COMPOUNDS AS TYROSINE KINASE MODULATORS

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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.

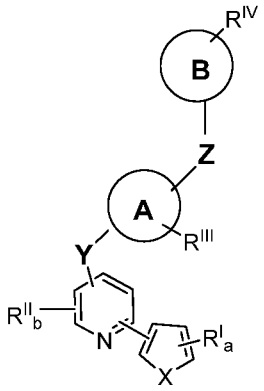
In addition, other small molecules were studied as tyrosine kinase inhibitors, such as the compounds disclosed in U.S. Pat. Nos. 6,765,012; 6,541,504; 6,747,025; 5,792,783; 5,834,504; 5,883,113; 5,883,116 and 5,886,020, all of which are incorporated by reference in their entireties.

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—$S(O)_n$—(CH_2)h—;
(4') —(CH_2)g—$SO_2N\ R^2$—(CH_2)h—;
(5') —(CH_2)g—NR^2SO_2—(CH_2)h—;
(6') —(CH_2)g— CO—(CH_2)h—;
(7') —(CH_2)g— $C(O)NR^2$—(CH_2)h—;
(8') —(CH_2)g— $NR^2C(O\ )$—(CH_2)h—;
(9') —(CH_2)g—C≡C—(CH_2)h—;
(10') —(CH_2)g— $NR^2C(O)NR^3$—(CH_2)h—;
(11') —(CH_2)g—(CH_2)h—;
(12') —(CH_2)g—CF_2—(CH_2)h—;
(13') —(CH_2)g—CCl_2—(CH_2)h—;
(14') —(CH_2)g—CHF—(CH_2)h—;
(15') —(CH_2)g—CH(OH)—(CH_2)h—;
(16') —(CH_2)g—CR^2R^3—(CH_2)h—;
(17') —(CH_2)g—C═C—(CH_2)h—;
and (18') a single bond;

wherein

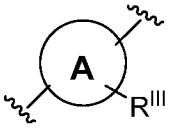
g is 0 or an integer of from 1 to 3;

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 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 cyclic ring;

Ring A is selected from the group consisting of:



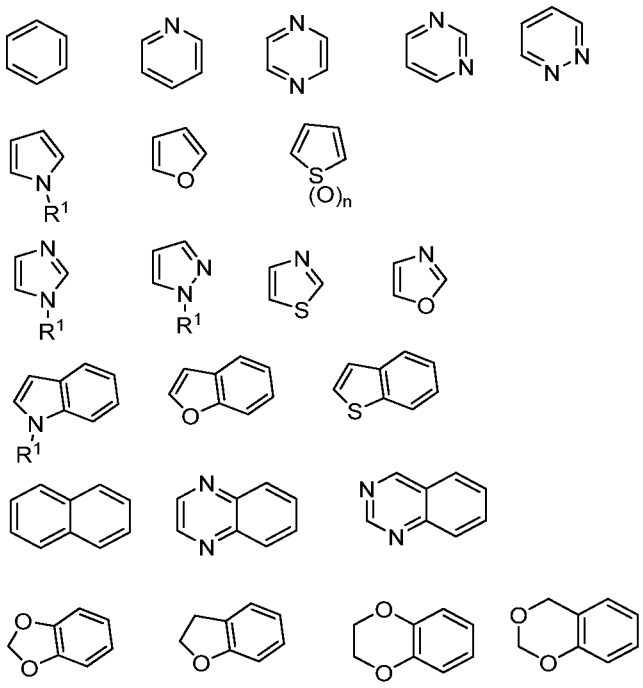
(i) Phenyl;

(ii) Naphthyl;

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

Ring A can be illustrated but not limited to the following:



wherein

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

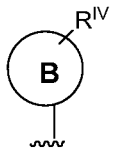
wherein

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:



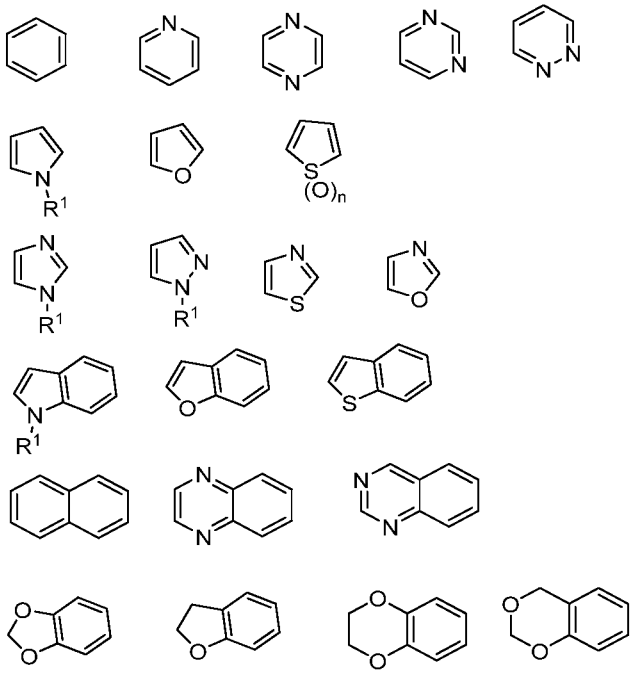
(i') Phenyl;

(ii') Naphthyl;

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

Ring B can be illustrated but not limited to the following:



wherein

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^{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 paragraphs:

(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, and any mixture of different crystal forms.

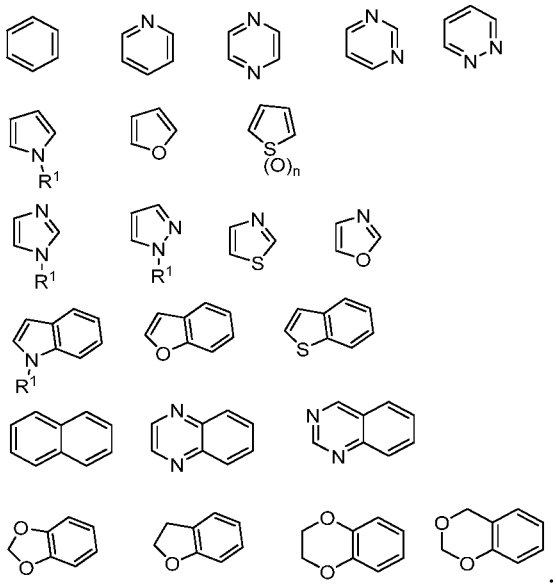
(2) A compound of Formula I in the form of a prodrug.

(3) The compound according to paragraph 1, wherein Z is selected from the group consisting of $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)S(O)_2$ and $S(O)_2N(R^8)(CH_2)_j$.

(4) The compound according to paragraphs 1 – 3, wherein Y is selected from the group consisting of —$(CH_2)g$—O—$(CH_2)h$—; —$(CH_2)g$—NR^1—$(CH_2)h$—;

—$(CH_2)g$—$S(O)_n$—$(CH_2)h$—; —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;
—$(CH_2)g$—NR^2SO_2—$(CH_2)h$—; —$(CH_2)g$— CO—$(CH_2)h$—;
—$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—; —$(CH_2)g$— $NR^2C(O\ )$—$(CH_2)h$—;
—$(CH_2)g$—C≡C—$(CH_2)h$—; —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$ and a single bond.

(5) The compound according to paragraphs 1 – 4, wherein Ring A and Ring B are independently selected from the group consisting of



(6) The compound according to paragraphs 1 – 5, wherein Y is selected from the group consisting of —$(CH_2)g$—$(CH_2)h$—; —$(CH_2)g$—CF_2—$(CH_2)h$—; —$(CH_2)g$—CCl_2—$(CH_2)h$—; —$(CH_2)g$—CHF—$(CH_2)h$—; —$(CH_2)g$—CH(OH)—$(CH_2)h$—;

—$(CH_2)g$—CR^2R^3—$(CH_2)h$—; and —$(CH_2)g$—C=C—$(CH_2)h$—.

(7) The compound according to paragraphs 1 – 6, wherein X is NH.

(8) A compound selected from the group consisting of

(1') [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid;

(2') methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate;

(3') ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid;

(4') methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate;

(5') 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(6') methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(7') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(8') 4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(9) N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy) pyridin-2-yl]-1H-pyrrole-3-carboxamide;

(10) N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(11') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(12') methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(13') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(14') N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(15') N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(16') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(17') N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(18') N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(19') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(20') methyl 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(21') 2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(22') 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(23') methyl 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(24') 2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(25') 2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(26') 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(27') methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(28') 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(29') methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(30') N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(31') N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(32') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(33') methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(34') 3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide;

(35') methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate;

(36') 2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide; and (37') 3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide.

(9) The compound according to paragraph 1, wherein Z is $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ or $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$, provided that when Ring B is pyrazole, R^{IV} is not a phenyl or substituted phenyl.

(10) The compound according to paragraph 9, wherein Y is selected from the group consisting of —(CH_2)g—O—(CH_2)h—; —(CH_2)g—NR^1—(CH_2)h—;

—(CH_2)g—$S(O)_n$—(CH_2)h—; —(CH_2)g—$SO_2N\ R^2$—(CH_2)h—;

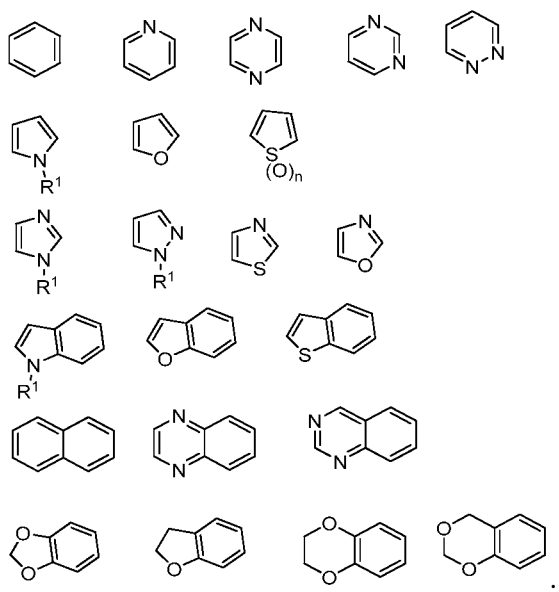
—(CH_2)g—NR^2SO_2—(CH_2)h—; —(CH_2)g— CO—(CH_2)h—;

—(CH_2)g— $C(O)NR^2$—(CH_2)h—; —(CH_2)g— $NR^2C(O\ )$—(CH_2)h—;

—(CH_2)g—C≡C—(CH_2)h—; —(CH_2)g— $NR^2C(O)NR^3$—(CH_2)h, and a single bond.

(11) The compound according to paragraph 9, wherein Y is selected from the group consisting of —(CH_2)g—(CH_2)h—; —(CH_2)g—CF_2—(CH_2)h—; —(CH_2)g—CCl_2—(CH_2)h—; —(CH_2)g—CHF—(CH_2)h—; —(CH_2)g—CH(OH)—(CH_2)h—; —(CH_2)g—CR^2R^3—(CH_2)h—; and —(CH_2)g—C═C—(CH_2)h—.

(12) The compound according to paragraphs 9 – 11, wherein Ring A and Ring B are independently selected from the group consisting of

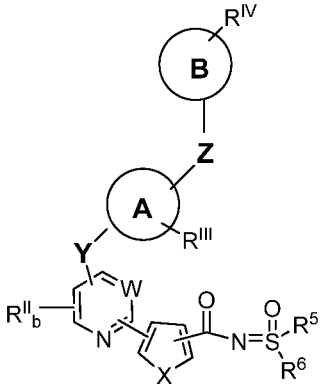


(13) The compound according to paragraphs 9 – 12, wherein X is NH.

(14) The compound according to paragraphs 9 – 12, wherein X is S.

(15) The compound according to paragraphs 9-14, wherein R^I is selected from the group consisting of hydrogen, halogen, C_1 to C_8 alkyl, $(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $(CR^5R^6)_dOR^4$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N=S(O)R^5R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, 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.

(16) A compound of Formula II:



Formula II

wherein

W is C or N;

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

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^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;

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') —$(CH_2)g—S(O)_n—(CH_2)h$—;
(4') —$(CH_2)g—SO_2N\ R^2—(CH_2)h$—;
(5') —$(CH_2)g—NR^2SO_2—(CH_2)h$—;
(6') —$(CH_2)g—\ CO—(CH_2)h$—;
(7') —$(CH_2)g—\ C(O)NR^2—(CH_2)h$—;
(8') —$(CH_2)g—\ NR^2C(O\ )—(CH_2)h$—;
(9') —$(CH_2)g—C\equiv C—(CH_2)h$—;
(10') —$(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h$—;
(11') —$(CH_2)g—(CH_2)h$—;
(12') —$(CH_2)g—CF_2—(CH_2)h$—;
(13') —$(CH_2)g—CCl_2—(CH_2)h$—;
(14') —$(CH_2)g—CHF—(CH_2)h$—;
(15') —$(CH_2)g—CH(OH)—(CH_2)h$—;
(16') —$(CH_2)g—CR^2R^3—(CH_2)h$—;
(17') —$(CH_2)g—C{=}C—(CH_2)h$—;
and (18') a single bond;

wherein

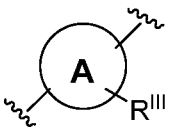
g is 0 or an integer of from 1 to 3;

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 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 cyclic ring;

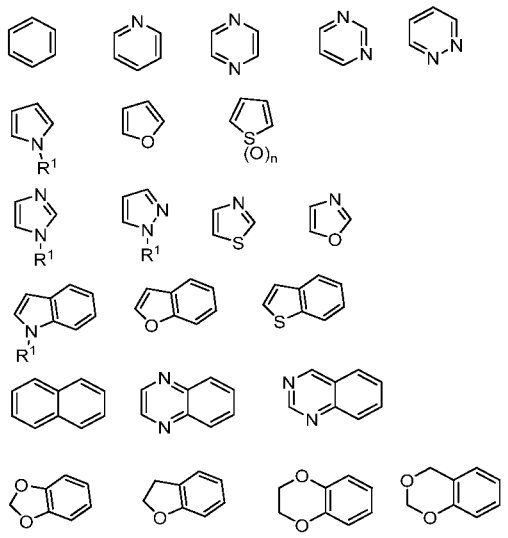
Ring A is selected from the group consisting of:



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

Ring A can be illustrated but not limited to the following:



wherein

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;

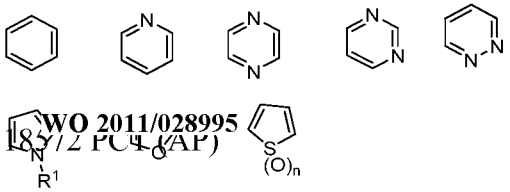
R^{III} represents optionally 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 alkoxy, hydroxy, amino, C_1-C_5 alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

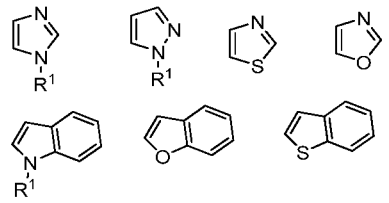
Z is selected from the group consisting of

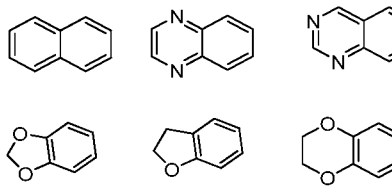
(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;
(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;
(3') $(CH_2)_iN(R^7)C(O)$;
(4') $C(O)N(R^8)(CH_2)_j$;
(5') $(CH_2)_iN(R^7)S(O)_2$;
and (6') $S(O)_2N(R^8)(CH_2)_j$;

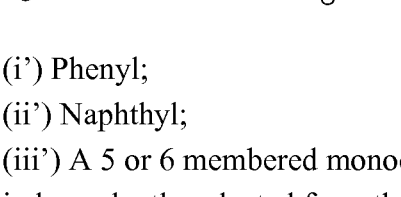
wherein

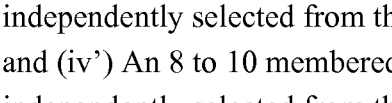
i is 0 or 1;
j is 0 or 1;

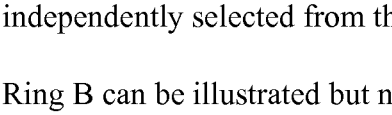


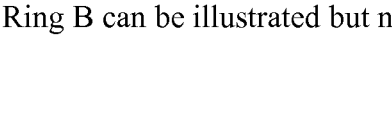




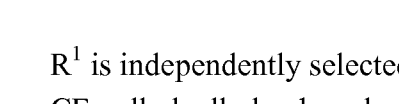


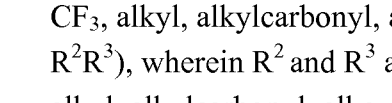


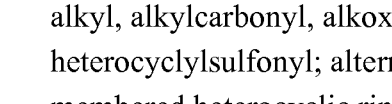


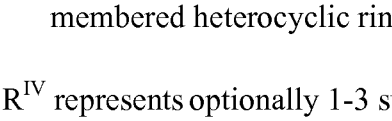


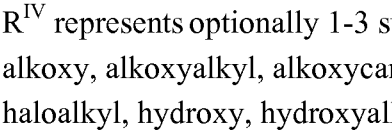


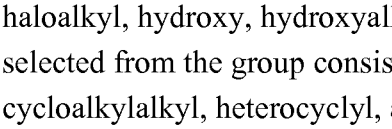


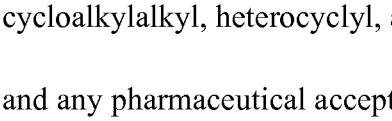


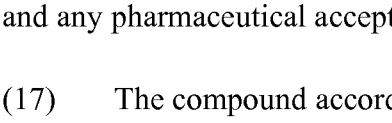


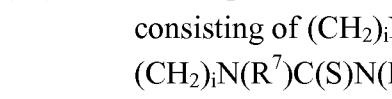






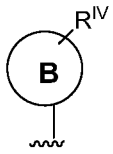






R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl;

Ring B is selected from the group consisting of:



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

Ring B can be illustrated but not limited to the following:

wherein

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;

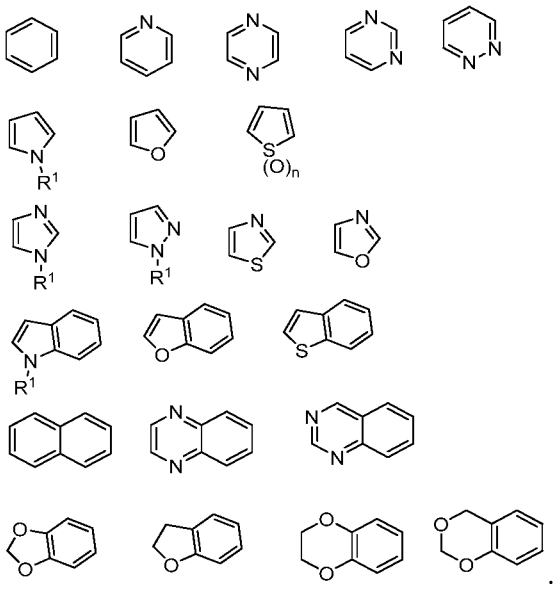
R^{IV} represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —NR^9R^{10}; wherein R^9 and R^{10} are independently selected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

and any pharmaceutical acceptable salt or prodrug.

(17) The compound according to paragraph 16, 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 $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.

(18) The compound according to paragraphs 16 – 17, wherein Y is selected from the group consisting of —$(CH_2)g$—O—$(CH_2)h$—; —$(CH_2)g$—NR^1—$(CH_2)h$—; —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—; —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—; —$(CH_2)g$—NR^2SO_2—$(CH_2)h$—; —$(CH_2)g$— CO—$(CH_2)h$—; —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—; —$(CH_2)g$— $NR^2C(O\ )$—$(CH_2)h$—; —$(CH_2)g$—C≡C—$(CH_2)h$—; —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$ and a single bond.

(19) The compound according to paragraphs 16 – 18, wherein Ring A and Ring B are independently selected from the group consisting of



(20) The compound according to paragraphs 16-19, wherein W is C.

(21) A method of use of the compounds of paragraphs 1 – 20, wherein the compounds are used as tyrosine kinase modulators;

(22) Use of the compounds of paragraphs 1 – 20 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 – 20 together with a pharmaceutically acceptable carrier;

(23) The use of paragraph 22, wherein the diseases 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.

(24) The use of paragraphs 22 – 23 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.

(25) The use of paragraphs 22 – 23 wherein the conditions and diseases are wound healing or to alleviate transplant rejection.

(26) A pharmaceutical composition comprising a therapeutic effective amount of a compound according to paragraphs 1 – 20 together with a pharmaceutically acceptable carrier which is suitable for systematic, parenteral, local or topical delivery.

(27) The pharmaceutical composition of paragraph 26, which are in the form selected from the group comprising 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.

(28) Use of the compounds of paragraphs 1-20 in the preparation of a medicament for the treatment of diseases and conditions, wherein the medicament contains pharmaceutical acceptable composition according to paragraphs 26 and 27.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a powder X-Ray Diffraction (XRPD) of Example 78;

Fig 2 shows a powder X-Ray Diffraction (XRPD) of Example 69;

Fig 3 shows a fluorescein angiography (blood-retinal barrier breakdown) of Example 121, Example 84 Sodium, Example 83, Example 78, Example 75 Sodium, Example 69, and Example 66; and

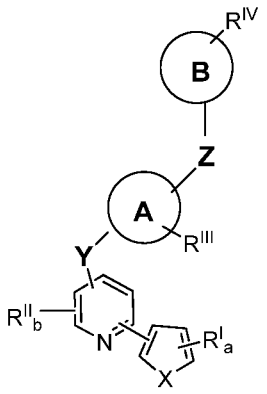
Fig 4 shows a fundus photography (retinal vasodilation and vessel tortuosity) of Example 121, Example 84 Sodium, Example 83, Example 78, Example 75 Sodium, Example 69, and Example 66.

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, transplant rejection, inflammation, neurodegenerative diseases and immune disorders.

1. Compounds of the Invention

In one aspect of the invention, the compounds of the present invention can be represented by the general formula I:



Formula I

wherein

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

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—$S(O)_n$—(CH_2)h—;

(4') —(CH_2)g—SO_2N R^2—(CH_2)h—;

(5') —$(CH_2)g$—NR^2SO_2—$(CH_2)h$—;

(6') —$(CH_2)g$— CO—$(CH_2)h$—;

(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;

(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;

(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;

(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;

(11') —$(CH_2)g$—$(CH_2)h$—;

(12') —$(CH_2)g$—CF_2—$(CH_2)h$—;

(13') —$(CH_2)g$—CCl_2—$(CH_2)h$—;

(14') —$(CH_2)g$—CHF—$(CH_2)h$—;

(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;

(16') —$(CH_2)g$—CR^2R^3—$(CH_2)h$—;

(17') —$(CH_2)g$—C=C—$(CH_2)h$—;

and (18') a single bond.

wherein

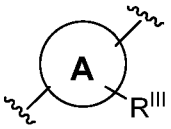
g is 0 or an integer of from 1 to 3;

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 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 cyclic ring;

Ring A is selected from the group consisting of:



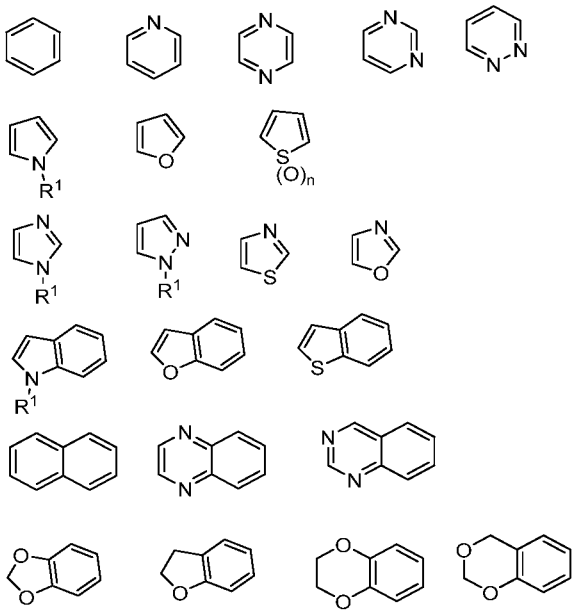
(i) Phenyl;

(ii) Naphthyl;

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

Ring A can be illustrated but not limited to the following:



wherein

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

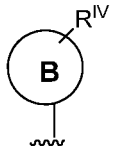
wherein

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:



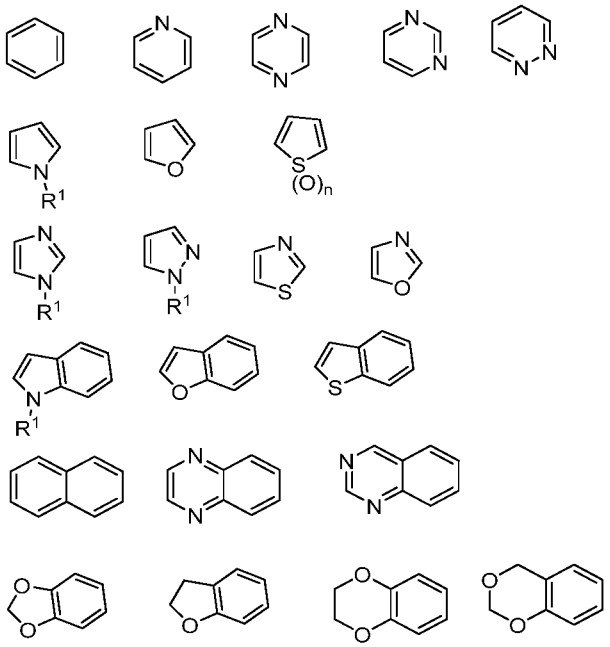
(i') Phenyl;

(ii') Naphthyl;

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

Ring B can be illustrated but not limited to the following:

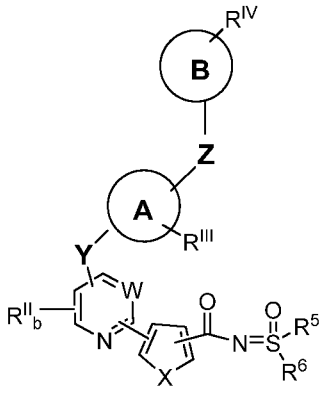


wherein

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^{IV} represents optionally 1-3 substituents, independently selected from the group consisting of hydrogen, 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;

In another aspect of the invention, the compounds of the present invention can be represented by the general formula II:



Formula II

wherein

W is C or N;

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

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^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, and sulfonate;

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—$S(O)_n$—(CH_2)h—;
(4') —(CH_2)g—$SO_2N\ R^2$—(CH_2)h—;
(5') —(CH_2)g—NR^2SO_2—(CH_2)h—;
(6') —(CH_2)g— CO—(CH_2)h—;
(7') —(CH_2)g— $C(O)NR^2$—(CH_2)h—;
(8') —(CH_2)g— $NR^2C(O\ )$—(CH_2)h—;
(9') —(CH_2)g—C≡C—(CH_2)h—;
(10') —(CH_2)g— $NR^2C(O)NR^3$—(CH_2)h—;
(11') —(CH_2)g—(CH_2)h—;
(12') —(CH_2)g—CF_2—(CH_2)h—;
(13') —(CH_2)g—CCl_2—(CH_2)h—;
(14') —(CH_2)g—CHF—(CH_2)h—;
(15') —(CH_2)g—CH(OH)—(CH_2)h—;
(16') —(CH_2)g—CR^2R^3—(CH_2)h—;
(17') —(CH_2)g—C═C—(CH_2)h—;
and (18') a single bond;

wherein

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

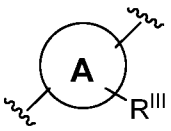
h is 0 or an integer of from 1 to 3;

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 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 cyclic ring;

Ring A is selected from the group consisting of:



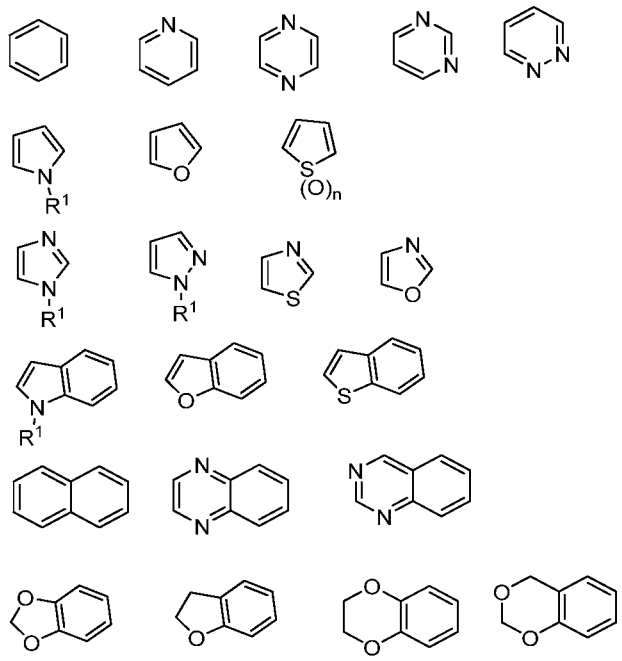
(i) Phenyl;

(ii) Naphthyl;

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

Ring A can be illustrated but not limited to the following:



wherein

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,

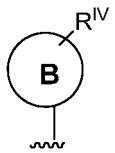
haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively R^2 and R^3 and may be taken together to form a 5-7 membered heterocyclic ring with N;

R^{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

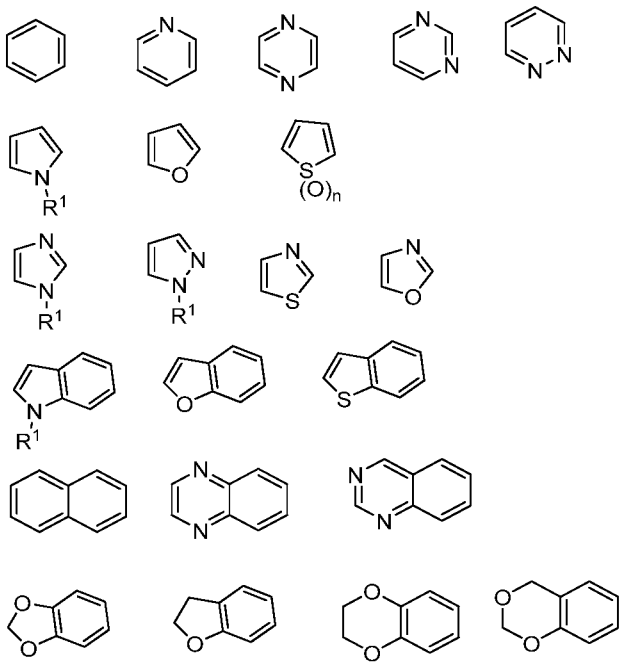
(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;
(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;
(3') $(CH_2)_iN(R^7)C(O)$;
(4') $C(O)N(R^8)(CH_2)_j$;
(5') $(CH_2)_iN(R^7)S(O)_2$;
and (6') $S(O)_2N(R^8)(CH_2)_j$;
wherein
i is 0 or 1;
j is 0 or 1;
R^7 and R^8 are independently selected from the group consisting of hydrogen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

Ring B can be illustrated but not limited to the following:



wherein

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^{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;
and including any pharmaceutically acceptable salt or prodrug.

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. Whenever

there is a conflict between chemical name and its structure drawing, the structure drawing should be used to interpret the compound of the present invention.

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, transplant rejection, inflammation, neurodegenerative diseases and immune disorders in the human being.

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

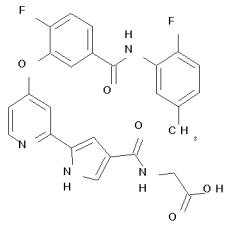
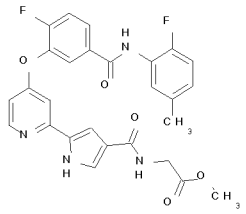
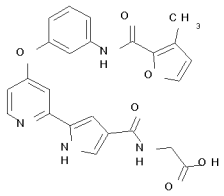
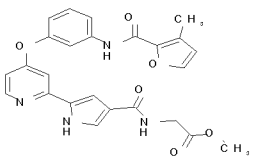
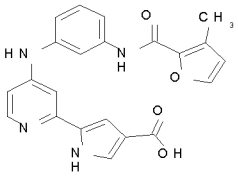
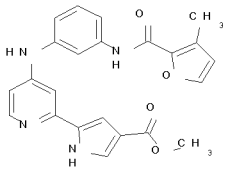
The present invention is also directed to the preparation of a medicament for the treatment and prevention of diseases and conditions related with abnormal activities of tyrosine kinase receptors. The medicament contains a pharmaceutical acceptable composition, which comprises the therapeutic effective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

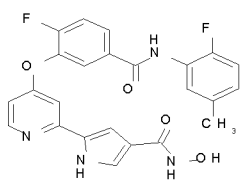
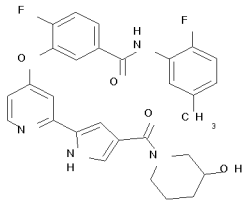
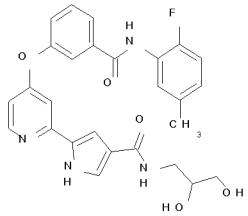
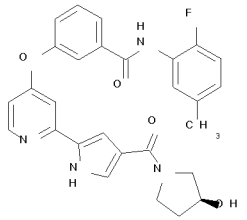
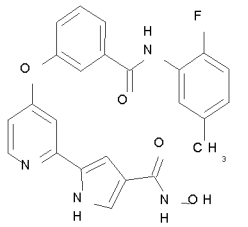
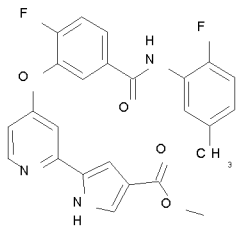
The pharmaceutical acceptable compositions contain therapeutic effective amount of the compounds of the present invention. These compositions can be used as a medicament and administered to a mammal, such as a person, in need thereof. Different types of suitable dosage forms and medicaments are well 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.

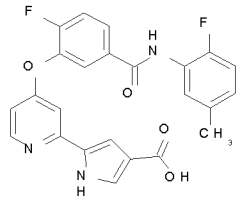
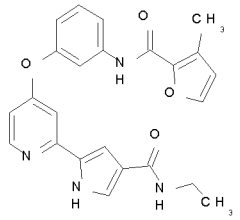
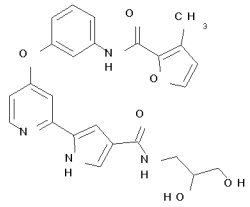
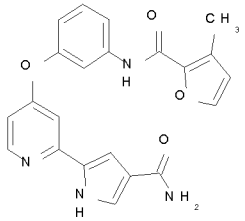
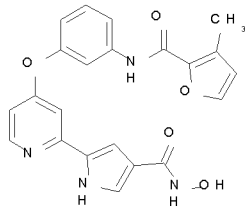
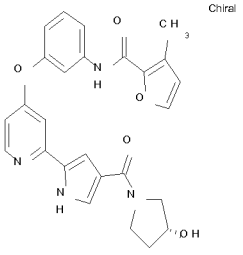
3. Examples

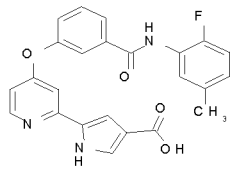
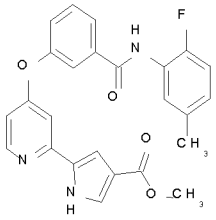
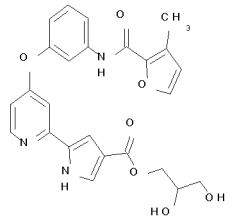
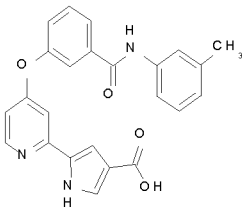
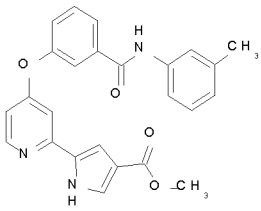
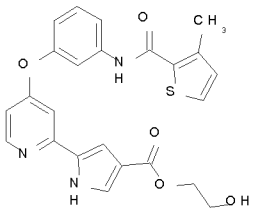
Some of the compounds of the present invention are listed in Table I.

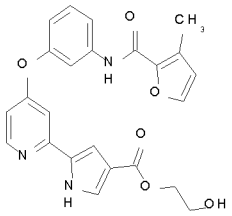
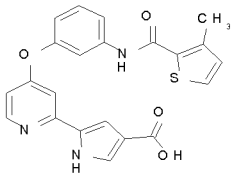
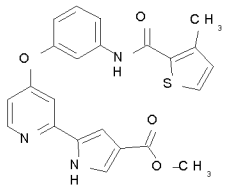
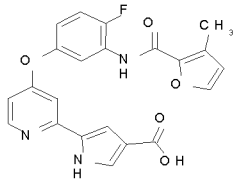
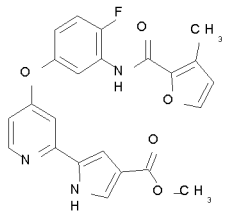
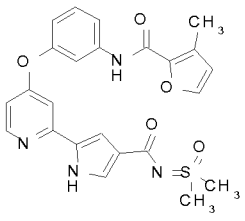
Table 1: Exemplified Compounds of the Present Invention

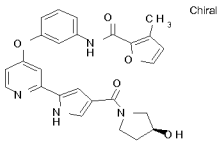
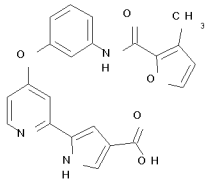
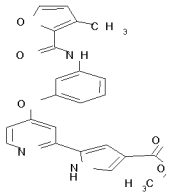
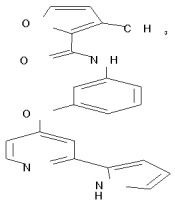
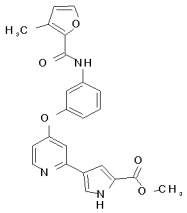
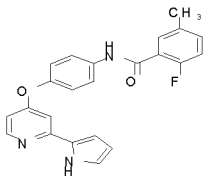
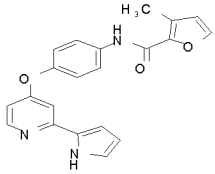
Example #	Chemical Sructure	MW	Chemical Name
1		506	[({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid
2		520	methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate
3		460	({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid
4		474	methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate
5		402	5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid
6		416	methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate

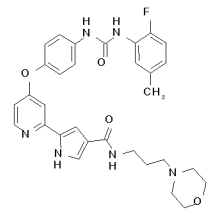
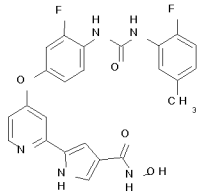
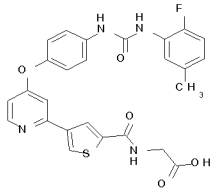
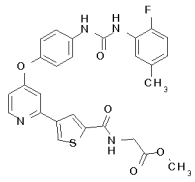
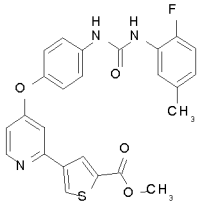
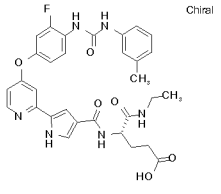
7		464	5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide
8		533	4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide
9		505	N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxamide
10		501	N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide
11		446	5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide
12		463	methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate

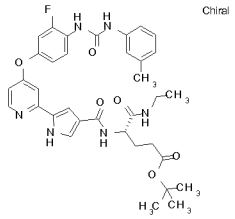
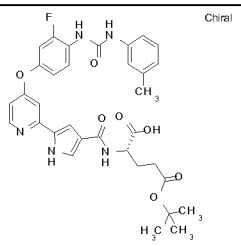
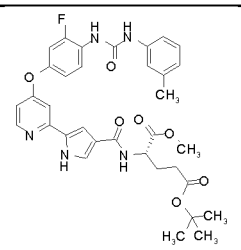
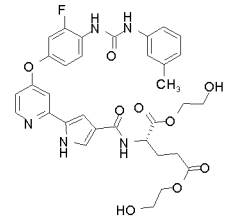
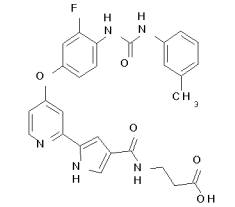
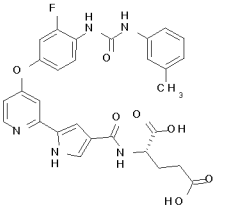
13		449	5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid
14		430	N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide
15		476	N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide
16		402	5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide
17		418	N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide
18		472	N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide

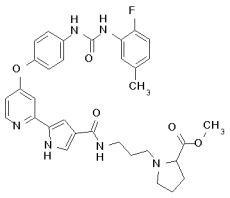
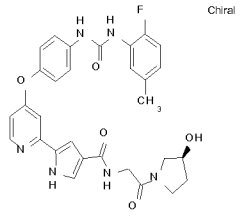
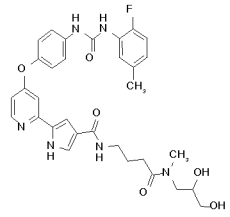
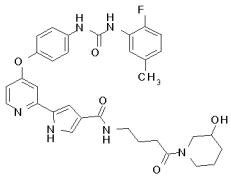
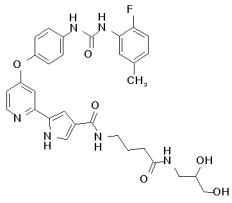
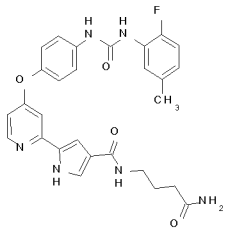
19		431	5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid
20		445	methyl 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate
21		477	2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate
22		413	5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid
23		427	methyl 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate
24		464	2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate

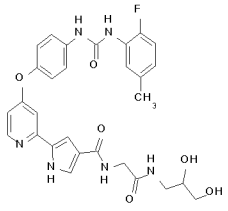
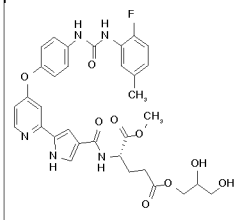
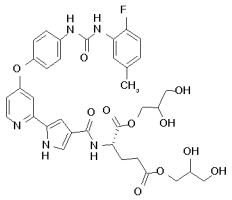
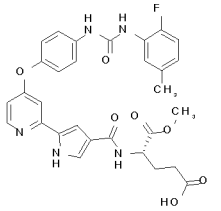
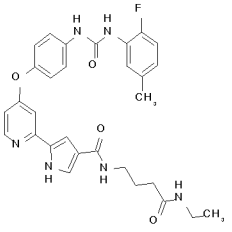
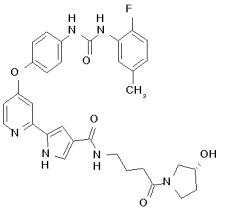
25		447	2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate
26		419	5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid
27		433	methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate
28		421	5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid
29		435	methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate
30		479	N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide

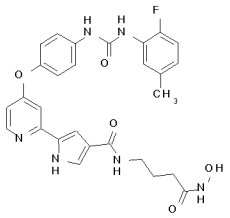
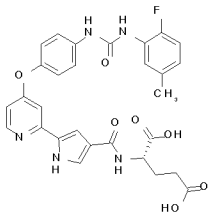
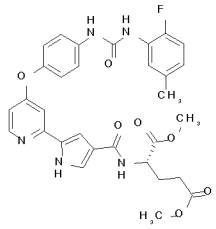
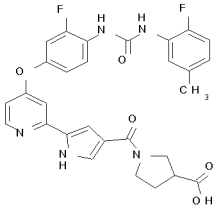
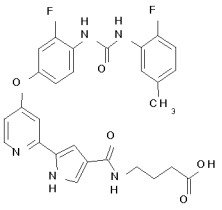
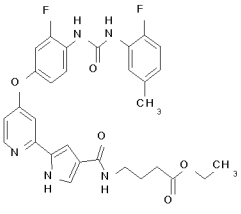
31		472	N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide
32		403	5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid
33		417	methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate
34		359	3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide
35		417	methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate
36		387	2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide
37		359	3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide

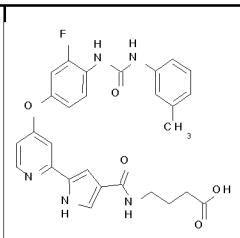
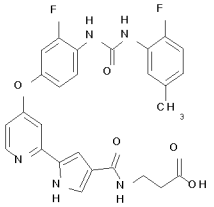
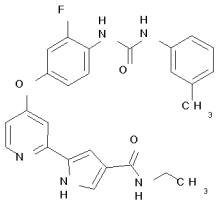
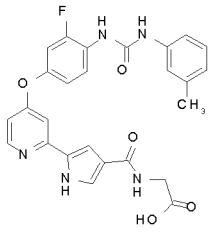
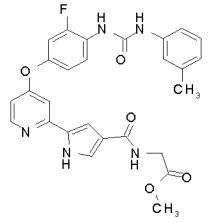
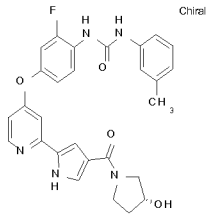
Example #	Chemical Sructure	MW	Chemical Name
38		573	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(3-morpholin-4-ylpropyl)-1H-pyrrole-3-carboxamide
39		479	5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-hydroxy-1H-pyrrole-3-carboxamide
40		521	{[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetic acid
41		535	methyl {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetate
42		478	methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylate
43		603	(4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid

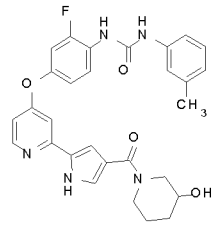
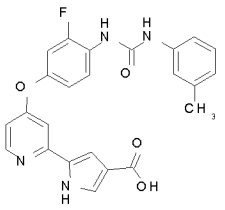
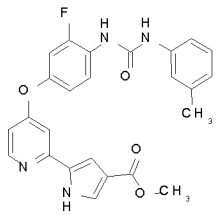
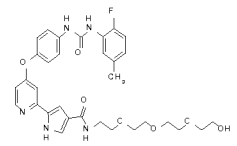
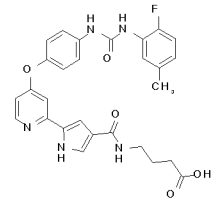
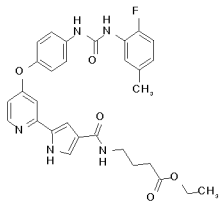
44		659	tert-butyl (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoate
45		632	(2S)-5-tert-butoxy-2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid
46		646	5-tert-butyl 1-methyl 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate
47		664	bis(2-hydroxyethyl) 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate
48		518	3-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid
49		576	2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid

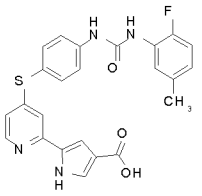
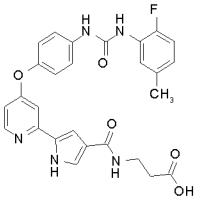
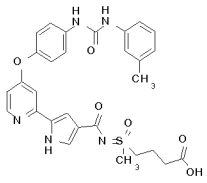
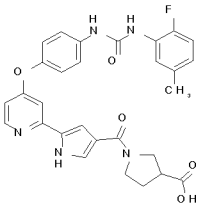
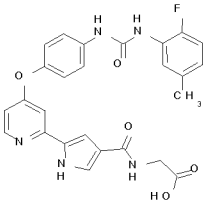
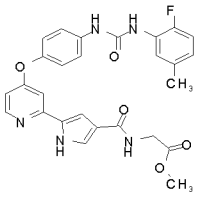
50		615	methyl 1-(3-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propyl)pyrrolidine-2-carboxylate
51		573	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-{2-[(3S)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}-1H-pyrrole-3-carboxamide
52		619	N-{4-[(2,3-dihydroxypropyl)(methyl)amino]-4-oxobutyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
53		615	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypiperidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide
54		605	N-{4-[(2,3-dihydroxypropyl)amino]-4-oxobutyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
55		531	N-(4-amino-4-oxobutyl)-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide

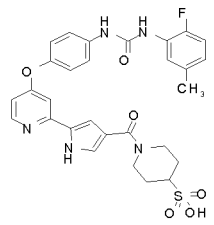
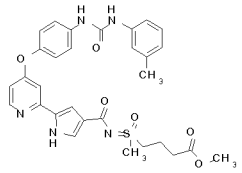
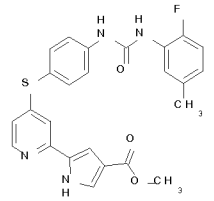
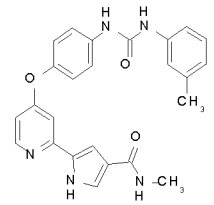
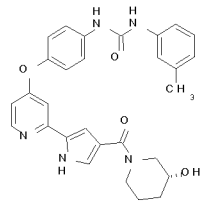
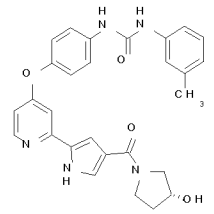
56		577	N-{2-[(2,3-dihydroxypropyl)amino]-2-oxoethyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
57		664	5-(2,3-dihydroxypropyl) 1-methyl 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate
58		724	bis(2,3-dihydroxypropyl) 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate
59		590	4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-methoxy-5-oxopentanoic acid
60		559	N-[4-(ethylamino)-4-oxobutyl]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
61		601	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypyrrolidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide

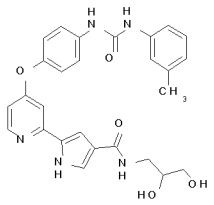
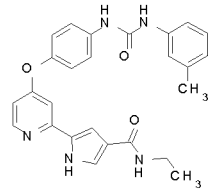
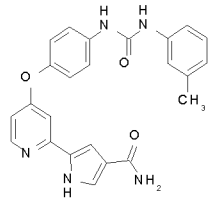
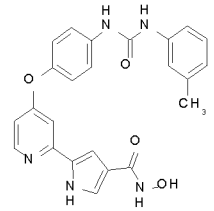
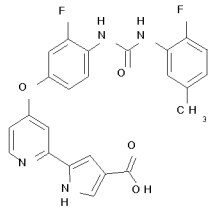
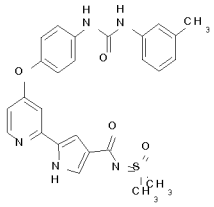
62		547	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(hydroxyamino)-4-oxobutyl]-1H-pyrrole-3-carboxamide
63		576	2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid
64		604	dimethyl 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate
65		562	1-[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]pyrrolidine-3-carboxylic acid
66		550	4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid
67		578	ethyl 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate

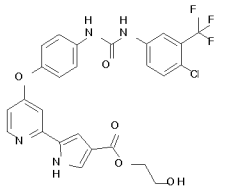
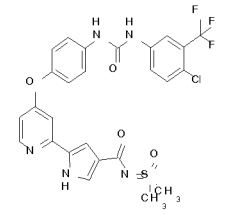
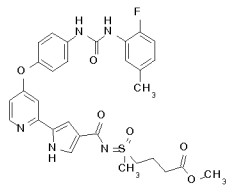
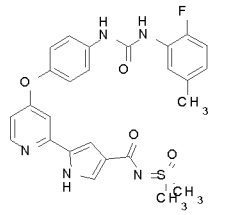
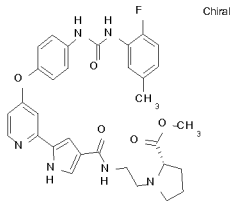
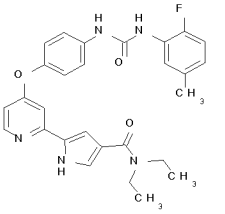
68		532	4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid
69		536	3-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid
70		474	N-ethyl-5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
71		503	{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetic acid
72		518	methyl {[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetate
73		516	1-(2-fluoro-4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-(3-methylphenyl)urea

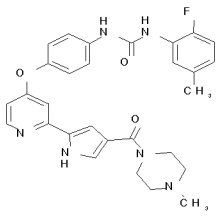
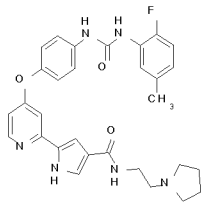
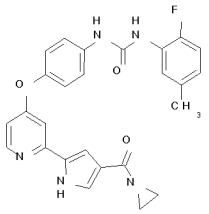
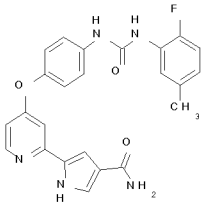
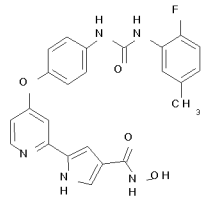
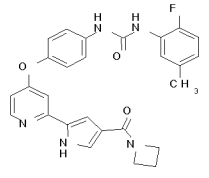
74		530	1-{2-fluoro-4-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea
75		446	5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid
76		460	methyl 5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate
77		622	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}ethyl)-1H-pyrrole-3-carboxamide
78		532	4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid
79		560	ethyl 4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate

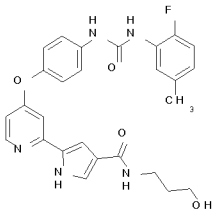
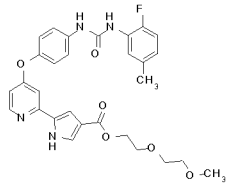
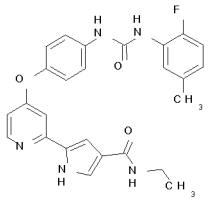
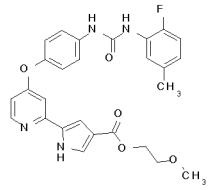
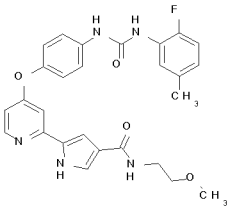
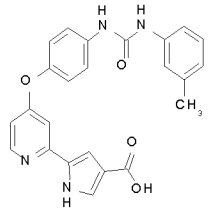
80		463	5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid
81		518	3-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid
82		576	4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoic acid
83		544	1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]pyrrolidine-3-carboxylic acid
84		503	{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetic acid
85		518	methyl {[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetate

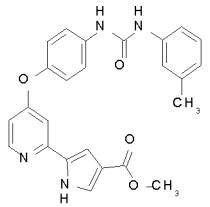
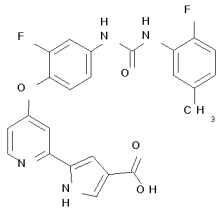
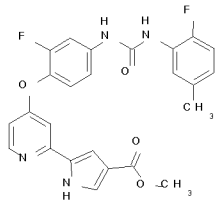
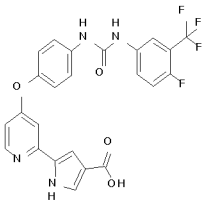
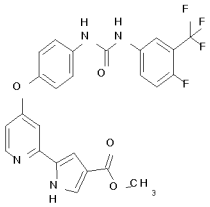
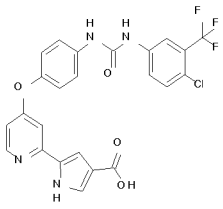
86		594	1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidine-4-sulfonic acid
87		590	methyl 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoate
88		477	methyl 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylate
89		441	N-methyl-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
90		512	1-{4-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea
91		498	1-{4-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea

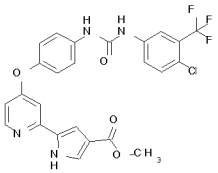
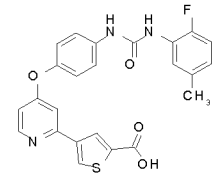
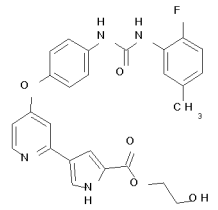
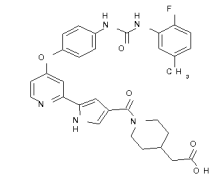
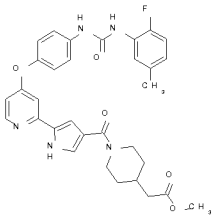
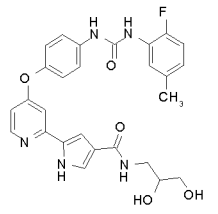
92		502	N-(2,3-dihydroxypropyl)-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
93		456	N-ethyl-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
94		427	5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
95		443	N-hydroxy-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
96		464	5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid
97		504	N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide

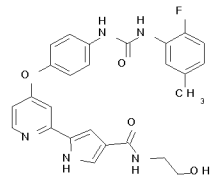
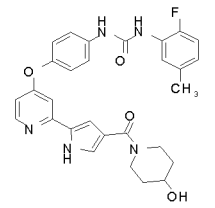
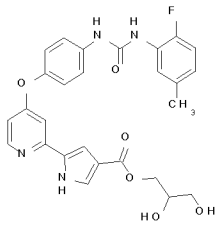
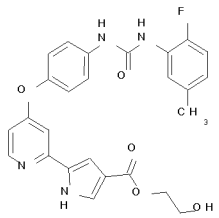
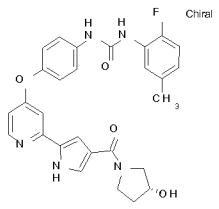
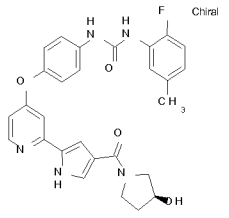
98		561	2-hydroxyethyl 5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate
99		592	5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-1H-pyrrole-3-carboxamide
100		608	methyl 4-{N-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]-S-methylsulfonimidoyl}butanoate
101		522	N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
102		601	methyl (2S)-1-(2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)pyrrolidine-2-carboxylate
103		502	N,N-diethyl-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide

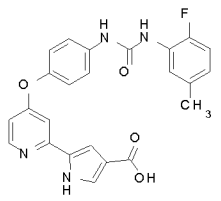
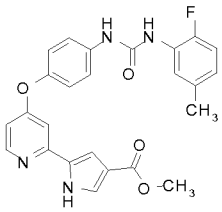
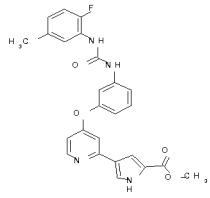
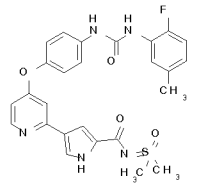
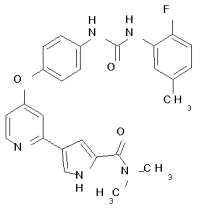
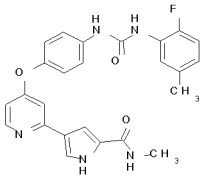
104		529	1-(2-fluoro-5-methylphenyl)-3-{4-[(2-{4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}urea
105		543	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-pyrrolidin-1-ylethyl)-1H-pyrrole-3-carboxamide
106		471	1-[4-({2-[4-(aziridin-1-ylcarbonyl)-1H-pyrrol-2-yl]pyridin-4-yl}oxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea
107		445	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
108		461	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-hydroxy-1H-pyrrole-3-carboxamide
109		486	1-[4-({2-[4-(azetidin-1-ylcarbonyl)-1H-pyrrol-2-yl]pyridin-4-yl}oxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea

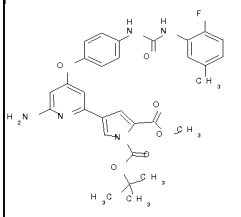
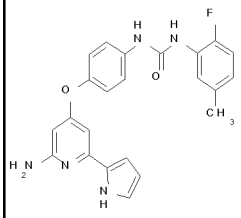
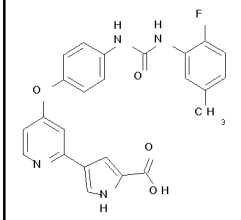
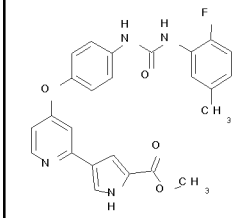
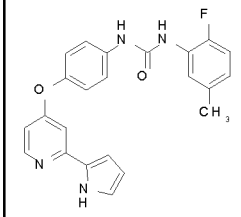
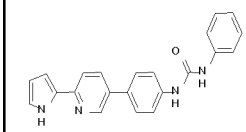
110		504	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(3-hydroxypropyl)-1H-pyrrole-3-carboxamide
111		549	2-(2-methoxyethoxy)ethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate
112		474	N-ethyl-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide
113		505	2-methoxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate
114		504	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-methoxyethyl)-1H-pyrrole-3-carboxamide
115		428	5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid

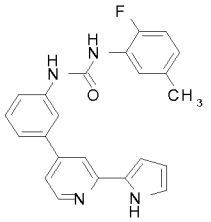
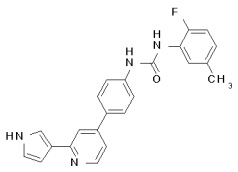
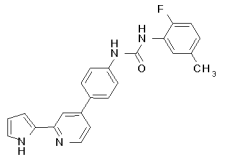
116		442	methyl 5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate
117		464	5-{4-[2-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid
118		478	methyl 5-{4-[2-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate
119		500	5-(4-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid
120		514	methyl 5-(4-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate
121		517	5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid

122		531	methyl 5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate
123		463	4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylic acid
124		490	2-hydroxyethyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate
125		572	{1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetic acid
126		586	methyl {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetate
127		520	N-(2,3-dihydroxypropyl)-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide

128		490	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-hydroxyethyl)-1H-pyrrole-3-carboxamide
129		530	1-(2-fluoro-5-methylphenyl)-3-{4-[(2-{4-[(4-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}urea
130		521	2,3-dihydroxypropyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate
131		490	2-hydroxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate
132		516	1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea
133		516	1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea

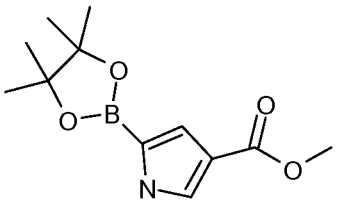
134		446	5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid
135		460	methyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate
136		460	methyl 4-{4-[3-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate
137		522	N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxamide
138		474	4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N,N-dimethyl-1H-pyrrole-2-carboxamide
139		459	4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-methyl-1H-pyrrole-2-carboxamide

140		576	1-tert-butyl 2-methyl 4-{6-amino-4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-1,2-dicarboxylate
141		417	1-(4-{[2-amino-6-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-(2-fluoro-5-methylphenyl)urea
142		446	4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylic acid
143		460	methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate
144		402	1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea
145		354	1-phenyl-3-{4-[6-(1H-pyrrol-2-yl)pyridin-3-yl]phenyl}urea

146		386	1-(2-fluoro-5-methylphenyl)-3-{3-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea
147		386	1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-3-yl)pyridin-4-yl]phenyl}urea
148		386	1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea

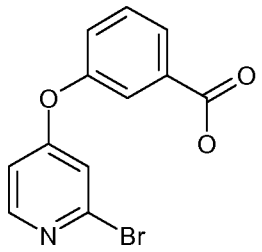
3.1 Compound Synthesis and Characterization

Preparation of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate



To a mixture of methyl-1H-pyrrole-3-carboxylate (5.0 g, 39.9 mmol), bis(pinacolato)diboron (5.37 g, 21.1 mmol), 4,4'-di-tert-butyl-2,2'-bipyridine (0.054 g, 0.20 mmol) and $[Ir(OMe)(COD)]_2$ (0.067 g, 0.099 mmol) was added cyclohexane (60 mL). The mixture stirred at 90°C for 5 hours. The mixture was cooled to room temperature and filtered, washing with ample amounts of water and twice with hexanes. The light orange solid was collected and dried in a vacuum oven at 55°C to afford methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (6.99 g, 70% yield).

Preparation of 3-(2-Bromo-pyridin-4-yloxy)-benzoic acid

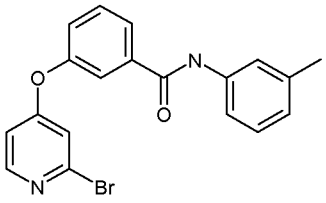


A mixture of 2-bromo-4-chloro-pyridine (200mg, 1.04mmol), methyl-3-hydroxybenzoate (158mg, 1.04mmol), cesium carbonate (507mg, 1.56mmol) in 10ml of anhydrous DMSO was heated at 66°C for 5 hours. The mixture was diluted with ethyl acetate (100ml), washed with brine (3x50ml), dried over Na_2SO_4 and evaporated to give a colorless oil. The oil was dissolved in MeOH (8ml), and 2M NaOH solution (4ml, 8mmol) was added. The mixture was heated at 60°C for 20 minutes, poured into 50ml of water, and acidified to pH = 4. The precipitates were filtered, washed with water and dried *in vacuo* to give 3-(2-bromo-pyridin-4-yloxy)-benzoic acid as white solid. Yield: 170mg, 56%.

^{1}H NMR (DMSO-d_6) δ: 13.24 (br. s., 1H), 8.27 (d, J = 5.9 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.58 - 7.68 (m, 2H), 7.45 - 7.52 (m, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 5.7, 2.2 Hz, 1H)

LR MS (ES-): 292 (M-H), 294

Preparation of 3-(2-Bromo-pyridin-4-yloxy)-N-m-tolyl-benzamide



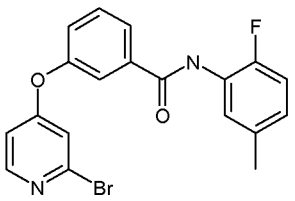
A mixture of 3-(2-bromo-pyridin-4-yloxy)-benzoic acid (170mg, 0.58mmol), HATU (265mg, 0.69mmol),) m-toluidine (93mg, 0.87mmol) and *N,N*-diisopropylethylamine (164mg, 1.28mmol) in anhydrous DMF (10ml) was stirred at room temperature for 20 minutes. The mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give 3-(2-Bromo-pyridin-4-yloxy)-N-m-tolyl-benzamide as off-white solid. Yield: 150mg, 68%.

^{1}H NMR (DMSO-d_6) δ: 10.18 (s, 1H), 8.29 (d, J = 5.9 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.78 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.50 - 7.60 (m, 2H), 7.45 (dd, J = 7.9, 1.8 Hz, 1H), 7.16 - 7.25 (m, 2H), 7.02 (dd, J = 5.7, 2.2 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 2.29 (s, 3H)

LR MS (ES+): 405 ($M+Na^+$), 407

LR MS (ES-): 381 (M-H), 383

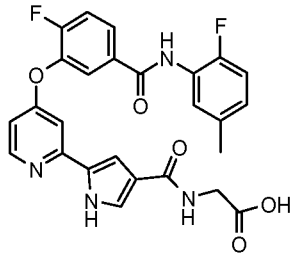
Preparation of 3-(2-Bromo-pyridin-4-yloxy)-N-(2-fluoro-5-methyl-phenyl)-benzamide



A mixture of 3-(2-bromo-pyridin-4-yloxy)-benzoic acid (200mg, 0.68mmol), HATU (312mg, 0.82mmol),) 2-fluoro-5-methylaniline (125mg, 1.0mmol) and *N,N*-diisopropylethylamine (193mg, 1.5mmol) in anhydrous DMF (10ml) was stirred at 60°C for 90 minutes. The mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give 3-(2-bromo-pyridin-4-yloxy)-N-(2-fluoro-5-methyl-phenyl)-benzamide as off-white solid. Yield: 200mg, 74%.

Example 1

[({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid



To a stirred solution of methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate (110mg, 0.21mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 1M NaOH solution (1ml, 1mmol). The mixture was stirred at room temperature for 1 hour, and poured into 100ml of water. 2M HCl was added until pH = 4. The precipitates were filtered, washed with water and dried *in vacuo* to give [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid as white solid. Yield: 100mg, 93%.

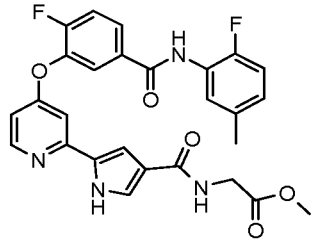
^{1}H NMR (DMSO-d_6) δ: 12.41 (br. s., 1H), 11.87 (br. s., 1H), 10.12 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 8.19 (t, J = 6.0 Hz, 1H), 7.95 - 8.04 (m, 2H), 7.63 (dd, J = 10.1, 8.7 Hz, 1H), 7.41 (dd, J = 3.1, 1.6 Hz, 1H), 7.35 (dd, J = 7.3, 1.8 Hz, 1H), 7.27 (d, J = 2.3 Hz, 1H), 7.09 - 7.18 (m, 2H),

7.04 (td, J = 5.3, 2.3 Hz, 1H), 6.81 (dd, J = 5.9, 2.3 Hz, 1H), 3.82 (d, J = 5.9 Hz, 2H), 2.27 (s, 3H)

LR MS (ES-): 505 (M-H)

Example 2

methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate



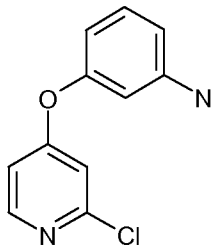
Similar procedure as Example 1.

^{1}H NMR (DMSO-d_6) δ: 11.95 (br. s., 1H), 10.12 (s, 1H), 8.44 (d, J = 5.9 Hz, 1H), 8.33 (t, J = 5.9 Hz, 1H), 7.97 - 8.03 (m, 2H), 7.61 - 7.67 (m, 1H), 7.45 (br. s., 1H), 7.33 - 7.37 (m, 1H), 7.30 (s, 1H), 7.18 (br. s., 1H), 7.14 (dd, J = 10.3, 8.5 Hz, 1H), 7.02 - 7.08 (m, 1H), 6.86 (br. s., 1H), 3.91 (d, J = 5.9 Hz, 2H), 3.61 (s, 3H), 2.27 (s, 3H)

LR MS (ES+): 521 (MH), 543 ($M+Na^+$)

LR MS (ES-): 519 (M-H)

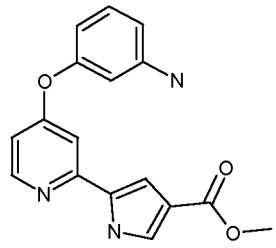
Preparation of 4-(3-Aminophenoxy)-2-chloropyridine



To a mixture of 3-aminophenol (3.7 g, 34.09 mmol) in DMSO (50 mL) was added Cs2CO3 (30.7 g, 94.46 mmol). The mixture stirred for 10 minutes and then 2,4-dichloropyridine (5.0 g, 33.79 mmol) was added. The mixture was stirred at 120°C for 1.5 h. The mixture was cooled and diluted with water. The aqueous solution was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over MgSO4 and concentrated to afford a dark oil. The

oil was purified via column chromatography, eluting with 30-40% EtOAc/hexanes, to afford 4-(3-Aminophenoxy)-2-chloropyridine (6.63 g, 89%) as a brown solid.

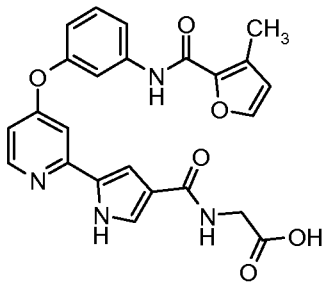
Preparation of methyl 5-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



A mixture of 4-(3-aminophenoxy)-2-chloropyridine (4.0 g, 18.13mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (6.82 g, 27.16mmol) and Pd(PPh3)4 (4.20 g, 3.63mmol) was added to a thick walled reaction vessel and purged with N2. A solution of 2M K2CO3 (13.59 mL) was added, followed by DME (70 mL). The reaction vessel was sealed and the mixture stirred at 92°C for 18 h. The reaction vessel was cooled to room temperature and the mixture was filtered over celite, washing with EtOAc. The filtrate was concentrated and the resultant dark oil was purified via column chromatography, eluting with 40-80% EtOAc/hexanes to afford methyl 5-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate (2.85 g, 51% yield).

Example 3

({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid



Similar procedure as Example 1.

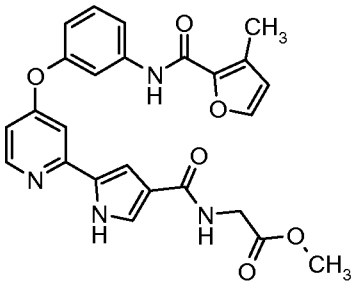
^{1}H NMR (DMSO-d_6) δ: 12.42 (br. s., 1H), 11.91 (br. s., 1H), 10.20 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 8.21 (t, J = 5.4 Hz, 1H), 7.76 (s, 1H), 7.65 - 7.73 (m, 2H), 7.36 - 7.47 (m, 2H), 7.26 (br. s.,

1H), 7.12 (br. s., 1H), 6.86 - 6.98 (m, 1H), 6.77 (br. s., 1H), 6.56 (s, 1H), 3.81 (d, J = 5.9 Hz, 2H), 2.29 (s, 3H)

LR MS (ES-): 459 (M-H)

Example 4

methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate



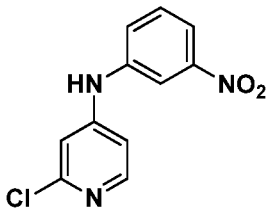
Similar procedure as Example 3.

^{1}H NMR (DMSO-d_6) δ: 11.88 (br. s., 1H), 10.19 (s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 8.32 (t, J = 5.6 Hz, 1H), 7.76 (s, 1H), 7.65 - 7.72 (m, 2H), 7.36 - 7.44 (m, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.08 (br. s., 1H), 6.90 (d, J = 7.3 Hz, 1H), 6.75 (dd, J = 5.6, 1.8 Hz, 1H), 6.56 (s, 1H), 3.89 (d, J = 5.6 Hz, 2H), 3.60 (s, 3H), 2.29 (s, 3H)

LR MS (ES+): 475 (MH), 497 ($M+Na^+$)

LR MS (ES-): 473 (M-H)

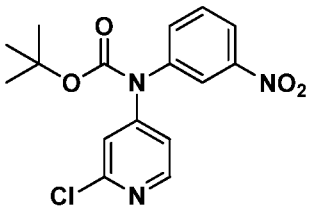
Preparation of 2-Chloro-*N*-(3-nitrophenyl)pyridine-4-amine



To a degassed (15 min, N_2) suspension of 2-chloro-4-iodopyridine (3.0 g, 12.53 mmol), 3-nitroaniline (1.82 g, 13.18 mmol), BINAP (0.39 g, 0.626 mmol) and Cs_2CO_3 (8.16 g, 25.04 mmol) in toluene (72 mL) was added $Pd(OAc)_2$ (0.084 g, 0.374 mmol). The reaction tube was sealed and the mixture stirred at 90°C for 18 h. The mixture was cooled to rt and filtered, washing with EtOAc. The orange/yellow solid collected was washed with CH_2Cl_2 until all the product washed through into the filtrate. The filtrate was concentrated to afford 2-Chloro-*N*-(3-

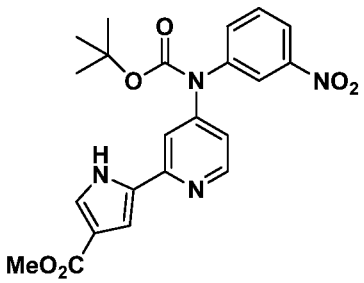
nitrophenyl)pyridine-4-amine as a bright yellow solid. Additional product was collected from the solid collected upon concentration of the previous filtrate, after washing with CH_2Cl_2. No further purification. Total amount of product collected was 2.85 g (91% yield).

Preparation of *tert*-Butyl 2-chloropyridin-4-yl(3-nitrophenyl)carbamate



To a stirring solution of 2-Chloro-*N*-(3-nitrophenyl)pyridine-4-amine (2.70 g, 10.82 mmol) in THF (45 mL) was added Et_3N (6.32 mL, 45.3 mmol). The mixture was cooled to 0°C, and DMAP (0.0135 g, 0.110 mmol) and BOC_2O (2.84 g, 12.99 mmol) were added. The mixture was warmed to rt and stirred for 18 h. The mixture was quenched with ice and diluted with water. Extracted with EtOAc (3 x 200 mL), washed with brine and water, dried ($MgSO_4$), and concentrated. A dark oil was afforded, which was passed through a pad of silica gel, eluting with 1:1 EtOAc/hexanes. Concentrated and dried under high vacuum to afford *tert*-Butyl 2-chloropyridin-4-yl(3-nitrophenyl)carbamate (3.65 g, 96.5% yield).

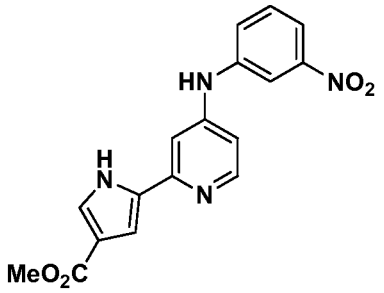
Preparation of methyl 5-(4-(*tert*-butoxycarbonyl(3-nitrophenyl)amino)pyridine-2-yl)-1*H*-pyrrole-3-carboxylate



A mixture of *tert*-Butyl 2-chloropyridin-4-yl(3-nitrophenyl)carbamate (3.65 g, 10.43 mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (5.48 g, 21.82 mmol), xantphos (0.72 g, 1.25 mmol) and Pd_2dba_3 (0.72 g, 0.79 mmol) was added to a thick walled reaction vessel and purged with N_2. A solution of 2M K_2CO_3 (8.76 mL) was added, followed by dioxane (67 mL). The reaction vessel was sealed and the mixture stirred at 105°C for 18 h. The reaction vessel was cooled to rt and the mixture was filtered over celite, washing with EtOAc. The filtrate was concentrated to afford a dark oil, which was purified via column chromatography eluting with 30-50% EtOAc/hexanes to afford methyl 5-(4-(*tert*-

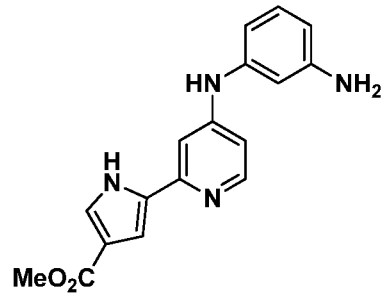
butoxycarbonyl(3-nitrophenyl)amino)pyridine-2-yl)-1*H*-pyrrole-3-carboxylate (2.98 g, 65% yield) as an orange oil.

Preparation of methyl 5-(4-((3-nitrophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate



Methyl 5-(4-(*tert*-butoxycarbonyl(3-nitrophenyl)amino)pyridine-2-yl)-1*H*-pyrrole-3-carboxylate (0.40 g, 0.91 mmol) was taken up in toluene (38 mL) and SiO_2 (9.0 g) was added. The mixture stirred at reflux for 20 h. The mixture was cooled to rt and filtered over celite, washing with EtOAc. The filtrate was concentrated to a bright orange color. The solid was taken up in hexanes and filtered. The solid was then washed with CH_2Cl_2/hexanes to afford methyl 5-(4-((3-nitrophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate (0.15 g, 49% yield) as a bright yellow solid.

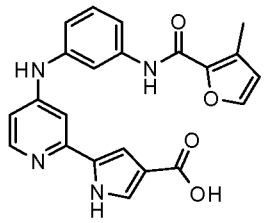
Preparation of methyl 5-(4-((3-aminophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate



Methyl 5-(4-((3-nitrophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate (1.32 g, 3.9 mmol) was taken up in EtOAc/EtOH (1:1; 90 mL) and purged with N_2. Pd/C (10%, 0.145 g) was added and the mixture was stirred under an atmosphere of H_2 at rt for 18 h. The mixture was filtered over celite, washing with EtOAc/EtOH. The filtrate was concentrated, taken back up in EtOAc and filtered over celite again to remove any residual catalyst. The filtrate was concentrated again and taken back up in EtOAc. The solution was filtered and the filtrate was concentrated to afford a tan solid. The solid was washed with CH_2Cl_2/hexanes (1:2) and dried under high vacuum to afford methyl 5-(4-((3-aminophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate (1.15 g, 96% yield) as a tan solid.

Example 5

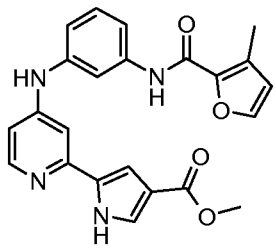
5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid



To a stirred solution of methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate (10mg, 0.024mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 2ml of 1M NaOH (2mmol) solution. The mixture was heated in a 60°C bath for 16 hours, cooled to room temperature and poured into 100ml of water. 2M HCl was added until pH = 5. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid as light brown solid. Yield: 2mg.

Example 6

methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate



A mixture of 3-methyl-2-furoic acid (22 mg, 0.18mmol), HATU (73mg, 0.19mmol) and *N,N*-diisopropylethylamine (45mg, 0.35mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of methyl 5-(4-((3-aminophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate (50mg, 0.16mmol). The mixture was stirred at room temperature for 3 hours and poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate as off-white solid. Yield: 10mg, 15%.

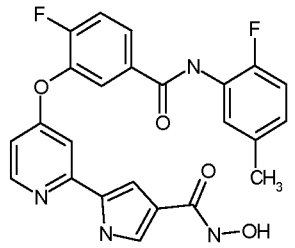
^{1}H NMR (DMSO-d_6) δ: 13.60 (br. s., 1H), 12.37 (br. s., 1H), 10.14 (s, 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.86 (t, J = 1.9 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.58 (br. s., 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.32 - 7.38 (m, 2H), 7.22 (br. s., 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.86 (dd, J = 6.2, 2.1 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 3.71 (s, 3H), 2.32 (s, 3H)

LR MS (ES+): 417 (MH)

LR MS (ES-): 415 (M-H)

Example 7

5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide



Similar procedure as Example 1.

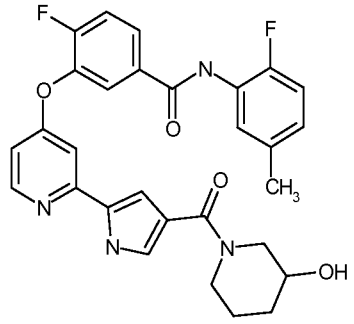
^{1}H NMR (DMSO-d_6) δ: 11.85 (br. s., 1H), 10.56 (br. s., 1H), 10.12 (s, 1H), 8.66 (br. s., 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.99 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 9.4 Hz, 1H), 7.30 - 7.40 (m, 2H), 7.27 (br. s., 1H), 7.10 - 7.18 (m, 1H), 7.01 - 7.10 (m, 2H), 6.75 - 6.85 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 487 ($M+Na^+$)

LR MS (ES-): 463 (M-H)

Example 8

4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide



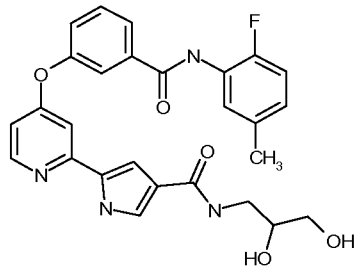
Similar procedure as Example 1.

LR MS (ES+): 533 (MH), 555 ($M+Na^+$)

LR MS (ES-): 531 (M-H)

Example 9

N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxamide



Similar procedure as Example 1.

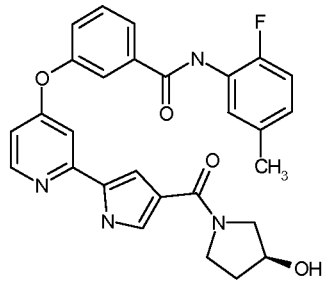
^1H NMR (DMSO-d_6) δ: 11.83 (br. s., 1H), 10.11 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.83 (t, J = 5.6 Hz, 1H), 7.77 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.42 - 7.46 (m, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.09 - 7.16 (m, 2H), 7.02 - 7.06 (m, 1H), 6.76 (dd, J = 5.7, 2.5 Hz, 1H), 4.77 (d, J = 5.0 Hz, 1H), 4.53 (t, J = 6.0 Hz, 1H), 3.50 - 3.56 (m, 1H), 3.25 - 3.30 (m, 3H), 3.08 - 3.14 (m, 1H), 2.27 (s, 3H)

LR MS (ES+): 505 (MH), 527 ($M+Na^+$)

LR MS (ES-): 503 (M-H)

Example 10

N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide



A mixture of 5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (50mg, 0.12mmol), HATU (55mg, 0.14mmol) and *N,N*-diisopropylethylamine (34mg, 0.26mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes, followed by addition of (S)-3-pyrrolidinol (16mg, 0.18mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide as white solid. Yield: 40mg, 69%.

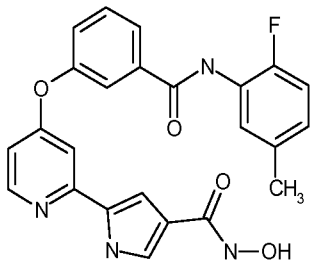
^{1}H NMR (DMSO-d_6) δ: 11.91 (br. s., 1H), 10.12 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.76 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.32 - 7.51 (m, 3H), 7.26 (d, J = 6.7 Hz, 1H), 6.99 - 7.20 (m, 3H), 6.73 (dd, 1H), 4.91 (br. s., 1H), 4.30 (br. s., 1H), 3.76 (br. s., 2H), 3.50 (br. s., 2H), 2.28 (s, 3H), 1.86 (br. s., 2H)

LR MS (ES+): 501 (MH), 523 ($M+Na^+$)

LR MS (ES-): 499 (M-H)

Example 11

5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide



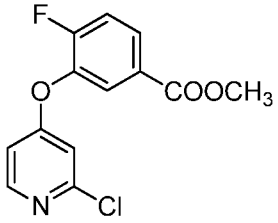
Similar procedure as Example 10.

^{1}H NMR (DMSO-d_6) δ: 11.84 (br. s., 1H), 10.56 (br. s., 1H), 10.10 (s, 1H), 8.65 (br. s., 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.76 (br. s., 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.44 (dd, J = 7.9, 1.5 Hz, 1H), 7.35 (d, J = 6.7 Hz, 1H), 7.31 (br. s., 1H), 7.25 (d, J = 1.8 Hz, 1H), 7.13 (dd, J = 10.3, 8.5 Hz, 1H), 7.01 - 7.07 (m, 2H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 2.27 (s, 3H)

LR MS (ES+): 469 ($M+Na^+$)

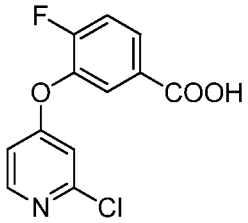
LR MS (ES-): 445 (M-H)

Preparation of 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid methyl ester



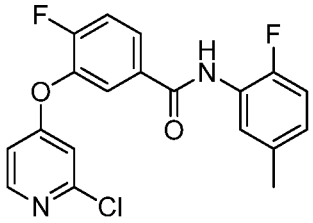
4-Fluoro-3-hydroxybenzoic acid methyl ester (1.70 g, 10.0 mmol) was dissolved in dimethylformamide (9 mL) under nitrogen at room temperature. Sodium hydride (60% oil dispersion, 0.48 g, 12 mmol) was added in portions over 30 min. The reaction was stirred for 90 minutes and then cooled in an ice bath. 2-Chloro-4-nitropyridine (1.58 g, 10.0 mmol) was added in small portions over 50 min. The reaction was stirred at room temperature for 17.5 h. Water (200 ml) was added and the mixture stirred until a brown lump formed. The water was decanted and the residue dissolved in EtOAc (150 mL). The solution was washed with brine, dried ($MgSO_4$), filtered and evaporated to give 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid methyl ester. Yield: 3.10 g.

Preparation of 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid



3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid methyl ester (2.81 g, 10.0 mmol) was dissolved in tetrahydrofuran (15 mL) and mixed with 2M lithium hydroxide (15 mL, 30 mmol). The suspension was stirred for 5 h. To the reaction was added water, then extracted with EtOAc. The aqueous layer was treated with 6M HCl (5 mL, 30 mmol) and then extracted with EtOAc (3x25 mL). The extract was dried ($MgSO_4$), filtered and evaporated to 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid. Yield: 2.22 g, 83%.

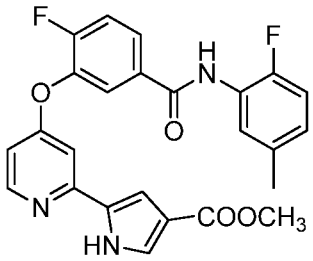
Preparation of 3-(2-Chloropyridin-4-yloxy)-4-fluoro-N-(2-fluoro-5-methylphenyl)benzamide



A solution of 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid (2.22 g, 8.29 mmol), 2-fluoro-5-methylaniline (1.56 g, 12.4 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 3.78 g, 9.95 mmol) and N-methylmorpholine (2.00 mL, 18.2 mmol) in dimethylformamide (22 mL) was heated at 90°C for 2 h. The solvent was evaporated *in vacuo* at 50°C. To the residue was added water resulting in a thick oil. The water was decanted and the oil dissolved in EtOAc then extracted twice with water, 1M hydrochloric acid and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated to crude 6 (3.37 g). Trituration with dichloromethane (25 mL) gave 3-(2-Chloropyridin-4-yloxy)-4-fluoro-N-(2-fluoro-5-methylphenyl)benzamide as white solid. Yield: 1.788 g, 58%.

Example 12

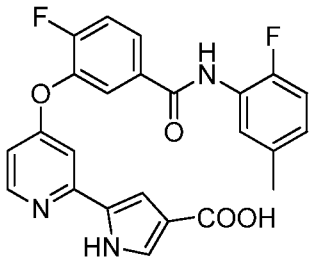
methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



A mixture of 3-(2-Chloropyridin-4-yloxy)-4-fluoro-N-(2-fluoro-5-methylphenyl)benzamide (1.217 g, 3.25 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (1.63 g, 6.50 mmol) and potassium carbonate (0.67 g, 4.87 mmol) in water (2.5 mL) and dioxane (15 mL) was purged with nitrogen for several minutes. To the mixture was added tetrakis-triphenylphosphine palladium(0) (0.18 g, (0.16 mmol). The reaction was sealed under nitrogen and heated at 100°C for 15 h. The cooled reaction was mixed with dichloromethane and filtered through Celite. The red solution was evaporated. The resulting oil was dissolved in dichloromethane, put on a column of silica gel (80 g) and eluted with hexane/EtOAc (1:1) to afford methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate as white solid. Yield: 1.162 g, 77%.

Example 13

5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid



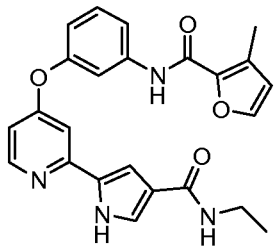
Similar procedure as Example 12.

^{1}H NMR (DMSO-d_6) δ: 12.03 (br. s., 1H), 11.85 (br. s., 1H), 10.11 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.98 (d, J = 6.2 Hz, 2H), 7.62 (t, J = 9.4 Hz, 1H), 7.43 (br. s., 1H), 7.30 - 7.39 (m, 2H), 7.08 - 7.19 (m, 2H), 7.04 (br. s., 1H), 6.79 (d, J = 3.2 Hz, 1H), 2.26 (s, 3H)

LR MS (ES-): 448 (M-H)

Example 14

N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide

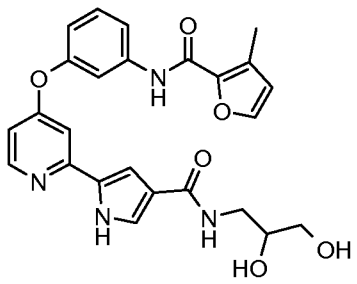


Similar procedure as Example 31.

LR MS (ES+): 453 ($M+Na^+$)

Example 15

N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 31.

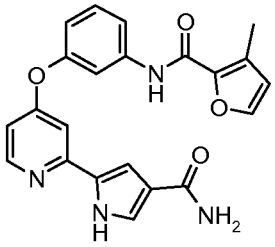
^{1}H NMR (DMSO-d_6) δ: 11.83 (br. s., 1H), 10.21 (s, 1H), 8.40 (d, J = 5.9 Hz, 1H), 7.85 (t, J = 6.0 Hz, 1H), 7.78 (s, 1H), 7.63 - 7.74 (m, 2H), 7.35 - 7.48 (m, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.10 (s, 1H), 6.85 - 6.96 (m, 1H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (s, 1H), 4.78 (d, J = 4.7 Hz, 1H), 4.53 (t, J = 5.9 Hz, 1H), 3.48 - 3.61 (m, 1H), 3.24 – 3.33 (m, 3H), 3.04 - 3.19 (m, 1H), 2.30 (s, 3H)

LR MS (ES+): 499 ($M+Na^+$)

LR MS (ES-): 475 (M-H)

Example 16

5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide



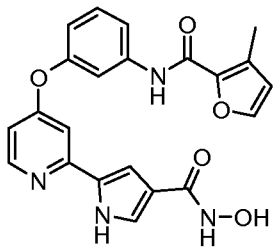
Similar procedure as Example 31.

^{1}H NMR (DMSO-d_6) δ: 11.83 (br. s., 1H), 10.21 (s, 1H), 8.40 (d, J = 5.9 Hz, 1H), 7.77 (s, 1H), 7.65 - 7.74 (m, 2H), 7.31 - 7.48 (m, 3H), 7.23 (d, J = 1.2 Hz, 1H), 7.07 (br. s., 1H), 6.86 - 6.95 (m, 1H), 6.75 (d, J = 3.5 Hz, 2H), 6.57 (s, 1H), 2.30 (s, 3H)

LR MS (ES-): 401 (M-H)

Example 17

N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide

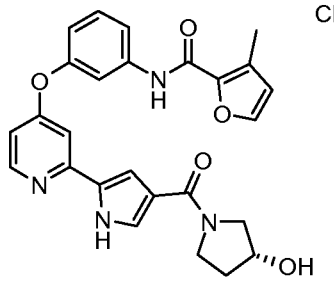


Similar procedure as Example 31.

^{1}H NMR (DMSO-d_6) δ: 11.84 (br. s., 1H), 10.49 - 10.64 (m, 1H), 10.20 (s, 1H), 8.60 - 8.74 (m, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.65 - 7.81 (m, 3H), 7.41 (t, J = 7.9 Hz, 1H), 7.32 (br. s., 1H), 7.23 (s, 1H), 7.02 (br. s., 1H), 6.85 - 6.94 (m, 1H), 6.69 - 6.78 (m, 1H), 6.57 (s, 1H), 2.30 (s, 3H)
LR MS (ES-): 417 (M-H)

Example 18

N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide

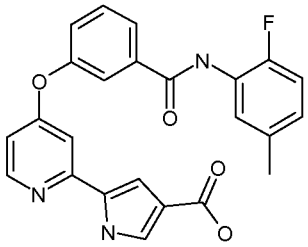


Similar procedure as Example 31.

^{1}H NMR (DMSO-d_6) δ: 11.90 (br. s., 1H), 10.20 (s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.64 - 7.73 (m, 2H), 7.36 - 7.46 (m, 2H), 7.21 - 7.30 (m, 1H), 7.03 - 7.13 (m, 1H), 6.85 - 6.93 (m, 1H), 6.70 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (d, J = 1.5 Hz, 1H), 4.90 (br. s., 1H), 4.30 (m, 1H), 3.76 (m, 1H), 3.49 (m, 2H), 2.30 (s, 3H), 1.86 (m, 2H)
LR MS (ES-): 471 (M-H)

Example 19

5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid



To a stirred solution of 5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid methyl ester (140mg, 0.31mmol) in THF (8ml) was added 5M NaOH solution (1ml, 5mmol). The mixture was heated at 70°C for 3 hours, cooled to room

temp, and poured into 100ml of water. 2M HCl was added until pH = 4. The precipitates were filtered, washed with water, and dried to give 5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid as white solid. Yield: 120mg, 92%.

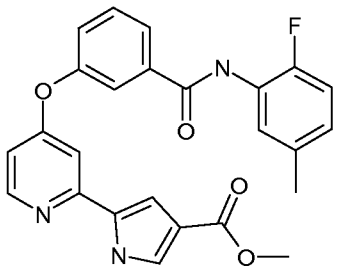
^{1}H NMR (d_6-DMSO): 12.03 (br. s., 1H), 11.89 (br. s., 1H), 10.11 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.77 (s, 1H), 7.56 - 7.71 (m, 1H), 7.30 - 7.54 (m, 4H), 6.97 - 7.23 (m, 3H), 6.75 (dd, J = 5.6, 2.1 Hz, 1H), 2.28 (s, 3H)

LR MS (ES+): 454 ($M+Na^+$)

LR MS (ES-): 430 (M-H)

Example 20

5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid methyl ester



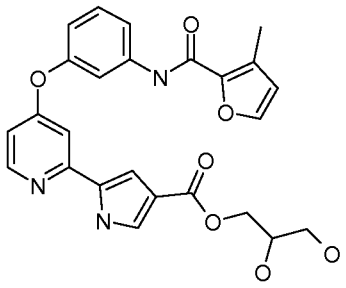
A mixture of 3-(2-bromo-pyridin-4-yloxy)-N-(2-fluoro-5-methyl-phenyl)-benzamide (200mg, 0.50 mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (251mg, 1.0 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10mg, 0.012 mmol) was added to a thick-walled reaction vessel and purged with N_2. A solution of 2M Na_2CO_3 (0.5 mL) was added, followed by DMSO (8 mL). The reaction vessel was sealed and the mixture stirred at 95°C for 16 h. The reaction vessel was cooled to room temperature and the mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude, which was purified via column chromatography eluting with 30-40% EtOAc/hexanes to afford 5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid methyl ester (150mg, 58% yield).

^{1}H NMR (d_6-DMSO): 12.14 (br. s., 1H), 10.11 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.77 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.41 - 7.50 (m, 3H), 7.35 (s, 1H), 7.09 - 7.21 (m, 2H), 7.06 (dd, J = 5.1, 1.9 Hz, 1H), 6.76 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 3H)

LR MS (ES+): 468 ($M+Na^+$)

LR MS (ES-): 444 (M-H)

Example 21

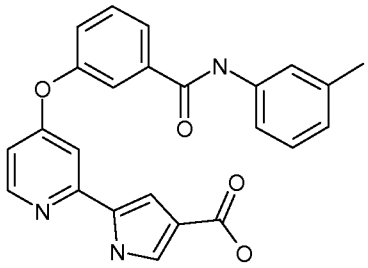


Similar procedure as Example 25.

2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate

Example 22

5-[4-(3-m-Tolylcarbamoyl-phenoxy)-pyridin-2-yl]-1H-pyrrole-3-carboxylic acid

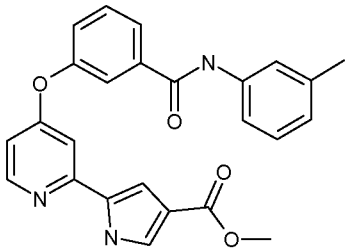


Similar procedure as Example 19.

^{1}H NMR (DMSO-d_6) δ: 12.03 (br. s., 1H), 11.86 (br. s., 1H), 10.19 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 7.50 - 7.69 (m, 3H), 7.32 - 7.46 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 7.06 (s, 1H), 6.91 (d, J = 7.3 Hz, 1H), 6.74 (dd, J = 5.6, 2.3 Hz, 1H), 2.28 (s, 3H)

Example 23

5-[4-(3-m-Tolylcarbamoyl-phenoxy)-pyridin-2-yl]-1H-pyrrole-3-carboxylic acid methyl ester

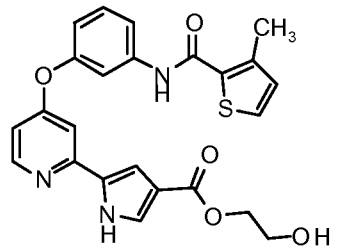


Similar procedure as Example 20.

^{1}H NMR (DMSO-d_6) δ: 12.14 (br. s., 1H), 10.18 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 7.50 - 7.68 (m, 3H), 7.38 - 7.48 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 7.12 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 3H)
LR MS (ES+): 450 ($M+Na^+$)
LR MS (ES-): 426 (M-H)

Example 24

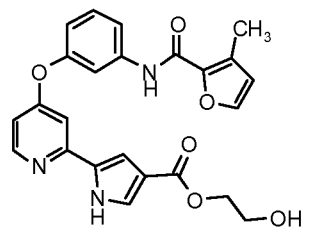
2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



Similar procedure as Example 25.
^{1}H NMR (d_6-DMSO): 12.13 (br. s., 1H), 10.13 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.68 (d, J = 5.0 Hz, 1H), 7.56 - 7.64 (m, 2H), 7.40 - 7.52 (m, 3H), 7.14 (s, 1H), 7.03 (d, J = 5.0 Hz, 1H), 6.89 - 6.98 (m, 1H), 6.76 (dd, J = 5.7, 2.2 Hz, 1H), 4.83 (t, J = 5.9 Hz, 1H), 4.15 (t, J = 5.1 Hz, 2H), 3.64 (q, J = 5.6 Hz, 2H), 2.44 (s, 3H)
LR MS (ES+): 486 ($M+Na^+$)
LR MS (ES-): 462 (M-H)

Example 25

2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



A mixture of 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid (70mg, 0.17mmol), ethylene glycol (1ml), 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC• HCl, 40mg, 0.21mmol) and 4-dimethylaminopyridine (DMAP, 10mg, 0.08mmol) in anhydrous DMF (10ml) was stirred at 70°C for 3 hours then room temperature for 16 hours. The mixture was poured into 100ml of water. Saturated $NaHCO_3$ solution was added until pH = 9. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with a gradient of 3~4% MeOH/$CHCl_3$ to give 2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate as white solid. Yield: 40mg, 51%.

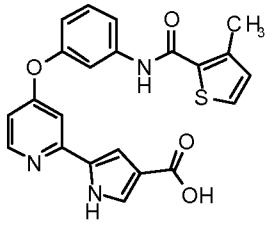
^{1}H NMR (d_6-DMSO): 12.13 (br. s., 1H), 10.22 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.79 (s, 1H), 7.70 (s, 2H), 7.36 - 7.54 (m, 3H), 7.13 (br. s., 1H), 6.86 - 6.97 (m, 1H), 6.72 - 6.80 (m, 1H), 6.59 (s, 1H), 5.75 (s, 1H), 4.83 (t, J = 5.3 Hz, 1H), 4.14 (t, J = 4.7 Hz, 2H), 3.58 - 3.69 (m, 2H), 2.32 (s, 3H)

LR MS (ES+): 470 ($M+Na^+$)

LR MS (ES-): 446 (M-H)

Example 26

5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid



Similar procedure as Example 32.

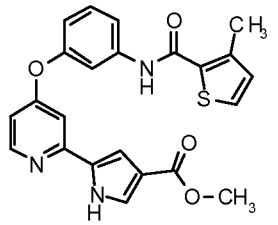
^{1}H NMR (d_6-DMSO): 12.04 (br. s., 1H), 11.87 (s, 1H), 10.13 (s, 1H), 8.42 (d, J = 6.2 Hz, 1H), 7.68 (d, J = 4.7 Hz, 1H), 7.57 - 7.64 (m, 2H), 7.40 - 7.49 (m, 2H), 7.38 (dd, J = 3.2, 1.5 Hz, 1H), 7.05 - 7.09 (m, 1H), 7.03 (d, J = 5.0 Hz, 1H), 6.90 - 6.97 (m, 1H), 6.75 (dd, J = 5.7, 2.5 Hz, 1H), 2.44 (s, 3H)

LR MS (ES+): 442 ($M+Na^+$)

LR MS (ES-): 418 (M-H)

Example 27

methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



Similar procedure as Example 33.

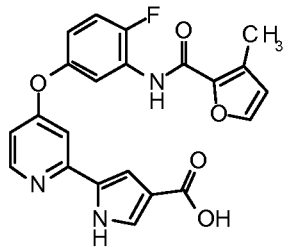
^{1}H NMR (DMSO-d_6) δ: 12.12 (br. s., 1H), 10.10 (s, 1H), 8.35 - 8.45 (m, 1H), 7.65 (d, J = 5.0 Hz, 1H), 7.55 - 7.60 (m, 2H), 7.37 - 7.45 (m, 3H), 7.10 (s, 1H), 7.00 (d, J = 5.0 Hz, 1H), 6.87 - 6.93 (m, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.41 (s, 3H)

LR MS (ES+): 456 ($M+Na^+$)

LR MS (ES-): 432 (M-H)

Example 28

5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid

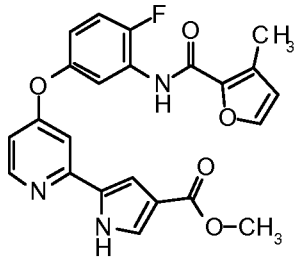


To a stirred solution of methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate (20mg, 0.046mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 3ml of 1M NaOH (3mmol) solution. The mixture was heated in a 72°C bath for 3 hours, cooled to room temperature and poured into 50ml of water. 2M HCl was added until pH = 4. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid as light gray solid. Yield: 19mg, 100%.

LR MS (ES-): 420 (M-H)

Example 29

methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



Similar procedure as Example 33.

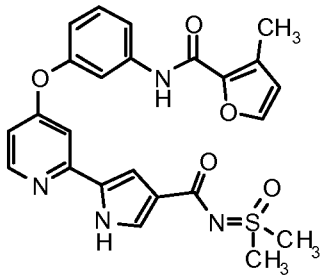
^{1}H NMR (d_6-DMSO): 12.15 (br. s., 1H), 9.74 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.60 (dd, J = 6.4, 2.9 Hz, 1H), 7.34 - 7.50 (m, 3H), 7.02 - 7.18 (m, 2H), 6.75 (dd, J = 5.6, 2.3 Hz, 1H), 6.60 (d, J = 1.5 Hz, 1H), 3.72 (s, 3H), 2.31 (s, 3H)

LR MS (ES+): 458 ($M+Na^+$)

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

Example 30

N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 101.

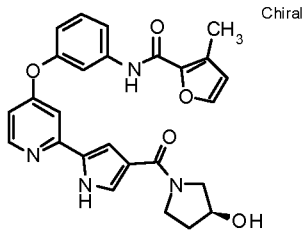
^{1}H NMR (d_6-DMSO): 11.83 (br. s., 1H), 10.20 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.65 - 7.72 (m, 2H), 7.37 - 7.45 (m, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.27 (dd, J = 2.9, 1.5 Hz, 1H), 6.96 - 6.99 (m, 1H), 6.87 - 6.92 (m, 1H), 6.71 (dd, J = 5.6, 2.3 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 3.35 (s, 6H), 2.30 (s, 3H)

LR MS (ES+): 501 ($M+Na^+$)

LR MS (ES-): 477 (M-H)

Example 31

N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide



A mixture of 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid (60mg, 0.15mmol), HATU (68mg, 0.18mmol) and *N,N*-diisopropylethylamine (43mg, 0.33mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of (S)-3-pyrrolidinol (16mg, 0.18mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide as white solid. Yield: 40mg, 56%.

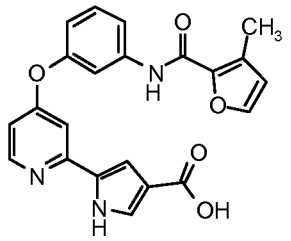
^{1}H NMR (d_6-DMSO): 11.95 (br. s., 1H), 10.21 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.64 - 7.74 (m, 2H), 7.35 - 7.51 (m, 2H), 7.29 (br. s., 1H), 7.12 (br. s., 1H), 6.90 (dd, J = 8.1, 1.3 Hz, 1H), 6.73 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 4.20 - 4.36 (m, 1H), 3.66 - 3.88 (m, 2H), 3.42 - 3.60 (m, 3H), 2.30 (s, 3H), 1.66 - 2.03 (m, 2H)

LR MS (ES+): 495 ($M+Na^+$)

LR MS (ES-): 471 (M-H)

Example 32

5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid



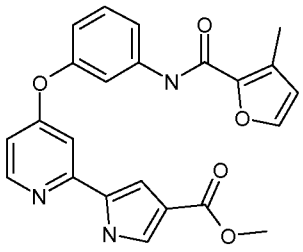
To a stirred solution of methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate (1.30g, 3.12mmol) in a mixture of solvents THF/MeOH (10ml/10ml) was added 2ml of 5M NaOH (10mmol) solution. The mixture was heated in a 68°C bath for 8 hours, cooled to room temperature and poured into 200ml of water. 2M HCl was added until pH = 3. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid as white solid. Yield: 1.20g, 95%.

^{1}H NMR (d_6-DMSO): 11.98 (br. s., 1H), 10.22 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.61 - 7.76 (m, 2H), 7.27 - 7.51 (m, 3H), 7.04 (br. s., 1H), 6.85 - 6.98 (m, 1H), 6.73 (dd, J = 5.7, 2.2 Hz, 1H), 6.59 (d, J = 1.5 Hz, 1H), 2.32 (s, 3H)

LR MS (ES-): 402 (M-H)

Example 33

methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



A mixture of 3-methyl-2-furoic acid (490 mg, 3.88mmol), HATU (1.71 g, 4.5mmol) and *N,N*-diisopropylethylamine (1.0g, 7.8mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of methyl 5-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate (1.0g, 3.24mmol). The mixture was stirred at 50°C for 2 hours and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate as white solid. Yield: 1.30g, 96%.

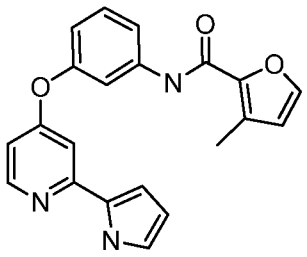
^{1}H NMR (d_6-DMSO): 12.15 (br. s., 1H), 10.22 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.68 - 7.74 (m, 2H), 7.38 - 7.47 (m, 3H), 7.09 - 7.14 (m, 1H), 6.88 - 6.94 (m, 1H), 6.75 (dd, J = 5.6, 2.3 Hz, 1H), 6.59 (d, J = 1.5 Hz, 1H), 3.72 (s, 3H), 2.32 (s, 3H)

LR MS (ES+): 440 ($M+Na^+$)

LR MS (ES-): 416 (M-H)

Example 34

3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide



A mixture of 3-methyl-2-furoic acid (60 mg, 0.48mmol), HBTU (198 mg, 0.52mmol) and *N,N*-diisopropylethylamine (129mg, 1.0mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of 3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}aniline (100mg, 0.40mmol). The mixture was stirred at 70°C for 3 hours and poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with 3-5% MeOH/$CHCl_3$ to give 3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide as white solid. Yield: 52mg, 36%.

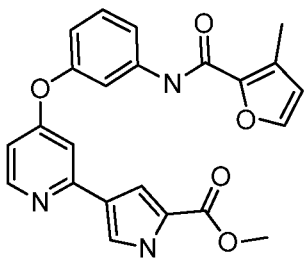
^{1}H NMR (d_6-DMSO): 11.46 (br. s., 1H), 10.19 (s, 1H), 8.36 (d, J = 6.2 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.64 - 7.72 (m, 2H), 7.35 - 7.44 (m, 1H), 7.28 (d, J = 2.1 Hz, 1H), 6.86 - 6.91 (m, 1H), 6.81 - 6.86 (m, 1H), 6.68 - 6.74 (m, 1H), 6.65 (dd, J = 5.7, 2.5 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 6.06 - 6.13 (m, 1H), 2.30 (s, 3H)

LR MS (ES+): 360 (M+H)

LR MS (ES-): 358 (M-H)

Example 35

methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate



Similar procedure as Example 33.

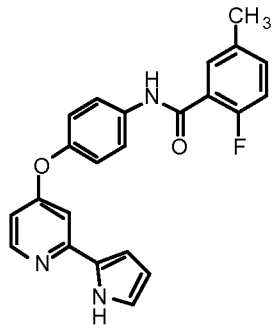
^{1}H NMR (d_6-DMSO): 12.18 (br. s., 1H), 10.19 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.59 - 7.72 (m, 3H), 7.33 - 7.44 (m, 2H), 7.25 - 7.32 (m, 1H), 6.83 - 6.93 (m, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 6.57 (d, J = 1.2 Hz, 1H), 3.76 (s, 3H), 2.30 (s, 3H)

LR MS (ES+): 440 ($M+Na^+$)

LR MS (ES-): 416 (M-H)

Example 36

2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide



Similar procedure as Example 37.

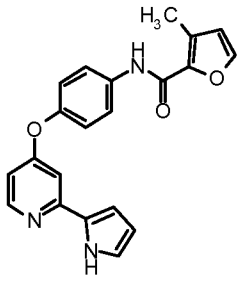
^{1}H NMR (d_6-DMSO): 11.44 (br. s., 1H), 10.47 (s, 1H), 8.33 (d, J = 5.6 Hz, 1H), 7.76 - 7.86 (m, 2H), 7.46 (dd, J = 6.4, 2.1 Hz, 1H), 7.36 (ddd, J = 7.9, 5.3, 2.1 Hz, 1H), 7.13 - 7.27 (m, 4H), 6.80 - 6.87 (m, 1H), 6.66 - 6.73 (m, 1H), 6.60 (dd, J = 5.6, 2.3 Hz, 1H), 6.06 - 6.15 (m, 1H), 2.34 (s, 3H)

LR MS (ES+): 388 (M+H)

LR MS (ES-): 386 (M-H)

Example 37

3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide

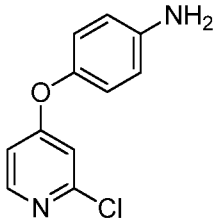


A mixture of 3-methyl-2-furoic acid (70mg, 0.55mmol), HATU (243mg, 0.64mmol),) tert-butyl 2-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1-carboxylate (160mg, 0.46mmol) and *N,N*-diisopropylethylamine (148mg, 1.15mmol) in anhydrous DMF (10ml) was stirred at 45°C for 2 hours. The mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was dissolved in 5ml of methylene chloride, followed by addition of trifluoroacetic acid (3ml). The mixture was stirred at room temperature for 16 hours. The solvents were evaporated under reduced pressure. The residue was purified by reversed-phase chromatography with a gradient of 10~50% acetonitrile/water to give 3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide as white solid. Yield: 56mg, 34%.

LR MS (ES+): 360 (M+H)

LR MS (ES-): 358 (M-H)

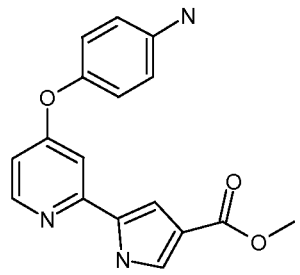
Preparation of 4-((2-chloropyridin-4-yl)oxy)aniline



A stirred solution of 4-aminophenol (740mg, 6.8mmol) in anhydrous DMSO (8ml) was flushed with nitrogen and treated with 1M $KOBu^t$ / THF solution (10ml, 10mmol). The mixture was stirred at room temperature under nitrogen for 10 minutes. 2,4-dichloropyridine (1.0g, 6.8mmol) was added and the mixture was heated at 60°C for 30 minutes, cooled to room temperature and poured into 100ml of water. The resulting precipitates were filtered, washed with water and dried to give 4-((2-chloropyridin-4-yl)oxy)aniline as light brown solid. The material was used for the following reactions without further purification. Yield: 1.15g, 77%.

^{1}H NMR (d_6-DMSO): 8.21 (d, 1H), 6.77 - 6.91 (m, 4H), 6.54 - 6.68 (m, 2H), 5.16 (s, 2H)

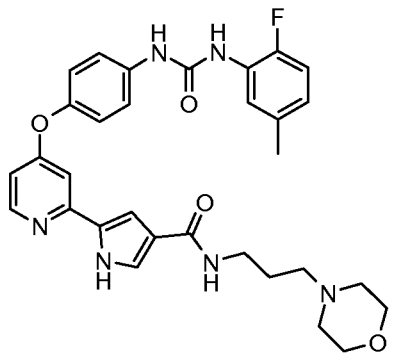
Preparation of methyl 5-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



A mixture of 4-((2-chloropyridin-4-yl)oxy)aniline (2.6 g, 11.78 mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (6.0 g, 23.90 mmol) and Pd(PPh3)4 (2.72 g, 2.35 mmol) was added to a thick walled reaction vessel and purged with N_2. A solution of 2M K_2CO_3 (17.68 mL) was added, followed by DME (90 mL). The reaction vessel was sealed and the mixture stirred at 92°C for 18 h. The reaction vessel was cooled to room temperature and the mixture was filtered over celite, washing with EtOAc. The filtrate was concentrated to afford a dark oil, which was purified via column chromatography eluting with 40-80% EtOAc/hexanes to afford methyl 5-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate (2.4 g, 65% yield).

Example 38

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(3-morpholin-4-ylpropyl)-1H-pyrrole-3-carboxamide

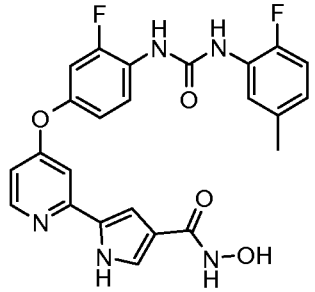


Similar procedure as Example 132.

LR MS (ES+): 573 (MH)

Example 39

5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-hydroxy-1H-pyrrole-3-carboxamide



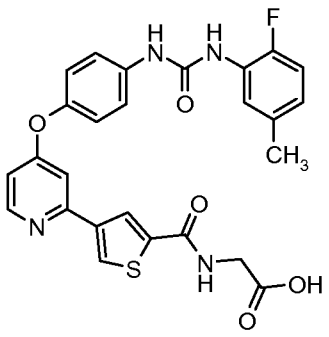
Similar procedure as Example 132.

^{1}H NMR (DMSO-d_6) δ: 11.82 (br. s., 1H), 10.55 (br. s., 1H), 9.05 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 2.3 Hz, 1H), 8.64 (br. s., 1H), 8.37 (d, J = 5.6 Hz, 1H), 8.23 (t, J = 9.2 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.31 (br. s., 1H), 7.26 (dd, J = 11.7, 2.6 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 6.98 - 7.05 (m, 2H), 6.76 - 6.83 (m, 1H), 6.73 (dd, J = 5.7, 2.5 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 478 (M-H)

Example 40

{[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thien



acid

To a stirred solution of methyl {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetate (60mg, 0.11mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 1ml of 1M NaOH (1.0mmol) solution. The mixture was stirred at room temperature for 1 hour and poured into 100ml of water. 2M HCl was added until pH = 3. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give {[(4-{4-[4-({[(2-fluoro-5-

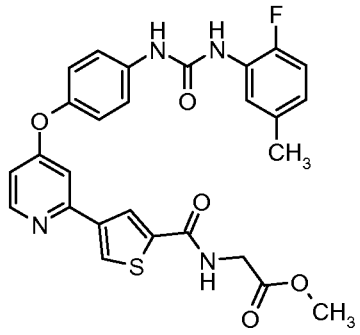
methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetic acid as white solid. Yield: 50mg, 86%.

^{1}H NMR (DMSO-d_6) δ: 12.61 (br s, 1H), 9.15 (s, 1H), 8.98 (t, J = 5.9 Hz, 1H), 8.43 - 8.48 (m, 2H), 8.40 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 1.2 Hz, 1H), 7.95 (dd, J = 7.6, 1.8 Hz, 1H), 7.50 - 7.58 (m, 2H), 7.40 (d, J = 2.3 Hz, 1H), 7.12 - 7.19 (m, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.73 - 6.81 (m, 2H), 3.88 (d, J = 5.9 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 519 (M-H)

Example 41

methyl {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetate



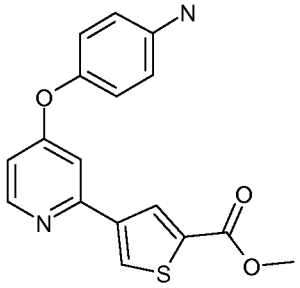
A mixture of 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylic acid (100mg, 0.22mmol), HATU (100mg, 0.26mmol) and *N,N*-diisopropylethylamine (85mg, 0.66mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of glycine methyl ester hydrochloride (41mg, 0.33mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give methyl {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetate as white solid. Yield: 90mg, 78%.

^{1}H NMR (DMSO-d_6) δ: 9.17 (s, 1H), 9.10 (t, J = 5.9 Hz, 1H), 8.44 - 8.49 (m, 2H), 8.37 - 8.42 (m, 2H), 7.92 - 7.98 (m, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 2.1 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.84 (m, 2H), 3.98 (d, J = 5.9 Hz, 2H), 3.63 (s, 3H), 2.25 (s, 3H)

LR MS (ES+): 557 ($M+Na^+$)

LR MS (ES-): 533 (M-H)

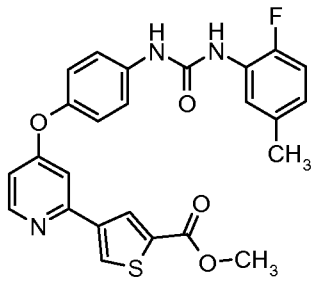
Preparation of methyl 4-(4-(4-aminophenoxy)pyridine-2-yl)thiophene-2-carboxylate



A mixture of 4-(4-aminophenoxy)-2-chloropyridine (5.0 g, 22.66mmol), methyl-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-thiophene-2-carboxylate (9.73 g, 36.25 mmol) and $Pd(PPh_3)_4$ (5.24 g, 4.53 mmol) was added to a thick walled reaction vessel and purged with N_2. A solution of 2M K_2CO_3 (17.0 mL) was added, followed by dioxane (120 mL). The reaction vessel was sealed and the mixture stirred at 92°C for 18 h. The reaction vessel was cooled to room temperature and the mixture was filtered over celite, washing with EtOAc. The filtrate was concentrated and the resultant dark oil was purified via column chromatography, eluting with 40-60% EtOAc/hexanes to afford methyl 4-(4-(4-aminophenoxy)pyridine-2-yl)thiophene-2-carboxylate (6.1 g, 82% yield).

Example 42

methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylate



To a stirred solution of methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]thiophene-2-carboxylate (500 mg, 1.53 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (255mg, 1.68mmol). The mixture was stirred at room temperature for one hour and poured into 200ml of water. The resulting precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with 3-5% $MeOH/CHCl_3$ to give methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylate as off-white solid. Yield: 560mg, 76%.

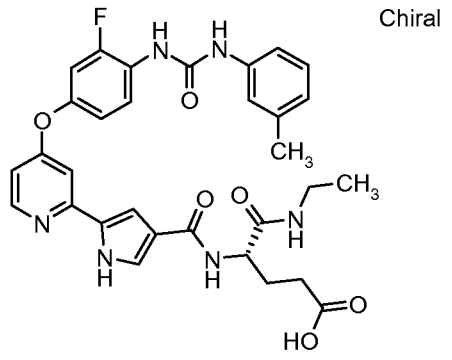
^1H NMR (DMSO-d_6) δ: 9.14 (s, 1H), 8.51 (d, J = 1.5 Hz, 1H), 8.41 - 8.47 (m, 2H), 8.33 (d, J = 1.8 Hz, 1H), 7.96 (d, J = 6.2 Hz, 1H), 7.48 - 7.57 (m, 3H), 7.13 (d, J = 9.1 Hz, 2H), 7.08 (dd, J = 11.4, 8.5 Hz, 1H), 6.76 - 6.81 (m, 1H), 6.74 (dd, J = 5.6, 2.3 Hz, 1H), 3.83 (s, 3H), 2.25 (s, 3H)

LR MS (ES+): 500 ($M+Na^+$)

LR MS (ES-): 476 (M-H)

Example 43

(4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid



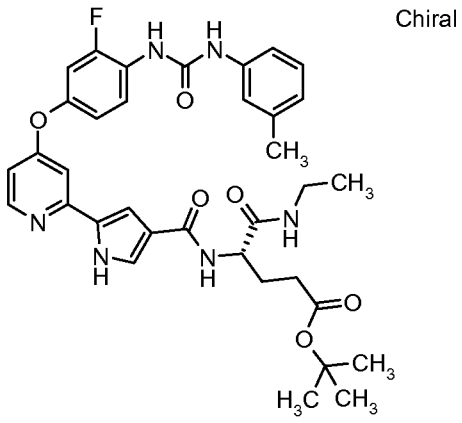
To a stirred solution of tert-butyl (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoate (30mg, 0.046mmol) in 5ml of methylene chloride was added 2ml of TFA. The mixture was stirred at room temperature for 1 hour, and evaporated to dryness. The residue was dissolved in MeOH (3ml), which was added dropwise into 100ml of water with vigorous stirring. The precipitates were filtered, washed with water and dried to give (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid as white solid. Yield: 20mg, 74%.

^{1}H NMR (DMSO-d_6) δ: 12.04 (br. s., 1H), 11.86 (br. s., 1H), 8.97 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.82 (t, J = 5.6 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.46 (br. s., 1H), 7.12 - 7.29 (m, 5H), 6.99 - 7.04 (m, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 4.7 Hz, 1H), 4.31 (td, J = 8.6, 5.4 Hz, 1H), 2.97 - 3.11 (m, 2H), 2.26 (s, 3H), 2.17 - 2.25 (m, 2H), 1.87 - 1.98 (m, 1H), 1.74 - 1.84 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H)

LR MS (ES-): 601 (M-H)

Example 44

tert-butyl (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoate



A mixture of (2S)-5-tert-butoxy-2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid (80mg, 0.13mmol), HATU (57mg, 0.15mmol) and *N,N*-

diisopropylethylamine (49mg, 0.38mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes, followed by addition of 2M ethylamine in THF solution (0.1ml, 0.2mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 5. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with 4~5% MeOH/$CHCl_3$ to give tert-butyl (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoate as white solid. Yield: 40mg, 48%.

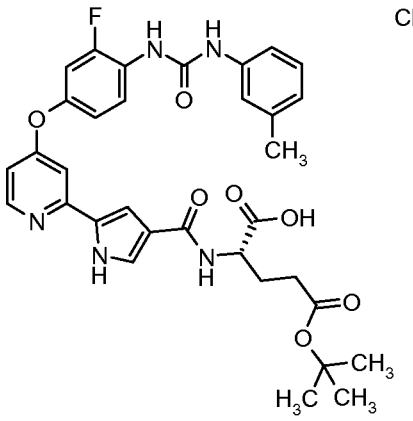
^{1}H NMR (DMSO-d_6) δ: 11.83 (br. s., 1H), 8.95 (s, 1H), 8.56 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.81 (t, J = 5.3 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 1.5 Hz, 1H), 7.23 - 7.30 (m, 2H), 7.18 - 7.23 (m, 2H), 7.12 - 7.18 (m, 2H), 6.98 - 7.04 (m, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 4.27 - 4.35 (m, 1H), 3.01 - 3.08 (m, 2H), 2.26 (s, 3H), 2.17 - 2.23 (m, 2H), 1.87 - 1.95 (m, 1H), 1.78 (m, 1H), 1.34 (s, 9H), 0.97 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 681 ($M+Na^+$)

LR MS (ES-): 657 (M-H)

Example 45

(2S)-5-tert-butoxy-2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid



To a stirred solution of (S)-5-tert-butyl 1-methyl 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate (120mg, 0.19mmol) in a mixture of solvents THF/MeOH

(5ml/5ml) was added 1ml of 1M NaOH (1mmol) solution. The mixture was stirred at room temperature for 30 minutes, and poured into 100ml of water. 2M HCl was added dropwise until pH = 4. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give (2S)-5-tert-butoxy-2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid as white solid. Yield: 100mg, 85%.

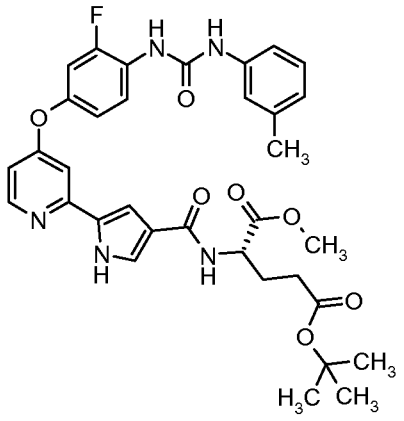
^{1}H NMR (DMSO-d_6) δ: 12.49 (br. s., 1H), 11.84 (br. s., 1H), 8.98 (s, 1H), 8.58 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.89 (br. s., 1H), 7.42 (br. s., 1H), 7.28 (s, 1H), 7.25 (dd, J = 11.7, 2.6 Hz, 1H), 7.20 - 7.23 (m, 2H), 7.11 - 7.18 (m, 2H), 7.01 (dd, J = 9.0, 1.6 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 4.23 - 4.34 (m, 1H), 2.23 - 2.28 (m, 2H), 2.26 (s, 3H), 1.95 - 2.03 (m, 1H), 1.80 - 1.88 (m, 1H), 1.35 (s, 9H)

LR MS (ES+): 654 ($M+Na^+$)

LR MS (ES-): 630 (M-H)

Example 46

(S)-5-tert-butyl 1-methyl 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate



A mixture of 5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (500mg, 1.1mmol), HATU (500mg, 1.32mmol) and *N,N*-diisopropylethylamine (426mg, 3.3mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes, followed by addition of L-Glutamic acid 5-tert-butyl 1-methyl ester hydrochloride (334mg, 1.32mmol). The mixture was stirred for another 10 minutes and poured into 200ml of water. 2M HCl was added dropwise until pH = 5. The precipitates were filtered,

washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with 3~5% MeOH/$CHCl_3$ to give (S)-5-tert-butyl 1-methyl 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate as off-white solid. Yield: 380mg, 52%.

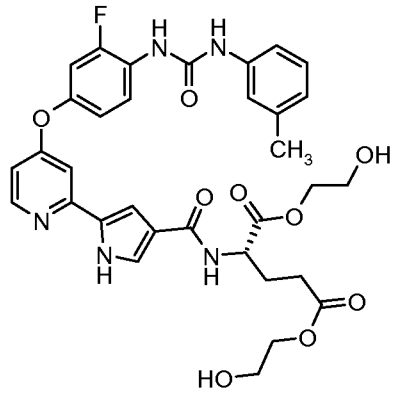
^{1}H NMR (DMSO-d_6) δ: 11.87 (br. s., 1H), 8.96 (s, 1H), 8.56 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 8.9 Hz, 1H), 8.08 (d, J = 7.0 Hz, 1H), 7.44 (br. s., 1H), 7.23 - 7.29 (m, 2H), 7.18 - 7.23 (m, 2H), 7.11 - 7.17 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.70 - 6.76 (m, 1H), 4.32 - 4.41 (m, 1H), 3.60 (s, 3H), 2.23 - 2.31 (m, 5H), 1.93 - 2.03 (m, 1H), 1.81 - 1.91 (m, 1H), 1.35 (s, 9H)

LR MS (ES+): 646 (MH), 668 ($M+Na^+$)

LR MS (ES-): 644 (M-H)

Example 47

bis(2-hydroxyethyl) 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate

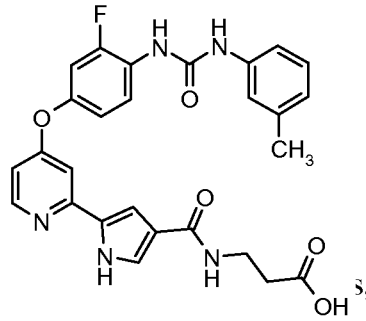


LR MS (ES+): 686 ($M+Na^+$)

LR MS (ES-): 662 (M-H), 561

Example 48

3-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid

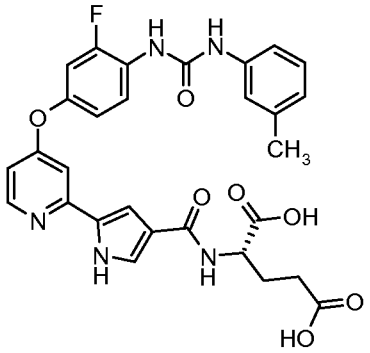
Similar procedure as 

^{1}H NMR (DMSO-d_6) s, 1H), 8.59 (br. s., 1H), 8.40 (d, J = 5.9 Hz, 1H), 8.22 (t, J = 9.0 Hz, 1H), 7.90 - 7.96 (m, 1H), 7.40 (br. s., 1H), 7.25 - 7.30 (m, 2H), 7.21 (d, J = 7.0 Hz, 2H), 7.15 (t, J = 7.8 Hz, 2H), 7.03 (d, J = 9.1 Hz, 1H), 6.79 (d, J = 7.0 Hz, 2H), 3.32 - 3.37 (m, 2H), 2.43 (t, J = 7.0 Hz, 2H), 2.26 (s, 3H)

LR MS (ES-): 516 (M-H)

Example 49

2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid

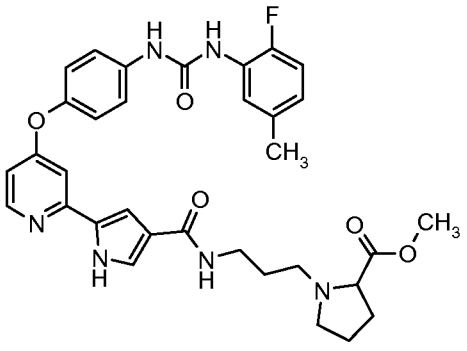


^{1}H NMR (DMSO-d_6) δ: 12.43 (br. s., 2H), 11.89 (br. s., 1H), 8.97 (br. s., 1H), 8.57 (br. s., 1H), 8.39 (d, J = 5.3 Hz, 1H), 8.20 (t, J = 8.8 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.46 (br. s., 1H), 7.11 - 7.31 (m, 4H), 7.02 (d, J = 9.1 Hz, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.75 (br. s., 1H), 4.32 (br. s., 1H), 2.30 (t, J = 7.2 Hz, 2H), 2.26 (s, 3H), 2.01 (m, 2H), 1.86 (m, 2H)

LR MS (ES-): 574 (M-H)

Example 50

methyl 1-(3-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propyl)pyrrolidine-2-carboxylate



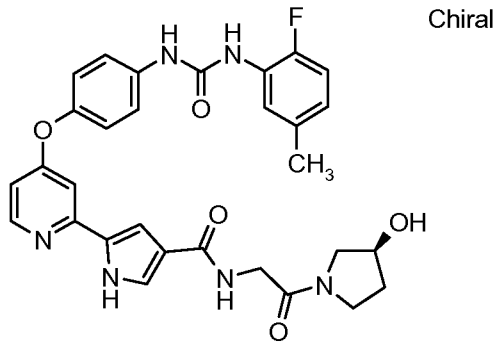
Similar procedure as Example 132.

LR MS (ES+): 615 (MH), 637 ($M+Na^+$)

LR MS (ES-): 613 (M-H)

Example 51

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-{2-[(3S)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}-1H-pyrrole-3-carboxamide



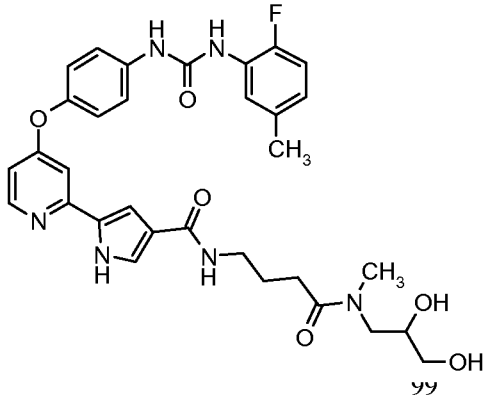
Similar procedure as Example 132.

LR MS (ES+): 573 (MH), 595 ($M+Na^+$)

LR MS (ES-): 571 (M-H)

Example 52

N-{4-[(2,3-dihydroxypropyl)(methyl)amino]-4-oxobutyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

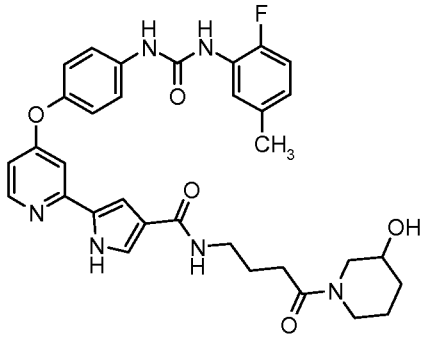
^{1}H NMR (DMSO-d_6) δ: 11.70 - 11.82 (m, 1H), 9.24 (s, 1H), 8.50 (d, J = 2.1 Hz, 1H), 8.35 (d, J = 5.9 Hz, 1H), 7.93 - 7.98 (m, 1H), 7.85 (dt, J = 14.5, 5.5 Hz, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.34 (br. s., 1H), 7.10 - 7.15 (m, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 7.01 - 7.05 (m, 1H), 6.73 - 6.82 (m, 1H), 6.67 (dd, J = 5.6, 2.3 Hz, 1H), 4.87 (d, J = 5.3 Hz, 1H), 4.60 - 4.69 (m, 1H), 4.46 (t, J = 5.9 Hz, 1H), 3.55 - 3.65 (m, 2H), 3.20 - 3.27 (m, 2H), 3.10 - 3.19 (m, 2H), 2.96 (s, 1H), 2.79 (s, 2H), 2.27 - 2.35 (m, 1H), 2.24 (s, 3H), 1.62 - 1.72 (m, 2H)

LR MS (ES+): 619 (MH), 641 ($M+Na^+$)

LR MS (ES-): 617 (M-H)

Example 53

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypiperidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide



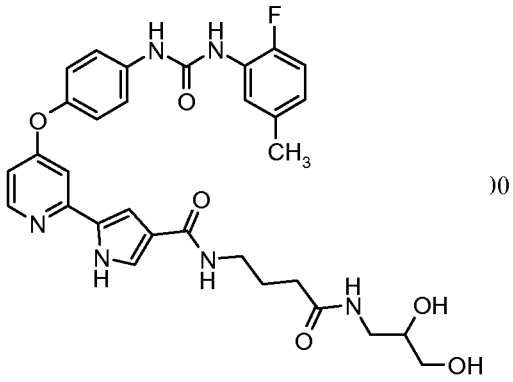
Similar procedure as Example 61.

LR MS (ES+): 637 ($M+Na^+$)

LR MS (ES-): 613 (M-H)

Example 54

N-{4-[(2,3-dihydroxypropyl)amino]-4-oxobutyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

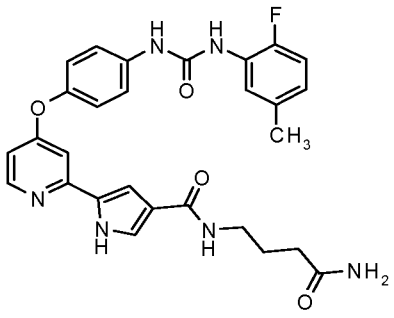
^{1}H NMR (DMSO-d_6) δ: 11.77 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.35 (d, J = 5.9 Hz, 1H), 7.96 (dd, J = 7.9, 2.1 Hz, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.77 (t, J = 5.9 Hz, 1H), 7.51 - 7.57 (m, 2H), 7.33 (dd, J = 3.1, 1.6 Hz, 1H), 7.11 - 7.16 (m, 3H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 7.01 - 7.05 (m, 1H), 6.75 - 6.82 (m, 1H), 6.68 (dd, J = 5.7, 2.5 Hz, 1H), 4.68 (d, J = 5.0 Hz, 1H), 4.46 (t, J = 5.9 Hz, 1H), 3.41 - 3.47 (m, 1H), 3.20 - 3.26 (m, 2H), 3.09 - 3.19 (m, 3H), 2.90 - 2.97 (m, 1H), 2.25 (s, 3H), 2.10 (t, J = 7.6 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 605 (MH), 627 ($M+Na^+$)

LR MS (ES-): 603 (M-H)

Example 55

N-(4-amino-4-oxobutyl)-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

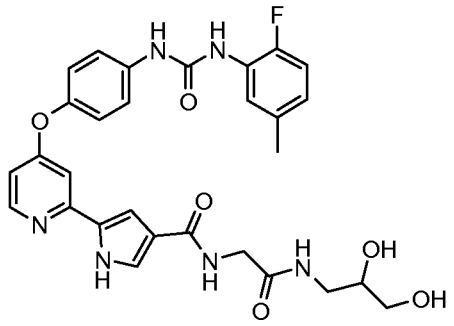
^{1}H NMR (DMSO-d_6) δ: 11.92 (br. s., 1H), 9.20 (br. s., 1H), 8.48 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.89 (br. s., 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.42 (br. s., 1H), 7.18 - 7.28 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.4, 8.5 Hz, 1H), 6.78 (ddd, J = 7.5, 5.0, 2.2 Hz, 2H), 6.68 (br. s., 1H), 3.14 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 2.05 (t, J = 7.5 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 553 ($M+Na^+$)

LR MS (ES-): 529 (M-H)

Example 56

N-{2-[(2,3-dihydroxypropyl)amino]-2-oxoethyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

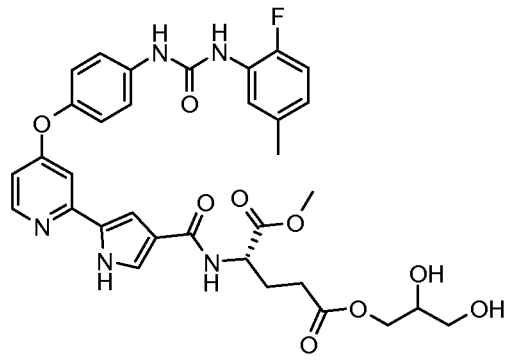
^{1}H NMR (DMSO-d_6) δ: 11.83 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.36 (d, J = 5.9 Hz, 1H), 8.14 (t, J = 6.0 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 5.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.38 (br. s., 1H), 7.13 (d, J = 8.8 Hz, 3H), 7.03 - 7.11 (m, 2H), 6.75 - 6.82 (m, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.70 (d, J = 5.0 Hz, 1H), 4.47 (t, J = 5.7 Hz, 1H), 3.76 (d, J = 5.6 Hz, 2H), 3.45 (dq, J = 11.2, 5.5 Hz, 1H), 3.16 - 3.27 (m, 3H), 2.93 - 3.00 (m, 1H), 2.25 (s, 3H)

LR MS (ES+): 577 (MH), 599 ($M+Na^+$)

LR MS (ES-): 575 (M-H)

Example 57

5-(2,3-dihydroxypropyl) 1-methyl 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate



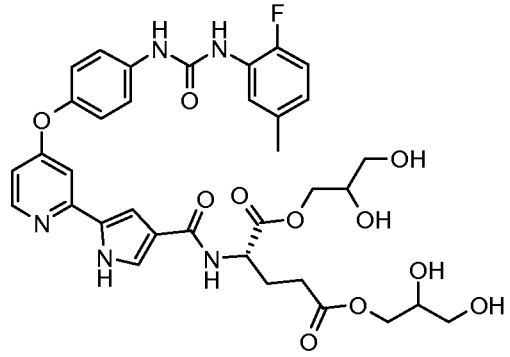
Similar procedure as Example 58.

^{1}H NMR (DMSO-d_6) δ: 11.86 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 8.08 - 8.17 (m, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.43 (br. s., 1H), 7.04 - 7.21 (m, 4H), 6.78 (dt, J = 5.7, 2.7 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 4.83 (d, J = 5.3 Hz, 1H), 4.58 (t, J = 5.7 Hz, 1H), 4.36 - 4.45 (m, 1H), 3.95 - 4.06 (m, 2H), 3.88 (dd, J = 11.0, 6.6 Hz, 1H), 3.60 (s, 3H), 3.28 - 3.35 (m, 2H), 2.40 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.99 - 2.10 (m, 1H), 1.88 - 1.95 (m, 1H), 1.15 (t, J = 7.0 Hz, 1H)

LR MS (ES+): 664 (MH), 686 ($M+Na^+$)

Example 58

bis(2,3-dihydroxypropyl) 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate



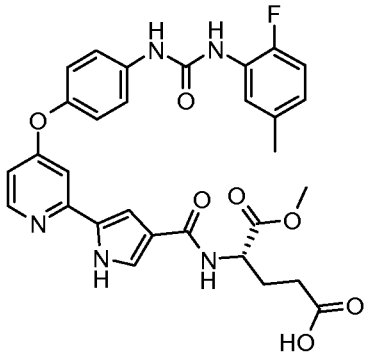
A mixture of 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid (60mg, 0.10mmol), glycerol (0.5ml), 1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC• HCl, 37mg, 0.19mmol) and 4-dimethylaminopyridine (DMAP, 5mg, 0.04mmol) in anhydrous THF (10ml) was stirred at 60°C for 3 hours. The mixture was cooled to room temperature, concentrated and purified by silica gel chromatography eluting with a gradient of 10~15% MeOH/$CHCl_3$ to give bis(2,3-dihydroxypropyl) 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate as colorless oil. Yield: 40mg, 53%.

LR MS (ES+): 746 ($M+Na^+$)

LR MS (ES-): 722 (M-H)

Example 59

4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-methoxy-5-oxopentanoic acid



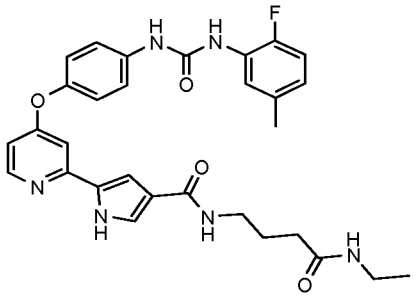
Similar procedure as Example 132.

^{1}H NMR (DMSO-d_6) δ: 11.98 (br. s., 1H), 9.19 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.13 (d, J = 7.3 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.53 - 7.57 (m, 2H), 7.47 - 7.52 (m, 1H), 7.24 (br. s., 1H), 7.19 (br. s., 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.72 - 6.81 (m, 2H), 4.38 (ddd, J = 9.5, 7.5, 5.3 Hz, 1H), 3.60 (s, 3H), 2.31 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.95 - 2.05 (m, 1H), 1.82 - 1.93 (m, J = 14.0, 9.6, 7.0, 7.0 Hz, 1H)

LR MS (ES-): 588 (M-H)

Example 60

N-[4-(ethylamino)-4-oxobutyl]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

^{1}H NMR (DMSO-d_6) δ: 11.96 (br. s., 1H), 9.20 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.89 (br. s., 1H), 7.76 (t, J = 5.3 Hz, 1H), 7.53 - 7.58 (m,

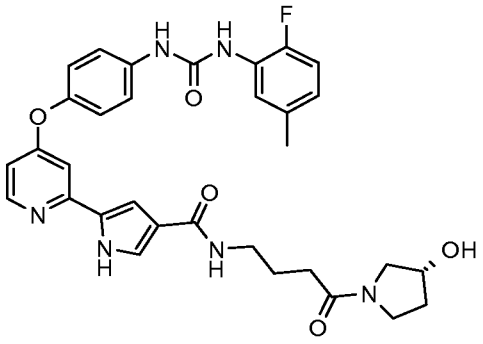
2H), 7.44 (br. s., 1H), 7.23 (br. s., 1H), 7.13 - 7.19 (m, 3H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.84 (m, 2H), 3.11 - 3.17 (m, 2H), 3.01 (qd, J = 7.2, 5.6 Hz, 2H), 2.25 (s, 3H), 2.05 (t, J = 7.5 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 559 (MH), 581 ($M+Na^+$)

LR MS (ES-): 557 (M-H)

Example 61

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypyrrolidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide



A mixture of 4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid (60mg, 0.11mmol), HATU (50mg, 0.13mmol) and *N,N*-diisopropylethylamine (43mg, 0.33mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes, followed by addition of (R)-3-pyrrolidinol (14mg, 0.16mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypyrrolidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide as white solid. Yield: 40mg, 59%.

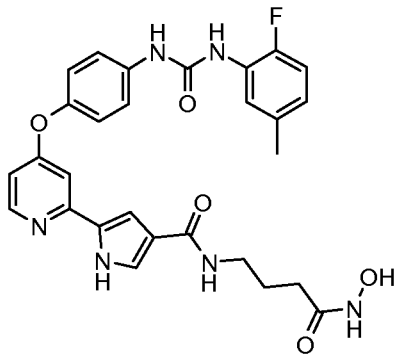
^{1}H NMR (DMSO-d_6) δ: 11.97 (br. s., 1H), 9.31 (s, 1H), 8.53 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.91 (d, J = 4.4 Hz, 1H), 7.54 - 7.59 (m, 2H), 7.42 - 7.48 (m, 1H), 7.24 (br. s., 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.05 - 7.10 (m, 1H), 6.78 (ddd, J = 7.5, 5.0, 2.2 Hz, 2H), 4.24 - 4.28 (m, 0H), 4.16 - 4.21 (m, 1H), 3.40 - 3.48 (m, 2H), 3.35 (ddd, J = 11.6, 8.4, 3.5 Hz, 1H), 3.25 - 3.30 (m, 1H), 3.14 - 3.25 (m, 4H), 2.25 (s, 3H), 2.23- 2.27 (m, 1H), 2.20 (t, J = 7.9 Hz, 1H), 1.84 - 1.92 (m, 1H), 1.75 - 1.82 (m, 1H), 1.65 - 1.73 (m, 2H)

LR MS (ES+): 601 (MH), 623 ($M+Na^+$)

LR MS (ES-): 599 (M-H)

Example 62

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(hydroxyamino)-4-oxobutyl]-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

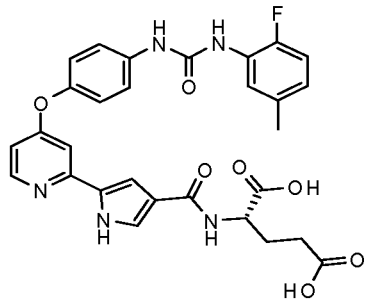
^{1}H NMR (DMSO-d_6) δ: 11.92 (br. s., 1H), 10.33 (s, 1H), 9.18 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 - 7.92 (m, 1H), 7.51 - 7.58 (m, 2H), 7.38 - 7.46 (m, 1H), 7.21 (br. s., 1H), 7.11 - 7.18 (m, 3H), 7.05 - 7.11 (m, 1H), 6.72 - 6.82 (m, 2H), 3.14 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 1.96 (t, J = 7.6 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 547 (MH), 569 ($M+Na^+$)

LR MS (ES-): 545 (M-H)

Example 63

2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid



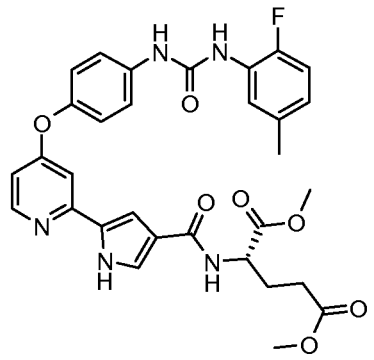
Similar procedure as Example 132.

^{1}H NMR (DMSO-d_6) δ: 12.42 (br. s., 1H), 12.12 (br. s., 1H), 11.86 (br. s., 1H), 9.15 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.93 - 8.01 (m, 2H), 7.51 - 7.58 (m, 2H), 7.44 (br. s., 1H), 7.18 (s, 1H), 7.11 - 7.16 (m, 3H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.82 (m,

1H), 6.69 (d, J = 3.8 Hz, 1H), 4.32 (ddd, J = 9.7, 7.9, 5.0 Hz, 1H), 2.30 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.96 - 2.05 (m, 1H), 1.80 - 1.91 (m, J = 14.0, 9.8, 7.2, 7.2 Hz, 1H)
LR MS (ES-): 574 (M-H)

Example 64

dimethyl 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate

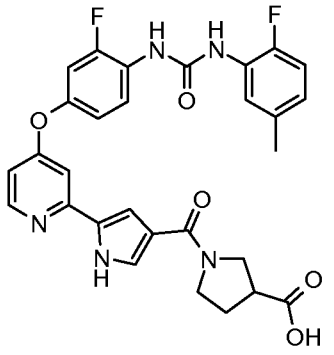


Similar procedure as Example 132.

^{1}H NMR (DMSO-d_6) δ: 12.27 (br. s., 1H), 9.33 (br. s., 1H), 8.50 - 8.57 (m, 1H), 8.44 (d, J = 6.2 Hz, 1H), 8.23 (d, J = 6.7 Hz, 1H), 7.95 (d, J = 6.5 Hz, 1H), 7.64 (br. s., 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.39 (br. s., 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.2, 8.2 Hz, 1H), 6.92 (br. s., 1H), 6.79 (d, J = 5.6 Hz, 1H), 4.35 - 4.43 (m, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 2.22 - 2.28 (m, 3H), 2.00 - 2.10 (m, 1H), 1.88 - 1.97 (m, 1H)
LR MS (ES+): 626 ($M+Na^+$)
LR MS (ES-): 602 (M-H)

Example 65

1-[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]pyrrolidine-3-carboxylic acid



Similar procedure as Example 132.

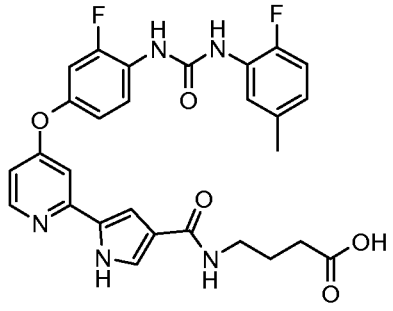
^{1}H NMR (DMSO-d_6) δ: 12.47 (br. s., 1H), 11.85 - 12.01 (m, 1H), 9.05 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.22 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.41 (br. s., 1H), 7.21 - 7.32 (m, 2H), 7.06 - 7.14 (m, 2H), 7.01 (dd, J = 9.0, 1.6 Hz, 1H), 6.79 (ddd, J = 7.6, 5.1, 1.9 Hz, 1H), 6.65 - 6.76 (m, 1H), 2.97 - 3.93 (m, 5H), 2.25 (s, 3H), 1.93 - 2.19 (m, 2H)

LR MS (ES+): 562 (MH), 584 ($M+Na^+$)

LR MS (ES-): 560 (M-H)

Example 66

4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid



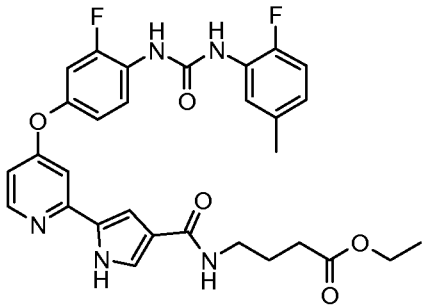
To a stirred solution of ethyl 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate (45mg, 0.078mmol) in 10ml of THF was added 3ml of 1M NaOH (3.0mmol). The mixture was heated at 60°C for 3 hours, cooled to room temperature and poured into 100ml of water. 2M HCl was added until pH = 5. The precipitates were filtered, washed with water, and dried to give 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid as grey solid. Yield: 40mg, 93%.

^{1}H NMR (DMSO-d_6) δ: 11.99 (br. s., 1H), 11.82 (br. s., 1H), 9.06 (d, J = 2.1 Hz, 1H), 8.94 (d, J = 2.6 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.23 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.9, 2.1 Hz, 1H), 7.85 (t, J = 5.7 Hz, 1H), 7.37 (br. s., 1H), 7.27 (dd, J = 11.7, 2.6 Hz, 1H), 7.19 (s, 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 2H), 7.02 (dd, J = 8.9, 1.6 Hz, 1H), 6.77 - 6.82 (m, 1H), 6.73 - 6.77 (m, 1H), 3.16 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 2.22 (t, J = 7.3 Hz, 2H), 1.67 (quin, J = 7.2 Hz, 2H)

LR MS (ES-): 548 (M-H)

Example 67

ethyl 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate



Similar procedure as Example 132.

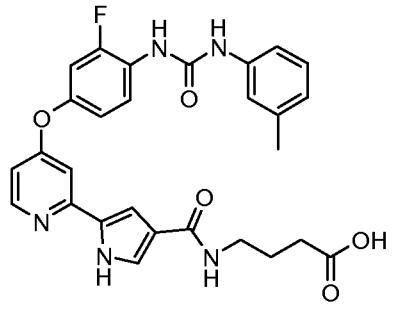
^{1}H NMR (DMSO-d_6) δ: 11.99 (br. s., 1H), 9.09 (d, J = 1.5 Hz, 1H), 8.96 (d, J = 2.3 Hz, 1H), 8.42 (d, J = 6.2 Hz, 1H), 8.26 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.8, 2.2 Hz, 1H), 7.86 - 7.94 (m, 1H), 7.46 (br. s., 1H), 7.25 - 7.34 (m, 2H), 7.22 (br. s., 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 7.02 - 7.07 (m, 1H), 6.87 (br. s., 1H), 6.76 - 6.82 (m, 1H), 4.01 (q, J = 7.1 Hz, 2H), 3.13 - 3.21 (m, 2H), 2.30 (t, J = 7.5 Hz, 2H), 2.25 (s, 3H), 1.70 (quin, J = 7.2 Hz, 2H), 1.14 (t, J = 7.04 Hz, 3H)

LR MS (ES+): 578 (MH), 600 ($M+Na^+$)

LR MS (ES-): 576 (M-H)

Example 68

4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid



Similar procedure as Example 66.

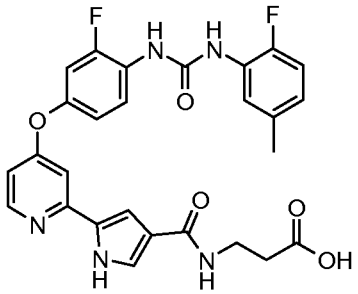
^{1}H NMR (DMSO-d_6) δ: 12.00 (br. s., 1H), 11.82 (br. s., 1H), 8.97 (s, 1H), 8.57 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.21 (t, J = 9.1 Hz, 1H), 7.85 (t, J = 5.7 Hz, 1H), 7.37 (br. s., 1H), 7.24 - 7.29 (m, 2H), 7.17 - 7.23 (m, 2H), 7.13 - 7.17 (m, 1H), 7.10 (br. s., 1H), 7.02 (dd, J = 8.8, 1.8 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.75 (br. s., 1H), 3.16 (q, J = 6.7 Hz, 2H), 2.26 (s, 3H), 2.22 (t, J = 7.3 Hz, 2H), 1.67 (quin, J = 7.2 Hz, 2H)

LR MS (ES+): 532 (MH), 554 ($M+Na^+$)

LR MS (ES-): 530 (M-H)

Example 69

3-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid



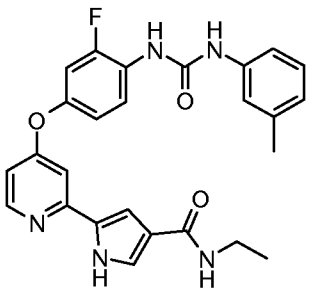
Similar procedure as Example 66.

^{1}H NMR (DMSO-d_6) δ: 11.93 (br. s., 2H), 9.08 (br. s., 1H), 8.96 (d, J = 1.8 Hz, 1H), 8.41 (d, J = 5.9 Hz, 1H), 8.25 (t, J = 8.9 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.94 (br. s., 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 10.3 Hz, 1H), 7.24 (br. s., 1H), 7.17 (br. s., 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.83 (br. s., 1H), 6.76 - 6.81 (m, 1H), 3.33 - 3.38 (m, 2H), 2.44 (t, J = 7.0 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 534 (M-H)

Example 70

N-ethyl-5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

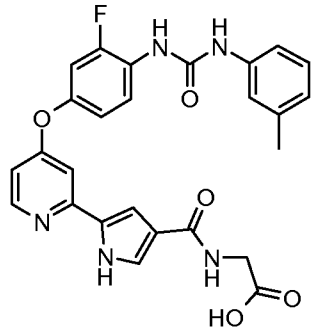
^{1}H NMR (DMSO-d_6) δ: 11.98 (br. s., 1H), 9.11 (s, 1H), 8.67 (br. s., 1H), 8.41 (d, J = 5.9 Hz, 1H), 8.23 (t, J = 9.1 Hz, 1H), 7.87 (t, J = 5.0 Hz, 1H), 7.44 (br. s., 1H), 7.25 - 7.32 (m, 3H), 7.18 - 7.25 (m, 2H), 7.12 - 7.17 (m, 1H), 7.04 (dd, J = 9.0, 1.6 Hz, 1H), 6.85 (br. s., 1H), 6.79 (d, J = 7.3 Hz, 1H), 3.15 - 3.22 (m, 2H), 2.26 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 474 (MH), 496 ($M+Na^+$)

LR MS (ES-): 472 (M-H)

Example 71

{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetic acid



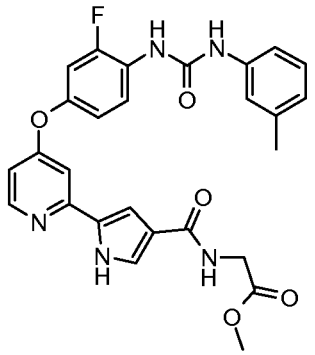
Similar procedure as Example 66.

^{1}H NMR (DMSO-d_6) δ: 11.84 (br. s., 1H), 9.23 (s, 1H), 8.73 (d, J = 1.5 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.18 (t, J = 9.1 Hz, 1H), 8.12 (t, J = 5.4 Hz, 1H), 7.38 (dd, J = 2.9, 1.8 Hz, 1H), 7.28 (s, 1H), 7.21 - 7.26 (m, 2H), 7.19 (d, J = 2.3 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.08 - 7.11 (m, 1H), 7.01 (dd, J = 9.0, 2.5 Hz, 1H), 6.78 (d, J = 7.3 Hz, 1H), 6.73 (dd, J = 5.9, 2.3 Hz, 1H), 3.78 (d, J = 5.9 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 502 (M-H)

Example 72

methyl {[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetate



Similar procedure as Example 132.

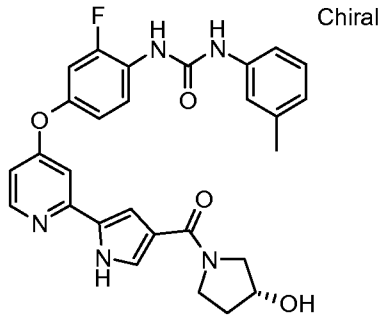
^{1}H NMR (DMSO-d_6) δ: 11.87 (br. s., 1H), 8.96 (s, 1H), 8.56 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.31 (t, J = 6.0 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.39 (dd, J = 3.2, 1.8 Hz, 1H), 7.24 - 7.29 (m, 2H), 7.21 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.13 - 7.17 (m, 1H), 7.08 - 7.10 (m, 1H), 7.01 (dd, J = 8.5, 2.1 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.74 (dd, J = 5.9, 2.3 Hz, 1H), 3.90 (d, J = 5.9 Hz, 2H), 3.60 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)

LR MS (ES-): 516 (M-H)

Example 73

1-(2-fluoro-4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-(3-methylphenyl)urea



Similar procedure as Example 132.

^{1}H NMR (DMSO-d_6) δ: 11.87 (br. s., 1H), 8.97 (s, 1H), 8.56 (d, J = 2.1 Hz, 1H), 8.37 (d, J = 5.9 Hz, 1H), 8.18 (t, J = 9.1 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.18 - 7.30 (m, 4H), 7.12 - 7.17 (m, 1H), 7.08 (d, J = 18.8 Hz, 1H), 6.99 (dt, J = 7.6, 1.5 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.68 (dd, J

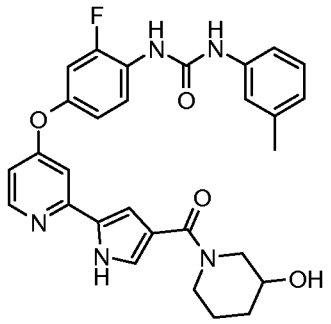
= 5.6, 2.3 Hz, 1H), 4.90 (d, J = 9.4 Hz, 1H), 4.30 (br. s., 1H), 3.68 - 3.82 (m, 2H), 3.42 - 3.54 (m, 2H), 2.26 (s, 3H), 1.72 - 1.97 (m, 2H)

LR MS (ES+): 516 (MH), 538 ($M+Na^+$)

LR MS (ES-): 514 (M-H)

Example 74

1-{2-fluoro-4-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea



Similar procedure as Example 132.

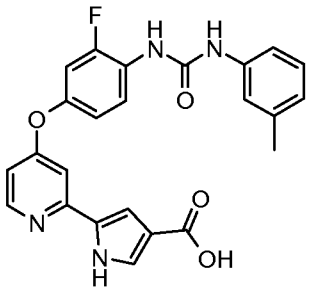
^1H NMR (DMSO-d_6) δ: 11.83 (br. s., 1H), 8.96 (s, 1H), 8.55 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 8.19 (t, J = 9.1 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.27 (s, 1H), 7.19 - 7.25 (m, 2H), 7.15 (t, J = 7.8 Hz, 1H), 7.12 (br. s., 1H), 6.97 - 7.01 (m, 1H), 6.90 (s, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.68 (dd, J = 5.7, 2.2 Hz, 1H), 4.87 (br. s., 1H), 4.04 (br. s., 1H), 3.85 (br. s., 1H), 3.41 - 3.52 (m, 1H), 3.07 (t, J = 10.1 Hz, 1H), 2.26 (s, 3H), 1.78 - 1.90 (m, 1H), 1.67 (td, J = 8.8, 4.7 Hz, 1H), 1.30 - 1.43 (m, 2H)

LR MS (ES+): 530 (MH), 552 ($M+Na^+$)

LR MS (ES-): 528 (M-H)

Example 75

5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid



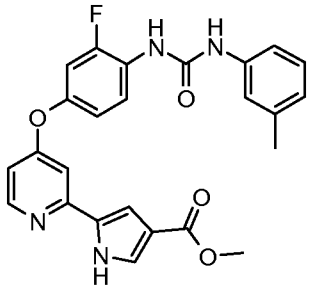
Similar procedure as Example 134.

^{1}H NMR (DMSO-d_6) δ: 12.04 (br. s., 1H), 11.87 (br. s., 1H), 8.97 (br. s., 1H), 8.56 (br. s., 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.36 (br. s., 2H), 7.19 - 7.30 (m, 3H), 7.12 - 7.17 (m, 1H), 7.08 (br. s., 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.73 (br. s., 1H), 2.26 (s, 3H)

LR MS (ES+): 469 (MH)

Example 76

methyl 5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

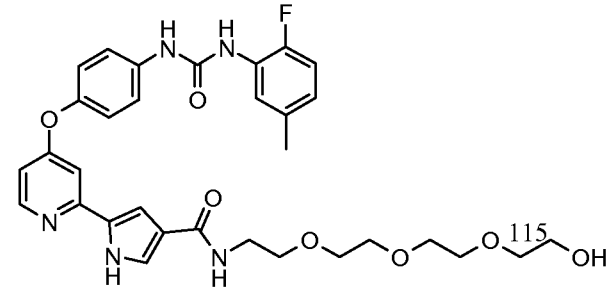
^{1}H NMR (DMSO-d_6) δ: 12.11 (br. s., 1H), 8.96 (s, 1H), 8.55 (s, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.19 (t, J = 9.1 Hz, 1H), 7.42 (dd, J = 3.1, 1.6 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.28 (s, 1H), 7.19 - 7.26 (m, 2H), 7.12 - 7.17 (m, 1H), 7.09 - 7.12 (m, 1H), 7.00 (dd, J = 9.1, 2.3 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.72 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 461 (MH), 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Example 77

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}ethyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

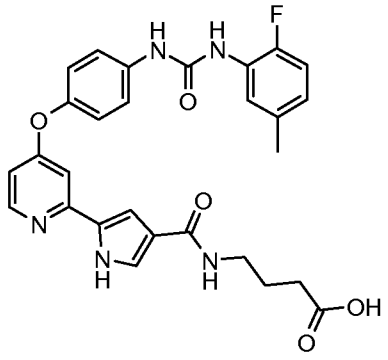
^{1}H NMR (DMSO-d_6) δ: 11.92 (br. s., 1H), 9.20 (s, 1H), 8.48 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.92 (br. s., 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.43 (br. s., 1H), 7.20 (br. s., 1H), 7.11 - 7.17 (m, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 6.73 - 6.81 (m, 2H), 3.41 - 3.48 (m, 12H), 3.34 - 3.39 (m, 2H), 3.31 (q, J = 5.8 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 622 (MH), 644 ($M+Na^+$)

LR MS (ES-): 620 (M-H)

Example 78

4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid



Similar procedure as Example 66.

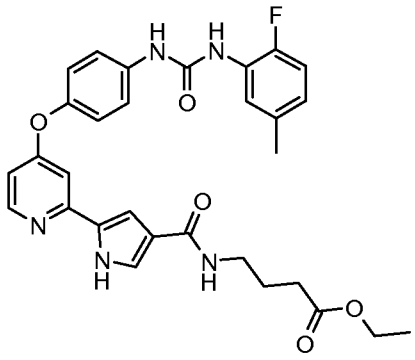
^{1}H NMR (DMSO-d_6) δ: 11.83 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 - 8.02 (m, 1H), 7.88 (t, J = 5.6 Hz, 1H), 7.57 (d, J = 9.1 Hz, 2H), 7.38 (br. s., 1H), 7.16 (d, J = 9.1 Hz, 2H), 7.06 - 7.17 (m, 3H), 6.77 - 6.85 (m, 1H), 6.67 - 6.76 (m, 1H), 3.16 - 3.22 (m, 2H), 2.28 (s, 3H), 2.25 (t, J = 7.3 Hz, 2H), 1.70 (quin, J = 7.2 Hz, 2H)

LR MS (ES+): 532 (MH)

LR MS (ES-): 530 (M-H)

Example 79

ethyl 4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate

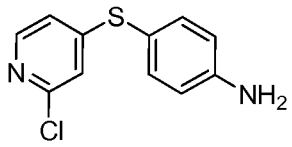


Similar procedure as Example 132.

LR MS (ES+): 560 (MH), 582 ($M+Na^+$)

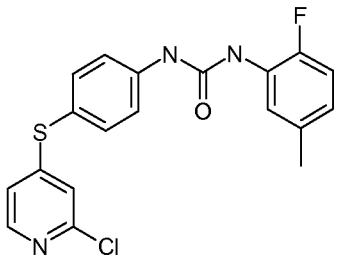
LR MS (ES-): 558 (M-H)

Preparation of 4-(2-Chloro-pyridin-4-ylsulfanyl)-phenylamine



2,4-Dichloropyrdine (4.44 g, 30.0 mmol) and potassium carbonate (8.28 g, 60.0 mmol) in dimethylformamide (60 mL) was purged with nitrogen for 10 min. 4-Aminothiophenol (3.76 g, 30.0 mmol) was added and the mixture stirred under nitrogen at room temperature for 18 h. Water (300 mL) was added and the slurry stirred for 30 min. The resulting solid was filtered, washed with water and vacuum dried at room temperature. Recrystallization from ethyl acetate (35 mL), filtered hot, then cooled gave 4-(2-Chloro-pyridin-4-ylsulfanyl)-phenylamine (3.946 g, 56% yield).

Preparation of 1-[4-(2-Chloro-pyridin-4-ylsulfanyl)-phenyl]-3-(2-fluoro-5-methyl-phenyl)-urea

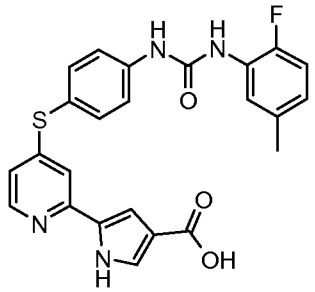


To a stirred solution of 4-(2-Chloro-pyridin-4-ylsulfanyl)-phenylamine (300 mg, 1.27 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (210mg, 1.39mmol). The mixture was stirred at 60°C for 5 hours, and poured into 100ml of water. The precipitates were filtered, washed with water (50ml), and dried to give the crude, which was purified by silica gel chromatography eluting with 2-3% MeOH/$CHCl_3$ to give 1-[4-(2-Chloro-pyridin-4-ylsulfanyl)-phenyl]-3-(2-fluoro-5-methyl-phenyl)-urea as white solid. Yield: 410mg, 83%.

^{1}H NMR (DMSO-d_6) δ: 9.37 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 5.9 Hz, 1H), 7.89 - 8.01 (m, 1H), 7.58 - 7.70 (m, 2H), 7.47 - 7.59 (m, 2H), 7.10 (dd, J = 11.4, 8.2 Hz, 1H), 6.94 - 7.03 (m, 2H), 6.82 (dd, J = 4.8, 2.2 Hz, 1H), 2.26 (s, 3H)

Example 80

5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid



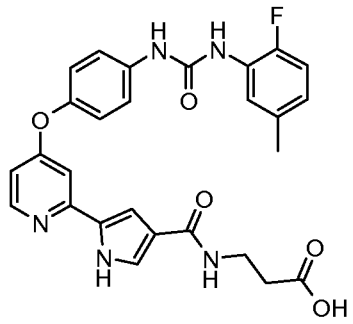
To a stirred solution of methyl 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylate (86mg, 0.18mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 2ml of 1M NaOH (2mmol) solution. The mixture was heated in a 66°C bath for 7 hours, cooled to room temperature and poured into 100ml of water. 2M HCl was added until pH = 3. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid as light brown solid. Yield: 73mg, 88%.

^{1}H NMR (DMSO-d_6) δ: 12.01 (br. s., 1H), 9.37 (s, 1H), 8.56 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 5.6 Hz, 1H), 7.95 (s, 1H), 7.44 - 7.68 (m, 5H), 7.36 (br. s., 1H), 7.10 (dd, J = 11.1, 8.5 Hz, 1H), 6.94 (br. s., 1H), 6.81 (br. s., 1H), 6.69 (d, J = 5.3 Hz, 1H), 2.26 (s, 3H)

LR MS (ES-): 461 (M-H)

Example 81

3-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid



Similar procedure as Example 66.

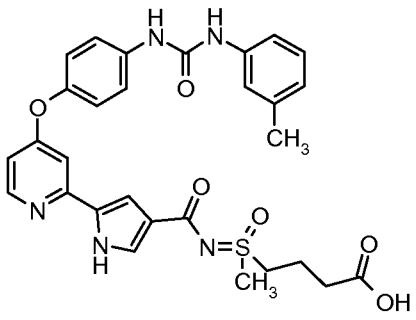
^{1}H NMR (DMSO-d_6) δ: 12.12 (br. s., 1H), 11.81 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.92 (t, J = 5.3 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.35 (br. s., 1H), 7.13 (dd, J = 6.6, 2.2 Hz, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 7.04 (br. s., 1H), 6.75 - 6.82 (m, 1H), 6.70 (d, J = 3.2 Hz, 1H), 3.32 - 3.41 (m, 2H), 2.43 (t, J = 7.0 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)

LR MS (ES-): 516 (M-H)

Example 82

4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoic acid



To a stirred solution of methyl 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoate (5mg, 0.0087mol) in MeOH (3ml) was added 1M NaOH

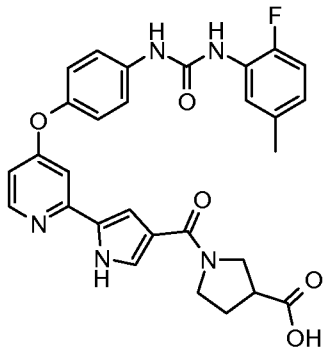
(0.5ml, 0.5mmol). The mixture was stirred at room temperature for 30 minutes, and poured into 30ml of water. 2M HCl was added dropwise until pH = 4. The precipitates were filtered, washed with water and dried to give 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoic acid as off-white solid. Yield: 5mg, 100%.

LR MS (ES+): 576 (MH), 598 ($M+Na^+$)

LR MS (ES-): 574 (M-H)

Example 83

1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]pyrrolidine-3-carboxylic acid



Similar procedure as Example 132.

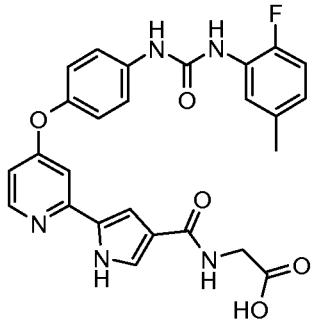
^1H NMR (DMSO-d_6) δ: 12.04 (br. s., 1H), 9.16 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.93 - 7.99 (m, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.41 (br. s., 1H), 7.33 (br. s., 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.82 (m, 1H), 6.72 (br. s., 1H), 2.98 - 3.93 (m, 5H), 2.25 (s, 3H), 1.93 - 2.19 (m, 2H)

LR MS (ES+): 544 (MH), 566 ($M+Na^+$)

LR MS (ES-): 542 (M-H)

Example 84

{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetic acid



Similar procedure as Example 66.

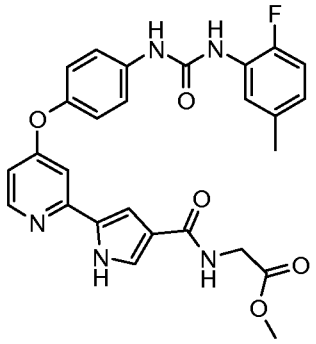
^{1}H NMR (DMSO-d_6) δ: 12.42 (br. s., 1H), 11.85 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.37 (d, J = 5.9 Hz, 1H), 8.21 (t, J = 6.0 Hz, 1H), 7.90 - 8.03 (m, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.38 (br. s., 1H), 7.02 - 7.21 (m, 5H), 6.74 - 6.84 (m, 1H), 6.70 (dd, J = 5.6, 2.3 Hz, 1H), 3.82 (d, J = 5.9 Hz, 2H), 2.26 (s, 3H)

LR MS (ES+): 504 (MH), 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Example 85

methyl {[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetate



Similar procedure as Example 132.

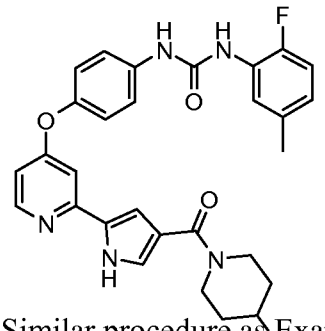
^{1}H NMR (DMSO-d_6) δ: 12.00 (br. s., 1H), 9.18 (s, 1H), 8.48 (d, J = 2.1 Hz, 1H), 8.29 - 8.44 (m, 2H), 7.97 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.46 (br. s., 1H), 7.02 - 7.27 (m, 5H), 6.79 (d, J = 2.1 Hz, 2H), 3.91 (d, J = 6.2 Hz, 2H), 3.61 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)

LR MS (ES-): 516 (M-H)

Example 86

1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidine-4-sulfonic acid



Similar procedure as Example 132.

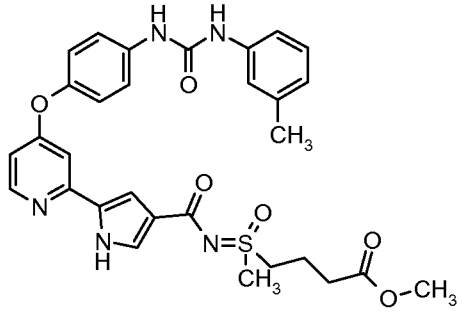
^{1}H NMR (DMSO-d$_6$) δ: 12.41 (br. s., 1H), 9.24 (s, 1H), 8.46 - 8.53 (m, 2H), 7.91 - 7.98 (m, 1H), 7.54 - 7.64 (m, 3H), 7.45 (br. s., 1H), 7.30 (br. s., 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.2, 8.2 Hz, 1H), 7.02 (br. s., 1H), 6.75 - 6.82 (m, 1H), 4.29 (br. s., 2H), 3.52 (br. s., 2H), 2.48 - 2.56 (m, 1H), 2.25 (s, 3H), 1.93 (d, J = 12.6 Hz, 2H), 1.45 (br. s., 2H)

LR MS (ES+): 616 (M+Na$^+$)

LR MS (ES-): 592 (M-H)

Example 87

methyl 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoate

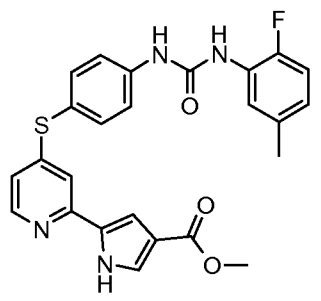


Similar procedure as Example 101.

LR MS (ES+): 590 (MH), 612 (M+Na$^+$)

Example 88

methyl 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylate

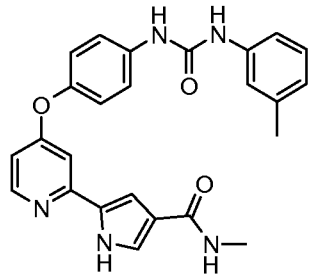


A mixture of 1-[4-(2-Chloro-pyridin-4-ylsulfanyl)-phenyl]-3-(2-fluoro-5-methyl-phenyl)-urea (410mg, 1.06 mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (532mg, 2.12 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10mg, 0.012 mmol) was added to a thick-walled reaction vessel and purged with N_2. A solution of 2M Na_2CO_3 (1.0 mL) was added, followed by DMSO (10 mL). The reaction vessel was sealed and the mixture stirred at 95°C for 16 h. The reaction vessel was cooled to room temperature and the mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude, which was purified via silica gel chromatography eluting with 2-5% MeOH/$CHCl_3$ to afford methyl 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylate as off-white solid. Yield: 100mg, 20% yield.

LR MS (ES+): 477 (MH), 499 ($M+Na^+$)

Example 89

N-methyl-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

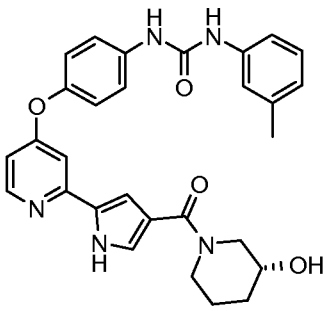
^1H NMR (DMSO-d_6) δ: 11.88 (br. s., 1H), 8.89 (s, 1H), 8.69 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.82 (d, J = 4.4 Hz, 1H), 7.52 - 7.58 (m, 2H), 7.37 (br. s., 1H), 7.27 (s, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.18 (br. s., 1H), 7.11 - 7.15 (m, 3H), 7.08 (br. s., 1H), 6.71 - 6.80 (m, 2H), 2.67 (d, J = 4.7 Hz, 3H), 2.25 (s, 3H)

LR MS (ES+): 442 (MH), 464 ($M+Na^+$)

LR MS (ES-): 440 (M-H)

Example 90

1-{4-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea



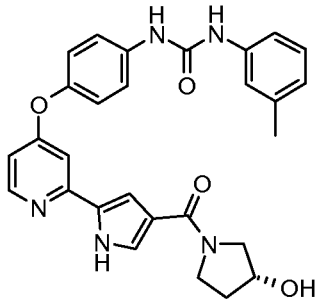
Similar procedure as Example 132.

LR MS (ES+): 512 (MH), 534 ($M+Na^+$)

LR MS (ES-): 510 (M-H)

Example 91

1-{4-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea



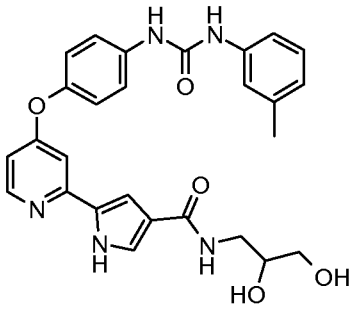
Similar procedure as Example 132.

^1H NMR (DMSO-d_6) δ: 11.88 (br. s., 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 6.99 - 7.39 (m, 8H), 6.78 (d, J = 7.0 Hz, 1H), 6.62 (dd, J = 5.6, 2.3 Hz, 1H), 4.91 (br. s., 1H), 4.31 (br. s., 1H), 3.67 - 3.87 (m, 2H), 3.49 (br. s., 2H), 2.26 (s, 3H), 1.88 (br. s., 2H)

LR MS (ES+): 520 ($M+Na^+$)

Example 92

N-(2,3-dihydroxypropyl)-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



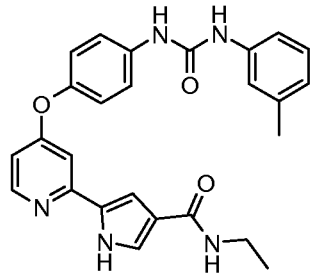
Similar procedure as Example 132.

^{1}H NMR (DMSO-d_6) δ: 11.86 (br. s., 1H), 8.78 (s, 1H), 8.61 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.87 (t, J = 5.7 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.41 (br. s., 1H), 7.05 - 7.32 (m, 7H), 6.75 (dd, J = 17.7, 6.6 Hz, 2H), 3.49 - 3.61 (m, 1H), 3.22 - 3.35 (m, 3H), 3.04 - 3.18 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 524 ($M+Na^+$)

Example 93

N-ethyl-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

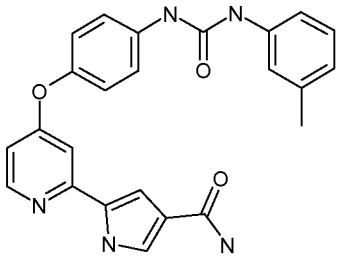
^{1}H NMR (DMSO-d_6) δ: 12.09 (br. s., 1H), 8.98 (s, 1H), 8.76 (s, 1H), 8.42 (d, J = 5.9 Hz, 1H), 7.91 (br. s., 1H), 7.45 - 7.65 (m, 3H), 7.05 - 7.38 (m, 7H), 6.82 - 6.94 (m, 1H), 6.78 (d, J = 7.6 Hz, 1H), 3.09 - 3.27 (m, 2H), 2.26 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 478 ($M+Na^+$)

LR MS (ES-): 454 (M-H)

Example 94

5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

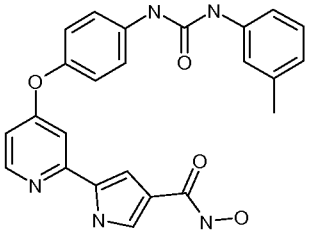
^{1}H NMR (d_6-DMSO,300MHz) δ: 11.81 (br. s., 1H), 8.76 (s, 1H), 8.59 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 9.1 Hz, 2H), 7.37 (br. s., 2H), 7.28 (s, 1H), 7.19 - 7.26 (m, 1H), 7.09 - 7.18 (m, 4H), 7.04 (br. s., 1H), 6.78 (d, J = 7.3 Hz, 2H), 6.69 (dd, J = 5.4, 1.9 Hz, 1H), 2.26 (s, 3H)

LR MS (ES+): 428 (MH), 450 ($M+Na^+$)

LR MS (ES-): 426 (M-H)

Example 95

N-hydroxy-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

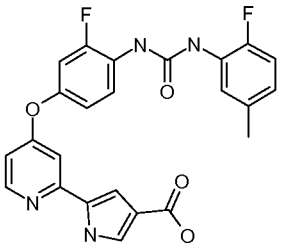
^{1}H NMR (d_6-DMSO,300MHz): 11.98 (br. s., 1H), 10.62 (br. s., 1H), 8.87 (s, 1H), 8.68 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.58 (d, J = 9.1 Hz, 2H), 7.04 - 7.46 (m, 8H), 6.80 (d, J = 7.6 Hz, 2H), 2.28 (s, 3H)

LR MS (ES+): 444 (MH), 466 ($M+Na^+$)

LR MS (ES-): 442 (M-H)

Example 96

5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid



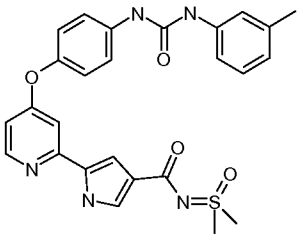
Similar procedure as Example 134.

^{1}H NMR (d_6-DMSO,300MHz): 12.04 (br. s., 1H), 11.88 (br. s., 1H), 9.08 (s, 1H), 8.97 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 8.25 (t, J = 9.2 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.38 (s, 2H), 7.27 (dd, J = 11.9, 2.5 Hz, 1H), 6.95 - 7.18 (m, 3H), 6.78 - 6.88 (m, 1H), 6.74 (dd, J = 5.6, 2.1 Hz, 1H), 2.28 (s, 3H)

LR MS (ES+): 465 (MH), 487 ($M+Na^+$)

LR MS (ES-): 463 (M-H)

Example 97



N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide

Similar procedure as Example 101.

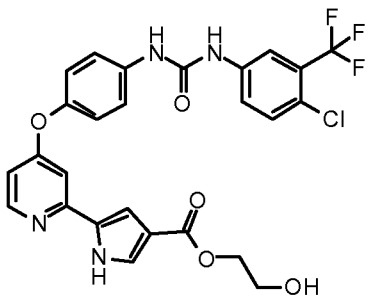
^{1}H NMR (d_6-DMSO,300MHz): 11.82 (none, 1H), 11.83 (br. s., 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.21 - 7.35 (m, 4H), 7.08 - 7.20 (m, 3H), 6.95 (s, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 3.37 (s, 6H), 2.28 (s, 3H)

LR MS (ES+): 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Example 98

2-hydroxyethyl 5-{4-[4-({[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 131.

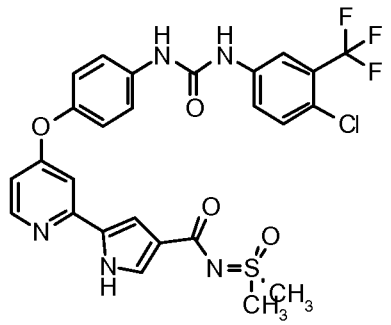
^{1}H NMR (d_6-DMSO,300MHz): 12.12 (br. s., 1 H), 9.19 (s, 1 H), 8.97 (s, 1 H), 8.40 (d, *J*=5.9 Hz, 1 H), 8.12 (d, *J*=2.1 Hz, 1 H), 7.53 - 7.70 (m, 4 H), 7.48 (dd, *J*=3.1, 1.6 Hz, 1 H), 7.35 (d, *J*=2.1 Hz, 1 H), 7.16 (d, *J*=9.1 Hz, 2 H), 7.09 (d, *J*=2.3 Hz, 1 H), 6.68 (dd, *J*=5.6, 2.3 Hz, 1 H), 4.83 (t, *J*=5.9 Hz, 1 H), 4.15 (t, *J*=5.0 Hz, 2 H), 3.59 - 3.69 ppm (m, 2 H)

LR MS (ES+): 583 ($M+Na^+$), 585

LR MS (ES-): 559 (M-H), 561

Example 99

N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



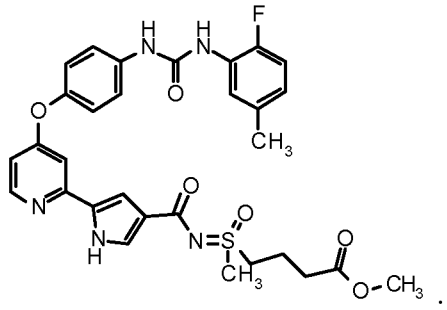
Similar procedure as Example 101.

^{1}H NMR (d_6-DMSO,300MHz) 11.83 (br. s., 1 H), 9.19 (s, 1 H), 8.97 (s, 1 H), 8.37 (d, *J*=5.9 Hz, 1 H), 8.12 (d, *J*=2.3 Hz, 1 H), 7.54 - 7.69 (m, 4 H), 7.23 - 7.31 (m, 2 H), 7.12 - 7.19 (m, 2 H), 6.93 - 6.97 (m, 1 H), 6.67 (dd, *J*=5.9, 2.3 Hz, 1 H), 3.37 ppm (s, 6 H)

LR MS (ES-): 590 (M-H)

Example 100

methy 4-(N-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxyl)-S-methylsulfonimidoyl)butanoate

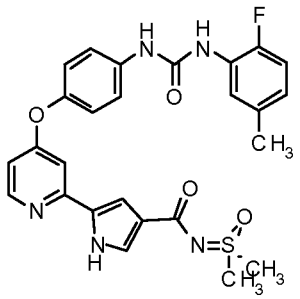


LR MS (ES+): 630 ($M+Na^+$)

LR MS (ES-): 606 (M-H)

Example 101

N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide

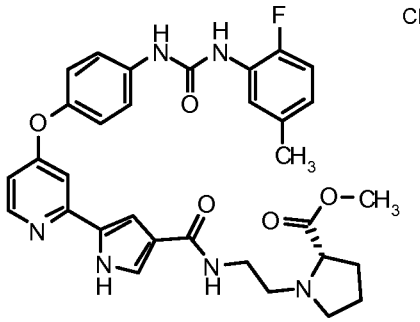


A mixture of 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (60mg, 0.13mmol), HATU (60mg, 0.16mmol), sulfonimidoyldimethane (24mg, 0.26mmol), *N,N*-diisopropylethylamine (37mg, 0.29mmol), 200mg of 4Å molecular sieves and 5ml of anhydrous 1,4-dioxane was added to a thick walled reaction vessel and purged with N_2. The reaction vessel was sealed and the mixture stirred at 90°C for 18 hours. The reaction vessel was cooled to room temperature and the mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude, which was purified by silica gel chromatography eluting with 3~5% MeOH/$CHCl_3$ to give N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide as white solid. Yield: 38mg, 54%.

^{1}H NMR (d_6-DMSO): 11.83 (br. s., 1H), 9.16 (s, 1H), 8.48 (br. s., 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.98 (d, J = 6.7 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 8.6, 1.6 Hz, 2H), 7.05 - 7.19 (m, 3H), 6.96 (s, 1H), 6.75 - 6.85 (m, 1H), 6.66 (dd, J = 5.4, 1.6 Hz, 1H), 3.37 (s, 6H), 2.27 (s, 3H)
LR MS (ES+): 544 ($M+Na^+$)
LR MS (ES-): 520 (M-H)

Example 102

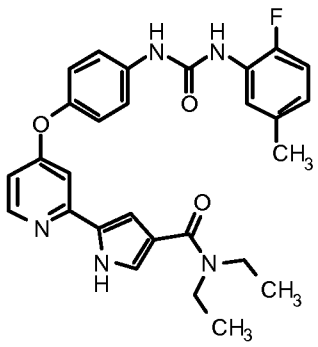
methyl (2S)-1-(2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)pyrrolidine-2-carboxylate



Similar procedure as Example 132.
LR MS (ES+): 623 ($M+Na^+$)
LR MS (ES-): 599 (M-H)

Example 103

N,N-diethyl-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

^{1}H NMR (d_6-DMSO): 11.97 (br. s., 1H), 9.19 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.40 (d, J = 6.2 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.53 - 7.61 (m, 2H), 7.40 (d, J = 1.5 Hz, 1H), 7.05 - 7.25 (m, 4H), 7.01 (br. s., 1H), 6.76 - 6.86 (m, 1H), 6.67 - 6.76 (m, 1H), 3.26 - 3.64 (m, 4H), 2.27 (s, 3H), 1.13 (t, J = 7.0 Hz, 6H)

LR MS (ES+): 524 ($M+Na^+$)

LR MS (ES-): 500 (M-H)

Example 104

1-(2-fluoro-5-methylphenyl)-3-{4-[(2-{4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}urea

Similar procedure as Example 132.

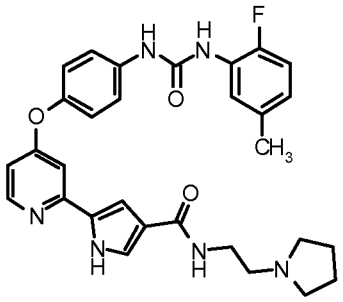
^{1}H NMR (d_6-DMSO): 11.87 (br. s., 1H), 9.16 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.98 (dd, J = 8.1, 1.9 Hz, 1H), 7.50 - 7.59 (m, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.08 - 7.19 (m, 4H), 6.87 - 6.95 (m, 1H), 6.80 (ddd, J = 7.7, 5.1, 2.2 Hz, 1H), 6.63 (dd, J = 5.9, 2.3 Hz, 1H), 3.60 (d, J = 4.1 Hz, 4H), 2.23 - 2.35 (m, 7H), 2.18 (s, 3H)

LR MS (ES+): 551 ($M+Na^+$)

LR MS (ES-): 527 (M-H)

Example 105

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-pyrrolidin-1-ylethyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

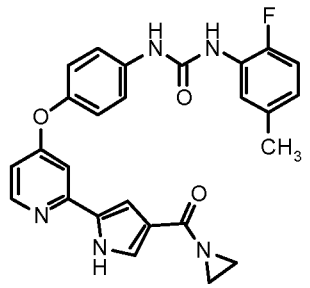
^{1}H NMR (d_6-DMSO): 11.80 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.98 (dd, J = 7.9, 2.1 Hz, 1H), 7.82 (t, J = 5.7 Hz, 1H), 7.50 - 7.63 (m, 2H), 7.35 (dd, J = 2.9, 1.8 Hz, 1H), 7.00 - 7.20 (m, 5H), 6.80 (dt, J = 7.9, 2.2 Hz, 1H), 6.70 (dd, J = 5.9, 2.3 Hz, 1H), 3.21 - 3.35 (m, 2H), 2.37 - 2.57 (m, 6H), 2.27 (s, 3H), 1.65 (dt, J = 6.6, 3.1 Hz, 4H)

LR MS (ES+): 565 ($M+Na^+$)

LR MS (ES-): 541 (M-H)

Example 106

1-[4-({2-[4-(aziridin-1-ylcarbonyl)-1H-pyrrol-2-yl]pyridin-4-yl}oxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea



Similar procedure as Example 132.

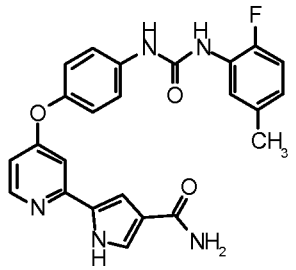
^1H NMR (d_6-DMSO): 11.90 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.36 (d, J = 5.9 Hz, 1H), 7.97 (dd, J = 8.2, 2.1 Hz, 1H), 7.50 - 7.58 (m, 2H), 7.28 (d, J = 2.1 Hz, 1H), 7.23 (br. s., 1H), 7.04 - 7.17 (m, 3H), 6.97 (br. s., 1H), 6.79 (ddd, J = 7.5, 5.1, 2.3 Hz, 1H), 6.65 (dd, J = 5.7, 2.5 Hz, 1H), 4.17 - 4.31 (m, 2H), 3.82 (t, J = 9.2 Hz, 2H), 2.26 (s, 3H)

LR MS (ES+): 494 ($M+Na^+$)

LR MS (ES-): 470 (M-H)

Example 107

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

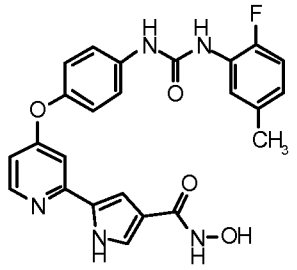
^1H NMR (d_6-DMSO): 11.89 (br. s., 1H), 9.21 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.98 (dd, J = 8.1, 1.9 Hz, 1H), 7.53 - 7.62 (m, 2H), 7.43 (br. s., 2H), 7.05 - 7.24 (m, 5H), 6.71 - 6.86 (m, 3H), 2.27 (s, 3H)

LR MS (ES+): 468 ($M+Na^+$)

LR MS (ES-): 444 (M-H)

Example 108

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-hydroxy-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

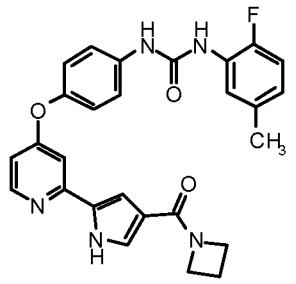
^{1}H NMR (d_6-DMSO): 12.10 (br. s., 1H), 10.66 (br. s., 1H), 9.29 (s, 1H), 8.53 (br. s., 1H), 8.43 (d, J = 6.2 Hz, 1H), 7.93 - 8.03 (m, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.39 - 7.50 (m, 1H), 7.30 (br. s., 1H), 7.05 - 7.26 (m, 4H), 6.75 - 6.91 (m, 2H), 2.27 (s, 3H)

LR MS (ES+): 484 ($M+Na^+$)

LR MS (ES-): 460 (M-H)

Example 109

1-[4-({2-[4-(azetidin-1-ylcarbonyl)-1H-pyrrol-2-yl]pyridin-4-yl}oxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea



Similar procedure as Example 132.

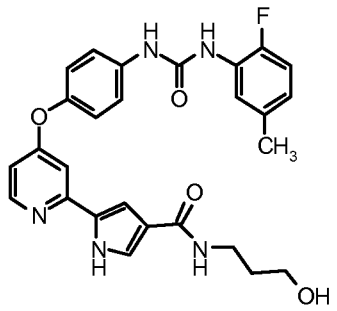
^{1}H NMR (d_6-DMSO): 11.67 (br. s., 1H), 9.16 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.34 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 5.9 Hz, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.02 - 7.23 (m, 5H), 6.86 (br. s., 1H), 6.74 - 6.83 (m, 1H), 6.64 (dd, J = 5.9, 2.3 Hz, 1H), 4.14 - 4.28 (m, 2H), 3.33 - 3.42 (m, 2H), 2.26 (s, 3H), 1.83 (br. s., 2H)

LR MS (ES+): 486 (M+H)

LR MS (ES-): 484 (M-H)

Example 110

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(3-hydroxypropyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

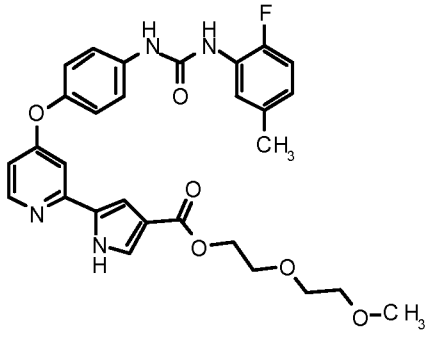
^{1}H NMR (d_6-DMSO): 11.78 (br. s., 1H), 9.20 (s, 1H), 8.51 (d, J = 2.1 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.83 (t, J = 5.7 Hz, 1H), 7.55 (d, J = 9.1 Hz, 2H), 7.32 - 7.36 (m, 1H), 7.02 - 7.17 (m, 5H), 6.78 (td, J = 5.3, 2.6 Hz, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.42 (t, J = 5.3 Hz, 1H), 3.41 (q, J = 6.2 Hz, 2H), 3.15 - 3.26 (m, 2H), 2.26 (s, 3H), 1.60 (quin, J = 6.7 Hz, 2H)

LR MS (ES+): 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Example 111

2-(2-methoxyethoxy)ethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 131.

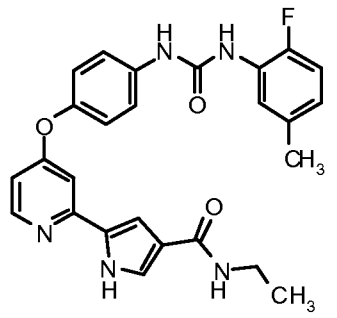
^{1}H NMR (d_6-DMSO): 12.12 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.97 (dd, J = 8.1, 1.9 Hz, 1H), 7.49 - 7.59 (m, 2H), 7.41 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.03 - 7.17 (m, 4H), 6.74 - 6.84 (m, 1H), 6.67 (dd, J = 5.7, 2.5 Hz, 1H), 4.20 - 4.28 (m, 2H), 3.62 - 3.70 (m, 2H), 3.51 - 3.59 (m, 2H), 3.39 - 3.46 (m, 2H), 3.18 - 3.24 (m, 3H), 2.26 (s, 3H)

LR MS (ES+): 571 ($M+Na^+$)

LR MS (ES-): 547 (M-H)

Example 112

N-ethyl-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

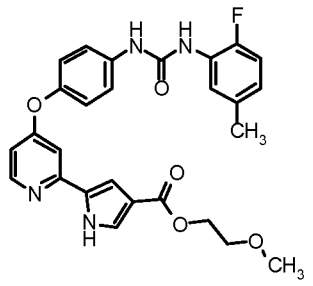
^{1}H NMR (d_6-DMSO): 11.93 (br. s., 1H), 9.23 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 6.2 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 (t, J = 5.6 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.42 (br. s., 1H), 7.02 - 7.27 (m, 5H), 6.72 - 6.86 (m, 2H), 3.09 - 3.25 (m, 2H), 2.26 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 496 ($M+Na^+$)

LR MS (ES-): 472 (M-H)

Example 113

2-methoxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 131.

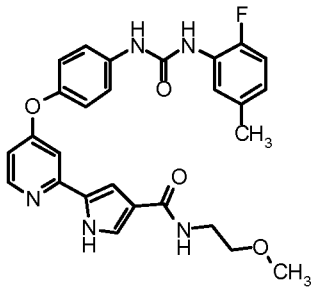
^{1}H NMR (d_6-DMSO): 12.12 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.98 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 1.2 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.01 - 7.19 (m, 4H), 6.78 (d, J = 5.9 Hz, 1H), 6.66 (dd, J = 5.9, 2.1 Hz, 1H), 4.17 - 4.32 (m, 2H), 3.51 - 3.65 (m, 2H), 3.29 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 527 ($M+Na^+$)

LR MS (ES-): 503 (M-H)

Example 114

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-methoxyethyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

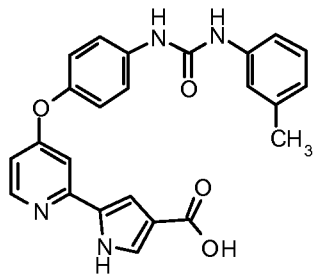
^{1}H NMR (d_6-DMSO): 11.86 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.86 - 8.02 (m, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.40 (br. s., 1H), 7.02 - 7.21 (m, 5H), 6.67 - 6.84 (m, 2H), 3.26 - 3.50 (m, 7H), 2.26 (s, 3H)

LR MS (ES+): 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Example 115

5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid



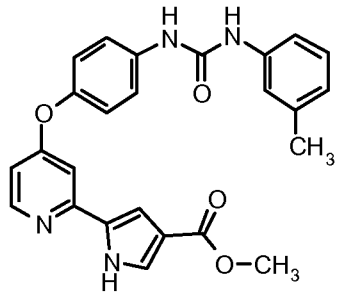
Similar procedure as Example 134.

^{1}H NMR (d_6-DMSO): 12.05 (br. s., 1H), 8.79 (s, 1H), 8.62 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.52 - 7.61 (m, 2H), 7.39 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.30 (s, 1H), 7.21 - 7.27 (m, 1H), 7.10 - 7.20 (m, 3H), 7.05 (s, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 2.28 (s, 3H)

LR MS (ES-): 427 (M-H)

Example 116

methyl 5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

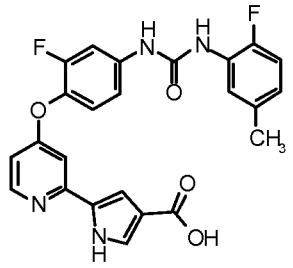
^{1}H NMR (d_6-DMSO): 12.12 (br. s., 1H), 9.02 (br. s., 1H), 8.85 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.50 - 7.59 (m, 2H), 7.41 (d, J = 1.5 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.29 (s, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.08 - 7.18 (m, 3H), 7.06 (d, J = 1.5 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.65 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 465 ($M+Na^+$)

LR MS (ES-): 441 (M-H)

Example 117

5-{4-[2-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid



Similar procedure as Example 134.

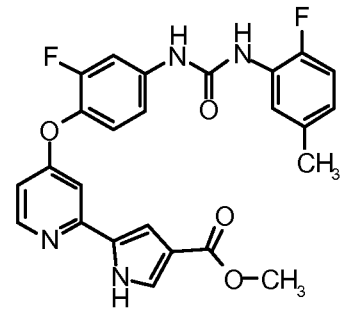
^{1}H NMR (d_6-DMSO): 12.03 (br. s., 1H), 11.86 (br. s., 1H), 9.62 (s, 1H), 8.65 (s, 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.94 (dd, J = 7.9, 1.8 Hz, 1H), 7.72 (dd, J = 13.2, 2.3 Hz, 1H), 7.26 - 7.40 (m, 3H), 7.15 - 7.24 (m, 1H), 7.01 - 7.14 (m, 2H), 6.81 (td, J = 5.3, 2.3 Hz, 1H), 6.68 (dd, J = 5.7, 2.2 Hz, 1H), 2.26 (s, 3H)

LR MS (ES+): 487 ($M+Na^+$)

LR MS (ES-): 463 (M-H)

Example 118

methyl 5-{4-[2-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

^{1}H NMR (d_6-DMSO): 12.13 (br. s., 1H), 9.34 (s, 1H), 8.55 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.94 (dd, J = 7.8, 1.6 Hz, 1H), 7.72 (dd, J = 13.5, 2.3 Hz, 1H), 7.43 (dd, J = 3.2, 1.8 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.26 - 7.36 (m, 1H), 7.18 (dd, J = 8.9, 1.6 Hz, 1H), 7.05 - 7.15 (m, 2H), 6.77 - 6.87 (m, 1H), 6.70 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H), 2.26 (s, 3H)

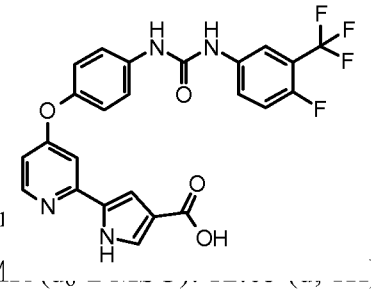
LR MS (ES+): 501 ($M+Na^+$)

LR MS (ES-): 477 (M-H)

Example 119

5-(4-{4-[({[4-fluoro-3

-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid



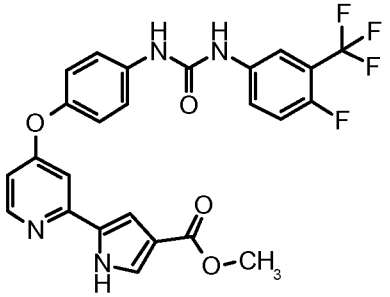
Similar

^{1}H NM[illegible]), 9.11 (s, 1H), 8.96 (s, 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.99 (dd, J = 6.4, 2.3 Hz, 1H), 7.60 - 7.72 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.27 - 7.49 (m, 3H), 7.14 (d, J = 9.1 Hz, 2H), 7.03 (br. s., 1H), 6.67 (dd, J = 5.7, 2.2 Hz, 1H)

LR MS (ES-): 499 (M-H)

Example 120

methyl 5-(4-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

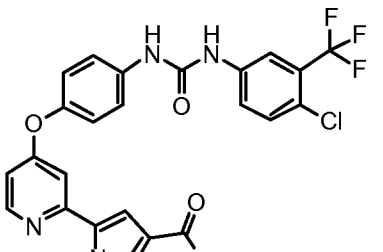
^{1}H NMR (d_6-DMSO): 12.12 (br. s., 1H), 9.04 (s, 1H), 8.91 (s, 1H), 8.37 (d, J = 6.2 Hz, 1H), 7.99 (dd, J = 6.4, 2.6 Hz, 1H), 7.60 - 7.69 (m, 1H), 7.51 - 7.61 (m, 2H), 7.37 - 7.49 (m, 2H), 7.34 (d, J = 2.1 Hz, 1H), 7.09 - 7.18 (m, 2H), 7.01 - 7.09 (m, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H)

LR MS (ES+): 537 ($M+Na^+$)

LR MS (ES-): 513 (M-H)

Example 121

5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid



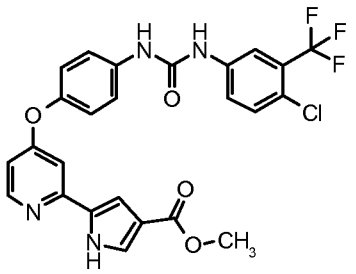
Similar procedure as Example 134.

^{1}H NMR (d_6-DMSO): 12.08 (br. s., 1H), 9.23 (s, 1H), 9.00 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 8.10 (s, 1H), 7.48 - 7.72 (m, 4H), 7.27 - 7.47 (m, 2H), 7.00 - 7.23 (m, 3H), 6.69 (br. s., 1H)

LR MS (ES-): 515 (M-H)

Example 122

methyl 5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

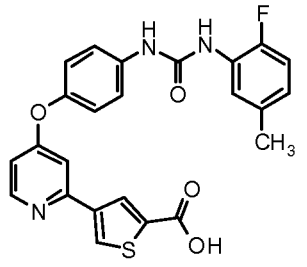
^{1}H NMR (d_6-DMSO): 12.12 (br. s., 1H), 9.17 (s, 1H), 8.94 (s, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.51 - 7.69 (m, 4H), 7.42 (dd, J = 3.2, 1.8 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.10 - 7.18 (m, 2H), 7.03 - 7.09 (m, 1H), 6.66 (dd, J = 5.9, 2.3 Hz, 1H), 3.70 (s, 3H)

LR MS (ES+): 553 ($M+Na^+$)

LR MS (ES-): 529 (M-H)

Example 123

4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylic acid



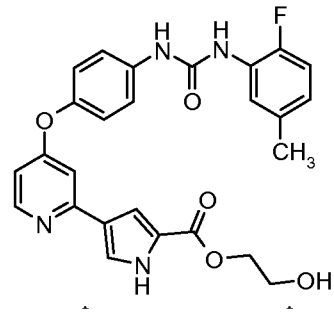
To a stirred solution of methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylate (550mg, 1.15mmol) in a mixture of solvents - THF/MeOH (20ml/20ml) was added 1ml of 5M NaOH (5mmol) solution. The mixture was heated in a 66°C bath for 2 hours, cooled to room temperature and poured into 200ml of water. 2M HCl was added until pH = 5. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylic acid as off-white solid. Yield: 520mg, 97%.

^{1}H NMR (d_6-DMSO): 9.30 (s, 1H), 8.59 (d, J = 2.6 Hz, 1H), 8.43 (d, J = 5.9 Hz, 1H), 8.35 (br. s., 1H), 8.13 (br. s., 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.59 (m, 2H), 7.45 (s, 1H), 7.03 - 7.18 (m, 3H), 6.75 - 6.83 (m, 1H), 6.72 (dd, J = 5.6, 2.3 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 462 (M-H)

Example 124

2-hydroxyethyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate



31.

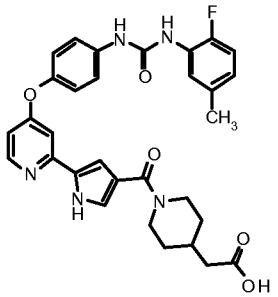
^{1}H NMR (DMSO-d_6) δ: 12.11 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.33 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.9, 1.8 Hz, 1H), 7.63 (dd, J = 2.9, 1.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.22 - 7.37 (m, 2H), 7.01 - 7.18 (m, 3H), 6.72 - 6.85 (m, 1H), 6.58 (dd, J = 5.6, 2.3 Hz, 1H), 4.83 (t, J = 5.9 Hz, 1H), 4.19 (t, J = 5.1 Hz, 2H), 3.57 - 3.73 (m, 2H), 2.25 (s, 3H)

LR MS (ES+): 491 (MH), 513 ($M+Na^+$)

LR MS (ES-): 489 (M-H)

Example 125

{1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetic acid

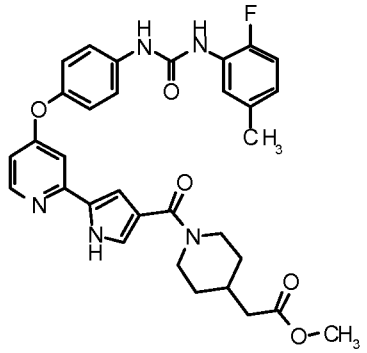


To a stirred solution of methyl {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetate (50mg, 0.085mmol) in THF/MeOH (5ml/5ml) was added 1M NaOH solution (3ml, 3mmol). The mixture was stirred at room temperature for one hour, and poured into 50ml of water. 2M HCl was added until pH = 4. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetic acid as white solid. Yield: 47mg, 96%.

LR MS (ES-): 570 (M-H)

Example 126

methyl {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetate



Similar procedure as Example 132.

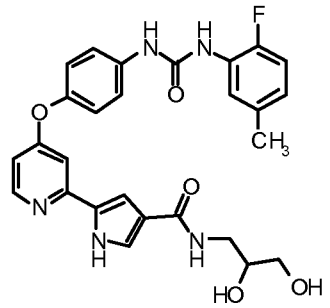
^{1}H NMR (d_6-DMSO): 11.83 (br. s., 1H), 9.14 (s, 1H), 8.46 (br. s., 1H), 8.35 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 1.8 Hz, 1H), 7.01 - 7.18 (m, 4H), 6.86 (s, 1H), 6.80 (d, J = 4.4 Hz, 1H), 6.61 (dd, J = 5.9, 2.1 Hz, 1H), 4.26 (br. s., 2H), 3.57 (s, 3H), 2.87 (br. s., 2H), 2.18 - 2.32 (m, 5H), 1.93 (br. s., 1H), 1.65 (br. s., 2H), 1.14 (br. s., 2H)

LR MS (ES+): 608 ($M+Na^+$)

LR MS (ES-): 584 (M-H)

Example 127

N-(2,3-dihydroxypropyl)-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

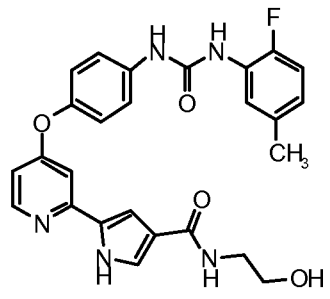
^1H NMR (d_6-DMSO): 11.81 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.8, 1.9 Hz, 1H), 7.86 (t, J = 5.7 Hz, 1H), 7.51 - 7.60 (m, 2H), 7.38 (dd, J = 3.1, 1.6 Hz, 1H), 7.10 - 7.19 (m, 3H), 7.07 (td, J = 4.3, 2.5 Hz, 2H), 6.74 - 6.84 (m, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.78 (d, J = 5.0 Hz, 1H), 4.54 (t, J = 5.9 Hz, 1H), 3.48 - 3.60 (m, 1H), 3.23 - 3.36 (m, 3H), 3.05 - 3.18 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 542 ($M+Na^+$)

LR MS (ES-): 518 (M-H)

Example 128

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-hydroxyethyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

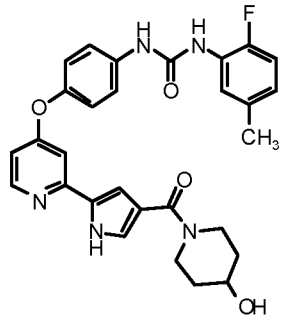
^{1}H NMR (d_6-DMSO): 11.79 (br. s., 1H), 9.30 (s, 1H), 8.57 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.95 (dd, J = 7.9, 1.8 Hz, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.50 - 7.63 (m, 2H), 7.35 (d, J = 1.5 Hz, 1H), 7.00 - 7.21 (m, 5H), 6.79 (td, J = 5.3, 2.5 Hz, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.66 (t, J = 5.6 Hz, 1H), 3.38 - 3.51 (m, 2H), 3.22 (q, J = 6.1 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 512 ($M+Na^+$)

LR MS (ES-): 488 (M-H)

Example 129

1-(2-fluoro-5-methylphenyl)-3-{4-[(2-{4-[(4-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}urea



Similar procedure as Example 132.

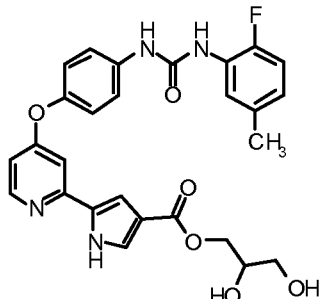
^{1}H NMR (d_6-DMSO): 11.84 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.99 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.3 Hz, 1H), 7.04 - 7.20 (m, 4H), 6.89 (s, 1H), 6.81 (td, J = 5.3, 2.3 Hz, 1H), 6.63 (dd, J = 5.9, 2.3 Hz, 1H), 4.73 (d, J = 4.1 Hz, 1H), 3.90 - 4.06 (m, 2H), 3.71 (dt, J = 8.4, 4.3 Hz, 1H), 3.25 (d, J = 2.6 Hz, 2H), 2.27 (s, 3H), 1.73 (d, J = 4.1 Hz, 2H), 1.21 - 1.44 (m, 2H)

LR MS (ES+): 552 ($M+Na^+$)

LR MS (ES-): 528 (M-H)

Example 130

2,3-dihydroxypropyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 131.

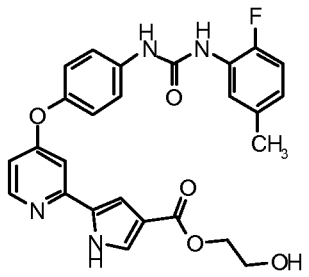
^{1}H NMR (d_6-DMSO): 12.12 (br. s., 1H), 9.24 (s, 1H), 8.54 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.62 (m, 2H), 7.48 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 - 7.40 (m, 1H), 7.05 - 7.20 (m, 4H), 6.75 - 6.87 (m, 1H), 6.68 (dd, J = 5.9, 2.3 Hz, 1H), 4.92 (d, J = 5.3 Hz, 1H), 4.64 (t, J = 5.7 Hz, 1H), 4.11 - 4.22 (m, 1H), 3.97 - 4.09 (m, 1H), 3.67 - 3.79 (m, 1H), 3.38 - 3.46 (m, 2H), 2.28 (s, 3H)

LR MS (ES+): 543 ($M+Na^+$)

LR MS (ES-): 519 (M-H)

Example 131

2-hydroxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



A mixture of 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (50mg, 0.11mmol), ethylene glycol (1ml), 1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC• HCl, 25mg, 0.13mmol) and 4-dimethylaminopyridine (DMAP, 5mg, 0.04mmol) in anhydrous THF (10ml) was stirred at 60°C for 16 hours. The mixture was 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 the crude, which was purified by silica gel chromatography with a gradient of 3~5% MeOH/$CHCl_3$ to give 2-hydroxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate as white solid. Yield: 36mg, 67%.

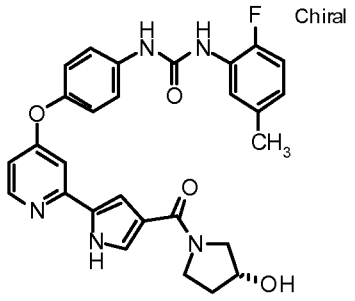
^{1}H NMR (d_6-DMSO): 12.12 (br. s., 1H), 9.18 (s, 1H), 8.49 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.94 - 8.05 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.48 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.03 - 7.23 (m, 4H), 6.75 - 6.86 (m, 1H), 6.69 (dd, J = 5.7, 2.2 Hz, 1H), 4.83 (t, J = 5.7 Hz, 1H), 4.15 (t, J = 5.1 Hz, 2H), 3.64 (q, J = 5.4 Hz, 2H), 2.27 (s, 3H)

LR MS (ES+): 513 ($M+Na^+$)

LR MS (ES-): 489 (M-H)

Example 132

1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea



A mixture of 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (50mg, 0.11mmol), HATU (51mg, 0.13mmol) and *N,N*-diisopropylethylamine (31mg, 0.24mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of (R)-3-pyrrolidinol (14mg, 0.16mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give 1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea as white solid. Yield: 40mg, 71%.

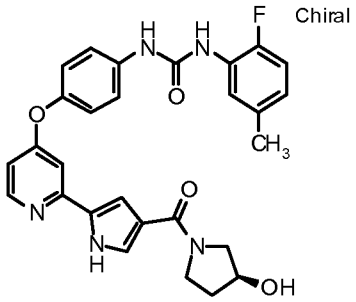
^{1}H NMR (d_6-DMSO): 11.90 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.99 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.62 (m, 2H), 7.37 (d, J = 2.3 Hz, 1H), 7.25 (br. s., 1H), 7.02 - 7.19 (m, 4H), 6.76 - 6.86 (m, 1H), 6.64 (dd, J = 5.6, 2.3 Hz, 1H), 4.93 (br. s., 1H), 4.22 - 4.38 (m, 1H), 3.69 - 3.87 (m, 1H), 3.43 - 3.59 (m, 2H), 3.35 - 3.42 (m, 1H), 2.27 (s, 3H), 1.90 (br. s., 2H)

LR MS (ES+): 538 ($M+Na^+$)

LR MS (ES-): 514 (M-H)

Example 133

1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea



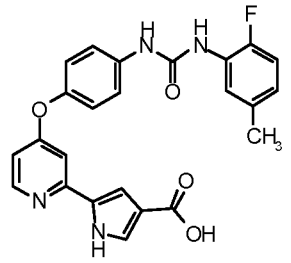
Similar procedure as Example 132.

LR MS (ES+): 538 ($M+Na^+$)

LR MS (ES-): 514 (M-H)

Example 134

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid



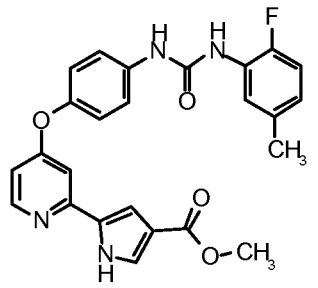
To a stirred solution of methyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate (1.38g, 3.00mmol) in a mixture of solvents THF/MeOH (20ml/20ml) was added 2ml of 5M NaOH (10mmol) solution. The mixture was heated in a 72°C bath for 5 hours, cooled to room temperature and poured into 200ml of water. 2M HCl was added until pH = 3. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid as light brown solid. Yield: 1.28g, 96%.

^1H NMR (d_6-DMSO): 12.04 (br. s., 1H), 11.88 (br. s., 1H), 9.18 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.94 - 8.05 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.31 - 7.42 (m, 2H), 7.01 - 7.21 (m, 4H), 6.81 (td, J = 5.2, 2.2 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 2.27 (s, 3H)

LR MS (ES-): 467 (M-H)

Example 135

methyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



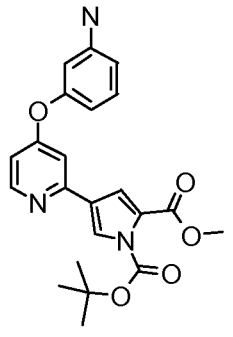
To a stirred solution of methyl 5-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate (1.0g, 3.23mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (488mg, 3.23mmol). The mixture was stirred at room temperature for one hour and poured into 200ml of 0.02M HCl solution with vigorous stirring. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give methyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate as white solid. Yield: 1.38g, 93%.

^{1}H NMR (d_6-DMSO): 12.14 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.99 (dd, J = 7.9, 1.8 Hz, 1H), 7.53 - 7.59 (m, 2H), 7.44 (dd, J = 3.2, 1.5 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.06 - 7.18 (m, 4H), 6.77 - 6.85 (m, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 3.72 (s, 3H), 2.28 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Preparation of1-tert-butyl 2-methyl 4-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate



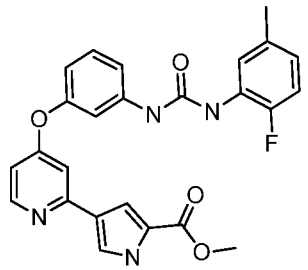
Similar procedure as 1-tert-butyl 2-methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate.

^{1}H NMR (d_6-DMSO): 8.38 (d, 1H), 8.01 (d, J = 1.5 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.06 (t, J = 7.9 Hz, 1H), 6.67 (dd, J = 5.7, 2.2 Hz, 1H), 6.43 (d, J = 7.9 Hz, 1H), 6.20 - 6.33 (m, 2H), 5.32 (br. s., 2H), 3.72 - 3.85 (m, 3H), 1.53 (s, 9H)

LR MS (ES+): 432 ($M+Na^+$)

Example 136

methyl 4-{4-[3-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate



To a stirred solution of 1-tert-butyl 2-methyl 4-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate (150 mg, 0.37 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (67mg, 0.44mmol). The mixture was stirred at room temperature for 3 hours and poured into 100ml of water. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give the Boc-protected intermediate as brown solid. This intermediate was dissolved in 5ml of methylene chloride, and 3ml of trifluoroacetic acid was added. Stirring was continued for 20 minutes. The mixture was evaporated to dryness to give the crude product, which was purified by silica gel chromatography eluting with 5% MeOH/$CHCl_3$ to give methyl 4-{4-[3-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate as white solid. Yield: 67mg, 39%.

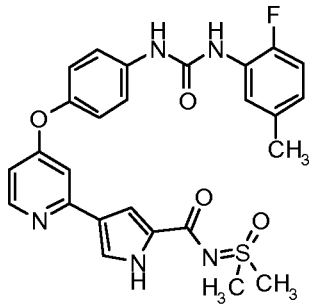
^{1}H NMR (d_6-DMSO): 12.18 (br. s., 1H), 9.23 (s, 1H), 8.47 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.63 (br. s., 1H), 7.25 - 7.47 (m, 4H), 7.16 (d, J = 7.9 Hz, 1H), 7.07 (dd, J = 11.4, 8.5 Hz, 1H), 6.72 - 6.85 (m, 2H), 6.65 (dd, J = 5.6, 2.1 Hz, 1H), 3.76 (s, 3H), 2.22 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Example 137

N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxamide



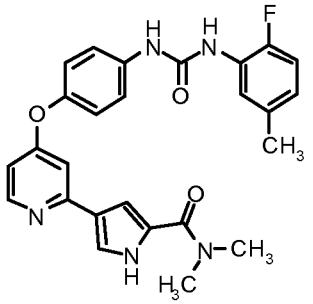
Similar procedure as Example 101.

LR MS (ES+): 544 ($M+Na^+$)

LR MS (ES-): 520 (M-H)

Example 138

4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N,N-dimethyl-1H-pyrrole-2-carboxamide



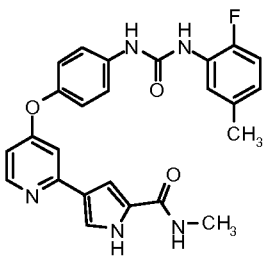
The title compound was isolated as a side product in the synthesis of Example 137.

LR MS (ES+): 474 (M+H)

LR MS (ES-): 472 (M-H

Example 139

4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-methyl-1H-pyrrole-2-carboxamide



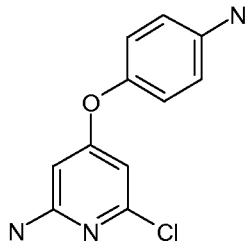
A mixture of 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylic acid (50mg, 0.11mmol), HATU (50mg, 0.13mmol), 2M methylamine/ THF solution (0.1ml, 0.2mmol) and *N,N*-diisopropylethylamine (31mg, 0.24mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes. The mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude, which was purified by silica gel chromatography with 3~5% MeOH/$CHCl_3$ to give 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-methyl-1H-pyrrole-2-carboxamide as white solid. Yield: 21mg, 41%.

^{1}H NMR (d_6-DMSO): 11.69 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 8.01 - 8.12 (m, 1H), 7.96 (dd, J = 7.8, 1.9 Hz, 1H), 7.48 - 7.61 (m, 2H), 7.43 (dd, J = 2.9, 1.5 Hz, 1H), 7.03 - 7.23 (m, 5H), 6.79 (dt, J = 8.1, 2.3 Hz, 1H), 6.61 (dd, J = 5.6, 2.3 Hz, 1H), 2.71 (d, J = 4.7 Hz, 3H), 2.26 (s, 3H)

LR MS (ES+): 482 ($M+Na^+$)

LR MS (ES-): 458 (M-H)

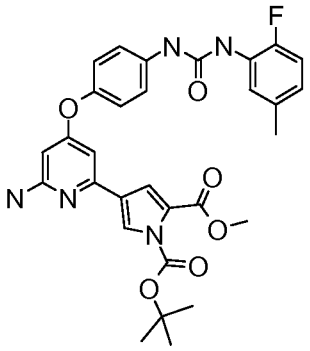
Preparation of 4-(4-aminophenoxy)-6-chloropyridin-2-amine



A stirred solution of 4-aminophenol (335mg, 3.1mmol) in anhydrous DMSO (8ml) was flushed with nitrogen and treated with 1M $KOBu^t$ / THF solution (3.1ml, 3.1mmol). The mixture was stirred at room temperature under nitrogen for 10 minutes. 4,6-dichloropyridin-2-ylamine (500mg, 3.1mmol) was added and the mixture was heated at 88°C for 16 hours, cooled to room temperature and poured into 100ml of water. The resulting precipitates were filtered, washed with water and dried to give the crude product, which was purified by silica gel chromatography with 2~5% MeOH/$CHCl_3$ to give 4-(4-aminophenoxy)-6-chloropyridin-2-amine as light brown solid. Yield: 350mg, 49%.

Example 140

1-tert-butyl 2-methyl 4-{6-amino-4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-1,2-dicarboxylate

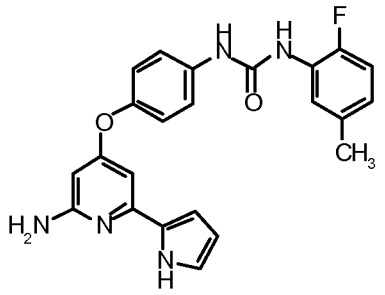


Similar procedure as Example 148.

LR MS (ES+): 598 ($M+Na^+$)

Example 141

1-(4-{[2-amino-6-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-(2-fluoro-5-methylphenyl)urea



Similar procedure as Example 148.

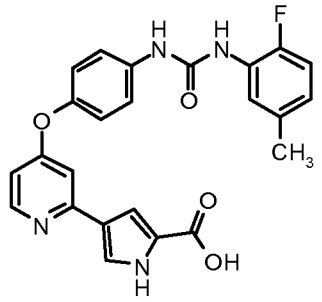
^1H NMR (d_6-DMSO): 11.02 (br. s., 1H), 9.11 (s, 1H), 8.44 (br. s., 1H), 7.97 (d, 1H), 7.50 (d, J = 8.8 Hz, 2H), 6.98 - 7.17 (m, 3H), 6.78 (br. s., 2H), 6.53 (br. s., 2H), 6.05 (br. s., 1H), 5.74 (br. s., 2H), 5.61 (s, 1H), 2.25 (s, 3H)

LR MS (ES+): 418 (M+H)

LR MS (ES-): 416 (M-H)

Example 142

4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylic acid

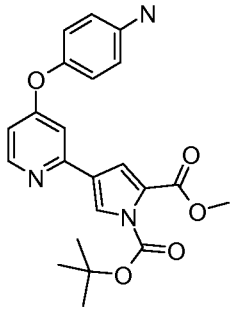


To a stirred solution of methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate (220mg, 0.48mmol) in THF/MeOH (3ml/10ml) was added 1M NaOH (4.0ml, 4.0mmol). The mixture was heated at 70°C for 2 hours, cooled to room temperature and poured into 100ml of water. 1M HCl was added until pH = 4 and the resulting precipitates were filtered, washed with water and dried *in vacuo* to give 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylic acid. Yield: 200mg, 94%.

^{1}H NMR (d_6-DMSO): 12.38 (br. s., 1H), 12.04 (br. s., 1H), 9.14 - 9.23 (m, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.34 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.9, 2.1 Hz, 1H), 7.60 (br. s., 1H), 7.50 - 7.58 (m, 2H), 7.30 (d, J = 2.1 Hz, 1H), 7.22 (s, 1H), 7.03 - 7.18 (m, 3H), 6.73 - 6.84 (m, 1H), 6.60 (dd, J = 5.6, 2.3 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 445 (M-H)

Preparation of 1-tert-butyl 2-methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate

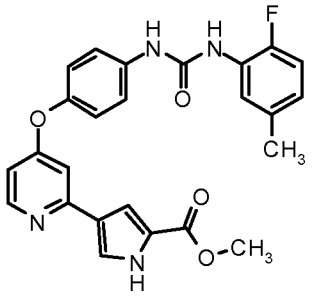


A 100ml flask was charged with 4-((2-chloropyridin-4-yl)oxy)aniline (150mg, 0.68mmol), 1-tert-butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2-dicarboxylate (260mg, 0.81mmol), 2M Na_2CO_3 solution (0.5ml, 1.0mmol), $PdCl_2(PPh_3)_2$ (5mg, 0.007mmol), 10ml of 1,4-dioxane and 3ml of water. The mixture was flushed with nitrogen and heated at 70°C for 30 minutes. The mixture was cooled to room temperature and poured into

100ml of water. The precipitates were filtered and dried to give the crude, which was further purified by silica gel chromatography eluting with 2-3% MeOH/$CHCl_3$ to give 1-tert-butyl 2-methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate as light brown oil. Yield: 240mg, 86%.

Example 143

Methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate



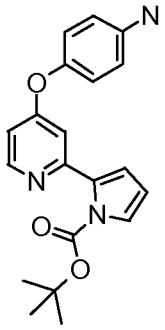
To a stirred solution of 1-tert-butyl 2-methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate (240 mg, 0.59 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (107mg, 0.71mmol). The mixture was stirred at room temperature for 30 minutes and poured into 100ml of water. The resulting precipitates were filtered, washed with water and dried to give a brown oil. Purification by silica gel chromatography eluting with 2-3% MeOH/$CHCl_3$ gave the Boc-protected intermediate as light green oil, which was dissolved in 5ml of methylene chloride, followed by addition of 3ml of trifluoroacetic acid. The mixture was stirred at room temperature for 10 minutes, evaporated to dryness, and purified by silica gel chromatography eluting with 2-5% MeOH/$CHCl_3$ to give methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate as white solid. Yield: 135mg, 50%.

^{1}H NMR (d_6-DMSO): 12.17 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.33 (d, J = 5.9 Hz, 1H), 7.91 - 8.04 (m, 1H), 7.61 (dd, J = 3.1, 1.6 Hz, 1H), 7.53 (d, J = 9.1 Hz, 2H), 7.22 - 7.31 (m, 2H), 7.02 - 7.17 (m, 3H), 6.73 - 6.85 (m, 1H), 6.58 (dd, J = 5.7, 2.5 Hz, 1H), 3.76 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

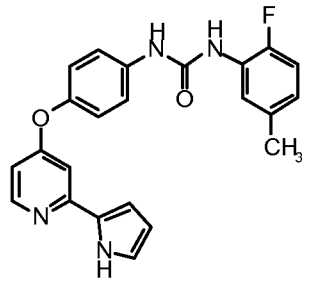
Preparation of tert-butyl 2-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1-carboxylate



To a stirred mixture of *N*-Boc-pyrrole-2-boronic acid (114mg, 0.54mmol) and 4-((2-chloropyridin-4-yl)oxy)aniline (100mg, 0.45mmol) in 8ml of 1,4-dioxane, was added $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) and 1M Na_2CO_3 aqueous solution (0.5ml, 1.0mmol). The mixture was heated at 72°C under N_2 for one hour, cooled to room temperature and poured into 100ml of water. The resulting mixture was extracted with EtOAc (2x50ml). The organic layers were combined, washed with brine (50ml), dried over Na_2SO_4, and evaporated to give a brown oil, which was purified by silica gel chromatography with a gradient of 20~50% EtOAc/hexanes to give tert-butyl 2-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1-carboxylate as colorless oil. Yield: 110mg, 70%.

Example 144

1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea

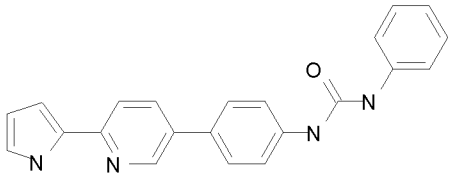


To a stirred solution of tert-butyl 2-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1-carboxylate (100 mg, 0.28 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (51mg, 0.34mmol). The mixture was stirred at room temperature for one hour and poured into 100ml of water. The resulting mixture was extracted with EtOAc (2x50ml). The organic layers were combined, washed with brine (50ml), dried over Na_2SO_4, and evaporated to give a brown oil, which was purified by silica gel chromatography with 2-5% MeOH/$CHCl_3$ to give the Boc-

protected intermediate as light green oil. The oil was dissolved in 5ml of methylene chloride, and 3ml of trifluoroacetic acid was added. Stirring was continued for 10 hours, and the mixture was evaporated to dryness. The brown residue was dissolved in methanol (5ml). This methanol solution was then added dropwise into 100ml of 1M $NaHCO_3$ solution with stirring. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea as light grey solid.
^{1}H NMR (d_6-DMSO): 11.43 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.48 - 7.58 (m, 2H), 7.20 (d, J = 2.1 Hz, 1H), 7.04 - 7.16 (m, 3H), 6.75 - 6.86 (m, 2H), 6.67 (dt, J = 3.8, 1.9 Hz, 1H), 6.57 (dd, J = 5.9, 2.3 Hz, 1H), 6.05 - 6.13 (m, 1H), 2.25 (s, 3H)

Example 145

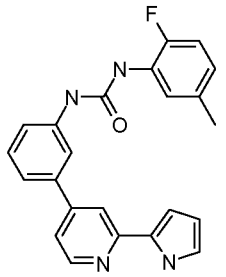
1-phenyl-3-{4-[6-(1H-pyrrol-2-yl)pyridin-3-yl]phenyl}urea



Similar procedure as Example 148.
^{1}H NMR (DMSO-d_6) δ: 11.46 (br. s., 1H), 8.79 (s, 1H), 8.75 (d, J = 1.8 Hz, 1H), 8.67 (s, 1H), 7.98 (dd, J = 8.4, 2.5 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.27 (t, J = 7.9 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 6.84 - 6.88 (m, 1H), 6.77 (t, J = 3.8 Hz, 1H), 6.11 - 6.16 (m, 1H)

Example 146

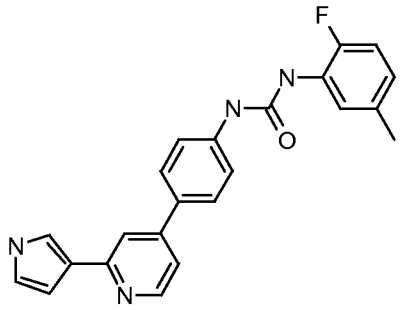
1-(2-fluoro-5-methylphenyl)-3-{3-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea



Similar procedure as Example 148.
LR MS (ES+): 387 ($M+H^+$)

Example 147

1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-3-yl)pyridin-4-yl]phenyl}urea

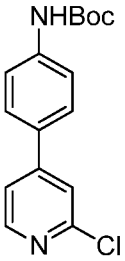


Similar procedure as Example 148.

^{1}H NMR (d_6-DMSO): 11.72 (br. s., 1H), 9.49 (br. s., 1H), 8.63 (s, 1H), 8.53 (d, J = 6.4 Hz, 1H), 8.38 (br. s., 1H), 8.07 (d, J = 8.5 Hz, 2H), 8.00 - 8.04 (m, 1H), 7.97 (dd, J = 7.9, 1.8 Hz, 1H), 7.81 - 7.90 (m, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.13 (dd, J = 11.3, 8.4 Hz, 1H), 7.03 (d, J = 2.1 Hz, 1H), 6.98 (br. s., 1H), 6.84 (ddd, J = 7.8, 5.3, 2.1 Hz, 1H), 2.21 - 2.36 (m, 3H)

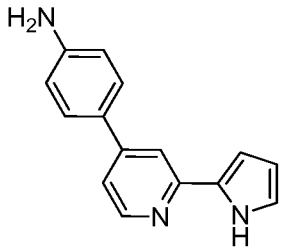
LR MS (ES+): 387 (M+H)

tert-butyl (4-(2-chloropyridin-4-yl)phenyl)carbamate



To a mixture of (4-boc-aminophenyl)boronic acid (200mg, 0.84mmol) and 2-chloro-4-bromopyridine (162mg, 0.84mmol) in 10ml of 1,4-dioxane, was added $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) and 1M Na_2CO_3 aqueous solution (0.5ml, 1.0mmol). The mixture was heated at 70°C under N_2 for 2 hours, cooled to room temperature and poured into 100ml of water. The brown precipitates were filtered, washed with water and dried to give tert-butyl (4-(2-chloropyridin-4-yl)phenyl)carbamate as the crude product.

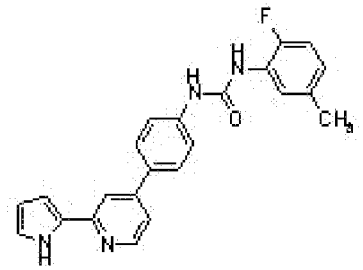
4-(2-(1H-pyrrol-2-yl)pyridin-4-yl)aniline



To a mixture of N-Boc-pyrrole-2-boronic acid (210mg, 1.0mmol) and tert-butyl (4-(2-chloropyridin-4-yl)phenyl)carbamate (250mg, 0.82mmol) in 10ml of 1,4-dioxane, was added $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) and 1M Na_2CO_3 aqueous solution (0.75ml, 1.5mmol). The mixture was heated at 60°C under N_2 for 3 hours, cooled to room temperature and poured into 100ml of water. The precipitates were filtered, dried and purified by silica gel chromatography with 1-5% MeOH/$CHCl_3$ to give the intermediate as light yellow oil. This intermediate was dissolved in 10ml of methylene chloride and 3ml of trifluoroacetic acid was added. The mixture was stirred at room temperature for 16 hours and evaporated to dryness to give 4-(2-(1H-pyrrol-2-yl)pyridin-4-yl)aniline TFA salt as light brown solid. Yield: 290mg, 100%.

Example 148

1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea



To a stirred suspension of 4-(2-(1H-pyrrol-2-yl)pyridin-4-yl)aniline TFA salt (60 mg, 0.17 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (48mg, 0.32mmol) and *N,N*-diisopropylethylamine (40 mg, 0.31 mmol). After 1 hour, the reaction mixture was evaporated and purified by silica gel chromatography with 2-3% MeOH/$CHCl_3$ to give 1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea as off-white solid. Yield: 28mg.

^{1}H NMR (d_6-DMSO): 11.49 (br. s., 1H), 9.29 (br. s., 1H), 8.52 - 8.60 (m, 1H), 8.48 (d, J = 5.3 Hz, 1H), 7.94 - 8.04 (m, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.42 (dd, J = 5.3, 1.5 Hz, 1H), 7.12 (dd, J = 11.4, 8.2 Hz, 1H), 6.89 (s, 2H), 6.82 (dt, J = 5.4, 2.6 Hz, 1H), 6.16 (t, J = 2.9 Hz, 1H), 2.29 (s, 3H)

LR MS (ES+): 409 ($M+Na^+$)

LR MS (ES-): 385 (M-H)

3.2 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. Compounds of the current invention have the IC50 value in the range of 0.01 to 500 nM.

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).

The foregoing description can be employed to practice the present invention, and represents the best mode contemplated. It should not be construed as limiting the overall scope hereof.

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 and III present the biodata of some of the compounds of the present invention.

Table II: Biodata of Compounds of the Present Invention with Amide Linker

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
1		28		
2	8	28		
3		28		
4	6	29		
5		2956		
6		506		
7	12	34		
8	8	28		
9	30	47		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
10	46	41		
11	28	23	34	
12				
13	16	27		
14	15	33	15	
15	51	26		73
16	17	21		
17	22	20		61
18	10	31		
19	30	37		135
20	83	28		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
21	12	24		39
22	18	29	13	105
23	13	35		
24	55	24		
25	30	25		
26	39	120		
27	45	66		
28	38	52		
29	18	55		
30	29	37		94

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
31	14	29	20	
32	22	46		
33	18	56		
34	7	70		
35	27	29		
36		10028		
37	1005	2610		

Table 1II: Biodata of Compounds of the Present Invention with Urea Linker

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
38		10		
39		23		
40		11		
41		11		
42		60		
43		16		
44		24		
45		17		
46	2	28		
47	107	17		
48	16	12		
49	145	27		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
50	5	32		
51		16		
52		25		
53	43	28		44
54	130	29		191
55	32	23		26
56	81	20		
57	102	45		
58	211	36		
59	34	29		
60	27	23		
61	91	39		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
62	122	43		
63	111	30		
64	16	39		
65		15	4	
66		17	3	
67	31	31		
68		16		
69		24	5	
70	2	20		
71		20		
72	7	15		
73		11		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
74	7	12		
76	2	14	3	
76	3	14		
77	8	10		
78	25	15	4	
79	13	38		
80	176	69		
81		19		
82	17	19		
83		22	5	
84		13		
85	6	30		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
86		27		
87	5	25		
88	374	477		
89	5	23		
90	8	17	6	21
91	17	14		38
92	37	9		39
93	6	5	5	14
94	10	6		10
95	30	32		
96	3	17		69
97	8	18		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
98	62	51		
99	49	46		
100	12	13		
101	4	8		82
102	10	35		8
103	24	20		
104	23	27		
105	87	15		
106	16	21		
107	13	21		
108	17	14	13	43
109	16	23		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
110	8	38	10	32
111	13	71		
112	13	18		
113	23	25		
114	13	22		
115	2	15	2	44
116	12	17		
117	6	18		
118	22	85		
119	12	54		
120	43	98		
121	37	14	20	102

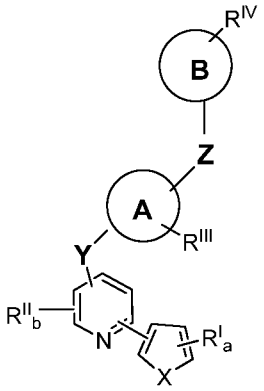
Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
122	142	130		
123	13	24		85
124	23	36		
125	22	31		
126	16	116		
127	20	21		91
128	10	53		
129	12	102		
130	5	43	16	32
131	8	31		
132	22	15		
133	66	15		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
134	4	31	4	
135	11	47		
136	29	22		
137	14	33		
138		30		
139	14	30		
140		10000		
141		2704		
142	111	28		
143	16	12		
144	28	26		
145	10000	10000		

Example#	VEGFR2 Cellular IC_{50} (nM)	VEGFR2 Enzyme IC_{50} (nM)	VEGFR1 Enzyme IC_{50} (nM)	PDGFβ Cellular IC_{50} (nM)
146	10000	7007		
147	10000	3505		
148	10000	1382		

We claim:

1. A compound represented by Formula I:



Formula I

wherein

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

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—$S(O)_n$—(CH_2)h—;

(4') —(CH_2)g—SO_2N R^2—(CH_2)h—;

(5') —$(CH_2)g—NR^2SO_2—(CH_2)h$—;

(6') —$(CH_2)g$— CO—$(CH_2)h$—;

(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;

(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;

(9') —$(CH_2)g—C\equiv C—(CH_2)h$—;

(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;

(11') —$(CH_2)g—(CH_2)h$—;

(12') —$(CH_2)g—CF_2—(CH_2)h$—;

(13') —$(CH_2)g—CCl_2—(CH_2)h$—;

(14') —$(CH_2)g$—CHF—$(CH_2)h$—;

(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;

(16') —$(CH_2)g—CR^2R^3—(CH_2)h$—;

(17') —$(CH_2)g—C{=}C—(CH_2)h$—;

and (18') a single bond;

wherein

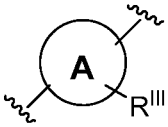
g is 0 or an integer of from 1 to 3;

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 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 cyclic ring;

Ring A is selected from the group consisting of:



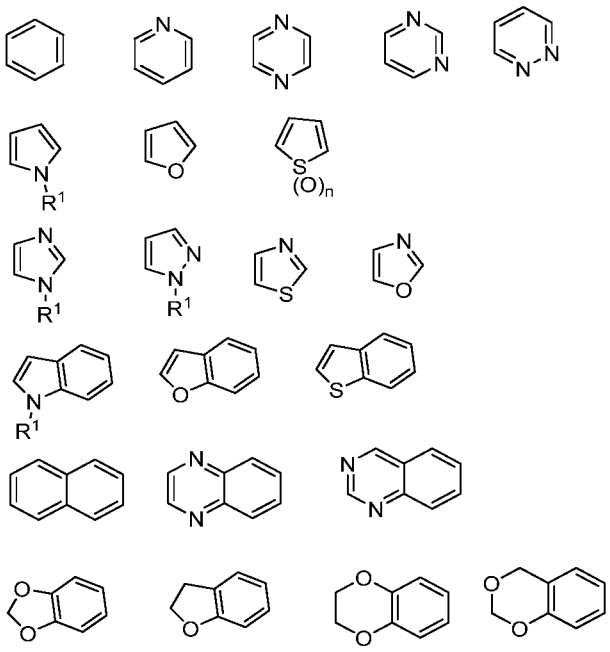
(i) Phenyl;

(ii) Naphthyl;

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

Ring A can be illustrated but not limited to the following:



wherein

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^{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, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

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

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

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

and (4') $S(O)_2N(R^8)(CH_2)_j$.

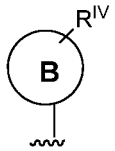
wherein:

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;

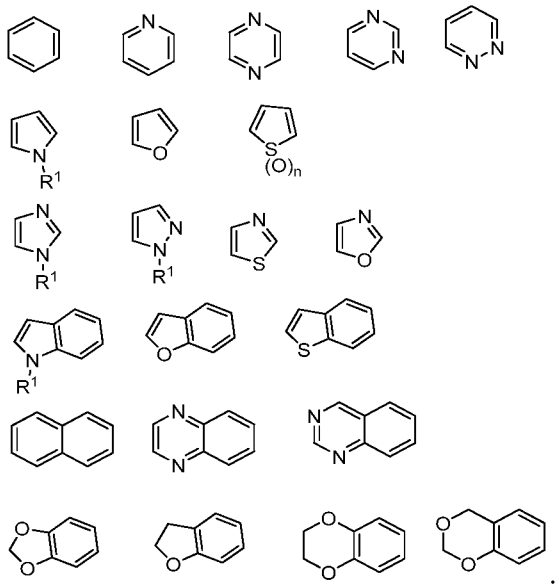
R^{IV} represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —NR^9R^{10}; wherein R^9 and R^{10} are independently selected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

and including any pharmaceutically acceptable salt or prodrug.

2. The compound according to claim 1, wherein X is NH.

3. The compound according to claim 1, wherein X is S.

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



5. A compound according to claim 1 selected from the group consisting of :

(1') [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid;

(2') methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate;

(3') ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid;

(4') methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate;

(5') 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(6') methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(7') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(8') 4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(9) N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy) pyridin-2-yl]-1H-pyrrole-3-carboxamide;

(10) N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(11') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(12') methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(13') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(14') N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(15') N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(16') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(17') N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(18') N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(19') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(20') methyl 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(21') 2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(22') 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(23') methyl 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(24') 2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(25') 2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(26') 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(27') methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(28') 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(29') methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(30') N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(31') N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(32') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(33') methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(34') 3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide;

(35') methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate;

(36') 2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide;
and (37') 3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide.

6. The compound according to claim 1 provided that when Ring B is pyrazole, R^{IV} is not a phenyl or substituted phenyl.

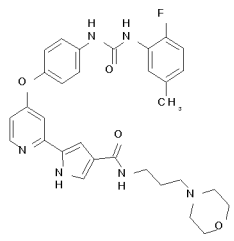
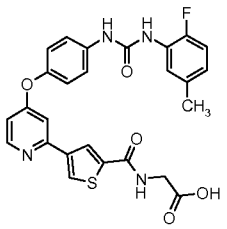
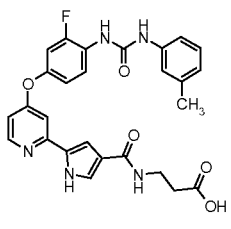
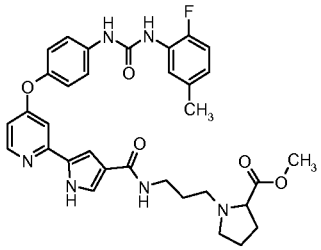
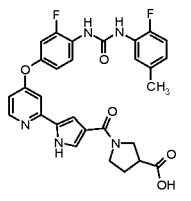
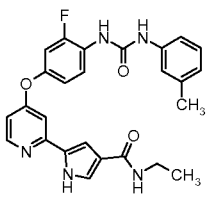
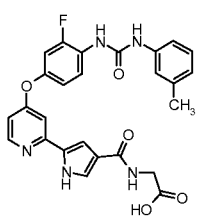
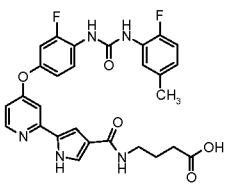
7. A compound according to claim 6, wherein Y is selected from the group consisting of

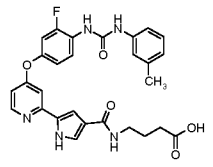
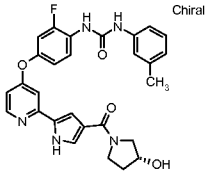
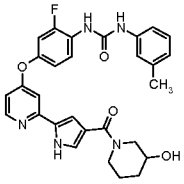
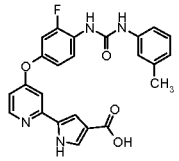
(1') —$(CH_2)g$—O—$(CH_2)h$—;
(2') —$(CH_2)g$—NR^1—$(CH_2)h$—;
(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;
(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;
(5') —$(CH_2)g$—NR^2SO_2—$(CH_2)h$—;
(6') —$(CH_2)g$— CO—$(CH_2)h$—;
(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;
(8') —$(CH_2)g$— $NR^2C(O\ )$—$(CH_2)h$—;
(9') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
and (10') a single bond.

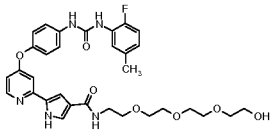
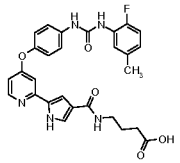
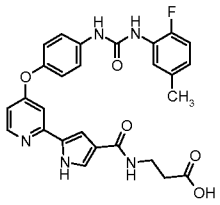
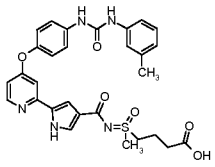
8. The compound according to claim 1, wherein X is S.

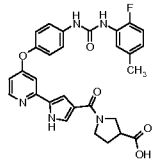
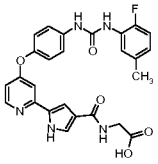
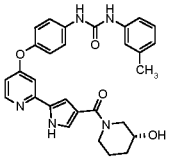
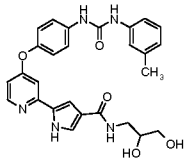
9. The compound according to claim 1, wherein X is NH.

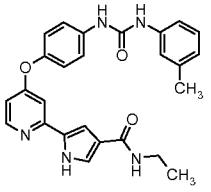
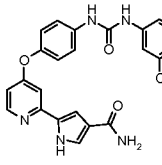
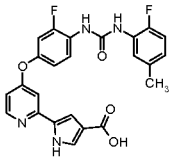
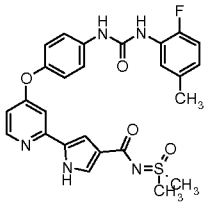
10. A compound according to claim 1 selected from the group consisting of

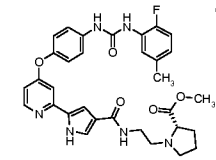
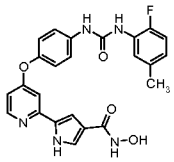
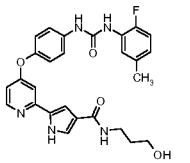
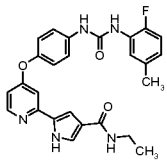









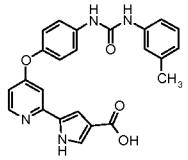
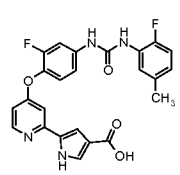

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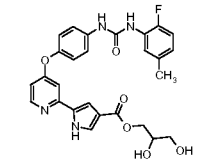

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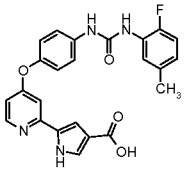
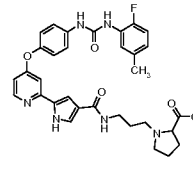

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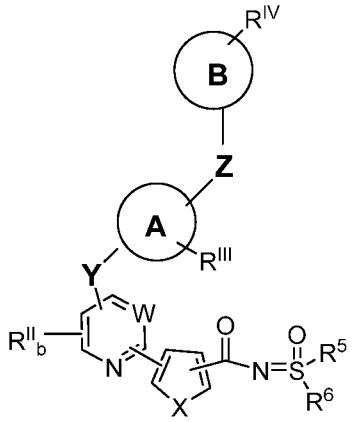
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11. A compound represented by Formula II:



Formula II

wherein

W is C or N;

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

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^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, and sulfonate;

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') —$(CH_2)g—S(O)_n—(CH_2)h$—;
(4') —$(CH_2)g—SO_2N\ R^2—(CH_2)h$—;
(5') —$(CH_2)g—NR^2SO_2—(CH_2)h$—;
(6') —$(CH_2)g—\ CO—(CH_2)h$—;
(7') —$(CH_2)g—\ C(O)NR^2—(CH_2)h$—;
(8') —$(CH_2)g—\ NR^2C(O\ )—(CH_2)h$—;
(9') —$(CH_2)g—C\equiv C—(CH_2)h$—;
(10') —$(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h$—;
(11') —$(CH_2)g—(CH_2)h$—;
(12') —$(CH_2)g—CF_2—(CH_2)h$—;
(13') —$(CH_2)g—CCl_2—(CH_2)h$—;
(14') —$(CH_2)g—CHF—(CH_2)h$—;
(15') —$(CH_2)g—CH(OH)—(CH_2)h$—;
(16') —$(CH_2)g—CR^2R^3—(CH_2)h$—;
(17') —$(CH_2)g—C{=}C—(CH_2)h$—;
and (18') a single bond;

wherein

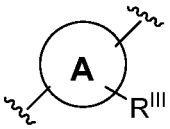
g is 0 or an integer of from 1 to 3;

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 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 cyclic ring;

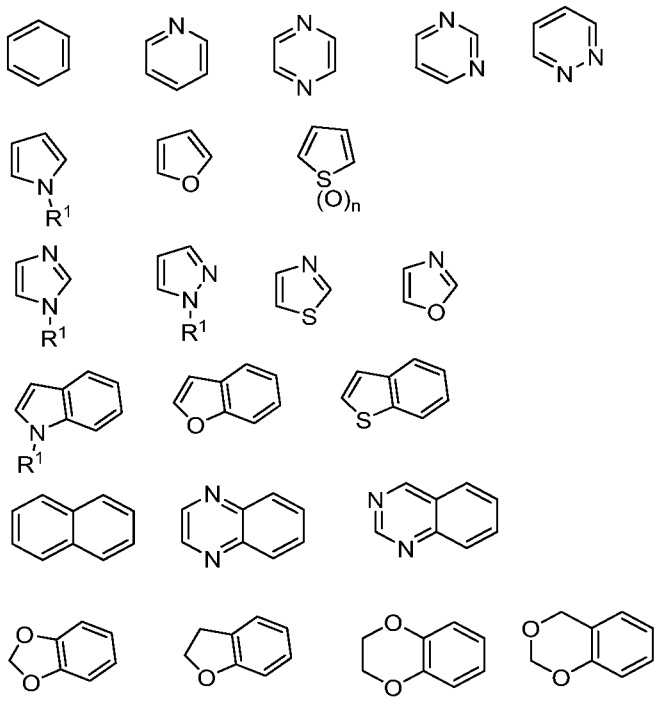
Ring A is selected from the group consisting of:



(i) Phenyl;
(ii) Naphthyl;

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

Ring A can be illustrated but not limited to the following:



wherein

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;

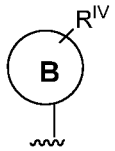
R^{III} represents optionally 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_5 alkoxy, hydroxy, amino, C_1-C_5 alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

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

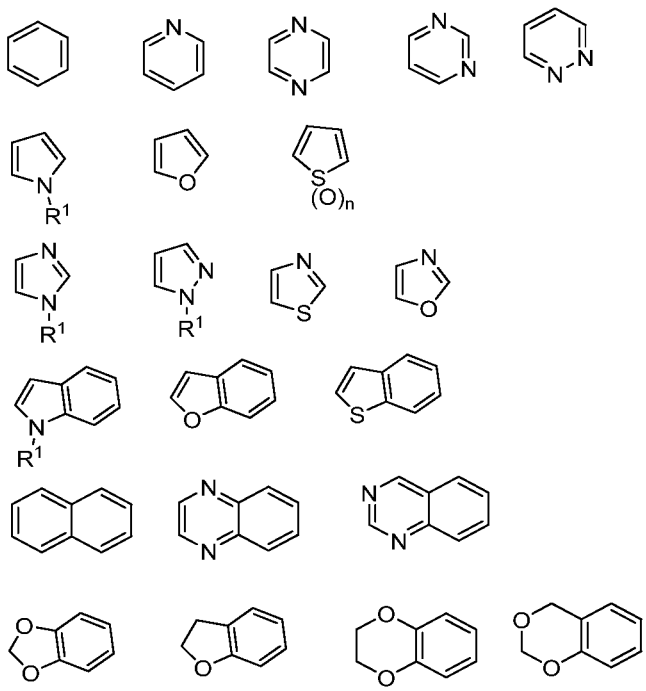
(5') $(CH_2)_iN(R^7)S(O)_2$;
and (6') $S(O)_2N(R^8)(CH_2)_j$;
wherein
i is 0 or 1;
j is 0 or 1;
R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl.

Ring B is selected from the group consisting of:



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

Ring B can be illustrated but not limited to the following:



wherein

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^{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;

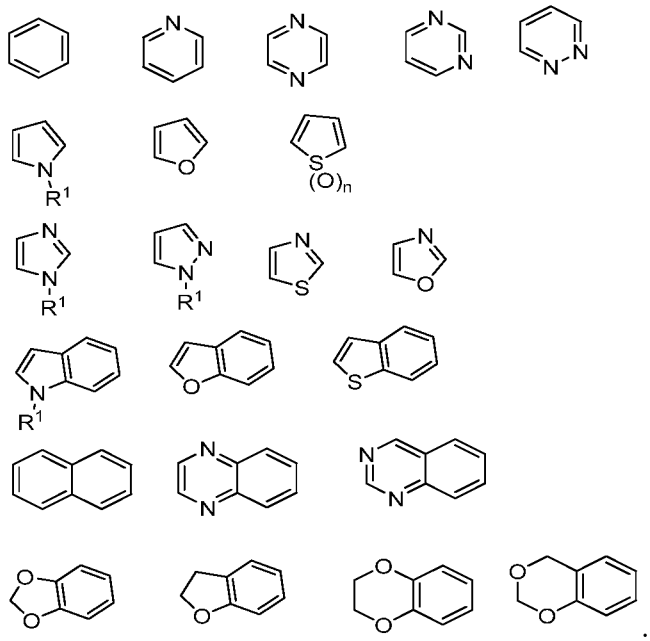
and including any pharmaceutically acceptable salt or prodrug.

12. The compound of claim 12, 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 $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.

13. The compound of claim 12, wherein 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') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;
(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;
(5') —$(CH_2)g$—NR^2SO_2—$(CH_2)h$—;
(6') —$(CH_2)g$— CO—$(CH_2)h$—;
(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;
(8') —$(CH_2)g$— $NR^2C(O\ )$—$(CH_2)h$—;
(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;
(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
and (11') a single bond.

14. The compound of claim 12, wherein W is C.

15. The compound of claim 12, wherein Ring A and Ring B are independently selected from the group consisting of



16. The compounds of claims 1 for use as a tyrosine kinase inhibitor.

17. 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.

18. A pharmaceutical composition comprising of a therapeutic effective amount of the compounds of claim 1 , together with a pharmaceutically acceptable carrier therefor.

19. The pharmaceutical composition of claim 18, 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.