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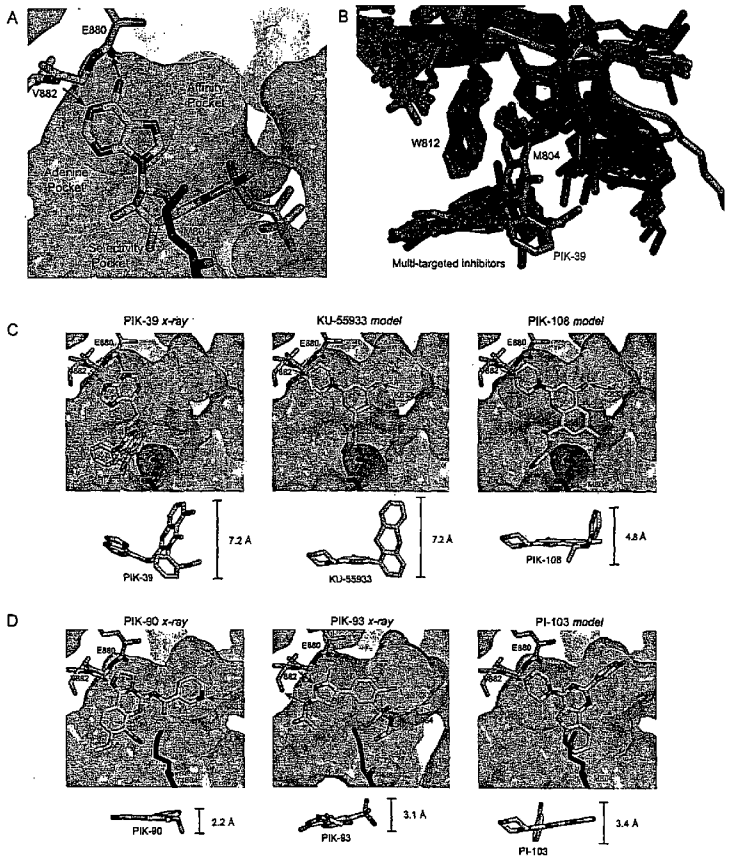

FIG. 2

(57) Abstract: The present invention provides novel PB -Kinase antagonists and methods of use thereof.

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PI3 KINASE ANTAGONISTS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 60/744,269, filed April 4, 2006, and U.S. Provisional Patent Application No. 60/744,270, filed April 4, 2006, both of which are incorporated herein by reference in their entirety for all purposes.

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 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/PDK1 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 (mTORC1) 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] The present invention meets these and other needs in the art by providing a new class of PI3-Kinase antagonists.

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention provides certain qnovel compounds found to be effective as antagonists of PI3-Kinases.

[0007] In one aspect, the present invention provides a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket quinazolinone antagonist) or a PI3-kinase antagonist as set forth in Formula (I), defined below.

[0008] In another aspect, the present invention provides methods of decreasing the catalytic activity of a PI3-Kinase. The method includes the step of contacting the PI3-Kinase with an activity decreasing amount of a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket quinazolinone antagonist) or a PI3-Kinase antagonist of Formula (I).

[0009] In another aspect, the present invention provides methods of treating disease mediated by treating a condition mediated by PI3-Kinase activity in a subject in need of such treatment. The method includes administering to the subject a therapeutically effective amount of a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket quinazolinone antagonist) or a PI3-Kinase antagonist of Formula (I).

[0010] 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 a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket quinazolinone antagonist) or a PI3-Kinase antagonist of Formula (I).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figure 1 illustrates structures of representative compounds from eleven chemotypes of PI3-K inhibitors.

[0012] Figure 2 illstrates 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 PI3-K inhibitors bound to p110γ.

[0013] 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.

[0014] Figure 4. Structures of additional PI3-K inhibitors and inactive analogs.

[0015] Figure 5. IC50 values (μM) for selected PI3-K inhibitors against lipid kinases.

[0016] 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).

[0017] Figure 7 sets forth the sequence of a human p110δ kinase.

[0018] Figure 8 sets forth the sequence of a human p110γ kinase.

[0019] Figure 9 sets forth the sequence of a human p110α kinase.

[0020] Figure 10 sets forth the sequence of a human p110β kinase.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0021] Abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0022] 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 $-OCH_2-$.

[0023] 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.

[0024] 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. An "alkynylene" is a subset of an alkylene in which the alkylene includes at least on triple bond between adjacent carbon atoms.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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 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, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. 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.

[0029] 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.

[0030] 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.

[0031] The term "oxo" as used herein means an oxygen that is double bonded to a carbon atom.

[0032] 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.

[0033] 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).

[0034] 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', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -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.

[0035] 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 -$S(O)_2$NR'-. 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.

[0036] As used herein, the term "heteroatom" or "ring heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0037] 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.

[0038] A "substituent group," as used herein, means a group selected from the following moieties:

[0039] (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

[0040] (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0041] (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

[0042] (ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0043] (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

[0044] (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.

[0045] 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.

[0046] 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.

[0047] 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 (e.g. (+)-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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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.

[0062] As used herein, the "antagonist" or "the compound of the present invention" refers to a compound fo Formula (I), or a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket quinazolinone antagonist). A "compound of Formula (I)" includes all embodiments of Formula (I) as described below.

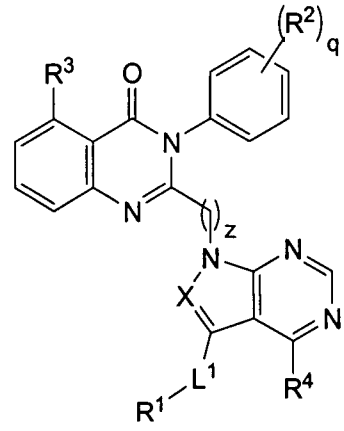
II. PI3-Kinase Antagonists

[0063] In one aspect, the present invention provides novel PI3-kinase antagonists. In some embodiments, the PI3-kinase antagonist is a PI3-Kinase affinity pocket binding antagonist (e.g. a PI3-Kinase affinity pocket quinazolinone antagonist). The PI3-Kinase affinity pocket binding antagonist of the present invention is a compound containing a PI3-Kinase affinity pocket binding moiety. The PI3-Kinase affinity pocket quinazolinone antagonists of the present invention are substituted quinazolinone compounds containing a PI3-Kinase affinity pocket binding moiety. 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.

[0064] In some embodiments, the PI3-Kinase affinity pocket quinazolinone antagonist further include a pyrazolopyrimidine substituent or a pyrrolopyrimidine substituent. In some related embodiments, the pyrazolopyrimidine substituent or pyrrolopyrimidine substituent is covalently bonded to the quinazolinone core, and the PI3-Kinase affinity pocket binding

moiety is covalently attached to the pyrazolopyrimidine substituent or pyrrolopyrimidine substituent.

[0065] In some embodiments, the PI3-kinase antagonist of the present invention has the formula:



(I).

[0066] In Formula (I) above, q is an integer from 0 to 5 (e.g. 1); z is an integer from 0 to 10 (e.g. 1); and X is =CH- or =N-. L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0067] R^1 and R^2 are independently halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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, where n is an integer from 0 to 2. R^1 may also be a PI3-Kinase affinity pocket binding moiety. R^3 and R^4 are independently hydrogen, halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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, where n is an integer from 0 to 2.

[0068] R^5 is independently hydrogen, $-C(O)R^{10}$, 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^6 is independently hydrogen, $-NR^{11}R^{12}$, 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. Where n is 1 or 2, R^6 is other than hydrogen.

[0069] R^7 is 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. R^8 is independently hydrogen, $-S(O)_nR^{13}$, $-C(O)R^{14}$, 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.

[0070] R^9 is independently $-NR^{15}R^{16}$, 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. R^{10} is independently hydrogen, $-NR^{17}R^{18}$, 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.

[0071] R^{14} is independently hydrogen, $-NR^{19}R^{20}$, 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; and

[0072] R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} 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.

[0073] In some embodiments, the PI3-Kinase affinity pocket binding moiety is capable of forming a hydrogen bond with the side chain amine of K833, an amino acid within the PI3-Kinase affinity pocket.

[0074] In some embodiments, R^1 is halogen, substituted or unsubstituted halo(C_1-C_6)alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl(C_1-C_6)alkyl, or substituted or unsubstituted heteroaryl(C_1-C_6)alkyl. R^1 may also be halogen, substituted or unsubstituted phenyl, substituted or unsubstituted furanyl,

substituted or unsubstituted pyrrolyl, substituted or unsubstituted thiophenyl, or substituted or unsubstituted benzothiophenyl, substituted or unsubstituted indolyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted 1H-pyrrolo[2,3-*c*]pyridinyl, substituted or unsubstituted 1H-pyrrolo[2,3-*b*]pyridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted cylcohexyl, substituted or unsubstituted morpholino, substituted or unsubstituted piperidinyl, or substituted or unsubstituted tetrahydropyridinyl.

[0075] In other embodiments, R^1 is phenyl, furanyl, pyrrolyl, thiophenyl, or benzothiophenyl, each of which are optionally substituted with one or more R^{21} substituent(s). R^{21} is independently (1) or (2) as defined in this paragraph. Thus, R^{21} may be (1) halogen, -CN, $-OR^{22}$, $-C(O)R^{23}$, $-NR^{24}R^{25}$, $-S(O)_wNR^{26}R^{27}$, or $-S(O)_wR^{28}$. The symbol w is an integer from 0 to 2. R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, or heteroarylalkyl, optionally substituted with unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl. R^{21} may also be (2) $(C_1\text{-}C_{10})$alkyl, 2 to 10 membered heteroalkyl, $C_3\text{-}C_8$ cycloalkyl, 3 to 8 membered heterocycloalkyl, aryl or heteroaryl optionally substituted with halogen, -OH, -CN, $-NH_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl.

[0076] In some embodiments, R^1 is phenyl substituted at the meta and para positions, or substituted at the meta and meta positions. That is, R^1 is a 4,5-substituted phenyl or a 3,5-substituted phenyl. In some related embodiments, the 4,5-substituted phenyl or 3,5-substituted phenyl is substituted, independently, with R^{21} (as defined in the previous paragraph). In some embodiments, R^{21} is halogen or $-OR^{22}$. R^{21} may also be fluorine and R^{22} may be hydrogen or unsubstituted $C_1\text{-}C_4$ alkyl (e.g. methyl). In other embodiments, R^1 is phenyl substituted para position (i.e. a 4-substituted phenyl).

[0077] In some embodiments, L^1 is substituted or unsubstituted alkylene (e.g. a substituted or unsubstituted alkynylene. In other embodiments, L^1 is substituted or unsubstituted methylene, substituted or unsubstituted ethylene, substituted or unsubstituted propylene, substituted or unsubstituted butylenes, substituted or unsubstituted ethynylene, or substituted or unsubstituted prop-2-ynylene. In some related embodiments, R^1 is –CN, -OR^5, NR^7R^8, R^{21}-substituted or unsubstituted cycloalkyl, R^{21}-substituted or unsubstituted aryl, R^{21}-substituted or unsubstituted heteroaryl, R^{21}-substituted or unsubstituted C_1-C_4 alkyl. R^{21} may be halogen, –OR^{22}, -$NR^{24}R^{25}$, or unsubstituted C_1-C_4 alkyl. R^5, R^7, R^8, R^{22}, R^{24} and R^{25} may independently be hydrogen or unsubstituted C_1-C_4 alkyl (e.g. methyl).

[0078] In some embodiments, R^2 is halogen, -OH, -CN, -NH_2, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl. R^2 may also be halogen or unsubstituted alkyl. In some embodiments, R^2 is fluorine or unsubstituted C_1-C_4 alkyl (e.g. methyl).

[0079] R^3 may be halogen, -OH, -CN, -NH_2, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl. R^3 may also be unsubstituted C_1-C_4 alkyl (e.g. methyl).

[0080] In some embodiments, R^4 is halogen, -OH, -CN, -NH_2, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl.

[0081] In some embodiments, R^2 and R^3 are independently unsubstituted C_1-C_4 alkyl, R^4 is NH_2, q is 1, and z is 1.

[0082] In some embodiments, each substituted group described above in the compound of Formula (I) 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, substituted cycloalkyl-alkyl, substituted heterocycloalkyl-alkyl, substituted arylalkyl, and/or substituted

heteroarylalkyl, described above in the compounds of Formula (I) 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.

[0083] In other embodiments of the compounds of Formula (I), each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, including those alkyl groups forming part of a cycloalkyl-alkyl (i.e. a cycloalkyl-(C_1-C_{20})alkyl), heterocycloalkyl-alkyl (i.e. a heterocycloalkyl-(C_1-C_{20})alkyl), arylalkyl (i.e. an aryl-(C_1-C_{20})alkyl), or substituted heteroarylalkyl (i.e. a heteroaryl-(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, including those cycloalkyl groups forming part of a cycloalkyl-alkyl (i.e. a C_4-C_8 cycloalkyl-alkyl, or a C_4-C_8 cycloalkyl-(C_1-C_{20})alkyl). Each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl, including those heterocycloalkyl groups forming part of a heterocycloalkyl-alkyl (i.e. a 4 to 8 membered heterocycloalkyl-alkyl, or a 4 to 8 membered heterocycloalkyl-(C_1-C_{20})alkyl).

[0084] 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, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl, including cycloalkyl-alkyl groups, heterocycloalkyl-alkyl groups, heteroarylalkyl groups, and arylalkyl groups, as described in the preceding paragraph.

[0085] In another embodiment, the compounds of the present invention include the compounds of any one or all of those listed in Table 1 below.

III. The PI3-Kinase Affinity Pocket

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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 p110δ 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. In some embodiments, the antagonist interact with or displaces the side chain of methionine 804 of p110γ, or the equivalent methionine present in p110α, p110β, or p110δ (See Figures 7-10).

[0090] 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

[0091] 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).

[0092] 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.

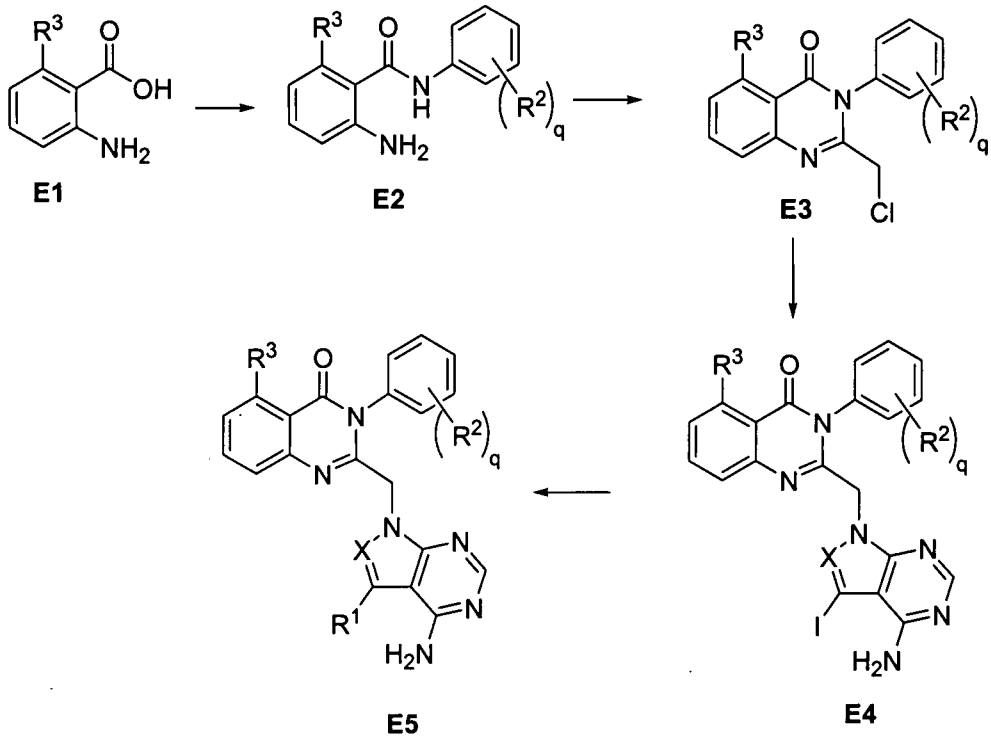
[0093] In some embodiments, the query PI3-Kinase affinity pocket binding antagonist is analyzed to determine whether at least one bond (e.g. a hydrogen bond) is formed between the query PI3-Kinase affinity pocket binding antagonist and an amino acid that form part of the PI3-Kinase affinity pocket. Using 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

[0094] 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 1



In Scheme 1, R^1, R^2, R^3, X, and q are as defined above. The anthranilic acid **E1** may be converted to the acid chloride using, for example, $SOCl_2$ and then directly reacted with the amino functionality of an aniline to yield the corresponding amide **E2**. Subsequent cyclization of **E2** may be accomplished using chloroacetylchloride. Substitution of the **E3** chlorine with the iodo-pyrazolopyrimidine or iodo-pyrrolopyrimidine is performed in the presence of base to form **E4**. Finally, the iodine of **E4** is substituted with R^1 by a Suzuki-Miyaura coupling with the appropriate boronic acid.

VI. Methods

[0095] In another aspect, the present invention provides methods of decreasing the catalytic activity of a PI3 kinase, such as p110δ kinase or p110γ kinase. The method includes the step of contacting the PI3 kinase (e.g. p110δ kinase) with an activity decreasing amount of a PI3-Kinase antagonist (i.e. a PI3-Kinase affinity pocket binding antagonist or a PI3-Kinase

antagonist of Formula (I)). In some embodiments, the antagonist is a PI3-Kinase affinity pocket quinazolinone antagonist. In some embodiments, the PI3-Kinase antagonist is specific to p110δ relative to the antagonist action against p110α, p110β, and/or p110γ. In some embodiments, the PI3-Kinase antagonist is specific to p110δ relative to the antagonist action against p110α and/or p110β. In some embodiments, the PI3-Kinase antagonist is specific to p110δ relative to the antagonist action against p110α. In some embodiments, the PI3-Kinase antagonist is specific to p110γ relative to the antagonist action against p110α and/or p110β. In some embodiments, the PI3-Kinase antagonist is specific to p110γ relative to the antagonist action against p110α.

[0096] In some embodiments, where the PI3-Kinase antagonist is specific to p110γ relative to the antagonist action against p110β, and/or p110α, the PI3-Kinase antagonist is the PI3-Kinase antagonist of Formula (I), where R^1 is a 4,5-substituted phenyl. In some related embodiments, the 4,5-substituted phenyl is substituted, independently, with R^{21}. R^{21} may be halogen or $-OR^{22}$. R^{21} may also be fluorine and R^{22} may be hydrogen or unsubstituted C_1-C_4 alkyl (e.g. methyl).

[0097] In other embodiments, where the PI3-Kinase antagonist is specific to p110δ relative to the antagonist action against p110α, p110β, and/or p110γ, the PI3-Kinase antagonist is the PI3-Kinase antagonist of Formula (I), where R^1 is a 3,5-substituted phenyl. In some related embodiments, the 3,5-substituted phenyl is substituted, independently, with R^{21}. R^{21} may be halogen or $-OR^{22}$. R^{21} may also be fluorine and R^{22} may be hydrogen or unsubstituted C_1-C_4 alkyl (e.g. methyl).

[0098] In some embodiments, the IC50 against the p110δ kinase and/or p110γ 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 100 fold lower than the IC50 against p110α, and/or p110β. In other embodiments, the IC50 of the antagonist against p110δ kinase and/or p110γ 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.

[0099] In another aspect, the present invention provides methods of treating a disease mediated by PI3-Kinase activity (e.g. p110δ kinase activity or p110γ kinase activity) in a subject in need of such treatment. The method includes administering to the subject a therapeutically effective amount of a PI3-Kinase antagonist (i.e. a PI3-Kinase affinity pocket

antagonist or PI3-Kinase antagonist of Formula (I)). In some embodiments, the antagonist is a PI3-Kinase affinity pocket quinazolinone antagonist.

[0100] In some embodiments, the disease is a hematologic malignancy, inflammation, autoimmune disease, or cardiovascular disease. In some embodiments, the disease is a hematologic malignancy or autoimmune disease. Examples of hematologic malignancies include acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), mastocytosis, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and myelodysplastic syndrome (MDS). Examples of inflammation disorders and autoimmune disease include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and asthma. Other disorders include bone-resorption disorders and thromobsis.

[0101] The disorder 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. A detailed description of conditions and disorders mediated by p110δ kinase activity is set forth in Sadu et al., WO 01/81346, which is incorporated herein by reference in its entirety for all purposes.

[0102] 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 a PI3-Kinase antagonist (i.e. a PI3-Kinase affinity pocket antagonist or PI3-Kinase antagonist of Formula (I)). In some embodiments, the antagonist is a PI3-Kinase affinity pocket quinazolinone antagonist.

VII. Pharmaceutical Formulations

[0103] In another aspect, the present invention provides a pharmaceutical composition including a PI3-Kinase affinity pocket binding antagonist or a compound of Formula (I) 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.

[0104] 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).

[0105] 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.

[0106] 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] 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, cyclophophamide, 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.

[0118] These additional agents may be administered separately, as part of a multiple dosage regimen, from the inhibitor-containing composition. Alternatively, these agents may be part of a single dosage form, mixed together with the inhibitor in a single composition.

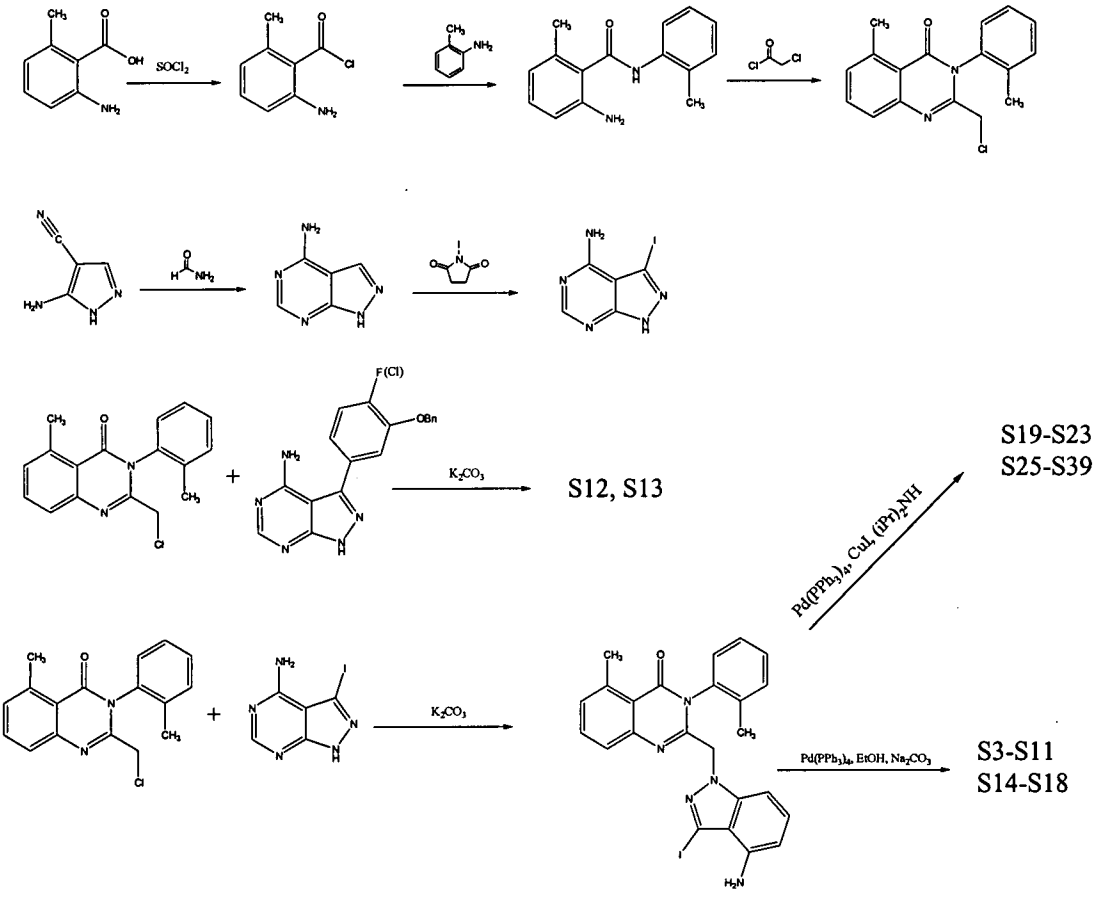
[0119] The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention. Indeed, various modifications of the invention in addition to those described herein will become apparent to those having skill in the art 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 agonists 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 and are hereby incorporated by reference herein in their entirety for all purposes, whether previously specifically incorporated or not.

VIII. Examples

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

A. Exemplary Synthesis Scheme

Scheme 2



Scheme 2 illustrates synthetic routes to certain compounds listed in Table 1 below. Using the information provided in Schemes 1 and 2, and the detailed synthesis information of certain compounds provided below, one skilled in the art would immediately recognize the synthetic routes to the compounds of the present invention.

B. Detailed Synthesis of Certain Compounds

1. Synthesis of 2-amino-6-methyl-N-o-tolylbenzamide

[0120] 2-amino-6-methylbenzoic acid (25 g, 165 mmol) was dissolved in benzene (250 mL). Thionyl chloride (37.5 mL, 500 mmol) was added and the reaction heated to reflux

overnight. The following day the reaction was concentrated in vacuo, and then taken up twice in benzene (200 mL) and solvent removed in vacuo again to give a black oil. The oil was dissolved in $CHCl_3$ (400 mL), o-toluidine (44 mL, 412 mmol) was added and the reaction heated to reflux. Reaction was complete after two hours, and the product was purified by three silica gel chromatographies (15% EtOAc/Hexanes) to yield a tan solid (29 g, 73.4% yield). LR-ESI MS $(M+H)^+$ *m/z* calcd 241.1, found 240.9.

2. Synthesis of 2-(chloromethyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one

[0121] Chloroacetylchloride (29 mL, 363 mmol) was added to a solution of 2-amino-6-methyl-N-o-tolylbenzamide (29 g, 121 mmol) in acetic acid (600 mL) and the reaction heated to reflux. After two hours the reaction was cooled to RT, and concentrated in vacuo. The product was purified by three silica gel chromatographies (twice in 15% EtOAc/Hexanes followed by 10% diethylether/hexanes) to yield a white solid (8.3 g, 23% yield). LR-ESI MS $(M+H)^+$ *m/z* calcd 299.1, found 298.8.

3. Synthesis of 2-((4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one

[0122] 2-(chloromethyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (0.15 g, 0.5 mmol) and 1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.101 g, 0.05 mmol) were added to DMF (10 mL) and K_2CO_3 (0.138 g, 1 mmol) and allowed to stir at RT in the dark for 24 hours. The product was precipitated by addition of water (800 mL) and collected by filtration. The precipitate was further purified by RP-HPLC ($MeCN:H_2O$:0.1% TFA). LR-ESI MS $(M+H)^+$ *m/z* calcd 398.2, found 398.1.

4. Synthesis of Compound S2

[0123] 2-(chloromethyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (3 g, 10.0 mmol) and 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (3.91 g, 15.05 mmol) were added to DMF (50 mL) and K_2CO_3 (2.77 g, 20 mmol) and allowed to stir at RT in the dark for 24 hours. The product was precipitated by addition of water (900 mL) and collected by filtration. The precipitate was further purified by silica gel chromatography (2% $MeOH/CH_2Cl_2$). LR-ESI MS $(M+H)^+$ *m/z* calcd 524.1, found 523.9.

5. Synthesis of Compound S3

[0124] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (50 mg, 0.096 mmol), *m*-phenol boronic acid (14.5 mg, 0.105 mmol) and tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol) were dissolved in a solution of DME (10 mL), EtOH (1.6 mL) and saturated aqueous Na_2CO_3 (2.75 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). LR-ESI MS $(M+H)^+$ *m/z* calcd 490.2, found 490.1.

6. Synthesis of Compound S4

[0125] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (50 mg, 0.096 mmol), 5-formylbenzo[b]thiophene-2-boronic ester (30.3 mg, 0.105 mmol) and tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol) were dissolved in a solution of DME (10 mL), EtOH (1.6 mL) and saturated aqueous Na_2CO_3 (2.75 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). LR-ESI MS $(M+H)^+$ *m/z* calcd 558.2, found 558.0.

7. Synthesis of Compound S5

[0126] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (50 mg, 0.096 mmol), 5-formyl-3-methylthiophene-2-boronic acid (18.9 mg, 0.105 mmol) and tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol) were dissolved in a solution of DME (10 mL), EtOH (1.6 mL) and saturated aqueous Na_2CO_3 (2.75 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). LR-ESI MS $(M+H)^+$ *m/z* calcd 522.2, found 522.0.

8. Synthesis of S6

[0127] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (100 mg, 0.192 mmol), 3,4-dimethoxyphenyl boronic ester (38.2

mg, 0.21 mmol) and tetrakis(triphenylphosphine)palladium (44 mg, 0.038 mmol) were dissolved in a solution of DME (20 mL), EtOH (3.2 mL) and saturated aqueous Na_2CO_3 (5.5 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). LR-ESI MS $(M+H)^+$ *m/z* calcd 534.2, found 534.0.

9. Synthesis of S7

2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (100 mg, 0.192 mmol), 4-phenoxyphenyl boronic acid (44.9 mg, 0.21 mmol) and tetrakis(triphenylphosphine)palladium (44 mg, 0.038 mmol) were dissolved in a solution of DME (20 mL), EtOH (3.2 mL) and saturated aqueous Na_2CO_3 (5.5 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). LR-ESI MS $(M+H)^+$ *m/z* calcd 566.2, found 566.0.

10. Synthesis of S8

[0128] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (100 mg, 0.192 mmol), 4-benzyloxyphenyl boronic acid (47.9 mg, 0.21 mmol) and tetrakis(triphenylphosphine)palladium (44 mg, 0.038 mmol) were dissolved in a solution of DME (20 mL), EtOH (3.2 mL) and saturated aqueous Na_2CO_3 (5.5 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA).

11. Synthesis of S33

[0129] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (50 mg, 0.096 mmol), 3-cyanophenyl boronic acid (15.8 mg, 0.105 mmol) and tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol) were dissolved in a solution of DME (10 mL), EtOH (1.6 mL) and saturated aqueous Na_2CO_3 (2.75 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the

reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). LR-ESI MS $(M+H)^+$ *m/z* calcd 499.2, found 499.0.

12. Synthesis of 2-amino-N-(2-chlorophenyl)-6-methylbenzamide

[0130] 2-amino-6-methylbenzoic acid (2.5 g, 16.5 mmol) was dissolved in benzene (75 mL). Thionyl chloride (3.0 mL, 41.1 mmol) was added and the reaction heated to reflux overnight. The following day the reaction was concentrated in vacuo, and then taken up twice in benzene (75 mL) and solvent removed in vacuo again to give a black oil. The oil was dissolved in $CHCl_3$ (75 mL), 2-chloroaniline (3.5 mL) was added and the reaction heated to reflux. Reaction was complete after four hours, at which point the reaction was filtered, the filtrate concentrated in vacuo, and the the product was purified by silica gel chromatography (25% EtOAc/Hexanes) to yield a brown oil (1.94 g, 45% yield). HR-EI MS $(M)^+$ *m/z* calcd 260.07, found 260.0715 .

13. Synthesis of 2-(chloromethyl)-3-(2-chlorophenyl)-5-methylquinazolin-4(3H)-one

[0131] Chloroacetylchloride (0.72 mL, 9 mmol) was added to a solution of 2-amino-N-(2-chlorophenyl)-6-methylbenzamide (0.8 g, 3.06 mmol) in acetic acid (10 mL) and the reaction heated to reflux. After 2.5 hours the reaction was cooled to RT, and concentrated in vacuo. The product was purified by silica gel chromatography (10% EtOAc/Hexanes) to yield a white solid (0.353 g, 36% yield). HR-EI MS $(M)^+$ *m/z* calcd 318.0327, found 318.0321.

14. Synthesis of 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(2-chlorophenyl)-5-methylquinazolin-4(3H)-one

[0132] 2-(chloromethyl)-3-(2-chlorophenyl)-5-methylquinazolin-4(3H)-one (0.112 g, 0.35 mmol) and 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.138 g, 0.053 mmol) were added to DMF (5 mL) and K_2CO_3 (0.096 g, 0.7 mmol) and allowed to stir at RT in the dark for 72 hours. The product was precipitated by addition of water (50 mL) and collected by filtration. The precipitate was further purified by RP-HPLC (MeCN:H_2O:0.1% TFA).

15. Synthesis of S1

[0133] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(2-chlorophenyl)-5-methylquinazolin-4(3H)-one (60 mg, 0.11 mmol), m-phenol boronic acid (17 mg, 0.121 mmol) and tetrakis(triphenylphosphine)palladium (25 mg, 0.022 mmol) were dissolved in a solution of DME (10 mL), EtOH (1.6 mL) and saturated aqueous Na_2CO_3 (2.75 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H_2O:0.1% TFA). LR-ESI MS $(M+H)^+$ *m/z* calcd 510.1, found 510.0.

16. Synthesis of S34

[0134] 2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-o-tolylquinazolin-4(3H)-one (50 mg, 0.096 mmol), benzene 3-sulphonamide boronic ester (29.7 mg, 0.105 mmol) and tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol) were dissolved in a solution of DME (10 mL), EtOH (1.6 mL) and saturated aqueous Na_2CO_3 (2.75 mL). The reaction was heated to reflux overnight under an argon atmosphere. The following day the reaction was poured into water, and the aqueous phase extracted three times with CH_2Cl_2. LR-ESI MS $(M+H)^+$ *m/z* calcd 553.2, found 553.0.

C. PI3-Kinase Structural Studies

[0135] 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).

[0136] 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.

[0137] 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).

[0138] 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.

[0139] 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.

[0140] 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).

[0141] 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.

[0142] 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.

[0143] 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).

[0144] 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.

[0145] 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.

[0146] 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.

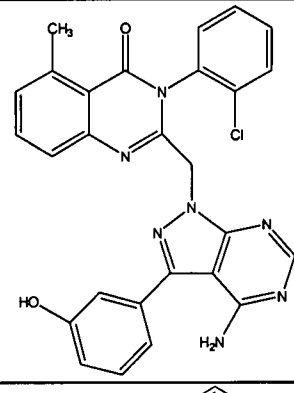
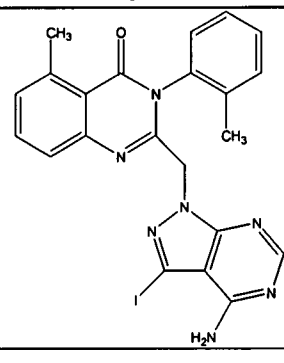
D. Expression and Assays of p110α/p85α, p110β/p85α, p110δ/p85α, and p110γ

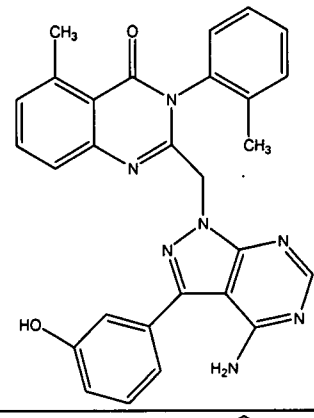
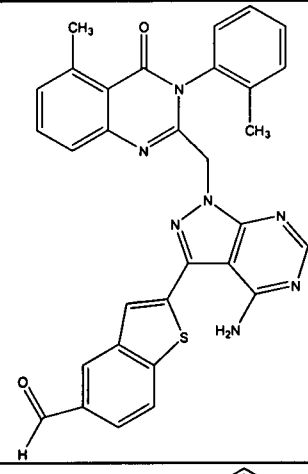
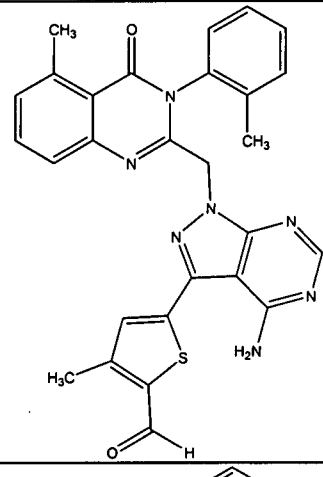
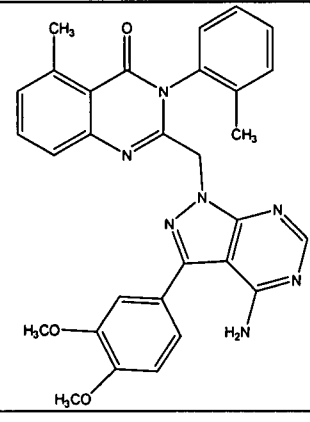
[0147] The class I PI3-Ks were either purchased (p110α/p85α, p110β/p85α, p110δ/p85α from Upstate, and p110γ from Sigma) or expressed as previously described (Knight et al., 2004). IC50 values were measured using either a standard TLC assay for lipid kinase activity (described below) or a high-throughput 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

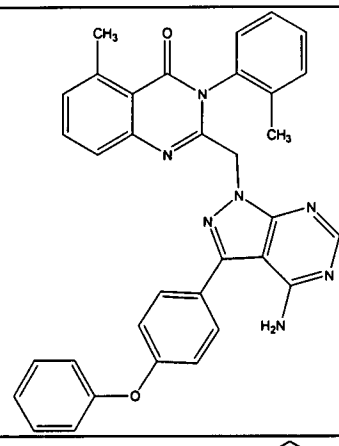
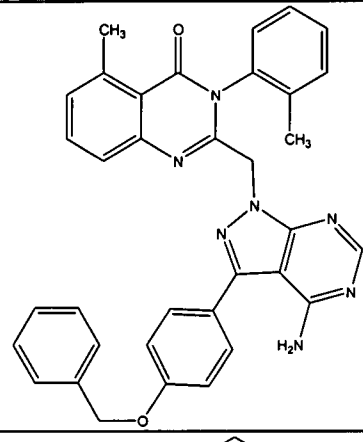
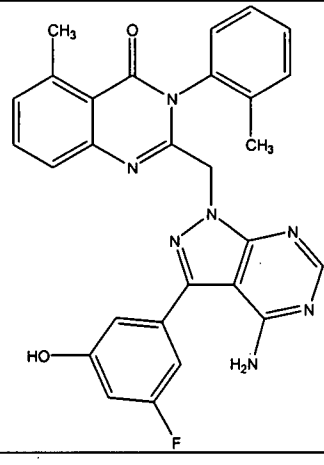
were then terminated by the addition of 105 µl 1N HCl followed by 160 µl CHCl3:MeOH (1:1). The biphasic mixture was vortexed, briefly centrifuged, and the organic phase transferred to a new tube using a gel loading pipette tip precoated with $CHCl_3$. This extract was spotted on TLC plates and developed 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.

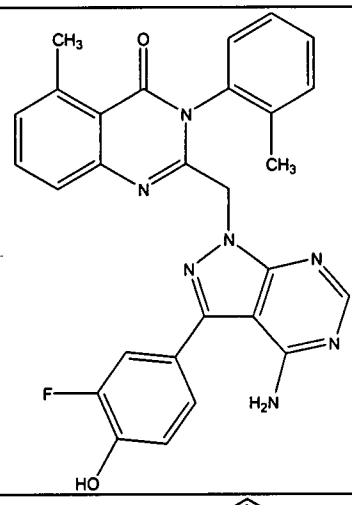
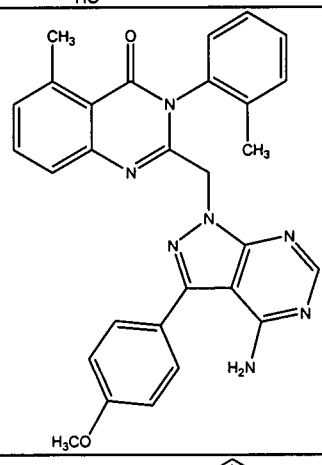
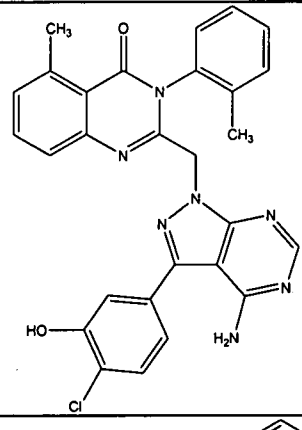
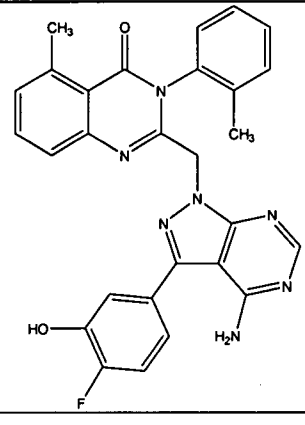
[0148] Results are set forth in Table 1 below.

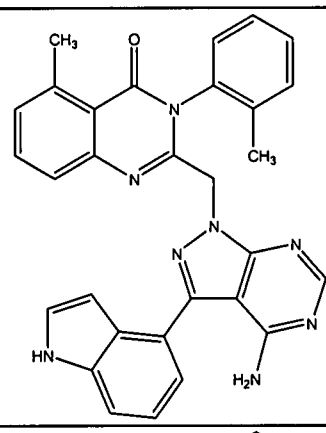
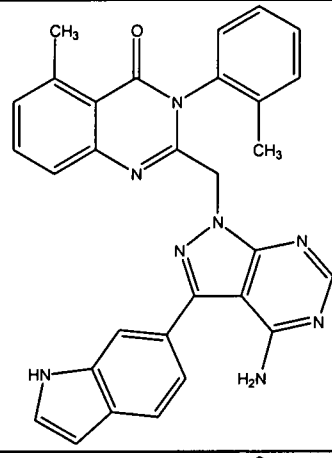
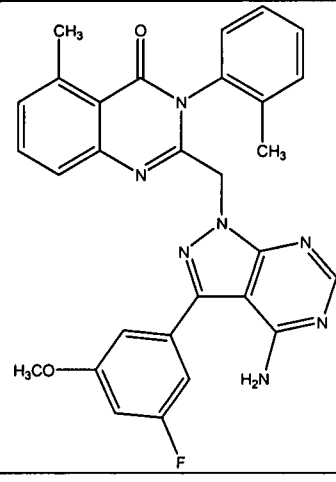
Table 1

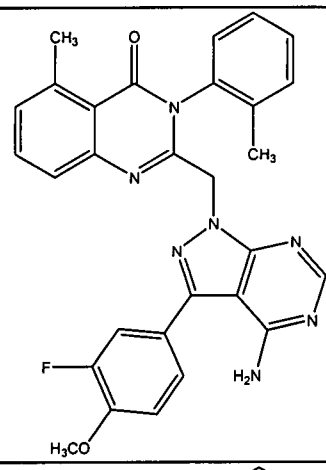
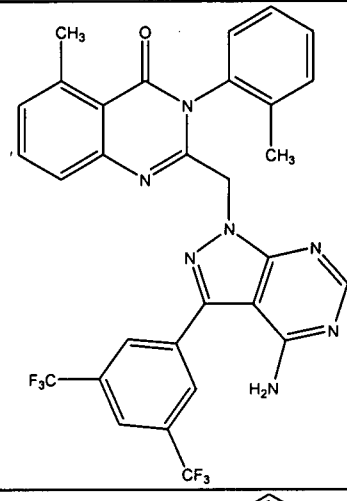
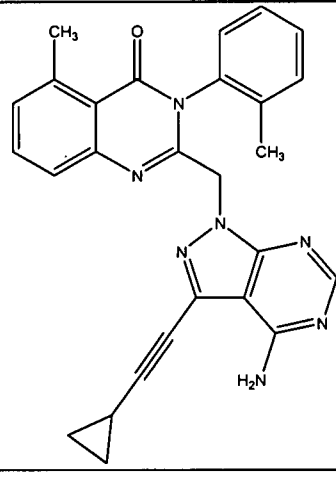
Compound	Structure	IC50			
MW		p110α	p110β	p110γ	p110δ
S1 (509.9464)		+	++	+++	+++
S2 (523.33)		++	++	+++	+++

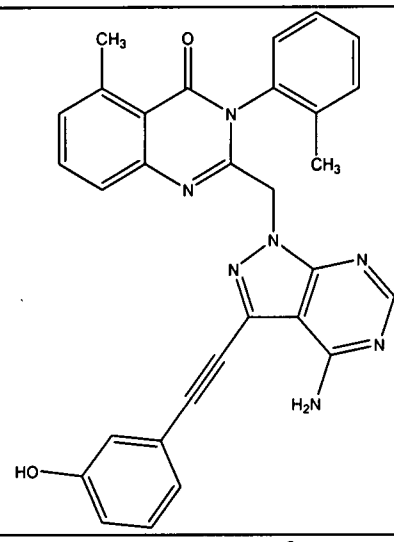
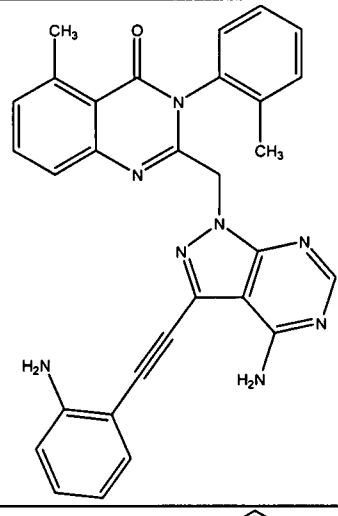
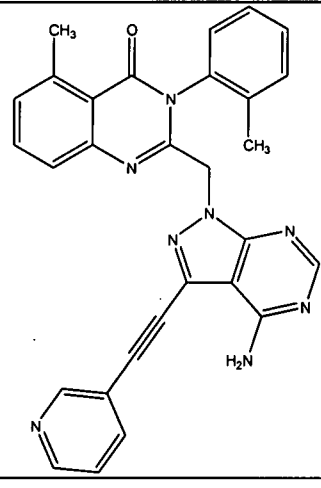
Compound MW	Structure	IC50 p110α	p110β	p110γ	p110δ
S3 (489.53)		+	+++	+++	+++
S4 (557.63)		+	+	++	+++
S5 (521.59)		+	++	+++	+++
S6 (533.58)		+	++	+++	+++

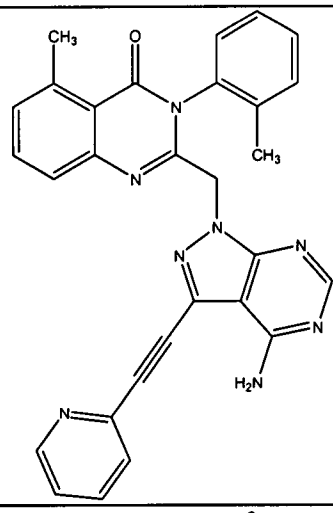
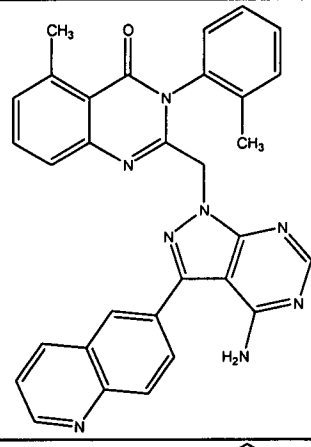
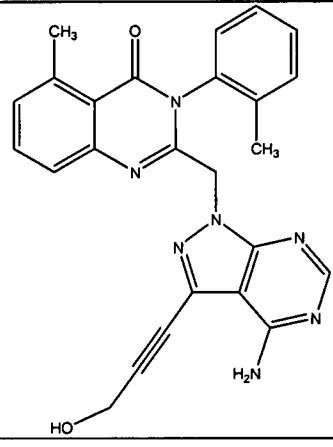
Compound MW	Structure	IC50 p110α	p110β	p110γ	p110δ
S7 (565.62)		+	++	++	+++
S8 (579.65)		++	++	++	+++
S9 (507.52)		++	+++	+++	+++

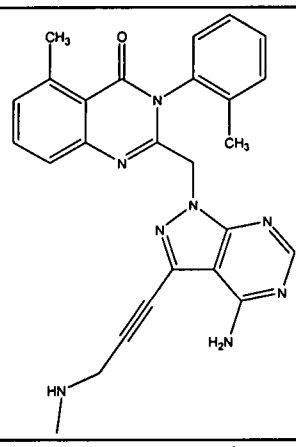
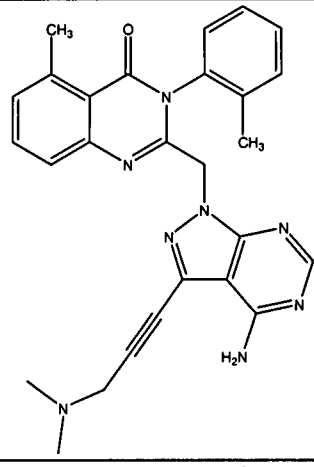
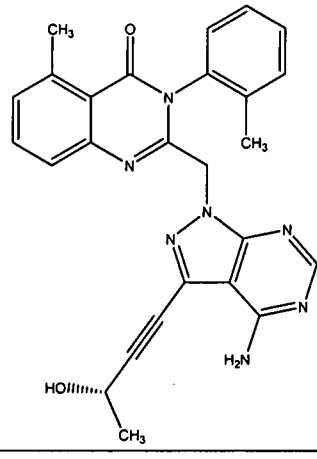
Compound	Structure	IC50			
MW		p110α	p110β	p110γ	p110δ
S10 (507.52)		++	+++	+++	+++
S11 (503.55)		++	++	+++	+++
S12 (523.97)		++	++	+++	+++
S13 (507.52)		++	++	+++	+++

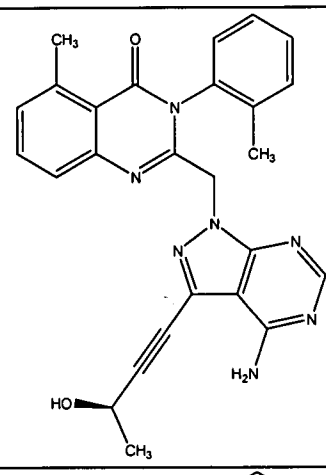
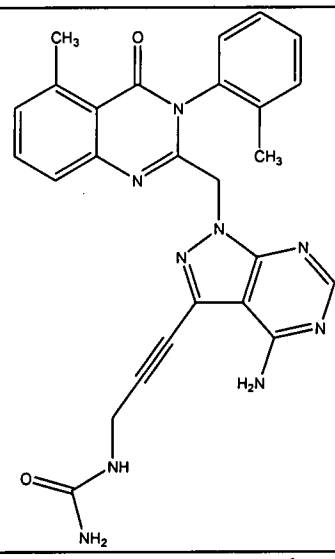
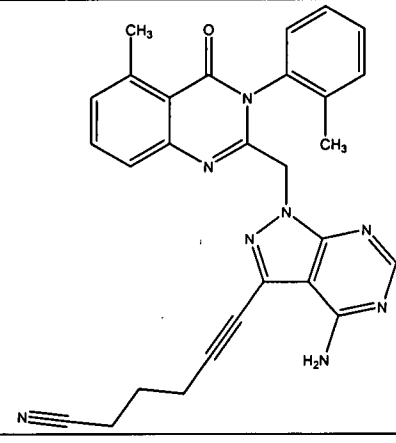
Compound	Structure	IC50			
MW		p110α	p110β	p110γ	p110δ
S14 (512.56)		+	++	+++	+++
S15 (512.56)		+	++	++	+++
S16 (521.55)		+	++	++	+++

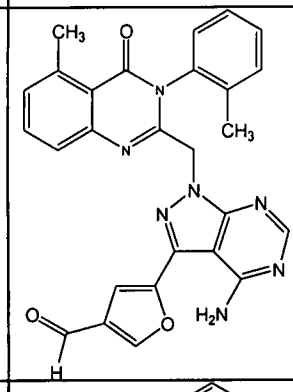
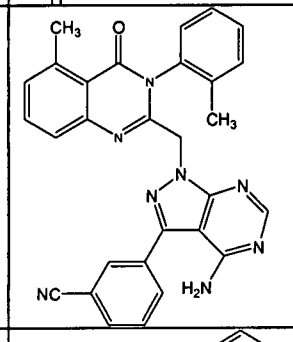
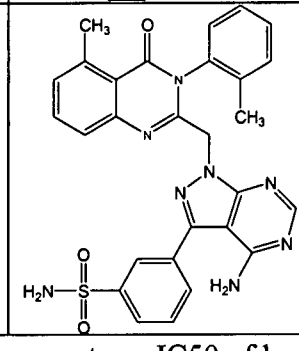
Compound MW	Structure	IC50 p110α	p110β	p110γ	p110δ
S17 (521.55)		++	++	+++	+++
S18 (608.52)		+	+	+	++
S19 (461.52)		+	++	++	+++

Compound	Structure	IC50			
MW		p110α	p110β	p110γ	p110δ
S20 (513.55)		++	++	+++	+++
S21 (512.56)		+	++	++	+++
S22 (498.54)		+	++	++	+++

Compound MW	Structure	IC50 p110α	p110β	p110γ	p110δ
S23 (498.54)		+	++	+++	+++
S24 (524.58)		++	++	+++	+++
S25 (451.48)		++	+++	++	+++

Compound MW	Structure	IC50 p110α	p110β	p110γ	p110δ
S26 (464.52)					+++
S27 (478.55)					++
S28 (465.51)		+	++	++	+++

Compound	Structure	IC50			
MW		p110α	p110β	p110γ	p110δ
S29 (465.51)		++	+++	+++	+++
S30 (493.52)		++	+	++	+++
S31 (488.54)					+++

Compound MW	Structure	IC50 p110α	 p110β	 p110γ	 p110δ
S32					
S33					
S34					

The symbol +++ represents an IC50 of less than 1 μM; the symbol ++ represents an IC50 value from1 μM to 100 μM; and + represents an IC50 value of more than 100 μM.

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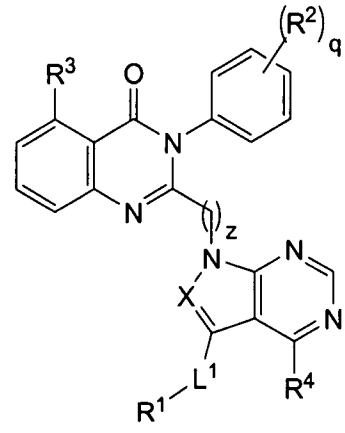
WHAT IS CLAIMED IS:

1. A compound having the formula:



(I),

wherein

q is an integer from 0 to 5;

z is an integer from 0 to 10;

X is =CH- or =N-;

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1 and R^2 are independently halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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, wherein n is independently an integer from 0 to 2;

R^3, and R^4 are independently hydrogen, halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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^5 is independently hydrogen, $-C(O)R^{10}$, 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^6 is independently hydrogen, $-NR^{11}R^{12}$, 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, wherein if n is 1 or 2 then R^6 is other than hydrogen;

R^7 is 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;

R^8 is independently hydrogen, $-S(O)_nR^{13}$, $-C(O)R^{14}$, 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^9 is independently $-NR^{15}R^{16}$, 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;

R^{10} is independently hydrogen, $-NR^{17}R^{18}$, 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^{14} is independently hydrogen, $-NR^{19}R^{20}$, 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; and

R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} 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.

2. The compound of claim 1, wherein R^1 is halogen, substituted or unsubstituted halo(C_1-C_6)alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl(C_1-C_6)alkyl, or substituted or unsubstituted heteroaryl(C_1-C_6)alkyl.

3. The compound of claim 1, wherein R^1 is halogen, substituted or unsubstituted phenyl, substituted or unsubstituted furanyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted thiophenyl, or substituted or unsubstituted benzothiophenyl, substituted or unsubstituted indolyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted 1H-pyrrolo[2,3-*c*]pyridinyl, substituted or unsubstituted 1H-pyrrolo[2,3-*b*]pyridinyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted cylcohexyl, substituted or unsubstituted morpholino, substituted or unsubstituted piperidinyl, or substituted or unsubstituted tetrahydopyridinyl.

4. The compound of claim 3, wherein R^1 is phenyl, furanyl, pyrrolyl, thiophenyl, or benzothiophenyl, each of which are optionally substituted with one or more R^{21} substituent(s), wherein R^{21} is independently

(1) halogen, -CN, $-OR^{22}$, $-C(O)R^{23}$, $-NR^{24}R^{25}$, $-S(O)_wNR^{26}R^{27}$, or $-S(O)_wR^{28}$, wherein w is an integer from 0 to 2, and R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, or heteroarylalkyl, optionally substituted with unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl; or

(2) $(C_1\text{-}C_{10})$alkyl, 2 to 10 membered heteroalkyl, $C_3\text{-}C_8$ cycloalkyl, 3 to 8 membered heterocycloalkyl, aryl or heteroaryl optionally substituted with halogen, -OH, -CN, $-NH_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl.

5. The compound of claim 4, wherein R^1 is phenyl substituted at the meta and para positions, or substituted at the meta and meta positions.

6. The compound of claim 5, wherein R^{21} is halogen or $-OR^{22}$.

7. The compound of claim 6, wherein R^{21} is fluorine and R^{22} is hydrogen or methyl.

8. The compound of claim 1, wherein q is 1.

9. The compound of claim 1, wherein z is 1.

10. The compound of claim 1, wherein R^2 is halogen, -OH, -CN, $-NH_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl.

11. The compound of claim 1, wherein R^2 is halogen or unsubstituted alkyl.

12. The compound of claim 1, wherein R^2 is fluorine or unsubstituted C_1-C_4 alkyl.

13. The compound of claim 1, wherein R^3 is halogen, -OH, -CN, $-NH_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocycloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl.

14. The compound of claim 1, wherein R^3 is unsubstituted alkyl.

15. The compound of claim 1, wherein R^3 is unsubstituted C_1-C_4 alkyl.

16. The compound of claim 1, wherein R^4 is halogen, -OH, -CN, $-NH_2$, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, or heteroarylalkyl.

17. The compound of claim 1, wherein R^2 and R^3 are independently unsubstituted C_1-C_4 alkyl; R^4 is NH_2; q is 1; and z is 1.

18. The compound of claim 1, wherein L^1 is substituted or unsubstituted alkylene.

19. The compound of claim 1, wherein L^1 is substituted or unsubstituted alkynylene.

20. The compound of claim 1, wherein L^1 is substituted or unsubstituted methylene, substituted or unsubstituted ethylene, substituted or unsubstituted propylene, substituted or unsubstituted butylenes, substituted or unsubstituted ethynylene, or substituted or unsubstituted prop-2-ynylene.

21. The compound of claim 20, wherein R^1 is –CN, -OR^5, -NR^7R^8, R^{21}-substituted or unsubstituted cycloalkyl, R^{21}-substituted or unsubstituted aryl, R^{21}-substituted or unsubstituted heteroaryl, R^{21}-substituted or unsubstituted C_1-C_4 alkyl, wherein

R^{21} is halogen, –OR^{22}, -$NR^{24}R^{25}$, or unsubstituted C_1-C_4 alkyl, and

R^5, R^7, R^8, R^{22}, R^{24} and R^{25} are independently hydrogen or unsubstituted C_1-C_4 alkyl.

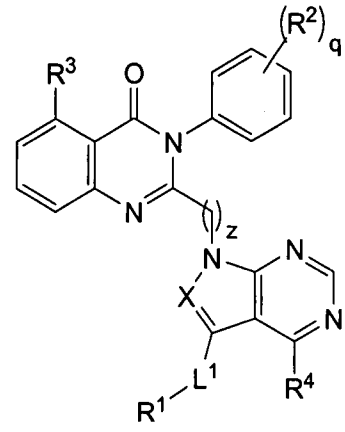
22. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.

23. A method of decreasing the catalytic activity of a PI3-Kinase, the method comprising the step of contacting said PI3-Kinase with an activity decreasing amount of a PI3-Kinase affinity pocket binding antagonist.

24. The method of claim 23, wherein said antagonist is a PI3-Kinase affinity pocket quinazolinone antagonist.

25. The method of claim 23, wherein the PI3-Kinase is p110δ kinase.

26. A method of decreasing the catalytic activity of a PI3-Kinase, the method comprising the step of contacting said PI3-Kinase with an activity decreasing amount of a compound having the formula:



(I),

wherein

q is an integer from 0 to 5;

z is an integer from 0 to 10;

X is =CH- or =N-;

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1 and R^2 are independently halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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, wherein n is independently an integer from 0 to 2;

R^3, and R^4 are independently hydrogen, halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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^5 is independently hydrogen, $-C(O)R^{10}$, 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^6 is independently hydrogen, $-NR^{11}R^{12}$, 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, wherein if n is 1 or 2 then R^6 is other than hydrogen;

R^7 is 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;

R^8 is independently hydrogen, $-S(O)_nR^{13}$, $-C(O)R^{14}$, 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^9 is independently $-NR^{15}R^{16}$, 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;

R^{10} is independently hydrogen, $-NR^{17}R^{18}$, 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^{14} is independently hydrogen, $-NR^{19}R^{20}$, 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; and

R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} 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.

27. A method of treating a disease mediated by p110δ kinase activity in a subject in need of such treatment, said method comprising administering to said subject a therapeutically effective amount of a PI3-Kinase affinity pocket binding antagonist.

28. The method of claim 27, wherein said antagonist is a PI3-Kinase affinity pocket quinazolinone antagonist.

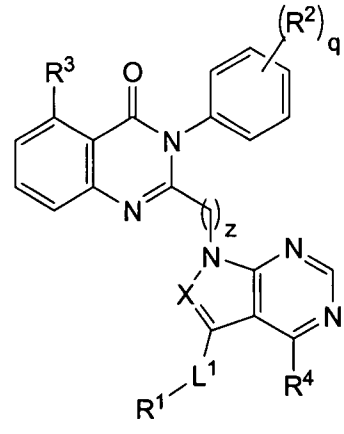
29. The method of claim 27, wherein the disease is a hematologic malignancy, inflammation, autoimmune disease, or cardiovascular disease.

30. The method of claim 27, wherein the disease is a hematologic malignancy, or autoimmune disease.

31. The method of claim 27, wherein the disease is acute myelogenous leukemia, chronic myelogenous leukemia, mastocytosis, chronic lymphocytic leukemia, multiple myeloma, or myelodysplastic syndrome.

32. The method of claim 27, wherein the disease is rheumatoid arthritis, systemic lupus erythematosus, or asthma.

33. A method of treating a disease mediated by p110δ kinase activity in a subject in need of such treatment, said method comprising administering to said subject a therapeutically effective amount of a compound having the formula:



(I),

wherein

q is an integer from 0 to 5;

z is an integer from 0 to 10;

X is =CH- or =N-;

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1 and R^2 are independently halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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, wherein n is independently an integer from 0 to 2;

R^3, and R^4 are independently hydrogen, halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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^5 is independently hydrogen, $-C(O)R^{10}$, 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^6 is independently hydrogen, $-NR^{11}R^{12}$, 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, wherein if n is 1 or 2 then R^6 is other than hydrogen;

R^7 is 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;

R^8 is independently hydrogen, $-S(O)_nR^{13}$, $-C(O)R^{14}$, 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^9 is independently $-NR^{15}R^{16}$, 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;

R^{10} is independently hydrogen, $-NR^{17}R^{18}$, 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;

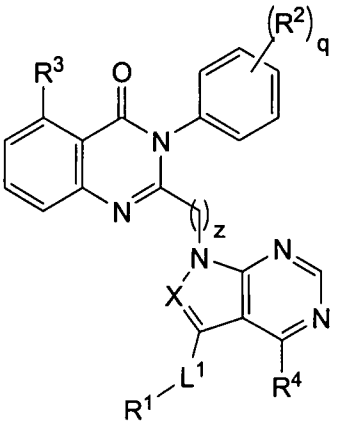
R^{14} is independently hydrogen, $-NR^{19}R^{20}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} 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.

34. A method of disrupting the function of a leukocyte or disrupting a function of an osteoclast, said method comprising contacting said leukocyte or said osteoclast with a function disrupting amount of a PI3-Kinase affinity pocket binding antagonist.

35. The method of claim 34, wherein said antagonist is a PI3-Kinase affinity pocket quinazolinone antagonist.

36. A method of disrupting the function of a leukocyte or disrupting a function of an osteoclast, said method comprising contacting said leukocyte or said osteoclast with a function disrupting amount of a compound having the formula



(I),

wherein

q is an integer from 0 to 5;

z is an integer from 0 to 10;

X is =CH- or =N-;

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or

unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1 and R^2 are independently halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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, wherein n is independently an integer from 0 to 2;

R^3, and R^4 are independently hydrogen, halogen, -CN, $-OR^5$, $-S(O)_nR^6$, $-NR^7R^8$, $-C(O)R^9$, 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^5 is independently hydrogen, $-C(O)R^{10}$, 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^6 is independently hydrogen, $-NR^{11}R^{12}$, 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, wherein if n is 1 or 2 then R^6 is other than hydrogen;

R^7 is 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;

R^8 is independently hydrogen, $-S(O)_nR^{13}$, $-C(O)R^{14}$, 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^9 is independently $-NR^{15}R^{16}$, 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;

R^{10} is independently hydrogen, $-NR^{17}R^{18}$, 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^{14} is independently hydrogen, $-NR^{19}R^{20}$, 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; and

R^{11}, R^{12}, R^{13}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} 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.

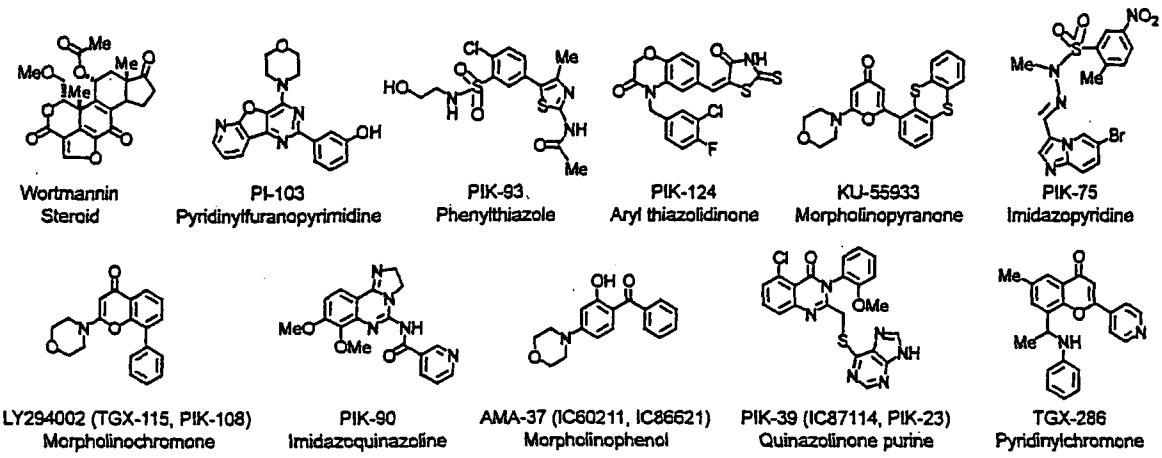

Wortmannin
Steroid
PI-103
Pyridinylfuranopyrimidine
PIK-93
Phenylthiazole
PIK-124
Aryl thiazolidinone
KU-55933
Morpholinopyranone
PIK-75
Imidazopyridine
LY294002 (TGX-115, PIK-108)
Morpholinochromone
PIK-90
Imidazoquinazoline
AMA-37 (IC60211, IC86621)
Morpholinophenol
PIK-39 (IC87114, PIK-23)
Quinazolinone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

FIG. 1

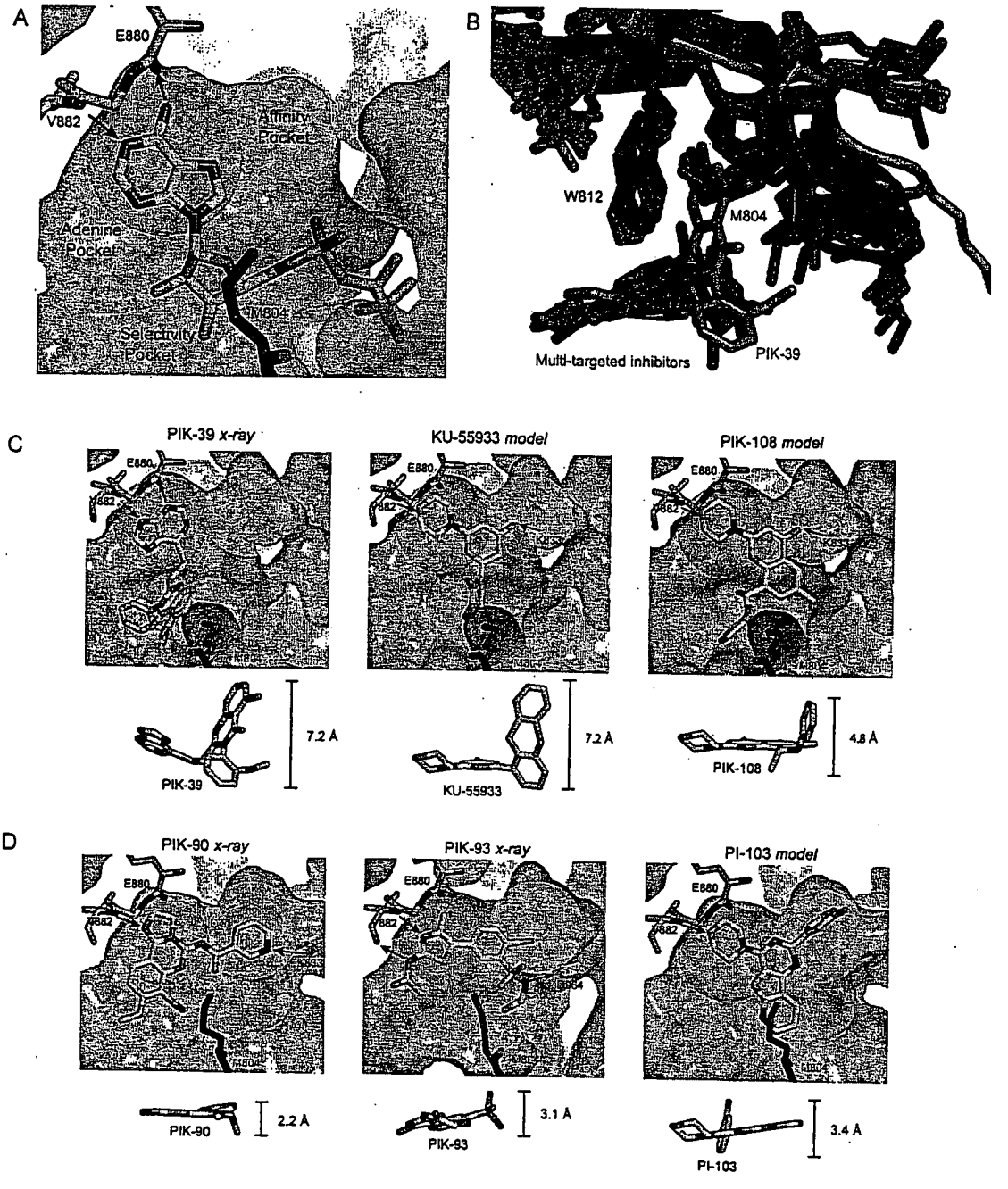

A
E880
V882
Affinity Pocket
Adenine Pocket
M804
Selectivity Pocket
B
W812
M804
Multi-targeted inhibitors
PIK-39
C
PIK-39 x-ray
KU-55933 model
PIK-108 model
7.2 Å
7.2 Å
4.8 Å
PIK-39
KU-55933
PIK-108
D
PIK-90 x-ray
PIK-93 x-ray
PI-103 model
2.2 Å
3.1 Å
3.4 Å
PIK-90
PIK-93
PI-103

FIG. 2

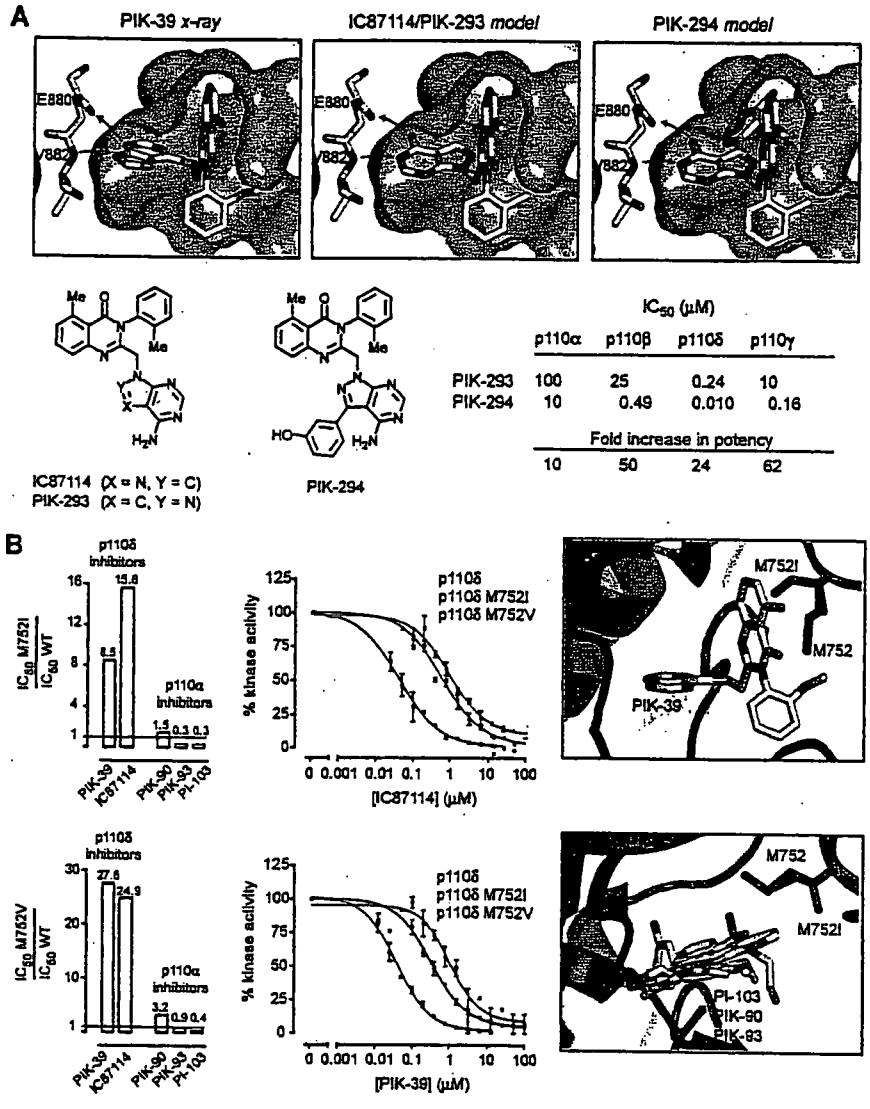
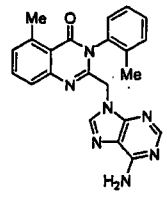

A
PIK-39 x-ray
IC87114/PIK-293 model
PIK-294 model
E880
V882
IC87114 (X = N, Y = C)
PIK-293 (X = C, Y = N)
PIK-294
IC50 (μM)
p110α p110β p110δ p110γ
PIK-293 100 25 0.24 10
PIK-294 10 0.49 0.010 0.16
Fold increase in potency
10 50 24 62
B
p110δ inhibitors
IC50 M752I / IC50 WT
p110α inhibitors
PIK-39
IC87114
PIK-90
PIK-93
PI-103
% kinase activity
p110δ
p110δ M752I
p110δ M752V
[IC87114] (μM)
M752I
M752
PIK-39
IC50 M752V / IC50 WT
[PIK-39] (μM)

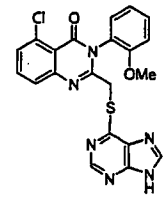
FIG. 3

PI3-K Inhibitor

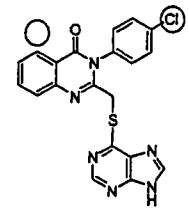
Inactive analog



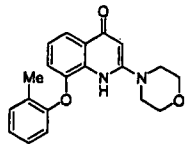
IC87114



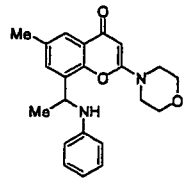
PIK-39



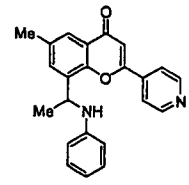
PIK-31



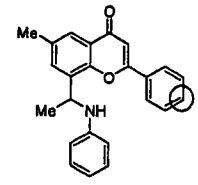
TGX-115



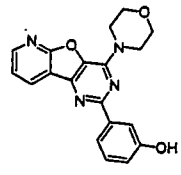
PIK-108



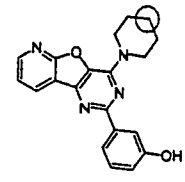
TGX-286



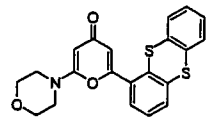
PIK-73



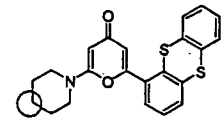
PI-103



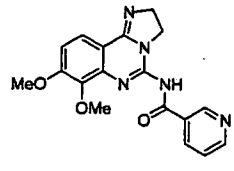
PIK-112



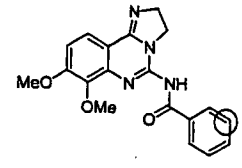
KU-55933



KU-58050



PIK-90



PIK-95

FIG. 4

	PIK23	TGX115	AMA37	PIK39	IC87114	TGX286	PIK75	PIK90	PIK93	PIK108	PI-103	PIK124	KU-55399
PI3Ks													
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	105.6	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	106.5	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
```

FIG. 7

```
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 nyksflgink ervpfvltpd flfvmgtsgk ktsphfqkfq dicvkaylal
1021 rhhtnlliil fsmmlmtgmp qltskediey irdaltvgkn eedakkyfld qievcrdkgw
1081 tvqfnwflhl vlgikqgekh sa
```

FIG. 8

```
1    MPPRPSSGEL WGIHLMPPRI LVEQLLPNGM 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
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FIG. 10