University of Hamburg
Department of Chemistry

1,4-Benzothiazepines, 3-Hydroxy-benzo[*b*]thiophene-2-carboxamides and Benzothieno[2,3-*e*][1,3]oxazines Derived from Thiosalicylic Acid

Dissertation submitted in partial satisfaction of the requirements for the degree
Doctor of Philosophy in pharmaceutical chemistry

by

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from
Homs-Syria

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Referees: Prof. Dr. D. Geffken
Prof. Dr. C. S. Leopold
Disputation: 17 April 2009

To My Parents,
Brothers
And Beloved Wife

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Hamburg, April 2009 Ibrahim Tolaymat

Standard Abbreviations and Acronyms

Ac_2O	acetic anhydride
aq.	aqueous
aromat.	aromatic
t-Bu	*tert*-butyl
°C	degrees Celsius
Calcd.	calculated
CDI	1,1`-carbonyldiimidazole
CH_2Cl_2	dichloromethane
cm^{-1}	wavenumbers
Δ	reflux
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	*N*,*N*-dimethylformamide
DMSO-d_6	dimethylsulfoxide deuterated
e.g.	for example (latin: exampli gratia)
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Fig.	figure
g	grams
h	hour(s)
HCl	hydrochloric acid
Hz	hertz
Im	Imidazole
IR	infrared
J	coupling constant (in NMR spectroscopy)
Lit.	literature
m	multiplet (spectral)
Me	methyl

MeOH	methanol
min	minute(s)
mmol	millimole(s)
M.p.	melting point
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
ppm	part(s) per million
quart.	quartiary (spectral)
RT	room temperature
s	singlet (spectral)
s.	see
t	triplet (spectral)
TCDI	1,1`-thiocarbonyldiimidazole
TEA	triethylamine
tert.	tertiary (spectral)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane
p-TsOH	*p*-toluenesulfonic acid

Table of Contents

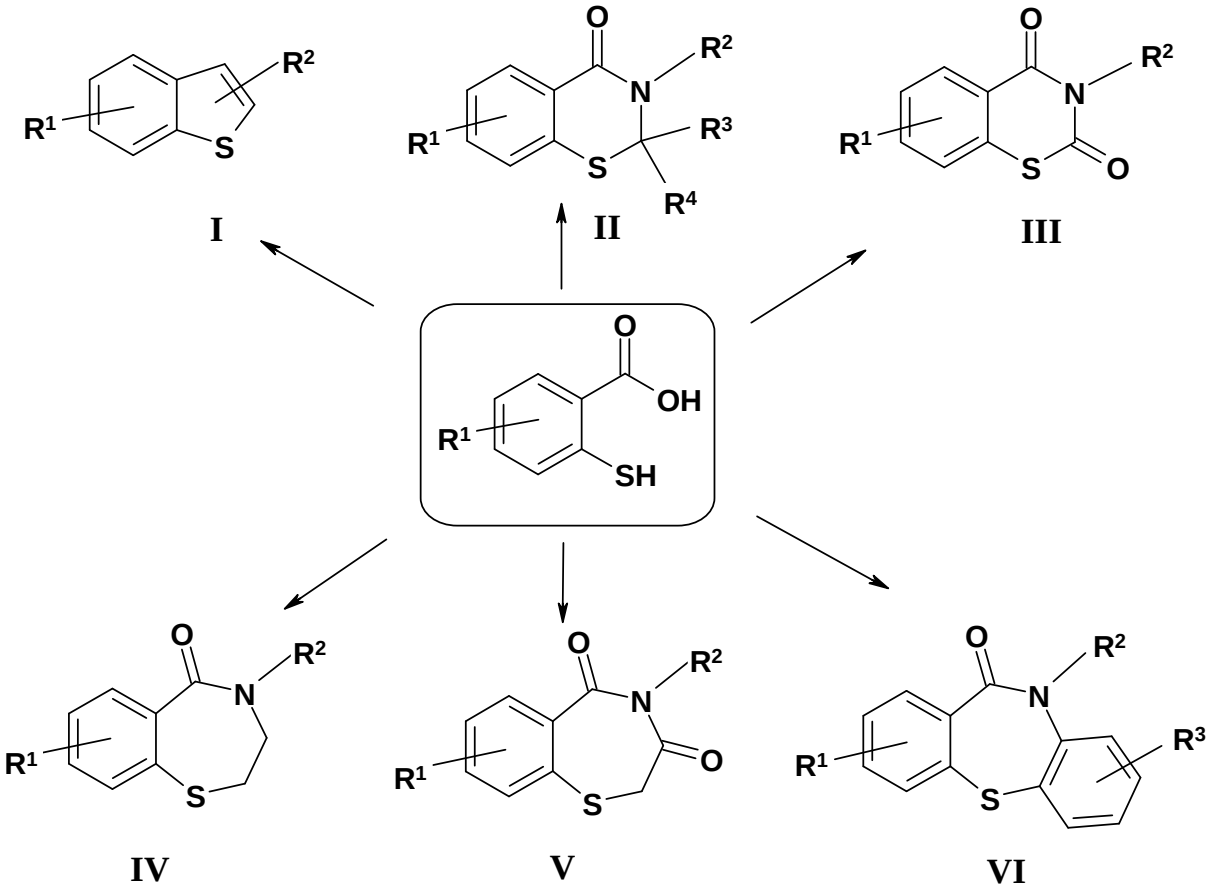
1 Introduction

1.1 Preface

Thiosalicylic acid, which is the sulfur analogue of salicylic acid, represents an important building block in organic synthesis as well as in the search for new bioactive substances.

It was synthesized for the first time in 1889 from *o*-toluenesulfonamide[1], and has been used as a starting material for different classes of sulfur containing heterocycles for industrial and medicinal purposes ever since.

E.g., benzothiophenes **I**[2,3], benzothiazinones **II**[4], benzothiazindiones **III**[5,6], benzothiazepinones **IV**[7,8], benzothiazepindiones **V**[9], dibenzothiazepines **VI**[10] and many more examples of heterocycles[11-14] have been derived from cyclization reactions of thiosalicylic acid.

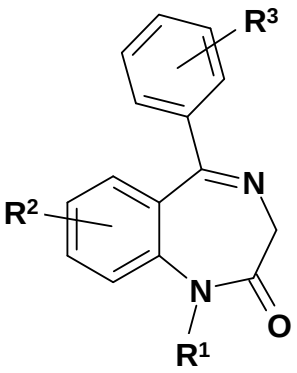


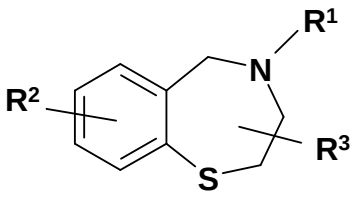
1.2 Bioactive Benzothiazepines and Benzothiophenes

As this thesis focuses on the synthesis of new compounds belonging to two types of sulfur containing heterocycles, namely benzothiazepine and benzothiophene, some well known representatives of these compounds will be mentioned below.

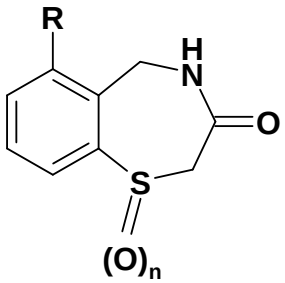
1.2.1 Bioactive benzothiazepines

Benzothiazepines have gained considerable attention because of their diversity of biological activity.
As structural analogues of benzodiazepines, benzothiazepine derivatives represent a significant class of neurologically active agents[15].





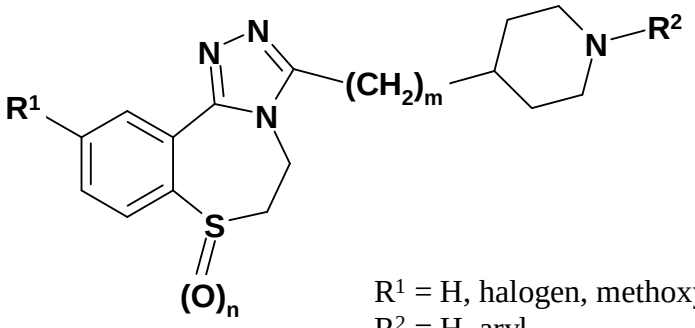
1,4-benzothiazepines-3-ones of type **VII** were described to possess anticonvulsant properties and might be useful in seizure therapy[16].



R = halogen, methyl, methoxy
n = 0, 1, 2

VII

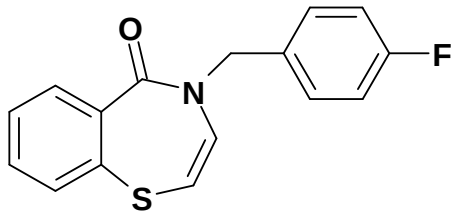
1,2,4-Triazolo-condensed 1,4-benzothiazepines of type **VIII** display antipsychotic activity based on dopamine antagonism[17].



R^1 = H, halogen, methoxy
R^2 = H, aryl
m = 0, 1, 2
n = 0, 1, 2

VIII

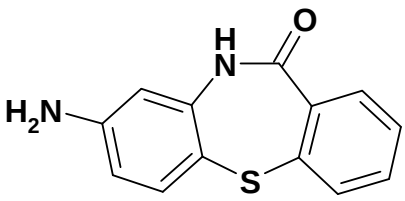
1,4-Benzothiazepine-5-one derivative **IX** prepared by *Mesaros* in our research group showed potent analgesic activity in the formalin test[a][18,19].



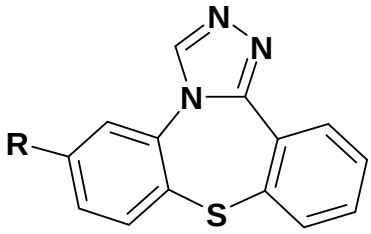
IX

8-Amino-10,11-dibenzo[*b*,*e*][1,4]thiazepin-11-ones (**X)** and their 1,2,4-triazolo condensed tetracyclic systemes **XI** were found to exhibit antidepressant activity[21].

[a] Administration of 5% formalin solution into the experimental animal's hind paw evokes two spontaneous responses: shaking and licking/biting of the injected paw. Standardization of this test allows the evaluation of analgesics[20].



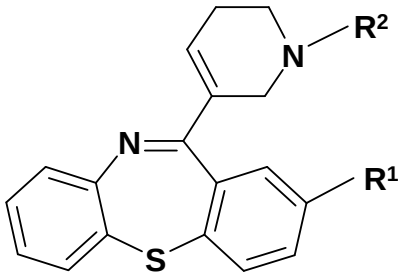
X



R = amino, mercapto, chloro

XI

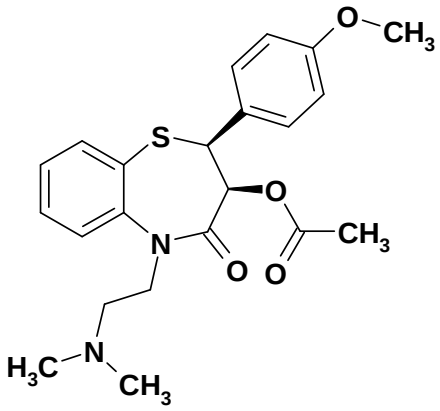
And dibenzothiazepines **XII**, fitted with a basic tetrahydropyridinyl residue, showed antipsychotic effects[22].



R^1 = halogen
R^2 = H, methyl, ethyl

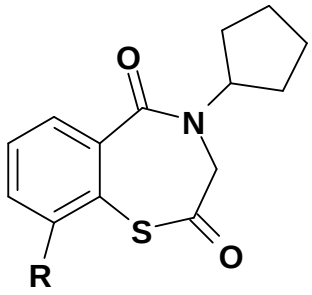
XII

Benzothiazepine derivatives can also affect the cardio vascular system, as demonstrated by the calcium channel blocker *Diltiazem*, which is used as an antihypertensive drug[23].



Diltiazem

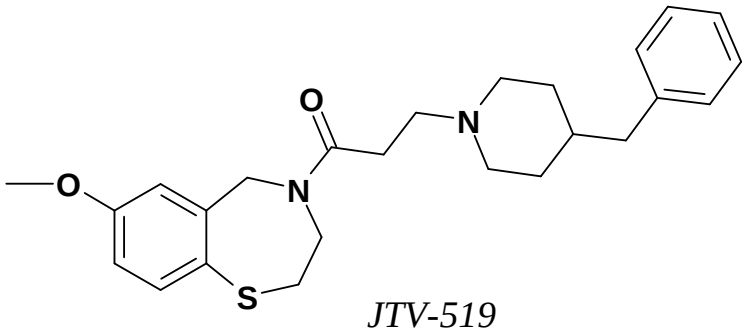
Derivatives of 4-cyclopentyl-[1,4]benzothiazepine-2,5-dione (**XIII**) were found to inhibit ACE[b] and are therefore of potential interest for antihypertensive therapy[24].



R = H, chloro, methoxy

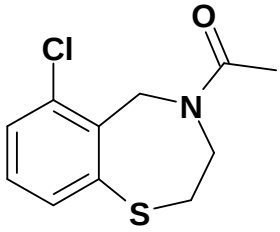
XIII

JTV-519, a 1,4-benzothiazepine derivative, developed by *Kaneko et al.*[25], has cardioprotective[26], antiarrhythmic[27] and anti-ischemic[28] properties.



JTV-519

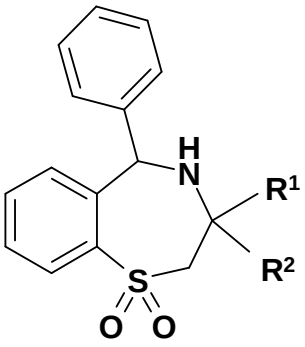
Furthermore, some benzothiazepines were found to be useful for the treatment of metabolism-related dysfunctions: e.g., 4-acetyl-6-chloro-2,3,4,5-tetrahydro-[1,4]benzothiazepine (**XIV**) was described as a very potent antiobesity agent[29].



XIV

[b] ACE: Angiotensin Converting Enzyme.

Some derivatives of 5-phenyl-[1,4]benzothiazepine-1,1-dioxide (**XV)** exhibited antihyperlipidemic[30,31] and blood glucose lowering[32] properties.



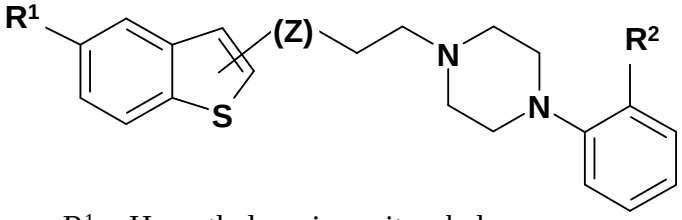
R^1, R^2 = H, alkyl

XV

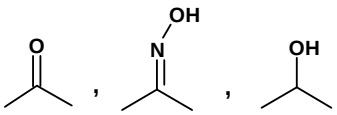
In addition, several benzo- and dibenzothiazepine derivatives showed insecticide[33], virucide[34], and antiparasite[35] properties.

1.2.2 Bioactive benzothiophenes

The benzothiophene motif represents another important example of sulfur containing heterocycles which generate a wide array of biological activities. For example, benzothiophenes of type **XVI**, fitted with a piperazine moiety in C2 or C3 inhibit serotonin reuptake and might become useful as antidepressants[36].

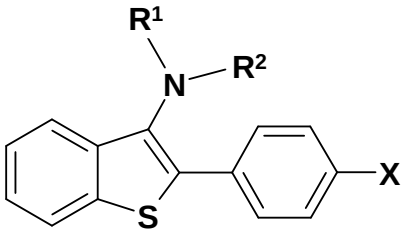


R^1 = H, methyl, amino, nitro, halogen
R^2 = H, hydroxyl, methoxy, halogen

Z = 

XVI

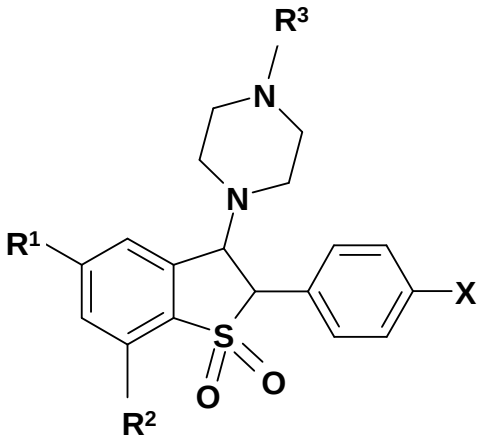
2-Phenyl-3-disubstituted amino-benzothiophenes of type **XVII** demonstrated lipid lowering properties[37,38].



X = H, chloro
R^1, R^2 = alkyl, aralkyl

XVII

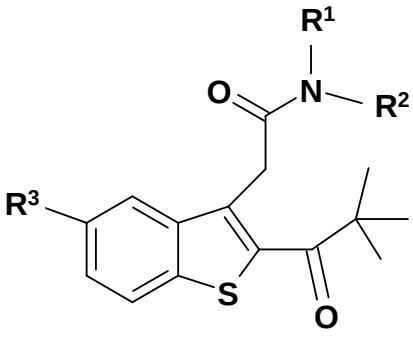
Derivatives of 2,3-dihydro-benzothiophen-1,1-dioxide of type **XVIII** displayed analgesic and antiinflammatory effects[39,40].



R^1, R^2 = H, methyl, chloro, N
R^3 = alkyl, aralkyl
X = H, chloro

XVIII

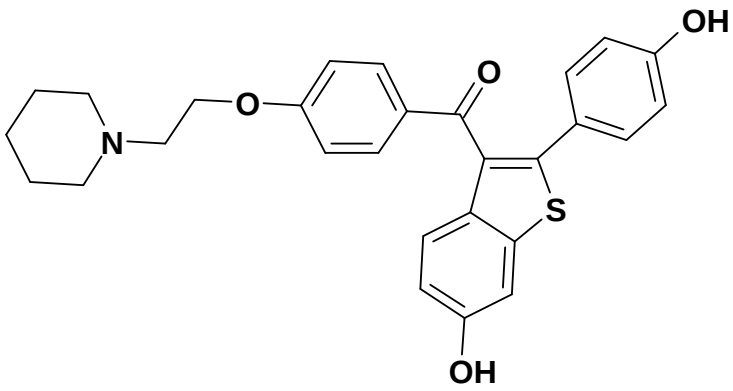
Benzothiophene derivatives belonging to type **XIX** are potassium channel blockers which reduce the intraocular pressure and are therefore of interest as potential agents for glaucoma therapy[41].



R^1, R^2 = alkyl
R^3 = H, floro, methoxy

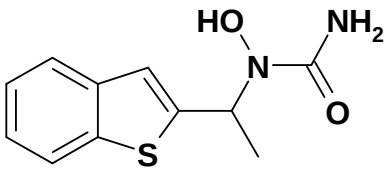
XIX

Raloxifene is a selective estrogen receptor modulator[42] and is used in the prevention of osteoporosis in postmenopausal women[43]. It also reduces the incidence of breast cancer in high risk group of females[44].



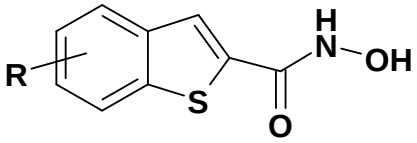
Raloxifene

Zileuton, a benzothiophene derivative with a hydroxyurea side chain is a potent 5-lipoxygenase inhibitor and is used in asthma therapy[45].



Zileuton

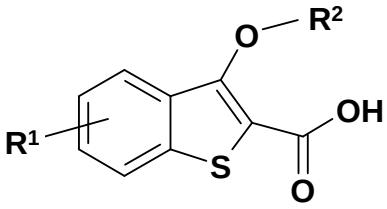
Benzothienyl-hydroxamic acids, with various substituents in C5 or C6 position of the benzothiophene core (**XX**), were described as potent histone deacetylase inhibitors, potentially valuable as antitumor agents [46].



R = aromatic amine or amide

XX

3-Alkoxy(Aralkoxy)-benzothiophene-2-carboxylic acid derivatives of type **XXI** are immunomodulators which could be helpful in treating autoimmune diseases[47].

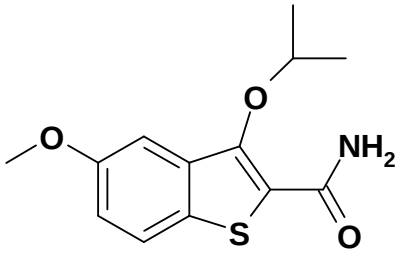


R^1 = H, chloro, nitro, methoxy

R^2 = alkyl, aryl, aralkyl

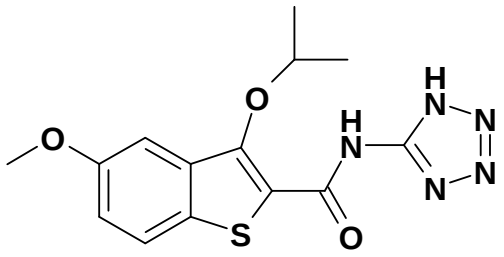
XXI

3-Isopropoxy-5-methoxy-benzothiophene-2-carboxamide (**XXII**) is an inhibitor of neutrophil-endothelial cell adhesion and has therefore antiinflammatory properties[48,49].



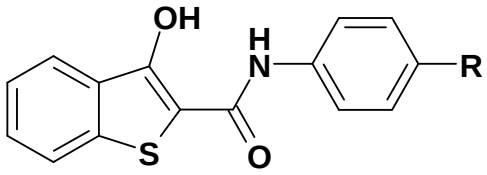
XXII

Interestingly, attachment of a tetrazole ring to the amide group in compound **XXII** delivered the antihistaminic agent *CI-959*[50], which also exhibits gastric cytoprotective properties[51].



CI-959

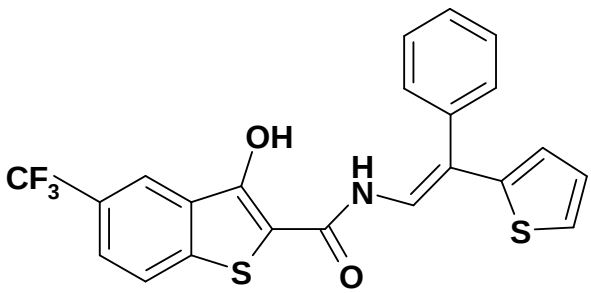
Antiinflammatory activity, based on inhibition of 5-lipoxygenase, was also observed for 3-hydroxy-benzothiophene-2-carboxanilides of type **XXIII**[52].



R = H, chloro, methoxy

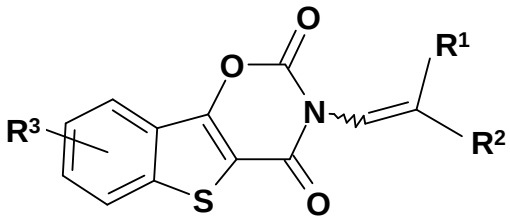
XXIII

Compound *L-652,343* shows a similar effect by acting as a dual cyclooxygenase and 5-lipoxygenase inhibitor[53,54].



L-652,343

From cyclic carbonylation of the before mentioned compound, *N*-alkenyl-benzothieno[2,3-*e*][1,3]oxazin-2,4-diones (**XXIV**) were obtained. The tricyclic compounds were found to act as prodrugs of *L-652-343*[55].



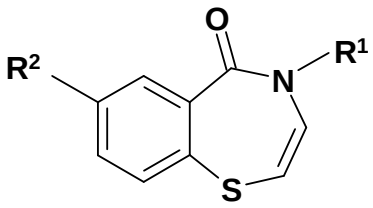
R^1, R^2 = alkyl, aryl
R^3 = H, halogen, trifluromethyl, methoxy

XXIV

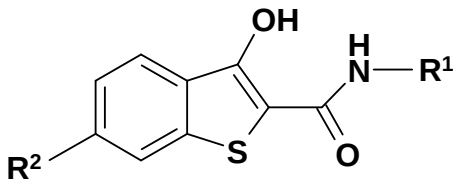
Further benzothiophene derivatives demonstrated virucide[56], molluscicide[57], endoparasiticide[58] and antidiabetic[59] activities.

1.3 Aim of Thesis

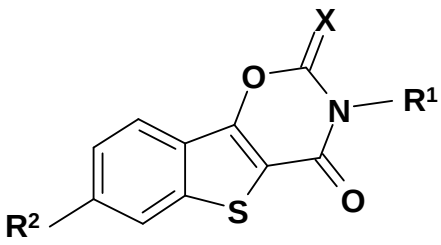
The established pharmacological importance and the wide diversity of biological activities exhibited by both benzothiazepines and benzothiophenes prompted me to carry out the present research work, which focuses mainly on the synthesis of novel 1,4-benzothiazepine derivatives of type **XXV,** 3-hydroxy-benzo[*b*]thiophene-2-carboxamides of type **XXVI** and the corresponding tricyclic compounds of type **XXVII**. Some additional results of the biological testing will also be discussed.



XXV



XXVI



XXVII

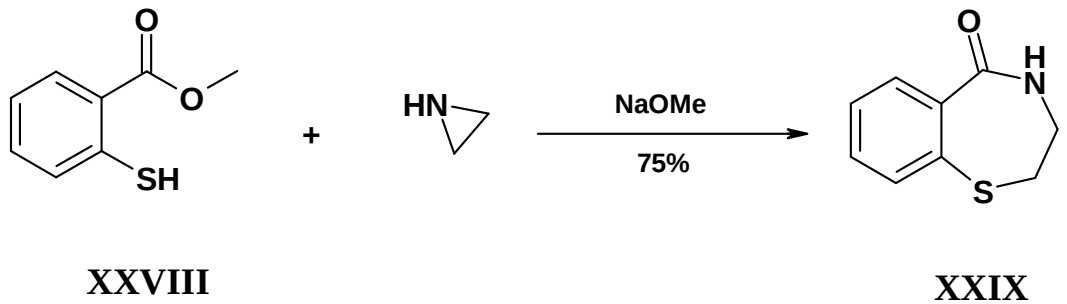
X = O , S
R^2 = H, chloro

2 1,4-Benzothiazepine-5-ones

2.1 Litreature review

Various synthetic methods for 1,4-benzothiazepine-5-ones were reported in the literature and selected examples are discussed below.
The reaction of thiosalicylic acid methyl ester (**XXVIII**) with aziridine in the presence of sodium methoxide produced compound **XXIX**, as reported by *Jakob* and *Schlack*[60] (Scheme 2-1).

Scheme 2-1 *Synthesis of Tetrahydro-[1,4]benzothiazepine-5-one* (**XXIX**)

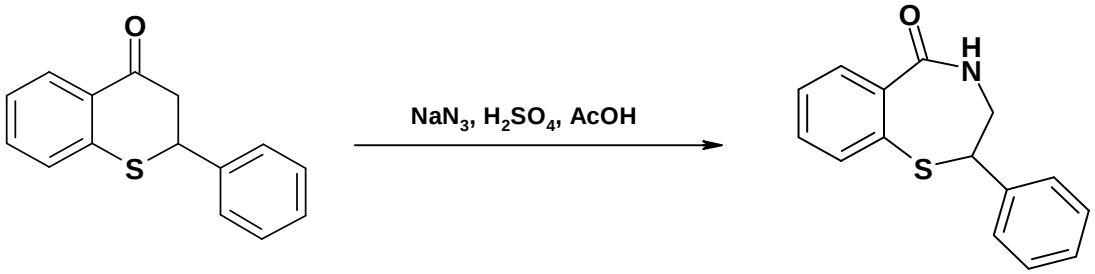


XXVIII **XXIX**

Jakob, F., Schlack, P., *Chem. Ber*. (1963) **96**, 88.

In 1980 *Levai* synthesized 2-phenyl-[1,4]benzothiazepine-5-one (**XXXI**) by ring expansion of 2-phenyl thioflavanone with sodium azide in acidic media[61] (Scheme 2-2).

Scheme 2-2 *Synthesis of 2-Phenyl-[1,4]benzothiazepine-5-one* (**XXXI**)

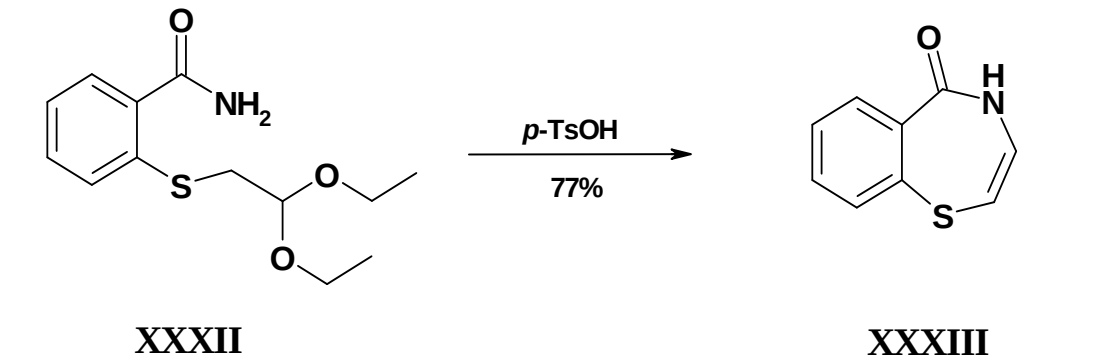


XXX **XXXI**

Levai, A., *Acta Chim. Acad. Sci. Hung.* (1980) **104**, 385

In 1988 *Hoffman* and *Fischer* synthesized the unsubstituted 1,4-benzothiazepine-5-one (**XXXIII**)[62]. The intramolecular cyclocondensation of **XXXII** was accomplished in refluxing toluene in the presence of catalytic amount of *p*-toluenesulfonic acid providing the targeted **XXXIII** in 77% yield (Scheme 2-3).

Scheme 2-3 *Synthesis of 1,4-Benzothiazepine-5-one* (**XXXIII**)

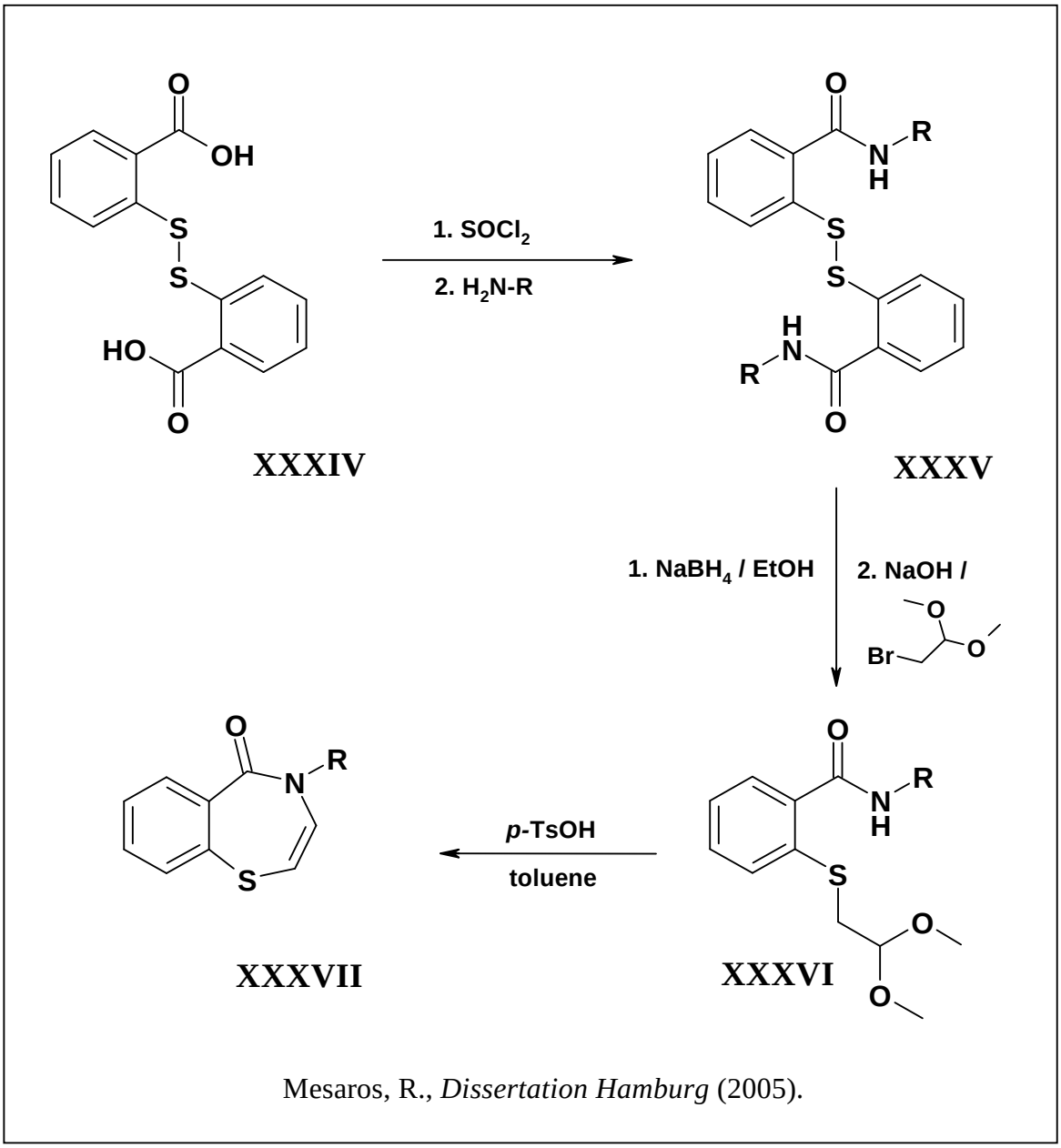


XXXII **XXXIII**

Hofmann, H., Fisher, H., *Chem. Ber*. (1988) **121**, 2147.

Mesaros reported the synthesis of *N*-alkylated derivatives of compound **XXXIII**[18,19]. As outlined in scheme 2-4, the activation of 2,2´-dithiodibenzoic acid by thionyl chloride and subsequent reaction with different amines afforded the disulfanediylbis-benzamides **XXXV,** which upon reduction and alkylation with 2-bromo-1,1-dimethoxyethane, followed by cyclocondensation of the intermediates **XXXVI** delivered the desired heterocycles **XXXVII**.

Scheme 2-4 *Synthesis of N-Alkylated-[1,4]benzothiazepine-5-ones* (**XXXVII**)



Mesaros, R., *Dissertation Hamburg* (2005).

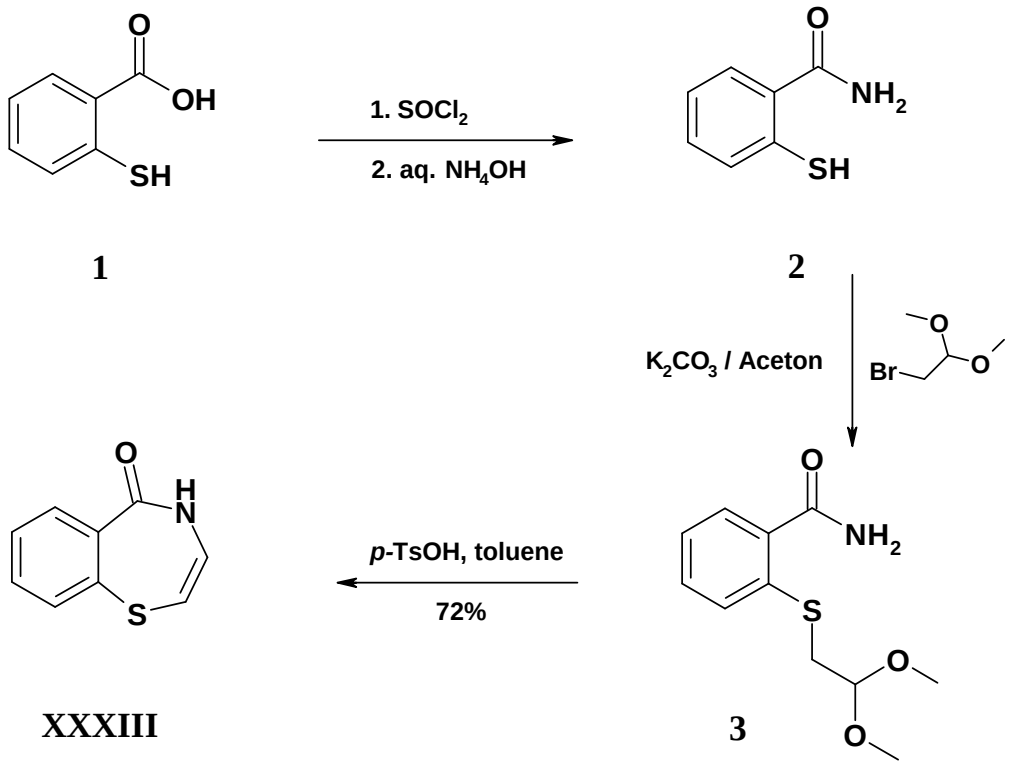
As some of the benzothiazepines **XXXVII** prepared by *Mesaros* were found to exhibit pronounced analgesic activity, it was of interest to synthesize a variety of differently substituted 1,4-benzothiazepine-5-ones, starting from thiosalicylic acid, in order to get information about structure-activity relationship.

2.2 Modification of compound XXXIII

2.2.1 Preparation of 1,4-Benzothiazepine-5-one (**XXXIII)**

Thiosalicylic acid was treated with an excess amount of thionyl chloride under reflux. The resulting acid chloride was then dissolved in dry tetrahydrofuran and added dropwise to a cooled aq. solution of ammonia (25%) to afford 2-mercapto-benzamide (**2**) as light brown precipitate. The benzamide was *S*-alkylated with 2-bromo-1,1-dimethoxyethane in dry acetone to give 2-[(2,2-dimethoxyethyl)sulfanyl]-benzamide (**3**) which finally provided 1,4-benzothiazepine-5-one (**XXXIII**) in 72% yield upon cyclic condensation in the presence of *p*-toluenesulfonic acid (Scheme 2-5).

Scheme 2-5 *Preparation of 1,4-Benzothiazepine-5-one* (**XXXIII**)



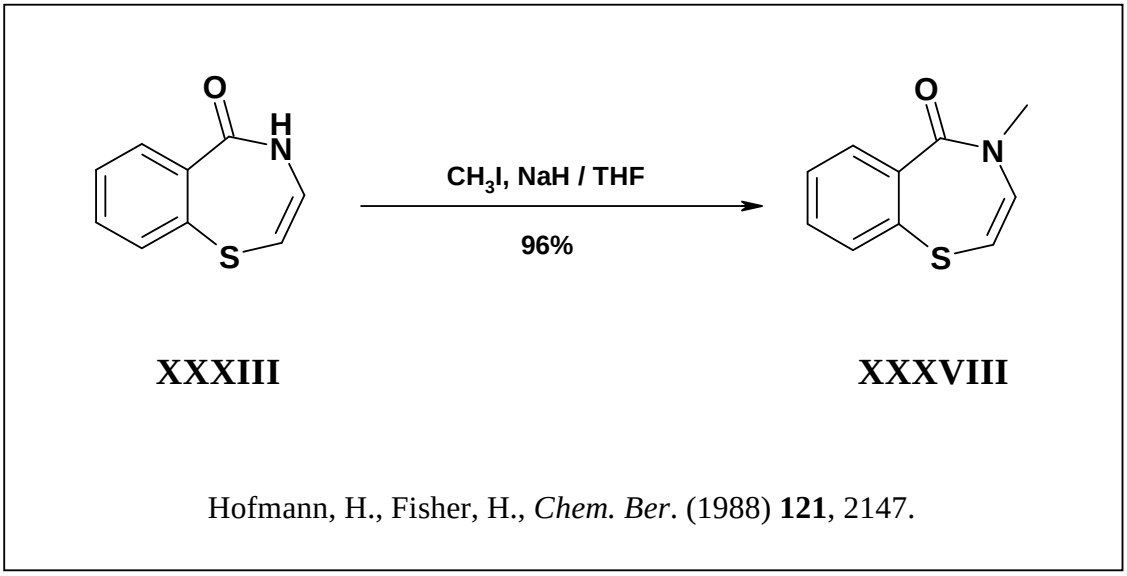
The IR spectrum of compound **XXXIII** is characterized by a strong (C=O) absorption band at 1658 cm^{-1} and a (N-H) band at 3210 cm^{-1}. (For ^{1}H-NMR and ^{13}C-NMR spectral data of **XXXIII** see experimental part)

2.2.2 *N*-Alkylation of compound **XXXIII**

Alkylation of the lactam functionality may occur at the N- or (and) O-atom, giving rise to the formation of *N*-alkyllactams or (and) cyclic imido esters[62-65].

Regioselective *N*-alkylation has been well documented in the literature[62,65-68]. For example, *Hofmann* and *Fischer* reported a selective *N*-methylation of **XXXIII** to afford 4-methyl-[1,4]benzothiazepine-5-one (**XXXVIII**) in 96% yield[62] (Scheme 2-6).

Scheme 2-6 *Synthesis of 4-Methyl-[1,4]benzothiazepine-5-one* (**XXXVIII**)

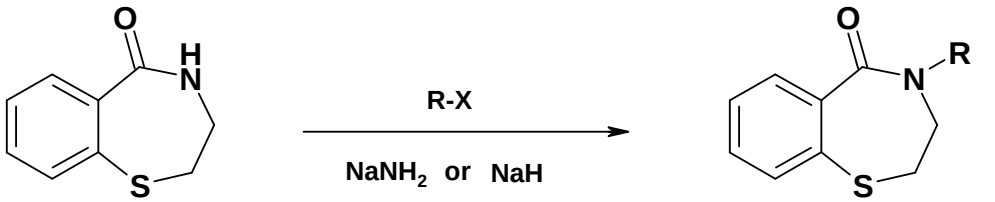


XXXIII **XXXVIII**

Hofmann, H., Fisher, H., *Chem. Ber*. (1988) **121**, 2147.

Similarly, alkylation of **XXIX** with methyl iodide or benzyl chloride furnished the corresponding **XXXIX** in 49/ 78% yield, respectively[7] (Scheme 2-7).

Scheme 2-7 *Alkylation of Compound* **XXIX**



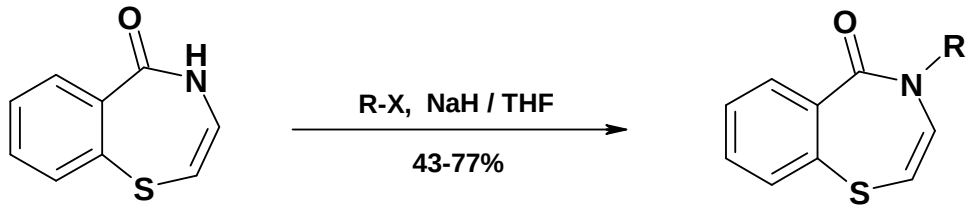
XXIX **XXXIX**

R = methyl, benzyl

Wünsch, K. H., Ehlers, A., Beyer, H., *Chem. Ber*. (1969) **102**, 1618.

In a similar fashion, **XXXIII** was converted as part of this thesis to the aimed 4-alkyl(aralkyl)-1,4-benzothiazepine-5-ones (**4**) by treating an ice-cooled mixture of **XXXIII** and sodium hydride in dry tetrahydrofuran with one equivalent of the appropriate alkylating agent. After stirring the mixture for 18 h at ambient temperature, the heterocyclic compounds **4a-d** were isolated as solid and stable substances in 43-77% yield (Scheme 2-8, Table 2-1).

Scheme 2-8 *Synthesis of 1,4-Benzothiazepine-5-ones* (**4**)



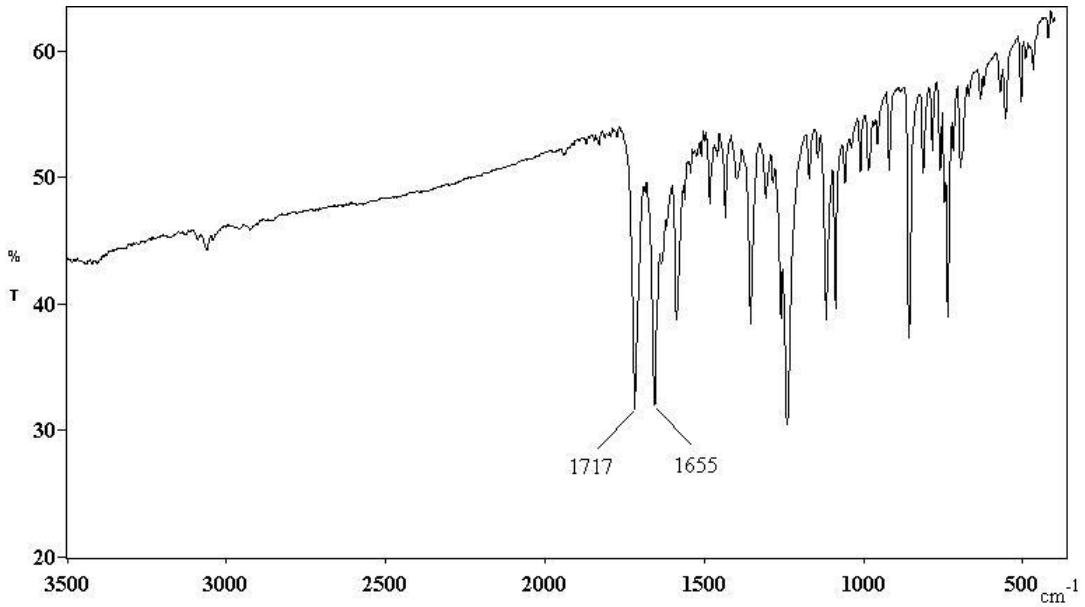
XXXIII **4a-d**

Table 2-1 *Prepared 1,4-Benzothiazepine-5-ones* (**4**)

4	**R**	**Yield (%)**
a	$C_6H_5COCH_2$	43
b	C_6H_5CO	66
c	4-$CH_3C_6H_4CO$	68
d	4-Cl-C_6H_4CO	77

The IR spectra of **4** are characterized by the presence of two strong (C=O) bands at 1627-1676 cm^{-1} and 1695-1717 cm^{-1} (Fig. 2-1).

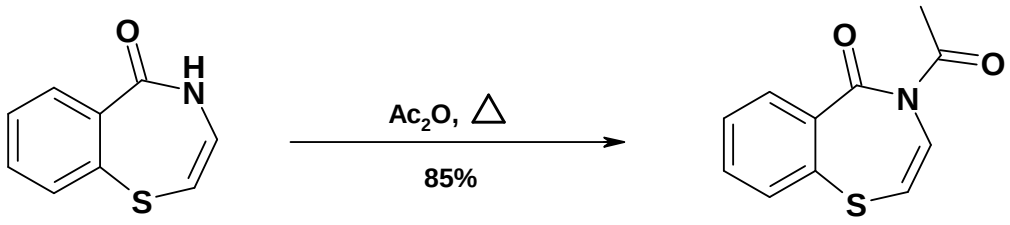
Fig. 2-1 *IR (KBr) Spectrum of 4-(4-Chloro-benzoyl)-[1,4]benzothiazepine-5-one* (**4d**)



2.2.3 Preparation of 4-Acetyl-[1,4]benzothiazepine-5-one (**5**)

Heating compound **XXXIII** with excess amount of acetic anhydride provided compound **5**. The product was obtained as a yellow solid after simple work up in 85% yield (Scheme 2-9).

Scheme 2-9.*Synthesis of 4-Acetyl-[1,4]benzothiazepine-5-one* (**5**)



XXXIII **5**

The IR spectrum of compound **5** shows two (C=O) absorption bands at 1676 and 1707 cm^{-1} which are typical for an imide group[69].

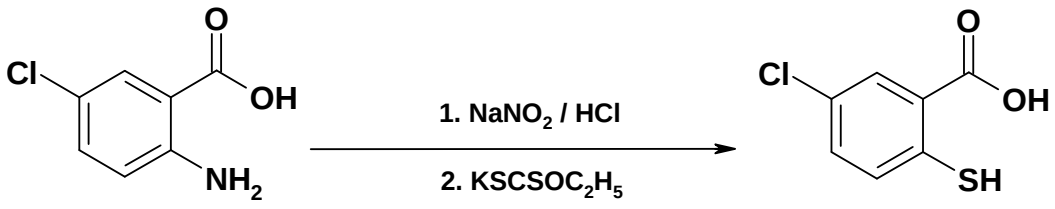
2.3 Synthesis of 7-Chloro-[1,4]benzothiazepine-5-ones

After the successful synthesis of *N*-substituted benzothiazepines **XXXVII** reported by *Mesaros* (Scheme 2-4)**,** this procedure was extended to the preparation of the 7-chloro analogs of **XXXVII** starting from 5-chloro-thiosalicyclic acid (**7**).

2.3.1 Synthesis of 5-Chlorothiosalicylic acid (**7**)

5-Chlorothiosalicylic (**7**) acid was synthesized according to the procedure described by *Katz et al*[70]. Diazotization of the corresponding anthranilic acid (**6)**, subsequent reaction with potassium ethyl xanthate and final hydrolysis with aq. sodium hydroxide (10%) produced **7** as yellow fine powder in 78% yield (Scheme 2-10).

Scheme 2-10 *Synthesis of 5-Chlorothiosalicylic acid* (**7**)

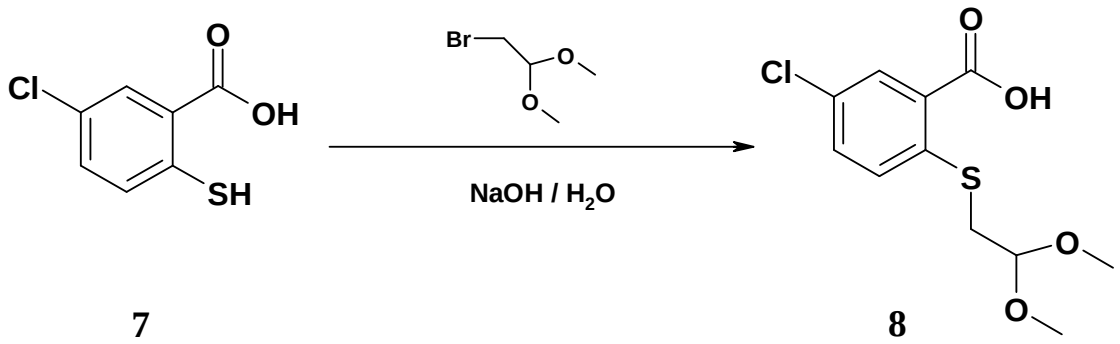


6 **7**

2.3.2 Preparation of 5-Chloro-2-[(2,2-dimethoxyethyl)sulfanyl]-benzoic acid (**8**)

5-Chlorothiosalicylic acid (**7**) was dissolved in a 10% aq. solution of sodium hydroxide and treated with 2-bromo-1,1-dimethoxyethane. The reaction mixture was heated to 70 °C and stirred for another 2 hours. Upon cooling and acidification with aq. HCl (10%), 5-chloro-2-[(2,2-dimethoxyethyl)sulfanyl]-benzoic acid (**8**) was obtained in 87% yield (Scheme 2-11).

Scheme 2-11 *Synthesis of 5-Chloro-2-[(2,2-dimethoxyethyl)sulfanyl]-benzoic acid* (**8**)



7 **8**

2.3.3 Preparation of 5-Chloro-2-[(2,2-dimethoxyethyl)-sulfanyl]-benzamides (**10**)

Compound **8** was converted to the corresponding azolide by treatment with 1,1`-carbonyldiimidiazole (CDI) in dry tetrahydrofuran. The formation of the intermediate **9** was confirmed by IR spectroscopy of the reaction mixture showing a strong (C=O) absorption at 1740 cm^{-1}. Subsequent addition of the respective benzylamine to the mixture afforded the corresponding amides **10a-c** in 52-83% yield (Scheme 2-12, Table 2-2).

Scheme 2-12 *Synthesis of 5-Chloro-2-[(2,2-dimethoxyethyl)sulfanyl]-benzamides* (**10**)

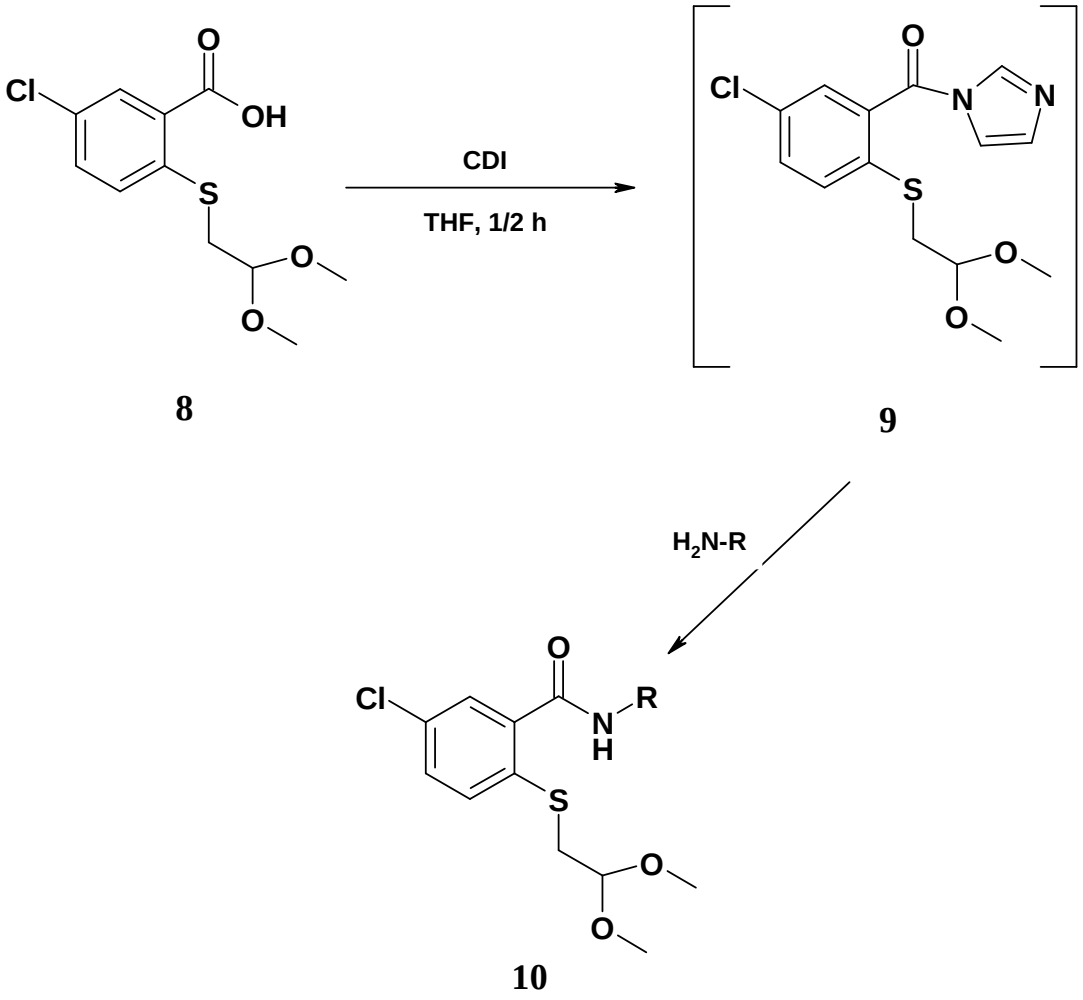


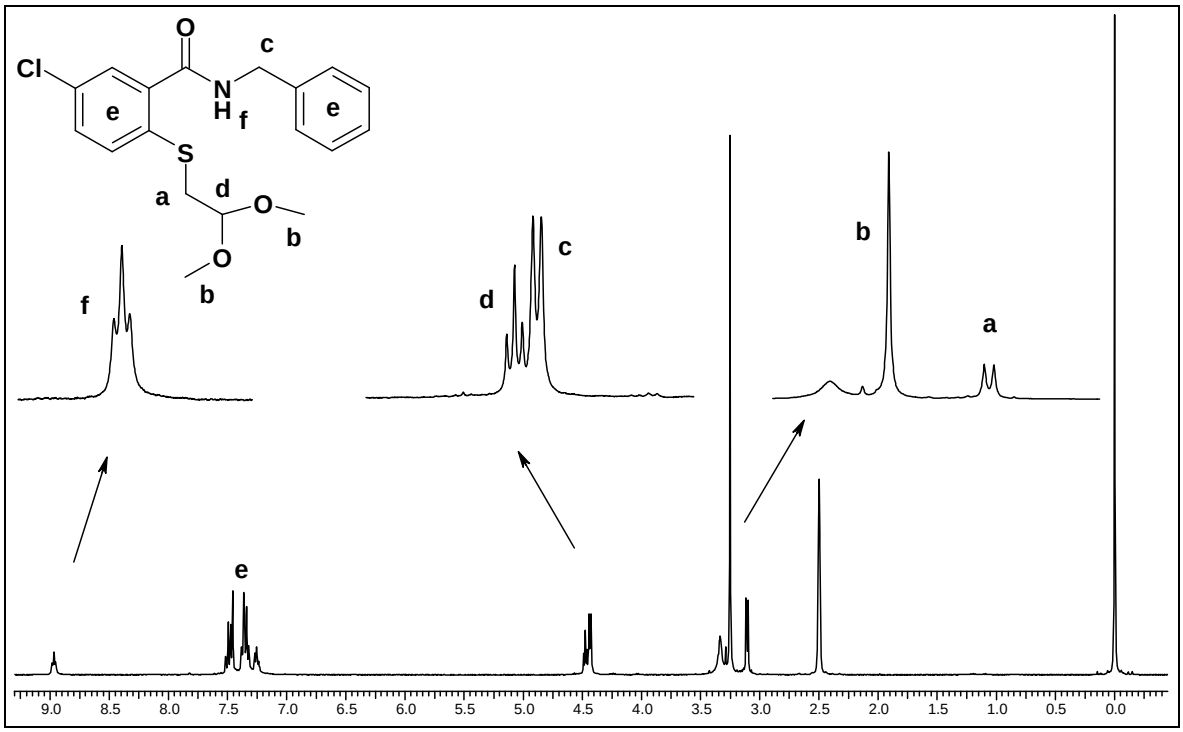
Table 2-2 *Prepared 5-Chloro-2-[(2,2-dimethoxyethyl)sulfanyl]-benzamides* (**10**)

10	**R**	**Yield (%)**
a	$C_6H_5CH_2$	85
b	4-F-$C_6H_4CH_2$	63
c	2,4-di-Cl-$C_6H_3CH_2$	52

Compounds **10a-c** were obtained as white stable solids, which display in the IR spectra a strong (C=O) absorption band at 1636 cm^{-1} and a broad (NH) absorption band at 3275 cm^{-1}.

The ^{1}H-NMR spectrum of compound **10a** is characterized by a doublet at 3.11 ppm (S-CH_2), a singlet at 3.34 ppm (O-CH_3), a doublet at 4.43 ppm (Ph-CH_2), a triplet at 4.48 (CH) and a triplet at 8.97 ppm (NH) (Fig. 2-2).

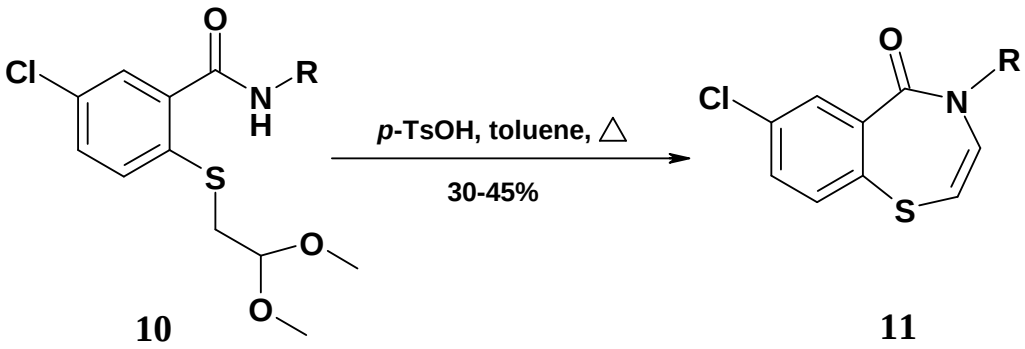
Fig. 2-2 *^{1}H-NMR Spectrum of N-Benzyl-5-chloro-2-[(2,2-dimethoxyethyl)-sulfanyl]-benzamide* (**10a**)



2.3.4 Cyclocondensation of **10a-c** to *N*-Substituted 7-chloro-[1,4]benzothiazepine-5-ones (**11**)

A mixture of **10** and catalytic amounts of *p*-toluenesulfonic acid in toluene was refluxed for 18 hours. After cooling, the mixture was extracted with saturated solution of $NaHCO_3$, the organic phase was collected, dried over magnesium sulfate and evaporated under reduced pressure.
Column chromatography of the crude products provided the desired 4-(arylmethyl)-[1,4]benzothiazepine-5-ones (**11a-c**) as solid substances[c] in 30-45% yields (Scheme 2-13, Table 2-3).

Scheme 2-13 *Synthesis of 4-(Arylmethyl)-7-chloro-[1,4]benzothiazepine-5-ones* (**11**)



10 **11**

Table 2-3 *Prepared 4-(Arylmethyl)-7-chloro-[1,4]benzothiazepine-5-ones (11)*

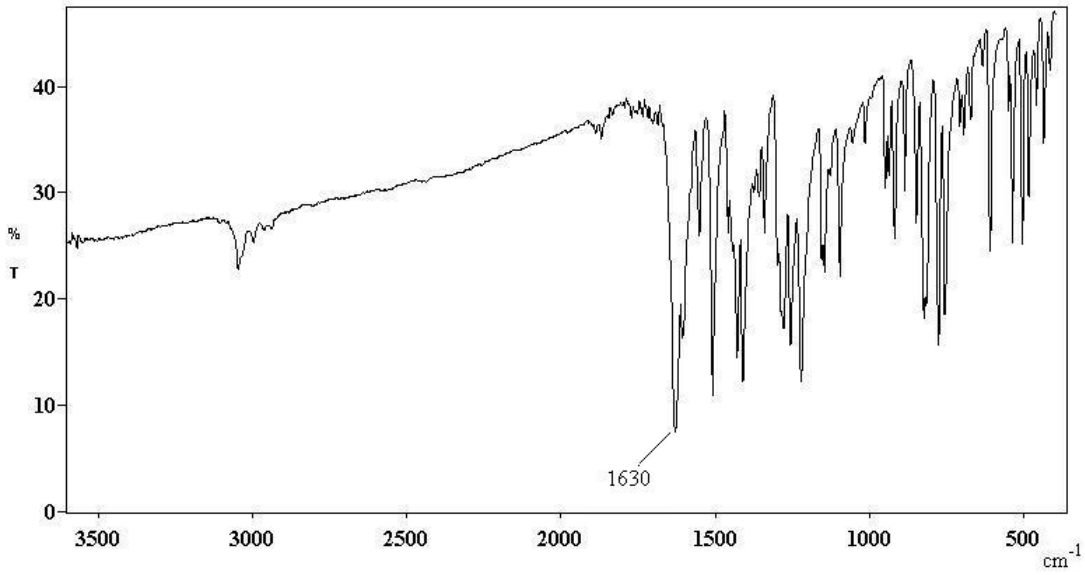
11	**R**	**Yield (%)**
a	$C_6H_5CH_2$	43
b	4-F-$C_6H_4CH_2$	45
c	2,4-di-Cl-$C_6H_3CH_2$	30

[c] The 1,4-benzothiazepine-5-one derivatives (XXXVII) (R = alkyl, aralkyl) prepared by *Mesaros* were described as oily substances.

2.3.5 Properties of 4-(Arylmethyl)-7-chloro-[1,4]benzothiazepine-5-ones (**11**)

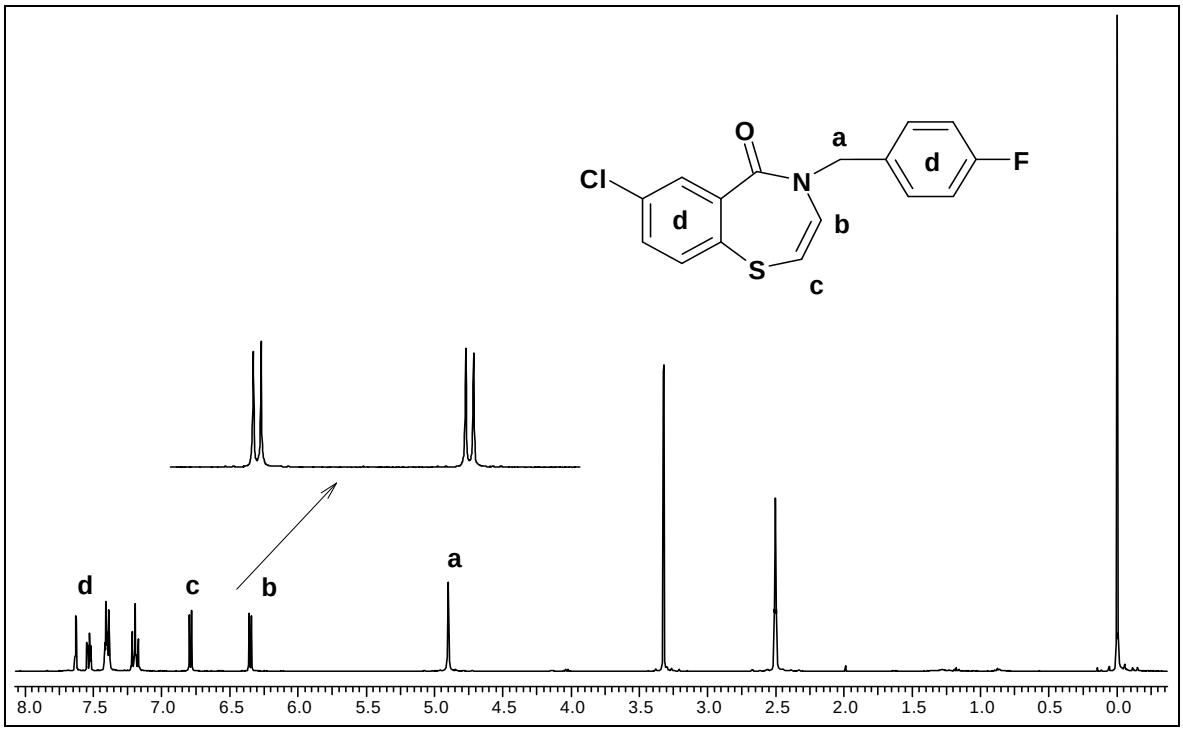
The IR spectra of compounds **11** are characterized by a sharp (C=O) absorption band between 1625-1636 cm^{-1} (Fig. 2-3).

Fig. 2-3 *IR (KBr) Spectrum of 7-Chloro-4-(4-flurobenzyl)-[1,4]benzo-thiazepine-5-one* (**11b**)



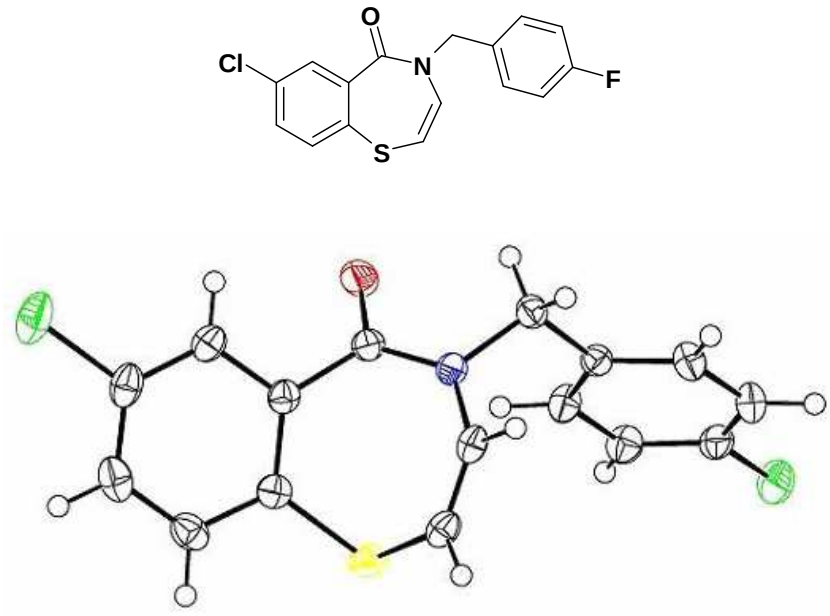
The ^{1}H-NMR spectrum of compound **11b** is characterized by a singlet at 4.90 ppm (aryl-CH_2) and two doublets at 6.35 and 6.79 ppm (S-CH=CH-N) (Figure 2-4).

Fig. 2-4 *^{1}H-NMR Spectrum of 7-Chloro-4-(4-flurobenzyl)-[1,4]benzothiazepine-5-one* (**11b**)



Finally, the molecular structure of **11b** could be unambiguously proven by X-ray crystallography (Figure 2-5).

Fig. 2-5 *Molecular Structure of 7-Chloro-4-(4-flurobenzyl)-[1,4]benzothiazepine-5-one* (**11b**)

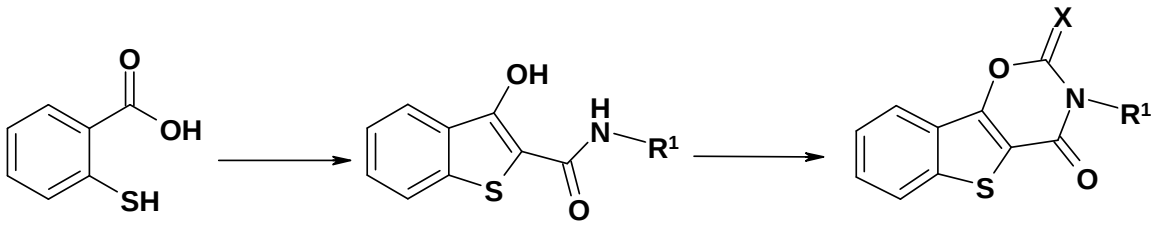


3 3-Hydroxy-benzo[*b*]thiophene-2-carboxamides and Heterocycles Thereof

The benzothiophene moiety represents an important pharmacophore-/toxophore in drug chemistry and agrochemistry[71-73].

As already mentioned before (s. page 20), the present work is focused on structural modifications of 3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**XXVI**) as well as their heterocyclization to benzothieno[2,3-*e*][1,3]oxazines (**XXVII**) (Scheme 3-1).

Scheme 3-1



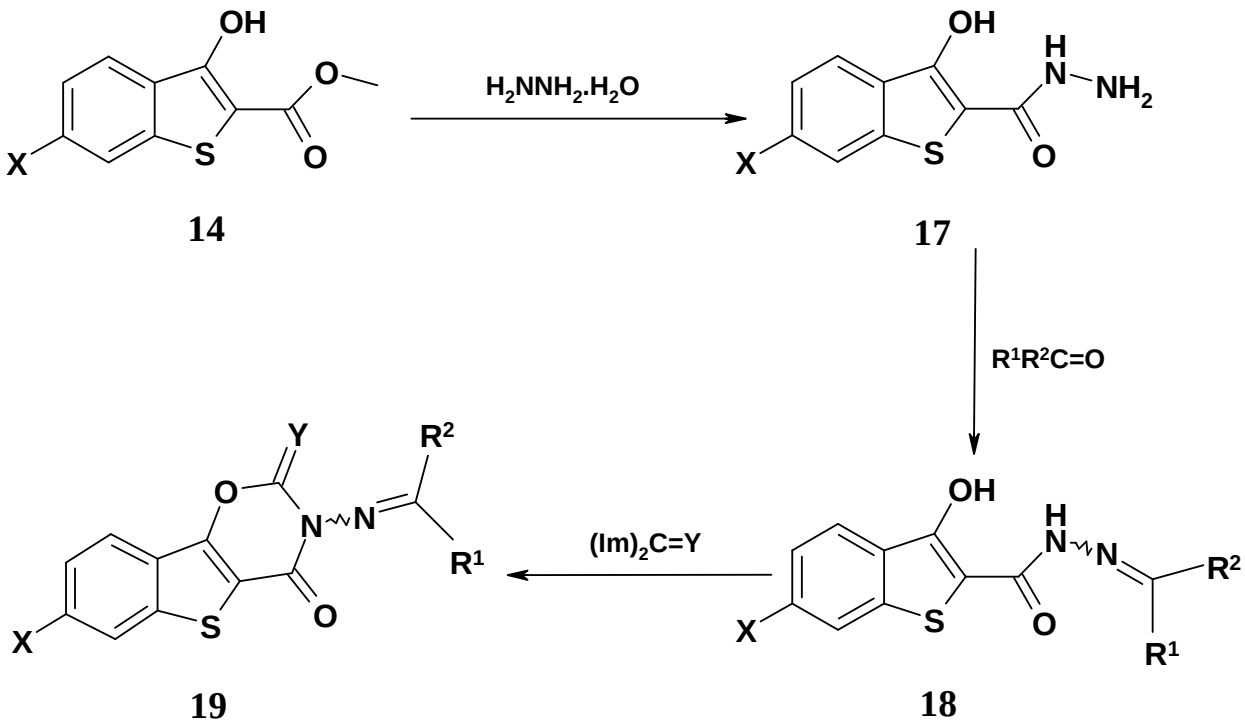
1 **XXVI** **XXVII**

R^1 = alkoxy or aralkoxy
alkenylamine
substituted amine

3.1 Synthesis of *N*-Aminoalkenyl-3-hydroxy-benzo[*b*]thiophene-2-carboxamides and their corresponding condensed 1,3-oxazine derivatives

Methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylates (**14**) were anticipated to undergo hydrazinolysis giving 3-hydroxy-beno[*b*]thiophene-2-carbohydrazides (**17**), which upon successive condensation with various ketones and aldehydes were expected to deliver *N*-aminoalkenyl-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**18**)[d]. Finally, subsequent cyclization of the hydrazones **18** was thought to produce 3-aminoalkenyl-benzothieno[2,3-*e*][1,3]oxazines (**19**) (Scheme 3-2).

Scheme 3-2



Im = Imidazole
Y = O, S

[d] Hydrazides and hydrazones may serve as pharmacophores in medicinal chemistry. E.g., isonicotinic acid hydrazide (*Isoniazid*) is still used in tuberculosis therapy since 1952, when its action against Mycobacterium tuberculosis was first discovered[74]. Hydrazone derivatives of *Isoniazid* were also found to exhibit comparable antimicrobial activity[75]. *Nifuroxazide* is a benzohydrazide derivative, which used as an antiseptic agent[76]. Further acylated hydrazones were reported to demonstrate antihypertensive effects[77]

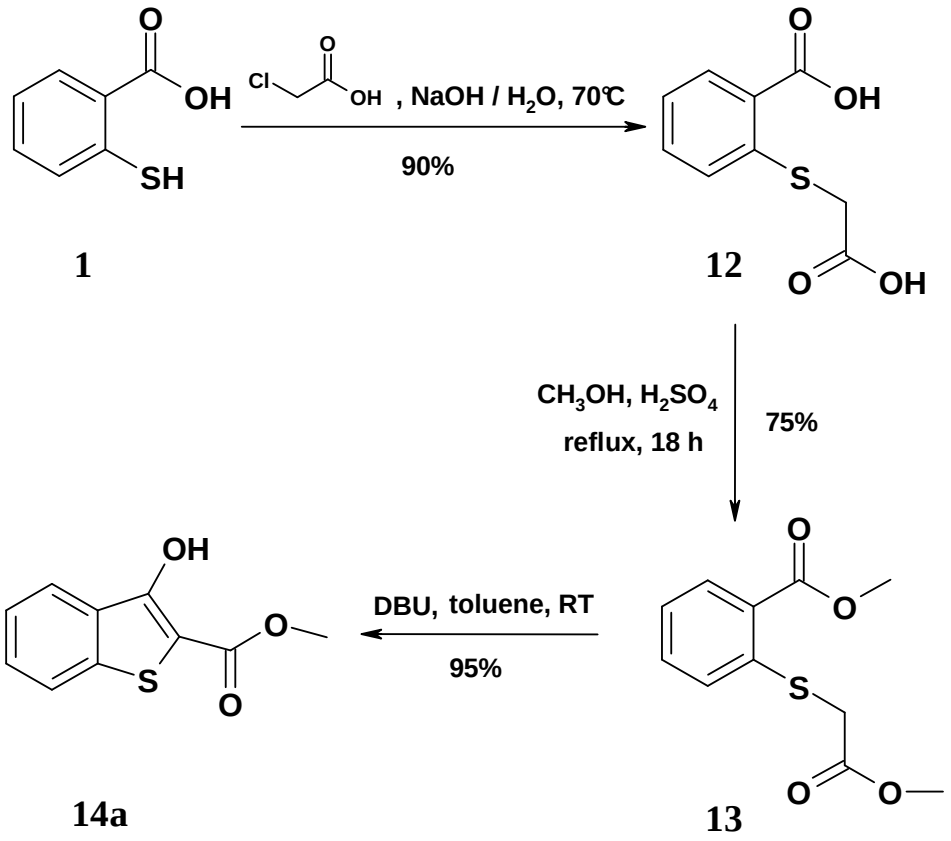
3.1.1 Synthesis of Methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylates (**14**)

The first synthesis of **14** was reported in 1907 by *Friedlaender*[78]. Starting from thiosalicylic acid (**1**), he was able to prepare methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylate (**14a**) in a three step reaction sequence.
Later, a number of slightly modified procedures have been published that are summarized in a review[79].
In this work, the desired compounds **14** have been prepared by the following routes A/B.

Procedure A

In this slightly modified *Friedlaender*'s procedure, thiosalicylic acid (**1**) was *S*-alkylated with chloroacetic acid in aqueous sodium hydroxide (10%). After cooling and acidification of the reaction mixture, 2-carboxymethylsulfanyl-benzoic acid (**12**) was obtained. The dicarboxylic acid was dissolved in a mixture of methanol/sulfuric acid (10%) and refluxed for 18 hours to give methyl 2-[(2-methoxy-2-oxoethyl)-sulfanyl]benzoate (**13)** which was subsequently cyclized in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to furnish the desired methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylates (**14a**) in overall yield of 75% (Scheme 3-3).

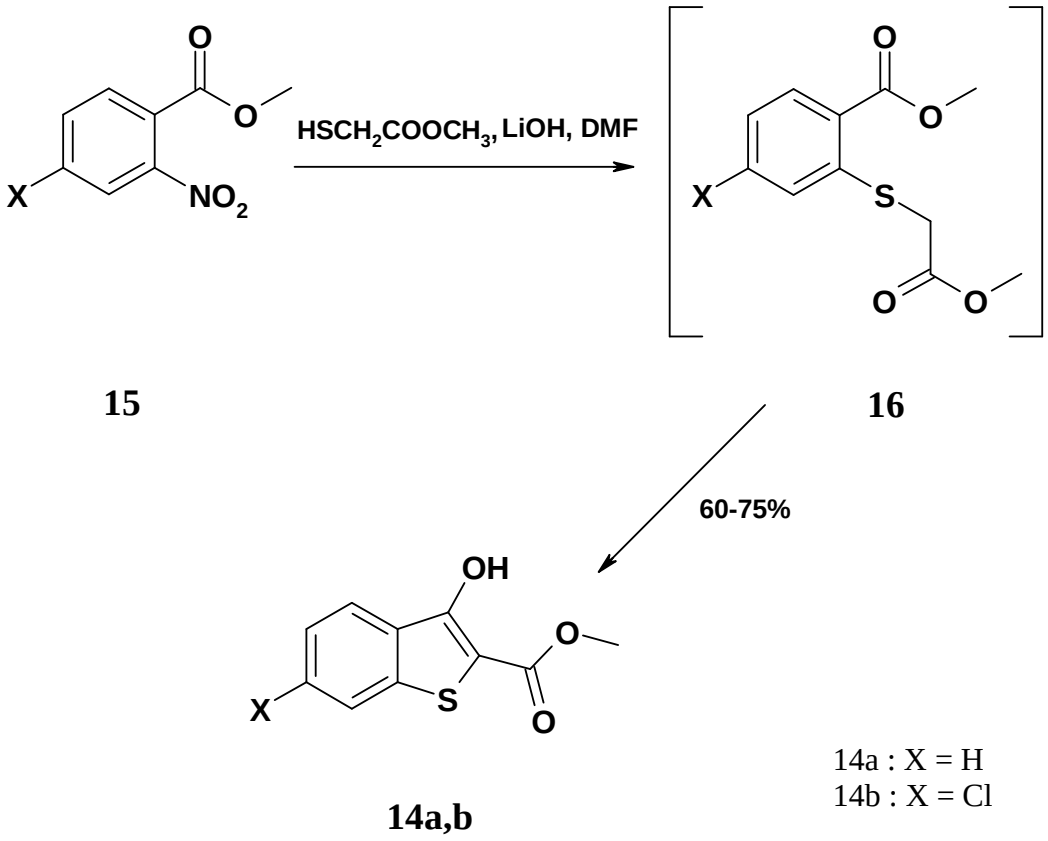
Scheme 3-3 *Synthesis of Methyl 3-hydroxy-benzo[b]thiopene-2-carboxylate* (**14a**); *Procedure A*



Procedure B

This procedure was described by *Beck* in 1973[80]: nucleophilic displacement of the nitro group in methyl *o*-nitrobenzoates (**15**) by methyl thioglycolate anion (lithium salt) in DMF, followed by base catalyzed cyclization of the intermediates **16**, furnished the targeted methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylates (**14a,b)** in 60 or 75% yield, respectively (Scheme 3-4).

Scheme 3-4 *Synthesis of Methyl 3-hydroxy-benzo[b]thiopene-2-carboxylates* (**14**); *Procedure B*

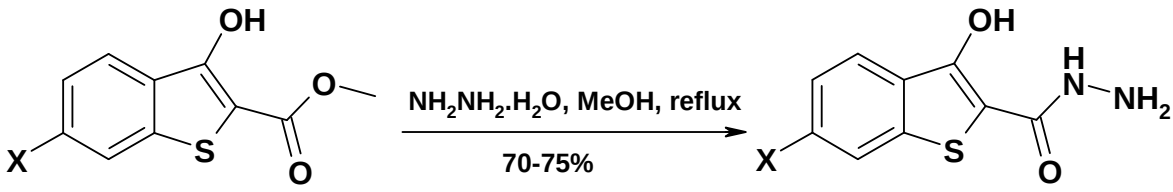


The methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylates (**14a,b**), prepared as part of my thesis, are stable solid compounds and their IR spectra are characterized by a strong (C=O) absorption band at 1660-1665 cm^{-1}.

3.1.2 Synthesis of 3-Hydroxy-benzo[*b*]thiophene-2-carbohydrazides (**17**)

When a mixture of compounds **14** with hydrazine hydrate in methanol was refluxed for 2 hours, the corresponding 3-hydroxy-benzo[*b*]thiophene-2-carbohydrazides (**17a,b**) were obtained in 70-75% yield as pale yellow stable solids (Scheme 3-5).

Scheme 3-5 *Synthesis of 3-Hydroxy-benzo[b]thiophene-2-carbohydrazides* (**17**)

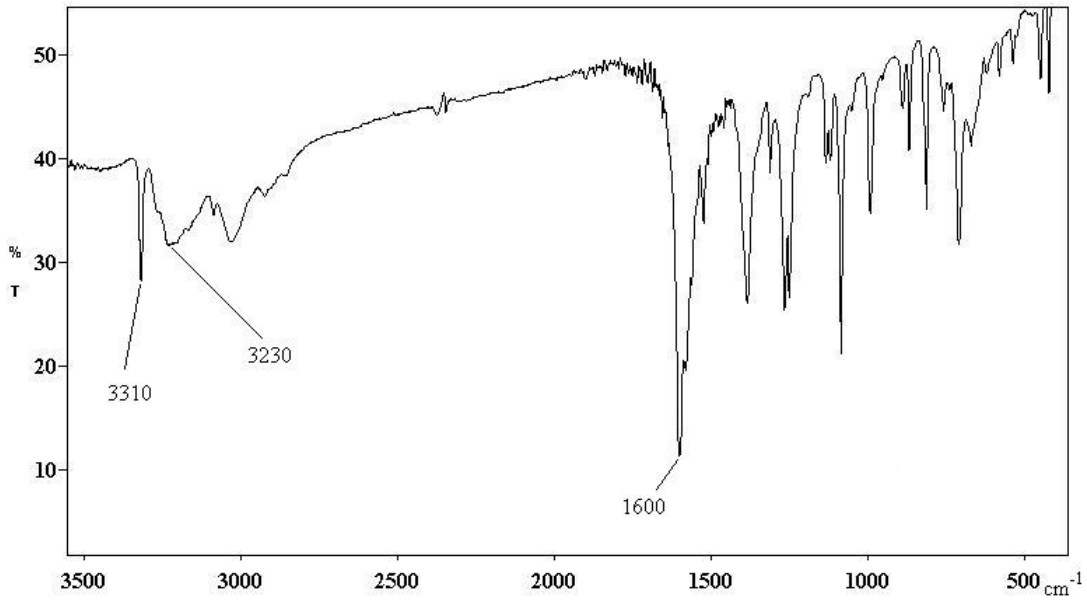


14a,b **17a,b**

17a: X = H
17b: X = Cl

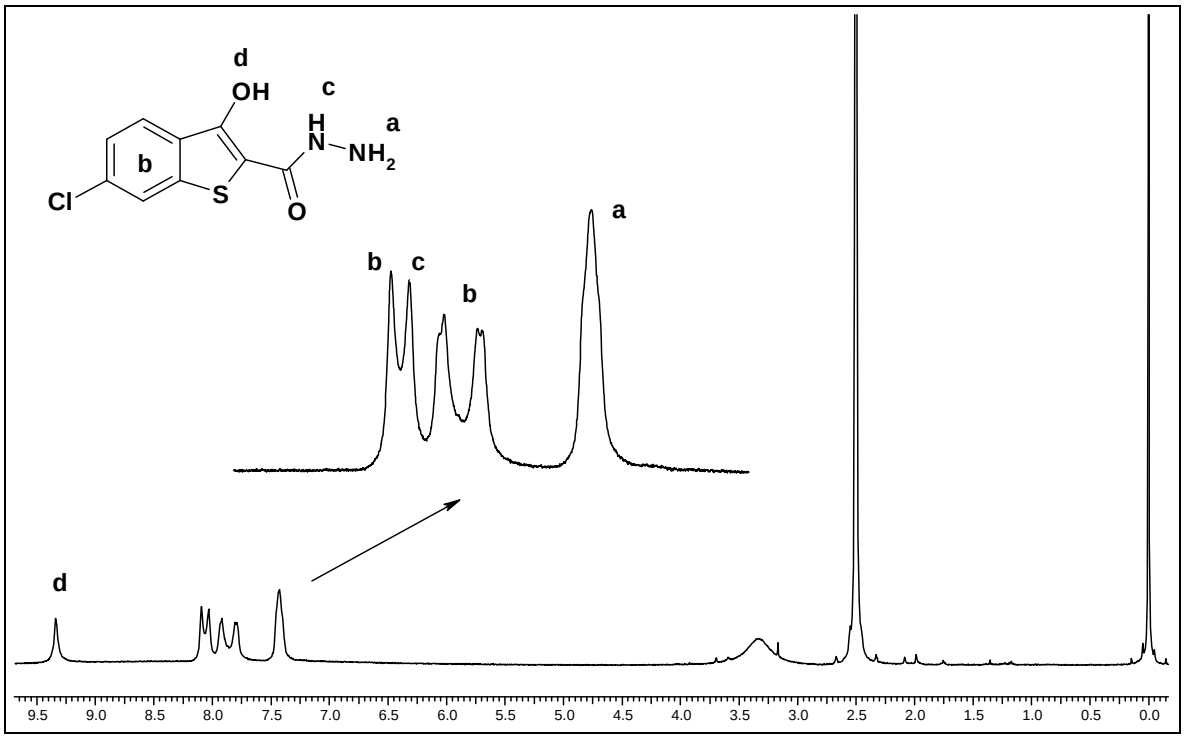
The IR spectra of compounds **17** display a sharp (C=O) absorption band at 1600 cm^{-1} and two (NH) absorption bands at 3230 and 3310 cm^{-1} (Fig. 3-1).

Fig. 3-1 *IR (KBr) Spectrum of 6-Chloro-3-hydroxy-benzo[b]thiophene-2-carbohydrazide* (**17b**)



The ^{1}H-NMR spectrum of compound **17b** is shown in Fig. 3-2 and exhibits three singlets at 7.43 ppm (NH_2), 8.04 ppm (NH) and 9.34 ppm (OH) besides multiplets of the aromatic protons at 7.80-8.10 ppm.

Fig. 3-2 *[1]H-NMR Spectrum of 6-Chloro-3-hydroxy-benzo[b]thiophene-2-carbohydrazide* (**17b**)



3.1.3 Condensation of 3-Hydroxy-benzo[*b*]thiophene-2-carbohydrazides (**17**) with ketones and aldehydes

After having successfully prepared the carbohydrazides **17**, it was of interest to study their behaviour towards ketones and aldehydes. When a mixture of **17** and ketone/aldehyde in a molar ratio of 1:2 was refluxed in methanol for 1 h, the *N*-aminoalkenyl-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**18**) were obtained as solid materials in 85-92% yield (Scheme 3-6, Table 3-1).

Scheme 3-6 *Preparation of N-Aminoalkenyl-3-hydroxy-benzo[b]thiophene-2-carboxamides* (**18**)

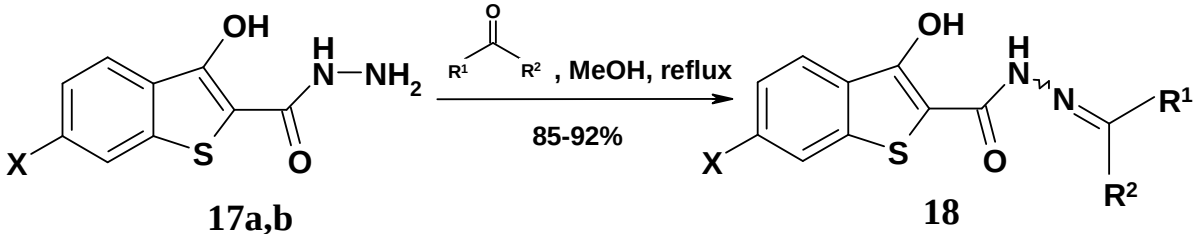
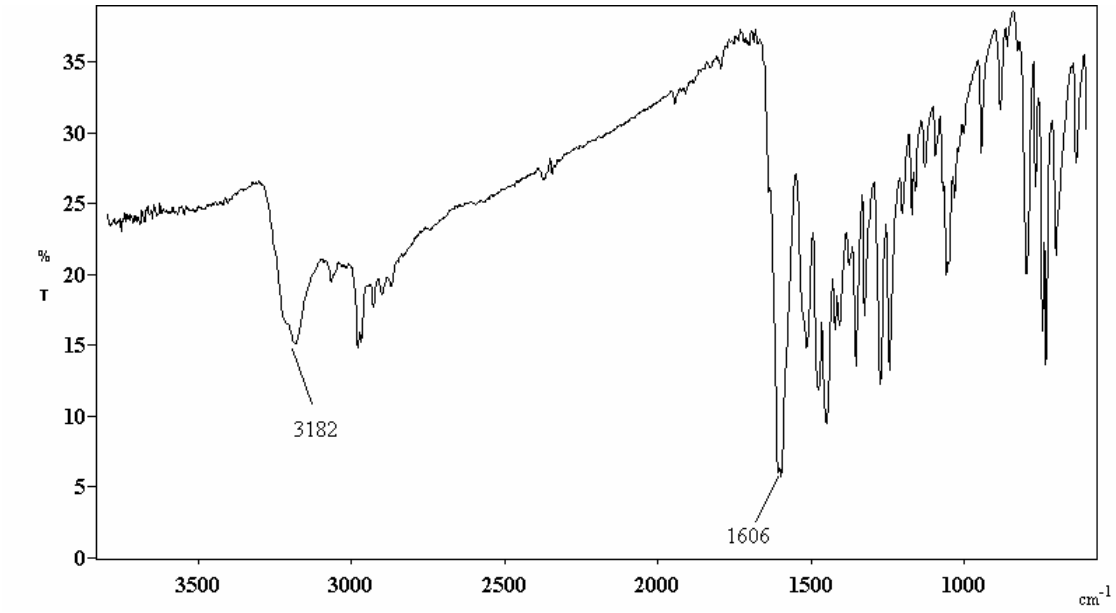


Table 3-1 *Prepared N-Aminoalkenyl-3-hydroxy-benzo[b]thiophene-2-carboxamides* (**18**)

18	**X**	**R^1**	**R^2**	**Yield (%)**
a	H	CH_3	CH_3	87
b	Cl	CH_3	CH_3	90
c	H	C_2H_5	C_2H_5	85
d	Cl	C_2H_5	C_2H_5	86
e	H	H	C_6H_5	89
f	Cl	H	C_6H_5	90
g	H	CH_3	C_6H_5	90
h	Cl	CH_3	C_6H_5	92

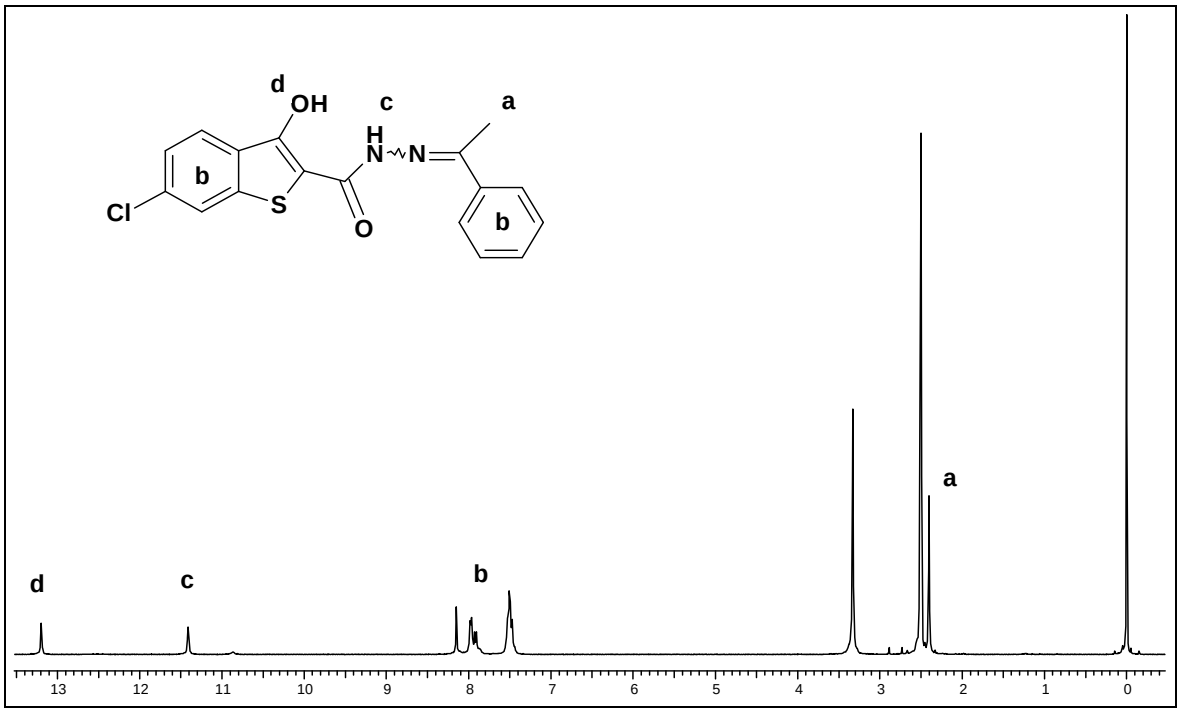
The IR spectra of compounds **18** display absorption bands at 1605-1635 cm^{-1} (C=O) and 3150-3185 cm^{-1} (NH) (Fig. 3-3).

Fig. 3-3 *IR (KBr) Spectrum of 3-Hydroxy-N-(pentan-3-ylideneamino)-benzo[b]thiophene-2-carboxamide* (**18c**)



The ^{1}H-NMR spectrum of compound **18h** offers singlets at 2.41 ppm (CH_3), 11.41 ppm (NH) and 13.20 ppm (OH) in addition to the signals of the arylic protons between 7.51-8.15 ppm (Fig. 3-4).

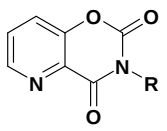
Fig. 3-4 *[1]H-NMR Spectrum of 6-Chloro-3-hydroxy-N-(1-phenylethylidene-amino)-benzo[b]thiophene-2-carboxamide* (**18h**)



3.1.4 Cyclic carbonylation (thiocarbonylation) of compounds **18** to 3-Aminoalkenyl-benzothieno[2,3-*e*][1,3]oxazines (**19**)

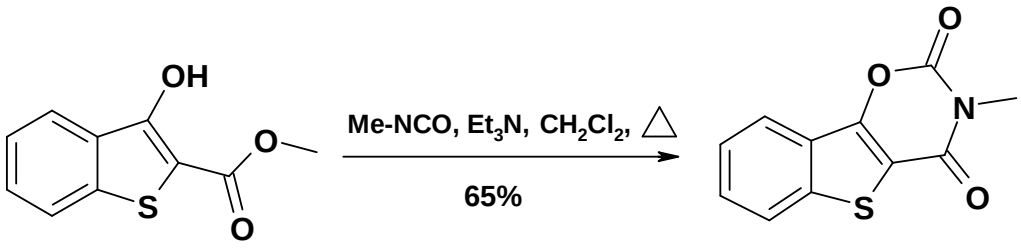
After the successful preparation of compounds **18**, their cyclic carbonylation to give benzothieno[2,3-*e*][1,3]oxazines of type **19** became of interest to me. The first examples of such fused heterocycles[e] were reported by *Beck* in 1975[81] when methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylate (**14a**) was reacted with methyl isocyanate in the presence of triethylamine to produce 3-methyl-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**XLI**) in 65% yield (Scheme 3-7).

[e] Oxazino anellated heterocycles are an interesting class of compounds from the perspective of medicinal chemists. As an example, Pyrido[2,3-*e*][1,3]-oxazine-2,4-diones (**XL**) have a broad spectrum of biological effects including analgesic, antipyretic, bacteriostatic, fungistatic, and monoaminoxidase inhibitory activity[82,83].



XL

Scheme 3-7 *Synthesis of 3-Methyl-benzothieno[2,3-e][1,3]oxazine-2,4-dione* (**XLI**)

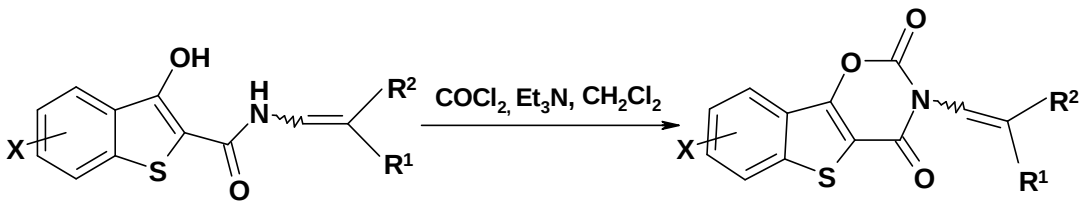


14a **XLI**

Beck, J. R., *J. Heterocycl. Chem.* (1975) **12**, 1037.

Later, *Marfat* described the synthesis of 3-alkenyl-benzothieno[2,3-*e*][1,3]oxazine-2,4-diones[f] (**XLIII**) from base catalyzed phosgenation of *N*-alkenyl-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**XLII**)[55] (Scheme 3-8).

Scheme 3-8 *Synthesis of 3-Alkenyl-benzothieno[2,3-e][1,3]oxazine-2,4-diones* (**XLIII**)



XLII **XLIII**

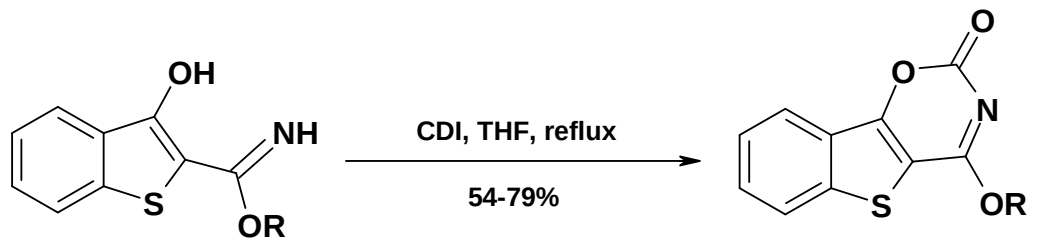
R^1, R^2 = alkyl, aryl, heterocycle
X = H, alkyl, haloalkyl

Marfat, A. EP 391732 *Chem. Abstr*. (1991) **114**, 122390.

[f] Compounds **XLIII** were described as cyclic prodrugs of *N*-alkenyl-3-hydroxy-benzo[*b*]thiophene-2-carboxamides which exhibit cyclooxygenase and 5-lipoxygenase inhibitory activity[53-55].

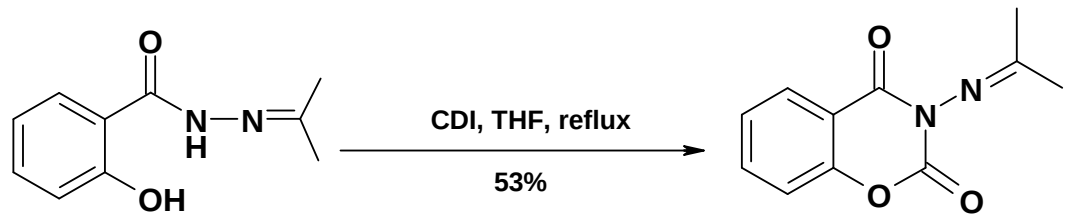
As reported by *Stoss*[84] and *Davidson*[85], treatment of 3-hydroxy-benzo[*b*]thiophene-2-carboximidates (**XLIV**) or 2-hydroxy-*N'*-(propan-2-ylidene)-benzohydrazide (**XLVI)** with 1,1`-carbonyldiimidiazole (CDI) in refluxing tetrahydrofuran provided the corresponding 4-alkoxy-benzothieno-[2,3-*e*][1,3]oxazine-2-ones (**XLV**) and 3-(propan-2-ylideneamino)-benzo[*e*]-[1,3]oxazine-2,4-dione (**XLVII**), respectively in moderate to good yields (Scheme 3-9).

Scheme 3-9 *Synthesis of 4-Alkoxy-benzothieno[2,3-e][1,3]oxazine-2-ones* (**XLV**) *and 3-(Propan-2-ylideneamino)-benzo[e][1,3]oxazine-2,4-dione* (**XLVII**)



XLIV **XLV**

Stoss, P., *Chem. Ber*. (1978) **111**, 314.

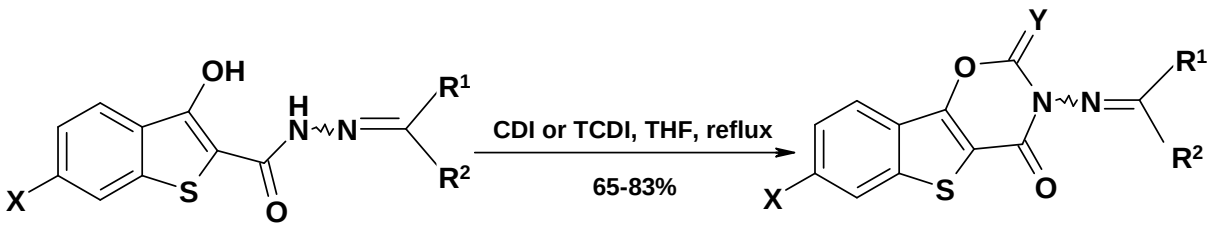


XLVI **XLVII**

Davidson, J. S., *Chem. Ind.* (1982) **17**, 660.

These reports prompted me to perform the cyclic carbonylation analogously by reacting **18** with 1.1 equivalents of 1,1`-carbonyldiimidiazole (CDI) or 1,1`-thiocarbonyldiimidiazole (TCDI) in refluxing dry tetrahydrofuran for 1 hour. As a matter of fact, the formation of the desired 3-aminoalkenyl-benzothieno[2,3-*e*][1,3]oxazines (**19**) was achieved in 65-83% yield (Scheme 3-10, Table 3-2).

Scheme 3-10 *Synthesis of 3-Aminoalkenyl-benzothieno[2,3-e][1,3]oxazines* (**19**)



18 **19**

Table 3-2 *Prepared 3-Aminoalkenyl-benzothieno[2,3-e][1,3]oxazines* (**19**)

19	**X**	**Y**	**R^1**	**R^2**	**Yield (%)**
a	H	O	CH_3	CH_3	75
b	Cl	O	CH_3	CH_3	70
c	H	S	CH_3	CH_3	72
d	Cl	S	CH_3	CH_3	65
e	H	O	C_2H_5	C_2H_5	74
f	Cl	O	C_2H_5	C_2H_5	71
g	H	O	H	C_6H_5	81
h	Cl	O	H	C_6H_5	75
i	H	O	CH_3	C_6H_5	83
j	Cl	O	CH_3	C_6H_5	78

The IR spectra of compounds **19a,b,e,f,g,h,i,j** are characterized by two sharp (C=O) absorption bands at 1700-1710 cm^{-1} and at 1760-1770 cm^{-1} (Fig. 3-5), whereas the IR spectra of the corresponding thioxo derivatives **19c,d** show a (C=O) absorption band at 1716 cm^{-1} and a sharp (C=S) band at 1280 cm^{-1} (Fig.3-6).

Fig. 3-5 *IR (KBr) Spectrum of 3-(1-Phenylethylideneamino)-benzothieno-[2,3-e][1,3]oxazine-2,4-dione* (**19i**)

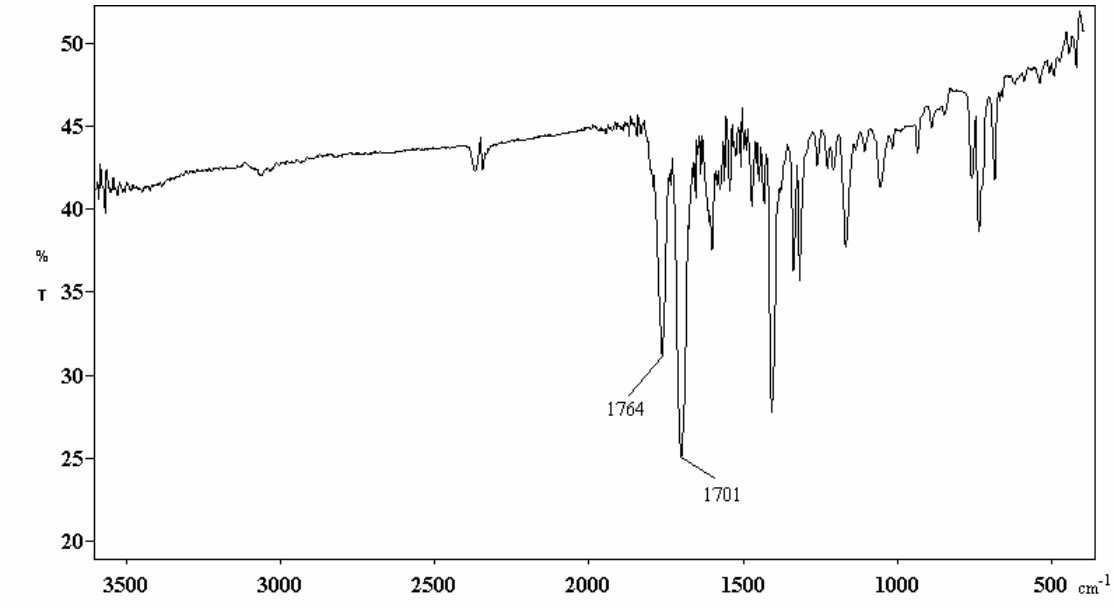
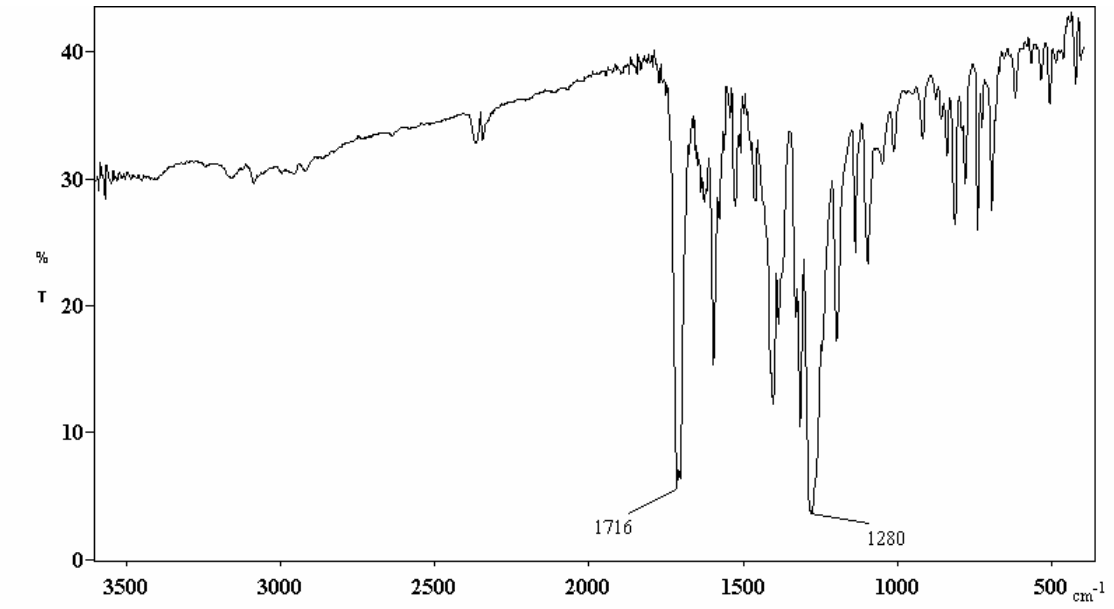


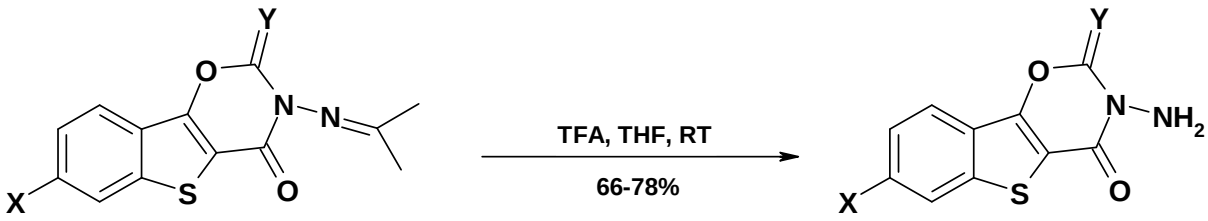
Fig. 3-6 *IR (KBr) Spectrum of 7-Chloro-3-(propan-2-ylideneamino)-2-thioxo-benzothieno[2,3-e][1,3]oxazine-4-one* (**19d**)



3.1.5 Preparation of 3-Amino-benzothieno[2,3-*e*][1,3]oxazines (**20**)

Cleavage of the hydrazono functionality in compounds **19a-d** could be achieved smoothly by treatment with trifluoroacetic acid in tetrahydrofuran at ambient temperature furnishing the desired 3-amino-benzothieno[2,3-*e*][1,3]oxazines (**20**) as solid substances in 66-78% yield (Scheme 3-11, Table 3-3).

Scheme 3-11 *Synthesis of 3-Amino-benzothieno[2,3-e][1,3]oxazines* (**20**)



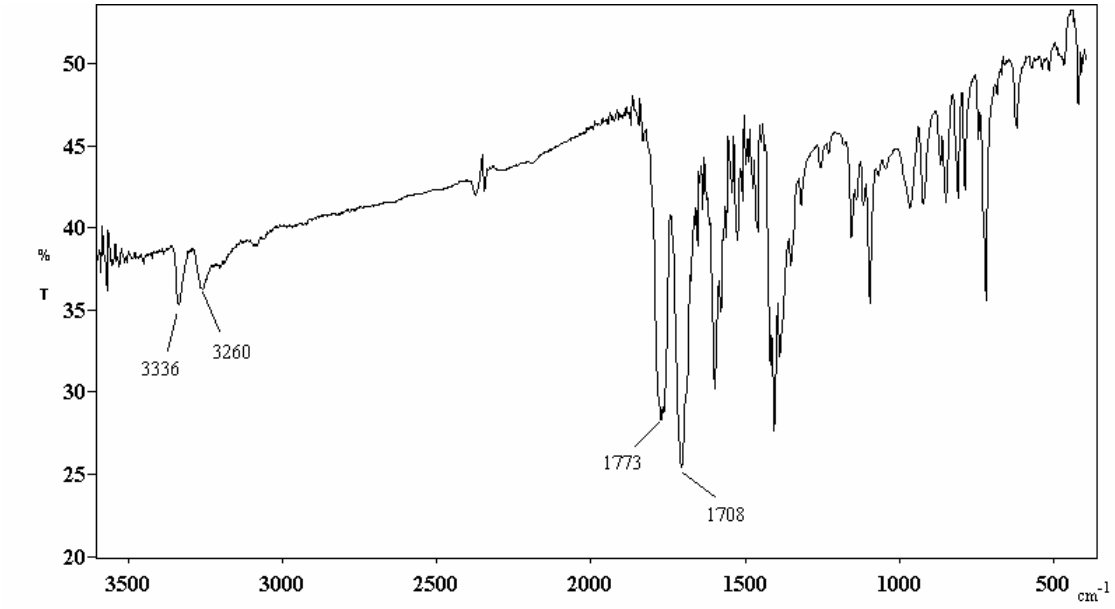
19 **20**

Table 3-3 *Prepared 3-Amino benzothieno[2,3-e][1,3]oxazines* (**20**)

20	**X**	**Y**	**Yield (%)**
a	H	O	78
b	Cl	O	73
c	H	S	70
d	Cl	S	66

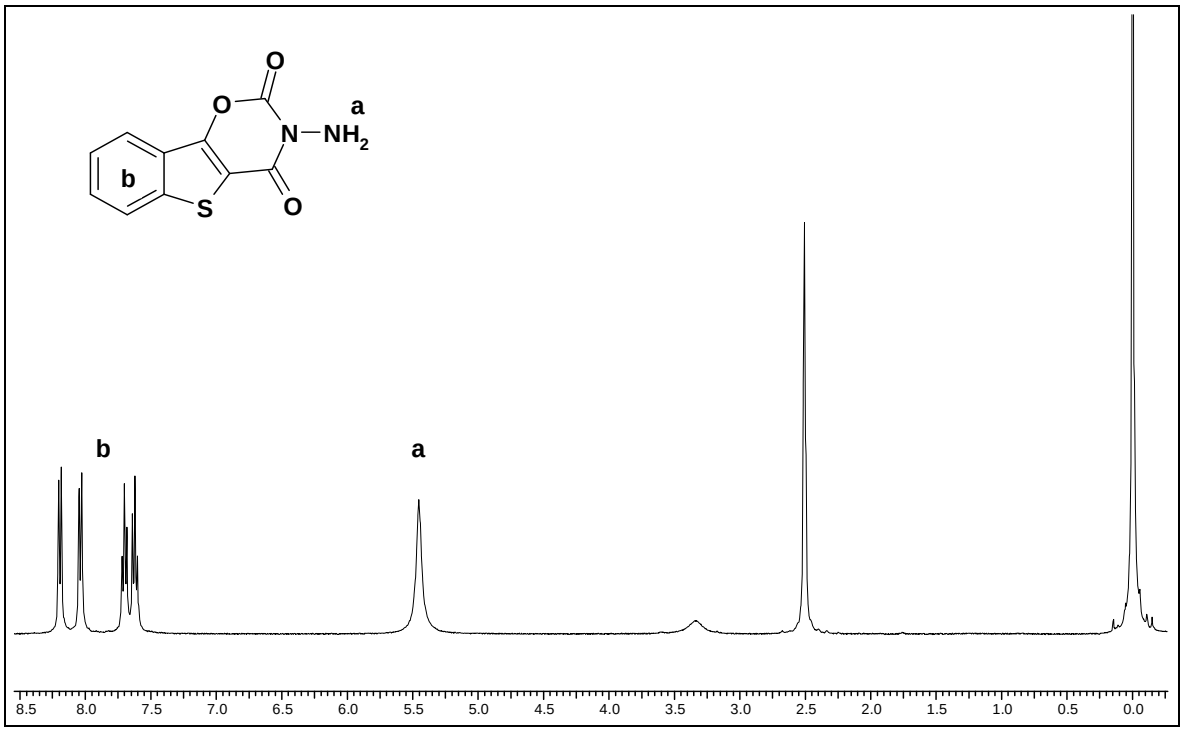
The IR spectra of **20** are characterized by (NH) absorption bands at 3250-3260 cm^{-1} and 3330-3340 cm^{-1} in addition to two sharp (C=O) bands in compounds **20a,b** (Fig. 3-7). For 3-amino-2-thioxo-benzothieno[2,3-*e*][1,3]oxazine-4-ones (**20c,d**), a characteristic (C=S) absorption bands are found at 1254-1271 cm^{-1}.

Fig. 3-7 *IR (KBr) Spectrum of 3-Amino-7-chloro-benzothieno[2,3-e][1,3]-oxazine-2,4-dione* (**20b**)



Additional structure prove for **20** was provided by the ^{1}H-NMR spectra. As exemplified in Fig. 3-8, compound **20a** depicts a singlet at 5.45 ppm (NH_2) and multiplets at 7.62-8.20 ppm (aromatic protons).

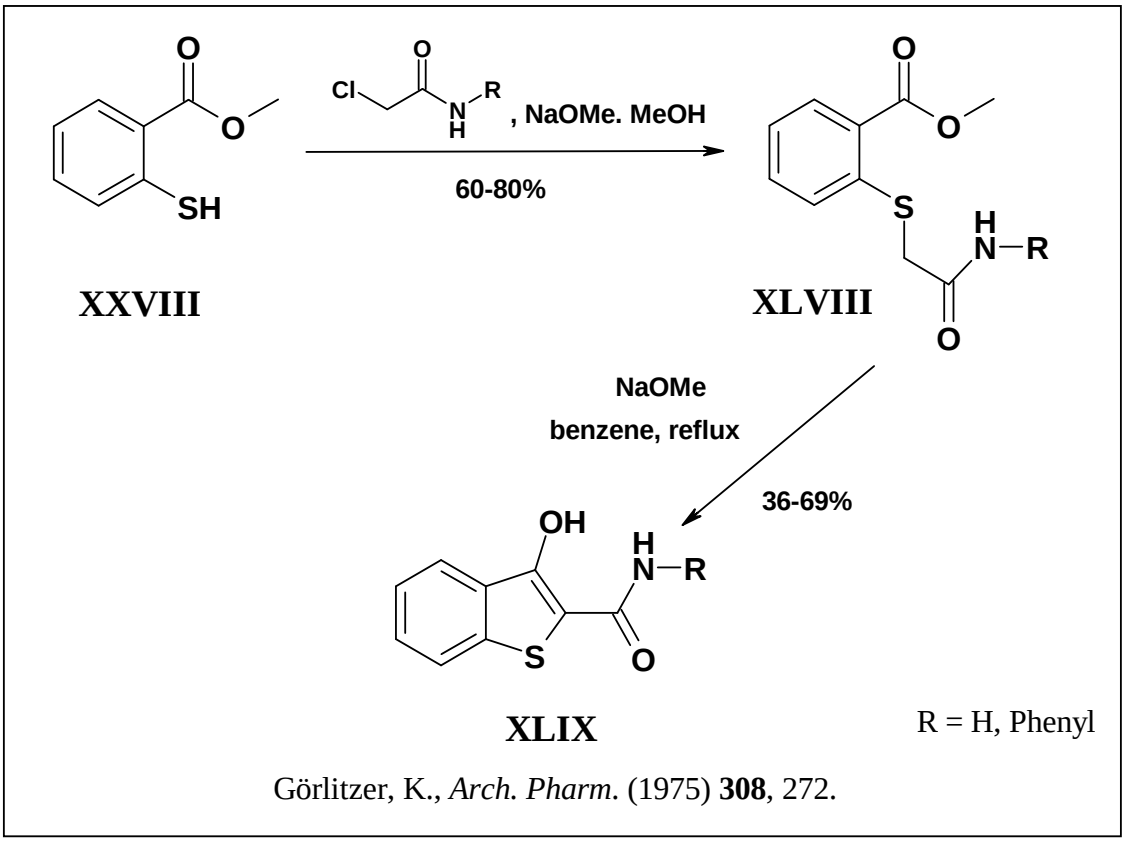
Fig. 3-8 *[1]H-NMR Spectrum of 3-Amino-benzothieno[2,3-e][1,3]oxazine-2,4-dione* (**20a**)



3.2 Synthesis and Cyclization of *N*-Alkoxy(Aralkoxy)-3-hydroxy-benzo[*b*]thiophene-2-carboxamides and 3-Hydroxy-benzo[*b*]thiophene-2-carbohydrazides

Having established an expedient synthetic route towards *N*-aminoalkenyl-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**18**) and their cyclic derivatives **19**, I confidently expected an analogous formation of the *N*-alkoxy-(aralkoxy)-3-hydroxy-benzo[*b*]thiophene-2-carboxamides **27** and 3-hydroxy-benzo[*b*]thiophene-2-carbohydrazides **28**-**30**, according to literature:
Görlitzer[86] reported the preparation of 3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**XLIX**) according to Scheme 3-12 by *S*-alkylation of thiosalicylic acid methyl ester (**XXVIII**) with chloroacetamide or chloroacetanilide and subsequent base catalyzed cyclization of the intermediates **XLVIII** in 36-69% yield.

Scheme 3-12 *Synthesis of 3-Hydroxy-benzo[b]thiophene-2-carboxamides* (**XLIX**)



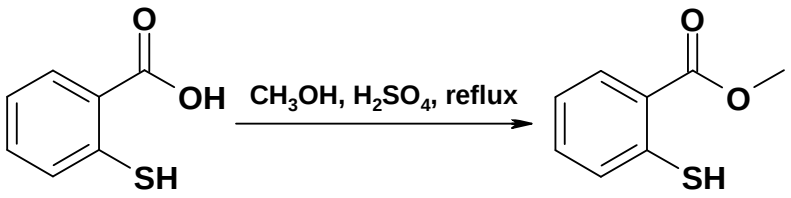
Görlitzer, K., *Arch. Pharm.* (1975) **308**, 272.

This method was also thought to provide an easy access to the targeted 3-hydroxy[*b*]benzothiophen-2-carbohydroxamates (**27**) and 3-hydroxy-benzo-[*b*]thiophene-2-carbohydrazides (**28-30**) as outlined in Schemes 3-13, 3-15 and 3-16.

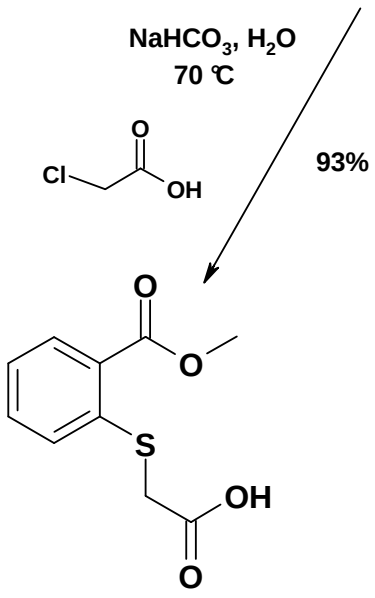
3.2.1 Synthesis of Methyl 2-carboxymethylsulfanyl-benzoate (**21**)

First, thiosalicylic acid (**1**) was converted to its methyl ester **XXVIII** with a mixture of methanol/sulfuric acid (10%), followed by reaction with chloroacetic acid in aqueous sodium bicarbonate solution. Acidification of the reaction mixture with aqueous HCl (10%) provided methyl 2-carboxymethylsulfanyl-benzoate (**21**) in 93% yield as white solid (Scheme 3-13).

Scheme 3-13 *Synthesis of Methyl 2-carboxymethylsulfanyl-benzoate* (**21**)



1 **XXVIII**



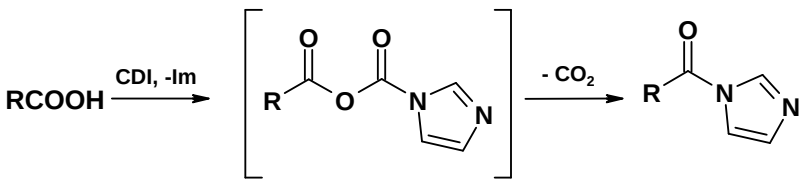
21

3.2.2 Synthesis of the Open-chained Precursors **23-26**

Compound **21** could be easily converted to the corresponding imidazolide **22** as an intermediate by treatment with one equivalent of 1,1`-carbonyldiimidiazole in dry tetrahydrofuran at ambient temperature[g]. Subsequent in-situ addition of various alkoxy(aralkoxy)amines, di- and monosubstituted hydrazines provided the desired methyl 2-[(2-alkoxy(aralkoxy)amino-2-oxoethyl)sulfanyl]benzoates (**23**), methyl 2-[(2-(2,2-disubstituted-hydrazinyl)-2-oxoethyl)sulfanyl]benzoates (**24**) and methyl 2-[(2-(alkylhydrazinyl)-2-oxoethyl)sulfanyl]benzoates (**25**, **26**), respectively, in 60-78% yield (Scheme 3-15).

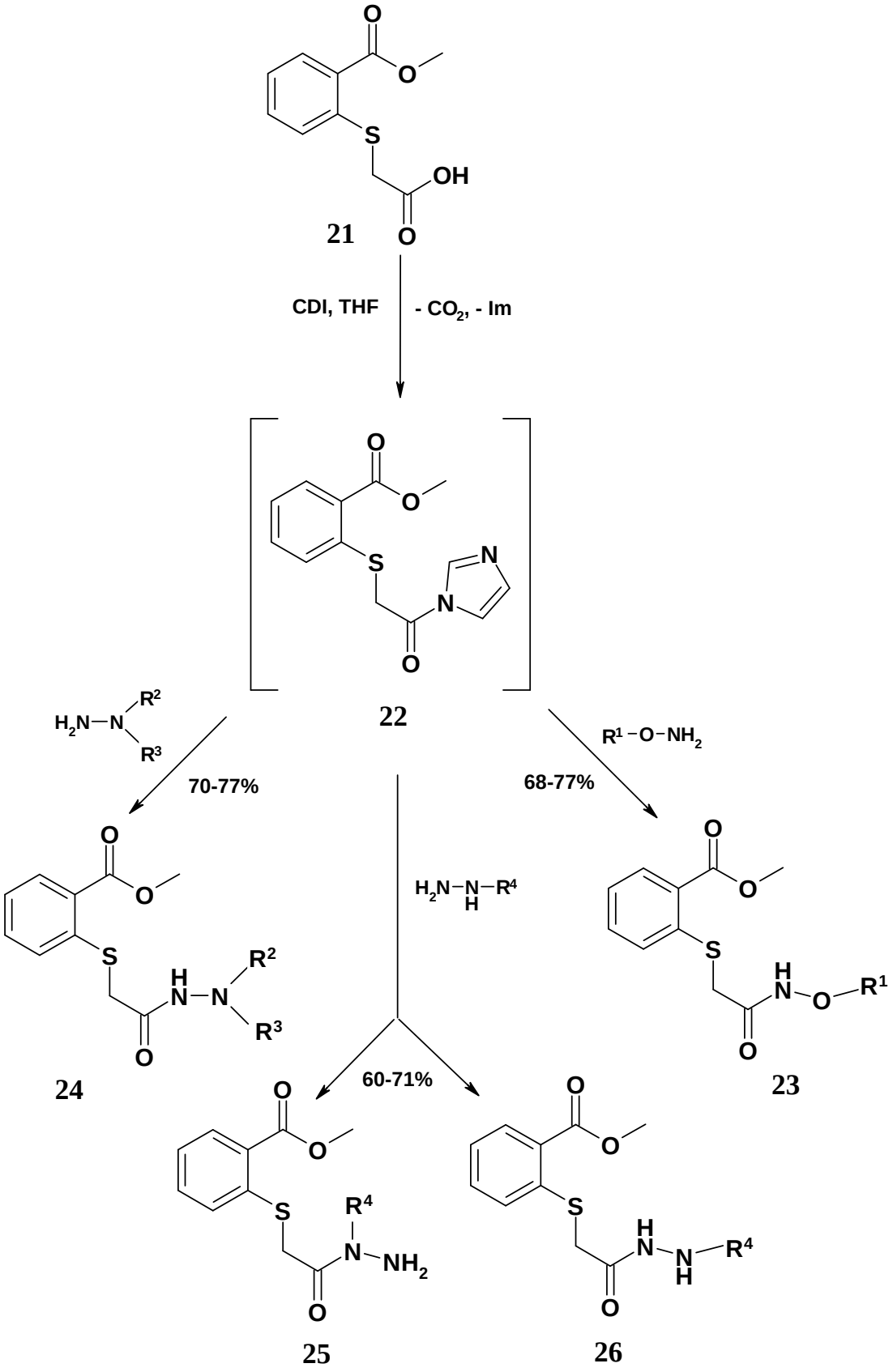
[g] As outlined in Scheme 3-14, a two step mechanism must be assumed for the reaction of carboxylic acid with CDI[87]. The first step is a nucleophilic attack of the carboxylic acid on the carbonyl group of CDI affording the transient anhydride **XLXI,** which upon subsequent liberation of carbon dioxide yields the imidazolide **XLXII.**

Scheme 3-14 *Reaction mechanism of a carboxylic acid with CDI*



XLX **XLXI** **XLXII**

Scheme 3-15 *Synthesis of Methyl 2-substituted-sulfanyl-benzoates* (**23**-**26**)



3.2.2.1 Synthesis of Methyl 2-[(2-alkoxy(aralkoxy)amino-2-oxoethyl) sulfanyl]benzoates (**23**)

By dropwise addition of a solution of alkoxy(aralkoxy)amines[h] in tetrahydrofuran to a freshly prepared suspension of the appropriate imidazolide **22** in tetrahydrofuran and stirring of the reaction mixture at ambient temperature, the desired methyl 2-[(2-alkoxy(aralkoxy)amino-2-oxoethyl)sulfanyl]benzoates (**23**) were obtained as white stable solids in 68-77% yield (Scheme 3-15, Table 3-4).

Table 3-4 *Prepared Methyl 2-[(2-alkoxy(aralkoxy)amino-2-oxoethyl) sulfanyl]benzoates* (**23**)

23	**R^1**	**Yield (%)**
a	CH_3	74
b	CH_2CHCH_2	77
c	$C_6H_5CH_2$	75
d	$C_6H_5CH_2CH_2$	72
e	$C_6H_5CH_2CH_2CH_2$	70
f	4-CH_3-$C_6H_4CH_2$	71
g	4-Br-$C_6H_4CH_2$	68
h	$C_{10}H_7CH_2$	71

The IR spectra of the prepared methyl 2-[(2-alkoxy(aralkoxy)amino-2-oxo-ethyl)sulfanyl]benzoates (**23**) exhibit two (C=O) bands at 1649-1668 cm^{-1} (hydroxamic acid), at 1705-1711 cm^{-1} (ester) and a broad (NH) band at 3200-3220 cm^{-1} (Fig. 3-9).

The ^{1}H-NMR of compound **23c** displays four singlets at 3.60 ppm (S-CH_2), 3.84 ppm (O-CH_3), 4.77 ppm (O-CH_2) and 11.38 ppm (NH), and a multiplet for the aromatic protons at 7.25-7.90 ppm (Fig. 3-10).

[h] Methoxyamine and allyloxyamine were used as hydrochlorides, and were added portionwise to the reaction mixture with equivalent amount of triethylamine.

Fig. 3-9 *IR (KBr) Spectrum of Methyl 2-[(2-methoxyamino-2-oxoethyl)-sulfanyl]benzoate* (**23a**)

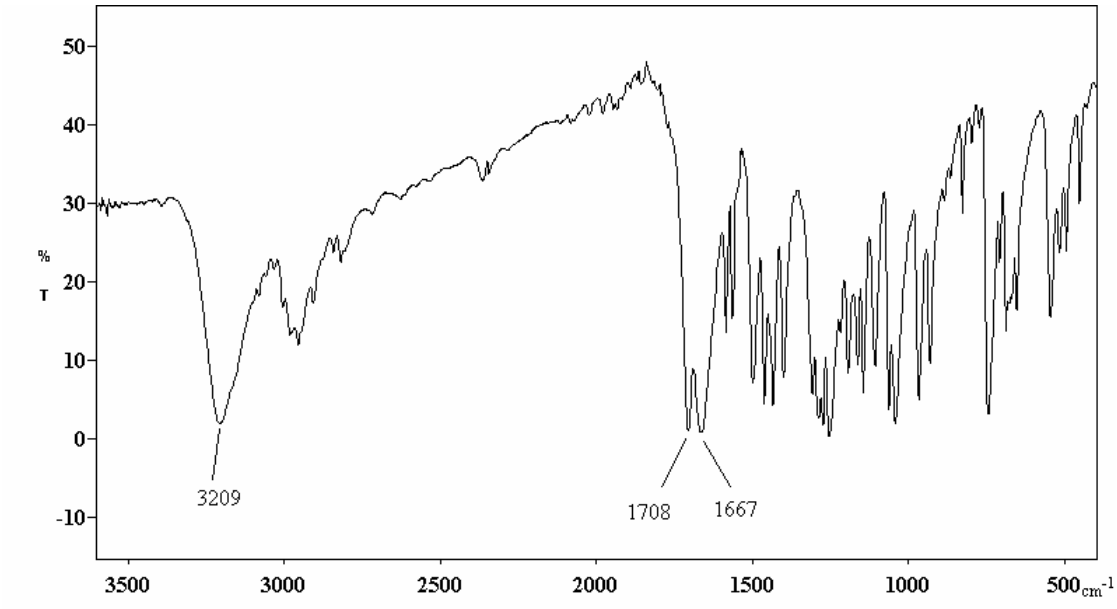
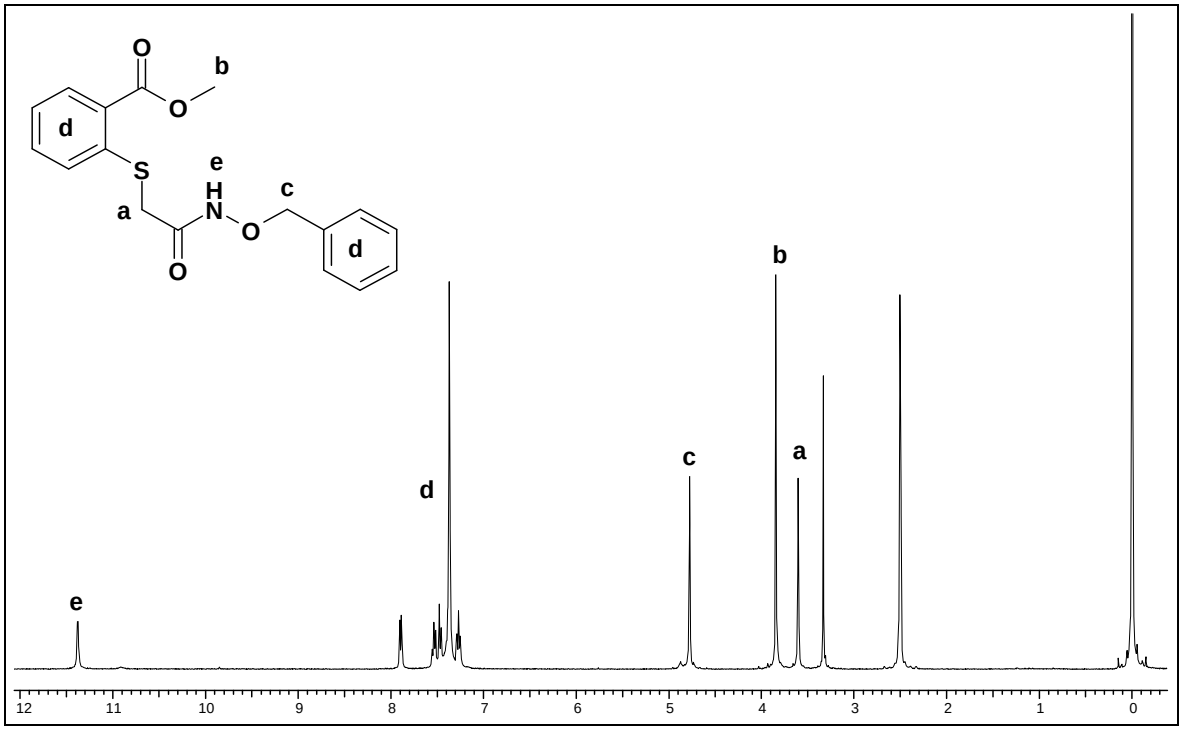


Fig. 3-10 *^{1}H-NMR Spectrum of Methyl 2-[(2-benzyloxyamino-2-oxoethyl)-sulfanyl]benzoate* (**23c**)



3.2.2.2 Synthesis of Methyl 2-[(2-(2,2-disubstituted-hydrazinyl)-2-oxo-ethyl)sulfanyl]benzoates (**24**)

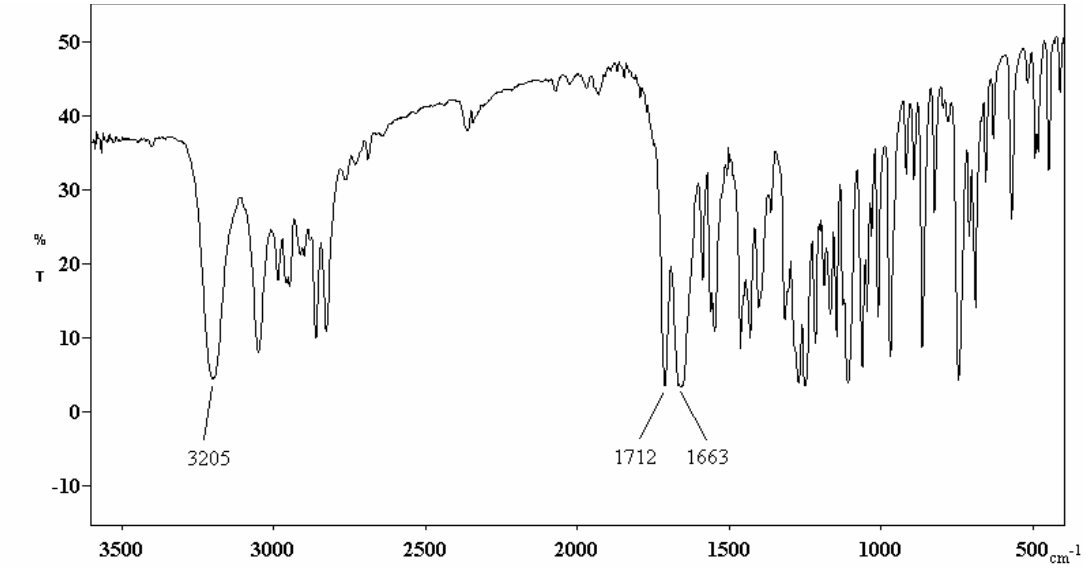
Treatment of the imidazolide **22** with equivalent amount of *N,N*-disubstituted hydrazines, dissolved in tetrahydrofuran, at room temperature realized methyl 2-[(2-(2,2-disubstituted-hydrazinyl)-2-oxoethyl)sulfanyl]benzoates (**24**) as white stable solids in 70-77% yield (Scheme 3-15, Table 3-5).

Table 3-5 *Prepared Methyl 2-[(2-(2,2-disubstituted-hydrazinyl)-2-oxoethyl)-sulfanyl]benzoates* (**24**)

24	**R^2**	**R^3**	**Yield (%)**
a	CH_3	CH_3	70
b	$-(CH_2)_5-$		75
c	$-(CH_2)_2-O-(CH_2)_2-$		77
d	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		72

The IR spectra of the prepared methyl 2-[(2-(2,2-disubstituted-hydrazinyl)-2-oxoethyl)sulfanyl]benzoates (**24**) show two (C=O) bands at 1650-1663 cm^{-1} (carbohydrazide), 1702-1713 cm^{-1} (carboxylic ester) and a (NH) band between 3200-3220 cm^{-1} (Fig. 3-11).

Fig. 3-11 *IR (KBr) Spectrum of Methyl 2-[(2-(morpholinoamino)-2-oxo-ethyl)sulfanyl]benzoate* (**24c**)



3.2.2.3 Synthesis of Methyl 2-[(2-(alkylhydrazinyl)-2-oxoethyl)sulfanyl]-benzoates (**25, 26**)

Depending on the size of the alkyl group[i], the reaction of the imidazolide **22** with alkylhydrazines[j] led to the formation of either methyl 2-[(2-(1-alkylhydrazinyl)-2-oxoethyl)sulfanyl]benzoates (**25a,b**; R^4 = Me, Et[k]) or methyl 2-[(2-(2-*tert*-butylhydrazinyl)-2-oxoethyl)sulfanyl]benzoate (**26**; R^4 = *t*-Bu) (Scheme 3-15).

Compounds **25a,b** and **26** were isolated as white stable crystalline solids in 71, 62, 60% yield and their structure was unambiguously proven by microanalysis and spectroscopic data (IR and ^{1}H NMR, ^{13}C NMR).

For example, the ^{1}H-NMR spectrum of compound **25a** depicts four singlets at 3.04 ppm (N-CH_3), 3.83 ppm (O-CH_3), 4.03 (S-CH_2), and 4.91 ppm (NH_2). (Fig 3-12).

Contrary, the ^{1}H-NMR spectrum of compound **26** is characterized by two singlets at 4.63 and 9.49 ppm, attributable to the (NH) protons and additional three singlets at 0.94 ppm (*t*-Bu), 3.70 ppm (S-CH_2) and 3.84 ppm (O-CH_3) (Fig. 3-13).

---

[i] Selective N^1 acylation of methylhydrazine with carboxylic acid imidazolide was reported in the literature[88]. The same result was also observed when acetic anhydride was used as the acylating agent[89]. However, concomitant acylation took place in 1- and 2- position when dimethyl- and diethyl carbonate were used as acylating agents [90].

[j] Ethyl- and *tert*-butylhydrazine were used as oxalate or hydrochloride salt with addition of equivalent amount of triethylamine.

[k] The formation of methyl 2-[(2-(2-ethylhydrazinyl)-2-oxoethyl)sulfanyl]benzoate was also observed. However it was not isolated due to its very low yield.

Fig. 3-12 *[1]H-NMR Spectrum of Methyl 2-[(2-(1-methylhydrazinyl)-2-oxo-ethyl)sulfanyl]benzoate* (**25a**)

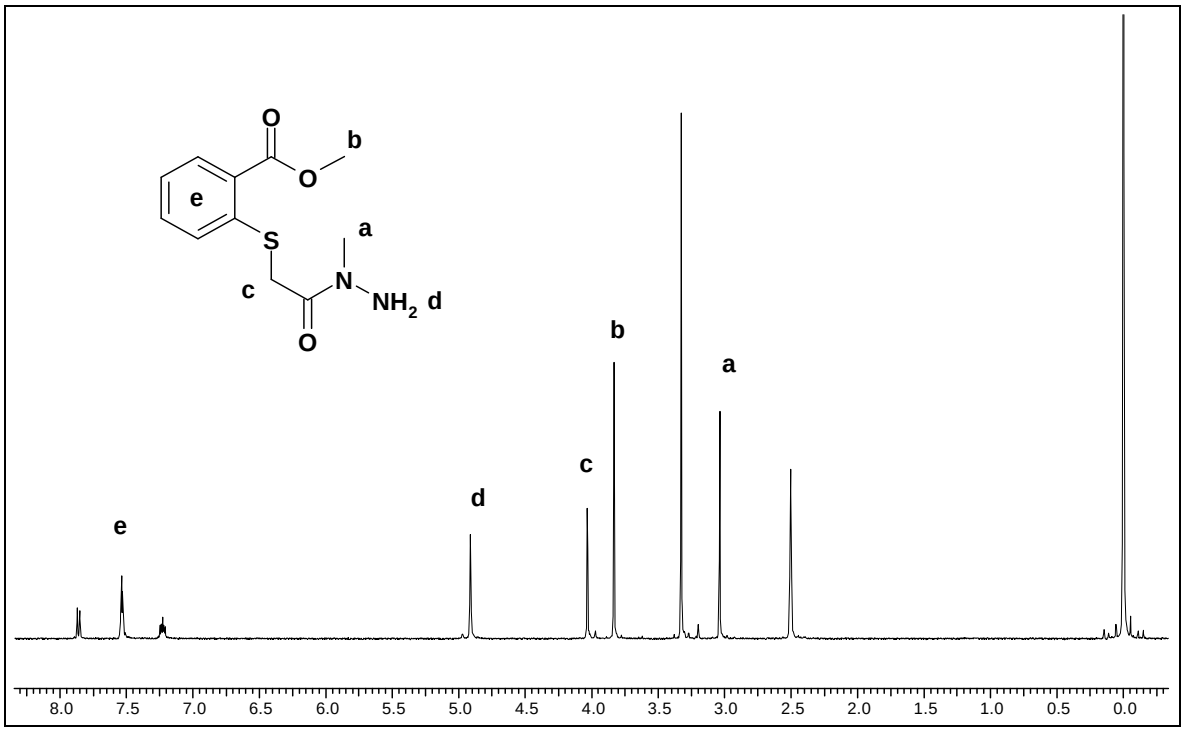
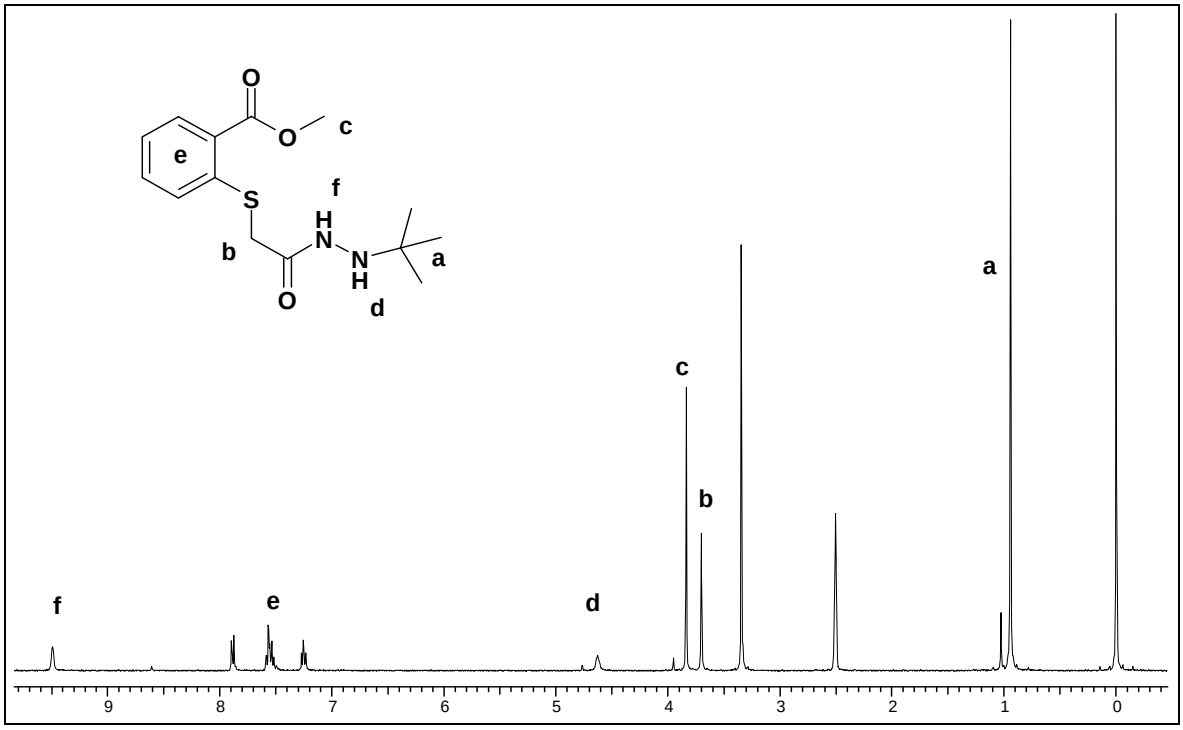


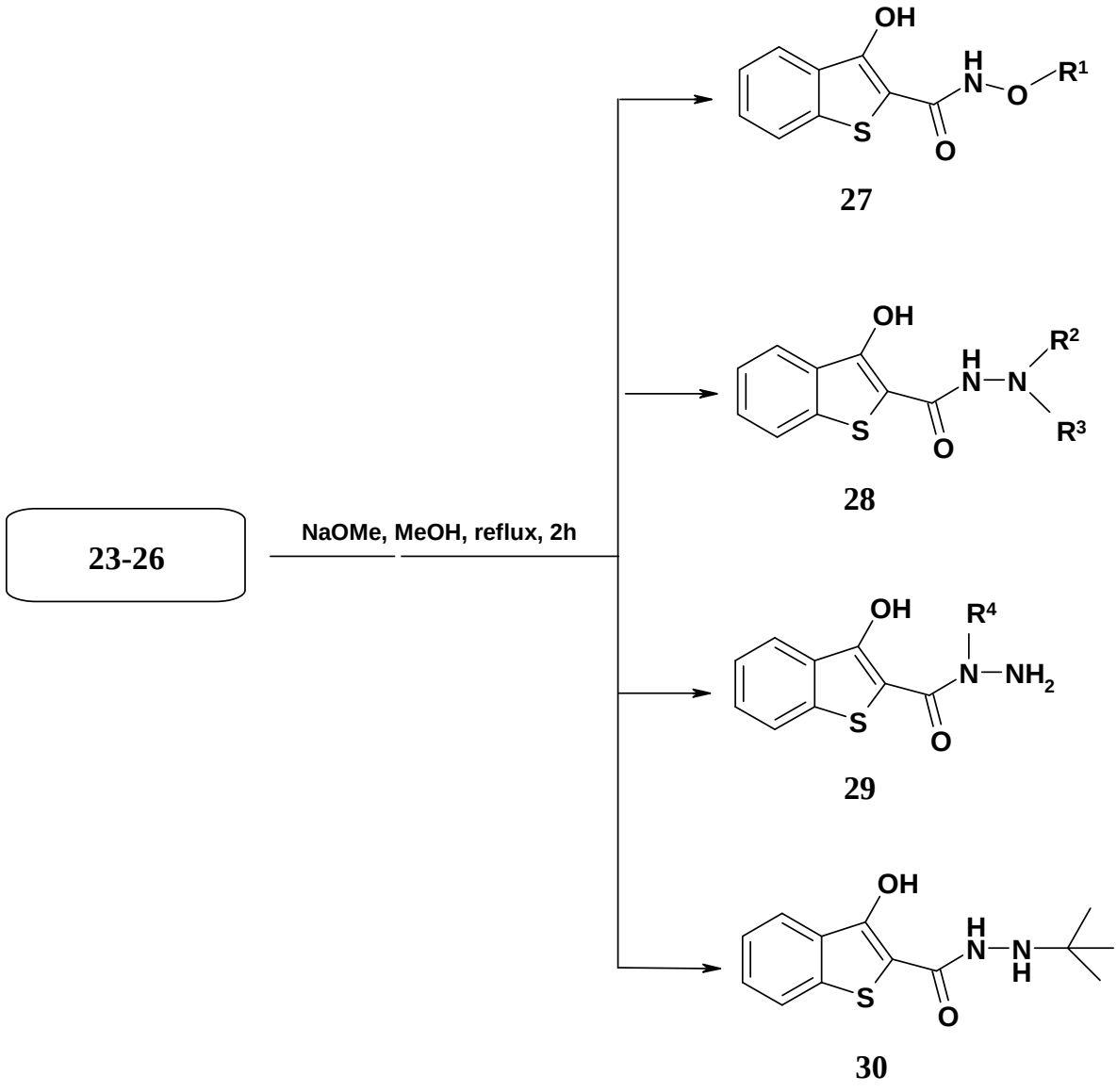
Fig. 3-13 *[1]H-NMR Spectrum of Methyl 2-[(2-(2-tert-butylhydrazinyl)-2-oxo-ethyl)sulfanyl]benzoate* (**26**)



3.2.3 Synthesis of *N*-Alkoxy(Aralkoxy)-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**27**) and 3-Hydroxy-benzo[*b*]thiophene-2-carbo-hydrazides (**28-30**)

The base catalyzed intramolecular cyclization of the intermediates **23-26** occurred smoothly by refluxing a mixture of **23-26** and sodium methoxide in methanol for two hours, followed by evaporation under reduced pressure and treatment of the oily residue with aqueous hydrochloride acid (Scheme 3-16).

Scheme 3-16 *Synthesis of 3-Hydroxy-benzo[b]thiophene-2-carboxamide derivatives* (**27-30**)



3.2.3.1 Preparation of N-Alkoxy(Aralkoxy)-3-hydroxy-benzo[b]thiophene-2-carboxamides (**27**)

Cyclization of compounds **23** provided the desired *N*-alkoxy(aralkoxy)-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**27**) in 65-80% yield as white or light pink crystalline solids[l] which were purified by recrystallization from ethanol (Scheme 3-16, Table 3-6).

Table 3-6 *Prepared N-Alkoxy(Aralkoxy)-3-hydroxy-benzo[b]thiophene-2-carboxamides* (**27**)

27	**R^1**	**Yield (%)**
a	CH_3	69
b	CH_2CHCH_2	75
c	$C_6H_5CH_2$	80
d	$C_6H_5CH_2CH_2$	70
e	$C_6H_5CH_2CH_2CH_2$	72
f	4-CH_3-$C_6H_4CH_2$	68
g	4-Br-$C_6H_4CH_2$	65
h	$C_{10}H_7CH_2$	72

The IR spectra of compounds **27** are characterized by a (C=O) absorption band at 1610-1620 cm^{-1} and (NH) absorption bands between 3120-3200 cm^{-1} (Fig. 3-14).

Additional structural proof comes from the ^{1}H-NMR spectra. For example, the ^{1}H-NMR spectrum of compound **27c** reveals three singlets at 4.98 ppm (O-CH_2), 11.32 ppm (NH) and at 11.80 ppm (OH), besides a multiplet for the arylic protons 7.38-7.98 ppm (Fig. 3-15).

[l] However, it was observed that these derivatives are not stable in room temperature and must be stored in the refrigerator.

Fig. 3-14 *IR (KBr) Spectrum of 3-Hydroxy-N-(3-phenylpropoxy)-benzo[b]-thiophene-2-carboxamide* (**27e**)

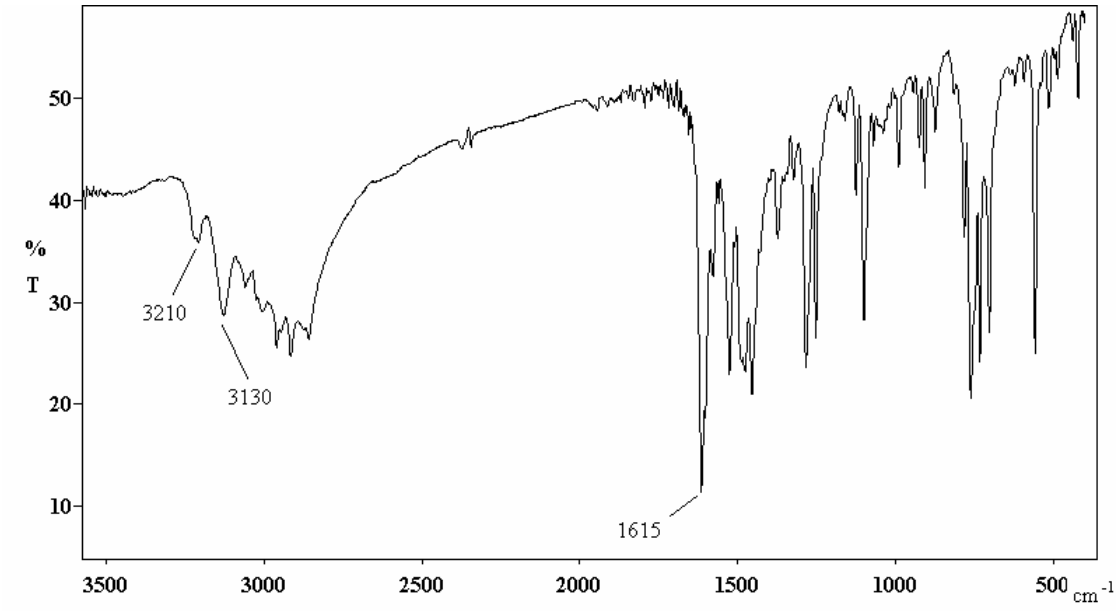
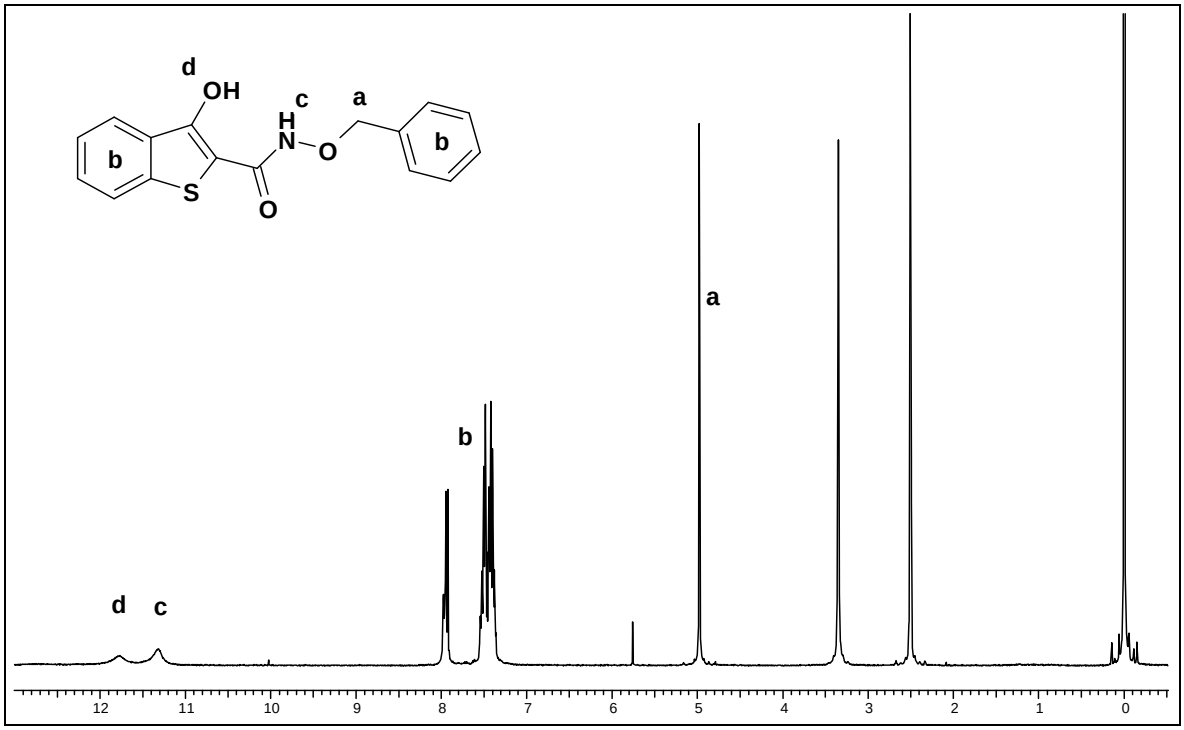
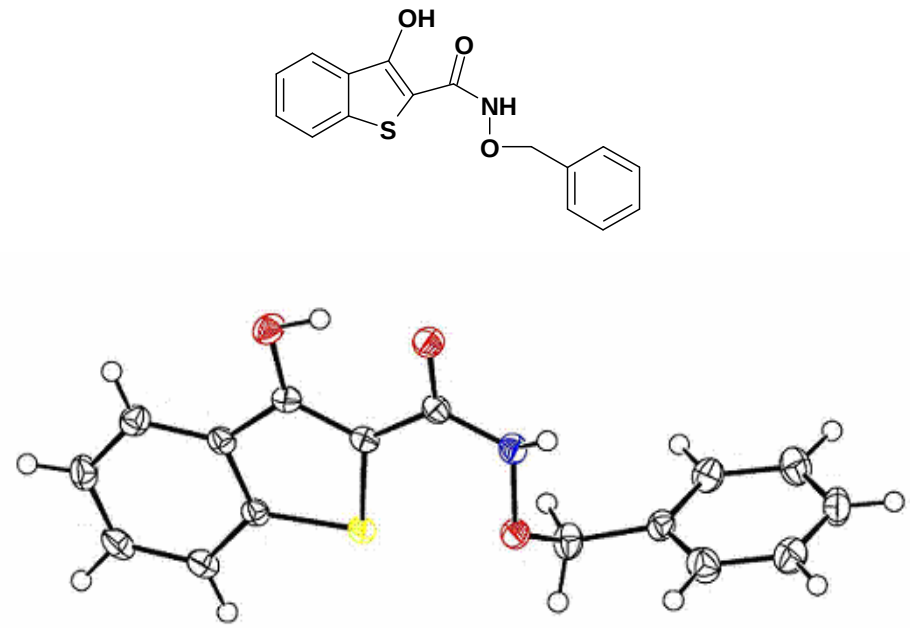


Fig. 3-15 *^{1}H-NMR Spectrum of N-Benzyloxy-3-hydroxy-benzo[b]thiophene-2-carboxamide* (**27c**)



Unambiguous structural proof of **27c** was obtained from X-ray crystallography (Fig. 3-16), that clearly exemplifies the 3-hydroxy-benzothiophene-2-carbohydroxamic acid structure.

Fig. 3-16 *Molecular Structure of N-Benzyloxy-3-hydroxy-benzo[b]thiophene-2-carboxamide* (**27c**)



3.2.3.2 *Preparation of N`,N`-Disubstituted-3-hydroxy-benzo[b]thiophene-2-carbohydrazides* (**28**)

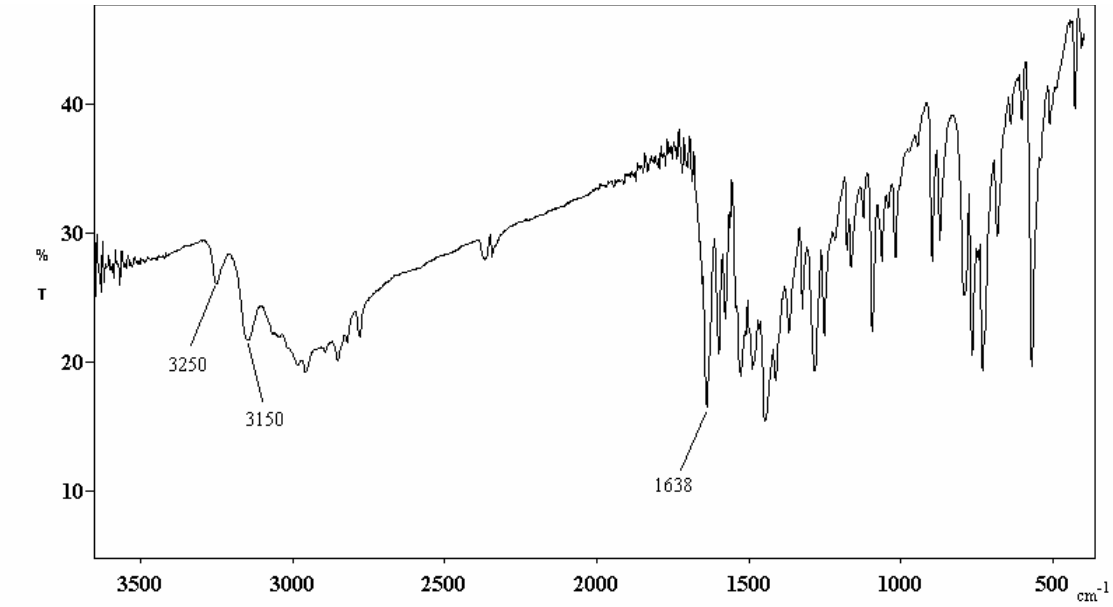
From the intramolecular cyclization of compounds **24** the targeted *N`,N`*-disubstituted-3-hydroxy-benzo[*b*]thiophene-2-carbohydrazides (**28**) were obtained in good yields of 73-87% as white stable solids. (Scheme 3-16, Table 3-7).

Table 3-7 *Prepared N`,N`-Disubstituted-3-hydroxy-benzo[b]thiophene-2-carbohydrazides* (**28**)

28	**R^2**	**R^3**	**Yield (%)**
a	CH_3	CH_3	73
b	$-(CH_2)_5-$		77
c	$-(CH_2)_2-O-(CH_2)_2-$		78
d	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		87

The IR spectra of compounds **28** offer a (C=O) band at 1630-1640 cm^{-1} and (NH) bands between 3150-3250 cm^{-1} (Fig 3-17).

Fig. 3-17 *IR (KBr) Spectrum of N`,N`-Dimethyl-3-hydroxy-benzo[b]thiophene-2-carbohydrazide* (**28a)**



The ^{1}H-NMR spectrum of compound **28a** displays singlets at 2.62 ppm ($N(CH_3)_2$), 9.52 ppm (NH) and 13.30 ppm (OH) (Fig. 3-18).
Unambiguous structural proof for **28a** was again obtained from X-ray crystallography (Fig. 3-19).

Fig. 3-18 *^{1}H-NMR Spectrum of N`,N`-Dimethyl-3-hydroxy-benzo[b]thiophene-2-carbohydrazide* (**28a**)

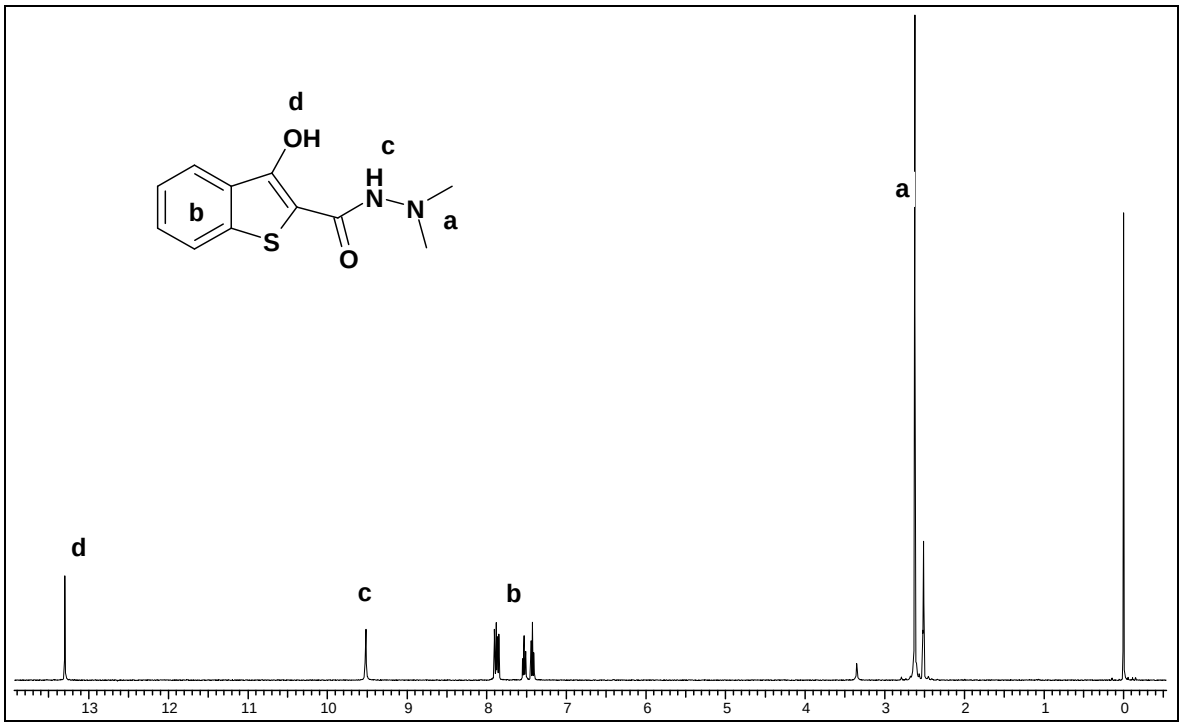
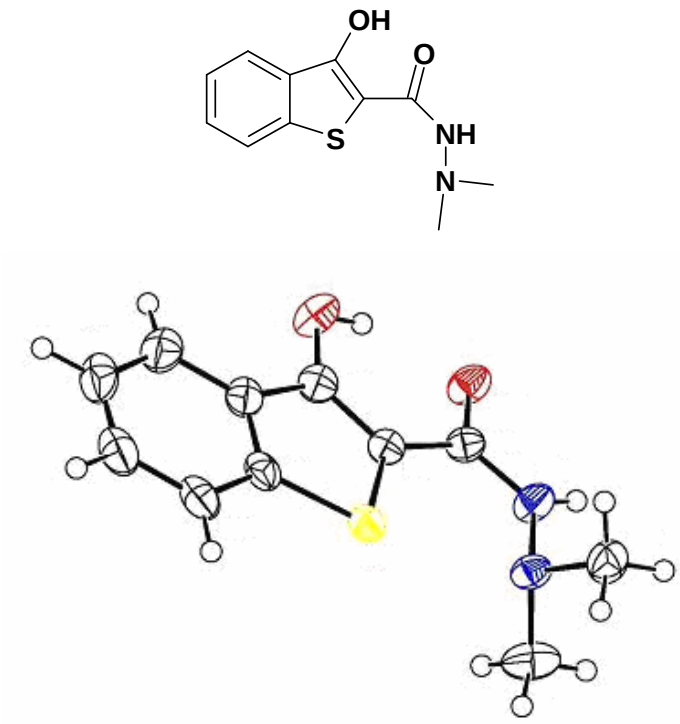


Fig. 3-19 *Molecular Structure of N`,N`-Dimethyl-3-hydroxy-benzo[b]thiophene-2-carbohydrazide* (**28a**)



3.2.3.3 Preparation of N(N`)-Alkyl-3-hydroxy-benzo[b]thiophene-2-carbohydrazides (**29**, **30**)

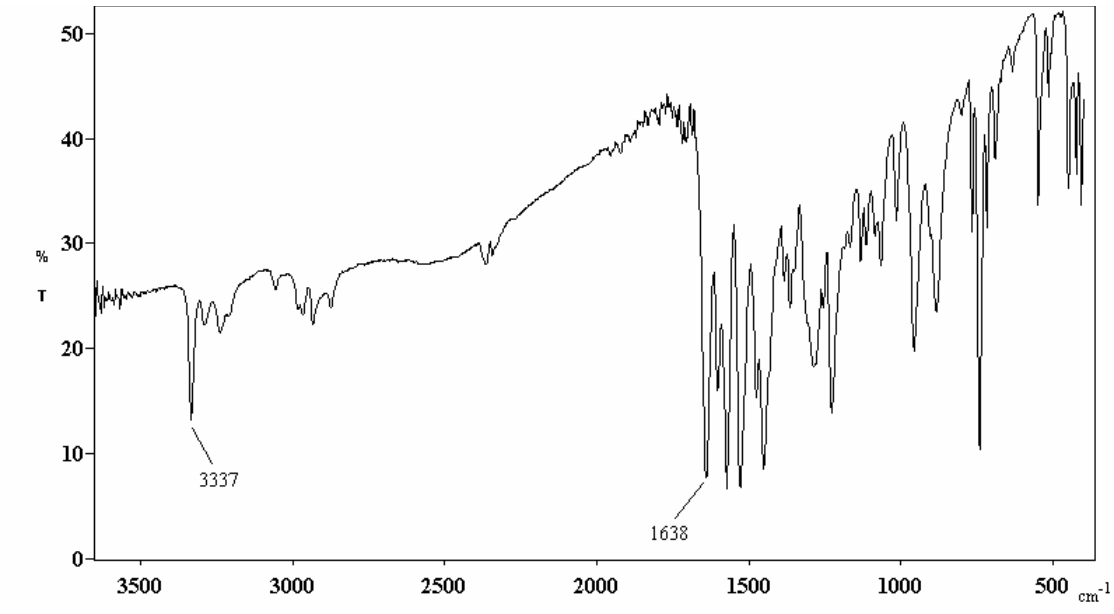
As outlined in scheme 3-16, internal cyclization of compounds **25a,b** afforded the corresponding *N*-alkyl-3-hydroxy-benzo[*b*]thiophene-2-carbohydrazides (**29a**,**b**) in 68, 60% yield respectively (Table 3-8). Similarly, *N'-tert*-butyl-3-hydroxy-benzo[*b*]thiophene-2-carbohydrazide (**30**) was obtained in 72% yield from compound **26**.

Table 3-8 *Prepared N-Alkyl-3-hydroxy-benzo[b]thiophene-2-carbohydrazides* (**29**)

29	**R^4**	**Yield (%)**
a	CH_3	68
b	C_2H_5	60

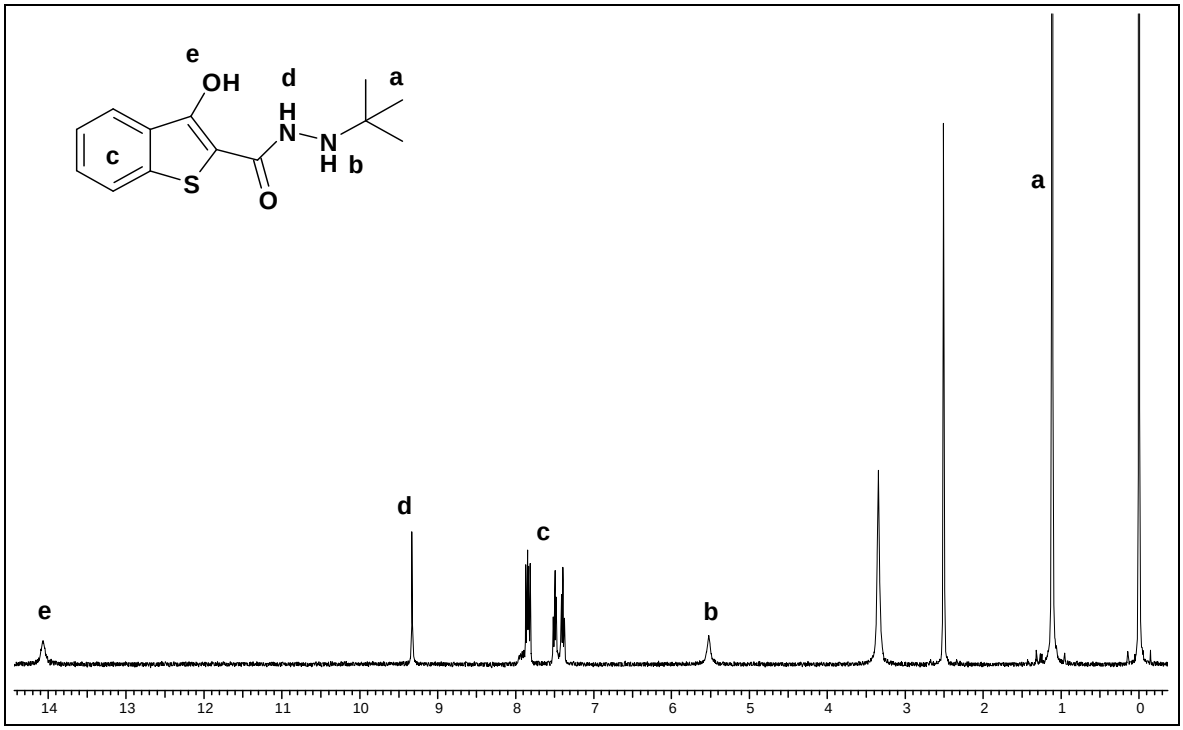
N(*N`*)-Alkyl-3-hydroxy-benzo[*b*]thiophene-2-carbohydrazides (**29**, **30**) are stable solids and characterized by their IR spectra which display a (C=O) band at 1638 cm^{-1} and a sharp (NH) band at 3320-3340 cm^{-1} (Fig. 3-20).

Fig. 3-20 *IR (KBr) Spectrum of N-Ethyl-3-hydroxy-benzo[b]thiophene-2-carbohydrazide* (**29b**)



The ^{1}H-NMR of *N'-tert*-butyl-3-hydroxy-benzo[*b*]thiophene-2-carbohydrazide (**30**) exhibits singlets at 1.11 ppm (*t*-Bu), 5.52 ppm (NH-*t*-Bu), 9.33 ppm (NH-CO) and 14.06 ppm (OH) (Fig. 3-21).

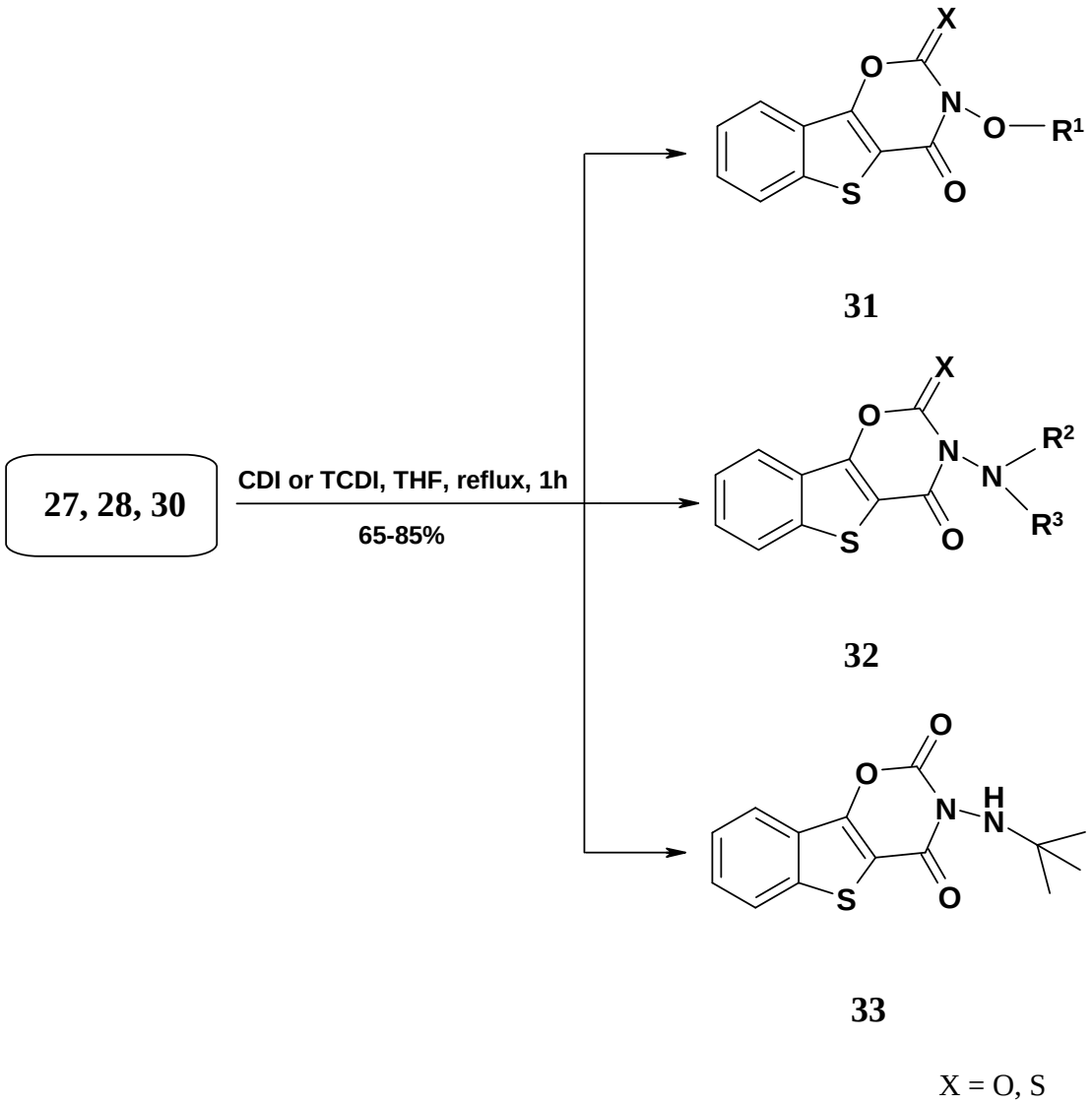
Fig. 3-21 *^{1}H-NMR Spectrum of N'-tert-Butyl-3-hydroxy-benzo[b]thiophene-2-carbohydrazide* (**30**)



3.2.4 Cyclic carbonylation (thiocarbonylation) of compounds **27**, **28**, **30** to 3-substituted-benzothieno[2,3-*e*][1,3]oxazines (**31**, **32**, **33**)

The successful preparation of the above described benzothiophene derivatives **27**-**30** prompted me to study their cyclic carbonylation towards the targeted 3-alkoxy(aralkoxy)-benzothieno[2,3-*e*][1,3]oxazines (**31)**, as well as the 3-aminosubstituted-benzothieno[2,3-*e*][1,3]oxazines (**32**, **33**) (Scheme 3-17).

Scheme 3-17 *Synthesis of 3-Substituted-benzothieno[2,3-e][1,3]oxazines* (**31-33**)



3.2.4.1 Synthesis and properties of 3-Alkoxy(Aralkoxy)-benzothieno[2,3-e][1,3]oxazines (**31**)

Thus, treatment of **27a-h** with 1,1 equivalent of 1,1`-carbonyldiimidazole (CDI) afforded cleanly the aimed 3-alkoxy(aralkoxy)-benzothieno[2,3-*e*][1,3]oxazine-2,4-diones (**31a-h**) as white to light pink solids in 72-85% yield, and reaction of compound **27e** with 1,1`-thiocarbonyldiimidazole (TCDI) furnished 3-(3-phenylpropoxy)-2-thioxo-benzothieno[2,3-*e*][1,3]-oxazine-4-one (**31i**) as light pink needles in 69% yield (Scheme 3-17, Table 3-9).

Table 3-9 *Prepared 3-Alkoxy(Aralkoxy)-benzothieno[2,3-e][1,3]oxazines* (**31**)

31	**R^1**	**X**	**Yield (%)**
a	CH_3	O	79
b	CH_2CHCH_2	O	85
c	$C_6H_5CH_2$	O	81
d	$C_6H_5CH_2CH_2$	O	77
e	$C_6H_5CH_2CH_2CH_2$	O	78
f	4-CH_3-$C_6H_4CH_2$	O	72
g	4-Br-$C_6H_4CH_2$	O	74
h	$C_{10}H_7CH_2$	O	72
i	$C_6H_5CH_2CH_2CH_2$	S	69

The IR spectra of compounds **31a-h** show two strong (C=O) bands at 1703-1718 cm^{-1} and at 1774-1780 cm^{-1} (Fig. 3-22). The IR spectrum of 3-(3-phenylpropoxy)-2-thioxo-benzothieno[2,3-*e*][1,3]oxazine-4-one (**31i**) displays one (C=O) absorption at 1718 cm^{-1} and a characteristic (C=S) band at 1290 cm^{-1} (Fig. 3-23).

The ^{1}H-NMR spectrum of compound **31f** offers singlets at 2.34 ppm (CH_3) and 5.13 ppm (CH_2) beside the multiplet of the aromatic protons between 7.25-8.23 ppm (Fig. 24).

Fig. 3-22 *IR (KBr) Spectrum of 3-Allyloxy-benzothieno[2,3-e][1,3]oxazines-2,4-dione* (**31b**)

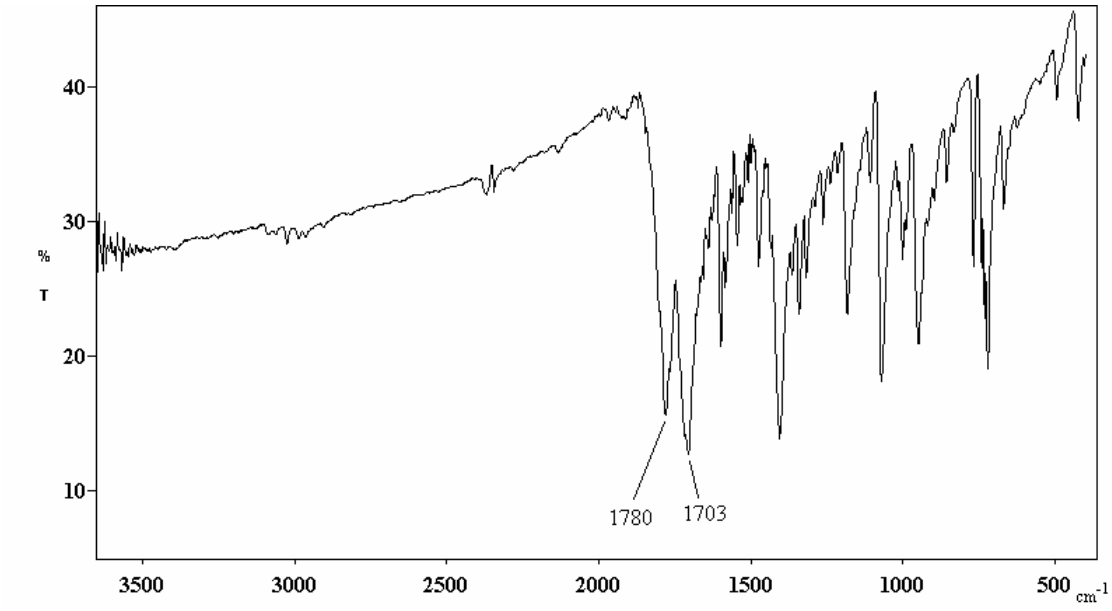


Fig. 3-23 *IR (KBr) Spectrum of 3-(3-Phenylpropoxy)-2-thioxo-benzothieno-[2,3-e][1,3]oxazine-4-one* (**31i)**

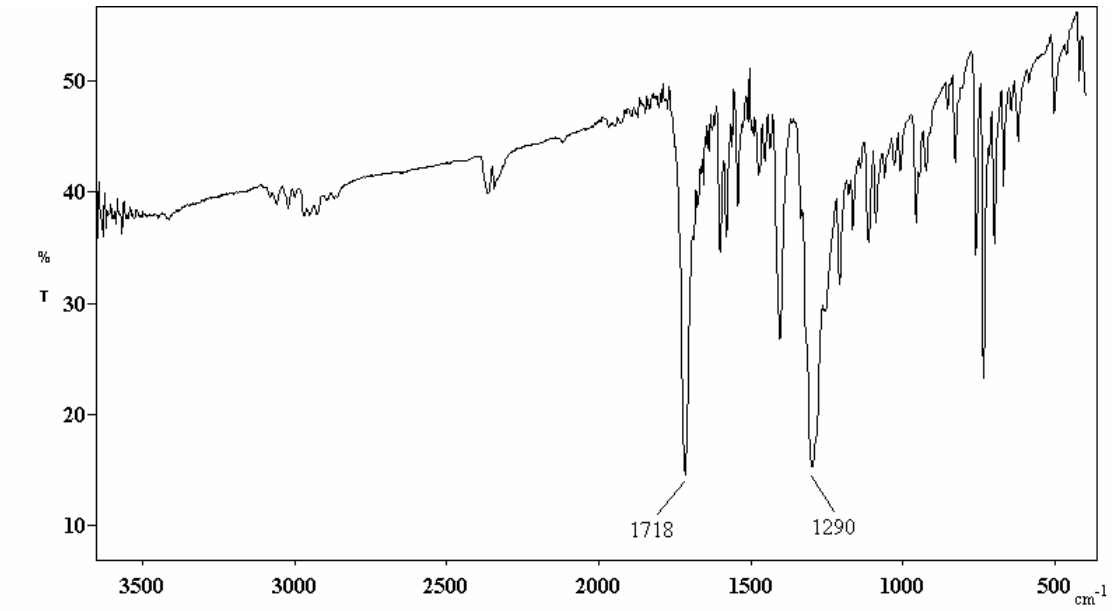
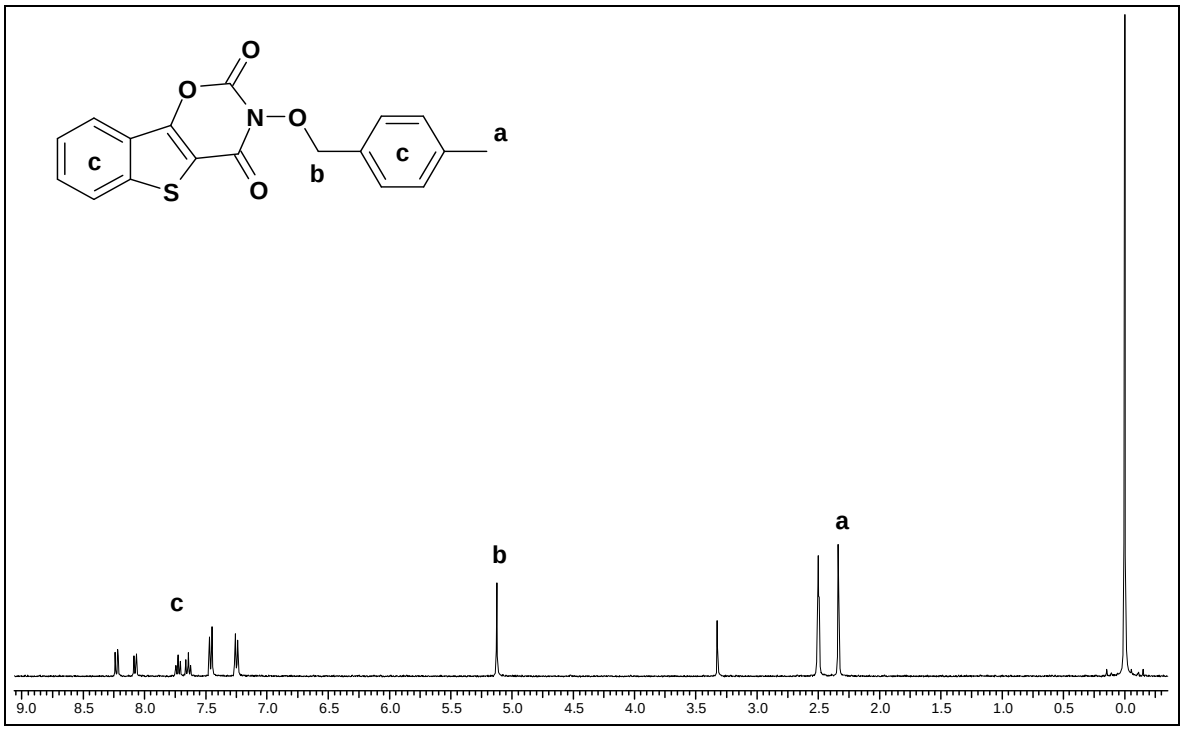


Fig. 3-24 *^{1}H-NMR Spectrum of 3-(4-Methyl-benzyloxy)-benzothieno[2,3-e]-[1,3]oxazine-2,4-dione* (**31f**)



3.2.4.2 Synthesis and properties of 3-(Aminosubstituted)-benzothieno[2,3-e][1,3]oxazines (**32, 33**)

Cyclization of compounds **28a-d** with 1,1`-carbonyldiimidazole (CDI) in refluxing THF produced the desired 3-aminosubstituted-benzothieno[2,3-*e*][1,3]oxazine-2,4-diones (**32a-d**) as white stable solids in 70-83% yields. Similarly, 3-*tert*-butylamino-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**33**) was accessible as white solid in 67% yield. 3-(Dimethylamino)-2-thioxo-benzothieno[2,3-*e*][1,3]oxazine-4-one (**32e**) was obtained as pale yellow solid in 65% yield after treating compound **28a** with 1,1`-thiocarbonyldiimidazole (TCDI) (Scheme 3-17, Table 3-10).

Table 3-10 *Prepared 3-(Aminosubstituted)-benzothieno[2,3-e][1,3]oxazines* (**32**)

32	**R^2**	**R^3**	**X**	**Yield (%)**
a	CH_3	CH_3	O	70
b	$-(CH_2)_5-$		O	74
c	$-(CH_2)_2-O-(CH_2)_2-$		O	76
d	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		O	83
e	CH_3	CH_3	S	65

The IR spectrum of **33** shows two (C=O) absorption bands at 1692, 1784 cm^{-1} and a (NH) band at 3300 cm^{-1} (Fig. 3-25), whereas the IR spectrum of 3-(dimethylamino)-2-thioxo-benzothieno[2,3-*e*][1,3]oxazine-4-one (**32e**) is characterized by a strong (C=S) band at 1280 cm^{-1} and a (C=O) band at 1708 cm^{-1} (Fig. 3-26).

The ^{1}H-NMR spectrum of compound **33** exhibits singlets at 1.13 ppm (*t*-Bu) and 5.45 ppm (NH) in addition to four multiplets (aromatic protons) (Fig. 3-27).

Fig. 3-25 *IR (KBr) Spectrum of 3-tert.-Butylamino-benzothieno[2,3-e][1,3]-oxazine-2,4-dione* (**33**)

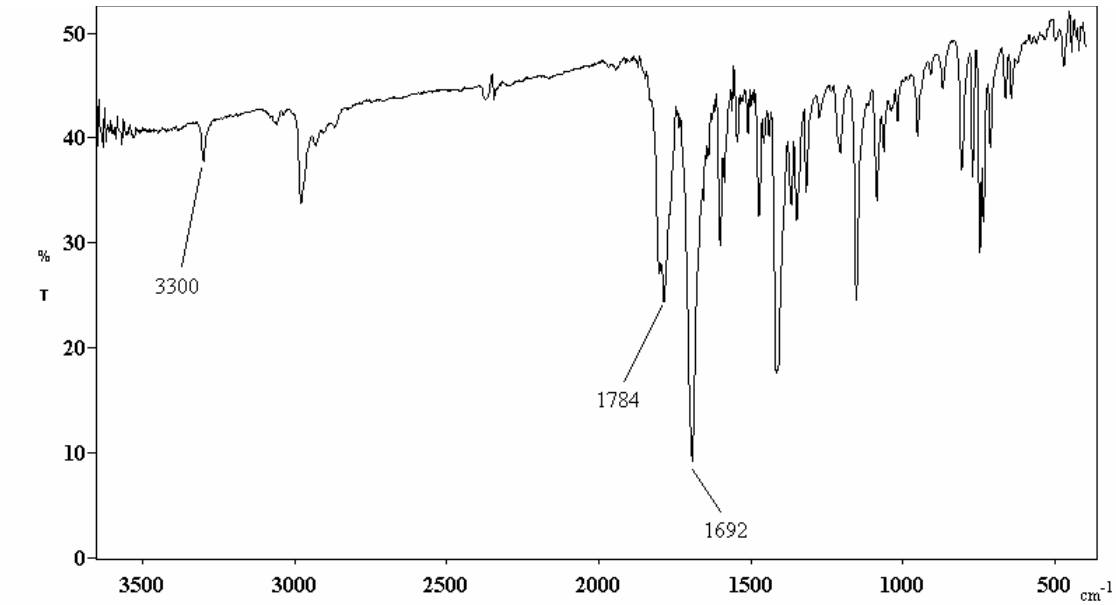


Fig. 3-26 *IR (KBr) Spectrum of 3-(Dimethylamino)-2-thioxo-benzothieno-[2,3-e][1,3]oxazine-4-one* (**32e**)

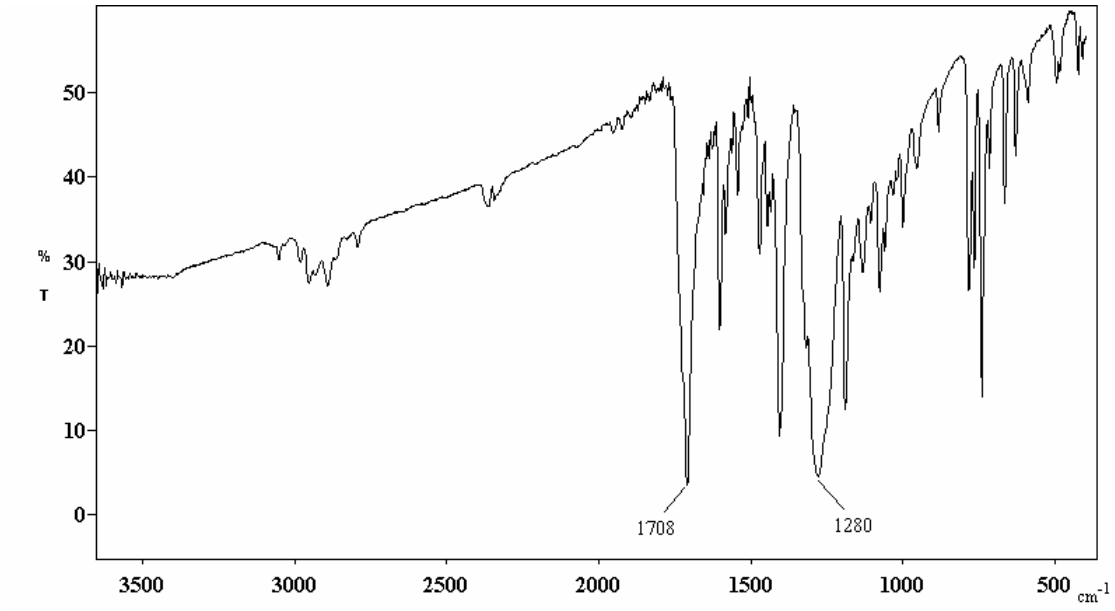
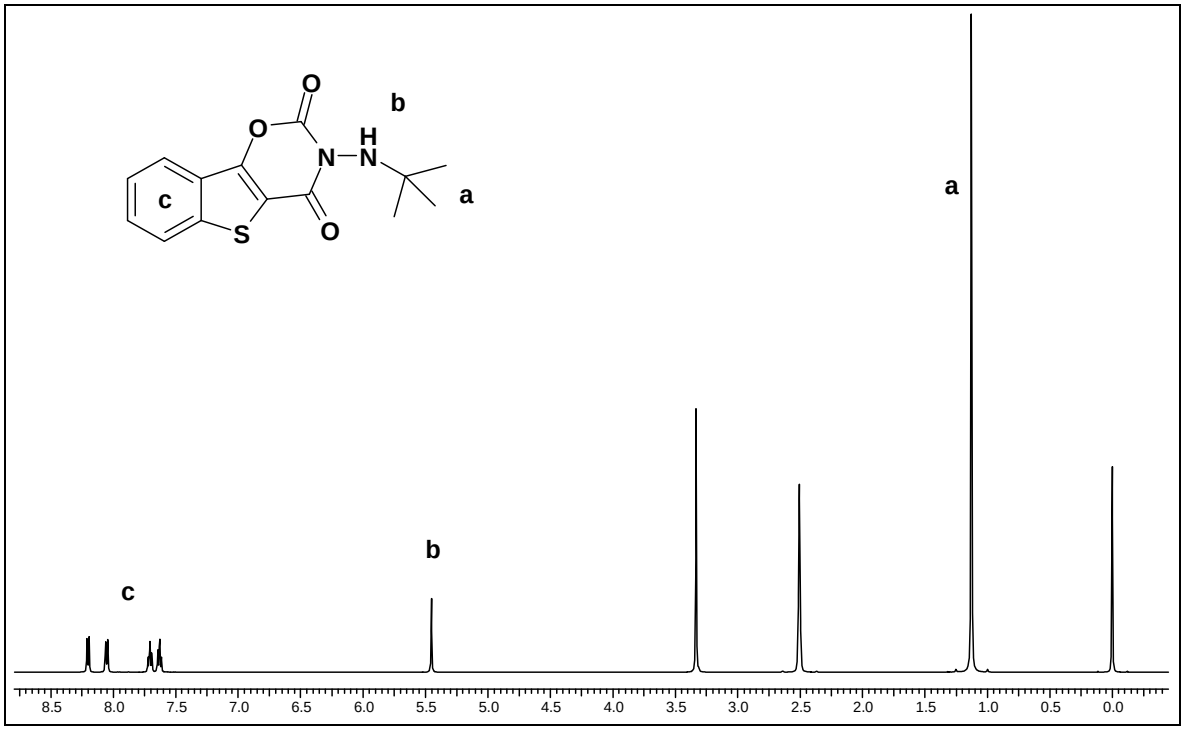


Fig. 3-27 *[1]H-NMR Spectrum of 3-tert.-Butylamino-benzothieno[2,3-e][1,3]-oxazine-2,4-dione* (**33**)



4 Biological Studies

4.1 Antiinflammatory Activity

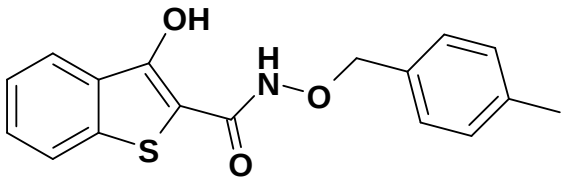
Several selected compounds (**18b,h**, **19a,d**, **27b,d,h,f**, **28c,d**, **29a**, **30** and **32a)** have been tested for COX/LOX[m] inhibitory activities. The in vitro tests were carried out in collaboration with Prof. Dr. Dannhardt (University of Mainz, Institute of Pharmacy).

4.1.1 Performed Assays

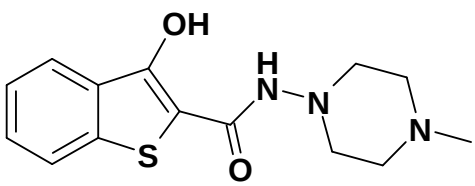
MDA (12-HHT) assay[91,92] and full blood assay were used to evaluate the inhibitory effect of the tested substances on COX-1 and COX-2, respectively.
The 5-LOX antagonistic properties were studied using a reversed phase HPLC method[93].

4.1.2 Results

All the tested compounds showed no inhibitory effect on COX-2.
Low 5-LOX inhibition was observed (22-36% inhibition at 10 µmol/L) for compounds **18b,h**, **19d**, **28d**, **30.**
Notably, compounds **27f**, **28d** showed good COX-1 inhibition with IC_{50} values of 1.5 and 5.3, respectively.



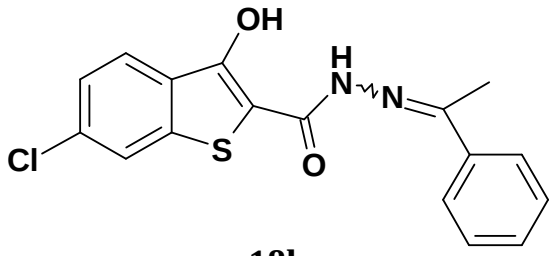
27f



28d

[m] COX-1 and COX-2 are subtypes of the enzyme cyclooxygenase which mediates the biosynthesis of prostaglandines starting from arachidonic acid. 5-LOX (5-Lipoxygenase) catalyses the biosynthesis of leuketrienes.

The best inhibitory effect towards COX-1 was achieved by compound **18h** which showed 94% inhibition at 0.1 µmol/L.



18h

4.2 Herbicidal and Fungicidal Activity

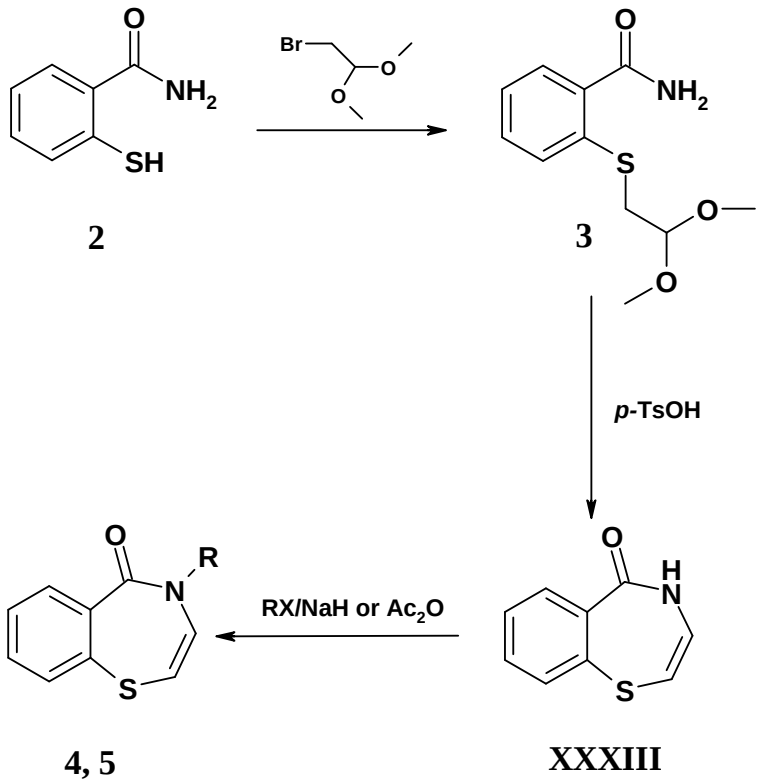
Screening of **4a,b**, **11a-c**, **19e-j**, **28c,d**, **29a**, **30**, **31b,e,f** and **32c,d** towards herbicidal and fungicidal activity (in collaboration with E.I. DuPont de Nemours, New York-Wilmington/USA) is still in progress.

5 Summary

This work deals with the synthesis of two types of sulfur containing heterocycles, namely 1,4-benzothiazepine-5-one as well as 3-hydroxy-benzothiophene-2-carboxamide derivatives.

In the first part, 1,4-benzothiazepine-5-one (**XXXIII**) was accessible by cyclocondensation of compound **3**, which in turn was obtained from 2-mercapto benzamide (**2**) and 2-bromo-1,1-dimethoxyethane. *N*-Alkylation (Acylation) of compound **XXXIII** provided the products **4** and **5** (Scheme 1).

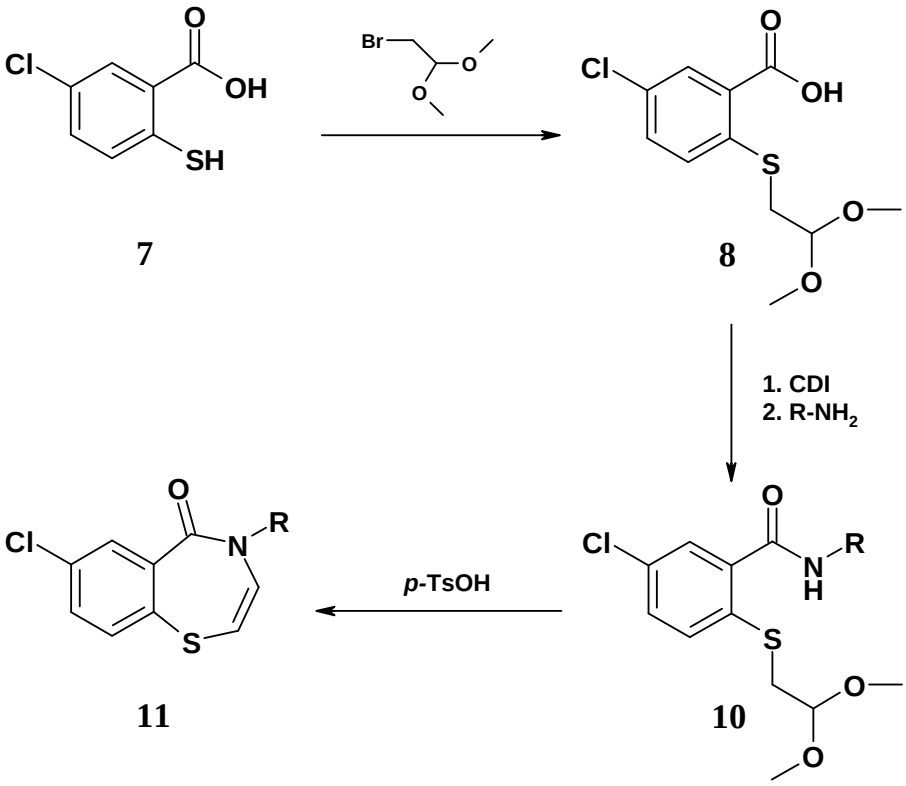
Scheme 1



As outlined in Scheme 2, *S*-alkylation of 5-chlorothiosalicylic acid (**7**) with 2-bromo-1,1-dimethoxyethane gave compound **8**. Subsequent reaction of **8** with 1,1`-carbonyldiimidazole (CDI), followed by the addition of different benzylamines furnished the corresponding amides **10**, which underwent

cyclocondensation providing the desired 4-arylmethyl-7-chloro-[1,4]benzo-thiazepine-5-ones (**11**).

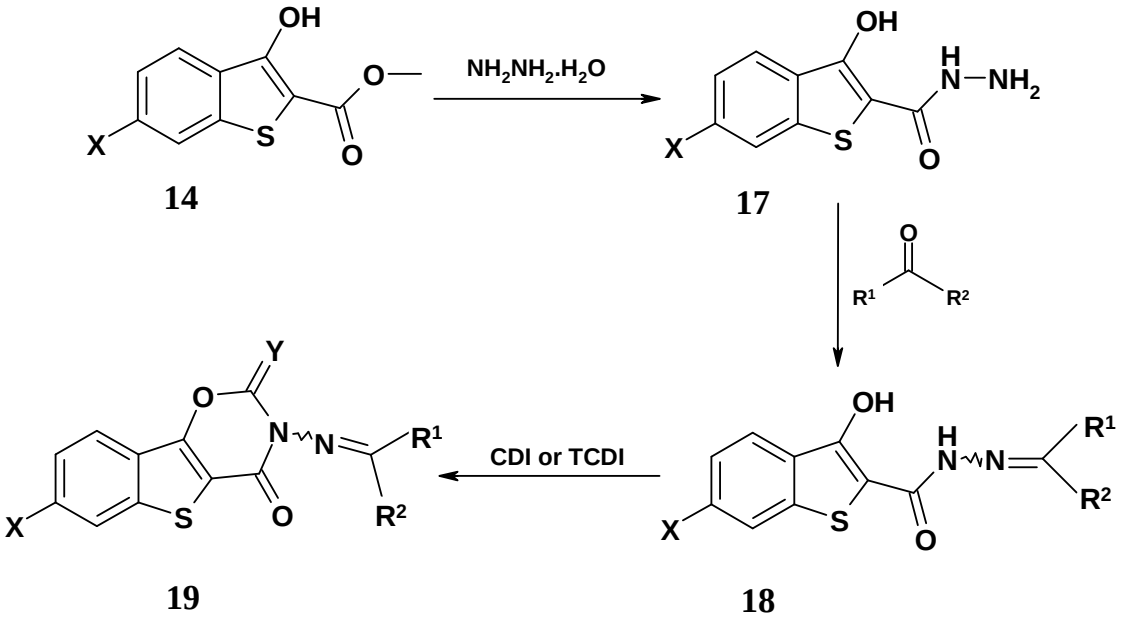
Scheme 2



In the second part, the synthesis of new 3-hydroxy-benzo[*b*]thiophene-2-carboxamides and their cyclization to the corresponding 3-substituted-benzothieno[2,3-*e*][1,3]oxazines was reported.

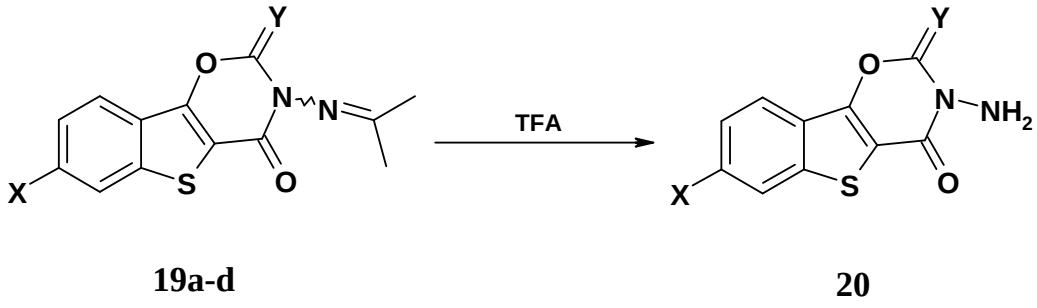
Hydrazinolysis of methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylates (**14**) realized the corresponding hydrazides **17**. Condensation of **17** with ketones and aldehydes occurred easily to provide *N*-aminoalkenyl-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**18**), which were successfully converted to the corresponding 3-aminoalkenyl-benzothieno[2,3-*e*][1,3]oxazines (**19**) by the reaction with 1,1`-carbonyldiimidazole (CDI) or 1,1`-thiocarbonyldiimidazole (TCDI) (Scheme 3).

Scheme 3



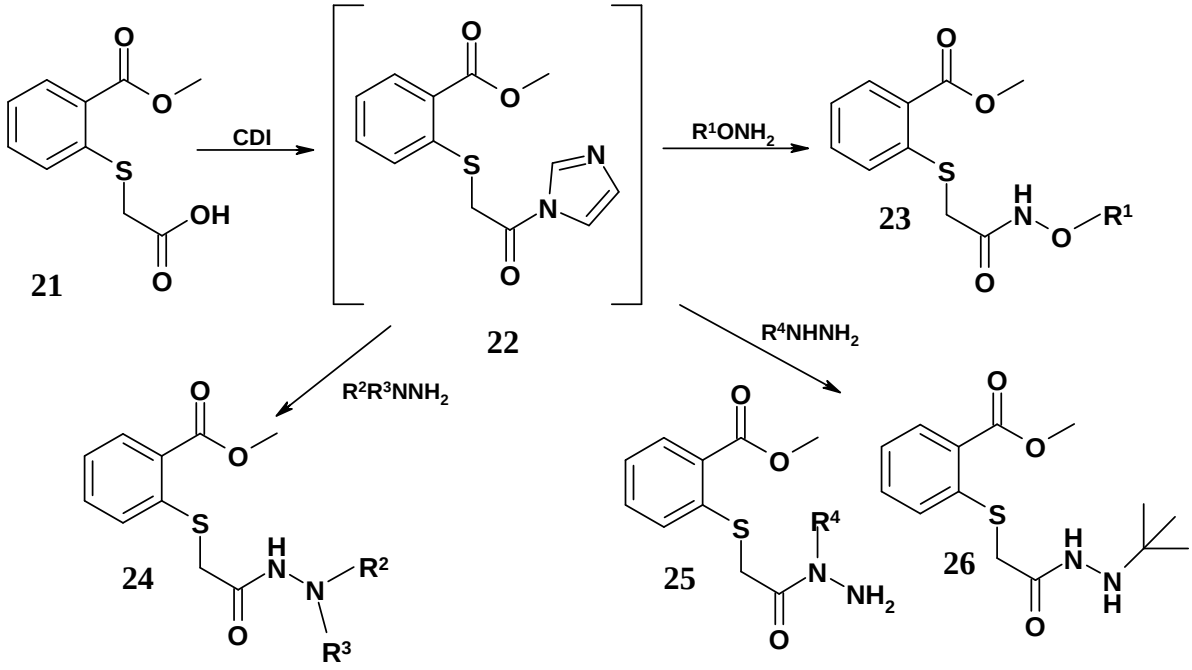
Cleavage of the alkenyl group in **19a-d** upon treatment with trifluoroacetic acid occurred smoothly to provide 3-amino-benzothieno[2,3-*e*][1,3]oxazines (**20**) (Scheme 4).

Scheme 4



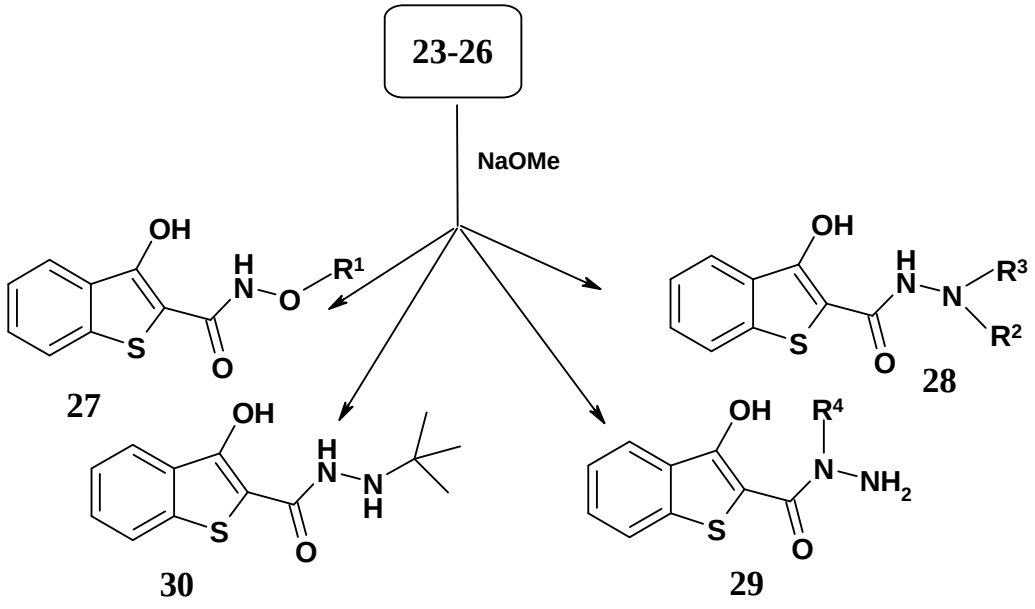
The reaction of methyl 2-carboxymethylsulfanyl benzoate (**21**) with CDI provided the imidazolide intermediate **22**. In situ addition of various alkoxy(aralkoxy)amines and hydrazines furnished the open chained precursors **23-26** (Scheme 5).

Scheme 5



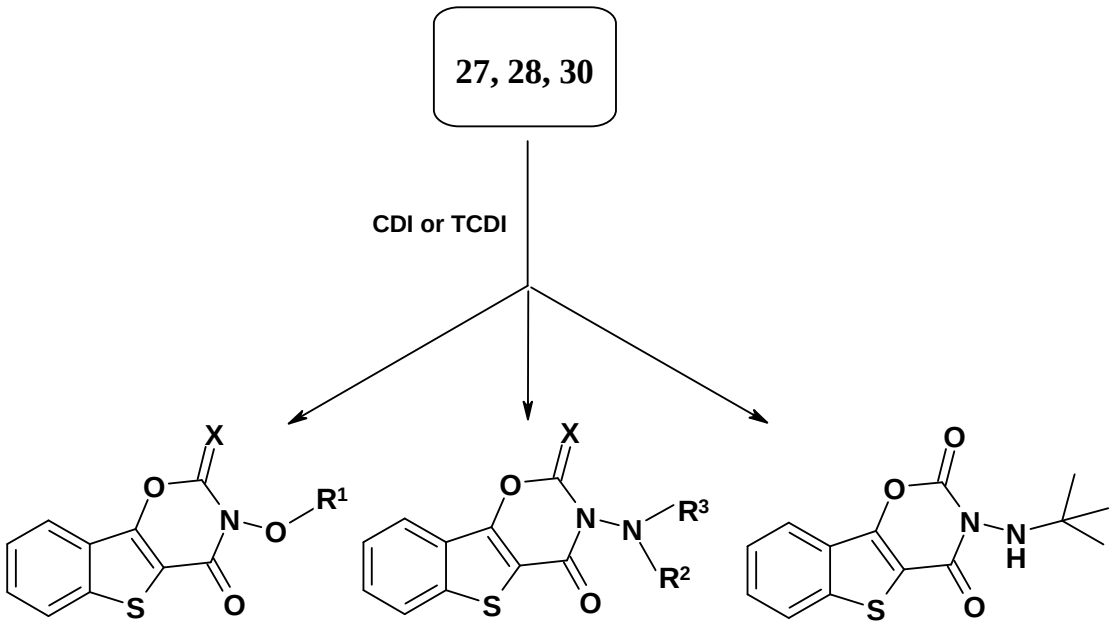
Cyclization of **23-26** was accomplished in refluxing sodium methoxide solution to give *N*-alkoxy(aralkoxy)-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**27**) as well as 3-hydroxy-benzo[*b*]thiophene-2-carbohydrazides (**28**-**30**) (Scheme 6).

Scheme 6



Finally, ring closure of **27**, **28**, **30** with CDI or TCDI effectively afforded the desired benzothieno[2,3-*e*][1,3]oxazines (**31-33**) (Scheme 7).

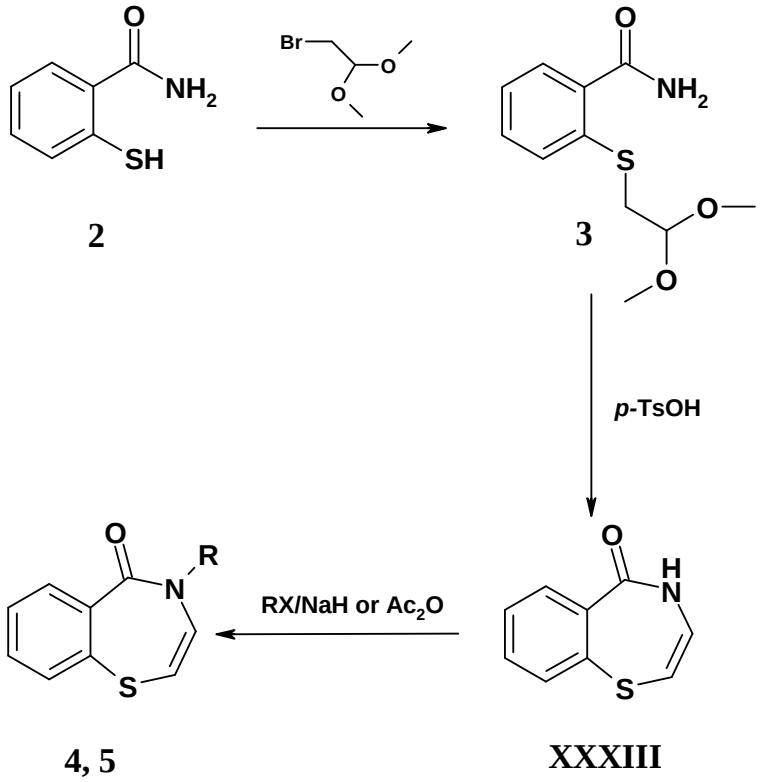
Scheme 7



6 Zusammenfassung

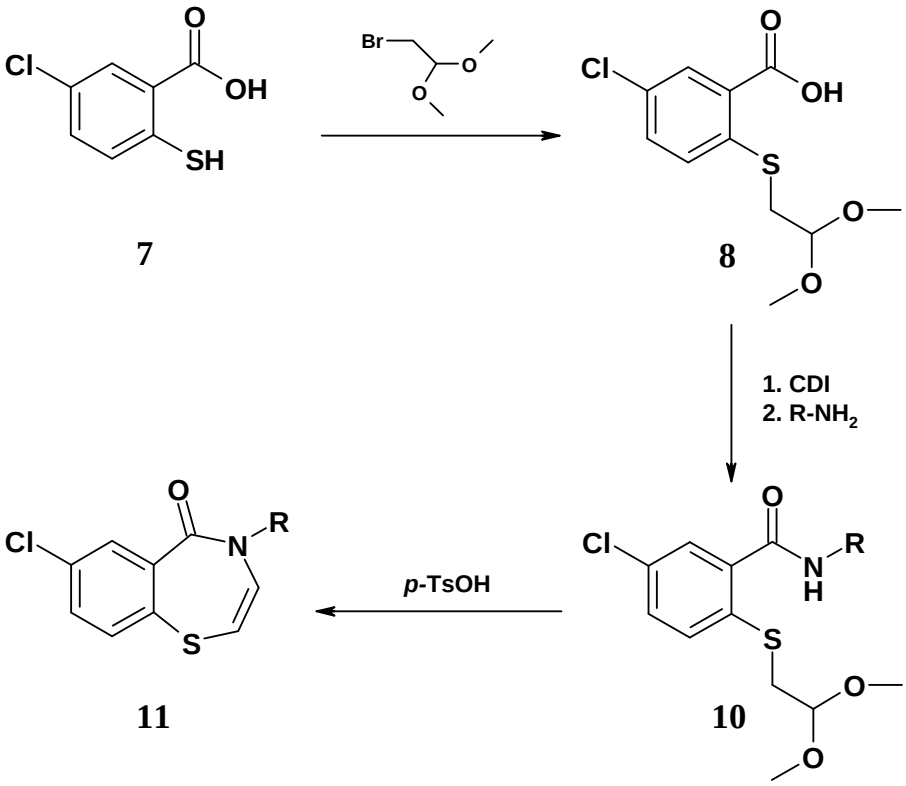
Die vorliegende Arbeit befasst sich mit der Synthese von 1,4-Benzothiazepin-5-onen und 3-Hydroxy-benzo[*b*]thiophen-2-carboxamiden. Die Verbindung **3** wurde durch *S*-Alkylierung von 2-Mercaptobenzamid (**2**) erhalten. Cyclokondensation von **3** ergab das unsubstituierte 1,4-Benzothiazepin-5-on (**XXXIII**), welches durch Alkylierung in die Verbindungen **4**, **5** überführt wurde (Schema 1).

Schema 1



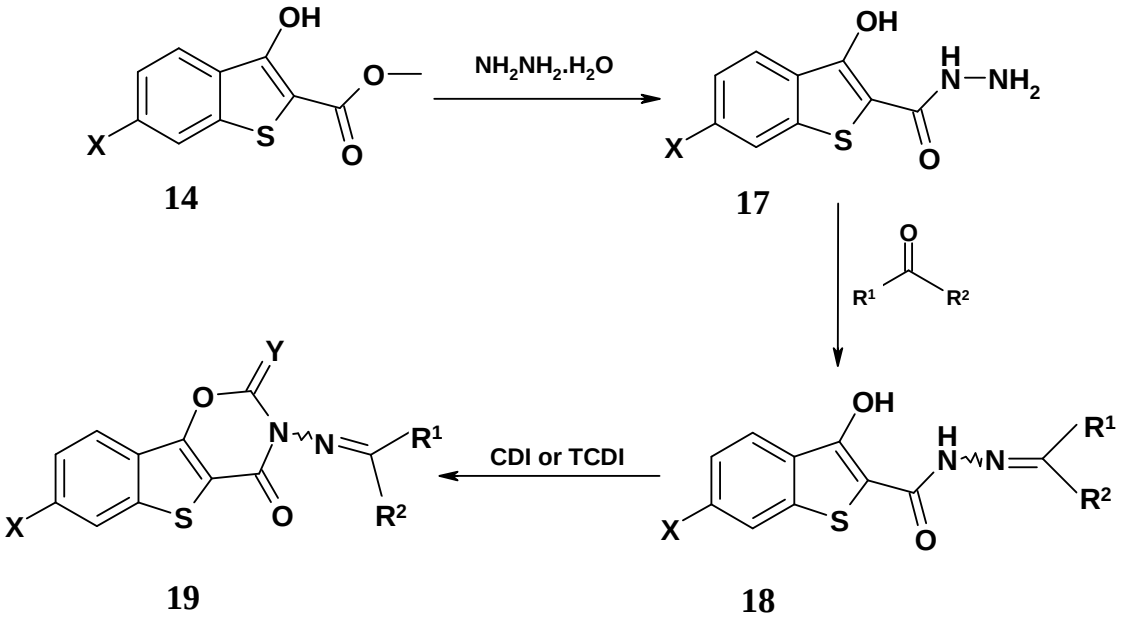
Gemäß Schema 2 ergab die *S*-Alkylierung von 5-Chlorothiosalicylsäure (**7**) durch Behandlung mit 2-Bromo-1,1-dimethoxyethan die Verbindung **8**. Diese lieferte nach Aktivierung mit 1,1`-Carbonyldiimidazol (CDI) durch Umsetzung mit verschiedenen Benzylaminen die Carboxamide **10**, welche durch Ringschlussreaktion die gewünschten 4-Arylmethyl-7-chloro-[1,4]benzothiazepin-5-one (**11**) erbrachten.

Schema 2



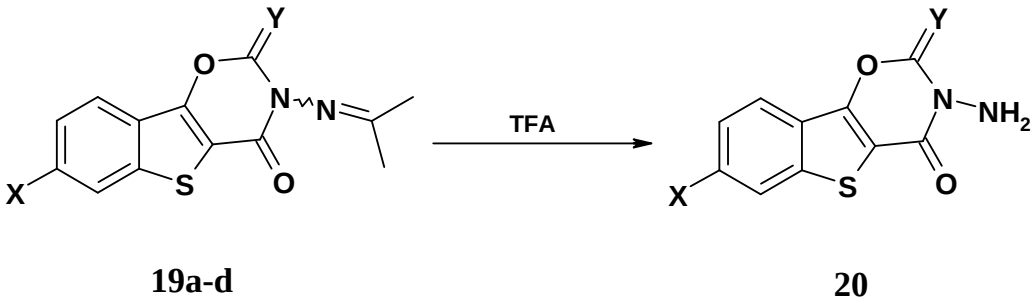
Im zweiten Teil dieser Arbeit wird die Herstellung von 3-Hydroxy-benzo[*b*]thiophen-2-carboxamid Derivaten und deren Cylclisierung zu den entsprechenden 3-substituierte-benzothieno[2,3-*e*][1,3]oxazinen beschrieben. Hydrazinolyse von Methyl 3-hydroxy-benzo[*b*]thiophen-2-carboxylate (**14**) lieferte die korrespondierenden Hydrazide **17**. Durch Umsetzung von **17** mit verschiedenen Ketonen und Aldehyden wurden die *N*-Aminoalkenyl-3-hydroxy-benzo[*b*]thiophen-2-carboxamide (**18**) erhalten.
Mit 1,1`-Carbonyldiimidazol (CDI) oder 1,1`-Thiocarbonyldiimidazol (TCDI) reagierten die Verbindungen **18** zu den entsprechenden 3-Aminoalkenyl-benzothieno[2,3-*e*][1,3]oxazine (**19**) (Schema 3).

Schema 3



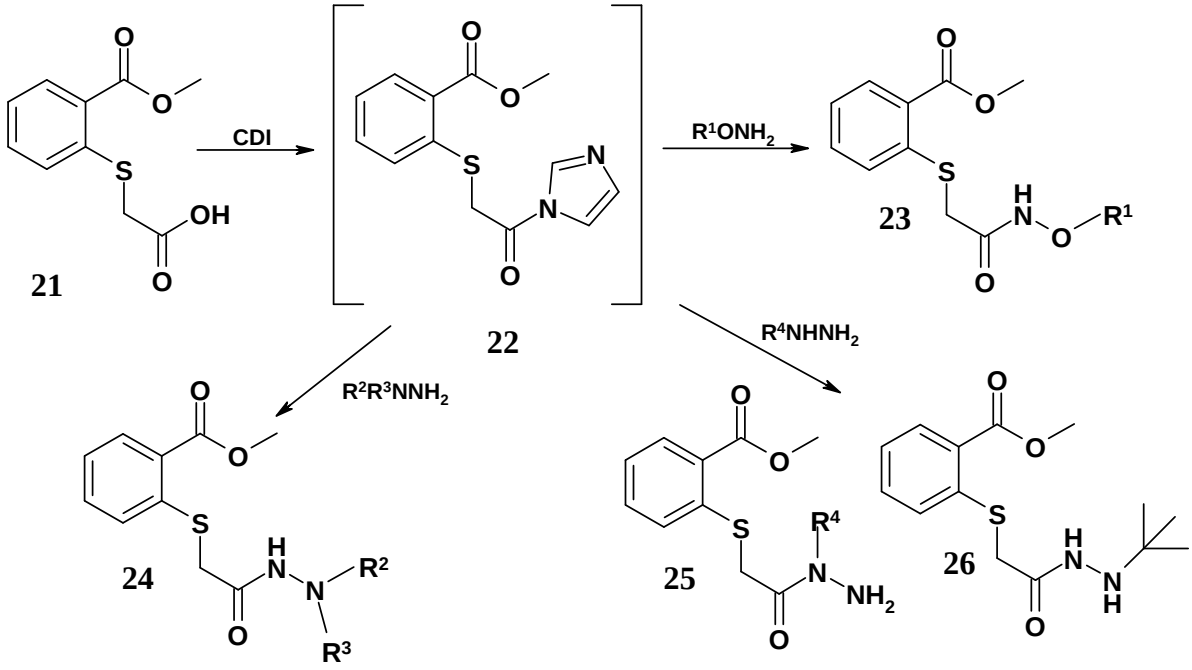
3-Amino-benzothieno[2,3-*e*][1,3]oxazine (**20**) konnten durch Behandlung von **19a-d** mit Trifluoroessigsäure erhalten werden (Schema 4).

Schema 4



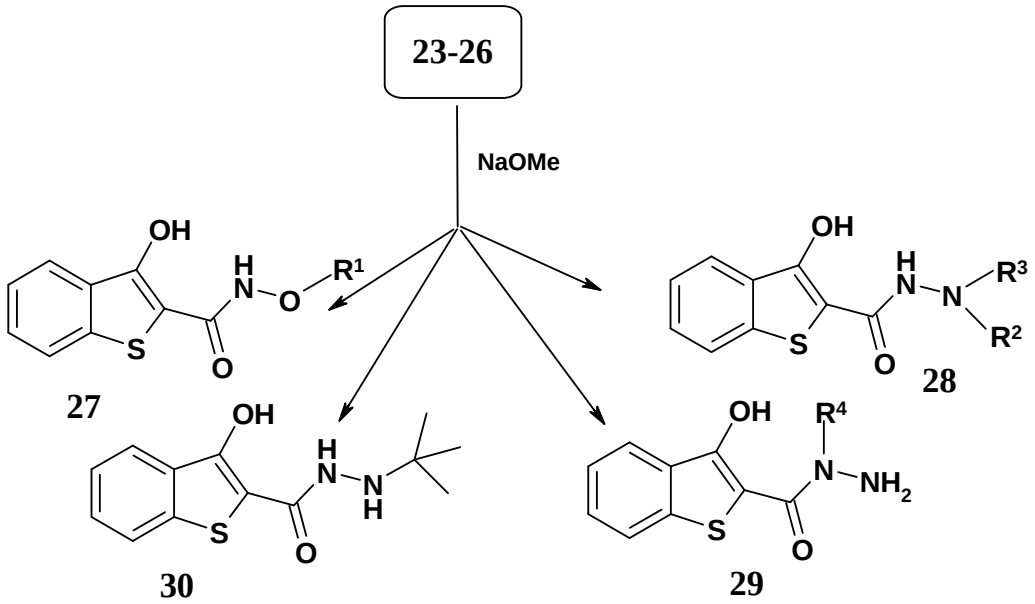
Die Umsetzung von Methyl 2-carboxymethylsulfanylbenzoat (**21**) mit 1,1`-Carbonyldiimidazol (CDI) ergab das Imidazolid-Intermediat **22**. Nachfolgende Addition von *O*-substituierten Hydroxylaminen und Hydrazinen lieferte **23-26** (Schema 5).

Schema 5



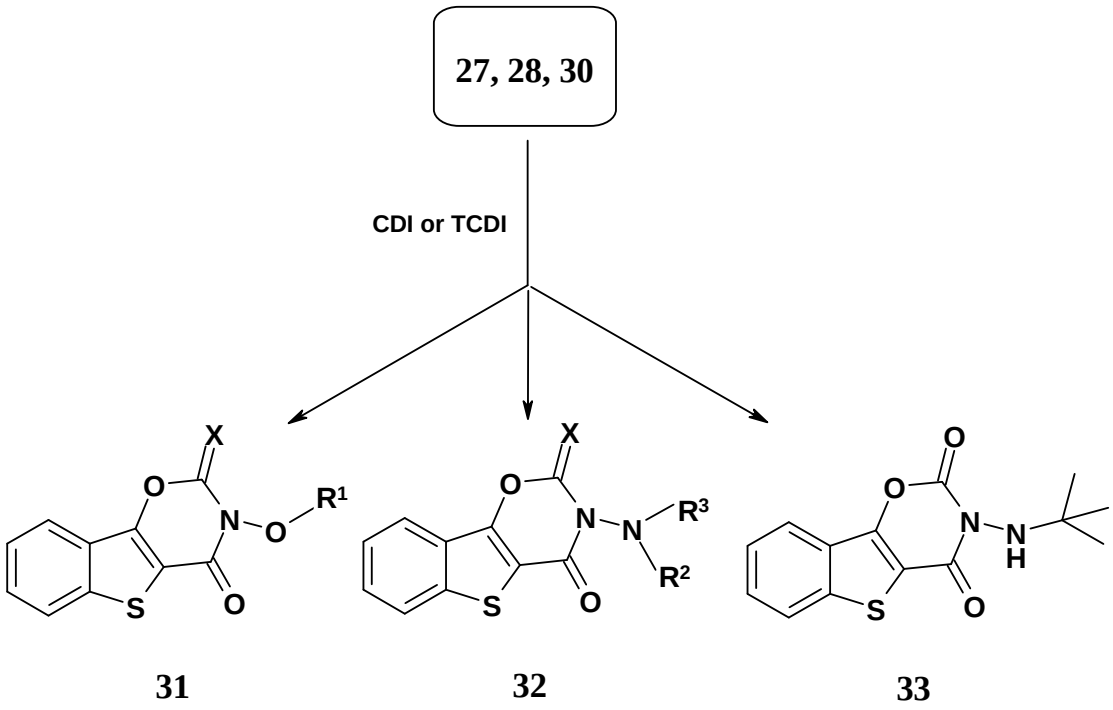
Die Cyclisierung von **23-26** mit Natriummethoxid in Methanol unter Rückfluss erbrachte die gewünschten *N*-Alkoxy(Aralkoxy)-3-hydroxy-benzo[*b*]thiophen-2-carboxamide (**27**) bzw. 3-Hydroxy-benzo[*b*]thiophen-2-carbohydrazide (**28**-**30**) (Schema 6).

Schema 6



Schließlich konnten die entsprechenden Benzothieno[2,3-*e*][1,3]oxazine (**31**-**33**) durch Behandlung von **27**, **28**, **30** mit CDI oder TCDI erhalten werden (Schema 7).

Schema 7



7 Experimental

7.1 General Information

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus.

IR Spectra were recorded on a Shimadzu FT-IR 8300.

^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6 as a solvent.

Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument.

Column chromatography was conducted on silica gel (ICN Silica 100-200, active 60 Å).

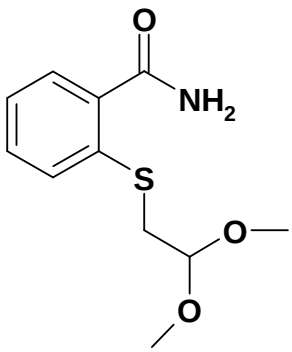
Magnesium sulfate was used as drying agent for organic phases.

7.2 Procedures and Analytical Data for Chapter 2

7.2.1 Preparation of 2-[(2,2-dimethoxyethyl)sulfanyl]benzamide (**3**)

A mixture of thiosalicylic acid (**1**) (50 mmol) and thionyl chloride (150 mL), was refluxed for 2 h. After removal of the solvent under reduced pressure, the resulting oily residue was dissolved in dry THF and added dropwise to a cooled aqueous solution of ammonia (25%) to afford 2-mercapto benzamide (**2**) as light brown precipitate. The product was collected by filtration, dried and used in the next synthetic step without further purification.
A stirred mixture of 2-mercapto benzamide (**2**) (30 mmol), K_2CO_3 (75 mmol), and 2-bromo-1,1-dimethoxyethane (30 mmol) in dry acetone (60 mL) was refluxed for 12h. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was taken up in dichloromethane (40 mL) and the resulting solution was washed with water (2 x 10 mL) and dried over $MgSO_4$. The solvent was evaporated to afford 2-[(2,2-dimethoxyethyl)sulfanyl]benzamide (**3**) after recrystallization from ether/ Petrolether.

2-[(2,2-dimethoxyethyl)sulfanyl]benzamide (**3**)



Yield: 65% white solid
M.P.: 92 °C
IR (KBr): 1683 cm^{-1} (C=O); 3406 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.06 (d, 2H, CH_2); 3.22 (s, 6H, CH_3); 4.47 (m, 1H, CH); 7.18-7.46 (m, 4H, aromat.); 7.66 (s, 2H, NH_2).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

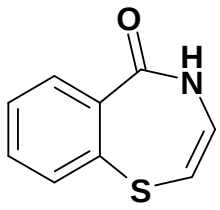
33.15 (CH_2); 51.29 (CH_3); 101.63 (CH); 126.23, 127.54, 128.12, 128.69 (4C tert., aroamt.); 128.47, 130.22 (2C quart., aromat.); 162.45 (C=O).

$C_{11}H_{15}NO_3S$ [241.31]

7.2.2 Preparation of 1,4-Benzothiazepine-5-one (**XXXIII**)

2-[(2,2-Dimethoxyethyl)sulfanyl]benzamide (**3**) (10 mmol) and *p*-toluene-sulphonic acid (0.5 mmol) were dissolved in toluene (40 mL) and heated to reflux for 18 hours. After cooling, the mixture was washed with saturated solution of $NaHCO_3$ (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford 1,4-benzothiazepine-5-one (**XXXIII**).

1,4-Benzothiazepine-5-one (**XXXIII**)



Yield: 72%, yellow solid

M.p.: 142 °C (Lit.[62] 141-143 °C)

IR (KBr): 1658 cm^{-1} (C=O); 3210 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

5.94 (d, *J* = 5.94 Hz, 1H); 6.55 (m, 1H); 7.33-7.64 (m, 4H, aromat.); 9.79 (s, 1H, NH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

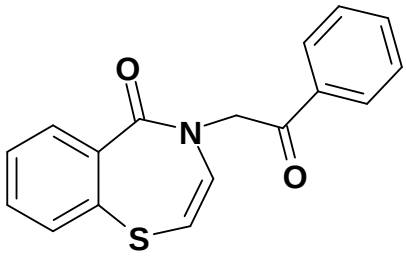
108.87 (S-CH); 128.29 (N-CH); 130.91, 131.52, 132.23, 133.19 (4C tert., aromat.); 138.00, 139.08 (2C quart., aromat.); 169.30 (C=O).

C_9H_7NOS [172.23]

7.2.3 Preparation of compounds **4**

To an ice-cooled suspension of 1,4-benzothiazepine-5-one (**XXXIII**) (2 mmol) and sodium hydride (2 mmol) in dry THF (10 mL), a solution of the appropriate alkylating agent (2 mmol) in dry THF (5 mL) was added dropwise. After stirring for 18 hours at room temperature, the solvent was removed under reduced pressure and the residue was taken up in CH_2Cl_2 (15 mL). The solution was washed with saturated solution of $NaHCO_3$ (5 mL) and dried over $MgSO_4$. Evaporation in vacuo resulting in a solid residue that was purified via column chromatography on silica gel (EtOAc/ n-hexan 1:1) to yield compounds **4**.

4-(2-Oxo-phenylethyl)-[1,4]benzothiazepine-5-one (**4a**)



Yield: 43%, white solid

M.p.: 143 °C

IR (KBr): 1695, 1627 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

5.23 (s, 2H, CH_2); 6.27 (d, *J* = 6.36 Hz, 1H, S-CH); 6.71 (d, *J* = 6.61 Hz, 1H, N-CH); 7.40-8.06 (m, 9H, aromat.).

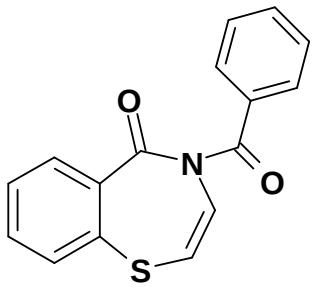
^{13}C-NMR (DMSO-*d6*): δ(ppm):

55.23 (CH_2); 112.52 (S-CH); 127.86, 128,24, 128.78, 130.66, 131.72, 131.88, 133.71 (9C tert., aromat.); 137.75 (N-CH); 134.63, 138.46, 139.47 (3C quart., aromat.); 168.43 (C=O); 192.79 (C=O).

$C_{17}H_{13}NO_2S$ [295.36]

Calcd.	[%]	C 69.13	H 4.44	N 4.47	S 10.86
Found	[%]	C 68.60	H 4.61	N 4.58	S 10.68

4-Benzoyl-[1,4]benzothiazepine-5-one (**4b**)



Yield: 66%, yellow solid

M.p.: 101 °C

IR (KBr): 1652, 1706 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

6.74 (d, *J* = 6.36 Hz, 1H, S-CH); 7.13 (d, *J* = 6.36 Hz, 1H, N-CH); 7.50-7.84 (m, 9H, aromat.).

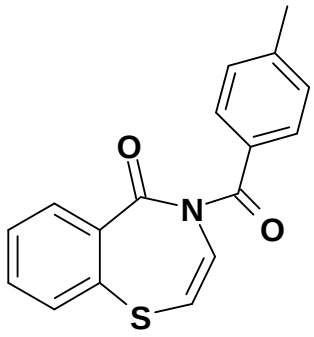
^{13}C-NMR (DMSO-*d6*): δ(ppm):

118.21 (S-CH); 128.62, 128,74, 128.87, 131.39, 132.05, 132.65, 133.19 (9C tert., aromat.); 133.46 (N-CH); 133.33, 136.30, 139.21 (3C quart., aromat.); 168.87 (C=O); 172.96 (C=O).

$C_{16}H_{11}NO_2S$ [281.34]

Calcd.	[%]	C 68.31	H 3.94	N 4.98	S 11.40
Found	[%]	C 68.43	H 4.18	N 4.92	S 11.04

4-(4-Methyl-benzoyl)-[1,4]benzothiazepine-5-one (**4c**)



Yield: 68%, yellow solid

M.p.: 89°C

IR (KBr): 1676, 1708 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.39 (s, 3H, CH_3); 6.69 (d, *J* = 6.61 Hz, 1H, S-CH); 7.10 (d, *J* = 6.36 Hz, 1H, N-CH); 7.37-7.76 (m, 8H, aromat.).

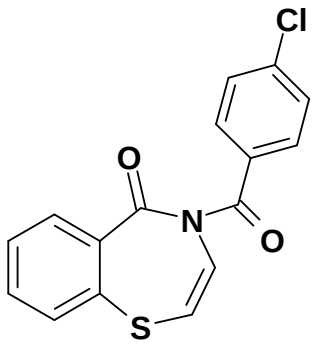
^{13}C-NMR (DMSO-*d6*): δ(ppm):

21.12 (CH_3); 117.78 (S-CH); 128.74, 128,96, 129.47, 131.37, 132.00, 132.62 (8C tert., aromat.); 133.46 (N-CH); 130.35, 136.47, 139.14, 144.02 (4C quart., aromat.); 168.81 (C=O); 172.73 (C=O).

$C_{17}H_{13}NO_2S$ [295.36]

Calcd.	[%]	C 69.13	H 4.44	N 4.74	S 10.86
Found	[%]	C 69.07	H 4.70	N 4.64	S 10.66

4-(4-Chloro-benzoyl)-[1,4]benzothiazepine-5-one (**4d**)



Yield: 77%, yellow solid

M.p.: 107°C

IR (KBr): 1654, 1718 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

6.78 (d, *J* = 6.62 Hz, 1H, S-CH); 7.13 (s, *J* = 6.35 Hz, 1H, N-CH); 7.50-7.83 (m, 8H, aromat.).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

118.65 (S-CH); 128.74, 129,03, 130.32, 131.40, 132.10, 132.37, (8C tert., aromat.); 133.40 (N-CH); 132.70, 136.15, 137.80, 139.23 (4C quart., aromat.); 168.97 (C=O); 171.98 (C=O).

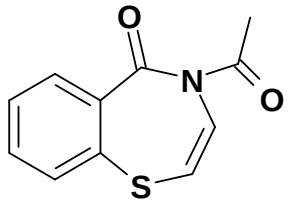
$C_{16}H_{10}ClNO_2S$ [315.78]

Calcd.	[%]	C 60.86	H 3.19	N 4.44	S 10.15
Found	[%]	C 60.74	H 3.45	N 4.41	S 10.20

7.2.4 Preparation of 4-Acetyl-[1,4]benzothiazepine-5-one (**5**)

A mixture of 1,4-benzothiazepine-5-one (**XXXIII**) (5mmol) and acetic anhydride (15 mL) was refluxed for 2h. After cooling, the mixture was purred into ice-water (20 mL) and the desired product precipitated as yellow solid after neutralization by dropwise addition of saturated solution of $NaHCO_3$.

4-Acetyl-[1,4]benzothiazepine-5-one (**5**)



Yield: 85%, yellow solid

M.p.: 82 °C

IR (KBr): 1676, 1706 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.59 (s, 3H, CH_3); 6.81 (d, *J* = 6.60 Hz, 1H, S-CH); 6.93 (d, *J* = 6.34 Hz, 1H, N-CH); 7.56-7.87 (m, 4H, aromat.).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

26.98 (CH_3); 119.45 (S-CH); 128.45, 130.85, 131.62, 131.85 (4C tert., aromat.); 133.68 (N-CH); 137.12, 139.74 (2C quart., aromat.); 168.53 (C=O); 172.89 (C=O).

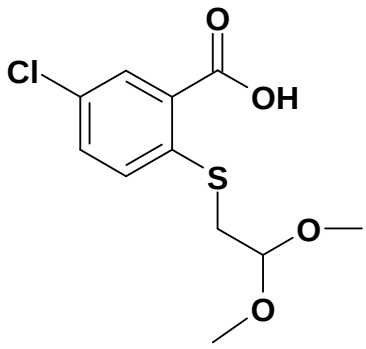
$C_{11}H_9NO_2S$ [219.26]

Calcd.	[%]	C 60.26	H 4.14	N 6.39	S 14.62
Found	[%]	C 60.25	H 4.35	N 6.33	S 14.53

7.2.5 Preparation of 5-Chloro-2-[(2,2-dimethoxyethyl)sulfanyl]benzoic acid (**8**)

A solution of 2-bromo-1,1-dimethoxyethan (30 mmol) in EtOH (7 mL) was added to 5-chlorothiosalicylic acid (**7**) (25 mmol) dissolved in 10% aq. solution of NaOH (50 mL). The mixture was stirred at 70 °C for 2 hours. After cooling and acidification with aq. HCl (10%), the product **8** was obtained as yellow precipitate which was filtered, washed with cold water and dried.

5-Chloro-2-[(2,2-dimethoxyethyl)sulfanyl]benzoic acid (**8**)



Yield: 87%, yellow solid

M.p.: 89 °C

IR (KBr): 1680 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.15 (d, 2H, CH_2); 3.29 (s, 6H, CH_3); 4.57 (t, 1H, CH); 7.45-7.82 (m, 3H, aromat.); 13.42 (s, 1H, OH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

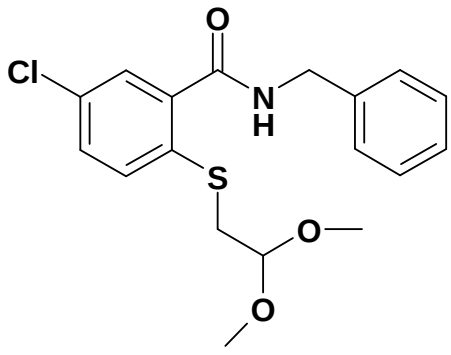
34.25 (CH_2); 53.15 (CH_3); 102.22 (CH); 127.75, 128.06, 131.76 (3C tert., aromat.); 128.55, 130.18, 139.27 (3C quart., aromat.); 166.23 (C=O).

$C_{11}H_{13}ClO_4S$ [276.74]

7.2.6 Preparation of 5-Chloro-2-[(2,2-dimethoxyethyl)sulfanyl]benzamides (**10**)

To a stirred solution of compound **8** (5 mmol) in dry THF, CDI (5,5 mmol) was added and the mixture was stirred at RT for 1h.
A solution of the appropriate amine (8 mmol) in THF (5 mL) was added and the reaction mixture was stirred at RT overnight.
The solvent was removed under reduced pressure and the residue was taken up in EtOAc (20 mL). The organic phase was extracted with a saturated solution of $NaHCO_3$ (7 mL) then with HCl 1N (7 mL), collected and dried over $MgSO_4$.
The solvent was removed and the residue was recrystallized from Et_2O/Petrolether to afford the benzamides **10.**

N-Benzyl-5-chloro-2-[(2,2-dimethoxyethyl)sulfanyl]benzamide (**10a**)



Yield: 85%, white solid
M.p.: 83 °C
IR (KBr): 1636 cm^{-1} (C=O); 3276 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.11 (d, *J* = 5.59 Hz, 2H, S-CH_2); 3.34 (s, 6H, CH_3); 4.43 (d, *J* = 5.85 Hz, 2H, Ph-*CH_2*); 4.48 (t, *J* = 5.46 Hz, 1H, CH); 7.24-7.52 (m, 8H, aromat.); 8.97 (t, *J* = 5.80 Hz, 1H, NH).

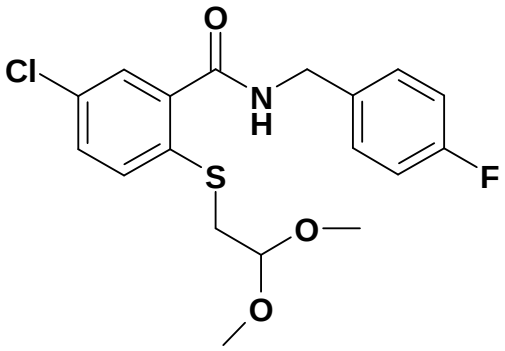
^{13}C-NMR (DMSO-*d6*): δ(ppm):

35.53 (S-CH_2); 42.43 (Ph-CH_2); 53.16 (CH_3); 102.52 (CH); 126.71, 127.11, 127.18, 128.16, 129.74, 130.36 (8C tert., aromat.); 129.63, 134.37, 138.55, 138.97 (4C quart., aromat.); 166.25 (C=O).

$C_{18}H_{20}ClNO_3S$ [365.88]

Calcd.	[%]	C 61.62	H 5.17	N 4.23	S 9.68
Found	[%]	C 61.51	H 5.21	N 4.33	S 9.10

5-Chloro-2-[(2,2-dimethoxyethyl)sulfanyl]-*N*-(4-fluoro-benzyl)benzamide (**10b**)



Yield: 63%, white solid

M.p.: 86 °C

IR (KBr): 1636 cm^{-1} (C=O); 3275 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.10 (d, *J* = 5.60 Hz, 2H, S-CH_2); 3.33 (s, 6H, CH_3); 4.42 (d, *J* = 6.11 Hz, 2H, Ph-CH_2); 4.47 (t, *J* = 5.60 Hz, 1H, CH); 7.24-7.52 (m, 7H, aromat.); 8.98 (t, *J* = 5.85 Hz, 1H, NH).

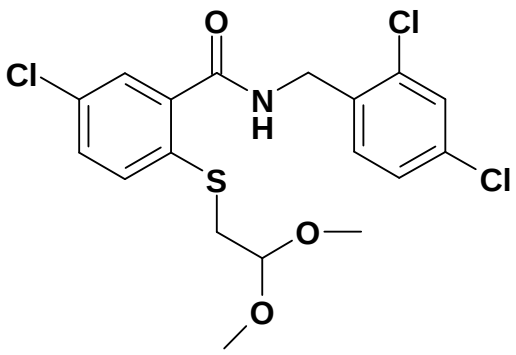
^{13}C-NMR (DMSO-*d6*): δ(ppm):

35.46 (S-CH_2); 41.74 (Ph-CH_2); 53.13 (CH_3); 102.46 (CH); 114.87 (d, $^{2}J_{CF}$ = 21.36 Hz); 129.15 (d, $^{3}J_{CF}$ = 7.63 Hz); 127.09, 129.67, 130.33 (3C tert., aromat.); 129.74, 134.37, 138.44 (3C quart., aromat.); 135.15 (d, $^{4}J_{CF}$ = 3.05 Hz); 159.91, 162.32 (d, $^{1}J_{CF}$ = 241.86 Hz); 166.25 (C=O).

$C_{18}H_{19}ClFNO_3S$ [383.87]

Calcd.	[%]	C 51.84	H 2.72	N 3.78	S 8.65
Found	[%]	C 51.30	H 2.76	N 3.77	S 8.47

5-Chloro-*N*-(2,4-dichloro-benzyl)-2-[(2,2-dimethoxyethyl)sulfanyl]-benzamide (**10c**)



Yield: 52%, yellow solid

M.p.: 100 °C

IR (KBr): 1630 cm^{-1} (C=O); 3260 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.10 (d, *J* = 5.50 Hz, 2H, S-CH_2); 3.26 (s, 6H, CH_3); 4.47 (d, *J* = 5.46 Hz, 2H, Ph-CH_2); 4.66 (t, *J* = 5.58 Hz, 1H, CH); 7.31-7.55 (m, 6H, aromat.); 8.72 (t, *J* = 5.54 Hz, 1H, NH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

35.39 (S-CH_2); 40.06 (Ph-CH_2); 53.14 (CH_3); 102.50 (CH); 127.35, 128.43, 129.67, 130.06, 130.11, 130.16 (6C tert., aromat.); 129.39, 132.85, 134.68, 134.75, 135.63, 137,82 (6C quart., aromat.); 165.89 (C=O).

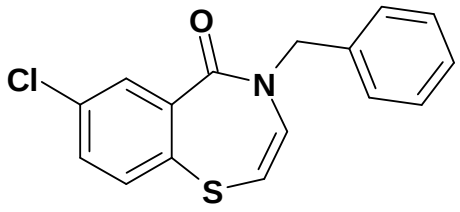
$C_{18}H_{18}Cl_3NO_3S$ [434.77]

Calcd.	[%]	C 61.62	H 5.17	N 4.23	S 9.68
Found	[%]	C 61.51	H 5.21	N 4.33	S 9.10

7.2.7 Preparation of 4-(Arylmethyl)-7-chloro-[1,4]benzothiazepines-5-ones (**11**)

A solution of the benzamides **10 (**4 mmol), *p*-toluenesulphonic acid (0.2 mmol) in toluene (15 mL) was heated to reflux for 18 h. After cooling, the mixture was washed with saturated solution of $NaHCO_3$ (10 mL). The organic layer was collected, dried over $MgSO_4$ and the solvent was removed under reduced pressure.
Column chromatography on silica gel of the resulting residue (EtOAc/n-hexan 1:1) afforded the targeted benzothiazepines derivatives **11.**

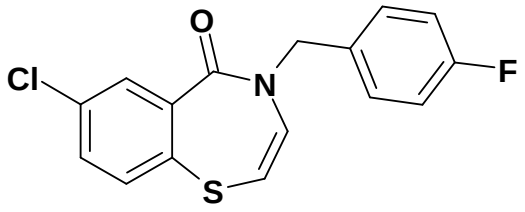
4-Benzyl-7-chloro-[1,4]benzothiazepine-5-one (**11a**)



Yield: 43%, yellow solid
M.p.: 112 °C
IR (KBr): 1625 cm^{-1} (C=O)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
4.93 (s, 2H, CH_2); 6.34 (d, *J* = 6.61 Hz, 1H, S-CH); 6.79 (d, *J* = 6.61 Hz, 1H, N-CH); 7.26-7.64 (m, 8H, aromat.).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
51.44 (CH_2); 114.65 (S-CH); 126.96, 127.15, 128.41, 130.95, 131.15, 132.46 (8C tert., aromat.); 137.47 (N-CH); 133.01, 136.62, 138.68, 140.38 (4C quart., aromat.); 167.10 (C=O).
$C_{16}H_{12}ClNOS$ [301.80]

Calcd.	[%]	C 63.68	H 4.01	N 4.64	S 10.62
Found	[%]	C 63.62	H 4.15	N 4.58	S 10.53

7-Chloro-4-(4-flurobenzyl)-[1,4]benzothiazepine-5-one (**11b**)



Yield: 45%, yellow solid

M.p.: 103 °C

IR (KBr): 1630 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*):δ(ppm):

4.90 (s, 2H, CH_2); 6.35 (d, *J* = 6.36 Hz, 1H, S-CH); 6.79 (d, *J* = 6.61 Hz, 1H, N-CH); 7.17-7.63 (m, 7H, aromat.).

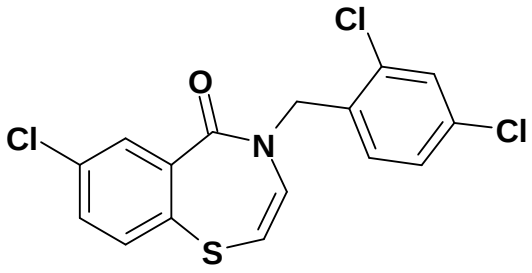
^{13}C-NMR (DMSO-*d6*): δ(ppm):

50.73 (CH_2); 114.85 (S-CH); 115.20 (d, $^{2}J_{CF}$ = 21.36 Hz); 129.15 (d, $^{3}J_{CF}$ = 8.39 Hz); 130.93, 131.71, 132.46 (3C tert., aromat.); 133.05 (d, $^{4}J_{CF}$ = 3.05 Hz); 133.02, 138.64, 140.31 (3C quart., aromat.); 137.34 (N-CH); 160.13, 162.54 (d, $^{1}J_{CF}$ = 242.63 Hz); 167.09 (C=O).

$C_{16}H_{11}ClFNOS$ [319.79]

Calcd.	[%]	C 60.10	H 3.47	N 4.38	S 10.03
Found	[%]	C 59.85	H 3.67	N 4.24	S 9.67

7-Chloro-4-(2,4-dichlorobenzyl)-[1,4]benzothiazepine-5-one (**11c**)



Yield: 30%, yellow needles
M.p.: 163 °C
IR (KBr): 1636 cm^{-1} (C=O)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
4.82 (s, 2H, CH_2); 6.32 (d, *J* = 6.35 Hz, 1H, S-CH); 6.82 (d, *J* = 6.62 Hz, 1H, N-CH); 7.15-7.56 (m, 6H, aromat.).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
47.93 (CH_2); 114.72 (S-CH); 125.73, 128.15, 130.03, 130.18, 131.11, 132.46 (6C tert., aromat.); 135.60 (N-CH); 129.87, 133.21, 133.75, 134.07, 138.52, 140.38 (6C quart., aromat.); 167.36 (C=O).
$C_{16}H_{10}Cl_3NOS$ [370.69]

Calcd.	[%]	C 51.84	H 2.72	N 3.78	S 8.65
Found	[%]	C 51.30	H 2.76	N 3.77	S 8.47

7.3 Procedures and Analytical Data for Chapter 3

7.3.1 Preparation of Methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylates (**14**)

Procedure A:

As outlined in scheme 3-3, thiosalicylic acid (**1**) (50 mmol) was dissolved in 10% aq. solution of NaOH (75 mL). Chloroacetic acid (60 mmol) dissolved in water (15 mL) was added and the mixture was heated to 70 °C for 2 h.
Acidification under ice cooling with HCl (2N) provided the product **12** as white precipitate which was filtered, washed with cold water and dried.
Compound **12** (40 mmol) was dissolved in mixture of H_2SO_4/MeOH (10%) (100 mL) and the solution was refluxed for 18 hours.
The solvent was removed and the residue was taken up in water (70 mL). Under stirring and ice cooling, $NaHCO_3$ was added to pH = 8-9.
The mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the organic phases were combined, dried over $MgSO_4$, and evaporated under reduced pressure to afford methyl 2-[(2-methoxy-2-oxoethyl)sulfanyl]benzoate (**13)** as white

crystalline material, which was used without further purification in the next synthetic step.

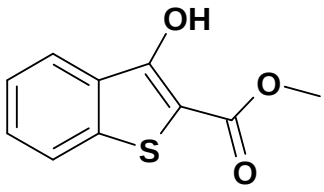
The diester **13** (30mmol) was dissolved in toluene (30 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (30 mmol) was added and the mixture was stirred for 24 hours at RT.

The reaction mixture was washed with HCl 1N (20 mL) and the organic layer was collected, dried over $MgSO_4$ and the solvent was removed to give methyl-3-hydroxy-benzo[*b*]thiophene-2-carboxylate (**14a**).

Procedure B:

To a stirred, cold solution (ice bath), containing methyl-2-nitrobenzoates (**15**) (30 mmol) and methyl thioglycolate (4 mL) in DMF (60 mL) was added slowly LiOH (2.5 g). The mixture was stirred under cooling for ½ h and then in RT for 1-2.5 h. It was poured into ice water and the solution was acidified. The crude product was collected and crystallized from EtOH.

Methyl 3-hydroxy-benzo[*b*]thiophene-2-carboxylate (**14a**)



Yield: 95% (Procedure A), 60% (Procedure B)

M.p.: 105 °C (Lit.[80] M.p. 109-110 °C)

IR (KBr): 1665 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

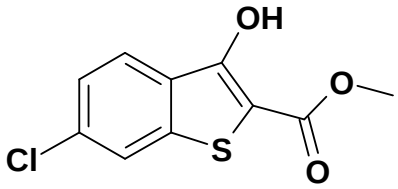
3.87 (s, 3H, CH_3); 7.45-7.95 (m, 4H, aromat.); 10.58 (s, 1H, OH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

51.86 (CH_3); 103.07, 131.33, 137.50, 155.67 (4C quart., aromat.); 122.66, 123.29, 124.59, 128.68 (4C tert., aromat.); 164.03 (C=O).

$C_{10}H_8O_3S$ [208.23]

Methyl 6-chloro-3-hydroxy-benzo[*b*]thiophene-2-carboxylate (**14b**)



Yield: 75% (Procedure B)

M.p.: 147 °C (Lit.[80] M.p. 149 °C)

IR (KBr): 1660 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.85 (s, 3H, CH_3); 7.47-8.15 (3H, aromat.); 10.63 (s, 1H, OH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

51.94 (CH_3); 103.24, 130.37, 133.52, 138.69, 155.84 (5C quart., aromat.); 122.92, 124.18, 125.28 (3C tert., aromat.); 163.56 (C=O).

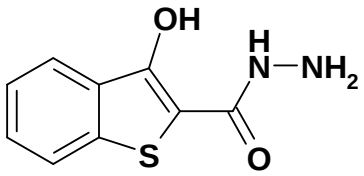
$C_{10}H_7ClO_3S$ [242.68]

7.3.2 Preparation of 3-Hydroxy-benzo[*b*]thiophene-2-carbohydrazides (**17**)

To a solution of **14** (10 mmol) in methanol (20 mL), hydrazine hydrate (7 mL) was added dropwise under ice cooling. The mixture was then refluxed for 4 h.

After completion of the reaction (monitored by TLC), the mixture was acidified with HCl (2N) to pH = 4-4.5 under ice cooling. The precipitated products were collected, washed with cold water and recrystallized from methanol.

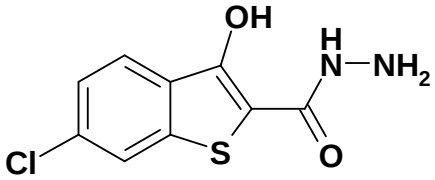
3-Hydroxy-benzo[*b*]thiophene-2-carbohydrazide (**17a**)



Yield: 75% pale yellow solid
M.p.: 98 °C
IR (KBr): 1600 cm^{-1} (C=O); 3300 cm^{-1} ($NH-NH_2$)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
7.40 (s, 2H, NH_2); 7.51-7.83 (m, 4H, aromat.); 7.69 (s, 1H, NH); 9.28 (s, 1H, OH).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
103.26, 131.96, 136.30, 154.48 (4C quart., aromat.); 123.25, 123.83, 124.76, 125.41 (4C tert., aromat.); 162.14 (C=O).
$C_9H_8N_2O_2S$ [208,24]

Calcd.	[%]	C 51.91	H 3.87	N 13.45	S 15.40
Found	[%]	C 51.25	H 3.96	N 13.28	S 14.97

6-Chloro-3-hydroxy-benzo[*b*]thiophene-2-carbohydrazide (**17b**)



Yield: 70% pale yellow solid
M.p.: 127 °C
IR (KBr): 1600 cm^{-1} (C=O); 3310 cm^{-1} ($NH-NH_2$)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

7.43 (s, 2H, NH_2); 7.80-8.10 (m, 3H, aromat.); 8.04 (s, 1H, NH); 9.43 (s, 1H, OH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

102.68, 131.42, 133.93, 138.21, 155.06 (5C quart., aromat.); 122.81, 124.79, 126.38 (3C tert., aromat.); 163.49 (C=O).

$C_9H_8N_2O_2S$ [242,69]

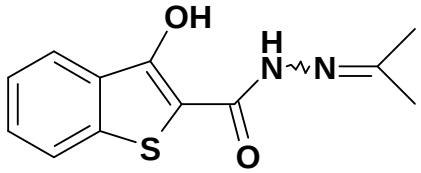
Calcd.	[%]	C 44.54	H 2.91	N 11.54	S 13.21
Found	[%]	C 43.50	H 3.00	N 11.09	S 13.26

7.3.3 Preparation of *N*-Aminoalkenyl-3-hydroxy-benzo[*b*]thiophene-2-carboxamides (**18**)

To a suspension of the hydrazides **17** (5 mmol) in MeOH (10 mL), the appropriate reagent (aldehyde or ketone) (10 mmol) was added and the mixture was heated to reflux for 1 hour.

After cooling, the precipitated solid product was collected by filtration and recrystalized from EtOH.

3-Hydroxy-*N*-(propan-2-ylideneamino)-benzo[*b*]thiophene-2-carboxamide (**18a**)



Yield: 87%, white solid

M.p.: 240 °C

IR (KBr): 1624 cm^{-1} (C=O); 3157-3236 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.99 (s, 3H, CH_3); 2.09 (s, 3H, CH_3); 7.43-7.92 (m, 4H, aromat.); 11.05 (s, 1H, NH); 13.22 (s, 1H, OH).

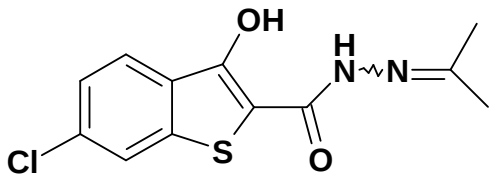
^{13}C-NMR (DMSO-*d6*): δ(ppm):

17.39, 24.51 (2C, CH_3); 101.65, 125.98, 134.08, 141.44 (4C quart., aromat.); 121.95, 122.73, 124.16, 128.39 (4C tert., aromat.); 161.36 (C=O); 168.01 (1C quart., C=N).

$C_{12}H_{12}N_2O_2S$ [248.31]

Calcd.	[%]	C 58.05	H 4.87	N 11.28	S 12.91
Found	[%]	C 57.85	H 5.01	N 11.24	S 12.67

6-Chloro-3-hydroxy-*N*-(propan-2-ylideneamino)-benzo[*b*]thiophene-2-carboxamide (**18b**)



Yield: 90%, white solid

M.p.: 254 °C

IR (KBr): 1625 cm^{-1} (C=O); 3156 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.98 (s, 3H, CH_3); 2.07 (s, 3H, CH_3); 7.43 (d, 1H, aromat.); 7.88 (d, 1H, aromat.); 8.09 (s, 1H, aromat.); 11.15 (s, 1H, NH); 13.29 (s, 1H, OH).

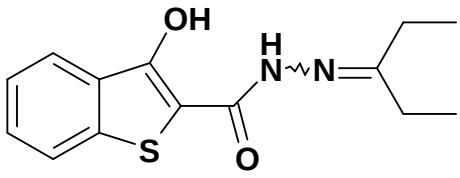
^{13}C-NMR (DMSO-*d6*): δ(ppm):

17.46, 24.50 (2C, CH_3); 101.14, 126.26, 128.15, 133.01, 142.82 (5C quart., aromat.); 122.33, 123.53, 124.97 (3C tert., aromat.); 161.42 (C=O); 167.66 (C=N).

$C_{12}H_{11}ClN_2O_2S$ [282.75]

Calcd.	[%]	C 50.98	H 3.92	N 9.91	S 11.34
Found	[%]	C 50.72	H 4.08	N 9.77	S 11.50

3-Hydroxy-*N*-(pentan-3-ylideneamino)-benzo[*b*]thiophene-2-carboxamide (**18c**)



Yield: 85%, white solid

M.p.: 192 °C

IR (KBr): 1605 cm^{-1} (C=O); 3182 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.04-1.22 (m, 6H, CH_3); 2.42 (m, 4H, CH_2); 7.44-7.92 (m, 4H, aromat.); 11.06 (s, 1H, NH); 13.34 (s, 1H, OH).

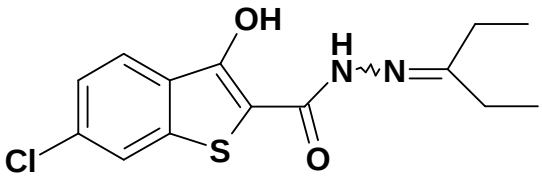
^{13}C-NMR (DMSO-*d6*): δ(ppm):

10.29, 11.66 (2C, CH_3); 22.67, 29.44 (2C, CH_2); 102.68, 125.66, 135.56, 139.06 (4C quart., aromat.); 122.40, 123.22, 124.65, 128.91 (4C tert., aromat.); 162.07 (C=O); 169.23 (C=N).

$C_{14}H_{16}N_2O_2S$ [276.36]

Calcd.	[%]	C 60.85	H 5.84	N 10.14	S 11.60
Found	[%]	C 60.32	H 5.96	N 10.22	S 11.42

6-Chloro-3-hydroxy-*N*-(pentan-3-ylideneamino)-benzo[*b*]thiophene-2-carboxamide (**18d**)



Yield: 86%, white solid

M.p.: 220 °C

IR (KBr): 1617 cm^{-1} (C=O); 3168 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.03-1.22 (m, 6H, CH_3); 2.42 (m, 4H, CH_2); 7.46 (d, 1H, aromat.); 7.89 (d, 1H, aromat.); 8.11 (s, 1H, aromat.); 11.17 (s, 1H, NH); 13.34 (s, 1H, OH).

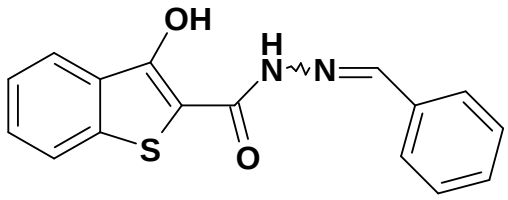
^{13}C-NMR (DMSO-*d6*): δ(ppm):

9.87, 11.25 (2C, CH_3); 22.23, 29.01 (2C, CH_2); 101.17, 126.34, 128.23, 133.23, 142.56 (5C quart., aromat.); 122.46, 123.40, 124.87 (3C tert., aromat.); 161.91 (C=O); 167.90 (C=N).

$C_{14}H_{15}ClN_2O_2S$ [310.80]

Calcd.	[%]	C 54.10	H 4.86	N 9.01	S 10.32
Found	[%]	C 54.02	H 5.05	N 8.90	S 10.28

<u>*N*-Benzylideneamino-3-hydroxy-benzo[*b*]thiophene-2-carboxamide (**18e**)</u>



Yield: 89%, white solid

M.p.: 246 °C

IR (KBr): 1635 cm^{-1} (C=O); 3150 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

7.28-7.9 (m, 9H, aromat.); 8.11 (s, 1H, N=*CH*); 12.13 (s, 1H, NH); 13.1 (s, 1H, OH).

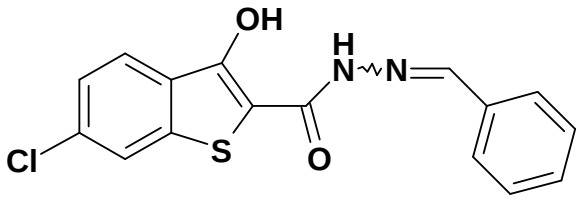
^{13}C-NMR (DMSO-*d6*): δ(ppm):

100.10, 129.90, 134.07, 134.11, 141.49 (5C quart., aromat.); 146.31 (1C, N=*CH*); 159.50 (C=O).

$C_{16}H_{12}N_2O_2S$ [296.35]

Calcd.	[%]	C 64.85	H 4.08	N 9.45	S 10.82
Found	[%]	C 64.31	H 4.22	N 9.41	S 10.88

N-Benzylideneamino-6-chloro-3-hydroxy-benzo[*b*]thiophene-2-carbox-amide (**18f**)



Yield: 90%, white solid

M.p.: 250 °C

IR (KBr): 1638 cm^{-1} (C=O); 3144 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

7.50-7.92 (m, 7H, aromat.); 8.19 (s, 1H, aromat.); 8.22 (s, 1H, N=*CH*).

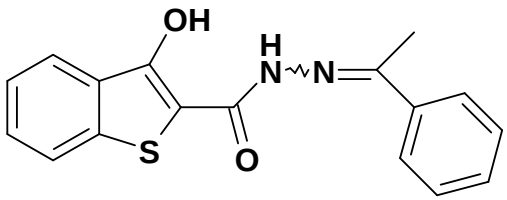
^{13}C-NMR (DMSO-*d6*): δ(ppm):

100.42, 128.16, 133.50, 133.54, 142.28, 16735 (6C quart., aromat.); 122.70, 123.52, 125.11, 127.54, 128.94, 130.37 (8C tert., aromat.); 146.02 (1C, N=*CH*); 160.41 (C=O).

$C_{16}H_{11}ClN_2O_2S$ [330.80]

Calcd.	[%]	C 58.10	H 3.35	N 8.47	S 9.69
Found	[%]	C 58.01	H 3.77	N 8.03	S 9.40

3-Hydroxy-*N*-(1-phenylethylideneamino)-benzo[*b*]thiophene-2-carbox-amide (**18g**)



Yield: 90%, white solid

M.p.: 242 °C

IR (KBr): 1614 cm^{-1} (C=O); 3172 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.41 (s, 3H, CH_3); 7.45-8 (m, 9H, aromat.); 11.33 (s, 1H, NH); 13.24 (s, 1H, OH).

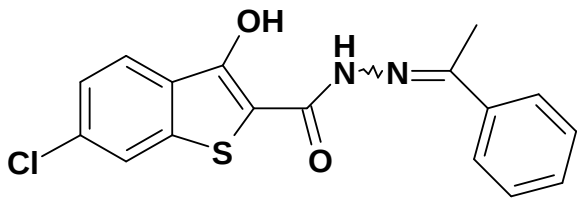
^{13}C-NMR (DMSO-*d6*): δ(ppm):

14.99 (CH_3); 102.54, 129.69, 134.65, 135.02, 142.16 (5C quart., aromat.); 122.54, 123.40, 124.84, 127.32, 128.91, 129.19, 129.93 (9C tert., aromat.); 162.02 (C=O); 168.80 (C=N).

$C_{17}H_{14}N_2O_2S$ [310.38]

Calcd.	[%]	C 65.79	H 4.55	N 9.03	S 10.33
Found	[%]	C 64.84	H 4.62	N 8.89	S 10.34

6-Chloro-3-hydroxy-*N*-(1-phenylethylideneamino)-benzo[*b*]thiophene-2-carboxamide (**18h**)



Yield: 92%, white solid

M.p.: 265 °C

IR (KBr): 1620 cm^{-1} (C=O); 3163 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.41 (s, 3H, CH_3); 7.51-7.97 (m, 7H, aromat.); 7.51 (s, 1H, aromat.); 11.41 (s, 1H, NH); 13.20 (s, 1H, OH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

14.59 (CH_3); 102.54, 123.47, 129.69, 134.65, 135.02, 142.16 (6C quart., aromat.); 122.60, 123.52, 125.04, 126.91, 128.48, 129.50 (8C, tert., aromat.); 162.32 (C=O); 168.67 (C=N).

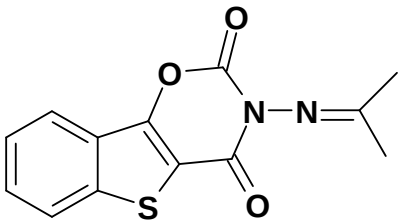
$C_{17}H_{13}ClN_2O_2S$ [344.82]

Calcd.	[%]	C 59.22	H 3.80	N 8.12	S 9.30
Found	[%]	C 58.48	H 3.88	N 8.05	S 9.40

7.3.4 General Procedure for Preparation of Benzothieno[2,3-e][1,3]oxazines (**19, 31-33**)

To a solution of 3-hydroxy-benzo[*b*]thiophene derivatives (**18**, **27**, **28**, **30**) (2 mmol) in dry THF (10 mL), CDI or TCDI (2,2 mmol) was added and the mixture was heated to reflux for 1 hour. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (15 mL) and extracted with HCl (10 mL, 0.1 N). The organic layer was collected, dried over $MgSO_4$ and evaporated under reduced pressure to furnish the targeted heterocyclic compound.
Recrystallization from hot EtOH provided analytically pure samples.

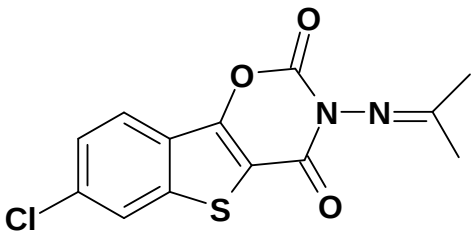
3-(Propan-2-ylideneamino)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**19a**)



Yield: 75%, white solid
M.p.: 209 °C
IR (KBr): 1699, 1761 cm^{-1} (C=O)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
1.92 (s, 3H, CH_3); 2.24 (s, 3H, CH_3); 7.60-8.22 (m, 4H, aromat.).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
19.46 (CH_3); 24.51 (CH_3); 110.89, 127.06, 138.76, 144.96 (4C quart., aromat.); 121.99, 124.30, 126.08, 129.47 (4C tert., aromat.); 149.78, 154.04 (2C, C=O); 182.03 (C=N).
$C_{13}H_{10}N_2O_3S$ [274.30]

Calcd.	[%]	C 56.92	H 3.67	N 10.21	S 11.69
Found	[%]	C 56.58	H 3.64	N 10.02	S 11.72

7-Chloro-3-(propan-2-ylideneamino)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**19b**)



Yield: 70%, white solid
M.p.: 203 °C
IR (KBr): 1698, 1760 cm^{-1} (C=O)
^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.92 (s, 3H, CH_3); 2.24 (s, 3H, CH_3); 7.66 (d, 1H, aromat.); 8.09 (d, 1H, aromat.); 8.42 (s, 1H, aromat.).

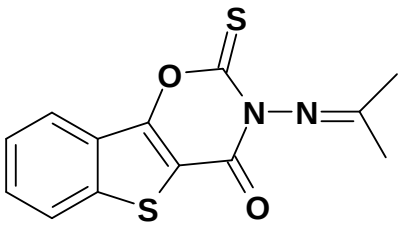
^{13}C-NMR (DMSO-*d6*): δ(ppm):

19.49 (CH_3); 24.51 (CH_3); 111.83, 125.89, 134.24, 139.89, 144.82 (5C quart., aromat.); 121.99, 124.30, 126.08, 129.47 (4C tert., aromat.); 149.78 (C=O); 153.89 (C=O); 182.17 (C=N).

$C_{13}H_9ClN_2O_3S$ [308.75]

Calcd.	[%]	C 50.57	H 2.94	N 9.07	S 10.39
Found	[%]	C 50.12	H 3.14	N 9.06	S 10.40

3-(Propan-2-ylideneamino)-2-thioxo-benzothieno[2,3-*e*][1,3]oxazine-4-one (**19c**)



Yield: 72%, yellow solid
M.p.: 213 °C
IR (KBr): 1282 cm^{-1} (C=S); 1710 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.89 (s, 3H, CH_3); 2.27 (s, 3H, CH_3); 7.66-8.24 (m, 4H, aromat.).

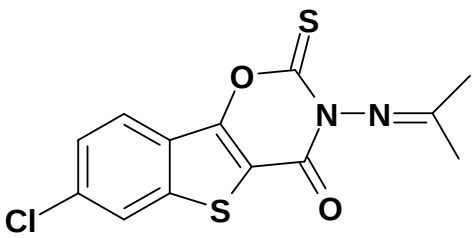
^{13}C-NMR (DMSO-*d6*): δ(ppm):

19.46 (CH_3); 24.34 (CH_3); 113.15, 126.25, 139.09, 150.93 (4C quart., aromat.); 122.16, 124.33, 126.33, 129.95 (4C tert., aromat.); 152.72 (C=O); 175.30 (C=S); 182.15 (C=N).

$C_{13}H_{10}N_2O_2S_2$ [290.36]

Calcd.	[%]	C 53.78	H 3.47	N 9.65	S 22.09
Found	[%]	C 53.24	H 3.64	N 9.50	S 21.16

7-Chloro-3-(propan-2-ylideneamino)-2-thioxo-benzothieno[2,3-*e*][1,3]-oxazine-4-one (**19d**)



Yield: 65%, yellow solid

M.p.: 173 °C

IR (KBr): 1278 cm^{-1} (C=S); 1716 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.88 (s, 3H, CH_3); 2.26 (s, 3H, CH_3); 7.70 (d, 1H, aromat.); 8.13 (d, 1H, aromat.); 8.45 (s, 1H, aromat.).

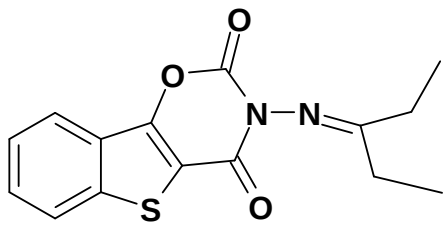
^{13}C-NMR (DMSO-*d6*): δ(ppm):

19.50 (CH_3); 24.32 (CH_3); 113.82, 126.36, 134.75, 140.23, 150.78 (5C quart., aromat.); 123.56, 124.00, 127.03 (3C tert., aromat.); 152.21 (C=O); 175.15 (C=S); 182.32 (C=N).

$C_{13}H_9ClN_2O_2S_2$ [324.81]

Calcd.	[%]	C 48.07	H 2.79	N 8.62	S 19.74
Found	[%]	C 48.50	H 2.98	N 8.48	S 19.10

3-(Pentan-3-ylideneamino)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**19e**)



Yield: 74%, white solid

M.p.: 127 °C

IR (KBr): 1698, 1760 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

0.99 (t, *J* = 7.36 Hz, 3H, CH_3); 1.19 (t, *J* = 7.37 Hz, 3H, CH_3); 2.26 (q, *J* = 14.75 Hz, 2H, CH_2); 2.50 (q, *J* = 14.75 Hz, 2H, CH_2); 7.62 (m, 2H, aromat.); 8.20 (m, 2H, aromat.).

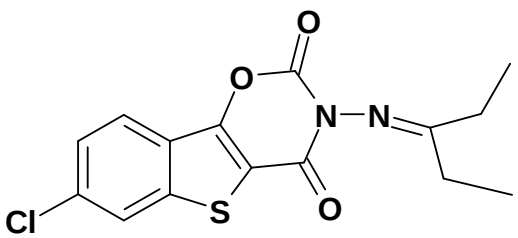
^{13}C-NMR (DMSO-*d6*): δ(ppm):

9.96 (CH_3); 10.23 (CH_3); 24.40 (CH_2); 28.21 (CH_2); 111.12, 127.09, 138.78, 145.00 (4C quart., aromat.); 122.01, 124.28, 126.07, 129.46 (4C tert., aromat.); 149.80 (C=O); 155.91 (C=O); 189.05 (C=N).

$C_{15}H_{14}N_2O_3S$ [302.35]

Calcd.	[%]	C 59.59	H 4.67	N 9.27	S 10.60
Found	[%]	C 59.55	H 4.91	N 9.15	S 10.76

7-Chloro-3-(pentan-3-ylideneamino)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**19f**)



Yield: 71%, white solid

M.p.: 197 °C

IR (KBr): 1698, 1760 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

0.98 (t, *J* = 7.63 Hz, 3H, CH_3); 1.18 (t, *J* = 7.37 Hz, 3H, CH_3); 2.24 (q, *J* = 14.73 Hz, 2H, CH_2); 2.60 (q, *J* = 14.75 Hz, 2H, CH_2); 7.67 (d, 1H, aromat.); 8.02 (d, 1H, aromat.); 8.42 (s, 1H, aromat.).

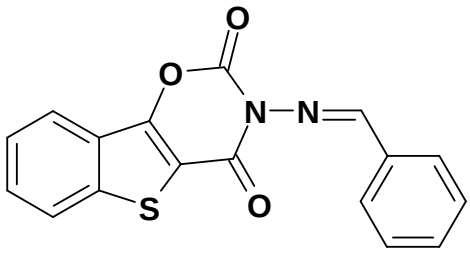
^{13}C-NMR (DMSO-*d6*): δ(ppm):

10.01 (CH_3); 10.22 (CH_3); 24.39 (CH_2); 28.18 (CH_2); 111.84, 125.91, 134.22, 139.88, 144.87 (5C quart., aromat.); 123.42, 123.98, 126.77 (3C tert., aromat.); 149.32 (C=O); 154.07 (C=O); 189.19 (C=N).

$C_{15}H_{13}ClN_2O_3S$ [336.80]

Calcd.	[%]	C 53.49	H 3.89	N 8.32	S 9.52
Found	[%]	C 53.40	H 4.01	N 8.27	S 9.47

3-Benzylideneamino-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**19g**)



Yield: 81%, white solid

M.p.: 224 °C

IR (KBr): 1700, 1764 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

7.58-8.25 (m, 9H, aromat.); 8.86 (s, 1H, N=CH).

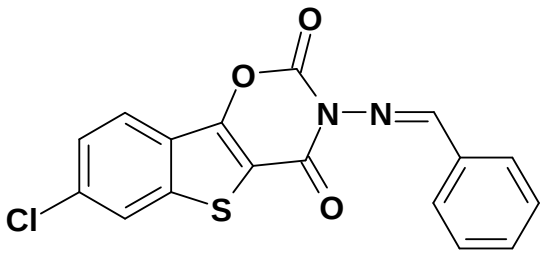
^{13}C-NMR (DMSO-*d6*): δ(ppm):

111.28, 126.96, 131.76, 138.29, 145.62 (5C quart., aromat.); 122.10, 124.39, 126.21, 128.85, 129.13, 129.64, 133.00 (9C tert., aromat.); 149.32 (C=O); 154.83 (C=O); 172.26 (C=N).

$C_{17}H_{10}N_2O_3S$ [322.34]

Calcd.	[%]	C 63.35	H 3.13	N 8.69	S 9.95
Found	[%]	C 62.90	H 3.27	N 8.58	S 9.94

3-Benzylideneamino-7-chloro-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione **(19h)**



Yield: 75%, white solid

M.p.: 237 °C

IR (KBr): 1694, 1757 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

7.60-8.09 (m, 6H, aromat.); 8.45 (s, 1H, aromat.); 8.85 (s, 1H, N=CH).

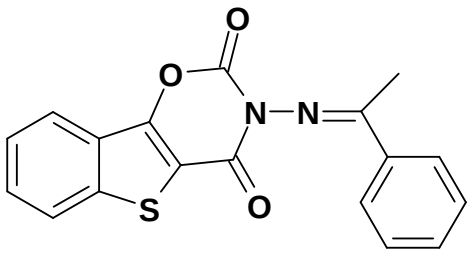
^{13}C-NMR (DMSO-*d6*): δ(ppm):

112.01, 125.74, 131.71, 134.43, 140.06, 145.46 (6C quart., aromat.); 123.51, 124.09, 126.93, 128.80, 129.13, 133.03 (8C tert., aromat.); 148.84 (C=O); 154.67 (C=O); 172.30 (C=N).

$C_{17}H_9ClN_2O_3S$ [356.79]

Calcd.	[%]	C 57.23	H 2.54	N 7.85	S 8.99
Found	[%]	C 57.14	H 2.67	N 7.78	S 9.16

3-(1-Phenylethylideneamino)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**19i**)



Yield: 83%, white solid

M.p.: 236 °C

IR (KBr): 1695, 1751 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.36 (s, 3H, CH_3); 7.54-8.23 (m, 9H, aromat.).

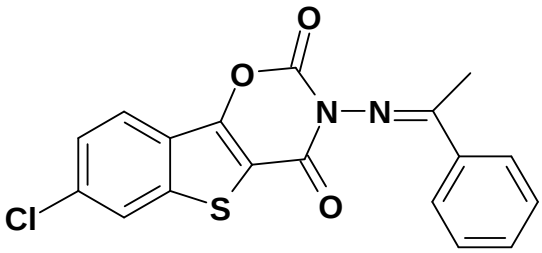
^{13}C-NMR (DMSO-*d6*): δ(ppm):

16.68 (CH_3); 111.13, 127.07, 135.46, 138.80, 144.95 (5C quart., aromat.); 122.07, 124.33, 126.12, 127.43, 127.54, 128.60, 131.86 (9C tert., aromat.); 149.90 (C=O); 154.08 (C=O); 178.31 (C=N).

$C_{18}H_{12}N_2O_3S$ [336.37]

Calcd.	[%]	C 64.27	H 3.60	N 8.33	S 9.53
Found	[%]	C 63.74	H 3.72	N 8.20	S 9.70

7-Chloro-3-(1-phenylethylideneamino)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**19j**)



Yield: 78%, white solid

M.p.: 245 °C

IR (KBr): 1694, 1754 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.36 (s, 3H, CH_3); 7.53-8.13 (m, 7H, aromat.); 8.45 (s, 1H, aromat.).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

17.16 (CH_3); 112.35, 126.38, 134.76, 135.89, 140.41, 145.27 (6C quart., aromat.); 123.93, 124.50, 127.30, 127.96, 129.08, 132.34 (8C tert., aromat.); 149.89 (C=O); 154.39 (C=O); 178.87 (C=N).

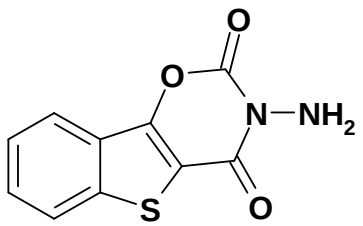
$C_{18}H_{11}ClN_2O_3S$ [370.82]

Calcd.	[%]	C 58.30	H 2.99	N 7.55	S 8.65
Found	[%]	C 58.11	H 3.09	N 7.47	S 8.76

7.3.5 Preparation of 3-Amino-benzothieno[2,3-*e*][1,3]oxazines (**20**)

To a solution of **19a-d** in THF (3 mmol), trifluoroacetic acid (5 mmol) was added dropwise under ice cooling. The mixture was stirred at RT for 4 h. Afterwards, the solvent was removed under reduced pressure and the resulting solid recrystallized from hot EtOH.

3-Amino-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**20a**)



Yield: 78%, white solid

M.p.: 238 °C

IR (KBr): 1687, 1766 cm^{-1} (C=O); 3273, 3347 cm^{-1} (NH_2)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

5.45 (s, 2H, NH_2); 7.62-8.20 (m, 4H, aromat.).

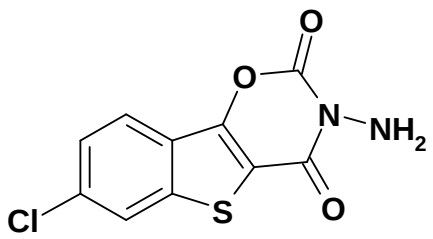
^{13}C-NMR (DMSO-*d6*): δ(ppm):

110.73, 126.07, 138.74, 147.65 (4C quart., aromat.); 121.95, 124.29, 126.90, 129.41 (4C tert., aromat.); 149.04 (C=O); 156.55 (C=O).

$C_{10}H_6N_2O_3S$ [234.23]

Calcd.	[%]	C 51.28	H 2.58	N 11.96	S 13.69
Found	[%]	C 50. 80	H 2.69	N 11.68	S 13.71

3-Amino-7-chloro-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**20b**)



Yield: 73%, white solid

M.p.: 227°C

IR (KBr): 1708, 1773 cm^{-1} (C=O); 3260, 3336 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

5.45 (s, 2H. NH_2); 7.46 (d, 1H, aromat.); 8.04 (d, 1H, aromat.); 8.40 (s, 1H, aromat.).

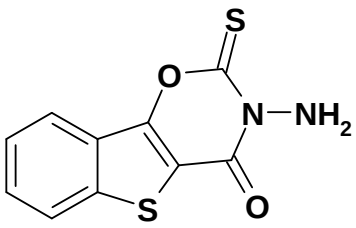
^{13}C-NMR (DMSO-*d6*): δ(ppm):

111.52, 125.81, 134.28, 139.97, 147.54 (5C quart., aromat.); 123.42, 124.02, 126.81 (3C tert., aromat.); 148.64 (C=O); 156.43 (C=N).

$C_{10}H_5N_2O_3S$ [268.68]

Calcd.	[%]	C 44.70	H 1.88	N 10.43	S 11.93
Found	[%]	C 44.47	H 1.86	N 10.20	S 12.17

3-Amino-2-thioxo-benzothieno[2,3-*e*][1,3]oxazine-4-one (**20c**)



Yield: 70%, yellow solid

M.p.: 180 °C

IR (KBr): 1254 cm^{-1} (C=S); 1716 cm^{-1} (C=O); 3219, 3296 cm^{-1} (NH_2)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

6.34 (s, 2H, NH_2); 7.65-8.25 (m, 4H, aromat.).

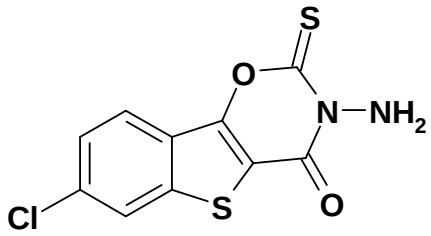
^{13}C-NMR (DMSO-*d6*): δ(ppm):

112.65, 126.15, 138.96, 151.77 (4C quart., aromat.); 122.12, 124.37, 126.37, 129.95 (4C tert., aromat.); 151.86 (C=O); 175.86 (C=S).

$C_{10}H_6N_2O_2S_2$ [250.30]

Calcd.	[%]	C 47.99	H 2.42	N 11.19	S 25.62
Found	[%]	C 47.95	H 2.46	N 10.83	S 25.18

3-Amino-7-chloro-2-thioxo-benzothieno[2,3-*e*][1,3]oxazine-4-one (**20d**)



Yield: 66%, yellow solid

M.p.: 218 °C

IR (KBr): 1271 cm^{-1} (C=S); 1717 cm^{-1} (C=O); 3212, 3302 cm^{-1} (NH_2)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

6.31 (s, 2H, NH_2); 7.66 (d, 1H, aromat.); 8.17 (d, 1H, aromat.); 8.43 (s, 1H, aromat.).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

113.01, 125.28, 134.76, 140.15, 151.36 (5C quart., aromat.); 123.56, 124.06, 127.05 (3C tert., aromat.); 151.64 (C=O); 175.77 (C=S).

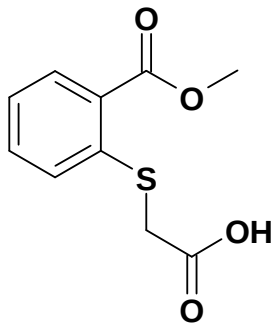
$C_{10}H_5ClN_2O_2S_2$ [284.74]

Calcd.	[%]	C 42.18	H 1.77	N 9.84	S 22.52
Found	[%]	C 42.37	H 1.89	N 9.51	S 22.28

7.3.6 Preparation of Methyl 2-Carboxymethylsulfanyl-benzoate (**21**)

To a suspension of salicylic acid methyl ester (50 mmol) in aq. solution of $NaHCO_3$ (10%) (100 mL), a solution of chloroacetic acid (50 mmol) in water (20 mL) was added and the mixture was then stirred at 70 °C for 2H. After cooling , the reaction mixture was acidified with HCl (10%) and the resulting solid product was collected by filtration.

Methyl 2-carboxymethylsulfanyl-benzoate (**21**)



Yield: 93%, white solid
M.p.: 144 °C
IR (KBr): 1680 cm^{-1} (COOH), 1711 cm^{-1} ($COOCH_3$)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.85 (s, 3H, CH_3); 3.87 (s, 2H, CH_2); 7.26-7.89 (m, 4H, aromat.); 12.86 (s, 1H, OH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

34.03 (CH_2); 52.05 (CH_3); 124.32, 125.75, 130.69, 132.68 (4C tert., aromat.); 126.93, 140.06 (2C quart., aromat.); 165.98, 170.40 (C=O).

$C_{10}H_{10}O_4S$ [226.25]

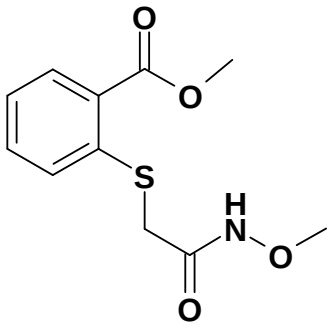
7.3.7 General procedure for the preparation of **23-26**

To a solution of methyl 2-carboxymethylsulfanyl-benzoate (**21**) (5 mmol in dry THF (10 mL) CDI (5.5 mmol) was added and the mixture was stirred at RT. Evolvement of CO_2 and the transformation of the solution into thick suspension indicated the formation of the imidazolide intermediate **22**.

The appropriate reagent[n] (*O*-substituted hydroxylamines or hydrazines) (6 mmol) was added and the mixture was stirred for additional 18 h at RT.

The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (15 mL). The organic layer was washed with (10%) aq. solution of $NaHCO_3$ (10 mL) then with (0.1 N) HCl (10 mL), collected, and dried over $MgSO_4$. Recrystallization from Et_2O provided the desired products.

Methyl 2-[(2-methoxyamino-2-oxoethyl)sulfanyl]benzoate (**23a**)



[n] Methoxy- and allayoxyamine, ethyl- and *tert*-butylhydrazine were used as hydrochloride or oxalate salt with addition of equivalent amount of triethylamine.

Yield: 74%, white solid

M.p.: 110 °C

IR (KBr): 1667, 1706 cm^{-1} (C=O); 3205 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.57 (s, 3H, CH_3); 3.59 (s, 2H, CH_2); 3.84 (s, 3H, CH_3); 7.27-7.90 (m, 4H, aromat.); 11.38 (s, 1H, NH).

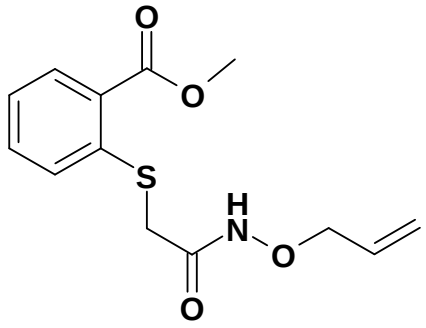
^{13}C-NMR (DMSO-*d6*): δ(ppm):

32.83 (CH_2); 52.08 (CH_3); 63.11 (CH_3); 124.47, 126.09, 130.61, 132.63 (4C tert., aromat.); 127.05, 140.06 (2C quart., aromat.); 164.64 (C=O); 165.96 (C=O).

$C_{11}H_{13}NO_4S$ [255.29]

Calcd.	[%]	C 51.75	H 5.13	N 5.49	S 12.56
Found	[%]	C 51.39	H 5.19	N 5.30	S 12.50

Methyl 2-[(2-allyloxyamino-2-oxoethyl)sulfanyl]benzoate (**23b**)



Yield: 77%, white solid

M.p.: 77 °C

IR (KBr): 1668, 1707 cm^{-1} (C=O); 3203 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.59 (s, 2H, S-CH_2); 3.84 (s, 3H, CH_3); 4.26 (d, *J* = 6.10 Hz, 2H, CH_2-CH=*CH_2*); 5.25 (t, *J* = 14.85 Hz, 2H, *CH_2*-CH=CH_2); 5.90 (m, 1H, CH_2-*CH*=CH_2); 7.25-7.90 (m, 4H, aromat.); 11.32 (s, 1H, NH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

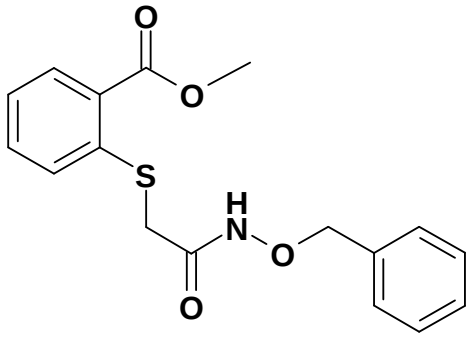
32.80 (S-CH_2); 52.07 (CH_3); 75.85 (CH_2-CH=CH_2); 119.30 (CH_2-CH=*CH_2*); 124.44, 126.06, 130.61, 132.61 (4C tert.,

aromat.); 132.79 (CH_2-*CH*=CH_2); 127.01, 140.12 (2C quart., aromat.); 164.80 (C=O); 165.96 (C=O).

$C_{13}H_{15}NO_4S$ [281.33]

Calcd.	[%]	C 55.50	H 5.37	N 4.98	S 11.40
Found	[%]	C 55.37	H 5.50	N 4.99	S 11.65

Methyl 2-[(2-benzyloxyamino-2-oxoethyl)sulfanyl]benzoate (**23c**)



Yield: 75%, white solid

M.p.: 81 °C

IR (KBr): 1667, 1706 cm^{-1} (C=O); 3213 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.60 (s, 2H, S-CH_2); 3.84 (s, 3H, CH_3); 4.77 (s, 2H, O-CH_2); 7.28-7.90 (m, 9H, aromat.); 11.38 (s, 1H, NH).

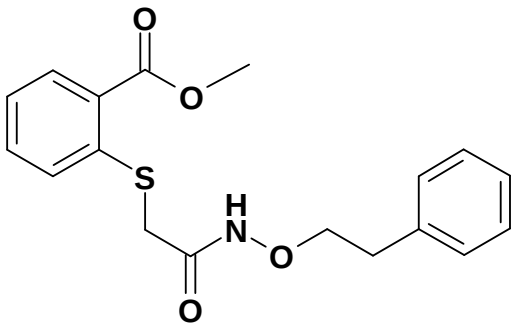
^{13}C-NMR (DMSO-*d6*): δ(ppm):

32.77 (S-CH_2); 52.08 (CH_3); 76.79 (O-CH_2); 124.44, 126.04, 128.22, 128.76, 130.62, 132.63 (9C tert., aromat.); 127.00, 135.70, 140.13 (3C quart., aromat.); 164.98 (C=O); 165.96 (C=O).

$C_{17}H_{17}NO_4S$ [331.39]

Calcd.	[%]	C 61.62	H 5.17	N 4.23	S 9.68
Found	[%]	C 61.51	H 5.21	N 4.33	S 9.10

Methyl 2-[(2-oxo-2-phenylethoxyamino-ethyl)sulfanyl]benzoate (**23d**)



Yield: 72%, white solid

M.p.: 79 °C

IR (KBr): 1664, 1705 cm^{-1} (C=O); 3238 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.74 (t, 2H, Ph-*CH_2*); 3.67 (s, 2H, S-CH_2); 3.83 (s, 3H, CH_3); 3.97 (t, 2H, O-CH_2); 7.22-7.89 (m, 9H, aromat.); 11.35 (s, 1H, NH).

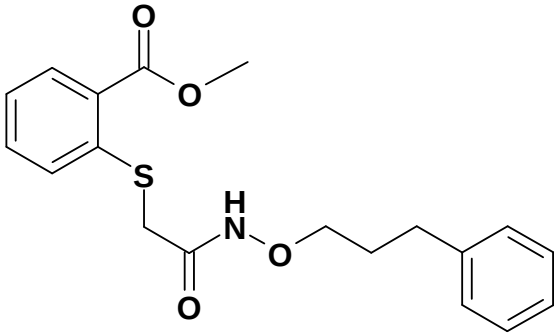
^{13}C-NMR (DMSO-*d6*): δ(ppm):

32.85 (S-CH_2); 33.69 (Ph-*CH_2*); 52.06 (CH_3); 75.57 (O-CH_2); 124.39, 126.11, 128.17, 128.82, 130.74, 132.53 (9C tert., aromat.); 127.13, 135.73, 140.06 (3C quart., aromat.); 164.88 (C=O); 165.62 (C=O).

$C_{18}H_{19}NO_4S$ [345.42]

Calcd.	[%]	C 62.59	H 5.54	N 4.05	S 9.28
Found	[%]	C 62.40	H 5.61	N 4.05	S 9.39

Methyl 2-[(2-oxo-2-phenylpropoxyamino-ethyl)sulfanyl]benzoate (**23e**)



Yield: 70%, white solid

M.p.: 77 °C

IR (KBr): 1649, 1705 cm^{-1} (C=O); 3276 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.79 (m, 2H, O-CH_2- *CH_2*- CH_2); 2.64 (t, *J* = 7.78 Hz, 2H, O-CH_2- CH_2- *CH_2*); 3.60 (s, 2H, S-CH_2); 3.74 (t, *J* = 6.36 Hz, 2H, O-*CH_2*- CH_2- CH_2); 3.84 (s, 3H, O-CH_3); 7.28-7.90 (m, 9H, aromat.); 11.30 (s, 1H, NH).

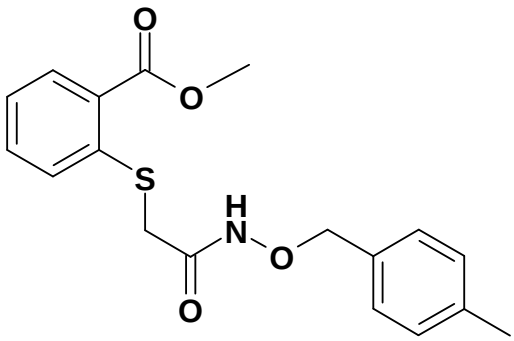
^{13}C-NMR (DMSO-*d6*): δ(ppm):

29.30, 31.23 (2C, CH_2); 32.83 (S-CH_2); 52.08 (O-CH_3); 74.38 (O-CH_2); 124.46, 125.68, 126.06, 128.18, 128.23, 130.64, 132.61 (9C tert., aromat.); 127.03, 140.10, 141.41 (3C quart., aromat.); 164.78 (C=O); 165.96 (C=O).

$C_{19}H_{21}NO_4S$ [359.45]

Calcd.	[%]	C 63.49	H 5.89	N 3.90	S 8.92
Found	[%]	C 63.39	H 5.94	N 3.90	S 8.46

Methyl 2-[(2-(4-methylbenzyloxyamino)-2-oxoethyl)sulfanyl]benzoate (**23f**)



Yield: 71%, white solid

M.p.: 94 °C

IR (KBr): 1665, 1706 cm^{-1} (C=O); 3215 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.30 (s, 3H, CH_3); 3.59 (s, 2H, S-CH_2); 3.84 (s, 3H, O-CH_3); 4.72 (s, 2H, O-CH_2); 7.16-7.90 (m, 8H, aromat.); 11.31 (s, 1H, NH).

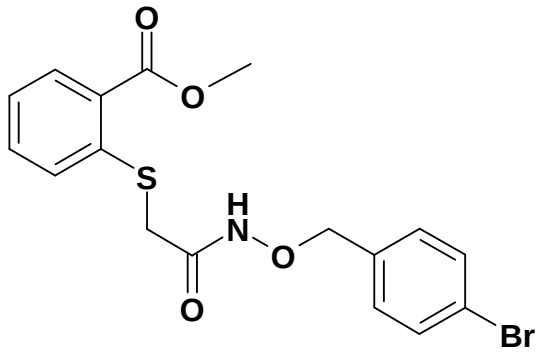
^{13}C-NMR (DMSO-*d6*): δ(ppm):

20.70 (CH_3); 32.75 (S-CH_2); 52.07 (O-CH_3); 76.61 (O-CH_2); 124.42, 126.02, 128.76, 128.90, 130.62, 132.62 (8C tert., aromat.); 126.97, 129.01, 137.53, 140.15 (4C quart., aromat.); 164.90 (C=O); 165.95 (C=O).

$C_{18}H_{19}NO_4S$ [345.42]

Calcd.	[%]	C 62.59	H 5.54	N 4.05	S 9.28
Found	[%]	C 62.40	H 5.61	N 4.05	S 9.38

Methyl 2-[(2-(4-bromobenzyloxyamino)-2-oxoethyl)sulfanyl]benzoate (**23g**)



Yield: 68%, white solid

M.p.: 121 °C

IR (KBr): 1663, 1708 cm^{-1} (C=O); 3212 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.59 (s, 2H, S-CH_2); 3.84 (s, 3H, O-CH_3); 4.75 (s, 2H, O-CH_2); 7.25-7.90 (m, 8H, aromat.); 11.38 (s, 1H, NH).

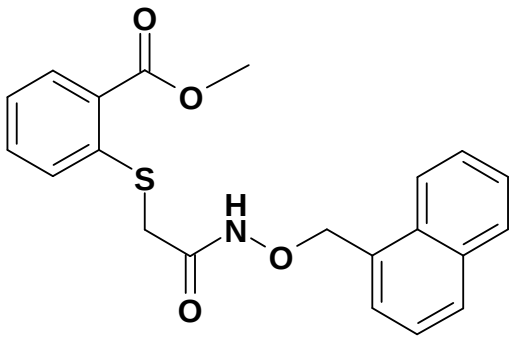
^{13}C-NMR (DMSO-*d6*): δ(ppm):

33.19 (S-CH_2); 52.55 (O-CH_3); 76.75 (O-CH_2); 124.91, 126.44, 131.09, 131.24, 131.46, 133.09 (8C tert., aromat.); 127.43, 135.60, 140.52, 159.98 (4C quart., aromat.); 165.51 (C=O); 166.41 (C=O).

$C_{17}H_{16}BrNO_4S$ [410.29]

Calcd.	[%]	C 49.77	H 3.93	N 3.41	S 7.81
Found	[%]	C 49.15	H 3.96	N 3.34	S 7.72

Methyl 2-[(2-(naphthalen-1-ylmethoxyamino)-2-oxoethyl)sulfanyl]benzoate (**23h**)



Yield: 71%, white solid

M.p.: 110 °C

IR (KBr): 1659, 1711 cm^{-1} (C=O); 3179 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.65 (s, 2H, S-CH_2); 3.85 (s, 3H, O-CH_3); 5.24 (s, 2H, O-CH_2); 7.25-8.45 (m, 11H, aromat.); 11.50 (s, 1H, NH).

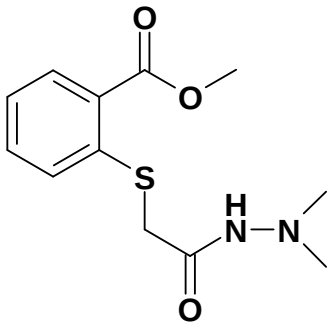
^{13}C-NMR (DMSO-*d6*): δ(ppm):

32.81 (S-CH_2); 52.08 (O-CH_3); 75.19 (O-CH_2); 124.47, 125.15, 125.92, 126.06, 126.35, 128.17, 128.50, 129.31, 130.65, 130.70, 132.67 (11C tert., aromat.); 127.05, 131.12, 131.78, 133.20, 140.13 (5C quart., aromat.); 165.21 (C=O); 165.98 (C=O).

$C_{21}H_{19}NO_4S$ [381.45]

Calcd.	[%]	C 66.12	H 5.02	N 3.67	S 8.41
Found	[%]	C 66.70	H 5.05	N 3.55	S 8.25

Methyl 2-[(2-(2,2-dimethylhydrazinyl)-2-oxoethyl)sulfanyl]benzoate (**24a**)



Yield: 70%, white solid

M.p.: 147 °C

IR (KBr): 1650, 1702 cm^{-1} (C=O); 3204 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.47 (s, 3H, CH_3); 2.53 (s, 3H, CH_3); 3.62 (s, 2H, CH_2); 3.87 (s, 3H, O-CH_3); 7.22-7.87 (m, 4H, aromat.); 8.64, 9.17 (NH).

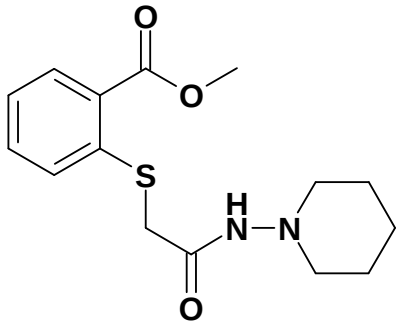
^{13}C-NMR (DMSO-*d6*): δ(ppm):

33.11 (S-CH_2); 46.14 (CH_3); 47.64 (CH_3); 52.04 (O-CH_3); 124.34, 127.14, 130.56, 132.53 (4C tert., aromat.); 127.14, 140.87 (2C quart., aromat.); 166.07 (C=O); 169.85 (C=O).

$C_{16}H_{12}N_2O_3S$ [268.34]

Calcd.	[%]	C 53.71	H 6.01	N 10.44	S 11.95
Found	[%]	C 53.64	H 6.13	N 10.22	S 11.95

Methyl 2-[(2-oxo-2-(piperidin-1-ylamino)-ethyl)sulfanyl]benzoate (**24b**)



Yield: 75%, white solid

M.p.: 124 °C

IR (KBr): 1662, 1713 cm^{-1} (C=O); 3207 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.06-1.62 (m, 6H); 2.64 (m, 4H); 3.57 (s, 2H, CH_2); 3.84 (s, 3H, CH_3); 7.22-7.88 (m, 4H, aromat.); 8.75, 9.11 (NH).

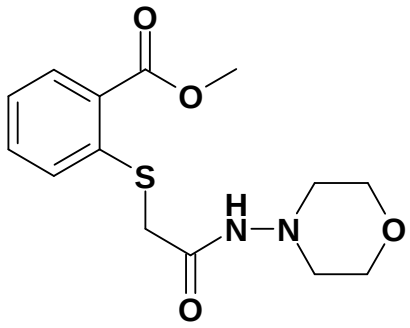
^{13}C-NMR (DMSO-*d6*): δ(ppm):

22.87, 25.25, 56.61 (5C, CH_2); 34.34 (S-CH_2); 52.05 (CH_3); 124.28, 126.37, 130.57, 132.51 (4C tert., aromat.); 127.53, 140.52 (2C quart., aromat.); 164.53 (C=O); 170.05 (C=O).

$C_{15}H_{20}N_2O_3S$ [308.40]

Calcd.	[%]	C 58.42	H 6.54	N 9.08	S 10.40
Found	[%]	C 58.32	H 6.62	N 9.01	S 10.33

Methyl 2-[(2-(morpholinoamino)-2-oxoethyl)sulfanyl]benzoate (**24c**)



Yield: 77%, white solid

M.p.: 169 °C

IR (KBr): 1661, 1713 cm^{-1} (C=O); 3200 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.72 (m, 4H); 3.60 (m, 4H); 3.82 (s, 2H, CH_2); 3.84 (s, 3H, CH_3); 7.24-7.88 (m, 4H, aromat.); 8.85, 9.29 (NH).

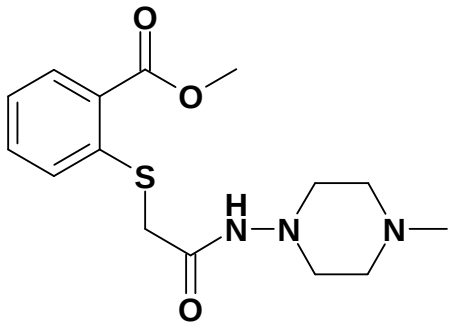
^{13}C-NMR (DMSO-*d6*): δ(ppm):

34.32 (S-CH_2); 52.06 (CH_3); 55.71 (2C, CH_2); 65.82 (2C, CH_2); 124.34, 126.46, 130.60, 132.56 (4C tert., aromat.); 127.15, 140.80 (2C quart., aromat.); 166.05 (C=O); 170.22 (C=O).

$C_{14}H_{18}N_2O_4S$ [310.37]

Calcd.	[%]	C 54.18	H 5.85	N 9.03	S 10.33
Found	[%]	C 53.75	H 5.90	N 8.77	S 10.20

Methyl 2-[(2-(4-methylpiperazin-1-ylamino)-2-oxoethyl)sulfanyl]benzoate (**24d**)



Yield: 72%, white solid

M.p.: 127 °C

IR (KBr): 1660, 1713 cm^{-1} (C=O); 3220 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.18 (m, 4H); 2.73 (m, 4H); 3.67 (s, 2H, CH_2); 3.82 (s, 3H, CH_3); 3.89 (s, 3H, CH_3); 7.24-7.82 (m, 4H, aromat.); 8.74, 9.13 (NH).

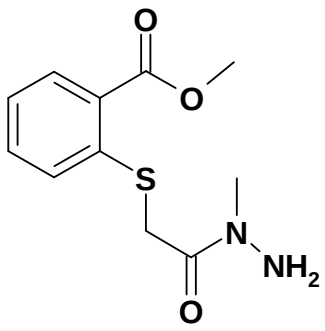
^{13}C-NMR (DMSO-*d6*): δ(ppm):

34.33 (CH_2); 45.26 (N-CH_3); 52.05 (O-CH_3); 54.01, 54.96 (4C); 124.31, 126.42, 130.58, 132.53 (4C tert., aromat.); 127.13, 140.91 (2C quart., aromat.); 165.96 (C=O); 170.21 (C=O).

$C_{15}H_{21}N_3O_3S$ [323.42]

Calcd.	[%]	C 55.71	H 6.54	N 12.99	S 9.91
Found	[%]	C 54.97	H 6.58	N 12.97	S 9.63

Methyl 2-[(2-(1-methylhydrazinyl)-2-oxoethyl)sulfanyl]benzoate (**25a**)



Yield: 71%, white solid

M.p.: 101 °C

IR (KBr): 1668, 1693 cm^{-1} (C=O); 3210, 3310 cm^{-1} (NH_2)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.04 (s, 3H, N-CH_3); 3.83 (s, 3H, O-CH_3); 4.03 (s, 2H, CH_2); 4.91 (s, 2H, NH_2); 7.2-7.86 (m, 4H, aromat.).

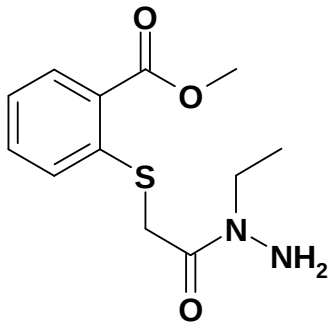
^{13}C-NMR (DMSO-*d6*): δ(ppm):

33.71 (CH_2); 37.41 (N-CH_3); 51.99 (O-CH_3); 123.94, 126.18, 130.47, 132.58 (4C tert., aromat.); 126.82, 141.33 (2C quart., aromat.); 166.03 (C=O); 169.41 (C=O).

$C_{11}H_{14}N_2O_3S$ [254.31]

Calcd.	[%]	C 51.95	H 5.55	N 11.02	S 12.61
Found	[%]	C 51.94	H 5.64	N 10.85	S 12.62

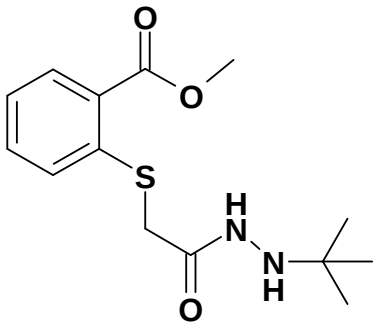
Methyl 2-[(2-(1-ethylhydrazinyl)-2-oxoethyl)sulfanyl]benzoate (**25b**)



Yield: 62%, white solid
M.p.: 86 °C
IR (KBr): 1665, 1697 cm^{-1} (C=O); 3210, 3310 cm^{-1} (NH_2)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
1.06 (t, 3H, CH_2-*CH_3*); 3.47 (q, 2H, *CH_2*-CH_3); 3.83 (s, 3H, O-CH_3); 4.04 (s, 2H, CH_2); 4.85 (s, 2H, NH_2); 7.23-7.87 (m, 4H, aromat.).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
11.22 (CH_2-*CH_3*); 33.91 (S-CH_2); 43.59 (*CH_2*-CH_3); 51.96 (O-CH_3); 123.95, 126.13, 130.42, 132.51 (4C tert., aromat.); 127.06, 141.23 (2C quart., aromat.); 166.45 (C=O); 168.95 (C=O).
$C_{12}H_{16}N_2O_3S$ [268.34]

Calcd.	[%]	C 53.71	H 6.01	N 10.44	S 11.95
Found	[%]	C 53.15	H 6.25	N 10.15	S 11.74

Methyl 2-[(2-(2-*tert*-butylhydrazinyl)-2-oxoethyl)sulfanyl]benzoate (**26**)



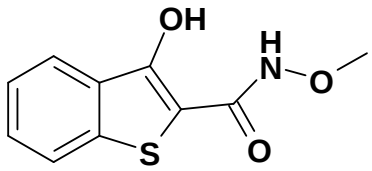
Yield: 60%, white solid
M.p.: 67 °C
IR (KBr): 1685, 1720 cm^{-1} (C=O); 3252, 3410 cm^{-1} (NH).
^{1}H-NMR (DMSO-*d6*): δ(ppm):
0.94 (s, 9H, $C(CH_3)_3$); 3.70 (s, 2H, CH_2); 3.84 (s, 3H, CH_3); 4.63 (s, 1H, N*H*-*tert*.-Bu); 7.25-7.88 (m, 4H, aromat.); 9.49 (s, 1H, CO-N*H*).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
26.92 (3C, CH_3); 33.81 (*C*$(CH_3)_3$); 52.03 (O-CH_3); 54.24 (CH_2); 124.31, 126.17, 130.45, 132.51 (4C tert., aromat.); 127.05, 140.43 (2C quart., aromat.); 165.97 (C=O); 166.30 (C=O).
$C_{14}H_{20}N_2O_3S$ [269.39]

Calcd.	[%]	C 56.73	H 6.80	N 9.45	S 10.82
Found	[%]	C 55.72	H 7.00	N 9.15	S 10.62

7.3.8 General procedure for the preparation of **27-30**

23-26 (3 mmol) were refluxed in commercially available solution of sodium methoxide in methanol (10 mL) for 2 h. Removal of the solvent under reduced pressure afforded oily residues which were taken up in cold water (5 mL) and the solution was acidified with few drops of 1N HCl to afford the desired products **27-30** as solid precipitates. Recrystallization of the crude products from hot EtOH furnished analytically pure samples.

3-Hydroxy-*N*-methoxy-benzo[*b*]thiophene-2-carboxamide (**27a**)



Yield: 69%, white solid
M.p.: 129 °C
IR (KBr): 1612 cm^{-1} (C=O); 3120 cm^{-1} (NH)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
3.76 (s, 3H, CH_3); 7.43-7.97 (m, 4 H, aromat.); 11.42 (s, 1H, NH); 11.82 (s, 1H, OH).

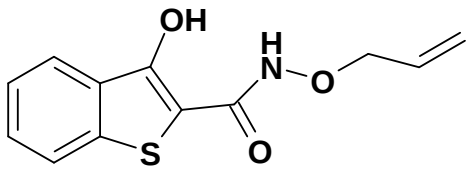
^{13}C-NMR (DMSO-*d6*): δ(ppm):

62.79 (CH_3); 107.07, 126.53, 132.55, 145.72 (4C quart., aromat.); 122.14, 123.24, 124.43, 128.18 (4C tert., aromat.); 164.01 (C=O).

$C_{10}H_9NO_3S$ [223.25]

Calcd.	[%]	C 53.80	H 4.06	N 6.27	S 14.36
Found	[%]	C 54.05	H 4.25	N 6.15	S 14.18

N-Allyloxy-3-hydroxy-benzo[*b*]thiophene-2-carboxamide (**27b**)



Yield: 75%, white solid

M.p.: 112 °C

IR (KBr): 1616 cm^{-1} (C=O); 3125 (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

4.46 (d, *J* = 5.85 Hz, 2H, O-CH_2); 5.36 (m, 2H, O-CH_2-CH-*CH_2*); 6.04 (m, 1H, O-CH_2-*CH*-CH_2); 7.45-7.95 (m, 4H, aromat.); 11.30 (s, 1H, NH); 11.80 (s, 1H, OH).

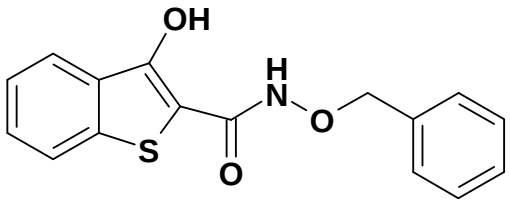
^{13}C-NMR (DMSO-*d6*): δ(ppm):

76.40 (O-*CH_2*-CH=CH_2); 107.03, 126.08, 137.26, 147.88 (4C quart., aromat.); 122.14, 123.24, 124.43, 129.20 (4C tert., aromat.); 119.80 (CH_2-CH=*CH_2*); 130.43 (CH_2-*CH*=CH_2); 165.95 (C=O).

$C_{12}H_{11}NO_3S$ [249.29]

Calcd.	[%]	C 57.82	H 4.45	N 5.62	S 12.86
Found	[%]	C 57.94	H 4.65	N 5.52	S 13.04

N-Benzyloxy-3-hydroxy-benzo[*b*]thiophene-2-carboxamide (**27c**)



Yield: 80%, pink solid

M.p.: 156 °C

IR (KBr): 1597 cm^{-1} (C=O); 3133 (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

4.98 (s, 2H, CH_2); 7.38-7.98 (m, 9H, aromat.); 11.32 (s, 1H, NH); 11.80 (s, 1H, OH).

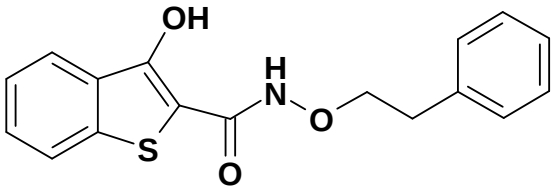
^{13}C-NMR (DMSO-*d6*): δ(ppm):

75.42 (CH_2); 113.23, 126.59, 131.06, 141.43, 154.48 (5C quart., aromat.); 122.20, 123.29, 124.44, 127.72, 128.31, 128.93, 134.49 (9C tert., aromat.); 165.88 (C=O).

$C_{16}H_{13}NO_3S$ [299.35]

Calcd.	[%]	C 64.20	H 4.38	N 4.68	S 10.71
Found	[%]	C 63.85	H 4.55	N 4.61	S 10.60

3-Hydroxy-*N*-phenethoxy-benzo[*b*]thiophene-2-carboxamide (**27d**)



Yield: 70%, pink solid

M.p.: 142 °C

IR (KBr): 1606 cm^{-1} (C=O); 3140 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.01 (m, 2H, CH_2-Ph); 4.17 (s, 2H, O-CH_2); 7.22-7.95 (m, 9H, aromat.); 11.37 (s, 1H, NH); 11.80 (s, 1H, OH).

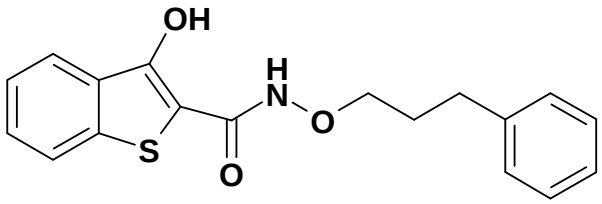
^{13}C-NMR (DMSO-*d6*): δ(ppm):

33.77 (Ph-CH_2); 75.42 (O-CH_2); 110.80, 126.03, 131.74, 141.23, 154.19 (5C quart., aromat.); 122.13, 123.23, 124.44, 126.19, 128.25, 128.84, 133.91 (9C tert., aromat.); 166.86 (C=O).

$C_{17}H_{15}NO_3S$ [313.38]

Calcd.	[%]	C 65.16	H 4.82	N 4.47	S 10.23
Found	[%]	C 64.50	H 4.89	N 4.40	S 10.07

3-Hydroxy-*N*-(3-phenylpropoxy)-benzo[*b*]thiophene-2-carboxamide (**27e**)



Yield: 72%, white solid

M.p.: 89 °C

IR (KBr): 1614 cm^{-1} (C=O); 3209 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.96 (m, 2H, O-CH_2-*CH_2*-CH_2); 2.73 (t, *J* = 7.78 Hz, 2H, O-CH_2-CH_2-*CH_2*); 4.17 (t, *J* = 6.61 Hz, 2H, O-*CH_2*-CH_2-CH_2); 7.17-7.96 (m, 9H, aromat.); 11.32 (s, 1H, NH); 11.80 (s, 1H, OH).

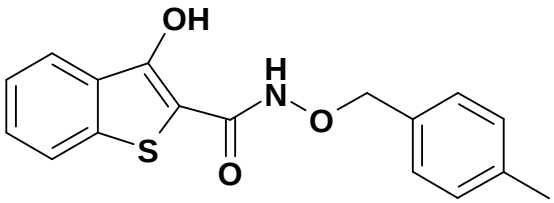
^{13}C-NMR (DMSO-*d6*): δ(ppm):

29.40 (CH_2); 31.30 (CH_2); 76.27 (O-CH_2); 107.16, 126.03, 131.08, 141.37, 154.50 (5C quart., aromat.); 122.15, 123.26, 124.46, 127.72, 128.24, 128.73, 134.51 (9C tert., aromat.); 165.67 (C=O).

$C_{18}H_{17}NO_3S$ [327.41]

Calcd.	[%]	C 66.03	H 5.23	N 4.28	S 9.79
Found	[%]	C 65.77	H 5.34	N 4.24	S 10.06

3-Hydroxy-*N*-(4-methylbenzyloxy)-benzo[*b*]thiophene-2-carboxamide (**27f**)



Yield: 68%, pink solid

M.p.: 171 °C

IR (KBr): 1611 cm^{-1} (C=O); 3134 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.32 (s, 3H, CH_3); 4.96 (s, 2H, CH_2); 7.21-7.97 (m, 8H, aromat.); 11.31 (s, 1H, NH); 11.81 (s, 1H, OH).

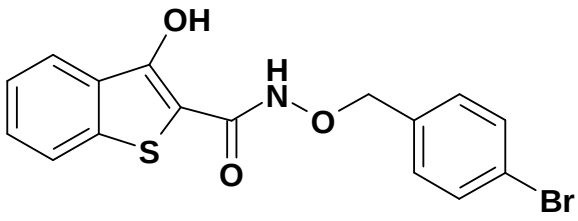
^{13}C-NMR (DMSO-*d6*): δ(ppm):

20.75 (CH_3); 76.10 (CH_2); 111.33, 125.89, 131.38, 137.73 141.82, 155.23 (6C quart., aromat.); 122.16, 123.27, 124.42, 127.72, 128.85, 129.05 (8C tert., aromat.); 164.34 (C=O).

$C_{17}H_{15}NO_3S$ [313.38]

Calcd.	[%]	C 65.16	H 4.82	N 4.47	S 10.23
Found	[%]	C 64.71	H 4.95	N 4.40	S 10.24

N-(4-Bromobenzyloxy)-3-hydroxy-benzo[*b*]thiophene-2-carboxamide (**27g**)



Yield: 65%, white solid

M.p.: 146 °C

IR (KBr): 1612 cm^{-1} (C=O); 3125 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

4.95 (s, 2H, CH_2); 7.43-7.98 (m, 8H, aromat.); 11.32 (s, 1H, NH); 11.76 (s, 1H, OH).

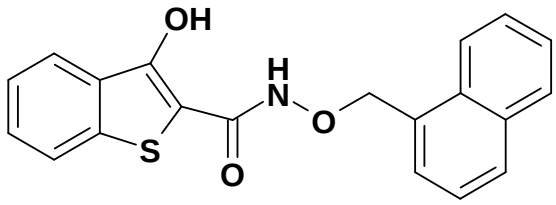
^{13}C-NMR (DMSO-*d6*): δ(ppm):

76.46 (CH_2); 112.58, 127.47, 132.74, 137.52, 141.92, 155.18 (6C quart., aromat.); 122.21, 123.28, 124.43, 128.73, 131.04, 131.23, 134.29 (8C tert., aromat.); 165.24 (C=O).

$C_{16}H_{12}BrNO_3S$ [378.25]

Calcd.	[%]	C 50.81	H 3.20	N 3.70	S 8.48
Found	[%]	C 50.52	H 3.33	N 3.67	S 8.44

3-Hydroxy-*N*-(naphthalen-1-ylmethoxy)-benzo[*b*]thiophene-2-carboxamide (**27h**)



Yield: 72%, white solid

M.p.: 174 °C

IR (KBr): 1622 cm^{-1} (C=O); 3124, 3218 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

5.44 (s, 2H, CH_2); 7.45-8.06 (m, 10H, aromat.); 8.62 (s, 1H, aromat.); 11.48 (s, 1H, NH); 11.78 (s, 1H, OH).

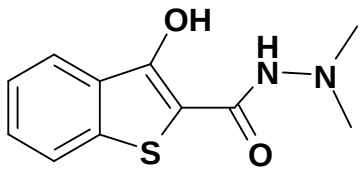
^{13}C-NMR (DMSO-*d6*): δ(ppm):

75.42 (CH_2); 112.28, 131.87, 131.90, 133.21, 142.58, 153.80 (7C quart., aromat.); 122.24, 123.31, 124.23, 125.22, 125.97, 126.41, 127.88 128.19, 128.57, 129.41 (11C tert, aromat.); 164.33 (C=O).

$C_{20}H_{15}NO_3S$ [349.41]

Calcd.	[%]	C 68.75	H 4.33	N 4.01	S 9.18
Found	[%]	C 68.40	H 4.45	N 3.97	S 9.11

3-Hydroxy-*N'*,*N'*-dimethyl-benzo[*b*]thiophene-2-carbohydrazide (**28a)**



Yield: 73%, colourless crystals

M.p.: 114 °C

IR (KBr): 1637cm^{-1} (C=O); 3148-3250 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.62 (s, 6H, CH_3); 7.41-7.90 (m, 4H, aromat.); 9.52 (s, 1H, NH); 13.30 (s, 1H, OH).

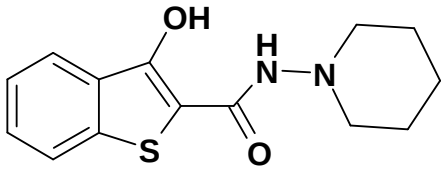
^{13}C-NMR (DMSO-*d6*): δ(ppm):

47.05 (2C, CH_3); 100.12, 129.71, 140.69, 159.81 (4C quart., aromat.); 121.69, 122.81, 124.09, 128.25 (4C tert., aromat.); 168.03 (C=O).

$C_{11}H_{12}N_2O_2S$ [236.29]

Calcd.	[%]	C 55.91	H 5.12	N 11.86	S 13.57
Found	[%]	C 55.99	H 5.24	N 11.74	S 13.62

3-Hydroxy-*N*-(piperidin-1-yl)-benzo[*b*]thiophene-2-carboxamide (**28b**)



Yield: 77%, white solid

M.p.: 181 °C

IR (KBr): 1616 cm^{-1} (C=O); 3159-3232 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.13-1.81 (m, 6H, CH_2); 2.58 (m, 2H, CH_2); 3.01 (m, 4H, CH_2); 7.40-7.90 (m, 4H, aromat.); 9.56 (s, 1H, NH); 13.38 (s, 1H, OH).

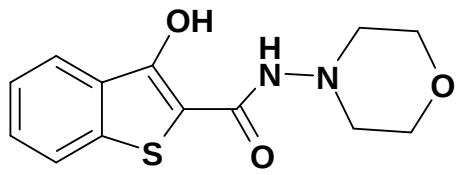
^{13}C-NMR (DMSO-*d6*): δ(ppm):

22.96, 25.05, 56.94 (5C, CH_2); 100.36, 130.18, 140.99, 160.49 (4C quart., aromat.); 122.08, 123.27, 124.54, 128.73 (4C tert., aromat.); 168.57 (C=O).

$C_{14}H_{16}N_2O_2S$ [276.36]

Calcd.	[%]	C 60.85	H 5.84	N 10.14	S 11.60
Found	[%]	C 60.41	H 5.89	N 9.93	S 11.57

3-Hydroxy-*N*-morpholino-benzo[*b*]thiophene-2-carboxamide (**28c**)



Yield: 78%, white solid

M.p.: 191 °C

IR (KBr): 1625cm^{-1} (C=O); 3146-3239 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.78-2.98 (m, 4H, CH_2); 3.65-3.88 (m, 4H, CH_2); 7.40-7.92 (m, 4H, aromat.); 9.65 (s, 1H, NH); 13.23 (s, 1H, OH).

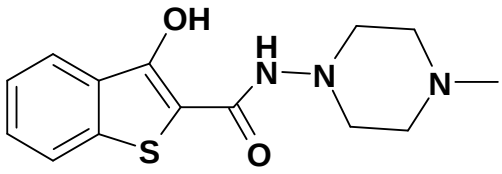
^{13}C-NMR (DMSO-*d6*): δ(ppm):

55.58, 65.37 (4C, CH_2); 99.44, 129.57, 140.41, 160.51 (4C quart., aromat.); 121.67, 122.86, 124.28, 128.44 (4C tert., aromat.); 168.42 (C=O).

$C_{13}H_{14}N_2O_3S$ [278.33]

Calcd.	[%]	C 56.10	H 5.07	N 10.06	S 11.52
Found	[%]	C 55.65	H 5.15	N 9.77	S 11.45

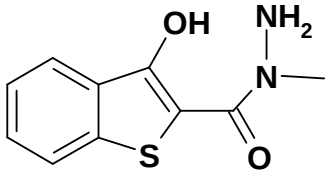
3-Hydroxy-*N*-(4-methylpiperazin-1-yl)-benzo[*b*]thiophene-2-carboxamide (**28d**)



Yield: 87%, white solid
M.p.: 210 °C
IR (KBr): 1616 cm^{-1} (C=O); 3125, 3201 cm^{-1} (NH)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
2.26 (s, 3H, CH_3); 2.39 (m, 2H); 2.78-2.95 (m, 6H); 7.42-7.92 (m, 4H, aromat.); 9.55 (s, 1H, NH); 13.30 (s, 1H, OH).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
45.27 (CH3); 53.57 (2C, CH_2); 54.98 (2C, CH_2); 99.58, 129.63, 140.43, 160.31 (4C quart., aromat); 121.66, 122.84, 124.14, 128.38 (4C tert., aromat.); 168.30 (C=O).
$C_{14}H_{17}N_3O_2S$ [291.37]

Calcd.	[%]	C 57.71	H 5.88	N 14.42	S 11.00
Found	[%]	C 57.53	H 5.97	N 14.32	S 10.96

3-Hydroxy-*N*-methyl-benzo[*b*]thiophene-2-carbohydrazide (**29a**)



Yield: 68%, white needles
M.p.: 182 °C
IR (KBr): 1640 cm^{-1} (C=O); 3320 cm^{-1} (NH_2)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.2 (s, 3H, CH_3); 5.50 (s, 2H, NH_2); 7.39-7.85 (m, 4H, aromat.); 14.05 (s, 1H, OH).

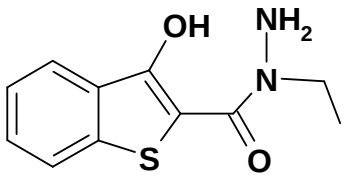
^{13}C-NMR (DMSO-*d6*): δ(ppm):

37.37 (CH_3); 101.39, 130.08, 140.10, 158.16 (4C quart., aromat.); 121.69, 122.47, 123.84, 127.81 (4C tert., aromat.); 167.46 (C=O).

$C_{10}H_{10}N_2O_2S$ [222.27]

Calcd.	[%]	C 54.04	H 4.53	N 12.60	S 14.43
Found	[%]	C 53.93	H 4.76	N 12.45	S 14.49

N-Ethyl-3-hydroxy-benzo[*b*]thiophene-2-carbohydrazide (**29b**)



Yield: 60%, white needles

M.p.: 145 °C

IR (KBr): 1638 cm^{-1} (C=O); 3337 cm^{-1} (NH_2).

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.19 (t, *J* = 7.12 Hz, 3H, CH_3); 3.64 (q, *J* = 14.24 Hz, 2H, CH_2); 5.42 (s, 2H, NH_2); 7.38-7.87 (m, 4H, aromat.); 13.70 (s, 1H, OH).

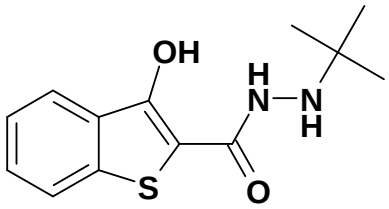
^{13}C-NMR (DMSO-*d6*): δ(ppm):

11.11 (CH_3); 44.02 (CH_2); 101.87, 130.06, 140.16, 158.50 (4C quart., aromat.); 121.65, 122.46, 123.82, 127.81 (4C tert., aromat.); 167.17 (C=O).

$C_{11}H_{12}N_2O_2S$ [236.29]

Calcd.	[%]	C 55.91	H 5.12	N 11.86	S 13.57
Found	[%]	C 55.87	H 5.28	N 11.75	S 13.55

N'-*tert*-Butyl-3-hydroxy-benzo[*b*]thiophene-2-carbohydrazide (**30**)



Yield: 72%, white needles

M.p.: 189 °C

IR (KBr): 1638 cm^{-1} (C=O); 3162, 3280 (NH).

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.11 (s, 9H, CH_3); 5.52 (s, 1H, N*H*-C$(CH_3)_3$); 7.39-7.85 (m, 4H, aromat.); 9.33 (s, 1H, CO-N*H*); 14.06 (s, 1H, OH).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

26.20 (CH_3); 54.13 (*C*$(CH_3)_3$); 121.85, 122.60, 123.86, 127.97 (4C tert., aromat); 102.21, 124.48, 130.28, 140.39 (4C quart., aromat.); 169.97 (C=O).

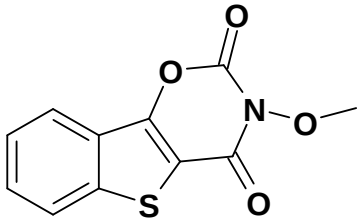
$C_{13}H_{16}N_2O_2S$ [264.35]

Calcd.	[%]	C 59.07	H 6.10	N 10.60	S 12.13
Found	[%]	C 58.22	H 6.09	N 10.36	S 12.11

7.3.9 Preparation of Benzthieno[2,3-e][1,3]oxazine derivatives (**31**, **32**, **33**)

Compounds **31**, **32**, **33** were prepared according to the general procedure described in 7.3.4 (s. page 110).

3-Methoxy-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**31a**)



Yield: 79%, pink solid

M.p.: 171 °C

IR (KBr): 1715, 1774 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.95 (s, 3H, CH_3); 7.64-8.22 (m, 4H, aromat.).

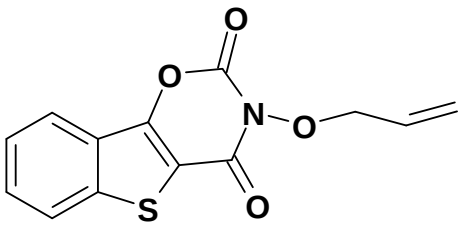
^{13}C-NMR (DMSO-*d6*): δ(ppm):

63.57 (CH_3); 104.74, 126.80, 138.91, 145.83 (4C quart., aromat.); 122.02, 124.38, 126.24, 129.58 (4C tert., aromat.); 151.81 (C=O); 156.32 (C=O).

$C_{11}H_7NO_4S$ [249.25]

Calcd.	[%]	C 53.01	H 2.83	N 5.62	S 12.86
Found	[%]	C 52.50	H 2.92	N 5.48	S 12.98

3-Allyloxy-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**31b**)



Yield: 85%, white solid

M.p.: 151 °C

IR (KBr): 1703, 1780 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

4.68 (d, *J* = 6.36 Hz, 2H, CH_2-CH=CH_2); 5.42 (m, 2H, CH_2-CH=CH_2); 6.07 (m, 1H, CH_2-CH=CH_2); 7.64-8.22 (m, 4H, aromat.).

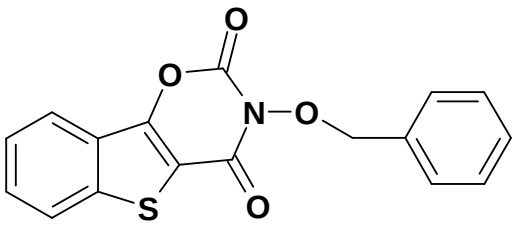
^{13}C-NMR (DMSO-*d6*): δ(ppm):

76.88 (O-CH_2-CH=CH_2); 111.09, 126.77, 138.95, 146.15 (4C quart., aromat.); 122.03, 124.38, 126.25, 129.61 (4C tert., aromat.); 121.50 (CH_2-CH=CH_2); 131.21 (CH_2-CH=CH_2); 149.10 (C=O); 154.75 (C=O).

$C_{13}H_9NO_4S$ [275.28]

Calcd.	[%]	C 56.72	H 3.30	N 5.09	S 11.65
Found	[%]	C 56.60	H 3.31	N 5.05	S 11.69

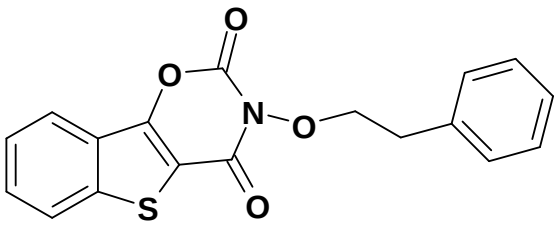
3-Benzyloxy-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**31c**)



Yield: 81%, white solid
M.p.: 189 °C
IR (KBr): 1716, 1778cm^{-1} (C=O)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
5.18 (s, 2H, CH_2); 7.44-8.22 (m, 9H, aromat.).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
77.83 (CH_2); 111.18, 126.80, 133.83, 138.96, 146.15 (5C quart., aromat.); 122.04, 124.38, 126.26, 128.41, 129.01, 129.53, 129.60 (9C tert., aromat.); 149.14 (C=O); 154.73 (C=O).
$C_{17}H_{11}NO_4S$ [325.35]

Calcd.	[%]	C 62.76	H 3.41	N 4.31	S 9.86
Found	[%]	C 62.64	H 3.48	N 4.23	S 9.84

3-Phenethyloxy-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**31d**)



Yield: 77%, pink solid
M.p.: 102 °C
IR (KBr): 1713, 1777 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

3.11 (t, 2H, CH_2); 4.36 (t, 2H, CH_2); 7.20-8.17 (m, 9H, aromat.).

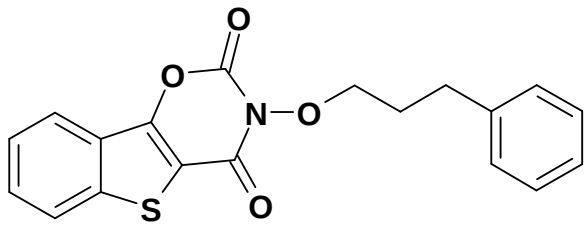
^{13}C-NMR (DMSO-*d6*): δ(ppm):

33.69 (CH_2); 76.17 (CH_2); 111.19, 126.81, 137.31, 138.93, 146.13 (5C quart., aromat.); 122.20, 124.36, 126.24, 128.23, 128.68, 129.56 (9C tert., aromat.); 149.09 (C=O); 154.75 (C=O).

$C_{18}H_{13}NO_4S$ [339.37]

Calcd.	[%]	C 63.71	H 3.86	N 4.13	S 9.45
Found	[%]	C 64.19	H 4.35	N 3.94	S 9.03

3-(3-Phenylpropoxy)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**31e**)



Yield: 78%, white solid

M.p.: 115 °C

IR (KBr): 1715, 1779 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.00 (m, 2H, O-CH_2-*CH_2*-CH_2); 2.78 (t, *J* = 7.63 Hz, 2H, O-CH_2-CH_2-*CH_2*); 4.19 (t, *J* = 6.24 Hz, 2H, O-*CH_2*-CH_2-CH_2); 7.17-8.22 (m, 9H, aromat.).

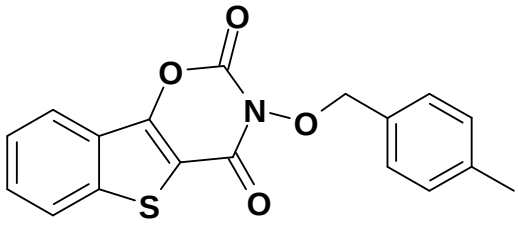
^{13}C-NMR (DMSO-*d6*): δ(ppm):

29.88 (O-CH_2-*CH_2*-CH_2); 31.68 (O-CH_2-CH_2-*CH_2*); 75.88 (O-*CH_2*-CH_2-CH_2); 111.32, 127.28, 139.38, 141.70, 146.64 (5C quart., aromat.); 122.46, 124.82, 126.24, 126.68, 128.70, 128.77, 130.00 (9C tert., aromat.); 149.58 (C=O); 155.26 (C=O).

$C_{19}H_{15}NO_4S$ [353.40]

Calcd.	[%]	C 64.58	H 4.28	N 3.96	S 9.07
Found	[%]	C 64.62	H 4.40	N 3.91	S 9.13

3-(4-Methylbenzyloxy)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**31f**)



Yield: 72%, pink solid

M.p.: 185 °C

IR (KBr): 1715, 1781 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.34 (s, 3H, CH_3); 5.13 (s, 2H, CH_2); 7.25-8.23 (m, 8H, aromat.).

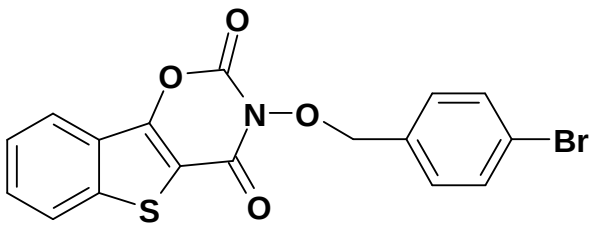
^{13}C-NMR (DMSO-*d6*): δ(ppm):

20.80 (CH_3); 77.66 (CH_2); 111.19, 126.81, 130.84, 138.45, 138.94, 146.16 (6C quart., aromat); 122.05, 124.39, 126.26, 128.94, 129.60, 129.62 (6C tert., aromat.); 149.14 (C=O); 154.76 (C=O).

$C_{17}H_{11}NO_4S$ [325.35]

Calcd.	[%]	C 63.71	H 3.86	N 4.13	S 9.45
Found	[%]	C 63.34	H 4.03	N 4.06	S 9.51

3-(4-Bromobenzyloxy)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**31g**)



Yield: 74%, white solid

M.p.: 184°C

IR (KBr): 1718, 1779 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

5.17 (s, 2H, CH_2); 7.54-8.24 (m, 8H, aromat.).

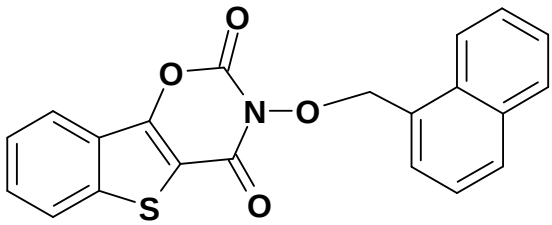
^{13}C-NMR (DMSO-*d6*): δ(ppm):

76.98 (CH_2); 111.65, 122.33, 126.78, 133.33, 138.95, 146.15 (6C quart., aromat.); 122.06, 124.40, 126.28, 129.63, 131.39, 131.62 (8C tert., aromat.); 149.15 (C=O); 154.73 (C=O).

$C_{17}H_{10}BrNO_4S$ [404.24]

Calcd.	[%]	C 50.51	H 2.49	N 3.46	S 7.93
Found	[%]	C 50.42	H 2.49	N 3.40	S 7.99

3-(Naphthalen-1-ylmethoxy)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**31h**)



Yield: 72%, white solid

M.p.: 237 °C

IR (KBr): 1708, 1784 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

5.61 (s, 2H, CH_2); 7.55-8.70 (m, 11H, aromat.).

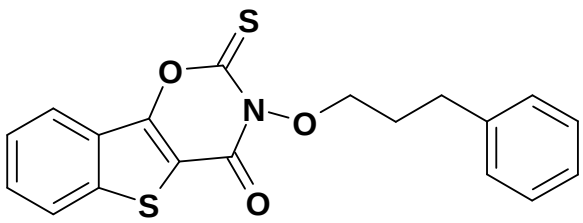
^{13}C-NMR (DMSO-*d6*): δ(ppm):

75.62 (CH_2); 111.85, 126.82, 130.22, 131.97, 133.16, 139.01, 146.24 (7C quart., aromat.); 122.08, 124.43, 124.50, 125.29, 126.10, 126.30, 126.63, 128.26, 129.61, 129.64, 130.08 (11C tert., aromat.); 149.22 (C=O); 153.39 (C=O).

$C_{21}H_{13}NO_4S$ [375.41]

Calcd.	[%]	C 67.19	H 3.49	N 3.73	S 8.54
Found	[%]	C 66.98	H 3.57	N 3.67	S 8.58

3-(3-Phenylpropoxy)-2-thioxo-benzothino[2,3-*e*][1,3]oxazine-4-one (**31i**)



Yield: 69%, pink needles

M.p.: 156 °C

IR (KBr): 1296 cm^{-1} (C=S); 1715 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.04 (m, 2H, CH_2-*CH_2*-CH_2); 2.81 (t, *J* = 7.64 Hz, 2H, *CH_2*-Ph); 4.29 (t, *J* = 6.23 Hz, 2H, O-*CH_2*); 7.20-8.24 (m, 9H, aromat.).

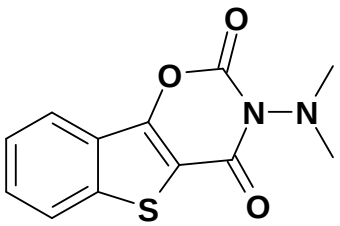
^{13}C-NMR (DMSO-*d6*): δ(ppm):

29.36 (CH_2-*C*H_2-CH_2); 31.26 (*C*H_2-Ph); 74.08 (O-*C*H_2); 113.60, 126.28, 139.23, 141.19, 151.23 (5C quart., aromat.); 122.11, 124.41, 125.80, 126.46, 128.26, 128.28, 129.97 (9C tert., aromat.); 151.93 (C=O); 177.35 (C=S).

$C_{19}H_{17}NO_3S_2$ [371.48]

Calcd.	[%]	C 61.77	H 4.09	N 3.79	S 17.36
Found	[%]	C 61.30	H 4.30	N 3.70	S 16.85

3-(Dimethylamino)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**32a**)



Yield: 70%, white solid

M.p.: 215 °C

IR (KBr): 1717, 1761 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.87 (s, 6H, CH_3); 7.60-8.20 (m, 4H, aromat.).

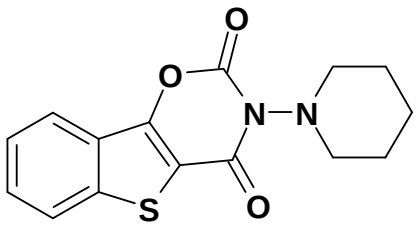
^{13}C-NMR (DMSO-*d6*): δ(ppm):

42.45 (2C, CH_3); 111.64, 126.93, 138.89, 147.22 (4C quart., aromat.); 121.930, 124.31, 126.09, 129.40 (4C tert., aromat.); 149.43 (C=O); 157.28 (C=O).

$C_{12}H_{10}N_2O_3S$ [262.29]

Calcd.	[%]	C 54.95	H 3.84	N 10.68	S 12.22
Found	[%]	C 54.75	H 3.95	N 10.55	S 12.18

3-(Piperidin-1-yl)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**32b**)



Yield: 74%, white solid

M.p.: 212 °C

IR (KBr): 1701, 1785 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.40-1.45 (m, 2H); 1.64 (m, 4H); 3.20-3.26 (m, 4H); 7.60-8.18 (m, 4H, aromat.).

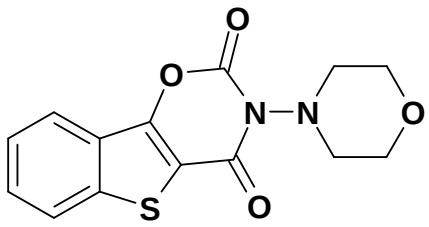
^{13}C-NMR (DMSO-*d6*): δ(ppm):

23.01, 25.83, 50.83, 56.49, 60.97 (5C, CH_2); 111.68, 126.95, 138.89, 147.38 (4C quart., aromat.); 121.94, 124.31, 126.09, 129.39 (4C tert., aromat.); 149.44 (C=O); 157.35 (C=O).

$C_{15}H_{14}N_2O_3S$ [302.35]

Calcd.	[%]	C 59.59	H 4.67	N 9.27	S 10.60
Found	[%]	C 59.58	H 4.87	N 9.01	S 10.39

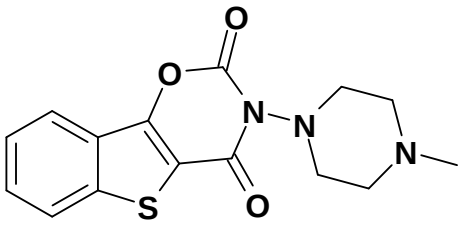
3-Morpholino-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione **(32c**)



Yield: 76%, white solid
M.p.: 252 °C
IR (KBr): 1698, 1760 cm^{-1} (C=O)
^{1}H-NMR (DMSO-*d6*): δ(ppm):
3.72 (s, 8H); 7.65-8.21 (m. 4H, aromat.).
^{13}C-NMR (DMSO-*d6*): δ(ppm):
50.18 (2C, CH_2); 66.48 (2C, CH_2); 110.42, 126.91, 138.89, 147.37 (4C quart., aromat.); 121.96, 124.34, 126.14, 129.46 (4C tert., aromat.); 151.07 (C=O); 157.32 (C=O).
$C_{14}H_{11}N_2O_4S$ [304.33]

Calcd.	[%]	C 55.26	H 3.97	N 9.21	S 10.54
Found	[%]	C 54.91	H 4.11	N 9.02	S 10.57

3-(4-Methylpiperazin-1-yl)-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione (**32d**)



Yield: 83%, white solid
M.p.: 234 °C
IR (KBr): 1710, 1765 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.21 (s, 3H, CH_3); 2.4 (m, 4H, CH_2); 3.2 (m, 4H, CH_2); 7.62-8.19 (m, 4H, aromat.).

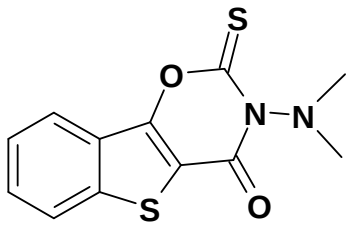
^{13}C-NMR (DMSO-*d6*): δ(ppm):

45.50 (CH_3); 49.25 (2C, CH_2); 54.76 (2C, CH_2); 111.65, 126.92, 138.88, 147.32 (4C quart., aromat.); 121.94, 124.32, 126.10, 129.42 (4C tert., aromat.); 149.45 (C=O); 157.35 (C=O).

$C_{15}H_{15}N_3O_3S$ [317.37]

Calcd.	[%]	C 56.77	H 4.76	N 13.24	S 10.10
Found	[%]	C 56.37	H 4.85	N 13.10	S 9.97

3-(Dimethylamino)-2-thioxo-benzothieno[2,3-*e*][1,3]oxazine-4-one (**32e**)



Yield: 65%, white solid

M.p.: 183 °C

IR (KBr): 1280 cm^{-1} (C=S); 1708 cm^{-1} (C=O)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

2.97 (s, 6H, CH_3); 7.64-8.22 (m, 4H, aromat.).

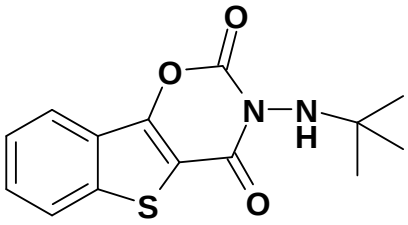
^{13}C-NMR (DMSO-*d6*): δ(ppm):

41.75 (CH_3); 113.78, 126.30, 139.20, 151.97 (4C quart., aromat.); 122.06, 124.38, 126.36, 129.87 (4C tert., aromat.); 155.00 (C=O); 181.35 (C=S).

$C_{12}H_{10}N_2O_2S_2$ [278.35]

Calcd.	[%]	C 51.78	H 3.62	N 10.06	S 23.04
Found	[%]	C 51.43	H 3.76	N 9.88	S 23.02

3-*tert*-Butylamino-benzothieno[2,3-*e*][1,3]oxazine-2,4-dione **(33)**



Yield: 67%, white solid

M.p.: 142 °C

IR (KBr): 1692, 1784 cm^{-1} (C=O); 3300 cm^{-1} (NH)

^{1}H-NMR (DMSO-*d6*): δ(ppm):

1.13 (s, 9H, *t*-Bu); 5.45 (s, 1H, NH); 7.63-8.21 (m, 4H, aromat.).

^{13}C-NMR (DMSO-*d6*): δ(ppm):

27.84 (C*(CH$_3$)$_3$*); 56.89 (*C*(CH$_3$)$_3$); 110.83, 126.98, 138.98, 149.17 (4C quart., aromat.); 122.03, 124.29, 126.07, 129.46 (4C tert., aromat.); 149.31 (C=O); 158.17 (C=O).

$C_{14}H_{14}N_2O_3S$ [290.34]

Calcd.	[%]	C 57.92	H 4.86	N 9.65	S 11.04
Found	[%]	C 57.24	H 4.92	N 9.37	S 11.01

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Hazard Information

Concerning the toxological characteristics of the compounds synthesized within the scope of this thesis, no information are available. Hence, hazardous properties cannot be excluded.
These chemicals should therefore be regarded as hazardous substances and treated with the appropriate caution.
Toxicological properties of the solvents and the chemicals employed within the course of this project are summarized in the tables below.

Solvents	Category of danger	Safety phrases
Acetone	F, Xi	S 9-16-26
Dichloromethane	Xn	S 23.2-24/25-36/37
Diethyl ether	F^+, Xn	S 9-16-29-33
N,*N*-Dimethylformamide	T	S 53.1-45
Ethanol	F	S 7-16
Ethyl acetate	F, Xn	S 16-26-33
n-Hexane	F, Xn, N	S 9-16-29-33-36/37-61-62
Methanol	F, T	S 7-16-36/37-45
Tetrahydrofuran	F, Xn	S 16-29-33
Toluene	F, Xn	S 16-25-29-33

Chemicals	Category of danger	Safety phrases
Acetic anhydride	C	S 26-36/37/39-45
2-Amino 5-chlorobenzoic acid	Xi	S 26-36/37/38
N-Aminomorpholine	Xi	S 36/37/38
N-Aminopipyridine	Xi	S 10-36/37/38
Ammonia	T	S7/9-16-38
Benzoyl chloride	C	S 26-45/34
Benzylamine	C	S 26
2-Bromo-1,1-dimethoxy-ethane	Xn	S 26-36/39

tert-Butylhydrazine hydrochloride	Xi	S 36/37/38
1,1`-Carbonyldiimidazole	Xn	S 22-36/37/38
Chloroacetic acid	T, N	S 23-37-45-61
4-Chloro 2-nitrobenzoic acid	Xi	S 26-36/37/38
1,8-Diazabicyclo[5.4.0]-undec-7-en	C	S 26-36/37/39-45
N,*N*-Dimethylhydrazine	F, T, N	S 53.1-45-61
Hydrazine hydrate	T, N	S 23/24/25-34-43-50/53
Hydrochloric acid	C	S 26-36/37/39-45
Lithium hydroxide	C	S 35
Methoxyamine hydrochloride	Xn	S 26-36/37/39-45
Methylhydrazine	F, T	S 53-16-24/25-45
Methyl thioglycolate	Xi	S 26-36/37
2-Nitrobenzoic acid	Xi	S 26-36/37/38
Potassium ethyl xanthate	Xi	S 26-36
Sodium hydride	F, Xi	S 24/25-26-43.11-7/8
Sodium hydroxide	C	S 26-37/39-45
Sodium methoxide	C, F	S 3-16-26-29-36/37-45
Sodium nitrite	N, O, T	S 45-61
Sulphuric acid	C	S 26-30-45
1,1`-Thiocarbonyl-diimidazole	-	S 22-24/25
Thionyl chloride	C	S 26-36/37/39-45
Thiosalicylic acid	Xi	-
p-Toluenesulfonic acid	Xi	36/37/38
Triethylamine	C, F	S 3-16-26-29-36/37-45
Trifluroacetic acid	C	S 20-35-52/53

Curriculum Vitae

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