The present invention provides novel PI3-Kinase antagonists and methods of use thereof.
FIG. 1

- Wortmannin Steroid
- PT-103 Pyridinylthiazopyrimidine
- PIK-53 Phenylthiazole
- PIK-124 Aryl thiazolidinone
- KU-55533 Morpholinopyranone
- PIK-75 Imidazopyridine
- LY294002 (TGX-115, PK-106) Morpholinocromone
- PIK-90 Imidazoquinazoline
- AMA-37 (IC85221, IC86621) Morpholinophenol
- PIK-39 (IC87114, PIK-23) Quinazolinone purine
- TGX-256 Pyridinylchromone
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FIG. 7

1 MPFGVDCPME FWTKENQSV YYDFLLPTGV YLLFPFSQSA NLSNITKQLLW HRAQYEPLFH
61 MLSGPEAYVF TCIINQTAEQQ ELEDSEQRLC DVQFPLEVLR LVAREDCRVDK KLINQISLLE
121 IGKLHEFDS LCPDEVNDPFR AKHCQFCEEA AARQROLLGE AWLQYSFPLQ LEPSAQIWWGP
181 GTLRPNRAL LVNKXFCGSE ESPFQVSTK DVLSTALMACA LRKATVFRQ FLVEQPEDVT
241 LQVNGRHEYL YGNYPFLOQPQ YTCSCKLHSGL TPHILMNVHS SIALMRDDEQSP NFAPQVQKPR
301 AKRQFPIPAK PSSISMLWYSL QPSFRFIEIO QSKVADNERRK LVVQAGLFLHR NELNMCSTVSS
361 SEVSVCSEFPV WKQLRELDFIN ICDLMRFNARL CFALYAVTIEK AKKARSTKKK SNKADCPIAM
421 ANMLFDFYKD QLKTQGERIL MWPSVPDEKG ELINPSTGVR SNPNTDGAAA LLICLFVNSP
481 HPPYYPALEK IDELGRHSEC VRHTEEQQLQ LREILERGS GELYEHEKDIL NWIRLHEQVE
541 HPEALARLL LUTTWNKRED VAOMLYLLCS WPELPLVSLAL ELLEPSFSFDC HQGSPAISKSL
601 RLRTDDELFO YLLQIVQVLK YSEYLOCEIT KFLDRALAN RKIGHFLFWR LSEWHPSV
661 ALRDQGLULA YCRCSTHEDK VLMQKQGEALS KLKALNDFVK LSSQKTTPKQR TKELMHLCMR
721 QAEVLAISH LQSPPLDSTL LAEVCFEQCT FMDSWKKPLW IMSYNSEEAGS GSVGIIIFKN
781 GDDLRQOMLT LQMQIYLDVL MWQLGEQLERM TVYGCQPFGD RTGQITVEVLRR SDTIANIQLN
841 KSNAATAAFF NKDATNLWLK SKNPGSALDR AIEEFETLSCA GYCVDATVLLG IGDRHDSNIM
901 IRESQGLFHI DPFHNGIRFR PVFLINTDFHH VIQQQKTNNS EKFERFQYGC
961 ERAAYLIRRH GLLFHLHFAL MRAAGLPFELS CSKDIQYKLK SLALGKTEBKE AKHIFVFKFN
1021 EALRESWKTK VNWLIAHQHSV DNRQ

(SEQ ID NO:1)
FIG. 10

1  MCFSFIMPPA MADILDIWAV DSQIASDGGI PVDFLLPTG I YIQLEVEREA TISYIKQMLW
61  KQVINYPMFN LLMWIDSYM ACVMQTAVYE ELEDRETTRL C DVRPLPVLSK TVRSCDPGE
121  KLNSKIGVLI GKLHFEFDSL KDFEVNEFRR KMRKFSEESK L SLVGLSWMD WLVQYTFPEEH
181  EPSIPENLED KLYAGKLIVA VHFGNQSDVP SFPVCPNMNIP IKVNEILAIQK RLTHGKEDDE
241  VSPYDVLQV SGRCYFYFGD HPLJQFYQIR NCVNMRLPFL PIEVCCCKIK KMYEQBMIAI
301  BAAIINNSSSN LFLFSLPKKT RIISHVWENN NFPQIVLTKG NKLNTTEBTVK VHVRLFLFHLG
361  TELLCKTIVS SEVSGKDHII WNEPLLFPDFIN ICADLRPAFL CFAVAVLTKI VTTKSKTI
421  NPSKYQTIRK AGKCVIPVAV VNTRMTDFKG QRLTGDILILH SWSSSFPEDE ELMLPMGTVQ
481  TNYFENATA LHVKFPENNK QPYYPFFDK ITKAAABIAS SDSANVSSRG GKSKPFLVLEK
541  ILDRDPLSQL CENMELIIWT LRQDCREIFP QSLPKLLLLI KWNNLTVQAL SQALLIQWPK
601  LPREALELL DFNYPDQYVR EYAVGCQYQM SDELSQYQL QLQVQVLKYP FLDICALSRPL
661  LERALGNRRI QGFLLWHRRLS EHPIAPSVQV FGVILEAYCR GSVGINKVLW DQVEALNKLK
721  TNLNIKLNA VKNRAKIGKE AMHTCLSQLSA YREALSDLQS PLNPCVILSE LLYVEKCKYM
781  SNNKPLWLY NNNQFEGDSV GVIPKNNDDL RQDMILTQML RNLMLWKEA GLDLRMFLYG
841  CLOTDRSGL IEVYSTSETI ADIQNSSLNNN AAAAAFKNDA LLWNLKYES GDDLORAILE
901  PTIACGAYCV ASYVLGIGDR HSDHNMKKT QQLPHFDPFGH IQLNFKSFPQ FKREVRVFPIL
961  TYDFIHIIVQQ GKTGNMTKFG FRPOQCCEDAY LILRRMGMLT TVLFAIMLTA GLQFLEXSVKD
1021  IYQLKELSLT GKESEEALKQ FKQKFLDEAL BSWTRKWMW AHVRLKDYSR

(SEQ ID NO: 4)
P13 KINASE ANTAGONISTS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 11/732,857, filed Apr. 4, 2007, which claims the benefit of U.S. Provisional Patent Application No. 60/744,269, filed Apr. 4, 2006, and U.S. Provisional Patent Application No. 60/744,270, filed Apr. 4, 2006, all of which are incorporated herein by reference in their entireties and for all purposes.

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

[0002] This invention was made with Government support under grant AI44009 awarded by the National Science Foundation. The Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

[0003] Phosphoinositide 3-kinases (P13-Ks) catalyze the synthesis of the phosphatidylinositol (PI) second messengers P(3)P, P(3,4)P2, and P(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 P13-K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation (Katso et al., 2001). The class I P13-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 Tcc family kinases, and the Rho family GTPases. The class II and III P13-Ks play a key role in intracellular trafficking through the synthesis of P(3)P and P(3,4)P2. The PIKKs are proteins that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and HsSmg-1).

[0004] The importance of these enzymes in diverse pathophysiology has made the P13-K family the focus of intense interest as a new class of drug targets (Ward et al., 2005). 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 P13-K signaling, is a commonly inactivated tumor suppressor (Cantley and Neel, 1999). Efforts are underway to develop small molecule P13-K inhibitors for the treatment of inflammation and autoimmune disease (p110 δ, 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; Condilffe 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 P13-Kinase antagonists.

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention provides certain novel compounds found to be effective as antagonists of P13-Kinases.

[0007] In one aspect, the present invention provides a P13-Kinase affinity pocket binding antagonist (e.g. a P13-Kinase affinity pocket quinazolinone antagonist) or a P13-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 P13-Kinase. The method includes the step of contacting the P13-Kinase with an activity decreasing amount of a P13-Kinase affinity pocket binding antagonist (e.g. a P13-Kinase affinity pocket quinazolinone antagonist) or a P13-Kinase antagonist of Formula (I).

[0009] In another aspect, the present invention provides methods of treating disease mediated by treating a condition mediated by P13-Kinase activity in a subject in need of such treatment. The method includes administering to the subject a therapeutically effective amount of a P13-Kinase affinity pocket binding antagonist (e.g. a P13-Kinase affinity pocket quinazolinone antagonist) or a P13-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 P13-Kinase affinity pocket binding antagonist (e.g. a P13-Kinase affinity pocket quinazolinone antagonist) or a P13-Kinase antagonist of Formula (I).

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. 1 illustrates structures of representative compounds from eleven chemotypes of P13-K inhibitors.


[0013] FIG. 3 illustrates the probing of selectivity and the P13-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 P13-Ks. B. (Left) Ratio of IC50 values between mutant and wild-type for p110 δ inhibitors and p110ε/multi-target inhibitors. (Center) Dose response curves for binding of two p110 δ inhibitors to wild-type, M7521, and M752V p110 δ (Right) Models suggesting the impact of the M7521 and M752V mutations in p110 δ on the binding of the different classes of inhibitors.


[0015] FIG. 5. IC50 values (µM) for selected P13-K inhibitors against lipid kinases.

[0016] FIG. 6. Inhibition of protein kinases by P13-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] FIG. 7 sets forth the sequence of a human p110 δ kinase (SEQ ID NO:1).

[0018] FIG. 8 sets forth the sequence of a human p110γ kinase (SEQ ID NO:2).

[0019] FIG. 9 sets forth the sequence of a human p110ε kinase (SEQ ID NO:3).
FIG. 10 sets forth the sequence of a human p110β kinase (SEQ ID NO:4).

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

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

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., —CH2O is equivalent to —OCH2—.

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 polysaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e., C1-C10 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, cyclohexylmethyl, 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, 2-butynyl, and the higher homologs and isomers.

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, —CH2—CH2—S—CH2—CH2— and —CH2—S—CH2—CH2—NH—CH2—. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylendioxy, alkyleneamino, alkylendiamino, 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 the —C(O)R’— and —R’C(=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,R’—. Where “heteroalkyl” is recited, followed by recitation 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.

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, cyclopentyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1,2,3,4-tetrahydropyridyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydropyranyl-2-yl, tetrahydrofuran-3-yl, tetrahydrothienyl-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.

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(C1- C4)alkyl” is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term “aryl” means, unless otherwise stated, a polysaturated, 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 heteroatom is 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-pyrydyl, 2-pyrydyl, 3-pyrydyl, 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, 5-benzimidazolyl, 5-indolyl, 1-isquinolinyl, 5-isquinolinyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinoline, and 6-quinoline. 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., arylthio, aryldithio, 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-pyridylmethyl, 3-(1-naphthyl)oxo)propyl, and the like). However, the term “heteroaryl,” as used herein is meant to cover only aryls substituted with one or more heteroatoms.

[0030] Where a heteroaryl, heterocycloalkyl or heteroaryl includes a specific number of members (e.g., “3 to 7 members”), the term “membered” refers to a carbon or heterocycle.

[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, heterocycloalkyl, alkenyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: —OR′, —O—NR′R″, —N—OR′, —NRR′, —SR′, —halogen, —SR′R″, —OC(O)R′, —C(O)R′, —CO2R′, —C(O)NR′R″, —OC(O)NR′R″, —NRC(O)R′, —NR′—C(O) NR′R″, —NR′C(O)NR′R″, —NR′—C(NR′R″)—NR′—, —S(O) R′, —S(O)2R′, —S(O)NRR′, —NRSO2R′, —CN and —NO2 in a number ranging from zero to (2m+1), where m is the total number of carbon atoms in such radical. R′, R″ and R‴ each preferably independently refer to hydrogen, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocycloalkyl.

[0034] As used herein, the term “heteroatom” or “ring heteroatom” is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0035] An “aminocycloalkyl” 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 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkyl, or a substituted or unsubstituted aryl, and substituted or unsubstituted heterocycloalkyl.

[0036] A “substituent group,” as used herein, means a group selected from the following moieties:

[0039] (A) —OH, —NH2, —SH, —CN, —CF3, —NO2, oxo, halogen, unsubstituted alkyl, unsubstituted heterocycloalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heterocycloalkyl, and

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

[0041] (i) oxo, —OH, —NH2, —SH, —CN, —CF3, —NO2, halogen, unsubstituted alkyl, unsubstituted hetero-
eralkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

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

(a) o xo, —OH, —NH₂, —SH, —CN, —C≡S, —NO₂, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from o xo, —OH, —NH₂, —SH, —CN, —C≡S, —NO₂, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

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 C₁-C₅ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted C₁-C₅ alkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₅-C₆ cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted C₅-C₆ heterocycloalkyl.

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 C₁-C₅ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted C₁-C₅ heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₅-C₆ cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted C₅-C₆ heterocycloalkyl.

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 the 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, hydroiodic, or phosphorous acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, malic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, pthalic, benzoic, nesulic, p-tolsulic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginine and the like, and salts of organic acids like glucuronic or galacturonic 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.

The neutral forms of the compounds 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.

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 use contemplated by the present invention and are intended to be within the scope of the present invention.

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 syntheses 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.

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.

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.

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.

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 ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

The compounds of the present invention may contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radio labeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.
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 amine, 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, laetic, mandelic, pthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginine and the like, and salts of organic acids like glutaric or galacturonic 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.

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 on a transdermal patch reservoir with a suitable enzyme or chemical reagent.

The terms "a," "an," or "(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.

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.

The terms "treating" or "treatment" refers to any indication 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.

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 recurrence) a disease, or reducing the likelihood of the onset (or recurrence) 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 enzyme relative 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.

As used herein, the "antagonist" or "the compound of the present invention" refers to a compound of Formula (I), or a P13-Kinase affinity pocket binding antagonist (e.g. a P13-Kinase affinity pocket quinazolinone antagonist). A "compound of Formula (I)") includes all embodiments of Formula (I) as described below.

II. P13-Kinase Antagonists

In one aspect, the present invention provides novel P13-Kinase antagonists. In some embodiments, the P13-kinase antagonist is a P13-Kinase affinity pocket binding antagonist (e.g. a P13-Kinase affinity pocket quinazolinone antagonist). The P13-Kinase affinity pocket binding antagonist of the present invention is a compound containing a P13-Kinase affinity pocket binding moiety. The P13-Kinase affinity pocket quinazolinone antagonists of the present invention are substituted quinazolinone compounds containing a P13-Kinase affinity pocket binding moiety. The P13-Kinase affinity pocket binding moiety is a substituent which, upon contacting a p110α, p110β, p110γ, or p110δ kinase, fills space within the corresponding P13-Kinase affinity pocket. In some embodiments, the P13-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 quinazoline 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 quinazoline 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:

![Chemical Structure](image)

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 is a bond, substituted or unsubstituted alkylenylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted arylenylene, or substituted or unsubstituted heteroarylene.

[0066] R'1 and R'2 are independently halogen, —CN, —OR', —S(O)R', —NR'R', —OC(O)R, —C(O)NR'R', substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryle. Where n is an integer from 0 to 2. R'1 may also be a PI3-Kinase affinity pocket binding moiety. R'2 and R'4 are independently hydrogen, halogen, —CN, —OR', —S(O)R', —NR'R', —OC(O)R, —C(O)NR'R', substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryle. Where n is an integer from 0 to 2.

[0067] R'3 is independently hydrogen, —C(O)R', substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylyl, or substituted or unsubstituted heteroaryle. Where n is 1 or 2. R'3 is independently hydrogen, —NR'R', substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylyl, or substituted or unsubstituted heteroaryle. Where n is 1 or 2. R'3 is independently hydrogen, —S(O)NR'R', —S(O)R', or —S(O)R. 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, heterocyloalkyl, aryl, heteroaryl, cycloalkyl-alkyl, heterocyloalkyl-alkyl, arylalkyl, or heteroarylalkyl, optionally substituted with unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocyloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocyloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl.

In some embodiments, R^1 is phenyl substituted at the meta and para positions, or substituted at the meta and para 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^2^1 may also be fluorine and R^2^2 may be hydrogen or unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl (e.g. methyl). In other embodiments, R^1 is phenyl substituted para position (i.e. a 4-substituted phenyl).

In some embodiments, L^1 is substituted or unsubstituted alkylene (e.g. a substituted or unsubstituted alkenylene. In other embodiments, L^1 is substituted or unsubstituted methylene, substituted or unsubstituted ethylene, substituted or unsubstituted propylene, substituted or unsubstituted butylene, substituted or unsubstituted ethynylene, or substituted or unsubstituted prop-2-ynylene.

In some embodiments, R^3 is —CN, —OR, NR^4R^4, R^21-substituted or unsubstituted cycloalkyl, R^2^3-substituted or unsubstituted aryl, R^2^3-substituted or unsubstituted heteroaryl, or R^2^3-substituted or unsubstituted heteroaralkyl. R^2^3 may be halogen, —OR^22, —NR^2^4R^4, or unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl. R^2^3 may be hydrogen or unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl (e.g. methyl).

In some embodiments, R^2^ is halogen, —OH, —CN, —NH\textsubscript{2}, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocyloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocyloalkyl-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\textsubscript{1}-C\textsubscript{4} alkyl (e.g. methyl).

In some embodiments, R^3 is halogen, —OH, —CN, —NH\textsubscript{2}, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocyloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocyloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl. R^2 may also be unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl (e.g. methyl).

In some embodiments, R^4 is halogen, —OH, —CN, —NH\textsubscript{2}, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocyloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted cycloalkyl-alkyl, unsubstituted heterocyloalkyl-alkyl, unsubstituted arylalkyl, or unsubstituted heteroarylalkyl. R^2 may also be unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl (e.g. methyl).

In some embodiments, R^5 and R^6 are independently unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl, R^7 is NH\textsubscript{2}, q is 1, and z is 1.

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 heterocyloalkyl, substituted aryl, substituted heteroaryl, substituted cycloalkyl-alkyl, substituted heterocyloalkyl-alkyl, substituted arylalkyl, 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.

In other embodiments of the compounds of Formula (I), each substituted or unsubstituted alkyl is a substituted or unsubstituted C\textsubscript{1}-C\textsubscript{20} alkyl, including those alkyl groups forming part of a cycloalkyl-alkyl (i.e. a cycloalkyl-(C\textsubscript{1}-C\textsubscript{20}) alkyl), heterocyloalkyl-alkyl (i.e. a heterocyloalkyl-(C\textsubscript{1}-C\textsubscript{20}) alkyl), arylalkyl (i.e. an aryl-(C\textsubscript{1}-C\textsubscript{20}) alkyl), or substituted heteroarylalkyl (i.e. a heteroaryl-(C\textsubscript{1}-C\textsubscript{20}) alkyl).

Each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 2 to 20 membered heteroaryl. Each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C\textsubscript{1}-C\textsubscript{6} cycloalkyl, including those cycloalkyl groups forming part of a cycloalkyl-alkyl (i.e. a C\textsubscript{1}-C\textsubscript{6} cycloalkyl-alkyl, or a C\textsubscript{1}-C\textsubscript{6} cycloalkyl-(C\textsubscript{1}-C\textsubscript{20}) alkyl). Each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 2 to 20 membered heteroaryl. Each substituted or unsubstituted heteroarylalkyl is a substituted or unsubstituted C\textsubscript{1}-C\textsubscript{6} heteroarylalkyl, including those heteroarylalkyl groups forming part of a heteroarylalkyl-alkyl (i.e. a C\textsubscript{1}-C\textsubscript{6} heteroarylalkyl-alkyl, or a C\textsubscript{1}-C\textsubscript{6} heteroarylalkyl-(C\textsubscript{1}-C\textsubscript{20}) alkyl).

Alternatively, each substituted or unsubstituted alkyl is a substituted or unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted C\textsubscript{1}-C\textsubscript{20} alkyl, each substituted or unsubstituted heteroaryl is a substituted or unsubstituted C\textsubscript{1}-C\textsubscript{20} aryl, or each substituted or unsubstituted heteroarylalkyl is a substituted or unsubstituted C\textsubscript{1}-C\textsubscript{20} alkyl. Each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted 4 to 8 membered cycloalkyl, including those cycloalkyl groups forming part of a cycloalkyl-alkyl (i.e. a C\textsubscript{1}-C\textsubscript{6} cycloalkyl-alkyl, or a C\textsubscript{1}-C\textsubscript{6} cycloalkyl-(C\textsubscript{1}-C\textsubscript{20}) alkyl).

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

The term "PI3-Kinase affinity pocket," as used herein, refers to a cavity within p110α, p110β, p110γ, and p110 δ corresponding to the lightly shaded region shown in FIGS. 2A, 2C, and 2D labeled “Affinity Pocket.” FIGS. 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, 1879, and D841 (p110γ numbering, see FIG. 8). The surface of the corresponding cavity in p110δ is bound, at least in part, by the side chains of K779, D911, 1825, and D787 (p110 δ numbering, see FIG. 7). The corresponding cavity within p110α is bound, at least in part, by the side chains of K802, D933, 1848, and D810 (p110α numbering, see FIG. 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 FIG. 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 (FIG. 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 FIG. 2C, PIK-39 does not contain a PI3-Kinase binding pocket moiety. And as shown in FIG. 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 pyrazolo-pyrimidine 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 FIGS. 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.

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](image-url)

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 FIG. 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.
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, 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 chloroacetaldehyde. Substitution of the E3 chlorine with the iodo-pyrazolopyrimidine or iodo-pyrazolopyrimidinyl 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

In another aspect, the present invention provides methods of decreasing the catalysis activity of a P33 kinase, such as p110 $\delta$ kinase or p110 $\gamma$ kinase. The method includes the step of contacting the P33 kinase (e.g., p110 $\delta$ kinase) with an activity decreasing amount of a P33-Kinase antagonist (i.e., a P33-Kinase affinity pocket binding antagonist or a P33-Kinase antagonist of Formula (1)). In some embodiments, the antagonist is a P33-Kinase affinity pocket quinazolinoine antagonist. In some embodiments, the P33-Kinase antagonist is specific to p110 $\delta$ relative to the antagonist action against p110 $\alpha$, p110 $\beta$, and/or p110 $\gamma$. In some embodiments, the P33-Kinase antagonist is specific to p110 $\delta$ relative to the antagonist action against p110 $\alpha$ and/or p110 $\gamma$. In some embodiments, the P33-Kinase antagonist is specific to p110 $\delta$ relative to the antagonist action against p110 $\alpha$ and p110 $\beta$. In some embodiments, the P33-Kinase antagonist is specific to p110 $\delta$ relative to the antagonist action against p110 $\alpha$ and p110 $\beta$. In some embodiments, the P33-Kinase antagonist is specific to p110 $\delta$ relative to the antagonist action against p110 $\alpha$ and p110 $\beta$.

In some embodiments, the P33-Kinase antagonist is specific to p110 $\delta$ relative to the antagonist action against p110 $\beta$, and/or p110 $\alpha$, the P33-Kinase antagonist is the P33-Kinase antagonist of Formula (1), 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 fluorne and $R^{22}$ may be hydrogen or unsubstituted $C_1-C_4$ alkyl (e.g., methyl).

In other embodiments, where the P33-Kinase antagonist is specific to p110 $\delta$ relative to the antagonist action against p110 $\alpha$, p110 $\beta$, and/or p110 $\gamma$, the P33-Kinase antagonist is the P33-Kinase antagonist of Formula (1), where $R'$ is a 3,5-substituted phenyl. In some related embodiments, the 3,5-substituted phenyl is substituted, independently, with $R^{23}$. $R^{23}$ may be halogen or $-OR^{24}$. $R^{23}$ may also be fluorne and $R^{24}$ may be hydrogen or unsubstituted $C_1-C_4$ alkyl (e.g., methyl).

In some embodiments, the IC$_{50}$ against the p110 $\delta$ kinase and/or p110 $\gamma$ 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 IC$_{50}$ against p110 $\alpha$ and/or p110 $\gamma$. In other embodiments, the IC$_{50}$ of the antagonist against p110 $\delta$ kinase and/or p110 $\gamma$ is less than 100 $\mu$M, 50 $\mu$M, 40 $\mu$M, 30 $\mu$M, 20 $\mu$M, 10 $\mu$M, 5 $\mu$M, 1 $\mu$M, 0.5 $\mu$M, 0.1 $\mu$M, 50 nM, 10 nM, 5 nM, 0.5 nM, or 0.1 nM.

In another aspect, the present invention provides methods of treating a disease mediated by P33-Kinase activity (e.g., p110 $\delta$ kinase activity or p110 $\gamma$ kinase activity) in a subject in need of such treatment. The method includes administering to the subject a therapeutically effective amount of a P33-Kinase antagonist (i.e., a P33-Kinase affinity pocket antagonist or P33-Kinase antagonist of Formula (1)). In some embodiments, the antagonist is a P33-Kinase affinity pocket quinazolinoine antagonist.

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 thrombosis.

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 insulnoma, 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 p110 $\delta$ kinase activity is set forth in Sadu et al., WO 01/81346, which is incorporated herein by reference in its entirety for all purposes.

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 P33-Kinase antagonist (i.e., a P33-Kinase affinity pocket antagonist or P33-Kinase antagonist of Formula (1)). In some embodiments, the antagonist is a P33-Kinase affinity pocket quinazolinoine antagonist.

VII. Pharmaceutical Formulations

In another aspect, the present invention provides a pharmaceutical composition including a P33-Kinase affinity pocket binding antagonist or a compound of Formula (1) in admixture with a pharmaceutically acceptable excipient. One of skill in the art will recognize that the pharmaceutical com-
positions include the pharmaceutically acceptable salts of the PI3-Kinase antagonists of the present invention described above.

[0105] 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).

[0106] 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.

[0107] 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, camyslate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylamylate, hydroxyisouronate, hydramine, hydrobromide, hydrochloride, hydroxychloroacetate, isethionate, lactate, lactobionate, maleate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygallacturonate, salicylate, stearate, subacetate, succinate, sulfate, tartrate, tetrionate, or urate. 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.

[0108] 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-articular, intra-dermal, intradendritic, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

[0109] For injection, the agents of the invention may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hanks’s solution, Ring-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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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-1RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating diabetes such as insulin, insulin analogues, alpha glucosidase inhibitors, biguanides, and insulin sensitizers; and agents for treating immunodeficiency disorders such as gamma globulin.

[0119] 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.

[0120] 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

[0121] The following examples are meant to illustrate certain embodiments of the invention, and not to limit the scope of the invention.
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-tolylenzamide

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 CHCl₃ (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-tolyquinazolin-4(3H)-one

Chloroacetyl chloride (29 mL, 363 mmol) was added to a solution of 2-amino-6-methyl-N-o-tolylenzamide (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% diethyl ether/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-tolyquinazolin-4(3H)-one

Chloroacetyl chloride (29 mL, 363 mmol) was added to a solution of 2-amino-6-methyl-N-o-tolylenzamide (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% diethyl ether/hexanes) to yield a white solid (8.3 g, 23% yield). LR-ESI MS (M+H)+ m/z calcd 299.1, found 298.8.

4. Synthesis of Compound S2

5. Synthesis of Compound S3

6. Synthesis of Compound S4

7. Synthesis of Compound S5
concentrated in vacuo and purified by RP-HPLC (MeCN: H₂O:0.1% TEA). LR-ESI MS (M+H)⁺/m/z calcd 558.2, found 558.0.

7. Synthesis of Compound S5

[0131] 2-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-O— tolyquinazolin-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 Na₂CO₃ (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 CH₂Cl₂. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN: H₂O:0.1% TEA). LR-ESI MS (M+H)⁺/m/z calcd 522.2, found 522.0.

8. Synthesis of S6

[0132] 2-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-O— tolyquinazolin-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 Na₂CO₃ (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 CH₂Cl₂. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN: H₂O:0.1% TEA). LR-ESI MS (M+H)⁺/m/z calcd 534.2, found 534.0.

9. Synthesis of S7

[0133] 2-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-tolyquinazolin-4(3H)-one (100 mg, 0.192 mmol), 4-phenoxypyphenyl 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 Na₂CO₃ (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 CH₂Cl₂. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN: H₂O:0.1% TEA). LR-ESI MS (M+H)⁺/m/z calcd 566.2, found 566.0.

10. Synthesis of S8

[0134] 2-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-O— tolyquinazolin-4(3H)-one (100 mg, 0.192 mmol), 4-benzoxypbenyl 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 Na₂CO₃ (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 CH₂Cl₂. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN: H₂O:0.1% TEA). LR-ESI MS (M+H)⁺/m/z calcd 558.2, found 558.0.

11. Synthesis of S33

[0135] 2-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-5-methyl-3-O— tolyquinazolin-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 Na₂CO₃ (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 CH₂Cl₂. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN: H₂O:0.1% TEA). LR-ESI MS (M+H)⁺/m/z calcd 499.2, found 499.0.

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

[0136] 2-amino-6-methylbenzoic acid (2.5 g, 16.5 mmol) was dissolved in benzene (75 mL). Thiouyl 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 in benzene (75 mL) and solvent removed in vacuo again to give a black oil. The oil was dissolved in CHCl₃ (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 product was purified by silica gel chromatography (25% EtOAc/Hexanes) to yield a brown oil (1.94 g, 45% yield). HR-ESI MS (M+H)⁺/m/z calcd 260.07, found 260.0715.

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

[0137] 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-ESI MS (M+H)⁺/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

[0138] 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 DME (5 mL) and K₂CO₃ (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:H₂O:0.1% TEA).

15. Synthesis of S1

[0139] 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 Na₂CO₃ (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 CH₂Cl₂. The organic extract was concentrated in vacuo and purified by RP-HPLC (MeCN:H₂O:0.1% TFA). LR-ESI MS (M+H)⁺ m/z calc. 510.1, found 510.0.

16. Synthesis of S34

[0140] 2-(4-amino-3-iodo-1H-pyrazolo[3,4-d][1,2,4]triazin-1-yl)methyl)-5-methyl-3-O—tolyquinazolin-4(3H)-one (50 mg, 0.096 mmol), benzene 3-sulphonamido boronic ester (29.7 mg, 0.155 mmol) and tetraakis(triphenylphosphine)palladium (22 mg, 0.019 mmol) were dissolved in a solution of DME (10 mL), EtOH (1.6 mL) and saturated aqueous Na₂CO₃ (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 CH₂Cl₂. LR-ESI MS (M+H)⁺ m/z calc. 553.2, found 553.0.

[0141] C. PI3-Kinase-Structural Studies

[0142] Crystal structures of p110γ have been reported, alone and in complex with ATP or p38-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 imidazole PIK-93 (FIG. 2).

[0143] Based on these co-crystal structures and a conserved ary/minorpholine pharmacophore model, structural models were generated for three additional chemotypes bound to p110γ: the pyridylfluoropyrimidine PIK-103, the morpholinonoclone PIK-108, and the morpholinopyranone KU-55933 (FIG. 2). Model-building for these inhibitors was guided by the observation that each compound contains the key ary/minorpholine pharmacophore found in LY294002.

[0144] PIK-39 is an isouquinoline 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 (FIG. 5). The biochemical selectivity of this compound is achieved through an unusual binding mode revealed in its co-crystal structure with p110γ (FIG. 2C). Only the mercaptopurine moiety of PIK-39 makes contacts within the interior of the ATP binding pocket, and this ring system is rotated by 110° with respect to each other.

[0150] Unlike other inhibitor chemotypes, PIK-39 does not exploit the PI3-kinase affinity pocket (FIG. 2C). The pyrazolopyrimidine analog of CH-717114 (PIK-293) as well as a novel analog containing an α-phenol (PIK-294, FIG. 3A) were then tested for inhibition of the class I PI-3k. PIK-294 was up to 60-fold more potent than PIK-293 (FIG. 3A).

[0151] 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-specific 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 this residue (FIG. 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 (FIG. 3B). We find that M752V and M752V p110δ are resistant to the p110δ-specific 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.

[0152] 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 (1E9O), 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.

[0153] 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 arylmorpholine-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.

[0154] D Expression and Assays of p110α/p85α, p110β/p85α, p110α/p85γ, and p110γ

[0155] The class I PI3-Ks were either purchased (p110α/ p85α, p110β/p85α, p110β/p85γ, p110 δ/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 FIG. 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 precleaned with CHCl₃. 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.

[0156] Results are set forth in Table 1 below.

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


beta regulatory subunits of phosphoinositide 3-kinase in
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unit of phosphoinositide 3-kinase. Proc Natl Acad Sci USA
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Thr Ser Val Ala Ala Asp Phe Tyr His Arg Leu Gly Pro His His Phe
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1060 1065 1070
What is claimed is:

1. A compound having the formula:

![Chemical structure](image)

wherein

$q$ is an integer from 0 to 5;
$r$ is an integer from 0 to 10;
$L^1$ is a bond, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkyne, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

$R^1$ and $R^2$ are independently halogen, $-$CN, $-$OR$,^1$ $-$S(O)$_2$R$,^2$ $-$NR$,^3$R$^4$, $-$C(O)R$,^5$, 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;

$R^3$, and $R^4$ are independently halogen, $-$CN, $-$OR$,^6$ $-$S(O)$_2$R$,^7$ $-$NR$,^8$R$^9$, $-$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;

$R^5$ is independently hydrogen, $-$C(O)R$,^11$ 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$,^12$R$,^13$, 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)$_2$R$,^14$, $-$C(O)R$,^15$, 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 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, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkyne, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkyne, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;
The compound of claim 4, wherein R¹ is phenyl substituted at the meta and para positions, or substituted at the meta and meta positions.

6. The compound of claim 5, wherein R² is halogen or —OR².

7. The compound of claim 6, wherein R² is fluorine and R² 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 R³ is halogen, —OH, —CN, —NH₂, 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 R³ is halogen or unsubstituted alkyl.

12. The compound of claim 1, wherein R³ is fluorine or unsubstituted C₁-C₄ alkyl.

13. The compound of claim 1, wherein R⁴ is halogen, —OH, —CN, —NH₂, 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 R⁴ is unsubstituted alkyl.

15. The compound of claim 1, wherein R⁴ is unsubstituted C₁-C₄ alkyl.

16. The compound of claim 1, wherein R⁵ is halogen, —OH, —CN, —NH₂, alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkyl-alkyl, heterocycloalkyl-alkyl, arylalkyl, or heteroarylalkyl.

17. The compound of claim 1, wherein R¹ and R² are independently unsubstituted C₁-C₄ alkyl; R³ is NH₂; q is 1; and z is 1.

18. The compound of claim 1, wherein L¹ is substituted or unsubstituted alkylene.

19. The compound of claim 1, wherein L¹ is substituted or unsubstituted alkyne.

20. The compound of claim 1, wherein L¹ is substituted or unsubstituted methylene, substituted or unsubstituted ethylene, substituted or unsubstituted propylene, substituted or unsubstituted butylene, substituted or unsubstituted ethynylene, or substituted or unsubstituted prop-2-ynylene.

21. The compound of claim 20, wherein R¹ is —CN, —OR¹, —NR¹R⁴, R¹-substituted or unsubstituted cycloalkyl, R¹-substituted or unsubstituted aryl, R³-substituted or unsubstituted heteroaryl, R³-substituted or unsubstituted C₁-C₄ alkyl, wherein R³ is halogen, —OR², —NR²R⁵, or unsubstituted C₁-C₄ alkyl and

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 p110 δ 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:

$$\begin{align*}
\text{R}^1 & \quad \text{O} \\
\text{L}^1 & \quad \text{R}^3 \\
\text{N} & \quad \text{R}^4
\end{align*}$$

wherein

- q is an integer from 0 to 5;
- z is an integer from 0 to 10;
- X is —CH₂ or =N—;
- L¹ 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;
- R¹ and R² are independently halogen, —CN, —OR¹, —SO₃H, —NR²R⁵, —C(O)R⁵, —C(O)R⁵, 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;
- R³ and R⁴ are independently halogen, —CN, —OR³, —SO₃H, —NR³R⁵, —C(O)R⁵, 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;
33. A method of treating a disease mediated by p110 δ 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:

\[
\text{I}
\]

wherein

- q is an integer from 0 to 5;
- z is an integer from 0 to 10;
- X is \(-\text{CH}=-\) or \(-\text{N}=-\);
- L is a bond, substituted or unsubstituted alkyne, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;
- R, and R are independently halogen, \(-\text{CN}, -\text{OR}^3, -\text{O}^3, -\text{S}^3, -\text{NR}^3, -\text{C}^3(\text{O})^3,\) substituted or unsubstituted alky, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
- R, R, R, R, R, R, and R are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl.

27. A method of treating a disease mediated by p110 δ 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 quinazolinedione 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 malignacy, 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.
R² is independently hydrogen, —S(O)²R¹³, —C(O)R¹⁴, 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; R² is independently —NR¹⁵R¹⁶, 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; R¹⁰ is independently hydrogen, —NR¹⁷R¹⁸, 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; R¹⁴ is independently hydrogen, —NR¹⁹R²⁰, 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 R¹¹, R¹², R¹³, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ 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 quinazoline 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

\[
R¹\text{ is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted aryle, or substituted or unsubstituted heteroaryl; }
\]

\[
R²\text{ and } R³\text{ are independently hydrogen, halogen, }-\text{CN, }-\text{OR},
\]

\[
-\text{S(O)}_n\text{R}^5, -\text{NR}^5\text{R}^6, -\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein } n \text{ is an integer from 0 to 2; }
\]

\[
R⁴, \text{ and } R⁵\text{ are independently hydrogen, halogen, }-\text{CN, }-\text{OR},
\]

\[
-\text{S(O)}_n\text{R}^5, -\text{NR}^5\text{R}^6, -\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R⁶\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R⁷\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R⁸\text{ and } R⁹\text{ are independently hydrogen, halogen, }-\text{CN, }-\text{OR},
\]

\[
-\text{S(O)}_n\text{R}^5, -\text{NR}^5\text{R}^6, -\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein } n \text{ is an integer from 0 to 2; }
\]

\[
R¹⁰, \text{ and } R¹¹\text{ are independently hydrogen, halogen, }-\text{CN, }-\text{OR},
\]

\[
-\text{S(O)}_n\text{R}^5, -\text{NR}^5\text{R}^6, -\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R¹²\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R¹³\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R¹⁴\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R¹⁵\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R¹⁶\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R¹⁷\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R¹⁸\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R¹⁹\text{ is independently hydrogen, }-\text{C(O)R}^6, \text{substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
R²⁰\text{ are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; }
\]

\[
\text{wherein}
\]

\[
q \text{ is an integer from 0 to 5;}
\]

\[
z \text{ is an integer from 0 to 10;}
\]

\[
X = -\text{CH} - \text{ or } -\text{N} - ;
\]