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CA 2474322 A1 2003/07/31

(21) 2 474 322

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2003/01/27
(87) Date publication PCT/PCT Publication Date: 2003/07/31
(85) Entrée phase nationale/National Entry: 2004/07/23
(86) N° demande PCT/PCT Application No.: EP 2003/000810
(87) N° publication PCT/PCT Publication No.: 2003/062215
(30) Priorités/Priorities: 2002/01/25 (10/057,747) US;
2002/01/25 (02075367.9) EP

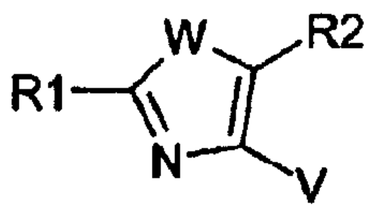
(51) Cl.Int.^{7}/Int.Cl.^{7} C07D 277/38, A61K 31/425, A61K 31/42, A61P 35/04, C07D 413/12, C07D 413/14, C07D 263/48, C07D 413/04

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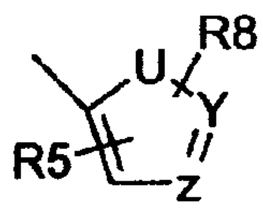
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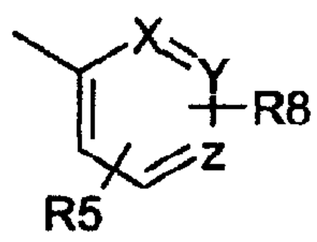
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(54) Titre : (THIA-/OXA-/PYRA) ZOLES SUBSTITUES 4(HETERO-) ARYLE POUR INHIBITION DE TIE-2
(54) Title: 4(HETERO-) ARYL SUBSTITUTED (THIA-/OXA-/PYRA) ZOLES FOR INHIBITION OF TIE-2



(I)





(57) Abrégé/Abstract:
The inventione relates to a compound of formula (I), wherein V is H or, or, R_1 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, N-R_6R_7, N- (CO) R_6R_7, N-R_6 (CO) R_7 or N- (CO) -O-R_6R_7 , R_8 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, N-R_3R_4, N- (CO) R_3R_4, N-R_3 (CO) R_4, N- (CO) -O-R_3R_4, O-R_3, CO-R_3, CO-OR_3 or O-CO-R_3, R_2, R_5, can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, carboxyl, Br, C1, F, CF_3, R_3, R_4, R_6, R_7 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, COOR_5 and CO-R_5, and may form a ring structure, X, Y, Z can be independently CH or N, and U can be independently S or NH, W can be independently NH, O or S, and racemic-diastereomeric mixtures, optical isomers, and pharmaceutically acceptable salts thereof, to a method of inhibiting the activity of one or more protein kinases by using these compounds in vitro or in cell culture, and to a pharmaceutical composition comprising such a compound and to their use as a medicament.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 July 2003 (31.07.2003)

PCT

(10) International Publication Number
WO 03/062215 A1

(51) International Patent Classification[7]: C07D 277/38, 263/48, 413/04, 413/12, 413/14, A61K 31/42, 31/425, A61P 35/04

(21) International Application Number: PCT/EP03/00810

(22) International Filing Date: 27 January 2003 (27.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

02075367.9	25 January 2002 (25.01.2002)	EP
10/057,747	25 January 2002 (25.01.2002)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

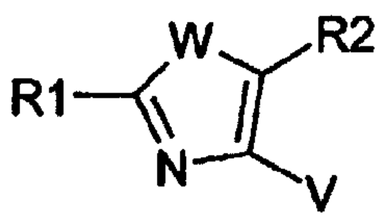
Published:

— *with international search report*

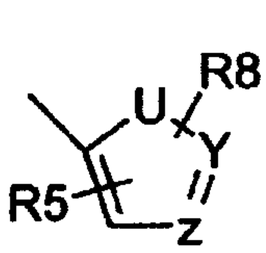
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

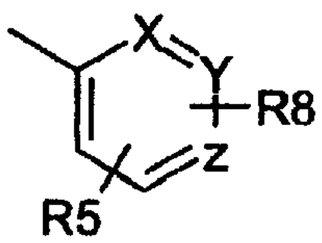
[Continued on next page]

(54) Title: 4(HETERO-) ARYL SUBSTITUTED (THIA-/OXA-/PYRA) ZOLES FOR INHIBITION OF TIE-2



(I)





(57) Abstract: The inventione relates to a compound of formula (I), wherein V is H or, or, R_1 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, N-R_6R_7, N- (CO) R_6R_7, N-R_6 (CO) R_7 or N- (CO) -O-R_6R_7 , R_8 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, N-R_3R_4, N- (CO) R_3R_4, N-R_3 (CO) R_4, N- (CO) -O-R_3R_4, O-R_3, CO-R_3, CO-OR_3 or O-CO-R_3, R_2, R_5, can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, carboxyl, Br, C1, F, CF_3, R_3, R_4, R_6, R_7 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, $COOR_5$ and CO-R_5, and may form a ring structure, X, Y, Z can be independently CH or N, and U can be independently S or NH, W can be independently NH, O or S, and racemic-diastereomeric mixtures, optical isomers, and pharmaceutically acceptable salts thereof, to a method of inhibiting the activity of one or more protein kinases by using these compounds in vitro or in cell culture, and to a pharmaceutical composition comprising such a compound and to their use as a medicament.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

4(HETERO-)ARYL SUBSTITUTED (THIA-/OXA-/PYRA)ZOLES FOR INHIBITION OF TIE-2

The invention relates to a novel compound having Tie2 and KDR inhibiting activity, to a method of inhibiting the activity of one or more protein kinases by using the compound, to a pharmaceutical composition comprising such a compound, to the use of the compound as a medicament particular as an inhibitor of protein kinase activity most preferably as an protein kinase inhibitor of both Tie-2 and KDR, accordingly an eminent use for the inhibition of the progression of a disease state in a patient, preferably cancer, venous malformations and angiogenesis dependent disorders.

Angiogenesis is a multistep process for the formation of new blood vessels from existing vasculature that normally occurs only during embryonic development, breast lactation, endometrail regulation and wound repair. During angiogenesis endothelial cells release enzymes that degrade the basement membrane, migrate through the membrane to form a sprout, and proliferate to extend the vessel (for review see Carmeliet and Jain, 2000).

All of these processes are strictly regulated by factors that either induce or inhibit angiogenesis. When the production and action of these factors is unbalanced, angiogenic factors can be released from tumor cells, migrate to the nearby endothelial cells and induce an angiogenic response cascade. This process is required for the growth of tumors beyond a certain size since they undergo

neovascularization and enter a phase of rapid cell growth that may lead to metastasis. Without neovascularizaion tumors enter necrotic and/or apoptotic processes. Increasing vessel density correlates with the likelihood that a patient would develop a metastastic disease (Weidner et al., 1991). This finding illustrates the important role of angiogenesis in cancer.

A number of growth factors are involved in vascular development (reviewed in Yancopoulos et al., 2000). They include at least five members of the vascular endothelium growth factor (VEGF) family, at least four members of the angiopoietin (Ang) family, and at least one member of the large ephrin family. To form functional vessels all of these factors have to act in a coordinated manner. VEGF can initiate vessel formation in adult animals, and Ang-1 further stabilizes and protects the adult vasculature.

Their corresponding receptors are exclusively members of the receptor tyrosine kinase (RTK) family of protein kinases. They are membrane-spanning proteins with an extracellular domain responsible for ligand binding, and a well conserved cytoplasmic tyrosine kinase domain. Signal transduction from the outer to the inner side of the cell is facilitated by a conformational change of the receptor after ligand binding, followed by dimerization and autophosphorylation of the receptor. Autophosphorylation of tyrosines in the activation loop of the tyrosine kinase (TK) domain leads to stimulation of catlytic activity, while autophosphorylation of other tyrosines generates binding sites for proteins with either SH2 or PTB domains. Engagement of these downstream effectors with this autophosphorylation leads to phosphorylation by the receptor which is the starting point for triggering a

cascade of downstream signalling events (reviewed in Hubbard, 1999).

The receptors that respond to VEGFs form a family of three closely related RTKs termed VEGFR-1 (Flt-1), VEGFR-2 (KDR or Flk-1) and VEGFR-3 (Flt-4) (reviewed in Tallquist et al., 1999). Their extracellular portion all contain seven immunglobulin-like (Ig) domains and a split intracellular kinase domain. While the major growth and permeability actions of VEGF are mediated by VEGFR-2, growth factor signalling is suppressed by VEGFR-1 because it probably acts as a decoy receptor. Mice lacking VEGFR-2 die between day 8.5 and 9.5 during embryogenesis due to very few enothelial cells and failure to develop a vasculature. Mice lacking VEGFR-1 form excess endothelial cells and disorganized blood vessels also die between E8.5 and E9.5. VEGFR-3 knockout embryos show a cardiovascular failure between E10 and E12 from defects in remodeling the primary vessel networks into larger blood vessels. VEGFR-3 seems to play a role in lymphangiogenesis since its expression is critical for lymphatic vessels (Valtola et al., 1999).

Another group of angiogenic receptors is formed by the two closely related RTKs, Tie-1 (Partanen et al., 1992) and Tie-2 (Ziegler et al., 1993). These are proteins of approximately 125 kD with a single putative transmembrane region. The extracellular domain contains at least three epidermal growth factor (EGF)-like regions of cystein expression, at least two immunglobulin G (IgG)-like domains and at least three regions with fibronectin III-like repeats. The intracellular portion of Tie-2 contains a tyrosine kinase domain with about 40 % sequence identity to that of FGFR-1, PDGFR and c-Kit with the typical motifs for

ATP binding (GXGXXG) and tyrosine phosphorylation (HRDLAARN and DFGL).

The Tie receptors are specifically expressed in developing vascular endothelial cells. Embryos deficient in Tie-1 fail to establish structural integrity of vascular endothelial cells, resulting in oedema and subsequently localized haemorrhage. However, analyses of embryos deficient in Tie-2 showed that it is important in angiogenesis, particularly for vascular network formation in endothelial cells, indicating that the structurally related receptor tyrosine kinases Tie-1 and Tie-2 have important but distinct roles in the formation of blood vessels (Dumont et al., 1994; Korhonen et al., 1994; Puri et al., 1995; Sato et al., 1995).

Two ligands for the Tie-2 receptor have been reported. While Angiopoietin-1 (Ang-1) binds and induces the tyrosine phosphorylation of Tie-2, it does not directly promote the growth of cultured endothelial cells but is essential for normal vascular development in the mouse (Davis et al., 1996). Mice engineered to lack Angiopoietin-1 display angiogenic deficits reminiscent of those previously seen in mice lacking Tie-2, demonstrating that Angiopoietin-1 is a primary physiologic ligand for Tie-2 and that it has critical in vivo angiogenic actions that are distinct from VEGF (Suri et al., 1996). Transgenic overexpression of Ang-1 in the skin of mice produces larger, more numerous, and more highly branched vessels (Suri et al., 1998). This finding supports a more direct role of Ang-1 in angiogenesis and vascular remodelling.

Angiopoietin-2 (Ang-2) was identified by homology screening and showed to be a naturally occurring antagonist for Ang-1 and Tie-2. Therefore, transgenic overexpression of

Ang-2 disrupts blood vessel formation in the mouse embryo. In adult mice and humans, Ang-2 is expressed only at sites of vascular remodeling (Maisonpierre et al., 1997).

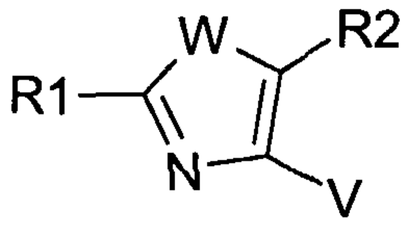
Interestingly, mice embryos knocked out for VEGFR-2 (Flk-1) show lethal defects in vasculogenesis that are earlier than a corresponding disruption of Tie-2. This and the other findings described above indicate that the VEGF/VEGFR signalling system seems to be necessary for the early stages of vascular development, while the Ang-1/Tie-2 system is required for the later stages of vascular remodeling.

These results raise the possibility that angiopoietins can be used, alone or in combination with VEGF, to promote therapeutic angiogenesis. On the other hand, blocking or moderating of the Tie receptor system may block or moderate angiogenesis and further proliferation of tumor cells. By in situ hybridization only a weak Tie-1 mRNA signal was obtained from adult skin, except during wound healing, when the proliferating capillaries in the granulation tissue contained abundant Tie RNA (Korhonen et al., 1992). However, capillaries and medium-sized vessels within cutaneous and brain metastases of melanoma were strongly positive for Tie mRNA. A Tie-specific amplified cDNA band was obtained by RT-PCR from melanoma metastases but not from normal skin. These results suggest a role for the Tie receptor system in angiogenesis associated with melanoma metastases (Kaipainen et al., 1994).

Administration of Ad-ExTek, a soluble adenoviral expressed extracellular domain of Tie-2, inhibited tumor metastasis when delivered at the time of surgical excision of primary tumors in a clinically relevant mouse model of tumor metastasis (Lin et al., 1998). The inhibition of Tie-2

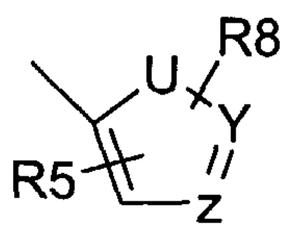
function by ExTek may be a consequence of sequestration of the angiopoietin ligand and/or heterodimerisation with the native Tie-2 receptor. This study demonstrates that disruption of Tie-2 signalling pathways, first, may be well tolerated in healthy organisms and, second, may provide therapeutic benefit.

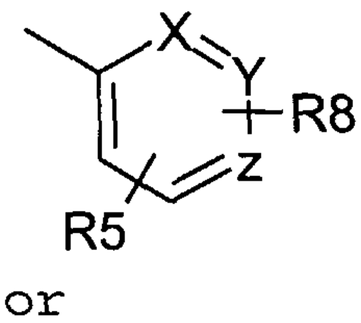
Summary of the invention



(I)

wherein V is H or





R5

or

R_1 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, N-R_6R_7, N-(CO)R_6R_7, N-R_6(CO)R_7 or N-(CO)-O-R_6R_7,

R_8 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, N-R_3R_4, N-(CO)R_3R_4, N-R_3(CO)R_4, N-(CO)-O-R_3R_4, O-R_3, CO-R_3, CO-OR_3 or O-CO-R_3,

R_2, R_5, can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, carboxyl, Br, C1, F, CF_3,

R_3, R_4, R_6, R_7 can be independently H, alkyl, alkenyl, cycloalkyl, heteroalkyl, aryl, heteroaryl, arylalkyl, alkylaryl, COOR_5 and CO-R_5, and may form a ring

structure,

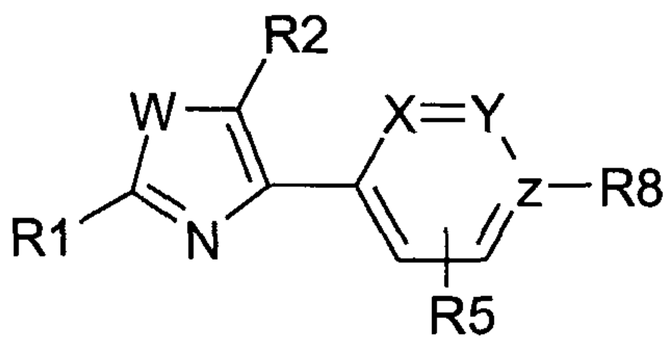
X, Y, Z can be independently CH or N, and

U can be independently S or NH,

W can be independently NH, O or S, and

racemic-diastereomeric mixtures, optical isomers, and pharmaceutically acceptable salts thereof.

In a prefered embodiment the invention relates to a compound according to formula II,



(II)

wherein W is S,

R_1 is N-R_6R_7,

R_6 is H,

R_7 is a substituted or unsubstituted alkyl, cycloalkyl, phenyl, arylalkyl, naphtyl, heteroaryl or heterocycloalkyl.

X and Y are CH or N,

Z is C,

R_8 is an amine group or a mono-substituted or di-substituted alkylamine, alkylene-amine or cycloalkylamine or heterocycloalkylamine, which (cyclo)alkylamine may be substituted with an alkyl, cycloalkyl, hydroxyl, halogen, pyridinyl or alkylpyridinyl group.

R_2 is hydrogen, heteroaryl, aralkyl or carboxylgroup, and

R_5 is hydrogen, hydroxyl, halogen or alkoxy group.

More prefered to a compound, wherein R_7 is:

- phenyl C_1-C_3 carboxylic acid, preferably para-carboxylic acid;
- 2-methyl- 5-fluorine phenyl;
- methoxy pyridinyl;
- halogen pyridinyl;
- isoquinolinyl;
- tri-methoxy phenyl;
- phenyl hydroxy-pyrrolidinyl
- phenyl piperazinyl
- phenyl n-methyl-piperazinyl
- napthenyl sulfonic acid
- ortho bromine phenyl and/or,

wherein R_8 is:

- alkylamine, preferably di-ethyl;
- hydroxypyrrolidinyl;
- methyl-butenylamine and or,

wherein R_2 is a carboxyl group or a tetrazole group. These compounds show best Tie-2 and KDR inhibiting activity.

The present invention provides a method of inhibiting or moderating the kinase activity of tyrosine kinases comprising the administration of a compound represented by formula (I) or (II) to said kinase in sufficient concentration to inhibit or moderate the enzyme activity of said kinase.

The present invention further provides the use of compounds in pharmaceutical compositions with a pharmaceutically acceptable carrier or excipient. These pharmaceutical compositions can be administered to individuals to slow or halt the process of angiogenesis in angiogenesis-aided diseases or cancer in general.

Definitions of the various terms

Listed below definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (useless they are otherwise limited in specific instances) either individually or as part of a larger group.

It should be noted that any heteroatom with unsatisfied valances is assumed to have the hydrogen-atom to satisfy the valances.

The term "alkyl" or "alk" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 20 carbon atoms unless otherwise defined. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. When substituted, alkyl groups may substituted with R at any available point of attachment. R is defined as R_1. When the alkyl group is said to be substituted with alkyl group this is used interchangeably with "branched alkyl group". Exemplary unsubstitute such groups may include but are not limited to methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. Exemplary substituents may include but are not limited to one or more of the following groups: halogen (such as F, Cl, Br, I), haloalkyl (such as CCl_3 and CF_3), alkoxy, alkylthio, hydroxy, carboxy (-COOH), alkyloxycarbonyl (-C(O)R), alkylcarbonyloxy (-OCOR), amino ($-NH_2$), alkylamino, dialkylamino, carbamoyl (-NHCOOR- or - OCONHR-), urea (-NHCONHR) or thiol (-SH). R is defined as R_6.

Alkyl groups as defined may also comprise one or more carbon to carbon double bonds or one or more carbon to carbon triple bonds.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 20 carbon atoms and at least one carbon to carbon double bond.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 20 carbon atoms and at least one carbon to carbon triple bond.

Cycloalkyl is a specie of alkyl containing from 3 to 15 carbon atoms, without alterning or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, etc. Exemplary substituents may include but are not limited to one or more of the following groups: halogen, alkyl, alkoxy, alkyl hydroxy, amino, alkylamino, dialkylamino, nitro, cyano, thiol and/or alkylthio.

Cycloalkenyl is a specie of alkenyl containing from 3 to 15 carbon atoms, without alterning or resonating double bonds between carbon atoms and at least one carbon to carbon double bond. It may contain from 1 to 4 rings. Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, etc. Exemplary substituents may include but are not limited to one or more of the following groups: halogen, alkyl, alkoxy, alkyl hydroxy, amino, alkylamino, dialkylamino, nitro, cyano, thiol and/or alkylthio.

Cycloalkynyl is a specie of alkyl containing from 3 to 15 carbon atoms, without alterning or resonating double bonds between carbon atoms and at least one carbon to carbon triple bond. It may contain from 1 to 4 rings. Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, etc. Exemplary substituents may include but are not limited to one or more of the following groups: halogen, alkyl, alkoxy, alkyl hydroxy, amino, alkylamino, dialkylamino, nitro, cyano, thiol and/or alkylthio.

The term "heterocycloalkyl" refers to a cycloalkyl group (nonaromatic) in which one to three of the carbon atoms in the ring are replaced by a heteroatom selected from O, S or N.

The term "heterocycloalkenyl" refers to a cycloalkenyl group (nonaromatic) in which one to three of the carbon atoms in the ring are replaced by a heteroatom selected from O, S or N.

The term "heterocycloalkynyl" refers to a cycloalkynyl group (nonaromatic) in which one to three of the carbon atoms in the ring are replaced by a heteroatom selected from O, S or N.

The term "aryl" refers to monocyclic, bicyclic, tricyclic or tetracyclic aromatic rings, e.g. phenyl, substituted phenyl and the like, as well as groups which are fused, e.g. naphtyl, substituted naphtyl, phenanthrenyl or substituted phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between

adjacent carbon atoms or suitable heteroatoms. Aryl groups may optionally be substituted with one or more groups including, but not limited to halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, nitro, trifluoromethyl, amino, NH-R_7, NR_6R_7, cycloalkyl, cyano, alkyl $S(O)_m$ (m = 0,1,2), SO_2-NR_6R_7, NR_6-SO_2-R_7, or thiol.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, a bicyclic aromatic group having 8 to 10 atoms, or a tricyclic aromatic group having 11 to 14 atoms containing at least one heteroatom, O, S, or N, in which a carbon or nitrogen atom is the point of attachment, and in which one to three additional carbon atoms is optionally replaced by a heteroatom selected from O, N, or S, said heteroaryl group being optionally substituted as described herein. Exemplary heteroaryl groups may include but are not limited to the following: thienyl, furyl, pyrrolyl, pyridinyl, imidazolyl, oxazolyl, pyrrolidinyl, piperidinyl, thiazolyl, pyrazinyl, pyridazinyl, pyrimidinal, triazinylazepinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzoxadiazolyl, benzofuranzanyl tetrahydropyranyl and the like. Exemplary substituents may include but are not limited to one or more of the following: halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, trifluoromethyl, cycloalkyl, nitro, cyano, amino, NH-R_7, NR_6R_7, alkyl-$S(O)_m$ (m = 0,1,2), or thiol and the like.

The term "arylalkyl", as used herein, denotes an aromatic ring bonded to an alkyl group as described above.

The term "alkylaryl", as used herein, denotes an alkyl group bonded to an aromatic ring as described above.

The terms "alkoxy" or "alkylthio", as used herein, denote an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "alkenyloxy" or "alkenylthio", as used herein, denote an alkenyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "alkynyloxy" or "alkynylthio", as used herein, denote an alkynyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively. The terms "alkynyloxy" or "alkynylthio", as used herein, denote an alkynyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "cycloalkoxy" or "cycloalkylthio", as used herein, denote an cycloalkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "cycloalkenyloxy" or "cycloalkenylthio", as used herein, denote a cycloalkenyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "cycloalkynyloxy" or "cycloalkynylthio", as used herein, denote a cycloalkynyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "heterocycloalkoxy" or "heterocycloalkylthio", as used herein, denote a heterocycloalkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "heterocycloalkenyloxy" or "heterocycloalkenylthio", as used herein, denote a heterocycloalkenyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "heterocycloalkynyloxy" or "heterocycloalkynylthio", as used herein, denote an heterocycloalkynyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "aryloxy" or "arylthio", as used herein, denote an aryl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "heteroalkyloxy" or "heteroalkylthio", as used herein, denote an heteroalkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "heteroalkenyloxy" or "heteroalkenylthio", as used herein, denote an heteroalkenyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "heteroalkynyloxy" or "heteroalkynylthio", as used herein, denote an heteroalkynyl group as described

above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "arylalkoxy" or "arylalkylthio", as used herein, denote an arylalkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "alkylaryloxy" or "alkylarylthio", as used herein, denote an alkylaryl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The terms "alkylamin" or "alkyloxycarbonyl", as used herein, denote an alkyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "alkenylamin" or "alkenyloxycarbonyl", as used herein, denote an alkenyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "alkynylamin" or "alkynyloxycarbonyl", as used herein, denote an alkynyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "cycloalkamin" or "cycloalkyloxycarbonyl", as used herein, denote an cycloalkyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "cycloalkenylamin" or "cycloalkenyloxycarbonyl", as used herein, denote a cycloalkenyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "cycloalkynylamin" or "cycloalkynyloxycarbonyl", as used herein, denote a cycloalkynyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "heterocycloalkamin" or "heterocycloalkyloxycarbonyl", as used herein, denote a heterocycloalkyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively, such as piperazinyl, morpholinyl, thiomorpholinyl

The terms "heterocycloalkenylamin" or "heterocycloalkenyloxycarbonyl", as used herein, denote a heterocycloalkenyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "heterocycloalkynylamin" or "heterocycloalkynyloxycarbonyl", as used herein, denote an heterocycloalkynyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "arylamin" or "arylloxycarbonyl", as used herein, denote an aryl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "heteroalkylamin" or "heteroalkylloxycarbonyl", as used herein, denote an heteroalkyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "heteroalkenylamin" or "heteroalkenylloxycarbonyl", as used herein, denote an heteroalkenyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "heteroalkynylamin" or "heteroalkynylloxycarbonyl", as used herein, denote an heteroalkynyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "arylalkamin" or "arylalkyloxycarbonyl", as used herein, denote an arylalkyl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The terms "alkylarylamin" or "alkylarylloxycarbonyl", as used herein, denote an alkylaryl group as described above bonded through an nitrogen linkage (-N-) or denotes an alkoxy group bonded through a carbonyl group, respectively.

The term "heteroatom" means O, S or N, selected on an independent basis.

The term "halogen" refers to chlorine, bromine, fluorine or iodine.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups of the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T.W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

Suitable examples of salts of the compounds according to the invention with inorganic or organic acids are hydrochloride, hydrobromide, hydrosulfate, sulfate, hydrophosphate, phosphate and the like. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds or their acceptable salts, are also included.

Suitable salts of carboxylic groups, if present, like sodium, potassium, lithium or magnesium or other pharmaceutically acceptable salts are also included.

All stereoisomers of the compounds of the instant invention are contemplated, either in a mixture or in pure or substantially pure form. The definition of the compounds according to the invention embraces all possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be dissolved by physical methods, such as, for example fractional crystallisation, separation or crystallisation of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by conventional methods, such

as, salt formation with an optically active acid followed by crystallisation.

It should be understood that solvates (e.g. hydrates) of the compounds of formula (I) and (II) are also within the scope of the present invention. Methods of solvation are generally known in the art. Accordingly, the compounds of the instant invention may be in the free or hydrate form, and may be obtained by methods exemplified.

Detailed Description of the Invention

The present invention relates to a new class of compounds that block or moderate kinase activity of tyrosine kinases

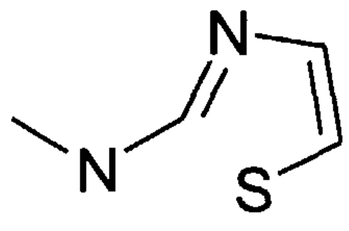
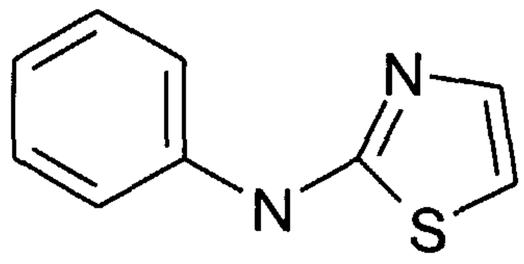
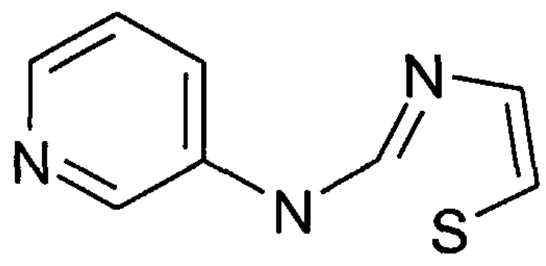
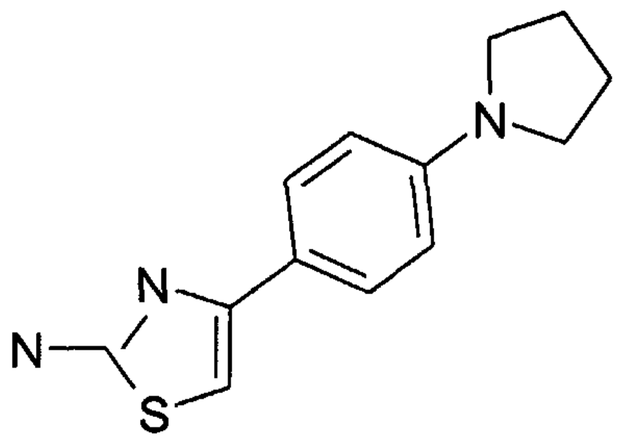
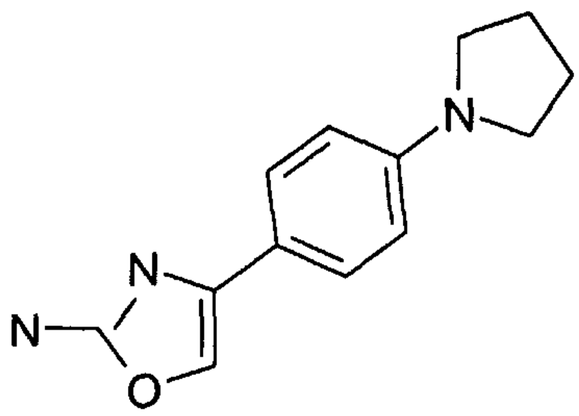
An embodiment of the invention relates to a new class of compounds that block or moderate kinase activity of the tyrosine kinase Tie-2 and KDR.

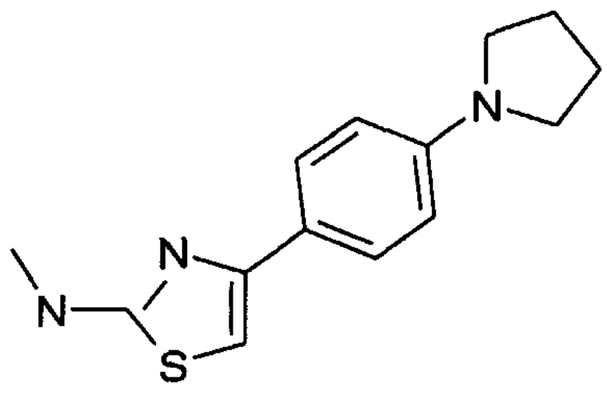
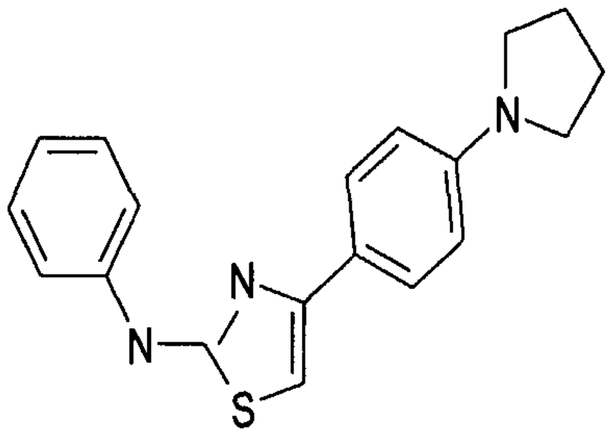
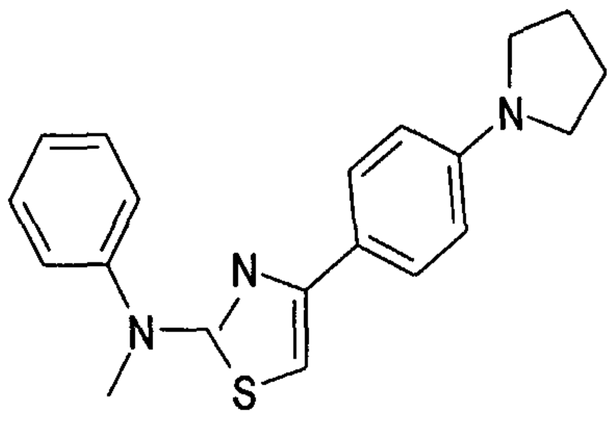
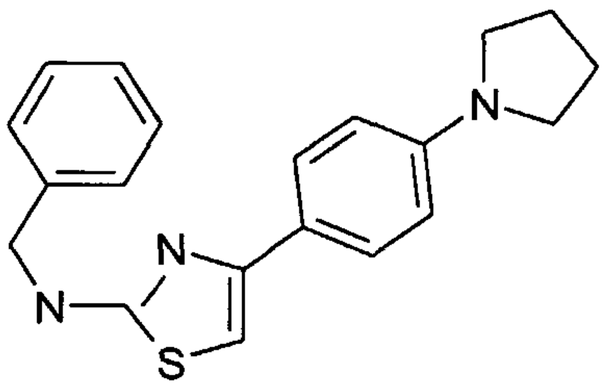
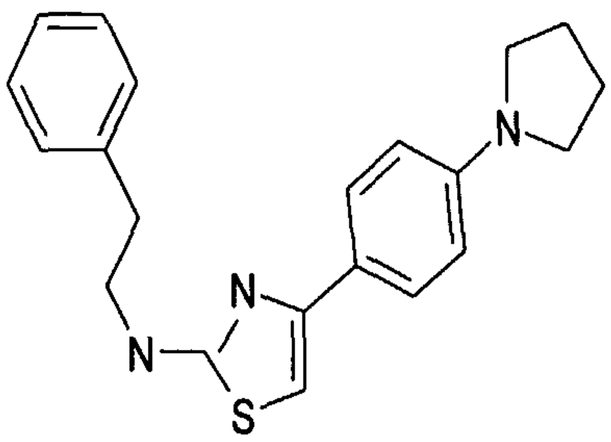
The simultaneous impairment of the VEGF/VEGF-R and of the Ang/Tie receptor systems is advantageous for cancer treatment. The improved effect can be attributed probably to the fact that the impairment of the Ang/Tie receptor system destabilizes the interaction between endothelial and periendothelial cells in the existing tumor blood vessels and thus sensitizes the endothelium for compounds which are directed against the VEGF/VEGF-R system.

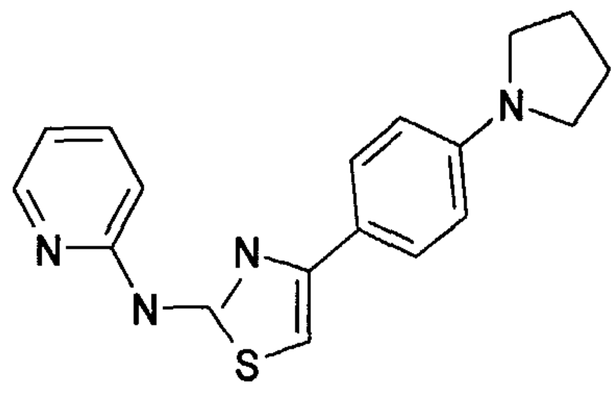
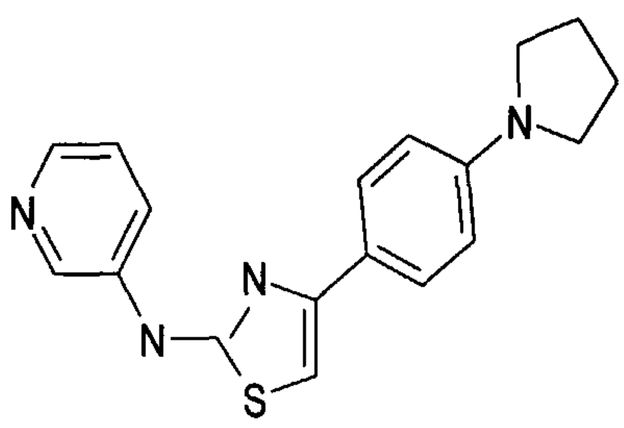
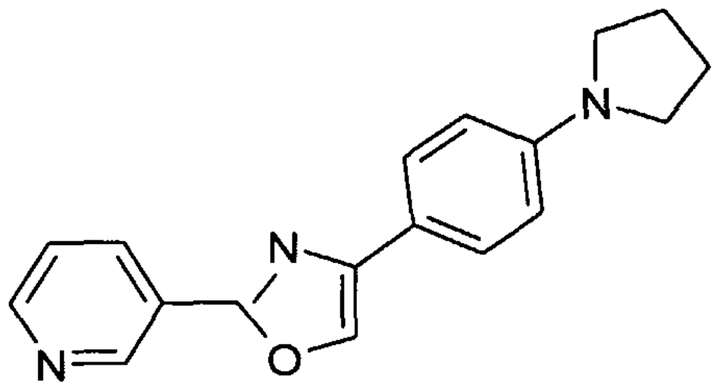
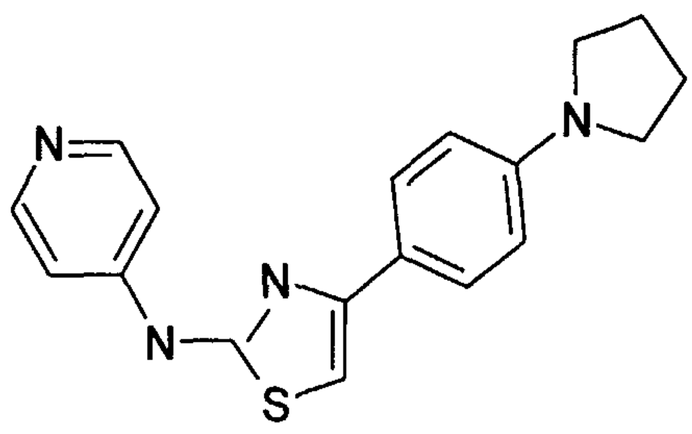
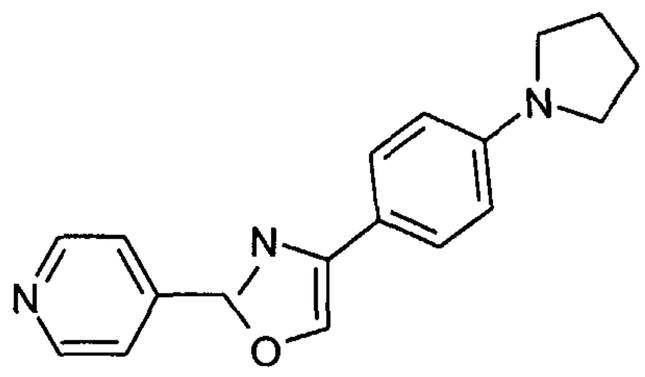
Follwing IC50 values were determined in the RTK ELISA using recombinant kinase domains of receptor tyrosine kinases which were expressed in baculovirus infected insect cells.

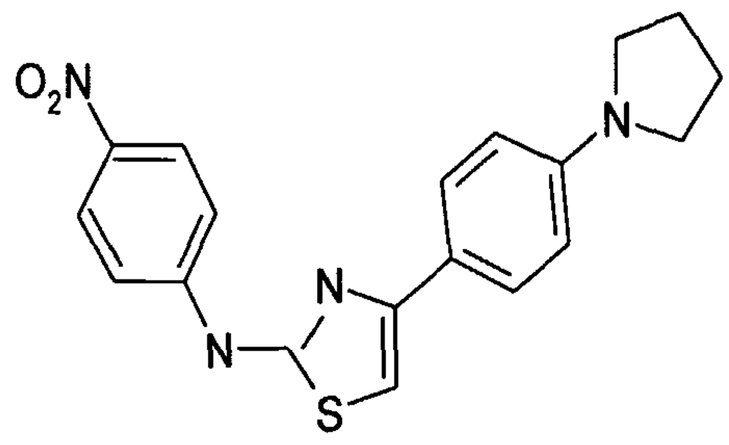
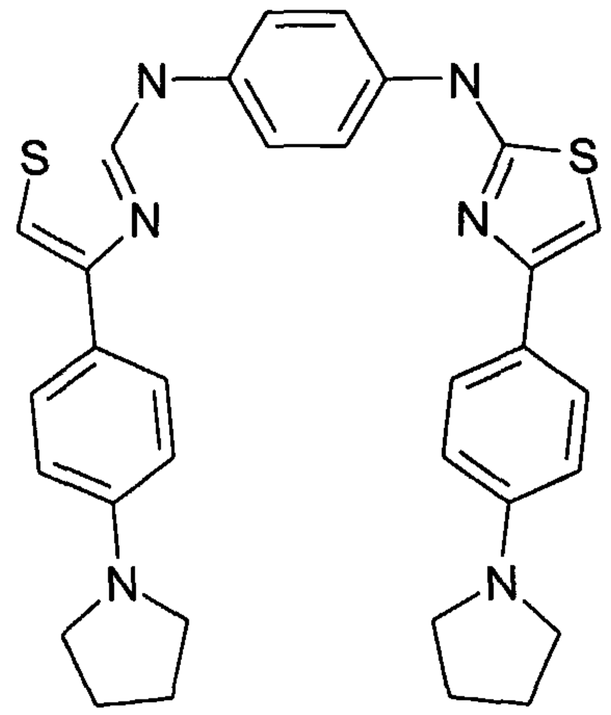
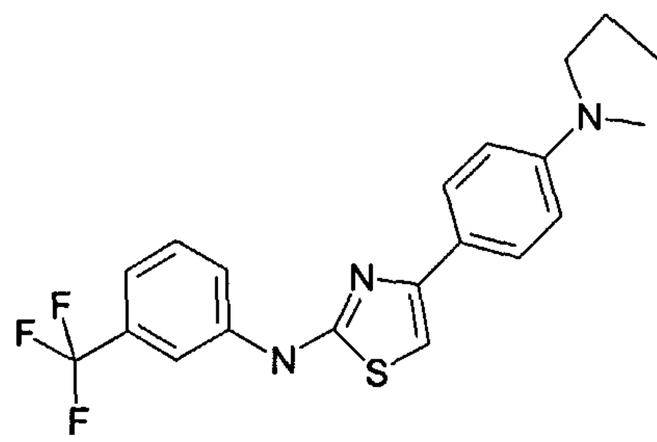
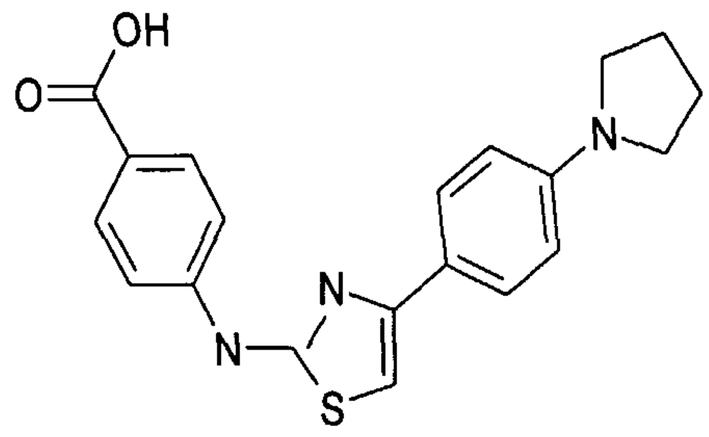
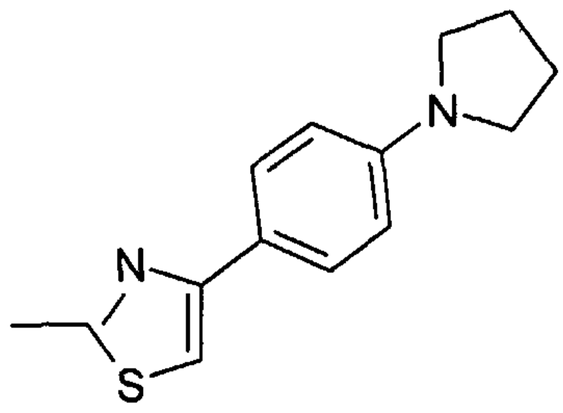
Compounds of the invention are comprised in the following listings including their kinase activity inhibiting activity.

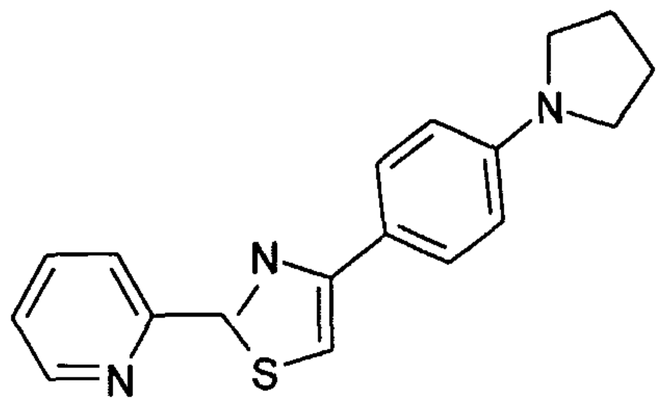
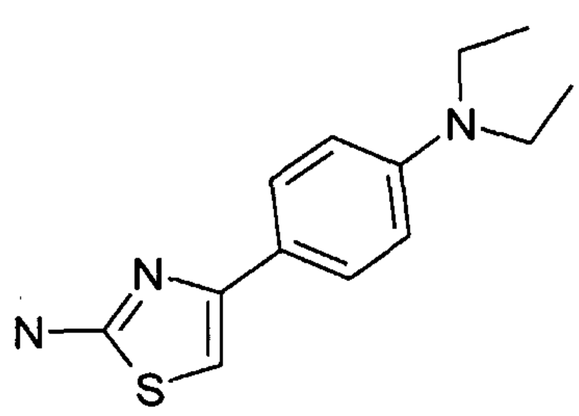
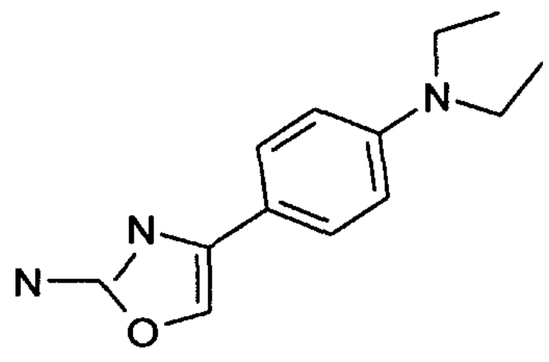
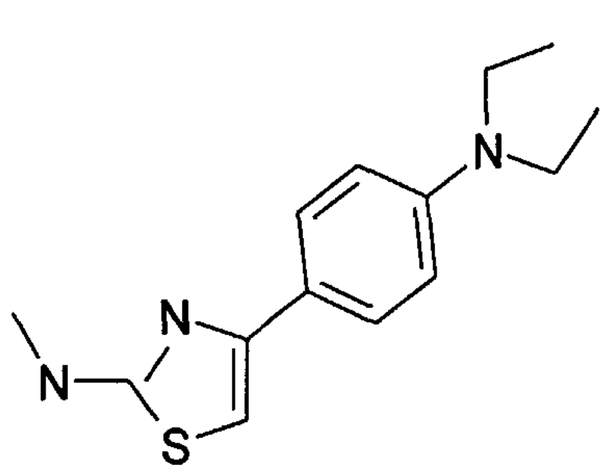
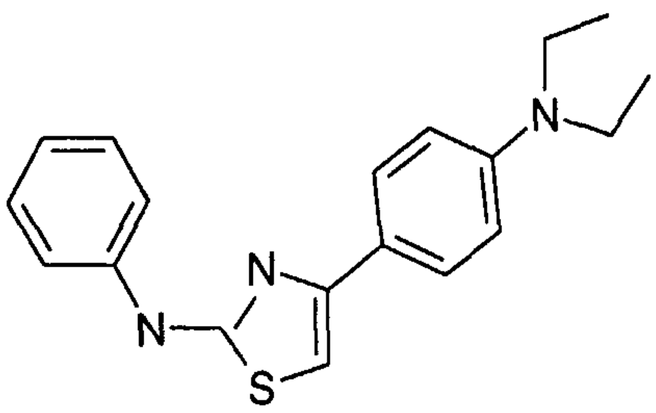
Number	Structure	IC50 [µM] Tie-2	KDR	c-Met

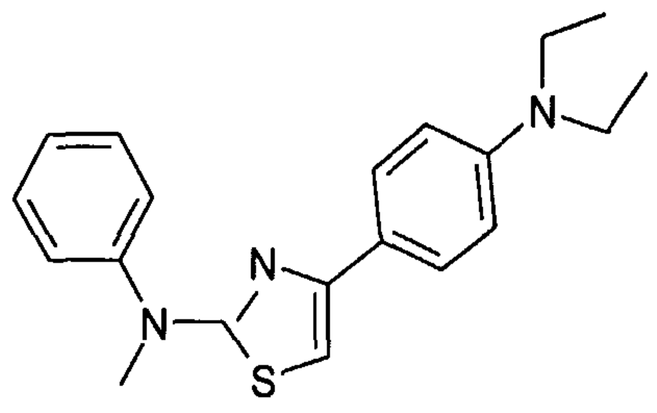
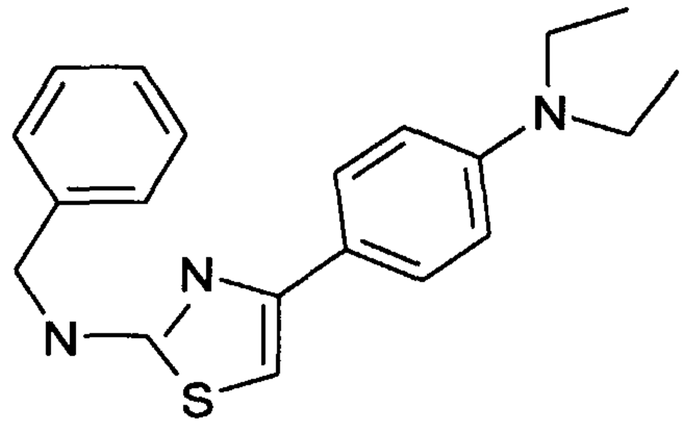
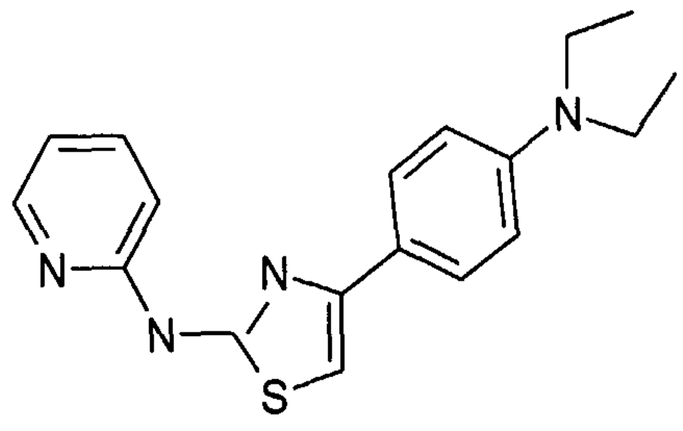
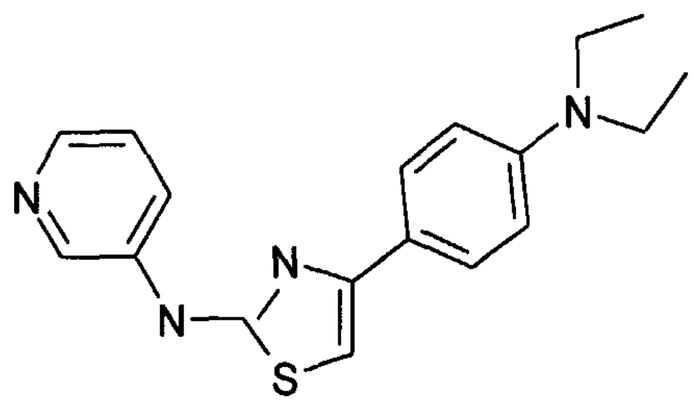
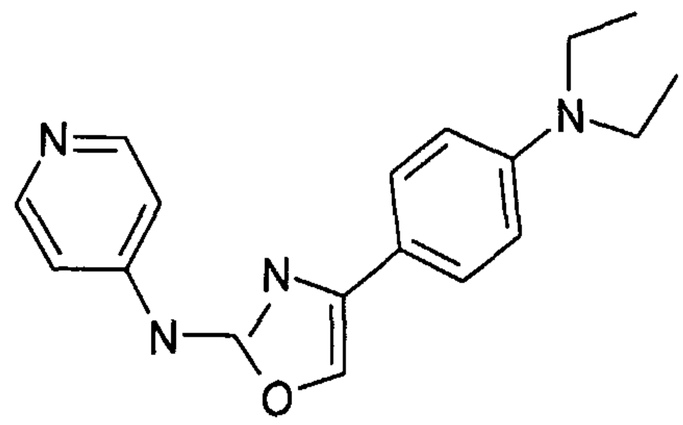
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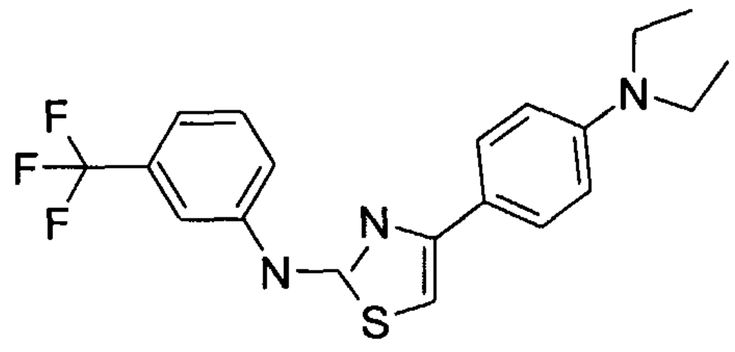
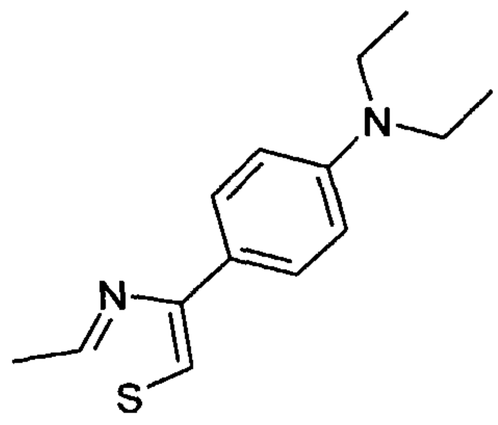
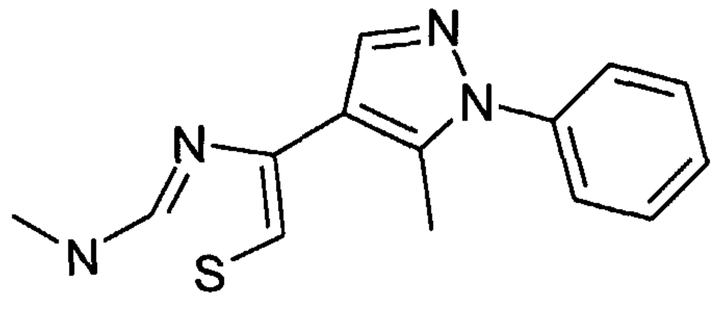
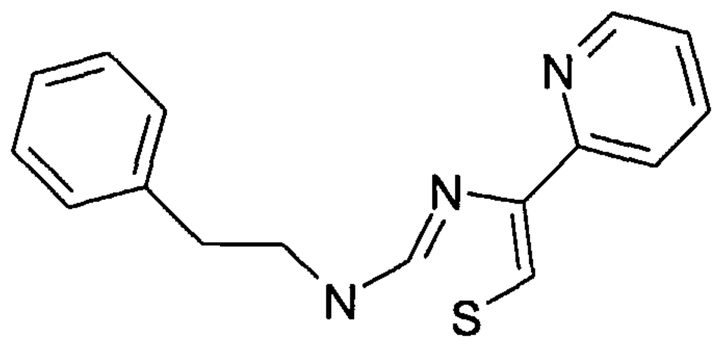
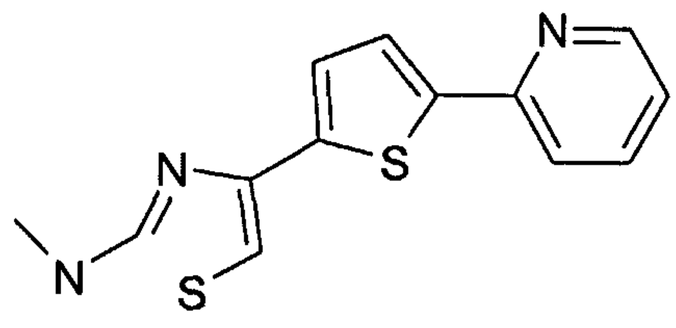
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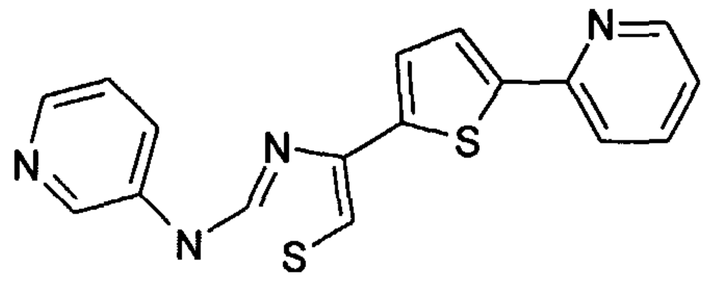
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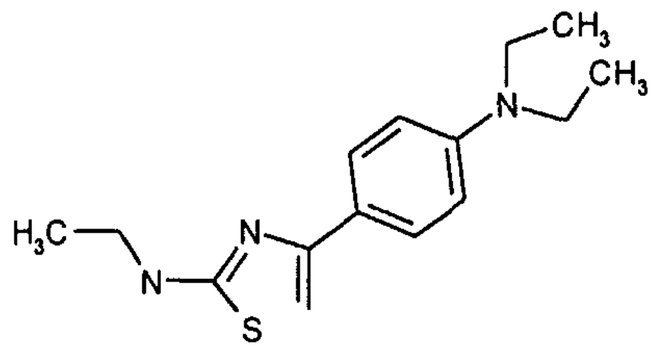
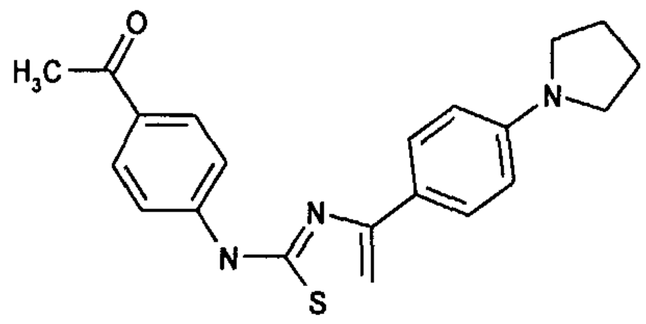
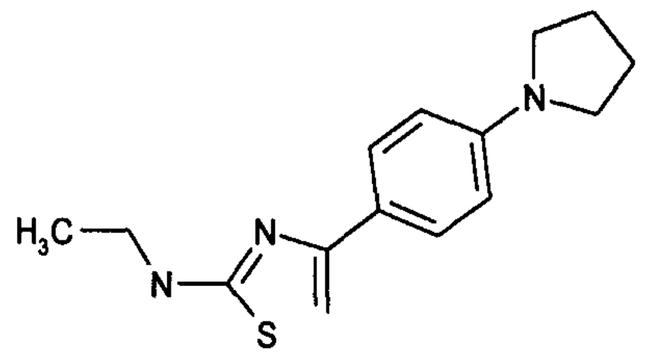
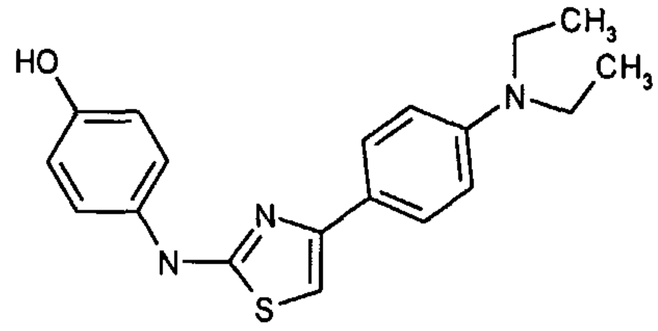
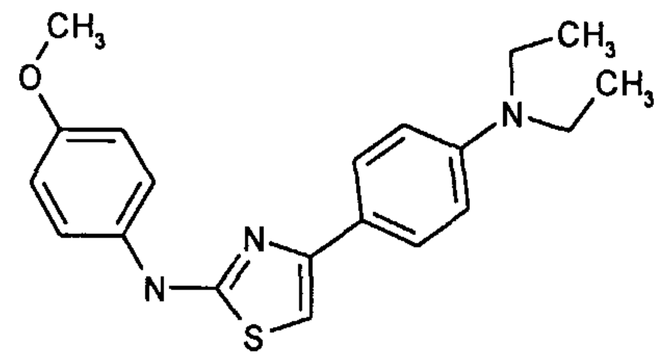
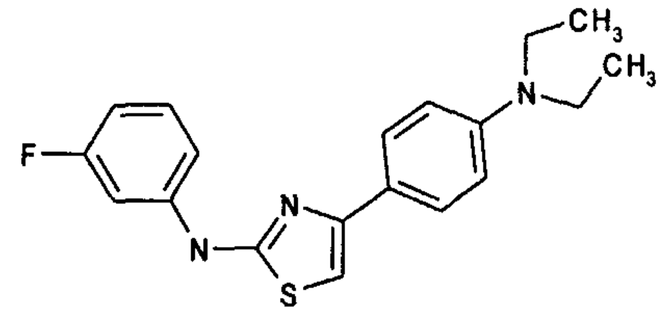
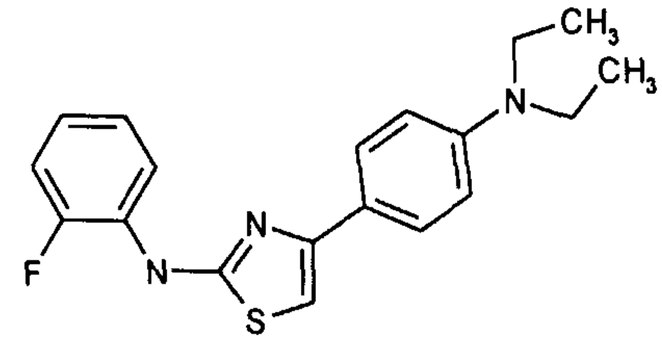
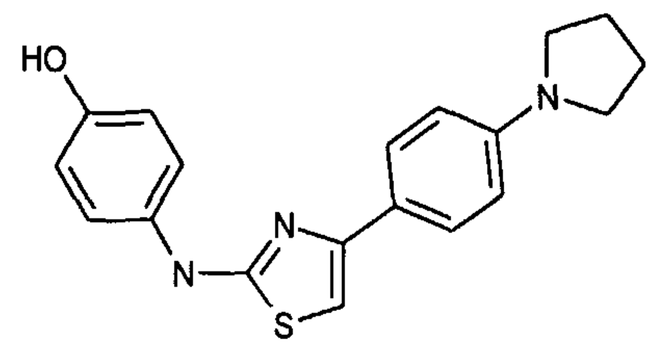
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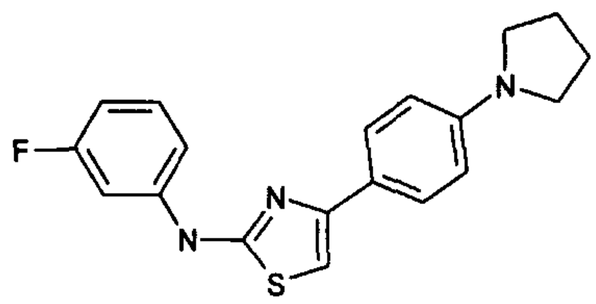
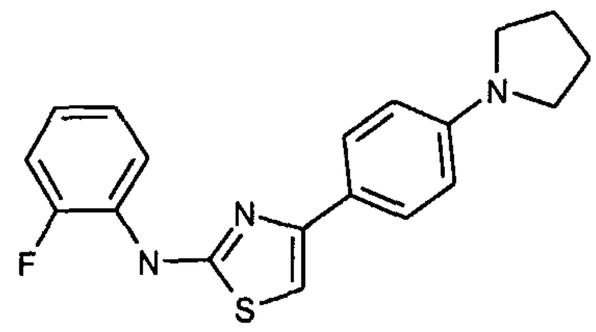
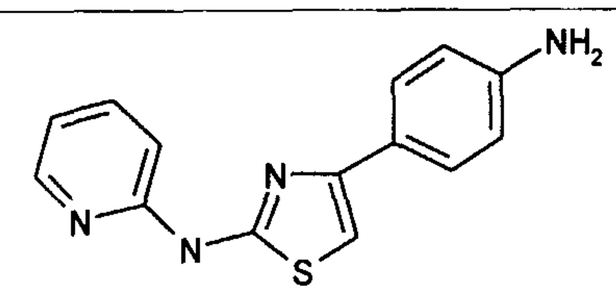
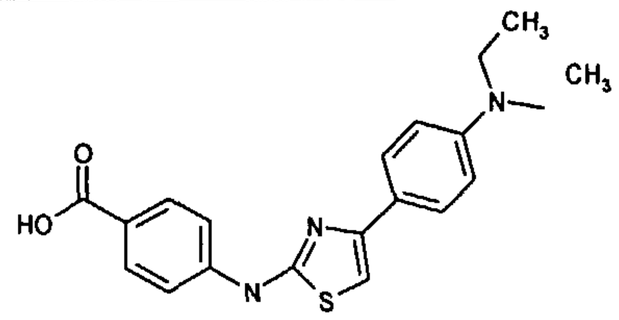
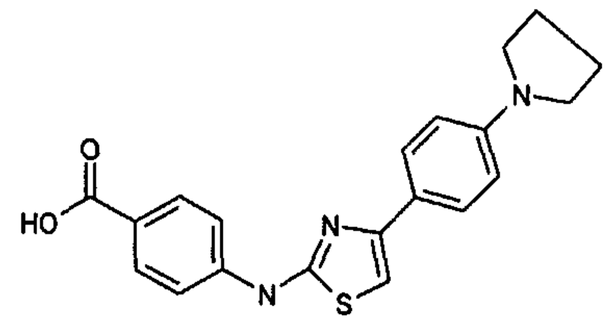
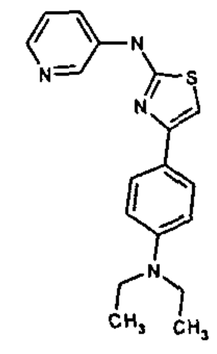
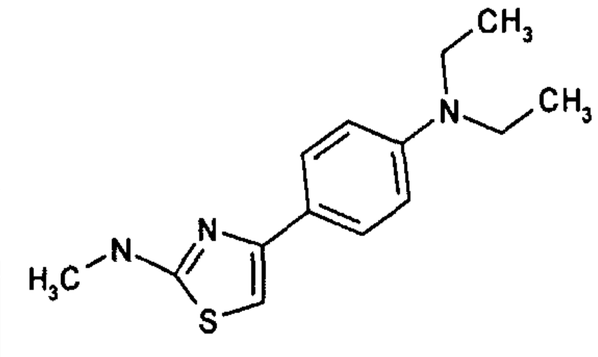
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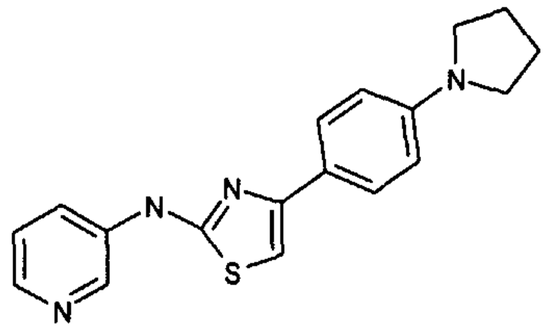
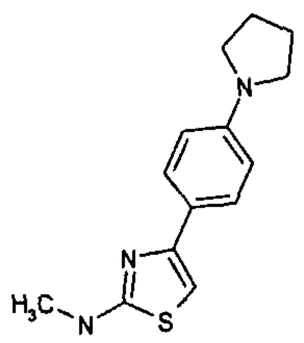
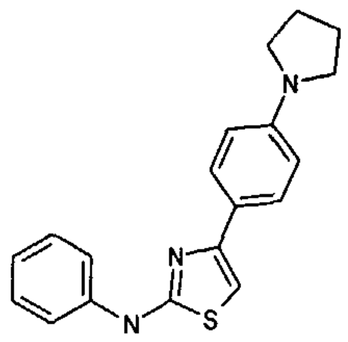
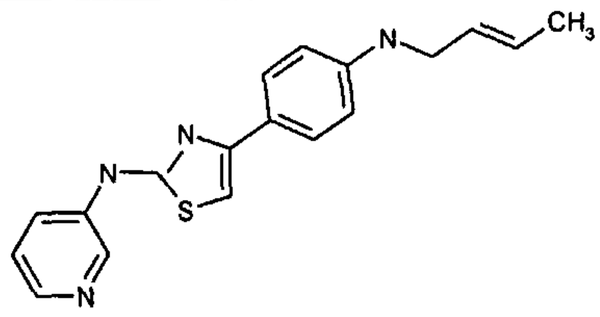
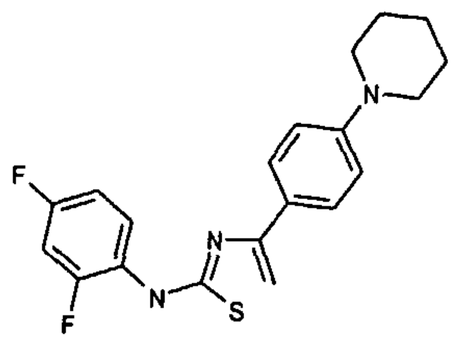
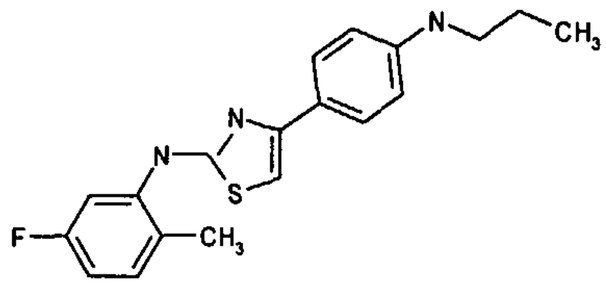
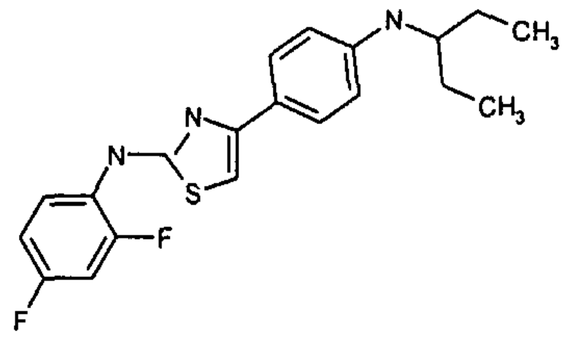
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31		>50	>25	>50

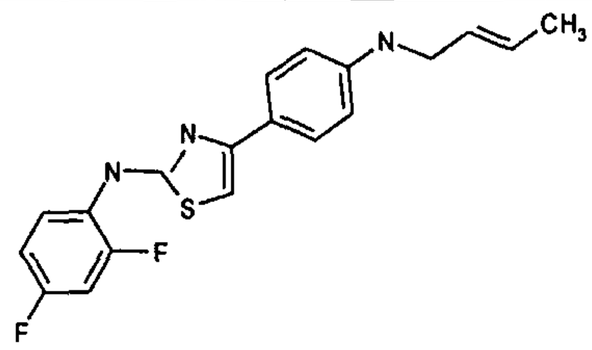
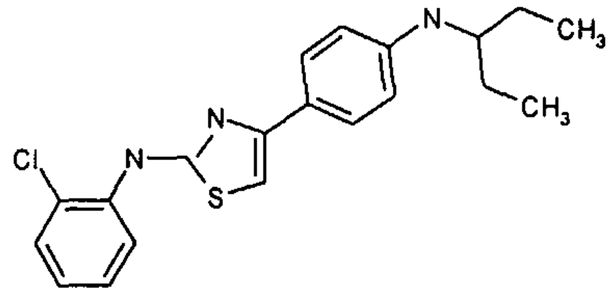
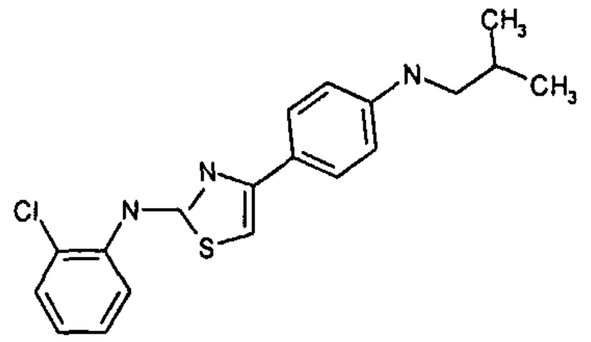
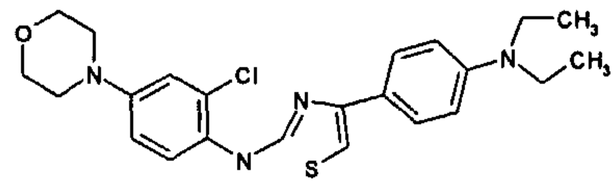
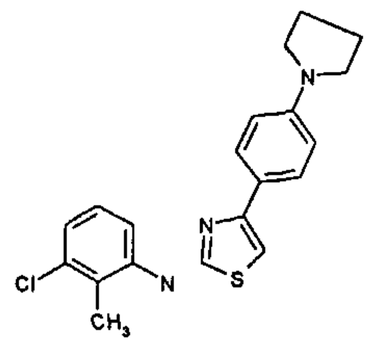
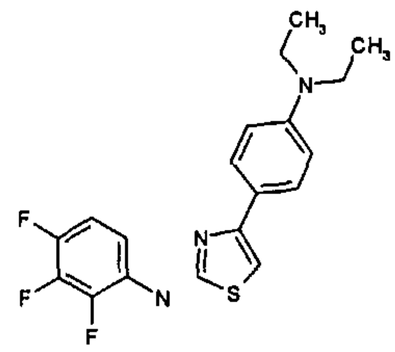
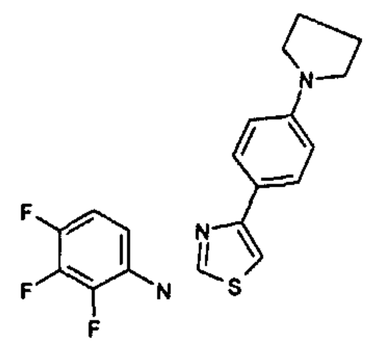
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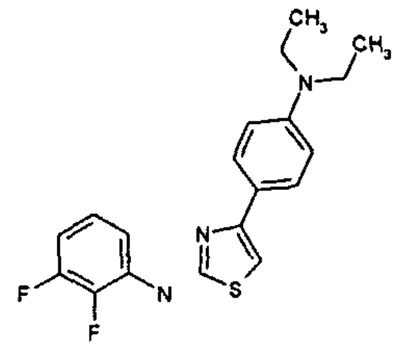
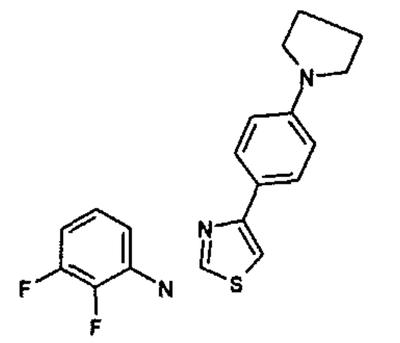
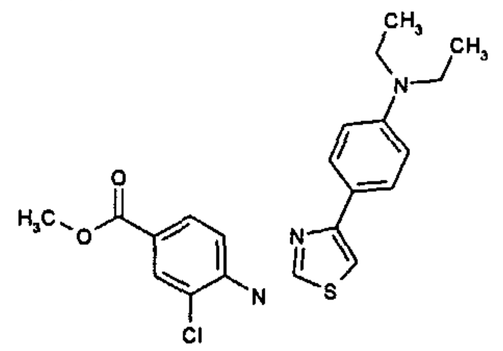
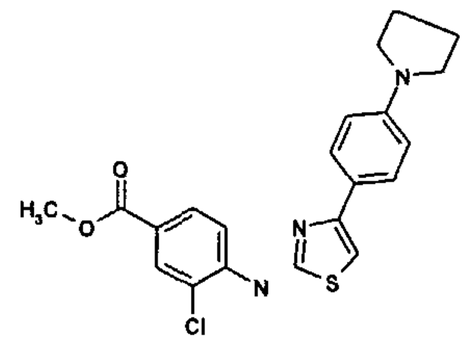
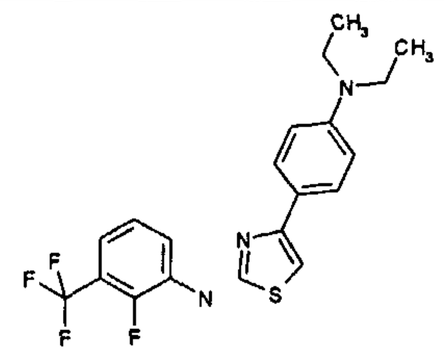
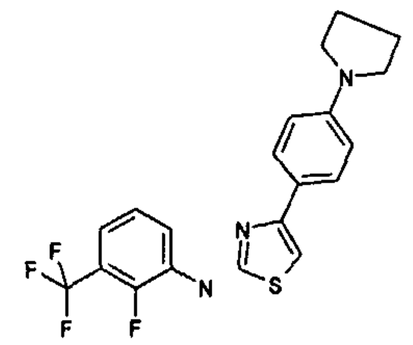
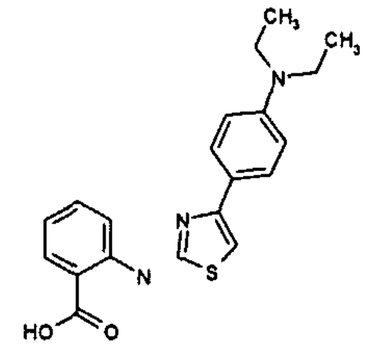
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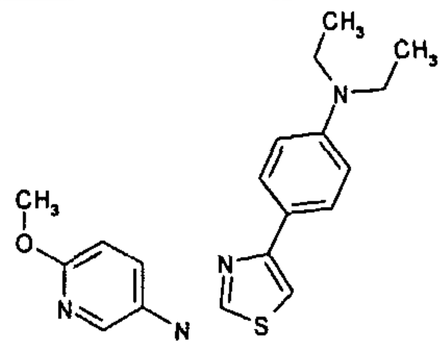
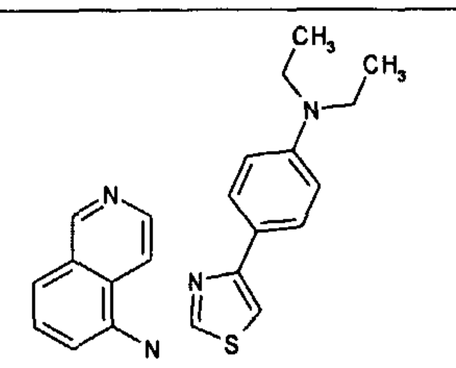
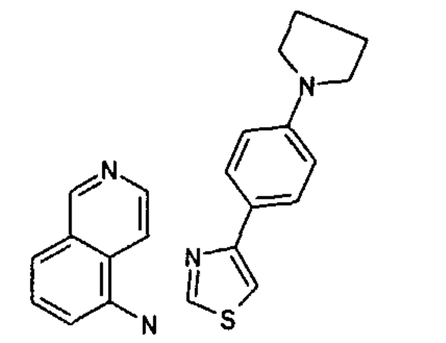
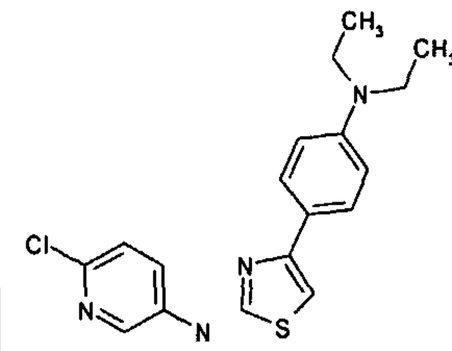
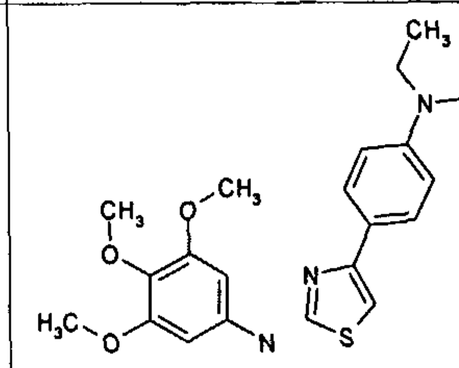
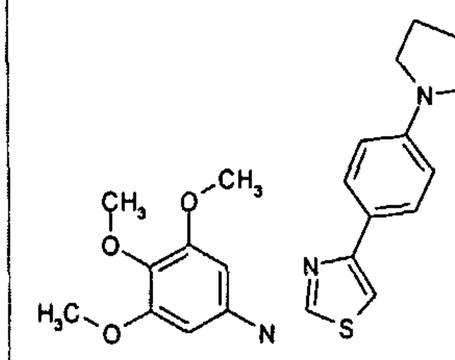
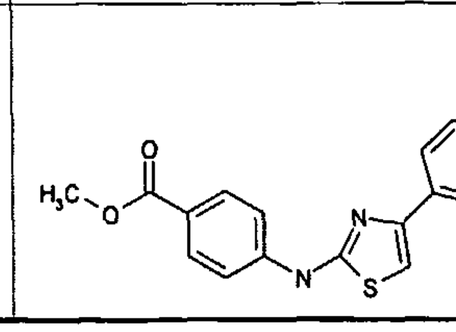
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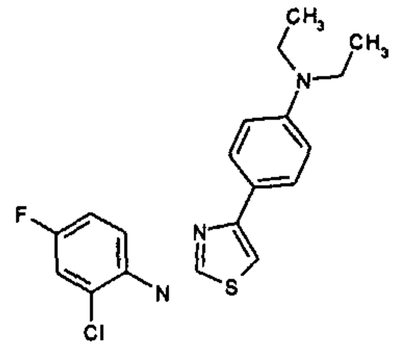
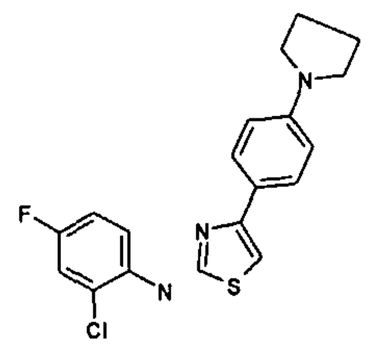
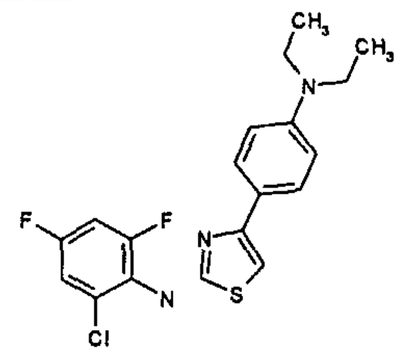
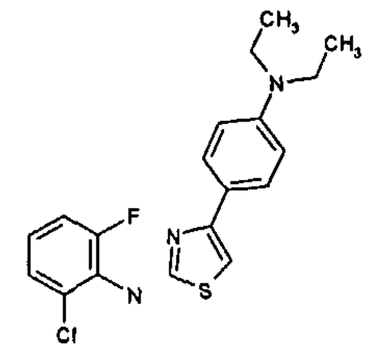
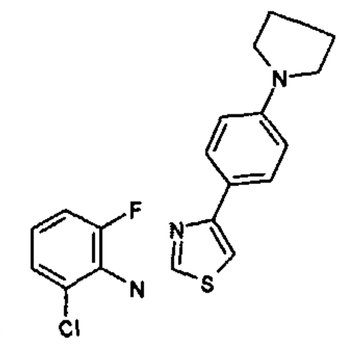
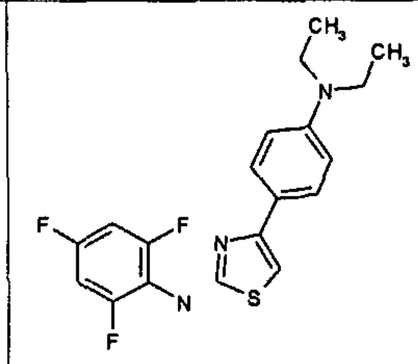
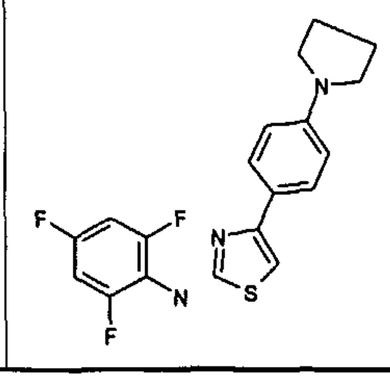
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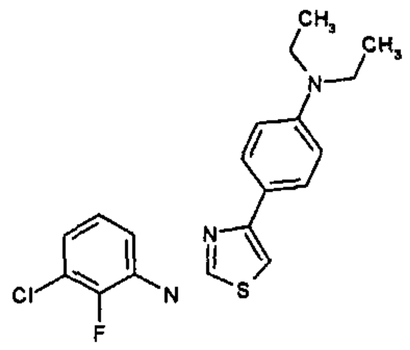
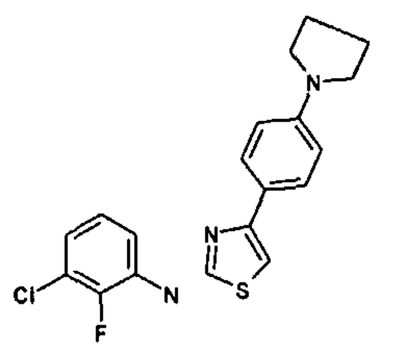
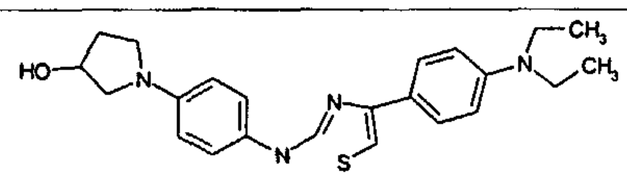
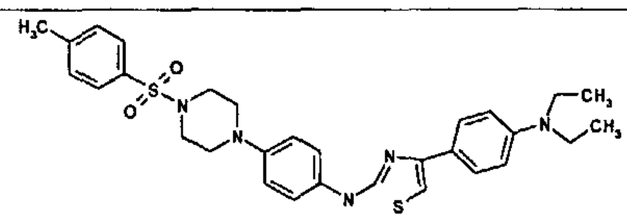
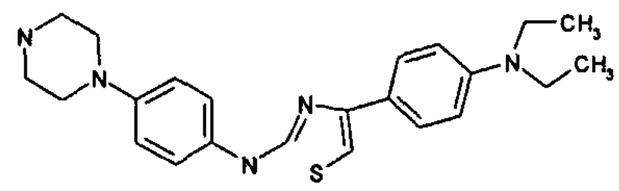
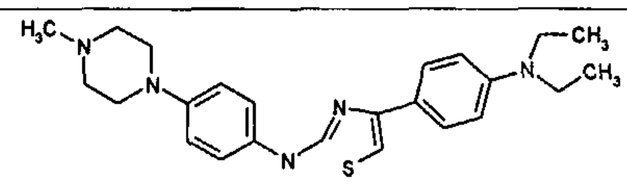
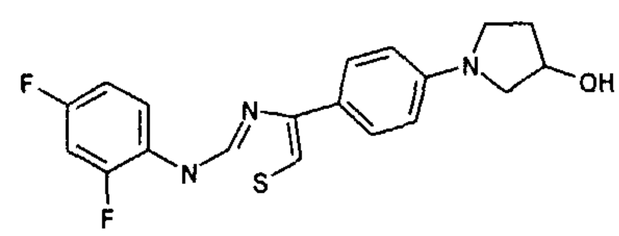
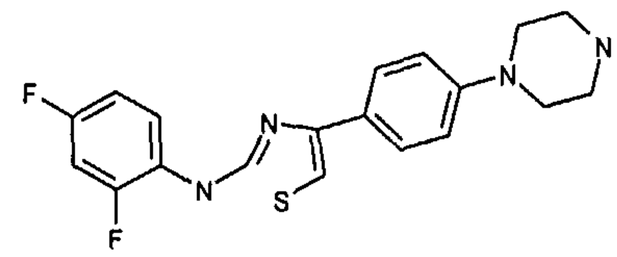
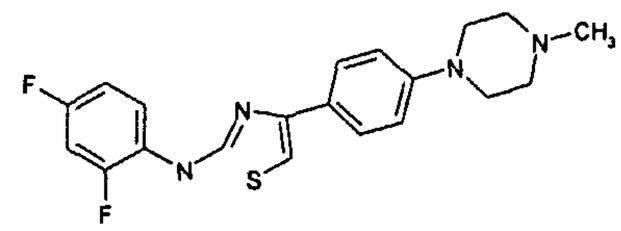
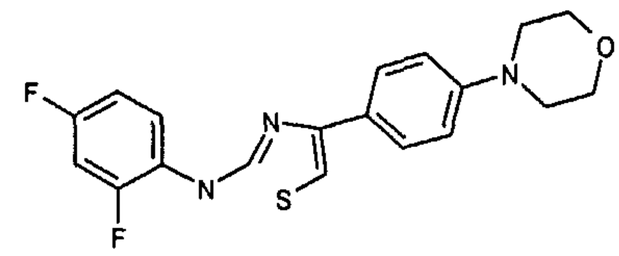
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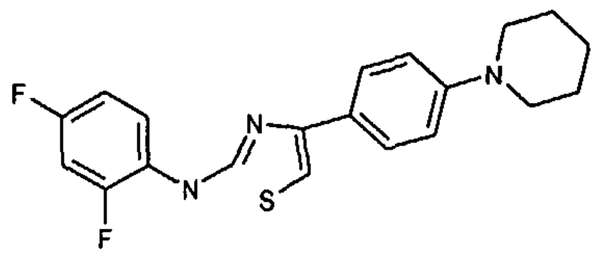
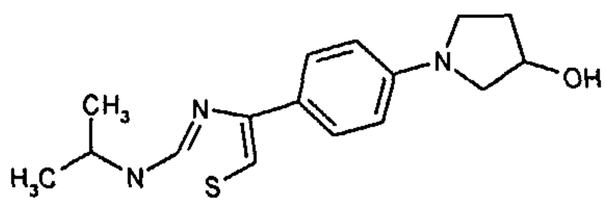
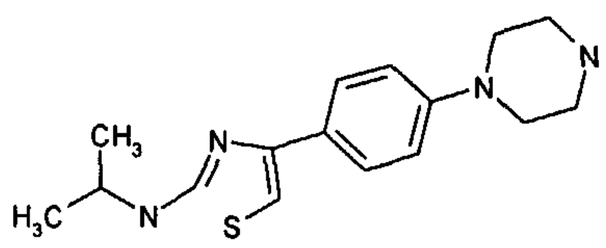
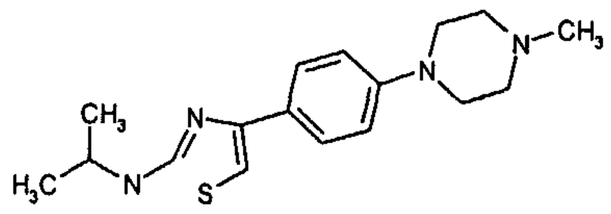
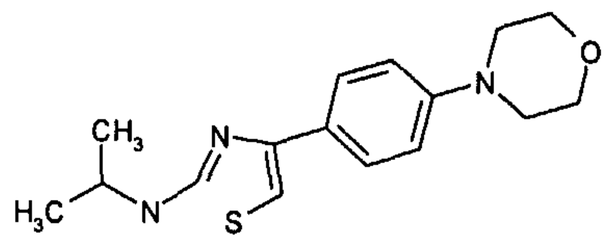
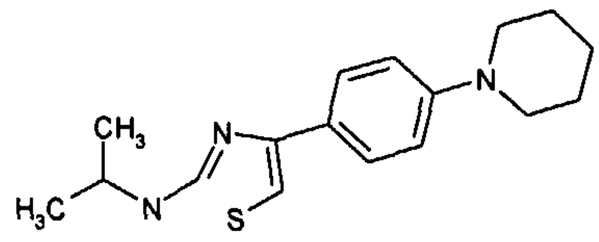
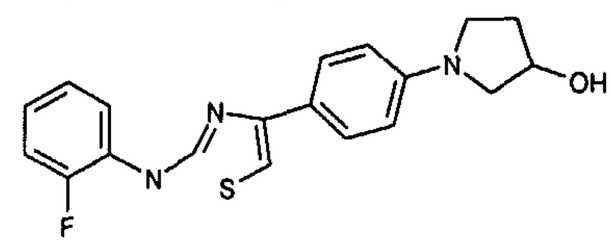
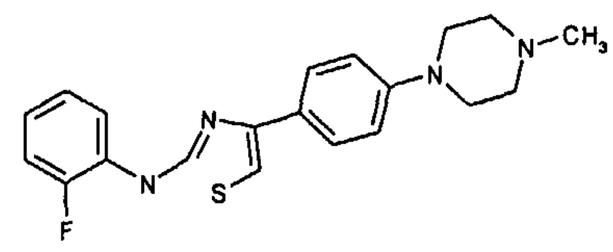
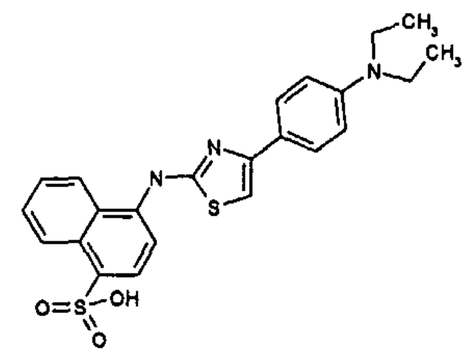
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SP6266		1,02	3,0
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SP5799		3,6	>50
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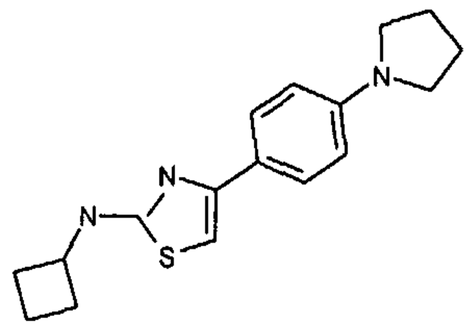
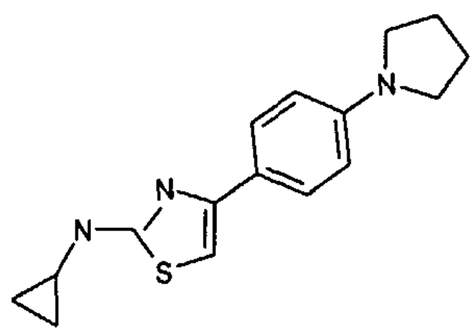
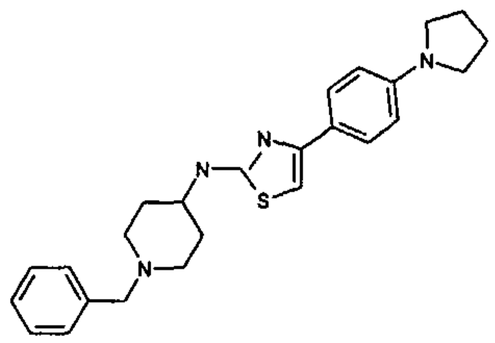
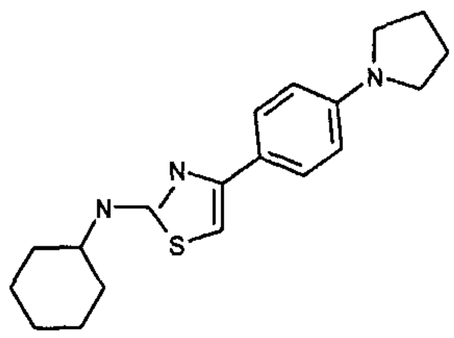
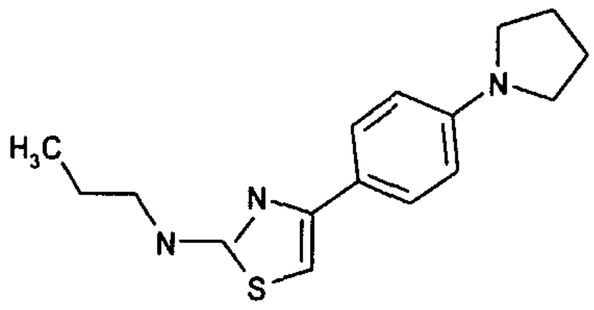
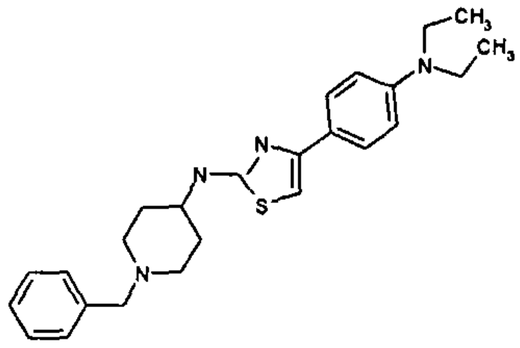
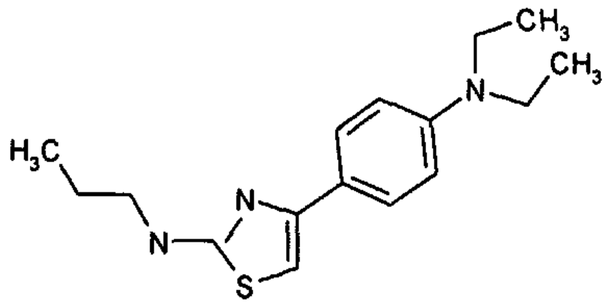
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SP5776		0,29	1,5
SP5775		0,34	3,6
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SP5760		0,27	0,42

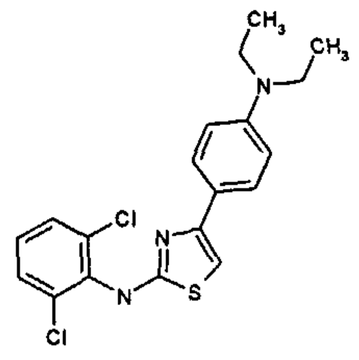
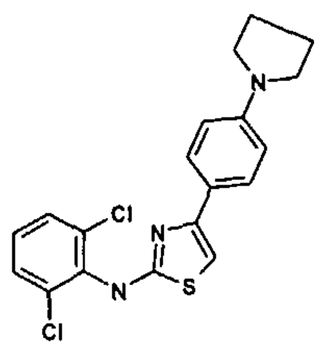
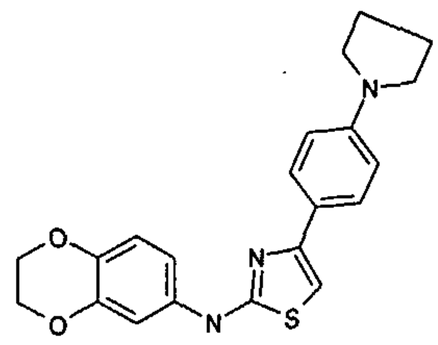
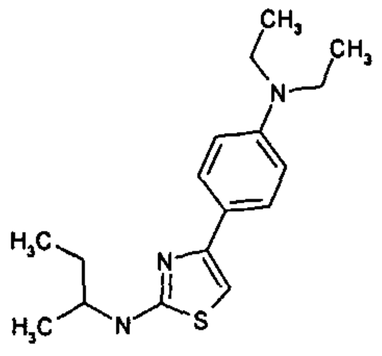
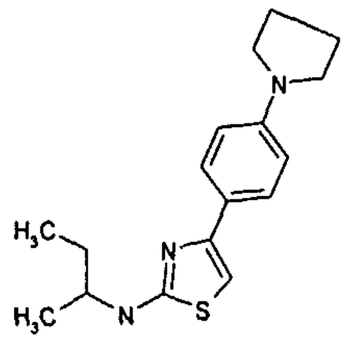
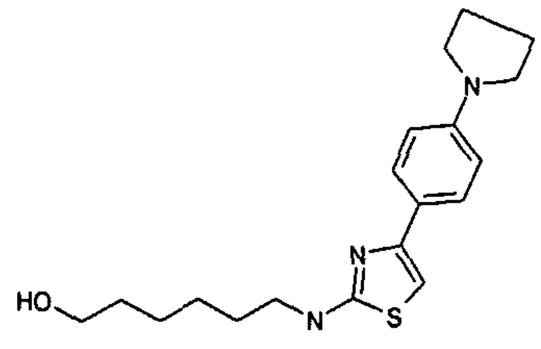
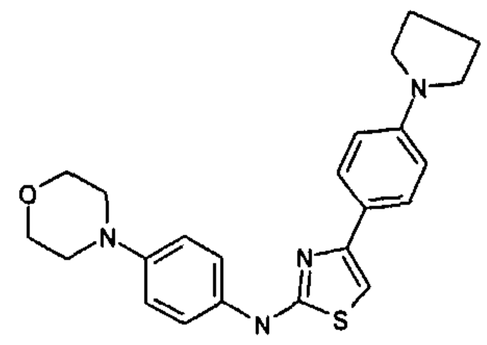
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SP5751		0,12	0,42
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SP5736		6,1	>100

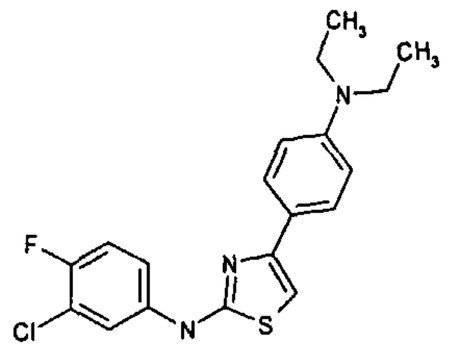
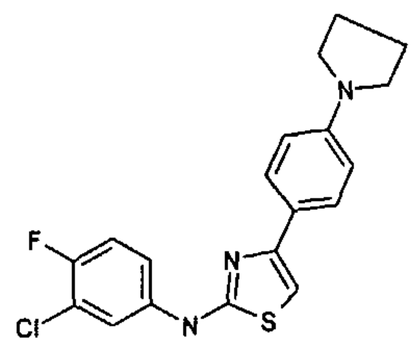
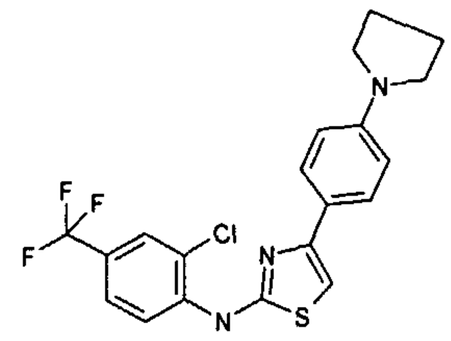
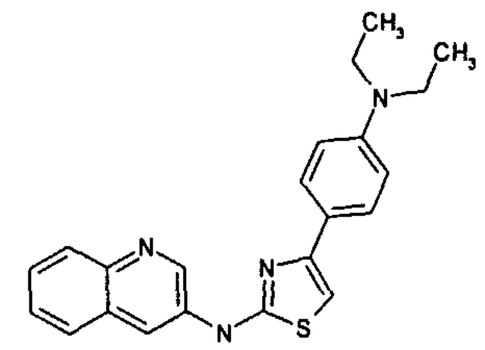
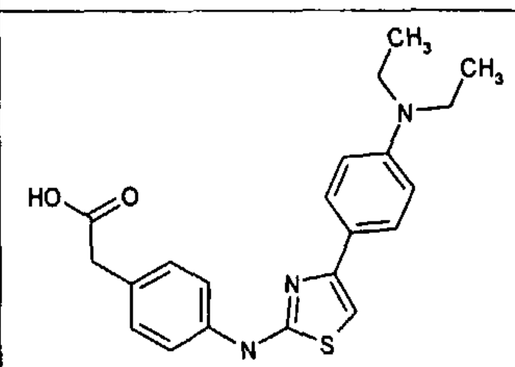
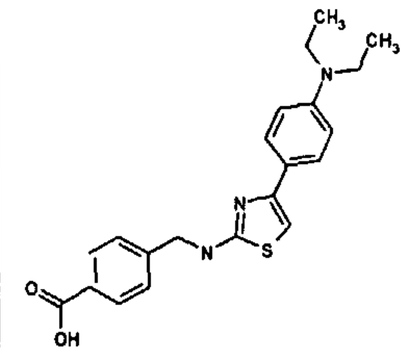
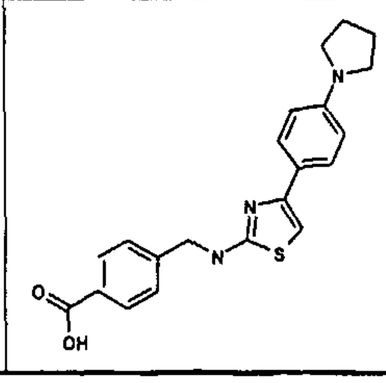
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SP5716		1,3	5,2
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SP5711		0,46	2,1

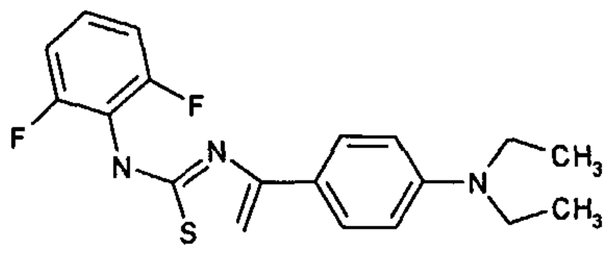
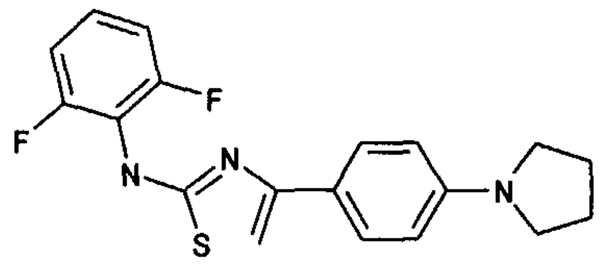
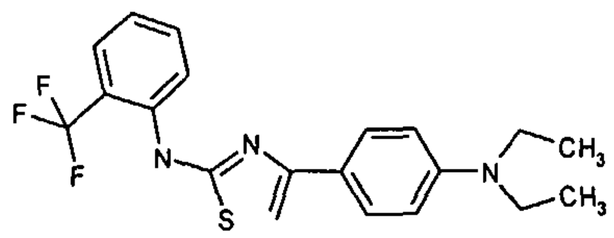
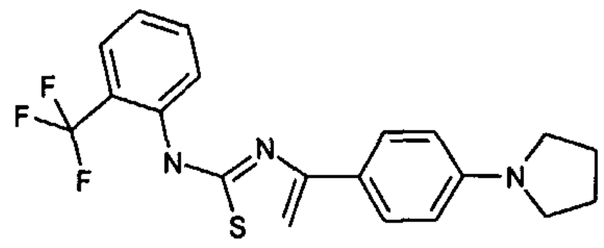
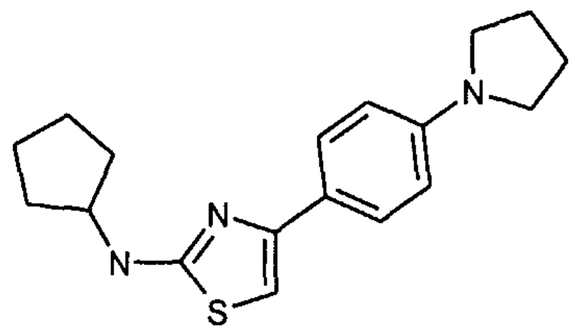
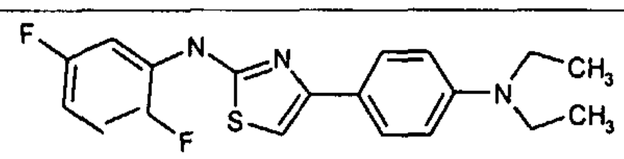
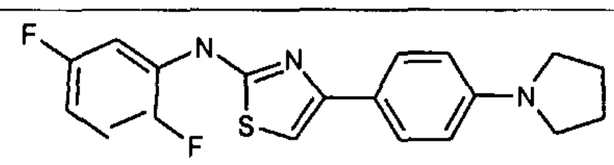
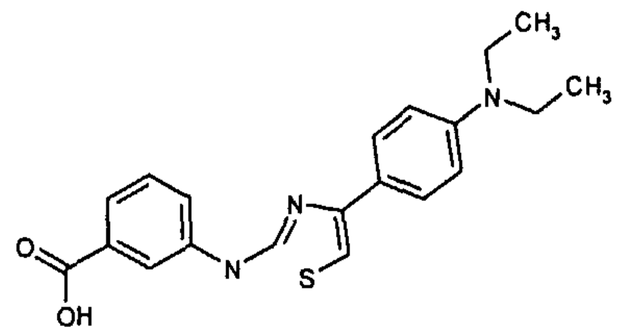
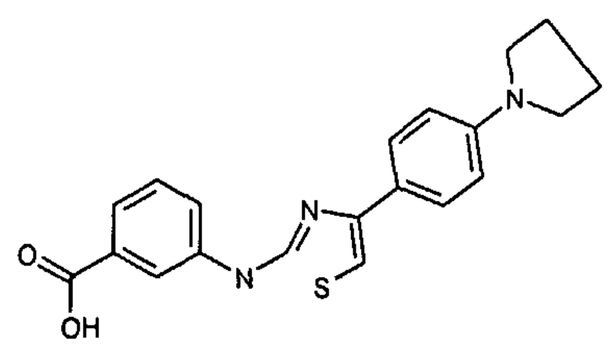
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SP5674		0,088	0,75
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SP5672		0,18	0,91
SP5671		0,26	1,45
SP5661		0,42	3,1
SP5659		0,41	3,9
SP5658		0,76	2,5
SP5657		3,5	>10

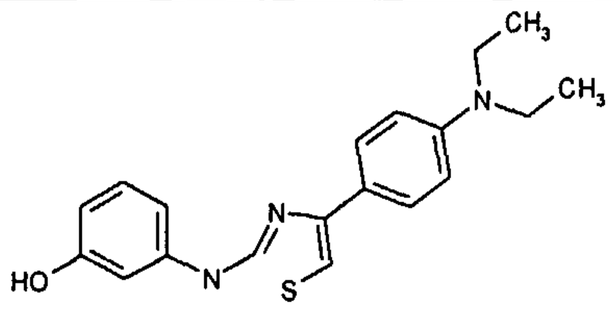
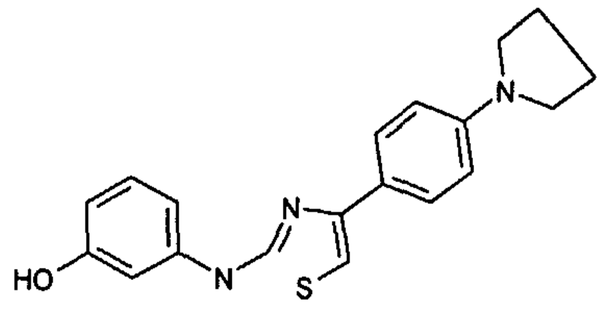
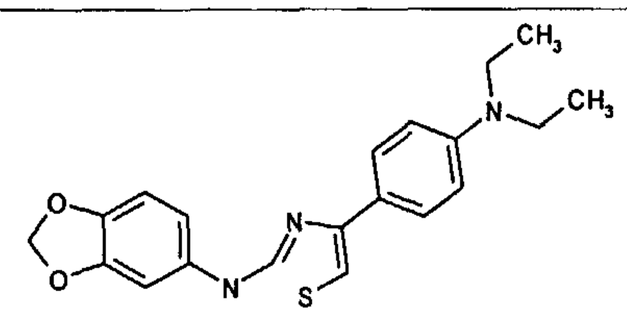
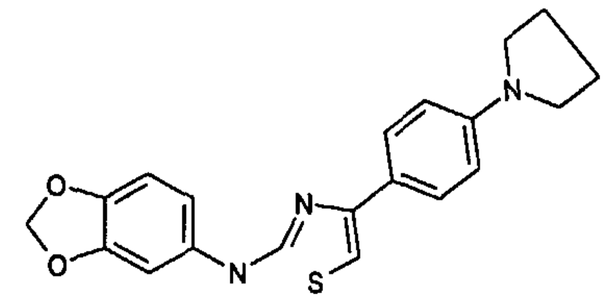
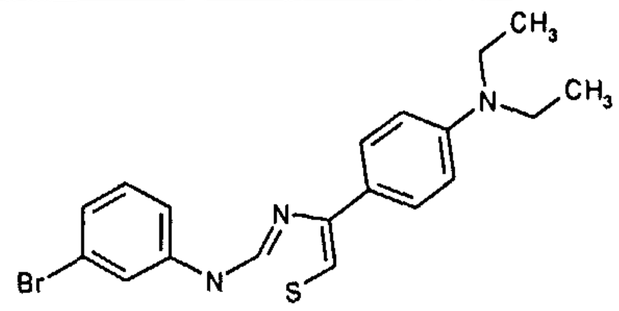
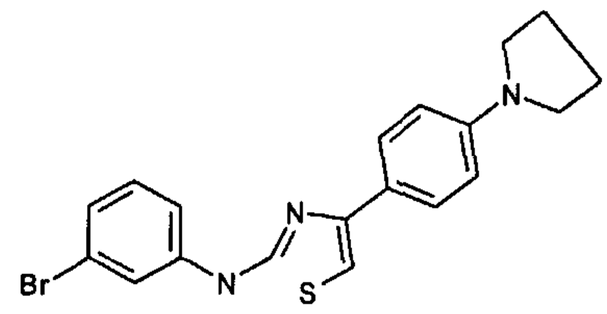
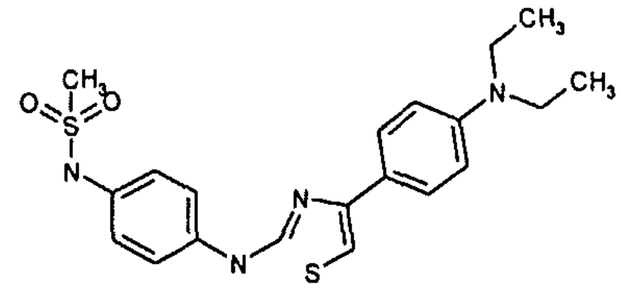
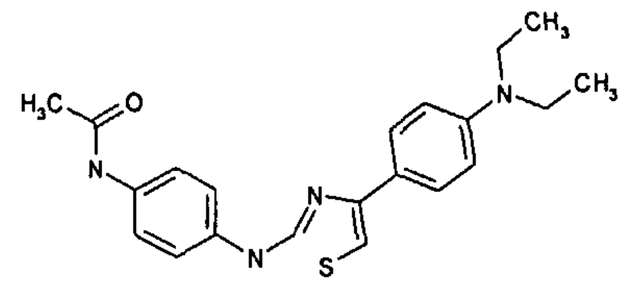
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SP5648		0,44	n.d.
SP5646		0,5	>100
SP5645		0,7	>100
SP5644		0,8	>100
SP5643		0,3	>100
SP5642		0,45	1,8
SP5615		2,7	12
SP5601		0,11	0,78

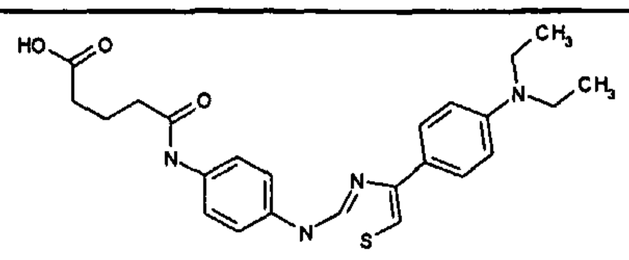
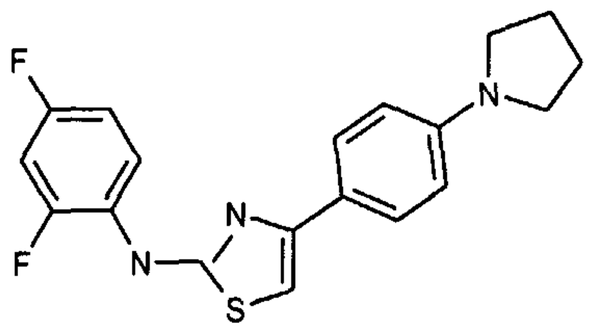
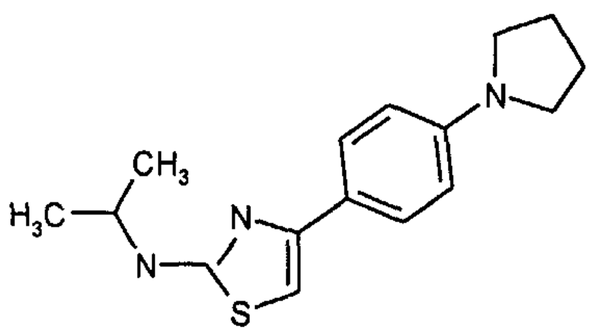
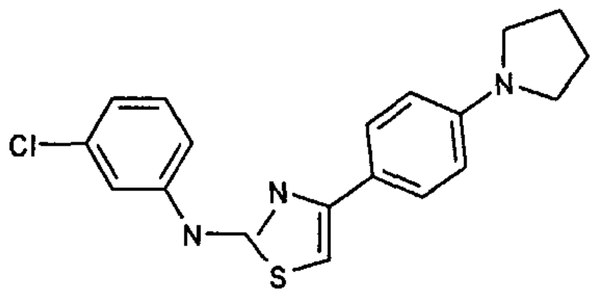
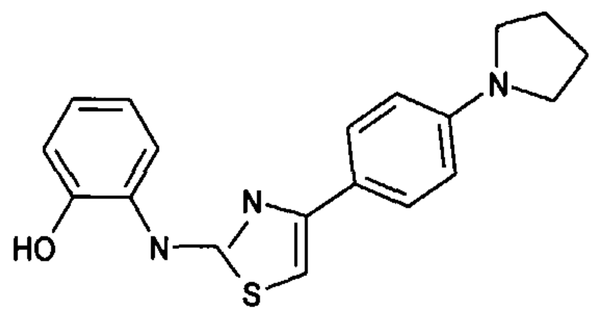
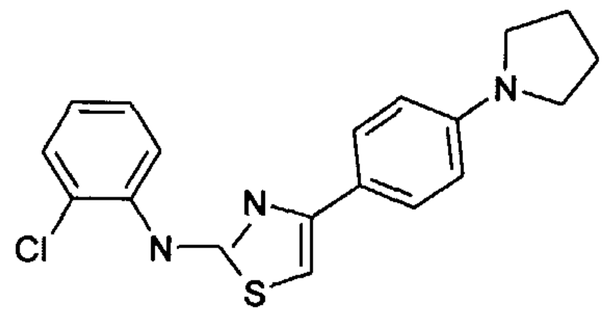
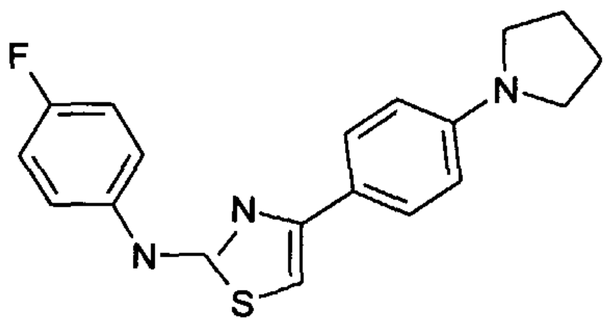
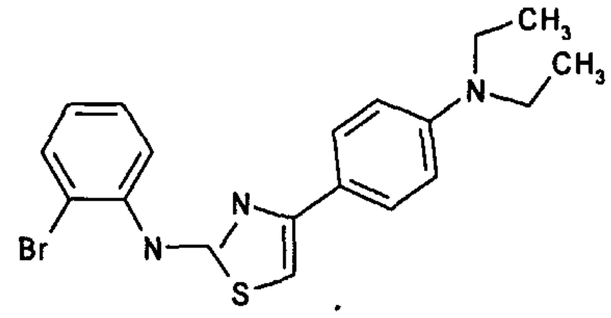
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SP5548		0,31	1,46
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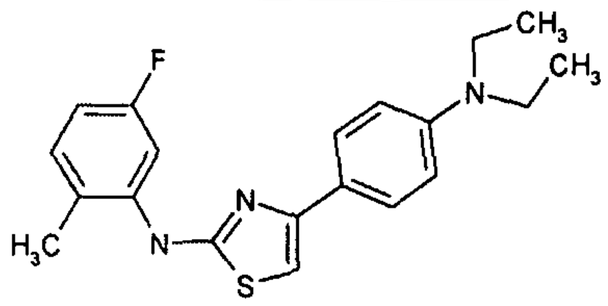
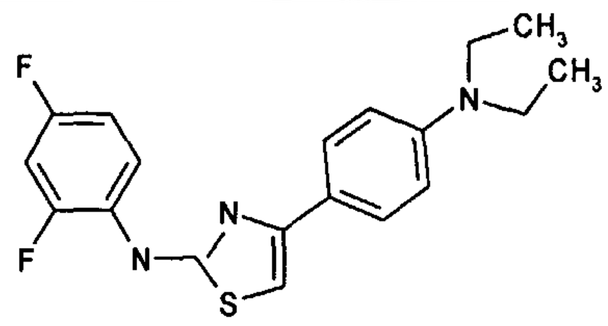
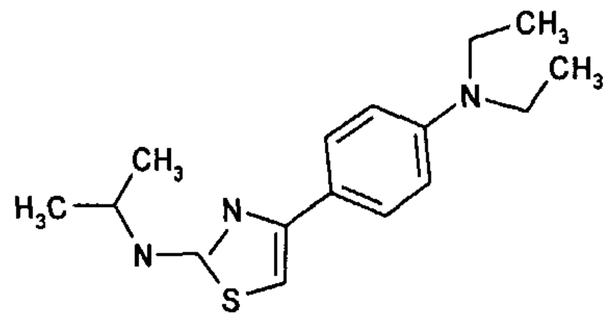
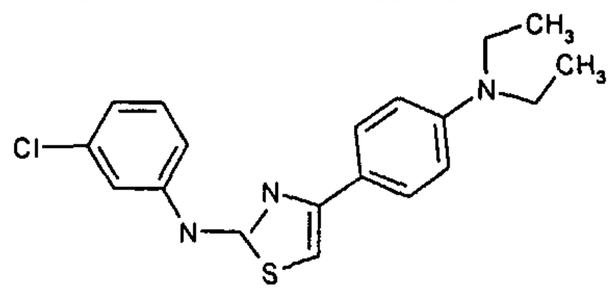
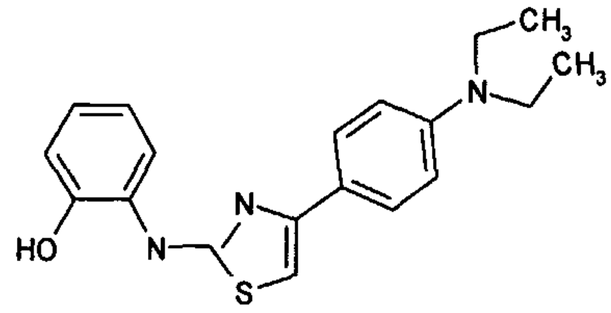
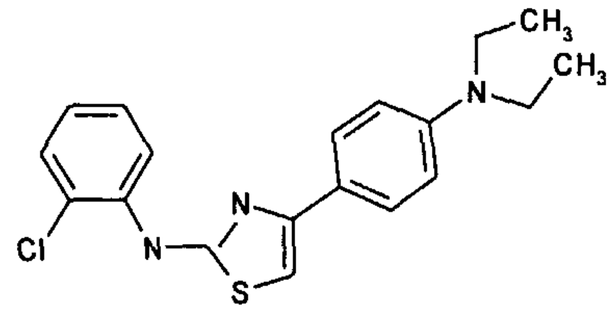
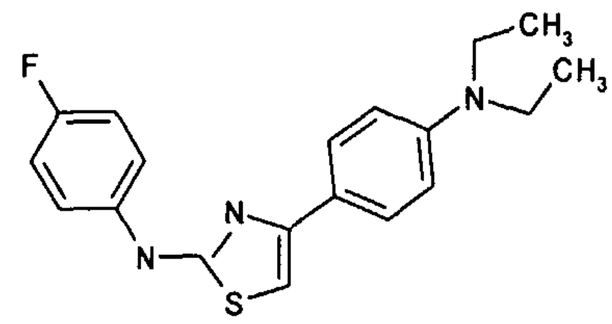
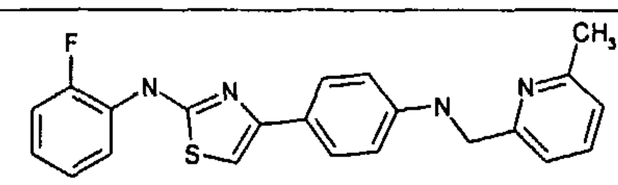
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SP5452		0,39	1,24
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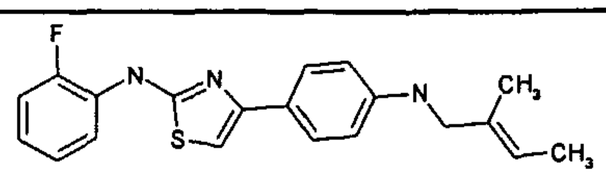
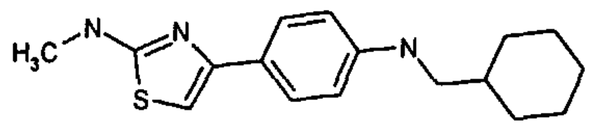
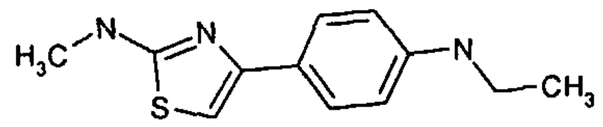
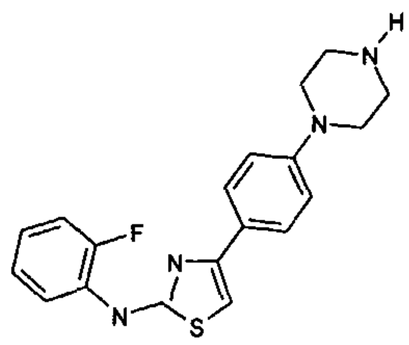
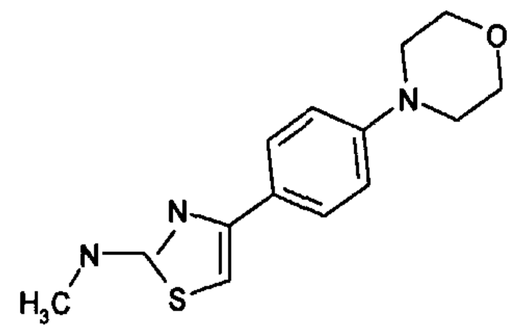
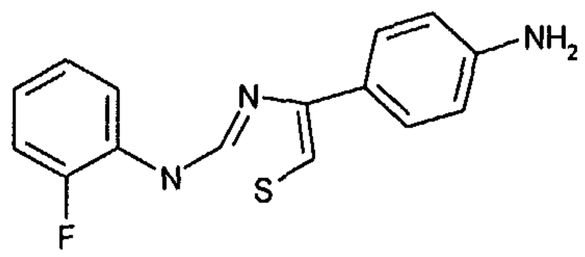
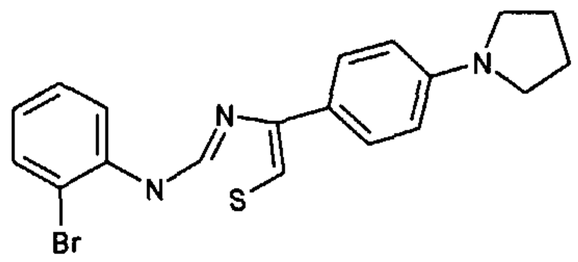
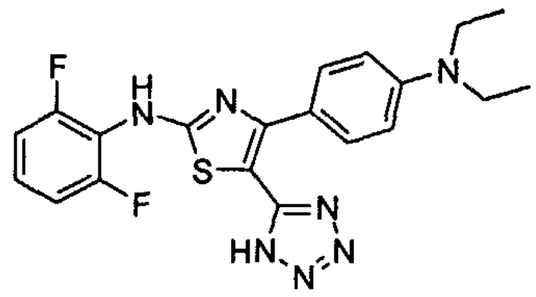
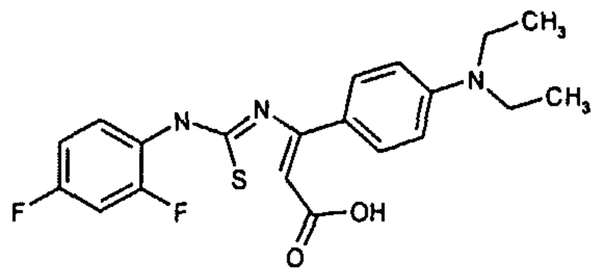
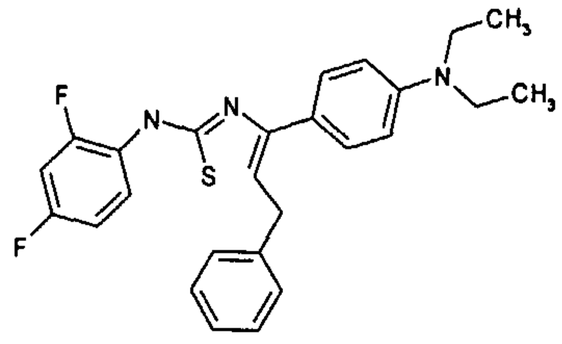
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SP5422		0,17	1,64
SP5421		0,11	1,06

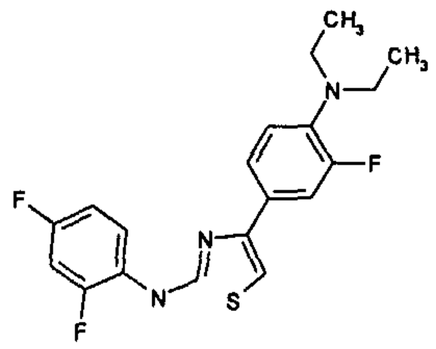
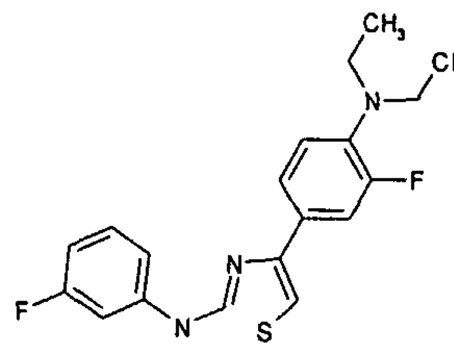
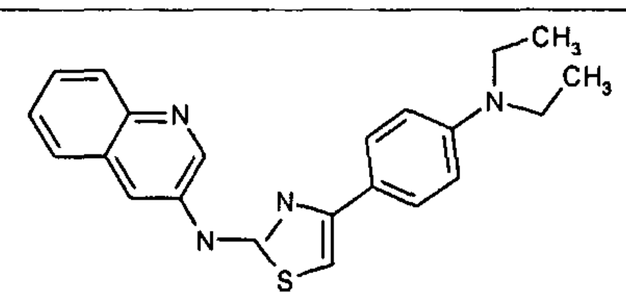
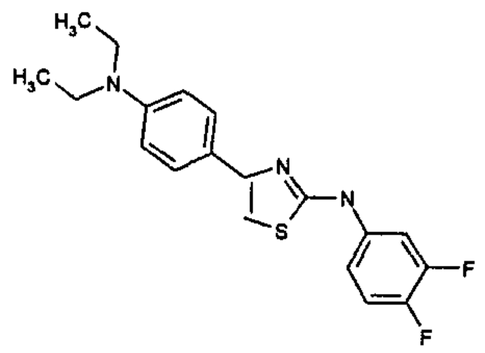
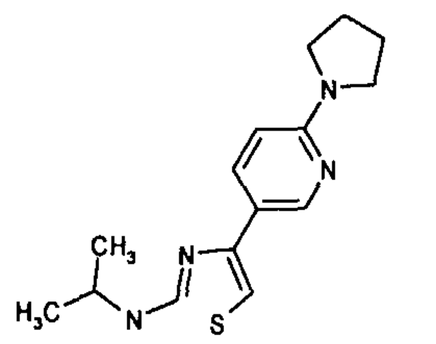
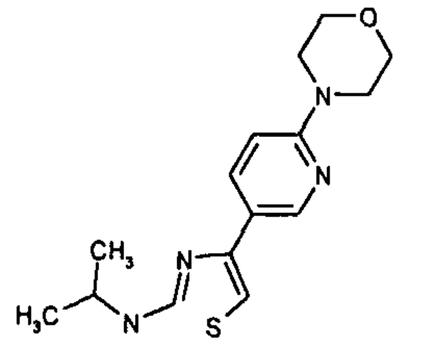
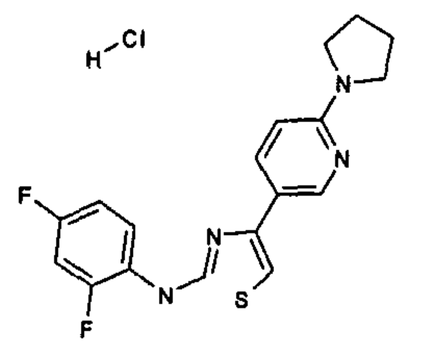
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SP5400		0,71	3,3
SP5377		0,58	1,9
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SP5341			>50
SP5330		0,24	0,52
SP5329		0,12	1,60

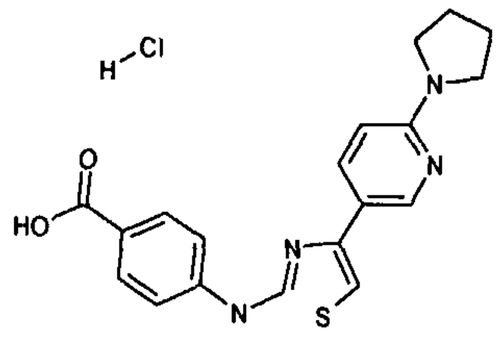
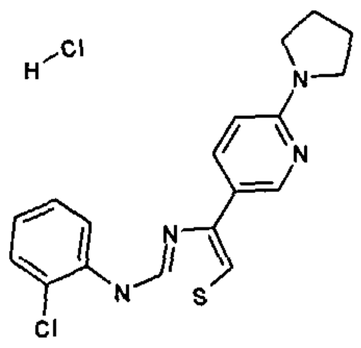
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SP5321		0,78	4,1
SP5308		0,8	7,3
SP5305		4,6	19

SP5304		2,0	8,0
SP5254		1,3	5,4
SP5253		0,53	2,1
SP5252		1,63	15
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SP5249		0,2	1,61
SP5248		0,8	2,4

SP5247		0,98	4,4
SP5246		0,88	5,1
SP5245		0,22	0,93
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SP5242		0,83	2,3
SP5241		0,21	1,9
SP5225		0,47	1,06

SP5224		0,29	0,71
SP5204		3,3	112
SP5202		0,62	10,0
SP5164		1,2	2,8
SP5116		1,65	4,9
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SP5053		0,31	0,84
SP4331		< 1	< 1
SP4267		0,26	0,64
SP4254		6,7	18

SP3507		14	>50
SP3505		2,1	>10
SP3309		0,38	1,28
SP3199		9,4	>15
SP2622		1,2	2,7
SP2621		4,3	5,4
SP2122		0,49	>100

SP2119		4,5	8,3
SP2115		2,1	5,6

Synthesis

Synthesis of the compound 1-37, may be as follows:

Synthesis of methyl-thiazol-2-yl-amine hydrochloride (2):

9.1 mg (0.1 mmol) N-methylthiourea and 12.9 µl (0.1 mmol) chloracetaldehyde solution in water (approx. 55%) were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 17.4 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 0.55 min, purity >95%.
HPLC-MS: 115.1 (M+H).

Synthesis of phenyl-thiazol-2-yl-amine hydrochloride (3):

15.2 mg (0.1 mmol) phenylthiourea and 12.9 µl (0.1 mmol) chloracetaldehyde solution in water (approx. 55%) were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 20.3 mg
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.22 min, purity >90%.
GCMS: 176 (M^+).

Synthesis of pyridin-3-yl-thiazol-2-yl-amine hydrochloride (4):

15.3 mg (0.1 mmol) 3-pyridylthiourea and 12.9 µl (0.1 mmol) chloracetaldehyde solution in water (approx. 55%) were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 20.4 mg
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 0.85 min, purity >80%.
HPLC-MS: 178 (M+H).

Synthesis of 4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-ylamine hydrobromide (5):

134 mg (0.5 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 38 mg (0.5 mmol) thiourea were dissolved in 5 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 139.2 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.83 min, purity >95%
HPLC-MS: 246 (M+H).

Synthesis of 4-(4-pyrrolidin-1-yl-phenyl)-oxazol-2-ylamine hydrobromide (6):

134 mg (0.5 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 30 mg (0.5 mmol) urea were dissolved in 5 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 163.7 mg
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.71 min, purity >85%.

Synthesis of methyl-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-amine hydrobromide (7):

805 mg (3 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 270 mg (3 mmol) *N*-methylthiourea were dissolved in 20 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 1.17 g.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.94 min, purity >95%.
GCMS: 259 (M^+).

Synthesis of phenyl-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-amine hydrobromide (8):

805 mg (3 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 570 mg (3 mmol) phenylthiourea were dissolved in 20 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 1.31 g.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.63 min, purity >90%.
HPLC-MS: 322 (M+H).

Synthesis of methyl-phenyl-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-amine hydrobromide (9):

268 mg (1 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 166 mg (1 mmol) N-methyl-N-phenylthiourea were dissolved in 20 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 442 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.94 min, purity >95%.
HPLC-MS: 336 (M+H).

Synthesis of benzyl-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-amine hydrobromide (10):

268 mg (1 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 166 mg (1 mmol) benzylthiourea were dissolved in 20 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 409 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.40 min, purity >98%.

Synthesis of phenylethyl-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-amine hydrobromide (11):

536 mg (2 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 360 mg (2 mmol) 2-phenylethylthiourea were dissolved in 5 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.

Yield: 850 mg.

HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.51 min, purity >99%

GCMS: 349 (M^+).

Synthesis of phenylethyl-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-amine hydrobromide (12):

268 mg (1 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 153 mg (1 mmol) 2-pyridylthiourea were dissolved in 5 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.

Yield: 382 mg.

HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.18 min, purity >95%

GCMS: 322 (M^+).

Synthesis of phenylethyl-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-amine hydrobromide (13):

268 mg (1 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 153 mg (1 mmol) 3-pyridylthiourea were dissolved in 20 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.

Yield: 397 mg.

HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.40 min, purity >98%.

GCMS: 322 (M^+).

Synthesis of 3-[4-(4-pyrrolidin-1-yl-phenyl)-oxazol-2-yl]-pyridine hydrobromide (14):

134 mg (0.5 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 61 mg (0.5 mmol) nicotinamide were dissolved in 10 ml

ethanol and stirred for 15 h at 90°C. The solvent was removed and the residue was dried in vacuo.
Yield: 183.5 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.66 min, purity >90%.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 9.88 (s, 1H, arom. CH), 9.03 (d, ^3J(H,H) = 7 Hz, 2H, arom. CH), 8.98 (d, ^3J(H,H) = 7 Hz, 2H, arom. CH), 7.92 (m, 1H, arom. CH), 7.73 (d, ^3J(H,H) = 9 Hz, 2H, arom. CH), 6.39 (d, ^3J(H,H) = 9 Hz, 2H, arom. CH), 6.33 (s, 1H, oxazole-CH), 3.23 (m, 4H, N-$\underline{CH_2}$-C), 1.89 (m, 4H, N-CH_2-$C\underline{H_2}$-C).

Synthesis of pyridin-4-yl-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-amine hydrobromide (15):

134 mg (0.5 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 76.6 mg (0.5 mmol) 4-pyridylthiourea were dissolved in 15 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 201.1 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.77 min, purity >80%

Synthesis of 4-[4-(4-pyrrolidin-1-yl-phenyl)-oxazol-2-yl]-pyridine hydrobromide (16):

134 mg (0.5 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 61 mg (0.5 mmol) isonicotinamide were dissolved in 10 ml ethanol and stirred for 15 h at 90°C. The solvent was removed and the residue was dried in vacuo.
Yield: 195.3 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.65 min, purity >98%.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 9.14 (d, ^3J(H,H) = 7 Hz, 2H, arom. CH), 8.50 (d, ^3J(H,H) = 7 Hz, 2H, arom. CH), 7.87 (d, ^3J(H,H) = 9 Hz, 2H, arom. CH), 6.68 (d, ^3J(H,H) = 9 Hz, 2H, arom. CH), 6.40 (s, 1H, oxazole-CH), 3.37 (q, ^3J(H,H) = 7 Hz, 4H, N-$\underline{CH_2}$-C), 1.99 (m, 4H, N-CH_2-$C\underline{H_2}$-C).

Synthesis of N,N'-bis-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-benzene-1,4-diamine dihydrobromide (17):

268 mg (1 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 197 mg (1 mmol) 4-nitrophenylthiourea were dissolved in 20 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 270.3 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.79 min, purity >99%.
HPLC-MS: 367 (M+H).

Synthesis of N,N'-bis-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-benzene-1,4-diamine dihydrobromide (18):

268 mg (1 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 113 mg (0.5 mmol) 1,4-phenylenbisthiourea were dissolved in 20 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 376.4 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.80 min, purity >95%.
HPLC-MS: 565 (M+H).

Synthesis of [4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-(3-trifluoromethyl-phenyl)-amine hydrobromide (19):

27.5 mg (0.1 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 22.0 mg (0.1 mmol) 3-(trifluormethyl)-phenylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 51 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min., hold 0.5 min at 90% B, Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 3.51min, purity >80%.
HPLC-MS: 390 (M+H).

Synthesis of 4-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-ylamino]-benzoic acid hydrobromide (20):

27.5 mg (0.1 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 19.6 mg (0.1 mmol) 4-carboxyphenylthiourea were dissolved in 10 ml Ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 46.2 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.56 min, purity >98%.
HPLC-MS: 366 (M+H).

Synthesis of 2-methyl-4-(4-pyrrolidin-1-yl-phenyl)-thiazole hydrobromide (21):

134 mg (0.5 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 38 mg (0.5 mmol) thioacetamide were dissolved in 10 ml ethanol and stirred for 15 h at 90°C. The solvent was removed and the residue was dried in vacuo.
Yield: 170.6 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.36 min, purity >90%.
HPLC-MS: 245 (M+H).

Synthesis of 3-[4-(4-pyrrolidin-1-yl-phenyl)-thiazol-2-yl]-pyridine hydrobromide (22):

134 mg (0.5 mmol) 2-bromo-4´-(1-pyrrolidino)-acetophenone and 69 mg (0.5 mmol) thionicotinamide were dissolved in 10 ml ethanol and stirred for 15 h at 90°C. The solvent was removed and the residue was dried in vacuo.
Yield: 204.7 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.02 min, purity >90%.
GC-MS: 307 (M^+).

Synthesis of 4-(4-diethylamino-phenyl)-thiazol-2-ylamine hydrobromide (23):

136 mg (0.5 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 38 mg (0.5 mmol) thiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 168.9 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 0.94 min, purity >95%.
GC-MS: 247 (M^+).

Synthesis of 4-(4-diethylamino-phenyl)-oxazol-2-ylamine hydrobromide (24):

136 mg (0.5 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 30 mg (0.5 mmol) urea were dissolved in 5 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 159.4 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.68 min, purity >90%.
HPLC-MS: 270 (M+K).

Synthesis of [4-(4-diethylamino-phenyl)-thiazol-2-yl]-methyl-amine hydrobromide (25):

54.1 mg (0.2 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 18 mg (0.2 mmol) N-methylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 64.3 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.12 min, purity >90%.
GC-MS: 261 (M^+).

Synthesis of [4-(4-Diethylamino-phenyl)-thiazol-2-yl]-phenyl-amine hydrobromide (26):

54.1 mg (0.2 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 38 mg (0.2 mmol) phenylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 78.3 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.08 min, purity >90%.
GC-MS: 323 (M^+).

Synthesis of [4-(4-diethylamino-phenyl)-thiazol-2-yl]-methyl-phenyl-amine hydrobromide (27):

27.0 mg (0.1 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 16.6 mg (0.1 mmol) N-methyl-N-phenylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 42 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.24 min, purity >99%.
GC-MS: 337 (M^+).

Synthesis of benzyl-[4-(4-diethylamino-phenyl)-thiazol-2-yl]-amine hydrobromide (28):

27.0 mg (0.1 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 16.6 mg (0.1 mmol) benzylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 44 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.86 min, purity >95%.
GC-MS: 337 (M^+).

Synthesis of [4-(4-diethylamino-phenyl)-thiazol-2-yl]-pyridin-2-yl-amine hydrobromide (29):

270 mg (1 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 153 mg (1 mmol) 2-pyridylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 443 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.49 min, purity >95%.
HPLC-MS: 325 (M+H).

Synthesis of [4-(4-diethylamino-phenyl)-thiazol-2-yl]-pyridin-2-yl-amine trifluoracetic acid (30):

108 mg (0.4 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 56 mg (0.4 mmol) 3-pyridylthiourea were dissolved in 20 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo. The crude product was purified by preparative HPLC.
Yield: 56 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.30 min, purity >98%.
GC-MS: 324 (M^+).

Synthesis of diethyl-[4-(2-pyridin-4-yl-oxazol-4-yl)-phenyl]-amine hydrobromide (31):

136 mg (0.5 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 61 mg (0.5 mmol) isonicotinamide were dissolved in 20 ml ethanol and stirred for 15 h at 90°C. The solvent was removed and the residue was dried in vacuo.
Yield: 160.2 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.67 min, purity >95%.
^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 9.10 (d, ^3J(H,H) = 7 Hz, 2H, arom. CH), 8.49 (d, ^3J(H,H) = 7 Hz, 2H, arom. CH), 7.84 (d,

^3J(H,H) = 9 Hz, 2H, arom. CH), 6.81 (d, ^3J(H,H) = 9 Hz, 2H, arom. CH), 6.35 (s, 1H, oxazole-CH), 3.47 (q, ^3J(H,H) = 7 Hz, 4H, N-C$\underline{H}_2$-C), 1.14 (t, 6H, N-CH$_2$-C$\underline{H}_3$.

Synthesis of [4-(4-diethylamino-phenyl)-thiazol-2-yl]-(3-trifluoromethyl-phenyl)-amine hydrobromide (32):

27.1 mg (0.1 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 22.0 mg (0.1 mmol) 3-(trifluormethyl)-phenylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 50.9 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 2.59 min, purity >99%.
GC-MS: 391 (M^+).

Synthesis of diethyl-[4-(2-methyl-thiazol-4-yl)-phenyl]-amine hydrobromide (33):

136 mg (0.5 mmol) 2-bromo-4´-(diethylamino)-acetophenone and 38 mg (0.5 mmol) thioacetamide were dissolved in 10 ml ethanol and stirred for 15 h at 90°C. The solvent was removed and the residue was dried in vacuo.
Yield: 164.5 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.62 min, purity >95%.
HPLC-MS: 247 (M+H).
GC-MS: 246 (M^+).

Synthesis of methyl-[4-(5-methyl-1-phenyl-1H-pyrazol-4-yl)-thiazol-2-yl]-amine hydrochloride (34):

27.9 mg (0.1 mmol) 2-bromo-1-[3-(4-chlorophenyl)-5-isoxazolyl]-1-ethanone and 9.0 mg (0.1 mmol) N-methylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 24.7 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1%

trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.70 min, purity >99%.
GC-MS: 270 (M^+).

Synthesis of phenylethyl-(4-pyridin-2-yl-thiazol-2-yl)-amine hydrobromide (35):

28.0 mg (0.1 mmol) 2-bromo-1-(2-pyridinyl)-1-ethanone and 18.0 mg (0.1 mmol) 2-phenylethylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 45.7 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.85 min, purity >90%.
GC-MS: 282 (M+H).

Synthesis of methyl-[4-(5-pyridin-2-yl-thiophen-2-yl)-thiazol-2-yl]-amine hydrobromide (36):

26.6 mg (0.1 mmol) 2-bromo-1-[5-(2-pyidinyl)-2-thienyl]-1-ethanone and 9.0 mg (0.1 mmol) N-methylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 35.6 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1% trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.59 min, purity >95%.
GC-MS: 273 (M^+).

Synthesis of pyridin-3-yl-[4-(5-pyridin-2-yl-thiophen-2-yl)-thiazol-2-yl]-amine hydrobromide (37):

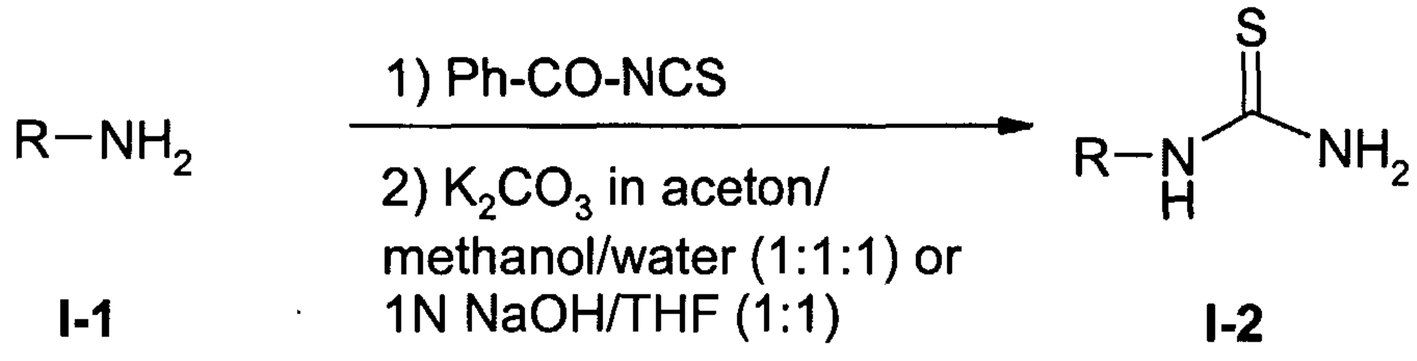
26.6 mg (0.1 mmol) 2-bromo-1-[5-(2-pyidinyl)-2-thienyl]-1-ethanone and 15.3 mg (0.1 mmol) 3-pyridylthiourea were dissolved in 10 ml ethanol and stirred for 15 h at 60°C. The solvent was removed and the residue was dried in vacuo.
Yield: 39.9 mg.
HPLC (Column: Xterra, MS C18, 5µm, 4.6*100 mm; 3 ml/min; 10% to 90% B gradient in 3.5 min. Solvent A: water + 0.1% trifluoroacetic acid, Solvent B: 100% acetonitrile + 0.1%

trifluoroacetic acid, UV: 214 nm, 254 nm, 301 nm): r_t = 1.59 min, purity >98%.
HPLC-MS: 337 (M+H).

The synthesis of the hereinbefore identified SP coded compounds may be as follows:

Synthesis I:

Preparation of Thioureas **I-2**:

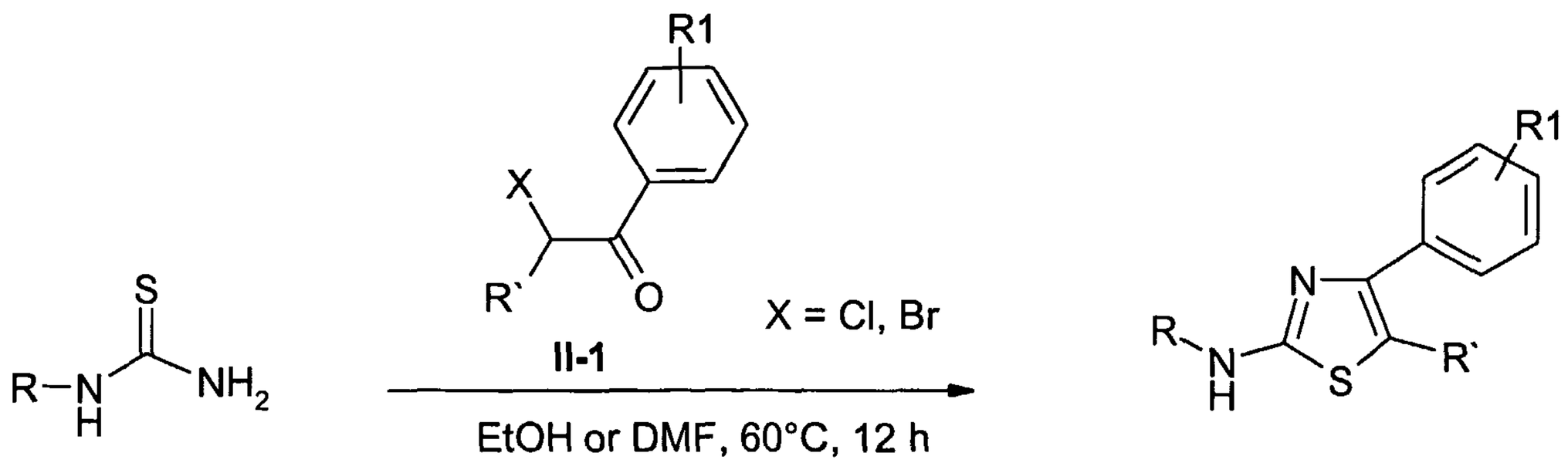


I-1 **I-2**

General procedure 1 for the preparation of the thioureas **I-2**:
The amine **I-1** was dissolved in acetone or methylene chloride (2-5 ml/mmol) and 1.1 equiv. of benzoyl isocyanate was added. The reaction was stirred overnight at room temperature. The solvent was removed, the residue was dissolved in THF/1N NaOH (1:1, 4 ml/mmol) and refluxed for 5 h. Alternatively the residue was dissolved in methanol/acetone/water (1:1:1, 3 ml/mmol), 5 equiv. of potassium carbonate were added and the mixture was stirred at room temperature overnight. The organic solvent was removed under reduced pressure and after cooling filtered if possible or extracted with methylene chloride, dried over $MgSO_4$ and concentrated. If acidic groups are present the organic solvent was removed, the aqueous layer was brought to neutral pH followed by filtration or extractive workup as described above. The crude thiourea was used without further purification.

Synthesis II:

Preparation of 2-aminothiazoles **II-2**:

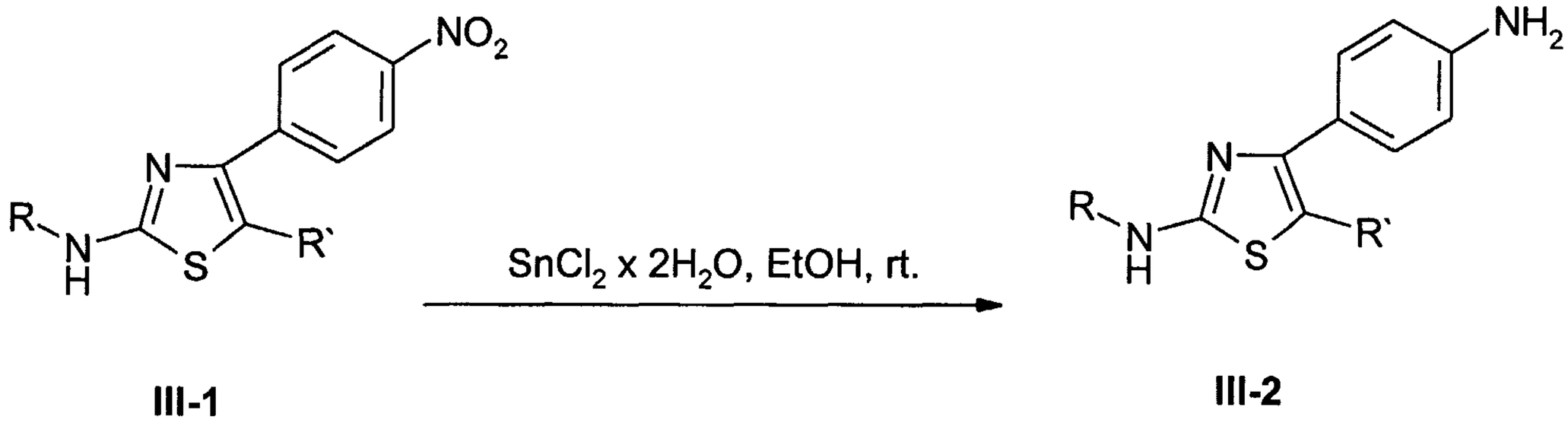


I-2 II-2

General procedure 2 for the preparation of 2-aminothiazoles **II-2**:
The thiourea **I-2** and 1 equiv. of the α-halogen carbonyl compound **II-1** were suspended in ethanol or DMF (2-20 ml/mmol) and stirred at 60°C for 12 h. The solvent was removed and the residue was purified using silica gel chromatography or preparative HPLC if necessary.

Synthesis III:

Preparation of 2-aminothiazoles **III-2**:

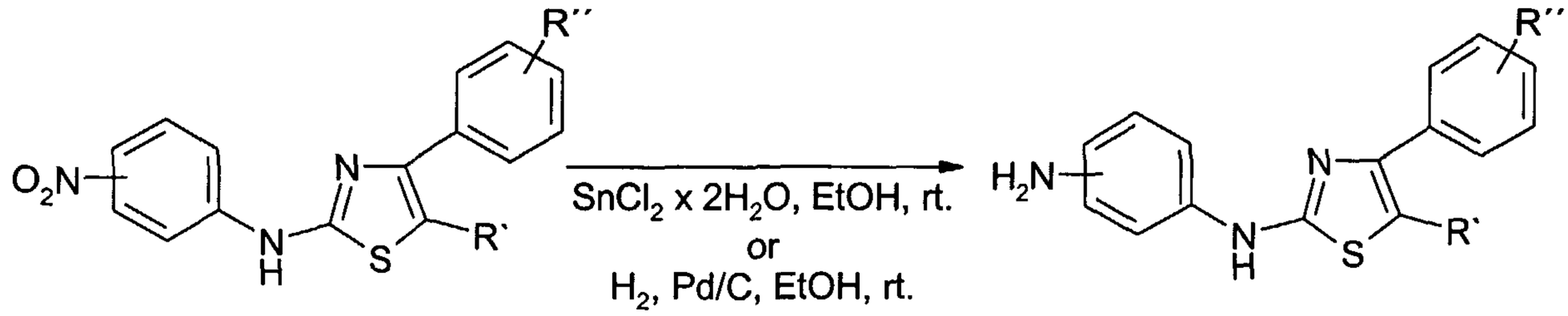


III-1 III-2

General procedure 3 for the preparation of 2-aminothiazoles **III-2**:
2-aminothiazole **III-1** and 1 equiv. tin dichloride dihydrate in ethanol were stirred at room temperature for 12 h. The solvent was removed and the residue was dissolved in ethyl acetate and 1 N NaOH. The organic layer was separated, dried over $MgSO_4$ and the solvent was removed.

Synthesis IV:

Preparation of 2-aminothiazoles **IV-2**:

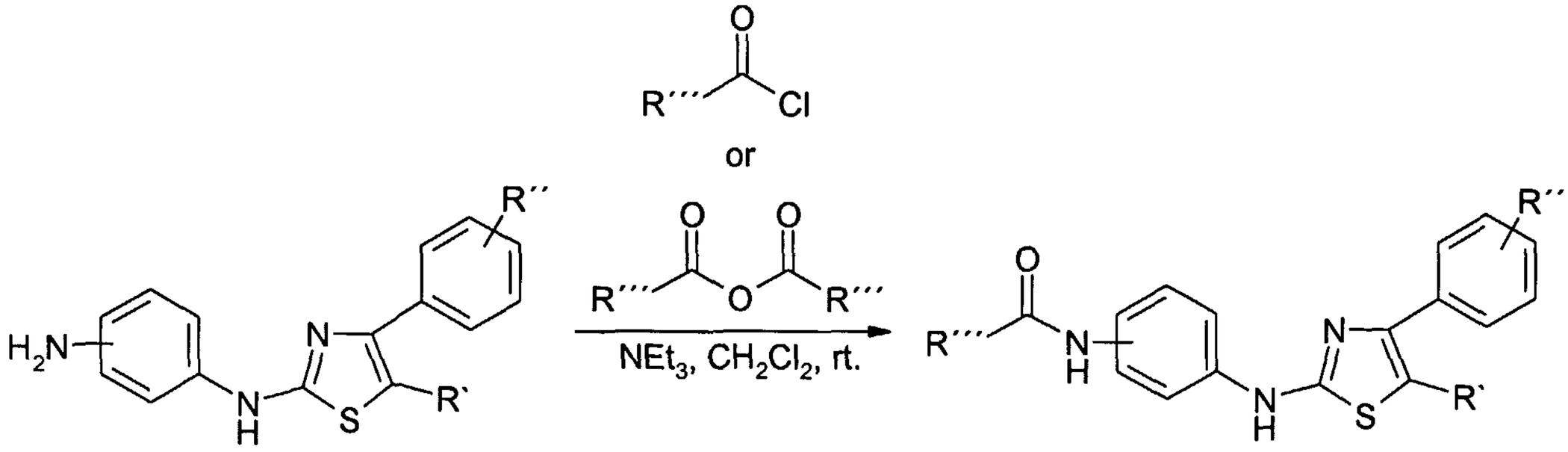


IV-1 **IV-2**

General procedure 4 for the preparation of 2-aminothiazoles **IV-2**: 2-aminothiazole **IV-1** and 1 equiv. tin dichloride dihydrate in ethanol were stirred at room temperature for 12 h. The solvent was removed and the residue was dissolved in ethyl acetate and 1 N NaOH. The organic layer was separated, dried over $MgSO_4$ and the solvent was removed. Alternatively, 2-aminothiazole **VI-1** was dissolved in ethanol and stirred with palladium on charcoal (10%) under hydrogen atmosphere for 12 h at room temperature. The mixture was filtered through a plug of celite and the filtrate was evaporated to dryness.

Synthesis V:

Preparation of 2-aminothiazoles **V-2**:

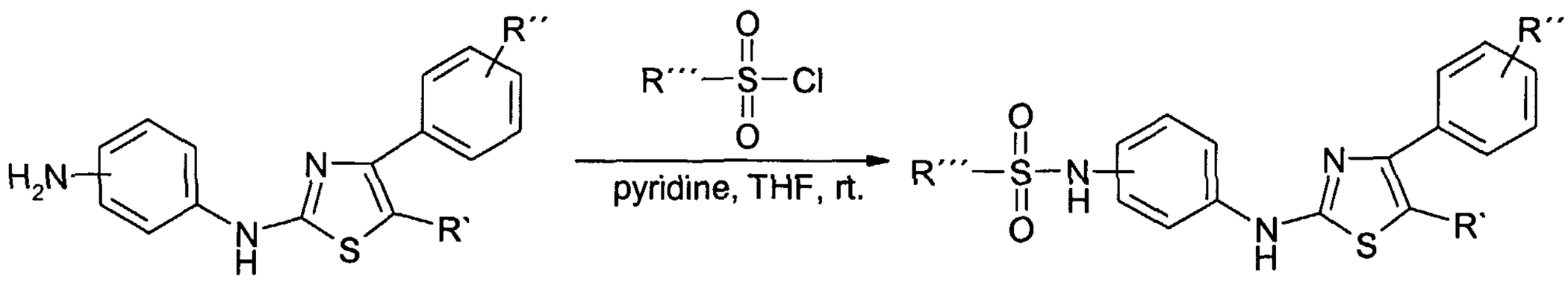


V-1 **V-2**

General procedure 5 for the preparation of 2-aminothiazoles **V-2**: 2-aminothiazole **V-1** was dissolved in methylene chloride and 2 equiv. triethylamine and 1.5 equiv. acid chloride or acid anhydride were added and stirred at room temperature for 12 h. The solvent was removed and the residue was dissolved in ethyl acetate and washed with sat. $NaHCO_3$- and NaCl-solutions. The organic layer was dried over $MgSO_4$, the solvent was removed and the residue was purified using silica gel chromatography or preparative HPLC if necessary.

Synthesis VI:

Preparation of 2-aminothiazoles **VI-2**:

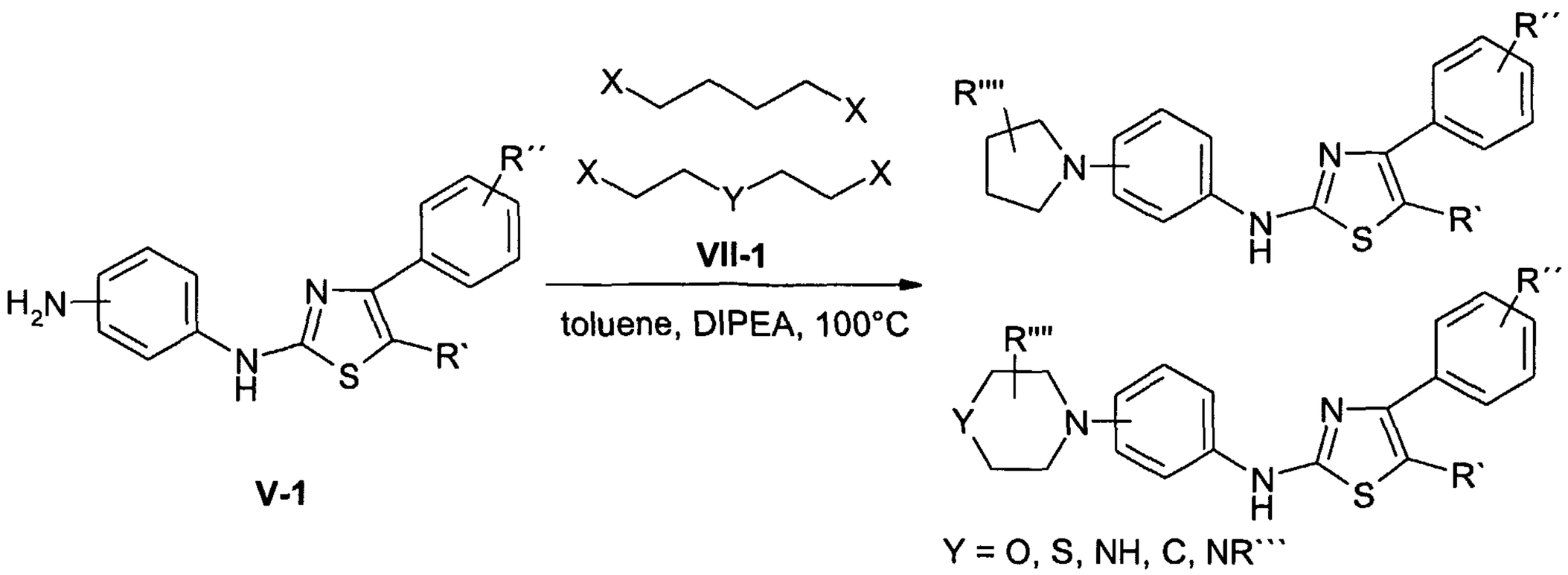


V-1 **VI-2**

General procedure 6 for the preparation of 2-aminothiazoles **VI-2**: 2-aminothiazole **V-1** was dissolved in THF/pyridine (10:1) and 1.1 equiv. sulfonyl chloride were added and stirred at room temperature for 12 h. The solvent was removed and the residue was dissolved in ethyl acetate and washed with sat. $NaHCO_3$- and NaCl-solutions. The organic layer was dried over $MgSO_4$, the solvent was removed and the residue was purified using silica gel chromatography or preparative HPLC if necessary.

Synthesis VII:

Preparation of 2-aminothiazoles **VII-2**:



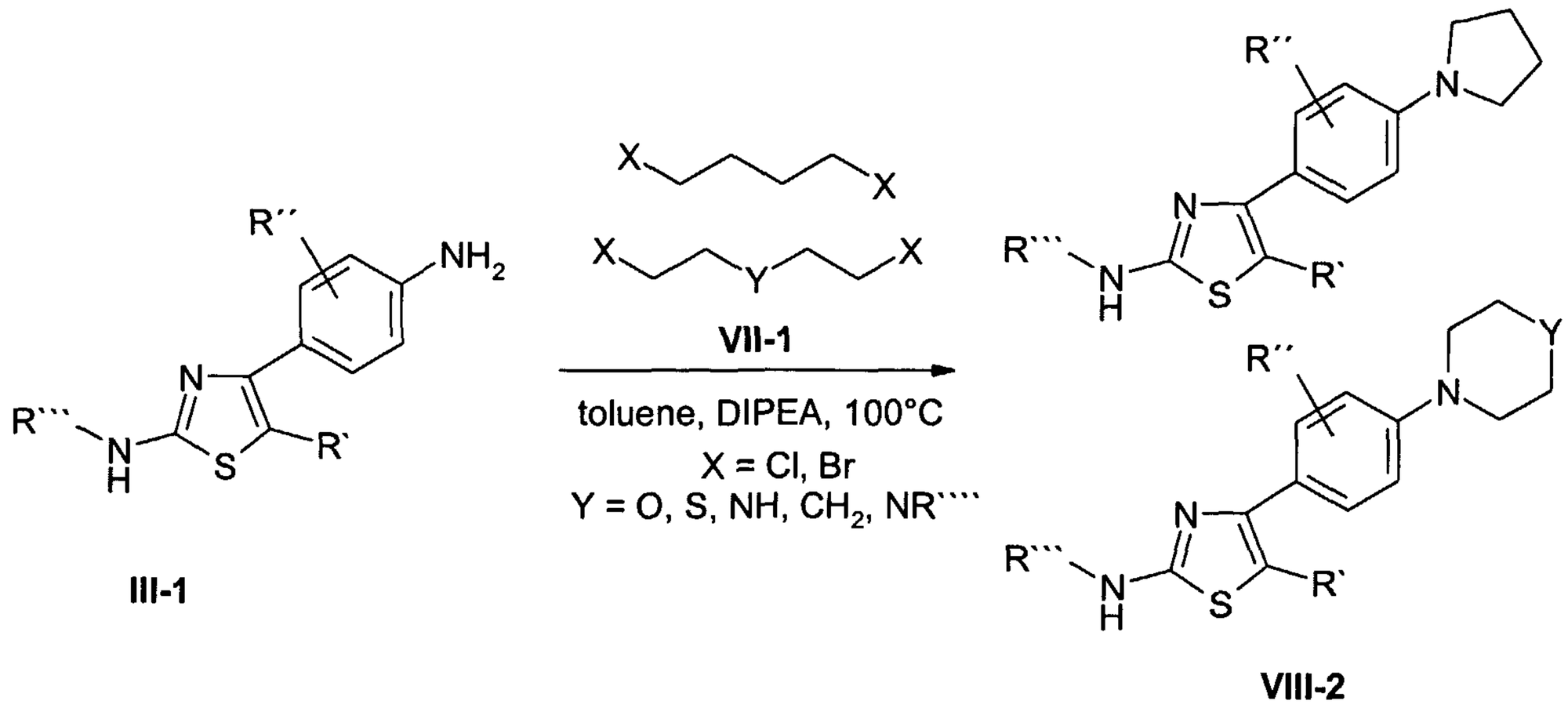
VII-2

General procedure 7 for the preparation of 2-aminothiazoles **VII-2**:

2-aminothiazole **V-1** and 1.5 equiv. dichloro or dibromo compound **VII-1** were dissolved in toluene and 6 equiv. *N,N*-diisopropyl-*N*-ethylamine were added. If the dichloro compound VII-1 was used, 0.2 equiv. tetrabutylammonium iodide were added. The mixture was stirred at 100 °C for 2 days. The solvent was removed and the residue was purified with preparative HPLC.

Synthesis VIII:

Preparation of 2-aminothiazoles **VIII-2**:

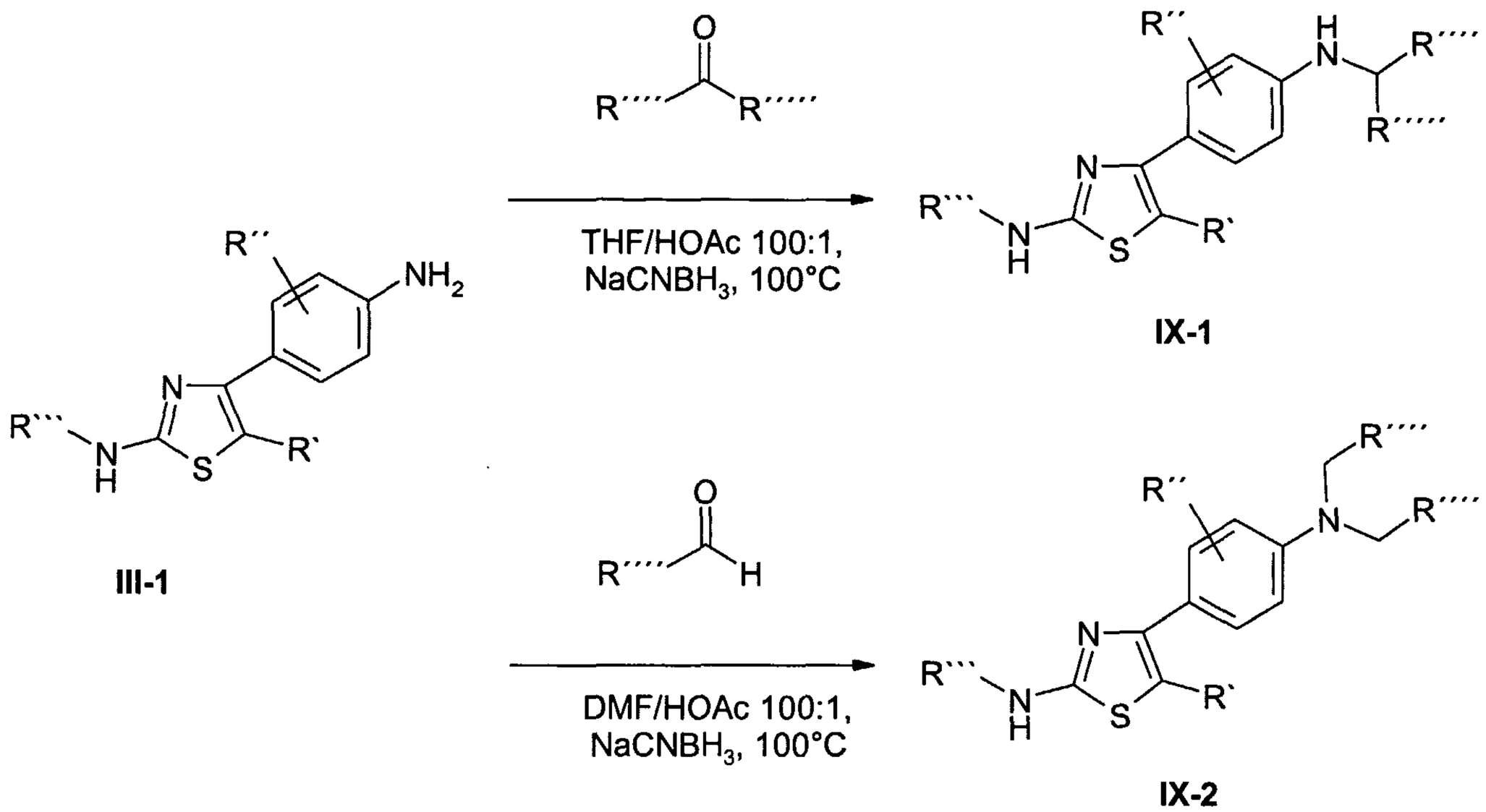


General procedure 8 for the preparation of 2-aminothiazoles **VIII-2**:

2-aminothiazole **III-1** and 1.5 equiv. dichloro or dibromo compound **VII-1** were dissolved in toluene and 6 equiv. *N,N*-diisopropyl-*N*-ethylamine were added. If the dichloro compound **VII-1** was used, 0.2 equiv. tetrabutylammonium iodide were added. The mixture was stirred at 100 °C for 2 days. The solvent was removed and the residue was purified with preparative HPLC.

Synthesis IX:

Preparation of 2-aminothiazoles **IX-1** and **IX-2**:



General procedure 9 for the preparation of 2-aminothiazoles **IX-1**:

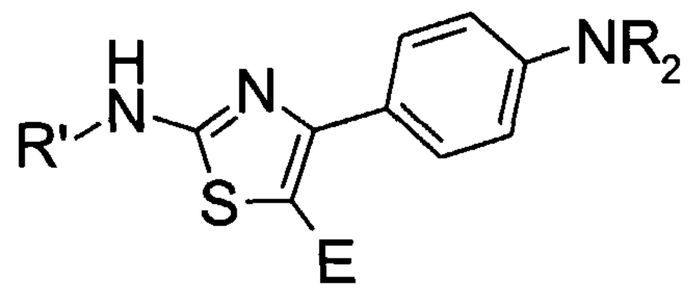
2-aminothiazole **III-1** and 5 equiv. aldehyde or ketone were dissolved in THF/HOAc (100:1) and 5 equiv. sodium cyanoborohydride were added. The mixture was stirred at room temperature overnight. The solvent was removed, ethyl acetate was added and washed with sat. $NaHCO_3$ and NaCl-solutions. After drying over $MgSO_4$ the solvent was removed and the crude product was purified by preparative HPLC.

General procedure 10 for the preparation of 2-aminothiazoles **IX-2**:

2-aminothiazole **III-1** and 10 equiv. aldehyde were dissolved in DMF/HOAc (100:1) and 20 equiv. sodium cyanoborohydride were added. The mixture was stirred at room temperature overnight. The solvent was removed, ethyl acetate was added and washed with sat. $NaHCO_3$ and NaCl-solutions. After drying over $MgSO_4$ the solvent was removed and if necessary the crude product was purified by preparative HPLC.

Synthesis X:

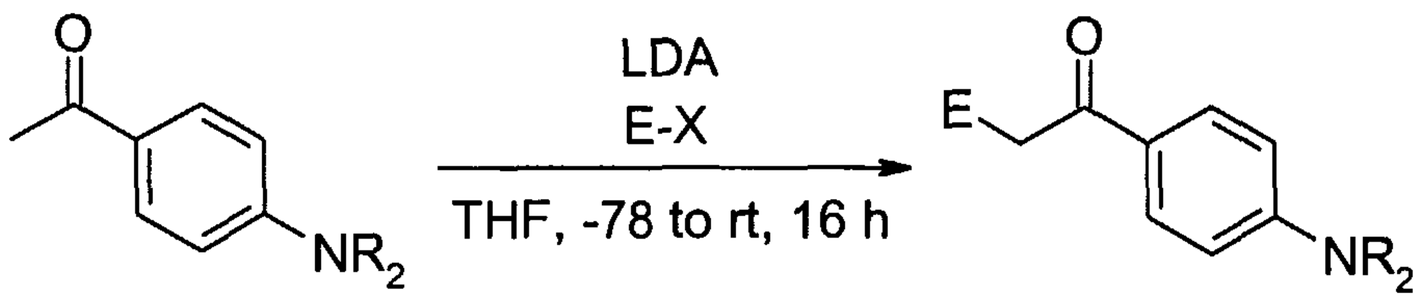
Preparation of 2-aminothiazoles **X-1**:



XI-1

General procedure 11 for the preparation of 5-substituted aminothiazoles starting from 4-dialkylamino acetophenone and elektrophiles :

Intermediates 1



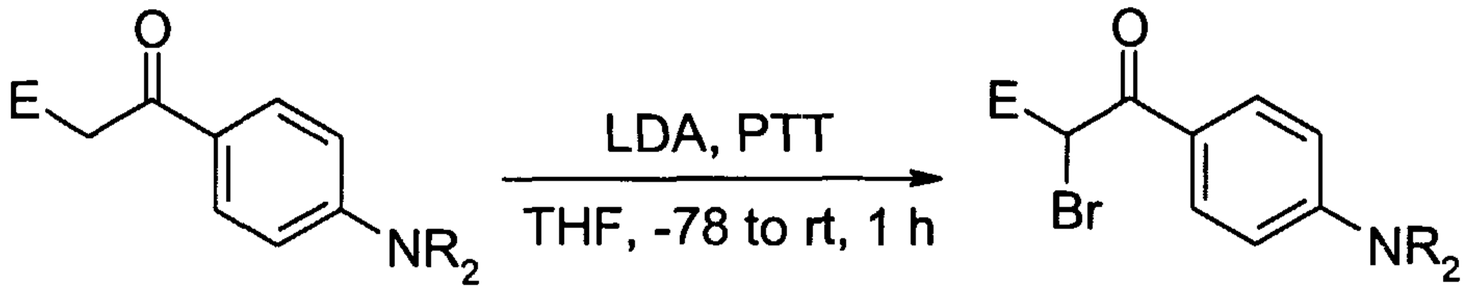
R = alkyl, …

E = elektrophile

X = leaving group (i.e. chloride, bromide, iodide)

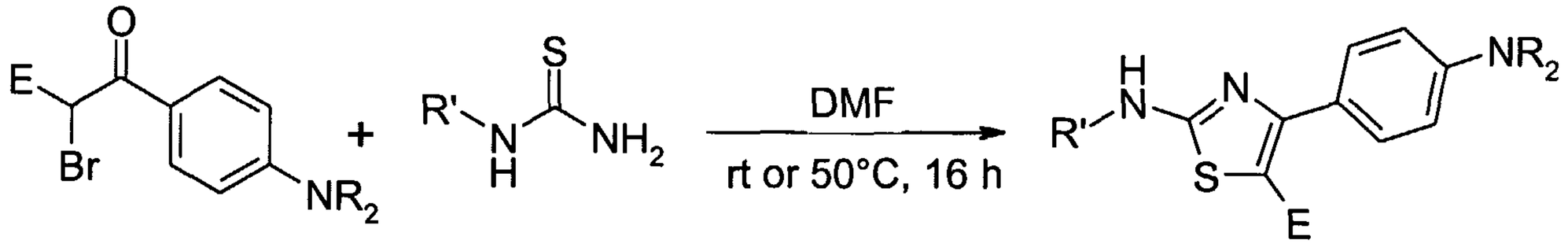
A solution of LDA (1.8 M in THF, 1 eq) was added to a solution of an 4-dialkylamino acetophenone (1 eq) in THF (5 ml/mmol) at -78°C. After stirring for 10 min an elektrophile was added (i.e. methyliodide, benzylbromide, allylbromide, allylchloroformate). The solution was warmed up to room temperature and the mixture was stirred for 16 hours. Water and a sat. solution of sodium hydrogencarbonate were added. The mixture was extracted twice with ethylacetate and the combined organic layers were washed with brine and dried over MgSO4. The solvent was filtered and evaporated to yield an -substituted acetophenone as intermediate **1**.

Intermediates 2



A solution of LDA (1.8 M in THF, 1 eq) was added to a solution of intermediate **1** (1 eq) in THF (5 ml/mmol) at -78°C. After stirring for 10 min a solution of phenyltrimethylammoniumtribromide (PTT, 1.5 eq) in THF (2 ml/mmol) was added. The solution was warmed up to room temperature and stirred for 1 h. Water and a sat. solution of sodium hydrogencarbonate were added. The mixture was extracted twice with ethylacetate and the combined organic layers were washed with brine and dried over MgSO4. The solvent was filtered and evaporated to yield intermediate **2**.

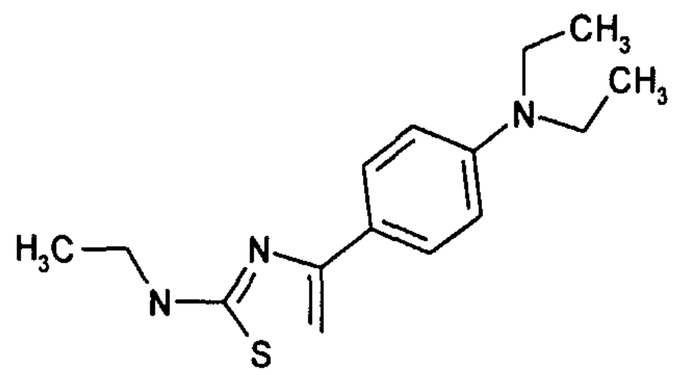
5-substituted aminothiazoles



A solution of intermediate **2** (1 eq) and a thiourea (1 eq) in DMF (5 ml/mmol) was stirred for 16 h at room temperature to 50°C. Water and a sat. solution of sodium hydrogencarbonate were added. The mixture was extracted twice with ethylacetate and the combined organic layers were washed with brine and dried over MgSO4. The solvent was filtered and evaporated to give crude products. The crude products were purified by preparative HPLC-MS to yield 5-substituted aminothiazoles.

Examples:

SP1342:



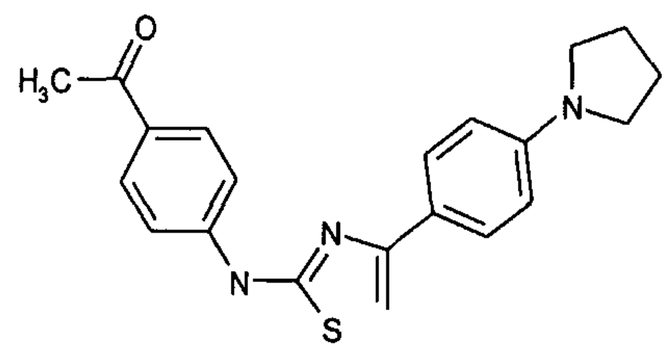
52 mg (0.5 mmol) ethylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 186 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 276 $[M+H]^+$

SP1336:



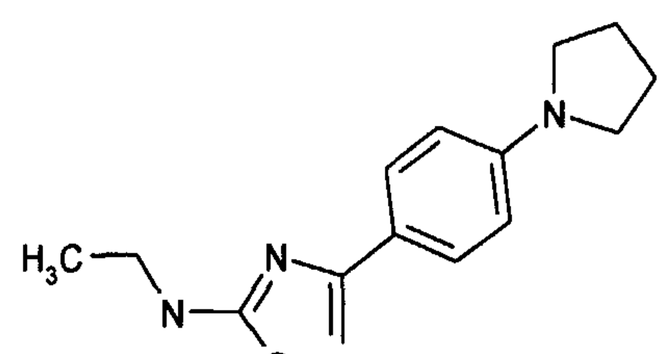
97 mg (0.5 mmol) 4-acetylphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 186 mg (hydrobromide)

Purity (HPLC): >98%

HPLC-MS: 364 $[M+H]^+$

SP1335:



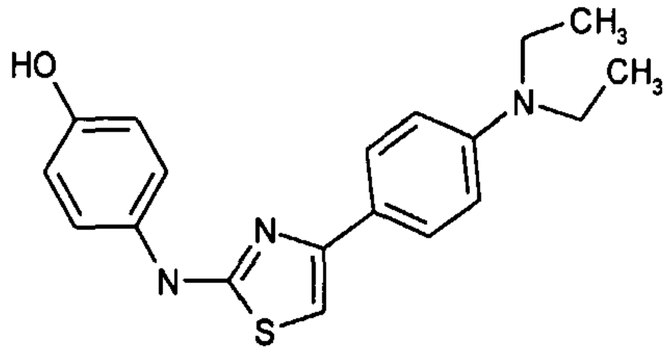
52 mg (0.5 mmol) ethylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 182 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 274 $[M+H]^+$

SP1319:



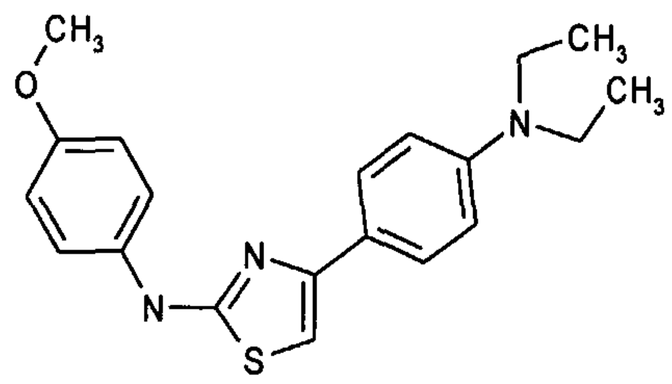
18 mg (0.1 mmol) hydroxyphenylthiourea and 27 mg (0.1 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 40 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 340 $[M+H]^+$

SP1318:



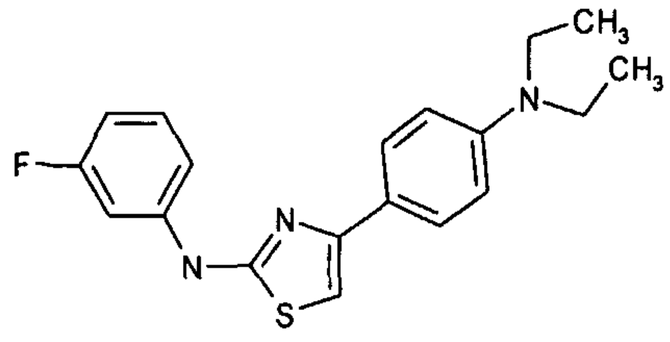
18 mg (0.1 mmol) methoxyphenylthiourea and 27 mg (0.1 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 41 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 353 $[M+H]^+$

SP1315:



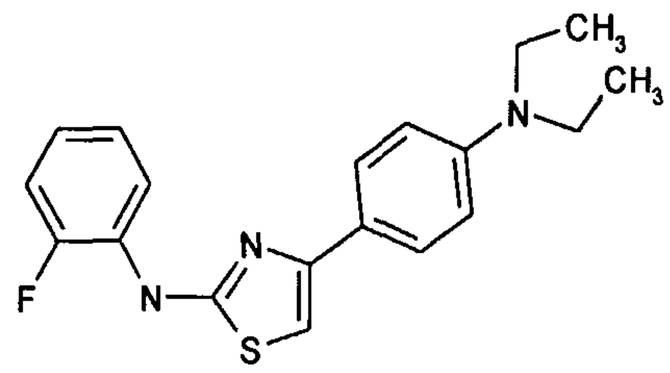
17 mg (0.1 mmol) 3-fluorophenylthiourea and 27 mg (0.1 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 43 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 342 $[M+H]^+$

SP1314:



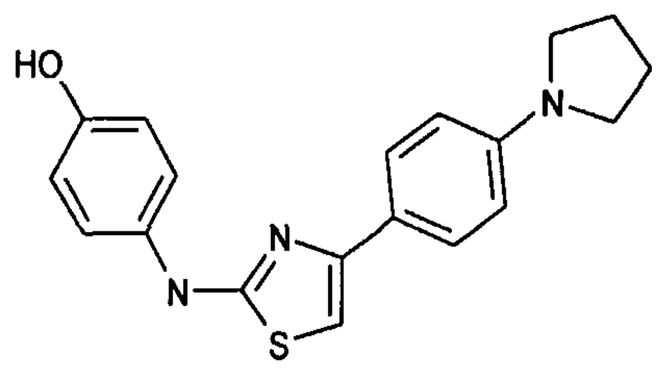
18 mg (0.1 mmol) methoxyphenylthiourea and 27 mg (0.1 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 43 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 342 $[M+H]^+$

SP1313:



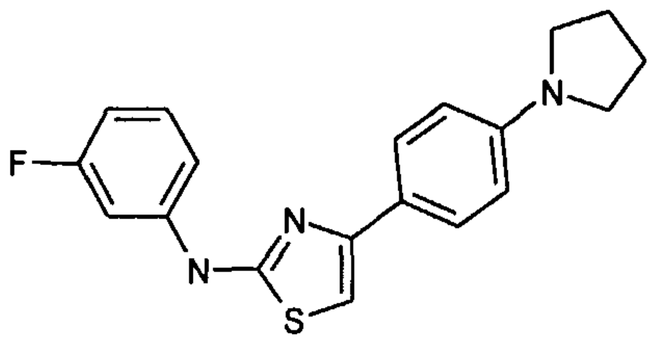
17 mg (0.1 mmol) hydroxyphenylthiourea and 27 mg (0.1 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 43 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 338 $[M+H]^+$

SP1309:



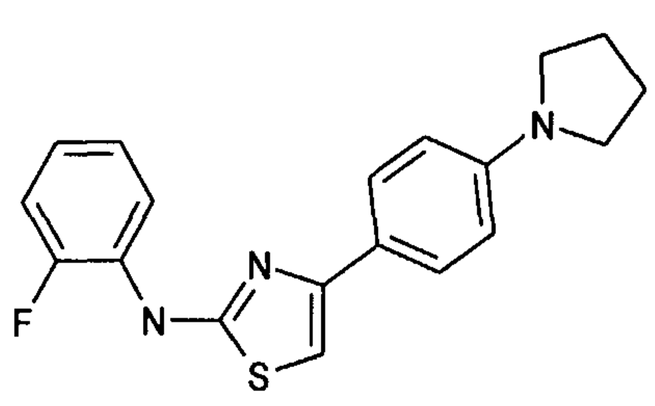
17 mg (0.1 mmol) 3-fluorphenylthiourea and 27 mg (0.1 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 41 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 340 $[M+H]^+$

SP1308:



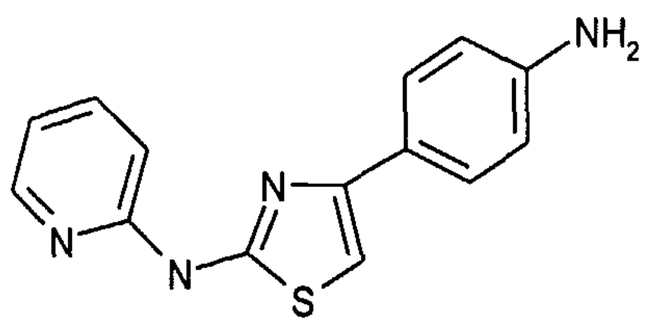
17 mg (0.1 mmol) 2-fluorphenylthiourea and 27 mg (0.1 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 40 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 340 $[M+H]^+$

SP1192:



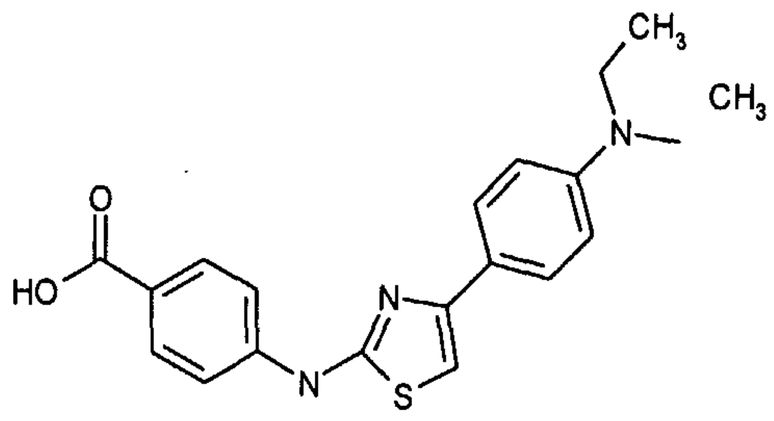
306 mg (2 mmol) 2-pyridylthiourea and 488 mg (2 mmol) *alpha*-bromo-4-nitroacetophenone in 20 ml ethanol were reacted according to general procedure 2. 30 mg (0.1 mmol) of the compound prepared above were reacted with 67 mg (0.3 mmol) tin(II)chloride in ethanol according to general procedure 3.

Yield: 23 mg

Purity (HPLC): >95%

HPLC-MS: 269 $[M+H]^+$

SP1155:



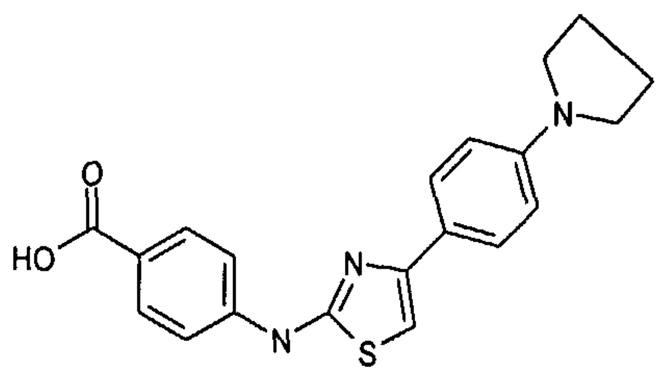
98 mg (0.5 mmol) 4-carboxyphenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 228 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 368 $[M+H]^+$

SP1153:



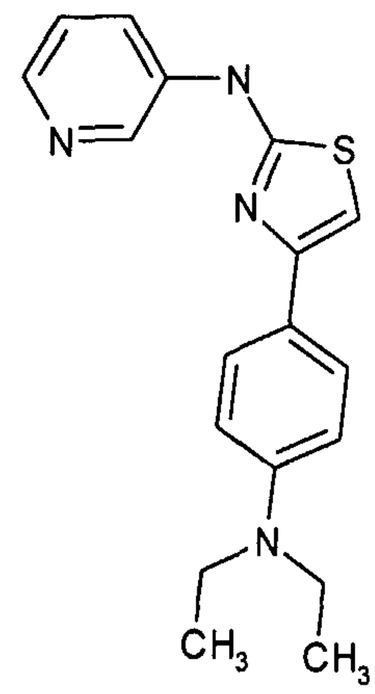
98 mg (0.5 mmol) 4-carboxyphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 3 ml ethanol were reacted according to general procedure 2.

Yield: 230 mg (hydrobromide)

Purity (HPLC): >98%

HPLC-MS: 366 $[M+H]^+$

SP0844:



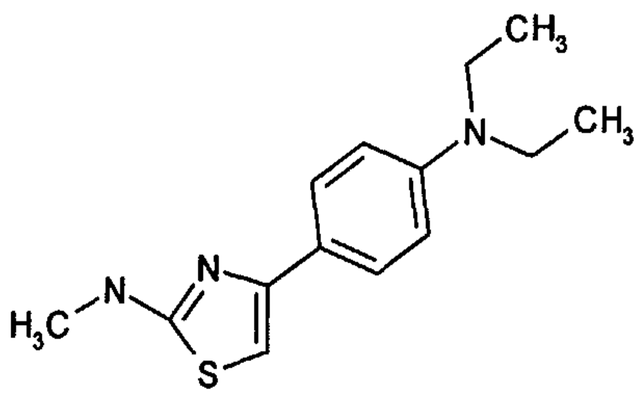
56 mg (0.4 mmol) 3-pyridylthiourea and 108 mg (0.1 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 172 mg (hydrobromide)

Purity (HPLC): >98%

HPLC-MS: 342 $[M+H]^+$

SP0750:



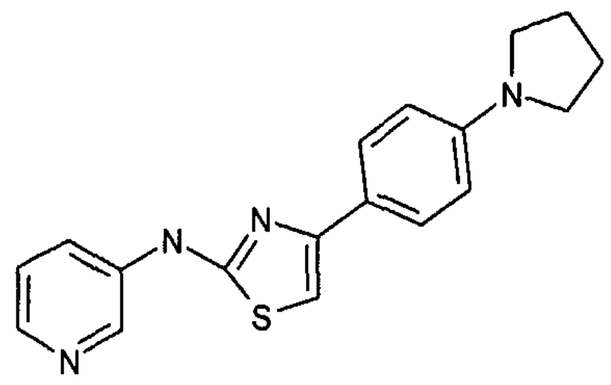
18 mg (0.2 mmol) N-methylthiourea and 54 mg (0.2 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 64 mg (hydrobromide)

Purity (HPLC): >95%

GC-MS: 261 $[M^+]$

SP0747:



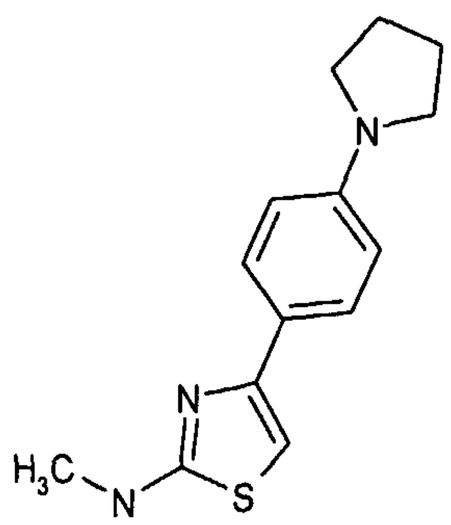
153 mg (1 mmol) 3-pyridylthiourea and 268 mg (1 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 20 ml ethanol were reacted according to general procedure 2.

Yield: 285 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 323 $[M+H]^+$

SP0704:



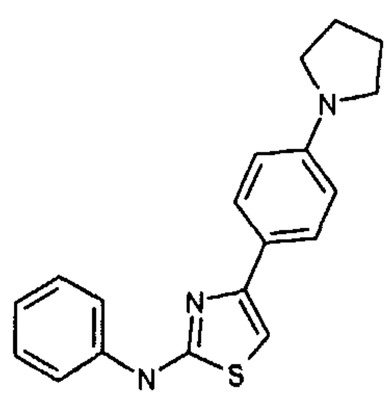
270 mg (3 mmol) N-methylthiourea and 804 mg (3 mmol) *alpha*-bromo-4-(pyrrolidino)-acetophenone in 20 ml ethanol were reacted according to general procedure 2.

Yield: 1.17 g (hydrobromide)

Purity (HPLC): >95%

GC-MS: 259 $[M^+]$

SP0694:



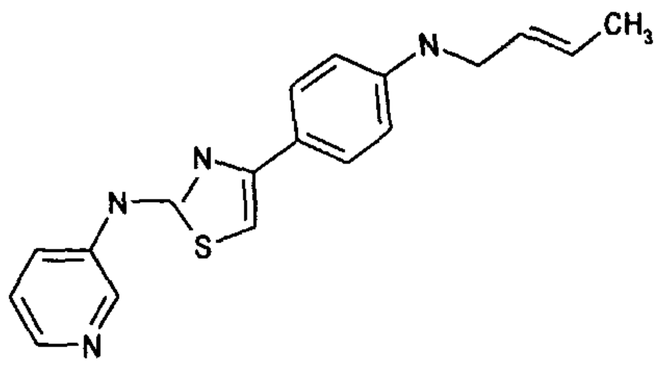
570 mg (3 mmol) phenylthiourea and 805 mg (3 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 20 ml ethanol were reacted according to general procedure 2.

Yield: 1.31 g (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 322 $[M+H]^+$

SP6538:



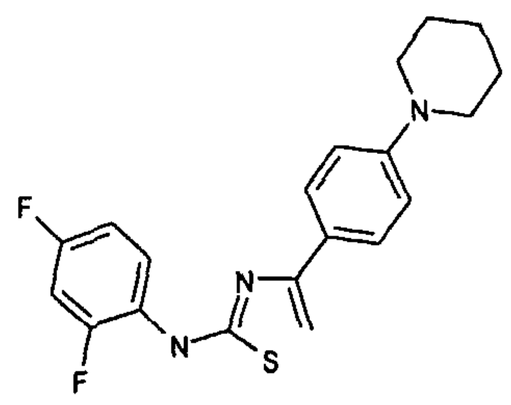
306 mg (2.0 mmol) 3-pyridylthiourea and 488 mg (2.0 mmol) 4-nitro-*alpha*-bromoacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 1.36 g (6.0 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 23 mg (0.1mmol) of the resulting amino compound were reacted with 41 μl (0.5 mmol) crotonaldehyde and 63 mg (0.5 mmol) sodium cyanoborohydride in 5 ml THF/HOAc (100/1) according to general procedure 9 followed by preparative HPLC.

Yield: 11 mg.

Purity (HPLC): >95%

HPLC-MS: 323 $[M+H]^+$

SP6406:



143 mg (0.5 mmol) dibromobarbituric acid and 151 mg (1mmol) 4-piperidino-acetophenone were dissolved in 4 ml diethyl ether and stirred at room temperature overnight. The reaction mixture was filtered and the filtrate was washed with sat. $NaHCO_3$-solution and water. The organic

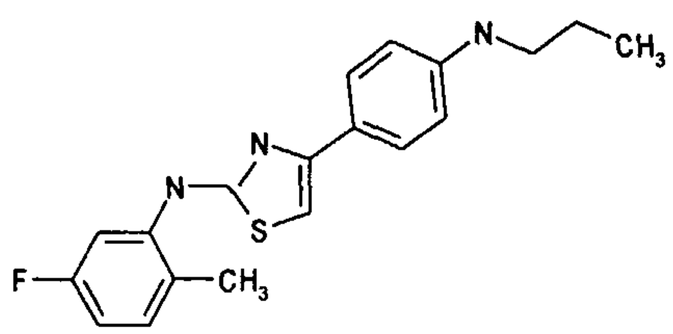
layer was dried over MgSO4 and the solvent was removed under reduced pressure to yield 172 mg of *alpha*-bromo-4-(1-piperidino)-acetophenone. 38 mg (0.2 mmol) 2,4-difluorophenylthiourea and 56,44 mg (0.2 mmol) *alpha*-bromo-4-(1-piperidino)-acetophenone were reacted in 5 ml ethanol according to general procedure 2 and purified using preparative HPLC.

Yield: 4.7 mg

Purity (HPLC): 90%

HPLC-MS: 372 $[M+H]^+$

SP6367:



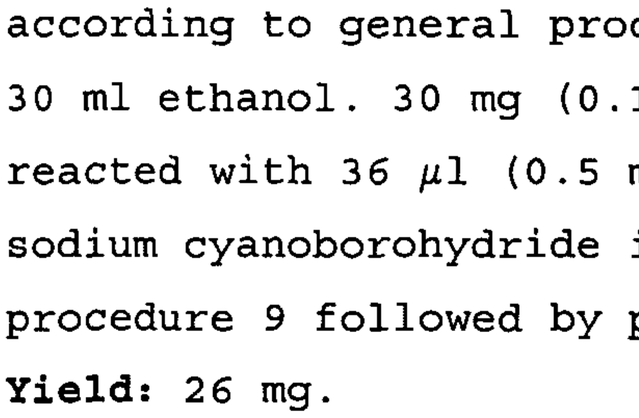
368 mg (2.0 mmol) 5-fluoro-2-methylphenylthiourea and 488 mg (2.0 mmol) 4-nitro-*alpha*-bromoacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 1.36 g (6.0 mmol) $SnCl_2 \times 2\ H_2O$ in 30 ml ethanol. 30 mg (0.1 mmol) of the resulting amino compound were reacted with 36 μl (0.5 mmol) propionaldehyde and 63 mg (0.5 mmol) sodium cyanoborohydride in 5 ml THF/HOAc (100/1) according to general procedure 9 followed by preparative HPLC.

Yield: 26 mg.

Purity (HPLC): 80%

HPLC-MS: 342 $[M+H]^+$

SP6282:



376 mg (2.0 mmol) 2,4-difluorophenylthiourea and 488 mg (2.0 mmol) 4-nitro-*alpha*-bromoacetophenone in 30 ml ethanol were reacted according to

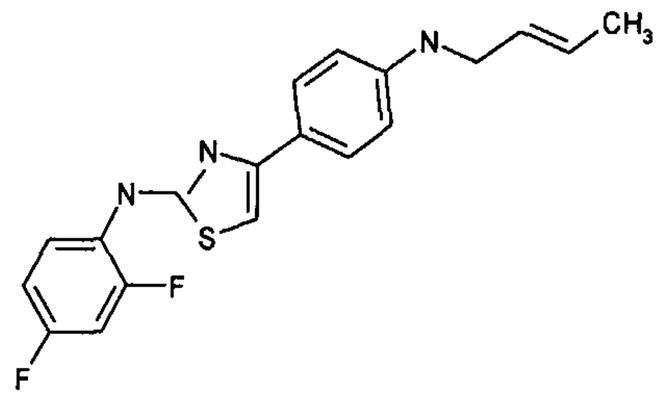
general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 1.36 g (6.0 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 30 mg (0.1mmol) of the resulting amino compound were reacted with 53 µl (0.5 mmol) 3-pentanone and 63 mg (0.5 mmol) sodium cyanoborohydride in 5 ml THF/HOAc (100/1) according to general procedure 9 followed by preparative HPLC.

Yield: 5 mg.

Purity (HPLC): >95%

HPLC-MS: 374 $[M+H]^+$

SP6280:



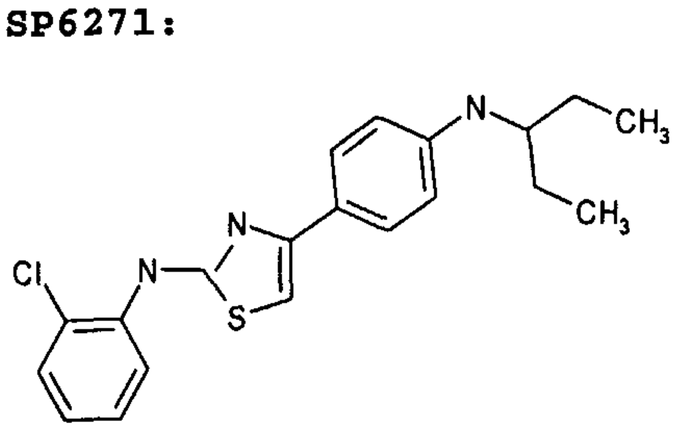
376 mg (2.0 mmol) 2,4-difluorophenylthiourea and 488 mg (2.0 mmol) 4-nitro-*alpha*-bromoacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 1.36 g (6.0 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 30 mg (0.1mmol) of the resulting amino compound were reacted with 41 µl (0.5 mmol) crotonaldehyde and 63 mg (0.5 mmol) sodium cyanoborohydride in 5 ml THF/HOAc (100/1) according to general procedure 9.

Yield: 27 mg.

Purity (HPLC): >95%

HPLC-MS: 358 $[M+H]^+$

SP6271:



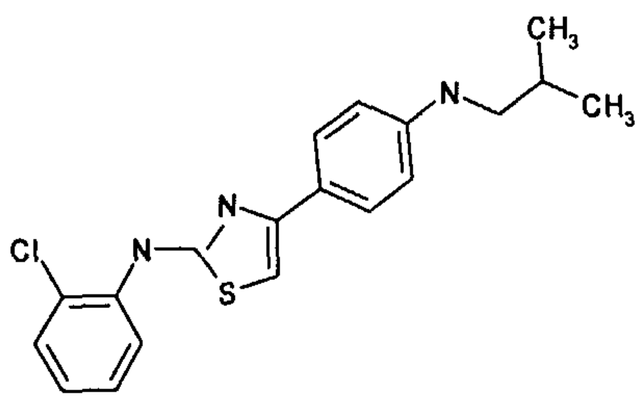
374 mg (2.0 mmol) 2-chlorophenylthiourea and 488 mg (2.0 mmol) 4-nitro-*alpha*-bromoacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 1.36 g (6.0 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 30 mg (0.1mmol) of the resulting amino compound were reacted with 53 µl (0.5 mmol) 3-pentanone and 63 mg (0.5 mmol) sodium cyanoborohydride in 5 ml THF/HOAc (100/1) according to general procedure 9.

Yield: 5 mg.

Purity (HPLC): >95%

HPLC-MS: 373 $[M+H]^+$

SP6266:



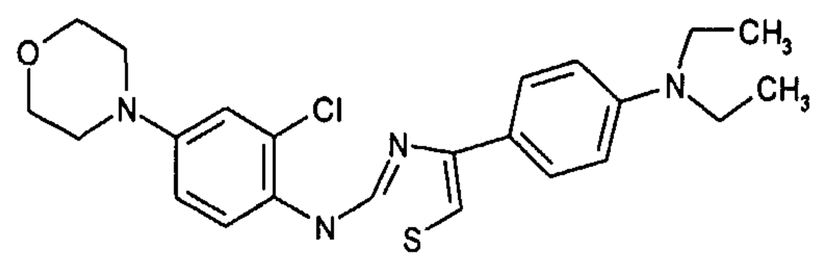
374 mg (2.0 mmol) 2-chlorophenylthiourea and 488 mg (2.0 mmol) 4-nitro-*alpha*-bromoacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 1.36 g (6.0 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 30 mg (0.1mmol) of the resulting amino compound were reacted with 46 µl (0.5 mmol) isobutyraldehyde and 63 mg (0.5 mmol) sodium cyanoborohydride in 5 ml THF/HOAc (100/1) according to general procedure 9.

Yield: 29 mg.

Purity (HPLC): >95%

HPLC-MS: 358 $[M+H]^+$

SP5875:



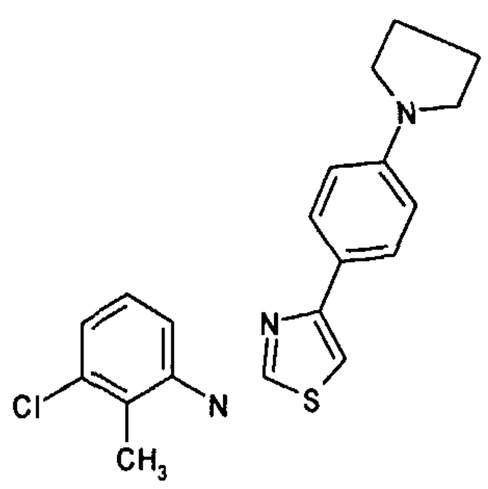
3.45 g (20 mmol) 2-chloro-4-nitroaniline and 2.96 ml (22 mmol) benzoylisothiocyanate in 40 ml acetone were reacted according to general procedure 1. 463 mg (2.0 mmol) 2-chloro-4-nitrophenylthiourea and 540 mg (2 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 1.36 g (6.0 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 75 mg (0.2mmol) of the resulting amino compound were reacted with 38 µl (0.3 mmol) 1-bromo-2-(2-bromo-ethoxy)-ethane and 209 µl (1.2 mmol) *N,N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Yield: 16 mg.

Purity (HPLC): >95%

HPLC-MS: 444 $[M+H]^+$

SP5799:



1.21 ml (10 mmol) 3-chloro-2-methylaniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 20 ml acetone were reacted according to general procedure 1.

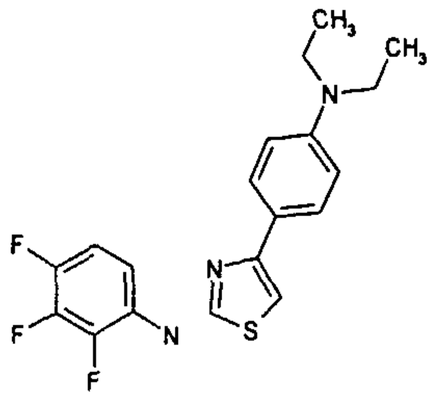
100 mg (0.5 mmol) 3-chloro-2-methylphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 189 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 370 $[M+H]^+$

SP5780:



1.06 ml (10 mmol) 2,3,4-trifluoraniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 20 ml acetone were reacted according to general procedure 1.

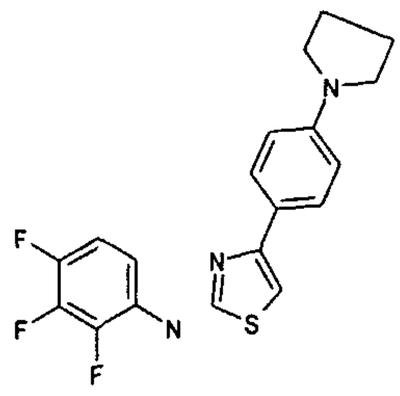
103 mg (0.5 mmol) 2,3,4-trifluorphenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 195 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 378 $[M+H]^+$

SP5779:



1.06 ml (10 mmol) 2,3,4-trifluoraniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 20 ml acetone were reacted according to general procedure 1.

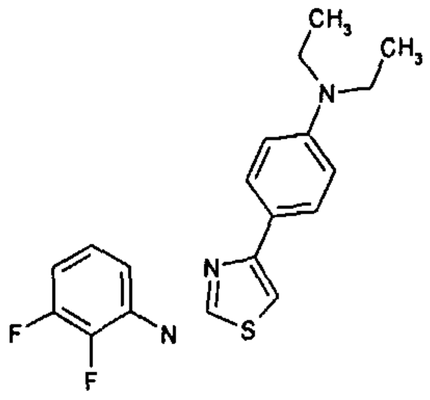
103 mg (0.5 mmol) 2,3,4-trifluorphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 181 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 376 $[M+H]^+$

SP5778:



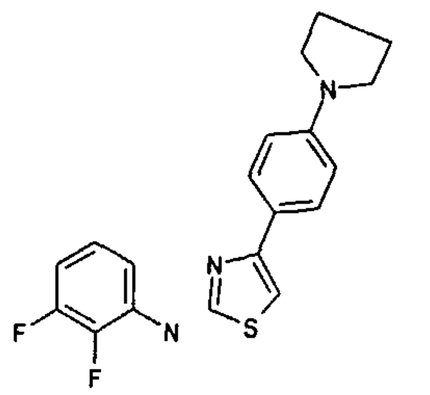
507 µl (5 mmol) 2,3-difluoraniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 10 ml acetone were reacted according to general procedure 1. 94 mg (0.5 mmol) 2,3-difluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 172 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 360 $[M+H]^+$

SP5777:



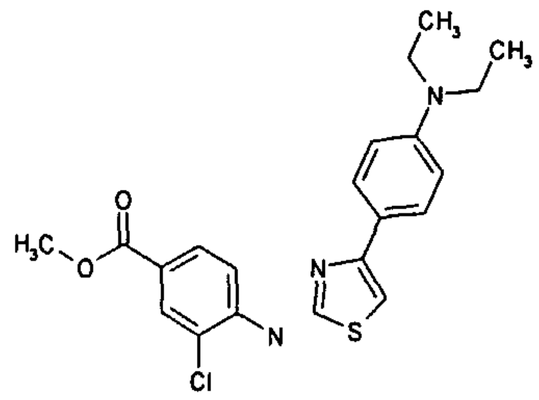
507 µl (5 mmol) 2,3-difluoraniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 10 ml acetone were reacted according to general procedure 1. 94 mg (0.5 mmol) 2,3-difluorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 156 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 358 $[M+H]^+$

SP5776:



1.86 g (10 mmol) methyl-4-amino-3-chlorobenzoate and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml acetone were reacted according to general procedure 1.

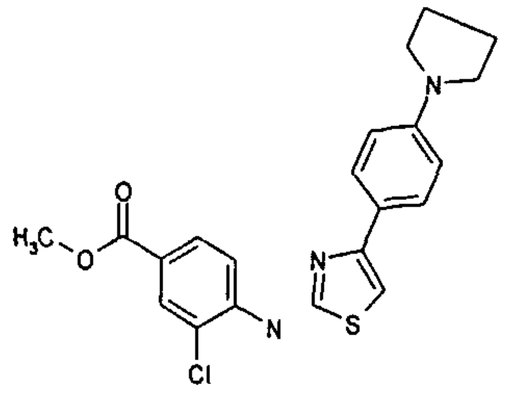
122 mg (0.5 mmol) 3-chloro-4-carboxylic acid methyl ester phenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 228 mg.

Purity (HPLC): >95%

HPLC-MS: 416 $[M+H]^+$

SP5775:



1.86 g (10 mmol) methyl-4-amino-3-chlorobenzoate and 1.48 ml (11 mmol) benzoyl isothiocyanate in 20 ml acetone were reacted according to general procedure 1.

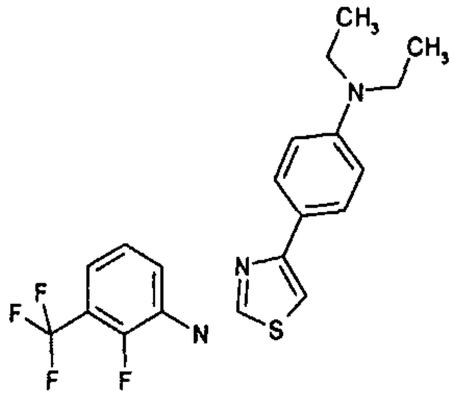
122 mg (0.5 mmol) 3-chloro-4-carboxylic acid methyl ester phenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 234 mg.

Purity (HPLC): >95%

HPLC-MS: 414 $[M+H]^+$

SP5774:



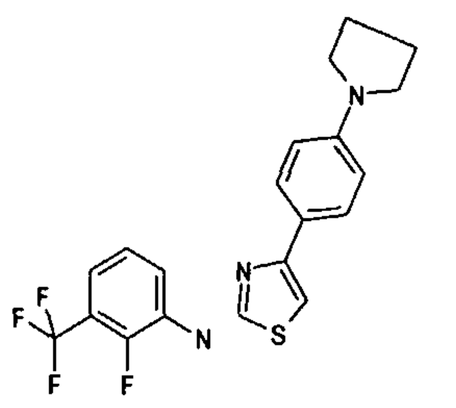
1.28 ml (10 mmol) 2-fluoro-3-(trifluoromethyl)-aniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 20 ml acetone were reacted according to general procedure 1.

119 mg (0.5 mmol) 2-fluoro-3-(trifluoromethyl)phenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Purity (HPLC): >95%

HPLC-MS: 410 $[M+H]^+$

SP5773:



1.28 ml (10 mmol) 2-fluoro-3-(trifluoromethyl)-aniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 20 ml acetone were reacted according to general procedure 1.

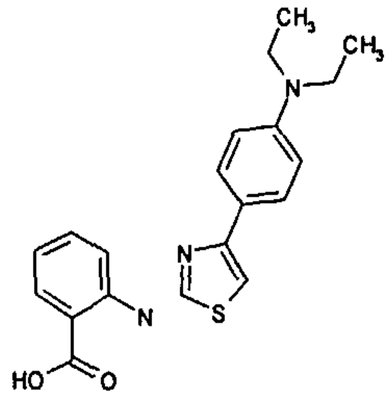
119 mg (0.5 mmol) 2-fluoro-3-(trifluoromethyl)phenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 164 mg (hydrobromide)

Purity (HPLC): 90%

HPLC-MS: 408 $[M+H]^+$

SP5760:



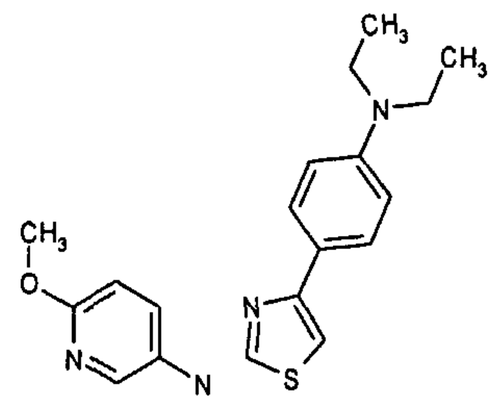
1.37 g (10 mmol) anthranilic acid and 1.48 ml (11 mmol) benzoyl isothiocyanate in 20 ml acetone were refluxed for 3 h. The precipitate was filtered and suspended in 20 ml methanol/acetone/water (1:1:1). 690 mg (50 mmol) K_2CO_3 were added and the mixture was stirred at room temperature for 4 h. The organic solvents were removed under reduced pressure and the remaining solution was poured into an solution of 1 N HCl in ice. The precipitate was filtered, carefully washed with water and dried in high vacuum. 89 mg (0.5 mmol of this compound were reacted with 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol according to general procedure 2 followed by purification using preparative HPLC.

Yield: 13 mg.

Purity (HPLC): >95%

HPLC-MS: 368 $[M+H]^+$

SP5756:



1.24 g (10 mmol) 5-amino-2-methoxypyridine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml acetone were reacted according to general procedure 1.

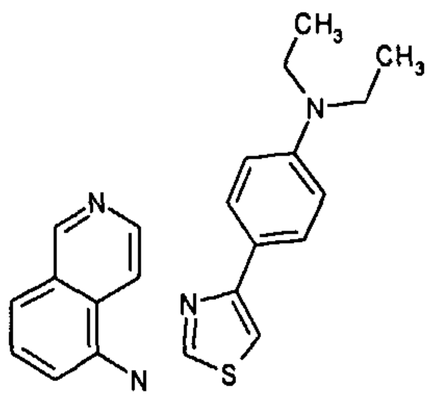
92 mg (0.5 mmol) 2-methoxy-5-thioureapyridine and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 184 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 355 $[M+H]^+$

SP5752:



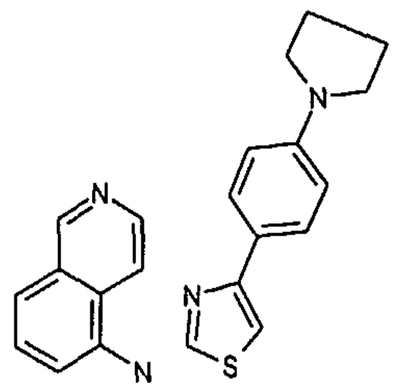
1.44 g (10 mmol) 5-aminoisochinoline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml acetone were reacted according to general procedure 1. 102 mg (0.5 mmol) 5-quinolinylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 214 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 375 $[M+H]^+$

SP5751:



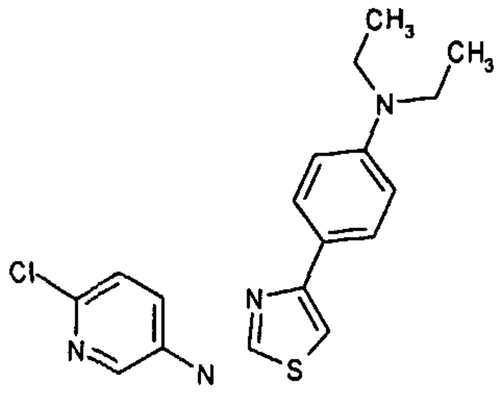
1.44 g (10 mmol) 5-aminoisochinoline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml acetone were reacted according to general procedure 1. 102 mg (0.5 mmol) 5-quinolinylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 216 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 373 $[M+H]^+$

SP5748:



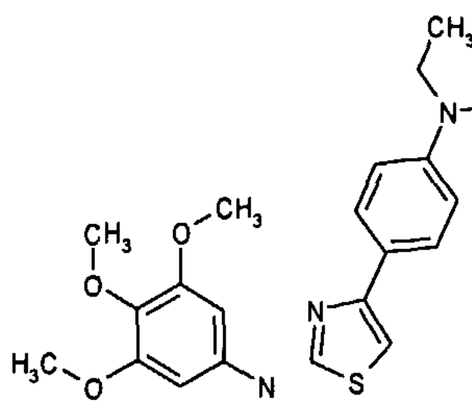
386 mg (3 mmol) 5-amino-2-chloropyridine and 440 µl (3 mmol) benzoyl isothiocyanate in 10 ml acetone were reacted according to general procedure 1. 37.5 mg (0.2 mmol) 6-chloropyridinyl-3-thiourea and 54 mg (0.2 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 98 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 359 $[M+H]^+$

SP5746:



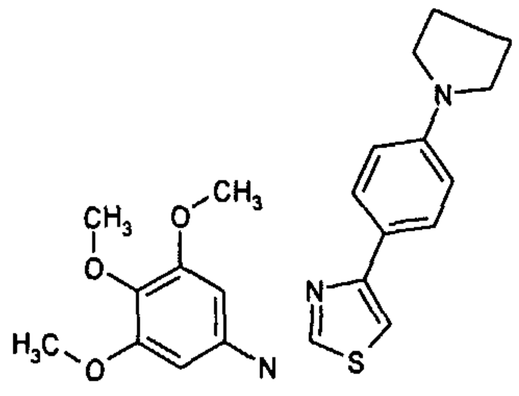
916 mg (5 mmol) 3,4,5-trimethoxyaniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 10 ml acetone were reacted according to general procedure 1. 128 mg (0.5 mmol) 3,4,5-trimethoxyphenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 257 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 414 $[M+H]^+$

SP5745:



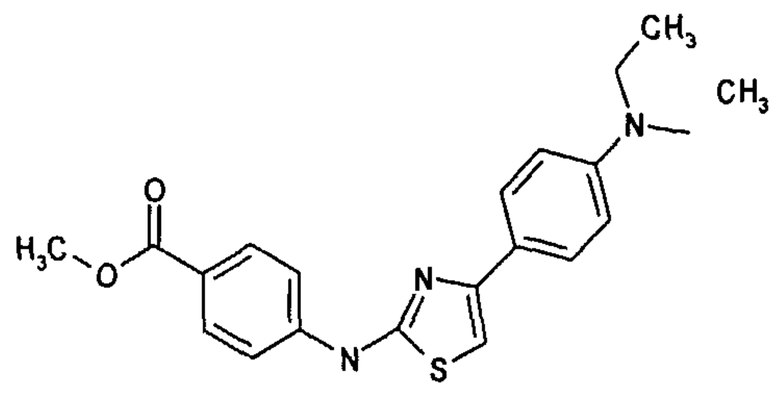
916 mg (5 mmol) 3,4,5-trimethoxyaniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 10 ml acetone were reacted according to general procedure 1. 128 mg (0.5 mmol) 3,4,5-trimethoxyphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 253 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 412 $[M+H]^+$

SP5736:



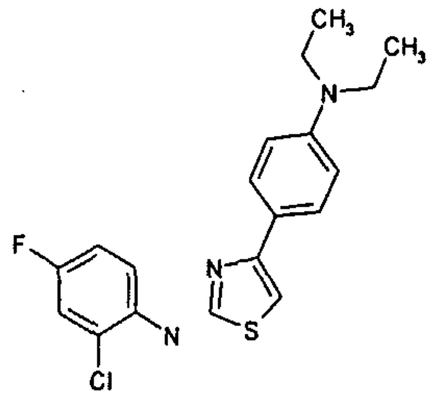
154 mg (0.34 mmol) SP1155xHBr were dissolved in 10 ml methanol and 50 µl (0.68 mmol) thionyl chloride were added carefully. The mixture was refluxed for 48 h and cooled to room temperature. The reaction mixture was concentrated, dissolved in 30 ml methylene chloride and washed with sat. $NaHCO_3$-solution. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure.

Yield: 34 mg (hydrobromide)

Purity (HPLC): 90%

HPLC-MS: 382 $[M+H]^+$

SP5718:



1.2 ml (10 mmol) 2-chloro-4-fluoroaniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml acetone were reacted according to general procedure 1.

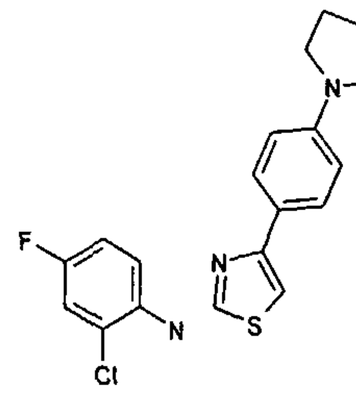
102 mg (0.5 mmol) 2-chloro-4-fluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 233 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 376 $[M+H]^+$

SP5717:



1.2 ml (10 mmol) 2-chloro-4-fluoroaniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml acetone were reacted according to general procedure 1.

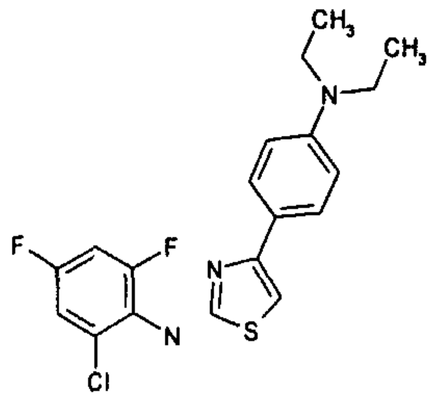
102 mg (0.5 mmol) 2-chloro-4-fluorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 230 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 374 $[M+H]^+$

SP5716:



818 mg (5 mmol) 6-chloro-2,4-difluoroaniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 15 ml acetone were reacted according to general procedure 1.

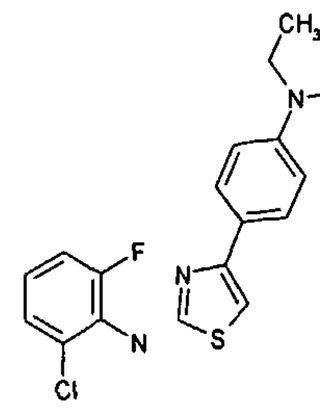
111 mg (0.5 mmol) 6-chloro-2,4-difluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 248 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 395 $[M+H]^+$

SP5714:



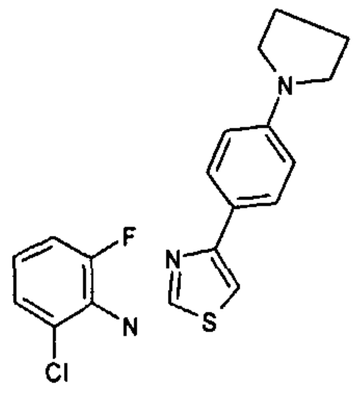
600 µl (5 mmol) 2-chloro-6-fluoroaniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 15 ml acetone were reacted according to general procedure 1. 61 mg (0.3 mmol) 2-chloro-6-fluorophenylthiourea and 81 mg (0.3 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 141 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 376 $[M+H]^+$

SP5713:



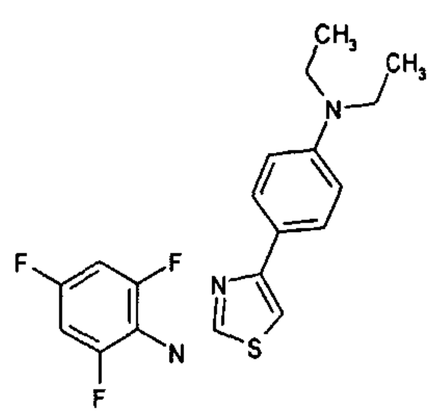
600 µl (5 mmol) 2-chloro-6-fluoroaniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 15 ml acetone were reacted according to general procedure 1. 61 mg (0.3 mmol) 2-chloro-6-fluorophenylthiourea and 81 mg (0.3 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 143mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 374 $[M+H]^+$

SP5712:



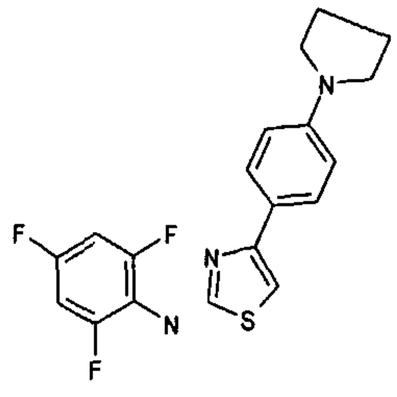
441 mg (3 mmol) 2,4,6-trifluoroaniline and 444 µl (3.3 mmol) benzoyl isothiocyanate in 10 ml acetone were reacted according to general procedure 1. 62 mg (0.3 mmol) 2,4,6-trifluorophenylthiourea and 81 mg (0.3 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 151 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 378 $[M+H]^+$

SP5711:



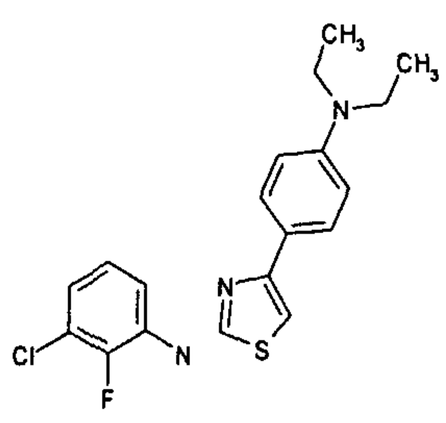
441 mg (3 mmol) 2,4,6-trifluoroaniline and 444 µl (3.3 mmol) benzoyl isothiocyanate in 10 ml acetone were reacted according to general procedure 1. 62 mg (0.3 mmol) 2,4,6-trifluorophenylthiourea and 81 mg (0.3 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 153 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 376 $[M+H]^+$

SP5710:



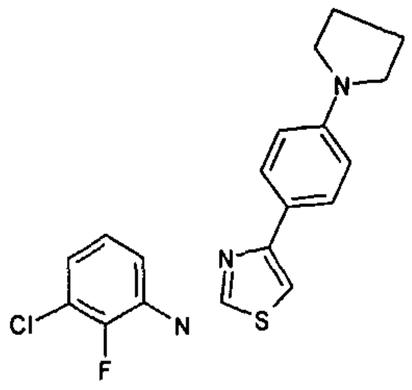
1.2 ml (10 mmol) 3-chloro-2-fluoraniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 102 mg (0.5 mmol) 3-chlor-2-fluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 229 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 376 $[M+H]^+$

SP5709:



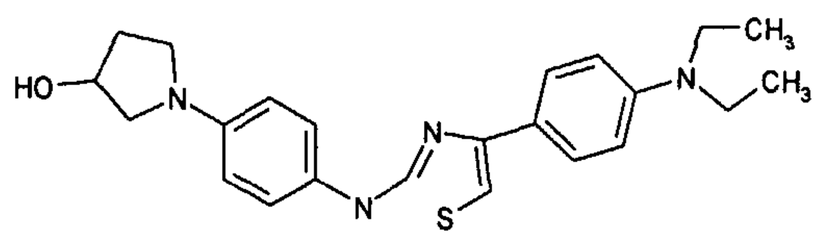
1.2 ml (10 mmol) 3-chloro-2-fluoraniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 102 mg (0.5 mmol) 3-chlor-2-fluorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 239 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 374 $[M+H]^+$

SP5674:



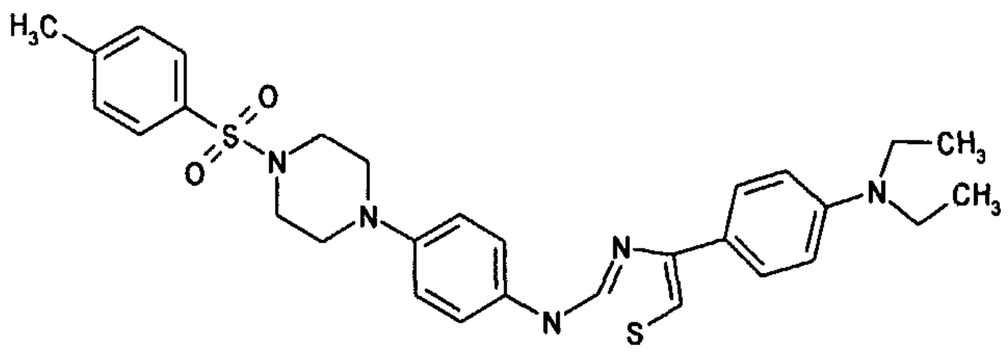
943 mg (4.78 mmol) 4-nitrophenylthiourea and 1.29 g (4.78 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.2 g (14.3 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 68 mg (0.2 mmol) of the resulting amino compound were reacted with 35 μl (0.3 mmol) 1,4-dibromo-2-butanol and 209 μl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Yield: 24 mg

Purity (HPLC): >95%

HPLC-MS: 409 $[M+H]^+$

SP5673:



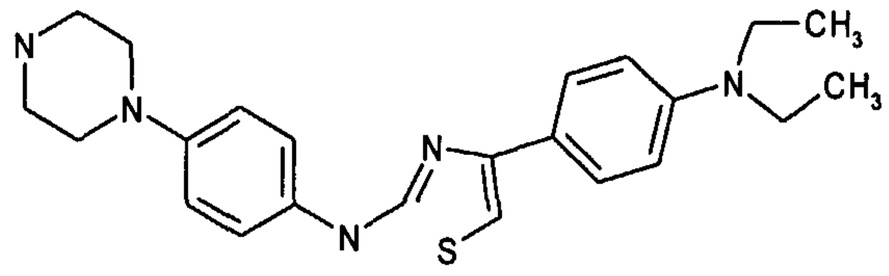
943 mg (4.78 mmol) 4-nitrophenylthiourea and 1.29 g (4.78 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.2 g (14.3 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 68 mg (0.2 mmol) of the resulting amino compound were reacted with 88.8 mg (0.3 mmol) *N,N*-bis-(2-chloroethyl)-*p*-toluenesulfonamide, 15 mg (0.04 mmol) tetrabutylammonium iodide and 209 µl (1.2 mmol) *N,N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Yield: 14 mg.

Purity (HPLC): >95%

HPLC-MS: 562 $[M+H]^+$

SP5672:

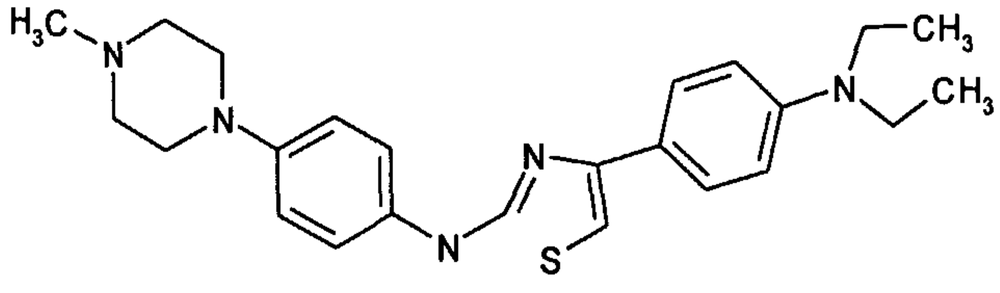


943 mg (4.78 mmol) 4-nitrophenylthiourea and 1.29 g (4.78 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.2 g (14.3 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 68 mg (0.2 mmol) of the resulting amino compound were reacted with 53.6 mg (0.3 mmol) bis-(2-chloroethyl)-amine, 15 mg (0.04 mmol) tetrabutylammonium iodide and 209 µl (1.2 mmol) *N,N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 408 $[M+H]^+$

SP5671:

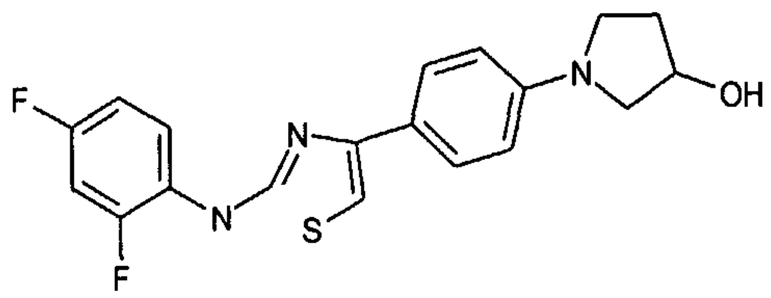


943 mg (4.78 mmol) 4-nitrophenylthiourea and 1.29 g (4.78 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.2 g (14.3 mmol) $SnCl_2$ x $2H_2O$ in 50 ml ethanol. 68 mg (0.2 mmol) of the resulting amino compound were reacted with 57.8 mg (0.3 mmol) *N*-methyl-*N*,*N*-bis-(chlorethyl)-amine, 15 mg (0.04 mmol) tetrabutylammonium iodide and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 422 $[M+H]^+$

SP5661:

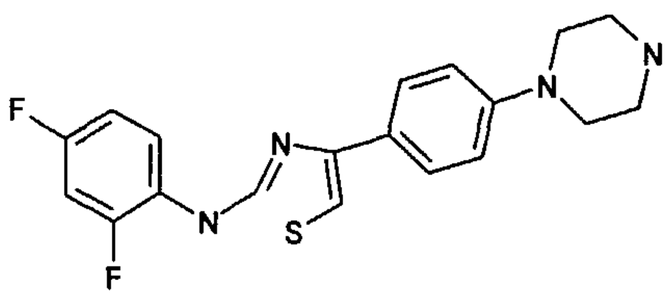


941 mg (5 mmol) 2,4-difluorophenylthiourea and 1.22 g (5 mmol) *alpha*-bromo-4-nitroacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.4 g (15 mmol) $SnCl_2$ x $2H_2O$ in 50 ml ethanol. 61 mg (0.2 mmol) of the resulting amino compound were reacted with 35 µl (0.3 mmol) 1,4-dibromo-2-butanol and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 374 $[M+H]^+$

SP5659:

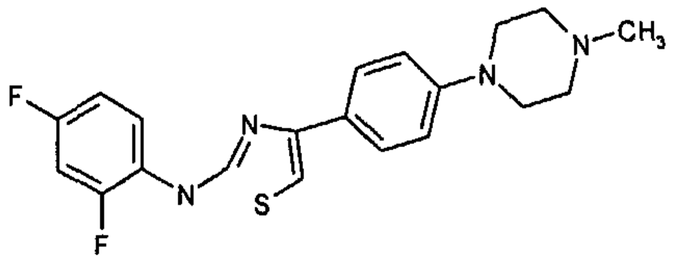


941 mg (5 mmol) 2,4-difluorophenylthiourea and 1.22 g (5 mmol) *alpha*-bromo-4-nitroacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.4 g (15 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 61 mg (0.2 mmol) of the resulting amino compound were reacted with 53.6 mg (0.3 mmol) bis-(2-chloroethyl)-amine, 15 mg (0.04 mmol) tetrabutylammonium iodide and 209 µl (1.2 mmol) *N,N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 373 $[M+H]^+$

SP5658:

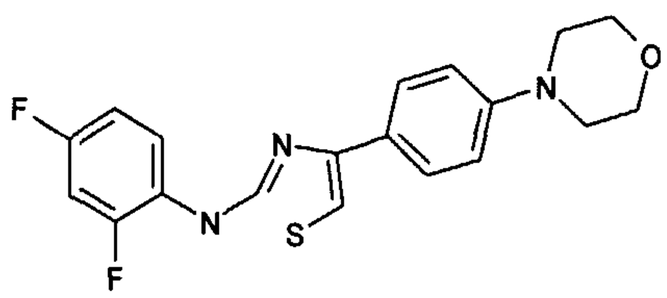


941 mg (5 mmol) 2,4-difluorophenylthiourea and 1.22 g (5 mmol) *alpha*-bromo-4-nitroacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.4 g (15 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 61 mg (0.2 mmol) of the resulting amino compound were reacted with 57.8 mg (0.3 mmol) *N*-methyl-*N,N*-bis-(chlorethyl)-amine, 15 mg (0.04 mmol) tetrabutylammonium iodide and 209 µl (1.2 mmol) *N,N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 387 $[M+H]^+$

SP5657:

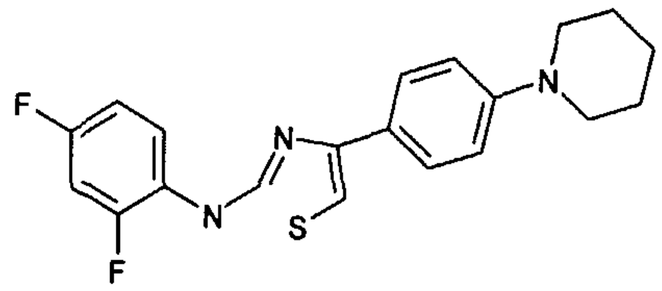


941 mg (5 mmol) 2,4-difluorophenylthiourea and 1.22 g (5 mmol) *alpha*-bromo-4-nitroacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.4 g (15 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 61 mg (0.2 mmol) of the resulting amino compound were reacted with 38 µl (0.3 mmol) 1-bromo-2-(2-bromo-ethoxy)-ethane and 209 µl (1.2 mmol) *N,N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 374 $[M+H]^+$

SP5656:

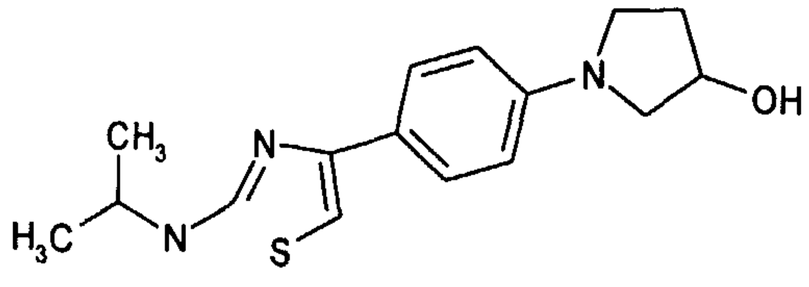


941 mg (5 mmol) 2,4-difluorophenylthiourea and 1.22 g (5 mmol) *alpha*-bromo-4-nitroacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.4 g (15 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 61 mg (0.2 mmol) of the resulting amino compound were reacted with 41 µl (0.3 mmol) 1,5-dibromopentane and 209 µl (1.2 mmol) *N,N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 372 $[M+H]^+$

SP5648:

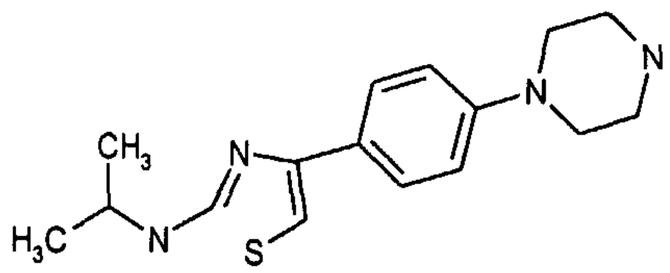


1.19 g (10 mmol) isopropylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 47 mg (0.2 mmol) of the resulting amino compound were reacted with 35 µl (0.3 mmol) 1,4-dibromo-2-butanol and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 304 $[M+H]^+$

SP5646:

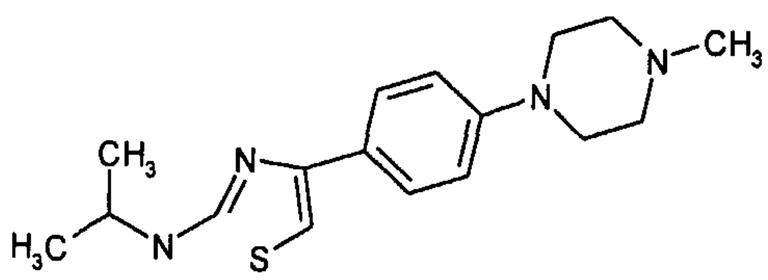


1.19 g (10 mmol) isopropylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 47 mg (0.2 mmol) of the resulting amino compound were reacted with 53.6 mg (0.3 mmol) bis-(2-chloroethyl)-amine, 15 mg (0.04 mmol) tetrabutylammonium iodide and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 303 $[M+H]^+$

SP5645:

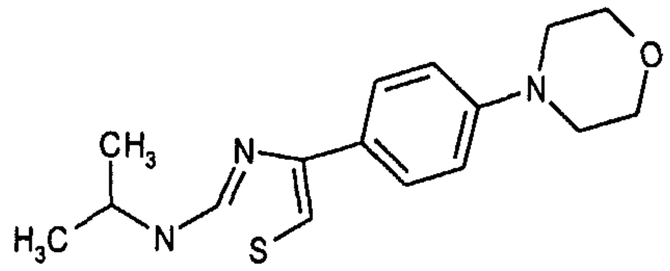


1.19 g (10 mmol) isopropylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 47 mg (0.2 mmol) of the resulting amino compound were reacted with 58 mg (0.3 mmol) *N*-methyl-*N*,*N*-bis-(chlorethyl)-amine, 15 mg (0.04 mmol) tetrabutylammonium iodide and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 317 $[M+H]^+$

SP5644:

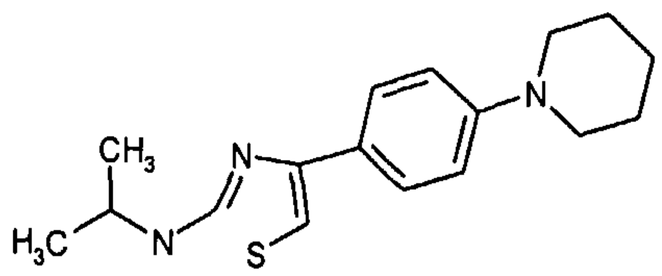


1.19 g (10 mmol) isopropylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 47 mg (0.2 mmol) of the resulting amino compound were reacted with 38 µl (0.3 mmol) 1-bromo-2-(2-bromo-ethoxy)-ethane and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 344 $[M+H]^+$

SP5643:

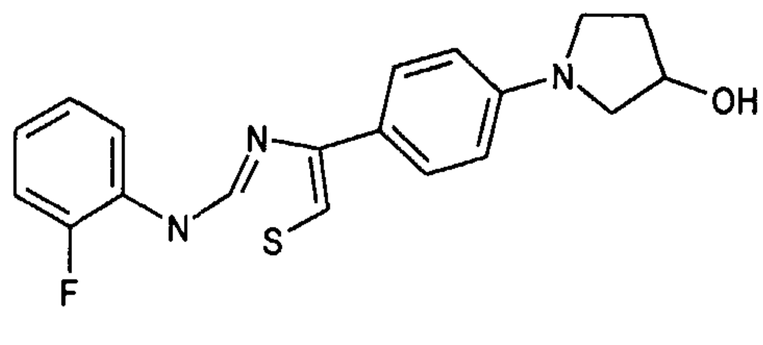


1.19 g (10 mmol) isopropylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 47 mg (0.2 mmol) of the resulting amino compound were reacted with 41 µl (0.3 mmol) 1,5-dibromopentane and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 302 $[M+H]^+$

SP5642:

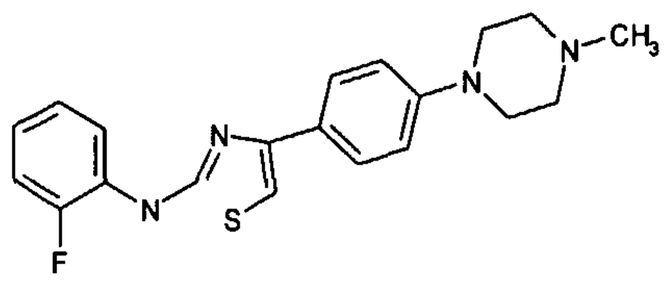


1.7 g (10 mmol) 2-fluorophenylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 57 mg (0.2 mmol) of the resulting amino compound were reacted with 35 µl (0.3 mmol) 1,4-dibromo-2-butanol and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 356 $[M+H]^+$

SP5615:

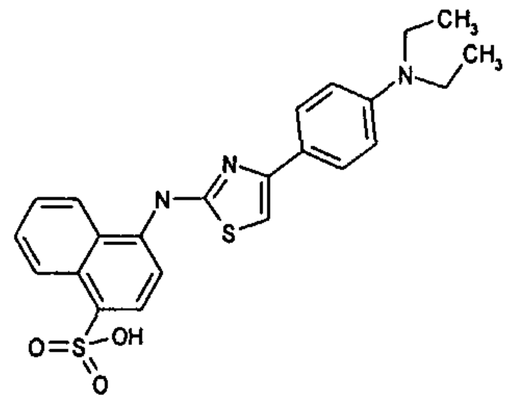


1.7 g (10 mmol) 2-fluorophenylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 57 mg (0.2 mmol) of the resulting amino compound were reacted with 58 mg (0.3 mmol) *N*-methyl-*N*,*N*-bis-(chlorethyl)-amine, 15 mg (0.04 mmol) tetrabutylammonium iodide and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Purity (HPLC): >95%

HPLC-MS: 369 $[M+H]^+$

SP5601:



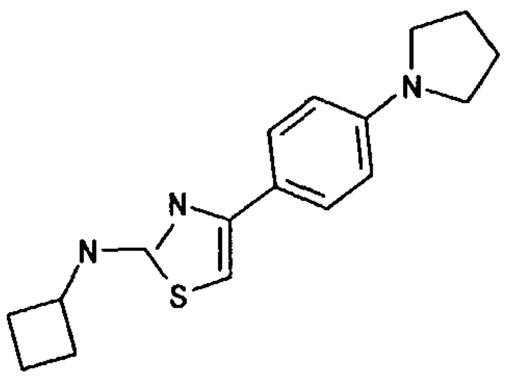
2.23 g (10 mmol) 4-amino-1-naphthalenesulfonic acid and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were stirred for 3 days at room temperature. The solvent was removed and the residue was dissolved in 20 ml THF and 20 ml 1 N NaOH. The mixture was refluxed for 5 h, cooled to room temperature and the organic solvent was removed. The precipitate was filtered, and the filtrate was evaporated to dryness under reduced pressure. 140 mg (0.5 mmol) of the crude 1-naphthalenesulfonic acid-4-thiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 29 mg.

Purity (HPLC): 95%

HPLC-MS: 454 $[M+H]^+$

SP5551:



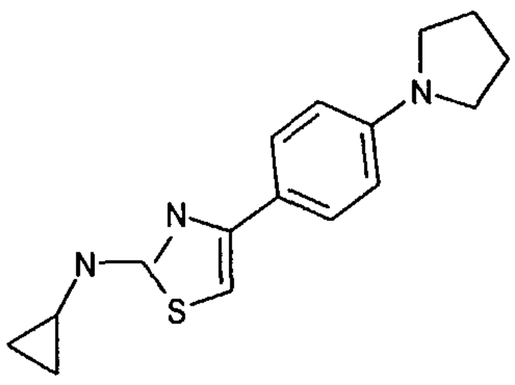
428 µl (5 mmol) cyclobutylamine and 740 µl (5.5 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 26 mg (0.2 mmol) cyclobutylthiourea and 54 mg (0.2 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 102 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 300 $[M+H]^+$

SP5550:



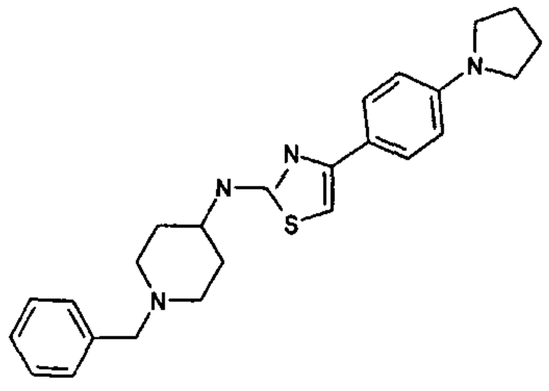
692 µl (10 mmol) cyclopropylamine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 24 mg (0.2 mmol) cyclobutylthiourea and 54 mg (0.2 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 100 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 286 $[M+H]^+$

SP5548:



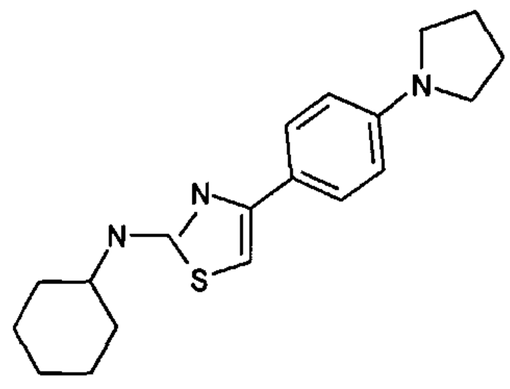
2.04 ml (10 mmol) 4-amino-1-benzylpiperidine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 50 mg (0.2 mmol) cyclobutylthiourea and 54 mg (0.2 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 92 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 419 $[M+H]^+$

SP5547:



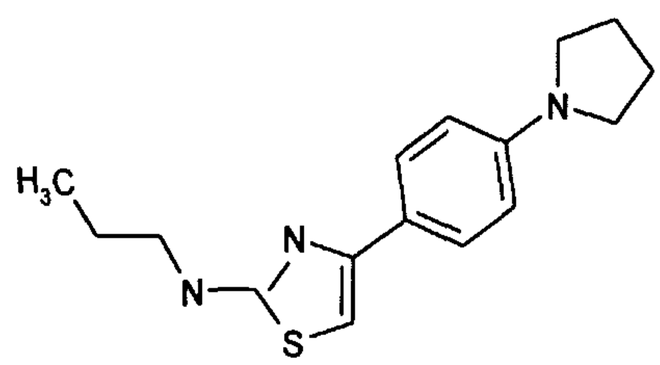
1.15 ml (10 mmol) cyclohexylamine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 32 mg (0.2 mmol) cyclobutylthiourea and 54 mg (0.2 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 87 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 328 $[M+H]^+$

SP5546:



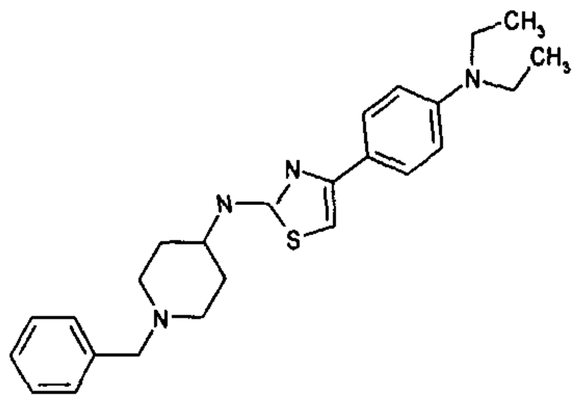
821 µl (10 mmol) *n*-propylamine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 24 mg (0.2 mmol) *n*-propyllthiourea and 54 mg (0.2 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 77 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 288 $[M+H]^+$

SP5541:



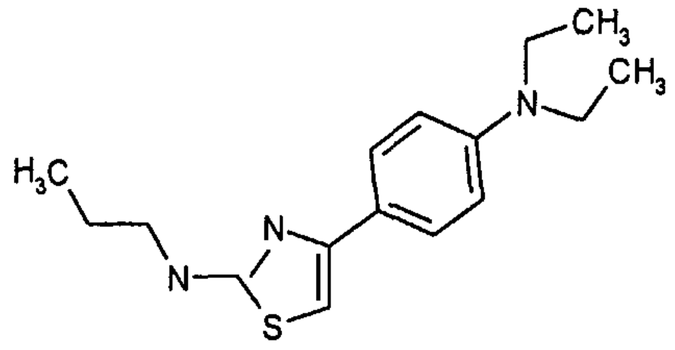
2.04 ml (10 mmol) 4-amino-1-benzylpiperidine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 50 mg (0.2 mmol) 4-thiourea-1-benzylpiperidine and 53.5 mg (0.2 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 89 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 421 $[M+H]^+$

SP5539:



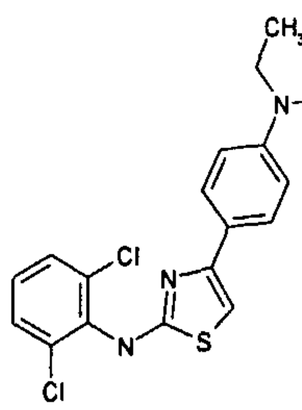
821 µl (10 mmol) *n*-propylamine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 24 mg (0.2 mmol) *n*-propylthiourea and 53.5 mg (0.2 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 91 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 290 $[M+H]^+$

SP5484:

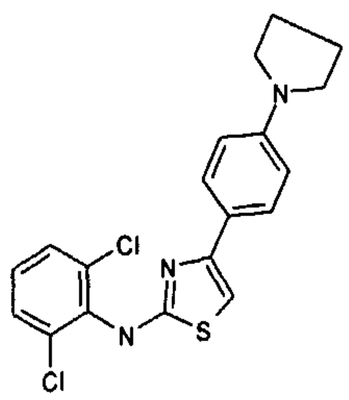


1.62 g (10 mmol) 2,6-dichloroaniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 111 mg (0.5 mmol) 2,6-dichlorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1- diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Purity (HPLC): 95%

HPLC-MS: 392, 394 $[M+H]^+$

SP5483:



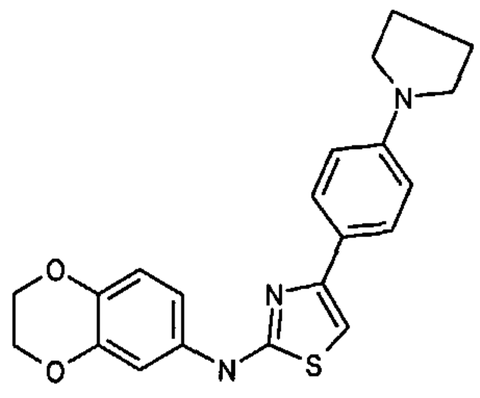
1.62 g (10 mmol) 2,6-dichloroaniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 111 mg (0.5 mmol) 2,6-dichlorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 91 mg.

Purity (HPLC): 95%

HPLC-MS: 390, 392 $[M+H]^+$

SP5467:

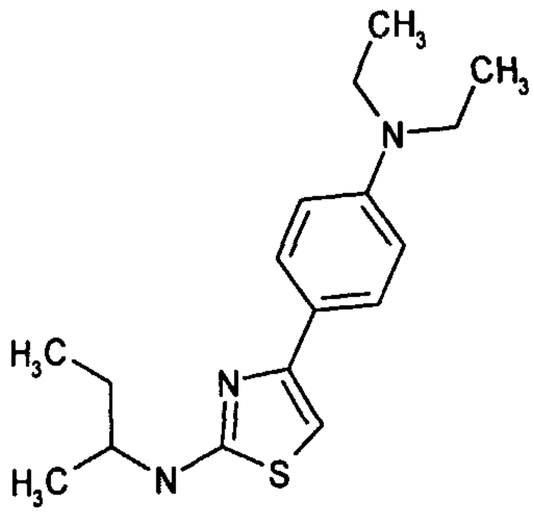


1.2 ml (10 mmol) 1,4-benzodioxane-6-amine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 66 mg (0.5 mmol) (2,3-dihydro-benzo[1,4]dioxin-6-yl)-thiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Purity (HPLC): 95%

HPLC-MS: 380 $[M+H]^+$

SP5466:



1.0 ml (10 mmol) sec-butylamine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 66 mg (0.5 mmol) sec-butylthiourea and 135 mg (0.5

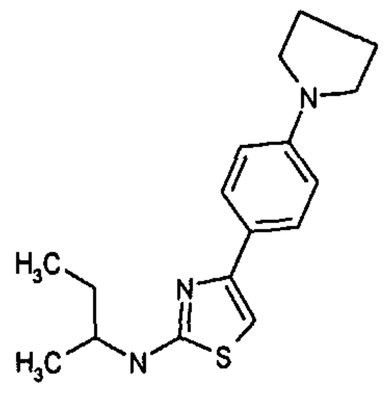
mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 211 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 304 $[M+H]^+$

SP5465:



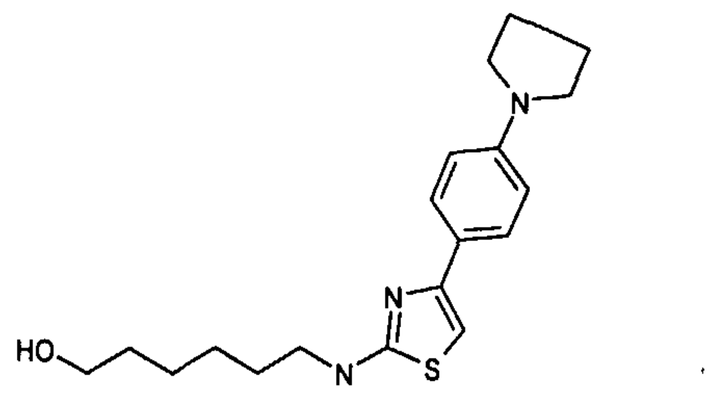
1.0 ml (10 mmol) sec-butylamine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 66 mg (0.5 mmol) sec-butylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 201 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 302 $[M+H]^+$

SP5452:



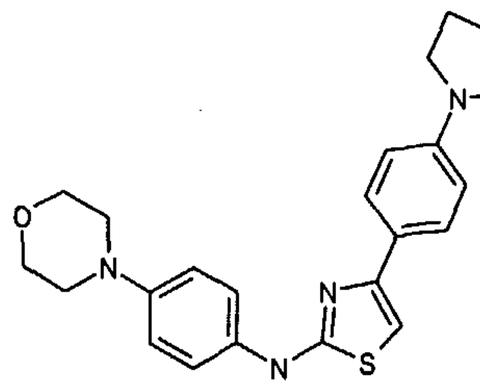
1.2 ml (10 mmol) 6-amino-1-hexanol and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 88 mg (0.5 mmol) 6-hydroxyhexylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 214 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 346 $[M+H]^+$

SP5450:



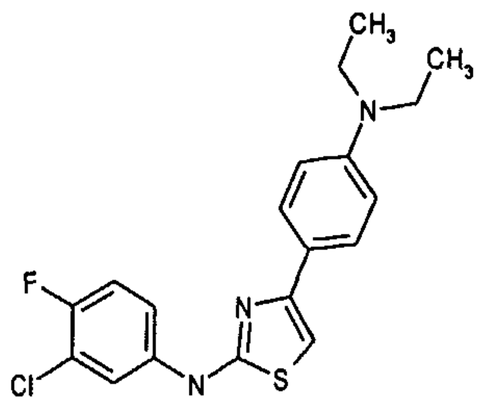
1.5 ml (10 mmol) 4-morpholinoaniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 119 mg (0.5 mmol) 4-morpholinophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 241 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 407 $[M+H]^+$

SP5447:



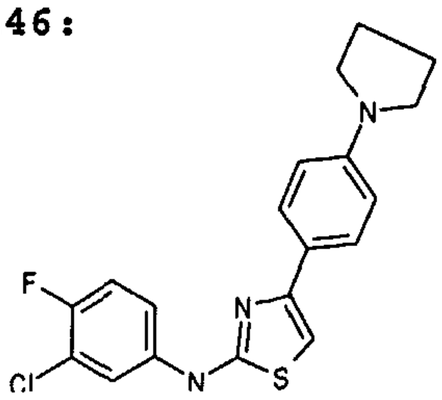
1.5 ml (10 mmol) 3-chloro-4-fluoroaniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 102 mg (0.5 mmol) 3-chloro-4-fluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 245 mg.

Purity (HPLC): >95%

HPLC-MS: 376 $[M+H]^+$

SP5446:



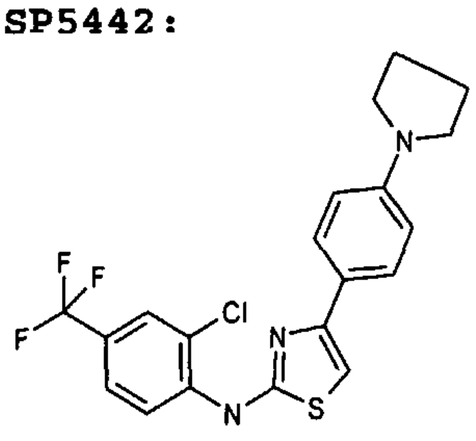
1.5 ml (10 mmol) 3-chloro-4-fluoroaniline and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 102 mg (0.5 mmol) 3-chloro-4-fluorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 229 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 374 $[M+H]^+$

SP5442:



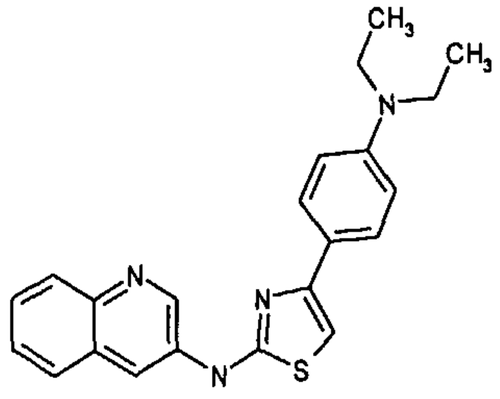
1.3 ml (10 mmol) 4-amino-3-chlorobenzotrifluorid and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 127 mg (0.5 mmol) 2-chloro-4-trifluoromethylphenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 94 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 361 $[M+H]^+$

SP5430:



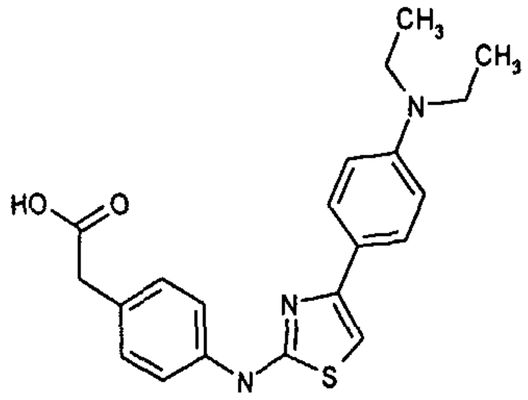
720 mg (5 mmol) 3-aminoquinoline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 15 ml methylene chloride were reacted according to general procedure 1. 102 mg (0.5 mmol) quinoline-3-thiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 224 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 375 $[M+H]^+$

SP5424:



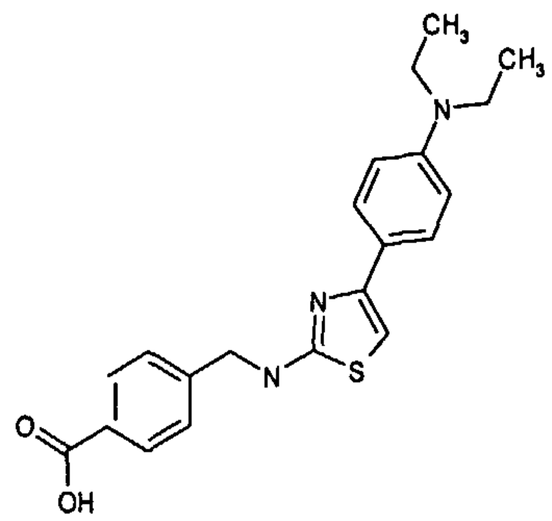
1.51 g (10 mmol) 4-Aminophenylessigsäure and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 105 mg (0.5 mmol) (4-thioureido-phenyl)-acetic acid and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 228 mg

Purity (HPLC): 95%

HPLC-MS: 382 $[M+H]^+$

SP5422:



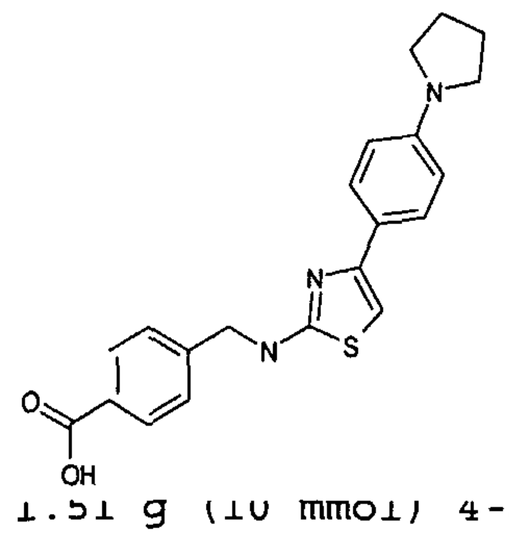
1.51 g (10 mmol) 4-aminomethylbenzoic acid and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 105 mg (0.5 mmol) 4-aminomethylphenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 45 mg.

Purity (HPLC): 95%

HPLC-MS: 382 $[M+H]^+$

SP5421:



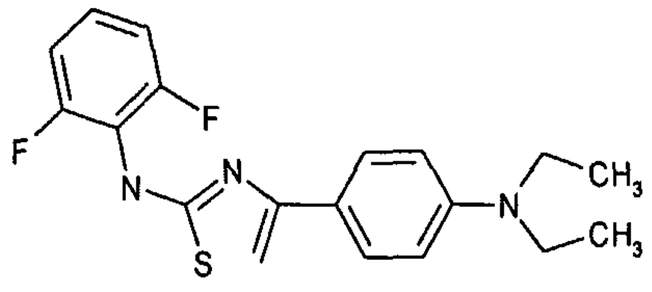
1.51 g (10 mmol) 4-aminomethylbenzoic acid and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 105 mg (0.5 mmol) 4-aminomethylphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 31 mg.

Purity (HPLC): 95%

HPLC-MS: 380 $[M+H]^+$

SP5410:



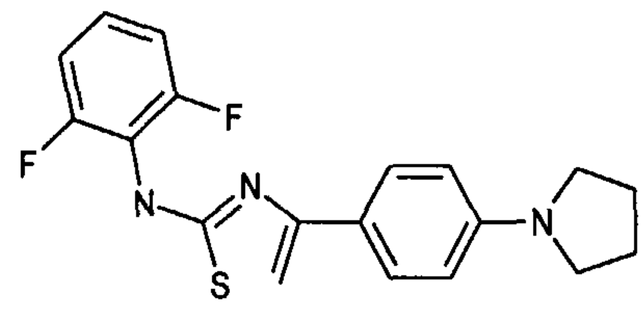
500 µl (5 mmol) 2,6-difluoraniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 15 ml methylene chloride were reacted according to general procedure 1. 75.3 mg (0.4 mmol) 2,6-difluorophenylthiourea and 108 mg (0.4 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 181 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 360 $[M+H]^+$

SP5409:



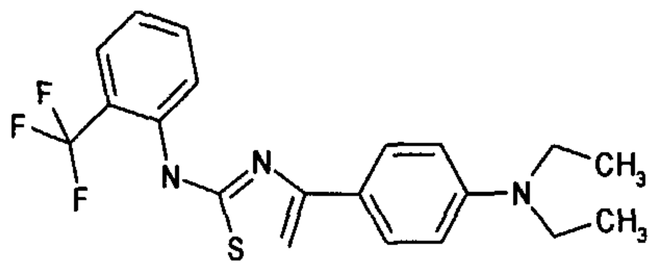
500 µl (5mmol) 2,6-difluoraniline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 15 ml methylene chloride were reacted according to general procedure 1. 75.3 mg (0.4 mmol) 2,6-difluorophenylthiourea and 107 mg (0.4 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 179 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 358 $[M+H]^+$

SP5401:



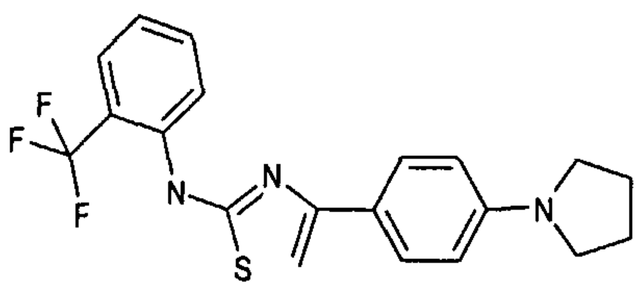
800 mg (10.5 mmol) ammoniumthiocyanate and 70 mg (0.67 mmol) sodium hydrogensulfite were dissolved in 2 ml 20% HCl. 1.24 g (10 mmol) 2-trifluoromethylaniline and additionally 2 ml 20% HCl were added and the mixture was stirred overnight at 90°C. After cooling to room temperature the precipitate was filtered and washed with 150 ml water and 30 ml diethyl ether and dried in vacuo. 220 mg (1 mmol) 2-trifluoromethylphenylthiourea and 270 mg (1 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 505 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 392 $[M+H]^+$

SP5400:



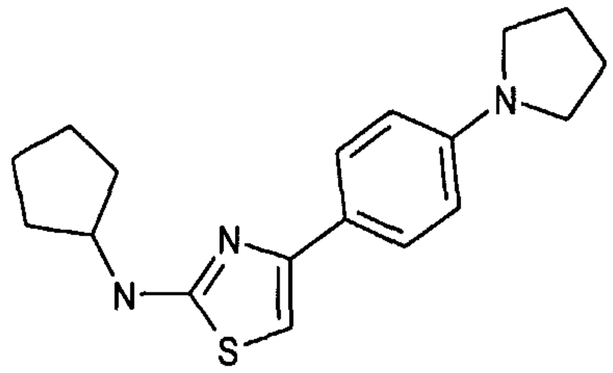
800 mg (10.5 mmol) ammoniumthiocyanate and 70 mg (0.67 mmol) sodium hydrogensulfite were dissolved in 2 ml 20% HCl. 1.24 g (10 mmol) 2-trifluoromethylaniline and additionally 2 ml 20% HCl were added and the mixture was stirred overnight at 90°C. After cooling to room temperature the precipitate was filtered and washed with 150 ml water and 30 ml Ether and dried in vacuo. 220 mg (1 mmol) 2-trifluoromethylphenylthiourea and 268 mg (1 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2

Yield: 466 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 390 $[M+H]^+$

SP5377:



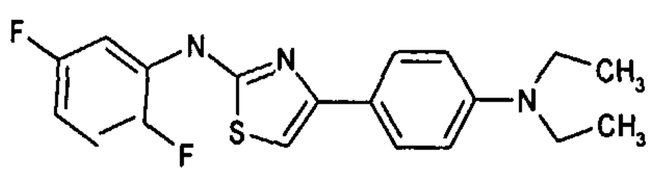
990 µl (10 mmol) cyclopentylamine and 1.48 ml (11 mmol) benzoyl isothiocyanate in 30 ml methylene chloride were reacted according to general procedure 1. 72 mg (0.5 mmol) cyclopentylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 166 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 302 $[M+H]^+$

SP5342:

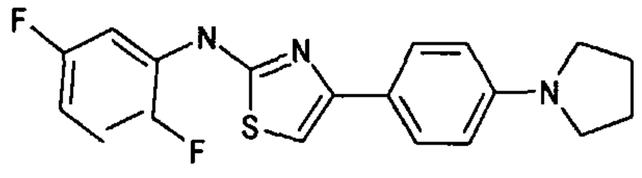


94 mg (0.5 mmol) 2,5-difluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Purity (HPLC): 95%

HPLC-MS: 360 $[M+H]^+$

SP5341:

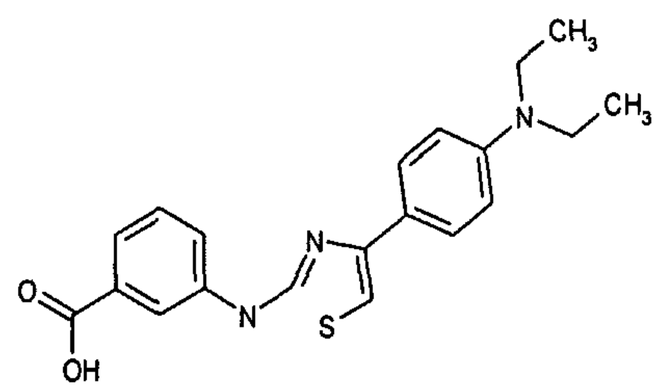


94 mg (0.5 mmol) 2,5-difluorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Purity (HPLC): 95%

HPLC-MS: 358 $[M+H]^+$

SP5330:



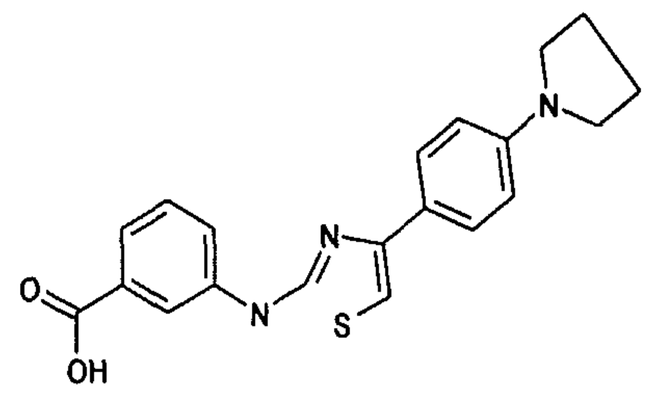
98 mg (0.5 mmol) 3-carboxyphenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 177 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 368 $[M+H]^+$

SP5329:



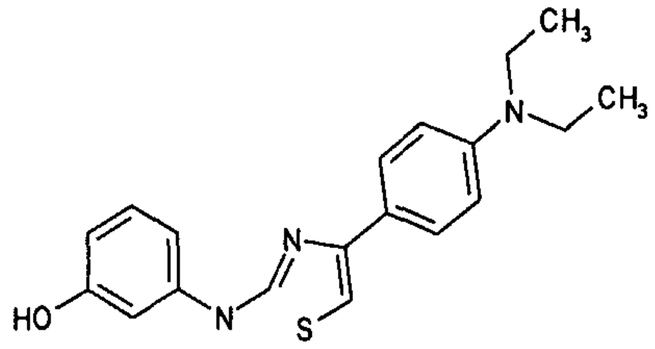
98 mg (0.5 mmol) 3-carboxyphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 178 mg (hydrobromide)

Purity (HPLC): 95%

HPLC-MS: 366 $[M+H]^+$

SP5328:



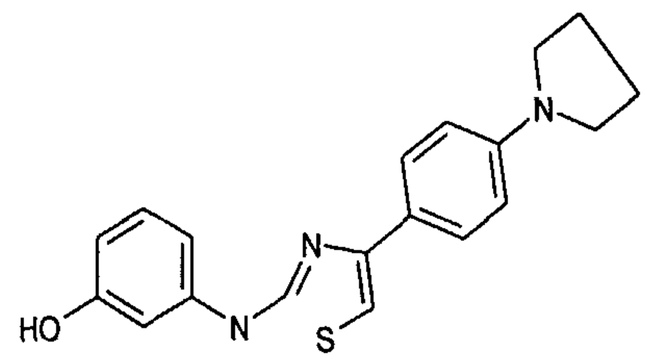
84 mg (0.5 mmol) 3-hydroxyphenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 159 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 340 $[M+H]^+$

SP5327:



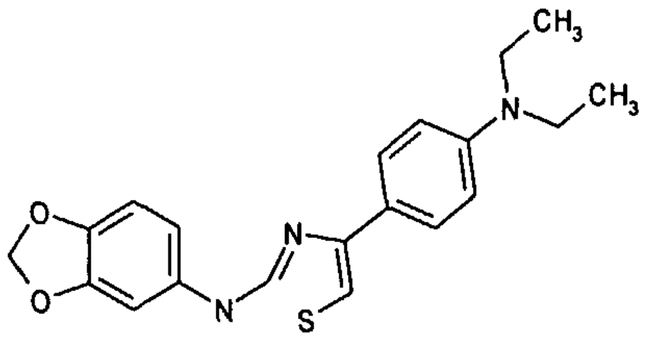
84 mg (0.5 mmol) 3-hydroxyphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 156 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 338 $[M+H]^+$

SP5326:



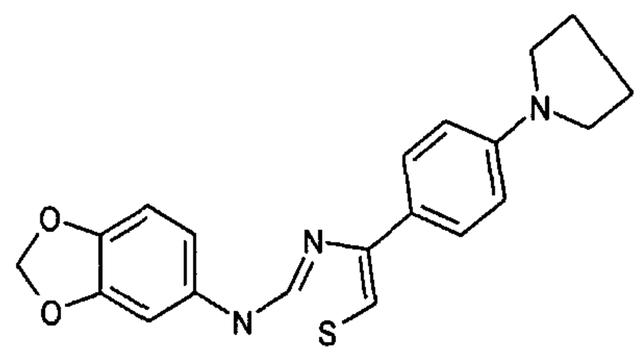
98.1 mg (0.5 mmol) 3,4-methylenedioxythiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 188 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 368 $[M+H]^+$

SP5325:



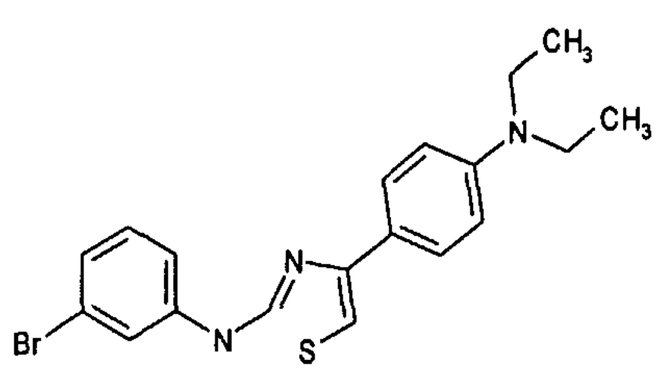
98.1 mg (0.5 mmol) 3,4-methylenedioxythiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 187 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 366 $[M+H]^+$

SP5322:



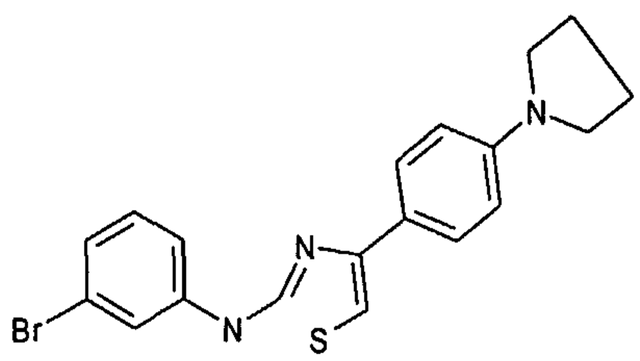
115.5 mg (0.5 mmol) 3-bromophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 197 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 402, 404 $[M+H]^+$

SP5321:



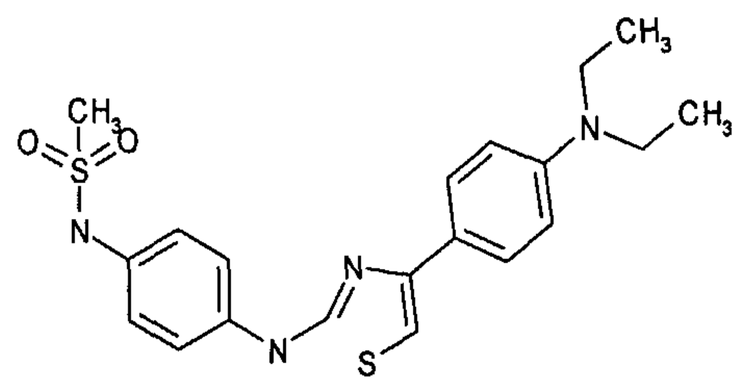
115.5 mg (0.5 mmol) 3-bromophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 194 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 400, 402 $[M+H]^+$

SP5308:



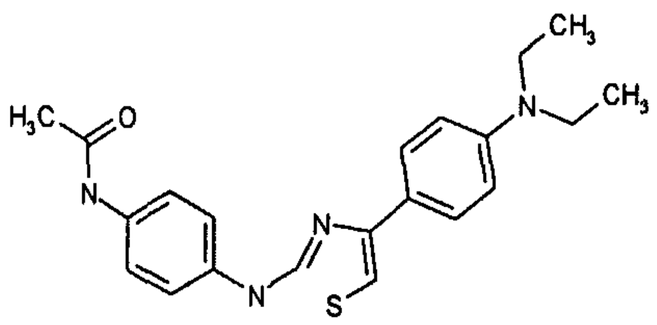
enylthiourea and 1.29 g (4.78 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.2 g (14.3 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 68 mg (0,2mmol) of the resulting amino compound were reacted with 17 µl (0.22 mmol) methanesulfonylchloride in 5 ml methylene chloride and 500 µl pyridine according to general procedure 6.

Yield: 33 mg.

Purity (HPLC): >95%

HPLC-MS: 417 $[M+H]^+$

SP5305:



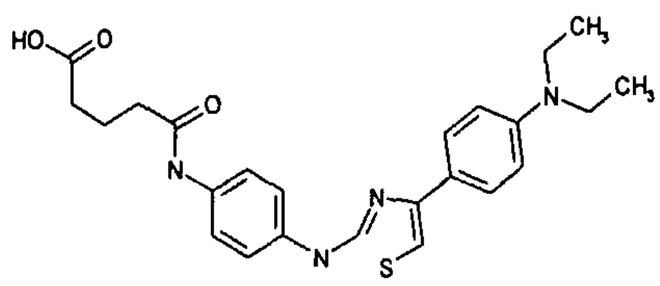
943 mg (4.78 mmol) 4-nitrophenylthiourea and 1.29 g (4.78 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.2 g (14.3 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 68 mg (0.2 mmol) of the resulting amino compound were stirred with 31 mg (0.3 mmol) acetic anhydride and 56 µl (0.4 mmol) triethylamine in 5 ml methylene chloride at room temperature overnight. The mixture was diluted with 30 ml ethylacetate, washed with sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over $MgSO_4$ and the solvent was removed.

Yield: 71 mg.

Purity (HPLC): >95%

HPLC-MS: 381 $[M+H]^+$

SP5304:



943 mg (4.78 mmol) 4-nitrophenylthiourea and 1.29 g (4.78 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 3.2 g (14.3 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 68 mg (0.2 mmol) of the resulting amino compound were stirred with 34 mg (0.3 mmol) glutaric acid anhydride and 56 µl (0.4 mmol) triethylamine in 5 ml methylene chloride at room temperature overnight. The mixture was diluted with 30 ml ethylacetate, washed with

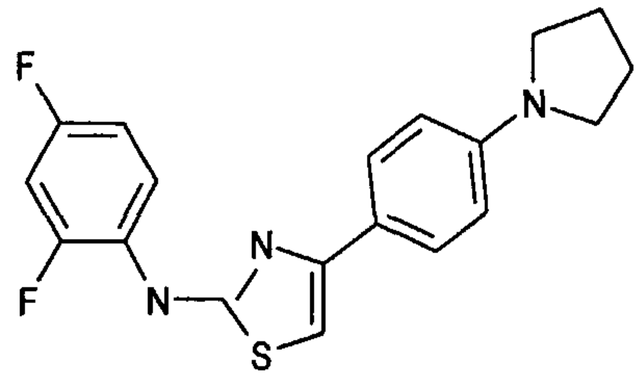
sat. $NaHCO_3$-solution and sat. NaCl-solution, dried over $MgSO_4$ and the solvent was removed.

Yield: 71 mg.

Purity (HPLC): >95%

HPLC-MS: 453 $[M+H]^+$

SP5254:



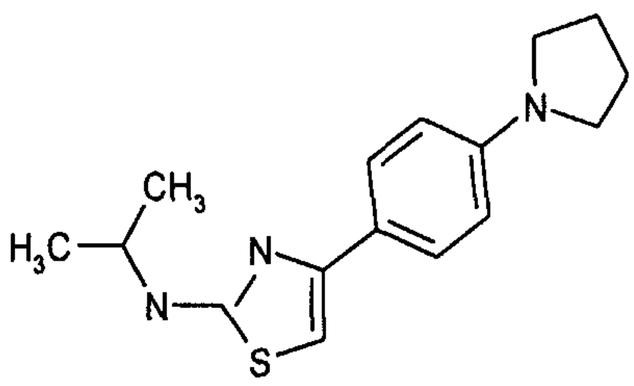
94 mg (0.5 mmol) 2,4-difluorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 115 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 358 $[M+H]^+$

SP5253:



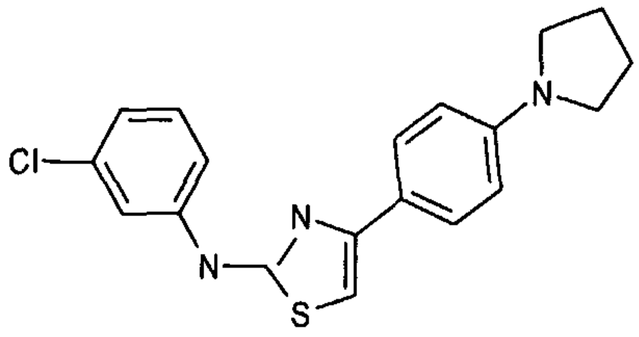
59 mg (0.5 mmol) isopropylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1- pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 187 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 288 $[M+H]^+$

SP5252:



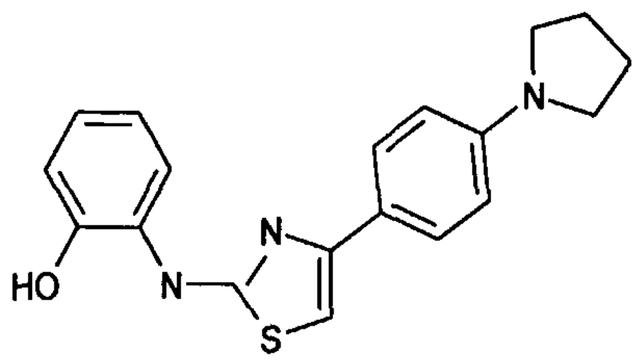
94 mg (0.5 mmol) 3-chlorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 181 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 356 $[M+H]^+$

SP5251:



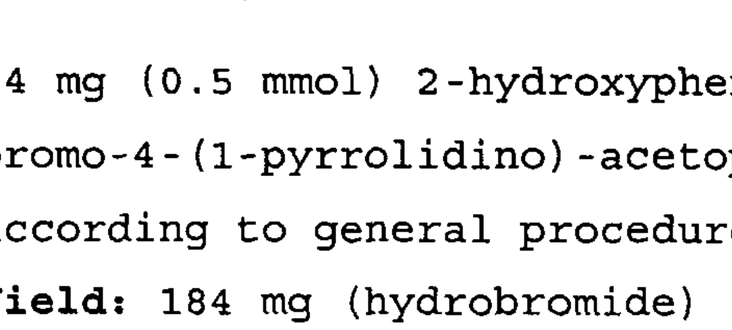
84 mg (0.5 mmol) 2-hydroxyphenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 184 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 338 $[M+H]^+$

SP5250:



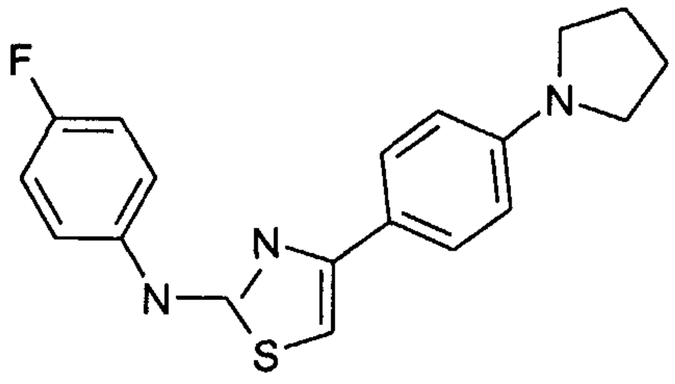
93 mg (0.5 mmol) 2-chlorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 180 mg (hydrobromide)

Purity (HPLC): 85%

HPLC-MS: 356 $[M+H]^+$

SP5249:



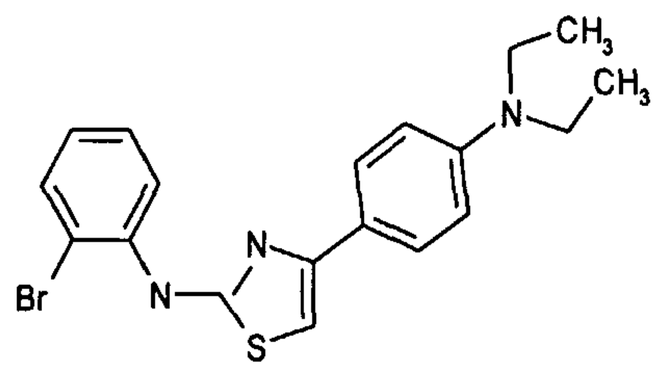
85 mg (0.5 mmol) 4-fluorophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-pyrrolidino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 176 mg (hydrobromide)

Purity (HPLC): 85%

HPLC-MS: 340 $[M+H]^+$

SP5248:



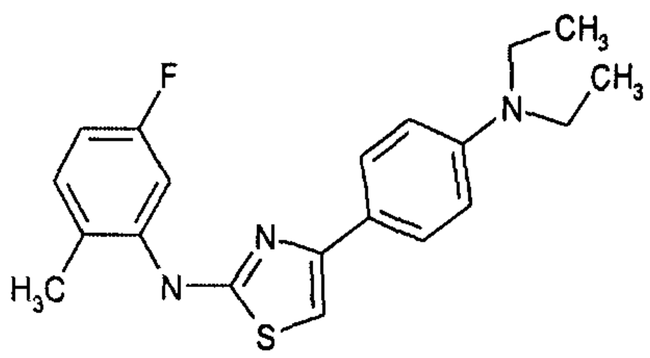
116 mg (0.5 mmol) 2-bromophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 231 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 402, 404 $[M+H]^+$

SP5247:



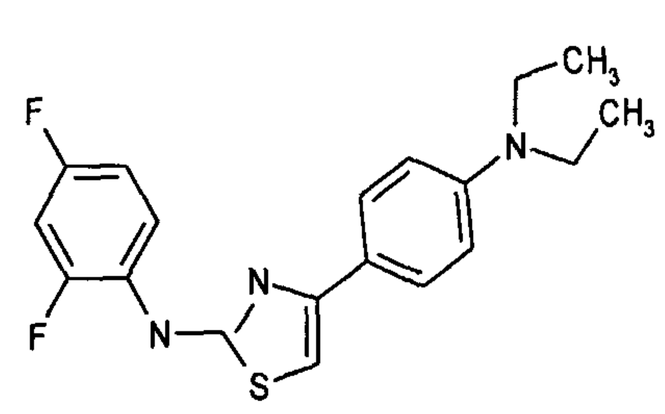
92 mg (0.5 mmol) 2-methyl-5-fluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 256 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 356 $[M+H]^+$

SP5246:



94 mg (0.5 mmol) 2,4-difluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 232 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 360 $[M+H]^+$

SP5245:

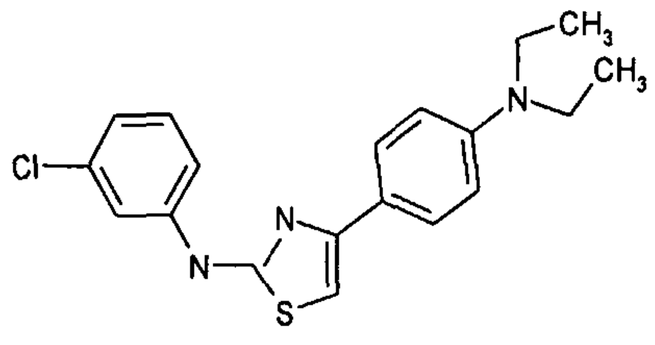
59 mg (0.5 mmol) isopropylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 191 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 290 $[M+H]^+$

SP5244:



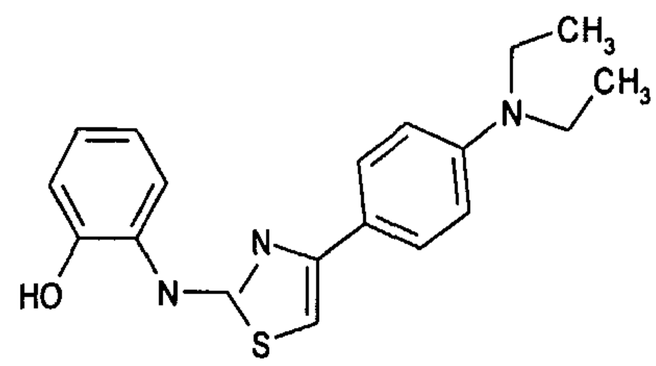
93 mg (0.5 mmol) 3-chlorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 222 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 358 $[M+H]^+$

SP5243:



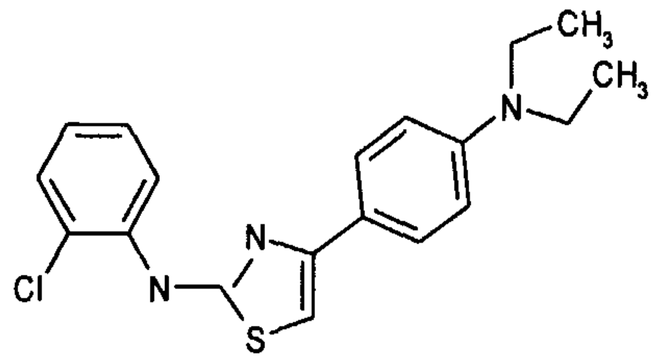
84 mg (0.5 mmol) 2-hydroxyphenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 240 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 340 $[M+H]^+$

SP5242:



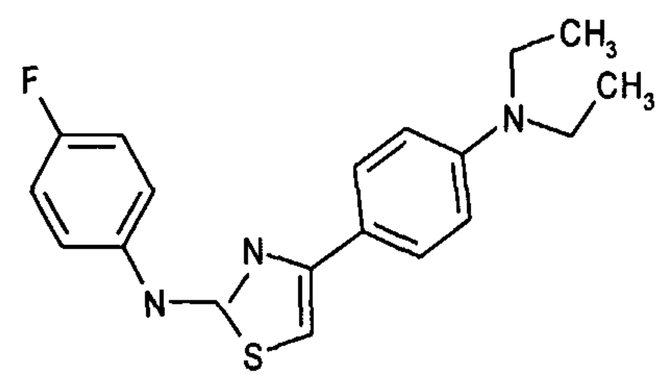
93 mg (0.5 mmol) 3-chlorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 226 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 358 $[M+H]^+$

SP5241:



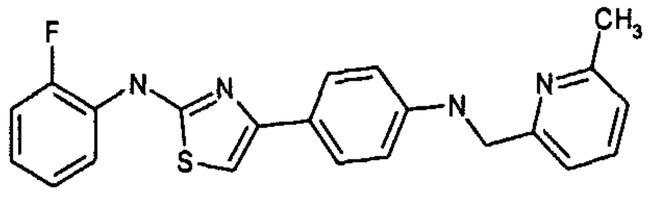
85 mg (0.5 mmol) 4-fluorophenylthiourea and 135 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2.

Yield: 199 mg (hydrobromide)

Purity (HPLC): >95%

HPLC-MS: 342 $[M+H]^+$

SP5225:



1.7 g (10 mmol) 2-fluorophenylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to

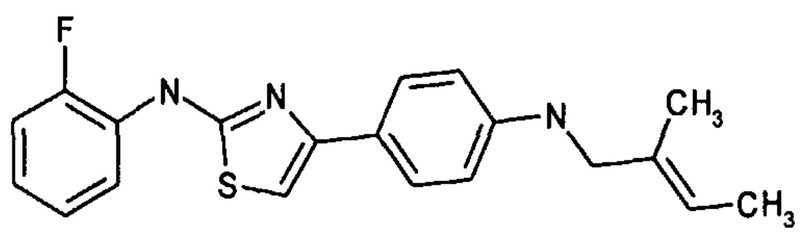
general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 41 mg (0.14 mmol) of the resulting amino compound were reacted with 24 mg (0.2 mmol) 6-methyl-2-pyridinecarboxaldehyde and 25 mg (0.4 mmol) sodium cyanoborohydride in 5 ml THF and 23 µl (0.4 mmol) HOAc according to general procedure 9.

Yield: 61 mg

Purity (HPLC): 90%

HPLC-MS: 391 $[M+H]^+$

SP5224:



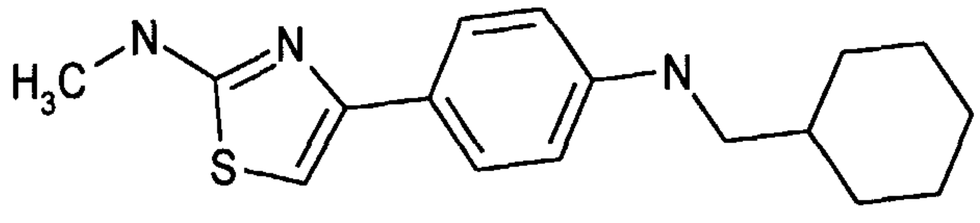
1.7 g (10 mmol) 2-fluorophenylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol. 40 mg (0.14 mmol) of the resulting amino compound were reacted with 97 µl (1 mmol) tiglic aldehyde and 25 mg (0.4 mmol) sodium cyanoborohydride in 5 ml THF and 23 µl (0.4 mmol) HOAc according to general procedure 9.

Yield: 51 mg

Purity (HPLC): 90%

HPLC-MS: 354 $[M+H]^+$

SP5204:



900 mg (10 mmol) methylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 41 mg (0.2 mmol) of the resulting amino compound were reacted with 121 µl (1.0 mmol) cyclohexanecarboxaldehyde and 25 mg (0.4 mmol) sodium

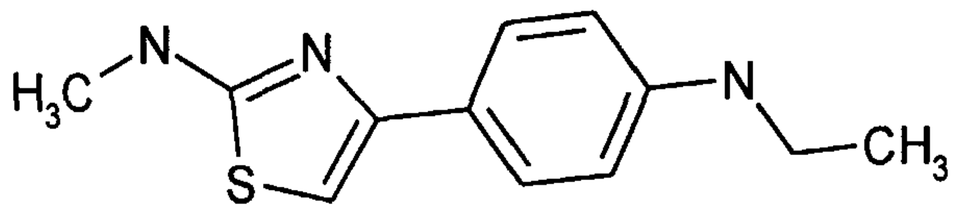
cyanoborohydride in 5 ml THF and 23 µl (0.4 mmol) HOAc according to general procedure 9.

Yield: 66 mg

Purity (HPLC): 85%

HPLC-MS: 302 $[M+H]^+$

SP5202:

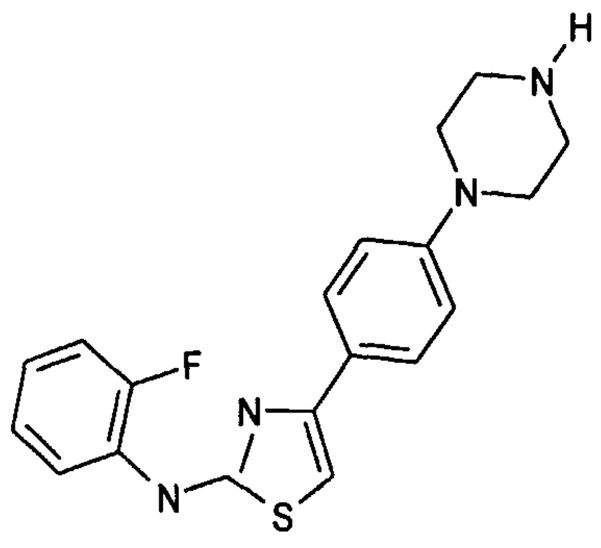


900 mg (10 mmol) methylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 41 mg (0.2 mmol) of the resulting amino compound were reacted with 11 µl (0.2 mmol) acetaldehyde and 25 mg (0.4 mmol) sodium cyanoborohydride in 5 ml THF and 23 µl (0.4 mmol) HOAc according to general procedure 9.

Purity (HPLC): 95%

HPLC-MS: 234 $[M+H]^+$

SP5164:



1.7 g (10 mmol) 2-fluorophenylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 30 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 30 ml ethanol. 29 mg (0.1 mmol) of the resulting amino compound were reacted with 53.6 mg (0.3 mmol) bis-(2-chloroethyl)-amine, 15 mg (0.04 mmol)

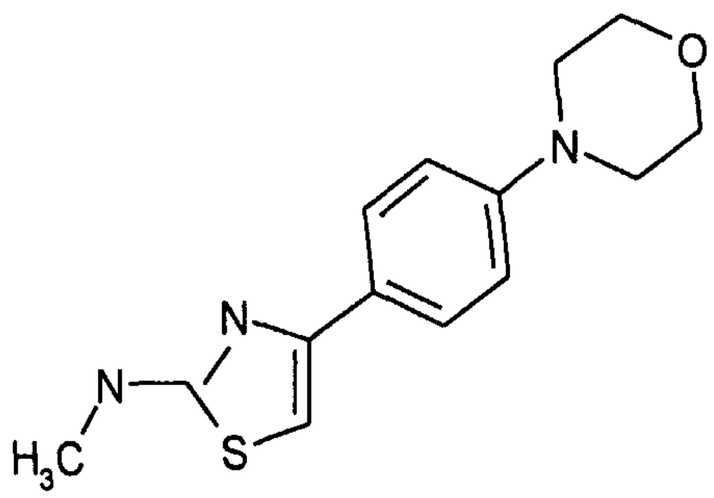
tetrabutylammonium iodide and 209 µl (1.2 mmol) *N*,*N*-diisopropyl-*N*-ethylamine in 3 ml toluene according to general procedure 8.

Yield: 6 mg

Purity (HPLC): 95%

HPLC-MS: 355 $[M+H]^+$

SP5116:



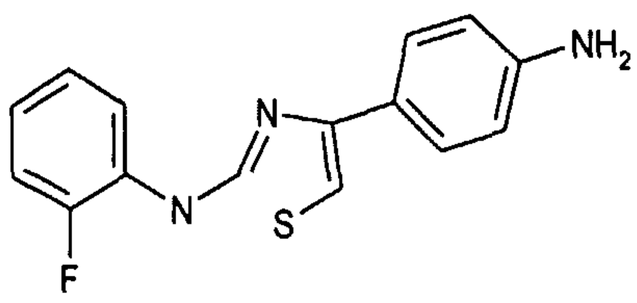
900 mg (10 mmol) methylthiourea and 2.78 g (10 mmol) 2,4´-dibromoacetophenone in 30 ml ethanol were reacted according to general procedure 2. 135 mg (0.5 mmol) of the resulting aminothiazole, 67.3 mg (0.7 mmol) NaOtBu and 6 mg (0.02 mmol) di-tert-butylbiphenylphosphine were dissolved in 1 ml DME under Argon atmosphere. 53 µl (0.6 mmol) morpholine and 10 mg palladium(II)-acetate were added and the mixture was stirred at 100 °C. After 2 h 4 ml DME were added and the mixture was stirred at 100 °C overnight. After cooling to room temperature 15 ml diethyl ether were added and the mixture was filtered through celite and washed with diethyl ether. The filtrate was evaporated to dryness and the residue was purified using preparative HPLC.

Yield: 7 mg.

Purity (HPLC): 95%

HPLC-MS: 276 $[M+H]^+$

SP5054:



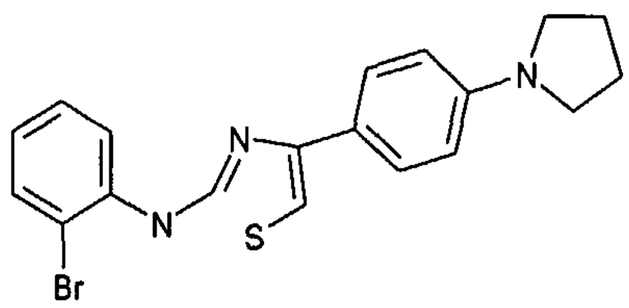
1.7 g (10 mmol) 2-fluorophenylthiourea and 2.44 g (10 mmol) 2-bromo-4-nitroacetophenone in 50 ml ethanol were reacted according to general procedure 2. The nitro group of the product was reduced according to general procedure 3 using 6.8 g (30 mmol) $SnCl_2 \times 2H_2O$ in 50 ml ethanol.

Yield: 2.1 g

Purity (HPLC): 95%

HPLC-MS: 286 $[M+H]^+$

SP5053:



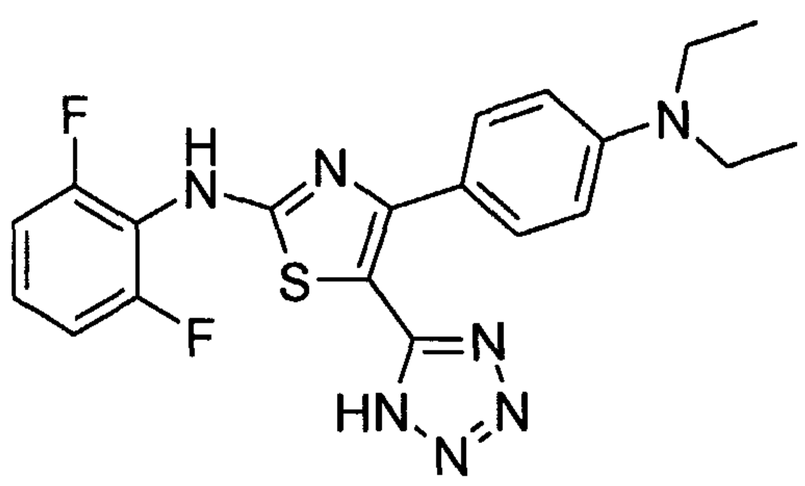
116 mg (0.5 mmol) 2-bromophenylthiourea and 134 mg (0.5 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 10 ml ethanol were reacted according to general procedure 2.

Yield: 254 mg.

Purity (HPLC): >95%

HPLC-MS: 400, 402 $[M+H]^+$

SP4331



A solution of *alpha*-bromo-4-diethylaminoacetophenone (544 mg, 2 mmol) in DMF (10 ml) was added drop by drop to a solution of sodium cyanide (1 g, 20 mmol) in DMF (40 ml) at 50°C. After stirring the suspension for 1 h at 50°C water was added and the mixture was extracted 3 times with ethyl acetate. The combined organic layers were washed with brine, dried

over $MgSO_4$, filtered and the solvents were evaporated yielding *alpha*-cyano-4-diethylaminoacetophenone (510 mg, HPLC-MS: 217 $[M+H]^+$). A solution of phenyltrimethylammoniumtribromide (900 mg, 2.4 mmol) in THF (10 ml) was added to a solution of *alpha*-cyano-4-diethylaminoacetophenone (510 mg) in THF (10 ml). After stirring fro 1 h at room temperature water was added and the mixture was extracted twice with ether. The combined org. layers were washed with brine, dried over $MgSO_4$, filtered and the solvents were evaporated yielding *alpha*-bromo-*alpha*-cyano-4-diethylaminoacetophenone (643 mg, HPLC-MS: 296 $[M+H]^+$). The obtained *alpha*-bromo- *alpha*-cyano-4-diethylaminoacetophenone (643 mg) and 2,6-difluorophenylthiourea (470 mg, 2.5 mmol) in 30 ml DMF stirred at room temperature for 16 h. The solvent was removed in vacuo and the resulting aminothiazole was purified by flash chromatography (20 g SiO_2, cyclohexane/ethyl acetate, 0-20% ethyl acetate in 40 min @ 15 ml/min, Rf = 0.2, Cy/EE = 5/1).

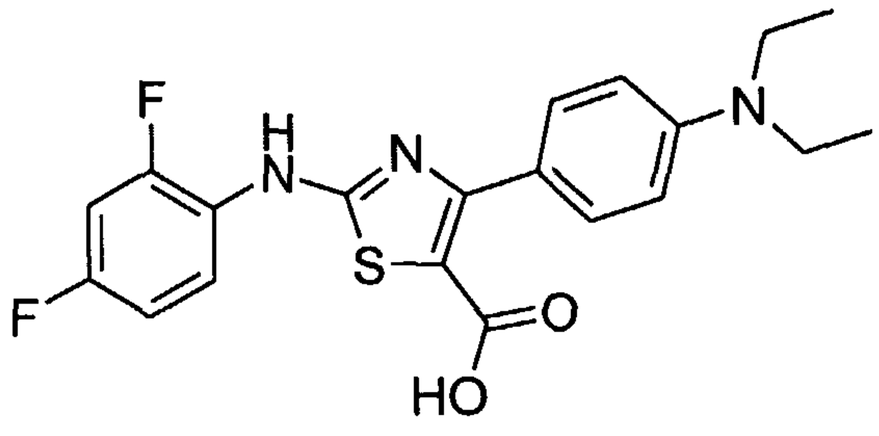
Yield: 366 mg, Purity (HPLC-MS): > 95%, HPLC-MS: 385 $[M+H]^+$

A solution of trimethylaluminum (2 M in toluene, 520 µl) was added to a solution of the aminothiazole prepared above (100 mg, 260 µmol) and azidotrimethylsilane (350 µl, 2.6 mmol) in 5 ml dry toluene under argon. The solution was stirred at 110°C for 22 hours, then cooled to room temperature and quenched with water. The mixture was acidified with 1 N hydrochloric acid to pH 4 and extracted with a mixture of ethyl acetate and ether (1:1, 3 times). The pH of the aqueous layer was increased to 7 and the solution was saturated with sodium chloride. The solution was extracted again with a mixture of ethyl acetate and ether (1:1, 3 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvents were evaporated. The resulting residue was purified by preparative HPLC-MS.

Yield: 35 mg

Purity (HPLC-MS): > 95%

HPLC-MS: 428 $[M+H]^+$



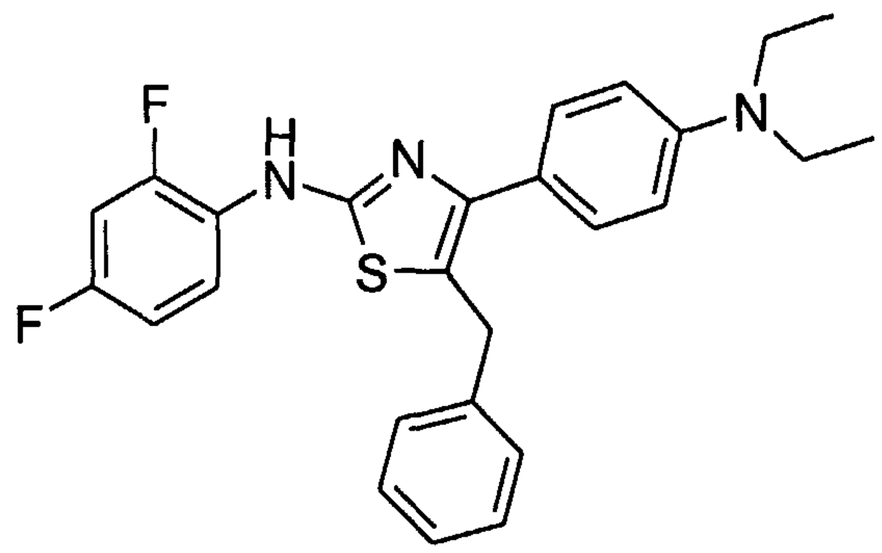
300 mg (1.57 mmol) 4-diethylaminoacetophenone, 189 mg (1.57 mmol) allylchloroformate and 62 mg (0.33 mmol) 2,4-difluorophenylthiourea were reacted according to general procedure 11 (Yield: 82 mg, purity (HPLC-MS): > 95%, HPLC-MS: 444 $[M+H]^+$). Palladium-tetrakis-triphenylphosphine (cat. amount) was added under argon to a oxygen-free solution of 48 mg (0.11 mmol) of the aminothiazole prepared above und morpholine (0.1 ml) in DMF (1 ml). The mixture was stirred at room temperature for 30 min. Water (5 ml) and a sat. solution of sodium hydrogen carbonate (5 ml) were added. The mixture was extracted with ethyl acetate (2x 20 ml) and the combined organic layers were washed with brine and dried over MgSO4. The solvent was filtered and evaporated to give a solid. The solid was washed with cold methanol and dried in high vacuum to yield pure acid.

Yield: 30 mg

Purity (HPLC-MS): > 90 %

HPLC-MS: 404 $[M+H]^+$

SP4254



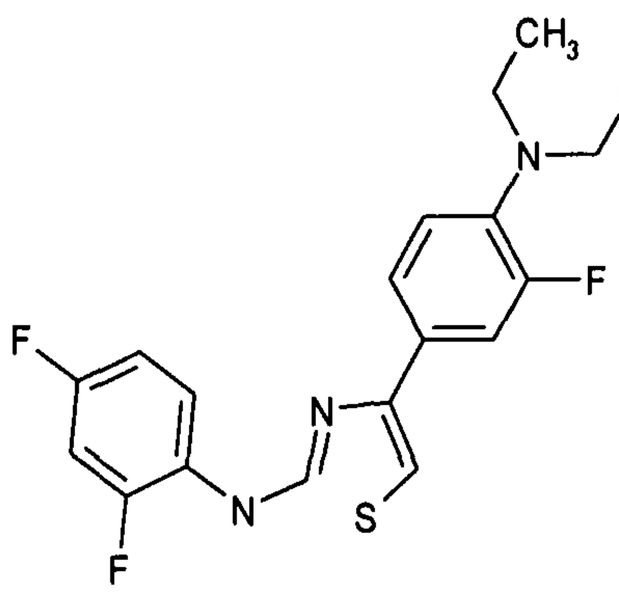
100 mg (0.52 mmol) 4-diethylaminoacetophenone, 90 mg (0.52 mmol) benzyl bromide and 110 mg (0.59 mmol) 2,4-difluorophenylthiourea were reacted according to general procedure 11.

Yield: 8.2 mg

Purity (HPLC-MS): > 90%

HPLC-MS: 450 $[M+H]^+$

SP3507:



To a solution of 4-bromo-2-fluoroaniline (1.90 g, 10 mmol) in 50 ml dry THF added sodium hexamethyldisilazide (25 mmol) at room temperature followed by iodoethane (3.9 g, 25 mmol). After stirring for 3 h, the mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$-solution. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give quantitative yield of the desired 4-diethylamino-3-fluorobromobenzene.

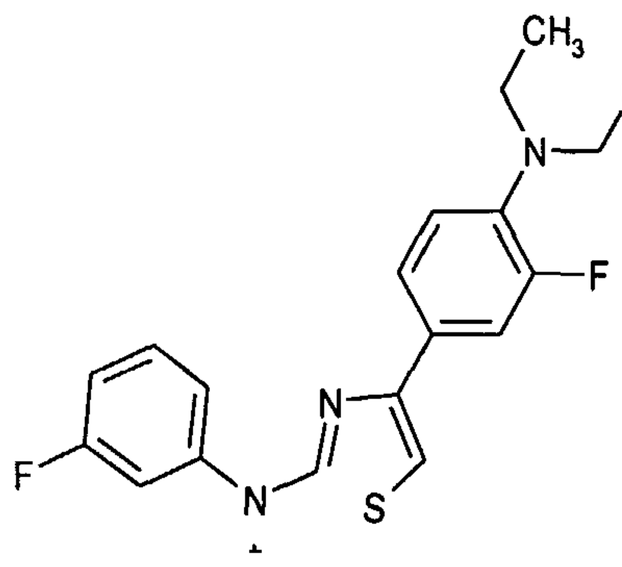
To a suspension of 4-diethylamino-3-fluorobromobenzene (1.07 g, 4.37 mmol) in dry MTBE (15 ml) at -20° C added *n*-butyllithium (2.0 ml, 5.0 mmol 2.5 M in hexane) drop by drop. After stirring for 10 min at -20° C, 2-chloro-*N*-methoxy-*N*-methylacetamide (0.69 g, 5.0 mmol) in MTBE (5 ml) was added and stirred at -20° C for 30 min. After warming to room temperature the mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and the solvents were evaporated and the residue was purified using silica gel chromatography. Yield: 1.1 g of 2-chloro-4'-diethylamino-3'-fluoroacetophenone. HPLC-MS: 244.22 $[M+H]^+$. 2-Chloro-4'-diethylamino-3'-fluoroacetophenone (24 mg, 0.1 mmol) and 2,4-difluorophenylthiourea (19 mg, 0.1 mmol) in 5 ml of ethanol was heated to 70°C overnight. Evaporated the solvent gave the desired substituted aminothiozole.

Yield: 41 mg

HPLC: 95%

HPLC-MS: 378 [M+H].

SP3505:



ethylamino-3-fluorobromobenzene produced for SP3507 (1.07 g, 4.37 mmol) in dry MTBE (15 ml) at -20° C added *n*-butyllithium (2.0 ml, 5.0 mmol 2.5 M in hexane) drop by drop. After stirring for 10 min at -20° C, 2-chloro-*N*-methoxy-*N*-methylacetamide (0.69 g, 5.0 mmol) in MTBE (5 ml) was added and stirred at -20° C for 30 min. After warming to room temperature the mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and the solvents were evaporated and the crude product was purified using silica gel chromatography.

Yield: 1.1 g

HPLC-MS: 244.22 $[M+H]^+$

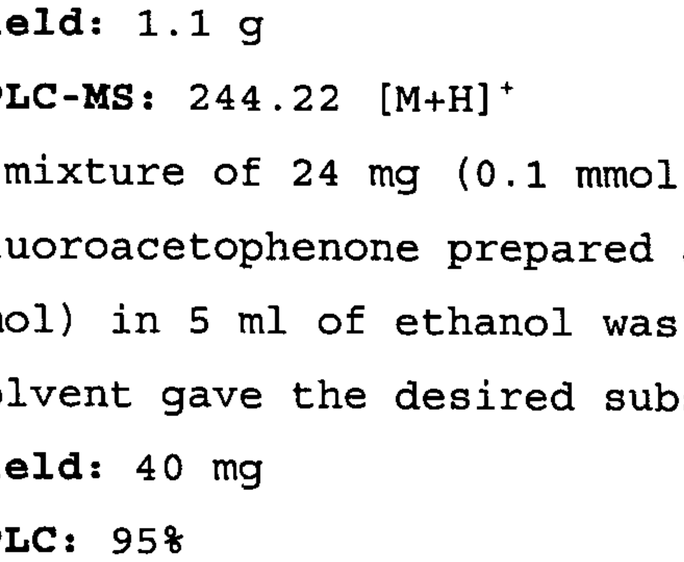
A mixture of 24 mg (0.1 mmol) 2-chloro-4'-diethylamino-3'-fluoroacetophenone prepared above and 3-fluorophenylthiourea (17 mg, 0.1 mmol) in 5 ml of ethanol was heated to 70°C overnight. Evaporated the solvent gave the desired substituted aminothiazole.

Yield: 40 mg

HPLC: 95%

HPLC-MS: 360 [M+H].

SP3309:



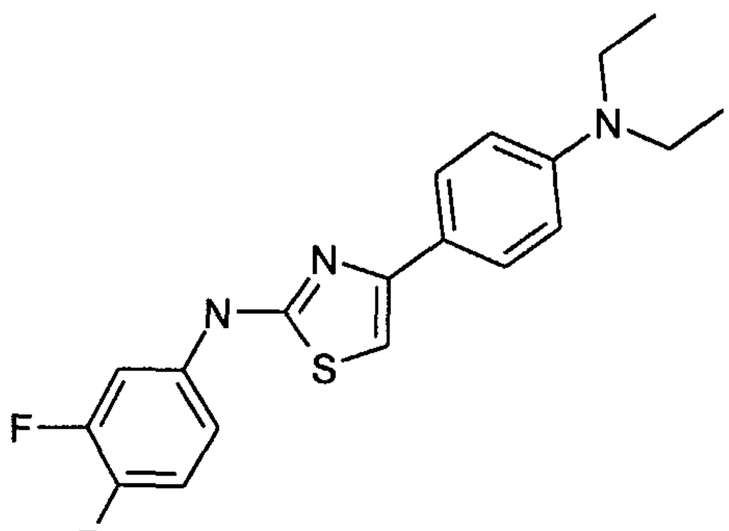
720 mg (5 mmol) 3-aminoquinoline and 740 µl (5.5 mmol) benzoyl isothiocyanate in 15 ml DMF were reacted according to general procedure 1. 41 mg (0.2 mmol) quinoline-3-thiourea and 54 mg (0.2 mmol) *alpha*-bromo-4-(1-diethylamino)-acetophenone in 5 ml ethanol were reacted according to general procedure 2 and purified using preparative HPLC.

Yield: 98 mg.

Purity (HPLC): 95%

HPLC-MS: 375 $[M+H]^+$

SP3199:



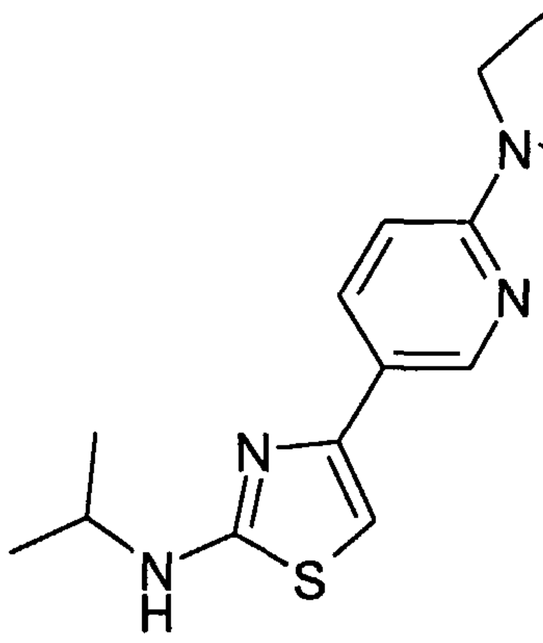
A solution of 2.44 g (10 mmol) 2-bromo-4'-nitroacetophenone and sodium thiocyanate in acetonitrile was stirred at 45° C for 3h. The solvent was evaporated and the residue was dissolved in ethyl acetate and water, extracted twice with ethyl acetate. The organic layer was separated, dried over Na_2SO_4 and the solvent was removed. (yield: 2.25 g, HPLC: >95%). 49 mg (0.22 mmol) of the 1-(4-nitro-phenyl)-2-thiocyanato-ethanone prepared above and 26 mg (0.20 mmol) 3,4-difluoroaniline in 3 ml ethanol were stirred at 50°C overnight. After cooling to room temperature 135 mg (0.6 mmol) $SnCl_2 \times 2H_2O$ were added and the mixture was stirred at 60°C overnight. The solvent was removed and the residue was dissolved in ethyl acetate and 1 N NaOH. The organic layer was separated, dried over $MgSO_4$ and the solvent was removed. 49 mg (0.16 mmol) of the aminothiazole prepared above were reacted with 113 µl (2 mmol) acetaldehyde and 255 mg (2 mmol) sodium cyanoborohydride in 5 ml DMF/HOAc (100/1) according to general procedure 10.

Yield: 45 mg.

Purity (HPLC): 95%

HPLC-MS: 360 $[M+H]^+$

SP2622



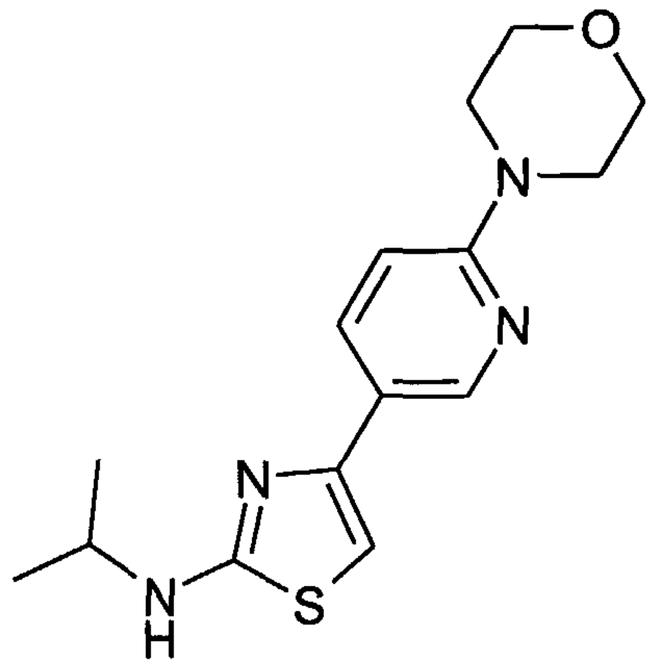
To a solution of 550 mg (3.53 mmol) 3-acetyl-6-chloropyridine (D. Kuo, *Tetrahedron* **1992**, *48*, 9233 - 9236) in 15 ml THF were added portionwise 600 mg (2.10 mmol) 5,5-dibromobarbituric acid (G. Grundke *et al.*, *Chem. Ber.* **1985**, *118*, 4288 - 4291). After 16 h the reaction was concentrated *in vacuo* and partitioned between ethyl acetate and sat. $NaHCO_3$ solution. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*.(Yield: 662 mg, HPLC-MS: 234/236/238 $[M+H]^+$). According to the general procedure 2 100 mg (426 µmol) 3-bromoacetyl-6-chloropyridine and 50 mg (426 µmol) isopropylthiourea were reacted in 5 ml ethanol (Yield: 150 mg, HPLC-MS: 254/256 $[M+H]^+$). In a sealed vessel 21 mg (85 µmol) of the aminothiazole prepared above and 3 ml pyrrolidine were placed at room temperature then heated to 120 °C with stirring for 72 h. After cooling the reaction was concentrated in vacuo and purified using preparative HPLC.

Yield: 13 mg

Purity (HPLC): >95%

HPLC-MS: 289 $[M+H]^+$

SP2621



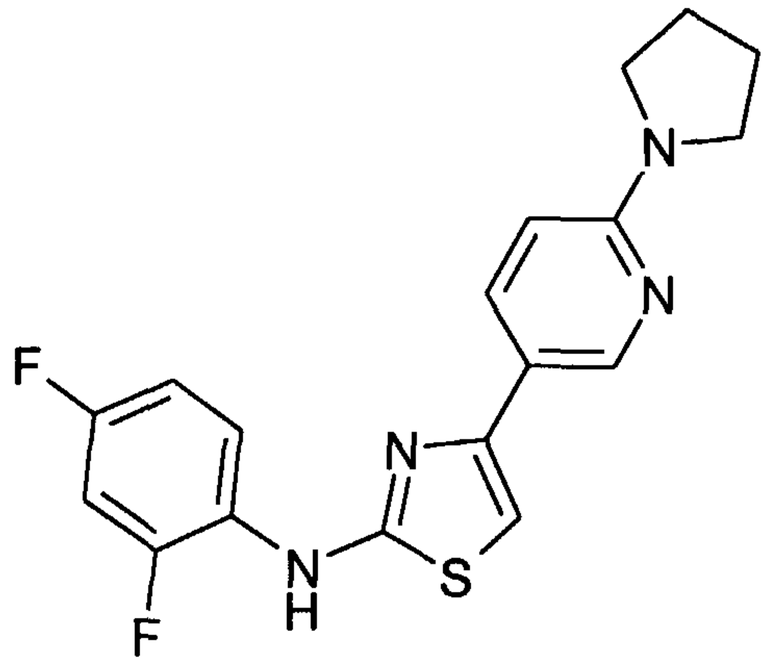
To a solution of 550 mg (3.53 mmol) 3-acetyl-6-chloropyridine (D. Kuo, *Tetrahedron* **1992**, *48*, 9233 - 9236) in 15 ml THF were added portionwise 600 mg (2.10 mmol) 5,5-dibromobarbituric acid (G. Grundke *et al.*, *Chem. Ber.* **1985**, *118*, 4288 - 4291). After 16 h the reaction was concentrated *in vacuo* and partitioned between ethyl acetate and sat. $NaHCO_3$ solution. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*.(Yield: 662 mg, HPLC-MS: 234/236/238 $[M+H]^+$). According to the general procedure 2 100 mg (426 µmol) 3-bromoacetyl-6-chloropyridine and 50 mg (426 µmol) isopropylthiourea were reacted in 5 ml ethanol (Yield: 150 mg, HPLC-MS: 254/256 $[M+H]^+$). In a sealed vessel 21 mg (85 µmol) of the aminothiazole prepared above and 3 ml morpholine were placed at room temperature then heated to 120 °C with stirring for 72 h. After cooling the reaction was concentrated in vacuo and purified using preparative HPLC.

Yield: 18 mg

Purity (HPLC): >95%

HPLC-MS: 305 $[M+H]^+$

SP2122



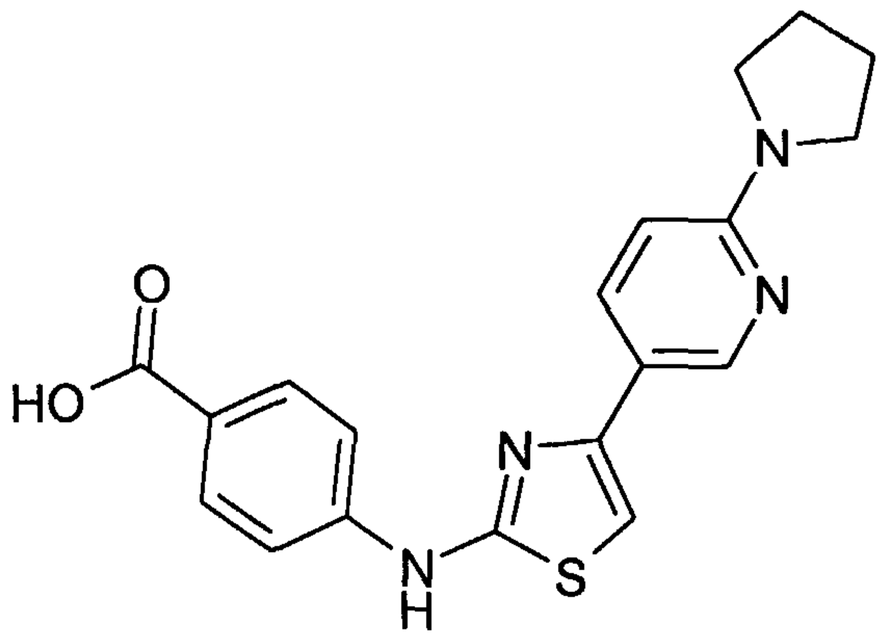
To a solution of 550 mg (3.53 mmol) 3-acetyl-6-chloropyridine (D. Kuo, *Tetrahedron* **1992**, *48*, 9233 - 9236) in 15 ml THF were added portionwise 600 mg (2.10 mmol) 5,5-dibromobarbituric acid (G. Grundke *et al.*, *Chem. Ber.* **1985**, *118*, 4288 - 4291). After 16 h the reaction was concentrated *in vacuo* and partitioned between ethyl acetate and sat. $NaHCO_3$ solution. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*.(Yield: 662 mg, HPLC-MS: 234/236/238 $[M+H]^+$). 50 mg (213 µmol) 3-bromoacetyl-6-chloropyridine and 40 mg (213 µmol) 2,4-difluorophenylthiourea were reacted in 5 ml ethanol according to the general procedure 2 (Yield: 90 mg, HPLC-MS: 324/326 $[M+H]^+$). In a sealed vessel 20 mg (60 µmol) the aminothiazole prepared above and 3 ml pyrrolidine were placed at room temperature then heated to 120 °C with stirring for 4 h. After cooling the reaction was concentrated in vacuo and purified using preparative HPLC.

Yield: 10 mg

Purity (HPLC): >95%

HPLC-MS: 359 $[M+H]^+$

SP2119



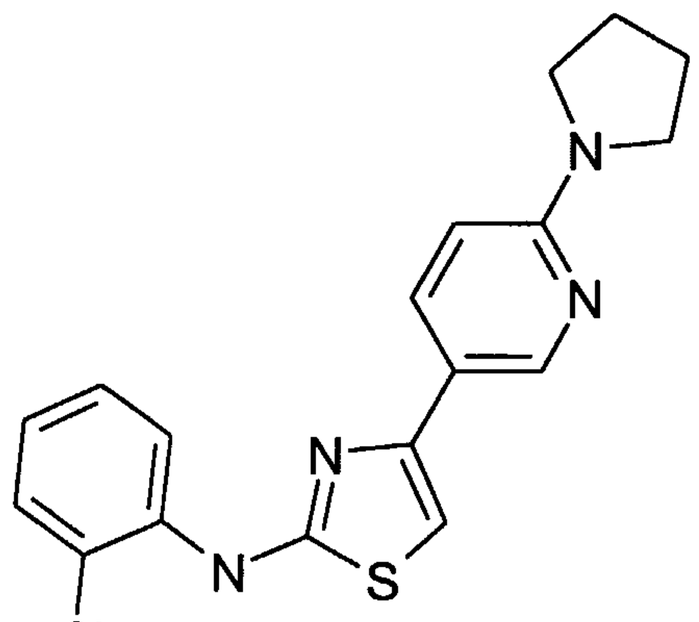
To a solution of 550 mg (3.53 mmol) 3-acetyl-6-chloropyridine (D. Kuo, *Tetrahedron* **1992**, *48*, 9233 - 9236) in 15 ml THF were added portionwise 600 mg (2.10 mmol) 5,5-dibromobarbituric acid (G. Grundke *et al.*, *Chem. Ber.* **1985**, *118*, 4288 - 4291). After 16 h the reaction was concentrated *in vacuo* and partitioned between ethyl acetate and sat. $NaHCO_3$ solution. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO4, filtered and evaporated *in vacuo*.(Yield: 662 mg, HPLC-MS: 234/236/238 $[M+H]^+$). According to the general procedure 2 200 mg (900 µmol) 3-bromoacetyl-6-chloropyridine and 177 mg (900 µmol) 4-carboxyphenylthiourea were reacted in 5 ml ethanol (yield: 377 mg; HPLC-MS: 332 $[M+H]^+$). In a sealed vessel 50 mg (150 µmol) of the aminothiazole prepared above and 3 ml pyrrolidine were placed at room temperature then heated to 120 °C with stirring for 72 h. After cooling the reaction was concentrated in vacuo and purified using preparative HPLC.

Yield: 40 mg

Purity (HPLC): >95%

HPLC-MS: 367 $[M+H]^+$

SP2115



Cl

To a solution of 550 mg (3.53 mmol) 3-acetyl-6-chloropyridine (D. Kuo, *Tetrahedron* **1992**, *48*, 9233 - 9236) in 15 ml THF were added portionwise 600 mg (2.10 mmol) 5,5-dibromobarbituric acid (G. Grundke *et al.*, *Chem. Ber.* **1985**, *118*, 4288 - 4291). After 16 h the reaction was concentrated *in vacuo* and partitioned between ethyl acetate and sat. $NaHCO_3$ solution. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*.(Yield: 662 mg, HPLC-MS: 234/236/238 $[M+H]^+$). 200 mg (900 µmol) 3-bromoacetyl-6-chloropyridine and 167 mg (900 µmol) 2-chlorophenylthiourea were reacted in 5 ml ethanol according to the general procedure 2 (Yield: 367 mg, HPLC-MS: 322/324 $[M+H]^+$ (Int: 100:65). In a sealed vessel 50 mg (150 µmol) of the aminothiazole prepared above and 3 ml pyrrolidine were placed at room temperature then heated to 120 °C with stirring for 72 h. After cooling the reaction was concentrated in vacuo and purified using preparative HPLC.

Yield: 45 mg

Purity (HPLC): >95%

HPLC-MS: 357/359 $[M+H]^+$(Int: 100:35)

Examples

Example 1: Receptor Tyrosine Kinase Assay

The following in vitro assays are used to determine the ability of different compounds to inhibit the transfer of phosphate groups onto tyrosine residues of downstream substrates. The level of phosphorylation is measured by a monoclonal antibody which is specific for phosphorylated tyrosine residues in an enzyme-linked immunosorbent assay (ELISA).

Materials:

The following recombinant kinases were expressed in baculovirus infected insect cells Sf9 and purchased from ProQuinase, Freiburg:

1.) GST-Tie2/Tek (aa 771-1124)

2.) GST-KDR (aa807-1356)

3.) GST-cMet (aa956-1390)

4.) GST-FGFR1 (aa400-822)

5.) GST-IGF1R (aa905-1337)

6.) GST-cKit (aa544-976)

7.) GST-cAbl (aa118-535)

8.) GST-His6-ErbB2 (aa679-1255)

9.) GST-FLT4 (aa725-1298)

The following recombinant kinase was expressed in baculovirus infected insect cells and purchased from MoBiTec, Göttingen:

10.) Src, partially purified (Panvera P2903)

The following reagents and supplies were used:

96-well LIA plates (Greiner 655074)

Poly-Glu-Tyr 4:1 (Sigma P0275)

Adenosin Triphosphate (Sigma A2383)

Dimethylsulfoxide DMSO (Roth A994.2)

Mouse monoclonal antiphosphotyrosin antibody PY20 coupled to horseradish peroxidase (Calbiochem 525320)

Bovine Serum Albumine (BSA) (Calbiochem 12659)

PBS buffer:

- 137 mM Sodium chloride (Roth 3957.1)
- 3 mM Potassium chloride (Roth 6781.1)
- 1.5 mM Potassium dihydrogenphosphate (Roth 3904.1)
- 8.2 mM Disodium hydrogenphosphate (Roth P030.2)

Sodium ortho vanadate (Sigma S6508)

Manganese dichloride tetrahydrate (Roth T881.1)

HEPES (Roth 9105.2)

Tween 20 (Roth A9127.1)

BM Chemoluminescent ELISA Substrate (Roche 1582950)

Procedure:

If not otherwise indicated all steps are performed at room temperature.

1.) Coat wells of ELISA plate with 10 mg/ml Poly-Glu-Tyr 4:1 in 100 µl/well PBS buffer (137 mM NaCl, 3 mM KCl, 1.5 mM KH_2PO_4, 8.2 mM Na_2HPO_4) overnight at 4 °C

2.) Wash 2 times for 5 min each with PBS + 0.05 % Tween20

3.) Kinase assay:

a.) Add 5-30 ng/well kinase in 50 µl/well kinase buffer (100 mM HEPES pH 7.4, 100 mM NaCl, 0.1 mM Na_3VO_4)

b.) Add 25 µl/well compound (50 and 5 µM) in 5 % DMSO

c.) Add 25 µl/well 100 µM ATP in 40 mM $MnCl_2$

d.) Incubate 30 min

4.) Wash 3 times for 5 min each with PBS + 0.05 % Tween20

5.) Add anti phosphotyrosin antibody /HRP 1:10.000 in 100 µl/well PBS + 0.05 % Tween + 0.1% BSA, incubate for 1 h

6.) Wash 3 times for 5 min each with PBS + 0.05 % Tween20

7.) Chemoluminescence reaction:

a.) Premix 25 µl/well BM CLS Solution 1 with 0.25 µl/well BM CLS Solution 2

b.) Preincubate for 15 min

c.) Add 25 µl/well PBS

d.) Add 50 µl/well substrate solution to microtiter wells

e.) Incubate for at least 1 min

8.) Detect chemoluminescence signals in Tecan Genios reader

a.) Mode : luminescence

b.) Integration time : 100 ms

c.) Enhancement factor : 125-150

d.) Shaking time: 5 s

Example 2: Generation of ligand

Materials:

293T cells

Dulbeccos modified eagle medium (DMEM) (Life Technologies)

Fetal Calf Serum (Life Technologies)

Cell culture tissue dishes (Greiner)

Escort Transfection Reagent (Sigma)

Procedure:

293T cells are plated at 1 x 106 cells per well in a six well plate in DMEM medium supplemented with 10 % fetal calf serum (FCS), incubated overnight at 37 °C and transfected with 1 μg plasmid DNA of pCB ANG1 by the Escort transfection reagent according to the manufacturer's protocol. After one day medium is changed to DMEM without FCS, and cell culture supernatants are harvested by centrifugation after additional 3 days.

Example 3: Cell-based assay

Materials:

Human umbilical vein endothelial cells (HUVEC) (Promocell C-12200)

Endothelial cell growth (ECG) medium (Promocell C-22010) supplemented with:

- 2 % Fetal Calf Serum
- 0.4 % Endothelial Cell Growth Fator (ECGF)
- 0.1 ng/ml Epidermal Growth factor (EGF)
- 1 µg/ml Hydrocortison
- 1 ng/ml bascic Fibroblast Growth Factor (bFGF)
- 50 ng/ml Amphotericin B
- 50 µg/ml Gentamicin

M199 medium (Life Technologies)

Detach Kit (Promocell C-41210) contains:

- HepesBSS
- Trypsin/EDTA solution
- Trypsin neutralisation solution (TNS)

Cell culture tissue dishes (Greiner)

PBS buffer:

RIPA buffer:

- 20 mM Tris/HCl pH 7,5

- 150 mM NaCl

- 2 mM EDTA

- 1 % Triton X100

- 1 % SDS

- 0,5 % deoxycholat (DOC)

- 10 % glycerol

4 x SDS sample buffer:

- 250 mM disodium hydrogenphosphate / sodium dihydrogenphosphate pH 7.0

- 8 % SDS

- 40 % glycerol

- 20 % mercaptoethanol

- 0.01 % bromophenol blue

PVDF membranes Immobilon-P (Millipore)

Bovine Serum Albumine (BSA) (Calbiochem 12659)

Tween 20 (Roth A9127.1)

Mouse monoclonal antiphosphotyrosin antibody PY20 coupled to horseradish peroxidase (Calbiochem 525320)

Rabbit polyclonal anti-Tie-2 antibody C-20 (Santa Cruz Biotechnology sc-324)

Goat anti rabbit IgG secondary antibody coupled to horseradish peroxidase (Dianova 111-035-003)

Enhanced chemoluminescence detection kit Supersignal Pico (Pierce 37070)

Procedure:

Endothelial cells e. g. HUVECs between passage 2 and 12 are plated at between 2 x 105 and 1 x 106 cells per well in a six well plate in supplemented ECG medium. After 24 to 48 hours the medium is changed to M199 medium containing increasing concentrations of the inhibitory compound in the individual wells. The cells are incubated at 37 °C and then treated with cell culture supernatants containing the ligand for 5 to 30 min.

Afterwards the cells are placed on ice, washed once with 1 ml PBS, lysed by the addition of 300 µl RIPA buffer and removed from the plate by a cell scraper. The suspension is transferred into a microcentrifuge tube, sonicated for 5 sec and boiled after addition of 100 µl 4 x SDS sample buffer for 5 min at 95 °C.

30 µl of the lysate are run on a 8 % SDS-PAGE gel. The separated proteins are then transferred to PVDF membranes according to the manufacturer's instructions for Western blotting.

The blots are blocked with PBS / 0.05 % Tween 20 / 1 % BSA for 1 h at room temperature, incubated with either

antiphosphotyrosin or anti-Tie-2 antibody diluted 1:2000 in PBS/Tween for 1 hour and washed 3 times with PBS/Tween. In the second case the blot is incubated with a goat anti rabbit IgG secondary antibody/ HRP conjugate diluted 1:4000 in PBS/Tween. After washing 3 times in PBS/Tween the blot is developed by the ECL method according to the manufacturer's instruction.

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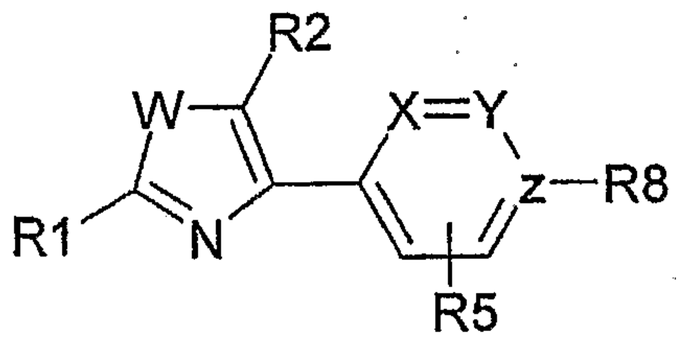
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(76)

NEW SET OF CLAIMS

1. Compound according to formula II,



(II)

wherein W is S,

R_1 is N-R_6R_7,

R_6 is H,

R_7 is a substituted or unsubstituted alkyl, cycloalkyl, phenyl, arylalkyl, naphtyl, heteroaryl or heterocycloalkyl.

X and Y are CH or N,

Z is C,

R_8 is an amine group or a mono-substituted or di-substituted alkylamine, alkylene-amine or cycloalkylamine or heterocycloalkylamine, which (cyclo)alkylamine may be substituted with an alkyl, cycloalkyl, hydroxyl, halogen, pyridinyl or alkylpyridinyl group.

R_2 is hydrogen, heteroaryl, aralkyl or carboxylgroup, and

R_5 is hydrogen, hydroxyl, halogen or alkoxy group;

2. Compound according to claim 1, wherein X and Y are CH.

3. Compound according to claim 1-2, wherein R_7 is C_1-C_7 alkyl or C_3-C_7 cycloalkyl optionally substituted with a hydroxyl or halogen group.

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4. Compound according to claim 1-2, wherein R_7 is a phenyl group substituted with at least one group selected from ketone, acylated amine, carboxyl, ester, sulfonic acid, amide, sulfon amide, alkyl sulfon amide, hydroxyl, alkoxyl, halogen and/or alkyl group such as trifluormethyl or optionally substituted with a carboxyl, hydroxyl or halogen group.

5. Compound according to claim 1-2, wherein R_7 is a phenyl group substituted with an amine, diketal, morpholinyl, piperazinyl or pyrrolidinyl group, which is optionally substituted with an alkyl, acyl, hydroxyl or sulfonyl group.

6. Compound according to claim 1-2, wherein R_7 is an arylalkyl group substituted with a carboxyl group.

7. Compound according to claim 1-2, wherein R_7 is a naphtyl group, substituted with an organic acid group, preferably a carboxylic acid or sulfonic acid group.

8. Compound according to claim 1-2, wherein the heteroaryl group of R_7 is a substituted or unsubstituted pyridinyl, quinolinyl or isoquinolinyl group.

9. Compound according to claim 8, wherein R_7 is a pyridinyl group substituted with an alkoxyl group or a halogen group, preferably chlorine.

10. Compound according to claim 1-2, wherein the heterocycloalkyl group of R_7 is piperidinyl, preferably substituted with an arylalkyl group.

AMENDED SHEET

11. Compound according to claim 1-10, wherein R_7 is:

- phenyl C_1-C_3 carboxylic acid, preferably para-carboxylic acid;
- 2-methyl- 5-fluorine phenyl;
- methoxy pyridinyl;
- halogen pyridinyl;
- isoquinolinyl;
- tri-methoxy phenyl;
- phenyl hydroxy-pyrrolidinyl
- phenyl piperazinyl
- phenyl n-methyl-piperazinyl
- napthenyl sulfonic acid
- ortho bromine phenyl

12. Compound according to claim 1-11, wherein the cycloalkylamine or heterocycloalkylamine group of R_8 is a pyrrolidinyl, piperazinyl, piperidinyl, morpholinyl or thiomorpholinyl, which is optionally substituted with an alkyl, hydroxyl or halogen group.

13. Compound according to claim 1-12 wherein R_8 is:

- alkylamine, preferably di-ethyl;
- hydroxypyrrolidinyl;
- methyl-butenylamine

14. Compound according to claim 1-13 wherein R_2 is a carboxyl group or a tetrazole group.

15. Compound according to claim 1-11 wherein Y is N.

16. Compound according to claim 1-15 being chosen from the group consisting of the compounds, SP1153, SP5421, SP5251,

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SP5601, SP5250, SP844, SP5748, SP5751, SP5672, SP5674, SP1335, SP5245, SP4267, SP1313, SP1319, SP1155, SP6367, SP5760, SP5756, SP5751, SP5748, SP5752, SP5746, SP5745, SP5672, SP5601, SP5424, SP5330, SP5245 SP5224, SP5053, SP4267

17. Method of inhibiting the activity of one or more protein kinases by using a compound of claim 1-16 in vitro or in cell culture.

18. Pharmaceutical composition comprising a pharmaceutically acceptable additive, such as a diluent or carrier and a compound according to claim 1-16.

19. Use of a compound according to claim 1-16 as a medicament.

20. Use of a compound according to claim 1-16 as an inhibitor of protein kinase activity.

21. Use of a compound according to claim 20, wherein the protein kinase is selected from the group of tyrosine kinases consisting of Tie-2, KDR, c-Met, FGFR-1, IGF-1R, c-Kit, Flt-4, ErbB-2, c-Abl, c-Src, and oncogenic variants thereof.

22. Use according to claim 20 or 21, wherein the protein kinase is Tie-2 or KDR.

23. Use according to claim 20 or 21, wherein the protein kinase is Tie-2 and KDR.

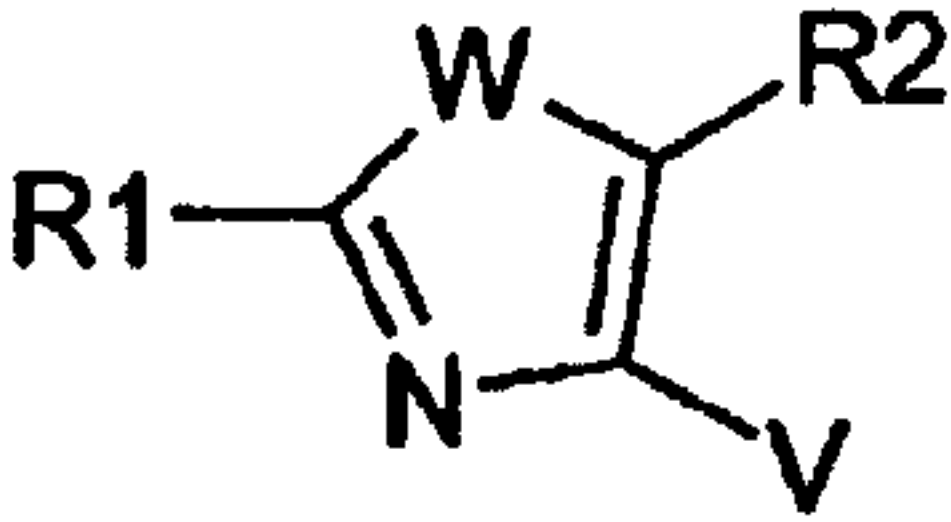
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24. Use of a compound according to claim 20, wherein the protein kinase is a serine/threonine kinase.

25. A compound according to claim 1-16 for use to inhibit the progression of a disease state in a patient.

26. A compound as claimed in claim 1-16 for use in the treatment of a disease selected from the group of cancer, venous malformations and angiogenesis dependent disorders.

AMENDED SHEET



(I)

