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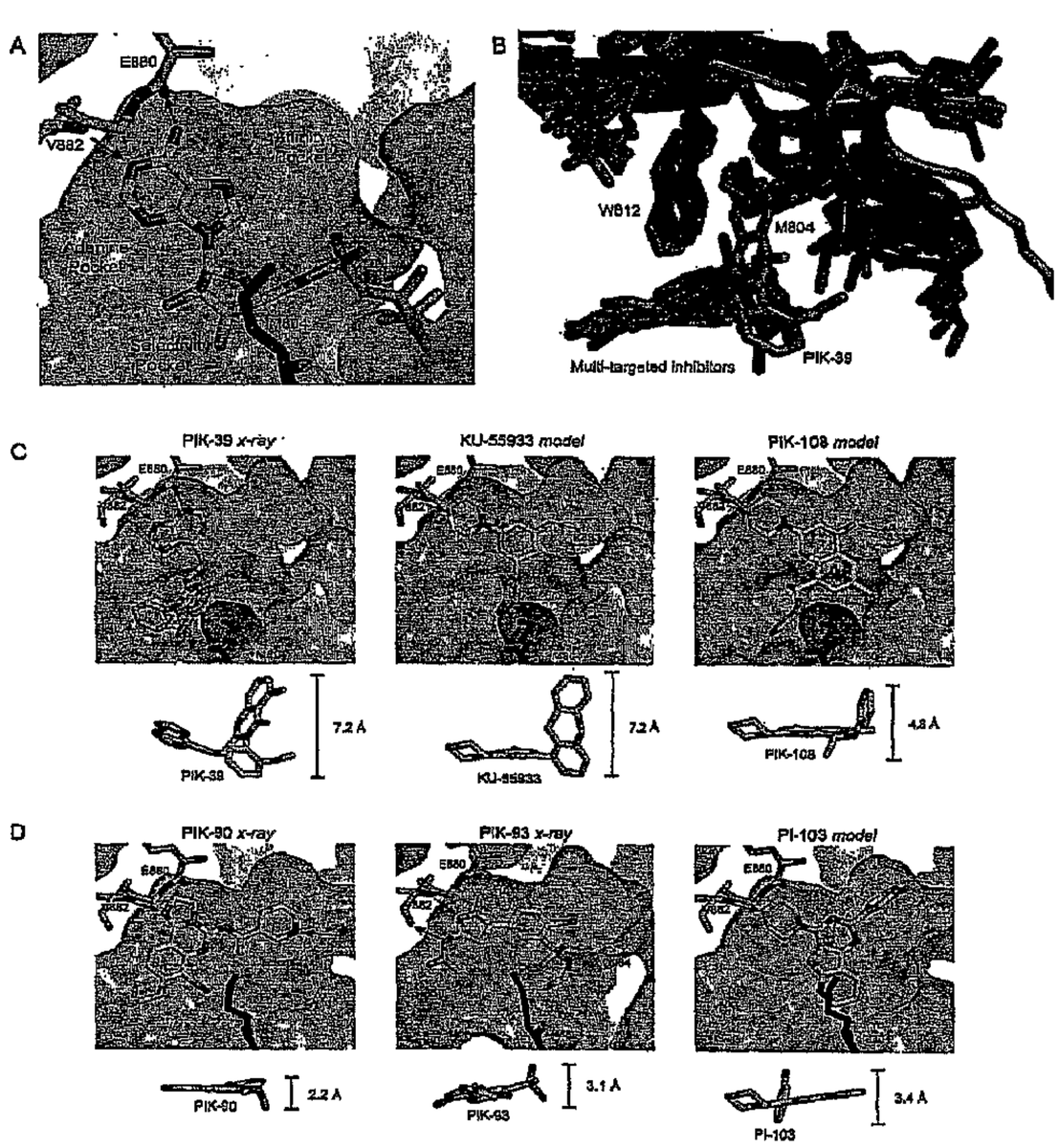
(54) **Titre : ANTAGONISTES DE LA KINASE**
(54) **Title: KINASE ANTAGONISTS**



(57) **Abrégé/Abstract:**
The present invention provides novel compounds that are antagonists of PI3 kinase, PI3 kinase and tryosine kinase, PDKinase and mTOR, or PI3Kinase, mTOR and tryosine kinase.

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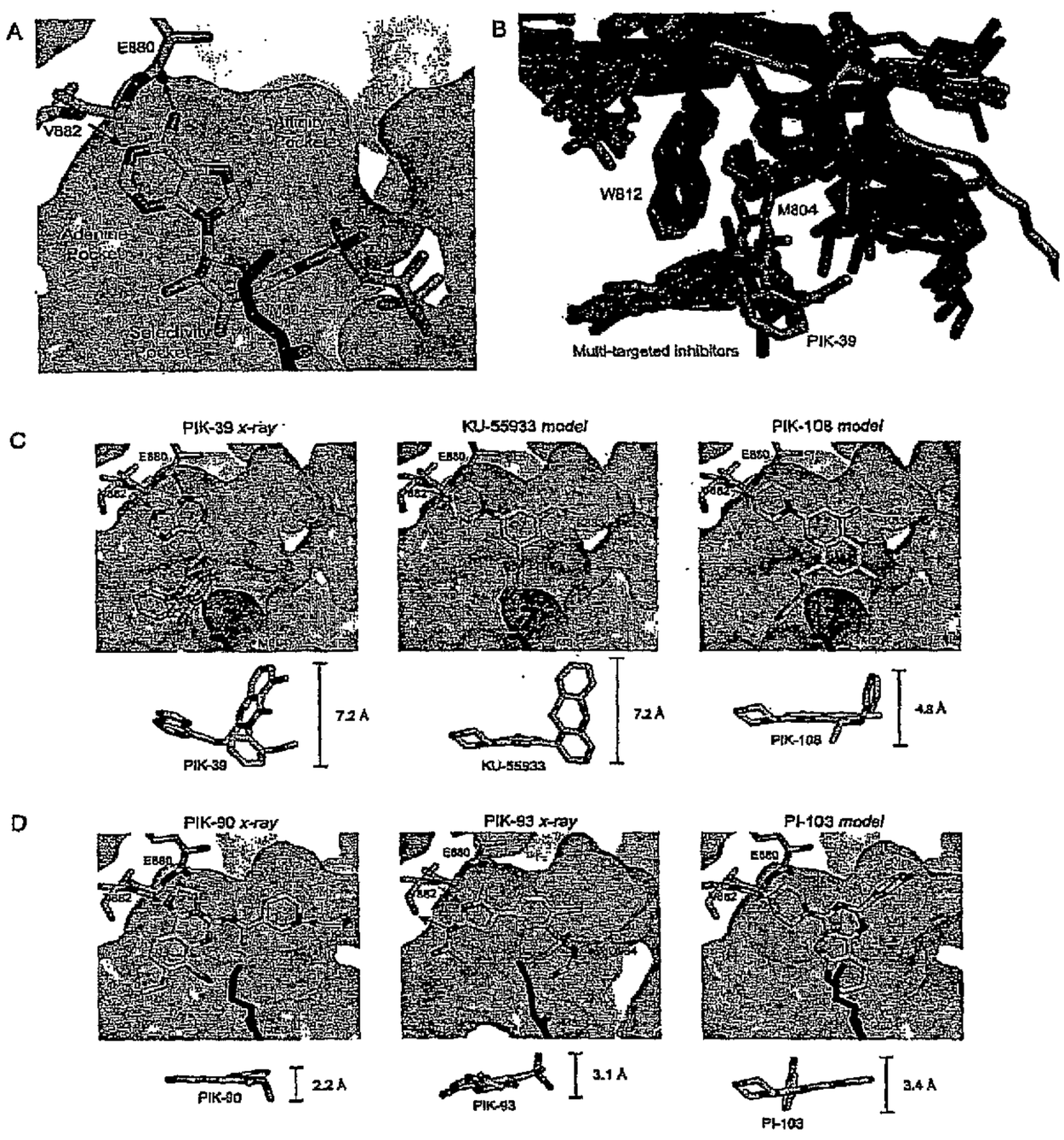

FIG. 2

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KINASE ANTAGONISTS

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STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] The present invention was supported by a grant from the National Institutes of Health (AI44009). The United States Government has certain rights to the invention.

BACKGROUND OF THE INVENTION

[0003] Phosphoinositide 3-kinases (PI3-Ks) catalyze the synthesis of the phosphatidylinositol (PI) second messengers PI(3)P, PI(3,4)P2, and PI(3,4,5)P3 (PIP3) (Fruman et al., 1998). In the appropriate cellular context, these three lipids control diverse physiological processes including cell growth, survival, differentiation and chemotaxis (Katso et al., 2001). The PI3-K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation (Katso et al., 2001). The class I PI3-Ks (p110α, p110β, p110δ, and p110γ) are activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as the Akt/PDKl pathway, the Tec family kinases, and the Rho family GTPases. The class II and III PI3-Ks play a key role in intracellular trafficking through the synthesis of PI(3)P and PI(3,4)P2. The PIKKs are protein kinases that control cell growth (mTORCl) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

[0004] The importance of these enzymes in diverse pathophysiology has made the PI3-K family the focus of intense interest as a new class of drug targets (Ward et al., 2003). This interest has been fueled by the recent discovery that p110α is frequently mutated in primary tumors (Samuels et al., 2004) and evidence that the lipid phosphatase PTEN, an inhibitor of PI3-K signaling, is a commonly inactivated tumor suppressor (Cantley and Neel, 1999). Efforts are underway to develop small molecule PI3-K inhibitors for the treatment of inflammation and autoimmune disease (p110δ, p110γ, and mTOR), thrombosis (p110β), viral infection (the PIKKs) and cancer (p110α, mTOR, and others). Recently, the first selective

inhibitors of these enzymes have been reported (Camps et al., 2005; Condliffe et al., 2005; Jackson et al., 2005; Knight et al., 2004; Lau et al., 2005; Sadhu et al., 2003).

[0005] Protein tyrosine kinases, protein serine/threonine kinases, and lipid kinases are distinct classes of proteins that play critical roles in regulation and proliferation of cellular activity. Small molecules that inhibit these protein classes have the potential to disrupt dysfunctional/pathological pathways at two distinct points. For example, signaling through tyrosine kinase receptors is known to be disregulated in several types of cancer. This signaling pathway involves downstream proteins such as PI3 Kinase. Signaling through the serine/threonine protein kinase mTOR (also known as the mammalian target of rapamycin) is known to regulate cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. Disruption of the mTOR pathway is implicated as a contributing factor to various human disease processes, especially various types of cancer. An inhibitor that blocks activity of protein tyrosine kinase and PI3 Kinase, mTOR and PI3Kinase, or mTOR, protein tyrosine kinase and PI3 Kinase, has the potential to stop the aberrant signaling at two or three different levels. Double or triple inhibition by a small molecule may magnify drug potency, increasing the compound's therapeutic potential.

[0006] The present invention meets these and other needs in the art by providing a new class of PI3 kinase antagonists, PI3 kinase and tryosine kinase antagonists, PI3Kinase and mTOR antagonists, and PI3Kinase, mTOR and tryosine kinase antagonists.

BRIEF SUMMARY OF THE INVENTION

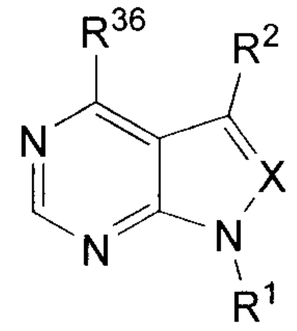
[0007] It has been discovered that certain compounds described herein are potent antagonists of PI3 kinase, PI3 kinase and tryosine kinase, PI3Kinase and mTOR, or PI3Kinase, mTOR and tryosine kinase.

[0008] In one aspect, the present invention provides novel kinase antagonists that are PI3-Kinase affinity pocket binding antagonists (e.g. a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonist or a PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonist). The PI3-Kinase affinity pocket binding antagonist is a compound containing a PI3-Kinase affinity pocket binding moiety. The PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists of the present invention are substituted pyrazolopyrimidine compounds containing a PI3-Kinase affinity pocket binding moiety. Likewise, the PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonists of the present invention are

substituted pyrrolopyrimidine compounds containing a PI3-Kinase affinity pocket binding moiety.

[0009] In another aspect, the present invention provides the novel kinase antagonists of Formula (I), defined below.

[0009A] Various embodiments of this invention relate to a compound having the formula:



wherein, X is =N-; R^1 is hydrogen, R^3-substituted or unsubstituted alkyl, R^3-substituted or unsubstituted heteroalkyl, R^3-substituted or unsubstituted cycloalkyl, R^3-substituted or unsubstituted heterocycloalkyl, or R^3-substituted or unsubstituted heteroaryl; R^2 is R^4-substituted heteroaryl; R^3 is halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, $=N-NH_2$, $-NR^{10}-C(O)R^{11}$, $-NR^{12}-C(O)-OR^{13}$, $-C(O)NR^{14}R^{15}$, $-NR^{16}S(O)_2R^{17}$, $-S(O)_2NR^{18}$, R^{19}-substituted or unsubstituted alkyl, R^{19}-substituted or unsubstituted heteroalkyl, R^{19}-substituted or unsubstituted cycloalkyl, R^{19}-substituted or unsubstituted heterocycloalkyl, R^{19}-substituted or unsubstituted aryl, or R^{19}-substituted or unsubstituted heteroaryl, wherein n is an integer from 0 to 2; R^{36} is NH_2; R^4 is halogen, -CN, $-OR^{20}$, or $-NR^{22}R^{23}$; R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} are independently hydrogen, R^{35}-substituted or unsubstituted alkyl, R^{35}-substituted or unsubstituted heteroalkyl, unsubstituted cycloalkyl, R^{35}-substituted or unsubstituted heterocycloalkyl, R^{35}-substituted or unsubstituted aryl, or R^{35}-substituted or unsubstituted heteroaryl; R^{20}, R^{22} and R^{23} are independently hydrogen, unsubstituted alkyl or unsubstituted heteroalkyl; R^{19} and R^{35} are independently hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl; and $R^{37}$and R^{38} are hydrogen, as well as use of a compound as a kinase antagonist as described herein. Some embodiments involve relate to use of a compound in treatment of a disorder or condition as described herein or in manufacture of a medicament for such treatment.

[0010] In another aspect, the present invention provides methods of decreasing the catalytic activity of a PI3 Kinase (e.g. a p110δ kinase). The method includes the step of contacting said

PI3 kinase with an activity decreasing amount of a compound of the present invention (i.e. a PI3-Kinase affinity pocket binding antagonists, or an antagonist of Formula I).

[0011] In another aspect, the present invention provides a method of treating a condition mediated by PI3 kinase activity, PI3 Kinase activity and tyrosine Kinase Activity, PI3 Kinase activity and mTOR activity, or PI3 Kinase activity, tyrosine kinase activity, and mTOR activity in a subject in need of such treatment. The method includes administering to the subject a therapeutically effective amount of a compound of the present invention (i.e. a PI3-Kinase affinity pocket binding antagonists, or an antagonist of Formula T).

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 illustrates structures of representative compounds from eleven chemotypes of PI3-K inhibitors.

[0013] Figure 2 illustrates structures of isoform-selective PI3-K inhibitors. A. Structure of ATP in the active site of p110γ, highlighting different regions of the ATP binding pocket. B. An alignment of all reported PI3-K inhibitor co-crystal structures. Met 804 adopts an up conformation in all structures except PIK-39. C. Structures or models of isoform-selective PI3-K inhibitors bound to p110γ. D. Structures or models of multi-targeted PB-K inhibitors bound to p110γ.

[0014] Figure 3 illustrates the probing of selectivity and an the PI3-Kinase affinity pocket. A. The structure of PIK-39 bound to p110γ suggests a model for the binding of IC87114. PIK-293 and PIK-294 are pyrazolopyrimidine analogs of IC87114. PIK-294 projects a *m*-phenol into the affinity pocket, and this compound is more potent against the class I PI3-Ks. B. (Left) Ratio of IC50 values between mutant and wild-type for p110δ inhibitors and p110α/multi-targeted inhibitors. (Center) Dose response curves for binding of two p110δ inhibitors to wild-type, M752I, and M752V p110δ (Right) Models suggesting the impact of

the M752I and M752V mutations in p110δ on the binding of the different classes of inhibitors.

[0015] Figure 4. Structures of additional PI3-K inhibitors and inactive analogs.

[0016] Figure 5. IC50 values (μM) for selected PI3-K inhibitors against lipid kinases.

[0017] Figure 6. Inhibition of protein kinases by PI3-K inhibitors. Values represent % activity remaining in the presence of 10 μM inhibitor. Values are average of triplicate measurements. IC50 values are in parenthesis where appropriate (μM).

[0018] Figure 7 sets forth the sequence of a human p110δ kinase.

[0019] Figure 8 sets forth the sequence of a human p110γ kinase.

[0020] Figure 9 sets forth the sequence of a human p110α kinase.

[0021] Figure 10 sets forth the sequence of a human p110β kinase.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0022] Abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0023] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0024] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e. unbranched) or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups

include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers.

[0025] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkyl, as exemplified, but not limited, by $-CH_2CH_2CH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2C\equiv CCH_2-$, $-CH_2CH_2CH(CH_2CH_2CH_3)CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0026] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of at least one carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and –CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxo, alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula –C(O)OR'- represents both –C(O)OR'- and –R'OC(O)-. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl

and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0027] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1 –(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 –piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

[0028] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0029] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (preferably from 1 to 3 rings) which are fused together (e.g. naphthyl) or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 6-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-

quinolyl, and 6-quinolyl. Thus, the term "heteroaryl" include fused ring structures in which at least one ring includes at least two double bonds. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent radicals of aryl and heteroaryl, respectively.

[0030] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxo, arylthioxo, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like). However, the term "haloaryl," as used herein is meant to cover only aryls substituted with one or more halogens.

[0031] Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" referrers to a carbon or heteroatom.

[0032] The term "oxo" as used herein means an oxygen that is double bonded to a carbon atom.

[0033] Each of above terms (*e.g.*, "alkyl," "heteroalkyl," "cycloalkyl, and "heterocycloalkyl", "aryl," "heteroaryl" as well as their divalent radical derivatives) are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0034] Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent and divalent derivative radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$,-C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"C(O)OR', -NR-C(NR'R")=NR"', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -CN and $-NO_2$ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R", R"' and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. As used herein, an "alkoxy" group is an alkyl attached to the remainder of the molecule through a divalent oxygen radical. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R""" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, -CF_3 and –CH_2CF_3) and acyl (*e.g.*, -$C(O)CH_3$, -$C(O)CF_3$, -$C(O)CH_2OCH_3$, and the like).

[0035] Similar to the substituents described for alkyl radicals above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, -OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"C(O)OR', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"", -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and –NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxo, and fluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R", R"' and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R"" groups when more than one of these groups is present.

[0036] Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently –NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently –CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C''R''')_d-$, where s and d are independently integers of from 0 to 3, and X' is –O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', R" and R"' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0037] As used herein, the term "heteroatom" or "ring heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0038] An "aminoalkyl" as used herein refers to an amino group covalently bound to an alkylene linker. The amino group is -NR'R", wherein R' and R" are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0039] A "substituent group," as used herein, means a group selected from the following moieties:

[0040] (A) -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0041] (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0042] (i) oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0043] (ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0044] (a) oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0045] (b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0046] A "size-limited substituent" or " size-limited substituent group," as used herein means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_4-C_8 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

[0047] A "lower substituent" or " lower substituent group," as used herein means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5-C_7 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0048] The compounds of the present invention may exist as salts. The present invention includes such salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived organic acids like

acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0049] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0050] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0051] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0052] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0053] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0054] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0055] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0056] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0057] The term "pharmaceutically acceptable salts" is meant to include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the

salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0058] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0059] The terms "a," "an," or "a(n)", when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

[0060] Description of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0061] The terms "treating" or "treatment" refers to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective

parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, the certain methods presented herein successfully treat cancer by decreasing the incidence of cancer and or causing remission of cancer.

[0062] An "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease. An "effective amount" may also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) a disease, or reducing the likelihood of the onset (or reoccurrence) of a disease or its symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An "activity decreasing amount," as used herein, refers to an amount of antagonist required to decrease the activity of an enzymne relateive to the absence of the antagonist. A "function disrupting amount," as used herein, refers to the amount of antagonist required to disrupt the function of an osteoclast or leukocyte relative to the absence of the antagonist.

[0063] As used herein, the "antagonist" or "the compound of the present invention" refers to a compound of Formula (I), or a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists, or a PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonist). A "compound of Formula (I)" includes the compounds of Formulae (I)-(X) as described below.

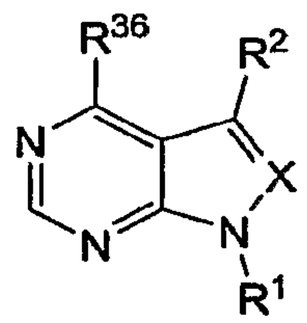
II. Kinase Antagonists

[0064] In one aspect, the present invention provides novel kinase antagonists. The kinase antagonists may be a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity

pocket binding pyrazolopyrimidine antagonist, or PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonist) or a compound of Formula (I). The PI3-Kinase affinity pocket binding antagonists of the present invention are compounds containing a PI3-Kinase affinity pocket binding moiety. The PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists of the present invention are substituted pyrazolopyrimidine compounds containing a PI3-Kinase affinity pocket binding moiety. Likewise, the PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonists of the present invention are substituted pyrrolopyrimidine compounds containing a PI3-Kinase affinity pocket binding moiety.

[0065] The PI3-Kinase affinity pocket binding moiety is a substituent which, upon contacting a p110α, p110β, p110γ, or p110δ kinase, fills space within the corresponding PI3-Kinase affinity pocket. In some embodiments, the PI3-Kinase affinity pocket binding moiety displaces at least one water molecule within the PI3-Kinase affinity pocket. The PI3-Kinase affinity pocket binding moiety may also interact with one or more amino acids that from part of the PI3-Kinase affinity pocket. A description of the PI3-Kinase affinity pocket and methods of determining whether a substituent fills space within the PI3-Kinase affinity pocket are set forth below.

[0066] In some embodiments, the kinase antagonist of the present invention has the formula:

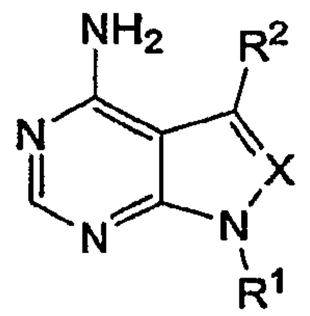


(I).

In Formula (I), R^1 is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^2 is halogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X is =N- or =C(H)-. R^{36} is halogen, $-NR^{37}R^{38}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

R^{37} and R^{38} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^{37} and R^{38} are independently hydrogen, or unsubstituted alkyl. R^2 may be a PI3-Kinase affinity pocket binding moiety.

[0067] In some embodiments, R^{36} is $-NH_2$. Thus, the kinase antagonist may have the formula:



(II).

[0068] In some embodiments, R^1, R^2, and X are as defined above in Formula (I). In certain embodiments, X is =N-.

[0069] In some embodiments of Formulae (I) and (II), R^1 is hydrogen, R^3-substituted or unsubstituted alkyl, R^3-substituted or unsubstituted heteroalkyl, R^3-substituted or unsubstituted cycloalkyl, R^3-substituted or unsubstituted heterocycloalkyl, R^3-substituted or unsubstituted aryl, or R^3-substituted or unsubstituted heteroaryl. R^2 is halogen, R^4-substituted aryl, or substituted or unsubstituted heteroaryl;

[0070] R^3 is halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, $=N-NH_2$, $-NR^{10}-C(O)R^{11}$, $-NR^{12}-C(O)-OR^{13}$, $-C(O)NR^{14}R^{15}$, $-NR^{16}S(O)_2R^{17}$, $-S(O)_2NR^{18}$, R^{19}-substituted or unsubstituted alkyl, R^{19}-substituted or unsubstituted heteroalkyl, R^{19}-substituted or unsubstituted cycloalkyl, R^{19}-substituted or unsubstituted heterocycloalkyl, R^{19}-substituted or unsubstituted aryl, or R^{19}-substituted or unsubstituted heteroaryl. Then symbol n is an integer from 0 to 2.

[0071] R^4 is halogen, -CN, $-OR^{20}$, $-S(O)_qR^{21}$, $-NR^{22}R^{23}$, $-C(O)R^{24}$, $=N-NH_2$, $-NR^{25}-C(O)R^{26}$, $-NR^{27}-C(O)-OR^{28}$, $-C(O)NR^{29}R^{30}$, $-NR^{31}S(O)_2R^{32}$, $-S(O)_2NR^{33}$, R^{34}-substituted or unsubstituted alkyl, R^{34}-substituted or unsubstituted heteroalkyl, R^{34}-substituted or unsubstituted cycloalkyl, R^{34}-substituted or unsubstituted heterocycloalkyl, R^{34}-substituted or unsubstituted aryl, or R^{34}-substituted or unsubstituted heteroaryl. The symbol q represents an integer from 0 to 2.

[0072] R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, and R^{33} are independently hydrogen, R^{35}-substituted or unsubstituted alkyl, R^{35}-substituted or unsubstituted heteroalkyl, unsubstituted cycloalkyl, R^{35}-substituted or unsubstituted heterocycloalkyl, R^{35}-substituted or unsubstituted aryl, or R^{35}-substituted or unsubstituted heteroaryl. R^{19}, R^{34} and R^{35} are independently hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0073] In some embodiments, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, and R^{33} are independently hydrogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, and R^{33} may independently be hydrogen, unsubstituted alkyl, or unsubstituted heteroalkyl.

[0074] R^1 may be R^3-substituted or unsubstituted alkyl, R^3-substituted or unsubstituted cycloalkyl, or R^3-substituted or unsubstituted aryl. R^1 may also be R^3-substituted or unsubstituted alkyl, or R^3-substituted or unsubstituted cycloalkyl. In some embodiments, R^1 is R^3-substituted or unsubstituted C_1-C_4 alkyl, or R^3-substituted or unsubstituted C_3-C_6 cycloalkyl. In other embodiments, R^1 is R^3-substituted or unsubstituted C_1-C_4 alkyl, or R^3-substituted or unsubstituted cyclopentyl. R^1 may also be methyl or unsubstituted C_3-C_6 branched alkyl (e.g. isopropyl, isobutyl, etc.).

[0075] In certain embodiments, R^3 is R^{19}-substituted or unsubstituted alkyl, R^{19}-substituted or unsubstituted cycloalkyl, or R^{19}-substituted or unsubstituted aryl. R^3 may also be R^{19}-substituted or unsubstituted alkyl, R^{19}-substituted or unsubstituted cycloalkyl, or R^{19}-substituted or unsubstituted aryl. In some embodiments, R^3 is R^{19}-substituted or unsubstituted alkyl, or R^{19}-substituted or unsubstituted cycloalkyl.

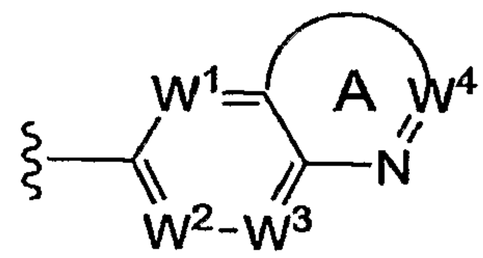
[0076] R^{19} may be unsubstituted alkyl or unsubstituted cycloalkyl. In come embodiments, R^{19} is unsubstituted C_1-C_4 alkyl or unsubstituted cyclopentyl.

[0077] In some embodiments, R^2 is R^4-substituted aryl, or R^4-substituted or unsubstituted heteroaryl. R^2 may be R^4-substituted phenyl, R^4-substituted or unsubstituted naphthyl, R^4-substituted or unsubstituted pyridinyl, R^4-substituted or unsubstituted pyrimidinyl, R^4-substituted or unsubstituted thiophenyl, R^4-substituted or unsubstituted furanyl, R^4-

substituted or unsubstituted indolyl, R^4-substituted or unsubstituted benzoxadiazolyl, R^4-substituted or unsubstituted benzodioxolyl, R^4-substituted or unsubstituted benzodioxanyl, R^4-substituted or unsubstituted thianaphthanyl, R^4-substituted or unsubstituted pyrrolopyridinyl, R^4-substituted or unsubstituted indazolyl, R^4-substituted or unsubstituted tetrahydronaphthalenyl, R^4-substituted or unsubstituted quinolinyl, R^4-substituted or unsubstituted quinoxalinyl, R^4-substituted or unsubstituted pyridopyrazinyl, R^4-substituted or unsubstituted quinazolinonyl, R^4-substituted or unsubstituted chromenonyl, R^4-substituted or unsubstituted benzoisoxazolyl, R^4-substituted or unsubstituted imidazopyridinyl, R^4-substituted or unsubstituted benzofuranyl, R^4-substituted or unsubstituted dihydro-benzofuranyl, R^4-substituted or unsubstituted dihydro-benzodioxinyl, R^4-substituted or unsubstituted benzoimidazolonyl, or R^4-substituted or unsubstituted benzothiophenyl.

[0078] In certain embodiments, R^2 is R^4-substituted phenyl, R^4-substituted or unsubstituted pyrrolepyridinyl, R^4-substituted or unsubstituted quinolinyl, R^4-substituted or unsubstituted indazolyl, R^4-substituted or unsubstituted quinolinyl indolyl, or R^4-substituted or unsubstituted naphthyl. R^4 may be halogen, -CN, $-OR^{20}$, or $-NR^{22}R^{23}$. R^4 may also simply be halogen, or $-OR^{20}$.

[0079] In certain embodiments, R^2 is has the formula:

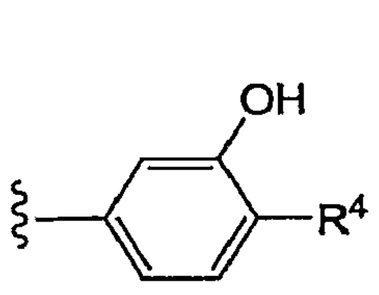
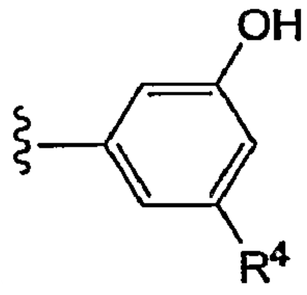
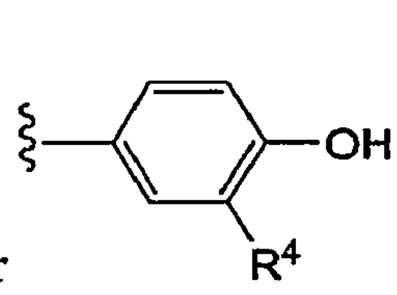


(III).

In Formula (III), W^1, W^2, W^3, and W^4 are independently =CH-, $=CR^4$-, or =N-. Each R^4 is as defined above in the description of Formulae (I) and (II). Ring A is a substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl. In some embodiments, ring A is a 6 to 7 membered heterocycloalkyl or 6 to 7 membered heteroaryl. Thus, in some embodiments, ring A is partially or fully unsaturated 6- or 7- membered ring.

[0080] R^{20} may be hydrogen or unsubstituted C_1-C_{10} alkyl. In some embodiments, R^{20} is hydrogen or unsubstituted C_1-C_4 alkyl. R^{20} may also simply be hydrogen or methyl.

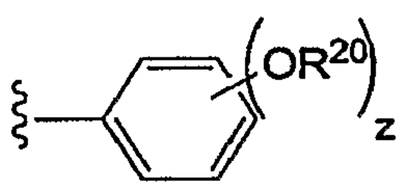
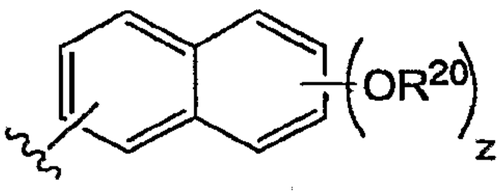
[0081] In some embodiments, R^2 has the formula:


(IV),

(V), or

(VI).

In Formulae (IV), (V) and (VI), R^4 is absent, halogen, unsubstituted C_1-C_4 alkyl, or $-OR^{20}$. The halogen may be F, Cl, or Br. In some embodiments, the halogen is F or Cl. In other embodiments, the halogen is F. R^{20} may be hydrogen or unsubstituted C_1-C_4 alkyl.

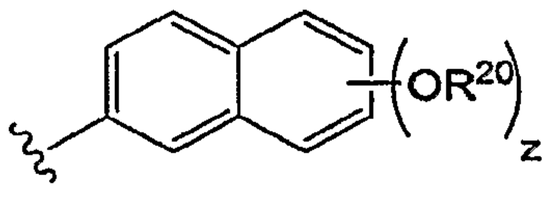
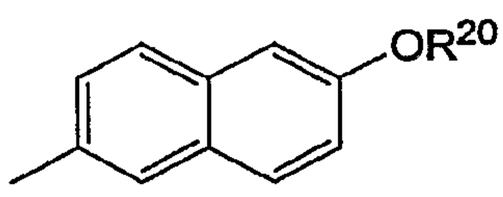
[0082] In some embodiments, R^2 is 6-hydroxynaphthyl, unsubstituted 7-azaindole, unsubstituted indolyl, unsubstituted indazolyl, or unsubstituted quinolinyl.

[0083] In some embodiments, R^2 has the formula:


(VII) or

(VIII).

In Formulae (VII) and (VIII), R^{20} is as defined above. It is noted that, in accordance with the description of R^{20} above, each R^{20} is optionally different. The symbol z is an integer from 1 to 5 (e.g. 1 or 2). In some embodiments, R^{20} is hydrogen or unsubstituted C_1-C_{10} alkyl (e.g. C_1-C_5 alkyl such as methyl or ethyl).

[0084] In some embodiments, R^2 has the formula:


(IX), or

(X).

In Formulae (IX) and (X), above, R^{20} is as defined above, for example, in the description of Formulae (I), (II), (VI), and (VII) above.

[0085] In some embodiments, each substituted group described above for the compounds of the present invention is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, aryl(C_1-C_6)alkyl, and heteroaryl(C_1-C_6)alkyl described above is substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. Alternatively, at least one or all of these groups are substituted with at least one lower substituent group.

[0086] In other embodiments of the compounds described above, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_4-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

[0087] Alternatively, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5-C_7 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0088] In another embodiment, the compounds of Formula (I) include any or all of the compounds listed in Table 1 below.

III. The PI3-Kinase Affinity Pocket

[0089] The term "PI3-Kinase affinity pocket," as used herein, refers to a cavity within p110α, p110β, p110γ, and p110δ corresponding to the lightly shaded region shown in Figures 2A, 2C, and 2D labeled "Affinity Pocket." Figures 2A, 2C, and 2D illustrate a computer model of the p110γ crystal structure. In p110γ, the surface of the PI3-Kinase affinity pocket is bound, at least in part, by the side chain of K833, D964, I879, and D841 (p110γ numbering, see Figure 8). The surface of the corresponding cavity in p110δ is bound, at least in part, by the side chain of K779, D911, I825, and D787 (p110δ numbering, see Figure 7). The corresponding cavity within p110α is bound, at least in part, by the side chains of K802, D933, I848, and D810 (p110α numbering, see Figure 9). The corresponding cavity within p110β is bound, at least in part, by the side chains of K805, D937, I851, and D813 (p110β numbering, see Figure 10). The PI3-Kinase affinity pocket is not accessed by ATP.

[0090] The PI3-Kinase affinity pocket of p110δ may be referred to herein as the p110δ affinity pocket. Likewise, the PI3-Kinase affinity pocket of p110γ may be referred to herein as the p110γ affinity pocket. The PI3-Kinase affinity pocket includes lysine 779, which, according to computer models, forms a hydrogen bond with the pyridine nitrogen of PIK-90 and the phenol oxygen of PI 103 (Figure 2D), both of which are inhibitors of p110δ. Based

on these computer modeling results, a novel antagonist was designed based on the chemical structure of PIK-39 and IC87114, as detailed below.

[0091] As shown in Figure 2C, PIK-39 does not contain a PI3-Kinase binding pocket moiety. And as shown in Figure 3A, IC87114 maintains contacts to E880 and V882 in the ATP binding region of p110δ, but is also missing a PI3-Kinase binding pocket moiety. By inserting *m*-phenol (a PI3-Kinase binding pocket moiety) at the C3 of the pyrazolopyrimidine of IC87114, the PI3-Kinase affinity pocket is accessed (FIG. 3A) resulting in a 60-fold increase in p110δ inhibition potency.

[0092] As described above, a PI3-Kinase binding pocket moiety is a substituent which, upon contacting upon contacting p110α, p110β, p110γ, or p110δ, fills space within the corresponding PI3-Kinase binding pocket. For example, a PI3-Kinase affinity pocket binding moiety is a substituent which, upon contacting upon contacting p110δ, fills space within the p110α affinity pocket. Likewise, a p110α affinity pocket binding moiety is a substituent which, upon contacting upon contacting p110α, fills space within the p110α affinity pocket.

[0093] In some embodiments, the PI3-Kinase binding pocket moiety additionally interacts (e.g. bonds) with an amino acid that forms part of the PI3-Kinase binding pocket. In some related embodiments, the interaction is a hydrogen bond, van der Waals interaction, ionic bond, covalent bond (e.g. disulfide bond) or hydrophobic interaction.

IV. Determining Space Filling Within the PI3-Kinase Affinity Pocket

[0094] To determine whether the PI3-Kinase affinity pocket binding moiety fills space within the PI3-Kinase affinity pocket, computer modeling techniques are employed. A query PI3-Kinase affinity pocket binding antagonist (i.e. a test compound) is fit into a computer image of p110γ. The p110γ computer image is derived from the solved co-crystal structure of human p110γ bound to PIK-39. The PyMOL Molecular Graphics System may be employed to generate the image. An example is presented in Figure 3A, wherein IC87114 and PIK-294 are built into the computer image of p110γ kinase, derived from the p110γ - PIK-39 co-crystal. See Knight, et al., Cell 125: 733-745 (2006).

[0095] The computer models are typically analyzed to prevent any gross steric clashes and to satisfy key hydrogen bonds between the query PI3-Kinase affinity pocket binding antagonist and the p110γ protein (e.g. V882 and M804). In some embodiments, energy

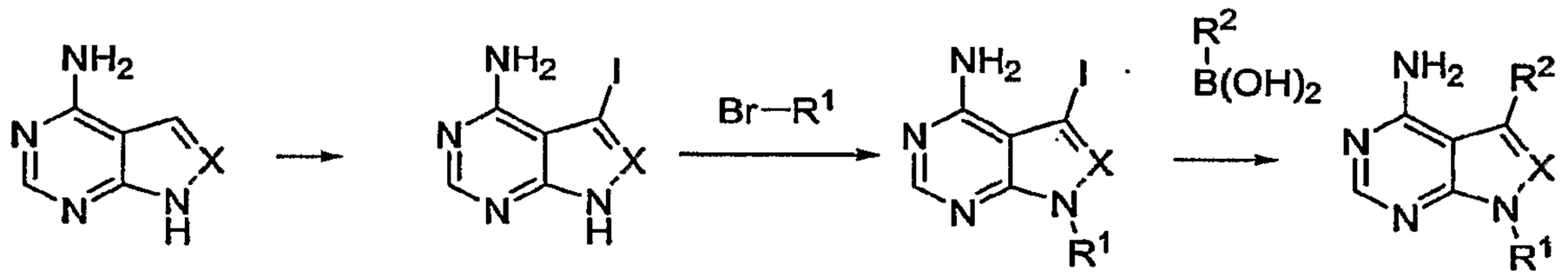
minimization calculations are performed to optimize binding energy. Using these techniques, one skilled in the art can easily determine whether a query PI3-Kinase affinity pocket binding antagonist includes a PI3-Kinase affinity pocket binding moiety that fills space within the PI3-Kinase affinity pocket.

[0096] In some embodiments, the query PI3-Kinase affinity pocket binding antagonist is analyzed to determine whether at least one bond (e.g. a hydrogen bond) is formed between the query PI3-Kinase affinity pocket binding antagonist and an amino acid that form part of the PI3-Kinase affinity pocket. Using a computer modeling technique as described above, the distance between one or more amino acids that form part of the PI3-Kinase affinity pocket and a potential contact point on the PI3-Kinase affinity pocket binding moiety is determined. Based on this distance, one skilled in the art may determine whether at least one bond is formed between one or more amino acids that form part of the PI3-Kinase affinity pocket and a PI3-Kinase affinity pocket binding moiety.

V. General Syntheses

[0097] The compounds of the invention are synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing the compounds of the invention are both readily apparent and accessible to those of skill in the relevant art. The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds of the invention. However, the discussion is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds of the present invention.

Scheme I



[0098] In Scheme I above, iodination of the pyrazolo- or pyrrolo-pyrimidine is accomplished using an appropriate iodination reagent, such as n-iodo-succinamide. Elaboration of the 1-position may be accomplished via halogen displacement of a brominated substituent (e.g. a substituted or unsubstituted alkylbromide). Palladium-catalyzed cross coupling between organoboronic acid and the iodo halide (i.e. Suzuki coupling), is then used

to elaborate the 3-position. Recent catalyst and method developments have broadened the possible Suzuki coupling applications enormously, so that the scope of the reaction partners is not restricted to aryls. Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic acids. Some pseudohalides (for example triflates) may also be used as coupling partners. Further information regarding Suzuki coupling may be found, for example in Kudo et al., *Angew. Chem. Int. Ed.* **45**: 1282-1284 (2006); Kirchhoffet al., *J. Am. Chem. Soc.*, **124**: 13662-13663 (2002); Wu et al., J. *Org. Chem.*, **68**: 670-673 (2003); and Molander et al., *J. Org. Chem.*, **67**: 8424-8429 (2002).

VI. Methods

[0099] In another aspect, the present invention provides methods of decreasing the catalytic activity of a PI3 Kinase (e.g. a p110α kinase). The method includes the step of contacting the PI3 kinase with an activity decreasing amount of a compound of the present invention (i.e. a PI3-Kinase affinity pocket binding antagonist or the compound of Formula (I)). In some embodiments, the antagonist is capable of decreasing the catalytic activity of a tyrosine kinase. In some embodiments, the antagonist is a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists, or PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonists.

[0100] In some embodiments, the antagonist is specific to p110α relative to the antagonist action against p110δ, p110β, and/or p110γ. In some embodiments, the IC50 for p110α is at least 1.5, 2.0, 3.0, 4.0, 5.0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, or 1000 fold lower than the IC50 against p110δ, p110β, and/or p110γ. In other embodiments, the IC50 of the antagonist against the p110α is less than 100 μM, 50 μM, 40 μM, 30 μM, 20 μM, 10 μM, 5 μM, 1 μM, 0.5 μM, 0.1 μM, 50 nM, 10 nM, 1 nM. 0.5 nM, 0.1 nM, 50 pM, 10 pM, or 1 pM.

[0101] In some embodiments, the antagonist is specific to p110α relative to the antagonist action against insulin receptor tyrosine kinase. In some embodiments, the IC50 for p110α is at least 1.5, 2.0, 3.0, 4.0, 5.0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, or 1000 fold lower than the IC50 against insulin receptor tyrosine kinase. In other embodiments, the IC50 of the antagonist against the p110α is less than 100 μM, 50 μM, 40 μM, 30 μM, 20 μM, 10 μM, 5 μM, 1 μM, 0.5 μM, 0.1 μM, 50 nM, 10 nM, 1 nM. 0.5 nM, 0.1 nM, 50 pM, 10 pM, or 1 pM.

[0102] In some embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of a tyrosine kinase. In some embodiments, the IC50 of the antagonist against the tyrosine kinase is less than 100 μM, 50 μM, 40 μM, 30 μM, 20 μM, 10 μM, 5 μM, 1 μM, 0.5 μM, 0.1 μM, 50 nM, 10 nM, 1 nM. 0.5 nM, 0.1 nM, 50 pM, 10 pM, or 1 pM. Some tyrosine kinases include, for example, DNA-dependent protein kinase DNA-dependent protein kinase (pubmed protein accession number (PPAN) AAA79184), Abl tyrosine kinase (CAA52387), Bcr-Abl, hemopoietic cell kinase (PPAN CAI19695), Src (PPAN CAA24495), vascular endothelial growth factor receptor 2 (PPAN ABB82619), vascular endothelial growth factor receptor-2 (PPAN ABB82619), epidermal growth factor receptor (PPAN AG43241), EPH receptor B4 (PPAN EAL23820), stem cell factor receptor (PPAN AAF22141), Tyrosine-protein kinase receptor TIE-2 (PPAN Q02858), fms-related tyrosine kinase 3 (PPAN NP_004110), platelet-derived growth factor receptor alpha (PPAN NP_990080), RET (PPAN CAA73131), and functional mutants thereof. In some embodiments, the tyrosine kinase is Abl, Bcr-Abl, EGFR, or Flt-3.

[0103] In some embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of mTOR (PPAN AAI17167). In some embodiments, the IC50 of the antagonist against mTOR is less than 100 μM, 50 μM, 40 μM, 30 μM, 20 μM, 10 μM, 5 μM, 1 μM, 0.5 μM, 0.1 μM, 50 nM, 10 nM, 1 nM. 0.5 nM, 0.1 nM, 50 pM, 10 pM, or 1 pM.

[0104] In some embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of mTOR and p110α at an IC50 of less than 100 μM, 50 μM, 40 μM, 30 μM, 20 μM, 10 μM, 5 μM, 1 μM, 0.5 μM, 0.1 μM, 50 nM, 10 nM, 1 nM. 0.5 nM, 0.1 nM, 50 pM, 10 pM, or 1 pM. In other embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of a tyrosine kinase and p110α at an IC50 of less than 100 μM, 50 μM, 40 μM, 30 μM, 20 μM, 10 μM, 5 μM, 1 μM, 0.5 μM, 0.1 μM, 50 nM, 10 nM, 1 nM. 0.5 nM, 0.1 nM, 50 pM, 10 pM, or 1 pM. In other embodiments, the antagonist decreases, or is capable of decreasing, the catalytic activity of a tyrosine kinase, mTOR, and p110α at an IC50 of less than 100 μM, 50 μM, 40 μM, 30 μM, 20 μM, 10 μM, 5 μM, 1 μM, 0.5 μM, 0.1 μM, 50 nM, 10 nM, 1 nM. 0.5 nM, 0.1 nM, 50 pM, 10 pM, or 1 pM.

[0105] In another aspect, the present invention provides a method of treating a disease or condition mediated by PI3 kinase activity, PI3 Kinase activity and Tyrosine Kinase Activity, PI3 Kinase activity and mTOR Activity, or PI3 Kinase activity, mTOR activity, and Tyrosine

Kinase Activity in a subject in need of such treatment. The method includes administering to the subject a therapeutically effective amount of an antagonist. The antagonist is a PI3-Kinase affinity pocket binding antagonist or the compound of Formula (I). In some embodiments the antagonist is a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonists, or PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonists.

[0106] The disease may also be a bone-resorption disorder, chronic myelogenous leukemia, abnormal inflammation, autoimmune disease, thrombosis, or asthma. The disease may also be a type of cancer or cancer metastasis, including, for example, leukemia, carcinomas and sarcomas, such as cancer of the brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus and Medulloblastoma. Additional examples include, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine and exocrine pancreas, and prostate cancer. In some embodiments, the disease is selected from disease is liver cancer, colon cancer, breast cancer, melanoma, acute myelogenous leukemia, chronic myelogenous leukemia, or nonsmall-cell lung cancer.

[0107] In another aspect, the present invention provides methods of disrupting the function of a leukocyte or disrupting a function of an osteoclast. The method includes contacting the leukocyte or the osteoclast with a function disrupting amount of the antagonist. The antagonist is a PI3-Kinase affinity pocket binding antagonist or the compound of Formula (I). In some embodiments the antagonist is a PI3-Kinase affinity pocket binding pyrazolopyrimidine antagonist, or PI3-Kinase affinity pocket binding pyrrolopyrimidine antagonist.

VII. Pharmaceutical Formulations

[0108] In another aspect, the present invention provides a pharmaceutical composition including an antagonist in admixture with a pharmaceutically acceptable excipient. One of skill in the art will recognize that the pharmaceutical compositions include the

pharmaceutically acceptable salts of the PI3-Kinase antagonists of the present invention described above.

[0109] In therapeutic and/or diagnostic applications, the compounds of the invention can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

[0110] The compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A most preferable dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[0111] Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and may include, by way of example but not limitation, acetate, benzenesulfonate, besylate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Preferred pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoate (embonate), phosphate, salicylate, succinate, sulfate, or tartrate.

[0112] Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained- low release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

Suitable routes may include oral, buccal, by inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articullar, intra –sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

[0113] For injection, the agents of the invention may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0114] Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the invention into dosages suitable for systemic administration is within the scope of the invention. With proper choice of carrier and suitable manufacturing practice, the compositions of the present invention, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (e.g. patient) to be treated.

[0115] For nasal or inhalation delivery, the agents of the invention may also be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances such as, saline, preservatives, such as benzyl alcohol, absorption promoters, and fluorocarbons.

[0116] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0117] In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used

pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

[0118] Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross- linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0119] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0120] Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

[0121] Depending upon the particular condition, or disease state, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may be administered together with the inhibitors of this invention. For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the inhibitors of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

[0122] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation, anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating diabetes such as insulin, insulin analogues, alpha glucosidase inhibitors, biguanides, and insulin sensitizers; and agents for treating immunodeficiency disorders such as gamma globulin.

[0123] These additional agents may be administered separately, as part of a multiple dosage regimen, from the composition. Alternatively, these agents may be part of a single dosage form, mixed together with the inhibitor in a single composition.

[0124] The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those having skill in the art from the foregoing description. Such modifications are intended to fall within the scope of the invention. Moreover, any one or more features of any embodiment of the invention may be combined with any one or more other features of any other embodiment of the invention, without departing from the scope of the invention. For example, the PI3-Kinase antagonists of the present invention described above are equally applicable to the methods of treatment and methods of inhibiting kinases described herein. References cited throughout this application are examples of the level of skill in the art.

VIII. Examples

[0125] The following examples are meant to illustrate certain embodiments of the invention, and not to limit the scope of the invention.

[0126] General Methods. All chemicals, reagents and solvents used were purchased commercially and used as received. dH2O refers to deioinized water. Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. Compounds were purified by High Pressure Liquid Chromatography (HPLC) eluting with dH_2O-MeCN-trifluroacetic acid, 50:50:0.1, unless otherwise indicated. Analysis of products was carried out on a Liquid Chromatography Mass Spectrometer (LCMS) using MeCN-0.1% formic acid (varying ratios) as eluent.

A. Selected Reaction Procedures.

[0127] Synthesis of 1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA18)**. A solution of 250 mL of formamide and 3-amino-4-pyrazolecarbonitrile (25 g, 0.231 mol) was heated to 180°C overnight under an argon atmosphere. Reaction was cooled and 400 mL of dH_2O were added. The resulting solid was filtered and rinsed with cold dH_2O. White solid precipitate was collected and dried *in vacuo* overnight to yield BA18 (39g, 100% yield). ESI-MS $(M+H)^+$ *m/z* calcd 136.1, found 136.1.

[0128] Synthesis of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA19)**. A solution of 3H-pyrazolo[3,4-d]pyrimidin-4-amine (10g, 0.074 mol) and n-iodo-succinamide (25 g, 0.111 mol) in DMF (80 mL) was heated to 80°C overnight under an argon atmosphere. The resulting solid was filtered and rinsed with cold EtOH. Product was dried *in vacuo* overnight to yield BA19 (24g, 100% yield). ESI-MS $(M+H)^+$ *m/z* calcd 262.0, found 262.0

[0129] Synthesis of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA12)**. A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2 g, 0.0077 mol) and K_2CO_3 (4.2g, 0.031 mol) in DMF (50 mL) was brought to 80°C under an argon atmosphere. Isopropylbromide (1.0g, 0.0084 mol) was added with a syringe. Reaction was refluxed under argon atmosphere for 2 hours. Solid K_2CO_3 was removed by filtration. Solvent was partially removed *in vacuo*. Sodium citrate (50 mL) was added and reaction was extracted with EtOAc. Organic phases concentrated *in vacuo* and purified using silica gel column chromatography [MeOH—CH_2Cl_2, 5:95] yielding BA12 (1.68 g, 72% yield). ESI-MS $(M+H)^+$ *m/z* calcd 304.0, found 304.1.

[0130] General Suzuki coupling. Preparation of final products (see Table 1 for final product names and structures).

[0131] 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol, 1 equivalent) was dissolved in DME (12 ml). Boronic acid (1.1 equivalent) was dissolved in EtOH (3.3 ml) and added to reaction mixture. Pd(PPh3)4 (30 mg, 0.026 mmol, 0.2 equivalents) and saturated Na2CO3 (1.9 ml) were added to the reaction mixture and heated to 80°C under argon and refluxed for 8 hours. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined and solvent was removed. Resulting solid (or oil) was dissolved in dH2O—MeCN—trifluroacetic acid, 50:50:0.1 and purified by HPLC. Purified product (varying yields) was confirmed by LCMS.

[0132] Synthesis of 4-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-benzenesulfonamide **(BA14).** A solution of benzenesulfonamide-4-boronic acid pinacol ester (23 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA14 (2.2 mg, 10% yield). ESI-MS $(M+H)^+$ *m/z* calcd 333.1, found 333.1.

[0133] Synthesis of 1-isopropyl-3-(3-methoxy-4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA15).** A solution of 2 methoxy-4-(4,4,5,5-tetramethyl-1,3-2-dioxaborolan-2-yl) phenol (19 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA15 (4.3 mg, 20% yield). ESI-MS $(M+H)^+$ *m/z* calcd 300.1, found 300.2.

[0134] Synthesis of 6-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)naphthalen-2-ol **(BA17).** A solution of 6-hydroxynaphthalen-2-yl-2-boronic acid (15 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and

CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA15 (4.8 mg, 23% yield). ESI-MS $(M+H)^+$ *m/z* calcd 320.1, found 320.1.

[0135] Synthesis of tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate **(BA20).** A solution of 4 4-N-Boc-amino-3-methoxy-benzeneboronic acid (48 mg, 0.18 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.18 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (40 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA20. ESI-MS $(M+H)^+$ *m/z* calcd 399.2, found 399.1.

[0136] Synthesis of 3-(4-amino-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA20d).** A solution of tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate (BA20) (20 mg, 0.05 mmol) in CH_2Cl_2, TFA, $S(CH_2)_2$, H_2O (45:45:5:5) (1mL) was stirred at room temperature for 15 minutes. $NaHCO_3$ (2 mL) was added till reaction was alkaline. Reaction was extracted with H_2O and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA20d.

[0137] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridine-2-carbonitrile **(BA21).** A solution of 2-cyanopyridine 5-boronic acid pinocol ester (18 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA21 (2.5 mg, 14% yield). ESI-MS $(M+H)^+$ *m/z* calcd 280.1, found 280.1.

[0138] Synthesis of 3-(3-(benzyloxy)-5-fluorophenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine.. A solution of (3-Benzyloxy-5-fluorophenyl)boronic acid (29 mg, 5.80 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol)

and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA22 (15.6 mg, 60% yield). ESI-MS $(M+H)^+$ *m/z* calcd 378.1, found 378.0.

[0139] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol **(BA22).** A solution of -(3-(benzyloxy)-5-fluorophenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (15 mg, 0.04 mmol) in MeOH (0.9 mL) was flushed with argon. Pd on activated carbon (10 mL) was carefully added while keeping reaction under an argon atmosphere. Reaction was flushed with H_2 gas and left under H_2 atmosphere overnight at room temperature. The reaction was filtered through celite and rinsed with MeOH to yield BA22 (15 mg, 100% yield). ESI-MS $(M+H)^+$ *m/z* calcd 288.1, found 288.1.

[0140] Synthesis of 1-isopropyl-3-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA23).** A solution of 3,4-Dimethoxyphenylboronic acid (24 mg, 0.13 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA23 (13.1 mg, 60% yield). ESI-MS $(M+H)^+$ *m/z* calcd 314.0, found 314.1.

[0141] Synthesis of (3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)methanol **(BA26).** A solution of (3-Hydroxymethylphenyl)boronic acid (24 mg, 0.13 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA26 (8.4 mg, 42% yield). ESI-MS $(M+H)^+$ *m/z* calcd 283.1, found 284.2.

[0142] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-N-(4,5-dihydrothiazol-2-yl)benzamide **(BA30).** A solution of [3-((4,5-dihydrothiazol-2-

yl)carbamoyl)phenyl]boronic acid (19 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA30 (17.8 mg, 67% yield).

[0143] Synthesis of 1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone **(BA31).** A solution of 4-Acetylphenylboronic acid (12.7 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA31 (12.9 mg, 62% yield).

[0144] Synthesis of (3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)methanol **(BA32).** A solution of (4-Aminocarbonyl-3-chlorophenyl)boronic acid (16 mg, 0.08 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA32 (9.7 mg, 42% yield). ESI-MS $(M+H)^+$ *m/z* calcd 331.1, found 331.1.

[0145] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-methylthiophene-2-carbaldehyde **(BA34).** A solution of 5-Formyl-3-methylthiophene-2-boronic acid (26 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in*

vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA34 (14.7 mg, 38% yield). ESI-MS $(M+H)^+$ *m/z* calcd 302.1, found 302.0.

[0146] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)furan-3-carbaldehyde **(BA35).** A solution of 4-Formylfuran-2-boronic acid (20 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA35 (13.5 mg, 39% yield). ESI-MS $(M+H)^+$ *m/z* calcd 272.1, found 272.1.

[0147] Synthesis of N-[3-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-phenyl]-methanesulfonamide **(BA38).** A solution of 3-Methanesulfonylaminophenylboronic acid (32 mg, 0.15 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA38 (24.3 mg, 54% yield). ESI-MS $(M+H)^+$ *m/z* calcd 347.1, found 347.0.

[0148] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzonitrile **(BA39).** A solution of 3-Cyanophenylboronic acid (23 mg, 0.15 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA39 (14.9 mg, 41% yield). ESI-MS $(M+H)^+$ *m/z* calcd 279.1, found 279.0.

[0149] Synthesis of N-[4-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-phenyl]-methanesulfonamide **(BA40).** A solution of 4-Methanesulfonylaminophenylboronic acid (24 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30

mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA40 (0.9 mg, 3% yield). ESI-MS $(M+H)^+$ *m/z* calcd 347.1, found 347.0.

[0150] Synthesis of 3-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-benzenesulfonamide **(BA41).** A solution of Benzenesulfonamide-3-boronic acid pinacol ester (31 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA41 (9.2 mg, 28% yield). ESI-MS $(M+H)^+$ *m/z* calcd 333.1, found 333.0.

[0151] Synthesis of 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzo[b]thiophene-5-carbaldehyde **(BA42).** A solution of 5-Formylbenzo[b]thiophene-2-boronic acid pinacol ester (31 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA42 (15.2 mg, 45% yield). ESI-MS $(M+H)^+$ *m/z* calcd 338.1, found 338.0.

[0152] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-3-carbaldehyde **(BA43).** A solution of N-Boc-3-formyl-5-indoleboronic acid pinacol ester (40 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). The TFA from purification hydrolyzed the Boc to yield BA43. ESI-MS $(M+H)^+$ *m/z* calcd 321.1, found 321.0.

[0153] Synthesis of 3-(benzo[c][1,2,5]oxadiazol-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA44).** A solution of Benzo[c][1,2,5]oxadiazole-5-boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA44. ESI-MS $(M+H)^+$ *m/z* calcd 296.1, found 296.1.

[0154] Synthesis of 2-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)acetonitrile **(BA45).** A solution of (4-Cyanomethylphenyl)boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA45. ESI-MS $(M+H)^+$ *m/z* calcd 293.1, found 293.1.

[0155] Synthesis of 2-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)acetonitrile **(BA46).** A solution of (3-Cyanomethylphenyl)boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA45. ESI-MS $(M+H)^+$ *m/z* calcd 293.1, found 293.1.

[0156] Synthesis of 1-isopropyl-3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA48).** A solution of (4-Methoxyphenylboronic acid (17 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere

overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA48 (4.5mg, 16% yield). ESI-MS $(M+H)^+$ *m/z* calcd 284.1, found 284.1.

[0157] Synthesis of 1-isopropyl-3-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA49).** A solution of 3-Methoxyphenylboronic acid (17 mg, 0.11 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA49. ESI-MS $(M+H)^+$ *m/z* calcd 284.1, found 284.0.

[0158] Synthesis of 1-isopropyl-3-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA52).** A solution of 3-Pyridinylboronic acid (15 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (15 mg, 0.015 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O) to yield BA52. ESI-MS $(M+H)^+$ *m/z* calcd 255.1, found 255.0.

[0159] Synthesis of 1-isopropyl-3-(pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA53).** A solution of 5-Pyrimidinylboronic acid (15 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (15 mg, 0.015 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O) to yield BA53. ESI-MS $(M+H)^+$ *m/z* calcd 256.1, found 256.1.

[0160] Synthesis of 3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA54).** A solution of 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (26 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg,

0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA54 (6 mg, 15% yield). ESI-MS $(M+H)^+$ *m/z* calcd 312.1, found 312.0.

[0161] Synthesis of 1-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone **(BA55).** A solution of 3-Acetylphenylboronic acid (23 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA55 (7 mg, 18% yield). ESI-MS $(M+H)^+$ *m/z* calcd 296.1, found 296.1.

[0162] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol **(BA56).** A solution of 4-Hydroxyphenylboronic acid (30 mg, 0.14 mmol) in EtOH (3.3 mL) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and saturated Na_2CO_3 (1.9 mL) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH_2Cl_2. Organic phases were combined, concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield BA56 (12 mg, 32% yield). ESI-MS $(M+H)^+$ *m/z* calcd 270.1, found 270.1.

[0163] Synthesis of PI3-K/Tyrosine Kinase Dual Inhibitors

[0164] Synthesis of 1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA18).** A solution of 250 ml of formamide and 3-amino-4-pyrazolecarbonitrile (25 g, 0.231 mol) was heated to 180°C overnight under an argon atmosphere. Reaction was cooled and 400 ml of dH2O were added. The resulting solid was filtered and rinsed with cold dH2O. White solid precipitate was collected and dried in vacuo overnight to yield BA18 (39g, 100% yield). ESI-MS (M+H)+ m/z calcd 136.1, found 136.1.

[0165] Synthesis of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA19).** A solution of 3H-pyrazolo[3,4-d]pyrimidin-4-amine (10g, 0.074 mol) and n-iodo-succinamide (25 g, 0.111

mol) in DMF (80ml) was heated to 80°C overnight under an argon atmosphere. The resulting solid was filtered and rinsed with cold EtOH. Product was dried in vacuo overnight to yield BA19 (24g, 100% yield). ESI-MS (M+H)+ m/z calcd 262.0, found 262.0

[0166] Synthesis of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA12)**. A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2 g, 0.0077 mol) and K2CO3 (4.2g, 0.031 mol) in DMF (50 ml) was brought to 80°C under an argon atomosphere. Isopropylbromide (1.0g, 0.0084 mol) was added with a syringe. Reaction was refluxed under argon atmosphere for 2 hours. Solid K2CO3 was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH2Cl2, 5:95] yielding BA12 (1.68 g, 72% yield). ESI-MS (M+H)+ m/z calcd 304.0, found 304.1.

[0167] Synthesis of 4-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-benzenesulfonamide **(BA14)**. A solution of benzenesulfonamide-4-boronic acid pinacol ester (23 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA14 (2.2 mg, 10% yield). ESI-MS (M+H)+ m/z calcd 333.1, found 333.1.

[0168] Synthesis of 1-isopropyl-3-(3-methoxy-4-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA15)**. A solution of 2 methoxy-4-(4,4,5,5-tetramethyl-1,3-2-dioxaborolan-2-yl) phenol (19 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA15 (4.3 mg, 20% yield). ESI-MS (M+H)+ m/z calcd 300.1, found 300.2.

[0169] Synthesis of 6-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)naphthalen-2-ol **(BA17)**. A solution of 6-hydroxynaphthalen-2-yl-2-boronic acid (15 mg, 0.08 mmol) in

EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA15 (4.8 mg, 23% yield). ESI-MS (M+H)+ m/z calcd 320.1, found 320.1.

[0170] Synthesis of tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate **(BA20)**. A solution of 4 4-N-Boc-amino-3-methoxybenzeneboronic acid (48 mg, 0.18 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.18 mmol) in DME (12 ml). Pd(PPh3)4 (40 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA20. ESI-MS (M+H)+ m/z calcd 399.2, found 399.1.

[0171] Synthesis of 3-(4-amino-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA20d)**. A solution of tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate (BA20) (20 mg, 0.05 mmol) in CH2Cl2, TFA, S(CH2)2, H2O (45:45:5:5) (1ml) was stirred at room temperature for 15 minutes. NaHCO3 (2 ml) was added till reaction was alkaline. Reaction was extrated with H2O and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA20d.

[0172] Synthesis of 2-amino-5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol **(BA20dd)**. BA20 (tert-butyl 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylcarbamate, 7 mg, 0.018 mmol) was dissolved in CH2Cl2 (2.5 ml) and stirred under an argon atmosphere at room temperature. BBr3 (0.500 ml) was added slowly with a syringe. The reaction mixture was stirred overnight, under argon at room temperature. BBr3 was removed in vacuo and the remaining solid was purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA20dd.

[0173] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)pyridine-2-carbonitrile **(BA21)**. A solution of 2-cyanopyridine 5-boronic acid pinocol ester (18 mg,

0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA21 (2.5 mg, 14% yield). ESI-MS (M+H)+ m/z calcd 280.1, found 280.1.

[0174] Synthesis of 3-(3-(benzyloxy)-5-fluorophenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. A solution of (3-Benzyloxy-5-fluorophenyl)boronic acid (29 mg, 5.80 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3;4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA22 (15.6 mg, 60% yield). ESI-MS (M+H)+ m/z calcd 378.1, found 378.0.

[0175] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-fluorophenol **(BA22)**. A solution of -(3-(benzyloxy)-5-fluorophenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (15 mg, 0.04 mmol) in MeOH (0.9 ml) was flushed with argon. Pd on activated carbon (10 ml) was carefully added while keeping reaction under an argon atmosphere. Reaction was flushed with H2 gas and left under H2 atmosphere overnight at room temperature. The reaction was filtered through celite and rinsed with MeOH to yield BA22 (15 mg, 100% yield). ESI-MS (M+H)+ m/z calcd 288.1, found 288.1.

[0176] Synthesis of 1-isopropyl-3-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA23)**. A solution of 3,4-Dimethoxyphenylboronic acid (24 mg, 0.13 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA23 (13.1 mg, 60% yield). ESI-MS (M+H)+ m/z calcd 314.0, found 314.1.

[0177] Synthesis of tert-butyl 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-(benzyloxy)-1H-indole-1-carboxylate **(BA24)**. A solution of 5-Benzyloxy-1-BOC-indole-2-boronic acid (303mg, 0.83 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.33 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [EtOAc—hexanes, 5:95] to yield BA24. ESI-MS (M+H)+ m/z calcd 499.2, found 499.2.

[0178] Synthesis of 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indol-5-ol **(BA24dd)**. BA24 (3-(4-fluoro-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine, 30 mg, 0.10 mmol) was dissolved in a solution of formic acid (4.5 ml, 10 equivalents) and HCl (0.45 ml, 1 equivalent). The reaction was heated and stirred for one hour under an argon atmosphere. The reaction was then concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA24dd. ESI-MS (M+H)+ m/z calcd 309.1, found 309.1.

[0179] Synthesis of (3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)methanol **(BA26)**. A solution of (3-Hydroxymethylphenyl)boronic acid (24 mg, 0.13 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA26 (8.4 mg, 42% yield). ESI-MS (M+H)+ m/z calcd 283.1, found 284.2.

[0180] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-N-(4,5-dihydrothiazol-2-yl)benzamide **(BA30)**. A solution of [3-((4,5-dihydrothiazol-2-yl)carbamoyl)phenyl]boronic acid (19 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined,

concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA30 (17.8 mg, 67% yield).

[0181] Synthesis of 1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone **(BA31)**. A solution of 4-Acetylphenylboronic acid (12.7 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA31 (12.9 mg, 62% yield).

[0182] Synthesis of (3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)methanol **(BA32)**. A solution of (4-Aminocarbonyl-3-chlorophenyl)boronic acid (16 mg, 0.08 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (20 mg, 0.07 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA32 (9.7 mg, 42% yield). ESI-MS (M+H)+ m/z calcd 331.1, found 331.1.

[0183] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-methylthiophene-2-carbaldehyde **(BA34)**. A solution of 5-Formyl-3-methylthiophene-2-boronic acid (26 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA34 (14.7 mg, 38% yield). ESI-MS (M+H)+ m/z calcd 302.1, found 302.0.

[0184] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)furan-3-carbaldehyde **(BA35)**. A solution of 4-Formylfuran-2-boronic acid (20 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and

saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA35 (13.5 mg, 39% yield). ESI-MS (M+H)+ m/z calcd 272.1, found 272.1.

[0185] Synthesis of N-[3-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-phenyl]-methanesulfonamide **(BA38)**. A solution of 3-Methanesulfonylaminophenylboronic acid (32 mg, 0.15 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (16 mg, 0.014 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA38 (24.3 mg, 54% yield). ESI-MS (M+H)+ m/z calcd 347.1, found 347.0.

[0186] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzonitrile **(BA39)**. A solution of 3-Cyanophenylboronic acid (23 mg, 0.15 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA39 (14.9 mg, 41% yield). ESI-MS (M+H)+ m/z calcd 279.1, found 279.0.

[0187] Synthesis of N-[4-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-phenyl]-methanesulfonamide **(BA40)**. A solution of 4-Methanesulfonylaminophenylboronic acid (24 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA40 (0.9 mg, 3% yield). ESI-MS (M+H)+ m/z calcd 347.1, found 347.0.

[0188] Synthesis of 3-(4-Amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-benzenesulfonamide **(BA41)**. A solution of Benzenesulfonamide-3-boronic acid pinacol ester (31 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA41 (9.2 mg, 28% yield). ESI-MS (M+H)+ m/z calcd 333.1, found 333.0.

[0189] Synthesis of 2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzo[b]thiophene-5-carbaldehyde **(BA42)**. A solution of 5-Formylbenzo[b]thiophene-2-boronic acid pinacol ester (31 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA42 (15.2 mg, 45% yield). ESI-MS (M+H)+ m/z calcd 338.1, found 338.0.

[0190] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-3-carbaldehyde **(BA43)**. A solution of N-Boc-3-formyl-5-indoleboronic acid pinacol ester (40 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA). The TFA from purification hydrolyzed the Boc to yield BA43. ESI-MS (M+H)+ m/z calcd 321.1, found 321.0.

[0191] Synthesis of 3-(benzo[c][1,2,5]oxadiazol-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA44)**. A solution of Benzo[c][1,2,5]oxadiazole-5-boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C

under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA44. ESI-MS (M+H)+ m/z calcd 296.1, found 296.1.

[0192] Synthesis of 2-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)acetonitrile **(BA45)**. A solution of (4-Cyanomethylphenyl)boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA45. ESI-MS (M+H)+ m/z calcd 293.1, found 293.1.

[0193] Synthesis of 2-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)acetonitrile **(BA46)**. A solution of (3-Cyanomethylphenyl)boronic acid (18 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA45. ESI-MS (M+H)+ m/z calcd 293.1, found 293.1.

[0194] Synthesis of 1-isopropyl-3-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA48)**. A solution of (4-Methoxyphenylboronic acid (17 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA48 (4.5mg, 16% yield). ESI-MS (M+H)+ m/z calcd 284.1, found 284.1.

[0195] Synthesis of 1-isopropyl-3-(3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA49)**. A solution of 3-Methoxyphenylboronic acid (17 mg, 0.11 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.10 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA49. ESI-MS (M+H)+ m/z calcd 284.1, found 284.0.

[0196] Synthesis of 1-isopropyl-3-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA52)**. A solution of 3-Pyridinylboronic acid (15 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (15 mg, 0.015 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O) to yield BA52. ESI-MS (M+H)+ m/z calcd 255.1, found 255.0.

[0197] Synthesis of 1-isopropyl-3-(pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA53)**. A solution of 5-Pyrimidinylboronic acid (15 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (15 mg, 0.015 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O) to yield BA53. ESI-MS (M+H)+ m/z calcd 256.1, found 256.1.

[0198] Synthesis of 3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA54)**. A solution of 2,3-dihydro-1,4-benzodioxin-6-ylboronic acid (26 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and

purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA54 (6 mg, 15% yield). ESI-MS (M+H)+ m/z calcd 312.1, found 312.0.

[0199] Synthesis of 1-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone **(BA55)**. A solution of 3-Acetylphenylboronic acid (23 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA55 (7 mg, 18% yield). ESI-MS (M+H)+ m/z calcd 296.1, found 296.1.

[0200] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol **(BA56)**. A solution of 4-Hydroxyphenylboronic acid (30 mg, 0.14 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.13 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA56 (12 mg, 32% yield). ESI-MS (M+H)+ m/z calcd 270.1, found 270.1.

[0201] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol **(BA59)**. A solution of 3-fluoro-4-hydroxyphenylboronic acid (103 mg, 0.66 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.33 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP using silica gel column chromatography [MeOH—CH2Cl2, 2:98] to yield BA59 (26 mg, 27% yield). ESI-MS (M+H)+ m/z calcd 288, found 288.

[0202] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-3-methylphenol **(BA60)**. A solution of 4-hydroxy-2-methylphenylboronic acid (110 mg, 0.66 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.33 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol)

and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH2Cl2, 2:98] to yield BA60 (42 mg, 22% yield). ESI-MS (M+H)+ m/z calcd 284, found 284.

[0203] Synthesis of 3-(4-fluoro-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA62)**. A solution of 4-fluoro-3-methoxyphenylboronic acid (61 mg, 0.36 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (90 mg, 0.30 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH2Cl2, 2:98] to yield BA62 (40 mg, 44% yield). ESI-MS (M+H)+ m/z calcd 302, found 302.

[0204] Synthesis of 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorophenol **(BA62d)**. A solution of BA62 (3-(4-fluoro-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine, 30 mg, 0.10 mmol) was dissolved in CH2Cl2 (5 ml) and stirred under an argon atmosphere. BBr3 (500uL, 0.5 mol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for 3 hours then concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH2Cl2, 2:98] to yield BA62d (23 mg, 44% yield). ESI-MS (M+H)+ m/z calcd 288.1, found 288.1.

[0205] Synthesis of 3-(2,5-difluoro-4-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA63)**. A solution of 2,5-difluoro-4-methoxyphenylboronic acid (84 mg, 0.45 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (54 mg, 0.18 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH2Cl2, 2:98] to yield BA63 (50 mg, 17% yield). ESI-MS (M+H)+ m/z calcd 320.1, found 320.0.

[0206] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2,5-difluorophenol **(BA93)**. 3-(2,5-difluoro-4-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA63) (20 mg, 0.06 mmol) was dissolved in CH2Cl2 (2ml) and BBr3 (0.630 mL, 0.63 mmol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for overnight then concentrated in vacuo and purified using by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA93 (6.7 mg, 35% yield). ESI-MS (M+H)+ m/z calcd 306.1, found 306.0.

[0207] Synthesis of 1-isopropyl-3-(3,4,5-trimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA64)**. A solution of 3,4,5-trimethoxyphenylboronic acid (123 mg, 0.58 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (70 mg, 0.23 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH2Cl2, 2:98] to yield BA64 (70 mg, 89% yield). ESI-MS (M+H)+ m/z calcd 344.1, found 344.0.

[0208] Synthesis of 1-isopropyl-3-(2,3-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA65)**. A solution 2,3-dimethoxyphenylboronic acid (105 mg, 0.58 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (70 mg, 0.23 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by silica gel column chromatography [MeOH—CH2Cl2, 2:98] to yield BA65 (63 mg, 88% yield). ESI-MS (M+H)+ m/z calcd 314.1, found 314.1.

[0209] Synthesis of 1-isopropyl-3-(2,4-dimethoxypyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA66)**. A solution 2,4-dimethoxypyrimidin-5-yl-5-boronic acid (106 mg, 0.58 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (70 mg, 0.23 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and

purified by silica gel column chromatography [MeOH—CH2Cl2, 2:98] to yield BA66. ESI-MS (M+H)+ m/z calcd 316.1, found 316.0.

[0210] Synthesis of 1-cyclopentyl-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA79)**. 3-fluoro-5-methoxybenzoic acid (5 g, 0.029 mol) was stirred in CH2Cl2 (50ml) at 0°C under an argon atmosphere. DMF (9 drops, catalytic) was added, followed by oxalyl chloride (12.7 ml, 0.147 mol). Reaction was warmed to room temperature then stirred under argon for one hour. Reaction was concentrated in vacuo to yield 3-fluoro-5-methoxybenzoyl chloride (BA67).

[0211] A solution of malononitrile (2.87 g, 0.044 mol) in dry THF (50 ml) was stirred at 0°C under an argon atmosphere. NaH in paraffin oil (4.64 g, 0.116 mol) was added piece-wise to solution. 3-fluoro-5-methoxybenzoyl chloride (BA67, 0.029 mol) was dissolved in 50 ml dry THF and added slowly to reaction. Reaction was warmed to room temperature and stirred under argon for 24 hours. 1N HCl (200 ml) was slowly added, then reaction mixture was extracted with EtOAc. Organic phases were combined, dried with magnesium sulfate, then concentrated in vacuo to yield 2-((3-fluoro-5-methoxyphenyl)(methoxy)methylene)malononitrile (BA69).

[0212] 2-((3-fluoro-5-methoxyphenyl)(methoxy)methylene)malononitrile (BA69, 0.029 mol) stirred in EtOH (20ml) at room temperature under an argon atmosphere. Hydrazine (1.4 ml, 29 mmol) was added and reaction was left stirring for 90 minutes. Reaction mixture was concentrated in vacuo and dried on vacuum pump overnight to yield intermediate 5-amino-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazole-4-carbonitrile (BA73). Formamide (20ml) was added and reaction was heated to 180°C under an argon atmosphere overnight. Reaction was cooled and dH2O was added (40ml) forcing a white precipitate out of solution. Precipitate was collected and washed with dH2O. Solid was dried and purified by silica gel column chromatography [MeOH—CH2Cl2, 10:90] to yield 3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA75).

[0213] 3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA75, 100 mg, 0.386 mmol) was dissolved in DMF (10 ml). K2CO3 (250 mg, 1.54 mmol) was added and reaction was stirred at room temperature under an argon atmosphere. Iodocyclopentane (0.134 ml, 1.16 mmol) was added with a syringe and reaction was stirred for 2 hours. Solid K2CO3 was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate

(50 ml) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA79.

[0214] Synthesis of 1-cyclopentyl-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA79d)**. 1-cyclopentyl-3-(3-fluoro-5-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA79, 0.386 mmol) was dissolved in CH2Cl2 (2 ml). BBr3 (4 mL, 4 mol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for 2 hours then concentrated in vacuo and purified using by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA79 (69 mg, 57% yield).

[0215] Synthesis of 1-cyclopentyl-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA80)**. A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (400 mg, 1.53 mmol) and K2CO3 (1 g, 6 mmol) in DMF (5 ml) was stirred at room temperature under an argon atomosphere. Iodocyclopentane (1.0g, 0.0084 mol) was added with a syringe. Reaction was refluxed under argon atmosphere for 2 hours. Solid K2CO3 was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH2Cl2, 5:95] yielding BA80 (300 mg, 60% yield). ESI-MS (M+H)+ m/z calcd 330.0, found 330.0.

[0216] Synthesis of 1-(3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)ethanone **(BA81, BA81d & BA81dd)**. A solution of tert-butyl 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (200 mg, 0.76 mmol) in EtOH (3.3 ml) was added to a solution of 1-cyclopentyl-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA80, 100 mg, 0.30 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH2Cl2, 5:95] yielding BA81. BA81 was dissolved in 50:50 CH2Cl2:TFA and stirred for one hour at room temperature. The reaction mixture was concentrated in vacuo and purified using by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA81d. BA81d was dissolved in CH2Cl2 (2ml) and BBr3 (4 mL, 4 mol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for 2 hours then concentrated in vacuo and purified using by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA81dd.

[0217] Synthesis of 3-(3-bromo-5-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA85)**. A solution of 2-(3-bromo-5-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (137 mg, 0.43 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (65 mg, 0.216 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA85 (28mg, 36% yield). ESI-MS (M+H)+ m/z calcd 362.1, found 362.0.

[0218] Synthesis of 3-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-5-bromophenol **(BA87)**. 3-(3-bromo-5-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA85, 0.1 mmol) was dissolved in CH2Cl2 (1 ml) and BBr3 (1 mL, 1 mol) was added slowly with a syringe, while stirring. The reaction was stirred at room temperature for 35 minutes then concentrated in vacuo and purified using by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA87 (10.7 mg, 31% yield). ESI-MS (M+H)+ m/z calcd 348.0, found 348.0.

[0219] Synthesis of tert-butyl 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-1-carboxylate **(BA86)**. A solution of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate (212 mg, 0.61 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (75 mg, 0.25 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O) to yield BA86 (9.3 mg, 9% yield). ESI-MS (M+H)+ m/z calcd 362.1, found 362.0.

[0220] Synthesis of 3-(1H-indol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA89)**. Tert-butyl 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-1-carboxylate (BA86, 9 mg, 0.022 mmol) was dissolved in 50:50 CH2Cl2:TFA and stirred for one hour at room temperature. The reaction mixture was concentrated in vacuo and purified using by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA89 (4.8 mg, 75% yield). ESI-MS (M+H)+ m/z calcd 293.1, found 293.0.

[0221] Synthesis of tert-butyl 5-(4-amino-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-1-carboxylate **(BA88)**. A solution of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate (130 mg, 0.38 mmol) in EtOH (3.3 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.15 mmol) in DME (12 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (1.9 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O) to yield BA88. ESI-MS (M+H)+ m/z calcd 419.2, found 419.1.

[0222] Synthesis of 3-(1H-indol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA94)**. Tert-butyl 5-(4-amino-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indole-1-carboxylate (BA88) was dissolved in 50:50 CH2Cl2:TFA and stirred for one hour at room temperature. The reaction mixture was concentrated in vacuo and purified using by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA89 (6.3 mg). ESI-MS (M+H)+ m/z calcd 319.1, found 319.2.

[0223] Synthesis of 1-cyclopentyl-3-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA90)**. A solution of 3,4-dimethoxyphenylboronic acid (41 mg, 0.23 mmol) in EtOH (1.65ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.09 mmol) in DME (6 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (0.95 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O) to yield BA90 (8.4 mg, 28% yield). ESI-MS (M+H)+ m/z calcd 340.2, found 340.1.

[0224] Synthesis of 3-(1H-indol-4-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA91)**. A solution of 1H-indol-4-yl-4-boronic acid (40 mg, 0.25 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.1 mmol) in DME (6 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (0.95 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA91 (14.6 mg, 50% yield). ESI-MS (M+H)+ m/z calcd 293.1, found 293.1.

[0225] Synthesis of 1-cyclopentyl-3-(1H-indol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA92)**. A solution of 1H-indol-4-yl-4-boronic acid (30 mg, 0.19 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (25 mg, 0.076 mmol) in DME (6 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (0.95 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA92 (23 mg, 95% yield). ESI-MS (M+H)+ m/z calcd 319.2, found 319.1.

[0226] Synthesis of 3-(2,3-dihydrobenzofuran-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA95)**. A solution of 2,3-dihydro-1-benzofuran-5-ylboronic acid (38 mg, 0.23 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.1 mmol) in DME (6 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (0.95 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA95 (15.7 mg, 59% yield). ESI-MS (M+H)+ m/z calcd 296.1, found 296.1.

[0227] Synthesis of 3-(benzofuran-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA96)**. A solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzofuran (56 mg, 0.23 mmol) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (30 mg, 0.1 mmol) in DME (6 ml). Pd(PPh3)4 (30 mg, 0.03 mmol) and saturated Na2CO3 (0.95 ml) were added and the reaction was heated to 80°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA96 (19 mg, 72% yield). ESI-MS (M+H)+ m/z calcd 296.1, found 296.1.

[0228] Synthesis of 5-(4-amino-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-ethoxyphenol **(BA98)**. 1-cyclopentyl-3-(4-ethoxy-3-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (ZK359, 25 mg, 0,071 mmol) was dissolved in CH2Cl2 (5 ml) and stirred at -10°C under an argon atmosphere. After 30 minutes, reaction was brought to 0°C and stirred for 2.5 hours. Reaction was stirred for additional 4 hours at room temperature,

then concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA98 (3 mg, 13 % yield). ESI-MS (M+H)+ m/z calcd 340.1, found 340.1.

[0229] Synthesis of 2-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenylamino)propan-1-ol **(BA99)**. 3-(4-amino-3-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA20d) (30 mg, 0.10 mmol) was dissolved in DMF (0.400 ml). K2CO3 (55 mg, 0.4 mmol) was added and reaction was stirred at 70°C. 3-bromo-1-propanol (0.050 ml, 0.6 mmol) was added and reaction was stirred overnight. Solid K2CO3 was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with saturated NaCl and CH2Cl2. Organic phases concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA99 (8.4 mg, 24 % yield). ESI-MS (M+H)+ m/z calcd 357.2, found 357.1.

[0230] Synthesis of 3-iodo-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA109)**. A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2 g, 7.69 mmol) and K2CO3 (4.25 g, 30.8 mmol) in DMF (5 ml) was stirred at room temperature under an argon atomosphere. Iodomethane (1.17 ml, 7.69 mmol) was added with a syringe. Reaction was stirred under an argon atmosphere at room temperature for 2 hours. Solid K2CO3 was removed by filtration. Solvent was partially removed in vacuo. Sodium citrate (50 ml) was added and reaction was extracted with EtOAc. Organic phases concentrated in vacuo and purified using silica gel column chromatography [MeOH—CH2Cl2, 5:95] yielding BA109 (212 mg, 10% yield). ESI-MS (M+H)+ m/z calcd 275.9, found 275.9

[0231] General synthetic scheme for BA102, BA105-108, BA110, BA118, BA128-BA135, BA137, BA139-140, BA143, BA147, BA149-BA152, BA156, BA158, BA160-BA162. A solution of boronic acid (2.5 equivalents) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA12, 1 equivalent) in DME (6 ml). Pd(PPh3)4 (15 mg, 0.15 mmol) and saturated Na2CO3 (0.95 ml) were added and the reaction was heated to 90°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield desired products. Products were analyzed by LC-MS.

[0232] General synthetic scheme for BA112, BA115, BA121, BA122, BA124, BA136, BA138. BA141, and BA144. A solution of boronic acid (2.5 equivalents) in EtOH (1.65 ml) was added to a solution of 1-cyclopentyl-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

(BA80, 1 equivalent) in DME (6 ml). Pd(PPh3)4 (15 mg, 0.15 mmol) and saturated Na2CO3 (0.95 ml) were added and the reaction was heated to 90°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield desired products. Products were analyzed by LC-MS.

[0233] General synthetic scheme for BA111, BA114, BA116, BA117, BA119, and BA120. A solution of boronic acid (2.5 equivalents) in EtOH (1.65 ml) was added to a solution of 3-iodo-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA109, 1 equivalent) in DME (6 ml). Pd(PPh3)4 (15 mg, 0.15 mmol) and saturated Na2CO3 (0.95 ml) were added and the reaction was heated to 90°C under an argon atmosphere overnight. After cooling, the reaction was extracted with saturated NaCl and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield desired products. Products were analyzed by LC-MS.

[0234] Synthesis of 6-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)quinolin-2-amine **(BA146)**. 3-(2-chloroquinolin-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA130, 50 mg, 0.15 mmol), acetamide (174 mg, 3.0 mmol) and K2CO3 (104 mg, 0.75 mmol) were combined and heated to 200°C under an argon atmosphere for one hour. Reaction was cooled, then extracted with H2O and CH2Cl2. Organic phases were combined, concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA146 (22 mg, 46 % yield). ESI-MS (M+H)+ m/z calcd 320.2, found 320.4.

[0235] Synthesis of 3-(3-amino-1H-indazol-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA154)**. 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorobenzonitrile (BA150, 20 mg, 0.07 mmol) was dissolved in n-BuOH (2 ml). Hydrazine monohydrate (0.400 ml) was added and the reaction was heated to 110°C under an argon atomosphere and left stirring over night. Reaction mixture was concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA154 (15 mg, 70 % yield). ESI-MS (M+H)+ m/z calcd 309.2, found 309.4.

[0236] Synthesis of 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-hydroxybenzonitrile **(BA155_2)**. 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorobenzonitrile (BA150, 25 mg, 0.1 mmol) was dissolved in DMF (1 ml). t-BuOK (24 mg, 0.21 mmol) was added and the reaction was stirred at room temperature overnight. Reaction was then heated to 150°C for 24 hours. The reaction was then concentrated in

vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA155_2 (21 mg, 89 % yield). ESI-MS (M+H)+ m/z calcd 295.1, found 295.4.

[0237] Synthesis of 3-(3-aminobenzo[d]isoxazol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (BA157_2) & 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-hydroxybenzonitrile **(BA157_3)**. 5-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-fluorobenzonitrile (BA151, 20 mg, 0.07 mmol) was dissolved in DMF (1 ml). t-BuOK (24 mg, 0.21 mmol) was added and the reaction was stirred at room temperature overnight. Reaction was then heated to 150°C for 24 hours. The reaction was then concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA157_2 (7 mg), ESI-MS (M+H)+ m/z calcd 295.1, found 295.4 and BA157_3 (8 mg), ESI-MS (M+H)+ m/z calcd 310.1, found 310.4.

[0238] Synthesis of 3-(3-amino-1H-indazol-6-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(BA159)**. 4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2,6-difluorobenzaldehyde (BA149, 20 mg, 0.063 mmol) was dissolved in n-BuOH (1 ml). Hydrazine monohydrate (0.400 ml) was added and the reaction was heated to 100°C under an argon atomosphere and left stirring for 2.5 hours. Reaction mixture was concentrated in vacuo and purified by RP-HPLC (MeCN:H2O:0.1% TFA) to yield BA159 (15 mg, 77 % yield). ESI-MS (M+H)+ m/z calcd 312.1, found 312.4.

[0239] Synthesis of 4-chloro-7-methyl-5-(naphthalen-2-yl)-7H-pyrrolo[2,3-d]pyrimidine **(ZK102)**. A solution of 4-chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (19 mg, 0.065 mmol), naphthalen-2-yl-2-boronic acid (12.2 mg, 0.071 mmol), Na_2CO_3 (68.9 mg, 0.65 mmol) and $PdCl_2$(dppf) (26.5 mg, 0.00325 mmol) in THF (3 mL) was heated to reflux overnight under an argon atmosphere. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield ZK102 (5 mg, 26% yield). ESI-MS $(M+H)^+$ *m/z* calcd 294.1, found 294.3.

[0240] Synthesis of 4-chloro-7-methyl-5-(3-biphenyl)-7H-pyrrolo[2,3-d]pyrimidine **(ZK103)**. A solution of 4-chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (10 mg, 0.034 mmol), 3-biphenyl-boronic acid (7.4 mg, 0.038 mmol), Na_2CO_3 (36.1 mg, 0.34 mmol) and $PdCl_2$(dppf) (1.4 mg, 0.0017 mmol) in THF (10 mL) was heated to reflux overnight under an argon atmosphere. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield ZK103 (3 mg, 28% yield). ESI-MS $(M+H)^+$ *m/z* calcd 320.1, found 320.0.

[0241] Synthesis of 3-(4-*tert*-butylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK125)**. 1-*tert*-butyl-3-(4-*tert*-butylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux for 2 hours. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA) to yield ZK125 (quant.). ESI-MS $(M+H)^+$ *m/z* calcd 268.2, found 268.4.

[0242] Synthesis of 3-(3-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK126)**. 1-*tert*-butyl-3-(3-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.16 mmol) was dissolved in a solution of formic acid (5 mL) and conc. HCl (0.1 mL) and heated to reflux for 2.5 hours. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 304.1, found 304.3.

[0243] Synthesis of 3-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK127)**. 1-*tert*-butyl-3-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (23 mg, 0.1 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.3 mL) and heated to reflux for 2.5 hours. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 226.1, found 226.3.

[0244] Synthesis of 3-(3-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK128)**. 1-*tert*-butyl-3-(3-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (23 mg, 0.055 mmol) was dissolved in a solution of formic acid (5 mL) and conc. HCl (0.1 mL) and heated to reflux for 2 hours. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 257.1, found 257.3.

[0245] Synthesis of 3-(benzo[d][1,3]dioxol-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK129)**. 1-*tert*-butyl-3-(benzo[d][1,3]dioxol-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (21 mg, 0.082 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.2 mL) and heated to reflux for 2 hours. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 256.1, found 256.3.

[0246] Synthesis of 3-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK130)**. 1-*tert*-butyl-3-(4-nitrophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (21 mg, 0.082 mmol) was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 257.1, found 257.3.

[0247] Synthesis of 3-(3-(2,6-dichlorobenzyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK131)**. 1-*tert*-butyl-3-(3-(2,6-dichlorobenzyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (19.5 mg, 0.05 mmol) was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 386.1, found 386.2.

[0248] Synthesis of 3-(2,3-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK132)**. 1-*tert*-butyl-3-(2,3-dimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (34 mg, 0.14 mmol) was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 240.1, found 240.4.

[0249] Synthesis of 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol **(ZK133)**. 1-*tert*-butyl-2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol (5 mg, 0.014 mmol) was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 228.1, found 228.3.

[0250] Synthesis of 3-o-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK134)**. 1-*tert*-butyl-3-o-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 226.1, found 226.3.

[0251] Synthesis of 3-(3-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK135)**. 1-*tert*-butyl-3-(3-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was dissolved in a solution of formic acid (2 mL) and conc. HCl (0.2 mL) and heated to reflux for 30 min. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 227.1, found 227.3.

[0252] Synthesis of 3-(3-(benzyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK136)**. 1-*tert*-butyl-3-(3-(benzyloxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (19 mg, 0.052 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux for 30 min. Reaction yielded a mixture of **ZK136** and 3-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol **(ZK138)**. Reaction was concentrated in vacuo and the

products purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ZK136: ESI-MS $(M+H)^+$ *m/z* calcd 318.1, found 318.3. ZK138: ESI-MS $(M+H)^+$ *m/z* calcd 228.1, found 228.3.

[0253] Synthesis of 3-(4-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK137)**. 1-*tert*-butyl-3-(4-aminophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (9 mg, 0.032 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.2 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 227.1, found 227.3.

[0254] Synthesis of 3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK139)**. 1-*tert*-butyl-3-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (9 mg, 0.029 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 266.1, found 266.4.

[0255] Synthesis of 5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine **(ZK140)**. 4-chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (90 mg, 0.31 mmol) was taken up in 7N NH_3/MeOH and heated in a sealed tube at 110° C overnight. Reaction was concentrated in vacuo to give a brown/off-white solid.

[0256] Synthesis of 3-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK141)**. 1-*tert*-butyl-3-p-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 226.1, found 226.3.

[0257] Synthesis of 3-(4-biphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK142)**. 1-*tert*-butyl-3-(4-biphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (22 mg, 0.066 mmol) was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 288.1, found 288.3.

[0258] Synthesis of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK143)**. 1-*tert*-butyl-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (19 mg, 54.1 mmol)

was dissolved in a solution of formic acid (1 mL) and conc. HCl (0.1 mL) and heated to reflux. The reaction was allowed to proceed 30 min., then concentrated in vacuo and the products purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 304.1, found 304.3.

[0259] Synthesis of 1-benzyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK147)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (110 mg, 0.42 mmol) was dissolved in DMF (2 mL) and K_2CO_3 (220 mg, 1.6 mmol) and benzyl bromide (71.8 mg, 0.42 mmol) were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration and then purified further by silica gel chromatography (5% MeOH/CH_2Cl_2) to yield a white solid.

[0260] Synthesis of 5-(4-(benzyloxy)phenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine **(ZK150)**. A solution of 5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (5 mg, 0.018 mmol), 4-(benzyloxy)phenylboronic acid (21 mg, 0.091 mmol), K_3PO_4 (19.3 mg, 0.091 mmol) and $Pd(PPh_3)_4$ (12.5 mg, 0.011 mmol) in DMF (3 mL) was heated to 60° C under an argon atmosphere. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 331.1, found 331.3.

[0261] Synthesis of 5-(3-biphenyl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine **(ZK151)**. A solution of 5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (5 mg, 0.018 mmol), 3-biphenylboronic acid (18 mg, 0.091 mmol), K_3PO_4 (19.3 mg, 0.091 mmol) and $Pd(PPh_3)_4$ (12.5 mg, 0.011 mmol) in DMF (3 mL) was heated to 60° C under an argon atmosphere. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 301.1, found 301.3.

[0262] Synthesis of 5-(benzo[b]thiophen-2-yl)-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine **(ZK152)**. A solution of 5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-amine (5 mg, 0.018 mmol), benzo[b]thiophen-2-yl-2-boronic acid (16 mg, 0.091 mmol), K_3PO_4 (19.3 mg, 0.091 mmol) and $Pd(PPh_3)_4$ (12.5 mg, 0.011 mmol) in DMF (3 mL) was heated to 60° C under an argon atmosphere. Reaction was concentrated *in vacuo* and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). ESI-MS $(M+H)^+$ *m/z* calcd 281.1, found 281.3.

[0263] Synthesis of 3-(naphthalen-2-yl)-1-phenethyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK155)**. 2-(methoxy(naphthalen-6-yl)methylene)malononitrile (100 mg, 0.43 mmol) and phenethylhydrazine hydrogen chloride (58.5 mg, 0.43 mmol) were dissolved in EtOH (3 mL)

and TEA (60 μL, 0.43 mmol) and heat to reflux for one hour. The product was extracted with diethylether and concentrated *in vacuo*. This concentrate was then dissolved in formamide (10 mL) and heated to 160-180° C overnight. The following day the reaction was cooled, poured into water, and the precipitated product collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 366.2, found 366.2.

[0264] Synthesis of 1-isopropyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK156)**. 2-(methoxy(naphthalen-6-yl)methylene)malononitrile (100 mg, 0.43 mmol) and isopropylhydrazine hydrogen chloride (47.3 mg, 0.43 mmol) were dissolved in EtOH (3 mL) and TEA (1 eq.) and heat to reflux for one hour. The product was extracted with diethylether and concentrated *in vacuo*. This concentrate was then dissolved in formamide (10 mL) and heated to 160-180° C overnight. The following day the reaction was cooled, poured into water, and the precipitated product collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 304.2, found 304.2.

[0265] Synthesis of 1-ethyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK157)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.42 mmol) was dissolved in DMF (3 mL) and K_2CO_3 (220 mg, 1.6 mmol) and ethyl iodide (37 μL, 0.46 mmol) were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 290.1, found 290.2.

[0266] Synthesis of 1-cyclopentyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK158)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (100 mg, 0.42 mmol) was dissolved in DMF (3 mL) and K_2CO_3 (220 mg, 1.6 mmol) and cyclopentyl bromide (49.5 μL, 0.46 mmol) were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 330.2, found 330.2.

[0267] Synthesis of 1-allyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK159)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K_2CO_3 (110 mg, 0.8 mmol) and allyl iodide (23 μL, 0.25 mmol) were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 302.1, found 302.2.

[0268] Synthesis of 2-(4-amino-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetamide **(ZK162)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K_2CO_3 (110 mg, 0.8 mmol) and iodoacetamide (46 mg, 0.25 mmol) were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 319.1, found 319.2.

[0269] Synthesis of 1-(cyclopropylmethyl)-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK165)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K_2CO_3 (110 mg, 0.8 mmol) and cyclopropyl methyl bromide (22 μL, 0.25 mmol) were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 316.2, found 316.2.

[0270] Synthesis of 1-isopentyl-3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK161)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K_2CO_3 (110 mg, 0.8 mmol) and isobutyl bromide were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 332.2, found 332.3.

[0271] Synthesis of 3-(naphthalen-2-yl)-1-((E)-3-phenylprop-1-enyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK167)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K_2CO_3 (110 mg, 0.8 mmol) and 1-((E)-3-bromoprop-1-enyl)benzene were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 378.2, found 378.2.

[0272] Synthesis of 3-(naphthalen-2-yl)-1-(prop-2-ynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK168)**. 3-(naphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.21 mmol) was dissolved in DMF (1.5 mL) and K_2CO_3 (110 mg, 0.8 mmol) and propargylbromide were added. The reaction was heated to 60° C overnight, then cooled to RT and poured into water (30 mL). The precipitate was collected by filtration. ESI-MS $(M+H)^+$ *m/z* calcd 300.1, found 300.2

[0273] Synthesis of 3-ethoxy-4-methoxybenzoyl chloride **(ZK299)**. 3-ethoxy-4-methoxybenzoic acid (5 g, 25.5 mmol) was added to a solution of CH_2Cl_2 (40 mL) and benzene (20 mL) in a flame-dried 150 mL round bottom flask. Anhydrous DMF (9 drops) was added and the solution was cooled on ice. Oxalyl chloride (11 mL, 128 mmol) was added dropwise, and the reaction was then allowed to warm to RT. The reaction was stirred at RT for 90 minutes, then concentrated *in vacuo* yield an off-white solid. The solid was placed on a high-vacuum line for 2 hours, and then taken onto the next step without further characterization.

[0274] Synthesis of 2-((3-ethoxy-4-methoxyphenyl)(hydroxy)methylene)malononitrile **(ZK301).** NaH (2.2 g, 56 mmol, 60% dispersion in paraffin oil) was added to a solution of malononitrile (1.85 g, 28 mmol) in THF (30 mL) on ice. 3-ethoxy-4-methoxybenzoyl chloride (25.5 mmol) was dissolved in THF (50 mL) and added the first solution dropwise by syringe at 0° C. The ice was then removed and the reaction was allowed to proceed at RT for 60 min. 1N HCl (100 mL) was added and the solution was extracted three times with EtOAc. The organic phase was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give an orange solid that was taken onto the next step without further characterization.

[0275] Synthesis of 2-((3-ethoxy-4-methoxyphenyl)(methoxy)methylene)malononitrile **(ZK302).** 2-((3-ethoxy-4-methoxyphenyl)(hydroxy)methylene)malononitrile (25.5 mmol) and sodium bicarbonate (17 g, 204 mmol) were combined in a solution of 1,4-dioxane (48 mL) and water (8 mL). Dimethylsulphate (17 mL, 178 mmol) was slowly added and the reaction was heated to 80-90° C for 2 hours. The reaction was cooled to RT, water was added, and the aqueous phase extracted three times with EtOAc (200 mL). The organic phases were combined, dried with $MgSO_4$, and filtered to give a red oil. The oil was purified by silica gel chromatography (10% EtOAc/Hexanes, $R_f \sim 0.1$) to give a white solid (3.59 g, 54.5% yield over three steps). ESI-MS $(M+H)^+$ *m/z* calcd 259.1, found 259.0.

[0276] Synthesis of 5-amino-3-(3-ethoxy-4-methoxyphenyl)-1-isopropyl-1H-pyrazole-4-carbonitrile **(ZK303).** 2-((3-ethoxy-4-methoxyphenyl)(methoxy)methylene)malononitrile (200 mg, 0.78 mmol), isopropylhydrazine hydrogen chloride (86 mg, 0.78 mmol), and triethylamine (0.10 mL, 0.78 mmol) were combined in ethanol (5 mL) and heated to reflux for 90 minutes. The reaction was then cooled to RT, water was added and the aqueous phase was extracted three times with EtOAc. The organic phase was concentrated and carried onto the next step without further characterization. ESI-MS $(M+H)^+$ *m/z* calcd 301.1, found 301.0

[0277] Synthesis of 3-(3-ethoxy-4-methoxyphenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine **(ZK305)**. 5-amino-3-(3-ethoxy-4-methoxyphenyl)-1-isopropyl-1H-pyrazole-4-carbonitrile was dissolved in formamide (20 mL) and heated to 180° C overnight. The next day the reaction was cooled to RT, water was added, and the precipitate was collected by filtration. The precipitate was then dissolved in CH_2Cl_2/MeOH and passed through a silica plug. The product was then lyophilized from benzene to yield an off-white solid (48 mg, 19% over two steps). ESI-MS $(M+H)^+$ *m/z* calcd 328.2, found 328.0.

[0278] Synthesis of 5-amino-3-(3-ethoxy-4-methoxyphenyl)-1-(2-hydroxyethyl)-1H-pyrazole-4-carbonitrile **(ZK304)**. 2-((3-ethoxy-4-methoxyphenyl)(methoxy)methylene)malononitrile (200 mg, 0.78 mmol), 2-hydroxyethylhydrazine (0.056 mL, 0.78 mmol), and triethylamine (0.10 mL, 0.78 mmol) were combined in ethanol (5 mL) and heated to reflux for 90 minutes. The reaction was then cooled to RT, water was added and the aqueous phase was extracted three times with EtOAc, CH_2Cl_2, and $CHCl_3$. The organic phase was concentrated and carried onto the next step without further characterization. ESI-MS $(M+H)^+$ *m/z* calcd 303.1, found 303.0.

[0279] 2-(4-amino-3-(3-ethoxy-4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethanol **(ZK306)** . 5-amino-3-(3-ethoxy-4-methoxyphenyl)-1-(2-hydroxyethyl)-1H-pyrazole-4-carbonitrile was dissolved in formamide (20 mL) and heated to 180° C overnight. The next day the reaction was cooled to RT, water was added, and the precipitate was collected by filtration. The precipitate was then dissolved in CH_2Cl_2/MeOH and passed through a silica plug. The product was then lyophilized from benzene to yield a brown solid (6.4 mg, 2.5% over two steps). ESI-MS $(M+H)^+$ *m/z* calcd 330.1, found 330.0.

B. Structural Studies

[0280] Crystal structures of p110γ have been reported, alone and in complex with ATP or pan-specific inhibitors such as LY294002 and wortmannin (Walker et al., 2000; Walker et al., 1999). To explore how potent and selective inhibitors bind, the crystal structures of PI3-K inhibitors from three chemotypes bound to human p110γ were determined at 2.5 - 2.6 Å resolution: the quinazoline purine PIK-39, the imidazopyridine PIK-90 and the phenylthiazole PIK-93 (Figure 2).

[0281] Based on these co-crystal structures and a conserved arylmorpholine pharmacophore model, structural models were generated for three additional chemotypes

bound to p110γ: the pyridinylfuranopyrimidine PI-103, the morpholinochromone PIK-108, and the morpholinopyranone KU-55933 (Figure 2). Model-building for these inhibitors was guided by the observation that each compound contains the key arylmorpholine pharmacophore found in LY294002.

[0282] PIK-39 is an isoquinoline purine that inhibits p110δ at mid-nanomolar concentrations, p110γ and p110β at concentrations ~100-fold higher, and shows no activity against any other PI3-K family member, including p110α, at concentrations up to 100 μM (Figure 5). The biochemical selectivity of this compound is achieved through an unusual binding mode revealed in its co-crystal structure with p110γ (Figure 2C). Only the mercaptopurine moiety of PIK-39 makes contacts within the interior of the ATP binding pocket, and this ring system is rotated ~110° and twisted ~35° out of the plane relative to the adenine of the ATP. In this orientation, it satisfies hydrogen bonds to the backbone amides of Val 882 and Glu 880 (thereby recapitulating the hydrogen bonds made by N1 and N6 of adenine).

[0283] In contrast to other PI3-K inhibitor structures, PIK-39 does not access the deeper pocket in the active site interior (Figure 2C, lightly shaded area labeled as "Affinity Pocket"). Instead, the aryl-isoquinoline moiety of PIK-39 extends out to the entrance of the ATP binding pocket (Figure 2B). In this region, the kinase accommodates the inhibitor by undergoing a conformational rearrangement in which Met 804 shifts from an "up" position, in which it forms the ceiling of the ATP binding pocket, to a "down" position which it packs against the isoquinoline moiety. The effect of this movement, which is unique to the PIK-39 structure (Figure 2B), is to create a novel hydrophobic pocket between Met 804 and Trp 812 at the entrance to the ATP binding site. This induced-fit pocket buries ~180 Å2 of solvent accessible inhibitor surface area, enabling PIK-39 to achieve nanomolar affinity despite limited contacts within the active site core.

[0284] Co-crystal structures of PIK-90 and PIK-93 compounds bound to p110γ were determined. PIK-90 and PIK-93 both make a hydrogen bond to the backbone amide nitrogen of Val 882 (Figure 2D), an interaction conserved among all known PI3-K inhibitors (Walker et al., 2000). In addition to this hydrogen bond, PIK-93 makes a second hydrogen bond to the backbone carbonyl of Val 882 and a third between its sulphonamide moiety and the side chain of Asp 964. PIK-93 is one of the most polar inhibitors in our panel (clogP = 1.69) and these extended polar interactions may compensate for its limited hydrophobic surface area.

[0285] PIK-90 binds in a mode similar to PIK-93, although this larger compound makes more extensive hydrophobic interactions, burying 327 $Å^2$ of solvent accessible surface area. To achieve this, PIK-90 projects its pyridine ring into a deeper cavity that is partially accessed by PIK-93 but not occupied by ATP (Figure 2D, lightly shaded circle). In this region, the pyridine ring of PIK-90 is poised to make a hydrogen bond to Lys 833, and we find that replacement of this pyridine nitrogen with carbon results in a 100-fold loss in affinity (PIK-95, Figure 4). PI-103, a third multi-targeted PI3K inhibitor, projects a phenol into the same pocket based on an arylmorpholine pharmacophore model (Figure 2D).

[0286] Two structural features distinguish these potent, multi-targeted inhibitors from the more selective compounds in our panel. First, these compounds adopt a flat conformation in the ATP binding pocket, whereas highly selective inhibitors project out of the plane occupied by ATP (Figure 2). Second, the most potent inhibitors project into a deeper binding pocket that is not accessed by ATP (Figure 2A). Much of the surface of this affinity pocket is contributed by the side-chain of Ile 879.

[0287] The mercaptopurine in the PIK-39 structure was replaced with adenine to yield a model of IC87114 (Figure 3A). This substitution provided the adenine of IC87114 in the correct orientation to make the same hydrogen bonds as the mercaptopurine of PIK-39, even though these two ring systems are rotated by 110° with respect to each other.

[0288] Unlike other inhibitor chemotypes, PIK-39 does not exploit the PI3-kinase affinity pocket (Figure 2C). The pyrazolopyrimidine analog of IC87114 (PIK-293) as well as a novel analog containing an m-phenol (PIK-294, Figure 3A) were then tested for inhibition of the class I PI3-Ks. PIK-294 was up to 60-fold more potent than PIK-293 (Figure 3A).

[0289] The structure of PIK-39 bound to p110γ reveals a conformational rearrangement of Met 804 that creates an induced pocket, and we have hypothesized that this conformational rearrangement underlies the selectivity of PIK-39 for p110δ. A prediction of this model is that mutation of Met 804 should perturb the binding of p110δ-selective inhibitors (which access the induced pocket), but not affect other classes of inhibitors (which do not access this pocket). Modeling suggests that mutation of Met 804 to a β-branched amino acid (such as valine or isoleucine) should restrict the pocket formed by rearrangement of that residue (Figure 3B, right). Therefore, we mutated the corresponding residue in p110δ (Met 752) to valine or isoleucine, expressed and purified these kinases, and tested them for sensitivity to

PI3-K inhibitors (Figure 3B). We find that M752I and M752V p110δ are resistant to the p110δ-selective inhibitors PIK-39 and IC87114, but retain sensitivity to the p110α/multi-targeted inhibitors PIK-90, PIK-93, and PI-103. This chemotype-specific resistance supports the unique role of Met 752 in gating an inducible selectivity pocket.

[0290] Antagonist modeling was performed using the PyMOL Molecular Graphics System. All p110γ crystal structures (PDB codes in parentheses), including the Apo (1E8Y), ATP (1E8X), Wortmannin (1E7U), LY294002 (1E7V), Quercetin (1E8W), Myricetin (1E90), and Staurosporine (1E8Z), PIK-90, PIK-93, and PIK-39 bound forms were structurally aligned using PyMOL's align function. Models for the inhibitors PIK-108, KU-55933, and PI-103 were built on top of the LY294002 arylmorpholine scaffold (1E7V) using PyMOL's fragment building function. A model for the inhibitor IC87114 was similarly built on top of the PIK-39 aryl-isoquinoline scaffold.

[0291] The model for PI-103 was built into the protein structure of p110γ bound to PIK-90, because the PIK-90 structure contains the enlarged affinity pocket that is necessary to accommodate PIK-103's phenolic moiety (the PIK-90 p110γ structure otherwise does not exhibit any conformational differences in the arymorpholine-binding region in comparison to the LY294002-bound p110γ structure). The models for PIK-108, KU-55933, and IC87114 were built into the protein structure of p110γ bound to PIK-39 because these inhibitors possess bulky groups that project out of the adenine plane and are likely to exploit the unique "Met 804 down" induced-fit pocket. In all inhibitor models, the choice of protein structure and inhibitor binding mode is based on extensive biochemical SAR as well as inhibitor geometry. The protein structures and inhibitor models have not been minimized to optimize binding energy, but care was taken to prevent any gross steric clashes and to satisfy key hydrogen bonds.

C. p110α/p85α, p110β/p85α, p110δ/p85α, and p110γ Assay

[0292] The class I PI3-Ks were either purchased (p110α/p85α, p110β/p85α, p110δ/p85α from Upstate, and p110γ from Sigma) or expressed as previously described (Knight et al., 2004). IC50 values were measured using either a standard TLC assay for lipid kinase activity (described below) or a high-throughput membrane capture assay. Kinase reactions were performed by preparing a reaction mixture containing kinase, inhibitor (2% DMSO final concentration), buffer (25 mM HEPES, pH 7.4, 10 mM MgCl2), and freshly sonicated

phosphatidylinositol (100 μg/ml). Reactions were initiated by the addition of ATP containing 10 μCi of γ-32P-ATP to a final concentration 10 or 100 μM, as indicated in Figure 5, and allowed to proceed for 5 minutes at room temperature. For TLC analysis, reactions were then terminated by the addition of 105 μl 1N HCl followed by 160 μl CHCl3:MeOH (1:1). The biphasic mixture was vortexed, briefly centrifuged, and the organic phase transferred to a new tube using a gel loading pipette tip precoated with $CHCl_3$. This extract was spotted on TLC plates and developed for 3 – 4 hours in a 65:35 solution of n-propanol:1M acetic acid. The TLC plates were then dried, exposed to a phosphorimager screen (Storm, Amersham), and quantitated. For each compound, kinase activity was measured at 10 – 12 inhibitor concentrations representing two-fold dilutions from the highest concentration tested (typically, 200 μM). For compounds showing significant activity, IC50 determinations were repeated two to four times, and the reported value is the average of these independent measurements.

[0293] Results are set forth below in Table 2.

D. Abl Assay

[0294] Inhibitors (final concentration: 10 μM) were assayed in triplicate against recombinant full-length Abl or Abl (T315I) (Upstate) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 200 μM ATP (2.5 μCi of γ-32P-ATP), and 0.5 mg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK was used as phosphoacceptor (200 μM) . Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0295] Results are set forth below in Table 3.

E. Hck Assay

[0296] Hck: Inhibitors (final concentration: 10 μM) were assayed in triplicate against recombinant full-length Hck in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 200 μM ATP (2.5 μCi of γ-32P-ATP), and 0.5 mg/mL BSA. The optimized Src family kinase peptide substrate EIYGEFKKK was used as phosphoacceptor (200 μM) . Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5%

phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0297] Results are set forth below in Table 3.

F. Inulsin Receptor (IR) Assay

[0298] IInhibitors (final concentration: 10 μM) were assayed in triplicate against recombinant insulin receptor kinase domain (Upstate) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 10 mM MnCl2, 200 μM ATP (2.5 μCi of γ-32P-ATP), and 0.5 mg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0299] Results are set forth below in Table 4.

G. Src Assay

[0300] Src, Src (T338I): Inhibitors (final concentration: 10 μM) were assayed in triplicate against recombinant full-length Src or Src (T338I) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 200 μM ATP (2.5 μCi of γ-32P-ATP), and 0.5 mg/mL BSA. The optimized Src family kinase peptide substrate EIYGEFKKK was used as phosphoacceptor (200 μM) . Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0301] Results are set forth below in Table 3.

H. DNA-PK (DNAK) Assay

[0302] DNA-PK was purchased from Promega and assayed using the DNA-PK Assay System (Promega) according to the manufacturer's instructions.

[0303] Results are shownin Table 2.

I. mTOR Assay

Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant mTOR (Invitrogen) in an assay containing 50 mM HEPES, pH 7.5, 1mM EGTA, 10 mM MgCl2, 2.5 mM, 0.01% Tween, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Rat recombinant PHAS-1/4EBP1 (Calbiochem; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0304] Results are set forth in Table 4 below.

J. Vascular endothelial growth receptor

[0305] Vascular endothelial growth receptor 2(KDR): Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant KDR receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 0.1% BME, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0306] Results are set forth in Table 3 below.

K. Ephrin receptor B4 (EphB4) Assay

[0307] Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant Ephrin receptor B4 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 0.1% BME, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0308] Results are set forth in Table 3 below.

L. Epidermal growth factor receptor (EGFR) Assay

Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant EGF receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 0.1% BME, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0309] Results are set forth in Table 3 below.

M. KIT Assay

[0310] Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant KIT kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 1mM DTT, 10mM MnCl2, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0311] Results are set forth in Table 4 below.

N. RET Assay

[0312] Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant RET kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 2.5mM DTT,10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK was used as phosphoacceptor (200 μM) . Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0313] Results are set forth in Table 4 below.

O. Platelet derived growth factor receptor (PDGFR) Assay

[0314] Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant PDG receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 2.5mM DTT,10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK was used as phosphoacceptor (200 μM) . Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

[0315] Results are set forth in Table 4 below.

P. FMS-related tyrosine kinase 3 (FLT-3) Assay

[0316] Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant FLT-3 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 2.5mM DTT,10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK was used as phosphoacceptor (200 μM) . Reactions were terminated by spotting onto phosphocellulose sheets, which were washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

Results are set forth in Table 4 below.

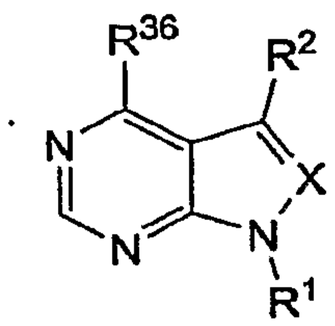
Q. TEK receptor tyrosine kinase (TIE2) Assay

[0317] Inhibitors (final concentrations 50 μM -0.003 μM) were tested against recombinant TIE2 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl2, 2mM DTT, 10mM MnCl2, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) was used as a substrate. Reactions were terminated by spotting onto nitrocellulose, which was washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

Results are set forth in Table 4 below.

R. Results

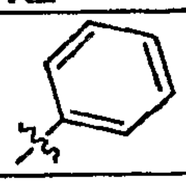
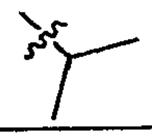
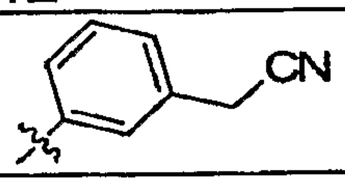
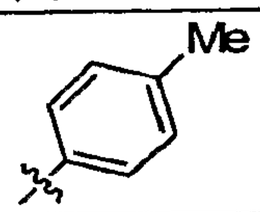
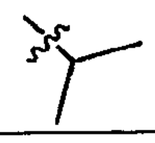
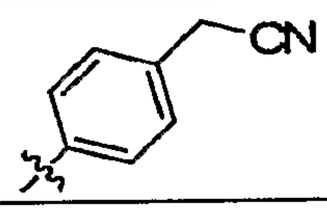
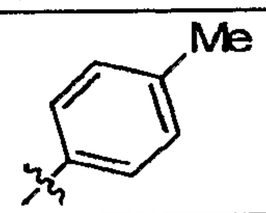
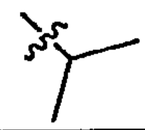
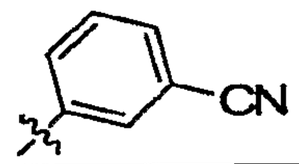
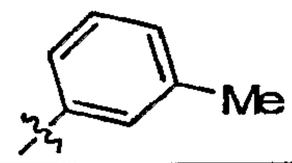
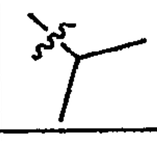
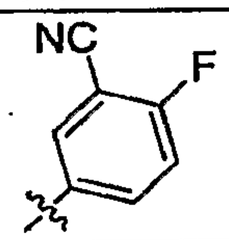
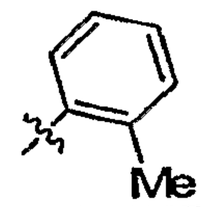
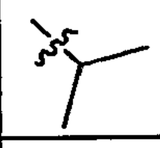
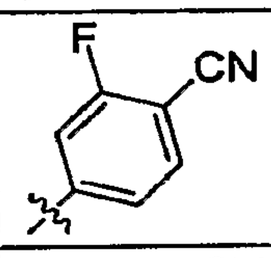
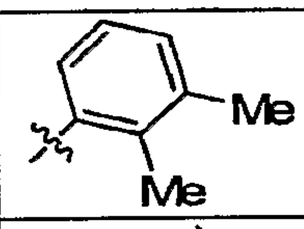
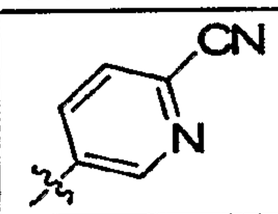
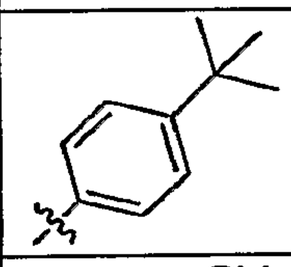
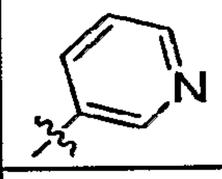
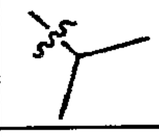
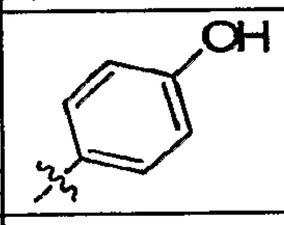
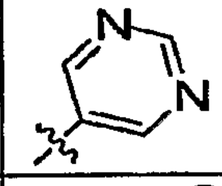
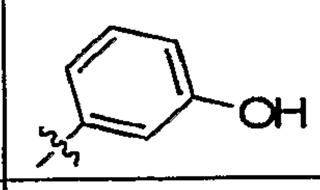
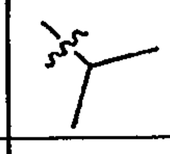
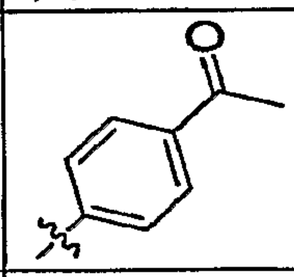
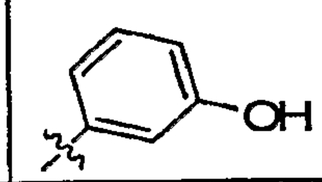
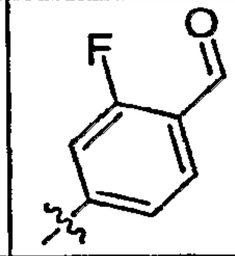
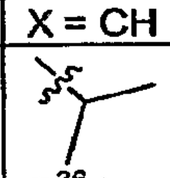
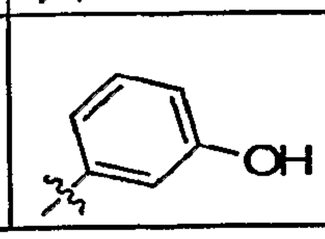
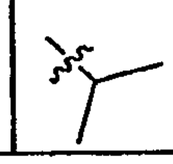
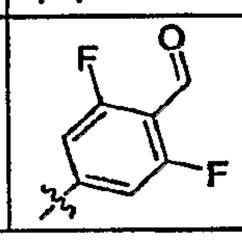
[0318] In Table 1, the compounds have the formula:

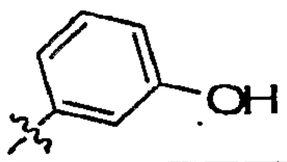
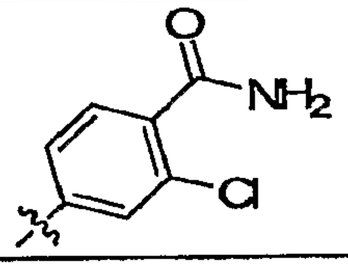
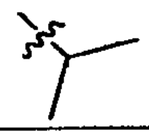
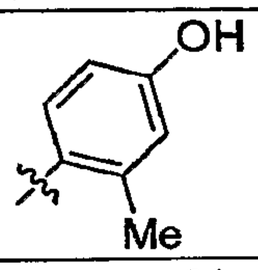
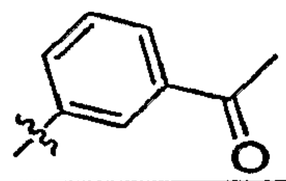
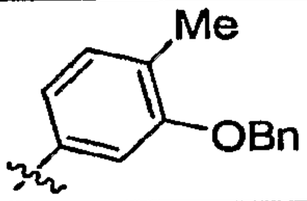
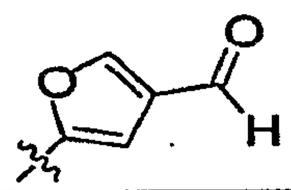
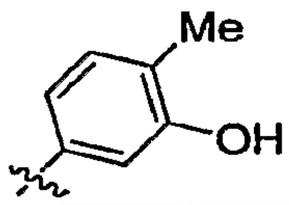
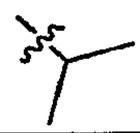
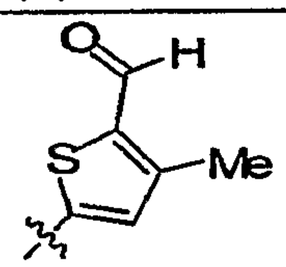
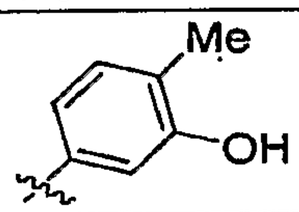
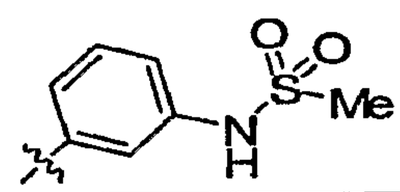
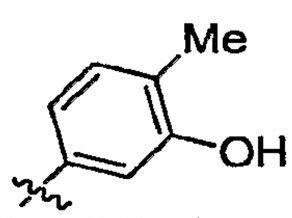
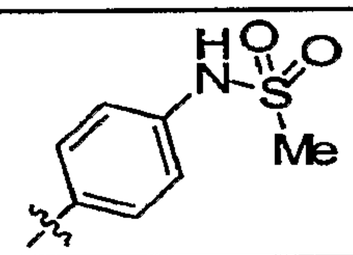
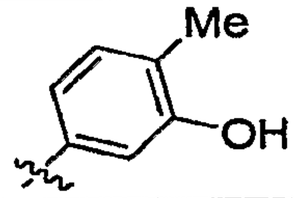
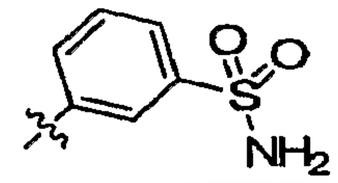
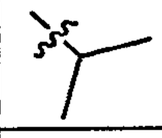
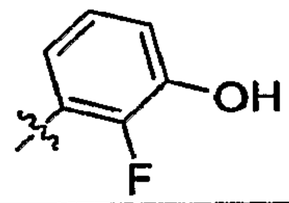
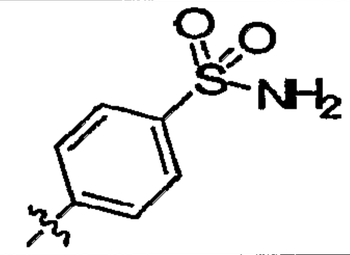
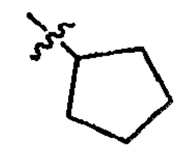
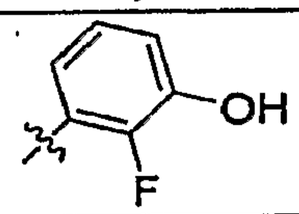
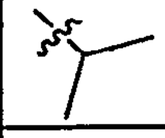
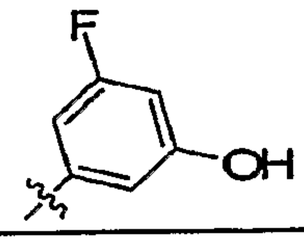
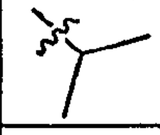
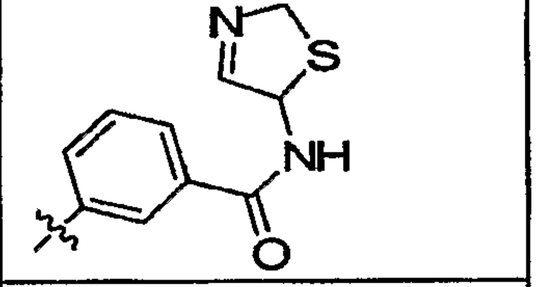
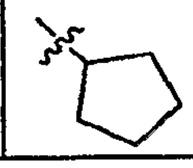
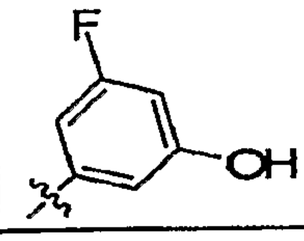
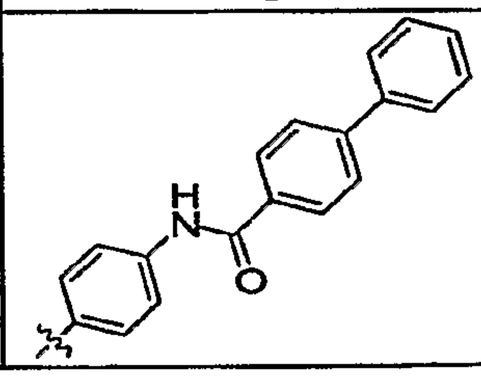


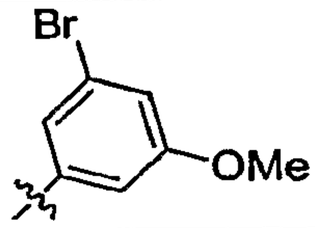
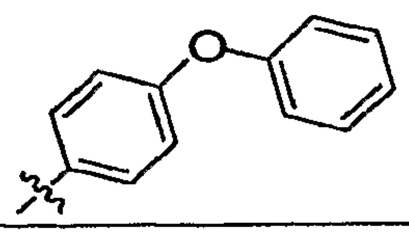
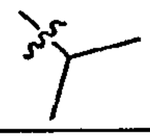
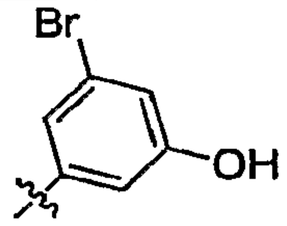
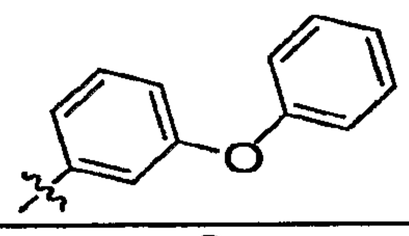
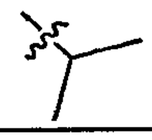
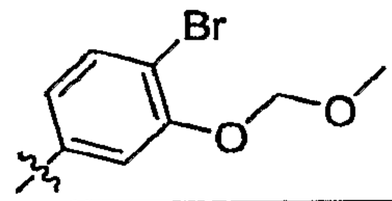
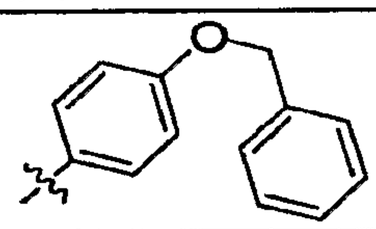
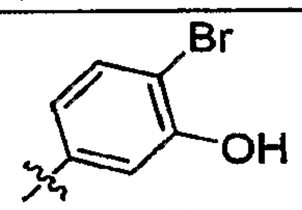
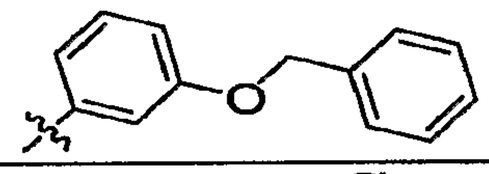
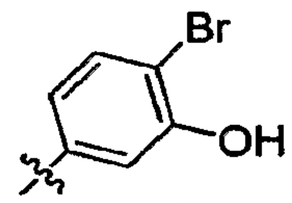
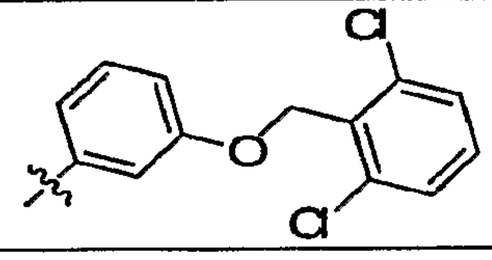
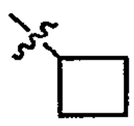
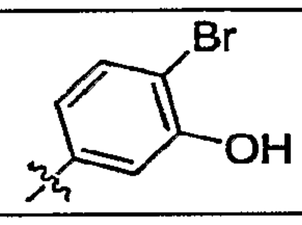
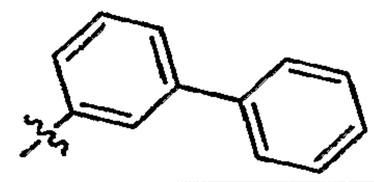
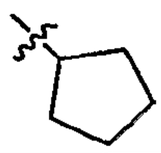
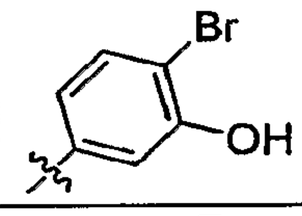
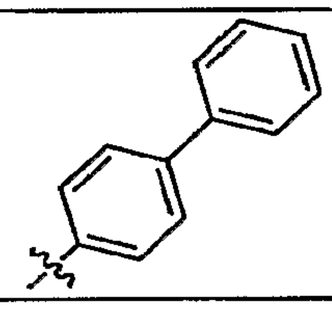
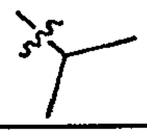
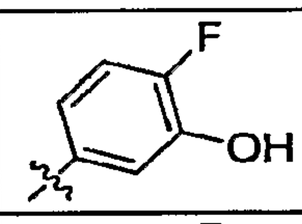
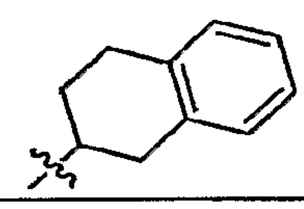
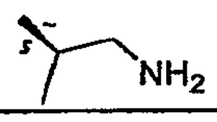
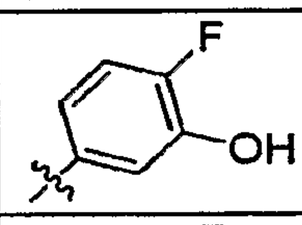
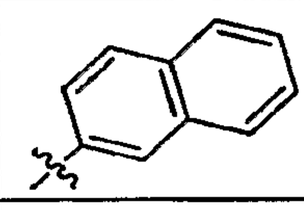
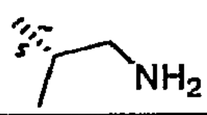
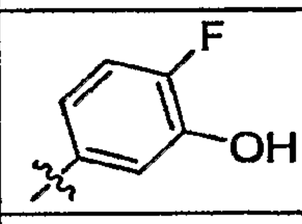
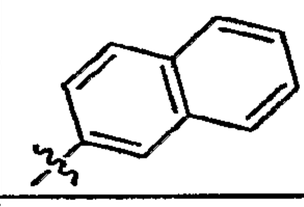
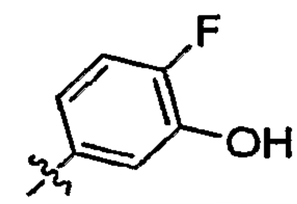
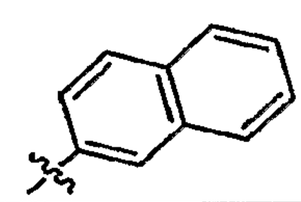
(I).

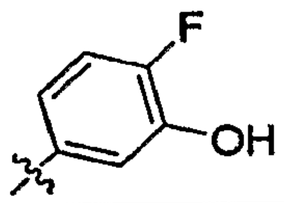
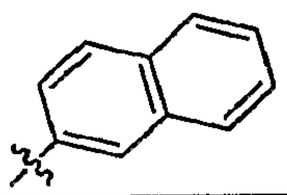
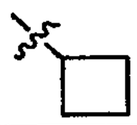
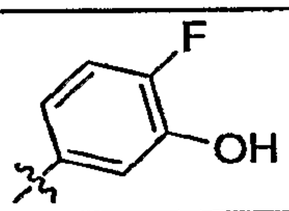
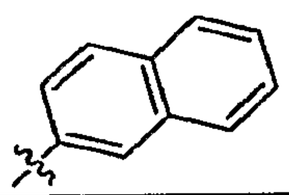
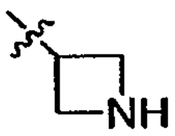
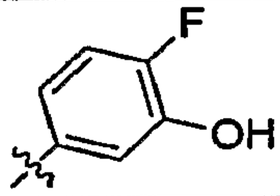
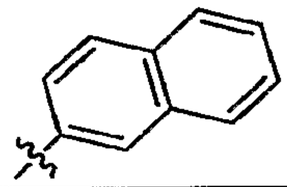
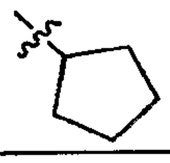
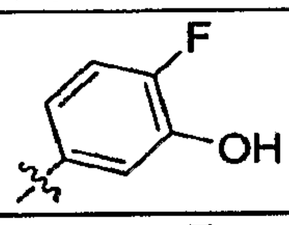
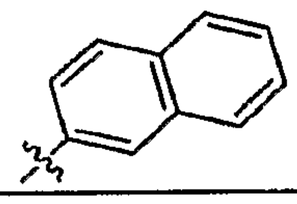
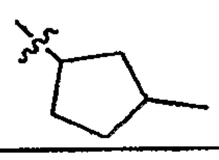
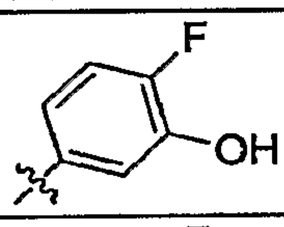
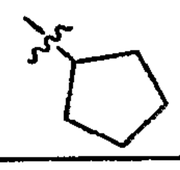
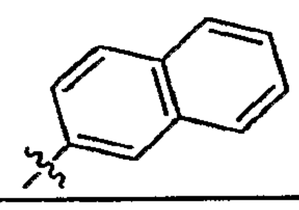
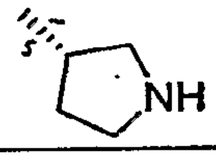
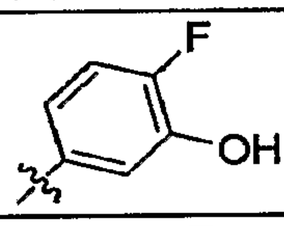
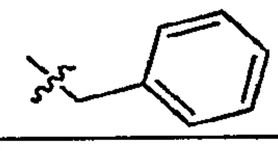
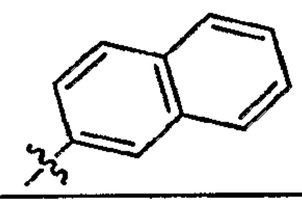
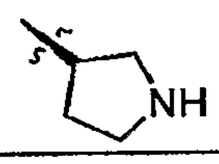
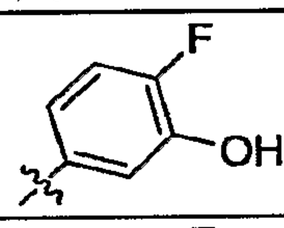
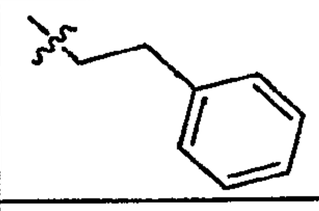
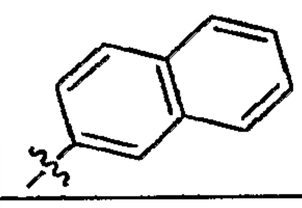
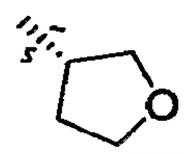
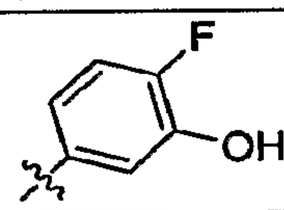
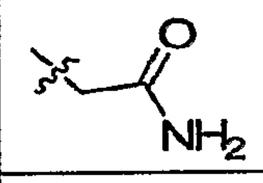
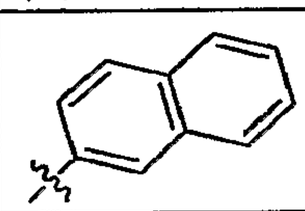
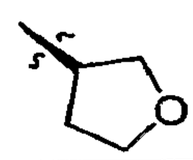
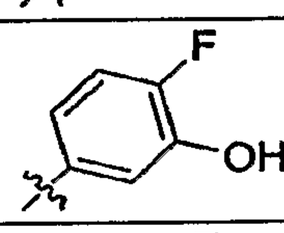
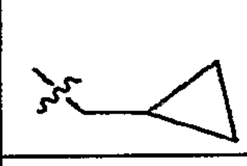
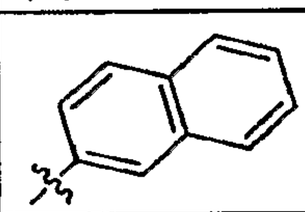
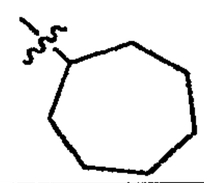
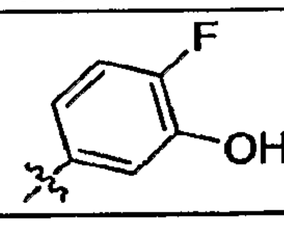
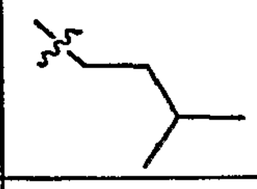
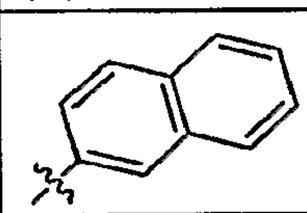
R^1 and R^2 are as defined in Table 1. X is =N- except where indicated. R^{36} is $-NH_2$ except where indicated.

Table 1

Cpd	R1	R2	Cpd	R1	R2
KS167	-H		BA46		
ZK141	-H		BA45		
KS84			BA39		
ZK127	-H		BA150		
ZK134	-H		BA151		
ZK132	-H		BA21		
ZK125	-H		BA52		
BA56			BA53		
ZK138	-H		BA31		
KS287	 X = CH		BA152		
KS288	 R^{36} is N-Methyl		BA149		

Cpd	R1	R2	Cpd	R1	R2
KS284			BA32		
BA60			BA55		
ZK318	-H		BA35		
ZK320	-H		BA34		
ZK333	-Me		BA38		
ZK323			BA40		
ZK327			BA41		
BA77d			BA14		
BA78d			BA12		-I
BA22			BA30		
BA79d			ZK149	-H	

Cpd	R1	R2	Cpd	R1	R2
BA85			ZK126	-H	
BA87			ZK143	-H	
ZK502			ZK150	-Me X = CH	
ZK489	-Me		ZK136	-H	
ZK487			ZK131	-H	
Zk491			ZK151	-Me X = CH	
Zk493			ZK142	-H	
BA62d			ZK139	-H	
ZK450			KS207	-H	
ZK454			KS208	-Me	
ZK469			ZK102	-Me (R^{36} is Cl)	

Cpd	R1	R2	Cpd	R1	R2
ZK471			ZK157		
ZK461			ZK159		
ZK413			ZK156		
ZK379			KS63		
ZK421			ZK158		
ZK403			ZK147		
ZK405			ZK155		
ZK432			ZK162		
ZK434			ZK165		
ZK465			ZK161		
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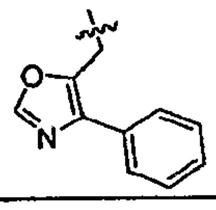
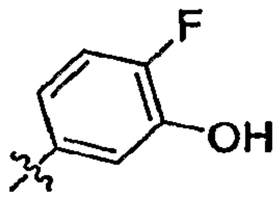
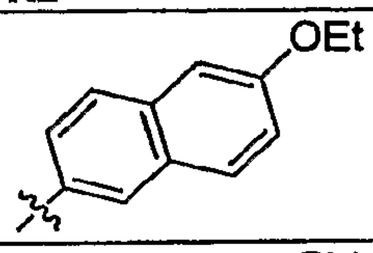
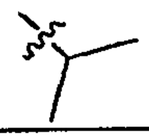
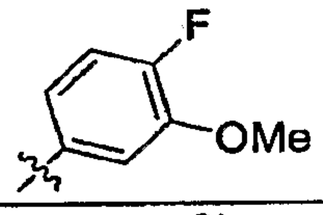
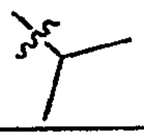
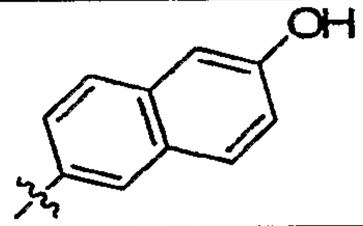
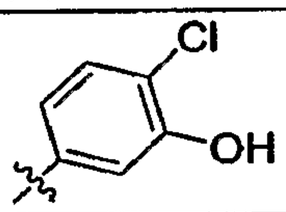
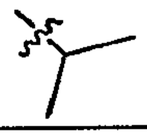
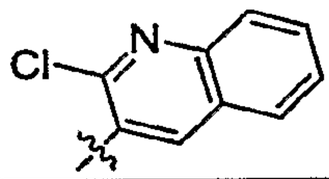
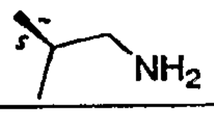
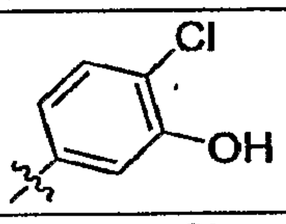
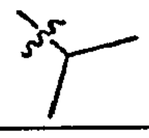
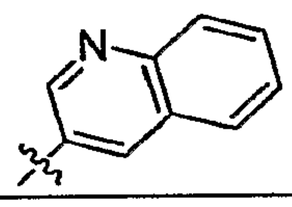
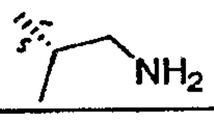
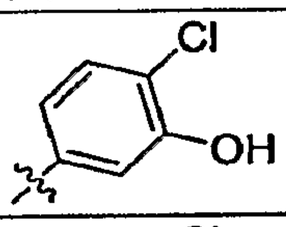
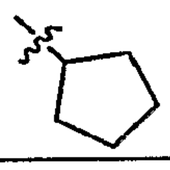
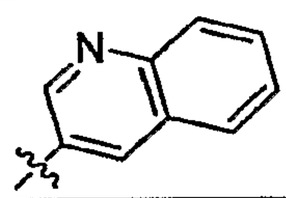
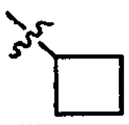
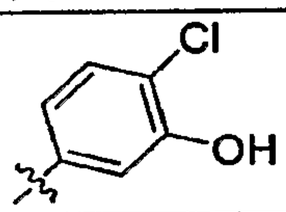
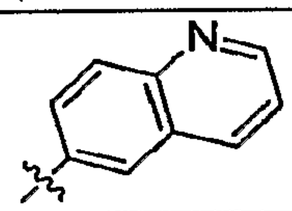
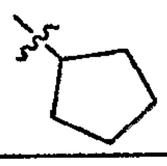
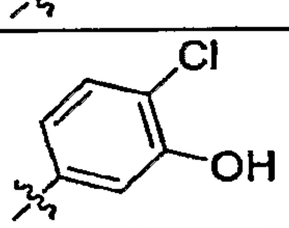
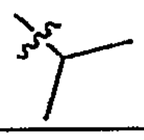
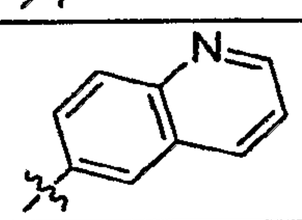
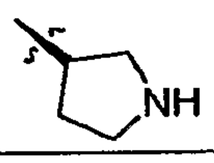
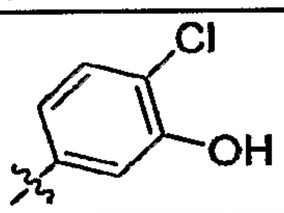
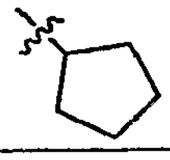
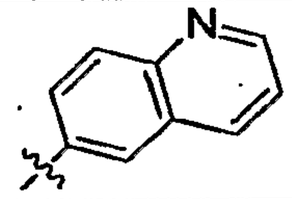
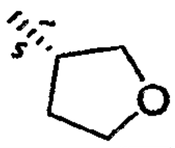
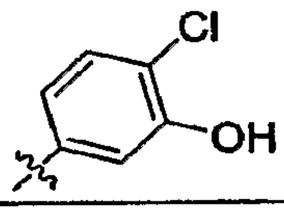
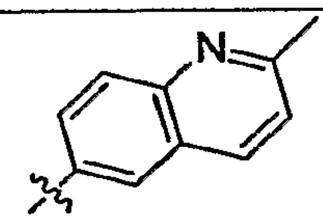
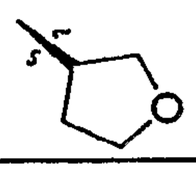
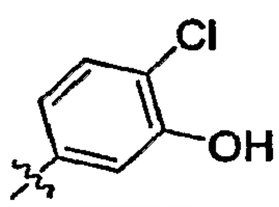
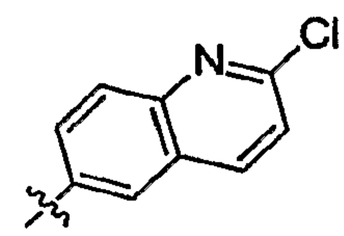
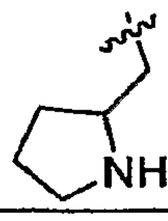
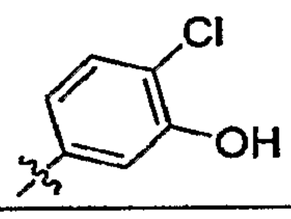
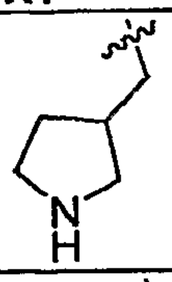
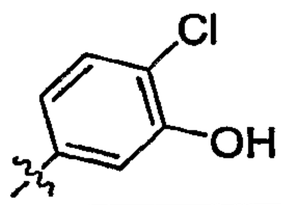
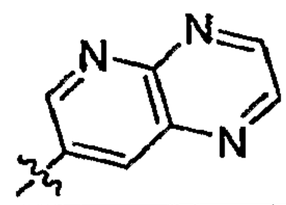
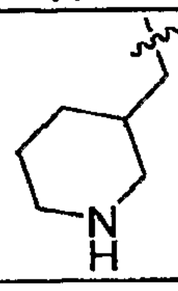
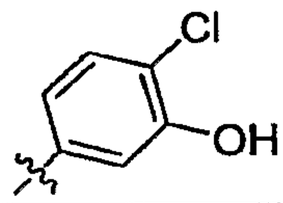
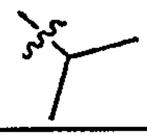
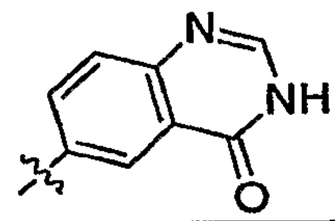
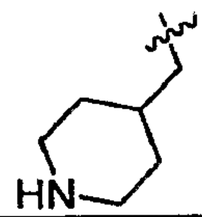
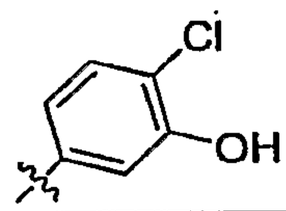
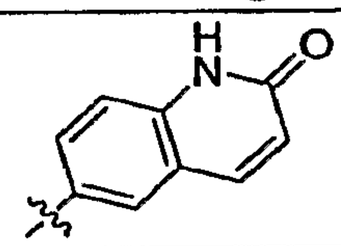
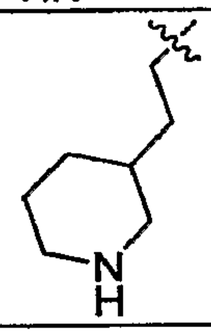
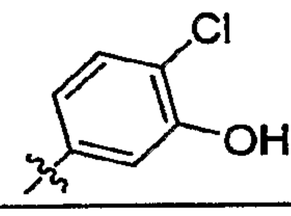
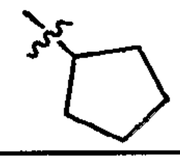
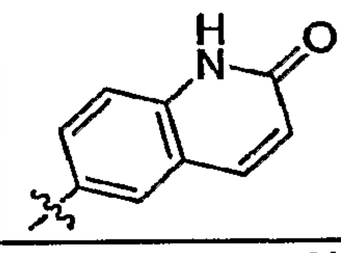
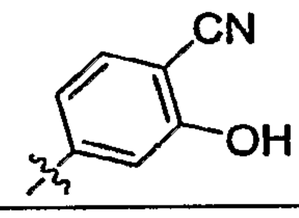
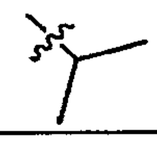
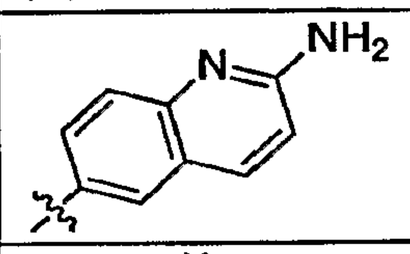
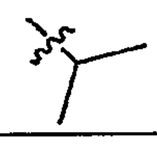
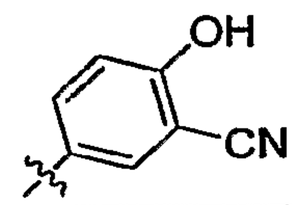
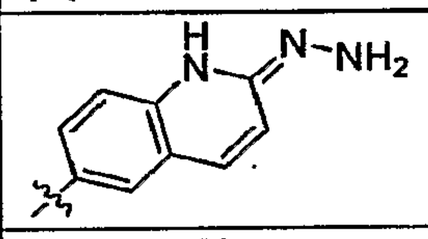
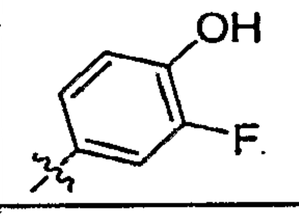
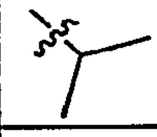
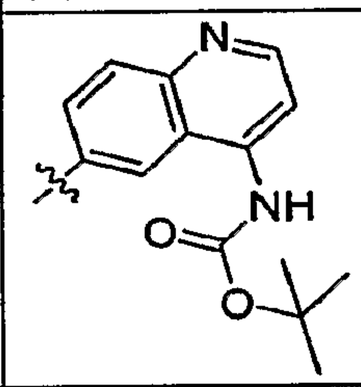
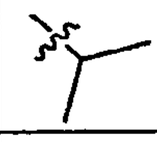
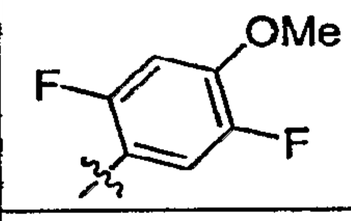
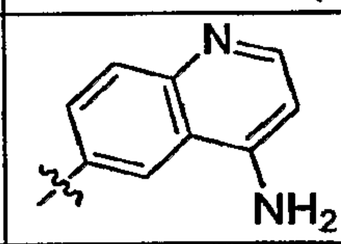
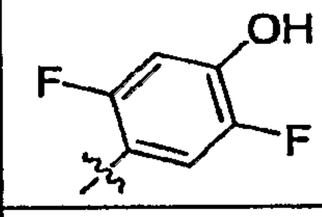
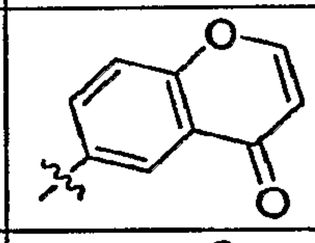
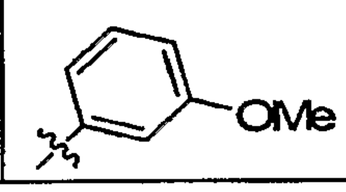
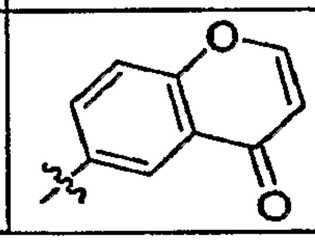
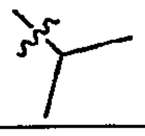
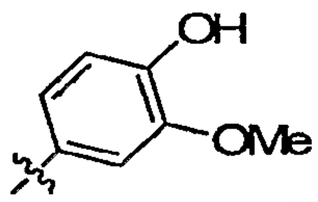
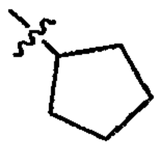
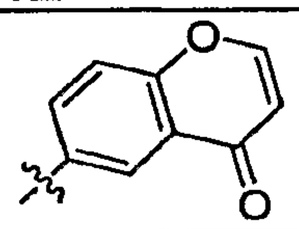
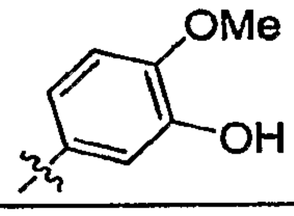
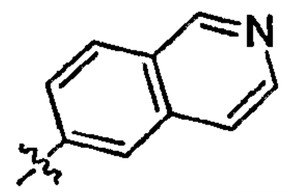
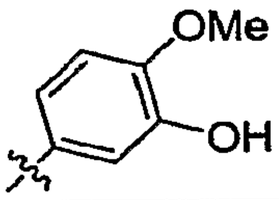
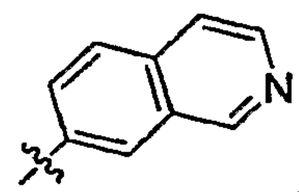
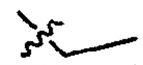
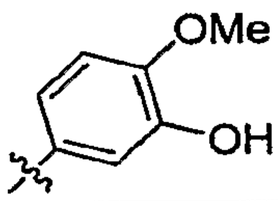
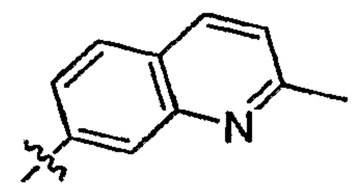
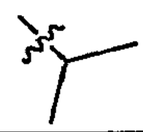
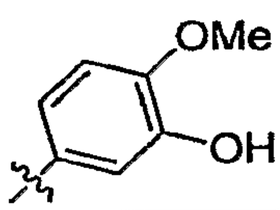
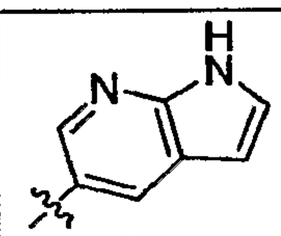
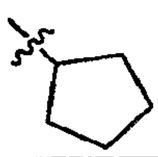
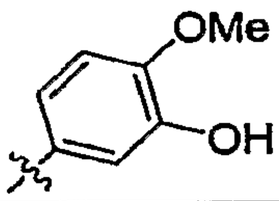
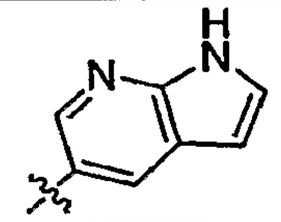
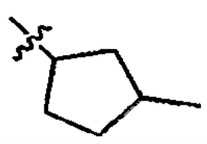
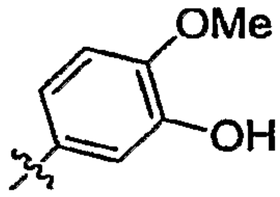
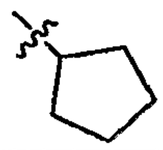
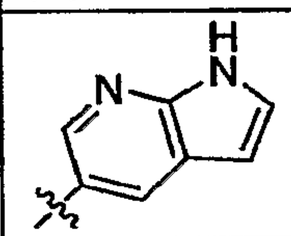
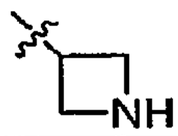
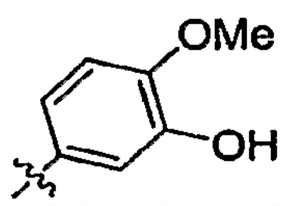
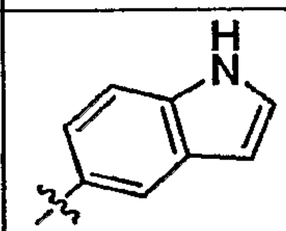
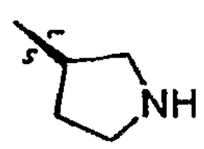
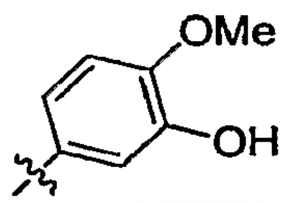
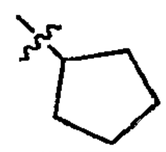
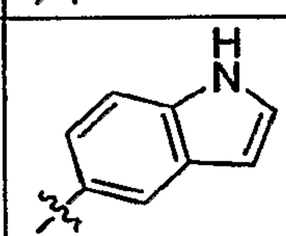
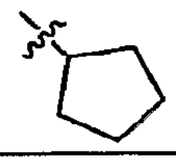
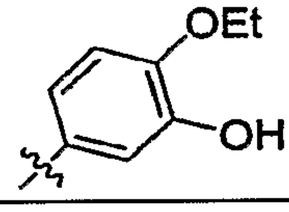
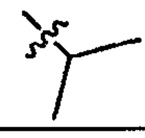
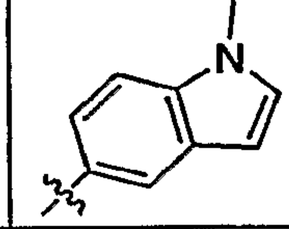
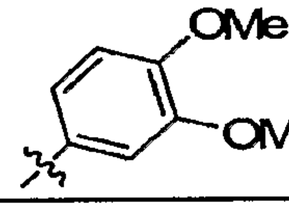
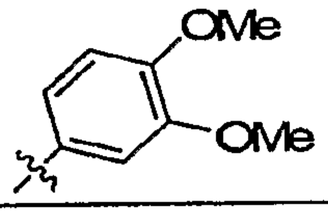
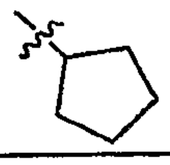
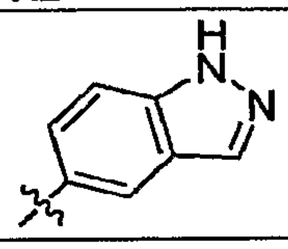
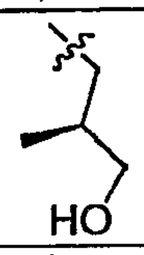
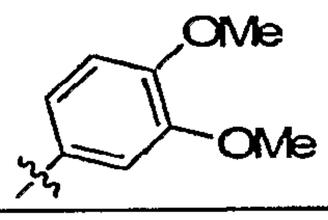
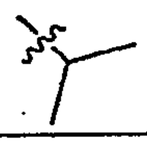
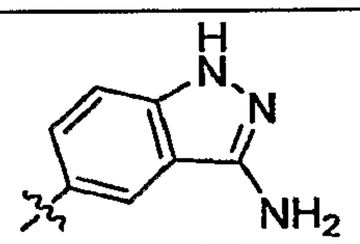
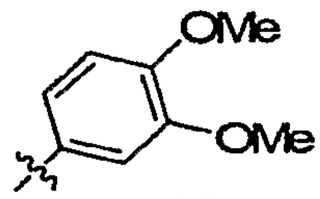
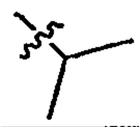
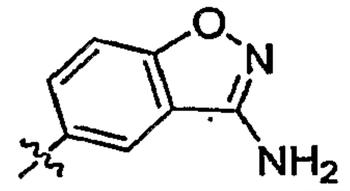
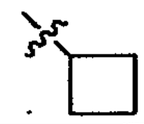
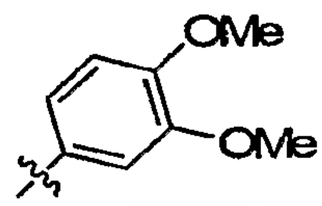
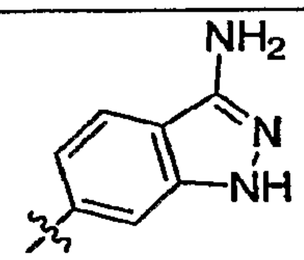
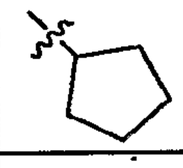
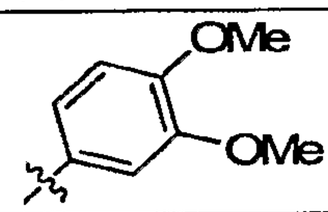
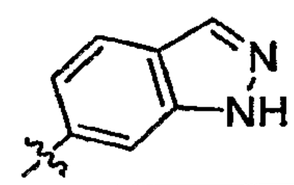
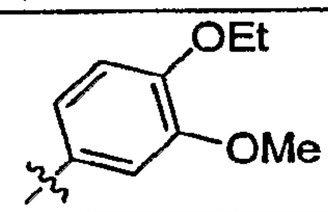
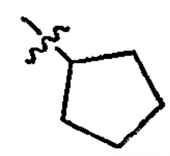
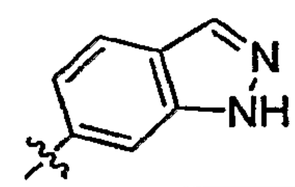
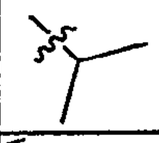
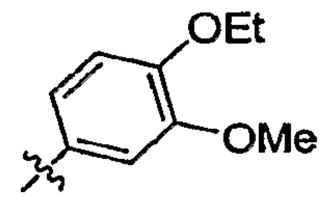
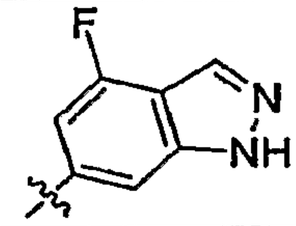
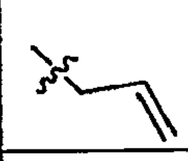
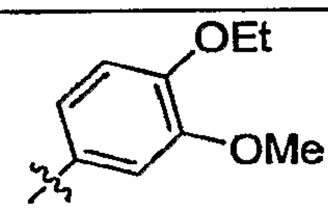
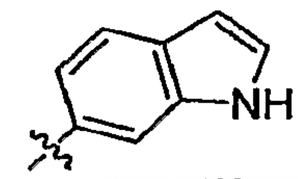
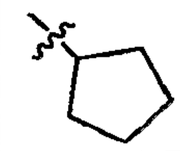
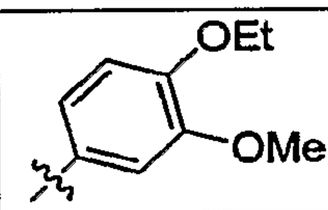
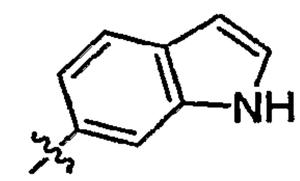
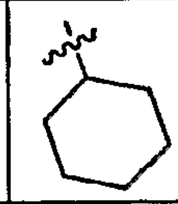
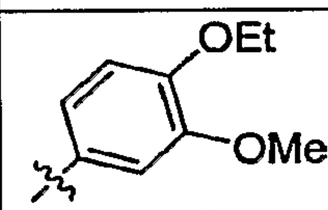
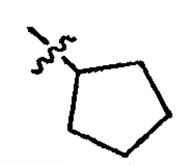
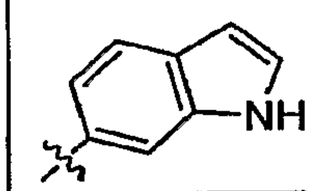
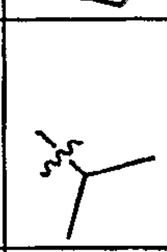
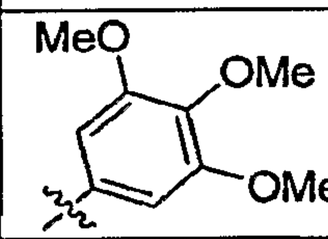
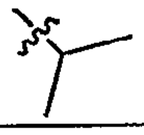
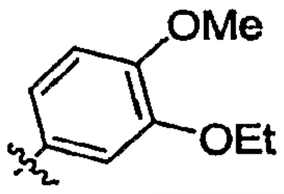
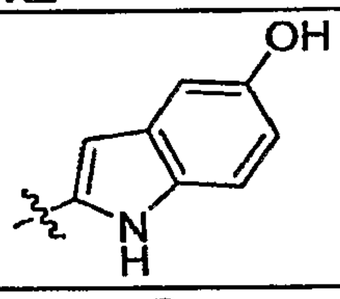
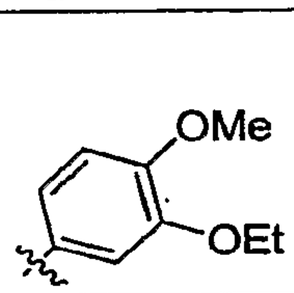
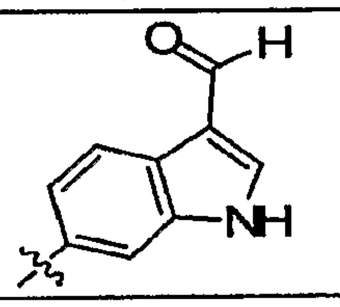
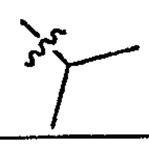
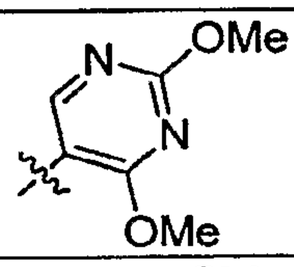
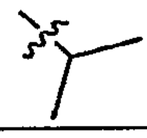
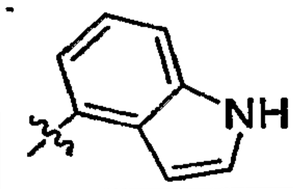
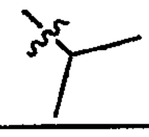
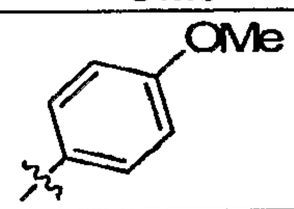
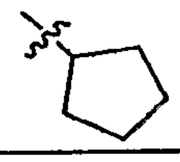
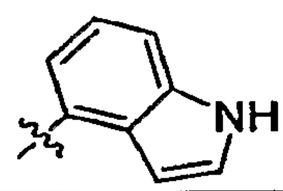
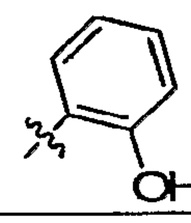
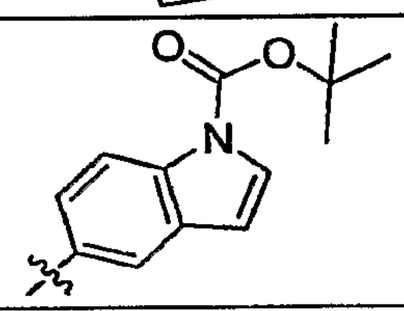
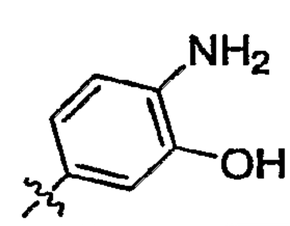
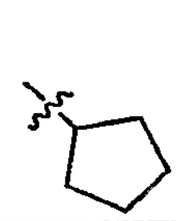
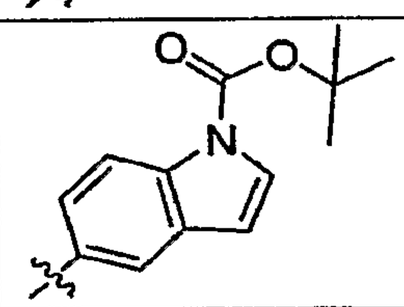
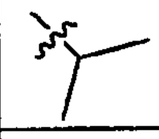
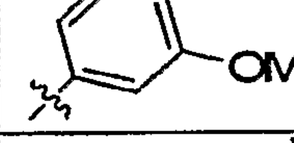
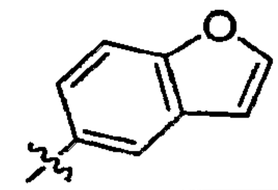
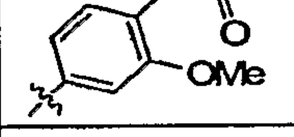
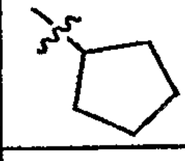
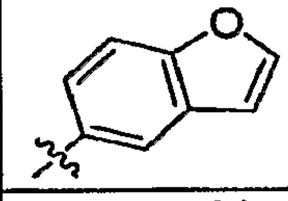
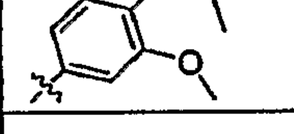
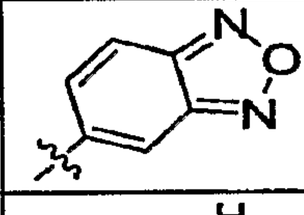
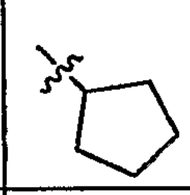
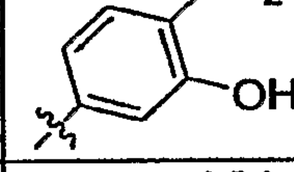
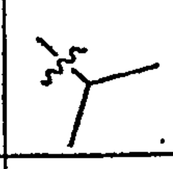
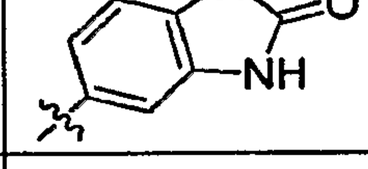
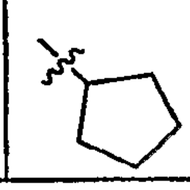
ZK401			BA116	-Me	
BA62			BA17		
ZK358			BA134		
ZK452			BA105		
ZK456			BA122		
ZK463			BA111	-Me	
ZK371			BA102		
ZK409			BA112		
ZK428			BA118		
ZK430			BA130		
ZK387			BA132		

Cpd	R1	R2	Cpd	R1	R2
ZK389			BA139		
ZK369			BA158		
ZK385			BA140		
ZK391			BA141		
BA155_2			BA146		
BA157_2			BA142		
BA59			BA145		
BA63			BA147		
BA93			BA148	-Me	
BA49			BA143		

Cpd	R1	R2	Cpd	R1	R2
BA15			BA144		
ZK321	-H		BA129		
ZK337	-Me		BA131		
ZK347			BA133		
ZK325			BA120	-Me	
ZK349			BA108		
ZK423			BA121		
ZK411			BA89		
ZK407			BA94		
BA98			BA135		
BA23			BA137		

Cpd	R1	R2	Cpd	R1	R2
ZK485			BA138		
ZK495			BA160		
ZK496			BA157_3		
ZK494			BA154		
BA90			BA110		
ZK341	-H		BA115		
ZK343			BA159		
ZK361			BA119	-Me	
ZK359			BA107		
ZK362			BA124		
BA64			BA161		
BA65			BA162		

Cpd	R1	R2	Cpd	R1	R2
ZK305			BA24dd		
ZK306			BA43		
BA66			BA91		
BA48			BA92		
ZK133	-H		BA86		
BA20dd			BA88		
BA20d			BA96		
BA20			BA97		
BA99			BA44		
BA81dd			BA156		
BA81d			BA95		

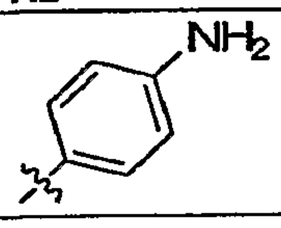
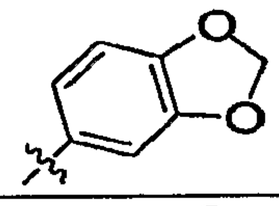
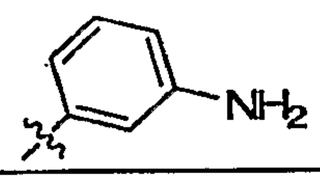
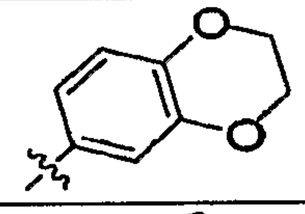
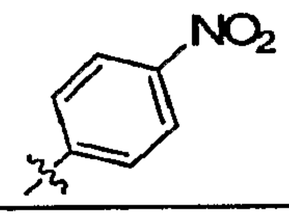
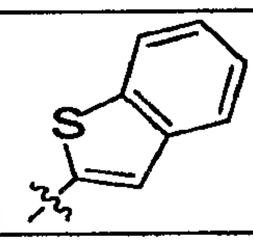
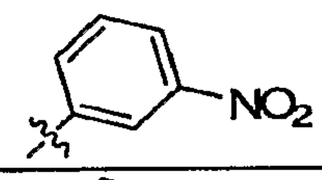
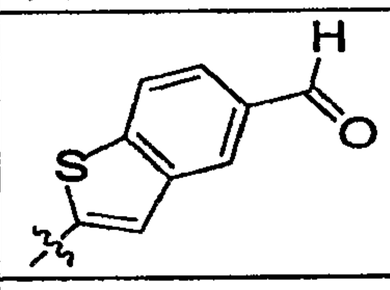
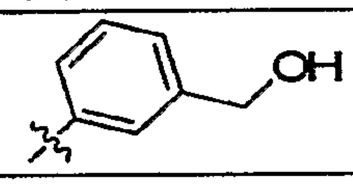
Cpd	R1	R2	Cpd	R1	R2
ZK137	-H		ZK129	-Me X = CH	
ZK135	-H		BA54		
ZK130	-H		ZK152	-Me X = CH	
ZK128	-H		BA42		
BA26					

Table 2

Cpd	110α	110β	110δ	110γ	DPK	Cpd	110α	110β	110δ	110γ	DPK
KS167	++	+	++	++	++	BA46	++	++	+++	++	+++
ZK141	++	++	++	++	+++	BA45	++	+	++	++	++
KS84	++	+	++	+	+++	BA39	++		+++	++	++
ZK127	++	++	++	++	+++	BA150	++	+	++	++	++
ZK134	++	+	++	++	+++	BA151	++	+	++	++	++
ZK132	++	++	++	++	+++	BA21	++	++	++		++
ZK125	++	+	++	++	+++	BA52	++	++	++	++	++
BA56	+++	+++	+++	+++	+++	BA53	++	+	+	+	++
ZK138	++	++	++	++	+++	BA31	++	++	+++	+++	++
KS287	++	++	++	++	++	BA152	++	++	+++	++	+++
KS288		+	+	+	+++	BA149	++	++	++	++	+
KS284	+++	++	+++	++	+++	BA32	++	++	+++		+++
BA60	++	++	+++	++	+++	BA55	++	++	+++	++	++
ZK318	++	+	++	++	++	BA35	++		+++	+++	+++
ZK320	++	++	+++	+++	++	BA34	++	++	+++	++	+++
ZK333	+++	++	+++	+++	+++	BA38	++		+++	+++	+++
ZK323	+++	++	+++	+++	+++	BA40	++		++	++	+++
ZK327	+++	++	+++	+++	+++	BA41	++	++	+++	+++	+++
BA77d	++	++	+++	++	++	BA14	++	++	+++	++	+++
BA78d	++	++	+++	++	+++	BA12	++	++	+++	++	++
BA22	+++	+++	+++	+++	+++	BA30	++	++	+++	+++	+++
BA79d	+++	+++	+++	+++	+++	ZK149	+	++	++	++	+
BA85	++	++	++	++	+++	ZK126	++	+	++	+	++
BA87	+++	+++	+++	+++	+++	ZK143	+	+	+	+	+
ZK502	++	++	+++	++	+++	ZK150	++	+	+	+	++
ZK489	+++	+++	+++	+++	+++	ZK136	++	+	+	++	+++
ZK487	+++	+++	+++	+++	+++	ZK131	+	+	+	+	+
Zk491	+++	+++	+++	+++	++	ZK151	+	+	+	+	+++
Zk493	+++	+++	+++	+++	+++	ZK142	+	+	+	+	+
BA62d	+++	+++	+++	+++	++	ZK139	+	+	+	++	++
ZK450	++	++	++	+++	+	KS207	++	+	+++	+++	+++
ZK454	++	++	++	+++	+++	KS208	++	++	++	+++	+++
ZK469	+++	+++	++	+++	+++	ZK102	+	+	+	+	+++
ZK471	+++	+++	+++	+++	++	ZK157			+++		+++
ZK461	+++	++	+++	++	++	ZK159	++	++	++	++	+++
ZK413	++	+++	+++	+++	+++	ZK156	++	++	++	++	+++
ZK379	+++	++	+++	+++	+++	KS63	+	+	+	+	+++
ZK421	+++	++	+++	+++	+++	ZK158	++	++	++	++	+++
ZK403	++	+++	+++	+++	++	ZK147	+	++	++	++	++
ZK405	++	++	+++	++	+++	ZK155	++	++	++	++	+++
ZK432	+++	++	+++	+++	+++	ZK162	++	+	++	++	+++
ZK434	+++	+++	+++	+++	+++	ZK165	++	+	++	++	+++
ZK465	+++	+	+++	+++	+++	ZK161	++	+	++	++	++
ZK377	++	++	++	++	+++	ZK167			++		++
ZK399	++	++	+++	++	+++	ZK168			++		+++
ZK401	++	+	++	+	+++	BA116	+	++	++	++	+++
BA62	+++	++	+++	+++	+++	BA17	+++	++	+++	++	+++
ZK358	+++	++	+++	+++	+++	BA134	++	+	++	+	++
ZK452	++	++	++	+++	+++	BA105	++	++	+++	++	+++
ZK456	+++	++	++	+++	+++	BA122	++	++	+++	++	+++
ZK463	+++	++	+++	+++	+++	BA111	+++	++	+++	+++	+++
ZK371	+++	+++	+++	+++	+++	BA102	+++	+++	+++	+++	+++
ZK409	+++	+++	+++	+++	+++	BA112	+++	++	+++	+++	+++
ZK428	+++	+++	+++	+++	+++	BA118	+++	++	+++	+++	+++

Cpd	110α	110β	110δ	110γ	DPK	Cpd	110α	110β	110δ	110γ	DPK
ZK430	+++	+++	+++	+++	+++	BA130	+++	++	+++	+++	+++
ZK387	++	++	++	++	+++	BA132	+++	+++	+++	+++	+++
ZK389	++	+++	+++	++	+++	BA139	++	++	+++	+	++
ZK369	++	+	++	++	++	BA158	+++	+++	+++	+++	+++
ZK385	++	++	+++	++	+++	BA140	+	++	+	+	++
ZK391	++	++	+++	++	+++	BA141	+	+	+	+	+
BA155_2	+++	+++	+++	+++	+++	BA146	+++	+++	+++	+++	+++
BA157_2	+++	+++	+++	+++	+++	BA142	+++	++	++	+++	+++
BA59	+++	++	+++	+++	+++	BA145	++	++	++	++	++
BA63		++		+++	+++	BA147	++	++	++	++	++
BA93	+++	++	+++	+++	+++	BA148	++	++	++	++	+++
BA49	++	+	++	++	++	BA143	++	++	++	++	+++
BA15	+++	++	+++	+++	+++	BA144	+++	++	+++	+++	+++
ZK321	+++	++	+++	+++	+++	BA129	++	+	++	+	++
ZK337	+++	+++	+++	+++	+++	BA131	+++	++	+++	+++	+++
ZK347	+++	+++	+++	+++	+++	BA133	+++	+++	+++	+++	+++
ZK325	+++	+++	+++	+++	+++	BA120	+++	++	+++	+++	+++
ZK349	+++	+++	+++	+++	+++	BA108	+++	++	+++	++	+++
ZK423	+++	+++	+++	+++	+++	BA121	+++	++	+++	++	+++
ZK411	++	+++	+++	+++	+++	BA89	+++	++	+++	+++	+++
ZK407	++	+++	+++	++	++	BA94	+++	++	+++	+++	+++
BA98	+++	+++	+++	+++	+++	BA135	+++	+++	+++	+++	+++
S1	++	+	++	+	+	BA136	+++	++	+++	++	+++
BA23	+++	+++	+++	+++	+++	BA137	+++	+++	+++	+++	+++
ZK485	+++	+++	+++	++	++	BA138	+++	++	+++	+++	+++
ZK495	+++	++	+++	++	+++	BA160	++	++	+++	+++	+++
ZK496	++	++	+++	++	+++	BA157_3	+++	++	+++	+++	+++
ZK494	+++	+++	+++	+++	+++	BA154	+++	+++	+++	+++	+++
BA90	+++	+++	+++	+++	+++	BA110	+++	++	+++	+++	+++
ZK341	++	++	+++	+++	++	BA115	+++	++	+++	+++	+++
ZK343	+++	++	+++	++	+++	BA159	+++	+++	+++	+++	++
ZK361	++	++	+++	+++	+++	BA119	++	++	+++	++	+++
ZK359	+++	+++	+++	+++	+++	BA107	++	++	+++	++	+++
ZK362	+++	+++	+++	+++	++	BA124	++	++	+++	++	+++
BA64	+	+	++	+	++	BA161	+	+	+	+	+++
BA65	+	+	++	+	++	BA162	++	++	++	++	+++
ZK305	+++	+++	+++	+++	+++	BA24dd	++	++	+++	++	+++
ZK306	++	+	++	++	++	BA43	+++		+++	+++	+++
BA66	++	++	+++	++	+++	BA91	++	++	++	++	+++
BA48	++	++	+++	++	+++	BA92	++	++	+++	++	+++
ZK133	+	+	+	++	++	BA86	++	++	++	+++	+++
BA20dd	++	++	++	++	+++	BA88	+	+	++	+++	+++
BA20d	++	++	+++	+++	+++	BA96	++	+	+++	+++	+++
BA20	++		++	++	++	BA97	++	++	+++	+++	+++
BA99	++	+	++	+	++	BA44	++	+++	++	++	++
BA81dd	+++	++	+++	+++	+	BA156	++	++	++	++	+++
BA81d	+++	++	+++	+++	+++	BA95	++	++	+++	+++	+++
ZK137	++	+	++	++	+++	ZK129	++	++	++	++	+++
ZK135	++	+	+	++	++	BA54	++	++	++	++	+++
ZK130	+	+	+	+	+	ZK152	++	++	++	++	+++
ZK128	++	+	++	++	++	BA42	++	++	++	++	+++
BA26	++	++	+++	+++	++	PIK294	++	+++	+++	+++	++
SU11248	++	+	++	++	+	Iressa	+	+	+	+	+
BAY43-9006	++	+	+	+	+	PIK103	+++	+++	+++	+++	+++
Dasatinib	++	+	++	+	++	PIK90	+++	+++	+++	+++	+++

Table 3

Cpd	Abl	Hck	Src	Src (T/I)	VEGFR	EGFR	EphB4
KS84	+++	+++	+++	++	+++	+++	+++
BA56	++	+++	+++	++	++	+++	++
KS284	+++	+++	+++	++	+++	+++	+++
BA60	++	+++	+++	+++	++	+	++
ZK318	++	++	+++	++	+		++
ZK320	+++	+++	+++	++	+++	++	++
ZK333	+++	+++	+++	++	+++	++	++
ZK323	+++	+++	+++	+++	+++	+++	+++
ZK327	+++	+++	+++	++	+++	++	++
BA77d	+++	+++	+++	++	++	++	+++
BA78d	+++	+++	+++	++	+++	++	++
BA22	+++	+++	+++	++	+++	+++	+++
BA79d	+++	+++	+++	++	+++	+++	+++
BA85	++	+++	+++	++	++	++	++
BA87	+++	+++	+++	+++	+++	+++	+++
ZK502	+++	+++	+++	++	++	++	+
ZK489	+++	+++	+++	+	++	+	++
ZK487	+++	+++	+++	++	+++	+++	+++
Zk491	+++	+++	+++	++	+++	+++	+++
Zk493	+++	+++	+++	++	+++	+++	+++
BA62d	+++	+++	+++	+++	+++	++	+++
ZK450	+++	+++	+++	+	++	+	++
ZK454	+++	++	+++	+	++	++	+
ZK469	+++	+++	+++	+	++	++	++
ZK471	+++	+++	+++	+	++	++	+
ZK461	+++	+++	+++	+	+++	++	++
ZK413	+++	+++	+++	+	++	++	
ZK379	+++	+++	+++	++	+++	+++	+++
ZK421	+++	+++	+++	+++	+++	+++	+++
ZK403	+++	+++	+++	++	+++	++	+++
ZK405	+++	+++	+++	++	++	++	+
ZK432	+++	+++	+++	++	+++	++	+++
ZK434	+++	+++	+++	++	+++	++	+++
ZK465	+++	+++	+++	+	+++	+++	+++
ZK377	++	++	+++	+	++	+	+
ZK399	+++	+++	+++	+	+	+	++
ZK401	+++	+++	+++	+	+	+	+
BA62	+++	+++	+++	+	+	++	+++
ZK358	+++	+++	+++	++	+++	+++	+++
ZK452	+++	+++	+++	++	+++	++	++
ZK456	+++	+++	+++	+	++	++	++
ZK463	+++	+++	+++	++	+++	++	++
ZK371	+++	+++	+++	++	+++	+++	+++
ZK409	+++	+++	+++	++	+++	++	+++
ZK428	+++	+++	+++	++	+++	++	+++
ZK430	+++	+++	+++	++	+++	++	+++
ZK387	+++	+++	+++	+	++	++	++
ZK389	+++	+++	+++	++	+++	++	+++
ZK369	++	++	+++	+	++	++	+
ZK385	++	+++	+++	+	++	+	++
ZK391	++	+++	+++	+	++	++	++
BA155_2	++	+++	+++	++	++	++	++
BA157_2	++	++	++	++	++	++	++

Cpd	Abl	Hck	Src	Src (T/I)	VEGFR	EGFR	EphB4
BA59	+++	+++	+++	+++	++	++	+++
BA63	++	+++	+++	++	++	++	++
BA93	++	+++	+++	++	++	++	++
BA49	++	+++	+++	++	+	++	+++
BA15	++	+++	+++	++	+	+++	++
ZK321	+++	+++	+++	++	++	+	++
ZK337	+++	+++	+++			+	++
ZK347	+++	+++	+++	++	+++	++	++
ZK325	+++	+++	+++	++	+++	++	+++
ZK349	+++	+++	+++	+++	+++	+++	+++
ZK423	+++	+++	+++	++	+++	+++	+++
ZK411	++	++	+++	+	++	++	++
ZK407	++	+++	+++	+	+++	++	+
BA98	+++	+++	+++	++	+++	+++	++
S1.	+++	+	++	+	+	+	+
BA23	++	++	+++	++	+	++	++
ZK485	++	+++	+++	+	+	++	++
ZK495	++	+++	++	++	+	++	++
ZK496	++	++	++	++	++	++	++
ZK494	+++	+++	+++	++	++	++	++
BA90	++	+++	+++	++	++	++	++
ZK341	++	++	+	+	+	+	+
ZK343	++	+++	+++	+	++	++	++
ZK361	++	++	++	+	+	++	+
ZK359	+++	+++	+++	++	++	++	+++
ZK362	++	+++	+++	+	+	++	+
BA64	+++	+++	+++	++	+	++	+++
BA65	++	+++	+++	++	++	++	++
ZK305	++	++	++	++	+	+	++
ZK306	+	++	++	++	++	++	+
BA66	++	++	++	+		+	++
BA48	++	+++	+++	++	++	++	++
BA20dd	+++	+++	+++	++	++	++	++
BA20d	+++	+++	+++	++	++	++	++
BA20	+++	+++	+++	+++	++	+++	+
BA99	++	+++	+++	++	+++	++	++
BA81dd	+++	+++	+++	++	+++	+++	+++
BA81d	+++	+++	+++	++	+++	+++	+++
BA26	++	++	+++	++	+	+	+
BA46	++	++	++	+	++	++	++
BA45	++	+++	+++	++	++	++	+
BA39	++	++	++	++	++	+	++
BA150	++	++	++	+	++	+	++
BA151	++	++	++	+	+	++	++
BA21	++	++	++	+	+	+	+
BA52	++	++	++	+	+	+	+
BA53	++	++	++	+	+	+	+
BA31	++	++	++	+	+	++	+
BA152	+++	+++	+++	+	++	++	++
BA149	++	+++	+++	++	++	++	++
BA32	++	++	++	+	+	+	++
BA55	++	++	++	+	+	++	++
BA35	++	++	++	++	++	++	++
BA34	++	++	++	++	++	++	++
BA38	++	++	++	++	+	+	+
BA40	++	++	++	++	++	++	+

Cpd	Abl	Hck	Src	Src (T/I)	VEGFR	EGFR	EphB4
BA41	++	++	++	++	++	+	++
BA14	++	++	++	++	+	+	++
BA12	++	++	++	++	++	++	++
BA30	++	++	++	++	++	+++	++
KS208	++	+++	++	++	++	+++	++
BA116	++	+++	++		+++	++	++
BA17	+++	+++	+++	+++	+++	+++	+++
BA134	++	++	++	++	+	+	++
BA105	++	+++	++	++	++	++	++
BA122	+++	+++	+++	++	++	+++	+++
BA111	+	+	++	++	++	++	++
BA102	+++	+++	+++	++	+++	+++	+++
BA112	++	+++	+++	++	++	++	++
BA118	++	++	+	++	++	+	++
BA130	++	+++	++	++	+++	+	++
BA132	++	+++	++	+	++	++	++
BA139	++	++	++	+	++	++	+
BA158	+++	+++	+++	++	++	++	++
BA140	++	++	++	++	+	++	++
BA141	+	++	+	+	+	++	+
BA146	++	++	++	+	++	++	++
BA142	++	++	+++	+	++	++	++
BA145	+	++	++	+	+	+	++
BA147	++	++	++	+	++	+	++
BA148	+	++	++	+	+	++	+
BA143	++	++	++	++	+	++	++
BA144	++	++	+++	+	++	+	++
BA129	++	+	+++	+	++	++	++
BA131	++	++	11	+	++	+	++
BA133	++	++	+++	+	+	++	++
BA120	+++	+++	+++	++	+++	++	++
BA108	+++	+++	+++	+++	+++	+++	+++
BA121	+++	+++	+++	+++	+++	+++	+++
BA89	+++	+++	+++	+++	+++	+++	+++
BA94	+++	+++	+++	+++	+++	+++	+++
BA135	+++	+++	+++	++	+++	+++	+
BA136	+++	+++	+++	++	+++		++
BA137	+++	+++	+++	+++	+++	++	++
BA138	+++	+++	+++	+++	+++	+++	++
BA160	+++	+++	+++	++	++	+++	++
BA157_3	++	+++	+++	++	+	++	++
BA154	+++	+++	+++	++	++	++	++
BA110	+++	+++	+++	++	+++	++	++
BA115	+++	+++	+++	+++	+++	+++	
BA159	+++	+++	+++	++	+++	++	++
BA119	++	+++	+++	++	++	++	++
BA107	+++	+++	+++	++	+++	+++	+++
BA124	+++	+++	+++	+++	+++	+++	+++
BA161	++	+	++	+	+	++	+
BA162	++	++	++	+	+	++	++
BA24dd	++	++	++	++	++	++	++
BA43	++	+++	++	++	++	++	++
BA91	++	++	+++	++	++	++	++
BA92	++	+++	+++	++	++	++	++
BA86	+++	+++	+++	+++	+++	+++	+++
BA88	+++	+++	+++	+++	+++	+++	+++

Cpd	Abl	Hck	Src	Src (T/I)	VEGFR	EGFR	EphB4
BA96	+++	+++	+++	++	++	+++	+++
BA97	+++	+++	+++	++	++	+++	+++
BA44	++	++	++	++	+	++	+
BA156	++	++	++	++	++	+++	++
BA95	++	+++	++	+	+	++	++
BA54	++	++	+++	++	++	++	++
BA42	+	++	++	++	++	+	++
SU11248	+++	+++	+++	+++	+++	++	+
BAY43-9006	+++	+++	+++	+++	+++	+	++
Dasatinib				++	+	+++	
Iressa	++	+++	+++	++	++		++
PIK103	+	+	+	+	+	+	+
PIK90	+	+	+	+	+	+	+
PIK294	++	+	++	+	+	+	+

Table 4

Cpd	cKIT	Tie2	FLT3	PDGFR	RET	IR	mTOR
ZK358	+++	++	+++	+++	+++	++	+++
ZK487	+++	+++	+++	+++	+++	+	+++
ZK349	+++	+++	+++	+++	+++	++	+++
ZK494	+++	++	++	+++	+++	+	+++
BA102	+++	+++	+++	+++	+++	+	+++
BA121	+++	+++	+++	+++		++	+++
KS84	+++	+	+++	+++	+++	++	++
SU11248	+++	++	+++	+++	+++	++	+
BAY43-9006	+++	+++	+	+++	+++	++	+
Dasatinib	+++	++	+++	+++	++	+	+
Iressa	+	++	+++	+++	++	+	+

In Tables 2-4 above, a +++ indicates an IC50 of less than 1 μM; a ++ indicates an IC50 of from 1 μM to 50 μM; and a + indicates and IC50 of more than 50 μM.

IX. References

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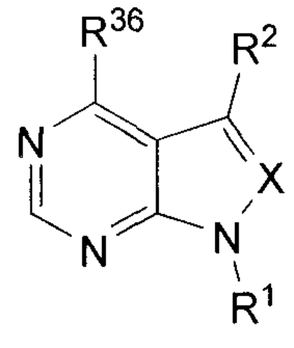
WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

wherein,

X is =N-;

R^1 is hydrogen, R^3-substituted or unsubstituted alkyl, R^3-substituted or unsubstituted heteroalkyl, R^3-substituted or unsubstituted cycloalkyl, R^3-substituted or unsubstituted heterocycloalkyl, or R^3-substituted or unsubstituted heteroaryl;

R^2 is R^4-substituted heteroaryl;

R^3 is halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, $=N-NH_2$, $-NR^{10}-C(O)R^{11}$, $-NR^{12}-C(O)-OR^{13}$, $-C(O)NR^{14}R^{15}$, $-NR^{16}S(O)_2R^{17}$, $-S(O)_2NR^{18}$, R^{19}-substituted or unsubstituted alkyl, R^{19}-substituted or unsubstituted heteroalkyl, R^{19}-substituted or unsubstituted cycloalkyl, R^{19}-substituted or unsubstituted heterocycloalkyl, R^{19}-substituted or unsubstituted aryl, or R^{19}-substituted or unsubstituted heteroaryl, wherein n is an integer from 0 to 2;

R^{36} is NH_2;

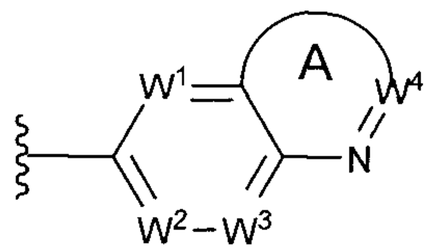
R^4 is halogen, -CN, $-OR^{20}$, or $-NR^{22}R^{23}$;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} and R^{18} are independently hydrogen, R^{35}-substituted or unsubstituted alkyl, R^{35}-substituted or unsubstituted heteroalkyl, unsubstituted cycloalkyl, R^{35}-substituted or unsubstituted heterocycloalkyl, R^{35}-substituted or unsubstituted aryl, or R^{35}-substituted or unsubstituted heteroaryl;

R^{20}, R^{22} and R^{23} are independently hydrogen, unsubstituted alkyl or unsubstituted heteroalkyl; and

R^{19} and R^{35} are independently hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

2. A compound as defined in claim 1, wherein R^2 is:



(III),

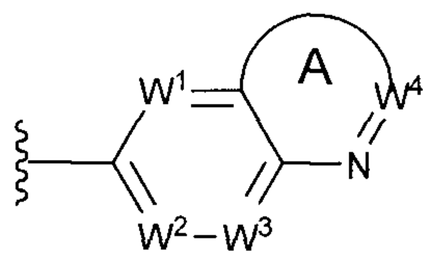
wherein,

W^1, W^2, W^3, and W^4 are independently =CH-, =CR^4- or =N- and

at least one of W^1, W^2, W^3, and W^4 is =CR^4-; and

ring A is a substituted or unsubstituted heteroaryl.

3. A compound as defined in claim 1, wherein R^2 is:



(III),

wherein,

W^1, W^2, W^3, and W^4 are independently =CH-, =CR^4- or =N-; and

at least one of W^1, W^2, W^3, and W^4 is =CR^4-; and

ring A is a partially or fully unsaturated 6- or 7- membered heteroaryl.

4. A compound as defined in claim 1, wherein:

R^2 is R^4-substituted pyridinyl, R^4-substituted pyrimidinyl, R^4-substituted thiophenyl, R^4-substituted furanyl, R^4-substituted indolyl, R^4-substituted benzoxadiazolyl, R^4-substituted benzodioxolyl, R^4-substituted benzodioxanyl, R^4-substituted thianaphthanyl, R^4-substituted pyrrolopyridinyl, R^4-substituted indazolyl, R^4-substituted quinolinyl, R^4-substituted quinoxalinyl, R^4-substituted pyridopyrazinyl, R^4-substituted quinazolinonyl, R^4-substituted chromenonyl, R^4-substituted benzoisoxazolyl, R^4-substituted imidazopyridinyl, R^4-substituted benzofuranyl, R^4-substituted dihydro-benzofuranyl, R^4-substituted dihydro-benzodioxinyl, R^4-substituted benzoimidazolonyl, or R^4-substituted benzothiophenyl.

5. A compound as defined in claim 1, wherein R^2 is R^4-substituted pyrrolopyridinyl, R^4-substituted quinolinyl, R^4-substituted indazolyl, or R^4-substituted indolyl.

6. A compound as defined in any one of claims 1 to 5, wherein R^1 is R^3-substituted or unsubstituted alkyl, or R^3-substituted or unsubstituted cycloalkyl.

7. A compound as defined in any one of claim 1 to 5, wherein R^1 is R^3-substituted or unsubstituted C_1-C_4 alkyl, or R^3-substituted or unsubstituted C_3-C_6 cycloalkyl.

8. A compound as defined in any one of claims 1 to 5, wherein R^1 is R^3-substituted or unsubstituted C_1-C_4 alkyl, or R^3-substituted or unsubstituted C_3-C_6 cyclopentyl.

9. A compound as defined in any one of claims 1 to 8, wherein R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} are independently hydrogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

10. A compound as defined in any one of claims 1 to 5, wherein R^1 is methyl or unsubstituted C_3-C_6 branched alkyl.

11. A compound as defined in any one of claims 1 to 5, wherein R^1 is isopropyl.

12. A compound as defined in any one of claims 1 to 5, wherein R^3 is R^{19}-substituted or unsubstituted alkyl, R^{19}-substituted or unsubstituted cycloalkyl, or R^{19}-substituted or unsubstituted aryl.

13. A compound as defined in any one of claims 1 to 5 and 12, wherein R^{19} is unsubstituted alkyl or unsubstituted cycloalkyl.

14. A compound as defined in any one of claims 1 to 5 and 12, wherein R^{19} is unsubstituted C_1-C_4 alkyl or unsubstituted cyclopentyl.

15. A compound as defined in claim 1, wherein R^1 is isopropyl and R^2 is 5-hydroxyindol-2-yl.

16. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 15 and a pharmaceutically acceptable excipient.

17. A compound as defined in any one of claims 1 to 15 or a composition as defined in claim 16, for use as a kinase antagonist.

18. The compound or composition as defined in claim 17, wherein the kinase is a P13-kinase.

19. A compound as defined in any one of claims 1 to 15 for use in treatment of a bone resorption disorder, chronic myelogenous leukemia, abnormal inflammation, an autoimmune disease, thrombosis, asthma, or a cancer.

20. A compound as defined in any one of claims 1 to 15 for use in treatment of a cancer.

21. The compound as defined in claim 20, wherein the cancer is Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine and exocrine pancreas, prostate cancer or kidney cancer.

22. A compound as defined in any one of claims 1 to 15 for use in treatment of liver cancer, colon cancer, breast cancer, melanoma, acute myelogenous leukemia, chronic myelogenous leukemia, or non small-cell lung cancer.

23. Use of a compound as defined in any one of claims 1 to 15 in manufacture of a medicament for treatment of: a bone resorption disorder, chronic myelogenous leukemia, abnormal inflammation, an autoimmune disease, thrombosis, asthma, or a cancer.

24. Use of a compound as defined in any one of claims 1 to 15 in manufacture of a medicament for treatment of a cancer.

25. The use as defined in claim 24, wherein the cancer is Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine and exocrine pancreas, prostate cancer or kidney cancer.

26. Use of a compound as defined in any one of claims 1 to 15 in manufacture of a medicament for treatment of liver cancer, colon cancer, breast cancer, melanoma, acute myelogenous leukemia, chronic myelogenous leukemia or non small-cell lung cancer.

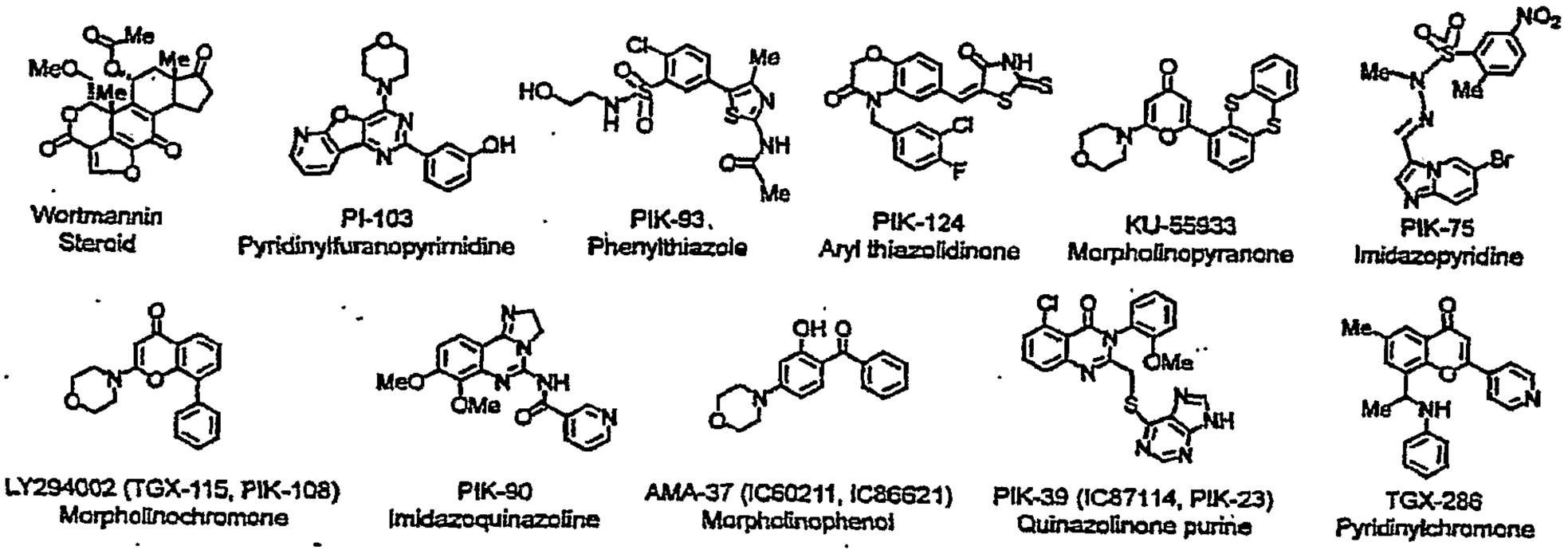

Wortmannin
Steroid
PI-103
Pyridinylfuranopyrimidine
PIK-93
Phenylthiazole
PIK-124
Aryl thiazolidinone
KU-55933
Morpholinopyranone
PIK-75
Imidazopyridine
LY294002 (TGX-115, PIK-108)
Morpholinochromone
PIK-90
Imidazoquinazoline
AMA-37 (IC60211, IC86621)
Morpholinophenol
PIK-39 (IC87114, PIK-23)
Quinazolinone purine
TGX-286
Pyridinylchromone

FIG. 1

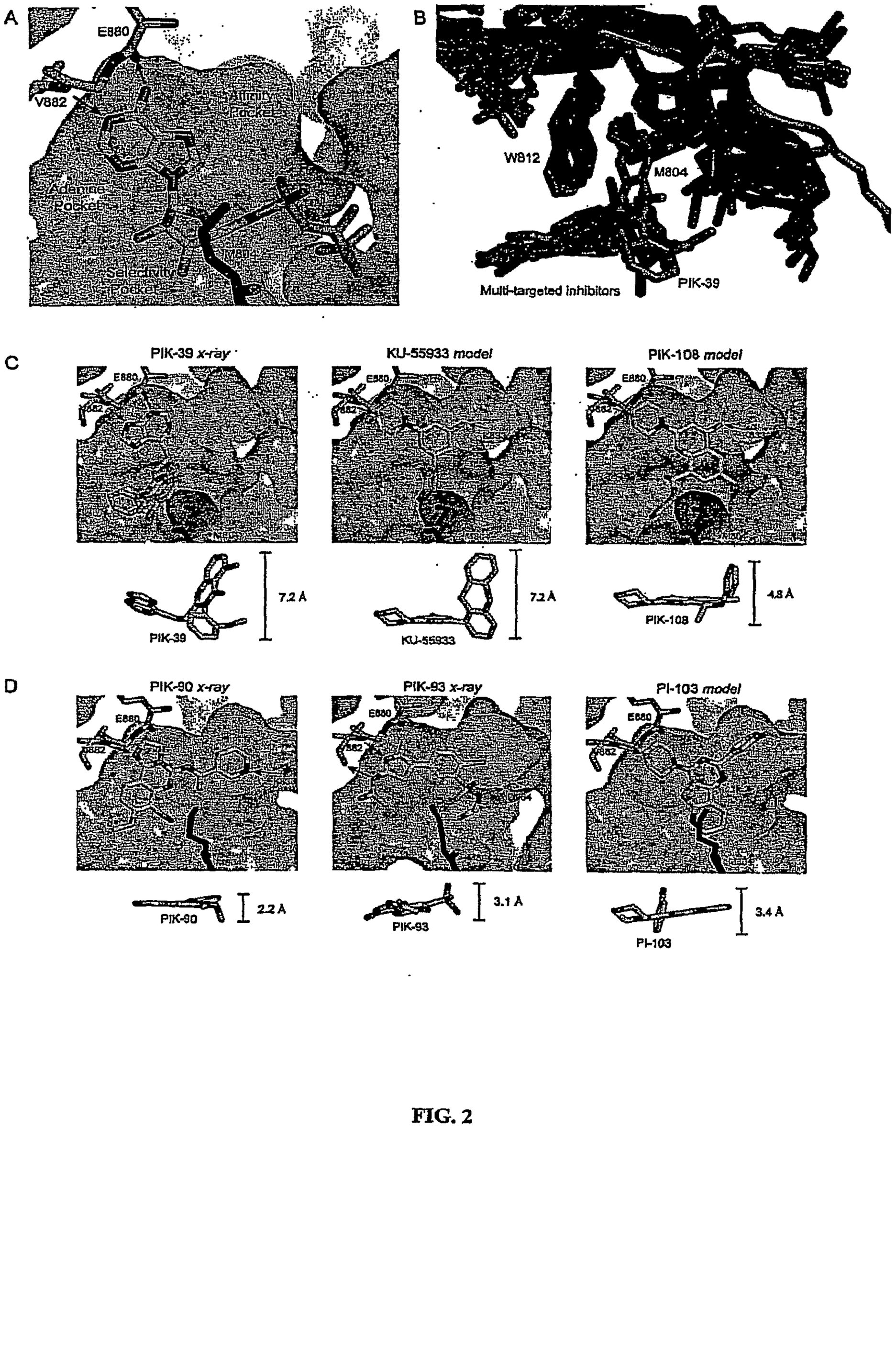

A
E880
V882
Affinity Pocket
Adenine Pocket
M804
Selectivity Pocket
B
W812
M804
Multi-targeted inhibitors
PIK-39
C
PIK-39 x-ray
KU-55933 model
PIK-108 model
E880
V882
7.2 Å
7.2 Å
4.8 Å
PIK-39
KU-55933
PIK-108
D
PIK-90 x-ray
PIK-93 x-ray
PI-103 model
E880
V882
M804
2.2 Å
3.1 Å
3.4 Å
PIK-90
PIK-93
PI-103

FIG. 2

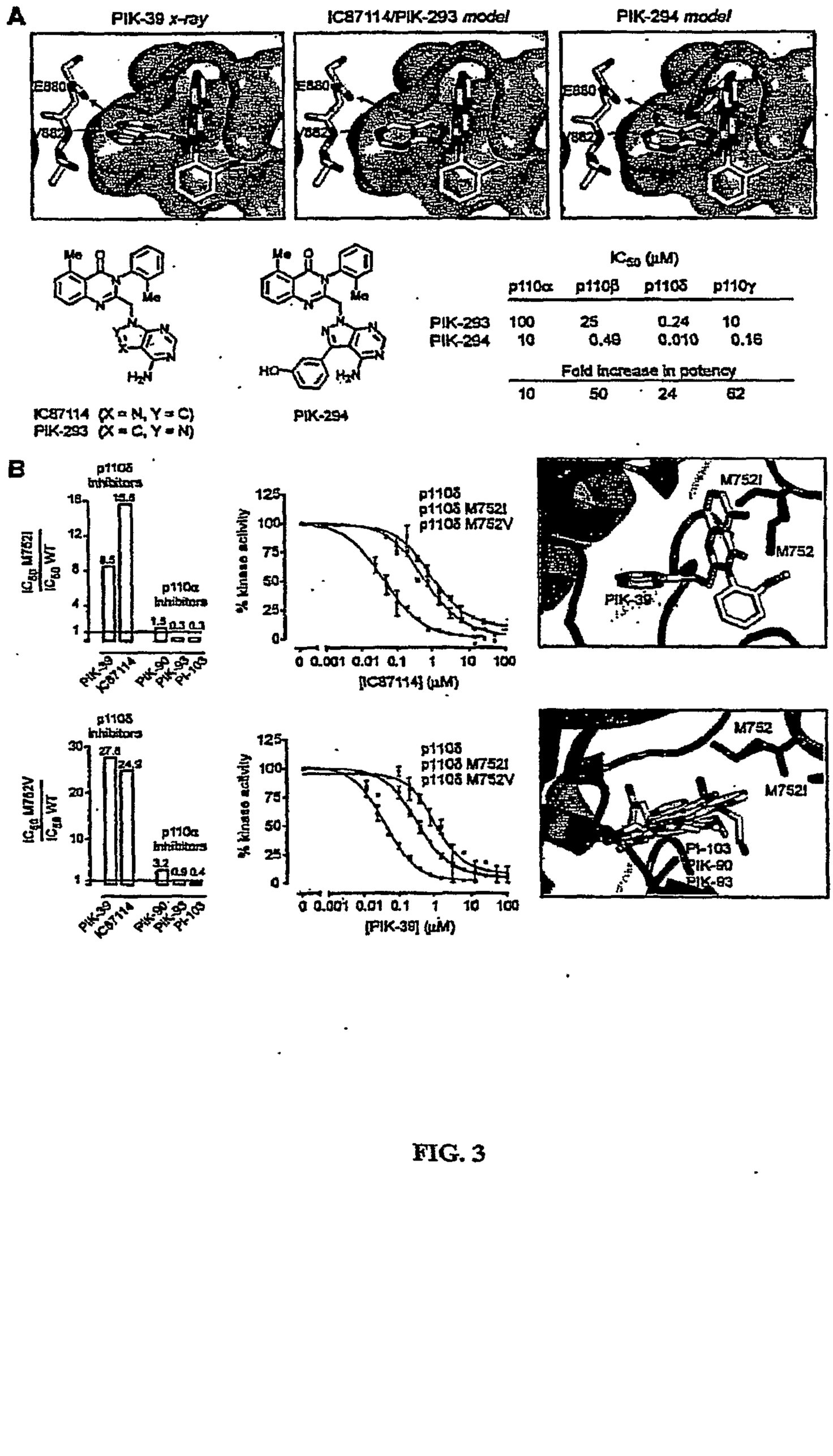
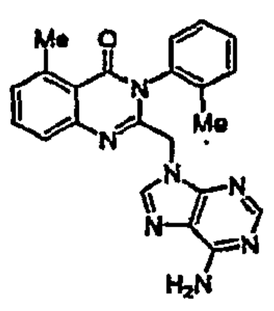
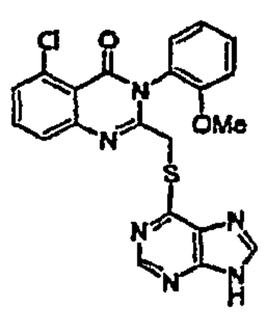

A
PIK-39 x-ray
IC87114/PIK-293 model
PIK-294 model
E880
V882
Me
Me
N
N
X
N
N
H_2N
HO
IC87114 (X = N, Y = C)
PIK-293 (X = C, Y = N)
PIK-294
IC_{50} (μM)
p110α p110β p110δ p110γ
PIK-293 100 25 0.24 10
PIK-294 10 0.49 0.010 0.16
Fold increase in potency
10 50 24 62
B
p110δ inhibitors
IC_{50} M752I / IC_{50} WT
18
12
6
4
1
15.5
8.5
p110α inhibitors
1.5 0.3 0.3
PIK-39
IC87114
PIK-90
PIK-93
PI-103
p110δ inhibitors
IC_{50} M752V / IC_{50} WT
30
20
10
1
27.8
24.2
p110α inhibitors
3.2 0.9 0.4
PIK-39
IC87114
PIK-90
PIK-93
PI-103
% kinase activity
125
100
75
50
25
0
p110δ
p110δ M752I
p110δ M752V
0 0.001 0.01 0.1 1 10 100
[IC87114] (μM)
[PIK-39] (μM)
M752I
M752
PIK-39
M752
M752I
PI-103
PIK-90
PIK-93

FIG. 3

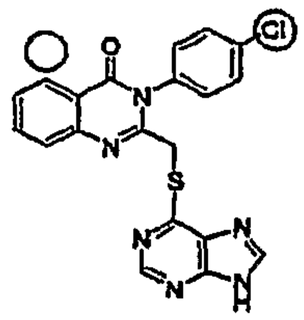
PI3-K Inhibitor | Inactive analog



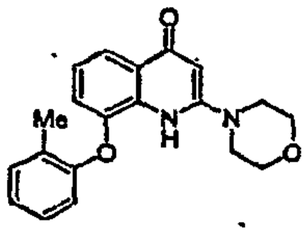
IC87114



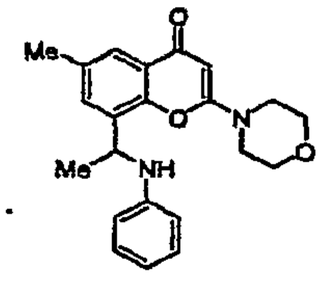
PIK-39



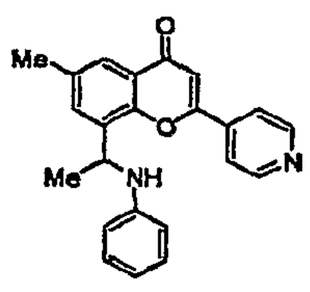
PIK-31



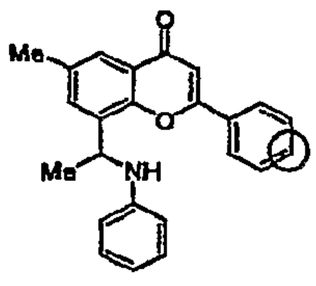
TGX-115



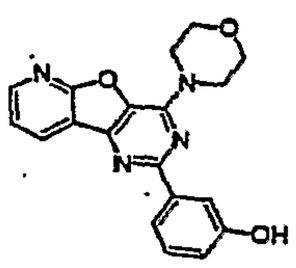
PIK-108



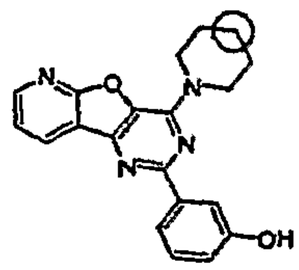
TGX-286



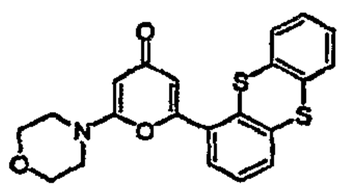
PIK-73



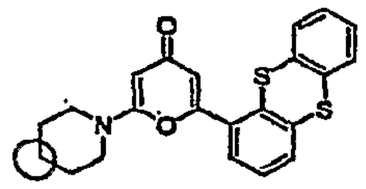
PI-103



PIK-112



KU-55933



KU-58050

PIK-90

PIK-95

FIG. 4

	PIK23	TGX115	AMA37	PIK39	IC87114	TGX286	PIK75	PIK90	PIK93	PIK108	PI-103	PIK124	KU-55399
PI3Kα													
p110α	*>200*	*61*	*32*	*>200*	*>200*	4.5	0.0058	0.011	0.039	2.6	0.008	0.023	3.3
p110β	*42*	*0.13*	*3.7*	*11*	*16*	0.12	1.3	0.35	0.59	0.057	0.088	1.1	1.2
p110δ	*0.097*	*0.63*	*22*	*0.18*	*0.13*	1	0.51	0.058	0.12	0.26	0.048	0.34	0.72
p110γ	*50*	*100*	*100*	*17*	*61*	10	0.076	0.018	0.016	4.1	0.15	0.054	9.9
PI3KC2α	*>100*	*>100*	*>100*	*>100*	*>100*	>100	~10	0.047	~16	~100	~1	0.14	ND
PI3KC2β	*100*	*50*	*>100*	*100*	*>100*	~100	~1	0.064	0.14	~20	0.026	0.37	ND
PI3KC2γ	*>100*	*100*	*50*	*100*	*>100*	ND	ND	ND	ND	ND	ND	ND	ND
hsVPS34	~50	5.2	>100	>100	>100	3.1	2.6	0.83	0.32	~5	2.3	10	~10
PI4Ks													
PI4KIIα	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
PI4KIIIα	>100	>100	>100	>100	>100	>100	>100	0.83	1.1	~50	>100	>100	>100
PI4KIIIβ	>100	>100	>100	>100	>100	>100	~50	3.1	0.019	>100	~50	>100	>100
PIKKs													
ATR	>100	>100	>100	>100	>100	>100	21	15	17	>100	0.85	2	20
ATM	>100	20	ND	>100	>100	>100	2.3	0.61	0.49	35	0.92	3.9	0.005
DNA-PK	*>100*	*1.2*	*0.27*	*>100*	*>100*	~50	0.002	0.013	0.064	0.12	0.002	1.5	10
mTORC1	*>100*	*>100*	*>100*	*>100*	*>100*	*>100*	*~1*	*1.05*	*1.38*	*~10*	*0.02*	*9*	~20
mTORC2	*>101*	*>100*	*>100*	*>100*	*>100*	*ND*	*~10*	ND	ND	ND	*0.083*	ND	>100
PIPKs													
PI4P5KIα	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
PI4P5KIβ	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
PI5P4KIIβ	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	ND

FIG. 5

	TGX115	AMA37	PIK39	IC87114	TGX286	PIK75	PIK90	PIK93	PI103	PIK124	KU55933
Abl	121.2	128.5	99.9	103.6	100.0	97.9	103.4	99.6	100.8	109.1	100.3
Abl (T315I)	141.2	127.4	110.5	99.4	108.5	121.6	111.3	126.0	108.1	87.5	105.3
Akt1	126.6	125.7	136.4	122.2	114.0	(10)	140.2	112.6	108.5	94.8	114.0
Akt1 (ΔPH)	91.4	77.3	81.0	89.6	94.7	(10)	122.4	122.2	123.1	93.3	116.5
Akt2	98.8	115.0	110.5	116.5	109.7	80.7	119.8	117.4	114.7	114.7	98.2
Akt2 (ΔPH)	104.4	94.4	111.3	117.8	117.3	95.0	108.5	110.7	112.6	98.7	100.2
Akt3	97.6	106.6	94.2	111.0	102.9	(2.9)	113.3	96.4	103.5	93.0	95.1
CamKII	111.4	121.9	122.1	115.4	118.8	119.8	116.1	120.4	127.6	135.5	121.8
CDK1/cyc.B	103.0	114.0	115.5	116.0	120.3	61.6	126.6	124.5	142.3	110.7	101.2
CDK2/cyc.A	105.3	99.7	105.6	102.4	103.1	(1.2)	100.9	98.1	98.5	104.9	97.4
Chk1	119.9	104.0	105.2	103.0	104.1	98.4	102.9	99.7	92.3	107.9	81.4
CK1	99.7	99.2	100.1	98.1	91.3	(3.0)	97.8	100.2	84.8	104.6	94.1
CK2	103.3	106.6	99.6	111.7	111.2	82.2	103.1	113.2	108.1	78.5	105.4
Erk1	96.7	99.3	97.6	93.7	99.0	77.9	98.8	98.6	92.0	97.8	104.6
Erk2	107.7	102.5	109.2	104.7	106.9	94.3	102.0	103.2	98.8	98.0	102.1
FAK	105.5	105.5	106.4	110.1	102.8	(10)	100.0	101.8	101.8	102.8	107.3
Fyn	145.7	131.3	115.7	105.3	111.3	(10)	126.1	127.2	114.2	113.4	116.0
GRK2	113.5	117.3	112.6	118.7	118.1	115.6	120.2	110.9	110.3	87.8	108.6
GSK3β	114.0	107.3	101.5	104.7	96.1	(4.4)	85.6	104.0	105.5	97.6	102.0
Hck	104.9	102.2	101.1	93.0	84.9	(10)	94.7	94.9	94.9	87.2	104.1
Insulin R.	108.4	113.4	113.6	115.7	112.1	99.5	102.8	109.8	106.0	109.9	109.7
JNK1α1	99.9	95.5	92.1	88.5	93.8	97.8	94.2	87.2	83.6	96.9	99.6
JNK2α1	104.8	104.8	116.7	107.1	88.1	88.1	90.5	88.1	81.0	85.7	85.7
JNK2α2	95.4	101.6	90.8	87.7	89.3	86.2	83.1	98.5	76.9	89.3	95.4
IRAK4	112.7	98.9	100.1	93.1	95.0	(0.9)	94.9	95.9	105.8	175.4	74.2
NEK2	125.2	99.1	98.6	114.3	126.4	106.9	103.4	110.1	120.0	118.5	106.5
PKA	105.4	94.0	108.1	108.6	107.3	(10)	103.1	105.6	102.5	104.3	104.1
PKCδ	103.9	104.9	103.9	104.6	104.9	114.3	100.7	103.7	101.2	105.5	103.7
PKCε	108.9	111.9	111.9	114.1	111.5	(10)	105.2	103.4	103.4	106.0	104.8
PDK1	111.2	101.9	97.4	113.4	114.4	111.0	110.4	118.7	107.5	109.4	130.7
PLK1	122.7	118.9	117.4	109.6	107.6	93.7	107.6	111.1	106.2	96.0	84.9
p38	101.2	102.8	108.5	104.1	100.9	100.3	98.5	102.9	99.8	102.6	101.4
Src	111.7	109.0	109.6	113.3	96.4	(10)	103.7	116.1	100.6	102.7	114.7
Src (T338I)	112.8	101.3	97.9	95.7	96.4	80.4	109.5	111.5	113.4	112.5	113.0
WNK1	107.5	108.0	109.6	109.0	119.3	101.1	108.6	110.0	104.1	108.3	104.7
Zap70	123.8	121.1	130.4	110.5	130.0	179.5	115.8	115.4	117.7	100.4	99.3

FIG. 6

```
   1 MPPGVDCPME FWTKEENQSV VVDFLLPTGV YLNFPVSRNA NLSTIKQLLW HRAQYEPLFH
  61 MLSGPEAYVF TCINQTAEQQ ELEDEQRRLC DVQPFLPVLR LVAREGDRVK  KLINSQISLL
 121 IGKGLHEFDS LCDPEVNDFR AKMCQFCEEA AARRQQLGWE AWLQYSFPLQ LEPSAQTWGP
 181 GTLRLPNRAL LVNVKFEGSE ESFTFQVSTK DVPLALMACA LRKKATVFRQ PLVEQPEDYT
 241 LQVNGRHEYL YGNYPLCQFQ YICSCLHSGL TPHLTMVHSS SILAMRDEQS NPAPQVQKPR
 301 AKPPPIPAKK PSSVSLWSLE QPFRIELIQG SKVNADERMK LVVQAGLFHG NEMLCKTVSS
 361 SEVSVCSEPV WKQRLEFDIN ICDLPRMARL CFALYAVIEK AKKARSTKKK SKKADCPIAW
 421 ANLMLFDYKD QLKTGERCLY MWPSVPDEKG ELLNPTGTVR SNPNTDSAAA LLICLPEVAP
 481 HPVYYPALEK ILELGRHSEC VHVTEEEQLQ LREILERRGS GELYEHEKDL VWKLRHEVQE
 541 HFPEALARLL LVTKWNKHED VAQMLYLLCS WPELPVLSAL ELLDFSFPDC HVGSFAIKSL
 601 RKLTDDELFQ YLLQLVQVLK YESYLDCELT KFLLDRALAN RKIGHFLFWH LRSEMHVPSV
 661 ALRFGLILEA YCRGSTHHMK VLMKQGEALS KLKALNDFVK LSSQKTPKPQ TKELMHLCMR
 721 QEAYLEALSH LQSPLDPSTL LAEVCVEQCT FMDSKMKPLW IMYSNEEAGS GGSVGIIFKN
 781 GDDLRQDMLT LQMIQLMDVL WKQEGLDLRM TPYGCLPTGD RTGLIEVVLR SDTIANIQLN
 841 KSNMAATAAF NKDALLNWLK SKNPGEALDR AIEEFTLSCA GYCVATYVLG IGDRHSDNIM
 901 IRESGQLFHI DFGHFLGNFK TKFGINRERV PFILTYDFVH VIQQGKTNNS EKFERFRGYC
 961 ERAYTILRRH GLLFLHLFAL MRAAGLPELS CSKDIQYLKD SLALGKTEEE ALKHFRVKFN
1021 EALRESWKTK VNWLAHNVSK DNRQ
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FIG. 7

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1     melenykqpv vlredncrrr rrmkprsaaa slssmelipi efvlptsqrk ckspetallh
61    vaghgnveqm kaqvwlrale tsvaadfyhr lgphhfllly qkkgqwyeiy dkyqvvqtld
121   clrywkathr spgqihlvqr hppseesqaf qrqltaligy dvtdvsnvhd deleftrrgl
181   vtprmaevas rdpklyamhp wvtskplpey lwkkiannci fivihrstts qtikvspddt
241   pgailqsfft kmakkkslmd ipesqseqdf vlrvcgrdey lvgetpiknf qwvrhclkng
301   eeihvvldtp pdpaldevrk eewplvddct gvtgyheqlt ihgkdhesvf tvslwdcdrk
361   frvkirgidi pvlprntdlt vfveaniqhg qqvlcqrrts pkpfteevlw nvwlefsiki
421   kdlpkgalln lqiycgkapa lsskasaesp sseskgkvql lyyvnlllid hrfllrrgey
481   vlhmwqisgk gedqgsfnad kltsatnpdk ensmsisill dnychpialp khqptpdpeg
541   drvraempnq lrkqleaiia tdplnpltae dkellwhfry eslkhpkayp klfssvkwgq
601   qeivaktyql larrevwdqs aldvgltmql ldcnfsdenv raiavqkles ledddvlhyl
661   lqlvqavkfe pyhdsalarf llkrglrnkr ighflfwflr seiaqsrhyq qrfavileay
721   lrgcgtamlh dftqqvqvie mlqkvtldik slsaekydvs sqvisqlkqk lenlqnsqlp
781   esfrvpydpg lkagalaiek ckvmaskkkp lwlefkcadp talsnetigi ifkhgddlrq
841   dmlilqilri mesiwetesl dlcllpygci stgdkigmie ivkdattiak iqqstvgntg
901   afkdevlnhw lkekspteek fqaaverfvy scagycvatf vlgigdrhnd nimitetgnl
961   fhidfghilg nyksflginк ervpfvltpd flfvmgtsgk ktsphfqkfq dicvkaylal
1021  rhhtnlliil fsmmlmtgmp qltskediey irdaltvgkn eedakkyfld qievcrdkgw
1081  tvqfnwflhl vlgikqgekh sa
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FIG. 8

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1     MPPRPSSGEL WGIHLMPPRI LVECLLPNGM IVTLECLREA TLITIKHELF KEARKYPLHQ
61    LLQDESSYIF VSVTQEAERE EFFDETRRLC DLRLFQPFLK VIEPVGNREE KILNREIGFA
121   IGMPVCEFDM VKDPEVQDFR RNILNVCKEA VDLRDLNSPH SRAMYVYPPN VESSPELPKH
181   IYNKLDKGQI IVVIWVIVSP NNDKQKYTLK INHDCVPEQV IAEAIRKKTR SMLLSSEQLK
241   LCVLEYQGKY ILKVCGCDEY FLEKYPLSQY KYIRSCIMLG RMPNLMLMAK ESLYSQLPMD
301   CFTMPSYSRR ISTATPYMNG ETSTKSLWVI NSALRIKILC ATYVNVNIRD IDKIYVRTGI
361   YHGGEPLCDN VNTQRVPCSN PRWNEWLNYD IYIPDLPRAA RLCLSICSVK GRKGAKEEHC
421   PLAWGNINLF DYTDTLVSGK MALNLWPVPH GLEDLLNPIG VTGSNPNKET PCLELEFDWF
481   SSVVKFPDMS VIEEHANWSV SREAGFSYSH AGLSNRLARD NELRENDKEQ LKAISTRDPL
541   SEITEQEKDF LWSHRHYCVT IPEILPKLLL SVKWNSRDEV AQMYCLVKDW PPIKPEQAME
601   LLDCNYPDPM VRGFAVRCLE KYLTDDKLSQ YLIQLVQVLK YEQYLDNLLV RFLLKKALTN
661   QRIGHFFFWH LKSEMHNKTV SQRFGLLLES YCRACGMYLK HLNRQVEAME KLINLTDILK
721   QEKKDETQKV QMKFLVEQMR RPDFMDALQG FLSPLNPAHQ LGNLRLEECR IMSSAKRPLW
781   LNWENPDIMS ELLFQNNEII FKNGDDLRQD MLTLQIIRIM ENIWQNQGLD LRMLPYGCLS
841   IGDCVGLIEV VRNSHTIMQI QCKGGLKGAL QFNSHTLHQW LKDKNKGEIY DAAIDLFTRS
901   CAGYCVATFI LGIGDRHNSN IMVKDDGQLF HIDFGHFLDH KKKKFGYKRE RVPFVLTQDF
961   LIVISKGAQE CTKTREFERF QEMCYKAYLA IRQHANLFIN LFSMMLGSGM PELQSFDDIA
1021  YIRKTLALDK TEQEALEYFM KQMNDAHHGG WTTKMDWIFH TIKQHALN
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FIG. 9

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1     MCFSFIMPPA MADILDIWAV DSQIASDGSI PVDFLLPTGI YIQLEVPREA TISYIKQMLW
61    KQVHNYPMFN LLMDIDSYMF ACVNQTAVYE ELEDETRRLC DVRPFLPVLK LVTRSCDPGE
121   KLDSKIGVLI GKGLHEFDSL KDPEVNEFRR KMRKFSEEKI LSLVGLSWMD WLKQTYPPEH
181   EPSIPENLED KLYGGKLIVA VHFENCQDVF SFQVSPNMNP IKVNELAIQK RLTIHGKEDE
241   VSPYDYVLQV SGRVEYVFGD HPLIQFQYIR NCVMNRALPH FILVECCKIK KMYEQEMIAI
301   EAAINRNSSN LPLPLPPKKT RIISHVWENN NPFQIVLVKG NKLNTEETVK VHVRAGLFHG
361   TELLCKTIVS SEVSGKNDHI WNEPLEFDIN ICDLPRMARL CFAVYAVLDK VKTKKSTKTI
421   NPSKYQTIRK AGKVHYPVAW VNTMVFDFKG QLRTGDIILH SWSSFPDELE EMLNPMGTVQ
481   TNPYTENATA LHVKFPENKK QPYYYPPFDK IIEKAAEIAS SDSANVSSRG GKKFLPVLKE
541   ILDRDPLSQL CENEMDLIWT LRQDCREIFP QSLPKLLLSI KWNKLEDVAQ LQALLQIWPK
601   LPPREALELL DFNYPDQYVR EYAVGCLRQM SDEELSQYLL QLVQVLKYEP FLDCALSRFL
661   LERALGNRRI GQFLFWHLRS EVHIPAVSVQ FGVILEAYCR GSVGHMKVLS KQVEALNKLK
721   TLNSLIKLNA VKLNRAKGKE AMHTCLKQSA YREALSDLQS PLNPCVILSE LYVEKCKYMD
781   SKMKPLWLVY NNKVFGEDSV GVIFKNGDDL RQDMLTLQML RLMDLLWKEA GLDLRMLPYG
841   CLATGDRSGL IEVVSTSETI ADIQLNSSNV AAAAAFNKDA LLNWLKEYNS GDDLDRAIEE
901   FTLSCAGYCV ASYVLGIGDR HSDNIMVKKT GQLFHIDFGH ILGNFKSKFG IKRERVPFIL
961   TYDFIHVIQQ GKTGNTEKFG RFRQCCEDAY LILRRHGNLF ITLFALMLTA GLPELTSVKD
1021  IQYLKDSLAL GKSEEEALKQ FKQKFDEALR ESWTTKVNWM AHTVRKDYRS
```
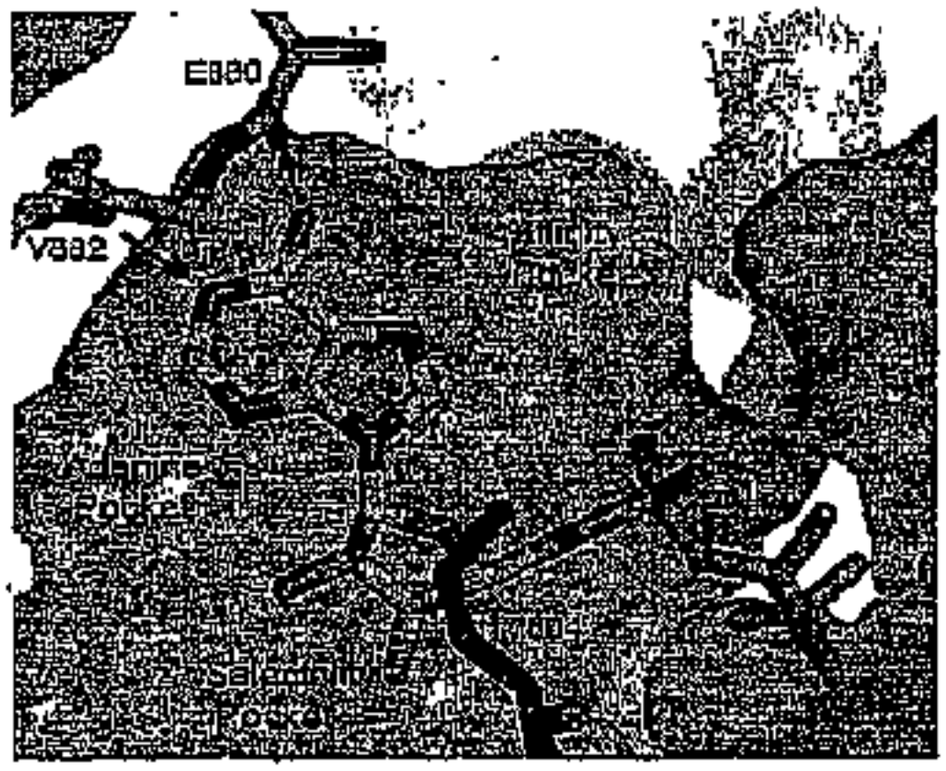
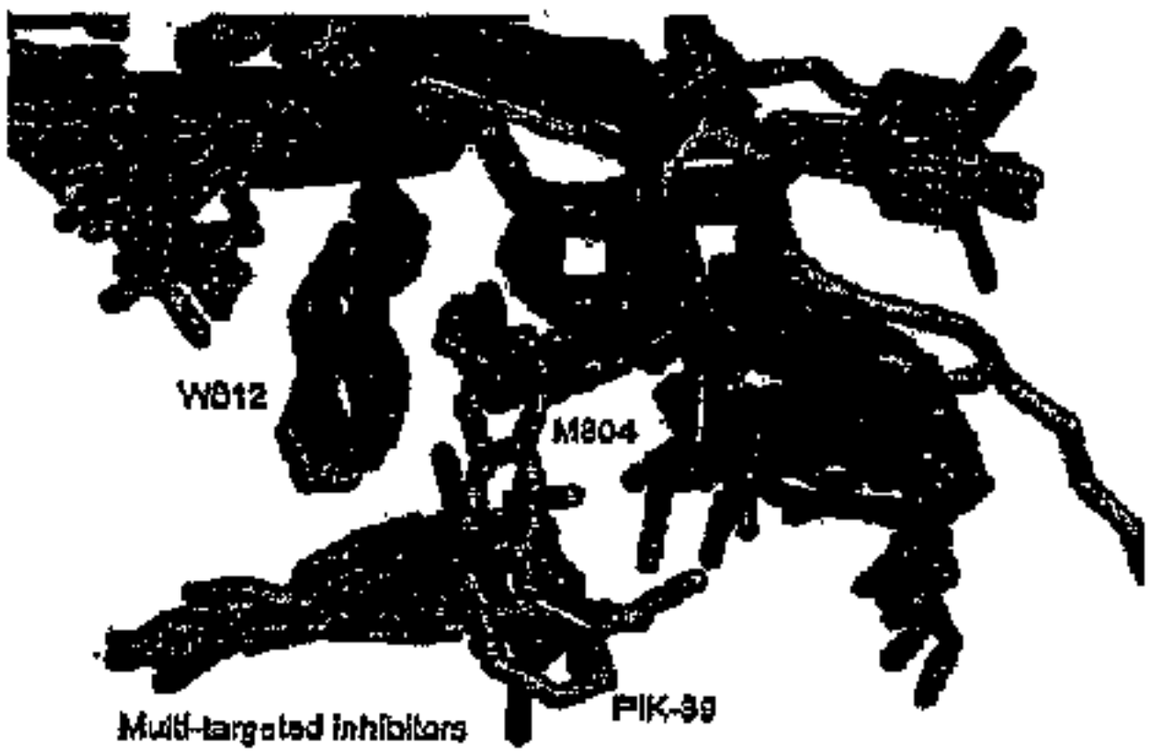

FIG. 10

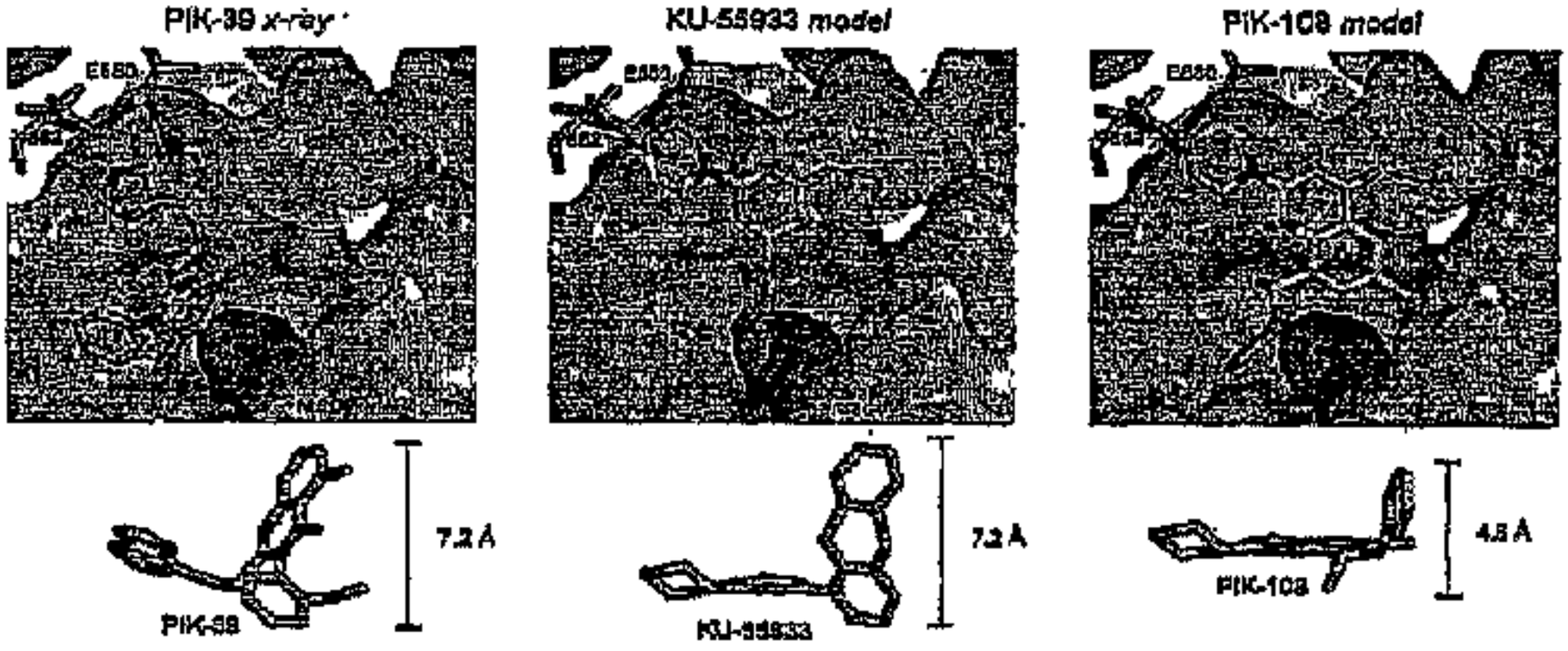
A


E880
V882

B


W812
M804
Multi-targeted inhibitors
PIK-39

C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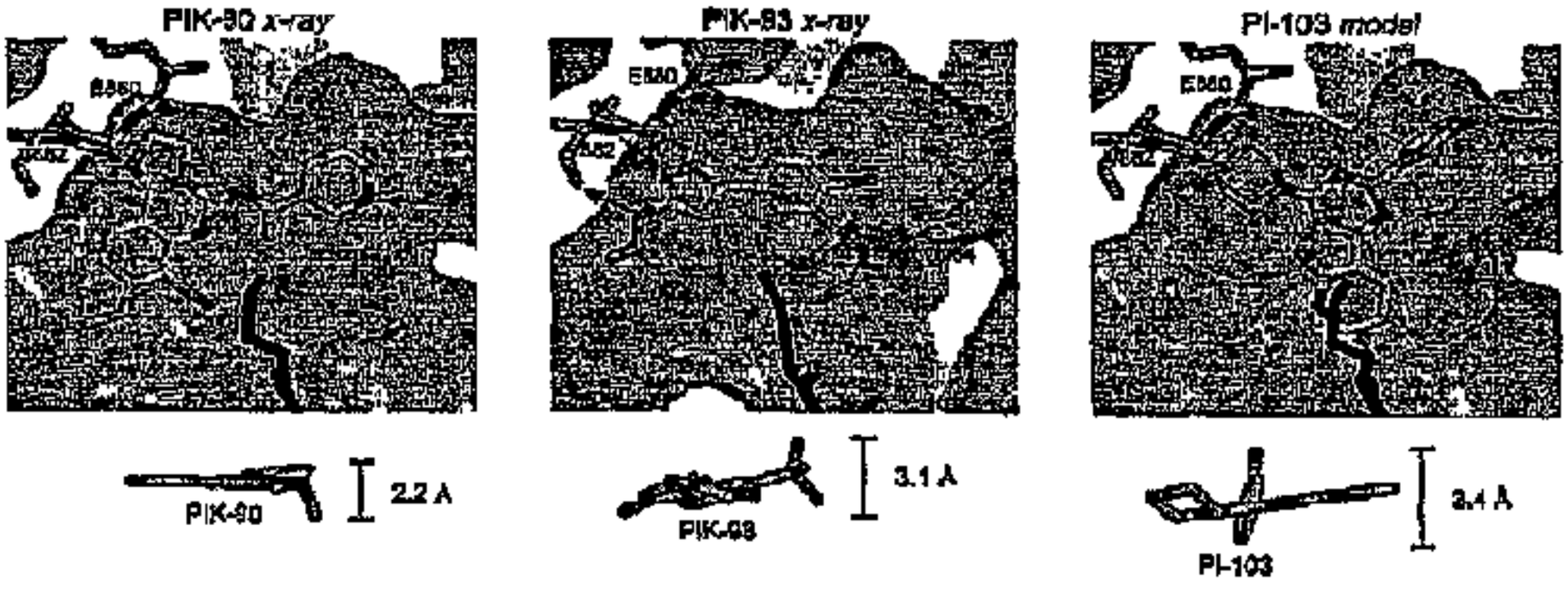
KU-55933 model
PIK-108 model
7.2 Å
7.2 Å
4.8 Å
PIK-108

D


PIK-90 x-ray
PIK-93 x-ray
PI-103 model
E880
2.2 Å
3.1 Å
3.4 Å
PIK-90
PIK-93
PI-103