, C-5′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$), 138.9 (1C, C-1′$_{\text{phenylsulfonylpyrrolidine-2-carboxylate}}$), 140.1 (1C, C-4″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 174.3 (1C, CO_2CH_3);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3401, 2952, 2810, 2216, 1732, 1590, 1438, 1333, 1209, 1157, 1111, 1031, 1005, 864, 836, 794, 710, 629, 592, 560, 538;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{28}N_2O_6S$: 485.1668, found: 485.165;

HPLC (method 1): t_R = 16.2, purity 98.5%.

(2*S*,4*R*)-*N*,4-dihydroxy-1-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]sulfonyl}pyrrolidine-2-carboxamide (72)



$C_{24}H_{28}N_2O_7S$

Mr = 488.6

An aqueous solution of hydroxylamine solution (50 wt%, 3.6 mL) was added to a solution of **72a** (67 mg, 0.14 mmol) dissolved in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture for 48 h at ambient temperature, water was added and the mixture

was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **72** (32 mg, 0.07mmol, 47%) as colorless solid.

m.p.= 113-114°C (decomposition);

TLC: R_f = 0.10 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -114.0 (1.0, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.52 – 1.66 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.82 (dt, *J*= 13.8/6.5 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 1.98 - 2.05 (m, 1H $CHC\mathit{H}_2CH$), 2.09 (m, *J* = 12.8/8.3/4.4 Hz, 1H, $CHC\mathit{H}_2CH$), 3.31 - 3.35 (m, 1H, $NC\mathit{H}_2$), 3.59 (t, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.61 - 3.68 (m, 1H, $NC\mathit{H}_2$), 4.03 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.12 (t, *J* = 7.9 Hz, 1H, NC*H*), 4.33 (m, *J* = 3.8 Hz, 1H, C*H*OH), 6.92 – 6.96 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 7.45 – 7.50 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 7.66 (m, *J* = 8.4 Hz, 2H, 3′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$, 5′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 7.84 – 7.89 (m, 2H, 2′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$, 6′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$);

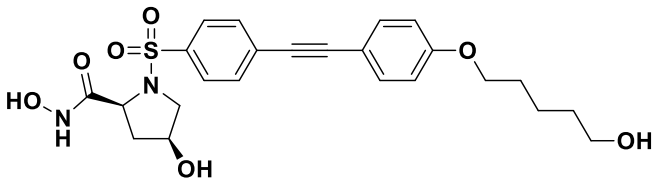
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 30.2 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 33.4 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 40.6 (1C, $CH\mathit{C}H_2CH$), 58.2 (1C, NCH_2), 60.5 (1C, N*C*H), 62.9 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 69.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 70.6 (1C, C*H*OH), 87.6 (1C, Ar*C*≡CAr), 94.2 (1C, ArC≡*C*Ar), 115.6 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 115.9 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 129.3 (2C, C-2′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$, C-6′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 130.1 (1C, C-4′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 132.8 (2C, C-3′ $_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$, C-5′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 134.4 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 137.4 (1C, C-1′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 161.4 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl]}$), 171.3 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3227, 2943, 2869, 2215, 1644, 1567, 1328, 1251, 1156, 1136, 1009, 975, 833, 715, 626, 592;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{28}N_2O_7S$: 489.1617, found 489.173;

HPLC (method 2): t_R = 14.6 min, purity 99.7%.

(2*S*,4*S*)-*N*,4-dihydroxy-1-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]sulfonyl}pyrrolidine-2-carboxamide (73)



$C_{24}H_{28}N_2O_7S$

Mr = 488.6

An aqueous solution of hydroxylamine solution (50 wt%, 4.0 mL) was added to a solution of **73a** (74 mg, 0.15 mmol) dissolved in a mixture of THF (6 mL) and isopropanol (6 mL). After stirring the reaction mixture for 48 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **73** (21 mg, 0.04mmol, 29%) as colorless solid.

m.p.= 156-157 °C (decomposition);

TLC: R_f = 0.13 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -136.0 (0.5, methanol);

^{1}H NMR (600 MHz, MeOD-d_4) δ [ppm]= 1.52 – 1.66 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.83 (dt, *J*= 13.9/6.6Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.97 - 2.13 (m, 2H $CHCH_2CH$), 3.36 (dd, *J* = 10.6, 4.6 Hz, 1H, NCH_2), 3.46 (m, *J* =10.6/2.5/1.3 Hz, 1H, NCH_2), 3.60 (t, *J*= 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.03 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.10 - 4.18 (m, 1H, NC*H*), 4.10 - 4.18 (m, 1H, C*H*OH), 6.93 – 6.99 (m, 2H, 3′′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl}$, 5′′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl}$), 7.45 – 7.51 (m, 2H, 2′′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl}$, 6′′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\}ethynyl)phenyl}$), 7.70 - 7.74

(m, *J*= 8.4 Hz, 2H, 3′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide,}$ 5′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 7.85 – 7.93 (m, 2H, 2′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide,}$ 6′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$);

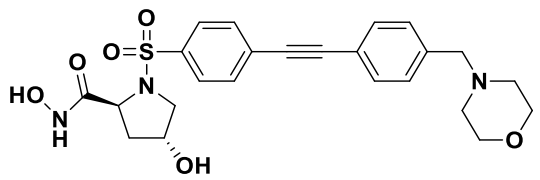
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 30.2 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 33.4 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 39.3 (1C, CH*C*H$_2$CH), 58.2 (1C, N*C*H$_2$), 60.7 (1C, N*C*H), 62.9 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 69.2 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 71.1 (1C, C*H*OH), 87.4 (1C, Ar*C*≡CAr), 94.6 (1C, ArC≡*C*Ar), 115.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl\}ethynyl)phenyl}$), 115.9 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl\}ethynyl)phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl\}ethynyl)phenyl}$), 129.1 (2C, C-2′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$, C-6′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 130.5 (1C, C-4′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 133.1 (2C, C-3′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$, C-5′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 134.5 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl\}ethynyl)phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl\}ethynyl)phenyl}$), 136.8 (1C, C-1′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxamide}$), 161.5 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl\}ethynyl)phenyl}$), 171.3 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3185, 2941, 2868, 2209, 1678, 1589, 1511, 1342, 1245, 1156, 1133, 1100, 1089, 1022, 831, 809, 724, 629, 589;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{24}H_{28}N_2O_7S$: 489.1617, found 489.170;

HPLC (method 2): t_R = 14.9 min, purity 95.5%.

(2*S*,4*R*)-*N*,4-dihydroxy-1-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)sulfonyl]pyrrolidine-2-carboxamide (78)



$C_{24}H_{27}N_3O_6S$

Mr = 485.6

An aqueous solution of hydroxylamine solution (50 wt%, 10.0 mL) was added to a solution of **78a** (181 mg, 0.37 mmol) dissolved in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture for 48 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by automatic flash

column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **78** (62 mg, 0.13 mmol, 35%) as colorless solid.

m.p.= 150-152 °C (decomposition);

TLC: R_f = 0.13 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -112.2 (2.7, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 2.01 (m, *J* = 12.8/7.5/3.1/1.7 Hz, 1H, CHC*H*$_2$CH), 2.09 (m, *J* = 12.9/8.3/4.4 Hz, 1H, CHC*H*$_2$CH), 2.46 (t, *J* = 4.8 Hz, 4H, NC*H*$_2$CH$_2$O), 3.34 (m, 1H, NC*H*$_2$), 3.55 (s, 2H, ArC*H*$_2$), 3.62 (dd, 1H, NC*H*$_2$), 3.69 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 4.12 (t, *J* = 7.9 Hz, 1H, NC*H*), 4.33 (m, 1H, C*H*OH), 7.38 – 7.45 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.50 – 7.55 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.67 – 7.72 (m, 2H, 3′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, 5′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 7.86 – 7.93 (m, 2H, 2′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, 6′- H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$);

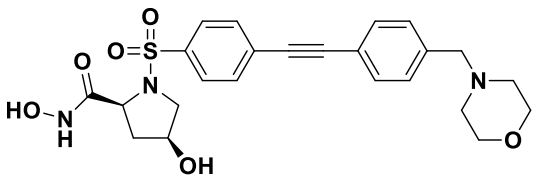
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 40.6 (1C, CH*C*H$_2$CH), 54.8 (2C, N*C*H$_2$CH$_2$O), 58.3 (1C, N*C*H$_2$), 60.5 (1C, N*C*H), 64.0 (1C, Ar*C*H$_2$), 67.9 (2C, NCH$_2$*C*H$_2$O), 70.6 (1C, C*H*OH), 88.9 (1C, Ar*C*≡CAr), 93.6 (1C, ArC≡*C*Ar), 122.8 (1C, C-1″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 129.3 (2C, C-2′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, C-6′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 129.5 (1C, C-4′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate)}$, 130.9 (2C, C-3″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.8 (2C, C-2″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 133.0 (2C, C-3′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, C-5′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 137.9 (1C, C-1′$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 140.0 (1C, C-4″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 171.2 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3230, 2915, 2861, 2815, 1669, 1334, 1263, 1237, 1199, 1003, 863, 838, 711, 628, 591, 562;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{27}N_3O_6S$: 486.1621, found: 486.169;

HPLC (method 2): t_R = 12.4 min, purity 99.6%.

(2*S*,4*S*)-*N*,4-dihydroxy-1-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)sulfonyl]pyrrolidine-2-carboxamide (79)



$C_{24}H_{27}N_3O_6S$

M_r = 485.6

An aqueous solution of hydroxylamine solution (50 wt%, 6.5 mL) was added to a solution of **79a** (120 mg, 0.25 mmol) dissolved in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture for 48 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **79** (60 mg, 0.12 mmol, 49%) as colorless solid.

m.p.= 159-160 °C (decomposition);

TLC: R_f = 0.15 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -74.8 (1.4, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.96 – 2.09 (m, 2H, CHC*H*$_2$CH), 2.46 (t, *J* = 4.4 Hz, 4H, NC*H*$_2$CH$_2$O), 3.36 (dd, *J* = 10.5/4.6 Hz, 1H, NC*H*$_2$), 3.46 (m, *J* = 10.6/2.3/1.3 Hz, 1H, NC*H*$_2$), 3.55 (s, 2H, ArC*H*$_2$), 3.69 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 4.13 – 4.19 (m, 1H, C*H*OH), 4.13 - 4.19 (m, 1H, NC*H*), 7.38 – 7.42 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.51 – 7.55 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.71 – 7.77 (m, 2H, 3′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, 5′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$), 7.87 – 7.93 (m, 2H, 2′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$, 6′-H$_{phenylsulfonylpyrrolidine\text{-}2\text{-}carboxylate}$);

^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 39.4 (1C, CH*C*H$_2$CH), 54.8 (2C, N*C*H$_2$CH$_2$O), 58.4 (1C, N*C*H$_2$), 60.8 (1C, N*C*H), 64.0 (1C, Ar*C*H$_2$), 67.9 (2C, NCH$_2$*C*H$_2$O), 71.1 (1C, C*H*OH), 88.7 (1C, Ar*C*≡CAr), 94.0 (1C, ArC≡*C*Ar), 122.7 (1C, C-1″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 129.1 (2C,

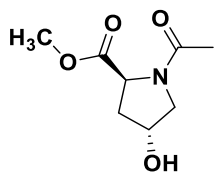
C-2′$_{phenylsulfonylpyrrolidine-2-carboxylate}$, C-6′$_{phenylsulfonylpyrrolidine-2-carboxylate}$), 129.9 (1C, C-4′$_{phenylsulfonylpyrrolidine-2-carboxylate}$), 130.9 (2C, C-3″$_{4-[(4-(morpholinomethyl)phenyl}$, C-5″$_{4-\{[4-(morpholinomethyl)phenyl}$) , 132.9 (2C, C-2″$_{4-\{[4-(morpholinomethyl)phenyl}$, C-6″$_{4-\{[4-(morpholinomethyl)phenyl}$), 133.4 (2C, C-3′$_{phenylsulfonylpyrrolidine-2-carboxylate}$, C-5′$_{phenylsulfonylpyrrolidine-2-carboxylate}$), 137.4 (1C, C-1′$_{phenylsulfonylpyrrolidine-2-carboxylate}$), 140.2 (1C, C-4″$_{4-\{[4-(morpholinomethyl)phenyl}$), 171.0 (1C, *C*ONHOH);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3204, 2849, 2804, 1347, 1160, 1114, 1093, 1010, 856, 831, 730, 709, 640, 561, 518, 487;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{24}H_{27}N_3O_6S$: 486.1621, found: 486.166;

HPLC (method 2): t_R = 12.6 min, purity 97.7%.

Methyl (2*S*,4*R*)-1-acetyl-4-hydroxypyrrolidine-2-carboxylate (104)



$C_8H_{13}NO_4$

M_r = 187.2

Triethylamine (7.4 mL, 5381 mg, 44.05 mmol) was added to an ice-cooled solution of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (57) (4 g, 22.02 mmol) in dichloromethane (30 mL) and the mixture was stirred for 15 min at 0 °C. Then, 4-dimethylaminopyridine (269 mg, 2.2 mmol) and acetyl chloride (1.9 mL, 2074 mg, 26.43 mmol) were added and the mixture was stirred for 3 h at ambient temperature. Afterwards, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V.= 60 mL, dichloromethane/methanol, 1/0 → 9/1) to give **104** (999 mg, 18.76 mmol, 24%) as pale-yellow oil.

TLC: R_f = 0.13 (dichloromethane/methanol, 95/5);

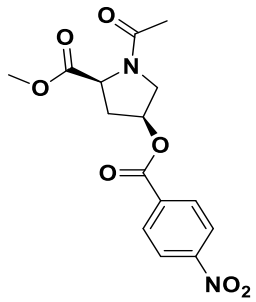
Specific rotation: $[\alpha]_D^{20}$ = -72.5 (3.1, methanol);

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]= 1.89 (m, *J* = 12.9/8.1/4.8 Hz, 1H, CHC*H*$_2$CH), 1.95 (s, 3H, NCOC*H*$_3$), 2.10 (m, *J* = 12.9/8.1/3.5/1.5 Hz, 1H, CHC*H*$_2$CH), 3.38 (m, *J* = 10.7/2.6/1.5 Hz, 1H, NC*H*$_2$), 3.60 (s, 3H, CO$_2$C*H*$_3$), 3.63 (dd, *J* = 10.7/4.5 Hz ,1H, NC*H*$_2$), 4.25 (m, 1H, NC*H*), 4.33 (m, *J* = 4.5, 2.1 Hz, 1H, C*H*OH), 5.18 (d, *J* = 3.9 Hz, 1H, CHO*H*), the signals of the major rotamer are given;

^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]= 22.0 (1C, NCO*C*H$_3$), 37.5 (1C, CHC*H*$_2$CH), 51.7 (1C, CO$_2$*C*H$_3$), 55.4 (1C, N*C*H$_2$), 57.0 (1C, N*C*H), 68.8 (1C, *C*HOH), 168.5 (1C, N*C*OCH$_3$), 172.5 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;
IR (neat): ṽ [cm^{-1}] = 3362, 3272, 2938, 2916, 1742, 1643, 1610, 1418, 1363, 1340, 1173, 1081, 1008, 964, 875, 699, 558;

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_8H_{13}NO_4$: 210.0845, found: 210.074.

Methyl (2*S*,4*S*)-1-acetyl-4-[(4-nitrobenzoyl)oxy]pyrrolidine-2-carboxylate (105)



$C_{15}H_{16}N_2O_7$

Mr = 336.3

Under N_2 atmosphere, DIAD (1.9 mL, 1744 mg, 8.62 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (2262 mg, 2.2 mmol) in dry THF (30 mL) and the mixture was stirred for 15 min at 0 °C. Then, a solution of *p*- nitrobenzoic acid (1310 mg, 7.84 mmol) and **104** (977 mg, 3.92 mmol) in dry THF (20 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V.= 60 mL, petroleum ether/ethyl acetate, 3/1 → 0/1) to give **105** (950 mg, 2.82 mmol, 72%) as colorless solid.

m.p. = 123-124 °C;

TLC: R_f = 0.25 (ethyl acetate);

Specific rotation $[\alpha]_D^{20}$ = -40.3 (4.0, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.13 (s, 3H, NCOC*H*$_3$), 2.44 – 2.66 (m, 2H, CHC*H*$_2$CH), 3.70 (s, 2H, CO_2C*H*$_3$), 3.84 – 3.91 (m, 1H, NC*H*$_2$), 3.97 (dd, *J* = 12.0/5.0 Hz, 1H, NC*H*$_2$), 4.82 (dd, *J* = 9.3/2.3 Hz, 1H, NC*H*), 5.66 (m, *J* = 5.0/1.7 Hz, 1H, C*H*O), 8.13 – 8.19 (m, 2H, 2′-H$_{4\text{-nitrobenzoyl}}$, 6′-H$_{4\text{-nitrobenzoyl}}$), 8.29 (m, 2H, 3′-H$_{4\text{-nitrobenzoyl}}$, 5′-H$_{4\text{-nitrobenzoyl}}$), the signals of the major rotamer are given;

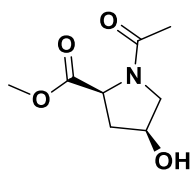
^{13}C NMR (126.MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, NCO*C*H$_3$), 35.3 (1C, CHC*H*$_2$CH), 52.6 (1C, *C*O$_2$CH$_3$), 53.6 (1C, NC*H*$_2$), 57.3 (1C, N*C*H), 74.6 (1C, C*H*O), 123.8 (2C, C-3′$_{4\text{-nitrobenzoyl}}$, C-5′ $_{4\text{-nitrobenzoyl}}$), 131.1 (2C, C-2′$_{4\text{ nitrobenzoyl}}$, C-6′$_{4\text{-nitrobenzoyl}}$), 135.0 (1C, C-1′$_{4\text{-nitrobenzoyl}}$), 151.0 (1C, C-4′$_{4\text{-nitrobenzoyl}}$), 164.2 (1C, Ar*C*O$_{2\ 4\text{-nitrobenzoyl}}$), 169.6 (1C, N*C*OCH$_3$), 171.6 (*C*O$_2CH_3$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3120, 3013, 2954, 1736, 1715, 1637, 1607, 1526, 1419, 1341, 1281, 1200, 1105, 1060, 1047, 862, 717, 564;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{16}N_2O_7$: 337.0958, found: 337.102;

HPLC (method 1): t_R = 18.2 min, purity 90.2%.

Methyl (2*S*,4*S*)-1-acetyl-4-hydroxypyrrolidine-2-carboxylate (106)



$C_8H_{13}NO_4$

M_r = 187.2

At ambient temperature, potassium carbonate (3.7 g, 26.76 mmol) was added to a solution of **105** (900 mg, 2.68 mmol) in dry methanol (50 ml). After stirring the reaction mixture for about 20 min, the mixture was filtered and the filtrate was acidified by adding 0.5N HCl. Then, a saturated aqueous solution of $NaHCO_3$ was added in excess to render the mixture alkaline and

the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol,1/0 → 9/1) to give **106** (161 mg, 0.86 mmol, 32%) as yellow oil.

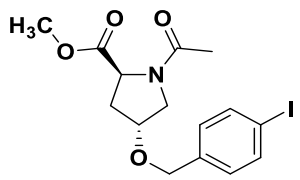
TLC: R_f = 0.33 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -80.9 (7.1, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.06 – 2.16 (s, 3H, NCOC*H*$_3$), 2.06- 2.16 (m, 1H, CHC*H*$_2$CH), 2.24 – 2.40 (m, 1H, CHC*H*$_2$CH), 3.64 – 3.72 (m, 2H, NC*H*$_2$), 3.79 (s, 3H, CO_2C*H*$_3$), 4.43 (m, *J* = 5.1 Hz, 1H, C*H*OH), 4.51 (dd, *J* = 9.9/1.8 Hz, 1H, NC*H*), the signals of the major rotamer are given;
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 22.4 (1C, NCO*C*H$_3$), 37.3 (1C, CHC*H*$_2$CH), 53.0 (1C, CO_2*C*H$_3$), 57.2 (1C, N*C*H$_2$), 57.7 (1C, N*C*H), 71.6 (1C, *C*HOH), 170.2 (1C, N*C*OCH$_3$), 175.4 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;
IR (neat): ṽ [cm^{-1}] = 3365, 2952, 1735, 1620, 1418, 1358, 1335, 1195, 1178, 1117, 1090, 1071, 1038, 970, 723, 541;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_8H_{13}NO_4$: 210.0845, found: 210.075;

Methyl (2*S*,4*R*)-1-acetyl-4-[(4-iodobenzyl)oxy]pyrrolidine-2-carboxylate (107)



$C_{15}H_{18}INO_4$

M_r =403.2

Under N_2 atmosphere, 4-iodobenzylbromide (825 mg, 2.78 mmol), silver(I) oxide (966 mg, 4.17 mmol), and potassium iodide (46 mg, 0.28 mmol) were added to a solution of **104** (260 mg, 1.39 mmol) in dichloromethane/cyclohexane (1/1) (20 mL). After stirring the reaction mixture for 48 h at ambient temperature, the mixture was filtered, and the solvent was concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h

= 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/3 → 0/1) to give **107** (302 g, 0.75 mmol, 54%) as colorless oil.

TLC: R_f = 0.30 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -30.2 (2.2, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.04 (s, 3H, NCOC*H*$_3$), 2.06 – 2.12 (m, 1H, CHC*H*$_2$CH), 2.36 (m, *J* = 13.5/8.2/4.1/1.3 Hz, 1H, CHC*H*$_2$CH), 3.55 (m, *J* = 10.9/3.2/1.4 Hz, 1H, NC*H*$_2$), 3.73 (s, 3H, CO_2C*H*$_3$), 3.74 – 3.81 (m, 1H, NC*H*$_2$), 4.22 – 4.29 (m, 1H, C*H*O), 4.34 – 4.49 (m, 2H, OC*H*$_2$Ar), 4.49 – 4.57 (m, 1H, NC*H*), 7.04 (m, *J* = 8.4/1.9 Hz, 2H, 2′-H$_{4\text{-iodobenzyl}}$, 6′-H$_{4\text{-iodobenzyl}}$), 7.67 (m, *J* = 8.3/2.2 Hz, 2H, 3′-H$_{4\text{-iodobenzyl}}$, 5′-H$_{4\text{-iodobenzyl}}$), the signals of the major rotamer are given;

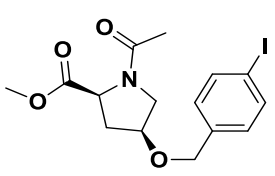
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 22.4 (1C, NCO*C*H$_3$), 35.1 (1C, CHC*H*$_2$CH), 52.5 (1C, CO_2*C*H$_3$), 53.2 (1C, N*C*H$_2$), 57.5 (1C, N*C*H), 70.8 (1C, O*C*H$_2$Ar), 77.4 (1C, C*H*O), 93.5 (1C, C-4′$_{4\text{-iodobenzyl}}$), 129.5 (2C, C-2′$_{4\text{-iodobenzyl}}$, C-6′$_{4\text{-iodobenzyl}}$), 137.4 (1C, C-1′$_{4\text{-iodobenzyl}}$), 137.8 (2C, C-3′$_{4\text{-iodobenzyl}}$, C-5′$_{4\text{-iodobenzyl}}$), 169.6 (1C, N*C*OCH$_3$), 172.9 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2949, 2870, 1737, 1645, 1413, 1355, 1198, 1176, 1085, 1058, 1005, 780, 611, 470;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{18}INO_4$: 404.0281, found: 404.032;

HPLC (method 1): t_R = 20.8 min, purity 99.3%.

Methyl (2*S*,4*S*)-1-acetyl-4-[(4-iodobenzyl)oxy]pyrrolidine-2-carboxylate (108)



$C_{15}H_{18}INO_4$

Mr = 403.2

Sodium hydride (60%) (196 mg, 4.91 mmol) was added to an ice-cooled solution of **106** (613 mg, 3.27 mmol) in dry DMF (15 mL) and the mixture was stirred for 30 min at ambient

temperature. Then, a solution of 4-iodobenzylbromide (1945 mg, 6.55 mmol) in dry DMF (15 mL) was added slowly over a period of 5 min. After stirring the reaction mixture for 18 h at ambient temperature, water was added to the mixture and extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4) and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **108** (402 mg, 1.00 mmol, 31%) as colorless oil.

TLC: R_f = 0.30 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -7.6 (1.5, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 2.02 – 2.13 (s, 3H, NCOC*H*$_3$), 2.02 - 2.13 (m, 1H, CHC*H*$_2$CH), 2.47 (m, *J* = 13.5/8.0/3.1/1.5 Hz, 1H, CHC*H*$_2$CH), 3.71 – 3.78 (s, 3H, CO_2CH_3), 3.71- 3.78 (m, 2H, NC*H*$_2$), 4.32 (m, *J* = 4.8/2.9 Hz, 1H, C*H*O), 4.42 – 4.58 (m, 1H, NC*H*), 4.42-4.58 (m, 2H, OC*H*$_2$Ar), 7.11 – 7.18 (m, 2H, 2′-H$_{4\text{-iodobenzyl}}$, 6′-H$_{4\text{-iodobenzyl}}$), 7.65 – 7.74 (m, 2H, 3′-H$_{4\text{-iodobenzyl}}$, 5′-H$_{4\text{-iodobenzyl}}$), the signals of the major rotamer are given;

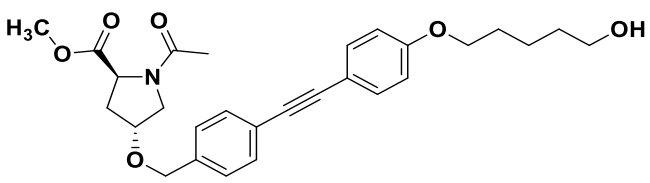
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 22.1 (1C, NCO*C*H$_3$), 36.2 (1C, CHC*H*$_2$CH), 52.9 (1C, CO_2CH_3), 54.4 (1C, N*C*H$_2$), 59.1 (1C, N*C*H), 71.4 (1C, O*C*H$_2$Ar), 78.8 (1C, C*H*O), 93.8 (1C, C-4′$_{4\text{-iodobenzyl}}$), 130.8 (2C, C-2′$_{4\text{-iodobenzyl}}$, C-6′$_{4\text{-iodobenzyl}}$), 138.8 (2C, C-3′$_{4\text{-iodobenzyl}}$, C-5′$_{4\text{-iodobenzyl}}$), 139.5 (1C, C-1′$_{4\text{-iodobenzyl}}$), 172.4 (1C, NCOCH$_3$), 174.4 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2949, 2869, 1739, 1644, 1414, 1355, 1198, 1176, 1086, 1059, 1032, 1005, 799, 470;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{18}INO_4$: 404.0281, found: 404.026;

HPLC (method 1): t_R = 20.8 min, purity 85.4%.

Methyl (2*S*,4*R*)-1-acetyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (109a)



$C_{28}H_{33}NO_6$

M_r = 479.6

Under N_2 atmosphere of nitrogen, tetrakis(triphenylphosphine)palladium(0) (4 mg, 0.003 mmol), copper(I) iodide (2 mg, 0.01 mmol), triethylamine (0.13 mL, 94 mg, 0.93 mmol), and **71** (88 mg, 0.43 mmol) were added to a solution of **107** (125 mg, 0.31 mmol) in dry acetonitrile (5 mL) and the reaction mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **109a** (104 mg, 0.22 mmol, 70 %) as yellow oil.

TLC: R_f = 0.18 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -3.0 (3.1, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.51 – 1.69 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.83 (m, *J* = 14.0, 6.6 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 2.01 – 2.14 (s, 3H, $NCOC\mathit{H}_3$), 2.01-2.14 (m, 1H, $CHC\mathit{H}_2CH$), 2.40 (m, *J* = 13.5/8.3/4.1/1.3 Hz, 1H, $CHC\mathit{H}_2CH$), 3.55 – 3.62 (m, 1H, $NC\mathit{H}_2$), 3.69 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.74 (s, 3H, $CO_2C\mathit{H}_3$), 3.76 – 3.83 (m, 1H, $NC\mathit{H}_2$), 3.99 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.28 (m, *J* = 4.9/3.2 Hz, 1H, C*H*O), 4.43 – 4.62 (m, 1H, NC*H*), 4.43 - 4.62 (m, 2H, $OC\mathit{H}_2Ar$), 6.82 – 6.90 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.27 (m, *J* = 9.3 Hz, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.43 – 7.47 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.47 – 7.51 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), the signals of the major rotamer are given;

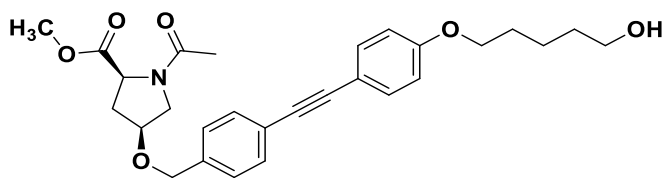
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $NCOC\mathit{H}_3$), 22.5 (1C, $OCH_2CHC\mathit{H}_2CH_2CH_2OH$), 29.2 (1C, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2C\mathit{H}_2CH_2OH$), 35.2 (1C, $CHC\mathit{H}_2CH$), 52.6 (1C, $CO_2C\mathit{H}_3$), 53.3 (1C, $NC\mathit{H}_2$), 57.7 (1C, NC*H*), 63.0 (1C, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 68.1 (1C, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 71.2

(1C, O*C*H$_2$Ar), 77.4 (1C, C*H*O), 87.9 (1C, Ar*C*≡CAr), 90.0 (1C, ArC≡*C*Ar), 114.7 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 115.2 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 123.5 (1C, C-4′$_{benzyl}$), 127.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.8 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 137.5 (1C, C-1′$_{benzyl}$), 159.4 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, the signals for N*C*OCH$_3$, and *C*O$_2$CH$_3$ cannot be observed in the spectrum, the signals of the major rotamer are given;
IR (neat): ṽ [cm^{-1}] = 3340, 2936, 2868, 1740, 1632, 1602, 1516, 1435, 1358, 1283, 1244, 1202, 1173, 1086, 1018, 830, 539, 524;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{28}H_{33}NO_6$: 480.2308, found: 480.236;

HPLC (method 1): t_R = 22.3 min, purity 99.1%.

Methyl (2*S*,4*S*)-1-acetyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (110a)



$C_{28}H_{33}NO_6$

M_r = 479.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.01 mmol), copper(I) iodide (5 mg, 0.03 mmol), triethylamine (0.4 mL, 270 mg, 2.66 mmol), and **71** (291 mg, 1.42 mmol) were added to solution of **108** (358 mg, 0.89 mmol) in dry acetonitrile (20 mL) and the reaction mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/0 → 0/1) to give **110a** (233 mg, 0.49 mmol, 55%) as yellow oil.

TLC: R_f = 0.40 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = +25.4 (6.3, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.51 – 1.72 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.77 – 1.87 (m, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 2.05 (s, 3H, $NCOC\mathit{H}_3$), 2.07 – 2.14 (m, 1H, $CHC\mathit{H}_2CH$), 2.39 (m, *J* = 13.6/8.2/4.1/1.3 Hz, 1H, $CHC\mathit{H}_2CH$), 3.58 (m, *J* = 10.7/3.0/1.2 Hz, 1H, $NC\mathit{H}_2$), 3.68 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.74 (s, 2H, $CO_2C\mathit{H}_3$), 3.76 – 3.81 (m, 1H, $NC\mathit{H}_2$), 3.99 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.26 – 4.31 (m, 1H, $C\mathit{H}O$), 4.42 – 4.59 (m, 2H, $OC\mathit{H}_2Ar$), 4.42 - 4.59 (m, 1H, $NC\mathit{H}$), 6.81 – 6.89 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.27 (m, *J* = 8.6 Hz, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.43 – 7.47 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.47 – 7.51 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), the signals of the major rotamer are given;

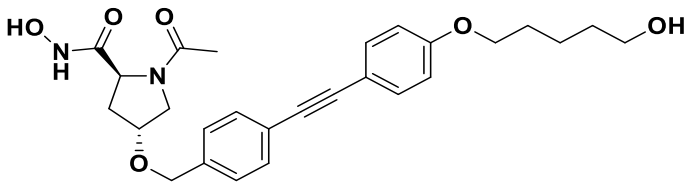
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 22.4 (1C, $NCOC\mathit{H}_3$), 22.5 (1C, $OCH_2CH_2C\mathit{H}_2CH_2CH_2OH$), 29.2 (1C, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2C\mathit{H}_2CH_2OH$), 35.2 (1C, $CHC\mathit{H}_2CH$), 52.5 (1C, $CO_2C\mathit{H}_3$), 53.3 (1C, $NC\mathit{H}_2$), 57.6 (1C, $NC\mathit{H}$), 63.0 (1C, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 68.1 (1C, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 71.2 (1C, $OC\mathit{H}_2Ar$), 77.4 (1C, $C\mathit{H}O$), 87.9 (1C, $ArC\mathit{C}{\equiv}CAr$), 90.0 (1C, $ArC{\equiv}C\mathit{C}Ar$), 115.0 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 114.7 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 123.5 (1C, C-4′$_{benzyl}$), 127.8 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.8 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 137.5 (1C, C-1′$_{benzyl}$), 159.3 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 169.7 (1C, $NC\mathit{O}CH_3$), 173.0 (1C, $\mathit{C}O_2CH_3$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3410, 2937, 2867, 1734, 1630, 1602, 1516, 1435, 1283, 1243, 1173, 1084, 1030, 1018, 830, 539, 522;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{33}NO_6$: 480.2308, found: 480.232;

HPLC (method 1): t_R = 20.8 min, purity 85.7%.

(2*S*,4*R*)-1-acetyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (109)



$C_{27}H_{32}N_2O_6$

M_r = 480.6

An aqueous solution of hydroxylamine solution (50 wt%, 5,6 mL) was added to a solution of **109a** (104 mg, 0.22 mmol) in a mixture of THF (4 mL) and isopropanol (4 mL). After stirring the reaction mixture for 24 h at ambient temperature, brine was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **109** (52 mg, 0.11 mmol, 52%) as colorless solid.

m.p. = 123-124 °C;

TLC: R_f = 0.15 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +86.2 (1.3, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.51 – 1.68 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.83 (m, *J* = 6.6 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.06 (s, 3H, $NCOCH_3$), 2.17 (m, 1H, $CHCH_2CH$), 2.39 (m, *J* = 13.0/8.0/3.1/1.5 Hz, 1H, $CHCH_2CH$), 3.60 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.69 – 3.81 (m, 2H, NCH_2), 4.03 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.29 - 4.40 (m, 1H, CHO), 4.29 – 4.40 (m, 1H, NCH), 4.53-4.65 (m, 2H, OCH_2Ar), 6.89 – 6.96 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.36 (m, *J* = 7.8 Hz, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.42 – 7.46 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.47 (m, *J* = 7.1/5.1 Hz, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}); the signals of the major rotamer are given;

^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 22.4 (1C, $NCOCH_3$), 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.5 (1C,

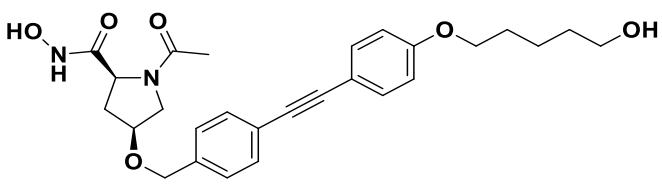
$OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 36.8 (1C, $CHC\mathit{H}_2CH$), 54.8 (1C, NCH_2), 58.1 (1C, NCH), 62.9 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 69.1 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 71.7 (1C, $O\mathit{C}H_2Ar$), 78.7 (1C, $C\mathit{H}O$), 88.6 (1C, $Ar\mathit{C}{\equiv}CAr$), 90.6 (1C, $ArC{\equiv}\mathit{C}Ar$), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 124.5 (1C, C-4′$_{benzyl}$), 128.9 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 139.7 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 171.6 (1C, $\mathit{C}ONHOH$), 172.6 (1C, $NCOCH_3$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3209, 2936, 2866, 1671, 1624, 1517, 1457, 1245, 1083, 1033, 828, 639, 569, 525;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{32}N_2O_6$: 481.2260, found: 481.232;

HPLC (method 2): t_R = 14.9 min, purity 99.6%.

(2*S*,4*S*)-1-acetyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (110)



$C_{27}H_{32}N_2O_6$

M_r = 480.6

An aqueous solution of hydroxylamine solution (50 wt%, 7.0 mL) was added to a solution of **110a** (65 mg, 0.14 mmol) in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture for 7 d at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **110** (8 mg, 0.12 mmol, 12.0 %) as colorless solid.

m.p. = 98-100 °C (decomposition);

TLC: R_f = 0.38 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -5.9 (0.9, methanol);

^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ [ppm]= 1.51 – 1.68 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.83 (m, *J* = 6.7 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$,), 2.05 (s, 3H, $NCOC\mathit{H}_3$), 2.13 (m, *J* = 13.3/8.1/4.9 Hz, 1H, $CHC\mathit{H}_2CH$), 2.38 (m, *J* = 13.0/7.9/3.2/1.5 Hz, 1H, $CHC\mathit{H}_2CH$), 3.60 (t, *J* = 6.3 Hz, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.68 – 3.82 (m, 2H, $NC\mathit{H}_2$), 4.03 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.29 – 4.43 (m, 1H, C*H*O), 4.29 - 4.43 (m, 1H, NC*H*), 4.59 (m, *J* = 22.7, 12.5 Hz, 2H, $OC\mathit{H}_2Ar$), 6.88 – 6.97 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.35 (m, *J* = 7.9/5.8 Hz, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.41 – 7.45 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.47 (m, *J* = 7.2/5.5 Hz, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), the signals of the major rotamers are given;

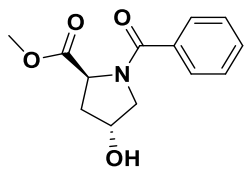
^{13}C NMR (126 MHz, MeOD-*d*$_4$) δ [ppm]= 22.4 (1C, $NCOC\mathit{H}_3$), 23.6 (1C, $OCH_2CH_2C\mathit{H}_2CH_2CH_2OH$), 30.3 (1C, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 33.5 (1C, $OCH_2CH_2CH_2C\mathit{H}_2CH_2OH$), 36.8 (1C, $CHC\mathit{H}_2CH$), 54.8 (1C, $NC\mathit{H}_2$), 58.1 (1C, N*C*H), 62.9 (1C, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 69.2 (1C, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 71.7 (1C, $OC\mathit{H}_2Ar$), 78.7 (1C, C*H*O), 88.6 (1C, Ar*C*≡CAr), 90.6 (1C, ArC≡*C*Ar), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.5 (1C, C-4′$_{benzyl}$), 128.9 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.7 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 171.5 (1C, *C*ONHOH), 172.6 (1C, N*C*OCH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3210, 2932, 2861, 1622, 1602, 1516, 1455, 1417, 1245, 1081, 1032, 828, 640, 536, 522;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{32}N_2O_6$: 481.2260, found: 481.233;

HPLC (method 2): t_R = 14.9 min, purity 97.8%.

Methyl (2*S*,4*R*)-1-benzoyl-4-hydroxypyrrolidine-2-carboxylate (111)



$C_{13}H_{15}NO_4$

Mr = 249.3

Triethylamine (1.8 mL, 1345 mg, 11.01 mmol) was added to an ice-cooled solution of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**57**) (1.0 g, 5.51 mmol) in dichloromethane (20 mL) and the mixture was stirred for 15 min at 0 °C. Then, 4-dimethylaminopyridine (67 mg, 0.55 mmol) and benzoyl chloride (0.7 mL, 851 mg, 6.06 mmol) were added and the mixture was stirred for 2 h at ambient temperature. Afterwards, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with dichloromethane (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/1 → 0/1) to give **111** (845 mg, 18.76 mmol, 62%) as colorless solid.

m.p.: 145-146 °C;

TLC: R_f = 0.35 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -140.5 (2.2, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.00 – 2.09 (m, 1H, CHC*H*$_2$CH), 2.27 – 2.36 (m, 1H, CHC*H*$_2$CH), 3.44 (m, *J* = 11.4/1.9 Hz, 1H, NC*H*$_2$), 3.71 (m, *J* = 4.0 Hz, 1H, NC*H*$_2$), 3.73 (s, 3H, CO_2CH_3), 4.39 (m, *J* = 4.5/2.2 Hz, 1H, C*H*OH), 4.78 (t, *J* = 8.4 Hz, 1H, NC*H*), 7.30 – 7.44 (m, 3H, 3′-H$_{benzoyl}$,4′-H$_{benzoyl}$,5′-H$_{benzoyl}$), 7.47 – 7.52 (m, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);

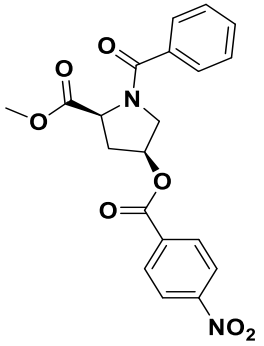
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 37.9 (1C, CH*C*H$_2$CH), 52.5 (1C, CO_2CH_3), 58.0 (1C, NCH$_2$), 58.1 (1C, NCH), 70.3 (1C, *C*HOH), 127.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.4 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.6 (1C, C-4′$_{benzoyl}$), 135.7 (1C, C-1′$_{benzoyl}$), 170.5 (1*C*, Ar*C*ON), 173.0 (1C, *C*O$_2$CH$_3$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3442, 2956, 2929, 1737, 1606, 1573, 1449, 1435, 1419, 1271, 1085, 1022, 795, 725, 702, 494;

HRMS (*m/z*): $[M+Na]^+$calcd for $C_{13}H_{15}NO_4$: 272.1001, found: 272.089;

HPLC (method 1): t_R = 12.8 min, purity 100%.

Methyl (2*S*,4*S*)-1-benzoyl-4-[(4-nitrobenzoyl)oxy]pyrrolidine-2-carboxylate (112)



$C_{20}H_{18}N_2O_7$

M_r = 398.5

Under N_2 atmosphere, DIAD (5.5 mL, 5.2 g, 25.63 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (6.7 g, 25.63 mmol) in dry THF (50 mL) and the mixture was stirred for 10 min at 0 °C. Then, a solution of *p*-nitrobenzoic acid (3.9 g, 23.30 mmol) and **111** (2.9 g, 11.65 mmol) in dry THF (20 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/2) to give **112** (2.3 g, 5.84 mmol, 50%) as pale-yellow oil.

TLC: R_f = 0.28 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = -5.8 (3.9, chloroform);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 2.33 (m, *J* = 14.3/3.0 Hz, 1H, CHC*H*$_2$CH), 2.74 (m, *J* = 29.2/14.6/9.6/5.3 Hz, 1H, CHC*H*$_2$CH), 3.68 (s, 3H, CO_2CH_3), 3.72 (d, *J* = 12.0 Hz, 1H, NC*H*$_2$), 3.97 (dd, *J* = 12.0/5.3 Hz, 1H, NC*H*$_2$), 4.87 (dd, *J* = 9.6/2.8 Hz, 1H, NC*H*), 5.52 (m, *J* = 5.3/2.3 Hz, 1H, C*H*O), 7.38 – 7.57 (m, 5H, 2′-$H_{benzoyl}$, 3′-$H_{benzoyl}$, 4′-$H_{benzoyl}$, 5′-$H_{benzoyl}$, 6′-

$H_{benzoyl}$), 8.09 - 8.14 (m, 2H, 2″-$H_{4\text{-nitrobenzoyl}}$, 6″-$H_{4\text{-nitrobenzoyl}}$), 8.35 – 8.40 (m, 2H, 3″-$H_{4\text{-nitrobenzoyl}}$, 5″-$H_{4\text{-nitrobenzoyl}}$), the signals of the major rotamer are given;

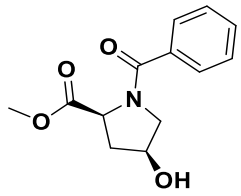
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 34.1 (1C, CH*C*H_2CH), 52.2 (1C, CO_2*C*H_3), 54.2 (1C, N*C*H_2), 57.3 (1C, N*C*H), 74.4 (1C, *C*HO), 123.9 (2C, C-3″$_{4\text{-nitrobenzoyl}}$, C-5″$_{4\text{-nitrobenzoyl}}$), 127.0 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.4 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.2 (1C, C-4′$_{benzoyl}$), 130.6 (2C, C-2″$_{4\text{-nitrobenzoyl}}$, C-6″$_{nitrobenzoyl}$), 134.7 (1C, C-1″$_{4\text{-nitrobenzoyl}}$), 135.8 (1C, C-1′$_{benzoyl}$), 150.4 (1C, C-4″$_{4\text{-nitrobenzoyl}}$), 163.5 (1C, Ar*C*O_2), 168.5 (1C, Ar*C*ON), 171.4 (1C, *C*O_2CH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2948, 2931, 1719, 1625, 1600, 1579, 1430, 1408, 1351, 1316, 1265, 1213, 1138, 1068, 1048, 893, 730, 717, 541, 504;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{18}N_2O_7$: 399.1114, found: 399.119;

HPLC (method 1): t_R = 21.5 min, purity 99.9%.

Methyl (2*S*,4*S*)-1-benzoyl-4-hydroxypyrrolidine-2-carboxylate (113)



$C_{13}H_{15}NO_4$

M_r = 249.3

At ambient temperature, potassium carbonate (7.8 g, 56.49 mmol) was added to a solution of **112** (2.0 g, 4.91 mmol) in dry methanol (50 mL). After stirring the reaction mixture for 30 min, the mixture was filtered and the filtrate was acidified by adding 0.5 N HCl. Then, a saturated aqueous solution of $NaHCO_3$ was added in excess to render the mixture alkaline and the mixture was extracted with dichloromethane (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **113** (813 mg, 3.26 mmol, 66%) as colorless solid.

m.p.= 98-99 °C;

TLC: R_f = 0.35 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = +15.4 (3.9, chloroform);

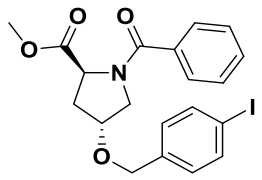
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.13 (d, *J* = 14.2 Hz, 1H, CHC*H*$_2$CH), 2.42 (m, *J* = 14.4/9.7/4.8 Hz, 1H, CHC*H*$_2$CH), 3.70 (d, *J* = 3.2 Hz, 2H, NC*H*$_2$), 3.85 (s, 3H, CO_2CH_3), 4.36 (m, *J* = 9.7 Hz, 1H, C*H*OH), 4.68 (dd, *J* = 9.8/2.2 Hz, 1H, NC*H*), 7.34 – 7.49 (m, 3H, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$), 7.50 – 7.57 (m, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);
^{13}C NMR (101.MHz, $CDCl_3$) δ [ppm]= 37.1 (1C, CH*C*H$_2$CH), 53.1 (1C, CO_2CH$_3$), 58.4 (1C, N*C*H), 58.7 (1C, N*C*H$_2$), 71.5 (1C, *C*HOH), 127.5 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.6 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.7 (1C, C-4′$_{benzoyl}$), 135.7 (1C, C-1′$_{benzoyl}$), 170.2 (1C, Ar*C*ON), 175.3 (1C, *C*O_2CH_3);

IR (neat): ṽ [cm^{-1}] = 3308, 2953, 2921, 1758, 1597, 1573, 1451, 1437, 1352, 1336, 1185, 1165, 1087, 790, 733, 698, 659, 541, 497;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{15}NO_4$: 272.1001, found: 272.090;

HPLC (method 1): t_R = 12.7 min, purity 89.5%.

Methyl (2*S*,4*R*)-1-benzoyl-4-[(4-iodobenzyl)oxy]pyrrolidine-2-carboxylate (114)



$C_{20}H_{20}INO_4$

Mr = 465.3

Under N_2 atmosphere, 4-iodobenzylbromide (810 mg, 2.73 mmol), silver(I) oxide (948 mg, 4.09 mmol), and potassium iodide (45 mg, 0.27 mmol) were added to a solution of **111** (340 mg, 1.36 mmol) in dichloromethane/cyclohexane (1/1) (15 mL). After stirring the reaction mixture for 36 h at ambient temperature, the mixture was filtered, and the solvent was concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 3/1 → 1/3) to give **114** (396 g, 0.85 mmol, 83%) as very sticky and colorless oil.

TLC: R_f = 0.38 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = -78.7 (3.6, methanol);

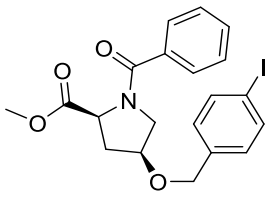
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.12 (m, *J* = 13.2/8.2/4.7 Hz, 1H, CHC*H*$_2$CH), 2.49 (m, *J* = 13.0/8.0/3.0/1.7 Hz, 1H, CHC*H*$_2$CH), 3.59 (m, *J* = 11.4/1.9 Hz, 1H, NC*H*$_2$), 3.72 – 3.84 (m, 1H, NC*H*$_2$), 3.72 - 3.84 (s, 3H. CO_2CH_3), 4.14 – 4.23 (m, 1H, C*H*O), 4.32 (d, *J* = 12.2 Hz, 1H, OC*H*$_2$Ar), 4.41 (d, *J* = 12.2 Hz, 1H, OC*H*$_2$Ar), 4.81 (t, *J* = 8.1 Hz, 1H, NC*H*), 6.98 (d, *J* = 8.2 Hz, 2H, 2″-H$_{4\text{-iodobenzyl}}$, 6″-H$_{4\text{-iodobenzyl}}$), 7.33 – 7.47 (m, 3H, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$), 7.51 – 7.59 (m, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), 7.59 – 7.70 (m, 2H, 3″-H$_{4\text{-iodobenzyl}}$, 5″-H$_{4\text{-iodobenzyl}}$);
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 35.0 (1C, CH*C*H$_2$CH), 52.6 (1C, CO_2*C*H$_3$), 55.1 (1C, N*C*H$_2$), 58.1 (1C, N*C*H), 70.6 (1C, O*C*H$_2$Ar), 77.3 (1C, *C*HO), 93.5 (1C, C-4″$_{4\text{-iodobenzyl}}$), 127.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.5 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.4 (2C, C-2″$_{4\text{-iodobenzyl}}$, C-6″$_{4\text{-iodobenzyl}}$), 130.6 (1C, C-4′$_{benzoyl}$), 135.8 (1C, C-1′$_{benzoyl}$), 137.4 (1C, C-1″$_{4\text{-iodobenzyl}}$), 137.8 (2C, C-3″$_{4\text{-iodobenzyl}}$, C-5″$_{4\text{-iodobenzyl}}$), 170.1 (1C, ArCON), 172.9 (1C, *C*O_2CH_3);

IR (neat): ṽ [cm^{-1}] = 2949, 2870, 1740, 1628, 1405, 1357, 1199, 1173, 1084, 1005, 790, 723, 670, 485, 472;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{20}INO_4$: 466.0437, found: 466.051;

HPLC (method 1): t_R = 23.5 min, purity 98.9%.

Methyl (2*S*,4*S*)-1-benzoyl-4-[(4-iodobenzyl)oxy]pyrrolidine-2-carboxylate (115)



$C_{20}H_{20}INO_4$

M_r = 465.3

Sodium hydride (60%) (67.40 mg, 1.20 mmol) was added to an ice-cooled solution of **113** (350 mg, 1.40 mmol) in dry DMF (15 mL) and the mixture was stirred for 30 min at ambient temperature. Then, a solution of 4-iodobenzylbromide (500 mg, 1.68 mmol) in dry DMF (10

mL) was added slowly over a period of 5 min. After stirring the reaction mixture for 18 h at ambient temperature, water was added to the mixture and extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4) and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 3/1 → 1/3) to give **115** (246 mg, 0.53 mmol, 38%) as colorless oil.

TLC: R_f = 0.38 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = +57.0 (4.1, chloroform);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.12 (m, *J* = 13.2/8.2/4.8 Hz, 1H, CHC*H*$_2$CH), 2.40 – 2.54 (m, 1H, CHC*H*$_2$CH), 3.59 (m, *J* = 11.5/3.1/2.5 Hz, 1H, NC*H*$_2$), 3.65 (d, *J* = 5.3 Hz, 1H, NC*H*$_2$), 3.79 (s, 3H, CO_2C*H*$_3$), 4.18 (m, *J* = 4.8, 2.5 Hz, 1H, C*H*O), 4.29 – 4.46 (m, 2H, OC*H*$_2$Ar), 4.81 (t, *J* = 8.1 Hz, 1H, NC*H*), 7.00 (m, *J* = 21.1/8.0 Hz, 2H, 2″-H$_{4\text{-iodobenzyl}}$, 6″-H$_{4\text{-iodobenzyl}}$), 7.35 – 7.47 (m, 3H, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$), 7.51 – 7.58 (m, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), 7.60 – 7.68 (m, 2H, 3″-H$_{4\text{-iodobenzyl}}$, 5″-H$_{4\text{-iodobenzyl}}$), the signals of the major rotamer are given;

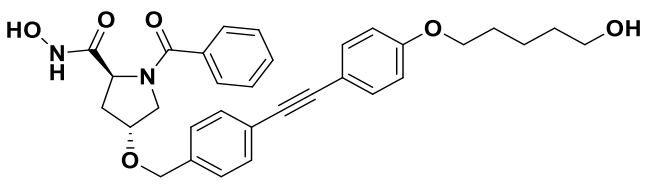
^{13}C NMR (126.MHz, $CDCl_3$) δ [ppm]= 35.1 (1C, CH*C*H$_2$CH), 52.6 (1C, CO_2*C*H$_3$), 55.1 (1C, N*C*H$_2$), 58.1 (1C, N*C*H), 70.6 (1C, O*C*H$_2$Ar), 77.5 (1C, *C*HO), 93.4 (1C, C-4″$_{4\text{-iodobenzyl}}$), 127.7 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.5 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.4 (2C, C-2″$_{4\text{-iodobenzyl}}$, C-6″$_{4\text{-iodobenzyl}}$), 130.6 (1C, C-4′$_{benzoyl}$), 135.8 (1C, C-1′$_{benzoyl}$), 137.4 (1C, C-1″$_{4\text{-iodobenzyl}}$), 137.8 (2C, C-3″$_{4\text{-iodobenzyl}}$, C-5″$_{4\text{-iodobenzyl}}$), 170.2 (1C, Ar*C*ON), 173.0 (1C, *C*O_2CH_3), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2948, 2872, 1742, 1628, 1405, 1357, 1198, 1175, 1087, 1006, 791, 725, 700, 487;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{20}INO_4$: 466.0437, found: 466.048;

HPLC (method 1): t_R = 23.5 min, purity 89.0%.

(2*S*,4*R*)-1-benzoyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenylethynyl}benzyl)oxy]pyrrolidine-2-carboxamide (116)



$C_{32}H_{34}N_2O_6$

M_r = 542.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (4 mg, 0.003 mmol), copper(I) iodide (2 mg, 0,01 mmol), triethylamine (0.13 mL, 91 mg, 0.90 mmol), and **71** (96 mg, 0.47 mmol) were added to a solution of **114** (170 mg, 0.30 mmol) in dry acetonitrile (15 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate, 3/2 → 0/1) to give **116a** (193 mg, 0.36 mmol, 96%) as brown oil.

An aqueous solution of hydroxylamine (50 wt%, 6 mL) was added to a solution of **116a** (64 mg, 0.14 mmol) in a mixture of THF (4 mL) and isopropanol (4 mL). After stirring the reaction mixture for 24 h at ambient temperature, brine was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **116** (59 mg, 0.11 mmol, 49%) as colorless solid.

m.p. = 52-53 °C;

TLC: R_f = 0.15 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -97.0 (1.2, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.50 – 1.66 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.81 (dt, *J* = 13.9/6.7 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.13 – 2.21 (m, 1H, $CHCH_2CH$), 2.46 (m, *J* = 13.5, 7.7, 1.9 Hz, 1H, $CHCH_2CH$), 3.52 – 3.64 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.52-3.64 (m, 1H, NCH_2), 3.75 – 3.85 (m, 1H, NCH_2), 4.01 (t, *J* = 6.4 Hz, 2H,

OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.23 (m, *J* = 4.1 Hz, 1H, C*H*O), 4.33 – 4.43 (d, 1H, OC*H*$_2$Ar), 4.51 (d, *J* = 12.4 Hz, 1H, OC*H*$_2$Ar), 4.56 – 4.68 (m, 1H, NC*H*), 6.86 – 6.96 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.20 – 7.26 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.35 – 7.52 (m, 3H, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$), 7.35 - 7.52 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.35 - 7.52 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$), 7.54 – 7.59 (m, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);

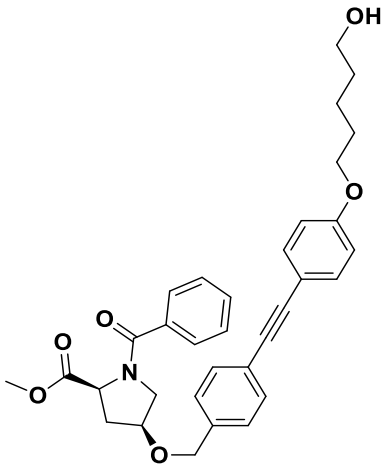
^{13}C NMR (151.MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH2OH), 30.2 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 33.4 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 36.7 (1C, CH*C*H$_2$CH), 57.0 (1C, N*C*H$_2$), 58.5 (1C, N*C*H), 62.9 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 69.1 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 71.5 (1C, O*C*H$_2$Ar), 79.0 (1C, *C*HO), 88.6 (1C, Ar*C*≡CAr), 90.6 (1C, ArC≡*C*Ar), 115.8 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.5 (1C, C-4″$_{benzyl}$), 128.7 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 128.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 129.6 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 131.9 (1C, C-4′$_{benzoyl}$), 132.4 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 134.1 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.0 (1C, C-1′$_{benzoyl}$), 139.6 (1C, C-1″$_{benzyl}$), 160.9 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 171.5 (1C, *C*ONHOH), 172.8 (1*C*, Ar*C*ON);

IR (neat): ṽ [cm^{-1}] = 3221, 2935, 2865, 1601, 1574, 1516, 1414, 1245, 1074, 1049, 1028, 1018, 829, 791, 723, 700, 539;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{32}H_{34}N_2O_6$: 543.2417, found: 543.248;

HPLC (method 2): t_R = 15.9 min, purity 100%.

Methyl (2*S*,4*S*)-1-benzoyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (117a)



$C_{33}H_{35}NO_6$

M_r = 541.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.004 mmol) copper(I) iodide (2 mg, 0.01 mmol), triethylamine (0.2 mL, 130 mg, 1.26 mmol), and **71** (138 mg, 0.68 mmol) were added to a solution of **115** (196 mg, 0.42 mmol) in dry acetonitrile (15 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate, 3/1 → 0/1) to give **117a** (153 mg, 0.22 mmol, 67%) as colorless oil.

TLC: R_f = 0.43 (petroleum ether/ethyl acetate, 1/3);

Specific rotation: $[\alpha]_D^{20}$ = +118.3 (1.2, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.50 – 1.60 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.60 – 1.69 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.77 – 1.89 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.17 (m, 1H, $CHCH_2CH$), 2.39 – 2.56 (m, 1H, $CHCH_2CH$), 3.59- 3.71 (m, 1H, NCH_2), 3.59- 3.71 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.76- 3.82 (m, 1H, NCH_2), 3.76 – 3.82 (s, 3H, CO_2CH_3), 3.98 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.16 – 4.26 (m, 1H, CHO), 4.35 – 4.53 (m, 2H, OCH_2Ar), 4.77 – 4.89 (m, 1H, NCH), 6.80 – 6.91 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.22 (m, 2H, 2″-$H_{benzyl}$, 6″-$H_{benzyl}$), 7.33 – 7.49 (m, 2H, 2‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.33- 7.49 (m, 2H, 3″-H_{benzyl}, 5″-

H_{benzyl}), 7.33 - 7.49 (m, 3H, 3′-H $_{benzoyl}$, 4′-$H_{benzoyl}$, 5′-$H_{benzoyl}$), 7.51 – 7.60 (m, 2H, 2′-$H_{benzoyl}$, 6′-$H_{benzoyl}$), the signals of the major rotamer are given;

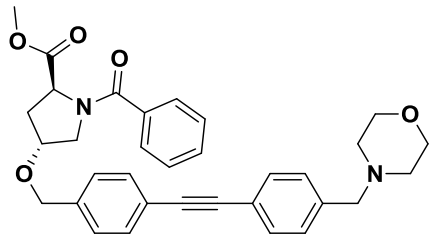
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 29.1 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 35.1 (1C, $CH\mathit{C}H_2CH$), 55.1 (1C, $N\mathit{C}H_2$), 58.2 (1C, $N\mathit{C}H$), 62.9 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 68.1 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 70.9 (1C, $O\mathit{C}H_2Ar$), 77.4 (1C, *C*HO), 87.8 (1C, Ar*C*≡CAr), 89.9 (1C, ArC≡*C*Ar), 114.7 (2C, C-3′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.3 (1C, C-1′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 123.4 (1C, C-4″$_{benzyl}$), 127.5 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 127.6 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 128.5 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.6 (1C, C-4′$_{benzoyl}$), 131.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 133.2 (2C, (2C, C-2′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.5 (1C, C-1″$_{benzyl}$), 159.4 (1C, C-4′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 170.2 (1C, Ar*C*ON), 173.0 (1C, $\mathit{C}O_2CH_3$), the signal for C-1′$_{benzoyl}$ cannot be observed in the spectrum, the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3403, 2938, 2865, 1739, 1625, 1601, 1516, 1413, 1244, 1204, 1173, 1073, 1018, 829, 726, 701, 538, 520;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{35}NO_6$: 542.2464, found: 542.252;

HPLC (method 1): t_R = 24.3 min, purity 93.4%.

Methyl (2*S*,4*R*)-1-benzoyl-4-({4-[(4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxylate (118a)



$C_{33}H_{34}N_2O_5$

M_r = 538.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (8 mg, 0.01mmol), copper(I) iodide (4 mg, 0.02 mmol), triethylamine (0.3 mL, 202 mg, 1.99 mmol), and **103** (200 mg, 1.00 mmol) were added to a solution of **114** (309 mg, 0.66 mmol) in dry acetonitrile (15 mL) and stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue

was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **118a** (97 mg, 0.18 mmol, 27%) as brown oil.

TLC: R_f = 0.28 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -82.2 (0.9, methanol);

^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ [ppm]= 2.15 (m, *J* = 13.7/9.3/4.4 Hz, 1H, CHC*H*$_2$CH), 2.50 (t, *J* = 4.7 Hz, 4H, NC*H*$_2$CH$_2$O), 2.59 (m, *J* = 13.6, 7.9, 2.1 Hz, 1H, CHC*H*$_2$CH), 3.55 – 3.64 (m, 1H, NC*H*$_2$), 3.55- 3.64 (s, 2H, ArC*H*$_2$), 3.71 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.80 (m, 1H, NC*H*$_2$), 3.80 (s, 3H, CO$_2$C*H*$_3$), 4.27 (m, *J* = 3.9, 1.7 Hz, 1H, C*H*O), 4.44 (d, *J* = 12.5 Hz, 1H, OC*H*$_2$Ar), 4.57 (d, *J* = 12.4 Hz, 1H, OC*H*$_2$Ar), 4.75 (dd, *J* = 9.3, 7.9 Hz, 1H, NC*H*), 7.28 (m, *J* = 7.9 Hz, 2H, 2″-H$_{benzyl,}$ 6″-H$_{benzyl}$), 7.39 (m, *J* = 8.1 Hz, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.41 – 7.60 (m, 2H, 3″-H$_{benzyl,}$ 5″-H$_{benzyl}$), 7.41 - 7.60 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.41 - 7.60 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);

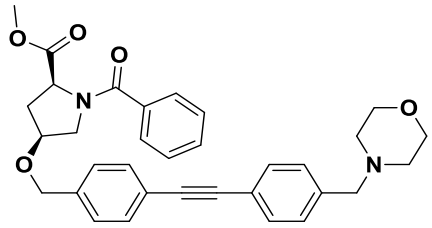
^{13}C NMR (126.MHz, MeOD-*d*$_4$) δ [ppm]= 36.1 (1C, CHC*H*$_2$CH), 53.0 (1C, CO$_2$*C*H3), 54.7 (2C, N*C*H$_2$CH$_2$O), 56.6 (1C, N*C*H$_2$), 59.6 (1C, N*C*H), 64.0 (1C, Ar*C*H$_2$), 67.8 (2C, NCH$_2$*C*H$_2$O), 71.6 (1C, O*C*H$_2$Ar), 79.0 (1C, *C*HO), 90.1 (1C, (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 128.5 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.8 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.7 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.9 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.0 (1C, C-4′$_{benzoyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 140.0 (1C, C-1″$_{benzyl}$), 172.5 (1*C*, Ar*C*ON), 174.3 (1C, *C*O$_2$CH$_3$), the signals for C-1′$_{benzoyl}$, C-4″$_{benzyl}$, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, and C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3030, 2952, 2853, 2809, 1742, 1632, 1409, 1200, 1175, 1114, 1088, 1007, 865, 820, 792, 722, 699, 517;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{34}N_2O_5$: 539.2468, found: 539.251;

HPLC (method 1): t_R = 19.5 min, purity 88.5%.

Methyl (2*S*,4*S*)-1-benzoyl-4-({4-[(4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxylate (119a)



$C_{33}H_{34}N_2O_5$

M_r = 538.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.01mmol), copper(I) iodide (7 mg, 0.04 mmol), triethylamine (0.5 mL, 360 mg, 3.56 mmol), and **103** (358 mg, 1.78 mmol) were added to a solution of **115** (552 mg, 1.19 mmol) in dry acetonitrile (15 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **119a** (546 mg, 1.01 mmol, 85%) as yellow oil.

TLC: R_f = 0.33 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$.= +101.3 (3.5, methanol);

^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ [ppm]= 2.17 (m, 1H, CHC*H*$_2$CH), 2.48 (t, *J* = 4.7 Hz, 4H, NC*H*$_2$CH$_2$O), 2.59 (m, *J* = 13.6/8.0/2.1 Hz, 1H, CHC*H*$_2$CH), 3.56 (s, 2H, ArC*H*$_2$), 3.60 (m, *J* = 11.8, 1.7 Hz, 1H, NC*H*$_2$), 3.71 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.80 (m, 1H, NC*H*$_2$), 3.80 (s, 3H, CO$_2$C*H*$_3$), 4.26 (m, *J* = 4.4/2.8/2.2 Hz, 1H, C*H*O), 4.43 (d, *J* = 12.5 Hz, 1H, OC*H*$_2$Ar), 4.56 (d, *J* = 12.5 Hz, 1H, OC*H*$_2$Ar), 4.71 – 4.79 (m, 1H, NC*H*), 7.28 (m, *J* = 8.1 Hz, 2H, 2″-H$_{benzyl,}$ 6″-H$_{benzyl}$), 7.39 (m, *J* = 8.1 Hz, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.42 - 7.60 (m, 2H, 3″-H$_{benzyl,}$ 5″-H$_{benzyl}$), 7.42 - 7.60 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.42 – 7.60 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);

^{13}C NMR (126.MHz, MeOD-*d*$_4$) δ [ppm]= 36.1 (1C, CHC*H*$_2$CH), 53.0 (1C, CO$_2$*C*H3), 54.8 (2C, N*C*H$_2$CH$_2$O), 56.6 (1C, N*C*H$_2$), 59.6 (1C, N*C*H), 64.1 (1C, Ar*C*H$_2$), 67.9 (2C, NCH$_2$*C*H$_2$O), 71.6 (1C, O*C*H$_2$Ar), 79.0 (1C, *C*HO), 90.1 (1C, (1C, Ar*C*≡CAr), 90.3 (1C,

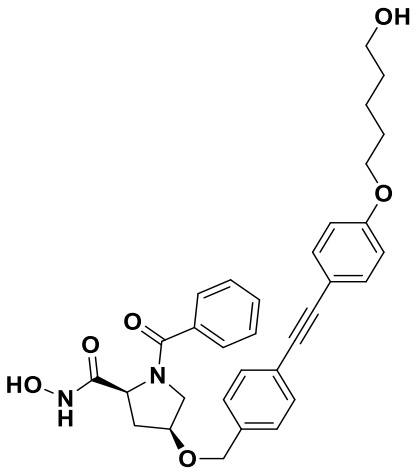
ArC≡*C*Ar), 123.7 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 124.0 (1C, C-4″$_{benzyl}$), 128.5 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.8 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.7 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.8 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.0 (1C, C-4′$_{benzoyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 136.8 (1C, C-1′$_{benzoyl}$), 139.2 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 140.0 (1C, C-1″$_{benzyl}$), 172.5 (1*C*, Ar*C*ON $_{benzoyl}$), 174.3 (1C, *C*O_2CH_3);

IR (neat): ṽ [cm^{-1}] = 3458, 3030, 2855, 2809, 1744, 1631, 1409, 1349, 1200, 1175, 1114, 1088, 1006, 865, 820, 722, 700, 541;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{34}N_2O_5$: 539.2468, found: 539.254;

HPLC (method 1): t_R = 19.4 min, purity 86.7%.

(2*S*,4*S*)-1-benzoyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (117)



$C_{32}H_{34}N_2O_6$

M_r = 542.6

An aqueous solution of hydroxylamine (50 wt%, 6 mL) was added to a solution of **117a** (130 mg, 0.24 mmol) in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture for 48 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-

HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **117** (67 mg, 0.12 mmol, 52%) as colorless solid.

m.p. = 68-70 °C;

TLC: R_f = 0.30 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +51.2 (3.3, methanol);

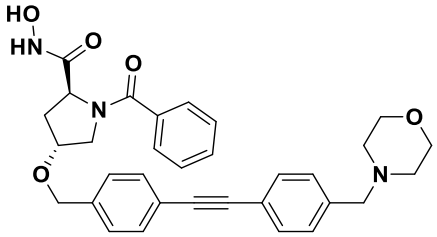
^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.51 – 1.67 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.82 (m, *J* = 6.6 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.14 – 2.25 (m, 1H, $CHCH_2CH$), 2.43 – 2.54 (m, 1H, $CHCH_2CH$), 3.54 – 3.64 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.54- 3.64 (m, 1H, NCH_2), 3.81 (dd, *J* = 11.9/3.5 Hz, 1H, NCH_2), 4.02 (t, *J* = 6.4/1.1 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.25 (m, *J* = 4.1 Hz, 1H, CHO), 4.39 (d, *J* = 12.4 Hz, 1H, OCH_2Ar), 4.45 – 4.64 (m, 1H, OCH_2Ar), 4.45 - 4.64 (m, 1H, NCH), 6.92 (m, *J* = 8.8/2.0 Hz, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.21 – 7.26 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.37 – 7.52 (m, 3H, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$), 7.37 – 7.52 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.37 - 7.52 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$), 7.55 – 7.59 (m, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), the signals of the major rotamer are given;
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.3 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 36.7 (1C, $CHCH_2CH$), 57.0 (1C, NCH_2), 58.5 (1C, NCH), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 69.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 71.6 (1C, OCH_2Ar), 79.0 (1C, CHO), 88.6 (1C, Ar*C*≡CAr), 90.6 (1C, ArC≡*C*Ar), 115.8 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.5 (1C, C-4″$_{benzyl}$), 128.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.8 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.6 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 131.9 (1C, C-4′$_{benzoyl}$), 132.5 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 134.1 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.0 (1C, C-1′$_{benzoyl}$), 139.6 (1C, C-1″$_{benzyl}$), 160.9 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 171.6 (1C, *C*ONHOH), 172.8 (1*C*, Ar*C*ON), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3210, 2934, 2868, 1601, 1573, 1516, 1415, 1245, 1075, 1051, 1018, 828, 791, 701, 538, 521;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{34}N_2O_6$: 543.2417, found: 543.250;

HPLC (method 2): t_R = 15.9 min, purity 99.7 %.

(2*S*,4*R*)-1-Benzoyl-*N*-hydroxy-4-({4-[(4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxamide (118)



$C_{32}H_{33}N_3O_5$

M_r = 539.6

An aqueous solution of hydroxylamine (50 wt%, 6.0 mL) was added to a solution of **118a** (128 mg, 0.29 mmol) in a mixture of THF (15 mL) and isopropanol (15 mL). After stirring the reaction mixture for 48 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **118** (60 mg, 0.12 mmol, 49%) as colorless solid.

m.p.= 121-122 °C;

TLC: R_f = 0.25 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -81.9 (2.1, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= δ 2.14 – 2.22 (m, 1H, CHC*H*$_2$CH), 2.46 (m, 1H, CHC*H*$_2$CH), 2.46 (t, 4H, NC*H*$_2$CH$_2$O), 3.53 (s, 2H, ArC*H*$_2$), 3.54 – 3.59 (m, 1H, NC*H*$_2$), 3.69 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.80 (dd, *J* = 11.9/3.5 Hz, 1H, NC*H*$_2$), 4.23 (m, 1H, C*H*O), 4.34 – 4.41 (d, 1H, OC*H*$_2$Ar), 4.52 (d, *J* = 12.5 Hz, 1H, OC*H*$_2$Ar), 4.60 (dd, *J* = 9.5/7.6 Hz, 1H, NC*H*), 7.24 (m, *J* = 8.0 Hz, 2H, 2″-H$_{benzyl,}$ 6″-H$_{benzyl}$), 7.36 (m, *J* = 8.1 Hz, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.40 – 7.59 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$), 7.40-7.59 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.40 - 7.59 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);

^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 36.7 (1C, CHC*H*$_2$CH), 54.7 (2C, N*C*H$_2$CH$_2$O), 57.0 (1C, N*C*H$_2$), 58.5 (1C, N*C*H), 64.0 (1C, Ar*C*H$_2$), 67.9 (2C, NCH$_2$*C*H$_2$O), 71.5 (1C, O*C*H$_2$Ar),

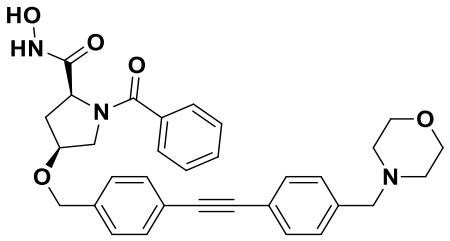
79.1 (1C, *C*HO), 90.1 (1C, Ar*C*≡CAr), 90.3 (1C, (1C, ArC≡*C*Ar), 123.6 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 124.0 (1C, C-4″$_{benzyl}$), 128.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.8 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.6 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.8 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.9 (1C, C-4′$_{benzoyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 137.0 (1C, C-1′$_{benzoyl}$), 139.2 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 140.1 (1C, C-1″$_{benzyl}$), 171.5 (1C, *C*ONHOH), 172.8 (1*C*, Ar*C*ON);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3201, 2947, 2856, 2812, 1411, 1115, 1089, 950, 820, 791, 722, 700, 664, 541;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{33}N_3O_5$: 540.2420, found: 540.248;

HPLC (method 2): t_R = 13.4 min, purity 99.0 %.

(2*S*,4*S*)-1-Benzoyl-*N*-hydroxy-4-({4-[(4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxamide (119)



$C_{32}H_{33}N_3O_5$

M_r = 539.6

An aqueous solution of hydroxylamine (50 wt%, 16.0 mL) was added to a solution of **119a** (320 mg, 0.59 mmol) in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture for 6 d at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **119** (130 mg, 0.24 mmol, 41%) as colorless solid.

m.p.= 101-102 °C;

TLC: R_f = 0.18 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +131.0 (1.5, methanol);

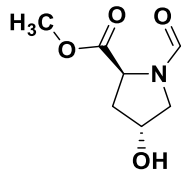
^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 2.11 – 2.19 (m, 1H, CHC*H*$_2$CH), 2.44 (m, 1H, CHC*H*$_2$CH), 2.44 (t, 4H, NC*H*$_2$CH$_2$O), 3.51 (s, 2H, ArC*H*$_2$), 3.54 (m, *J* = 11.9/1.4 Hz, 1H, NC*H*$_2$), 3.67 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.79 (dd, *J* = 11.9/3.5 Hz, 1H, NC*H*$_2$), 4.21 (m, 1H, C*H*O), 4.36 (d, *J* = 12.5 Hz, 1H, OC*H*$_2$Ar), 4.50 (d, *J* = 12.4 Hz, 1H, OC*H*$_2$Ar), 4.59 (dd, *J* = 9.5/7.5 Hz, 1H, NC*H*), 7.22 (m, *J* = 8.0 Hz, 2H, 2″-H$_{benzyl,}$ 6″-H$_{benzyl}$), 7.32 – 7.36 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.38 - 7.51 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$), 7.38 - 7.51 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl,}$ 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.38 – 7.51 (m, 3H, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$), 7.52 – 7.57 (m, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 36.7 (1C, CHC*H*$_2$CH), 54.7 (2C, N*C*H$_2$CH$_2$O), 57.0 (1C, N*C*H$_2$), 58.5 (1C, N*C*H), 64.0 (1C, Ar*C*H$_2$), 67.9 (2C, NCH$_2$*C*H$_2$O), 71.5 (1C, O*C*H$_2$Ar), 79.1 (1C, *C*HO), 90.1 (1C, Ar*C*≡CAr), 90.3 (1C, (1C, ArC≡*C*Ar), 123.6 (1C, C-1‴$_{4\text{-}[(4\text{-}(morpholinomethyl)phenyl}$), 124.0 (1C, C-4″$_{benzyl}$), 128.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.8 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.6 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.8 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.9 (1C, C-4′$_{benzoyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 137.0 (1C, C-1′$_{benzoyl}$), 139.2 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 140.1 (1C, C-1″$_{benzyl}$), 171.4 (1C, *C*ONHOH), 172.8 (1*C*, Ar*C*ON);

IR (neat): ṽ [cm^{-1}] = 3200, 2852, 2806, 1615, 1447, 1411, 1350, 1114, 1088, 1071, 1005, 864, 819, 791, 722, 700, 663, 541;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{32}H_{33}N_3O_5$: 540.2420, found: 540.247;

HPLC (method 2): t_R = 13.3 min, purity 100.0 %.

Methyl (2*S*,4*R*)-1-formyl-4-hydroxypyrrolidine-2-carboxylate (120)



$C_7H_{11}NO_4$

M_r =173.2

Triethylamine (0.9 mL, 674 mg, 6.66 mmol) was added to a solution of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (1.1 g, 6.08 mmol) in toluene (100 mL) and the mixture was stirred for 15 min at ambient temperature. Then, formic acid (0.3 mL, 308 mg, 6.69 mmol) was added and the mixture was refluxed for 18 h. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 3 cm, V = 60 mL, dichloromethane/methanol, 9/1) to give **120** (302 mg, 1.74 mmol, 29%) as brown oil.

TLC: R_f = 0.33 (dichloromethane/methanol, 95/5);

Specific rotation $[\alpha]_D^{20}$ = -1.8 (1.7, methanol);

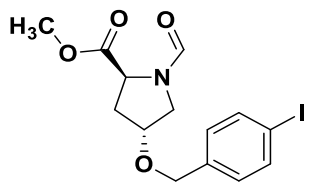
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 2.06 - 2.15 (m, 1H, CHC*H*$_2$CH), 2.37 (m, 1H, CHC*H*$_2$CH), 3.63 (m, 1H, NC*H*$_2$), 3.69 (m, 1H, NC*H*$_2$), 3.74 (s, 3H, CO_2CH_3), 4.52 (m, 1H, C*H*OH), 4.59 (m, 1H, NC*H*), 5.45 (d, 1H, CHO*H*), 8.23 (s, 1H, NC*H*O), the signals of the major rotamer are given;

^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 38.3 (CH*C*H$_2$CH), 52.7 (1C, *C*O_2CH_3), 54.7 (1C, N*C*H$_2$), 55.5 (1C, N*C*H), 69.6 (1C, *C*HOH), 161.6 (1C, N*C*HO), 172.3 (1C, *C*O_2CH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3396, 2955, 1738, 1650, 1424, 1382, 1172, 1082, 1057, 1016, 735, 662, 544;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_7H_{11}NO_4$: 196.0688, found: 196.059.

Methyl (2*S*,4*R*)-1-formyl-4-((4-iodobenzyl)oxy]pyrrolidine-2-carboxylate (123)



$C_{14}H_{16}INO_4$

Mr = 389.2

Under N_2 atmosphere, 4-iodobenzylbromide (2.3 g, 7.76 mmol), silver(I) oxide (2.7 g, 11.64 mmol), and potassium iodide (73 mg, 0.44 mmol) were added to a solution of **120** (672 mg, 3.88 mmol) in dichloromethane/cyclohexane (1/1) (20 mL). After stirring the reaction mixture for 36 h at ambient temperature, the mixture was filtered, and the solvent was concentrated *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/3 → 0/1) to give **123** (341 mg, 0.88 mmol, 23%) as colorless oil.

TLC: R_f = 0.35 (petroleum ether/ethyl acetate, 1/2);

Specific rotation: $[\alpha]_D^{20}$ = -37.0 (3.2, methanol);

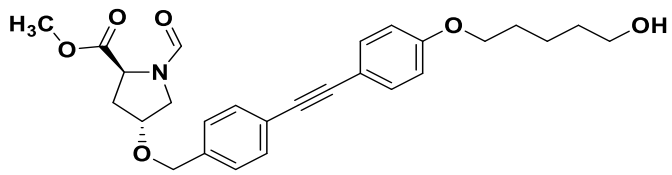
^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.01 – 2.14 (m, 1H, CHC*H*$_2$CH), 2.45 (m, *J* = 15.4/8.1/3.4/2.0 Hz, 1H, CHC*H*$_2$CH), 3.64 – 3.73 (m, 2H, NC*H*$_2$), 3.76 (s, 3H, CO_2CH_3), 4.21 (m, *J* = 5.9/2.6 Hz, 1H, C*H*O), 4.35 – 4.50 (m, 2H, OC*H*$_2$Ar), 4.56 (m, *J* = 9.8/7.9 Hz, 1H, NC*H*), 7.04 (m, *J* = 8.4/2.5 Hz, 2H, 2′-H$_{4\text{-iodobenzyl}}$, 6′-H$_{4\text{-iodobenzyl}}$), 7.67 (m, *J* = 8.7/2.3 Hz, 2H, 3′-H$_{4\text{-iodobenzyl}}$, 5′-H$_{4\text{-iodobenzyl}}$), 8.24 (s, 1H, NC*H*O), the signals of the major rotamer are given;
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 35.3 (1C, CH*C*H$_2$CH), 51.7 (1C, N*C*H$_2$), 52.7 (1C, CO_2CH_3), 55.5 (1C, N*C*H), 70.7 (1C, O*C*H$_2$Ar), 76.6 (1C, *C*HO), 93.6 (C-4′$_{4\text{-iodobenzyl}}$), 129.5 (2C, C-2′$_{4\text{-iodobenzyl}}$, C-6′$_{4\text{-iodobenzyl}}$), 137.3 (1C, C-1′$_{4\text{-iodobenzyl}}$), 137.8 (2C, C-3′$_{4\text{-iodobenzyl}}$, C-5′$_{4\text{-iodobenzyl}}$), 161.2 (1C, N*C*HO), 172.2 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2950, 2867, 1740, 1662, 1379, 1352, 1196, 1175, 1084, 1006, 800;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{16}INO_4$: 390.0124, found: 390.018;

HPLC (method 1): t_R = 20.7 min, purity 100%.

Methyl (2*S*,4*R*)-1-formyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy)pyrrolidine-2-carboxylate (125)



$C_{27}H_{31}NO_6$

Mr = 465.5

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (4 mg, 0.003mmol) copper(I) iodide (2 mg, 0,01 mmol), triethylamine (0.13 mL, 94 mg, 0.93 mmol), and **71** (81 mg, 0.40 mmol) were added to a solution of **123** (121 mg, 0.31 mmol) in acetonitrile (10 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate, 1/1 to 0/1) to give **125** (137 mg, 0.29 mmol, 95%) as yellowish-brown oil.

TLC: R_f = 0.28 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -26.7 (1.4, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 1.49 – 1.71 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.83 (m, *J* = 6.6 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 2.05 – 2.15 (m, 1H, $CHC\mathit{H}_2CH$), 2.41 – 2.54 (m, 1H, $CHC\mathit{H}_2CH$), 3.64 – 3.74 (t, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.64-3.74 (m, 2H, $NC\mathit{H}_2$), 3.75 (s, 3H, $CO_2C\mathit{H}_3$), 3.97 (t, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.16 – 4.27 (m, 1H, C*H*O), 4.43 – 4.63 (m, 1H, NC*H*), 4.43-4.63 (m, 2H, $OC\mathit{H}_2Ar$), 6.81 – 6.90 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 7.22 – 7.30 (m, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.40 – 7.52 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 7.40 - 7.52 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), 8.23 (s, 1H, NC*H*O), the signals of the major rotamer are given;

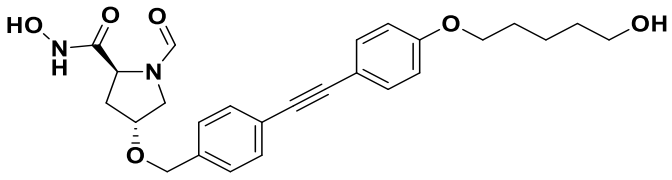
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $OCH_2CH_2C\mathit{H}_2CH_2CH_2OH$), 29.1 (1C, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2C\mathit{H}_2CH_2OH$), 35.3 (1C, $CHC\mathit{H}_2CH$), 51.7 (1C, $NC\mathit{H}_2$), 52.7 (1C, $CO_2C\mathit{H}_3$), 55.6 (1C, NC*H*), 62.9 (1C, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 68.0 (1C, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 71.1 (1C, $OC\mathit{H}_2Ar$), 76.5 (1C, C*H*O), 87.8 (1C,

Ar*C*≡CAr), 90.0 (1C, ArC≡*C*Ar), 114.7 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.2 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 123.5 (1C, C-4′$_{benzyl}$), 127.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.8 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.4 (1C, C-1′$_{benzyl}$), 159.4 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 161.2 (1C, N*C*HO), 172.2 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;
IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3435, 2935, 2865, 1742, 1664, 1602, 1384, 1244, 1209, 1174, 1075, 1017, 830, 539, 521;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{27}H_{31}NO_6$: 465.2151, found: 466.222;

HPLC (method 1): t_R = 22.3 min, purity 96.9 %.

(2S,4*R*)-1-formyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (126)



$C_{26}H_{30}N_2O_6$

M_r = 466.5

An aqueous solution of hydroxylamine (50 wt%, 3.5 mL) was added to a solution of **125** (122 mg, 0.26 mmol) in THF (8 mL). After stirring the reaction mixture for 48 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **126** (23 mg, 0.05 mmol, 19%) as colorless solid.

m.p. = 124-125 °C (decomposition);

TLC: R_f = 0.13 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +225 (0.9, methanol);

^{1}H NMR (600 MHz, DMSO-*d_6*) δ [ppm]= 1.39 – 1.50 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.63-1.80 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.98 (m, *J* = 13.2/8.3/4.7 Hz, 1H, $CHCH_2CH$), 2.29 (m, *J* = 12.6/7.6/2.2 Hz, 1H, $CHCH_2CH$), 3.41 (dt, *J*= 6.0 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.51 (dd, *J*= 11.6/3.7 Hz, 1H, NCH_2), 3.85 (m, *J* = 11.8/1.8 Hz, 1H, NCH_2), 4.00 (t, *J* = 6.5 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.15 – 4.23 (m, 1H, CHO), 4.15 – 4.23 (m, 1H, NCH), 4.38 (t, *J* = 5.1 Hz, 1H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.52 (m, *J* = 3.8 Hz, 2H, OCH_2Ar), 6.92 – 7.01 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.34 (m, 2H, 2′-$H_{benzyl}$, 6′-$H_{benzyl}$), 7.43 – 7.54 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.43 - 7.54 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), 8.18 (s, 1H, NCHO), 8.90 (1H, CONHOH), 10.66 (1H, CONHOH), the signals of the major rotamer are given;

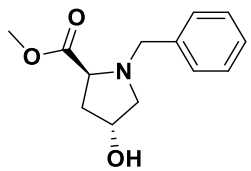
^{13}C NMR (151 MHz, DMSO-*d_6*) δ [ppm]= 22.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 28.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 35.4 (1C, $CHCH_2CH$), 51.4 (1C, NCH_2), 54.0 (1C, NCH), 60.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 67.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 69.3 (1C, OCH_2Ar), 76.3 (1C, CHO), 87.8 (1C, ArC≡CAr), 89.5 (1C, ArC≡CAr), 114.0 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 114.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy)phenyl})}$, 121.7 (1C, C-4′$_{benzyl}$), 127.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.1 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 132.9 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 138.6 (1C, C-1′$_{benzyl}$), 159.0 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 161.4 (1C, NCHO), 167.7 (1C, CONHOH), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2935, 2861, 2213, 1640, 1601, 1517, 1426, 1376, 1244, 1074, 828, 739, 643, 523;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{30}N_2O_6$: 467.2104, found: 467.215;

HPLC (method 2): t_R = 14.9 min, purity 100%.

Methyl (2*S*,4*R*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (133)



$C_{13}H_{17}NO_3$

M_r = 235.3

Triethylamine (1.5 mL, 1114 mg, 11.01 mmol) was added to a solution of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**57**) (1.0 g, 22.02 mmol) in acetonitrile (15 mL) and the mixture was stirred for 15 min at ambient temperature. Then, benzyl bromide (0.7 mL, 1036 mg, 6.06 mmol) was added and the reaction mixture was refluxed for 2 h. Afterwards, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/2 → 0/1) to give **133** (1.1 g, 4.81 mmol, 87%) as pale-yellow oil.

TLC: R_f = 0.30 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = -52.7 (4.2, methanol);

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ [ppm]= 1.89 (m, *J* = 12.9/7.9/3.8 Hz, 1H, CHC*H*$_2$CH), 2.02 (m, *J* = 13.0/7.3 Hz, 1H, CHC*H*$_2$CH), 2.24 (dd, *J* = 9.7/4.4 Hz, 1H, NC*H*$_2$), 3.06 (dd, *J* = 9.7/5.9 Hz, 1H, NC*H*$_2$), 3.46 (t, *J* = 7.8 Hz, 1H, NC*H*), 3.51 (d, *J* = 13.2 Hz, 1H, C*H*$_2$Ar), 3.57 (s, 3H, CO_2CH_3), 3.85 (d, *J* = 13.1 Hz, 1H, C*H*$_2$Ar), 4.20 (m, *J* = 10.1/8.3/4.2 Hz, 1H, C*H*OH), 4.87 (d, *J* = 4.3 Hz, 1H, CHO*H*), 7.20 - 7.25 (m, 1H, 4′-H$_{benzyl}$), 7.26 – 7.33 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$);

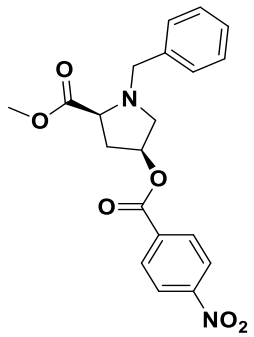
^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ [ppm]= 38.9 (1C, CH*C*H$_2$CH), 51.3 (1C, CO_2CH_3), 57.9 (1C, *C*H$_2$Ar), 61.0 (1C, N*C*H$_2$), 63.6 (1C, N*C*H), 68.4 (1C, *C*HOH), 126.8 (1C, C-4′$_{benzyl}$), 128.0 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.5 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 138.7 (1C, C-1′$_{benzyl}$), 173.5 (1C, *C*O_2CH_3);

IR (neat): ṽ [cm^{-1}] = 3411, 2950, 2807, 1731, 1454, 1436, 1198, 1173, 1084, 1028, 751, 699;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{17}NO_3$: 236.1208, found: 236.129;

HPLC (method 1): t_R = 11.4 min, purity 100%.

Methyl (2*S*,4*S*)-1-benzyl-4-[(4-nitrobenzoyl)oxy]pyrrolidine-2-carboxylate (134)



$C_{20}H_{20}N_2O_6$

M_r = 384.4

Under N_2 atmosphere, DIAD (13.7 mL, 12857 mg, 63.58 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (16.7 g, 63.58 mmol) in dry THF (80 mL) and the mixture was stirred for 10 min at 0 °C. Then, a solution of *p*- nitrobenzoic acid (9.7 g, 57.80 mmol) and **133** (6.8 g, 28.90 mmol) in dry THF (40 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 8 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 3/2). Fractions containing the desired product were combined and evaporated *in vacuo.* A share (200 mg, 0.9%) of the obtained residue (22.2 g) was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **134** as yellow oil for analysis.

TLC: R_f = 0.43 (petroleum ether/ethyl acetate, 3/1);

Specific rotation: $[\alpha]_D^{20}$ = -6.0 (1.3, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.21 (m, *J* = 14.3/6.7/3.1/1.0 Hz ,1H, CHC*H*$_2$CH), 2.61 (m, *J* = 14.3/8.6/7.4 Hz, 1H, CHC*H*$_2$CH), 2.80 (dd, *J* = 11.2/6.0 Hz, 1H, 1H, NC*H*$_2$), 3.16 (m, *J* = 11.1/1.4 Hz, 1H, NC*H*$_2$), 3.35 (dd, *J* = 8.6/6.7 Hz, 1H, NC*H*), 3.57 (d, *J* = 13.2 Hz, 1H, C*H*$_2$Ar), 3.64 (s, 3H, CO_2CH_3), 3.97 (d, *J* = 13.1 Hz, 1H, C*H*$_2$Ar), 5.30 – 5.42 (m, 1H, C*H*O),

7.15 – 7.30 (m, 5H, 2′-H_{benzyl}, 3′-H_{benzyl}, 4′-H_{benzyl}, 5′-H_{benzyl}, 6′-H_{benzyl}), 8.09 - 8.15 (m, 2H, 2″-$H_{4\text{-nitrobenzoyl}}$, 6″-$H_{4\text{-nitrobenzoyl}}$), 8.17- 8.23 (m, 2H, 3″-$H_{4\text{-nitrobenzoyl}}$, 5″-$H_{4\text{-nitrobenzoyl}}$);

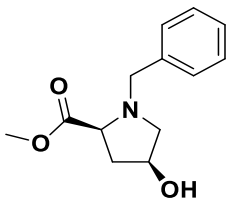
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 36.6 (1C, CH*C*H_2CH), 52.2 (1C, CO_2*C*H_3), 57.8 (1C, *C*H_2Ar), 58.5 (1C, N*C*H_2), 63.8 (1C, N*C*H), 74.4 (1C, *C*HO), 123.7 (2C, C-3″$_{4\text{-nitrobenzoyl}}$, C-5″$_{4\text{-nitrobenzoyl}}$), 127.6 (1C, C-4′$_{benzyl}$), 128.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.3 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.0 (2C, C-2″$_{4\text{-nitrobenzoyl}}$, C-6″$_{4\text{-nitrobenzoyl}}$), 135.7 (1C, C-1″$_{4\text{-nitrobenzoyl}}$), 137.5 (1C, C-1′$_{benzyl}$), 150.8 (1C, C-4″$_{4\text{-nitrobenzoyl}}$), 164.7 (1C, Ar*C*O_2), 173.4 (1C, *C*O_2CH_3);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2951, 2806, 1718, 1525, 1272, 1200, 1172, 1117, 1013, 873, 861, 838, 718, 700;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{20}N_2O_6$: 385.1321, found: 385.138;

HPLC (method 1): t_R = 19.2 min, purity 99.7%.

Methyl (2*S*,4*S*)-1-benzyl-4-hydroxypyrrolidine-2-carboxylate (135)



$C_{13}H_{17}NO_3$

M_r = 235.3

At ambient temperature, potassium carbonate (67.2 g, 138.20 mmol) was added to a solution of crude **134** (18.7 g, 48.65 mmol) in dry methanol (50 mL). After stirring the reaction mixture for 30 min, the mixture was filtered and the filtrate was acidified by adding 0.5 N HCl. Then, a saturated aqueous solution of $NaHCO_3$ was added in excess to render the mixture alkaline and the mixture was extracted with dichloromethane (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **135** (3.0 g, 3.26 mmol, 26%) as yellow oil.

TLC: R_f = 0.30 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = -67.1 (15.9, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 1.90 – 1.98 (m, 1H, CHC*H*$_2$CH), 2.38 (m, *J* = 14.2/10.1/5.8 Hz, 1H, CHC*H*$_2$CH), 2.62 (dd, *J* = 9.9/4.0 Hz, 1H, NC*H*$_2$), 3.01 (m, *J* = 9.9/1.6 Hz, 1H, NC*H*$_2$), 3.34 (dd, *J* = 10.1/3.8 Hz, 1H, NC*H*), 3.63 (s, 3H, CO_2CH_3), 3.71 (d, *J* = 13.1 Hz, 1H, C*H*$_2$Ar), 3.86 (d, *J* = 13.1 Hz, 1H, C*H*$_2$Ar), 4.24 (m, 1H, C*H*OH), 7.20 – 7.35 (m, 5H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 4′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$);

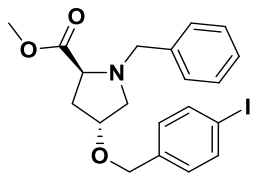
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 39.4 (1C, CH*C*H$_2$CH), 52.2 (1C, CO_2CH_3), 58.2 (1C, *C*H$_2$Ar), 62.0 (1C, N*C*H$_2$), 63.4 (1C, N*C*H), 71.2 (1C, *C*HO), 127.4 (1C, C-4′$_{benzyl}$), 128.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 138.1 (1C, C-1′$_{benzyl}$), 175.8 (1C, *C*O$_2$CH$_3$);

IR (neat): ṽ [cm^{-1}] = 3433, 2951, 2803, 1730, 1453, 1436, 1200, 1174, 1137, 1082, 1049, 745, 699;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{17}NO_3$: 236.1208, found: 236.131;

HPLC (method 1): t_R = 11.1 min, purity 100%.

Methyl (2*S*,4*R*)-1-benzyl-4-[(4-iodobenzyl)oxy]pyrrolidine-2-carboxylate (136)



$C_{20}H_{22}INO_3$

Mr= 451.3

Sodium hydride (60%) (510 mg, 12.75 mmol) was added to an ice-cooled solution of **133** (2.0 g, 8.50 mmol) in dry DMF (30 mL) and the mixture was stirred for 30 min at ambient temperature. Then, a solution of 4-iodobenzylbromide (3.0 g, 10.20 mmol) in dry DMF (15 mL) was added slowly over a period of 5 min. After stirring the reaction mixture for 18 h at ambient temperature, water was added to the mixture and extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4) and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/1 → 3/2) to give a crude product which was further purified by automatic

flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **136** (563 mg, 1.25 mmol, 15%) as yellow oil.

TLC: R_f = 0.30 (petroleum ether/ethyl acetate, 4/1);

Specific rotation: $[\alpha]_D^{20}$ = -38.6 (15.0, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.10 – 2.19 (m, 2H, CHC*H*$_2$CH), 2.45 (dd, *J* = 10.1/4.6 Hz, 1H, NC*H*$_2$), 3.26 (dd, *J* = 10.1/6.1 Hz, 1H, NC*H*$_2$), 3.47 (t, *J* = 7.9 Hz, 1H, NC*H*), 3.53 (d, *J* = 12.8 Hz, 1H, C*H*$_2$Ar), 3.60 (s, 3H, CO_2CH_3), 3.86 (d, *J* = 12.8 Hz, 1H, C*H*$_2$Ar), 4.07 – 4.15 (m, 1H, C*H*O), 4.28 – 4.36 (m, 2H, OC*H*$_2$Ar), 6.95 – 7.01 (m, 2H, 2″-H$_{4\text{-iodobenzyl}}$, 6″-H$_{4\text{-iodobenzyl}}$), 7.18 – 7.22 (m, 1H, 4′-H$_{benzyl}$), 7.23 – 7.28 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.55 – 7.63 (m, 2H, 3″-H$_{4\text{-iodobenzyl}}$, 5″-H$_{4\text{-iodobenzyl}}$);

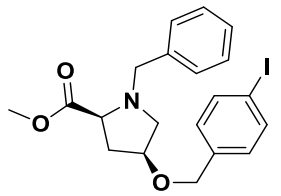
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 36.6 (1C, CH*C*H$_2$CH), 52.0 (1C, CO_2*C*H$_3$), 58.9 (1C, *C*H$_2$Ar), 58.9 (1C, N*C*H$_2$), 64.3 (1C, N*C*H), 70.8 (1C, OC*H*$_2$Ar), 77.3 (1C, *C*HO), 93.3 (1C, C-4″$_{benzyl}$), 127.4 (1C, C-4′$_{benzyl}$), 128.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.3 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.6 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 137. 7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 138.0 (1C, C-1″$_{benzyl}$), 138.1 (1C, C-1′$_{benzyl}$), 174.1 (1C, *C*O_2CH_3);

IR (neat): ṽ [cm^{-1}] = 2947, 2841, 2803, 1731, 1484, 1453, 1435, 1197, 1171, 1091, 1059, 1006, 798, 743, 699, 470;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{22}INO_3$: 452.0644, found: 452.095;

HPLC (method 1): t_R = 21.2 min, purity 96.6%.

Methyl (2S,4S)-1-benzyl-4-[(4-iodobenzyl)oxy]pyrrolidine-2-carboxylate (137)



$C_{20}H_{22}INO_3$

M_r = 451.3

Sodium hydride (60%) (464 mg, 11.60 mmol) was added to an ice-cooled solution of **135** (1820 mg, 7.74 mmol) in dry DMF (20 mL) and the mixture was stirred for 30 min at ambient temperature. Then, a solution of 4-iodobenzylbromide (3445 mg, 11.60 mmol) in dry DMF (10 mL) was added slowly over a period of 5 min. After stirring the reaction mixture for 18 h at ambient temperature, water was added to the mixture and extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4) and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/0 → 1/3) to give **137** (385 mg, 0.85 mmol, 11.0%) as pale-yellow oil.

TLC: R_f = 0.30 (petroleum ether/ethyl acetate, 4/1);

Specific rotation: $[\alpha]_D^{20}$ = +39.6 (4.6, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.15 – 2.26 (m, 2H, CHC*H*$_2$CH), 2.51 (dd, *J* = 10.1/4.7 Hz, 1H, NC*H*$_2$), 3.32 (dd, *J* = 10.1/6.0 Hz, 1H, NC*H*$_2$), 3.53 (t, *J* = 7.9 Hz, 1H, NC*H*), 3.59 (d, *J* = 12.8 Hz, 1H, C*H*$_2$Ar), 3.66 (s, 3H, CO_2CH_3), 3.92 (d, *J* = 12.8 Hz, 1H, C*H*$_2$Ar), 4.12 – 4.20 (m, 1H, C*H*O), 4.31 – 4.44 (m, 2H, OC*H*$_2$Ar), 7.01 – 7.06 (m, 2H, 2″-$H_{4\text{-iodobenzyl}}$, 6″-$H_{4\text{-iodobenzyl}}$), 7.20 – 7.38 (m, 5H, 2′-H_{benzyl}, 3′-H_{benzyl}, 4′-H_{benzyl}, 5′-H_{benzyl} , 6′-H_{benzyl}), 7.62 – 7.68 (m, 2H, 3″-$H_{4\text{-iodobenzyl}}$, 5″-$H_{4\text{-iodobenzyl}}$);

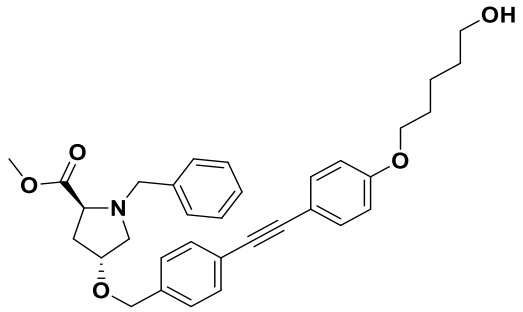
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 36.6 (1C, CH*C*H$_2$CH), 52.0 (1C, CO_2*C*H$_3$), 58.9 (1C, *C*H$_2$Ar), 58.9 (1C, N*C*H$_2$), 64.3 (1C, N*C*H), 70.8 (1C, OC*H*$_2$Ar), 77.3 (1C, *C*HO), 93.3 (1C, C-4″$_{benzyl}$), 127.4 (1C, C-4′$_{benzyl}$), 128.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.3 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.6 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 137.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 138.0 (1C, C-1″$_{benzyl}$), 138.1 (1C, C-1′$_{benzyl}$), 174.0 (1C, *C*O_2CH_3);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2947, 2841, 2802, 1730, 1484, 1453, 1435, 1378, 1358, 1197, 1171, 1092, 1059, 1006, 799, 743, 699, 470;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{22}INO_3$: 452.0644, found: 452.073;

HPLC (method 1): t_R = 21.3 min, purity 93.5%.

Methyl (2*S*,4*R*)-1-benzyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (138a)



$C_{33}H_{37}NO_5$

Mr = 527.7

Under N_2 atmosphere, copper(I) iodide (2 mg, 0,01 mmol), tetrakis(triphenylphosphine)palladium(0) (4 mg, 0.003 mmol), triethylamine (1.1 mL, 812 mg, 8.03 mmol), and **71** (168 mg, 0.82 mmol) were added to a solution of **136** (174 mg, 0.39 mmol) in dry acetonitrile (10 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate = 3/2 → 0/1) to give **138a** (104 mg, 0.20 mmol, 51%) as brown oil.

TLC: R_f = 0.23 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = -76.8 (1.0, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.51 – 1.69 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.78 – 1.88 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.19 – 2.24 (m, 2H, $CHCH_2CH$), 2.50 – 2.57 (m, 1H, NCH_2), 3.34 (dd, *J* = 10.1/6.1 Hz, 1H, NCH_2), 3.54 (t, *J* = 7.9 Hz, 1H, NCH), 3.60 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 3.66 (s, 3H, CO_2CH_3), 3.68 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.92 (d, *J* =

12.9 Hz, 1H, C*H*$_2$Ar), 3.99 (t, *J* = 6.4 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.15 – 4.21 (m, 1H, C*H*O), 4.38 – 4.48 (m, 2H, OC*H*$_2$Ar), 6.82 – 6.89 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy)phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.26 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.26 (m, 1H, 4′-H$_{benzyl}$), 7.29–7.34 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.43 – 7.49 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.43 - 7.49 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$);

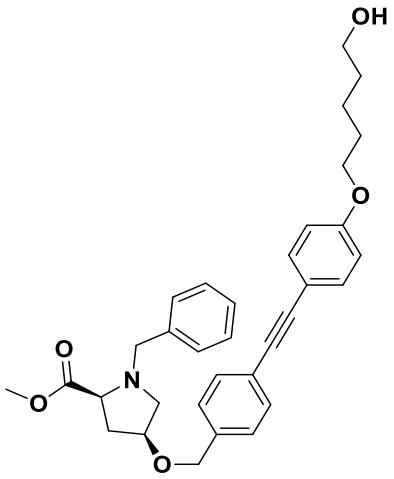
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 29.2 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 32.6 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 36.7 (1C, CH*C*H$_2$CH), 52.0 (1C, CO$_2$*C*H$_3$), 59.0 (1C, N*C*H$_2$), 59.0 (1C, *C*H$_2$Ar), 63.0 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 64.4 (1C, N*C*H), 68.0 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 71.1 (1C, O*C*H$_2$Ar), 77.3 (1C, *C*HO), 88.1 (1C, Ar*C*≡CAr), 89.7 (1C, ArC≡*C*Ar), 114.7 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.4 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 123.1 (1C, C-4″$_{benzyl}$), 127.4 (1C, C-4′$_{benzyl}$), 127.7 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 128.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.4 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 133.2 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$ 138.1 (1C, C-1″$_{benzyl}$), 138.1 (1C, C-1′$_{benzyl}$), 159.3 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 174.1 (1C, *C*O$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3412, 2939, 2865, 1733, 1602, 1516, 1283, 1244, 1203, 1172, 1091, 1058, 1018, 829, 744, 670, 539, 522;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{33}H_{37}NO_5$: 528.2672, found: 528.274;

HPLC (method 1): t_R = 22.6 min, purity 96.9%.

Methyl (2*S*,4*S*)-1-benzyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (139a)



$C_{33}H_{37}NO_5$

M_r = 527.7

Under N_2 atmosphere, copper(I) iodide (3 mg, 0,02 mmol), tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol), triethylamine (0.2 mL, 155 mg, 1.53 mmol), and **71** (167 mg, 0.82 mmol) were added to a solution of **137** (230 mg, 0.51 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 3/1 → 0/1) to give **139a** (260 mg, 0.49 mmol, 97%) as yellow oil.

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = +37.4 (5.8, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.51 – 1.71 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.79 – 1.88 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.17 – 2.26 (m, 2H, $CHCH_2CH$), 2.53 (dd, *J* = 10.1/4.7 Hz, 1H, NCH_2), 3.34 (dd, *J* = 10.1/6.1 Hz, 1H, NCH_2), 3.54 (t, *J* = 7.9 Hz, 1H, NC*H*), 3.60 (d, *J* = 12.8 Hz, 1H, CH_2Ar), 3.66 (s, 3H, CO_2CH_3), 3.69 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.92 (d, *J* = 12.8 Hz, 1H, CH_2Ar), 3.99 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.15 – 4.22 (m, 1H, C*H*O), 4.39 – 4.49 (m, 2H, OCH_2Ar), 6.83 – 6.89 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.26 (m, 2H, 2″-$H_{benzyl}$, 6″-$H_{benzyl}$), 7.26 (m, 1H, 4′-$H_{benzyl}$), 7.28 – 7.34 (m, 4H, 2′-H_{benzyl}, 3′-H_{benzyl},5′-H_{benzyl},

6′-H_{benzyl}), 7.42- 7.49 (m, 2H, 2‴-$H_{4-(\{4-[(5-hydroxypentyl)oxy]phenyl}$, 6‴-$H_{4-(\{4-[(5-hydroxypentyl)oxy]phenyl}$), 7.42 – 7.49 (m, 2H, 3″-H_{benzyl}, 5″-H_{benzyl});

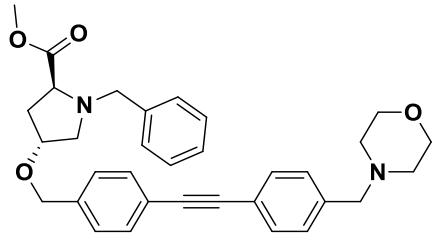
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 29.2 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 36.7 (1C, $CH\mathit{C}H_2CH$), 52.0 (1C, $CO_2\mathit{C}H_3$), 59.0 (1C, $N\mathit{C}H_2$), 59.0 (1C, $\mathit{C}H_2Ar$), 63.0 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 64.4 (1C, N*C*H), 68.0 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 71.1 (1C, $O\mathit{C}H_2Ar$), 77.3 (1C, *C*HO), 88.1 (1C, Ar*C*≡CAr), 89.7 (1C, ArC≡*C*Ar), 114.7 (2C, C-3‴$_{4-(\{4-[(5-hydroxypentyl)oxy]phenyl}$, C-5‴$_{4-(\{4-[(5-hydroxypentyl)oxy]phenyl}$), 115.4 (1C, C-1‴$_{4-(\{4-[(5-hydroxypentyl)oxy]phenyl}$), 123.1 (1C, C-4″$_{benzyl}$), 127.4 (1C, C-4′$_{benzyl}$), 127.7 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 128.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.3 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 133.2 (2C, C-2‴$_{4-(\{4-[(5-hydroxypentyl)oxy]phenyl}$, C-6‴$_{4-(\{4-[(5-hydroxypentyl)oxy]phenyl}$), 138.1 (1C, C-1″$_{benzyl}$), 138.2 (1C, C-1′$_{benzyl}$), 159.3 (1C, C-4‴$_{4-(\{4-[(5-hydroxypentyl)oxy]phenyl}$), 174.1 (1C, $\mathit{C}O_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3404, 2939, 2863, 1733, 1602, 1516, 1283, 1244, 1202, 1172, 1091, 1057, 1028, 1018, 829, 747, 700, 538, 522;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{37}NO_5$: 528.2672, found: 528.268;

HPLC (method 1): t_R = 22.6 min, purity 97.9%.

Methyl (2*S*,4*R*)-1-benzyl-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxylate (140a)



$C_{33}H_{36}N_2O_4$

M_r = 524.7

Under N_2 atmosphere, copper(I) iodide (5 mg, 0,02 mmol), tetrakis(triphenylphosphine)palladium(0) (9 mg, 0.008 mmol), triethylamine (0.34 mL, 249 mg, 2.46 mmol), and **103** (248 mg, 1.23 mmol) were added to a solution of **136** (370 mg, 0.82 mmol) in dry acetonitrile (10 mL) and the mixture was stirred for 18 h at ambient temperature.

Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/1 → 0/1) to give **140a** (97 mg, 0.18 mmol, 27%) as orange oil.

TLC: R_f = 0.18 (petroleum ether/ethyl acetate, 1/1);

Specific rotation $[\alpha]_D^{20}$ = -32.0 (3.8, methanol);

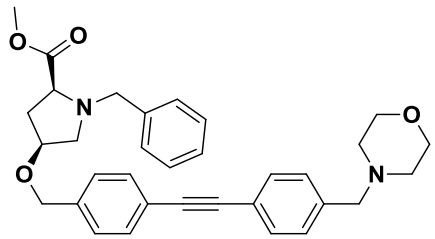
^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ [ppm]= 2.10 – 2.30 (m, 2H, CHC*H*$_2$CH), 2.46 – 2.52 (t, 4H, NC*H*$_2$CH$_2$O), 2.57 (dd, *J* = 10.3/4.4 Hz, 1H, NC*H*$_2$), 3.29 (dd, *J* = 10.4/6.0 Hz, 1H, NC*H*$_2$), 3.51 – 3.58 (m, 1H, NC*H*), 3.51- 3.58 (s, 2H, ArC*H*$_2$), 3.63 (d, *J* = 12.7 Hz, 1H, C*H*$_2$Ar), 3.67 (s, 3H, CO$_2$C*H*$_3$), 3.69 – 3.75 (t, 4H, NCH$_2$C*H*$_2$O), 3.91 (d, *J* = 12.8 Hz, 1H, C*H*$_2$Ar), 4.20 (m, 1H, C*H*O), 4.44 – 4.57 (m, 2H, OC*H*$_2$Ar), 7.25 – 7.32 (m, 1H, 4′-H$_{benzyl}$), 7.32 – 7.37 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.32-7.37 (m, 2H, 2″-H$_{benzyl,}$ 6″-H$_{benzyl}$), 7.37 – 7.41 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.47 – 7.55 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.47 - 7.55 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$);
^{13}C NMR (101 MHz, MeOD-*d*$_4$) δ [ppm]= 37.6 (1C, CHC*H*$_2$CH), 52.4 (1C, CO$_2$*C*H$_3$), 54.7 (2C, N*C*H$_2$CH$_2$O), 59.9 (1C, N*C*H$_2$), 59.9 (1C, C*H*$_2$Ar), 64.1 (1C, Ar*C*H$_2$), 65.4 (1C, N*C*H), 67.9 (2C, NCH$_2$*C*H$_2$O), 71.9 (1C, O*C*H$_2$Ar), 78.5 (1C, C*H*O), 90.2 (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 123.7 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 123.9 (1C, C-4″$_{benzyl}$), 128.5 (1C, C-4′$_{benzyl}$), 129.0 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 130.5 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.8 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 139.1 (1C, C-1′$_{benzyl}$), 139.2 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 140.3 (1C, C-1″$_{benzyl}$), 175.5 (1C, *C*O$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 2949, 2852, 2805, 1745, 1732, 1517, 1453, 1436, 1350, 1199, 1172, 1115, 1096, 1007, 914, 866, 820, 747, 700, 542;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{33}H_{36}N_2O_4$: 525.2675, found: 525.274;

HPLC (method 1): t_R = 17.1 min, purity 94.8%.

Methyl (2S,4S)-1-benzyl-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxylate (141a)



$C_{33}H_{36}N_2O_4$

M_r = 524.7

Under N_2 atmosphere, copper(I) iodide (7 mg, 0,04 mmol), tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.01 mmol), triethylamine (0.54 mL, 396 mg, 3.91 mmol), and **103** (393 mg, 1.95 mmol) were added to a solution of **137** (588 mg, 1.30 mmol) in dry acetonitrile (15 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/1 → 0/1) to give **141a** (607 mg, 1.16 mmol, 89%) as brown oil.

TLC: R_f = 0.18 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = +50.7 (5.9, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.15 (m, *J* = 8.0/5.4 Hz, 2H, CHC*H*$_2$CH), 2.39 (t, *J* = 4.6 Hz, 4H, NC*H*$_2$CH$_2$O), 2.47 (dd, *J* = 10.1/4.7 Hz, 1H, NC*H*$_2$), 3.28 (dd, *J* = 10.1/6.1 Hz, 1H, NC*H*$_2$), 3.46 (s, 2H, ArC*H*$_2$), 3.46 (m, 1H, NC*H*), 3.53 (d, *J* = 12.8 Hz, 1H, C*H*$_2$Ar), 3.60 (s, 3H, CO_2C*H*_3), 3.65 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.85 (d, *J* = 12.8 Hz, 1H, C*H*$_2$Ar), 4.12 (m, 1H, C*H*O), 4.33 – 4.44 (m, 2H, OC*H*$_2$Ar), 7.16 – 7.30 (m, 5H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 4′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.16 – 7.30 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.16- 7.30 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.42 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$), 7.42 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 36.6 (1C, CHC*H*$_2$CH), 52.0 (1C, CO_2*C*H_3), 53.8 (2C, NCH$_2$CH$_2$O), 58.9 (1C, C*H*$_2$Ar), 59.0 (1C, NCH$_2$), 63.3 (1C, ArCH$_2$), 64.3 (1C, NCH), 67.1 (2C, NCH$_2$CH$_2$O), 71.0 (1C, OCH$_2$Ar), 77.3 (1C, C*H*O), 89.3 (1C, ArC≡CAr), 89.5 (1C, ArC≡CAr), 122.2 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 122.7 (1C, C-4″$_{benzyl}$), 127.4 (1C, C-

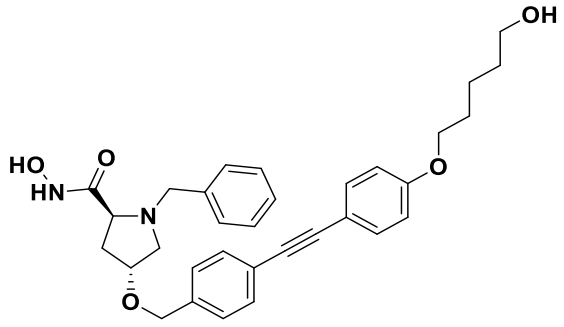
4′$_{benzyl}$), 127.6 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 128.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.3 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.3 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.7 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.8 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 138.1 (1C, C-1′$_{benzyl}$), 138.3 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 138.5 (1C, C-1″$_{benzyl}$), 174.1 (1C, *C*$O_2CH_3$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2949, 2852, 2805, 1732, 1453, 1436, 1349, 1115, 1097, 1070, 1007, 866, 819, 747, 699, 541;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{36}N_2O_4$: 525.2675, found: 525.274;

HPLC (method 1): t_R = 17.1 min, purity 97.4 %.

(2*S*,4*R*)-1-benzyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (138)



$C_{32}H_{36}N_2O_5$

M_r = 528.6

An aqueous solution of hydroxylamine solution (50 wt%, 7.0 mL) was added to a solution of **138a** (92 mg, 0.17 mmol) in THF (10 mL). After stirring the reaction mixture for 72 h at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **138** (16 mg, 0.03 mmol, 18 %) as colorless solid.

m.p. = 78-79 °C;

TLC: R_f = 0.28 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -49.6 (1.3, methanol);

^{1}H NMR (600 MHz, MeOD-*d_4*) δ [ppm]= 1.49 – 1.64 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.75 – 1.83 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.09 (m, *J* = 13.3/8.0/6.8 Hz, 1H, $CHCH_2CH$), 2.20 (m, *J* = 13.3/8.0/3.6 Hz, 1H, $CHCH_2CH$), 2.46 (dd, *J* = 10.4/4.5 Hz, 1H, NCH_2), 3.21 (dd, *J* = 10.4/5.6 Hz, 1H, NCH_2), 3.36 (t, *J* = 8.0 Hz, 1H, NC*H*), 3.50 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 3.58 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.87 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 3.98 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.11 – 4.16 (m, 1H, C*H*O), 4.38 – 4.48 (m, 2H, OCH_2Ar), 6.85 – 6.92 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.22- 7.25 (m, 1H, 4′-$H_{benzyl}$), 7.25 – 7.35 (m, 4H, 2′-H_{benzyl}, 3′-H_{benzyl}, 5′-H_{benzyl}, 6′-H_{benzyl}), 7.25- 7.35 (m, 2H, 2″-H_{benzyl}, 6″-H_{benzyl}), 7.38 – 7.46 (m, 2H, 2‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.38- 7.46 (m, 2H, 3″-$H_{benzyl}$, 5″-$H_{benzyl}$);

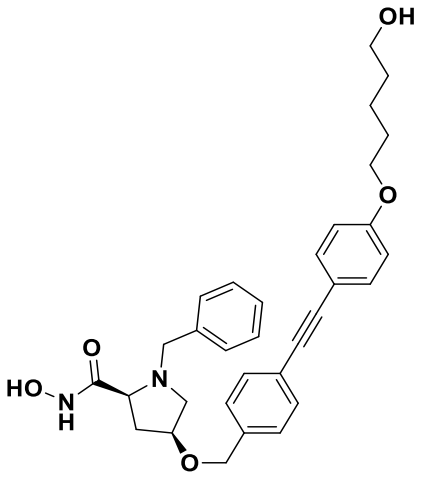
^{13}C NMR (151 MHz, MeOD-*d_4*) δ [ppm]= 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.4 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 38.0 (1C, $CHCH_2CH$), 59.5 (1C, NCH_2), 60.2 (1C, CH_2Ar), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 65.8 (1C, NCH), 69.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 71.8 (1C, OCH_2Ar), 78.9 (1C, CHO), 88.7 (1C, ArC≡CAr), 90.5 (1C, ArC≡CAr), 115.8 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 116.5 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 124.3 (1C, C-4″$_{benzyl}$), 128.4 (1C, C-4′$_{benzyl}$), 128.9 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 130.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 134.1 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 139.4 (1C, C-1′$_{benzyl}$), 139.8 (1C, C-1″$_{benzyl}$), 160.8 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 172.8 (1C, CONHOH);

IR (neat): ṽ [cm^{-1}] = 3255, 2936, 2863, 1649, 1603, 1515, 1247, 1130, 1087, 1072, 829, 759, 703, 540;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{36}N_2O_5$: 529.2624, found: 529.265;

HPLC (method 2): t_R = 14.6 min, purity 97.2%.

(2*S*,4*S*)-1-Benzyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (139)



$C_{32}H_{36}N_2O_5$

M_r = 528.6

An aqueous solution of hydroxylamine solution (50 wt%, 18.0 mL) was added to a solution of **139a** (181 mg, 0.34 mmol) in THF (10 mL). After stirring the reaction mixture for 10 d at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **139** (12 mg, 0.02 mmol, 7%) as colorless solid.

m.p. = 117-1190 °C;

TLC: R_f = 0.33 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +14.0 (2.4, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.45 – 1.61 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.76 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.06 (m, *J* = 13.3/8.0/6.8 Hz, 1H, $CHCH_2CH$), 2.17 (m, *J* = 13.3/8.0/3.6 Hz, 1H, $CHCH_2CH$), 2.43 (dd, *J* = 10.4/4.5 Hz, 1H, NCH_2), 3.18 (dd, *J* = 10.4/5.6 Hz, 1H, NCH_2), 3.33 (t, *J* = 8.0 Hz, 1H, NC*H*), 3.46 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 3.54 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.84 (d, *J* = 12.9 Hz, 1H, CH_2Ar), 3.95 (t, *J* =

6.4 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.11 (m, 1H, C*H*O), 4.34 – 4.47 (m, 2H, OC*H*$_2$Ar), 6.83 – 6.88 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.18 – 7.22 (m, 1H, 4′-H$_{benzyl}$), 7.23 – 7.32 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.23 - 7.32 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.35 – 7.42 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.35 - 7.42 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$);

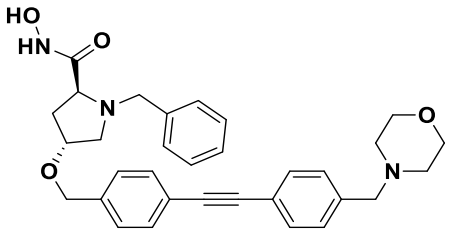
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 30.2 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 33.4 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 38.0 (1C, CH*C*H$_2$CH), 59.5 (1C, N*C*H$_2$), 60.2 (1C, *C*H$_2$Ar), 62.9 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 65.8 (1C, N*C*H), 69.1 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 71.8 (1C, O*C*H$_2$Ar), 78.9 (1C, *C*HO), 88.7 (1C, Ar*C*≡CAr), 90.5 (1C, ArC≡*C*Ar), 115.8 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.3 (1C, C-4″$_{benzyl}$), 128.4 (1C, C-4′$_{benzyl}$), 128.9 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 130.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 134.1 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.4 (1C, C-1′$_{benzyl}$), 139.8 (1C, C-1″$_{benzyl}$), 160.8 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 172.7 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3344, 3256, 2936, 2864, 1649, 1604, 1516, 1247, 1178, 1131, 1111, 1088, 1072, 829, 760, 703, 540;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{32}H_{36}N_2O_5$: 529.2624, found: 529.263;

HPLC (method 2): t_R = 14.5 min, purity 100%.

(2*S*,4*R*)-1-Benzyl-*N*-hydroxy-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxamide (140)



$C_{32}H_{35}N_3O_4$

M_r = 525.7

An aqueous solution of hydroxylamine solution (50 wt%, 14.0 mL) was added to a solution of **140a** (270 mg, 0.51 mmol) in THF (10 mL). After stirring the reaction mixture for 6 d at ambient

temperature, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **140** (18 mg, 0.03 mmol, 7%) as colorless solid.

m.p.= 64-65 °C;

TLC: R_f = 0.40 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +27.1 (0.7, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 2.04 – 2.13 (m, 1H, CHC*H*$_2$CH), 2.19 (m, *J* = 13.3/8.0/3.6 Hz, 1H, CHC*H*$_2$CH), 2.38 – 2.50 (t, 4H, NC*H*$_2$CH$_2$O), 2.38- 2.50 (dd, 1H, NC*H*$_2$), 3.21 (dd, *J* = 10.4/5.6 Hz, 1H, NC*H*$_2$), 3.35 (t, *J* = 8.0 Hz, 1H, NC*H*), 3.49 (s, 2H, ArC*H*$_2$), 3.49 (d, 1H, C*H*$_2$Ar), 3.66 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.86 (d, *J* = 12.9 Hz, 1H, C*H*$_2$Ar), 4.14 (m, *J* = 5.4/4.0 Hz, 1H, C*H*O), 4.37 – 4.50 (m, 2H, OC*H*$_2$Ar), 7.20 – 7.24 (m, 1H, 4′-H$_{benzyl}$), 7.26 – 7.36 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.26 - 7.36 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.26 – 7.36 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.42 – 7.48 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.42 - 7.48 (m, 2H, 3″-H$_{benzyl,}$ 5″-H$_{benzyl}$);

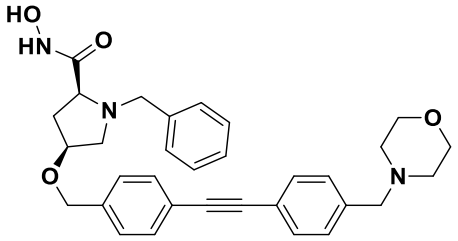
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 38.0 (1C, CHC*H*$_2$CH), 54.7 (2C, N*C*H$_2$CH$_2$O), 59.5 (1C, N*C*H$_2$), 60.2 (1C, C*H*$_2$Ar), 64.0 (1C, Ar*C*H$_2$), 65.8 (1C, N*C*H), 67.9 (2C, NCH$_2$*C*H$_2$O), 71.8 (1C, O*C*H$_2$Ar), 78.9 (1C, C*H*O), 90.2 (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 123.7 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 123.8 (1C, C-4″$_{benzyl}$), 128.4 (1C, C-4′$_{benzyl}$), 128.9 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 130.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.8 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 139.1 (1C, C-1′$_{benzyl}$), 139.4 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 140.3 (1C, C-1″$_{benzyl}$), 172.8 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3199, 2852, 2808, 1661, 1517, 1453, 1350, 1114, 1070, 1006, 914, 864, 819, 791, 751, 700, 516;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{35}N_3O_4$: 526.2628, found: 526.269;

HPLC (method 2): t_R = 12.8 min, purity 96.7%.

(2*S*,4*S*)-1-Benzyl-*N*-hydroxy-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxamide (141)



$C_{32}H_{35}N_3O_4$

M_r = 525.7

An aqueous solution of hydroxylamine solution (50 wt%, 18.0 mL) was added to a solution of **141a** (350 mg, 0.67 mmol) in THF (10 mL). After stirring the reaction mixture for 6 d at ambient temperature, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **141** (61 mg, 0.12 mmol, 17%) as colorless solid.

m.p.= 77-78 °C;

TLC: R_f = 0.40 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +3.8 (4.0, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 2.10 (m, *J* = 13.3/8.1/6.8 Hz, 1H, CHC*H*$_2$CH), 2.21 (m, *J* = 13.3/8.0/3.6 Hz, 1H, CHC*H*$_2$CH), 2.40 – 2.51 (m, 4H, NC*H*$_2$CH$_2$O), 2.40- 2.51 (m, 1H, NC*H*$_2$), 3.23 (dd, *J* = 10.4/5.6 Hz, 1H, NC*H*$_2$), 3.36 (t, *J* = 8.0 Hz, 1H, NC*H*), 3.49 – 3.54 (s, 2H, ArC*H*$_2$), 3.49- 3.54 (d, 1H, C*H*$_2$Ar), 3.69 (t, *J* = 4.7 Hz, 5H, NCH$_2$C*H*$_2$O), 3.88 (d, *J* = 12.9 Hz, 1H, C*H*$_2$Ar), 4.16 (m, *J* = 10.5/6.7/4.2 Hz, 1H, C*H*O), 4.40 – 4.53 (m, 2H, OC*H*$_2$Ar), 7.22 – 7.26 (m, 1H, 4′-H$_{benzyl}$), 7.28 – 7.38 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.28-7.38 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.28 - 7.38 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.45 – 7.50 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.45 - 7.50 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$);

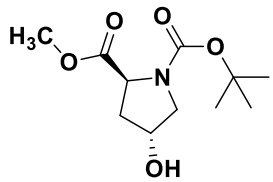
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 38.1 (1C, CHC*H*$_2$CH), 54.7 (2C, NC*H*$_2$CH$_2$O), 59.5 (1C, NC*H*$_2$), 60.2 (1C, C*H*$_2$Ar), 64.1 (1C, ArC*H*$_2$), 65.8 (1C, NC*H*), 67.9 (2C, NCH$_2$C*H*$_2$O), 71.8 (1C, OC*H*$_2$Ar), 78.9 (1C, C*H*O), 90.2 (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 123.7 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 123.9 (1C, C-4″$_{benzyl}$), 128.4 (1C, C-4′$_{benzyl}$), 128.9 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 130.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.8 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-3″$_{benzyl}$, C-5″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 139.1 (1C, C-1′$_{benzyl}$), 139.4 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 140.3 (1C, C-1″$_{benzyl}$), 172.8 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3188, 2855, 2807, 1662, 1516, 1453, 1114, 1070, 1006, 865, 819, 700, 544, 514;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{32}H_{35}N_3O_4$: 526.2628, found: 526.268;

HPLC (method 2): t_R = 12.6 min, purity 99.1 %.

1-(*tert*-butyl)-2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (142)



$C_{11}H_{19}NO_5$

Mr = 245.3

Triethylamine (3.70 mL, 2691 mg, 22.02 mmol) was added to a solution of methyl (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylate hydrochloride (**57**) (2.0 g, 11 mmol) in dichloromethane (30 mL) and the mixture was stirred for 15 min at ambient temperature. Then, di-*tert* butyl dicarbonate (2.9 g, 13.21 mmol) was added and the mixture was stirred for 18 h at ambient temperature. Afterwards, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with dichloromethane (3×). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo* to give **142** (2.7 g, 11.01 mmol, 100%) as colorless oil.

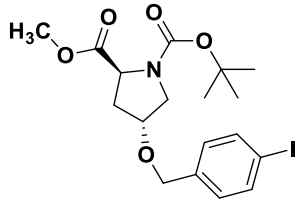
Specific rotation $[\alpha]_D^{20}$ = -51.6 (4.8, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 1.40 (s, 9H, OC(CH_3)$_3$), 2.03 (m, *J* = 13.1/8.3/4.7 Hz, 1H, CHCH_2CH), 2.16 – 2.34 (m, 1H, CHCH_2CH), 3.52 (m, *J* = 11.7/1.9 Hz, 1H, NCH_2), 3.59 (m, *J* = 11.7/4.1 Hz, 1H, NCH_2), 3.71 (s, 3H, CO_2CH_3), 4.33 – 4.42 (m, 1H, NC*H*), 4.45 (m, *J* = 4.7/2.4 Hz, 1H, C*H*OH), the signals of the major rotamer are given;
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 28.4 (3C, OC(CH_3)$_3$), 39.2 (1C, CHCH_2CH), 52.2 (1C, CO_2CH_3), 54.8 (1C, NCH_2), 58.1 (1C, N*C*H), 69.5 (1C, *C*HOH), 80.6 (1C, O*C*(CH_3)$_3$), 154.2 (1C, N$CO_2C(CH_3)_3$), 173.9 (1C, CO_2CH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3436, 2977, 2953, 1744, 1698, 1676, 1396, 1366, 1277, 1256, 1201, 1155, 1125, 1087, 895, 773;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{19}NO_5$: 268.1263, found: 268.117.

1-(*tert*-butyl)-2-methyl (2*S*,4*R*)-4-[(4-iodobenzyl)oxy]pyrrolidine-1,2-dicarboxylate (143)



$C_{18}H_{24}INO_5$

Mr = 461.3

Sodium hydride (60%) (799 mg, 19.97 mmol) was added to an ice-cooled solution of **142** (2.4 g, 13.31 mmol) in dry DMF (25 mL) and the mixture was stirred for 30 min at ambient temperature. Then, a solution of 4-iodobenzylbromide (1952 mg, 15.98 mmol) in dry DMF (15 mL) was added slowly over a period of 5 min. After stirring the reaction mixture for 18 h at ambient temperature, water was added to the mixture and extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4) and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/1 → 3/2) to give **143** (1360 mg, 2.95 mmol, 30%) as pale-yellow oil.

TLC: R_f = 0.25 (petroleum ether/ethyl acetate, 3/1);

Specific rotation: $[\alpha]_D^{20}$ = -17.9 (1.0, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.41 (m, 9H, OC(CH_3)$_3$), 2.04 (m, 1H, CHCH_2CH), 2.29 – 2.39 (m, 1H, CHCH_2CH), 3.50 - 3.64 (m, 2H, NCH_2), 3.66 (s, 3H, CO_2CH_3), 4.07 - 4.16 (m, 1H, C*H*O), 4.31 - 4.38 (m, 1H, NC*H*), 4.38 – 4.49 (m, 2H, OCH_2Ar), 7.00 - 7.08 (m, 2H, 2′-H$_{4\text{-iodobenzyl}}$, 6′-H$_{4\text{-iodobenzyl}}$), 7.66 (m, 2H, 3′-H$_{4\text{-iodobenzyl}}$, 5′-H$_{4\text{-iodobenzyl}}$), the signals of the major rotamer are given;

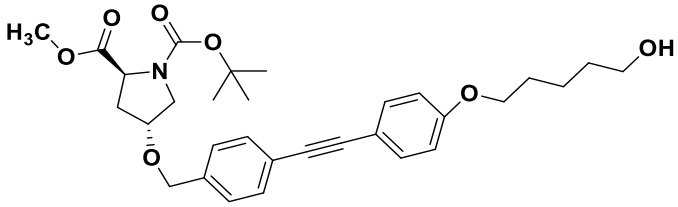
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 28.5 (3C, OC(CH_3)$_3$), 36.3 (1C, CHCH_2CH), 51.4 (1C, NCH_2), 52.2 (1C, CO_2CH_3), 57.9 (1C, NCH), 70.3 (1C, OCH_2Ar), 76.2 (1C, CHO), 80.4 (1C, OC(CH_3)$_3$), 93.3 (1C, C-4′$_{4\text{-iodobenzyl}}$), 129.5 (2C, C-2′$_{4\text{-iodobenzyl}}$, C-6′$_{4\text{-iodobenzyl}}$), 137.6 (2C, C-3′$_{4\text{-iodobenzyl}}$, C-5′$_{4\text{-iodobenzyl}}$), 137.6 (1C, C-1′$_{4\text{-iodobenzyl}}$), 154.1 (1C, NCO_2C(CH_3)$_3$), 173.0 (1C, CO_2CH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2975, 2950, 1748, 1694, 1393, 1364, 1200, 1156, 1115, 1088, 1006, 894, 799, 769;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}INO_5$: 484.0699, found: 484.060;

HPLC (method 1): t_R = 25.4 min, purity 97.6%.

1-(*tert*-butyl)-2-methyl (2*S*,4*R*)-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-1,2-dicarboxylate (150)



$C_{31}H_{39}NO_7$

Mr = 537.7

Under N_2 atmosphere, copper(I) iodide (15 mg, 0.08 mmol), tetrakis(triphenylphosphine)palladium(0) (31 mg, 0.03 mmol), triethylamine (1.11 mL, 812 mg, 8.03 mmol), and **71** (1168 mg, 5.72 mmol) were added to a solution of **143** (1234 mg, 2.68 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/2) to give **150** (1170 mg, 2.18 mmol, 81%) as brown oil.

TLC: R_f = 0.40 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = -8.0 (3.0, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.42 (s, 9H, OC(C*H*$_3$)$_3$), 1.51 – 1.69 (m, 4H, OCH$_2$CH$_2$C*H*$_2$C*H*$_2$CH$_2$OH), 1.83 (dt, *J* = 14.3/6.7 Hz, 2H, OCH$_2$C*H*$_2$CH$_2$CH$_2$CH$_2$OH), 2.04-2.11 (m, 1H, CHC*H*$_2$CH), 2.32 – 2.44 (m, 1H, CHC*H*$_2$CH), 3.56 – 3.71 (m, 2H, NC*H*$_2$), 3.56 – 3.71 (t, 2H, OCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$OH), 3.73 (s, 3H, CO$_2$C*H*$_3$), 3.98 (t, *J* = 6.4 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.10 – 4.21 (m, 1H, C*H*O), 4.31 – 4.39 (m, 1H, NC*H*), 4.42 – 4.57 (m, 2H, OC*H*$_2$Ar), 6.82 – 6.89 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.22 – 7.30 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.41 – 7.51 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.41 - 7.51 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$), the signals of the major rotamer are given;

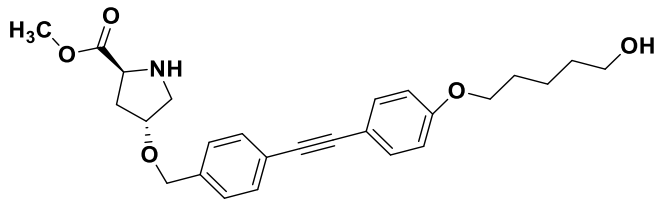
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 28.4 (3C, OC(*C*H$_3$)$_3$), 29.2 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 32.6 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 36.9 (1C, CH*C*H$_2$CH), 51.5 (1C, N*C*H$_2$), 52.2 (1C, CO$_2$*C*H$_3$), 58.2 (1C, N*C*H), 63.0 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 68.0 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 70.9 (1C, O*C*H$_2$Ar), 76.4 (1C, *C*HO), 80.3 (1C, O*C*(CH$_3$)$_3$), 114.7 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.3 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 123.3 (1C, C-4′$_{benzyl}$), 127.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.7 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.7 (1C, C-1′$_{benzyl}$), 159.3 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 173.7 (1C, *C*O$_2CH_3$), the signals for Ar*C*≡CAr, ArC≡*C*Ar, and N*C*O$_2$C(CH$_3$)$_3$ cannot be observed in the spectrum, the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3450, 2937, 2868, 1745, 1697, 1602, 1517, 1395, 1365, 1244, 1204, 1158, 1090, 894, 830, 770, 539;

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{31}H_{39}NO_7$: 560.2727, found: 560.264;

HPLC (method 1): t_R = 25.9 min, purity 98.9 %.

Methyl (2*S*,4*R*)-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (149)



$C_{26}H_{31}NO_5$

M_r = 437.5

Zinc bromide (1804 mg, 8.01 mmol) was added to a solution of **150** (1436 mg, 2.67 mmol) in dichloromethane (30 mL) and stirred for 3 h at ambient temperature. Then, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **149** (300 mg, 0.69 mmol, 26%) as yellowish-green oil.

TLC: R_f = 0.20 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +8.1 (1.6, chloroform);

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ [ppm]= δ 1.60 (m, *J* = 16.3/11.7/6.7/2.2 Hz, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.84 (m, *J* = 6.6 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.26 – 2.44 (m, 2H, $CHCH_2CH$), 3.06 (dd, *J* = 12.4/4.2 Hz, 1H, $NHCH_2$), 3.38 (dd, 1H, $NHCH_2$), 3.38 (s, 3H, CO_2CH_3), 3.61 (t, *J* = 6.3 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.76 (s, 1H, $NHCH_2$), 3.97 – 4.11 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.97- 4.11 (m, 1H, NHC*H*), 4.23 (m, *J* = 3.9/1.6 Hz, 1H, C*H*O), 4.45 – 4.58 (m, 2H, OCH_2Ar), 6.83 – 6.99 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.28 – 7.35 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.41 – 7.51 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.41 - 7.51 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$);

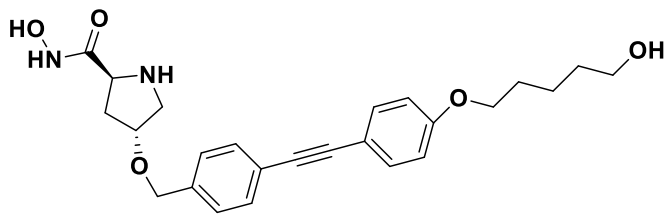
^{13}C NMR (101 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.3 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 36.6 (1C, $CHCH_2CH$), 50.0 (1C, CO_2CH_3), 53.2 (1C, $NHCH_2$), 60.0 (1C, NHCH), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 69.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 71.3 (1C, OCH_2Ar), 79.5 (1C, CHO), 88.6 (1C, ArC≡CAr), 90.5 (1C, ArC≡CAr), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-}}$

hydroxypentyl)oxy]phenyl, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.4 (1C, C-4′$_{benzyl}$), 128.8 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.6 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), the signal for *C*$O_2CH_3$ cannot be observed in the spectrum; **IR** (neat): ṽ [cm^{-1}] = 3338, 2939, 2866, 1735, 1602, 1517, 1283, 1243, 1173, 1070, 1019, 828, 538, 523;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{31}NO_5$: 438.2202, found: 438.227;

HPLC (method 1): t_R = 19.7 min, purity 87.9 %.

(2*S*,4*R*)-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (152)



$C_{25}H_{30}N_2O_5$

Mr = 438.5

Sodium methoxide in methanol (5.4 M, 0.9 mL) and hydroxylamine hydrochloride (337 mg, 4.85 mmol) were added to a solution of **149** (212 mg, 0.48 mmol) in dry methanol (6 mL) and the mixture was stirred for 24 h at ambient temperature. Then, water was added to the reaction mixture and extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **152** (63 mg, 0.14 mmol, 30%) as colorless solid.

m.p. = 85-87 °C (decomposition);

TLC: R_f = 0.25 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -1.8 (1.7, methanol);

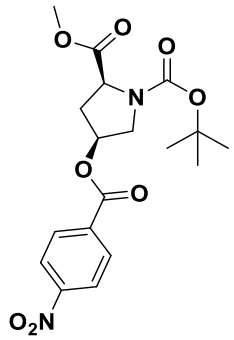
^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.51 – 1.65 (m, 4H, OCH$_2$CH$_2$C*H*$_2$C*H*$_2$CH$_2$OH), 1.81 (m, *J* = 14.1/6.6 Hz, 2H, OCH$_2$C*H*$_2$CH$_2$CH$_2$CH$_2$OH), 2.03 – 2.11 (m, 1H, CHC*H*$_2$CH), 2.30 - 2.38 (m, 1H, CHC*H*$_2$CH), 2.98 (dd, *J* = 10.4/6.2 Hz, 1H, NHC*H*$_2$), 3.12 – 3.19 (m, 1H, NHC*H*$_2$), 3.59 (t, *J* = 6.4 Hz, 2H, OCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$OH), 3.87 (dd, *J* = 9.4/4.1 Hz, 1H, NHC*H*), 4.01 (t, *J* = 6.4 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.09 – 4.17 (m, 1H, C*H*O), 4.44 – 4.58 (m, 2H, OC*H*$_2$Ar), 6.87 – 6.95 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.30 - 7.36 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.40 – 7.47 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.40 - 7.47 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$);
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 30.3 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 33.4 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 37.9 (1C, CH*C*H$_2$CH), 54.4 (1C, NH*C*H$_2$), 61.3 (1C, NH*C*H), 62.9 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 69.1 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 72.2 (1C, O*C*H$_2$Ar), 79.3 (1C, *C*HO), 88.7 (1C, Ar*C*≡CAr), 90.4 (1C, ArC≡*C*Ar), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.4 (1C, C-4′$_{benzyl}$), 128.9 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.8 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 172.5 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3205, 2936, 2865, 1692, 1602, 1518, 1372, 1246, 1174, 1108, 1073, 1030, 829, 523;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{25}H_{30}N_2O_5$: 439.2155, found: 439.222;

HPLC (method 2): t_R = 13.9 min, purity 100%.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-[(4-nitrobenzoyl)oxy]pyrrolidine-1,2-dicarboxylate (153)



$C_{18}H_{22}N_2O_8$

M_r = 394.4

Under N_2 atmosphere, DIAD (12.2 mL, 11.4 g, 56.51 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (14.8 g, 56.51 mmol) in dry THF (150 mL) and the mixture was stirred for 15 min at 0 °C. Then, a solution of *p*- nitrobenzoic acid (8.6 g, 51.37 mmol) and **142** (6.3 g, 25.69 mmol) in dry THF (40 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 8 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 3/2). Fractions containing the desired product were combined and evaporated *in vacuo.* A share (200 mg, 1.3%) of the obtained residue (15.3 g) was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **153** as colorless solid for analysis.

m.p. = 103-105 °C;

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 3/1);

Specific rotation: $[\alpha]_D^{20}$ = -20.7 (3.0, methanol);

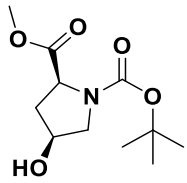
^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]= 1.39 (s, 9H, OC(C*H*$_3$)$_3$), 2.21 – 2.34 (m, 1H, CHC*H*$_2$CH), 2.67 (m, *J* = 21.6/14.5/9.7/4.9 Hz, 1H, CHC*H*$_2$CH), 3.49 – 3.61 (m, 1H, NC*H*$_2$), 3.63 (s, 3H, CO_2C*H*$_3$), 3.75 (m, *J* = 19.2/12.5/5.0 Hz, 1H, NC*H*$_2$), 4.48 (m, *J* = 18.6/9.8/1.6 Hz, 1H, NC*H*), 5.50 (m, *J* = 8.1/2.9 Hz, 1H, C*H*O), 8.09 (m, 2H, 2′-H$_{4\text{-nitrobenzoyl}}$, 6′-H$_{4\text{-nitrobenzoyl}}$), 8.33 – 8.40 (m, 2H, 3′-H$_{4\text{-nitrobenzoyl}}$, 5′-H$_{4\text{-nitrobenzoyl}}$), the signals of the major rotamer are given;

^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]= 27.9 (3C, OC(CH$_3$)$_3$), 35.7 (1C, CHCH$_2$CH), 52.1 (CO$_2$$CH_3$), 52.2 (1C, NCH$_2$), 57.4 (1C, NCH), 73.6 (1C, CHO), 79.2 (1C, OC(CH$_3$)$_3$), 123.9 (2C, C-3′$_{4\text{-nitrobenzoyl}}$, C-5′$_{4\text{-nitrobenzoyl}}$), 130.6 (2C, C-2′$_{4\text{-nitrobenzoyl}}$, C-6′$_{4\text{-nitrobenzoyl}}$), 134.8 (1C, C-1′$_{4\text{-nitrobenzoyl}}$), 150.4 (1C, C-4′$_{4\text{-nitrobenzoyl}}$), 152.9 (1C, NCO$_2$C(CH$_3$)$_3$), 163.5 (1C, ArCO$_{24\text{-nitrobenzoyl}}$), 172.3 (1C, CO$_2CH_3$), the signals of the major rotamer are given;
IR (neat): ṽ [cm^{-1}] = 2974, 1738, 1719, 1697, 1528, 1396, 1351, 1280, 1203, 1179, 1161, 1107, 1066, 1052, 888, 880, 860, 717, 539;

HRMS (*m/z*): [M+Na]$^+$ calcd for C$_{18}$H$_{22}$N$_2$O$_8$: 417.1376, found: 417.131;

HPLC (method 1): t$_R$ = 23.4 min, purity 92.1%.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (154)



C$_{11}$H$_{19}$NO$_5$

M$_r$ = 245.3

At ambient temperature, potassium carbonate (54.5 g, 394.32 mmol) was added to a solution of crude **153** (15 g, 39.43 mmol) in dry methanol (100 mL). After stirring the reaction mixture for 30 min, the mixture was filtered and the filtrate was acidified by adding 0.5 N HCl. Then, a saturated aqueous solution of NaHCO$_3$ was added in excess to render the mixture alkaline and the mixture was extracted with dichloromethane (3×). The combined organic phases were dried (Na$_2$SO$_4$), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/2) to give **154** (3.4 g, 13.78 mmol, 35%) as yellow oil.

TLC: R$_f$ = 0.33 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = -42.2 (5.9, methanol);

^{1}H NMR (400 MHz, CDCl$_3$) δ [ppm]= 1.43 (s, 9H, OC(CH_3)$_3$), 2.01 – 2.13 (m, 1H, CHCH_2CH), 2.32 (m, J = 18.9/14.3/9.8/4.7 Hz, 1H, CHCH_2CH), 3.43 – 3.73 (m, 2H, NCH_2),

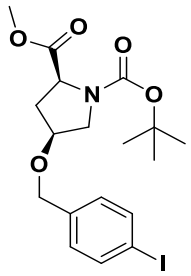
3.77 (s, 3H, CO_2CH_3), 4.25 – 4.40 (m, 1H, NC*H*), 4.25 - 4.40 (m, 1H, C*H*OH), the signals of the major rotamer are given;

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 28.5 (3C, OC(CH_3)$_3$), 38.7 (1C, $CHCH_2CH$), 52.7 (1C, CO_2CH_3), 55.6 (1C, NCH_2), 58.1 (1C, NCH), 70.5 (1C, CHOH), 80.6 (1C, OC(CH_3)$_3$), 153.9 (1C, $NCO_2C(CH_3)_3$), 175.6(1C, CO_2CH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3460, 2984, 2954, 2929, 1726, 1668, 1419, 1257, 1159, 1120, 1088, 981, 769, 593, 577;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{19}NO_5$: 268.1263, found: 268.116.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-[(4-iodobenzyl)oxy]pyrrolidine-1,2-dicarboxylate (155)



$C_{18}H_{24}INO_5$

Mr = 461.3

Sodium hydride (60%) (661 mg, 16.51 mmol) was added to an ice-cooled solution of **154** (2.7 g, 11.01 mmol) in dry DMF (25 mL) and the mixture was stirred for 30 min at ambient temperature. Then, a solution of 4-iodobenzylbromide (4903 mg, 16.51 mmol) in dry DMF (20 mL) was added slowly over a period of 5 min. After stirring the reaction mixture for 18 h at ambient temperature, water was added to the mixture and extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4) and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/0 → 3/1) to give **155** (3494 mg, 7.57 mmol, 69%) as yellow oil.

TLC: R_f = 0.38 (petroleum ether/ethyl acetate, 3/1);

Specific rotation $[\alpha]_D^{20}$ = +16.0 (8.9, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 1.36 – 1.52 (s, 9H, OC(CH_3)$_3$), 2.06 (m, *J* = 15.1/7.9/5.0 Hz, 1H, CHCH_2CH), 2.28 – 2.45 (m, 1H, CHCH_2CH), 3.49 – 3.65 (m, 2H, NCH_2), 3.73 (s, 3H, CO_2CH_3), 4.13 (m, *J* = 23.7/8.8/4.3 Hz, 1H, C*H*O), 4.28 – 4.38 (m, 1H, NC*H*), 4.38 – 4.51 (m, 2H, OCH_2Ar), 7.04 (m, 2H, 2′-H$_{4\text{-iodobenzyl}}$, 6′-H$_{4\text{-iodobenzyl}}$), 7.66 (m, 2H, 3′-H$_{4\text{-iodobenzyl}}$, 5′-H$_{4\text{-iodobenzyl}}$), the signals of the major rotamer are given;

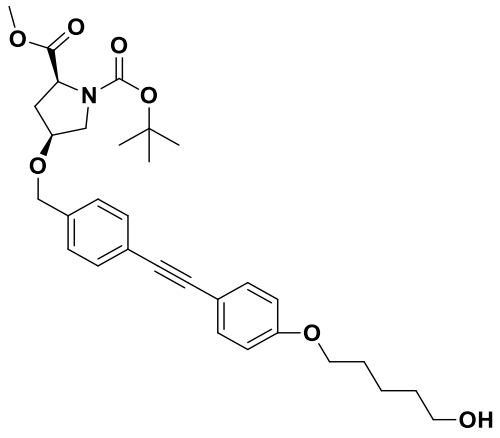
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 28.5 (3C, OC(CH_3)$_3$), 36.9 (1C, CHCH_2CH), 51.4 (1C, NCH_2), 52.2 (1C, CO_2CH_3), 58.2 (1C, NCH), 70.6 (1C, OCH_2Ar), 76.4 (1C, CHO), 80.3 (1C, OC(CH_3)$_3$), 93.3 (1C, C-4′$_{4\text{-iodobenzyl}}$), 129.5 (2C, C-2′$_{4\text{-iodobenzyl}}$, C-6′$_{4\text{-iodobenzyl}}$), 137.6 (1C, C-1′$_{4\text{-iodobenzyl}}$), 137.8 (2C, C-3′$_{4\text{-iodobenzyl}}$, C-5′$_{4\text{-iodobenzyl}}$), 153.9 (1C, NCO_2C(CH_3)$_3$), 173.7 (1C, CO_2CH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2975, 2950, 1748, 1694, 1393, 1364, 1200, 1157, 1115, 1089, 1006, 894, 800, 769, 463;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}INO_5$: 484.0699, found: 484.059;

HPLC (method 1): t_R = 25.3 min, purity 96.7%.

1-(*tert*-butyl)-2-methyl (2*S*,4*S*)-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-1,2-dicarboxylate (156)



$C_{31}H_{39}NO_7$

M_r = 537.7

Under N_2 atmosphere, copper(I) iodide (19 mg, 0.10 mmol), tetrakis(triphenylphosphine)palladium(0) (38 mg, 0.03 mmol), triethylamine (1.4 mL, 987 mg, 9.76 mmol), and **71** (1065 mg, 5.21 mmol) were added to a solution of **155** (1.5 g, 3.25 mmol)

in dry acetonitrile (50 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (*Ø* = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/2) to give **156** (943 mg, 1.75 mmol, 54.0%) as brown oil.

TLC: R_f = 0.30 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = +11.4 (1.8, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 1.36 – 1.50 (s, 9H, OC(C*H*$_3$)$_3$), 1.50 – 1.71 (m, 4H, OCH$_2$CH$_2$C*H*$_2$C*H*$_2$CH$_2$OH), 1.77 – 1.90 (m, 2H, OCH$_2$C*H*$_2$CH$_2$CH$_2$CH$_2$OH), 2.04 (m, 1H, CHC*H*$_2$CH), 2.29 – 2.46 (m, 1H, CHC*H*$_2$CH), 3.51 – 3.71 (m, 2H, NC*H*$_2$), 3.51 - 3.71 (t, 2H, OCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$OH), 3.73 (s, 3H, CO$_2$C*H*$_3$), 3.98 (t, *J* = 6.4 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.11 – 4.22 (m, 1H, C*H*O), 4.29 – 4.40 (m, 1H, NC*H*), 4.41 – 4.57 (m, 2H, OC*H*$_2$Ar), 6.82 – 6.89 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$ 7.23 – 7.30 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.41 – 7.51 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.41 - 7.51 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$), the signals of the major rotamer are given;

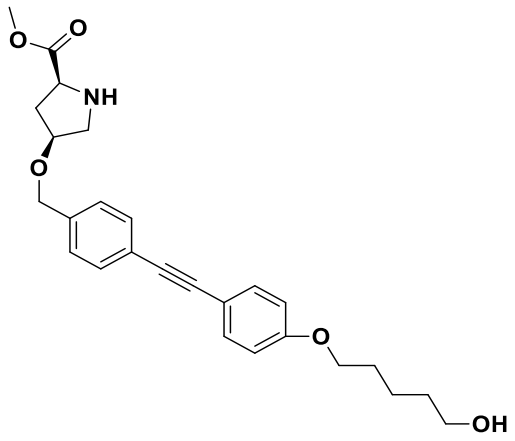
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 28.4 (3C, OC(*C*H$_3$)$_3$), 29.2 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 32.6 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 36.9 (1C, CH*C*H$_2$CH), 51.5 (1C, N*C*H$_2$), 52.2 (1C, CO$_2$*C*H$_3$), 58.2 (1C, N*C*H), 63.0 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 68.0 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 70.9 (1C, O*C*H$_2$Ar), 76.4 (1C, *C*HO), 80.4 (1C, O*C*(CH$_3$)$_3$), 88.0 (1C, Ar*C*≡CAr), 89.8 (1C, ArC≡*C*Ar), 114.7 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.3 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 123.3 (1C, C-4′$_{benzyl}$), 127.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.7 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.8 (1C, C-1′$_{benzyl}$), 159.3 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 173.9 (1C, *C*O$_2CH_3$), the signal for N*C*O$_2$C(CH$_3$)$_3$ cannot be observed in the spectrum, the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3447, 2937, 2868, 1747, 1697, 1517, 1395, 1365, 1244, 1204, 1173, 1158, 1108, 1090, 830, 539, 523;

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{31}H_{39}NO_7$: 560.2727, found: 560.264;

HPLC (method 1): t_R = 25.9 min, purity 95.7%.

Methyl (2*S*,4*S*)-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (157)



$C_{26}H_{31}NO_5$

Mr = 437.5

Zinc bromide (1495 mg, 6.64 mmol) was added to a solution of **156** (1190 mg, 2.21 mmol) in dichloromethane (30 mL) and stirred for 3 h at ambient temperature. Then, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **157** (101 mg, 0.23 mmol, 11%) as yellowish-green oil.

TLC: R_f = 0.20 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +10.4 (1.2, methanol);

^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ [ppm]= 1.49 – 1.68 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.77 – 1.87 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.20 – 2.34 (m, 2H, $CHCH_2CH$), 2.83 – 2.93 (m, 1H, $NHCH_2$), 3.23 (m, *J* = 12.3/1.4 Hz, 1H, $NHCH_2$), 3.36 (s, 3H, CO_2CH_3), 3.60 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.71 (s, 1H, $NHCH_2$), 3.79 (dd, *J* = 7.6/5.9 Hz, 1H, NHC*H*), 4.02 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.09 – 4.17 (m, 1H, C*H*O), 4.47 (m, *J* = 1.8 Hz, 2H, OCH_2Ar), 6.89 – 6.95 (m, 2H, 3′′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5′′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.29 – 7.32 (m, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.44 (m, 2H, 2′′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6′′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.44 (m, 2H, 3′-$H_{benzyl}$, 5′-$H_{benzyl}$);

^{13}C NMR (126 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.3 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 37.2 (1C, $CHCH_2CH$),

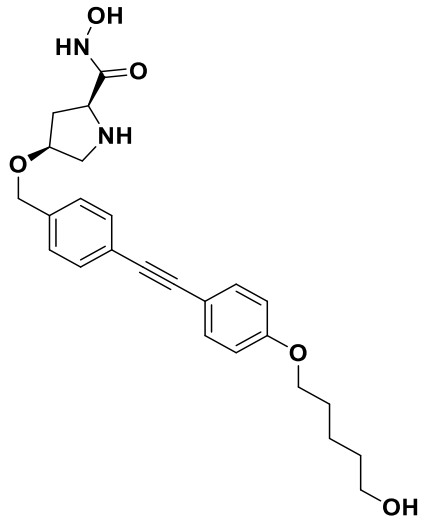
50.0 (1C, CO_2CH_3), 53.1 (1C, $NHCH_2$), 59.7 (1C, NHCH), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 69.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 71.2 (1C, OCH_2Ar), 80.2 (1C, CHO), 88.7 (1C, ArC≡CAr), 90.4 (1C, ArC≡CAr), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.3 (1C, C-4′$_{benzyl}$), 128.7 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.9 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 175.9 (1C, CO_2CH_3);

IR (neat): ṽ [cm^{-1}] = 3310, 2934, 2862, 1733, 1601, 1517, 1243, 1173, 1062, 1030, 980, 831, 820, 524;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{31}NO_5$: 438.2202, found: 438.225;

HPLC (method 1): t_R = 19.7 min, purity 96.0%.

(2*S*,4*S*)-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (158)



$C_{25}H_{30}N_2O_5$

Mr = 438.5

Sodium methoxide in methanol (5.4 M, 0.5 mL) and hydroxylamine hydrochloride (178 mg, 2.56 mmol) were added to a solution of **157** (112 mg, 0.26 mmol) in dry methanol (2 mL) and the mixture was stirred for 24 h at ambient temperature. Afterwards, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the

desired product were combined and subjected to lyophilization to give **158** (15 mg, 0.03 mmol, 13%) as colorless solid.

m.p. = 99-100 °C (decomposition);

TLC: R_f = 0.33 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +5.6 (1.4, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.50 – 1.65 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.82 (m, *J* = 6.7 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.01 (m, *J* = 13.4/6.9/4.8 Hz, 1H, $CHCH_2CH$), 2.35 (m, *J* = 13.3/9.3/7.1 Hz, 1H, $CHCH_2CH$), 2.82 – 2.90 (m, 1H, $NHCH_2$), 3.14 (dd, *J* = 9.6/5.2 Hz, 1H, $NHCH_2$), 3.59 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.83 (dd, *J* = 9.4/4.8 Hz, 1H, NHCH), 4.01 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.13 (m, *J* = 7.2/5.2 Hz, 1H, CHO), 4.48 – 4.63 (m, 2H, OCH_2Ar), 6.89 – 6.98 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.33 (m, *J* = 8.2 Hz, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.40 – 7.47 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.40 - 7.47 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl});

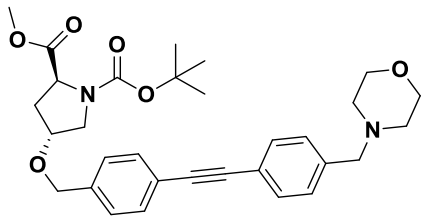
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.3 (1C, $CHCH_2CH$), 33.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 54.2 (1C, $NHCH_2$), 61.5 (1C, NHCH), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 69.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 72.4 (1C, OCH_2Ar), 79.2 (1C, CHO), 88.7 (1C, ArC≡CAr), 90.4 (1C, ArC≡CAr), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.4 (1C, C-4′$_{benzyl}$), 128.9 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.9 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 166.3 (1C, CONHOH);

IR (neat): ṽ [cm^{-1}] = 3260, 2939, 2866, 1651, 1602, 1518, 1412, 1392, 1246, 1108, 1074, 1058, 1031, 830, 644, 523;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{30}N_2O_5$: 439.2155, found: 439.222;

HPLC (method 2): t_R = 13.7 min, purity 95.7%.

1-(*tert*-butyl)-2-methyl (2*S*,4*R*)-4-({4-[(4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-1,2-dicarboxylate (159)



$C_{31}H_{38}N_2O_6$

Mr = 534.7

Under N_2 atmosphere, copper(I) iodide (18 mg, 0.10 mmol), tetrakis(triphenylphosphine)palladium(0) (37 mg, 0.03 mmol), triethylamine (1.33 mL, 974 mg, 9.63 mmol), and **103** (969 mg, 4.81 mmol) were added to a solution of **143** (1480 mg, 3.21 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 3/1 → 0/1) to give **159** (1619 mg, 3.03 mmol, 94%) as brown oil.

TLC: R_f = 0.20 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = -8.6 (4.0, methanol);

^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ [ppm]= 1.41 – 1.51 (s, 9H, OC(C*H*$_3$)$_3$), 2.03 – 2.14 (m, 1H, CHC*H*$_2$CH), 2.33 – 2.42 (m, 1H, CHC*H*$_2$CH), 2.44 – 2.53 (t, 4H, NC*H*$_2$CH$_2$O), 3.56 (s, 2H, ArC*H*$_2$), 3.56 (m, 1H, NC*H*$_2$), 3.58 – 3.65 (m, 1H, NC*H*$_2$), 3.71 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.75 (s, 3H, CO$_2$C*H*$_3$), 4.23 (m, *J* = 15.7/4.9/2.5 Hz, 1H, C*H*O), 4.39 (m, *J* = 7.7 Hz, 1H, NC*H*), 4.49 – 4.64 (m, 2H, OC*H*$_2$Ar), 7.31 – 7.41 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5″-4$_{\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.31 - 7.41 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.47 – 7.53 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.47 - 7.53 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$), the signals of the major rotamer are given;

^{13}C NMR (126 MHz, MeOD-*d*$_4$) δ [ppm]= 28.6 (3C, OC(*C*H$_3$)$_3$), 37.5 (1C, CHC*H*$_2$CH), 52.9 (1C, CO$_2$*C*H$_3$), 52.9 (1C, N*C*H$_2$), 54.7 (2C, N*C*H$_2$CH$_2$O), 59.6 (1C, N*C*H), 64.0 (1C, Ar*C*H$_2$), 67.9 (2C, NCH$_2$*C*H$_2$O), 71.6 (1C, OC*H*$_2$Ar), 77.9 (1C, *C*HO), 81.7 (1C, O*C*(CH$_3$)$_3$), 90.1 (Ar*C*≡CAr), 90.2 (ArC≡*C*Ar), 123.7 (1C, C-1″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 124.0 (1C, C-4′ $_{benzyl}$), 128.9 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.8 (1C, C-3″$_{4\text{-}((4\text{-}(morpholinomethyl)phenyl}$, C-5″$_{4\text{-}\{[4\text{-}}$

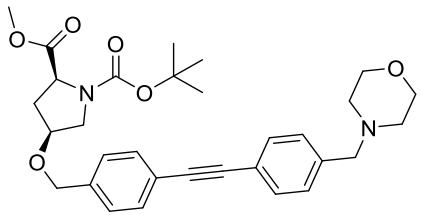
$_{(morpholinomethyl)phenyl}$), 132.6 (2C, C-2″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.7 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 149.8 (1C, N*C*O$_2$C(CH$_3$)$_3$), 175.3 (1C, *C*O$_2CH_3$), the signals for C-1′$_{benzyl}$ and C-4″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$ cannot be observed in the spectrum, the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2952, 2854, 2809, 1748, 1697, 1394, 1365, 1202, 1157, 1114, 1091, 1007, 913, 894, 865, 820, 794, 770, 542;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{31}H_{38}N_2O_6$: 535.2730, found: 535.277;

HPLC (method 1): t_R = 20.9 min, purity 99.5%.

1-(*tert*-butyl)-2-methyl (2*S*,4*S*)-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-1,2-dicarboxylate (160)



$C_{31}H_{38}N_2O_6$

Mr = 534.7

Under N_2 atmosphere, copper(I) iodide (32 mg, 0.17 mmol), tetrakis(triphenylphosphine)palladium(0) (65 mg, 0.06 mmol), triethylamine (2.34 mL, 1711 mg, 16.91 mmol), and **103** (1702 mg, 8.45 mmol) were added to a solution of **155** (2.6 g, 5.64 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 3/1 → 0/1) to give **160** (2.7 g, 5.05 mmol, 90%) as brown oil.

TLC: R_f = 0.20 (petroleum ether/ethyl acetate, 1/1);

Specific rotation: $[\alpha]_D^{20}$ = +10.3 (2.0, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 1.37 – 1.52 (s, 9H, OC(CH_3)$_3$), 2.03 – 2.13 (m, 1H, CHCH_2CH), 2.31 – 2.57 (m, 1H, CHCH_2CH), 2.31 - 2.57 (t, 4H, NCH_2CH_2O), 3.54 (s, 2H, ArCH_2), 3.54 (m, 2H, NCH_2), 3.73 (t, 4H, NCH$_2$CH_2O), 3.73 (s, 3H, CO_2CH_3), 4.08 – 4.21 (m, 1H, C*H*O), 4.31 – 4.40 (m, 1H, NC*H*), 4.41 – 4.60 (m, 2H, OCH_2Ar), 7.23 – 7.38 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, 5″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 7.23 – 7.38 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.43 – 7.55 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, 6″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 7.43 – 7.55 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$); the signals of the major rotamer are given;

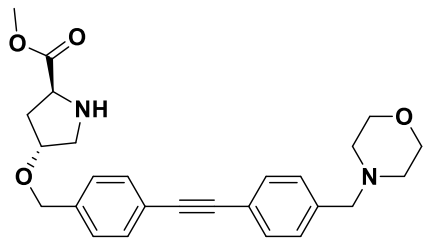
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 28.4 (3C, OC(*C*H$_3$)$_3$), 36.9 (1C, CHCH_2CH), 51.5 (1C, N*C*H$_2$), 52.2 (1C, CO_2CH_3), 53.7 (2C, N*C*H$_2$CH$_2$O), 58.2 (1C, N*C*H), 63.2 (1C, Ar*C*H$_2$), 67.0 (2C, NCH$_2$*C*H$_2$O), 70.9 (1C, OCH_2Ar), 76.4 (1C, *C*HO), 80.3 (1C, O*C*(CH$_3$)$_3$), 127.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 127.7 (1C, C-3″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-5″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 131.8 (2C, C-2″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-6″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 131.9 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 151.3 (1C, N*C*O$_2$C(CH$_3$)$_3$), 173.6 (1C, *C*O$_2CH_3$), the signals for Ar*C*≡CAr, ArC≡*C*Ar, C-1′$_{benzyl}$, C-4″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-1″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, and C-4′$_{benzyl}$ cannot be observed in the spectrum, the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2952, 2855, 2809, 1748, 1697, 1394, 1365, 1350, 1201, 1158, 1114, 1091, 1070, 1007, 865, 820, 770, 567;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{31}H_{38}N_2O_6$: 535.2730, found: 535.277;

HPLC (method 1): t_R = 20.9 min, purity 83.6%.

Methyl (2*S*,4*R*)-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxylate (161a)



$C_{26}H_{30}N_2O_4$

Mr = 434.5

Zinc bromide (1820 mg, 8.08 mmol) was added to a solution of **159** (1440 mg, 2.69 mmol) in dichloromethane (20 mL) and stirred for 3 h at ambient temperature. Then, water was added

and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **161a** (140 mg, 0.32 mmol, 12.0%) as brown oil.

TLC: R_f = 0.28 (dichloromethane/methanol, 95/5);

Specific rotation $[\alpha]_D^{20}$ = +2.1 (7.5, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.97 – 2.04 (m, 1H, CHC*H*$_2$CH), 2.29 (m, *J* = 13.7/8.0/2.3/1.2 Hz, 1H, CHC*H*$_2$CH), 2.39 – 2.48 (t, 4H, NC*H*$_2$CH$_2$O), 3.08 – 3.17 (m, 2H, NHC*H*$_2$), 3.49 (s, 2H, ArC*H*$_2$), 3.70 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.72 (s, 3H, CO$_2$C*H*$_3$), 4.01 (t, *J* = 7.9 Hz, 1H, NHC*H*), 4.08- 4.16 (m, 1H, C*H*O), 4.48 (s, 2H, OC*H*$_2$Ar), 7.27 – 7.32 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.27 – 7.32 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.44 – 7.50 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.44 – 7.50 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$);

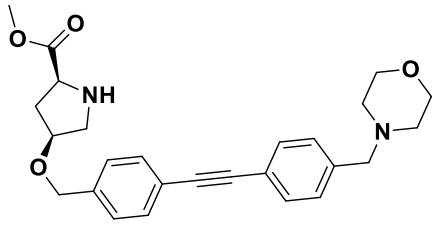
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 36.7 (1C, CHC*H*$_2$CH), 52.3 (1C, CO$_2$*C*H$_3$), 52.6 (1C, NH*C*H$_2$), 53.7 (2C, N*C*H$_2$CH$_2$O), 58.8 (1C, NH*C*H), 63.2 (1C, Ar*C*H$_2$), 67.1 (2C, NCH$_2$*C*H$_2$O), 70.7 (1C, OC*H*$_2$Ar), 79.6 (1C, *C*HO), 89.3 (Ar*C*≡CAr), 89.5 (ArC≡*C*Ar), 122.1 (1C, C-1″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 122.7 (1C, C-4′$_{benzyl}$), 127.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.3 (1C, C-3″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.7 (2C, C-2″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.8 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 138.3 (1C, C-4″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 138.5 (1C, C-1′$_{benzyl}$), 175.2 (1C, *C*O$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3029, 2933, 2854, 2807, 1733, 1606, 1517, 1453, 1368, 1348, 1289, 1242, 1207, 1113, 1084, 1007, 914, 865, 819, 794, 514;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{30}N_2O_4$: 435.2206, found: 435.223;

HPLC (method 1): t_R = 14.4 min, purity 85.9%.

Methyl (2*S*,4*S*)-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxylate (162a)



$C_{26}H_{30}N_2O_4$

Mr = 434.5

Zinc bromide (2243 mg, 9.96 mmol) was added to a solution of **160** (2663 mg, 4.98 mmol) in dichloromethane (20 mL) and stirred for 3 h at ambient temperature. Then, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **162a** (1258 mg, 2.90 mmol, 58%) as yellow oil.

TLC: R_f = 0.38 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +9.1 (2.8, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.02 (m, *J* = 13.6/7.8/5.8 Hz, 1H, CHC*H*$_2$CH), 2.30 (m, *J* = 13.7/8.0/2.3/1.0 Hz, 1H, CHC*H*$_2$CH), 2.41 – 2.50 (m, 4H, NC*H*$_2$CH$_2$O), 3.08 – 3.21 (m, 2H, NHC*H*$_2$), 3.51 (s, 2H, ArC*H*$_2$), 3.72 (t, 4H, NCH$_2$C*H*$_2$O), 3.72 (s, 3H, CO$_2$C*H*$_3$), 4.02 (t, *J* = 7.9 Hz, 1H, NHC*H*), 4.15 (m, *J* = 7.6/3.2 Hz, 1H, C*H*O), 4.49 (s, 2H, OC*H*$_2$Ar), 7.26 – 7.35 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, 5″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 7.26 – 7.35 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.44 – 7.53 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, 6″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 7.44 – 7.53 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$);

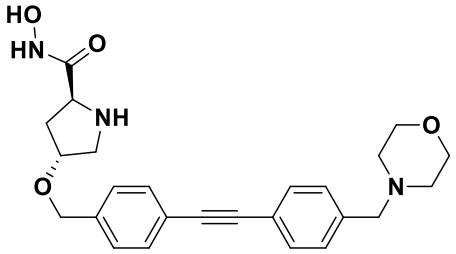
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 36.7 (1C, CHC*H*$_2$CH), 52.4 (1C, CO$_2$*C*H$_3$), 52.6 (1C, NH*C*H$_2$), 53.7 (2C, N*C*H$_2$CH$_2$O), 58.9 (1C, NH*C*H), 63.3 (1C, Ar*C*H$_2$), 67.1 (2C, NCH$_2$*C*H$_2$O), 70.8 (1C, OC*H*$_2$Ar), 79.6 (1C, *C*HO), 89.3 (Ar*C*≡CAr), 89.5 (ArC≡*C*Ar), 122.2 (1C, C-1″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 122.7 (1C, C-4′$_{benzyl}$), 127.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.3 (1C, C-3″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-5″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 131.7 (2C, C-2″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-6″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 131.8 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 138.2 (1C, C-4″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 138.5 (1C, C-1′$_{benzyl}$), 175.1 (1C, *C*O$_2CH_3$);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3030, 2854, 2808, 1733, 1348, 1204, 1173, 1114, 1085, 1070, 1007, 865, 819, 795; 541, 515;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{30}N_2O_4$: 435.2206, found: 435.227;

HPLC (method 1): t_R = 14.4 min, purity 96.9%.

(2*S*,4*R*)-*N*-hydroxy-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxamide (161)



$C_{25}H_{29}N_3O_4$

M_r = 435.5

Sodium methoxide in methanol (5.4 M, 0.3 mL) and hydroxylamine hydrochloride (120 mg, 1.73 mmol) were added to a solution of **161a** (150 mg, 0.35 mmol) in dry methanol (2 mL) and the mixture was stirred for 24 h at ambient temperature. Afterwards, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **161** (52 mg, 0.12 mmol, 34%) as colorless solid.

m.p. = 119-120 °C;

TLC: R_f = 0.20 (dichloromethane/methanol, 9/1);

Specific rotation $[\alpha]_D^{20}$ = +19.6 (1.3, methanol);

^{1}H NMR (500 MHz, MeOD-d_4) δ [ppm]= 2.17 – 2.32 (m, 2H, CHC*H*$_2$CH), 2.46 (t, *J* = 4.8 Hz, 4H, NC*H*$_2$CH$_2$O), 2.81 (dd, *J* = 10.6/3.9 Hz, 1H, NHC*H*$_2$), 3.15 – 3.22 (m, 1H, NHC*H*$_2$), 3.53 (s, 2H, ArC*H*$_2$), 3.66 – 3.72 (m, 4H, NCH$_2$C*H*$_2$O), 3.99 (dd, *J* = 9.3/5.4 Hz, 1H, NHC*H*), 4.12 – 4.17 (m, 1H, C*H*O), 4.51 – 4.55 (m, 2H, OC*H*$_2$Ar), 7.38 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl},}$

5″-$H_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.38 (m, 2H, 2′-$H_{benzyl}$, 6′-$H_{benzyl}$), 7.48 (m, 2H, 2″-$H_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6″-$H_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.48 (m, 2H, 3′-$H_{benzyl}$, 5′-$H_{benzyl}$);

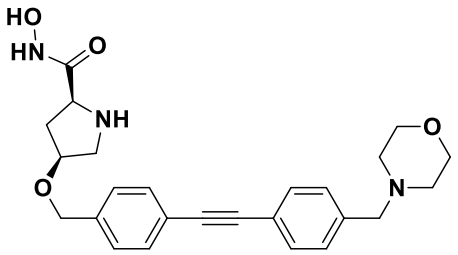
^{13}C NMR (126 MHz, MeOD-*d_4*) δ [ppm]= 34.2 (1C, CHC*H_2*CH), 54.2 (1C, NH*C*H_2), 54.7 (2C, N*C*H_2CH_2O), 61.6 (1C, NH*C*H), 64.1 (1C, Ar*C*H_2), 67.9 (2C, NCH_2*C*H_2O), 71.5 (1C, OC*H_2*Ar), 79.9 (1C, *C*HO), 90.1 (Ar*C*≡CAr), 90.2 (ArC≡*C*Ar), 123.7 (1C, C-1″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 123.8 (1C, C-4′$_{benzyl}$), 129.0 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.8 (1C, C-3″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-2″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 139.2 (1C, C-4″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 140.4 (1C, C-1′$_{benzyl}$), 168.9 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3178, 2861, 2811, 1652, 1517, 1453, 1411, 1350, 1114, 1086, 1070, 1035, 1008, 868, 820, 793, 514;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{29}N_3O_4$: 436.2158, found: 436.220;

HPLC (method 2): t_R = 11.8 min, purity 100 %

(2*S*,4*S*)-*N*-hydroxy-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)oxy]pyrrolidine-2-carboxamide (162)



$C_{25}H_{29}N_3O_4$

M_r = 435.5

Sodium methoxide in methanol (5.4 M, 0.3 mL) and hydroxylamine hydrochloride (114 mg, 1.65 mmol) were added to a solution of **162a** (143 mg, 0.33 mmol) in dry methanol (1.5 mL) and the mixture was stirred for 24 h at ambient temperature. Afterwards, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **162** (12 mg, 0.03 mmol, 8%) as colorless solid.

m.p.= 123-125 °C (decomposition);

TLC: R_f = 0.23 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = +15.7 (1.2, methanol);

^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ [ppm]= 2.20 (m, *J* = 14.4/5.6 Hz, 1H, CHC*H*$_2$CH), 2.30 (m, *J* = 12.5/9.5/1.6 Hz, 1H, CHC*H*$_2$CH), 2.44 – 2.49 (t, 4H, NC*H*$_2$CH$_2$O), 2.82 (dd, *J* = 10.7/3.9 Hz, 1H, NHC*H*$_2$), 3.15 – 3.23 (m, 1H, NHC*H*$_2$), 3.54 (s, 2H, ArC*H*$_2$), 3.67 – 3.72 (t, 4H, NCH$_2$C*H*$_2$O), 3.99 (dd, *J* = 9.3/5.3 Hz, 1H, NHC*H*), 4.13 – 4.18 (m, 1H, C*H*O), 4.51 – 4.59 (m, 2H, OC*H*$_2$Ar), 7.33 – 7.42 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.33 – 7.42 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.46 – 7.53 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.46 – 7.53 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$);

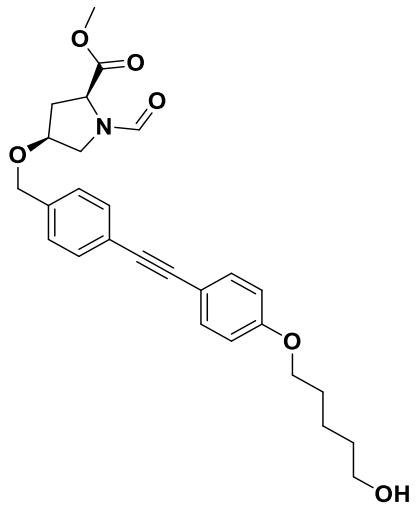
^{13}C NMR (126 MHz, MeOD-*d*$_4$) δ [ppm]= 34.2 (1C, CHC*H*$_2$CH), 54.3 (1C, NH*C*H$_2$), 54.7 (2C, N*C*H$_2$CH$_2$O), 61.5 (1C, NH*C*H), 64.1 (1C, Ar*C*H$_2$), 67.9 (2C, NCH$_2$*C*H$_2$O), 71.5 (1C, OC*H*$_2$Ar), 79.9 (1C, *C*HO), 90.1 (Ar*C*≡CAr), 90.2 (ArC≡*C*Ar), 123.7 (1C, C-1″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 123.8 (1C, C-4′$_{benzyl}$), 129.0 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.8 (1C, C-3″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-2″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 139.2 (1C, C-4″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 140.4 (1C, C-1′$_{benzyl}$), 169.6 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3219, 2857, 2808, 1652, 1516, 1453, 1349, 1112, 1069, 1007, 866, 819, 793, 516;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{29}N_3O_4$: 436.2158, found: 436.220;

HPLC (method 2): t_R = 11.8 min, purity 98.0 %.

Methyl (2*S*,4*S*)-1-formyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (127)



$C_{27}H_{31}NO_6$

Mr = 465.6

Triethylamine (0.6 mL, 432 mg, 4.27 mmol) and formic acid (98%) (0.33 mL, 401 mg, 8.55 mmol) were added to **157** (1.87 g, 4.27 mmol) in dry toluene (30 mL) and the reaction mixture was refluxed overnight. Then, the solvent was removed in vacuo and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/2 → 0/1) to give **127** (640 mg, 1.37 mmol, 32%) as brown oil.

TLC: R_f = 0.28 (ethyl acetate);

Specific rotation $[\alpha]_D^{20}$ = +12.5 (3.6, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.46 – 1.66 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.81 (m, *J* = 6.8 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.22 (m, *J* = 13.3/8.8/4.2 Hz, 1H, $CHCH_2CH$), 2.72 (m, *J* = 13.6/1.6 Hz, 1H, $CHCH_2CH$), 3.36 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.58 – 3.64 (m, 1H, NCH_2), 3.65 (s, 2H, CO_2CH_3), 3.67 – 3.73 (m, 2H, NCH_2), 3.93 – 4.02 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.15 – 4.23 (m, 1H, CHO), 4.42 – 4.55 (m, 2H, OCH_2Ar), 4.42 - 4.55 (m, 1H, NCH), 6.81 – 6.89 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.20 – 7.24 (m, 1H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.41 – 7.50 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.41 - 7.50 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), 8.30 – 8.33 (s, 1H, NCHO), the signals of the major rotamer are given;

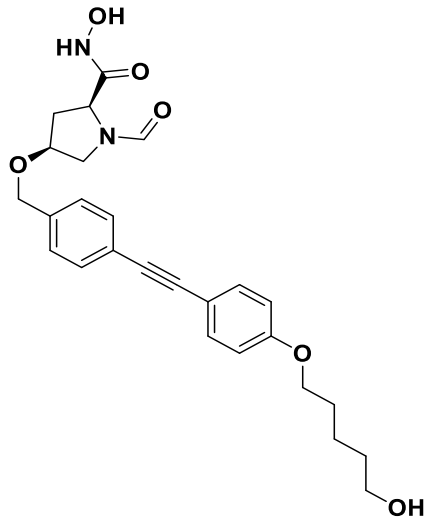
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 23.0 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 29.3 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 30.6 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 35.2 (1C, $CHC\mathit{H}_2CH$), 49.9 (1C, NCH_2), 53.0 (1C, $CO_2\mathit{C}H_3$), 57.7 (1C, N*C*H), 61.5 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 68.2 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 70.3 (1C, $O\mathit{C}H_2Ar$), 75.6 (1C, C*H*O), 87.9 (1C, Ar*C*≡CAr), 114.7 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.2 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 123.1 (1C, C-4′$_{benzyl}$), 127.5 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.6 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.4 (1C, C-1′$_{benzyl}$), 159.4 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 162.3 (1C, N*C*HO), 171.9 (1C, *C*O_2CH_3), the signal for ArC≡*C*Ar cannot be observed in the spectrum, the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2940, 2867, 1738, 1670, 1602, 1516, 1435, 1417, 1244, 1197, 1173, 1087, 1045, 1018, 830, 540, 523;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{31}NO_6$: 465.2151, found: 466.221;

HPLC (method 1): t_R = 27.0 min, purity 87.0%.

(2*S*,4*S*)-1-Formyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (163)



$C_{26}H_{30}N_2O_6$

Mr = 466.5

An aqueous solution of hydroxylamine (50 wt%, 0.8 mL) was added to a solution of **127** (58 mg, 0.12 mmol) in acetonitrile (1 mL) and the mixture was stirred for 18 h at ambient

temperature. Afterwards, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **163** (14 mg, 0.03 mmol, 25%) as colorless solid.

m.p. = 119-120 °C;

TLC: R_f = 0.18 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -12.0 (1.0, methanol);

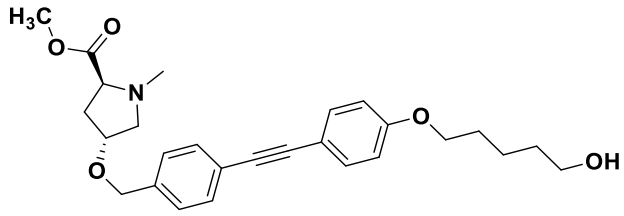
^{1}H NMR (600 MHz, MeOD-*d_4*) δ [ppm]= 1.49 – 1.65 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.74 – 1.86 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.24 – 2.53 (m, 2H, $CHCH_2CH$), 3.42 (t, *J* = 6.3 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.65 (dd, *J* = 10.9/4.4 Hz, 1H, NCH_2), 3.91 (dd, *J* = 10.9/5.6 Hz, 1H, NCH_2), 4.01 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.24 (m, *J* = 10.0/5.5/3.4 Hz, 1H, CHO), 4.42 (m, *J* = 9.1/4.8/1.1 Hz, 1H, NCH), 4.47 – 4.60 (m, 2H, OCH_2Ar), 6.89 – 6.94 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.32 – 7.38 (m, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.40 – 7.48 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.40 – 7.48 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), 8.19 – 8.20 (m, 1H, NCHO), the signals of the major rotamer are given;
^{13}C NMR (151 MHz, MeOD-*d_4*) δ [ppm]= 24.0 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.3 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 31.4 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 35.8 (1C, $CHCH_2CH$), 52.9 (1C, NCH_2), 56.6 (1C, NCH), 62.7 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 69.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 72.0 (1C, OCH_2Ar), 77.5 (1C, CHO), 88.7 (1C, ArC≡CAr), 90.4 (1C, ArC≡CAr), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 124.4 (1C, C-4′$_{benzyl}$), 129.0 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 139.5 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 164.4 (1C, NCHO), 170.2 (1C, CONHOH), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3209, 2972, 2937, 2865, 1651, 1602, 1517, 1388, 1360, 1245, 1198, 1173, 1081, 1047, 1019, 830, 537, 525;

HRMS (*m/z*): $[M+K]^+$ calcd for $C_{26}H_{30}N_2O_6$: 505.2104, found: 505.231;

HPLC (method 2): t_R = 17.6 min, purity 95.0%.

Methyl (2*S*,4*R*)-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}-1-methylpyrrolidine-2-carboxylate (164a)



$C_{27}H_{33}NO_5$

M_r = 451.56

Formaldehyde (37%) (0.33 mL) was added to an ice-cooled solution of **151** (645 mg, 1.47 mmol) in dichloroethane (15 mL) and the mixture was stirred for 30 min at 0 °C. The reaction mixture was stirred for a further 30 min at ambient temperature. Then, sodium triacetoxyborohydride (3749 mg, 17.69 mmol) was added to the reaction mixture and stirred at ambient temperature for 36 h. Afterwards, water was added to the mixture and extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, dichloromethane/methanol, 1/0 → 9/1) to give **164a** (215 mg, 0.48 mmol, 32%) as pale-yellow oil.

TLC: R_f = 0.45 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +30.0 (1.0, chloroform);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= δ 1.50 – 1.69 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.76 – 1.89 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.19 (m, 1H, $CHCH_2CH$), 2.52 (m, 1H, $CHCH_2CH$), 2.52 (s, 3H, NCH_3), 3.34 (d, *J* = 10.7 Hz, 1H, NCH_2), 3.68 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.75 (s, 3H, CO_2CH_3), 3.98 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.12 (m, 1H, C*H*O), 4.42 – 4.53 (m, 2H, OCH_2Ar), 6.83 – 6.88 (m, 2H, 3″-$H_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.26 – 7.31 (m, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.42 – 7.51 (m, 2H, 2″-$H_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.42 – 7.51 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), the signals for NC*H* and NCH_2 cannot be observed in the spectrum;

^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 29.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 37.0 (1C, $CHCH_2CH$),

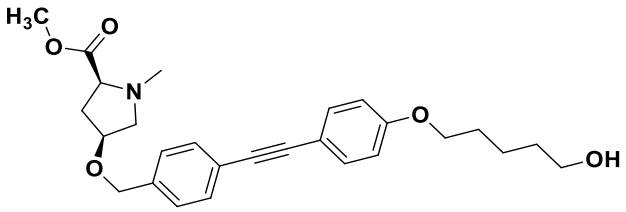
63.0 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 68.1 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 70.9 (1C, $O\mathit{C}H_2Ar$), 76.7 (1C, *C*HO), 88.1 (1C, Ar*C*≡CAr), 114.7 (2C, C-3″$_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.4 (1C, C-1″$_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$) , 127.7 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.6 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 159.3 (1C, C-4″$_{4\text{-}\{(4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), the signals for NCH_3, NCH, $\mathit{C}O_2CH_3$, NCH_2, ArC≡*C*Ar, C-4′ $_{benzyl}$, and C-1′ $_{benzyl}$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3383, 2939, 2861, 1743, 1601, 1517, 1468, 1338, 1283, 1244, 1204, 1173, 1108, 1093, 1066, 1019, 821, 524;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{33}NO_5$: 452.2359, found: 452.239;

HPLC (method 1): t_R= 20.1 min, purity = 87.4%.

Methyl (2*S*,4*S*)-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}-1-methylpyrrolidine-2-carboxylate (165a)



$C_{27}H_{33}NO_5$

M_r = 451.56

Formaldehyde (37%) (0.37 mL) was added to an ice-cooled solution of **157** (720 mg, 1.65 mmol) in dichloroethane (15 mL) and the mixture was stirred for 30 min at 0 °C. The reaction mixture was stirred for a further 30 min at ambient temperature. Then, sodium triacetoxyborohydride (4185 mg, 19.75 mmol) was added to the reaction mixture and stirred at ambient temperature for 72 h. Afterwards, water was added to the mixture and extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, dichloromethane/methanol, 1/0 → 9/1) to give **165a** (161 mg, 0.36 mmol, 24%) as pale-yellow oil.

TLC: R_f = 0.45 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +10.9 (3.8, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.50 – 1.71 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.83 (dt, *J* = 14.3/6.7 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 2.17 – 2.31 (m, 2H, $CHC\mathit{H}_2CH$), 2.41 – 2.55 (m, 3H, $NC\mathit{H}_3$), 2.41 - 2.55 (m, 1H, $NC\mathit{H}_2$), 3.34 (m, *J* = 17.4/9.4 Hz, 1H, $NC\mathit{H}$), 3.55 (dd, *J* = 10.2/6.1 Hz, 1H, $NC\mathit{H}_2$), 3.68 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.75 (s, 3H, $CO_2C\mathit{H}_3$), 3.98 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.21 (m, *J* = 6.6/3.5 Hz, 1H, $C\mathit{H}O$), 4.47 (m, *J* = 12.0 Hz, 2H, $OC\mathit{H}_2Ar$), 6.79 – 6.89 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.28 (m, *J* = 8.0 Hz, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.39 – 7.53 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.39 – 7.53 (m, 2H, 3′-H_{benzyl}, 5-H_{benzyl});

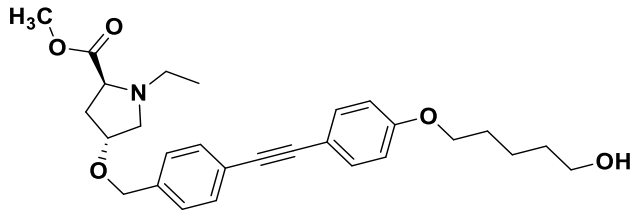
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 29.2 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 37.0 (1C, $CH\mathit{C}H_2CH$), 41.3 (1C, NCH_3), 62.2 (1C, NCH_2), 63.0 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 66.3 (1C, NCH), 68.0 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 71.3 (1C, OCH_2Ar), 77.2 (1C, *C*HO), 88.0 (1C, Ar*C*≡CAr), 89.8 (1C, ArC≡*C*Ar), 114.7 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.3 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 123.2 (1C, C-4′$_{benzyl}$), 127.7 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.7 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.9 (1C, C-1′$_{benzyl}$), 159.3 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), the signal for $\mathit{C}O_2CH_3$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3389, 2939, 2861, 1736, 1602, 1469, 1456, 1437, 1283, 1245, 1203, 1108, 1093, 1019, 830, 539, 524;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{33}NO_5$: 452.2359, found: 452.244;

HPLC (method 1): t_R= 20.3 min, purity = 76.3%.

Methyl (2*S*,4*R*)-1-ethyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (166a)



$C_{28}H_{35}NO_5$

M_r = 465.6

Triethylamine (0.26 mL, 193 mg, 1.91 mmol) was added to a solution of **151** (418 mg, 0.96 mmol) in acetonitrile (15 mL) and the mixture was stirred for 30 min at ambient temperature. Then, ethyl bromide (0.14 ml, 208 mg, 1.19 mmol) was added to the reaction mixture and refluxed overnight. Afterwards, the solvent was removed in vacuo and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, dichloromethane/methanol, 1/0 → 95/5) to give **166a** (345 mg, 0.74 mmol, 77%,) as brown oil.

TLC: R_f = 0.25 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = +24.7 (1.6, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.11 (t, *J* = 7.3 Hz, 3H, NCH$_2$C*H*$_3$), 1.52 – 1.67 (m, 4H, OCH$_2$CH$_2$C*H*$_2$C*H*$_2$CH$_2$OH), 1.83 (dt, *J* = 14.0, 6.5 Hz, 2H, OCH$_2$C*H*$_2$CH$_2$CH$_2$CH$_2$OH), 2.04 – 2.12 (m, 1H, CHC*H*$_2$CH), 2.40 (m, *J* = 11.8, 7.2 Hz, 1H, NC*H*$_2$CH$_3$), 2.45 – 2.55 (m, 1H, CHC*H*$_2$CH), 2.45 - 2.55 (m, 1H, NC*H*$_2$), 2.82 (m, *J* = 11.9/7.3 Hz, 1H, NC*H*$_2$CH$_3$), 3.19 (t, *J* = 8.2 Hz, 1H, NC*H*), 3.32 (m, 1H, NC*H*$_2$), 3.60 (t, *J* = 6.4 Hz, 2H, OCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$OH), 3.73 (s, 3H, CO$_2$C*H*$_3$), 4.03 (t, *J* = 6.4 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.16 (m, *J* = 7.2/5.5/3.4/1.8 Hz, 1H, C*H*O), 4.46 – 4.55 (m, 2H, OC*H*$_2$Ar), 6.89 – 6.96 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 7.33 – 7.37 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.42 – 7.47 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 7.42 – 7.47(m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$);

^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 13.4 (1C, NCH$_2$*C*H$_3$), 23.6 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 30.3 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 33.5 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 37.6 (1C, CH*C*H$_2$CH), 50.5 (1C, N*C*H$_2$CH$_3$), 59.7 (1C, N*C*H$_2$), 62.9 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 66.5 (1C, N*C*H), 69.1 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH),

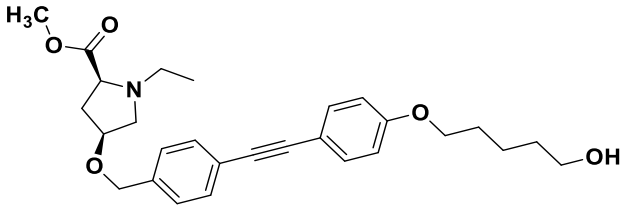
71.7 (1C, O*C*H$_2$Ar), 78.2 (1C, *C*HO), 88.7 (1C, Ar*C*≡CAr), 90.4 (1C, ArC≡*C*Ar), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 116.6 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 124.3 (1C, C-4′$_{benzyl})$, 128.9 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl})$, 132.3 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl})$, 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 140.0 (1C, C-1′$_{benzyl})$, 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 175.3 (1C, *C*O$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3340, 2935, 2860, 1740, 1601, 1518, 1468, 1436, 1391, 1357, 1284, 1243, 1199, 1174, 1108, 1094, 1071, 1038, 1018, 832, 820, 524;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{28}H_{35}NO_5$: 466.2515, found: 466.260;

HPLC (method 1): t_R = 20.6 min, purity 95.7%.

Methyl (2*S*,4*S*)-1-ethyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxylate (167a)



$C_{28}H_{35}NO_5$

M_r = 465.6.

Triethylamine (0.22 mL, 158 mg, 1.56 mmol) was added to a solution of **157** (342 mg, 0.78 mmol) in acetonitrile (15 mL) and the mixture was stirred for 30 min at ambient temperature. Then, ethyl bromide (0.12 ml, 170 mg, 1.56 mmol) was added to the reaction mixture and refluxed overnight. Afterwards, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 3/1 → 0/1) to give **167a** (182 mg, 0.39 mmol, 50%,) as yellow oil.

TLC: R_f = 0.30 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -31.3 (3.5, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.13 (t, 3H, NCH$_2$C*H*$_3$), 1.50 – 1.71 (m, 4H, OCH$_2$CH$_2$C*H*$_2$C*H*$_2$CH$_2$OH), 1.77 – 1.87 (m, 2H, OCH$_2$C*H*$_2$CH$_2$CH$_2$CH$_2$OH), 2.17 (m, 1H,

CHC*H*$_2$CH), 2.44 (m, 1H, CHC*H*$_2$CH), 3.34 (d, *J* = 10.5 Hz, 1H, NC*H*$_2$), 3.69 (m, *J* = 6.1 Hz, 2H, OCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$OH), 3.74 (s, 3H, CO$_2$C*H*$_3$), 3.98 (t, *J* = 6.4 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.49 (s, 2H, OC*H*$_2$Ar), 6.81 – 6.91 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.29 (m, *J* = 8.0 Hz, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.42 – 7.49 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.42 – 7.49 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$), the signals for NC*H*$_2$, NC*H*, NC*H*$_2$CH$_3$, and C*H*O cannot be observed in the spectrum;

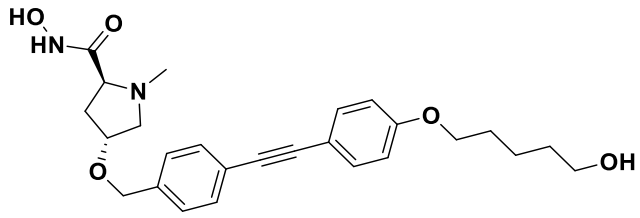
^{13}C NMR (151 MHz, CDCl$_3$) δ [ppm]= 22.5 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 29.2 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 32.6 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 36.6 (1C, CH*C*H$_2$CH), 58.5 (1C, N*C*H$_2$), 63.0 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 68.0 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 70.8 (1C, O*C*H$_2$Ar), 76.6 (1C, *C*HO), 88.1 (1C, Ar*C*≡CAr), 89.6 (1C,ArC≡*C*Ar), 114.7 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.4 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 122.9 (1C, C-4′$_{benzyl}$), 127.7 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.7 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 133.2 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 159.3 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), the signals for *C*O$_2CH_3$, NCH$_2$*C*H$_3$, N*C*H$_2CH_3$, N*C*H, and C-1′ $_{benzyl}$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3342, 2936, 2863, 1743, 1602, 1518, 1284, 1245, 1200, 1175, 1109, 1094, 1074, 833, 821, 525;

HRMS (*m/z*): [M+H]$^+$ calcd for C$_{28}$H$_{35}$NO$_5$: 466.2515, found: 466.257;

HPLC (method 1): t_R = 20.6 min, purity 86.1%.

(2*S*,4*R*)-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}-1-methylpyrrolidine-2-carboxamide (164)



$C_{26}H_{32}N_2O_5$

Mr = 452.6

Sodium methoxide in methanol (5.4 M, 0.4 mL) and hydroxylamine hydrochloride (138 mg, 1.99 mmol) were added to a solution of **164a** (180 mg, 0.40 mmol) in dry methanol (2 mL) and the mixture was stirred for 24 h at ambient temperature. Afterwards, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **164** (41 mg, 0.02 mmol, 23%) as colorless solid.

m.p.= 119-121 °C;

TLC: R_f = 0.25 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +4.2 (1.7, chloroform);

^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ [ppm]= 1.49 – 1.65 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.75 – 1.85 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.04 (m, *J* = 13.9/6.9/2.6/1.4 Hz, 1H, $CHCH_2CH$), 2.32 (s, 3H, NCH_3), 2.39 – 2.44 (m, 1H, NCH_2), 2.44 – 2.49 (m, 1H, $CHCH_2CH$), 2.84 (dd, *J* = 9.2/6.9 Hz, 1H, NC*H*), 3.24 (m, *J* = 10.7/1.4 Hz, 1H, NCH_2), 3.58 (t, *J* = 6.3 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.00 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.10 (m, *J* = 6.4/3.8/1.3 Hz, 1H, C*H*O), 4.48 (s, 2H, OCH_2Ar), 6.87 – 6.93 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 7.29 - 7.37 (m, *J* = 8.2 Hz, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.38 – 7.48 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-}hydroxypentyl)oxy]phenyl}$), 7.38 – 7.48 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl});

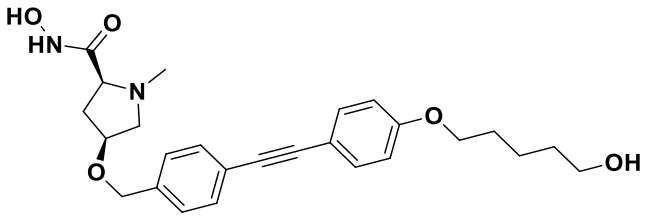
^{13}C NMR (126 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 30.2 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 33.5 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 38.5 (1C, CH*C*H$_2$CH), 41.5 (1C, N*C*H$_3$), 62.5 (1C, N*C*H$_2$), 62.9 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 68.5 (1C, N*C*H), 69.2 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 71.6 (1C, O*C*H$_2$Ar), 79.2 (1C, *C*HO), 88.7 (1C, Ar*C*≡CAr), 90.4 (1C, ArC≡*C*Ar), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.3 (1C, C-4′$_{benzyl}$), 129.0 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.9 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 171.8 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3167, 2933, 2857, 1658, 1601, 1517, 1469, 1284, 1244, 1070, 1054, 1031, 830, 658, 522;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{26}H_{32}N_2O_5$: 453.2311, found: 453.232;

HPLC (method 2): t_R = 13.6 min, purity 99.2%.

(2*S*,4*S*)-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}-1-methylpyrrolidine-2-carboxamide (165)



$C_{26}H_{32}N_2O_5$

M_r = 452.6

An aqueous solution of hydroxylamine (50 wt%, 1.4 mL) was added to a solution of **165a** (97 mg, 0.34 mmol) in a mixture of THF (0.5 mL) and isopropanol (0.5 mL). After stirring the reaction mixture for 18 h at ambient temperature, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **165** (16 mg, 0.04 mmol, 17%) as colorless solid.

m.p. = 127-128 °C (decomposition);

TLC: R_f = 0.20 (dichloromethane/methanol, 95/5);

Specific rotation $[\alpha]_D^{20}$ = +15.9 (1.1, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.51 – 1.64 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.76 – 1.86 (m, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 2.10 – 2.17 (m, 2H, $CHC\mathit{H}_2CH$), 2.34 (s, 3H, $NC\mathit{H}_3$), 2.39 – 2.47 (m, 1H, $NC\mathit{H}_2$), 3.04 (t, *J* = 8.1 Hz, 1H, NC*H*), 3.40 (dd, *J* = 10.1/5.9 Hz, 1H, $NC\mathit{H}_2$), 3.59 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 4.01 (t, *J* = 6.4 Hz, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.19 (m, *J* = 6.0/4.7 Hz, 1H, C*H*O), 4.44 – 4.54 (m, 2H, $OC\mathit{H}_2Ar$), 6.88 – 6.93 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.30 – 7.37 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.39 – 7.47 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.39 – 7.47 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$);

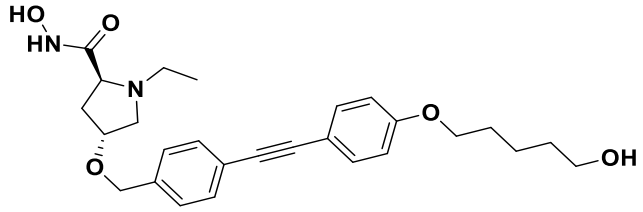
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 30.3 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 33.5 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 38.3 (1C, $CH\mathit{C}H_2CH$), 41.4 (1C, $N\mathit{C}H_3$), 62.9 (1C, $N\mathit{C}H_2$), 62.9 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 67.5 (1C, N*C*H), 69.1 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 71.9 (1C, $O\mathit{C}H_2Ar$), 78.8 (1C, *C*HO), 88.7 (1C, Ar*C*≡CAr), 90.4 (1C, ArC≡*C*Ar), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.4 (1C, C-4′$_{benzyl}$), 129.0 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.9 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 170.9 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3194, 2936, 2859, 1656, 1601, 1517, 1469, 1285, 1245, 1108, 1059, 1032, 822, 524;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{32}N_2O_5$: 453.2311, found: 453.236;

HPLC (method 2): t_R = 13.6 min, purity 99.2%.

(2*S*,4*R*)-1-Ethyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (166)



$C_{27}H_{34}N_2O_5$

M_r =466.6

Sodium methoxide in methanol (5.4 M, 0.2 mL) and hydroxylamine hydrochloride (84 mg, 1.21 mmol) were added to a solution of **166a** (113 mg, 0.24 mmol) in dry methanol (1.5 mL) and the mixture was stirred for 24 h at ambient temperature. Afterwards, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **166** (10 mg, 0.02 mmol, 9%) as colorless solid.

m.p.= 163-164 °C (decomposition);

TLC: R_f = 0.33 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +286.0 (1.0, chloroform);

^{1}H NMR (600 MHz, MeOD-d_4) δ [ppm]= 1.10 (t, *J* = 7.3 Hz, 3H, NCH_2CH_3), 1.51 – 1.66 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.78 – 1.86 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.06 (m, 1H, $CHCH_2CH$), 2.25 – 2.40 (m, 1H, $CHCH_2CH$), 2.25 - 2.40 (m, 1H, NCH_2CH_3), 2.25 - 2.40 (m, 1H, NCH_2), 2.74 (m, *J* = 11.8/7.3 Hz, 1H, NCH_2CH_3), 2.88 (dd, *J* = 9.4/7.1 Hz, 1H, NC*H*), 3.31 (m, 1H, NCH_2), 3.59 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.02 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.10 (m, *J* = 3.7/1.3 Hz, 1H, C*H*O), 4.51 (m, *J* = 12.4 Hz, 2H, OCH_2Ar), 6.89 – 6.94 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.31 – 7.38 (m, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.39 – 7.49 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.39 - 7.49 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl});

^{13}C NMR (151 MHz, MeOD-d_4) δ [ppm]= 14.1 (1C, NCH_2CH_3), 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.3 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.5 (1C,

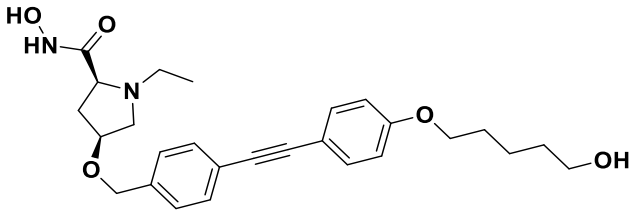
$OCH_2CH_2CH_2CH_2CH_2OH$), 37.8 (1C, $CHCH_2CH$), 50.4 (1C, NCH_2CH_3), 59.6 (1C, NCH_2), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 67.4 (1C, NCH), 69.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 71.6 (1C, OCH_2Ar), 79.0 (1C, CHO), 88.7 (1C, ArC≡CAr), 90.3 (1C, ArC≡CAr), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 116.6 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-}}$ $_{hydroxypentyl)oxy]phenyl})$, 124.2 (1C, C-4′$_{benzyl}$), 129.0 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 140.1 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 168.3 (1C, CONHOH);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3227, 2937, 2866, 1639, 1602, 1517, 1438, 1285, 1246, 1058, 1033, 880, 830, 564, 450;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{34}N_2O_5$: 467.2468, found: 467.249;

HPLC (method 2): t_R = 13.9 min, purity 99.4%.

(2*S*,4*S*)-1-Ethyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]oxy}pyrrolidine-2-carboxamide (167)



$C_{27}H_{34}N_2O_5$

M_r =466.6

Sodium methoxide in methanol (5.4 M, 0.3 mL) and hydroxylamine hydrochloride (132 mg, 1.90 mmol) were added to a solution of **167a** (177 mg, 0.38 mmol) in dry methanol (1.0 mL) and the mixture was stirred for 24 h at ambient temperature. Afterwards, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **167** (6 mg, 0.01 mmol, 3%) as colorless solid.

m.p. = 131-132 °C (decomposition);

TLC: R_f = 0.33 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +13.6 (0.6, methanol);

^{1}H NMR (500 MHz, MeOD-*d*$_4$) δ [ppm]= 1.12 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3), 1.52 – 1.68 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.77 – 1.88 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.09 (m, *J* = 14.0/5.7/1.9 Hz, 1H, $CHCH_2CH$), 2.38 – 2.50 (m, 1H, $CHCH_2CH$), 2.38 – 2.50 (m, 1H, NCH_2CH_3), 2.38 – 2.50 (m, 1H, NCH_2), 2.70 (m, *J* = 11.9/7.3 Hz, 1H, NCH_2CH_3), 3.05 (dd, *J* = 9.7/5.7 Hz, 1H, NCH), 3.32 (m, 1H, NCH_2), 3.60 (t, *J* = 6.3 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.02 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.14 (m, *J* = 6.0/4.8/2.4/1.2 Hz, 1H, CHO), 4.46 – 4.55 (m, 2H, OCH_2Ar), 6.90 – 6.94 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.36 (m, *J* = 8.2 Hz, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.41 – 7.48 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.41- 7.48 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl});

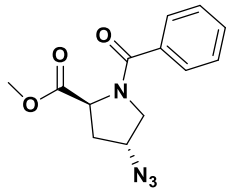
^{13}C NMR (126 MHz, MeOD-*d*$_4$) δ [ppm]= 14.0 (1C, NCH_2CH_3), 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.3 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 37.7 (1C, $CHCH_2CH$), 50.7 (1C, NCH_2CH_3), 59.6 (1C, NCH_2), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 66.9 (1C, NCH), 69.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 71.6 (1C, OCH_2Ar), 79.3 (1C, CHO), 88.7 (1C, ArC≡CAr), 90.4 (1C, ArC≡CAr), 115.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.6 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.3 (1C, C-4′$_{benzyl}$), 129.0 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 134.1 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.9 (1C, C-1′$_{benzyl}$), 160.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 173.0 (1C, CONHOH);

IR (neat): ṽ [cm^{-1}] = 3204, 2935, 2861, 1654, 1601, 1517, 1470, 1284, 1244, 1074, 1053, 1030, 832, 658, 531;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{34}N_2O_5$: 467.2468, found: 467.252;

HPLC (method 2): t_R = 13.8 min, purity 98.9 %.

Methyl (2*S*,4*R*)-4-azido-1-benzoylpyrrolidine-2-carboxylate (168)



$C_{13}H_{14}N_4O_3$

$M_r = 274.3$

Under N_2 atmosphere, DIAD (4.04 mL, 3797 mg, 18.78 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (4925 mg, 18.78 mmol) in dry THF (30 mL) and the mixture was stirred for 10 min at 0 °C. Then, a solution of diphenylphosphoryl azide (4.05 mL, 5167 mg, 18.78 mmol) and **111** (3.6 g, 14.44 mmol) in dry THF (20 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 1/2) to give **168** (3370 mg, 12.29 mmol, 85%) as colorless solid.

TLC: R_f = 0.55 (petroleum ether/ethyl acetate, 1/2);

Specific rotation: $[\alpha]_D^{20}$ = -100.9 (2.2, methanol);

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]= 2.26 (m, *J* = 13.2/7.5/5.4 Hz, 1H, CHC*H*$_2$CH), 2.45 (m, *J* = 13.3/8.5/3.9 Hz, 1H, CHC*H*$_2$CH), 3.54 (dd, *J* = 11.4/2.7 Hz, 1H, NC*H*$_2$), 3.80 (s, 3H, $CO_2C\mathit{H}_3$), 3.86 (dd, *J* = 11.4/4.9 Hz, 1H, NC*H*$_2$), 4.25 (m, *J* = 4.2 Hz, 1H, C*H*N_3), 4.80 (t, *J* = 7.8 Hz, 1H, NC*H*), 7.43 (m, 3H, 3′-$H_{benzoyl}$, 4′-$H_{benzoyl}$, 5′-$H_{benzoyl}$), 7.52 – 7.59 (m, 2H, 2′-$H_{benzoyl}$, 3′-$H_{benzoyl}$);

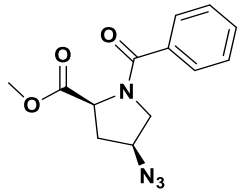
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]= 34.9 (1C, CH*C*H$_2$CH), 52.7 (1C, $CO_2\mathit{C}H_3$), 54.7 (1C, N*C*H$_2$), 57.8 (1C, N*C*H), 60.0 (1C, *C*HN_3), 127.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.6 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.8 (1C, C-4′$_{benzoyl}$) 135.5 (1C, C-1′$_{benzoyl}$), 170.0 (1C, Ar*C*ON), 172.4 (1C, *C*O_2CH_3);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2953, 2101, 1742, 1632, 1404, 1262, 1198, 1174, 1026, 936, 722, 699, 541;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{14}N_4O_3$: 297.1066, found: 297.097;

HPLC (method 1): t_R = 18.5 min, purity 87.8%.

Methyl (2*S*,4*S*)-4-azido-1-benzoylpyrrolidine-2-carboxylate (169)



$C_{13}H_{14}N_4O_3$

M_r = 274.3

Under N_2 atmosphere, DIAD (1.24 mL, 1590 mg, 5.78 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (1.5 g, 5.78 mmol) in dry THF (20 mL) and the mixture was stirred for 10 min at 0 °C. Then, a solution of diphenylphosphoryl azide (1.24 mL, 1590 mg, 5.78 mmol) and **113** (1.2 g, 4.81 mmol) in dry THF (20 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 4/1 → 0/1) to give **169** (332 mg, 1.21 mmol, 25%) as colorless solid.

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 1/2);

Specific rotation: $[\alpha]_D^{20}$ = -31.40 (4.3, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.16 (m, 1H, CHC*H*$_2$CH), 2.53 – 2.68 (m, 1H, CHC*H*$_2$CH), 3.51 – 3.86 (m, 2H, NC*H*$_2$), 3.51 - 3.86 (s, 3H, CO_2CH_3), 4.09 (m, *J* = 15.8/9.3 Hz, 1H, C*H*N_3), 4.82 (t, *J* = 7.7 Hz, 1H, NC*H*), 7.29 – 7.65 (m, 5H, 2′-$H_{benzoyl}$, 3′-$H_{benzoyl}$, 4′-$H_{benzoyl}$, 5′-$H_{benzoyl,}$ 6′-$H_{benzoyl}$);

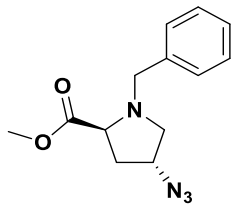
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 34.5 (1C, CH*C*H_2CH), 52.8 (1C, CO_2CH_3), 54.0 (1C, N*C*H_2), 57.5 (1C, N*C*H), 59.1 (1C, *C*HN_3), 127.5 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.6 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.8 (1C, C-4′$_{benzoyl}$) 135.5 (1C, C-1′ $_{benzoyl}$), 171.5 (1C, *C*O_2CH_3), the signal for Ar*C*ON cannot be observed in the spectrum;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2953, 2102, 1744, 1634, 1602, 1403, 1359, 1261, 1199, 1174, 1073, 787, 725, 701, 655, 623;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{14}N_4O_3$: 297.1066, found: 297.100;

HPLC (method 1): t_R = 18.2 min, purity 100%.

Methyl (2*S*,4*R*)-4-azido-1-benzylpyrrolidine-2-carboxylate (170)



$C_{13}H_{16}N_4O_2$

Mr = 260.3

Under N_2 atmosphere, DIAD (1.89 mL, 1944 mg, 9.61 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (2522 mg, 1.30 mmol) in dry THF (30 mL) and the mixture was stirred for 5 min at 0 °C. Then, a solution of diphenylphosphoryl azide (2.07 mL, 2646 mg, 9.61 mmol) and **133** (1740 mg, 7.40 mmol) in dry THF (15 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/diethyl ether = 1/0 → 6/1) to give **170** (1572 mg, 6.04 mmol, 82%) as pale-yellow oil.

TLC: R_f = 0.25 (petroleum ether/diethyl ether, 6/1);

Specific rotation: $[\alpha]_D^{20}$ = -42.6 (2.8, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 2.17 (m, *J* = 13.3/8.3/4.4 Hz, 1H, CHC*H*$_2$CH), 2.35 (m, *J* = 14.2/7.3 Hz, 1H, CHC*H*$_2$CH), 2.55 (dd, *J* = 10.2/5.0 Hz, 1H, NC*H*$_2$), 3.33 (dd, *J* = 10.2/6.4 Hz, 1H, NC*H*$_2$), 3.57 (m, 1H, NC*H*), 3.67 (s, 3H, CO_2CH_3), 3.67 (d, 1H, C*H*$_2$Ar), 3.93 (d, *J* = 13.0 Hz, 1H, C*H*$_2$Ar), 4.10 (m, *J* = 5.6 Hz, 1H, C*H*N_3), 7.23 – 7.34 (m, 5H, 2′-H_{benzyl}, 3′-H_{benzyl}, 4′-H_{benzyl}, 5′-H_{benzyl}, 6′-H_{benzyl});

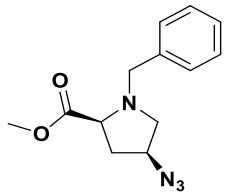
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 36.0 (1C, CH*C*H_2CH), 52.1 (1C, CO_2*C*H_3), 57.9 (1C, *C*H_2Ar), 58.0 (1C, NCH_2), 59.1 (1C, *C*HN_3), 63.8 (1C, NC*H*), 127.6 (1C, C-4′$_{benzyl}$), 128.6 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 137.5 (1C, C-1′$_{benzyl}$), 173.3 (1C, *C*$O_2$$CH_3$);

IR (neat): ṽ [cm^{-1}] = 2952, 2170, 2099, 1732, 1489, 1262, 1200, 1180, 1161, 1026, 1010, 961, 753, 699, 689, 598, 510, 471;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{16}N_4O_2$: 261.1273, found: 261.131;

HPLC (method 1): t_R = 14.7 min, purity 77.4 %.

Methyl (2*S*,4*S*)-4-azido-1-benzylpyrrolidine-2-carboxylate (171)



$C_{13}H_{16}N_4O_2$

Mr = 260.3

Under N_2 atmosphere, DIAD (2.50 mL, 2578 mg, 12.75 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (3344 mg, 12.75 mmol) in dry THF (30 mL) and the mixture was stirred for 5 min at 0 °C. Then, a solution of diphenylphosphoryl azide (2.75 mL, 3509 mg, 12.75 mmol) and **135** (2.0 g, 8.50 mmol) in dry THF (15 mL) was added dropwise at 0 °C. After stirring the mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/diethyl ether = 1/0 → 6/1) to give **171** (1840 mg, 7.07 mmol, 84%) as pale-yellow oil.

TLC: R_f = 0.25 (petroleum ether/diethyl ether, 6/1);

Specific rotation: $[\alpha]_D^{20}$ = -52.1 (6.4, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.15 (m, 1H, CHC*H*$_2$CH), 2.45 – 2.58 (m, 1H, CHC*H*$_2$CH), 2.64 (m, 1H, NC*H*$_2$), 3.08 (m, 1H, NC*H*$_2$), 3.35 (m, 1H, NC*H*), 3.52 – 3.64 (d, 1H,

C*H*$_2$Ar), 3.72 (s, 3H, CO_2CH_3), 3.84 – 3.95 (m, 1H, C*H*N_3), 4.03 (d, *J* = 13.1 Hz, 1H, C*H*$_2$Ar), 7.21 – 7.42 (m, 5H, 2′-H_{benzyl}, 3′-H_{benzyl}, 4′-H_{benzyl}, 5′-H_{benzyl}, 6′-H_{benzyl});

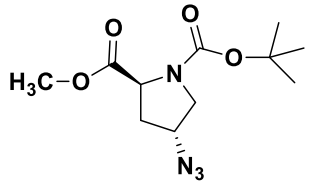
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 36.0 (1C, CH*C*H_2CH), 52.2 (1C, CO_2CH_3), 57.8 (1C, *C*H_2Ar), 58.1 (1C, N*C*H_2), 58.6 (1C, *C*HN_3), 63.9 (1C, N*C*H), 127.5 (1C, C-4′$_{benzyl}$), 128.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 137.7 (1C, C-1′$_{benzyl}$), the signal for *C*O_2CH_3 cannot be observed in the spectrum;

IR (neat): [cm^{-1}] = 2952, 2804, 2100, 1732, 1453, 1436, 1265, 1200, 1175, 1047, 1009, 746, 699, 470;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{16}N_4O_2$: 261.1273, found: 261.128;

HPLC (method 1): t_R = 13.5 min, purity 81.4%.

1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-azidopyrrolidine-1,2-dicarboxylate (172)



$C_{11}H_{18}N_4O_4$

Mr = 270.3

Under N_2 atmosphere, DIAD (9.72 mL, 10017 mg, 49.54 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (12993 mg, 49.54 mmol), diphenylphosphoryl azide (10.68 mL, 13633 mg, 49.54 mmol), and **142** (8.1 g, 33.02 mmol) in dry THF (100 mL). After stirring the reaction mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 8 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/0 → 3/2) to give **172** (7586 mg, 28.07 mmol, 85.0%) as pale-yellow oil.

TLC: R_f = 0.43 (petroleum ether/ethyl acetate, 3/1)

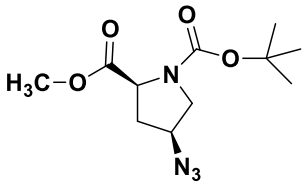
Specific rotation: $[\alpha]_D^{20}$ = -42.3 (8.2, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.33 (s, 9H, OC(CH_3)$_3$), 2.14 (m, 1H, CHCH_2CH), 2.33 (m, 1H, CHCH_2CH), 3.39 (m, J = 11.6/2.0 Hz, 1H, NCH_2), 3.54 (m, J = 16.7/11.5/5.0 Hz, 1H, NCH_2), 3.67 (s, 3H, CO_2CH_3), 4.22 (m, J = 18.2/7.7 Hz, 1H, NCH), 4.36 (m, J = 13.7/5.1/2.2 Hz, 1H, CHN$_3$), the signals of the major rotamer are given;
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 27.8 (3C, OC(CH_3)$_3$), 35.6 (1C, CHCH_2CH), 51.1 (1C, NCH_2), 52.0 (1C, CO_2CH_3), 57.3 (1C, NCH), 58.5 (1C, CHN$_3$), 79.5 (1C, OC(CH$_3$)$_3$), 152.6 (1C, NCO_2C(CH$_3$)$_3$), 172.5 (1C, CO_2CH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2979, 2102, 1747, 1698, 1393, 1366, 1257, 1201, 1179, 1156, 1123, 960, 769;

HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{11}H_{18}N_4O_4$: 293.1328, found: 293.122.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-azidopyrrolidine-1,2-dicarboxylate (173)



$C_{11}H_{18}N_4O_4$

Mr = 270.3

Under N_2 atmosphere, DIAD (1.22 mL, 1260 mg, 6.23 mmol) was added dropwise to an ice-cooled solution of triphenylphosphine (1635 mg, 6.23 mmol), diphenylphosphoryl azide (1.34 mL, 1715 mg, 6.23 mmol), and **154** (1019 mg, 4.15 mmol) in dry THF (20 mL). After stirring the reaction mixture at ambient temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/0 → 3/2) to give **173** (960 mg, 3.55 mmol, 86%) as colorless oil.

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 3/1);

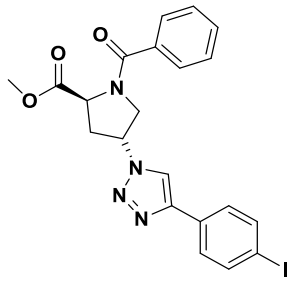
Specific rotation: $[\alpha]_D^{20}$ = -34.0 (8.7, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 1.44 (s, 9H, OC(CH_3)$_3$), 2.17 (m, *J* = 13.1/5.9/3.6 Hz, 1H, CHCH_2CH), 2.46 (m, 1H, CHCH_2CH), 3.47 (m, *J* = 21.4/11.6/4.1 Hz, 1H, NCH_2), 3.75 (m, 1H, NCH_2), 3.75 (s, 3H, CO_2CH_3), 4.09 – 4.16 (m, 1H, C*H*N_3), 4.32 (dd, *J* = 8.8/4.4 Hz, 1H, NC*H*), the signals of the major rotamer are given;
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 28.5 (3C, OC(*C*H_3)$_3$), 36.2 (1C, CH*C*H_2CH), 51.0 (1C, N*C*H_2), 52.4 (1C, CO_2*C*H_3), 57.9 (1C, N*C*H), 58.4 (1C, *C*HN_3), 80.8 (1C, O*C*(CH_3)$_3$), 172.4 (1C, *C*O_2CH_3), (1C, N*C*O_2C(CH_3)$_3$, the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2978, 2102, 1752, 1697, 1392, 1365, 1258, 1200, 1156, 1053, 892, 769, 561;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{18}N_4O_4$: 293.1328, found: 293.123.

Methyl (2*S*,4*R*)-1-benzoyl-4-[4-(4-iodophenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylate (174)



$C_{21}H_{19}IN_4O_3$

M_r = 502.3

1-ethynyl-4-iodobenzene (569 mg, 2.50 mmol), L-sodium ascorbate (99 mg, 0.50 mmol), and copper(II) sulfate pentahydrate (25 mg, 0.10 mmol) were added to a solution of **168** (685 mg, 2.50 mmol) in a mixture of *tert*- butanol (10 mL) and water (10 mL). After heating the reaction mixture for 18 h at 40 °C, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/0 → 0/1) to give **174** (349 mg, 0.69 mmol, 28%) as colorless oil.

TLC: R_f = 0.35 (petroleum ether/ethyl acetate, 1/2);

Specific rotation: $[\alpha]_D^{20}$ = -104.8 (1.2, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 2.66 (m, *J* = 13.0/5.9 Hz, 1H, CHC*H*$_2$CH), 2.99 (m, *J* = 14.4/7.4 Hz, 1H, CHC*H*$_2$CH), 3.84 (s, 3H, CO_2C*H*$_3$), 4.05 – 4.14 (m, 1H, NC*H*$_2$), 4.23 (dd, *J* = 11.7/6.3 Hz, 1H, NC*H*$_2$), 5.01 (dd, *J* = 8.7/5.3 Hz, 1H, NC*H*), 5.31 (m, 1H, CH_2C*H*CH_2), 7.37 – 7.47 (m, 3H, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$), 7.54 (m, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), 7.54 (m, 2H, 2‴-H$_{4\text{-}iodophenyl}$, 6‴-H$_{4\text{-}iodophenyl}$), 7.71 (s, 1H, 5″-H$_{triazole}$), 7.76 (m, *J* = 8.1 Hz, 2H, 3‴-H$_{4\text{-}iodophenyl}$, 5‴-H$_{4\text{-}iodophenyl}$);

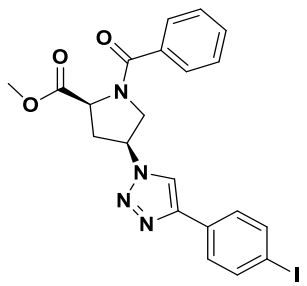
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 35.2 (1C, CH*C*H$_2$CH), 53.0 (1C, CO_2*C*H$_3$), 54.7 (1C, N*C*H$_2$), 58.0 (1C, N*C*H), 58.9 (1C, CH_2*C*HCH$_2$), 94.2 (1C, C-4‴$_{4\text{-}iodophenyl}$), 118.7 (1C, C-5″$_{triazole}$), 127.5 (2C, C-2‴$_{4\text{-}iodophenyl}$, C-6‴$_{4\text{-}iodophenyl}$), 127.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.8 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.7 (1C, C-1‴$_{4\text{-}iodophenyl}$), 131.1 (1C, C-4′$_{benzoyl}$), 135.2 (1C, C-4′$_{benzoyl}$), 138.2 (1C, C-3‴$_{4\text{-}iodophenyl}$, C-5‴$_{4\text{-}iodophenyl}$), 147.5 (1C, C-4″$_{triazole}$), 170.0 (1C, Ar*C*ON), 172.2 (1C, *C*O_2CH_3);

IR (neat): ṽ [cm^{-1}] = 2950, 1739, 1628, 1398, 1360, 1201, 1175, 1028, 1005, 970, 819, 792, 723, 700, 514;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{19}IN_4O_3$: 503.0502, found:503.058;

HPLC (method 1): t_R = 22.6 min, purity 100%.

Methyl (2*S*,4*S*)-1-benzoyl-4-[4-(4-iodophenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylate (175)



$C_{21}H_{19}IN_4O_3$

M_r = 502.3

1-ethynyl-4-iodobenzene (758 mg, 3.33 mmol), L-sodium ascorbate (110 mg, 0.55 mmol), and copper(II) sulfate pentahydrate (28 mg, 0.11 mmol) were added to a solution of **169** (760 mg, 2.77 mmol) in a mixture of *tert*- butanol (10 mL) and water (10 mL). After stirring the reaction mixture at ambient temperature overnight, water was added and the mixture was extracted with

ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/2 → 1/2) to give **175** (1071 mg, 2.13 mmol, 77%) as brown oil.

TLC: R_f = 0.20 (petroleum ether/ethyl acetate, 1/2);

Specific rotation: $[\alpha]_D^{20}$ = +6.5 (5.1, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.57 - 2.74 (m, 1H, CHC*H*$_2$CH), 3.04 (m, 1H, CHC*H*$_2$CH), 3.79 (s, 3H, CO_2C*H*$_3$), 4.18 (m, 2H, NC*H*$_2$), 4.95 (m, 1H, NC*H*), 5.16 (m, 1H, CH_2C*H*CH_2), 7.43 (m, 5H, 2′-$H_{benzoyl}$, 3′-$H_{benzoyl}$, 4′-$H_{benzoyl}$, 5′-$H_{benzoyl}$, 6′ -$H_{benzoyl}$), 7.51 - 7.57 (m, 2H, 2‴-$H_{4\text{-iodophenyl}}$, 6‴-$H_{4\text{-iodophenyl}}$), 7.69 – 7.81 (m, 2H, 3‴-$H_{4\text{-iodophenyl}}$, 5‴-$H_{4\text{-iodophenyl}}$), 7.90 (s, 1H, 5″-$H_{triazole}$);

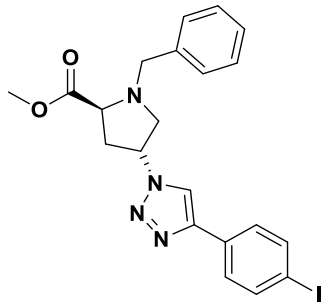
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 34.5 (1C, CH*C*H_2CH), 52.9 (1C, CO_2*C*H_3), 54.0 (1C, N*C*H_2), 57.4 (1C, N*C*H), 59.0 (1C, CH_2*C*HCH_2), 94.1 (1C, C-4‴$_{4\text{-iodophenyl}}$), 118.9 (1C, C-5″$_{triazole}$), 127.6 (2C, C-2‴$_{4\text{-iodophenyl}}$, C-6‴$_{4\text{-iodophenyl}}$), 128.7 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.7 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.8 (1C, C-1‴$_{4\text{-iodophenyl}}$), 131.1 (1C, C-4′$_{benzoyl}$), 138.2 (1C, C-3‴$_{4\text{-iodophenyl}}$, C-5‴$_{4\text{-iodophenyl}}$), 147.4 (1C, C-4″$_{triazole}$), 171.5 (1C, *C*O_2CH_3), the signals for C-4′$_{benzoyl}$ and Ar*C*ON cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3067, 2949, 2877, 2104, 1740, 1629, 1600, 1446, 1408, 1266, 1203, 1174, 1136, 1004, 820, 786, 732, 699, 507;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{19}IN_4O_3$: 503.0502, found:503.057;

HPLC (method 1): t_R = 22.6 min, purity 84.3%.

Methyl (2*S*,4*R*)-1-benzyl-4-[4-(4-iodophenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylate (176)



$C_{21}H_{21}IN_4O_2$

Mr = 488.3

1-ethynyl-4-iodobenzene (1064 mg, 4.67 mmol), L-sodium ascorbate (154 mg, 0.78 mmol), and copper(II) sulfate pentahydrate (39 mg, 0.16 mmol) were added to a solution of **170** (1012 mg, 3.89 mmol) in a mixture of *tert*- butanol (15 mL) and water (15 mL). After heating the reaction mixture for 72 h at 55 °C, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/1 → 1/1) to give **176** (766 mg, 1.57 mmol, 40%) as colorless solid.

m.p. = 131-133 °C;

TLC: R_f = 0.20 (petroleum ether/ethyl acetate, 1/2);

Specific rotation: $[\alpha]_D^{20}$ = -46.3 (1.8, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 2.55 – 2.64 (m, 2H, CHC*H*$_2$CH), 2.83 (dd, *J* = 9.7/5.9 Hz, 1H, NC*H*$_2$), 3.43 (dd, *J* = 9.7/6.9 Hz, 1H, NC*H*$_2$), 3.66 (s, 3H, CO_2CH_3), 3.68 (d, *J* = 13.2 Hz, 1H, C*H*$_2$Ar), 3.81 (dd, *J* = 8.0/6.4 Hz, 1H, NC*H*), 3.93 (d, *J* = 13.2 Hz, 1H, C*H*$_2$Ar), 5.26 (m, *J* = 12.4/7.2/4.0 Hz, 1H, CH_2CHCH_2), 7.24 (m, *J* = 8.6/6.4/3.8 Hz, 1H, 4′-H$_{benzyl}$), 7.27 – 7.33 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.61 – 7.67 (m, 2H, 2‴-H$_{4\text{-iodophenyl}}$, 6‴-H$_{4\text{-iodophenyl}}$), 7.79 – 7.84 (m, 2H, 3‴-H$_{4\text{-iodophenyl}}$, 5‴-H$_{4\text{-iodophenyl}}$), 8.70 (s, 1H, 5″-H$_{triazole}$);

^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 35.4 (1C, CH*C*H$_2$CH), 51.6 (1C, CO_2CH_3), 56.3 (1C, *C*H$_2$Ar), 57.7 (1C, CH_2CHCH_2), 57.8 (1C, NCH$_2$), 62.9 (1C, NCH), 93.7 (1C, C-4‴$_4$-

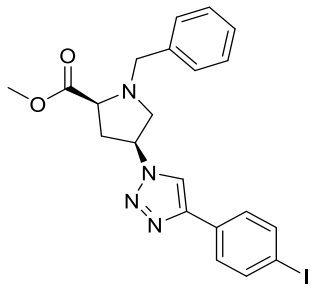
$_{\text{iodophenyl}}$), 120.8 (1C, C-5″$_{\text{triazole}}$), 127.1 (2C, C-2‴$_{\text{4-iodophenyl}}$, C-6‴$_{\text{4-iodophenyl}}$), 127.1 (1C, C-4′$_{\text{benzyl}}$), 128.2 (2C, C-3′$_{\text{benzyl}}$, C-5′$_{\text{benzyl}}$), 128.6 (2C, C-2′$_{\text{benzyl}}$, C-6′$_{\text{benzyl}}$), 130.3 (1C, C-1‴$_{\text{4-iodophenyl}}$), 137.7 (2C, C-3‴$_{\text{4-iodophenyl}}$, C-5‴$_{\text{4-iodophenyl}}$), 138.2 (1C, C-1′$_{\text{benzyl}}$), 145.5 (1C, C-4″$_{\text{triazole}}$), 172.7 (1C, *C*O_2CH_3);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3115, 2956, 2796, 1749, 1437, 1379, 1199, 1167, 1006, 975, 818, 764, 702, 515;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{21}IN_4O_2$: 489.0709, found: 489.078;

HPLC (method 1): t_R = 21.5 min, purity 97.4%.

Methyl (2*S*,4*S*)-1-benzyl-4-[4-(4-iodophenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylate (177)



$C_{21}H_{21}IN_4O_2$

Mr = 488.3

1-ethynyl-4-iodobenzene (648 mg, 2.84 mmol), L-sodium ascorbate (94 mg, 0.47 mmol), and copper(II) sulfate pentahydrate (24 mg, 0.09 mmol) were added to a solution of **171** (616 mg, 2.37 mmol) in a mixture of *tert*- butanol (10 mL) and water (10 mL). After stirring the reaction mixture at ambient temperature overnight, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 3/1 → 1/1) to give **177** (819 mg, 1.68 mmol, 71%) as colorless oil.

TLC: R_f = 0.20 (petroleum ether/ethyl acetate, 2/1);

Specific rotation: $[\alpha]_D^{20}$ = +55.3 (1.6, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 2.26 – 2.34 (m, 1H, CHCH_2CH), 2.85 – 2.96 (m, 2H, CHCH_2CH), 2.85 – 2.96 (m, 1H, NCH_2), 3.05 – 3.11 (m, 1H, NCH_2), 3.50 (dd, J = 9.5/6.6 Hz, 1H, NCH), 3.61 (s, 3H, CO_2CH_3), 3.61 (d, 1H, CH_2Ar), 3.97 (d, J = 13.3 Hz, 1H, CH_2Ar), 5.27 (m, J = 8.6/5.9/3.1 Hz, 1H, CH_2CHCH_2), 7.24 (m, J = 8.7/6.4/2.0 Hz, 1H, 4′-H_{benzyl}), 7.27 – 7.35 (m, 4H, 2′-H_{benzyl}, 3′-H_{benzyl}, 5′-H_{benzyl}, 6′-H_{benzyl}), 7.59 – 7.64 (m, 2H, 2‴-$H_{4\text{-iodophenyl}}$, 6‴-$H_{4\text{-iodophenyl}}$), 7.80 – 7.86 (m, 2H, 3‴-$H_{4\text{-iodophenyl}}$, 5‴-$H_{4\text{-iodophenyl}}$), 8.70 (s, 1H, 5″-$H_{triazole}$);

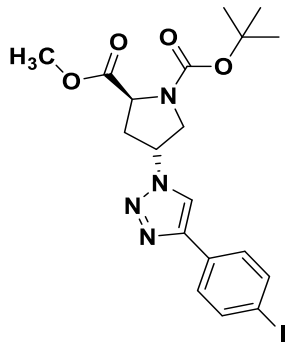
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 35.9 (1C, CHCH$_2$CH), 51.8 (1C, CO_2CH_3), 56.7 (1C, CH$_2$Ar), 57.9 (1C, CH_2CHCH_2), 58.0 (1C, NCH$_2$), 63.0 (1C, NCH), 93.7 (1C, C-4‴$_{4\text{-iodophenyl}}$), 119.9 (1C, C-5″$_{triazole}$), 127.0 (2C, C-2‴$_{4\text{-iodophenyl}}$, C-6‴$_{4\text{-iodophenyl}}$), 127.1 (1C, C-4′$_{benzyl}$), 128.2 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.7 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.3 (1C, C-1‴$_{4\text{-iodophenyl}}$), 137.8 (2C, C-3‴$_{4\text{-iodophenyl}}$, C-5‴$_{4\text{-iodophenyl}}$), 137.8 (1C, C-1′$_{benzyl}$), 145.5 (1C, C-4″$_{triazole}$), 173.0 (1C, CO$_2$CH$_3$);

IR (neat): ṽ [cm^{-1}] = 2953, 2928, 2854, 2806, 1739, 1453, 1333, 1304, 1200, 1175, 1111, 1069, 1007, 817, 756, 701, 523;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{21}IN_4O_2$: 489.0709, found: 489.077;

HPLC (method 1): t_R = 21.8 min, purity 94.6%.

1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-[4-(4-iodophenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-1,2-dicarboxylate (178)



$C_{19}H_{23}IN_4O_4$

Mr = 498.3

1-ethynyl-4-iodobenzene (2953 mg, 12.95 mmol), L-sodium ascorbate (733 mg, 3.70 mmol), and copper(II) sulfate pentahydrate (185 mg, 0.74 mmol) were added to a solution of **172** (5.0 g, 18.50 mmol) in a mixture of *tert*- butanol (50 mL) and water (50 mL). After heating the reaction mixture overnight at 50 °C, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/0 → 1/1) to give **178** (5.8 g, 11.64 mmol, 63%) as colorless solid.

m.p.= 154-156 °C;

TLC: R_f = 0.20 (petroleum ether/ethyl acetate, 2/1);

Specific rotation: $[\alpha]_D^{20}$ = -13.9 (2.3, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.34 (s, 9H, OC(CH_3)$_3$), 2.50 – 2.61 (m, 1H, CHCH_2CH), 2.86 (m, *J* = 27.3/13.9/8.4/5.2 Hz, 1H, CHCH_2CH), 3.72 (s, 3H, CO_2CH_3), 3.75 – 3.82 (m, 1H, NCH_2), 3.94 (m, *J* = 11.7/6.2 Hz, 1H, NCH_2), 4.52 (m, *J* = 14.9/8.4/6.2 Hz, 1H, NC*H*), 5.32 (m, 1H, CH_2CHCH_2), 7.60 – 7.71 (m, 2H, 2″-$H_{4\text{-iodophenyl}}$, 6″-$H_{4\text{-iodophenyl}}$), 7.82 (m, *J* = 8.7/2.2 Hz, 2H, 3″-$H_{4\text{-iodophenyl}}$, 6″-$H_{4\text{-iodophenyl}}$), 8.75 (s, 1H, 5′-H_{triazole}), the signals of the major rotamer are given;

^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 27.9 (3C, OC(*C*H_3)$_3$), 35.4 (1C, CHCH_2CH), 51.8 (1C, N*C*H_2), 52.2 (1C, CO_2CH_3), 57.5 (1C, N*C*H), 57.8 (1C, CH_2CHCH_2), 79.7 (1C,

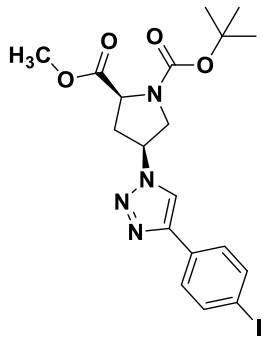
O*C*(CH_3)$_3$), 93.8 (1C, C-4″$_{4\text{-iodobenzyl}}$), 121.2 (1C, C-5′$_{triazole}$), 127.2 (1C, C-2″$_{4\text{-iodobenzyl}}$, C-6″$_{4\text{-iodobenzyl}}$), 130.1 (1C, C-1″$_{4\text{-iodobenzyl}}$), 137.7 (2C, C-3″$_{4\text{-iodobenzyl}}$, C-5″$_{4\text{-iodobenzyl}}$), 145.5 (1C, C-4′$_{triazole}$), 172.6 (1C, *C*O_2CH_3), 152.7 (1C, N*C*$O_2C(CH_3)_3$), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2983, 2953, 2933, 1740, 1694, 1407, 1368, 1264, 1146, 1114, 1030, 816, 764, 556, 522;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{23}IN_4O_4$: 499.0764, found: 499.082;

HPLC (method 1): t_R = 24.1 min, purity 100%.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-[4-(4-iodophenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-1,2-dicarboxylate (179)



$C_{19}H_{23}IN_4O_4$

Mr = 498.3

1-ethynyl-4-iodobenzene (7424 mg, 32.56 mmol), L-sodium ascorbate (1290 mg, 6.51 mmol), and copper(II) sulfate pentahydrate (325 mg, 1.30 mmol) were added to a solution of **173** (8.8 g, 32.56 mmol) in a mixture of *tert*- butanol (50 mL) and water (50 mL). After stirring the reaction mixture at ambient temperature overnight, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/0 → 1/1) to give **179** (4030 mg, 8.09 mmol, 25%) as colorless solid.

m.p. = 171-172 °C;

TLC: R_f = 0.30 (petroleum ether/ethyl acetate, 2/1);

Specific rotation: $[\alpha]_D^{20}$ = -22.1 (1.9, methanol);

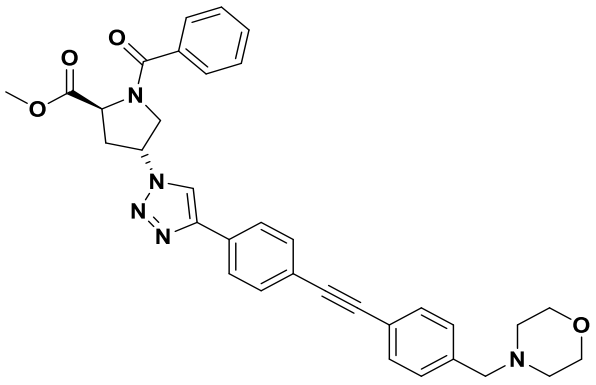
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.46 (s, 9H, OC(CH_3)$_3$), 2.62 – 2.71 (m, 1H, CHCH_2CH), 2.98 (m, 1H, CHCH_2CH), 3.71 (s, 3H, CO_2CH_3), 3.85 – 3.99 (m, 1H, NCH_2), 4.19 (dd, *J* = 11.9/7.2 Hz, 1H, NCH_2), 4.45 (m, 1H, NC*H*), 5.19 – 5.32 (m, 1H, CH_2CHCH_2), 7.54 – 7.60 (m, 2H, 2″-H$_{4\text{-iodophenyl}}$, 6″-H$_{4\text{-iodophenyl}}$), 7.71 – 7.78 (m, 2H, 3″-H$_{4\text{-iodophenyl}}$, 6″-H$_{4\text{-iodophenyl}}$), 7.96 (s, 1H, 5′-H$_{\text{triazole}}$), the signals of the major rotamer are given;
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 28.4 (3C, OC(CH_3)$_3$), 36.6 (1C, CHCH_2CH), 51.5 (1C, NCH_2), 52.6 (1C, CO_2CH_3), 57.9 (1C, NCH), 58.5 (1C, CH_2CHCH_2), 81.4 (1C, OC(CH_3)$_3$), 94.0 (1C, C-4″$_{4\text{-iodobenzyl}}$), 118.7 (1C, C-5′$_{\text{triazole}}$), 127.6 (1C, C-2″$_{4\text{-iodobenzyl}}$, C-6″$_{4\text{-iodobenzyl}}$), 130.0 (1C, C-1″$_{4\text{-iodobenzyl}}$), 138.2 (2C, C-3″$_{4\text{-iodobenzyl}}$, C-5″$_{4\text{-iodobenzyl}}$), 147.5 (1C, C-4′$_{\text{triazole}}$), 172.4 (1C, CO_2CH_3), the signal for N$CO_2C(CH_3)_3$ cannot be observed in the spectrum, the signal of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2971, 2936, 2880, 1709, 1387, 1363, 1203, 1160, 1151, 973, 821, 5112;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{23}IN_4O_4$: 499.0764, found 499.083;

HPLC (method 1): t_R = 23.9 min, purity 99.3 %.

Methyl (2*S*,4*R*)-1-benzoyl-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylate (180)



$C_{34}H_{33}N_5O_4$

M_r = 575.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (8 mg, 0.01 mmol), copper(I) iodide (4 mg, 0.02 mmol), triethylamine (1.0 mL, 705 mg, 6.97 mmol), and **103** (210 mg, 1.05

mmol) were added to a solution of **174** (350 mg, 0.70 mmol) in dry acetonitrile (25 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 3/2 → 0/1) to give **180** (319 mg, 0.55 mmol, 79%) as colorless solid.

m.p. = 206-207 °C;

TLC: R_f = 0.30 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -74.5 (2.9, methanol);

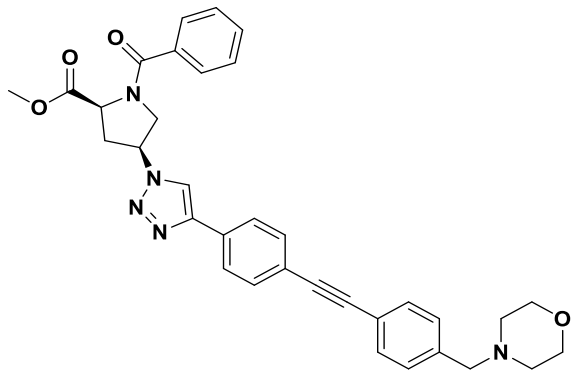
^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 2.36 (t, *J* = 4.6 Hz, 4H, NCH_2CH$_2$O), 2.60 – 2.68 (m, 1H, CHCH_2CH), 2.96 (m, *J* = 13.3/8.6/4.3 Hz, 1H, CHCH_2CH), 3.49 (s, 2H, ArCH_2), 3.58 (t, *J* = 4.6 Hz, 4H, NCH$_2$CH_2O), 3.74 (s, 3H, CO$_2$CH_3), 3.95 – 4.00 (m, 1H, NCH_2), 4.22 (dd, *J* = 11.5/5.7 Hz, 1H, NCH_2), 4.83 (m, *J* = 9.4/8.6 Hz, 1H, NC*H*), 5.36 (m, *J* = 6.0/3.0 Hz, 1H, CH$_2$C*H*CH$_2$), 7.33 – 7.40 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.43 – 7.55 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.43 - 7.55 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), 7.60 – 7.67 (m, 2H, 3‴-H$_{phenyl}$, 5‴-H$_{phenyl}$), 7.85 – 7.90 (m, 2H, 2‴-H$_{phenyl}$, 6‴-H$_{phenyl}$), 8.76 (s, 1H, 5″-H$_{triazole}$);
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 34.0 (1C, CHCH_2CH), 52.2 (1C, CO$_2$*C*H$_3$), 53.1 (2C, N*C*H$_2$CH$_2$O), 54.6 (1C, N*C*H$_2$), 57.8 (1C, N*C*H), 58.8 (1C, CH$_2$*C*HCH_2), 62.0 (1C, Ar*C*H$_2$), 66.2 (2C, NCH$_2$*C*H$_2$O), 89.0 (1C, Ar*C*≡CAr), 90.1 (1C, ArC≡*C*Ar), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.6 (1C, C-5″$_{triazole}$), 121.7 (1C, C-4‴$_{phenyl}$), 125.3 (1C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.2 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.5 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 130.6 (1C, C-4′$_{benzoyl}$), 130.6 (1C, C-1‴$_{phenyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.0 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 135.2 (1C, C-1′$_{benzoyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.7 (1C, C-4″$_{triazole}$), 168.5 (1C, Ar*C*ON), 171.6 (1C, *C*O$_2$CH$_3$);

IR (neat): ṽ [cm^{-1}] = 3102, 2852, 2806, 1742, 1628, 1405, 1202, 1175, 1113, 1031, 1007, 865, 838, 792, 725, 700, 543, 527;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{34}H_{33}N_5O_4$: 576.2533, found:576.260;

HPLC (method 1): t_R = 18.9 min, purity 100%.

Methyl (2*S*,4*S*)-1-benzoyl-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl} phenyl)-1H-1,2,3-triazol-1-yl] pyrrolidine-2-carboxylate (181)



$C_{34}H_{33}N_5O_4$

M_r = 575.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.004 mmol), copper(I) iodide (3 mg, 0.01 mmol), triethylamine (0.65 mL, 475 mg, 4.70 mmol), and **103** (189 mg, 0.94 mmol) were added to a solution of **175** (236 mg, 0.47 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 3/2 → 0/1) to give **181** (199 mg, 0.35 mmol, 74%) as colorless solid.

m.p. = 169-170 °C;

TLC: R_f = 0.18 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = +41.2 (0.9, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 2.36 (t, 4H, NC*H*$_2$CH$_2$O), 2.59 – 2.68 (m, 1H, CHC*H*$_2$CH), 3.03 (m, *J* = 13.8/7.5 Hz, 1H, CHC*H*$_2$CH), 3.50 (s, 2H, ArC*H*$_2$), 3.58 (t, *J* = 4.7 Hz, 4H, NCH$_2$C*H*$_2$O), 3.68 (s, 3H, CO$_2$C*H*$_3$), 4.11 (m, *J* = 10.9/7.9 Hz, 2H, NC*H*$_2$), 4.78 (t, *J* = 8.4 Hz, 1H, NC*H*), 5.33 (m, *J* = 7.9 Hz, 1H, CH$_2$C*H*CH$_2$), 7.35 – 7.39 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.47 – 7.54 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$),

7.47 - 7.54 (m, 3H, 3′-$H_{benzoyl}$, 4′-$H_{benzoyl}$, 5′-$H_{benzoyl}$), 7.58 – 7.65 (m, 2H, 2′-$H_{benzoyl}$, 6′-$H_{benzoyl}$), 7.58 - 7.65 (m, 2H, 3‴-H_{phenyl}, 5‴-H_{phenyl}), 7.88 (m, *J* = 8.0 Hz, 2H, 2‴-H_{phenyl}, 6‴-H_{phenyl}), 8.83 (s, 1H, 5″-$H_{triazole}$);

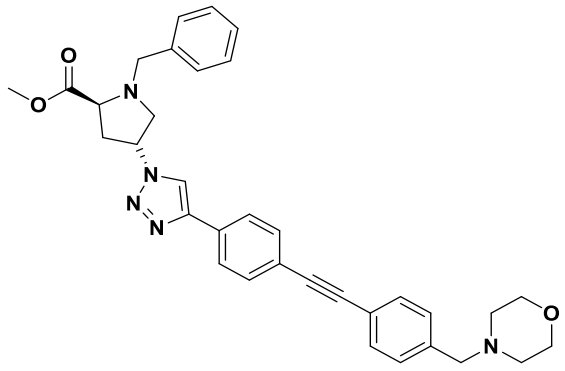
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 33.5 (1C, CHC*H*$_2$CH), 52.1 (1C, CO_2CH_3), 53.1 (2C, NCH_2CH_2O), 53.5 (1C, NCH_2), 57.3 (1C, CH_2CHCH_2), 57.4 (1C, NCH), 62.0 (1C, ArCH_2), 66.2 (2C, NCH_2CH_2O), 89.0 (1C, Ar*C*≡CAr), 90.1 (1C, ArC≡*C*Ar), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 121.5 (1C, C-5″$_{triazole}$), 121.6 (1C, C-4‴$_{phenyl}$), 125.3 (1C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.4 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.4 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-5‴$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 130.6 (1C, C-1‴$_{phenyl}$), 130.7 (1C, C-4′$_{benzoyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-6‴$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 132.0 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 135.2 (1C, C-1′$_{benzoyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 145.7 (1C, C-4″$_{triazole}$), 168.4 (1C, Ar*C*ON), 171.2 (1C, *C*O_2CH_3);

IR (neat): ṽ [cm^{-1}] = 3446, 2878, 2799, 2759, 1737, 1647, 1435, 1417, 1366, 1263, 1232, 1217, 1099, 1006, 865, 841, 827, 730, 699, 530, 505;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{33}N_5O_4$: 576.2533, found:576.259;

HPLC (method 1): t_R = 18.8 min, purity 90.4%.

Methyl (2*S*,4*R*)-1-benzyl-4-(4-[4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylate (182)



$C_{34}H_{35}N_5O_3$

M_r = 561.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.01 mmol), copper(I) iodide (3 mg, 0.02 mmol), triethylamine (0.75 mL, 549 mg, 5.43 mmol), and **103** (164 mg, 0.81 mmol) were added to a solution of **176** (265 mg, 0.54 mmol) in dry acetonitrile (20 mL) and

the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **182** (210 mg, 0.37 mmol, 69%) as colorless solid.

m.p. = 150-151 °C;

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 1/3);

Specific rotation: $[\alpha]_D^{20}$ = -56.3 (1.2, methanol);

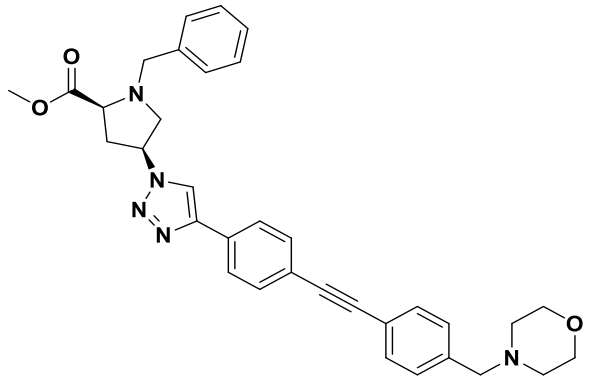
^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 2.36 (t, *J* = 4.7 Hz, 4H, NCH_2CH_2O), 2.57 – 2.66 (m, 2H, CHCH_2CH), 2.85 (dd, *J* = 9.7/5.8 Hz, 1H, NCH_2), 3.44 (dd, *J* = 9.7/6.9 Hz, 1H, NCH_2), 3.49 (s, 2H, ArCH_2), 3.58 (t, *J* = 4.6 Hz, 4H, NCH$_2$CH_2O), 3.66 (s, 3H, CO$_2$CH_3), 3.69 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 3.82 (dd, *J* = 8.0/6.4 Hz, 1H, NC*H*), 3.94 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 5.28 (m, *J* = 13.5/7.2/4.1 Hz, 1H, CH$_2$C*H*CH), 7.25 (m, *J* = 8.6/5.6/2.7 Hz, 1H, 4′-H$_{benzyl}$), 7.29 – 7.34 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.35 – 7.39 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.50 – 7.55 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.61 – 7.65 (m, 2H, 3′′-H$_{phenyl}$, 5′′-H$_{phenyl}$), 7.88 – 7.92 (m, 2H, 2′′-H$_{phenyl}$, 6′′-H$_{phenyl}$), 8.74 (s, 1H, 5″-H$_{triazole}$);
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 35.4 (1C, CHCH_2CH), 51.6 (1C, CO$_2$*C*H$_3$), 53.1 (2C, N*C*H$_2$CH$_2$O), 56.3 (1C, CH_2Ar), 57.8 (1C, CH$_2$C*H*CH$_2$), 57.8 (1C, NCH_2), 62.0 (1C, Ar*C*H$_2$), 62.9 (1C, N*C*H), 66.2 (2C, NCH$_2$*C*H$_2$O), 89.0 (1C, Ar*C*≡CAr), 90.0 (1C, ArC≡*C*Ar), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.1 (1C, C-5″$_{triazole}$), 121.5 (1C, C-4′′$_{phenyl}$), 125.3 (2C, C-2′′$_{phenyl}$, C-6′′$_{phenyl}$), 127.1(1C, C-4′$_{benzyl}$), 128.2 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 130.9 (1C, C-1′′$_{phenyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.9 (2C, C-3′′$_{phenyl}$, C-5′′$_{phenyl}$), 138.2 (1C, C-1′$_{benzyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.7 (1C, C-4″$_{triazole}$), 172.7 (1C, *C*O$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 2955, 2924, 2853, 2800, 1738, 1451, 1203, 1167, 1115, 1008, 867, 841, 826, 755, 673, 544, 531;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{34}H_{35}N_5O_3$: 562.2740, found: 562.279;

HPLC (method 1): t_R = 17.8 min, purity 92.0%.

Methyl (2*S*,4*S*)-1-benzyl-4-([4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl] pyrrolidine-2-carboxylate (183)



$C_{34}H_{35}N_5O_3$

M_r = 561.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.01 mmol), copper(I) iodide (3 mg, 0.02 mmol), triethylamine (0.75 mL, 549 mg, 5.43 mmol), and **103** (164 mg, 0.81 mmol) were added to a solution of **177** (265 mg, 0.54 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **183** (227 mg, 0.40 mmol, 75%) as brown solid.

m.p. = 145-146 °C;

TLC: R_f = 0.28 (petroleum ether/ethyl acetate, 1/3);

Specific rotation: $[\alpha]_D^{20}$ = +74.8 (2, methanol);

^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]= 2.21 – 2.30 (m, 1H, CHC*H*$_2$CH), 2.48 (s, 4H, NC*H*$_2$CH$_2$O), 2.84 (dd, *J* = 10.6/5.8 Hz, 1H, NC*H*$_2$), 2.94 (m, *J* = 14.8/10.0/8.7 Hz, 1H, CHC*H*$_2$CH), 3.13 (m, *J* = 10.5/1.5 Hz, 1H, NC*H*$_2$), 3.45 (dd, *J* = 9.9/6.5 Hz, 1H, NC*H*), 3.51-3.61 (d, 1H, C*H*$_2$Ar), 3.55 (s, 2H, ArC*H*$_2$), 3.72 (s, 3H, CO_2CH_3), 3.72 (t, 4H, NCH_2CH_2O), 4.07 (d, *J* = 13.0 Hz, 1H, C*H*$_2$Ar), 5.33 (m, *J* = 8.2/6.0/1.8 Hz, 1H, CH_2CHCH_2), 7.21 – 7.41 (m, 5H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 4′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.21 - 7.41 (m, 2H, 3‴′-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴′-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.47 – 7.55 (m, 2H, 2‴′-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴′-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.57 – 7.63 (m, 2H, 3‴-H$_{phenyl}$, 5‴-H$_{phenyl}$), 7.82 – 7.88 (m, 2H, 2‴-H$_{phenyl}$, 6‴-H$_{phenyl}$), 8.57 (s, 1H, 5″-H$_{triazole}$);

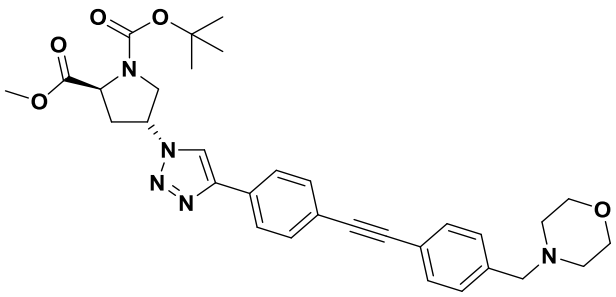
^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]= 37.5 (1C, CHC*H*$_2$CH), 52.4 (1C, CO_2*C*H_3), 53.7 (2C, NCH$_2$CH$_2$O), 57.8 (1C, C*H*$_2$Ar), 58.5 (1C, CH$_2$C*H*CH$_2$), 59.1 (1C, NC*H*$_2$), 63.9 (1C, Ar*C*H$_2$), 67.1 (2C, NCH$_2$*C*H$_2$O), 119.1 (1C, C-5″$_{triazole}$), 125.7 (2C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.8 (1C, C-4′$_{benzyl}$), 128.7 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.1 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.1 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.0 (1C, C-1‴$_{phenyl}$), 131.8 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.3 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 137.3 (1C, C-1′$_{benzyl}$), 147.8 (1C, C-4″$_{triazole}$), 173.5 (1C, *C*$O_2CH_3$), the signals for N*C*H, C-4‴$_{phenyl}$, Ar*C*≡CAr, ArC≡*C*Ar, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, and C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3142, 2953, 2927, 2855, 2802, 1740, 1411, 1332, 1200, 1176, 1111, 1067, 1032, 1007, 866, 842, 814, 762, 749, 701, 524, 499;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{35}N_5O_3$: 562.2740, found: 562.278;

HPLC (method 1): t_R = 18.2 min, purity 93.3%.

1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl] pyrrolidine-1,2-dicarboxylate (184)



$C_{32}H_{37}N_5O_5$

Mr = 571.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (54 mg, 0.05 mmol), copper(I) iodide (27 mg, 0.14 mmol), triethylamine (6.5 mL, 4719 mg, 46.64 mmol), and **103** (1408 mg, 7.00 mmol) were added to a solution of **178** (2324 mg, 4.66 mmol) in dry acetonitrile (60 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 3/1 → 0/1) to give **184** (2376 mg, 4.15 mmol, 89%) as brown solid.

m.p. = 158-159 °C;

TLC: R_f = 0.38 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -8.6 (3.0, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 1.35 (s, 9H, OC(C*H*$_3$)$_3$), 2.36 (t, *J* = 4.6 Hz, 4H, NC*H*$_2$CH$_2$O), 2.56 (m, *J* = 14.5/7.0 Hz, 1H, CHC*H*$_2$CH), 2.87 (m, *J* = 27.7/13.9/8.6/5.3 Hz, 1H, CHC*H*$_2$CH), 3.49 (s, 2H, ArC*H*$_2$), 3.58 (t, *J* = 4.6 Hz, 4H, NCH$_2$C*H*$_2$O), 3.73 (s, 3H, CO$_2$C*H*$_3$), 3.80 (dd, *J* = 11.6/3.9 Hz, 1H, NC*H*$_2$), 3.95 (m, *J* = 11.6/6.2 Hz, 1H, NC*H*$_2$), 4.53 (m, *J* = 15.0/8.4/6.2 Hz, 1H, NC*H*), 5.34 (m, *J* = 4.8/4.4 Hz, 1H, CH$_2$C*H*CH$_2$), 7.35 – 7.39 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.50 – 7.55 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.60 – 7.66 (m, 2H, 3″-H$_{phenyl}$, 5″-H$_{phenyl}$), 7.88 – 7.95 (m, 2H, 2″-H$_{phenyl}$, 6″-H$_{phenyl}$), 8.79 (s, 1H, 5′-H$_{triazole}$), the signals of the major rotamer are given;

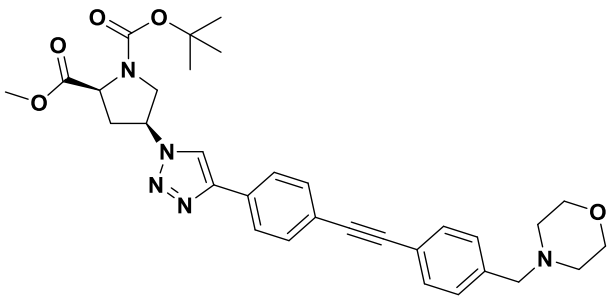
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 27.8 (3C, OC(*C*H$_3$)$_3$), 35.4 (1C, CHC*H*$_2$CH), 51.8 (1C, NC*H*$_2$), 52.2 (1C, CO$_2$*C*H$_3$), 53.1 (2C, N*C*H$_2$CH$_2$O), 57.6 (1C, N*C*H), 57.8 (1C, CH$_2$C*H*CH$_2$), 62.0 (1C, Ar*C*H$_2$), 66.2 (2C, NCH$_2$*C*H$_2$O), 79.7 (1C, O*C*(CH$_3$)$_3$), 89.0 (1C, Ar*C*≡CAr), 90.0 (1C, ArC≡*C*Ar), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.4 (1C, C-5′$_{triazole}$), 121.6 (1C, C-4″$_{phenyl}$), 125.3 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 130.7 (1C, C-1″$_{phenyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.0 (2C, (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.7 (1C, C-4′$_{triazole}$), 152.7 (1C, N*C*O$_2$C(CH$_3$)$_3$), 172.6 (1C, *C*O$_2CH_3$), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2892, 2853, 2811, 1736, 1704, 1442, 1400, 1290, 1163, 1153, 1119, 1035, 1008, 869, 830, 795, 544, 525;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{32}H_{37}N_5O_5$: 572.2795, found: 572.285;

HPLC (method 1): t_R = 20.2 min, purity 98.6%.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-1,2-dicarboxylate (185)



$C_{32}H_{37}N_5O_5$

Mr = 571.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.04 mmol), copper(I) iodide (23 mg, 0.12 mmol), triethylamine (5.60 mL, 4061 mg, 40.13 mmol), and **103** (1212 mg, 6.02 mmol) were added to a solution of **179** (2.0 g, 4.01 mmol) in dry acetonitrile (70 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 3/2 → 0/1) to give **185** (1936 mg, 3.39 mmol, 85%) as brown solid.

m.p. = 185-186 °C;

TLC: R_f = 0.38 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -13.7 (4.2, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.39 (s, 9H, OC(CH_3)$_3$), 2.36 (t, *J* = 4.7 Hz, 4H, NCH_2CH$_2$O), 2.56 – 2.67 (m, 1H, CHCH_2CH), 2.91 – 2.99 (m, 1H, CHCH_2CH), 3.50 (s, 2H, ArCH_2), 3.56 – 3.63 (t, 4H, NCH$_2$CH_2O), 3.56 - 3.63 (s, 3H, CO$_2$CH_3), 3.80 (m, *J* = 11.5/6.6 Hz, 1H, NCH_2), 4.01 – 4.13 (m, 1H, NCH_2), 4.39 – 4.46 (m, 1H, NC*H*), 5.29 (m, *J* = 10.8/6.9 Hz, 1H, CH$_2$C*H*CH$_2$), 7.37 (m, *J* = 8.1 Hz, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.48 – 7.54 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.60 – 7.65 (m, 2H, 3″-H$_{phenyl}$, 5″-H$_{phenyl}$), 7.86 – 7.93 (m, 2H, 2″-H$_{phenyl}$, 6″-H$_{phenyl}$), 8.83 (s, 1H, 5′-H$_{triazole}$), the signals of the major rotamer are given;

^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 27.9 (3C, OC(*C*H$_3$)$_3$), 35.1 (1C, CHCH_2CH), 50.7 (1C, NCH_2), 52.0 (1C, CO$_2$*C*H$_3$), 53.1 (2C, N*C*H$_2$CH$_2$O), 56.7 (1C, CH$_2$C*H*CH$_2$), 57.5 (1C,

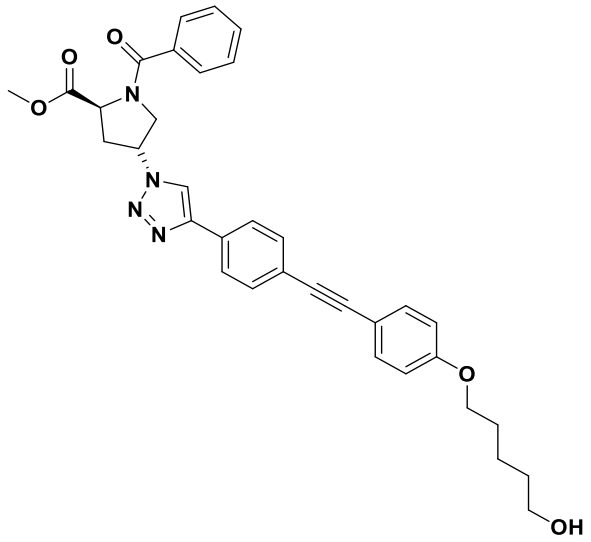
NCH), 62.0 (1C, ArCH_2), 66.2 (2C, NCH_2CH_2O), 79.5 (1C, O$C(CH_3)_3$), 89.0 (1C, ArC≡CAr), 90.0 (1C, ArC≡CAr), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.4 (1C, C-5′$_{triazole}$), 121.6 (1C, C-4″$_{phenyl}$), 125.3 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 130.8 (1C, C-1″$_{phenyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.0 (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.8 (1C, C-4′$_{triazole}$), 152.6 (1C, N$CO_2C(CH_3)_3$), 172.0 (1C, CO_2CH_3), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2953, 2928, 2853, 2802, 1749, 1698, 1399, 1365, 1173, 1153, 1114, 844, 805, 544, 526;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{37}N_5O_5$: 572.2795, found: 572.280;

HPLC (method 1): t_R = 20.2 min, purity 89%.

Methyl (2S,4*R*)-1-benzoyl-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl} pyrrolidine-2-carboxylate (186)



$C_{34}H_{34}N_4O_5$

M_r = 578.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.01 mmol), copper(I) iodide (3 mg, 0.02 mmol), triethylamine (0.22 mL, 160 mg, 1.58 mmol), and **71** (173 mg, 0.85 mmol) were added to a solution of **174** (265 mg, 0.53 mmol) in dry acetonitrile (30 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL,

petroleum ether/ethyl acetate = 3/2 → 0/1) to give **186** (314 mg, 0.54 mmol, 100%) as yellow solid.

m.p. = 188-190 °C;

TLC: R_f = 0.38 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -101.5 (2.1, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 1.46 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.72 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.59 – 2.68 (m, 1H, $CHCH_2CH$), 2.96 (m, 1H, $CHCH_2CH$), 3.41 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.74 (s, 3H, CO_2CH_3), 3.93 – 4.05 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.93 - 4.05 (dd, 1H, NCH_2), 4.22 (dd, *J* = 11.5/5.7 Hz, 1H, NCH_2), 4.38 (t, 1H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.82 (m, 1H, NCH), 5.35 (m, 1H, CH_2CHCH_2), 6.91 – 7.02 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.42 – 7.53 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), 7.42 - 7.53 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.57 – 7.61 (m, 2H, 3‴-H$_{phenyl}$, 5‴-H$_{phenyl}$), 7.82 – 7.90 (m, 2H, 2‴-H$_{phenyl}$, 6‴-H$_{phenyl}$), 8.74 (s, 1H, 5″-H$_{triazole}$);

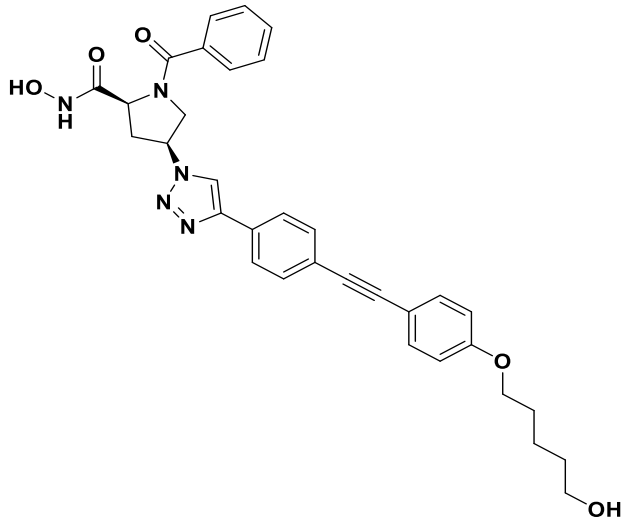
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 22.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 28.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 34.0 (1C, $CHCH_2CH$), 52.2 (1C, CO_2CH_3), 54.5 (1C, NCH_2), 57.7 (1C, NCH), 58.8 (1C, CH_2CHCH_2), 60.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 67.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 87.8 (1C, ArC≡CAr), 90.3 (1C, ArC≡CAr), 113.9 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 114.8 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 121.5 (1C, C-5″$_{triazole}$), 122.0 (1C, C-4‴$_{phenyl}$), 125.3 (2C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.1 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.4 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.6 (1C, C-4′$_{benzoyl}$), 131.4 (1C, C-1‴$_{phenyl}$), 131.7 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 132.9 (1C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 135.2 (1C, C-1′$_{benzoyl}$), 145.7 (1C, C-4″$_{triazole}$), 159.0 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 168.5 (1C, ArCON), 171.6 (1C, CO_2CH_3);

IR (neat): ṽ [cm^{-1}] = 3501, 2936, 2864, 1741, 1621, 1601, 1510, 1420, 1282, 1244, 1161, 1025, 830, 815, 700, 540, 530;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{34}N_4O_5$: 579.2529, found:579.257;

HPLC (method 1): t_R = 23.4 min, purity 94.1%.

(2*S*,4*S*)-1-benzoyl-*N*-hydroxy-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl}pyrrolidine-2-carboxamide (197)



$C_{33}H_{33}N_5O_5$

M_r = 579.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.004 mmol), copper(I) iodide (2 mg, 0.01 mmol), triethylamine (0.2 mL, 122 mg, 1.21 mmol), and **71** (176 mg, 0.86 mmol) were added to a solution of **175** (202 mg, 0.40 mmol) in dry acetonitrile (30 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **187** (94 mg, 0.16 mmol, 41%) as yellow solid.

An aqueous solution of hydroxylamine (50 wt%, 4 mL) was added to a solution of **187** (92 mg, 0.16 mmol) in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture at ambient temperature overnight, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **197** (36 mg, 0.06 mmol, 39%) as colorless solid.

m.p. = 137-138 °C;

TLC: R_f = 0.15 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +57.3 (1.7, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.37 – 1.54 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.72 (m, *J* = 6.7 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.50 (m, 1H, $CHCH_2CH$), 2.92 (m, 1H, $CHCH_2CH$), 3.41 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.00 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.00 (m, 2H, NCH_2), 4.39 (t, 1H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.59 (m, 1H, NCH), 5.29 (m, 1H, CH_2CHCH_2), 6.93 – 7.01 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.31 – 7.66 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.31 - 7.66 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), 7.31 - 7.66 (m, 2H, 3‴-H$_{phenyl}$, 5‴-H$_{phenyl}$), 7.87 (m, *J* = 8.1 Hz, 2H, 2‴-H$_{phenyl}$, 6‴-H$_{phenyl}$), 8.80 (s, 1H, 5″-H$_{triazole}$);

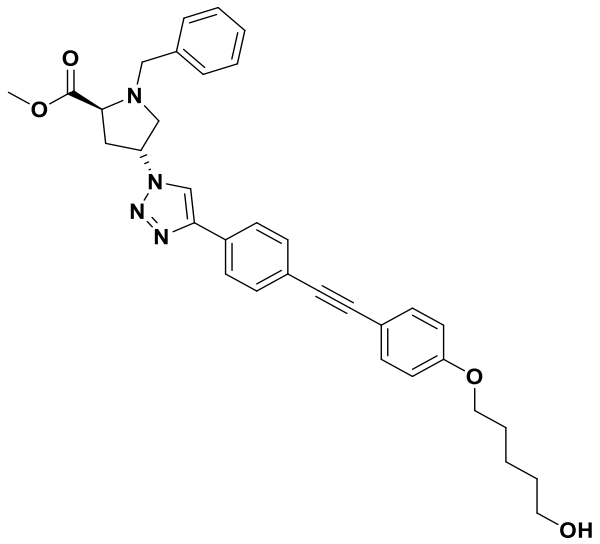
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 22.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 28.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 34.5 (1C, $CHCH_2CH$), 54.1 (1C, NCH_2), 56.8 (1C, CH_2CHCH_2), 56.9 (NCH), 60.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 67.7 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 87.9 (1C, ArC≡CAr), 90.3 (1C, ArC≡CAr), 114.0 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.9 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 121.4 (1C, C-5″$_{triazole}$), 122.0 (1C, C-4‴$_{phenyl}$), 125.3 (2C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.6 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.2 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.4 (1C, C-4′$_{benzoyl}$), 131.4 (1C, C-1‴$_{phenyl}$), 131.7 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 132.9 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 145.7 (1C, C-4″$_{triazole}$), 159.1 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 167.4 (1C, ArCON), 168.5 (1C, CONHOH), the signal for C-1′$_{benzoyl}$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3227, 1624, 1602, 1511, 1624, 1602, 1511, 1448, 1414, 1247, 1030, 830, 793, 668, 531;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{33}N_5O_5$: 580.2482, found 580.254;

HPLC (method 1): t_R = 15.9 min, purity 98.6%.

Methyl (2*S*,4*R*)-1-benzyl-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl}pyrrolidine-2-carboxylate (188)



$C_{34}H_{36}N_4O_4$

M_r = 564.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.004 mmol), copper(I) iodide (3 mg, 0.01 mmol), triethylamine (0.61 mL, 448 mg, 4.42 mmol), and **71** (145 mg, 0.71 mmol) were added to a solution of **176** (216 mg, 0.44 mmol) in dry acetonitrile (15 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **188** (228 mg, 0.40 mmol, 92%) as yellow solid.

m.p. = 135-136°C;

TLC: R_f = 0.48 (petroleum ether/ethyl acetate, 1/3);

Specific rotation: $[\alpha]_D^{20}$ = -53.1 (2.3, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.45 (m, *J* = 22.6/8.9/4.6/2.1 Hz, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.72 (m, *J* = 6.7 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.56 – 2.65 (m, 2H, $CHCH_2CH$), 2.85 (dd, *J* = 9.7/5.8 Hz, 1H, NCH_2), 3.38 – 3.46 (m, 1H, NCH_2), 3.38 - 3.46 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.65 (s, 3H, CO_2CH_3), 3.69 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 3.81 (dd, *J* = 8.0/6.4 Hz, 1H, NCH), 3.94 (d, *J* = 13.2 Hz, 1H, CH_2Ar), 4.00 (t, *J* = 6.5

Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.38 (t, *J* = 5.1 Hz, 1H, OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$O*H*), 5.27 (m, *J* = 13.3/7.2/4.0 Hz, 1H, CH$_2$C*H*CH$_2$), 6.94 – 7.01 (m, 2H, 3‴′-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴′-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.25 (m, *J* = 6.8/6.0/3.3 Hz, 1H, 4′-H$_{benzyl}$), 7.28 – 7.34 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.45 – 7.51 (m, 2H, 2‴′-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴′-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.57 – 7.62 (m, 2H, 3‴-H$_{phenyl}$, 5‴-H$_{phenyl}$), 7.85 – 7.90 (m, 2H, 2‴-H$_{phenyl}$, 6‴-H$_{phenyl}$), 8.73 (s, 1H, 5″-H$_{triazole}$);

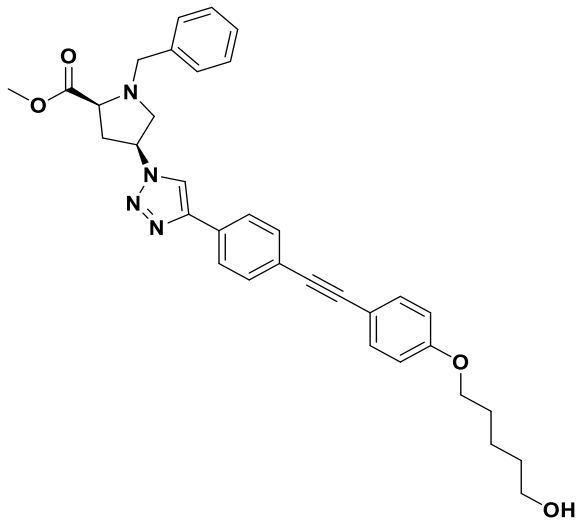
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 22.0 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 28.4 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 32.1 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 35.3 (1C, CH*C*H$_2$CH), 51.6 (1C, CO$_2$*C*H$_3$), 56.3 (1C, *C*H$_2$Ar), 57.7 (1C, 1C, CH$_2$C*H*CH$_2$), 57.7 (1C, N*C*H$_2$), 60.5 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 62.8 (1C, N*C*H), 67.6 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 87.8 (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 113.9 (1C, C-1‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.8 (2C, C-3‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 120.9 (1C, C-5″$_{triazole}$), 121.9 (1C, C-4‴$_{phenyl}$), 125.2 (1C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.0 (1C, C-4′$_{benzyl}$), 128.1 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.5 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.5 (1C, C-1‴$_{phenyl}$), 131.7 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 132.9 (2C, C-2‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 138.1 (1C, C-1′$_{benzyl}$), 145.7 (1C, C-4″$_{triazole}$), 172.7 (1C, *C*O$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3377, 2940, 2861, 1741, 1603, 1511, 1246, 1172, 1054, 1037, 826, 754, 698, 530;

HRMS (*m/z*): [M+H]$^+$ calcd for C$_{34}$H$_{36}$N$_4$O$_4$: 565.2737, found: 565.280;

HPLC (method 1): t$_R$ = 22.6 min, purity 97.8%.

Methyl (2*S*,4*S*)-1-benzyl-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl}pyrrolidine-2-carboxylate (189)



$C_{34}H_{36}N_4O_4$

M_r = 564.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (5 mg, 0.004 mmol), copper(I) iodide (3 mg, 0.01 mmol), triethylamine (0.2 mL, 143 mg, 1.41 mmol), and **71** (154 mg, 0.75 mmol) were added to a solution of **177** (220 mg, 0.45 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **189** (248 mg, 0.44 mmol, 93%) as yellow solid.

m.p. = 138-139 °C;

TLC: R_f = 0.48 (petroleum ether/ethyl acetate, 1/3);

Specific rotation: $[\alpha]_D^{20}$ = +73.3 (1.8, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.40 – 1.52 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.73 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.31 (m, *J* = 14.2/6.8/3.4 Hz, 1H, $CHCH_2CH$), 2.88 – 2.97 (m, 1H, $CHCH_2CH$), 2.88 – 2.97 (m, 1H, NCH_2), 3.07 – 3.12 (m, 1H, NCH_2), 3.39 – 3.46 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.51 (dd, *J* = 9.5/6.6 Hz, 1H, NC*H*), 3.62 (s, 3H, CO_2CH_3), 3.62 (d, 1H, CH_2Ar), 3.93 – 4.04 (d, 1H, CH_2Ar), 3.93 - 4.04 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.38 (t, *J* = 5.0 Hz, $OCH_2CH_2CH_2CH_2CH_2OH$), 5.28 (m, *J* =

8.6/6.0/3.2 Hz, 1H, CH_2CHCH_2), 6.96 – 7.01 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.21 – 7.27 (m, 1H, 4′-H_{benzyl}), 7.29 – 7.37 (m, 4H, 2′-H_{benzyl}, 3′-H_{benzyl}, 5′-H_{benzyl}, 6′-H_{benzyl}), 7.47 – 7.52 (m, 2H, 2‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.59 – 7.64 (m, 2H, 3‴-H_{phenyl}, 5‴-H_{phenyl}), 7.82 – 7.87 (m, 2H, 2‴-H_{phenyl}, 6‴-H_{phenyl}), 8.73 (s, 1H, 5″-$H_{triazole}$);

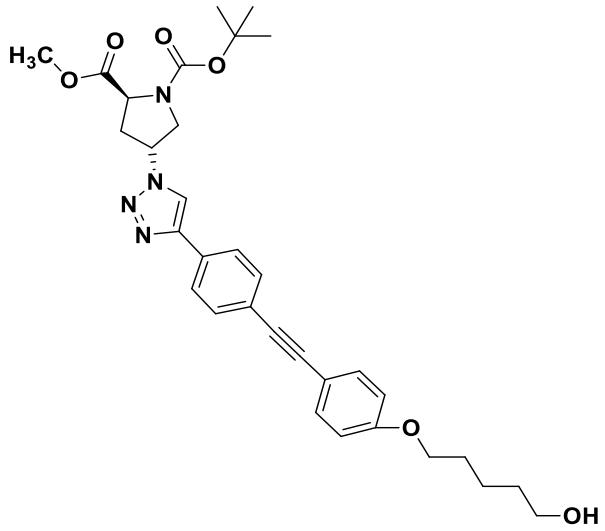
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 22.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 28.4 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 35.9 (1C, $CHCH_2CH$), 51.8 (1C, CO_2CH_3), 56.6 (1C, CH_2Ar), 57.9 (1C, 1C, CH_2CHCH_2), 58.0 (1C, NCH_2), 60.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 63.0 (1C, NCH), 67.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 87.8 (1C, ArC≡CAr), 90.2 (1C, ArC≡CAr), 114.0 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.8 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 120.1 (1C, C-5″$_{triazole}$), 121.9 (1C, C-4‴$_{phenyl}$), 125.1 (1C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.1 (1C, C-4′$_{benzyl}$), 128.2 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.7 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.5 (1C, C-1‴$_{phenyl}$), 131.8 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 132.9 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.8 (1C, C-1′$_{benzyl}$), 145.7 (1C, C-4″$_{triazole}$), 173.0 (1C, CO_2CH_3);

IR (neat): ṽ [cm^{-1}] = 2950, 2857, 2808, 1742, 1510, 1451, 1198, 1174, 1136, 1111, 1070, 975, 817, 745, 699, 523, 499;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{36}N_4O_4$: 565.2737, found: 525.278;

HPLC (method 1): t_R = 22.9 min, purity 93.9%.

1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl} pyrrolidine-1,2-dicarboxylate (190)



$C_{32}H_{38}N_4O_6$

M_r =574.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (53mg, 0.05 mmol), copper(I) iodide (26 mg, 0.14 mmol), triethylamine (6.31 mL, 4610 mg, 45.55 mmo), and **71** (1861 mg, 9.11 mmol) were added to a solution of **178** (2270 mg, 4.56 mmol) in dry acetonitrile (70 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/1 → 0/1) to give **190** (2100 mg, 3.65 mmol, 80%) as yellowish-brown solid.

m.p. = 157-158 °C;

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 1/3);

Specific rotation: $[\alpha]_D^{20}$ = -5.8 (1.8, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.35 (s, 9H, OC(CH_3)$_3$), 1.39 – 1.52 (m, 4H, OCH$_2$CH$_2$CH_2CH_2CH$_2$OH), 1.72 (m, 2H, OCH$_2$CH_2CH$_2$CH$_2$CH$_2$OH), 2.51 – 2.60 (m, 1H, CHCH_2CH), 2.87 (m, *J* = 27.7/13.8/8.5/5.0 Hz, 1H, CHCH_2CH), 3.41 (m, 2H, OCH$_2$CH$_2$CH$_2$CH$_2$CH_2OH), 3.73 (s, 3H, CO$_2$CH_3), 3.80 (dd, *J* = 11.5/3.9 Hz, 1H, NCH_2), 3.94 (dd, *J* = 11.7/6.1 Hz, 1H, NCH_2), 4.00 (t, *J* = 6.5 Hz, 2H, OCH_2CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.38 (t,

1H, $OCH_2CH_2CH_2CH_2CH_2O\mathit{H}$), 4.53 (m, *J* = 15.0/8.4/6.2 Hz, 1H, $NC\mathit{H}$), 5.34 (m, *J* = 5.6 Hz, 1H, $CH_2C\mathit{H}CH_2$), 6.93 – 7.02 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.46 – 7.52 (m, 2H, 2‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.58 – 7.63 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 7.86 – 7.91 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 8.78 (s, 1H, 5′-$H_{triazole}$), the signals of the major rotamer are given;

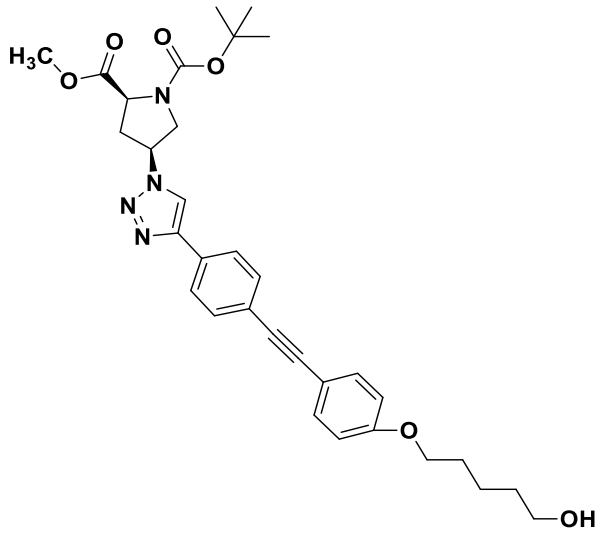
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 22.1 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 27.8 (3C, $OC(\mathit{C}H_3)_3$), 28.5 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 35.4 (1C, $CH\mathit{C}H_2CH$), 51.9 (1C, $N\mathit{C}H_2$), 52.2 (1C, $CO_2\mathit{C}H_3$), 57.7 (1C, $N\mathit{C}H$), 57.8 (1C, $CH_2C\mathit{H}CH_2$), 60.6 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 67.7 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 79.7 (1C, $O\mathit{C}(CH_3)_3$), 87.8 (1C, $Ar\mathit{C}{\equiv}CAr$), 90.3 (1C, $ArC{\equiv}\mathit{C}Ar$), 114.0 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.9 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 121.3 (1C, C-5′$_{triazole}$), 122.0 (1C, C-4″$_{phenyl}$), 125.3 (1C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 130.4 (1C, C-1″$_{phenyl}$), 131.8 (1C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 132.9 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 145.8 (1C, C-4′$_{triazole}$), 152.7 (1C, $N\mathit{C}O_2C(CH_3)_3$), 159.1 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 172.6 (1C, $\mathit{C}O_2CH_3$), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3338, 2935, 2873, 1733, 1702, 1511, 1399, 1366, 1285, 1245, 1162, 1125, 1028, 828, 547;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{38}N_4O_6$: 575.2791, found: 575.280;

HPLC (method 1): t_R = 24.8 min, purity 100%.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl}pyrrolidine-1,2-dicarboxylate (191)



$C_{32}H_{38}N_4O_6$

M_r =574.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (46mg, 0.04 mmol), copper(I) iodide (23 mg, 0.12 mmol), triethylamine (5.6 mL, 4061 mg, 40.13 mmol), and **71** (1314 mg, 6.43 mmol) were added to a solution of **179** (2000 mg, 4.01 mmol) in dry acetonitrile (50 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate = 1/0 → 0/1) to give **191** (2041 mg, 3.55 mmol, 89%) as yellowish-brown solid.

m.p. = 174-176 °C;

TLC: R_f = 0.33 (petroleum ether/ethyl acetate, 1/3);

Specific rotation: $[\alpha]_D^{20}$ = +15.7 (2.3, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.41 – 1.52 (s, 9H, OC(CH_3)$_3$), 1.52 – 1.73 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.77 – 1.93 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.67 – 2.72 (m, 1H, $CHCH_2CH$), 2.95 – 3.03 (m, 1H, $CHCH_2CH$), 3.64 – 3.78 (s, 3H, CO_2CH_3), 3.64 - 3.78 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.99 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.99 (m,

2H, NCH_2), 4.19 (m, 1H, NCH_2), 4.40 – 4.49 (m, 1H, NCH), 5.27 (m, 1H, CH_2CHCH_2), 6.82 – 6.91 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.46 (m, 2H, 2‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.53 – 7.59 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 7.79 – 7.84 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 7.96 – 8.04 (m, 1H, 5′-$H_{triazole}$), the signals of the major rotamer are given;

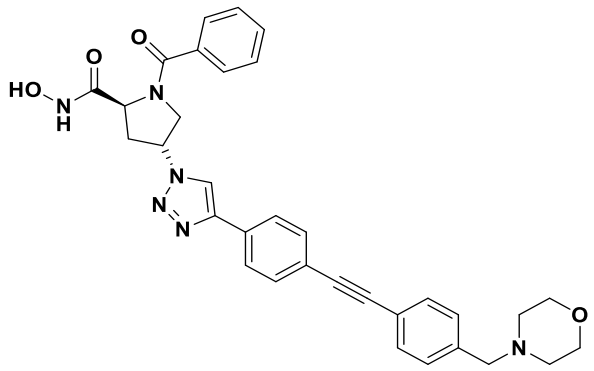
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 28.4 (3C, $OC(CH_3)_3$), 29.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 36.6 (1C, $CHCH_2CH$), 51.4 (1C, NCH_2), 52.4 (1C, CO_2CH_3), 57.8 (1C, NCH), 57.9 (1C, CH_2CHCH_2), 63.0 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 68.0 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 81.4 (1C, $OC(CH_3)_3$), 88.0 (1C, ArC≡CAr), 90.7 (1C, ArC≡CAr), 114.7 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 115.2 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 118.9 (1C, C-5′$_{triazole}$), 123.8 (1C, C-4″$_{phenyl}$), 125.8 (1C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 129.6 (1C, C-1″$_{phenyl}$), 132.2 (1C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 133.3 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 159.4 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 172.4 (1C, CO_2CH_3), the signals for C-4′$_{triazole}$ and $NCO_2C(CH_3)_3$ cannot be observed in the spectrum, the signal of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2933, 2866, 1751, 1698, 1510, 1399, 1364, 1244, 1200, 1172, 1153, 1120, 1021, 831, 808, 762, 541;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{38}N_4O_6$: 575.2791, found: 575.286;

HPLC (method 1): t_R = 24.6 min, purity 81.7%.

(2*S*,4*S*)-1-benzoyl-*N*-hydroxy-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxamide (192)



$C_{33}H_{32}N_6O_4$

M_r = 576.7

An aqueous solution of hydroxylamine (50 wt%, 3.0 mL) was added to a solution of **180** (291 mg, 0.51 mmol) in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture at ambient temperature overnight, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **192** (173 mg, 0.30 mmol, 60%) as colorless solid.

m.p. = 166-167 °C;

TLC: R_f = 0.33 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -50.5 (1.0, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 2.35 (t, *J* = 4.7 Hz, 4H, NC*H*$_2$CH$_2$O), 2.50 (m, 1H, CHC*H*$_2$CH), 2.82 (m, *J* = 13.1/8.4/4.1 Hz, 1H, CHC*H*$_2$CH), 3.49 (s, 2H, ArC*H*$_2$), 3.57 (t, *J* = 4.6 Hz, 4H, NCH$_2$C*H*$_2$O), 3.91 – 3.96 (m, 1H, NC*H*$_2$), 4.20 (dd, *J* = 11.5/5.6 Hz, 1H, NC*H*$_2$), 4.64 (t, *J* = 7.7 Hz, 1H, NC*H*), 5.35 (m, *J* = 5.9/3.0 Hz, 1H, CH$_2$C*H*CH$_2$), 7.34 – 7.39 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.40 – 7.56 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.40 - 7.56 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl,}$ 6′-H$_{benzoyl}$), 7.58 – 7.68 (m, 2H, 3‴-H$_{phenyl}$, 5‴-H$_{phenyl}$), 7.84 – 7.90 (m, 2H, 2‴-H$_{phenyl}$, 6‴-H$_{phenyl}$), 8.70 (s, 1H, 5″-H$_{triazole}$);

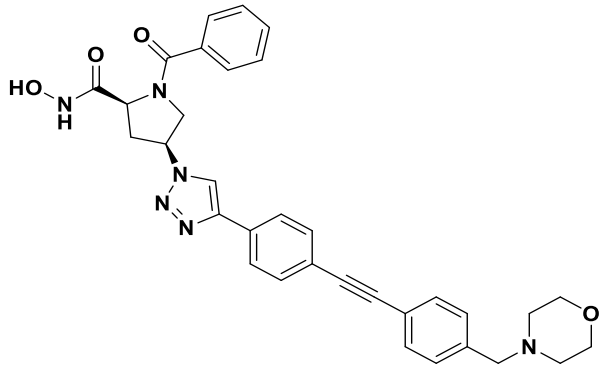
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 35.3 (1C, CHCH_2CH), 53.2 (2C, NCH_2CH_2O), 54.9 (1C, NCH_2), 56.9 (1C, NCH), 58.9 (1C, CH_2CHCH_2), 62.0 (1C, ArCH_2), 66.2 (2C, NCH_2CH_2O), 89.0 (1C, ArC≡CAr), 90.1 (1C, ArC≡CAr), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.6 (1C, C-5″$_{triazole}$), 121.7 (1C, C-4‴$_{phenyl}$), 125.3 (1C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.2 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.3 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 130.3 (1C, C-4′$_{benzoyl}$), 130.7 (1C, C-1‴$_{phenyl}$), 131.3 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.0 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 135.8 (1C, C-1′$_{benzoyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.7 (1C, C-4″$_{triazole}$), 167.8 (1C, *C*ONHOH), 168.8 (1C, Ar*C*ON);

IR (neat): ṽ [cm^{-1}] = 3244, 3213, 2857, 1668, 1615, 1447, 1411, 1114, 1006, 972, 865, 842, 793, 702, 545, 529;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{32}N_6O_4$: 577.2485, found: 577.256;

HPLC (method 2): t_R = 13.2 min, purity 100%.

(2*S*,4*S*)-1-benzoyl-*N*-hydroxy-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxamide (193)



$C_{33}H_{32}N_6O_4$

M_r = 576.7

An aqueous solution of hydroxylamine (50 wt%, 4.0 mL) was added to a solution of **181** (92 mg, 0.16 mmol) in a mixture of THF (5 mL) and isopropanol (5 mL). After stirring the reaction mixture at ambient temperature overnight, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-

HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **193** (28 mg, 0.05 mmol, 30%) as colorless solid.

m.p. = 148-149 °C;

TLC: R_f = 0.18 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +46.5 (1, methanol);

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ [ppm]= 2.26 – 2.42 (t, 4H, NC*H*$_2$CH$_2$O), 2.50 (m, 1H, CHC*H*$_2$CH), 2.93 (m, *J* = 13.9/7.6 Hz, 1H, CHC*H*$_2$CH), 3.49 (s, 2H, ArC*H*$_2$), 3.58 (t, *J* = 4.6 Hz, 4H, NCH$_2$C*H*$_2$O), 4.06 (m, 2H, NC*H*$_2$), 4.59 (t, *J* = 8.6 Hz, 1H, NC*H*), 5.23 – 5.35 (m, 1H, CH$_2$C*H*CH$_2$), 7.37 (m, *J* = 8.1 Hz, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.40 – 7.67 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.40 – 7.67 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl,}$ 6′-H$_{benzoyl}$), 7.40 – 7.67 (m, 2H, 3‴-H$_{phenyl}$, 5‴-H$_{phenyl}$), 7.89 (m, *J* = 8.1 Hz, 2H, 2‴-H$_{phenyl}$, 6‴-H$_{phenyl}$), 8.83 (s, 1H, 5″-H$_{triazole}$);

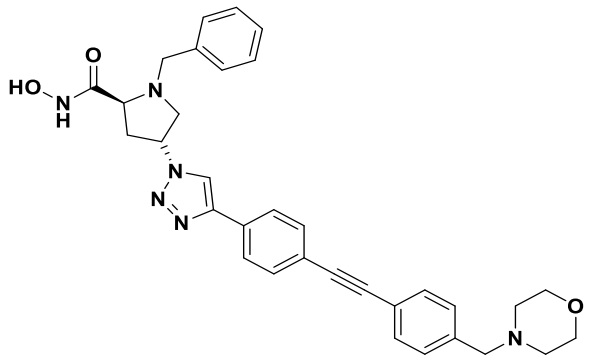
^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ [ppm]= 34.4 (1C, CHC*H*$_2$CH), 53.1 (2C, N*C*H$_2$CH$_2$O), 62.0 (1C, Ar*C*H$_2$), 56.7 (1C, CH$_2$*C*H*C*H$_2$), 56.9 (1C, N*C*H), 66.2 (2C, NCH$_2$*C*H$_2$O), 89.0 (1C, Ar*C*≡CAr), 89.9 (1C, (1C, ArC≡*C*Ar), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.5 (1C, C-5″$_{triazole}$), 121.6 (1C, C-4‴$_{phenyl}$), 125.3 (1C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.5 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.2 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.9 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.6 (1C, C-4″$_{triazole}$), 167.4 (1C, *C*ONHOH), 168.4 (1C, Ar*C*ON), the signals for C-1′$_{benzoyl}$, C-4′$_{benzoyl}$, C-1‴$_{phenyl}$, and N*C*H$_2$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3213, 2850, 2804, 1623, 1448, 1411, 1113, 1006, 974, 864, 840, 793, 725, 700, 546, 530;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{33}H_{32}N_6O_4$: 577.2485, found: 577.256;

HPLC (method 2): t_R = 13.1 min, purity 100%.

(2*S*,4*R*)-1-benzyl-*N*-hydroxy-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxamide (194)



$C_{33}H_{34}N_6O_3$

M_r = 562.7

An aqueous solution of hydroxylamine (50 wt%, 7.5 mL) was added to a solution of **182** (160 mg, 0.28 mmol) in a mixture of THF (2 mL) and isopropanol (2 mL). After stirring the reaction mixture at ambient temperature overnight, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **194** (74 mg, 0.13 mmol, 47%) as colorless solid.

m.p. = 146-147 °C;

TLC: R_f = 0.45 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -50.9 (1.6, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 2.35 (d, *J* = 4.6 Hz, 4H, NC*H*$_2$CH$_2$O), 2.54 (m, *J* = 8.2/5.9 Hz, 2H, CHC*H*$_2$CH), 2.76 (dd, *J* = 9.6/6.1 Hz, 1H, NC*H*$_2$), 3.42 (dd, *J* = 9.5/7.0 Hz, 1H, NC*H*$_2$), 3.48 (s, 2H, ArC*H*$_2$), 3.53 – 3.59 (m, 4H, NCH$_2$C*H*$_2$O), 3.53 - 3.59 (m, 1H, NC*H*), 3.61 (d, *J* = 13.3 Hz, 1H, C*H*$_2$Ar), 3.84 (d, *J* = 13.4 Hz, 1H, C*H*$_2$Ar), 5.30 (m, *J* = 8.3/6.3 Hz, 1H, CH$_2$C*H*CH$_2$), 7.22 – 7.26 (m, 1H, 4′-H$_{benzyl}$), 7.29 – 7.38 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.29- 7.38 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.49 – 7.54 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.58 – 7.65 (m, 2H, 3′′-H$_{phenyl}$, 5′′-H$_{phenyl}$), 7.86 – 7.91 (m, 2H, 2′′-H$_{phenyl}$, 6′′-H$_{phenyl}$), 8.71 (s, 1H, 5″-H$_{triazole}$);

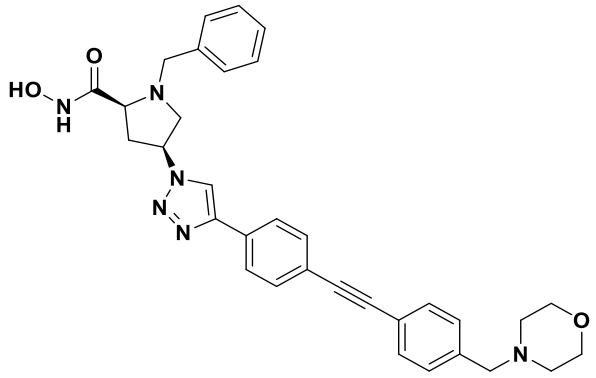
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 35.7 (1C, CHCH_2CH), 53.2 (2C, NCH_2CH_2O), 56.5 (1C, CH_2Ar), 57.7 (1C, NCH_2), 58.1 (1C, CH_2CHCH_2), 62.0 (1C, ArCH_2), 63.0 (1C, NCH), 66.2 (2C, NCH_2CH_2O), 89.1 (1C, ArC≡CAr), 90.0 (1C, ArC≡CAr), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.1 (1C, C-5″$_{triazole}$), 121.6 (1C, C-4‴$_{phenyl}$), 125.3 (2C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.1 (1C, C-4′$_{benzyl}$), 128.2 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.5 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 130.9 (1C, C-1‴$_{phenyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.0 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 138.3 (1C, C-1′$_{benzyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.7 (1C, C-4″$_{triazole}$), 168.4 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3128, 2950, 2812, 1646, 1510, 1453, 1114, 1071, 1006, 865, 843, 827, 794, 750, 700, 544, 529;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{34}N_6O_3$: 563.2692, found: 563.275;

HPLC (method 2): t_R = 13.4 min, purity 98.1%.

(2*S*,4*S*)-1-benzyl-*N*-hydroxy-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxamide (195)



$C_{33}H_{34}N_6O_3$

M_r = 562.7

An aqueous solution of hydroxylamine (50 wt%, 1.1 mL) was added to a solution of **183** (180 mg, 0.32 mmol) in a mixture of THF (1 mL) and isopropanol (1 mL) and the mixture was stirred at ambient temperature overnight. Then, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **195** (78 mg, 0.14 mmol, 43%) as colorless solid.

m.p. = 97-99°C;

TLC: R_f = 0.43 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +84.6 (1.3, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 2.15 (m, *J* = 14.0/7.0/3.1 Hz, 1H, CHC*H*$_2$CH), 2.31 – 2.41 (m, 4H, NC*H*$_2$CH$_2$O), 2.71 (dd, *J* = 10.4/6.0 Hz, 1H, NC*H*$_2$), 2.81 – 2.93 (m, 1H, NC*H*$_2$), 2.81 - 2.93 (m, 1H, CHC*H*$_2$CH), 3.18 (dd, *J* = 9.1/7.0 Hz, 1H, NC*H*), 3.37 – 3.42 (d, 1H, C*H*$_2$Ar), 3.49 (s, 2H, ArC*H*$_2$), 3.58 (t, *J* = 4.6 Hz, 4H, NCH$_2$C*H*$_2$O), 3.98 (d, *J* = 13.5 Hz, 1H, C*H*$_2$Ar), 5.25 – 5.31 (m, 1H, CH$_2$C*H*CH$_2$), 7.19 – 7.23 (m, 1H, 4′-H$_{benzyl}$), 7.29 (m, *J* = 8.4/6.9 Hz, 2H, 3′-H$_{benzyl,}$ 5′-H$_{benzyl}$), 7.35 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.35 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.51 – 7.55 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.63 – 7.68 (m, 2H, 3′′-H$_{phenyl}$, 5′′-H$_{phenyl}$), 7.86 – 7.90 (m, 2H, 2′′-H$_{phenyl}$, 6′′-H$_{phenyl}$), 9.18 (s, 1H, 5′′-H$_{triazole}$);

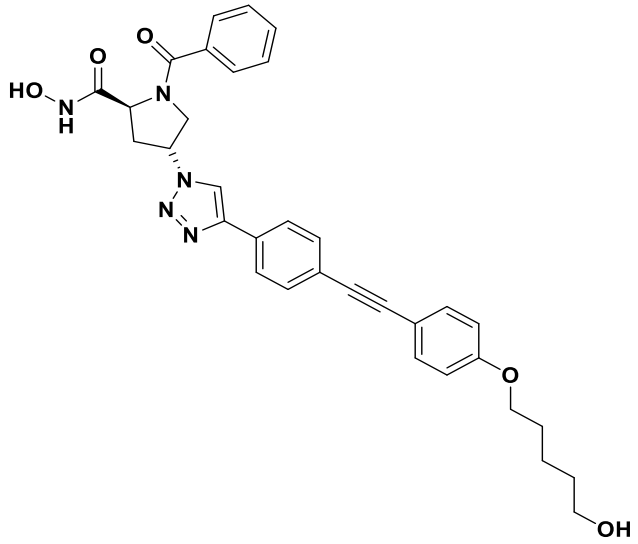
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 36.5 (1C, CHC*H*$_2$CH), 53.2 (2C, N*C*H$_2$CH$_2$O), 56.3 (1C, C*H*$_2$Ar), 58.0 (1C, CH$_2$C*H*CH$_2$), 58.3 (1C, NC*H*$_2$), 62.0 (1C, Ar*C*H$_2$), 63.4 (1C, N*C*H), 66.2 (2C, NCH$_2$*C*H$_2$O), 89.1 (1C, Ar*C*≡CAr), 90.0 (1C, ArC≡*C*Ar), 120.5 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 120.8 (1C, C-5′′$_{triazole}$), 121.5 (1C, C-4‴$_{phenyl}$), 125.2 (2C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.1 (1C, C-4′$_{benzyl}$), 128.2 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.5 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.1 (1C, C-1‴$_{phenyl}$), 131.3 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.0 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 137.8 (1C, C-1′$_{benzyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.8 (1C, C-4′′$_{triazole}$), 168.2 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3138, 2852, 2807, 1665, 1510, 1453, 1113, 1069, 1006, 864, 841, 794, 701, 545, 529;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{34}N_6O_3$: 563.2692, found: 563.271;

HPLC (method 2): t_R = 13.5 min, purity 100%.

(2*S*,4*R*)-1-benzoyl-*N*-hydroxy-4-{4-[4-({4-[(5-hydroxypentyl)oxy)phenyl)ethynyl)phenyl)-1H-1,2,3-triazol-1-yl)pyrrolidine-2-carboxamide (196)



$C_{33}H_{33}N_5O_5$

M_r = 579.7

An aqueous solution of hydroxylamine (50 wt%, 0.6 mL) was added to a solution of **186** (105 mg, 0.18 mmol) in a mixture of THF (1 mL) and isopropanol (1 mL) and the mixture was stirred at ambient temperature overnight. Then, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **196** (10 mg, 0.02 mmol, 10%) as colorless solid.

m.p. = 165-166 °C;

TLC: R_f = 0.19 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -28.1 (1.1, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.38 – 1.52 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.72 (m, *J* = 6.7 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.50 (m, 1H, $CHCH_2CH$), 2.82 (m, *J* = 13.2/8.3/4.1 Hz, 1H, $CHCH_2CH$), 3.41 (m, *J* = 5.8 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.91 – 3.96 (m, 1H, NCH_2), 4.00 (t, *J* = 6.5 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.20 (dd, *J* = 11.5/5.6 Hz, 1H, NCH_2), 4.39 (t, *J* = 5.1 Hz, 1H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.64 (t, *J* = 7.7 Hz, 1H,

NC*H*), 5.35 (m, 1H, $CH_2C\mathit{H}CH_2$), 6.94 – 7.03 (m, 2H, 3‴′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5⁗′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.32 – 7.65 (m, 2H, 2‴′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6⁗′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.32 - 7.65 (m, 5H, 2′-$H_{benzoyl}$, 3′-$H_{benzoyl}$, 4′-$H_{benzoyl}$, 5′-$H_{benzoyl}$, 6′-$H_{benzoyl}$), 7.32 - 7.65 (m, 2H, 3‴-H_{phenyl}, 5‴-H_{phenyl}), 7.80 – 7.94 (m, 2H, 2‴-H_{phenyl}, 6‴-H_{phenyl}), 8.70 (s, 1H, 5″-$H_{triazole}$);

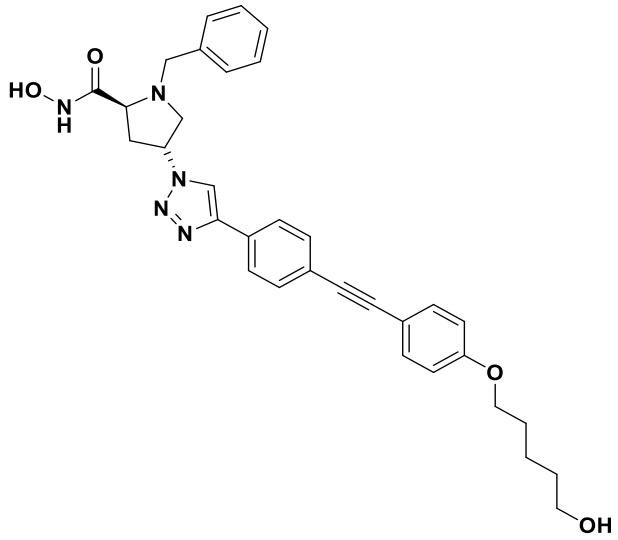
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 22.1 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 28.5 (1C, (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 35.3 (1C, $CHC\mathit{H}_2CH$), 54.9 (1C, NCH_2), 56.9 (1C, NC*H*), 58.9 (1C, $CH_2C\mathit{H}CH_2$), 60.6 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 67.7 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 87.8 (1C, Ar*C*≡CAr), 90.3 (1C, ArC≡*C*Ar), 114.0 (1C, C-1⁗′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.9 (2C, C-3⁗′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5⁗′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 121.5 (1C, C-5″$_{triazole}$), 122.1 (1C, C-4‴$_{phenyl}$), 125.3 (2C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.2 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.3 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.3 (1C, C-4′$_{benzoyl}$), 131.4 (1C, C-1‴$_{phenyl}$), 131.8 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 132.9 (1C, C-2⁗′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6⁗′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 135.8 (1C, C-1′$_{benzoyl}$), 145.7 (1C, C-4″$_{triazole}$), 159.1 (1C, C-4⁗′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 167.8 (1C, *C*ONHOH), 168.7 (1C, Ar*C*ON);

IR (neat): ṽ [cm^{-1}] = 3211, 2935, 2865, 1618, 1602, 1510, 1434, 1411, 1247, 1174, 1027, 831, 720, 695, 537;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{33}N_5O_5$: 580.2482, found: 580.254;

HPLC (method 2): t_R = 15.7 min, purity 95.7%.

(2*S*,4*R*)-1-benzyl-*N*-hydroxy-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxamide (198)



$C_{33}H_{35}N_5O_4$

M_r = 565.7

An aqueous solution of hydroxylamine (50 wt%, 3.9 mL) was added to a solution of **188** (83 mg, 0.15 mmol) in a mixture of THF (2 mL) and isopropanol (2 mL). After stirring the reaction mixture at ambient temperature overnight, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **198** (22 mg, 0.04 mmol, 26%) as colorless solid.

m.p. = 198-199 °C;

TLC: R_f = 0.20 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -15.4 (1.3, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.46 (m, *J* = 17.3/12.6/7.2/3.1 Hz, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.72 (m, *J* = 6.6 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.46 – 2.58 (m, 2H, $CHCH_2CH$), 2.76 (dd, *J* = 9.5/6.1 Hz, 1H, NCH_2), 3.38 – 3.44 (m, 2H, NCH_2), 3.38 – 3.44 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.55 (dd, *J* = 8.1/6.0 Hz, 1H, NC*H*), 3.61 (d, *J* = 13.3

Hz, 1H, C*H*$_2$Ar), 3.84 (d, *J* = 13.4 Hz, 1H, C*H*$_2$Ar), 4.00 (t, *J* = 6.5 Hz, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.38 (t, *J* = 5.3 Hz, 1H, OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$O*H*), 5.29 (m, *J* = 8.4/6.4 Hz, 1H, CH$_2$C*H*CH$_2$), 6.95 – 7.00 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.23 – 7.27 (m, 1H, 4′-H$_{benzyl}$), 7.30 – 7.36 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.46 – 7.51 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.56 – 7.62 (m, 2H, 3‴-H$_{phenyl}$, 5‴-H$_{phenyl}$), 7.83 – 7.94 (m, 2H, 2‴-H$_{phenyl}$, 6‴-H$_{phenyl}$), 8.70 (s, 1H, 5″-H$_{triazole}$);

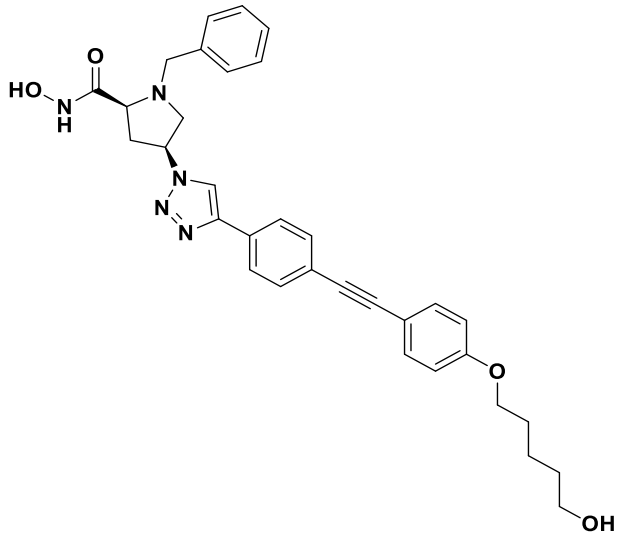
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 22.1 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 28.5 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 32.2 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 35.7 (1C, CH*C*H$_2$CH), 56.5 (1C, *C*H$_2$Ar), 57.8 (1C, N*C*H$_2$), 58.1 (1C, 1C, CH$_2$C*H*CH$_2$), 60.6 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 63.0 (1C, N*C*H), 67.7 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 87.9 (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 114.0 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.9 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 121.1 (1C, C-5″$_{triazole}$), 121.9 (1C, C-4″$_{phenyl}$), 125.2 (1C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 127.0 (1C, C-4′$_{benzyl}$), 128.2 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.5 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.5 (1C, C-1″$_{phenyl}$), 131.7 (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 132.9 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 138.3 (1C, C-1′$_{benzyl}$), 145.7 (1C, C-4″$_{triazole}$), 168.4 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3340, 3144, 2931, 2862, 1663, 1603, 1511, 1286, 1254, 1077, 1026, 831, 702, 530;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{33}H_{35}N_5O_4$: 566.2689, found:566.277;

HPLC (method 2): t_R = 16.3 min, purity 94.6%.

(2*S*,4*S*)-1-benzyl-*N*-hydroxy-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl} pyrrolidine-2-carboxamide (199)



$C_{33}H_{35}N_5O_4$

M_r = 565.7

An aqueous solution of hydroxylamine (50 wt%, 1.2 mL) was added to a solution of **189** (198 mg, 0.35 mmol) in a mixture of THF (1 mL) and isopropanol (1 mL) and the mixture was stirred at ambient temperature overnight. Then, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **199** (49 mg, 0.09 mmol, 25%) as colorless solid.

m.p. = 183-184 °C (decomposition);

TLC: R_f = 0.30 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +31.4 (1.8, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.39 – 1.52 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.69 – 1.77 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.16 (m, *J* = 14.0/7.1/3.0 Hz, 1H, $CHCH_2CH$), 2.69 (dd, *J* = 10.4/5.9 Hz, 1H, NCH_2), 2.82 (m, *J* = 14.2/9.0 Hz, 1H, $CHCH_2CH$), 2.88 (dd, 1H, NCH_2), 3.15 (dd, *J* = 9.1/7.0 Hz, 1H, NC*H)*, 3.32 – 3.46 (d, 1H, CH_2Ar), 3.32- 3.46 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.94 – 4.04 (d, 1H, CH_2Ar), 3.94 - 4.04 (t, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 5.24 – 5.30 (m, 1H, CH_2CHCH_2), 6.95 – 7.01 (m, 2H, 3‴′-H4-({4-

[(5-hydroxypentyl)oxy]phenyl, 5‴′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.18 – 7.23 (m, 1H, 4′-H_{benzyl}), 7.28 (m, *J* = 7.6 Hz, 2H, 3′-H_{benzyl}, 5′-H_{benzyl}), 7.31 – 7.35 (m, 2H, 2′-H_{benzyl}, 6′-H_{benzyl}), 7.46 – 7.52 (m, 2H, 2‴′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.57 – 7.65 (m, 2H, 3‴-H_{phenyl}, 5‴-H_{phenyl}), 7.84 – 7.89 (m, 2H, 2‴-H_{phenyl}, 6‴-H_{phenyl}), 9.25 (s, 1H, 5″-$H_{triazole}$);

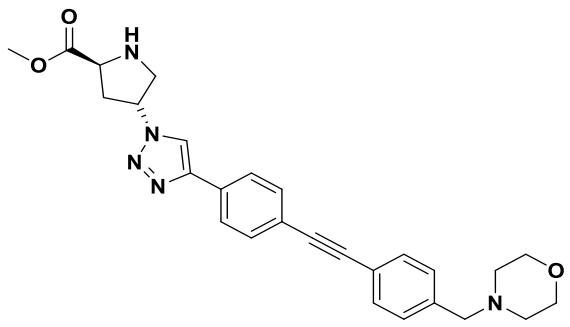
^{13}C NMR (151 MHz, DMSO-*d_6*) δ [ppm]= 22.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 28.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 36.3 (1C, $CHCH_2CH$), 56.2 (1C, CH_2Ar), 58.0 (1C, 1C, CH_2CHCH_2), 58.4 (1C, NCH_2), 60.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 63.5 (1C, NCH), 67.7 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 87.9 (1C, ArC≡CAr), 90.2 (1C, ArC≡CAr), 114.0 (1C, C-1‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.9 (2C, C-3‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 120.6 (1C, C-5″$_{triazole}$), 121.9 (1C, C-4‴$_{phenyl}$), 125.1 (1C, C-2‴$_{phenyl}$, C-6‴$_{phenyl}$), 127.0 (1C, C-4′$_{benzyl}$), 128.2 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.5 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.8 (1C, C-1‴$_{phenyl}$), 131.8 (2C, C-3‴$_{phenyl}$, C-5‴$_{phenyl}$), 132.9 (2C, C-2‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 138.0 (1C, C-1′$_{benzyl}$), 145.8 (1C, C-4″$_{triazole}$), 168.0 (1C, CONHOH);

IR (neat): ṽ [cm^{-1}] = 3197, 2938, 2863, 1665, 1603, 1511, 1453, 1285, 1246, 1174, 1057, 1027, 830, 701, 531;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{35}N_5O_4$: 566.2689, found: 566.285;

HPLC (method 2): t_R = 16.5 min, purity 98.6%.

Methyl (2*S*,4*R*)-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylate (200)



$C_{27}H_{29}N_5O_3$

Mr = 471.6

Zinc bromide (2742 mg, 12.17 mmol) was added to a solution of **184** (2320 mg, 4.06 mmol) in dichloromethane (80 mL) and stirred for 18 h at ambient temperature. Then, water was added

and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **200** (967 mg, 2.05 mmol, 51%) as pale-brown solid.

m.p. = 192-193 °C;

TLC: R_f = 0.38 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = +19.8 (4.1, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 2.36 (t, *J* = 4.8 Hz, 4H, NC*H*$_2$CH$_2$O), 2.42 – 2.58 (m, 2H, CHC*H*$_2$CH), 3.13 – 3.18 (m, 1H, NHC*H*$_2$), 3.39 (dd, *J* = 11.6/5.9 Hz, 1H, NHC*H*$_2$), 3.50 (s, 2H, ArC*H*$_2$), 3.58 (t, *J* = 4.6 Hz, 4H, NCH$_2$C*H*$_2$O), 3.68 (s, 3H, CO$_2$C*H*$_3$), 4.11 (t, *J* = 7.6 Hz, 1H, NHC*H*), 5.24 (m, *J* = 9.5/3.6 Hz, 1H, CH$_2$C*H*CH$_2$), 7.35 – 7.39 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.50 – 7.55 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.60 – 7.65 (m, 2H, 3″-H$_{phenyl}$, 5″-H$_{phenyl}$), 7.88 – 7.93 (m, 2H, 2″-H$_{phenyl}$, 6″-H$_{phenyl}$), 8.73 (s, 1H, 5′-H$_{triazole}$);

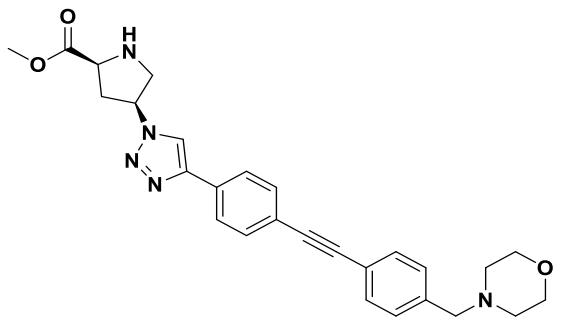
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 36.0 (1C, CHC*H*$_2$CH), 51.8 (1C, CO$_2$*C*H$_3$), 53.2 (1C, NHC*H*$_2$), 53.1 (2C, N*C*H$_2$CH$_2$O), 58.3 (1C, NH*C*H), 60.7 (1C, CH$_2$C*H*CH$_2$), 62.0 (1C, Ar*C*H$_2$), 66.2 (2C, NCH$_2$*C*H$_2$O), 89.1 (1C, Ar*C*≡CAr), 90.0 (1C, ArC≡*C*Ar), 120.8 (1C, C-5′$_{triazole}$), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.5 (1C, C-4″$_{phenyl}$), 125.3 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.0 (1C, C-1″$_{phenyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.9 (2C, (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.7(1C, C-4′$_{triazole}$), 174.3 (1C, *C*O$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3354, 3291, 3103, 2961, 2933, 2866, 2804, 2760, 1733, 1413, 1226, 1207, 1172, 1129, 1054, 1037, 913, 862, 839, 814, 711, 532;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{27}H_{29}N_5O_3$: 472.2270, found: 472.232;

HPLC (method 1): t_R = 14.2 min, purity 97.9%.

Methyl (2*S*,4*S*)-4-[4-(4-{[4-(morpholinomethyl)phenyl]ethynyl}phenyl)-1H-1,2,3-triazol-1-yl]pyrrolidine-2-carboxylate (201)



$C_{27}H_{29}N_5O_3$

Mr = 471.6

Zinc bromide (2140 mg, 9.50 mmol) was added to a solution of **185** (1820 mg, 3.17 mmol) in dichloromethane (100 mL) and stirred for 18 h at ambient temperature. Then, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **201** (1082 mg, 2.29 mmol, 72%) as pale-brown solid.

m.p. = 199-200 °C;

TLC: R_f = 0.30 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -19.7 (1.7, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 2.31 – 2.39 (t, 4H, NC*H*$_2$CH$_2$O), 2.77 (m, *J* = 13.7/9.1/8.1 Hz, 1H, CHC*H*$_2$CH), 3.25 (dd, *J* = 11.4/4.8 Hz, 1H, NHC*H*$_2$), 3.29 – 3.34 (dd, 1H, NHC*H*$_2$), 3.50 (s, 2H, ArC*H*$_2$), 3.58 (t, *J* = 4.6 Hz, 4H, NCH$_2$C*H*$_2$O), 3.65 (s, 3H, CO$_2$C*H*$_3$), 3.91 (dd, *J* = 9.0/6.5 Hz, 1H, NHC*H*), 5.10 – 5.17 (m, 1H, CH$_2$C*H*CH$_2$), 7.35 – 7.39 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.50 – 7.55 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.60 – 7.65 (m, 2H, 3″-H$_{phenyl}$, 5″-H$_{phenyl}$), 7.86 – 7.91 (m, 2H, 2″-H$_{phenyl}$, 6″-H$_{phenyl}$), 8.73 (s, 1H, 5′-H$_{triazole}$);

^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 36.0 (1C, CHC*H*$_2$CH), 51.8 (1C, CO$_2$*C*H$_3$), 52.7 (1C, NHC*H*$_2$), 53.1 (2C, N*C*H$_2$CH$_2$O), 58.4 (1C, NH*C*H), 60.2 (1C, CH$_2$C*H*CH$_2$), 62.0 (1C, Ar*C*H$_2$), 66.2 (2C, NCH$_2$*C*H$_2$O), 89.0 (1C, Ar*C*≡CAr), 90.0 (1C, ArC≡*C*Ar), 120.8 (1C, C-

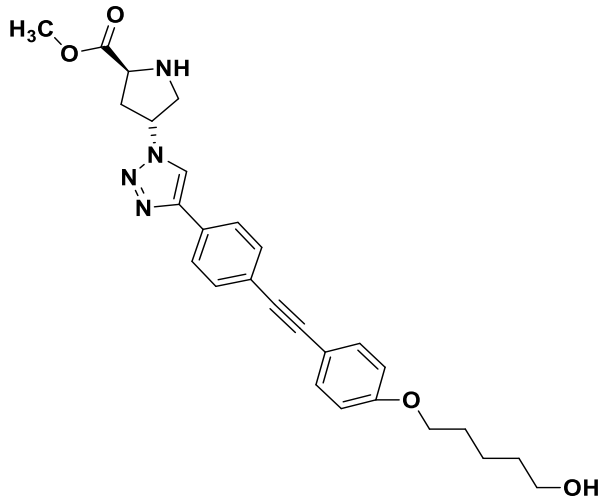
5′$_{triazole}$), 120.8 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 121.5 (1C, C-4″$_{phenyl}$), 125.2 (2C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 130.9 (1C, C-1″$_{phenyl}$), 131.2 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.9 (2C, (2C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 138.9 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 145.6 (1C, C-4′$_{triazole}$), 173.9 (1C, *C*$O_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3362, 2931, 2860, 2805, 2762, 1733, 1699, 1454, 1438, 1398, 1365, 1202, 1115, 1009, 839, 819, 758, 529;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{29}N_5O_3$: 472.2270, found:472.234;

HPLC (method 1): t_R = 14.1 min, purity 100%.

Methyl (2S,4R)-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl}pyrrolidine-2-carboxylate (202)



$C_{27}H_{30}N_4O_4$

M_r = 474.6

Zinc bromide (2351 mg, 10.44 mmol) was added to a solution of **190** (2.0 g, 3.48 mmol) in dichloromethane (100 mL) and stirred for 18 h at ambient temperature. Then, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **202** (850 mg, 1.79 mmol, 52%) as pale-yellow solid.

m.p. = 141-142 °C;

TLC: R_f = 0.30 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = +47.8 (2.9, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 1.39 – 1.52 (m, 4H, $OCH_2CH_2C\mathit{H}_2C\mathit{H}_2CH_2OH$), 1.72 (m, *J* = 6.6 Hz, 2H, $OCH_2C\mathit{H}_2CH_2CH_2CH_2OH$), 2.41 – 2.60 (m, 2H, $CHC\mathit{H}_2CH$), 3.15 (dd, *J* = 11.5, 3.4 Hz, 1H, $NHC\mathit{H}_2$), 3.37 – 3.48 (m, 1H, $NHC\mathit{H}_2$), 3.37- 3.48 (m, 2H, $OCH_2CH_2CH_2CH_2C\mathit{H}_2OH$), 3.68 (s, 3H, $CO_2C\mathit{H}_3$), 4.00 (m, 2H, $OC\mathit{H}_2CH_2CH_2CH_2CH_2OH$), 4.11 (dd, *J* = 8.4/6.8 Hz, 1H, $NHC\mathit{H}$), 4.38 (t, *J* = 5.1 Hz, 1H, $OCH_2CH_2CH_2CH_2CH_2O\mathit{H}$), 5.24 (m, *J* = 9.6/3.5 Hz, 1H, $CH_2C\mathit{H}CH_2$), 6.94 – 7.01 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.45 – 7.51 (m, 2H, 2‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.57 – 7.62 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 7.87 – 7.92 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 8.72 (s, 1H, 5′-$H_{triazole}$);

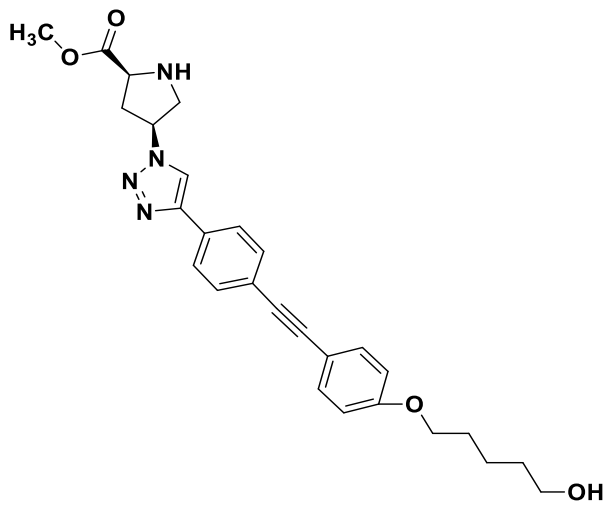
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 22.1 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 28.4 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 36.0 (1C, $CH\mathit{C}H_2CH$), 51.8 (1C, $CO_2\mathit{C}H_3$), 53.2 (1C, $NH\mathit{C}H_2$), 58.3 (1C, $NH\mathit{C}H$), 60.6 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 60.7 (1C, $CH_2C\mathit{H}CH_2$), 67.7 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 87.9 (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 114.0 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.9 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 120.7 (1C, C-5′$_{triazole}$), 121.9 (1C, C-4″$_{phenyl}$), 125.2 (1C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 130.6 (1C, C-1″$_{phenyl}$), 131.7 (1C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 132.9 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 145.7 (1C, C-4′$_{triazole}$), 159.0 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 174.3 (1C, $\mathit{C}O_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3299, 2933, 2865, 1737, 1602, 1511, 1246, 1173, 1107, 1032, 829, 801, 532;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{30}N_4O_4$: 475.2267, found: 475.231;

HPLC (method 1): t_R = 19.2 min, purity 83.8%.

Methyl (2*S*,4*S*)-4-{4-[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)phenyl]-1H-1,2,3-triazol-1-yl}pyrrolidine-2-carboxylate (203)



$C_{27}H_{30}N_4O_4$

M_r = 474.6

Zinc bromide (2351 mg, 10.44 mmol) was added to a solution of **191** (2.0 g, 3.48 mmol) in dichloromethane (100 mL) and stirred for 18 h at ambient temperature. Then, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **203** (1351 mg, 2.85 mmol, 82%) as pale-yellow solid.

m.p. = 225-226 °C;

TLC: R_f = 0.30 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -41.0 (2.1, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.39 – 1.52 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.67 – 1.76 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 2.35 (m, *J* = 13.6/6.0 Hz, 1H, $CHCH_2CH$), 2.77 (m, *J* = 13.6/8.3 Hz, 1H, $CHCH_2CH$), 3.25 (dd, *J* = 11.4/4.8 Hz, 1H, $NHCH_2$), 3.32 (dd, 1H, $NHCH_2$), 3.37 – 3.44 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.65 (s, 3H, CO_2CH_3), 3.91 (dd, *J* = 9.0/6.5 Hz, 1H, NHC*H*), 4.00 (t, *J* = 6.5 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.38 (t, *J* = 5.1 Hz, 1H, $OCH_2CH_2CH_2CH_2CH_2OH$), 5.13 (m, *J* = 7.6/5.3 Hz, 1H, CH_2CHCH_2), 6.94 – 7.01 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 7.45 – 7.51 (m, 2H, 2‴-

$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″′-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 7.57 – 7.62 (m, 2H, 3″-H_{phenyl}, 5″-H_{phenyl}), 7.85 – 7.90 (m, 2H, 2″-H_{phenyl}, 6″-H_{phenyl}), 8.71 (s, 1H, 5′-$H_{triazole}$);

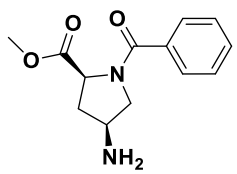
^{13}C NMR (151 MHz, DMSO-*d_6*) δ [ppm]= 22.1 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 28.5 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 36.0 (1C, $CH\mathit{C}H_2CH$), 51.8 (1C, $CO_2\mathit{C}H_3$), 52.7 (1C, $NH\mathit{C}H_2$), 58.4 (1C, NH*C*H), 60.2 (1C, $CH_2C\mathit{H}CH_2$), 60.6 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 67.7 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 87.9 (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 114.0 (1C, C-1″′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 114.9 (2C, C-3″′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 120.7 (1C, C-5′$_{triazole}$), 121.9 (1C, C-4″$_{phenyl}$), 125.2 (1C, C-2″$_{phenyl}$, C-6″$_{phenyl}$), 130.6 (1C, C-1″$_{phenyl}$), 131.7 (1C, C-3″$_{phenyl}$, C-5″$_{phenyl}$), 132.9 (2C, C-2″′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 145.7 (1C, C-4′$_{triazole}$), 159.0 (1C, C-4″′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})$, 173.9 (1C, *C*$O_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3366, 3090, 2939, 2864, 1739, 1604, 1513, 1474, 1436, 1243, 1210, 1177, 1036, 833, 823, 584, 528;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{30}N_4O_4$: 475.2267, found:475.232;

HPLC (method 1): t_R = 19.1 min, purity 95.1%.

Methyl (2*S*,4*S*)-4-amino-1-benzoylpyrrolidine-2-carboxylate (208)



$C_{13}H_{16}N_2O_3$

Mr = 248.3

Under N_2 atmosphere, palladium on activated charcoal (10%, 572 mg) was added to a solution of **169** (2950 mg, 10.76 mmol) in methanol (30 mL). The reaction mixture was stirred under hydrogen atmosphere (balloon) at ambient temperature for 18 h. Then, the mixture was filtered through Celite® and the filtrate was concentrated *in vacuo* to give **208** (2435 mg, 9.81 mmol, 91%) as colorless oil.

TLC: R_f = 0.20 (dichloromethane/methanol, 95/5);

Specific rotation: $[\alpha]_D^{20}$ = -46.4 (2.2, methanol);

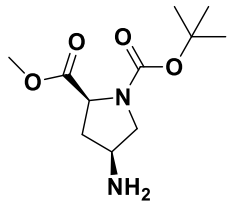
^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.61 (m, *J* = 12.2/9.0 Hz, 1H, CHC*H*$_2$CH), 2.37 – 2.46 (m, 1H, CHC*H*$_2$CH), 3.22 (dd, *J* = 9.9/8.2 Hz, 1H, NC*H*$_2$), 3.32 – 3.39 (m, 1H, C*H*NH$_2$), 3.47 – 3.57 (m, 1H, NC*H*$_2$), 3.67 (s, 3H, CO$_2$C*H*$_3$), 4.48 (t, *J* = 8.5 Hz, 1H, NC*H*), 7.35 – 7.58 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 37.5 (1C, CH*C*H$_2$CH), 51.2 (1C, *C*HNH$_2$), 51.8 (1C, CO$_2$*C*H$_3$), 57.3 (1C, NCH$_2$), 57.9 (1C, N*C*H), 127.1 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.3 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.2 (1C, C-4′$_{benzoyl}$), 135.9 (1C, C-1′$_{benzoyl}$), 168.1 (1C, Ar*C*ON), 172.3 (1C, *C*O$_2$CH$_3$);

IR (neat): ṽ [cm^{-1}] = 3362, 2951, 2874, 1737, 1622, 1575, 1447, 1412, 1200, 1175, 1029, 726, 701, 660;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{13}H_{16}N_2O_3$: 249.1161, found: 249.123;

HPLC (method 1): t_R = 9.9 min, purity 75.7%.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (209)



$C_{11}H_{20}N_2O_4$

M_r = 244.3

Under N_2 atmosphere, palladium on activated charcoal (10%, 82 mg) was added to a solution of **173** (415 mg, 1.54 mmol) in methanol (10 mL). The reaction mixture was stirred under hydrogen atmosphere (balloon) at ambient temperature for 18 h. Then, the mixture was filtered through Celite® and the filtrate was concentrated *in vacuo*. The residue was further purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, dichloromethane/methanol, 1/0 →9/1) to give **209** (171 mg, 0.70 mmol, 46%) as colorless oil.

TLC: R_f = 0.43 (dichloromethane/methanol, 9/1);

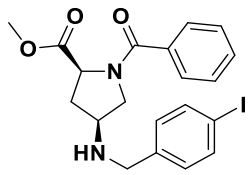
Specific rotation: $[\alpha]_D^{20}$ = -4.0 (4.5, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.43 (s, 9H, OC(C*H*$_3$)$_3$), 1.80 – 1.91 (m, 1H, CHC*H*$_2$CH), 2.36 – 2.52 (m, 1H, CHC*H*$_2$CH), 3.32 (m, 1H, NC*H*$_2$), 3.57 (m, 1H, C*H*NH$_2$), 3.69 (dd, 1H, NC*H*$_2$), 3.75 (s, 3*H*, CO_2C*H*$_3$), 4.23 (dd, *J* = 9.1/5.2 Hz, 1H, NC*H*), the signals of the major rotamer are given;
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 28.4 (3C, OC(*C*H$_3$)$_3$), 39.3 (1C, CH*C*H$_2$CH), 50.5 (1C, *C*HNH$_2$), 52.3 (1C, *C*O$_2$CH$_3$), 54.9 (1C, N*C*H$_2$), 58.4 (1C, N*C*H), 80.5 (1C, O*C*(CH$_3$)$_3$), 153.8 (1C, N*C*O$_2$C(CH$_3$)$_3$), 174.2 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3369, 2976, 2952, 1744, 1691, 1394, 1365, 1201, 1155, 1112, 893, 863, 770;

HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{20}N_2O_4$: 267.1423, found:267.134;

Methyl (2*S*,4*S*)-1-benzoyl-4-[(4-iodobenzyl)amino]pyrrolidine-2-carboxylate (210)



$C_{20}H_{21}IN_2O_3$

M_r = 464.3

4-iodobenzaldehyde (830 mg, 3.58 mmol) was added to an ice-cooled solution of **208** (740 mg, 2.98 mmol) in dichloroethane (30 mL) and the mixture was stirred for 30 min at 0 °C. The reaction mixture was stirred for a further 30 min at ambient temperature. Then, sodium triacetoxyborohydride (1011 mg, 4.77 mmol) was added to the reaction mixture and stirred at ambient temperature for 24 h. Afterwards, water was added to the mixture and extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **210** (428 mg, 0.92 mmol, 31%,) as brown oil.

TLC: R_f = 0.33 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -44.3 (3.5, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.96 – 2.09 (m, 1H, CHC*H*$_2$CH), 2.54 (m, *J* = 14.2/7.6 Hz, 1H, CHC*H*$_2$CH), 3.38 (m, *J* = 11.2/8.7 Hz, 1H, C*H*NH), 3.53 (m, 1H, NC*H*$_2$), 3.68 (m, 1H, NC*H*$_2$), 3.68 (d, 1H, NHC*H*$_2$Ar), 3.74 (d, *J* = 12.8 Hz, 1H, NHC*H*$_2$Ar), 3.79 (s, 3H, CO_2CH_3), 4.66 – 4.72 (m, 1H, NC*H*), 7.05 (m, *J* = 7.9 Hz, 2H, 2″-H$_{4\text{-iodobenzyl}}$, 6″-H$_{4\text{-iodobenzyl}}$), 7.33 – 7.49 (m, 3H, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$), 7.53 (m, *J* = 7.4 Hz, 2H, 2′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), 7.62 (m, *J* = 7.9 Hz, 2H, 3″-H$_{4\text{-iodobenzyl}}$, 5″-H$_{4\text{-iodobenzyl}}$);

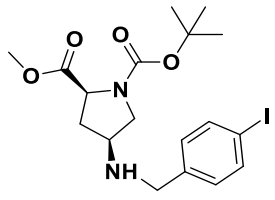
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 34.8 (1C, CH*C*H$_2$CH), 51.4 (NH*C*H$_2$Ar), 52.8 (1C, CO_2*C*H$_3$), 55.2 (1C, N*C*H$_2$), 57.2 (1C, *C*HNH), 58.1 (1C, N*C*H), 93.1 (1C, C-4″$_{4\text{-iodobenzyl}}$), 127.6 (1C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.5 (1C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.4 (1C, C-2″$_{4\text{-iodobenzyl}}$, C-6″$_{4\text{-iodobenzyl}}$), 130.7 (1C, C-4′$_{benzoyl}$), 135.7 (1C, C-1′$_{benzoyl}$), 137.7 (1C, C-1″$_{4\text{-iodobenzyl}}$), 137.8 (1C, C-3″$_{4\text{-iodobenzyl}}$, C-5″$_{4\text{-iodobenzyl}}$), 169.9 (1C, Ar*C*ON), 173.0 (1C, *C*O_2CH_3);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3305, 2948, 2874, 1739, 1624, 1576, 1408, 1360, 1200, 1175, 1028, 1005, 791, 725, 700, 662;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{21}IN_2O_3$: 465.0597, found: 465.066;

HPLC (method 1): t_R = 17.8 min, purity 90.7 %.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-[(4-iodobenzyl)amino]pyrrolidine-1,2-dicarboxylate (211)



$C_{18}H_{25}IN_2O_4$

Mr = 460.3

4-iodobenzaldehyde (2810 mg, 12.11 mmol) was added to an ice-cooled solution of **209** (4226 mg, 17.30 mmol) in dichloroethane (60 mL) and the mixture was stirred for 30 min at 0 °C. The reaction mixture was stirred for a further 30 min at ambient temperature. Then, sodium triacetoxyborohydride (5500 mg, 25.95 mmol) was added to the reaction mixture and stirred at ambient temperature for 24 h. Afterwards, water was added to the mixture and extracted with

dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 3/1 → 0/1) to give **211** (3051 mg, 6.63 mmol, 55%,) as pale-yellow oil.

TLC: R_f = 0.63 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -26.7 (1.8, methanol);

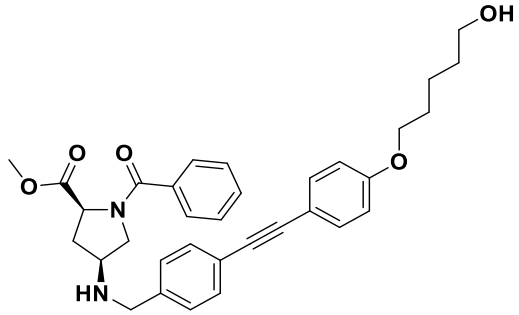
^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.40 (s, 9H, OC(C*H*$_3$)$_3$), 1.94 – 2.02 (m, 1H, CHC*H*$_2$CH), 2.38 (m, 1H, CHC*H*$_2$CH), 3.33 (m, 1H, C*H*NH), 3.39 (dd, *J* = 11.0/4.9 Hz, 1H, NC*H*$_2$), 3.63- 3.75 (m, 1H, NC*H*$_2$), 3.63 – 3.75 (s, 3H, CO_2C*H*$_3$), 3.63 - 3.75 (m, 2H, NHC*H*$_2$Ar), 4.22 (dd, *J* = 8.9/5.2 Hz, 1H, NC*H*), 7.05 (m, 2H, 2′-H$_{4\text{-iodobenzyl}}$, 6′-H$_{4\text{-iodobenzyl}}$), 7.63 (m, 2H, 3′-H$_{4\text{-iodobenzyl}}$, 5′-H$_{4\text{-iodobenzyl}}$), the signals of the major rotamer are given;
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 28.4 (3C, OC(*C*H$_3$)$_3$), 36.5 (1C, CH*C*H$_2$CH), 51.3 (1C, NH*C*H$_2$Ar), 51.9 (1C, N*C*H$_2$), 52.3 (1C, *C*O$_2$CH$_3$), 55.7 (1C, *C*HNH), 58.2 (1C, N*C*H), 80.4 (1C, O*C*(CH$_3$)$_3$), 92.7 (1C, C-4′$_{4\text{-iodobenzyl}}$), 130.3 (2C, C-2′$_{4\text{-iodobenzyl}}$, C-6′$_{4\text{-iodobenzyl}}$), 137.7 (2C, C-3′$_{4\text{-iodobenzyl}}$, C-5′$_{4\text{-iodobenzyl}}$), 139.3 (1C, C-1′$_{4\text{-iodobenzyl}}$), 153.9 (1C, N*C*O$_2$C(CH$_3$)$_3$), 174.0 (1C, *C*O$_2$CH$_3$), the signals of the major rotamer are given;

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2976, 2949, 2873, 1744, 1695, 1481, 1397, 1365, 1256, 1201, 1158, 1108, 1007, 797, 768;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{25}IN_2O_4$: 461.0859, found: 461.091;

HPLC (method 1): t_R = 19.4 min, purity 90.8%.

Methyl (2*S*,4*S*)-1-benzoyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]amino}pyrrolidine-2-carboxylate (212)



$C_{33}H_{36}N_2O_5$

M_r = 540.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (3 mg, 0.002 mmol), copper(I) iodide (2 mg, 0.01 mmol), triethylamine (0.4 mL, 270 mg, 2.67 mmol), and **71** (87 mg, 0.43 mmol) were added to a solution of **210** (124 mg, 0.27 mmol) in dry acetonitrile (20 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **212** (134 mg, 0.25 mmol, 92%) as yellow oil.

TLC: R_f = 0.23 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -24.3 (6.5, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.52 – 1.66 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.80 – 1.85 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.86 – 1.93 (m, 1H, $CHCH_2CH$), 2.59 – 2.67 (m, 1H, $CHCH_2CH$), 3.34 – 3.42 (m, 2H, NCH_2), 3.34 - 3.42 (m, 1H, CHNH), 3.60 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.62 – 3.65 (m, 1H, NCH_2), 3.68 (d, *J* = 13.4 Hz, 1H, $NHCH_2Ar$), 3.79 (d, 1H, $NHCH_2Ar$), 3.79 (s, 3H, CO_2CH_3), 4.02 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.62 (t, *J* = 8.3 Hz, 1H, NCH), 6.88 – 6.96 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.28 – 7.32 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.39 – 7.55 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.39 – 7.55 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$), 7.39 – 7.55 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$);

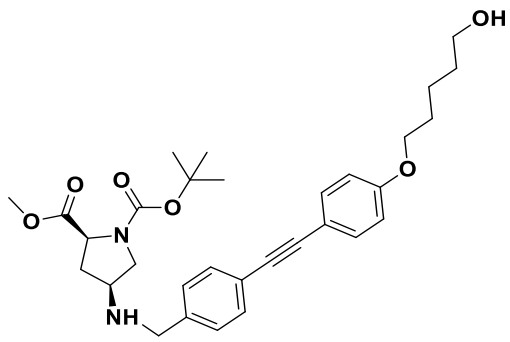
^{13}C NMR (151 MHz, MeOD-d_4) δ [ppm]= 23.6 (1C, $OCH_2CH_2\mathit{C}H_2CH_2CH_2OH$), 30.3 (1C, $OCH_2\mathit{C}H_2CH_2CH_2CH_2OH$), 33.5 (1C, $OCH_2CH_2CH_2\mathit{C}H_2CH_2OH$), 36.0 (1C, $CH\mathit{C}H_2CH$), 52.8 (1C, $NH\mathit{C}H_2Ar$), 53.0 (1C, $CO_2\mathit{C}H_3$), 56.4 (1C, $N\mathit{C}H_2$), 58.1 (1C, *C*HNH), 59.5 (1C, N*C*H), 62.9 (1C, $OCH_2CH_2CH_2CH_2\mathit{C}H_2OH$), 69.2 (1C, $O\mathit{C}H_2CH_2CH_2CH_2CH_2OH$), 88.7 (1C, Ar*C*≡CAr), 90.4 (1C, ArC≡*C*Ar), 115.8 (2C, C-3′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 116.7 (1C, C-1′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 124.1 (1C, C-4″$_{benzyl}$), 128.4 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 129.7 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.7 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 131.9 (1C, C-4′$_{benzoyl}$), 132.5 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 134.1 (2C, (2C, C-2′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 136.9 (1C, C-1′$_{benzoyl}$), 141.0 (1C, C-1″$_{benzyl}$), 160.9 (1C, C-4′″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 172.0 (1*C*, Ar*C*ON), 174.2 (1C, $\mathit{C}O_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3398, 2937, 2866, 1738, 1624, 1601, 1515, 1413, 1244, 1203, 1173, 1018, 830, 727, 701, 540, 524;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{36}N_2O_5$: 541.2624, found: 541.268;

HPLC (method 1): t_R = 20.1 min, purity 97.5%.

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]amino}pyrrolidine-1,2-dicarboxylate (213)



$C_{31}H_{40}N_2O_6$

M_r = 536.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (54mg, 0.05 mmol), copper(I) iodide (27 mg, 0.14 mmol), triethylamine (6.5 mL, 4726 mg, 46.71 mmol), and **71** (1908 mg, 9.34 mmol) were added to a solution of **211** (2150 mg, 4.67 mmol) in dry acetonitrile (30 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V

= 60 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **213** (2342 mg, 4.36 mmol, 94%) as brown oil.

TLC: R_f = 0.30 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -13.7 (3.8, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 1.32 (s, 9H, OC(C*H*$_3$)$_3$), 1.45 (m, 4H, OCH$_2$CH$_2$C*H*$_2$C*H*$_2$CH$_2$OH), 1.68 – 1.81 (m, 2H, OCH$_2$C*H*$_2$CH$_2$CH$_2$CH$_2$OH), 1.68 – 1.81 (m, 1H, CHC*H*$_2$CH), 2.26 – 2.41 (m, 1H, CHC*H*$_2$CH), 2.98 – 3.09 (m, 1H, NC*H*$_2$), 3.41 (m, 2H, OCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$OH), 3.49 – 3.57 (m, 1H, NC*H*$_2$), 3.64 (s, 3H, CO$_2$C*H*$_3$), 3.97 – 4.01 (m, 2H, OC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 4.16 (m, 1H, NC*H*), 4.37 (t, *J* = 5.1 Hz, 1H, OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$O*H*), 6.96 (m, 2H, 3″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.34 (m, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.43 – 7.48 (m, 2H, 2″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.43 – 7.48 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$), the signals for C*H*NH and NHC*H*$_2$Ar cannot be observed in the spectrum, the signals of the major rotamer are given;

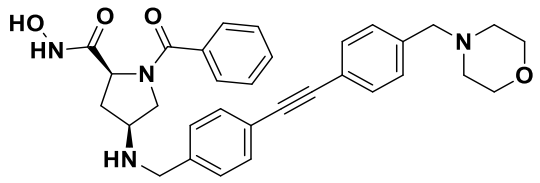
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 22.1 (1C, OCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$OH), 27.8 (3C, OC(*C*H$_3$)$_3$), 28.4 (1C, OCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$OH), 32.1 (1C, OCH$_2$CH$_2$CH$_2$*C*H$_2$CH$_2$OH), 51.7 (1C, CO$_2$*C*H$_3$), 57.6 (1C, N*C*H), 60.6 (1C, OCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$OH), 67.6 (1C, O*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$OH), 78.8 (1C, O*C*(CH$_3$)$_3$), 88.0 (1C, Ar*C*≡CAr), 89.1 (1C, ArC≡*C*Ar), 114.1 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 120.8 (1C, C-4′$_{benzyl}$), 128.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.9 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 132.8 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 140.4 (1C, C-1′$_{benzyl}$), 152.8 (1C, N*C*O$_2$C(CH$_3$)$_3$), 158.9 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 173.1 (1C, *C*O$_2CH_3$), the signals for CH*C*H$_2$CH, *C*HNH, N*C*H$_2$, and NH*C*H$_2$Ar cannot be observed in the spectrum, the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 3264, 2937, 2871, 2837, 1739, 1699, 1519, 1401, 1366, 1245, 1167, 1105, 1083, 1022, 981, 899, 827, 769, 564, 536;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{31}H_{40}N_2O_6$: 537.2886, found: 537.296;

HPLC (method 1): t_R = 21.3 min, purity 87.8%.

(2*S*,4*S*)-1-Benzoyl-*N*-hydroxy-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)amino]pyrrolidine-2-carboxamide (217)



$C_{32}H_{34}N_4O_4$

M_r = 538.6

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (3 mg, 0.003 mmol), copper(I) iodide (2 mg, 0.01 mmol), triethylamine (0.42 mL, 305 mg, 3.02 mmol), and **103** (91 mg, 0.45 mmol) were added to a solution of **210** (140 mg, 0.30 mmol) in dry acetonitrile (15 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 3 cm, h = 15 cm, V = 5 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **214** (76 mg, 0.14 mmol, 47%) as yellow oil.

An aqueous solution of hydroxylamine (50 wt%, 0.5 mL) was added to a solution of **214** (76 mg, 0.14 mmol) in a mixture of THF (1 mL) and isopropanol (1 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the reaction mixture was purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **217** (7 mg, 0.01 mmol, 9%) as colorless solid.

m.p. = 105-106 °C;

TLC: R_f = 0.33 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = +310.5 (1.0, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.70 (m, *J* = 12.4/8.5 Hz, 1H, CHC*H*$_2$CH), 2.30 – 2.41 (m, 1H, CHC*H*$_2$CH), 2.30 – 2.41 (t, 4H, NC*H*$_2$CH$_2$O), 3.17 (m, 1H, C*H*NH), 3.36 (m, 1H, NC*H*$_2$), 3.48 (s, 2H, ArC*H*$_2$), 3.51 – 3.60 (m, 1H, NC*H*$_2$), 3.51 – 3.60 (t, 4H, NCH$_2$C*H*$_2$O), 3.61 – 3.70 (m, 2H, NHC*H*$_2$Ar), 4.29 (t, *J* = 8.2 Hz, 1H, NC*H*), 7.34 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.34 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.42 – 7.53 (m, 5H, 2′-H$_{benzoyl}$, 3′-H$_{benzoyl}$, 4′-H$_{benzoyl}$, 5′-H$_{benzoyl}$, 6′-H$_{benzoyl}$), 7.42 – 7.53 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}}$

(morpholinomethyl)phenyl, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.42 - 7.53 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$), 8.88 (s, 1H, CON*H*OH), 10.71 (s, 1H, CONHO*H*);

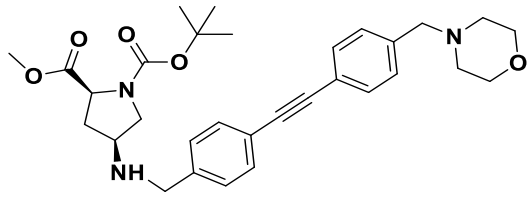
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]= 35.5 (1C, CH*C*H$_2$CH), 50.9 (1C, NH*C*H$_2$Ar), 53.2 (2C, N*C*H$_2$CH$_2$O), 55.4 (1C, N*C*H$_2$), 56.6 (1C, *C*HNH), 57.1 (1C, N*C*H), 62.0 (1C, Ar*C*H$_2$), 66.2 (2C, NCH$_2$*C*H$_2$O), 88.3 (1C, ArC≡*C*Ar), 88.9 (1C, (1C, Ar*C*≡CAr), 120.5 (1C, C-4″$_{benzyl}$), 121.0 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 127.3 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.2 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 128.2 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 129.2 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 130.1 (1C, C-4′$_{benzoyl}$), 131.1 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 131.2 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 136.3 (1C, C-1′$_{benzoyl}$), 138.7 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 141.8 (1C, C-1″$_{benzyl}$), 168.4 (1*C*, Ar*C*ON), 168.7 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3235, 3029, 2915, 2854, 2810, 1620, 1574, 1516, 1448, 1412, 1350, 1114, 1006, 915, 865, 837, 792, 700, 662, 542;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{32}H_{34}N_4O_4$: 539.2580, found: 539.261;

HPLC (method 2): t_R = 11.9 min, purity 99.0%

1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)amino]pyrrolidine-1,2-dicarboxylate (215)



$C_{31}H_{39}N_3O_5$

Mr = 533.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.05 mmol), copper(I) iodide (29 mg, 0.15 mmol), triethylamine (7.10 mL, 5166 mg, 51.05 mmol), and **103** (2055 mg, 10.21 mmol) were added to a solution of **211** (2350 mg, 5.11 mmol) in dry acetonitrile (30 mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **215** (2.2 g, 4.12 mmol, 81%) as yellow oil.

TLC: R_f = 0.20 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -28.0 (2.0, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.42 (s, 9H, OC(C*H*$_3$)$_3$), 1.90 (m, *J* = 12.8/7.1 Hz, 1H, CHC*H*$_2$CH), 2.41 – 2.54 (m, 5H, CHC*H*$_2$CH), 2.41 - 2.54 (t, 4H, NC*H*$_2$CH$_2$O), 3.23 (m, *J* = 14.0/10.6/6.5 Hz, 1H, NC*H*$_2$), 3.35 (m, C*H*NH), 3.55 (s, 2H, ArC*H*$_2$), 3.70 (t, 4H, NCH$_2$C*H*$_2$O), 3.70 (m, 1H, NC*H*$_2$), 3.72 – 3.79 (s, 3H, CO$_2$C*H*$_3$), 3.72 – 3.79 (m, 2H, NHC*H*$_2$Ar), 4.27 (dd, *J* = 8.4/6.8 Hz, 1H, NC*H*), 7.37 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.37 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.49 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6″-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.49 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$), the signals of the major rotamer are given;

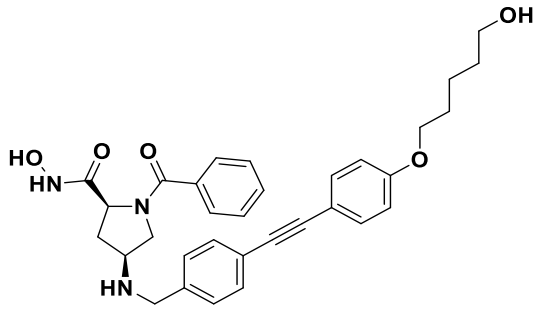
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 28.6 (3C, OC(*C*H$_3$)$_3$), 37.2 (1C, CH*C*H$_2$CH), 52.7 (1C, NHC*H*$_2$Ar), 52.8 (1C, CO$_2$*C*H$_3$), 53.4 (1C, N*C*H$_2$), 54.8 (2C, N*C*H$_2$CH$_2$O), 56.9 (1C, *C*HNH), 59.6 (1C, N*C*H), 64.1 (1C, Ar*C*H$_2$), 67.9 (2C, NCH$_2$*C*H$_2$O), 81.8 (1C, O*C*(CH$_3$)$_3$), 90.1 (1C, ArC≡*C*Ar), 90.2 (1C, Ar*C*≡CAr), 123.5 (1C, C-4′$_{benzyl}$), 123.7 (1C, C-1″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 129.7 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.8 (1C, C-3″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-2″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.7 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 139.1 (1C, C-4″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 141.5 (1C, C-1′$_{benzyl}$), 155.7 (1C, N*C*O$_2$C(CH$_3$)$_3$), 175.4 (1C, *C*O$_2CH_3$), the signals of the major rotamer are given;

IR (neat): ṽ [cm^{-1}] = 2951, 2856, 2811, 1744, 1694, 1396, 1365, 1201, 1157, 1113, 1033, 1007, 865, 833, 794, 769, 542;

HRMS (*m/z*): [M+H]$^+$ calcd for C$_{31}$H$_{39}$N$_3$O$_5$: 534.2890, found:534.298;

HPLC (method 1): t_R = 16.5 min, purity 96.8%.

(2*S*,4*S*)-1-Benzoyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]amino}pyrrolidine-2-carboxamide (216)



$C_{32}H_{35}N_3O_5$

M_r = 541.6

An aqueous solution of hydroxylamine (50 wt%, 6.7 mL) was added to a solution of **212** (276 mg, 0.51mmol) in a mixture of THF (1 mL) and isopropanol (1 mL) and the mixture was stirred at ambient temperature overnight. Then, the reaction mixture was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, dichloromethane/methanol, 1/0 → 9/1) to give the product (**216**) which was further purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **216** (132 mg, 0.24 mmol, 48%) as colorless solid.

m.p. = 102-103 °C;

TLC: R_f = 0.38 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -5.5 (1.7, methanol);

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]= 1.46 (m, *J* = 22.2/12.4/7.4/5.3/2.1 Hz, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.71 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 171 (m, 1H, $CHCH_2CH$), 2.36 (m, *J* = 14.4/8.1/7.7/4.0 Hz, 1H, $CHCH_2CH$), 3.14 (m, *J* = 7.1 Hz, 1H, CHNH), 3.35 (m, 1H, NCH_2), 3.41 (m, *J* = 6.2 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.53 (dd, *J* = 10.1/6.4 Hz, 1H, NCH_2), 3.65 (m, *J* = 14.1 Hz, 2H, $NHCH_2Ar$), 3.99 (t, *J* = 6.5 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 4.30 (t, *J* = 8.2 Hz, 1H, NCH), 4.39 (t, 1H, $OCH_2CH_2CH_2CH_2CH_2OH$), 6.92 – 7.00 (m, 2H, 3‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.31 (m, *J* = 7.9 Hz, 2H, 2″-H_{benzyl}, 6″-H_{benzyl}), 7.41 (m, *J* = 8.0 Hz, 2H, 3″-H_{benzyl}, 5″-H_{benzyl}), 7.43 – 7.49 (m, 2H, 2‴-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-$H_{4\text{-}(\{4\text{-}[(5\text{-}}$

hydroxypentyl)oxy]phenyl), 7.43 – 7.49 (m, 3H, 3′-$H_{benzoyl}$, 4′-$H_{benzoyl}$, 5′-$H_{benzoyl}$), 7.50 – 7.55 (m, 2H, 2′-$H_{benzoyl}$, 6′-$H_{benzoyl}$);

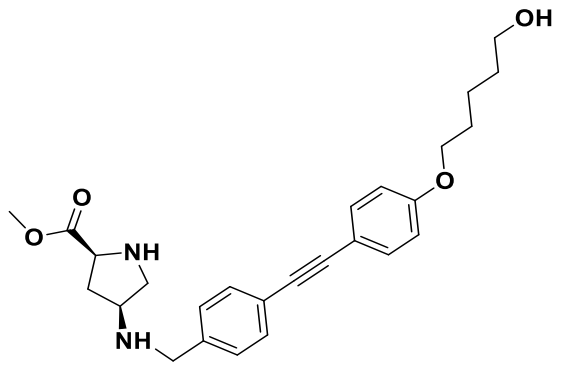
^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 22.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 28.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 35.5 (1C, $CHCH_2CH$), 50.9 (1C, $NHCH_2Ar$), 55.4 (1C, NCH_2), 56.6 (1C, *C*HNH), 57.1 (1C, NCH), 60.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 67.7 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 88.0 (1C, Ar*C*≡CAr), 89.1 (1C, ArC≡*C*Ar), 114.2 (1C, C-1′′′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 114.8 (2C, C-3′′′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5′′′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 120.8 (1C, C-4′′$_{benzyl}$), 127.3 (2C, C-2′$_{benzoyl}$, C-6′$_{benzoyl}$), 128.1 (2C, C-2′′$_{benzyl}$, C-6′′$_{benzyl}$), 128.2 (2C, C-3′$_{benzoyl}$, C-5′$_{benzoyl}$), 130.0 (1C, C-4′$_{benzoyl}$), 130.9 (2C, C-3′′$_{benzyl}$, C-5′′$_{benzyl}$), 132.9 (2C, (2C, C-2′′′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6′′′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 136.3 (1C, C-1′$_{benzoyl}$), 141.4 (1C, C-1′′$_{benzyl}$), 158.9 (1C, C-4′′′$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 168.4 (1*C*, Ar*C*ON), 168.7 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3211, 2936, 2867, 1668, 1602, 1573, 1516, 1448, 1413, 1284, 1246, 1050, 1028, 828, 703, 529;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{35}N_3O_5$: 542.2577, found:542.266;

HPLC (method 2): t_R = 13.7 min, purity 100%.

Methyl (2*S*,4*S*)-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]amino}pyrrolidine-2-carboxylate (218)



$C_{26}H_{32}N_2O_4$

M_r = 436.6

Zinc bromide (2351 mg, 10.44 mmol) was added to a solution of **213** (2187 mg, 4.08 mmol) in dichloromethane (40 mL) and stirred for 24 h at ambient temperature. Then, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were

dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **218** (520 mg, 1.19 mmol, 29%) as brown oil.

TLC: R_f = 0.25 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -18.3 (4.1, methanol);

^{1}H NMR (600 MHz, DMSO-*d_6*) δ [ppm]= 1.39 – 1.51 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.72 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.86 – 1.91 (m, 1H, $CHCH_2CH$), 2.22 – 2.29 (m, 1H, $CHCH_2CH$), 2.91 – 3.00 (m, 2H, $NHCH_2$), 3.28 (m, 1H, CHNH), 3.41 (t, *J* = 6.2 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.66 (s, 3H, CO_2CH_3), 3.76 (m, 2H, $NHCH_2Ar$), 3.93 (dd, *J* = 8.8/6.0 Hz, 1H, NHCH), 3.99 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 6.91 – 6.99 (m, 2H, 3″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.37 (m, 2H, 2′-$H_{benzyl}$, 6′-$H_{benzyl}$), 7.42 – 7.52 (m, 2H, 2″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6″-$H_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 7.42 – 7.52 (m, 2H, 3′-H_{benzyl}, 5′-H_{benzyl});

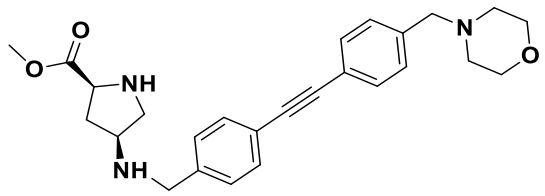
^{13}C NMR (151 MHz, DMSO-*d_6*) δ [ppm]= 22.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 28.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 34.8 (1C, $CHCH_2CH$), 50.3 (1C, $NHCH_2Ar$), 51.1 (1C, $NHCH_2$), 52.1 (1C, CO_2CH_3), 56.9 (1C, CHNH), 58.1 (1C, NHCH), 60.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 67.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 87.9 (1C, ArC≡CAr), 89.4 (1C, ArC≡CAr), 114.0 (1C, C-1″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 114.8 (2C, C-3″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 121.3 (1C, C-4′$_{benzyl}$), 128.6 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 131.0 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 132.9 (2C, C-2″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 159.0 (1C, C-4″$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl})}$, 173.0 (1C, CO_2CH_3), the signal for C-1′$_{benzyl}$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 3364, 2927, 2859, 1731, 1602, 1517, 1443, 1285, 1246, 1174, 1107, 1021, 829, 529;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{32}N_2O_4$: 437.2362, found: 437.239;

HPLC (method 1): t_R = 16.5 min, purity 66.8%.

Methyl (2*S*,4*S*)-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)amino]pyrrolidine-2-carboxylate (219)



$C_{26}H_{31}N_3O_3$

M_r = 433.6

Zinc bromide (2026 mg, 8.99 mmol) was added to a solution of **215** (1.6 g, 3.00 mmol) in dichloromethane (30 mL) and stirred for 24 h at ambient temperature. Then, water was added and the mixture was extracted with dichloromethane (3x). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (Ø = 6 cm, h = 15 cm, V = 60 mL, dichloromethane/methanol, 1/0 → 9/1)) to give **219** (794 mg, 1.83 mmol, 61%) as yellow oil.

TLC: R_f = 0.25 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -7.6 (4, methanol);

^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ [ppm]= 1.90 – 1.99 (m, 1H, CHC*H*$_2$CH), 2.27 (m, *J* = 13.2/8.9/6.4 Hz, 1H, CHC*H*$_2$CH), 2.35 (t, *J* = 4.6 Hz, 4H, NC*H*$_2$CH$_2$O), 2.99 – 3.03 (m, 2H, NHC*H*$_2$), 3.32 (m, *J* = 5.1 Hz, 1H, C*H*NH), 3.49 (s, 2H, ArC*H*$_2$), 3.57 (t, *J* = 4.6 Hz, 4H, NCH$_2$C*H*$_2$O), 3.67 (s, 3H, CO$_2$C*H*$_3$), 3.78 (s, 2H, NHC*H*$_2$Ar), 3.98 (dd, *J* = 8.8/5.9 Hz, 1H, NHC*H*), 7.34 – 7.37 (m, 2H, 3″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, 5″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 7.39 – 7.42 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.50 (m, 2H, 2″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, 6″-H$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 7.50 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$);

^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ [ppm]= 34.5 (1C, CH*C*H$_2$CH), 50.1 (1C, NHC*H*$_2$C$_6$H$_4$), 50.9 (1C, NH*C*H$_2$), 52.2 (1C, CO$_2$*C*H$_3$), 53.1 (2C, N*C*H$_2$CH$_2$O), 56.7 (1C, *C*HNH), 58.1 (1C, NH*C*H), 62.0 (1C, Ar*C*H$_2$), 66.2 (2C, NCH$_2$*C*H$_2$O), 89.1 (1C, ArC≡*C*Ar), 89.2 (1C, Ar*C*≡CAr), 120.8 (1C, C-4′$_{benzyl}$), 121.0 (1C, C-1″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 128.8 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 129.2 (1C, C-3″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-5″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 131.2 (2C, C-2″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$, C-6″$_{4\text{-}\{[4\text{-(morpholinomethyl)phenyl}}$), 131.2 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 138.9 (1C, C-

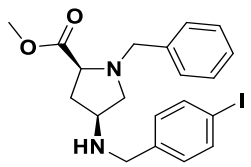
4″$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 172.5 (1C, *C*$O_2CH_3$), the signal for C-1′ $_{benzyl}$ cannot be observed in the spectrum;

IR (neat): ṽ [cm^{-1}] = 2951, 2923, 2853, 2805, 1734, 1441, 1348, 1333, 1231, 1113, 1068, 1006, 864, 864, 823, 794, 543;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{26}H_{31}N_3O_3$: 434.2365, found: 434.241;

HPLC (method 1): t_R = 12.0 min, purity 72.9%.

Methyl (2*S*,4*S*)-1-benzyl-4-[(4-iodobenzyl) amino]pyrrolidine-2-carboxylate (223)



$C_{20}H_{23}IN_2O_2$

Mr = 450.3

Triphenylphosphine (563 mg, 2.15 mmol) was added to **171** (559 mg, 2.15 mmol) in dry THF (20 ml) and stirred for 3 h at ambient temperature. Then, the reaction mixture was refluxed for 15 min and allowed to cool to ambient temperature, whereupon 4-iodobenzaldehyde (498 mg, 2.15 mmol) was added and refluxed for 3 h. Afterwards, the mixture was cooled to 0 °C and sodium triacetoxyborohydride (455 mg, 2.15 mmol) was added and stirred for 30 min at 0°C. After finally warming to ambient temperature and stirring for 18 h, the solvent was removed *in vacuo*. The residue obtained was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/0 → 0/1) to give a crude product which was further purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **223** (467 mg, 1.04 mmol, 48%) as yellow oil.

TLC: R_f = 0.38 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -22.7 (8.5, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.89 (m, *J* = 13.7/6.0/3.4/1.0 Hz, 1H, CHC*H*$_2$CH), 2.34 (m, *J* = 13.7/9.1/7.5 Hz, 1H, CHC*H*$_2$CH), 2.52 (dd, *J* = 9.8/5.9 Hz, 1H, NC*H*$_2$), 2.96 (m, *J* = 9.7/2.6/1.0 Hz, 1H, CHC*H*$_2$CH), 3.25 (m, 1H, C*H*NH), 3.25 (m, 1H, NC*H*), 3.54 (d, *J* = 13.0 Hz, 1H, C*H*$_2$Ar), 3.60 (s, 3H, CO_2CH_3), 3.62 – 3.68 (m, 2H, NHC*H*$_2$Ar), 3.83 (d, *J* = 13.0 Hz, 1H, C*H*$_2$Ar), 7.02 – 7.07 (m, 2H, 2″-$H_{4\text{-iodobenzyl}}$, 6″-$H_{4\text{-iodobenzyl}}$), 7.19 – 7.23 (m, 1H, 4′-H_{benzyl}), 7.26 (m, 4H, 2′-H_{benzyl}, 3′-H_{benzyl}, 5′-H_{benzyl}, 6′-H_{benzyl}), 7.57 – 7.60 (m, 2H, 3″-$H_{4\text{-iodobenzyl}}$, 5″-$H_{4\text{-iodobenzyl}}$);

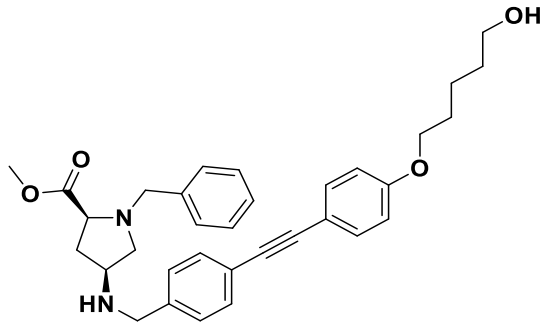
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 36.3 (1C, CH*C*H$_2$CH), 51.1 (1C, NH*C*H$_2$Ar), 52.1 (1C, CO_2CH_3), 56.0 (1C, *C*HNH), 58.3 (1C, *C*H$_2$Ar), 58.4 (1C, N*C*H$_2$), 64.1 (1C, N*C*H), 92.6 (1C, C-4″$_{benzyl}$), 127.4 (1C, C-4′$_{benzyl}$), 128.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.2 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.6 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 137. 7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 138.2 (1C, C-1′$_{benzyl}$), 139.3 (1C, C-1″$_{benzyl}$), 174.8 (1C, *C*O_2CH_3);

IR (neat): ṽ [cm^{-1}] = 2947, 2800, 1731, 1667, 1482, 1453, 1435, 1197, 1172, 1006, 742, 698, 470;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{23}IN_2O_2$: 451.0804, found: 451.087;

HPLC (method 1): t_R = 20.2 min, purity 85.6%.

Methyl (2*S*,4*S*)-1-benzyl-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]amino}pyrrolidine-2-carboxylate (224)



$C_{33}H_{38}N_2O_4$

M_r = 526.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.01 mmol), copper(I) iodide (5 mg, 0.03 mmol), triethylamine (1.2 mL, 872 mg, 8.62 mmol), and **71** (376 mg, 1.84 mmol) were added to a solution of **223** (388 mg, 0.86 mmol) in dry acetonitrile (15 mL) and

the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 1/1 → 0/1) to give **224** (255 mg, 0.48 mmol, 56%) as sticky brown oil.

TLC: R_f = 0.28 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -7.6 (1.1, methanol);

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]= 1.51 (m, *J* = 14.7/9.4/6.4/3.3 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.61 (m, *J* = 8.5/6.3 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.75 – 1.82 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.95 (m, 1H, $CHCH_2CH$), 2.36 (m, *J* = 13.8/9.1/7.4 Hz, 1H, $CHCH_2CH$), 2.56 (dd, *J* = 10.0/5.8 Hz, 1H, NCH_2), 3.01 – 3.06 (m, 1H, NCH_2), 3.27 (dd, *J* = 9.1/5.7 Hz, 1H, NCH), 3.32 (m, *J* = 4.6/3.0 Hz, 1H, CHNH), 3.57 (d, *J* = 13.1 Hz, 1H, CH_2Ar), 3.59 (s, 3H, CO_2CH_3), 3.64 (t, *J* = 6.5 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.72 – 3.78 (m, 2H, $NHCH_2Ar$), 3.82 (d, *J* = 13.0 Hz, 1H, CH_2Ar), 3.94 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 6.79 – 6.85 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.19 – 7.31 (m, 5H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 4′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.19 - 7.31 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.41 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.41 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$);

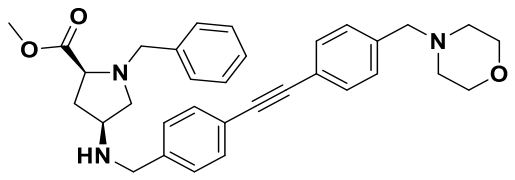
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]= 22.5 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 29.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 32.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 36.0 (1C, $CHCH_2CH$), 51.2 (1C, $NHCH_2Ar$), 52.2 (1C, CO_2CH_3), 56.2 (1C, CHNH), 58.1 (1C, NCH_2), 58.2 (1C, CH_2Ar), 63.0 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 63.9 (1C, NCH), 68.0 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 88.1 (1C, ArC≡CAr), 89.7 (1C, ArC≡CAr), 114.7 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 115.4 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 122.9 (1C, C-4″$_{benzyl}$), 127.5 (1C, C-4′$_{benzyl}$), 128.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 128.7 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 129.2 (2C, C-2′$_{benzyl}$, C-6$_{benzyl}$), 131.8 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 133.2 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 137.7 (1C, C-1′$_{benzyl}$), 138.0 (1C, C-1″$_{benzyl}$), 159.3 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 175.0 (1C, CO_2CH_3);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3311, 2937, 2863, 1734, 1602, 1515, 1470, 1454, 1283, 1244, 1200, 1172, 1057, 1028, 829, 744, 700, 538;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{38}N_2O_4$: 527.2832, found:527.289;

HPLC (method 1): t_R = 22.0 min, purity 90.1%

Methyl (2*S*,4*S*)-1-benzyl-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)amino]pyrrolidine-2-carboxylate (225)



$C_{33}H_{37}N_3O_3$

M_r = 523.7

Under N_2 atmosphere, tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.01 mmol), copper(I) iodide (6 mg, 0.03 mmol), triethylamine (1.52 mL, 1112 mg, 10.99 mm), and **103** (442 mg, 2.20 mmol) were added to a solution of **223** (495 mg, 1.10 mmol) in dry acetonitrile (20mL) and the mixture was stirred for 18 h at ambient temperature. Then, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, petroleum ether/ethyl acetate, 3/1 → 0/1) to give **225** (533 mg, 1.02 mmol, 93%) as brown oil

TLC: R_f = 0.13 (ethyl acetate);

Specific rotation: $[\alpha]_D^{20}$ = -7.6 (2.5, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.85 – 1.92 (m, 1H, CHC*H*$_2$CH), 2.41 – 2.50 (m, 1H, CHC*H*$_2$CH), 2.41 – 2.50 (t, 4H, NC*H*$_2$CH$_2$O), 2.57 (dd, *J* = 10.0/6.3 Hz, 1H, NC*H*$_2$), 2.98 (m, *J* = 10.0/2.7/0.9 Hz, 1H, NC*H*$_2$), 3.26 – 3.31 (m, 1H, NC*H*), 3.26 – 3.31 (m, 1H, C*H*NH), 3.56 (d, 1H, C*H*$_2$Ar), 3.56 (s, 2H, ArC*H*$_2$), 3.64 (s, 3H, CO$_2$C*H*$_3$), 3.71 (t, 4H, NCH$_2$C*H*$_2$O), 3.71 (m, 2H, NHC*H*$_2$Ar), 3.87 (d, *J* = 12.8 Hz, 1H, C*H*$_2$Ar), 7.23 – 7.27 (m, 1H, 4′-H$_{benzyl}$), 7.29 – 7.35 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.29 – 7.35 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.36 – 7.39 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.45 – 7.51 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$), 7.45 – 7.51 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$);

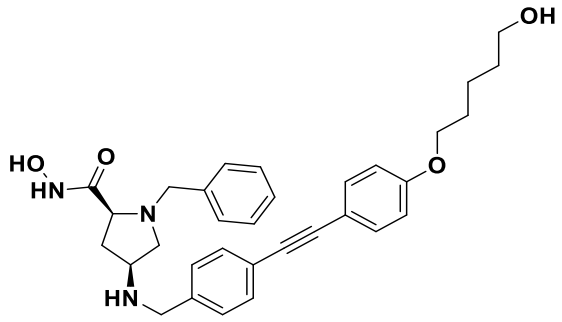
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 37.1 (1C, CH*C*H$_2$CH), 52.2 (1C, NH*C*H$_2$Ar), 52.5 (1C, CO$_2$*C*H$_3$), 54.8 (2C, N*C*H$_2$CH$_2$O), 57.1 (1C, C*H*NH), 59.3 (1C, N*C*H$_2$), 59.6 (1C, C*H*$_2$Ar), 64.1 (1C, Ar$_4$*C*H$_2$), 65.6 (1C, N*C*H), 67.9 (2C, NCH$_2$*C*H$_2$O), 90.2 (1C, Ar*C*≡CAr), 90.1 (1C, ArC≡*C*Ar), 123.5 (1C, C-4″$_{benzyl}$), 123.7 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 128.5 (1C, C-4′$_{benzyl}$), 129.4 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.9 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.4 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 130.8 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 139.1 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 139.5 (1C, C-1′$_{benzyl}$), 141.2 (1C, C-1″$_{benzyl}$), 176.2 (1C, *C*O$_2CH_3$);

IR (neat): ṽ [cm^{-1}] = 3028, 2950, 2851, 2804, 1732, 1453, 1260, 1198, 1172, 1114, 1070, 1007, 866, 818, 795, 745, 699, 542;

HRMS (*m/z*): [M+H]$^+$ calcd for $C_{33}H_{37}N_3O_3$: 524.2835, found: 524.289;

HPLC (method 1): t_R = 16.9 min, purity 97.5%.

(2*S*,4*S*)-1-Benzyl-*N*-hydroxy-4-{[4-({4-[(5-hydroxypentyl)oxy]phenyl}ethynyl)benzyl]amino}pyrrolidine-2-carboxamide (226)



$C_{32}H_{37}N_3O_4$

M_r = 527.7

An aqueous solution of hydroxylamine (50 wt%, 11 mL) was added to a solution of **224** (227 mg, 0.43 mmol) in a mixture of THF (4 mL) and isopropanol (4 mL) and the mixture was stirred at ambient temperature overnight. Then, the reaction mixture was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, dichloromethane/methanol, 1/0 → 9/1) to give the product (**226**) which was further purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-

HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **226** (86 mg, 0.16 mmol, 38%) as colorless solid.

m.p. = 85-87 °C;

TLC: R_f = 0.38 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -6.2 (3.9, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.48 – 1.65 (m, 4H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.74 – 1.85 (m, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 1.74 - 1.85 (m, 1H, $CHCH_2CH$), 2.35 – 2.45 (m, 1H, $CHCH_2CH$), 2.35 – 2.45 (m, 1H, NCH_2), 2.87 – 2.94 (m, 1H, NCH_2), 3.09 (dd, *J* = 9.0/6.7 Hz, 1H, NC*H*), 3.22 (m, *J* = 7.7/5.8/3.4/2.2 Hz, 1H, C*H*NH), 3.35 (d, *J* = 13.0 Hz, 1H, CH_2Ar), 3.56 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 3.62 (d, *J* = 13.1 Hz, 1H, $NHCH_2Ar$), 3.68 (d, *J* = 13.1 Hz, 1H, $NHCH_2Ar$), 3.88 (d, *J* = 13.0 Hz, 1H, CH_2Ar), 3.97 (t, *J* = 6.4 Hz, 2H, $OCH_2CH_2CH_2CH_2CH_2OH$), 6.85 – 6.92 (m, 2H, 3‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, 5‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.20 – 7.24 (m, 1H, 4′-H$_{benzyl}$), 7.26 – 7.31 (m, 2H, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$), 7.26 – 7.31 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.31 – 7.34 (m, 2H, 2′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.37 – 7.42 (m, 2H, 2‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl\ phenyl}$, 6‴-H$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 7.37 – 7.42 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$);

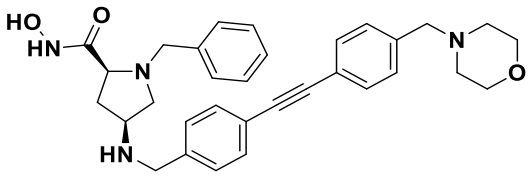
^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 23.6 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 30.2 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 33.4 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 37.5 (1C, $CHCH_2CH$), 52.3 (1C, $NHCH_2Ar$), 57.1 (1C, *C*HNH), 58.9 (1C, NCH_2), 59.5 (1C, CH_2Ar), 62.9 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 66.4 (1C, N*C*H), 69.1 (1C, $OCH_2CH_2CH_2CH_2CH_2OH$), 88.7 (1C, Ar*C*≡CAr), 90.4 (1C, ArC≡*C*Ar), 115.8 (2C, C-3‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-5‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 116.5 (1C, C-1‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 124.0 (1C, C-4″$_{benzyl}$), 128.4 (1C, C-4′$_{benzyl}$), 129.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 129.9 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 130.1 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 132.5 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 134.1 (2C, C-2‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$, C-6‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 139.5 (1C, C-1′$_{benzyl}$), 140.4 (1C, C-1″$_{benzyl}$), 160.8 (1C, C-4‴$_{4\text{-}(\{4\text{-}[(5\text{-hydroxypentyl})oxy]phenyl}$), 173.2 (1C, *C*ONHOH);

IR (neat): ṽ [cm^{-1}] = 3201, 2934, 2863, 1653, 1602, 1516, 1470, 1453, 1284, 1246, 1056, 1029, 829, 740, 700, 538;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{37}N_3O_4$: 528.2784, found:528.284;

HPLC (method 2): t_R = 14.1 min, purity 99.3%.

(2*S*,4*S*)-1-Benzyl-*N*-hydroxy-4-[(4-{[4-(morpholinomethyl)phenyl]ethynyl}benzyl)amino]pyrrolidine-2-carboxamide (227)



$C_{32}H_{36}N_4O_3$

M_r = 524.7

An aqueous solution of hydroxylamine (50 wt%, 11 mL) was added to a solution of **225** (215 mg, 0.41 mmol) in a mixture of THF (5 mL) and isopropanol (5 mL) and the mixture was stirred at ambient temperature overnight. Then, the reaction mixture was purified by flash column chromatography (Ø = 4 cm, h = 15 cm, V = 20 mL, dichloromethane/methanol, 1/0 → 9/1) to give the product (**227**) which was further purified by automatic flash column chromatography using a Biotage® Isolera™ One system (0% → 100% MeCN in H_2O, Biotage® SNAP KP-C18-HS 30 g). Fractions containing the desired product were combined and subjected to lyophilization to give **227** (65 mg, 0.12 mmol, 30%) as colorless solid.

m.p. = 95-97 °C;

TLC: R_f = 0.35 (dichloromethane/methanol, 9/1);

Specific rotation: $[\alpha]_D^{20}$ = -6.4 (2.1, methanol);

^{1}H NMR (600 MHz, MeOD-*d*$_4$) δ [ppm]= 1.82 (m, *J* = 13.6/6.3/3.3 Hz, 1H, CHC*H*$_2$CH), 2.35 – 2.48 (m, 1H, CHC*H*$_2$CH), 2.35 – 2.48 (m, 4H, NC*H*$_2$CH$_2$O), 2.35 – 2.48 (m, 1H, NC*H*$_2$), 2.90 (d, 1H, NC*H*$_2$), 3.09 (dd, *J* = 9.0/6.6 Hz, 1H, NC*H*), 3.18 – 3.24 (m, 1H, C*H*NH), 3.34 (d, 1H, C*H*$_2$Ar), 3.49 (s, 2H, ArC*H*$_2$), 3.59 – 3.72 (m, 4H, NCH$_2$C*H*$_2$O), 3.59 – 3.72 (m, 2H, NHC*H*$_2$Ar), 3.87 (d, *J* = 13.0 Hz, 1H, C*H*$_2$Ar), 7.19 – 7.23 (m, 1H, 4′-H$_{benzyl}$), 7.24 – 7.35 (m, 4H, 2′-H$_{benzyl}$, 3′-H$_{benzyl}$, 5′-H$_{benzyl}$, 6′-H$_{benzyl}$), 7.24 – 7.35 (m, 2H, 3‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 5‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.24 – 7.35 (m, 2H, 2″-H$_{benzyl}$, 6″-H$_{benzyl}$), 7.41 – 7.48 (m, 2H, 2‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, 6‴-H$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 7.41 – 7.48 (m, 2H, 3″-H$_{benzyl}$, 5″-H$_{benzyl}$);

^{13}C NMR (151 MHz, MeOD-*d*$_4$) δ [ppm]= 37.5 (1C, CH*C*H$_2$CH), 52.3 (1C, NH*C*H$_2$Ar), 54.7 (2C, N*C*H$_2$CH$_2$O), 57.1 (1C, C*H*NH), 58.9 (1C, N*C*H$_2$), 59.5 (1C, C*H*$_2$Ar), 64.0 (1C, Ar*C*H$_2$),

66.4 (1C, N*C*H), 67.8 (2C, NCH_2CH_2O), 90.2 (1C, Ar*C*≡CAr), 90.2 (1C, ArC≡*C*Ar), 123.5 (1C, C-4″$_{benzyl}$), 123.7 (1C, C-1‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 128.4 (1C, C-4′$_{benzyl}$), 129.5 (2C, C-3′$_{benzyl}$, C-5′$_{benzyl}$), 130.0 (2C, C-2′$_{benzyl}$, C-6′$_{benzyl}$), 130.1 (2C, C-2″$_{benzyl}$, C-6″$_{benzyl}$), 130.8 (2C, C-3‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-5‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.6 (2C, C-2‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$, C-6‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 132.7 (2C, C-3″$_{benzyl}$, C-5″$_{benzyl}$), 139.1 (1C, C-4‴$_{4\text{-}\{[4\text{-}(morpholinomethyl)phenyl}$), 139.5 (1C, C-1′$_{benzyl}$), 140.9 (1C, C-1″$_{benzyl}$), 173.2 (1C, *C*ONHOH);

IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3236, 2913, 2852, 2806, 1659, 1516, 1453, 1114, 1070, 1006, 865, 822, 742, 700, 543;

HRMS (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{36}N_4O_3$: 525.278, found:525.283;

HPLC (method 2): t_R = 12.4 min, purity 95.4%.

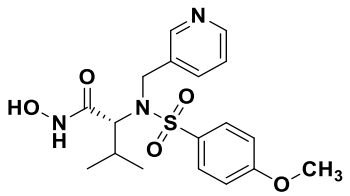
6.3 Biological evaluation

6.3.1 MMP-13 inhibitors

6.3.1.1 *In vitro* MMP inhibition assay

The synthetic fluorometric substrate (7-methoxycoumarin-4-yl)acetyl-Pro-Leu-Gly-Leu-[3-(2,4-dinitrophenyl)-L-2,3-diamino-propionyl]-Ala-Arg-NH_2 (Mca-PLGL-Dpa-AR-NH_2 Fluorogenic MMP Substrate, R & D Systems, Minneapolis, MN, USA) was used to assay activated MMP-2, MMP-8, MMP-9, and MMP-13 as described previously.[19,188,189] The inhibition of human active MMP-2, MMP-8, MMP-9, and MMP-13 was assayed by preincubating MMP-2, MMP-8, MMP-9 or MMP-13 (each at 2 nM) and inhibitor compounds at varying concentrations (10 pM – 1 mM) in 50 mM Tris·HCl, pH 7.5, containing 0.2 M NaCl, 5 mM $CaCl_2$, 20 μM $ZnSO_4$, and 0.05% Brij 35 at 37 °C for 30 min. An aliquot of substrate (10 μL of a 50 μM solution) was then added to 90 μL of the preincubated MMP/inhibitor mixture, and the fluorescence was determined at 37 °C by following product release over time. The changes in fluorescence were monitored using a Fusion Universal Microplate Analyzer (Tristar^2 Multimode Reader LB 942, Berthold Technologies, Bad Wildbad, Germany) with excitation and emission wavelengths set to 330 nm and 390 nm, respectively. Reaction rates were measured from the initial 10 min of the reaction profile where product release was linear with time and plotted as a function of inhibitor dose. From the resulting inhibition curves, the IC_{50} values for each inhibitor were calculated by non-linear regression analysis, performed using the Grace 5.1.25 software (Linux).

The potent MMP inhibitor CGS27023A (**228**) (Figure 24), possessing proven *in vivo* efficacy[190,191], was used as positive control.



CGS 27023A (228)

Figure 28. Chemical structure of CGS 27023A used as a positive control.

6.3.2 LpxC inhibitors

6.3.2.1 Disc diffusion assay

Liquid cultures of *E. coli* BL21(DE3) and the defective strain *E. coli* D22[192] were grown overnight in lysogeny broth (LB)[193] at 37 °C, 200 rpm. Then, 150 µL of an overnight cell suspension was spread evenly onto LB agar plates. 0.15 µmol of each compound (dissolved in 10 µL or 15 µL DMSO) was applied onto circular filter paper (Ø = 6 mm, GE Healthcare). Pure DMSO, serving as a negative control and CHIR-090,[194] serving as a positive control were also spotted. The agar plates were incubated overnight at 37 °C and the diameter of the zone of growth inhibition was measured for each compound. Each assay was performed at least three times on separate days.

6.3.2.2 Minimum Inhibitory concentration (MIC)

The MIC values of the compounds were determined by means of the microdilution method using 96-well plates. To determine the MIC values against *E. coli* BL21(DE3) and *E. coli* D22, the bacteria were grown overnight in LB at 37 °C and 200 rpm. The overnight suspension was diluted 1:1000 in fresh LB. 10 µL of a twofold dilution series of the compounds in DMSO and 90 µL of LB were dispensed to each well of a 96-well plate. Then, 100 µL of the inoculated medium was added, resulting in $5 \cdot 10^5$ cfu mL^{-1}, 5% DMSO, and a final concentration range of the test compounds between 64 µg mL^{-1} and 0.031 µg mL^{-1}. The plates were incubated for 20 h at 37 °C. The MIC was defined as the lowest concentration of the compounds that prevented visible growth after incubation. Each assay was performed at least three times on separate days.

6.3.2.3 LpxC enzyme assay

6.3.2.3.1 Protein expression

The expression of LpxCC63A was performed essentially as previously described.[144,195] The C63A mutation lowers the undesired influence of the Zn^{2+}-concentration on the enzymatic activity. The plasmid pETEcLpxCC63A, which was kindly provided by CAROL FIERKE,[196] was transformed into *E. coli* BL21(DE3) cells. The overnight culture was prepared by growing a single colony in 50 mL LB supplemented with carbenicillin (0.1 mM) and glucose (0.5%) at 37 °C and 200 rpm. The next day, 2 mL of this culture was used to inoculate 400 mL of fresh LB, containing carbenicillin (0.1 mM) and glucose (0.5%). After reaching an OD_{600} of 0.6–0.8, the culture was cooled to 30 °C and induced with IPTG (1 mM) and $ZnCl_2$ (100 µM). After being

grown for additional 4 h at 30 °C, the cells were cooled on ice for 20 min and then harvested by centrifugation (4 °C, 5000 × g, 15 min) and stored at -20 °C.

6.3.2.3.2 Protein purification

Unless otherwise specified, all steps were carried out at 4 °C. The harvested cells were thawed on ice and resuspended in 50 mL anion exchange (AEX)-buffer (25 mM Hepes, 2 mM DTT, pH = 7.0), containing benzamidine (15 μg mL^{-1}) and PMSF (1 mM) as protease inhibitors. Afterwards, the cells were disrupted by sonication (5× 40 s). Then, the cellular debris were removed by centrifugation (4 °C, 5000 × g, 90 min) and the supernatant was filtered (0.2 μm). The cleared lysate was loaded onto a 20 mL-AEX-column (HiPrep Q HP 16/10, GE Healthcare) and eluted at a flow rate of 0.5 mL min^{-1} using a linear potassium chloride gradient (0 M → 0.5 M) in AEX-buffer. The fractions containing LpxC were concentrated using molecular weight cut off (MWCO) spin columns (10 kDa), loaded onto a 120 mL-size exclusion (SEC)-column (HiLoad 16/600 Superdex 200, GE Healthcare) and eluted at a flowrate of 0.5 mL min^{-1} in SEC-buffer (50 mM Bis/Tris, 150 mM NaCl, pH = 6.0). The presence of the enzyme during the purification progress was confirmed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDSPAGE) with Coomassie brilliant blue staining. The purified enzyme was quantified by the use of a Nanodrop 2000C, diluted with SEC-buffer to 0.5 mg mL^{-1} and stored at -80 °C.

6.3.2.3.3 Fluorescence-based assay

A fluorescence-based microplate assay for LpxC activity was performed as described by CLEMENTS *et al.*[145] with minor modifications by WIMMER *et al.*[195] The wells in a black, non-binding, 96-well fluorescence microplate (Greiner Bio One, Frickenhausen) were filled with 93 μL of 26.9 μM UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**27a**) in assay buffer (40 mM sodium morpholinoethanesulfonic acid, 80 μM dithiothreitol, 0.02% Brij 35 (pH 6.0)). In order to assay the inhibitors at final concentrations ranging from 200 nM up to 200 μM, 2 μL of a respective dilution of the compounds in DMSO was added. The addition of 5 μL of a solution of purified LpxC (10 μg mL^{-1}) in an assay buffer led to final concentrations of 25 μM UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**27a**), 14.7 nM LpxC, 2% DMSO, and from 200 nM up to 200 μM inhibitor. The microplate was incubated for 30 min at 37 °C in a plate shaker. Then, the biochemical reaction was stopped by adding 40 μL of 0.625 M sodium hydroxide. The reaction mixture was further incubated for 10 min and neutralized by adding 40 μL of 0.625 M acetic acid. The deacetylated product UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]glucosamine (**27b**) was converted into a fluorescing isoindole **229** by adding

120 µL of a *o*-phthaldialdehyde-2-mercaptoethanol solution, which was prepared by dissolving 10 mg *o*-phthaldialdehyde in 1 mL methanol, diluting the mixture with 24 mL sodium borate buffer (0.1 M), and finally adding 2.5 µL 2-mercaptoethanol.[197] Fluorescence was measured with a Tristar^2 plate reader (Berthold, Bad Wildbad) at 340 nm excitation and 460 nm emission wavelengths. Each assay was performed at least three times on separate days. For a complete inhibition of the LpxC enzyme, CHIR-090 was used at a concentration of 200 µM, while pure DMSO served as negative control resulting in no enzyme inhibition. The IC_{50} values were calculated *via* Probit-log concentration graphs with the aid of the software Origin, which were then converted into K_i-values using the CHENG-PRUSOFF equation:[146]

$K_i = IC_{50}/ (1 + [S]/ K_M)$

K_i = enzyme-inhibitor dissociation constant;

IC_{50}: half maximal inhibitory concentration;

[S]: Substrate concentration

K_M = MICHAELIS-MENTEN constant (concentration of the substrate at which the reaction velocity is equal to one half of the maximal velocity for the reaction).

6.3.2.3.5 LC-MS/ MS-based assay

The wells in a black, non-binding, 96-well fluorescence microplate (Greiner Bio One, Frickenhausen) were filled with 93 µL of 26.9 µM UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**27a**) in assay buffer (40 mM sodium morpholinoethanesulfonic acid (pH 6.0), 80 µM dithiothreitol, 0.02% Brij 35). In order to assay the inhibitors at final concentrations from 20 nM up to 20 µM, 2 µL of a respective dilution of the compounds in DMSO were added. The addition of 5 µL of a solution of purified LpxC (10 µg · mL^{-1}) in assay buffer led to final concentrations of 25 µM UDP-3-*O*-[(*R*)-3-hydroxymyristoyl]-*N*-acetylglucosamine (**27a**), 15 nM *E. coli* LpxCC63A, 2% DMSO, and from 20 nM up to 20 µM inhibitor. The microplate was incubated for 30 min at 37 °C in a plate shaker. Then, the biochemical reaction was stopped by adding 40 µL of 0.625 M hydrochloric acid. The reaction mixtures were further incubated for 10 min, sealed and stored at -80 °C until analysis. The reaction mixtures were separated by ultra-high-performance liquid-chromatography (1920 Infinity UHPLC, Agilent Technologies) and the eluted compounds were analyzed by mass spectrometry using electro spray ionization in the negative ion mode with a triple quadrupole mass spectrometer (QTRAP 5500, AB Sciex LLC).

UHPLC method: column: Nucleodur® C18 Gravity-SB (*Ø* = 3 µm, *h* = 100 mm, Macherey-Nagel), coupled to a Universal RP-guard column (*Ø* = 2 mm, *h* = 4 mm, Macherey-Nagel);

flow rate: 0.3 µL · min^{-1}; injection volume: 3.0 µL; solvents: A: 20 mM ammonium formate in water; B: 1 mM ammonium formate in acetonitrile/isopropanol/water (47.5/42.75/9.75); gradient elution: (B%): 0 – 1 min: 30%, 1 – 16 min: gradient from 30% to 90%, 16 – 17 min: 90%, 17 – 17.5 min: gradient from 90% to 30%, 17.5 – 21.5 min: 30%; detection: 12 – 19 min; t_R (**27a**) = 12.2 min, t_R (**27b**) = 13.0 min.

To analyze the eluted compounds by mass spectrometry, a multiple reaction monitoring (MRM) method was applied. The specific parameters of this method are given in Table 1. After detection and selection of the precursor ions (**27a**: *m*/*z* 832; **27b**: *m*/*z* 790), both analytes were fragmented, leading to three identical product ions (*m*/*z* (product 1) 385, collision energy = -60 V; *m*/*z* (product 2) 159, collision energy = -80 V; *m*/*z* (product 3) 79, collision energy = -140 V). The mass transitions 832 → 79 (substrate **27a**) and 790 → 79 (product **27b**) were used as quantifiers, the other mass transitions were used as qualifiers. The ratio between substrate **27a** and product **27b** was quantified by comparing the peak areas of the quantifiers. The percentual inhibition caused by each inhibitor concentration was determined with respect to the amount of the product formed in the non-inhibited reaction after 30 min.

Each assay was performed at least three times on separate days. The IC_{50}-values were calculated *via* Probit-log concentration graphs with the aid of the software Origin and were subsequently converted into K_i-values using the CHENG-PRUSOFF equation.[146]

Table 15. Parameters of the MS/MS-method using the triple quadrupole mass spectrometer QTRAP 5500 (AB Sciex LLC).

scan time	**12 – 19 min**
curtain gas (CUR)	20 psi
collision gas (CAD)	Medium
ion spray voltage (IS)	-4500 V
temperature (TEM)	450 °C
ion source gas 1	60 psi
ion source gas 2	50 psi
declustering potential (DP)	-170 V
entrance potential (EP)	-10 V
dwell time	150 ms

7.0 BIBLIOGRAPHY

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8.0 APPENDIX

8.1 Hazards and precautionary statements

Compound	GHS code	Hazard (H) statement	Precautionary (P) statement
Acetone	02, 07	225, 319, 336	210, 305+351+338, 403+233
Acetonitrile	02, 07	225, 302 +312 +332, 319	210, 280, 305 +351 +338, 403+235
Acetyl chloride	02, 05	225, 314, 318	210, 260, 280, 303+361+353, 305 +351+338, 310, 370+378, 403+235,
Ammonium chloride (saturated solution)	07	302, 319	270, 305+351+338
Ammonium molybdate (TLC dipping bath)	07	302, 315, 319, 335	280, 302+352, 305+351+338, 337+313
4-Benzenesulfonyl chloride	05, 07	302, 314, 318	270, 280, 301+312, 303+361+353, 304+340+310, 305+351+ 338
Benzoyl chloride	05, 06	227 302 +312, 331, 314, 318, 317	260, 280, 302+352, 303+361+353, 305+351+338, 370+378, 403+ 233
Benzyl bromide	05, 07	290, 315, 319, 335,	261, 264, 271, 280, 302+352, 305+351+338, 312

Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
1-Bromo-4-iodobenzene	07	315, 319, 335, 413	264, 280, 261, 271, 273, 302+352, 321, 332+317, 362+364, 305+351+338, 304+340, 319, 403+233, 405, 501
5-Bromopentan-1-ol	02, 05, 07	226, 302, 315, 318, 335	210, 233, 240, 241, 242, 243, 261, 264, 270, 271, 280, 301+312, 302+352, 303+361+353, 304+340, 305+351+338, 310, 312, 321, 330, 362+364, 370+378, 403+233, 403+235, 405
Cerium sulfate	05, 09	314, 410	260, 273, 280, 303+361+353, 304+340+310, 305+351+338
$CDCl_3$	06, 08	302, 315, 319, 331, 336, 351, 361d, 372	201, 301+312, 302+352, 304+340+311, 305+351+338, 308+313
Copper iodide	07, 09	302, 315, 319, 335 410	273, 280, 302+352, 305+351+338

Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
Copper sulfate pentahydrate	05, 07, 09	302, 318, 410	273 280, 301+312, 305+351+338
Cyclohexane	02, 07, 08, 09	225, 304, 315, 336, 410	210, 273, 301+330+331, 302+352, 403+233
Dichloroethane	02, 06, 08	225, 302, 304, 315, 319, 331, 335, 350,	210, 301+310, 303+361+353, 304+340+311,305+351 +338, 331
Dichloromethane	07, 08	315, 319, 336, 351	261, 280, 302+352, 305+351+338, 308+313
Diethylaminosulfur trifluoride	02, 05	226, 242, 314	210, 280, 303+361+353, 305+351+338, 370+378, 403+235
Diethylether	02, 07	224, 302, 336	210, 243, 261, 303+361+353, 304+340, 312
1,4-Diiodobenzene	07	315, 319, 335	None
Diisopropylazodicarboxylate	07,08, 09	315, 319 335, 351, 373, 411	261, 273, 281, 305+351+338
4-Dimethylaminopyridine	06	301, 310, 315, 319, 335	261, 280, 302+350, 305+351+338, 310
Dimethylformamide	02, 07, 08	226, 312+332, 319, 360D	280, 302+352, 305+351+338, 308+313

Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
Dimethylsulfoxide	none	227, 412	210, 273, 280, 370+378, 403+235, 501
Dimethylsulfoxide-d_6	none	227	210, 280, 370+378, 403+235, 501
Diphenylphosphoryl azide	06, 07	301+311+ 331, 315, 319	280, 261, 264, 270, 312, 301+310, 330, 304+340, 302+352, 332+313, 305+351+338, 337+313, 362, 271, 403+233, 405, 501
Di-*tert* butylcarbonate	02, 05, 06,	226, 315, 317, 318, 330, 335	210, 233, 280, 303+361+353, 304+340, 310, 305+351+338,
4-Ethinylbenzaldehyde	07	315, 319, 335	261, 264, 271, 280, 302+352, 305+351+338
1-Ethinyl-4-iodobenzene	07	315, 319, 335	261, 305+351+338, 302+352
Ethyl acetate	02, 07	225, 319, 336	210, 233, 240, 241, 242, 305+351+338
Ethyl bromide	02, 07, 08	225, 302+332, 351	210,233, 261, 312,370+378, 403+235, 501

Compound	GHS code	Hazard (H) statement	Precautionary (P) statement
Ethylenediamine	02, 05, 06, 08	226, 302+332, 311, 314, 317, 334, 412	210, 280
Formaldehyde (37%)	05, 06, 08	301+311+ 331, 314, 317, 335, 341, 350, 370	260, 280, 303+361+353, 304+340, 305+351+338, 308+311
Formic acid	02, 05, 06	226, 290, 302, 314, 331	210, 280, 303+361+353, 304+340, 305+351+338, 310
Hex-5-yn-1-ol	07	227, 315, 319, 335	261, 264, 271, 280, 302+352, 305+351+338
Hydrochloric acid (0.5N aq. solution)	05, 07	290, 314, 335	280, 303+361+353, 304+340, 305+351+338, 310
Hydroxylamine (50%)	02, 05, 07, 08, 09	208, 290, 302, 315, 317, 318, 335, 351, 373, 400	210, 212, 230, 233, 280, 305+351+338, 371+380+375, 501

Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
Hydroxylamine hydrochloride	05, 07, 08, 09	290, 302+312, 315, 317, 319, 351, 373, 410	273, 280, 301+312, 302+352+312, 305+351+338, 308+313
Iodine	07, 08, 09	302+312+ 332, 315, 319, 335, 372, 400	273, 302+352, 304+340, 305+351+338
4-Iodoaniline	07	302, 315, 319, 335	261, 305+351+338
4-Iodobenzaldehyde	07	315, 319, 335	261, 264, 271, 280, 302 +352, 305+351+338
4-Iodobenzoyl chloride	05	314	260, 280, 303+361+353, 304+340+310,305+351+338, 363
4-Iodobenzyl bromide	05, 07	314, 318	260, 264, 280, 301+330+331, 303+361+353, 304+340, 305+351+338, 310, 321, 363, 405, 501
4-Iodophenol	05, 07	302+312, 314	260, 270, 280, 301+312, 303+361+353, 305+351+338

Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
Isopropanol	02, 07	225, 319, 336	P210, 305+351+338, 312, 370+378, 403+233, 403+235, 501
Methanol	02, 06, 08	225, 301+311+ 331, 370	210, 270, 280, 303+361+353, 304+340, 308+311
Methanol-d_4	02, 06, 08	225, 301+311+ 331, 370	210, 233, 280, 302+352, 310, 403+235
Methyl (2*S*, 4*R*)-4-hydroxyproline-2-carboxylate hydrochloride	07	315, 319	264, 280, 302+352, 305+351+338, 337+313
Morpholine	02, 05, 06, 08	226, 302, 311+331, 314, 361fd	210, 260, 280, 302+352, 303+361+353, 305+351+338, 370+378, 403+233, 403+235
Ninhydrin (TLC dipping bath)	07	302, 315, 319, 335	280, 302+352, 304+340, 305+351+338, 312
Palladium acetate	05, 07, 09	317, 318, 410	261, 272, 273, 280, 302+352, 305+351+338
Palladium on carbon	02, 07	228, 315, 319	210, 305+351+338

Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
Tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) hexaflurophosphate	07	315, 319, 335	261, 264, 271, 280, 312, 302+352, 304+340, 337+313, 305+351+338, 332+313
Petroleum ether	02, 07, 08, 09	224, 304, 315, 336, 411	210, 233, 273, 301+310, 331, 403+233
p-Nitrobenzoic acid	05, 07	302, 318, 319	280, 305+351+338
Potassium carbonate	07	315, 319, 335, 412	261, 273, 280, 312, 302+352, 305+351+338, 337+313, 403+233, 501
Potassium iodide	08	372	260, 264, 270, 314, 501
Silical gel	08	350,360, 373, 400, 410	260, 202, 285, 501
Silver (I) oxide	03, 05, 09	271, 318, 410	210, 273, 280, 305+351+338, 310
Sodium ascorbate	none	none	none
Sodium bicarbonate (saturated solution)	07	none	none
Sodium chloride (saturated solution)	none	none	none
Sodium hydride	02, 05	228, 260, 290, 314	210, 231+232, 260, 280, 303+361+353, 305+351+338

Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
Sodium methoxide in methanol	02, 05, 06, 07, 08	225, 301+311+ 331, 315, 318, 336, 370	280, 210, 240, 241, 242, 243, 260, 264, 270, 271, 330, 301+310, 303+361+353, 304+340, 305+351+338, 307+311, 332+313, 362, 370+378, 403+233, 403+235, 405, 501
Sodium sulfate	none	none	None
Sodium triacetoxyborohydride	02, 07	228, 261, 315, 335	210, 223, 231+232, 240, 241 261, 264, 271, 280, 302+352, 304+340, 312, 321, 332+313, 335+334, 362, 370+378, 402+404, 403+233, 405, 501
Sulfuric acid (TLC dipping bath)	05	290, 314	234, 280 301+330+331, 303+361+353, 305+351+338, 310, 363
tert-Butanol	02, 07	225, 319, 332, 335	210, 280, 304+340, 305+351+338, 312
tert-Butylammonium fluoride trihydrate	07	302, 315, 319, 412	264, 273, 280, 301+312, 302+352, 305+351+338

Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
tert-Butylnitrite	02, 07	225, 302+332	210, 243, 271, 260, 280, 301+312, 303 +361+353, 304+340
Tetrahydrofuran	02, 07, 08	225, 302, 319, 335, 336, 351	202, 210, 233, 301+312, 305+351+338, 308+313
Tetrakis palladium triphenylphosphine	07	302, 413	231, 264, 270, 273, 305+351+338, 403+233, 411+235, 422, 501
Toluene	02, 07, 08	225, 304, 315, 336, 361, 373, 412	202, 210, 273, 301+310, 303+361+353, 331
tri-(2-Furyl) phosphine	07	315, 319, 335	261, 305+351+338
Triethoxysilane	02, 05, 06	226, 302, 315, 318, 330	280, 210, 233, 240, 241, 242, 243, 301+312, 303+361+353, 304+340+310, 305+351+338, 310, 370+378, 403+235, 501

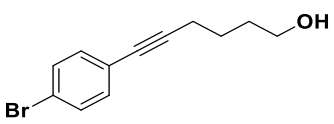
Compound	**GHS code**	**Hazard (H) statement**	**Precautionary (P) statement**
Triethylamine	02, 05, 06, 07	225, 302, 311+331, 314, 318, 335, 401	210, 233, 261, 264, 273, 280, 301+330+331, 303+361+353, 304+340, 305+351+338, 370+378, 403+233, 310
Trimethylsilyl acetylene	02, 07	225 335 315 319	210, 271, 240, 241, 242, 243, 261, 280, 264, 370+378, 305+351+338, 312, 337+313, 302+352, 303+361+353, 304+340, 332+313, 362+364, 403+235, 405, 501
Triphenylphosphine	05, 07, 08	302, 317, 318, 372	260, 270, 280, 301+302, 305+351+338, 302+353, 310, 314
Vanillin (TLC dipping bath)	07	319	280, 305+351+338, 312
Zinc bromide	05, 07, 09	302, 314, 317, 410	273, 280, 303+361+353, 305+351+338, 310

Legend:

GHS code	Pictogram	GHS code	Pictogram
01	 Explosive	06	 Toxic
02	 Flammable	07	 Harmful
GHS code	**Pictogram**	**GHS code**	**Pictogram**
03	 Oxidizing	08	 Health hazard
04	 Compressed gas	09	 Environmental hazard
05	 Corrosive		

8.2 Compound index

The following is a list of all synthesized compounds and the pages on which they can be found.



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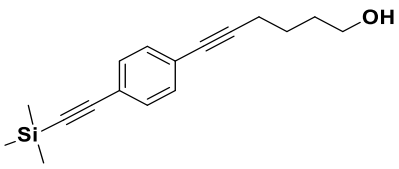

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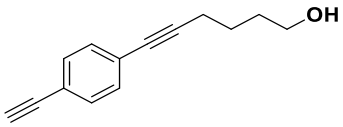

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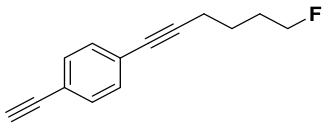

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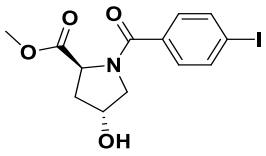
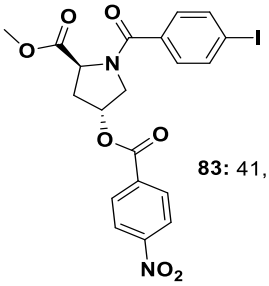


58: 33, 41, 94, 123



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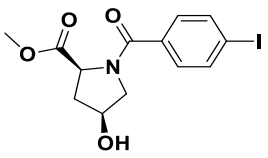
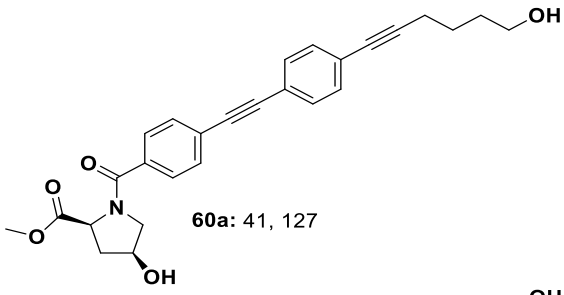


59: 33, 41, 45, 52, 94, 126



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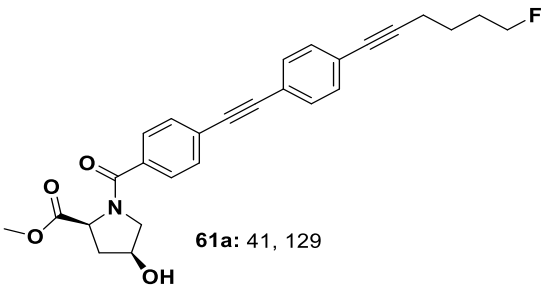

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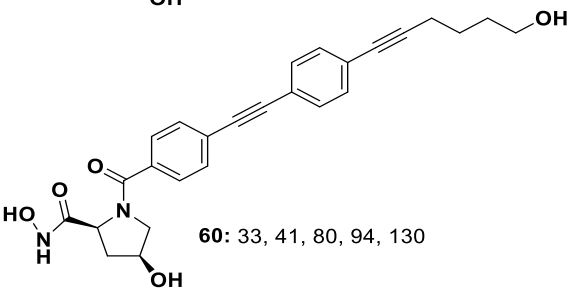
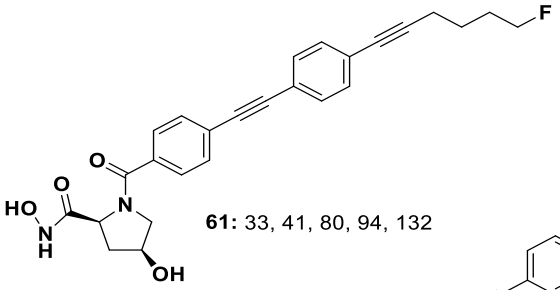


60: 33, 41, 80, 94, 130



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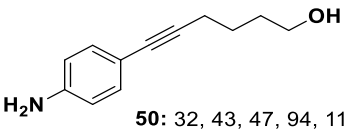
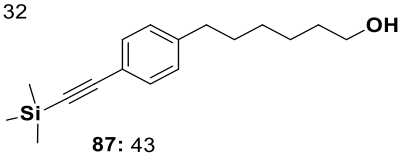


50: 32, 43, 47, 94, 116



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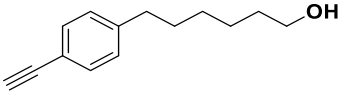
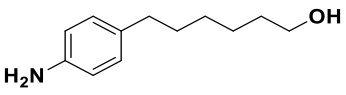


52: 32, 43, 94, 118



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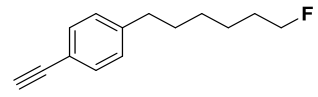

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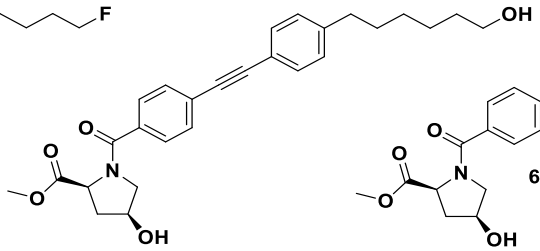

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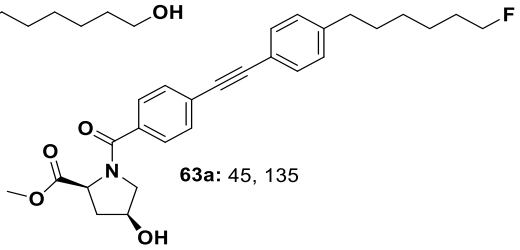

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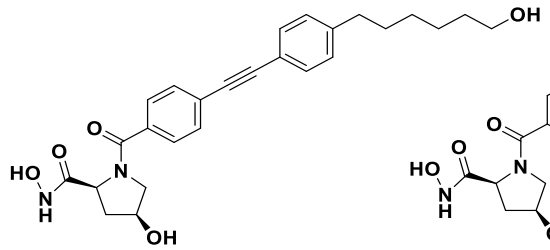

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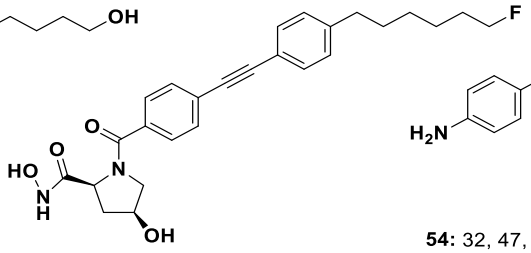
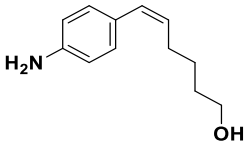


63: 33, 45, 80, 94, 138



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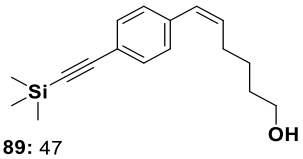

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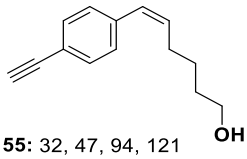

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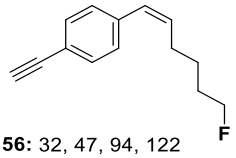

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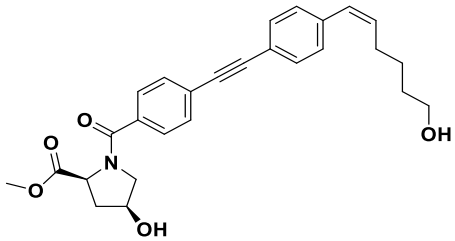

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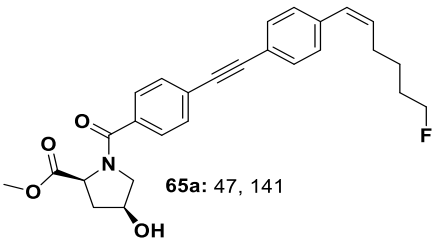

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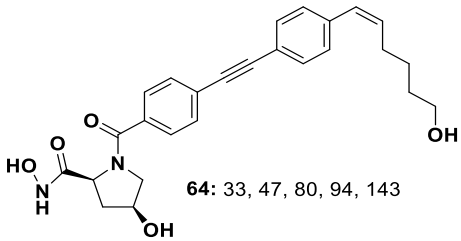

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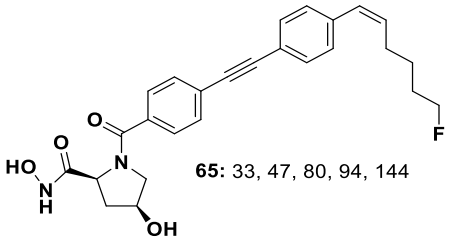

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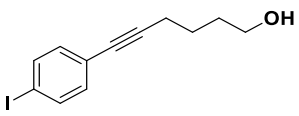

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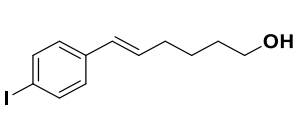

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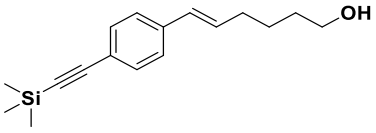

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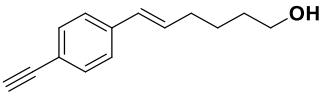

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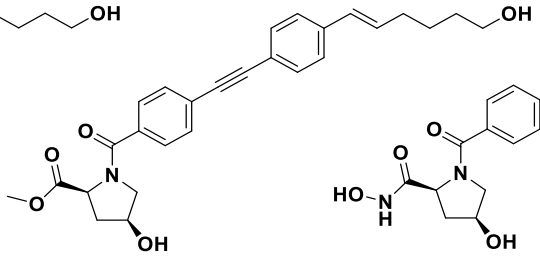

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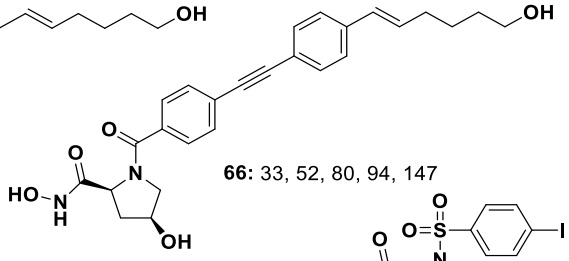
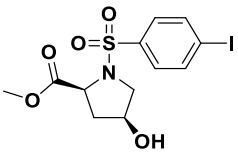


66: 33, 52, 80, 94, 147



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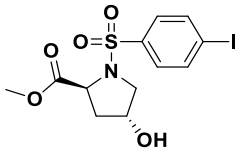

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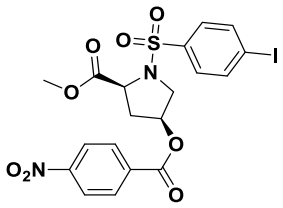

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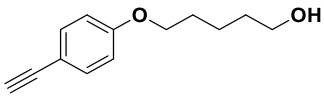

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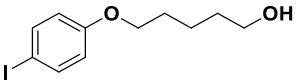

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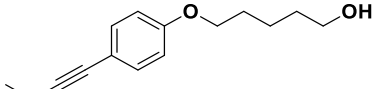

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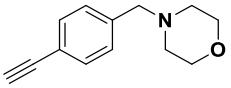

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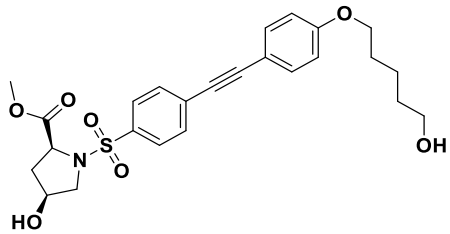

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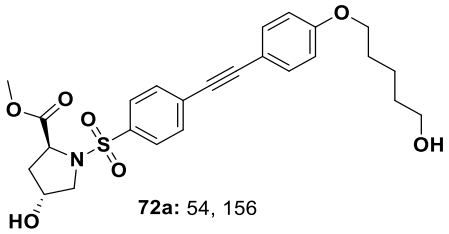
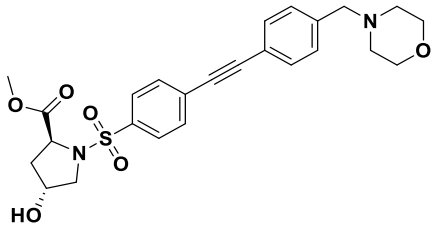
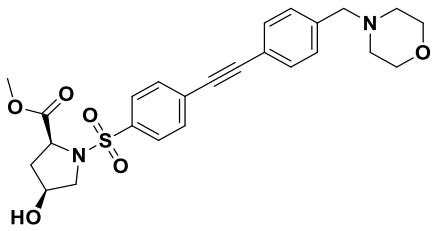


72a: 54, 156



78a: 54, 159



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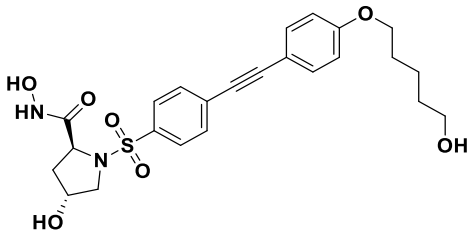

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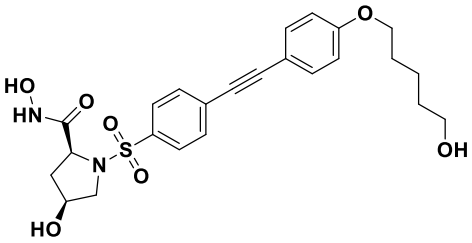
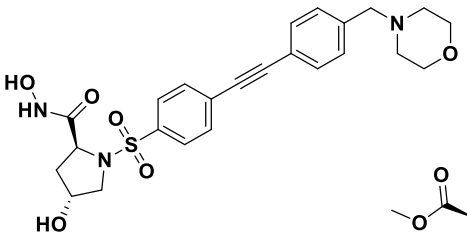
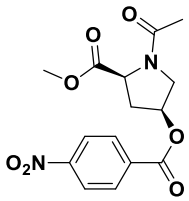


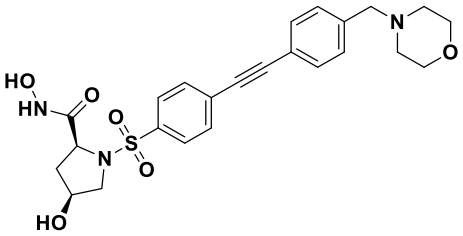
73: 34, 54, 82, 95, 163



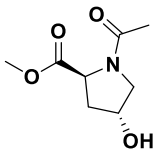
78: 38, 54, 87, 100, 164



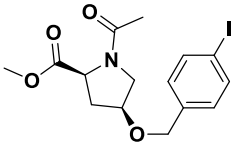
105: 55, 168



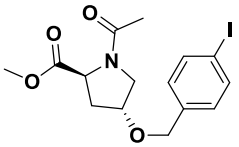
79: 38, 54, 87, 100, 166



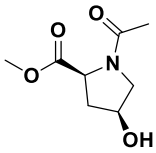
104: 55, 167



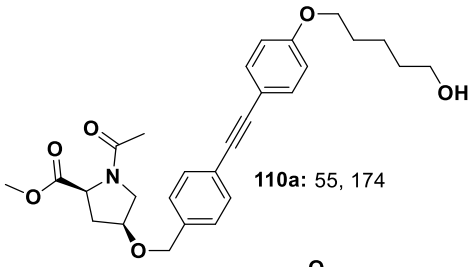
108: 55, 171



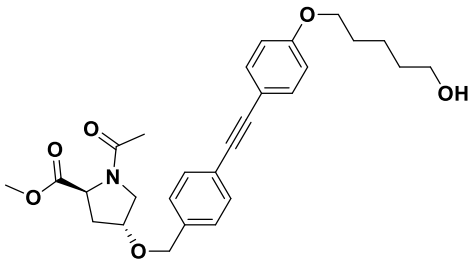
107: 55, 170



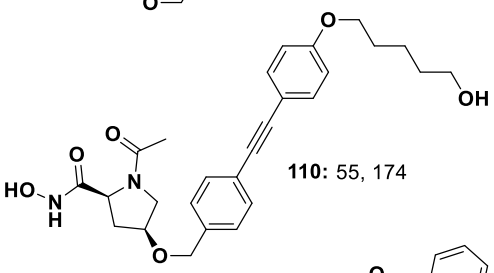
106: 55, 169



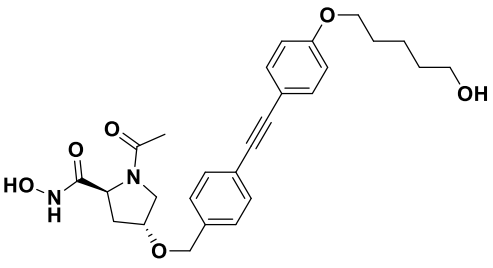
110a: 55, 174



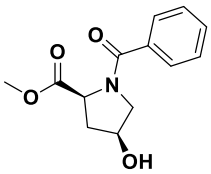
109a: 55, 173



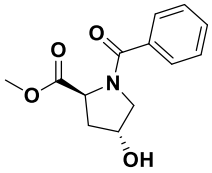
110: 55, 174



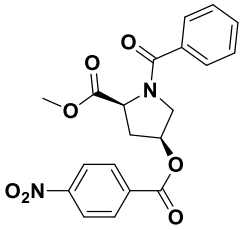
109: 55, 83, 97, 176



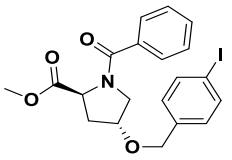
113: 57, 181



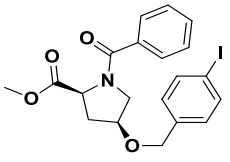
111: 57, 179



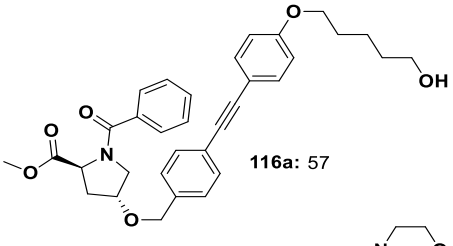
112: 57, 180



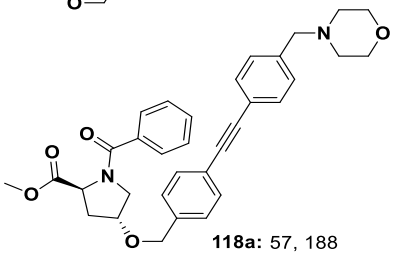
114: 57, 182



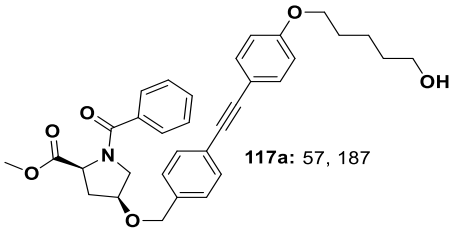
115: 57, 183



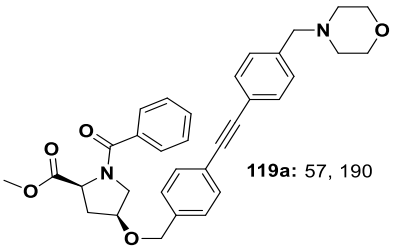
116a: 57



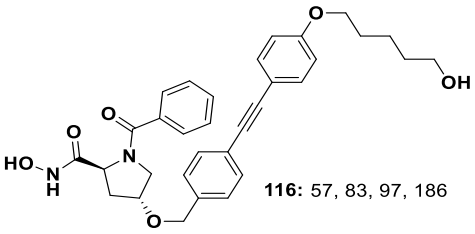
118a: 57, 188



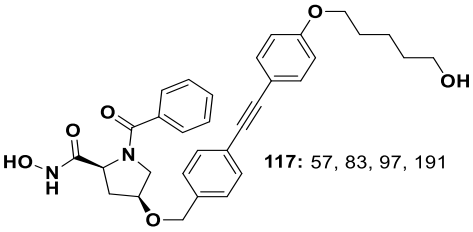
117a: 57, 187



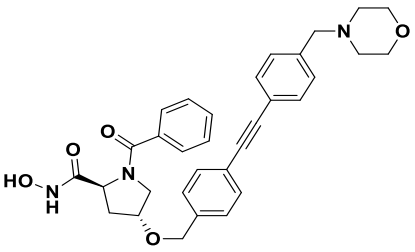
119a: 57, 190



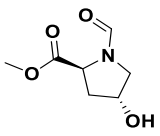
116: 57, 83, 97, 186



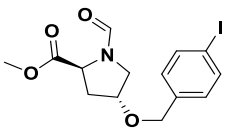
117: 57, 83, 97, 191



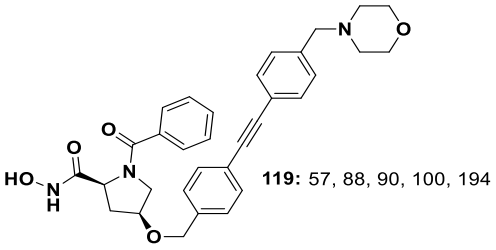
118: 57, 88, 90, 100, 193



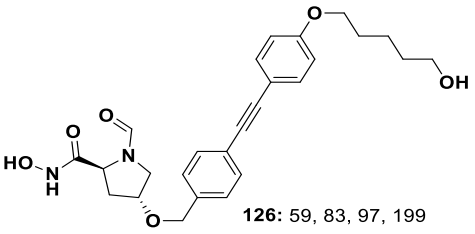
120: 59, 196



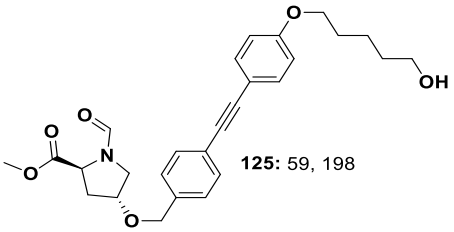
123: 59, 197



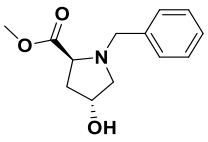
119: 57, 88, 90, 100, 194



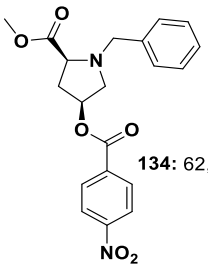
126: 59, 83, 97, 199



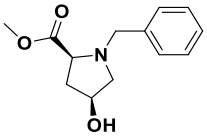
125: 59, 198



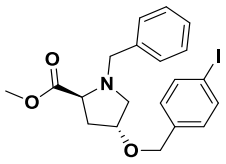
133: 62, 201



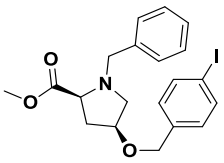
134: 62, 202



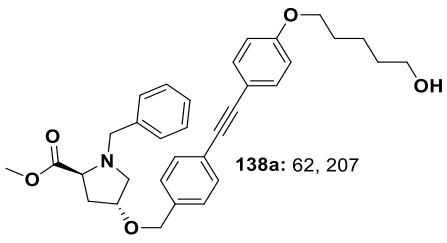
135: 62, 203



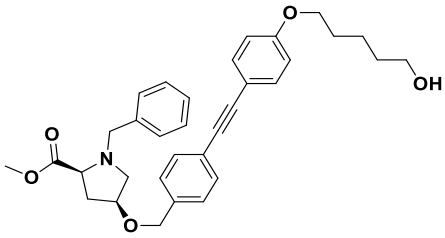
136: 62, 204



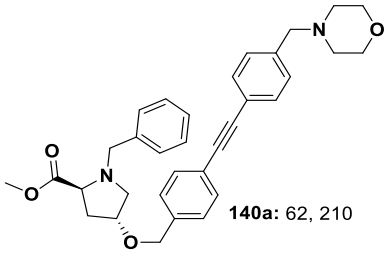
137: 62, 206



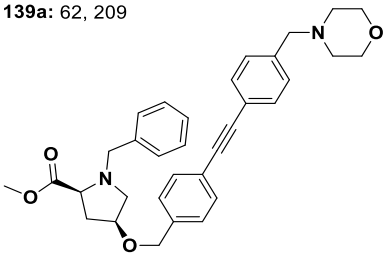
138a: 62, 207



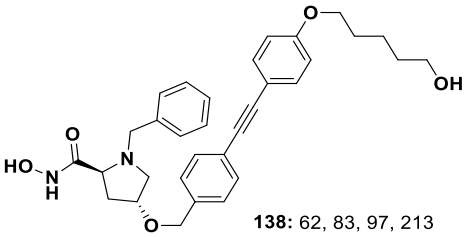
139a: 62, 209



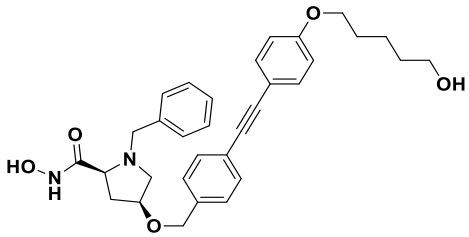
140a: 62, 210



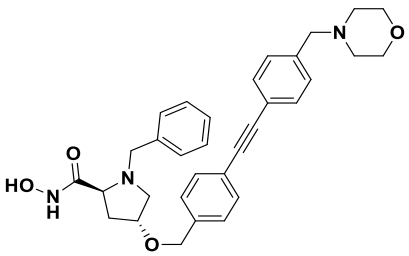
141a: 62, 212



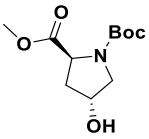
138: 62, 83, 97, 213



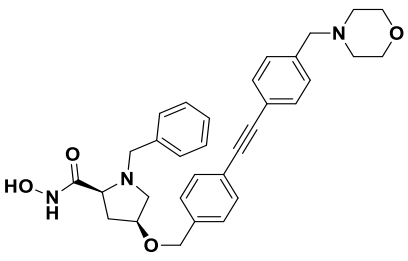
139: 62, 83, 97, 215



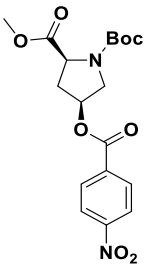
140: 62, 88, 90, 100, 216



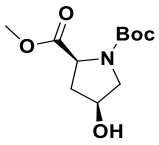
142: 63, 68, 219



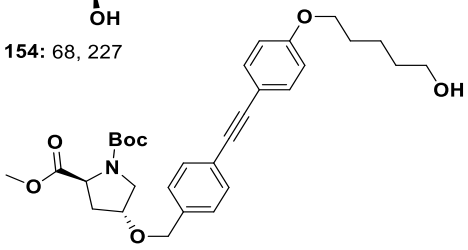
141: 62, 88, 90, 100, 218



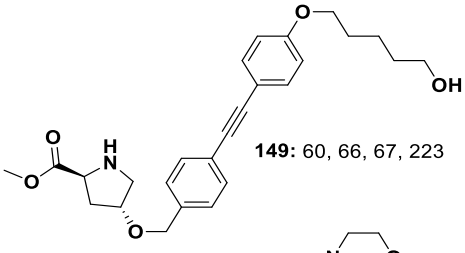
153: 68, 226



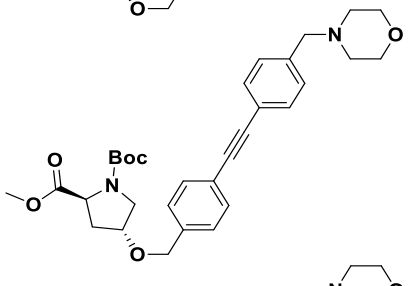
154: 68, 227



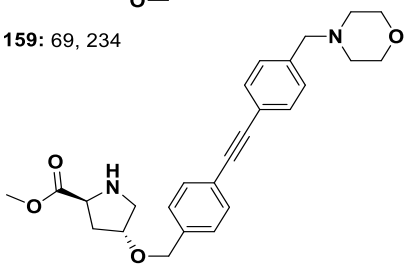
150: 67, 221



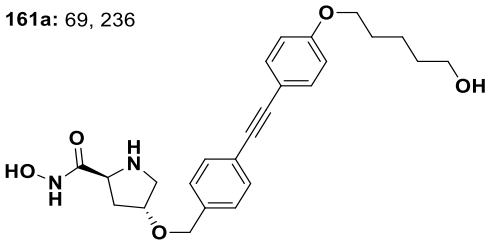
149: 60, 66, 67, 223



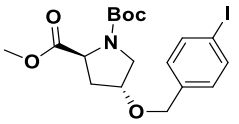
159: 69, 234



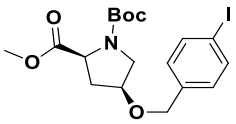
161a: 69, 236



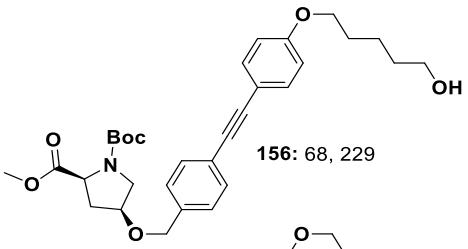
152: 67, 83, 97, 224



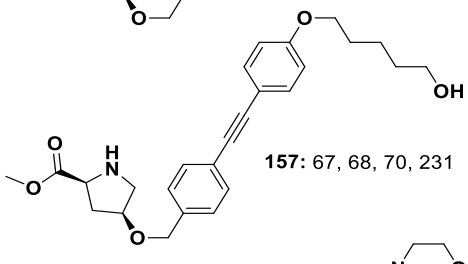
143: 63, 66, 67, 69, 220



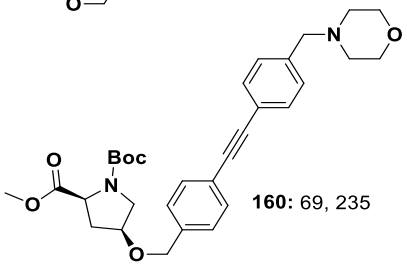
155: 68, 69, 228



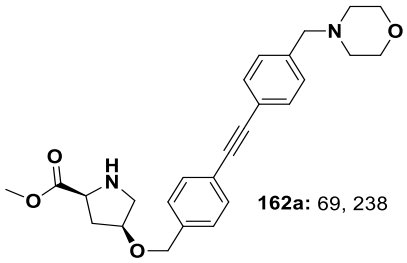
156: 68, 229



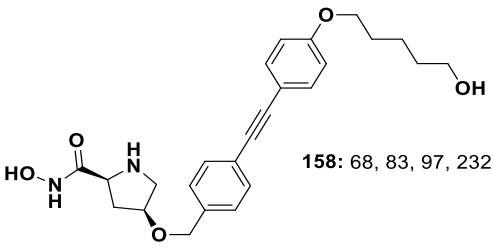
157: 67, 68, 70, 231



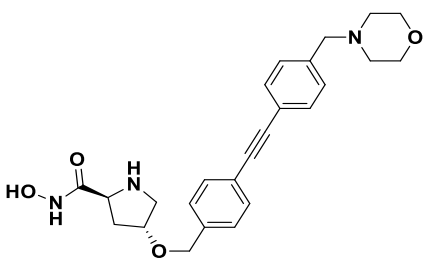
160: 69, 235



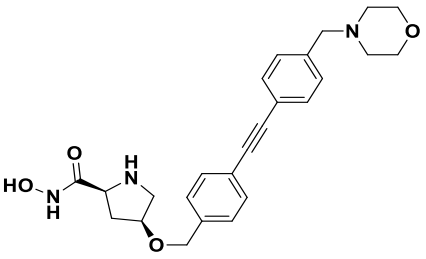
162a: 69, 238



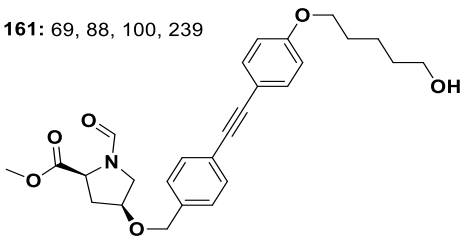
158: 68, 83, 97, 232



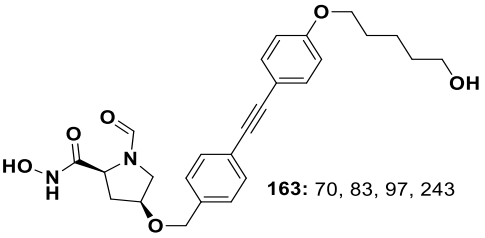
161: 69, 88, 100, 239



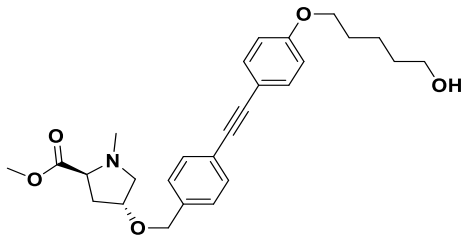
162: 69, 88, 100, 240



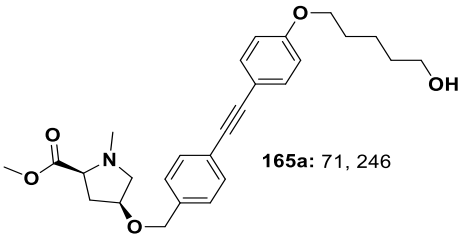
127: 59, 70, 242



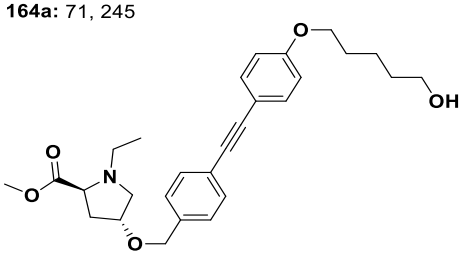
163: 70, 83, 97, 243



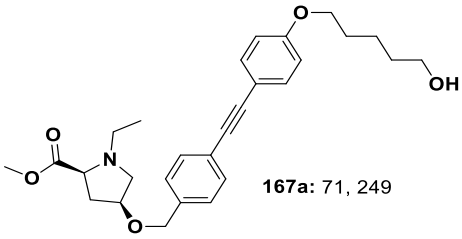
164a: 71, 245



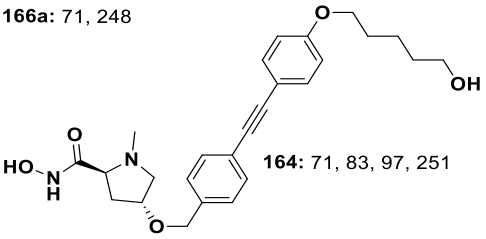
165a: 71, 246



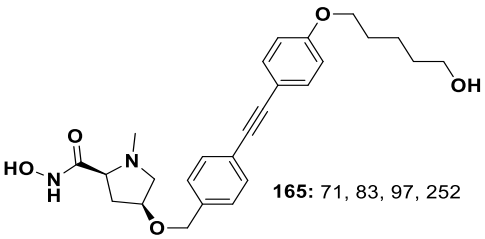
166a: 71, 248



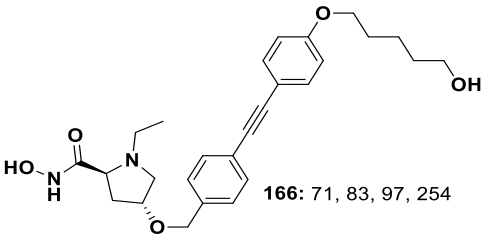
167a: 71, 249



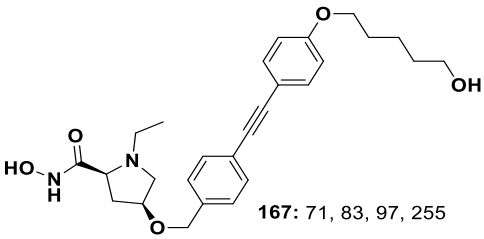
164: 71, 83, 97, 251



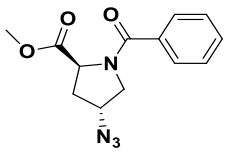
165: 71, 83, 97, 252



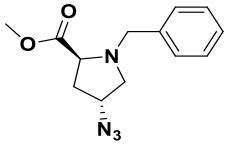
166: 71, 83, 97, 254



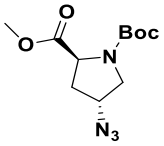
167: 71, 83, 97, 255



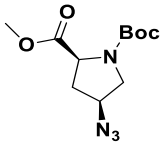
168: 73, 257



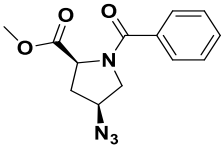
170: 73, 259



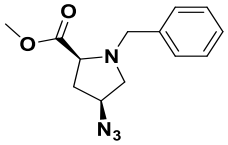
172: 73, 261



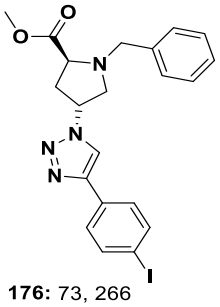
173: 73, 99, 262



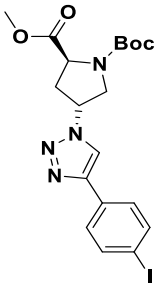
169: 73, 99, 258



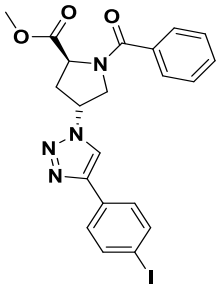
171: 73, 99, 260



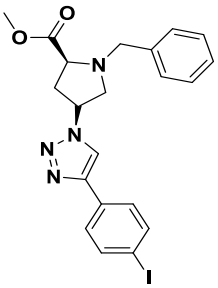
176: 73, 266



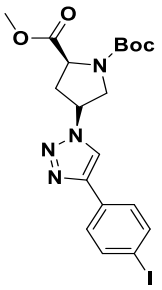
178: 73, 269



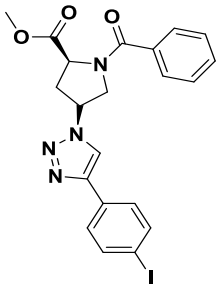
174: 73, 263



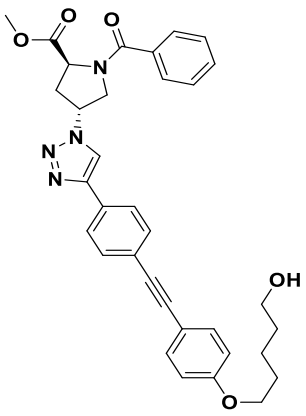
177: 73, 267



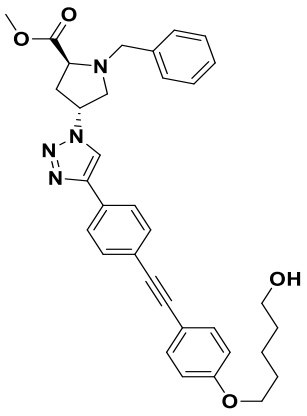
179: 73, 270



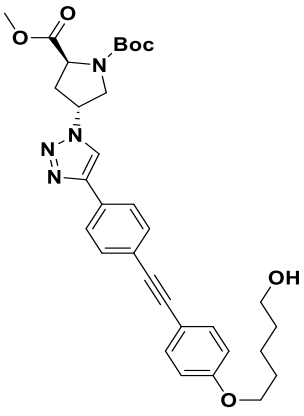
175: 73, 264



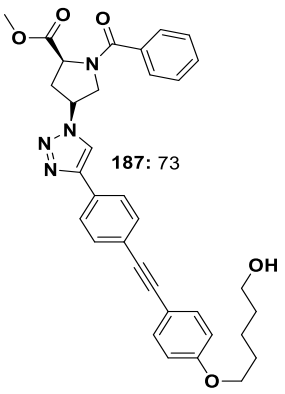
186: 73, 280



188: 73, 284



190: 73, 74, 288


187: 73
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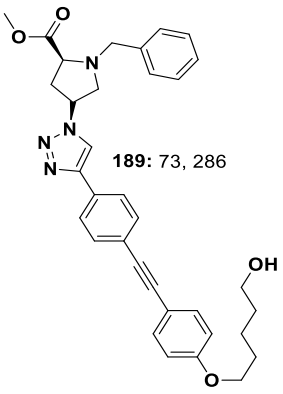
189: 73, 286
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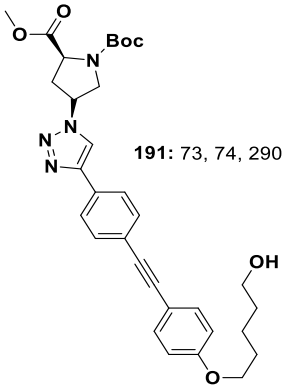
Boc
191: 73, 74, 290
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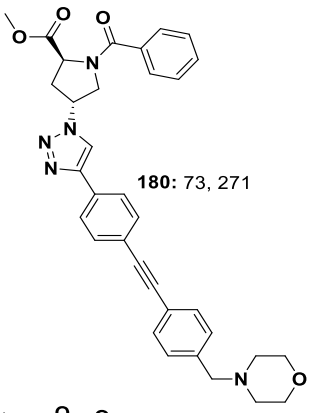
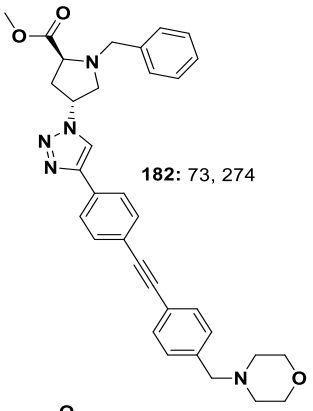
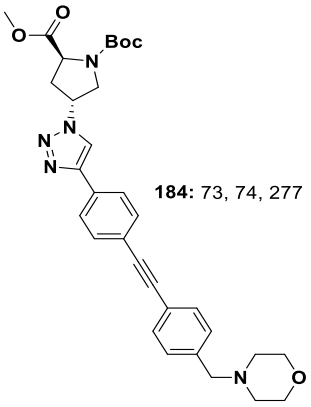

180: 73, 271


182: 73, 274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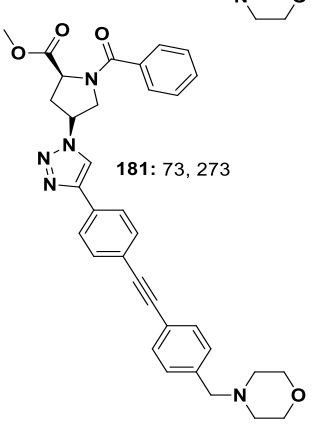
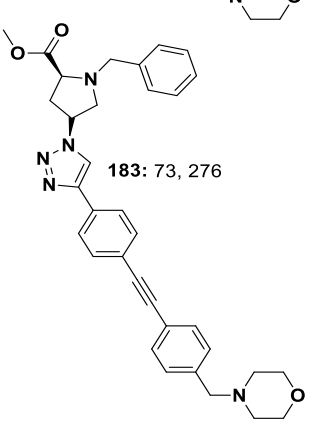
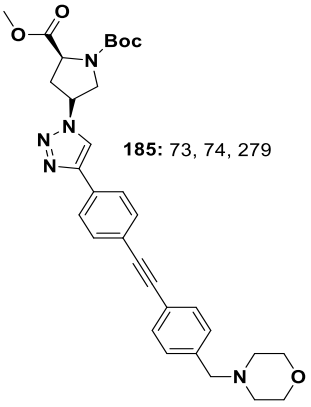
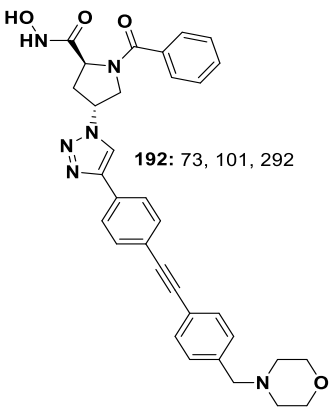
184: 73, 74, 277


181: 73, 273


183: 73, 276


Boc
185: 73, 74, 279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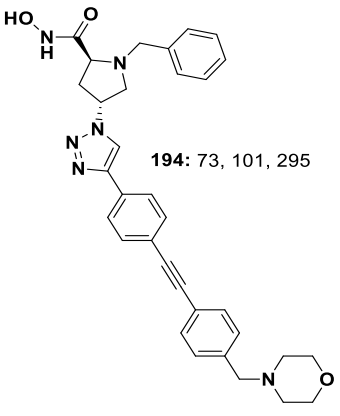
HN
192: 73, 101, 292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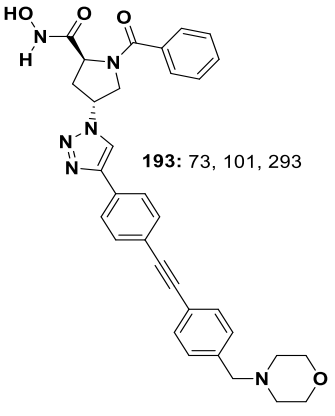
194: 73, 101, 295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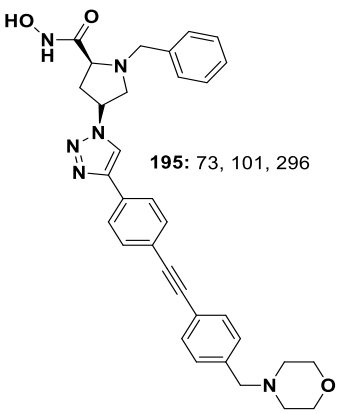
193: 73, 101, 293



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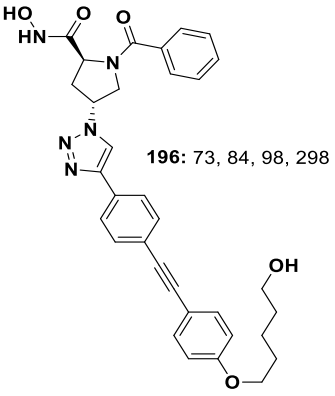
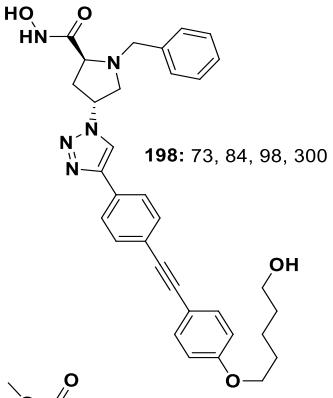


196: 73, 84, 98, 298



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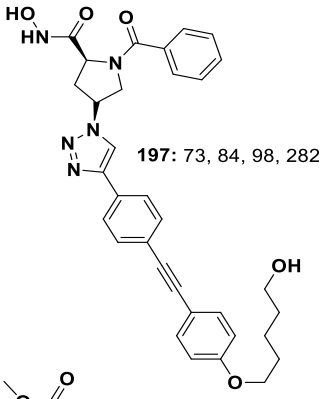

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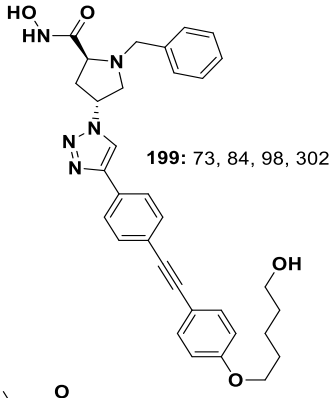

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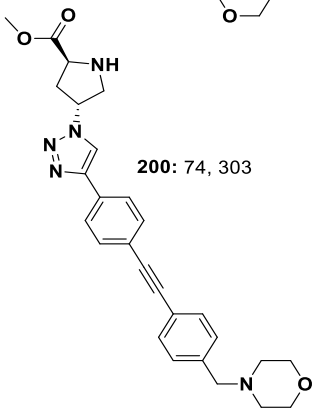

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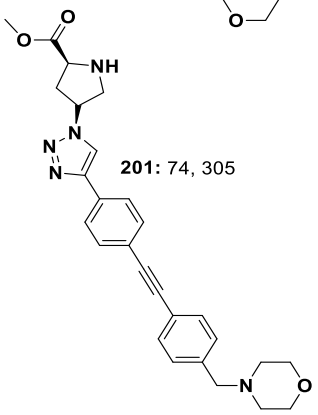

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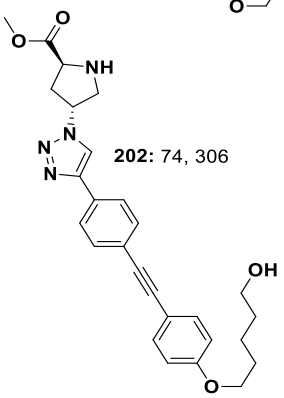

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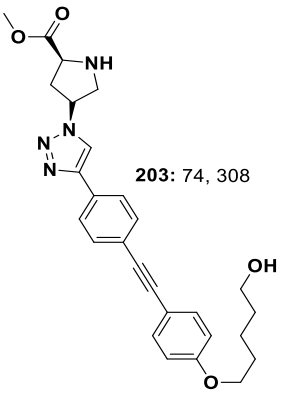

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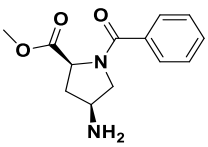

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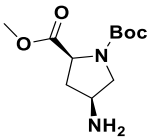

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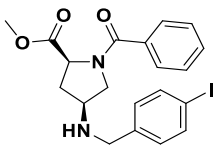

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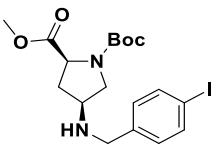

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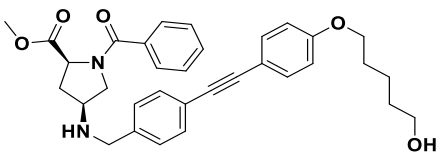

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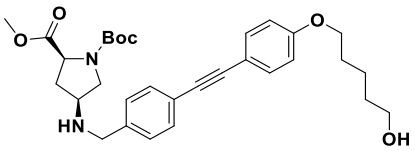

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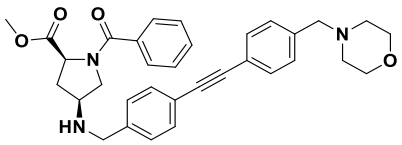

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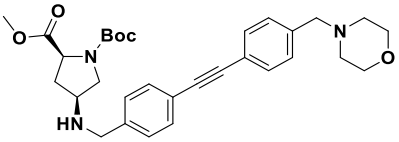

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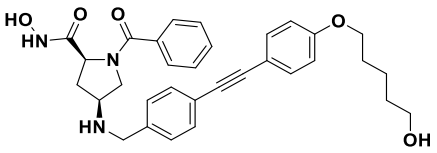

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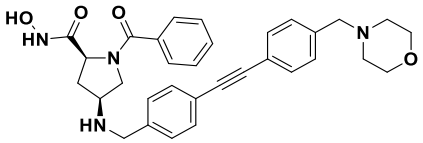

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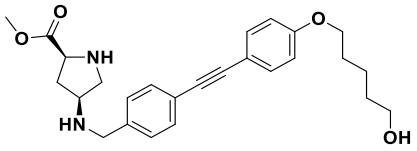

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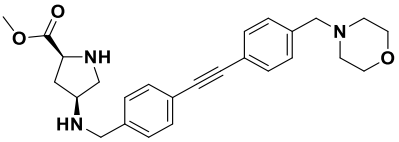

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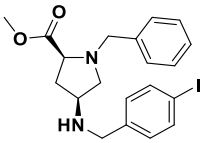

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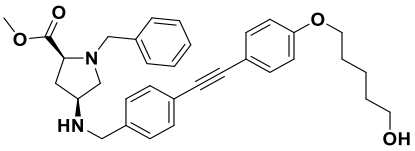

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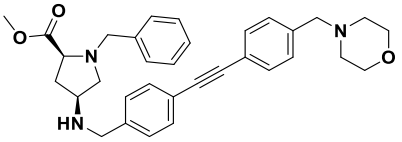

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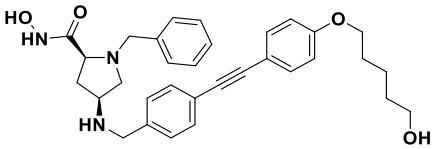

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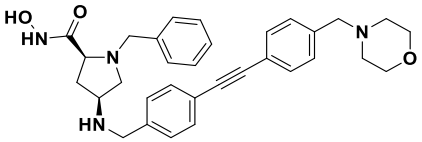

227: 78, 91, 102, 330

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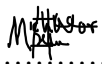
10.0 DECLARATION ON OATH

I hearby declare on oath that this doctoral dissertation was written independently and solely on my own based on the original work of my PhD and has not been used other than the acknowledged resources and aids.

Hamburg, 20.07.2023 ……

Place, Date



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Michael Worlako Klu