COMPOUNDS AS TYROSINE KINASE MODULATORS

Inventors: Xialing Guo and Zhen Zhu

CROSS REFERENCE TO RELATED APPLICATIONS

The present invention claims priority under 35 U.S.C. 119(e) to United States Provisional Application Nos. 61/239,603, filed on Sep 03, 2009, 61/306,616, filed on Feb 22, 2010, 61/356,699 filed on June 21, 2010 and 61/360,531 filed on July 01, 2010, all of which are expressly incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention is directed to novel compounds with multiple aromatic components capable of modulating, regulating and/or inhibiting tyrosine kinase signal transduction. The present invention is also directed to methods of prevention and/or treatment of disorders related to unregulated tyrosine kinase signal transduction, including but not limited to, cell growth disorders, metabolic disorders, blood vessel proliferative disorders, inflammatory disorders, neurodegenerative diseases and immune disorders.

BACKGROUND OF THE INVENTION

Protein tyrosine kinases ("PTKs") play an important role in the control of cell growth and differentiation. PTKs comprise a large and diverse class of proteins having enzymatic activity. PTKs can be of the receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular). For example, signal transduction mediated by receptor tyrosine kinases ("RTKs") is initiated by extracellular interaction with a specific growth factor (i.e., a ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic homeostasis, and responses to the extracellular microenvironment).

With respect to RTKs, it has been shown also that tyrosine phosphorylation sites function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Several intracellular substrate proteins that associate with RTKs have been identified and are divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack a catalytic domain but serve as adapters and associate with catalytically active molecules. The specificity of the interactions between receptors or proteins and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. These observations suggest that the function of each RTK is determined not only by its pattern of expression and ligand availability, but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

The RTKs comprise a large family of transmembrane receptors with diverse biological activities. The intrinsic function of RTKs is activated upon ligand binding, which results in phophorylation of the receptor and multiple cellular substrates, and subsequently in a variety of cellular responses. At present, at least nineteen distinct RTK subfamilies have been identified. One RTK subfamily, designated the HER subfamily, is believed to be comprised of EGFR, HER2, HER3 and HER4. Ligands to the HER subfamily of receptors include epithelial growth factor (EGF), TGF-α, amphiregulin, HB-EGF, betacellulin and heregulin. The second subfamily of RTKs, designated the insulin subfamily, is comprised of the INS-R, the IGF-1R and the IR-R. The third RTK subfamily, the "PDGF" family, includes the PDGF α and β receptors, CSFIR, c-kit and FLK-II. Another subfamily of RTKs, identified as the FLK family, is believed to be comprised of the kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1), the fetal liver kinase 4 (FLK-4) and the fms-like tyrosine kinase 1 (flt-1). Each of these receptors was initially believed to be a receptor for hematopoietic growth factors. Two other subfamilies of RTKs have been designated as the FGF receptor family (FGFR1, FGFR2, FGFR3 and FGFR4) and the Met subfamily (c-met and Ron). Because of the similarities between the PDGF and FLK subfamilies, the two

subfamilies are often considered together. The known RTK subfamilies are identified in Plowman et al, 1994, DN&P 7(6): 334-339, which is incorporated herein by reference.

The non-receptor tyrosine kinases represent a collection of cellular enzymes which lack extracellular and transmembrane sequences. At present, over twenty-four individual non-receptor tyrosine kinases, comprising eleven subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack and LIMK) have been identified. At present, the Src subfamily of non-receptor tyrosine kinases is comprised of the largest number of PTKs, and include Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. A more detailed discussion of non-receptor tyrosine kinases is provided in Bolen, 1993, Oncogen 8: 2025-2031, which is incorporated herein by reference.

Many of the protein tyrosine kinases (PTKs), whether an RTK or non-receptor tyrosine kinase, have been found to be involved in cellular signaling pathways leading to cellular signal cascades and pathogenic conditions such as cancer, psoriasis and hyper immune responses. In view of the importance of PTKs to the control, regulation and modulation of cell proliferation and the diseases and disorders associated with abnormal cell proliferation, many attempts have been made to identify receptor and non-receptor tyrosine kinase "inhibitors" using a variety of approaches, including the use of mutant ligands (U.S. Patent No. 4,966,849), soluble receptors and antibodies (Kendall & Thomas, 1994, Proc. Nat'l Acad. Sci 90: 10705-09; Kim, et al, 1993, Nature 362: 841-844), RNA ligands (Jellinek, et al, Biochemistry 33: 10450-56); Takano, et al, 1993, Mol. Bio. Cell 4:358A; Kinsella, et al, 1992, Exp. Cell Res. 199: 56-62; Wright, et al, 1992, J. Cellular Phys. 152: 448-57) and tyrosine kinase inhibitors (U.S. Patent No. 5,330,992; Mariani, et al, 1994, Proc. Am. Assoc. Cancer Res. 35: 2268).

More recently, attempts have been made to identify small molecules which act as tyrosine kinase inhibitors. For example, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT Application No. WO 92/20642), vinylene-azaindole derivatives (PCT Application No. WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolones (U.S. Patent No. 5,330,992) have been described generally as tyrosine kinase inhibitors. Styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1), seleoindoles and selenides (PCT Application No. WO 94/03427), tricyclic polyhydroxylic compounds (PCT Application No. WO 92/21660) and benzylphosphonic acid compounds (PCT

Application No. WO 91/15495) have been described as compounds for use as tyrosine kinase inhibitors for use in the treatment of cancer.

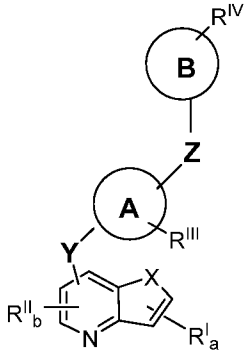
In addition, other small molecules were studied as tyrosine kinase inhibitors, such as the compounds disclosed in U.S. Pat. Nos. 6,765,012; 6,541,504; 6,747,025; 5,792,783; 5,834,504; 5,883,113; 5,883,116 and 5,886,020, all of which are incorporated by reference in their entireties.

The identification and use of compounds which specifically inhibit signal transduction by modulating the activity of receptor and non-receptor tyrosine is one aspect of the present invention.

SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by Formula I capable of modulating, regulating and/or inhibiting tyrosine kinase signal transduction, and uses of the compounds and compositions incorporating the compounds for disease treatment and prevention.

The compounds of the present invention can be found in general Formula I:



Formula I

wherein

X is selected from the group consisting of NR^1, O, $S(O)_n$;

n is 0 or an integer of from 1 to 2;

R^1 is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, CF_3, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N R^2R^3), wherein R^2 and R^3 are independently selected from

the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

R^I is selected from the group consisting of hydrogen, halogen, C_1 to C_8 alkyl, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5 R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5 R^6)_dOSO_2R^4$, $S(O)_f(CR^5 R^6)_eOSO_2R^4$, $(CR^5 R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5 R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N=S(O)R^5 R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f (CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each R^4 is independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_8 alkyl, aryl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of R^5; wherein R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, hydroxyl, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and CR^5R^6 may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate;

a is 0 or an integer of from 1 to 3;

d is 0 or an integer of from 1 to 5;

e is an integer of from 1 to 4;

f is 0 or an integer of from 1 to 2;

R^{II} is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, (NR^2R^3)alkoxy, (NR^2R^3)alkenyl, (NR^2R^3)alkyl, (NR^2R^3)carbonylalkenyl, and (NR^2R^3)carbonylalkyl, wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of

(1) —(CH_2)g—O—(CH_2)h—;
(2) —(CH_2)g—NR^1—(CH_2)h—;
(3) —(CH_2)g— CO—(CH_2)h—;
(4) —(CH_2)g— C(O)NR^2—(CH_2)h—;
(5) —(CH_2)g— NR^2C(O)—(CH_2)h—;
(6) —(CH_2)g—(CH_2)h—;
(7) —(CH_2)g—CH(OH)—(CH_2)h—;
(8) —(CH_2)g—C═C—(CH_2)h—;
and (9) a single bond;

wherein

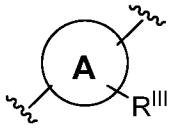
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

R^1 is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, CF_3, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N R^2R^3), wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

R^2 is selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl;

Ring A is selected from the group consisting of:



(i) Phenyl;

(ii) Naphthyl;

(iii) A 5 or 6 membered monocyclic heteroaryl group which has 1-5 heteroatoms independently selected from the group consisting of O, N and S;

and (iv) An 8 to 10 membered bicyclic heteroaryl group which has 1-6 heteroatoms independently selected from the group consisting of O, N and S;

R^{III} represents optionally 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 alkoxy, hydroxy, amino, C_1-C_5 alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)S(O)_2$;

and (6') $S(O)_2N(R^8)(CH_2)_j$;

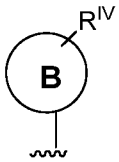
wherein

i is 0 or 1;

j is 0 or 1;

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl.

Ring B is selected from the group consisting of:



(i') Phenyl;

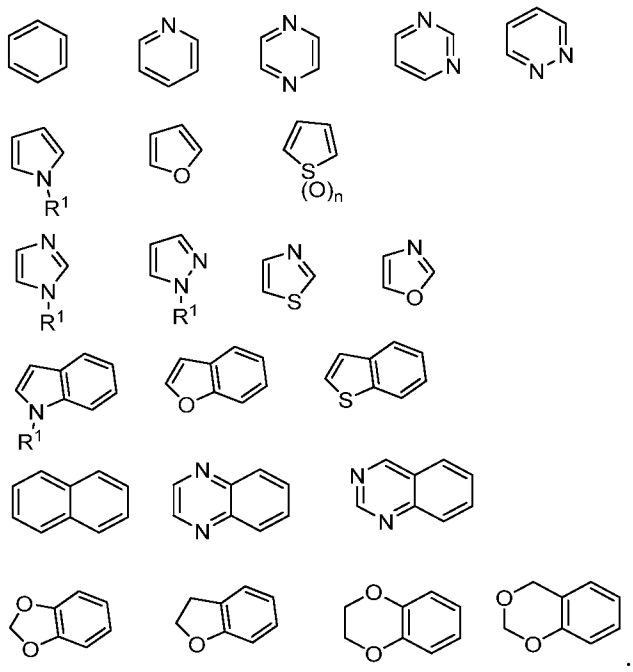
(ii') Naphthyl;

(iii') A 5 or 6 membered monocyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;
and (iv') An 8 to 10 membered bicyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;

R^{IV} represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —NR^9R^{10}; wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl.

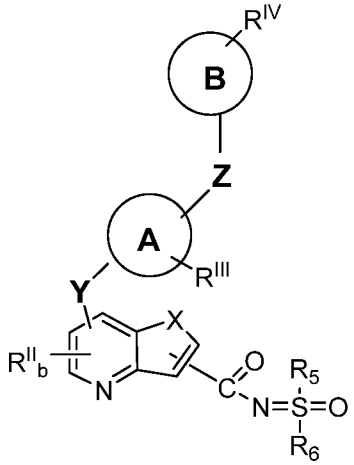
Some embodiments of the present invention are included in the following paragrpahs:

1) A compound according to Formula I, including any tautomer, stereoisomer, diastereoisomeric form, polymorphic form, crystal form, a solvate, a hydrate, a metabolite, a pharmaceutically acceptable salt or prodrug, mixture of different stereoisomers, mixture of different crystal forms.
2) A compound of Formula I in the form of a prodrug.
3) The compound according to paragraph 1, wherein Y is selected from the group consisting of
   (a) —(CH_2)g—C=C—(CH_2)h—;
   (b) —(CH_2)g—NR^1—(CH_2)h—;
   (c) —(CH_2)g— CO—(CH_2)h—;
   (d) —(CH_2)g— C(O)NR^2—(CH_2)h—;
   (e) —(CH_2)g— NR^2C(O)—(CH_2)h—;
   (f) —(CH_2)g—(CH_2)h—;
   (g) —(CH_2)g—CH(OH)—(CH_2)h—;
   (h) —(CH_2)g—O—(CH_2)h—;
   and (i) a single bond.
4) The compound according to paragraphs 1 – 3, wherein Z is selected from the group consisting of $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(O)$, and $C(O)N(R^8)(CH_2)_j$.
5) The compound according to paragraphs 1 – 4, wherein X is NH.
6) The compound according to paragraphs 1 – 5, wherein Ring A and Ring B are independently selected from the group consisting of



7) The compound according to paragraph 6, wherein X is S.

8) The compound according to paragraph 1 , which can be further represented by Formula II:

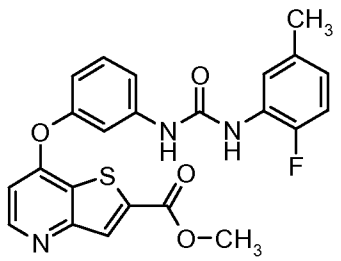


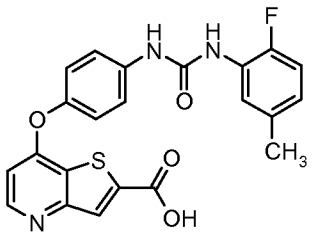
Formula II

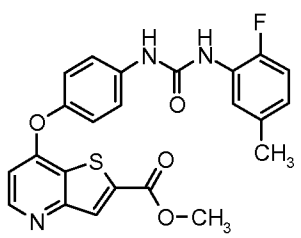
including any tautomer, stereoisomer, diastereoisomeric form, crystal form, polymorphic form, mixture of stereoisomers, mixture of polymorphic forms, mixture of crystal forms, a solvate, a hydrate, a metabolite, a pharmaceutically acceptable salt or a prodrug.

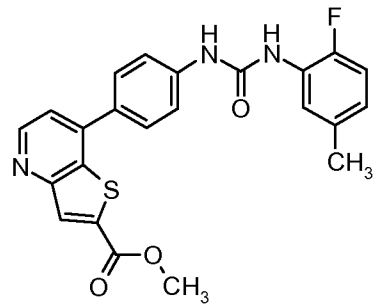
9) The compound according to paragraphs 1 – 8, wherein R^I is selected from the group consisting of hydrogen, halogen, C_1 to C_8 alkyl, $(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $(CR^5\ R^6)_dOR^4$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HNC(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each R^4 is independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_8 alkyl, aryl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of R^5; wherein R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, hydroxyl, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and CR^5R^6 may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate.

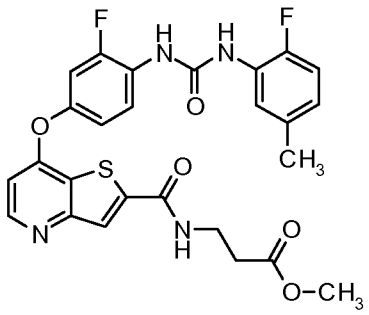
10) A compound selected from the group consisting of

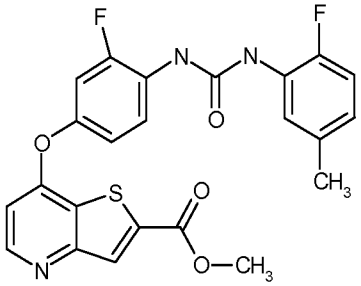


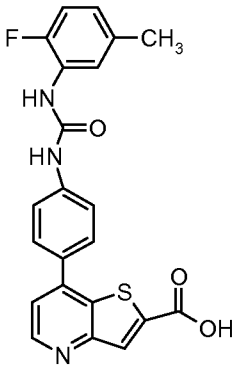


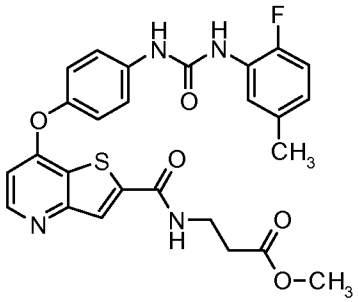


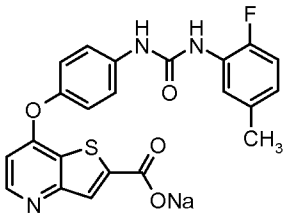


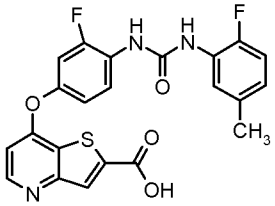


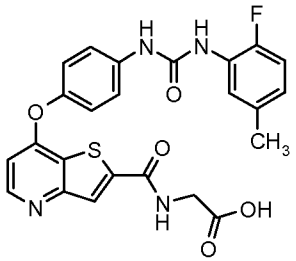


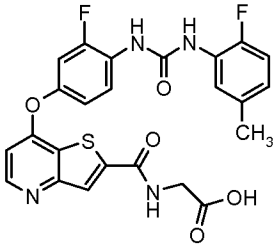


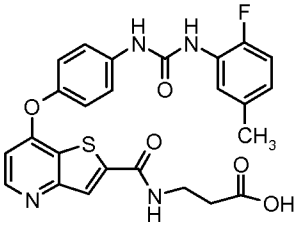


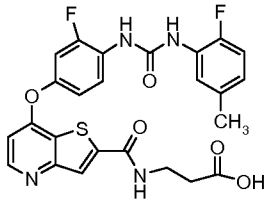


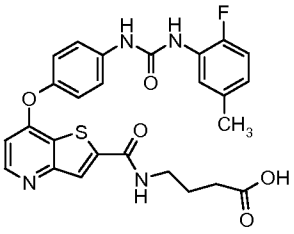


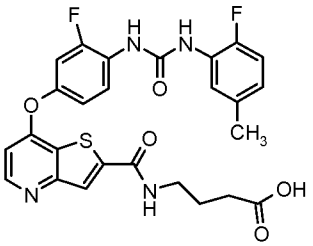


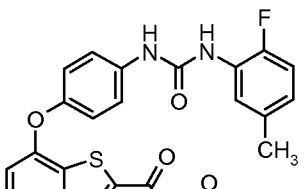


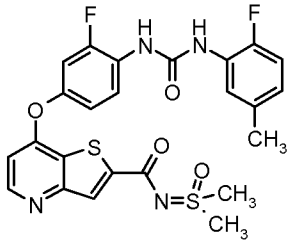


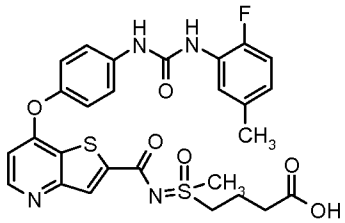


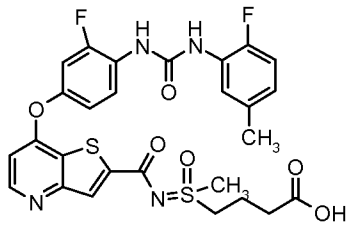












11) A method of use of the compounds of paragraphs 1 – 10, wherein the compounds are used as tyrosine kinase modulators.

12) Use of the compounds of paragraphs 1 – 10 in the preparation of a medicament for the treatment or prevention of diseases or conditions related with unregulated tyrosine kinase activities, comprising administering a therapeutically effective amount of the compound of paragraphs 1 – 10 together with a pharmaceutically acceptable carrier;

13) The use of paragraph 12, wherein the iseases or conditions are selected from the group consisting of cell growth and metabolic disorders, blood vessel proliferative disorders, inflammatory disorders, neurodegenerative diseases, and immune disorders.

14) The use of paragraphs 12 – 13 wherein the diseases or conditions are selected from the group consisting of colorectal cancer, lung cancer, hematological cancer, renal cancer, liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases and immune disorders.

15) A pharmaceutical composition comprising a therapeutic effective amount of a compound according to paragraphs 1 – 10 together with a pharmaceutically acceptable carrier which is suitable for systematic, parenteral, local or topical delivery.

16) The pharmaceutical composition of paragraph 15 which are in the form selected from the group consisting of tablets, capsules, intravenous injections, intramuscular injections, local injections, topical creams, gels and ointments, eye drops, ophthalmic solutions, ophthalmic suspensions, ophthalmic emulsions, intravitreal injections, subtenon

injections, ophthalmic biodrodible implant, and non-bioeordible ophthalmic inserts or depots.

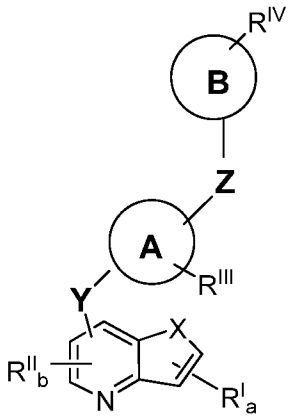
17) Use of the compounds of paragraph 10 in the preparation of a medicament for the treatment of diseases and conditions, wherein the medicament contains a pharmaceutical acceptable composition according to paragraphs 15 and 16.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a series of compounds with multiple aromatic components useful as protein tyrosine kinase inhibitors. The compounds of the present invention are useful for treating diseases related to unregulated tyrosine kinase signal transduction, for example, cancer, blood vessel proliferative disorders, fibrotic disorders, and neurodegenerative diseases. In particular, compounds of the present invention are useful for the treatment of colorectal cancer, lung cancer, hematological cancer, renal cancer, liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases and immune disorders.

1. Compounds of the Invention

The present invention is directed to a compound of Formula I:



Formula I

wherein

X is selected from the group consisting of NR^1, O, $S(O)_n$;

n is 0 or an integer of from 1 to 2;

R^1 is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, CF_3, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N R^2R^3), wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

R^I is selected from the group consisting of hydrogen, halogen, C_1 to C_8 alkyl, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d$ $S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5\ R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5\ R^6)_dOSO_2R^4$, $S(O)_f(CR^5\ R^6)_eOSO_2R^4$, $(CR^5\ R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5\ R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N{=}S(O)R^5\ R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f\ (CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each R^4 is independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_8 alkyl, aryl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of R^5; wherein R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, hydroxyl, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and CR^5R^6 may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of

hydroxyl, halo, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate;

a is 0 or an integer of from 1 to 3;

d is 0 or an integer of from 1 to 5;

e is an integer of from 1 to 4;

f is 0 or an integer of from 1 to 2;

R^{II} is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, (NR^2R^3)alkoxy, (NR^2R^3)alkenyl, (NR^2R^3)alkyl, (NR^2R^3)carbonylalkenyl, and (NR^2R^3)carbonylalkyl, wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of

(1') —(CH_2)g—O—(CH_2)h—;
(2') —(CH_2)g—NR^1—(CH_2)h—;
(3') —(CH_2)g— CO—(CH_2)h—;
(4') —(CH_2)g— C(O)NR^2—(CH_2)h—;
(5') —(CH_2)g— NR^2C(O)—(CH_2)h—;
(6') —(CH_2)g—(CH_2)h—;
(7') —(CH_2)g—CH(OH)—(CH_2)h—;
(8') —(CH_2)g—C=C—(CH_2)h—;
and (9') a single bond;

wherein

g is 0 or an integer of from 1 to 3;

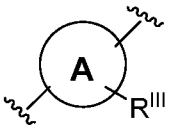
h is 0 or an integer of from 1 to 3;

R^1 is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, CF_3, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N R^2R^3), wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl,

arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively R^2 and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

R^2 is selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl;

Ring A is selected from the group consisting of:



(i) Phenyl;

(ii) Naphthyl;

(iii) A 5 or 6 membered monocyclic heteroaryl group which has 1-5 heteroatoms independently selected from the group consisting of O, N and S;

and (iv) An 8 to 10 membered bicyclic heteroaryl group which has 1-6 heteroatoms independently selected from the group consisting of O, N and S;

R^{III} represents optionally 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 alkoxy, hydroxy, amino, C_1-C_5 alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)S(O)_2$;

and (6') $S(O)_2N(R^8)(CH_2)_j$.

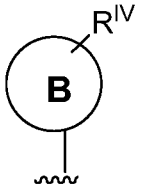
wherein

i is 0 or 1;

j is 0 or 1;

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl;

Ring B is selected from the group consisting of:



(i') Phenyl;

(ii') Naphthyl;

(iii') A 5 or 6 membered monocyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;

and (iv') An 8 to 10 membered bicyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;

R^{IV} represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —NR^9R^{10}; wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl.

Unless otherwise indicated, reference to a compound should be construed broadly to include compounds, pharmaceutically acceptable salts, prodrugs, tautomers, stereoisomers, diastereoisomers, alternate solid forms, crystal forms, polymorphic forms, hydrates, solvates, metabolites, mixtures of stereoisomers, mixtures of crystal forms, non-covalent complexes, and combinations thereof, of a chemical entity of a depicted structure or a chemical name.

A pharmaceutically acceptable salt is any salt of the parent compound that is suitable for administration to an animal or human. A pharmaceutically acceptable salt also refers to any salt which may form *in vivo* as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt. A salt comprises one or more ionic forms of the compound, such as a conjugate acid or base, associated with one or more corresponding counter-ions. Salts can form from or incorporate one or more deprotonated acidic groups (e.g. carboxylic acids), one or more protonated basic groups (e.g. amines), or both (e.g. zwitterions).

A "prodrug" is a compound, which when administered to the body of a subject (such as a mammal), breaks down in the subject's metabolic pathway to provide an active compound of Formula I. More specifically, a prodrug is an active or inactive "masked" compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a subject or patient. One common form of a prodrug is a masked carboxylic acid group. Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bundgaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, Apr. 11, 1981) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.For example, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Prodrug preparation is well known in the art. For example, "Prodrugs and Drug Delivery Systems," which is a chapter in Richard B. Silverman, *Organic Chemistry of Drug Design and Drug Action*, 2d Ed., Elsevier Academic Press: Amsterdam, 2004, pp. 496-557, provides further detail on the subject.

Tautomers are isomers that are in rapid equilibrium with one another. For example, tautomers may be related by transfer of a proton, hydrogen atom, or hydride ion. Unless stereochemistry is explicitly and unambiguously depicted, a structure is intended to include every possible stereoisomer, both pure or in any possible mixture.

Alternate solid forms are different solid forms than those that may result from practicing the procedures described herein. For example, alternate solid forms may be amorphous forms, crystal forms, polymorphs, and the mixtures thereof.

Non-covalent complexes are complexes that may form between the compound and one or more additional chemical species that do not involve a covalent bonding interaction between the compound and the additional chemical species. They may or may not have a

specific ratio between the compound and the additional chemical species. Examples might include solvates, hydrates, charge transfer complexes, and the like.

2. Uses, Formulation and Administration

The present invention is also directed to the use of the compounds as protein tyrosine kinase modulators and inhibitors. These compounds can be used to treat diseases related to unregulated tyrosine kinase signal transduction, for example, various cancers, blood vessel proliferative disorders, fibrotic disorders, and neurodegenerative diseases. In particular, compounds of the present invention are useful for the treatment and/or prevention of colorectal cancer, lung cancer, hematological cancer, renal cancer, liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases and immune disorders in the human being.

The present invention is also directed to the preparation of a medicament for the treatment and prevention of diseases and conditions related with abnormal activities of tyrosine kinase receptors. The medicament contains a pharmaceutical acceptable composition, which comprises the therapeutic effective amount of the compounds of present invention, together with a pharmaceutical acceptable carrier.

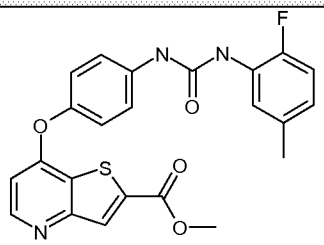
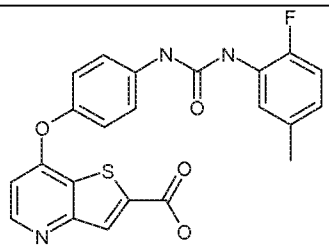
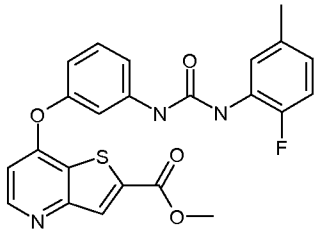
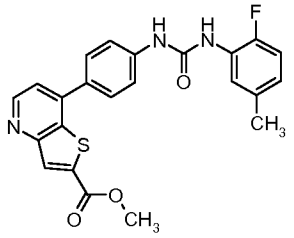
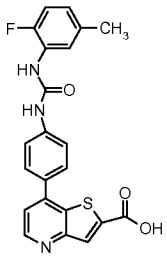
For the purposes of this disclosure, “treat,” “treating,” or “treatment” refer to the diagnosis, cure, mitigation, treatment, or prevention of disease or other undesirable conditions.

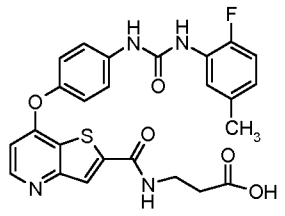
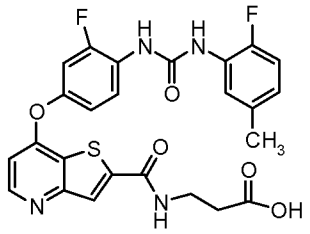
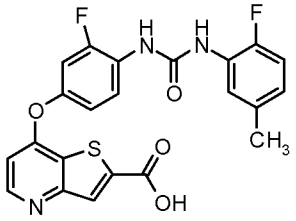
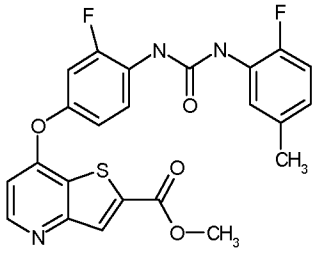
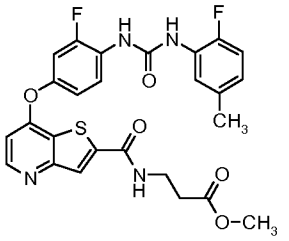
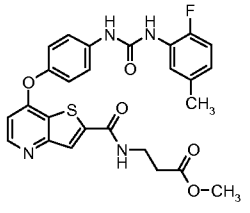
The pharmaceutical acceptable compositions contain therapeutic effective amount of the compounds of the present invention. These compositions can be used as a medicament and administered to a mammal, such as a person, in need thereof. Different types of suitable dosage forms and medicaments are well known in the art, and can be readily adapted for delivery of the compounds of the present invention, such as, but not limited to, systematic, parenteral, local and topical delivery. The dosage forms can be tablets, capsules, intravenous injections, intramuscular injections, local injections, topical creams, gels and ointments, eye drops, ophthalmic solutions, ophthalmic suspensions, ophthalmic emulsions, intravitreal injections, subtenon injections, ophthalmic biodrodible implant, and non-bioeordible

ophthalmic inserts or depots, nasal sprays and ointment, various rectal or vaginal preparations.

3. Examples

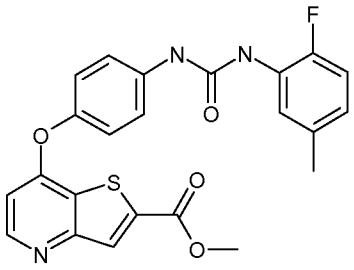
Table 1: Exemplified Compounds of the Present Invention

Compound	Structure	MW	Chemical Name
F1		451	methyl 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylate
F2		437	7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylic acid
F3		451	methyl 7-[3-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylate
F4		435	methyl 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-b]pyridine-2-carboxylate
F5		421	7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-b]pyridine-2-carboxylic acid

F6		509	3-[({7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoic acid
F7		527	3-[({7-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoic acid
F8		455	7-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylic acid
F9		469	methyl 7-(3-fluoro-4-(3-(2-fluoro-5-methylphenyl)ureido)phenoxy)thieno[3,2-b]pyridine-2-carboxylate
F10		541	methyl 3-[({7-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoate
F11		523	methyl 3-[({7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoate

3.1 Compound Synthesis and Characterization

Compound F1
Methyl 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylate

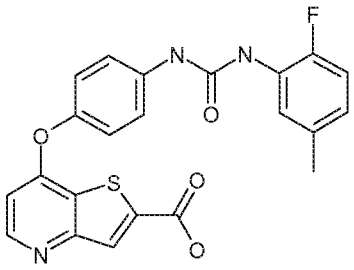


To a stirred solution of methyl 7-bromothieno[3,2-b]pyridine-2-carboxylate (200mg, 0.74mmol) in 8ml of DMSO, were added CuBr (10mg, 0.074mmol), ethyl 2-cyclohexanonecarboxylate (26mg, 0.15mmol), cesium carbonate (500mg, 1.54mmol) and 4-aminophenol (96mg, 0.88mmol). The mixture was purged with nitrogen for 10 minutes, and then heated at 70°C under N_2 for 3 hours. The reaction was cooled to room temperature and poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude aniline intermediate as a pale green solid (~140mg). This crude material was dissolved in 10ml of THF, and 2-fluoro-5-methylphenyl isocyanate (70mg, 0.46mmol) was added. The mixture was stirred at room temperature for 5 hours, and poured into 100ml of water. The brown precipitates were filtered, washed with water and dried to give the crude product, which was purified by silica gel chromatography, eluting with 2-3% MeOH/$CHCl_3$ to give methyl 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylate as light brown solid. Yield: 90mg, 27%.

^{1}H NMR (d_6-DMSO) d: 9.25 (s, 1H), 8.61 (d, J = 5.3 Hz, 1H), 8.50 (br. s., 1H), 8.21 (s, 1H), 7.96 (d, J = 6.7 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.09 (dd, J = 11.4, 8.2 Hz, 1H), 6.71 - 6.85 (m, 2H), 3.91 (s, 3H), 2.26 (s, 3H)
LR MS (ES+): 452 (MH), 474 ($M+Na^+$)
LR MS (ES-): 450 (M-H)

Compound F2

7-[4-({[(2-Fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylic acid



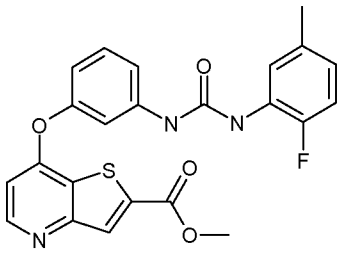
To a stirred suspension of methyl 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)-phenoxy]thieno[3,2-b]pyridine-2-carboxylate (50mg, 0.11mmol) in MeOH (3ml), was added 0.4M LiOH/MeOH solution (10ml, 4.0mmol). The mixture was heated at 50°C for 7 hours, and poured into 100ml of water. 1M HCl was added until pH = 4. The resulting precipitates were filtered, washed with water and dried *in vacuo* to give 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylic acid as light grey solid. Yield: 40mg, 83%.

^{1}H NMR (DMSO-d_6) δ: 13.88 (br. s., 1H), 9.19 (s, 1H), 8.58 (d, J = 5.3 Hz, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.10 (s, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.53 - 7.59 (m, 2H), 7.22 - 7.27 (m, 2H), 7.08 (dd, 1H), 6.77 - 6.80 (m, 1H), 6.73 (d, J = 5.6 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 436 (M-H)

Compound F3

Methyl 7-[3-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylate



prepared using procedures similar to Compound F1.

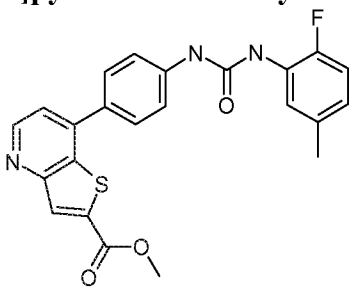
^{1}H NMR (DMSO-d_6) δ: 9.51 (s, 1H), 8.64 (d, J = 5.3 Hz, 1H), 8.60 (s, 1H), 8.21 (s, 1H), 7.87 (dd, J = 7.8, 1.6 Hz, 1H), 7.58 (t, J = 2.1 Hz, 1H), 7.41 (t, J = 8.1 Hz, 1H), 7.23 (dd, J = 8.2, 1.2 Hz, 1H), 7.06 (dd, J = 11.3, 8.4 Hz, 1H), 6.91 (dd, J = 7.9, 1.8 Hz, 1H), 6.85 (d, J = 5.3 Hz, 1H), 6.77 (td, J = 5.2, 2.2 Hz, 1H), 3.91 (s, 3H), 2.21 (s, 3H)

LR MS (ES+): 452 (MH), 474 ($M+Na^+$)

LR MS (ES-): 450 (M-H)

Compound F4

Methyl 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-b]pyridine-2-carboxylate



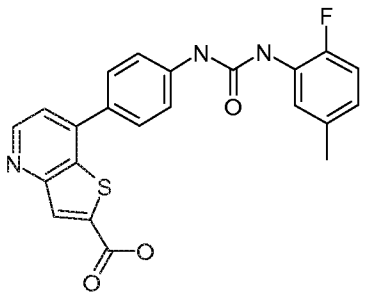
To a mixture of methyl 7-bromothieno[3,2-b]pyridine-2-carboxylate (68mg, 0.25mmol) and 1-(2-fluoro-5-methylphenyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea (102mg, 0.28mmol) in 8ml of 1,4-dioxane, was added $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) and 1M Na_2CO_3 aqueous solution (0.25ml, 0.5mmol). The mixture was heated at 70°C under N_2 for 1 hour, cooled to room temperature and poured into 100ml of water. The brown precipitates were filtered, washed with water and dried to give the crude product, which was purified by silica gel chromatography, eluting with 2-3% MeOH/$CHCl_3$ to give methyl 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-b]pyridine-2-carboxylate as light yellow solid. Yield: 30mg, 28%.

^1H NMR (d_6-DMSO) d: 9.38 (s, 1H), 8.84 (d, J = 4.7 Hz, 1H), 8.58 (d, J = 2.1 Hz, 1H), 8.28 (s, 1H), 7.60 - 8.06 (m, 6H), 7.06 - 7.19 (m, 1H), 6.82 (br. s., 1H), 3.93 (s, 3H), 2.28 (s, 3H)

LR MS (ES-): 434 (M-H)

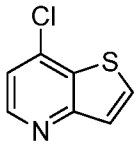
Compound F5

7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-b]pyridine-2-carboxylic acid



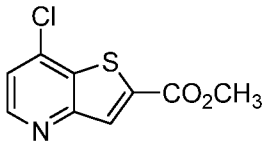
To a stirred solution of methyl 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-b]pyridine-2-carboxylate (20mg, 0.046mmol) in THF/MeOH (5ml/5ml) was added 1M NaOH (2.0ml, 2.0mmol). The mixture was heated at 70°C for 30 minutes, cooled to room temperature and poured into 50ml of water. 1M HCl was added until pH = 4 and the resulting precipitates were filtered, washed with water and dried in vacuo to give 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thieno[3,2-b]pyridine-2-carboxylic acid.
Yield: 20mg, 100%.
LR MS (ES-): 420 (M-H)

Preparation of 7-chlorothieno[3,2-b]pyridine



Thieno[3,2-b]pyridin-7-ol (20 g, 0.132 mol) was suspended in phosphorous oxy chloride (80.9 g, 0.528 mol) and stirred at 100 C for 2 hours. The solution was cooled to room temperature and was poured over ice. The aqueous solution was neutralized with sodium hydroxide and the resulting precipitate was collected by filtration and washed with water. The filter cake was taken up in dichloromethane and dried over magnesium sulfate. The solution was filtered and the filtrate was concentrated to dryness to give 7-chlorothieno[3,2-b]pyridine as a brown liquid which solidified to a beige solid under high vacuum. Yield: 20.4 g (91%); MS $[M+H]^+$ 169.9; ^{1}HNMR ($CDCl_3$) δ: 8.7 (d, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 7.3 (d,1H) ppm.

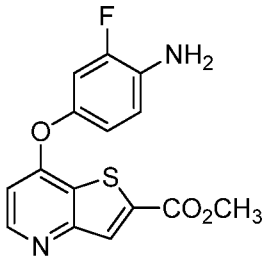
Preparation of methyl 7-chlorothieno[3,2-b]pyridine-2-carboxylate



7-chlorothieno[3,2-b]pyridine (19.7 g, 0.116 mol) was taken up in THF (400 mL) and cooled to approximately -70 C. The *n*-butyllithium (1.6M, 80 mL, 0.128 mol) was added dropwise with stirring under an atmosphere of nitrogen. The solution was stirred at -70 C for 1 hour at which time neat methyl chloroformate was added via dropwise addition. The reaction mixture gradually warmed to room temperature and was stirred for over the weekend. The reaction mixture was treated with 25 mL of methanol and then concentrated to dryness

leaving a maroon residue. The crude solid was taken up in dichloromethane and passed through a silica gel column eluting with 1:1 hexane/ethyl acetate. Fractions containing the product were combined and concentrated to give a red solid. Trituration with 9:1 hexane/diethyl ether afforded methyl 7-chlorothieno[3,2-b]pyridine-2-carboxylate as a pink solid after filtration. Yield: 14.5 g (55%); MS $[M+H]^+$ 227.9; ^{1}HNMR ($CDCl_3$) δ: 8.7 (d, 1H), 8.3 (s, 1H), 7.4 (d, 1H) ppm.

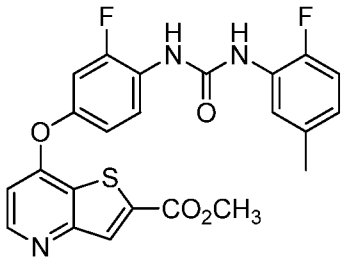
Preparation of methyl 7-(4-amino-3-fluorophenoxy)thieno[3,2-b]pyridine-2-carboxylate



Methyl 7-chlorothieno[3,2-b]pyridine-2-carboxylate (5 g, 0.022 mol) and the 4-amino-3-fluorophenol (3.3 g, 0.026 mol) were added to a round bottom flask containing cesium carbonate (14.8 g, 0.045 mol), ethyl-2-cyclohexanone carboxylate (0.73 g, 0.004 mol), and copper (I) chloride (0.22 g, 0.002 mol). The mixture was diluted with DMSO (250 mL) and stirred at 70 C under an atmosphere of nitrogen for 2 hours. The dark reaction mixture was cooled to room temperature and poured into ethyl acetate (500 mL)/ water (1 L) with vigorous stirring. The mixture was filtered through celite and the organic portion of the filtrate was separated and dried over magnesium sulfate. The solution was filtered and the filtrate was concentrated to give a purple viscous liquid. The crude product was taken up in dichloromethane and passed through a silica gel column eluting with 1:1 hexane /ethyl acetate. Fractions containing the product were combined and concentrated to afford methyl 7-(4-amino-3-fluorophenoxy)thieno[3,2-b]pyridine-2-carboxylate as red solid. Yield: 1.62 g (23 %); MS $[M+H]^+$ 319.1

Compound F9

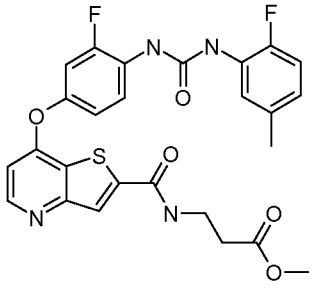
methyl 7-(3-fluoro-4-(3-(2-fluoro-5-methylphenyl)ureido)phenoxy)thieno[3,2-b]pyridine-2-carboxylate



Methyl 7-(4-amino-3-fluorophenoxy)thieno[3,2-b]pyridine-2-carboxylate (1.62 g, 5.1 mmol) was taken up in 55 mL of ethyl acetate followed by the dropwise addition of 2-fluoro-5-methylphenyl isocyanate (0.85 g, 5.6 mmol) in 5 mL ethyl acetate. The solution afforded a lavender solid after stirring at room temperature for overnight. The solid was collected by filtration and washed with diethyl ether to give methyl 7-(3-fluoro-4-(3-(2-fluoro-5-methylphenyl)ureido)phenoxy)thieno[3,2-b]pyridine-2-carboxylate as an off white solid. Yield: 1.75 g (73 %); MS $[M+H]^+$ 470.1; ^{1}HNMR (DMSO-d_6) δ: 9.2 (s, 1H), 9.0 (s, 1H), 8.6 (d, 1H), 8.3 (t, 1H, 8.1 (s, 1H), 8.0 (d, 1H), 7.5 (d, 1H), 7.2 (m, 2H), 6.8 (m, 2H), 3.9 (s, 3H), 2.1 (s, 3H) ppm.

Compound F10

methyl 3-[({7-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino) phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoate



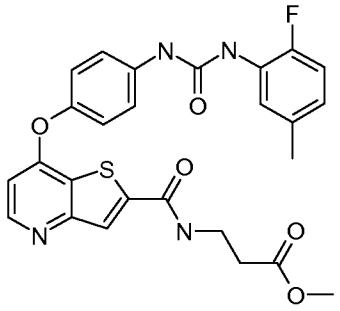
^{1}H NMR (DMSO-d_6) δ: 9.10 (br. s., 1H), 9.03 (t, J = 5.4 Hz, 1H), 8.96 (br. s., 1H), 8.56 (d, J = 5.3 Hz, 1H), 8.26 (t, J = 9.1 Hz, 1H), 8.21 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.40 (dd, J = 11.6, 2.5 Hz, 1H), 7.06 - 7.16 (m, 2H), 6.74 - 6.84 (m, 2H), 3.60 (s, 3H), 3.48 - 3.55 (m, 2H), 2.62 (t, J = 6.9 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 563 $(M+Na^+)$

LR MS (ES-): 539 (M-H)

Compound F11

methyl 3-[({7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino) phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoate



A mixture of 7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylic acid (120mg, 0.27mmol), HATU (122mg, 0.32mmol) and *N,N*-diisopropylethylamine (105mg, 0.81mmol) in anhydrous THF (10ml) was stirred at room temperature for 10 minutes, followed by addition of (R)-3-pyrrolidinol (56mg, 0.40mmol). The mixture was heated and stirred at 60°C for 30 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4. The precipitates were filtered, washed with water and dried *in vacuo* to give methyl 3-[({7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoate as white solid. Yield: 128mg, 90%.

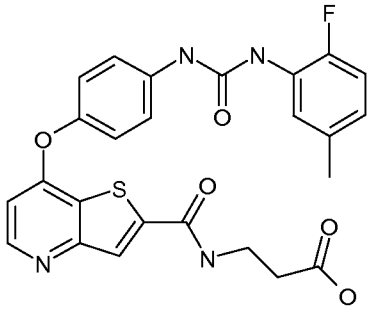
^{1}H NMR (DMSO-d_6) δ: 9.18 (s, 1H), 9.01 (t, 1H), 8.54 (br. s., 1H), 8.47 (br. s., 1H), 8.20 (br. s., 1H), 7.95 (d, J = 6.7 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.08 (dd, J = 11.0, 8.7 Hz, 1H), 6.78 (br. s., 1H), 6.69 (d, J = 5.0 Hz, 1H), 3.60 (s, 3H), 3.46 - 3.55 (m, 2H), 2.62 (t, J = 6.7 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 545 ($M+Na^+$)

LR MS (ES-): 521 (M-H)

Compound F6

3-[({7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoic acid



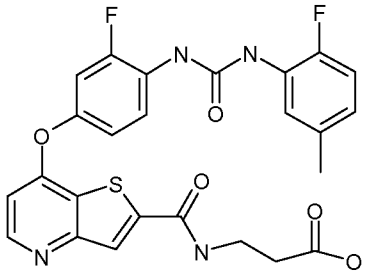
To a stirred solution of methyl 3-[({7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoate (98mg, 0.19mmol) in a mixture of solvents THF/MeOH (10ml/10ml) was added 2ml of 1M NaOH (2mmol) solution. The mixture was stirred at room temperature for 1 hour and poured into 100ml of water. 2M HCl was added until pH = 4. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 3-[({7-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoic acid as off-white solid. Yield: 90mg, 95%.

^{1}H NMR (DMSO-d_6) δ: 12.25 (br. s., 1H), 9.18 (s, 1H), 8.99 (t, J = 5.1 Hz, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.47 (br. s., 1H), 8.21 (s, 1H), 7.95 (d, J = 6.5 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.0, 8.4 Hz, 1H), 6.78 (br. s., 1H), 6.68 (d, J = 5.3 Hz, 1H), 3.42 - 3.53 (m, 2H), 2.53 (t, J = 6.9 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 507 (M-H)

Compound F7

3-[({7-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridin-2-yl}carbonyl)amino]propanoic acid



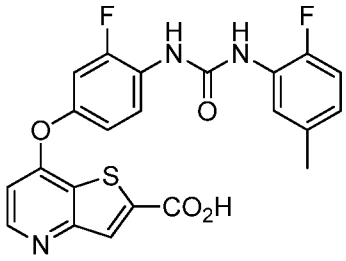
^{1}H NMR (DMSO-d_6) δ: 12.26 (br. s., 1H), 9.09 (br. s., 1H), 9.00 (t, J = 4.7 Hz, 1H), 8.96 (br. s., 1H), 8.56 (d, J = 5.3 Hz, 1H), 8.25 (t, J = 9.0 Hz, 1H), 8.22 (s, 1H), 7.98 (d, J = 7.0 Hz,

1H), 7.35 - 7.44 (m, 1H), 7.05 - 7.16 (m, 2H), 6.71 - 6.85 (m, 2H), 3.42 - 3.54 (m, 2H), 2.53 (t, J = 6.7 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 525 (M-H)

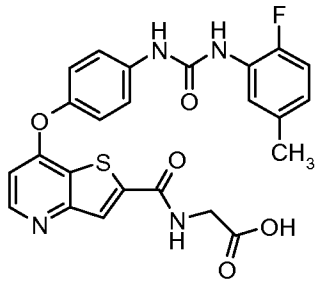
Compound F8

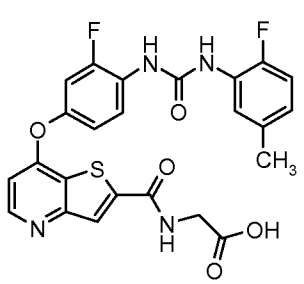
7-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylic acid

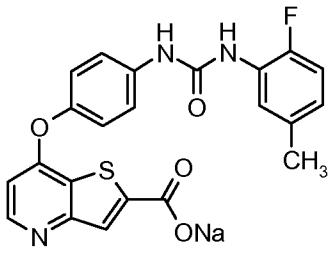


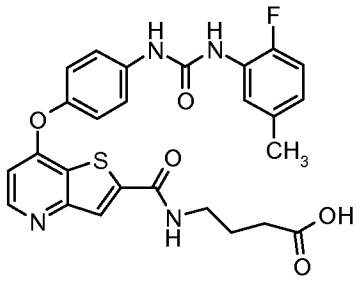
Methyl 7-(3-fluoro-4-(3-(2-fluoro-5-methylphenyl)ureido)phenoxy)thieno[3,2-b]pyridine-2-carboxylate (1.84 g, 3.92 mmol) was taken up in 100 mL THF followed by the dropwise addition of 1N sodium hydroxide (4.8 mL, 4.8 mmol). The solution was stirred at room temperature for 3 hours, at which time an additional 2.4 mL of 1N sodium hydroxide was added. The solution was stirred at room temperature for overnight and the resulting mixture was diluted with 75 mL of water and acidified using 1N HCl. The insoluble material was separated by filtration and the filter cake was suspended in ethyl acetate and stirred for several minutes before filtering. The filter cake was washed several times with ethyl acetate and dried under high vacuum to give 7-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]thieno[3,2-b]pyridine-2-carboxylic acid as an off white solid. Yield: 1.6 g (90 %); MS $[M+H]^+$ 456.1; ^{1}HNMR (DMSO-d_6) δ: 13.9 (bs, 1H),9.2 (s, 1H), 9.0 (s, 1H), 8.6 (d, 1H), 8.3 (t, 1H), 8.1 (s, 1H), 8.0 (d, 1H), 7.5 (d, 1H), 7.2 (m, 2H), 6.8 (m, 2H), 2.1 (s, 3H) ppm.

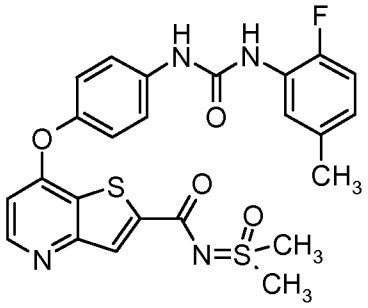
Other compounds which may be made according to the teachings of the present application include:

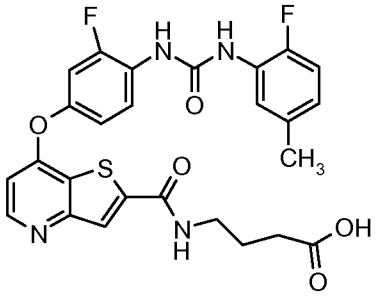


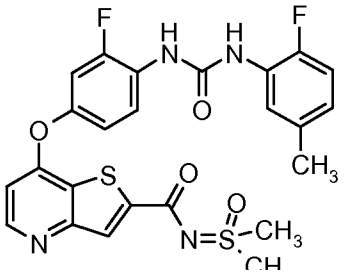


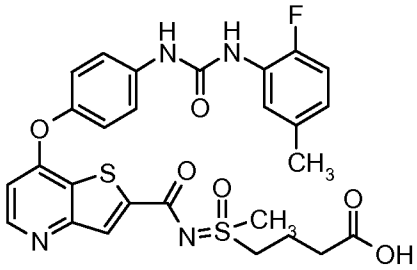


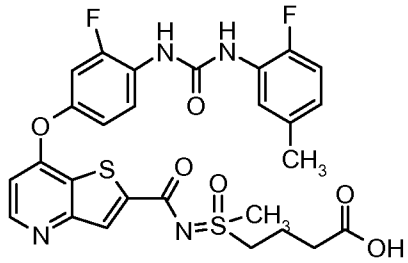












4. Biological Testing

Biological data for the compounds of the present invention was generated by the use of one or more of the following assays.

VEGF Stimulated Ca.sup.++ Signal in Vitro

Automated FLIPR (Fluorometric Imaging Plate Reader) technology was used to screen for inhibitors of VEGF induced increases in intracellular calcium levels in fluorescent dye loaded endothelial cells. HUVEC (human umbilical vein endothelial cells) (Clonetics) were seeded in 96-well fibronectin coated black-walled plates overnight at 37.degree. C./5% CO.sub.2. Cells were loaded with calcium indicator Fluo-4 for 45 minutes at 37.degree. C. Cells were washed 4 times (Original Cell Wash, Labsystems) to remove extracellular dye. Test compounds were reconstituted in 100% DMSO and added to the cells to give a final DMSO concentration of 0.1%. For screening, cells were pre-incubated with test agents for 30 minutes, at a single concentration (10 .mu.M) or at concentrations ranging from 0.01 to 10.0 .mu.M followed by VEGF stimulation (5 ng/mL). Changes in fluorescence at 516 nm were measured simultaneously in all 96 wells using a cooled CCD camera. Data were generated by

determining max-min fluorescence levels for unstimulated, stimulated, and drug treated samples. IC.sub.50 values for test compounds were calculated from % inhibition of VEGF stimulated responses in the absence of inhibitor.

VEGFR2 Kinase Assay

The cytoplasmic domain of the human VEGF receptor (VEGFR-2) was expressed as a Histidine-tagged fusion protein following infection of insect cells using an His engineered baculovirus. His-VEGFR-2 was purified to homogeneity, as determined by SDS-PAGE, using nickel resin chromatography. Kinase assays were performed in 96 well microtiter plates that were coated overnight with 30 .mu.g of poly-Glu-Tyr (4:1) in 10 mM Phosphate Buffered Saline (PBS), pH 7.2-7.4. The plates were incubated with 1% BSA and then washed four times with PBS prior to starting the reaction. Reactions were carried out in 120 .mu.L reaction volumes containing 3.6 .mu.M ATP in kinase buffer (50 mM Hepes buffer pH 7.4, 20 mM MgCl.sub.2, 0.1 mM MnCl.sub.2 and 0.2 mM Na.sub.3 VO.sub.4). Test compounds were reconstituted in 100% DMSO and added to the reaction to give a final DMSO concentration of 5%. Reactions were initiated by the addition 0.5 ng of purified protein. Following a ten minute incubation at 25.degree. C., the reactions were washed four times with PBS containing 0.05% Tween-20. 100 .mu.l of a monoclonal anti-phosphotyrosine antibody-peroxidase conjugate was diluted 1:10000 in PBS-Tween-20 and added to the wells for 30 minutes. Following four washes with PBS-Tween-20, 100 .mu.l of O-phenylenediamine Dihydrochloride in Phosphate-citrate buffer, containing urea hydrogen peroxide, was added to the wells for 7 minutes as a colorimetric substrate for the peroxidase. The reaction was terminated by the addition of 100 .mu.l of 2.5N H.sub.2 SO.sub.4 to each well and read using a microplate ELISA reader set at 492 nm. IC.sub.50 values for compound inhibition were calculated directly from graphs of optical density (arbitrary units) versus compound concentration following subtraction of blank values.

VEGF-induced Dermal Extravasation in Guinea Pig (Miles Assay)

Male Hartley guinea pigs (300-600 g) were anesthetized with isofluorane, sheared, and given a single dose of drug or the respective vehicle. The guinea pigs were dosed orally unless indicated otherwise in Table 3. Ten minutes prior to the end of drug treatment, guinea pigs were anesthetized with isofluorane, and 0.5% Evans blue dye (EBD) in PBS (13-15 mg/kg dose of EBD) was injected intravenously. After 5 minutes, triplicate intradermal injections of 100 ng rhVEGF.sub.165 in 100 .mu.l PBS and of 100 .mu.l PBS alone were

administered on the flank. After 20 minutes, each animal was cuthanized with Pentosol, and the skin containing the intradermal injection sites was removed for image analysis. Using an analog video camera coupled to a PC, an image of each trans-illuminated skin sample was captured, and the integrated optical density of each injection site was measured using ImagePro 4. For each skin sample, the difference between the mean optical density of the VEGF sites and mean optical density of the PBS sites is the measure of VEGF-induced EBD extravasation in that animal. These measured values were averaged per study group to determine the mean VEGF-induced EBD extravasation for each experimental condition, and the group means were then compared to assess inhibition of VEGF-induced EBD extravasation in the drug-treated groups relative to the vehicle-treated controls. To determine the dose required for 50% inhibition (ID.sub.50), the percent inhibition data was plotted as a function of oral dose, using the `best-fit` analysis within MicroSoft Excel software. The ID.sub.50 value was verified visually by using the plotted data (horizontal line from 50% y value, at intersection with best-fit line drop vertical line to x axis (dose).

Laser-induced Choroidal Neovascularization (CNV) in Rat (CNV Assay)

CNV was induced and quantified in this model as previously described (Edelman and Castro. Exp. Eye Res. 2000; 71:523-533). On day 0, male Brown Norway rats (200-300 g) were anesthetized with 100 mg/kg Ketamine and 10 mg/kg Xylazine, and pupils were dilated with 1% Tropicamide. Using the blue-green setting of a Coherent Novus Argon Laser, 3 laser bums (90 mW for 0.1 s; 100 .mu.m diameter) were given to each eye between the retinal vessels around the optic nerve head. Rats were dosed with test compounds in their indicated vehicles orally once daily.

On day 10, rats were sacrificed with 100% CO.sub.2, and blood vessels were labeled by vascular perfusion with 10 mg/ml FITC-dextran (MW 2.times.10.sup.6). Using an epifluorescence microscope (20.times.) coupled to a spot digital camera and a PC, images were obtained from the flat mounts of the RPE-choroid-sclera from each eye, and the area occupied by hyperfluorescent neovessels within each laser lesion was measured using ImagePro 4 software.

To determine the dose required for 50% inhibition (ID.sub.50), the percent inhibition data was plotted as a function of oral dose, using the `best-fit` analysis within MicroSoft Excel software. The ID.sub.50 value was verified visually by using the plotted data (horizontal line from 50% y value, at intersection with best-fit line drop vertical line to x axis (dose).

Rabbit Eye VEGF Permeability Model

Assay used was detailed by Jeffrey Edelman, etc in Exp. Eye. Res. 80(2005), Pg 249-258.

PDGF Stimulated Ca^{2+} Signal in Vitro

Automated FLIPR (Fluorometric Imaging Plate Reader) technology was used to screen for inhibitors of PDGF induced increases in intracellular calcium levels in fluorescent dye loaded endothelial cells. NHDF-Ad (Normal human dermal fibroblasts) (Lonza) were seeded in 384-well fibronectin coated black-walled plates overnight at 37° C/5% CO_2 . Cells were loaded with calcium indicator Fluo-4 for 45 minutes at 37° C. Cells were washed 4 times (ELx405-CW, Bio-Tek) to remove extracellular dye. Test compounds were reconstituted in 100% DMSO and added to the cells to give a final DMSO concentration of 0.1%. For screening, cells were pre-incubated with test agents for 30 minutes, at a single concentration (10 μM) or at concentrations ranging from 0.001nM to 10 μM followed by PDGF stimulation (10 ng/mL). Changes in fluorescence at 515nm were measured simultaneously in all 384 wells using a cooled CCD camera. Data were generated by determining max-min fluorescence levels for unstimulated, stimulated, and drug treated samples. IC_{50} values for test compounds were calculated from % inhibition of PDGF stimulated responses in the absence of inhibitor.

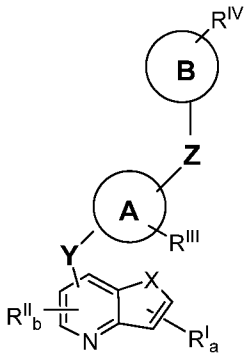
Table II: Biological Activities of Compounds of the Present Invention

Compound	Cellular VEGFR2 IC_{50} (nM)	Enzymic VEGFR2 IC_{50} (nM)	Enzymic VEGFR1 IC_{50} (nM)	In Vivo Rabbit Eye VEGF Permeability
F1	2	18		
F2	29	20	16	efficacious
F3	35	21		
F4	10^4	10^4		
F5	10^4	10^4		

F6		**11**		
F7		**10**		
F8		**11**		

What is claimed is:

1. A compound represented by Formula I:



Formula I

wherein

X is selected from the group consisting of NR^1, O, $S(O)_n$;

n is 0 or an integer of from 1 to 2;

R^1 is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, CF_3, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N R^2R^3), wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

R^I is selected from the group consisting of hydrogen, halogen, C_1 to C_8 alkyl, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d$ $S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5\ R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5\ R^6)_dOSO_2R^4$, $S(O)_f(CR^5\ R^6)_eOSO_2R^4$, $(CR^5\ R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5$ $R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N{=}S(O)R^5\ R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f\ (CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each R^4 is independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_8 alkyl, aryl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-

dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of R^5; wherein R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, hydroxyl, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and CR^5R^6 may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate;

a is 0 or an integer of from 1 to 3;

d is 0 or an integer of from 1 to 5;

e is an integer of from 1 to 4;

f is 0 or an integer of from 1 to 2;

R^{II} is selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, (NR^2R^3)alkoxy, (NR^2R^3)alkenyl, (NR^2R^3)alkyl, (NR^2R^3)carbonylalkenyl, and (NR^2R^3)carbonylalkyl, wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of

(a) $—(CH_2)g—O—(CH_2)h—$;
(b) $—(CH_2)g—NR^1—(CH_2)h—$;
(c) $—(CH_2)g— CO—(CH_2)h—$;
(d) $—(CH_2)g— C(O)NR^2—(CH_2)h—$;
(e) $—(CH_2)g— NR^2C(O)—(CH_2)h—$;
(f) $—(CH_2)g—(CH_2)h—$;
(g) $—(CH_2)g—CH(OH)—(CH_2)h—$;
(h) $—(CH_2)g—C=C—(CH_2)h—$;
and (i) a single bond;

wherein

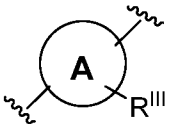
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

R^1 is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, CF_3, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N R^2R^3), wherein R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

R^2 is selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl;

wherein Ring A is selected from the group consisting of:

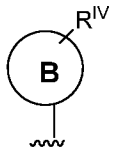


(i) Phenyl;
(ii) Naphthyl;
(iii) A 5 or 6 membered monocyclic heteroaryl group which has 1-5 heteroatoms independently selected from the group consisting of O, N and S;
and (iv) An 8 to 10 membered bicyclic heteroaryl group which has 1-6 heteroatoms independently selected from the group consisting of O, N and S;

R^{III} represents optionally 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 alkoxy, hydroxy, amino, C_1-C_5 alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of
(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;
(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;
(3') $(CH_2)_iN(R^7)C(O)$;
(4') $C(O)N(R^8)(CH_2)_j$;
(5') $(CH_2)_iN(R^7)S(O)_2$;
and (6') $S(O)_2N(R^8)(CH_2)_j$;
wherein:
i is 0 or 1;
j is 0 or 1;
R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl;

wherein Ring B is selected from the group consisting of:



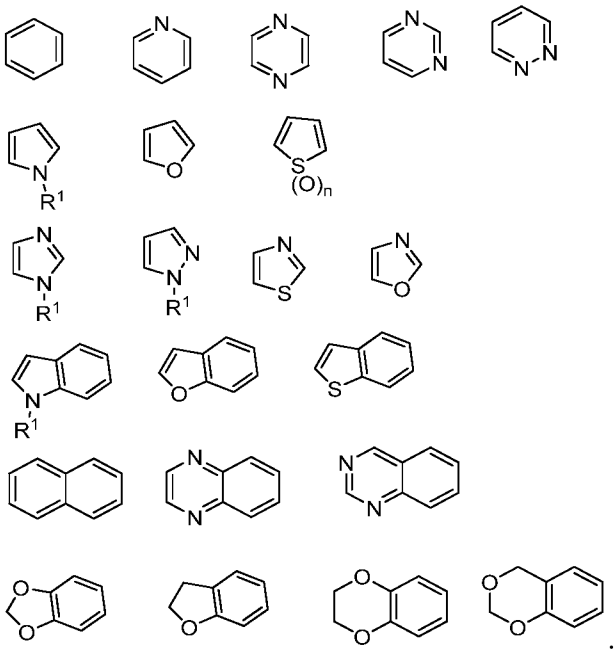
(i') Phenyl;
(ii') Naphthyl;
(iii') A 5 or 6 membered monocyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;
and (iv') An 8 to 10 membered bicyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;

R^{IV} represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —NR^9R^{10}; wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalky;

and including any pharmaceutically acceptable salt or prodrug.

2. A compound according to claim 1, wherein Z is selected from the group consisting of $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ and $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.

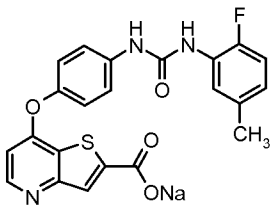
3. A compound according to claim 1, wherein Ring A and Ring B are independently selected from the group consisting of

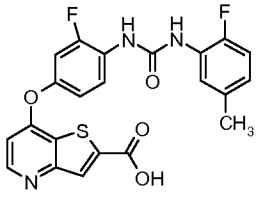


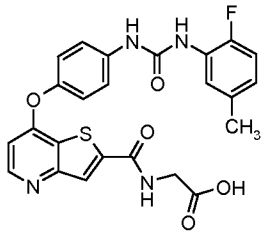
4. A compound according to claim 1, wherein X is S.

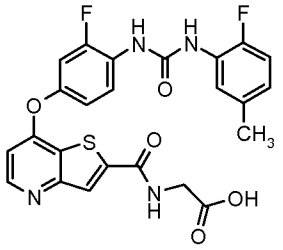
5. A compound according to claim 1, wherein R^I is selected from the group consisting of hydrogen, halogen, C_1 to C_8 alkyl, $(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $(CR^5R^6)_dOR^4$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N=S(O)R^5\ R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each R^4 is independently selected from the group consisting of hydrogen, hydroxyl, C_1-C_8 alkyl, aryl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of R^5; wherein R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, hydroxyl, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and CR^5R^6 may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, C_1-C_8 alkyl, C_1-C_8 hydroxyalkyl, C_1-C_8 alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate.

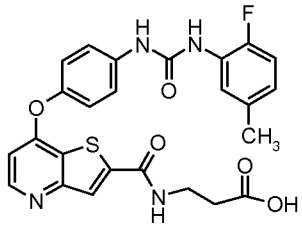
6. A compound according to claim 1, selected from the group consisting of

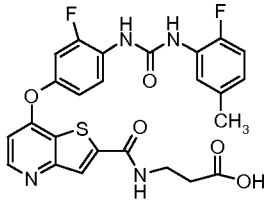


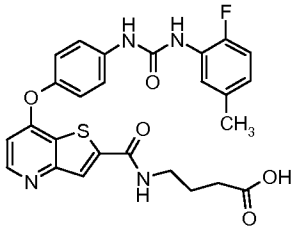


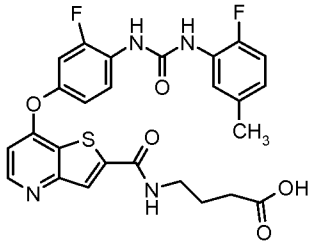


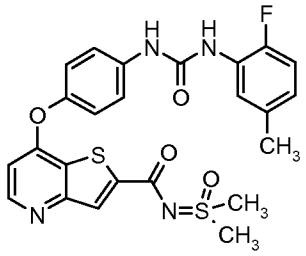


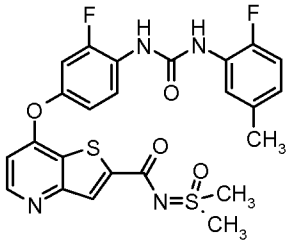


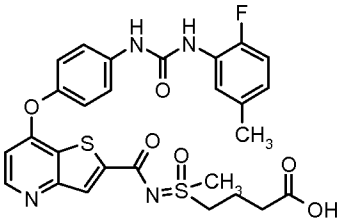


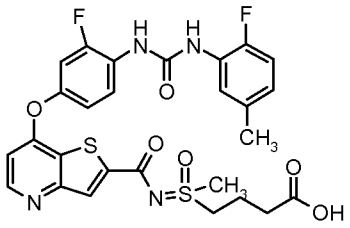


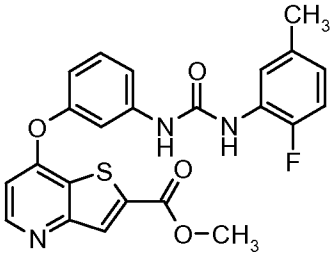


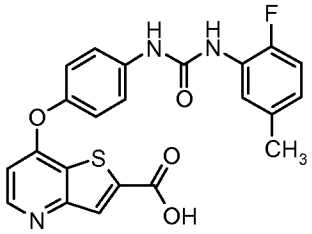


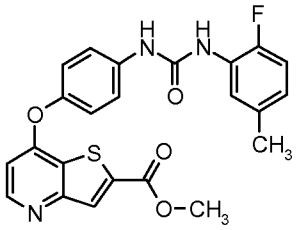


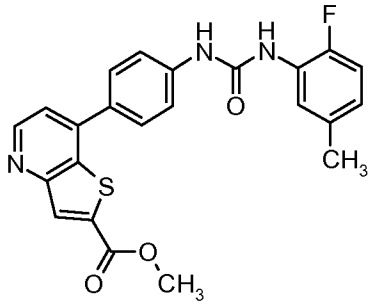


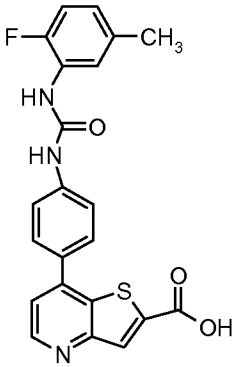


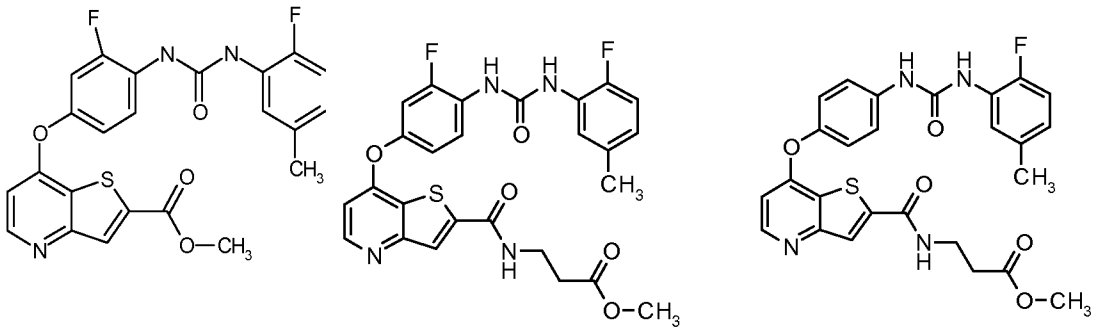












7. The compound of claim 1 for use as a tyrosine kinase inhibitor.

8. The compound according to claim 1, which is used for the treatment of one of the diseases or conditions selected from the group consisting of colorectal cancer, lung cancer, hematological cancer, renal cancer, liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases and immune disorders in the human being.

9. A pharmaceutical composition comprising of a therapeutic effective amount of a compound of claim 1, together with a pharmaceutically acceptable carrier therefor.

10. The composition of claim 9, wherein the composition comprises of tablets, capsules, intravenous injections, intramuscular injections, local injections, topical creams, gels and ointments, eye drops, eye ointments, eye sprays, ophthalmic suspensions, ophthalmic emulsions, intravitreal injections, subtenon injections, ophthalmic biodrodible implant, and non-bioeordible ophthalmic inserts and depots.