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(54) **Title:** PYRROLOPYRIMIDINE DERIVATIVES AND ANALOGS AND THEIR USE IN THE TREATMENT AND PREVENTION OF DISEASES

(57) **Abstract:** Described herein are compounds and compositions for modulating kinase activity, and methods for modulating kinase activity using the compounds and compositions. Also described herein are methods of using the compounds and/or compositions in the treatment and prevention of a variety of diseases and unwanted conditions in subjects.

PYRROLOPYRIMIDINE DERIVATIVES AND ANALOGS AND THEIR USE IN THE TREATMENT AND PREVENTION OF DISEASES

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/536,301 filed January 13, 2004, U.S. Provisional Application No. 60/602,460 filed August 18, 2004, U.S. Provisional Application No. 60/602,584 filed August 18, 2004, and U.S. Provisional Application No. 60/602,586 filed August 18, 2004, the disclosures of each of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

The protein kinases (PKs) are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The PKs are categorized into two classes: the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs). The activity of PTKs is primarily associated with growth factor receptors. Growth factor receptors are cell-surface proteins that are converted to an active form upon the binding of a growth factor ligand. The active form interacts with proteins on the inner surface of a cell membrane leading to phosphorylation on tyrosine residues of the receptor and other proteins (Schlessinger and Ullrich (1992) Neuron **9**:303-391). The serine-threonine kinases (STKs) are predominantly intracellular, and are the most common of the cytosolic kinases. The protein kinases have been implicated in a host of pathogenic conditions including, cancer, psoriasis, hepatic cirrhosis, diabetes, angiogenesis, restenosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, immunological disorders such as autoimmune disease, cardiovascular disease such as atherosclerosis and a variety of renal disorders.

Growth factor receptors with PTK activity are known as receptor tyrosine kinases (RTKs). At present, at least nineteen (19) distinct subfamilies of RTKs have been identified, including the "HER" subfamily which includes EGFR (epidermal growth factor receptor), HER2, HER3 and HER4. These RTKs consist of an extracellular glycosylated ligand binding domain, a transmembrane domain and an intracellular cytoplasm catalytic domain that can phosphorylate tyrosine residues on proteins. Other RTK subfamily consists of insulin receptor (IR); insulin-like growth factor I receptor (IGF-1R); insulin receptor related receptor (IRR); the platelet derived growth factor receptor (PDGFR) group, which includes PDGFR-α, PDGFR-β, CSFIR, c-kit and c-fms; the fetus liver kinase (flk) receptor subfamily which includes fetal liver kinase-1 (KDR/FLK-1, VEGFR-2), flk-1R, flk-4 and fms-like tyrosine kinase 1 (flt-1); the tyrosine kinase growth factor receptor family is the fibroblast growth factor (FGF) receptor subgroup; and the vascular endothelial growth factor (VEGF) receptor subgroup. In addition to the RTKs, there also exists a family of intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine kinases" (CTK). At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk, Abll, Zap70, Fes, Fps, Fak, Jak and Ack) have been identified. The Src subfamily is the largest group and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk (Bolen (1993) Oncogene, **8**:2025-2031).

One class of compounds known to inhibit certain tyrosine kinases include pyrimidine compounds. For example, U.S. Patent No. 6,635,762 to Blumenkopf *et al.* describes pyrrolo[2,3-d]pyrimidine compounds. The compounds can be used to inhibit protein tyrosine kinases, especially Janus Kinase 3 (JAK3). U.S. Patent No. 6,627,754 to Blumenkopf *et al.* describes 4-aminopyrrolo[2,3-d]pyrimidine compounds, where the amine is at least a secondary amine, and use of the compounds to inhibit protein tyrosine kinases, especially Janus Kinase 3 (JAK3). The patent also discloses use of the compounds for treating diseases such as diabetes, cancer, autoimmune diseases, and the like.

Various pyrimidine compounds have also been identified as inhibitors of EGFR. U.S. Patent No. 6,395,733 to Arnold *et al.* describes 4-aminopyrrolo[2,3-d]pyrimidine compounds. The compounds are also said to inhibit EGFR. U.S. Patent No. 6,251,911 to Bold *et al.* describes 4-amino-1H-pyrazolo[3,4-d]pyrimidine compounds having EGFR and c-erb B2 activity. U.S. Patent 6,140,317 to Traxler *et al.* describes 4-substituted pyrrolo[2,3-d]pyridmidine compounds, and U.S. Patent Nos. 6,140,332, 6,096,749, and 5,686,457, all to Traxler *et al.* describes 4-aminopyrrolo[2,3-d]pyrimidine compounds, 4-aniline pyrrolo[2,3-d]pyrimidine compounds, and 4-aniline pyrrolo[2,3-d]pyrimidine compounds respectively. The compounds are said to inhibit EGFR.

U.S. Patent No. 6,207,669 to Cockerill *et al.* describes substituted bicyclic heteroaromatic compounds and their use as inhibitors of protein tyrosine kinase activity, such as EGFR.

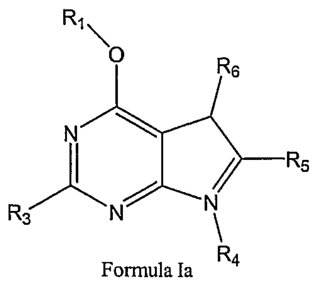
SUMMARY OF THE INVENTION

Provided herein are compounds which modulate at least one kinase activity, and in further embodiments modulate at least one protein tyrosine kinase activity, and in further embodiments modulate at least one receptor tyrosine kinase activity, and in further embodiments modulate the activity of at least one member of the HER subfamily of receptor tyrosine kinases, and in other or further embodiments modulate the activity of a specific kinase or kinase class. In some embodiments, the compositions are useful in methods for treating and preventing conditions and diseases, such as cancer, hematologic malignancies, cardiovascular disease, inflammation or multiple sclerosis. The compounds provided herein can be delivered alone or in combination with additional agents, and are used for the treatment and/or prevention of conditions and diseases. Unless otherwise stated, each of the substituents presented below is as defined earlier in the specification.

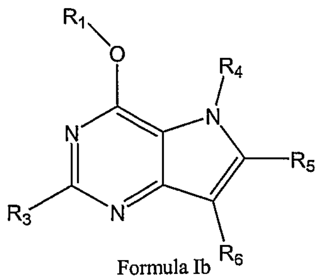
Provided herein are methods and compositions for treating and/or preventing conditions and diseases associated with kinase activity, e.g., EGFR, PDGFR, ABL, KIT, TNIK, PLK4, MARK2, VEGFR-2, and/or FLT3 activity. In some embodiments, the compounds achieve this result by modulating at least one protein kinase activity. In other embodiments, the compounds achieve this result by modulating at least one protein tyrosine kinase activity, in further embodiments the compounds achieve this result by modulating at least one receptor tyrosine kinase activity, in other embodiment the compounds achieve this result by modulating the activity of at least one member the HER subfamily of receptor tyrosine kinases. In other embodiments, the compounds achieve this result by modulating EGFR, PDGFR, ABL, KIT, TNIK, PLK4, MARK2, VEGFR-2, and/or FLT3 activity.

In one aspect, methods for preventing further progression of the conditions or diseases, or, optionally for treating and/or preventing such conditions and diseases in a subject in need thereof are provided. In one embodiment the conditions or diseases are associated with at least one kinase activity, in further embodiments the conditions or diseases are associated with at least one protein tyrosine kinase activity, in further embodiments the conditions or diseases are associated with at least one receptor tyrosine kinase activity, in further embodiments the conditions or diseases are associated with at least one activity of a kinase in the HER subfamily of receptor tyrosine kinases, and in further embodiments the conditions or diseases are associated with at least one EGFR, PDGFR, ABL, KIT, TNIK, PLK4, MARK2, VEGFR-2, and/or FLT3 activity.

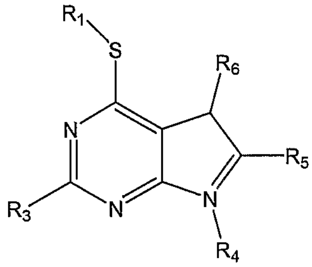
Provided herein are compositions and methods of treating a disease comprising providing an effective amount of a compound of Formula Ia, Formula Iaa, Formula Ib or Formula Ibb:



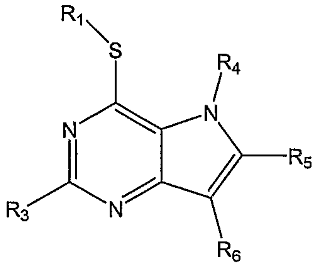
Formula Ia



Formula Ib



Formula Iaa



Formula Ibb

;

wherein

(a) R_1 is selected from one of the following options:

a. R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$,

i. wherein z is a number selected from the group consisting of 0, 1, 2, 3 and 4;

ii. R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy;

iii. R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$; or

b. R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$,

i. wherein z is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-

C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy;

iii. R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3; and

(b) R_3 is L_3-(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; L_3 is a bond, NH, O or S; R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine;

(c) R_4 is a moiety having the structure –(CHR_{4a})$_y$-R_{4b},

i. wherein y is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{4a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine;

iii. R_{4b} is a moiety selected from the group consisting of H, -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, an optionally substituted phenyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle;

(d) R_5 is H or phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and

R_6 is a moiety selected from the group consisting of H, heteroaryl, and phenyl, wherein the phenyl and the heteroaryl are optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or when the compound has the structure of Formula Ia or Formula Iaa, R_1 and R_6 together form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, -(C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; or

when the compound has the structure of Formula Ib or Formula Ibb, R_1 and R_4 together form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, -(C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; or

R_4 and R_5 together form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; or

R_5 and R_6 together form a 5- or 6-membered carbocyclic or heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine;

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, $-L_1$-OH, $-L_1-NH_2$, $-L_1-(C_1-C_4)$alkyl, $-L_1-(C_3-C_6)$cycloalkyl, $-L_1-(C_1-C_4)$fluoroalkyl, $-L_1-(C_1-C_4)$alkoxy, $-L_1-(C_1-C_4)$alkylamine, $-L_1-(C_1-C_4)$dialkylamine and $-L_1$-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$, are provided herein. In some embodiments, z is 0; or z is 1 or 2 and R_{1a} is H; or z is 1 or 2 and R_{1a} is (C_1-C_4)alkyl.

Compositions and methods of treating a disease comprising contacting providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_4 is a moiety having the structure $-(CHR_{4a})_y-R_{4b}$, wherein y is a number selected from the group consisting of 0, 1, 2 and 3; R_{4a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine; and R_{4b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, an optionally substituted phenyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{4b} is H when y is 1, 2, or 3, are also provided herein. In some embodiments, y is 0 or 1 and R_{4a} is H; or y is 0 or 1 and R_{4a} is (C_1-C_4)alkyl. In other embodiments, R_6 is an H; or R_6 is an optionally substituted phenyl; or R_6 is an optionally substituted heteroaryl.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3, are provided herein. In some embodiments, z is 0; or z is 1 and R_{1a} is H or (C_1-C_4)alkyl.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_5 is a phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy, are provided herein. In some embodiments, R_6 is an H; or R_6 is an optionally substituted phenyl; or R_6 is an optionally substituted heteroaryl. In other embodiments, R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$. In other embodiments, R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3. In still other embodiments, z is 0; or z is 1 and R_{1a} is H or (C_1-C_4)alkyl.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_4 is a moiety having the structure $-(CHR_{4a})_y-R_{4b}$, wherein y is a number selected from the group consisting of 0, 1, 2 and 3; R_{4a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine; R_{4b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, an optionally substituted phenyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{4b} is H when y is 1, 2, or 3; R_5 is H or phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_6 is a moiety selected from the group consisting of H, heteroaryl, and phenyl, wherein the phenyl and the heteroaryl are optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or R_5 and R_6 together form a 6-membered carbocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine, are provided herein. In some embodiments, R_5 is the optionally substituted phenyl. In other embodiments, R_6 is an H; or R_6 is an optionally substituted phenyl; or R_6 is an optionally substituted heteroaryl. In other embodiments, R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, and $-C(O)-(C_1-C_4)$alkoxy; and R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, $-L_1-OH$, $-L_1-NH_2$, $-L_1-(C_1-C_4)$alkyl, $-L_1-(C_3-C_6)$cycloalkyl, $-L_1-(C_1-C_4)$fluoroalkyl, $-L_1-(C_1-C_4)$alkoxy, $-L_1-(C_1-C_4)$alkylamine, $-L_1-(C_1-C_4)$dialkylamine and $-L_1$-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$. In still other embodiments, z is 0; or z is 1 or 2 and R_{1a} is H; or z is 1 or 2 and R_{1a} is (C_1-C_4)alkyl. In yet other embodiments, R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, $-(C_1-C_4)$dialkylamine, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, and $-C(O)-(C_1-C_4)$alkoxy; and R_{1b} is a moiety selected from the group consisting of $-(C_1-C_4)$alkyl, an optionally substituted $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_4, R_5 and R_6 are each H. In some embodiments, R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, and $-C(O)-(C_1-C_4)$alkoxy; and R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, $-L_1-OH$, $-L_1-NH_2$, $-L_1-(C_1-C_4)$alkyl, $-L_1-(C_3-C_6)$cycloalkyl, $-L_1-(C_1-C_4)$fluoroalkyl, $-L_1-(C_1-C_4)$alkoxy, $-L_1-(C_1-C_4)$alkylamine, $-L_1-(C_1-C_4)$dialkylamine and $-L_1$-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$. In still other embodiments, R_{1b} is phenyl, optionally substituted with 1 moiety selected from the group consisting of halogen, -CN, $-L_1-OH$, $-L_1-NH_2$, $-L_1-(C_1-C_4)$alkyl, $-L_1-(C_3-C_6)$cycloalkyl, $-L_1-(C_1-C_4)$fluoroalkyl, $-L_1-(C_1-$

C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_4 is -(C_1-C_4)alkyl; R_5 is phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_6 is a moiety selected from the group consisting of H and phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are provided herein. In some embodiments, R_6 is H. In other embodiments, R_5 is phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of -OH, and -(C_1-C_4)alkoxy; or R_5 is phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_4 is an optionally substituted -(C_3-C_6)cycloalkyl; R_5 is H or phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_6 is a moiety selected from the group consisting of H and phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are provided herein. In some embodiments, R_6 is H. In other embodiments, R_5 is phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of -OH, and -(C_1-C_4)alkoxy. In still other embodiments, R_5 is phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine,

-C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_4 is a CH_2 group substituted by an optionally substituted phenyl; R_5 is H or phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_6 is a moiety selected from the group consisting of H and phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are provided herein. In some embodiments, R_6 is H. In other embodiments, R_5 is phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of -OH, and -(C_1-C_4)alkoxy. In still other embodiments, R_5 is phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy. In yet other embodiments, R_1 is a moiety having the structure –$(CHR_{1a})_z$-R_{1b}, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$. And still in other embodiments, R_1 is a moiety having the structure –$(CHR_{1a})_z$-R_{1b}, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3.

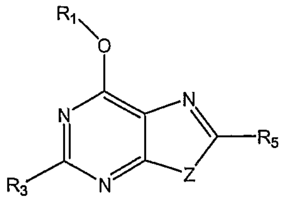
Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_3 is -(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are also provided herein.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_3 is –NH-(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are also provided herein.

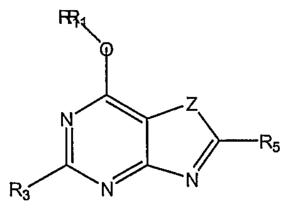
Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_3 is –O-(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are also providedherein.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula Ia, Formula Iaa, Formula Ib and Formula Ibb wherein R_3 is –S-(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are provided herein.

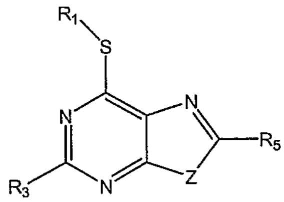
Provided herein are compositions and methods of treating a disease comprising providing an effective amount of a compound of Formula IIa, IIaa, IIb or IIbb:



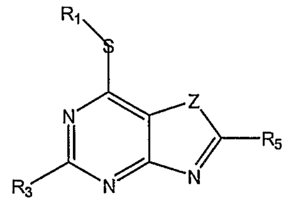
Formula IIa



Formula IIb



Formula IIaa



Formula IIbb ;

wherein Z is selected from the group consisting of O, S, and NR_4;

(a) R_1 is selected from one of the following options:

a. R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$,

i. wherein z is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and

iii. R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, –L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$; or

b. R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$,

i. wherein z is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-

(C_1-C_4)fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, and $-C(O)-(C_1-C_4)$alkoxy; and

iii. R_{1b} is a moiety selected from the group consisting of $-(C_1-C_4)$alkyl, an optionally substituted $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3; and

(b) R_3 is $L_3-(CHR_{3a})_x-R_{3b}$, wherein x is 0, 1, 2, or 3; L_3 is a bond, NH, O or S; R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine;

(c) R_4 is H or a moiety having the structure $-(CHR_{4a})_y-R_{4b}$,

i. wherein y is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{4a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, $-(C_1-C_4)$dialkylamine; and

iii. R_{4b} is a moiety selected from the group consisting of $-(C_1-C_4)$alkyl, an optionally substituted $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, an optionally substituted phenyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{4b} is H when y is 1, 2, or 3; and

(d) R_5 is H or phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, $-(C_1-C_4)$dialkylamine, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, and $-C(O)-(C_1-C_4)$alkoxy;or

R_1 and R_4 together, when the compound has the structure of Formula IIb form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -

NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

R_4 and R_5 together form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine;

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

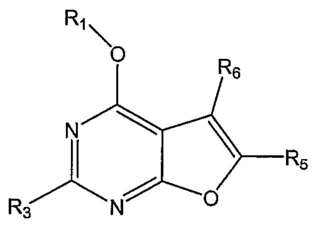
Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula IIa, IIaa, IIb or IIbb wherein R_4 is a moiety having the structure –(CHR_{4a})$_y$-R_{4b}, wherein y is a number selected from the group consisting of 0, 1, 2 and 3; R_{4a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine; and R_{4b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, an optionally substituted phenyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{4b} is H when y is 1, 2, or 3, are provided herein. In some embodiments, R_1 is a moiety having the structure –(CHR_{1a})$_z$-R_{1b}, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$. In other embodiments, z is 0; or z is 1 and R_{1a} is a moiety selected from the group consisting of H and (C_1-C_4)alkyl.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula IIa, IIaa, IIb or IIbb wherein R_1 is a moiety having the structure –(CHR_{1a})$_z$-R_{1b}, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-

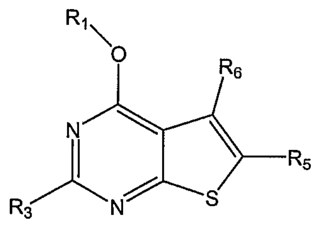
C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3; are provided herein. In some embodiments, z is 0; or z is 1 and R_{1a} is a moiety selected from the group consisting of H and (C_1-C_4)alkyl. In other embodiments, R_1 is a moiety having the structure –(CHR_{1a})$_z$-R_{1b}, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$. In still other embodiments, R_1 is a moiety having the structure –(CHR_{1a})$_z$-R_{1b}, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula IIa, IIaa, IIb or IIbb wherein R_3 is -(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are provided herein. In some embodiments, R_3 is –NH-(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine. In other embodiments, R_3 is –O-(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, $(C_1\text{-}C_4)$alkyl, F, $(C_1\text{-}C_4)$fluoroalkyl, $(C_1\text{-}C_4)$alkoxy, $-(C_1\text{-}C_4)$alkylamine, and $-(C_1\text{-}C_4)$dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, $-(C_1\text{-}C_4)$alkyl, $-(C_1\text{-}C_4)$fluoroalkyl, $-(C_1\text{-}C_4)$alkoxy, $-(C_1\text{-}C_4)$alkylamine, and $-(C_1\text{-}C_4)$dialkylamine. In still other embodiments, R_3 is $-S\text{-}(CHR_{3a})_x\text{-}R_{3b}$, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, $(C_1\text{-}C_4)$alkyl, F, $(C_1\text{-}C_4)$fluoroalkyl, $(C_1\text{-}C_4)$alkoxy, $-(C_1\text{-}C_4)$alkylamine, and $-(C_1\text{-}C_4)$dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, $-(C_1\text{-}C_4)$alkyl, $-(C_1\text{-}C_4)$fluoroalkyl, $-(C_1\text{-}C_4)$alkoxy, $-(C_1\text{-}C_4)$alkylamine, and $-(C_1\text{-}C_4)$dialkylamine.

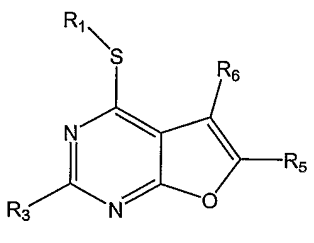
Provided herein are compositions and methods of treating a disease comprising providing an effective amount of a compound of Formula IIIa, IIIaa, IIIb or IIIbb:



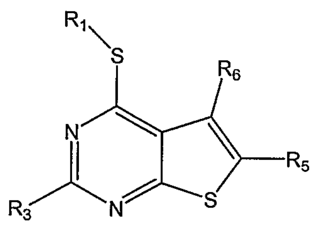
Formula IIIa



Formula IIIb



Formula IIIaa



Formula IIIbb ;

wherein

(a) R_1 is selected from one of the following options:

a. R_1 is a moiety having the structure $-(CHR_{1a})_z\text{-}R_{1b}$,

i. wherein z is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{1a} is a moiety selected from the group consisting of H, $(C_1\text{-}C_4)$alkyl, F, $(C_1\text{-}C_4)$fluoroalkyl, $(C_1\text{-}C_4)$alkoxy, -C(O)OH, $-C(O)\text{-}NH_2$, $-C(O)\text{-}(C_1\text{-}C_4)$alkyl, $-C(O)\text{-}(C_1\text{-}C_4)$fluoralkyl, $-C(O)\text{-}(C_1\text{-}C_4)$alkylamine, and $-C(O)\text{-}(C_1\text{-}C_4)$alkoxy; and

iii. R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, $-L_1$-OH, $-L_1$-NH_2, $-L_1$-(C_1-C_4)alkyl, $-L_1$-(C_3-C_6)cycloalkyl, $-L_1$-(C_1-C_4)fluoroalkyl, $-L_1$-(C_1-C_4)alkoxy, $-L_1$-(C_1-C_4)alkylamine, $-L_1$-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$; or

a. R_1 is a moiety having the structure –$(CHR_{1a})_z$-R_{1b},

i. wherein z is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and

iii. R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3; and

(b) R_3 is L_3-$(CHR_{3a})_x$-R_{3b}, wherein x is 0, 1, 2, or 3; L_3 is a bond, NH, O or S; R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine;

(c) R_5 is H or phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and –C(O)-(C_1-C_4)alkoxy; and

R_6 is a moiety selected from the group consisting of H and a phenyl or heteroaryl, wherein the phenyl and the heteroaryl are optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

R_1 and R_6 together, when the compound has the structure of Formula IIb form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

R_5 and R_6 together form a 5 or 6-membered carbocyclic or heterocyclic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are provided herein;

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

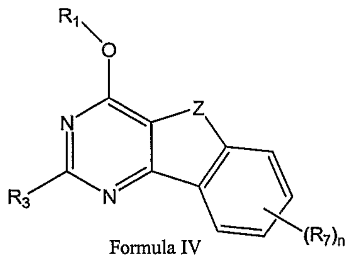
Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula IIIa, IIIaa, IIIb or IIIbb wherein R_5 is a phenyl, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy, are provided herein. In some embodiments, the 1-2 optional moieties are independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine. In other embodiments, R_6 is H. In still other embodiments, R_6 is the optionally substituted heteroaryl group. In still other embodiments, the phenyl group is substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine. In yet other embodiments, R_5 and R_6 together form a 6-membered carbocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula IIIa, IIIaa, IIIb or IIIbb wherein R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$, are provided herein.

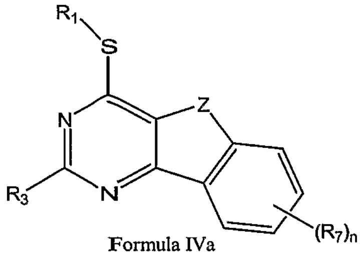
Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula IIIa, IIIaa, IIIb or IIIbb wherein R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3, are provided herein.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of Formula IIIa, IIIaa, IIIb or IIIbb wherein R_3 is $-(CHR_{3a})_x-R_{3b}$, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, are also provided herein. In some embodiments, R_3 is $-NH-(CHR_{3a})_x-R_{3b}$, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine. In other embodiments, R_3 is $-O-(CHR_{3a})_x-R_{3b}$, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine. In still other embodiments, R_3 is –S-(CHR_{3a})$_x$-R_{3b}, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine.

Provided herein are compositions and methods of treating a disease comprising providing an effective amount of a compound of the Formula IV or IVa:



Formula IV



Formula IVa

;

wherein Z is selected from the group consisting of O, S, and NR_4;

(a) R_1 is selected from one of the following options:

a. R_1 is a moiety having the structure –(CHR_{1a})$_z$-R_{1b},

i. wherein z is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and

iii. R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$; or

b. R_1 is a moiety having the structure –(CHR_{1a})$_z$-R_{1b},

i. wherein z is a number selected from the group consisting of 0, 1, 2 and 3;

ii. R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and

iii. R_{1b} is a moiety selected from the group consisting of -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3; and

(b) R_3 is L_3-$(CHR_{3a})_x$-R_{3b}, wherein x is 0, 1, 2, or 3; L_3 is a bond, NH, O or S; R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; and

(c) n is 0, 1, 2, or 3; and each R_7 is independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy;

or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of the Formula IV or IVa wherein R_1 is a moiety having the structure $-(CHR_{1a})_z$-R_{1b}, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy; and R_{1b} is phenyl, optionally substituted with 1-4 moieties independently selected from the group consisting of halogen, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-

phenyl, wherein L_1 is a bond, –C(O)- and $S(O)_2$, are provided herein. In some embodiments, z is 0; or z is 1 and R_{1a} is a moiety selected from the group consisting of H and (C_1-C_4)alkyl. In other embodiments, R_1 is a moiety having the structure $-(CHR_{1a})_z-R_{1b}$, wherein z is a number selected from the group consisting of 0, 1, 2 and 3; R_{1a} is a moiety selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, $-(C_1-C_4)$dialkylamine, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, and $-C(O)-(C_1-C_4)$alkoxy; and R_{1b} is a moiety selected from the group consisting of $-(C_1-C_4)$alkyl, an optionally substituted $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, and an optionally substituted 5-membered or 6-membered unsaturated heterocycle; or R_{1b} is H when z is 1, 2, or 3.

Compositions and methods of treating a disease comprising providing an effective amount of one of the following compounds of the Formula IV or IVa wherein R_3 is $-(CHR_{3a})_x-R_{3b}$, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine. In some embodiments, R_3 is hydrogen. In other embodiments, R_3 is $-NH-(CHR_{3a})_x-R_{3b}$, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine. In yet other embodiments, R_3 is $-O-(CHR_{3a})_x-R_{3b}$, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine. In still other embodiments, R_3 is $-S-(CHR_{3a})_x-R_{3b}$, wherein x is 0, 1, 2, or 3; and R_{3a} is selected from the group consisting of H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; and R_{3b} is H or a phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine.

In certain embodiments, isomers, diastereomers, enantiomers, metabolites, prodrugs, salts, or esters of the compounds described herein are administered to the patient. In certain embodiments involving the use of compounds having the structure of any of Formula Ia, Formula Iaa, Formula Ib, Formula Ibb, Formula IIa, Formula IIaa, Formula IIb, Formula IIbb, Formula IIIa, Formula IIIaa, Formula IIIb, Formula IIIbb, Formula IV, or Formula IVa, the conditions or diseases are associated with at least one kinase activity, in further embodiments the conditions or diseases are associated with at least one protein tyrosine kinase activity, in further embodiments the conditions or diseases are associated with at least one receptor tyrosine kinase activity, in further embodiments the conditions or diseases are associated with at least one activity of a kinase in the HER subfamily of receptor tyrosine kinases, and in further embodiments the conditions or diseases are associated with at least one of EGFR, PDGFR, ABL, KIT, TNIK, PLK4, MARK2, VEGFR-2, and/or FLT3 activity. In some embodiments, the kinase is a class III receptor tyrosine kinase (RTKIII). In other embodiments, the kinase is a tyrosine kinase receptor intimately involved in the regulation and stimulation of cellular proliferation. In still other embodiments, the kinase is a fms-like tyrosine kinase 3 receptor (FLT3 kinase). In one embodiment, compositions and methods provided herein are effective to modulate the activity of PDGFR. In other embodiments, compositions and methods provided herein are effective to selectively modulate the activity of PDGFR. In one embodiment, compositions and methods provided herein are effective to modulate the activity of Bcr-Abl. In other embodiments, compositions and methods provided herein are effective to selectively modulate the activity of Bcr-Abl. In some embodiments, the compounds disclosed herein directly inhibit EGFR activity. In other embodiments, the compounds disclosed herein indirectly inhitit EGFR activity. As used herein, EGFR activity includes the activity of one or more of the tyrosine kinase activities of EGFR, such as ErbB2, ErbB3, or ErbB4.

In some embodiments, the method involving the use of compounds having the structure of any of Formula Ia, Formula Iaa, Formula Ib, Formula Ibb, Formula IIa, Formula IIaa, Formula IIb, Formula IIbb, Formula IIIa, Formula IIIaa, Formula IIIb, Formula IIIbb, Formula IV, or Formula IVa comprises contacting the epidermal growth factor receptor with an effective amount of the compound. In other embodiments, the contacting occurs in vivo. In other embodiments, the contacting occurs within a human patient, wherein the human patient has an EGFR-mediated disease or condition. In various embodiments, the effective amount is an amount effective for treating an EGFR-mediated disease or condition within the body of the person. In some embodiments the EGFR-mediated disease or condition is selected from the group consisting of blood vessel growth, cancer, benign hyperplasia, keloid formation, and psoriasis.

Compositions described herein may be administered in a pharmaceutical composition containing one or more pharmaceutically acceptable excipients suitable. In some embodiments, the composition is in the form of a tablet, a capsule, or a soft-gel capsule. In other embodiments, the excipient is a liquid suited for administration by injection, including intravenous, intramuscular, or subcutaneous administration. And, in yet other embodiments, the excipient is suited to topical, transdermal, or buccal administration, or as a suppository.

Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg (1992) "ADVANCED ORGANIC CHEMISTRY 3RD ED." Vols. A and B, Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art are employed.

The term "agonist" means a molecule such as a compound, a drug, an enzyme activator or a hormone that enhances the activity of another molecule or the activity of a receptor site.

The term "alkenyl group" includes a monovalent unbranched or branched hydrocarbon chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to, (C_2-C_8)alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted.

The term "alkoxy" as used herein includes -O-(alkyl), wherein alkyl is defined herein.

The term "alkyl" means a straight chain or branched, saturated or unsaturated chain having from 1 to 10 carbon atoms. Representative saturated alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl, and longer alkyl groups, such as heptyl, and octyl. An alkyl group can be unsubstituted or substituted. Unsaturated alkyl groups include alkenyl groups and alkynyl groups, discussed herein. Alkyl groups containing three or more carbon atoms may be straight, branched or cyclized.

The term “alkynyl group” includes a monovalent unbranched or branched hydrocarbon chain having one or more triple bonds therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkynyl groups include, but are not limited to, (C_2-C_6)alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl. An alkynyl group can be unsubstituted or substituted.

The term “antagonist” means a molecule such as a compound, a drug, an enzyme inhibitor, or a hormone, that diminishes or prevents the action of another molecule or the activity of a receptor site.

The term “aryl” includes a carbocyclic or heterocyclic aromatic group containing from 5 to 30 ring atoms. The ring atoms of a carbocyclic aromatic group are all carbon atoms, and include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. A carbocyclic aromatic group can be unsubstituted or substituted. Preferably, the carbocyclic aromatic group is a phenyl group. The ring atoms of a heterocyclic aromatic group contains at least one heteroatom, preferably 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. Illustrative examples of heterocyclic aromatic groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl, phienyl, isoxazolyl, indolyl, oxetanyl, azepinyl, piperazinyl, morpholinyl, dioxanyl, thietanyl and oxazolyl. A heterocyclic aromatic group can be unsubstituted or substituted. Preferably, a heterocyclic aromatic is a monocyclic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms.

The term “aryloxy” includes -O-aryl group, wherein aryl is as defined herein. An aryloxy group can be unsubstituted or substituted.

The term “cycloalkyl” includes a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon-carbon multiple bonds. Examples of cycloalkyl groups include, but are not limited to, (C_3-C_7)cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl group can be unsubstituted or substituted. Preferably, the cycloalkyl group is a monocyclic ring or bicyclic ring.

The terms “effective amount” or “therapeutically effective amount” refer to a sufficient amount of the agent to provide the desired biological result. That result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in a disease. An appropriate “effective” amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

The term “halogen” includes fluorine, chlorine, bromine, and iodine.

The term “modulate” means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

The term “modulator” means a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, agonist, antagonist, and the like.

By “pharmaceutically acceptable” or “pharmacologically acceptable” is meant a material which is not biologically or otherwise undesirable, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

The term “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4’-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

A "prodrug" refers to a drug or compound in which the pharmacological action results from conversion by metabolic processes within the body. Prodrugs are generally drug precursors that, following administration to a subject and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by a metabolic pathway. Some prodrugs have a chemical group present on the prodrug that renders it less active and/or confers solubility or some other property to the drug. Once the chemical group has been cleaved and/or modified from the prodrug the active drug is generated. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. The design of prodrugs to date has been to increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent. See, e.g., Fedorak et al., *Am. J. Physiol.*, 269:G210-218 (1995); McLoed et al., *Gastroenterol*, 106:405-413 (1994); Hochhaus et al., *Biomed. Chrom.*, 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics*, 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula et al., *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987. Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth herein are included within the scope of the claims. Indeed, some of the herein-described derivatives may be a prodrug for another derivative or active compound. The optical isomers of the compounds disclosed herein, especially those resulting from the chiral carbon atoms in the molecule. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion may also be useful for the applications described herein.

The term "subject" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

The term "sulfonyl" refers to the presence of a sulfur atom, which is optionally linked to another moiety such as an aliphatic group, an aromatic group, an aryl group, an alicyclic group, or a heterocyclic group. Aryl or alkyl sulfonyl moieties have the formula $-SO_2R'$, and alkoxy moieties have the formula -O-R', wherein R' is alkyl, as defined herein, or is aryl wherein aryl is phenyl, optionally substituted with 1-3 substituents independently selected from halo (fluoro, chloro, bromo or iodo), lower alkyl (1-6C) and lower alkoxy (1-6C).

The terms "treat" or "treatment" are synonymous with the term "prevent" and are meant to indicate a postponement of development of diseases, preventing the development of diseases, and/or reducing severity of such symptoms that will or are expected to develop. Thus, these terms include ameliorating existing disease symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disorder or disease, e.g., arresting the development of the disorder or disease, relieving the disorder or disease, causing regression of the disorder or disease, relieving a condition caused by the disease or disorder, or stopping the symptoms of the disease or disorder.

Unless otherwise indicated, when a substituent is deemed to be "optionally substituted," it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from, for example, alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, perhaloalkyl, perfluoroalkyl, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art.

The compounds described herein may be labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Molecular embodiments provided herein may possess one or more chiral centers and each center may exist in the R or S configuration. The compositions and methods provided herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns. Additionally, the compounds and methods provided herein may exist as geometric isomers. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. In some situations, compounds may exist as tautomers. All tautomers are included within the formulas described herein are provided by compounds and methods herein.

In addition, the compounds provided herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

These and other aspects of the present invention will become evident upon reference to the following detailed description. In addition, various references are set forth herein which describe in more detail certain procedures or compositions, and are incorporated by reference in their entirety.

DISCLOSURE OF THE INVENTION

Compounds

Compounds and methods for modulating the activity of at least one of EGFR, PDGFR, ABL, VEGFR-2, and/or FLT3 are discussed throughout. Salts of the compounds may be used for therapeutic and prophylactic purposes, where the salt is preferably a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example Q-toluenesulphonic, acids. In another aspect, compositions containing the herein-described analogs and derivatives are provided. Preferably, the compositions are formulated to be suitable for pharmaceutical or clinical use by the inclusion of appropriate carriers or excipients. In yet another embodiment, pharmaceutical formulations are provided comprising at least one compound described herein, or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients are described herein.

Synthesis of Compounds

The compounds described herein can be obtained from commercial sources, such as Aldrich Chemical Co. (Milwaukee, Wis.), Sigma Chemical Co. (St. Louis, Mo.), or Maybridge (Cornwall, England), or the compounds can be synthesized. The compounds described herein, and other related compounds having different substituents can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 3rd Ed., Vols. A and B (Plenum 1992), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999) (all of which are incorporated by reference in their entirety). General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein. As a guide the following synthetic methods may be utilized.

Selected examples of covalent linkages and precursor functional groups which yield them are given in the Table entitled "Examples of Covalent Linkages and Precursors Thereof." Precursor functional groups are shown as electrophilic groups and nucleophilic groups. The functional group on the organic substance may be attached directly, or attached via any useful spacer or linker as defined below.

Table 1: Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	amines/anilines
Carboxamides	acyl azides	amines/anilines
Carboxamides	acyl halides	amines/anilines
Esters	acyl halides	alcohols/phenols

Covalent Linkage Product	Electrophile	Nucleophile
Esters	acyl nitriles	alcohols/phenols
Carboxamides	acyl nitriles	amines/anilines
Imines	Aldehydes	amines/anilines
Hydrazones	aldehydes or ketones	Hydrazines
Oximes	aldehydes or ketones	Hydroxylamines
Alkyl amines	alkyl halides	amines/anilines
Esters	alkyl halides	carboxylic acids
Thioethers	alkyl halides	Thiols
Ethers	alkyl halides	alcohols/phenols
Thioethers	alkyl sulfonates	Thiols
Esters	alkyl sulfonates	carboxylic acids
Ethers	alkyl sulfonates	alcohols/phenols
Esters	Anhydrides	alcohols/phenols
Carboxamides	Anhydrides	amines/anilines
Thiophenols	aryl halides	Thiols
Aryl amines	aryl halides	Amines
Thioethers	Azindines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	carboxylic acids	amines/anilines
Esters	carboxylic acids	Alcohols
hydrazines	Hydrazides	carboxylic acids
N-acylureas or Anhydrides	carbodiimides	carboxylic acids
Esters	diazoalkanes	carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	haloacetamides	Thiols
Ammotriazines	halotriazines	amines/anilines
Triazinyl ethers	halotriazines	alcohols/phenols
Amidines	imido esters	amines/anilines
Ureas	Isocyanates	amines/anilines
Urethanes	Isocyanates	alcohols/phenols
Thioureas	isothiocyanates	amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	phosphoramidites	Alcohols
Silyl ethers	silyl halides	Alcohols
Alkyl amines	sulfonate esters	amines/anilines
Thioethers	sulfonate esters	Thiols
Esters	sulfonate esters	carboxylic acids
Ethers	sulfonate esters	Alcohols
Sulfonamides	sulfonyl halides	amines/anilines
Sulfonate esters	sulfonyl halides	phenols/alcohols

In general, carbon electrophiles are susceptible to attack by complementary nucleophiles, including carbon nucleophiles, wherein an attacking nucleophile brings an electron pair to the carbon electrophile in order to form a new bond between the nucleophile and the carbon electrophile.

Suitable carbon nucleophiles include, but are not limited to alkyl, alkenyl, aryl and alkynyl Grignard, organolithium, organozinc, alkyl-, alkenyl , aryl- and alkynyl-tin reagents (organostannanes), alkyl-, alkenyl-, aryl- and alkynyl-borane reagents (organoboranes and organoboronates); these carbon nucleophiles have the advantage of being kinetically stable in water or polar organic solvents. Other carbon nucleophiles include phosphorus ylids, enol and enolate reagents; these carbon nucleophiles have the advantage of being relatively easy to generate from precursors well known to those skilled in the art of synthetic organic chemistry. Carbon nucleophiles, when used in conjunction with carbon electrophiles, engender new carbon-carbon bonds between the carbon nucleophile and carbon electrophile.

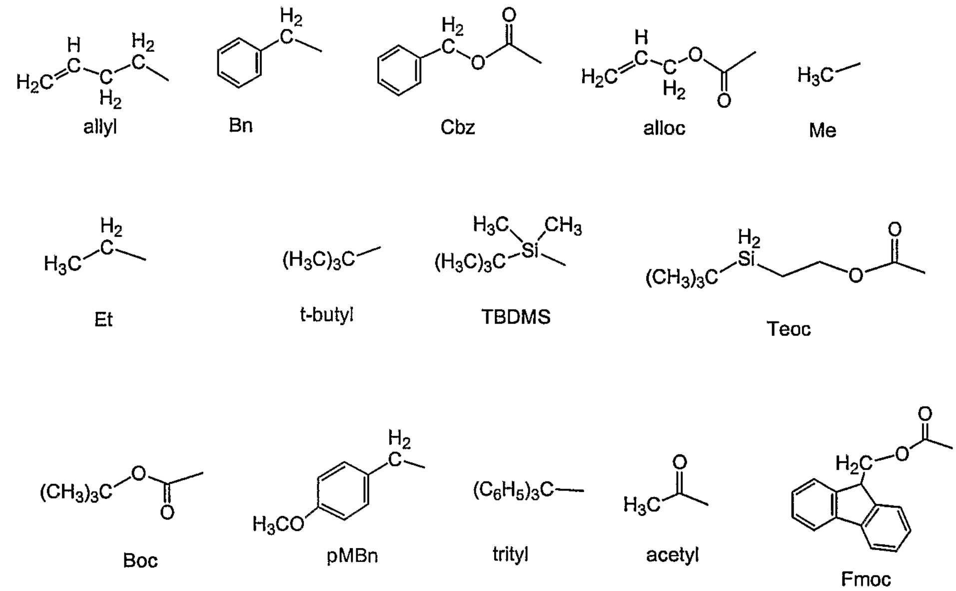
Non-carbon nucleophiles suitable for coupling to carbon electrophiles include but are not limited to primary and secondary amines, thiols, thiolates, and thioethers, alcohols, alkoxides, azides, semicarbazides, and the like. These non-carbon nucleophiles, when used in conjunction with carbon electrophiles, typically generate heteroatom linkages (C-X-C), wherein X is a hetereoatom, e. g, oxygen or nitrogen.

The term “protecting group” refers to chemical moieties that block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. It is preferred that each protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. Protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester derivatives as exemplified herein, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

Allyl blocking groups are useful in then presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd_0-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

Typically blocking/protecting groups may be selected from:



Other protecting groups are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

Methods of Formulation and Therapeutic/Prophylactic Administation and Dosing

In practicing the methods of treatment or use provided herein, the therapeutically effective amount of the compound provided herein is administered in a pharmaceutical composition to a mammal having a condition to be treated. Preferably, the mammal is a human. The compounds described herein are preferably used to prepare a medicament, such as by formulation into pharmaceutical compositions for administration to a subject using techniques generally known in the art. A summary of such pharmaceutical and veterinary compositions as well as further information on various pharmaceutical compositions described herein may be found, for example, in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975;

Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage F*orms *and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

Additionally, the compounds can be used singly or as components of mixtures. In some embodiments, the compounds are those for systemic administration as well as those for topical or transdermal administration. In other embodiments, the formulations are designed for timed release. In still other embodiments, the formulation is in unit dosage form.

The composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulation, solution, or suspension; for parenteral injection as a sterile solution, suspension or emulsion; for topical administration as an ointment or cream; or for rectal administration as a suppository, enema, foam, or gel. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical compositions will include a conventional pharmaceutically acceptable carrier or excipient and a compound described herein as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Pharmaceutical compositions described herein may contain 0.1%-95% of the compound. In any event, the composition or formulation to be administered will contain a quantity of a compound in an amount effective to alleviate or reduce the signs in the subject being treated, i.e., proliferative diseases, over the course of the treatment.

In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packeted tablets or capsules, and powders in vials or ampoules.

Methods for the preparation of compositions comprising the compounds described herein include formulating the derivatives with one or more inert, pharmaceutically acceptable carriers to form either a solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. The compositions may be in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. Suitable excipients or carriers are, for example, water, saline, dextrose, glycerol, alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like. These compositions may also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

A carrier can be one or more substances which also serve to act as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, or tablet disintegrating agent. A carrier can also be an encapsulating material.

In powder forms, the carrier is preferably a finely divided solid in powder form that is interdispersed as a mixture with a finely divided powder from of one or more compound. In tablet forms of the compositions, one or more compounds is intermixed with a carrier with appropriate binding properties in suitable proportions followed by compaction into the shape and size desired. Powder and tablet form compositions preferably contain between about 5 to about 70% by weight of one or more compound. Carriers that may be used in the practice include, but are not limited to, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Carriers also include any commonly used excipients in pharmaceutics and should be selected on the basis of compatibility with the compounds disclosed herein and the release profile properties of the desired dosage form. Exemplary carriers include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. Pharmaceutically acceptable carriers may comprise, e.g., acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like.

The compounds described herein may also be encapsulated or microencapsulated by an encapsulating material, which may thus serve as a carrier, to provide a capsule in which the derivatives, with or without other carriers, is surrounded by the encapsulating material. In an analogous manner, cachets comprising one or more compounds are also provided. Tablet, powder, capsule, and cachet forms of the may be formulated as single or unit dosage forms suitable for administration, optionally conducted orally. For intravenous injections, the compounds described herein may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer.

In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted. One or more compounds are then dispersed into the melted material by, as a non-limiting example, stirring. The non-solid mixture is then placed into molds as desired and allowed to cool and solidify.

Non-limiting compositions in liquid form include solutions suitable for oral, injection, or parenteral administration, as well as suspensions and emulsions suitable for oral administration. Sterile aqueous based solutions of one or more compounds, optionally in the presence of an agent to increase solubility of the derivative(s), are also provided. Non-limiting examples of sterile solutions include those comprising water, ethanol, and/or propylene glycol in forms suitable for parenteral administration. A sterile solution comprising a compound described herein may be prepared by dissolving one or more compounds in a desired solvent followed by sterilization, such as by filtration through a sterilizing membrane filter as a non-limiting example. In another embodiment, one or more compounds are dissolved into a previously sterilized solvent under sterile conditions.

A water based solution suitable for oral administration can be prepared by dissolving one or more compounds in water and adding suitable flavoring agents, coloring agents, stabilizers, and thickening agents as desired. Water based suspensions for oral use can be made by dispersing one or more compounds in water together with a viscous material such as, but not limited to, natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical field.

The compound may be administered with the methods herein either alone or in combination with other therapies such as treatments employing other treatment agents or modalities including anti-angiogenic agents, chemotherapeutic agents, radionuclides, anti-proliferative agents, inhibitors of protein kinase C, inhibitors of other tyrosine kinases, cytokines, negative growth regulators, for example TGFβ or IFNβ, cytolytic agents, immunostimulators, cytostatic agents and the like. When co-administered with one or more biologically active agents, the compound provided herein may be administered either simultaneously with the biologically active agent(s), or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein in combination with the biologically active agent(s).

Toxicity and therapeutic efficacy of such therapeutic regimens can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.* for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

The compounds can be administered before, during or after the occurrence of a condition of a disease, and the timing of administering the composition containing a compound can vary. Thus, for example, the compounds can be used as a prophylactic and can be administered continuously to subjects with a propensity to conditions and diseases in order to prevent the occurrence of the disorder. The compounds and compositions can be administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the compounds can be initiated within the first 48 hours of the onset of the symptoms, preferably within the first 48 hours of the onset of the symptoms, more preferably within the first 6 hours of the onset of the symptoms, and most preferably within 3 hours of the onset of the symptoms. The initial administration can be via any route practical, such as, for example, an intravenous injection, a bolus injection, infusion over 5 minutes to about 5 hours, a pill, a capsule, transdermal patch, buccal delivery, and the like, or combination thereof. A compound is preferably administered as soon as is practicable after the onset of a condition of a condition or a disease is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. The length of treatment can vary for each subject, and the length can be determined using the known criteria. For example, the compound or a formulation containing the compound can be administered for at least 2 weeks, preferably about 1 month to about 5 years, and more preferably from about 1 month to about 3 years.

The dosage appropriate for the compounds described here will be in the range of less than 0.1 mg/kg to over 10 mg/kg per day. The dosage may be a single dose or repetitive. In other embodiments using the compounds for therapeutic use, the compounds described herein are administered to a subject at dosage levels of from about 0.5 mg/kg to about 8.0 mg/kg of body weight per day. For a human subject of approximately 70 kg, this is a dosage of from 40 mg to 600 mg per day. Such dosages, however, may be altered depending on a number of variables, not limited to the activity of the compound used, the condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the condition being treated, and the judgment of the practitioner.

The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon.

Methods of Use: Biological Activity

Protein kinases (PKs) play a role in signal transduction pathways regulating a number of cellular functions, such as cell growth, differentiation, and cell death. PKs are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. Abnormal PK activity has been related to disorders ranging from relatively non life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer). In addition, a variety of tumor types have dysfunctional growth factor receptor tyrosine kinases, resulting in inappropriate mitogenic signaling. Protein kinases are believed to be involved in many different cellular signal transduction pathways. In particular, protein tyrosine kinases (PTK) are attractive targets in the search for therapeutic agents, not only for cancer, but also against many other diseases. Blocking or regulating the kinase phosphorylation process in a signaling cascade may help treat conditions such as cancer or inflammatory processes.

Protein tyrosine kinases are a family of tightly regulated enzymes, and the aberrant activation of various members of the family is one of the hallmarks of cancer. The protein-tyrosine kinase family includes Bcr-Abl tyrosine kinase, and can be divided into subgroups that have similar structural organization and sequence similarity within the kinase domain. The members of the type III group of receptor tyrosine kinases include the platelet-derived growth factor (PDGF) receptors (PDGF receptors α and β), colony-stimulating factor (CSF-1) receptor (CSF-1R, c-Fms), FLT3, and stem cell or steel factor receptor (c-kit).

The compounds, compositions, and methods provided herein are useful to modulate the activity of kinases including, but not limited to, ERBB2, ABL, AURKA, CDK2, EGFR, FGFR1, LCK, MAPK14, PDGFR, KDR, ABL, BRAF, ERBB4, FLT3, KIT, and RAF1. In some embodiments, the compositions and methods provided herein modulate the activity of a mutant kinase.

Inhibition by the compounds provided herein can be determined using any suitable assay. In one embodiment, inhibition is determined in vitro. In a specific embodiment, inhibition is assessed by phosphorylation assays. Any suitable phosphorylation assay can be employed. For example, membrane autophosphorylation assays, receptor autophosphorylation assays in intact cells, and ELISA's can be employed. See, e.g., Gazit, et al., J. Med. Chem. (1996) 39:2170-2177, Chapter 18 in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Ausubel, et al., eds. 2001). Cells useful in such assays include cells with wildtype or mutated forms. In one embodiment, the wildtype is a kinase that is not constitutively active, but is activated with upon dimerization. For example, the mutant FLT3 kinase is constitutively active via internal tandem duplication mutations or point mutations in the activation domain. Suitable cells include those derived through cell culture from patient samples as well as cells derived using routine molecular biology techniques, e.g., retroviral transduction, transfection, mutagenesis, etc. Exemplary cells include Ba/F3 or 32Dc13 cells transduced with, e.g., MSCV retroviral constructs FLT3-ITD (Kelly et al., 2002); Molm-13 and Molm14 cell line (Fujisaki Cell Center, Okayama, Japan); HL60 (AML-M3), AML193 (AML-M5), KG-1, KG-la, CRL-1873, CRL-9591, and THP-1 (American Tissue Culture Collection, Bethesda, MD); or any suitable cell line derived from a patient with a hematopoietic malignancy.

In some embodiments, the compounds described herein significantly inhibit receptor tyrosine kinases. A significant inhibition of a receptor tyrosine kinase activity refers to an IC_{50} of less than or equal to 100 μM. Preferably, the compound can inhibit activity with an IC_{50} of less than or equal to 50 μM, more preferably less than or equal to 10 μM, more preferably less than 1 μM, or less than 100 nM, most preferably less than 50 nM. Lower IC_{50}'s are preferred because the IC_{50} provides an indication as to the in vivo effectiveness of the compound. Other factors known in the art, such as compound half-life, biodistribution, and toxicity should also be considered for therapeutic uses. Such factors may enable a compound with a lower IC_{50} to have greater in vivo efficacy than a compound having a higher IC_{50}. Preferably, a compound that inhibits activity is administered at a dose where the effective tyrosine phosphorylation, i.e., IC_{50}, is less than its cytotoxic effects, LD_{50}.

In some embodiments, the compounds selectively inhibit one or more kinases. Selective inhibition of a kinase, such as FLT3, EGFR, p38 kinase, STK10, MKNK2, Bcr-Abl, c-kit, or PDGFR, is achieved by inhibiting activity of one kinase, while having an insignificant effect on other members of the superfamily.

FLT3

FLT3 kinase is a tyrosine kinase receptor involved in the regulation and stimulation of cellular proliferation. *See e.g.*, Gilliland et al., *Blood* 100:1532-42 (2002). The FLT3 kinase is a member of the class III receptor tyrosine kinase (RTKIII) receptor family and belongs to the same subfamily of tyrosine kinases as c-kit, c-fms, and the platelet-derived growth factor α and ß receptors. *See e.g.*, Lyman et al., *FLT3 Ligand in The Cytokine Handbook* 989 (Thomson et al., eds. 4th Ed.) (2003). The FLT3 kinase has five immunoglobulin-like domains in its extracellular region as well as an insert region of 75-100 amino acids in the middle of its cytoplasmic domain. FLT3 kinase is activated upon the binding of the FLT3 ligand, which causes receptor dimerization. Dimerization of the FLT3 kinase by FLT3 ligand activates the intracellular kinase activity as well as a cascade of downstream substrates including Stat5, Ras, phosphatidylinositol-3-kinase (PI3K), PLCγ, Erk2, Akt, MAPK, SHC, SHP2, and SHIP. *See e.g.*, Rosnet et al., *Acta Haematol.* 95:218 (1996); Hayakawa et al., *Oncogene* 19:624 (2000); Mizuki et al., *Blood* 96:3907 (2000); and Gilliand et al., *Curr. Opin. Hematol.* 9: 274-81 (2002). Both membrane-bound and soluble FLT3 ligand bind, dimerize, and subsequently activate the FLT3 kinase.

In normal cells, immature hematopoietic cells, typically CD34+ cells, placenta, gonads, and brain express FLT3 kinase. *See, e.g.*, Rosnet, et al., *Blood* 82:1110-19 (1993); Small et al., *Proc. Natl. Acad. Sci. U.S.A.* 91:459-63 (1994); and Rosnet et al., *Leukemia* 10:238-48 (1996). However, efficient stimulation of proliferation via FLT3 kinase typically requires other hematopoietic growth factors or interleukins. FLT3 kinase also plays a critical role in immune function through its regulation of dendritic cell proliferation and differentiation. *See e.g.*, McKenna et al., Blood 95:3489-97 (2000).

Numerous hematologic malignancies express FLT3 kinase, the most prominent of which is AML. See e.g., Yokota et al., Leukemia 11:1605-09 (1997). Other FLT3 expressing malignancies include B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias. See e.g., Rasko et al., Leukemia 9:2058-66 (1995).

FLT3 kinase mutations associated with hematologic malignancies are activating mutations. In other words, the FLT3 kinase is constitutively activated without the need for binding and dimerization by FLT3 ligand, and therefore stimulates the cell to grow continuously.

Several studies have identified inhibitors of FLT3 kinase activity that also inhibit the kinase activity of related receptors, *e.g.*, VEGF receptor (VEGFR), PDGF receptor (PDGFR), and kit receptor kinases. *See e.g.*, Mendel et al., *Clin. Cancer Res.* 9:327-37 (2003); O'Farrell et al., *Blood* *101*:3597-605 (2003); and Sun et al., *J. Med. Chem.* 46:1116-19 (2003). Such compounds effectively inhibit FLT3 kinase-mediated phosphorylation, cytokine production, cellular proliferation, resulting in the induction of apoptosis. *See e.g.*, Spiekermann et al., *Blood* 101:1494-1504 (2003). Moreover, such compounds have potent antitumor activity *in vitro* and *in vivo*.

Compounds described herein are contacted with FLT3 expressing cells in any suitable manner. The cell may constitutively or inducibly express FLT3 following exogenous or endogenous stimuli or recombinant manipulation. The cell can be *in vitro* or *in vivo* in a tissue or organ. The cell and the compounds disclosed herein can be contacted for any period of time where undesirable toxicity results. Contacting a FLT3-expressing cell *in vivo* includes systemic, localized, and targeted delivery mechanisms known in the art. *See e.g.*, *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

Compounds provided herein are useful in treating conditions characterized by inappropriate FLT3 activity such as proliferative disorders. FLT3 activity includes, but is not limited to, enhanced FLT3 activity resulting from increased or *de novo* expression of FLT3 in cells, increased FLT3 expression or activity, and FLT3 mutations resulting in constitutive activation. Thus, inhibition and reduction of the activity of FLT3 kinase refers to a lower level of measured activity relative to a control experiment in which the protein, cell, or subject is not treated with the test compound, whereas an increase in the activity of FLT3 kinase refers to a higher level of measured activity relative to a control experiment. In particular embodiments, the reduction or increase is at least 10%. Reduction or increase in the activity of FLT3 kinase of at least 20%, 50%, 75%, 90% or 100% or any integer between 10% and 100% may be preferred for particular applications.

The existence of inappropriate or abnormal FLT3 ligand and FLT3 levels or activity can be determined using well known methods in the art. For example, abnormally high FLT3 levels can be determined using commercially available ELISA kits. FLT3 levels can be determined using flow cytometric analysis, immunohistochemical analysis, and in situ hybridization techniques. Further, an inappropriate activation of the FLT3 can be determined by an increase in one or more of the activities occurring subsequent to FLT3 binding: (1) phosphorylation or autophosphorylation of FLT3; (2) phosphorylation of a FLT3 substrate, *e.g.*, Stat5, Ras; (3) activation of a related complex, *e.g.*, PI3K; (4) activation of an adaptor molecule; and (5) cellular proliferation. These activities are readily measured by well known methods in the art.

In addition to or instead of inhibiting the FLT3 kinase, the compounds disclosed herein can, in one embodiment, also inhibit other tyrosine protein kinases that are involved in the signal transmission mediated by other trophic factors which function in growth regulation and transformation in mammal cells, including human cells. Exemplary kinases include, but are limited to the abl kinase, *e.g.*, the v-abl kinase (Lydon et al., *Oncogene Res.* 5:161-73 (1990) and Geissler et al., *Cancer Res.* 52:4492-98 (1992)); kinases of the "HER" subfamily which includes EGFR (epidermal growth factor receptor), HER2, HER3 and HER4; kinases of the src kinase family, *e.g.*, the c-src kinase, lck kinase and fyn kinase; other members of the PDGFR tyrosine kinase family, *e.g.*, PDGFR, CSF-1R, Kit, VEGFR and FGFR; and the insulin-like growth factor receptor kinase (IGF-1-kinase), and serine/threonine kinases, *e.g.*, protein kinase C.

PDGFR

Platelet-Derived Growth factor Receptors ($PDGFR_ds$) are receptor tyrosine kinases that regulate proliferative and chemotatic responses. $PDGFR_ds$ have two forms- PDGFR-α (CD140a) and PDGFR-β (CD140b). PDGFRs are normally found in connective tissue and glia but are lacking in most epithelia, and PDGF expression has been shown in a number of different solid tumors, from glioblastomas to prostate carcinomas. For instance, PDGFR kinases are involved in various cancers such as T- cell lymphoma, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), melanoma, glioblastoma and others (see Bellamy W. T. et al. , Cancer Res. 1999,59, 728-733). In these various tumor types, the biological role of PDGF signaling can vary from autocrine stimulation of cancer cell growth to more subtle paracrine interactions involving adjacent stroma and angiogenesis. Furthermore, PDGF has been implicated in the pathogenesis of several nonmalignant proliferation diseases, including atherosclerosis, restenosis following vascular angioplasty and fibroproliferative disorders such as obliterative bronchiolitis. Therefore, inhibiting the PDGFR kinase activity with small molecules may interfere with tumor growth and angiogenesis.

The binding of PDGFR to its receptor activates the intracellular tyrosine kinase, resulting in the autophorylation of the receptor as well as other intracellular substrates such as Src, GTPase Activating Protein (GAP), and phosphatidylinositol-3-phosphate. Upon autophorylation the PDGFR also forms complexes with other signaling moieties including phospholipase C-γ (PLC-γ), phosphatidylinositol-3-kinase (PI3K), and raf-1. It appears to be involved in communication between endothelial cells and pericytes, a communication that is essential for normal blood vessel development.

It has been found previously that the disruption of the PDGFR-β in mice oblates neovascular pericytes that from part of the capillary wall. See Lindahl, P., *et al., Science* (1997) 227:242-245; Hellstrom, M., ., *et al., Development* (1999) 126:3047-3055. A recent study by Bergers, G., *et al., J. Clin. Invest.* (2003) 111:1287-1295 has suggested that inhibition of PDGFR kinase activity by certain compounds such as SU6668 or ST1571/Gleevec inhibits tumor growth and that these compounds combined with VEGFR inhibitor SU5416 were very effective in reducing tumor growth. Further, inhibition of PDGFR-β by Gleevec enhanced tumor chemotherapeutic efficacy in mice. Pietras, K., *et al., Cancer Res.* (2002) 62:5476-5484. A review of PDGFR receptors as cancer drug targets by Pietras, K., *et al.*, appears in *Cancer Cell.* (2003) 3:439-443. Inhibition of this kinase activity is also effective where abnormal forms of PDGFR, such as the TEL/PDGFR-β fusion protein associated with chronic myelomonocytic leukemia (CMML) is produced. See also, Grisolano, J. L., *et al., Proc. Natl. Acad. Sci. USA.* (2003) 100:9506-9511.

Inhibitors of PDGFR-β frequently also inhibit additional kinases involved in tumor growth such as BCR-ABL, TEL-ABL, and PDGFR-α. See, Carroll, M., *et al., Blood* (1997) 90:4947-4952 and Cools, J., *et al., Cancer Cell* (2003) 3:450-469. One class of established inhibitors of PDGFR kinase activity includes quinazoline derivatives which comprise piperazine substitutions. Such compounds are disclosed in Yu, J-C., *et al., J. Pharmacol. Exp. Ther.* (2001) 298:1172-1178; Pandey, A., *et al., J. Med. Chem.* (2002) 45:3772-3793 Matsuno, K., *et al., J. Med. Chem.* (2002) 45: 4413-4523 and Matsuno, K., *et al., ibid.*, 3057-3066. Still another class is represented by 2-phenyl pyrimidines as disclosed by Buchdunger, E., *et al., Proc. Natl. Acad. Sci. USA.* (1995) 92:2558-2562. However, there remains a need for additional compounds that are effective in inhibiting PDGFR kinase activity. Given the complexities of signal transduction with the redundancy and crosstalk between various pathways, the identification of specific PDGFR tyrosine kinase inhibitors permits accurate targeting with limited or no unwanted inhibition of the pathways, thus reducing the toxicity of such inhibitory compounds.

Compounds described herein are contacted with PDGFR expressing cells in any suitable manner. The cell may constitutively or inducibly express PDGFR following exogenous or endogenous stimuli or recombinant manipulation. The cell can be *in vitro* or *in* *vivo* in a tissue or organ. The cell and the compounds disclosed herein can be contacted for any period of time where undesirable toxicity results. Contacting a PDGFR-expressing cell *in vivo* includes systemic, localized, and targeted delivery mechanisms known in the art. *See e.g., Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

Compounds provided herein are useful in treating conditions characterized by inappropriate PDGFR activity such as proliferative disorders. PDGFR activity includes, but is not limited to, enhanced PDGFR activity resulting from increased or *de novo* expression of PDGFR in cells, increased PDGFR expression or activity, and PDGFR mutations resulting in constitutive activation. Thus, inhibition and reduction of the activity of PDGFR refers to a lower level of measured activity relative to a control experiment in which the protein, cell, or subject is not treated with the test compound, whereas an increase in the activity of PDGFR refers to a higher level of measured activity relative to a control experiment. In particular embodiments, the reduction or increase is at least 10%. Reduction or increase in the activity of PDGFR of at least 20%, 50%, 75%, 90% or 100% or any integer between 10% and 100% may be preferred for particular applications.

The existence of inappropriate or abnormal PDGFR ligand and PDGFR levels or activity can be determined using well known methods in the art. For example, abnormally high PDGFR levels can be determined using commercially available ELISA kits. PDGFR levels can be determined using flow cytometric analysis, immunohistochemical analysis, and in situ hybridization techniques. These activities are readily measured by well known methods in the art.

In addition to or instead of inhibiting PDGFR, the compounds disclosed herein can, in one embodiment, also inhibit other tyrosine protein kinases that are involved in the signal transmission mediated by other trophic factors which function in growth regulation and transformation in mammal cells, including human cells. Exemplary kinases include, but are limited to the abl kinase, *e.g.*, the v-abl kinase (Lydon et al., *Oncogene Res.* 5:161-73 (1990) and Geissler et al., *Cancer Res.* 52:4492-98 (1992)); kinases of the "HER" subfamily which includes EGFR (epidermal growth factor receptor), HER2, HER3 and HER4; kinases of the src kinase family, *e.g.*, the c-src kinase, lck kinase and fyn kinase; other members of the

PDGFR tyrosine kinase family, *e.g.*, FLT3, CSF-1R, Kit, VEGFR and FGFR; and the insulin-like growth factor receptor kinase (IGF-1-kinase), and serine/threonine kinases, *e.g.*, protein kinase C.

Bcr-Abl

c-Abl is a nonreceptor tyrosine kinase that contributes to several leukogenic fusion proteins, including the deregulated tyrosine kinase, Bcr-Abl. Chronic myeloid leukemia (CML) is a clonal disease involving the pluripotent hematopoietic stem cell compartment and is associated with the Philadelphia chromosome [Nowell P. C. and Hungerford D. A., Science 132,1497 (1960)], a reciprocal translocation between chromosomes 9 and 22 ([(9:22) (q34; q11)]) [Rowley J. D., Nature 243,290-293 (1973)]. The translocation links the c-Abl tyrosine kinase oncogene on chromosome 9 to the 5_d half of the bcr (breakpoint cluster region) gene on chromosome 22 and creates the fusion gene bcr/abl. The fusion gene produces a chimeric 8.5 kB transcript that codes for a 210-kD fusion protein ($p210^{bcr\text{-}abl}$), and this gene product is an activated protein tyrosine kinase. Thus, the Abelson tyrosine kinase is improperly activated by accidental fusion of the bcr gene with the gene encoding the intracellular non-receptor tyrosine kinase, c-Abl.

The Bcr domain interferes with the intramolecular Abl inhibitory loop and unveils a constitutive kinase activity that is absent in the normal Abl protein. Bcr-Abl tyrosine kinase is a potent inhibitor of apoptosis, and it is well accepted that the oncoprotein expresses a constitutive tyrosine kinase activity that is necessary for its cellular transforming activity. Constitutive activity of the fusion tyrosine kinase Bcr-Abl has been established as the characteristic molecular abnormality present in virtually all cases of chronic myeloid leukemia (CML) and up to 20 percent of adult acute lymphoblastic leukemia (ALL) [Faderl S. et al., N Engl J Med 341, 164-172 (1999); Sawyers C. L., N Engl J Med 340,1330-1340 (1999)].

Mutations present in the kinase domain of the Bcr-Abl gene of patients suffering from CML or Ph+ ALL account for the biological resistance of these patients towards STI571 treatment in that said mutations lead to resistance of the Bcr- Abl tyrosine kinase towards inhibition by STI571. Novel therapies for CML need to address this emerging problem of clinical resistance to STI571 (Gleevec). Because tumor progression in patients receiving STI571 seem to be mediated by amplification of or mutation in the Bcr-Abl gene that causes the tyrosine kinase to be less efficiently inhibited by the drug, newer tyrosine kinase inhibitors may be susceptible to the same mechanisms of resistance. None the less, these findings are extremely valuable in the development of new compounds or combinations of compounds which are capable to overcome resistance towards treatment with STI571. Furthermore, in view of the large number of protein kinase inhibitors and the multitude of proliferative and other PK-related diseases, there is an ever-existing need to provide novel classes of compounds that are useful as PK inhibitors and thus in the treatment of these PTK related diseases.

Compounds described herein are contacted with Bcr-Abl expressing cells in any suitable manner. The cell may constitutively or inducibly express Bcr-Abl following exogenous or endogenous stimuli or recombinant manipulation. The cell can be *in vitro* or *in vivo* in a tissue or organ. The cell and the compounds disclosed herein can be contacted for any period of time where undesirable toxicity results. Contacting a Bcr-Abl expressing cell *in vivo* includes systemic, localized, and targeted delivery mechanisms known in the art. *See e.g., Remington: The Science and Practice of Pharmacy,* Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences,* Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms,* Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

Compounds provided herein are useful in treating conditions characterized by inappropriate Bcr-Abl activity such as proliferative disorders. Thus, inhibition and reduction of the activity of Bcr-Abl refers to a lower level of measured activity relative to a control experiment in which the protein, cell, or subject is not treated with the test compound, whereas an increase in the activity of Bcr-Abl refers to a higher level of measured activity relative to a control experiment. In particular embodiments, the reduction or increase is at least 10%. Reduction or increase in the activity of Bcr-Abl of at least 20%, 50%, 75%, 90% or 100% or any integer between 10% and 100% may be preferred for particular applications.

The existence of inappropriate or abnormal Bcr-Abl levels or activity can be determined using well known methods in the art. For example, abnormally high Bcr-Abl levels can be determined using commercially available ELISA kits. Bcr-Abl levels can be determined using flow cytometric analysis, immunohistochemical analysis, and in situ hybridization techniques. These activities are readily measured by well known methods in the art.

In addition to or instead of inhibiting Bcr-Abl, the compounds disclosed herein can, in one embodiment, also inhibit other tyrosine protein kinases that are involved in the signal transmission mediated by other trophic factors which function in growth regulation and transformation in mammal cells, including human cells. Exemplary kinases include, but are limited to the abl kinase, *e.g.*, the v-abl kinase (Lydon et al., *Oncogene Res.* 5:161-73 (1990) and Geissler et al., *Cancer Res.* 52:4492-98 (1992)); kinases of the "HER" subfamily which includes EGFR (epidermal growth factor receptor), HER2, HER3 and HER4; kinases of the src kinase family, *e.g.*, the c-src kinase, lck kinase and fyn kinase; other members of the PDGFR tyrosine kinase family, *e.g.*, FLT3, CSF-1R, Kit, VEGFR and FGFR; and the insulin-like growth factor receptor kinase (IGF-1-kinase), and serine/threonine kinases, *e.g.*, protein kinase C.

EGFR

The compounds disclosed herein are useful in treating conditions characterized by any inappropriate EGFR activity, such as particularly proliferative disorders. Such activity includes, but is not limited to enhanced or decreased EGFR activity resulting from increased or *de novo* expression of EGFR in cells, increased EGFR-ligand expression or activity, and EGFR mutations resulting in constitutive activation. The existence of inappropriate or abnormal EGFR –ligand and EGFR levels or activity can be determined using well known methods in the art. For example, abnormally high EGFR ligand levels can be determined using commercially available ELISA kits. EGFR levels can be determined using flow cytometric analysis, immunohistochemical analysis, *in situ* hybridization techniques.

The compounds, compositions, and methods described can be used to treat a variety of diseases and unwanted conditions associated EGFR activity, including, but not limited to, blood vessel growth (angiogenesis), cancer, benign hyperplasia, keloid formation, and psoriasis. In one aspect, the compounds are used to reduce the likelihood of occurrence of a cancer. In other embodiments, the compounds are used to treat non-small cell lung cancer or other solid tumors that overexpress EGF receptors. In still other embodiments, the compounds are useful for treating head cancer, neck cancer, pancreatic cancer, hepatocellular carcinoma, esophageal cancer, breast cancer, ovarian cancer, gynealogical cancer, colorectal cancer, and glioblastoma.

Compounds identified herein as inhibitors of EGFR activity can be used to prevent or treat a variety of diseases and unwanted conditions, including, but not limited to benign or malignant tumors, *e.g.*, carcinoma of the kidneys, liver, adrenal glands, bladder, breast, stomach, ovaries, colon, rectum, prostate, pancreas, lungs, vagina or thyroid, sarcoma, glioblastomas, numerous tumors of the neck and head, and leukemia. In one embodiment, the malignancy is of epithelial origin. In another embodiment, the compounds are used to treat or prevent non-small cell lung carcinoma. In still another embodiment, the disease treated by the compounds disclosed herein is pancreatic cancer. The compounds may be useful in inducing the regression of tumors as well as preventing the seeding and outgrowth of tumor metastases. These compounds are also useful in therapeutically or prophylactically in diseases or disorders associated with non-malignant hyperplasia, *e.g.*, epidermal hyperproliferation (*e.g.*, psoriasis), keloid formation, prostate hyperplasia, and cardiac hypertrophy. It is also possibly to use the compounds disclosed herein in the treatment of diseases of the immune system and the central and peripheral nervous systems insofar as EGFR or EGFR-related receptors are involved.

Activity towards EGFR refers to one or more of the biologically relevant activity associated with EGFR, including but not limited to autophosphorylation, phosphorylation of other substrates, anti-apoptotic activity, proliferative activity, and differentiation activity. In this context, inhibition and reduction of the activity of EGFR refers to a lower level of measured activity relative to a control experiment in which the protein, cell, or subject is not treated with the test compound or is treated with a compound that does not inhibit EGFR activity, whereas an increase in the activity of EGFR refers to a higher level of measured activity relative to a control experiment. In particular embodiments, the reduction or increase is at least 10%. Reduction or increase in the activity of EGFR of at least 20%, 50%, 75%, 90% or 100% or any integer between 10% and 100%, may be preferred for particular applications. The compounds disclosed herein modulate at least one of the activities mediated by EGFR, *e.g.* anti-apoptotic activity, and can modulate one or more or all of the known EGFR activities.

Aberrant or inappropriate EGFR activity can be determined by an increase in one or more of the activities occurring subsequent to binding of a ligand, *e.g.*, EGF, TGFα, amphiregulin, HB-EGF, betacellulin, epiregulin, or epigen: 1) phosphorylation or autophosphorylation of EGFR; 2) phosphorylation of a EGFR substrate, *e.g.*, Stat5b, phospholipase gamma (PLCγ); 3) activation of a related complex, *e.g.* PI3K; 4) activation of other genes, *e.g.*, c-fos; and 5) cellular proliferation. These activities are readily measured by well known methods in the art. For example, tyrosine phosphorylation can be determined using *e.g.*, immunoblotting with anti-phosphotyrosine antibodies. *See, e.g.*, Chapter 18 in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Ausubel, *et al.*, eds. 2001). Cell proliferation can be determined using, *e.g.*, ^{3}H-thymidine uptake.

Compounds described herein are contacted with EGFR expressing cells in any suitable manner. The cell may constitutively or inducibly express EGFR following exogenous or endogenous stimuli or recombinant manipulation. The cell can be *in vitro* or *in* *vivo* in a tissue or organ. The cell and the compounds disclosed herein can be contacted for any period of time where undesirable toxicity results. Contacting an EGFR-expressing cell *in vivo* includes systemic, localized, and targeted delivery mechanisms known in the art. *See e.g.*, *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

The action of the compounds disclosed herein on the EGFR ligand-stimulated cellular tyrosine phosphorylation of EGFR can be also determined in the human A431. In one embodiment, the compounds disclosed exhibit inhibition at concentrations in the nanomolar to micromolar range. Additionally, inhibition can be determined by examining gene expression profiles of EGFR-ligand treated cells. For example, the stimulation of dormant BALB-c3T3 cell by EGF rapidly induces the expression of c-fos mRNA. Pretreatment of the cells with a compound disclosed herein prior to the stimulation with EGF can inhibit the c-fos expression. *See* Trinks et al., *J. Med. Chem.* 37(7), 1015-27 (1994).

EGFR inhibition by the compounds provided herein can be determined using any suitable assay. In one embodiment, EGFR inhibition is determined *in vitro*. In a specific embodiment, EGFR inhibition is assessed by phosphorylation assays. Any suitable phosphorylation assay can be employed. For example, membrane autophosphorylation assays, receptor autophosphorylation assays in intact cells, and ELISA's can be employed. *See, e.g.*, McGlynn et al., *Eur. J. Biochem.* 207:265-75(1992); Trinks et al., *J. Med. Chem.* 37(7), 1015-27(1994); Posner et al., *J. Biol. Chem.* 267(29):20638-47 (1992); Chapter 18 in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Ausubel, *et al.*, eds. 2001). Cells useful in such assays include, but are not limited to MDA-MB-231, Hs578T, A431, MCF-7, T-47D, ZA-75-1, SUM44, epidermoid Balb/c mouse keratinocyte cells, and cells recombinantly engineered to express EGFR, including NIH-3T3, CHO and COS cells (American Type Culture Collection, Rockville, MD). *See e.g.*, Roos et al., *Proc. Natl. Acad. Sci. U.S.A.* 83:991-95 (1986).

In some embodiments, the compounds selectively inhibit one or more kinases. For example, selective inhibition of EGFR is achieved by significantly inhibiting EGFR activity, while having an insignificant effect (*i.e.*, an IC_{50} for tyrosine phosphorylation greater than 100 μM on PDGFR) on other members of the PDGFR superfamily. The compounds described can inhibit the activation of the EGFR by one or more of the ligands or EGFR receptors, *i.e.*, erbB2, erbB3, or erbB4. Members of the PDGFR superfamily, besides PDGFR, include EGFR. KDR, and Flt1. In some embodiments, no other member of the PDGFR super family, is significantly inhibited. In one embodiment, compounds inhibit EGFR significantly more than erbB2, erbB3, or erbB4.

In addition to or instead of inhibiting the EGFR tyrosine kinase, the compounds disclosed herein can, in one embodiment, also inhibit other tyrosine protein kinases that are involved in the signal transmission mediated by other trophic factors which function in growth regulation and transformation in mammal cells, including human cells. Exemplary kinases include, but are limited to the abl kinase, *e.g.*, the v-abl kinase (Lydon et al., *Oncogene Res.* 5:161-73 (1990) and Geissler et al., *Cancer Res.* 52:4492-98 (1992)); kinases of the src kinase family, *e.g.*, the c-src kinase, lck kinase and fyn kinase; other members of the PDGFR tyrosine kinase family, *e.g.*, PDGFR, CSF-1R, Kit, VEGFR and FGFR; and the insulin-like growth factor receptor kinase (IGF-1-kinase), and serine/threonine kinases, *e.g.*, protein kinase C.

In one embodiment, the efficacy of the EGFR modulation is determined using cellular proliferation assays. Briefly, cells expressing EGFR are co-cultured in the presence of the inhibitor and EGF, TGF-α, or other appropriate EGFR ligand. *See*, *e.g.*, Weissmann et al., *Cell* 32, 599 (1983) and Carpenter et al., *Anal. Biochem.* 153:279-82 (1985). The compound is inhibitory for proliferation if it inhibits the proliferation of cells relative to the proliferation of cells in the absence of the compound or in the presence of a non-EGFR inhibitor. Proliferation may be quantified using any suitable methods. Typically, the proliferation is determined by assessing the incorporation of radioactive-labeled nucleotides into DNA (*e.g.*, ^{3}H-thymidine) *in vitro*. In one embodiment, proliferation is determined by ATP luminescence, *e.g.*, CellTiter-Glo™ Luminescent Cell Viability Assay (Promega). In another embodiment, inhibition of EFGR by the compounds presented herein is determined by cell cycle analysis. *See generally* CYTOKINE CELL BIOLOGY: A PRACTICAL APPROACH (F. Balkwell, ed. 2000). Analogous methods may be used with the other protein kinases described herein, including by way of example only, FLT3, PDGFR, and Bcr-Abl.

In one embodiment, the compounds disclosed herein can be used to treat cell proliferative disorders. Cell proliferative disorders are disorders wherein undesirable cell proliferation of one or more cellular subset in an organism occurs and results in harm, *e.g.*, discomfort, reduction or loss of function, or decreased life expectancy, to the organism. A cellular proliferative disorder mediated by EGFR activation can be determined by examining the level of EGFR activity using the methods disclosed herein. Analogous methods may be used with the other protein kinases described herein, including by way of example only, FLT3, PDGFR, and Bcr-Abl.

In another embodiment, EGFR inhibition is determined *in vivo*. In one embodiment, animal models of tumor growth are used to assess the efficacy of EGFR inhibitors against tumor growth and metastasis *in vivo*. Any suitable animal model may be employed to assess the anti-tumor activity of EGFR inhibitors. The murine recipient of the tumor can be any suitable strain. The tumor can be syngeneic, allogeneic, or xenogeneic to the tumor. The tumor can express endogenous or exogenous EGFR. Exogenous EGFR expression can be achieved using well known methods of recombinant expression via transfection or transduction of the cells with the appropriate nucleic acid. The recipient can be immunocompetent or immunocompromised in one or more immune-related functions, included but not limited to nu/nu, SCID, and beige mice. In one specific embodiment, the mouse is a Balb/c or C57BL/6 mouse. Any suitable tumor cells from fresh tumor samples, and short term polyclonal tumor cells. Exemplary tumor cell lines include EGFR transfected NIH3T3, MCF7 (human mammary), and A431 (human epidermoid) cells. *See e.g.*, Santon et al., *Cancer Res.* 46:4701-05 (1986) and Ozawa et al, *Int. J. Cancer* 40:706-10 (1987). The dosage of EGFR inhibitory compound ranges from 1 μg/mouse to 1 mg/mouse in at least one administration. The compound can be administered by any suitable route, including subcutaneous, intravenous, intraperitoneal, intracerebral, intradermal, or implantation of tumor fragments. In one embodiment, the dose of compound is 100 μg/mouse twice a week. In one specific embodiment, the tumor is injected subcutaneously at day 0, and the volume of the primary tumor is measured at designated time points by using calipers. Any suitable control compound can be used. Pharmacokinetics, oral bioavailability, and dose proportionality studies can be performed in these animals using well known methods. *See, e.g.*, Klutchko, *et al.*, *J. Med. Chem.* (1998) 41:3276-3292. Analogous methods may be used with the other protein kinases described herein, including by way of example only, FLT3, PDGFR, and Bcr-Abl.

Aberrant activity of protein tyrosine kinases, such as c-erbB2, c-src, c-met, EGFR and PDGFR have been implicated in human malignancies. Elevated EGFR activity has, for example, been implicated in non-small cell lung, bladder and head and neck cancers, and increased c-erbB2 activity in breast, ovarian, gastric and pancreatic cancers. Inhibition of protein tyrosine kinases should therefore provide a treatment for tumors such as those described herein.

Methods of Use

By modulating kinase activity, the compounds disclosed herein can be used to treat a variety of diseases. Suitable conditions characterized by undesirable protein-kinase activity can be treated by the compounds presented herein. As used herein, the term "condition" refers to a disease, disorder, or related symptom where inappropriate kinase activity is present. In some embodiments, these conditions are characterized by aggressive neovasculaturization including tumors, especially acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs). In some embodiments, a FLT3-, a PDGFR-, a Bcr-Abl-, and/or an EGFR-modulating compounds may be used to treat tumors. The ability of compounds that inhibit FLT3 kinase activity to treat tumors has been established.

Compounds presented herein are useful in the treatment of a variety of biologically aberrant conditions or disorders related to tyrosine kinase signal transduction. Such disorders pertain to abnormal cell proliferation, differentiation, and/or metabolism. Abnormal cell proliferation may result in a wide array of diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis).

In various embodiments, compounds presented herein regulate, modulate, and/or inhibit disorders associated with abnormal cell proliferation by affecting the enzymatic activity of one or more tyrosine kinases and interfering with the signal transduced by said kinase. More particularly, provided herein are compounds which regulate, modulate said kinase mediated signal transduction pathways as a therapeutic approach to cure leukemia and many kinds of solid tumors, including but not limited to carcinoma, sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreas cancers, colon cancers, blood cancers, lung cancers and bone cancers.

In other embodiments, compounds herein are useful in the treatment of cell proliferative disorders including cancers, blood vessel proliferative disorders, fibrotic disorders, and mesangial cell proliferative disorders. Blood vessel proliferation disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration. They also play a pivotal role in cancer development. Other examples of blood vessel proliferation disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage, and ocular diseases, like diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness. Conversely, disorders related to the shrinkage, contraction or closing of blood vessels, such as restenosis, are also implicated.

Fibrotic disorders refer to the abnormal formation of extracellular matrix. Examples of fibrotic disorders include hepatic cirrhosis and mesangial cell proliferative disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar. Hepatic cirrhosis can cause diseases such as cirrhosis of the liver. An increased extracellular matrix resulting in a hepatic scar can also be caused by viral infection such as hepatitis. Lipocytes appear to play a major role in hepatic cirrhosis. Other fibrotic disorders implicated include atherosclerosis.

Mesangial cell proliferative disorders refer to disorders brought about by abnormal proliferation of mesangial cells. Mesangial proliferative disorders include various human renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies. The cell proliferative disorders which are indications of the compounds and methods provided herein are not necessarily independent. For example, fibrotic disorders may be related to, or overlap, with blood vessel proliferative disorders. For example, atherosclerosis results, in part, in the abnormal formation of fibrous tissue within blood vessels.

Compounds provided herein can be administered to a subject upon determination of the subject as having a disease or unwanted condition that would benefit by treatment with said derivative. The determination can be made by medical or clinical personnel as part of a diagnosis of a disease or condition in a subject. Non-limiting examples include determination of a risk of acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs).

The methods provided herein can comprise the administration of an effective amount of one or more compounds as disclosed herein, optionally in combination with one or more other active agents for the treatment of a disease or unwanted condition as disclosed herein. The subject is preferably human, and repeated administration over time is within the scope of the methods provided herein.

Also provided herein are compounds described throughout and their salts or solvates and pharmaceutically acceptable salts or solvates thereof for use in the prevention or treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned herein. The compounds provided herein are especially useful for the treatment of disorders caused by aberrant kinase activity such as breast, ovarian, gastric, pancreatic, non-small cell lung, bladder, head and neck cancers, and psoriasis. The cancers include hematologic cancers, for example, acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs).

A further aspect provided herein are methods of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity, including susceptible malignancies, which comprises administering to the subject an effective amount of a compound described herein or a pharmaceutically acceptable salt or solvate thereof.

A further aspect provided herein is the use of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of cancer and malignant tumors. The cancer can be stomach, gastric, bone, ovary, colon, lung, brain, larynx, lymphatic system, genitourinary tract, ovarian, squamous cell carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, lung cancer, bladder cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, breast cancer, small-cell lung cancer, leukemia, acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs), glioma, colorectal cancer, genitourinary cancer gastrointestinal cancer, or pancreatic cancer.

Compounds provided herein are useful for preventing and treating conditions associated with ischemic cell death, such as myocardial infarction, stroke, glaucoma, and other neurodegenerative conditions. Various neurodegenerative conditions which may involve apoptotic cell death, include, but are not limited to, Alzheimer's Disease, ALS and motor neuron degeneration, Parkinson's disease, peripheral neuropathies, Down's Syndrome, age related macular degeneration (ARMD), traumatic brain injury, spinal cord injury, Huntington's Disease, spinal muscular atrophy, and HIV encephalitis. The compounds described in detail herein can be used in methods and compositions for imparting neuroprotection and for treating neurodegenerative diseases.

The compounds described herein, can be used in a pharmaceutical composition for the prevention and/or the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis and rheumatoid arthritis), common cold, dysmenorrhea, menstrual cramps, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familiar adenomatous polyposis), tissue ulceration, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding, coagulation, anemia, synovitis, gout, ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neurodegenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic retinopathy, neuropathy and nephropathy), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders, and septic shock, arthritis, fever, common cold, pain and cancer in a mammal, preferably a human, cat, livestock or a dog, comprising an amount of a compound described herein or a pharmaceutically acceptable salt thereof effective in such prevention and/or treatment optionally with a pharmaceutically acceptable carrier.

A further aspect provided herein is the use of a compound described herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of psoriasis.

Kits/Articles of Manufacture

For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

For example, the container(s) can comprise one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

A kit will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

The terms "kit" and "article of manufacture" may be used as synonyms.

For the sake of brevity, all patents and other references cited herein are incorporated by reference in their entirety.

EXAMPLES

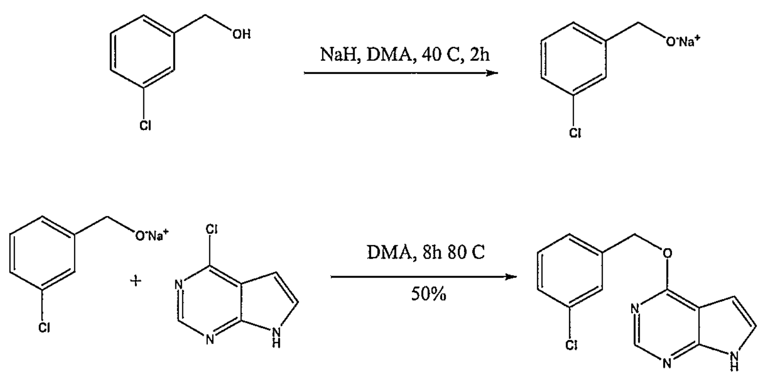
The compounds and methods provided herein are further illustrated by the following examples, which should not be construed as limiting in any way. The experimental procedures to generate the data shown are discussed in more detail below. For all formulations herein, multiple doses may be proportionally compounded as is known in the art.

The compounds and methods provided herein have been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation.

Compound A1

4-(3-Chloro-benzyloxy)-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 260 (M^++H)

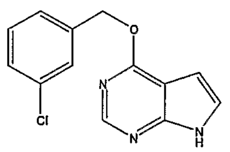
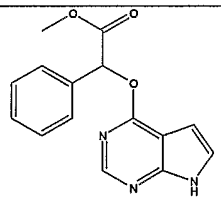
Compound A1 may be synthesized by the following procedure:

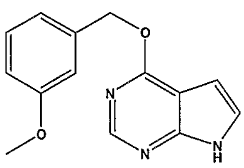
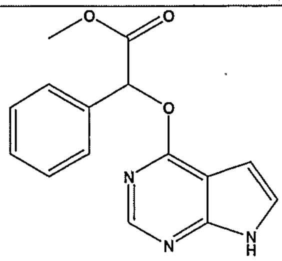
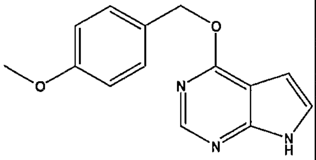
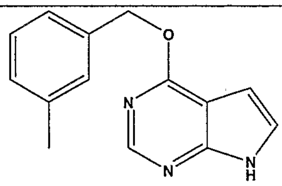
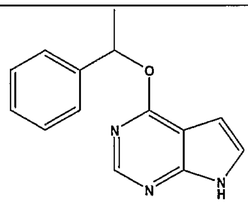
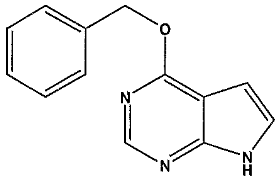
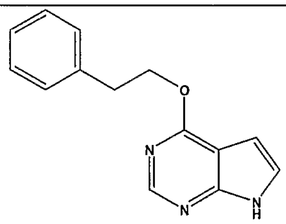


To a 1mM solution of 3-chlorobenzyl alcohol was added 1.5 eq of NaH in DMA and stirred at 40 °C for 2 hours. The solution was cooled and 0.95 eq of 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine in 0.5 ml DMA was added and the reaction heated at 80 °C for 8 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 2mg (50%) of compound A1.

Compounds A2 through A9 were synthesized in a manner analogous to Compound A1 using similar starting materials and reagents. The structures are shown below in Table A:

Table A

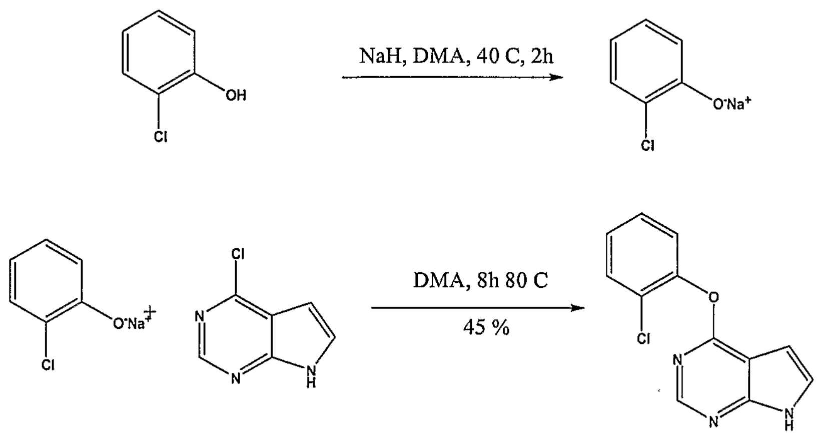
NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
A1			A6	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
A2		A7	
A3		A8	
A4		A9	
A5			

Compound B1

4-(2-Chloro-phenoxy)-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 246 (M^++H)

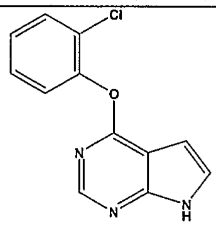
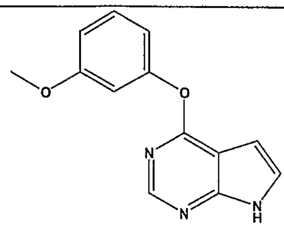
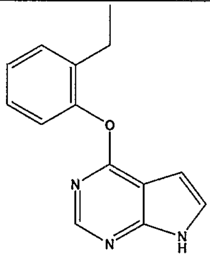
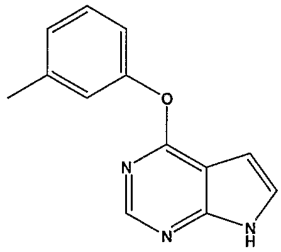
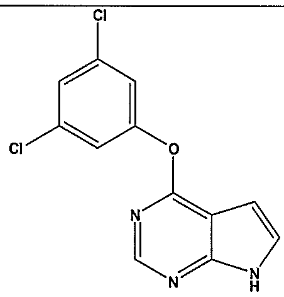
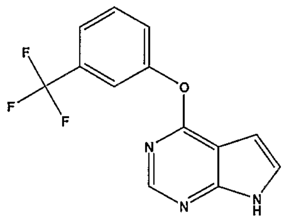
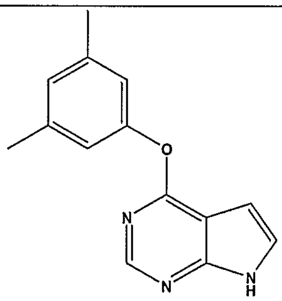
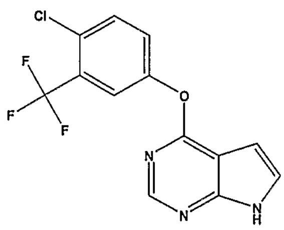
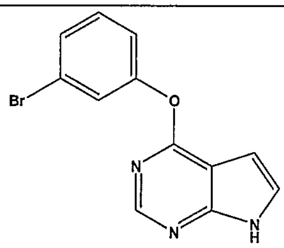
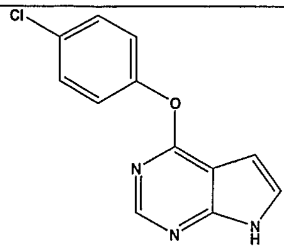
Compound B1 was synthesized by the following procedure:

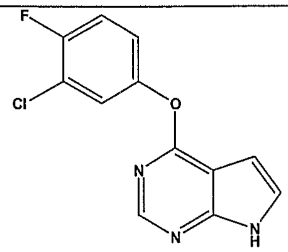
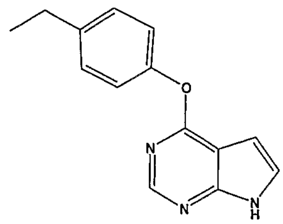
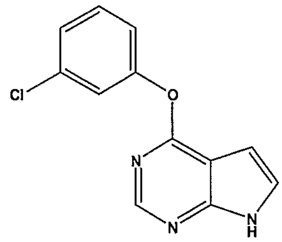
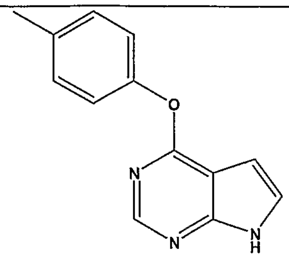
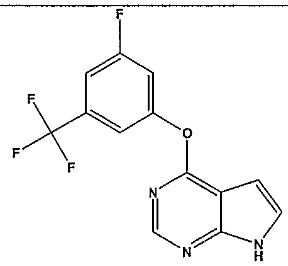
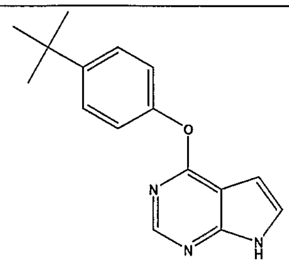
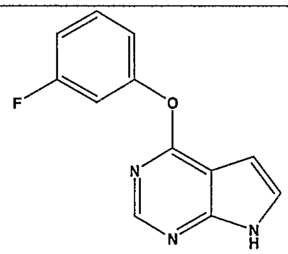
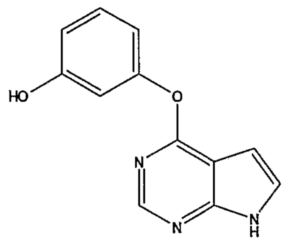
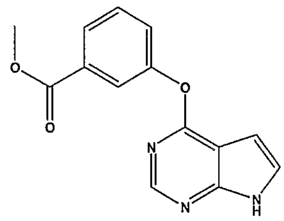
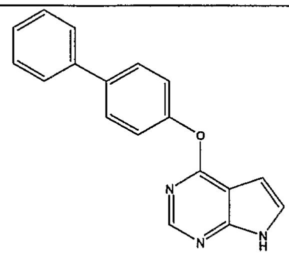
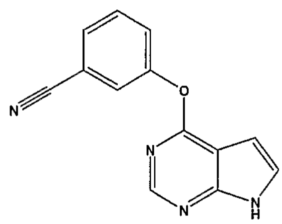
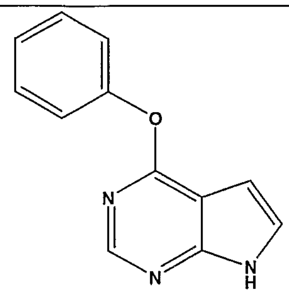


To a 1mM solution of 2-chlorophenol was added 1.5 eq of NaH in DMA and stirred at 40 °C for 2 hours. The solution was cooled and 0.95 eq of 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine in 0.5 ml DMA was added and the reaction heated at 80 °C for 8 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 2mg (45%) of compound B1.

Compounds B2 through B22 were synthesized in a manner analogous to Compound B1 using similar starting materials and reagents. The structures are shown below in Table B:

Table B

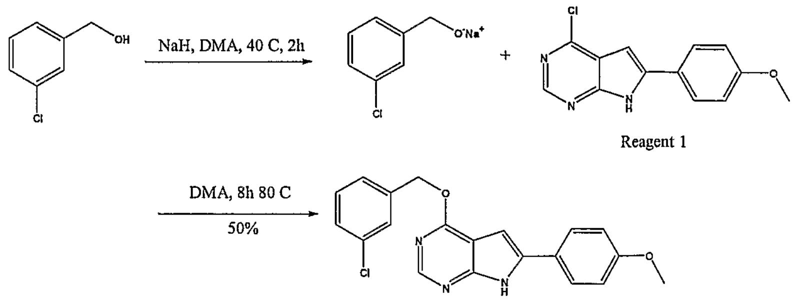
NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
B1			B12	
B2			B13	
B3			B14	
B4			B15	
B5			B16	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
B6		B17	
B7		B18	
B8		B19	
B9		B20	
B10		B21	
B11		B22	

<u>Compound C1</u>

4-(3-Chloro-benzyloxy)-6-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 367 (M^++H)

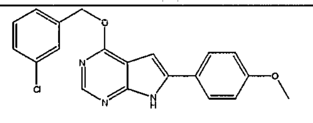
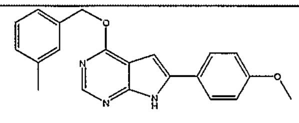
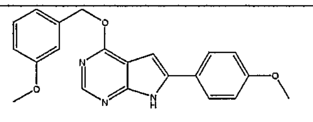
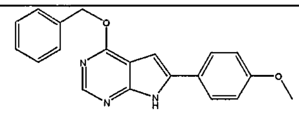
Compound C1 was synthesized by the following procedure:



To a 1mM solution of 3-chlorobenzyl alcohol was added 1.5 eq of NaH in DMA and stirred at 40 °C for 2 hours. The solution was cooled and 0.95 eq of reagent 1 in 0.5 ml DMA was added and the reaction heated at 80 °C for 8 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 2mg (50%) of compound C1.

Compounds C2 through C4 were synthesized in a manner analogous to Compound C1 using similar starting materials and reagents. The structures are shown below in Table C:

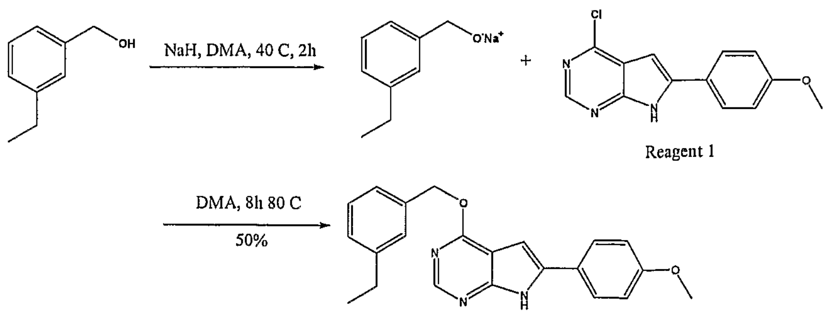
Table C

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
C1			C3	
C2			C4	

<u>Compound D1</u>

4-(2-Ethyl-phenoxy)-6-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 347 (M^++H)

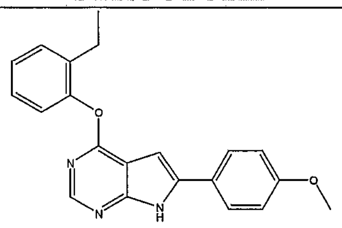
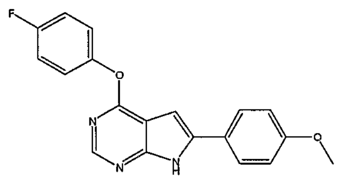
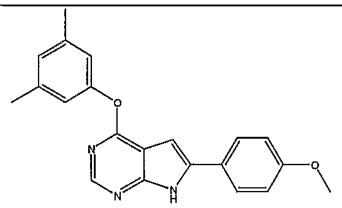
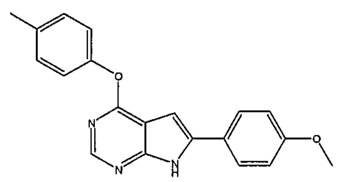
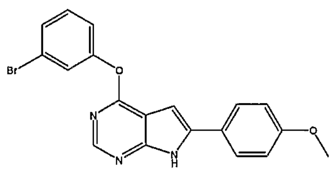
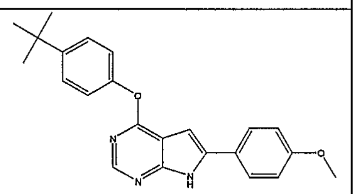
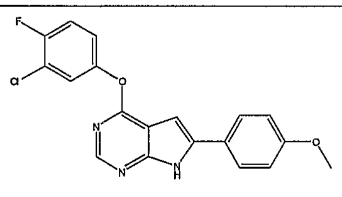
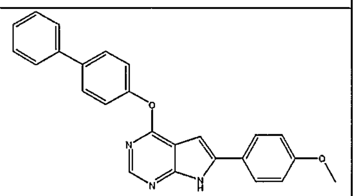
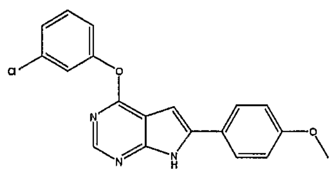
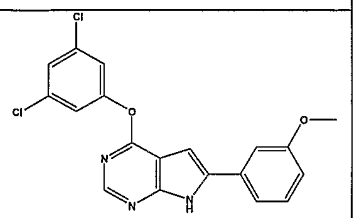
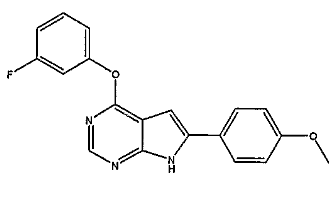
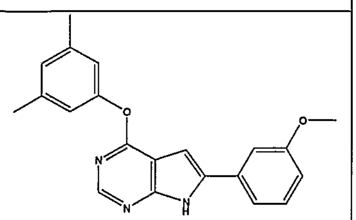
Compound D1 was synthesized by the following procedure:

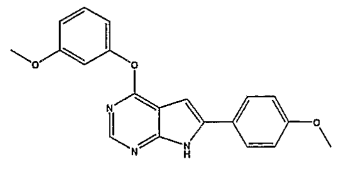
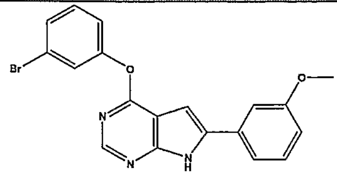
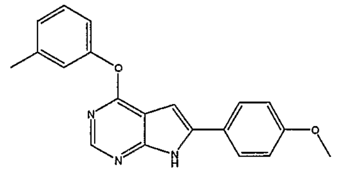
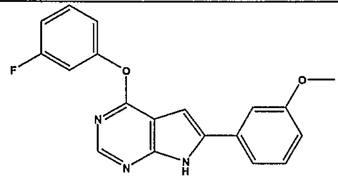
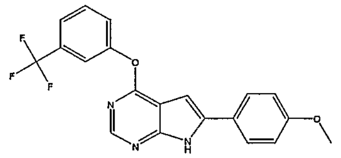
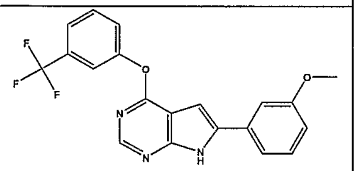
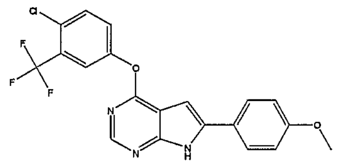
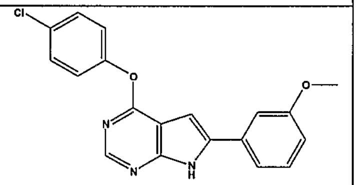
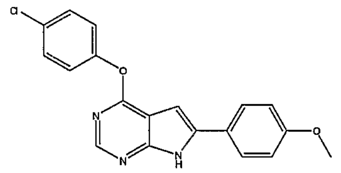
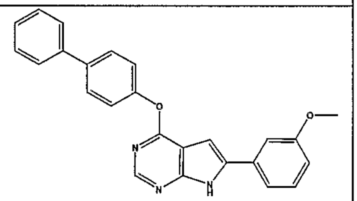
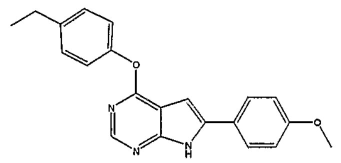
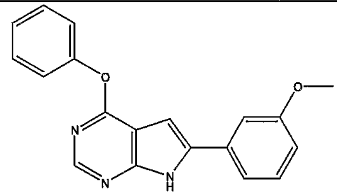


To a 1mM solution of 2-chlorophenol was added 1.5 eq of NaH in DMA and stirred at 40 °C for 2 hours. The solution was cooled and 0.95 eq reagent 1 in 0.5 ml DMA was added and the reaction heated at 80 °C for 8 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 2mg (45%) of compound D1.

Compounds D2 through D24 were synthesized in a manner analogous to Compound D1 using similar starting materials and reagents. The structures are shown below in Table D:

Table D

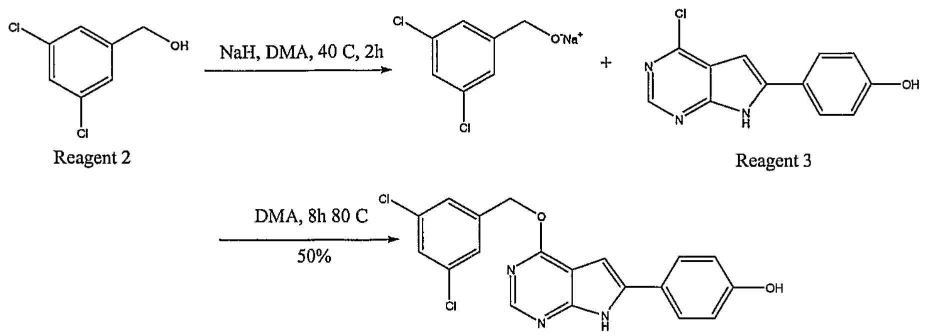
NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
D1			D13	
D2			D14	
D3			D15	
D4			D16	
D5			D17	
D6			D18	

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
D7			D19	
D8			D20	
D9			D21	
D10			D22	
D11 AB40145			D23	
D12			D24	

Compound E1

4-[4-(3,5-Dichloro-phenoxy)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol; LC-MS: 373 (M^{+}+H)

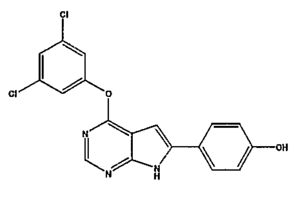
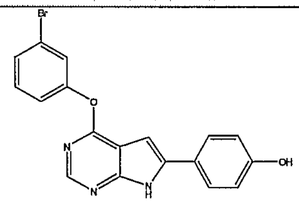
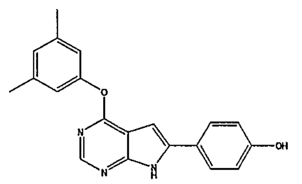
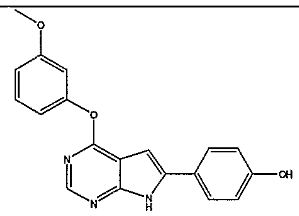
Compound E1 was synthesized by the following procedure:



To a 1mM solution of reagent 2 was added 1.5 eq of NaH in DMA and stirred at 40 °C for 2 hours. The solution was cooled and 0.95 eq Reagent 3 in 0.5 ml DMA was added and the reaction heated at 80 °C for 8 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitirlie solvent system) to obtain 2mg (45%) of compound E1.

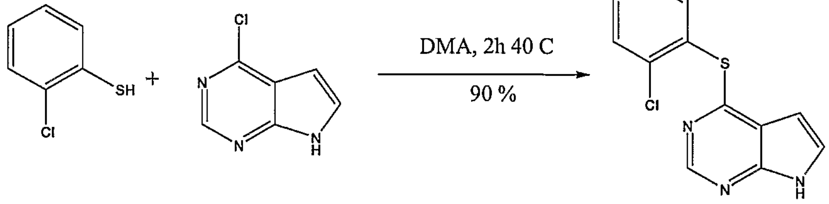
Compounds E2 through E4 were synthesized in a manner analogous to Compound E1 using similar starting materials and reagents. The structures are shown below in Table E:

Table E

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
E1			E3	
E2			E4	

4-(2-Chloro-phenylsulfanyl)-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 263 (M^++H)

Compound F1 was synthesized by the following procedure:

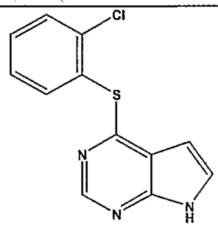
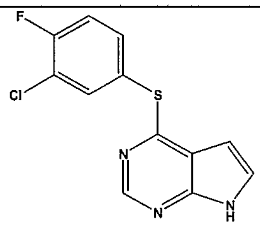
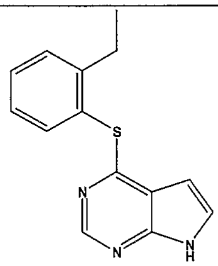
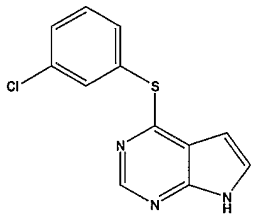
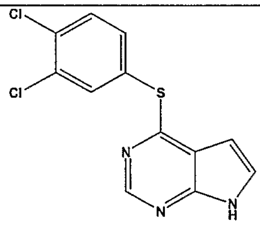
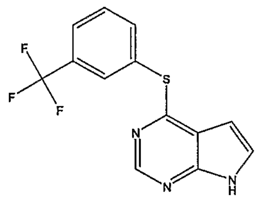
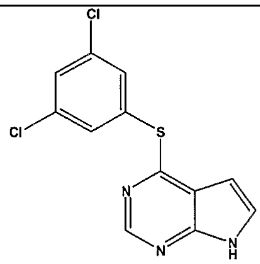
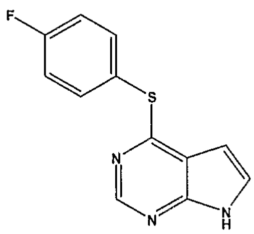
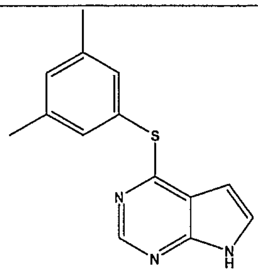
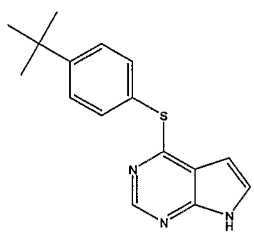


To a 1mM solution of 2-chlorothiophenol in DMA was added 0.95 eq of 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours.

The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 8mg (90%) of compound F1.

Compounds F2 through F10 were synthesized in a manner analogous to Compound F1 using similar starting materials and reagents. The structures are shown below in Table F:

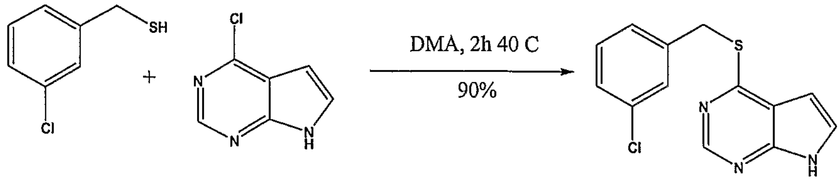
Table F

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
F1		F6	
F2		F7	
F3		F8	
F4		F9	
F5		F10	

Compound G1

4-Benzylsulfanyl-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 243 (M^++H)

Compound G1 was synthesized by the following procedure:

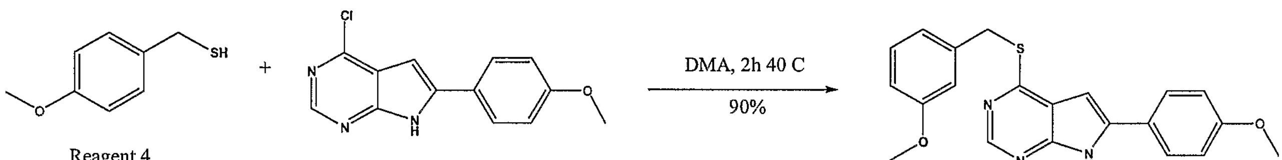


To a 1mM solution of 3-chlorothiobenzyl alcohol in DMA was added 0.95 eq of 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 9mg (90%) of compound G1.

<u>Compound H1</u>

4-(4-Methoxy-benzylsulfanyl)-6-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 379 (M^++H)

Compound H1 was synthesized by the following procedure:

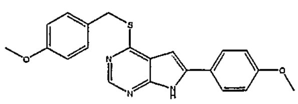
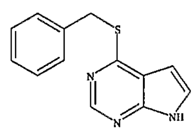
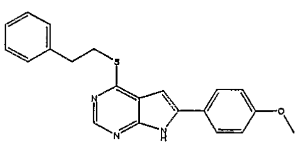
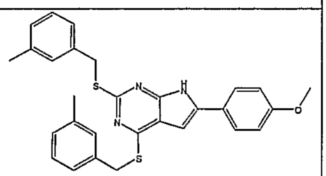


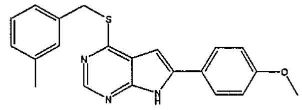
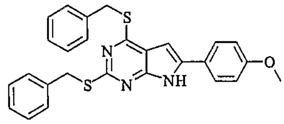
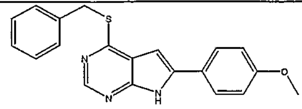
Reagent 4 Reagent 5

To a 1mM solution of reagent 4 in DMA was added 0.95 eq of reagent 5 in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 9mg (90%) of compound H1.

Compounds H2 through H7 were synthesized in a manner analogous to Compound H1 using similar starting materials and reagents. The structures are shown below in Table H:

<u>Table H</u>

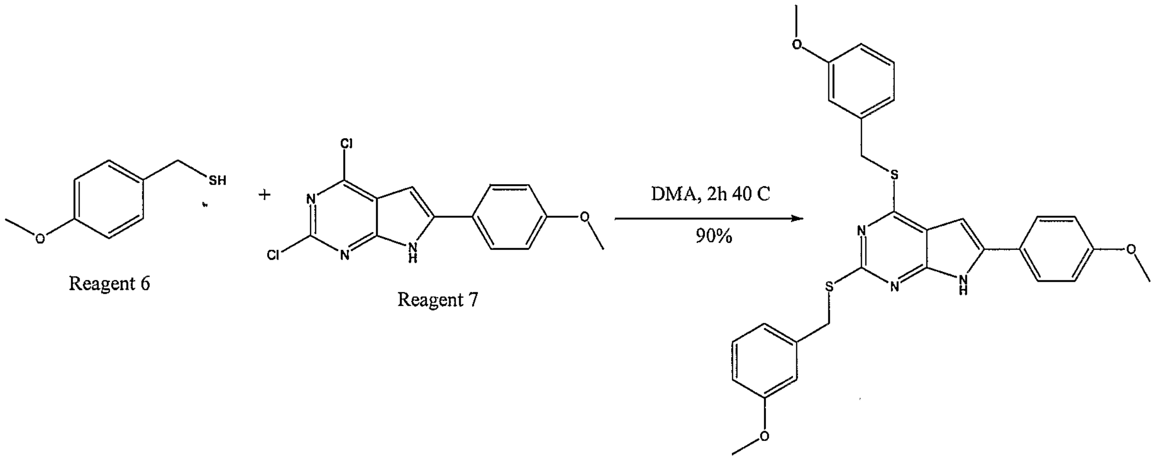
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
H1		H5	
H2		H6	

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
H3			H7	
H4				

Compound I1

2,4-Bis-(4-methoxy-benzylsulfanyl)-6-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 531 (M^{+}+H)

Compound I1 was synthesized by the following procedure:

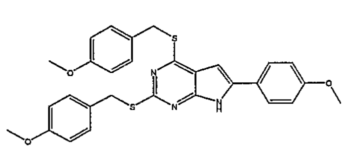
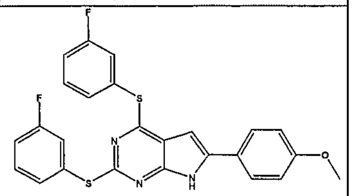
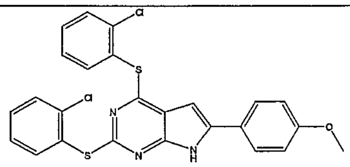
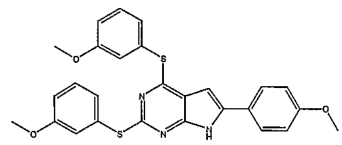
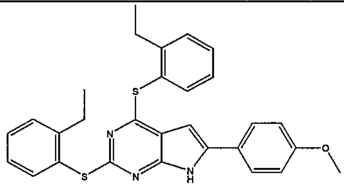
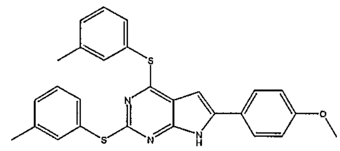
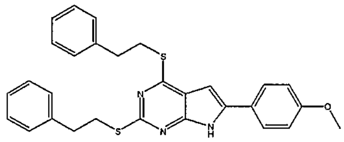
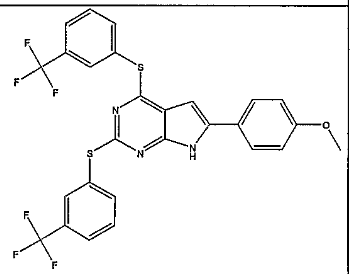
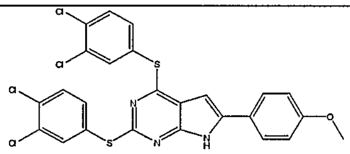
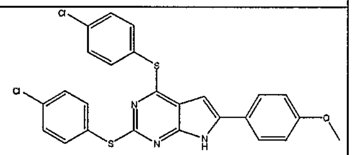
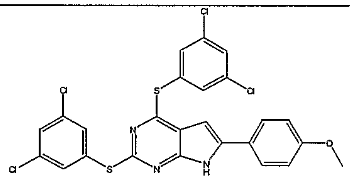
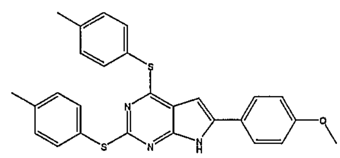
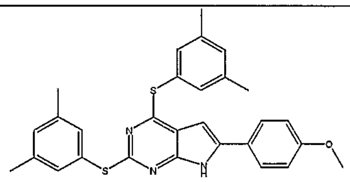
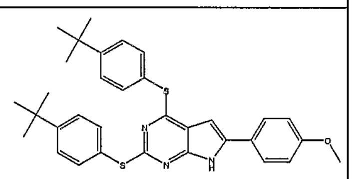
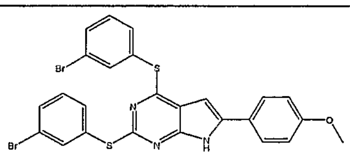
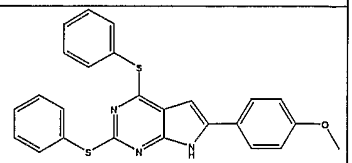


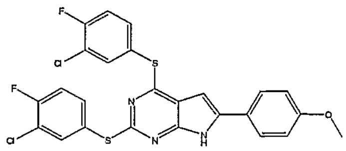
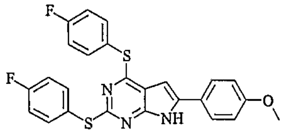
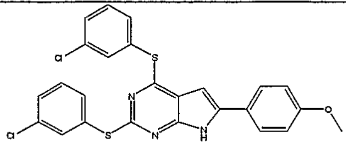
To a 1mM solution of reagent 6 in DMA was added 0.95 eq of reagent 7 in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 9mg (90%) of compound I1.

Compounds I2 through I19 were synthesized in a manner analogous to Compound I1 using similar starting materials and reagents. The structures are shown below in Table I:

Table I

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE

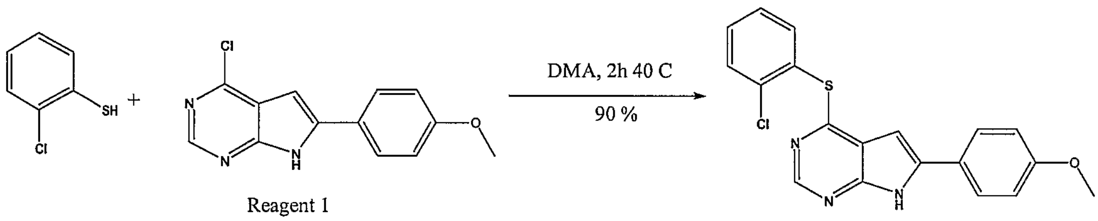
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
I1		I11	
I2		I12	
I3		I13	
I4		I14	
I5		I15	
I6		I16	
I7		I17	
I8		I18	

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
I9			I19	
I10				

Compound J1

4-(2-Chloro-phenylsulfanyl)-6-(4-methoxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine; LC-MS: 369 (M^++H)

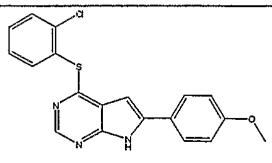
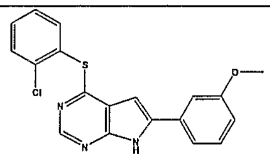
Compound J1 was synthesized by the following procedure:

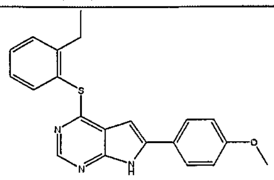
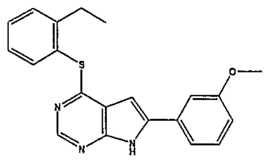
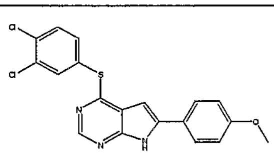
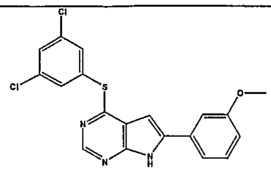
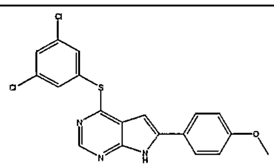
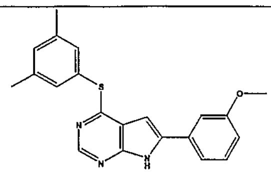
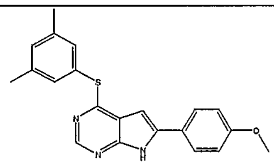
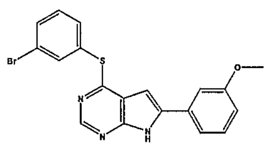
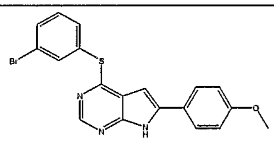
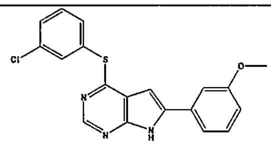
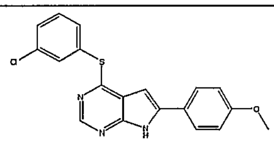
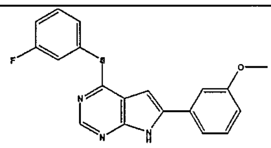
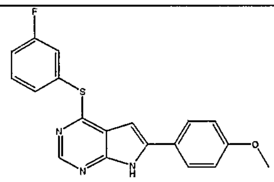
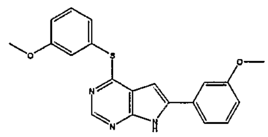
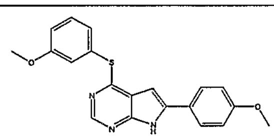
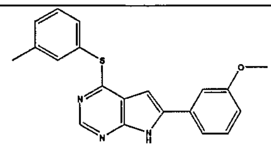
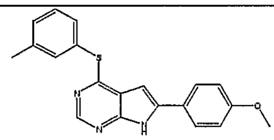
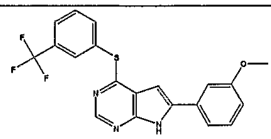
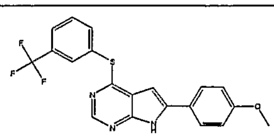
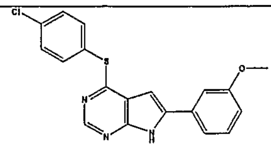


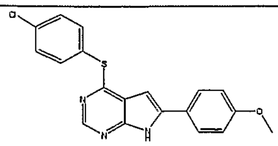
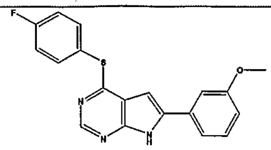
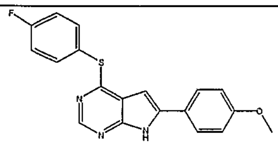
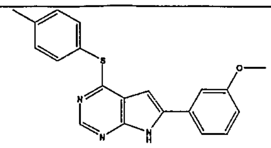
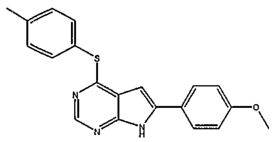
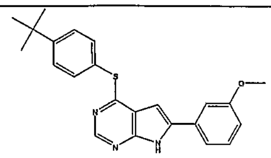
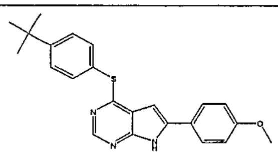
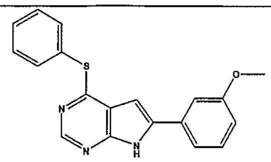
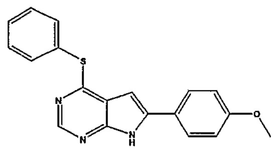
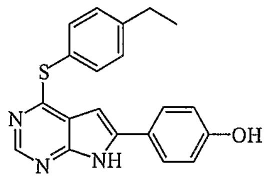
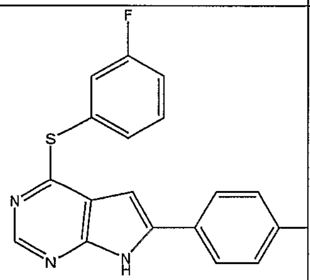
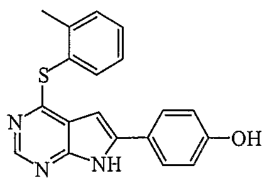
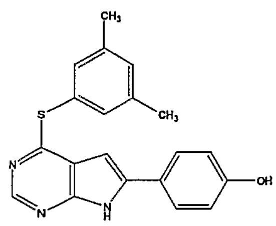
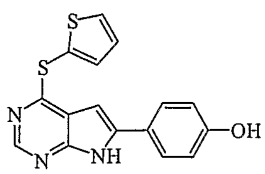
To a 1mM solution of 2-chlorothiophenol in DMA was added 0.95 eq of reagent 1 in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was then cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 8mg (90%) of compound J1.

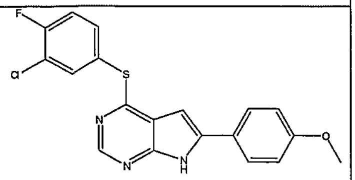
Compounds J2 through J37 were synthesized in a manner analogous to Compound J1 using similar starting materials and reagents. The structures are shown below in Table J:

Table J

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
J1			J19	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
J2		J20	
J3		J21	
J4		J22	
J5		J23	
J6		J24	
J7		J25	
J8		J26	
J9		J27	
J10		J28	
J11		J29	

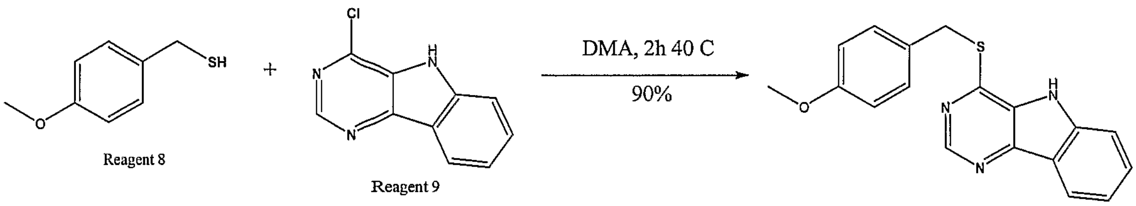
NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
J12			J30	
J13			J31	
J14			J32	
J15			J33	
J16			J34	
J17			J35	
J18			J36	

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
			J37	

Compound K1

1-(4-Methoxy-benzylsulfanyl)-9H-2,4,9-triaza-fluorene; LC-MS: 322 (M^++H)

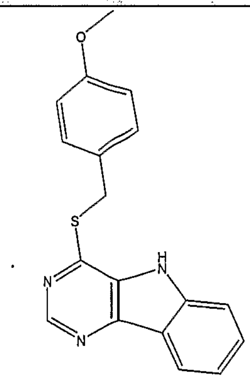
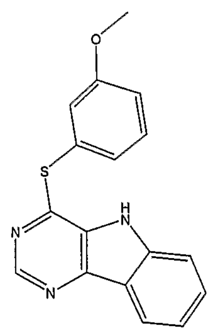
Compound K1 was synthesized by the following procedure:

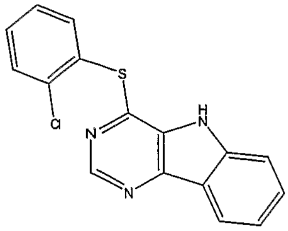
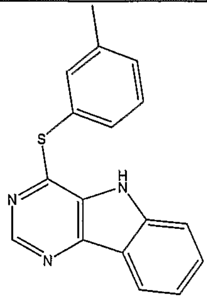
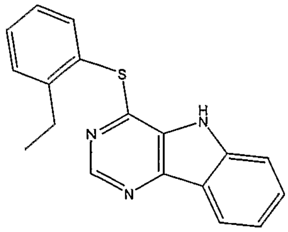
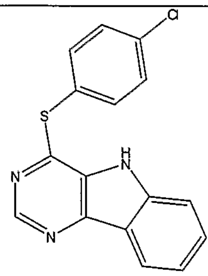
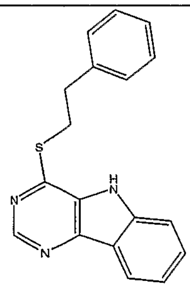
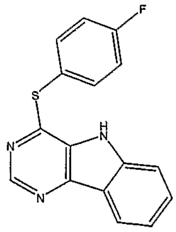
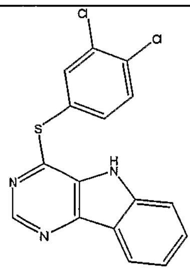
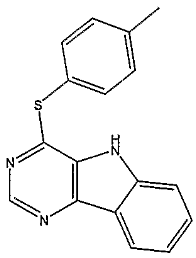
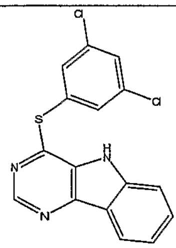
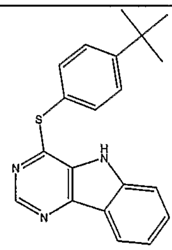
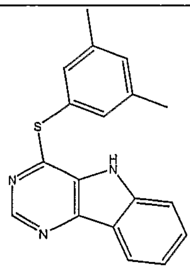
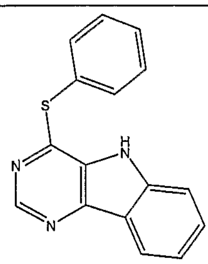


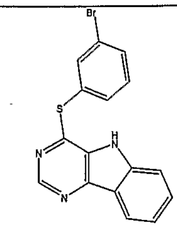
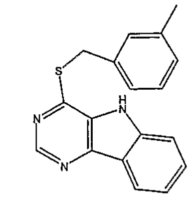
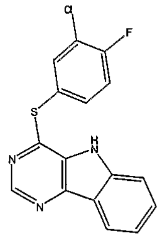
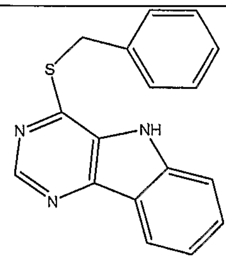
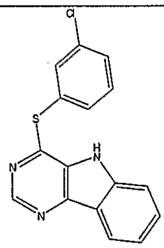
To a 1mM solution of reagent 8 in DMA was added 0.95 eq of reagent 9 in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 9mg (90%) of compound K1.

Compounds K2 through K19 were synthesized in a manner analogous to Compound K1 using similar starting materials and reagents. The structures are shown below in Table K:

Table K

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
K1			K11	

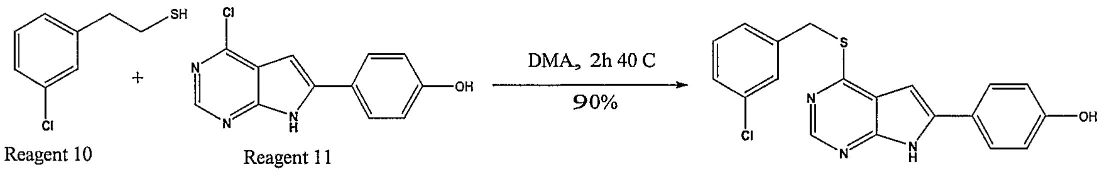
NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
K2			K12	
K3			K13	
K4			K14	
K5			K15	
K6			K16	
K7			K17	

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
K8			K18	
K9			K19	
K10				

<u>Compound L1</u>

4-(4-Phenethylsulfanyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-phenol; LC-MS: 349 (M^{+}+H)

Compound L1 was synthesized by the following procedure:

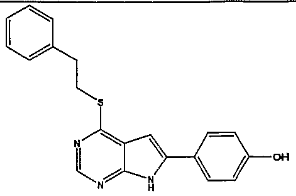
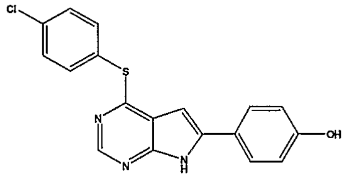
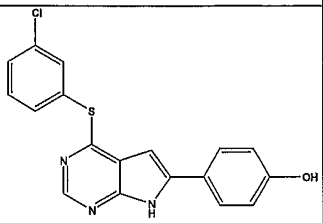
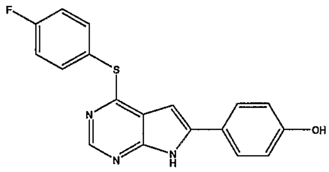
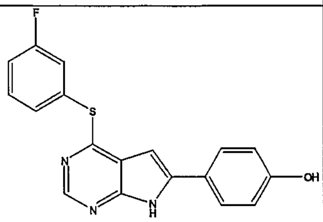
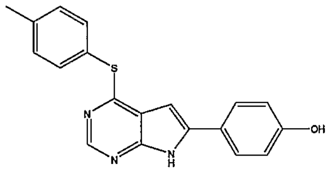
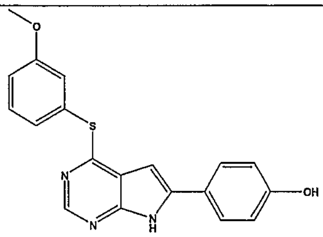
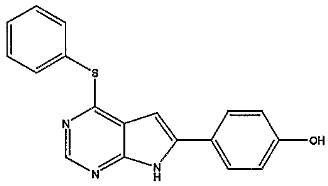
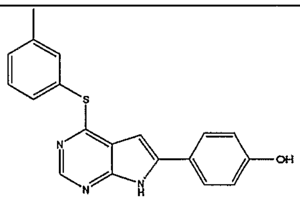
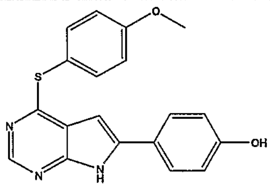
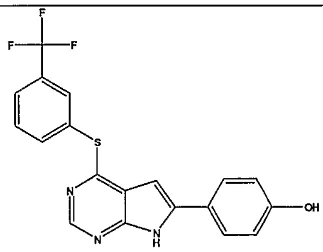


To a 1mM solution of reagent 10 in DMA was added 0.95 eq of reagent 11 in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 9mg (90%) of compound L1.

Compounds L1 through L11 were synthesized in a manner analogous to Compound L1 using similar starting materials and reagents. The structures are shown below in Table L:

<u>Table L</u>

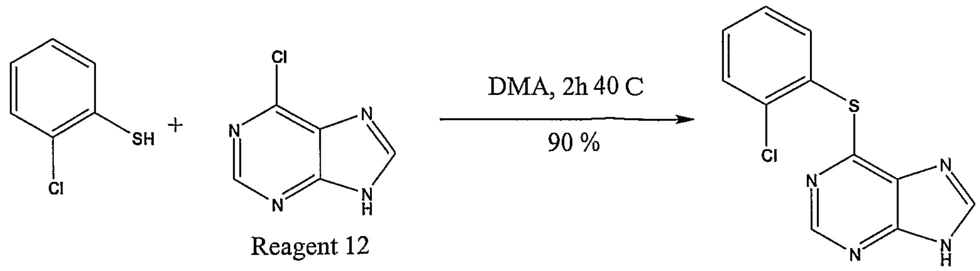
NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
L1		L7	
L2		L8	
L3		L9	
L4		L10	
L5		L11	
L6			

Compound M1

6-(2-Chloro-phenylsulfanyl)-9H-purine; LC-MS: 264 (M^++H)

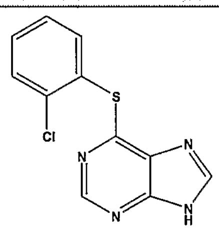
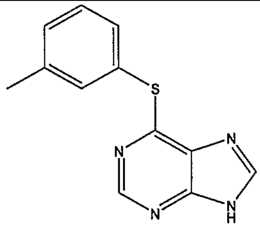
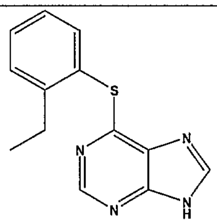
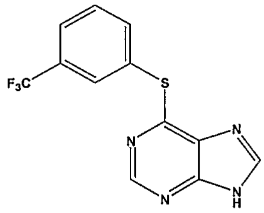
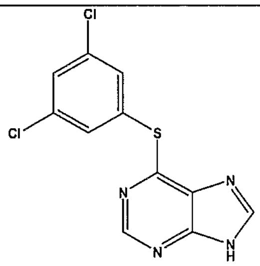
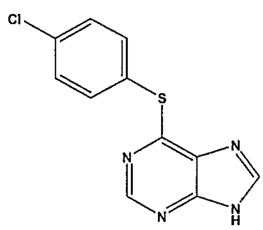
Compound M1 was synthesized by the following procedure:

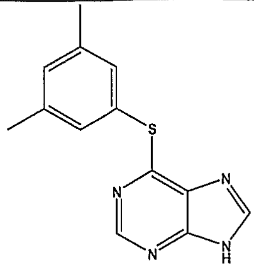
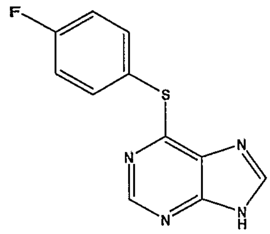
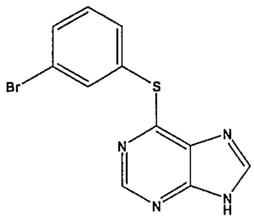
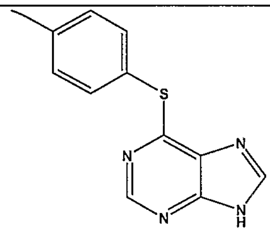
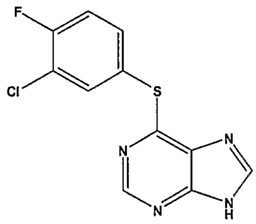
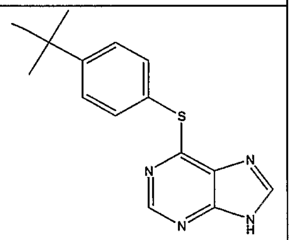
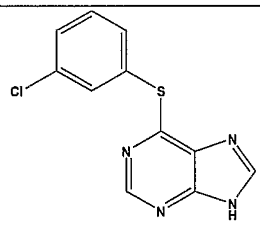
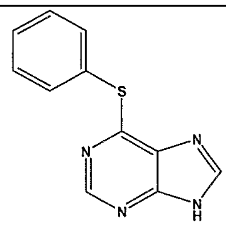
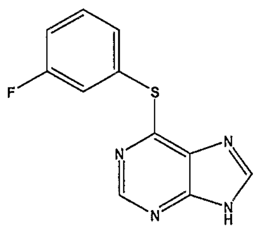
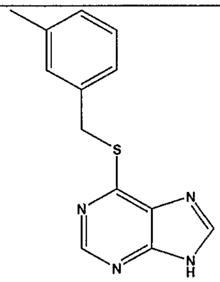
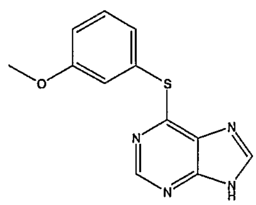
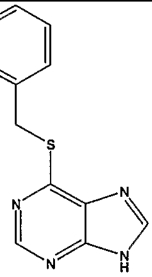


To a 1mM solution of 2-chlorothiophenol in DMA was added 0.95 eq of reagent 12 in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 8mg (90%) of compound M1.

Compounds M2 through M18 were synthesized in a manner analogous to Compound M1 using similar starting materials and reagents. The structures are shown below in Table M:

Table M

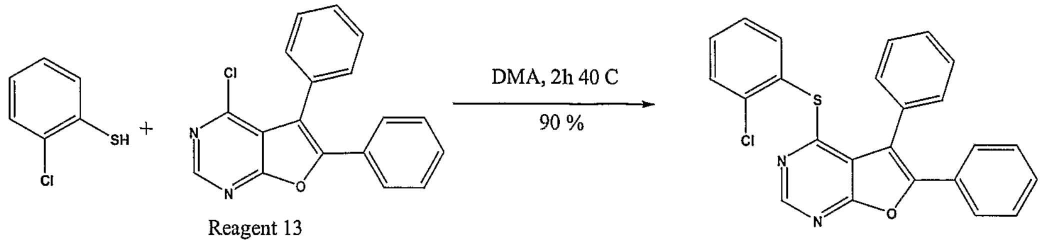
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
M1		M10	
M2		M11	
M3		M12	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
M4		M13	
M5		M14	
M6		M15	
M7		M16	
M8		M17	
M9		M18	

Compound N1

4-(2-Chloro-phenylsulfanyl)-5,6-diphenyl-furo[2,3-d]pyrimidine; LC-MS: 416 (M^{+}+H)

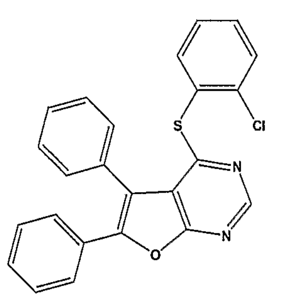
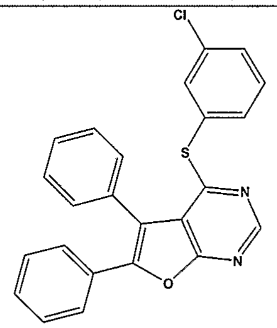
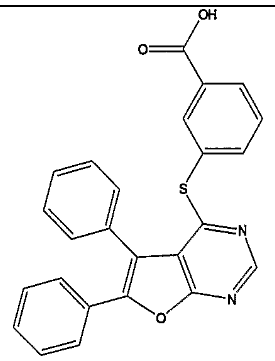
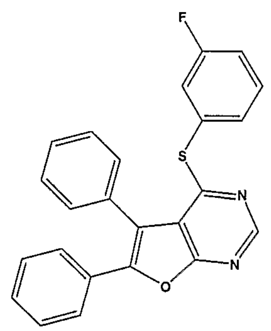
Compound N1 was synthesized by the following procedure:

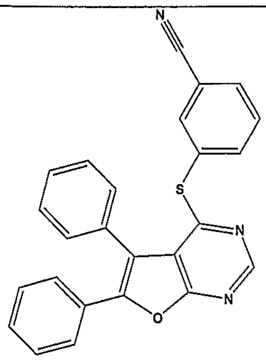
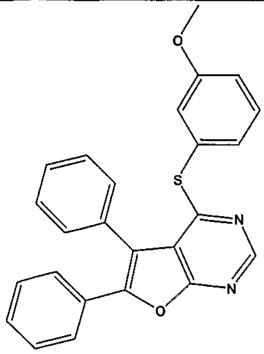
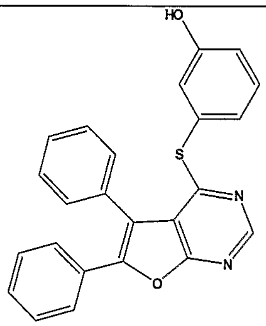
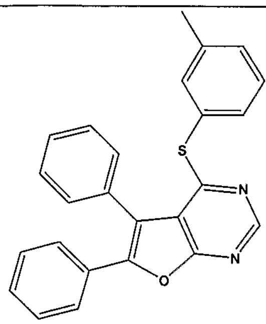
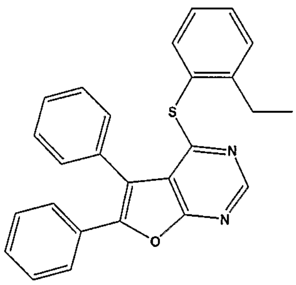
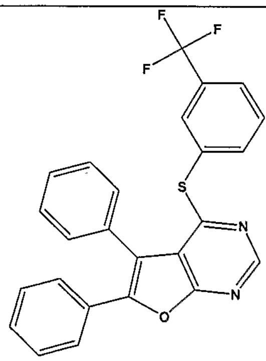
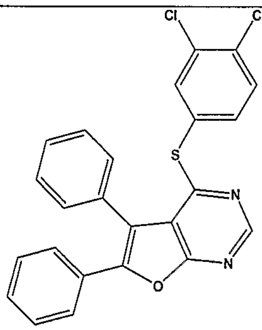
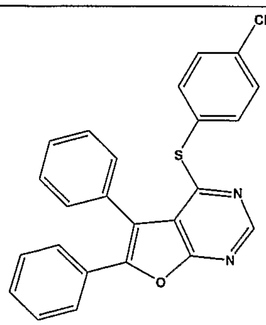


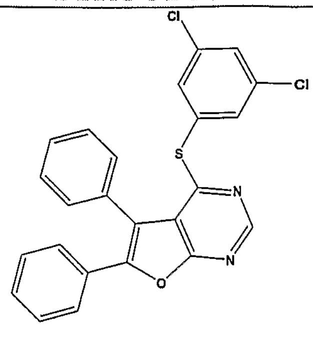
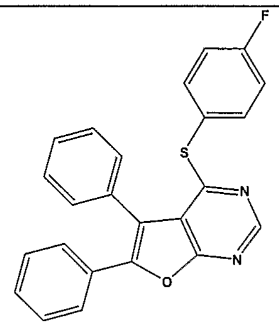
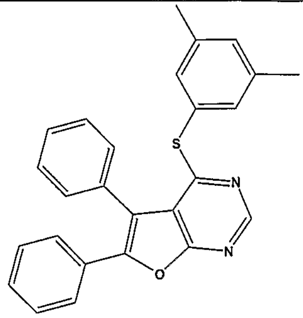
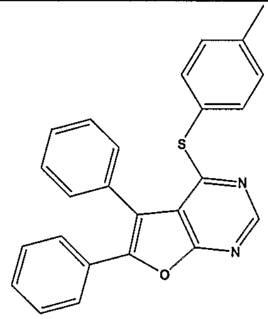
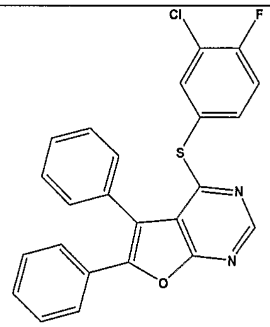
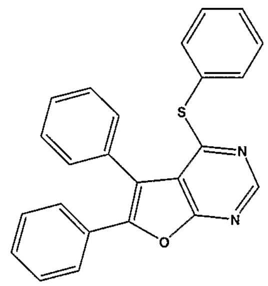
To a 1mM solution of 2-chlorothiophenol in DMA was added 0.95 eq of reagent 13 in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 8mg (90%) of compound N1.

Compounds N2 through N18 were synthesized in a manner analogous to Compound N1 using similar starting materials and reagents. The structures are shown below in Table N:

Table N

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
N1		N10	
N2		N11	

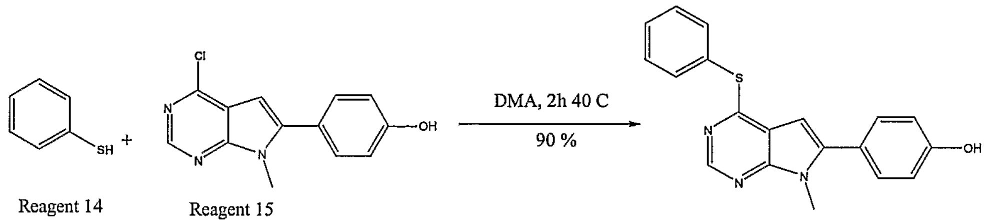
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
N3		N12	
N4		N13	
N5		N14	
N6		N15	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
N7		N16	
N8		N17	
N9		N18	

Compound O1

4-(7-Methyl-4-phenylsulfanyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-phenol; LC-MS: 335 (M^{+}+H)

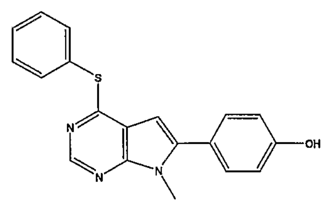
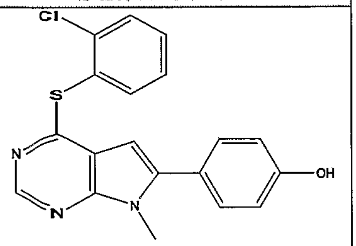
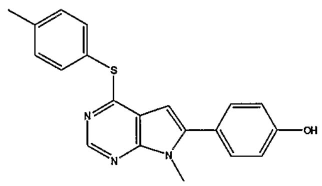
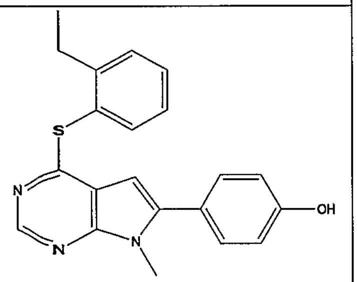
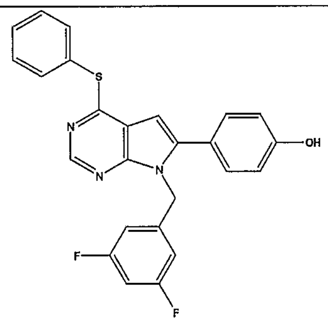
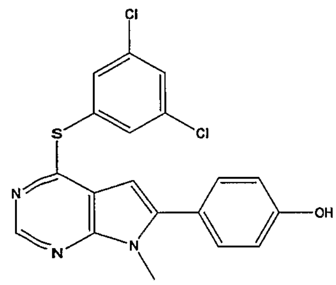
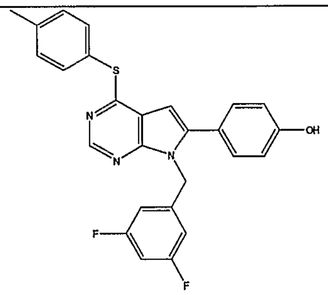
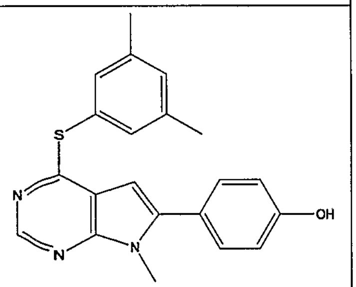
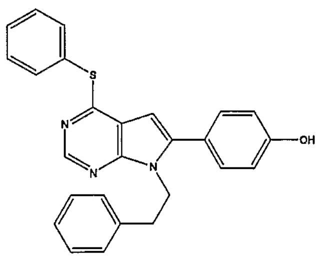
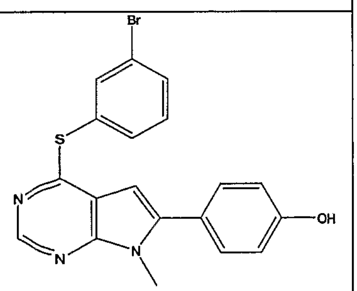
Compound O1 was synthesized by the following procedure:

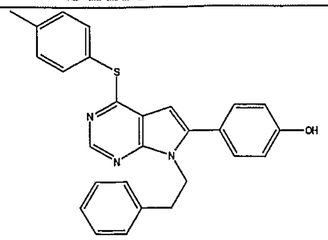
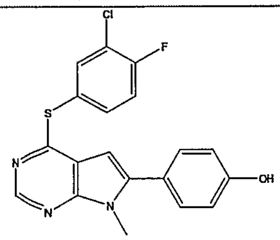
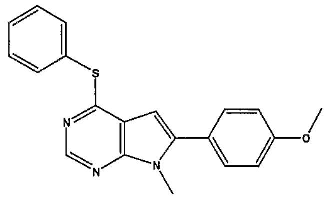
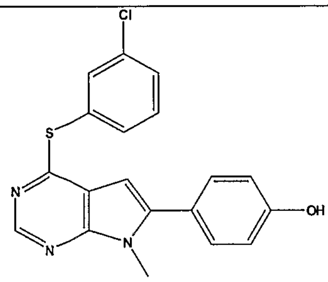
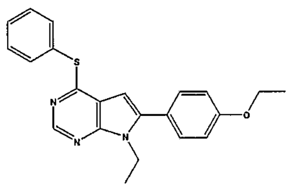
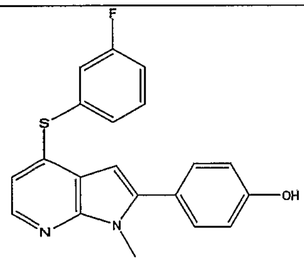
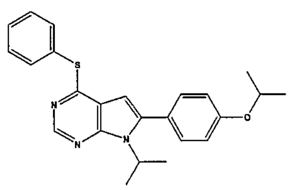
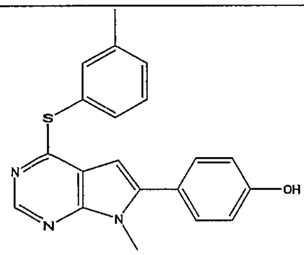
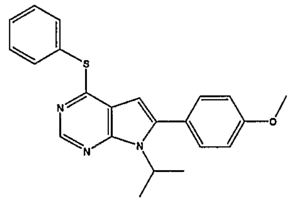
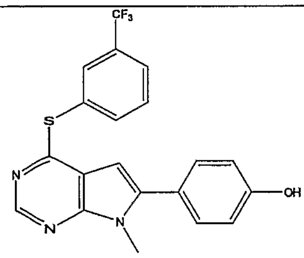
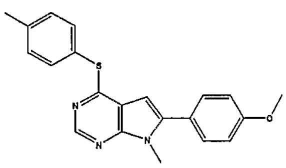
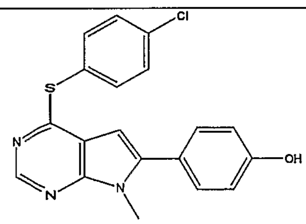


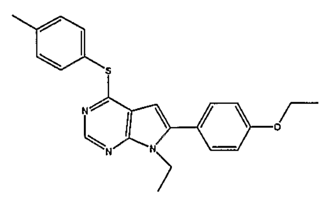
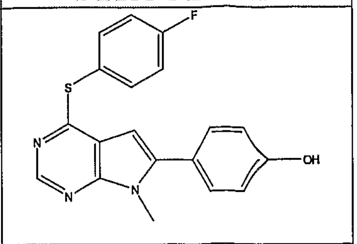
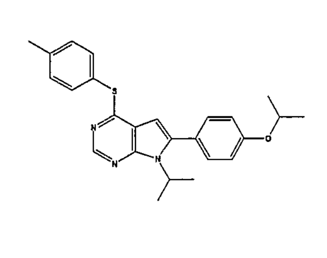
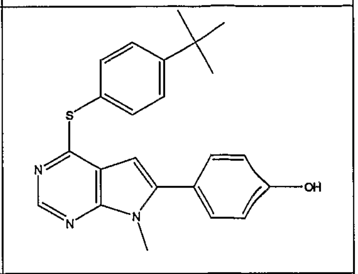
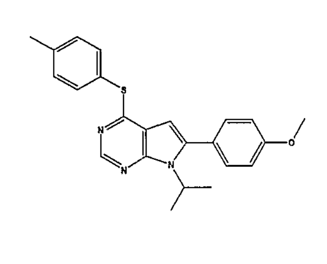
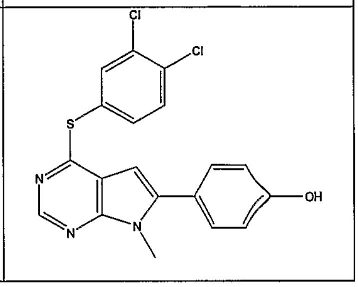
To a 1mM solution of reagent 14 in DMA was added 0.95 eq of reagent 15 in 0.5 ml DMA and the reaction heated at 40 °C for 2 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 8mg (90%) of compound O1.

Compounds O2 through O28 were synthesized in a manner analogous to Compound O1 using similar starting materials and reagents. The structures are shown below in Table O:

Table O

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
O1		O15	
O2		O16	
O3		O17	
O4		O18	
O5		O19	

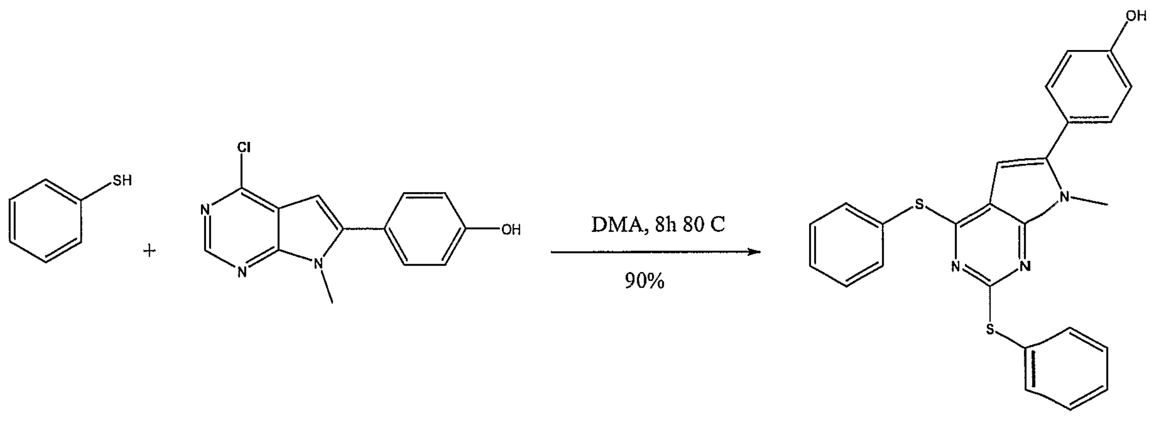
NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
O6		O20	
O7		O21	
O8		O22	
O9		O23	
O10		O24	
O11		O25	

NO.	CHEMICAL STRUCTURE	NO.	CHEMICAL STRUCTURE
O12		O26	
O13		O27	
O14		O28	

Compound P1

4-(7-Methyl-2,4-bis-phenylsulfanyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-phenol; LC-MS: 443 (M^{+}+H)

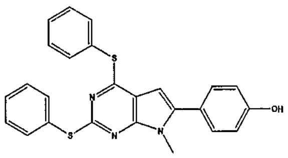
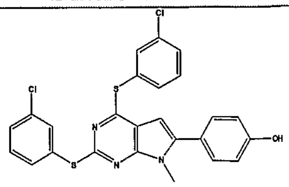
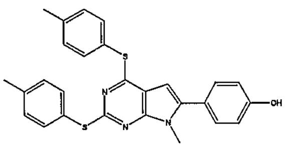
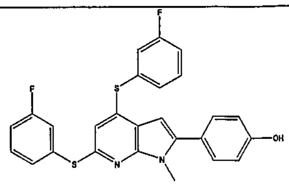
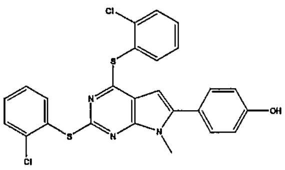
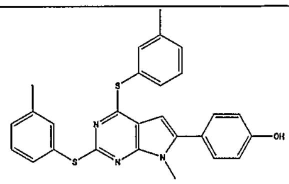
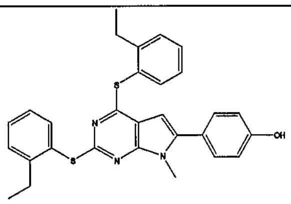
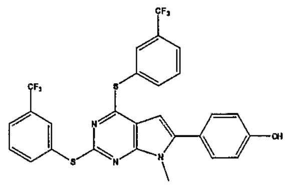
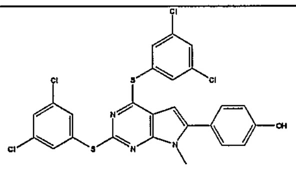
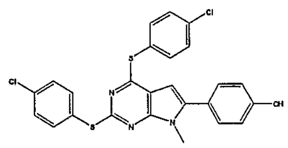
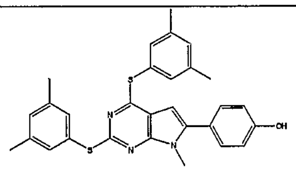
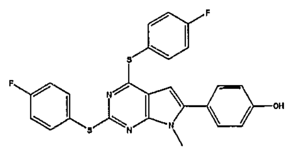
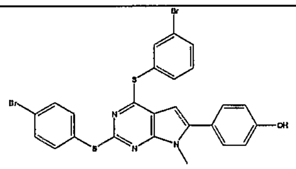
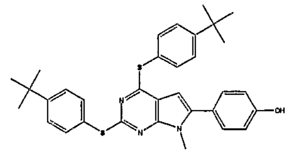
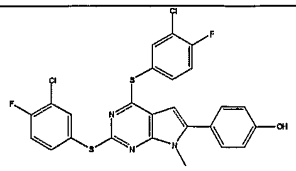
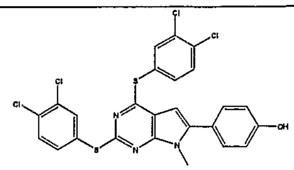
Compound P1 was synthesized by the following procedure:



To a 1mM solution of thiophenol was added 0.95 eq of 4-(4-Chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-phenol in 0.5 ml DMA and the reaction heated at 80 °C for 8 hours. The reaction was cooled to room temperature and purified by reverse phase HPLC (Water:Acetonitrile solvent system) to obtain 2mg (50%) of compound P1.

Compounds P2 through P16 were synthesized in a manner analogous to Compound P1 using similar starting materials and reagents. The structures are shown below in Table P:

Table P

NO.	CHEMICAL STRUCTURE		NO.	CHEMICAL STRUCTURE
P1			P9	
P2			P10	
P3			P11	
P4			P12	
P5			P13	
P6			P14	
P7			P15	
P8			P16	

Binding Constant (K_d) Measurements for Small-Molecule- Kinase Interactions

Methods for measuring binding affinities for interactions between small molecules and kinases including FLT3, c-KIT, ABL(T334I) [a.k.a. ABL(T315I)], VEGFR-2 (a.k.a. KDR), and EGFR are described in detail in US Application No. 10/873,835, which is incorporated by reference herein in its entirety. The components of the assays include human kinases expressed as fusions to T7 bacteriophage particles and immobilized ligands that bind to the ATP site of the kinases. For the assay, phage-displayed kinases and immobilized ATP site ligands are combined with the compound to be tested. If the test compound binds the kinase it competes with the immobilized ligand and prevents binding to the solid support. If the compound does not bind the kinase, phage-displayed proteins are free to bind to the solid support through the interaction between the kinase and the immobilized ligand. The results are read out by quantitating the amount of fusion protein bound to the solid support, which is accomplished by either traditional phage plaque assays or by quantitative PCR (qPCR) using the phage genome as a template. To determine the affinity of the interactions between a test molecule and a ,kinase, the amount of phage-displayed kinase bound to the solid support is quantitated as a function of test compound concentration. The concentration of test molecule that reduces the number of phage bound to the solid support by 50% is equal to the K_d for the interaction between the kinase and the test molecule. Typically, data are collected for twelve concentrations of test compound and, the resultant binding curve is fit to a non-cooperative binding isotherm to calculate K_d.

Described in the exemplary assays below is data from binding with varying kinases. Binding values are reported as follows "+" for representative compounds exhibiting a binding dissociation constant (Kd) of 10,000 nM or higher; "++"for representative compounds exhibiting a Kd of 1,000 nM to 10,000 nM; "+++"for representative compounds exhibiting a Kd of 100 nM to 1,000 nM; and "++++"for representative compounds exhibiting a Kd of less than 100 nM. The term "ND" represents non-determined values.

The Affinity of the Compounds for FLT3

The ability of FLT3 kinase inhibitors to inhibit cellular proliferation was also examined. MV4:11 was a cell line derived from a patient with acute myelogenous leukemia. It expressed a mutant FLT3 protein that was constitutively active. MV4:11 cells were grown in the presence of candidate FLT3 inhibitor molecules, resulting in significantly decreased proliferation of the leukemia-derived cells in the presence of compound. Inhibition of FLT3 kinase activity prevented proliferation of these cells, and thus the MV4:11 cell line can be used a model for cellular activity of small molecule inhibitors of FLT3.

FLT3 assay using MV4,11 cells

MV4,11 cells were grown in an incubator @ 37°C in 5% CO_2 in Medium 2 (RPMI, 10%FBS, 4mM glutamine, Penn/Strep). The cells were counted daily and the cell density was kept between 1e5 and 8e5 cells/ml.

Day One: Enough cells were harvested for experiments to be conducted in 50ml conical tubes. The harvested cells were spun at 500g for 5 min at 4°C, the supernatant was then aspirated and the cells were resuspended in the starting volume of 1 x PBS. The cells were again spun at 500g for 5 min at 4°C and the supernatant again aspirated. The cells were then resuspended in medium 3 (DMEM w/ glut, 10% FBS, Penn/Strep) to a density of $4e^5$ cells/ml and incubated @ 37°C in 5% CO_2 O/N.

Day Two: The cells were counted and enough medium 3 was added to decrease density to 2e5 cells/ml. 50ul (10,000 cells) was aliquoted into each well of a 96 well optical plate using multichannel pipetman. The compound plate was then set up by aliquoting 3 μl of negative control (DMSO) into column 1 of a 96 well 300ul polypropylene plate, aliquoting 3 μl of positive control (10mM AB20121) into column 12 of plate, and aliquoting 3 μl of appropriate compounds from serial dilutions into columns 2-11. To each well, 150 μl of Medium 3 was added and 50 μl of compound/medium mixture from compound plate into rows of optical plate in duplicate. The cells were then incubated @ 37°C in 5% CO_2 for 3 days.

Day Five: MTS was thawed in a H_2O bath. 20 μl of MTS was added to each well of optical plate and the cells were incubated @ 37°C in 5% CO_2 for 2 hours. The plate was then placed on a plate shaker for 30 seconds on high speed.

Data for some of the compounds is provided below:

Compound No.	Kd for FLT3(DKIN) Binding (nM)
F1	+
J5	+
J37	+++
J16	+++
D13	+++
D14	++
D24	+++
L9	+++
O7	+++
O8	+++
O9	+++
O10	+++

Compound No.	Kd for FLT3(DKIN) Binding (nM)
O11	+++
O12	+++
O13	++
O14	++

Compound No.	(MV 4,11) Cell Proliferation Assay with 0.5% Serum IC50 (nM) "CS0001"
J5	++++
J37	+++
J16	++++
K5	+

The Affinity of the Compounds for PDGFR

Kd values for the interactions between PDGFR-β and candidate small molecule ligands were measured by a phage-display-based competitive binding assay that is described in detail in U.S. Serial No. 10/406,797 filed 2 April 2003 and incorporated herein by reference. Briefly, T7 phage displaying human PDGFR-β were incubated with an affinity matrix coated with known PDGFR-β inhibitor in the presence of various concentrations of the soluble competitor molecules. Soluble competitor molecules that bind PDGFR-β prevent binding of PDGFR-β phage to the affinity matrix, hence, after washing, fewer phage are recovered in the phage eluate in the presence of an effective competitor than in the absence of an effective competitor. The Kd for the interaction between the soluble competitor molecule and PDGFR-β is equal to the concentration of soluble competitor molecule that causes a 50% reduction in the number of phage recovered in the eluate compared to a control sample lacking soluble competitor. Since this assay is generic, and any molecule can be used as a soluble competitor, we have determined Kd values for the interaction between PDGFR-β and several small molecules, including those shown below.

Compound No.	Kd for PDGFR-β (DKIN) Binding (nM)
J37	+++
J12	++
J14	+++
J16	+++
D7	+++
D8	++
D11	+++
D13	+++
D14	++
D22	+++
D24	++

Compound No.	Kd for PDGFR-β (DKIN) Binding (nM)
L9	++

The Affinity of the Compounds for Abl

Compound No.	Kd for ABL1 Binding (nM)
J3	++++
J9	+++
J17	++
J18	++
J26	+++
L4	+++
L9	+++

In addition, compound L2 exhibited (++) activity in a binding assay termed "ABL2 (DKIN:Kd (nM)".

The Affinity of the Compounds for VEGFR-2

Compound No.	Kd for VEGFR2(DKIN) Binding (nM)
J14	+++
E4	++
L4	+++
L5	+
L7	++
L8	+
L9	+++
L10	+

The Affinity of the Compounds for EGFR

To measure the Kd values, the T7 phage displaying human EGFR were incubated with an atorvastatin-coated affinity matrix in the presence of various concentrations of a soluble (non-immobilized) compounds provided herein, as described in detail herein. Soluble compounds that bind EGFR prevent binding of EGFR phage to the affinity matrix; hence, fewer phage are recovered in the phage eluate in the presence of an effective competitor than in the absence of an effective competitor. The Kd for the interaction between the soluble compound (competitor) molecule and EGFR is equal to the concentration of soluble competitor molecule that causes a 50% reduction in the number of phage recovered in the eluate compared to a control sample lacking soluble competitor.

EGFR Autophosphorylation Inhibition Assay

Tyrosine 1173 is a major autophosphorylation site resulting from activation of EGFR by epidermal growth factor (EGF). To determine the capacity of a compound to inhibit this phosphorylation activity of EGFR upon itself, the following methodology was used: 4 x 10^4 A431 cells/well in a 96-well culture plate or 3.6 x 10^5 A549 cells/well in a 24-well culture plate were cultured overnight at 37°C in 5% CO_2 in low serum culture medium (DMEM supplemented with 0.5 % fetal calf serum, 4,500 mg/L glucose and 100 units/ml penicillin-streptomycin). After 16 hours, the cells were pre-incubated in eight serial 3-fold dilutions of test compound (3.3 μM – 0.0017 μM) in addition to vehicle control (final concentration on DMSO vehicle was 1%) for two hours. Cells were stimulated by the addition of 5 ng/ml of EGF for five minutes. Cells were then washed with cold phosphate buffered saline (PBS), and incubated for 30 minutes at 4°C in lysis buffer. Subsequently, the samples were centrifuged at 6000 x RCF for 15 minutes, and the level of phosphorylation of EGFR tyrosine 1173 was measured using a sandwich enzyme-linked immunosorbent assay following the manufacturer's recommended protocols (Biosource, Camarillo, CA). Total EGFR levels were also measured in the same manner to control for protein level differences. The reported values are those concentrations of compound required to inhibit EGF-induced phosphorylation of tyrosine 1173 by 50%.

A431 Proliferation Inhibition Assay

To examine the ability of a compound to inhibit proliferation of the A431 cell line, the following methodology was used: 2000 cells/well in a 96-well culture plate were cultured overnight at 37°C in 5% CO_2 in low serum medium (DMEM supplemented with 0.5 % fetal calf serum, 4,500 mg/L glucose and 100 units/ml penicillin-streptomycin).After 16 hours, medium was replaced with low serum medium containing 10 serial 3-fold dilutions of compound plus a vehicle control (final concentration of DMSO vehicle was 1%), and the cells were incubated at 37°C in 5% CO_2 for 72 hours. Relative cell number was using 3-(4,5-dimethylthiazol-2-yl)-5(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) following the manufacturer's recommended protocol (Promega, Madison, WI). The reported values are those concentrations of compound required to inhibit cell proliferation by 50%.

Data for some of the compounds is provided below.

Binding of wildtype-EGFR

Compound No.	Kd for EGFR(DKIN) Binding (nM)
F3	+++
J3	+++
J37	++++
J7	++++
J8	++++
J9	+++
J10	+++

Compound No.	Kd for EGFR(DKIN) Binding (nM)
J11	+++
J13	++++
J14	++++
J16	+++
D3	+++
D5	++++
D8	++++
C3	+
C4	+++
J17	+++
J18	+++
K5	++++
K8	++++
K10	++++
K12	+++
K13	++++
K14	++++
K15	++++
K17	++++
D18	+++
D19	++++
D20	+++
D21	+++
J19	++++
J20	++++
J21	+
J22	+++
J23	++++
J24	++++
J25	++++
J26	+++
J27	+++
J28	++++
J30	++++
J31	++++
J32	++
J33	++++
E1	+++
E2	++++
E3	++++
E4	+++
L1	++
L2	++++
L3	++++
L4	+++
L5	++++
L7	++++
L8	++++
L9	++++
N4	+++
N12	+++
L11	+++

<u>Binding Data of mutant-EGFR- Kd Expressed in nM</u>

Assay	Compound No.	Compound No.	Compound No.
	K5	E3	L2
(L861Q)	+++	++++	++++
(G719C)	++++	++++	++++
(G719S)	++++	++++	++++
(S752-1759del)	++++	++++	++++
(L747-T751del, Sins)	++++	++++	++++
(L747-T752del, P753S)	++++	++++	++++
(L747-E749del, A750P)	++++	++++	++++
(L858R)	++++	++++	++++
(E746-A750del)	++++	++++	++++

Cell Assay Data for EGFR Phosphorylation in Epidermoid Carcinoma Cell Line A431

Compound No.	IC50 (nM)
J37	+++
J7	++
J8	++
J13	++
J14	++
D5	+++
K5	+++
K8	+++
K10	+++
K13	+++
K14	+++
K15	+++
D19	+++
J19	++
J20	++
J23	+++
J24	+++
J25	+++
J27	+++
J28	++
J30	++
J31	++
J33	+++
E1	+++
E3	++++
L2	++++
L3	++++
L5	++++
L7	+++
L8	++++
L9	+++

Cell Assay Data for EGFR Phosphorylation in Lung Cancer Cell Line A459

Compound No.	IC50 (nM)

Compound No.	IC50 (nM)
J7	++
J8	++
J14	++
K5	+++
K10	+++
K14	+++
D19	++
J19	++
J23	+++
J24	+++
J25	++
J27	++
J30	++
J31	+
J33	++
E3	+++
L2	+++
L3	++
L5	++
L7	++
L8	++
L9	++

The Affinity of the Compounds for other Kinases

KIT (DKIN) Binding Assay: Assay for the inactive form of KIT, which contains the autoinhibitory juxtamembrane domain. Compound J16 exhibited (++) activity in the Kd assay measured in nM.

TNIK (DKIN) Binding Assay: Compound L2 exhibited (++++) activity in the Kd assay measured in nM.

PLK 4 (SKIN) Binding Assay: Compound L2 exhibited (+) activity in the Kd assay measured in nM.

MARK2 (SKIN) Binding Assay: Compound L2 exhibited (+) activity in the Kd assay measured in nM.

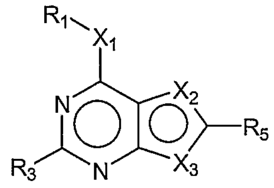
All references cited herein, including patents, patent applications, and publications, are herby incorporated by reference in their entireties, whether previously specifically incorporated or not.

Having now fully described compounds and methods provided herein, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters, concentrations, and conditions without departing from the spirit and scope of the invention and without undue experimentation.

While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth.

WHAT IS CLAIMED IS:

1. A compound corresponding to Formula (I):



(I)

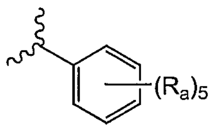
wherein:

a. R_1 is $-(CHR_{1a})_z-R_{1b}$, where

i. each R_{1a} is independently H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, or -C(O)-(C_1-C_4)alkoxy,

ii. z is 0, 1, 2, or 3, and

iii. R_{1b} is



,

where each R_a is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)-, or -$S(O)_2$-;

b. R_3 is H or $L_3-(CHR_{3a})_x-R_{3b}$, where

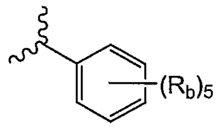
i. L_3 is a bond, NH, O, or S,

ii. R_{3a} is H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, or -(C_1-C_4)dialkylamine,

iii. x is 0, 1, 2, or 3, and

iv. R_{3b} is phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine;

c. R_5 is H or

, where each R_b is independently H, halogen, -CN, -OH, -NH_2, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamine, substituted or unsubstituted dialkylamine, -C(O)OH, -C(O)NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, or -C(O)-(C_1-C_4)alkoxy;

d. X_1 is S or O;

e. X_2 is CR_6 when X_3 is NR_4, or X_2 is NR_4 when X_3 is CR_6, provided that neither X_2 and X_3 are both CR_6, nor X_2 and X_3 are both NR_4, wherein

f. R_4 is H or –$(CHR_{4a})_y$-R_{4b}, where

i. R_{4a} is halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamine, substituted or unsubstituted dialkylamine,

ii. y is 0, 1, 2, or 3, and

iii. R_{4b} is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5-membered or 6-membered unsaturated heterocycle; or

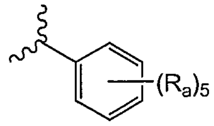
R_4 and R_5, taken together, form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine

g. R_6 is H, heteroaryl, or phenyl, wherein the phenyl and the heteroaryl are optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

R_6 and R_5, taken together, form a 5- or 6-membered carbocyclic or heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamine, and substituted or unsubstituted dialkylamine;

or pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

2. The compound of claim 1, wherein R_1 is

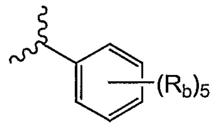


.

3. The compound of claim 2, wherein each R_a is independently H, halogen, substituted or unsubstituted alkyl, or substituted or unsubstituted alkoxy.

4. The compound of claim 1, wherein R_3 is H.

5. The compound of claim 1, wherein R_5 is



.

6. The compound of claim 5, wherein each R_b is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, or -OH.

7. The compound of claim 1, wherein X_1 is S.

8. The compound of claim 1, wherein X_1 is O.

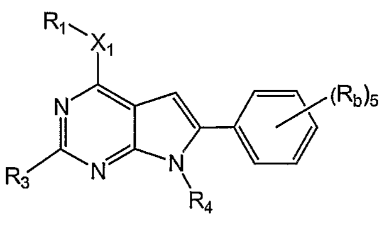
9. The compound of claim 1, wherein X_2 is CR_6 and X_3 is NR_4.

10. The compound of claim 9, wherein R_4 is H or substituted or unsubstituted alkyl.

11. The compound of claim 9, wherein R_6 is H.

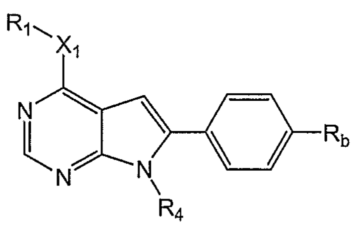
12. The compound of claim 9, wherein each of R_6 and R_3 is H.

13. The compound of claim 1, corresponding to Formula (A):



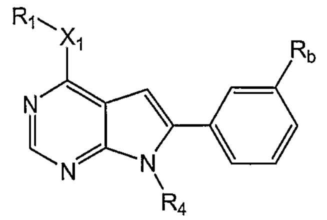
(A).

14. The compound of claim 13, corresponding to Formula (B):



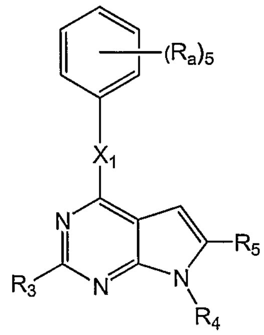
(B).

15. The compound of claim 13, corresponding to Formula (C):



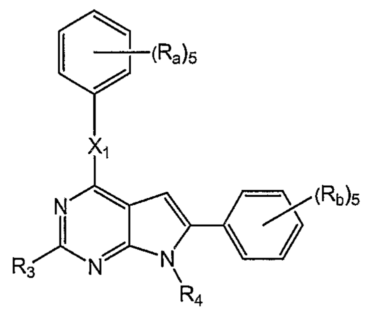
(C).

16. The compound of claim 1, corresponding to Formula (D):



(D).

17. The compound of claim 16, corresponding to Formula (E):

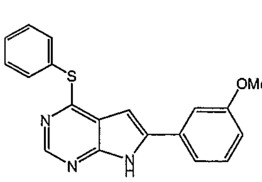
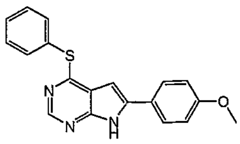
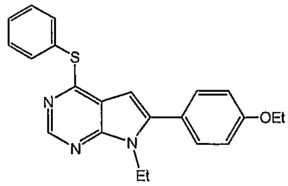
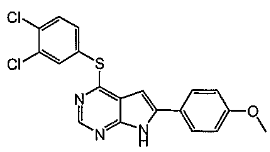


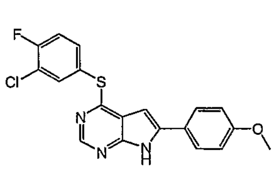
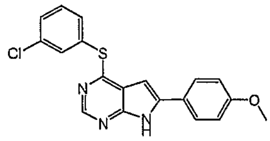
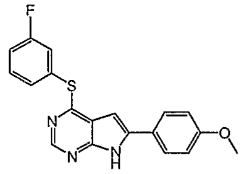
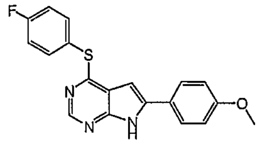
(E).

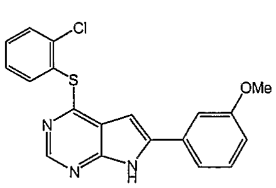
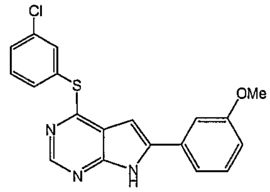
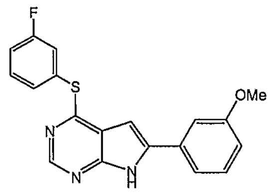
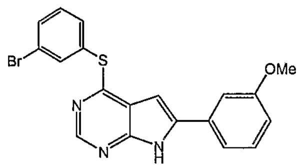
18. The compound of claim 17, wherein each R_a is independently H, halogen, C_1-C_4 alkyl, C_1-C_4 fluoroalkyl, or C_1-C_4 alkoxy.

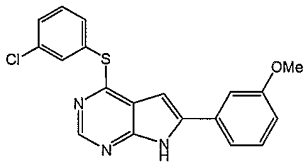
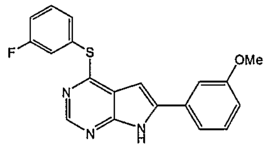
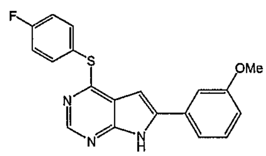
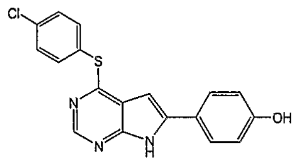
19. The compound of claim 17, wherein each R_b is independently H, halogen, -OH, C_1-C_4 alkyl, or C_1-C_4 alkoxy.

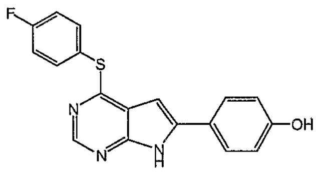
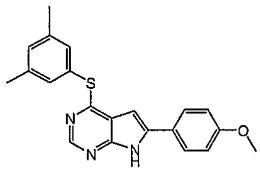
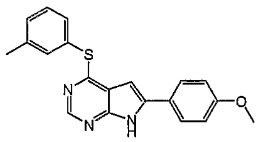
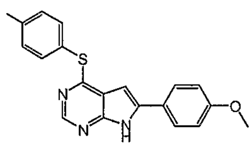
20. The compound of claim 1, selected from the group consisting of:

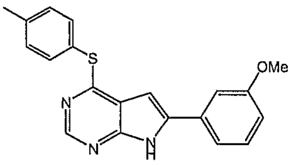
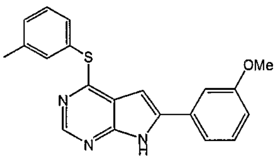
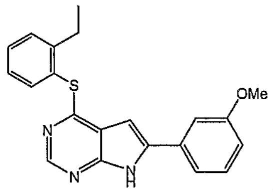
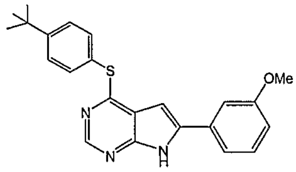
,
,
,
,

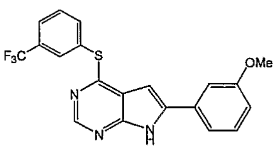
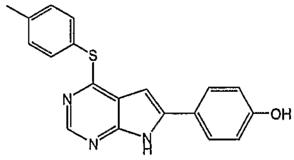
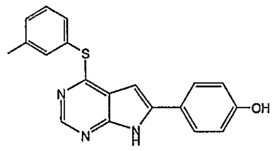
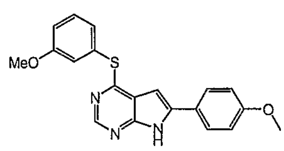
,
,
,
,

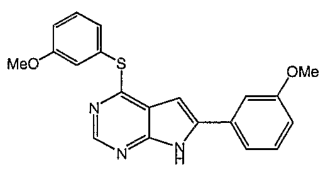
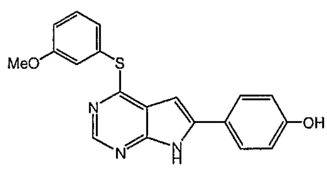
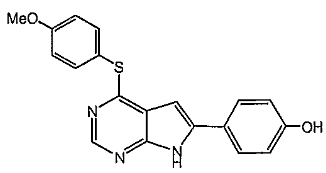
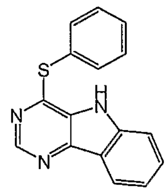
,
,
,
,

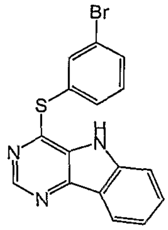
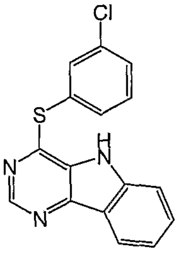
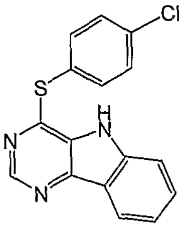
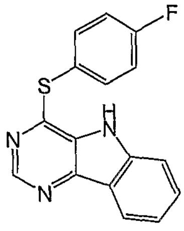
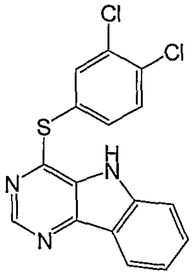
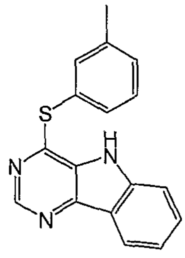
,
,
,
,

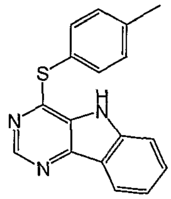
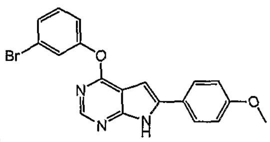
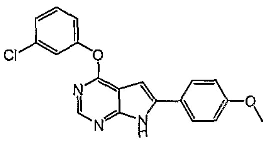
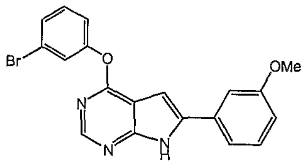
,
,
,
,

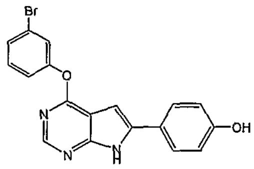
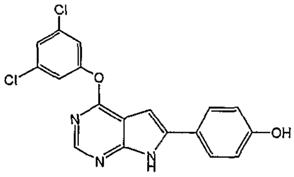
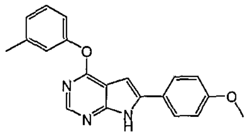
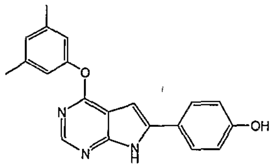
,
,
,
,

,
,
,
,

,
,
,
,

, , , , , ,

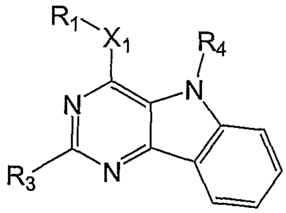
, , , ,

, ,  and .

21. The compound of claim 1, wherein X_2 is NR_4 and X_3 is CR_6.

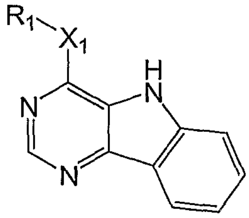
22. The compound of claim 21, wherein R_5 and R_6 are taken together to form a phenyl ring optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, substituted or unsubstituted C_3-C_{20} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted C_2-C_{20} alkoxy, substituted or unsubstituted alkylamine, and substituted or unsubstituted dialkylamine.

23. The compound of claim 21, corresponding to Formula (F):



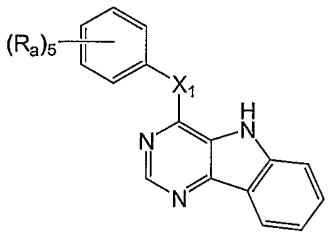
(F).

24. The compound of claim 23, corresponding to Formula (G):



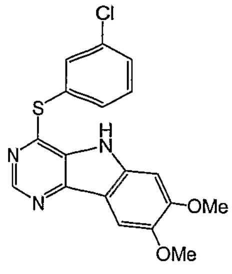
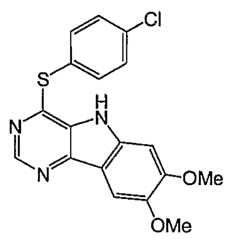
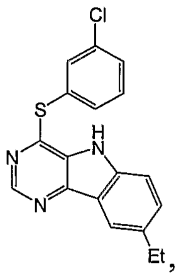
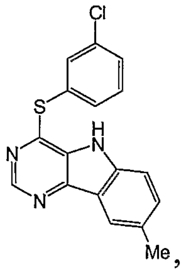
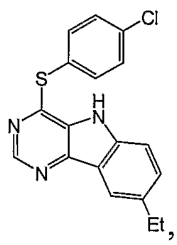
(G).

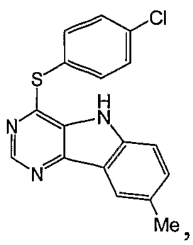
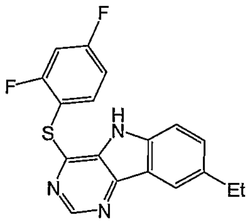
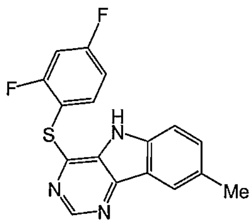
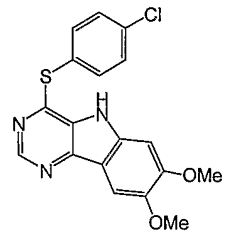
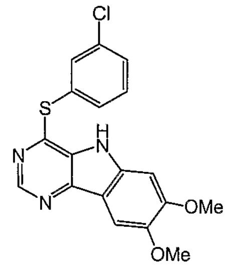
25. The compound of claim 24, corresponding to Formula (H):

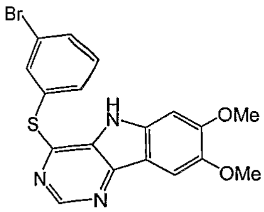
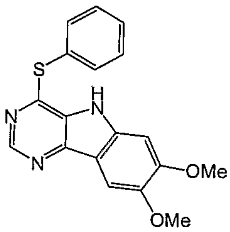
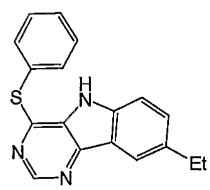
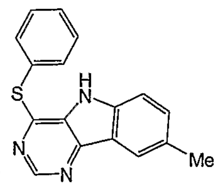


(H).

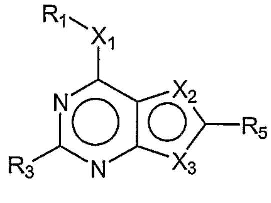
26. The compound of claim 1, wherein said compound is not:

,
,
,
,
,

,
,
,
,
,

,
,
, or
.

27. A method for treating a disease comprising administering to a subject in need thereof an effective amount of an flt-3 kinase modulating compound corresponding to Formula (I):



(I)

wherein:

a. X_1 is S or O;

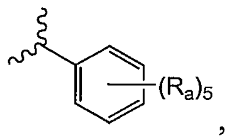
b. each of X_2 and X_3 is independently N, O, S, NR_4, or CR_6;

c. R_1 is $-(CHR_{1a})_z-R_{1b}$, where

i. each R_{1a} is independently H, $(C_1\text{-}C_4)$alkyl, F, $(C_1\text{-}C_4)$fluoroalkyl, $(C_1\text{-}C_4)$alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-$(C_1\text{-}C_4)$alkyl, -C(O)-$(C_1\text{-}C_4)$fluoralkyl, -C(O)-$(C_1\text{-}C_4)$alkylamine, -$(C_1\text{-}C_4)$alkylamine, -$(C_1\text{-}C_4)$dialkylamine, or -C(O)-$(C_1\text{-}C_4)$alkoxy,

ii. z is 0, 1, 2, or 3, and

iii. R_{1b} is



where each R_a is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, -CN, -L_1-OH, -L_1-NH_2, -L_1-$(C_1\text{-}C_4)$alkyl, -L_1-$(C_3\text{-}C_6)$cycloalkyl, -L_1-$(C_1\text{-}C_4)$fluoroalkyl, -L_1-$(C_1\text{-}C_4)$alkoxy, -L_1-$(C_1\text{-}C_4)$alkylamine, -L_1-$(C_1\text{-}C_4)$dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)-, or -$S(O)_2$-; or

R_{1b} is H, -$(C_1\text{-}C_4)$alkyl, an optionally substituted -$(C_3\text{-}C_6)$cycloalkyl, -$(C_1\text{-}C_4)$fluoroalkyl, or an optionally substituted 5-membered or 6-membered unsaturated heterocycle;

d. R_3 is H or L_3-$(CHR_{3a})_x$-R_{3b}, where

i. L_3 is a bond, NH, O, or S,

ii. R_{3a} is H, $(C_1\text{-}C_4)$alkyl, F, $(C_1\text{-}C_4)$fluoroalkyl, $(C_1\text{-}C_4)$alkoxy, -$(C_1\text{-}C_4)$alkylamine, or -$(C_1\text{-}C_4)$dialkylamine,

iii. x is 0, 1, 2, or 3, and

iv. R_{3b} is phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -$(C_1\text{-}C_4)$alkyl, -$(C_1\text{-}C_4)$fluoroalkyl, -$(C_1\text{-}C_4)$alkoxy, -$(C_1\text{-}C_4)$alkylamine, and -$(C_1\text{-}C_4)$dialkylamine;

e. R_4 is H or –$(CHR_{4a})_y$-R_{4b}, where

i. R_{4a} is H, $(C_1\text{-}C_4)$alkyl, F, $(C_1\text{-}C_4)$fluoroalkyl, $(C_1\text{-}C_4)$alkoxy, -$(C_1\text{-}C_4)$alkylamine, or -$(C_1\text{-}C_4)$dialkylamine;

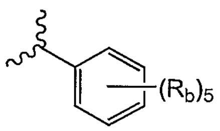
ii. y is 0, 1, 2, or 3, and

iii. R_{4b} is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5-membered or 6-membered unsaturated heterocycle; or

R_4 and R_5, taken together, form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; or

when X_2 is NR_4 and X_3 is CR_6, R_1 and R_4, taken together, form a 5- or 6-membered aromatic heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; or

f. R_5 is H or



, where each R_b is independently H, halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, $-(C_1-C_4)$dialkylamine, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, or $-C(O)-(C_1-C_4)$alkoxy; and

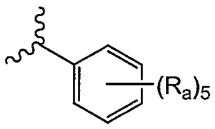
g. R_6 is H, heteroaryl, or phenyl, wherein the phenyl and the heteroaryl are optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; or

R_6 and R_5, taken together, form an aromatic carbocycle or heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine, or

when X_2 is CR_6 and X_3 is NR_4, R_6 and R_1, taken together, form a 5- or 6-membered aromatic heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine;

or pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

28. The method of claim 27, wherein R_1 of said compound is

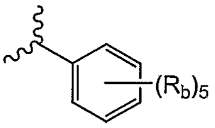


.

29. The method of claim 28, wherein each R_a of said compound is independently H, halogen, $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxy.

30. The method of claim 27, wherein R_3 of said compound is H.

31. The method of claim 27, wherein R_5 of said compound is H or



.

32. The method of claim 31, wherein each R_b of said compound is independently H, halogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or -OH.

33. The method of claim 27, wherein X_1 of said compound is S.

34. The method of claim 27, wherein X_1 of said compound is O.

35. The method of claim 27, wherein X_2 of said compound is CR_6 and X_3 of said compound is NR_4.

36. The method of claim 27, wherein X_2 of said compound is CR_6 and X_3 of said compound is O.

37. The method of claim 27, wherein X_2 of said compound is CR_6 and X_3 of said compound is S.

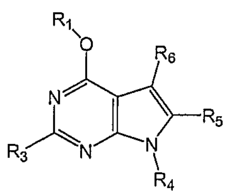
38. The method of claim 27, wherein X_2 of said compound is N and X_3 of said compound is NR_4.

39. The method of claim 27, wherein R_4 of said compound is H or $(C_1\text{-}C_4)$alkyl.

40. The method of claim 27, wherein R_6 of said compound is H.

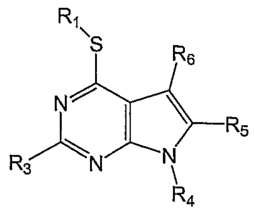
41. The method of claim 27, wherein each of R_6 and R_3 of said compound is H.

42. The method of claim 27, wherein said compound corresponds to Formula (Ia-O):



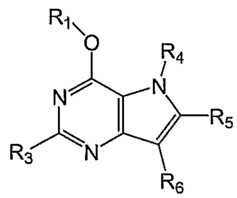
(Ia-O).

43. The method of claim 27, wherein said compound corresponds to Formula (Ia-S):



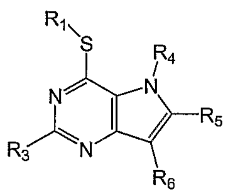
(Ia-S).

44. The method of claim 27, wherein said compound corresponds to Formula (Ib-O):



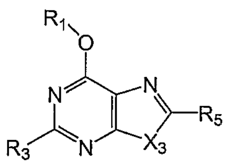
(Ib-O).

45. The method of claim 27, wherein said compound corresponds to Formula (Ib-S):



(Ib-S).

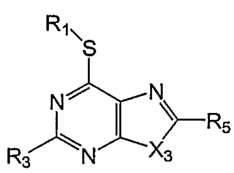
46. The method of claim 27, wherein said compound corresponds to Formula (IIa-O):



(IIa-O),

wherein X_3 is O, S, or NR_4.

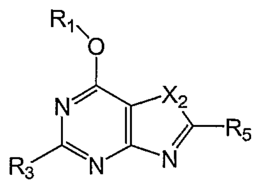
47. The method of claim 27, wherein said compound corresponds to Formula (IIa-S):



(IIa-S),

wherein X_3 is O, S, or NR_4.

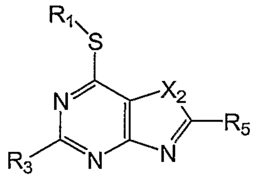
48. The method of claim 27, wherein said compound corresponds to Formula (IIb-O):



(IIb-O),

wherein X_2 is O, S, or NR_4.

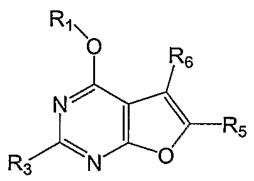
49. The method of claim 27, wherein said compound corresponds to Formula (IIb-S):



(IIb-S),

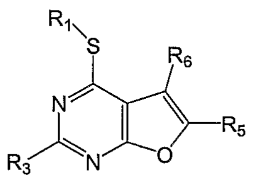
wherein X_2 is O, S, or NR_4.

50. The method of claim 27, wherein said compound corresponds to Formula (IIIa-O):



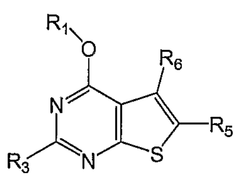
(IIIa-O).

51. The method of claim 27, wherein said compound corresponds to Formula (IIIa-S):



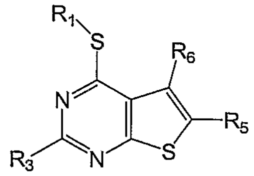
(IIIa-S).

52. The method of claim 27, wherein said compound corresponds to Formula (IIIb-O):



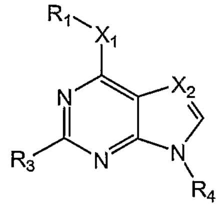
(IIIb-O).

53. The method of claim 27, wherein said compound corresponds to Formula (IIIb-S):



(IIIb-S).

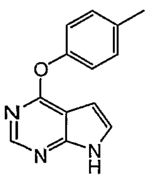
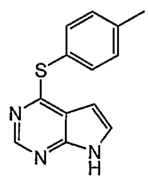
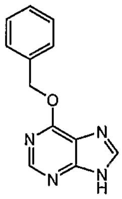
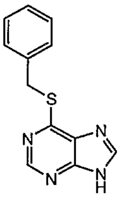
54. The method of claim 27, wherein said compound corresponds to Formula (A1):



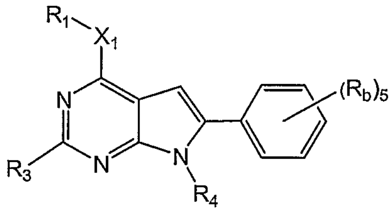
(A1),

wherein X_2 is N or CR_6.

55. The method of claim 54, wherein said compound is selected from the group consisting of:

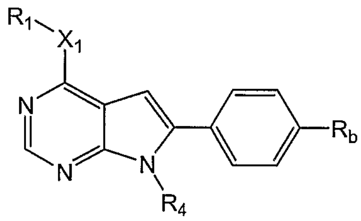
 ,  ,  , and  .

56. The method of claim 27, wherein said compound corresponds to Formula (A):



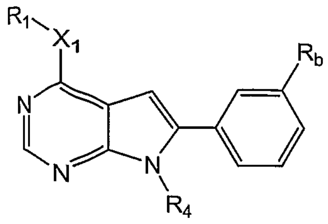
(A).

57. The method of claim 56, wherein said compound corresponds to Formula (B):



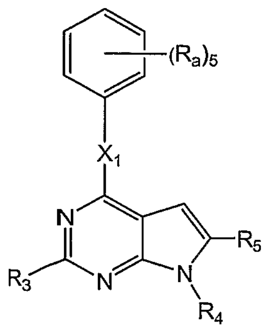
(B).

58. The method of claim 56, wherein said compound corresponds to Formula (C):



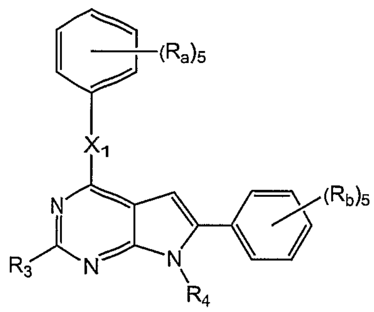
(C).

59. The method of claim 27, wherein said compound corresponds to Formula (D):



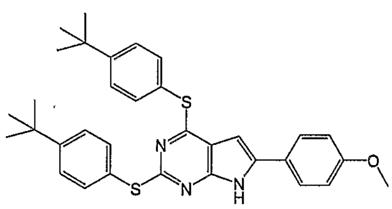
(D).

60. The method of claim 59, corresponding to Formula (E):



(E).

61. The method of claim 56, wherein said compound is selected from the group consisting of: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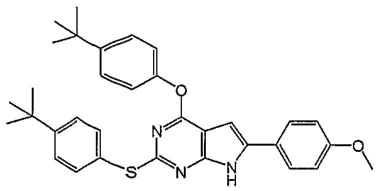
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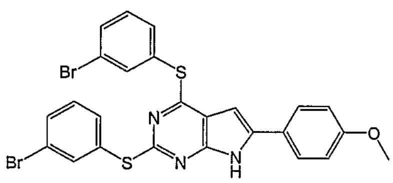
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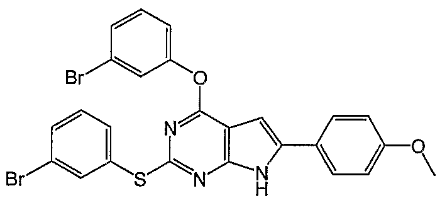
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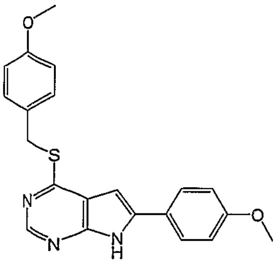
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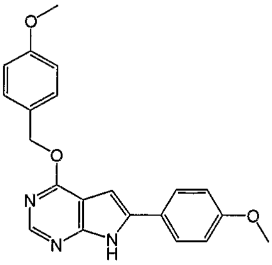
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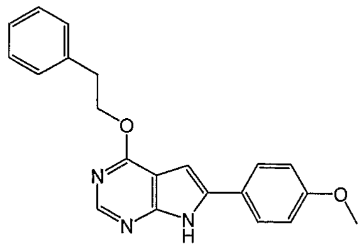
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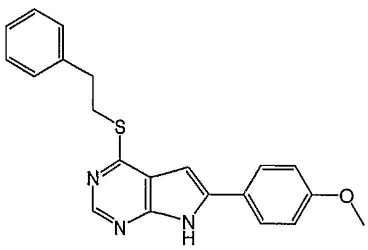
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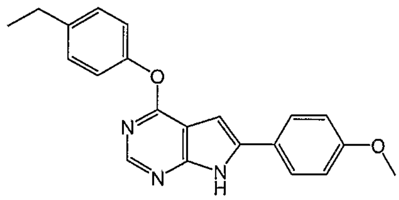
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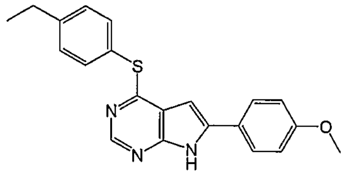
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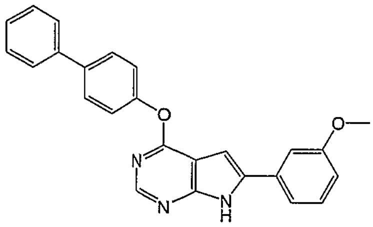
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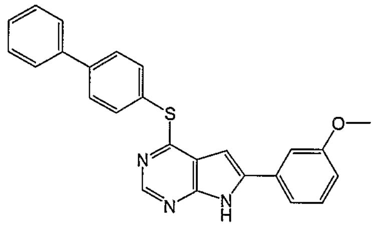
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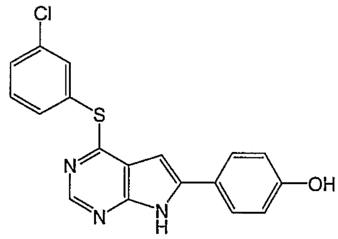
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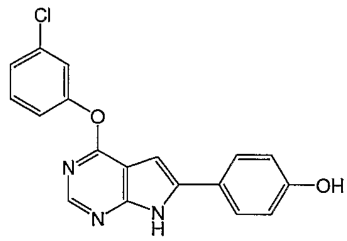
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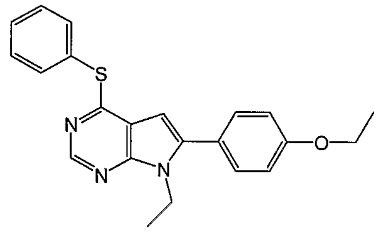
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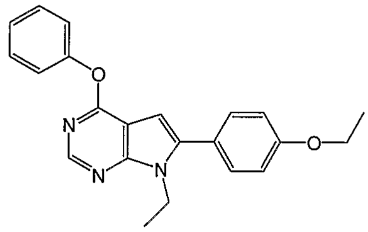
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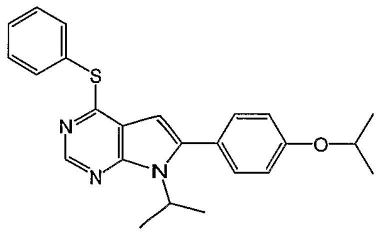
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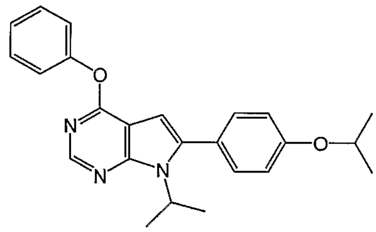
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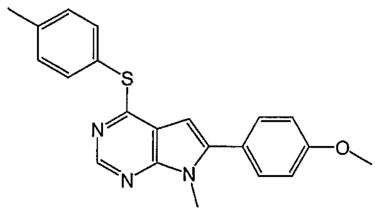
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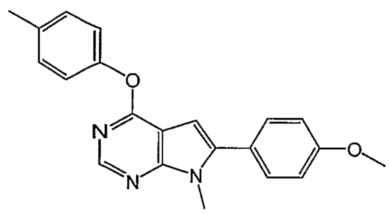
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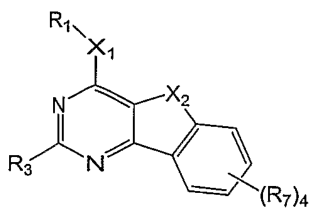
62. The method of claim 27, wherein X_2 is NR_4 and X_3 is CR_6.

63. The method of claim 62, wherein R_5 and R_6 are taken together to form an optionally substituted phenyl ring.

64. The method of claim 27, wherein said compound corresponds to Formula (IV):



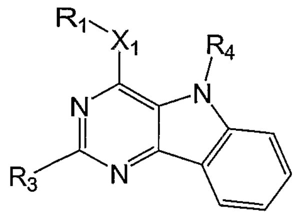
(IV),

wherein

X_2 is O, S, or NR_4; and

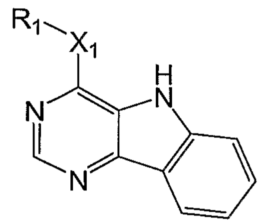
each R_7 is independently selected from the group consisting of H, halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, $-(C_1-C_4)$dialkylamine, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, and $-C(O)-(C_1-C_4)$alkoxy.

65. The method of claim 64, wherein said compound corresponds to Formula (F):



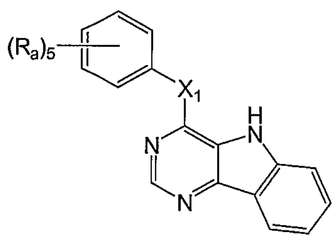
(F).

66. The method of claim 65, wherein said compound corresponds to Formula (G):



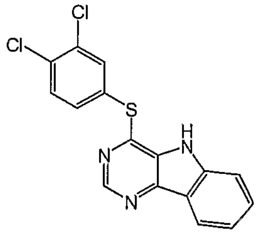
(G).

67. The method of claim 66, wherein said compound corresponds to Formula (H):

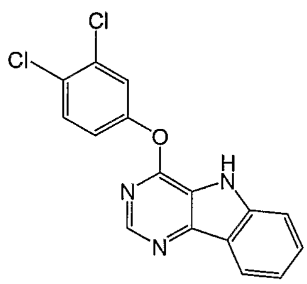


(H).

68. The method of claim 67, wherein said compound is selected from the group consisting of:



and



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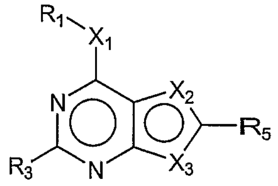
69. A method for modulating flt-3 activity comprising contacting flt-3 with an effective amount of a flt-3 modulating compound corresponding to Formula (I):



(I)

wherein:

a. X_1 is S or O;

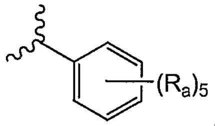
b. each of X_2 and X_3 is independently N, O, S, NR_4, or CR_6;

c. R_1 is $-(CHR_{1a})_z-R_{1b}$, where

i. each R_{1a} is independently H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, $-(C_1-C_4)$alkylamine, $-(C_1-C_4)$dialkylamine, or $-C(O)-(C_1-C_4)$alkoxy,

ii. z is 0, 1, 2, or 3, and

iii. R_{1b} is



,

where each R_a is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, -CN, $-L_1-OH$, $-L_1-NH_2$, $-L_1-(C_1-C_4)$alkyl, $-L_1-(C_3-C_6)$cycloalkyl, $-L_1-(C_1-C_4)$fluoroalkyl, $-L_1-(C_1-C_4)$alkoxy, $-L_1-(C_1-C_4)$alkylamine, $-L_1-(C_1-C_4)$dialkylamine and $-L_1$-phenyl, wherein L_1 is a bond, –C(O)–, or $-S(O)_2-$; or

R_{1b} is H, $-(C_1-C_4)$alkyl, an optionally substituted $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, or an optionally substituted 5-membered or 6-membered unsaturated heterocycle;

d. R_3 is H or $L_3-(CHR_{3a})_x-R_{3b}$, where

i. L_3 is a bond, NH, O, or S,

ii. R_{3a} is H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, $-(C_1-C_4)$alkylamine, or $-(C_1-C_4)$dialkylamine,

iii. x is 0, 1, 2, or 3, and

iv. R_{3b} is phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine;

e. R_4 is H or –$(CHR_{4a})_y$-R_{4b}, where

i. R_{4a} is H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, or -(C_1-C_4)dialkylamine;

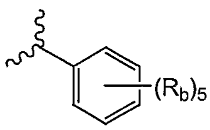
ii. y is 0, 1, 2, or 3, and

iii. R_{4b} is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5-membered or 6-membered unsaturated heterocycle; or

R_4 and R_5, taken together, form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

when X_2 is NR_4 and X_3 is CR_6, R_1 and R_4, taken together, form a 5- or 6-membered aromatic heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

f. R_5 is H or



, where each R_b is independently H, halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, or -C(O)-(C_1-C_4)alkoxy; and

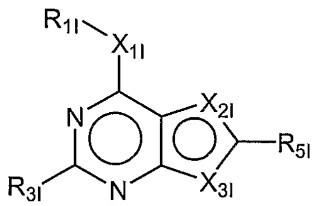
g. R_6 is H, heteroaryl, or phenyl, wherein the phenyl and the heteroaryl are optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

R_6 and R_5, taken together, form an aromatic carbocycle or heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine, or

when X_2 is CR_6 and X_3 is NR_4, R_6 and R_1, taken together, form a 5- or 6-membered aromatic heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine;

or pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

70. A method for treating a disease comprising administering to a subject in need thereof an effective amount of FLT-3 modulating compound corresponding to:



wherein:

a. X_{1I} is S or O;

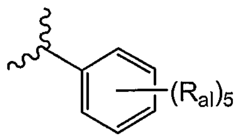
b. each of X_{2I} and X_{3I} is independently N, O, S, NR_{4I}, or CR_{6I};

c. R_{1I} is $-(CHR_{1aI})_{zI}-R_{1bI}$, where

i. each R_{1aI} is independently H, halogen or a substituted or unsubstituted moiety selected from alkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, alkoxy, alkylamine, dialkylamine, -C(O)OH, $-C(O)NH_2$, -C(O)-alkyl, -C(O)-haloalkyl, -C(O)-alkylamine, and -C(O)-alkoxy,

ii. z_I is 0, 1, 2, 3, or 4 and

iii. R_{1bI} is



,

where each R_{aI} is independently H, halogen, -CN, -OH, or a substituted or unsubstituted moiety selected from the group consisting of alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, heteroalkyl, $-L_1$-OH, $-L_1-NH_2$, $-L_1$-alkyl, $-L_1$-cycloalkyl, $-L_1$-haloalkyl, $-L_1$-alkoxy, $-L_1$-alkylamine, $-L_1$-dialkylamine and $-L_1$-phenyl, wherein L_1 is a bond, –C(O)-, or $-S(O)_2$-; or

R_{1bI} is H, alkyl, or a substituted or unsubstituted moiety selected from cycloalkyl, haloalkyl, and heterocycle;

d. R_{3I} is H or $L_{3I}-(CHR_{3aI})_x-R_{3bI}$, where

i. L_{3I} is a bond, NH, O, or S,

ii. R_{3aI} is H, alkyl, halogen, haloalkyl, alkoxy, alkylamine, or dialkylamine,

iii. x_I is 0, 1, 2, 3, or 4 and

iv. R_{3bI} is H or substituted or unsubstituted aryl or heteroaryl group;

e. R_{4I} is H or $-(CHR_{4aI})_{yI}-R_{4bI}$, where

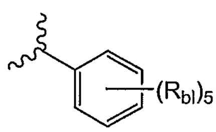
i. R_{4aI} is H, alkyl, halogen, haloalkyl, alkoxy, alkylamine, or dialkylamine;

ii. y_I is 0, 1, 2, 3, or 4 and

iii. R_{4bI} is a substituted or unsubstituted moiety selected from alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; or

R_{4I} and R_{5I}, taken together, form a substituted or unsubstitued heteroaryl moiety; or when X_{1I} is NR_{4I} and X_{2I} is CR_{6I}, R_{1I} and R_{4I}, taken together, form a substituted or unsubstituted heterocycle; or

f. R_{5I} is H or



, where each R_{bI} is independently H, halogen, -CN, -OH, -NH_2, or a substituted or unsubstituted moiety selected from alkyl, cycloalkyl, haloalkyl, alkoxy, alkylamine, dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-alkyl, -C(O)-haloalkyl, -C(O)-alkylamine, and -C(O)-alkoxy; and

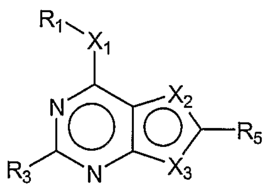
g. R_{6I} is H, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; or

R_{6I} and R_{5I}, taken together, form a substituted or unsubstituted aryl or heteroaryl moiety, or

when X_{1I} is CR_{6I} and X_{2I} is NR_{4I}, R_{6I} and R_{1I}, taken together, form a substituted or unsubstituted heterocycle;

or pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

71. A method for treating a disease comprising administering to a subject in need thereof an effective amount of an epidermal growth factor receptor modulating compound corresponding to Formula (I):



(I)

wherein:

a. X_1 is S or O;

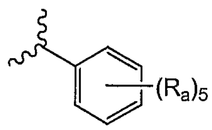
b. each of X_2 and X_3 is independently N, O, S, NR_4, or CR_6;

c. R_1 is $-(CHR_{1a})_z-R_{1b}$, where

i. each R_{1a} is independently H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, or -C(O)-(C_1-C_4)alkoxy,

ii. z is 0, 1, 2, or 3, and

iii. R_{1b} is



,

where each R_a is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)-, or -$S(O)_2$-; or

R_{1b} is H, -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, or an optionally substituted 5-membered or 6-membered unsaturated heterocycle;

d. R_3 is H or L_3-(CHR_{3a})$_x$-R_{3b}, where

i. L_3 is a bond, NH, O, or S,

ii. R_{3a} is H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, or -(C_1-C_4)dialkylamine,

iii. x is 0, 1, 2, or 3, and

iv. R_{3b} is phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine;

e. R_4 is H or –(CHR_{4a})$_y$-R_{4b}, where

i. R_{4a} is H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, or -(C_1-C_4)dialkylamine;

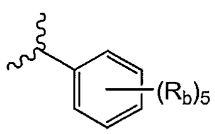
ii. y is 0, 1, 2, or 3, and

iii. R_{4b} is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5-membered or 6-membered unsaturated heterocycle; or

R_4 and R_5, taken together, form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

when X_2 is NR_4 and X_3 is CR_6, R_1 and R_4, taken together, form a 5- or 6-membered aromatic heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

f. R_5 is H or



, where each R_b is independently H, halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -

(C_1-C_4)alkylamine, $-(C_1-C_4)$dialkylamine, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-C_4)$alkyl, $-C(O)-(C_1-C_4)$fluoralkyl, $-C(O)-(C_1-C_4)$alkylamine, or $-C(O)-(C_1-C_4)$alkoxy; and

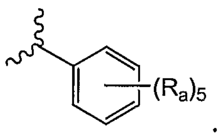
g. R_6 is H, heteroaryl, or phenyl, wherein the phenyl and the heteroaryl are optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine; or

R_6 and R_5, taken together, form an aromatic carbocycle or heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine, or

when X_2 is CR_6 and X_3 is NR_4, R_6 and R_1, taken together, form a 5- or 6-membered aromatic heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, and $-(C_1-C_4)$dialkylamine;

or a pharmaceutically acceptable salt, pharmaceutcaly acceptable N-oxide, pharmaceutically acitve metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

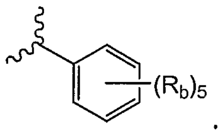
72. The method of claim 71, wherein R_1 of said compound is



73. The method of claim 72, wherein each R_a of said compound is independently H, halogen, (C_1-C_4)alkyl, or (C_1-C_4)alkoxy.

74. The method of claim 71, wherein R_3 of said compound is H.

75. The method of claim 71, wherein R_5 of said compound is H or



76. The method of claim 75, wherein each R_b of said compound is independently H, halogen, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, or -OH.

77. The method of claim 71, wherein X_1 of said compound is S.

78. The method of claim 71, wherein X_1 of said compound is O.

79. The method of claim 71, wherein X_2 of said compound is CR_6 and X_3 of said compound is NR_4.

80. The method of claim 71, wherein X_2 of said compound is CR_6 and X_3 of said compound is O.

81. The method of claim 71, wherein X_2 of said compound is CR_6 and X_3 of said compound is S.

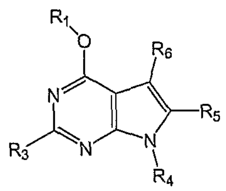
82. The method of claim 71, wherein X_2 of said compound is N and X_3 of said compound is NR_4.

83. The method of claim 71, wherein R_4 of said compound is H or $(C_1\text{-}C_4)$alkyl.

84. The method of claim 71, wherein R_6 of said compound is H.

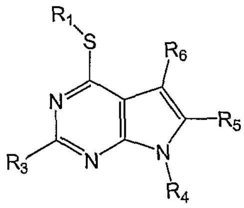
85. The method of claim 71, wherein each of R_6 and R_3 of said compound is H.

86. The method of claim 71, wherein said compound corresponds to Formula (Ia-O):



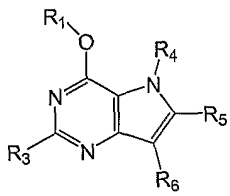
(Ia-O).

87. The method of claim 71, wherein said compound corresponds to Formula (Ia-S):



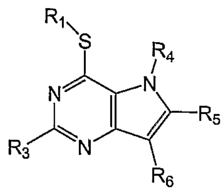
(Ia-S).

88. The method of claim 71, wherein said compound corresponds to Formula (Ib-O):



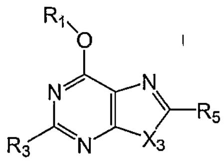
(Ib-O).

89. The method of claim 71, wherein said compound corresponds to Formula (Ib-S):



(Ib-S).

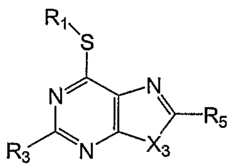
90. The method of claim 71, wherein said compound corresponds to Formula (IIa-O):



(IIa-O).

91. The method of claim 90, wherein X_3 of said compound corresponding to Formula (IIa-O) is O, S, or NR_4.

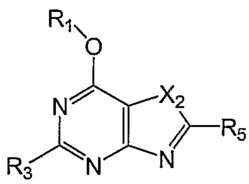
92. The method of claim 71, wherein said compound corresponds to Formula (IIa-S):



(IIa-S).

93. The method of claim 92, wherein X_3 of said compound corresponding to Formula (IIa-S) is O, S, or NR_4.

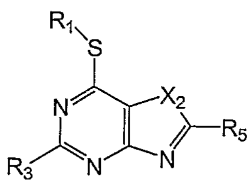
94. The method of claim 71, wherein said compound corresponds to Formula (IIb-O):



(IIb-O).

95. The method of claim 94, wherein X_3 of said compound corresponding to Formula (IIb-O) is O, S, or NR_4.

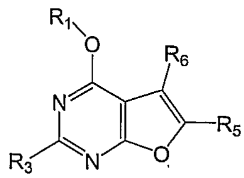
96. The method of claim 71, wherein said compound corresponds to Formula (IIb-S):



(IIb-S).

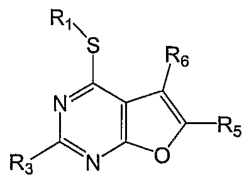
97. The method of claim 96, wherein X_3 of said compound corresponding to Formula (IIa) is O, S, or NR_4.

98. The method of claim 71, wherein said compound corresponds to Formula (IIIa-O):



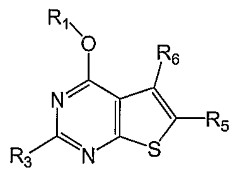
(IIIa-O).

99. The method of claim 71, wherein said compound corresponds to Formula (IIIa-S):



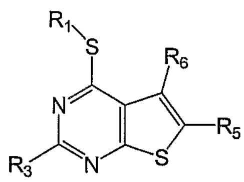
(IIIa-S).

100. The method of claim 71, wherein said compound corresponds to Formula (IIIb-O):



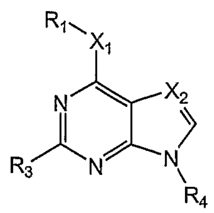
(IIIb-O).

101. The method of claim 71, wherein said compound corresponds to Formula (IIIb-S):



(IIIb-S).

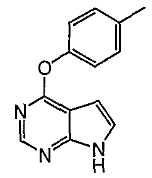
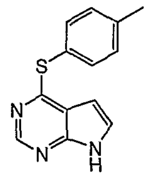
102. The method of claim 71, wherein said compound corresponds to Formula (A1):



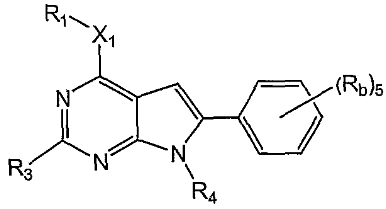
(A1).

103. The method of claim 71, wherein X_2 of said compound corresponding to Formula (A1) is N or CR_6.

104. The method of claim 103, wherein said compound is selected from the group consisting of:

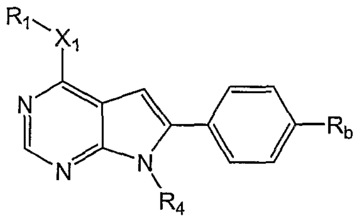
 and  .

105. The method of claim 71, wherein said compound corresponds to Formula (A):



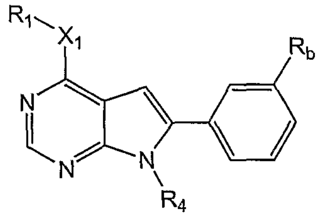
(A).

106. The method of claim 105, wherein said compound corresponds to Formula (B):



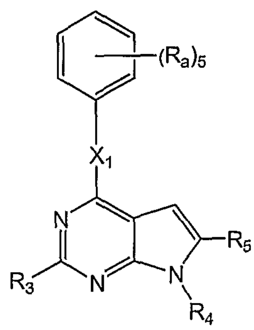
(B).

107. The method of claim 105, wherein said compound corresponds to Formula (C):



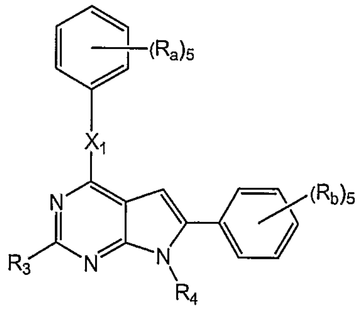
(C).

108. The method of claim 71, wherein said compound corresponds to Formula (D):



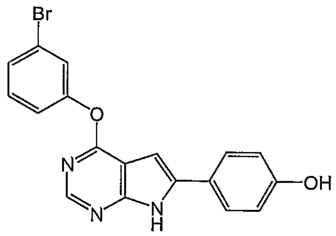
(D).

109. The compound of claim 108, corresponding to Formula (E):



(E).

110. The method of claim 109, wherein said compound is selected from the group consisting of: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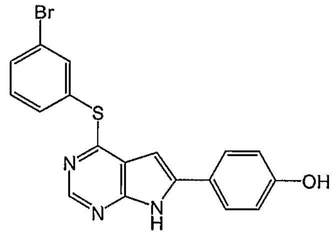
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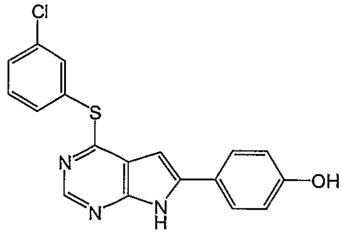
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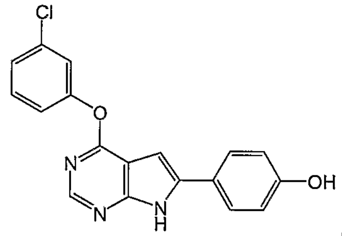
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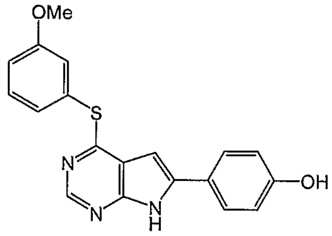
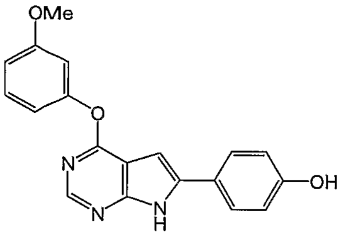
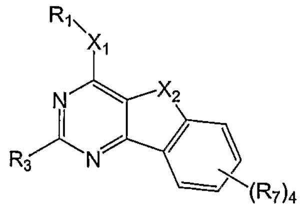

, and

.

111. The method of claim 71, wherein X_2 is NR_4 and X_3 is CR_6.

112. The method of claim 111, wherein R_5 and R_6 are taken together to form an optionally substituted phenyl ring.

113. The method of claim 71, wherein said compound corresponds to Formula (IV):



(IV),

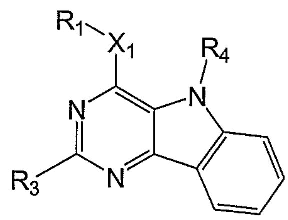
wherein

X_2 is O, S, or NR_4; and

each R_7 is independently selected from the group consisting of H, halogen, -CN, -OH, $-NH_2$, $-(C_1-C_4)$alkyl, $-(C_3-C_6)$cycloalkyl, $-(C_1-C_4)$fluoroalkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$alkylamine, $-(C_1-C_4)$dialkylamine, -C(O)OH, $-C(O)-NH_2$, $-C(O)-(C_1-$

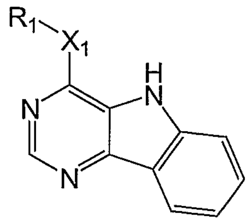
C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, and -C(O)-(C_1-C_4)alkoxy.

114. The method of claim 113, wherein said compound corresponds to Formula (F):



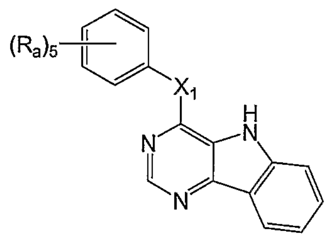
(F).

115. The method of claim 114, wherein said compound corresponds to Formula (G):



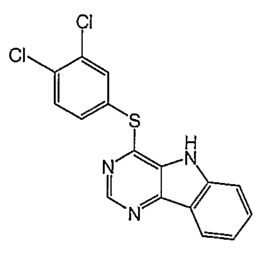
(G).

116. The method of claim 115, wherein said compound corresponds to Formula (H):

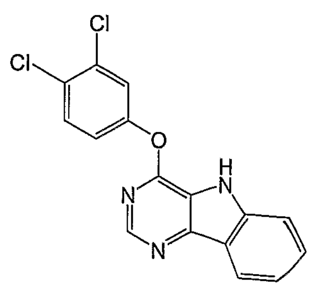


(H).

117. The method of claim 116, wherein said compound is selected from the group consisting of:

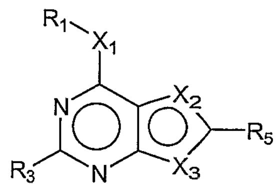


and



.

118. A method for treating a disease comprising administering to a subject in need thereof an effective amount of an EGFR kinase modulating compound corresponding to Formula (I):



(I)

wherein:

a. X_1 is S or O;

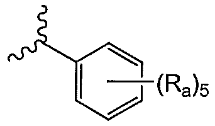
b. each of X_2 and X_3 is independently N, O, S, NR_4, or CR_6;

c. R_1 is $-(CHR_{1a})_z-R_{1b}$, where

i. each R_{1a} is independently H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, or -C(O)-(C_1-C_4)alkoxy,

ii. z is 0, 1, 2, or 3, and

iii. R_{1b} is



,

where each R_a is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, -CN, -L_1-OH, -L_1-NH_2, -L_1-(C_1-C_4)alkyl, -L_1-(C_3-C_6)cycloalkyl, -L_1-(C_1-C_4)fluoroalkyl, -L_1-(C_1-C_4)alkoxy, -L_1-(C_1-C_4)alkylamine, -L_1-(C_1-C_4)dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)-, or -$S(O)_2$-; or

R_{1b} is H, -(C_1-C_4)alkyl, an optionally substituted -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, or an optionally substituted 5-membered or 6-membered unsaturated heterocycle;

d. R_3 is H or $L_3-(CHR_{3a})_x-R_{3b}$, where

i. L_3 is a bond, NH, O, or S,

ii. R_{3a} is H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, or -(C_1-C_4)dialkylamine,

iii. x is 0, 1, 2, or 3, and

iv. R_{3b} is phenyl, optionally substituted with 1-2 substituents independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -$(C_1-$

C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine;

e. R_4 is H or –$(CHR_{4a})_y$-R_{4b}, where

i. R_{4a} is H, (C_1-C_4)alkyl, F, (C_1-C_4)fluoroalkyl, (C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, or -(C_1-C_4)dialkylamine;

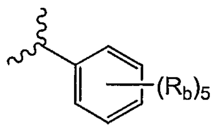
ii. y is 0, 1, 2, or 3, and

iii. R_{4b} is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5-membered or 6-membered unsaturated heterocycle; or

R_4 and R_5, taken together, form a 5- or 6-membered heterocyclic aromatic ring structure, optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

when X_2 is NR_4 and X_3 is CR_6, R_1 and R_4, taken together, form a 5- or 6-membered aromatic heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

f. R_5 is H or



, where each R_b is independently H, halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, -(C_1-C_4)dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)fluoralkyl, -C(O)-(C_1-C_4)alkylamine, or -C(O)-(C_1-C_4)alkoxy; and

g. R_6 is H, heteroaryl, or phenyl, wherein the phenyl and the heteroaryl are optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -(C_1-C_4)alkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine; or

R_6 and R_5, taken together, form an aromatic carbocycle or heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-

C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine, or

when X_2 is CR_6 and X_3 is NR_4, R_6 and R_1, taken together, form a 5- or 6-membered aromatic heterocycle optionally substituted with 1-2 moieties independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -(C_1-C_4)alkyl, -(C_3-C_6)cycloalkyl, -(C_1-C_4)fluoroalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)alkylamine, and -(C_1-C_4)dialkylamine;

or a pharmaceutically acceptable salt, pharmaceutcaly acceptable N-oxide, pharmaceutically acitve metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

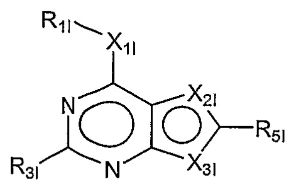
119. The method of claim 118, wherein the contacting occurs in vivo.

120. The method of claim 119, wherein the contacting occurs within a human patient, wherein the human patient has an EGFR-mediated disease or condition.

121. The method of claim 120, wherein the effective amount is an amount effective for treating an EGFR-mediated disease or condition within the body of the person.

122. The method of claim 121 wherein the EGFR-mediated disease or condition is selected from the group consisting of blood vessel growth, cancer, benign hyperplasia, keloid formation, and psoriasis.

123. A method for treating a disease comprising administering to a subject in need thereof an effective amount of an epidermal growth factor receptor modulating compound corresponding to:



wherein:

a. X_{1I} is S or O;

b. each of X_{2I} and X_{3I} is independently N, O, S, NR_{4I}, or CR_{6I};

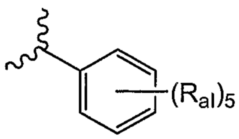
c. R_{1I} is –(CHR_{1aI})$_{zI}$-R_{1bI}, where

i. each R_{1aI} is independently H, halogen or a substituted or unsubstituted moiety selected from alkyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkenyl, alkynyl, alkoxy, alkylamine, dialkylamine, -

C(O)OH, -C(O)NH_2, -C(O)-alkyl, -C(O)-haloalkyl, -C(O)-alkylamine, and -C(O)-alkoxy,

ii. z_I is 0, 1, 2, 3, or 4 and

iii. R_{1bI} is



,

where each R_{aI} is independently H, halogen, -CN, -OH, or a substituted or unsubstituted moiety selected from the group consisting of alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, heteroalkyl, -L_1-OH, -L_1-NH_2, -L_1-alkyl, -L_1-cycloalkyl, -L_1-haloalkyl, -L_1-alkoxy, -L_1-alkylamine, -L_1-dialkylamine and –L_1-phenyl, wherein L_1 is a bond, –C(O)-, or -S$(O)_2$-; or

R_{1bI} is H, alkyl, or a substituted or unsubstituted moiety selected from cycloalkyl, haloalkyl, and heterocycle;

d. R_{3I} is H or L_{3I}-$(CHR_{3aI})_x$-R_{3bI}, where

i. L_{3I} is a bond, NH, O, or S,

ii. R_{3aI} is H, alkyl, halogen, haloalkyl, alkoxy, alkylamine, or dialkylamine,

iii. x_I is 0, 1, 2, 3, or 4 and

iv. R_{3bI} is H or substituted or unsubstituted aryl or heteroaryl group;

e. R_{4I} is H or –$(CHR_{4aI})_{yI}$-R_{4bI}, where

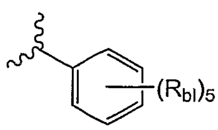
i. R_{4aI} is H, alkyl, halogen, haloalkyl, alkoxy, alkylamine, or dialkylamine;

ii. y_I is 0, 1, 2, 3, or 4 and

iii. R_{4bI} is a substituted or unsubstituted moiety selected from alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; or

R_{4I} and R_{5I}, taken together, form a substituted or unsubstitued heteroaryl moiety; or when X_{1I} is NR_{4I} and X_{2I} is CR_{6I}, R_{1I} and R_{4I}, taken together, form a substituted or unsubstituted heterocycle; or

f. R_{5I} is H or



, where each R_{bI} is independently H, halogen, -CN, -OH, -NH_2, or a substituted or unsubstituted moiety selected from alkyl, cycloalkyl, haloalkyl, alkoxy, alkylamine, dialkylamine, -C(O)OH, -C(O)-NH_2, -C(O)-alkyl, -C(O)-haloalkyl, -C(O)-alkylamine, and -C(O)-alkoxy; and

g. R_{6I} is H, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; or

R_{6I} and R_{5I}, taken together, form a substituted or unsubstituted aryl or heteroaryl moiety, or

when X_{1I} is CR_{6I} and X_{2I} is NR_{4I}, R_{6I} and R_{1I}, taken together, form a substituted or unsubstituted heterocycle;

or a pharmaceutically acceptable salt, pharmaceutcaly acceptable N-oxide, pharmaceutically acitve metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

124. The method of claim 123, wherein the disease is selected from the group consisting of blood vessel growth, cancer, benign hyperplasia, keloid formation, and psoriasis.