INHIBITORS OF VEGF RECEPTOR AND HGF RECEPTOR SIGNALING

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to the inhibition of VEGF receptor signaling and HGF receptor signaling. More particularly, the invention relates to compounds and methods for the inhibition of VEGF receptor signaling and HGF receptor signaling.

Summary of the Related Art

[0002] Angiogenesis is an important component of certain normal physiological processes such as embryogenesis and wound healing, but aberrant angiogenesis contributes to some pathological disorders and in particular to tumor growth.[1,2] VEGF-A (vascular endothelial growth factor A) is a key factor promoting neovascularization (angiogenesis) of tumors.[3-7] VEGF induces endothelial cell proliferation and migration by signaling through two high affinity receptors, the fms-like tyrosine kinase receptor, Flt-1, and the kinase insert domain-containing receptor, KDR.[8,9,10]. These signaling responses are critically dependent upon receptor dimerization and activation of intrinsic receptor tyrosine kinase (RTK) activity. The binding of VEGF as a disulfide-linked homodimer stimulates receptor dimerization and activation of the RTK domain [11]. The kinase activity autophosphorylates cytoplasmic receptor tyrosine residues, which then serve as binding sites for molecules involved in the propagation of a signaling cascade. Although multiple pathways are likely to be elucidated for both receptors, KDR signaling is most extensively studied, with a mitogenic response suggested to involve ERK-1 and ERK-2 mitogen-activated protein kinases [12].

[0003] Disruption of VEGF receptor signaling is a highly attractive therapeutic target in cancer, a CLIENT-HOST DIVIDED ARCHITECTURE FOR INPUT-OUTPUT COORDINATION ure endothelium remains relatively quiescent (with the exception of the female reproductive system and wound healing). A number of experimental approaches to inhibiting VEGF signaling have been examined, including use of neutralizing antibodies [13,14,15], receptor antagonists [16], soluble receptors [17], antisense constructs [18] and dominant-negative strategies [19].

[0004] Despite the attractiveness of anti-angiogenic therapy by VEGF inhibition alone, several issues may limit this approach. VEGF expression levels can themselves be elevated by numerous diverse stimuli and perhaps most importantly, the hypoxic state of tumors resulting from VEGFr inhibition, can lead to the induction of factors that themselves

promote tumor invasion and metastasis thus, potentially undermining the impact of VEGF inhibitors as cancer therapeutics [20].

[0005] The HGF (hepatocyte growth factor) and the HGF receptor, c-met, are implicated in the ability of tumor cells to undermine the activity of VEGF inhibition [20]. HGF derived from either stromal fibroblasts surrounding tumor cells or expressed from the tumor itself has been suggested to play a critical role in tumor angiogenesis, invasion and metastasis [21,22]. For example, invasive growth of certain cancer cells is drastically enhanced by tumor-stromal interactions involving the HGF/c-Met (HGF receptor) pathway [23,24,25]. HGF, which was originally identified as a potent mitogen for hepatocytes [26,27] is primarily secreted from stromal cells, and the secreted HGF can promote motility and invasion of various cancer cells that express c-Met in a paracrine manner [28,29,30]. Binding of HGF to c-Met leads to receptor phosphorylation and activation of Ras/mitogen-activated protein kinase (MAPK) signaling pathway, thereby enhancing malignant behaviors of cancer cells [30,31]. Moreover, stimulation of the HGF/c-met pathway itself can lead to the induction of VEGF expression, itself contributing directly to angiogenic activity[32].

[0006] Thus, anti-tumor anti-angiogenic strategies or approaches that target both VEGF/VEGFr signaling and HGF/c-met signaling may circumvent the ability of tumor cells to overcome VEGF inhibition alone and may represent improved cancer therapeutics.

[0007] Here we describe small molecules that are potent inhibitors of both the VEGF receptor KDR and the HGF receptor c-met.

BRIEF SUMMARY OF THE INVENTION

[0008] The present invention provides new compounds and methods for treating cell proliferative diseases. The compounds of the invention are dual function inhibitors, capable of inhibiting both VEGF and HGF. Accordingly, the invention provides new inhibitors of VEGF receptor signaling and HGF receptor signaling, including the VEGF receptor KDR and the HGF receptor c-met.

[0009] In a first aspect, the invention provides compounds of formula A that are useful as inhibitors of VEGF receptor signaling and HGF receptor signaling.

[0010] In a second aspect, the invention provides compounds of formula B that are useful as inhibitors of VEGF receptor signaling and HGF receptor signaling.

[0011] In a third aspect, the invention provides compositions comprising a compound of the present invention that is an inhibitor of VEGF receptor signaling and HGF receptor

signaling, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0012] In a fourth aspect, the invention provides a method of simultaneously inhibiting VEGF receptor signaling and HGF receptor signaling in a cell, comprising contacting a cell in which inhibition of VEGF receptor signaling and HGF receptor signaling is desired with a compound of the invention.

[0013] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0014] The invention provides compounds and methods for inhibiting the VEGF receptor KDR and the HGF receptor c-met. The invention also provides compositions and methods for treating cell proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

[0015] For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

[0016] The terms " inhibitor of VEGF receptor signaling " and "inhibitor of HGF receptor signaling" are used to identify a compound having a structure as defined herein, which is capable of interacting with a HGF receptor and a VEGF receptor and inhibiting the activity of HGF and VEGF. In some preferred embodiments, such reduction of activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%.

[0017] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (*e.g.* CH_3-CH_2-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene."

(Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-. Also, a number of moieties disclosed herein exist in multiple tautomeric forms, all of which are intended to be encompassed by any given tautomeric structure.

[0018] The term "hydrocarbyl" refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A "C_0" hydrocarbyl is used to refer to a covalent bond. Thus, "C_0-C_3-hydrocarbyl" includes a covalent bond, methyl, ethyl, ethenyl, ethynyl, propyl, propenyl, propynyl, and cyclopropyl.

[0019] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A "C_0" alkyl (as in "C_0-C_3-alkyl") is a covalent bond (like "C_0" hydrocarbyl).

[0020] The term "alkenyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0021] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0022] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation,

ethenylene, propenylene, and butenylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0023] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0024] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, NH, N-alkyl, SO, SO_2, SO_2NH, or $NHSO_2$.

[0025] An "aryl" group is a C_6-C_{14} aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C_6-C_{10} aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C_1-C_6)alk(C_6-C_{10})aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0026] A "heterocyclyl" or "heterocyclic" group is a ring structure having from about 3 to about 12 atoms, wherein one or more atoms are selected from the group consisting of N, O, S, SO, and SO_2. The heterocyclic group is optionally substituted on carbon at one or more positions. The heterocyclic group is also independently optionally substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, or aralkoxycarbonyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocyles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds where an annular O or S atom is adjacent to another O or S atom.

[0027] As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π-electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring

selected from the group consisting of N, O, and S. The term "heteroaryl" is also meant to encompass monocyclic and bicyclic groups. For example, a heteroaryl group may be pyrimidinyl, pyridinyl, benzimidazolyl, thienyl, benzothiazolyl, benzofuranyl and indolinyl. A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which is independently optionally substituted or unsubstituted. Preferred heteroalkyl groups comprise a C_1-C_6 alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms. Examples of preferred heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, and thiazolylethyl. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0028] For simplicity, reference to a "C_n-C_m" heterocyclyl or heteroaryl means a heterocyclyl or heteroaryl having from "n" to "m" annular atoms, where "n" and "m" are integers. Thus, for example, a C_5-C_6-heterocyclyl is a 5- or 6- membered ring having at least one heteroatom, and includes pyrrolidinyl (C_5) and piperidinyl (C_6); C_6-hetoaryl includes, for example, pyridyl and pyrimidyl.

[0029] An "arylene," "heteroarylene," or "heterocyclylene" group is an aryl, heteroaryl, or heterocyclyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0030] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, pyridotriazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl,

quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0031] As employed herein, when a moiety (*e.g.*, cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (*e.g.*, an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

(a) halo, hydroxy, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,

(b) C_1-C_5 alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, C_2-C_8 acyl, C_2-C_8 acylamino, C_1-C_8 alkylthio, arylalkylthio, arylthio, C_1-C_8 alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0-C_6 *N*-alkyl carbamoyl, C_2-C_{15} *N,N*-dialkylcarbamoyl, C_3-C_7 cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3-C_7 heterocycle, C_5-C_{14} heteroaryl, or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and

(c) $-(CH_2)_s-NR^{30}R^{31}$, wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R^{30} and R^{31} are each independently hydrogen, cyano, oxo, carboxamido, amidino, C_1-C_8 hydroxyalkyl, C_1-C_3 alkylaryl, aryl-C_1-C_3 alkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, aryl-C_1-C_3 alkoxycarbonyl, C_2-C_8 acyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl, aryl,

cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

R^{30} and R^{31} taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

[0032] Especially preferred substituents on alkyl groups include halogen and hydroxy.

[0033] Especially preferred substituents or ring groups, such as aryl, heteroaryl, cycloalkyl and heterocyclyl, include halogen, alkoxy and alkyl.

[0034] A "halohydrocarbyl" is a hydrocarbyl moiety in which from one to all hydrogens have been replaced with one or more halo.

[0035] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (*i.e.*, R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (*i.e.*, NH_2-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH_2, alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0036] The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons.

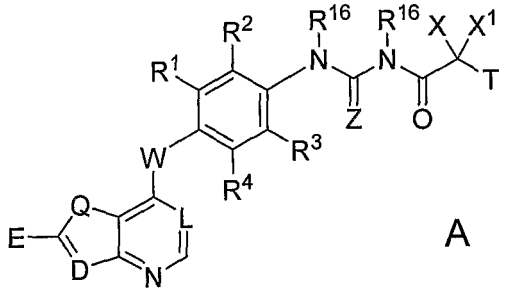
[0037] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluoro-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4-dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH_2-) substituted with oxygen to form carbonyl -CO-).

[0038] An "unsubstituted" moiety as defined above (*e.g.*, unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

[0039] Throughout the specification, preferred embodiments of one or more chemical substituents are identified. Also preferred are combinations of preferred embodiments. For example, paragraph [0048] describes preferred embodiments of X and X^1 in the compounds of formula (A) and paragraph [0053] describes preferred embodiments of R^1 in the compounds of formula (A). Thus, also contemplated as within the scope of the invention are compounds of formula (A) in which X and X^1 are as described in paragraph [0048] and R^1 is as described in paragraph [0053]. Furthermore, compounds excluded from any one particular genus of compounds (*e.g.*, through a proviso clause) are intended to be excluded from the scope of the invention entirely, including from other disclosed genera, unless expressly stated to the contrary.

Compounds

[0040] In the first aspect, the invention comprises compounds of formula (A), that are inhibitors of VEGF receptor signaling and HGF receptor signaling:



A

and pharmaceutically acceptable salts and complexes thereof, wherein

T is selected from the group consisting of arylalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said arylalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl is optionally substituted with 1 to 3 independently selected R^{20};

each R^{20} is independently selected from the group consisting of -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^{17}$, $-OCF_3$, $-NR^{17}R^{18}$, $-S(O)_{0-2}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-N(R^{17})SO_2R^{17}$, $-N(R^{17})C(O)R^{17}$, $-N(R^{17})C(O)OR^{17}$, $-C(O)R^{17}$, $-C(O)SR^{17}$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, $-O(CH_2)_n$aryl, $-O(CH_2)_n$heteroaryl, $-(CH_2)_{0-5}$(aryl), $-(CH_2)_{0-5}$(heteroaryl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-CH_2(CH_2)_{0-4}$-T^2, an optionally substituted C_{1-4} alkylcarbonyl, C_{1-4} alkoxy, an amino optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy and a saturated or unsaturated three- to seven-membered carboxyclic or heterocyclic group, wherein T^2 is selected from the group consisting of -OH, -OMe, -OEt, $-NH_2$, -NHMe, $-NMe_2$, -NHEt and $-NEt_2$, and wherein the aryl, heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted;

W is selected from the group consisting of O, S, NH and NMe;

Z is selected from the group consisting of O, or S and NH;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano, or nitro, wherein C_1-C_6 alkyl is optionally substituted, or

X and X^1 taken together with the atom to which they are attached, form a C_3-C_7 cycloalkyl;

R^1, R^2, R^3 and R^4 independently represent hydrogen, halo, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^{17}$, $-NR^{17}R^{18}$, $-C(O)OR^{17}$, $-C(O)R^{17}$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^{17} is selected from the group consisting of H and R^{18};

R^{18} is selected from the group consisting of a (C_1-C_6)alkyl, an aryl, a aryl(C_1-C_6)alkyl, a heterocyclyl and a heterocyclyl(C_1-C_6)alkyl, each of which is optionally substituted, or

R^{17} and R^{18}, taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, the optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from the group consisting of N, O, S and P;

R^{16} is selected from the group consisting of -H, -CN, $-(CH_2)_{0-5}$(aryl), $-(CH_2)_{0-5}$(heteroaryl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-CH_2(CH_2)_{0-4}$-T^2, an optionally substituted C_{1-4} alkylcarbonyl, and a saturated or unsaturated three- to seven-membered carboxyclic or heterocyclic group, wherein T^2 is selected from the group consisting of -OH, -OMe, -OEt, $-NH_2$, -NHMe, $-NMe_2$, -NHEt and $-NEt_2$, and wherein the aryl, heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted;

Q is selected from the group consisting of CH_2, O, S, N(H), N(C_1-C_6 alkyl), N-Y-(aryl), -N-OMe, $-NCH_2OMe$ and -N-Bn;

D is selected from the group consisting of C-E and N;

L is N, or CR, wherein R is selected from the group consisting of -H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

E is selected from the group consisting of E^1, E^2 and E^3, wherein

E^1 is selected from the group consisting of -H, halogen, nitro, azido, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-C(O)NR^{42}R^{43}$, -Y-$NR^{42}R^{43}$, $-NR^{42}C(=O)R^{43}$, $-SO_2R^{42}$, $-SO_2NR^{42}R^{43}$, $-NR^{37}SO_2R^{42}$, $-NR^{37}SO_2NR^{42}R^{43}$, $-C(=N-OR^{42})R^{43}$, $-C(=NR^{42})R^{43}$, $-NR^{37}C(=NR^{42})R^{43}$,

$-C(=NR^{42})NR^{37}R^{43}$, $-NR^{37}C(=NR^{42})NR^{37}R^{43}$, $-C(O)R^{42}$, $-CO_2R^{42}$, -C(O)(heterocyclyl), $-C(O)(C_6\text{-}C_{10}$ aryl), -C(O)(heteroaryl), $-Y\text{-}(C_6\text{-}C_{10}$ aryl), -Y-(heteroaryl), -Y-(5-10 membered heterocyclic), $-NR^{6a}R^{6b}$, $-NR^{6a}SO_2R^{6b}$, $-NR^{6a}C(O)R^{6b}$, $-OC(O)R^{6b}$, $-NR^{6a}C(O)OR^{6b}$, $-OC(O)NR^{6a}R^{6b}$,$-OR^{6a}$, $-SR^{6a}$, $-S(O)R^{6a}$, $-SO_2R^{6a}$, $-SO_3R^{6a}$, $-SO_2NR^{6a}R^{6b}$, $-SO_2NR^{42}R^{43}$, $-COR^{6a}$, $-CO_2R^{6a}$, $-CONR^{6a}R^{6b}$, $-(C_1\text{-}C_4)$fluoroalkyl, $-(C_1\text{-}C_4)$fluoroalkoxy, $-(CZ^3Z^4)_aCN$, wherein n is an integer ranging from 0 to 6, and the aforementioned E^1 groups other than -H and halogen are optionally substituted by 1 to 5 independently selected R^{38}, or E^1 is selected from a moiety selected from the group consisting of $-(CZ^3Z_4)_a$-aryl, $-(CZ^3Z^4)_a$-heterocycle, $(C_2\text{-}C_6)$alkynyl, $-(CZ^3Z^4)_a\text{-}(C_3\text{-}C_6)$cycloalkyl, $-(CZ^3Z^4)_a\text{-}(C_5\text{-}C_6)$cycloalkenyl, $(C_2\text{-}C_6)$ alkenyl and $(C_1\text{-}C_6)$alkyl, which is optionally substituted with 1 to 3 independently selected Y^2 groups, where a is 0,1, 2, or 3, and wherein when a is 2 or 3, the CZ^3Z^4 units may be the same or different; wherein

each R^{38} is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-NR^{36}R^{39}$, $-OR^{37}$, $-SO_2NR^{36}R^{39}$, $C_1\text{-}C_6$ alkyl, $-(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nOR^{37}$, $-S(O)_j(C_1\text{-}C_6$ alkyl), $-(CH_2)_n(C_6\text{-}C_{10}$ aryl), $-(CH_2)_n(C_5\text{-}C_{10}$ heteroaryl), $-(CH_2)_n$(5-10 membered heterocyclyl); $-C(O)(CH_2)_n(C_6\text{-}C_{10}$ aryl), $-(CH_2)_nO(CH_2)_j(C_6\text{-}C_{10}$ aryl), $-(CH_2)_nO(CH_2)_i$(5-10 membered heterocyclyl), $-C(O)(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_jNR^{39}CH_2C(O)NR^{36}R^{39}$, $-(CH_2)_jNR^{39}(CH_2)_iNR^{37}C(O)R^{40}$, $-(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_jNR^{39}(CH_2)_iS(O)_j(C_1\text{-}C_6$ alkyl), $-(CH_2)_jNR^{39}(CH_2)_nR^{36}$, $-SO_2(CH_2)_n(C_6\text{-}C_{10}$ aryl), $-SO_2(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_nNR^{36}R^{39}$, $-NR^{37}SO_2NR^{36}R^{39}$, SO_2R^{36}, $C_2\text{-}C_6$ alkenyl, $C_3\text{-}C_{10}$ cycloalkyl and $C_1\text{-}C_6$ alkylamino, wherein j is an integer ranging from 0 to 2, n is an integer ranging from 0 to 6, i is an integer ranging from 0 to 6, the $-(CH_2)_i$- and $-(CH_2)_n$- moieties of the foregoing R^{38} groups optionally include a carbon-carbon double or triple bond where n is an integer between 2 and 6, and the alkyl, aryl, heteroaryl and heterocyclyl moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, $C_1\text{-}C_6$ alkyl, $C_3\text{-}C_{10}$ cycloalkyl, $-(CH_2)_n(C_6\text{-}C_{10}$ aryl), $-(CH_2)_n$(5-10 membered

heterocyclyl), -$(CH_2)_nO(CH_2)_iOR^{37}$, and -$(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6;

each R^{42} and R^{43} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -Y-(C_3-C_{10} cycloalkyl), -Y-(C_6-C_{10} aryl), -Y-(C_6-C_{10} heteroaryl), -Y-(5-10 membered heterocyclic), -Y-O-Y^1-OR^{37}, -Y^1-CO_2-R^{37}, and -Y-OR^{37}, wherein the alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclic moieties of the foregoing R^{42} and R^{43} groups are optionally substituted by 1 or more substituents independently selected from R^{44}, wherein

Y is a bond or is -$(C(R^{37})(H))_n$,

n is an integer ranging from 1 to 6, and

Y^1 is -$(C(R^{37})(H))_n$, or

R^{42} and R^{43} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted by 1 to 5 independently selected R^{44} substituents, with the proviso that R^{42} and R^{43} are not both bonded to the nitrogen directly through an oxygen;

each R^{44} is independently selected from the group consisting of halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, -$C(O)R^{40}$, -$C(O)OR^{40}$, -$OC(O)R^{40}$, -$OC(O)OR^{40}$, -$NR^{36}C(O)R^{39}$, -$C(O)NR^{36}R^{39}$, -$NR^{36}R^{39}$, -OR^{37}, -$SO_2NR^{36}R^{39}$, -SO_2R^{36}, -$NR^{36}SO_2R^{39}$, -$NR^{36}SO_2NR^{37}R^{41}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, -C_1-C_6 alkylamino, -$(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, -$(CH_2)_nO(CH_2)_iOR^{37}$, -$(CH_2)_nOR^{37}$, -$S(O)_j$($C_1$-$C_6$ alkyl), -$(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_n$(5-10 membered heterocyclic), -$C(O)(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_nO(CH_2)$j(C_6-C_{10} aryl), -$(CH_2)_nO(CH_2)_i$(5 to 10 membered heterocyclic), -$C(O)(CH_2)_n$(5 to 10 membered heterocyclic), -$(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, -$(CH_2)_jNR^{39}CH_2C(O)NR^{36}R^{39}$, -$(CH_2)_jNR^{39}(CH_2)_iNR^{37}C(O)R^{40}$, -$(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$, -$(CH_2)_jNR^{39}(CH_2)_iS(O)_j$($C_1$-$C_6$ alkyl), -$(CH_2)_jNR^{39}(CH_2)_nR^{36}$, -$SO_2(CH_2)_n$($C_6$-$C_{10}$ aryl), and -$SO_2(CH_2)_n$(5 to 10 membered heterocyclic) wherein, j is an integer from 0 to 2, n is an integer from 0 to 6 and i is an integer ranging from 2 to 6, the -$(CH_2)_i$- and -$(CH_2)_{n1}$- moieties of the foregoing R^{44} groups optionally include a carbon-carbon double or triple bond wherein n is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{44} groups are optionally substituted by 1 or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, -$C(O)R^{40}$, -$C(O)OR^{40}$, -$OC(O)R^{40}$, -$OC(O)OR^{40}$,-$NR^{36}C(O)R^{39}$, -$C(O)NR^{36}R^{39}$, -$(CH_2)_nNR^{36}R^{39}$, -SO_2R^{36}, -$SO_2NR^{36}R^{39}$, C_1-C_6 alkyl,

C_3-C_{10} cycloalkyl, -$(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_n$(5 to 10 membered heterocyclic), -$(CH_2)_nO(CH_2)_iOR^{37}$ and -$(CH_2)_nOR^{37}$, wherein n is an integer from 0 to 6 and i is an integer from 2 to 6; and

each R^{40} is independently selected from H, C_1-C_{10} alkyl, -$(CH_2)_n$(C_6-C_{10} aryl), C_3-C_{10} cycloalkyl, and -$(CH_2)_n$(5-10 membered heterocyclic), wherein n is an integer ranging from 0 to 6;

each R^{36} and R^{39} is independently selected from the group consisting of H, -OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_n$(5-10 membered heterocyclic), -$(CH_2)_nO(CH_2)_iOR^{37}$, -$(CH_2)_nCN(CH_2)_nOR^{37}$, -$(CH_2)_nCN(CH_2)_nR^{37}$, and -$(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{36} and R^{39} groups are optionally substituted by one or more substituents independently selected from -OH, halo, cyano, nitro, trifluoromethyl, azido, -$C(O)R^{40}$, -$C(O)OR^{40}$, -$CO(O)R^{40}$, -$OC(O)OR^{40}$, -$NR^{37}C(O)R^{41}$, -$C(O)NR^{37}R^{41}$, -$NR^{37}R^{41}$, -C_1-C_6 alkyl, -$(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_n$(5 to 10 membered heterocyclic), -$(CH_2)_nO(CH_2)_iOR^{37}$, and -$(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, with the proviso that when R^{36} and R^{39} are both attached to the same nitrogen, then R^{36} and R^{39} are not both bonded to the nitrogen directly through an oxygen;

each R^{37} and R^{41} is independently selected from the group consisting of H, OR^{36}, C_1-C_6 alkyl and C_3-C_{10} cycloalkyl;

each R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, -$(CZ^5Z^6)_u$-(C_3-C_6)cycloalkyl, -$(CZ^5Z^6)_u$-(C_5-C_6)cycloalkenyl, -$(CZ^5Z^6)_u$-aryl, -$(CZ^5Z^6)_u$-heteroaryl, -$(CZ^5Z^6)_u$-heterocycle, (C_2-C_6)alkenyl, and (C_1-C_6)alkyl, each of which is optionally substituted with 1 to 3 independently selected Y^3 groups, where u is 0,1, 2, or 3, and wherein when u is 2 or 3, the CZ^5Z^6 units may be the same or different, or

R^{6a} and R^{6b} taken together with adjacent atoms can form a heterocycle;

each Z^3, Z^4, Z^5 and Z^6 is independently selected from the group consisting of H, F and (C_1-C_6)alkyl, or

each Z^3 and Z^4, or Z^5 and Z^6 are selected together to form a carbocycle, or

two Z^3 groups on adjacent carbon atoms are selected together to optionally form a carbocycle;

each Y^2 and Y^3 is independently selected from the group consisting of halogen, cyano, nitro, tetrazolyl, guanidino, amidino, methylguanidino, azido, $-C(O)Z^7$, $-OC(O)NH_2$, $-OC(O)NHZ^7$, $-OC(O)NZ^7Z^8$, $-NHC(O)Z^7$, $-NHC(O)NH_2$, $-NHC(O)NHZ^7$, $-NHC(O)NZ^7Z^8$, $-C(O)OH$, $-C(O)OZ^7$, $-C(O)NH_2$, $-C(O)NHZ^7$, $-C(O)NZ^7Z^8$, $-P(O)_3H_2$, $-P(O)_3(Z^7)_2$, $-S(O)_3H$, $-S(O)Z^7$, $-S(O)_2Z^7$, $-S(O)_3Z^7$, $-Z^7$, $-OZ^7$, $-OH$, $-NH_2$, $-NHZ^7$, $-NZ^7Z^8$, $-C(=NH)NH_2$, $-C(=NOH)NH_2$, -N-morpholino, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)haloalkyl, (C_2-C_6)haloalkenyl, (C_2-C_6)haloalkynyl, (C_1-C_6)haloalkoxy, $-(CZ^9Z^{10})_rNH_2$, $-(CZ^9Z^{10})_rNHZ^3$, $-(CZ^9Z^{10})_rNZ^7Z^8$, $-X^6(CZ^9Z^{10})_r-(C_3-C_8)$cycloalkyl, $-X^6(CZ^9Z^{10})_r-(C_5-C_8)$cycloalkenyl, $-X^6(CZ^9Z^{10})_r$-aryl and $-X^6(CZ^9Z^{10})_r$-heterocycle, wherein

r is 1, 2, 3 or 4;

X^6 is selected from the group consisting of O, S, NH, -C(O)-, -C(O)NH-, -C(O)O-, -S(O)-, $-S(O)_2-$ and $-S(O)_3-$;

Z^7 and Z^8 are independently selected from the group consisting of an alkyl of 1 to 12 carbon atoms, an alkenyl of 2 to 12 carbon atoms, an alkynyl of 2 to 12 carbon atoms, a cycloalkyl of 3 to 8 carbon atoms, a cycloalkenyl of 5 to 8 carbon atoms, an aryl of 6 to 14 carbon atoms, a heterocycle of 5 to 14 ring atoms, an aralkyl of 7 to 15 carbon atoms, and a heteroaralkyl of 5 to 14 ring atoms, or

Z^7 and Z^8 together may optionally form a heterocycle;

Z^9 and Z^{10} are independently selected from the group consisting of H, F, a (C_1-C_{12})alkyl, a (C_6-C_{14})aryl, a (C_5-C_{14})heteroaryl, a (C_7-C_{15})aralkyl and a (C_5-C_{14})heteroaralkyl, or

Z^9 and Z^{10} are taken together form a carbocycle, or

two Z^9 groups on adjacent carbon atoms are taken together to form a carbocycle; or

any two Y^2 or Y^3 groups attached to adjacent carbon atoms may be taken together to be $-O[C(Z^9)(Z^{10})]_rO$ or $-O[C(Z^9)(Z^{10})]_{r+1}$, or

any two Y^2 or Y^3 groups attached to the same or adjacent carbon atoms may be selected together to form a carbocycle or heterocycle; and wherein

any of the above-mentioned substituents comprising a CH_3 (methyl), CH_2 (methylene), or CH (methine) group which is not attached to a halogen, SO or SO_2 group or to a N, O or S atom optionally bears on said group a substituent selected from hydroxy, halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy and an $-N[(C_1-C_4)alkyl][(C_1-C_4)alkyl]$;

E^2 is $-C\equiv CH$ or $-C\equiv C-(CR^{45}R^{45})_n-R^{46}$;

R^{45} is independently selected from the group consisting of H, a (C_1-C_6)alkyl and a (C_3-C_8)cycloalkyl;

R^{46} is selected from the group consisting of heterocyclyl, $-N(R^{47})-C(O)-N(R^{47})(R^{48})$, $-N(R^{47})-C(S)-N(R^{47})(R^{48})$, $-N(R^{47})-C(O)-OR^{48}$, $-N(R^{47})-C(O)-(CH_2)_n-R^{48}$, $-N(R^{47})-SO_2R^{47}$, $-(CH_2)_nNR^{47}R^{48}$, $-(CH_2)_nOR^{48}$, $-(CH_2)_nSR^{49}$, $-(CH_2)_nS(O)R^{49}$, $-(CH_2)_nS(O)_2R^{49}$, $-OC(O)R^{49}$, $-OC(O)OR^{49}$, $-C(O)NR^{47}R^{48}$, heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, and aryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$;

R^{47} and R^{48} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, heterocyclyl, $-(CH_2)_nNR^{50}R^{51}$, $-(CH_2)_nOR^{50}$, $-(CH_2)_nC(O)R^{49}$, $-C(O)_2R^{49}$, $-(CH_2)_nSR^{49}$, $-(CH_2)_nS(O)R^{49}$, $-(CH_2)_nS(O)_2R^{49}$, $-(CH_2)_nR^{49}$, $-(CH_2)_nCN$, aryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-(CH_2)_nOR^{49}$, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$heteroaryl, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, and heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-(CH_2)_nOR^{49}$, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$heteroaryl, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, or

R^{47} and R^{48}, together with the atom to which they are attached, form a 3-8 membered ring;

R^{49} is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkylene, aryl(C_1-C_6)alkylene wherein the aryl is optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, heteroaryl(C_1-C_6)alkylene wherein the heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, aryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, and heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$;

R^{50} and R^{51} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl and $-C(O)R^{45}$, or

R^{50} and R^{51}, together with the atom to which they are attached, form a 3-8 membered ring; and

E^3 is the group defined by $-(Z^{11})-(Z^{12})_m-(Z^{13})_{m1}$, wherein

Z^{11} is heterocyclyl or heterocyclylene;

Z^{12} is selected from the group consisting of OC(O), OC(S) and C(O);

Z^{13} is selected from the group consisting of heterocyclyl, aralkyl, $N(H)R^{52}$, $(C_1\text{-}C_3)$alkyl, $-OR^{52}$, halo, $S(O)_2R^{56}$, $(C_1\text{-}C_3)$hydroxyalkyl and $(C_1\text{-}C_3)$haloalkyl;

m is 0 or 1;

m1 is 0 or 1;

R^{52} is selected from the group consisting of H, $-(CH_2)_qS(O)_2R^{54}$, $R^{55}NR^{53}R^{53}$, $(C_1\text{-}C_3)$alkyl, $-(CH_2)_qOR^{53}$, $-C(O)R^{54}$ and $-C(O)OR^{53}$;

q is 0, 1, 2, 3 or 4;

R^{53} is $(C_1\text{-}C_3)$alkyl;

R^{54} is $(C_1\text{-}C_3)$alkyl or $N(H)R^{53}$;

R^{55} is $(C_1\text{-}C_6)$ alkyl; and

R^{56} is selected from the group consisting of NH_2, $(C_1\text{-}C_3)$alkyl and OR^{52}.

[0041] In a preferred embodiment of the compounds according to paragraph [0040], T is aryl or heteroaryl, wherein each of said aryl and heteroaryl is optionally substituted with 1 to 3 independently selected R^{20}.

[0042] In a preferred embodiment of the compounds according to paragraph [0040], T is selected from the group consisting of arylalkyl, cycloalkyl and heterocyclyl, wherein each of said arylalkyl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 3 independently selected R^{20}.

[0043] In a preferred embodiment of the compounds according to paragraphs [0040] to [0042], R^{20} is selected from the group consisting of H, halogen, $-OR^{17}$ and $-C(O)OR^{17}$.

[0044] In a preferred embodiment of the compounds according to paragraphs [0040] to [0043], R^{20} is fluorine or chloride.

[0045] In a preferred embodiment of the compounds according to paragraphs [0040] to [0044], W is O.

[0046] In a preferred embodiment of the compounds according to paragraphs [0040] to [0045], Z is S or O.

[0047] In a preferred embodiment of the compounds according to paragraphs [0040] to [0046], Z is S.

[0048] In a preferred embodiment of the compounds according to paragraphs [0040] to [0047], X and X^1 are independently selected from the group consisting of H and C_1-C_6alkyl, wherein the C_1-C_6alkyl is optionally substituted.

[0049] In a preferred embodiment of the compounds according to paragraphs [0040] to [0048], X and X^1 are both H.

[0050] In a preferred embodiment of the compounds according to paragraphs [0040] to [0048], X and X^1 taken together with the atom to which they are attached, form a C_3-C_7cycloalkyl.

[0051] In a preferred embodiment of the compounds according to paragraphs [0040] to [0050], R^1, R^2, R^3 and R^4 are independently selected from the group consisting of H, halogen, trihalomethyl, OR^{17}, $-NR^{17}R^{18}$ and C_1-C_6alkyl.

[0052] In a preferred embodiment of the compounds according to paragraphs [0040] to [0051], R^1, R^2 and R^4 are independently selected from the group consisting of H, halo and $-OR^{17}$.

[0053] In a preferred embodiment of the compounds according to paragraphs [0040] to [0052], R^1 is H or halogen.

[0054] In a preferred embodiment of the compounds according to paragraphs [0040] to [0053], R^1 is halogen.

[0055] In a preferred embodiment of the compounds according to paragraphs [0040] to [0054], R^2, R^3 and R^4 are each H.

[0056] In a preferred embodiment of the compounds according to paragraphs [0040] to [0055], R^{17} is a C_1-C_6alkyl.

[0057] In a preferred embodiment of the compounds according to paragraphs [0040] to [0056], R^{16} is H or C_1-C_6alkyl.

[0058] In a preferred embodiment of the compounds according to paragraphs [0040] to [0057], Q is selected from the group consisting of CH_2, S, -N-(C_1-C_6alkyl), N-Y-(aryl) and -N-OMe.

[0059] In a preferred embodiment of the compounds according to paragraphs [0040] to [0058], Q is S.

[0060] In a preferred embodiment of the compounds according to paragraphs [0040] to [0058], Q is CH_2.

[0061] In a preferred embodiment of the compounds according to paragraphs [0040] to [0058], Q is -N-(C_1-C_6alkyl).

[0062] In a preferred embodiment of the compounds according to paragraphs [0040] to [0058], Q is -N-Y-(aryl).

[0063] In a preferred embodiment of the compounds according to paragraphs [0040] to [0058], Q is -N-OMe.

[0064] In a preferred embodiment of the compounds according to paragraphs [0040] to [0063], D is C-E.

[0065] In a preferred embodiment of the compounds according to paragraphs [0040] to [0064], D is CH.

[0066] In a preferred embodiment of the compounds according to paragraphs [0040] to [0065], L is C-R.

[0067] In a preferred embodiment of the compounds according to paragraphs [0040] to [0065], R is H or halogen.

[0068] In a preferred embodiment of the compounds according to paragraphs [0040] to [0065], L is N.

[0069] In a preferred embodiment of the compounds according to paragraphs [0040] to [0068], E is selected from the group consisting of E^1 and E^2.

[0070] In a preferred embodiment of the compounds according to paragraphs [0040] to [0069], E is E^1.

[0071] In a preferred embodiment of the compounds according to paragraphs [0040] to [0070], E is E^1, wherein E^1 is selected from the group consisting of H, halogen, -$C(O)NR^{42}R^{43}$, -$SO_2NR^{42}R^{43}$, $C(=NR^{42})NR^{37}R^{43}$, -CO_2R^{42}, -C(O)(heterocyclyl), -C(O)(heteroaryl), -Y-(C_6-C_{10} aryl), -Y-(heteroaryl), -Y-(5 to 10 membered heterocyclic), -SR^{6a}, -$S(O)R^{6a}$, -SO_2R^{6a}, wherein each of said E^1 other than H and halogen are optionally substituted with 1 to 5 independently selected R^{38}, or E1 is (C1-C6)alkyl, which is optionally substituted with 1 to 3 independently selected Y2 groups.

[0072] In a preferred embodiment of the compounds according to paragraphs [0040] to [0071], R^{38} is selected from the group consisting of halogen, -$C(O)OR^{40}$, -$NR^{36}C(O)R^{39}$, -$C(O)NR^{36}R^{39}$, -$NR^{36}R^{39}$, -OR^{37}, C_1-C_6alkyl, -$C(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, -$(CH_2)_nOR^{37}$, -$S(O)_j(C_1$-$C_6$alkyl), -$(CH_2)_n$-(5 to 10 membered heterocyclic), -$(CH_2)O(CH_2)_i$(5 to 10 membered heterocyclic), -$(CH_2)_n$(5 to 10 membered heteroaryl), -$(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, -$(CH_2)_jNR^{39}(CH_2)_nR^{36}$, -$(CH_2)_nNR^{36}R^{39}$, wherein j is an integer ranging from 0 to 2, n is an integer ranging from 0 to 6, i is an integer ranging from 1 to 6, , the -$(CH_2)_i$- and -$(CH_2)_n$- moieties of the foregoing R^{38} groups optionally include a carbon-carbon double or triple bond where n is an integer between 2 and 6, and the alkyl, aryl,

heteroaryl, and heterocyclic moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_nO(CH_2)_iOR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6.

[0073] In a preferred embodiment of the compounds according to paragraphs [0040] to [0072], the alkyl, aryl, heteroaryl, and heterocyclic moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from the group consisting of -OH and $-C(O)OR^{40}$.

[0074] In a preferred embodiment of the compounds according to paragraphs [0040] to [0073], each R^{42} and R^{43} is independently selected from the group consisting of H, -Y-(C_3-C_{10} cycloalkyl), -Y-(C_6-C_{10} aryl), -Y-(C_6-C_{10} heteroaryl) and -Y-(5 to 10 membered heterocyclic), wherein the cycloalkyl, aryl, heteroaryl and heterocyclic moieties of the foregoing R^{42} and R^{43} groups are optionally substituted by 1 or more substituents independently selected from R^{44}.

[0075] In a preferred embodiment of the compounds according to paragraphs [0040] to [0073], each R^{42} and R^{43} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $-Y^1-CO_2-R^{37}$ and $-Y-OR^{37}$.

[0076] In a preferred embodiment of the compounds according to paragraphs [0040]to [0075], one of R^{42} and R^{43} is H.

[0077] In a preferred embodiment of the compounds according to paragraphs [0040] to [0076], one of R^{42} and R^{43} is -(C_6-C_{10} heteroaryl) or -Y-(5 to 10 membered heterocyclic).

[0078] In a preferred embodiment of the compounds according to paragraphs [0040] to [0077], Y is a bond.

[0079] In a preferred embodiment of the compounds according to paragraphs [0040] to [0077] Y is $-(C(R^{37})(H))_n$.

[0080] In a preferred embodiment of the compounds according to paragraphs [0040] to [0079], R^{42} and R^{43} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted by 1 to 5 independently selected R^{44} substituents, with the proviso that R^{42} and R^{43} are not both bonded to the nitrogen directly through an oxygen.

[0081] In a preferred embodiment of the compounds according to paragraphs [0040] to [0080], R^{44} is independently selected from the group consisting of $-C(O)NR^{36}R^{39}$, $-OR^{37}$ and C_1-C_6alkyl.

[0082] In a preferred embodiment of the compounds according to paragraphs [0040] to [0081], each R^{40} is independently selected from the group consisting of H and C_1-C_{10} alkyl.

[0083] In a preferred embodiment of the compounds according to paragraphs [0040] to [0082], each R^{36} and R^{39} is independently selected from the group consisting of H, C_1-C_6alkyl, $-(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_nOR^{37}$ and $-C(O)OR^{40}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, with the proviso that when R^{36} and R^{39} are both attached to the same nitrogen, then R^{36} and R^{39} are not both bonded to the nitrogen directly through an oxygen.

[0084] In a preferred embodiment of the compounds according to paragraphs [0040] to [0083], each R^{37} and R^{41} is independently selected from the group consisting of H and C_1-C_6alkyl.

[0085] In a preferred embodiment of the compounds according to paragraphs [0040] to [0084], R^{6a} is selected from the group consisting of $-(CZ^5Z^6)_u$-aryl, $-(CZ^5Z^6)_u$-heteroaryl and C_1-C_6alkyl, each of which is optionally substituted with 1 to 3 indepedently selected Y^3 groups, wherein u is 0, 1, 2 or 3, and wherein when u is 2 or 3, the CZ^5Z^6 units may be the same or different.

[0086] In a preferred embodiment of the compounds according to paragraphs [0040] to [0085], R^{6a} is selected from the group consisting of $-(CZ^5Z^6)_u$-aryl and $-(CZ^5Z^6)_u$-heteroaryl, each of which is optionally substituted with 1 to 3 indepedently selected Y^3 groups, wherein u is 0.

[0087] In a preferred embodiment of the compounds according to paragraphs [0040] to [0086], Y^2 is -OH.

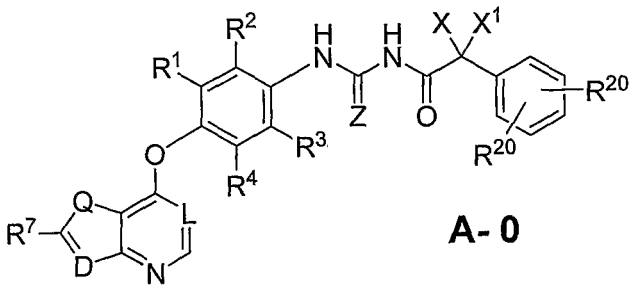
[0088] In a preferred embodiment of the compounds according to paragraphs [0040] to [0086], Y^3 is -OH.

[0089] In a preferred embodiment of the compounds according to paragraphs [0040] to [0069], E^2 is $-C\equiv C-(CR^{45}R^{45})_n-R^{46}$, wherein n is an integer ranging from 1 to 6.

[0090] In a preferred embodiment of the compounds according to paragraph [0089], R^{45} is H.

[0091] In a preferred embodiment of the compounds according to paragraph [0089] to [0090], R^{46} is a heterocyclyl.

[0092] In a preferred embodiment of the compounds according to paragraph [0040], the compounds are represented by the formula A-0:



A- 0

and pharmaceutically acceptable salts and complexes thereof, wherein

Z is O or S;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano and nitro, wherein C_1-C_6 alkyl is optionally substituted;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, halo, trihalomethyl, -OR^{17}, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

Q is O, S, NH, N(C_1-C_6 alkyl), or N-Y-(aryl);

D is CR^{11}, or N;

L is N, or CR, wherein R is H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

R^7 is H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$ or CO_2R^9, wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted;

R^9 and R^{10} are independently selected from H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11}, and -Y-O-R^{11}, wherein C_1-C_6 alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted;

Y is a bond or is -($C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y^1 is -($C(R^{11})(H))_t$-,

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted,

each R^{20} is independently selected from the group consisting of hydrogen, halo, trihalomethyl, OR^{17}, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted, and

each R^{17} is an independently selected C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted.

[0093] In a preferred embodiment of the compounds according to paragraph [0092], X and X^1 are both hydrogen.

[0094] In a preferred embodiment of the compounds according to paragraphs [0092] to [0093], R^1 is hydrogen or halogen.

[0095] In a preferred embodiment of the compounds according to paragraphs [0092] to [0094], R^1 is fluorine.

[0096] In a preferred embodiment of the compounds according to paragraphs [0092] to [0095], R^4 is hydrogen or halogen.

[0097] In a preferred embodiment of the compounds according to paragraphs [0092] to [0096], R^4 is fluorine.

[0098] In a preferred embodiment of the compounds according to paragraphs [0092] to [0097], R^2 is selected from the group consisting of H, halogen, trihalomethyl and $-OR^{17}$.

[0099] In a preferred embodiment of the compounds according to paragraphs [0092] to [0098], R^3, and R^{20} are each hydrogen.

[0100] In a preferred embodiment of the compounds according to paragraphs [0092] to [0098], R^{20} is $-OR^{17}$.

[0101] In a preferred embodiment of the compounds according to paragraphs [0092] to [0100], Q is S, N(C_1-C_6 alkyl), or N-Y-(aryl).

[0102] In a preferred embodiment of the compounds according to paragraphs [0092] to [0100], Q is NH.

[0103] In a preferred embodiment of the compounds according to paragraphs [0092] to [0102], D is CR^{11}.

[0104] In a preferred embodiment of the compounds according to paragraphs [0092] to [0103], L is CH or N.

[0105] In a preferred embodiment of the compounds according to paragraphs [0092] to [0104], R^7 is H, halogen, C_1-C_6 alkyl, $-CONR^9R^{10}$, $-SO_2NH_2$, $-SO_2NR^9R^{10}$, -Y-heterocyclyl, -Y-heteroaryl, -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, or $-SO_2$-C_1-C_6 alkyl, wherein C_1-C_6

alkyl, is unsubstituted or is substituted with one or two of hydroxy or halogen, and heterocyclyl, and heteroaryl are unsubstituted or substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0106] In a preferred embodiment of the compounds according to paragraphs [0092] to [0105], R^7 is $-CONR^9R^{10}$.

[0107] In a preferred embodiment of the compound according to paragraphs [0092] to [0105], R^7 is Y-heteroaryl.

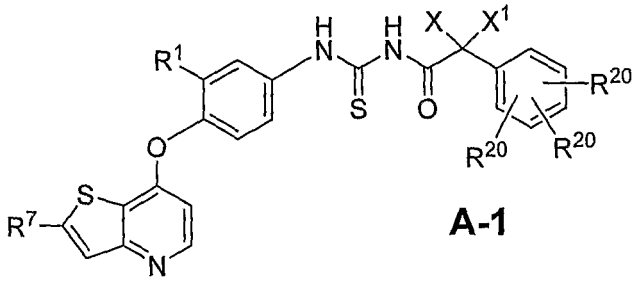
[0108] In a preferred embodiment of the compounds according to paragraph [0106], R^9 and R^{10} are independently H, C_1-C_6 alkyl, -Y-O-R^{11}, -Y-(heterocycle), -Y^1-CO_2-R^{11}, or -Y-(aryl), wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and heterocyclyl, and aryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0109] In a preferred embodiment of the compounds according to paragraph [0106], R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said ring is unsubstituted or is substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0110] In a preferred embodiment of the compounds according to paragraphs [0092] to [0105], R^7 is H, halogen, C_1-C_6 alkyl, $-SO_2NR^9R^{10}$, -C(=O)(heterocyclyl), -Y-(heterocyclyl), or -Y-(heteroaryl), wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0111] In a preferred embodiment of the compounds according to paragraphs [0092] to [0110], Z is sulfur.

[0112] In a preferred embodiment of the compounds according to paragraph [0040], the compounds are represented by the formula A-1:



A-1

and pharmaceutically acceptable salts and complexes thereof, wherein

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

X and X^1 are independently selected from the group consisting of H and C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted, or

X and X^1 taken together with the atom to which they are attached, form a C_3-C_7 cycloalkyl;

R^7 is H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -SR^{6a}, -S-aryl, -S-(heteroaryl), -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$, CO_2R^9, -C≡C-$(CR^{45}R^{45})_n$-R^{46} and –C(=NR^{42})$NR^{37}R^{43}$, wherein n is an integer ranging from 0 to 6 and wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted with 1 to 5 independently selected R^{38};

R^9 and R^{10} are independently selected from H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(C_1-C_6 heteroalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11}, Y-C(O)OR^{37} and -Y-O-R^{11}, wherein said C_1-C_6 alkyl,heteroalkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted with one or more independently selected R^{44}, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted with 1 to 5 independently selected R^{44};

each R^{20} is independently selected from the group consisting of H, halo, -OR^{17} and -C(O)OR^{17};

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y^1 is -$(C(R^{11})(H))_t$-, and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

[0113] In a preferred embodiment of the compounds according to paragraph [0112], R^1 is hydrogen or halogen.

[0114] In a preferred embodiment of the compounds according to paragraph [0112] to [0113], R^1 is fluorine.

[0115] In a preferred embodiment of the compounds according to paragraphs [0112] to [0114], R^7 is selected from the group consisting of H, -C(=O)NR^9R^{10}, -Y-(aryl), -Y-(heteroaryl) and -S-C_1-C_6 alkyl, wherein said -Y-(aryl), -Y-(heteroaryl) and -S-C_1-C_6 alkyl are optionally substituted with 1 to 5 independently selected R^{38}.

[0116] In a preferred embodiment of the compounds according to paragraphs [0112] to [0115], R^7 is -C(=O)NR^9R^{10}, optionally substituted with one or more independently selected R^{44}.

[0117] In a preferred embodiment of the compounds according to paragraphs [0112] to [0115], R^7 is -Y-(aryl), optionally substituted with 1 to 5 independently selected R^{38}.

[0118] In a preferred embodiment of the compounds according to paragraphs [0112] to [0115], R^7 is -Y-(heteroaryl), optionally substituted with 1 to 5 independently selected R^{38}.

[0119] In a preferred embodiment of the compounds according to paragraphs [0112] to [0118], R^{38} is selected from the group consisting of halogen, -OR^{37}, C_1-C_6alkyl, -$(CH_2)_n$-(5 to 10 membered heterocyclyl), -$(CH_2)_j NR^{39}(CH_2)_n R^{36}$, -$(CH_2)_j NR^{39}(CH_2)_i NR^{36}R^{39}$, -$(CH_2)_n$-heteroaryl, -C(O)$NR^{36}R^{39}$, -$(CH_2)_n O(CH_2)_i$(5to 10 membered heterocyclyl) and -$(CH2)_j O(CH_2)_i NR^{36}R^{39}$, wherein n is an integer ranging from 0 to 6, j is an integer ranging from 0 to 2 , j is an integer ranging from 1 to 6 and wherein the alkyl, heteroaryl and heterocyclyl moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, -C(O)R^{40}, -C(O)OR^{40}, -OC(O)R^{40}, -OC(O)OR^{40}, -NR^{36}C(O)R^{39}, -C(O)$NR^{36}R^{39}$, -$(CH_2)_n NR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_n$(5-10 membered heterocyclyl), -$(CH_2)_n O(CH_2)_i OR^{37}$, and -$(CH_2)_n OR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6.

[0120] In a preferred embodiment of the compounds according to paragraphs [0112] to [0119], R^{38} is selected from the group consisting of -OR^{37}, C_1-C_6alkyl, -$(CH_2)_n$(5 to 10 membered heterocyclyl) and -$(CH_2)_n O(CH_2)_i$(5 to10 membered heterocyclyl).

[0121] In a preferred embodiment of the compounds according to paragraphs [0112] to [0120], R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -C_1-C_6 heteroalkyl, -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-R^{11} and Y-C(O)OR^{37}, wherein a C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, heterocyclcyl and heteroaryl are each optionally substituted with 1 or more independently selected R^{44}.

[0122] In a preferred embodiment of the compounds according to paragraphs [0112] to [0121], R^{44} is selected from the group consisting of C_1-C_6 alkyl, -OR^{37}, -C(O)$NR^{36}R^{39}$ and -C(O)OR^{46}.

[0123] In a preferred embodiment of the compounds according to paragraphs [0112] to [0122], R^{36} is selected from the grouip consisting of H, C_1-C_6 alkyl, -$(CH_2)_n OR^{37}$ and -$(CH_2)_n$(heterocyclyl).

[0124] In a preferred embodiment of the compounds according to paragraphs [0112] to [0123], R^{39} is H or C_1-C_6 alkyl.

[0125] In a preferred embodiment of the compounds according to paragraphs [0112] to [0124], R^{37} is H or C_1-C_6 alkyl.

[0126] In a preferred embodiment of the compounds according to paragraphs [0112] to [0125], R^{20} is selected from the group consisting of H, halogen, -OR^{17} and -$C(O)OR^{17}$.

[0127] In a preferred embodiment of the compounds according to paragraphs [0112] to [0126], R^{17} is H or C_1-C_6 alkyl.

[0128] In a preferred embodiment of the compounds according to paragraphs [0112] to [0127], R^{20} is halogen.

[0129] In a preferred embodiment of the compounds according to paragraphs [0112] to [0128], R^{20} is Cl or F.

[0130] In a preferred embodiment of the compounds according to paragraphs [0112] to [0129], R^{6a} is -$(CZ^5Z^6)_u$-aryl.

[0131] In a preferred embodiment of the compounds according to paragraph [0112] to [0114], R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$CONR^9R^{10}$, -SO_2NH_2, -$SO_2NR^9R^{10}$, -Y-heterocyclyl, -Y-heteroaryl, -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

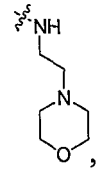
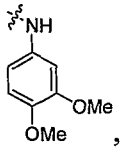
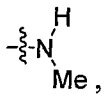
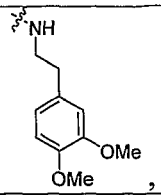
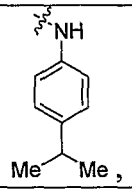
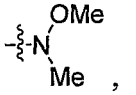
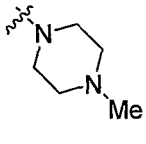
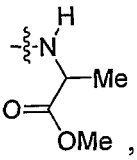
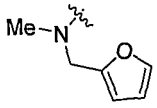
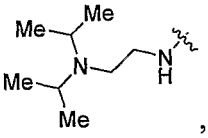
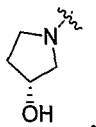
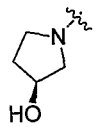
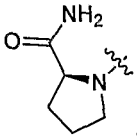
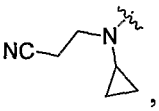
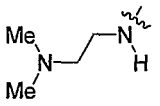
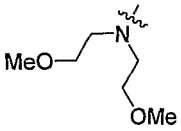
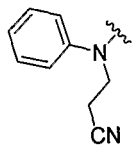
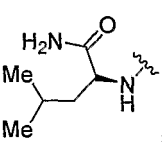
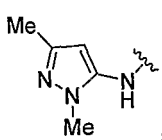
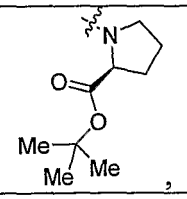
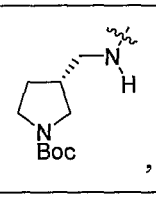
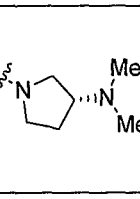
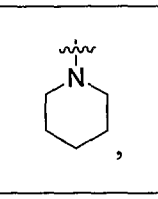
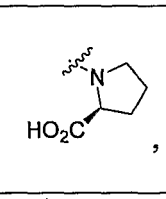
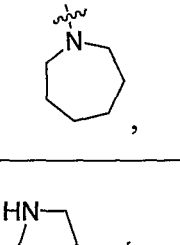
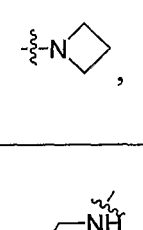
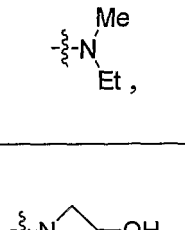
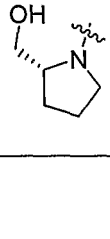
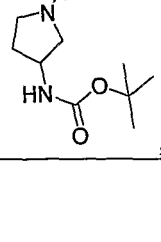
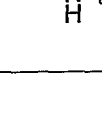
[0132] In a preferred embodiment of the compounds according to paragraphs [0112] to [0114], R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$SO_2NR^9R^{10}$, -C(=O)(heterocyclyl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0133] In a preferred embodiment of the compounds according to paragraph [0116], R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -Y-O-R^{11}, -Y-(heterocycle), -Y-CO_2-R^{11}, -Y-(aryl) and -Y-(heteroaryl), wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, aryl and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0134] In a preferred embodiment of the compounds according to paragraph [0116], R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a

pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said ring is unsubstituted or is substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0135] In a preferred embodiment of the compounds according to paragraph [0116], NR^9R^{10} is selected from:

<table>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>

[0136] In a preferred embodiment of the compounds according to paragraph [0118] R^7 is unsubstituted heteroaryl.

[0137] In a preferred embodiment of the compounds according to paragraph [0136], R^7 is thiazolyl, pyridinyl, pyrimidinyl, and imidazolyl, each of which is preferably unsubstituted or is substituted with one or two of alkoxy, or alkyl.

[0138] In a preferred embodiment of the compounds according to paragraphs [0131] to [0132], R^7 is C_1-C_6 alkyl, unsubstituted or substituted with hydroxy.

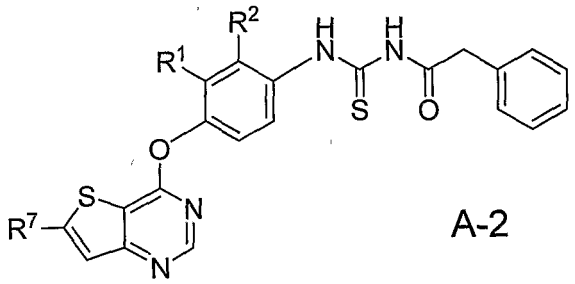
[0139] In a preferred embodiment of the compounds according to paragraphs [0112] to [0138], X and X^1 are both H.

[0140] In a preferred embodiment of the compounds according to paragraphs [0112] to [0139], R^{17} is selected from the group consisting of H and C_1-C_6 alkyl.

[0141] In a preferred embodiment of the compounds according to paragraphs [0112] to [0140], R^{38} is selected from the group consisting of -OR^{37}, C_1-C_6 alkyl and -$(CH_2)_n$(5 to 10 membered heterocylic), wherein n is an integer ranging from 0 to 6.

[0142] In a preferred embodiment of the compounds according to paragraphs [0112] to [0141], R^{37} is selected from the group consisting of H and C_1-C_6 alkyl.

[0143] In a preferred embodiment of the compounds according to paragraph [0040], the compounds are represented by the formula A-2:



A-2

and pharmaceutically acceptable salts and complexes thereof, wherein

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^4 is selected from the group consisting of H and halogen;

R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$C(=O)NR^9R^{10}$, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$ and CO_2R^9, wherein C_1-C_6 alkyl, aryl, heterocycle and

heteroaryl are each independently optionally substituted with 1 to 5 independently selected R^{38};

R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11} and -Y-O-R^{11}, wherein C_1-C_6 alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted with one or more independently selected R^{44}, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted;

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y_1 is -($C(R^{11})(H))_t$-, and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

[0144] In a preferred embodiment of the compounds according to paragraph [0143], R1 is hydrogen or halogen.

[0145] In a preferred embodiment of the compounds according to paragraphs [0143] to [0144], R1 is fluorine.

[0146] In a preferred embodiment of the compounds according to paragraphs [0143] to [0145], R4 is selected from the group consisting of H and halogen.

[0147] In a preferred embodiment of the compounds according to paragraphs [0143] to [0146], R4 is fluorine.

[0148] In a preferred embodiment of the compounds according to paragraphs [0143] to [0147], R7 is selected from the group consisting of H, halogen, C1-C6 alkyl, -C(=O)NR9R10, -SO2NH2, -SO2NR9R10, -Y-heterocyclyl -Y-heteroaryl, -S-aryl, -S-C1-C6 alkyl, -SO-C1-C6 alkyl and -SO2-C1-C6 alkyl, wherein C1-C6 alkyl, heterocyclyl, heteroaryl and aryl are each optionally substituted with 1 to 5 independently selected R38.

[0149] In a preferred embodiment of the compounds according to paragraphs [0143] to [0147], R7 is selected from the group consisting of H, halogen, C1-C6 alkyl, -C(=O)NR9R10, -SO2NH2, -SO2NR9R10, -Y-heterocyclyl -Y-heteroaryl, -S-aryl, -S-C1-C6 alkyl, -SO-C1-C6 alkyl and -SO2-C1-C6 alkyl, wherein C1-C6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, haloalkyl or (CH2)jNR39(CH2)nO(CH2)iOR37.

[0150] In a preferred embodiment of the compounds according to paragraphs [0143] to [0147], R7 is selected from the group consisting of H, halogen, C1-C6 alkyl, -SO2NR9R10, -C(=O)(heterocyclyl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C1-C6 alkyl, -SO-C1-C6 alkyl, or -SO2-C1-C6 alkyl, wherein C1-C6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, haloalkyl or (CH2)jNR39(CH2)nO(CH2)iOR37.

[0151] In a preferred embodiment of the compounds according to paragraphs [0143] to [0150], R7 is selected from the group consisting of C1-C6 alkyl, -C(=O)NR9R10, -Y-(heterocyclyl, -Y-(heteroaryl), -S-C1-C6 alkyl and -SO-C1-C6 alkyl, wherein C1-C6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, haloalkyl or (CH2)jNR39(CH2)nO(CH2)iOR37.

[0152] In a preferred embodiment of the compounds according to paragraphs [0143] to [0151], R7 is CONR9R10.

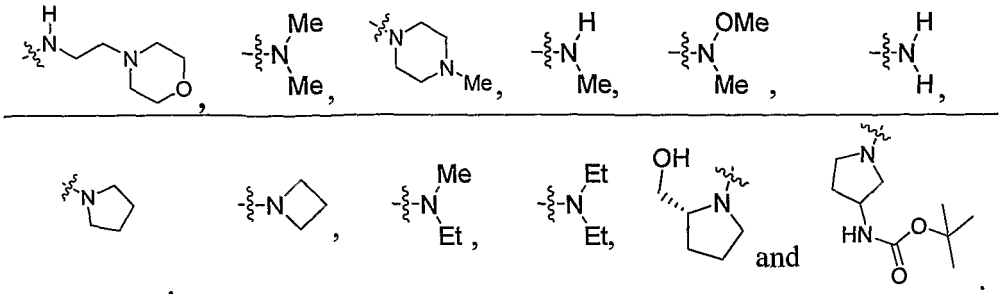
[0153] In a preferred embodiment of the compounds according to paragraph [0152], R9 and R10 are independently selected from the group consisting of H, C1-C6 alkyl, -Y-O-R11, -Y-(heterocycle), -Y1-CO2-R11 and -Y-(aryl), wherein the alkyl, heterocyclyl and aryl moieties of the foregoing R9 and R10 groups are optionally substituted with 1 or more substituents independently selected from R44.

[0154] In a preferred embodiment of the compounds according to paragraphs [0152] to [0153], R9 and R10 are independently selected from the group consisting of H, C1-C6 alkyl, -Y-O-R11, -Y-(heterocycle), -Y1-CO2-R11 and -Y-(aryl), wherein C1-C6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and aryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, haloalkyl or (CH2)jNR39(CH2)nO(CH2)iOR37.

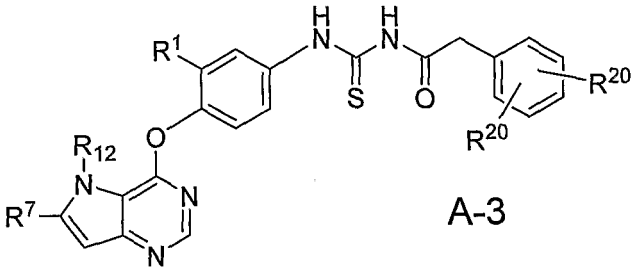
[0155] In a preferred embodiment of the compounds according to paragraph [0152], R9 and R10 taken together with the nitrogen to which they are attached form a C5-C9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted.

[0156] In a preferred embodiment of the compounds according to paragraph [0155], R9 and R10 are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said ring is unsubstituted or is substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0157] In a preferred embodiment of the compounds according to paragraph [0152], NR9R10 is selected from the group consisting of:



[0158] In a preferred embodiment of the compounds according to paragraph [0040], the compounds are represented by the formula A-3:



A-3

and pharmaceutically acceptable salts and complexes thereof, wherein

R^7 is selected from the group consisting of H, -Y-(aryl) and -Y-(heteroaryl), wherein -Y-(aryl) and -Y-(heteroaryl) are optionally substituted with 1 to 5 independently selected R^{38};

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^{12} is selected from the group consisting of H, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -Y-(aryl), wherein C_1-C_6 alkyl and aryl are optionally substituted;

Y is a bond or is -(C(R^{11})(H))$_t$-, wherein t is an integer from 1 to 6;

R^{11} is H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted; and

each R_{20} is independently selected from the group consisting of H and halogen.

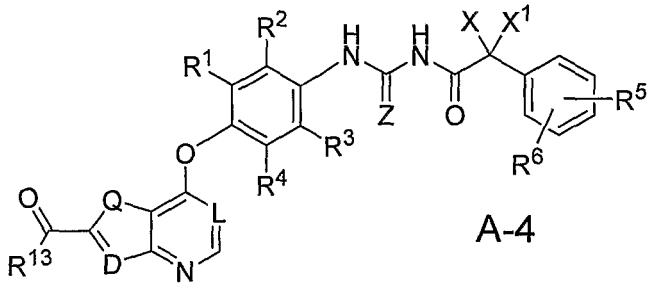
[0159] In a preferred embodiment of the compounds according to paragraph [0158], R^1 is hydrogen or halogen.

[0160] In a preferred embodiment of the compounds according to paragraphs [0158] to [0159], R^1 is fluorine.

[0161] In a preferred embodiment of the compounds according to paragraphs [0158] to [0160], R^{12} is unsubstituted C_1-C_3 alkyl or unsubstituted -Y-phenyl.

[0162] In a preferred embodiment of the compounds according to paragraphs [0158] to [0161], R^{20} is Cl.

[0163] In a preferred embodiment of the compounds according to paragraph [0040], the compounds are represented by the formula A-4:



A-4

and pharmaceutically acceptable salts and complexes thereof, wherein

Z is O or S;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano and nitro, wherein C_1-C_6 alkyl is optionally substituted;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and $NR^{17}R^{18}$, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^{17} and R^{18} are independently C_1-C_6alkyl;

Q is O, S, NH, N(C_1-C_6 alkyl), or N-Y-(aryl);

D is CR^{11}, or N;

L is N, or CR, wherein R is selected from the group consisting of H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

R^{13} is heterocyclyl or heteroaryl, wherein heterocyclyl and heteroaryl are optionally substituted with 1 to 5 independently selected R^{38};

Y is a bond or is $-(C(R^{11})(H))_t-$, wherein t is an integer from 1 to 6; and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

[0164] In a preferred embodiment of the compounds according to paragraph [0163], X and X^1 are both hydrogen.

[0165] In a preferred embodiment of the compounds according to paragraphs [0163] to [0164], R^1, R^2, R^3 and R^4 are independently H or halogen.

[0166] In a preferred embodiment of the compounds according to paragraphs [0163] to [0165], R^1 is hydrogen or halogen.

[0167] In a preferred embodiment of the compounds according to paragraphs [0163] to [0166], R^1 is fluorine or chlorine.

[0168] In a preferred embodiment of the compounds according to paragraphs [0163] to [0167], R^4 is hydrogen or halogen.

[0169] In a preferred embodiment of the compounds according to paragraphs [0163] to [0168], R^4 is fluorine or chlorine.

[0170] In a preferred embodiment of the compounds according to paragraphs [0163] to [0169], R^2, R^3, R^5, and R^6 are each hydrogen.

[0171] In a preferred embodiment of the compounds according to paragraphs [0163] to [0170], Q is selected from the group consisting of S, N(C_1-C_6 alkyl) and N-Y-(aryl).

[0172] In a preferred embodiment of the compounds according to paragraphs [0163] to [0171], Q is S.

[0173] In a preferred embodiment of the compounds according to paragraphs [0163] to [0172], D is CR^{11}.

[0174] In a preferred embodiment of the compounds according to paragraphs [0163] to [0173], R11 is H.

[0175] In a preferred embodiment of the compounds according to paragraphs [0163] to [0174], L is CH or N.

[0176] In a preferred embodiment of the compounds according to paragraphs [0163] to [0175], L is CH.

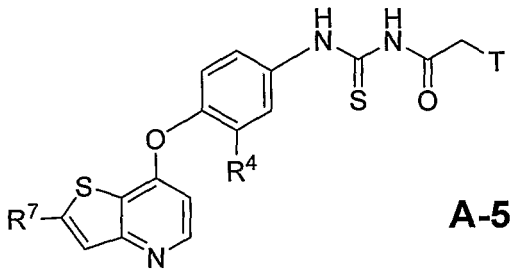
[0177] In a preferred embodiment of the compounds according to paragraphs [0163]-[0175], Z is sulfur.

[0178] In a preferred embodiment of the compounds according to paragraphs [0163] to [0177], R^{38} is selected from $C(O)OR^{40}$ and $NR^{36}R^{39}$.

[0179] In a preferred embodiment of the compounds according to paragraphs [0163] to [0178], R^{40} is H or C_1-C_{10} alkyl.

[0180] In a preferred embodiment of the compounds according to paragraphs [0163] to [0179], R^{36} and R^{39} are independently C_1-C_6 alkyl.

[0181] In a preferred embodiment of the compounds according to paragraph [0040], the compounds are represented by the formula A-5:



A-5

and pharmaceutically acceptable salts and complexes thereof, wherein

R^7 is selected from the group consisting of H, -C(O)$NR^{42}R^{43}$, -Y-(aryl), -Y-(heteroaryl), -C(O)-(C_3-C_{10} cycloalkyl), -C(O)-(heterocyclyl), -C(O)-(C_6-C_{10} aryl) and -C(O)-(heteroaryl), wherein the aforementioned R^7 groups other than H are optionally substituted with 1 to 5 independently selected R^{38};

R^4 is selected from the group consisting of H and halogen; and

T is selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl and arylalkyl, each of which is optionally substituted with 1 to 3 independently selected R^{20};

[0182] In a preferred embodiment of the compounds according to paragraph [0181], R^7 is selected from the group consisting of H, C(O)$NR^{42}R^{43}$ and -Y-(heteroaryl), wherein -Y-(heteroaryl) is optionally substituted with 1 to 5 independently selected R^{38};

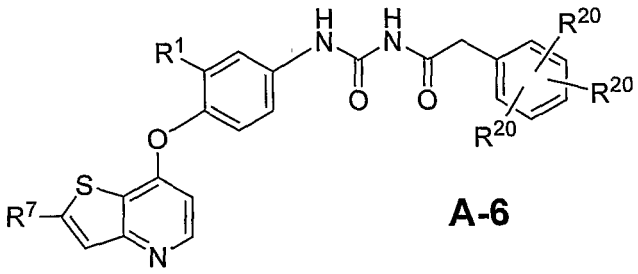
[0183] In a preferred embodiment of the compounds according to paragraphs [0181] to [0182], R^7 is C(O)$NR^{42}R^{43}$;

[0184] In a preferred embodiment of the compounds according to paragraphs [0181] to [0183], R^{42} and R^{43} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring, wherein said ring is optionally substituted with 1 to 5 independently selected R^{44} substituents, with the proviso that R^{42} and R^{43} are not both bonded to the nitrogen directly through and oxygen.

[0185] In a preferred embodiment of the compounds according to paragraphs [0181] to [0184], R^4 is halogen.

[0186] In a preferred embodiment of the compounds according to paragraphs [0181] to [0185], R^4 is fluorine.

[0187] In a preferred embodiment of the compounds according to paragraph [0040], the compounds are represented by the formula A-6:



A-6

and pharmaceutically acceptable salts and complexes thereof, wherein

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -SR^{6a}, -S-aryl, -S-(heteroaryl), -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$, CO_2R^9, -C≡C-$(CR^{45}R^{45})_n$-R^{46} and -C(=NR^{42})$NR^{37}R^{43}$, wherein n is an integer ranging from 0 to 6 and wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted with 1 to 5 independently selected R^{38};

R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(C_1-C_6 heteroalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11}, Y-C(O)OR^{37} and -Y-O-R^{11}, wherein said C_1-C_6 alkyl,heteroalkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted with one or more independently selected R^{44}, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted with 1 to 5 independently selected R^{44};

each R^{20} is independently selected from the group consisting of H, halo, -OR^{17} and -C(O)OR^{17};

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y^1 is -$(C(R^{11})(H))_t$-; and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

[0188] In a preferred embodiment of the compounds according to paragraph [0187], R^7 is selected from the group consisting of H, C(O)NR^9R^{10} and -Y-(heteroaryl), wherein -Y-(heteroaryl) is optionally substituted with 1 to 5 independently selected R^{38};

[0189] In a preferred embodiment of the compounds according to paragraphs [0187] to [0188], R^7 is $C(O)NR^9R^{10}$;

[0190] In a preferred embodiment of the compounds according to paragraphs [0187] to [0189], R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring, wherein said ring is optionally substituted with 1 to 5 independently selected R^{44} substituents.

[0191] In a preferred embodiment of the compounds according to paragraphs [0187] to [0190], R^7 is -Y-(heteroaryl), wherein said -Y-(heteroaryl) is optionally substituted with 1 to 5 independently selected R^{38}.

[0192] In a preferred embodiment of the compounds according to paragraphs [0187] to [0191], R^7 is -Y-(heteroaryl), wherein said -Y-(heteroaryl) is optionally substituted with one C_1-C_6 alkyl.

[0193] In a preferred embodiment of the compounds according to paragraphs [0187] to [0192], R^1 is halogen.

[0194] In a preferred embodiment of the compounds according to paragraphs [0187] to [0193], R^1 is fluorine.

[0195] In a preferred embodiment of the compounds according to paragraphs [0187] to [0194], R^{17} is selected from the group consisting of H and C_1-C_6 alkyl.

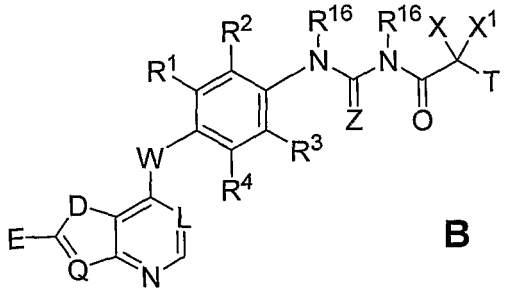
[0196] In a preferred embodiment of the compounds according to paragraphs [0187] to [0195], R^{38} is selected from the group consisting of $-OR^{37}$, C_1-C_6 alkyl and $-(CH_2)_n$(5 to 10 membered heterocylic), wherein n is an integer ranging from 0 to 6.

[0197] In a preferred embodiment of the compounds according to paragraphs [0187] to [0196], R^{37} is selected from the group consisting of H and C_1-C_6 alkyl.

[0198] In a preferred embodiment of the compounds according to paragraphs [0187] to [0197], each R^{20} is independently selected from the group consisting of H, halogen and -O-(C_1-C_6)alkyl.

[0199] In a preferred embodiment of the compounds according to paragraphs [0187] to [0198], two R^{20} are H and the third R^{20} is selected from the group consisting of H, halogen and -O-(C_1-C_6 alkyl).

[0200] In a second aspect, the invention comprises compounds of formula (B), which are inhibitors of VEGF receptor signaling and HGF receptor signaling:



B

and pharmaceutically acceptable salts and complexes thereof, wherein

T is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl is optionally substituted with 1 to 3 R^{20};

each R^{20} is independently selected from the group consisting of -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^{17}$, $-OCF_3$, $-NR^{17}R^{18}$, $-S(O)_{0-2}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-N(R^{17})SO_2R^{17}$, $-N(R^{17})C(O)R^{17}$, $-N(R^{17})C(O)OR^{17}$, $-C(O)R^{17}$, $-C(O)SR^{17}$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, $-O(CH_2)_n$aryl, $-O(CH_2)_n$heteroaryl, $-(CH_2)_{0-5}$(aryl), $-(CH_2)_{0-5}$(heteroaryl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-CH_2(CH_2)_{0-4}$-T^2, an optionally substituted C_{1-4} alkylcarbonyl, C_{1-4} alkoxy, an amino optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy and a saturated or unsaturated three- to seven-membered carboxyclic or heterocyclic group, wherein T^2 is selected from the group consisting of -OH, -OMe, -OEt, $-NH_2$, -NHMe, $-NMe_2$, -NHEt and $-NEt_2$, and wherein the aryl, heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted;

W is selected from the group consisting of O, S and NH;

Z is selected from the group consisting of O, or S and NH;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano, or nitro, wherein C_1-C_6 alkyl is optionally substituted, or

X and X^1 taken together with the atom to which they are attached, form a C_3-C_7 cycloalkyl;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, halo, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^{17}$, $-NR^{17}R^{18}$, $-C(O)OR^{17}$, $-C(O)R^{17}$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^{17} is selected from the group consisting of H and R^{18};

R^{18} is selected from the group consisting of a C_1-C_6 alkyl, an aryl, an aryl(C_1-C_6 alkyl), a heterocyclyl and a heterocyclyl(C_1-C_6 alkyl), each of which is optionally substituted, or

R^{17} and R^{18}, taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, the optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from the group consisting of N, O, S and P;

R^{16} is selected from the group consisting of -H, -CN, $-(CH_2)_{0-5}$(aryl), $-(CH_2)_{0-5}$(heteroaryl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-CH_2(CH_2)_{0-4}-T^2$, an optionally substituted C_{1-4} alkylcarbonyl, and a saturated or unsaturated three- to seven-membered carboxyclic or heterocyclic group, wherein T^2 is selected from the group consisting of -OH, -OMe, -OEt, $-NH_2$, -NHMe, $-NMe_2$, -NHEt and $-NEt_2$, and wherein the aryl, heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted;

D is selected from the group consisting of CH_2, O, S, NH, N-(C_1-C_6 alkyl), or N-Y-(aryl), -N-OMe, $-NCH_2OMe$ and -N-Bn;

Q is selected from the group consisting of C-E and N;

L is N, or CR, wherein R is selected from the group consisting of -H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

E is selected from the group consisting of E^1, E^2 and E^3, wherein

E^1 is selected from the group consisting of -H, halogen, nitro, azido, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-C(O)NR^{42}R^{43}$, $-Y-NR^{42}R^{43}$, $-NR^{42}C(=O)R^{43}$, $-SO_2R^{42}$, $-SO_2NR^{42}R^{43}$, $-NR^{37}SO_2R^{42}$, $-NR^{37}SO_2NR^{42}R^{43}$, $-C(=N-OR^{42})R^{43}$, $-C(=NR^{42})R^{43}$, $-NR^{37}C(=NR^{42})R^{43}$, $-C(=NR^{42})NR^{37}R^{43}$, $-NR^{37}C(=NR^{42})NR^{37}R^{43}$, $-C(O)R^{42}$, $-CO_2R^{42}$, -C(O)(heterocyclyl), -C(O)(C_6-C_{10} aryl), -C(O)(heteroaryl), -Y-(C_6-C_{10} aryl), -Y-(heteroaryl), -Y-(5-10 membered heterocyclic), $-NR^{6a}R^{6b}$, $-NR^{6a}SO_2R^{6b}$, $-NR^{6a}C(O)R^{6b}$, $-OC(O)R^{6b}$, $-NR^{6a}C(O)OR^{6b}$, $-OC(O)NR^{6a}R^{6b}$,$-OR^{6a}$, $-SR^{6a}$, $-S(O)R^{6a}$, $-SO_2R^{6a}$, $-SO_3R^{6a}$, $-SO_2NR^{6a}R^{6b}$, $-SO_2NR^{42}R^{43}$, $-COR^{6a}$, $-CO_2R^{6a}$, $-CONR^{6a}R^{6b}$, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)fluoroalkoxy, $-(CZ^3Z^4)_aCN$, wherein n is an integer ranging from 0 to 6, and the aforementioned E^1 groups other than -H and halogen are optionally substituted by 1 to 5 independently selected R^{38}, or E^1 is selected from a moiety selected from the group consisting of $-(CZ^3Z_4)_a$-aryl, $-(CZ^3Z^4)_a$-heterocycle, (C_2-C_6)alkynyl, $-(CZ^3Z^4)_a$-(C_3-C_6)cycloalkyl, $-(CZ^3Z^4)_a$-(C_5-C_6)cycloalkenyl, (C_2-C_6) alkenyl and (C_1-C_6)alkyl, which is optionally substituted with 1 to 3 independently selected Y^2 groups, where a is 0,1, 2, or 3, and wherein when a is 2 or 3, the CZ^3Z^4 units may be the same or different; wherein

each R^{38} is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-NR^{36}R^{39}$, $-OR^{37}$, $-SO_2NR^{36}R^{39}$, C_1-C_6 alkyl, $-(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nOR^{37}$, $-S(O)_j(C_1$-C_6 alkyl), $-(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_n(C_5$-C_{10} heteroaryl), $-(CH_2)_n$(5-10 membered heterocyclyl); $-C(O)(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_nO(CH_2)_j(C_6$-C_{10} aryl), $-(CH_2)_nO(CH_2)_i$(5-10 membered heterocyclyl), $-C(O)(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_jNR^{39}CH_2C(O)NR^{36}R^{39}$, $-(CH_2)_jNR^{39}(CH_2)_iNR^{37}C(O)R^{40}$, $-(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_jNR^{39}(CH_2)_iS(O)_j(C_1$-$C_6$ alkyl), $-(CH_2)_jNR^{39}(CH_2)_nR^{36}$, $-SO_2(CH_2)_n(C_6$-C_{10} aryl), $-SO_2(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_nNR^{36}R^{39}$, $-NR^{37}SO_2NR^{36}R^{39}$, SO_2R^{36}, C_2-C_6 alkenyl, C_3-C_{10} cycloalkyl and C_1-C_6 alkylamino, wherein j is an integer ranging from 0 to 2, n is an integer ranging from 0 to 6, i is an integer ranging from 0 to 6, the $-(CH_2)_i$- and $-(CH_2)_n$- moieties of the foregoing R^{38} groups optionally include a carbon-carbon double or triple bond where n is an integer between 2 and 6, and the alkyl, aryl, heteroaryl and heterocyclyl moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_nO(CH_2)_iOR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6;

each R^{42} and R^{43} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -Y-(C_3-C_{10} cycloalkyl), -Y-(C_6-C_{10} aryl), -Y-(C_6-C_{10} heteroaryl), -Y-(5-10 membered heterocyclic), $-Y\text{-}O\text{-}Y^1\text{-}OR^{37}$, $-Y^1\text{-}CO_2\text{-}R^{37}$, and $-Y\text{-}OR^{37}$, wherein the alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclic moieties of the foregoing R^{42} and R^{43} groups are optionally substituted by 1 or more substituents independently selected from R^{44}, wherein

Y is a bond or is $-(C(R^{37})(H))_n$,

n is an integer ranging from 1 to 6, and

Y^1 is $-(C(R^{37})(H))_n$, or

R^{42} and R^{43} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted by 1

to 5 R^{44} substituents, with the proviso that R^{42} and R^{43} are not both bonded to the nitrogen directly through an oxygen;

each R^{44} is independently selected from the group consisting of halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-NR^{36}R^{39}$, $-OR^{37}$, $-SO_2NR^{36}R^{39}$, $-SO_2R^{36}$, $-NR^{36}SO_2R^{39}$, $-NR^{36}SO_2NR^{37}R^{41}$, C1-$C_6$ alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, -C_1-C_6 alkylamino, $-(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nOR^{37}$, $-S(O)_j(C_1$-C_6 alkyl), $-(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_n$(5-10 membered heterocyclic), $-C(O)(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_nO(CH_2)j(C_6$-C_{10} aryl), $-(CH_2)_nO(CH_2)_i$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_jNR^{39}CH_2C(O)NR^{36}R^{39}$, $-(CH_2)_jNR^{39}(CH_2)_iNR^{37}C(O)R^{40}$, $-(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_jNR^{39}(CH_2)_iS(O)_j(C_1$-$C_6$ alkyl), $-(CH_2)_jNR^{39}(CH_2)_nR^{36}$, $-SO_2(CH_2)_n(C_6$-C_{10} aryl), and $-SO_2(CH_2)_n$(5 to 10 membered heterocyclic) wherein, j is an integer from 0 to 2, n is an integer from 0 to 6 and i is an integer ranging from 2 to 6, the $-(CH_2)_i-$ and $-(CH_2)_{n1}-$ moieties of the foregoing R^{44} groups optionally include a carbon-carbon double or triple bond wherein n is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{44} groups are optionally substituted by 1 or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$,-$NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, $-SO_2R^{36}$, $-SO_2NR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$ and $-(CH_2)_nOR^{37}$, wherein n is an integer from 0 to 6 and i is an integer from 2 to 6; and

each R^{40} is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_n(C_6$-C_{10} aryl), C_3-C_{10} cycloalkyl, and $-(CH_2)_n$(5-10 membered heterocyclic), wherein n is an integer ranging from 0 to 6;

each R^{36} and R^{39} is independently selected from the group consisting of H, -OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_n$(5-10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nCN(CH_2)_nOR^{37}$, $-(CH_2)_nCN(CH_2)_nR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{36} and R^{39} groups are optionally substituted by one or more substituents independently selected from -OH, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, -

$CO(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{37}C(O)R^{41}$, $-C(O)NR^{37}R^{41}$, $-NR^{37}R^{41}$, $-C_1$-C_6 alkyl, $-(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, with the proviso that when R^{36} and R^{39} are both attached to the same nitrogen, then R^{36} and R^{39} are not both bonded to the nitrogen directly through an oxygen;

each R^{37} and R^{41} is independently selected from the group consisting of H, OR^{36}, C_1-C_6 alkyl and C_3-C_{10} cycloalkyl;

each R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, $-(CZ^5Z^6)_u$-$(C_3$-$C_6)$cycloalkyl, $-(CZ^5Z^6)_u$-$(C_5$-$C_6)$cycloalkenyl, $-(CZ^5Z^6)_u$-aryl, $-(CZ^5Z^6)_u$-heterocycle, $(C_2$-$C_6)$alkenyl, and $(C_1$-$C_6)$alkyl, which is optionally substituted with 1 to 3 independently selected Y^3 groups, where u is 0,1, 2, or 3, and wherein when u is 2 or 3, the CZ^5Z^6 units may be the same or different, or

R^{6a} and R^{6b} taken together with adjacent atoms can form a heterocycle;

each Z^3, Z^4, Z^5 and Z^6 is independently selected from the group consisting of H, F and $(C_1$-$C_6)$alkyl, or

each Z^3 and Z^4, or Z^5 and Z^6 are selected together to form a carbocycle, or

two Z^3 groups on adjacent carbon atoms are selected together to optionally form a carbocycle;

each Y^2 and Y^3 is independently selected from the group consisting of halogen, cyano, nitro, tetrazolyl, guanidino, amidino, methylguanidino, azido, $-C(O)Z^7$, $-OC(O)NH_2$, $-OC(O)NHZ^7$, $-OC(O)NZ^7Z^8$, $-NHC(O)Z^7$, $-NHC(O)NH_2$, $-NHC(O)NHZ^7$, $-NHC(O)NZ^7Z^8$, $-C(O)OH$, $-C(O)OZ^7$, $-C(O)NH_2$, $-C(O)NHZ^7$,$-C(O)NZ^7Z^8$, $-P(O)_3H_2$, $-P(O)_3(Z^7)_2$, $-S(O)_3H$, $-S(O)Z^7$, $-S(O)_2Z^7$, $-S(O)_3Z^7$, $-Z^7$, $-OZ^7$, $-OH$, $-NH_2$, $-NHZ^7$, $-NZ^7Z^8$, $-C(=NH)NH_2$,$-C(=NOH)NH_2$, -N-morpholino, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$haloalkenyl, $(C_2$-$C_6)$haloalkynyl, $(C_1$-$C_6)$haloalkoxy, $-(CZ^9Z^{10})_rNH_2$, $-(CZ^9Z^{10})_rNHZ^3$, $-(CZ^9Z^{10})_rNZ^7Z^8$, $-X^6(CZ^9Z^{10})_r$-$(C_3$-$C_8)$cycloalkyl, $-X^6(CZ^9Z^{10})_r$-$(C_5$-$C_8)$cycloalkenyl, $-X^6(CZ^9Z^{10})_r$-aryl and $-X^6(CZ^9Z^{10})_r$-heterocycle, wherein

r is 1, 2, 3 or 4;

X^6 is selected from the group consisting of O, S, NH, -C(O)-, -C(O)NH-, -C(O)O-, -S(O)-, $-S(O)_2$- and $-S(O)_3$-;

Z^7 and Z^8 are independently selected from the group consisting of an alkyl of 1 to 12 carbon atoms, an alkenyl of 2 to 12 carbon atoms, an alkynyl of 2 to 12 carbon atoms, a

cycloalkyl of 3 to 8 carbon atoms, a cycloalkenyl of 5 to 8 carbon atoms, an aryl of 6 to 14 carbon atoms, a heterocycle of 5 to 14 ring atoms, an aralkyl of 7 to 15 carbon atoms, and a heteroaralkyl of 5 to 14 ring atoms, or

Z^7 and Z^8 together may optionally form a heterocycle;

Z^9 and Z^{10} are independently selected from the group consisting of H, F, a $(C_1\text{-}C_{12})$alkyl, a $(C_6\text{-}C_{14})$aryl, a $(C_5\text{-}C_{14})$heteroaryl, a $(C_7\text{-}C_{15})$aralkyl and a $(C_5\text{-}C_{14})$heteroaralkyl, or

Z^9 and Z^{10} are taken together form a carbocycle, or

two Z^9 groups on adjacent carbon atoms are taken together to form a carbocycle; or

any two Y^2 or Y^3 groups attached to adjacent carbon atoms may be taken together to be $-O[C(Z^9)(Z^{10})]_rO$ or $-O[C(Z^9)(Z^{10})]_{r+1}$, or

any two Y^2 or Y^3 groups attached to the same or adjacent carbon atoms may be selected together to form a carbocycle or heterocycle; and wherein

any of the above-mentioned substituents comprising a CH_3 (methyl), CH_2 (methylene), or CH (methine) group which is not attached to a halogen, SO or SO_2 group or to a N, O or S atom optionally bears on said group a substituent selected from hydroxy, halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy and an $-N[(C_1\text{-}C_4)\text{alkyl}][(C_1\text{-}C_4)\text{alkyl}]$;

E^2 is $-C\equiv CH$ or $-C\equiv C\text{-}(CR^{45}R^{45})_n\text{-}R^{46}$;

R^{45} is independently selected from the group consisting of H, a $(C_1\text{-}C_6)$alkyl and a $(C_3\text{-}C_8)$cycloalkyl;

R^{46} is selected from the group consisting of heterocyclyl, $-N(R^{47})\text{-}C(O)\text{-}N(R^{47})(R^{48})$, $-N(R^{47})\text{-}C(S)\text{-}N(R^{47})(R^{48})$, $-N(R^{47})\text{-}C(O)\text{-}OR^{48}$, $-N(R^{47})\text{-}C(O)\text{-}(CH_2)_n\text{-}R^{48}$, $-N(R^{47})\text{-}SO_2R^{47}$, $-(CH_2)_nNR^{47}R^{48}$, $-(CH_2)_nOR^{48}$, $-(CH_2)_nSR^{49}$, $-(CH_2)_nS(O)R^{49}$, $-(CH_2)_nS(O)_2R^{49}$, $-OC(O)R^{49}$, $-OC(O)OR^{49}$, $-C(O)NR^{47}R^{48}$, heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, $(C_1\text{-}C_6)$alkoxy, $-NO_2$, $(C_1\text{-}C_6)$alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, and aryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, $(C_1\text{-}C_6)$alkoxy, $-NO_2$, $(C_1\text{-}C_6)$alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$;

R^{47} and R^{48} are independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, heterocyclyl, $-(CH_2)_nNR^{50}R^{51}$, $-(CH_2)_nOR^{50}$, $-(CH_2)_nC(O)R^{49}$, $-C(O)_2R^{49}$, $-(CH_2)_nSR^{49}$, $-(CH_2)_nS(O)R^{49}$, $-(CH_2)_nS(O)_2R^{49}$, $-(CH_2)_nR^{49}$, $-(CH_2)_nCN$, aryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, $(C_1\text{-}C_6)$alkoxy, $-NO_2$, $(C_1\text{-}C_6)$alkyl, -CN, $-(CH_2)_nOR^{49}$, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$heteroaryl, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, and heteroaryl

optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-(CH_2)_nOR^{49}$, $-(CH_2)_n$heterocyclyl, $-(CH_2)_n$heteroaryl, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, or

R^{47} and R^{48}, together with the atom to which they are attached, form a 3-8 membered ring;

R^{49} is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkylene, aryl(C_1-C_6)alkylene wherein the aryl is optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, heteroaryl(C_1-C_6)alkylene wherein the heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, aryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$, and heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$;

R^{50} and R^{51} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl and $-C(O)R^{45}$, or

R^{50} and R^{51}, together with the atom to which they are attached, form a 3-8 membered ring; and

E^3 is the group defined by $-(Z^{11})-(Z^{12})_m-(Z^{13})_{m1}$, wherein

Z^{11} is heterocyclyl or heterocyclylene;

Z^{12} is selected from the group consisting of OC(O), OC(S) and C(O);

Z^{13} is selected from the group consisting of heterocyclyl, aralkyl, $N(H)R^{52}$, (C_1-C_3)alkyl, $-OR^{52}$, halo, $S(O)_2R^{56}$, (C_1-C_3)hydroxyalkyl and (C_1-C_3)haloalkyl;

m is 0 or 1;

m1 is 0 or 1;

R^{52} is selected from the group consisting of H, $-(CH_2)_qS(O)_2R^{54}$, $R^{55}NR^{53}R^{53}$, (C_1-C_3)alkyl, $-(CH_2)_qOR^{53}$, $-C(O)R^{54}$ and $-C(O)OR^{53}$;

q is 0, 1, 2, 3 or 4;

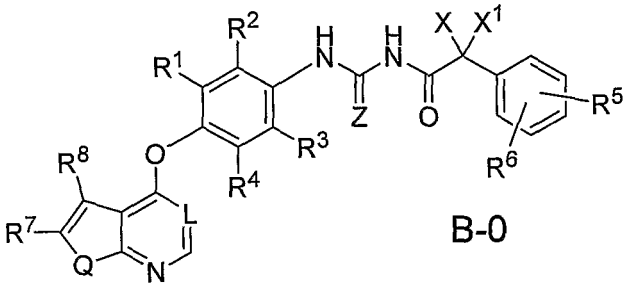
R^{53} is (C_1-C_3)alkyl;

R^{54} is (C_1-C_3)alkyl or $N(H)R^{53}$;

R^{55} is (C_1-C_6) alkyl; and

R^{56} is selected from the group consisting of NH_2, (C_1-C_3)alkyl and OR^{52}.

[0201] In a preferred embodiment of the compounds according to paragraph [0200], the compounds are represented by the formula B-0:



B-0

and pharmaceutically acceptable salts and complexes thereof, wherein

Z is O or S;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano, or nitro, wherein C_1-C_6 alkyl is optionally substituted;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

Q is O, S, NH, N(C_1-C_6 alkyl), or N-Y-(aryl);

L is N, or CR, wherein R is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$ and CO_2R^9, wherein C_1-C_6 alkyl, aryl, heterocyclyl and heteroaryl are each optionally substituted;

R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11}, and -Y-O-R^{11}, wherein C_1-C_6 alkyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl are each optionally substituted, or

R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted;

R^8 is selected from the group consisting of H, halo and C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted;

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y^1 is -$(C(R^{11})(H))_t$-, and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

[0202] In a preferred embodiment of the compounds according to paragraph [0201], X and X^1 are both hydrogen.

[0203] In a preferred embodiment of the compounds according to paragraphs [0201] to [0202], R^1 is hydrogen or halogen.

[0204] In a preferred embodiment of the compounds according to paragraphs [0201] to [0203], R^1 is fluorine.

[0205] In a preferred embodiment of the compounds according to paragraphs [0201] to [0204], R^4 is hydrogen or halogen.

[0206] In a preferred embodiment of the compounds according to paragraphs [0201] to [0205] R^4 is fluorine.

[0207] In a preferred embodiment of the compounds according to paragraphs [0201] to [0206], R^2, R^3, R^5, and R^6 are each hydrogen.

[0208] In a preferred embodiment of the compounds according to paragraphs [0201] to [0207], Q is S, N(C_1-C_6 alkyl), or N-Y-(aryl).

[0209] In a preferred embodiment of the compounds according to paragraphs [0201] to [0208], L is CH or N.

[0210] In a preferred embodiment of the compounds according to paragraphs [0201] to [0209], R^8 is selected from the group consisting of H, halo and C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted with OH or $NR^{14}R^{15}$, where R^{14} and R^{15} are independently H or C_1-C_6 alkyl, or R^{14} and R^{15} are taken together with the nitrogen to which they are attached to form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted.

[0211] In a preferred embodiment of the compounds according to paragraphs [0201] to [0210], R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$CONR^9R^{10}$, -SO_2NH_2, -$SO_2NR^9R^{10}$, -Y-heterocycle -Y-heteroaryl, -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl and -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocycle, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0212] In a preferred embodiment of the compounds according to paragraphs [0201] to [0211], R^7 is -$CONR^9R^{10}$.

[0213] In a preferred embodiment of the compounds according to paragraph [0212], R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-O-R^{11}, -

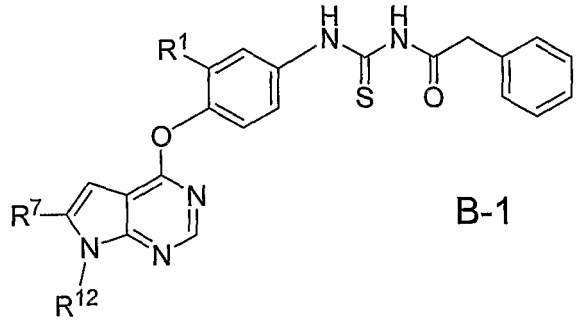
Y-(heterocycle), -Y^1-CO_2-R^{11} and -Y-(aryl), wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocycle, and aryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0214] In a preferred embodiment of the compounds according to paragraph [0212], R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said ring is unsubstituted or is substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0215] In a preferred embodiment of the compounds according to paragraphs [0201] to [0209], R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$SO_2NR^9R^{10}$, -C(=O)(heterocyclyl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl and -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

[0216] In a preferred embodiment of the compounds according to paragraphs [0201] to [0215], Z is sulfur.

[0217] In a preferred embodiment of the compounds according to paragraph [0200], the compounds are represented by the formula B-1:



B-1

and pharmaceutically acceptable salts and complexes thereof, wherein

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -C(=O)NR_9R_{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$ and CO_2R^9, wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted;

R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-

CO_2-R^{11}, and -Y-O-R^{11}, wherein C_1-C_6 alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted;

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y_1 is -($C(R^{11})(H))_t$-;

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted; and

R^{12} is selected from the group consisting of H, C_1-C_6 alkyl and -Y-(aryl), wherein C_1-C_6 alkyl and aryl are optionally substituted.

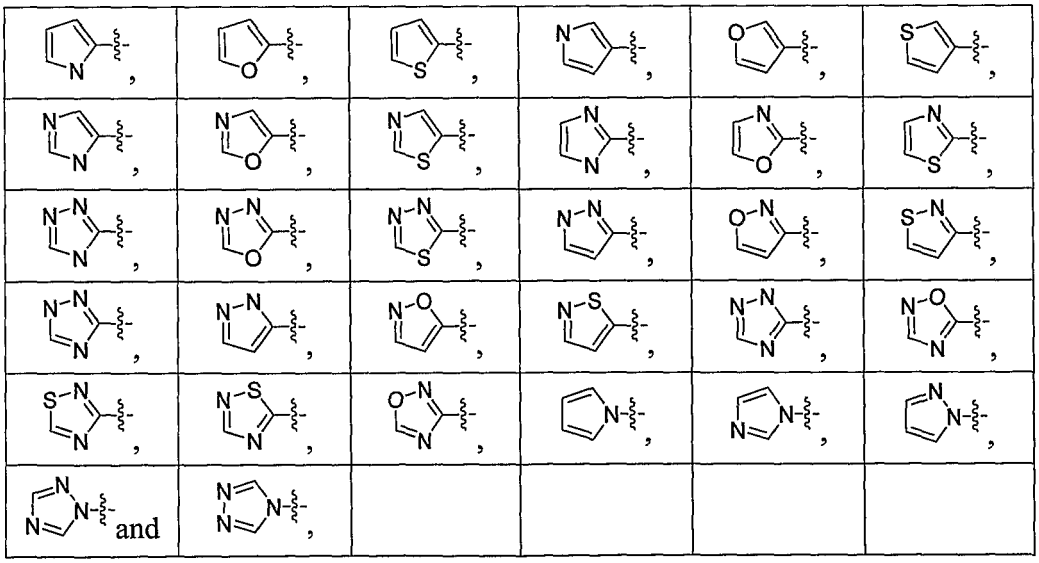
[0218] In a preferred embodiment of the compounds according to paragraph [0217], R^1 is hydrogen or halogen.

[0219] In a preferred embodiment of the compounds according to paragraphs [0217] to [0218], R^1 is fluorine.

[0220] In a preferred embodiment of the compounds according to paragraphs [0217] to [0219], R^{12} is unsubstituted C_1-C_3 alkyl or unsubstituted benzyl.

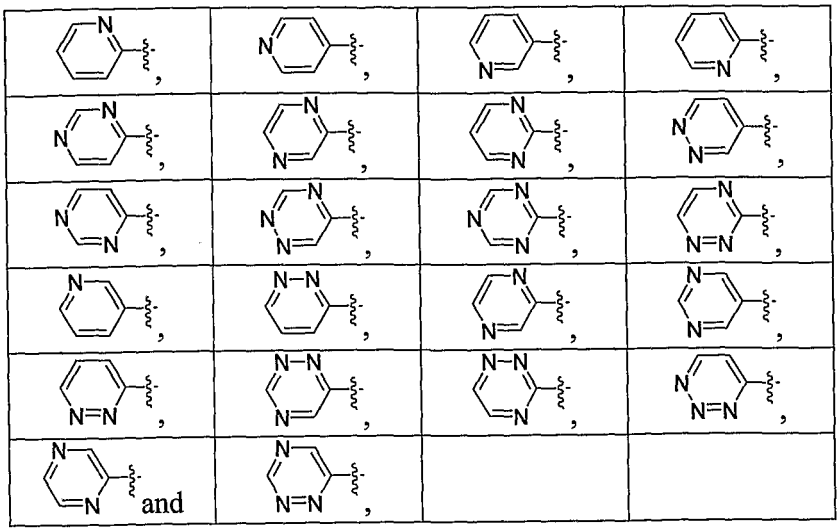
[0221] In a preferred embodiment of the compounds according to paragraphs [0217] to [0220], R^7 is -$C(O)NR^9R^{10}$.

[0222] In a preferred embodiment of the compounds according to paragraphs [0217] to [0220] R^7 is selected from the group consisting of



wherein the members of said group are optionally substituted by 1 to 3 independently selected R^{38}.

[0223] In a preferred embodiment of the compounds according to paragraphs [0217] to [0220] R^7 is selected from the group consisting of



wherein the members of said group are optionally substituted with 1 to 3 independently selected R^{38}.

[0224] In the third aspect, the invention provides a composition comprising a compound according to any one of paragraphs [0040] - [0223] or as depicted in any of the tables and examples herein together with a pharmaceutically acceptable excipient.

[0225] The fourth aspect of the invention provides a method of inhibiting VEGF receptor signaling and HGF receptor signaling, the method comprising contacting the receptor with a compound according to any one of paragraphs [0040] - [0223] or as depicted in any of the tables herein, or with a composition according to paragraph [0224]. Inhibition of VEGF and HGF activity can be in a cell or a multicellular organism. If in a multicellular organism, the method according to this aspect of the invention comprises administering to the organism a compound according to any one of paragraphs [0040] - [0223] or as depicted in any of the tables herein, or a composition according to paragraph [0224]. Preferably the organism is a mammal, more preferably a human.

[0226] The data presented herein demonstrate the inhibitory effects of the VEGF and HGF inhibitors of the invention. These data lead one to reasonably expect that the compounds of the invention are useful not only for inhibition of VEGF receptor signaling and HGF receptor signaling, but also as therapeutic agents for the treatment of proliferative diseases, including cancer and tumor growth.

[0227] Preferred compounds according to the invention include those described in the examples below. Compounds were named using Chemdraw Ultra version 6.0.2 or version

8.0.3, which are available through Cambridgesoft.com, 100 Cambridge Park Drive, Cambridge, MA 02140, Namepro version 5.09, which is available from ACD labs, 90 Adelaide Street West, Toronto, Ontario, M5H, 3V9, Canada, or were derived therefrom.

Synthetic Schemes and Experimental Procedures

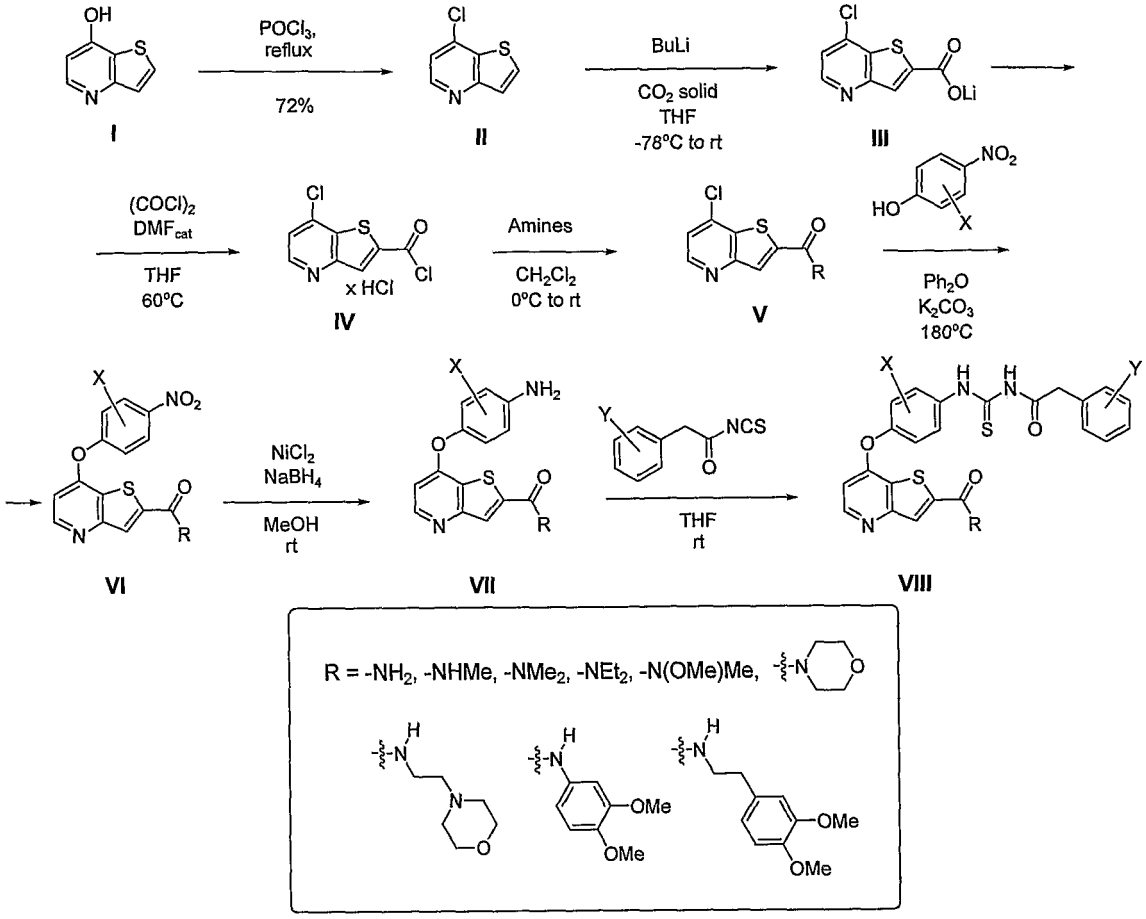
[0228] The compounds of the invention can be prepared according to the reaction schemes or the examples illustrated below utilizing methods known to one of ordinary skill in the art. These schemes serve to exemplify some procedures that can be used to make the compounds of the invention. One skilled in the art will recognize that other general synthetic procedures may be used. The compounds of the invention can be prepared from starting components that are commercially available. Any kind of substitutions can be made to the starting components to obtain the compounds of the invention according to procedures that are well known to those skilled in the art.

I. Synthesis (general schemes)

[0229] Thieno[3,2-b]pyridine based compounds of formula **A-0** may be prepared according to the procedures illustrated in the scheme A. Thus, thieno[3,2-b]pyridine-7-ol (**I**) upon treatment with $POCl_3$ is converted to the chloride **II**. Treatment of this material with a strong base such as *n*-BuLi followed by an addition of carbon dioxide affords the carboxylate **III** which is used without purification in the next step, providing the acyl chloride **IV** (presumably as a hydrochloride salt) upon its reaction with oxalyl chloride. The acyl chloride **IV** is used for the next step without further purification as well: upon its reaction with different primary and secondary amines the compound **IV** is converted to a variety of primary and secondary amides **V** which can further be derivatized via a substitution of the chlorine atom in the pyridine ring.

[0230] Thus, **V** reacting with substituted 4-nitrophenols in a high boiling point solvent, such as diphenyl ether in the presence of a base such as potassium carbonate, produced the nitro derivatives **VI** which then are reduced to the amines **VII** upon treatment with a mixture $NiCl_2/NaBH_4$ (or other conventional reagents). The amines **VII** also may be used for the next step without further purification, and upon treatment with 2-phenylacetyl isothiocyanates afford phenylacetylthioureas **VIII** bearing the amido-substituents such as the ones shown in the scheme A.

Scheme A

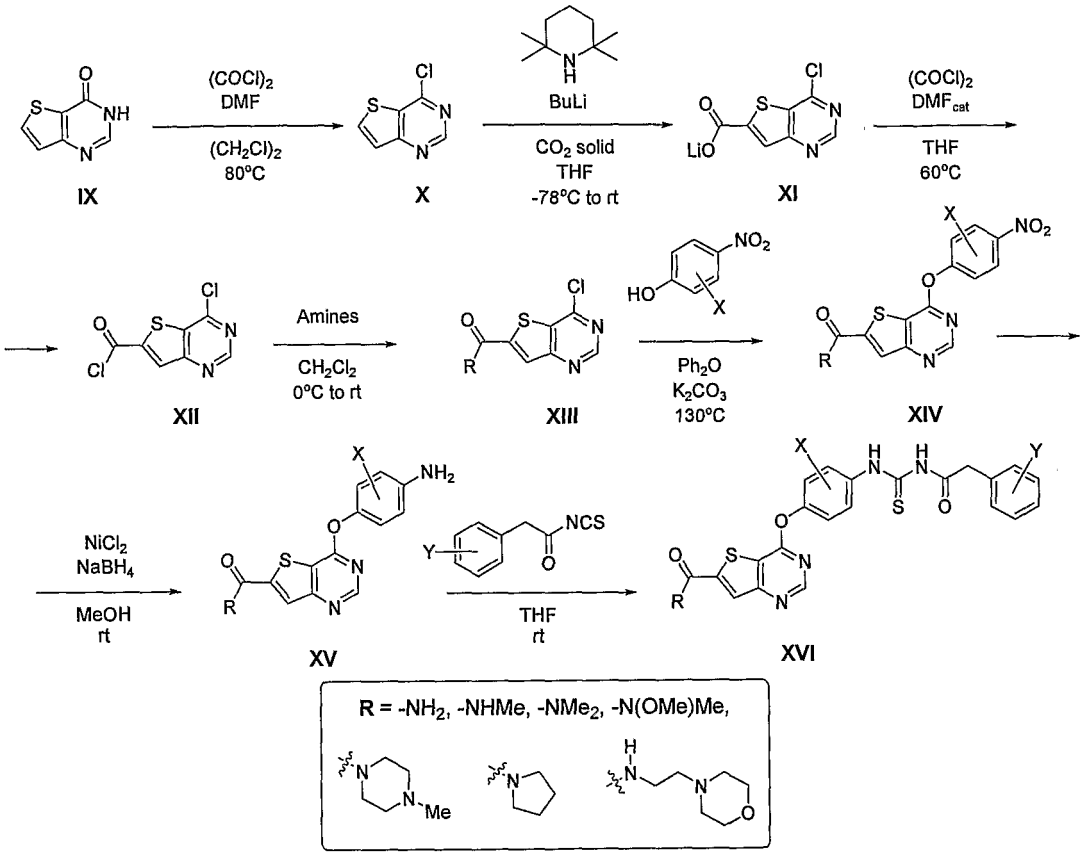


[0231] Substituents X and Y (up to three, same or different in each of the indicated benzene rings)are independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, nitro, hydroxy, amino, C_1-C_6 alkylamino

[0232] Thieno[3,2-d]pyrimidine based compounds of formula **A-0** may be prepared according to the procedures illustrated in the scheme B. Thus, thieno[3,2-d]pyrimidine-7-ol (**IX**) upon treatment with $POCl_3$ is converted to the chloride **X**. Treatment of this material with a strong base such as lithium tetramethylpiperidide (LiTMP) generated *in situ* followed by an addition of carbon dioxide affords the carboxylate **XI** which is used without purification in the next step, providing the acyl chloride **XII** (presumably as a hydrochloride salt) upon its reaction with oxalyl chloride. The acyl chloride **XII** reacting with different primary and secondary amines is converted to a variety of primary and secondary amides **XIII** which can further be derivatized via a substitution of the chlorine atom in the pyrimidine ring.

[0233] Thus, **XIII** reacting with substituted 4-nitrophenols in a high boiling point solvent, such as diphenyl ether in the presence of a base such as potassium carbonate, produce the nitro derivatives **XIV** which are then reduced to the amines **XV** upon treatment with a mixture $NiCl_2/NaBH_4$ (or other conventional reagents). The amines **XV** upon treatment with 2-phenylacetyl isothiocyanates afford the phenylacetylthioureas **XVI** bearing the amido-substituents such as the ones shown in the scheme B.

Scheme B

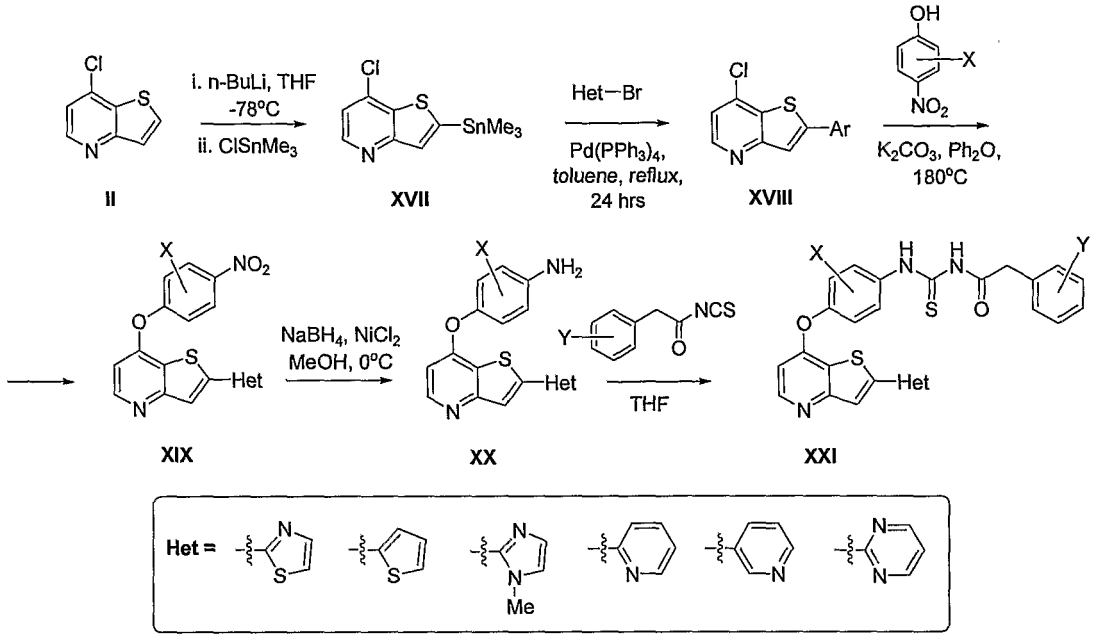


[0234] Substituents X and Y (up to three, same or different in each of the indicated benzene rings) are independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, nitro, hydroxy, amino, C_1-C_6 alkylamino

[0235] Thieno[3,2-b]pyridine based phenylacetylureas of formula **A-0** bearing heteroaryl substituents instead of the amido moieties may be prepared according to the procedures illustrated in the scheme C. Thus, treatment of the chloride **II** with a strong base such as *n*-BuLi followed by an addition of trimethyltin (or tributyltin) chloride affords the trimethylstannyl (or tributylstannyl) derivative **XVII.** This material reacting with different heteroaryl bromides in the presence of a Pd-catalyst (Stille coupling reaction or similar type

reactions) produces heteroaryl-substituted thienopyridines **XVIII** which can further be derivatized via a substitution of the chlorine atom in the pyridine ring.

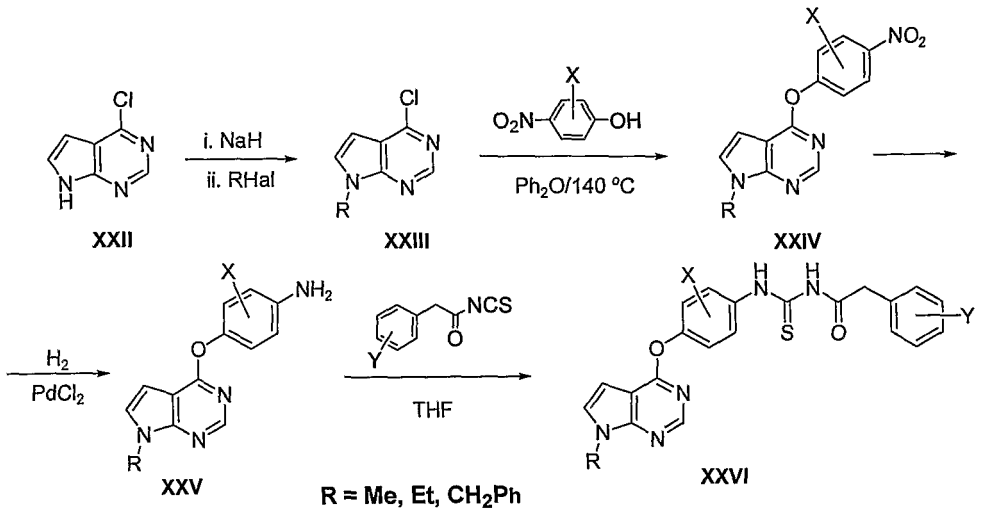
Scheme C



[0236] Substituents X and Y (up to three, same or different in each of the indicated benzene rings) are independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, nitro, hydroxy, amino, C_1-C_6 alkylamino

[0237] Thus, **XVIII** reacting with substituted 4-nitrophenols in a high boiling point solvent, such as diphenyl ether in the presence of a base such as potassium carbonate, produced the nitro derivatives **XIX** which are then reduced to the amines **XX** upon treatment with a mixture $NiCl_2/NaBH_4$ (or other conventional reagents). The amines **XX** could be used for the next step without further purification, and upon treatment with 2-phenylacetyl isothiocyanates afford the phenylacetylthioureas **XXI** bearing the heteroaryl substituents such as the ones shown in the scheme C. Heteroaryls shown in the scheme B, in turn may bear additional substituents exemplified (but not limited to) alkyls, amines, alkylamino, aminoalkyls, alkoxyalkyls, hydroxyalkyls, alkylsulfonylalkyls, etc.- known in the art as solubilizing functionalities.

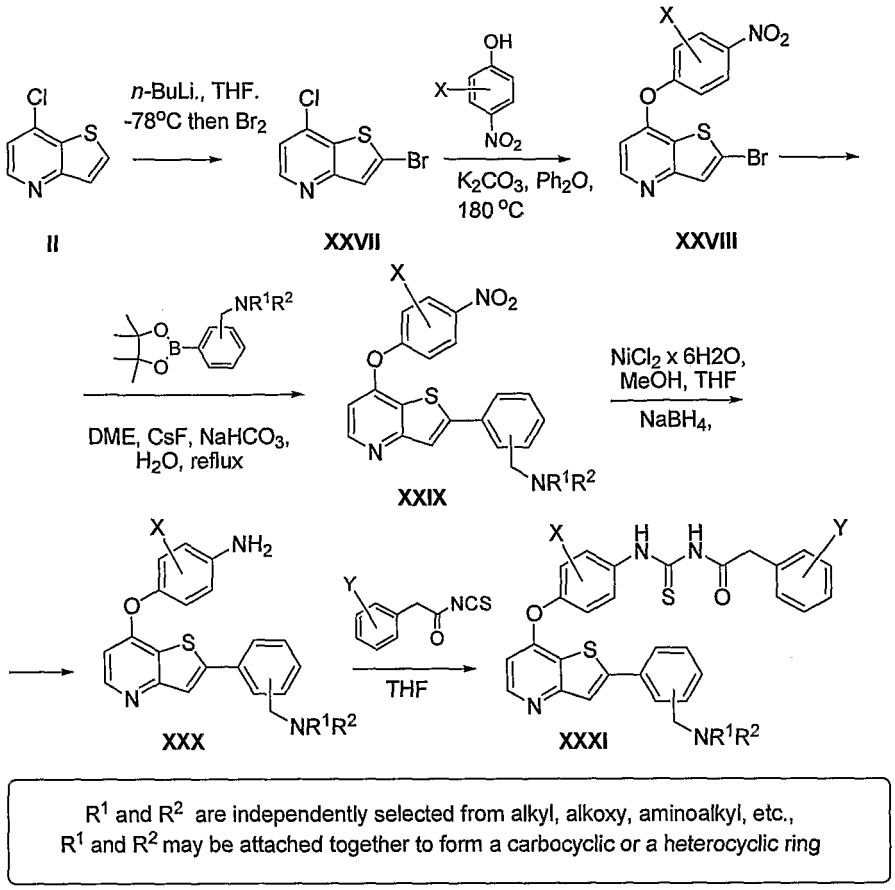
Scheme D



[0238] Substituents X and Y (up to three, same or different in each of the indicated benzene rings)are independently selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, nitro, hydroxy, amino, C_1-C_6 alkylamino

[0239] Pyrrolo[2,3-d]pyrimidine based compounds of formula **B-0** may be prepared according to the procedures illustrated in the scheme D. Treatment of the 4-chloro-7*H*-pyrrolo[2,3-d]pyrimidine (**XXII**) with an alkyl halide in the presence of a base such as sodium hydride affords the alkylated chlorides **XXIII**, which reacting with substituted 4-nitrophenols in a high boiling point solvent, such as diphenyl ether in the presence of a base such as cesium carbonate, produced the nitro derivatives **XXIV** reduced to the amines **XXV** upon hydrogenation (or treatment with conventional reducing agents). The amines **XXV** reacting with 2-phenylacetyl isothiocyanates afford the phenylacetylthioureas **XXVI** bearing the alkyl substituents such as the ones shown in the scheme D.

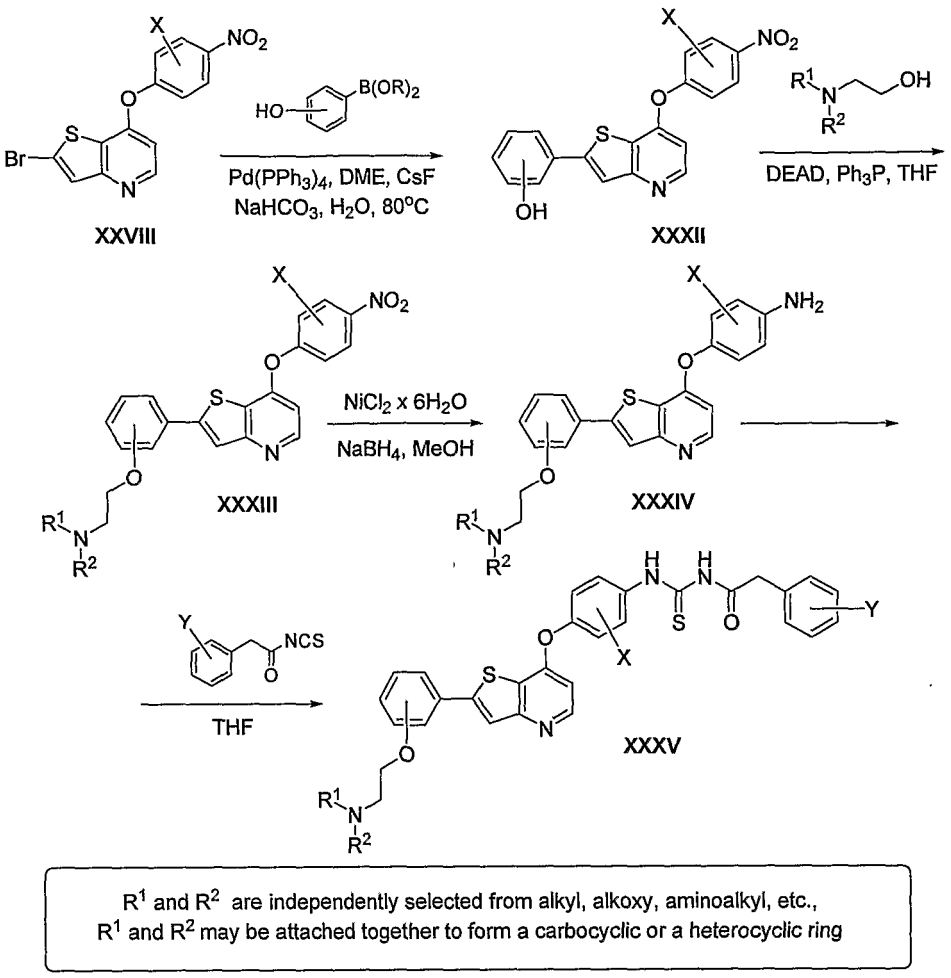
Scheme E



[0240] Substituents X and Y (up to three, same or different in each of the indicated benzene rings) are independently selected from halo, C_1-C_6alkyl, C_1-C_6alkoxy, cyano, nitro, hydroxy, amino, C_1-C_6alkylamino

[0241] Thieno[3,2-b]pyridine based phenylacetylureas of formula **A-0** bearing aryl substituents may be prepared according to the procedures illustrated in the scheme E. Thus vhloride **II** upon lithiation and subsequent bromination is converted to the bromide **XXVII** that reacting with substituted 4-nitrophenols produces more elaborated compound **XXVIII**. This material can be used for Suzuki type (and like) reactions with a variety of aryl boronic acids (or boronates), in particular with the ones functionalized with basic groups, thus providing compounds **XXIX**. Reduction of **XXIX** with a mixture $NiCl_2/NaBH_4$ (or other conventional reagents) affords amines **XXX**. The latter upon treatment with 2-phenylacetyl isothiocyanates afford the phenylacetylthioureas **XXXI** bearing aryl substituents such as the ones shown in the scheme E.

Scheme F

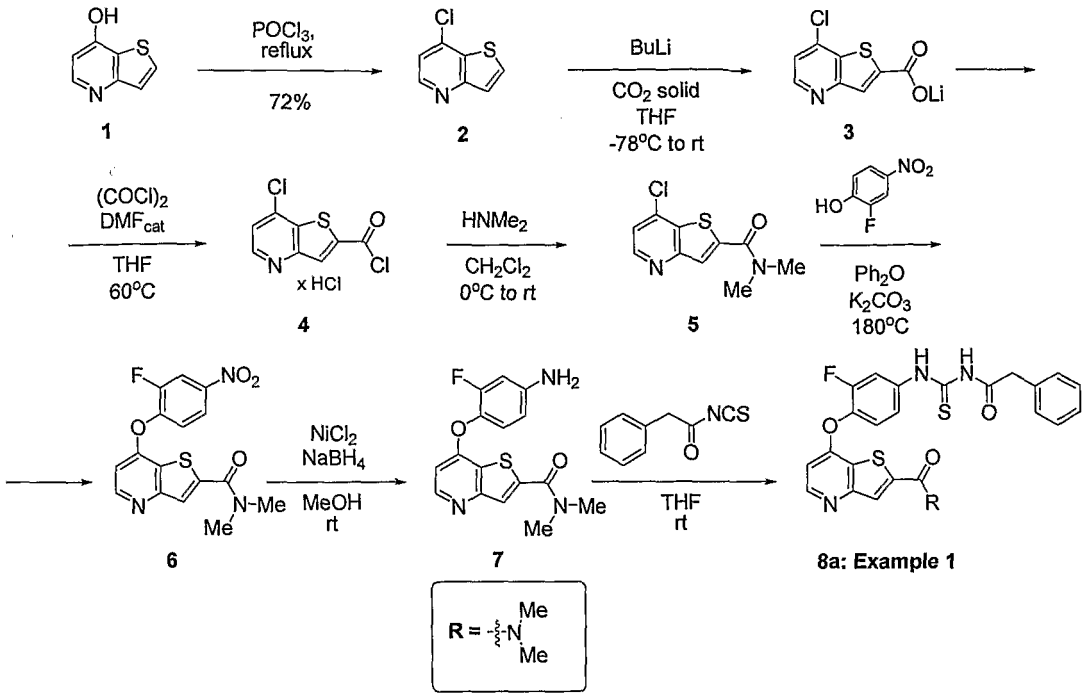


[0242] Substituents X and Y (up to three, same or different in each of the indicated benzene rings) are independently selected from halo, C_1-C_6alkyl, C_1-C_6alkoxy, cyano, nitro, hydroxy, amino, C_1-C_6alkylamino

[0243] Bromides **XXVIII** also can be used for Suzuki type (and like) reactions with a variety of hydroxyphenyl boronic acids (boronates), to form phenolic compounds **XXXII**. These phenols reacting with different alcohols (Mitsunobu reaction), in particular functionalized with basic groups, provide compounds **XXXIII**. Reduction of **XXXIII** with a mixture $NiCl_2/NaBH_4$ (or other conventional reagents) affords amines **XXXIV** which upon treatment with 2-phenylacetyl isothiocyanates afford the phenylacetylthioureas **XXXV** bearing the aryl substituents such as the ones shown in the scheme F.

II. Specific examples

Scheme 1



Example 1

1-(4-(2-(Dimethylcarbamoyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (8a)

Step 1: 7-Chlorothieno[3,2-*b*]pyridine (**2**)

[0244] A stirred suspension of thieno[3,2-b]pyridin-7-ol (**1**, 5.0 g, 33.1 mmol) in $POCl_3$ (15 mL) was heated to 105°C in an oil bath for 4 hrs. The resultant solution was cooled to room temperature and the $POCl_3$ was removed under reduced pressure. The residue was cooled in an ice/water bath and cold water was added. The water was made basic with concentrated NH_4OH solution and extracted with EtOAc. The organic extract was dried over anhydrous sodium sulfate and concentrated to produce an oil which was purified by column chromatography (eluent EtOAc-hexane, 1:4) to afford the title compound as a brown solid (4.5 g, 72% yield). ^1H NMR (400 MHz, $CDCl_3$) **δ** (ppm): 8.60 (d, J = 4.9 Hz, 1H), 7.80 (d, J = 5.5 Hz, 1H), 7.60 (d, J = 5.5 Hz, 1H), 7.30 (d, J = 4.9 Hz, 1H).

Steps 2-4: 7-Chloro-*N*,*N*-dimethylthieno[3,2-*b*]pyridine-2-carboxamide (**5**)

[0245] To a stirred solution of **2** (3.0 g, 17.8 mmol) in dry THF (60 mL) at -78°C was added n-BuLi (7.8 mL, 19.6 mmol, 2.5 M solution in hexanes) and the resultant suspension was stirred for 15 minutes. Solid carbon dioxide (excess) was added and the mixture was allowed to warm to room temperature over a period of 1 hour. The solvent was removed under reduced pressure and the resultant lithium carboxylate **3** was used without further purification (3.88 g, quantitative).

[0246] To a stirred suspension of **3** (3.5 g, 15.9 mmol) in dry DCM (50 mL) was added $(COCl)_2$ (3.96 g, 31.2 mmol) and dry DMF (1 drop). The reaction mixture was heated to reflux for 2 hrs. The solvents were evaporated to produce **4** (presumably as an HCl salt) which was used directly in the next step.

[0247] Acyl chloride **4** (2.42 g, 10.5 mmol) was suspended in dry DCM (105 mL) at 0°C and Me_2NH (15.7 mL, 2M solution in THF, 31.4 mmol) was added and the reaction mixture was stirred overnight. The solvent was removed and the residue was dissolved in EtOAc and washed with water. The organic phase was collected and dried over anhydrous sodium sulfate then filtered and concentrated under reduced pressure to produce a residue, which was purified by column chromatography (eluent EtOAc-hexane, 9:1) to afford **5** as a yellow solid (1.65 g, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.62 (d, *J*= 4.8 Hz, 1H), 7.76 (s, 1H), 7.37 (d, *J*= 4.8 Hz, 1H), 3.35-3.25 (m, 3H), 3.25-3.20 (m, 3H).

Step 5: 7-(2-Fluoro-4-nitrophenoxy)-*N*,*N*-dimethylthieno[3,2-*b*]pyridine-2-carboxamide (**6**)

[0248] A mixture of **5** (1.65 g, 6.85 mmol), potassium carbonate (5.68 g, 41.1 mmol) and 2-fluoro-4-nitrophenol (1.65 g, 10.3 mmol) were heated to 170°C in diphenyl ether (20 mL) for 5 hrs. The mixture was cooled to room temperature, diluted with EtOAc and washed with water. The organic phase was collected, dried over anhydrous sodium sulfate and the solvents were removed under reduced pressure. The residue was purified by column chromatography (eluents EtOAc-hexane 9:1, then MeOH-EtOAc 1:4) to afford **6** as a yellow solid (1.02 g, 41% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.64 (d, *J*= 5.3 Hz, 1H), 8.46 (dd, *J*= 2.8 and 10.3 Hz, 1H), 8.20 (ddd, *J*= 1.3 and 2.6 and 9.0 Hz, 1H), 7.98 (s, 1H), 7.73 (dd, *J*= 8.3 Hz, 1H), 6.99 (dd, *J*= 0.9 and 4.8 Hz, 1H), 3.25-3.30 (m, 3H), 3.02-3.11 (m, 3H).

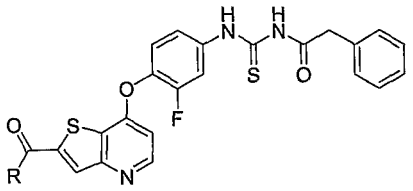
Steps 6-7: 1-(4-(2-(Dimethylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**8a**)

[0249] To a solution of **6** (190 mg, 0. 55 mmol) in MeOH (10 mL) at 0°C was added $NiCl_2$ x $6H_2O$ (241 mg, 1.02 mmol) and $NaBH_4$ (81.4 mg, 2.2 mmol). The reaction mixture was stirred for 1 hr, concentrated to dryness and the resultant solid was dissolved in 1 M HCl. The aqueous solution was then made basic with concentrated NH_4OH solution and extracted with EtOAc. The organic phase was collected, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure and the resultant solid was triturated with diethyl ether to afford **7** as a white solid that was used immediately in the next step.

[0250] To a suspension of 7 (465.8 mg, 1.41 mmol) in THF (20 mL) was added benzyl isothiocyanate (374 mg, 2.12 mmol) and the reaction mixture was stirred for 1 hr, concentrated under reduced pressure and the resultant residue was purified by column chromatography (eluent EtOAc-MeOH 19:1) to afford a yellow solid which was triturated with Et_2O to afford **8a** as an off-white solid (534 mg, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.47 (s, 1H), 11.78 (s, 1H), 8.57 (d, *J*= 4.2 Hz, 1H), 8.05-7.95 (m, 1H), 7.93 (s, 1H), 7.52 (s, 2H), 7.33 (d, *J*= 3.9 Hz, 1H), 7.28-7.23 (m, 1H), 6.72 (d, *J*= 5.3 Hz, 1H), 3.83 (s, 2H), 3.26 (s broad, 3H), 3.05 (s broad, 3H).

Examples 2-11:

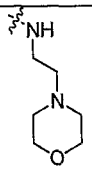
[0251] Examples 2-11 (compounds **8b-k**) were prepared using the same procedures as described for the compound **8a**, example 1 (scheme 1). Characterization of **8b-k** is provided in table 1.

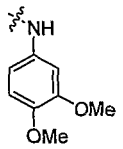
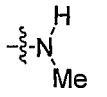
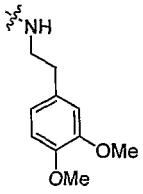
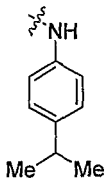


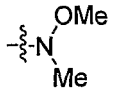
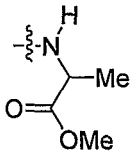
8b-k: Examples 2-11

Table 1.

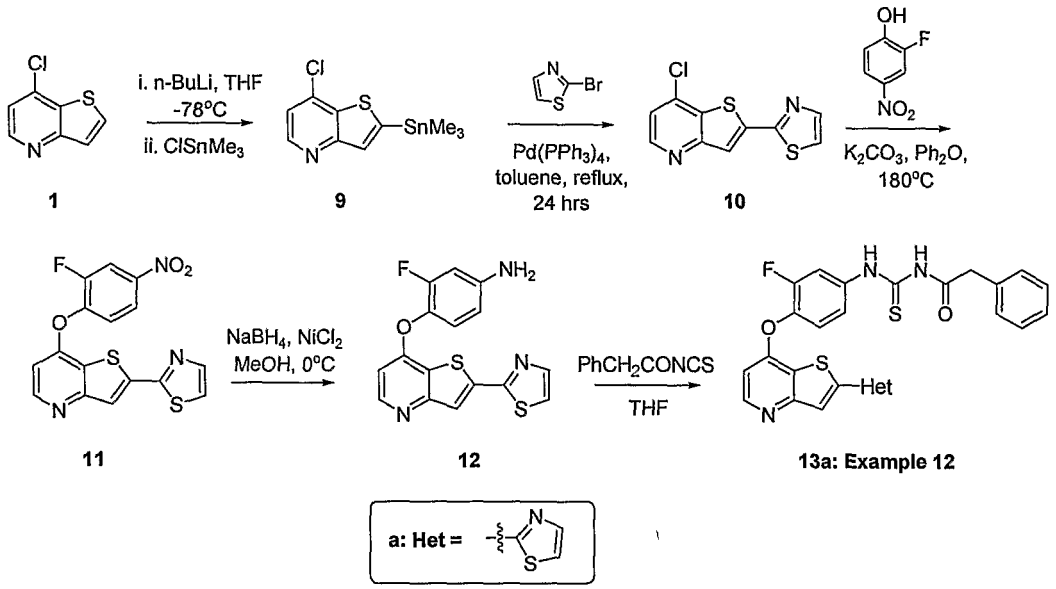
Characterization of compounds 8b-k (examples 2-11)

Cpd	Ex	R	Name	Characterization
8b	**2**		1-(4-(2-(2-morpholinoethylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δppm:** 12.52 (s, 1H), 11.85 (s, 1H), 8.96 (t, *J*= 5.3 Hz, 1H), 8.62 (d, *J*= 5.5 Hz, 1H), 8.28 (s, 1H), 8.06 (d, *J*= 10.9 Hz, 1H), 7.57 (d, *J*= 6.5 Hz, 2H), 7.38-7.30 (m, 5H), 6.77 (d, *J*= 5.2 Hz, 1H), 3.86 (s, 2H), 3.61 (t, *J*= 4.4 Hz, 4H), 3.46 (q, *J*= 6.6 Hz, 2H), 3.39-3.36 (m, 6H).
8c	**3**		1-(4-(2-(morpholinylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6). δ ppm:** 12.52 (s, 1H), 8.72 (s, 1H), 8.54 (d, *J*= 6.1 Hz, 1H), 8.0-7.98 (m, 2H), 7.38-7.26 (m, 7H), 6.73 (d, *J*= 5.7 Hz, 1H), 3.72 (s, 8H), 2.02 (s, 2H).

Cpd	Ex	R	Name	Characterization
8d	**4**		1-(4-(2-(3,4-dimethoxyphenylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d$_6$). δ ppm:** 10.64 (s, 1H), 8.61 (d, *J*= 5.4 Hz, 1H), 8.51 (s, 1H), 8.03 (d, *J*=12.7 Hz, 1H), 7.92 (s, 1H), 7.54 (m, 2H), 7.44 (d, *J*= 2.4 Hz, 1H), 7.29 (m, 7H), 6.96 (d, *J*= 8.8 Hz, 1H), 6.76 (d, *J*= 6.1 Hz, 1H), 3.82 (s, 2H), 3.76 (d, *J*= 8.3 Hz, 6H).
8e	**5**		1-(4-(2-(methylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.47 (s, 1H), 11.80 (s, 1H), 8.92 (s, 1H), 8.55 (d, *J*= 3.7 Hz, 1H), 8.18 (s, 1H), 8.01 (d, *J*= 11.9 Hz, 1H), 7.52 (s, 2H), 7.32 (s, 4H), 7.25 (s, 1H), 6.71 (d, *J*= 4.9 Hz, 1H), 3.81 (s, 2H), 2.83 (d, *J*= 3.3 Hz, 3H).
8f	**6**		1-(4-(2-(3,4-dimethoxyphenethylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d$_6$). δ ppm:** 12.47 (s, 1H), 11.81 (s, 1H), 9.03 (t, *J*= 5.7 Hz, 1H), 8.56 (d, *J*= 5.5 Hz, 1H), 8.22 (s, 1H), 8.02 (d, *J*= 11.4 Hz, 1H), 7.53 (s, 2H), 7.33 (m, 4H), 7.27 (m, 1H), 6.84 (m, 2H), 6.73 (m, 2H), 3.82 (s, 2H), 3.70 (d, *J*= 4.5 Hz, 6H), 3.50 (q, *J*=6.6 Hz, 2H), 2.80 (t, *J*= 7.0 Hz, 2H).
8g	**7**		1-(4-(2-(diethylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.58 (s, 1H), 8.71 (s, 1H), 8.59 (s, 1H), 8.05-7.92 (m, 2H), 7.40 (m, 4H), 7.33 (m, 3H), 6.71 (s, 1H), 3.80 (s, 2H), 3.59 (q, *J*= 7.2 Hz, 4H), 1.29 (m, 6H).
8h	**8**		1-(4-(2-(4-isopropylphenylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d$_6$). δ ppm:** 12.48 (s, 1H), 11.81 (s, 1H), 10.56 (s, 1H), 8.61 (d *J*= 5.4 Hz, 1H), 8.53 (s, 1H), 8.03 (d, *J*= 12.3 Hz, 2), 7.66 (d, *J*= 8.4 Hz, 2H), 7.54 (m, 2H), 7.33 (m, 4H), 7.23 (m, 3H), 6.75 (d, *J*= 5.3 Hz, 1H), 3.82 (s, 2H), 2.87 (m, 1H), 1.20 (d, *J*= 6.8 Hz, 6H).
8i	**9**		1-(4-(2-carbamoylthieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d$_6$). δ ppm:** 12.48 (s, 1H), 11.81 (s, 1H), 8.56 (dd, *J* = 0.6Hz and 5.5Hz, 1H), 8.40 (s, 1H), 8.25 (d, *J* = 0.8 Hz, 1H), 8.01 (d, *J* = 13.3 Hz, 1H), 7.86 (s, 1H), 7.33 (m, 4H), 7.25 (m, 1H), 6.72 (d, *J*= 5.3 Hz, 1H), 3.82 (s, 2H).

Cpd	Ex	R	Name	Characterization
8j	10		1-(4-(2-(N-methoxy-N-methylcarbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d$_6$). δ ppm:** 12.51 (s, 1H), 11.85 (s, 1H), 8.63 (d, *J* = 5.3 Hz, 1H), 8.22 (s, 1H), 8.04 (d, *J* = 13.1 Hz, 1H), 7.57 (m, 2H), 7.36 (m, 4H), 7.30 (m, 1H), 6.77 (d, *J*= 5.3 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.39 (s, 3H).
8k	11		Methyl 2-(1-(4-(2-(carbamoyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thioureido)propanoate	**^{1}H NMR (400 MHz, DMSO-d$_6$). δ ppm:** 12.48 (s, 1H), 11.80 (s, 1H), 9.28 (d, *J* = 6.9 Hz, 1H), 8.59 (d, *J* = 5.3 Hz, 1H), 8.38 (s, 1H), 8.02 (d, *J* = 12.9 Hz, 1H), 7.53 (m, 2H), 7.33 (m, 4H), 7.28 (m, 1H), 6.75 (d, *J*= 5.3 Hz, 1H), 4.49 (m, 1H), 3.82 (s, 2H), 3.66 (s, 3H), 1.44 (d, *J* = 7.4 Hz, 3H).

Scheme 2



Example 12

1-(4-(2-(Thiazol-2-yl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (13a)

Step 1: 7-Chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine

[0252] To a solution of **2** (1.0 g, 5.9 mmol) in dry THF (60 mL) at -78°C was added n-BuLi (2.36 mL, 5.9 mmol, 2.5 M solution in hexanes) and the resultant brown precipitate was stirred for 10 min. Trimethytin chloride (1.18 g, 5.9 mmol) in dry THF (10 mL) was added slowly and the mixture was allowed to stir at –78°C for 2 hrs, quenched with methanol at -78°C and the solvents were removed under reduced pressure. The residue was

dissolved in EtOAc and washed with water; the organic phase was collected, dried over anhydrous sodium sulfate and filtered. The EtOAc was evaporated under reduced pressure and the resultant oil was purified by column chromatography (eluent EtOAc-hexane 1:4) to afford **9** (1.2 g, 63% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.21 (d, J = 5.1 Hz, 1H), 7.36 (s, 1H), 6.91 (m, 1H), 0.16 (s, 9H).

Step 2: 7-Chloro-2-(thiazol-2-yl)thieno[3,2-*b*]pyridine (**10**)

[0253] To a solution of **9** (175 mg, 0.53 mmol) and 2-bromothiazole (94 mg, 0.58 mmol) in dry toluene (6 mL) was added $Pd(PPh_3)_4$ (62 mg, 0.053 mmol) and the reaction mixture was refluxed overnight, cooled to room temperature and the solvents were removed under reduced pressure. The resultant solid was triturated with hexane/Et_2O and then purified by column chromatography (eluent EtOAc-hexane 1:1) to give **10** as a white solid (75 mg, 56% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.65 (d, J = 5.1 Hz), 8.2 (s, 1H), 7.97 (s, 2H), 7.61 (d, J = 5.1 Hz).

Step 3: 7-(2-Fluoro-4-nitrophenoxy)-2-(thiazol-2-yl)thieno[3,2-b]pyridine (**11**)

[0254] To a suspension of **10** (194 mg, 0.77 mmol) in Ph_2O (10 mL) was added 2-fluoro-4-nitrophenol (240 mg, 1.53 mmol) and potassium carbonate (425 mg, 3.08 mmol) and the reaction mixture was heated at 180°C for 4 hrs. The reaction mixture was cooled to room temperature and diluted with EtOAc. The resultant solution was washed with water and the organic layer was collected, dried over anhydrous sodium sulfate and filtered. The solvents were removed under reduced pressure; the residue was dissolved in DCM, and purified by column chromatography (eluent EtOAc-hexane 4:1) to afford **11** (190 mg, 66 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.61 (d, J = 5.5 Hz, 1H), 8.46 (dd, J = 2.74 and 10.37 Hz), 8.24 (s, 1H), 8.20-8.10 (m, 1 H), 7.95 (s, 2H), 7.73 (t, J = 8 Hz, 1H), 6.98 (d, J = 5.3 Hz, 1H).

Steps 4-5. 1-(4-(2-(Thiazol-2-yl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**13a**)

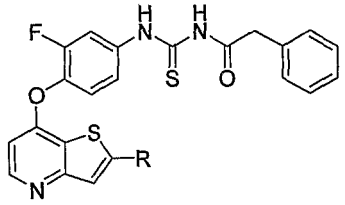
[0255] To a suspension of **11** (190 mg, 0. 55 mmol) in MeOH (10 mL) at 0°C was added $NiCl_2.6H_2O$ (241 mg, 1.02 mmol) and $NaBH_4$ (81.4 mg, 2.2 mmol). The reaction mixture was allowed to stir for 1 hr, concentrated to dryness and the resultant solid was dissolved in 1 M HCl. The aqueous solution was then made basic with concentrated ammonium hydroxide solution whereupon **12** precipitated as a grey solid, which was collected by filtration and used crude in the next step.

[0256] To a suspension of the amine **12** (152 mg, 0.44 mmol) in THF (10 mL) was added benzyl isothiocyanate (118 mg, 0.66 mmol) and the reaction mixture was stirred for 1

hr, concentrated under reduced pressure and purified by column chromatography (eluents EtOAc-hexane 3:1, then EtOAc) to afford a yellow solid. Trituration of this material with Et_2O/hexane gave **13a** (100 mg, 43 % yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 12.48 (s, 1H), 11.81 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.19 (s, 1H), 8.00 (d, J = 13.3 Hz, 1H), 7.95 (d, J = 3.1 Hz, 1H), 7.94 (d, J = 3.1 Hz, 1H), 7.53 (m, 2H), 7.33 (m, 3 H), 7.25 (m, 2H), 6.72 (d, J = 5.5 Hz, 1H), 3.82 (s, 2H).

Example 13

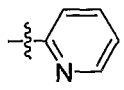
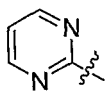
[0257] Examples 13-19 (compounds **13b-h**) were prepared using the same procedures as described for the compound **13a** (example 12, scheme 2). Characterization of compounds **13b-h** (examples 13-19) is provided in table 2.

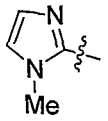
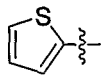
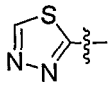
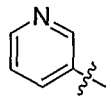


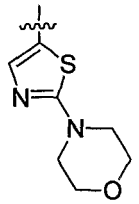
13 b-h: examples 13-19

Table 2

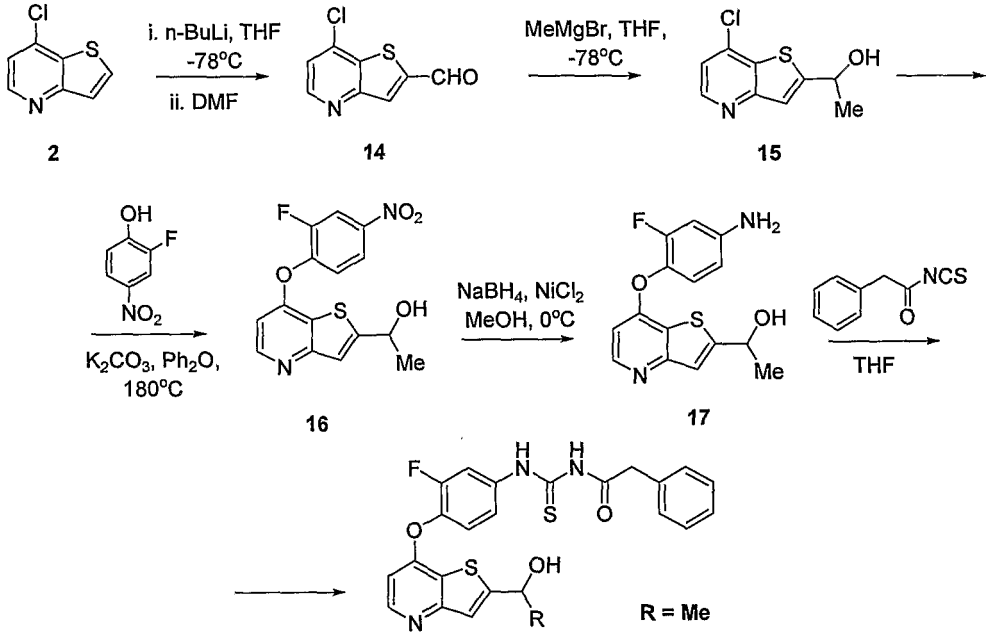
Characterization of compounds 13b-h (examples 13-19)

Cpd	Ex	R	Name	Characterization
13b	**13**		1-(4-(2-(Pyridin-2-yl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^1H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.47 (s, 1H), 11.81 (s, 1H), 8.61 (d, *J* = 2.9 Hz, 1H), 8.51 (d, *J* = 5.5 Hz, 1H), 8.36 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.0 (d, *J* = 17 Hz, 1H), 7.93 (dt, *J* = 1.76 and 7.82 Hz, 1H), 7.51 (m, 2H), 7.32 (m, 4H), 7.26 (m, 1H), 6.65 (d, *J* = 5.5 Hz, 1H), 3.82 (s, 2H). MS (m/z) 515.2 (M+H)
13c	**14**		N-(3-Fluoro-4-(2-(pyrimidin-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^1H NMR** (400 MHz, DMSO-d_6) δ ppm: 12.51 (s, 1H), 11.82 (s, 1H), 8.95 (m, 2H), 8.59 (m, 1H), 8.34 (s, 1H), 8.04 (m, 1H), 7.55 (m, 3H), 7.34 (m, 4H), 7.28 (m, 1H), 6.75 (m, 1H), 3.82 (s, 2H). MS (m/z) 516.2 (M+H)

Cpd	Ex	R	Name	Characterization
13d	**15**		N-(3-Fluoro-4-(2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 12.48 (s, 1H), 11.84 (s, 1H), 8.50 (m, 1H), 8.1 (s, 1H), 8.04 (d, *J* = 12.1 Hz, 1H), 7.63 (s, 1H), 7.56 (m, 2H), 7.39 (s, 1H), 7.33 (m, 4H), 7.27 (m, 1H), 7.19 (m, 1H), 6.77 (d, *J* = 5.7 Hz, 1H). MS (m/z) 518.2 (M+H)
13e	**16**		N-(3-Fluoro-4-(2-(thiophen-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm:12.48 (s, 1H), 11.84 (s, 1H), 8.50 (m, 1H), 8.04 (m, 1H), 7.79, (s, 1H), 7.73 (s, 1H), 7.63 (m, 2H), 7.39 (s, 4H), 7.27 (m, 1H), 7.19 (m, 1H), 6.65 (m, 1H), 5.74 (m, 1H), 3.81 (s, 2H). MS (m/z) 520.0 (M+H)
13f	**17**		N-(4-(2-(1,3,4-Thiadiazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm:12.47 (s, 1H), 11.82 (s, 1H), 8.57 (d, *J* = 5.5 Hz, 1H), 8.16 (s, 1H), 8.0 (d, *J* = 13 Hz, 1H), 7.56 (m, 1H), 7.36 (m, 4H), 7.26 (m, 2H), 6.71 (d, *J* = 5.3 Hz, 1H), 3.82 (s, 2H). MS (m/z) 522 (M+H)
13g	**18**		N-(3-fluoro-4-(2-(pyridin-3-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR** (400 MHz,DMSO-d_6) δ ppm: 12.49 (s, 1H), 11.85 (s, 1H), 9.12 (dd, *J* = 0.8 and 2.3 Hz), 8.63 (dd, *J* = 1.6 and 4,7 Hz, 1H), 8.55 (d, *J* = 5.5 Hz, 1H), 8.27 (m, 1H), 8.23 (s, 1H), 8.0 (d, *J* = 13.1 Hz, 1H), 7.54 (m, 3H), 7.32 (m, 4H), 7.26 (m, 2H), 6.69 (dd, *J* = 0.9 and 5.5 Hz, 1H), 3.81 (s, 2H). MS (m/z) 515.2 (M+H)

Cpd	Ex	R	Name	Characterization
13h	19		N-(3-fluoro-4-(2-(2-morpholinothiazol-5-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (400 MHz,DMSO-d_6) δ ppm:12.45 (s, 1H), 11.81 (s, 1H), 8.44 (dd, J = 1.2, 5.48 Hz, 1H), 7.98 (d, J = 12 Hz, 1H), 7.74 (s, 1H), 7.50 (s, 3H), 7.33 (m, 4H), 7.27 (m, 2H), 6.59 (d, J = 5.5 Hz, 1H), 3.82 (s, 2H), 3.72 (t, J = 4.7 Hz, 4H), 3.47 (t, J = 4.9 Hz, 4H). MS (m/z) 606.2 (M+H)

Scheme 3



18a: Example 20

Example 20

1-(4-(2-(1-Hydroxyethyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (18a)

Step 1. 7-Chlorothieno[3,2-b]pyridine-2-carbaldehyde (**14**)

[0258] To a solution of **2** (200 mg, 1.18 mmol) in dry THF (10 mL) at -78°C was added n-BuLi (0.57 mL, 1.42 mmol, 2.5 M solution in hexanes) and the resultant suspension was stirred for 20 min. Dry DMF (0.5 mL, excess) was added and the reaction mixture was stirred for an additional 2 hrs. The reaction mixture was quenched with methanol at -78°C and water was added. The mixture was extracted with EtOAc and the organic extracts were combined, dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure and the resultant yellow solid was triturated with hexane to afford

14 (250 mg, 100 % yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.2 (s, 1H), 8.78 (d, J = 5.1 Hz, 1H), 8.61 (s, 1H), 7.78 (d, J = 5.1 Hz, 1 H).

Steps 2-3. 1-(7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-**b**]pyridin-2-yl)ethanol (**16**)

[0259] To a solution of **14** (200 mg, 1 mmol) in dry THF (5 mL) at -78°C was added methylmagnesium bromide (0.51 mL, 1 mmol, 2 M solution in dibutyl ether) and the reaction mixture was stirred at -78°C for 1 hr. The reaction was quenched with water and extracted with EtOAc. The organic phase was dried over anhydrous sodium sulfate and evaporated. The resultant solid was washed with hexane to give **15** as a white solid (177 mg, 83% yield), which was used crude in the next step.

[0260] To a suspension of **15** (170 mg, 0.79 mmol) in Ph_2O (10 mL) was added 2-fluoro-4-nitrophenol (250 mg, 1.58 mmol) and potassium carbonate (436 mg, 3.16 mmol) and the reaction mixture was heated at 180°C for 4 hrs, cooled to room temperature and diluted with EtOAc. The solution was washed with water and the organic layer was collected, dried over anhydrous sodium sulfate and filtered. The solvents were removed under reduced pressure. The residue was dissolved in DCM, and purified by column chromatography (eluent EtOAc-hexane, 4:1) to afford **16** (125 mg, 47 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm: 8.52 (dd, J = 0.8 and 5.5 Hz, 1H), 8.44 (dd, J = 2.5 and 10.2 Hz, 1H), 8.15 (d, J = 10.2 Hz, 1H), 7.63 (t, J = 8.2 Hz, 1H), 7.41 (s, 1H), 6.86 (d, J = 5.3 Hz, 1H), 5.96 (dd, J = 0.4 Hz and 4.9 Hz), 5.09 (m, 1H), 1.49 (d, J = 6.5 Hz, 3H).

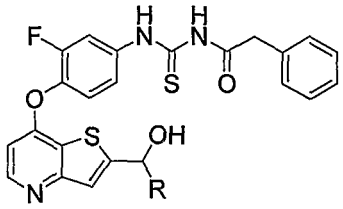
Steps 4-5. 1-(4-(2-(1-Hydroxyethyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**18a**)

[0261] To a suspension of **16** (129 mg, 0. 39 mmol) in MeOH (5 mL) at 0°C was added $NiCl_2.6H_2O$ (183 mg, 0.77 mmol) and sodium borohydride (57 mg, 1.5 mmol). The reaction mixture was allowed to stir for 1 hr, concentrated to dryness and the resultant solid was dissolved in 1 M HCl. The aqueous solution was then made basic with concentrated ammonium hydroxide solution, extracted with EtOAc and the organic extract was dried over anhydrous sodium sulfate then filtered. The solvent was removed under reduced pressure to give **17** (110 mg, 94% yield) as brown oil, which was used immediately in the next step.

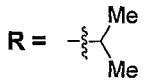
[0262] To an emulsion of **17** (110 mg, 0.36 mmol) in THF (10 mL) was added 2-phenylacetyl isothiocyanate (76 mg, 0.43 mmol) and the reaction mixture was stirred for 1 hr, concentrated and the residue was purified by column chromatography (eluents EtOAc-hexane 3:1, then EtOAc) to afford a yellow solid which upon trituration with diethyl

ether/hexane gave **18a** as an off-white solid (90 mg, 52 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.47 (s, 1H), 11.81 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.2 (s, 1H), 7.9 (d, J = 12.3 Hz, 1H), 7.51-7.44 (m, 2H), 7.30 (d, J = 0.9 Hz, 1H), 7.33 – 7.31 (m, 3H), 7.30-7.24 (m, 1H), 6.57 (d, J = 5.3 Hz, 1H), 5.91 (d, J = 4.9 Hz, 1H), 5.09 (m, 1H), 3.9 (s, 2H), 1.49 (d, J = 6.3 Hz, 3H).

Example 21



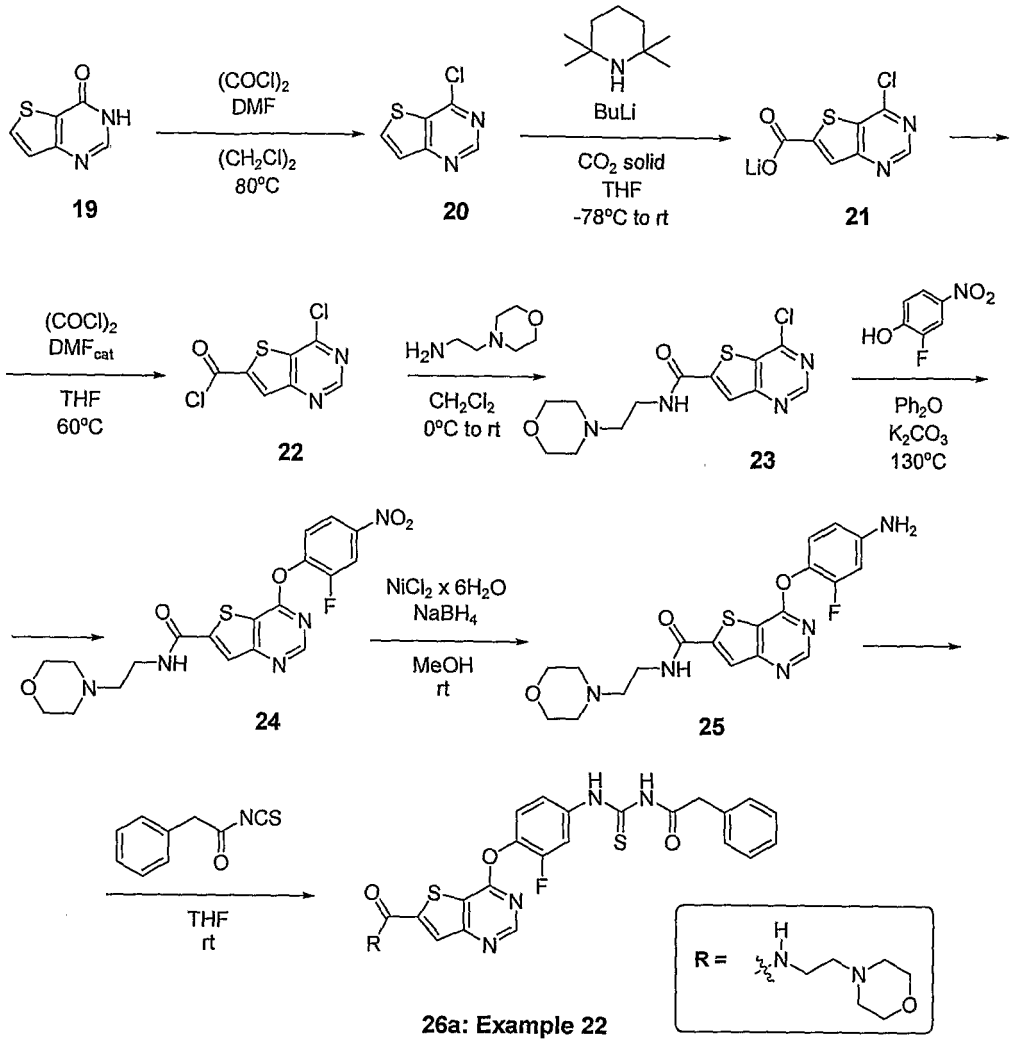
18 b: Example 21



1-(4-(2-(1-Hydroxy-2-methylpropyl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (18b)

[0263] Title compound was prepared using the same procedures as described for the compound **18a** (example 20, scheme 3). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.46 (s, 1H), 11.80 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.52-7.45 (m, 2H), 7.35 (s, 1H), 7.32 (m, 3H), 7.28 (m, 1H), 6.55 (d, J = 5.5 Hz, 1H), 5.91 (d, J = 4.7 Hz, 1H), 4.70 (t, J = 5.1 Hz, 1H), 3.8 (s, 2H), 1.95 (m, 1H), 0.9 (dd, J = 0.7 and 10.2 Hz, 6H).

Scheme 4



19 20 21 22 23 24 25

26a: Example 22

Example 22

1-(4-(6-(2-Morpholinoethylcarbamoyl)thieno[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (26a)

Step 1: 4-Chlorothieno[3,2-*d*]pyrimidine (**20**)

[0264] To a stirred solution of $(COCl)_2$ (7.33 mL, 84.11 mmol) in anhydrous $(CH_2Cl)_2$ (20 mL) at 0°C under nitrogen was added DMF (4.47 mL, 57.18 mmol). After 20 min a solution of thieno[3,2-*d*]pyrimidin-4(3H)-one (**19**) (4 g, 26.28 mmol) in anhydrous $(CH_2Cl)_2$ (5 mL) was added drop wise to the reaction mixture which was stirred for 20 min at 0°C, warmed to room temperature over another 20 min, heated at 80°C for 1.5 hours, and cooled to room temperature. Finally, the reaction mixture was poured into water and extracted with DCM. The extract was washed sequentially with water, brine, dried over Na_2SO_4, filtered and evaporated to afford the title compound **20** (4.36 g, 97% yield) as a

yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.02 (s, 1H), 8.59 (d, J = 5.2 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H).

Step 2: 4-Chlorothieno[3,2-*d*]pyrimidine-6-carbonyl chloride (**22**)

[0265] To a stirred solution of 2,2,6,6-tetramethylpiperidine (4.45 mL, 26.37 mmol) in anhydrous THF (50 mL) at 0°C under nitrogen was added n-BuLi (10.55 mL, 26.37 mmol, 2.5 M in hexanes). The reaction mixture was stirred for 30 min, then a solution of **20** (3 g, 17.58 mmol) in anhydrous THF (10 mL) was added drop wise at -78°C over 30 min followed by dry ice (10 g). The resultant suspension was warmed to the room temperature over 2 hours and filtered to afford the lithium carboxylate **21** as a yellow solid (4.5 g), which was used for the next step without further purification.

[0266] To a stirred solution of $(COCl)_2$ (2.95 mL, 33.82 mmol) in anhydrous DCM (30 mL) at 0°C under nitrogen was added DMF (0.5 mL, 6.45 mmol). The reaction mixture was stirred for 20 min and treated with a solution of the carboxylate **21** (3.71 g, 16.89 mmol) in anhydrous DCM (5 mL) (drop wise addition at 0°C), stirred for additional 10 min and heated at 60°C for 3 hours, cooled to room temperature and concentrated under reduced pressure to afford the title compound **22** (3.90 g, 99% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.02 (s, 1H), 8.59 (d, J = 5.2 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H).

Step 3: 4-Chloro-*N*-(2-morpholinoethyl)thieno[3,2-*d*]pyrimidine-6-carboxamide (**23**)

[0267] To a stirred solution of **22** (500 mg, 2.15 mmol) in anhydrous DCM (20 mL) at 0°C under nitrogen was added 4-(2-aminoethyl)-morpholine (307 mg, 2.36 mmol). The reaction mixture was allowed to warm to the room temperature over 3 hours and was stirred for additional 14 hours, treated with saturated aqueous solution of $NHCO_3$ and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residues was purified by flash chromatography on silica gel (eluents MeOH- DCM, 5:95, then 1:9) to afford the title compound **23** (458 mg, 65% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 9.13 (t, J = 5.6 Hz, 1H), 9.08 (s, 1H), 8.32 (s, 1H), 3.60-3.54 (m, 4H), 3.44 (q, J = 6.8 Hz, 2H), 2.54-2.48 (m, 2H), 2.46-2.40 (m, 4H).

Step 4: 4-(2-Fluoro-4-nitrophenoxy)-*N*-(2-morpholinoethyl)thieno[3,2-*d*]pyrimidine-6-carboxamide (**24**)

[0268] To a stirred solution of compound **23** (458 mg, 1.40 mmol) in Ph_2O (6 mL) was added 2-fluoro-4-nitrophenol (242 mg, 1.54 mmol). The reaction mixture was heated at 120°C for 2.5 hours, treated with K_2CO_3 (80 mg, 0.56 mmol) and heated at the same

temperature for additional 18 hours. After cooling, the reaction mixture was purified by flash chromatography on a silica gel column (eluents EtOAc-hexane 5:95, 1:1, then MeOH-DCM, 5:95 and 1:9), to afford the title compound **24** (570 mg, 91% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 9.09 (t, J = 5.6 Hz, 1H), 8.77 (s, 1H), 8.41 (dd, J = 2.4 and 10.4 Hz, 1H), 8.30 (s, 1H), 8.22 (dd, J = 2.4 and 8.8 Hz, 1H), 7.88 (t, J = 8.8 Hz, 1H), 3.60-3.52 (m, 4H), 3.45 (q, J = 6.8 Hz, 2H), 2.50 (q, J = 6.8 Hz, 2H), 2.46-2.40 (m, 4H).

Step 5: 4-(4-Amino-2-fluorophenoxy)-*N*-(2-morpholinoethyl)thieno[3,2-*d*]pyrimidine-6-carboxamide (**25**)

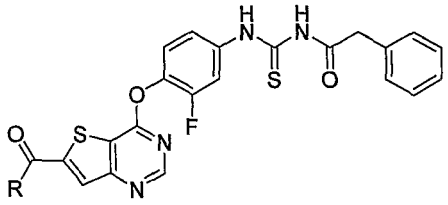
[0269] To a stirred solution of **24** (1.30 g, 2.72 mmol) in anhydrous MeOH (15 mL) at room temperature under nitrogen were added $NiCl_2$ x $6H_2O$ (605 mg, 2.54 mmol) and $NaBH_4$ (192 mg, 5.08 mmol), respectively. The reaction mixture was stirred for 50 min, concentrated, cooled to 0°C, treated with HCl (10 mL, 1M) followed by addition of NH_4OH (29%) (pH 9-10), and finally extracted with AcOEt. The organic extract was successively washed with water and brine, dried over Na_2SO_4, filtered, and concentrated to afford the title compound **25** (450 mg, 85% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 9.04 (t, J = 5.6 Hz, 1H), 8.73 (s, 1H), 8.23 (s, 1H), 7.07 (t, J = 8.8 Hz, 1H), 6.48 (dd, J = 2.4 and 13.2 Hz, 1H), 6.40 (dd, J = 2.4 and 8.8 Hz, 1H), 5.47 (s, 2H), 3.62-3.52 (m, 4H), 3.44 (q, J = 6.8 Hz, 2H), 2.56-2.48 (m, 2H), 2.46-2.40 (m, 4H).

Step 6: 1-(4-(6-(2-Morpholinoethylcarbamoyl)thieno[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**26a**)

[0270] To a stirred solution of **25** (450 mg, 1.07 mmol) in anhydrous THF (10 mL) under nitrogen was slowly added benzyl isothiocyanate (0.5 mL). The reaction mixture was stirred for 18 hours and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (eluent MeOH-DCM, 5:95→10:90) followed by reversed phase chromatography purification (column Phenomene X, C18, eluent H_2O-MeOH, 50:50→5:95, 10 mL/min) to afford the title compound **26a** (104 mg, 16% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ((ppm): 12.43(s, 1H), 11.80(s, 1H), 9.07(t, J = 5.6 Hz, 1H), 8.76(s, 1H), 8.28(s, 1H), 7.93(dd, J = 2.4 and 12.0 Hz, 1H), 7.54(t, J = 8.8 Hz, 1H), 7.48(dd, J = 1.2 and 8.8 Hz, 1H), 7.39-7.30(m, 4H), 7.30-7.20(m, 1H), 3.82(s, 2H), 3.60-3.54(m, 4H), 3.45(q, J = 6.4 Hz, 2H), 2.50(m, 2H), 2.48-2.40(m, 4H).

Examples 23-27

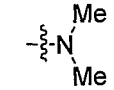
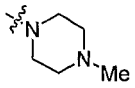
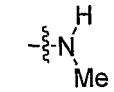
[0271] Examples 23-27 (compounds **26b-e**) were prepared using the same procedures as described for the compound **26a**, example 22 (scheme 4). Characterization of compounds 26b-e (examples 23-27) is provided in table 3.

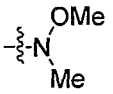


26 b-e: Examples 23-27

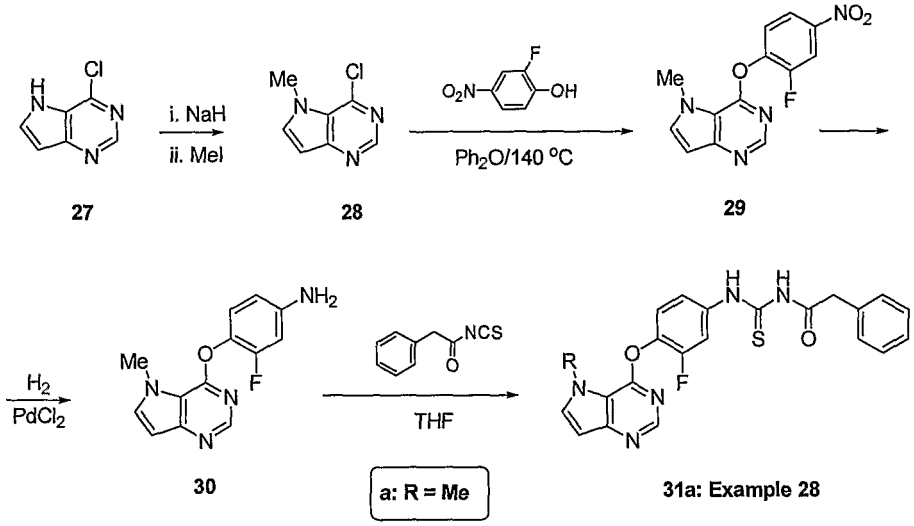
Table 3

Characterization of compounds 26b-e (examples 23-27)

Cpd	Ex	R	Name	Characterization
26b	**23**		1-(4-(6-(Dimethylcarbamoyl)thieno[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 8.77 (s, 1H), 8.01 (s, 1H), 7.93 (dd, J = 2.4 and 12.4 Hz, 1H), 7.54 (t, J = 8.4 Hz, 1H), 7.50-7.44 (m, 1H), 7.38-7.30 (m, 4H), 7.30-7.23 (m, 1H), 3.82 (s, 2H), 3.24 (s, 3H), 3.07 (s, 3H).
26c	**24**		1-(4-(6-(4-*N*-Methylpiperazylcarbamoyl)thieno[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.43 (s, 1H), 11.80 (s, 1H), 8.77 (s, 1H), 7.93 (s, 1H), 7.93 (dd, J = 2.0 and 12.0 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.48 (dd, J = 2.0 and 8.4 Hz, 1H), 7.38-7.30 (m, 4H), 7.30-7.24 (m, 1H), 3.82 (s, 2H), 3.74-3.62 (m, 4H), 2.48-2.36 (m, 4H), 2.25 (bs, 3H).
26d	**25**		1-(4-(6-(Methylcarbamoyl)thieno[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.42 (s, 1H), 11.80 (s, 1H), 9.10 (q, J = 4.4 Hz, 1H), 8.76 (s, 1H), 8.23 (s, 1H), 7.92 (dd, J = 2.0 and 12.0 Hz, 1H), 7.54 (t, J = 8.8 Hz, 1H), 7.48 (dd, 2.0 and 8.8 Hz, 1H), 7.36-7.30 (m, 4H), 7.30-7.24 (m, 1H), 3.82 (s, 2H), 2.87 (d, J = 4.4 Hz, 1H).

Cpd	Ex	R	Name	Characterization
26e	26		1-(4-(6-(*N*-Methoxy-N-methylcarbamoyl)thieno[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 8.79 (s, 1H), 8.23 (s, 1H), 7.93 (dd, J = 2.0 and 11.6 Hz, 1H), 7.55 (t, J = 8.8 Hz, 1H), 7.48 (dd, J = 2.0 and 8.8 Hz, 1H), 7.36-7.30 (m, 4H), 7.30-7.24 (m, 1H), 3.87 (s, 3H), 3.82 (s, 2H), 3.39 (s, 3H).
26f	27		1-(4-(6-Carbamoylthieno[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.43 (s, 1H), 11.80 (s, 1H), 8.76 (s, 1H), 8.55 (bs, 1H), 8.29 (s, 1H), 8.07 (bs, 1H), 7.93 (dd, J = 2.0 and 12 Hz, 1H), 7.54 (t, J = 8.8 Hz, 1H), 7.48 (dd, J = 2.0 and 8.8 Hz, 1H), 7.36-7.30 (m, 4H), 7.30-7.23 (m, 1H), 3.82 (s, 2H).

Scheme 5



Example 28

1-(4-(5-Methyl-*5H*-pyrrolo[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (31a)

Step 1: 4-Chloro-5-methyl-*5H*-pyrrolo[3,2-*d*]pyrimidine (**28**)

[0272] To a stirred solution of 4-chloro-*5H*-pyrrolo[3,2-*d*]pyrimidine (**27**) (*J. Org. Chem.*, 2001, *66*, 17, 5723-5730) (643 mg, 4.15 mmol) in DMF (41 mL) was added NaH (60% in mineral oil, 330 mg, 8.3 mmol) in one portion at 0°C and the mixture was stirred for 1 h followed by addition of methyl iodide (0.28 mL, 4.5 mmol). The reaction mixture was allowed to warm up to the room temperature, stirred for an additional hour and

quenched with AcOH (1 mL) to form a suspension which was stirred for 10 min and concentrated under reduced pressure to give a solid. This material was dissolved in AcOEt, the solution was washed with cold saturated $NaHCO_3$ solution and water, dried over Na_2SO_4, and concentrated to produce the title compound **28** as a pale yellow solid (640 mg, 93% yield). ^1H NMR (400 MHz, CD_3OD) δ(ppm): 8.51 (s, 1H), 7.75 (d, J = 3.3 Hz, 1H), 6.62 (d, J = 3.3 Hz, 2H), 4.15 (s, 1H). LRMS (M+1) 168.1 (100%), 170.1 (34%).

Step 2: 4-(2-Fluoro-4-nitrophenoxy)-5-methyl-*5H*-pyrrolo[3,2-*d*]pyrimidine (**29**)

[0273] A suspension of 4-chloro-5-methyl-*5H*-pyrrolo[3,2-*d*]pyrimidine (**28**) (300 mg, 1.79 mmol), 4-nitro-2-fluorophenol (422 mg, 2.69 mmol) and cesium carbonate (1.2 g, 3.58 mmol) in diphenyl ether (18 mL) was stirred overnight at 140°C. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and the residue was triturated with Et_2O, filtered, and dried to afford the title compound **29** as a grey solid (258 mg, 49% yield). LRMS (M+1) 289.1 (100%).

Step 3: 4-(5-Methyl-*5H*-pyrrolo[3,2-*d*]pyrimidin-4-yloxy)-3-fluorobenzenamine (**30**)

[0274] To a solution of 4-(2-fluoro-4-nitrophenoxy)-5-methyl-*5H*-pyrrolo[3,2-*d*] pyrimidine (**29**) (253.6 mg, 0.879 mmol) in AcOH (3 mL) at 90°C was added iron powder (245 mg, 4.4 mmol). The mixture was stirred vigorously for 10 min and filtered. The filtrate was concentrated under reduced pressure to produce a solid, which was dissolved in DCM. The resultant solution was washed with cold $NaHCO_3$ solution and water, dried over Na_2SO_4 and concentrated to provide a residue which was purified by column chromatography (eluent MeOH-CH_2Cl_2 1:20) to afford the title compound **30** as a brown solid (120.6 mg, 53% yield). LRMS (M+1) 240.1 (100%).

Step 4: 1-(4-(5-Methyl-*5H*-pyrrolo[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**31a**)

[0275] To a solution of 4-(5-methyl-*5H*-pyrrolo[3,2-*d*]pyrimidin-4-yloxy)-3-fluorobenzenamine (**30**) (120.8 mg, 0.5 mmol) and benzyl isothiocyanate (0.1 mL, 0.55 mmol) in THF (5 mL) was stirred 2 h at room temperature, concentrated under reduced pressure and the residue was subjected to a column chromatography on silica gel, (eluent EtOAc-hexane 1:1) to afford the title compound **31a** as a white solid (97.6 mg, 45%). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.42 (s, 1H), 11.79 (s,1H), 8.28 (d, J=0.6 Hz, 1H), 7.88 (dd, J=2.3 Hz, J=12.1 Hz, 1H), 7.81 (d, J=3.1 Hz, 1H), 7.50 (t, J=8.4 Hz, 1H), 7.44 (dd, J=2.1 Hz, J=8.8 Hz, 1H), 7.33 (m, 4H), 7.28 (m, 1H), 6.65 (dd, J=0.6 Hz, J=2.9 Hz, 1H), 4.10 (s, 3H), 3.83 (s, 2H). LRMS (M+1) 436.1 (100%).

Example 29

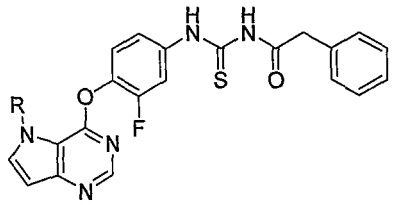
1-(4-(5-Ethyl-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (31b)

[0276] Title compound **31b** was obtained according to the scheme 5 using procedures similar to the ones described for example 28 but using ethyl iodide (instead of methyl iodide) in the step 1. Characterization of **31b** is provided in table 4.

Example 30

1-(4-(5-Benzyl-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (31c)

[0277] Title compound **31c** was obtained according to the scheme 5 using procedures similar to the ones described for the example 28 but using benzyl bromide (instead of methyl iodide) in the step 1. Characterization of **31c** is provided in table 4.



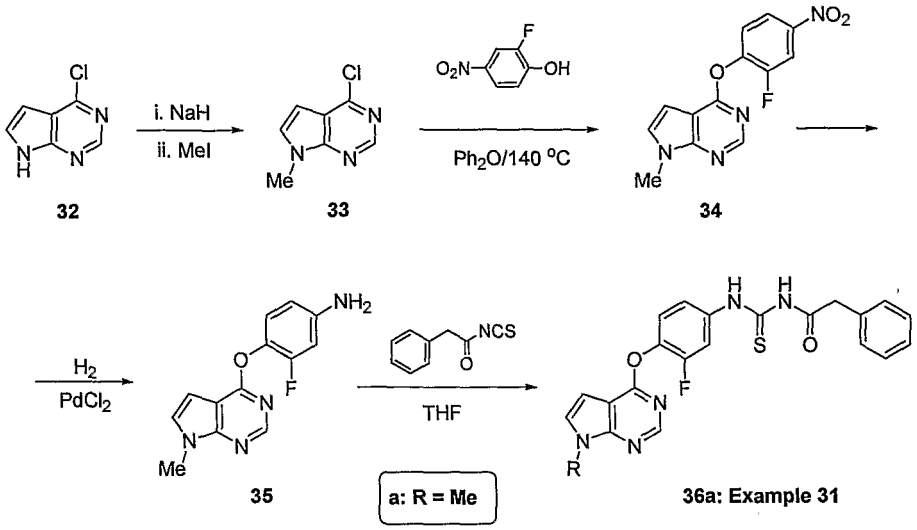
31b-c: Examples 29-30

Table 4

Characterization of 31b-c (examples 29-30)

Cpd	Ex	R	Name	Characterization
31b	**29**	**Et**	1-(4-(5-Ethyl-5H-pyrrolo[3,2-d]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm):** 12.4 (br, 1H), 11.8 (br, 1H), 8.3 (s, 1H), 7.90-7.85 (m, 2H), 7.54-7.41 (m, 2H), 7.40 (m, 4H), 7.29 (m, 1H), 6.63 (d, J=3.1 Hz, 1H), 4.46 (q, J=7.0 Hz, J=14.3 Hz, 2H), 3.83 (s, 2H), 1.46 (t, J=7.0 Hz, 3H). LRMS (M+1) 450.2 (100%).
31c	**30**	**-CH_2Ph**	1-(4-(5-Benzyl-5H-pyrrolo[3,2-d]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm):** 12.34 (s, 1H), 11.79 (s, 1H), 8.3 (s, 1H), 8.04 (d, J=3.1 Hz, 1H), 7.8 (dd, J=2.3 Hz, J=7.8 Hz, 1H), 7.4 (m, 1H), 7.35-7.76 (m, 11H), 6.7 (d, 3.1 Hz, 1H), 5.66 (s, 2H), 3.82 (s, 2H). LRMS (M+1) 512.3 (100%).

Scheme 6



Example 31

1-(4-(7-Methyl-*7H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenyl acetyl)thiourea (36a)

[0278] Title compound **36a** (scheme 6) was obtained according to the procedures similar to the ones described for the example 28 (scheme 5) but using as a starting material 4-chloro-*7H*-pyrrolo[2,3-*d*]pyrimidine **32** (instead of chloride **27**). Characterization of **36a** is provided in table 5.

Example 32

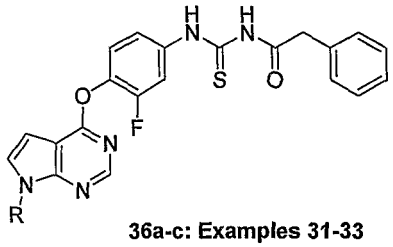
1-(4-(7-Ethyl-*7H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenyl acetyl)thiourea (36b)

[0279] Title compound **36b** was obtained according to the scheme 6 using the procedures similar to the ones described for the example 31 but using ethyl iodide (instead of methyl iodide) in the step 1. Characterization of **36b** is provided in table 5.

Example 33

1-(4-(7-Benzyl-*7H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenyl acetyl)thiourea (36c)

[0280] Title compound **36c** was obtained according to the scheme 6 using the procedures similar to the ones described for the example 31 but using benzyl bromide (instead of methyl iodide) in the step 1. Characterization of **36c** is provided in table 5.



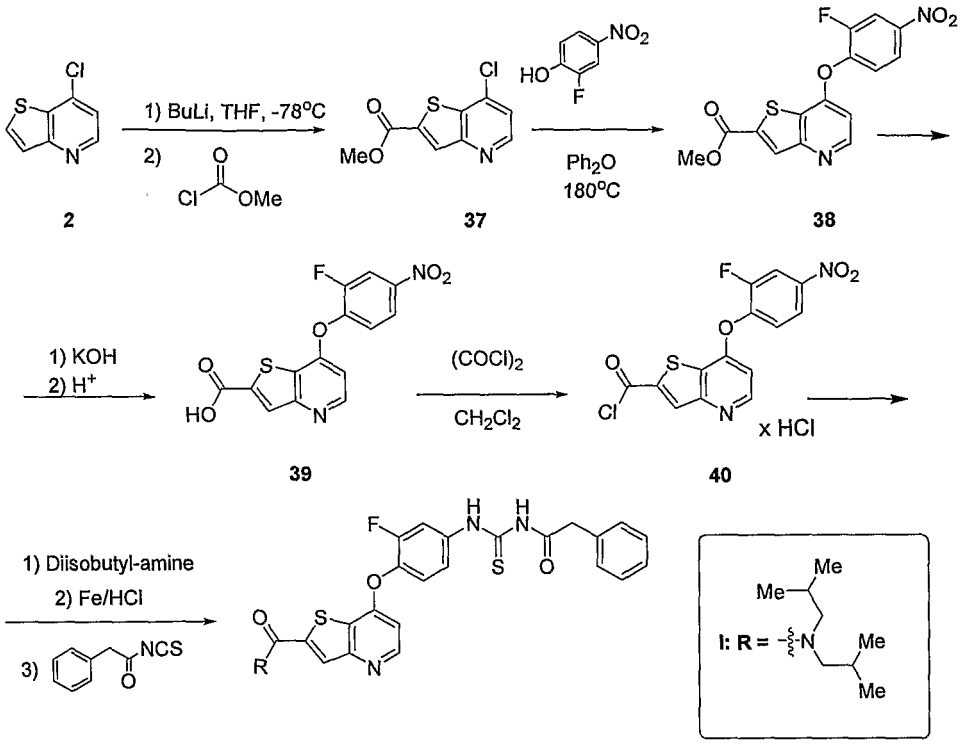
36a-c: Examples 31-33

Table 5

Characterization of 36a-c (examples 31-33)

Cpd	Ex	R	Name	Characterization
36a	**31**	**Me**	1-(4-(7-Methyl-*7H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenyl acetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.43 (s, 1H), 11.79 (s,1H), 8.34 (s, 1H), 7.87 (dd, J=1.8 Hz, J=13.1 Hz, 1H), 7.55 (d, J=3.5 Hz, 1H), 7.44 (m, 2H), 7.33 (m, 4H), 7.27 (m, 1H), 6.62 (d, J=3.5 Hz, 1H), 3.83 (m, 5H). LRMS (M+1) 436.1 (100%).
36b	**32**	**Et**	1-(4-(7-Ethyl-*7H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenyl acetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.41 (br, 1H), 11.78 (br, 1H), 8.32 (s, 1H), 7.87 (m, 1H), 7.63 (d, J=3.5, Hz, 1H), 7.43 (m, 2H), 7.33 (m, 4H), 7.27 (m, 1H), 6.63 (d, J=3.5 Hz, 1H), 4.29 (q, J=7.2 Hz, J=14.5 Hz, 2H), 3.82 (s, 2H), 1.40 (t, J=7.2 Hz, 3H). LRMS (M+1) 450.2 (100%).
36c	**33**	**-CH_2Ph**	1-(4-(7-Benzyl-*7H*-pyrrolo[2,3-*d*]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenyl acetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.41 (s, 1H), 11.79 (s, 1H), 8.35 (s, 1H), 7.87 (m,1H), 7.68 (d, J=3.5 Hz, 1H), 7.44 (m, 2H), 7.35-7.23 (m, 10H), 6.68 (d, 3.5 Hz, 1H), 5.48 (s, 2H), 3.82 (s, 2H). LRMS (M+1) 512.3 (100%).

Scheme 7



8I: Example 34

Example 34

7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-N,N-diisobutylthieno[3,2-b]pyridine-2-carboxamide (8l)

Step 1: Methyl 7-chlorothieno[3,2-*b*]pyridine-2-carboxylate (**37**)

[0281] To a stirred solution of **2** (7.0 g, 41.3 mmol) in anhydrous THF (100 mL) at -78°C under a nitrogen atmosphere was added *n*-BuLi (24.7 mL, 2.5 M in hexanes, 61.8 mmol). After 1 hour, methyl chloroformate (9.6 ml, 124 mmol) was added and the reaction mixture was stirred for an extra hour at the same temperature, quenched with excess methanol and allowed to warm to room temperature. The solvent was then evaporated and the residue was purified by flash chromatography using hexane – AcOEt (70:30) as an eluent. The product from the column was re-crystallized from ethyl acetate to afford title compound **37** (4.3g, 46% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 8.75 (dd, J = 0.8 and 4.8 Hz, 1H), 8.26 (d, J= 0.8 Hz, 1H), 7.74 (dd, J= 0.8 and 5.2 Hz, 1H), 3.93 (s, 3H).

Step 2: Methyl 7-(2-fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridine-2-carboxylate (**38**)

[0282] A mixture of **37** (4.0 g, 17.6 mmol), 2-fluoro-4-nitrophenol (5.5 g, 35.0 mmol) and K_2CO_3 (12.1 g, 87.5 mmol) in Ph_2O was heated at 180°C for 5 hours. The mixture was cooled to room temperature, diluted with EtOAc and washed with water. The organic phase was collected, dried over anhydrous sodium sulfate and the solvents were removed under

reduced pressure. The residue was purified by flash chromatography using hexane – AcOEt (70:30) as an eluent. The product from the column was re-crystallized from a mixture of ethyl acetate-hexanes to afford **38** (3.6 g, 59% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 8.69 (d, J = 5.2 Hz, 1H), 8.47 (dd, J = 2.4 and 10.0 Hz, 1H), 8.27 (s, 1H), 8.21 (m, 1H), 7.77 (dd, J = 8.0 and 9.2 Hz, 1H), 7.06 (dd, J = 0.8 and 5.2 Hz, 1H), 3.93 (s, 3H).

Step 3: 7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridine-2-carboxylic acid (**39**)

[0283] To a stirred solution of **38** (2.5 g, 7.18 mmol) in THF (50 ml) was added KOH (14.3 ml, 1.0 N in H_2O, 14.3 mmol). After 4 hours the reaction mixture was concentrated and the resultant residue was dissolved in H_2O (50 ml). The aqueous layer was then washed with ethyl acetate and acidified with 1N HCl (pH = 1). The precipitate that formed upon acidification was collected by filtration, washed with water and dried under high vacuum to afford title compound **39** (2.3 g, 96% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 8.68 (d, J = 5.2 Hz, 1H), 8.47 (dd, J = 2.8 and 10.4 Hz, 1H), 8.20 (m, 1H), 8.17 (s, 1H), 7.76 (dd, J = 8.0 and 8.8 Hz, 1H), 7.04 (d, J = 5.2 Hz, 1H).

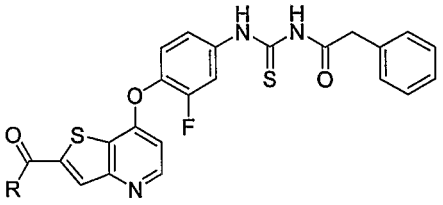
Step 4: 7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridine-2-carbonyl chloride (**40**)

[0284] To a solution of **39** (2.0 g, 5.98 mmol) in anhydrous CH_2Cl_2 (30 ml) under an atmosphere of nitrogen, was added oxalyl chloride (2.6 ml, 29.8 mmol). After stirring for 2 hours the solvent was evaporated, anhydrous toluene (10 mL) was added and the resultant mixture was evaporated (procedure of addition of toluene followed by evaporation was performed twice) to afford title compound **40** (2.2 g, 94% yield) as a white solid. The product was used without further purification and characterization and was assumed to be the mono-HCl salt.

Step 5: 7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-*N,N*-diisobutylthieno[3,2-b]pyridine-2-carboxamide (**8l**)

[0285] To a solution of **40** (150 mg, 0.385 mmol) and TEA (107 µl, 0.771 mmol) in anhydrous CH_2Cl_2 under an atmosphere of nitrogen was added diisobutylamine (67 µL, 0.385 mmol). After stirring for 1 hour, methanol (2 mL) was added followed by iron powder (150 mg) and HCl (conc., 0.4 mL). The reaction mixture was stirred for additional 2 hours and then partitioned between ethyl acetate (20 mL) and a mixture of H_2O (20 mL) and NH_4OH (2 mL). Organic phase was collected, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was treated with 2-phenylacetyl isothiocyanate (102 mg, 0.58 mmol) in THF (2 mL), the resultant mixture was allowed to stand for 2 hours

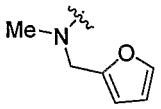
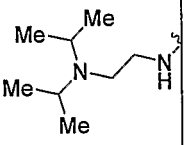
at ambient temperature, quenched with methanol (5.0 mL), loaded onto 5 ml of silica gel and purified by flash chromatography using hexane – AcOEt (70:30) as an eluent, to afford title compound **8l** (41 mg, 18%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 8.54 (d, J = 5.6 Hz, 1H), 8.08 (dd, J = 2.0 and 12.0 Hz, 1H), 7.69 (s, 1H), 7.38 – 7.49 (m, 2H), 7.28 – 7.35 (m, 5H), 6.77 (dd, J = 1.2 and 5.6 Hz, 1H), 3.77 (s, 2H), 3.46 (bs, 4H), 2.18 (bs, 1H), 2.02 (bs, 1H), 1.02 (bs, 6H), 0.87 (bs, 6H). LRMS (M+1):592.7 (calcd), 593.3 (found).

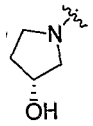
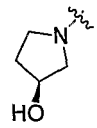
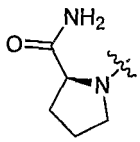
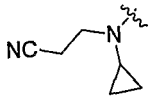


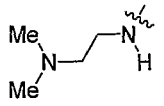
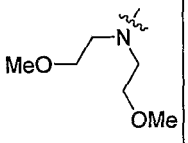
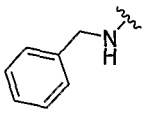
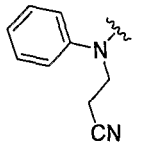
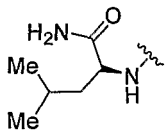
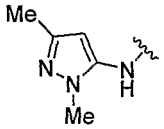
8m-y: Examples 35-47

Table 6

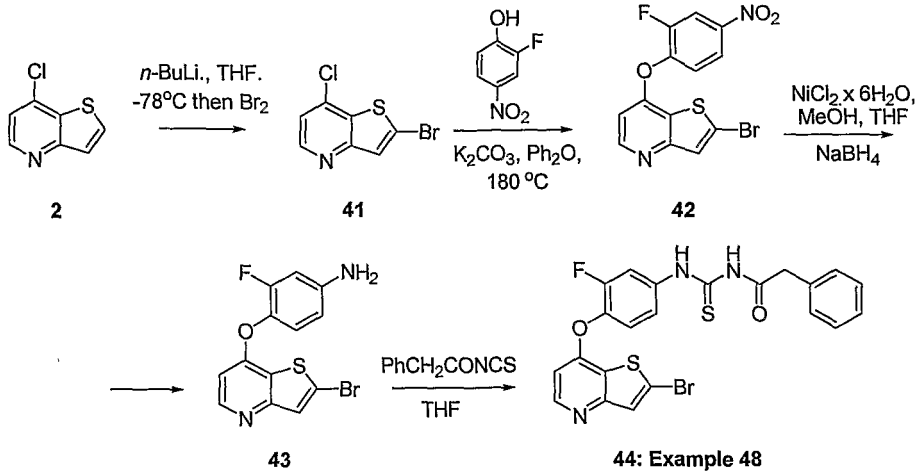
Characterization of compounds 8m-y (examples 35-47)

Cpd	Ex	R	Name	Characterization
8m	**35**		7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-carboxylic acid furan-2-ylmethyl-methyl-amide	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.49 (s, 1H), 11.82 (s, 1H), 8.59 (d, J= 5.6 Hz, 1H), 7.92-8.05 (m, 2H), 7.67 (bs, 1H), 7.54 (m, 2H), 7.25-7.37 (m, 5H), 6.75 (d, J=0.8, 5.2 Hz, 1H), 6.46 (s, 2H), 4.74 (bs, 2H), 3.83 (s, 2H), 3.27 (bs, 1.5H), 2.99 (bs, 1.5H). LRMS (M+1):574.6 (cald), 575.2 (found).
8n	**36**		7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-carboxylic acid (2-diisopropylamino-ethyl)-amide, formate salt	12.45 (s, 1H), 11.78 (s, 1H), 8.92 (t, J = 5.6 Hz, 1H), 8.53 (d, J = 5.6 Hz, 1H), 8.16 (s, 1H), 8.12 (s, 1H), 7.99 (m, 1H), 7.50 (m, 2H), 7.21-7.30 (m, 5H), 6.69 (d, J=5.2 Hz, 1H), 3.79 (s, 2H), 3.22 (m, 2H), 2.97 (m, 2H), 2.55 (t, J=7.6Hz, 2H), 0.964 (d, J=6.4 Hz, 12H). LRMS (M+1) .607.8 (calcd.), 608.3 (found).

Cpd	Ex	R	Name	Characterization
8o	**37**		1-{3-Fluoro-4-[2-(pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-phenyl}-3-phenylacetyl-thiourea	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.48 (s, 1H), 11.82 (s, 1H), 8.58 (d, J = 5.3 Hz, 1H), 8.03 (m, 2H), 8.00 (s, 1H), 7.53 (m, 2H), 7.33 (m, 4H), 7.28 (m, 1H), 6.73 (d, J=5.3 Hz, 1H), 3.86 (t, J =6.4 Hz, 2H), 3.83 (s, 2H), 3.53 (t, J – 6.84 Hz, 2H), 1.95-1.86 (m, 4H). LRMS (M+1) . 534. 6 (calcd.), 535.2 (found).
8p	**38**		(*R*)-N-(3-Fluoro-4-(2-(3-hydroxypyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.48 (s, 1H), 11.81 (s, 1H), 8.59 (d, J = 5.6 Hz, 1H), 8.04 (m, 2H), 7.54 (m, 2H), 7.22-7.34 (m, 5H), 6.74 (d, J=5.2 Hz, 1H), 5.07 (bs, 1H), 4.36 (bd, J=19.6 Hz, 1H), 3.99 (m, 1H), 3.82 (s, 2H), 3.38-3.68 (m, 3H), 1.80-2.06 (m, 2H). MS (m/z): 551.1(M+H) (found).
8q	**39**		(*S*)-*N*-(3-Fluoro-4-(2-(3-hydroxypyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy) phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (DMSO-d_6) δ (ppm): 12.51(s, 1H), 11.84(s, 1H), 8.62(d. 1H, J=5.3Hz), 8.08-8.01(m, 2H), 7.56-7.52(m, 2H), 7.36-7.31(m, 4H), 7.28-7.24(m, 1H), 6.77(d, 1H, J=5.7Hz), 4.38-4.32(m, 1H), 4.00-3.92(m, 1H), 3.81(s, 2H), 3.67-3.55(m, 4H), 2.06-1.83(m, 2H). MS (m/z): 551.1(M+H) (found).
8r	**40**		(S)-1-(7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carbonyl)pyrrolidine-2-carboxamide	LRMS (M+1) 577.6 (calcd.), 578.3 (found).
8s	**41**		7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-carboxylic acid (2-cyano-ethyl)-cyclopropyl-amide	LRMS (M+1): 573.7 (calcd.), 574.2 (found).

Cpd	Ex	R	Name	Characterization
8t	**42**		7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-carboxylic acid (2-dimethylamino-ethyl)-amide, formate salt	LRMS (M+1): 551.7 (cald), 552.2 (found)
8u	**43**		7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-carboxylic acid bis-(2-methoxy-ethyl)-amide	LRMS (M+1): 596.7 (cald), 597.3 (found).
8v	**44**		7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-carboxylic acid benzylamide	LRMS (M+1): 570.7 (calcd), 571.3 (found).
8w	**45**		7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-carboxylic acid (2-cyano-ethyl)-phenyl-amide	LRMS (M+1): 609.7 (calcd.), 610.2 found.
8x	**46**		(R)-N-(1-amino-4-methyl-1-oxopentan-2-yl)-7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carboxamide	LRMS (M+1): 593.6 (calcd), 594.2 (found).
8y	**47**		7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide	LRMS (M+1): 574.6 (calcd), 575.2 (found)

Scheme 8



Example 48

N-(4-(2-Bromothieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (44)

Step 1. 2-Bromo-7-chlorothieno[3,2-b]pyridine (**41**)

[0286] To a stirred solution of the chloride **2** (10.12 g, 5.59 mmol) in dry THF (200 ml) at -78°C was added *n*-BuLi (24 ml, 76.7 mmol, 2.5 M solution in hexanes) and the resultant suspension was stirred for 15 minutes. Bromine (18.9 g, 120 mmol) was added slowly and the reaction mixture was stirred for additional 30 min, quenched with water and diluted with EtOAc. The organic phase was collected, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography (9:1 EtOAc/hexane) afforded title compound **41** (10.5 g, 71% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.62 (d, *J*= 5.09 Hz, 1H), 7.92 (s, 1H), 7.59 (d, *J*= 5.09 Hz, 1H).

Step 2. 2-Bromo-7-(2-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine (**42**)

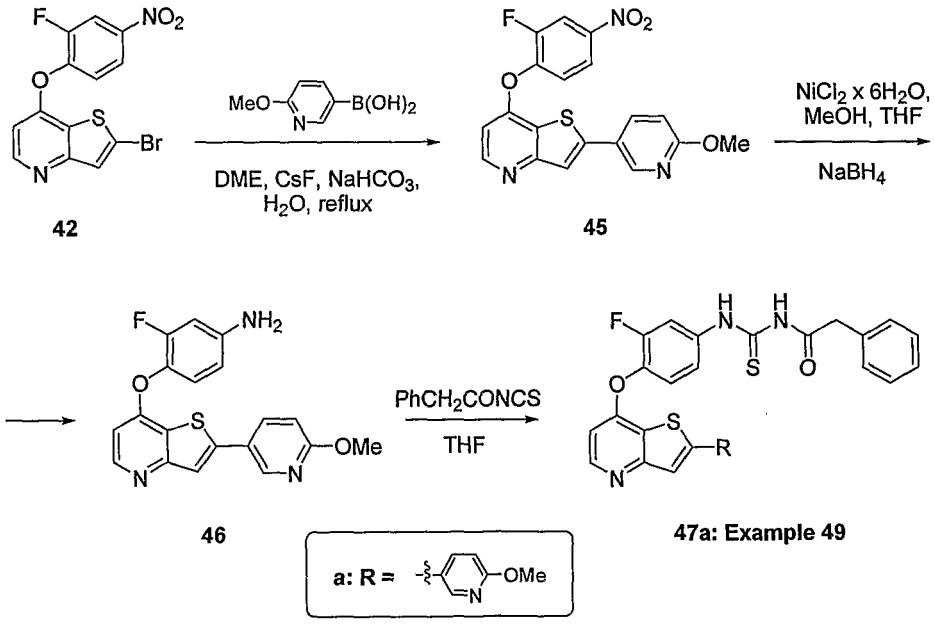
[0287] A mixture of the bromide **41** (5.1 g, 20.5 mmol), potassium carbonate (5.65 g, 4 mmol) and 2-fluoro-4-nitrophenol (4.82 g, 30.7 mmol) was heated at 190°C in diphenyl ether (25 ml) for 3 hrs. After cooling to room temperature it was diluted with DCM and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (eluent EtOAc:hexane, 3:1) to afford title compound **42** as a yellow solid (5.4 g, 71% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.55 (d, *J*= 5.28 Hz, 1H), 8.46 (dd, *J*= 2.5 and 10.4 Hz, 1H), 8.19 (d, *J*= 8.8 Hz, 1H), 7.87 (s, 1H), 7.72 (t, *J* = 8.4 Hz), 6.99 (d, *J*= 5.47 Hz, 1H).

Steps 3 - 4. 1-(4-(2-Bromothieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**44**)

[0288] To a solution of the nitro compound **42** (100 mg, 0.27 mmol) in THF (2 ml) and water (0.5 ml) was added $SnCl_2$ x $2H_2O$ (76.99 mg, 1.5 eq, 0.41 mmol) and the reaction mixture was refluxed for 3 hrs, cooled to room temperature, diluted with EtOAc and washed with conc. ammonium hydroxide solution. EtOAc-extract was collected and the aqueous fractions were combined and washed with DCM. DCM extract was combined with the AcOEt-extract, the mixture was dried over sodium sulfate, filtered and evaporated to form the amine **43** (92 mg, 100%), which was used without any further purification.

[0289] To a solution of the amine **43** (92 mg, 0.27 mmol) in THF (10 ml) was added benzyl isothiocyanate (72 mg, 1.5 eq, 0.407 mmol). The reaction mixture was stirred for 1 hr at room temperature, concentrated under reduced pressure and the residue was purifed by column chromatograpy (7:3 hexane:EtOAc to 1:1 MeOH:EtOAc) to afford the title compound **44** as a white solid (28 mg, 20% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.48 (s, 1H), 11.81 (s, 1H), 8.55 – 8.52 (m, 1H), 8.01 (d, *J*= 11.9 Hz, 1H), 7.85 (s, 1H), 7.55 – 7.49 (m, 2H), 7.45 – 7.19 (m, 5H), 6.73 (d, *J*= 5.7 Hz, 1H), 3.82 (s, 2H). MS (m/z): 518.2 / 520.2 (M+H).

Scheme 9



Example 49

N-(3-Fluoro-4-(2-(6-methoxypyridin-3-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (47a)

Step 1. 7-(2-Fluoro-4-nitrophenoxy)-2-(6-methoxypyridin-3-yl)thieno[3,2-b]pyridine (**45**)

[0290] A mixture of the nitro compound **42** (500 mg, 1.36 mmol), 6-methoxypyridin-3-ylboronic acid (312 mg, 2.04 mmol) and CsF (620 mg, 4.08 mmol) were suspended in DME (12 ml) and $NaHCO_3$ (342 mg, 4.08 mmol), dissolved in the minimum amount of water, was added. The mixture was de-aerated by bubbling N_2 through the solution for 10 min, heated at 80°C for 3 hrs and concentrated to dryness. The formed residue was dissolved in DCM and washed with water. The DCM was collected, dried over sodium sulfate, filtered and the DCM was removed by evaporation. The resultant solid was triturated with Et_2O to afford the title compound **45** (176 mg, 32% yield), which was used without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.71 (m, 1H), 8.56 (m 1H), 8.46 (m, 1H), 8.22 (m,2H), 8.01 (s, 1H), 7.72 (t, J = 8.6 Hz, 1H), 6.99 (d, J= 5.47 Hz, 1H), 6.90 (m, 1H), 3.97 (s, 3H).

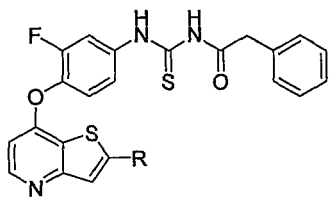
Step 2. *N*-(3-Fluoro-4-(2-(6-methoxypyridin-3-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**47a**)

[0291] To a solution of **45** (176 mg, 0. 44 mmol) in MeOH (10 ml) and THF (10 ml) at 0°C was added $NiCl_2$ x $6H_2O$ (210 mg, 0.89 mmol) and $NaBH_4$ (65 mg, 1.76 mmol). The reaction mixture was stirred for 1 hr, concentrated to dryness and the resultant solid was dissolved in 1 M HCl. The acidic solution was then made basic with aqueous ammonium hydroxide and extracted with EtOAc. The organic phase was collected, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated under reduced pressure and the residue was triturated with Et_2O to afford the amine **46** as a white solid which was used immediately in the next step.

[0292] To a suspension of the amine **46** (162 mg, 0.44 mmol) in THF (7 ml) was added 2-phenylacetyl isothiocyanate (117 mg, 0.66 mmol). The reaction mixture was stirred for 1 hr, concentrated under reduced pressure and the residue was purified by column chromatography (eluent EtOAc-MeOH, 95:5); a solid was obtained which was triturated with Et_2O to afford title compound **47a** (80 mg, 33% yield). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.50 (s, 1H), 11.85 (s, 1H), 8.70 (s, 1H), 8.68 (d, J= 6.07 Hz, 1H), 8.28 (m, 1H), 8.10 (s, 2H), 7.59 (s, 2H), 7.34-7.27 (m, 5H), 7.01 (d, J= 8.61 Hz, 1H), 6.93 (d, J= 5.7 Hz, 1H), 3.93 (s, 3H), 3.83 (s, 2H).

Examples 50-54

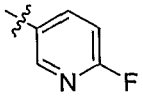
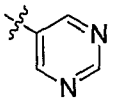
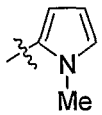
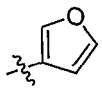
[0293] Examples 50-54 (compounds **47b-f**) were prepared similarly to the compound **47a** (example 49) according to the scheme 9.

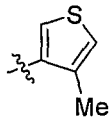


47b-f: Examples 50-54

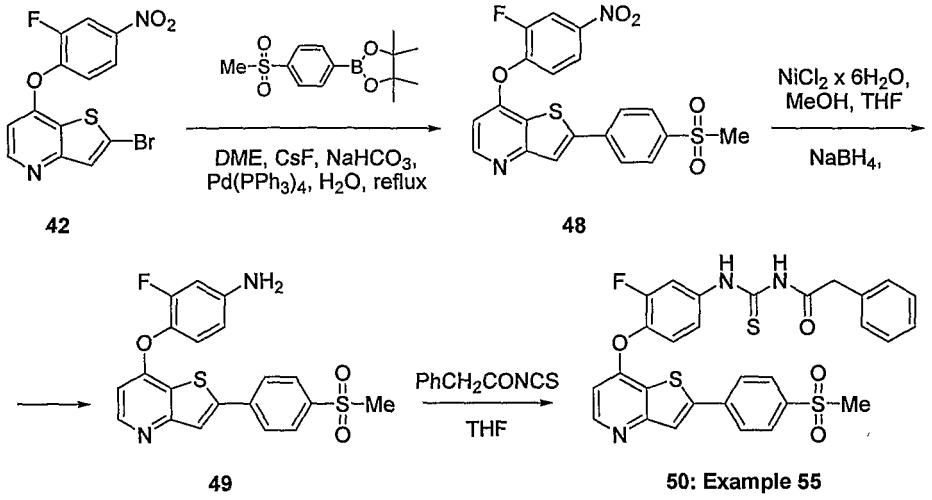
Table 7

Characterization of compounds 47b-f (examples 50-54)

Cpd	Ex	R	Name	Characterization
47b	50		N-(3-Fluoro-4-(2-(6-fluoropyridin-3-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm): 12.46 (s, 1H), 11.82 (s, 1H), 8.79 (m, 1H), 8.55 (d, J = 5.48 Hz, 1H), 8.50 (m, 1H), 8.19 (s, 1H), 8.02 (d, J = 13 Hz, 1H), 7.53 (m, 1H), 7.37-7.26 (m, 6H), 6.68 (m, 1H), 6.68 (m, 1H), 3.82 (s, 2H).
47c	51		N-(3-Fluoro-4-(2-(pyrimidin-5-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide dihydochloride.	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm): 12.48 (s, 1H), 11.83 (s, 1H), 9.2 (bs, 3H) 8.63 (m, 1H), 8.34 (s, 1H), 8.03 (d, J = 11 Hz, 1H), 7.55 (m, 2H), 7.30 (m, 6H), 6.68 (m, 1H), 3.82 (s, 2H).
47d	52		N-(3-Fluoro-4-(2-(1-methyl-1H-pyrrol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 8.46 (d, J = 5.9 Hz, 1H), 8.04 (m, 1H), 7.59 (s, 1H), 7.51 (m, 2H), 7.3 – 7.2 (m, 6H), 7.01 (s, 1H) 6.58 (d, J = 5.9 Hz, 1H), 6.53 (m, 1H), 6.10 (m, 1H), 3.87 (s, 3H), 3.81 (s, 2H).
47e	53		N-(3-Fluoro-4-(2-(furan-3-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	1H NMR (DMSO) δ (ppm): 12.49 (s, 1H), 11.84 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.36 (s, 1H), 8.00 (d, J = 11.3 Hz, 1H), 7.85-7.83 (m, 1H), 7.82 (s, 1H), 7.52-7.51 (m, 2H), 7.34-7.33 (m, 4H), 7.28-7.26 (m, 1H), 7.09 (brs, 1H), 6.62 (d, J = 5.3 Hz, 1H), 3.82 (s, 2H), MS (m/z) 504.0 (M+H)

Cpd	Ex	R	Name	Characterization
47f	54		1-(3-Fluoro-4-(2-(4-methylthiophen-3-yl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (DMSO) δ (ppm): 12.49 (s, 1H), 11.84 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.94 (d, J = 2.7 Hz, 1H), 7.70 (s, 1H), 7.54-7.52 (m, 2H), 7.41-7.40 (m, 1H), 7.35-7.34 (m, 3H), 7.33 (s, 1H), 7.27 (m, 1H), 6.64 (dd, J = 4.7 Hz, 1H), 3.82 (s, 2H), 2.43 (s, 3H), MS (m/z) 534.0 (M+H).

Scheme 10



Example 55

N-(3-Fluoro-4-(2-(4-(methylsulfonyl)phenyl)thieno[3,2-b]pyridin-7-yloxy) phenylcarbamothioyl)-2-phenylacetamide (50)

Step 1. 7-(2-Fluoro-4-nitrophenoxy)-2-(4-(methylsulfonyl)phenyl)thieno[3,2-b]pyridine (**48**)

[0294] To a solution of **42** (461 mg, 1.3 mmol, scheme 8) in DME (4 mL) was added 4,4,5,5-tetramethyl-2-(4-(methylsulfonyl)phenyl)-1,3,2-dioxaborolane (500 mg, 2.5 mmol), CsF (391 mg, 3.8 mmol), $Pd(PPh_3)_4$ (72 mg, 63 μmol) and $NaHCO_3$ (315 mg, 3.8 mmol) pre-dissolved in H_2O (1 ml). The reaction mixture was purged with nitrogen and refluxed for 2 hours. The DME was removed under reduced pressure and the aqueous layer was extracted with EtOAc. The extract was dried over sodium sulphate, filtered and evaporated to form a residue which was purified by column chromatography (eluent EtOAc/hexane, 1:1) to afford the title compound **48** (97 mg, 18% yield) as a white solid. ^{1}HNMR (DMSO) δ (ppm): 8.63 (d, J = 1.2 Hz, 1H), 8.49 (d-d, J = 2.7 Hz, 1H), 8.33 (s, 1H), 8.22-8.19 (m,

2H), 8.16 (s, 2H), 8.02 (d, J = 8.6 Hz, 2H), 7.75 (t, J = 8.0 Hz, 1H), 7.77-7.58 (m, 2H), 7.58-7.50 (m, 2H), 6.97 (d, J = 5.5 Hz, 1H), 3.33 (s, 3H), MS (m/z): 444.8 (M+H).

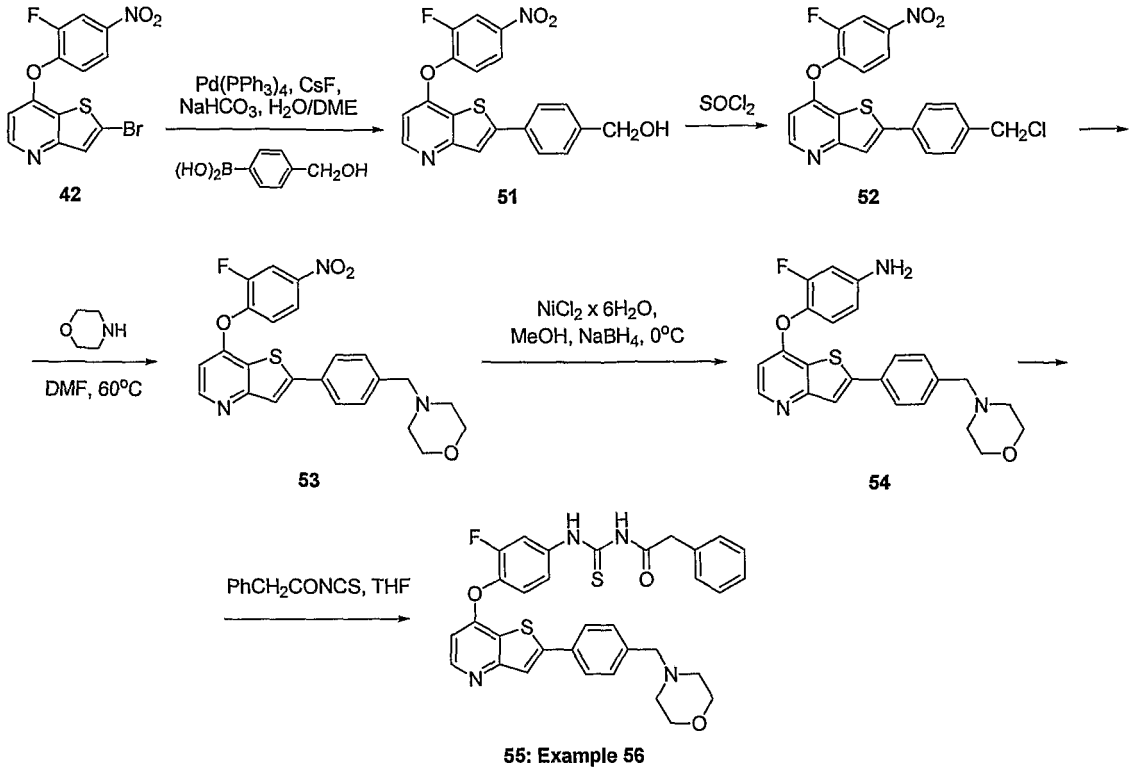
Step 2. 3-Fluoro-4-(2-(4-(methylsulfonyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)benzenamine (**49**)

[0295] Nitro compound **48** (97 mg, 2 mmol) was dissolved in a mixture of THF (7 mL) and MeOH (15 mL); $NiCl_2 . x 6H_2O$ (130 mg, 0.5 mmol) was added and the solution was cooled to 0°C. To the cooled mixture $NaBH_4$ (42 mg, 1.1 mmol) was added portion wise. The reaction was stirred for 20 min and quenched with 2 M HCl. The solvents were removed under reduced pressure and the residue was treated with concentrated ammonium hydroxide solution (pH 10) and extracted with EtOAc. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (eluent EtOAc) to afford the title compound **49** (46.7 mg, 51% yield) as a white solid. ^{1}H NMR (DMSO) δ (ppm): 8.52 (d, J = 5.5 Hz, 1H), 8.25 (s, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.63-7.58 (m, 2H), 7.56-7.52 (m, 2H), 7.13 (t, J = 8.6 Hz, 1H), 6.61 (d, J = 2.2 Hz, 1H), 6.56 (dd, J = 10 Hz, 1H), 6.46 (dd, J = 5.7 Hz, 1H), 5.57 (s, 2H), 3.29 (s, 3H), MS (m/z): 414.8 (M+H).

Step 3. N-(3-Fluoro-4-(2-(4-(methylsulfonyl)phenyl)thieno[3,2-b]pyridin-7-yloxy) phenylcarbamothioyl)-2-phenylacetamide (**50**)

[0296] To a solution of **49** (46.7 mg, 0.1mmol) in dry THF (5 mL), 2-phenylacetyl isothiocyanate (40 mg, 0.2 mmol) was added and the reaction was allowed to stir for 30 minutes. The THF was removed under reduced pressure and the resultant product was purified by column chromatography on silica gel, eluent hexane/EtOAc (1:1), to afford the title compound **50** (35.4 mg, 53% yield). ^{1}HNMR (DMSO) δ (ppm): 12.49 (s, 1H),11.85 (s, 1H), 8.57 (d, J = 5.5 Hz, 1H), 8.30 (s, 1H), 8.17 (d, J = 8.4Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.63-7.52 (m, 5H), 7.34 (d, J = 4.1 Hz, 2H), 6.71 (d, J = 5.3 Hz, 1H), 3.82 (brs, 2H), 3.27 (s, 3H) MS (m/z) 592.0 (M^+).

Scheme 11



Example 56

1-(3-Fluoro-4-(2-(4-(morpholinomethyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea (55)

Step 1. (4-(7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-b]pyridin-2-yl)phenyl)methanol (**51**)

[0297] To a solution of **42** (1.0 g, 2.71 mmol) in dry DME (20 ml) was added 4-(hydroxymethyl)phenylboronic acid (823 mg, 5.4 mmol), $NaHCO_3$ (682 mg, 8.13 mmol), CsF (820 mg, 5.4 mmol) and water (10 mL) and the reaction mixture was refluxed under nitrogen for 2 hrs. After cooling to room temperature the DME was removed under reduced pressure, the residue was dissolved in EtOAc and the organic solution was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated. The resultant solid residue was triturated with Et_2O to afford the title compound **51** as a white solid (880 mg, 82% yield). MS (m/z): 397.1 (M+H).

Step 2. 2-(4-(Chloromethyl)phenyl)-7-(2-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine (**52**)

[0298] The alcohol **51** (880 mg, 2.22 mmol) was suspended in $SOCl_2$ (10 ml) and the reaction mixture was refluxed for 1 hour, cooled and carefully poured onto ice/water. A precipitate was formed which was collected by filtration, washed with additional cold water

and dried under vacuum to afford the title compound **52** (919 mg, 100% yield), which was used without additional purification. MS (m/z): 415.1(100%) (M+H), 417.1 (36%) (M+H).

Step 3. 7-(2-Fluoro-4-nitrophenoxy)-2-(4-(morpholinomethyl)phenyl)thieno[3,2-b]pyridine (**53**)

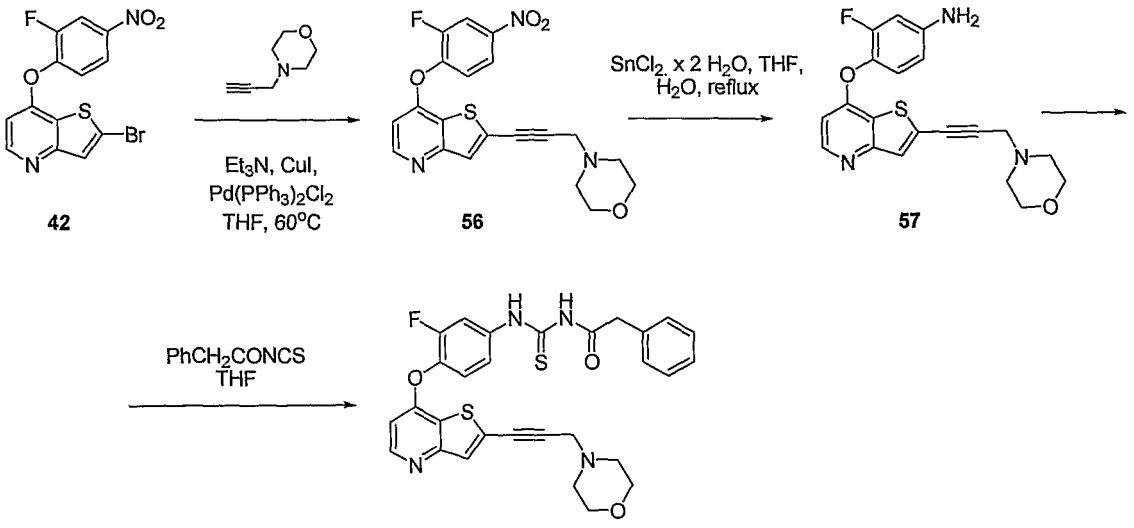
[0299] To a suspension of **52** (823 mg, 1.82 mmol) in DMF (10 ml) was added morpholine (317 mg, 3.65 mmol) and the reaction mixture was heated for 4 hours at 60°C, the solvent was removed under reduced pressure and the residual solid was triturated with EtOAc and collected by filtration. It was further washed with EtOAc until no color was observed in the filtrate, to form the title compound **53** (800 mg, 94% yield), which was used without additional purification. ^{1}HNMR (DMSO) δ (ppm): 8.57 (d, J = 4.7 Hz, 1H), 8.46 (dd, J = 2.7 and 10.4 Hz, 1H), 8.18 (m, 1H), 8.07 (s, 1H), 7.83 (d, J = 12.2 Hz, 1H), 7.71 (t, J = 8.02 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 5.3 Hz, 1H), 3.56 (m, 4H), 3.51 (m, 2H), 3.33 (m, 2H), 2.50 (m, 2H).

Step 4. 1-(3-Fluoro-4-(2-(4-(morpholinomethyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea (**55**)

[0300] To a solution of **53** (1.1 g, 2.37 mmol) in MeOH (20 mL) and THF (20 mL) at 0°C was added $NiCl_2$ x $6H_2O$ (1.12 g, 4.73 mmol) and $NaBH_4$ (350 mg, 9.48 mmol). The reaction mixture was allowed to stir for 1 hr, solvents were removed under reduced pressure and the resultant solid residue was dissolved in 1 M HCl. This solution was made basic with concentrated aqueous ammonium hydroxide and extracted with EtOAc. The organic phase was collected, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated under reduced pressure and the resultant solid was triturated with Et_2O to afford the amine **54** as a white solid (1.02 g, 100% yield), which was used in the next step without further purification.

[0301] To a suspension of the amine **54** (1.02 g, 2.34 mmol) in THF (10 mL) was added 2-phenylacetyl isothiocyanate (622 mg, 3.52 mmol) and the reaction mixture was stirred for 1 hr at room temperature, concentrated under reduced pressure and purified by column chromatograpy (eluent EtOAc:MeOH, 95:5) to afford title compound **55** as a yellow powder (288 mg, 12% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.48 (s, 1H), 11.84 (s, 1H), 8.63 (m, 1H), 8.18 (s, 1H), 8.01 (d, J = 7.8 Hz, 2H), 7.75 (m, 2H), 7.57 (s, 2H), 7.33 (m, 4H), 6.80 (d, J= 11.7 Hz, 2H), 3.83 (s, 5H), 3.37 (d, J = 11.7 Hz, 2H), 3.12 (m, 2H). MS (m/z) 613.3 (M+H).

Scheme 12



58: Example 57

Example 57

1-(3-Fluoro-4-(2-(3-morpholinoprop-1-ynyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea (58)

Step 1. 7-(2-Fluoro-4-nitrophenoxy)-2-(3-morpholinoprop-1-ynyl)thieno[3,2-b]pyridine (**56**)

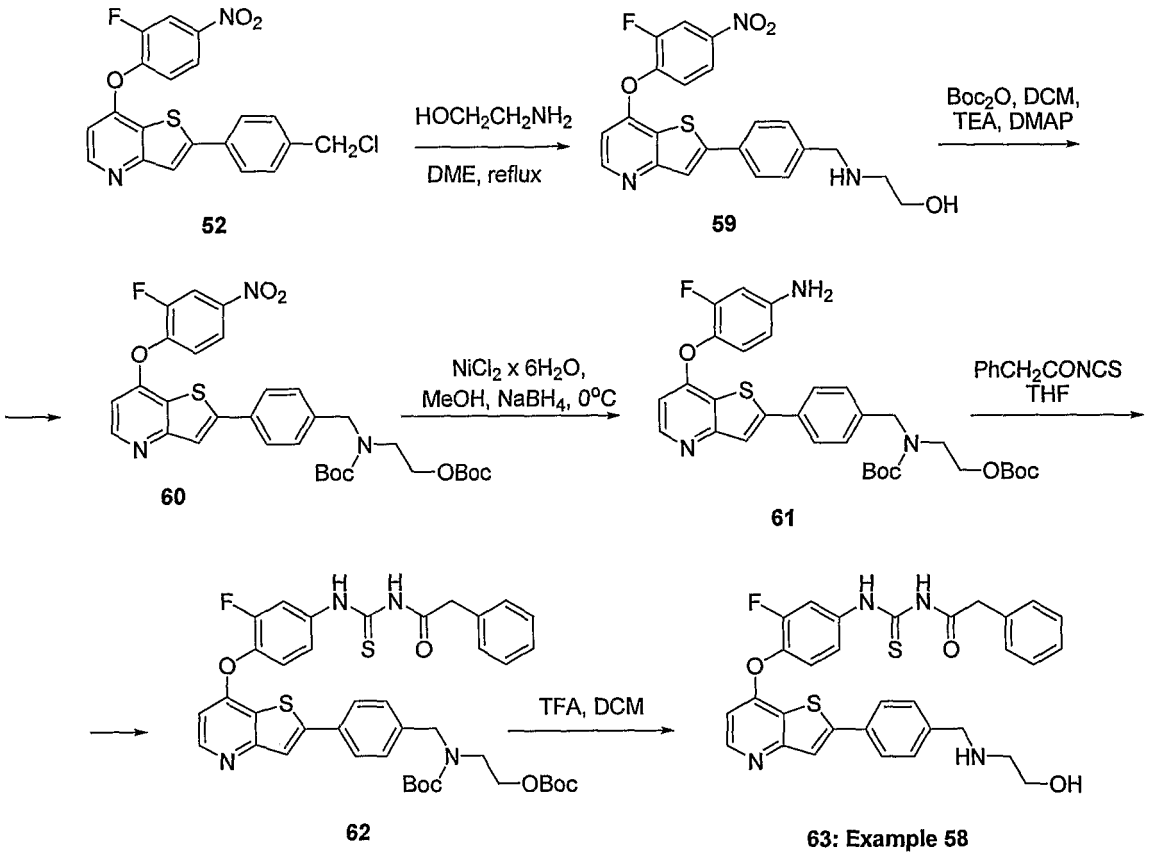
[0302] To a solution of bromide **42** (100 mg, 0.27 mmol) in THF (5 ml) was added 4-(prop-2-ynyl)morpholine (68 mg, 0.54 mmol) [H-W. Tsou, et. al. *J. Med. Chem.*, **2001**, *44*, 2719-2734], triethylamine (68 mg, 0.67mmol), CuI (5 mg, 0.03 mmol) and $Pd(PPh_3)_2Cl_2$ (5.3 mg, 7.56 μmol). The reaction mixture was degassed with nitrogen and refluxed for 2 hrs, cooled to room temperature and adsorbed onto silica. Purification by column chromatography (eluent EtOAc) afforded the title compound **56** as a beige solid (88 mg, 79%). MS (m/z): 397.1 (M+H).

Steps 2-3. 1-(3-Fluoro-4-(2-(3-morpholinoprop-1-ynyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea (**58**)

[0303] To a solution of the nitro compound **56** (300 mg, 0.724 mmol) in THF (10 mL) and NH_4Cl (6 mL) was added $SnCl_2$ x $2H_2O$ (489 mg, 2.17 mmol) and the reaction mixture was refluxed for 3 hrs. After cooling the mixture was diluted with EtOAc and washed with concentrated aqueous ammonium hydroxide. EtOAc phase was separated and the aqueous phase was extracted with DCM. Both EtOAc phase and DCM extract were combined, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated to dryness to afford the amine **57** (277 mg, 100% yield), which was used without further purification.

[0304] To a solution of the amine **57** (270 mg, 0.74 mmol) in THF (10 mL) was added 2-phenylacetyl isothiocyanate (188 mg, 1.06 mmol) and the reaction mixture was stirred for 1 hr, concentrated under reduced pressure and purified by column chromatography (eluent EtOAc) to afford title compound **58** (37 mg, 10% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.47 (s, 1H), 11.82 (s, 1H), 8.55 (d, J= 5.3 Hz, 1H), 8.01 (d, J= 13.2 Hz, 1H), 7.79 (s, 1H), 7.52 (s, 1H), 7.33 (m, 4H), 7.28 (m, 1H), 6.72 (d, J= 5.3 Hz, 1H), 3.82 (s, 2H), 3.64 (s, 2H), 3.61 (m, 5H), 2.51 (m, 4H). MS (m/z): 561.3 (M+H).

Scheme 13



Example 58

2-((4-(7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-b]pyridin-2-yl)phenyl)methylamino) ethanol (63)

Step 1. 2-{4-[7-(2-Fluoro-4-nitro-phenoxy)-thieno[3,2-b]pyridin-2-yl]-benzylamino}-ethanol (**59**)

[0305] To a suspension of the chloride **52** (500 mg, 1.1 mmol) in DME (10 mL) was added ethanolamine (336 mg, 5.5 mmol). The reaction mixture refluxed for 2 hrs, the solvent was removed under reduced pressure; the residue was dissolved in EtOAc and

washed with water. The organic phase was collected, dried over sodium sulfate, filtered and evaporated. The remaining solid was triturated with Et_2O to afford the title compound **59** as a yellow solid (200 mg, 41% yield). ^1H NMR (DMSO) δ (ppm): 8.57 (d, J = 5.5 Hz, 1H), 8.47 (dd, J = 2.7 and 10.4 Hz, 1H), 8.21 (m, 1H), 8.17 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 5.5 Hz, 1H), 4.48 (t, J = 5.5 Hz, 1H), 3.75 (s, 2H), 3.45 (q, J = 5.6 Hz, 2H), 3.33 (m, 1H), 3.15 (d, J = 5.1 Hz, 2H), 2.56 (t, J = 5.7 Hz, 2H).

Step 2. Carbonic acid 2-(*tert*-butoxycarbonyl-{4-[7-(2-fluoro-4-nitro-phenoxy)-thieno[3,2-b]pyridin-2-yl]-benzyl}-amino)-ethyl ester *tert*-butyl ester (**60**)

[0306] To a solution of **59** (200 mg, 0.45 mmol) in DCM (7 mL) at room temperature was added triethylamine (188 mg, 1.82 mmol), DMAP (cat) and Boc_2O (355 mg, 1.82 mmol). The reaction mixture was stirred at room temperature overnight, the DCM was removed under reduced pressure and the residue was dissolved in EtOAc, washed sequentially with dilute HCl solution, saturated $NaHCO_3$ and brine, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated and the residue was purified by column chromatography (eluent EtOAc:hexane, 3:7) to afford title compound **60** (200 mg, 69% yield) as a yellow oil. ^1H NMR (DMSO) δ (ppm): 8.58 (d, J = 5.3 Hz, 1H), 8.47 (dd, J = 2.7 and 10.3 Hz, 1H), 8.21 (m, 1H), 8.09 (s, 1H), 7.87 (m, 2H), 7.72 (t, J = 8.4 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 5.3 Hz, 1H), 4.44 (s, 2H), 4.07 (t, J = 5.5 Hz, 2H), 3.40 (m, 2H), 1.36 (m, 18H).

Steps 3-4. Carbonic acid 2-[*tert*-butoxycarbonyl-(4-{7-[2-fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridin-2-yl}-benzyl)-amino]-ethyl ester *tert*-butyl ester (**62**)

[0307] To a solution of **60** (500 mg, 1.1 mmol) in MeOH (10 mL) at 0°C was added $NiCl_2$ x $6H_2O$ (148 mg, 0.63 mmol) and $NaBH_4$ (46 mg, 1.24 mmol). The reaction mixture was allowed to stir for 1 hr, concentrated to dryness and the resultant solid was dissolved in 1 M HCl. The acidic solution was then made basic with concentrated ammonium hydroxide solution and extracted with EtOAc. The organic phase was collected, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated under reduced pressure and the resultant solid was triturated with Et_2O to afford the crude amine **61** as a white solid (190 mg, 100% yield), which was used for the next step without characterization and additional purification.

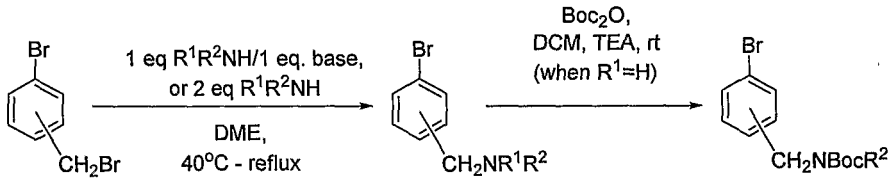
[0308] To a suspension of the amine **61** (190 g, 0.31 mmol) in THF (7 mL) was added 2-phenylacetyl isothiocyanate (118 mg, 0.62 mmol) and the reaction mixture was stirred for

1 hr at room temperature, concentrated under reduced pressure and purified by column chromatography (eluent EtOAc-MeOH, 6:4) to afford title compound **62** as a yellow powder (190 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.48 (s, 1H), 11.83 (s, 1H), 8.51 (s, 1H), 8.04 (s, 1H), 8.01 (d, J = 11.7 Hz, 1H), 7.86 (d, J = 7.7 Hz, 2H), 7.52 (m, 2H), 7.34 (m, 6H), 7.32 (m, 1H), 6.64 (d, J= 5.5 Hz, 1H), 4.43 (s, 2H), 4.07 (t, J = 5.3 Hz, 2H), 3.81 (s, 2H), 3.44 (m, 2H), 1.37 (m, 18H).

Step 5. 1-(3-Fluoro-4-(2-(4-((2-hydroxyethylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea (**63**)

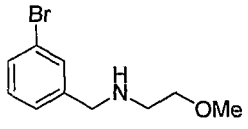
[0309] To a solution of 62 in DCM (190 mg, 0.24 mmol) was added TFA (excess) at room temperature and the reaction mixture was stirred for 3 hrs, evaporated under reduced pressure and the residual solid was triturated with Et_2O to afford the title compound **63** as the di-TFA salt (100 mg, 51% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.49 (s, 1H), 11.84 (s, 1H), 8.89 (s, 1H), 8.53 (d, J = 5.1 Hz, 1H), 8.14 (s, 1H), 8.01 (m, 1H), 7.62 (dd, J = 2.5 and 7.7 Hz, 2H), 7.54 (d, J = 2.7 Hz, 2H), 7.33 (m, 4H), 7.28 (m, 1H), 6.67 (d, J= 5.5 Hz, 1H), 4.64 (m, 1H), 4.30 (m, 1H), 4.22 (t, J = 5.3 Hz, 2H), 3.82 (s, 2H), 3.63 (t, J = 5.3 Hz, 2H), 2.98 (m, 1H). MS (m/z) 587.0 (M+H).

Scheme 14



Substituted aryl bromides (compounds 64-71)

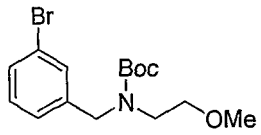
N-(3-Bromobenzyl)-2-methoxyethanamine (**64**)



64

[0310] To a solution of 2-methoxyethanamine (900 mg, 12 mmol) in DME (15 mL) was added 3-bromobenzylbromide (2.5 g, 10 mmol) and the reaction mixutre was stirred at 40°C (scheme 14). After 30 minutes, Et_3N (1.01 g, 10 mmol) was added and the reaction was allowed to stir for another 10 minutes, filtered and the filtrate was concentrated to afford bromide **64** as a colorless oil (2.0 g, 80% yield). MS (m/z): 244.1 / 246.1 (M+H).

tert-Butyl 3-bromobenzyl(2-methoxyethyl)carbamate (**65**)

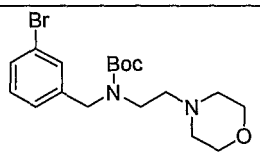
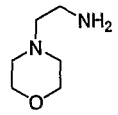
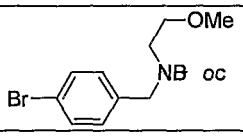
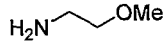
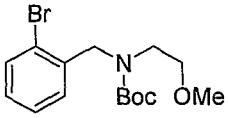
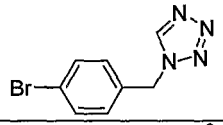
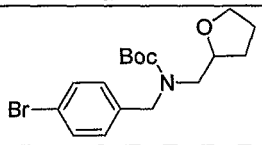
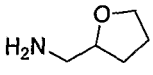


65

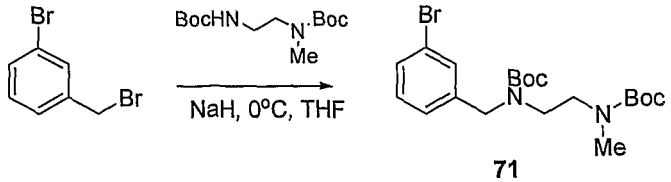
[0311] To a solution of compound **64** (997 mg, 4 mmol) in CH_2Cl_2 (12 mL), di-*tert*-butylcarbonate (1.8 g, 8 mmol) was added and the reaction mixture was stirred for 3 hrs (scheme 14). DMAP (cat.) was added to the solution and the reaction mixture was allowed to stir for additional 76 hours. Solvent was removed under reduced pressure and the crude product was purified by column chromatography, eluent EtOAc/hexane (1:10) to afford the title compound **65** (778 mg, 56% yield) as a colorless oil. MS (m/z): 368.1 / 370.1 (M+Na).

Table 8

Aryl bromides 66-70 prepared according to the scheme 14

Cpd	Aryl bromide	Chemical name	Characterization MS (m/z)	Amine reagent used to obtain the aryl bromides
66		*tert*-Butyl 3-bromobenzyl(2-morpholinoethyl)carbamate	399.1 / 401.1 (M+H)	
67		*tert*-Butyl 4-bromobenzyl(2-methoxyethyl)carbamate	344.1 / 346.1 (M+H)	
68		*tert*-Butyl 2-bromobenzyl(2-methoxyethyl)carbamate	365.9 / 367.9 (M+Na)	
69		1-(4-Bromobenzyl)-1*H*-tetrazole	238.9 / 240.9 (M+H)	
70		*tert*-Butyl 4-bromobenzyl((tetrahydrofuran-2-yl)methyl)carbamate	370.1 / 372.1 (M+H)	

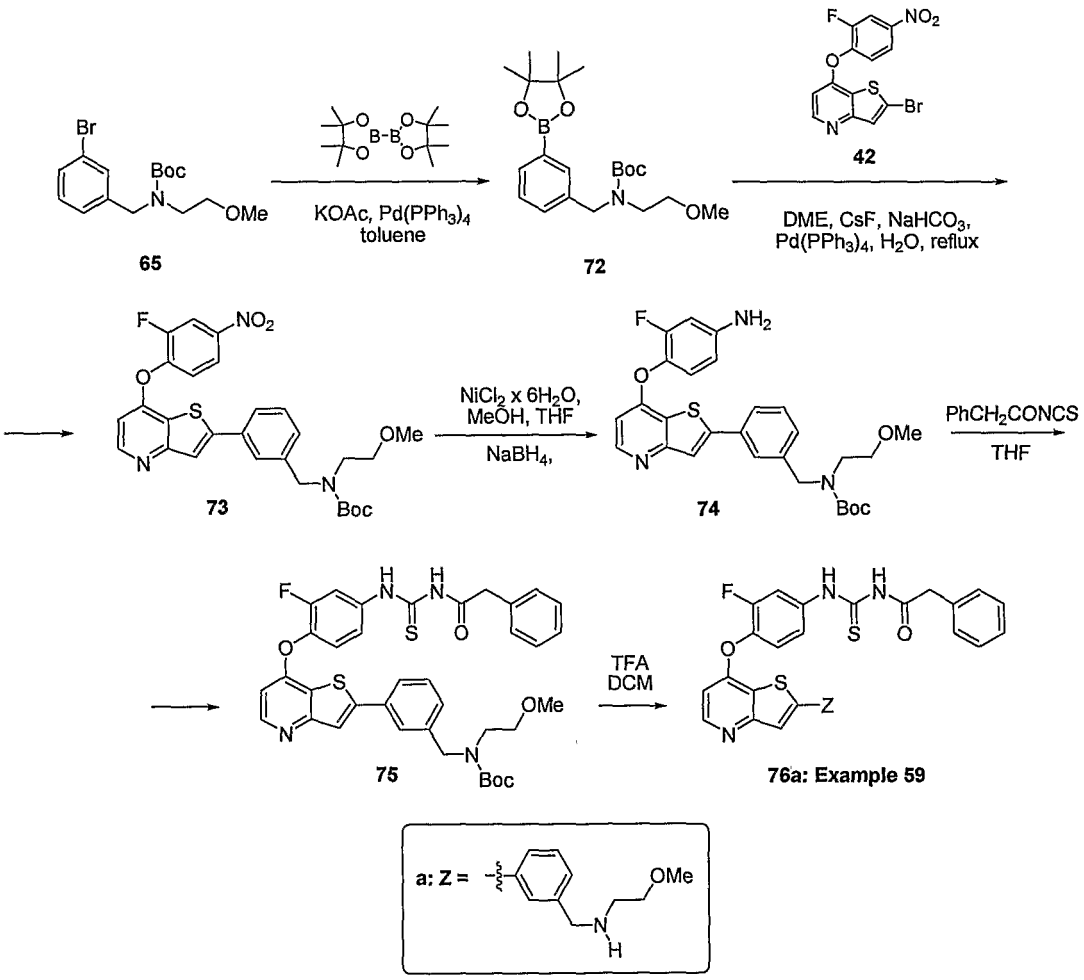
bis-*tert*-Butyl 2-(3-bromobenzylamino)ethyl(methyl)carbamate (**71**)



71

[0312] To a solution of tert-butyl 2-tert-butyloxycarbonylaminoethyl(methyl)carbamate (600 mg, 2.2 mmol) in dry THF (5 mL) at 0^0C, was added NaH (91 mg, 3.8 mmol) and the reaction was stired for 30 minutes. 3- Bromobenzylbromide was added and the reaction was refluxed for 3 hours, cooled to room temperature and poured into MeOH. Solvents were removed under reduced pressure and the product was partitioned between EtOAc and water. Organic phase was collected and dried over anhydrous sodium sulphate, filtered and evaporated. The crude product was purified by column chromatography on silica gel, eluent EtOAc/hexane (1:5), to afford the title compound **71** (672 mg, 80% yield) as a colourless oil. MS (m/z): 343.0/345.0 (M-Boc).

Scheme 15



Example 59

N-(3-Fluoro-4-(2-(3-((2-methoxyethylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (76a)

Step 1. *tert*-Butyl 2-methoxyethyl(3-(pinacolatoborolan-2-yl)benzyl)carbamate (**72**)

[0313] To a solution of bromide **65** (778 mg, 2.3 mmol), in dry toluene (12 mL), was added the bis(pinacolato)diboron (872 mg, 3.4 mmol), KOAc (677 mg, 6.9 mmol) and $Pd(PPh_3)_4$ (80 mg, 69 μmol). The reaction mixture was purged with nitrogen, refluxed for 2 hours and was allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue was partitioned between DCM and water (30mL/30mL). The organic phase was collected and dried over anhydrous sodium sulphate, filtered and evaporated.The remained solid was purified by column chromatography, eluent EtOAc/hexane (1:10) to afford title compound **72** (577 mg, 64% yield) as a colorless oil. ^{1}H NMR (DMSO) δ (ppm): 7.54-7.52 (m, 2H), 7.33-7.31 (m, 2H), 4.39 (s, 2H), 3.40-3.35 (m, 2H), 3.33-3.25 (m, 2H), 3.20 (s, 3H), 1.43-1.32 (m, 9H), 1.28 (s, 12H).

Step 2. *tert*-Butyl 3-(7-(2-fluoro-4-nitrophenoxy)thieno{3,2-b}pyridine-2-yl)benzyl(2-methoxyethyl)carbamate (**73**)

[0314] To a solution of the bromo-nitro compound **42** (272 mg, 0.7 mmol) in DME (4mL), was added pinacolate **72** (578 mg, 1.5 mmol), CsF (226 mg, 2.2 mmol), $Pd(PPh_3)_4$ (43 mg, 37 μmol) and $NaHCO_3$ (186 mg, 2.2 mmol) pre-dissolved in water (2mL). The reaction mixture was purged with nitrogen, refluxed for 1 hour, cooled to room temperature and the solvent was removed under reduced pressure. The residue was extracted with EtOAc, the extract was dried over anhydrous sodium sulfate, filtered and concentrated to produce a brown oil which was purified by chromatography on silica gel, eluent EtOAc, to afford the title compound **73** (347 mg, 85% yield) as a white solid. ^{1}H NMR (DMSO) δ (ppm): 8.60 (d, J = 5.3 Hz, 1H), 8.47 (d-d, J = 7.6 Hz, 1H), 8.19 (d, J = 6.5 Hz, 1H), 8.07 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.73-7.69 (m, 2H), 7.48 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 6.95 (d, J = 5.5 Hz, 1H), 4.48 (s, 2H), 3.21 (s,3H), 2.50 (q, J = 2.2 Hz, 4H), 1.44-1.33 (m, 9H), MS (m/z): 554.0 (M+H).

Step 3. *tert*-Butyl 3-(7-(4-amino-2-fluorophenoxy)thieno[3,2-b]pyridin-2-yl)benzyl(2-methoxyethyl)carbamate (**74**)

[0315] To a solution of **73** (347 mg, 0.6 mmol) in THF (4 mL) and MeOH (2 mL), $NiCl_2$ (372 mg, 1.6 mmol) was added and the solution was cooled to 0°C. $NaBH_4$ (95 mg, 2.5 mmol) was added portion wise. After 20 minutes, the reaction was treated with 2 M HCl and solvents were removed under reduced pressure. The concentrated mixture was basified

to pH 10 with ammonium hydroxide solution and the mixture was extracted with EtOAc, the extract was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by silica gel column chromatography, eluent EtOAc, to afford the title compound **74** (235 mg, 72% yield) as a white solid. ^{1}H NMR (DMSO) δ (ppm): 8.47 (d, J = 5.6 Hz, 1H), 7.97 (s, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.70 (s, 1H), 7.48 (t, J = 7.6 Hz, 1H), 6.56-6.51 (m, 2H), 6.44 (dd, J = 6.3 Hz, 1H), 5.54 (s, 2H), 4.84 (s, 2H), 3.43 (s, 2H), 3.23 (s, 3H), 2.50 (q, J = 2.2 Hz, 4H), 1.46-1.35 (m, 9H).

Step 4. *tert*-Butyl 3-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)benzyl(2-methoxyethyl)carbamate (**75**)

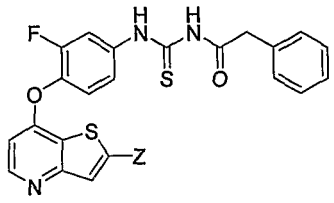
[0316] To a solution of **74** (235 mg, 0.5 mmol) in dry THF (5 mL), 2-phenylacetyl isothiocyanate (159 mg, 0.9 mmol) was added and the reaction was allowed to stir for 30 min. The solvent was removed under reduced pressure and the resulting product was purified by chromatography on silica gel using EtOAc/hexane (1:1) as eluting system to give the desired product (440 mg, 90%) as a white solid. ^{1}H NMR (DMSO) δ (ppm): 8.52 (d, J = 5.3 Hz, 1H), 8.01 (t, J = 6.5 Hz, 2H), 7.79 (d, J = 7.4 Hz, 1H), 7.70 (s, 1H), 7.53-7.52 (m, 2H), 7.47 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 4.5 Hz, 4H), 7.30-7.24 (m, 2H), 6.67 (d, J = 5.3 Hz, 1H), 4.49 (s, 2H), 3.83 (s, 2H), 3.42 (s, 2H), 3.22 (s, 3H), 2.50 (q, J = 2.2 Hz, 4H), 1.45-1.33 (m, 9H).

Step 5. *N*-(3-Fluoro-4-(2-(3-((2-methoxyethylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**76a**)

[0317] To a solution of **75** (440 mg, 0.6 mmol) in DCM (10 mL), TFA (145 µL, 1.9 mmol) was added and the reaction was stirred for 12 hours, concentrated under reduced pressure, and the residue was purified by silica gel column chromatography, eluent MeOH/EtOAc (1:10), to afford the title compound **76a** (227 mg, 63% yield) as a light yellow solid. ^{1}H NMR (DMSO) δ (ppm): 8.54 (d, J = 5.5 Hz, 1H), 8.07 (s, 1H), 8.02-8.0 (m, 2H), 7.93 (d-t, J = 2.0 Hz, 1H), 7.55-7.53 (m, 4H), 7.34-7.32 (m, 4H), 7.29-7.26 (m, 1H), 6.68 (d, J = 5.3 Hz, 1H),4.19 (s, 2H), 3.81 (s, 1H), 3.57 (t, J = 4.9 Hz, 2H), 3.33 (s, 2H), 3.29 (s, 3H), 3.08 (t, J = 4.9 Hz, 2H), 2.84 (q, J = 2.2 Hz, 4H).

Examples 60-65

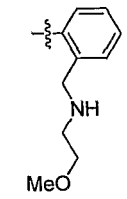
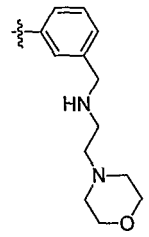
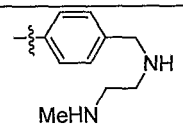
[0318] Compounds **76b-g** (examples 60-65) were synthesized similarly to the compound **76a** (example 59) according to the schemes 14-15, starting from bromides **66-69** and **71.** Characterization of **76b-g** is provided in Table 8a.

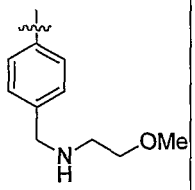
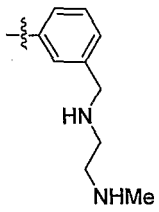
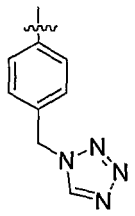


76b-g: Examples 60-65

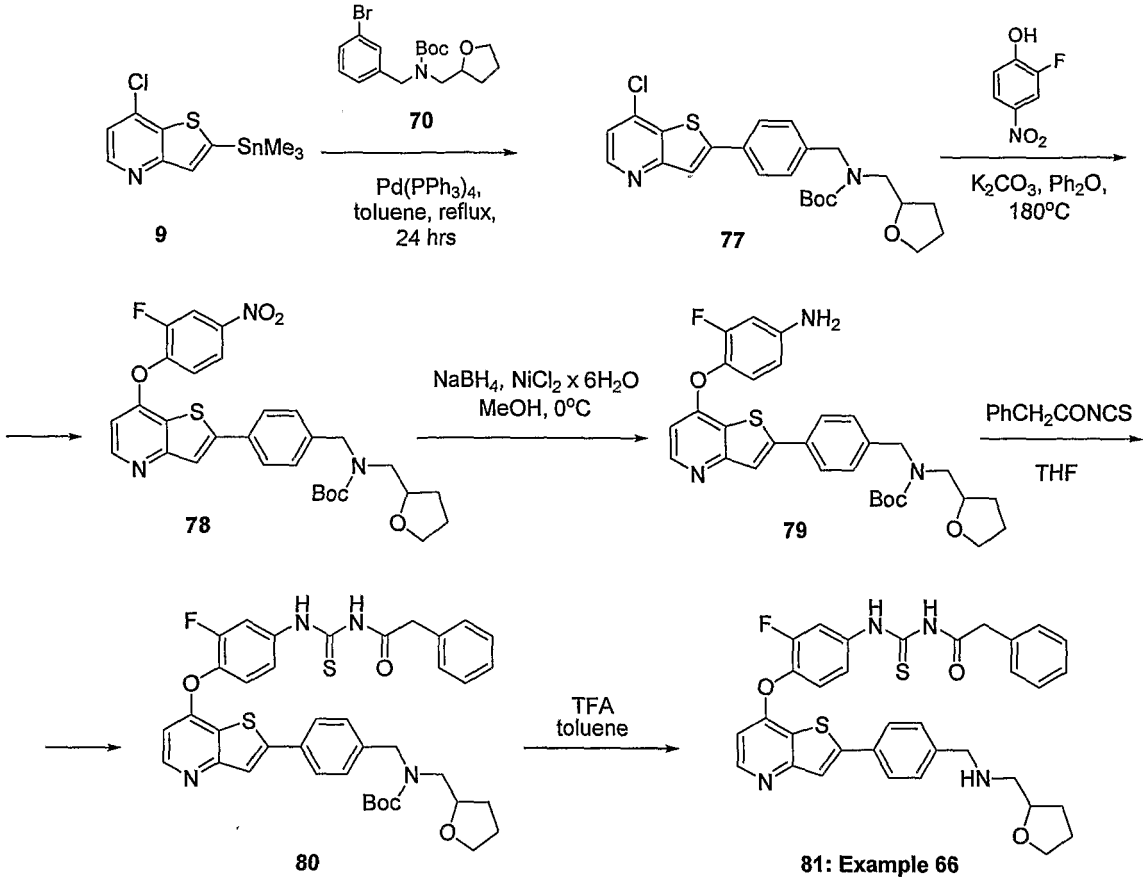
Table 8a

Characterization of compounds 76b-g (examples 60-65)

Cpd	Ex	Z	Chemical name	Characterization
76 b	60		1-(3-Fluoro-4-(2-(2-((2-methoxyethylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (400MHz, DMSO-d_6) δ ppm): 12.50 (s, 1H), 11.83 (s, 1H), 8.57 (d, J = 5.5 Hz, 1H), 8.03-8.00 (m, 1H), 7.76-7.74 (m, 2H), 7.61-7.50 (m, 5H), 7.36-7.25 (m, 5H), 6.70 (d, J = 5.3 Hz, 1H), 4.32 (s, 2H), 3.81 (s, 2H), 3.52 (t, J = 5.1 Hz, 2H), 3.16 (s, 3H), 3.08 (t, J = 4.7 Hz, 2H), MS (m/z): 601.0 (M+H).
76c	61		1-(3-Fluoro-4-(2-(3-((2-morpholinoethylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (400MHz, DMSO-d6) δ (ppm): 12.49 (s, 1H), 11.85 (s, 1H), 8.56 (d, J = 5.1 Hz, 1H), 8.09-7.98 (m, 5H), 7.61-7.55 (m, 5H), 7.33 (s, 1H), 7.27 (brs, 2H), 6.70 (d, J = 5.1 Hz, 1H), 4.30 (brs, 2H), 3.82 (brs, 2H), 3.73 (brs, 4H), MS (m/z) 656.2 (M+H).
76 d	62		N-(3-Fluoro-4-(2-(4-((2-(methylamino)ethylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	1H NMR (DMSO): 12.49 (s, 1H), 11.84 (s, 1H), 8.51 (d, J=5.5 Hz), 8.04-7.99 (m, 2H), 7.87 (d, J=7.6 Hz, 2H), 7.54-7.53 (m, 2H), 7.34-7.33 (m, 5H), 7.29-7.22 (m, 2H), 6.64 (d, J=5.5 Hz, 1H), 4.42-4.39 (m, 2H), 3.82 (s, 2H), 3.29 (brs, 2H), 3.23 (brs, 3H), 2.78-2.76 (m, 2H), MS: calcd 599.74, found 800.1 (M+H).

Cpd	Ex	Z	Chemical name	Characterization
76e	63		1-(3-Fluoro-4-(2-(4-((2-methoxyethylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (400MHz, DMSO-d_6) δ ppm): 12.48 (s, 1H), 11.83 (s, 1H), 9.02 (s, 2H), 8.54 (d, J = 5.5 Hz, 1H), 8.13 (s, 1H), 8.02 (d, J = 13.3 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.53 (m, 2H), 7.33 (m, 4H), 7.28 (m, 2H), 6.67 (d, J = 5.5 Hz, 1H), 4.22 (m, 2H), 3.83 (s, 2H), 3.59 (t, J = 4.9 Hz, 2H), 3.31 (s, 3H), 3.12 (m, 2H), MS (m/z): 601.2 (M+H).
76f	64		1-(3-Fluoro-4-(2-(3-((2-(methylamino)ethylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (DMSO) δ (ppm): 12.49 (s, 1H), 11.85 (s, 1H), 8.55 (d, J = 5.09 Hz, 1H), 8.08 (s, 1H), 8.04 (brs, 1H), 8.00-7.97 (m, 2H), 7.62-7.53 (m, 4H), 7.36-7.32 (m, 4H), 7.29-7.26 (m, 1H), 6.69 (d, J = 5.5 Hz, 1H), 4.31 (brs, 2H), 3.82 (s, 2H), 3.31-3.27 (m, 4H), 2.63 (s, 3H), MS (m/z) 600.2 (M+H).
76g	65		1-(4-(2-(4-((1H-Tetrazol-1-yl)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (DMSO) δ (ppm): 12.46 (s, 1H), 11.82 (s, 1H), 9.54 (s,1H), 8.51 (dd, J = 1.1 and 5.09 Hz, 1H), 8.1 (s, 1H), 7.96 (d, J = 23.3 Hz, 1H), 7.90 (d, J = 6.7 Hz, 2H), 7.53 (m, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.32 (m, 4H), 7.26 (m, 1H), 6.65 (d, J = 5.5 Hz, 1H), 5.78 (s, 2H), 3.82 (s, 2H). MS (m/z) 596.1 (M+H).

Scheme 16



Example 66

1-(3-Fluoro-4-(2-(4-(((tetrahydrofuran-2-yl)methylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea (81)

Step 1. *tert*-Butyl(4-(7-chlorothieno[3,2-b]pyridin-2-yl)phenyl)methyl((tetrahydrofuran-2-yl) methyl) carbamate (77)

[0319] To a solution of the trimethyltin compound **9** (1.4 g, 3.06 mmol) (scheme 2) and bromide **70** (2.25g, 6.11 mmol) (scheme 14, Table 8) in dry toluene (50 ml) was added $Pd(PPh_3)_4$ (176 mg, 0.153 mmol). The reaction mixture was refluxed overnight, cooled to room temperature and the solvents were removed under reduced pressure. The resultant solid was triturated with hexane/ether and then purified by column chromatography, eluents EtOAc/Hexane 1:9, then EtOAc:hexane 4:6, to afford title compound 77 as a white solid (1.2 g, 86% yield). MS (m/z): 459.2 / 461.2 (M+H).

Step 2. *tert*-Butyl (4-(7-(2-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridin-2-yl)phenyl)methyl((tetrahydrofuran-2-yl)methyl)carbamate (**78**)

[0320] To a solution of **77** (1.0 g, 2.18 mmol) in Ph_2O (10 ml) was added 2-fluoro-4-nitrophenol (856 mg, 5.45 mmol) and potassium carbonate (904 mg, 6.55 mmol). The reaction mixture was heated at 180°C for 4 hrs, cooled to room temperature, diluted with DCM, filtered and concentrated. The residue was purified by column chromatography, eluent EtOAc:hexane 8:2, to afford title compound **78** (250 mg, 20% yield). MS (m/z): 580.3 (M+H).

Steps 3-4. *tert*-Butyl (4-(7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)phenyl)methyl((tetrahydrofuran-2-yl)methyl)carbamate (**80**)

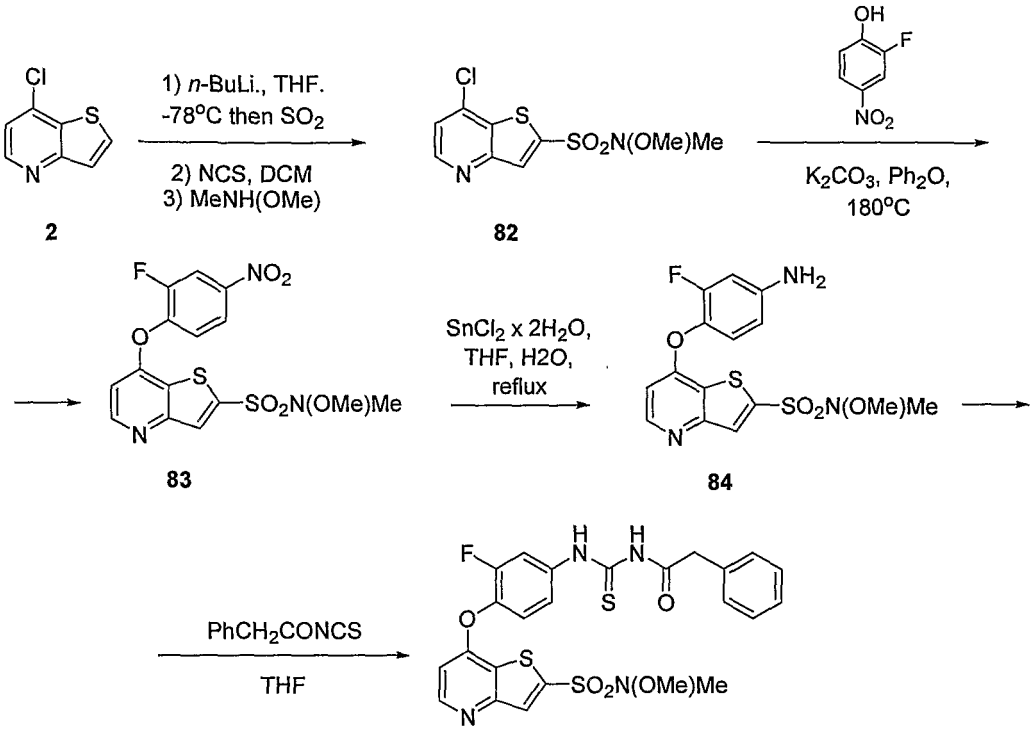
[0321] To a solution of **78** (250 mg, 0.431 mmol) in MeOH (10 mL) at 0°C was added $NiCl_2$ x $6H_2O$ (205 mg, 0.86 mmol) and $NaBH_4$ (64 mg, 1.72 mmol). The reaction mixture was allowed to stir for 1 hr, concentrated to dryness and the resultant solid was dissolved in 2 M HCl. This solution was then made basic with concentrated aqueous ammonium hydroxide and extracted with DCM. The DCM extract was dried over anhydrous sodium sulfate, filtered and evaporated to form the amine **79** (236 mg, 100% yield), which was used without characterization and further purification.

[0322] To a solution of the amine **79** (236 mg, 0.43 mmol) in THF (10 mL) was added 2-phenylacetyl isothiocyanate (114 mg, 6.44 mmol). The reaction mixture was stirred for 1 hr, concentrated and the residue was purified by column chromatograpy, eluent - gradient from EtOAc:hexane 1:1 to EtOAc, to afford title compound **80** (200 mg, 64 % yield) as a white solid. MS (m/z): 725.5 (M+H).

Step 5.1-(3-Fluoro-4-(2-(4-(((tetrahydrofuran-2-yl)methylamino)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-3-(2-phenylacetyl)thiourea (**81**)

[0323] To a solution of **80** (200 mg, 0.28 mmol) in toluene (5 mL), TFA (excess) was added. The reaction mixture was allowed to stir overnight, the solvent was removed under reduced pressure and the remained solid was triturated with diethyl ether to afford title compound **81** as the di-TFA salt (130 mg, 57% yield). ^{1}H NMR (DMSO) δ (ppm): 12.47 (s, 1H), 11.83 (s, 1H), 9.06 (s, 2H), 8.53 (dd, *J* = 2.0 and 5.5 Hz, 1H), 8.13 (s, 1H), 8.0 (d, J = 12.1 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.53 (m, 2H), 7.32 (m, 4H), 7.27 (m, 1H), 6.68 (d, *J* = 5.8 Hz, 1H), 4.23 (m, 1H), 3.82 (s, 2H), 3.78 (m, 1H), 3.71 (m, 1H), 3.11 (m, 1H), 2.95 (m, 1H), 2.0 (m, 1H), 1.98 (m, 2H), 1.56 (m, 1H). MS (m/z) 627.3 (M+H).

Scheme 16a



85: Example 67

Example 67

7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-sulfonic acid methoxy-methyl-amide (85)

Step 1. 7-Chloro-*N*-methoxy-*N*-methylthieno[3,2-b]pyridine-2-sulfonamide (**82**)

[0324] To a solution of chloride **2** (scheme 1) (700 mg, 4.14 mmol) in THF (20 ml) was added *n*-BuLi (2 ml, 4.97 mmol, 2.5 M solution in hexanes) at -78° C and the reaction mixture was stirred for 20 mins. SO_2-gas was passed over the surface of the solution for 3 hrs at the same temperature, then for an additional hr at 0°C. The reaction mixture was evaporated. DCM (20 ml) and NCS (605 mg, 4.55 mmol) were added and the reaction mixture was stirred at room temperature for 1.5 hrs, filtered through a celite pad and concentrated to produce a pink solid. The solid was dissolved in acetone (20 ml); MeNH(OMe) hydrochloride (608 mg, 6.21 mmol) and triethylamine (627 mg, 6.21 mmol) were added and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The EtOAc solution was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (eluent EtOAc:hexane,

1:1) to afford the title compound **82** (485 mg, 40% yield) as a pink solid. MS (m/z) 561.1 (M+H).

Step 2. 7-(2-Fluoro-4-nitrophenoxy)-*N*-methoxy-*N*-methylthieno[3,2-b]pyridine-2-sulfonamide (**83**)

[0325] A mixture of **82** (400 mg, 1.37 mmol), 2-fluoro-4-nitrophenol (321 mg, 2.05 mmol) and K_2CO_3 (756 mg, 5.48 mmol) were heated to 190°C in diphenyl ether (55 ml) for 3 hrs. The mixture was cooled to room temperature, diluted with DCM and filtered. The filtrate was concentrated and purified by column chromatography (eluent EtOAc:hexane, 1:1) to afford title compound **83** (225 mg, 40% yield). MS (m/z) 414.0 (M+H).

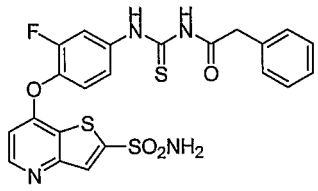
Steps 3-4. 7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-sulfonic acid methoxy-methyl-amide (**85**)

[0326] To a solution of the nitro compound **83** (225 mg, 0.54 mmol) in THF (5 ml) and water (2 ml) was added $SnCl_2$ x $2H_2O$ (742 mg, 3.3 mmol). The reaction mixture was refluxed for 3 hrs, diluted with EtOAc and washed with aqueous ammonium hydroxide. The washings were combined and extracted with DCM. Both EtOAc- and DCM- phases were combined, dried over anhydrous sodium sulfate, filtered and evaporated to produce the amine **84** (168 mg, 81% yield), which was used without characterization and further purification.

[0327] To a solution of the amine **84** (225 mg, 0.59 mmol) in THF (8 ml) was added phenyl-acetyl isothiocyanate (208 mg, 1.18 mmol). The reaction mixture was stirred for 1 hr, concentrated under reduced pressure and purified by column chromatography (eluent EtOAc) to afford **85** (323 mg, 98% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.52 (s, 1H), 11.86 (s, 1H), 8.74 (d, J = 5.3 Hz, 1H), 8.33 (s, 1H), 8.07 (d, J= 13.5 Hz, 1H), 7.61 (m, 2H), 7.36 (m, 4H), 7.29 (m, 1H), 3.86 (s, 3H), 3.84 (s, 2H), 2.96 (s, 3H). MS (m/z): 561.3 (M+H).

Example 68

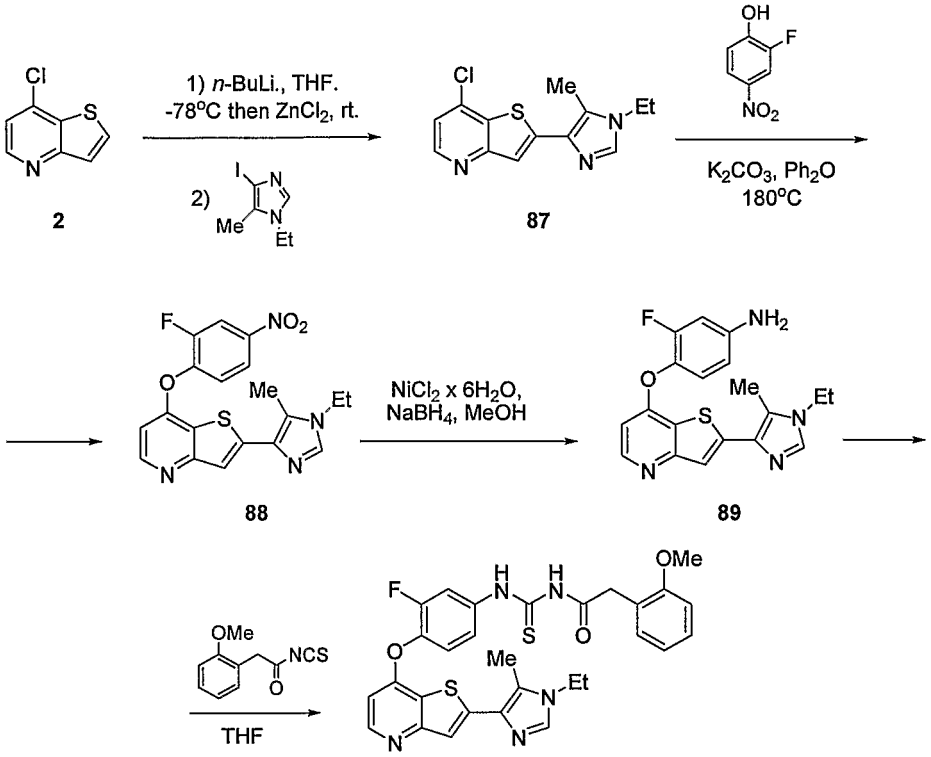
7-[2-Fluoro-4-(3-phenylacetyl-thioureido)-phenoxy]-thieno[3,2-b]pyridine-2-sulfonic acid amide (86)



86: Example 68

[0328] Title compound **86** was obtained following the procedures described for the compound **85** (example 67, scheme 16) but substituting in the first step O-methyl hydroxylamine for ammonia. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.82 (s, 1H), 13.15 (s, 1H), 9.98 (m, 1H), 9.4-9.2 (m, 4H), 8.87 (s, 2H), 8.64 (m, 5H), 8.15 (s, 1H), 3.82 (s, 2H). MS (m/z): 517.3 (M+H).

Scheme 17



90: Example 69

Example 69

1-(4-(2-(1-Ethyl-5-methyl-1H-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-(2-methoxyphenyl)acetyl)thiourea (90)

Step 1. 7-Chloro-2-(1-ethyl-5-methyl-1H-imidazol-4-yl)-thieno[3,2-b]pyridine (**87**)

[0329] To a solution of **2** (1.14 g, 6.76 mmol) in THF (60 ml) was added, at -78°C, *n*-BuLi (3.38 ml, 2.5 M soln in hexanes) and the reaction mixture was stirred at the same temperature for 10 min. A solution of $ZnCl_2$ (16.9 ml, 2.5 ml, 0.5M in THF) was added and the reaction mixture was warmed to room temperature. Then a solution of 1-ethyl-4-iodo-5-methyl-1*H*-imidazole (800 mg, 3.38 mmol) (Pyne, S.G and Cliff, M.D. *Synthesis* **1994**, 681) and $Pd(PPh_3)_4$ (390 mg, 0.34 mmol) in THF (15 ml) were added and the reaction mixture was refluxed for 3 hrs, cooled to room temperature, quenched with conc. ammonium

hydroxide solution and made neutral with concentrated aqueous HCl. The neutral solution was extracted with EtOAc, the extract was collected, dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated and the residue was purified by column chromatography (eluent MeOH:EtOAc, 1:9) to afford the title compound **87** (1.1g, 100% yield) as a brown oil. MS (m/z) 278.0 / 280.0 (M+H).

Step 2. 2-(1-Ethyl-5-methyl-1*H*-imidazol-4-yl)-7-(2-fluoro-4-nitro-phenoxy)-thieno[3,2-b]pyridine (**88**)

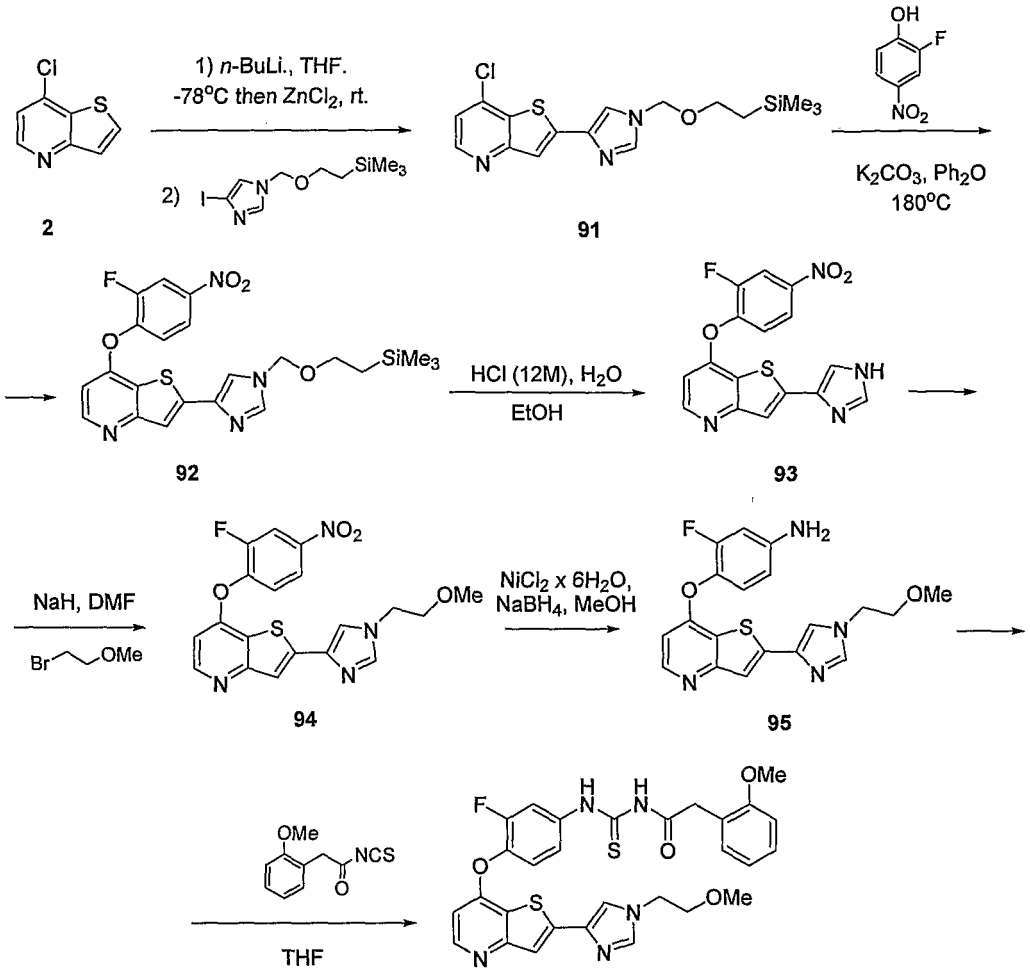
[0330] A suspension of **87** (650 mg, 2.35 mmol), potassium carbonate (970 mg, 7.04 mmol) and 2-fluoro-4-nitrophenol (738 mg, 4.7 mmol) were heated at 190°C in diphenyl ether (15 ml) for 3 hrs. The mixture was cooled to room temperature, diluted with DCM and filtered. The filtrate was concentrated and the residue was purified by column chromatography (eluents EtOAc, then MeOH:EtOAc, 1:9) to afford title compound **88** (600 mg, 64%) as a yellow solid. MS (m/z) 399.0 (M+H).

Steps 3-4. 1-(4-(2-(1-Ethyl-5-methyl-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-(2-methoxyphenyl)acetyl)thiourea (**90**)

[0331] To a solution of **88** (200 mg, 0.5 mmol) in MeOH (8 ml) and THF (2 ml) at 0°C was added $NiCl_2$ x $6H_2O$ (237 mg, 1 mmol) and $NaBH_4$ (74 mg, 2 mmol). The reaction mixture was allowed to stir for 1 hr, concentrated to dryness and the resultant solid was dissolved in 1 M HCl. The acidic solution was then made basic with concentrated aqueous ammonium hydroxide and extracted with EtOAc. The organic phase was collected, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated under reduced pressure and the residue was triturated with Et_2O to afford the crude amine **89** (184 mg, 100% yield) which was used immediately in the next step [without characterization].

[0332] To a solution of the amine **89** (180 mg, 0.49 mmol) in THF (10 ml) was added (2-methoxy-phenyl)-acetyl isothiocyanate (200 mg, 0.98 mmol). The reaction mixture was stirred for 10 min, concentrated and the residue was purified by column chromatography (eluents EtOAc, then to MeOH-EtOAc, 1:9), to afford title compound **90** (84 mg, 30% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.56 (s, 1H), 11.73 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.04 (d, J = 12.3 Hz, 1H), 7.71 (s, 1H), 7.51 (m, 4H), 7.25 (m, 2H), 6.97 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.2Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 5.5 Hz, 1H), 4.0 (q, J = 3.2 Hz, 2H), 3.80 (s, 2H), 3.77 (s, 3H), 2.47 (s, 3H), 1.31 (t, J = 3.2 Hz, 2H). MS (m/z) 576.1 (M+H).

Scheme 18



96: Example 70

Example 70

N-(3-Fluoro-4-(2-(1-(2-methoxyethyl)-1H-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide (96)

Step 1. 7-Chloro-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-yl)thieno[3,2-b]pyridine (**91**)

[0333] To a solution of **2** (9.4 g, 56.0 mmol) in THF (150 ml) at -78°C was added *n*-BuLi (28 ml, 70.0 mmol, 2.5 M soln in hexanes) and the reaction mixture was stirred at -78°C for 45 mins. A solution of $ZnCl_2$ (140 ml, 70.0 mmol, 0.5M in THF) was added and the reaction mixture was warmed to room temperature. To the warmed mixture a solution of 4-iodo-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole [Carl J. Lovey et al, *Tetrahedron Lett.*, **2004**, 45(28), 5529-5532] (9.0 g, 28.0 mmol) and $Pd(PPh_3)_4$ (2.5 g, 2.1 mmol) in THF (50 ml) were added. The reaction mixture was heated to reflux for 3 hrs, cooled to room

temperature, quenched with aqueous ammonium hydroxide and made neutral with aqueous HCl. The neutral solution was extracted with EtOAc, the organic phase was collected, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (eluent MeOH-EtOAc, 1:20) to afford the title compound **91** (7.5 g, 73% yield) as a brown oil. MS (m/z) 366.0/368.0 (M+H).

Step 2. 7-(2-Fluoro-4-nitrophenoxy)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-4-yl)thieno[3,2-b]pyridine (**92**)

[0334] A suspension of **91** (4.2 g, 11.5 mmol), potassium carbonate (7.95 g, 57.5 mmol) and 2-fluoro-4-nitrophenol (4.97 g, 31.6 mmol) was heated at 190°C in diphenyl ether (15 ml) for 4.5 hrs, cooled to room temperature, diluted with DCM and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (eluents hexane and acetone/hexane, 45:55) to afford title compound **92** (3.4 mg, 61% yield) as a yellow solid MS (m/z) 487.0 (M+H).

Step 3. 7-(2-Fluoro-4-nitrophenoxy)-2-(1H-imidazol-4-yl)thieno[3,2-b]pyridine (**93**)

[0335] To a suspension of **92** (3.3 g, 6.8 mmol) in EtOH (8 ml) was added concentrated HCl (7 ml) and distilled water (4 ml). The mixture was heated at 80-90°C for 2.5 h, cooled to room temperature and concentrated under reduced pressure. The remaining residue was subjected to azeotropic distillation with EtOH followed by neutralization with saturated aqueous $NaHCO_3$. The solid that precipitated was filtered and washed with water, and the filtrate was extracted with EtOAc. The solid and EtOAc extract were combined, evaporated under reduced pressure and the residue was collected and dried to afford the title compound **93** (2.4 g, 100% yield) as a yellow solid. MS (m/z) 357.0 (M+H).

Step 4. 7-(2-Fluoro-4-nitrophenoxy)-2-(1-(2-methoxyethyl)-1*H*-imidazol-4-yl)thieno[3,2-b]pyridine (**94**)

[0336] To a solution of **93** (300 mg, 0.84 mmol) in dry DMF (3 ml) at 0°C was added NaH (40 mg, 60 % dispersion in oil, 1.0 mmol). The mixture was allowed to warm to room temperature over 0.5 h then re-cooled to 0°C. Bromoethylmethyl ether (123 mg, 0.88 mmol) was added and mixture was allowed to warm to room temperature over 20 hours, concentrated and partitioned between EtOAc and water. The EtOAc phase was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography (eluents hexane and acetone/hexane 75:25) to afford the title compound **94** (126 mg, 36% yield) as a pale yellow solid. MS (m/z) 415.1.0 (M+H).

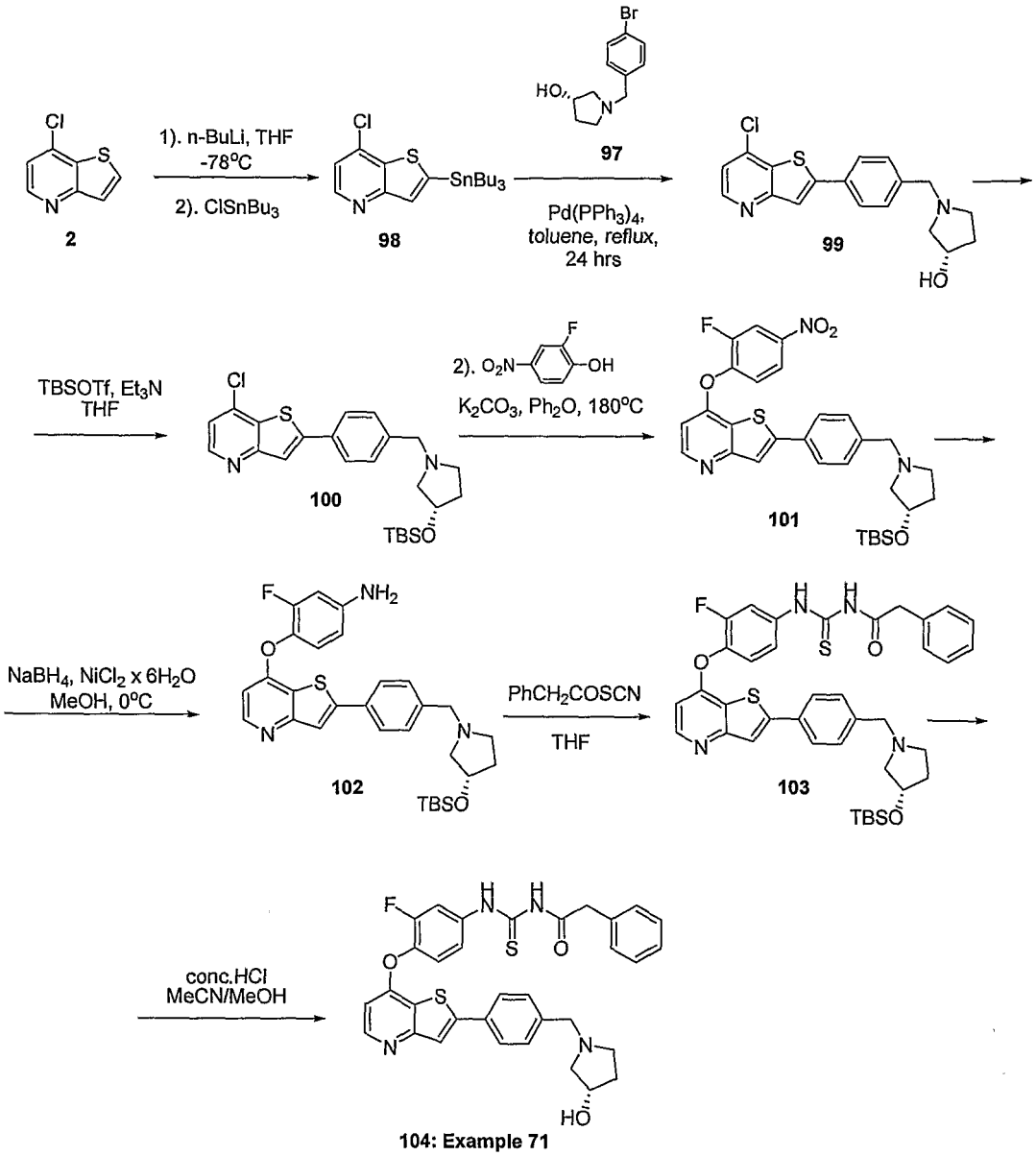
Step 5. 3-Fluoro-4-(2-(1-(2-methoxyethyl)-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine (**95**)

[0337] Following the procedure described above for compound **89** (scheme 17) but replacing the nitro compound **88** with the nitro compound **94,** title compound **95** was obtained as a beige solid (23 mg, 100% yield). MS (m/z) 385.2 (M+H).

Step 6. *N*-(3-Fluoro-4-(2-(1-(2-methoxyethyl)-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide (**96**)

[0338] Following the procedure described above for the compound **90** (scheme 17) but replacing the amine **89** with the amine **95** and using 2-(2-methoxyphenyl)acetyl isothiocyanate instead of 2-phenylacetyl isothiocyanate, title compound **96** was obtained as a beige solid (6 mg, 17% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.57 (1H, s), 11.77 (1H, s), 8.53 (1H, d, J=5.48 Hz), 8.08 (1H, d, J=12.03 Hz), 8.02 (1H, s), 7.91 (1H, s), 7.76 (1H, s), 7.59-7.52 (2H, m), 7.28-7.21 (2H, m), 6.98 (1H, d, J=8.22 Hz), 6.91 (1H, d, J=7.44 Hz), 6.71 (1H, d, J=5.67 Hz), 4.21 (2H, t, J=4.89 Hz), 3.80 (2H, s), 3.77 (3H, s), 3.65 (2H, t, J=4.89 Hz), 3.26 (3H, s). MS (m/z) 592.1 (M+H).

Scheme 19



Example 71

(S)-N-(3-Fluoro-4-(2-(4-((3-hydroxypyrrolidin-1-yl)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (104)

Step 1. (S)-1-(4-Bromobenzyl)pyrrolidin-3-ol (**97**)

[0339] Title compound **97** was obtained, according to the scheme 14 by reacting (S)-pyrrolidin-3-ol with 3-bromobenzylbromide, as a white solid (1.3g 63% yield). LRMS 256.1/258.1 (M+1).

Step 2. 7-Chloro-2-(tributylstannyl)thieno[3,2-*b*]pyridine (**98**)

[0340] To a solution of the chloride **2** (18.72 g, 110 mmol) in THF (200 mL) at -78°C *n*-BuLi (51 mL, 127 mmol) was added and the reaction mixture was stirred for about 30 minutes. The tributylchlorostannane (25.4 mL, 93 mmol) was added and the mixture was stirred at -78°C for another 60 minutes, quenched with water [at the same temperature] and allowed to warm up to room temperature. The warmed mixture was extracted with EtOAc, the extract was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography, eluents EtOAc-hexane (15:85), then EtOAc-hexane (25:75) to afford title compound **98** (30.2 g, 77% yield) as a yellow oil. LRMS (M+1) 459.1 (100%).

Step 3. (S)-1-(4-(7-Chlorothieno[3,2-b]pyridin-2-yl)benzyl)pyrrolidin-3-ol (**99**)

[0341] To a solution of **98** (2.44 g, 5.30 mmol) and bromide **97** (1.3g, 5.07 mmol) in dry toluene (30 mL) was added $Pd(PPh_3)_4$ (290 mg, 0.25 mmol). The reaction mixture was heated to reflux for 1.5 h, cooled to room temperature and the solvent was removed under reduced pressure. The resultant solid was purified by column chromatography, eluents EtOAc-Hexane (1:1) then MeOH/EtOAc (20:80), to afford title compound **99** (1.24 g, 71% yield) as a white solid. MS (m/z): 345.1/347.1 (M+H).

Step 4. (S)-2-(4-((3-(*tert*-Butyldimethylsilyloxy)pyrrolidin-1-yl)methyl)phenyl)-7-chlorothieno[3,2-b]pyridine (**100**)

[0342] To a suspension of **99** (0.5 g, 1.45 mmol) in dry THF (7 ml) at 0°C was added TBDMSOTf (0.5 ml, 2.2 mmol) and the reaction mixture was stirred for 20 min. Et_3N (0.61 ml, 4.4 mmol) was added and mixture was stirred at the same conditions for another hour, quenched by the addition of water (~2 ml) and concentrated to dryness. The remained solid was partitioned between EtOAc and water. Organic phase was collected, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography, eluents EtOAc/hexane (1:1) then MeOH/EtOAc (5:95) to afford title compound **100** (637 mg, 96% yield) as a white solid. MS (m/z): 459.2/461.2 (M+H).

Step 5. (S)-2-(4-((3-(*tert*-Butyldimethylsilyloxy)pyrrolidin-1-yl)methyl)phenyl)-7-(2-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine (**101**)

[0343] To a solution of **100** (250.0 mg, 0.54 mmol) in Ph_2O (4 ml) was added 2-fluoro-4-nitrophenol (171 mg, 1.1 mmol) and potassium carbonate (304 mg, 2.2 mmol). The the reaction mixture was heated to 195 °C for 3 hrs, cooled to room temperature, diluted with DCM, filtered and concentrated. The residue was purified by column chromatography, eluents EtOAc, then MeOH/EtOAc (20-80), to afford title compound **101** (94 mg, 30% yield) as a white solid. MS (m/z): 580.3 (M+H).

Step 6. (S)-N-(4-(2-(4-((3-(*tert*-Butyldimethylsilyloxy)pyrrolidin-1-yl)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (**103**)

[0344] To a solution of the nitro compound **101** (90 mg, 0.16 mmol) in MeOH (4 ml) at 0°C was added $NiCl_2$ x $6H_2O$ (74 mg, 0.31 mmol) and $NaBH_4$ (23 mg, 0.62 mmol). The reaction mixture was allowed to stir for 1 hr, concentrated to dryness and the resultant solid was dissolved in 2 M HCl. The acidic solution was then made basic with aqueous ammonium hydroxide solution and extracted with EtOAc. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated to form the amine **102** (80 mg, 95% yiled), which was used without further purification and characterization.

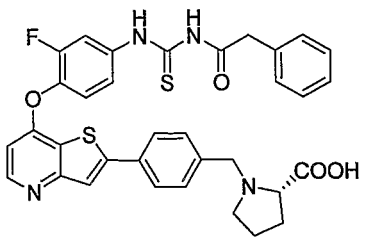
[0345] To a solution of the amine **102** (80 mg, 0.15 mmol) in THF (2 mL) was added 2-phenylacetyl isothiocyanate (64 mg, 0.36 mmol).The reaction mixture was stirred for 1 hr, concentrated and the residue was purified by column chromatography, eluents EtOAc:hexane (1:1), then EtOAc, to afford title compound **103** (34 mg, 30 % yield) as a white solid. MS (m/z): 727.5 (M+H).

Step 7. (S)-N-(3-fluoro-4-(2-(4-((3-hydroxypyrrolidin-1-yl)methyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**104**)

[0346] To a solution of **103** (34 mg, 0.047 mmol) in CH_3CN/MeOH (0.5 mL/2.0 mL), concentrated HCl (8 drops) was added and the reaction was allowed to stir 2 h. The solvents were removed under reduced pressure and the resultant solid was triturated with diethyl ether followed by purification by Gilson HPLC preparative system, column Aquasil C18 (25% MeOH in water to 100% MeOH), to afford title compound **104** (2.5 mg, 9% yield), as a white solid. ^{1}H NMR (DMSO) δ (ppm): 11.82 (1H, s), 8.51 (1H, d, J=5.28 Hz), 8.23 (1H, s), 8.02-7.98 (2H, m), 7.82 (2H, d, J=7.83 Hz), 7.52 (2H, br), 7.41 (2H, d, J=7.83 Hz), 7.33-7.25 (5H, m), 6.64 (1H, d, J=5.09 Hz), 4.20 (1H, br), 3.83 (2H, s), 3.38 (2H, s), 2.34-2.32 (2H, m), 2.03-1.96 (2H, m), 1.56 (2H, br). MS (m/z) 613.3 (M+H).

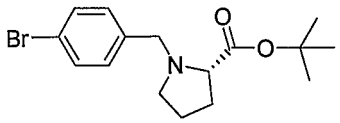
Example 72

(S)-1-(4-(7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)benzyl)pyrrolidine-2-carboxylic acid (106)



106: Example 72

Step 1. (S)-*tert*-Butyl 1-(4-bromobenzyl)pyrrolidine-2-carboxylate (**105**)



105

[0347] Title compound **105** was obtained, according to the scheme 14 by reacting (S)-*tert*-butyl pyrrolidine-2-carboxylate with 3-bromobenzylbromide, as a white solid (1.62g, 94% yield). LRMS 340.1/342.1 (M+1).

(S)-1-(4-(7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)benzyl)pyrrolidine-2-carboxylic acid (**106**)

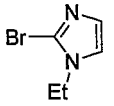
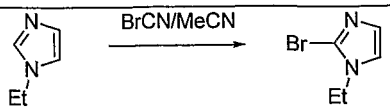
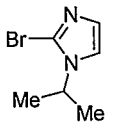
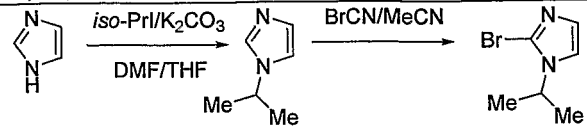
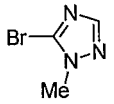
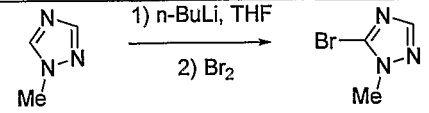
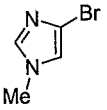
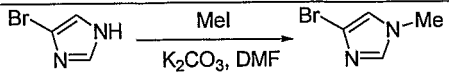
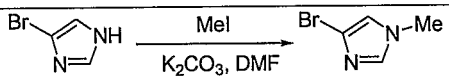
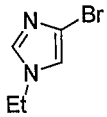
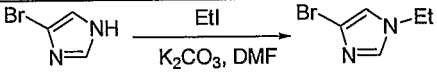
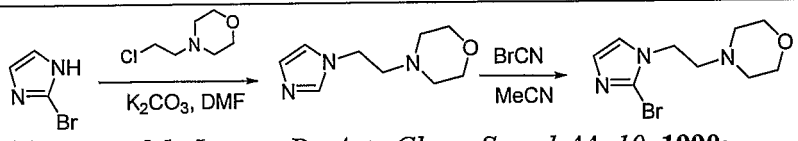
[0348] Title compound **106** was obtained following the procedures similar to the ones described above for the synthesis of compound **104** (example 71, scheme 19), replacing bromide **97** with the bromide **105** in the second step, skipping the step 4 (TBS-protection) and using in the last step TFA/DCM mixture for *tert*-butyl ester de-protection. ^{1}H NMR (400 MHz,DMSO-d_6); δ12.47 (1H, s), 11.82 (1H, s), 8.53 (1H, br), 8.13 (1H, s), 8.01 (1H, d, J=12.91 Hz), 7.96 (2H, d, J=7.02 Hz), 7.60 (2H, d, J=7.63 Hz), 7.54 (2H, br), 7.34-7.27 (5H, m), 6.67 (1H, d, J=5.09 Hz), 4.40 (1H, br), 4.23 (1H, br), 3.83 (2H, s), 3.38 (2H, s), 2.38 (1H, br), 2.00 (2H, br), 1.85 (1H, br). MS (m/z) 641.3 (M+H).

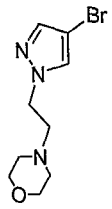
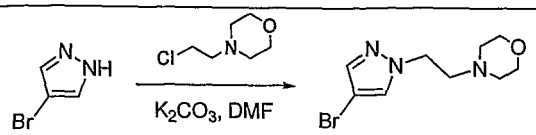
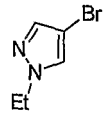
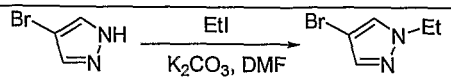
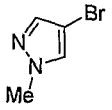
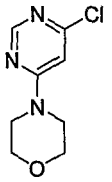
Examples 73-82 (compounds 13i-13r)

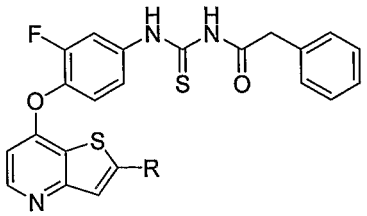
[0349] Following the procedures described above for the synthesis of compound **13a** (example 12, scheme 2) but substituting trimethyltin chloride in the step 1 for tributyltin chloride and 2-bromothiazole in the step 2 for heteroaryl bromides shown in the Table 9, title compounds **13i-13r** were synthesized. Characterization of compounds **13i-13r** (examples 73-82) is provided in the Table 10.

Table 9

Heteroaryl bromides used in the synthesis of compounds 13i-13r (examples 73-82)

Heteroaryl bromide	Preparation
	 McCullum, P., *et al.*, *Aust. J. Chem.* 52(3), **1999**, 159-166
	 McCullum, P., *et al.*, *Aust. J. Chem.* 52(3), **1999**, 159-166
	 Borai, M. El *et al. Pol J. Chem.* 55, **1981**, 1659
	 a) Begtrup, M.; Larsen, P.; *Acta Chem. Scand.* 44, *10*; **1990**; 1050-1057. b) Begtrup, M.; *Bull. Soc. Chim. Belg.*; 97; *8-9*; **1988**; 573-598. c) Begtrup, M.; Larsen, P.; *Chem. Pharm. Bull.* 42, *9*; **1994**; 1784-1790.
	 a) Begtrup, M.; Larsen, P.; *Acta Chem. Scand.* 44, *10*; **1990**; 1050-1057. b) Begtrup, M.; *Bull. Soc. Chim. Belg.*; 97; *8-9*; **1988**; 573-598. c) Begtrup, M.; Larsen, P.; *Chem. Pharm. Bull.* 42, *9*; **1994**; 1784-1790.
	 a) Begtrup, M.; Larsen, P.; *Acta Chem. Scand.* 44, *10*; **1990**; 1050-1057. b) Begtrup, M.; *Bull. Soc. Chim. Belg.*; 97; *8-9*; **1988**; 573-598. c) Begtrup, M.; Larsen, P.; *Chem. Pharm. Bull.* 42, *9*; **1994**; 1784-1790.
	 a) Begtrup, M.; Larsen, P.; *Acta Chem. Scand.* 44, *10*; **1990**; 1050-1057. b) Begtrup, M.; *Bull. Soc. Chim. Belg.*; 97; *8-9*; **1988**; 573-598. c) Begtrup, M.; Larsen, P.; *Chem. Pharm. Bull.* 42, *9*; **1994**; 1784-1790. d) Reference where BrCN is being used for such a purpose

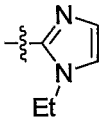
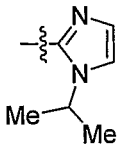
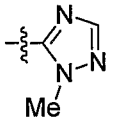
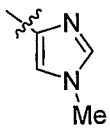
Heteroaryl bromide	Preparation
	 a) Begtrup, M.; Larsen, P.; *Acta Chem. Scand.* 44, *10*; **1990**; 1050-1057. b) Begtrup, M.; *Bull. Soc. Chim. Belg.*; 97; *8-9*; **1988**; 573-598. c) Begtrup, M.; Larsen, P.; *Chem. Pharm. Bull.* 42, *9*; **1994**; 1784-1790.
	 a) Begtrup, M.; Larsen, P.; *Acta Chem. Scand.* 44, *10*; **1990**; 1050-1057. b) Begtrup, M.; *Bull. Soc. Chim. Belg.*; 97; *8-9*; **1988**; 573-598. c) Begtrup, M.; Larsen, P.; *Chem. Pharm. Bull.* 42, *9*; **1994**; 1784-1790.
	A commercial product
	A commercial product

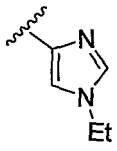
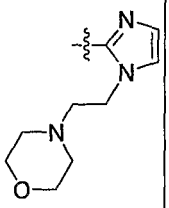
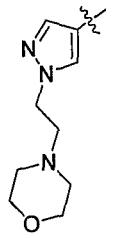
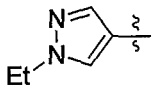
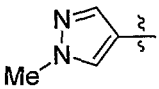


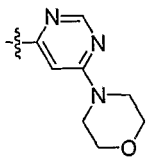
13i-13r: Examples 73-82

Table 10

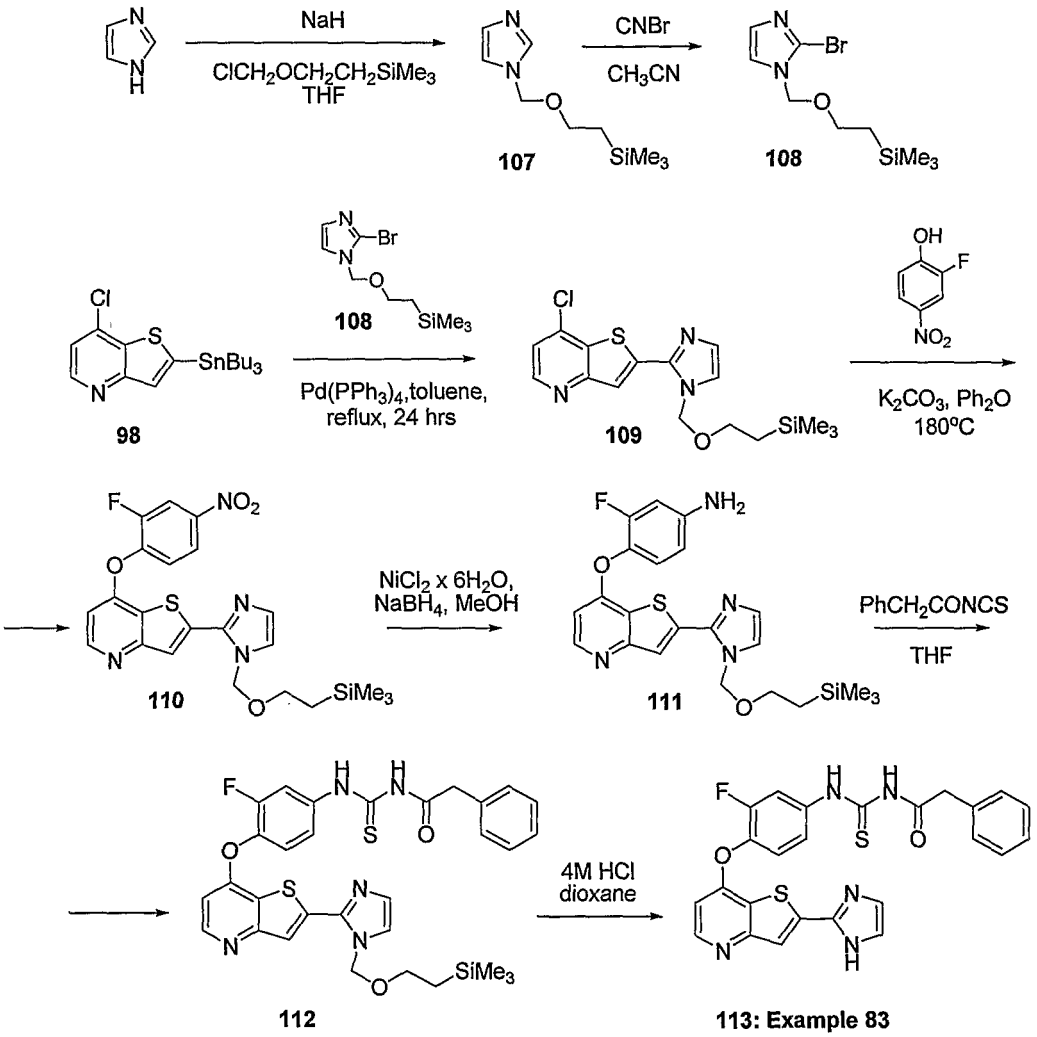
Characterization of compounds 13i-13r (examples 73-82)

Cpd	Ex	R	Name	Characterization
13i	73		N-(4-(2-(1-Ethyl-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.48 (1H, s), 11.81 (1H, s), 8.52 (1H, d, J=5.09 Hz), 8.02 (1H, d, J=12.13 Hz), 7.82 (1H, s), 7.53-7.46 (3H, m), 7.34-7.28 (5H, m), 7.06 (1H, s), 6.68 (1H, d, J=5.48 Hz), 4.37 (2H, q, J=6.85 Hz), 3.83 (2H, s), 1.43 (3H, t, J=7.24 Hz) MS (m/z) 532.3 (M+H)
13j	74		N-(3-Fluoro-4-(2-(1-isopropyl-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H nmr (400 MHz,DMSO-d_6) δ ppm 12.48 (1H, s), 11.82 (1H, s), 8.53 (1H, d, J=5.38 Hz), 8.02 (1H, d, J=12.13 Hz), 7.81 (1H, s), 7.60 (1H, s), 7.53 (2H, d, J=5.28 Hz), 7.34-7.26 (5H, m), 7.09 (1H, s), 6.68 (1H, d, J=5.28 Hz), 4.98 (1H, quintet, J=6.46 Hz), 3.83 (2H, s), 1.49 (6H, d, J=6.46 Hz) MS (m/z) 546.3 (M+H)
13k	75		N-(3-Fluoro-4-(2-(4-methyl-4H-1,2,4-triazol-3-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H nmr (400 MHz,DMSO-d_6) δ ppm 12.45 (1H, s), 11.78 (1H, s), 8.56 (1H, d, J=5.28 Hz), 8.16 (1H, s), 8.02 (s, 1H), 7.98 (1H, s), 7.52 (2H, s), 7.30-7.21 (5H, m), 6.72 (1H, d, J=5.09), 4.16 (3H, s), 3.78 (2H, s) . MS (m/z) 519.2 (M+H)
13l	76		N-(3-Fluoro-4-(2-(1-methyl-1H-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H nmr (400 MHz,DMSO-d_6) δ ppm 44 (1H, d, J=5.67 Hz), 8.01 (1H, d, J=12.13 Hz), 7.85 (1H, s), 7.71 (1H, s), 7.68 (1H, s), 7.51-7.50 (2H, m), 7.33-7.27 (5H, m), 6.57 (1H, d, J=5.48 Hz), 3.83 (2H, s), 3.72 (3H, s) . MS (m/z) 518.2 (M+H)

Cpd	Ex	R	Name	Characterization
13m	77		N-(4-(2-(1-Ethyl-1H-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide	^{1}H nmr (400 MHz,DMSO-d_6) δ ppm 12.50 (1H, s), 11.84 (1H, s), 8.56 (1H, d, J=5.87 Hz), 8.14 (1H, s), 8.11-8.04 (2H, m), 7.78 (1H, s), 7.57-7.56 (2H, m), 7.35-7.56 (5H, m), 6.76 (1H, d, J=5.48 Hz), 4.10 (2H, q, J=7.24 Hz), 3.84 (2H, s), 1.44 (3H, t, J=7.24 Hz). MS (m/z) 532.2 (M+H)
13n	78		N-(3-Fluoro-4-(2-(1-(2-morpholinoethyl)-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H nmr (400 MHz,DMSO-d_6) δ ppm 12.49 (1H, s), 11.82 (1H, s), 8.52 (1H, d, J=5.09 Hz), 8.02 (1H, d, J=11.93 Hz), 7.90 (1H, s), 7.54-7.48 (3H, m), 7.33-7.24 (5H, m), 7.06 (1H, s), 6.69 (1H, d, J=4.90 Hz), 4.44 (2H, s), 3.83 (2H, s), 3.55-3.51 (4H, m), 2.71 (2H, s), 2.50 (2H, s) . MS (m/z) 617.3 (M+H)
13o	79		N-(3-Fluoro-4-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (DMSO) δ (ppm): 12.46 (1H, s), 11.81 (1H, s), 8.45 (1H, d, J=5.48 Hz), 8.33 (1H, s), 8.01-7.99 (2H, m), 7.69 (1H, s), 7.51-7.49 (2H, m), 7.34-7.24 (5H, m), 6.59 (1H, d, J=5.48 Hz), 4.26 (2H, t, J=6.46 Hz), 3.82 (2H, s), 3.54 (4H, t, J=4.40 Hz), 2.74 (2H, t, J=6.46 Hz), 2.42 (4H, br). MS (m/z) 617.3 (M+H).
13p	80		N-(4-(2-(1-Ethyl-1H-pyrazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.49(s, 1H), 11.84(s, 1H), 8.47(d, J = 5.6 Hz, 1H), 8.36(s, 1H), 8.02-7.99(m, 2H), 7.70(s, 1H), 7.58-7.51(m, 2H), 7.39-7.32(m, 4H), 7.31-7.25(m, 1H), 6.60(d, J = 5.6 Hz, 1H), 4.18(q, J = 7.2 Hz, 2H), 3.83(s, 2H), 1.41(t, J = 7.2 Hz, 3H).
13q	81		N-(3-Fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.50(s, 1H), 11.85(s, 1H), 8.47(d, J = 5.6 Hz, 1H), 8.31(s, 1H), 8.02(d, J = 12.0 Hz, 1H), 7.99(s, 1H), 7.70(s, 1H), 7.55-7.52(m, 2H), 7.38-7.32(m, 4H), 7.31-7.28(m, 1H), 6.60(d, J = 5.6 Hz, 1H), 3.89(s, 3H), 3.83(s, 2H).

Cpd	Ex	R	Name	Characterization
13r	82		N-(3-Fluoro-4-(2-(6-morpholinopyrimidin-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 12.48(s, 1H), 11.82(s, 1H), 8.60(s, 1H), 8.56(d, J = 5.6 Hz, 1H), 8.55(s, 1H), 8.03(d, J = 12.0 Hz, 1H), 7.66(s, 1H), 7.58-7.52(m, 2H), 7.37-7.31(m, 4H), 7.31-7.24(m, 1H), 6.70(d, J = 5.6 Hz, 1H), 3.82(s, 2H), 3.78-3.68(m, 8H).

Scheme 20



Example 83

N-(4-(2-(1*H*-Imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (113)

Step 1. 1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (**107**)

[0350] To a stirred suspension of NaH (60% dispersion in oil, 0.65 g, 16.2 mmol) at 0°C was added imidazole (1 g, 14.7 mmol) in THF (14 mL). The mixture was warmed to room

temperature over 30 min, then re-cooled to 0°C followed by an addition of (2-(chloromethoxy)ethyl)trimethylsilane (2.73 ml, 15.4 mmol). The combined mixture was warmed to room temperature over 1h, quenched with saturated aqueous ammonium chloride, concentrated to dryness and partitioned between water and EtOAc. Organic phase was collected, dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by column chromatography (eluents EtOAc, then MeOH/EtOAc 20:80), to afford the title compound (2.04 g, 70% yield) as a white solid. MS (m/z) 199.3 (M+H).

Step 2. 2-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazole (**108**)

[0351] To a solution of **107** (100 mg, 0.50 mmol) in acetonitrile (1 mL) at room temperature was added cyanogen bromide (107 mg, 1.0 mmol) and the mixture was allowed to stir at room temperature for 3 h, concentrated to dryness and partitioned between EtOAc and water. The organic phase was collected, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by column chromatography (eluents EtOAc/hexane 25:75, then EtOAc), to afford the title compound **108** (45 mg, 32% yield) as a colorless oil. MS (m/z) 277.0/279.0 (M+H).

Step 3. 7-Chloro-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)thieno[3,2-b]pyridine (**109**)

[0352] Starting from the compound **98** (scheme 19) and following the procedure described above for the synthesis of compound **10** (example 12, scheme 2) but substituting 2-bromothiazole in the step 2 for the bromide **108**, title compound **109** was obtained as a white solid (22 mg, 41% yield). MS (m/z) 366.1/368.1 (M+H).

Step 4. 7-(2-Fluoro-4-nitrophenoxy)-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)thieno[3,2-b]pyridine (**110**)

[0353] Following the procedure described above for the synthesis of compound **11** (example 12, step 3, scheme 2) but substituting compound **10** for compound **109**, title compound **110** was obtained as a yellow solid (104 mg, 50% yield). MS (m/z) 487.3 (M+H).

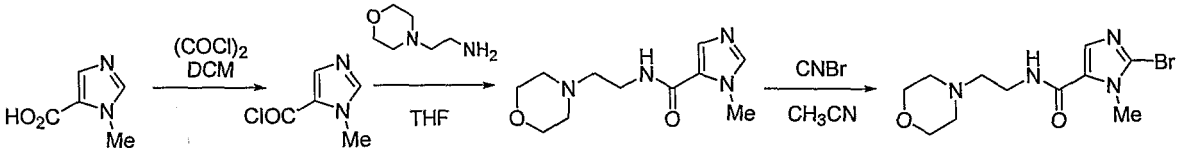
Steps 5-6. N-(3-Fluoro-4-(2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**112**)

[0354] Following the procedure described above for the synthesis of compound **13a** (example 12, steps 4-5, scheme 2) but substituting compound **11** for compound **110** and using intermediate amine **111** (instead of amine **12**), title compound **112** was obtained as a beige solid (48 mg, 33% yield). MS (m/z) 634.3 (M+H).

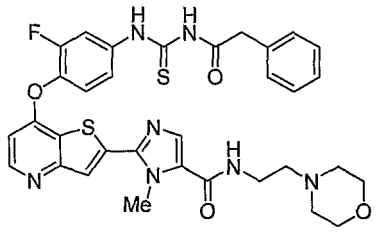
Step 7. *N*-(4-(2-(1*H*-Imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (**113**)

[0355] A solution of **112** (21 mg, 0.033 mmol) in 4N HCl in dioxane (3.5 mL) was allowed to stir at 55°C for 1 h. The mixture was then cooled and solvent was removed under reduced pressure. The resultant gum was triturated with ether several times to form a solid material that was dried under high vacuum to afford the product **113** as a beige solid (5 mg, 28% yield). ^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.50 (1H, s), 11.84 (1H, s), 8.66 (1H, d, J=5.67 Hz), 8.39 (1H, s), 8.06 (1H, d, J=12.72 Hz), 7.68 (2H, s), 7.59-7.58 (2H, m), 7.36-7.30 (5H, m), 6.86 (1H, d, J=5.48 Hz), 3.83 (2H, s). MS (m/z) 504.1 (M+H).

Scheme 21



114 **115** **116**



117: Example 84

Example 84

2-(7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)-1-methyl-N-(2-morpholinoethyl)-1*H*-imidazole-5-carboxamide (117)

Step 1. 1-Methyl-*N*-(2-morpholinoethyl)-1*H*-imidazole-5-carboxamide (**115**)

[0356] To a suspension of 1-methyl-1*H*-imidazole-5-carboxylic acid (0.92 g, 7.3 mmol) [Rapoport, H.; et al.; *Synthesis* **1988**; 767.] in dichloromethane (10 ml), was added oxalyl chloride (2.6 ml, 29.2 mmol) and the reaction mixture was heated to reflux for 1 h, cooled, concentrated to dryness to form acid chloride **114** (1.05 g, 100%) which was used without characterization and further purification.

[0357] To a suspension of the acid chloride **114** (1.05 g, 7.3 mmol) in THF (10 mL) was added 2-morpholinoethanamine (2.38 g, 18.5 mmol). The mixture was stirred at room temperature for 1h, concentrated to dryness and the residue was purified by column

chromatography (eluent chloroform/MeOH/ammonium hydroxide, 100:2:0.5), to afford the title compound **115** (551 mg, 32% yield) as a white solid. MS (m/z) 239.1 (M+H).

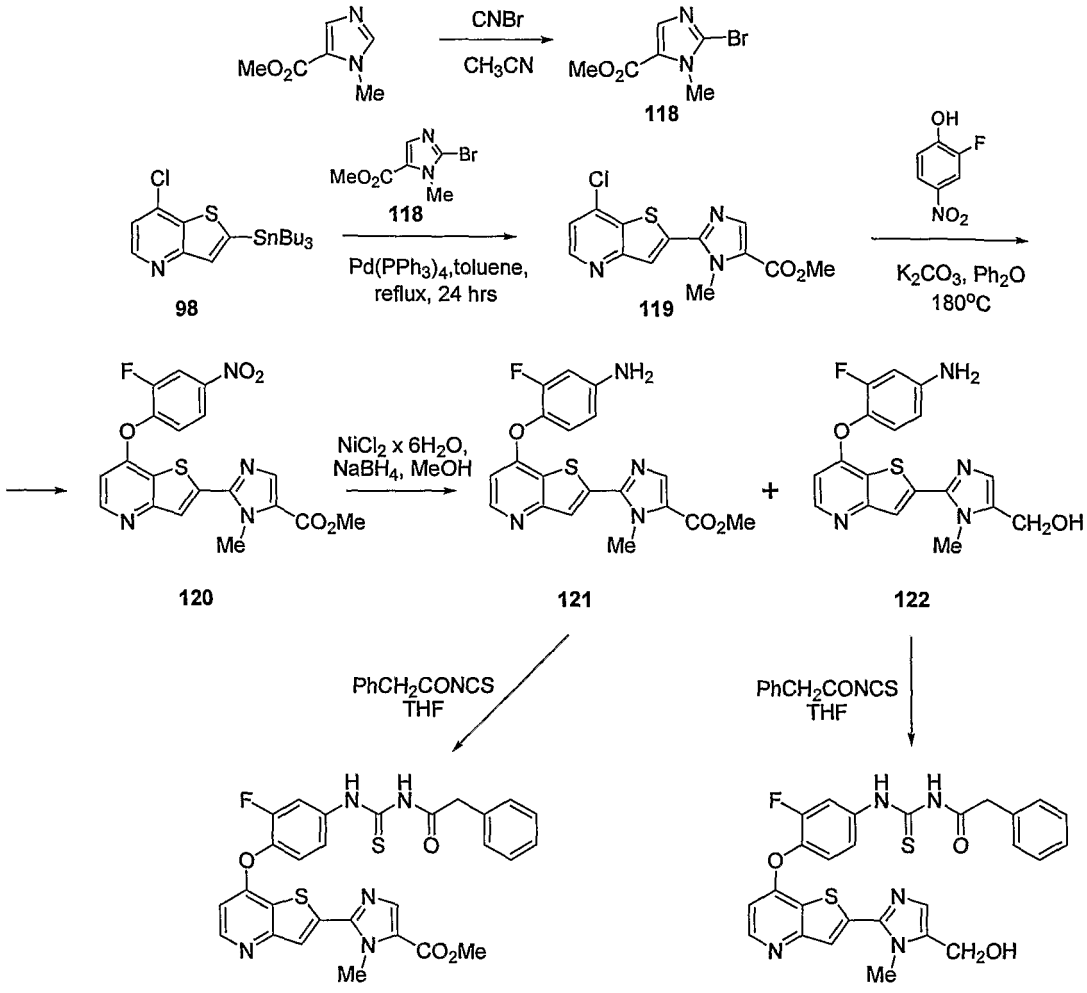
Step 2. 2-Bromo-1-methyl-*N*-(2-morpholinoethyl)-1*H*-imidazole-5-carboxamide (**116**)

[0358] To a solution of **115** (550 mg, 2.31 mmol) in acetonitrile (5 mL) was added cyanogen bromide (489 mg, 4.6 mmol). The reaction flask was covered with aluminum foil and the mixture was allowed to stir at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (eluents 100% EtOAc to 30%MeOH/EtOAc), to afford title compound **116** as a beige solid (230 mg (31%). MS (m/z) 317.1/319.1 (M+H).

Step 3. 2-(7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)-1-methyl-N-(2-morpholinoethyl)-1*H*-imidazole-5-carboxamide (**117**)

[0359] Following the procedures described above for the synthesis of compound **13a** (example 12, scheme 2) but substituting trimethyltin chloride in the step 1 for tributyltin chloride and 2-bromothiazole in the step 2 for the bromide **116**, title compound **117** was synthesized. ^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 8.55 (1H, d, J=5.28 Hz), 8.47 (1H, br), 8.04 (1H, s), 7.97 (1H, d, J=12.52 Hz), 7.67 (1H, s), 7.49 (2H, br), 7.33-7.32 (4H, m), 7.26 (1H, m), 6.70 (1H, d, J=5.09 Hz), 4.18 (3H, s), 3.84 (2H, s), 3.57 (4H, br), 2.47-2.33 (8H, m). MS (m/z) 674.3 (M+H).

Scheme 22



Examples 85 and 86

Methyl 2-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)-1-methyl-1*H*-imidazole-5-carboxylate (123), and

N-(3-Fluoro-4-(2-(5-(hydroxymethyl)-1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (124)

Step 1. Methyl 2-bromo-1-methyl-1*H*-imidazole-5-carboxylate (**118**)

[0360] Following the procedure described above for the compound **116** (scheme 21) but replacing compound **115** with methyl 1-methyl-1*H*-imidazole-5-carboxylate, title compound **118** was obtained as a beige solid (373 mg, 49% yield). MS (m/z) 219.1/221.1 (M+H).

Step 2. Methyl 2-(7-chlorothieno[3,2-b]pyridin-2-yl)-1-methyl-1*H*-imidazole-5-carboxylate (**119**)

[0361] Starting from the compound **98** (scheme 19) and following the procedure described above for the synthesis of compound **10** (example 12, scheme 2) but substituting 2-bromothiazole in the step 2 for the bromide **118**, title compound **119** was obtained as a white solid (580 mg, 100% yield). MS (m/z) 308.1/310.0 (M+H).

Step 3. Methyl 2-(7-(2-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridin-2-yl)-1-methyl-1*H*-imidazole-5-carboxylate (**120**)

[0362] Following the procedure described above for the synthesis of compound **11** (example 12, step 3, scheme 2) but substituting compound **10** for compound **119,** title compound **120** was obtained as a yellow solid (254 mg, 31% yield). MS (m/z) 429.1 (M+H).

Step 4. Methyl 2-(7-(4-amino-2-fluorophenoxy)thieno[3,2-b]pyridin-2-yl)-1-methyl-1*H*-imidazole-5-carboxylate (**121**) and (2-(7-(4-amino-2-fluorophenoxy)thieno[3,2-b]pyridin-2-yl)-1-methyl-1*H*-imidazol-5-yl)methanol (**122**)

[0363] Following the procedure described above for the synthesis of compound **12** (example 12, step 4, scheme 2) but substituting compound **11** for compound **120,** title compounds **121** and **122** were obtained as white solids (39 mg, 21% yield and 56 mg, 32% yield). MS (m/z) 399.1 (M+H) and MS (m/z) 371.1 (M+H) respectively.

Step 5. Methyl 2-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)-1-methyl-1*H*-imidazole-5-carboxylate (**123**)

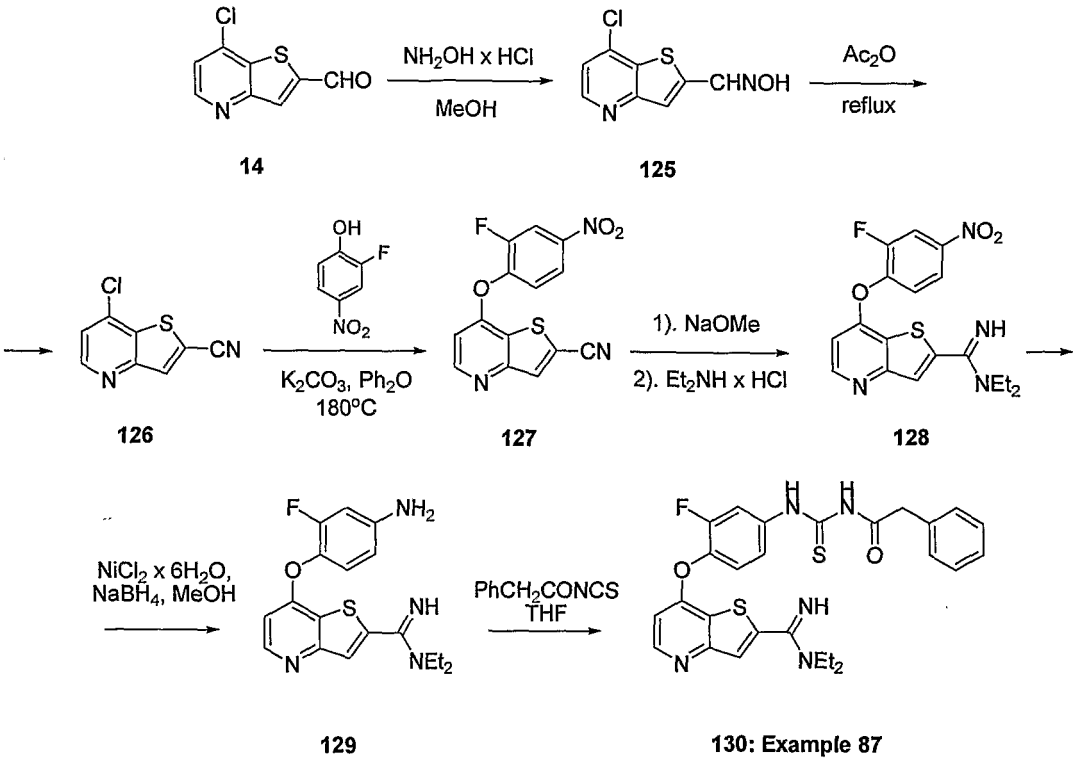
[0364] Following the procedure described above for the synthesis of compound **13a** (example 12, step 3, scheme 2) but substituting compound **12** for compound **121,** title compound **123** was obtained as a beige solid (35 mg, 63% yield). ^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.48 (1H, s), 11.82 (1H, s), 8.58 (1H, dd, 5.48, 0.98 Hz), 8.13 (1H, d, J=0.98 Hz), 8.03 (1H, d, J=12.52 Hz), 7.81 (1H, d, J=1.17 Hz), 7.55-7.54 (2H, m), 7.36-7.31 (4H, m), 7.27 (1H, m), 6.74 (1H, d, J=5.48 Hz), 4.21 (3H, s), 3.83 (3H, s), 3.83 (2H, s). MS (m/z) 576.2 (M+H).

Step 5a. *N*-(3-Fluoro-4-(2-(5-(hydroxymethyl)-1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**124**)

[0365] Following the procedure described above for the synthesis of compound **13a** (example 12, step 3, scheme 2) but substituting compound **12** for compound **122,** title compound **124** was obtained as a beige solid (32 mg, 39% yield). ^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.48 (1H, s), 11.82 (1H, s), 8.58 (1H, dd, 5.48, 0.98 Hz), 8.13 (1H, d, J=0.98 Hz), 8.03 (1H, d, J=12.52 Hz), 7.81 (1H, d, J=1.17 Hz), 7.55-7.54 (2H, m),

7.36-7.31 (4H, m), 7.27 (1H, m), 6.74 (1H, d, J=5.48 Hz), 4.21 (3H, s), 3.83 (3H, s), 3.83 (2H, s). MS (m/z) 576.2 (M+H).

Scheme 23



Example 87

N-(4-(2-(*N*,*N*-Diethylcarbamimidoyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (130)

Step 1. 7-Chlorothieno[3,2-b]pyridine-2-carbaldehyde oxime (**125**)

[0366] To a solution of aldehyde **14** (scheme 3) in MeOH was added NH_2OH x HCl (227 mg, 3.26 mmol) in water (0.5 mL) and the mixture was stirred at room temperature for 0.5 h. The solvents were removed by under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to afford the title compound **125** (458 mg, 85% yield) as a white solid. MS (m/z) 213.1/215.1 (M+H).

Step 2. 7-Chlorothieno[3,2-b]pyridine-2-carbonitrile (**126**)

[0367] A solution of the oxime **125** (100 mg, 0.47 mmol) in acetic anhydride (2 ml) was set to reflux for 3 h and then at 90°C for 48h. The acetic anhydride was removed under reduced pressure and the residue was partitioned between a cold aqueous K_2CO_3 solution and EtOAc. The organic phase was dried over anhydrous sodium sulfate, concentrated to dryness and remained solid was purified by column chromatography, eluents 25%

EtOAc/hexane (25:75), then 100% EtOAc, to afford the title compound **126** (65 mg, 71% yield). MS (m/z) 195.1/197.1 (M+H).

Step 3. 7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine-2-carbonitrile (**127**)

[0368] Following the procedure described above for the synthesis of compound **11** (example 12, step 3, scheme 2) but substituting compound **10** for compound **126,** title compound **127** was obtained as a yellow solid (114 mg, 60% yield). MS (m/z) 316.0 (M+H).

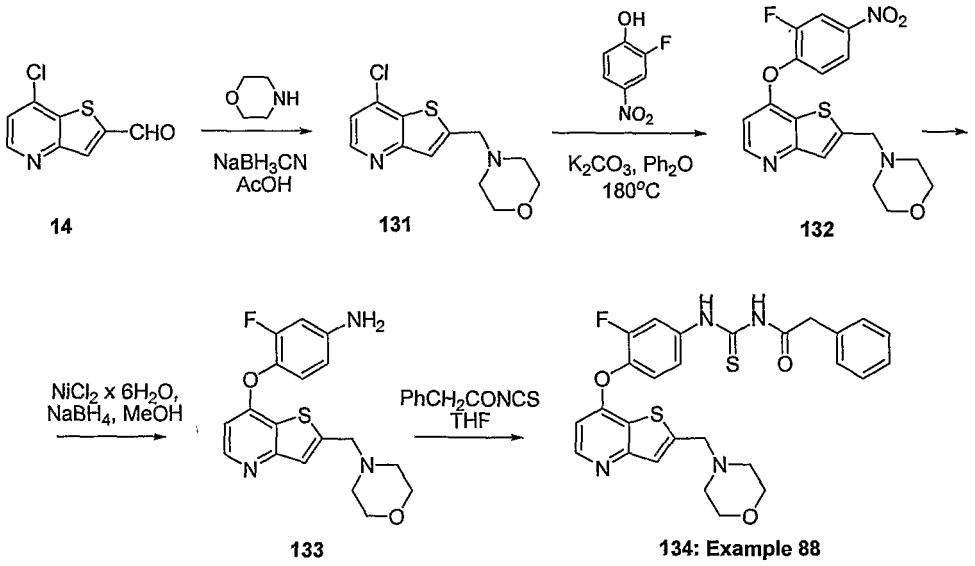
Step 4. *N,N*-Diethyl-7-(2-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine-2-carboximidamide (**128**)

[0369] To a solution of nitrile **127** (116 mg, 0.37 mmol) in MeOH (3 mL) was added NaOMe (25% in MeOH, 0.09 ml, 0.39 mmol) and the mixture was allowed to stir at room temperature for 18 h. Subsequently, Et_2NH x HCl (1.01 g, 9.25 mmol) was added and the mixture was heated to reflux for 12 h., cooled to room temperature and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and saturated aqueous ammonium chloride, the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The remained solid was purified by column chromatography (eluents EtOAc then $CHCl_3$/MeOH/NH_4OH 44:5:0.5), to afford the title compound **128** (30 mg, 21% yield) as a white solid. MS (m/z) 389.2 (M+H).

Steps 4-5. N-(4-(2-(*N,N*-Diethylcarbamimidoyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (**130**)

[0370] Following the procedure described above for the synthesis of compound **13a** (example 12, steps 4-5, scheme 2) but substituting compound **11** for compound **128** and using intermediate amine **129** (instead of amine **12**), title compound **130** was obtained as a beige solid (5 mg, 13% yield). ^1H NMR (DMSO) δ (ppm): 8.58 (1H, d, J=5.48 Hz), 8.29 (1H, s), 8.02 (1H, d, J=11.35 Hz), 7.81 (1H, d, J=2.54 Hz), 7.53 (2H, br), 7.34-7.33 (5H, m), 6.74 (1H, d, J=5.28 Hz), 3.83 (2H, s), 3.40 (4H, q, J=6.91 Hz), 1.16 (6H, t, J=6.95 Hz). MS (m/z) 536.2 (M+H).

Scheme 24



Example 88

N-(3-Fluoro-4-(2-(morpholinomethyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (134)

Step 1. 4-((7-Chlorothieno[3,2-b]pyridin-2-yl)methyl)morpholine (**131**)

[0371] To a solution of aldehyde **14** (scheme 3) (316 mg, 1.6 mmol) and morpholine (0.15 ml, 1.52 mmol) in MeOH (20 mL) was added acetic acid (0.88 ml, 15 mmol), followed by sodium cyanoborohydride (105 mg, 1.67 mmol). The resultant mixture was allowed to stir for 18 h, quenched with saturated aqueous potassium carbonate solution (5 mL), evaporated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was dried over anhydrous sodium sulfate, concentrated to dryness and the remained solid was purified by column chromatography, eluents EtOAc/hexane (30:70), then MeOH/EtOAc (1:99), to afford the title compound **131** (120 mg, 29% yield). MS (m/z) 269.0/271.0 (M+H).

Step 2. 4-((7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-b]pyridin-2-yl)methyl)morpholine (**132**)

[0372] Following the procedure described above for the synthesis of compound **11** (example 12, step 3, scheme 2) but substituting compound **10** for compound **131**, title compound **132** was obtained as a yellow solid (110 mg, 69% yield). MS (m/z) 390.1 (M+H).

Steps 3-4. *N*-(3-Fluoro-4-(2-(morpholinomethyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**134**)

[0373] Following the procedure described above for the synthesis of compound **13a** (example 12, steps 4-5, scheme 2) but substituting compound **11** for compound **132** and

using intermediate amine **133** (instead of amine **12**), title compound **134** was obtained as a white solid (38 mg, 27% yield). ^{1}H NMR (DMSO) δ (ppm): 12.89 (1H, s), 12.24 (1H, s), 8.87 (1H, d, J=4.71 Hz), 8.42 (1H, d, J=12.13 Hz), 7.95-7.88 (3H, m), 7.76-7.68 (5H, m), 7.00 (1H, d, J=5.28 Hz), 4.26-4.25 (4H, m), 4.02 (4H, br), 3.76 (2H, s), 2.90 (2H, s). MS (m/z) 537.2 (M+H).

Examples 89-92

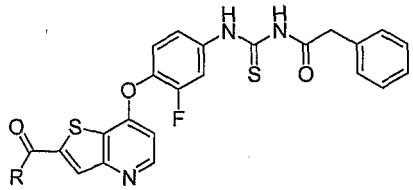
(S)-*tert*-Butyl 1-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carbonyl)pyrrolidine-2-carboxylate (135a),

(R)-*tert*-Butyl 3-((7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carboxamido)methyl)pyrrolidine-1-carboxylate (135b),

(R)-*N*-(4-(2-(3-(Dimethylamino)pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (135c), and

N-(3-Fluoro-4-(2-(piperidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (135d)

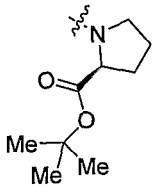
[0374] Compounds **135a-d** (examples 89-92) were obtained following the procedures described above for the synthesis of compound **8a** (example 1, scheme 1). Characterization of **135a-d** is provided in Table 11.

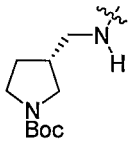
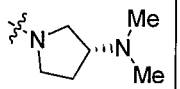
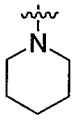


135 a-d: Examples 89-92

Table 11

Characterization of compounds 135a-d (examples 89-92)

Cpd	Ex	R	Name	Characterization
135a	**89**		(S)-*tert*-Butyl 1-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carbonyl)pyrrolidine-2-carboxylate	1H NMR (400 MHz, DMSO-d6) δ ppm: 12.48(s, 1H), 11.82(s, 1H), 8.61(d, J = 5.6 Hz, 0.7H), 8.58(d, J = 5.6 Hz, 0.3H), 8.10(s, 0.7H), 8.03(bd, J = 12.0 Hz, 1H), 7.86(s, 0.3H), 7.57-7.51(m, 2H), 7.47-7.20(m, 5H), 6.77(d, J = 5.6 Hz, 0.7H), 6.75(d, J = 5.6 Hz, 0.3H), 5.02-4.97(m, 0.3H), 4.20(dd, J = 3.2 and 8.4 Hz, 0.7H), 3.97(t, J = 6.8 Hz, 1.4H), 3.82(s, 1.4H), 3.80(t, J = 6.8 Hz, 0.6H), 3.55(s, 0.6H), 2.3-1.10(m, 5H), 1.41(s, 6.3H), 1.19(s, 2.7H).

Cpd	Ex	R	Name	Characterization
135b	**90**		(R)-*tert*-Butyl 3-((7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carboxamido)methyl)pyrrolidine-1-carboxylate	1H NMR (400 MHz, DMSO-d6) δ ppm: 12.48(s, 1H), 11.81(s,1H), 9.05-8.90(m, 1H), 8.58(d, J = 5.6 Hz, 1H), 8.32-8.22(m, 1H), 8.02(d, J = 11.6 Hz, 1H), 7.56-7.52(m, 2H), 7.36-7.30(m, 4H), 7.30-7.24(m, 1H), 6.73(d, J = 5.6 Hz, 1H), 4.00-3.90(m, 1H), 3.82(s, 2H), 3.54-3.20(m, 4H), 1.91-1.74(m, 4H), 1.39(bs, 9H).
135c	**91**		(R)-*N*-(4-(2-(3-(Dimethylamino) pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide	1H NMR (400 MHzCDCl3) δ ppm: 12.54 (s, 1H), 8.80 (s, 1H), 8.54 (d, 1H, J=5.5 Hz), 8.14 (s, 1H), 7.96 (dd, 1H, J=11.4/2.1 Hz), 7.52-7.26 (m, 6H), 6.63 (d, 1H, J=5.5 Hz), 4.35-3.52 (m, 5H), 3.80 (s, 2H), 2.79 (s, 6H), 2.70-2.40 (m, 2H).
135d	**92**		N-(3-Fluoro-4-(2-(piperidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	LRMS (M+1) 549.3 (100%), 550.3 (32%).

Example 93

N-(3-Fluoro-4-(2-(piperidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride (136a)

[0375] *N*-(3-Fluoro-4-(2-(piperidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**135d**, example 92) (686 mg, 1.25 mmol) was solubilized in THF (2 mL); dichloromethane (4 mL) and 1M hydrogen chloride in ether (1.5 mL, 1.5 mmol) were successfully added. The reaction mixture was stirred for1hour, the solvents were partially evaporated under reduced pressure to form a precipitate, which was collected by filtration, to afford the title compound **136a** (380 mg, 65% yield) as a light-yellow solid. Characterization of this material is provided in Table 12.

Example 94

N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride (136b)

[0376] Following the procedure described above for the synthesis of compound **136a** (example 93) but substituting compound **135d** (example 92, table 11) for the compound **8o**

(example 37, table 6), title compound **136b** was obtained. Characterization of this material is provided in Table 12.

Example 95

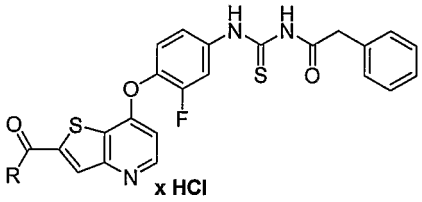
(S)-1-(7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carbonyl)pyrrolidine-2-carboxylic acid hydrochloride (136c)

[0377] Following the procedure described above for the synthesis of compound **136a** (Example 93) but substituting compound **135d** (example 92, table 11) for the compound **135a** (Example 89, Table 11), title compound **136c** was obtained. Characterization of this material is provided in Table 12.

Example 96

N-(4-(2-(Azepane-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide hydrochloride (136d)

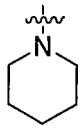
[0378] Title compound **136d** was obtained following the procedures described above for the synthesis of compound **136a** (example 93, table 12). Characterization of **136d** is provided in Table 12.

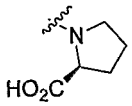
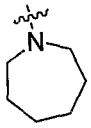


136 a-d: Examples 93-96

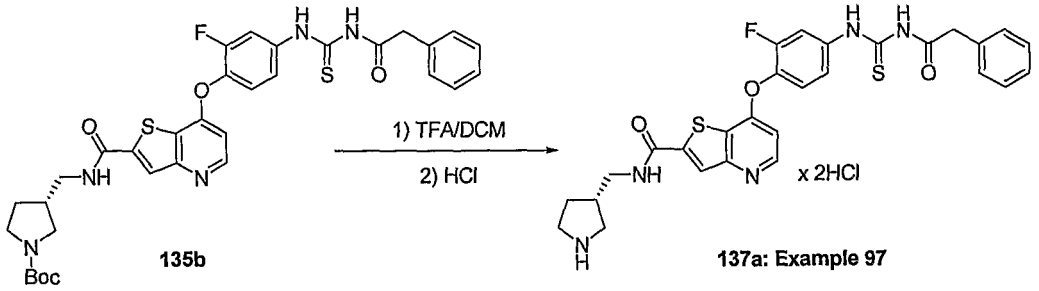
Table 12

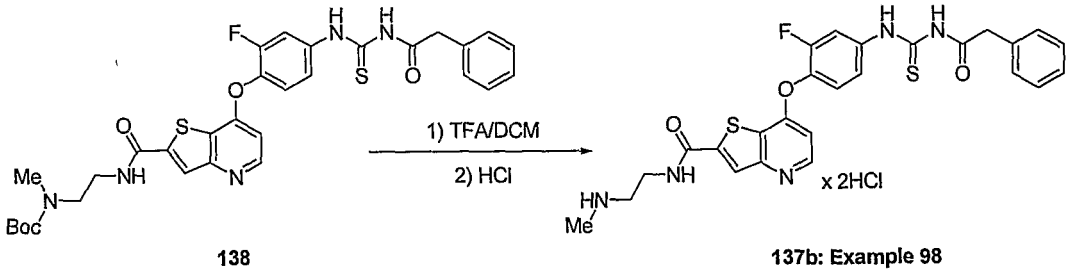
Characterization of compounds 136a-d (examples 93-96)

Cpd	Ex	R	Name	Characterization
136a	**93**		N-(3-Fluoro-4-(2-(piperidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride	1H NMR (400 MHzDMSO-d6) δ ppm: 12.49 (s, 1H), 11.83 (s, 1H), 8.65 (d, 1H, J=5.7 Hz), 8.05 (d, 1H, J=11.3 Hz), 7.82 (s, 1H), 7.56-7.55 (m, 2H), 7.34-7.26 (m, 5H), 6.84 (d, 1H, J=5.7 Hz), 3.83 (s, 2H), 3.61-3.58 (m, 4H), 1.65-1.09 (m, 6H).

Cpd	Ex	R	Name	Characterization
136b	94		N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride	1H NMR (400 MHz, DMSO-d6) δ ppm: 12.49(s, 1H), 11.82(s, 1H), 8.64(d, J = 5.6 Hz, 1H), 8.08-8.01(m, 1H), 8.05(s, 1H), 7.58-7.53(m, 1H), 7.36-7.31(m, 4H), 7.30-7.24(m, 1H), 6.82(d, J = 5.6 Hz, 1H), 3.85(t, J = 6.4 Hz, 2H), 3.82(s, 2H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
136c	95		(S)-1-(7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carbonyl)pyrrolidine-2-carboxylic acid hydrochloride	1H NMR (400 MHz, DMSO-d6) δ ppm: 12.49(s, 1H), 11.82(s, 1H), 8.67(d, J = 5.6 Hz, 0.7H), 8.63(d, J = 5.6 Hz, 0.3H), 8.12(s, 0.7H), 8.05(d, J = 21.0 Hz, 1H), 7.88(s, 0.3H), 7.58-7.54(m, 2H), 7.37-7.10(m, 4H), 7.30-7.24(m, 1H), 6.85(d, J = 5.6 Hz, 0.7H), 6.81(d, J = 5.6 Hz, 0.3H), 5.03-4.99(m, 0.3H), 4.48(dd, J = 4.4 and 8.0 Hz, 0.7H), 3.98(t, J = 7.2 Hz, 1.4 H), 3.82(s, 2H), 3.68-3.60(m, 0.6H), 2.32-2.25(m, 1H), 2.08-1.90(m, 3H).
136d	96		N-(4-(2-(Azepane-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide hydrochloride	1H NMR (400 MHzDMSO-d6) δ ppm: 12.49 (s, 1H), 11.83 (s, 1H), 8.64 (d, 1H, J=5.7 Hz), 8.04 (d, 1H, J=11.5 Hz), 7.85 (s, 1H), 7.56-7.55 (m, 2H), 7.34-7.26 (m, 5H), 6.81 (d, 1H, J=5.5 Hz), 3.83 (s, 2H), 3.67-3.56 (m, 4H), 1.76-1.57 (m, 8H).

Scheme 25





Example 97

(S)-7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-N-(pyrrolidin-3-ylmethyl)thieno[3,2-b]pyridine-2-carboxamide hydrochloride (137a)

[0379] To a solution of **135b** (table 11) (16 mg, 0.028 mmol) in CH_2Cl_2 (15 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature until the reaction is complete, then the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution a extracted with DCM. The extract was concentrated, the residue was dissolved in DCM (15 mL) and hydrogen chloride (0.5M in ether, 46 μL, 0.046 mmol) was added. The reaction mixture was stirred for one hour, the solvents were partially evaporated under reduced pressure to form a precipitate, which was collected by filtration, to afford the title compound **137a** (10 mg, 87% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.48(s, 1H), 11.82(s, 1H), 9.49-9.43(m, 1H), 9.24(bs, 1H), 8.74(bs, 1H), 8.62(d, J = 5.6 Hz, 1H), 8.38(s, 1H), 8.03(d, J = 12.0 Hz, 1H), 7.58-7.5(m, 2H), 7.3-7.30(m, 4H), 7.30-7.24(m, 1H), 6.79(d, J = 5.6 Hz, 1H), 3.80-3.54(m, 3H), 3.30-3.20(m, 1H), 3.20-3.10(m, 1H), 2.12-2.02(m, 1H), 2.00-1.95(m, 2H), 1.74-1.63(m, 1H).

Example 98

7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-N-(2-(methylamino)ethyl) thieno[3,2-b]pyridine-2-carboxamide hydrochloride (137b)

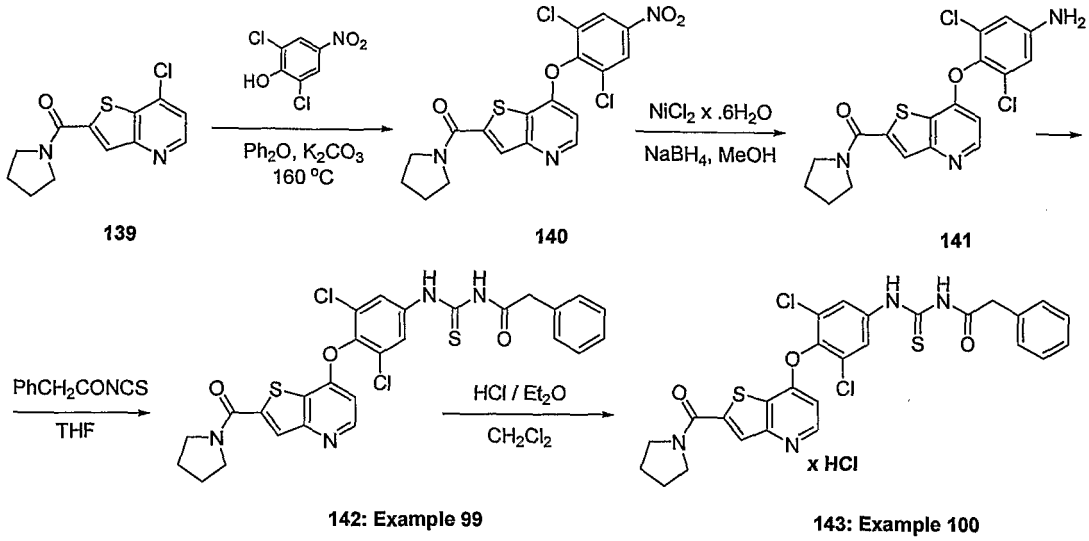
Steps 1-7. *tert*-Butyl 2-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridine-2-carboxamido)ethyl(methyl)carbamate (**138**)

[0380] Following the procedures described above for the synthesis of compound **8a** (Example 1, scheme 1) but replacing dimethyl amine with *tert*-butyl 2-aminoethyl(methyl)carbamate, title compound **138** was obtained (13%). LRMS (M+1) 638.2 (100%).

Step 8. 7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-N-(2-(methylamino)ethyl) thieno[3,2-b]pyridine-2-carboxamide hydrochloride (**137b**)

[0381] Following the procedure described above for the synthesis of **137a** but replacing compound **135b** with compound **138**, title compound **137b** was obtained as an HCl salt in 65% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.49(s, 1H), 11.83(s, 1H), 9.39(t, J = 5.2Hz, 1H), 8.80(bs, 1H), 8.62(d, J = 5.6 Hz, 1H), 8.39(s, 1H), 8.04(d, J = 11.6 Hz, 1H), 7.97(bs, 1H), 7.58-7.50(m, 2H), 7.37-7.31(m, 4H), 7.31-7.24(m, 1H), 6.80(d, J = 5.6 Hz, 1H), 3.78-3.71(m, 0.5H), 3.61(q, J = 6.0 Hz, 1H), 3.21-3.24(m, 0.5H), 3.18-3.04(m, 2H), 2.60(t, J = 4.8 Hz, 2H).

Scheme 26



139 140 141

142: Example 99 143: Example 100

Examples 99 and 100

N-(3,5-Dichloro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (142) and 7-(2,6-dichloro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-2-(pyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-4-ium chloride (143)

Steps 1-4. (7-Chlorothieno[3,2-*b*]pyridin-2-yl)(pyrrolidin-1-yl)methanone (**139**)

[0382] Following the procedures described above for the synthesis of compound **5** (scheme 1, example 1) but replacing dimethyl amine in the step 4 for pyrrolidine, title compound **139** was obtained. LRMS (M+1) 267.1 (100%).

Step 5. (7-(2,6-Dichloro-4-nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)(pyrrolidin-1-yl)methanone (**140**)

[0383] Starting from the compound **139** and following the procedure described above for the synthesis of compound **6** (scheme 1, example 1) but replacing 2-fluoro-4-nitrophenol with 2,6-dichloro-4-nitrophenol, title compound **140** was obtained in 69% yield. LRMS (M+1) 438.0 (100%), 439.1 (20%), 440.1 (70%).

Steps 6-7. *N*-(3,5-Dichloro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**142**)

[0384] Starting from the nitro compound **140** and following the procedures described above for the synthesis of **8a** (steps 6-7, scheme 1, example 1) title compound **142** was obtained in 49% yield. LRMS (M+1) 585.3 (100%), 586.2 (34%), 587.3 (72%).

7-(2,6-Dichloro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-2-(pyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-4-ium chloride (**143**)

[0385] Following the procedure described above for the synthesis of compound **136a** (Table 12, Example 93) but replacing compound **135d** with compound **142**, title compound **143** was obtained in 42% yield. Characterization of **143** is provided in the Table 13.

Examples 101 and 102

N-(3-Chloro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride (144) and

N-(3-Methyl-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride (145)

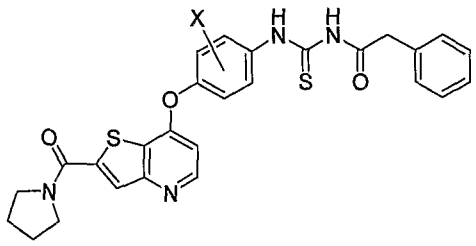
[0386] Compounds **144-145** (examples 101-102) were obtained following the procedures described above for the synthesis of compound **143** (example 100). Characterization of compounds **144-145** is provided in the Table 13.

Examples 103 and 104

2-Phenyl-N-(4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (146) and

N-(3-(Dimethylamino)-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (147)

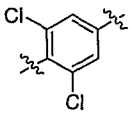
[0387] Compounds **146-147** (Examples 103-104) were obtained following the procedures described above for the synthesis of compound **142** (Example 99). Characterization of compounds **145-147** is provided in the Table 13.

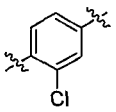
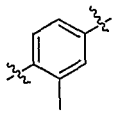
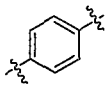
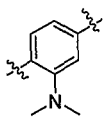


143-147: Examples 100-104

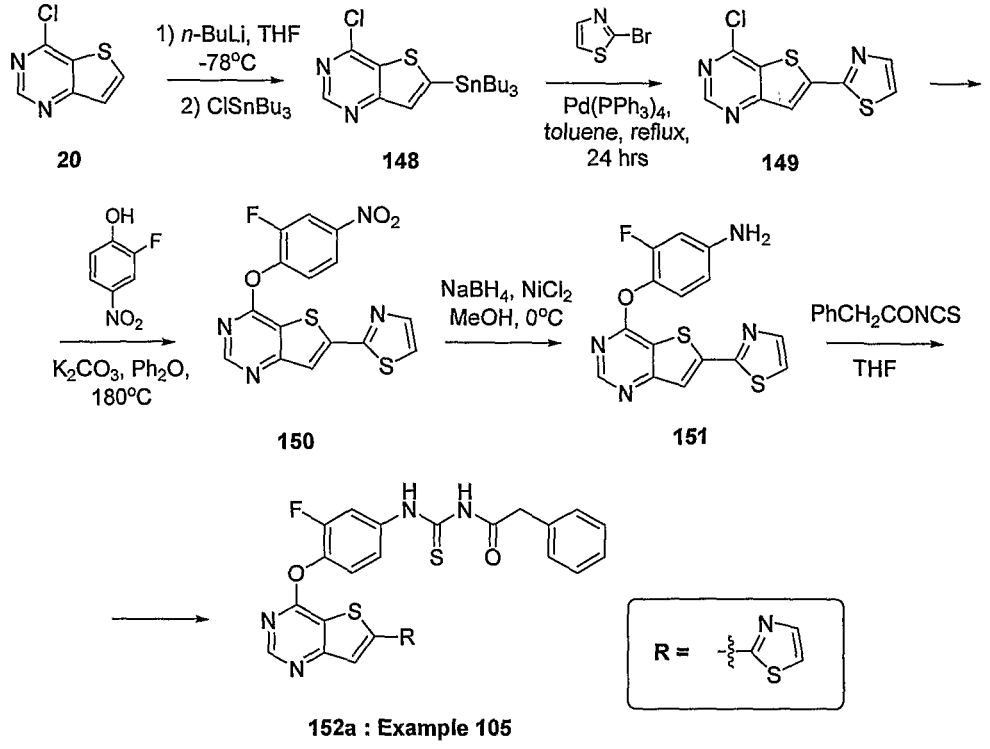
Table 13

Characterization of compounds 143-146 (examples 99-103)

Cpd	Ex	Ar	Name	Characterization
143	**100**		*N*-(3,5-Dichloro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.44 (s, 1H), 11.91 (s, 1H), 8.61 (d, 1H, J=5.5 Hz), 8.10 (s, 2H), 8.06 (s, 1H), 7.34-7.27 (m, 5H), 6.68 (d, 1H, J=5.5 Hz), 3.88-3.83 (m, 4H), 3.70-3.40 (m, 2H), 1.99-1.18 (m, 4H).

Cpd	Ex	Ar	Name	Characterization
144	101		N-(3-Chloro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.43 (s, 1H), 11.83 (s, 1H), 8.65 (d, 1H, J=5.7 Hz), 8.14 (d, 1H, J=2.3 Hz), 8.06 (s, 1H), 7.70 (dd, 1H, J=8.8/2.5 Hz), 7.55 (d, 1H, J=8.8 Hz), 7.34-7.26 (m, 5H), 6.74 (d, 1H, J=5.7 Hz), 3.87-3.83 (m, 4H), 3.56-3.53 (m, 2H), 1.99-1.88 (m, 4H).
145	102		N-(3-Methyl-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.43 (s, 1H), 11.74 (s, 1H), 8.62 (d, 1H, J=5.7 Hz), 8.04 (s, 1H), 7.69-7.65 (m, 2H), 7.43-7.26 (m, 6H), 6.67 (d, 1H, J=5.7 Hz), 3.87-3.82 (m, 4H), 3.67-3.38 (m, 2H), 2.13 (s, 3H), 1.99-1.18 (m, 4H).
146	103		2-Phenyl-N-(4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.41(s, 1H), 11.75(s, 1H), 8.68(d, J = 5.6 Hz, 1H), 8.06(s, 1H), 7.77(d, J = 8.8 Hz, 2H), 7.36(d, J = 8.8 Hz, 2H), 7.34-7.31(m, 4H), 7.30-7.24(m, 1H), 6.85(d, J = 5.6 Hz, 1H), 3.84(t, J = 6.4 Hz, 2H), 3.82(s, 2H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
147	104		N-(3-(Dimethylamino)-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, CDCl$_3$) δ ppm:** 8.48 (d, 1H, J=6.1 Hz), 8.27 (s, 1H), 7.56 (m, 8H), 6.67 (m, 1H), 3.91 (t, 2H, J=6.8 Hz), 3.78 (s, 2H), 3.74 (t, 2H, J=6.8 Hz), 2.73 (s, 6H), 2.19-2.01 (m, 4H).

Scheme 27



20 148 149 150 151

152a : Example 105

Example 105

N-(3-Fluoro-4-(6-(thiazol-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (152a)

Step 1. 4-Chloro-6-(tributylstannyl)thieno[3,2-d]pyrimidine (**148**)

[0388] Starting from 4-chloro-thieno[3,2-d]pyrimidine (**20**, scheme 4) and following the procedure described above for the synthesis of tributyltin compound **98** (scheme 19), title compound **148** was obtained in 79% yield. LRMS (M+1) 461.1 (100%).

Step 2. 4-Chloro-6-(thiazol-2-yl)thieno[3,2-d]pyrimidine (**149**)

[0389] Starting from the tributyltin compound **148** and following the procedure described above for the synthesis of compound 10 (scheme 2, example 12), title compound 149 was obtained in 81% yield. LRMS (M+1) 254.0 (100%).

Step 3. 4-(2-Fluoro-4-nitrophenoxy)-6-(thiazol-2-yl)thieno[3,2-d]pyrimidine (**150**)

[0390] Starting from the bis-aryl compound **149** and following the procedure described above for the synthesis of compound **11** (scheme 2, example 12) title compound **150** was obtained in 65% yield. LRMS (M+1) 375.0 (100%).

Steps 4-5. *N*-(3-Fluoro-4-(6-(thiazol-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**152a**)

[0391] Starting from the nitro compound **150**, following the procedure described above for the synthesis of compound **13a** (via the intermediate amine **12**, scheme 2, example 12), title compound **152a** was obtained [via intermediate 3-fluoro-4-(6-(thiazol-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)benzenamine (**151**)] in 7% yield. Characterization of **152a** is provided in the Table 14.

Examples 106-108

N-(3-Fluoro-4-(6-(pyridin-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (152b),

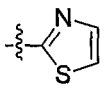
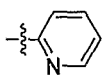
N-(3-Fluoro-4-(6-(thiophen-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (152c), and

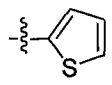
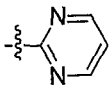
N-(3-Fluoro-4-(6-(thiophen-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (152d)

[0392] Compounds **152b-d** (Examples 106-108) were synthesized according to the Scheme 27, similarly to the compound **152a** (Example 105). Characterization of **152b-d** is provided in the Table 14.

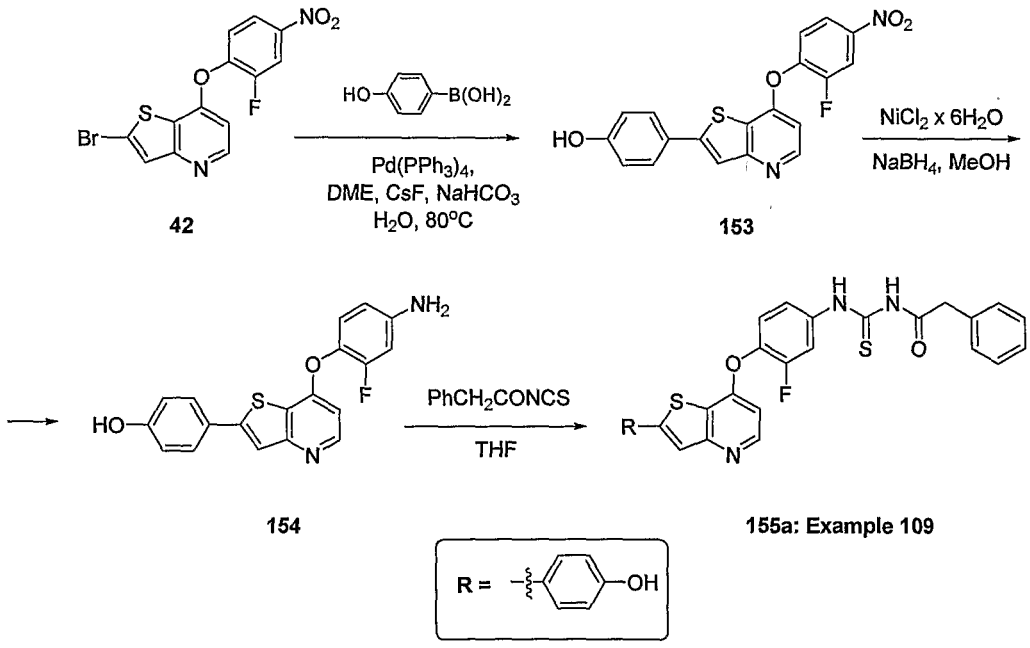
Table 14

Characterization of Compounds 152a-d (Examples 105-108)

Cpd	Ex	R	Name	Characterization
152a	**105**		*N*-(3-Fluoro-4-(6-(thiazol-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 8.75(s, 1H), 8.32(s, 1H), 8.05(d, J = 3.2 Hz, 1H), 8.03(d, J = 3.2 Hz, 1H), 7.96-7.88(m, 1H), 7.58-7.50(m, 1H), 7.50-7.43(m, 1H), 7.36-7.30(m, 4H), 7.30-7.23(m, 1H), 3.83(s, 2H).
152b	**106**		*N*-(3-Fluoro-4-(6-(pyridin-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.44(s, 1H), 11.80(s, 1H), 8.73(s, 1H), 8.70-8.64(m, 1H), 8.47(s, 1H), 8.38(m, J = 8.0 Hz, 1H), 8.00(td, J = 2.0 and 8.0 Hz, 1H), 7.92(dd, J = 2.0 and 12.0 Hz, 1H), 7.55(t, J = 8.8 Hz, 1H), 7.53-7.46(m, 2H), 7.36-7.31(m, 4H), 7.30-7.24(m, 1H), 3.82(s, 2H).

Cpd	Ex	R	Name	Characterization
152c	**107**		*N*-(3-Fluoro-4-(6-(thiophen-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.42(s, 1H), 11.80(s, 1H), 8.69(s, 1H), 7.92(dd, J = 2.4 and 10.4 Hz, 1H), 7.91(s, 1H), 7.82(dd, J = 1.2 and 4.8 Hz, 1H), 7.79(dd, J = 1.2 and 3.6 Hz, 1H), 7.54(t, J = 8.8 Hz, 1H), 7.47(dd, J = 2.4 and 8.8 Hz, 1H), 7.36-7.30(m, 4H), 7.30-7.25(m, 1H), 7.24(dd, J = 3.6 and 4.8 Hz, 1H), 3.82(s, 2H).
152d	**108**		*N*-(3-Fluoro-4-(6-(pyrimidin-2-yl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.44(s, 1H), 11.80(s, 1H), 9.00(s, 1H), 8.98(s, 1H), 8.77(s, 1H), 8.37(s, 1H), 7.94(dd, J = 2.4 and 12.0 Hz), 7.61(t, J = 5.2 Hz, 1H), 7.57(t, J = 8.8 Hz, 1H), 7.49(dd, J = 2.4 and 8.8 Hz, 1H), 7.38-7.31(m, 4H), 7.30-7.25(m 1H), 3.83(s, 2H).

Scheme 28



Example 109

N-(3-Fluoro-4-(2-(4-hydroxyphenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155a)

Step 1. 4-(7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenol (**153**)

[0393] To a solution of 2-bromo-7-(2-fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridine (**42**, scheme 8) (650 mg, 1.76 mmol) in ethylene glycol dimethyl ether (18 mL) were added 4-

hydroxyphenylboronic acid (486 mg, 3.52 mmol), tetrakis-triphenylphosphine palladium(0) (203 mg, 0.18 mmol), cesium fluoride (802 mg, 5.28 mmol) and a solution of sodium bicarbonate (444 mg, 5.28 mmol) in water (1 mL). The reaction mixture was purged with nitrogen, heated at 80°C for 4 hours, quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by trituration with methanol and ether to afford title compound **153** (418 mg, 62% yield) as a yellow solid. LRMS (M+1) 383.1 (100%).

Step 2. 4-(7-(4-Amino-2-fluorophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenol (**154**)

[0394] Following the procedure described above for the synthesis of the amine **49** (scheme 10, example 55) but substituting nitro compound **48** for the nitro compound **153**, title compound **154** was obtained in 99% yield (crude material, used in the next step without additional purification). LRMS (M+1) 353.1 (100%).

Step 3. *N*-(3-Fluoro-4-(2-(4-hydroxyphenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**155a**)

[0395] Following the procedure described above for the synthesis of Compound **50** (Scheme 10, Example 55) but substituting amine **49** for the amine **154**, title Compound **155a** was obtained in 3% yield. Characterization of **155a** is provided in the Table 14a.

Examples 110-118

N-(3-Fluoro-4-(2-(4-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155b),

N-(3-Fluoro-4-(2-(3-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155c),

N-(3-Fluoro-4-(2-(3-fluoro-4-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155d),

N-(3-Fluoro-4-(2-(4-morpholinophenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155e),

N-(3-Fluoro-4-(2-phenylthieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155f),

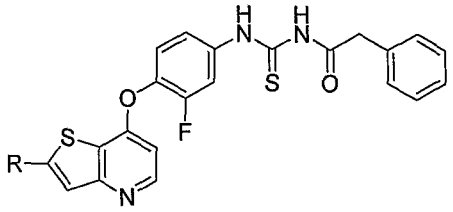
N-(3-Fluoro-4-(2-(2-morpholinopyrimidin-5-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155g),

N-(3-Fluoro-4-(2-(2-(2-morpholinoethoxy)pyrimidin-5-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155h),

N-(3-Fluoro-4-(2-(2-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155i), and

N-(3-Fluoro-4-(2-(4-hydroxy-3-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155j)

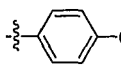
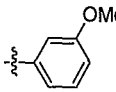
[0396] Compounds **155b-j** (Examples 110-118) were prepared similarly to the Compound **155a** (Example 109, Scheme 28). Characterization of **155b-j** is provided in the Table 14a.

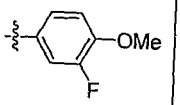
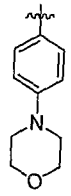
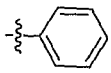
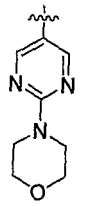
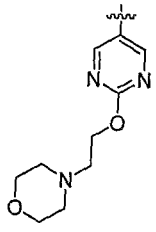


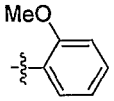
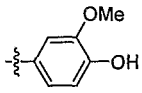
155a-j : Examples 109-118

Table 14a

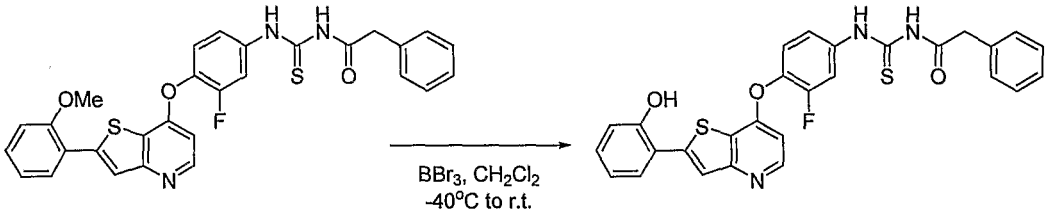
Characterization of compounds 152a-j (examples 109-118)

Cpd	Ex	R	Name	Characterization
155a	**109**		N-(3-Fluoro-4-(2-(4-hydroxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.46 (s, 1H), 11.82 (s, 1H), 9.95 (s, 1H), 8.46 (d, 1H, J=5.3 Hz), 7.99 (d, 1H, J=13.1 Hz), 7.83(s, 1H), 7.70 (d, 2H, J=13.1 Hz), 7.52-7.51 (m, 2H), 7.34-7.27 (m, 5H), 6.86 (d, 2H, J=8.6 Hz), 6.59 (d, 1H, J=5.5 Hz), 3.83 (s, 2H).
155b	**110**		N-(3-Fluoro-4-(2-(4-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.46(s, 1H), 11.82(s, 1H), 8.48(d, J = 5.6 Hz, 1H), 8.00(d, J = 7.6 Hz, 1H), 7.91(s, 1H), 7.81(d, J = 8.8 Hz, 2H), 7.66-7.60(m, 2H), 7.37-7.31(m, 4H), 7.31-7.24(m, 1H), 7.05(d, J = 8.8 Hz, 2H), 6.61(d, J = 5.6 Hz, 1H), 3.82(s, 3H).
155c	**111**		N-(3-Fluoro-4-(2-(3-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.46(s, 1H), 11.82(s, 1H), 8.52(d, J = 5.6 Hz, 1H), 8.10(s, 1H), 8.01(d, J = 12.4 Hz, 1H), 7.56-7.51(m, 2H), 7.46-7.37(m, 3H),7.37-7.31(m, 4H), 7.31-7.24(m, 1H), 7.05-7.00(m, 1H), 6.65(d, J = 5.6 Hz, 1H), 3.85(s, 3H), 3.82(s, 2H).

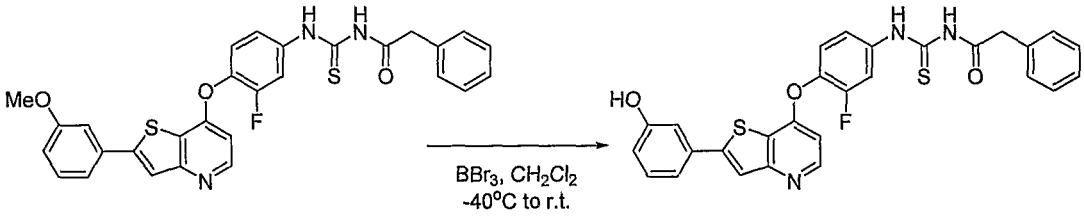
Cpd	Ex	R	Name	Characterization
155d	112		N-(3-Fluoro-4-(2-(3-fluoro-4-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.46(s, 1H), 11.82(s, H), 8.49(d, J = 5.6 Hz, 1H), 8.01(s, 1H), 8.2-7.76(m, 1H), 7.84(dd, J = 2.4 and 12.0 Hz, 1H), 7.66-7.61(m, 1H), 7.55-7.51(m, 2H), 7.38-7.10(m, 6H), 6.63(d, J = 5.6 Hz, 1H), 3.90(s, 3H), 3.82(s, 2H).
155e	113		N-(3-Fluoro-4-(2-(4-morpholinophenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.49(s, 1H), 11.85(s, 1H), 8.63(d, J = 5.6 Hz, 1H), 8.03(d, J = 11.6 Hz, 1H), 7.89(s, 1H), 7.79(d, J = 8.8 Hz, 2H), 7.63-7.56(m, 2H), 7.36-7.31(m, 4H), 7.31-7.25(m, 1H), 7.05(d, J = 8.8 Hz, 2H), 6.87(d, J = 5.6 Hz, 1H), 3.83(s, 2H), 3.78-3.73(m, 4H), 3.30-3.24(m, 4H).
155f	114		N-(3-Fluoro-4-(2-phenylthieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.46(s, H), 11.82(s, 1H), 8.52(d, J = 5.6 Hz, 1H), 8.06(s, 1H), 8.01(d, J = 12.4 hz, 1H), 7.88(d, J = 6.8 Hz, 2H), 7.58-7.41(m, 5H), 7.38-7.31(m, 4H), 7.31-7.24(m, 1H), 6.65(d, J = 5.6 Hz, 1H), 3.82(s, 2H).
155g	115		N-(3-Fluoro-4-(2-(2-morpholinopyrimidin-5-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.46(s, 1H), 11.82(s, 1H), 8.89(s, 2H), 8.49(d, J = 5.6 hz, 1H), 8.00(d, J = 12.0 Hz, 1H), 7.98(s, 1H), 7.56-7.51(m, 2H), 7.37-7.31(m, 4H), 7.31-7.24(m, 1H), 6.61(d, J = 5.6 Hz, 1H), 3.82(s, 2H), 3.82-3.76(m, 4H), 3.70-3.66(m, 4H).
155h	116		N-(3-Fluoro-4-(2-(2-(2-morpholinoethoxy)pyrimidin-5-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:** 12.49(s, 1H), 11.85(s, 1H), 9.13(s, 2H), 8.56(d, J = 5.6 Hz, 1H), 8.18(s, 1H), 8.03(d, J = 1.8 Hz, 1H), 7.60-7.54(m, 2H), 7.39-7.32(m, 4H), 7.32-7.25(m, 1H), 6.68(d, J = 5.6 Hz, 1H), 4.50(t, J = 5.6 Hz, 2H), 3.83(s, 2H), 3.57(t, J = 4.4 Hz, 4H), 2.73(t, J = 5.6 Hz,2H), 2.51-2.44(m, 4H).

Cpd	Ex	R	Name	Characterization
155i	117		N-(3-Fluoro-4-(2-(2-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.51 (s, 1H), 11.84 (s, 1H), 8.67 (d, 1H, J=6.1 Hz), 8.13 (s, 1H), 8.08 (d, 1H, J=13.1 Hz), 8.02 (dd, 1H, J=7.7 / 1.5 Hz), 7.61-7.60 (m, 2H), 7.50 (td, 1H, J=7.8 / 1.7 Hz), 7.35-7.32 (m, 4H), 7.29-7.26 (m, 2H), 7.13 (td, 1H, J=7.6 / 1.1 Hz), 6.88 (d, 1H, J=6.1 Hz), 4.00 (s, 3H), 3.83 (s, 2H).
155j	118		N-(3-Fluoro-4-(2-(4-hydroxy-3-methoxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.49 (s, 1H), 11.85 (s, 1H), 9.57 (s, 1H), 8.49 (d, 1H, J=5.5 Hz), 8.01 (d, 1H, J=13.5 Hz), 7.94 (s, 1H), 7.54-7.53 (m, 2H), 7.44 (d, 1H, J=2.3 Hz), 7.38-7.27 (m, 6H), 6.88 (d, 1H, J=8.2 Hz), 6.61 (d, 1H, J=4.9 Hz), 3.89 (s, 3H), 3.83 (s, 2H).

Scheme 29



155i : Example 117 155k : Example 119



155c : Example 111 155l : Example 120

Example 119

N-(3-Fluoro-4-(2-(2-hydroxyphenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155k)

[0397] To a cold (-40°C) solution of the compound **155i** (80 mg, 0.15 mmol) in DCM (3 mL) was added tribromoborane (1M in DCM, 0.60 mL, 0.60 mmol). The reaction mixture was stirred overnight at room temperature. Water and methanol were added and the mixture

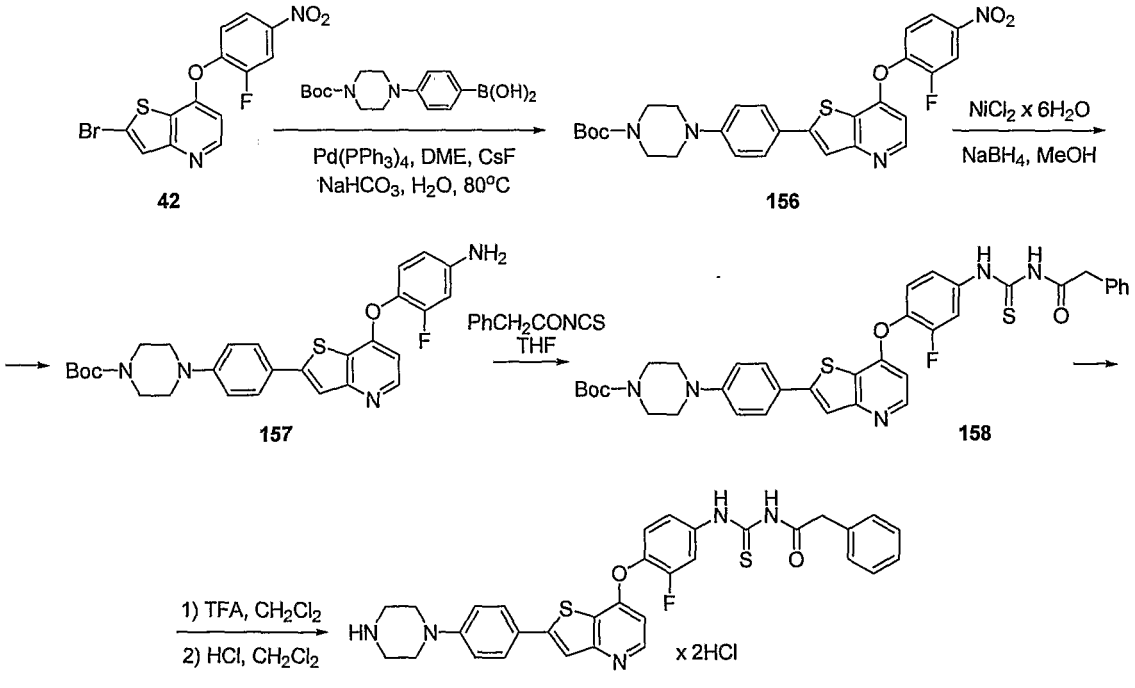
was stirred for additional 20 minutes. Organic phase was separated and the aqueous layer was extracted with EtOAc. Both organic phases were combined, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (eluent MeOH-DCM, 2:98) then triturated with methanol, to afford the title compound **155k** (6 mg, 7%yield), as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.47 (d, 1H, J=0.4 Hz), 11.82 (s, 1H), 10.65 (s, 1H), 8.48 (d, 1H, J=5.5 Hz), 8.07 (s, 1H), 8.01 (d, 1H, J=11.5 Hz), 7.84 (d, 1H, J=7.8 Hz), 7.53-7.49 (m, 2H), 7.38-7.23 (m, 6H), 7.01 (d, 1H, J=8.2 Hz), 6.93 (t, 1H, J=7.4 Hz), 6.58 (d, 1H, J=5.5 Hz), 3.83 (s, 2H). LRMS (M+1) 530.2 (100%).

Example 120

N-(3-Fluoro-4-(2-(3-hydroxyphenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (155l)

[0398] Following the procedure described above for the synthesis of compound **155k** (example 119, scheme 29) but substituting methoxy-compound **155i** for the methoxy-compound **155c**, title compound **155l** was prepared in 62% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.49(s, 1H), 11.84(s, 1H), 8.68(d, J = 5.6 Hz, 1H), 8.07(d, J = 12.0 Hz, 1H), 7.99(s, 1H), 7.64-7.56(m, 2H), 7.38-7.24(m, 8H), 6.96-6.88(m, 2H), 3.83(s, 2H).

Scheme 30



Example 121

N-(3-Fluoro-4-(2-(4-(piperazin-1-yl)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide di-hydrochloride (159)

Step 1. *tert*-Butyl 4-(4-(7-(2-fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenyl)piperazine-1-carboxylate (**156**)

[0399] Starting from the nitro-bromo compound **42**, following the procedure described above for the synthesis of compound **48** (scheme 10, example 55) but substituting 4,4,5,5-tetramethyl-2-(4-(methylsulfonyl)phenyl)-1,3,2-dioxaborolane for 4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)phenylboronic acid, title compound **156** was obtained in 70% yield. LRMS (M+1) 550.6 (100%).

Step 2. *tert*-Butyl 4-(4-(7-(4-amino-2-fluorophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenyl)piperazine-1-carboxylate (**157**)

[0400] Following the procedure described above for the synthesis of amine **49** (scheme 10, example 55) but substituting nitro compound **48** for the nitro compound **156**, title compound **157** was obtained in 99% yield (crude material, used in the next step without additional purification). LRMS (M+1) 520.2 (100%).

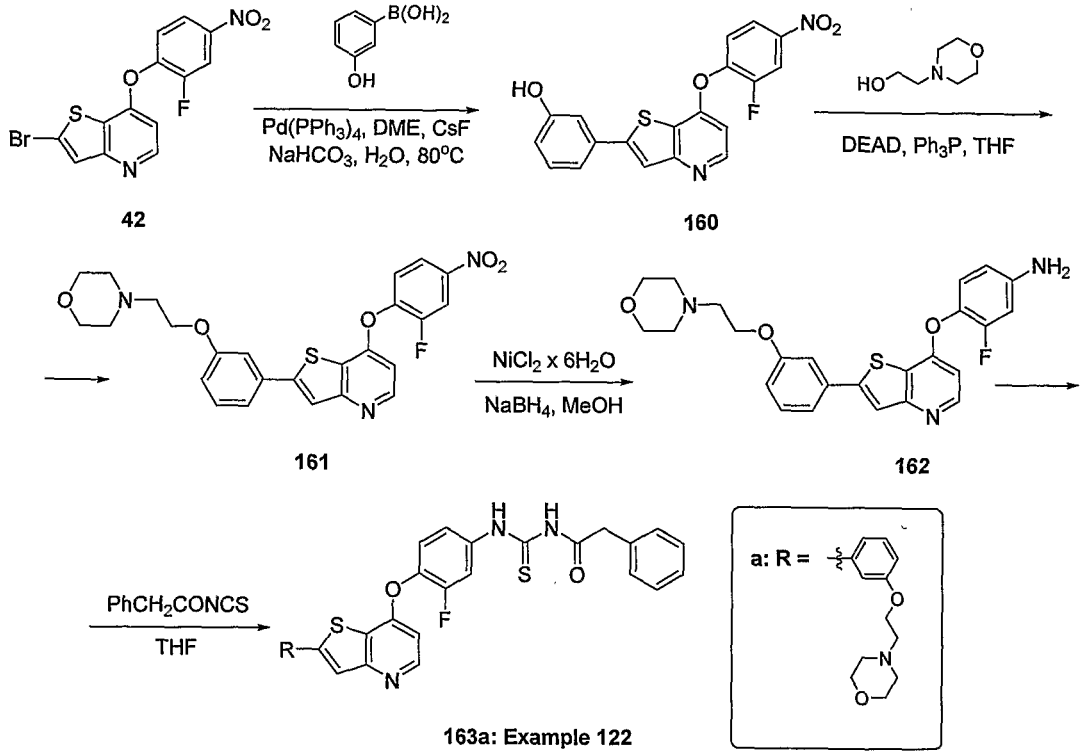
Step 3. t*ert*-Butyl 4-(4-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-*b*]pyridine-2-yl)phenyl)piperazine-1-carboxylate (**158**)

[0401] Following the procedure described above for the synthesis of compound **50** (scheme 10, example 55) but substituting amine **49** for the amine **157**, title compound **158** was obtained in 41% yield. LRMS (M+1) 697.2 (100%).

Step 4. *N*-(3-Fluoro-4-(2-(4-(piperazin-1-yl)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide di-hydrochloride (**159**)

[0402] Following the procedure described above for the synthesis of compound **137a** (scheme 25, example 97) but substituting compound **135b** for the compound **158**, title compound **159** was obtained in 21% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.48(s, 1H), 11.84(s, 1H), 9.26(bs, 1H), 8.62(d, J = 5.6 Hz, 1H), 8.05(d, J = 12.0 Hz, 1H), 7.94(s, 1H), 7.81(d, J = 8.8 Hz, 2H), 7.62-7.55(m, 2H), 7.37-7.31(m, 4H), 7.31-7.24(m, 1H), 7.10(d, J = 8.8 Hz, 2H), 6.85(d, J = 5.6 Hz, 1H), 3.83(s, 2H), 3.58-3.51(m, 4H), 3.26-3.18(m, 4H). LRMS (M+1) 597.2 (100%).

Scheme 31



163a: Example 122

Example 122

N-(3-Fluoro-4-(2-(3-(2-morpholinoethoxy)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (163a)

Step 1. 3-(7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenol (**160**)

[0403] Starting from the nitrobromo compound **42**, following the procedure described above for the synthesis of compound **153** (scheme 28, example 109) but substituting 4-hydroxyphenylboronic acid for 3-hydroxyphenylboronic acid, title compound **160** was obtained in 66% yield as a gray solid. LRMS (M+1) 383.1 (100%).

Step 2. 4-(2-(3-(7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenoxy)ethyl)morpholine (**161**)

[0404] Diethylazodicarboxylate (0.6 mL, 3.84 mmol) was added to the solution of **160** (1.05 g, 2.75 mmol), 2-morpholinoethanol (0.5 mL, 3.84 mmol) and triphenylphosphine (1.01 g, 3.84 mmol) in tetrahydrofuran (27 mL). The reaction mixture was stirred until its completion, quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The organic phase was washed with water and brine, dried over anhydrous magnesium sulfate, filtred and evaporated under reduced pressure. The residue was purified by flash chromatography, eluent MeOH-DCM (2:98) to afford title compound **161** (906 mg, 66%yield) as a light-yellow solid. LRMS (M+1) 496.3 (100%).

Step 3. 3-Fluoro-4-(2-(3-(2-morpholinoethoxy)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)benzenamine (**162**)

[0405] Following the procedure described above for the synthesis of amine **49** (scheme 10, example 55) but substituting nitro compound **48** for the nitro compound **161**, title compound **162** was obtained in 91% yield (crude material, used in the next step without additional purification). LRMS (M+1) 466.2 (100%).

Step 4. *N*-(3-Fluoro-4-(2-(3-(2-morpholinoethoxy)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**163a**)

[0406] Following the procedure described above for the synthesis of compound **50** (scheme 10, example 55) but substituting amine **49** for the amine **162**, title compound **163a** was obtained in 29% yield. Characterization of **163a** is provided in the table 15.[LRMS (M+1) 643.3 (100%).

Examples 123-127

N-(3-Fluoro-4-(2-(4-(2-morpholinoethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (163b)

N-(3-Fluoro-4-(2-(4-(2-(piperidin-1-yl)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (163c)

N-(3-Fluoro-4-(2-(4-(2-(pyridin-2-yl)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride (163d)

N-(3-Fluoro-4-(2-(4-(3-morpholinopropoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (163e)

tert-Butyl 2-(4-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)phenoxy)ethyl(methyl)carbamate (163f)

[0407] Starting from the phenol **153** (scheme 28, example 109) and following the procedures described above for the synthesis of **163a** (Scheme 31, Example 122) title compounds **163b-f** were obtained. Characterization of **163b-f** is provided in the Table 15.

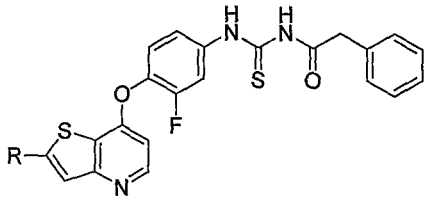
Examples 128-129

N-(3-Fluoro-4-(2-(3-methoxy-4-(2-morpholinoethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (163g)

N-(3-Fluoro-4-(2-(2-(2-morpholinoethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride (163h)

[0408] Following the procedures described above for the synthesis of **163a** (Scheme 31, example 122) but replacing in the first step 3-hydroxyphenylboronic acid with 4-hydroxy-3-

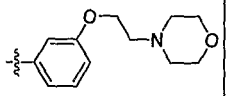
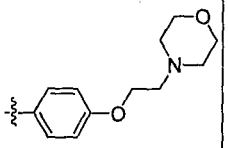
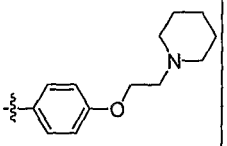
methoxyphenylboronic acid or 2-hydroxyphenylboronic acid, title compounds **163g-h** were obtained. Characterization of **163g-h** is provided in the table 15.

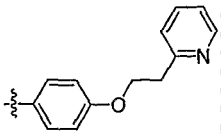
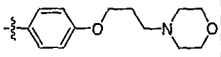
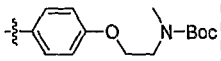
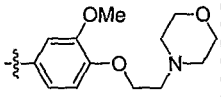


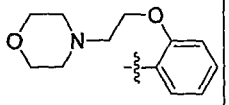
163a-h: Example 122-128

Table 15

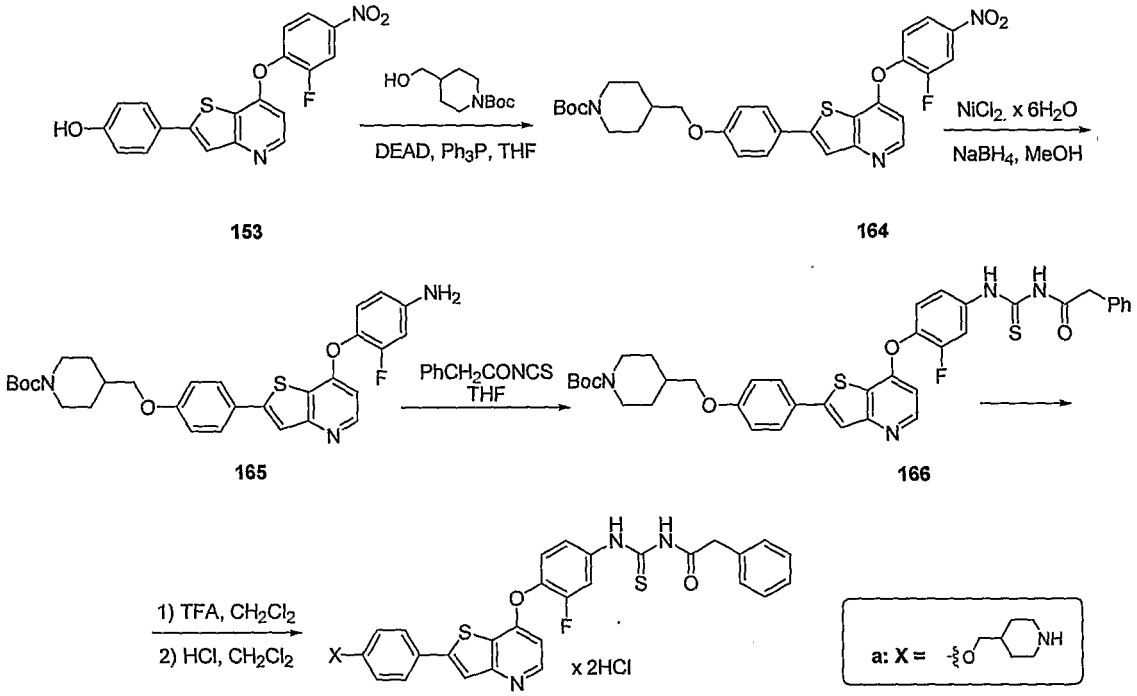
Characterization of compounds 163a-h (examples 122-128)

Cpd	Ex	R	Name	Characterization
163a	**122**		*N*-(3-Fluoro-4-(2-(3-(2-morpholinoethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.47 (s, 1H), 11.82 (s, 1H), 8.52 (d, 1H, J=5.5 Hz), 8.12 (s, 1H), 8.01 (d, 1H, J=12.1 Hz), 7.54-7.52 (m, 2H), 7.45-7.26 (m, 8H), 7.04-7.01 (m, 1H), 6.65 (d, 1H, J=5.3 Hz), 4.20 (t, 2H, J=5.8 Hz), 3.83 (s, 2H), 3.57 (t, 4H, J=4.6 Hz), 2.73 (t, 2H, J=5.6 Hz), 2.51-2.49 (m, 4H).
163b	**123**		*N*-(3-Fluoro-4-(2-(4-(2-morpholinoethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.46(s, 1H), 11.82(s, 1H), 8.49(s, J = 5.6 Hz, 1H), 8.00(d, J = 12.0 Hz, 1H), 7.94(s, 1H), 7.90-7.78(m, 2H), 7.56-7.38(m, 2H), 7.39-7.22(m, 5H), 7.16-7.02(m, 2H), 6.62(d, J = 5.6 H, 1H), 4.34-3.90(m, 3H), 3.82(s, 2H), 3.76-2.40(m, 9H).
163c	**124**		*N*-(3-Fluoro-4-(2-(4-(2-(piperidin-1-yl)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 8.52(bs, 1H), 8.38(d, J = 5.6 Hz, 1H), 8.0(dd, J = 2.0 and 12.0 Hz, 1H), 7.75(d, J = 8.4Hz, 2H), 7.64(s, 1H), 7.44-7.40(m, 1H), 7.38-7.29(m, 5H), 7.29-7.24(m, 1H), 7.07(d, J = 8.4 Hz, 2H), 6.60(d, J = 5.6 Hz, 1H), 4.39-4.31(m, 2H), 3.75(s, 2H), 3.39-3.33(m, 2H), 3.20-3.05(m, 4H), 1.89-1.79(m, 4H), 1.70-1.60(m, 2H).

Cpd	Ex	R	Name	Characterization
163d	125		*N*-(3-Fluoro-4-(2-(4-(2-(pyridin-2-yl)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.48(s, 1H), 11.84(s, 1H), 8.81(d, J = 4.8 Hz, 1H), 8.61(d, J = 5.6 Hz, 1H), 8.44(t, J = 7.6 Hz, 1H), 8.35-7.98(m, 2H), 7.97(s, 1H), 7.86(d, J = 8.8 Hz, 2H), 7.61-7.55(m, 2H), 7.38-7.31(m, 4H), 7.31-7.24(m, 1H), 7.07(d, J = 8.8 Hz, 2H), 6.82(d, J = 5.6 Hz, 1H), 4.51(t, J = 6.0 Hz, 2H), 3.83(s, 2H), 3.52(t, J = 6.0 Hz, 2H).
163e	126		*N*-(3-Fluoro-4-(2-(4-(3-morpholinopropoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.46 (s, 1H), 11.82 (s, 1H), 8.48 (d, 1H, J=5.3 Hz), 8.00 (d, 1H, J=12.5 Hz), 7.91 (s, 1H), 7.80 (d, 2H, J=8.8 Hz), 7.53 (m, 2H), 7.34-7.22 (m, 5H), 7.04 (d, 2H, J=8.6 Hz), 6.61 (d, 1H, J=5.7 Hz), 4.10-4.07 (m, 2H), 3.83 (s, 2H), 3.59-3.55 (m, 4H), 2.50-2.41 (m, 6H), 1.92 (m, 2H)
163f	127		*tert*-Butyl 2-(4-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)phenoxy)ethyl(methyl)carbamate	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.50 (S, 1H), 11.85 (s, 1H), 8.50 (d, 1H, J=5.5 Hz), 8.02 (d, 1H, J=13.3 Hz), 7.94 (s, 1H), 7.83 (d, 2H, J=8.8 Hz), 7.55-7.54 (m, 2H), 7.38-7.26 (m, 5H), 7.08 (d, 2H, J=8.8 Hz), 6.63 (d, 1H, J=5.3 Hz), 4.17 (br s, 2H), 3.83 (s, 2H), 3.56 (m, 2H), 2.90-2.86 (m, 3H), 1.40-1.36 (m, 9H).
163g	128		N-(3-Fluoro-4-(2-(3-methoxy-4-(2-morpholinoethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 8.51 (d, 1H, J=5.5 Hz), 8.03-8.01 (m, 2H), 7.55-7.53 (m, 2H), 7.47 (d, 1H, J=2.2Hz), 7.39-7.24 (m, 6H), 7.10 (d, 1H, J=8.6 Hz), 6.63 (d, 1H, J=5.5 Hz), 4.14 (t, 2H, J=5.9 Hz), 3.88 (s, 3H), 3.83 (s, 2H), 3.58 (t, 4H, J=4.6 Hz), 2.71 (t, 2H, J=5.9 Hz), 2.46-2.43 (m, 4H).

Cpd	Ex	R	Name	Characterization
163h	**129**		N-(3-Fluoro-4-(2-(2-(2-morpholinoethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide hydrochloride	1H NMR (400 MHz, DMSO-d6) δ ppm: 12.50 (s, 1H), 11.86 (s, 1H), 11.66-11.50 (br s, 1H), 8.79-8.76 (m, 1H), 8.37 (d, 1H, J=5.9 Hz), 8.08 (dd, 1H, J=11.3/2.0 Hz), 7.93 (dd, 1H, J=7.6/1.6 Hz), 7.63-7.52 (m, 3H), 7.35-7.16 (m, 7H), 6.99 (t, 1H, J=4.8 Hz), 4.71 (br s, 2H), 3.93-3.91 (m, 2H), 3.84 (s, 2H), 3.80-3.77 (m, 4H), 3.53-3.50 (m, 2H), 3.36-3.33 (m, 2H).

Scheme 32



167a: Example 130

Example 130

N-(3-Fluoro-4-(2-(4-(piperidin-4-ylmethoxy)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (167a)

Step 1. *tert*-Butyl-4-((4-(7-(2-fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenoxy)methyl)piperidine-1-carboxylate (**164**)

[0409] Starting from the compound **153** (shown in the scheme 28) and following the procedure described above for the synthesis of compound **161** (step 2, scheme 31, example 122), title compound **164** was obtained in 69% yield. LRMS (M+1) 579.2 (100%).

Step 2. *tert*-Butyl 4-((4-(7-(4-amino-2-fluorophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenoxy)methyl)piperidine-1-carboxylate (**165**)

[0410] Following the procedure described above for the synthesis of amine **157** (scheme 30, example 121) but substituting nitro compound **156** for the nitro compound **164**, title compound **165** was obtained in 99% yield (crude material, used in the next step without additional purification). LRMS (M+1) 549.2 (100%).

Step 3. *tert*-Butyl-4-((4-(7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-*b*]pyridin-2-yl)phenoxy)methyl)piperidine-1-carboxylate (**166**)

[0411] Following the procedure described above for the synthesis of compound **158** (scheme 30, example 121) but substituting amino compound **157** for the amino compound **165**, title compound **166** was obtained in 31% yield. LRMS (M+1) 726.2 (100%).

Step 4. *N*-(3-Fluoro-4-(2-(4-(piperidin-4-ylmethoxy)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide di-hydrochloride (**167a**)

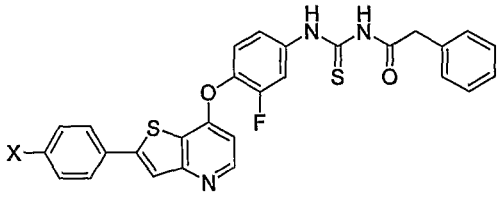
[0412] Following the procedure described above for the synthesis of compound **159** (scheme 30, example 121) but substituting Boc-protected amino compound **158** for the Boc-protected amino compound **166**, title compound **167a** (presumably as a di-hydrochloride salt) was obtained in 15% yield. Characterization of **167a** is provided in the table 16. LRMS (M+1) 626.2 (100%).

Example 131-132

(S)-N-(3-Fluoro-4-(2-(4-(pyrrolidin-2-ylmethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (167b) and

N-(4-(2-(4-(4-Aminobutoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (167c)

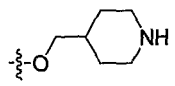
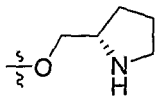
Following the procedures described above for the synthesis of **167a** (scheme 32, example 130) but replacing in the first step *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate with (S)-tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate or tert-butyl 4-hydroxybutylcarbamate, title compounds **167b-c** were obtained. Characterization of **167b-c** is provided in the table 16.



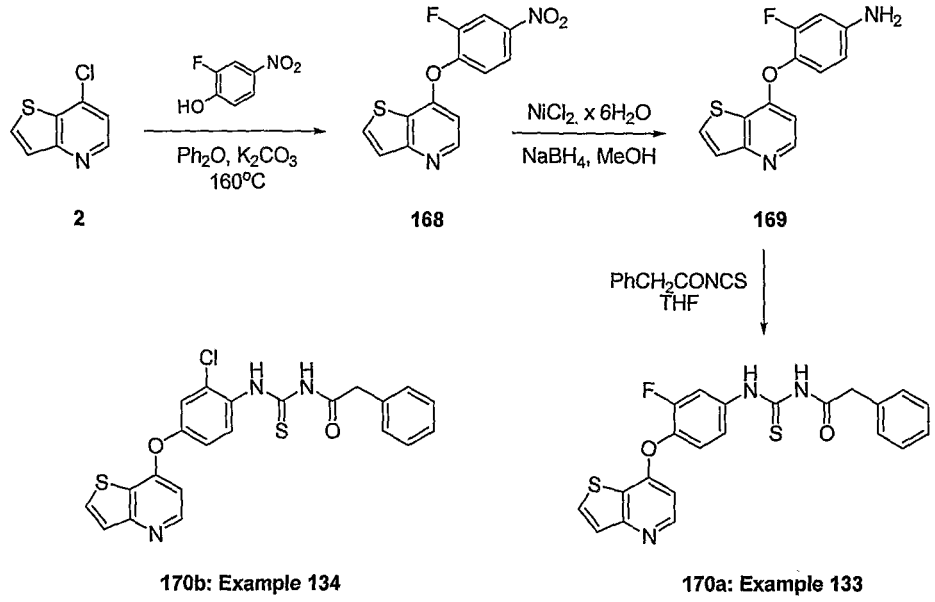
167a-c: Examples 130-132

Table 16

Characterization of compounds 167a-c (examples 130-132)

Cpd	Ex	X	Name	Characterization
167a	**130**		N-(3-Fluoro-4-(2-(4-(piperidin-4-ylmethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide di-hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 8.41(d, J = 5.6 hz, 1H), 8.06(dd, J = 3.2 and 12.4 Hz, 1H), 7.75(d, J = 8.8 Hz, 2H), 7.65(s, 1H), 7.37-7.43(m, 1H), 7.39(d, J = 8.4 Hz, 1H), 7.37-7.33(m, 4H), 7.33-7.25(m, 1H), 7.04(d, J = 8.8 Hz, 2H), 6.64(d, J = 5.6 Hz, 1H), 3.98(d, J = 5.6 Hz, 2H), 3.76(s, 2H), 3.50-3.42(m, 2H), 3.12-3.01(m, 2H), 2.25-2.16(m, 1H), 2.162.06(m, 2H), 1.92-1.58(m, 2H).
167b	**131**		(S)-N-(3-Fluoro-4-(2-(4-(pyrrolidin-2-ylmethoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide di-hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 12.46(s, 1H), 11.82(s, 1H), 8.49(d, J = 5.6 Hz, 1H), 8.04-7.88(m, 1H), 7.96(s, 1H), 7.86(d, J = 8.8 Hz, 1H), 7.56-7.51(m, 2H), 7.36-7.31(m, 4H), 7.31-7.24(m, 1H), 7.11(d, J = 8.8 Hz, 2H), 6.63(d, J = 5.6 Hz, 1H), 4.34(dd, J = 4.4 and 10.8 Hz, 1H), 4.20-4.12(m, 1H), 4.00-3.90(m, 1H), 3.82(s, 2H), 3.28-3.18(m, 2H), 2.20-2.10(m, 1H), 2.05-1.88(m, 2H), 1.82-1.70(m, 1H).
167c	**132**	-O(CH$_2$)$_4$NH$_2$	N-(4-(2-(4-(4-Aminobutoxy)phenyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide di-hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm:** 8.40(d, J = 5.6 Hz, 1H), 8.05(dd, J = 3.2 and 12.0 Hz, 1H), 7.75(d, J = 8.8 Hz, 2H), 7.64(s, H), 7.48-7.43(m, 1H), 7.39(d, J = 8.8 Hz, 1H), 7.37-7.31(m, 4H), 7.31-7.24(m, 1H), 7.03(d, J = 8.8 Hz, 2H), 6.64(d, j = 5.6 Hz, 1H), 4.11(t, J = 5.6 Hz,2H), 3.76(s, 2H), 3.03(t, J = 7.2 Hz, 2H), 1.99-1.83(m, 4H).

Scheme 33



2 168 169

170b: Example 134 170a: Example 133

Example 133

N-(3-Fluoro-4-(thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (170a)

Step 1. 7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridine (**168**)

[0413] Starting from the chloride **2** (scheme 1) and following the procedure described above for the synthesis of compound **6** (scheme 1, example 1), title compound **168** was obtained in 45% yield. LRMS (M+1) 290.3 (100%).

Step . 3-Fluoro-4-(thieno[3,2-*b*]pyridin-7-yloxy)benzenamine (**169**)

[0414] Starting from the nitro compound **168** and following the procedure described above for the synthesis of amine **49** (scheme 10, example 55), title compound **169** was obtained in 41% yield. LRMS (M+1) 260.3 (100%).

Step 3. *N*-(3-Fluoro-4-(thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**170a**)

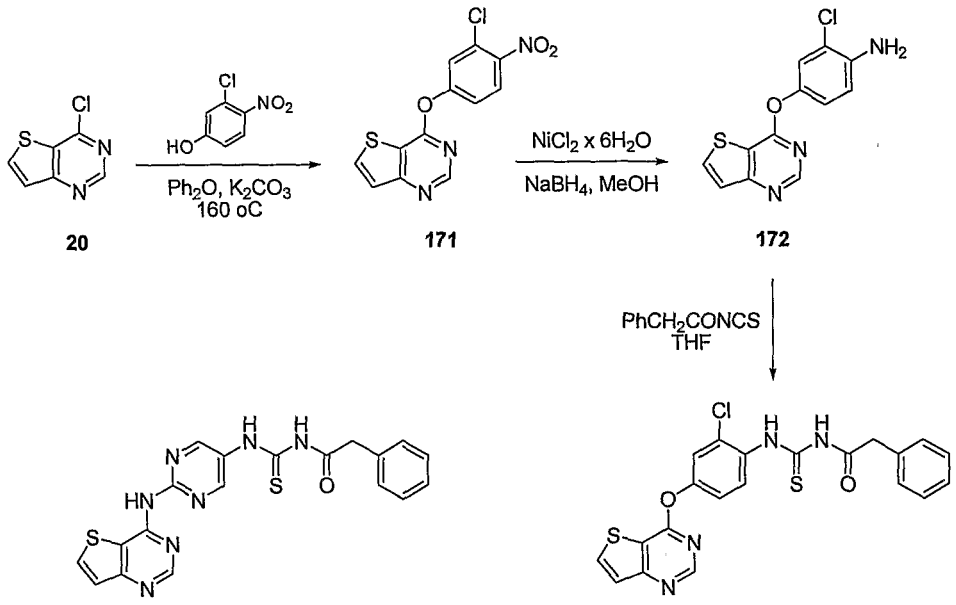
[0415] Starting from the amine **169** and following the procedure described above for the synthesis of compound **50** (scheme 10, example 55), title compound **170a** was obtained in 29 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.46(s, 1H), 11.81(s, 1H), 8.52(d, J = 5.2 Hz, 1H), 8.17(d, J = 5.2Hz, 1H), 8.01(dd, J = 2.0 and 11.2 Hz, 1H), 7.60(d, J = 5.2 Hz, 1H), 7.58-7.48(m, 2H), 7.36-7.30(m, 4H), 7.30-7.22(m, 1H), 6.64(d, J = 5.2Hz, 1H), 3.82(s, 2H). LRMS (M+1) 437.5 (100%).

Example 134

N-(2-Chloro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (170b)

[0416] Title compound **170b** (example 134) was obtained according to the scheme 33 via a 3-step synthesis starting from the chloride **2** and replacing 2-fluoro-4-nitrophenol [in the step 1] with 3-chloro-4-nitrophenol. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.36(s, H), 11.88(s, 1H), 8.55(d, J = 5.6 Hz, 1H), 8.159d, J = 5.6 Hz, 1H), 8.08(d, J = 8.8 Hz, 1H), 7.61(d, J = 2.8 Hz, 1H), 7.60(d, J = 5.6 Hz, 1H), 7.36-7.30(m, 4H), 7.32(m, J = 2.8 Hz, 1H), 7.30-7.24(m, 1H), 6.73(d, J = 5.6 Hz, 1H), 3.84(s, 2H).

Scheme 34



Example 135

N-(2-Chloro-4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (173)

Step 1. 4-(3-Chloro-4-nitrophenoxy)thieno[3,2-*d*]pyrimidine (**171**)

[0417] Starting from the chloride **20** (scheme 4) and following the procedure described above for the synthesis of compound **24** (scheme 4, example 22) remplacing 2-fluoro-4-nitrophenol with 3-chloro-4-nitrophenol, title compound **171** was obtained in 72% yield. LRMS (M+1) 307.7 (100%).

Step 2. 2-Chloro-4-(thieno[3,2-*d*]pyrimidin-4-yloxy)benzenamine (**172**)

[0418] Starting from the nitro compound **171** and following the procedure described above for the synthesis of amine **25** (scheme 4, example 22), title compound **172** was obtained in 80% yield. LRMS (M+1) 277.7 (100%).

Step 3. *N*-(2-Chloro-4-(thieno[3,2-*d*]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**173**)

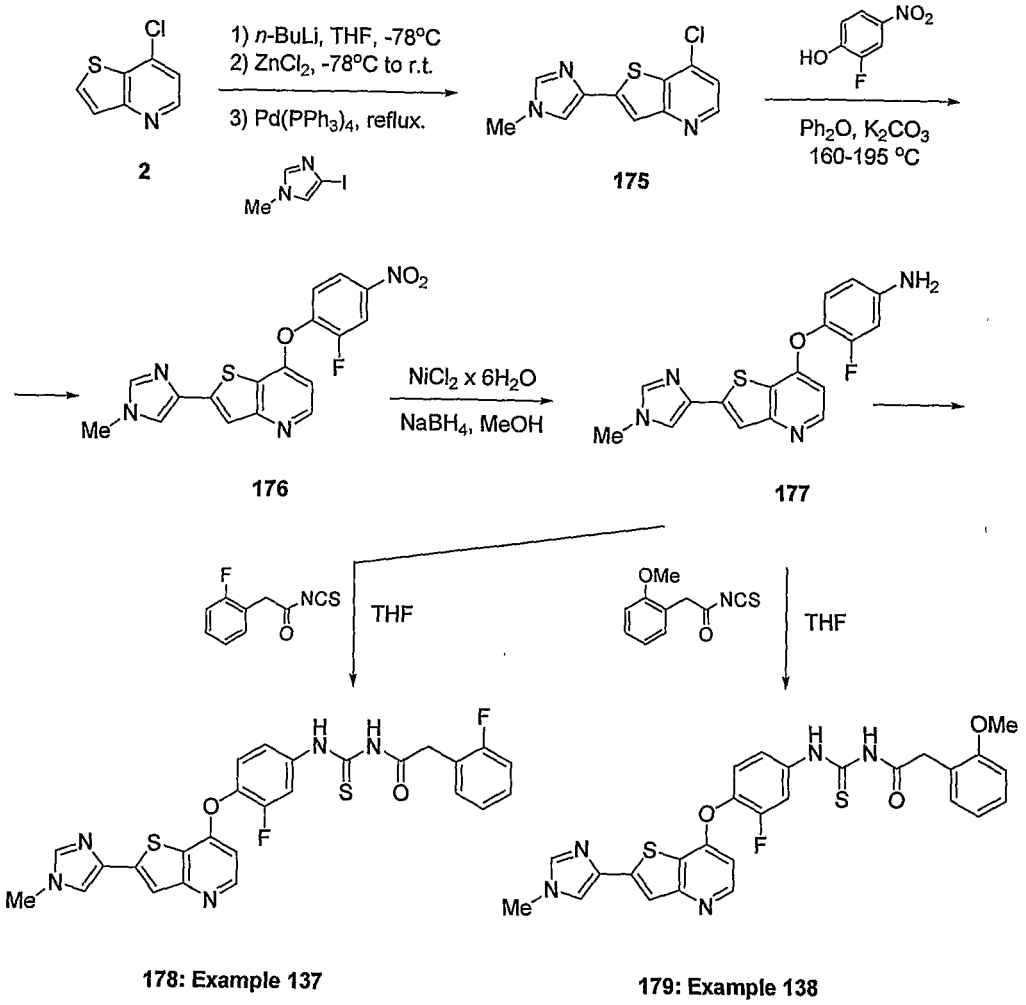
[0419] Starting from the amine **172** and following the procedure described above for the synthesis of compound **26a** (scheme 4, example 22), title compound **173** was obtained in 9% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.35(s, 1H), 11.89(s, 1H), 8.72(s, 1H), 8.48(d, J = 5.6 Hz, 1H), 8.04(d, J = 8.8 Hz, 1H), 7.69(d, J = 2.8 Hz, 1H), 7.68(d, J = 5.6 Hz, 1H), 7.40(dd, J = 2.8 and 8.8 Hz, 1H), 7.36-7.30(m, 4H), 7.30-7.24(m, 1H), 3.84(s, 2H). LRMS (M+1) (100%).

Example 136

2-Phenyl-*N*-(2-(thieno[3,2-d]pyrimidin-4-ylamino)pyrimidin-5-ylcarbamothioyl)acetamide (174)

[0420] Title compound **174** (example 136) was obtained according to the scheme 34 via a 3-step synthesis starting from the chloride **20** and replacing 3-chloro-4-nitrophenol [in the step 1] with 5-nitropyrimidin-2-amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.85(bs, 2H), 10.91(bs, 1H), 8.71(s, 1H),8.64(s, 2H), 8.63-8.61(m, 1H), 8.25(d, J = 5.6 Hz, 1H), 7.45(d, J = 5.6 Hz, 1H), 7.34-7.27(m, 4H), 7.27-7.21(m, 1H), 3.79(s, 2H).

Scheme 35



Example 137

N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-4-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-fluorophenyl)acetamide (178)

Step 1. 7-Chloro-2-(1-methyl-1*H*-imidazol-4-yl)thieno[3,2-*b*]pyridine (**175**)

[0421] To a solution of chloride **2** (scheme 1) (2.45 g, 14.4 mmol) in THF (48 mL) at -78°C was slowly added *n*-BuLi (2.5M in hexane, 7.2 mL, 18.0 mmol). The reaction mixture was stirred for one hour [at -78°C] followed by slow addition of ZnCl (0.5M in THF, 36 mL, 18.0 mmol). In a few minutes the reaction mixture was allowed to warm to room temperature and stirred for one hour.

[0422] A solution of 4-iodo-1-methyl-1*H*-imidazole (1.50 g, 7.2 mmol) [*Tet. Lett.* **2004**, 45, 5529] in THF (5 mL) and the tetrakis(triphenylphosphine) palladium (0) (0.83 g, 0.72 mmol) were added to the reaction mixture which was heated to reflux for 1 hour, cooled to room temperature, diluted with aqueous ammonium hydroxide and, finally neutralized with

a 1N HCl solution. The acidic solution was extracted with DCM, the extract was washed with water and brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (eluents DCM, then DCM-MeOH, 97:3) to afford title compound **175** (1.45 g, 81% yield) as a yellow solid. LRMS (M+1) 263.9 (100%), 265.9 (33%).

Step 2. 7-(2-Fluoro-4-nitrophenoxy)-2-(1-methyl-1*H*-imidazol-4-yl)thieno[3,2-*b*]pyridine (**176**)

[0423] Starting from the chloride **175** and following the procedure described above for the synthesis of compound **11** (scheme 2, example 12), title compound **176** was obtained in 47% yield. LRMS (M+1) 371.0 (100%).

Step 3. 3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-4-yl)thieno[3,2-*b*]pyridin-7-yloxy)benzenamine (**177**)

[0424] Starting from the nitro compound **176** and following the procedure described above for the synthesis of amine **49** (scheme 10, example 55), title compound **177** was obtained in 74% yield. LRMS (M+1) 341.0 (100%).

Step 4. *N*-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-4-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-fluorophenyl)acetamide (**178**)

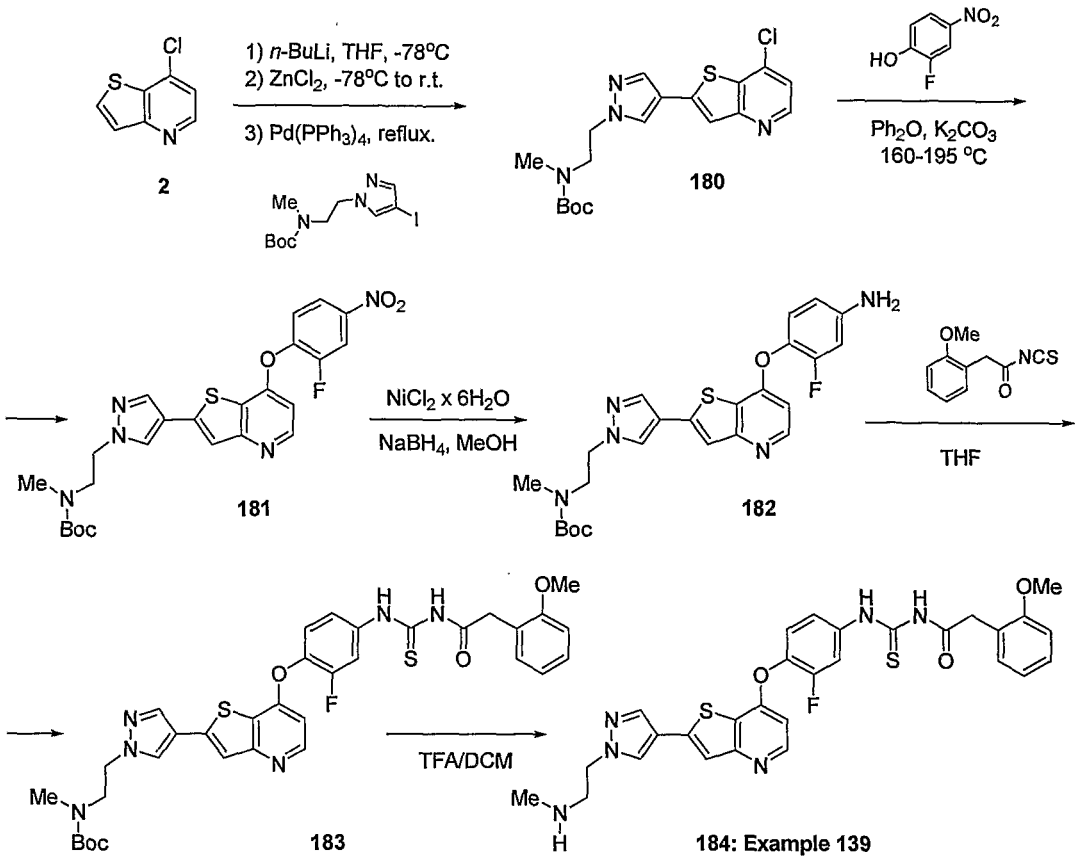
[0425] Starting from the amine **177**, following the procedure described above for the synthesis of compound **50** (scheme 10, example 55) but replacing 2-phenylacetyl isothiocyanate with 2-(2-fluorophenyl)acetyl isothiocyanate, title compound **178** was obtained in 24% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.44 (s, 1H), 11.88 (s, 1H), 8.46 (d, 1H, J=5.5 Hz), 8.34 (dd, 1H, J=12.3/2.2 Hz), 7.87 (d, 1H, J=1.2 Hz), 7.72 (d, 1H, J=1.2Hz), 7.69 (s, 1H), 7.57-7.49 (m, 2H), 7.43-7.31 (m, 2H), 7.23-7.15 (m, 2H), 6.59 (d, 1H, J=5.5 Hz), 3.94 (s, 2H), 3.73 (s, 3H). LRMS (M+1) 536.1 (100%).

Example 138

N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide (179)

[0426] Starting from the amine **177**, following the procedure described above for the synthesis of compound **50** (scheme 10, example 55) but replacing 2-phenylacetyl isothiocyanate with 2-(2-methoxyphenyl)acetyl isothiocyanate, title compound **179** was obtained in 52% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.58 (s, 1H), 11.75 (s, 1H), 8.46 (d, 1H, J=5.5 Hz), 8.72 (dd, 1H, J=12.3/2.2 Hz), 7.86 (d, 1H, J=1.2 Hz), 7.72 (d, 1H, J=0.8 Hz), 7.70 (s, 1H), 7.57-7.49 (m, 2H), 7.30-7.23 (m, 2H), 7.00 (d, 1H, J=7.8 Hz), 6.92 (dt, 1H, J=7.3/0.9 Hz), 6.58 (d, 1H, J=5.1 Hz), 3.82 (s, 2H), 3.79 (s, 3H), 3.72 (s, 3H).

Scheme 36



Example 139

N-(3-Fluoro-4-(2-(1-(2-(methylamino)ethyl)-1*H*-pyrazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide (184)

Step 1. *tert*-Butyl 2-(4-(7-chlorothieno[3,2-b]pyridin-2-yl)-1*H*-pyrazol-1-yl)ethyl(methyl)carbamate (**180**)

[0427] Starting from the chloride **2** and following the procedure described above for the synthesis of **175** (scheme 35, example 138), but replacing 4-iodo-1-methyl-1*H*-imidazole with *tert*-butyl 2-(4-iodo-1*H*-pyrazol-1-yl)ethyl(methyl)carbamate, title compound **180** was obtained in 75% yield. LRMS (M+1) 393.1 (100%).

Step 2. *tert*-Butyl 2-(4-(7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-b]pyridin-2-yl)-1*H*-pyrazol-1-yl)ethyl(methyl)carbamate (**181**)

[0428] Starting from the chloride **180** and following the procedure described above for the synthesis of compound **11** (scheme 2, example 12), title compound **181** was obtained in 37% yield. LRMS (M+1) 514.1 (100%).

Step 3. *tert*-Butyl 2-(4-(7-(4-amino-2-fluorophenoxy)thieno[3,2-b]pyridin-2-yl)-1*H*-pyrazol-1-yl)ethyl(methyl)carbamate (**182**)

[0429] Starting from the nitro compound **181** and following the procedure described above for the synthesis of amine **49** (scheme 10, example 55), title compound **182** was obtained in 22% yield. LRMS (M+1) 484.2 (100%).

Step 4. *tert*-Butyl 2-(4-(7-(2-fluoro-4-(3-(2-(2-methoxyphenyl)acetyl)thioureido)phenoxy)thieno[3,2-b]pyridin-2-yl)-1*H*-pyrazol-1-yl)ethyl(methyl)carbamate (**183**)

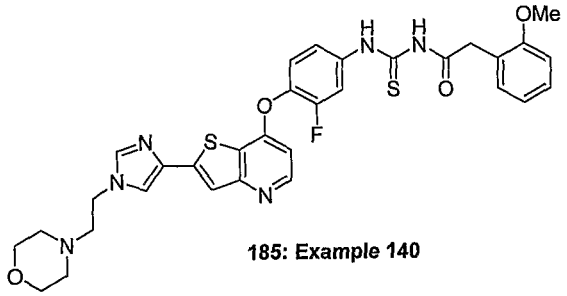
[0430] Starting from the amine **182,** following the procedure described above for the synthesis of compound **50** (scheme 10, example 55) but replacing 2-phenylacetyl isothiocyanate with 2-(2-methoxyphenyl)acetyl isothiocyanate, title compound **183** was obtained in 90% yield. LRMS (M+1) 691.2 (100%).

Step 5. *N*-(3-Fluoro-4-(2-(1-(2-(methylamino)ethyl)-1*H*-pyrazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide (**184**)

[0431] Starting from the compound **183** and following the procedure described above for the synthesis of compound **159** (scheme 30, step 4, example 121), title compound **184** was obtained in 66% yield. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 8.45(d, J = 5.6 Hz, 1H), 8.33(s, 1H), 8.00(s, 1H), 7.85-7.75(m, 1H), 7.69(s, 1H), 7.39(t, J = 8.4 Hz, 1H), 7.35-7.28(m, 1H), 7.28-7.22(m, 1H), 7.22(d, J = 7.6 Hz, 1H), 6.97(d, J = 8.4 Hz, 1H), 6.89(t, J = 7.6 Hz, 1H), 6.57(d, J = 5.6 Hz, 1H), 4.19(t, J = 6.4 Hz, 2H), 3.82(s, 2H), 3.77(s, 3H), 2.88(t, J = 6.4 Hz, 2H), 2.28(s, 3H).

Example 140

N-(3-Fluoro-4-(2-(1-(2-morpholinoethyl)-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide (185)

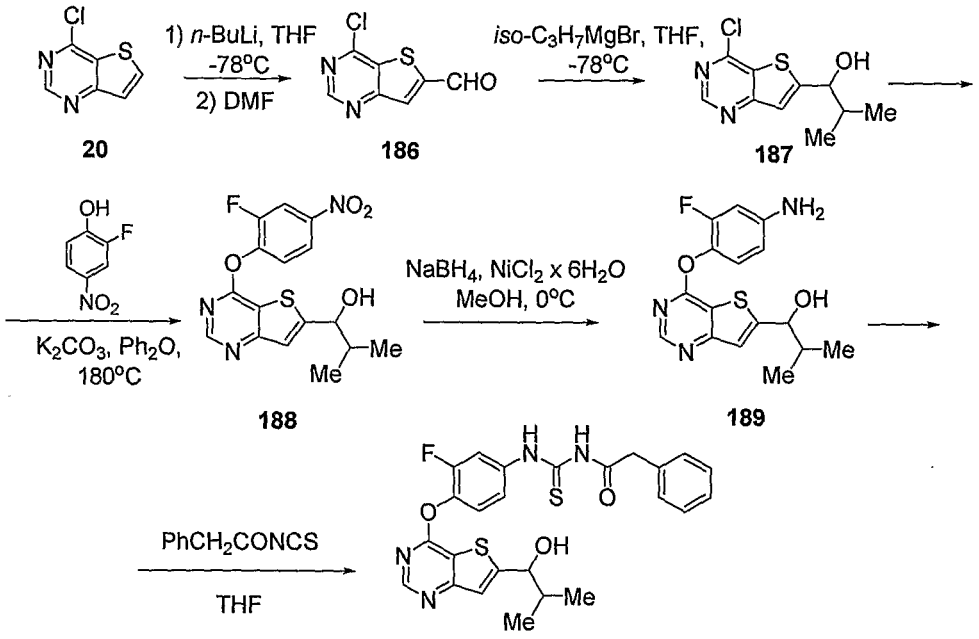


185: Example 140

[0432] Title compound **185** (example 140) was obtained following the procedures described above for compound **183** [according to the scheme 36] via a 4-step synthesis starting from chloride **2** and replacing *tert*-butyl 2-(4-iodo-1*H*-pyrazol-1-yl)ethyl(methyl)carbamate [in the step 1] with 4-(2-(4-iodo-1*H*-imidazol-1-yl)ethyl)morpholine [*Tet. Lett.* **2004,** 45, 5529]. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 12.56(s, 1H), 11.75(s, 1H), 8.55(d, J = 5.6 Hz, 1H), 8.50-8.20(m, 1H), 7.93(d, J = 1.2 Hz,

1H), 7.78(s, 1H), 7.60-7.55(m, 2H), 7.35(d, J = 1.2 Hz, 1H), 7.32-7.25(m, 1H), 7.23(dd, J = 1.6 and 7.2 Hz, 1H), 7.00(d, J = 7.6 Hz, 1H), 6.92(td, J = 0.8 and 7.6 Hz, 1H), 6.69(d, J = 5.6 Hz, 1H), 4.35(t, J = 6.0 Hz, 2H), 3.81(s, 2H), 3.78(s, 3H), 3.48(t, J = 4.4 Hz, 4H), 2.59(t, J = 6.0 Hz, 2H), 2.35(t, J = 4.4 Hz, 4H).

Scheme 37



190: Example 141

Example 141

N-(3-Fluoro-4-(6-(1-hydroxy-2-methylpropyl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (190)

Step 1. 4-Chloro-thieno[3,2-d]pyrimidine-6-carbaldehyde (**186**)

[0433] Starting from 4-chloro-thieno[3,2-d]pyrimidine (**20**, scheme 4) and following procedure described above for the synthesis of aldehyde **14** (scheme 3, step 1, example 20), title compound **186** was obtained in 84% yield. LRMS (M+1) 199.0 (100%).

Steps 2-3. 1-[4-(2-Fluoro-4-nitro-phenoxy)-thieno[3,2-d]pyrimidin-6-yl]-ethanol (**188**)

[0434] Starting from the aldehyde **186** and following procedures described above for the synthesis of nitro compound **16** (scheme 3, steps 2-3, example 20), title compound **188** was obtained [via the intermediate alcohol **187**], in 25% yield. LRMS (M+1) 336.0 (100%).

Steps 3-4. *N*-(3-Fluoro-4-(6-(1-hydroxy-2-methylpropyl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**190**)

[0435] Starting from the nitro compound **188** and following procedures described above for the synthesis of compound **18a** (scheme 3, steps 4-5, example 20), title compound **190**

was obtained [via the intermediate amino alcohol **189**], in 24% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.42(s, 1H), 11.80(s, 1H), 8.64(s, 1H), 7.90(dd, J = 2.0 and 12.0 Hz, 1H), 7.52(t, J = 8.4 Hz, 1H), 7.48(d, J = 0.8 Hz, 1H), 7.46(dd, J = 2.0 and 8.4 Hz, 1H), 7.36-7.31(m, 4H), 7.31-7.24(m, 1H), 6.15(d, 4.8 Hz, 1H), 4.82(td, J = 0.8 and 5.2 Hz, 1H), 3.82(s, 2H), 2.10-1.98(m, 1H), 0.93(d, J = 6.8 Hz, 3H), 0.90(d, J = 6.8 Hz, 3H).

Examples 142-148

N-(3-Fluoro-4-(6-(pyrrolidine-1-carbonyl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (26f)

N-(4-(2-(Azetidine-1-carbonyl)thieno[3,2-b]□yridine-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide hydrochloride (26g)

1-(4-(6-(*N*-Ethyl-*N*-methylcarbamoyl)thieno[3,2-d]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (26h)

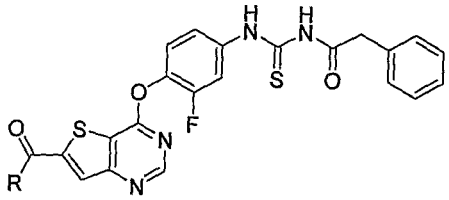
N,N-Diethyl-4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-d]pyrimidine-6-carboxamide (26i)

(R)-*N*-(3-Fluoro-4-(6-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (26j)

(S)-*N*-(4-(6-(3-(*tert*-Butyldimethylsilyloxy)pyrrolidine-1-carbonyl)thieno[3,2-d]pyrimidin-4-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (26k)

tert-Butyl 1-(4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-d]pyrimidine-6-carbonyl)pyrrolidin-3-ylcarbamate (26l)

[0436] Compounds **26f-l** (examples 142-148) were obtained by following the procedures described above for the compound **26a** (example 22, scheme 4). Characterization of **26f-l** is provided in the table 17.

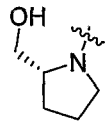
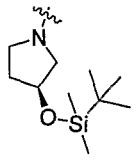
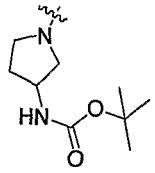


26f-l: Examples 142-148

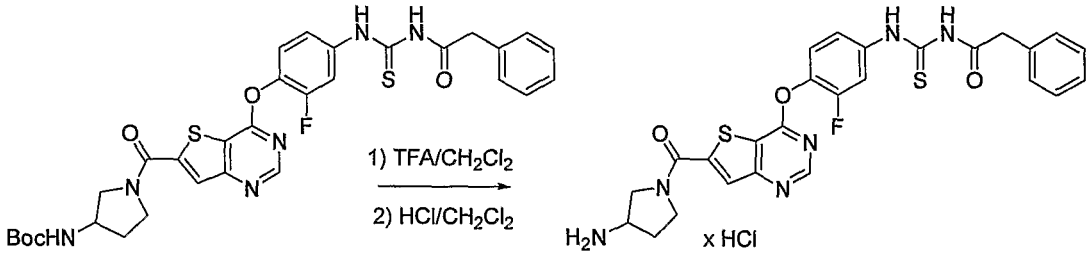
Table 17

Characterization of compounds 26f-l (examples 142-148)

Cpd	Ex	R	Name	Characterization
26f	**142**		N-(3-Fluoro-4-(6-(pyrrolidine-1-carbonyl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.42(s, 1H), 11.79(s, 1H), 8.77(s, 1H), 8.11(s, 1H), 7.92(dd, J = 2.0 and 11.6 Hz, 1H), 7.54(t, J = 8.4 Hz, 1H), 7.47(dd, J = 2.0 and 8.4 Hz, 1H), 7.36-7.31(m, 4H),7.30-7.32(m, 1H), 3.85(t, J = 6.4 Hz,2H), 3.82(s, 2H), 3.55(t, J = 6.4 Hz, 2H), 1.96(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
26g	**143**		N-(4-(2-(Azetidine-1-carbonyl)thieno[3,2-b]□yridine-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.48(s, 1H), 11.82(s, 1H), 8.64(d, J = 5.6 Hz, 1H), 8.03(db, J = 12.8 Hz, 1H), 7.91(s, 1H), 7.58-7.52(m, 2H), 7.37-7.31(m, 4H), 7.30-7.24(m, 1H), 6.82(d, J = 5.6 Hz, 1H), 4.62(t, J = 7.2 Hz, 2H), 4.11(t, J = 7.2 Hz, 2H), 3.82(s, 2H), 2.35(quin, J = 7.2 Hz, 2H).
26h	**144**		1-(4-(6-(N-Ethyl-N-methylcarbamoyl)thieno[3,2-d]pyrimidin-4-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.44 (s, 1H), 11.81 (s, 1H), 8.77 (s, 1H), 8.03 (s, 1/2H), 7.93 (dd, 1H, J=11.9/2.3 Hz), 7.89 (s, 1/2H), 7.54 (t, 1H, J=8.5 Hz), 7.48 (dd, 1H, J=8.8/2.2 Hz), 7.38-7.32 (m, 4H), 7.30-7.25 (m, 1H), 3.82 (s, 2H), 3.52 (m, 2H), 3.23 (s, 3/2H), 3.04 (s, 3/2H), 1.19 (m, 3H).
26i	**145**		N,N-Diethyl-4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-d]pyrimidine-6-carboxamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.44 (s, 1H), 11.80 (s, 1H), 8.77 (s, 1/3H), 8.77 (s, 2/3H), 7.93 (dd, 1H, J=2.2/11.9 Hz), 7.89 (s, 1/3H), 7.89 (s, 2/3H), 7.54 (t, 1H, J=8.5 Hz), 7.48 (dd, 1H, J=1.8/8.3 Hz), 7.34-7.33 (m, 4H), 7.29-7.26 (m, 1H), 3.83 (s, 2H), 3.53-3.48 (m, 4H), 1.21 (m, 6H).

Cpd	Ex	R	Name	Characterization
26j	**146**		®-N-(3-Fluoro-4-(6-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.41 (s, 1H); 11.80 (s, 1H); 8.77 (s, 1H); 8.08 (s, 1H); 7.92 (d, J= 11.6 Hz,1H); 7.54 (t, J= 8.8 Hz, 1H); 7.49-7.45 (m, 1H); 7.34-7.26 (m, 5H); 4.84 (t, J= 4.4Hz, 1H); 4.23-4.19 (m, 1H); 3.91-3.78 (m, 2H); 3.82 (s, 2H); 3.62-3.51 (m, 2H); 2.07-1.87 (m, 4H).
26k	**147**		(S)-N-(4-(6-(3-(*tert*-Butyldimethylsilyloxy)pyrrolidine-1-carbonyl)thieno[3,2-d]pyrimidin-4-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide	**^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):** 12.5 (s, 1H), 8.79 (s, 1H), 8.66 (d, 1H, J=0.4 Hz), 8.03-7.91 (m, 2H), 7.52-7.21 (m, 6H), 4.60-4.52 (m, 1H), 4.07-3.67 (m, 4H), 2.13-1.97 (m, 2H), 1.28-1.26 (m, 2H), 0.93-0.89 (m, 9H), 0.14-0.09 (m, 6H).
26l	**148**		*tert*-Butyl 1-(4-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-d]pyrimidine-6-carbonyl)pyrrolidin-3-ylcarbamate	1H NMR (400 MHz, DMSO-d6) δ (ppm): 8.77(s, 1H), 8.09(s, 0.5H), 8.05(s, 0.5H), 7.96-7.93(m, 0.5H), 7.93-7.90(m, 0.5H), 7.58-7.50(m, 1H), 7.50-7.46(m, 1H), 7.38-7.31(nm, 4H), 7.31-7.24(m, 1H), 3.82(s, 2H), 4.15-1.20(m, 7H).

Scheme 38



26l: Example 148 **191: Example 149**

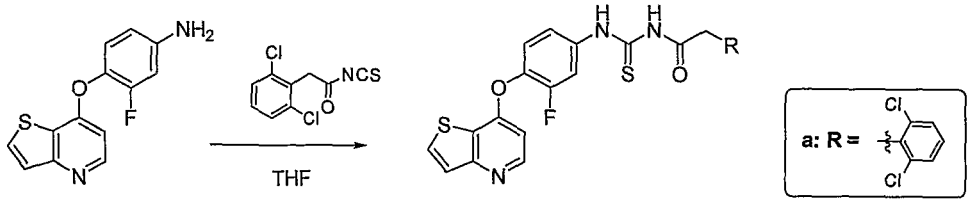
Example 149

N-(4-(6-(3-Aminopyrrolidine-1-carbonyl)thieno[3,2-*d*]pyrimidin-4-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide hydrochloride(191)

[0437] Following the procedure described above for the synthesis of compound **159** (scheme 30, example 121) but substituting Boc-protected amino compound **158** for the Boc-protected amino compound **26l**, title compound **191** was obtained in 40% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.77(s, 1H), 8.12(s, 0.5H), 8.06(s, 0.5H), 7.92(dd, J = 2.4 and 12.0 Hz, 1H), 7.54(t, J = 8.4 Hz, 1H), 7.48(dd, J = 2.4 and 8.4 Hz, 1H), 7.36-7.31(m,

4H), 7.30-7.25(m, 1H), 4.2-3.80(m, 1H), 3.08(s, 2H), 3.80-3.50(m, 4H), 2.10-1.98(m, 1H), 1.82-1.64(m, 1H). LRMS (M+1) 550.6 (100%).

Scheme 39



169 192a: Example 150

Example 150

2-(2,6-Dichlorophenyl)-*N*-(3-fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (192a)

[0438] Starting from the amine **169** (scheme 33), following the procedures described above for the synthesis of compound **170a** (example 133) but replacing 2-phenylacetyl isothiocyanate with 2-(2,6-dichlorophenyl)acetyl isothiocyanate, title compound **192a** was obtained in 7 % yield. Characterization of **192a** is provided in table 18.

Example 151

N-(3-Fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(thiophen-2-yl)acetamide (192b)

[0439] Starting from the amine **169** (scheme 33), following the procedures described above for the synthesis of compound **170a** (example 133) but replacing 2-phenylacetyl isothiocyanate with 2-(thiophen-2-yl)acetyl isothiocyanate, title compound **192b** was obtained in 9 % yield. Characterization of **192b** is provided in table 18.

Example 152

2-(2,6-Difluorophenyl)-*N*-(3-fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (192c)

[0440] Starting from the amine **169** (scheme 33), following the procedures described above for the synthesis of compound **170a** (example 133) but replacing 2-phenylacetyl isothiocyanate with 2-(2,6-difluorophenyl)acetyl isothiocyanate, title compound **192c** was obtained in 23 % yield. Characterization of **192c** is provided in table 18.

Example 153

N-(3-Fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-1-phenylcyclopropanecarboxamide (192d)

[0441] Starting from the amine **169** (scheme 33), following the procedures described above for the synthesis of compound **170a** (example 133) but replacing 2-phenylacetyl isothiocyanate with 1-phenylcyclopropanecarbonyl isothiocyanate, title compound **192d** was obtained in 41 % yield. Characterization of **192d** is provided in table 18.

Example 154

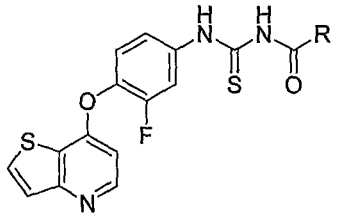
N-(3-Fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylpropanamide (192e)

[0442] Starting from the amine **169** (scheme 33), following the procedures described above for the synthesis of compound **170a** (example 133) but replacing 2-phenylacetyl isothiocyanate with 3-methyl-2-phenylbutanoyl isothiocyanate, title compound **192e** was obtained in 49 % yield. Characterization of **192e** is provided in table 18.

Example 155

N-(3-Fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-3-phenylpropanamide (192f)

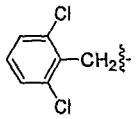
[0443] Starting from the amine **169** (scheme 33), following the procedures described above for the synthesis of compound **170a** (example 133) but replacing 2-phenylacetyl isothiocyanate with 3-phenylpropanoyl isothiocyanate, title compound **192f** was obtained in 59 % yield. Characterization of **192f** is provided in table 18.

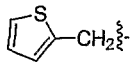
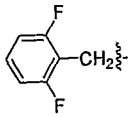
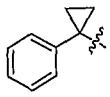
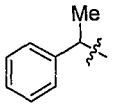
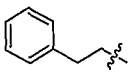


192a-f: Examples 150-155

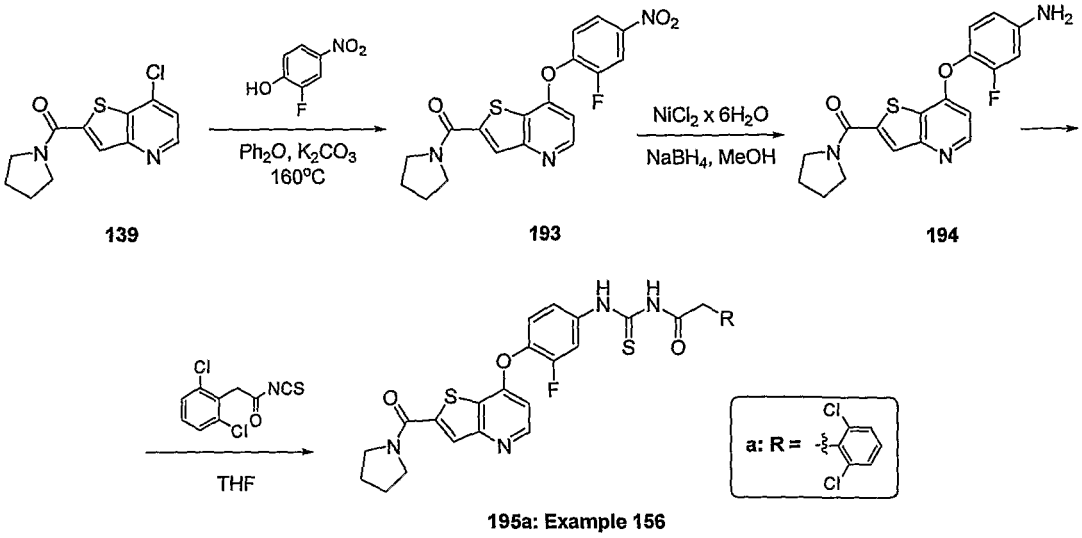
Table 18

Characterization of compounds 192a-f (examples 150-155)

Cpd	Ex	R	Name	Characterization
192a	**150**		2-(2,6-Dichlorophenyl)-N-(3-fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ(ppm):** 12.27(s, 1H), 12.01(s, 1H), 8.52(d, J = 5.6 Hz, 1H), 8.35-8.00(m, J = 12.0 Hz, 1H), 7.59(d, J = 5.6 Hz, 1H), 7.58-7.47(m, 4H), 7.36(t, J = 8.0 Hz, 1H), 6.64(d, J = 5.6 Hz, 1H), 4.21(s, 2H).

Cpd	Ex	R	Name	Characterization
192b	**151**		N-(3-Fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(thiophen-2-yl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.37(s, 1H), 11.80(s, 1H), 8.52(d, J = 5.6 Hz, 1H), 8.17(d, J = 5.6 Hz, 1H), 7.98(d, J = 12.4 Hz, 1H), 7.60(d, J = 5.6 Hz, 1H), 7.54-7.46(m, 2H), 7.42(dd, J= 1.6 and 5.2 Hz, H), 7.20-6.97(m, 2H), 6.64(d, J = 5.6 Hz, 1H), 4.07(s, 2H).
192c	**152**		2-(2,6-Difluorophenyl)-N-(3-fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide	^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.28(s, H), 11.93(s, 1H), 8.52(d, J = 5.6 Hz, H), 8.17(d, J = 5.6 Hz, 1H), 8.03-7.98(m, 1H), 7.60(d, J = 5.6 Hz, 1H), 7.57-7.48(m, 2H), 7.46-7.37(m, 1H), 7.12(t, J = 7.6 Hz, 2H), 6.65(d, J = 5.6 Hz, 1H), 3.96(s, 2H).
192d	**153**		*N*-(3-Fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-1-phenylcyclopropanecarboxamide	^{1}H NMR (DMSO) δ (ppm): 12.31 (1H, s), 9.26 (1H, s), 8.52 (1H, d, J=5.28 Hz), 8.17 (1H, d, J=5.28 Hz), 7.96 (1H, d, J=11.93 Hz), 7.60 (1H, d, J=5.28 Hz), 7.52-7.31 (7H, m), 6.64 (1H, d, J=5.09 Hz), 1.62 (2H, brd, J=1.96 Hz), 1.33 (2H, brd, J=2.35 Hz). MS (m/z) 464.2 (M+H).
192e	**154**		*N*-(3-Fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylpropanamide	^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.50 (1H, s), 11.77 (1H, s), 8.52 (1H, d, J=5.28 Hz), 8.16 (1H, d, J=5.48 Hz), 8.00 (1H, d, J=11.74), 7.60 (1H, d, J=5.48 Hz), 7.55-7.48 (2H, m), 7.41-7.33 (5H, m), 6.63 (d, J=5.48 Hz), 4.10 (1H, q, J=6.85 Hz), 1.44 (3H, d, J=6.85 Hz). MS (m/z) 452.1 (M+H)
192f	**155**		N-(3-Fluoro-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-3-phenylpropanamide	^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.58 (2, 1H), 11.62 (s, 1H), 8.53 (1H, d, J=5.48 Hz), 8.17 (1H, d, J=5.28 Hz), 8.03 (1H, d, J=11.35 Hz), 7.60 (1H, d, J=5.48 Hz), 7.53-7.52 (2H, br), 7.31-7.21 (5H, m), 6.66 (1H, d, J=5.28 Hz), 2.92-2.87 (2H, m), 2.83-2.79 (2H, m). MS (m/z) 452.1 (M+H)

Scheme 40



195a: Example 156

Example 156

2-(2,6-Dichlorophenyl)-*N*-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (195a)

Step 1. (7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)(pyrrolidin-1-yl)methanone (**193**)

[0444] Starting from (7-chlorothieno[3,2-*b*]pyridin-2-yl)(pyrrolidin-1-yl)methanone (**139**, scheme 26) and following the procedure described above for the synthesis of compound **6** (scheme 1, example 1), title compound **193** was obtained in (93% yield). LRMS (M+1) 387.4 (100%).

Step 2. (7-(4-Amino-2-fluorophenoxy)thieno[3,2-*b*]pyridin-2-yl)(pyrrolidin-1-yl)methanone (**194**)

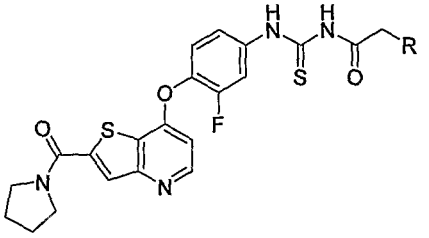
[0445] Starting from the nitro compound **193** and following the procedures described above for the synthesis of amine **7**, (scheme 1, example1) title compound **194** was obtained in 92% yield. LRMS (M+1) 357.4 (100%).

Step 3. 2-(2,6-Dichlorophenyl)-*N*-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (**195a**)

[0446] Starting from the amine **194** and following the procedure described above for the synthesis of compounds **50** (scheme 10), **170a** (scheme 33) or **192a-f** (scheme 39), title compound **195a** was obtained in 70% yield. Characterization of **195a** is provided in table 19.

Examples 157-181 (compounds 195b-q)

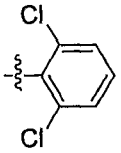
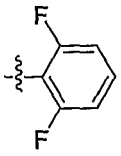
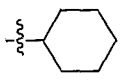
[0447] Compounds **195b-q** (examples 157-181) were obtained starting from the amine **194**, following the procedure described above for the synthesis of compound **195a** and replacing 2-(2,6-difluorophenyl)acetyl isothiocyanate with an appropriately substituted homologue. Characterization of **195b-q** is provided in the table 19.

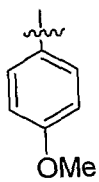
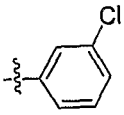
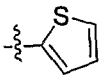
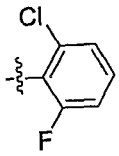
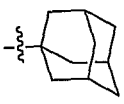


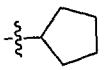
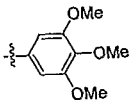
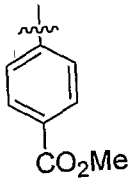
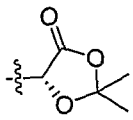
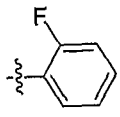
195a-q: Examples 156-181

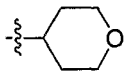
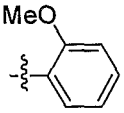
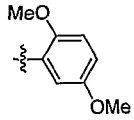
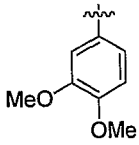
Table 19

Characterization of compounds 195a-q (examples 156-181)

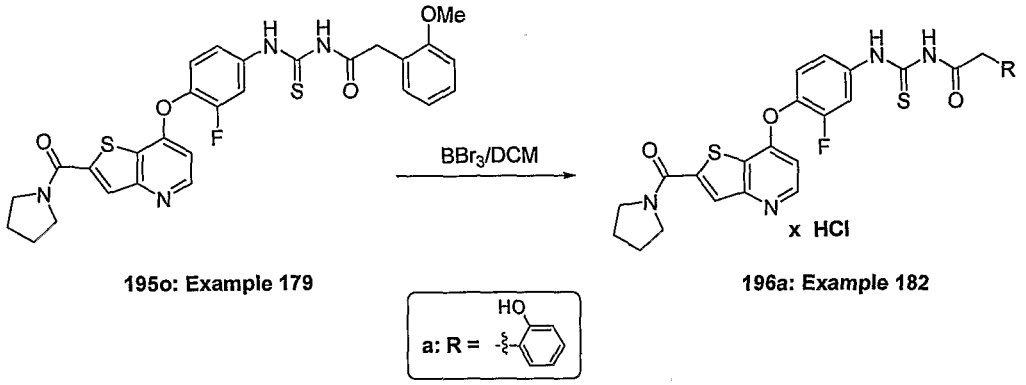
Cpd	Ex	R	Name	Characterization
195a	**156**		2-(2,6-Dichlorophenyl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.29(s, 1H), 12.02(s, 1H), 8.63(d, J = 5.6 Hz, 1H), 8.08-8.02(m, 1H), 8.04(s, 1H), 7.62(m, 4H), 7.36(dd, J = 7.2 and 8.4 Hz, 1H), 6.80(d, J = 5.6 Hz, 1H), 4.21(s, 2H), 3.85(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quint, J = 6.4 Hz, 2H), 1.88(quint, J = 6.4 Hz, 2H).
195b	**157**		2-(2,6-Difluorophenyl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.29(s, 1H), 11.94(s, 1H), 8.63(d, J = 5.6 Hz, 1H), 8.07-8.01(m, 1H), 8.05(s, 1H), 7.60-7.51(m, 2H), 7.46-7.37(m, 1H), 7.18-709(m, 2H), 6.80(d, J = 5.6 Hz, 1H), 3.97(s, 2H), 3.85(t, J = 6.4Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin,J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
195c	**158**		2-Cyclohexyl-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.67(s, 1H), 11.55(s, 1H), 8.65(d, J = 5.6 Hz, 1H), 8.12-8.06(m, 1H), 8.06(s, 1H), 7.60-7.53(m, 2H), 6.82(d, J = 5.6 Hz, 1H), 3.86(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 2.37(d, J = 6.8 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H), 1.71-1.58(m, 6H), 1.30-1.08(m, 3H), 1.07-0.92(m, 2H).

Cpd	Ex	R	Name	Characterization
195d	159		N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(4-methoxyphenyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.50(s, 1H), 11.77(s, 1H), 8.64(d, J = 5.6 Hz, 1H), 8.07-8.01(m, 1H), 8.05(s, H), 7.58-7.53(m, 2H), 7.28-7.22(m, 2H), 6.94-6.88(m, 2H), 6.81(d, J = 5.6 Hz, 1H), 3.85(t, J = 6.4 Hz, 2H), 3.73(s, 2H), 3.73(s, 3H), 3.54(t, J = 6.4 Hz, 2H), 1.97 (quin, J = 6.4 Hz, 2H0, 1.89(quin, J = 6.4 Hz, 2H).
195e	160		2-(3-Chlorophenyl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.42(s, 1H), 11.83(s, 1H), 8.65(d, J = 5.6 Hz, 1H), 8.07-8.01(m, 1H), 8.05(s, 1H), 7.59-7.52(m, 2H), 7.44-7.26(m, 4H), 6.82(d, J = 5.6 Hz, 1H), 3.86(s, 2H), 3.85(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
195f	161		N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(thiophen-2-yl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.39(s, 1H), 11.82(s, 1H), 8.65(d, J = 5.6 Hz, 1H), 8.08-8.00(m, 1H), 8.05(s, 1H), 7.60-.7.55(m, 2H), 7.46-7.42(m, 1H), 7.04-6.98(m, 2H), 6.83(d, J = 5.6 Hz, 1H), 4.06(s, 2H), 3.85(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 1.98(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
195g	162		2-(2-Chloro-6-fluorophenyl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.30(s, 1H), 11.99(s, 1H), 8.63(d, J = 5.6 Hz, 1H), 8.08-8.01(m, 1H), 8.05(s, 1H), 7.60-7.51(m, 2H), 7.44-7.36(m, 2H), 7.30-7.24(m, 1H), 6.80(d, J = 5.6 Hz, 1H), 4.07(s, 2H), 3.85(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 1.95(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
195h	163		1 -(2-Adamantan-1-yl-acetyl)-3-{3-fluoro-4-[2-(pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-phenyl}-thiourea	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.75(s, 1H), 11.45(s, 1H), 8.67(d, J = 5.6 Hz, 1H), 8.12(d, J = 12.4 Hz, 1H), 8.06(s, 1H), 7.62-7.53(m, 2H), 6.86(d, J = 5.6 Hz, 1H), 3.85(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 2.26(s, 2H), 2.02-1.92(m, 5H), 1.89(quin, J = 6.4 Hz, 2H), 1.70-1.57(m, 12H).

Cpd	Ex	R	Name	Characterization
195i	164		2-Cyclopentyl-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.66(s, 1H), 11.55(s, 1H), 8.65(d, J = 5.6 Hz, 1H), 8.10-8.03(m, 2H), 7.59-7.54(m, 2H), 6.82(d, J = 5.6 Hz, 1H), 3.86(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 2.20(quin, J = 7.6 Hz, 1H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H), 1.83-1.71(m, 2H), 1.68-1.47(m, 4H), 1.26-1.12(m, 2H).
195j	165		N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(3,4,5-trimethoxyphenyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.49(s, 1H), 11.76(s, 1H), 8.60(d, J = 5.6 Hz, 1H), 8.07-8.01(m, 2H), 7.58-7.54(m, 2H), 6.77(d, J = 5.6 Hz, 1H), 6.65(s, 2H), 3.86(t, J = 6.4 Hz, 2H), 3.76(s, 6H), 3.74(s, 2H), 3.63(s, 3H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2).
195k	166		Methyl 4-(2-(3-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenyl)thioureido)-2-oxoethyl)benzoate hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.41(s, 1H), 11.86(s, 1H), 8.60(d, J = 5.6 Hz, 1H), 8.04(s, 1H), 8.04-8.00(m, 1H), 7.93(d, J = 8.0 Hz, 2H), 7.58-7.50(m, 2H), 7.47(d, J = 8.0 Hz, 2H), 6.76(d, J = 5.6 Hz, 1H), 3.94(s, 2H), 3.86(t, J = 6.4 Hz, 2H), 3.84(s, H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 64 Hz, 2H).
195l	167		(R)-2-(2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamoyl)ethanethioamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.32(s, 1H), 11.73(s, 1H), 8.64(d, J = 5.6 Hz, 1H), 8.05(s, 1H), 8.04-8.00(m, 1H), 7.60-7.54(m, 2H), 6.81(d, J = 5.6 Hz, 1H), 4.93(t, J = 4.4 Hz, 1H), 3.86(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 3.16(dd, J = 4.4 and 16.8 Hz, 1H), 2.99(dd, J = 5.0 and 16.8 Hz, 1H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
195 m	168		N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-fluorophenyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm):** 12.42(s, 1H), 11.88(s, 1H), 8.67(d, J = 5.6 Hz, 1H), 8.08-8.02(m, 1H), 8.06(s, H), 7.60-7.52(m, 2H), 7.43-7.30(m, 2H), 7.24-7.16(m, 2H), 6.85(d, J = 5.6 Hz, 1H), 3.989s, 2H), 3.85(t, J = 6.4 Hz, 2H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).

Cpd	Ex	R	Name	Characterization
195n	**169**		N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(tetrahydro-2H-pyran-4-yl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.63(s, 1H), 11.59(s, 1H), 8.66(d, J = 5.2 Hz, 1H), 8.11-8.02(m, 1H), 8.06(s, 1H), 7.60-7.54(m, 2H), 6.84(d, J = 5.2 Hz, 1H), 3.85(t, J = 6.8 Hz, 2H), 3.85-3.79(m, 2H), 3.54(t, J = 6.8 Hz, 2H), 3.30(t, J = 12.0 Hz, 2H), 2.43(d, J = 6.8 Hz, 2H), 2.20-1.95(m, 1H), 1.97(quin, J = 6.8 Hz, 2H), 1.89(quin, J = 6.8 Hz, 2H), 1.61(d, J = 12.8 Hz, 2H), 1.25(qd, J = 4.0 and 12.0 Hz, 2H).
195o	**179**		N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.55(s, 1H), 11.73(s, 1H), 8.63(d, J = 5.6 Hz, 1H), 8.10-8.04(m, 2H), 7.60-7.51(m, 2H), 7.26(td, J = 1.6 and 8.0 Hz, 1H), 7.21(dd, J = 1.6 and 7.6 Hz, 1H), 6.99(d, J = 8.0 Hz, H), 6.90(ts, J = 1.2 and 7.6 Hz, 1H), 6.80(d, J = 5.6 Hz, 1H), 3.86(t, J = 6.4 Hz, 2H), 3.81(s, 2H), 3.78(s, 3H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
195p	**180**		2-(2,5-Dimethoxyphenyl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.53(s, 1H), 11.71(s, 1H), 6.64(d, J = 5.6 Hz, 1H)< 8.10-8.04(m, 1H), 8.05(s, 1H), 7.60-7.52(m, 2H), 6.93-6.78(m, 4H), 3.85(t, J = 6.4 Hz, 2H), 3.78(s, 2H), 3.72(s, 3H), 3.69(s, 3H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
195q	**181**		2-(3,4-Dimethoxyphenyl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.51(s, 1H), 11.76(s, 1H), 8.69(d, J = 5.6 Hz, 1H), 8.08-8.02(m, 1H), 8.07(s, 1H), 7.61-7.54(m, 2H), 6.98-6.82(m, 4H), 3.85(t, J = 6.4 Hz, 2H), 3.78-3.70(m, 8H), 3.54(t, J = 6.4 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).

Scheme 41



Example 182

N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-hydroxyphenyl)acetamide hydrochloride (196a)

[0448] Starting from the compound **195o** and following the procedure described above for the synthesis of compound **155k** (scheme 29, example 119), title compound **196a** was obtained in 62% yield. Characterization of **196a** is provided in table 20.

Example 183

2-(2,5-Dihydroxyphenyl)-*N*-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride (196b)

[0449] Starting from the compound **195p** and following the procedure described above for the synthesis of **196a**, title compound **196b** was obtained in 83% yield. Characterization of **196b** is provided in table 20.

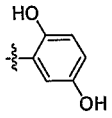
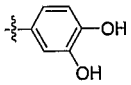
Example 184

2-(3,4-Dihydroxyphenyl)-*N*-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (196c)

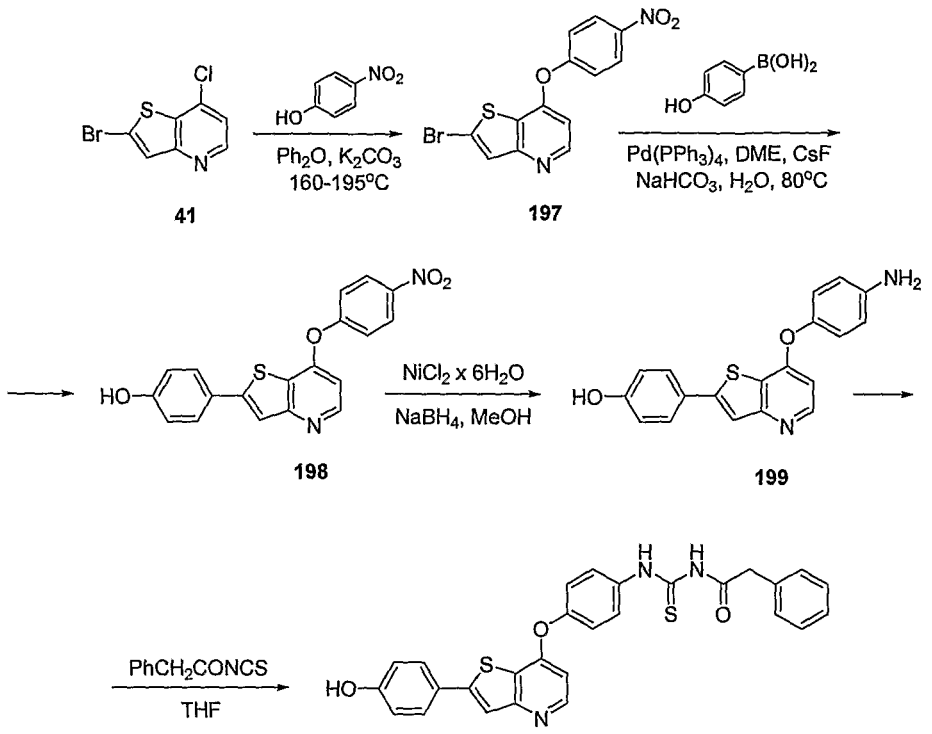
[0450] Starting from the compound **195q** and following the procedure described above for the synthesis of **196a**, title compound **196c** was obtained in 25% yield. Characterization of **196c** is provided in table 20.

Table 20

Characterization of compounds 196a-c (examples 182-184)

Cpd	Ex	R	Name	Characterization
196a	**182**		N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-hydroxyphenyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.60(s, 1H), 11.67(s, 1H), 9.63(bs, 1H), 8.63(d, J = 5.6 Hz, 1H), 8.09-8.00(m, H), 8.05(s, 1H), 7.60-7.50(m, 2H), 7.13(d, J = 7.6 Hz, 1H), 7.08(t, J = 7.6 Hz, 1H), 6.83-6.77(m, 2H), 6.74(t, J = 7.6 Hz, 1H), 3.85(t, J = 6.4 Hz, 2H), 3.76(s, 2H), 3.54(t, J = 6.4 Hz, 12H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
196b	**183**		2-(2,5-Dihydroxyphenyl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide hydrochloride	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 12.59(s, 1H), 11.59(s, 1H), 8.60(d, J = 5.6 Hz, 1H), 8.08-8.03(m ,1H), 8.04(s, 1H), 7.58-7.52(m, 2H), 6.77(d, J = 5.6 Hz, 1H), 6.60(d, J = 8.4 Hz, 1H), 6.57(d, J = 2.8 Hz, 1H), 6.49(dd, J = 2.8 and 8.4 Hz, 1H), 3.86(t, J = 6.4 Hz, 2H), 3.54(t, j = 6.54 Hz, 2H), 1.97(quin, J = 6.4 Hz, 2H), 1.89(quin, J = 6.4 Hz, 2H).
196c	**184**		2-(3,4-Dihydroxyphenyl)-N-(3-fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide	**^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):** 8.53(d, J = 5.6 Hz, 1H), 8.07(dd, J = 2.4 and 12.0 Hz, 1H), 7.94(s, 1H), 7.50-7.44(m, 1H), 7.40(t, J = 8.4 Hz, 1H), 6.82-6.71(m, 3H), 6.65(dd, J = 2.4 and 8.4 Hz, 1H), 3.92(t, J = 6.4 Hz, 2H), 3.67(t, J = 6.4 Hz, 1H), 3.59(s, 2H), 2.09(quin, J = 6.4 Hz, 2H), 2.02(quin, J = 6.4 Hz, 2H).

Scheme 42



Example 185

N-(4-(2-(4-Hydroxyphenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (200)

Step 1. 2-Bromo-7-(4-nitrophenoxy)thieno[3,2-b]pyridine (**197**)

[0451] Starting from the compound **41** (scheme 8) and following the procedure described above for the synthesis of compound **42** (scheme 8) but replacing 2-fluoro-4-nitrophenol for 4-nitrophenol, title compound **197** was obtained in 48% yield. LRMS (M+1) 350.9 (100%). 352.9 (100%).

Step 2. 4-(7-(4-Nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenol (**198**)

[0452] Starting from the compound **197** and following the procedure described above for the synthesis of compound **153** (scheme 28), title compound **198** was obtained in 81% yield. LRMS (M+1) 365.0 (100%).

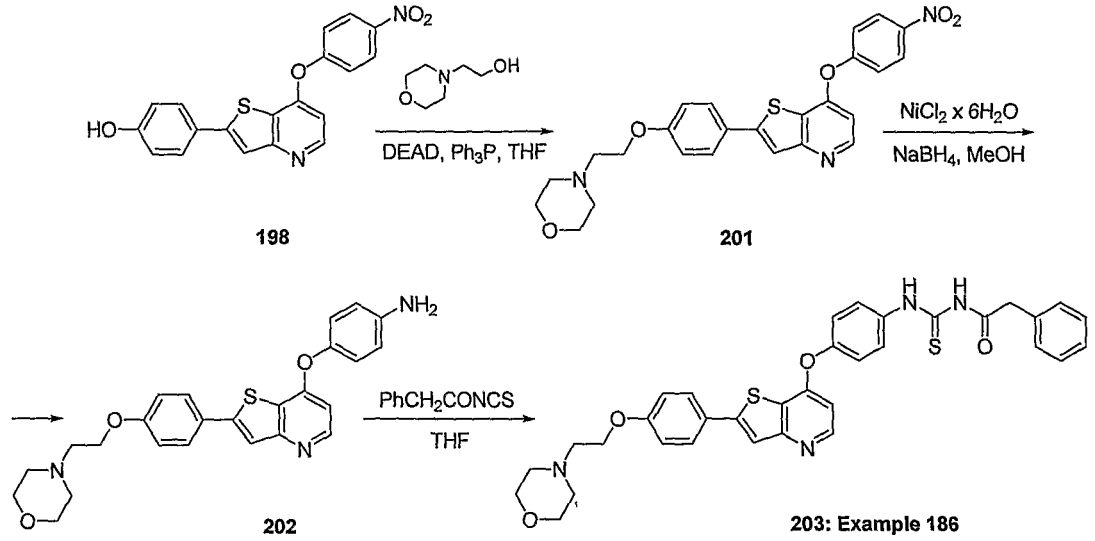
Step 3. 4-(7-(4-Aminophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenol (**199**)

[0453] Starting from the compound **198** and following the procedure described above for the synthesis of compound **154** (scheme 28), title compound **199** was obtained in 83% yield. LRMS (M+1) 335.0 (100%).

Step 4. *N*-(4-(2-(4-Hydroxyphenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (200)

[0454] Starting from the compound **199** and following the procedure described above for the compound **155a** (scheme 28, example 109), title compound **200** was obtained in 3% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.38 (s, 1H), 11.74 (s, 1H), 9.94 (s, 1H), 8.46 (d, 1H, J=5.3 Hz), 7.81 (s, 1H), 7.72 (d, 2H, J=9.0 Hz), 7.69 (dd, 2H, J=6.7/1.8 Hz), 7.34-7.27 (m, 7H), 6.86 (dd, 2H, J=6.7/1.8 Hz), 6.61 (d, 1H, J=5.5 Hz), 3.82 (s, 2H). LRMS (M+1) 512.1 (100%).

Scheme 43



Example 186

N-(4-(2-(4-(2-Morpholinoethoxy)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (203)

Step 1. 4-(2-(4-(7-(4-Nitrophenoxy)thieno[3,2-*b*]pyridin-2-yl)phenoxy)ethyl)morpholine (**201**)

[0455] Starting from the compound **198** (scheme 42) and following the procedure described above for the compound **161** (scheme 31), title compound **201** was obtained in 69% yield. LRMS (M+1) 478.1 (100%).

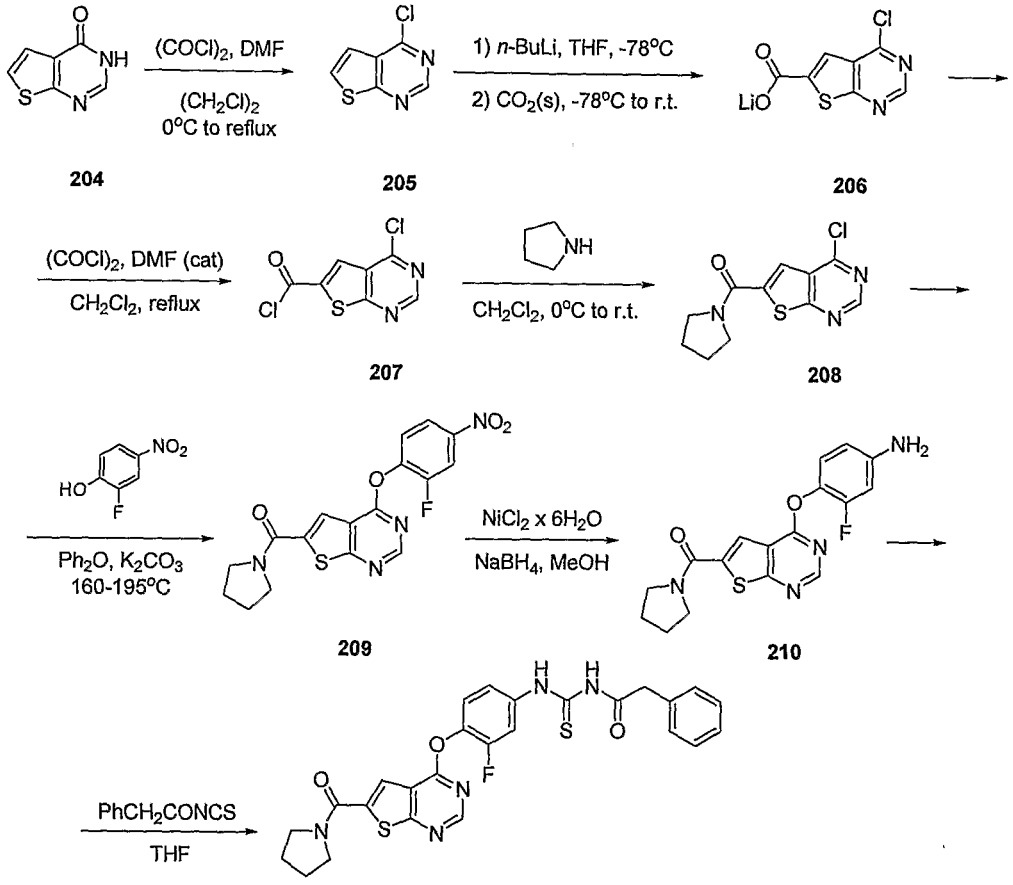
Step 2. 4-(2-(4-(2-Morpholinoethoxy)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)benzenamine (**202**)

[0456] Starting from the compound **201** and following the procedure described above for the compound **162** (scheme 31), title compound **202** was obtained in 69% yield. LRMS (M+1) 448.2 (100%).

Step 3. *N*-(4-(2-(4-(2-Morpholinoethoxy)phenyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**203**)

[0457] Starting from the compound **202** and following the procedure described above for the compound **163a** (scheme 31), title compound **203** was obtained in 30% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.38 (s, 1H), 11.73 (s, 1H), 8.47 (d, 1H, J=5.5 Hz), 7.90 (s, 1H), 7.79 (s, 2H, J=9.0), 7.36 (d, 2H, J=9.0 Hz), 7.43-7.27 (m, 7H), 7.05 (d, 2H, J=9.0 Hz), 6.63 (d, 1H, J=5.3 Hz), 4.15 (t, 2H, J=5.6 Hz), 3.82 (s, 2H), 3.58 (t, 4H, J=4.6 Hz), 2.71 (t, 2H, J=5.7 Hz), 2.51-2.46 (m, 4H). LRMS (M+1) 625.2 (100%).

Scheme 44



Example 187

N-(3-fluoro-4-(6-(pyrrolidine-1-carbonyl)thieno[2,3-*d*]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (211)

Step 1. 4-Chlorothieno[2,3-*d*]pyrimidine (**205**)

[0458] Starting from thieno[2,3-*d*]pyrimidin-4(3H)-one (**204**) [*J. Med. Chem.*, **1999**, 42, 26, 5437-5447, *Bull. Soc. Chim. Fr.*, **1975**, 587-591] and following the procedure described

above for the synthesis of compound **20** (scheme 4, example 22), title compound **205** was obtained in 93% yield. LRMS (M+1) 169.1 (100%), 171.1 (32%).

Steps 2-4. (4-Chlorothieno[2,3-*d*]pyrimidin-6-yl)(pyrrolidin-1-yl)methanone (**208**)

[0459] Starting from the compound **205** and following the procedures described above for the synthesis of amide **5** (scheme 1, steps 2-4, example 1), title compound **208** was obtained [via intermediates **206** and **207**], in 76% yield as dark-brown oil (crude material, was used for the next step without additional purification). LRMS (M+1) 268.2 (100%).

Step 5. (4-(2-Fluoro-4-nitrophenoxy)thieno[2,3-*d*]pyrimidin-6-yl)(pyrrolidin-1-yl)methanone (**209**)

[0460] Starting from the compound **208** and following the procedures described above for the synthesis of nitro compound **6** (scheme 1, step 5, example 1), title compound **209** was obtained in 24% yield. LRMS (M+1) 389.1 (100%).

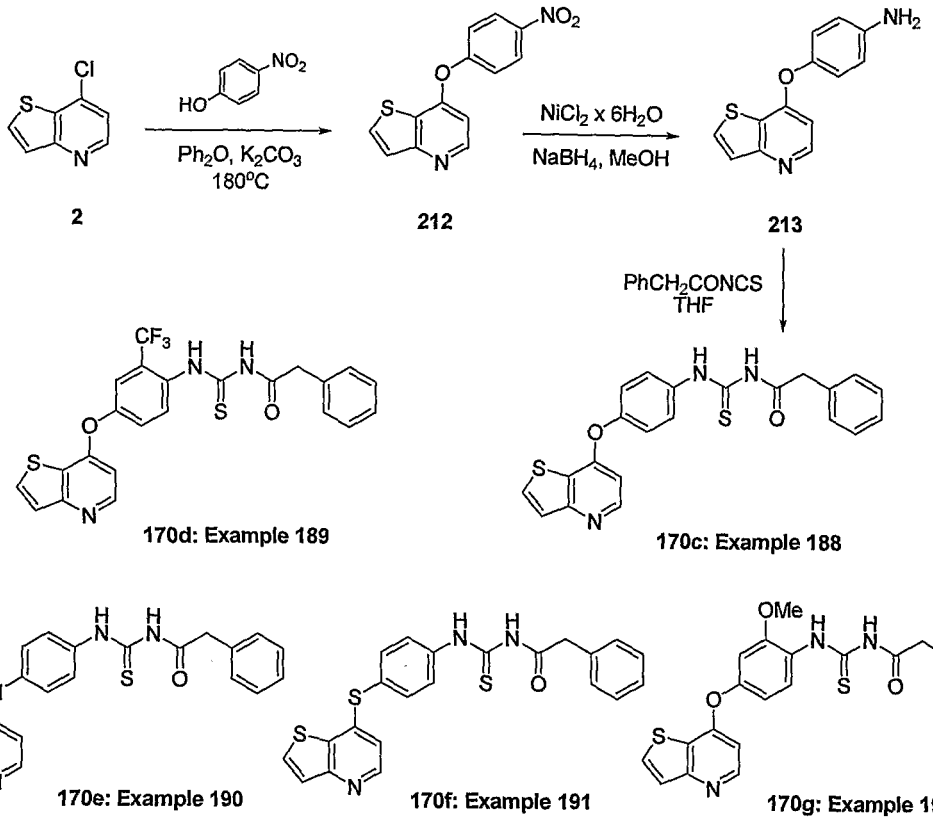
Step 6. (4-(4-Amino-2-fluorophenoxy)thieno[2,3-*d*]pyrimidin-6-yl)(pyrrolidin-1-yl)methanone (**210**)

[0461] Starting from the compound **209** and following the procedures described above for the synthesis of amine **7** (scheme 1, step 6, example 1), crude title compound **210** was obtained. It was purified by flash chromatography, eluents DCM followed by DCM-MeOH-Et_3N (97.75:2:0.25), to afford title compound **210** in 54% yield as a yellow solid. LRMS (M+1) 359.1 (100%).

Step 7. *N*-(3-Fluoro-4-(6-(pyrrolidine-1-carbonyl)thieno[2,3-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**211**)

[0462] Starting from the compound **210** and following the procedures described above for the synthesis of compound **8a** (scheme 1, step 7, example 1), crude title compound **211** was obtained. It was purified by flash chromatography, eluents DCM and DCM-MeOH-Et_3N (97.75:2:0.25) followed by trituration with a mixture of MeOH-EtOAc, to afford title compound **211** in 17% yield as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.43 (s, 1H), 11.80 (s, 1H), 8.70 (s, 1H), 8.06 (s, 1H), 7.93 (d, 1H, J=11.7/2.3 Hz), 7.53-7.47 (m, 2H), 7.34-7.26 (m, 5H), 3.90 (t, 2H, J=6.7 Hz), 3.83 (s, 2H), 3.55 (t, 2H, J=6.7 Hz), 1.99-1.85 (m, 4H). LRMS (M+1) 536.2 (100%).

Scheme 45



Example 188

2-Phenyl-*N*-(4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (170c)

Step 1. 7-(4-Nitrophenoxy)thieno[3,2-b]pyridine (**212**)

[0463] Staring from the chloride **2**, following the procedure described above for the synthesis of compound **6** (scheme 1, example 1) but substituting 2-fluoro-4-nitrophenol for 4-nitrophenol, title compound **212** was obtained in 89% yield. MS (m/z) 273.0 (M+H).

Step 2. 4-(Thieno[3,2-b]pyridin-7-yloxy)benzenamine (**213**)

[0464] Staring from the nitro compound **212**, following the procedure described above for the synthesis of amine **49** (scheme 10, example 55), title compound **213** was obtained in 90% yield. MS (m/z) 243.1 (M+H).

Step 3. 2-Phenyl-*N*-(4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (**170c**)

[0465] Staring from the amine **213**, following the procedure described above for the synthesis of compound **50** (scheme 10, example 55), title compound **170c** was obtained in 34% yield. ^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.35 (1H, s), 11.69 (1H, s), 8.47 (1H, d, J=5.28 Hz), 8.10 (1H, d, J=5.28 Hz), 7.70 (1H, s), 7.68 (1H, s), 7.54 (1H, d, J=5.28 Hz), 7.30-7.22 (7H, m), 6.61 (1H, d, J=5.28 Hz), 3.78 (2H, s). MS (m/z) 420.0 (M+H).

Example 189

2-Phenyl-*N*-(4-(thieno[3,2-b]pyridin-7-yloxy)-2-(trifluoromethyl)phenylcarbamothioyl)acetamide (170d)

[0466] Title compound **170d** was obtained according to the scheme 45 via a three-step synthesis starting from the chloride **2** and replacing 4-nitrophenol [in the first step] with 4-nitro-3-(trifluoromethyl)phenol. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.29 (s, 1H), 11.99 (s, 1H), 8.56 (d, *J* = 5.3 Hz, 1H), 8.17 (d, *J*= 5.3 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.74 (d, J = 2.7 Hz, 1H), 7.63 (m, 2H), 7.34 (m, 4H), 7.26 (m, 2H), 6.75 (d, *J*= 5.3 Hz, 1H), 3.85 (s, 1H). MS (m/z): 488.3 (M+H).

Example 190

2-Phenyl-*N*-(4-(thieno[3,2-b]pyridin-7-ylamino)phenylcarbamothioyl)acetamide (170e)

[0467] Title compound **170e** was obtained according to the scheme 45 via a three-step synthesis starting from the chloride **2** and replacing 4-nitrophenol [in the first step] with 4-nitrobenzenamine. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.39 (s, 1H), 11.72 (s, 1H), 8.97 (s, 1H), 8.35 (d, *J*= 5.1 Hz, 1H), 8.03 (d, *J* = 5.5 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 5.3 Hz, 1H), 7.38 (m, 4H), 7.32 (d, *J* = 8.4 Hz, 3H), 6.94 (d, *J*= 5.5 Hz, 1H), 3.87 (s, 1H). MS (m/z): 419.2 (M+H).

Example 191

2-Phenyl-*N*-(4-(thieno[3,2-b]pyridin-7-ylthio)phenylcarbamothioyl)acetamide (170f)

[0468] Title compound **170f** was obtained according to the scheme 45 via a three-step synthesis starting from the chloride **2** and replacing 4-nitrophenol [in the first step] with 4-nitrobenzenethiol. ^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.65 (1H, s), 11.91 (1H, s), 8.62 (1H, d, J=4.70 Hz), 8.28 (1H, d, J=5.28 Hz), 8.01-7.90 (2H, m), 7.79-7.68 (5H, m), 7.23 (1H, m), 3.95 (2H, m). MS (m/z) 436.0 (M+H)

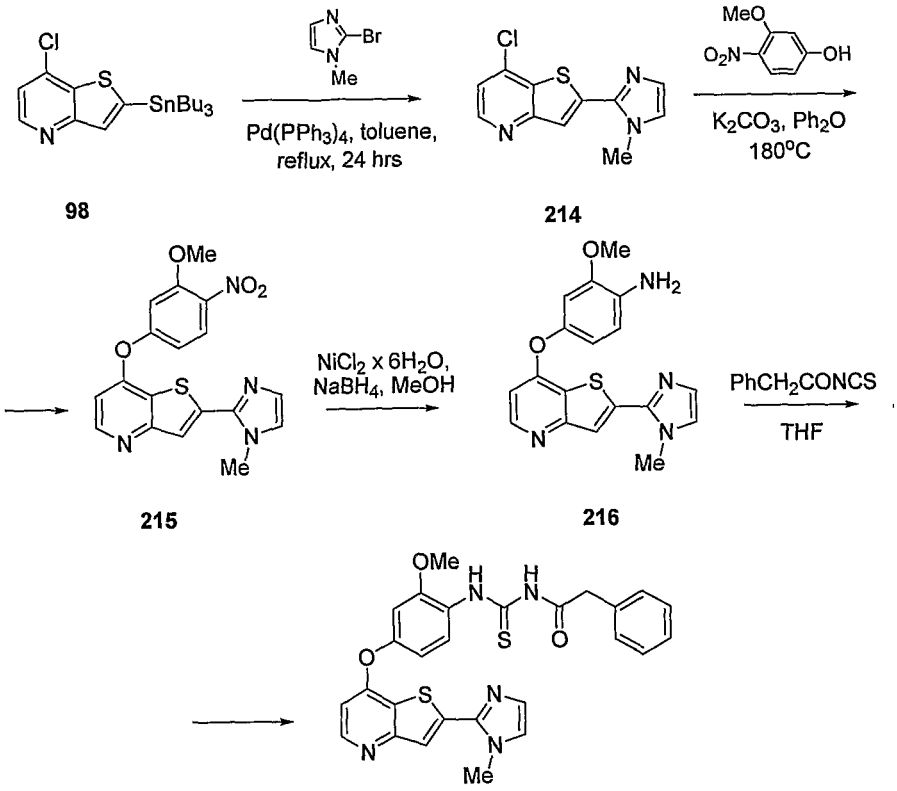
Example 192

N-(2-Methoxy-4-(thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (170g)

[0469] Title compound **170g** was obtained according to the scheme 45 via a three-step synthesis starting from the chloride **2** and replacing 4-nitrophenol [in the first step] with 3-methoxy-4-nitrophenol [Hodgson, C., *J. Chem. Soc.*, **1929**, 2778). ^{1}H NMR (DMSO) δ (ppm): 12.70 (1H, s), 11.71 (1H, s), 8.63 (1H, d, J=8.80 Hz), 8.51 (1H, d, J=5.28 Hz), 8.14 (1H, d, J=5.48 Hz), 7.50 (1H, dd, J=5.48, 0.78 Hz), 7.36-7.25 (5H, m), 7.13 (1H, d, J=2.54

Hz), 6.89 (1H, dd, J=8.80, 2.54 Hz), 6.69 (1H, d, J=5.48 Hz), 3.82 (5H, s). MS (m/z) 449.55 (M+H).

Scheme 46



Example 193

N-(2-Methoxy-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (217)

Step 1. 7-Chloro-2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridine (**214**)

[0470] Starting from tributyltin compound **98** (scheme 19) and following the procedure described above for the synthesis of compound **10** (scheme 2, step 2, example 12) but replacing 2-bromothiazole with 2-bromo-1-methyl-1*H*-imidazole, title compound **214** was obtained in 95% yield. MS (m/z) 250.1 (100%), 252.1 (37%), (M+H).

Step 2. 7-(3-Methoxy-4-nitrophenoxy)-2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridine (**215**)

[0471] Starting from compound **214**, following the procedure described above for the synthesis of compound **11** (scheme 2, step 3, example 12) but replacing 2-fluoro-4-nitrophenol with 3-methoxy-4-nitrophenol [Hodgson, C., *J. Chem. Soc.*, **1929**, 2778], title compound **215** was obtained in 9% yield. MS (m/z) 383.1 (M+H).

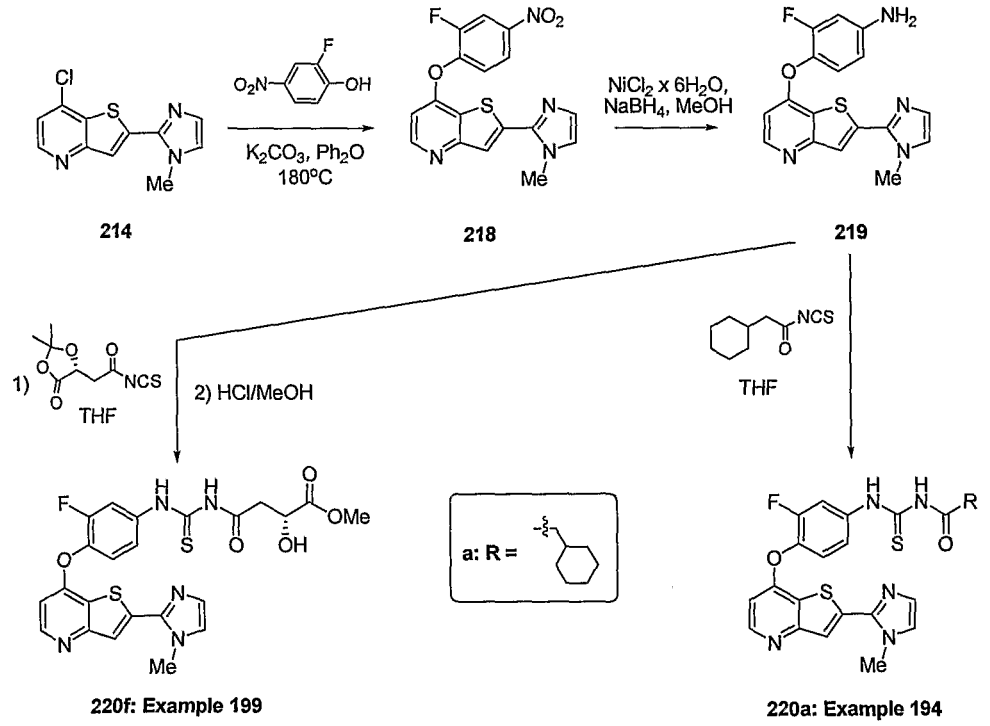
Step 3. 2-Methoxy-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine (**216**)

[0472] Starting from compound **215** and following the procedure described above for the synthesis of compound **12** (scheme 2, step 4, example 12), title compound **216** was obtained in 100% yield. MS (m/z) 353.1 (M+H).

Step 4. *N*-(2-Methoxy-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**217**)

[0473] Starting from compound **216** and following the procedure described above for the synthesis of compound 13a (scheme 2, step 5, example 12), title compound 217 was obtained in 48% yield. ^{1}H NMR (400 MHz,DMSO-d_6) δ ppm 12.07 (1H, s), 11.59 (1H, s), 8.45 (1H, d, J=5.48 Hz), 7.91 (1H, d, J=8.80 Hz), 7.85 (1H, s), 7.41 (1H, s), 7.24-6.98 (8H, m), 6.66 (1H, d, J=5.67 Hz), 3.99 (3H, s), 3.78 (3H, s), 3.59 (2H, s). MS (m/z) 530.2 (M+H).

Scheme 47



Example 194

2-Cyclohexyl-*N*-(3-fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (220a)

Step 1. 7-(2-Fluoro-4-nitrophenoxy)-2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridine (**218**)

[0474] Starting from compound **214** (scheme 46) and following the procedure described above for the synthesis of compound **11** (scheme 2, step 3, example 12), title compound **218** was obtained in 45% yield. MS (m/z) 371.1 (M+H).

Step 2. 3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine (**219**)

[0475] Starting from compound **218** and following the procedure described above for the synthesis of compound **12** (scheme 2, step 4, example 12), title compound **219** was obtained in 86% yield. MS (m/z) 341.1 (M+H).

Step 3: 2-Cyclohexyl-*N*-(3-fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (220a)

[0476] To a suspension of **219** (50 mg, 0.145 mmol) in THF (1.5 mL) was added 2-cyclohexylacetyl isothiocyanate (40 mg, 0,22 mmol) [P. A. S. Smith and R. O. Kan. *J. Org. Chem.*, **1964**, 2261] and the reaction mixture was stirred for 3 hours transferred onto a flash chromatography column and eluted with EtOAc-MeOH mixture (19:1), to afford title compound **220a** (27.5 mg, 31% yield) as a light yellow solid. Characterization of **220a** is provided in the table 21.

Example 195

2-Cyclopentyl-*N*-(3-fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (220b)

[0477] Title compound **220b** was obtained similarly to the compound **220a** from the amine **219** and 2-cyclopentylacetyl isothiocyanate [P. A. S. Smith and R. O. Kan. *J. Org. Chem.*, **1964**, 2261] in 47% yield. Characterization of **220b** is provided in the table 21.

Example 196

N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-oxopyrrolidin-1-yl)acetamide (220c)

[0478] Title compound **220c** was obtained similarly to the compound **220a** from the amine **219** and 2-(2-oxopyrrolidin-1-yl)acetyl isothiocyanate [prepared according to the reference P. A. S. Smith and R. O. Kan. *J. Org. Chem.*, **1964**, 2261] in 18% yield. Characterization of **220c** is provided in the table 21.

Example 197

N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(tetrahydro-2H-pyran-4-yl)acetamide (220d)

[0479] Title compound **220d** was obtained similarly to the compound **220a** from the amine **219** and 2-(tetrahydro-2*H*-pyran-4-yl)acetyl isothiocyanate [prepared according to

the reference P. A. S. Smith and R. O. Kan. *J. Org. Chem.*, **1964**, 2261] in 15% yield. Characterization of **220d** is provided in the table 21.

Example 198

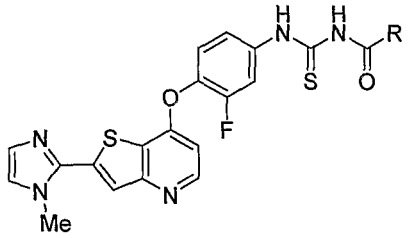
N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide (220e)

[0480] Title compound **220f** was obtained similarly to the compound **220a** from the amine **219** and acetyl isothiocyanate in 28% yield. Characterization of **220f** is provided in the table 21.

Example 199

(R)-Methyl 4-(3-(3-fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenyl)thioureido)-2-hydroxy-4-oxobutanoate (220f)

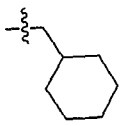
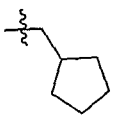
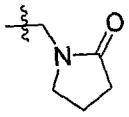
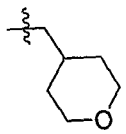
[0481] To a suspension of **219** (60 mg, 0.186 mmol) in THF (1.9 mL) was added (R)-2-(2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetyl isothiocyanate (60 mg, 0,28 mmol) [P. A. S. Smith and R. O. Kan. *J. Org. Chem.*, **1964**, 2261]. The reaction mixture was stirred for 3 hours, concentrated, purified by flash chromatography, eluent EtOAc-MeOH (19:1), to produce a solid material (29.5 mg) which was dissolved in MeOH, treated with HCl (1N in Et_2O, 0.1 mL) and the mixture was stirred for 10 min at room temperature. The solution was concentrated, and the residue was purified by preparative HPLC (Aquasil C18 column, gradient: 30% MeOH to 95% MeOH in water, 45 min), to afford title compound **220f** (15 mg, 13% yield) as a white solid. Characterization of **220f** is provided in the table 21.

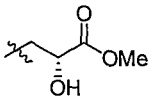


220a-f: Examples 194-199

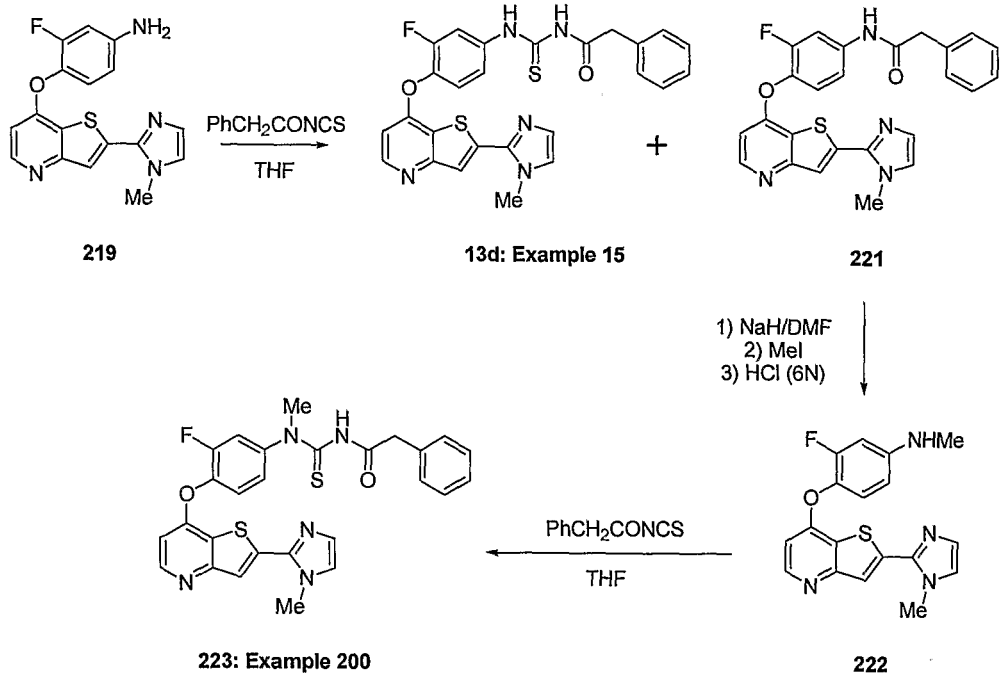
Table 21

Characterization of compounds 220a-f (examples 194-199)

Cpd	Ex	R	Name	Characterization
220a	194		2-Cyclohexyl-*N*-(3-fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide	^{1}HNMR: (DMSO-d_6) δ (ppm): 12.68 (s, 1H), 11.57 (s, 1H), 8.72 (d, 5.5 Hz, 1H), 8.40 (s, 1H), 8.1 (m, 1H), 7.88 (m, 1H), 7.75 (s, 1H), 7.61 (m, 2H), 6.90 (d, J=5.5Hz, 1H), 4.05 (s, 3H), 2.37 (d, J=6.8Hz, H), 1.79-1.60 (m, 6H), 1.28-1.12 (m, 3H), 1.02-0.94 (m, 2H). MS (m/z): 524.3(M+1).
220b	195		2-Cyclopentyl-N-(3-fluoro-4-(2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide	^{1}H NMR (DMSO-d_6) δ (ppm): 12.66 (s, 1H), 11.55 (s, 1H), 8.5 (m, 1H), 8.06 (d, J=12.5Hz, 1H), 7.9 (s, 1H), 7.55 (m, 2H), 7.41 (s, 1H), 7.05 (s, 1H), 6.69 (m, 1H), 4.0 (s, 3H), 2.5 (m, 2H), 2.2 (m, 1H), 1.78 (m, 2H), 1.61-1.52 (m, 4H), 1.18 (m, 2H). MS (m/z): 510.2 (M+1)
220c	196		N-(3-Fluoro-4-(2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-oxopyrrolidin-1-yl)acetamide	^{1}H NMR (DMSO-d_6) δ (ppm): 8.52 (d, J=5.4Hz, 1H), 7.98 (m, 1H), 7.89 (m, 1H), 7.46 (m, 2H), 7.40 (s, 1H), 7.04 (m, 1H), 6.68 (d, J=5.3Hz, 1H), 4.18 (s, 2H), 3.99 (s, 3H), 3.37 (m, 2H), 2.27 (m, 2H), 2.0 (m, 2H). MS (m/z): 525.3 (M+1).
220d	197		N-(3-Fluoro-4-(2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(tetrahydro-2H-pyran-4-yl)acetamide	^{1}H NMR (DMSO-d_6) δ (ppm): 8.53 (d, J=5.3Hz, 1H), 8.03 (d, J=12.5Hz, 1H), 7.89 (s, 1H), 7.52 (m, 2H), 7.41 (m, 1H), 7.04 (m, 1H), 6.69 (d, J=5.4Hz, 1H), 3.99 (s, 3H), 3.82 (m, 2H), 3.59 (m, 1H), 3.3 (m, 2H), 2.43 (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H). MS (m/z): 526.2 (M+1).
220e	198	CH_3	N-(3-Fluoro-4-(2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)acetamide	^{1}H NMR (DMSO-d_6) δ (ppm): 12.55 (br, 1H), 11.52 (br, 1H), 8.53 (m, 1H), 8.03 (m, 1H), 7.90 (s, 1H), 7.52 (m, 2H), 7.41 (s, 1H), 7.04 (s, 1H), 6.69 (m, 1H), 4.00 (s, 3H), 2.18 (s, 2H). MS (m/z): 442.1 (M+1).

Cpd	Ex	R	Name	Characterization
220f	**199**		(R)-Methyl 4-(3-(3-fluoro-4-(2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenyl)thioureido)-2-hydroxy-4-oxobutanoate	^{1}H NMR (DMSO-d_6) δ (ppm): 8.55 (d, J=5.5Hz, 1H), 8.04 (m, 1H), 7.92 (s, 1H), 7.55 (m, 2H), 7.43 (d, J=1Hz, 1H), 7.06 (d, J=1Hz, 1H), 6.70 (dd, J=5.5Hz, J=1Hz, 1H), 4.48 (dd, J=5.2Hz, J=7.2Hz, 1H), 4.0 (s, 3H), 3.67 (s, 3H), 2.92 (dd, J=5.2Hz, J=15.5Hz, 1H), 2.86 (dd, J=7.4Hz, J=15.5Hz, 1H). MS (m/z): 530.2 (M+1)

Scheme 48



219 **13d: Example 15** **221**

223: Example 200 **222**

Example 200

N-((3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenyl)(methyl)carbamothioyl)-2-phenylacetamide (223)

Step 1: *N*-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (13d) and *N*-(3-fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenyl)-2-phenylacetamide (221)

[0482] To a suspension of **219** (400 mg, 1.18 mmol) in THF (12 mL) was added 2- 2-phenylacetyl isothiocyanate (312 mg, 1.76 mmol) [P. A. S. Smith and R. O. Kan. *J. Org. Chem.*, **1964**, 2261], the reaction mixture was stirred for 3 hours, transferred onto a flash chromatography column and eluted with EtOAc/MeOH mixture (98:2), to afford title compounds **13d** (example 15, 254 mg, 42% yield) and **221** (96 mg, 17% yield).

[0483] Characterization of **13d** (example 15) is provided in the table 2. Compound **221** is characterized by its mass-spectrum: MS (m/z): 459.1 (M+1).

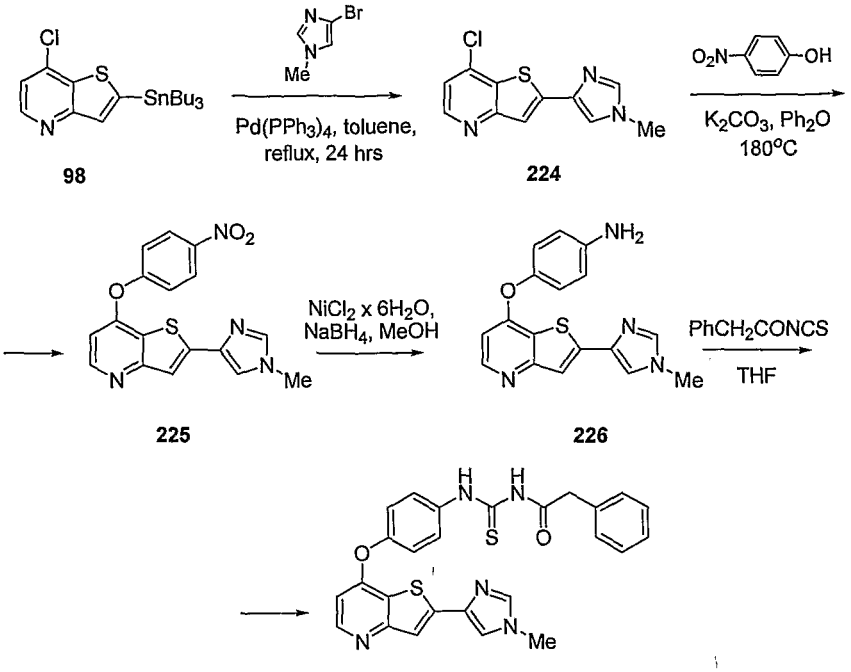
Step 2. 3-Fluoro-*N*-methyl-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine (**222**)

[0484] To a solution of **221** (274.8 mg, 0.6 mmol) in DMF (6 mL) NaH (60% in mineral oil, 36 mg, 0.9 mmol) was added in one portion at 0 ^{0}C and the reaction mixture was stirred for 1 h, followed by addition of MeI (0.037 mL, 0.6 mmol). The reaction mixture was allowed to warm up to room temperature, stirred overnight, diluted with EtOAc, washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was treated with 6N HCl (3 mL), and heated at 100°C for 3 h, cooled to room temperature and partitioned between water and DCM. Aqueous phase was collected, basified with 1N NaOH to pH 11 and extracted with EtOAc. The extract was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography (eluent EtOAc/MeOH, 9:1) to afford title compound **222** (102 mg, 46% yiled) as a syrup. MS (m/z): 355.1 (M+1).

Step 3: *N*-((3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenyl)(methyl)carbamothioyl)-2-phenylacetamide (223)

[0485] To a suspension of the **222** (102 mg, 2.88 mmol) in THF (3 ml) was added 2-phenylacetyl isothiocyanate (51 mg, 0.288 mmol). The reaction mixture was stirred for 1 hr, transferred onto a chromatography column and eluted with a mixture EtOAc/MeOH (19:1) to afford title compound **223** (30 mg, 20% yield) as a white solid. ^{1}HNMR: (DMSO-d_6) **δ** (ppm): 10.88 (s, 1H), 8.51 (d, J=5.3Hz, 1H), 7.91 (s, 1H), 7.41-7.18 (m, 6H), 7.04 (m, 4H), 6.5 (d, J=5.3Hz, 1H), 4.0 (s, 3H), 3.6 (s, 2H), 3.43 (s, 3H). MS (m/z): 532.3 (M+1).

Scheme 49



227: Example 201

Example 201

N-(4-(2-(1-Methyl-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (227)

Step 1: 7-Chloro-2-(1-methyl-1*H*-imidazol-4-yl)thieno[3,2-b]pyridine (**224**)

[0486] Starting from the compound **98** (scheme 19), following the procedure described above for the synthesis of compound **10** (scheme 2, step 2, example 12) but replacing 2-bromothiazole with 4-bromo-1-methyl-1*H*-imidazole, title compound **224** was obtained in 29% yield. MS (m/z): 250.1 (100%), 252.1 (37%) (M+1).

Step 2: 2-(1-Methyl-1*H*-imidazol-4-yl)-7-(4-nitrophenoxy)thieno[3,2-*b*]pyridine (**225**)

[0487] A mixture of **224** (950mg, 3.81 mmol), 4-nitrophenol (795 mg, 5.72 mmol), K_2CO_3 (1.05 g, 7.62 mmol) and Ph_2O (5 mL) was stirred at 190°C for 2 h in a sealed tube, cooled and treated with additional amount of 4-nitrophenol (795 mg, 5.72 mmol). The mixture was stirred for another hour at the same conditions, cooled to room temperature and diluted with DCM. The DCM solution was extracted with 2N HCl; the aqueous phase was collected, basified with concentrated ammonium hydroxide solution (pH~11) and extracted with EtOAc. The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **225** (860 mg, 64% yield) as an orange solid. MS (m/z): 353.1(M+1).

Step 3: 4-(2-(1-Methyl-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)benzenamine (**226**)

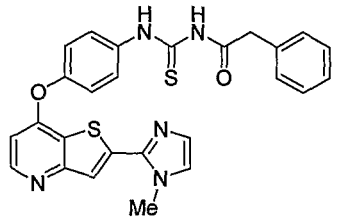
[0488] To a solution of **225** (860 mg, 2.44 mmol) and $NiCl_2$ x $6H_2O$ (1.16 mg, 4.88 mmol) in MeOH/THF (49/81 mL) $NaBH_4$ (278 mg, 7.32 mmol) was carefully added. The reaction mixture was stirred for 10 min, concentrated under reduced pressure and the residue was suspended in 10% HCl. The suspension was basified with concentrated NH_4OH solution (pH ~11) and extracted with EtOAc.

[0489] The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to produce a solid material. The aqueous phase (a suspension) was filtered; the precipitate was collected, washed with MeOH and dried under reduced pressure.

[0490] Both precipitate and the solid obtained from the organic phase, were combined to afford title compound **226** (947.4 mg, crude) as a brown solid that was used in the next step without further purification. MS (m/z): 323.1 (M+1).

Step 4: *N*-(4-(2-(1-Methyl-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**227**)

[0491] To a suspension of the **226** (385 mg, ~0.99 mmol) in THF (10 mL) was added 2-phenylacetyl isothiocyanate (263 mg, 1.49 mmol). The reaction mixture was stirred for 1 hr, transferred onto a chromatography column and eluted with EtOAc/MeOH (9:1) producing a solid material which was re-crystallized from MeCN to afford title compound **227** (74.3 mg, 15% yield) as a white solid. ^{1}HNMR: (DMSO-d_6) d(ppm): 12.39 (s, 1H), 11.73 (s, 1H), 8.43 (d, J=5.3Hz, 1H), 7.84 (s, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 7.34-7.27 (m, 7H), 6.69 (d, J=5.3Hz, 1H), 3.82 (s, 2H), 3.72 (s, 3H). MS (m/z): 500.1 (M+1).



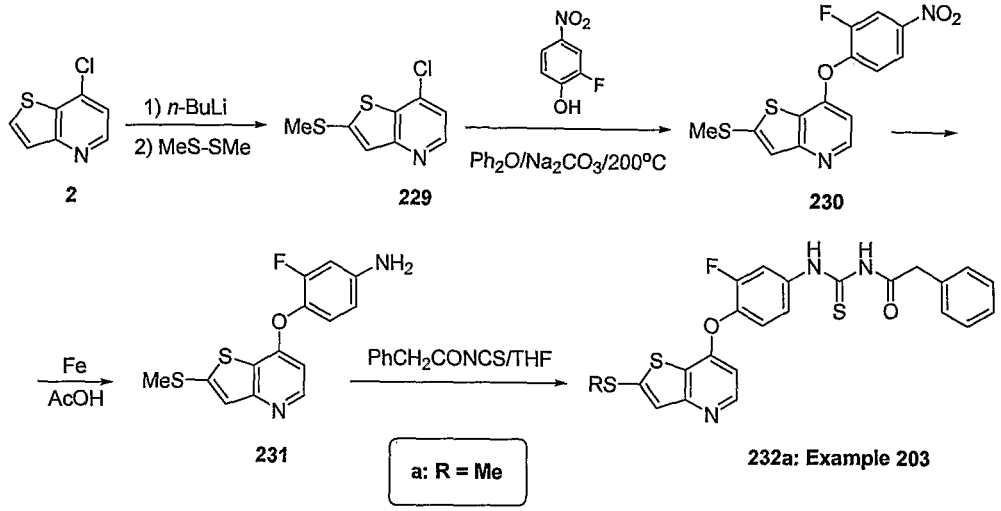
228: Example 202

Example 202

N-(4-(2-(1-Methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (228)

[0492] Title compound **228** was obtained starting from the compound **214** (scheme 46) and following the procedures described above for the synthesis of compound **227** (scheme 49, example 201). ^{1}H NMR (DMSO-d_6) **δ** (ppm): 12.42 (s, 1H), 11.77 (s, 1H), 8.74 (m, 1H), 8.37 (m, 1H), 7.87-7.78 (m, 1H), 7.70 (m, 1H), 7.42-7.20 (m, 7H), 6.90 (m, 1H), 4.05 (d, J=1Hz, 3H), 3.83 (s, 2H). MS (m/z): 500.3.

Scheme 50



Example 203

1-(4-(2-(Methylthio)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (232a)

Step 1: 7-Chloro-2-(methylthio)thieno[3,2-b]pyridine (229)

[0493] To a solution of **2** (200 mg, 1,18 mmol) in dry THF (11ml) at –78°C was added *n*-BuLi (0.57 mL, 2.5M solution on hexane, 1.41 mmol) and the resultant brown precipitate was stirred for 10 minutes. Methyl disulfide (0,16ml, 1,77mmol) was added slowly, the mixture was stirred at –78°C for 3 hours and partitioned between DCM and water. Organic phase was separated, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford title compound **229** (0,240g, 94% yield, crude) as a yellow solid. MS (m/z): 216.1 (100%), 218.1 (39%) (M+1).

Step 2: 7-(2-Fluoro-4-nitrophenoxy)-2-(methylthio)thieno[3,2-b]pyridine (230)

[0494] To a suspension of **229** (100 mg, 0,463 mmol) in diphenyl ether (4 mL), was added 2-fluoro-4-nitrophenol (109 mg, 0,695 mmol) and sodium carbonate (147 mg, 1,39 mmol). The reaction mixture was heated atr 200°C overnight, cooled to room temperature, loaded onto a flash chromatography column and eluted with EtOAc/hexane (1:1) to afford title compound **230** (0,135 mg, 86% yield) as a yellow solid. MS (m/z): 337.0 (M+1).

Step 3: 4-(2-(Methylthio)thieno[3,2-b]pyridin-7-yloxy)-3-fluorobenzenamine (231)

[0495] To as solution of **230** (84 mg, 0,250 mmol) in acetic acid (5 mL) at 100°C, was added iron powder (0,069g, 1,249mmol). The reaction mixture was allowed to stir for 5 minutes, filtered through a celite pad and concentrated under reduced pressure. The residue

was purified by column chromatography, eluent DCM/MeOH (50:1), to afford title compound **231** (61 mg, 80% yield) as yellow oil. MS (m/z): 307.1 (M+1).

Step 4: 1-(4-(2-(Methylthio)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**232a**)

[0496] To a suspension of **231** (61 mg) in THF (2 mL) was added 2-phenylacetyl isothiocyanate (42 mg, 0,199 mmol). The reaction mixture was stirred for 3 hours, concentrated under reduced pressure and the residue was purified by column chromatography, eluent EtOAc/hexane (35:65), to produce yellow oil. Purification of this material by preparative HPLC (column C-18 Aquasil, gradient: 60% MeOH to 95% MeOH) afforded title compound **232a** (25 mg, 26% yield) as a cream solid. Characterization of **232a** is provided in the table 22.

Example 204

1-(4-(2-(Butylthio)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (232b)

[0497] Starting from the compound **2**, following procedures described above for the synthesis of compound **232a** (example 203, scheme 50) but replacing methyl disulfide with *n*-butyl disulfide in the step 1, title compound **232b** was synthesized. Characterization of **232b** is provided in the table 22.

Example 205

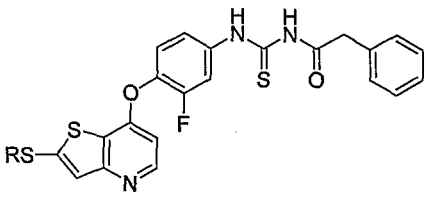
1-(4-(2-(Benzylthio)thieno [3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (232c)

[0498] Starting from the compound **2**, following procedures described above for the synthesis of compound **232a** (example 203, scheme 50) but replacing methyl disulfide with benzyl disulfide in the step 1, title compound **232c** was synthesized. Characterization of **232c** is provided in the table 22.

Example 206

1-(4-(2-(Pyridin-2-ylthio)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (232d)

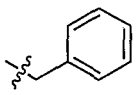
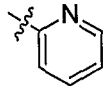
[0499] Starting from the compound **2**, following procedures described above for the synthesis of compound **232a** (example 203, scheme 50) but replacing methyl disulfide with 2-pyridyl disulfide in the step 1, title compound **232d** was synthesized. Characterization of **232d** is provided in the table 22.



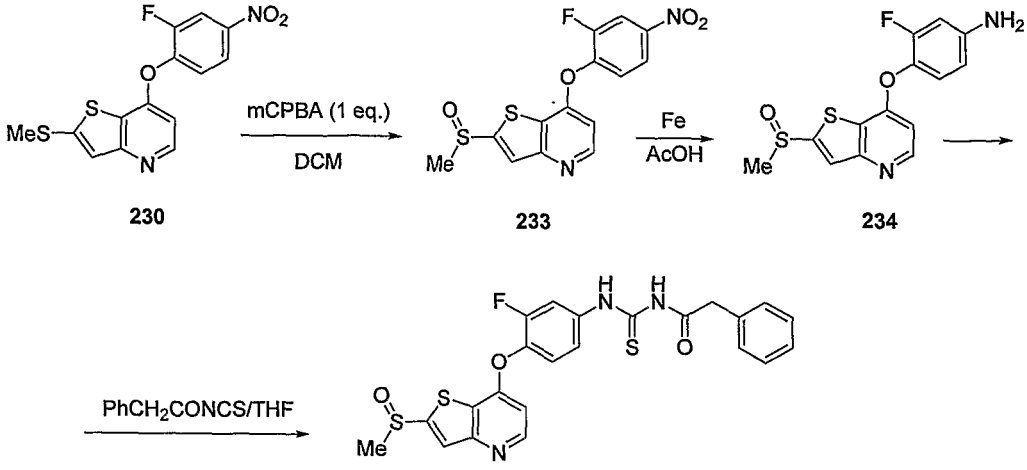
232a-d: Examples 203-206

Table 22

Characterization of compounds 232a-d (examples 203-206)

Cpd	Ex	R	Name	Characterization
232a	**203**	Me	1-(4-(2-(Methylthio)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	^{1}HNMR: (DMSO-d6) δ (ppm):12.46(s,1H), 11.81(s,1H), 8.45(s, 1H), 7.99(d, J=12.5, 1H), 7.51(s, 1H), 7.50(s, 1H), 7.46(s, 1H), 7.34-7.30(m, 2H), 7.30-7.27(m, 3H), 6.61(d, J=5.5Hz,1H), 3.82(s,2H), 2.71(s,3H). MS (m/z): 484.1.
232b	**204**	*n*-Bu	1-(4-(2-(Butylthio)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (DMSO-d_6) δ (ppm): 12.46 (s, 1H), 11.81(s, 1H), 8.46(d, J=5.5 Hz, 1H), 7.98 (d, J=12.44Hz, 1H), 7.54 (s, 1H), 7.53-7.47 (m, 2H), 7.35-7.31 (m, 4H), 7.31-7.24(m, 1H), 6.60 (d, J=5.5Hz, 1H), 3.82(s, 2H), 3.13 (t, J=7.24Hz, 2H), 1.64(q, J=7.43Hz, 2H), 1.42 (sextuplet, J=7.43Hz, 2H), 0.90 (t, J=7.24Hz, 3H). MS (m/z): 526.2
232c	**205**		1-(4-(2-(Benzylthio)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (DMSO-d_6) δ (ppm): 12.46 (s,1H), 11.81 (s, 1H), 8.44 (d, J=5.5 Hz, 1H), 7.98 (d, J=11.83Hz, 1H), 7.52-7.45 (m, 3H), 7.38-7.22 (m, 10H), 6.60 (d, J=5.5Hz, 1H), 4.39 (s, 2H), 3.82 (s, 2H). MS (m/z): 560.2
232d	**206**		1-(4-(2-(Pyridin-2-ylthio)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea	^{1}H NMR (DMSO-d6) δ (ppm): 8.55 (d, J=5.3Hz, 1H), 8.45 (d, J=3.91Hz, 1H), 8.00-7.95 (m, 2H), 7.74 (td, J=7.83Hz ; 1.76Hz, 1H), 7.50 (s, 2H), 7.35-7.23 (m, 8H), 6.70 (d, J=5.3Hz, 1H), 3.82 (s, 2H), 1.23 (s, 1H). MS (m/z): 547.2

Scheme 51



230 233 234

235: Example 207

Example 207

1-(4-(2-(Methylsulfinyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (207)

Step 1: 7-(2-Fluoro-4-nitrophenoxy)-2-(methylsulfinyl)thieno[3,2-b]pyridine (**233**)

[0500] To a solution of **230** (400 mg, 1.189mmol, scheme 50) in DCM (12 mL) at 0°C was added m-CPBA (77%, 272 mg, 1.189mmol). The reaction mixture was stirred at 0°C for 30 minutes, water was added and the phases were separated. The organic phase was collected, washed with a 1% sodium hydroxide solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography, eluent DCM/MeOH (20:1), to afford title compound **233** (414 mg, 90% yield, crude), which was used in the next step without further purification. MS (m/z): 353.0 (M+1).

Step 2: 4-(2-(Methylsulfinyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorobenzenamine (**234**)

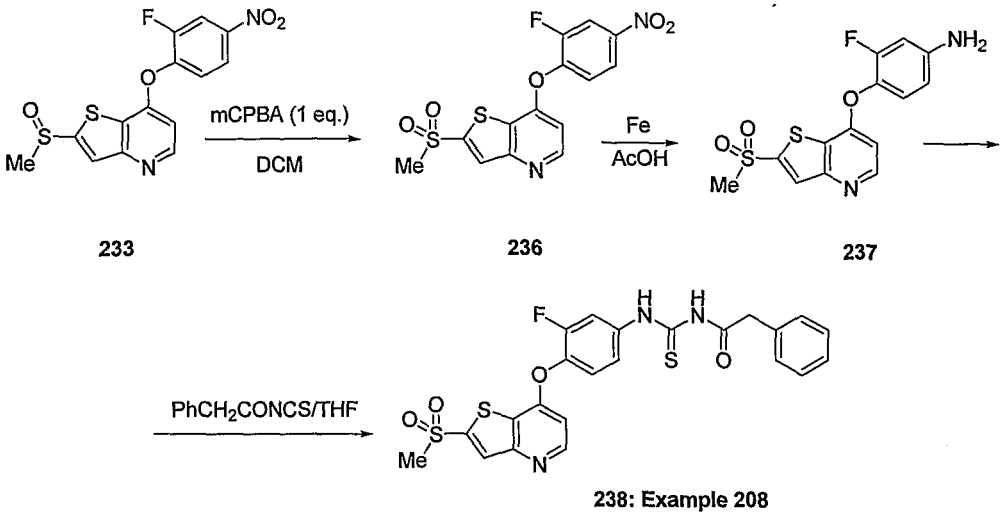
[0501] To as solution of **233** (400 mg, 1.135mmol) in acetic acid (10 mL) at 100°C, was added iron powder (317 mg, 5.675mmol). The reaction mixture was stirred for 5 minutes, filtered through a celite pad and concentrated under reduced pressure. The residue was purified by column chromatography, eluent EtOAc/hexane (4:1), to afford title compound **234** (0.285g, 69% yield) as a yellow solid. MS (m/z): 323.0 (M+1).

Step 3: 1-(4-(2-(Methylsulfinyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**235**)

[0502] To a suspension of **234** (280 mg, 0. 868mmol) in THF (8mL) was added 2-phenyl acetyl isothiocyanate (185 mg, 1.04 mmol). The reaction mixture was stirred for 3 hours, concentrated; the solid residue washed with Et_2O and dried, to afford title compound

235 (229 mg, 53% yileld) as a white-rose solid. ^{1}HNMR: (DMSO-d6) δ (ppm):12.41(s,1H), 11.75(s,1H), 8.54(d, J=5.3 Hz, 1H), 7.98 (s, 1H), 7.96(d, J=13.5Hz, 1H), 7.48(d, J=5.0Hz, 2H), 7.30-7.26(m, 2H), 7.26-7.18(m, 3H), 6.69(d, J=5.5Hz,1H), 3.25(s, 2H), 2.98(s, 3H). MS (m/z): 500.1 (M+1).

Scheme 52



238: Example 208

Example 208

1-(4-(2-(Methylsulfonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (238)

Step 1: 7-(2-Fluoro-4-nitrophenoxy)-2-(methylsulfonyl)thieno[3,2-b]pyridine (**236**)

[0503] To a solution of **233** (50 mg, 0.142mmol) in DCM (2mL), was added mCPBA (77%, 33 mg, 0.142 mmol) at **0°C**. The mixture was stirred at 0°C for 1 hour, water was added and the phases were separated. The organic layer was collected, **washed** with a 1% sodium hydroxide solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford title compound **236** (46 mg, 88% yield, crude) as a yellow solid which was used in the next step without additional purification. MS (m/z): 369.0 (M+1).

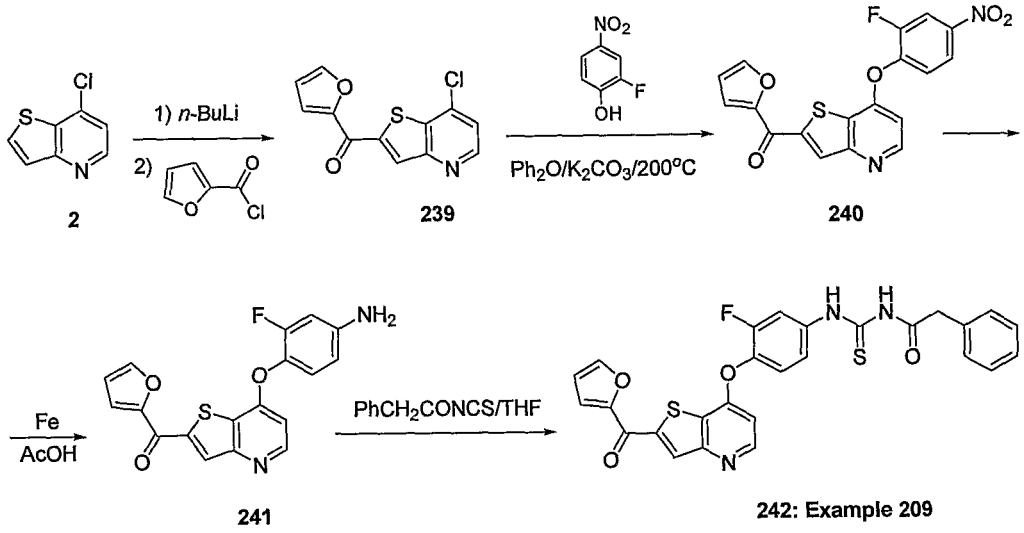
Step 2: 4-(2-(Methylsulfonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorobenzenamine (**237**)

[0504] To a solution of **236** (45 mg, 0.122 mmol) in acetic acid (4 mL) at 100°C, was added iron powder (34 mg, 0.611 mmol). The reaction mixture was stirred for 5 minutes, filtered through a celite pad and concentrated under reduced pressure to afford title compound **237** (20 mg, 48% yield, crude) as a yellow oil that was used in the next step without further purification. MS (m/z): 339.0 (M+1).

Step 3. 1-(4-(2-(Methylsulfonyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl)-3-(2-phenylacetyl)thiourea (**238**)

[0505] To a suspension of **237** (20 mg, 0.059mmol) in THF (10 mL) was added 2-phenylacetyl isothiocyanate (26 mg, 0.146 mmol). The reaction mixture was stirred for 2 hours, concentrated under reduced pressure and the residue was purified by column chromatography, eluent EtOAc/MeOH (19:1), to afford a solid material that was dissolved in a minimum MeOH and precipitated with hexane to afford title compound **238** (9.6 mg, 31%) as a white solid. ^{1}HNMR: (DMSO-d_6) δ (ppm):12.48(s,1H), 11.81(s,1H), 8.69(d,J=5.5 Hz, 1H), 8.36(s,1H), 8.03(d, J=12.13Hz, 1H), 7.55(s,2H), 7.36-7.30(m, 2H), 7.30-7.24(m, 3H), 6.86(d,J=5.5Hz,1H), 3.83(s,2H), 3.54(s,3H). MS (m/z): 516.2.

Scheme 53



Example 209

N-(3-Fluoro-4-(2-(furan-2-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (242)

Step1: (7-Chlorothieno[3,2-b]pyridin-2-yl)(furan-2-yl)methanone (239)

[0506] To a solution of **2** (100 mg, 0.589 mmol) in THF (6mL) at –78°C, was added *n*-BuLi (2.5 M in hexane, 0.259 mL, 8,84 mmol) and the reaction mixture was stirred 15 minutes. 2-Furoyl chloride (0.087 mL, 0.884 mmol) was added drop wise; the mixture was stirred for additional 2 hours and partitioned between DCM and water. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford title compound **239** (35 mg, 23% yield, crude) as a yellow solid, that was used in the next step without additional purification. MS (m/z): 264.0 (100%), 266.0 (40%) (M+1).

Step 2: (7-(2-Fluoro-4-nitrobenzyl)thieno[3,2-b]pyridin-2-yl)(furan-2-yl)methanone (240)

[0507] To a suspension of **239** (35 mg, 0.133mmol) in Ph_2O (2 mL) was added 2-fluoro-4-nitrophenol (42 mg, 0.265 mmol) and K_2CO_3 (73 mg, 0.530 mmol). The reaction

mixture was heated at 180°C in a sealed flask for 60 hrs, cooled down to room temperature, loaded onto a flash chromatography column and eluted with EtOAc/hexane mixture (1:1), to afford title compound **240** (20 mg 39% yield) as a yellow solid. MS (m/z): 385.1 (M+1).

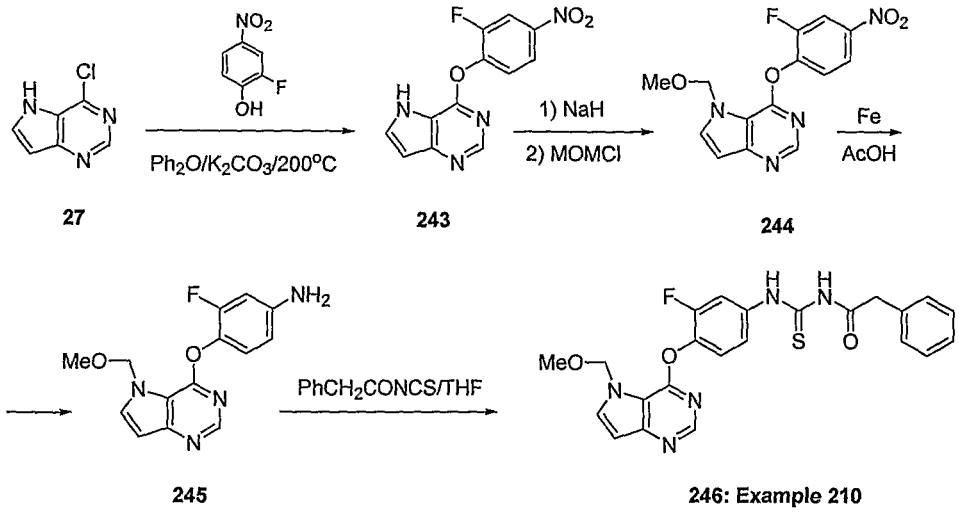
Step 3: (7-(4-Amino-2-fluorobenzyl)thieno[3,2-b]pyridin-2-yl)(furan-2-yl)methanone (**241**)

[0508] To as solution of **240** (20 mg, 0.052 mmol) in acetic acid (2 mL) at 100°C, was added iron powder (15 mg, 0.260 mmol). The reaction mixture was stirred for 3 minutes, filtered through a celite pad and concentrated under reduced pressure. The residue was purified by flash chromatography, eluent EtOAc/hexane (3:7) to afford title compound **241** (3.3 mg, 18% yield) as a yellow solid. MS (m/z): 355.1 (M+1).

Step 4: *N*-(3-Fluoro-4-(2-(furan-2-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**242**)

[0509] To a solution of **241** (3.3 mg, 0.0093mmol) in THF (1 mL) was added 2-phenylacetyl isothiocyanate (2 mg, 0.011 mmol). The reaction mixture was stirred for 3 hours, concentrated under reduced pressure and purified by column chromatography, eluent EtOAc/hexane (20:80), followed by precipitation from a mixture acetone/hexane. Thus, title compound **242** was obtained (2.2 mg, 44% yield) as a yellow solid. ^{1}HNMR: 1HNMR: (DMSO-d6) δ (ppm):12.49(s, 1H), 11.82(s, 1H), 8.67(d, J=5.5 Hz, 1H), 8.63(s, 1H), 8.22(s, 1H), 8.03(d, J=13.1 Hz, 1H), 7.79(d, J=3.7 Hz, 1H), 7.60-7.55(m, 2H), 7.55-7.25(m,5H), 6.89-6.87(m, 1H), 6.83(d, J=5.5Hz, 1H), 3.82(s, 2H). MS (m/z): 532.1 (M+1).

Scheme 54



27 243 244

245 246: Example 210

Example 210

N-(3-Fluoro-4-(5-(methoxymethyl)-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (246)

Step 1. 4-(2-Fluoro-4-nitrophenoxy)-5*H*-pyrrolo[3,2-d]pyrimidine (**243**)

[0510] To a suspension of **27** (0,400g, 2,60mmol) [G.B. Evans, R.H. Furneaux, et.al *J. Org. Chem.*, **2001**, 66, 17, 5723-5730] in diphenylether (25ml) was added 2-fluoro-4-nitrophenol (614 mg, 3.90mmol) and HCl (2N in Et_2O) (0.19 ml, 3.90mmol). The reaction mixture was heated at 120°C for 4 hours, cooled to room temperature and concentrated under reduced pressure, to afford title compound **243** (610 mg, 86% yield) as a black solid. MS (m/z): 274.1 (M+1).

Step 2: 4-(2-Fluoro-4-nitrophenoxy)-5-(methoxymethyl)-5*H*-pyrrolo[3,2-d]pyrimidine (**244**)

[0511] To a suspension of **243** (150 mg, 0.547 mmol in DMF (6 mL) was added NaH (66 mg, 1.64 mmol). and the reaction mixture was stirred at 0°C for 1 hour. Chloromethyl methyl ester (132 mg, 1.641 mmol) was added drop wise and the mixture was stirred at room temperature over night. MeOH (2 mL) was added and the mixture was stirred for an additional hour and partitioned between EtOAc and water. The organic phase was collected, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford title compound **244** (86 mg, 49% yield, crude) as an orange solid. MS (m/z): 319.1 (M+1).

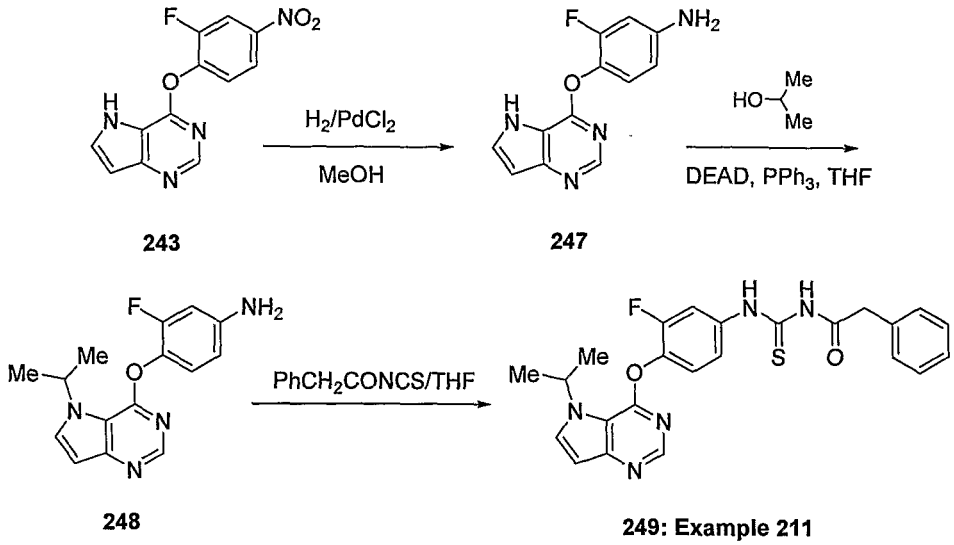
Step 3: 3-Fluoro-4-(5-(methoxymethyl)-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)benzenamine (**245**)

[0512] To as solution of **244** (85 mg, 0.267 mmol) in acetic acid (8 mL) at 100°C, was added iron powder (75 mg, 1.34 mmol). The reaction mixture was stirred for 5 minutes, filtered through Celite® pad and concentrated to dryness; the residue was purified by flash chromatography, eluent DCM/MeOH (30:1) to afford title compound **245** (18 mg, 23% yield) as an orange solid. MS (m/z): 289.1 (M+1).

Step 4: *N*-(3-Fluoro-4-(5-(methoxymethyl)-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**246**)

[0513] To a suspension of **245** (18 mg, 0.062 mmol) in THF (1 mL) was added 2-phenylacetyl isothiocyanate (12 mg, 0.069 mmol). The reaction mixture was stirred for 3 hours, concentrated under reduced pressure and the residue was purified by flash chromatography, eluent hexane/EtOAc (3:2) followed by recrystallization (MeCN/water), and preparative HPLC (Aquasil C-18, gradiend: 60% MeOH to 95% MeOH in water), to afford title compound **246** (9.2 mg, 33% yield) as a white solid. ^{1}HNMR: (CD_3OD) **δ** (ppm): 8.35(s, 1H), 8.03 (d, J=12.4Hz, 1H), 7.96(d, J=3.13Hz, 1H), 7.44-7.26(m, 6H), 6.69 (d, J=3.13Hz,1H), 5.29 (quintuplet, J=6.65Hz, 1H), 3.75(s, 2H), 3.60 (d, J=10.96Hz, 3H), 1.63(d, J=6.65Hz, 6H). MS (m/z): 464.16 (M+1).

Scheme 55



Example 211

N-(3-Fluoro-4-(5-isopropyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (249)

Step 1: 4-(5*H*-Pyrrolo[3,2-*d*]pyrimidin-4-yloxy)-3-fluorobenzenamine (**247**)

[0514] A solution of **243** (263 mg, 0.966 mmol, scheme 54) in MeOH (10mL) and $PdCl_2$ (1.8 mg, 0.01 mmol) was stirred in the atmosphere of hydrogen for 60 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Water was added to the residue and the aqueous solution was extracted with DCM. The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to afford title compound **247** (170 mg, 72% yield, crude) as a gray solid. MS (m/z): 243.08 (M+1).

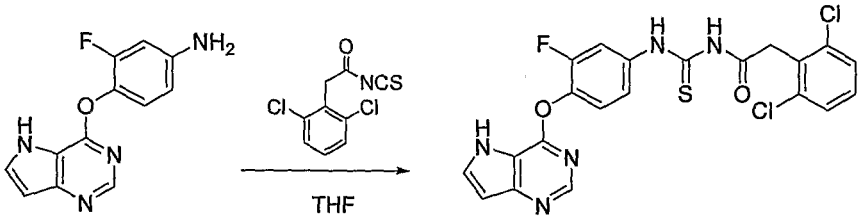
Step 2: 3-Fluoro-4-(5-isopropyl-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)benzenamine (**248**)

[0515] To a suspension of **247** (80 mg, 0.327mmol) in THF (4 mL), was added PPh_3 (258 mg, 0.983 mmol), DEAD (0.155ml, 0.983mmol) and isopropanol (0.075ml, 0.983 mmol), and the reaction mixture was allowed to stir for 48 hours. 3N HCl solution (1.0 mL) was added and the mixture was extracted with DCM. Aqueous phase was collected, neutralized with NaOH 10% (pH ~11) and extracted with DCM. The organic phase was collected, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified twice by column chromatography: eluents EtOAc/hexane (3:7) and MeOH/DCM (1:20), to afford title compound **248** (19 mg, 31% yield) as yellow solid. MS (m/z): 287.1 (M+1).

Step 3: *N*-(3-Fluoro-4-(5-isopropyl-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**249**)

[0516] To a suspension of **248** (10 mg, 0.035mmol) in THF (1 mL) was added 2-phenylacetyl isothiocyanate (0.007 mL, 0.038mmol). The reaction mixture was stirred for 3 hours, concentrated under reduced pressure and the residue was purified by flash chromatography, eluent EtOAc/hexane (1:1) and preparative HPLC (C-18 Aquasyl column, gradient: 60% to 95% MeOH in water, 45 min), to afford title compound **249** (4 mg, 26% yield) as a white solid. ^{1}HNMR: (CD_3OD) δ (ppm): 8.35(s, 1H), 8.03 (d, J=12.4Hz, 1H), 7.96(d, J=3.13Hz, 1H), 7.44-7.26(m, 6H), 6.69 (d, J=3.13Hz,1H), 5.29 (quintuplet, J=6.65Hz, 1H), 3.75(s, 2H), 3.60 (d, J=10.96Hz, 3H), 1.63(d, J=6.65Hz, 6H). MS (m/z): 464.2 (M+1).

Scheme 56



247 **250: Example 212**

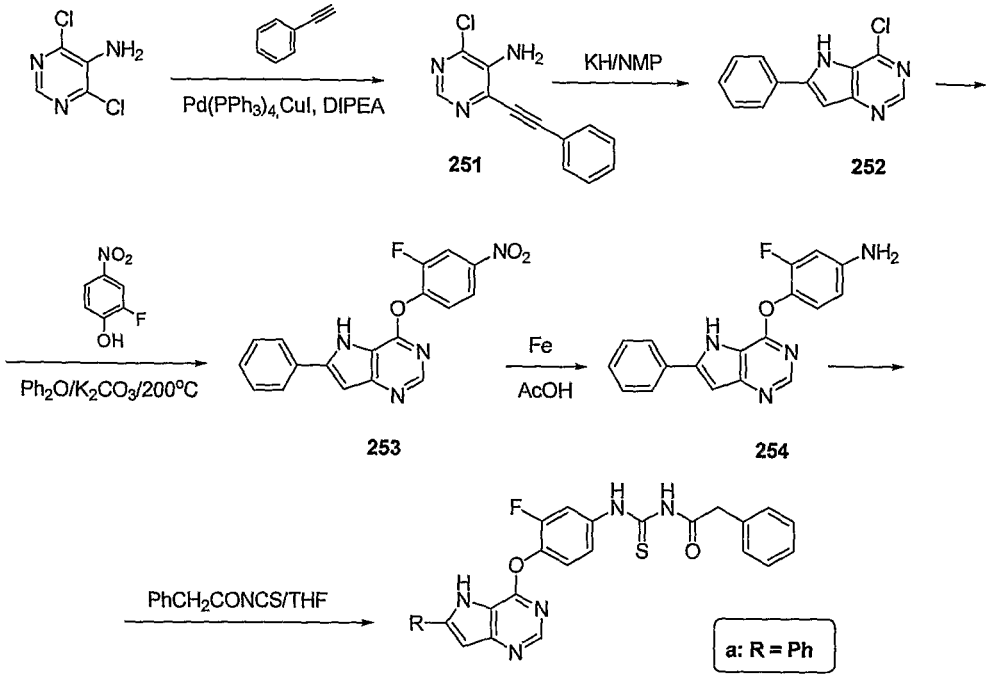
Example 212

N-(4-(5*H*-Pyrrolo[3,2-d]pyrimidin-4-yloxy)-3-fluorophenylcarbamothioyl)-2-(2,6-dichlorophenyl)acetamide (250)

Step 1: *N*-(4-(5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)-3-fluorophenylcarbamothioyl)-2-(2,6-dichlorophenyl)acetamide (**250**)

[0517] To a solution of **247** (200 mg, 0.819 mmol, scheme 55) in THF (8.2 mL) 2-(2,6-dichlorophenyl)acetyl isothiocyanate (302 mg, 1.33 mmol) was added. The mixture was stirred for 1 h at room temperature, transferred onto a flash chromatography column and eluted with EtOAc/hexane (1:1). The solid material obtained was triturated with diethyl ether, filtered and dried under reduced pressure, to afford title compound **250** (200 mg, 0.408, 50% yield) as a light brown solid. ^{1}HNMR: (DMSO-d_6) δ (ppm) 12.69 (s, 1H), 12.26 (s, 1H), 12.04 (s, 1H), 7.94 (m, 2H), 7.53 (m, 4H), 7.39 (m, 1H), 6.72 (m, 1H), 4.22 (s, 2H). MS (m/z): 490.1 (100%, 492.1 (77%) (M+1).

Scheme 57



255a: Example 213

Example 213

N-(3-Fluoro-4-(6-phenyl-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (255a)

Step 1: 4-Chloro-6-(phenylethynyl)pyrimidin-5-amine (**251**)

[0518] Ethynylbenzene (0.092 mL, 0.92 mmol) was added to a solution of 4,6-dichloropyrimidin-5-amine (100 mg, 0.61 mmol), $Pd(PPh_3)_4$ (140 mg, 0.12 mmol), CuI (116 mg, 0.61 mmol) and DIPEA (0.5 mL, 3.05 mmol) in DME (6.1 mL). The reaction mixture was stirred in the dark over night at room temperature, diluted with DCM, washed sequentially with dilute aqueous citric acid and water, dried over anhydrous Na_2SO_4 and concentrated under reduce pressure. The residue was purified by flash chromatography, eluent EtOAc/hexane (1:3), to afford title compound **251** (30.8 mg, 22% yield) as a yellow solid. MS (m/z): 230.1 (100.0%), 232.1 (33%) (M+1).

Step 2: 4-Chloro-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (**252**)

[0519] To a solution of **251** (30.8 mg, 0.134 mmol) in NMP (1.4 mL) a suspension of KH in mineral oil (35%, 31 mL, 0.268 mmol) was added in one portion. The mixture was stirred at room temperature overnight and partitioned between EtOAc and water. The organic phase was collected, dried over anhydrous Na_2SO_4 and concentrated. The residue

was purified by flash chromatography, eluent EtOAc/hexane (1:2) to afford title compound affording **252** (22.7 mg, 74% yield). MS (m/z): 230.1 (100%) 232.1 (33%) (M+1).

Step 3: 4-(2-Fluoro-4-nitrophenoxy)-6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (**253**)

[0520] A mixture of **252** (47.9mg, 0.21 mmol), 4-nitrophenol (50 mg, 0.32 mmol), K_2CO_3 (58 mg, 0.42 mmol) and Ph_2O (4 mL) was stirred at 190°C overnight in a sealed tube. The mixture was cooled down, more 4-nitrophenol (50 mg, 0.32 mmol) was added and the mixture was stirred at 190 ^{0}C for additional 8 h. It was cooled again, transferred onto a chromatography column and eluted sequentially with EtOAc/hexane (1:10) and EtOAc/hexane (1:3), to afford title compound **253** (71.4 mg, 97% yield) as a white foam. MS (m/z): 351.1 (M+1).

Step 4: 3-Fluoro-4-(6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yloxy)benzenamine (**254**)

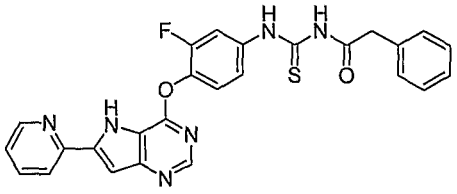
[0521] To a solution of **253** (71.4 mg, 0,21 mmol) in acetic acid (2.1 mL) at 100°C, was added iron powder (59 mg, 1.05 mmol). The reaction mixture was stired for 5 minutes, filtered through a Celite® pad and concentrated under reduced pressure. The residue was purified by column chromatography, eluent EtOAc/hexane (2:1), to afford title compound **254** (27.9 mg, 40% yield). MS (m/z): 321.1 (M+1).

Step 5: *N*-(3-Fluoro-4-(6-phenyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**255a**)

[0522] To a suspension of the **254** (26.8 mg, 0.84 mmol) in THF (1.6 ml) was added 2-phenylacetyl isothiocyanate (23 mg, 0.13 mmol). The mixture was stirred for 1 hr transferred onto a chromatography column and eluted sequentially with EtOAc/MeOH (9:1) and EtOAc/hexane (1:1), to afford title compound **255a** (30 mg, 72% yield) as a white solid. ^{1}HNMR: (DMSO-d_6) δ (ppm):12.65 (s, 1H), 12.43 (s, 1H), 11.79 (s, 1H), 8.31 (s, 1H), 8.06 (d, J=7.6Hz, 2H), 7.91 (m, 1H), 7.52 (m, 4H), 7.43 (m, 1H), 7.34, (m, 4H), 7.27 (m, 1H), 7.18 (m, 1H), 3.83 (s, 2H). MS (m/z): 498.2 (M+1).

Example 214

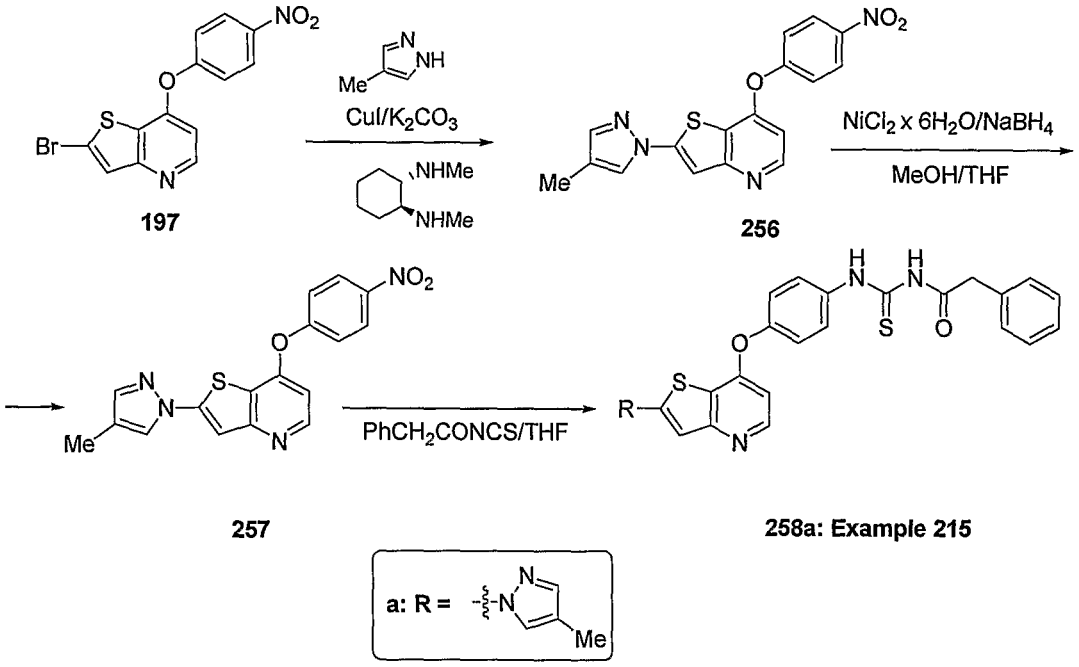
N-(3-Fluoro-4-(6-(pyridin-2-yl)-5*H*-pyrrolo[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (255b)



255b: Example 214

[0523] Following the procedures described above for the synthesis of compound **255a** (example 213, scheme 57) but replacing ethynylbenzene in the step 1 with 2-ethynylpyridine, title compound **255b** was obtained. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.85 (br, 1H), 12.65 (br, 1H), 11.75 (br, 1H), 8.71 (m, 1H), 8.33 (s, 1H), 8.21 (d, J=8Hz, 1H), 7.96 (m, 1H), 7.89 (m, 1H), 7.52-7.42 (m, 3H), 7.34-7.32 (m, 5H), 7.28 (m, 1H) , 3.83 (s, 2H). MS (m/z): 499.2 (M+1).

Scheme 58



Example 215

N-(4-(2-(4-Methyl-1*H*-pyrazol-1-yl)thieno[3,2-*b*]pyridin-7-yloxy) phenylcarbamothioyl)-2-phenylacetamide (258a)

Step 1: 2-(4-Methyl-1*H*-pyrazol-1-yl)-7-(4-nitrophenoxy)thieno[3,2-*b*]pyridine (**256**)

[0524] A mixture of **197** (300 mg, 0.86 mmol, scheme 42), 4-methyl-1*H*-pyrazole (69 mg, 0.86 mmol), CuI (16.4 mg, 0.086 mmol), trans-N^1,N^2-dimethylcyclohexane-1,2-diamine (24.4 mg, 0.172 mmol) [J.C. Antilla, A. Klapars, et. al. *JACS*, **2002**, 124, 11684-1688] and K_2CO_3 (238 mg, 1.72 mmol) in toluene (1.7 mL) was stirred at room temperature in an atmosphere of nitrogen nitrogen overnight, diluted with EtOAc (100 mL), filtered through a Celite® pad, and concentrated under reduced pressure. The residue was purified by flash chromatography with gradient elution with EtOAc/hexane (1:1) to EtOAc/hexane (2:1) to afford title compound **256** (88.8 mg, 37% yield) as a white solid. MS (m/z): 352.06 (M+1).

Step 2: 4-(2-(4-Methyl-1*H*-pyrazol-1-yl)thieno[3,2-*b*]pyridin-7-yloxy)benzenamine (**257**)

[0525] To a solution of **256** (168.4 mg, 0.478 mmol) and $NiCl_2$ x $6H_2O$ (226 mg, 0.956 mmol) in MeOH/THF (10/10 mL) $NaBH_4$ (72 mg, 1.92 mmol) was carefully added. The reaction mixture was stirred for 10 min, concentrated to dryness and the resultant solid was suspended in 10% HCl. The aqueous solution was basified (pH ~11) with concentrated aqueous NH_4OH and extracted with EtOAc. The organic extract was collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, to afford title compound **257** (134.6.mg, 87% yield) as a white solid. MS (m/z): 322.09 (M+1).

Step 3: *N*-(4-(2-(4-Methyl-*1H*-pyrazol-1-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**258a**)

[0526] To a suspension of the **257** (134.6 mg, 0.418 mmol) in THF (4.2 mL) was added 2-phenylacetyl isothiocyanate (111 mg, 0.627 mmol). The reaction mixture was stirred for 1 hr at room temperature, transferred onto a chromatography column and eluted wit a gradient of gradient EtOAc/hexane, 1:1 to 2:1, to provide a beige solid which was triturated with diethyl ether to afford title compound **258a** (31 mg, 15% yield) as a white solid. Characterization of **258a** is provided in the table 23.

Example 216

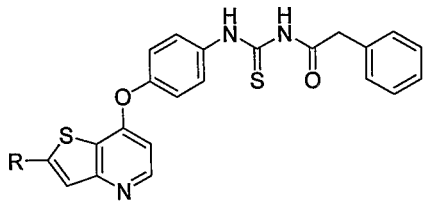
N-(4-(2-(1*H*-Pyrazol-1-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (258b)

[0527] Following the procedures described above for the synthesis of compound **258a** (example 215, scheme 58) but replacing 4-methyl-1*H*-pyrazole in the step 1 with 1*H*-pyrazole, title compound **258b** was obtained. Characterization of **258b** is provided in the table 23.

Example 217

N-(4-(2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (258c)

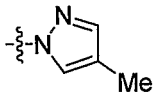
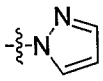
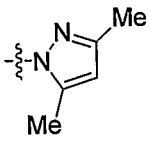
[0528] Following the procedures described above for the synthesis of compound **258a** (example 215, scheme 58) but replacing 4-methyl-1*H*-pyrazole in the step 1 with 3,5-dimethyl-1*H*-pyrazole, title compound **258c** was obtained. Characterization of **258c** is provided in the table 23.



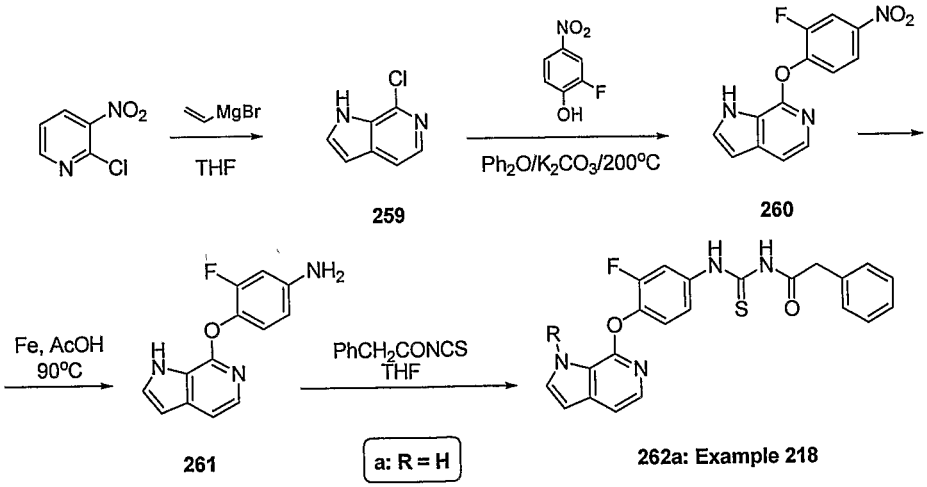
258a-c: Examples 215-217

Table 23

Characterization of compounds 258a-c (examples 215-217)

Cpd	Ex	R	Name	Characterization
258a	**215**		*N*-(4-(2-(4-Methyl-*1H*-pyrazol-1-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}HNMR: (DMSO-d_6) δ (ppm): 12.42 (br, 1H), 11.76 (br, 1H), 8.5 (m, 2H), 7.75 (m, 2H), 7.65 (s, 2H), 7.32 (m, 7H), 6.65 (m, 1H), 3.83 (s, 2H), 2.12 (s, 3H). MS (m/z): 500.0 (M+1).
258b	**216**		*N*-(4-(2-(1*H*-Pyrazol-1-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (DMSO-d_6) δ (ppm): 12.4 (s, 1H), 11.73 (s, 1H), 8.74 (d, J=2.5Hz, 1H), 8.45 (d, J=5.7Hz, 1H), 7.87 (s, 1H), 7.81 (m, 1H), 7.74 (d, J=8.8Hz, 1H), 7.34-7.31 (m, 7H), 6.66 (m, 2H), 3.82 (s, 2H). MS (m/z): 486.1
258c	**217**		*N*-(4-(2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide	^{1}H NMR (DMSO-d_6) δ (ppm): 12.44 (s, 1H), 11.77 (s, 1H), 8.6 (d, J=5.8, 1H), 7.78 (m, 2H), 7.49 (s, 1H), 7.38-7.28 (m, 7H), 6.80 (d, J=5.8Hz, 2H), 6.27 (s, 1H), 3.83 (s, 2H), 2.59 (s, 3H), 2.21 (s, 3H). MS (m/z): 514.1

Scheme 59



Example 218

N-(4-(1*H*-Pyrrolo[2,3-c]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (262a)

Step 1. 7-Chloro-1*H*-pyrrolo[2,3-*c*]pyridine (**259**)

[0529] To a solution of 2-chloro-3-nitropyridine (5g, 31.5mmol)) in THF (200mL) at -78°C, was added vinylmagnesium bromide (100mL, 1.0M in THF) The reaction mixture was stirred at -20°C for 8 hours, quenched with NH_4Cl solution (20%, 150mL), extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography, eluent EtOAc/hexane (1:5), to afford the title compound **259** (1.23g, 26% yield) as a white solid [Z. Zhang, et al., *J. Org. Chem.*, **2002**, 67, 2345-2347] . MS (m/z): 153.1(M+H) (found).

Step 2. 7-(2-Fluoro-4-nitrophenoxy)-1*H*-pyrrolo[2,3-c]pyridine (**260**)

[0530] A mixture of **259** (420mg, 2.76mmol), 2-fluoro-4-nitrophenol (651mg, 4.14mmol) and K_2CO_3(1.14g, 8.28mmol) in Ph_2O (15 mL) was heated at 200°C for 6 hours, cooled to room temperature and partitioned between EtOAc and water. Organic phase was collected, dried and concentrated. The residue was purified by flash column chromatography with gradient elution from hexane to hexane/EtOAc (3:1), to afford the title compound **260** (333 mg, 44% yield) as a yellowish solid. MS (m/z): 274.1(M+H) (found).

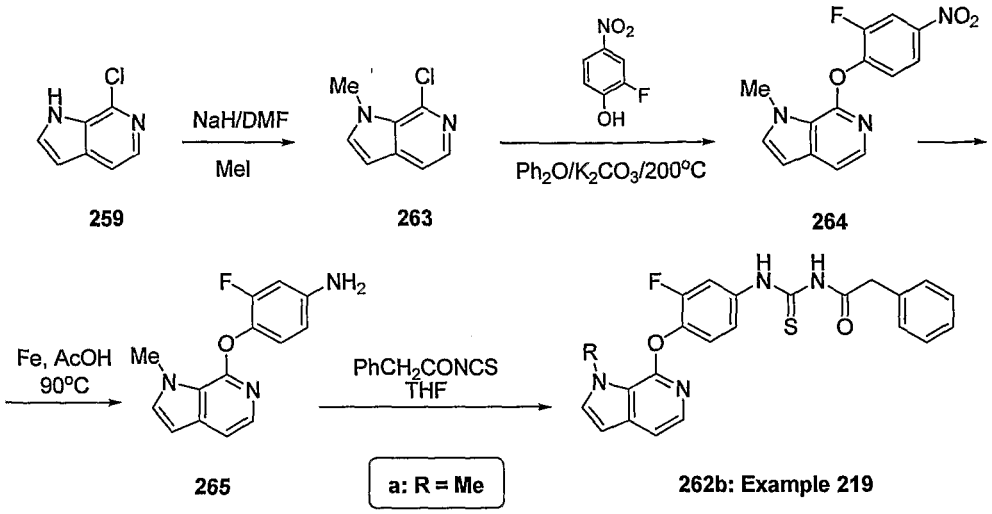
Step 3. 4-(1*H*-Pyrrolo[2,3-c]pyridin-7-yloxy)-3-fluorobenzenamine (**261**)

[0531] To a solution of **260** (100mg, 0.36mmol) in AcOH (4mL) at 90°C, was added iron powder (102mg, 2.1mmol). The reaction mixture was vigorously stirred for 10 min, cooled, filtered through a Celite pad and concentrated. The residue was purified by flash column chromatography, eluent EtOAc/hexane (1:1), to afford title compound **261** (87mg, 99% yield) as an off-white solid. MS (m/z): 244.1(M+H) (found).

Step 4. *N*-(4-(1*H*-Pyrrolo[2,3-c]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (**262a**)

[0532] A mixture of **261** (44mg, 0.18mmol) and 2-phenylacetyl isothiocyanate (36 □L, 0.19 mmol) in THF (2 mL) was stirred at room temperature for 2 hours, and concentrated. The residue was purified by flash column chromatography, eluent EtOAc/hexane (1:1), to afford the title compound **262a** (30mg, 40%) as an off-white solid. ^{1}H NMR (DMSO-d_6) **δ** (ppm): 12.41(s, 1H), 12.07(s, 1H), 11.77(s, 1H), 7.84(dd, 1H, J_1= 10.95Hz, J_2=2.0Hz), 7.58(t, 1H, J_1=J_2=2.7Hz), 7.51(d, 1H, J=5.7Hz), 7.43-7.39(m, 2H), 7.37-7.33(m, 4H), 7.31-7.26(m, 2H), 6.55(dd, 1H, J_1= 1.76Hz, J_2=2.9Hz), 3.84(s, 2H), MS (m/z): 421.1(M+H) (found).

Scheme 60



Example 219

N-(3-Fluoro-4-(1-methyl-1*H*-pyrrolo[2,3-c]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (262b)

Step 1. 7-Chloro-1-methyl-1*H*-pyrrolo[2,3-c]pyridine (**263**)

[0533] To a solution of **259** (250mg, 1.64mmol) in DMF (16mL) at 0°C was added NaH (197mg, 4.92 mmol, 60% in mineral oil), and the mixture was stirred for 30 min, followed by addition of MeI (112 □L, 1.80mmol). The reaction mixture was stirred at room temperature for 2 h before acetic acid (1mL) was added. Solvents were removed under reduced pressure, the residue was partitioned between water and EtOAc. Organic phase was collected, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography, eluent EtOAc/hexane (1:1), to afford the title compound **263** (200mg, 92% yield) as an off-white solid. MS (m/z): 167.1(M+H) (found).

Step 2. 7-(2-Fluoro-4-nitrophenoxy)-1-methyl-1H-pyrrolo[2,3-c]pyridine (**264**)

[0534] Starting from the compound **263** and following the procedure described above for the synthesis of nitro compound **260** (scheme 59, step 2, example 218), title compound **264** was obtained in 91% yield as a yellow solid. MS (m/z): 288.1(M+H) (found).

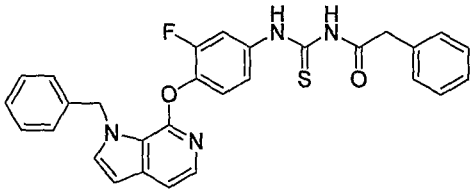
Step 3.-Fluoro-4-(1-methyl-1*H*-pyrrolo[2,3-c]pyridin-7-yloxy)benzenamine(**265**)

[0535] Starting from the compound **264** and following the procedure described above for the synthesis of amine **261** (scheme 59, step 3, example 218), title compound **265** was obtained in 89% yield as an off-white solid. MS (m/z): 258.1(M+H) (found).

Step 4. *N*-(3-Fluoro-4-(1-methyl-1*H*-pyrrolo[2,3-c]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**262b**)

[0536] Starting from the compound **265** and following the procedure described above for the synthesis of compound **262a** (scheme 59, step 4, example 218), title compound **262b** was obtained in 87% yield as an off-white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.40(s, 1H), 11.78(s, 1H), 7.83(dd, 1H, J_1= 10.95Hz, J_2=1.9Hz), 7.56(d, 1H, 2.7Hz), 7.49(d, 1H, J=5.5Hz), 7.43-7.39(m, 2H), 7.37-7.33(m, 4H), 7.31-7.26(m, 2H), 6.52(d,1H, J_2=2.9Hz), 4.11(s, 3H), 3.84(s, 2H), MS (m/z): 435.1(M+H) (found).

Example 220

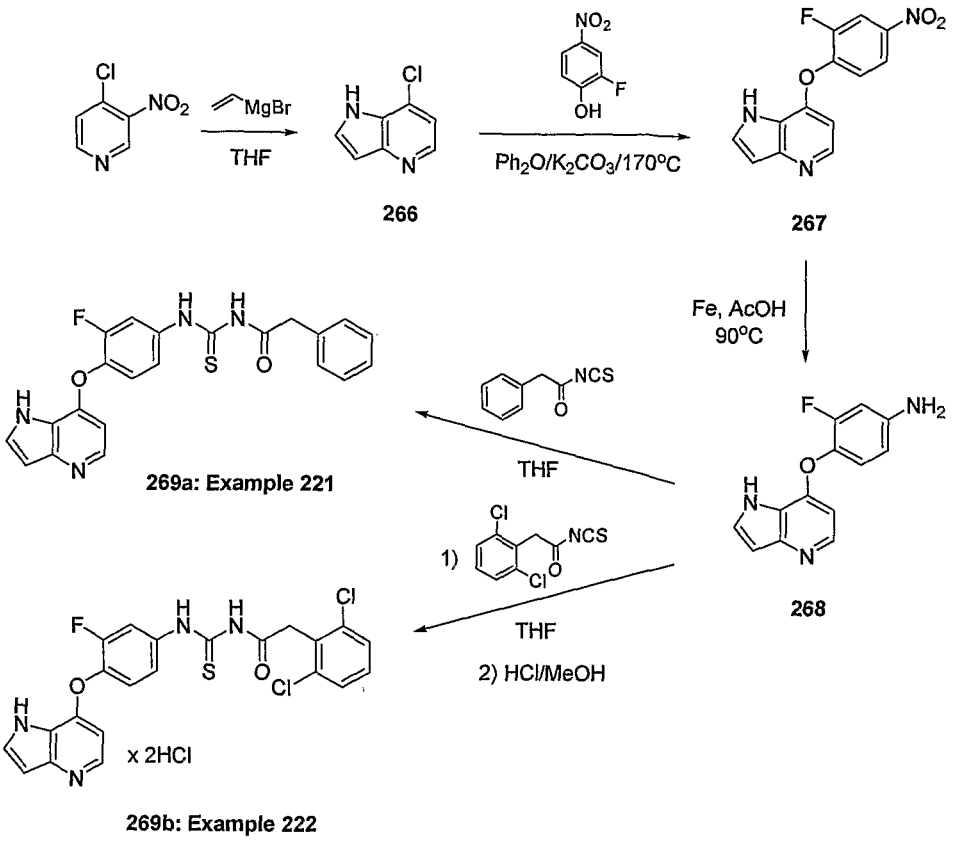


262c: Example 220

N-(4-(1-Benzyl-1*H*-pyrrolo[2,3-*c*]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (262c)

[0537] Starting from the compound **259** and following the procedures described above for the synthesis of compound **262b** (scheme 60, step 4, example 219) but using benzyl bromide in step 1 instead of methyl iodide, title compound **262c** was obtained. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.36 (s, 1H), 11.76(s, 1H), 7.78(m, 1H,), 7.58(t, 1H, J_1=J_2=2.7Hz), 7.50(d, 1H, J=5.7Hz), 7.34(m, 5H), 7.30-7.221(m, 5H), 7.15(dd, 1H, J_1= 8.1Hz, J_2=0.4Hz), 7.10(t, 1H), 6.60(d, 1H, J=2.9Hz), 5.68(s, 2H), 3.82(s, 2H). MS (m/z): 511.2(M+H) (found).

Scheme 61



Example 221

N-(4-(1*H*-Pyrrolo[3,2-*b*]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenyl acetamide (269a)

Step 1. 7-Chloro-1*H*-pyrrolo[3,2-b]pyridine (**266**)

[0538] To a solution of 2-chloro-3-nitropyridine (2.0g, 12.6mmol) [C. Almansa, et al., *J. Med. Chem.*, **2001**, 44, 350-361] in THF (80mL) at -78°C, was added vinylmagnesium bromide (80mL, 1.0M in THF), and the reaction mixture was stirred at -20°C for 8 hours, quenched with NH_4Cl solution (20%, 100mL), extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography, eluent EtOAc/Hexane (1:1), to afford the title compound **266** (240mg, 11%) as yellow crystals. MS (m/z): 153.1(M+H) (found).

Step 2. 7-(2-Fluoro-4-nitrophenoxy)-1H-pyrrolo[3,2-b]pyridine(**267**)

[0539] A mixture of **266** (180mg, 1.18mmol), 2-fluoro-4-nitrophenol (558mg, 3.55mmol) and K_2CO_3(981mg, 7.10mmol) in Ph_2O(4mL) was heated at 170°C for 8 hours, cooled to room temperature and partitioned between EtOAc and water. Organic phase was collected, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash

column chromatography with gradient elution of hexane, to hexane/EtOAc (1:1), to afford the title compound **267** (84 mg, 26% yield) as a yellowish solid. MS (m/z): 274.1(M+H) (found).

Step 3. 4-(1*H*-Pyrrolo[3,2-*b*]pyridin-7-yloxy)-3-fluorobenzenamine (**268**)

[0540] To a solution of **267** (35mg, 0.13mmol) in AcOH (1mL) at 90°C, was added iron powder (36mg, 0.65mmol). The reaction mixture was stirred vigorously for 10min, cooled, filtered through a Celite pad and concentrated. The residue was partitioned between DCM and $NaHCO_3$ saturated solution. Phases were separated; the aqueous phase was neutralized with AcOH and extracted with DCM. Primary organic phase and the extract were combined and concentrated to give the title compound **268** (31mg, 99%) as an off-white solid. MS (m/z): 244.1(M+H) (found).

Step 4. *N*-(4-(1*H*-Pyrrolo[3,2-*b*]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenyl acetamide (**269a**)

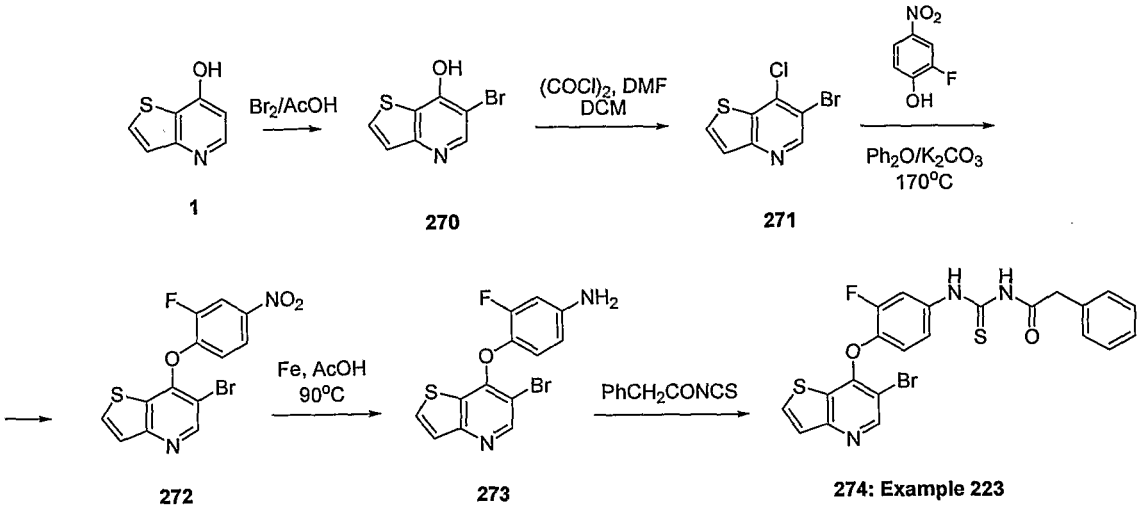
[0541] A mixture of **268** (20mg, 0.08mmol) and 2-phenylacetyl isothiocyanate (16 □L, 0.08mmol) in THF (1 mL) was stirred at room temperature for 2 hours and concentrated. The residue was purified by flash column chromatography (eluent EtOAc) followed by preparative HPLC (column Aqusil C18, gradient elution with 60-95% MeOH in water, 45 min) to afford the title compound **269a** (13mg, 40% yield) as an off-white solid. ^{1}H NMR (CD_3OD) δ (ppm): 8.41(s, 1H), 8.16(d. 1H, J= 5.6Hz), 8.02(dd, 1H, J_1=2.3Hz, J_2=12.2Hz), 7.62(d, 1H, J=3.3Hz), 7.44(m, 1H), 7.37-7.33(m, 4H) 7.31-7.26(m, 1H), 6.65(d, 1H, J=3.1Hz), 6.52(d, 1H, J=5.7Hz), 3.76(s, 2H), MS (m/z): 421.1(M+H) (found).

Example 222

N-(4-(1*H*-Pyrrolo[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-(2,6-dichlorophenyl)acetamide dihydrochloride (269b)

[0542] Starting from the compound **268** and following the procedure described above for the synthesis of compound **269a** (example 221) but replacing 2-phenylacethyl isothiocyanate with 2-(2,6-dichlorophenyl)acetyl isothiocyanate, a white solid was obtained. This material was dissolved in MeOH and treated with HCl (1mL, 1.0M in ether). Solvents were removed under the reduced pressure and the residue was lyophilized, to afford the title compound **269b** (48% yield) as a yellowish solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 13.29(s, 1H), 12.32(s, 1H), 12.05(s, 1H), 8.52(d, 1H,), 8.14(m, 2H), 7.64(m, 2H), 7.51(d, 1H), 7.37(dd, 1H), 6.86(m, 1H), 6.81(dd, 1H), 4.22(s, 2H), MS (m/z): 489.1(M+H) (found).

Scheme 62



Example 223

N-(4-(6-Bromothieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (274)

Step 1. 6-Bromothieno[3,2-b]pyridin-7-ol (**270**)

[0543] To a solution of thieno[3,2-b]pyridin-7-ol (**1**, 2.55g, 16.87 mmol) in acetic acid (50mL) was added bromine(1.7 mL, 32.72 mmol). The mixture was heated at 110°C for 1h, cooled and the resultant precipitate was separated by filtration, to afford the title compound **270** (4.47g, crude) as a dark brown powder, which was used in next step without further purification. M/S (m/z): 231.9(M+H) (found).

Step 2. 6-Bromo-7-chlorothieno[3,2-*b*]pyridine (**271**)

[0544] DMF (0.72mL) was added slowly to a solution of $(COCl)_2$ in DCE at 0°C and the mixture was stirred for 30 min, followed by addition of **270** (crude from above). The combined mixture was stirred for 10 min at the same conditions and was heated to reflux for 3h. After cooling the mixture was concentrated and partitioned between DCM and water. Organic phase was collected and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (eluent EtOAc), to afford the title compound **271** (0.66g, 70% yield based on compound **1**) as a yellowish solid. MS (m/z): 249.0(M+H) (found).

Step 3. 6-Bromo-7-(2-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine (**272**)

[0545] Starting from the compound **271** and following the procedure described above for the synthesis of compound **260** (scheme 59, example 218, step 2), title compound **272** was obtained in 61% yield as an off-white solid. MS (m/z): 368.9(M+H).

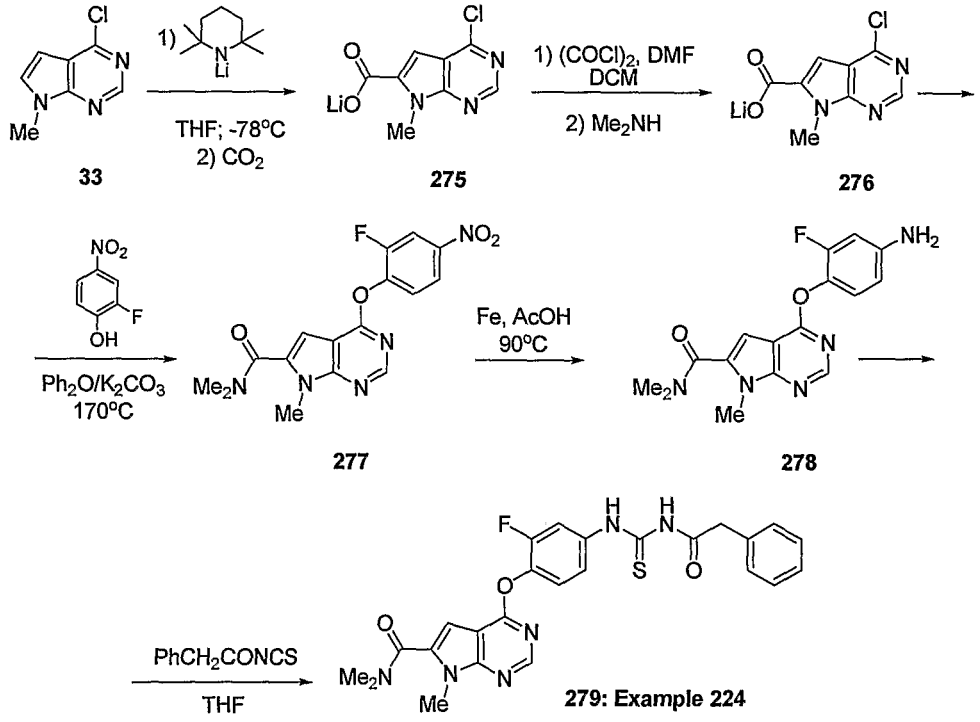
Step 4. 4-(6-Bromothieno[3,2-b]pyridin-7-yloxy)-3-fluorobenzenamine (**273**)

[0546] Starting from the compound **272** and following the procedure described above for the synthesis of compound **261** (scheme 59, example 218, step 3), title compound **273** was obtained in 92% yield as a light brown solid. MS (m/z): 340.0(M+H).

Step 5. *N*-(4-(6-Bromothieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (**274**)

[0547] Starting from the compound **273** and following the procedure described above for the synthesis of compound **262a** (scheme 59, example 218, step 4), title compound **274** was obtained in 99% yield as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm):12.44(s, 1H), 11.79(s, 1H), 8.82(s, 1H), 8.03(d, 1H), 7.99(dd, 1H), 7.54(d, 1H), 7.41(dd, 1H), 7.32-7.24(m, 6H), 3.80(s, 2H). MS (m/z):517.0 (M+H) (found).

Scheme 63



Example 224

4-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-*N*,*N*,7-trimethyl-7*H*-pyrrolo [2,3-*d*]pyrimidine-6-carboxamide (279)

Step 1. Lithium 4-chloro-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate (**275**)

[0548] To a solution of 2,2,6,6-tetramethylpiperidine (92 µL, 0.54mmol) in THF (4 mL) at -10°C, *n*-BuLi (338 µL, 1.6M in hexane, 0.54mmol) was added drop wise and the reaction mixture was stirred at -10°C for 10 min. Compound **33** (60mg, 0.36mmol) [G. B.

Evans et al. *J. Org. Chem.*, **2001**, 66, 17, 5723-5730 and shown in the scheme 6] was added drop wise maintaining the temperature below -70°C over a period of 15 min. Dried CO_2–gas was bubbled through the reaction mixture and stirred at room temperature overnight. The precipitate thus formed was collected by filtration and dried to afford the title compound **275** (78mg, 100% yield) as a yellow solid. MS (m/z): 209.9 (RCOOH, M-H) (found).

Step 2. 4-Chloro-*N,N*,7-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (**276**)

[0549] A reaction mixture containing carboxylate **275** (78mg, 0.36mmo), oxalyl chloride (63uL, 0.72mmol), and a drop of DMF in DCM was stirred for 2h. Solvents were removed under reduced pressure and the residue was re-dissolved in DCM (4mL). To this solution Me_2NH (360 µL, 0.72mmol, 2M in THF) in THF was added and the mixture was stirred at room temperature for 4h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (eluent EtOAc) to afford the title compound **276** (50mg, 58% yield) as a yellowish solid. MS (m/z): 239.1(M+H) (found).

Step 3. 4-(2-Fluoro-4-nitrophenoxy)-*N,N*,7-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (**277**)

[0550] Starting from the compound **276** and following the procedure described above for the synthesis of compound **260** (scheme 59, example 218, step 2) title compound **277** was obtained in 77% yield as an off-white solid. MS (m/z): 360.1(M+H) (found).

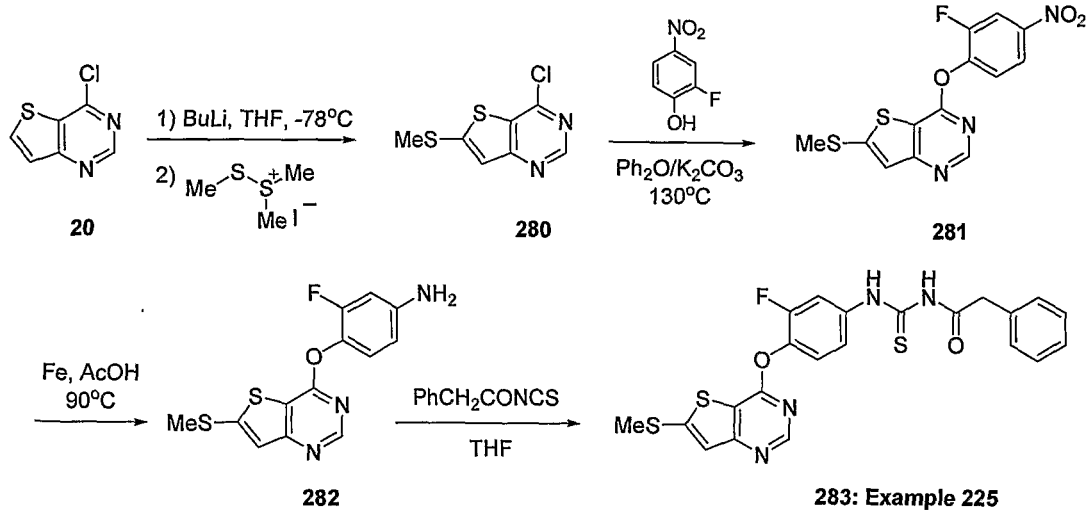
Step 4. 4-(4-Amino-2-fluorophenoxy)-*N,N*,7-trimethyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (**278**)

[0551] Starting from the compound **277** and following the procedure described above for the synthesis of compound **261** (scheme 59, example 218, step 3) title compound **278** was obtained in 72 % yield as an off-white solid. MS (m/z): 330.1(M+H) (found).

Step 5. 4-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-*N,N*,7-trimethyl-7*H*-pyrrolo [2,3-*d*]pyrimidine-6-carboxamide (**279**)

[0552] Starting from the compound 278 and following the procedure described above for the synthesis of compound 262a (scheme 59, example 218, step 4) title compound 279 was obtained in 98% yield as an off-white solid. 1H NMR (DMSO-d6) δ (ppm): 12.45(s, 1H), 11.81(s, 1H), 8.43(s, 1H), 7.89(m, 1H), 7.46(m, 2H), 7.34(m, 4H), 7.28(m, 1H), 6.93(m, 1H), 4.03(s, 3H), 3.82(s, 2H), 3.81(s, 3H), 3.14(s, 3H), 3.06(s, 3H). MS (m/z): 507.1(M+H) (found).

Scheme 64



Example 225

N-(3-Fluoro-4-(6-(methylthio)thieno[3,2-*d*]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (283)

Step 1. 4-chloro-6-(methylthio)thieno[3,2-*d*]pyrimidine (**280**)

[0553] To a solution of **20** (shown in the scheme 4) (200mg, 1.18mmol) in THF (11 mL) was added *n*-BuLi (566 µL, 1.42mmol, 2.5M in THF) very slowly at -78°C and the mixture was stirred for 15 min at the same conditions. A solutions of dimethyl disulfide (160uL, 1.77mmol) and MeI (110 µL, 1.77mmol) in THF (1 mL) was added drop wise. The reaction mixture was stirred for 2h at -78°C, quenched with saturated aqueus NH_4Cl solution, and extracted with DCM. The extract was dried over anhydrous Na_2SO_4 and concentrated to afford the title compound **280** (210mg, 82% yield) as a yellowish solid. MS (m/z): 217.0(M+H) (found).

Step 2. 4-(2-Fluoro-4-nitrophenoxy)-6-(methylthio)thieno[3,2-*d*]pyrimidine (**281**)

[0554] A mixture of **280** (210mg, 0.97mmol), 2-fluoro-4-nitrophenol (278mg, 1.77mmol) and K_2CO_3 (560mg, 3.54mmol) in Ph_2O (10mL) was heated at 130°C 60 hours, cooled to room temperature and partitioned between EtOAc and water. Organic phase was collected, dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography with a gradient elution (hexane to hexane/EtOAc, 1:1) to afford the title compound **281** (288 mg, 88% yield) as a yellowish solid. MS (m/z): 338.1(M+H) (found).

Step 3. 3-Fluoro-4-(6-(methylthio)thieno[3,2-*d*]pyrimidin-4-yloxy)benzenamine (**282**)

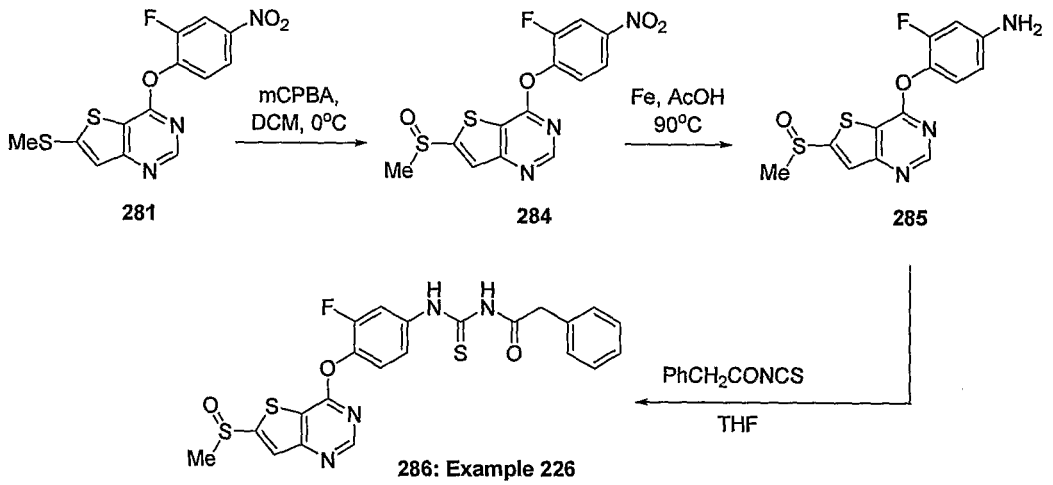
[0555] To a solution of **281** (288mg, 0.94mmol) in AcOH (25mL) at 90°C, was added iron powder (238mg, 4.25mmol), and the reaction mixture was stirred vigorously at 90°C

for 10 min, cooled, filtered through a Celite pad and concentrated. The residue was purified by flash column chromatography (eluent EtOAc) to afford the title compound **282** (248mg, 95%) as an off-white solid. MS (m/z): 308.1(M+H) (found).

Step 4. *N*-(3-Fluoro-4-(6-(methylthio)thieno[3,2-*d*]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (**283**)

[0556] A mixture of **282** (248mg, 0.80mmol) and 2-phenylacetyl isothiocyanate (214mg, 1.20mmol) in THF (8 mL) was stirred for 2 hours, and concentrated. The residue was purified by flash column chromatography, eluent EtOAc/hexane (3:7), to afford title compound **283** (200mg, 52% yield) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.42(s, 1H), 11.80(s, 1H), 8.63(s, 1H), 7.85(d, 1H), 7.54-7.44 (m, 3H), 7.35 (m, 4H), 7.30(m, 1H), 3.81(s, 2H), MS (m/z): 485.1(M+H) (found).

Scheme 65



Example 226

N-(3-Fluoro-4-(6-(methylsulfinyl)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl carbamothioyl)-2-phenylacetamide (286)

Step 1. 4-(2-Fluoro-4-nitrophenoxy)-6-(methylsulfinyl)thieno[3,2-*d*]pyrimidine (**284**)

[0557] A mixture of **281** (1.1g, 3.2mmol) and *m*-CPBA (77%, 890 mg, 12.8 mmol) in DCM at 0°C was stirred for 2 hours, diluted with DCM, washed with ice water, $NaHCO_3$ solution and water again; dried and concentrated to give the title compound **284** (1.15 g, quantitative) as a yellowish solid. MS (m/z): 354.0(M+H) (found).

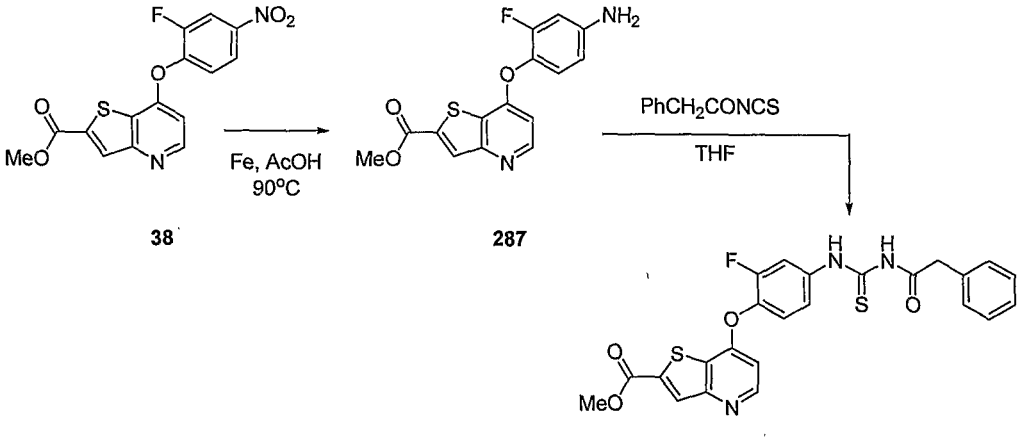
Step 2. 4-(2-Fluoro-4-nitrophenoxy)-6-(methylsulfinyl)thieno[3,2-*d*]pyrimidine (**285**)

[0558] Starting from the compound **284** and following the procedure described above for the synthesis of compound **282** (scheme 64, step 3, example 225), title compound **285** was obtained in 34% yield as an off-white solid. MS (m/z): 324.0 (M+H) (found).

Step 3. *N*-(3-Fluoro-4-(6-(methylsulfinyl)thieno[3,2-*d*]pyrimidin-4-yloxy)phenyl carbamothioyl)-2-phenylacetamide (**286**)

[0559] Starting from the compound **285** and following the procedure described above for the synthesis of compound **283** (scheme 64, step 4, example 225), title compound **286** was obtained in 36% yield as an off-white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 12.45(s, 1H), 11.83(s, 1H), 8.80(s, 1H), 8.13(s, 1H), 7.93(dd, 1H, J_1=2.3Hz, J_2=10.9Hz), 7.55 (t, 1H, J=8.6Hz), 7.48 (m, 1H), 7.34-7.31(m, 4H), 7.28-7.25(m, 1H), 3.81(s, 2H), 3.08(s, 3H). MS (m/z): 501.0(M+H) (found).

Scheme 66



288: Example 227

Example 227

Methyl 7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-*b*]pyridine-2-carboxylate hydrochloride (288)

Step 1. Methyl 7-(4-amino-2-fluorophenoxy)thieno[3,2-b]pyridine-2-carboxylate (**287**)

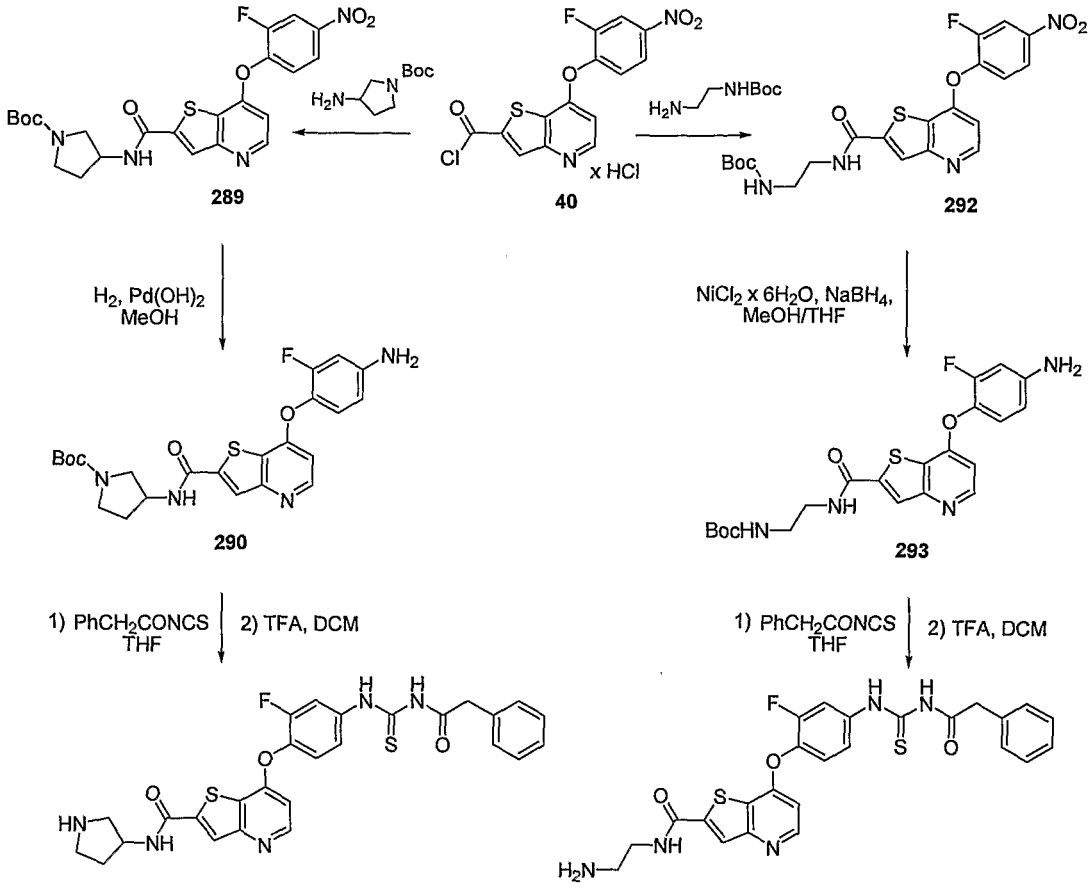
[0560] Starting from the nitro compound **38** (shown in the scheme 7) and following the procedure described above for the synthesis of compound **261** (scheme 59, step 3, example 218), title compound **287** was obtained in 86% yield as an off-white solid. MS (m/z):319.0 (M+H) (found).

Step 2. Methyl 7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-*b*]pyridine-2-carboxylate hydrochloride (**288**)

[0561] Starting from the amine **287**, following the procedure described above for the synthesis of compound **269b** (scheme 561, example 222) and replacing 2-(2,6-dichlorophenyl)acetyl isothiocyanate with 2-phenylacetyl isothiocyanate, title compound 288 was obtained in 72% yield as a yellowish solid. ^{1}H NMR (d-DMSO) δ (ppm): 12.51(s, 1H), 11.84(s, 1H), 8.64(dd, 1H, J_1=5.1Hz, J_2=0.4Hz), 8.24(s, 1H, J=0.4Hz), 8.02(dd, 1H,

J_1=1.8Hz, J_2=13.4Hz), 7.56-7.54(m, 2H), 7.36-7.31(m, 1H), 7.28-7.25(m, 1H), 6.81 (d, 1H, J = 5.5 Hz), 3.91 (s, 3H), 3.81 (s, 2H). MS (m/z):496.3 (M+H) (found).

Scheme 67



Example 228

7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-*N*-(pyrrolidin-3-yl)thieno[3,2-*b*]pyridine-2-carboxamide (291)

Step 1. *tert*-Butyl 3-(7-(2-fluoro-4-nitrophenoxy)thieno[3,2-b]pyridine-2-carboxamido) pyrrolidine-1-carboxylate (**289**)

[0562] A solution of **40** (shown in the scheme 7, 600 mg, 1.54 mmol), *tert*-butyl 3-aminopyrrolidine-1-carboxylate (369 mg, 2.0 mmol) in DCM (15 mL) was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography, eluents EtOAc and EtOAc/MeOH (10:1), to afford the title compound **289** (160mg, 20%) as an off-white solid. MS (m/z): 503.3 (M+H) (found).

Step 2. *tert*-Butyl 3-(7-(4-amino-2-fluorophenoxy)thieno[3,2-b]pyridine-2-carboxamido) pyrrolidine-1-carboxylate (**290**)

[0563] A mixture of **289** (90 mg, 0.18 mmol) and $Pd(OH)_2$ in MeOH (2 mL) was hydrogenated at 1 atm for 1h. The catalyst was filtered off and the filtrate was concentrated to afford the title compound **290** (60mg, 70% yield) as a yellowish solid. MS (m/z): 473.2 (M+H) (found).

Step 3. 7-(2-Fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-*N*-(pyrrolidin-3-yl)thieno[3,2-*b*]pyridine-2-carboxamide (**291**)

[0564] A solution of **290** (40 mg, 0.084 mmol) and 2-phenylacetyl isothiocyanate (22 mg, 0.126 mmol) in THF (2 mL) was stirred for 30min. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (eluent EtOAc), to afford a solid material, which was dissolved in a mixture of TFA/DCM (0.5 mL/0.5 mL) and stirred at room temperature for 2h. Solvents were removed under reduced pressure and the residue was purified by preparative HPLC (Aqusil C18, gradient eluent, 60-95% MeOH in water, 45 min) to afford the title compound **291** (8mg, 80% yield) as an off-white solid. ^{1}H NMR (d-DMSO) δ (ppm): 9.27(d, 1H), 8.57(d, 1H), 8.37(s, 1H), 8.30(s, 1H), 8.01(d, 1H), 7.53(m, 2H), 7.33-7.31(m, 4H), 7.29-7.25(m, 1H), 6.74(d, 1H), 4.46(m, 1H), 3.82(s, 2H), 3.11-3.03(m, 2H), 2.18-2.09(m, 2H), 1.93-1.89(m, 2H). MS (m/z): 550.2(M+H) (found).

Example 229

N-(2-Aminoethyl)-7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-*b*]pyridine-2-carboxamide (294)

Step 1. *tert*-Butyl 2-(7-(2-fluoro-4-nitrophenoxy)thieno[3,2-*b*]pyridine-2-carboxamido) ethylcarbamate (**292**)

[0565] A solution of **40** (shown in the scheme 7, 100 mg, 0.26 mmol), N-Boc-N-methylethylenediamine hydrochloride (50 mg, 0.26 mmol) and Et_3N (36 μL, 0.52 mmol) in DCM (2 mL) was stirred for 4h at room temperature and diluted with EtOAc (10mL). The combined mixture was washed with brine and phases were separated. The aqueous phase was extracted with EtOAc, and the extract was combined with the organic phase, dried over anhydrous Na_2SO_4 and concentrated to afford title compound **292** (119 mg, 96%, crude) as yellowish solid. MS (m/z): 477.1 (M+H) (found).

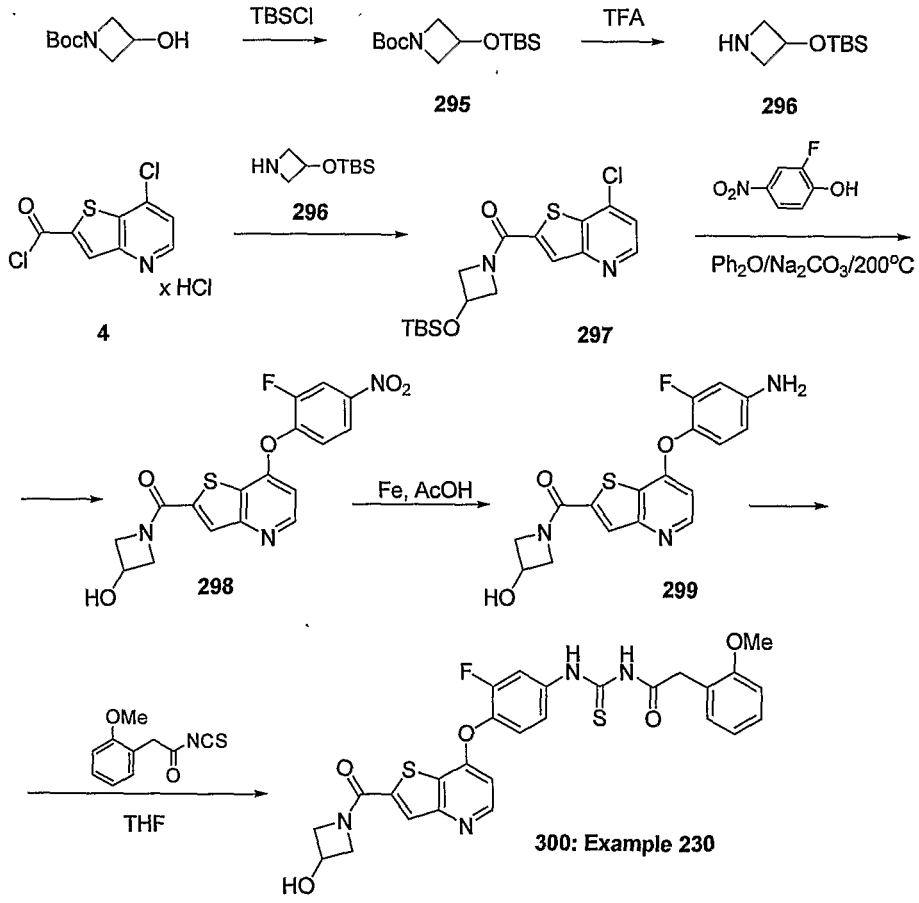
Step 2. *tert*-Butyl 2-(7-(4-amino-2-fluorophenoxy)thieno[3,2-b]pyridine-2-carboxamido) ethylcarbamate (**293**)

[0566] To a solution of **292** (80mg, 0.17mmol) in MeOH/THF (1.7 mL/1.7 mL) at 0°C, was added $NiCl_2$ x $6H_2O$ (85 mg, 0.35 mmol), followed by addition of $NaBH_4$ (26 mg, 0.68 mmol), portion wise. The reaction mixture was stirred for 15min, treated with 2N aqueous HCl (2 mL), filtered; the filtrate was neutralized with aqueous NH_4OH to pH 7 and partitioned between EtOAc and water. Organic phase was collected, dried over anhydrous Na_2SO_4 and concentrated. The residue (75 mg, quantitative yield, crude) was used directly in next step without further purification. MS (m/z): 447.1(M+H) (found).

Step 3. *N*-(2-Aminoethyl)-7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)thieno[3,2-*b*]pyridine-2-carboxamide (**294**)

[0567] Following the procedure described above for the synthesis of compound **291** (example 228), title compound was obtained in 3% yield as an off-white solid. ^1H NMR (d-DMSO) δ (ppm): 9.00(d, 1H), 8.50(m, 1H), 8.30(m, 1H), 8.20(d, 1H), 7.92(d, 1H), 7.44(m, 2H), 7.26-7.25(m, 3H), 7.21-7.18(m, 1H), 6.66(d, 1H), 3.75(s, 2H), 3.30-3.20(m, 6H). MS (m/z): 524.3(M+H).

Scheme 68



Example 230

N-(3-Fluoro-4-(2-(3-hydroxyazetidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide (300)

Step 1. *tert*-Butyl 3-(tert-butyldimethylsilyloxy)azetidine-1-carboxylate (**295**)

[0568] A solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (1 g, 5.77 mmol), TBSCl (6.35 mmol, 956 mg) in DCM (11.5 mL), was stirred for 72 hrs at room temperature. The solvent was removed under reduced pressure, EtOAc was added to the residue, and the solid material was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography with gradient elution wit EtOAc/hexane (9:1) to EtOAc/hexane (1:1), to afford title compound **295** (1.25 g, 75% yield) as a syrup. MS (m/z): 310.1 (M+23).

Step 2: 3-(*tert*-Butyldimethylsilyloxy)azetidine (**296**)

[0569] A mixture of **295** (200 mg, 0.696 mol), DCM (1 mL) and TFA (1mL) was stirred for 1 h at room temperature, concentrated under reduced pressure; NaOH (1M, 15 mL) was added to the residue and the suspension was extracted with DCM, the extract was dried (anhydrous Na_2SO_4) and concentrated, to afford title compound **296** (90.4 mg, 69% yield) as a syrup. MS (m/z): 188.1 (M+1).

Step 3: (3-(*tert*-Butyldimethylsilyloxy)azetidin-1-yl)(7-chlorothieno[3,2-b]pyridin-2-yl)methanone (**297**)

[0570] Starting from the acyl chloride **4** (scheme 1), replacing dimethyl amine with the amine **296** and following the procedure described for the synthesis of amide **5** (scheme 1 as well), title compound **297** was obtained in 64% yield as a syrup. MS (m/z): 383.0 (M+1).

Step 4: (7-(2-Fluoro-4-nitrophenoxy)thieno[3,2-b]pyridin-2-yl)(3-hydroxyazetidin-1-yl)methanone (**298**)

[0571] Starting from the amide **297** and following the procedure described above for the synthesis of compound **230** (scheme 50, example 203), title compound **298** was obtained in 39% yield as a syrup. MS (m/z): 389.05 (M+1).

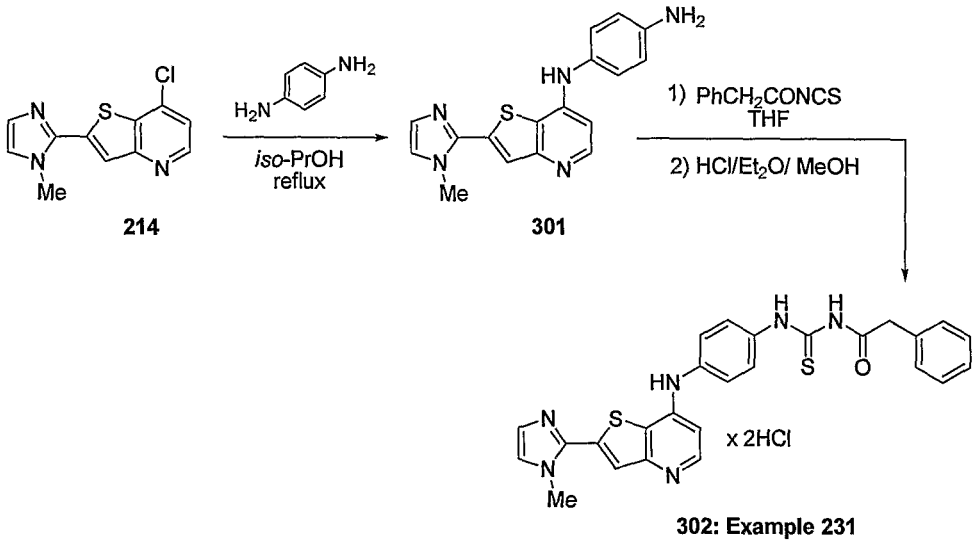
Step 5: (7-(4-Amino-2-fluorophenoxy)thieno[3,2-b]pyridin-2-yl)(3-hydroxyazetidin-1-yl)methanone (**299**)

[0572] Starting from the nitro compound **298** and following the procedure described above for the synthesis of the amine **231** (scheme 50, example 203), title compound **299** was obtained in 83% yield. MS (m/z): 359.07 (M+1).

Step 6: *N*-(3-Fluoro-4-(2-(3-hydroxyazetidine-1-carbonyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide (**300**)

[0573] Starting from the amine **299**, following the procedure described above for the synthesis of compound **232a** (scheme 50, example 203) but replacing 2-phenylacetyl isothiocyanate with (2-methoxy-phenyl)-acetyl isothiocyanate andtitle compound **300** was obtained in 39% yield as a creamy solid. ^{1}HNMR: (CD_3OD) δ (ppm): 12.58 (s, 1H), 11.77 (s, 1H), 8.62 (m, 1H), 8.09 (d, J=12.3Hz, 1H), 7.95 (s, 1H), 7.56 (m, 2H), 7.26 (m, 2H), 7.00 (m, 1H), 6.92 (m, 1H), 6.77 (m, 1H), 6.50 (d, J=5.9Hz, 1H), 4.81 (m, 1H), 4.59 (m, 1H), 4.35 (m, 2H), 3.87-3.78 (m, 6H). MS (m/z): 567.0 (M+1).

Scheme 69



Example 231

N-(4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-ylamino)phenyl carbamothioyl)-2-phenylacetamide (302)

Step 1. N^1-(2-(1-Methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl)benzene-1,4-diamine (**301**)

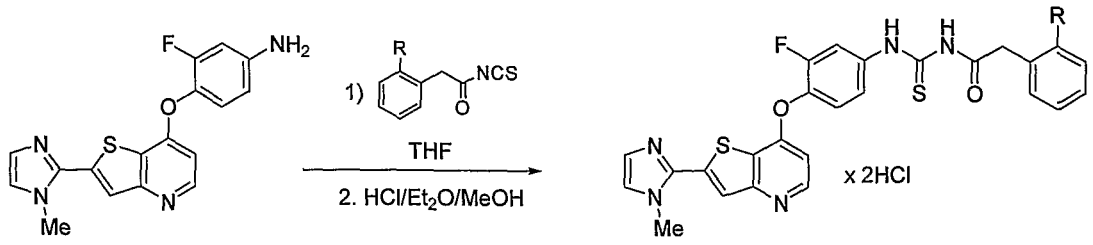
[0574] A mixture of **214** (500mg, 2.0mmol, scheme 46) and benzene-1,4-diamine (500mg, 4.62 mmol) in *iso*-PrOH (15 mL) was refluxed overnight, cooled to room temperature and filtered. The solid was collected, washed with *iso*-PrOH/H_2O mixture, to afford the title compound **301** (300mg, 44% yield) as a yellowish solid. MS (m/z): 322.1(M+H) (found).

Step 2. *N*-(4-(2-(1-Methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-ylamino)phenyl carbamothioyl)-2-phenylacetamide (**302**)

[0575] Starting from the compound **301**, following the procedures described above for the synthesis of compound **269b** (scheme 61, example 222) but replacing 2-(2,6-dichlorophenyl)acetyl isothiocyanate with 2-phenylacethyl isothiocyanate, title compound

302 was obtained in 12% yield, as a yellow solid. ^{1}H NMR (d-DMSO) δ (ppm): 12.47(s, 1H), 11.76(s, 1H), 10.83(s, 1H), 8.41(d, 1H, J=6.9Hz), 7.84(s, 1H), 7.80(s, 1H), 7.78(s, 1H), 7.55(s, 1H), 7.46(s, 1H), 7.43(s, 1H), 7.32(m, 4H), 7.28-7.20(m, 1H), 7.20(s, 1H), 6.94(d, 1H, J=6.8Hz), 3.98(s, 3H), 3.81(s, 2H). MS (m/z): 499.1(M+H) (found).

Scheme 70



219 (scheme 47)

a: R = F;
b: R = OMe;

303a: Example 232
303b: Example 233

Example 232

N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-b]pyridin-7-yloxy) phenyl carbamothioyl)-2-(2-fluorophenyl)acetamide di-hydrochloride (303a)

[0576] A mixture of aniline **219** (100 mg, 0.29 mmol, scheme 47) and 2-(2-fluorophenyl)acetyl isothiocyanate (115 mg, 0.58 mmol) in THF (3 mL) was stirred for 1 hour, loaded directly onto a column containing silica gel and eluted sequentially with EtOAc and EtOAc/MeOH (100:1), to produce a white solid. This material was suspended in MeOH (5 mL) and HCl (1.0M in ether, 1 mL) was added to form a clear solution that was evaporated to dryness. The residue was washed with ether, suspended in H_2O, and lyophilized to afford the title compound (80mg, 45% yield) as a yellowish solid. ^{1}H-NMR (DMSO-d_6) δ (ppm): 12.42(s, 1H), 11.88(s, 1H), 8.65(d. 1H, J= 5.5Hz), 8.20(s, 1H), 8.05(d, 1H, J=1.7Hz), 7.74(s, 1H), 7.58-7.55(m, 3H) 7.39-7.32(m, 2H), 7.21-7.16(m, 2H), 6.82(d, 1H, J=5.5Hz), 4.02(s, 3H), 3.93(s, 2H), MS (m/z): 536.2(M+H) (found).

Example 233

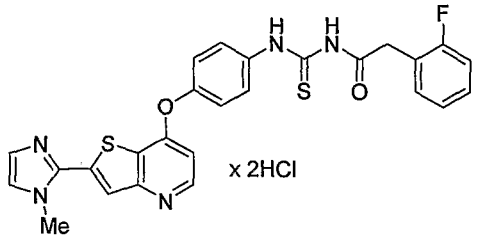
N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenylcarbamothioyl)-2-(2-methoxyphenyl)acetamide di-hydrochloride (303b)

[0577] Starting from the compound **219**, following the procedure described above for the synthesis of **303a** (example 232) but replacing 2-(2-fluorophenyl)acetyl isothiocyanate with 2-(2-methoxyphenyl)acetyl isothiocyanate, title compound **303b** was obtained in 44% as an off-white solid. ^{1}H NMR (d-DMSO) δ (ppm): 12.55 (s, 1H), 11.73(s, 1H), 8.62(m, 1H), 8.09(m, 1H), 7.65(s, 1H), 7.57(m, 1H), 7.43(s, 1H), 7.27-7.20(m, 1H), 6.98(d, 1H,

J=8.2Hz), 6.90(dt, 1H, J_1=1.0Hz, J_2=7.4Hz), 6.79(m, 1H), 4.02(s, 3H), 3.81(s, 2H), 3.77(s, 3H). MS (m/z): 548.3(M+H) (found).

Example 234

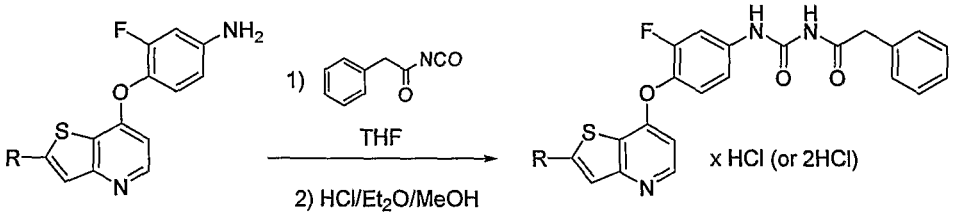
2-(2-Fluorophenyl)-*N*-(4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yloxy) phenylcarbamothioyl)acetamide dihydrochloride (304)



304: Example 234

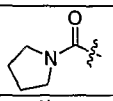
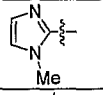
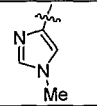
[0578] Starting from the compound **214** (scheme 46) and following the procedures described above for the synthesis of compound **228** (example 202) and **303a** (example 232), title compound **234** was obtained in 31% yield as an off-white solid. ^{1}H NMR (d-DMSO) δ (ppm): 12.34(s, 1H), 11.81(s, 1H), 8.68(m, 1H,) , 8.24(s, 1H), 7.79(m, 3H), 7.62(s, 1H), 7.40-7.13(m, 6H), 6.86(d, 1H), 4.02(s, 3H), 3.93(s, 2H). MS (m/z): 518.1(M+H) (found).

Scheme 71



194 (scheme 40)
219 (scheme 47)
177 (scheme 35)

305a: Example 235
305b: Example 236
305c: Example 237

R	Compound No
	**194 and 305a**
	**219 and 305b**
	**177 and 305c**

Examples 235

N-(3-Fluoro-4-(2-(pyrrolidine-1-carbonyl)thieno[3,2-*b*]pyridin-7-yloxy)phenyl carbamoyl)-2-phenylacetamide hydrochloride (305a)

[0579] A mixture of **194** (93 mg, 0.26 mmol, scheme 40) and 2-phenylacetyl isocyanate (83 mg, 0.62 mmoL) [J. Hill, et al. *JACS*, 62; **1940**; 1595] was stirred for 1h at room

temperature, loaded directly onto a flash chromatography column and eluted with EtOAc. A white solid was obtained, which was suspended in MeOH and treated with HCl (1 mL, 1.0M in Et_2O) to form a clear solution. The solution was concentrated to form a precipitate which was collected by filtration, to afford the title compound **305a** (48 mg, 33% yield) as a white solid. ^{1}H NMR (d-DMSO) δ (ppm): 11.05(s, 1H), 10.62(s, 1H), 8.57(d, 1H), 8.02(s, 1H), 7.81(d, 1H), 7.48-7.43(m, 2H), 7.33-7.25(m, 5H), 6.74(d, 1H), 3.85(t, 2H), 3.78(s, 2H), 3.51(t, 2H), 1.98-1.86(m, 2H). MS (m/z): 519.2(M+H) (found).

Example 236

N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenyl carbamoyl)-2-phenylacetamide dihydrochloride (305b)

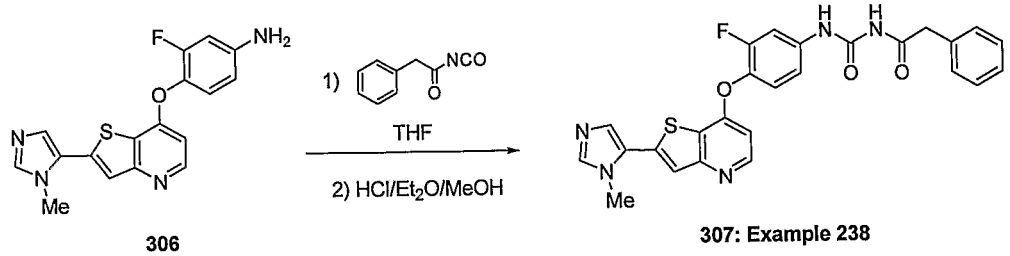
[0580] Starting from the compound **219** (scheme 47) and following the procedure described above for the synthesis of compound **305a**, title compound **305b** was obtained in 15% yield as a white solid. ^{1}H NMR (d-DMSO) δ (ppm): 11.07(s, 1H), 10.66(s, 1H), 8.67(d, 1H, J=5.5Hz), 8.27(s, 1H), 7.85-7.80(m, 2H), 7.65(s, 1H), 7.51(t, 1H, J=8.6Hz), 7.46(d, 1H), 7.34-7.28(m, 5H), 6.85(d, 1H, J=5.3Hz), 4.03(s, 3H), 3.74(s, 2H). MS (m/z): 502.2(M+H) (found).

Example 237

N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-4-yl)thieno[3,2-*b*]pyridin-7-yloxy)phenyl carbamoyl)-2-phenylacetamide dihydrochloride (305c)

[0581] Starting from the compound **177** (scheme 35) and following the procedure described above for the synthesis of compound **305a**, title compound **305c** was obtained in 54% yield as a white solid. ^{1}H NMR (d-DMSO) δ (ppm): 11.08(s, 1H), 10.67(s, 1H), 8.66 (d, 1H, J=6.2Hz), 8.26(s, 1H), 8.21(s, 1H), 7.93(s, 1H), 7.85(dd, 1H, J_1=12.9Hz, J_2=2.5Hz), 7.53(t, 1H, J=8.8Hz), 7.65(s, 1H), 7.48-7.45(m, 1H), 7.35-7.30(m, 4H), 7.28-7.24(m, 1H), 6.94(d, 1H, J=6.1Hz), 3.79(s, 3H), 3.75(s, 2H). MS (m/z): 502.1(M+H) (found).

Scheme 72



306 307: Example 238

Example 238

N-(3-Fluoro-4-(2-(1-methyl-1H-imidazol-5-yl)thieno[3,2-*b*]pyridin-7-yloxy) phenyl carbamoyl)-2-phenylacetamide (307)

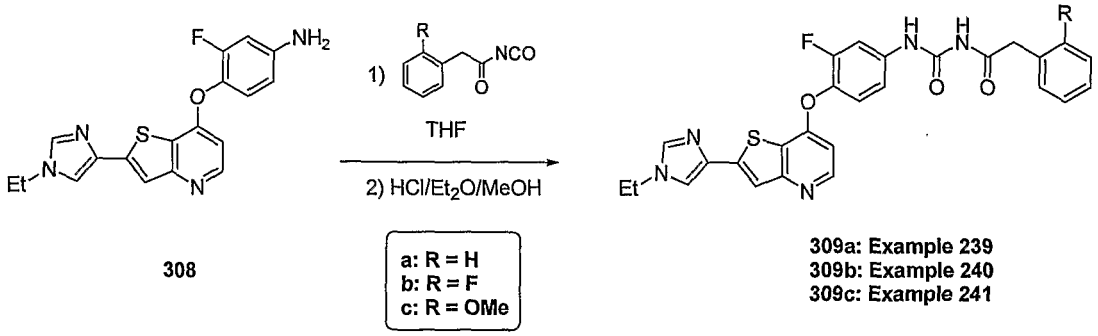
3-Fluoro-4-[2-(1-methyl-1*H*-imidazol-5-yl)-thieno[3,2-b]pyridin-7-yloxy]-phenylamine (**306**)

[0582] Starting from the compound **98** (scheme 19) and following the procedures described above for the synthesis of compound **12** (scheme 2, steps 1-4) but replacing 2-bromothiazole at the Stille coupling stage with 5-bromo-1-methyl-1*H*-imidazole (Table 9), title compound **306** was obtained. MS (m/z): 341.0M+H) (found).

N-(3-Fluoro-4-(2-(1-methyl-1*H*-imidazol-5-yl)thieno[3,2-*b*]pyridin-7-yloxy) phenyl carbamoyl)-2-phenylacetamide (**307**)

[0583] A mixture of **306** (99mg, 0.29 mmol) and 2-phenylacetyl isocyanate (97 mg, 0.60 mmoL) [A. J. Hill, et al. *JACS*, 62; **1940**; 1595] was stirred for 1h at room temperature, loaded directly onto a flash chromatography column and gradient eluted with EtOAc, to MeOH/EtOAc (10:90) to afford the title compound **307** (42% yield) as a white solid. ^{1}H NMR (d-DMSO) δ (ppm): 11.11(s, 1H), 10.68(s, 1H, J=5.5Hz), 8.49(d), 7.85(s, 1H), 7.82(dd, 1H, J_1=12.9Hz, J_2=2.4Hz), 7.76(s, 1H), 7.43(m, 2H), 7.40(s, 1H), 7.32(m, 4H), 7.28(m, 1H), 6.61(d, 1H, J=5.5Hz), 3.89(s, 3H), 3.74(s, 2H). MS (m/z):502.4 (M+H) (found).

Scheme 73



Example 239

N-(4-(2-(1-Ethyl-1*H*-imidazol-4-yl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl carbamoyl)-2-phenylacetamide (309a)

4-[2-(1-Ethyl-1*H*-imidazol-4-yl)-thieno[3,2-b]pyridin-7-yloxy]-3-fluoro-phenylamine (**308**)

[0584] Starting from the compound **98** (scheme 19) and following the procedures described above for the synthesis of compound **12** (scheme 2, steps 1-4) but replacing 2-

bromothiazole at the Stille coupling stage with 4-bromo-1-ethyl-1*H*-imidazole (Table 9), title compound **308** was obtained. MS (m/z): 355.1 (M+H) (found).

N-(4-(2-(1-Ethyl-1*H*-imidazol-4-yl)thieno[3,2-*b*]pyridin-7-yloxy)-3-fluorophenyl carbamoyl)-2-phenylacetamide (**309a**)

[0585] A mixture of **308** (300mg, 0.85 mmol) and 2-phenylacetyl isocyanate (164 mg, 1.02 mmoL) [Arthur J. Hill, et al. *JACS*, 62; **1940**; 1595] was stirred for 1h at room temperature, loaded directly onto a flash chromatography column and gradient eluted with EtOAc, to MeOH/EtOAc (20:80) to afford the title compound **309a** (45% yield) as a white solid. ^{1}H NMR (d-DMSO) δ (ppm): 11.07(s, 1H), 10.63(s, 1H), 8.41(d, 1H, J=5.5Hz), 7.94(d, 1H, J=1.4Hz), 7.80(dd, 1H, J_1=13.1Hz, J_2=2.4Hz), 7.77(d, 1H, J=1.1Hz), 7.65(s, 1H), 7.46-7.39(m, 2H), 7.35-7.19(m, 4H), 7.28-7.24(m, 1H), 6.54(dd, 1H, J_1=5.5Hz, J_2=0.8Hz), 4.03(q, 2H), 3.73(s, 2H), 1.38(t, 3H). MS (m/z): 516.1(M+H) (found).

Example 240

N-(4-(2-(1-Ethyl-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl carbamoyl)-2-(2-fluorophenyl)acetamide (309b)

[0586] A mixture of **308** (320 mg, 0.90 mmol) and (2-fluoro-phenyl)-acetyl isocyanate (600 mg, 3.35 mmoL) [A. J. Hill, et al. *JACS*, 62; **1940**; 1595] was stirred for 1h at room temperature, loaded directly onto a flash chromatography column and gradient eluted with EtOAc, to MeOH/EtOAc(20:80), to afford the title compound **309b** in 42% yield as a white solid. ^{1}H NMR (d-DMSO) δ (ppm): 11.10(s, 1H), 10.58(s, 1H), 8.42(d, 1H, J=5.5Hz), 7.94(d, 1H, J=1.1Hz), 7.82-7.77(m, 2H), 7.65(s, 1H), 7.45-7.30(m, 4H), 7.19-7.16(m, 2H), 6.54(dd, 1H, J_1=0.7Hz, J_2=5.4Hz), 4.04(q, 2H), 3.83(s, 2H), 1.38(t, 3H). MS (m/z): 534.1(M+H) (found).

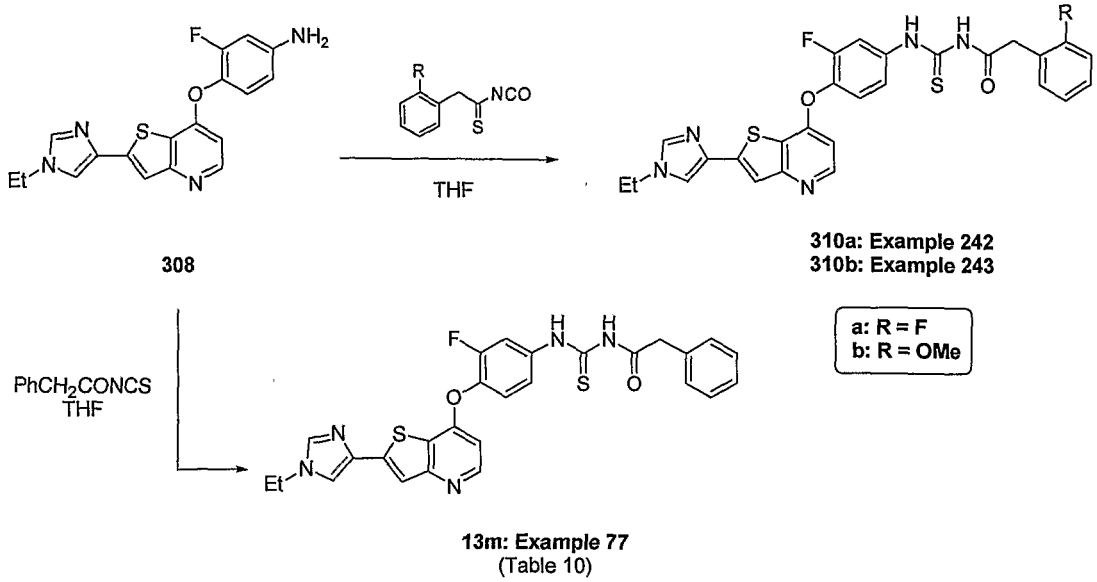
Example 241

N-(4-(2-(1-Ethyl-1*H*-imidazol-4-yl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenyl carbamoyl)-2-(2-methoxyphenyl)acetamide (309c)

[0587] A mixture of **308** (370 mg, 1.05 mmol) and (2-methoxy-phenyl)-acetyl isocyanate (240 mg, 1.25 mmoL) [A. J. Hill, et al. *JACS*, 62; **1940**; 1595] was stirred for 1h at room temperature, loaded directly onto a flash chromatography column and eluted with EtOAc, to afford the title compound **309c** in 42% yield as a white solid. ^{1}H NMR (d-DMSO) δ (ppm): 10.98(s, 1H), 10.69(s, 1H), 8.41(d, 1H, J=5.3Hz), 7.94(d, 1H, J=1.2Hz), 7.81(dd, 1H, J_1=13.1Hz, J_2=2.4Hz), 7.77(d, 1H, J=0.9Hz), 7.65(s, 1H), 7.45-7.40(m, 2H), 7.26-7.19(m, 2H), 6.97(d, 1H, J=8.0Hz), 6.89(dt, 1H, J_1=0.8Hz, J_2=8.2Hz), 6.54(d, 1H,

J=5.5Hz), 4.04(q, 2H), 3.75(s, 3H), 3.70(s, 2H), 1.38(t, 3H). MS (m/z): 546.1(M+H) (found).

Scheme 74



Example 242

1-{4-[2-(1-Ethyl-1*H*-imidazol-4-yl)-thieno[3,2-b]pyridin-7-yloxy]-3-fluoro-phenyl}-3-[2-(2-fluoro-phenyl)-acetyl]-thiourea (310a)

[0588] To a suspension of the **308** (385 mg, 0.99 mmol) in THF (10 mL) was added 2-(2-fluorophenyl)acetyl isothiocyanate (263 mg, 1.49 mmol) and the reaction mixture was stirred for1 hr, transferred onto a flash chromatography column and eluted with EtOAc/MeOH 19:1, to afford title compound **310a** (366.9 mg, 67% yield) as a creamy solid. ^{1}HNMR: (DMSO-d_6) δ (ppm): 12.42 (s, 1H), 11.87 (s, 1H), 8.44 (d, J=5.5Hz, 1H), 8.02 (d, J=11.5Hz, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.67 (s, 1H), 7.52 (m, 2H), 7.42 (m, 2H), 7.25 (m, 2H), 7.06 (d, J=5.5Hz, 1H), 4.04 (q, J=7.3Hz, 2H), 3.92 (s, 2H), 7.4 (t, J=7.3Hz, 3H). MS (m/z): 550.0 (M+1).

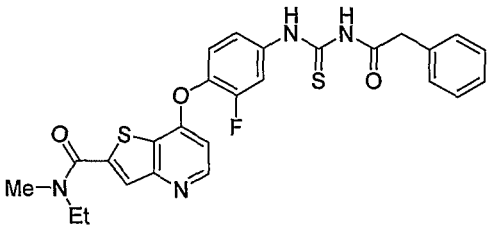
Example 243

1-{4-[2-(1-Ethyl-1*H*-imidazol-4-yl)-thieno[3,2-b]pyridin-7-yloxy]-3-fluoro-phenyl}-3-[2-(2-methoxy-phenyl)-acetyl]-thiourea (310b)

[0589] Starting from the compound **308**, following the procedure described above for the synthesis of **310a** but replacing 2-(2-fluorophenyl)acetyl isothiocyanate with (2-methoxy-phenyl)-acetyl isothiocyanate, title compound **310b** was obtained in 82% yield. ^{1}H NMR (DMSO-d_6) δ (ppm): 12,57 (s, 1H), 11.76 (s, 1H), 8.45 (d, J=5.5Hz, 1H), 8.07 (m, 1H), 7.96 (d, J=1Hz, 1H), 7.79 (d, J=1Hz, 1H), 7.69 (s, 1H), 7.6 (m, 2H), 7.26 (m, 2H), 7.0

(d, J=7.4Hz, 1H), 6.92 (m, 1H), 6.59 (d, J=5.5Hz, 1H), 4.06 (q, J=7.5Hz, 2H), 3.82 (s, 2H), 3.79 (s, 3H), 1.4 (t, J=7.4Hz, 3H). MS (m/z): 562.0 (M+1).

Example 244

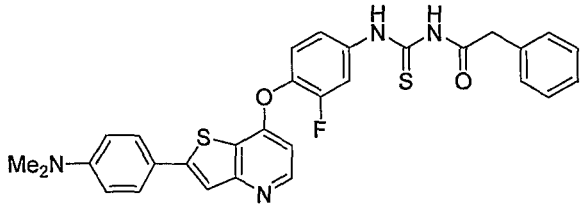


311: Example 244

N-Ethyl-7-(2-fluoro-4-(3-(2-phenylacetyl)thioureido)phenoxy)-*N*-methylthieno[3,2-b]pyridine-2-carboxamide (311)

[0590] Title compound 311 was obtained by following the procedures described above for the synthesis of compound 8a (scheme 1, example 1) but replacing dimethylamine in the step 4 with *N*-methylethanamine. ^{1}H NMR (400 MHz, DMSO-d6) (ppm) 12.49 (s, 1H), 11.82 (s, 1H), 8.64 (d, *J*= 5.48 Hz, 1H), 8.03 (d, *J* = 12.7 Hz, 1H) 7.85 (m, 1H), 7.54 (m, 2H), 7.32 (m, 4H), 7.24 (m, 1H), 6.82 (d, *J*= 5.3 Hz, 1H), 3.83 (s, 2H), 3.53 (m, 2H), 3.38 (m, 2H), 3.05 (s, 1H), 1.10 m, 3H). MS (calcd.) 522.1, found 523.2 (M+H).

Example 245

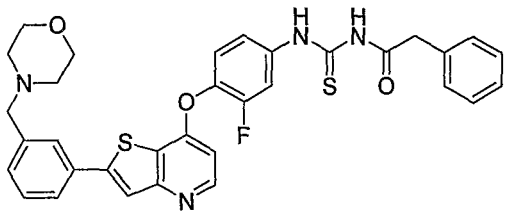


312: Example 245

N-(4-(2-(4-(Dimethylamino)phenyl)thieno[3,2-b]pyridin-7-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (312)

[0591] Title compound 312 was obtained by following the procedures described above for the synthesis of compound 50 (scheme 10, example 55) but replacing 4,4,5,5-tetramethyl-2-(4-(methylsulfonyl)phenyl)-1,3,2-dioxaborolane in the first step with 4-(dimethylamino)phenylboronic acid. ^{1}H NMR (DMSO): 12.48 (1H, s), 11,83 (1H, s), 8.44 (1H, d, J=5.48 Hz), 7.99 (1H, d, J=12.91 Hz), 7.77 (1H, s), 7.68 (2H, d, J=8.41 Hz), 7.51 (2H, br), 7.33-7.28 (5H, m), 6.77 (2H, d, J=8.22 Hz), 6.56 (1H, d, J=4.89 Hz), 3.81 (2H, s), 2.96 (6H, s). MS: calcd: 556.7, found: 556.9 (M+H).

Example 246

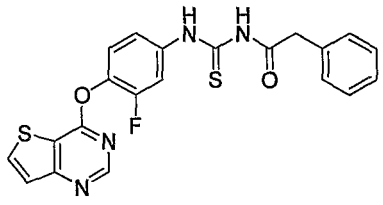


313: Example 246

N-(3-Fluoro-4-(2-(3-(morpholinomethyl)phenyl)thieno[3,2-b]pyridin-7-yloxy)phenylcarbamothioyl)-2-phenylacetamide (313)

[0592] Title compound 313 was obtained by following the procedures described above for the synthesis of compound 75 (scheme 15) but starting from 4-(3-bromobenzyl)morpholine instead of *tert*-butyl 3-bromobenzyl(2-methoxyethyl)carbamate (65). ^{1}H NMR (DMSO): 12.49 (1H, s), 11.84 (1H, s), 8.52 (1H, d, J=5.48 Hz), 8.05 (1H, s), 8.01 (1H, d, J=12.72 Hz), 7.79-7.78 (2H, m), 7.53 (2H, br), 7.46 (1H, t, J=7.63 Hz), 7.39 (1H, d, J=7.63 Hz), 7.34-7.26 (5H, m), 6.66 (1H, d, J=5.28 Hz), 3.82 (2H, s), 3.57 (4H, br), 3.32 (2H, s), 2.38 (4H, br). MS: calcd: 612.7, found: 613.3 (M+1).

Example 247

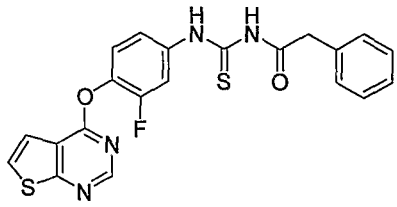


314: Example 247

N-(3-Fluoro-4-(thieno[3,2-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (314)

[0593] Title compound 314 was obtained by following the procedures described above for the synthesis of compound 173 (scheme 34, example 135) but replacing 3-chloro-4-nitrophenol in the step 1 with 2-fluoro-4-nitrophenol. ^{1}HNMR (DMSO-d_6) δ(ppm): 12.42 (bs, 1H), 11.79 (bs, 1H), 8.71 (s, 1H), 8.51 (d, J = 5.2 Hz, 1H), 7.91 (dd, J = 2.4 and 12.0 Hz, 1H), 7.70 (d, J = 5.2 Hz, 1H), 7.53 (dd, J = 8.4 Hz, 1H), 7.47 (dd, J = 2.4 and 8.4 Hz, 1H), 7.38-7.30 (m, 4H), 7.30-7.27 (m, 1H), 3.82 (s, 2H). LRMS: 438.1(calc) 439.1 (found).

Example 248

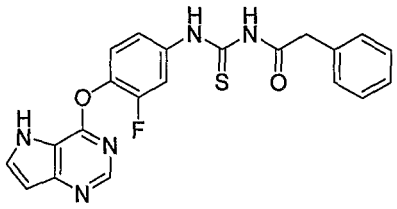


315: Example 248

N-(3-Fluoro-4-(thieno[2,3-d]pyrimidin-4-yloxy)phenylcarbamothioyl)-2-phenylacetamide (315)

[0594] Title compound 315 was obtained starting from the compound 205 (scheme 44) and following the procedures described above for the synthesis of compound 314. ^{1}HNMR (DMSO-d_6) δ(ppm): 12.42 (s, 1H), 11.80 (s, 1H), 8.63 (s, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.91 (dd, J = 2.0 and 12.0 Hz, 1H), 7.70 (d, J = 5.6 Hz, 1H), 7.50 (t, J = 8.4 Hz, 1H), 7.46 (dd, J = 2.4 and 8.4 Hz, 1H), 7.36-7.30 (m, 4H), 7.30-7.24 (m, 1H), 3.82 (s, 2H). LRMS: 438.4 (calc) 439.3 (found).

Example 249



316: Example 249

N-(4-(5*H*-Pyrrolo[3,2-d]pyrimidin-4-yloxy)-3-fluorophenylcarbamothioyl)-2-phenylacetamide (316)

[0595] Title compound 316 was obtained by following the procedures described above for the synthesis of compound 31a (scheme 5, example 28) but skipping *N*-methylation step. ^{1}HNMR (DMSO-d_6) δ(ppm): 12.41(s, 1H), 8.32 (s, 1H), 7.91 (d, J = 10 Hz, 1H), 7.48 (s, 1H), 7.56-7.42 (m, 2H), 7.39-7.32 (m , 4H), 7.30-7.22 (m, 1H), 6.66 (s, 1H), 3.83 (s, 2H). LRMS: 421.1 (calc) 422.1 (found).

ASSAY EXAMPLES

Assay Example 1

Inhibition of c-met and VEGF Activity

[0596] The following protocols were used to assay the compounds of the invention.

***In Vitro* Receptor Tyrosine Kinase Assays (c-Met/HGF receptor and VEGF receptor KDR)**

[0597] These tests measure the ability of compounds to inhibit the enzymatic activity of recombinant human c-Met/HGF receptor and VEGF receptor enzymatic activity.

[0598] A 1.3-kb cDNA corresponding to the intracellular domain of c-Met or c-Met IC (Genbank accession number NP000236-1 amino acid 1078 to 1337) was cloned into the BamHI/XhoI sites of the pBlueBacHis2A vector (Invitrogen) for the production of a histidine-tagged version of that enzyme. This constuct was used to generate recombinant baculovirus using the Bac-N-Blue^{TM} system according to the manucfacturer's instructions (Invitrogen)

[0599] The c-Met IC protein was expressed in Hi-5 cells (*Trichoplusia Ni*) upon infection with recombinant baculovirus construct. Briefly, Hi-5 cells grown in suspension and maintained in serum-free medium (Sf900 II supplemented with gentamycin) at a cell density of about 2 X 10^6 cells/ml were infected with the abovementioned viruses at a multiplicity of infection (MOI) of 0.2 during 72 hours at 27°C with agitation at 120 rpm on a rotary shaker. Infected cells were harvested by centrifugation at 398g for 15 min. Cell pellets were frozen at -80°C until purification was performed.

[0600] All steps described in cell extraction and purification were performed at 4°C. Frozen Hi-5 cell pellets infected with the C-Met IC recombinant baculovirus were thawed and gently resuspended in Buffer A (20mM Tris pH 8.0, 10% glycerol, 1µg/ml pepstatin, 2µg/ml Aprotinin and leupeptin, 50µg/ml PMSF, 50µg/ml TLCK and 10µM E64, 0.5mM DTT and 1mM Levamisole) using 3 ml of buffer per gram of cells. The suspension was Dounce homogenized after which it was centrifuged at 22500g, 30 min., 4°C. The supernatant (cell extract) was used as starting material for purification of c-Met IC.

[0601] The supernatant was loaded onto a QsepharoseFF column (Amersham Biosciences) equilibrated with Buffer B (20mM Tris pH 8.0, 10% glycerol) supplemented with 0.05M NaCl. Following a ten column volume (CV) wash with equilibration buffer, bound proteins were eluted with a 5 CV salt linear gradient spanning from 0.05 to 1M NaCl in Buffer B. Typically, the conductivity of selected fractions ranked between 6.5 and 37 mS/cm. This Qsepharose eluate had an estimated NaCl concentration of 0.33M and was supplemented with a 5M NaCl solution in order to increase NaCl concentration at 0.5M and also with a 5M Imidazole (pH 8.0) solution to achieve a final imidazole concentration of 15mM. This material was loaded onto a HisTrap affinity column (GE Healthcare) equilibrated with Buffer C (50mM $NaPO_4$ pH 8.0, 0.5M NaCl, 10% glycerol) supplemented

with 15mM imidazole. After a 10 CV wash with equilibration buffer and an 8 CV wash with buffer C + 40mM imidazole, bound proteins were eluted with an 8 CV linear gradient (15 to 500mM) of imidazole in buffer C. C-Met IC enriched fractions from this chromatography step were pooled based on SDS-PAGE analysis. This pool of enzyme underwent buffer exchange using PD-10 column (GE Healthcare) against buffer D (25mM HEPES pH 7.5, 0.1M NaCl, 10% glycerol and 2mM □-mercaptoethanol) Final C-Met IC protein preparations concentrations were about 0.5 mg/ml with purity approximating 80%. Purified c-Met IC protein stocks were supplemented with BSA at 1mg/ml, aliquoted and frozen at -80°C prior to use in enzymatic assay.

[0602] In the case of VEGF receptor KDR a 1.6-kb cDNA corresponding to the catalytic domain of VEGFR2 or KDR (Genbank accession number AF035121 amino acid 806 to 1356) was cloned into the Pst I site of the pDEST20 Gateway vector (Invitrogen) for the production of a GST-tagged version of that enzyme. This constuct was used to generate recombinant baculovirus using the Bac-to-Bac™ system according to the manucfacturer's instructions (Invitrogen)

[0603] The GST-VEGFR2$_{806-1356}$ protein was expressed in Sf9 cells (*Spodoptera frugiperda*) upon infection with recombinant baculovirus construct. Briefly, Sf9 cells grown in suspension and maintained in serum-free medium (Sf900 II supplemented with gentamycin) at a cell density of about 2 X 10^6 cells/ml were infected with the abovementioned viruses at a multiplicity of infection (MOI) of 0.1 during 72 hours at 27°C with agitation at 120 rpm on a rotary shaker. Infected cells were harvested by centrifugation at 398g for 15 min. Cell pellets were frozen at -80°C until purification was performed.

[0604] All steps described in cell extraction and purification were performed at 4°C. Frozen Sf9 cell pellets infected with the GST-VEGFR2$_{806-1356}$ recombinant baculovirus were thawed and gently resuspended in Buffer A (PBS pH 7.3 supplemented with 1μg/ml pepstatin, 2μg/ml Aprotinin and leupeptin, 50μg/ml PMSF, 50μg/ml TLCK and 10μM E64 and 0.5mM DTT) using 3 ml of buffer per gram of cells. Suspension was Dounce homogenized and 1% Triton X-100 was added to the homogenate after which it was centrifuged at 22500g, 30 min., 4°C. The supernatant (cell extract) was used as starting material for purification of GST-VEGFR2$_{806-1356}$.

[0605] The supernatant was loaded onto a GST-agarose column (Sigma) equilibrated with PBS pH 7.3. Following a four column volume (CV) wash with PBS pH 7.3 + 1% Triton X-100 and 4 CV wash with buffer B (50mM Tris pH 8.0, 20% glycerol and 100mM NaCl), bound proteins were step eluted with 5 CV of buffer B supplemented with 5mM

DTT and 15mM glutathion.GST-VEGFR2$_{806-1356}$ enriched fractions from this chromatography step were pooled based on U.V. trace i.e. fractions with high O.D.$_{280}$. Final GST-VEGFR2$_{806-1356}$ protein preparations concentrations were about 0.7 mg/ml with purity approximating 70%. Purified GST-VEGFR2$_{806-1356}$ protein stocks were aliquoted and frozen at -80°C prior to use in enzymatic assay.

[0606] Inhibition of c-Met/HGF receptor and VEGFR/KDR was measured in a DELFIA™ assay (Perkin Elmer). The substrate poly(Glu$_4$,Tyr) was immobilized onto black high-binding polystyrene 96-well plates. The coated plates were washed and stored at 4 °C. During the assay, enzymes were pre-incubated with inhibitor and Mg-ATP on ice in polypropylene 96-well plates for 4 minutes, and then transferred to the coated plates. The subsequent kinase reaction took place at 30 °C for 10-30 minutes. ATP concentrations in the assay were 10 uM for C-Met (5X the K_m) and 0.6 uM for VEGFR/KDR (2X the K_m). Enzyme concentration was 25 nM (C-Met) or 5 nM (VEGFR/KDR). After incubation, the kinase reactions were quenched with EDTA and the plates were washed. Phosphorylated product was detected by incubation with Europium-labeled anti-phosphotyrosine MoAb. After washing the plates, bound MoAb was detected by time-resolved fluorescence in a Gemini SpectraMax reader (Molecular Devices). Compounds were evaluated over a range of concentrations and IC$_{50}$'s (concentration of compounds giving 50% inhibition of enzymatic activity) were determined.

C-Met phosphorylation cell-based assay

[0607] This test measures the ability of compounds to inhibit HGF stimulated auto-phosphorylation of the c-Met/HGF receptor itself in a whole cell system.

[0608] MNNGHOS cell line expressing TPR-MET fusion protein were purchased from ATCC. The TPR-MET is the product of a chromosomal translocation placing the TPR locus on chromosome 1 upstream of the MET gene on chromosome 7 encoding for it's cytoplasmic region catalytic domain. Dimerization of the M_r 65,000 TPR-Met oncoprotein through a leucine zipper motif encoded by the TPR portion leads to constitutive activation of the met kinase. Constitutive autophosphorylation occurs on residues Tyr361/365/366 of TPR-Met. These residues are homologous to Tyr1230/1234/1235 of MET which become phosphorylated upon dimerization of the receptor upon HGF binding.

[0609] Inhibitor of c-Met formulated as 30 mM stocks in DMSO. For MNNGHOS treatments, cells, compounds were added to tissue culture media at indicated doses for 3 hours prior to cell lysis. Cells were lysed in ice-cold lysis buffer containing 50 mM HEPES (pH 7.5), 150 mM NaCl, 1.5 mM MgCl2, 10 % glycerol, 1 % Triton X-100, 1 mM 4-(2-

Aminoethyl)benzenesulfonyl fluoride hydrochloride, 200 μM sodium orthovanadate, 1 mM sodium fluoride, 10 μg/ml of leupeptin, 10 μg/ml of aprotinin/ml, 1 ug/ml of pepstatin and 50ug/ml Na-p-Tosyl-L-lysine chloromethyl ketone hydrochloride .

[0610] Lysate were separated on 5-20% PAGE-SDS and immunoblots were performed using Immobilon P polyvinylidene difluoride membranes (Amersham) according to the manufacturer's instructions for handling. The blots were washed in Tris-buffered saline with 0.1% Tween 20 detergent (TBST). Tyr361/365/366 of TPR-Met were detected with polyclonal rabbit antibodies against tyrosine phosphorylated Met (Biosource International) and secondary antibodies anti-rabbit -horseradish peroxidase (Sigma) by chemiluminescence assays (Amersham, ECL) were performed according to the manufacturer's instructions and followed by film exposure. Signal was quantitated by densitometry on Alpha-Imager. IC_{50} values were defined as the dose required to obtain 50% inhibition of the maximal HGF stimulated phosphorylated c-Met levels.

In Vivo Solid Tumor Disease Model

[0611] This test measures the capacity of compounds to inhibit solid tumor growth.

[0612] Tumor xenografts were established in the flank of female athymic CD1 mice (Charles River Inc.), by subcutaneous injection of $1X10^6$ U87, A431 or SKLMS cells/mouse. Once established, tumors were then serially passaged s.c. in nude mice hosts. Tumor fragments from these host animals were used in subsequent compound evaluation experiments. For compound evaluation experiments female nude mice weighing approximately 20g were implanted s.c. by surgical implantation with tumor fragments of ~30 mg from donor tumors. When the tumors were approximately 100 mm^3 in size (~7-10 days following implantation), the animals were randomized a separated into treatment and control groups. Each group contained 6-8 tumor-bearing mice, each of which was ear-tagged and followed individually throughout the experiment

[0613] Mice were weighed and tumor measurements are taken by calipers three times weekly, starting on Day 1. These tumor measurements were converted to tumor volume by the well-known formula $(L+W/4)^3 4/3\pi$. The experiment was terminated when the control tumors reached a size of approximately 1500 mm^3. In this model, the change in mean tumor volume for a compound treated group / the change in mean tumor volume of the control group (non-treated or vehicle treated) x 100 ($\Delta T / \Delta C$) was subtracted from 100 to give the percent tumor growth inhibition (%TGI) for each test compound. In addition to tumor volumes, body weight of animals were monitored twice weekly for up to 3 weeks.

[0614] The activities of a number of compounds according to the invention measured by various assays are displayed in the following table, Table 24. In the table, "a" indicates inhibitory activity at a concentration of less than 50 nanomolar; "b" indicates inhibitory activity at a concentration ≥ 50 but < 250 nanomolar, "c" indicates inhibitory activity at ≥ 250 but < 500 and "d" indicates inhibitory activity at a concentration of ≥ 500 nanomolar; and "e" indicates no activity as measured by that assay.

Table 24

Example No	Compound No	C-Met (enz.) (IC_{50}, μM)	VEGF(enz.) (IC_{50}, μM)	C-Met cell-based Y1230-34-35 tpr-met inhibition (IC_{50}, μM)
1	8a	b	a	a
2	8b	b	a	b
3	8c	b	c	b
5	8e	b	b	b
7	8g	b	c	b
9	8i	b	b	c
10	8j	b	b	b
11	8k	b	d	b
12	13a	b	a	a
13	13b	b	a	a
14	13c	b	b	b
15	13d	b	a	a
133	170a	b	b	b
16	13e	b	a	c
18	13g	b	b	b
20	18a	b	d	e
22	26a	b	b	a
23	26b	b	a	b
24	26c	b	c	d
25	26d	b	b	e
26	26e	b	b	e
27	26f	b	b	e
28	31a	b	d	e
29	31b	c	d	e
35	8m	b	b	a
36	8n	b	d	b
37	8o	b	a	a
40	8r	b	a	b
75	13k	b	a	a
142	26f	b	a	a
188	170c	c	d	d
221	269a	a	d	d

[0615] In the following table, Table 25, "a" indicates % TGI in the range of 75-100; "b" indicates % TGI in the range of 50-74; "c" indicates % TGI in the range of 25-49, and "d" indicates % TGI in the range of 0-24. Regiment of administration was once daily.

Table 25

Ex (Cpd)	Dosage mg/kg (once daily)	Vehicle	Tumor type	Duration of experiment (days)	Route of administration	Tumor Growth Inhibition (%)
1 (8a)	30	DMSO	A431	14	IP	d
	30	DMSO	A549	14	IP	b
	100	5% DMSO - 1% Tween-80 in water	U87MG	14	PO	c
	15	DMSO	MKN74	10	IP	d
	30	DMSO	MKN74	10	IP	c
	15	DMSO	U87MG	10	IP	c
	30	DMSO	U87MG	7	IP	c
	30	DMSO	A431	14	IP	c
	30	DMSO	U87MG	14	IP	c
	30	DMSO	SKLMS40	14	IP	b
	30	DMSO	SW48	14	IP	b
	30	DMSO	U87MG	14	IP	a*
	30	DMSO	HCT116	14	IP	c
7 (8g)	30	DMSO	SW48	14	IP	c
	30	DMSO	HCT116	14	IP	b
12 (13a)	30	DMSO	SW48	14	IP	b
	30	DMSO	U87MG	14	IP	b
	30	DMSO	HST116	14	IP	c
	30	DMSO	SW48	14	IP	d
13 (13b)	30	DMSO	A431	7	IP	b
	30	DMSO	SW48	14	IP	d
	30	DMSO	U87MG	14	IP	a
	30	DMSO	DU145	10	IP	d
	30	DMSO	SKLMS40	10	IP	b
37 (8o)	15	DMSO	DU145	10	IP	d
	30	DMSO	DU145	10	IP	d
	30	DMSO	A431	14	IP	b
	30	DMSO	A549	14	IP	c
	15	50/50 DMSO:40/60 PEG/0.2 N HCl in saline	U87MG	10	IV	b
	30	50/50 DMSO:40/60 PEG/0.2 N HCl in saline	U87MG	10	IV	c
15 (13d)	30	DMSO	DU145	10	IP	b
	30	DMSO	SKLMS40	10	IP	b
	30	DMSO	A431	14	IP	b
	30	DMSO	A549	14	IP	b

	15	DMSO	DU145	10	IP	d
	30	DMSO	DU145	10	IP	d
	15	50/50 DMSO:40/60 PEG/0.2 N HCl in saline	U87MG	10	IV	b
	30	50/50 DMSO:40/60 PEG/0.2 N HCl in saline	U87MG	10	IV	b
	100	5% DMSO - 1% Tween-80 in water	U87MG	14	PO	a
	30	DMSO	U87MG	14	IP	b
	75	5% DMSO - 1% Tween-80 in water	A549	12	PO	c
	50	5% DMSO - 1% Tween-80 in water	A549	11	PO	c
	75	5% DMSO - 1% Tween-80 in water	A549	10	PO	b
	15	DMSO	MKN74	10	IP	c
	30	DMSO	MKN74	10	IP	c
	15	DMSO	U87MG	10	IP	b
	30	DMSO	U87MG	10	IP	b
	15	DMSO	HCT116	10	IP	c
	30	DMSO	HCT116	10	IP	c
75 (13k)	15	DMSO	DU145	10	IP	c
	15	DMSO	SKLMS40	10	IP	b
	100	5% DMSO - 1% Tween-80 in water	U87MG	14	PO	b
	30	DMSO	U87MG	14	IP	c
	75	5% DMSO - 1% Tween-80 in water	A549	12	PO	b
	30	DMSO	U87MG	10	IP	c
	15	DMSO	U87MG	10	IP	d
73 (13j)	100	5% DMSO - 1% Tween-80 in water	U87MG	14	PO	c
38 (8p)	30	DMSO	A431	14	IP	c
	30	DMSO	A549	14	IP	c
39 (8q)	30	DMSO	A549	14	IP	b
148 (26l)	30	DMSO	DU145	10	IP	c
	30	50/50 DMSO:40/60 PEG/0.2 N HCl in saline	U87MG	10	IP	c
76 (13l)	75	5% DMSO - 1% Tween-80 in water	A549	10	PO	b
	75	5% DMSO - 1% Tween-80 in water	DU145	10	PO	c
	30	DMSO	A549	14	IP	b
	75	5% DMSO - 1% Tween-80 in water	A549	14	PO	c
157 (195b)	30	DMSO	A341	14	IP	c
	30	DMSO	A549	14	IP	c
56 (55)	30	DMSO	A549	12	IP	c
63 (76c)	30	DMSO	A549	10	IP	b
	30	DMSO	DU145	10	IP	c
77 (13m)	30	DMSO	A549	10	IP	b
	75	5% DMSO - 1% Tween-80 in water	A549	10	PO	b
	75	5% DMSO - 1% Tween-80 in water	U87MG	14	PO	b

	75	5% DMSO - 1% Tween-80 in water	SKLMS40	6	PO	d
201 (227)	30	DMSO	A549	10	IP	c
	75	5% DMSO - 1% Tween-80 in water	A549	10	PO	c
81 (13q)	75	5% DMSO - 1% Tween-80 in water	SKLMS40	14	PO	*c*
242 (310a)	75	5% DMSO - 1% Tween-80 in water	U87MG	14	PO	a
	75	5% DMSO - 1% Tween-80 in water	HCT116	14	PO	b
243 (310b)	75	5% DMSO - 1% Tween-80 in water	U87MG	14	PO	b
	75	5% DMSO - 1% Tween-80 in water	SKLMS40	11	PO	b
137 (178)	75	0.5% CMC in acetate buffer (pH 4.0)	MDA-MB-231	14	PO	b
138 (179)	75	0.5% CMC in acetate buffer (pH 4.0)	MDA-MB-231	14	PO	b

a* - greater than 100% tumor growth inhibition (i.e., tumor shrinkage)

REFERENCES

1. Fan, T. P. D.; Jaggar, R.; Bicknell, R. Controlling the vasculature: angiogenesis, anti-angiogenesis, and vascular targetting of gene therapy. *Trends Pharmacol. Sci.* **1995**, *16*, 57-66.

2. Folkman, J. Angiogenesis in cancer, vascular, rheumtoid and other disease. *Nat. Med.* **1995**, *1*, 27-31.

3. Jakeman, L. B.; Armanini, M.; Phillips, H. S.; Ferrara, N. Developmental expression of binding sites and messenger ribonucleic acid for vascular endothelial growth factor suggests a role for this protein in vasculogenesis and angiogenesis. *Endocrinology* **1993**, *133*, 848-859.

4. Connolly, D. T.; Olander, J. V.; Heuvelman, D.; Nelson, R.; Monsell, R.; Siegel, N.; Haymore, B. L.; Leimgruber, R.; Feder, J. Human vascular permeability factor. Isolation from U937 cells. *J. Biol. Chem.* **1989**, *264*, 20017-20024.

5. Plowman, G. D.; Ullrich, A.; Shawver, L. K. Receptor tyrosine kinases as targets for drug intervention. *Drug News Perspect.* **1994**, *7*, 334-339.

6. Straw, L. M.; Shawver, L. K. Tyrosine kinases in disease: overview of kinase inhibitors as therapeutic agents and current drugs in clinical trials. *Exp. Opin. Invest. Drugs* **1998**, *7*, 553-573.

7. Shawver, L. K.; Lipson, K. E.; Fong, T. A. T.; McMahon, G.; Plowman, G. D.; Strawn, L. M. Receptor tyrosine kinases as targets for inhibition of angiogenesis. *Drug Discov. Today* **1997**, *2*, 50-63.

8. De Vries, C.; Escobedo, J. A.; Ueno, H.; Houck, K.; Ferrara, N.; Williams, L. T. The fms-like tyrosine kinase, a receptor for vascular endothelial growth factor. *Science* **1992**, *255*, 989-991.

9. Terman, B. I.; Dougher-Vermazen, M.; Carrion, M. E.; Dimitrov, D.; Armellino, D. C.; Gospodarowicz, D.; Bohlen, P. Identification of the KDR tyrosine kinase as a receptor for vascular endothelial cell growth factor. *Biochem. Biophys. Res. Commun.* **1992**, *187*, 1579-1586.

10. Plate K. H., Breier G., Weich H. A., Mennel H. D., Risau W. Vascular endothelial growth factor and glioma angiogenesis: coordinate induction of VEGF receptors, distribution of VEGF protein and possible *in vivo* regulatory mechanisms. Int. J. Cancer, *59:* 520-529, 1994.

11. Fuh G., Li B., Crowley C., Cunningham B., Wells J. A. Requirements for binding and signaling of the kinase domain receptor for vascular endothelial growth factor. J. Biol. Chem., *273:* 11197-11204, 1998.

12. Wheeler-Jones C., Abu-Ghazaleh R., Cospedal R., Houliston R. A., Martin J., Zachary I. Vascular endothelial growth factor stimulates prostacyclin production and activation of cytosolic phospholipase A_2 in endothelial cells via p42/p44 mitogen-activated protein kinase. FEBS Lett., *420:* 28-32, 1997.

13. Kim K. J., Li B., Winer J., Armanini M., Gillett N., Phillips H. S., Ferrara N. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth *in vivo*. Nature (Lond.), *362:* 841-844, 1993.

14. Kanai T., Konno H., Tanaka T., Baba M., Matsumoto K., Nakamura S., Yukita A., Asano M., Suzuki H., Baba S. Anti-tumour and anti-metastatic effects of human-vascular-endothelial-growth-factor-neutralizing antibody on human colon and gastric carcinoma xenotransplanted orthotopically into nude mice. Int. J. Cancer, *77:* 933-936, 1998.

15. Zhu Z., Rockwell P., Lu D., Kotanides H., Pytowski B., Hicklin D. J., Bohlen P., Witte L. Inhibition of vascular endothelial growth factor-induced receptor activation with anti-kinase insert domain-containing receptor single chain antibodies from a phage display library. Cancer Res., *58:* 3209-3214, 1998.

16. Siemeister G., Schirner M., Reusch P., Barleon B., Marme D., Martiny-Baron G. An antagonistic vascular endothelial growth factor (VEGF) variant inhibits VEGF-stimulated receptor autophosphorylation and proliferation of human endothelial cells. Proc. Natl. Acad. Sci. USA, *95:* 4625-4629, 1998.

17. Lin P., Sankar S., Shan S., Dewhirst M. W., Polverini P. J., Quinn T. Q., Peters K. G. Inhibition of tumour growth by targeting tumour endothelium using a soluble vascular endothelial growth factor receptor. Cell Growth Differ., *9:* 49-58, 1998.

18. Cheng S-Y., Huang H-J. S., Nagane M., Ji X-D., Wang D., Shih C. C-Y., Arap W., Huang C-M., Cavenee W. K. Suppression of glioblastoma angiogenicity and tumorigenicity by inhibition of endogenous expression of vascular endothelial growth factor. Proc. Natl. Acad. Sci. USA, *93:* 8502-8507, 1996.

19. Millauer B., Longhi M. P., Plate K. H., Shawver L. K., Risau W., Ullrich A., Strawn L. M. Dominant-negative inhibition of Flk-1 suppresses the growth of many tumour types *in vivo*. Cancer Res., *56:* 1615-1620, 1996.

20. Pennacchietti S, Michieli P, Galluzzo M, Mazzone M, Giordano S, Comoglio PM. Hypoxia promotes invasive growth by transcriptional activation of the met protooncogene. Cancer Cell. 2003 Apr;3(4):347-61.

21. Camps JL, Chang SM, Hsu TC, et al Fibroblast-mediated acceleration of human epithelial tumor growth in vivo. Proc Natl Acad Sci USA, *87:* 75-9, 1990.

22. Nakamura T, Matsumoto K, Kiritoshi A, Tano Y Induction of hepatocyte growth factor in fibroblasts by tumor-derived factors affects invasive growth of tumor cells: in vitro analysis of tumor-stromal interactions. Cancer Res, *57:* 3305-13, 1997.

23. Nishimura K, Kitamura M, Takada S, et al Regulation of invasive potential of human prostate cancer cell lines by hepatocyte growth factor. Int J Urol, *5:* 276-81, 1998.

24. Bae-Jump V, Segreti EM, Vandermolen D, Kauma S Hepatocyte growth factor (HGF) induces invasion of endometrial carcinoma cell lines in vitro. Gynecol Oncol, *73:* 265-72, 1999.

25. Nakamura T, Nawa K, Ichihara A Partial purification and characterization of hepatocyte growth factor from serum of hepatectomized rats. Biochem Biophys Res Commun, *122:* 1450-9, 1984.

26. Nakamura T, Nishizawa T, Hagiya M, et al Molecular cloning and expression of human hepatocyte growth factor. Nature, *342:* 440-3, 1989.

27. Ebert M, Yokoyama M, Friess H, Buchler MW, Korc M Coexpression of the c-met proto-oncogene and hepatocyte growth factor in human pancreatic cancer. Cancer Res, *54:* 5775-8, 1994.

28. Di Renzo MF, Narsimhan RP, Olivero M, et al Expression of the Met/HGF receptor in normal and neoplastic human tissues. Oncogene, *6:* 1997-2003, 1991.

29. Di Renzo MF, Poulsom R, Olivero M, Comoglio PM, Lemoine NR Expression of the Met/hepatocyte growth factor receptor in human pancreatic cancer. Cancer Res, *55:* 1129-38, 1995.

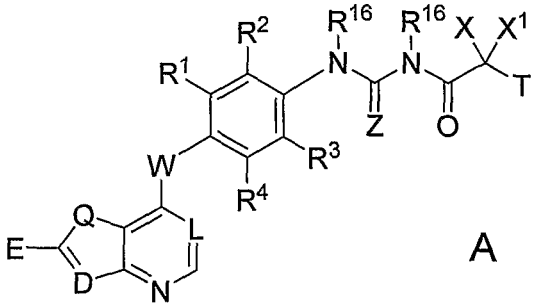
30. Delehedde M, Sergeant N, Lyon M, Rudland PS, Fernig DG Hepatocyte growth factor/scatter factor stimulates migration of rat mammary fibroblasts through both mitogen-activated protein kinase and phosphatidylinositol 3-kinase/Akt pathways. Eur J Biochem, *268:* 4423-9, 2001.

31. Bardelli A, Basile ML, Audero E, et al Concomitant activation of pathways downstream of Grb2 and PI 3-kinase is required for MET-mediated metastasis. Oncogene, *18:* 1139-46, 1999.

32. Saucier C, Khoury H, Lai KM, Peschard P, Dankort D, Naujokas MA, Holash J, Yancopoulos GD, Muller WJ, Pawson T, Park M. The Shc adaptor protein is critical for VEGF induction by Met/HGF and ErbB2 receptors and for early onset of tumor angiogenesis. Proc Natl Acad Sci U S A. 2004 Feb 24;101(8):2345-50.

WHAT IS CLAIMED IS:

1. A compound of the formula (A), that are inhibitors of VEGF receptor signaling and HGF receptor signaling:



A

and pharmaceutically acceptable salts and complexes thereof, wherein

T is selected from the group consisting of arylalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said arylalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl is optionally substituted with 1 to 3 independently selected R^{20};

each R^{20} is independently selected from the group consisting of -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^{17}$, $-OCF_3$, $-NR^{17}R^{18}$, $-S(O)_{0-2}R^{17}$, $-S(O)_2NR^{17}R^{17}$, $-C(O)OR^{17}$, $-C(O)NR^{17}R^{17}$, $-N(R^{17})SO_2R^{17}$, $-N(R^{17})C(O)R^{17}$, $-N(R^{17})C(O)OR^{17}$, $-C(O)R^{17}$, $-C(O)SR^{17}$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, $-O(CH_2)_n$aryl, $-O(CH_2)_n$heteroaryl, $-(CH_2)_{0-5}$(aryl), $-(CH_2)_{0-5}$(heteroaryl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-CH_2(CH_2)_{0-4}$-T^2, an optionally substituted C_{1-4} alkylcarbonyl, C_{1-4} alkoxy, an amino optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy and a saturated or unsaturated three- to seven-membered carboxyclic or heterocyclic group, wherein T^2 is selected from the group consisting of -OH, -OMe, -OEt, $-NH_2$, -NHMe, $-NMe_2$, -NHEt and $-NEt_2$, and wherein the aryl, heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted;

W is selected from the group consisting of O, S, NH and NMe;

Z is selected from the group consisting of O, or S and NH;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano, or nitro, wherein C_1-C_6 alkyl is optionally substituted, or

X and X^1 taken together with the atom to which they are attached, form a C_3-C_7 cycloalkyl;

R^1, R^2, R^3 and R^4 independently represent hydrogen, halo, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-OR^{17}$, $-NR^{17}R^{18}$, $-C(O)OR^{17}$, $-C(O)R^{17}$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^{17} is selected from the group consisting of H and R^{18};

R^{18} is selected from the group consisting of a (C_1-C_6)alkyl, an aryl, a aryl(C_1-C_6)alkyl, a heterocyclyl and a heterocyclyl(C_1-C_6)alkyl, each of which is optionally substituted, or

R^{17} and R^{18}, taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, the optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from the group consisting of N, O, S and P;

R^{16} is selected from the group consisting of -H, -CN, $-(CH_2)_{0-5}$(aryl), $-(CH_2)_{0-5}$(heteroaryl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-CH_2(CH_2)_{0-4}$-T^2, an optionally substituted C_{1-4} alkylcarbonyl, and a saturated or unsaturated three- to seven-membered carboxyclic or heterocyclic group, wherein T^2 is selected from the group consisting of -OH, -OMe, -OEt, $-NH_2$, -NHMe, $-NMe_2$, -NHEt and $-NEt_2$, and wherein the aryl, heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted;

Q is selected from the group consisting of CH_2, O, S, N(H), N(C_1-C_6 alkyl), N-Y-(aryl), -N-OMe, $-NCH_2OMe$ and -N-Bn;

D is selected from the group consisting of C-E and N;

L is N, or CR, wherein R is selected from the group consisting of -H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

E is selected from the group consisting of E^1, E^2 and E^3, wherein

E^1 is selected from the group consisting of -H, halogen, nitro, azido, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-C(O)NR^{42}R^{43}$, -Y-$NR^{42}R^{43}$, $-NR^{42}C(=O)R^{43}$, $-SO_2R^{42}$, $-SO_2NR^{42}R^{43}$, $-NR^{37}SO_2R^{42}$, $-NR^{37}SO_2NR^{42}R^{43}$, $-C(=N\text{-}OR^{42})R^{43}$, $-C(=NR^{42})R^{43}$, $-NR^{37}C(=NR^{42})R^{43}$, $-C(=NR^{42})NR^{37}R^{43}$, $-NR^{37}C(=NR^{42})NR^{37}R^{43}$, $-C(O)R^{42}$, $-CO_2R^{42}$, -C(O)(heterocyclyl), -C(O)(C_6-C_{10} aryl), -C(O)(heteroaryl), -Y-(C_6-C_{10} aryl), -Y-(heteroaryl), -Y-(5-10 membered heterocyclic), $-NR^{6a}R^{6b}$, $-NR^{6a}SO_2R^{6b}$, $-NR^{6a}C(O)R^{6b}$, $-OC(O)R^{6b}$, $-NR^{6a}C(O)OR^{6b}$, $-OC(O)NR^{6a}R^{6b}$,$-OR^{6a}$, $-SR^{6a}$, $-S(O)R^{6a}$, $-SO_2R^{6a}$, $-SO_3R^{6a}$, $-SO_2NR^{6a}R^{6b}$,

$-SO_2NR^{42}R^{43}$, $-COR^{6a}$, $-CO_2R^{6a}$, $-CONR^{6a}R^{6b}$, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$fluoroalkoxy, $-(CZ^3Z^4)_aCN$, wherein n is an integer ranging from 0 to 6, and the aforementioned E^1 groups other than -H and halogen are optionally substituted by 1 to 5 independently selected R^{38}, or E^1 is selected from a moiety selected from the group consisting of $-(CZ^3Z_4)_a$-aryl, $-(CZ^3Z^4)_a$-heterocycle, (C_2-C_6)alkynyl, $-(CZ^3Z^4)_a-(C_3-C_6)$cycloalkyl, $-(CZ^3Z^4)_a-(C_5-C_6)$cycloalkenyl, (C_2-C_6) alkenyl and (C_1-C_6)alkyl, which is optionally substituted with 1 to 3 independently selected Y^2 groups, where a is 0,1, 2, or 3, and wherein when a is 2 or 3, the CZ^3Z^4 units may be the same or different; wherein each R^{38} is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-NR^{36}R^{39}$, $-OR^{37}$, $-SO_2NR^{36}R^{39}$, C_1-C_6 alkyl, $-(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nOR^{37}$, $-S(O)_j(C_1-C_6$ alkyl), $-(CH_2)_n(C_6-C_{10}$ aryl), $-(CH_2)_n(C_5-C_{10}$ heteroaryl), $-(CH_2)_n$(5-10 membered heterocyclyl); $-C(O)(CH_2)_n(C_6-C_{10}$ aryl), $-(CH_2)_nO(CH_2)_j(C_6-C_{10}$ aryl), $-(CH_2)_nO(CH_2)_i$(5-10 membered heterocyclyl), $-C(O)(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_jNR^{39}CH_2C(O)NR^{36}R^{39}$, $-(CH_2)_jNR^{39}(CH_2)_iNR^{37}C(O)R^{40}$, $-(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_jNR^{39}(CH_2)_iS(O)_j(C_1-C_6$ alkyl), $-(CH_2)_jNR^{39}(CH_2)_nR^{36}$, $-SO_2(CH_2)_n(C_6-C_{10}$ aryl), $-SO_2(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_nNR^{36}R^{39}$, $-NR^{37}SO_2NR^{36}R^{39}$, SO_2R^{36}, C_2-C_6 alkenyl, C_3-C_{10} cycloalkyl and C_1-C_6 alkylamino, wherein j is an integer ranging from 0 to 2, n is an integer ranging from 0 to 6, i is an integer ranging from 0 to 6, the $-(CH_2)_i-$ and $-(CH_2)_n-$ moieties of the foregoing R^{38} groups optionally include a carbon-carbon double or triple bond where n is an integer between 2 and 6, and the alkyl, aryl, heteroaryl and heterocyclyl moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n(C_6-C_{10}$ aryl), $-(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_nO(CH_2)_iOR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6;

each R^{42} and R^{43} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -Y-(C_3-C_{10} cycloalkyl), -Y-(C_6-C_{10} aryl), -Y-(C_6-C_{10} heteroaryl), -Y-(5-10 membered heterocyclic), -Y-O-Y^1-OR^{37}, -Y^1-CO_2-R^{37}, and -Y-OR^{37}, wherein the alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclic moieties of the foregoing R^{42} and R^{43} groups are optionally substituted by 1 or more substituents independently selected from R^{44}, wherein

Y is a bond or is -($C(R^{37})(H)$)$_n$,

n is an integer ranging from 1 to 6, and

Y^1 is -($C(R^{37})(H)$)$_n$, or

R^{42} and R^{43} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted by 1 to 5 independently selected R^{44} substituents, with the proviso that R^{42} and R^{43} are not both bonded to the nitrogen directly through an oxygen;

each R^{44} is independently selected from the group consisting of halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, -$C(O)R^{40}$, -$C(O)OR^{40}$, -$OC(O)R^{40}$, -$OC(O)OR^{40}$, -$NR^{36}C(O)R^{39}$, -$C(O)NR^{36}R^{39}$, -$NR^{36}R^{39}$, -OR^{37}, -$SO_2NR^{36}R^{39}$, -SO_2R^{36}, -$NR^{36}SO_2R^{39}$, -$NR^{36}SO_2NR^{37}R^{41}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, -C_1-C_6 alkylamino, -$(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, -$(CH_2)_nO(CH_2)_iOR^{37}$, -$(CH_2)_nOR^{37}$, -$S(O)_j$($C_1$-$C_6$ alkyl), -$(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_n$(5-10 membered heterocyclic), -$C(O)(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_nO(CH_2)j$(C_6-C_{10} aryl), -$(CH_2)_nO(CH_2)_i$(5 to 10 membered heterocyclic), -$C(O)(CH_2)_n$(5 to 10 membered heterocyclic), -$(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, -$(CH_2)_jNR^{39}CH_2C(O)NR^{36}R^{39}$, -$(CH_2)_jNR^{39}(CH_2)_iNR^{37}C(O)R^{40}$, -$(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$, -$(CH_2)_jNR^{39}(CH_2)_iS(O)_j$($C_1$-$C_6$ alkyl), -$(CH_2)_jNR^{39}(CH_2)_nR^{36}$, -$SO_2(CH_2)_n$($C_6$-$C_{10}$ aryl), and -$SO_2(CH_2)_n$(5 to 10 membered heterocyclic) wherein, j is an integer from 0 to 2, n is an integer from 0 to 6 and i is an integer ranging from 2 to 6, the -$(CH_2)_i$- and -$(CH_2)_{n1}$- moieties of the foregoing R^{44} groups optionally include a carbon-carbon double or triple bond wherein n is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{44} groups are optionally substituted by 1 or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, -$C(O)R^{40}$, -$C(O)OR^{40}$, -$OC(O)R^{40}$, -$OC(O)OR^{40}$,-$NR^{36}C(O)R^{39}$, -

$C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, $-SO_2R^{36}$, $-SO_2NR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$ and $-(CH_2)_nOR^{37}$, wherein n is an integer from 0 to 6 and i is an integer from 2 to 6; and

each R^{40} is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_n$(C_6-C_{10} aryl), C_3-C_{10} cycloalkyl, and $-(CH_2)_n$(5-10 membered heterocyclic), wherein n is an integer ranging from 0 to 6;

each R^{36} and R^{39} is independently selected from the group consisting of H, -OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5-10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nCN(CH_2)_nOR^{37}$, $-(CH_2)_nCN(CH_2)_nR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{36} and R^{39} groups are optionally substituted by one or more substituents independently selected from -OH, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-CO(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{37}C(O)R^{41}$, $-C(O)NR^{37}R^{41}$, $-NR^{37}R^{41}$, $-C_1$-C_6 alkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, with the proviso that when R^{36} and R^{39} are both attached to the same nitrogen, then R^{36} and R^{39} are not both bonded to the nitrogen directly through an oxygen;

each R^{37} and R^{41} is independently selected from the group consisting of H, OR^{36}, C_1-C_6 alkyl and C_3-C_{10} cycloalkyl;

each R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, $-(CZ^5Z^6)_u$-(C_3-C_6)cycloalkyl, $-(CZ^5Z^6)_u$-(C_5-C_6)cycloalkenyl, $-(CZ^5Z^6)_u$-aryl, $-(CZ^5Z^6)_u$-heteroaryl, $-(CZ^5Z^6)_u$-heterocycle, (C_2-C_6)alkenyl, and (C_1-C_6)alkyl, each of which is optionally substituted with 1 to 3 independently selected Y^3 groups, where u is 0,1, 2, or 3, and wherein when u is 2 or 3, the CZ^5Z^6 units may be the same or different, or

R^{6a} and R^{6b} taken together with adjacent atoms can form a heterocycle;

each Z^3, Z^4, Z^5 and Z^6 is independently selected from the group consisting of H, F and (C_1-C_6)alkyl, or

each Z^3 and Z^4, or Z^5 and Z^6 are selected together to form a carbocycle, or

two Z^3 groups on adjacent carbon atoms are selected together to optionally form a carbocycle;

each Y^2 and Y^3 is independently selected from the group consisting of halogen, cyano, nitro, tetrazolyl, guanidino, amidino, methylguanidino, azido, $-C(O)Z^7$, $-OC(O)NH_2$, $-OC(O)NHZ^7$, $-OC(O)NZ^7Z^8$, $-NHC(O)Z^7$, $-NHC(O)NH_2$, $-NHC(O)NHZ^7$, $-NHC(O)NZ^7Z^8$, $-C(O)OH$, $-C(O)OZ^7$, $-C(O)NH_2$, $-C(O)NHZ^7$,$-C(O)NZ^7Z^8$, $-P(O)_3H_2$, $-P(O)_3(Z^7)_2$, $-S(O)_3H$, $-S(O)Z^7$, $-S(O)_2Z^7$, $-S(O)_3Z^7$, $-Z^7$, $-OZ^7$, $-OH$, $-NH_2$, $-NHZ^7$, $-NZ^7Z^8$, $-C(=NH)NH_2$,$-C(=NOH)NH_2$, -N-morpholino, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)haloalkyl, (C_2-C_6)haloalkenyl, (C_2-C_6)haloalkynyl, (C_1-C_6)haloalkoxy, $-(CZ^9Z^{10})_rNH_2$, $-(CZ^9Z^{10})_rNHZ^3$, $-(CZ^9Z^{10})_rNZ^7Z^8$, $-X^6(CZ^9Z^{10})_r-(C_3-C_8)$cycloalkyl, $-X^6(CZ^9Z^{10})_r-(C_5-C_8)$cycloalkenyl, $-X^6(CZ^9Z^{10})_r$-aryl and $-X^6(CZ^9Z^{10})_r$-heterocycle, wherein

r is 1, 2, 3 or 4;

X^6 is selected from the group consisting of O, S, NH, -C(O)-, -C(O)NH-, -C(O)O-, -S(O)-, $-S(O)_2-$ and $-S(O)_3-$;

Z^7 and Z^8 are independently selected from the group consisting of an alkyl of 1 to 12 carbon atoms, an alkenyl of 2 to 12 carbon atoms, an alkynyl of 2 to 12 carbon atoms, a cycloalkyl of 3 to 8 carbon atoms, a cycloalkenyl of 5 to 8 carbon atoms, an aryl of 6 to 14 carbon atoms, a heterocycle of 5 to 14 ring atoms, an aralkyl of 7 to 15 carbon atoms, and a heteroaralkyl of 5 to 14 ring atoms, or

Z^7 and Z^8 together may optionally form a heterocycle;

Z^9 and Z^{10} are independently selected from the group consisting of H, F, a (C_1-C_{12})alkyl, a (C_6-C_{14})aryl, a (C_5-C_{14})heteroaryl, a (C_7-C_{15})aralkyl and a (C_5-C_{14})heteroaralkyl, or

Z^9 and Z^{10} are taken together form a carbocycle, or

two Z^9 groups on adjacent carbon atoms are taken together to form a carbocycle; or

any two Y^2 or Y^3 groups attached to adjacent carbon atoms may be taken together to be $-O[C(Z^9)(Z^{10})]_rO$ or $-O[C(Z^9)(Z^{10})]_{r+1}$, or

any two Y^2 or Y^3 groups attached to the same or adjacent carbon atoms may be selected together to form a carbocycle or heterocycle; and wherein

any of the above-mentioned substituents comprising a CH_3 (methyl), CH_2 (methylene), or CH (methine) group which is not attached to a halogen, SO or SO_2 group or to a N, O or S atom optionally bears on said group a substituent selected from hydroxy, halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy and an $-N[(C_1-C_4)alkyl][(C_1-C_4)alkyl]$;

E^2 is -C≡CH or -C≡C-$(CR^{45}R^{45})_n$-R^{46};

R^{45} is independently selected from the group consisting of H, a (C_1-C_6)alkyl and a (C_3-C_8)cycloalkyl;

R^{46} is selected from the group consisting of heterocyclyl, -$N(R^{47})$-C(O)-$N(R^{47})(R^{48})$, -$N(R^{47})$-C(S)-$N(R^{47})(R^{48})$, -$N(R^{47})$-C(O)-OR^{48}, -$N(R^{47})$-C(O)-$(CH_2)_n$-R^{48}, -$N(R^{47})$-SO_2R^{47}, -$(CH_2)_nNR^{47}R^{48}$, -$(CH_2)_nOR^{48}$, -$(CH_2)_nSR^{49}$, -$(CH_2)_nS(O)R^{49}$, -$(CH_2)_nS(O)_2R^{49}$, -$OC(O)R^{49}$, -$OC(O)OR^{49}$, -$C(O)NR^{47}R^{48}$, heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -$(CH_2)_nNR^{50}R^{51}$, and aryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -$(CH_2)_nNR^{50}R^{51}$;

R^{47} and R^{48} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, heterocyclyl, -$(CH_2)_nNR^{50}R^{51}$, -$(CH_2)_nOR^{50}$, -$(CH_2)_nC(O)R^{49}$, -$C(O)_2R^{49}$, -$(CH_2)_nSR^{49}$, -$(CH_2)_nS(O)R^{49}$, -$(CH_2)_nS(O)_2R^{49}$, -$(CH_2)_nR^{49}$, -$(CH_2)_n$CN, aryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -$(CH_2)_nOR^{49}$, -$(CH_2)_n$heterocyclyl, -$(CH_2)_n$heteroaryl, -SO_2R^{50} and -$(CH_2)_nNR^{50}R^{51}$, and heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -$(CH_2)_nOR^{49}$, -$(CH_2)_n$heterocyclyl, -$(CH_2)_n$heteroaryl, -SO_2R^{50} and -$(CH_2)_nNR^{50}R^{51}$, or

R^{47} and R^{48}, together with the atom to which they are attached, form a 3-8 membered ring;

R^{49} is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkylene, aryl(C_1-C_6)alkylene wherein the aryl is optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -$(CH_2)_nNR^{50}R^{51}$, heteroaryl(C_1-C_6)alkylene wherein the heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -$(CH_2)_nNR^{50}R^{51}$, aryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -$(CH_2)_nNR^{50}R^{51}$, and heteroaryl optionally substituted with one or more substituents

selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$;

R^{50} and R^{51} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl and $-C(O)R^{45}$, or

R^{50} and R^{51}, together with the atom to which they are attached, form a 3-8 membered ring; and

E^3 is the group defined by $-(Z^{11})-(Z^{12})_m-(Z^{13})_{m1}$, wherein

Z^{11} is heterocyclyl or heterocyclylene;

Z^{12} is selected from the group consisting of OC(O), OC(S) and C(O);

Z^{13} is selected from the group consisting of heterocyclyl, aralkyl, $N(H)R^{52}$, (C_1-C_3)alkyl, $-OR^{52}$, halo, $S(O)_2R^{56}$, (C_1-C_3)hydroxyalkyl and (C_1-C_3)haloalkyl;

m is 0 or 1;

m1 is 0 or 1;

R^{52} is selected from the group consisting of H, $-(CH_2)_qS(O)_2R^{54}$, $R^{55}NR^{53}R^{53}$, (C_1-C_3)alkyl, $-(CH_2)_qOR^{53}$, $-C(O)R^{54}$ and $-C(O)OR^{53}$;

q is 0, 1, 2, 3 or 4;

R^{53} is (C_1-C_3)alkyl;

R^{54} is (C_1-C_3)alkyl or $N(H)R^{53}$;

R^{55} is (C_1-C_6) alkyl; and

R^{56} is selected from the group consisting of NH_2, (C_1-C_3)alkyl and OR^{52}.

2. The compound according to claim 1, wherein T is aryl or heteroaryl, wherein each of said aryl and heteroaryl is optionally substituted with 1 to 3 independently selected R^{20}.

3. The compound according to claim 1, wherein T is selected from the group consisting of arylalkyl, cycloalkyl and heterocyclyl, wherein each of said arylalkyl, cycloalkyl and heterocyclyl is optionally substituted with 1 to 3 independently selected R^{20}.

4. The compound according to claim 1, wherein R^{20} is selected from the group consisting of H, halogen, $-OR^{17}$ and $-C(O)OR^{17}$.

5. The compound according to claim 1, wherein R^{20} is fluorine or chloride.

6. The compound according to claim 1, wherein W is O.

7. The compound according to claim 1, wherein Z is S or O.

8. The compound according to claim 1, wherein Z is S.

9. The compound according to claim 1, wherein X and X^1 are independently selected from the group consisting of H and C_1-C_6alkyl, wherein the C_1-C_6alkyl is optionally substituted.

10. The compound according to claim 1, wherein X and X^1 are both H.

11. The compound according to claim 1, wherein X and X^1 taken together with the atom to which they are attached, form a C_3-C_7cycloalkyl.

12. The compound according to claim 1, wherein R^1, R^2, R^3 and R^4 are independently selected from the group consisting of H, halogen, trihalomethyl, OR^{17}, $-NR^{17}R^{18}$ and C_1-C_6alkyl.

13. The compound according to claim 1, wherein R^1, R^2 and R^4 are independently selected from the group consisting of H, halo and $-OR^{17}$.

14. The compound according to claim 1, wherein R^1 is H or halogen.

15. The compound according to claim 1, wherein R^1 is halogen.

16. The compound according to claim 1, wherein R^2, R^3 and R^4 are each H.

17. The compound according to claim 1, wherein R^{17} is a C_1-C_6alkyl.

18. The compound according to claim 1, wherein R^{16} is H or C_1-C_6alkyl.

19. The compound according to claim 1, wherein Q is selected from the group consisting of CH_2, S, -N-(C_1-C_6alkyl), N-Y-(aryl) and -N-OMe.

20. The compound according to claim 1, wherein Q is S.

21. The compound according to claim 1, wherein Q is CH_2.

22. The compound according to claim 1, wherein Q is -N-(C_1-C_6alkyl).

23. The compound according to claim 1, wherein Q is -N-Y-(aryl).

24. The compound according to claim 1, wherein Q is -N-OMe.

25. The compound according to claim 1, wherein D is C-E.

26. The compound according to claim 1, wherein D is CH.

27. The compound according to claim 1, wherein L is C-R.

28. The compound according to claim 1, wherein R is H or halogen.

29. The compound according to claim 1, wherein L is N.

30. The compound according to claim 1, wherein E is selected from the group consisting of E^1 and E^2.

31. The compound according to claim 1, wherein E is E^1.

32. The compound according to claim 1, wherein E is E^1, wherein E^1 is selected from the group consisting of H, halogen, $-C(O)NR^{42}R^{43}$, $-SO_2NR^{42}R^{43}$, $C(=NR^{42})NR^{37}R^{43}$, $-CO_2R^{42}$, -C(O)(heterocyclyl), -C(O)(heteroaryl), -Y-(C_6-C_{10} aryl), -Y-(heteroaryl), -Y-(5 to 10 membered heterocyclic), $-SR^{6a}$, $-S(O)R^{6a}$, $-SO_2R^{6a}$, wherein each of said E^1 other than H and halogen are optionally substituted with 1 to 5 independently selected R^{38}, or E1 is (C1-C6)alkyl, which is optionally substituted with 1 to 3 independently selected Y^2 groups.

33. The compound according to claim 1, wherein R^{38} is selected from the group consisting of halogen, $-C(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-NR^{36}R^{39}$, $-OR^{37}$, C_1-C_6alkyl, $-C(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_nOR^{37}$, $-S(O)_j(C_1$-C_6alkyl), $-(CH_2)_n$-(5 to 10 membered heterocyclic), $-(CH_2)O(CH_2)_i$(5 to 10 membered heterocyclic), $-(CH_2)_n$(5 to 10 membered heteroaryl), $-(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_jNR^{39}(CH_2)_nR^{36}$, $-(CH_2)_nNR^{36}R^{39}$, wherein j is an integer ranging from 0 to 2, n is an integer ranging from 0 to 6, i is an integer ranging from 1 to 6, , the $-(CH_2)_i$- and $-(CH_2)_n$- moieties of the foregoing R^{38} groups optionally include a carbon-carbon double or triple bond where n is an integer between 2 and 6, and the alkyl, aryl, heteroaryl, and heterocyclic moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_nO(CH_2)_iOR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6.

34. The compound according to claim 1, wherein the alkyl, aryl, heteroaryl, and heterocyclic moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from the group consisting of -OH and $-C(O)OR^{40}$.

35. The compound according to claim 1, wherein each R^{42} and R^{43} is independently selected from the group consisting of H, -Y-(C_3-C_{10} cycloalkyl), -Y-(C_6-C_{10} aryl), -Y-(C_6-C_{10} heteroaryl) and -Y-(5 to 10 membered heterocyclic), wherein the cycloalkyl, aryl, heteroaryl and heterocyclic moieties of the foregoing R^{42} and R^{43} groups are optionally substituted by 1 or more substituents independently selected from R^{44}.

36. The compound according to claim 1, wherein each R^{42} and R^{43} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, $-Y^1-CO_2-R^{37}$ and -Y-OR^{37}.

37. The compound according to claim 1, wherein one of R^{42} and R^{43} is H.

38. The compound according to claim 1, wherein one of R^{42} and R^{43} is -(C_6-C_{10} heteroaryl) or -Y-(5 to 10 membered heterocyclic).

39. The compound according to claim 1, wherein Y is a bond.

40. The compound according to claim 1, wherein Y is $-(C(R^{37})(H))_n$.

41. The compound according to claim 1, wherein R^{42} and R^{43} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted by 1 to 5 independently selected R^{44} substituents, with the proviso that R^{42} and R^{43} are not both bonded to the nitrogen directly through an oxygen.

42. The compound according to claim 1, wherein R^{44} is independently selected from the group consisting of $-C(O)NR^{36}R^{39}$, $-OR^{37}$ and C_1-C_6alkyl.

43. The compound according to claim 1, wherein each R^{40} is independently selected from the group consisting of H and C_1-C_{10} alkyl.

44. The compound according to claim 1, wherein each R^{36} and R^{39} is independently selected from the group consisting of H, C_1-C_6alkyl, $-(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_nOR^{37}$ and $-C(O)OR^{40}$, wherein n is an integer ranging from 0 to 6 and i is an integer

ranging from 2 to 6, with the proviso that when R^{36} and R^{39} are both attached to the same nitrogen, then R^{36} and R^{39} are not both bonded to the nitrogen directly through an oxygen.

45. The compound according to claim 1, wherein each R^{37} and R^{41} is independently selected from the group consisting of H and C_1-C_6alkyl.

46. The compound according to claim 1, wherein R^{6a} is selected from the group consisting of -$(CZ^5Z^6)_u$-aryl, -$(CZ^5Z^6)_u$-heteroaryl and C_1-C_6alkyl, each of which is optionally substituted with 1 to 3 indepedently selected Y^3 groups, wherein u is 0, 1, 2 or 3, and wherein when u is 2 or 3, the CZ^5Z^6 units may be the same or different.

47. The compound according to claim 1, wherein R^{6a} is selected from the group consisting of -$(CZ^5Z^6)_u$-aryl and -$(CZ^5Z^6)_u$-heteroaryl, each of which is optionally substituted with 1 to 3 indepedently selected Y^3 groups, wherein u is 0.

48. The compound according to claim 1, wherein Y^2 is -OH.

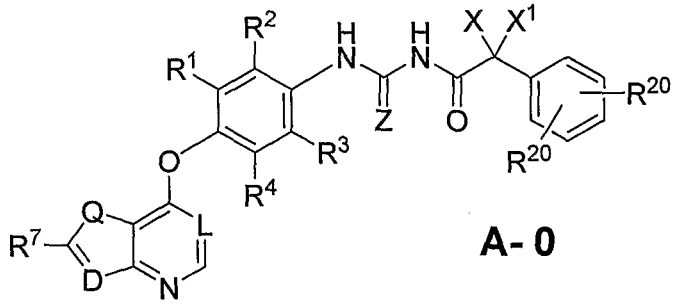
49. The compound according to claim 1, wherein Y^3 is -OH.

50. The compound according to claim 1, wherein E^2 is -C≡C-$(CR^{45}R^{45})_n$-R^{46}, wherein n is an integer ranging from 1 to 6.

51. The compound according to claim 50, wherein R^{45} is H.

52. The compound according to claim 50, wherein R^{46} is a heterocyclyl.

53. The compound according to claim 1, represented by the formula A-0:



A-0

and pharmaceutically acceptable salts and complexes thereof, wherein

Z is O or S;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano and nitro, wherein C_1-C_6 alkyl is optionally substituted;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, halo, trihalomethyl, $-OR^{17}$, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

Q is O, S, NH, N(C_1-C_6 alkyl), or N-Y-(aryl);

D is CR^{11}, or N;

L is N, or CR, wherein R is H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

R^7 is H, halogen, C_1-C_6 alkyl, $-C(=O)NR^9R^{10}$, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, $-SO_2$-C_1-C_6 alkyl, $-Y-NR^9R^{10}$, $-SO_2NR^9R^{10}$ or CO_2R^9, wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted;

R^9 and R^{10} are independently selected from H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), $-Y-O-Y^1-O-R^{11}$, $-Y^1-CO_2-R^{11}$, and $-Y-O-R^{11}$, wherein C_1-C_6 alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted;

Y is a bond or is $-(C(R^{11})(H))_t-$, wherein t is an integer from 1 to 6;

Y^1 is $-(C(R^{11})(H))_t-$,

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted,

each R^{20} is independently selected from the group consisting of hydrogen, halo, trihalomethyl, OR^{17}, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted, and

each R^{17} is an independently selected C_1-C_6alkyl, wherein said C_1-C_6alkyl is optionally substituted.

54. The compound according to claim 53, wherein X and X^1 are both hydrogen.

55. The compound according to claim 53, wherein R^1 is hydrogen or halogen.

56. The compound according to claim 53, wherein R^1 is fluorine.

57. The compound according to claim 53, wherein R^4 is hydrogen or halogen.

58. The compound according to claim 53, wherein R^4 is fluorine.

59. The compound according to claim 53, wherein R^2 is selected from the group consisting of H, halogen, trihalomethyl and $-OR^{17}$.

60. The compound according to claim 53, wherein R^3, and R^{20} are each hydrogen.

61. The compound according to claim 53, wherein R^{20} is $-OR^{17}$.

62. The compound according to claim 53, wherein Q is S, N(C_1-C_6 alkyl), or N-Y-(aryl).

63. The compound according to claim 53, wherein Q is NH.

64. The compound according to claim 53, wherein D is CR^{11}.

65. The compound according to claim 53, wherein L is CH or N.

66. The compound according to claim 53, wherein R^7 is H, halogen, C_1-C_6 alkyl, $-CONR^9R^{10}$, $-SO_2NH_2$, $-SO_2NR^9R^{10}$, -Y-heterocyclyl, -Y-heteroaryl, -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, or $-SO_2$-C_1-C_6 alkyl, wherein C_1-C_6 alkyl, is unsubstituted or is substituted with one or two of hydroxy or halogen, and heterocyclyl, and heteroaryl are unsubstituted or substituted with one or two of alkoxy, alkyl, or haloalkyl.

67. The compound according to claim 53, wherein R^7 is $-CONR^9R^{10}$.

68. The compound according to claim 53, wherein R^7 is Y-heteroaryl.

69. The compound according to claim 67, wherein R^9 and R^{10} are independently H, C_1-C_6 alkyl, -Y-O-R^{11}, -Y-(heterocycle), $-Y^1$-CO_2-R^{11}, or -Y-(aryl), wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and heterocyclyl, and aryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

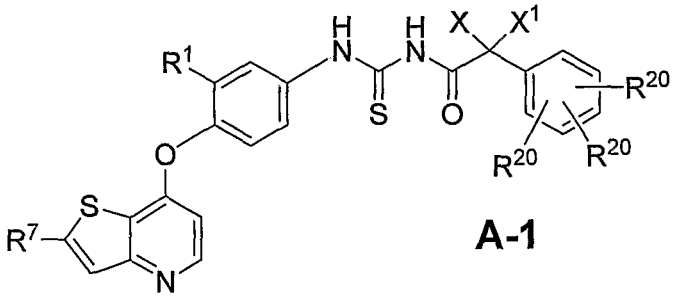
70. The compound according to claim 67, wherein R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said ring is unsubstituted or is substituted with one or two of alkoxy, alkyl, or haloalkyl.

71. The compound according to claim 53, wherein R^7 is H, halogen, C_1-C_6 alkyl, $-SO_2NR^9R^{10}$, -C(=O)(heterocyclyl), -Y-(heterocyclyl), or -Y-(heteroaryl), wherein C_1-C_6 alkyl is

unsubstituted or is substituted with one or two of hydroxy or halogen, and heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

72. The compound according to claim 53, wherein Z is sulfur.

73. The compound according to claim 1, represented by the formula A-1:



A-1

and pharmaceutically acceptable salts and complexes thereof, wherein

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

X and X^1 are independently selected from the group consisting of H and C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted, or

X and X^1 taken together with the atom to which they are attached, form a C_3-C_7 cycloalkyl;

R^7 is H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -SR^{6a}, -S-aryl, -S-(heteroaryl), -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$, CO_2R^9, -C≡C-$(CR^{45}R^{45})_n$-R^{46} and –C(=NR^{42})$NR^{37}R^{43}$, wherein n is an integer ranging from 0 to 6 and wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted with 1 to 5 independently selected R^{38};

R^9 and R^{10} are independently selected from H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(C_1-C_6 heteroalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11}, Y-C(O)OR^{37} and -Y-O-R^{11}, wherein said C_1-C_6 alkyl,heteroalkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted with one or more independently selected R^{44}, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted with 1 to 5 independently selected R^{44};

each R^{20} is independently selected from the group consisting of H, halo, -OR^{17} and -C(O)OR^{17};

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;
Y^1 is -($C(R^{11})(H))_t$-, and

74. R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

75. The compound according to claim 73, wherein R^1 is hydrogen or halogen.

76. The compound according to claim 73, wherein R^1 is fluorine.

77. The compound according to claim 73, wherein R^7 is selected from the group consisting of H, -C(=O)NR^9R^{10}, -Y-(aryl), -Y-(heteroaryl) and -S-C_1-C_6 alkyl, wherein said -Y-(aryl), -Y-(heteroaryl) and -S-C_1-C_6 alkyl are optionally substituted with 1 to 5 independently selected R^{38}.

78. The compound according to claim 73, wherein R^7 is -C(=O)NR^9R^{10}, optionally substituted with one or more independently selected R^{44}.

79. The compound according to claim 73, wherein R^7 is -Y-(aryl), optionally substituted with 1 to 5 independently selected R^{38}.

80. The compound according to claim 73, wherein R^7 is -Y-(heteroaryl), optionally substituted with 1 to 5 independently selected R^{38}.

81. The compound according to claim 73, wherein R^{38} is selected from the group consisting of halogen, -OR^{37}, C_1-C_6alkyl, -$(CH_2)_n$-(5 to 10 membered heterocyclyl), -$(CH_2)_jNR^{39}(CH_2)_nR^{36}$, -$(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, -$(CH_2)_n$-heteroaryl, -C(O)$NR^{36}R^{39}$, -$(CH_2)_nO(CH_2)_i$(5to 10 membered heterocyclyl) and -$(CH2)_jO(CH_2)_iNR^{36}R^{39}$, wherein n is an integer ranging from 0 to 6, j is an integer ranging from 0 to 2 , j is an integer ranging from 1 to 6 and wherein the alkyl, heteroaryl and heterocyclyl moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, -C(O)R^{40}, -C(O)OR^{40}, -OC(O)R^{40}, -OC(O)OR^{40}, -NR^{36}C(O)R^{39}, -C(O)$NR^{36}R^{39}$, -$(CH_2)_nNR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_n$(C_6-C_{10} aryl), -$(CH_2)_n$(5-10 membered heterocyclyl), -$(CH_2)_nO(CH_2)_iOR^{37}$, and -$(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6.

82. The compound according to claim 73, wherein R^{38} is selected from the group consisting of $-OR^{37}$, C_1-C_6alkyl, $-(CH_2)_n$(5 to 10 membered heterocyclyl) and $-(CH_2)_nO(CH_2)_i$(5 to10 membered heterocyclyl).

83. The compound according to claim 73, wherein R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -C_1-C_6 heteroalkyl, -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-R^{11} and Y-C(O)OR^{37}, wherein a C_1-C_6 alkyl, C_1-C_6 heteroalkyl, aryl, heterocyclcyl and heteroaryl are each optionally substituted with 1 or more independently selected R^{44}.

84. The compound according to claim 73, wherein R^{44} is selected from the group consisting of C_1-C_6 alkyl, $-OR^{37}$, $-C(O)NR^{36}R^{39}$ and $-C(O)OR^{46}$.

85. The compound according to claim 73, wherein R^{36} is selected from the grouip consisting of H, C_1-C_6 alkyl, $-(CH_2)_nOR^{37}$ and $-(CH_2)_n$(heterocyclyl).

86. The compound according to claim 73, wherein R^{39} is H or C_1-C_6 alkyl.

87. The compound according to claim 73, wherein R^{37} is H or C_1-C_6 alkyl.

88. The compound according to claim 73, wherein R^{20} is selected from the group consisting of H, halogen, $-OR^{17}$ and $-C(O)OR^{17}$.

89. The compound according to claim 73, wherein R^{17} is H or C_1-C_6 alkyl.

90. The compound according to claim 73, wherein R^{20} is halogen.

91. The compound according to claim 73, wherein R^{20} is Cl or F.

92. The compound according to claim 73, wherein R^{6a} is $-(CZ^5Z^6)_u$-aryl.

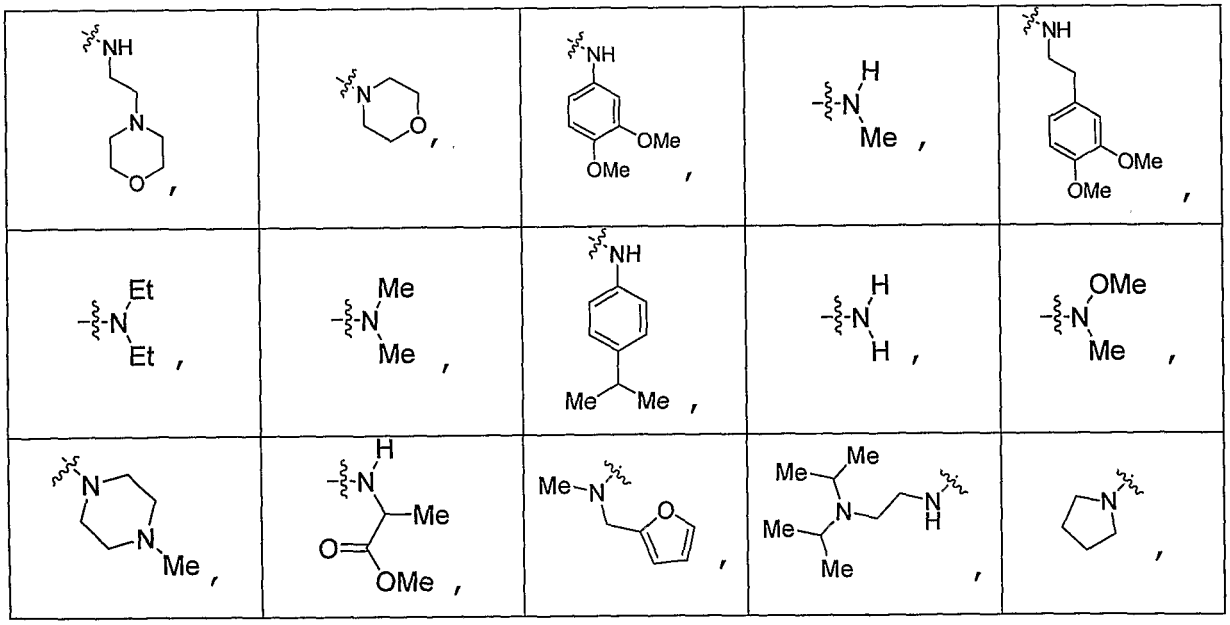
93. The compound according to claim 73, wherein R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, $-CONR^9R^{10}$, $-SO_2NH_2$, $-SO_2NR^9R^{10}$, -Y-heterocyclyl, -Y-heteroaryl, -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, or $-SO_2$-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

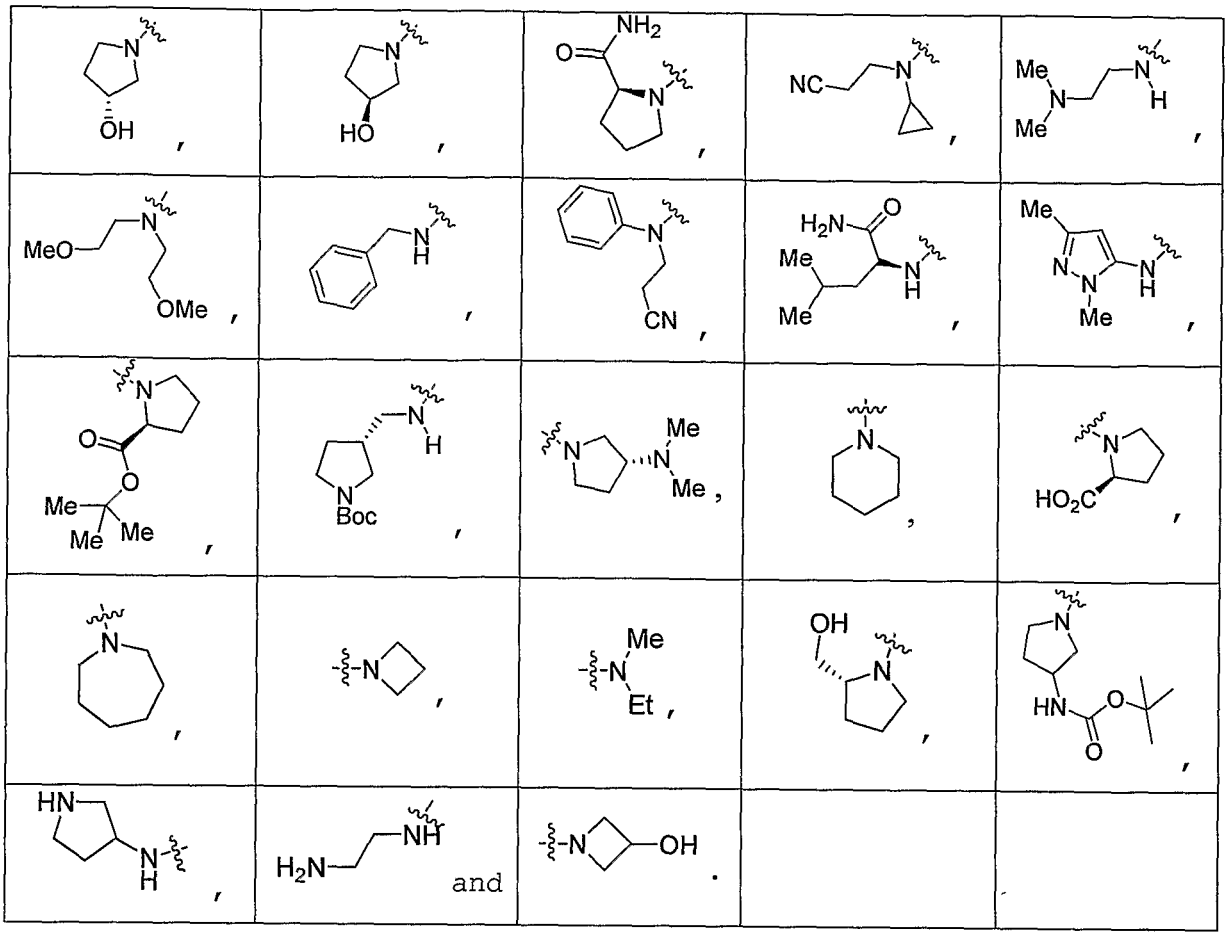
94. The compound according to claim 73, wherein R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$SO_2NR^9R^{10}$, -C(=O)(heterocyclyl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

95. The compound according to claim 77, wherein R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -Y-O-R^{11}, -Y-(heterocycle), -Y-CO_2-R^{11}, -Y-(aryl) and -Y-(heteroaryl), wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, aryl and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

96. The compound according to claim 77, wherein R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said ring is unsubstituted or is substituted with one or two of alkoxy, alkyl, or haloalkyl.

97. The compound according to claim 77, wherein NR^9R^{10} is selected from the group consistisng of:





98. The compound according to claim 73, wherein R^7 is unsubstituted heteroaryl.

99. The compound according to claim 73, wherein R^7 is thiazolyl, pyridinyl, pyrimidinyl, and imidazolyl, each of which is preferably unsubstituted or is substituted with one or two of alkoxy, or alkyl.

100. The compound according to claim 73, wherein R^7 is C_1-C_6 alkyl, unsubstituted or substituted with hydroxy.

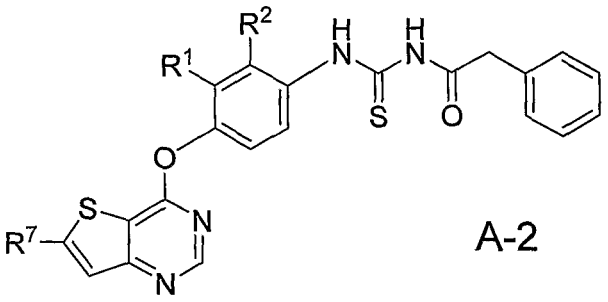
101. The compound according to claim 73, wherein X and X^1 are both H.

102. The compound according to claim 73, wherein R^{17} is selected from the group consisting of H and C_1-C_6 alkyl.

103. The compound according to claim 73, wherein R^{38} is selected from the group consisting of $-OR^{37}$, C_1-C_6 alkyl and $-(CH_2)_n$(5 to 10 membered heterocylic), wherein n is an integer ranging from 0 to 6.

104. The compound according to claim 73, wherein R^{37} is selected from the group consisting of H and C_1-C_6 alkyl.

105. The compound according to claim 1, represented by the formula A-2:



and pharmaceutically acceptable salts and complexes thereof, wherein

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^4 is selected from the group consisting of H and halogen;

R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, -SO_2-C_1-C_6 alkyl, -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$ and CO_2R^9, wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted with 1 to 5 independently selected R^{38};

R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11} and -Y-O-R^{11}, wherein C_1-C_6 alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted with one or more independently selected R^{44}, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted;

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y_1 is -$(C(R^{11})(H))_t$-, and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

106. The compound according to claim 104, wherein R^1 is hydrogen or halogen.

107. The compound according to claim 104, wherein R^1 is fluorine.

108. The compound according to claim 104, wherein R^4 is selected from the group consisting of H and halogen.

109. The compound according to claim 104, wherein R^4 is fluorine.

110. The compound according to claim 104, wherein R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -SO_2NH_2, -$SO_2NR^9R^{10}$, -Y-heterocyclyl -Y-heteroaryl, -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl and -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl, heterocyclyl, heteroaryl and aryl are each optionally substituted with 1 to 5 independently selected R^{38}.

111. The compound according to claim 104, wherein R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -SO_2NH_2, -$SO_2NR^9R^{10}$, -Y-heterocyclyl -Y-heteroaryl, -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl and -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, haloalkyl or $(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$.

112. The compound according to claim 104, wherein R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$SO_2NR^9R^{10}$, -C(=O)(heterocyclyl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, or -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, haloalkyl or $(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$.

113. The compound according to claim 104, wherein R^7 is selected from the group consisting of C_1-C_6 alkyl, -C(=O)NR_9R_{10}, -Y-(heterocyclyl, -Y-(heteroaryl), -S-C_1-C_6 alkyl and -SO-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, haloalkyl or $(CH_2)_jNR_{39}(CH_2)_nO(CH_2)_iOR_{37}$.

114. The compound according to claim 104, wherein R^7 is $CONR^9R^{10}$.

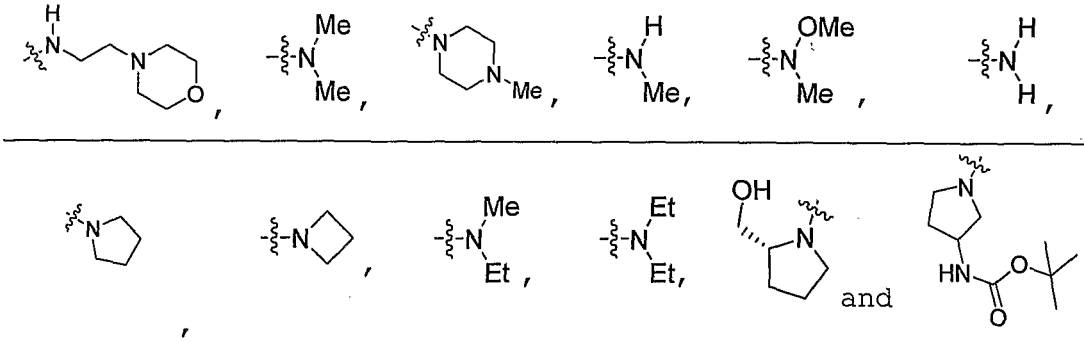
115. The compound according to claim 113, wherein R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-O-R^{11}, -Y-(heterocycle), -Y^1-CO_2-R^{11} and -Y-(aryl), wherein the alkyl, heterocyclyl and aryl moieties of the foregoing R^9 and R^{10} groups are optionally substituted with 1 or more substituents independently selected from R^{44}.

116. The compound according to claim 113, wherein R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-O-R^{11}, -Y-(heterocycle), -Y^1-CO_2-R^{11} and -Y-(aryl), wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and aryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, haloalkyl or $(CH_2)_jNR_{39}(CH_2)_nO(CH_2)_iOR_{37}$.

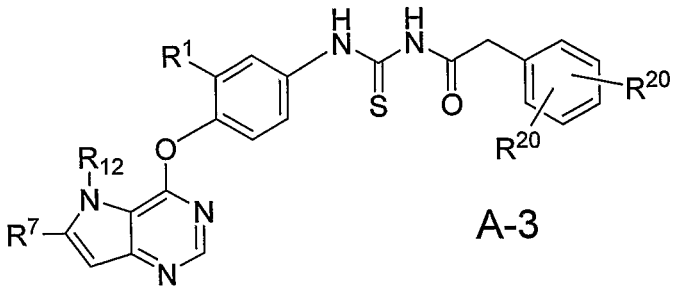
117. The compound according to claim 113, wherein R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted.

118. The compound according to claim 113, wherein R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said ring is unsubstituted or is substituted with one or two of alkoxy, alkyl, or haloalkyl.

119. The compound according to claim 113, wherein NR^9R^{10} is selected from the group consisting of:



120. The compound according to claim 1, represented by the formula A-3:



A-3

and pharmaceutically acceptable salts and complexes thereof, wherein

R^7 is selected from the group consisting of H, -Y-(aryl) and -Y-(heteroaryl), wherein -Y-(aryl) and -Y-(heteroaryl) are optionally substituted with 1 to 5 independently selected R^{38};

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^{12} is selected from the group consisting of H, C_1-C_6 alkyl, -O(C_1-C_6 alkyl) and -Y-(aryl), wherein C_1-C_6 alkyl and aryl are optionally substituted;

Y is a bond or is $-(C(R^{11})(H))_t-$, wherein t is an integer from 1 to 6;

R^{11} is H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted; and

each R_{20} is independently selected from the group consisting of H and halogen.

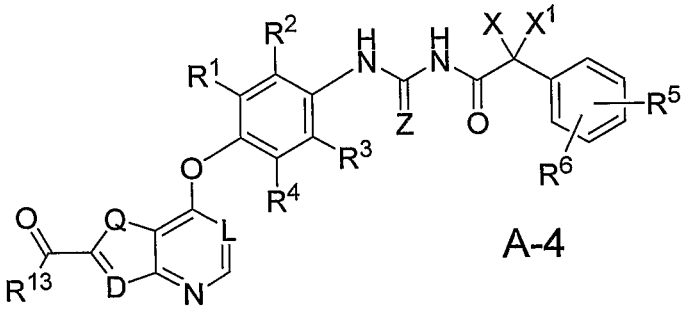
121. The compound according to claim 119, wherein R^1 is hydrogen or halogen.

122. The compound according to claim 119, wherein R^1 is fluorine.

123. The compound according to claim 119, wherein R^{12} is unsubstituted C_1-C_3 alkyl or unsubstituted -Y-phenyl.

124. The compound according to claim 119, wherein R^{20} is Cl.

125. The compound according to claim 1, represented by the formula A-4:



A-4

and pharmaceutically acceptable salts and complexes thereof, wherein

Z is O or S;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano and nitro, wherein C_1-C_6 alkyl is optionally substituted;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and $NR^{17}R^{18}$, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^{17} and R^{18} are independently C_1-C_6alkyl;

Q is O, S, NH, N(C_1-C_6 alkyl), or N-Y-(aryl);

D is CR^{11}, or N;

L is N, or CR, wherein R is selected from the group consisting of H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

R^{13} is heterocyclyl or heteroaryl, wherein heterocyclyl and heteroaryl are optionally substituted with 1 to 5 independently selected R^{38};

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6; and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

126. The compound according to claim 124, wherein X and X^1 are both hydrogen.

127. The compound according to claim 124, wherein R^1, R^2, R^3 and R^4 are independently H or halogen.

128. The compound according to claim 124, wherein R^1 is hydrogen or halogen.

129. The compound according to claim 124, wherein R^1 is fluorine or chlorine.

130. The compound according to claim 124, wherein R^4 is hydrogen or halogen.

131. The compound according to claim 124, wherein R^4 is fluorine or chlorine.

132. The compound according to claim 124, wherein R^2, R^3, R^5, and R^6 are each hydrogen.

133. The compound according to claim 124, wherein Q is selected from the group consisting of S, N(C_1-C_6 alkyl) and N-Y-(aryl).

134. The compound according to claim 124, wherein Q is S.

135. The compound according to claim 124, wherein D is CR^{11}.

136. The compound according to claim 124, wherein R^{11} is H.

137. The compound according to claim 124, wherein L is CH or N.

138. The compound according to claim 124, wherein L is CH.

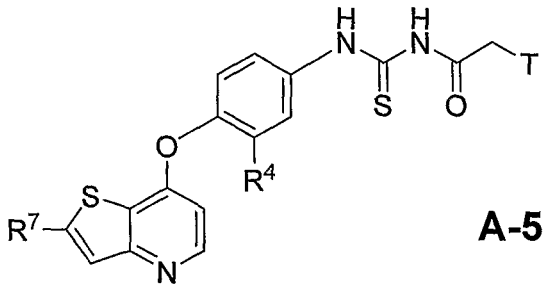
139. The compound according to claim 124, wherein Z is sulfur.

140. The compound according to claim 124, wherein R^{38} is selected from $C(O)OR^{40}$ and $NR^{36}R^{39}$.

141. The compound according to claim 124, wherein R^{40} is H or C_1-C_{10} alkyl.

142. The compound according to claim 124, wherein R^{36} and R^{39} are independently C_1-C_6 alkyl.

143. The compound according to claim 1, represented by the formula A-5:



A-5

and pharmaceutically acceptable salts and complexes thereof, wherein

R^7 is selected from the group consisting of H, $-C(O)NR^{42}R^{43}$, -Y-(aryl), -Y-(heteroaryl), -C(O)-(C_3-C_{10} cycloalkyl), -C(O)-(heterocyclyl), -C(O)-(C_6-C_{10} aryl) and -C(O)-(heteroaryl), wherein the aforementioned R^7 groups other than H are optionally substituted with 1 to 5 independently selected R^{38};

R^4 is selected from the group consisting of H and halogen; and

T is selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl and arylalkyl, each of which is optionally substituted with 1 to 3 independently selected R^{20};

144. The compound according to claim 142, wherein R^7 is selected from the group consisting of H, $C(O)NR^{42}R^{43}$ and -Y-(heteroaryl), wherein -Y-(heteroaryl) is optionally substituted with 1 to 5 independently selected R^{38}.

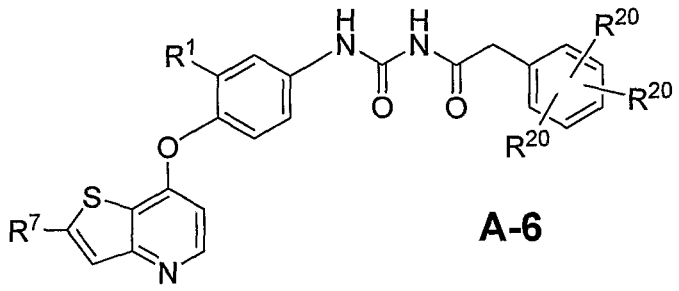
145. The compound according to claim 142, wherein R^7 is $C(O)NR^{42}R^{43}$.

146. The compound according to claim 142, wherein R^{42} and R^{43} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring, wherein said ring is optionally substituted with 1 to 5 independently selected R^{44} substituents, with the proviso that R^{42} and R^{43} are not both bonded to the nitrogen directly through and oxygen.

147. The compound according to claim 142, wherein R^4 is halogen.

148. The compound according to claim 142, wherein R^4 is fluorine.

149. The compound according to claim 1, represented by the formula A-6:



A-6

and pharmaceutically acceptable salts and complexes thereof, wherein

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, $-C(=O)NR^9R^{10}$, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), $-SR^{6a}$, -S-aryl, -S-(heteroaryl), -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl, $-SO_2$-C_1-C_6 alkyl, $-Y-NR^9R^{10}$, $-SO_2NR^9R^{10}$, CO_2R^9, $-C\equiv C-(CR^{45}R^{45})_n-R^{46}$ and $-C(=NR^{42})NR^{37}R^{43}$, wherein n is an integer ranging from 0 to 6 and wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted with 1 to 5 independently selected R^{38};

R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(C_1-C_6 heteroalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), $-Y-O-Y^1-O-R^{11}$, $-Y^1-CO_2-R^{11}$, $Y-C(O)OR^{37}$ and $-Y-O-R^{11}$, wherein said C_1-C_6 alkyl,heteroalkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted with one or more independently selected R^{44}, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted with 1 to 5 independently selected R^{44};

each R^{20} is independently selected from the group consisting of H, halo, $-OR^{17}$ and $-C(O)OR^{17}$;

Y is a bond or is $-(C(R^{11})(H))_t-$, wherein t is an integer from 1 to 6;

Y^1 is $-(C(R^{11})(H))_t-$; and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

150. The compound according to claim 148, wherein R^7 is selected from the group consisting of H, $C(O)NR^9R^{10}$ and -Y-(heteroaryl), wherein -Y-(heteroaryl) is optionally substituted with 1 to 5 independently selected R^{38}.

151. The compound according to claim 148, wherein R^7 is $C(O)NR^9R^{10}$.

152. The compound according to claim 148, wherein R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring, wherein said ring is optionally substituted with 1 to 5 independently selected R^{44} substituents.

153. The compound according to claim 148, wherein R^7 is -Y-(heteroaryl), wherein said -Y-(heteroaryl) is optionally substituted with 1 to 5 independently selected R^{38}.

154. The compound according to claim 148, wherein R^7 is -Y-(heteroaryl), wherein said -Y-(heteroaryl) is optionally substituted with one C_1-C_6 alkyl.

155. The compound according to claim 148, wherein R^1 is halogen.

156. The compound according to claim 148, wherein R^1 is fluorine.

157. The compound according to claim 148, wherein R^{17} is selected from the group consisting of H and C_1-C_6 alkyl.

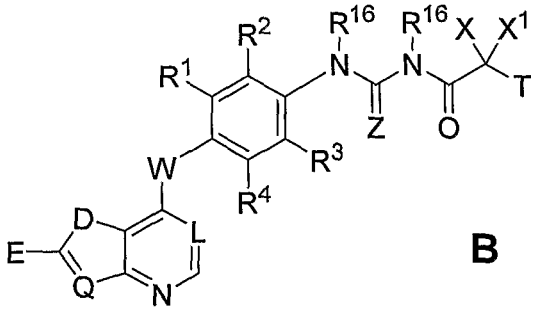
158. The compound according to claim 148, wherein R^{38} is selected from the group consisting of $-OR^{37}$, C_1-C_6 alkyl and $-(CH_2)_n$(5 to 10 membered heterocylic), wherein n is an integer ranging from 0 to 6.

159. The compound according to claim 148, wherein R^{37} is selected from the group consisting of H and C_1-C_6 alkyl.

160. The compound according to claim 148, wherein each R^{20} is independently selected from the group consisting of H, halogen and -O-(C_1-C_6)alkyl.

161. The compound according to claim 148, wherein two R^{20} are H and the third R^{20} is selected from the group consisting of H, halogen and -O-(C_1-C_6 alkyl).

162. A compound of the formula (B), that are inhibitors of VEGF receptor signaling and HGF receptor signaling:



B

and pharmaceutically acceptable salts and complexes thereof, wherein

T is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl, wherein each of said cycloalkyl, heterocyclyl, aryl and heteroaryl is optionally substituted with 1 to 3 R^{20};

each R^{20} is independently selected from the group consisting of -H, halogen, trihalomethyl, -CN, -NO_2, -NH_2, -OR^{17}, -OCF_3, -$NR^{17}R^{18}$, -$S(O)_{0-2}R^{17}$, -$S(O)_2NR^{17}R^{17}$, -$C(O)OR^{17}$, -$C(O)NR^{17}R^{17}$, -$N(R^{17})SO_2R^{17}$, -$N(R^{17})C(O)R^{17}$, -$N(R^{17})C(O)OR^{17}$, -$C(O)R^{17}$, -$C(O)SR^{17}$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, -$O(CH_2)_n$aryl, -$O(CH_2)_n$heteroaryl, -$(CH_2)_{0-5}$(aryl), -$(CH_2)_{0-5}$(heteroaryl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -$CH_2(CH_2)_{0-4}$-T^2, an optionally substituted C_{1-4} alkylcarbonyl, C_{1-4} alkoxy, an amino optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy and a saturated or unsaturated three- to seven-membered carboxyclic or heterocyclic group, wherein T^2 is selected from the group consisting of -OH, -OMe, -OEt, -NH_2, -NHMe, -NMe_2, -NHEt and -NEt_2, and wherein the aryl, heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted;

W is selected from the group consisting of O, S and NH;

Z is selected from the group consisting of O, or S and NH;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano, or nitro, wherein C_1-C_6 alkyl is optionally substituted, or

X and X^1 taken together with the atom to which they are attached, form a C_3-C_7 cycloalkyl;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of hydrogen, halo, trihalomethyl, -CN, -NO_2, -NH_2, -OR^{17}, -$NR^{17}R^{18}$, -$C(O)OR^{17}$, -$C(O)R^{17}$, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^{17} is selected from the group consisting of H and R^{18};

R^{18} is selected from the group consisting of a C_1-C_6alkyl, an aryl, a, aryl(C_1-C_6alkyl), a heterocyclyl and a heterocyclyl(C_1-C_6alkyl), each of which is optionally substituted, or

R^{17} and R^{18}, taken together with a common nitrogen to which they are attached, form an optionally substituted five- to seven-membered heterocyclyl, the optionally substituted five- to seven-membered heterocyclyl optionally containing at least one additional annular heteroatom selected from the group consisting of N, O, S and P;

R^{16} is selected from the group consisting of -H, -CN, -$(CH_2)_{0-5}$(aryl), -$(CH_2)_{0-5}$(heteroaryl), C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -$CH_2(CH_2)_{0-4}$-T^2, an optionally substituted C_{1-4} alkylcarbonyl, and a saturated or unsaturated three- to seven-membered carboxyclic or heterocyclic group, wherein T^2 is selected from the group consisting of -OH, -OMe, -OEt, -NH_2, -NHMe, -NMe_2, -NHEt and -NEt_2, and wherein the aryl, heteroaryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted;

D is selected from the group consisting of CH_2, O, S, NH, N-(C_1-C_6 alkyl), or N-Y-(aryl), -N-OMe, -NCH_2OMe and -N-Bn;

Q is selected from the group consisting of C-E and N;

L is N, or CR, wherein R is selected from the group consisting of -H, halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

E is selected from the group consisting of E^1, E^2 and E^3, wherein

E^1 is selected from the group consisting of -H, halogen, nitro, azido, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$C(O)NR^{42}R^{43}$, -Y-$NR^{42}R^{43}$, -$NR^{42}C(=O)R^{43}$, -SO_2R^{42}, -$SO_2NR^{42}R^{43}$, -$NR^{37}SO_2R^{42}$, -$NR^{37}SO_2NR^{42}R^{43}$, -$C(=N\text{-}OR^{42})R^{43}$, -$C(=NR^{42})R^{43}$, -$NR^{37}C(=NR^{42})R^{43}$, -

$C(=NR^{42})NR^{37}R^{43}$, $-NR^{37}C(=NR^{42})NR^{37}R^{43}$, $-C(O)R^{42}$, $-CO_2R^{42}$, -C(O)(heterocyclyl), -C(O)(C_6-C_{10} aryl), -C(O)(heteroaryl), -Y-(C_6-C_{10} aryl), -Y-(heteroaryl), -Y-(5-10 membered heterocyclic), $-NR^{6a}R^{6b}$, $-NR^{6a}SO_2R^{6b}$, $-NR^{6a}C(O)R^{6b}$, $-OC(O)R^{6b}$, $-NR^{6a}C(O)OR^{6b}$, $-OC(O)NR^{6a}R^{6b}$,$-OR^{6a}$, $-SR^{6a}$, $-S(O)R^{6a}$, $-SO_2R^{6a}$, $-SO_3R^{6a}$, $-SO_2NR^{6a}R^{6b}$, $-SO_2NR^{42}R^{43}$, $-COR^{6a}$, $-CO_2R^{6a}$, $-CONR^{6a}R^{6b}$, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)fluoroalkoxy, $-(CZ^3Z^4)_aCN$, wherein n is an integer ranging from 0 to 6, and the aforementioned E^1 groups other than -H and halogen are optionally substituted by 1 to 5 independently selected R^{38}, or E^1 is selected from a moiety selected from the group consisting of -$(CZ^3Z_4)_a$-aryl, $-(CZ^3Z^4)_a$-heterocycle, (C_2-C_6)alkynyl, $-(CZ^3Z^4)_a$-(C_3-C_6)cycloalkyl, $-(CZ^3Z^4)_a$-(C_5-C_6)cycloalkenyl, (C_2-C_6) alkenyl and (C_1-C_6)alkyl, which is optionally substituted with 1 to 3 independently selected Y^2 groups, where a is 0,1, 2, or 3, and wherein when a is 2 or 3, the CZ^3Z^4 units may be the same or different; wherein each R^{38} is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-NR^{36}R^{39}$, $-OR^{37}$, $-SO_2NR^{36}R^{39}$, C_1-C_6 alkyl, $-(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nOR^{37}$, $-S(O)_j$(C_1-C_6 alkyl), $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(C_5-C_{10} heteroaryl), $-(CH_2)_n$(5-10 membered heterocyclyl); $-C(O)(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_nO(CH_2)_j$(C_6-C_{10} aryl), $-(CH_2)_nO(CH_2)_i$(5-10 membered heterocyclyl), $-C(O)(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_jNR^{39}CH_2C(O)NR^{36}R^{39}$, $-(CH_2)_jNR^{39}(CH_2)_iNR^{37}C(O)R^{40}$, $-(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_jNR^{39}(CH_2)_iS(O)_j$($C_1$-$C_6$ alkyl), $-(CH_2)_jNR^{39}(CH_2)_nR^{36}$, $-SO_2(CH_2)_n$(C_6-C_{10} aryl), $-SO_2(CH_2)_n$(5-10 membered heterocyclyl), $-(CH_2)_nNR^{36}R^{39}$, $-NR^{37}SO_2NR^{36}R^{39}$, SO_2R^{36}, C_2-C_6 alkenyl, C_3-C_{10} cycloalkyl and C_1-C_6 alkylamino, wherein j is an integer ranging from 0 to 2, n is an integer ranging from 0 to 6, i is an integer ranging from 0 to 6, the $-(CH_2)_i$- and $-(CH_2)_n$- moieties of the foregoing R^{38} groups optionally include a carbon-carbon double or triple bond where n is an integer between 2 and 6, and the alkyl, aryl, heteroaryl and heterocyclyl moieties of the foregoing R^{38} groups are optionally substituted by one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5-10

membered heterocyclyl), $-(CH_2)_nO(CH_2)_iOR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6;

each R^{42} and R^{43} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, -Y-(C_3-C_{10} cycloalkyl), -Y-(C_6-C_{10} aryl), -Y-(C_6-C_{10} heteroaryl), -Y-(5-10 membered heterocyclic), $-Y-O-Y^1-OR^{37}$, $-Y^1-CO_2-R^{37}$, and $-Y-OR^{37}$, wherein the alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclic moieties of the foregoing R^{42} and R^{43} groups are optionally substituted by 1 or more substituents independently selected from R^{44}, wherein

Y is a bond or is $-(C(R^{37})(H))_n$,

n is an integer ranging from 1 to 6, and

Y^1 is $-(C(R^{37})(H))_n$, or

R^{42} and R^{43} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted by 1 to 5 R^{44} substituents, with the proviso that R^{42} and R^{43} are not both bonded to the nitrogen directly through an oxygen;

each R^{44} is independently selected from the group consisting of halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-NR^{36}R^{39}$, $-OR^{37}$, $-SO_2NR^{36}R^{39}$, $-SO_2R^{36}$, $-NR^{36}SO_2R^{39}$, $-NR^{36}SO_2NR^{37}R^{41}$, C1-$C_6$ alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, $-C_1$-C_6 alkylamino, $-(CH_2)_jO(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nOR^{37}$, $-S(O)_j(C_1$-C_6 alkyl), $-(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_n$(5-10 membered heterocyclic), $-C(O)(CH_2)_n(C_6$-C_{10} aryl), $-(CH_2)_nO(CH_2)j(C_6$-C_{10} aryl), $-(CH_2)_nO(CH_2)_i$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_jNR^{39}(CH_2)_iNR^{36}R^{39}$, $-(CH_2)_jNR^{39}CH_2C(O)NR^{36}R^{39}$, $-(CH_2)_jNR^{39}(CH_2)_iNR^{37}C(O)R^{40}$, $-(CH_2)_jNR^{39}(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_jNR^{39}(CH_2)_iS(O)_j(C_1$-$C_6$ alkyl), $-(CH_2)_jNR^{39}(CH_2)_nR^{36}$, $-SO_2(CH_2)_n(C_6$-C_{10} aryl), and $-SO_2(CH_2)_n$(5 to 10 membered heterocyclic) wherein, j is an integer from 0 to 2, n is an integer from 0 to 6 and i is an integer ranging from 2 to 6, the $-(CH_2)_i$- and $-(CH_2)_{n1}$- moieties of the foregoing R^{44} groups optionally include a carbon-carbon double or triple bond wherein n is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{44} groups are optionally substituted by 1 or more substituents

independently selected from the group consisting of halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-OC(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{36}C(O)R^{39}$, $-C(O)NR^{36}R^{39}$, $-(CH_2)_nNR^{36}R^{39}$, $-SO_2R^{36}$, $-SO_2NR^{36}R^{39}$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$ and $-(CH_2)_nOR^{37}$, wherein n is an integer from 0 to 6 and i is an integer from 2 to 6; and

each R^{40} is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_n$(C_6-C_{10} aryl), C_3-C_{10} cycloalkyl, and $-(CH_2)_n$(5-10 membered heterocyclic), wherein n is an integer ranging from 0 to 6;

each R^{36} and R^{39} is independently selected from the group consisting of H, -OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5-10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$, $-(CH_2)_nCN(CH_2)_nOR^{37}$, $-(CH_2)_nCN(CH_2)_nR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{36} and R^{39} groups are optionally substituted by one or more substituents independently selected from -OH, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{40}$, $-C(O)OR^{40}$, $-CO(O)R^{40}$, $-OC(O)OR^{40}$, $-NR^{37}C(O)R^{41}$, $-C(O)NR^{37}R^{41}$, $-NR^{37}R^{41}$, $-C_1$-C_6 alkyl, $-(CH_2)_n$(C_6-C_{10} aryl), $-(CH_2)_n$(5 to 10 membered heterocyclic), $-(CH_2)_nO(CH_2)_iOR^{37}$, and $-(CH_2)_nOR^{37}$, wherein n is an integer ranging from 0 to 6 and i is an integer ranging from 2 to 6, with the proviso that when R^{36} and R^{39} are both attached to the same nitrogen, then R^{36} and R^{39} are not both bonded to the nitrogen directly through an oxygen;

each R^{37} and R^{41} is independently selected from the group consisting of H, OR^{36}, C_1-C_6 alkyl and C_3-C_{10} cycloalkyl;

each R^{6a} and R^{6b} is independently selected from the group consisting of hydrogen, $-(CZ^5Z^6)_u$-(C_3-C_6)cycloalkyl, $-(CZ^5Z^6)_u$-(C_5-C_6)cycloalkenyl, $-(CZ^5Z^6)_u$-aryl, $-(CZ^5Z^6)_u$-heterocycle, (C_2-C_6)alkenyl, and (C_1-C_6)alkyl, which is optionally substituted with 1 to 3 independently selected Y^3 groups, where u is 0,1, 2, or 3, and wherein when u is 2 or 3, the CZ^5Z^6 units may be the same or different, or

R^{6a} and R^{6b} taken together with adjacent atoms can form a heterocycle;

each Z^3, Z^4, Z^5 and Z^6 is independently selected from the group consisting of H, F and (C_1-C_6)alkyl, or

each Z^3 and Z^4, or Z^5 and Z^6 are selected together to form a carbocycle, or

two Z^3 groups on adjacent carbon atoms are selected together to optionally form a carbocycle;

each Y^2 and Y^3 is independently selected from the group consisting of halogen, cyano, nitro, tetrazolyl, guanidino, amidino, methylguanidino, azido, $-C(O)Z^7$, $-OC(O)NH_2$, $-OC(O)NHZ^7$, $-OC(O)NZ^7Z^8$, $-NHC(O)Z^7$, $-NHC(O)NH_2$, $-NHC(O)NHZ^7$, $-NHC(O)NZ^7Z^8$, $-C(O)OH$, $-C(O)OZ^7$, $-C(O)NH_2$, $-C(O)NHZ^7$,$-C(O)NZ^7Z^8$, $-P(O)_3H_2$, $-P(O)_3(Z^7)_2$, $-S(O)_3H$, $-S(O)Z^7$, $-S(O)_2Z^7$, $-S(O)_3Z^7$, $-Z^7$, $-OZ^7$, $-OH$, $-NH_2$, $-NHZ^7$, $-NZ^7Z^8$, $-C(=NH)NH_2$,$-C(=NOH)NH_2$, -N-morpholino, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)haloalkyl, (C_2-C_6)haloalkenyl, (C_2-C_6)haloalkynyl, (C_1-C_6)haloalkoxy, $-(CZ^9Z^{10})_rNH_2$, $-(CZ^9Z^{10})_rNHZ^3$, $-(CZ^9Z^{10})_rNZ^7Z^8$, $-X^6(CZ^9Z^{10})_r-(C_3-C_8)$cycloalkyl, $-X^6(CZ^9Z^{10})_r-(C_5-C_8)$cycloalkenyl, $-X^6(CZ^9Z^{10})_r$-aryl and $-X^6(CZ^9Z^{10})_r$-heterocycle, wherein

r is 1, 2, 3 or 4;

X^6 is selected from the group consisting of O, S, NH, -C(O)-, -C(O)NH-, -C(O)O-, -S(O)-, $-S(O)_2-$ and $-S(O)_3-$;

Z^7 and Z^8 are independently selected from the group consisting of an alkyl of 1 to 12 carbon atoms, an alkenyl of 2 to 12 carbon atoms, an alkynyl of 2 to 12 carbon atoms, a cycloalkyl of 3 to 8 carbon atoms, a cycloalkenyl of 5 to 8 carbon atoms, an aryl of 6 to 14 carbon atoms, a heterocycle of 5 to 14 ring atoms, an aralkyl of 7 to 15 carbon atoms, and a heteroaralkyl of 5 to 14 ring atoms, or

Z^7 and Z^8 together may optionally form a heterocycle;

Z^9 and Z^{10} are independently selected from the group consisting of H, F, a (C_1-C_{12})alkyl, a (C_6-C_{14})aryl, a (C_5-C_{14})heteroaryl, a (C_7-C_{15})aralkyl and a (C_5-C_{14})heteroaralkyl, or

Z^9 and Z^{10} are taken together form a carbocycle, or

two Z^9 groups on adjacent carbon atoms are taken together to form a carbocycle; or

any two Y^2 or Y^3 groups attached to adjacent carbon atoms may be taken together to be $-O[C(Z^9)(Z^{10})]_rO$ or $-O[C(Z^9)(Z^{10})]_{r+1}$, or

any two Y^2 or Y^3 groups attached to the same or adjacent carbon atoms may be selected together to form a carbocycle or heterocycle; and wherein

any of the above-mentioned substituents comprising a CH_3 (methyl), CH_2 (methylene), or CH (methine) group which is not attached to a halogen, SO or SO_2 group or to a N, O or S

atom optionally bears on said group a substituent selected from hydroxy, halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy and an -N[(C_1-C_4)alkyl][(C_1-C_4)alkyl];

E^2 is -C≡CH or -C≡C-($CR^{45}R^{45}$)$_n$-R^{46};

R^{45} is independently selected from the group consisting of H, a (C_1-C_6)alkyl and a (C_3-C_8)cycloalkyl;

R^{46} is selected from the group consisting of heterocyclyl, -N(R^{47})-C(O)-N(R^{47})(R^{48}), -N(R^{47})-C(S)-N(R^{47})(R^{48}), -N(R^{47})-C(O)-OR^{48}, -N(R^{47})-C(O)-(CH_2)$_n$-R^{48}, -N(R^{47})-SO_2R^{47}, -(CH_2)$_n$N$R^{47}R^{48}$, -(CH_2)$_n$OR^{48}, -(CH_2)$_n$SR^{49}, -(CH_2)$_n$S(O)R^{49}, -(CH_2)$_n$S(O)$_2R^{49}$, -OC(O)R^{49}, -OC(O)OR^{49}, -C(O)N$R^{47}R^{48}$, heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -(CH_2)$_n$N$R^{50}R^{51}$, and aryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -(CH_2)$_n$N$R^{50}R^{51}$;

R^{47} and R^{48} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, heterocyclyl, -(CH_2)$_n$N$R^{50}R^{51}$, -(CH_2)$_n$OR^{50}, -(CH_2)$_n$C(O)R^{49}, -C(O)$_2R^{49}$, -(CH_2)$_n$SR^{49}, -(CH_2)$_n$S(O)R^{49}, -(CH_2)$_n$S(O)$_2R^{49}$, -(CH_2)$_n$$R^{49}$, -($CH_2$)$_n$CN, aryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -(CH_2)$_n$OR^{49}, -(CH_2)$_n$heterocyclyl, -(CH_2)$_n$heteroaryl, -SO_2R^{50} and -(CH_2)$_n$N$R^{50}R^{51}$, and heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -(CH_2)$_n$OR^{49}, -(CH_2)$_n$heterocyclyl, -(CH_2)$_n$heteroaryl, -SO_2R^{50} and -(CH_2)$_n$N$R^{50}R^{51}$, or

R^{47} and R^{48}, together with the atom to which they are attached, form a 3-8 membered ring;

R^{49} is selected from the group consisting of (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, heterocyclyl(C_1-C_6)alkylene, aryl(C_1-C_6)alkylene wherein the aryl is optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -(CH_2)$_n$N$R^{50}R^{51}$, heteroaryl(C_1-C_6)alkylene wherein the heteroaryl is optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and -(CH_2)$_n$N$R^{50}R^{51}$, aryl optionally substituted with one or more substituents selected from the group consisting of halo, -CF_3, (C_1-C_6)alkoxy, -NO_2, (C_1-C_6)alkyl, -CN, -SO_2R^{50} and

$-(CH_2)_nNR^{50}R^{51}$, and heteroaryl optionally substituted with one or more substituents selected from the group consisting of halo, $-CF_3$, (C_1-C_6)alkoxy, $-NO_2$, (C_1-C_6)alkyl, -CN, $-SO_2R^{50}$ and $-(CH_2)_nNR^{50}R^{51}$;

R^{50} and R^{51} are independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl and $-C(O)R^{45}$, or

R^{50} and R^{51}, together with the atom to which they are attached, form a 3-8 membered ring; and

E^3 is the group defined by $-(Z^{11})-(Z^{12})_m-(Z^{13})_{m1}$, wherein

Z^{11} is heterocyclyl or heterocyclylene;

Z^{12} is selected from the group consisting of OC(O), OC(S) and C(O);

Z^{13} is selected from the group consisting of heterocyclyl, aralkyl, $N(H)R^{52}$, (C_1-C_3)alkyl, $-OR^{52}$, halo, $S(O)_2R^{56}$, (C_1-C_3)hydroxyalkyl and (C_1-C_3)haloalkyl;

m is 0 or 1;

m1 is 0 or 1;

R^{52} is selected from the group consisting of H, $-(CH_2)_qS(O)_2R^{54}$, $R^{55}NR^{53}R^{53}$, (C_1-C_3)alkyl, $-(CH_2)_qOR^{53}$, $-C(O)R^{54}$ and $-C(O)OR^{53}$;

q is 0, 1, 2, 3 or 4;

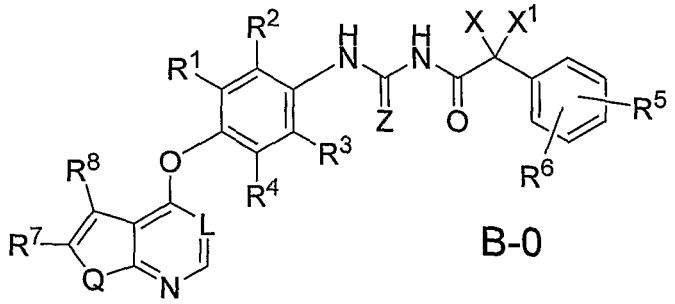
R^{53} is (C_1-C_3)alkyl;

R^{54} is (C_1-C_3)alkyl or $N(H)R^{53}$;

R^{55} is (C_1-C_6) alkyl; and

R^{56} is selected from the group consisting of NH_2, (C_1-C_3)alkyl and OR^{52}.

163. The compound according to claim 161, represented by the formula B-0:



B-0

and pharmaceutically acceptable salts and complexes thereof, wherein

Z is O or S;

X and X^1 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, cyano, or nitro, wherein C_1-C_6 alkyl is optionally substituted;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

Q is O, S, NH, N(C_1-C_6 alkyl), or N-Y-(aryl);

L is N, or CR, wherein R is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl are optionally substituted; and

R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -C(=O)NR^9R^{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$ and CO_2R^9, wherein C_1-C_6 alkyl, aryl, heterocyclyl and heteroaryl are each optionally substituted;

R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11}, and -Y-O-R^{11}, wherein C_1-C_6 alkyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl are each optionally substituted, or

R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted;

R^8 is selected from the group consisting of H, halo and C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted;

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y^1 is -$(C(R^{11})(H))_t$-, and

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted.

164. The compound according to claim 162, wherein X and X^1 are both hydrogen.

165. The compound according to claim 162, wherein R^1 is hydrogen or halogen.

166. The compound according to claim 162, wherein R^1 is fluorine.

167. The compound according to claim 162, wherein R^4 is hydrogen or halogen.

168. The compound according to claim 162, wherein R^4 is fluorine.

169. The compound according to claim 162, wherein R^2, R^3, R^5, and R^6 are each hydrogen.

170. The compound according to claim 162, wherein Q is S, N(C_1-C_6 alkyl), or N-Y-(aryl).

171. The compound according to claim 162, wherein L is CH or N.

172. The compound according to claim 162, wherein R^8 is selected from the group consisting of H, halo and C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted with OH or $NR^{14}R^{15}$, where R^{14} and R^{15} are independently H or C_1-C_6 alkyl, or R^{14} and R^{15} are taken together with the nitrogen to which they are attached to form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted.

173. The compound according to claim 162, wherein R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$CONR^9R^{10}$, -SO_2NH_2, -$SO_2NR^9R^{10}$, -Y-heterocycle -Y-heteroaryl, -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl and -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocycle, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

174. The compound according to claim 162, wherein R^7 is -$CONR^9R^{10}$.

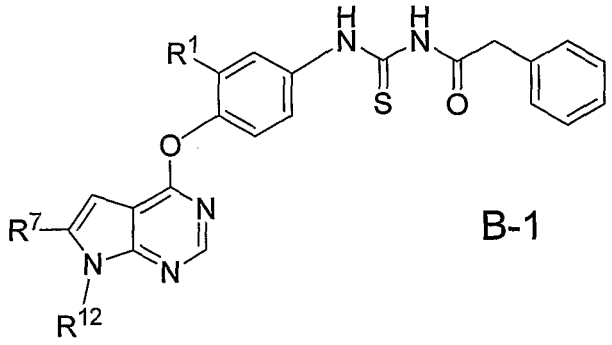
175. The compound according to claim 173, wherein R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-O-R^{11}, -Y-(heterocycle), -Y^1-CO_2-R^{11} and -Y-(aryl), wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocycle, and aryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

176. The compound according to claim 173, wherein R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said ring is unsubstituted or is substituted with one or two of alkoxy, alkyl, or haloalkyl.

177. The compound according to claim 162, wherein R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -$SO_2NR^9R^{10}$, -C(=O)(heterocyclyl), -Y-(heterocyclyl), -Y-(heteroaryl), -S-aryl, -S-C_1-C_6 alkyl, -SO-C_1-C_6 alkyl and -SO_2-C_1-C_6 alkyl, wherein C_1-C_6 alkyl is unsubstituted or is substituted with one or two of hydroxy or halogen, and the heterocyclyl, and heteroaryl are unsubstituted or are substituted with one or two of alkoxy, alkyl, or haloalkyl.

178. The compound according to claim 162, wherein Z is sulfur.

179. The compound according to claim 161, represented by the formula B-1:



B-1

and pharmaceutically acceptable salts and complexes thereof, wherein

R^1 is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl, wherein C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl are optionally substituted;

R^7 is selected from the group consisting of H, halogen, C_1-C_6 alkyl, -C(=O)NR_9R_{10}, -C(=O)(aryl), -C(=O)(heterocyclyl), -C(=O)(heteroaryl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-NR^9R^{10}, -$SO_2NR^9R^{10}$ and CO_2R^9, wherein C_1-C_6 alkyl, aryl, heterocycle and heteroaryl are each independently optionally substituted;

R^9 and R^{10} are independently selected from the group consisting of H, C_1-C_6 alkyl, -Y-(cycloalkyl), -Y-(aryl), -Y-(heterocyclyl), -Y-(heteroaryl), -Y-O-Y^1-O-R^{11}, -Y^1-CO_2-R^{11}, and -Y-O-R^{11}, wherein C_1-C_6 alkyl, cycloalkyl, aryl, heterocycle, and heteroaryl are each optionally substituted, or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a C_5-C_9 heterocyclyl ring or a heteroaryl ring, wherein said ring is optionally substituted;

Y is a bond or is -$(C(R^{11})(H))_t$-, wherein t is an integer from 1 to 6;

Y_1 is -$(C(R^{11})(H))_t$-;

R^{11} at each occurrence is independently H or C_1-C_6 alkyl, wherein C_1-C_6 alkyl is optionally substituted; and

R^{12} is selected from the group consisting of H, C_1-C_6 alkyl and -Y-(aryl), wherein C_1-C_6 alkyl and aryl are optionally substituted.

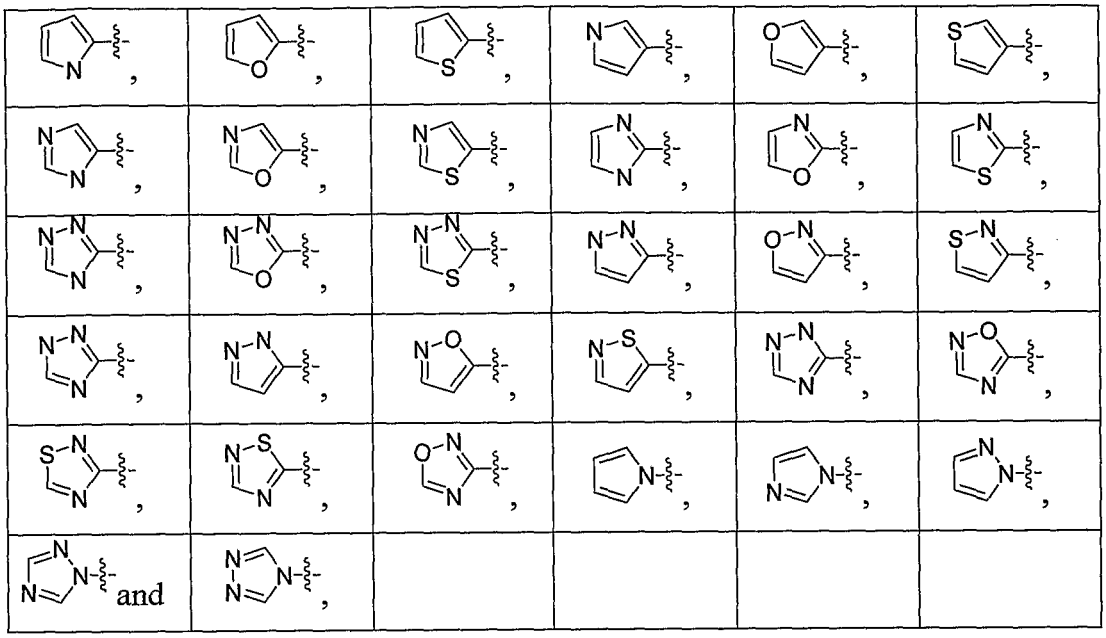
180. The compound according to claim 178, wherein R^1 is hydrogen or halogen.

181. The compound according to claim 178, wherein R^1 is fluorine.

182. The compound according to claim 178, wherein R^{12} is unsubstituted C_1-C_3 alkyl or unsubstituted benzyl.

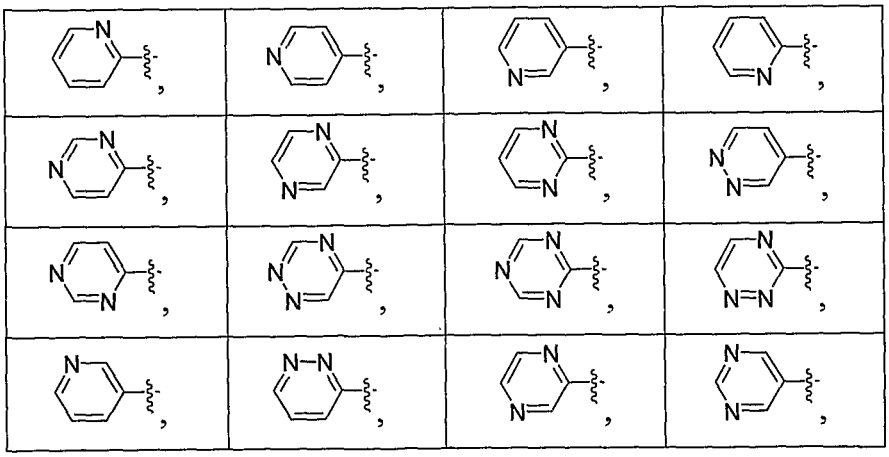
183. The compound according to claim 178, wherein R^7 is -C(O)NR^9R^{10}.

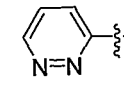
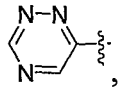
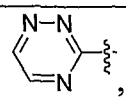
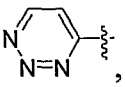
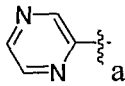
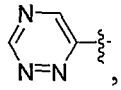
184. The compound according to claim 178, wherein R^7 is selected from the group consisting of



wherein the members of said group are optionally substituted by 1 to 3 independently selected R^{38}.

185. The compound according to claim 178, wherein R^7 is selected from the group consisting of



			
 and			

wherein the members of said group are optionally substituted with 1 to 3 independently selected R^{38}.

186. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.

187. A pharmaceutical compositioin comprising the compound according to claim 161 and a pharmaceutically acceptable carrier.

188. A method of inhibiting VEGF receptor signaling and HGF receptor signaling, the method comprising contacting the receptor with a receptor inhibiting amount of a compound according to claim 1.

189. A method of inhibiting VEGF receptor signaling and HGF receptor signaling, the method comprising contacting the receptor with a receptor inhibiting amount of a compound according to claim 161.

190. A method of inhibiting VEGF receptor signaling and HGF receptor signaling in a cell, the method comprising contacting the cell with a receptor inhibiting amount of a compound according to claim 1.

191. A method of inhibiting VEGF receptor signaling and HGF receptor signaling in a cell, the method comprising contacting the cell with a receptor inhibiting amount of a composition according to claim 185.

192. A method of inhibiting VEGF receptor signaling and HGF receptor signaling in a cell, the method comprising contacting the cell with a receptor inhibiting amount of a compound according to claim 161.

193. A method of inhibiting VEGF receptor signaling and HGF receptor signaling in a cell, the method comprising contacting the cell with a receptor inhibiting amount of a composition according to claim 186.

194. A method of inhibiting VEGF receptor signaling and HGF receptor signaling in an animal, the method comprising administering to the animal a receptor inhibiting amount of a composition according to claim 185.

195. A method of inhibiting VEGF receptor signaling and HGF receptor signaling in an animal, the method comprising administering to the animal a receptor inhibiting amount of a composition according to claim 186.

196. The method of claim 193, wherein the animal is a human.

197. The method of claim 194, wherein the animal is a human.

198. A method of inhibiting proliferative activity of a cell, the method comprising contacting the cell with an effective proliferative inhibiting amount of a compound according to claim 1.

199. A method of inhibiting proliferative activity of a cell, the method comprising contacting the cell with an effective proliferative inhibiting amount of a compound according to claim 161.

200. A method of treating a cell proliferative disease in a patient, the method comprising administering to the patient in need of such treatment an effective therapeutical amount of a composition according to claim 185.

201. A method of treating a cell proliferative disease in a patient, the method comprising administering to the patient in need of such treatment an effective therapeutical amount of a composition according to claim 186.

202. The method of claim 199, wherein the patient is a human.

203. The method of claim 201, wherein the cell proliferative disease is cancer.

204. The method of claim 200, wherein the patient is a human.

205. The method of claim 203, wherein the cell proliferative disease is cancer.

206. A method of inhibiting tumor growth in a patient, the method comprising administering to the patient in need thereoof an effective therapeutical amount of a composition according to claim 185.

207. A method of inhibiting tumor growth in a patient, the method comprising administering to the patient in need thereof an effective therapeutical amount of a composition according to claim 186.

208. The method of claim 205, wherein the patient is a human.

209. The method of claim 206, wherein the patient is a human.