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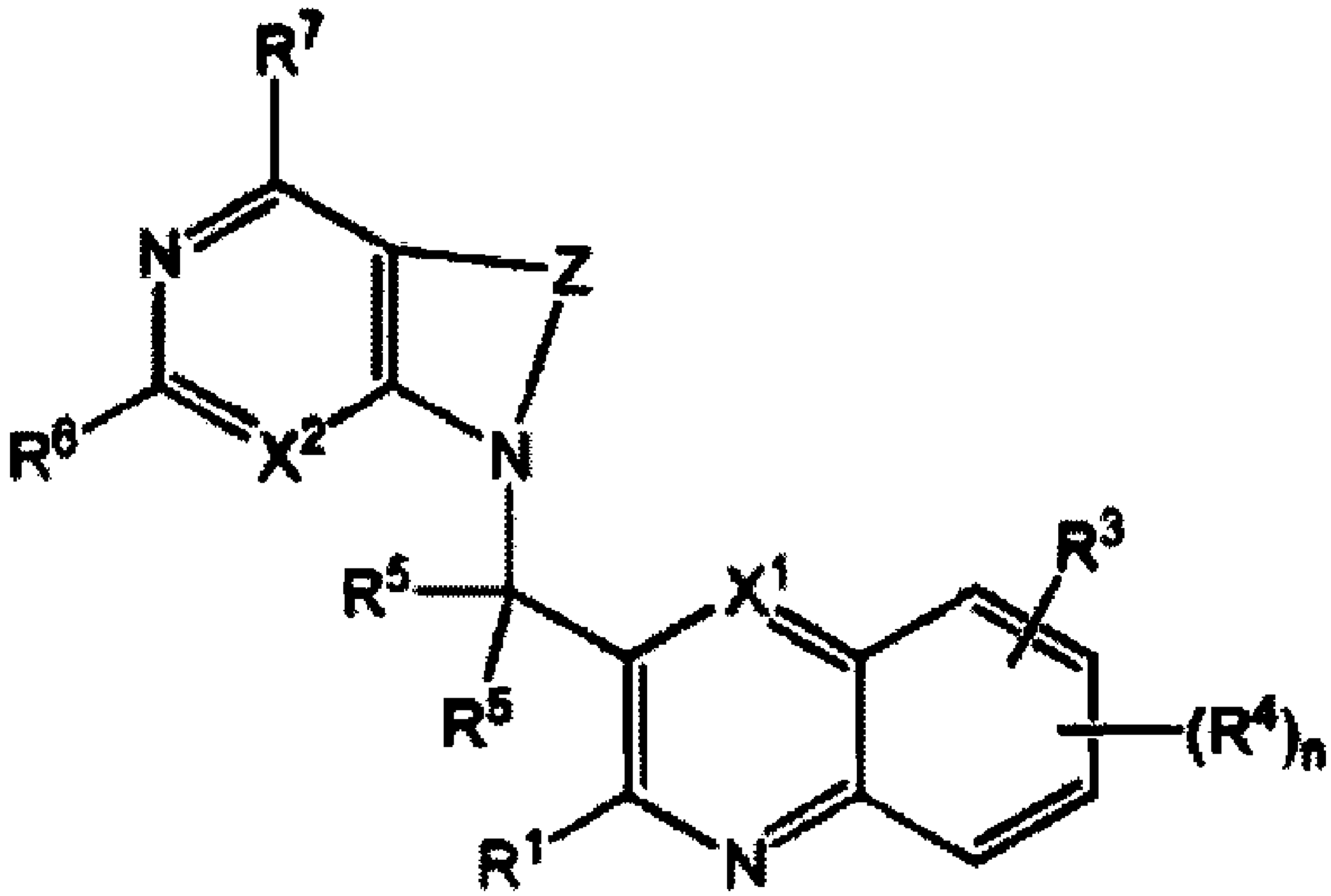
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(57) Abrégé/Abstract:
Substituted bicyclic heteroaryls of formula (see above Formula) and compositions containing them, for the treatment of general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, including

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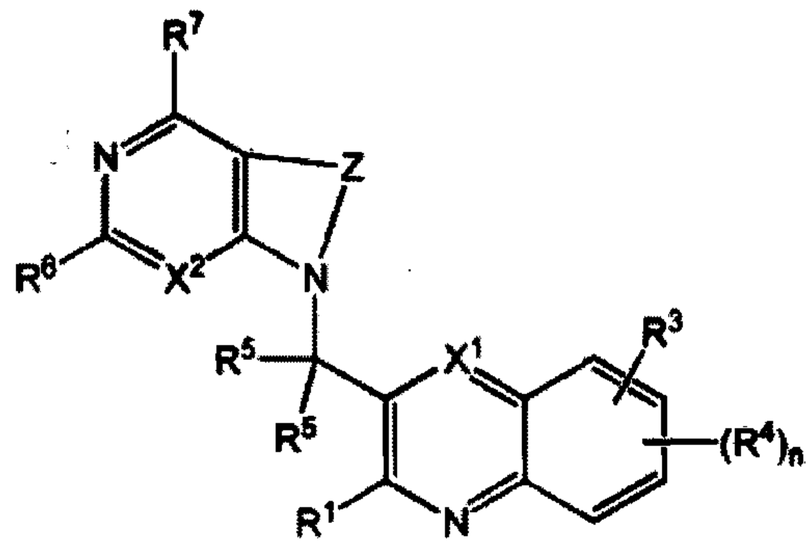
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but not restricted to autoimmune diseases such as systemic lupus erythematosis (SLE), myestenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis, Sjoegren's syndrome and autoimmune hemolytic anemia, allergic conditions including all forms of hypersensitivity, The present invention also enables methods for treating cancers that are mediated, dependent on or associated with p 110 activity, including but not restricted to leukemias, such as Acute Myeloid leukaemia (AML), Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-ALL), Non Hodgkins Lymphoma (NHL), B-cell lymphoma and solid tumors, such as breast cancer.

ABSTRACT

Substituted bicyclic heteroaryls of formula



and compositions containing them, for the treatment of general inflammation, arthritis, rheumatic diseases, osteoarthritis, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, psoriasis, skin complaints with inflammatory components, chronic inflammatory conditions, including but not restricted to autoimmune diseases such as systemic lupus erythematosis (SLE), myestenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis, Sjoegren's syndrome and autoimmune hemolytic anemia, allergic conditions including all forms of hypersensitivity, The present invention also enables methods for treating cancers that are mediated, dependent on or associated with p110 activity, including but not restricted to leukemias, such as Acute Myeloid leukaemia (AML), Myelo-dysplastic syndrome (MDS), myelo-proliferative diseases (MPD), Chronic Myeloid Leukemia (CML), T-cell Acute Lymphoblastic leukaemia (T-ALL), B-cell Acute Lymphoblastic leukaemia (B-ALL), Non Hodgkins Lymphoma (NHL), B-cell lymphoma and solid tumors, such as breast cancer.

HETEROCYCLIC COMPOUNDS AND THEIR USES

The present invention relates generally to phosphatidylinositol 3-kinase (PI3K) enzymes, and more particularly to selective inhibitors of PI3K activity and to methods of using such materials.

BACKGROUND OF THE INVENTION

Cell signaling via 3′-phosphorylated phosphoinositides has been implicated in a variety of cellular processes, e.g., malignant transformation, growth factor signaling, inflammation, and immunity (see Rameh et al., J. Biol Chem, 274:8347-8350 (1999) for a review). The enzyme responsible for generating these phosphorylated signaling products, phosphatidylinositol 3-kinase (PI 3-kinase; PI3K), was originally identified as an activity associated with viral oncoproteins and growth factor receptor tyrosine kinases that phosphorylates phosphatidylinositol (PI) and its phosphorylated derivatives at the 3′-hydroxyl of the inositol ring (Panayotou et al., Trends Cell Biol 2:358-60 (1992)).

The levels of phosphatidylinositol-3,4,5-triphosphate (PIP3), the primary product of PI 3-kinase activation, increase upon treatment of cells with a variety of stimuli. This includes signaling through receptors for the majority of growth factors and many inflammatory stimuli, hormones, neurotransmitters and antigens, and thus the activation of PI3Ks represents one, if not the most prevalent, signal transduction events associated with mammalian cell surface receptor activation (Cantley, Science 296:1655-1657 (2002); Vanhaesebroeck et al. Annu.Rev.Biochem, 70: 535-602 (2001)). PI 3-kinase activation, therefore, is involved in a wide range of cellular responses including cell growth, migration, differentiation, and apoptosis (Parker et al., Current Biology, 5:577-99 (1995); Yao et al., Science, 267:2003-05 (1995)). Though the downstream targets of phosphorylated lipids generated following PI 3-kinase activation have not been fully characterized, it is known that pleckstrin-homology (PH) domain- and FYVE-finger domain-containing proteins are activated when binding to various phosphatidylinositol lipids (Sternmark et al., J Cell Sci, 112:4175-83 (1999); .Lemmon et al., Trends Cell Biol, 7:237-42 (1997)). Two groups of PH-domain

containing PI3K effectors have been studied in the context of immune cell signaling, members of the tyrosine kinase TEC family and the serine/threonine kinases of te AGC family. Members of the Tec family containing PH domains with apparent selectivity for PtdIns (3,4,5)P_3 include Tec, Btk, Itk and Etk. Binding of PH to PIP_3 is critical for tyrsosine kinase activity of the Tec family members (Schaeffer and Schwartzberg, Curr.Opin.Immunol. 12: 282-288 (2000)) AGC family members that are regulated by PI3K include the phosphoinositide-dependent kinase (PDK1), AKT (also termed PKB) and certain isoforms of protein kinase C (PKC) and S6 kinase. There are three isoforms of AKT and activation of AKT is strongly associated with PI3K- dependent proliferation and survival signals. Activation of AKT depends on phosphorylation by PDK1, which also has a 3-phosphoinositide-selective PH domain to recruit it to the membrane where it interacts with AKT. Other important PDK1 substrates are PKC and S6 kinase (Deane and Fruman, Annu.Rev.Immunol. 22_563-598 (2004)). In vitro, some isoforms of protein kinase C (PKC) are directly activated by PIP3. (Burgering et al., Nature, 376:599-602 (1995)).

Presently, the PI 3-kinase enzyme family has been divided into three classes based on their substrate specificities. Class I PI3Ks can phosphorylate phosphatidylinositol (PI), phosphatidylinositol-4-phosphate, and phosphatidyl-inositol-4,5-biphosphate (PIP2) to produce phosphatidylinositol-3-phosphate (PIP), phosphatidylinositol-3,4-biphosphate, and phosphatidylinositol-3,4,5-triphosphate, respectively. Class II PI3Ks phosphorylate PI and phosphatidyl-inositol-4-phosphate, whereas Class III PI3Ks can only phosphorylate PI.

The initial purification and molecular cloning of PI 3-kinase revealed that it was a heterodimer consisting of p85 and p110 subunits (Otsu et al., Cell, 65:91-104 (1991); Hiles et al., Cell, 70:419-29 (1992)). Since then, four distinct Class I PI3Ks have been identified, designated PI3K α, β, δ, and γ, each consisting of a distinct 110 kDa catalytic subunit and a regulatory subunit. More specifically, three of the catalytic subunits, i.e., p110α, p110β and p110δ, each interact with the same regulatory subunit, p85; whereas p110γ interacts with a distinct regulatory subunit, p101. As described below, the patterns of expression of each of these PI3Ks in human cells and tissues are also distinct. Though a wealth of information

has been accumulated in recent past on the cellular functions of PI 3-kinases in general, the roles played by the individual isoforms are not fully understood.

Cloning of bovine p110α has been described. This protein was identified as related to the Saccharomyces cerevisiae protein: Vps34p, a protein involved in vacuolar protein processing. The recombinant p110α product was also shown to associate with p85α, to yield a PI3K activity in transfected COS-1 cells. See Hiles et al., Cell, 70, 419-29 (1992).

The cloning of a second human p110 isoform, designated p110β, is described in Hu et al., Mol Cell Biol, 13:7677-88 (1993). This isoform is said to associate with p85 in cells, and to be ubiquitously expressed, as p110β mRNA has been found in numerous human and mouse tissues as well as in human umbilical vein endothelial cells, Jurkat human leukemic T cells, 293 human embryonic kidney cells, mouse 3T3 fibroblasts, HeLa cells, and NBT2 rat bladder carcinoma cells. Such wide expression suggests that this isoform is broadly important in signaling pathways.

Identification of the p110δ isoform of PI 3-kinase is described in Chantry et al., J Biol Chem, 272:19236-41 (1997). It was observed that the human p110δ isoform is expressed in a tissue-restricted fashion. It is expressed at high levels in lymphocytes and lymphoid tissues and has been shown to play a key role in PI 3-kinase-mediated signaling in the immune system (Al-Alwan etl al. JI 178: 2328-2335 (2007); Okkenhaug et al JI, 177: 5122-5128 (2006); Lee et al. PNAS, 103: 1289-1294 (2006)). P110δ has also been shown to be expressed at lower levels in breast cells, melanocytes and endothelial cells (Vogt et al. Virology, 344: 131-138 (2006) and has since been implicated in conferring selective migratory properties to breast cancer cells (Sawyer et al. Cancer Res. 63:1667-1675 (2003)). Details concerning the P110δ isoform also can be found in U.S. Pat. Nos. 5,858,753; 5,822,910; and 5,985,589. See also, Vanhaesebroeck et al., Proc Nat. Acad Sci USA, 94:4330-5 (1997), and international publication WO 97/46688.

In each of the PI3Kα, β, and δ subtypes, the p85 subunit acts to localize PI 3-kinase to the plasma membrane by the interaction of its SH2 domain with phosphorylated tyrosine residues (present in an appropriate sequence context) in target proteins (Rameh et al., Cell, 83:821-30 (1995)). Five isoforms of p85 have

been identified (p85α, p85β, p55γ, p55α and p50α) encoded by three genes. Alternative transcripts of Pik3r1 gene encode the p85 α, p55 α and p50α proteins (Deane and Fruman, Annu.Rev.Immunol. 22: 563-598 (2004)). p85α is ubiquitously expressed while p85β, is primarily found in the brain and lymphoid tissues (Volinia et al., Oncogene, 7:789-93 (1992)). Association of the p85 subunit to the PI 3-kinase p110α, β, or δ catalytic subunits appears to be required for the catalytic activity and stability of these enzymes. In addition, the binding of Ras proteins also upregulates PI 3-kinase activity.

The cloning of p110γ revealed still further complexity within the PI3K family of enzymes (Stoyanov et al., Science, 269:690-93 (1995)). The p110γ isoform is closely related to p110α and p110β (45-48% identity in the catalytic domain), but as noted does not make use of p85 as a targeting subunit. Instead, p110γ binds a p101 regulatory subunit that also binds to the βγ subunits of heterotrimeric G proteins. The p101 regulatory subunit for PI3Kgamma was originally cloned in swine, and the human ortholog identified subsequently (Krugmann et al., J Biol Chem, 274:17152-8 (1999)). Interaction between the N-terminal region of p101 with the N-terminal region of p110γ is known to activate PI3Kγ through Gβγ. Recently, a p101-homologue has been identified, p84 or $p87^{PIKAP}$ (PI3Kγ adapter protein of 87 kDa) that binds p110γ (Voigt et al. JBC, 281: 9977-9986 (2006), Suire et al. Curr.Biol. 15: 566-570 (2005)). $p87^{PIKAP}$ is homologous to p101 in areas that bind p110γ and Gβγ and also mediates activation of p110γ downstream of G-protein-coupled receptors. Unlike p101, $p87^{PIKAP}$ is highly expressed in the heart and may be crucial to PI3Kγ cardiac function.

A constitutively active PI3K polypeptide is described in international publication WO 96/25488. This publication discloses preparation of a chimeric fusion protein in which a 102-residue fragment of p85 known as the inter-SH2 (iSH2) region is fused through a linker region to the N-terminus of murine p110. The p85 iSH2 domain apparently is able to activate PI3K activity in a manner comparable to intact p85 (Klippel et al., Mol Cell Biol, 14:2675-85 (1994)).

Thus, PI 3-kinases can be defined by their amino acid identity or by their activity. Additional members of this growing gene family include more distantly related lipid and protein kinases including Vps34 TOR1, and TOR2 of Saccharomyces cerevisiae (and their mammalian homologs such as FRAP and mTOR), the ataxia telangiectasia gene product (ATR) and the catalytic subunit of DNA-dependent protein kinase (DNA-PK). See generally, Hunter, Cell, 83:1-4 (1995).

PI 3-kinase is also involved in a number of aspects of leukocyte activation. A p85-associated PI 3-kinase activity has been shown to physically associate with the cytoplasmic domain of CD28, which is an important costimulatory molecule for the activation of T-cells in response to antigen (Pages et al., Nature, 369:327-29 (1994); Rudd, Immunity, 4:527-34 (1996)). Activation of T cells through CD28 lowers the threshold for activation by antigen and increases the magnitude and duration of the proliferative response. These effects are linked to increases in the transcription of a number of genes including interleukin-2 (IL2), an important T cell growth factor (Fraser et al., Science, 251:313-16 (1991)). Mutation of CD28 such that it can no longer interact with PI 3-kinase leads to a failure to initiate IL2 production, suggesting a critical role for PI 3-kinase in T cell activation.

Specific inhibitors against individual members of a family of enzymes provide invaluable tools for deciphering functions of each enzyme. Two compounds, LY294002 and wortmannin, have been widely used as PI 3-kinase inhibitors. These compounds, however, are nonspecific PI3K inhibitors, as they do not distinguish among the four members of Class I PI 3-kinases. For example, the IC_{50} values of wortmannin against each of the various Class I PI 3-kinases are in the range of 1-10nM. Similarly, the IC_{50} values for LY294002 against each of these PI 3-kinases is about 1μM (Fruman et al., Ann Rev Biochem, 67:481-507 (1998)). Hence, the utility of these compounds in studying the roles of individual Class I PI 3-kinases is limited.

Based on studies using wortmannin, there is evidence that PI 3-kinase function also is required for some aspects of leukocyte signaling through G-protein coupled receptors (Thelen et al., Proc Natl Acad Sci USA, 91:4960-64 (1994)). Moreover, it has been shown that wortmannin and LY294002 block

neutrophil migration and superoxide release. However, inasmuch as these compounds do not distinguish among the various isoforms of PI3K, it remains unclear from these studies which particular PI3K isoform or isoforms are involved in these phenomena and what functions the different Class I PI3K enzymes perform in both normal and diseased tissues in general. The co-expression of several PI3K isoforms in most tissues has confounded efforts to segregate the activities of each enzyme until recently.

The separation of the activities of the various PI3K isozymes has been advanced recently with the development of genetically manipulated mice that allowed the study of isoform-specific knock-out and kinase dead knock-in mice and the development of more selective inhibitors for some of the different isoforms. P110α and p110β knockout mice have been generated and are both embryonic lethal and little information can be obtained from these mice regarding the expression and function of p110 alpha and beta (Bi et al. Mamm.Genome, 13:169-172 (2002); Bi et al. J.Biol.Chem. 274:10963-10968 (1999)). More recently, p110α kinase dead knock in mice were generated with a single point mutation in the DFG motif of the ATP binding pocket (p110αD^{933A}) that impairs kinase activity but preserves mutant p110α kinase expression. In contrast to knock out mice, the knockin approach preserves signaling complex stoichiometry, scaffold functions and mimics small molecule approaches more realistically than knock out mice. Similar to the p110α KO mice, p110αD^{933A} homozygous mice are embryonic lethal. However, heterozygous mice are viable and fertile but display severely blunted signaling via insulin-receptor substrate (IRS) proteins, key mediators of insulin, insulin-like growth factor-1 and leptin action. Defective responsiveness to these hormones leads to hyperinsulinaemia, glucose intolerance, hyperphagia, increase adiposity and reduced overall growth in heterozygotes (Foukas, et al. Nature, 441: 366-370 (2006)). These studies revealed a defined, non-redundant role for p110α as an intermediate in IGF-1, insulin and leptin signaling that is not substituted for by other isoforms. We will have to await the description of the p110β kinase-dead knock in mice to further understand the

function of this isoform (mice have been made but not yet published; Vanhaesebroeck).

P110γ knock out and kinase-dead knock in mice have both been generated and overall show similar and mild phenotypes with primary defects in migration of cells of the innate immune system and a defect in thymic development of T cells (Li et al. Science, 287: 1046-1049 (2000), Sasaki et al. Science, 287: 1040-1046 (2000), Patrucco et al. Cell, 118: 375-387 (2004)).

Similar to p110γ, PI3K delta knock out and kinase-dead knock-in mice have been made and are viable with mild and like phenotypes. The $p110\delta^{D910A}$ mutant knock in mice demonstrated an important role for delta in B cell development and function, with marginal zone B cells and CD5+ B1 cells nearly undetectable, and B- and T cell antigen receptor signaling (Clayton et al. J.Exp.Med. 196:753-763 (2002); Okkenhaug et al. Science, 297: 1031-1034 (2002)). The $p110\delta^{D910A}$ mice have been studied extensively and have elucidated the diverse role that delta plays in the immune system. T cell dependent and T cell independent immune responses are severely attenuated in $p110\delta^{D910A}$ and secretion of TH1 (INF-γ) and TH2 cytokine (IL-4, IL-5) are impaired (Okkenhaug et al. J.Immunol. 177: 5122-5128 (2006)). A human patient with a mutation in p110δ has also recently been described. A taiwanese boy with a primary B cell immunodeficiency and a gamma-hypoglobulinemia of previously unkown aetiology presented with a single base-pair substitution, m.3256G to A in codon 1021 in exon 24 of p110δ. This mutation resulted in a mis-sense amino acid substitution (E to K) at codon 1021, which is located in the highly conserved catalytic domain of p110δ protein. The patient has no other identified mutations and his phenotype is consistent with p110δ deficiency in mice as far as studied. (Jou et al. Int.J.Immunogenet. 33: 361-369 (2006)).

Isoform-selective small molecule compounds have been developed with varying success to all Class I PI3 kinase isoforms (Ito et al. J. Pharm. Exp. Therapeut., 321:1-8 (2007)). Inhibitors to alpha are desirable because mutations in p110α have been identified in several solid tumors; for example, an amplification mutation of alpha is associated with 50% of ovarian, cervical, lung and breast

cancer and an activation mutation has been described in more than 50% of bowel and 25% of breast cancers (Hennessy et al. Nature Reviews, 4: 988-1004 (2005)). Yamanouchi has developed a compound YM-024 that inhibits alpha and delta equi-potently and is 8- and 28-fold selective over beta and gamma respectively (Ito et al. J.Pharm.Exp.Therapeut., 321:1-8 (2007)).

P110β is involved in thrombus formation (Jackson et al. Nature Med. 11: 507-514 (2005)) and small molecule inhibitors specific for this isoform are thought after for indication involving clotting disorders (TGX-221: 0.007uM on beta; 14-fold selective over delta, and more than 500-fold selective over gamma and alpha) (Ito et al. J.Pharm.Exp.Therapeut., 321:1-8 (2007)).

Selective compounds to p110γ are being developed by several groups as immunosuppressive agents for autoimmune disease (Rueckle et al. Nature Reviews, 5: 903-918 (2006)). Of note, AS 605240 has been shown to be efficacious in a mouse model of rheumatoid arthritis (Camps et al. Nature Medicine, 11: 936-943 (2005)) and to delay onset of disease in a model of systemic lupus erythematosis (Barber et al. Nature Medicine, 11: 933-935 (205)).

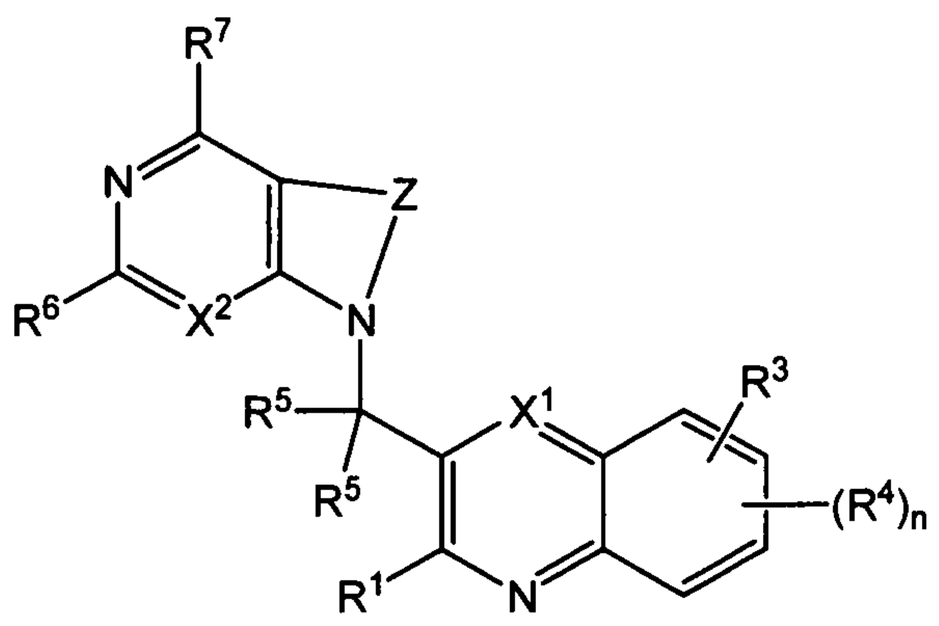
Delta-selective inhibitors have also been described recently. The most selective compounds include the quinazolinone purine inhibitors (PIK39 and IC87114). IC87114 inhibits p110δ in the high nanomolar range (triple digit) and has greater than 100-fold selectivity against p110α, is 52 fold selective against p110β but lacks selectivity against p110γ (approx. 8-fold). It shows no activity against any protein kinases tested (Knight et al. Cell, 125: 733-747 (2006)). Using delta-selective compounds or genetically manipulated mice ($p110\delta^{D910A}$) it was shown that in addition to playing a key role in B and T cell activation, delta is also partially involved in neutrophil migration and primed neutrophil respiratory burst and leads to a partial block of antigen-IgE mediated mast cell degranulation (Condliffe et al. Blood, 106: 1432-1440 (2005); Ali et al. Nature, 431: 1007-1011 (2002)). Hence p110δ is emerging as an important mediator of many key inflammatory responses that are also known to participate in aberrant inflammatory conditions, including but not limited to autoimmune disease and allergy. To support this notion, there is a growing body of p110δ target validation

data derived from studies using both genetic tools and pharmacologic agents. Thus, using the delta-selective compound IC 87114 and the p110δ^{D910A} mice, Ali et al. (Nature, 431: 1007-1011 (2002)) have demonstrated that delta plays a critical role in a murine model of allergic disease. In the absence of functional delta, passive cutaneous anaphylaxis (PCA) is significantly reduced and can be attributed to a reduction in allergen-IgE induced mast cell activation and degranulation. In addition, inhibition of delta with IC 87114 has been shown to significantly ameliorate inflammation and disease in a murine model of asthma using ovalbumin-induced airway inflammation (Lee et al. FASEB, 20: 455-465 (2006). These data utilizing compound were corroborated in p110δ^{D910A} mutant mice using the same model of allergic airway inflammation by a different group (Nashed et al. Eur.J.Immunol. 37:416-424 (2007)).

There exists a need for further characterization of PI3Kδ function in inflammatory and auto-immune settings. Furthermore, our understanding of PI3Kδ requires further elaboration of the structural interactions of p110δ, both with its regulatory subunit and with other proteins in the cell. There also remains a need for more potent and selective or specific inhibitors of PI3K delta, in order to avoid potential toxicology associated with activity on isozymes p110 alpha (insulin signaling) and beta (platelet activation). In particular, selective or specific inhibitors of PI3Kδ are desirable for exploring the role of this isozyme further and for development of superior pharmaceuticals to modulate the activity of the isozyme.

Summary

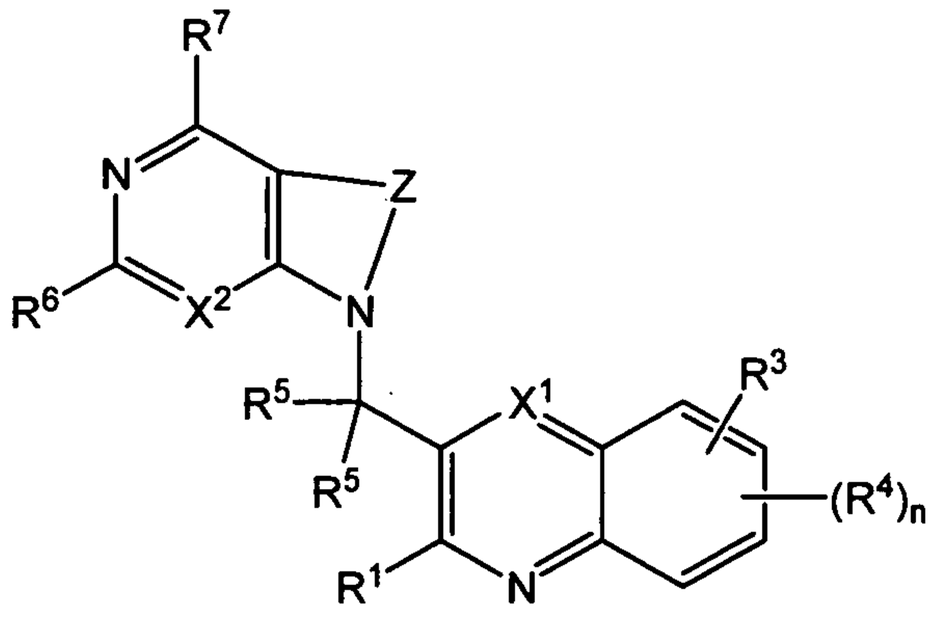
The present invention comprises a new class of compounds having the general formula



which are useful to inhibit the biological activity of human PI3Kδ. Another aspect of the invention is to provide compounds that inhibit PI3Kδ selectively while having relatively low inhibitory potency against the other PI3K isoforms. Another aspect of the invention is to provide methods of characterizing the function of human PI3Kδ. Another aspect of the invention is to provide methods of selectively modulating human PI3Kδ activity, and thereby promoting medical treatment of diseases mediated by PI3Kδ dysfunction. Other aspects and advantages of the invention will be readily apparent to the artisan having ordinary skill in the art.

Detailed Description

One aspect of the invention relates to compounds having the structure:



or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Z is $-CR^{11}=CR^{11}-$, $-CR^{11}=N-$, $-N=CR^{11}-$, $-CR^{11}=CR^{11}-C(=O)-$ and $-C(=O)-CR^{11}=CR^{11}-$;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, $-(C_{1-3}alkyl)$heteroaryl, $-(C_{1-3}alkyl)$heterocycle, $-O(C_{1-3}alkyl)$heteroaryl, $-O(C_{1-3}alkyl)$heterocycle, $-NR^a(C_{1-3}alkyl)$heteroaryl, $-NR^a(C_{1-3}alkyl)$heterocycle, $-(C_{1-3}alkyl)$phenyl, $-O(C_{1-3}alkyl)$phenyl and $-NR^a(C_{1-3}alkyl)$phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^6 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^7 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$,

$-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

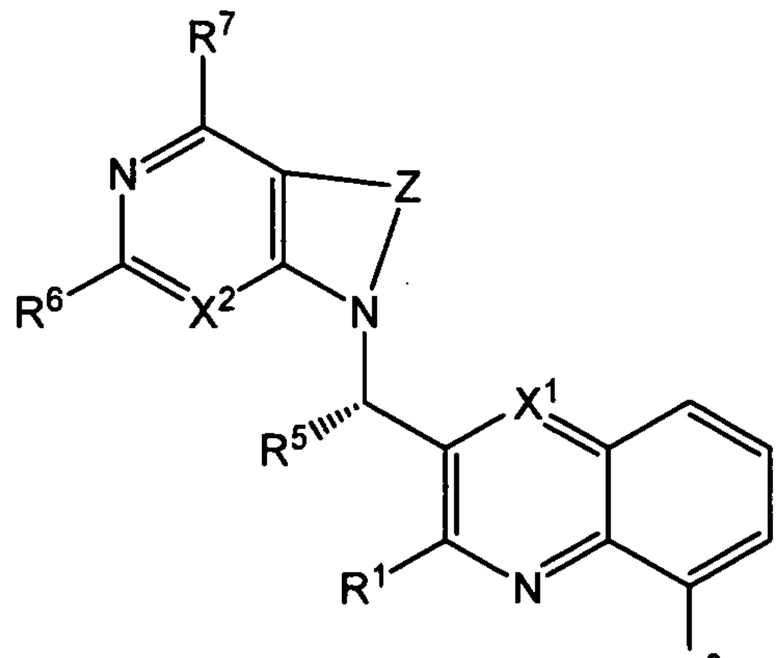
R^{11} is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^{11} is C_{1-9}alkyl or C_{1-4}alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$,

-$N(R^a)S(=O)_2NR^aR^a$, -NR^aC_{2-6}alkylNR^aR^a and -NR^aC_{2-6}alkylOR^a; and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or R^{11} is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, -$C(=O)R^a$, -$C(=O)OR^a$, -$C(=O)NR^aR^a$, -$C(=NR^a)NR^aR^a$, -OR^a, -$OC(=O)R^a$, -$OC(=O)NR^aR^a$, -$OC(=O)N(R^a)S(=O)_2R^a$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -$S(=O)R^a$, -$S(=O)_2R^a$, -$S(=O)_2NR^aR^a$, -$S(=O)_2N(R^a)C(=O)R^a$, -$S(=O)_2N(R^a)C(=O)OR^a$, -$S(=O)_2N(R^a)C(=O)NR^aR^a$, -$NR^aR^a$, -$N(R^a)C(=O)R^a$, -$N(R^a)C(=O)OR^a$, -$N(R^a)C(=O)NR^aR^a$, -$N(R^a)C(=NR^a)NR^aR^a$, -$N(R^a)S(=O)_2R^a$, -$N(R^a)S(=O)_2NR^aR^a$, -$NR^aC_{2-6}$alkyl$NR^aR^a$ and -NR^aC_{2-6}alkylOR^a;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6}alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3}haloalkyl, -OC_{1-4}alkyl, -NH_2, -NHC_{1-4}alkyl, -$N(C_{1-4}$alkyl$)C_{1-4}$alkyl.

Another aspect of the invention relates to compounds having the structure:



or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Z is $-CR^{11}=CR^{11}-$, $-CR^{11}=N-$, $-N=CR^{11}-$, $-CR^{11}=CR^{11}-C(=O)-$ and $-C(=O)-CR^{11}=CR^{11}-$;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, $-(C_{1-3}$alkyl)heteroaryl, $-(C_{1-3}$alkyl)heterocycle, $-O(C_{1-3}$alkyl)heteroaryl, $-O(C_{1-3}$alkyl)heterocycle, $-NR^a(C_{1-3}$alkyl)heteroaryl, $-NR^a(C_{1-3}$alkyl)heterocycle, $-(C_{1-3}$alkyl)phenyl, $-O(C_{1-3}$alkyl)phenyl and $-NR^a(C_{1-3}$alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl,

heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^6 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^7 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$,

$-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^{10} is H, $C_{1-3}alkyl$, $C_{1-3}haloalkyl$, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

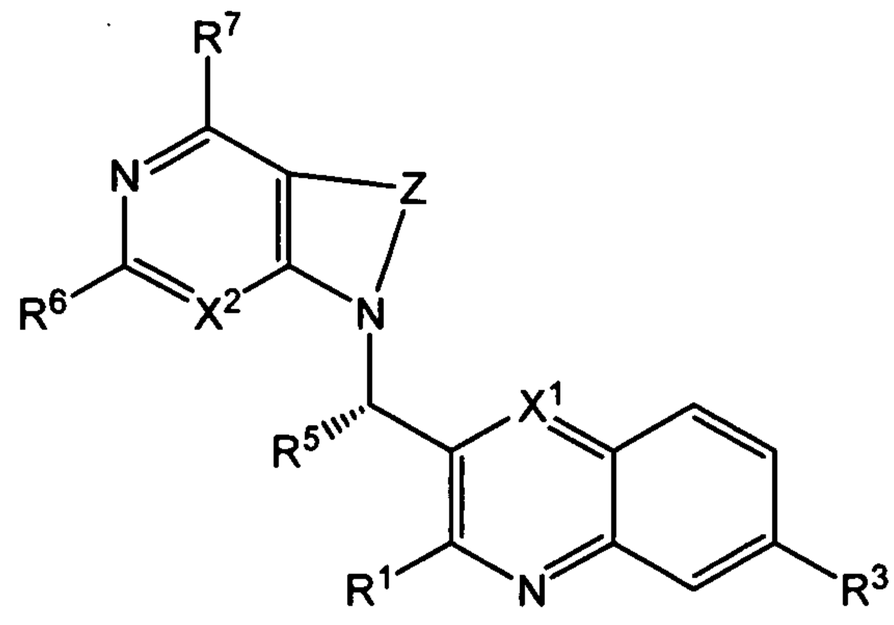
R^{11} is selected from H, halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^{11} is $C_{1-9}alkyl$ or $C_{1-4}alkyl(phenyl)$ wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$,

$-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or R^{11} is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or $C_{1-6}alkyl$, the phenyl, benzyl and $C_{1-6}alkyl$ being substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}alkyl$, $C_{1-3}haloalkyl$, $-OC_{1-4}alkyl$, $-NH_2$, $-NHC_{1-4}alkyl$, $-N(C_{1-4}alkyl)C_{1-4}alkyl$.

Another aspect of the invention relates to compounds having the structure:



or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Z is $-CR^{11}=CR^{11}-$, $-CR^{11}=N-$, $-N=CR^{11}-$, $-CR^{11}=CR^{11}-C(=O)-$ and $-C(=O)-CR^{11}=CR^{11}-$;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, $-(C_{1-3}alkyl)$heteroaryl, $-(C_{1-3}alkyl)$heterocycle, $-O(C_{1-3}alkyl)$heteroaryl, $-O(C_{1-3}alkyl)$heterocycle, $-NR^a(C_{1-3}alkyl)$heteroaryl, $-NR^a(C_{1-3}alkyl)$heterocycle, $-(C_{1-3}alkyl)$phenyl, $-O(C_{1-3}alkyl)$phenyl and $-NR^a(C_{1-3}alkyl)$phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl,

heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^6 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^7 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$,

$-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^{10} is H, $C_{1-3}alkyl$, $C_{1-3}haloalkyl$, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

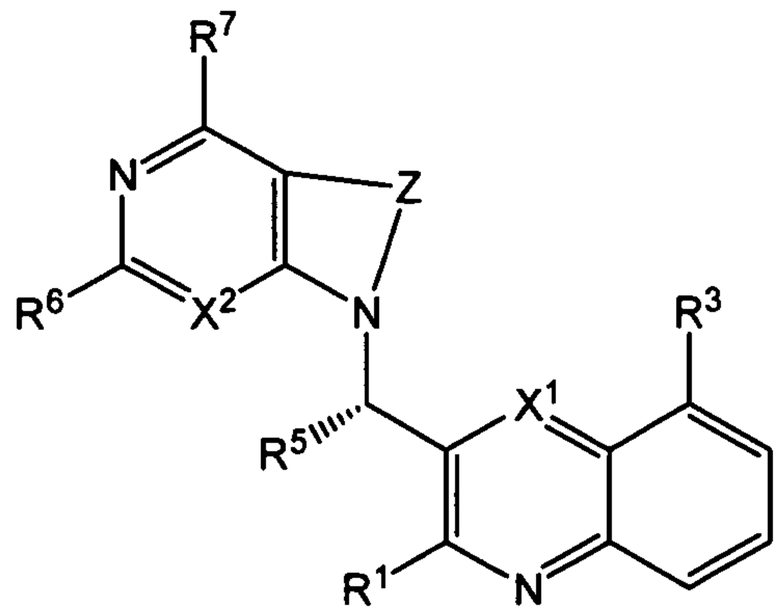
R^{11} is selected from H, halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^{11} is $C_{1-9}alkyl$ or $C_{1-4}alkyl(phenyl)$ wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$; $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$,

$-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or R^{11} is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or $C_{1-6}alkyl$, the phenyl, benzyl and $C_{1-6}alkyl$ being substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}alkyl$, $C_{1-3}haloalkyl$, $-OC_{1-4}alkyl$, $-NH_2$, $-NHC_{1-4}alkyl$, $-N(C_{1-4}alkyl)C_{1-4}alkyl$.

Another aspect of the invention relates to compounds having the structure:



or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Z is -CR^{11}=CR^{11}-, –CR^{11}=N-, –N=CR^{11}-, -CR^{11}=CR^{11}-C(=O)- and -C(=O)-CR^{11}=CR^{11}-;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^a, -OC(=O)NR^aR^a, -OC(=O)N(R^a)$S(=O)_2R^a$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^aR^a$, -$S(=O)_2N(R^a)C(=O)R^a$, -$S(=O)_2N(R^a)C(=O)OR^a$, -$S(=O)_2N(R^a)C(=O)NR^aR^a$, -$NR^aR^a$, -$N(R^a)C(=O)R^a$, -$N(R^a)C(=O)OR^a$, -$N(R^a)C(=O)NR^aR^a$, -$N(R^a)C(=NR^a)NR^aR^a$, -$N(R^a)S(=O)_2R^a$, -$N(R^a)S(=O)_2NR^aR^a$, -$NR^aC_{2-6}$alkyl$NR^aR^a$ and -NR^aC_{2-6}alkylOR^a; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle, -(C_{1-3}alkyl)heteroaryl, -(C_{1-3}alkyl)heterocycle, -O(C_{1-3}alkyl)heteroaryl, -O(C_{1-3}alkyl)heterocycle, -NR^a(C_{1-3}alkyl)heteroaryl, -NR^a(C_{1-3}alkyl)heterocycle, -(C_{1-3}alkyl)phenyl, -O(C_{1-3}alkyl)phenyl and -NR^a(C_{1-3}alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^a, -OC(=O)NR^aR^a, -OC(=O)N(R^a)$S(=O)_2R^a$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^aR^a$, -$S(=O)_2N(R^a)C(=O)R^a$, -$S(=O)_2N(R^a)C(=O)OR^a$, -$S(=O)_2N(R^a)C(=O)NR^aR^a$, -$NR^aR^a$, -$N(R^a)C(=O)R^a$, -$N(R^a)C(=O)OR^a$, -$N(R^a)C(=O)NR^aR^a$, -$N(R^a)C(=NR^a)NR^aR^a$, -$N(R^a)S(=O)_2R^a$, -$N(R^a)S(=O)_2NR^aR^a$, -$NR^aC_{2-6}$alkyl$NR^aR^a$, -$NR^aC_{2-6}$alkyl$OR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl,

heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^6 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^7 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$,

$-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^{10} is H, $C_{1-3}alkyl$, $C_{1-3}haloalkyl$, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

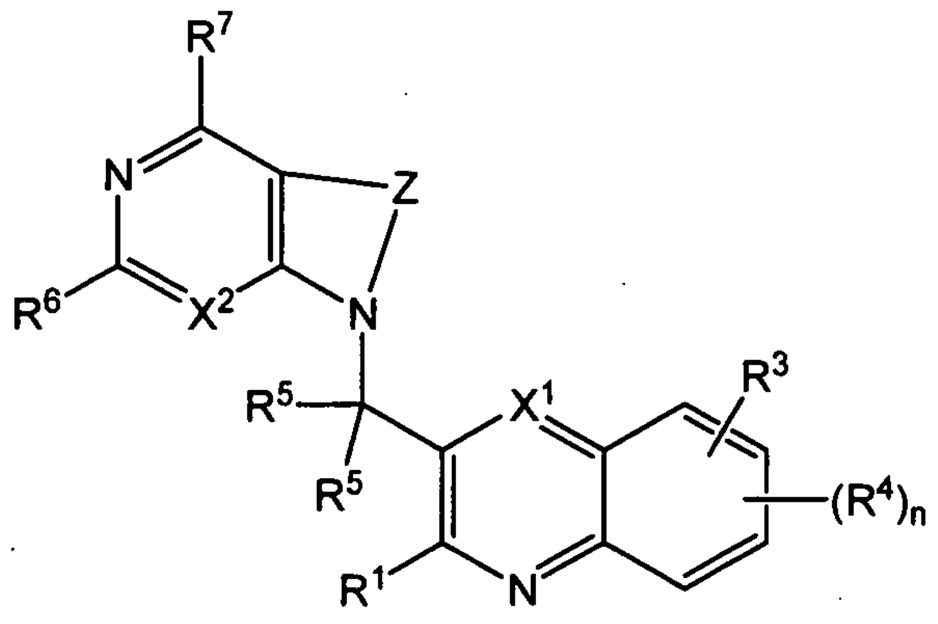
R^{11} is selected from H, halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^{11} is $C_{1-9}alkyl$ or $C_{1-4}alkyl(phenyl)$ wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$,

$-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or R^{11} is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, $C_{1-4}haloalkyl$, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or $C_{1-6}alkyl$, the phenyl, benzyl and $C_{1-6}alkyl$ being substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}alkyl$, $C_{1-3}haloalkyl$, $-OC_{1-4}alkyl$, $-NH_2$, $-NHC_{1-4}alkyl$, $-N(C_{1-4}alkyl)C_{1-4}alkyl$.

Another aspect of the invention relates to compounds having the structure:



or any pharmaceutically-acceptable salt or hydrate thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Z is $-CR^{11}=CR^{11}-$, $-CR^{11}=N-$, $-N=CR^{11}-$, $-CR^{11}=CR^{11}-C(=O)-$ and $-C(=O)-CR^{11}=CR^{11}-$;

n is 0, 1, 2 or 3;

R^1 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl;

R^6 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^7 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^8 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^8 is C_{1-9}alkyl or C_{1-4}alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or R^8 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N,

O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$,

$-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

R^{11} is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^{11} is C_{1-9}alkyl or C_{1-4}alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or R^{11} is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$,

$-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$;

R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6}alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3}haloalkyl, $-OC_{1-4}$alkyl, $-NH_2$, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)C_{1-4}$alkyl.

In another embodiment, in conjunction with any of the above or below embodiments, X^1 is $C(R^9)$ and X^2 is N.

In another embodiment, in conjunction with any of the above or below embodiments, X^1 is $C(R^9)$ and X^2 is $C(R^{10})$.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl substituted by 0 or 1 R^2 substituents, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is phenyl substituted by R^2, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is selected from 2-methylphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2-fluorophenyl and 2-methoxyphenyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the

available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is an unsaturated 5- or 6-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S.

In another embodiment, in conjunction with any of the above or below embodiments, R^1 is selected from pyridyl and pyrimidinyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^3 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$, $-NR^aC_{2-6}alkylOR^a$, C_{1-6}alkyl, phenyl,

benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^3 is H.

In another embodiment, in conjunction with any of the above or below embodiments, R^3 is selected from F, Cl, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl; or both R^5 groups together form a C_{3-6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^5 is H.

In another embodiment, in conjunction with any of the above or below embodiments, one R^5 is S-methyl, the other is H.

In another embodiment, in conjunction with any of the above or below embodiments, at least one R^5 is halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^6 is H.

In another embodiment, in conjunction with any of the above or below embodiments, R^6 is NR^bR^a.

In another embodiment, in conjunction with any of the above or below embodiments, R^6 is NH_2.

In another embodiment, in conjunction with any of the above or below embodiments, R^6 is NHC_{1-6}alkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^7 is selected from C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^7 is selected from C_{1-6}haloalkyl, Br, Cl, F, I and C_{1-6}alkyl.

In another embodiment, in conjunction with any of the above or below embodiments, R^7 is H.

In another embodiment, in conjunction with any of the above or below embodiments, R^8 is H.

In another embodiment, in conjunction with any of the above or below embodiments, R^8 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with any of the above or below embodiments, R^8 is C_{1-9}alkyl or C_{1-4}alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a; and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I.

In another embodiment, in conjunction with any of the above or below embodiments, R^8 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with any of the above or below embodiments, R^9 is H.

In another embodiment, in conjunction with any of the above or below embodiments, R^9 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with any of the above or below embodiments, R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a.

In another embodiment, in conjunction with any of the above or below embodiments, R^{10} is H.

In another embodiment, in conjunction with any of the above or below embodiments, R^{10} is cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$.

Another aspect of the invention relates to a method of treating PI3K-mediated conditions or disorders.

In certain embodiments, the PI3K-mediated condition or disorder is selected from rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases, and autoimmune diseases. In other embodiments, the PI3K- mediated condition or disorder is selected from cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease. In still other embodiments, the PI3K-mediated condition or disorder is selected from cancer, colon cancer, glioblastoma, endometrial carcinoma, hepatocellular cancer, lung cancer, melanoma, renal cell carcinoma, thyroid carcinoma, cell lymphoma,

lymphoproliferative disorders, small cell lung cancer, squamous cell lung carcinoma, glioma, breast cancer, prostate cancer, ovarian cancer, cervical cancer, and leukemia. In yet another embodiment, the PI3K- mediated condition or disorder is selected from type II diabetes. In still other embodiments, the PI3K-mediated condition or disorder is selected from respiratory diseases, bronchitis, asthma, and chronic obstructive pulmonary disease. In certain embodiments, the subject is a human.

Another aspect of the invention relates to the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases or autoimmune diseases comprising the step of administering a compound according to any of the above embodiments.

Another aspect of the invention relates to the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases and autoimmune diseases, inflammatory bowel disorders, inflammatory eye disorders, inflammatory or unstable bladder disorders, skin complaints with inflammatory components, chronic inflammatory conditions, autoimmune diseases, systemic lupus erythematosis (SLE), myestenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiples sclerosis, Sjoegren's syndrome and autoimmune hemolytic anemia, allergic conditions and hypersensitivity, comprising the step of administering a compound according to any of the above or below embodiments.

Another aspect of the invention relates to the treatment of cancers that are mediated, dependent on or associated with p110δ activity, comprising the step of administering a compound according to any of the above or below embodiments.

Another aspect of the invention relates to the treatment of cancers are selected from acute myeloid leukaemia, myelo-dysplastic syndrome, myelo-proliferative diseases, chronic myeloid leukaemia, T-cell acute lymphoblastic leukaemia, B-cell acute lymphoblastic leukaemia, non-hodgkins lymphoma, B-cell lymphoma, solid tumors and breast cancer, comprising the step of administering a compound according to any of the above or below embodiments.

Another aspect of the invention relates to a pharmaceutical composition comprising a compound according to any of the above embodiments and a pharmaceutically-acceptable diluent or carrier.

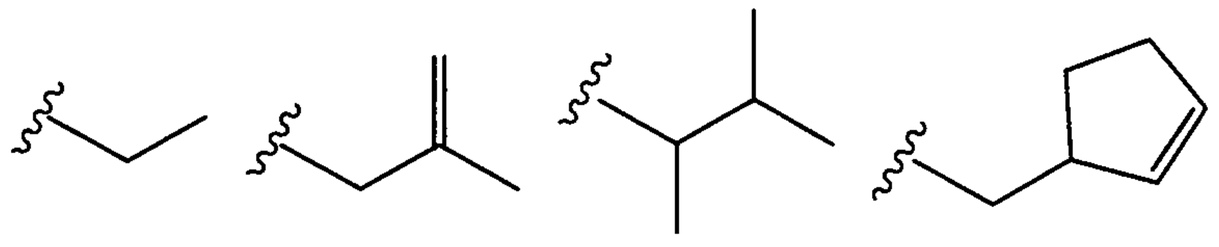
Another aspect of the invention relates to the use of a compound according to any of the above embodiments as a medicament.

Another aspect of the invention relates to the use of a compound according to any of the above embodiments in the manufacture of a medicament for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases, and autoimmune diseases.

The compounds of this invention may have in general several asymmetric centers and are typically depicted in the form of racemic mixtures. This invention is intended to encompass racemic mixtures, partially racemic mixtures and separate enantiomers and diasteromers.

Unless otherwise specified, the following definitions apply to terms found in the specification and claims:

"$C_{\alpha-\beta}$alkyl" means an alkyl group comprising a minimum of α and a maximum of β carbon atoms in a branched, cyclical or linear relationship or any combination of the three, wherein α and β represent integers. The alkyl groups described in this section may also contain one or two double or triple bonds. Examples of C_{1-6}alkyl include, but are not limited to the following:



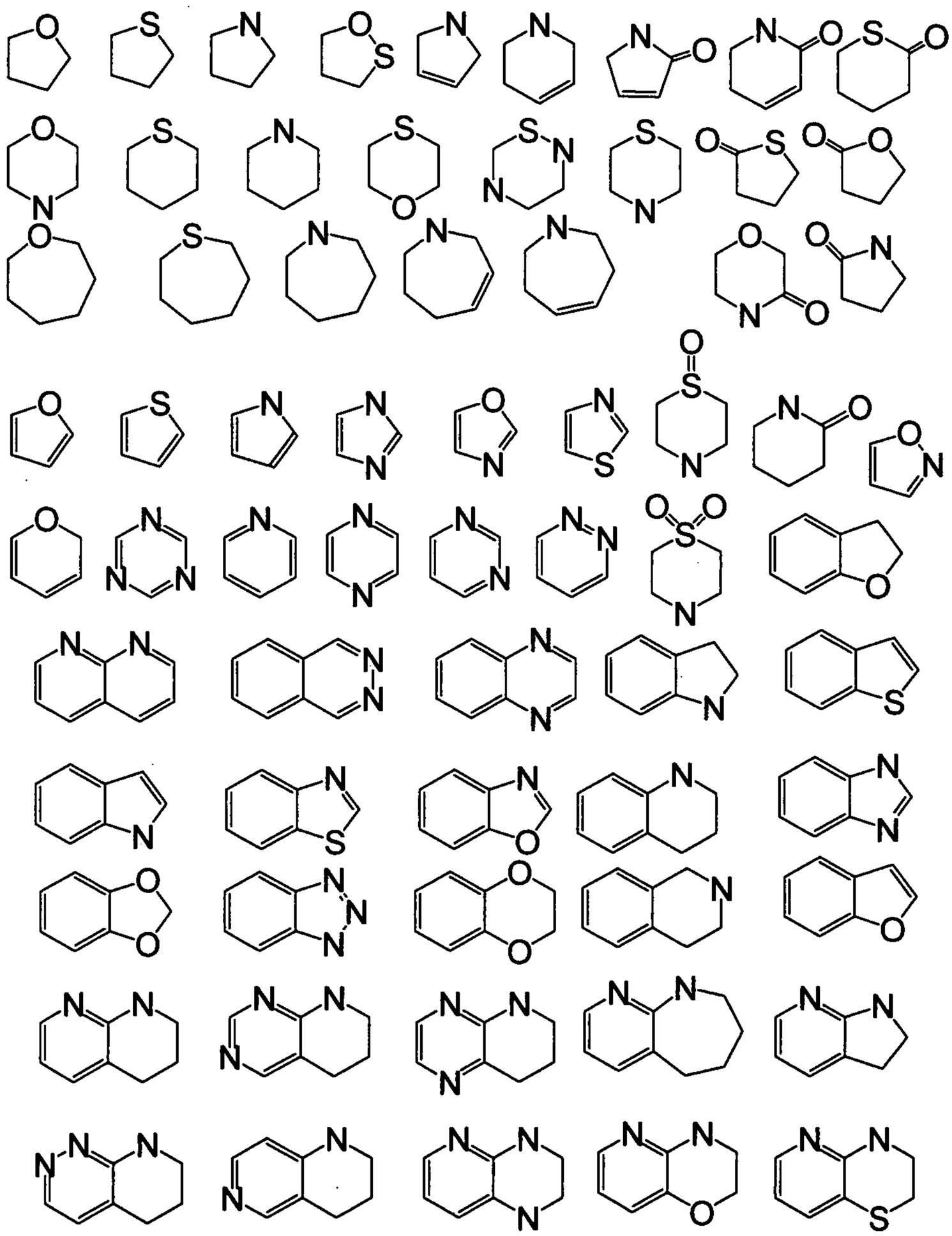
"Benzo group", alone or in combination, means the divalent radical C_4H_4=, one representation of which is -CH=CH-CH=CH-, that when vicinally attached to another ring forms a benzene-like ring--for example tetrahydronaphthylene, indole and the like.

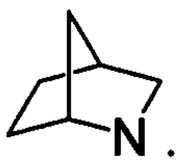
The terms "oxo" and "thioxo" represent the groups =O (as in carbonyl) and =S (as in thiocarbonyl), respectively.

"Halo" or "halogen" means a halogen atoms selected from F, Cl, Br and I.

"C_{v-w}haloalkyl" means an alkyl group, as described above, wherein any number--at least one--of the hydrogen atoms attached to the alkyl chain are replaced by F, Cl, Br or I.

"Heterocycle" means a ring comprising at least one carbon atom and at least one other atom selected from N, O and S. Examples of heterocycles that may be found in the claims include, but are not limited to, the following:



and .

"Available nitrogen atoms" are those nitrogen atoms that are part of a heterocycle and are joined by two single bonds (e.g. piperidine), leaving an external bond available for substitution by, for example, H or CH_3.

"Pharmaceutically-acceptable salt" means a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmacologically acceptable salts" include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," *see infra* and Berge et al., J. Pharm. Sci. 66:1 (1977).

"Saturated, partially saturated or unsaturated" includes substituents saturated with hydrogens, substituents completely unsaturated with hydrogens and substituents partially saturated with hydrogens.

"Leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

"Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include, but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl alkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho-

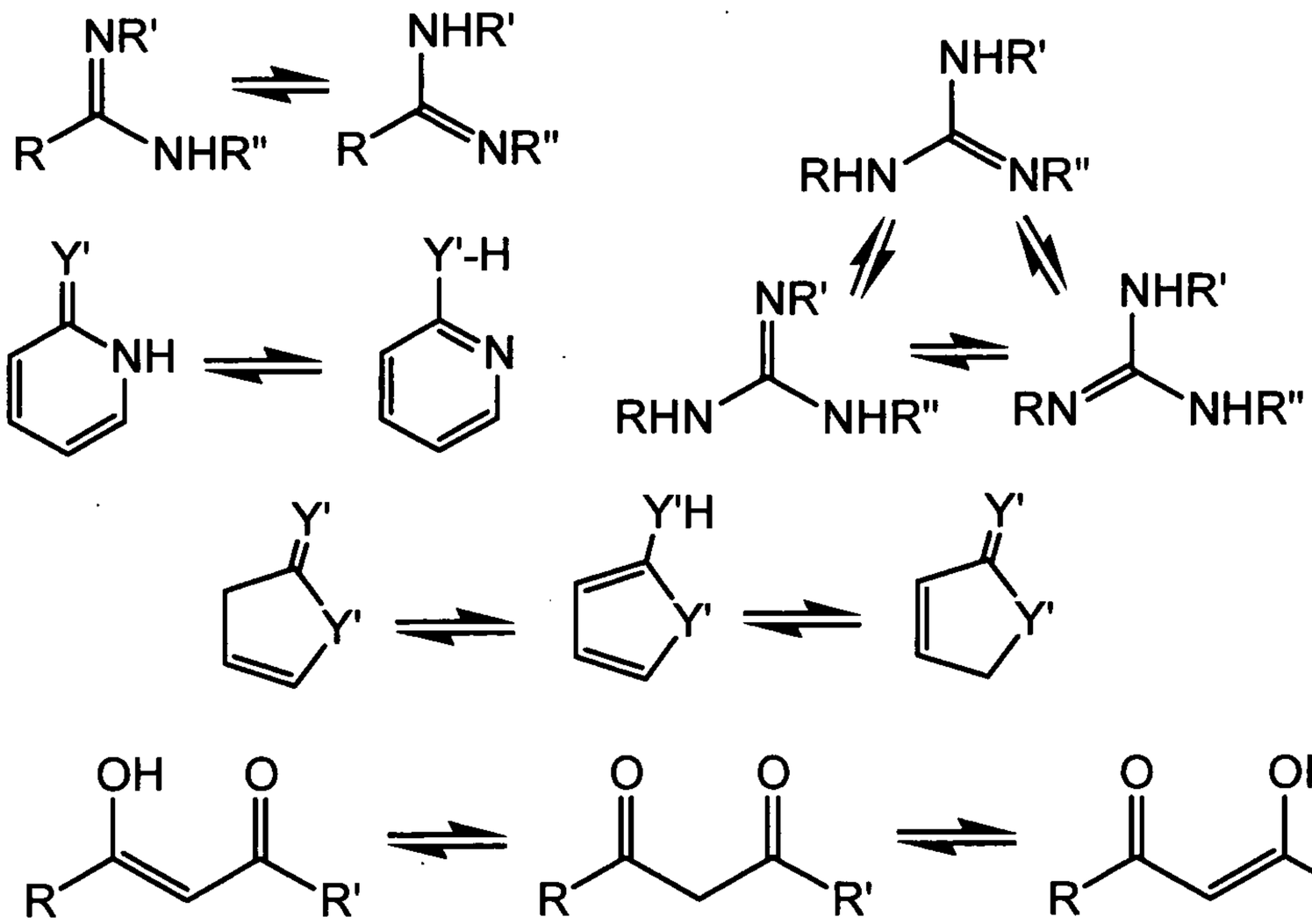
methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkylenylalkyl radicals, preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxycarbonyl and aralkoxycarbonyl groups include benzyloxycarbonyl, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, trifluoroacetyl, trichloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxycarbonyl group. Amino protecting groups can also form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many of the amino protecting groups are also suitable for protecting carboxy, hydroxy and mercapto groups. For example, aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-butyl.

Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of an amino groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-trisilyl derivative. Removal of the silyl function from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group. Suitable

silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethyl silyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzyloxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can readily be neutralized to yield the free amine. Carboxy protecting group, such as methyl, ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed under hydrolysis and hydrogenolysis conditions well known to those skilled in the art.

It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as cyclic and acyclic amidine and guanidine groups, heteroatom substituted heteroaryl groups (Y' = O, S, NR), and the like, which are illustrated in the following examples:



and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bungaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and

Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

The specification and claims contain listing of species using the language "selected from . . . and . . ." and "is . . . or . . ." (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is meant to include the group as a whole, or any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and is not meant in any way to limit the removal of individual elements or subgroups as needed.

Experimental

The following abbreviations are used:

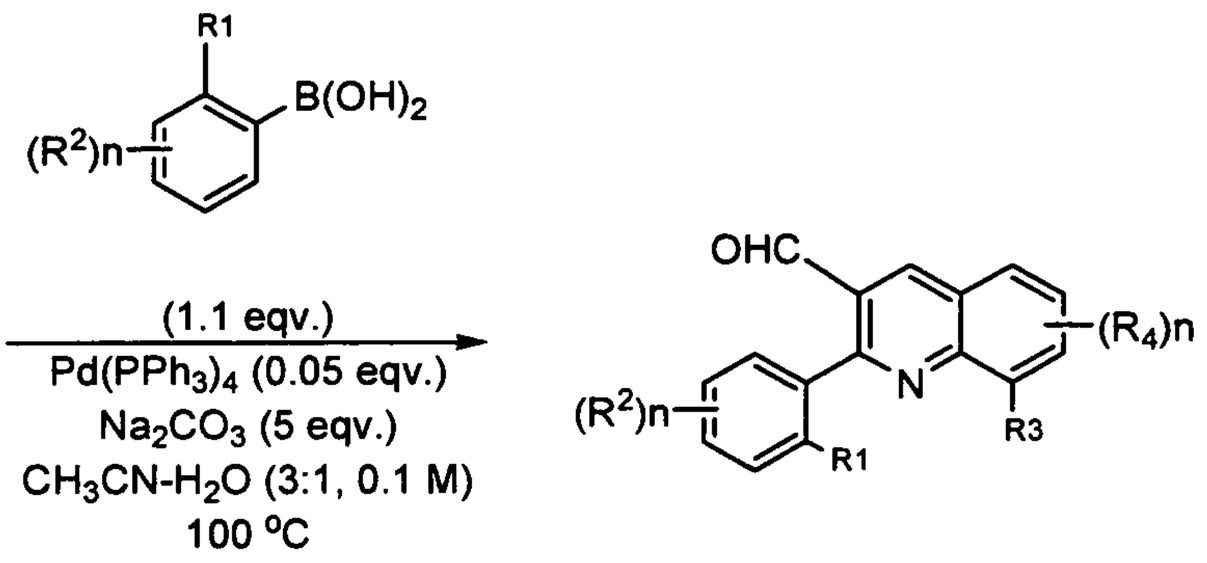
aq. - aqueous
BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
cond - concentrated
DCM dichloromethane
DMF - *N,N*-dimethylformamide
Et_2O - diethyl ether
EtOAc - ethyl acetate
EtOH - ethyl alcohol
h - hour(s)
min - minutes
MeOH - methyl alcohol
rt room temperature
satd - saturated
THF – tetrahydrofuran

General

Reagents and solvents used below can be obtained from commercial sources. ^{1}H-NMR spectra were recorded on a Bruker 400 MHz and 500 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet) , coupling constant(s) in Hertz (Hz) and number of protons. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Agilent 1100 series LC/MSD electrospray mass spectrometer. All compounds could be analyzed in the positive ESI mode using acetonitrile:water with 0.1% formic acid as the delivery solvent. Reverse phase analytical HPLC was carried out using a Agilent 1200 series on Agilent Eclipse XDB-C18 5μm column (4.6 x 150 mm) as the stationary phase and eluting with acetonitrile:H_2O with 0.1% TFA. Reverse phase Semi-Prep HPLC was carried out using a Agilent 1100 Series on a Phenomenex Gemini^{TM} 10μm C18 column

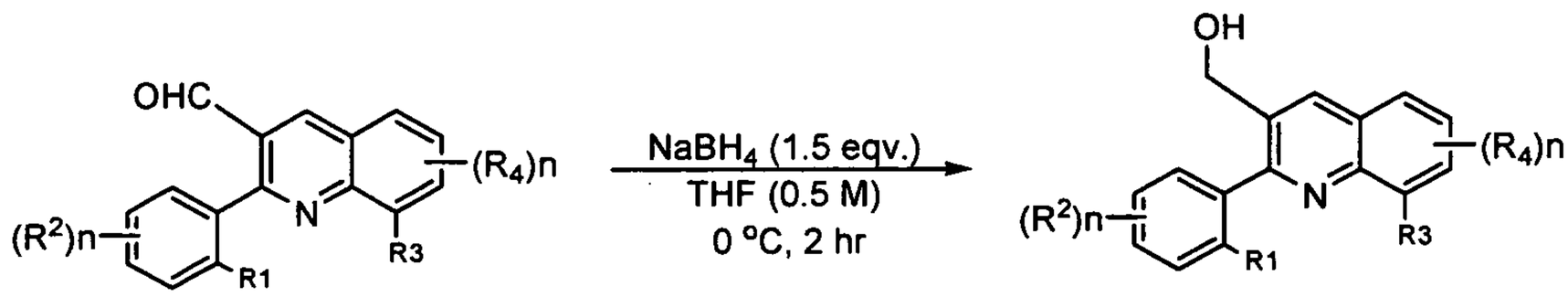
(250 x 21.20 mm) as the stationary phase and eluting with acetonitrile:H_2O with 0.1% TFA.

Procedure A



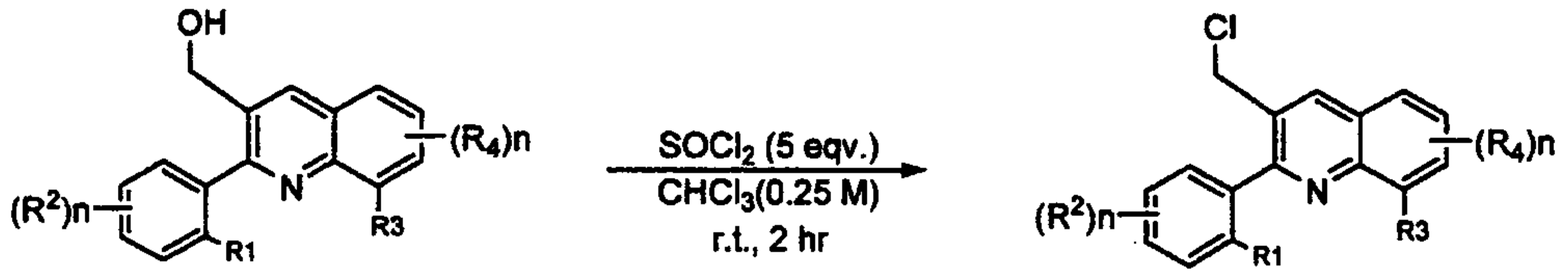
A mixture of 2-chloro-quinoline-3-carbaldehyde (1 eq), arylboronic acid (1.1 eq), tetrakis(triphenylphosphine)palladium (5 mol %), and sodium carbonate (2M aq. Sol., 5.0 eq) in CH_3CN-water (3:1, 0.1 M) was heated at 100 °C under N_2 for several hours. The mixture was partitioned between EtOAc and H_2O, the organic layer was separated, and the aqueous layer was extracted with EtOAc . The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by column chromatography on silica gel using 0% to 25% gradient of EtOAc in hexane to provide 2-arylquinoline-3-carbaldehydes.

Procedure B



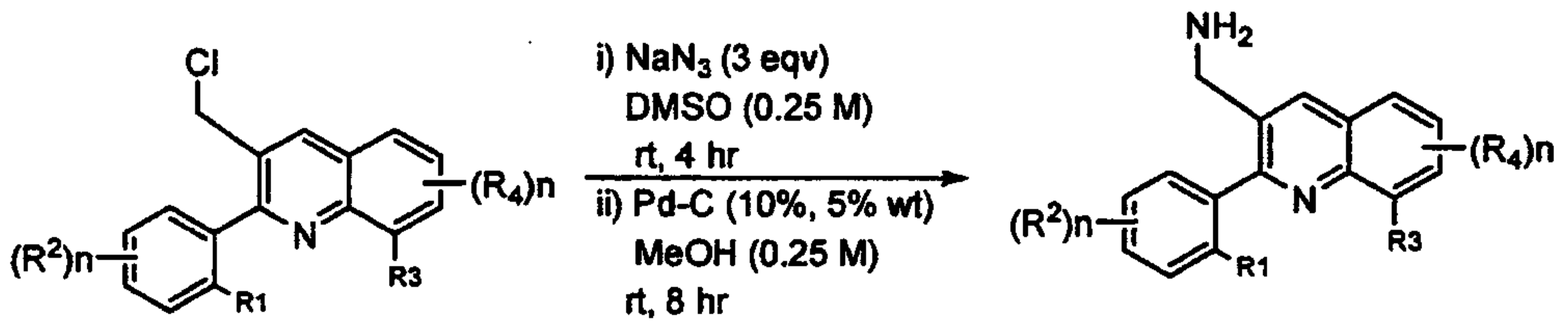
Solid sodium borohydride (1.5 eq) was added to a solution of 2-arylquinoline-3-carbaldehyde (1 eq) in THF (0.5M) at 0 °C and the mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc (3 times). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 50% of EtOAc in hexane to provide (2-arylquinolin-3-yl)methanols.

Procedure C



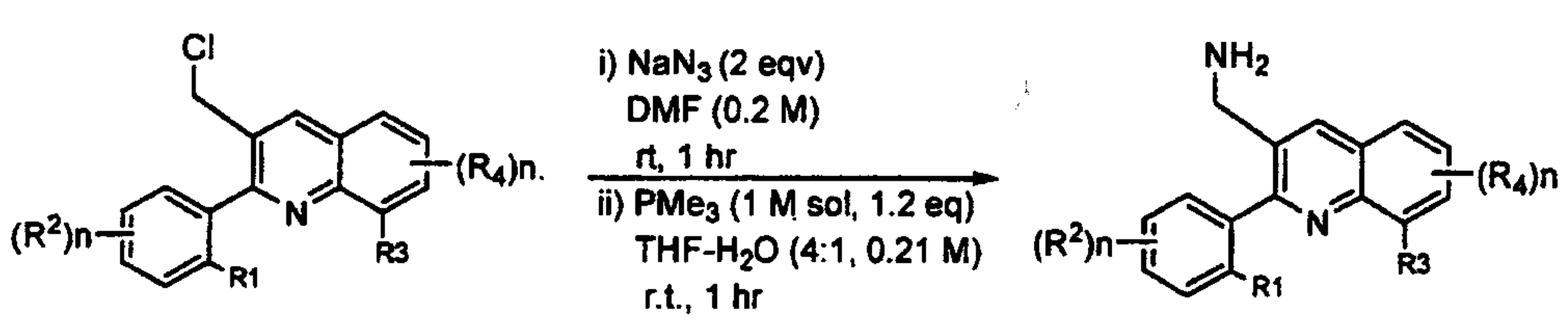
(2-Arylquinolin-3-yl)methanol (1 eq) in $CHCl_3$ (0.25M) was treated with $SOCl_2$ (5 eq) at rt for 2 h. Solvents were removed under reduced pressure and the residue was partitioned between EtOAc and saturated aq. $NaHCO_3$ solution. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on a Redi-Sep™ column using 0 to 100% gradient of EtOAc in hexane to provide 3-(chloromethyl)-2-arylquinolines.

Procedure D



To a solution of 3-(chloromethyl)-2-arylquinoline (1 eq) in DMSO (0.25 M) was added NaN_3 (3 eq) at rt and the mixture was stirred for 4 h at rt. The mixture was diluted with water, extracted with EtOAc (2 times) and the combined organic layers were washed with water (2 times), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH and treated with 10% Pd-C (5 wt %) and the mixture was then stirred under H_2 balloon over night. The mixture was filtered through a celite™ pad followed by removal of solvents to give (2-arylquinolin-3-yl)methanamines.

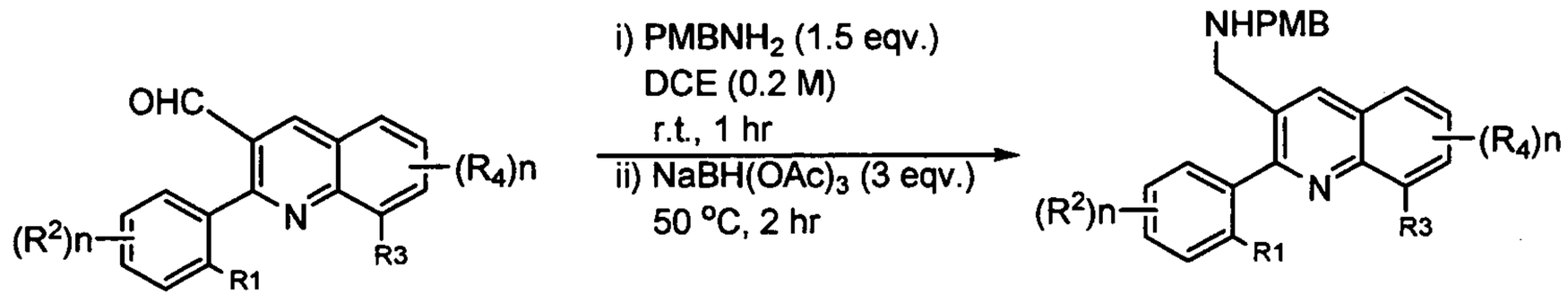
Procedure E



To a stirring solution of 3-(chloromethyl)-2-arylquinoline (1 eq) in 16 mL of DMF was added NaN_3 (2 eq) at rt. The mixture was stirred at rt for 1 h. The

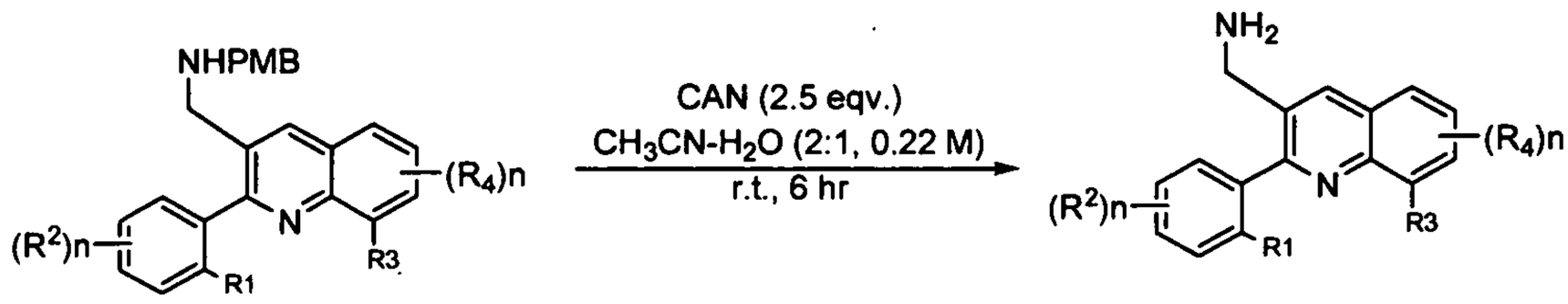
mixture was partitioned between EtOAc and H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide 3-(azidomethyl)-2-arylquinolines. The crude product was carried on without purification for the next step. To a stirring solution of 3-(azidomethyl)-2-arylquinoline in THF-H_2O (4:1, 0.21 M) was added dropwise PMe_3 (1.0 M solution in THF, 1.2 eq) at rt and the mixture was stirred at rt for 1 h. To the mixture was added EtOAc and the mixture was extracted with 1N HCl (2 times). The combined extracts were neutralized with solid sodium bicarbonate, and extracted with EtOAc (2 times). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give dark syrup. The crude product was purified by column chromatography on a Redi-Sep™ column using 0 to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 as eluent to provide (2-arylquinolin-3-yl)methanamines.

Procedure F



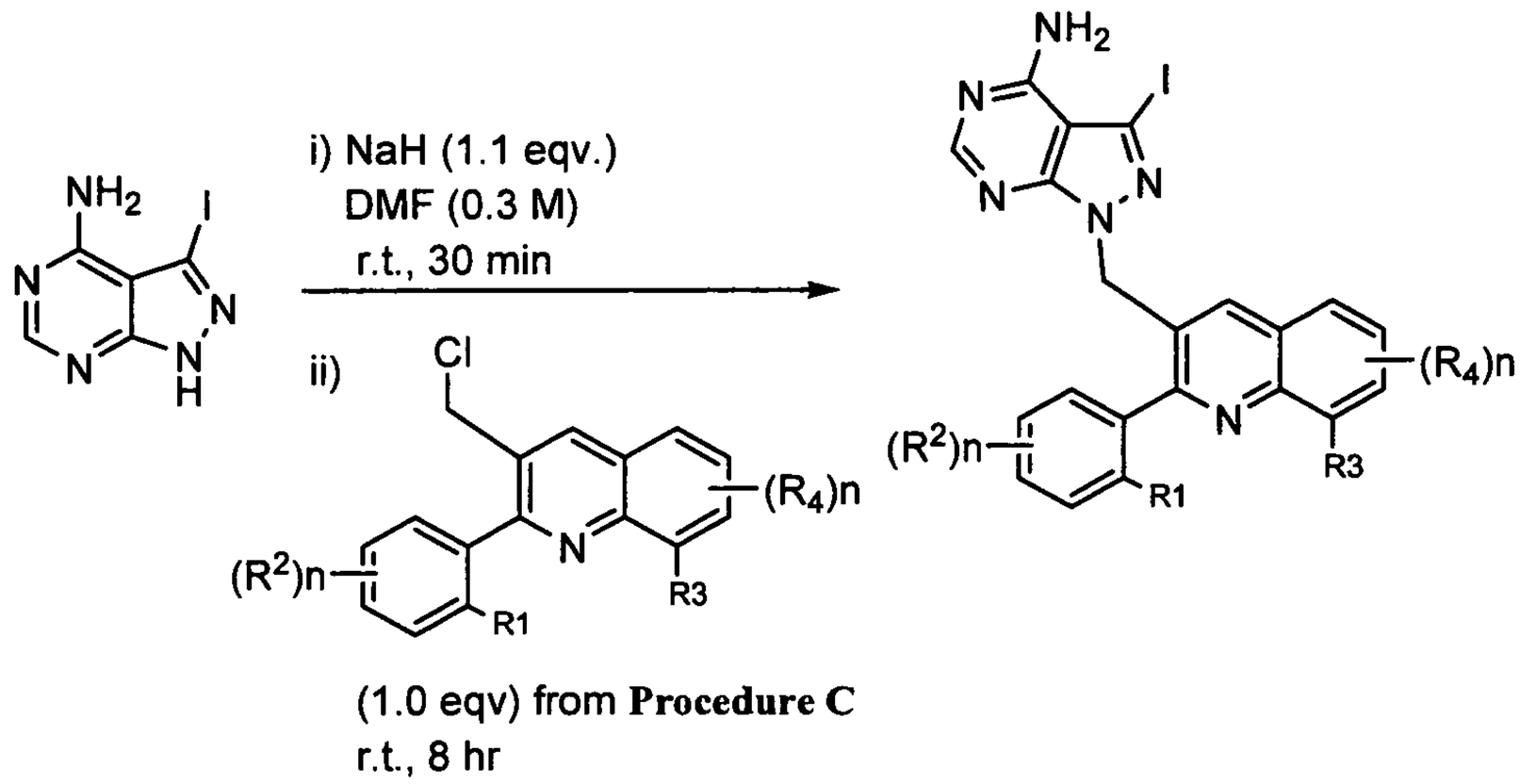
A mixture of 2-arylquinoline-3-carbaldehyde (1 eq), DCE (0.2 M), and $PMBNH_2$ (1.5 eq) was stirred at rt. After 1 h, to the mixture was added $NaBH(OAc)_3$ (3 eq) and the mixture was stirred at 50 °C for 2 h. To the mixture was added saturated aq. $NaHCO_3$ and the mixture was stirred for 15 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 times). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on a Redi-Sep™ column using 0 to 100% gradient of EtOAc in hexane to provide N-(4-methoxybenzyl)(2-arylquinolin-3-yl)methanamines.

Procedures G



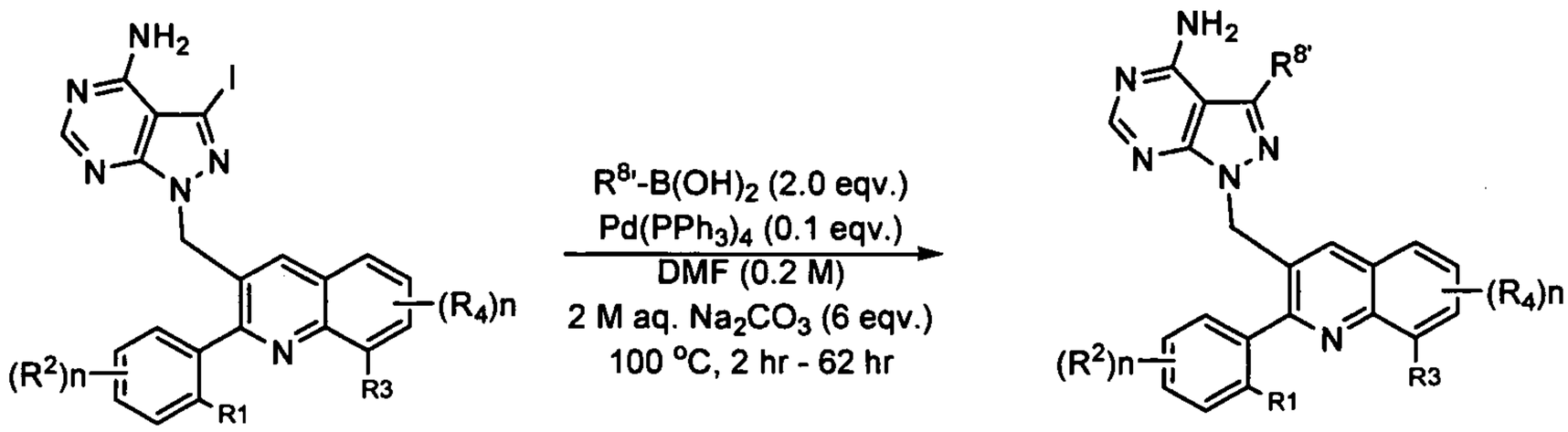
A mixture of N-(4-methoxybenzyl)(2-arylquinolin-3-yl)methanamine (1 eq) and ammonium cerium(iv) nitrate (3.5 eq) in CH_3CN-H_2O (2:1, 0.22M) was stirred at rt for 24 h. To the mixture wad added 0.5M HCl (12 eq) and the mixture was washed with CH_2Cl_2 (3 times) to remove 4-methoxybenzaldehyde produced. The organic fraction was then extracted with 0.5M HCl (2 times). The combined acidic aqueous layer was basified to pH 9.0 with 2N HaOH. The resulting precipitate was collected by filtration. The crude product was purified by column chromatography on a Redi-Sep™ column using 0 to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 as eluent to provide provide (2-arylquinolin-3-yl)methanamines.

Procedure I



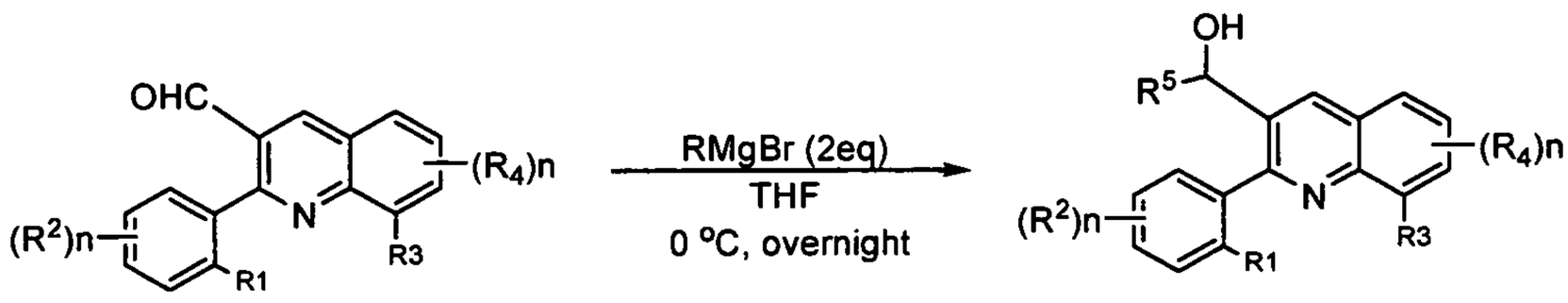
A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1 eq) in DMF (0.3M) at 0 °C was treated with NaH (60%, 2.2 eq) for 30 min before addition of a solution of 3-(chloromethyl)-2-arylquinolines (1 eq) in DMF (0.5M). The mixture was stirred at room temperature overnight. The mixture was poured onto ice-water. The resulting precipitate was collected by suction filtration, washed with water, and air-dried. The crude product was purified by column chromatography on a Redi-Sep™ column using 0 to 100% gradient of EtOAc in hexane and then 100% isocratic of EtOAc as eluent to provide 3-iodo-1-((2-arylquinolin-3-yl)-methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amines.

Procedure J



A mixture of 3-iodo-1-((2-arylquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1 eq), boronic acid (2.0 eq), tetrakis(triphenylphosphine)-palladium (10 mol %), and sodium carbonate (2M aq. Sol., 6 eq) in DMF (0.2M) was heated at 100 °C under N_2 for several hours. To the mixture was added water. The resulting precipitate was collected by suction filtration, washed with water, and air-dried. The crude product was purified by column chromatography on a Redi-Sep™ column using using 0 to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 14 min as eluent to provide 3-substituted-1-((2-phenylquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amines.

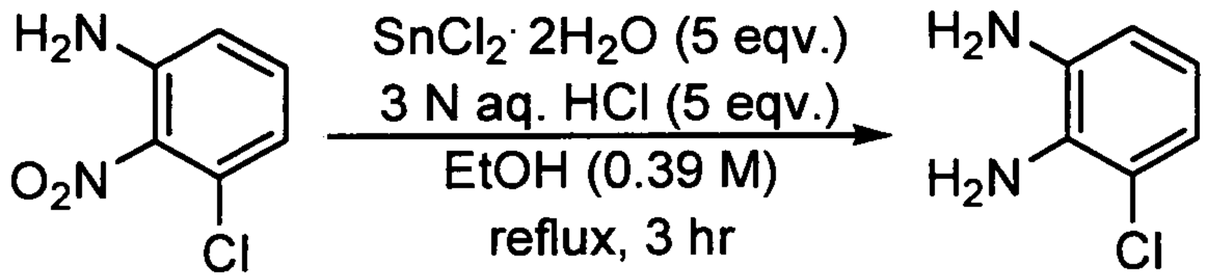
Procedure K



To a mixture of 2-phenylquinoline-3-carbaldehyde (1.0eq) in THF (0.28M) at 0 °C was added dropwise a solution of a Grignard reagent (3 M, 2eq) and the reaction was stirred overnight before being quenched with NH_4Cl saturated solution. The mixture was extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: EtOAc/hexane, 1/1) to provide1-(2-phenylquinolin-3-yl)alcohols.

Procedure L: Preparation of N-((5-Chloro-3-(2-chlorophenyl)quinoxalin-2-yl)methyl)-9H-purin-6-amine

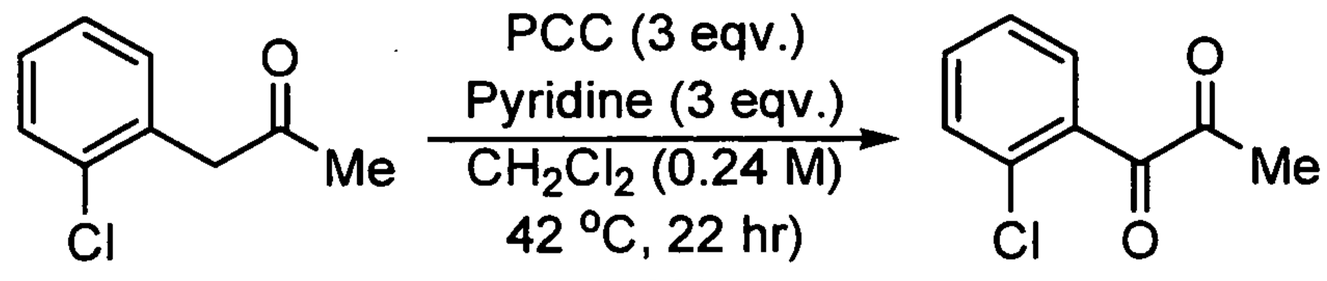
3-Chlorobenzene-1,2-diamine



79.09%

To s aolution of 3-chloro-2-nitroaniline (10.00 g, 57.95 mmol), 3 N aq. HCl (96.58 mL, 289.7 mmol), and ethyl alcohol (148.6 mL, 57.95 mmol) was added Tin(II) chloride dihydrate (65.96 g, 289.7 mmol) and the mixture was heated under reflux with stirring. After 3 h, the mixture was cooled to room temperature and concentrated under reduced pressure to give a brown syrup. The mixture was cautiously treated with an excess of 10 M KOH (115.9 mL, 1159 mmol, 20 eqv.). The mixture was diluted with EtOAc (200 mL), filtered through Celite™ pad, and washed the pad well with EtOAc (100 mL x 2). The filtrate was extracted with EtOAc (100 mL x 2). The combined organic layers were washed with water (100 mL x1), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 3-chlorobenzene-1,2-diamine as a red oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.43 - 6.53 (2 H, m), 6.38 (1 H, t, J=7.8 Hz), 4.80 (2 H, s), 4.60 (2 H, s); LC-MS (ESI) m/z 142.9 $[M+H]^+$. The crude product was carried on crude without purification for the next step.

1-(2-Chlorophenyl)propane-1,2-dione

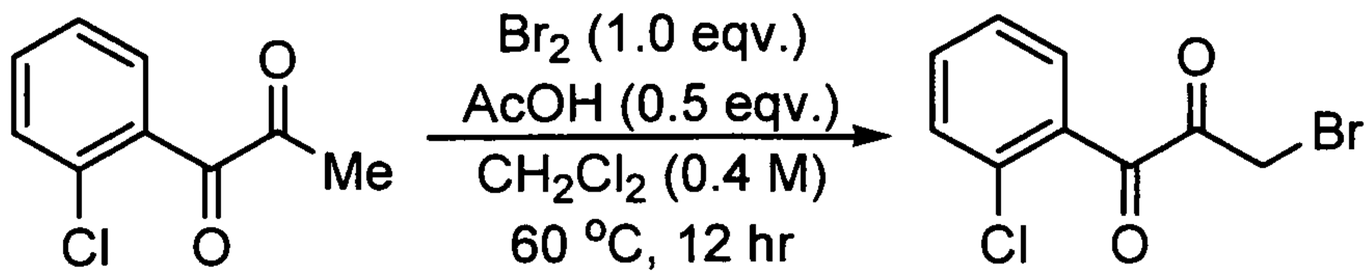


7.8%

To a solution of 2-chlorophenylacetone (10.800 g, 64.049 mmol) in 279 mL of CH_2Cl_2, pyridinium chlorochromate (41.418 g, 192.15 mmol), and pyidine (16 mL) in three portions were added over 2.5 hours and the mixture was refluxed under vigorous stirring. After 22 h, he mixture was removed from heat. The mixture was concentrated in vacuo to give a dark red syrup. The crude mixture

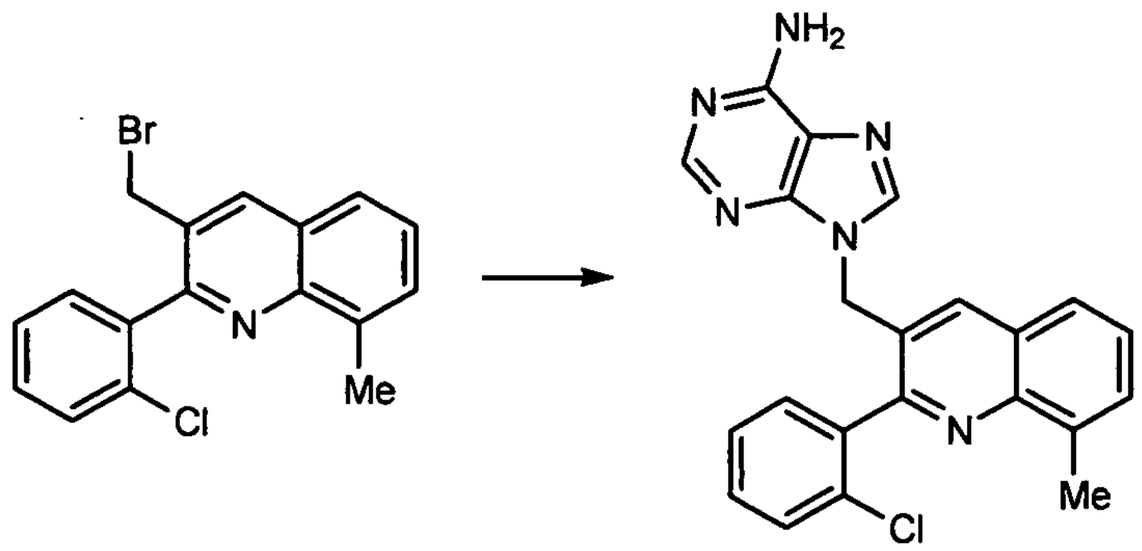
was purified by column chromatography on a 120 g of Redi-Sep™ column using 0-10% gradient of EtOAc in hexane over 28 min as eluent to give 1-(2-chlorophenyl)propane-1,2-dione as yellow liquid: ^{1}H NMR (400 MHz, choroform-d) δ ppm 7.66 (1 H, dd, J=7.6, 1.8 Hz), 7.49 - 7.54 (1 H, m), 7.38 - 7.45 (2 H, m), 2.58 (3 H, s); LC-MS: m/z 182.9 $[M+H]^+$.

3-Bromo-1-(2-chlorophenyl)propane-1,2-dione



A mixture of 1-(2-chlorophenyl)propane-1,2-dione (4.2379 g, 23.208 mmol), bromine (1.1891 mL, 23.208 mmol), and glacial acetic acid (0.67005 mL, 11.604 mmol) in chloroform (58.020 mL, 23.208 mmol) was heated at 60 °C. After 17 h of stirring at 60 °C, the mixture was removed from heat and concentrated under reduced pressure to give 3-bromo-1-(2-chlorophenyl)propane-1,2-dione as an orange liquid: LC-MS: a peak of m/z 261.0 $[M+H(^{79}Br)]^+$ and 262.9 $[M+H\ (^{81}Br)-]^+$. The orange liquid was carried on crude without purification for the next step.

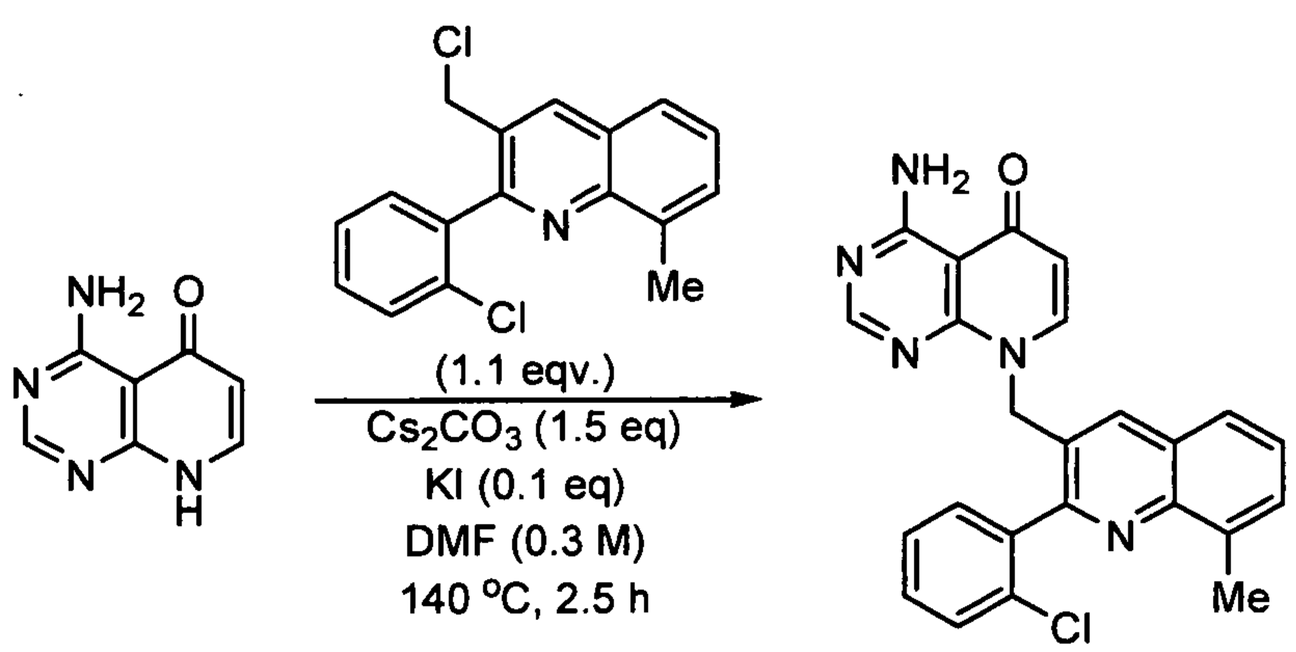
Example 1: 9-((2-(2-Chlorophenyl)-8-methylquinolin-3-yl)methyl)-9H-purin-6-amine



9-((2-(2-Chlorophenyl)-8-methylquinolin-3-yl)methyl)-9H-purin-6-amine. A mixture of 3-(bromomethyl)-2-(2-chlorophenyl)-8-methylquinoline (66 mg, 0.19 mmol), {prepared in a similar way as 3-(bromomethyl)-8-methyl-2-o-tolyl-quinoline, example 9} adenine (39 mg, 0.29 mmol), and cesium carbonate (124 mg, 0.38 mmol) in DMF (0.7 mL) was stirred at rt for 2 h. The crude mixture was evaporated onto silica gel and purified by flash chromatography (Biotage Si

25+M) eluting with MeOH/CH_2Cl_2 (5% to 10%). The resulting white solid was further purified by HPLC (Berger SFC) eluting with i-PrOH/CO_2/DEA to provide a white solid [PI3Kδ IC_{50} = 2130nM]. MS (ESI+) m/z = 401.1 (M+1).

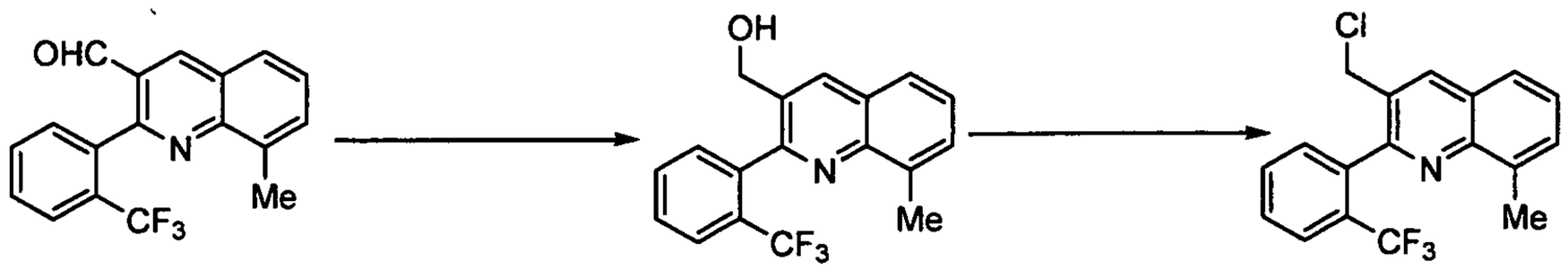
Example 2: Preparation of 4-Amino-8-((2-(2-chlorophenyl)-8-methyl-quinolin-3-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one



To a mixture of 4-aminopyrido[2,3-d]pyrimidin-5(8H)-one (0.1 g, 0.616 mmol), Cs_2CO_3 (0.3013 g, 0.925 mmol, 1.5 eq), and KI (0.0102 g, 0.0616 mmol, 0.1 eq) in DMF (2 mL) was added 3-(chloromethyl)-2-(2-chlorophenyl)-8-methyl-quinoline (0.2049 g, 0.678 mmol, 1.1 eq) and the mixture was stirred at 140 °C for 2.5 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on a 40 g of Redi-Sep™ column using 0 to 100% gradient of EtOAc in hexane over 14 min and then 100% isocratic of EtOAc for 10 min as eluent to provide 4-amino-8-((2-(2-chlorophenyl)-8-methyl-quinolin-3-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one as white solid. The white solid was triturated with EtOAc-Hexane (1:1) and filtered to provide 4-amino-8-((2-(2-chlorophenyl)-8-methylquinolin-3-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one [PI3Kδ IC_{50} = 58nM] as white solid. ^1H NMR (DMSO-d_6) δ ppm 9.53 (1 H, d, J=4.7 Hz), 8.13 (1 H, s), 8.04 - 8.11 (2 H, m), 7.84 (1 H, d, J=7.8 Hz), 7.78 (1 H, d, J=7.8 Hz), 7.64 (1 H, d, J=7.0 Hz), 7.38 - 7.59 (5 H, m), 6.12 (1 H, d, J=7.8 Hz), 5.40 (2 H, d, J=6.3 Hz), 2.64 (3 H, s). Mass Spectrum (ESI) m/e = 428.0 (M + 1).

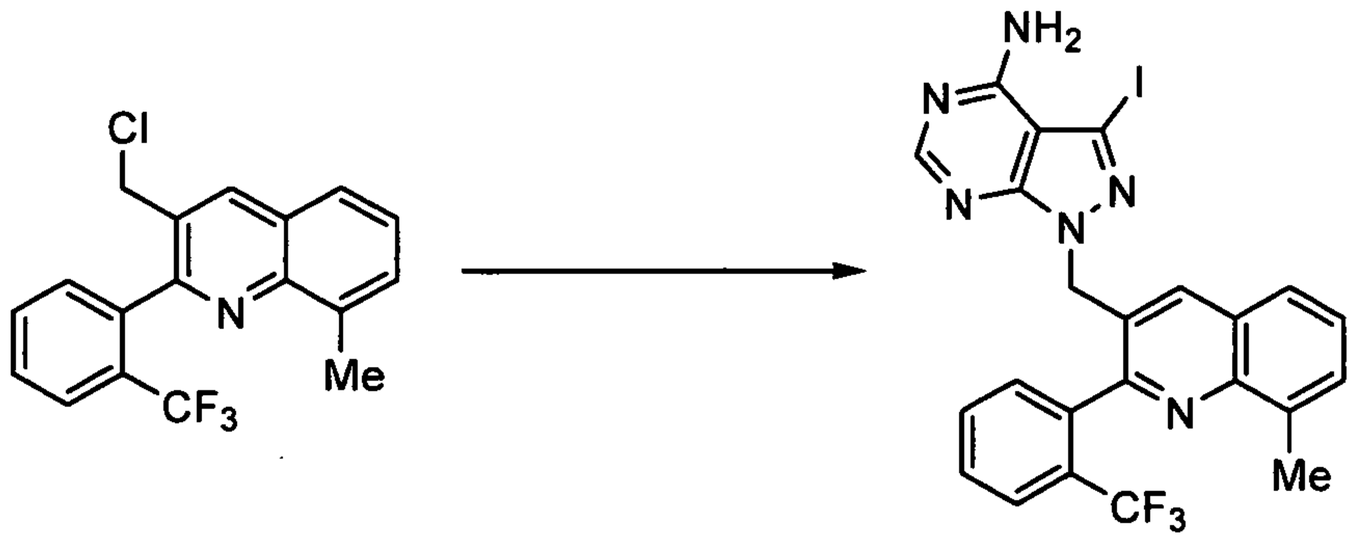
Example 3: 3-Iodo-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)-methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine:

3-(Chloromethyl)-8-methyl-2-(2-(trifluoromethyl)phenyl)quinoline



Prepared according to Procedure B using 8-methyl-2-(2-(trifluoromethyl)phenyl)-quinoline-3-carbaldehyde (1.6541 g, 5.25 mmol) and solid $NaBH_4$ (0.2977 g, 7.87 mmol, 1.5 eq) in THF (26 mL) followed by Procedure C using the crude (8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methanol and $SOCl_2$ (1.9 mL, 26.23 mmol, 5 eq) in $CHCl_3$ (26 mL). After purification, 3-(chloromethyl)-8-methyl-2-(2-(trifluoromethyl)phenyl)quinoline was obtained as as yellow syrup. ^1H NMR (DMSO-d_6) δ ppm 8.60 (1 H, s), 7.92 (2 H, dd, J=11.5, 8.0 Hz), 7.72 - 7.85 (2 H, m), 7.67 (2 H, dd, J=14.3, 7.2 Hz), 7.54 - 7.62 (1 H, m), 4.71 (2 H, dd, J=89.8, 11.9 Hz), 2.62 (3 H, s). Mass Spectrum (ESI) m/e = 336.1 (M + 1).

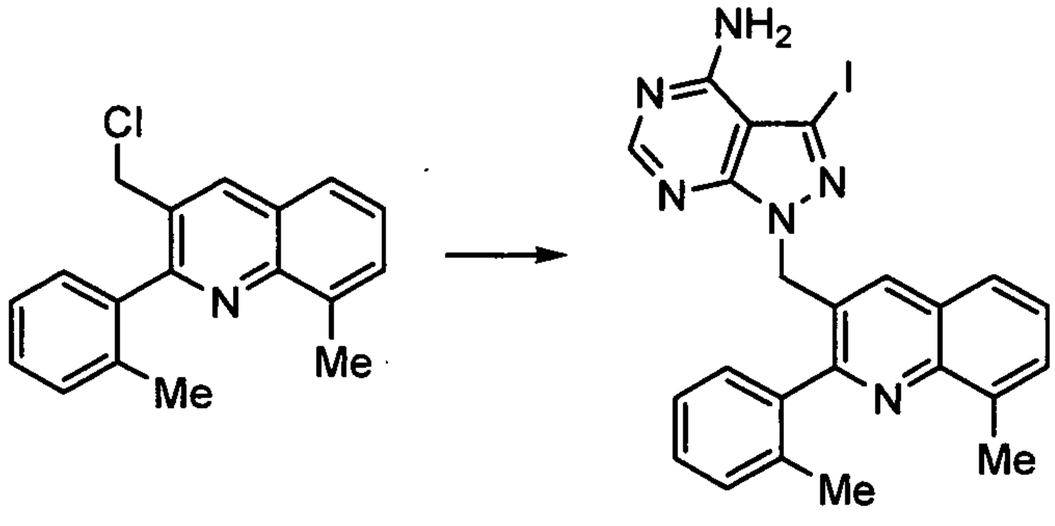
3-Iodo-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared according to Procedure I using 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.41 g, 1.6 mmol, 1 eq) in DMF (5 mL), NaH (60%, 0.138 g, 3.5 mmol, 2.2 eq), and 3-(chloromethyl)-8-methyl-2-(2-(trifluoromethyl)phenyl)quinoline (0.58 g, 1.7 mmol, 1 eq) in DMF (3 mL). After purification, 3-iodo-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was obtained as white solid. ^1H NMR (DMSO-d_6) δ ppm 8.27 (1 H, s), 7.99 (1 H, s), 7.88 (1 H, d, J=7.8 Hz), 7.73 - 7.79 (1 H, m), 7.65 (1 H, d, J=6.7

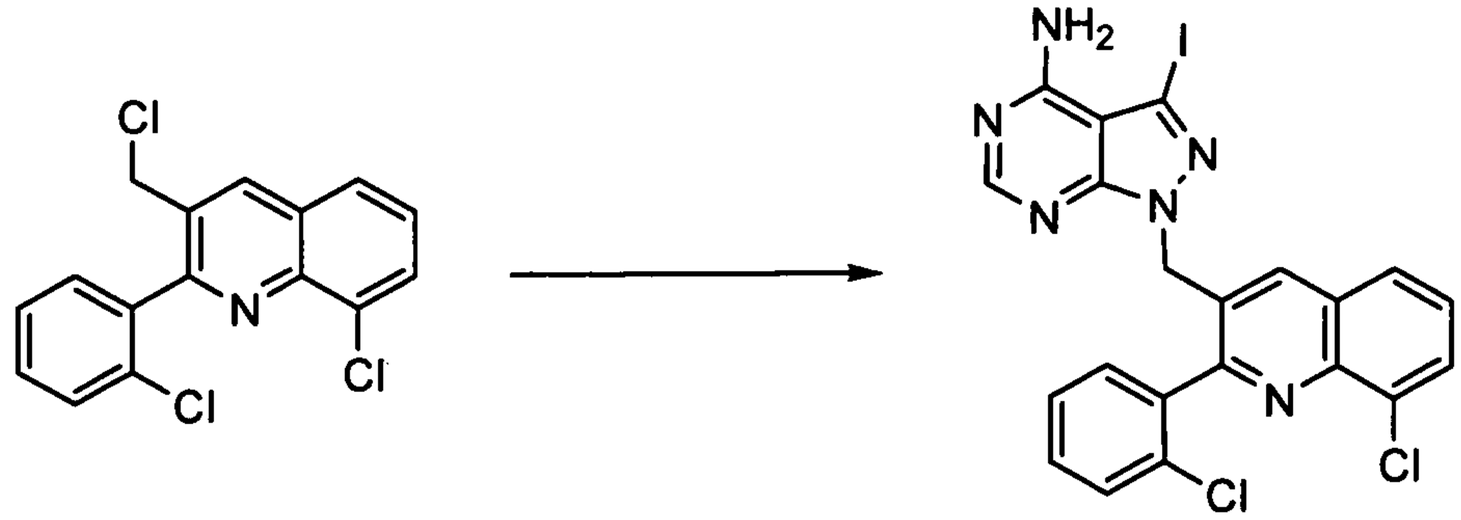
Hz), 7.51 - 7.61 (3 H, m), 7.28 - 7.35 (1 H, m), 5.41 - 5.54 (2 H, m), 2.60 (3 H, s). Mass Spectrum (ESI) m/e = 561.0 (M + 1).

Example 4: 3-Iodo-1-((8-methyl-2-o-tolylquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared according to Procedure I. A solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (400 mg, 1.5 mmol) in DMF (5 mL) at 0 °C was treated with NaH (60%, 67.4 mg, 1.1 eq) for 30 min before addition of a solution of 3-(chloromethyl)-8-methyl-2-o-tolylquinoline (435 mg, 1 eq) in DMF (2 mL). The mixture was stirred at room temperature over night. The reaction mixture was partitioned between DCM (50 mL) and water (50 mL). The insoluble was filtered and washed with DCM and water. The organic layer from the filtrate was separated, dried over Na_2SO_4, concentrated and purified by column chromatography on silica gel (eluent: DCM/MeOH, 25/1) to provide a white solid [PI3Kδ IC_{50} = 6nM]. ^{1}H-NMR (DMSO-d^6) δ 7.96 (s, 1H), 7.85 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 7.0 Hz, 1H), 7.31 (t, J = 7.1 Hz, 1H), 6.94-6.99 (m, 4H), 5.26(s, 2H), 2.45 (s, 3H), 1.79 (s, 3H). Mass Spectrum (ESI) m/e = 507 (M + 1).

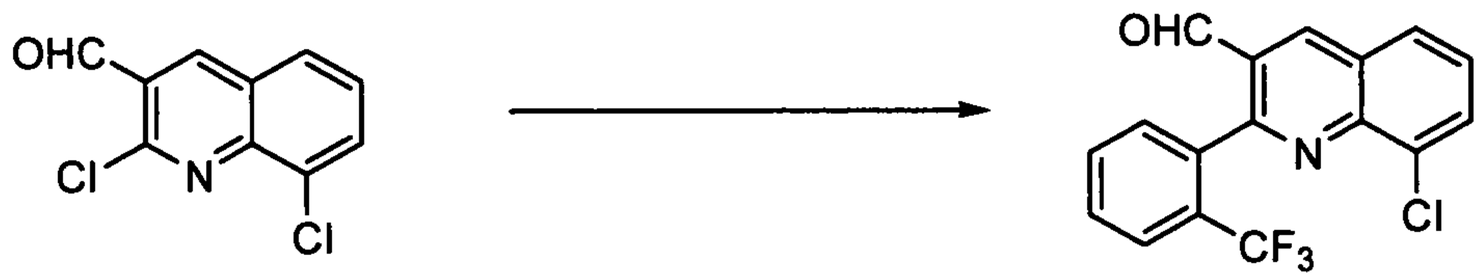
Example 5: Preparation of 1-((8-Chloro-2-(2-chlorophenyl)quinolin-3-yl)-methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared according to Procedure I using 8-chloro-3-(chloromethyl)-2-(2-chlorophenyl)quinoline (0.235 g, 0.73 mmol), NaH (0.047 g 60 % in oil, 1.17 mmol, 1.6 eq) and 3-iodo-1H-pyrazolo{3,4-d}pyrimidin-4-amine (0.209 g, 0.8 mmol, 1.1 eq) in DMF. 1-((8-chloro-2-(2-chlorophenyl)quinolin-3-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was obtained after purification as a white solid [PI3Kδ IC_{50} = 14nM]. 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.42 (1 H, s), 8.09 (1 H, dd, J=8.6, 1.2 Hz), 7.98 - 8.05 (2 H, m), 7.66 (1 H, t), 7.48 (1 H, dd, J=8.2, 0.8 Hz), 7.36 (1 H, dt, J=7.8, 1.6 Hz), 7.25 (1 H, dt, J=7.4, 1.2 Hz), 7.13 (1 H, dd, J=7.4, 1.6 Hz), 5.53 (2 H, s) Mass Spectrum (ESI) m/e = 547.0 and 549.0 (M+1)

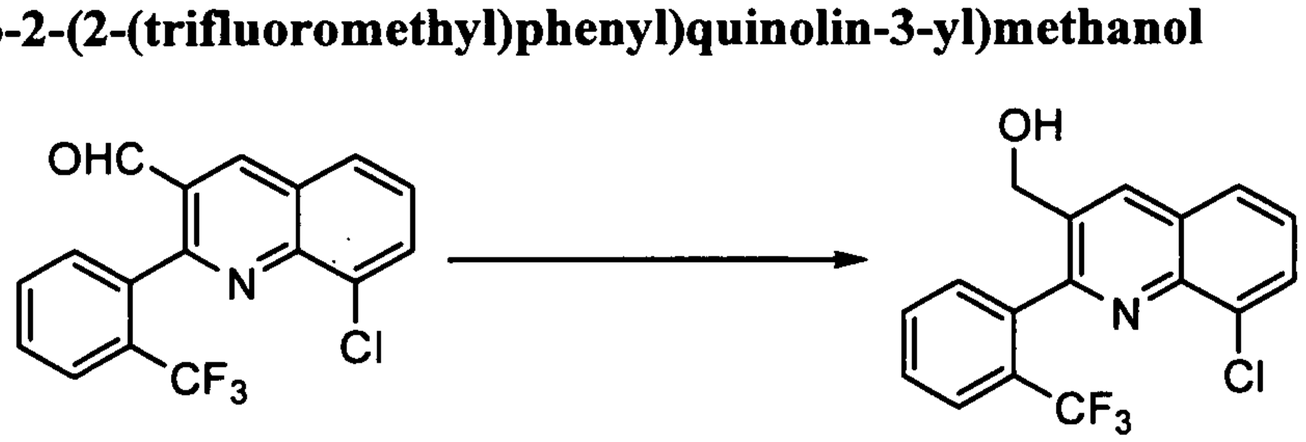
Example 6: Preparation of 1-((8-Chloro-2-(2-(trifluoromethyl)phenyl)-quinolin-3-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

8-Chloro-2-(2-(trifluoromethyl)phenyl)quinoline-3-carbaldehyde



Prepared according to Procedure A using 2,8-dichloroquinoline 3-carbaldehyde (1.0 g, 4.42 mmol), 2-trifluoromethylphenyl boronic acid (0.924 g, 4.87 mmol, 1.1 eq), tetrakis(triphenylphosphine)palladium (0.256 g, 0.221 mmol, 0.05 eq), and sodium carbonate (2.34 g, 22.1 mmol, 5 eq) in acetonitrile (30 mL) and water(10 mL). After purification, 2-(2-trifluoromethylphenyl)-8-chloroquinoline-3-carbaldehyde was obtained as a yellow solid. 1H NMR (500 MHz, DMSO-d_6) δ ppm 9.95 (1 H, s), 9.19 (1 H, s), 8.33 (1 H, dd, J=8.5, 1.2 Hz), 8.20 (1 H, dd, J=7.3, 1.2 Hz), 7.95 (1 H, d, J=7.3 Hz), 7.74 - 7.87 (2 H, m), 7.63 (1 H, d, J=7.3 Hz) Mass Spectrum (ESI) m/e = 336.1 and 338.0 (M+1)

(8-Chloro-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methanol



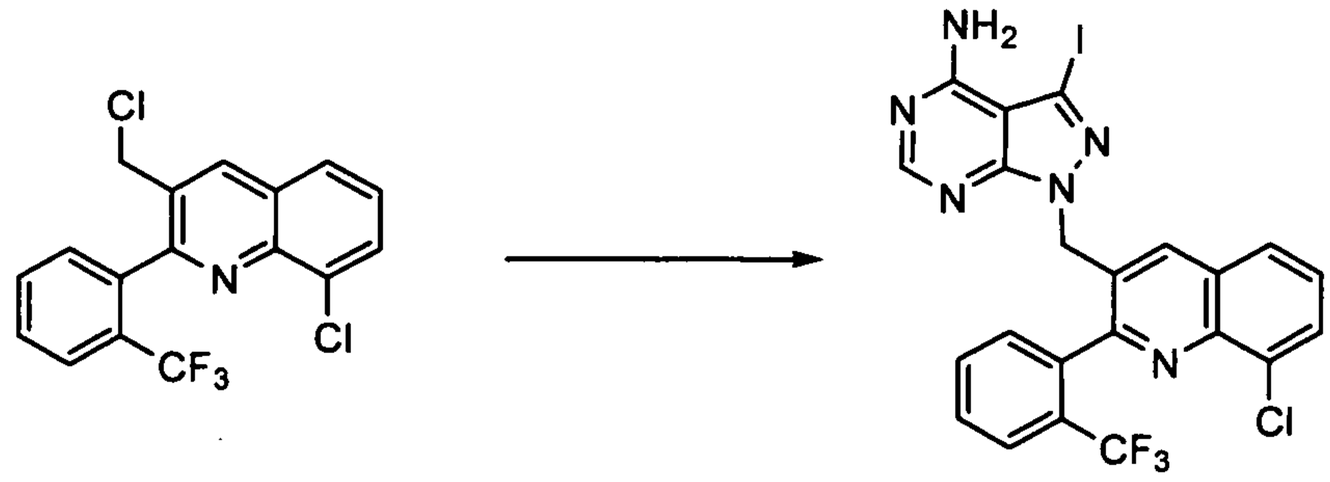
Prepared according to Procedure B using 8-chloro-2-(2-trifluoromethylphenyl) quinoline-3-carbaldehyde (1.10 g, 3.28 mmol) and sodium borohydride (0.186 g, 4.91 mmol, 1.5 eq) in THF (15 mL). (8-chloro-2-(2-trifluoromethylphenyl)-quinolin-3-yl)methanol was obtained as a white solid. 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.57 (1 H, s), 8.10 (1 H, dd, J=7.9, 1.2 Hz), 7.94 (2 H, t, J=6.4 Hz), 7.82 (1 H, t, J=7.6 Hz), 7.76 (1 H, t, J=7.6 Hz), 7.50 - 7.68 (4 H, m), 5.54 (1 H, t, J=5.2 Hz), 4.45 (1 H, br d), 4.28 (1 H, br d) Mass Spectrum (ESI) m/e = 338.0 and 340.0 (M+1)

8-Chloro-3-(chloromethyl)-2-(2-(trifluoromethyl)phenyl)quinoline



Prepared according to Procedure C using (8-chloro-2-(2-trifluoromethylphenyl)-quinolin-3-yl)methanol (1.10 g, 3.26 mmol) and $SOCl_2$ (1.19 mL, 16.3 mmol, 5 eq) in dichloromethane (5 mL). 8-chloro-3-(chloromethyl)-2-(2-trifluoromethyl-phenyl)quinoline was obtained as a yellow syrup. 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.75 (1 H, s), 8.10 (1 H, d, J=8.2 Hz), 8.02 (1 H, d, J=6.3 Hz), 7.95 (1 H, d, J=7.4 Hz), 7.72 - 7.87 (2 H, m), 7.58 - 7.71 (2 H, m), 4.71 (2 H, dd, J=82.2, 12.1 Hz) Mass Spectrum (ESI) m/e = 356.0 and 358.0 (M+1).

1-((8-Chloro-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine

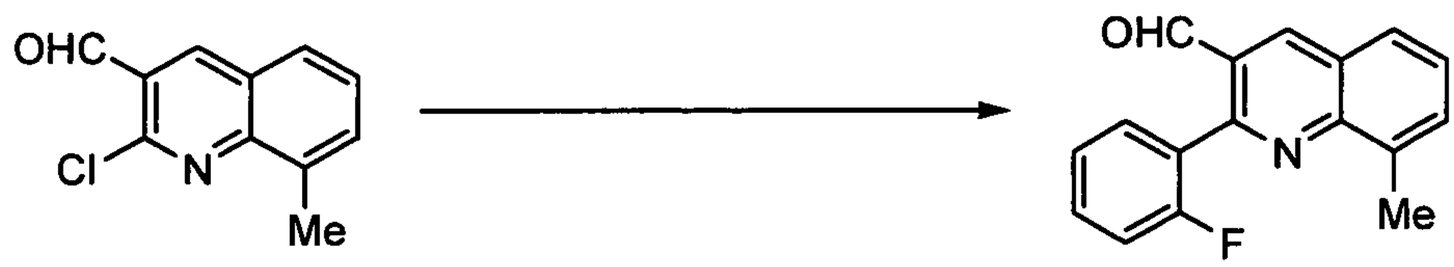


Prepared according to Procedure I using 8-chloro-3-(chloromethyl)-2-(2-trifluoro-methylphenyl)quinoline (0.356 g, 1.0 mmol), NaH (0.044g 60% in oil, 1.1 mmol, 1.1 eq) and 3-iodo-1H-pyrazolo{3,4-d}pyrimidin-4-amine (0.287 g, 1.1 mmol, 1.1

eq) in 5 mL DMF. 1-((8-Chloro-2-(2-trifluoromethylphenyl)quinolin-3-yl)-methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine [PI3Kδ IC_{50} = 7nM] was obtained after purification as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.40 (1 H, s), 8.08 (1 H, d, J=8.2 Hz), 7.96 - 8.03 (2 H, m), 7.74 - 7.84 (1 H, m), 7.56 - 7.70 (3 H, m), 7.26 - 7.37 (1 H, m), 5.47 (2 H, s) Mass Spectrum (ESI) m/e = 580.9 and 583.0 (M+1)

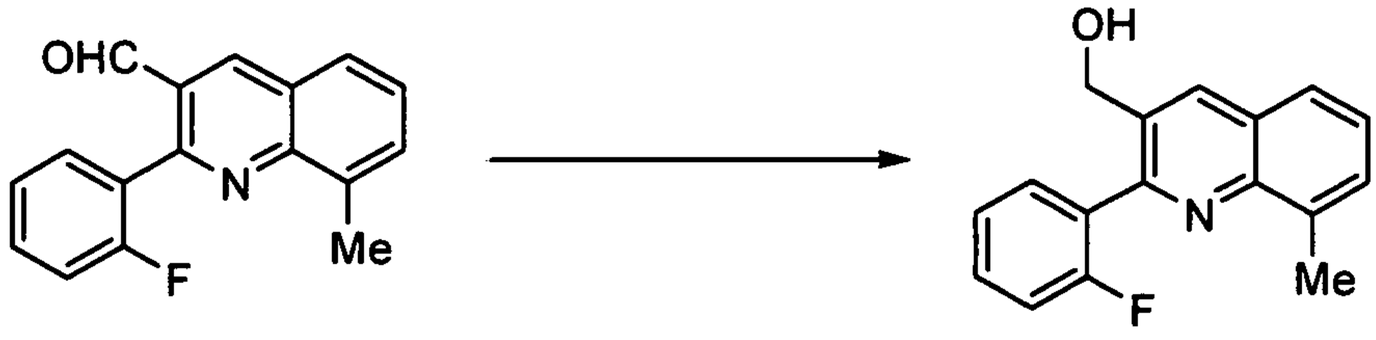
Example 7 Preparation of 1-((2-(2-Fluorophenyl)-8-methylquinolin-3-yl)-methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine:

2-(2-Fluorophenyl)-8-methylquinoline-3-carbaldehyde



Prepared according to Procedure A using 2-chloro-8-methylquinoline 3-carbaldehyde (1.0 g, 4.86 mmol), 2-fluorophenyl boronic acid (0.749 g, 5.35 mmol, 1.1 eq), tetrakis(triphenylphosphine)palladium (0.281 g, 0.24 mmol, 0.05 eq), and sodium carbonate (2.58 g, 24 mmol, 5 eq) in acetonitrile (36 mL) and water (12 mL). After purification, 2-(2-fluorophenyl)-8-methylquinoline-3-carbaldehyde was obtained as a yellow solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 10.03 (1 H, d, J=3.5 Hz), 8.99 (1 H, s), 8.12 (1 H, d, J=7.8 Hz), 7.85 (1 H, d, J=7.0 Hz), 7.76 (1 H, td, J=7.5, 1.8 Hz), 7.58 - 7.70 (2 H, m), 7.45 (2 H, td, J=7.5, 1.0 Hz), 7.38 (2 H, td, J=9.4, 1.2 Hz), 2.75 (3 H, s) Mass Spectrum (ESI) m/e = 266.0 (M+1)

(2-(2-Fluorophenyl)-8-methylquinolin-3-yl)methanol



Prepared according to Procedure B using 2-(2-fluorophenyl)-8-methylquinoline-3-carbaldehyde (0.725 g, 2.73 mmol), and sodium borohydride (0.155 g, 4.1 mmol, 1.5 eq) in THF (15 mL). (2-(2-fluorophenyl)-8-methylquinolin-3-yl)methanol was obtained as a yellow solid. 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.46 (1

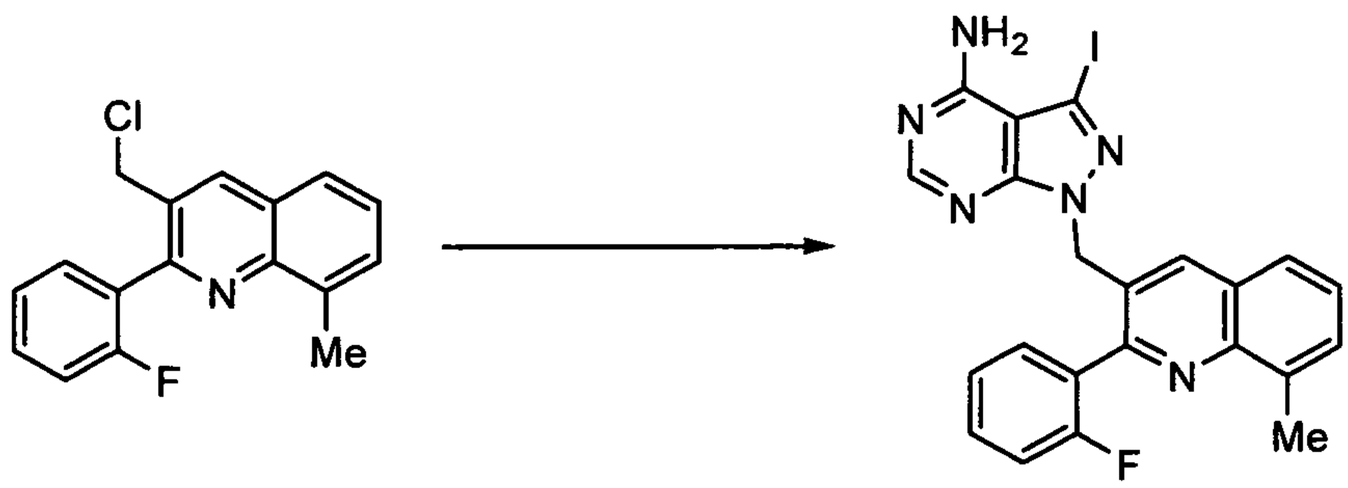
H, s), 7.90 (1 H, d, J=7.9 Hz), 7.63 (1 H, d, J=6.7 Hz), 7.50 - 7.60 (3 H, m), 7.38 (1 H, d, J=7.9 Hz), 7.35 - 7.37 (1 H, m), 5.42 (1 H, t, J=5.5 Hz), 4.50 (2 H, d, J=5.5 Hz), 2.69 (3 H, s) Mass Spectrum (ESI) m/e = 268.1 (M+1)

3-(Chloromethyl)-2-(2-fluorophenyl)-8-methylquinoline



Prepared according to Procedure C using (2-(2-fluorophenyl)-8-methylquinolin-3-yl)methanol (0.700g, 2.62 mmol) in $SOCl_2$ (2 mL, 27.4 mmol, 10.5 eq). 3-(chloromethyl)-2-(2-fluorophenyl)-8-methyl-quinoline (0.665g, 89%) was obtained after purification as a brown foam. 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.61 (1 H, s), 7.92 (1 H, d, J=7.9 Hz), 7.71 (1 H, d, J=6.7 Hz), 7.53 - 7.66 (3 H, m), 7.40 (2 H, t, J=7.9 Hz), 4.81 (2 H, s), 2.69 (3 H, s) Mass Spectrum (ESI) m/e = 286.1 and 288.1 (M+1)

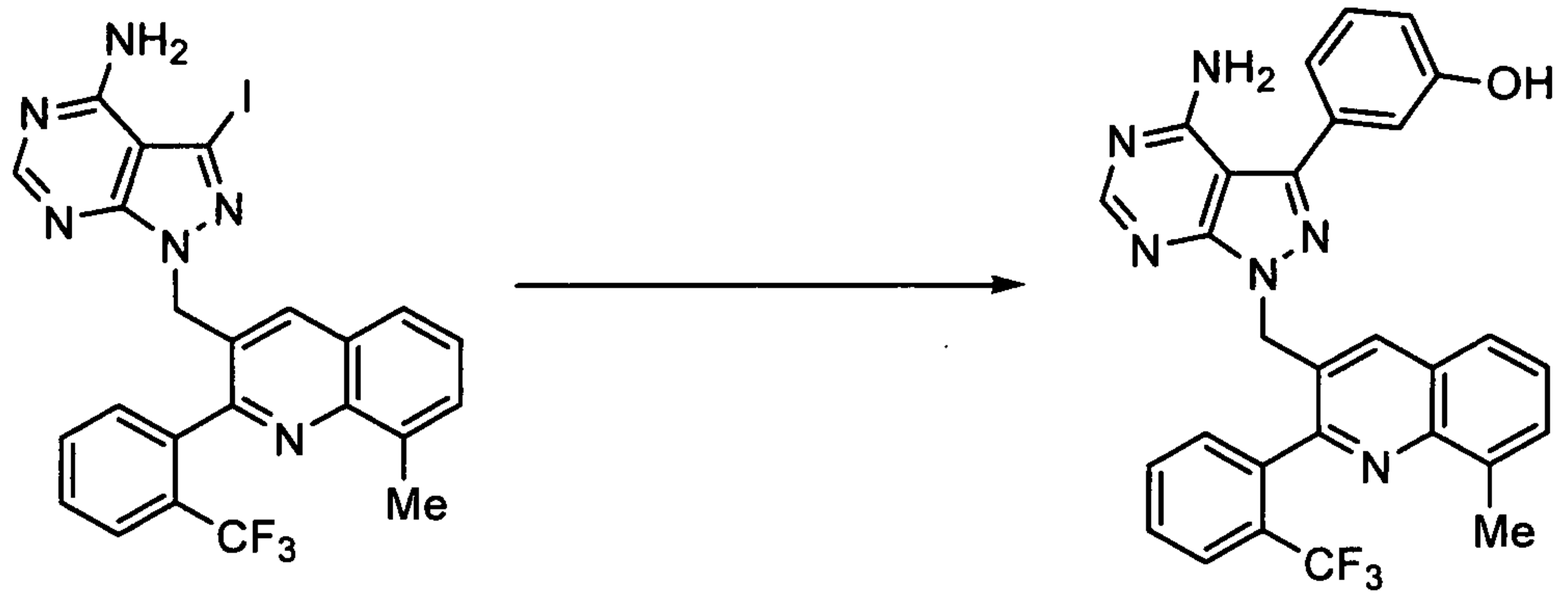
1-((2-(2-Fluorophenyl)-8-methylquinolin-3-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared according to Procedure I using (2-(2-fluorophenyl)-8-methylquinolin-3-yl)methanamine (0.200g, 0.7 mmol), NaH (0.031g, 60% in oil, 0.77 mmol, 1.1 eq) and 3-iodo-1H-pyrazolo{3,4-d}pyrimidin-4-amine (0.201g, 0.77 mmol, 1.1 eq) in DMF. 1-((2-(2-fluorophenyl)-8-methylquinolin-3-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine [PI3Kδ IC_{50} = 4nM] was obtained after purification as a white solid. 1H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (1 H, s), 8.00 (1 H, s), 7.96 (1 H, s), 7.80 (1 H, d, J=7.9 Hz), 7.63 (1 H, d, J=7.3 Hz), 7.46 - 7.53 (1 H, m), 7.30 (1 H, dt), 7.08 (1 H, dd, J=7.6, 1.5 Hz), 7.02 (1 H, d, J=7.9

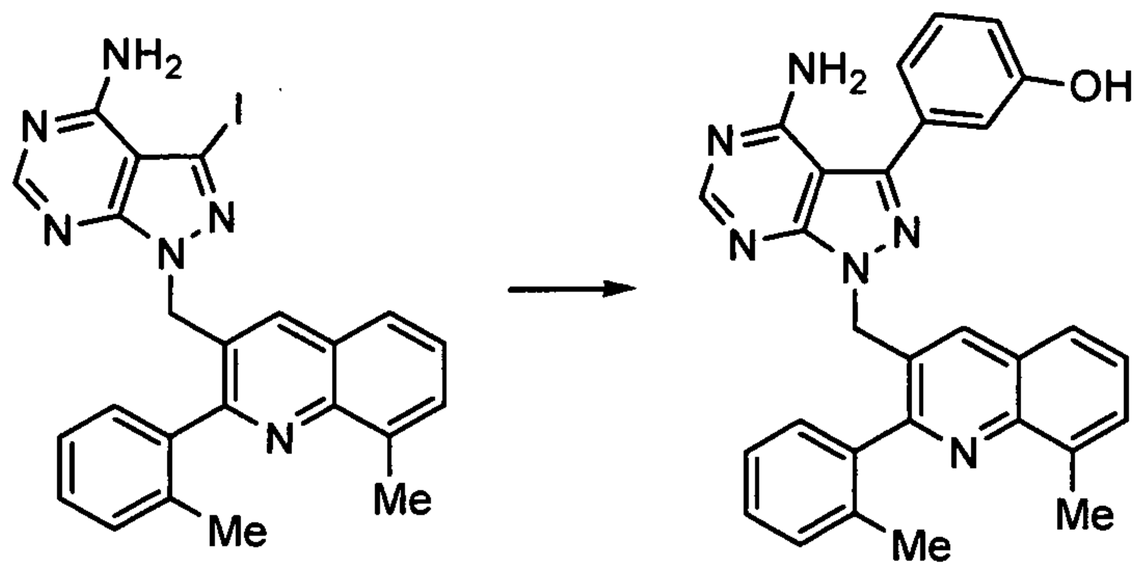
Hz), 6.91 (1 H, t, J=7.3 Hz), 5.46 - 5.54 (2 H, m), 2.90 (3 H, s) Mass Spectrum (ESI) m/e = 511.0 (M+1)

Example 8: 3-(4-Amino-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol:



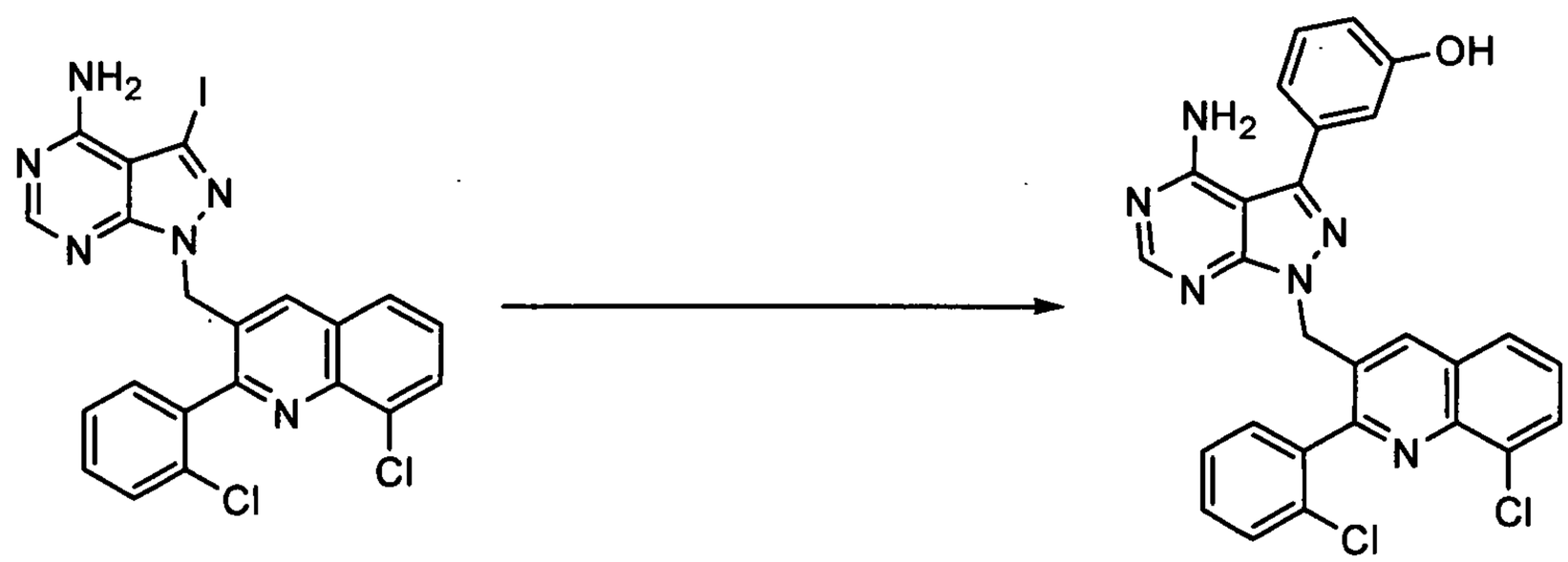
Prepared according to Procedure J using 3-iodo-1-((8-methyl-2-(2-(trifluoro-methyl)phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.1 g, 0.1785 mmol, 1 eq), 3-hydroxyphenylboronic aicd (0.0492 g, 0.357 mmol, 2.0 eq), tetrakis(triphenylphosphine)palladium (0.0206 g, 0.0178 mmol, 10 mol %), and sodium carbonate (2M aq. sol, 0.535 mL, 1.07 mmol., 6 eq) in DMF (1 mL). After purification, 3-(4-amino-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)-quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol was obtained as light gray solid. The gray solid was suspended in CH_2Cl_2 and filtered to provide 3-(4-amino-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol [PI3Kδ IC_{50} = 8nM] as off-white solid. ^1H NMR (DMSO-d_6) δ ppm 9.65 (1 H, s), 8.28 (1 H, s), 8.04 (1 H, s), 7.87 (1 H, d, J=7.8 Hz), 7.74 - 7.80 (1 H, m), 7.64 (1 H, d, J=7.0 Hz), 7.56 - 7.61 (2 H, m), 7.50 - 7.56 (1 H, m), 7.34 - 7.38 (1 H, m), 7.30 (1 H, t, J=7.8 Hz), 6.94 - 7.02 (2 H, m), 6.80 - 6.87 (1 H, m), 5.53 (2 H, s), 2.60 (3 H, s). Mass Spectrum (ESI) m/e = 527.2 (M + 1).

Example 9: 3-(4-Amino-1-((8-methyl-2-o-tolylquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol



Prepared according to Procedure J. A mixture of 3-iodo-1-((8-methyl-2-o-tolylquinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (51 mg, 0.1 mmol), 3-hydroxyphenylboronic acid (15.2 mg, 1.1 eq), sodium carbonate (55 mg, 5 eq), tetrakis(triphenylphosphine)palladium (6 mg, 5% mmol) in DMF (1 mL) and water (0.3 mL) was heated to 100 °C under N_2 for 4 h. The reaction mixture was cooled to room temperature, filtered and purified by reverse HPLC (MeCN/H_2O/0.1%TFA) on C18 to give a white solid [PI3Kδ IC_{50} = 7nM]. ^{1}H-NMR (DMSO-d^6) δ 8.37 (s, 1H), 8.35 (s, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.14-7.17 (m, 4H), 6.87-6.97 (m, 4H), 5.63(s, br, 2H), 2.63 (s, 3H), 1.91 (s, 3H). Mass Spectrum (ESI) m/e = 473 (M + 1).

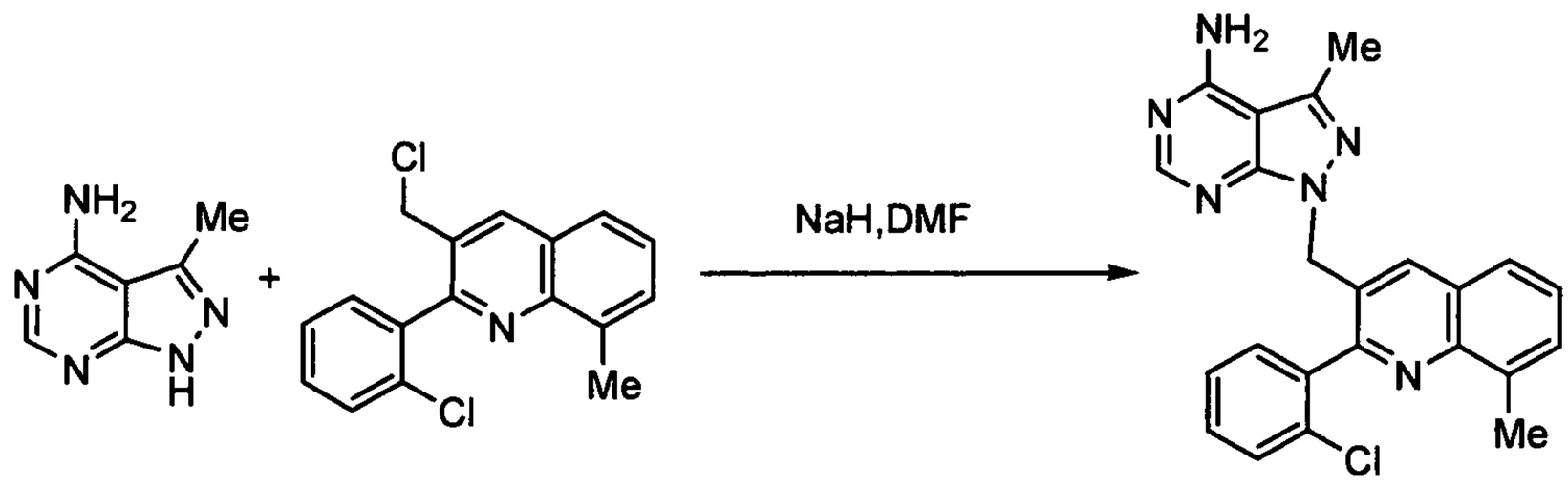
Example 10: Preparation of 3-(4-Amino-1-((8-chloro-2-(2-chlorophenyl)-quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol:



Prepared according to Procedure J using 1-((8-chloro-2-(2-chlorophenyl)quinolin-3-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.100 g, 0.18 mmol), 3-(hydroxyphenyl)boronic acid (0.050 g, 0.37 mmol, 2 eq), tetrakis(triphenyl-phosphine)palladium (0.021 g, 0.018 mmol, 0.1 eq) and 2M aq sodium carbonate (0.54 mL, 1.08 mmol, 6 eq) in DMF (1 mL). 3-(4-Amino-1-((8-chloro-2-(2-

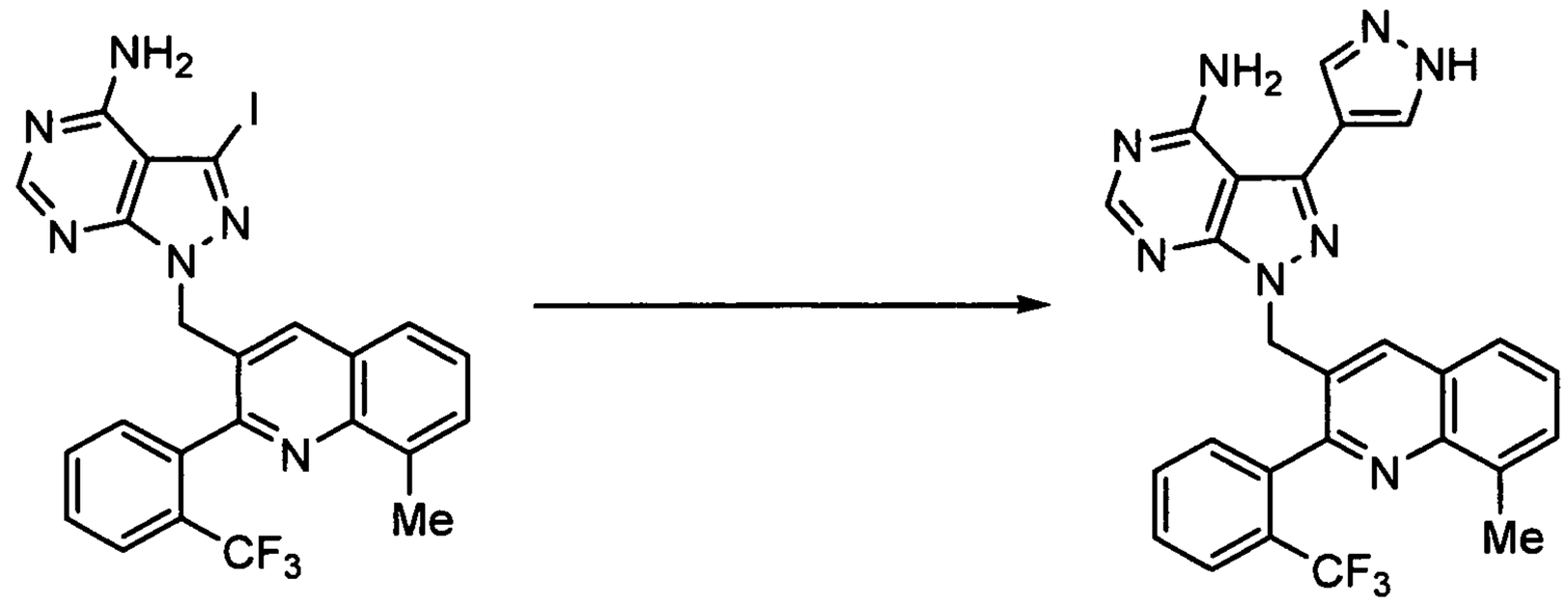
chlorophenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenol [PI3Kδ IC_{50} = 14nM] was obtained after purification as a white solid. 1H NMR (400 MHz, DMSO-d_6) δ ppm 9.52 (1 H, s), 8.31 (1 H, s), 7.91 - 8.00 (2 H, m), 7.86 (1 H, dd, J=7.4, 1.2 Hz), 7.52 (1 H, t, J=7.8 Hz), 7.35 (1 H, d, J=8.2 Hz), 7.07 - 7.28 (3 H, m), 6.97 - 7.05 (1 H, m), 6.78 - 6.93 (2 H, m), 6.70 (1 H, dd, J=8.2, 1.6 Hz), 5.36 - 5.57 (2 H, m) Mass Spectrum (ESI) m/e = 513.1 and 515.0 (M+1).

Example 11: 1-((2-(2-Chlorophenyl)-8-methylquinolin-3-yl)methyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine



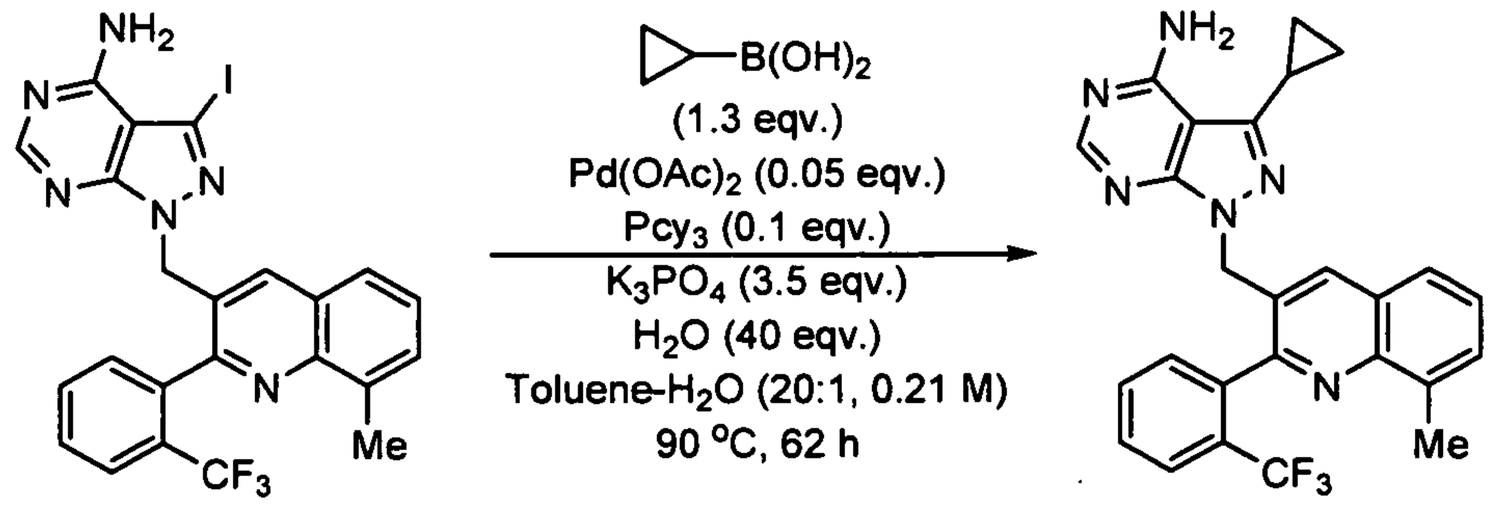
To a stirred solution of 3-methyl-1H-pyrazole[3,4-d]pyrimidin-4-amine[1] (59 mg, 0.397 mmol) in DMF (1.65 mL) at room temperature was added sodium hydride (26.5 mg, 0.662 mmol) at once. After 25 minutes, 3-(chloromethyl)-2-(2-chlorophenyl)-8-methylquinoline (100 mg, 0.331 mmol) was added, the mixture was stirred for several days. The reaction mixture was poured into H_2O and extracted with Et_2O washed with brine and dried over $MgSO_4$ [PI3Kδ IC_{50} = 137nM]. Chromatography: Gradient 89:9:1/DCM. ^{1}H NMR (DMSO-d_6) δ ppm 8.07 (1 H, s), 7.96 (1 H, s), 7.82 (1 H, d, J=7.8 Hz), 7.64 (1 H, d, J=7.0 Hz), 7.48-7.55 (2 H, d, m), 7.34-7.40 (1 H, m), 7.24-7.30 (1 H, m), 7.16-7.21 (1 H, m), 5.40 (2 H, s), 2.64 (3 H, s), 2,44 (3 H, s), 7.36 - 7.40 (2 H, m), 7.30 - 7.36 (1 H, m), 6.12 (1 H, d, J=5.5 Hz), 4.41 (2 H, d, J=4.7 Hz), 2.67 (3 H, s), 2.14 (3 H, s). Mass Spectrum (ESI) m/e = 415.1 (M + 1).

Example 12: 1-((8-Methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)-methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine:



Prepared according to Procedure J using 3-iodo-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.1000 g, 0.178 mmol, 1 eq), pyrazole-4-boronic acid pinacol ester (0.0693 g, 0.357 mmol, 2.0 eq), tetrakis(triphenylphosphine)palladium(0) (0.0206 g, 0.0178 mmol, 10 mol %), and sodium carbonate (2M aq. sol, 0.535 mL, 1.07 mmol., 6 eq) in DMF (1 mL). After purification, 1-((8-methyl-2-(2-(trifluoromethyl)-phenyl)quinolin-3-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was obtained as white solid. The white solid was suspended in CH_2Cl_2 and filtered to give the desired product as white solid [PI3Kδ IC_{50} = 8nM]. ^1H NMR (DMSO-d_6) δ ppm 13.17 (1 H, s), 8.22 (1 H, s), 7.97 - 8.08 (2 H, m), 7.71 - 7.90 (3 H, m), 7.56 - 7.66 (3 H, m), 7.52 (1 H, dd, J=7.8, 7.0 Hz), 7.35 - 7.44 (1 H, m), 6.82 (2 H, br. s.), 5.42 - 5.55 (2 H, m), 2.60 (3 H, s). Mass Spectrum (ESI) m/e = 501.1 (M + 1).

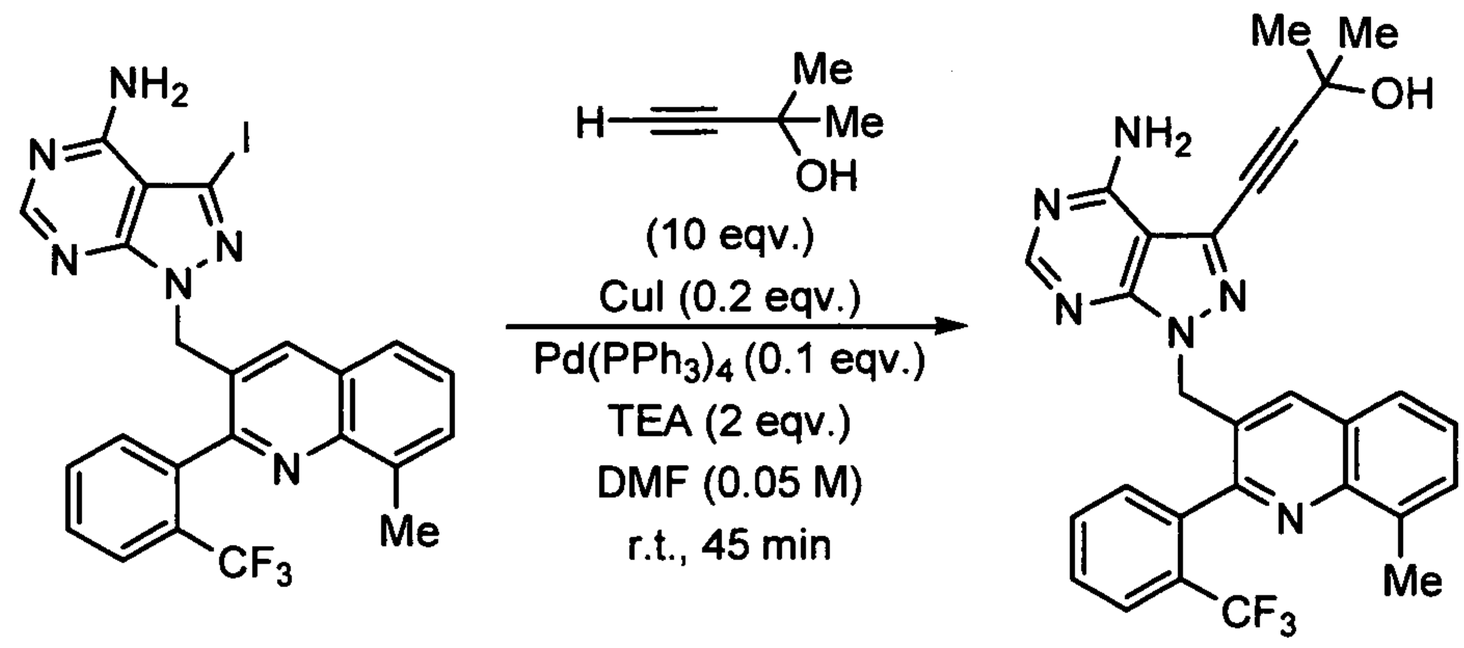
Example 13: 3-Cyclopropyl-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)-quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine:



To a solution of 3-iodo-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)-methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.1000 g, 0.18 mmol), cyclo-propylboronic acid (0.020 g, 0.23 mmol, 1.3 eq), tripotassium phosphate (0.13 g,

0.62 mmol, 3.5 eq), and tricyclohexylphosphine (0.0050 g, 0.018 mmol, 0.1 eq) in toluene (2 mL) and water (0.1 mL) under nitrogen atmosphere was added palladium acetate (0.0020 g, 0.0089 mmol, 5 mol %). The mixture was heated at 90 °C for 62 h. To the mixture was added water (30 mL). The mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (50 mL x 1), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a yellow syrup. The yellow syrup was purified by column chromatography on a 40 g of Redi-Sep™ column using 50 to 100% gradient of EtOAc in hexane over 9 min, 100% isocratic of EtOAc for 8 min, and then 0 to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 14 min as eluent to provide 3-cyclopropyl-1-((8-methyl-2-(2-(trifluoromethyl)-phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine [PI3Kδ IC_{50} = 149nM] as yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm 8.08 (1 H, s), 7.98 (1 H, s), 7.77 - 7.85 (2 H, m), 7.59 - 7.68 (3 H, m), 7.51 (1 H, dd, J=7.8, 7.0 Hz), 7.37 - 7.44 (1 H, m), 5.34 (2 H, s), 2.59 (3 H, s), 2.31 - 2.42 (1 H, m), 0.84 - 0.93 (2 H, m), 0.70 - 0.78 (2 H, m). Mass Spectrum (ESI) m/e = 475.1 (M + 1).

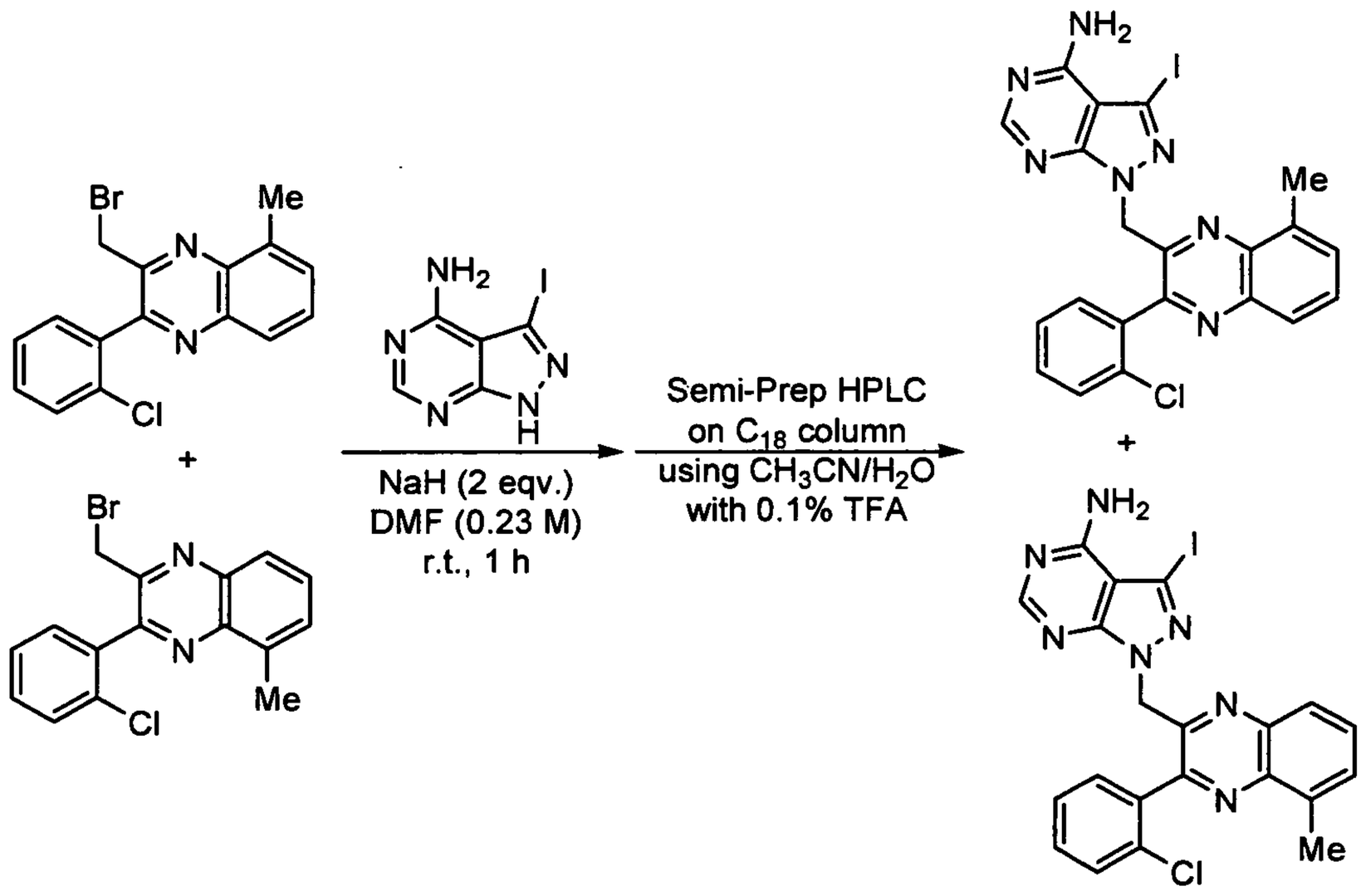
Example 14: 4-(4-Amino-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methylbut-3-yn-2-ol:



A suspension of 3-iodo-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)-methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.0569 g, 0.102 mmol) and copper(i) iodide (0.00387 g, 0.0203 mmol, 0.2 eq) in DMF (2 mL) was treated with 2-methyl-3-butyn-2-ol (0.0984 mL, 1.02 mmol, 10 eq), triethylamine (0.0282 mL, 0.203 mmol, 2 eq) and tetrakis(triphenylphosphine)palladium(0) (0.0117 g, 0.0102 mmol, 10 mol %) under Ar. The mixture was stirred under Ar at rt for 45

min. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on a 40 g of Redi-Sep™ column using 0 to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 14 min as eluent to provide 4-(4-amino-1-((8-methyl-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methylbut-3-yn-2-ol [PI3Kδ IC_{50} = 116nM] as a tan solid. ^{1}H NMR (DMSO-d_6) δ ppm 8.21 (1 H, s), 8.02 (1 H, s), 7.87 (1 H, d, J=7.8 Hz), 7.77 - 7.82 (1 H, m), 7.65 (1 H, d, J=6.7 Hz), 7.57 - 7.62 (2 H, m), 7.51 - 7.57 (1 H, m), 7.26 - 7.32 (1 H, m), 5.76 (1 H, s), 5.44 (2 H, s), 2.60 (3 H, s), 1.46 (6 H, s). Mass Spectrum (ESI) m/e = 517.2 (M + 1).

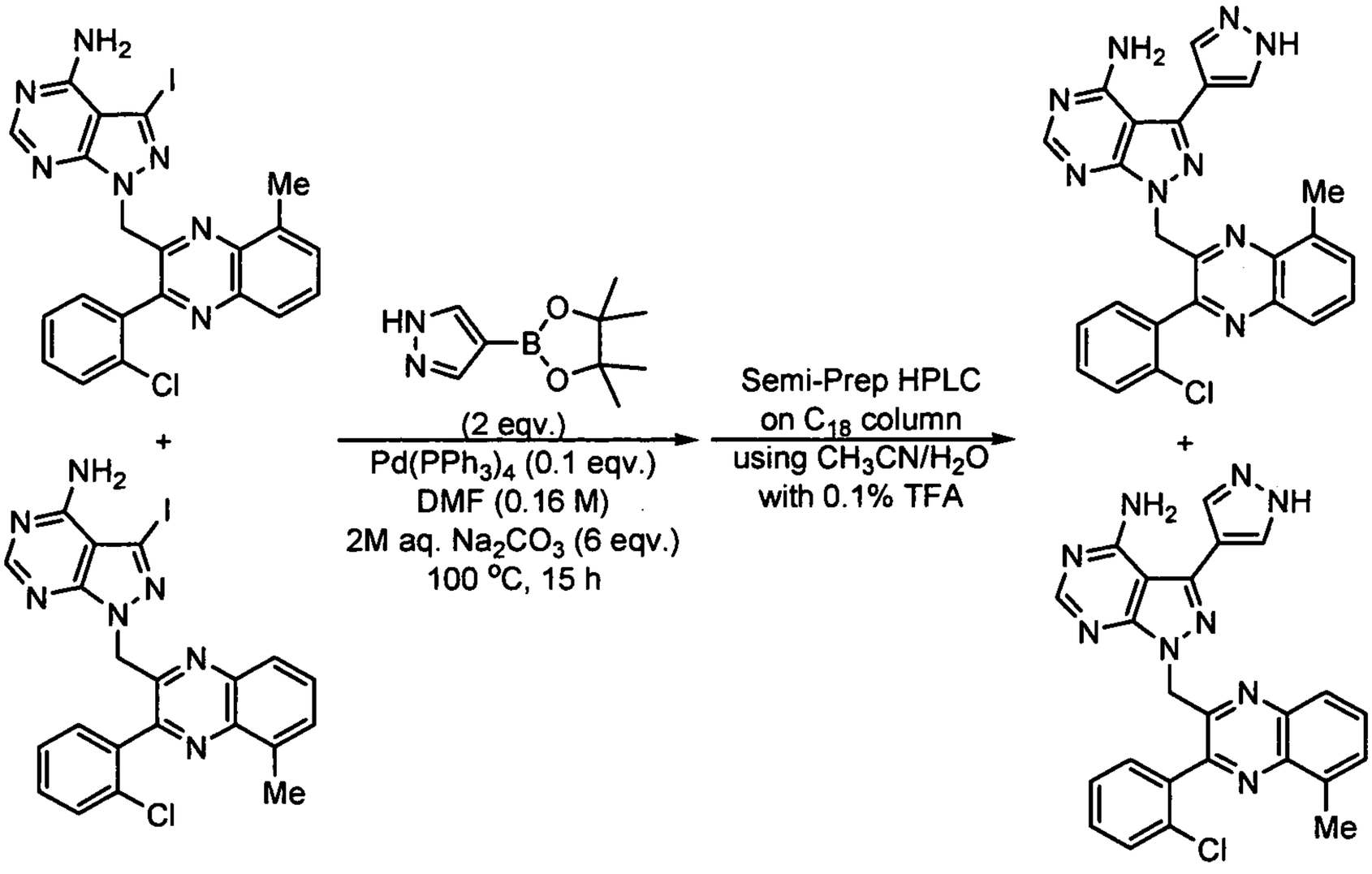
Examples 15 and 16: 1-((3-(2-Chlorophenyl)-8-methylquinoxalin-2-yl)-methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-Chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine:



To a solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.8909 g, 3.41 mmol, 1 eq) 10 mL of DMF (10 mL) was added sodium hydride, 60% dispersion in mineral oil (0.2730 g, 6.83 mmol, 2 eq) at 0 °C and the mixture was stirred at rt. After 10 min at rt, to the mixture was added a solution of 3-(bromomethyl)-2-(2-chlorophenyl)-5-methylquinoxaline and 2-(bromomethyl)-3-(2-chlorophenyl)-5-methylquinoxaline (prepared according to procedures shown in Example 15 and

16, 1.2458 g, 3.58 mmol) in DMF (5 mL) and the mixture was stirred at rt for 1 h. The mixture was poured into ice-water (100 mL). The resulting precipitate was collected by filtration to provide yellow solid. The yellow solid was purified by column chromatography on a 80 g of Redi-Sep™ column using 9% isocratic of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 for 20 min and then 9% to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 20 min as eluent to provide a mixture of 1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine as yellow foamy solid. The yellow foamy solid (0.1 g) was dissolved in 5 mL of MeOH-CH_3CN (0.1% of TFA) and purified by semi-prep-HPLC on C18 column using 30-90% gradient of CH_3CN (0.1% of TFA) in water (0.1% of TFA) over 40 min as eluent to provide 1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine [PI3Kδ IC_{50} = 38nM] as white solid and 1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine [PI3Kδ IC_{50} = 21nM] as a TFA salt. ^{1}H NMR (DMSO-d_6) δ ppm 8.05 (1 H, s), 7.93 (1 H, dd, J=8.0, 1.0 Hz), 7.77 - 7.82 (1 H, m), 7.72 - 7.77 (1 H, m), 7.48 (1 H, d, J=7.8 Hz), 7.33 - 7.39 (1 H, m), 7.27 - 7.32 (2 H, m), 5.74 (2 H, s), 2.54 (3 H, s); Mass Spectrum (ESI) m/e = 528.0 (M+1); HPLC: a peak at 7.834 min. ^{1}H NMR (DMSO-d_6) δ ppm 8.02 (1 H, s), 7.93 (1 H, d, J=8.5 Hz), 7.82 (1 H, t, J=7.6 Hz), 7.75 - 7.79 (1 H, m), 7.43 (1 H, d, J=7.9 Hz), 7.28 - 7.34 (1 H, m), 7.19 - 7.26 (2 H, m), 5.75 (2 H, br. s.), 2.68 (3 H, s); Mass Spectrum (ESI) m/e = 528.0 (M+1); HPLC: a peak at 8.039 min.

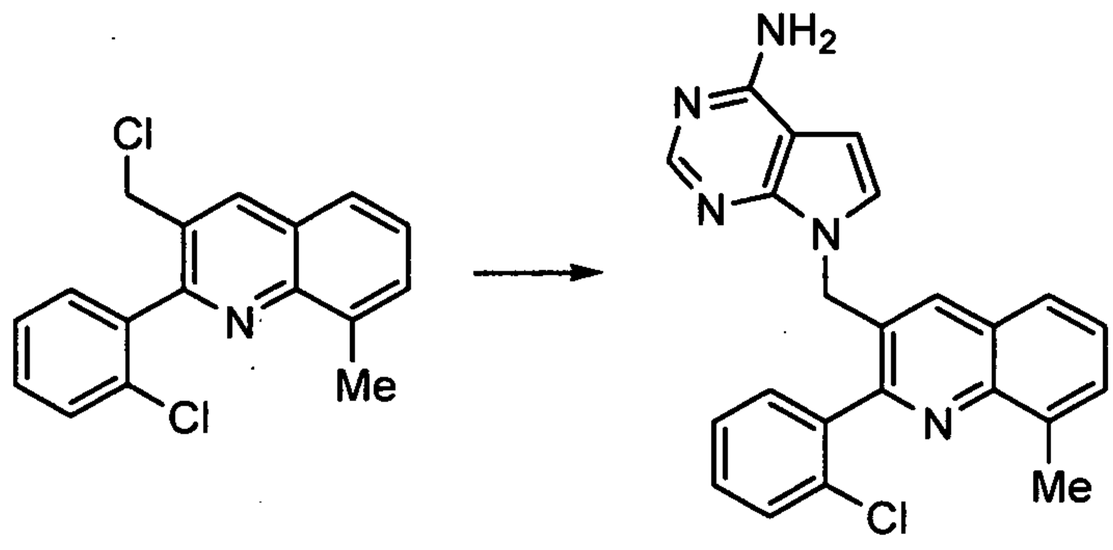
Example 17 and 18: 1-((3-(2-Chlorophenyl)-8-methylquinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-Chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine:



Prepared according to Procedure J using a mixture of 1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.2737 g, 0.52 mmol, 1 eq), 4-pyrazoleboronic acid pinacol ester (0.20 g, 1.0 mmol, 2.0 eq), tetrakis(triphenylphosphine)palladium(0) (0.060 g, 0.052 mmol, 10 mol %), and sodium carbonate (2M aq. sol, 1.6 mL, 3.1 mmol, 6 eq) in DMF (3.1 mL). After purification, a mixture of 1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was obtained as tan solid. The tan solid (0.1566 g) was dissolved in DMSO (8 mL) and purified by semi-prep-HPLC on C18 column using 20-70% gradient of CH_3CN (0.1% of TFA) in water (0.1% of TFA) over 40 min as eluent to provide 1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine [PI3Kδ IC_{50} = 18nM] as white solid as a TFA

salt and 1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine [PI3Kδ IC_{50} = 30nM] as white solid as a TFA salt. ^{1}H NMR (DMSO-d_6) δ ppm 8.18 (1 H, s), 7.88 - 7.96 (3 H, m), 7.77 - 7.82 (1 H, m), 7.72 - 7.77 (1 H, m), 7.49 (1 H, d, J=7.8 Hz), 7.27 - 7.38 (3 H, m), 5.82 (2 H, d, J=18.4 Hz), 2.54 (3 H, s); Mass Spectrum (ESI) m/e = 468.1 (M+1); HPLC: a peak at 6.522 min. ^{1}H NMR (DMSO-d_6) δ ppm 8.15 (1 H, s), 7.91 - 7.96 (1 H, m), 7.89 (2 H, s), 7.78 - 7.84 (1 H, m), 7.74 - 7.78 (1 H, m), 7.40 - 7.49 (1 H, m), 7.18 - 7.34 (3 H, m), 5.82 (2 H, d, J=27.4 Hz), 2.66 (3 H, s); Mass Spectrum (ESI) m/e = 468.1 (M+1); HPLC: a peak at 6.700 min.

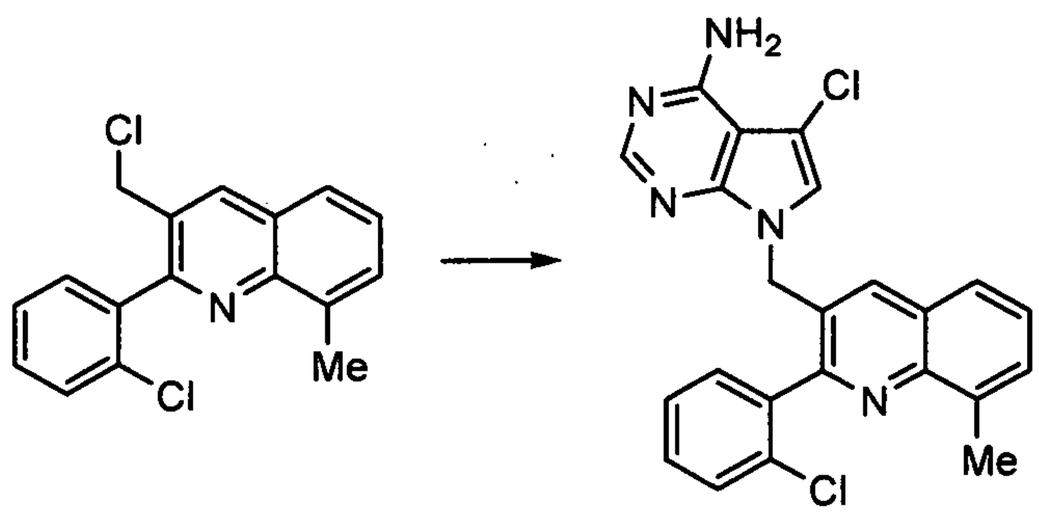
Example 19: 7-((2-(2-Chlorophenyl)-8-methylquinolin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine



A solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (280 mg, 1.1 eq) in DMF (3 mL) was treated with NaH (1.2 eq, 80 mg, 60%) and the reaction mixture was stirred at rt for 30 min before addition of 3-(chloromethyl)-2-(2-chlorophenyl)-8-methylquinoline (500 mg, 1.7 mmol) in DMF (2 mL). After 2 h at rt, the mixture was partitioned between EtOAc (50 mL) and H_2O (30 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) , concentrated and purified by flash chromatography (0% to 25% EtOAc/hexane) to provide 3-((4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl)-2-(2-chlorophenyl)-8-methylquinoline as a white foam. This material (60 mg, 0.14 mmol) was dissolved in EtOH (4 mL) and treated with NH_3 gas for 3 min. The sealed tube was heated at 80 °C for 4 days. The reaction mixture was concentrated and purified by column chromatography on silica gel (eluent: DCM/MeOH, 20/1) to provide a white solid [PI3Kδ IC_{50} =

1968nM]. ^{1}H-NMR (DMSO-d^6) δ 7.94 (s, 1H), 7.89 (s, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.37-7.62 (m, 6H), 6.96 (s, 2H), 6.86 (d, J = 3.6 Hz, 1H), 6.54 (d, J = 3.5 Hz, 1H), 5.30 (d, J = 5.9 Hz, 2H), 2.64 (s, 3H). Mass Spectrum (ESI) m/e = 400 (M + 1).

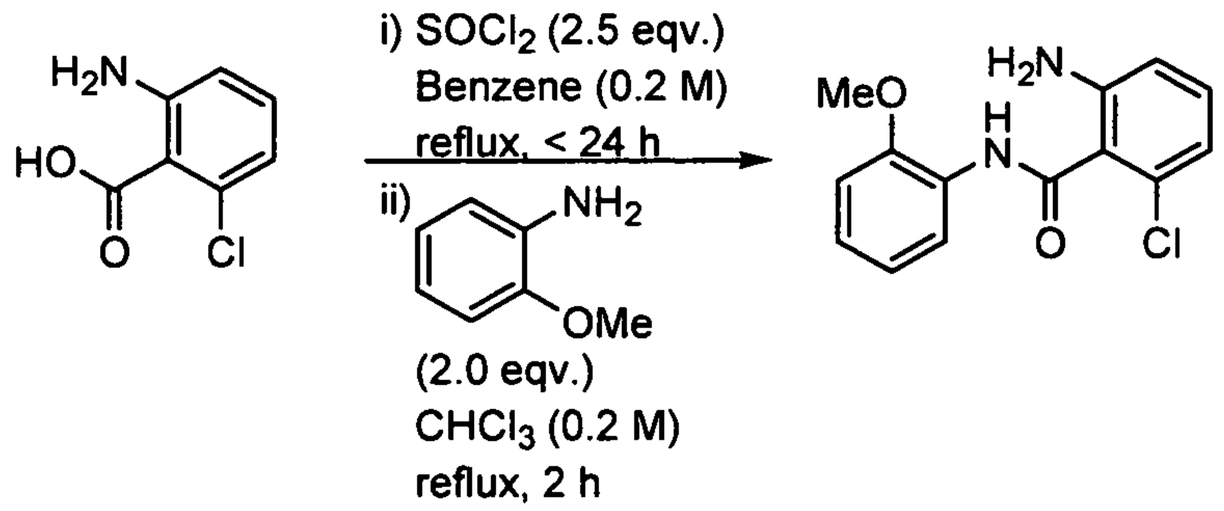
Example 20: 5-Chloro-7-((2-(2-chlorophenyl)-8-methylquinolin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine



5-Chloro-7-((2-(2-chlorophenyl)-8-methylquinolin-3-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine was prepared from 4,5-dichloro-7H-pyrrolo[2,3-d]pyrimidine according to the above procedure (example 44) as a white solid [PI3Kδ IC_{50} = 20nM]. ^{1}H-NMR ($CDCl_3$) δ 8.04 (s, 1H), 7.90 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 7.0 Hz, 1H), 7.15-7.43 (m, 6H), 5.23-5.45 (m, 4H), 2.69 (s, 3H). Mass Spectrum (ESI) m/e = 434 (M + 1).

Example 21: Preparation of 4-Amino-8-((5-chloro-3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one:

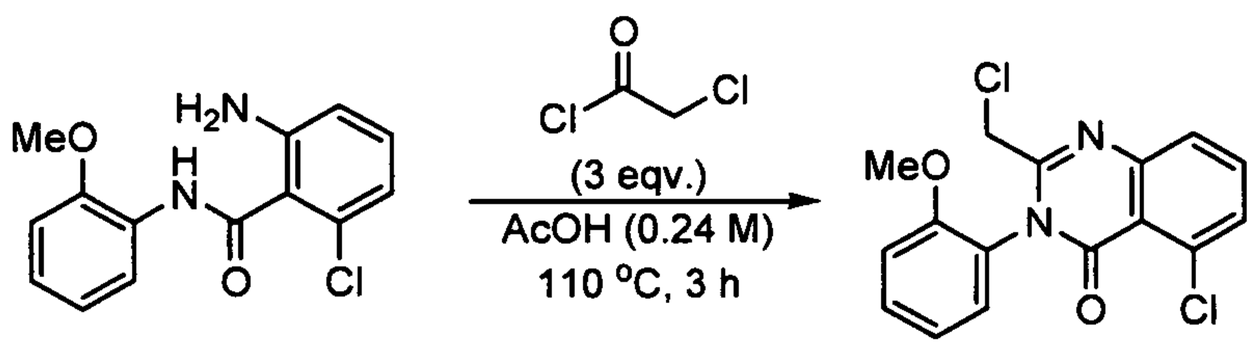
2-Amino-6-chloro-N-(2-methoxyphenyl)benzamide



SO_2Cl_2 (5.4 mL, 74 mmol, 2.5 eq) was added to a rapidly stirring solution of 2-amino-6-chlorobenzoic acid (5 g, 29.14 mmol) in benzene (146 mL) and the mixture was stirred at reflux for 24 h. The mixture was concentrated under reduced pressure, and stripped down twice with benzene to give brown oil. The result-

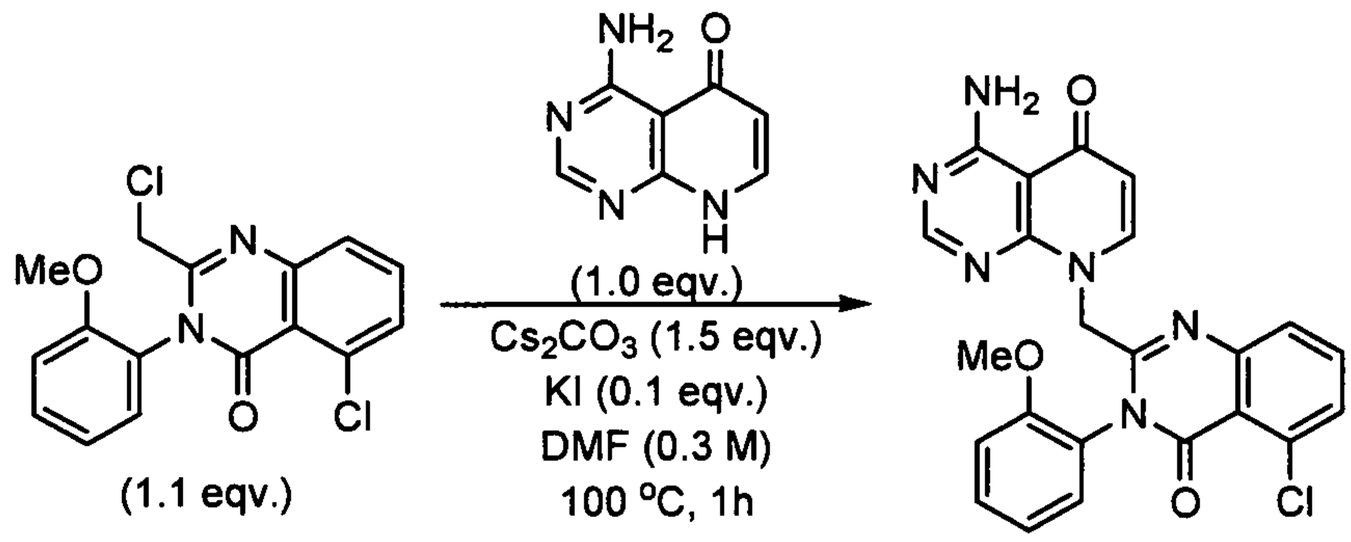
ing oil was dissolved in $CHCl_3$ (146 mL) and to that solution was added o-anisidine and the mixture was stirred at 65 °C for 2 h. The mixture was cooled to rt and the resulting precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and purified by column chromatography on a 120 g of Redi-Sep™ column using 0 to 100% gradient of EtOAc in hexane over 20 min as eluent to provide 2-amino-6-chloro-N-(2-methoxyphenyl)benzamide as yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm 9.44 (1 H, s), 7.86 (1 H, dd, J=7.9, 1.3 Hz), 7.13 - 7.21 (1 H, m), 7.04 - 7.11 (2 H, m), 6.97 (1 H, t, J=7.6 Hz), 6.66 (2 H, dd, J=28.0, 7.9 Hz), 5.37 (2 H, s), 3.81 (3 H, s). Mass Spectrum (ESI) m/e = 277.0 (M + 1).

5-Chloro-2-(chloromethyl)-3-(2-methoxyphenyl)quinazolin-4(3H)-one



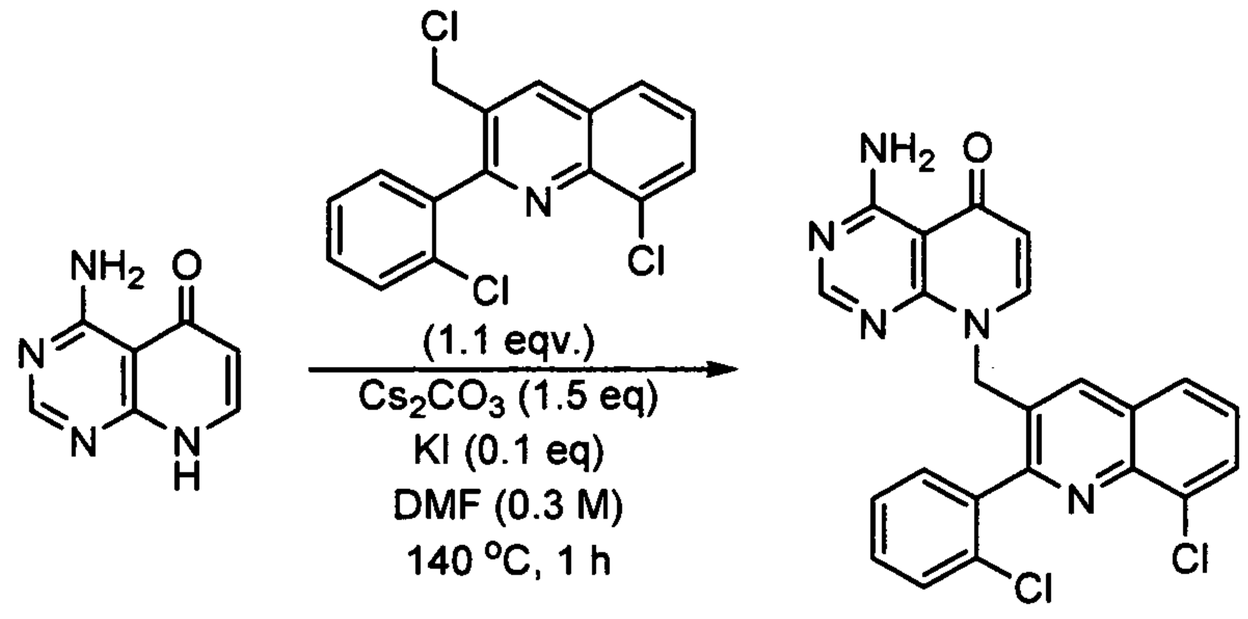
To a solution of 2-amino-6-chloro-N-(2-methoxyphenyl)benzamide (4.0813 g, 14.75 mmol) in AcOH (39 mL) was added dropwise chloroacetyl chloride (3.6 mL, 45.2 mmol, 3 eq), and then the mixture was stirred at 110 °C for 3 h. The mixture was cooled to rt and concentrated under reduce pressure. The residue was dissolved in H_2O and neutralized with K_2CO_3. The oily product was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried with K_2CO_3, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on a 120 g of Redi-Sep™ column using 0 to 100% gradient of EtOAc in hexane over 20 min as eluent to provide 5-chloro-2-(chloromethyl)-3-(2-methoxyphenyl)quinazolin-4(3H)-one as off-white solid. ^{1}H NMR (DMSO-d_6) δ ppm 7.83 (1 H, t, J=7.9 Hz), 7.69 - 7.74 (1 H, m), 7.64 (1 H, dd, J=7.9, 0.9 Hz), 7.51 - 7.58 (1 H, m), 7.47 (1 H, dd, J=7.7, 1.6 Hz), 7.26 (1 H, d, J=8.3 Hz), 7.09 - 7.17 (1 H, m), 4.28 (2 H, dd, J=51.8, 12.5 Hz), 3.77 (3 H, s). Mass Spectrum (ESI) m/e = 335.0 and 337.0 (M + 1).

4-Amino-8-((5-chloro-3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one



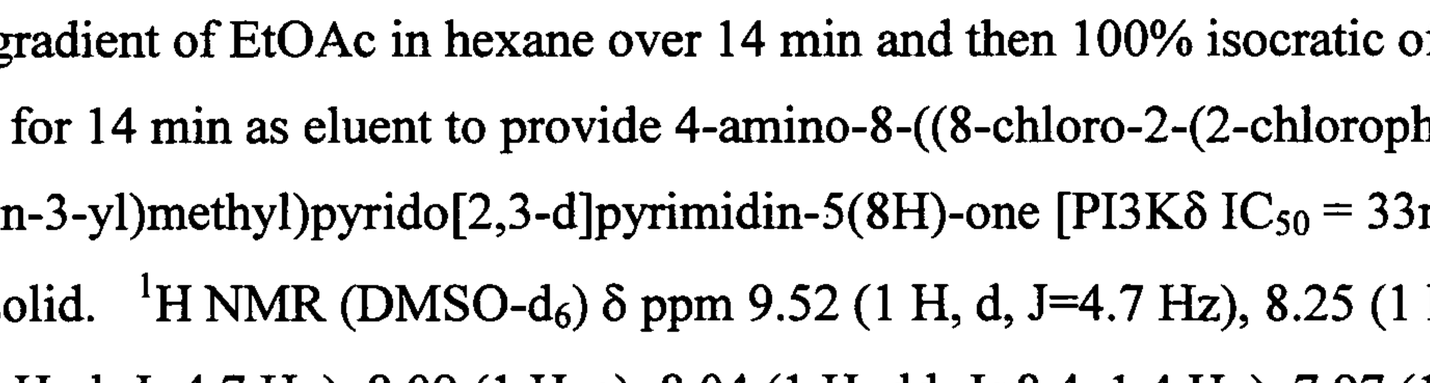
To a mixture of 4-aminopyrido[2,3-d]pyrimidin-5(8H)-one (0.1 g, 0.616 mmol), Cs_2CO_3 (0.3013 g, 0.925 mmol, 1.5 eq), and KI (0.0102 g, 0.0616 mmol, 0.1 eq) in DMF (2 mL) was added 5-chloro-2-(chloromethyl)-3-(2-methoxyphenyl)-quinazolin-4(3H)-one (0.2273 g, 0.678 mmol, 1.1 eq) and the mixture was stirred at 100 °C for 1 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on a 40 g of Redi-Sep™ column using 0 to 100% gradient of :MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 14 min as eluent to provide 4-amino-8-((5-chloro-3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one as yellow solid (0.1707 g, 60%). The yellow solid was triturated with MeOH and filtered to provide 4-amino-8-((5-chloro-3-(2-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one [PI3Kδ IC_{50} = 13nM] as yellow solid. ^1H NMR (DMSO-d_6) d ppm 9.53 (1 H, d, J=4.7 Hz), 8.20 (1 H, s), 8.14 (1 H, d, J=4.7 Hz), 7.88 (1 H, d, J=7.8 Hz), 7.65 - 7.72 (1 H, m), 7.49 - 7.59 (3 H, m), 7.37 (1 H, dd, J=8.2, 1.2 Hz), 7.31 (1 H, dd, J=8.6, 1.2 Hz), 7.15 - 7.21 (1 H, m), 6.20 (1 H, d, J=8.2 Hz), 4.91 - 5.13 (2 H, m), 3.85 (3 H, s). Mass Spectrum (ESI) m/e = 461.0 (M + 1).

Example 22: Preparation of 4-Amino-8-((8-chloro-2-(2-chlorophenyl)-quinolin-3-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one:



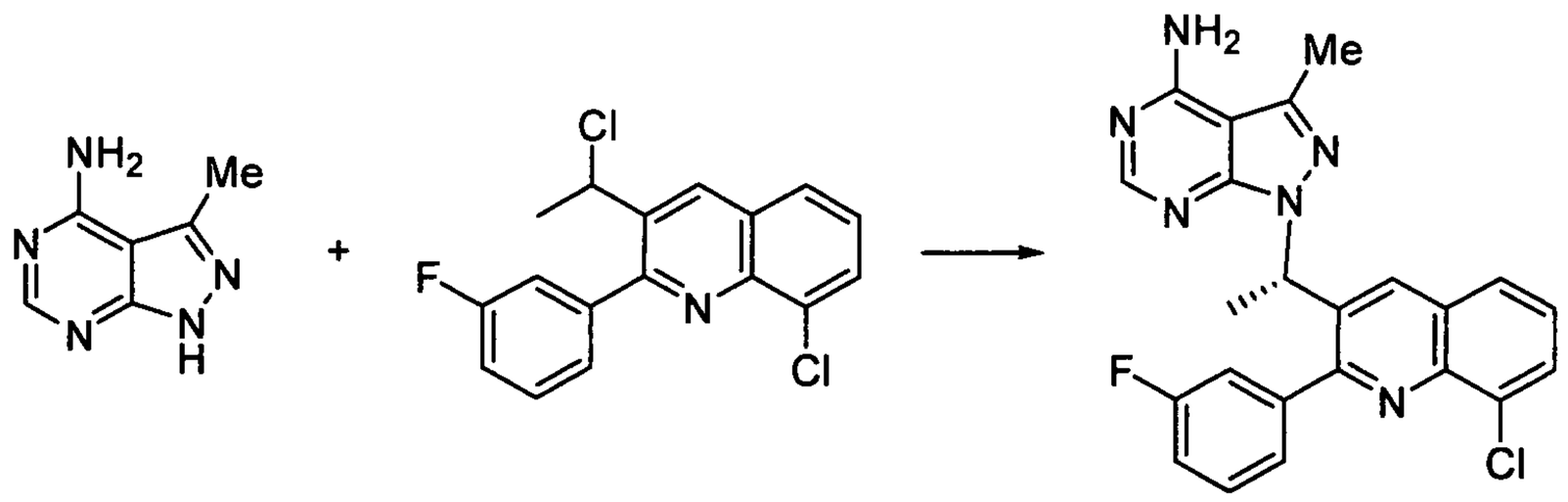
To a mixture of 4-aminopyrido[2,3-d]pyrimidin-5(8H)-one (0.05 g, 0.308 mmol), Cs_2CO_3 (0.1515 g, 0.46 mmol, 1.5 eq), and KI (0.0051 g, 0.0309 mmol, 0.1 eq) in DMF (1 mL) was added 8-chloro-3-(chloromethyl)-2-(2-chlorophenyl)quinoline (0.1 g, 0.309 mmol, 1.0 eq) and the mixture was stirred at 140 °C for 1 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on a 40 g of Redi-Sep™ column using 0 to 100% gradient of EtOAc in hexane over 14 min and then 100% isocratic of EtOAc for 14 min as eluent to provide 4-amino-8-((8-chloro-2-(2-chlorophenyl)-quinolin-3-yl)methyl)pyrido[2,3-d]pyrimidin-5(8H)-one [PI3Kδ IC_{50} = 33nM] as white solid. ^{1}H NMR (DMSO-d_6) δ ppm 9.52 (1 H, d, J=4.7 Hz), 8.25 (1 H, s), 8.11 (1 H, d, J=4.7 Hz), 8.09 (1 H, s), 8.04 (1 H, dd, J=8.4, 1.4 Hz), 7.97 (1 H, dd, J=7.6, 1.4 Hz), 7.81 (1 H, d, J=7.8 Hz), 7.63 (1 H, d, J=7.8 Hz), 7.57 - 7.61 (1 H, m), 7.42 - 7.53 (3 H, m), 6.14 (1 H, d, J=7.8 Hz), 5.40 (2 H, s). Mass Spectrum (ESI) m/e = 448.0 and 450.1 (M + 1).

Example 23:



1,3,5-Trichlorotriazine (94 mg, 510 μmol) was added to dimethylformamide (0.04 mL, 510 μmol) at 25 °C. After the formation of a white solid (10 min), DCM (3 mL) was added, followed by 1-(8-chloro-2-(3-fluorophenyl)quinolin-3-yl)ethanol

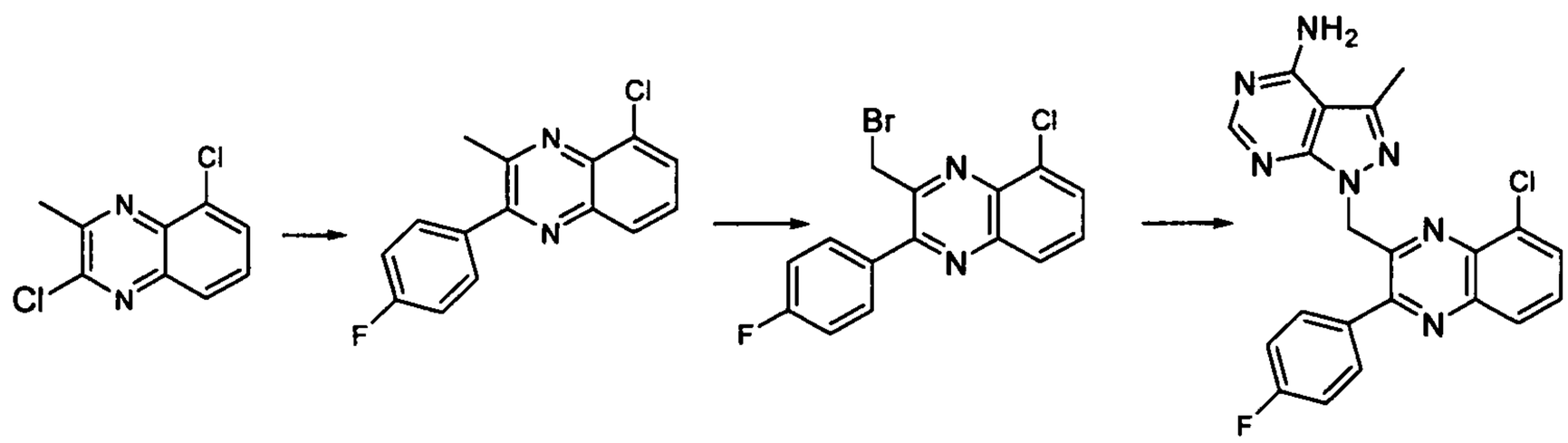
(140.0 mg, 464 μmol), made from procedure K. After the addition, the mixture was stirred at room temperature for 4 h. Water (10 mL) was added, and then diluted with DCM (10 mL), the organic phase was washed with 15 mL of a saturated solution of $NaHCO_3$, followed by water and brine. The organic layers were dried and concentrated. Purification of the residue by flash chromatography over silica gel, using 10% hexane in EtOAc, gave 8-chloro-3-(1-chloroethyl)-2-(3-fluorophenyl)quinoline, Mass Spectrum (ESI) m/e = 320.0 (M + 1).



To a solution of 3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine[1] (28 mg, 187 μmol) in DMF(2 mL) was added sodium hydride, 60% dispersion in mineral oil (15 mg, 375 μmol) at 0 °C and the mixture was stirred at rt for 10 min. To the mixture was added a solution of 8-chloro-3-(1-chloroethyl)-2-(3-fluorophenyl)-quinoline (60.0 mg, 187 μmol) in DMF (1 mL) and the mixture was stirred at rt for 24 hrs. The mixture was poured into ice-water and extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated. The residue was purified by flash chromatography over silica gel, using DCM and MeOH (95:5), then Chiral HPLC (Chiralpak IA column, 0.46 x 250mm, 5 mm), using 15% isopropanol in hexane as eluent, gave 1-((S)-1-(8-chloro-2-(3-fluorophenyl)-quinolin-3-yl)ethyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine, a fraction collected at 17 min, 99 %ee at 254 nm, ^{1}H NMR (DMSO-d_6) δ ppm 8.62 (1 H, s), 8.09 (1 H, d, J=8.2 Hz), 7.97 (1 H, d, J=8.2 Hz), 7.96 (1 H, s), 7.63 (1 H, t, J=8.0 Hz), 7.35-7.41 (1 H, m), 7.13-7.22 (3 H, m), 6.22-6.27 (1 H, m), 2.47 (3 H, s), 1.79 (3 H, d, J=6.8 Hz). Mass Spectrum (ESI) m/e = 433.1 (M + 1).

Example 24:

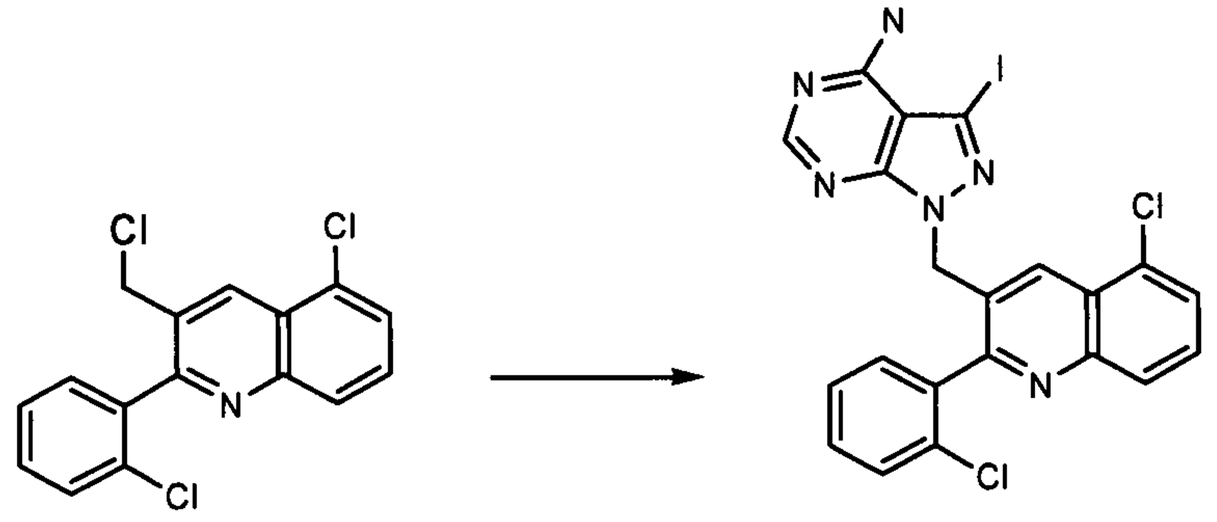
Using the same or analogous synthetic techniques and substituting with appropriate reagents as in Example 1, the following compound was prepared:



1-((8-chloro-3-(4-fluorophenyl)quinoxalin-2-yl)methyl)-3-methyl-1H-pyrazolo-[3,4-d]pyrimidin-4-amine, ^{1}H NMR (DMSO-d_6) δ ppm 8.08 (1 H, dd, J=8.0, 1.2 Hz), 8.02 (1 H, dd, J=8.0, 1.2 Hz), 8.01 (1 H, s), 7.85 (1 H, t, J=8.0 Hz), 7.58-7.64 (2 H, m), 7.11-7.18 (3 H, m), 2.38 (3 H, s). Mass Spectrum (ESI) m/e = 420.1 (M + 1).

Example 25:

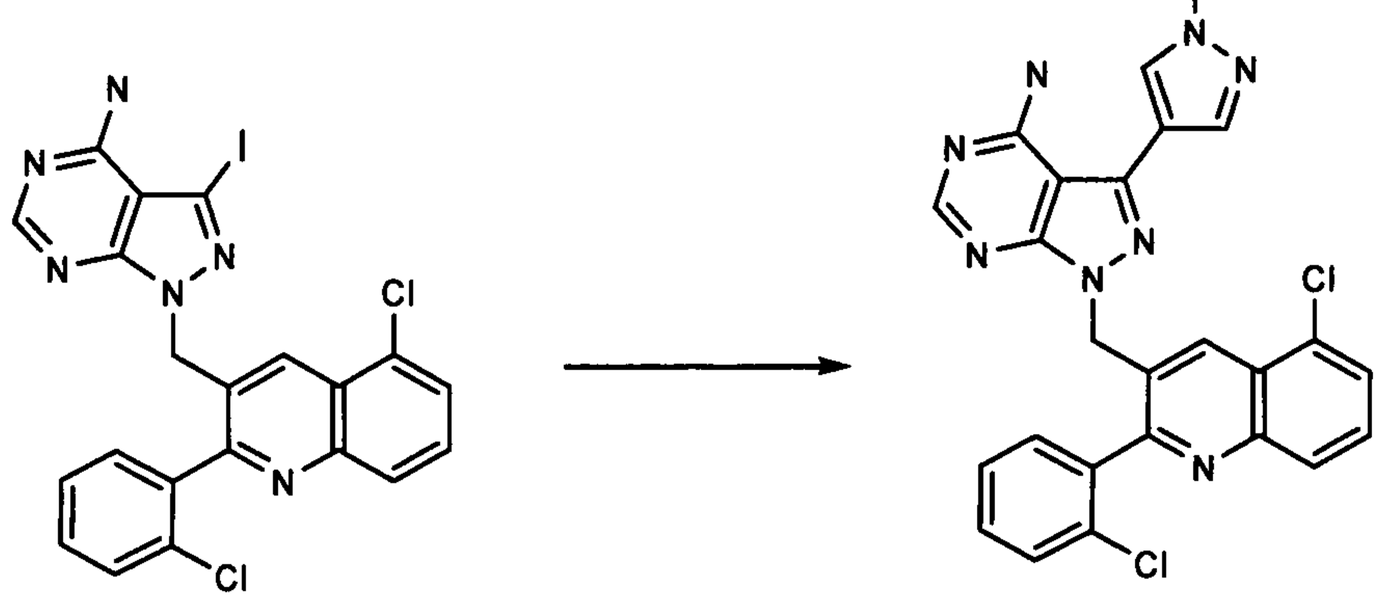
1-((5-Chloro-2-(2-chlorophenyl)quinolin-3-yl)methyl)-3-iodo-1H-pyrazolo-[3,4-d]pyrimidin-4-amine



Prepared according to Procedure **I** using 5-chloro-3-(chloromethyl)-2-(2-chloro-phenyl)quinoline (0.700 g, 2.17 mmol), 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.623 g, 2.39 mmol, 1.1 eq) and NaH (0.078 g, 3.26 mmol, 1.5 eq) in DMF (15 mL). N-((8-chloro-2-(3-fluorophenyl)quinolin-3-yl)methyl)-9H-purin-6-amine [PI3Kδ IC50 = 35 nM] was obtained after purification as a white solid. 1H-NMR (MeOD) δ ppm 8.62 (s, 1H), 8.00 (s, 1H), 7.89-7.91 (m, 1H), 7.82-7.85 (m, 1H), 7.43 (d, 1H, J=5.0 Hz), 7.29-7.32 (t, 1H), 7.18-7.22 (t, 1H), 7.06 (d, 1H, J=5.0 Hz), 5.63 (s, 2H), Mass Spectrum (ESI) m/e = 548 (M + 1).

Example 26

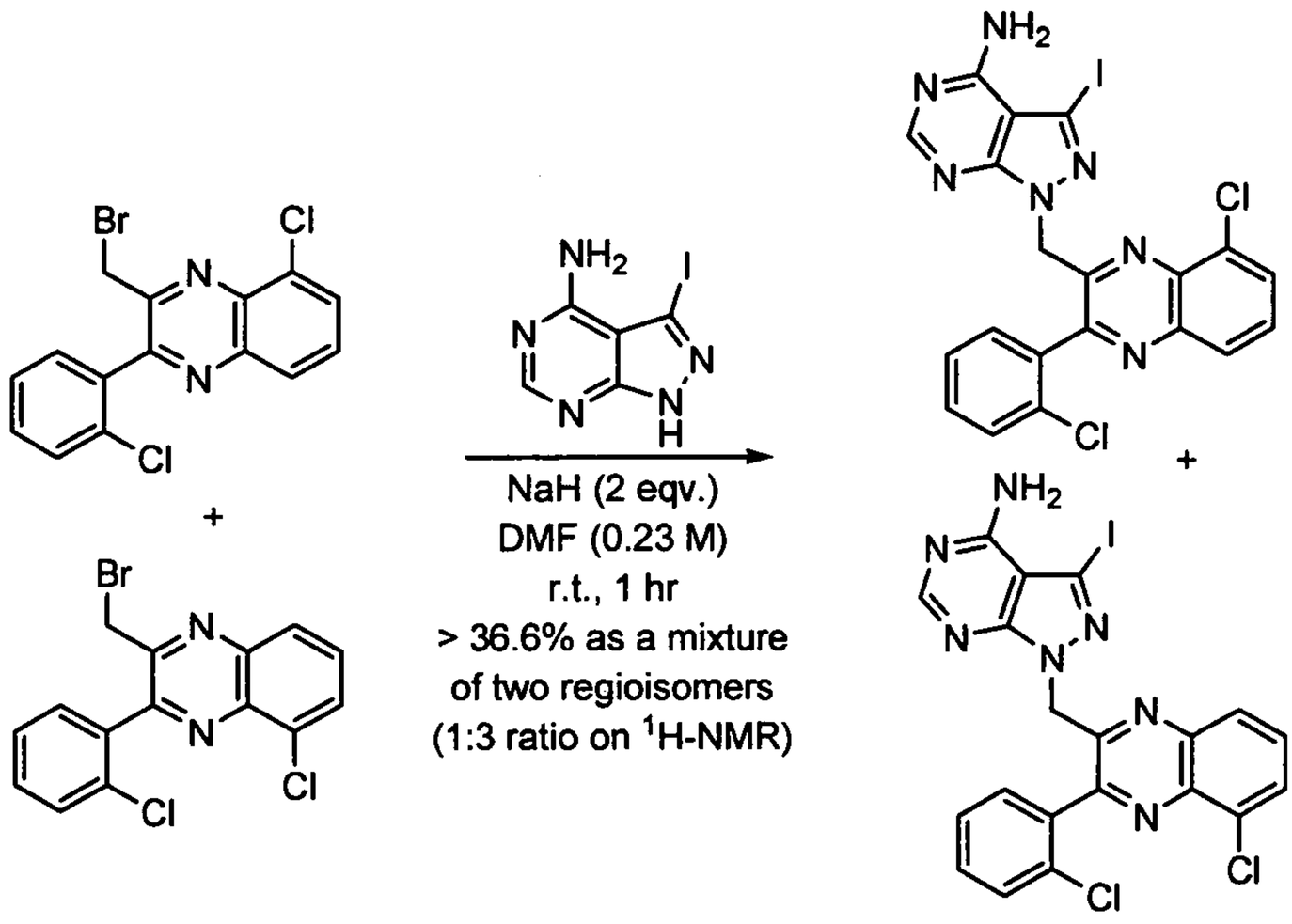
1-((5-chloro-2-(2-chlorophenyl)quinolin-3-yl)methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



Prepared according to Procedure **J** using 1-((5-chloro-2-(2-chlorophenyl)quinolin-3-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.060 g, 0.110 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.032 g, 0.164 mmol, 1.5 eq), tetrakis(triphenylphosphine)palladium (0.006 g, 10 mol %), and sodium carbonate (2M aq. Sol., 6 eq) in DMF (0.2M)). 1-((5-chloro-2-(2-chlorophenyl)quinolin-3-yl)methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine was obtained after purification as a white solid. 1H-NMR (MeOD) δ ppm 8.56 (s, 1H), 8.01-8.05 (m, 3H), 7.87 (d, 1H, J=5.0), 7.80-7.83 (m, 1H), 7.65 (s, 1H), 7.47 (d, 1H, J=5.0), 7.34 (t, 1H, J=5.0), 7.24 (t, 1H, J=5.0 Hz), 7.15 (d, 1H), 5.63 (s, 2H), 3.89 (s, 3H), Mass Spectrum (ESI) m/e = 502 (M + 1).

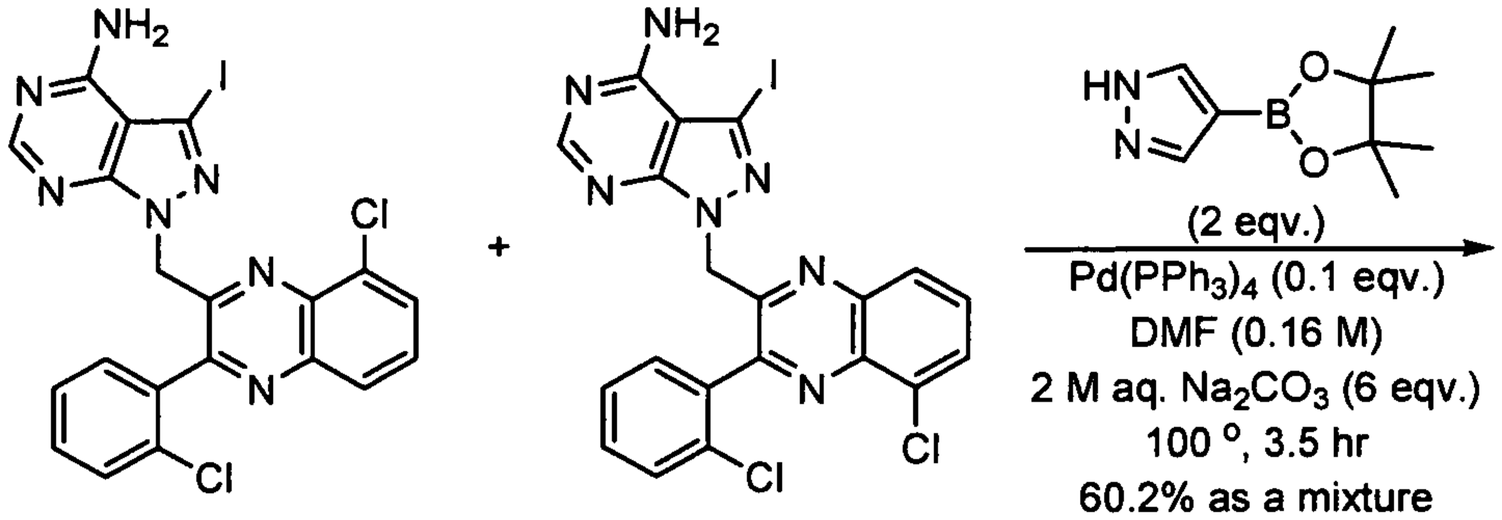
Example 27: Preparation of 1-((8-chloro-3-(2-chlorophenyl)quinoxalin-2-yl)-methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a TFA salt and 1-((5-chloro-3-(2-chlorophenyl)quinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a TFA salt:

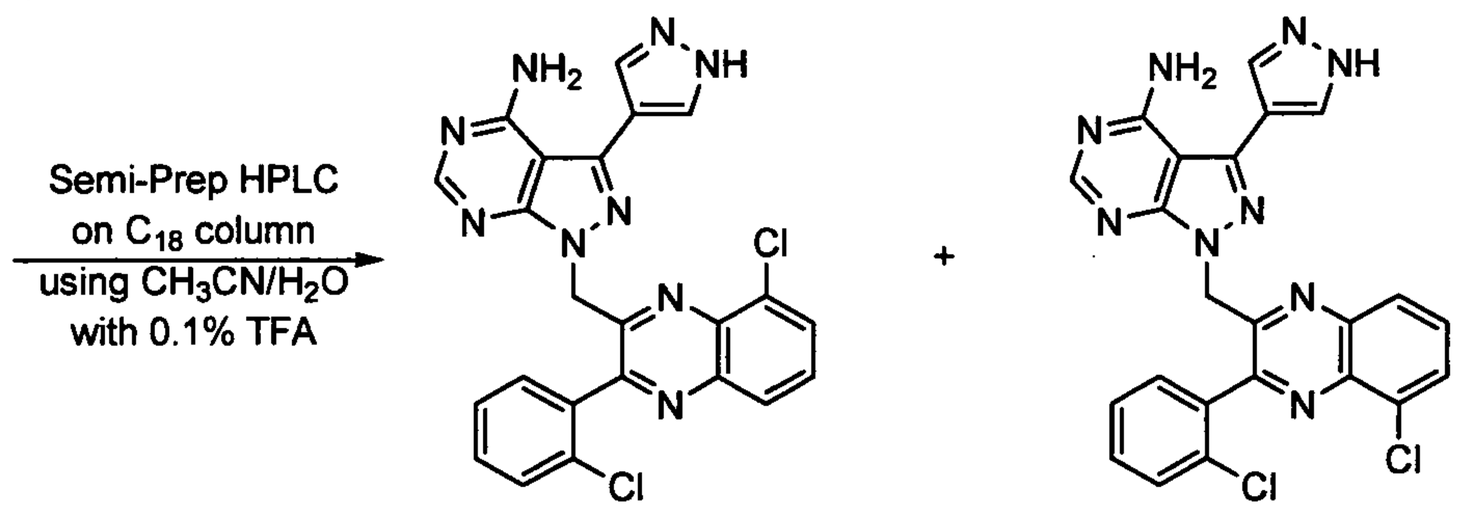
1-((8-Chloro-3-(2-chlorophenyl)quinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((5-chloro-3-(2-chlorophenyl)-quinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine



To a solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.7168 g, 2.746 mmol) in 6 mL of DMF was added sodium hydride, 60% dispersion in mineral oil (0.2197 g, 5.492 mmol) at 0 °C and the mixture was stirred at room temperature. After 10 min, to the mixture was added a solution of a mixture of 3-(bromomethyl)-5-chloro-2-(2-chlorophenyl)quinoxaline and 2-(bromomethyl)-5-chloro-3-(2-chlorophenyl)quinoxaline (1.061 g, 2.883 mmol) in 6 mL of DMF and the mixture was stirred at room temperature. After 1 hr, the mixture was poured into ice-water (100 mL). The resulting precipitate was colloected by filtration to give yellow solid (1.2805 g). The yellow solid was purified by column chromatography on a 40 g of Redi-Sep™ column using 0-100% gradient of EtOAc in hexane over 14 min and then 100% isocratic of EtOAc for 16 min as eluent to give a mixture of two regioisomers as yellow solid. The yellow solid was suspended in EtOAc and filtered to give 1-((8-chloro-3-(2-chlorophenyl)-quinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((5-chloro-3-(2-chlorophenyl)quinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine as tan solid: LC-MS (ESI) m/z 547.9 $[M+H]^+$.

1-((8-Chloro-3-(2-chlorophenyl)quinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a TFA salt and 1-((5-Chloro-3-(2-chlorophenyl)quinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a TFA salt

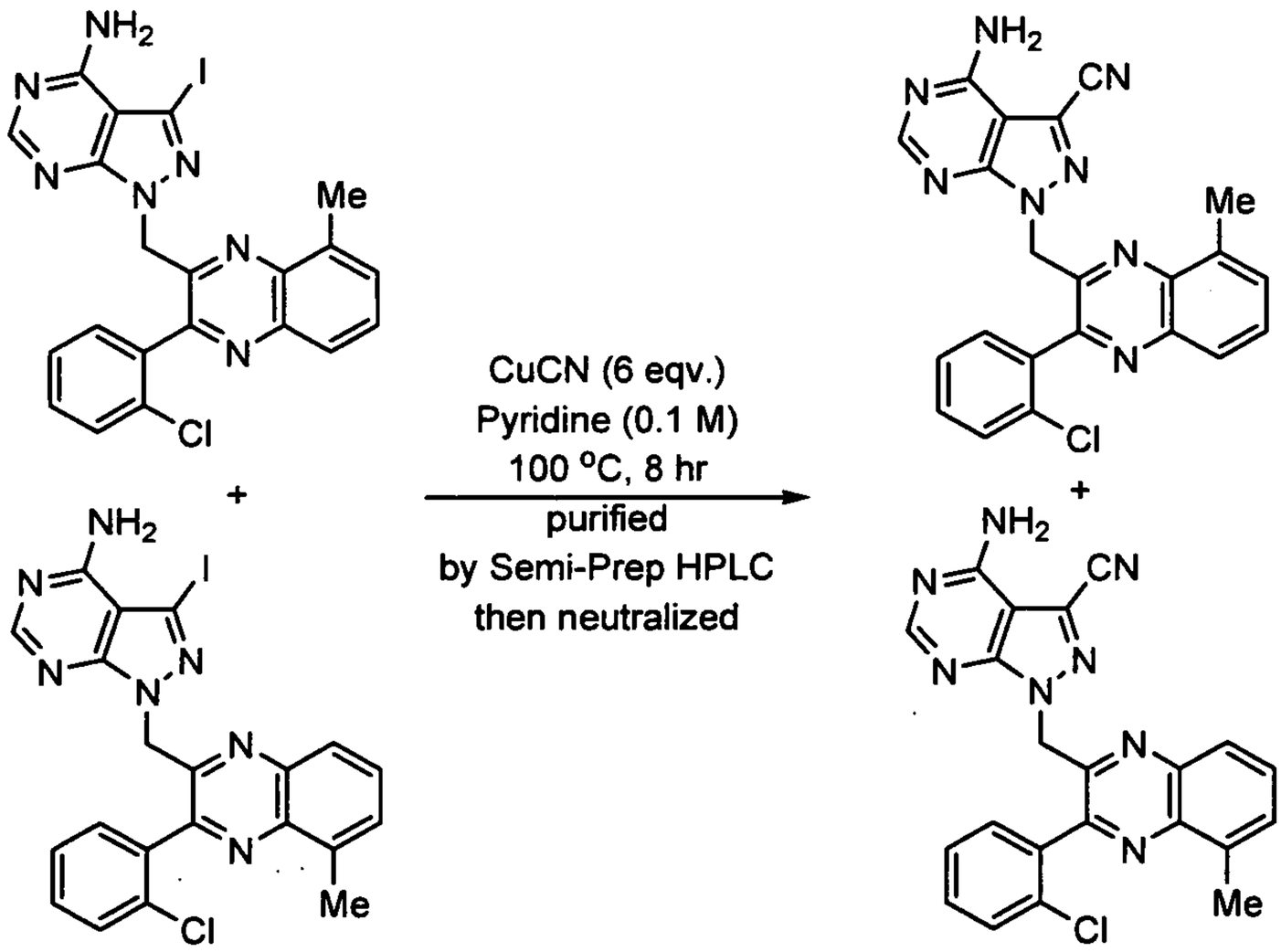




A solution of a mixture of 1-((8-chloro-3-(2-chlorophenyl)quinoxalin-2-yl)-methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((5-chloro-3-(2-chlorophenyl)quinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine in 3.2 mL of DMF was treated with 4-pyrazoleboronic acid pinacol ester (0.2124 g, 1.095 mmol), tetrakis(triphenylphosphine)palladium(0) (0.06324 g, 0.05473 mmol), and 2 M aq. sodium carbonate sol. (1.642 mL, 3.284 mmol). The mixture was heated at 100 °C. After 3.5 hr, the mixture was removed from the heat and poured onto ice-water (100 mL). The resulting precipitate was collected by suction filtration, washed with water, and air-dried to give tan solid. The tan solid was purified by column chromatography on a 40 g of Redi-Sep™ column using 0 to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 14 min and then 100% isocratic of CH_2Cl_2:MeOH:NH_4OH (89:9:1) for 8 min as eluent to give a product mixture of two regioisomers as off-white solid. The off-white solid was dissolved purified by semi-prep-HPLC on C18 column using 30-60% gradient of CH_3CN (0.1% of TFA) in water (0.1% of TFA) over 40 min as

eluent to give two separated regioisomers: **1-((8-chloro-3-(2-chlorophenyl)-quinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a TFA salt** as white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.14 (1 H, s), 8.12 - 8.13 (1 H, m), 8.11 (1 H, q, J=1.4 Hz), 7.85 - 7.94 (3 H, m), 7.44 (1 H, d, J=7.8 Hz), 7.22 - 7.33 (3 H, m), 5.89 (1 H, s), 5.85 (1 H, s); LC-MS: m/z 488.0 and 490.0 [M+1], (Exact Mass: 487.08) and **1-((5-chloro-3-(2-chlorophenyl)quinoxalin-2-yl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a TFA salt** as white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.16 (1 H, s), 8.12 (1 H, s), 8.10 (1 H, s), 7.87 - 7.95 (3 H, m), 7.44 - 7.50 (1 H, m), 7.25 - 7.37 (3 H, m), 5.87 (1 H, s), 5.83 (1 H, s); LC-MS: m/z 488.0 and 490.0 [M+1], (Exact Mass: 487.08).

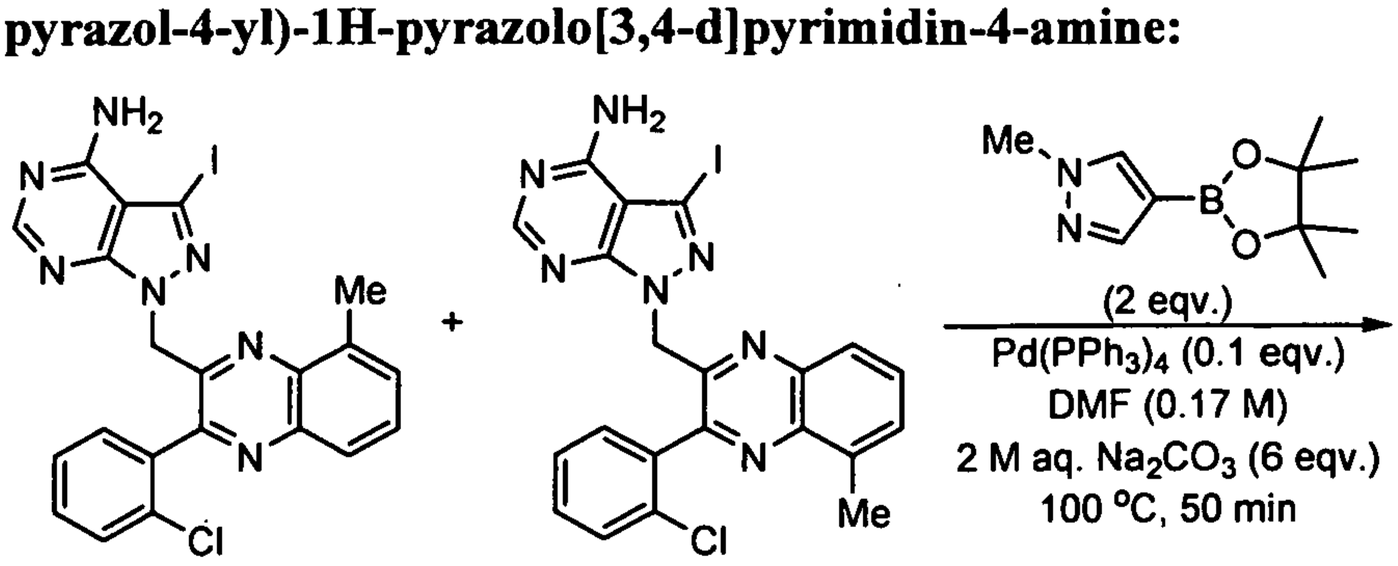
Example 28: Preparation of 4-Amino-1-((3-(2-chlorophenyl)-8-methyl-quinoxalin-2-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbonitrile and 4-Amino-1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbonitrile:

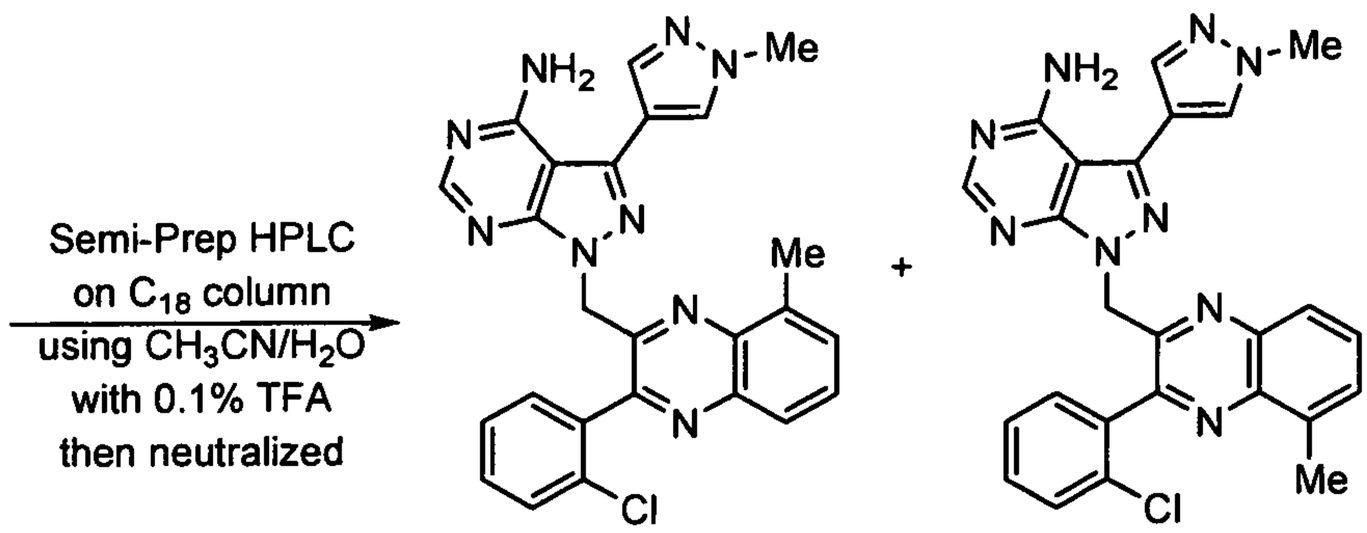


A suspension of a mixture of 1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)-methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-chloro-phenyl)-5-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**Prepared in Example 15**, 0.30000 g, 0.568 mmol) and copper(i) cyanide

(0.305 g, 3.41 mmol) in 5 mL of pyridine was stirred at 100 °C. After 8 hr, the mixture was cooled to room temperature. The mixture was concentrated under reduced pressure. The crude mixture was purified by column chromatography on a 40 g of Redi-Sep™ column using 0-100% gradient of EtOAc in hexane over 14 min and then 100% isocratic of EtOAc for 10 min as eluent to give a mixture of two regioisomers. The mixture was purified (1.5 mL (~50 mg) x 4 injections) by semi-prep-HPLC on a Gemini™ 10 μ C18 column (250 x 21.2 mm, 10 μm) using 30-70% gradient of CH_3CN (0.1% of TFA) in water (0.1% of TFA) over 40 min as eluent to give two fractions: each fraction was treated with saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (50 mL x 1). The each organic layer was washed with H_2O (30 mL x 2), dried over Na_2SO_4, filtered, concentrated under reduced pressure to give two separated regioisomers: **4-amino-1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbonitrile** as an off-white solid: ^1H NMR (500 MHz, DMF) δ ppm 8.16 (1 H, s), 7.95 (1 H, d, J=8.1 Hz), 7.78 - 7.83 (1 H, m), 7.73 - 7.78 (1 H, m), 7.50 - 7.56 (1 H, m), 7.39 - 7.45 (2 H, m), 7.32 - 7.38 (1 H, m), 5.86 (2 H, s), 2.50 (3 H, s); LC-MS (ESI) m/z 427.0 $[M+H]^+$ and **4-amino-1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbonitrile** as a white solid: ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.13 (1 H, s), 7.91 (1 H, dd, J=8.2, 0.9 Hz), 7.79 - 7.84 (1 H, m), 7.76 - 7.80 (1 H, m), 7.46 - 7.51 (1 H, m), 7.33 - 7.40 (2 H, m), 7.26 - 7.32 (1 H, m), 5.87 (2 H, s), 2.68 (3 H, s); LC-MS (ESI) m/z 427.1 $[M+H]^+$.

Example 29: Preparation of 1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)-methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine:

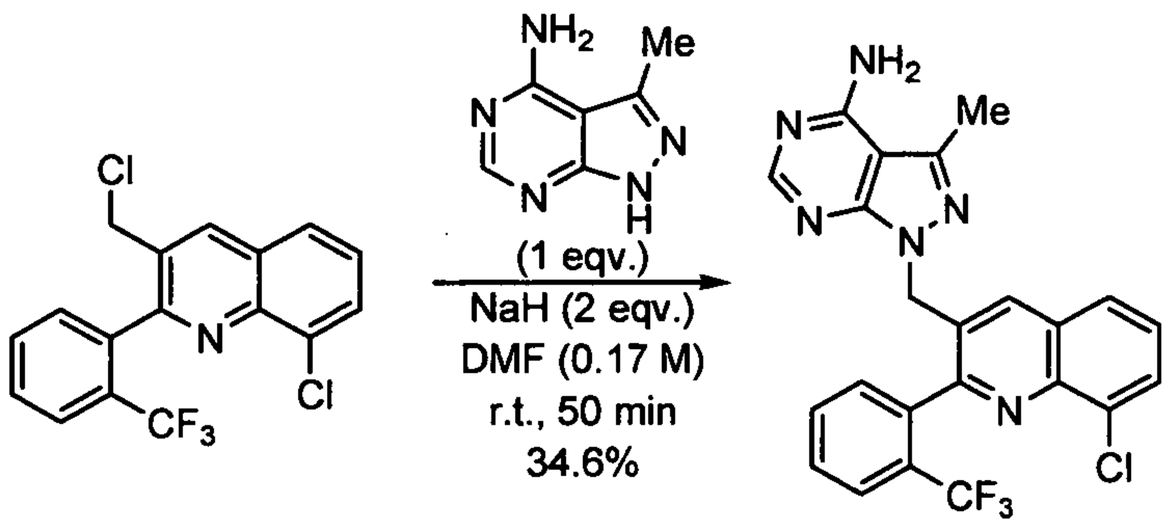




A solution of a mixture of 1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)-methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (**Prepared in Example 15**, 0.3000 g, 0.5685 mmol) in 3.3 mL of DMF was treated with 1-methylpyrazole-4-boronic acid pinacol ester (0.2366 g, 1.137 mmol), tetrakis(triphenylphosphine)palladium(0) (0.06569 g, 0.05685 mmol), and 2 M aq. sodium carbonate sol. (1.705 mL, 3.411 mmol). The mixture was stirred at 100 °C. After 50min, The mixture was cooled to room temperature. To the mixture was added water (50 mL) and the resulting precipitate was collected by filtration to give the products as a brown solid. The borwn solid was purified by column chromatography on a 40 g of Redi-Sep™ column using 0 to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 14 min and then 100% isocratic of CH_2Cl_2:MeOH:NH_4OH (89:9:1) for 10 min as eluent to give a mixture of two regioisomers as a dark brown solid. The dark brown solid was purified (1.5 mL (~53 mg) x 5 injections) by semi-prep-HPLC on a Gemini™ 10 μ C18 column (250 x 21.2 mm, 10 μm) using 20-60% gradient of CH_3CN (0.1% of TFA) in water (0.1% of TFA) over 40 min as eluent to give two fractions: each fraction was treated with saturated $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were respectively washed with H_2O (30 mL x 2), dried over Na_2SO_4, filtered, concentrated under reduced pressure to give two separated regioisomers: **1-((3-(2-chlorophenyl)-8-methylquinoxalin-2-yl)methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine** as an -off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.04 (1 H, s), 7.99 (1 H, s), 7.90 - 7.95 (1 H, m), 7.76 - 7.81 (1 H, m), 7.72 - 7.76 (1 H, m), 7.63 (1 H, d, J=0.8 Hz), 7.45 (1 H, dd, J=7.4, 0.8 Hz), 7.28 - 7.33 (1 H, m), 7.20 -

7.27 (2 H, m), 6.83 (2 H, br. s.), 5.62 - 5.93 (2 H, m), 3.87 (3 H, s), 2.57 (3 H, s); LC-MS (ESI) m/z 482.0 $[M+H]^+$ and **1-((3-(2-chlorophenyl)-5-methylquinoxalin-2-yl)methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine** as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.01 (1 H, s), 7.97 (1 H, s), 7.94 (1 H, dd, J=8.4, 1.0 Hz), 7.78 - 7.84 (1 H, m), 7.74 - 7.78 (1 H, m), 7.61 (1 H, d, J=0.8 Hz), 7.38 - 7.43 (1 H, m), 7.22 - 7.28 (1 H, m), 7.14 - 7.22 (2 H, m), 6.81 (2 H, br. s.), 5.59 - 5.95 (2 H, m), 3.86 (3 H, s), 2.66 (3 H, s); LC-MS (ESI) m/z 482.0 $[M+H]^+$.

Example 30: Preparation of 1-((8-chloro-2-(2-(trifluoromethyl)phenyl)-quinolin-3-yl)methyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine:

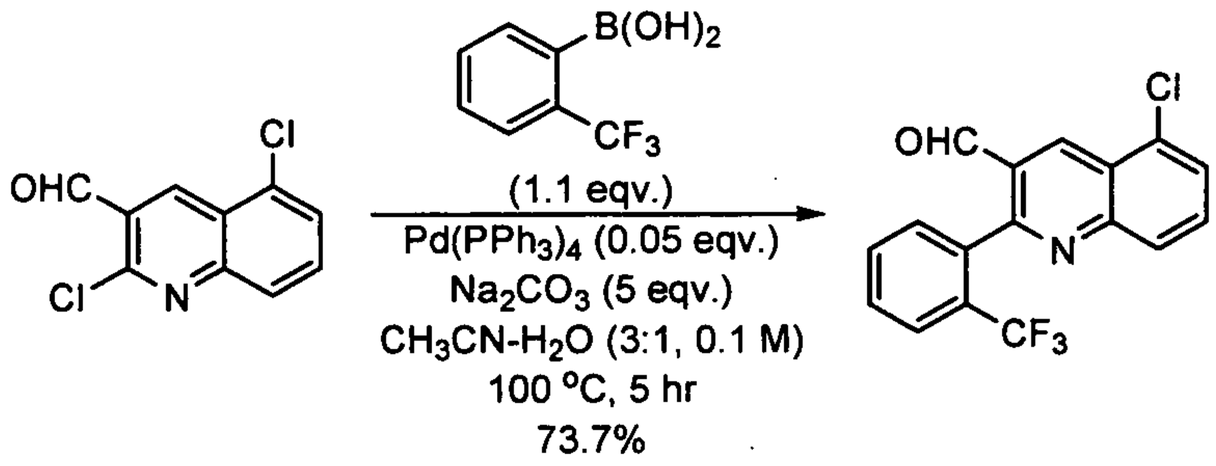


To a solution of 3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.07385 g, 0.4951 mmol) in 1 mL of DMF was added Sodium hydride, 60% dispersion in mineral oil (0.03960 g, 0.9902 mmol) at 0 °C and the mixture was stirred at room temperature. After 10 min at room temperature, to the mixture was added a solution of 8-chloro-3-(chloromethyl)-2-(2-(trifluoromethyl)phenyl)quinoline hydrochloride (**Prepared in Example 6**, 0.1944 g, 0.4951 mmol) in 2 mL of DMF and the mixture was stirred at room temperature. After 50 min, the mixture was poured into ice-water (100 mL). The resulting precipitate was colloected by filtration to give a brown solid (0.2185 g). The aq. filtrate also contained the desired product. The aq. filtrate was extracted with CH_2Cl_2 (50 mL x 3). The combined organis layers were washed with brine (50 mL x 1), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a colorless syrup (0.0346 g). The brown solid and the colorless syrup were combined and purified by column chromatography on a 40 g of Redi-Sep™ column using 0-100% gradient of EtOAc in hexane over 14 min, then 100% isocratic of EtOAc for 10 min, and then 0% to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 14

min as eluent to give 1-((8-chloro-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)-methyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine as an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.24 (1 H, s), 8.03 (1 H, dd, J=8.3, 1.3 Hz), 7.97 (1 H, dd, J=7.5, 1.3 Hz), 7.95 (1 H, s), 7.79 - 7.85 (1 H, m), 7.57 - 7.67 (3 H, m), 7.32 - 7.37 (1 H, m), 7.24 (2 H, br. s.), 5.30 - 5.42 (2 H, m), 2.46 (3 H, s); LC-MS (ESI) m/z 469.1 $[M+H]^+$.

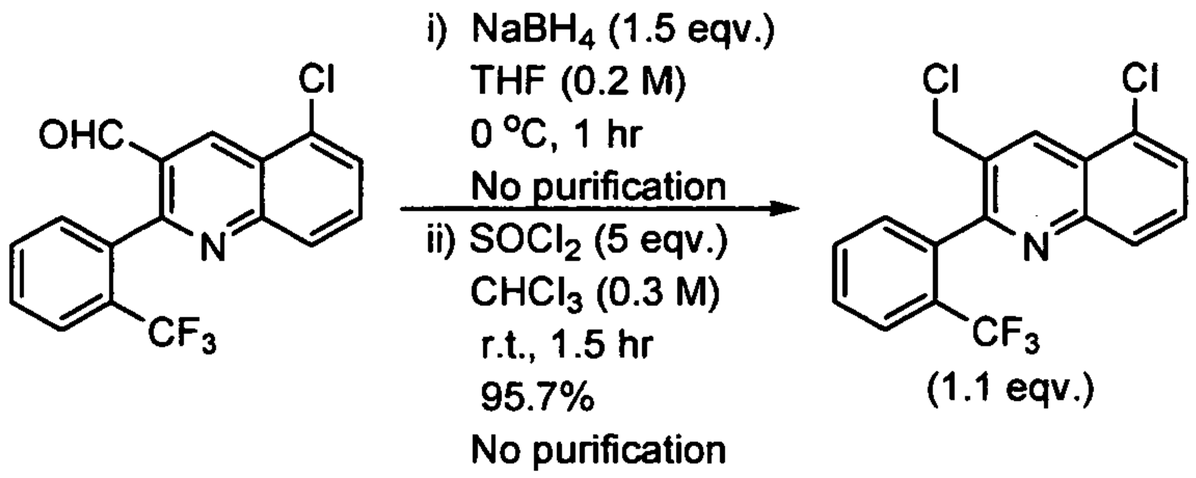
Example 31: Preparation of 1-((5-chloro-2-(2-(trifluoromethyl)phenyl)-quinolin-3-yl)methyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine:

5-Chloro-2-(2-(trifluoromethyl)phenyl)quinoline-3-carbaldehyde



A mixture of 2,5-dichloroquinoline-3-carbaldehyde (1.9948 g, 8.8243 mmol), 2-(trifluoromethyl)phenylboronic acid (1.8436 g, 9.7067 mmol), tetrakis(triphenyl-phosphine)palladium (0.50985 g, 0.44121 mmol), and sodium carbonate anhydrous (4.6763 g, 44.121 mmol) in 88 mL of CH_3CN-H_2O (3:1) was stirred at 100 °C. After 5 hr, the mixture was cooled to room temperature and partitioned between EtOAc (100 mL) and water (100 mL). The organic layer was washed with brine (50 mL x 2), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a red syrup. The red syrup was purified by silica gel column chromatography on a 80 g of Redi-Sep™ column using 0 to 50% gradient of EtOAc in hexane over 25 min and then 50% isocratic of EtOAc for 30 min as eluent to give 5-chloro-2-(2-(trifluoromethyl)phenyl)quinoline-3-carbaldehyde as a light-yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.01 (1 H, s), 9.19 (1 H, d, J=1.0 Hz), 8.08 - 8.14 (1 H, m), 7.97 - 8.03 (2 H, m), 7.89 - 7.95 (1 H, m), 7.73 - 7.84 (2 H, m), 7.55 - 7.61 (1 H, m); LC-MS (ESI) m/z 336.1 $[M+H]^+$.

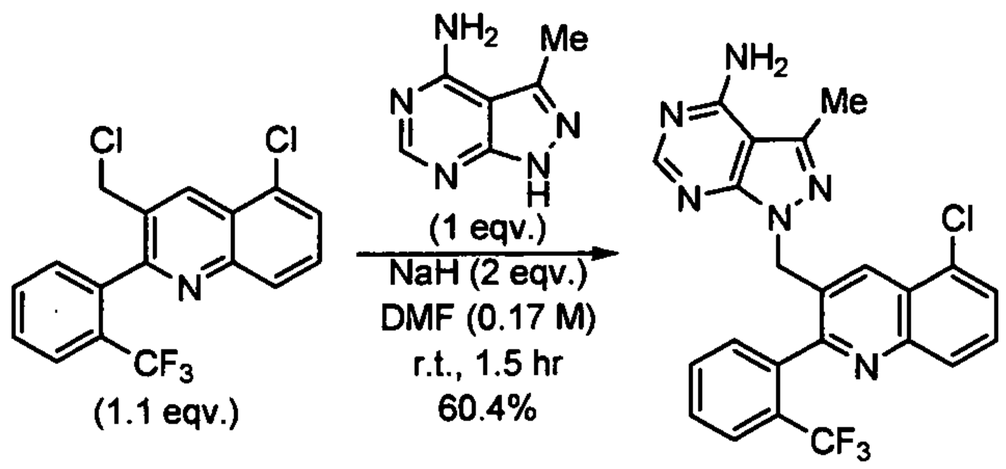
5-Chloro-3-(chloromethyl)-2-(2-(trifluoromethyl)phenyl)quinoline hydrochloride



To a solution of 5-chloro-2-(2-(trifluoromethyl)phenyl)quinoline-3-carbaldehyde (2.1673 g, 6.456 mmol) in 32 mL of THF at 0 °C was added sodium borohydride (0.3664 g, 9.684 mmol) and the mixture was stirred at 0 °C. After 1 hr at 0 °C, the mixture was partitioned between EtOAc (100 mL) and H_2O (100 mL), and the organic layer was washed with brine (50 mL x 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (5-chloro-2-(2-(trifluoromethyl)-phenyl)quinolin-3-yl)methanol as a yellow syrup: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.68 - 8.73 (1 H, m), 7.96 - 8.02 (1 H, m), 7.90 - 7.95 (1 H, m), 7.83 - 7.87 (1 H, m), 7.68 - 7.83 (3 H, m), 7.50 - 7.58 (1 H, m), 5.63 (1 H, t, J=5.3 Hz), 4.36 (2 H, br. s.); LC-MS (ESI) m/z 338.0 $[M+H]^+$. The product was carried on crude without purification for the next step.

A solution of (5-chloro-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methanol (2.180 g, 6.455 mmol) in 22 mL of $CHCl_3$ was treated with thionyl chloride (2.348 mL, 32.27 mmol) dropwise, and the reaction mixture was stirred at room temperature. After 1.5 hr, the mixture was concentrated under reduced pressure and co-evaporated three times with CH_2Cl_2 to give 5-chloro-3-(chloromethyl)-2-(2-(trifluoromethyl)phenyl)quinoline hydrochloride as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.86 (1 H, d, J=0.6 Hz), 7.99 - 8.05 (1 H, m), 7.94 (1 H, dd, J=7.4, 1.0 Hz), 7.88 - 7.92 (1 H, m), 7.81 - 7.87 (2 H, m), 7.74 - 7.81 (1 H, m), 7.61 - 7.66 (1 H, m), 4.77 (2 H, d, J=79.0 Hz); LC-MS (ESI) m/z 356.0 and 358.0 $[M+H]^+$ (Exact Mass of neutal form: 355.014). The yellow solid was carried on crude without purification for the next step.

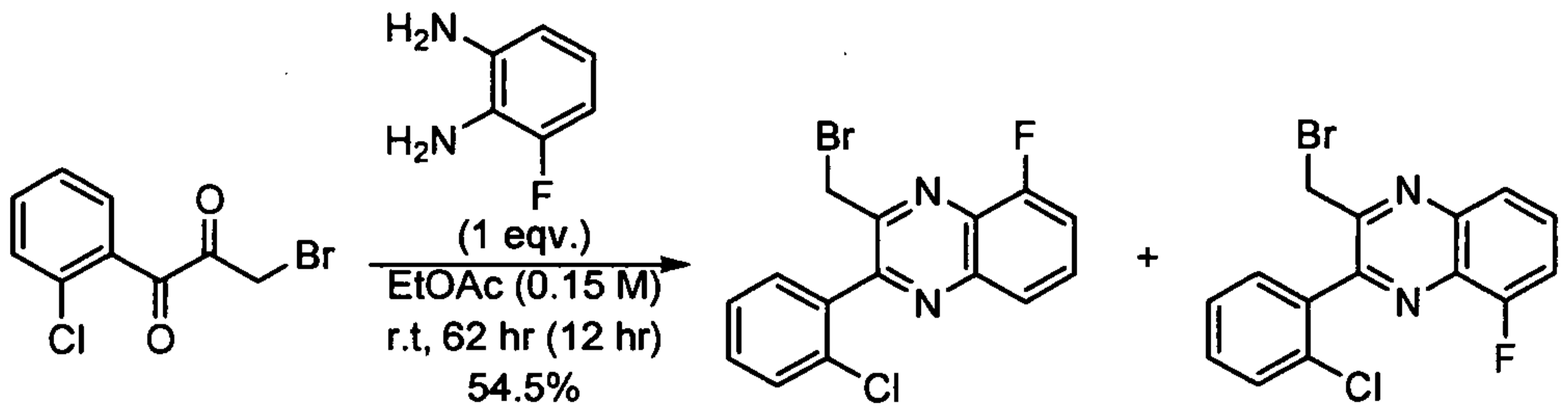
1-((5-Chloro-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)methyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine



To a solution of 3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.0956 g, 0.641 mmol) in 1 mL of DMF was added sodium hydride, 60% dispersion in mineral oil (0.0513 g, 1.28 mmol) at 0 °C and the mixture was stirred at room temperature. After 5 min at room temperature, to the mixture was added a solution of 5-chloro-3-(chloromethyl)-2-(2-(trifluoromethyl)phenyl)quinoline hydrochloride (0.2767 g, 0.705 mmol) in 3 mL of DMF and the mixture was stirred at room temperature. After 1.5 hr, the mixture was poured into ice-water (100 mL). The resulting precipitate was collected by filtration to give an off-white solid. The off white solid was purified by column chromatography on a 40 g of Redi-Sep™ column using 0-100% gradient of EtOAc in hexane over 14 min and then 0% to 100% gradient of CH_2Cl_2:MeOH:NH_4OH (89:9:1) in CH_2Cl_2 over 14 min as eluent to give an off-white solid. The off-white solid was suspended in CH_2Cl_2-hexane (1:1) and filtered to give 1-((5-chloro-2-(2-(trifluoromethyl)phenyl)quinolin-3-yl)-methyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.44 (1 H, d, J=0.8 Hz), 7.96 - 8.02 (1 H, m), 7.94 (1 H, s), 7.84 - 7.88 (1 H, m), 7.75 - 7.83 (2 H, m), 7.52 - 7.64 (2 H, m), 7.05 - 7.49 (3 H, m, J=6.7 Hz), 5.42 (2 H, s), 2.45 (3 H, s); LC-MS (ESI) m/z 469.1 $[M+H]^+$.

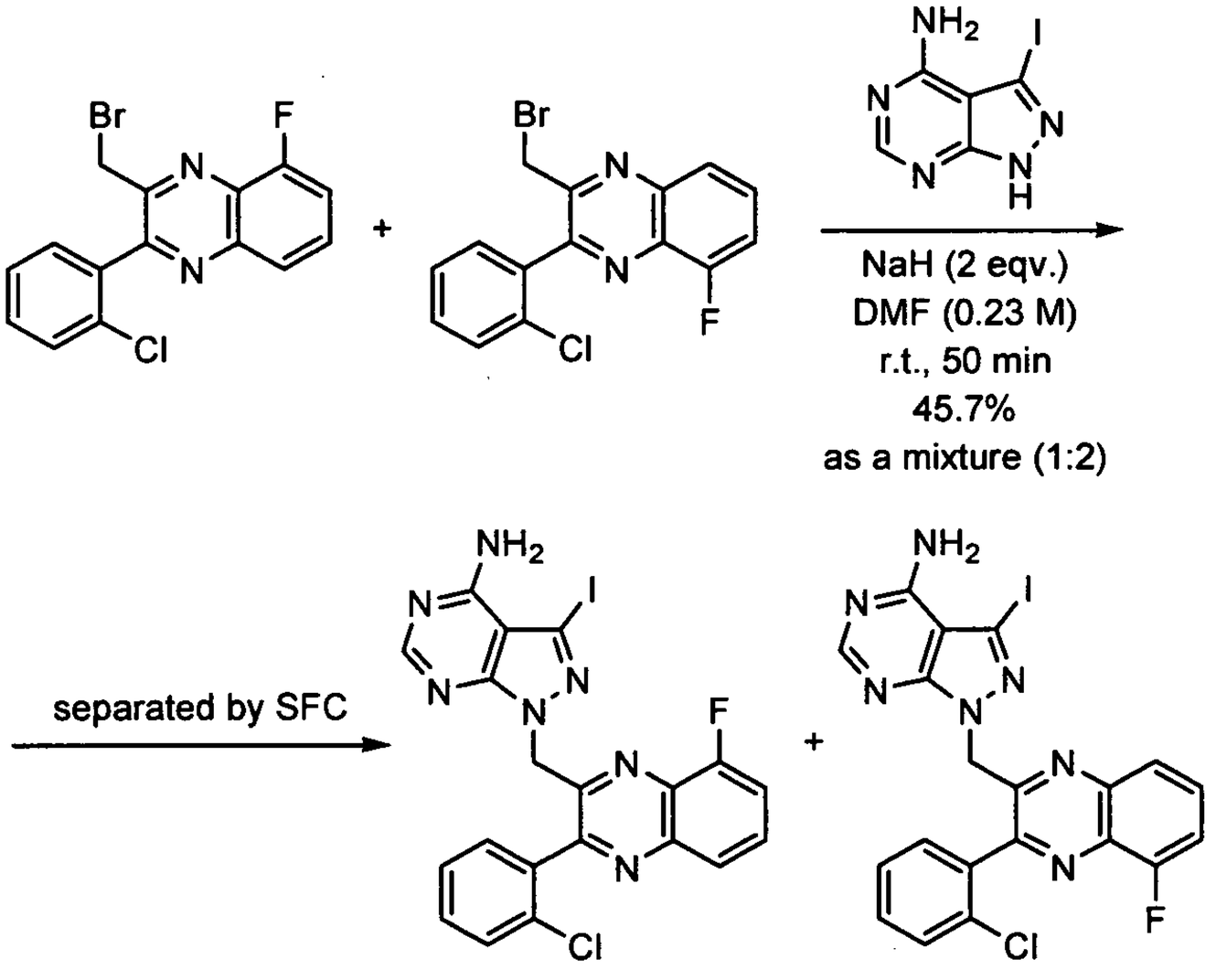
Example 32: Preparation of 1-((3-(2-chlorophenyl)-8-fluoroquinoxalin-2-yl)-methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-chlorophenyl)-5-fluoroquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine:

3-(Bromomethyl)-2-(2-chlorophenyl)-5-fluoroquinoxaline and 2-(Bromo-methyl)-3-(2-chlorophenyl)-5-fluoroquinoxaline



To a solution of 3-bromo-1-(2-chlorophenyl)propane-1,2-dione (**Prepared in Procedure L**, 2.3832 g, 9.114 mmol) in 61 mL of EtOAc was added a solution of 3-fluorobenzene-1,2-diamine (1.150 g, 9.114 mmol) at room temperature and the resulting red mixture was stirred at room temperature. After 3 hr, the mixture was concentrated in vacuo to give a mixture of two regioisomers as a black syrup. The black syrup was purified by column chromatography on a 80 g of Redi-Sep™ column using 0 to 50% gradient of EtOAc in hexane over 25 min and then 100% isocratic of EtOAc for 4 min as eluent to give a mixture of 3-(bromomethyl)-2-(2-chlorophenyl)-5-fluoroquinoxaline and 2-(bromomethyl)-3-(2-chlorophenyl)-5-fluoroquinoxaline as a red syrup: LC-MS (ESI) two peaks of m/z 351.0 [M+H (^{79}Br)]$^+$ and 352.9 [M+H (^{81}Br)]$^+$. The red syrup was carried on crude without further purification for the next step.

1-((3-(2-Chlorophenyl)-8-fluoroquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-Chlorophenyl)-5-fluoroquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine



To a solution of 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.6330 g, 2.425 mmol) 5 mL of DMF was added Sodium hydride, 60% dispersion in mineral oil (0.1940 g, 4.850 mmol) at 0 °C and the mixture was stirred at room temperature. After 10 min at room temperature, to the mixture was added a solution of a mixture of 3-(bromomethyl)-2-(2-chlorophenyl)-5-fluoroquinoxaline and 2-(bromomethyl)-3-(2-chlorophenyl)-5-fluoroquinoxaline (0.9379 g, 2.668 mmol) in 5 mL of DMF and the mixture was stirred at room temperature. After 50 min, the mixture was poured into ice-water (100 mL). The resulting precipitate was collected by filtration to give a yellow solid. The yellow solid was purified by silica gel column chromatography on a 40 g of Redi-Sep™ column using 0-100% gradient of EtOAc in hexane over 14 min and then 100% isocratic of EtOAc for 16 min as eluent to give a mixture of 1-((3-(2-chlorophenyl)-8-fluoroquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine and 1-((3-(2-chlorophenyl)-5-fluoroquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a tan solid. The tan solid was separated by supercritical fluid chromatography (SFC) to give two separated regioisomers: **1-((3-(2-**

chlorophenyl)-8-fluoroquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine as a white solid: ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.18 (1 H, s), 7.92 - 7.98 (1 H, m), 7.72 - 7.80 (1 H, m), 7.46 - 7.55 (1 H, m), 7.36 (1 H, dd, J=8.0, 1.0 Hz), 7.19 - 7.24 (1 H, m), 7.12 - 7.17 (1 H, m), 7.05 - 7.10 (1 H, m), 5.75 - 6.14 (4 H, m); LC-MS (ESI) m/z 532.0 $[M+H]^+$ and **1-((3-(2-chlorophenyl)-5-fluoroquinoxalin-2-yl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine** as a white solid: ^{1}H NMR (400 MHz, chloroform-d) δ ppm 8.20 (1 H, s), 7.86 - 7.92 (1 H, m), 7.70 - 7.78 (1 H, m), 7.45 - 7.53 (1 H, m), 7.37 - 7.42 (1 H, m), 7.24 - 7.30 (1 H, m), 7.16 - 7.23 (2 H, m), 5.76 - 6.04 (4 H, m); LC-MS (ESI) m/z 532.0 $[M+H]^+$.

Biological Assays

Recombinant expression of PI3Ks

Full length p110 subunits of PI3k α, β and δ, N-terminally labeled with polyHis tag, were coexpressed with p85 with Baculo virus expression vectors in sf9 insect cells. P110/p85 heterodimers were purified by sequential Ni-NTA, Q-HP, Superdex-100 chromatography. Purified α, β and δ isozymes were stored at -20 °C in 20mM Tris, pH 8, 0.2M NaCl, 50% glycerol, 5mM DTT, 2mM Na cholate. Truncated PI3Kγ, residues 114-1102, N-terminally labeled with polyHis tag, was expessed with Baculo virus in Hi5 insect cells. The γ isozyme was purified by sequential Ni-NTA, Superdex-200, Q-HP chromatography. The γ isozyme was stored frozen at -80 °C in NaH_2PO_4, pH 8, 0.2M NaCl, 1% ethylene glycol, 2mM β-mercaptoethanol.

	Alpha	Beta	Delta	gamma
50 mM Tris	pH 8	pH 7.5	pH 7.5	pH 8
MgCl2	15 mM	10 mM	10 mM	15 mM
Na cholate	2 mM	1 mM	0.5 mM	2 mM
DTT	2 mM	1 mM	1 mM	2 mM
ATP	1 uM	0.5 uM	0.5 uM	1 uM
PIP2	none	2.5 uM	2.5 uM	none
time	1 hr	2 hr	2 hr	1 hr
[Enzyme]	15 nM	40 nM	15 nM	50 nM

In vitro enzyme assays.

Assays were performed in 25 μL with the above final concentrations of components in white polyproplyene plates (Costar 3355). Phospatidyl inositol phosphoacceptor, PtdIns(4,5)P2 P4508, was from Echelon Biosciences. The ATPase activity of the alpha and gamma isozymes was not greatly stimulated by PtdIns(4,5)P2 under these conditions and was therefore omitted from the assay of these isozymes. Test compounds were dissolved in dimethyl sulfoxide and diluted with three-fold serial dilutions. The compound in DMSO (1 μL) was added per test well, and the inhibition relative to reactions containing no compound, with and without enzyme was determined. After assay incubation at room temperature, the reaction was stopped and residual ATP determined by addition of an equal volume of a commercial ATP bioluminescence kit (Perkin Elmer EasyLite) according to the manufacturer's instructions, and detected using a AnalystGT luminometer.

Human B Cells Proliferation stimulate by anti-IgM

Isolate human B Cells:

Isolate PBMCs from Leukopac or from human fresh blood. Isolate human B cells by using Miltenyi protocol and B cell isolation kit II. –human B cells were Purified by using AutoMacs.column.

Activation of human B cells

Use 96 well Flat bottom plate, plate 50000/well purified B cells in B cell proliferation medium (DMEM + 5% FCS, 10 mM Hepes, 50 μM 2-mercaptoethanol); 150 μL medium contain 250 ng/mL CD40L –LZ recombinant protein (Amgen) and 2 μg/mL anti-Human IgM antibody (Jackson ImmunoReseach Lab.#109-006-129), mixed with 50 μL B cell medium containing PI3K inhibitors and incubate 72 h at 37 °C incubator. After 72h, pulse labeling B cells with 0.5-1 uCi /well ^{3}H thymidine for overnight ~18 h, and harvest cell using TOM harvester.

Compound	IC50
1-((8-chloro-2-(2-fluorophenyl)-3-quinolinyl)methyl)-3-(1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.018171
4-amino-1-((3-(2-chlorophenyl)-8-methyl-2-quinoxalinyl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbonitrile	0.083816

4-amino-1-((3-(2-chlorophenyl)-5-methyl-2-quinoxalinyl)methyl)-1H-pyrazolo[3,4-d]pyrimidine-3-carbonitrile	0.001989
1-((3-(2-chlorophenyl)-8-methyl-2-quinoxalinyl)methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.01979
1-((3-(2-chlorophenyl)-5-methyl-2-quinoxalinyl)methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.037023
1-((5-chloro-2-(2-chlorophenyl)-3-quinolinyl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.093431
1-((8-chloro-2-(2-(trifluoromethyl)phenyl)-3-quinolinyl)methyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.044789
1-((5-chloro-2-(2-(trifluoromethyl)phenyl)-3-quinolinyl)methyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.135691
1-((3-(2-chlorophenyl)-8-fluoro-2-quinoxalinyl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.817616
1-((3-(2-chlorophenyl)-5-fluoro-2-quinoxalinyl)methyl)-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.55443
1-((5-chloro-2-(2-chlorophenyl)-3-quinolinyl)methyl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.046745
1-((1S)-1-(8-chloro-2-(3-fluorophenyl)-3-quinolinyl)ethyl)-3-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine	0.00157
2-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)-3-(3-fluorophenyl)-6-methyl-4H-pyrido[1,2-a]pyrimidin-4-one	0.512429

Human B Cells Proliferation stimulate by IL-4

Isolate human B Cells:

Isolate human PBMCs from Leukopac or from human fresh blood. Isolate human B cells using Miltenyi protocol – B cell isolation kit. Human B cells were Purified by AutoMacs.column.

Activation of human B cells

Use 96-well flat bottom plate, plate 50000/well purified B cells in B cell proliferation medium (DMEM + 5% FCS, 50 μM 2-mercaptoethanol, 10mM Hepes). The medium (150 μL) contain 250 ng/mL CD40L –LZ recombinant

protein (Amgen) and 10 ng/mL IL-4 (R&D system # 204-IL-025), mixed with 50 150 μL B cell medium containing compounds and incubate 72 h at 37 °C incubator. After 72 h, pulse labeling B cells with 0.5-1 uCi /well *3*H thymidine for overnight ~18 h, and harvest cell using TOM harvester.

Specific T antigen (Tetanus toxoid) induced human PBMC proliferation assays

Human PBMC are prepared from frozen stocks or they are purified from fresh human blood using a Ficoll gradient. Use 96 well round-bottom plate and plate $2x10^5$ PBMC/well with culture medium (RPMI1640 + 10% FCS, 50uM 2-Mercaptoethanol,10 mM Hepes). For IC_{50} determinations, PI3K inhibitors was tested from 10 μM to 0.001 μM, in half log increments and in triplicate. Tetanus toxoid ,T cell specific antigen (University of Massachusetts Lab) was added at 1 μg/mL and incubated 6 days at 37 °C incubator. Supernatants are collected after 6 days for IL2 ELISA assay , then cells are pulsed with ^{3}H-thymidine for ~18 h to measure proliferation.

GFP assays for detecting inhibition of Class Ia and Class III PI3K

AKT1 (PKBa) is regulated by Class Ia PI3K activated by mitogenic factors (IGF-1, PDGF, insulin, thrombin, NGF, etc.). In response to mitogenic stimuli, AKT1 translocates from the cytosol to the plasma membrane

Forkhead (FKHRL1) is a substrate for AKT1. It is cytoplasmic when phosphorylated by AKT (survival/growth). Inhibition of AKT (stasis/apoptosis) - forkhead translocation to the nucleus

FYVE domains bind to PI(3)P. the majority is generated by constitutive action of PI3K Class III

AKT membrane ruffling assay (CHO-IR-AKT1-EGFP cells/GE Healthcare)

Wash cells with assay buffer. Treat with compounds in assay buffer 1 h. Add 10 ng/mL insulin. Fix after 10 min at room temp and image

Forkhead translocation assay (MDA MB468 Forkhead-DiversaGFP cells)

Treat cells with compound in growth medium 1 h. Fix and image.

Class III PI(3)P assay (U2OS EGFP-2XFYVE cells/GE Healthcare)

Wash cells with assay buffer. Treat with compounds in assay buffer 1 h. Fix and image.

Control for all 3 assays is 10uM Wortmannin:

AKT is cytoplasmic

Forkhead is nuclear

PI(3)P depleted from endosomes

Biomarker assay: B-cell receptor stimulation of CD69 or B7.2 (CD86) expression

Heparinized human whole blood was stimulated with 10 μg/mL anti-IgD (Southern Biotech, #9030-01). 90 μL of the stimulated blood was then aliquoted per well of a 96-well plate and treated with 10 μL of various concentrations of blocking compound (from 10-0.0003 μM) diluted in IMDM + 10% FBS (Gibco). Samples were incubated together for 4 h (for CD69 expression) to 6 h (for B7.2 expression) at 37 °C. Treated blood (50 μL) was transferred to a 96-well, deep well plate (Nunc) for antibody staining with 10 μL each of CD45-PerCP (BD Biosciences, #347464), CD19-FITC (BD Biosciences, #340719), and CD69-PE (BD Biosciences, #341652). The second 50 μL of the treated blood was transferred to a second 96-well, deep well plate for antibody staining with 10 μL each of CD19-FITC (BD Biosciences, #340719) and CD86-PeCy5 (BD Biosciences, #555666). All stains were performed for 15-30 minutes in the dark at room temperature. The blood was then lysed and fixed using 450 μL of FACS lysing solution (BD Biosciences, #349202) for 15 minutes at room temperature. Samples were then washed 2X in PBS + 2% FBS before FACS analysis. Samples were gated on either CD45/CD19 double positive cells for CD69 staining, or CD19 positive cells for CD86 staining.

Gamma Counterscreen: Stimulation of human monocytes for phospho-AKT expression

A human monocyte cell line, THP-1, was maintained in RPMI + 10% FBS (Gibco). One day before stimulation, cells were counted using trypan blue exclusion on a hemocytometer and suspended at a concentration of 1 x 10^6 cells per mL of media. 100 μL of cells plus media (1 x 10^5 cells) was then aliquoted per well of 4-96-well, deep well dishes (Nunc) to test eight different compounds. Cells were rested overnight before treatment with various concentrations (from 10-0.0003μM) of blocking compound. The compound diluted in media (12 μL)

was added to the cells for 10 minutes at 37 °C. Human MCP-1 (12 µL, R&D Diagnostics, #279-MC) was diluted in media and added to each well at a final concentration of 50 ng/mL. Stimulation lasted for 2 minutes at room temperature. Pre-warmed FACS Phosflow Lyse/Fix buffer (1 mL of 37 °C) (BD Biosciences, #558049) was added to each well. Plates were then incubated at 37 °C for an additional 10-15 minutes. Plates were spun at 1500 rpm for 10 minutes, supernatant was aspirated off, and 1 mL of ice cold 90% MEOH was added to each well with vigorous shaking. Plates were then incubated either overnight at -70 °C or on ice for 30 minutes before antibody staining. Plates were spun and washed 2X in PBS + 2% FBS (Gibco). Wash was aspirated and cells were suspended in remaining buffer. Rabbit pAKT (50 µL, Cell Signaling, #4058L) at 1:100, was added to each sample for 1 h at rt with shaking. Cells were washed and spun at 1500 rpm for 10 minutes. Supernatant was aspirated and cells were suspended in remaining buffer. Secondary antibody, goat anti-rabbit Alexa 647 (50 µL, Invitrogen, #A21245) at 1:500, was added for 30 minutes at rt with shaking. Cells were then washed 1X in buffer and suspended in 150 µL of buffer for FACS analysis. Cells need to be dispersed very well by pipetting before running on flow cytometer. Cells were run on an LSR II (Becton Dickinson) and gated on forward and side scatter to determine expression levels of pAKT in the monocyte population.

Gamma Counterscreen: Stimulation of monocytes for phospho-AKT expression in mouse bone marrow

Mouse femurs were dissected from five female BALB/c mice (Charles River Labs.) and collected into RPMI + 10% FBS media (Gibco). Mouse bone marrow was removed by cutting the ends of the femur and by flushing with 1 mL of media using a 25 gauge needle. Bone marrow was then dispersed in media using a 21 gauge needle. Media volume was increased to 20 mL and cells were counted using trypan blue exclusion on a hemocytometer. The cell suspension was then increased to 7.5×10^6 cells per 1 mL of media and 100 µL (7.5×10^5 cells) was aliquoted per well into 4-96-well, deep well dishes (Nunc) to test eight different compounds. Cells were rested at 37 °C for 2 h before treatment with various concentrations (from 10-0.0003µM) of blocking compound. Compound diluted in

media (12 μL) was added to bone marrow cells for 10 minutes at 37 °C. Mouse MCP-1 (12 μL, R&D Diagnostics, #479-JE) was diluted in media and added to each well at a final concentration of 50 ng/mL. Stimulation lasted for 2 minutes at room temperature. 1 mL of 37 °C pre-warmed FACS Phosflow Lyse/Fix buffer (BD Biosciences, #558049) was added to each well. Plates were then incubated at 37°C for an additional 10-15 minutes. Plates were spun at 1500 rpm for 10 minutes. Supernatant was aspirated off and 1 mL of ice cold 90% MEOH was added to each well with vigorous shaking. Plates were then incubated either overnight at -70 °C or on ice for 30 minutes before antibody staining. Plates were spun and washed 2X in PBS + 2% FBS (Gibco). Wash was aspirated and cells were suspended in remaining buffer. Fc block (2 μL, BD Pharmingen, #553140) was then added per well for 10 minutes at room temperature. After block, 50 μL of primary antibodies diluted in buffer; CD11b-Alexa488 (BD Biosciences, #557672) at 1:50, CD64-PE (BD Biosciences, #558455) at 1:50, and rabbit pAKT (Cell Signaling, #4058L) at 1:100, were added to each sample for 1 h at RT with shaking. Wash buffer was added to cells and spun at 1500 rpm for 10 minutes. Supernatant was aspirated and cells were suspended in remaining buffer. Secondary antibody; goat anti-rabbit Alexa 647 (50 μL, Invitrogen, #A21245) at 1:500, was added for 30 minutes at rt with shaking. Cells were then washed 1X in buffer and suspended in 100 μL of buffer for FACS analysis. Cells were run on an LSR II (Becton Dickinson) and gated on CD11b/CD64 double positive cells to determine expression levels of pAKT in the monocyte population.

pAKT in vivo Assay

Vehicle and compounds are administered p.o. (0.2 mL) by gavage (Oral Gavage Needles Popper & Sons, New Hyde Park, NY) to mice (Transgenic Line 3751, female, 10-12 wks Amgen Inc, Thousand Oaks, CA) 15 min prior to the injection i.v (0.2 mLs) of anti-IgM FITC (50 ug/mouse) (Jackson Immuno Research, West Grove, PA). After 45 min the mice are sacrificed within a CO_2 chamber. Blood is drawn via cardiac puncture (0.3 mL) (1cc 25 g Syringes, Sherwood, St. Louis, MO) and transferred into a 15 mL conical vial (Nalge/Nunc International, Denmark). Blood is immediately fixed with 6.0 mL of BD Phosflow Lyse/Fix Buffer (BD Bioscience, San Jose, CA), inverted 3X's and placed in 37 °C water

bath. Half of the spleen is removed and transferred to an eppendorf tube containing 0.5 mL of PBS (Invitrogen Corp, Grand Island, NY). The spleen is crushed using a tissue grinder (Pellet Pestle, Kimble/Kontes, Vineland, NJ) and immediately fixed with 6.0 mL of BD Phosflow Lyse/Fix buffer, inverted 3X's and placed in 37 °C water bath. Once tissues have been collected the mouse is cervically-dislocated and carcass to disposed. After 15 min, the 15 mL conical vials are removed from the 37 °C water bath and placed on ice until tissues are further processed. Crushed spleens are filtered through a 70 μm cell strainer (BD Bioscience, Bedford, MA) into another 15 mL conical vial and washed with 9 mL of PBS. Splenocytes and blood are spun @ 2,000 rpms for 10 min (cold) and buffer is aspirated. Cells are resuspended in 2.0 mL of cold (-20 °C) 90% methyl alcohol (Mallinckrodt Chemicals, Phillipsburg, NJ). Methanol is slowly added while conical vial is rapidly vortexed. Tissues are then stored at -20 °C until cells can be stained for FACS analysis.

Multi-dose TNP immunization

Blood was collected by retro-orbital eye bleeds from 7-8 week old BALB/c female mice (Charles River Labs.) at day 0 before immunization. Blood was allowed to clot for 30 minutes and spun at 10,000 rpm in serum microtainer tubes (Becton Dickinson) for 10 minutes. Sera were collected, aliquoted in Matrix tubes (Matrix Tech. Corp.) and stored at -70 °C until ELISA was performed. Mice were given compound orally before immunization and at subsequent time periods based on the life of the molecule. Mice were then immunized with either 50 μg of TNP-LPS (Biosearch Tech., #T-5065), 50 μg of TNP-Ficoll (Biosearch Tech., #F-1300), or 100 μg of TNP-KLH (Biosearch Tech., #T-5060) plus 1% alum (Brenntag, #3501) in PBS. TNP-KLH plus alum solution was prepared by gently inverting the mixture 3-5 times every 10 minutes for 1 hour before immunization. On day 5, post-last treatment, mice were CO_2 sacrificed and cardiac punctured. Blood was allowed to clot for 30 minutes and spun at 10,000 rpm in serum microtainer tubes for 10 minutes. Sera were collected, aliquoted in Matrix tubes, and stored at -70 °C until further analysis was performed. TNP-specific IgG1, IgG2a, IgG3 and IgM levels in the sera were then measured via ELISA. TNP-BSA (Biosearch Tech., #T-5050) was used to capture the TNP-

specific antibodies. TNP-BSA (10 μg/mL) was used to coat 384-well ELISA plates (Corning Costar) overnight. Plates were then washed and blocked for 1 h using 10% BSA ELISA Block solution (KPL). After blocking, ELISA plates were washed and sera samples/standards were serially diluted and allowed to bind to the plates for 1 h. Plates were washed and Ig-HRP conjugated secondary antibodies (goat anti-mouse IgG1, Southern Biotech #1070-05, goat anti-mouse IgG2a, Southern Biotech #1080-05, goat anti-mouse IgM, Southern Biotech #1020-05, goat anti-mouse IgG3, Southern Biotech #1100-05) were diluted at 1:5000 and incubated on the plates for 1 h. TMB peroxidase solution (SureBlue Reserve TMB from KPL) was used to visualize the antibodies. Plates were washed and samples were allowed to develop in the TMB solution approximately 5-20 minutes depending on the Ig analyzed. The reaction was stopped with 2M sulfuric acid and plates were read at an OD of 450 nm.

For the treatment of PI3Kδ-mediated-diseases, such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases, and autoimmune diseases, the compounds of the present invention may be administered orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intramuscular, intrasternal, infusion techniques or intraperitoneally.

Treatment of diseases and disorders herein is intended to also include the prophylactic administration of a compound of the invention, a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (i.e., an animal, preferably a mammal, most preferably a human) believed to be in need of preventative treatment, such as, for example, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, psoriasis, inflammatory diseases, and autoimmune diseases and the like.

The dosage regimen for treating PI3Kδ-mediated diseases, cancer, and/or hyperglycemia with the compounds of this invention and/or compositions of this invention is based on a variety of factors, including the type of disease, the age, weight, sex, medical condition of the patient, the severity of the condition, the

route of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. Dosage levels of the order from about 0.01 mg to 30 mg per kilogram of body weight per day, preferably from about 0.1 mg to 10 mg/kg, more preferably from about 0.25 mg to 1 mg/kg are useful for all methods of use disclosed herein.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a capsule, a tablet, a suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a given amount of the active ingredient. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known are using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including

synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose.

For administration, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, acacia, gelatin, sodium alginate, polyvinyl-pyrrolidine, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The pharmaceutical compositions may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (e.g., solutions, suspensions, or emulsions). The pharmaceutical compositions may be subjected

to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be

obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Likewise, the compounds of this invention may exist as isomers, that is compounds of the same molecular formula but in which the atoms, relative to one another, are arranged differently. In particular, the alkylene substituents of the compounds of this invention, are normally and preferably arranged and inserted into the molecules as indicated in the definitions for each of these groups, being read from left to right. However, in certain cases, one skilled in the art will appreciate that it is possible to prepare compounds of this invention in which these substituents are reversed in orientation relative to the other atoms in the molecule. That is, the substituent to be inserted may be the same as that noted above except that it is inserted into the molecule in the reverse orientation. One skilled in the art will appreciate that these isomeric forms of the compounds of this invention are to be construed as encompassed within the scope of the present invention.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methansulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 2-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids that may be employed to from pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Also encompassed in the scope of the present invention are pharmaceutically acceptable esters of a carboxylic acid or hydroxyl containing group, including a metabolically labile ester or a prodrug form of a compound of this invention. A metabolically labile ester is one which may produce, for example, an increase in blood levels and prolong the efficacy of the corresponding non-esterified form of the compound. A prodrug form is one which is not in an active form of the molecule as administered but which becomes therapeutically active after some in vivo activity or biotransformation, such as metabolism, for example, enzymatic or hydrolytic cleavage. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bungaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use. Esters of a compound of this invention, may include, for example, the methyl, ethyl, propyl, and butyl esters, as well as other suitable esters formed between an acidic moiety and a hydroxyl containing moiety. Metabolically labile esters, may include, for example, methoxymethyl, ethoxymethyl, iso-propoxymethyl, α-methoxyethyl, groups such as α-((C_1-C_4)-

alkyloxy)ethyl, for example, methoxyethyl, ethoxyethyl, propoxyethyl, iso-propoxyethyl, etc.; 2-oxo-1,3-dioxolen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3,dioxolen-4-ylmethyl, etc.; C_1-C_3 alkylthiomethyl groups, for example, methylthiomethyl, ethylthiomethyl, isopropylthiomethyl, etc.; acyloxymethyl groups, for example, pivaloyloxymethyl, α-acetoxymethyl, etc.; ethoxycarbonyl-1-methyl; or α-acyloxy-α-substituted methyl groups, for example α-acetoxyethyl.

Further, the compounds of the invention may exist as crystalline solids which can be crystallized from common solvents such as ethanol, N,N-dimethyl-formamide, water, or the like. Thus, crystalline forms of the compounds of the invention may exist as polymorphs, solvates and/or hydrates of the parent compounds or their pharmaceutically acceptable salts. All of such forms likewise are to be construed as falling within the scope of the invention.

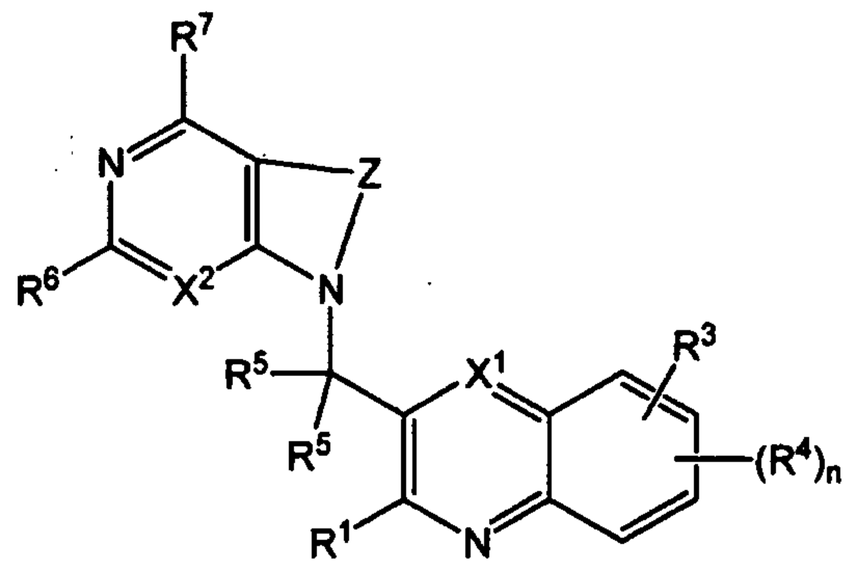
While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

We Claim:

1. A compound having the structure:



or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is $C(R^9)$ or N;

X^2 is $C(R^{10})$ or N;

Z is $-CR^{11}=CR^{11}-$, $-CR^{11}=N-$, $-N=CR^{11}-$, $-CR^{11}=CR^{11}-C(=O)-$ and $-C(=O)-CR^{11}=CR^{11}-$;

n is 0, 1, 2 or 3;

R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl;

R^2 is selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}alkylNR^aR^a$, $-OC_{2-6}alkylOR^a$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkylNR^aR^a$ and $-NR^aC_{2-6}alkylOR^a$; or R^2 is selected from C_{1-6}alkyl, phenyl, benzyl, heteroaryl, heterocycle,

-(C_{1-3}alkyl)heteroaryl, -(C_{1-3}alkyl)heterocycle, -O(C_{1-3}alkyl)heteroaryl, -O(C_{1-3}alkyl)heterocycle, -NR^a(C_{1-3}alkyl)heteroaryl, -NR^a(C_{1-3}alkyl)heterocycle, -(C_{1-3}alkyl)phenyl, -O(C_{1-3}alkyl)phenyl and -NR^a(C_{1-3}alkyl)phenyl all of which are substituted by 0, 1, 2 or 3 substituents selected from C_{1-4}haloalkyl, OC_{1-4}alkyl, Br, Cl, F, I and C_{1-4}alkyl;

R^3 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, -C(=O)R^a, -C(=O)OR^a, -C(=O)NR^aR^a, -C(=NR^a)NR^aR^a, -OR^a, -OC(=O)R^a, -OC(=O)NR^aR^a, -OC(=O)N(R^a)$S(=O)_2R^a$, -OC_{2-6}alkylNR^aR^a, -OC_{2-6}alkylOR^a, -SR^a, -S(=O)R^a, -$S(=O)_2R^a$, -$S(=O)_2NR^aR^a$, -$S(=O)_2$N(R^a)C(=O)R^a, -$S(=O)_2$N(R^a)C(=O)OR^a, -$S(=O)_2$N(R^a)C(=O)NR^aR^a, -NR^aR^a, -N(R^a)C(=O)R^a, -N(R^a)C(=O)OR^a, -N(R^a)C(=O)NR^aR^a, -N(R^a)C(=NR^a)NR^aR^a, -N(R^a)$S(=O)_2R^a$, -N(R^a)$S(=O)_2NR^aR^a$, -NR^aC_{2-6}alkylNR^aR^a, -NR^aC_{2-6}alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^4 is, independently, in each instance, halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, N(C_{1-4}alkyl)C_{1-4}alkyl or C_{1-4}haloalkyl;

R^5 is, independently, in each instance, H, halo, C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkyl substituted by 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, N(C_{1-4}alkyl)C_{1-4}alkyl; or both R^5 groups together form a C_{3-6}spiroalkyl substituted by 0, 1, 2 or 3 substituents selected from halo, cyano, OH, OC_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}haloalkyl, OC_{1-4}alkyl, NH_2, NHC_{1-4}alkyl, N(C_{1-4}alkyl)C_{1-4}alkyl;

R^6 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^7 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^8 is selected from H, C_{1-6}haloalkyl, Br, Cl, F, I, OR^a, NR^aR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from C_{1-6}haloalkyl, OC_{1-6}alkyl, Br, Cl, F, I and C_{1-6}alkyl;

R^9 is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a, C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle, wherein the C_{1-6}alkyl, phenyl, benzyl, heteroaryl and heterocycle are additionally substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a, $-NR^aC_{2-6}$alkylOR^a; or R^9 is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR^aR^a, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR^aR^a and $-NR^aC_{2-6}$alkylOR^a;

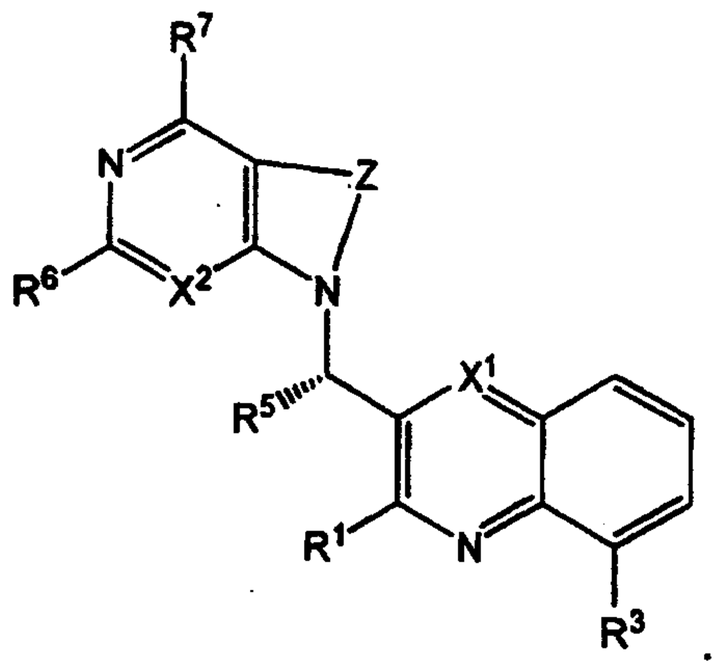
R^{10} is H, C_{1-3}alkyl, C_{1-3}haloalkyl, cyano, nitro, CO_2R^a, $C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $S(=O)R^b$, $S(=O)_2R^b$ or $S(=O)_2NR^aR^a$;

R^{11} is selected from H, halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ and $-NR^aC_{2-6}$alkylOR^a; or R^{11} is C_{1-9}alkyl or C_{1-4}alkyl(phenyl) wherein either is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ and $-NR^aC_{2-6}$alkylOR^a; and additionally substituted by 0, 1, 2, 3, 4 or 5 substituents independently selected from Br, Cl, F and I; or R^{11} is a saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0, 1, 2, 3 or 4 substituents selected from halo, C_{1-4}haloalkyl, cyano, nitro, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)NR^aR^a$, $-OC(=O)N(R^a)S(=O)_2R^a$, $-OC_{2-6}$alkylNR$^aR^a$, $-OC_{2-6}$alkylOR^a, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^aR^a$, $-S(=O)_2N(R^a)C(=O)R^a$, $-S(=O)_2N(R^a)C(=O)OR^a$, $-S(=O)_2N(R^a)C(=O)NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^a$, $-N(R^a)C(=O)OR^a$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^a$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkylNR$^aR^a$ and $-NR^aC_{2-6}$alkylOR^a;

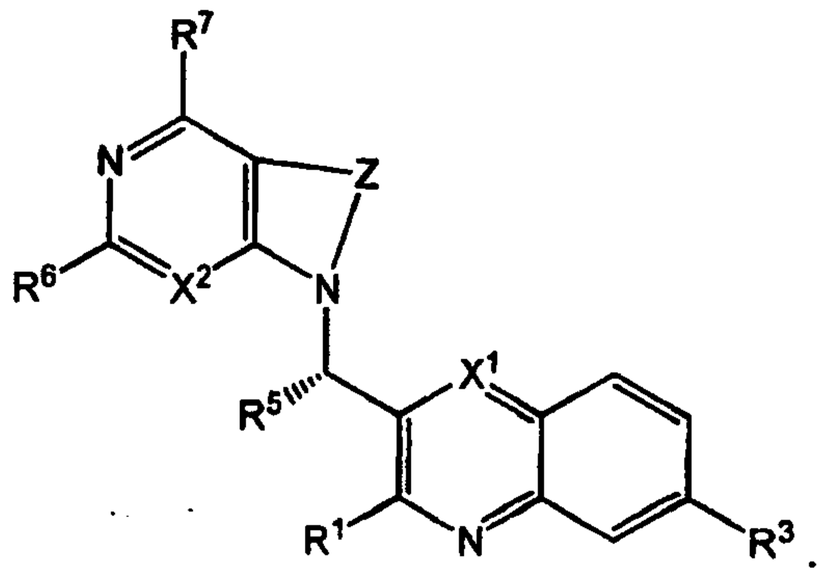
R^a is independently, at each instance, H or R^b; and

R^b is independently, at each instance, phenyl, benzyl or C_{1-6}alkyl, the phenyl, benzyl and C_{1-6}alkyl being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alkyl, C_{1-3}haloalkyl, -OC_{1-4}alkyl, -NH_2, -NHC_{1-4}alkyl, -$N(C_{1-4}alkyl)C_{1-4}$alkyl.

2. A compound according to Claim 1, having the structure:



3. A compound according to Claim 1, having the structure:



4. A compound according to Claim 1, wherein R^3 is F, Cl or Br; and n is 0.

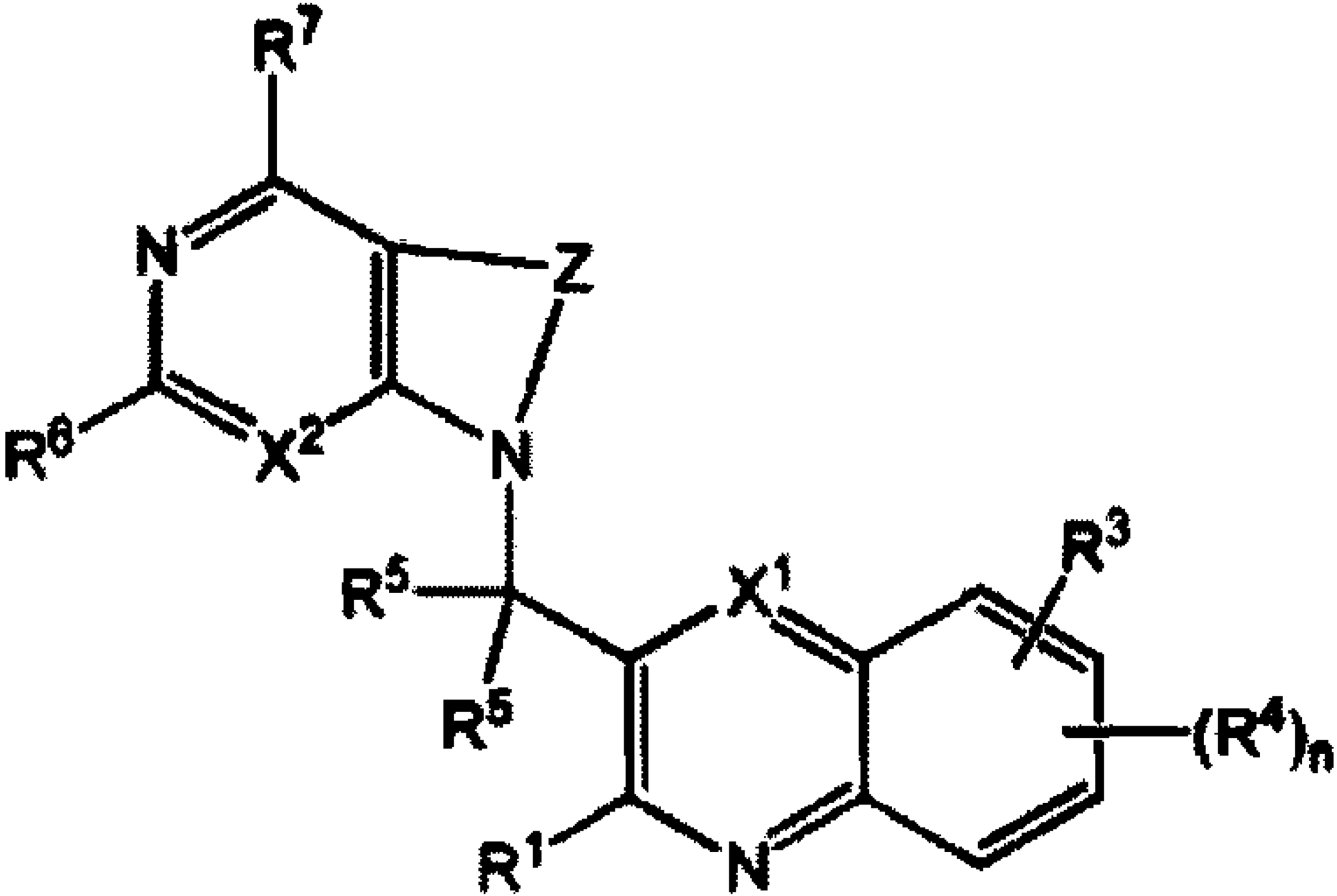
5. A compound according to Claim 1, wherein R^1 is phenyl substituted by 0 or 1 R^2 substituents, and the phenyl is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

6. A compound according to Claim 1, wherein R^1 is a direct-bonded or oxygen-linked saturated, partially-saturated or unsaturated 5-, 6- or 7-membered monocyclic ring containing 1, 2, 3 or 4 atoms selected from N, O and S, but containing no more than one O or S, wherein the available carbon atoms of the ring are substituted by 0, 1 or 2 oxo or thioxo groups, wherein the ring is substituted by 0 or 1 R^2 substituents, and the ring is additionally substituted by 0, 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_{1-4}alkyl, OC_{1-4}alkyl, OC_{1-4}haloalkyl, NHC_{1-4}alkyl, $N(C_{1-4}alkyl)C_{1-4}$alkyl and C_{1-4}haloalkyl.

7. A use of the compound defined in claim 1 for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, psoriasis, an inflammatory disease, an autoimmune disease, an inflammatory bowel disorder, an inflammatory eye disorder, an inflammatory or unstable bladder disorder, skin complaints with inflammatory components, a chronic inflammatory condition, an autoimmune disease, systemic lupus erythematosis (SLE), myestenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis, Sjoegren's syndrome, autoimmune hemolytic anemia, an allergic condition or hypersensitivity.

8. A use of the compound defined in claim 1 for preparing a medicament for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, psoriatic arthritis, psoriasis, an inflammatory disease, an autoimmune disease, an inflammatory bowel disorder, an inflammatory eye disorder, an inflammatory or unstable bladder disorder, skin complaints with inflammatory components, a chronic inflammatory condition, an autoimmune disease, systemic lupus erythematosis (SLE), myestenia gravis, rheumatoid arthritis, acute disseminated encephalomyelitis, idiopathic thrombocytopenic purpura, multiple sclerosis, Sjoegren's syndrome, autoimmune hemolytic anemia, an allergic condition or hypersensitivity.

9. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically-acceptable diluent or carrier.


R7
N
Z
R6
X2
N
R5
R5
X1
R3
(R4)n
R1
N