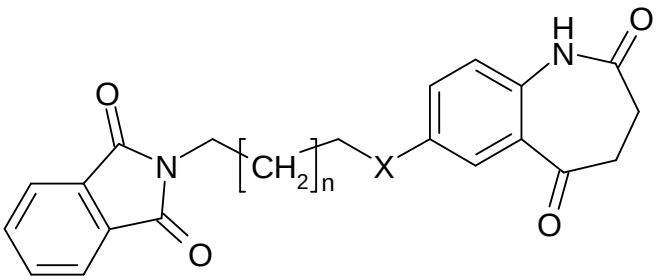
Summary

Protein kinases represent a family of enzymes which regulate fundamental cellular processes such as growth, differentiation, proliferation, motility and apoptosis. In this regard kinases constitute potential targets in tumor therapy. Based on lead structure **19**, a multiple protein kinase inhibitor, compounds were synthesized and provided for biological testing on 16 protein kinases.

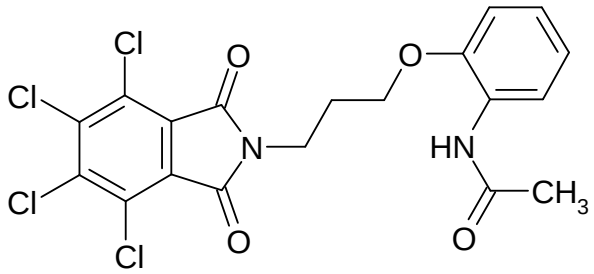


19	n = 1	X = CH_2
20a	n = 1	X = O
20b	n = 2	X = O

With a view to analyze structure-activity-relationships structural modifications in different parts of lead structure **19** were accomplished.

- Insertion of an ether-oxygen into the alkyl chain
- Lengthening or shortening of the alkyl chain
- Substitution of the phthalimide structure by succinimide, o-benzoic sulfimide, 4-aminophthalimide or 3,4,5,6-tetrachlorophthalimide
- Preparation of 7-alkyl- and 7-(2-phenylethyl)-substituted benzazepin-dione derivatives
- "Opening" of the azepindione structure: synthesis of *N*-(2-, 3- and 4-alkoxyphenyl)acetamide compounds as well as *N*-(4-alkoxyphenyl)-propanamide and *N*-(4-alkoxyphenyl)benzamide derivatives

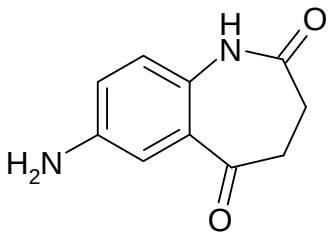
With respect to the protein kinases IGF1-R, VEGFR2 and especially SRC substance **111a** was found to be 7–30 fold more active than lead structure **19**. These enzymes are involved in the regulation of proliferation, angiogenesis and metastasis in tumors. Therefore **111a** represents a potent multiple protein kinase inhibitor. Furthermore the ether derivatives **20a** and **20b** exhibit higher inhibitory activities than **19**. They display a similar selectivity profile as compound **111a**.



111a

Altogether we found that 3,4,5,6-tetrachlorophthalimide substituted compounds as well as structure modifications of **19** containing an inserted ether oxygen are the most potent protein kinase inhibitors synthesized within the scope of this thesis. The *in vitro* antitumor activity of an assortment of compounds is presently under investigation at the National Cancer Institute.

Another compound (**33a**) synthesized within the scope of this thesis exhibited inhibitory activity against γ-Secretase, an enzyme that plays a major role in the development of "extracellular amyloid plaques", morphological hallmarks in the brains of Alzheimer patients.



33a