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(54) Title: CHEMICAL COMPOUNDS, COMPOSITIONS AND METHODS FOR KINASE MODULATION

(57) **Abrégé/Abstract:**

Chemical compounds that modulate kinase activity, including PI3 kinase activity, and chemical compounds, pharmaceutical compositions, and methods of treatment of diseases and conditions associated with kinase activity, including PI3 kinase activity, are described herein.



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(54) Title: CHEMICAL COMPOUNDS, COMPOSITIONS AND METHODS FOR KINASE MODULATION

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CHEMICAL COMPOUNDS, COMPOSITIONS AND METHODS FOR KINASE MODULATION**CLAIM OF PRIORITY**

[0001] This application claims priority from U.S.S.N. 61/347,370, filed May 21, 2010, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] The activity of cells can be regulated by external signals that stimulate or inhibit intracellular events. The process by which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response is referred to as signal transduction. Over the past decades, cascades of signal transduction events have been elucidated and found to play a central role in a variety of biological responses. Defects in various components of signal transduction pathways have been found to account for a vast number of diseases, including numerous forms of cancer, inflammatory disorders, metabolic disorders, vascular and neuronal diseases (Gaestel et al. *Current Medicinal Chemistry* (2007) 14:2214-2234).

[0003] Kinases represent a class of important signaling molecules. Kinases can generally be classified into protein kinases and lipid kinases, and certain kinases exhibit dual specificities. Protein kinases are enzymes that phosphorylate other proteins and/or themselves (*i.e.*, autophosphorylation). Protein kinases can be generally classified into three major groups based upon their substrate utilization: tyrosine kinases which predominantly phosphorylate substrates on tyrosine residues (*e.g.*, erb2, PDGF receptor, EGF receptor, VEGF receptor, src, abl), serine/threonine kinases which predominantly phosphorylate substrates on serine and/or threonine residues (*e.g.*, mTorC1, mTorC2, ATM, ATR, DNA-PK, Akt), and dual-specificity kinases which phosphorylate substrates on tyrosine, serine and/or threonine residues.

[0004] Lipid kinases are enzymes that catalyze the phosphorylation of lipids. These enzymes, and the resulting phosphorylated lipids and lipid-derived biologically active organic molecules, play a role in many different physiological processes, including cell proliferation, migration, adhesion, and differentiation. Certain lipid kinases are membrane associated and they catalyze the phosphorylation of lipids contained in or associated with cell membranes. Examples of such enzymes include phosphoinositide(s) kinases (*e.g.*, PI3-kinases, PI4-Kinases), diacylglycerol kinases, and sphingosine kinases.

[0005] The phosphoinositide 3-kinases (PI3Ks) signaling pathway is one of the most highly mutated systems in human cancers. PI3K signaling is also a key factor in many other diseases in humans. PI3K signaling is involved in many disease states including allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome.

[0006] PI3Ks are members of a unique and conserved family of intracellular lipid kinases that phosphorylate the 3'-OH group on phosphatidylinositols or phosphoinositides. The PI3K family comprises 15 kinases with distinct substrate specificities, expression patterns, and modes of regulation. The class I PI3Ks (p110 α , p110 β , p110 δ , and p110 γ) are typically activated by tyrosine kinases or G-protein coupled receptors to generate PIP3, which engages downstream effectors such as those in the Akt/PDK1 pathway, mTOR, the Tec family kinases, and the Rho family GTPases. The class II and III PI3Ks play a key role in intracellular trafficking through the synthesis of PI(3)P

and PI(3,4)P2. The PI3Ks are protein kinases that control cell growth (mTORC1) or monitor genomic integrity (ATM, ATR, DNA-PK, and hSmg-1).

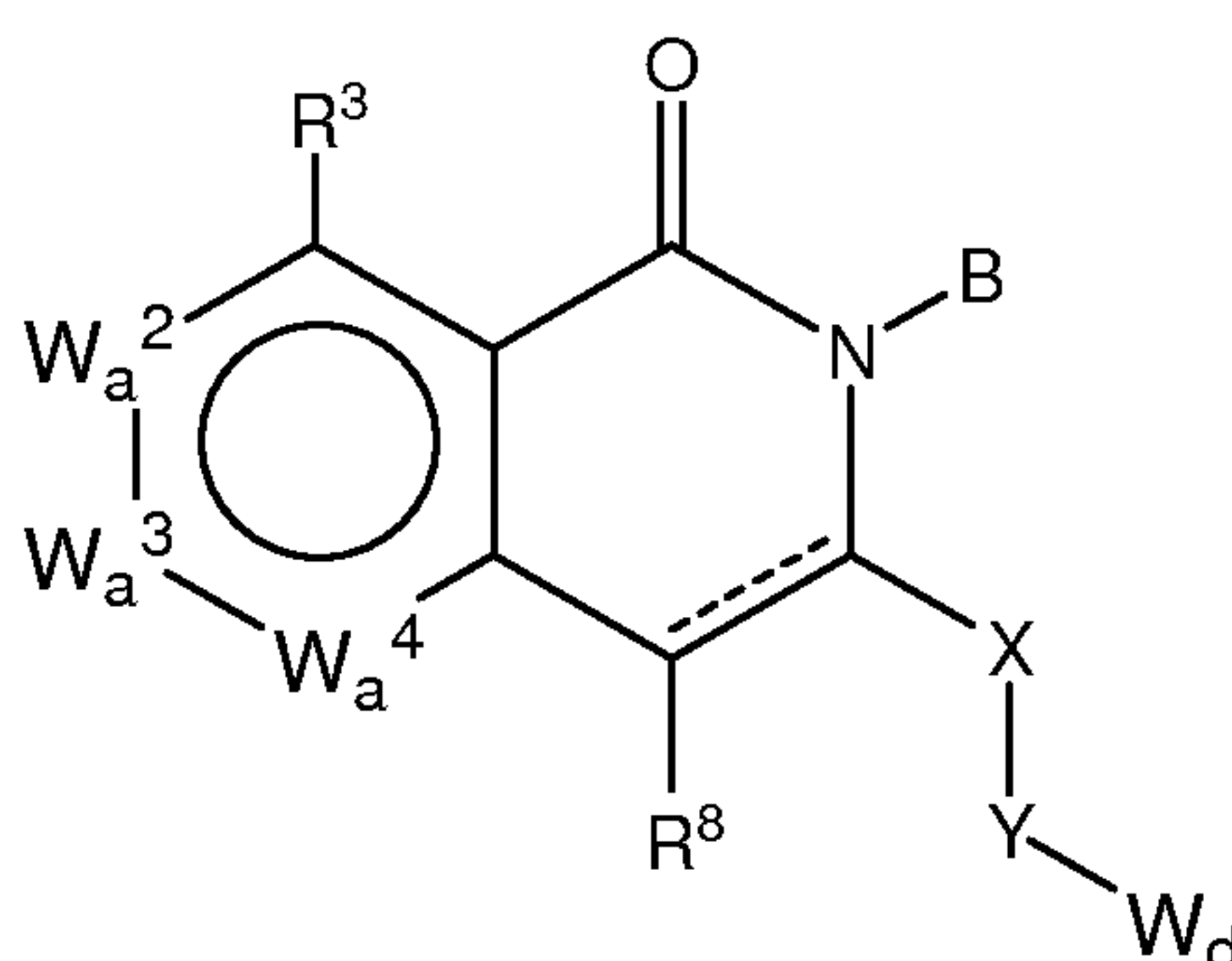
[0007] The delta (δ) isoform of class I PI3K has been implicated, in particular, in a number of diseases and biological processes. PI3K δ is expressed primarily in hematopoietic cells including leukocytes such as T-cells, dendritic cells, neutrophils, mast cells, B-cells, and macrophages. PI3K δ is integrally involved in mammalian immune system functions such as T-cell function, B-cell activation, mast cell activation, dendritic cell function, and neutrophil activity. Due to its integral role in immune system function, PI3K δ is also involved in a number of diseases related to undesirable immune response such as allergic reactions, inflammatory diseases, inflammation mediated angiogenesis, rheumatoid arthritis, and auto-immune diseases such as lupus, asthma, emphysema and other respiratory diseases. Other class I PI3K involved in immune system function includes PI3K γ , which plays a role in leukocyte signaling and has been implicated in inflammation, rheumatoid arthritis, and autoimmune diseases such as lupus.

[0008] Unlike PI3K δ , the beta (β) isoform of class I PI3K appears to be ubiquitously expressed. PI3K β has been implicated primarily in various types of cancer including PTEN-negative cancer (Edgar et al. *Cancer Research* (2010) 70(3):1164-1172), and HER2-overexpressing cancer such as breast cancer and ovarian cancer.

SUMMARY

[0009] As such, there remains a need for PI3K inhibitors capable of selectively inhibiting certain isoform(s) of class I PI3K without substantially affecting the activity of the remaining isoforms of the same class. In particular, inhibitors capable of selectively inhibiting PI3K δ and/or PI3K γ , but without substantially affecting the activity of PI3K β , would reduce one or more possible side effects associated with unnecessary down-regulation of PI3K β activity in a subject. Such inhibitors would be effective in ameliorating disease conditions mediated primarily by PI3K δ/γ . The present disclosure addresses this need and provides related advantages as well.

[0010] In one aspect, provided herein is a compound of Formula I:

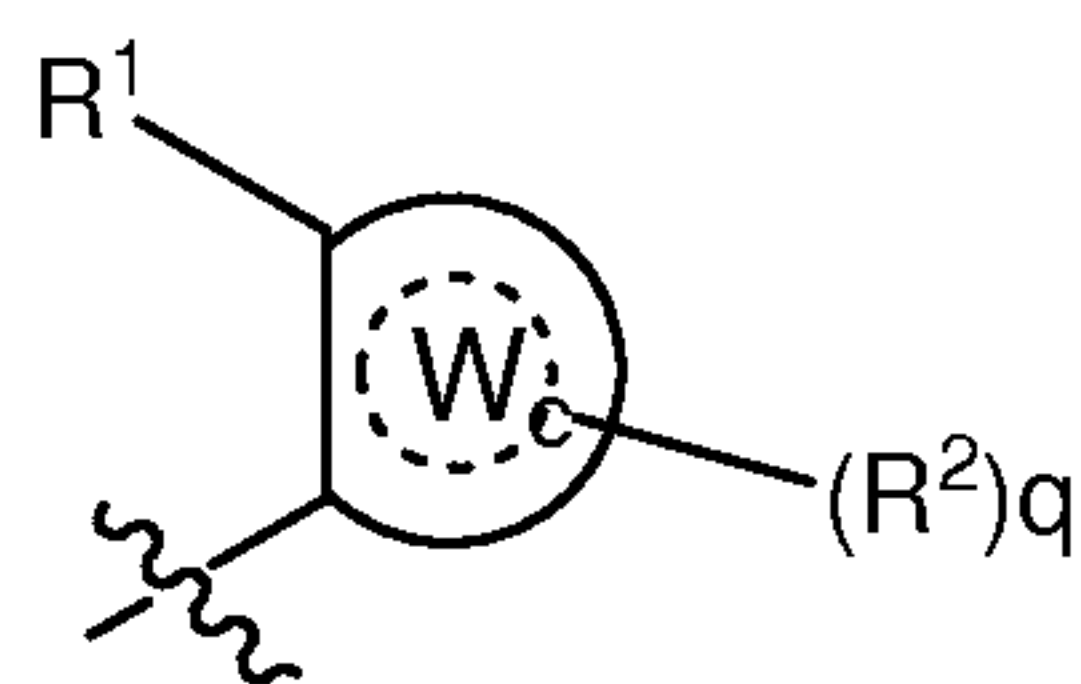


Formula I

or pharmaceutically acceptable forms thereof, wherein,

W_a^2 is CR⁵ or N; W_a^3 is CR⁶ or N; W_a^4 is CR⁷ or N; wherein no more than two adjacent ring atoms selected from W_a^2 , W_a^3 , and W_a^4 are heteroatoms;

B is hydrogen, alkyl, amino, heteroalkyl, or a moiety of formula II:



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

q is an integer of 0, 1, 2, 3, or 4;

X is absent or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3, or 4;

Y is absent, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)(CHR^9)_z-$, $-N(R^9)-$, $N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$, or $-N(R^9)C(R^9)_2-$, and z is an integer of 1, 2, 3, or 4;

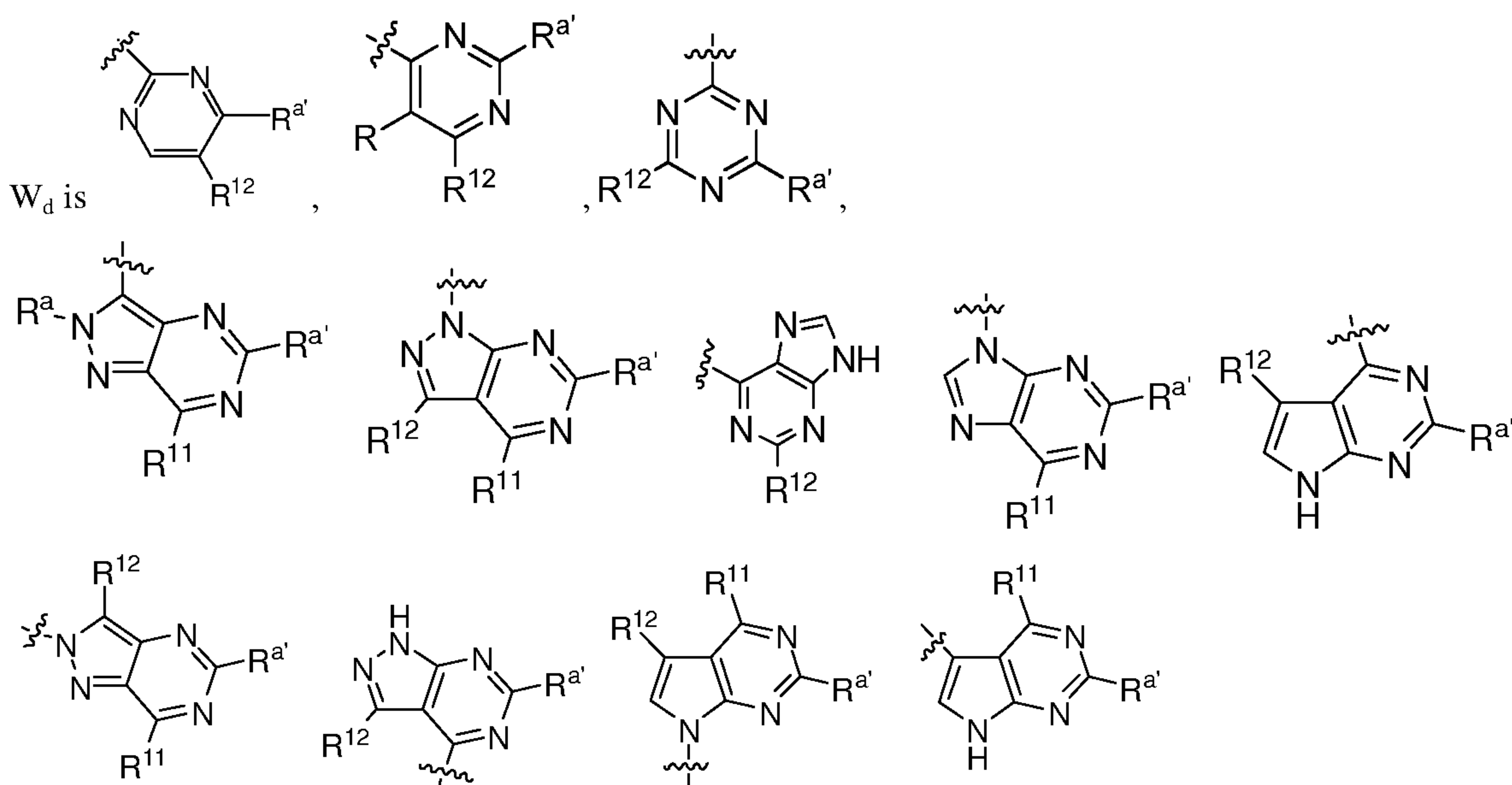
R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

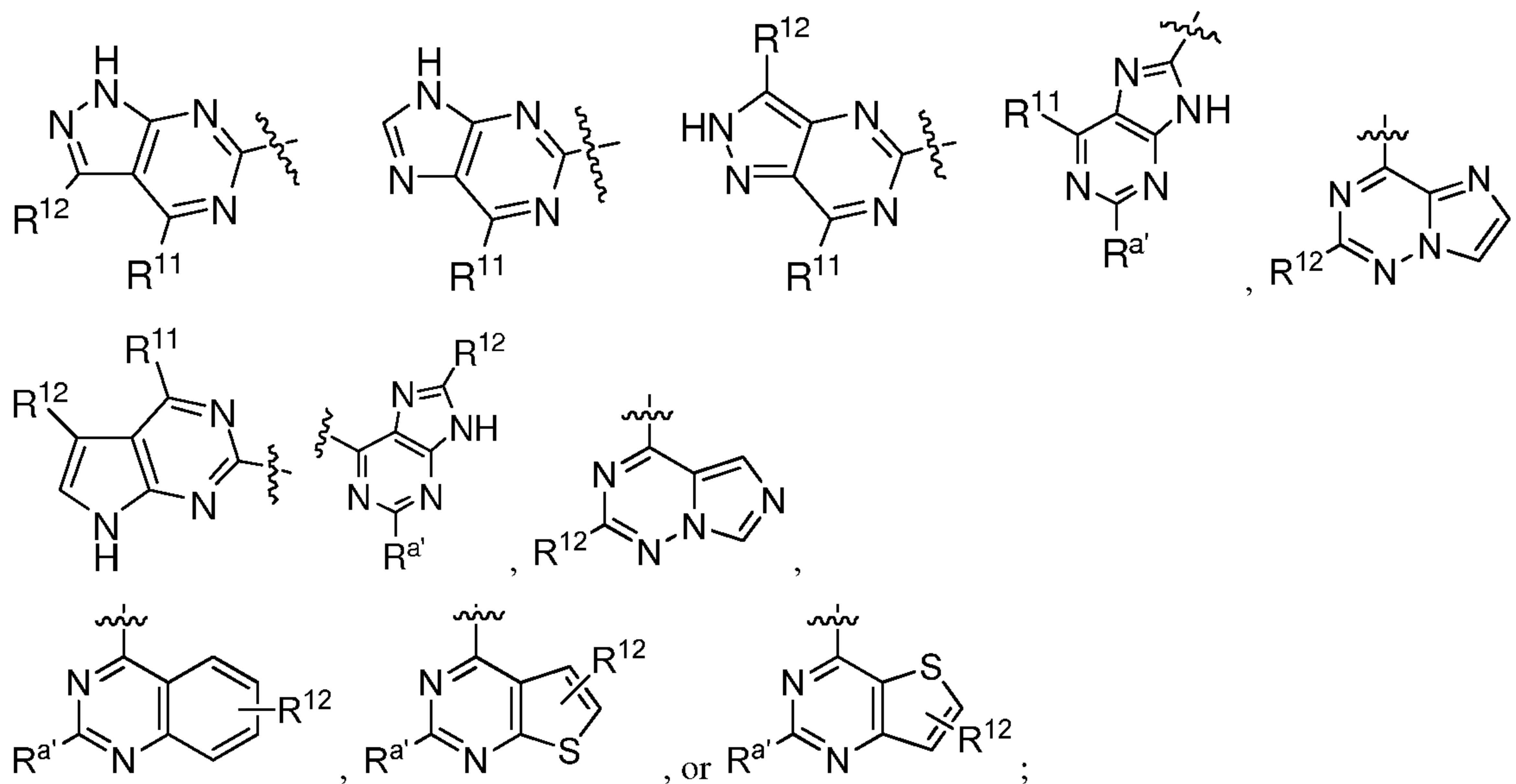
each R^2 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

R^3 is cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclalkyl, alkenyl, or alkynyl, or R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C_1-C_6 alkyl group to an aryl, heteroaryl or heterocyclyl, or R^3 and R^5 are taken together with the carbons to which they are attached form a 5- or 6-membered ring; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{13} ;

R^5 , R^6 , R^7 , and R^8 are independently hydrogen, halo, cyano, alkyl or amino;

each R^9 is independently hydrogen, alkyl, or heterocycloalkyl;





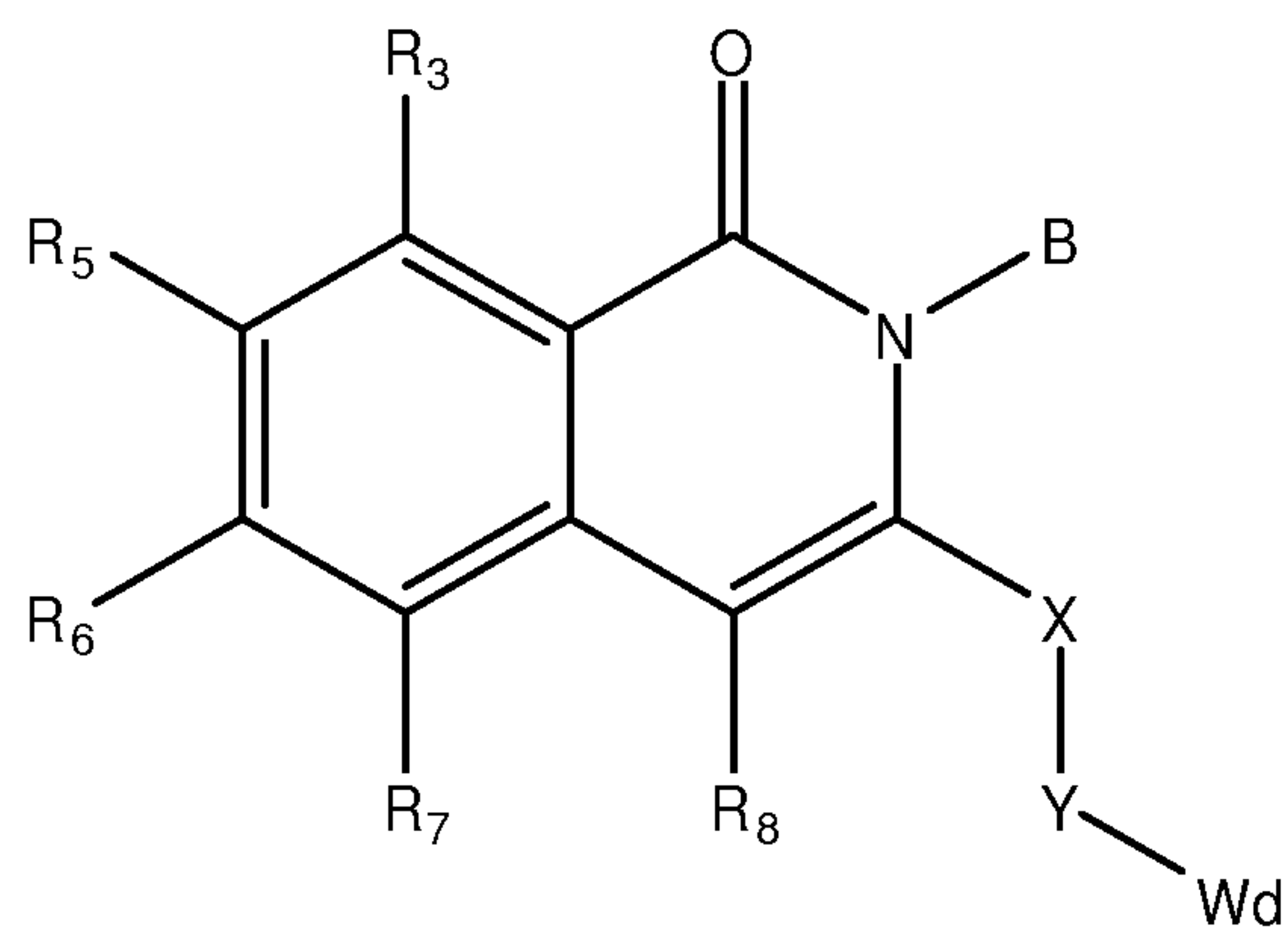
R^{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, alkoxy, phosphate, urea, or carbonate;

R^{12} is hydrogen, alkyl, haloalkyl, alkynyl, alkenyl, halo, $-C(O)NH_2$, aryl, heteroaryl, nonaromatic heterocyclyl, or cycloalkyl,

$R^{a'}$ is hydrogen, alkyl, $-NH_2$, cyano, or halogen; and

each R^{13} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or halogen.

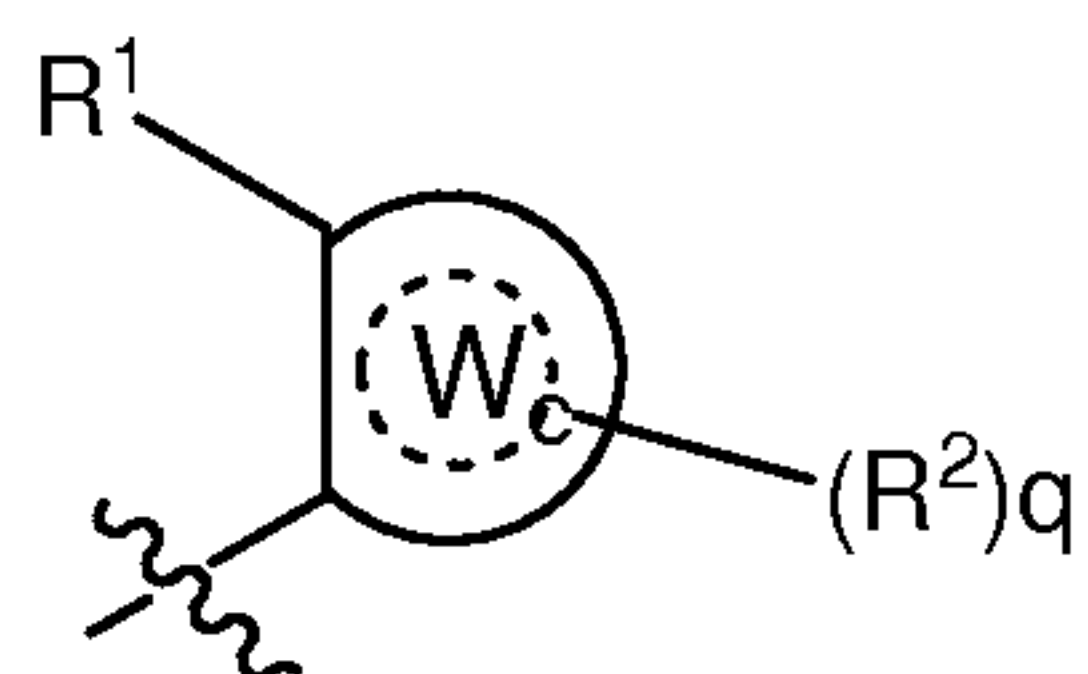
[0011] In certain embodiments, compounds are provided of the following Formula Ib:



Formula (Ib),

or pharmaceutically acceptable forms thereof, wherein

B is hydrogen, alkyl, amino, heteroalkyl, or a moiety of Formula II:



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

q is an integer of 0, 1, 2, 3, or 4;

X is absent or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3, or 4;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -C(=O)-, -C(=O)(CHR⁹)_z-, -N(R⁹)-, N(R⁹)-C(=O)-, -N(R⁹)-C(=O)NH-, or -N(R⁹)C(R⁹)₂-, and z is an integer of 1, 2, 3, or 4;

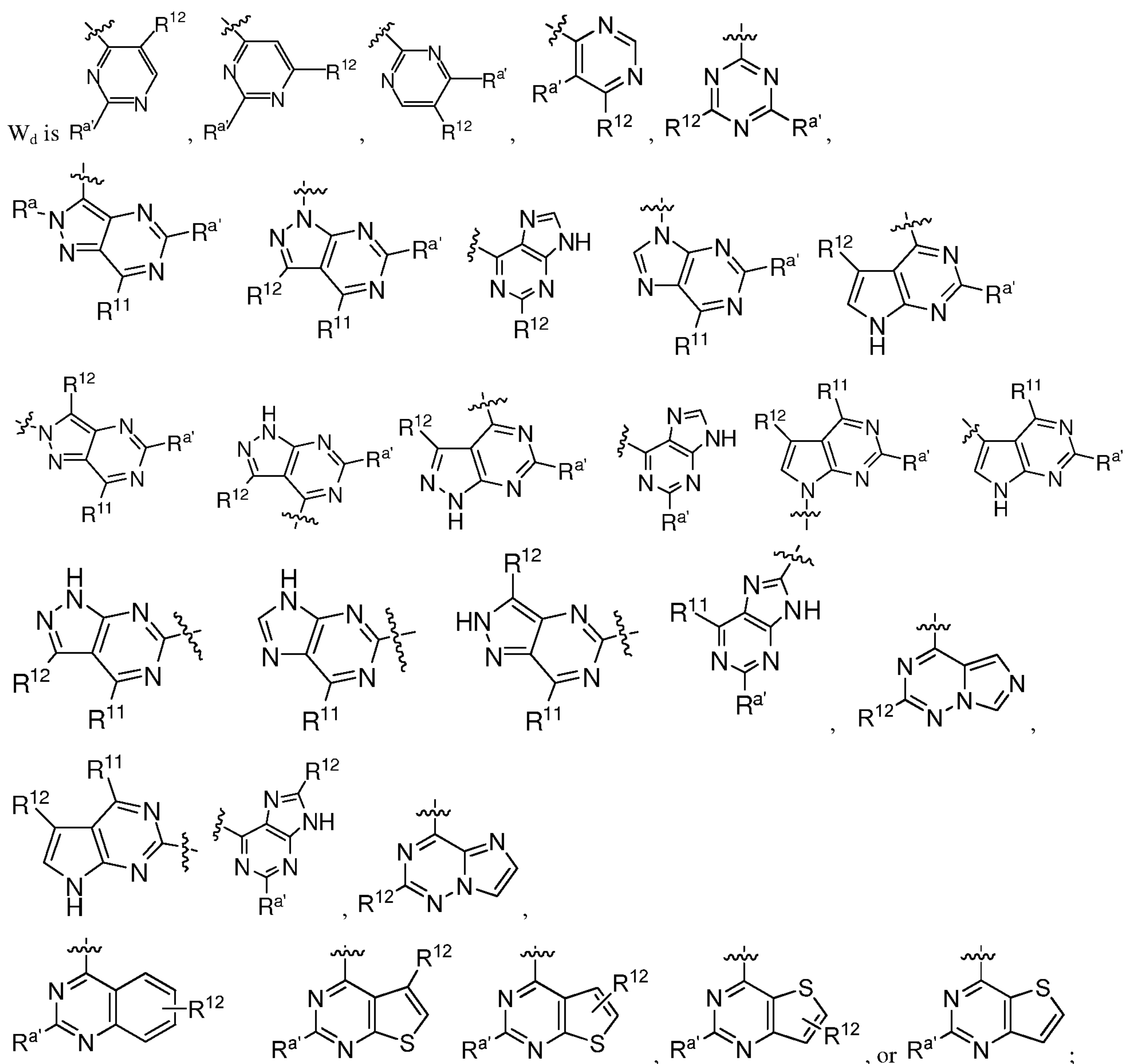
R¹ is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

each R² is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

R³ is cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, alkenyl, or alkynyl, or R³ is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C₁-C₆ alkyl group to an aryl, heteroaryl or heterocyclyl, or R³ and R⁵ are taken together with the carbons to which they are attached form a 5- or 6-membered ring; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R¹³;

R⁵, R⁶, R⁷, and R⁸ are independently hydrogen, halo, cyano, alkyl or amino;

each R⁹ is independently hydrogen, alkyl, or heterocycloalkyl;



R^{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, alkoxy, phosphate, urea, or carbonate;

R^{12} is hydrogen, alkyl, haloalkyl, alkynyl, alkenyl, halo, $-C(O)NH_2$, aryl, heteroaryl, nonaromatic heterocyclyl, or cycloalkyl,

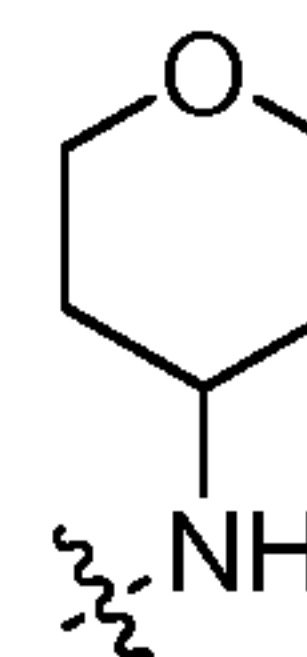
$R^{a'}$ is hydrogen, alkyl, $-NH_2$, cyano or halogen; and

each R^{13} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or halogen.

[0012] In certain embodiments, R^3 is selected from a 5-membered heteroaryl; 5-membered nonaromatic heterocycle; 6-membered aryl; 6-membered heteroaryl; 6-membered nonaromatic heterocycle; fused 5/6-bicyclic heteroaryl; fused 5/6-bicyclic nonaromatic heterocycle; C_1 - C_6 alkyl group substituted with a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered aryl or heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C_1 - C_6 alkyl group to a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered aryl or heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R^3 is a C_1 - C_6 alkyl group substituted with a fused polycyclic group, wherein the polycyclic group has greater than two rings and is carbocyclic or heterocyclic; C_1 - C_6 alkyl group substituted with a bridged cycloalkyl or bridged heterocyclic group. In some embodiments, R^3 is C_1 - C_6 alkyl group substituted with a spirocyclic cycloalkyl or spirocyclic heterocyclic group. In some embodiments, R^3 is a branched C_4 - C_{12} alkyl group, wherein said branched alkyl group contains at least one terminal t-butyl group.

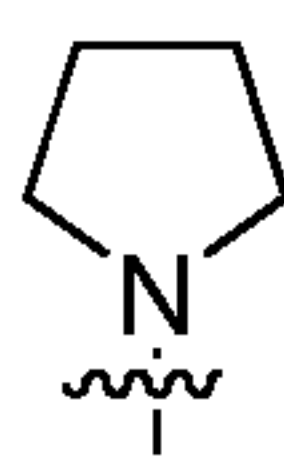
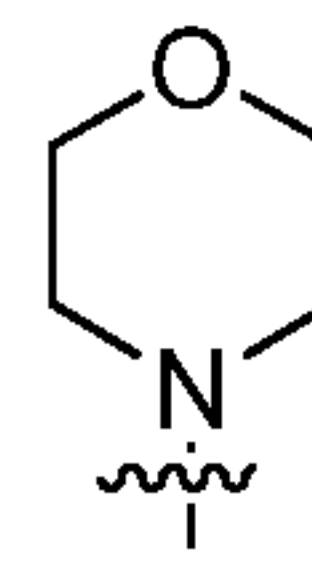
[0013] In some embodiments, R^3 is a 5-membered heteroaryl. In some embodiments, R^3 is a 5-membered nonaromatic heterocycle. In some embodiments, R^3 is a 6-membered aryl. In some embodiments, R^3 is a 6-membered heteroaryl. In some embodiments, R^3 is a 6-membered nonaromatic heterocycle. In some embodiments, R^3 is a fused 5/6-bicyclic heteroaryl. In some embodiments, R^3 is a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R^3 is a 5-membered heteroaralkyl. In some embodiments, R^3 is a 5-membered nonaromatic heterocyclalkyl. In some embodiments, R^3 is a 6-membered aralkyl. In some embodiments, R^3 is a 6-membered heteroaralkyl. In some embodiments, R^3 is a 6-membered nonaromatic heterocyclalkyl. In some embodiments, R^3 is a fused 5/6-bicyclic heteroaralkyl. In some embodiments, R^3 is a fused 5/6-bicyclic nonaromatic heterocyclalkyl.

[0014] In certain embodiments, R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C_1 - C_6 alkyl group to an aryl, heteroaryl or heterocyclyl. In some embodiments, R^3 is N, wherein the N has a covalent bond either directly or through a C_1 - C_6 alkyl group to an aryl, heteroaryl or heterocyclyl. In some embodiments, R^3 is N, wherein the N has a covalent bond directly to an aryl, heteroaryl or heterocyclyl. In some embodiments, R^3 is N, wherein N has a covalent bond directly to a heterocyclyl. In

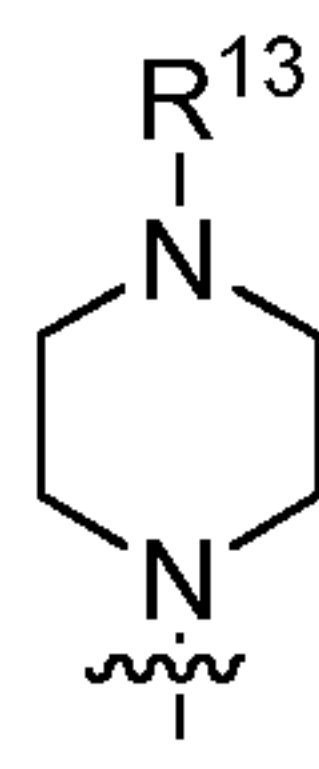


some embodiments, the heterocyclyl is 4-tetrahydro-2H-pyran. In some embodiments, R^3 is

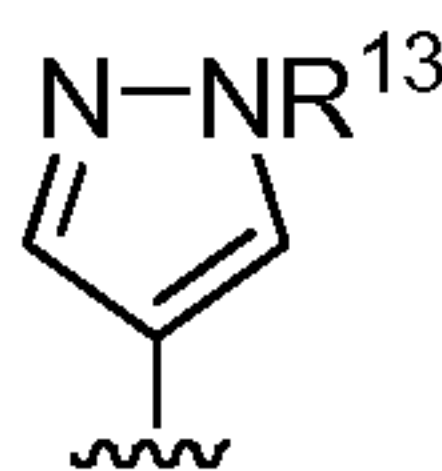
[0015]

In certain embodiments, R³ is. In some embodiments, R³ is

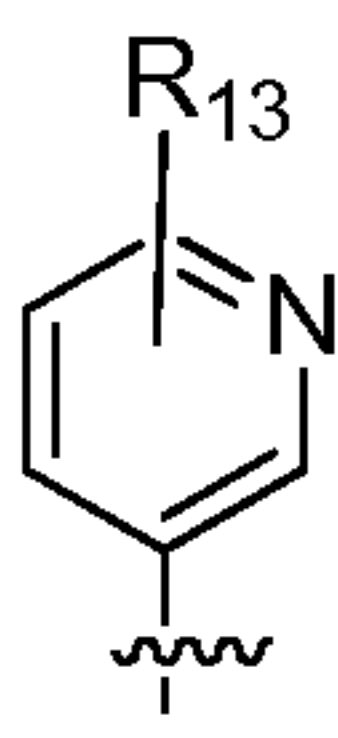
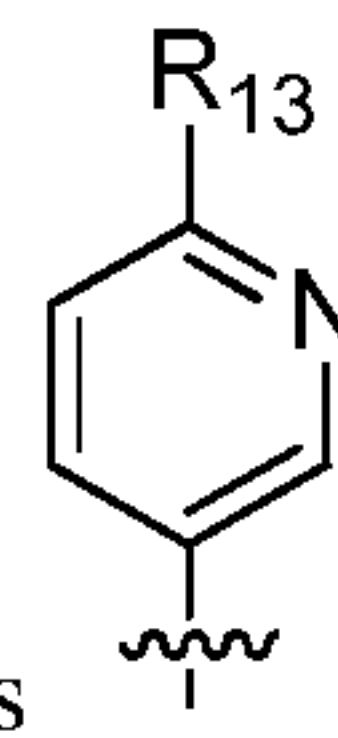
. In some

embodiments, R³ is. In some embodiments, R¹³ is C₁₋₆ alkyl (*e.g.*, methyl).

[0016]

In certain embodiments, R³ is. In some embodiments, R¹³ is H. In someembodiments, R¹³ is C₁₋₆ alkyl (*e.g.*, methyl).

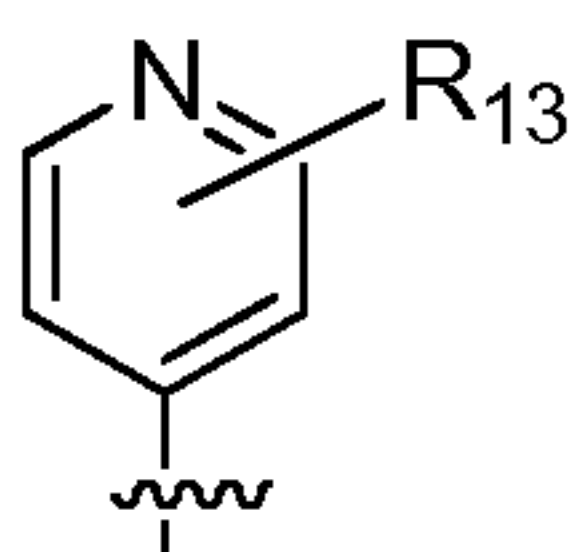
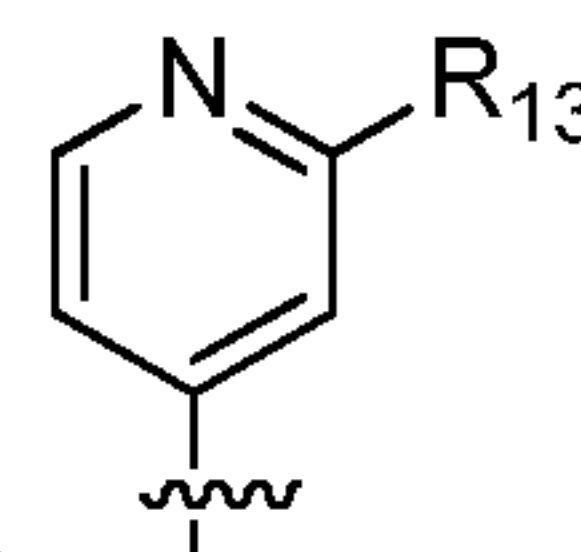
[0017]

In certain embodiments, R³ is. In some embodiments, R³ is

. In some

embodiments, R¹³ is H. In some embodiments, R¹³ is C₁₋₆ alkyl (*e.g.*, methyl).

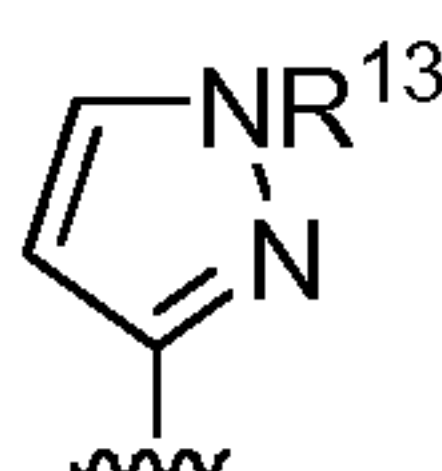
[0018]

In certain embodiments, R³ is. In some embodiments, R³ is

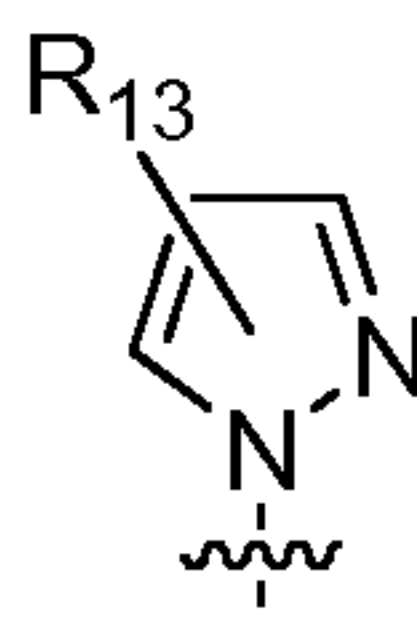
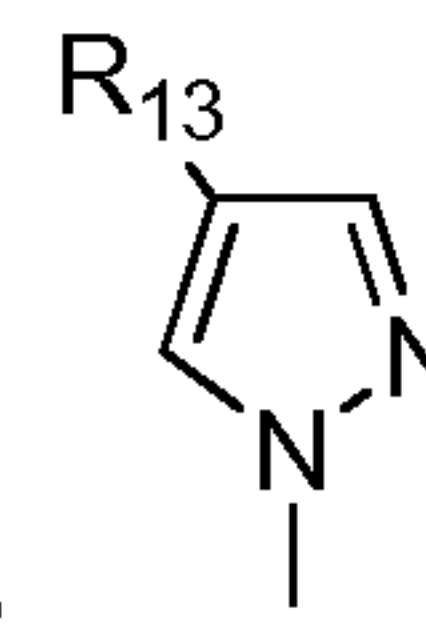
. In some

embodiments, R¹³ is H. In some embodiments, R¹³ is C₁₋₆ alkyl (*e.g.*, methyl).

[0019]

In certain embodiments, R³ is. In some embodiments, R¹³ is H.

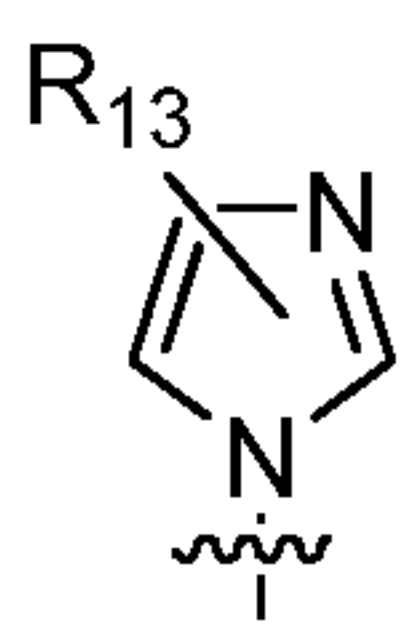
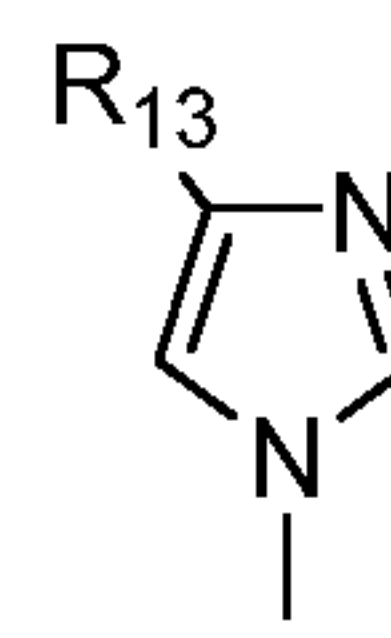
[0020]

In certain embodiments, R³ is. In some embodiments, R³ is

. In some

embodiments, R¹³ is C₁₋₆ alkyl (*e.g.*, methyl). In some embodiments R¹³ is H.

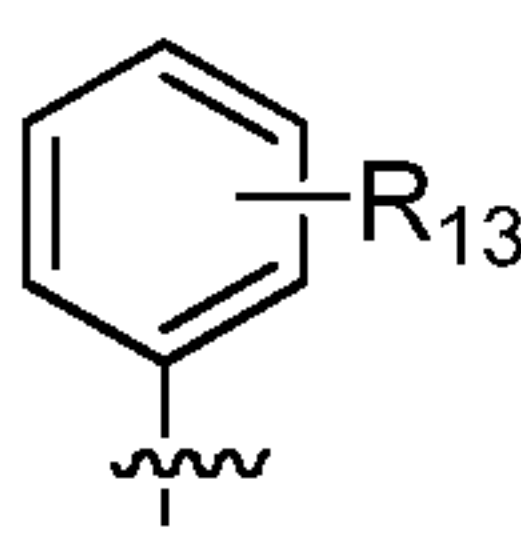
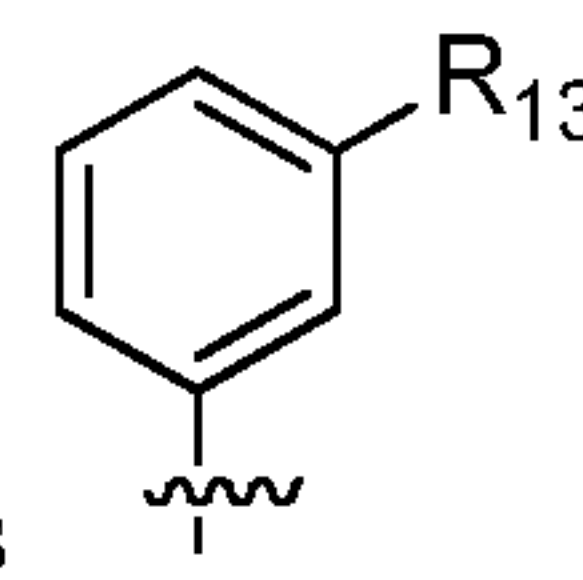
[0021]

In certain embodiments, R³ is. In some embodiments, R³ is

. In some

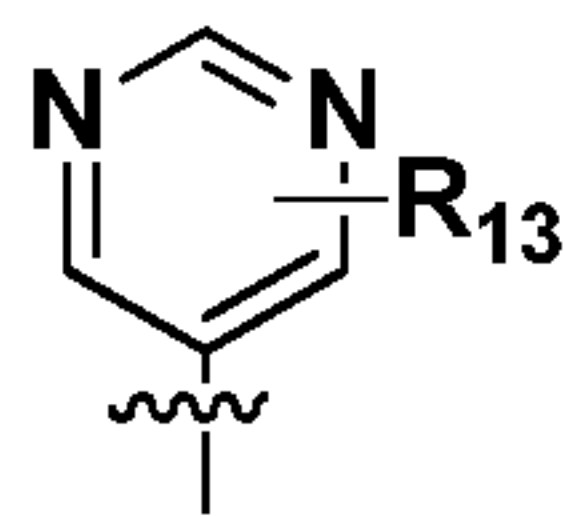
embodiments, R¹³ is H. In some embodiments, R¹³ is C₁₋₆ alkyl (*e.g.*, methyl).

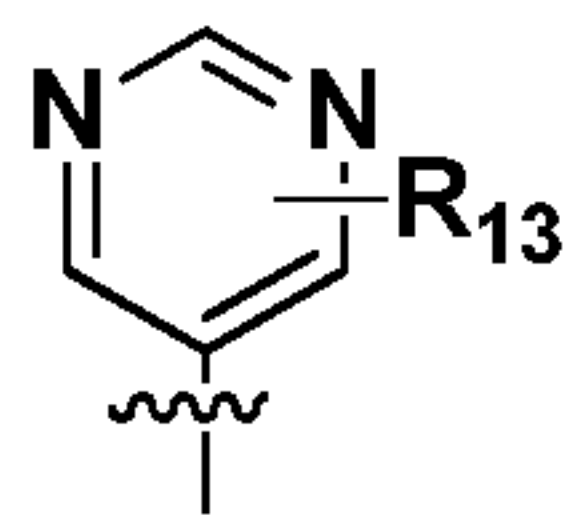
[0022]

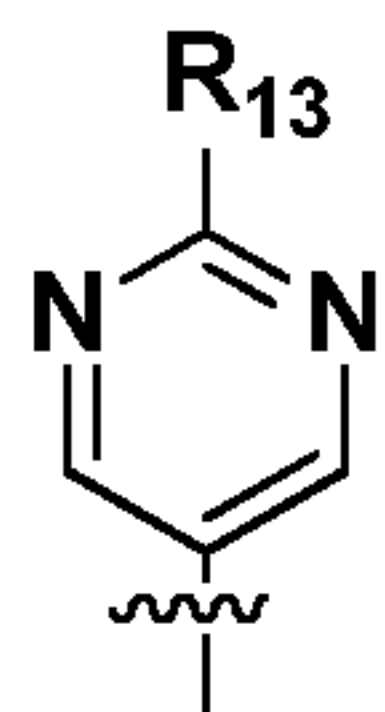
In certain embodiments, R³ is. In some embodiments, R³ is

. In some

embodiments, R¹³ is H. In some embodiments, R¹³ is halogen (*e.g.*, fluoro).



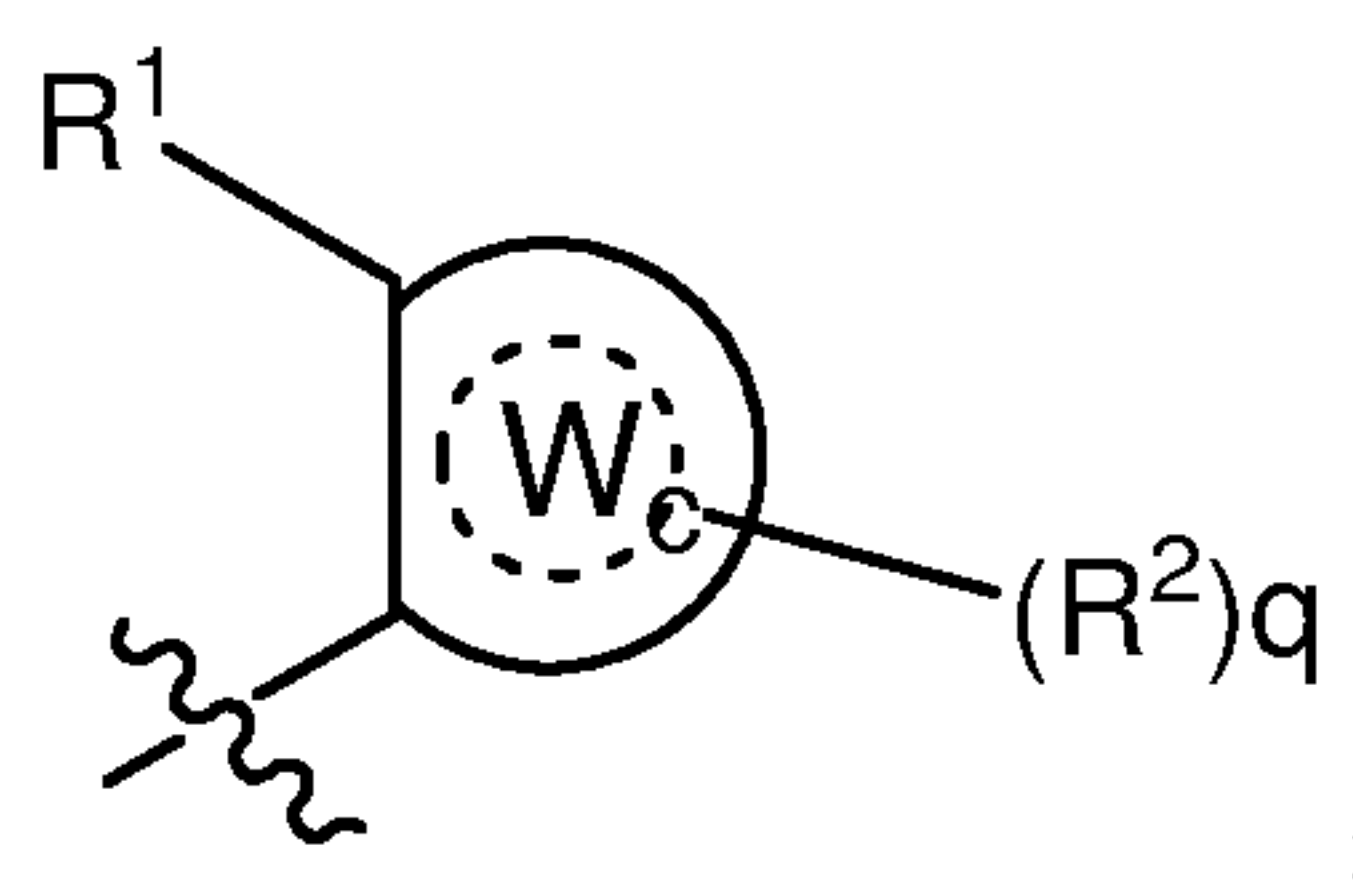
[0023] In certain embodiments, R^3 is . In some embodiments, R^3 is



. In some embodiments, R^{13} is H. In some embodiments, R^{13} is alkoxy (*e.g.*, methoxy).

[0024] In certain embodiments, R^3 and R^5 taken together with the carbons to which they are attached can form a 5- or 6-membered ring which can be substituted with 0, 1, 2, or 3 R^{13} groups.

[0025] In certain embodiments, B is hydrogen. In certain embodiments, a compound is provided of the previous formula wherein B is a moiety of Formula II:

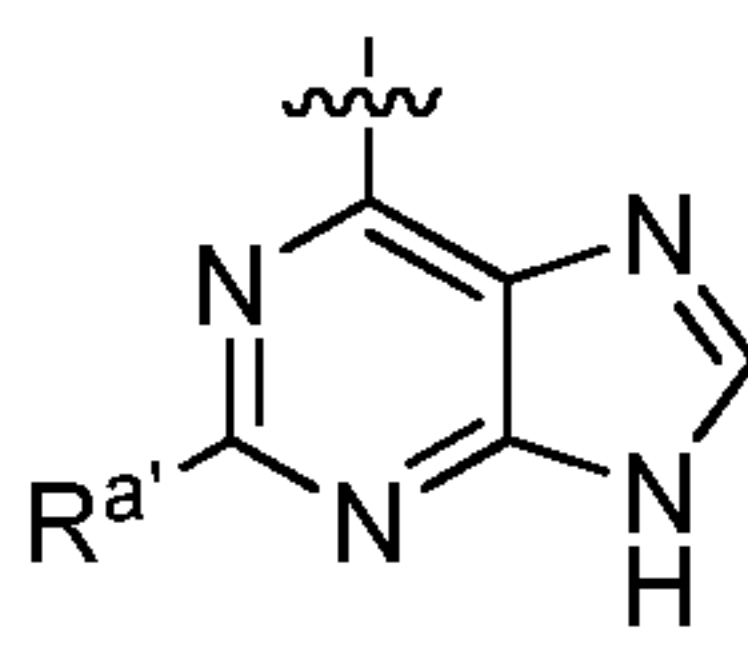


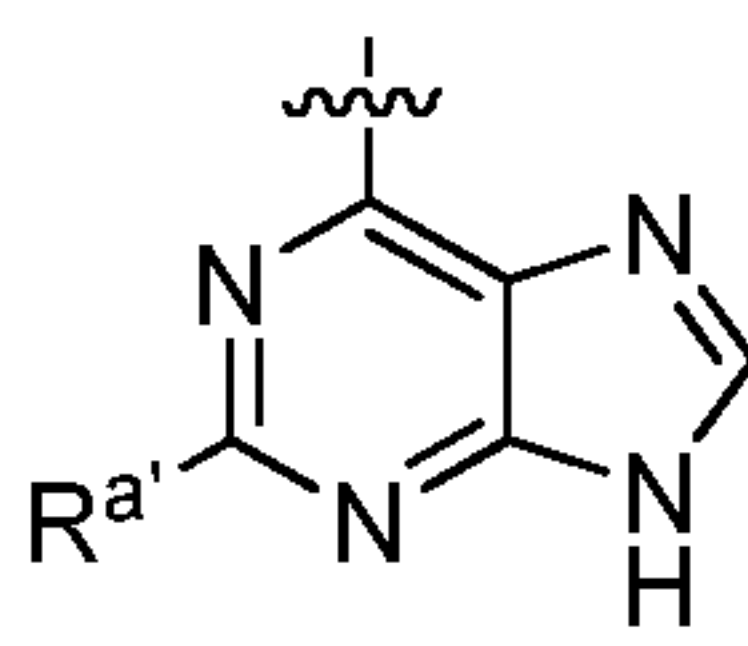
Formula II.

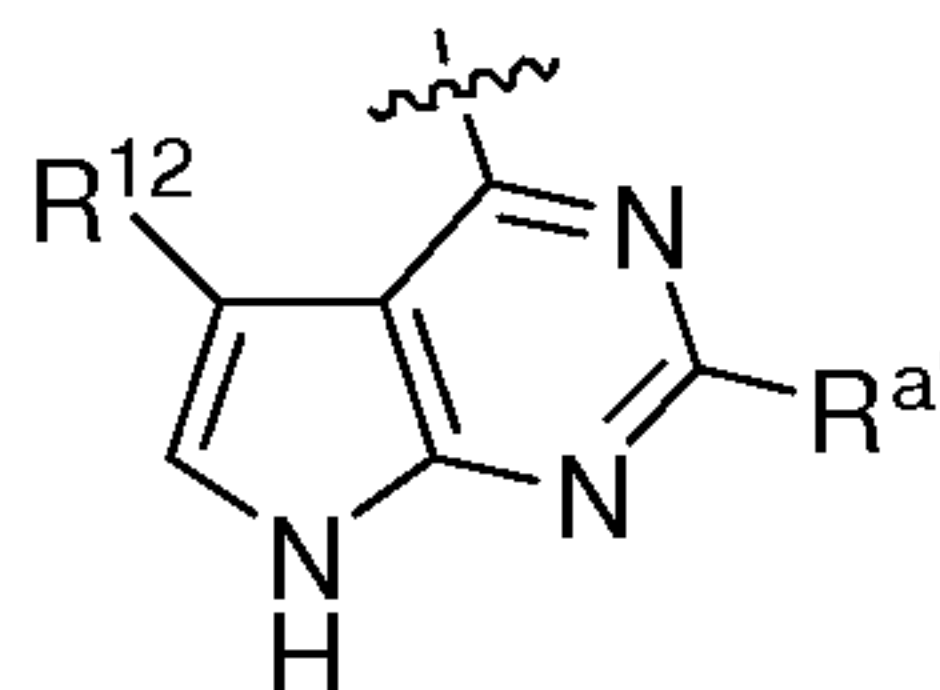
In some embodiments, W_c is aryl or heteroaryl. In some embodiments, W_c is 6-membered aryl (*e.g.*, phenyl). In some embodiments, q is 0. In some embodiments, R^1 is hydrogen. In some embodiments, q is 1. In some embodiments, R^2 is halo (*e.g.*, fluoro).

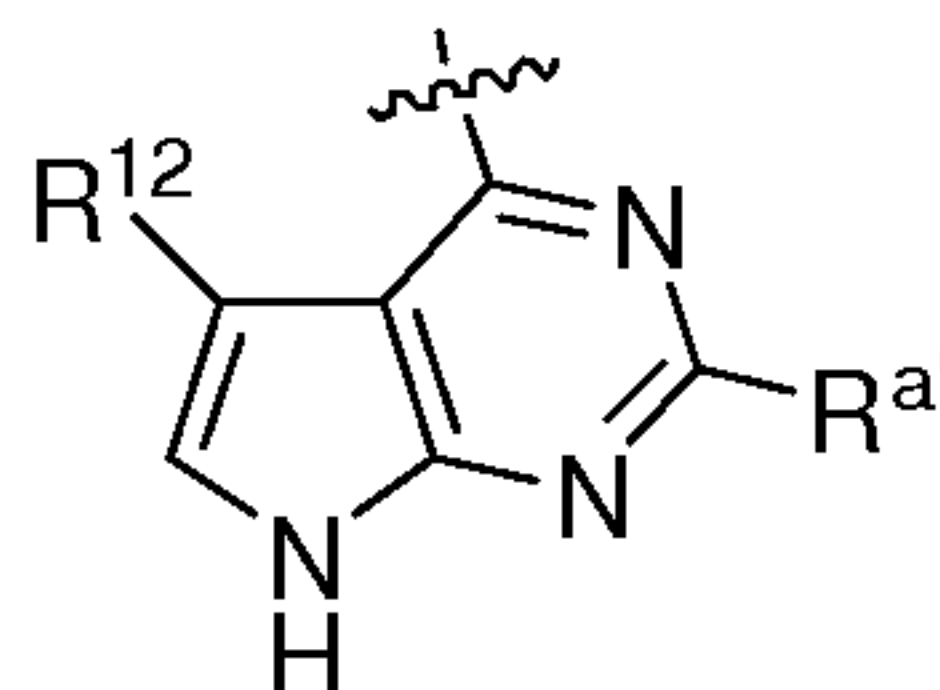
In some embodiments, W_c is cycloalkyl (*e.g.*, cyclopropyl). In some embodiments, q is 0. In some embodiments, R^1 is hydrogen.

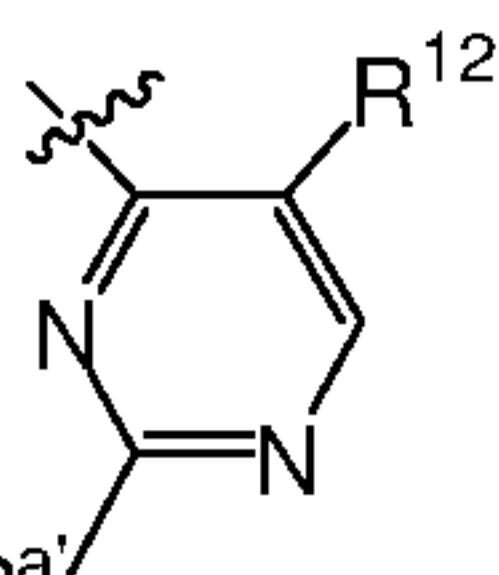
[0026] In certain embodiments, Y is absent. In some embodiments, X is $-(CH(R^9))_z-$. In some embodiments, z is 1. In some embodiments, R^9 is independently hydrogen. In some embodiments, R^9 is independently alkyl (*e.g.*, methyl).



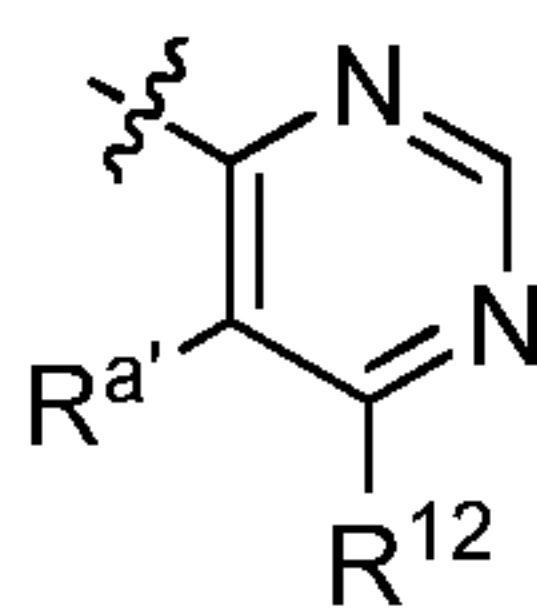
[0027] In certain embodiments, W_d is . In some embodiments, $R^{a'}$ is hydrogen. In some embodiments, $R^{a'}$ is $-NH_2$.



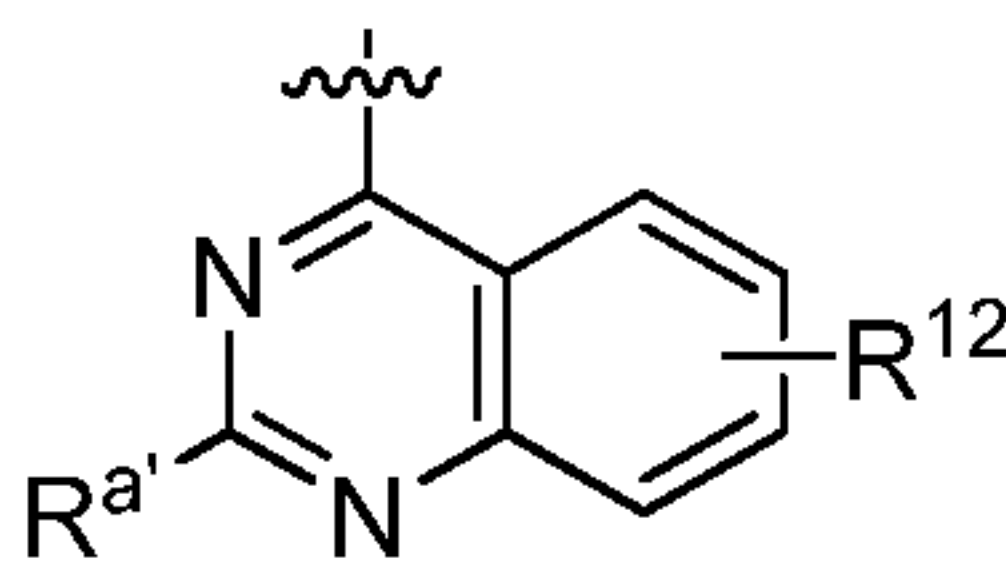
[0028] In some embodiments, W_d is . In some embodiments, R^{12} is halogen (*e.g.*, fluoro). In some embodiments, R^{12} is cyano. In some embodiments, R^{12} is $-C(O)NH_2$. In some embodiments, $R^{a'}$ is hydrogen.



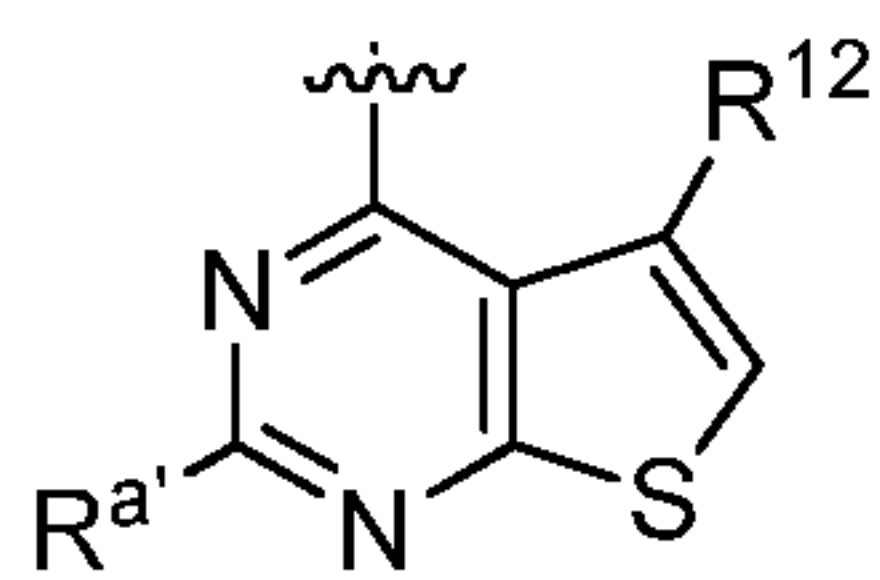
[0029] In some embodiments, W_d is $R^{a'}$. In some embodiments, $R^{a'}$ is $-NH_2$. In some embodiments, R^{12} is halo (*e.g.*, fluoro or iodo). In some embodiments, R^{12} is cyano. In some embodiments, R^{12} is haloalkyl (*e.g.*, trifluoromethyl).



[0030] In certain embodiments, W_d is $R^{a'}$. In some embodiments, $R^{a'}$ is cyano. In some embodiments, R^{12} is $-NH_2$.



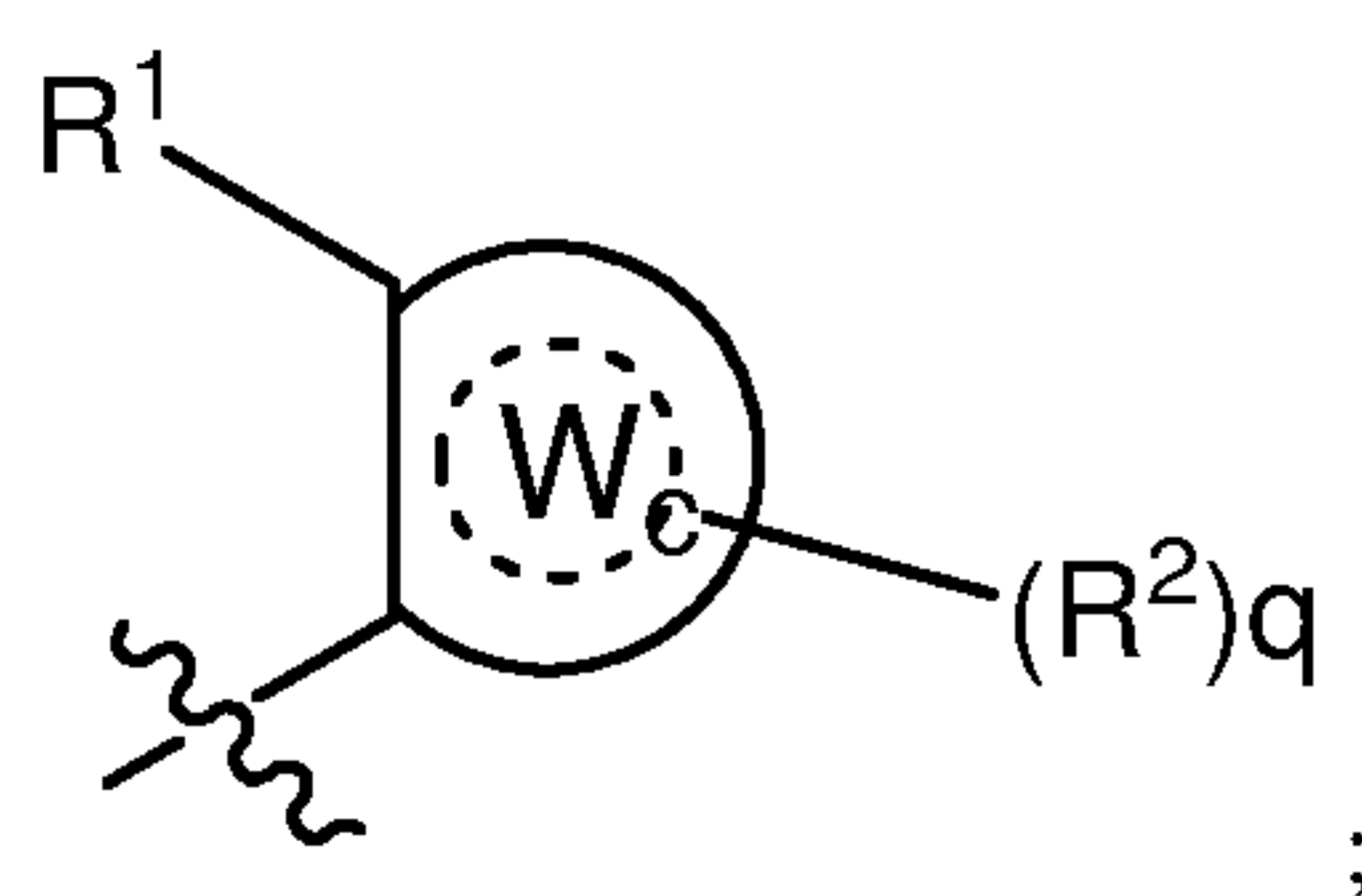
[0031] In some embodiments, W_d is $R^{a'}$. In some embodiments, W_d is



[0032] In certain embodiments, R^3 is R^{12} . In some embodiments, $R^{a'}$ is $-NH_2$. In some embodiments, R^{12} is hydrogen.

[0033] In certain embodiments, R^6 is hydrogen. In some embodiments, R^7 is hydrogen. In some embodiments, R^8 is hydrogen. In some embodiments, R^6 , R^7 and R^8 are hydrogen.

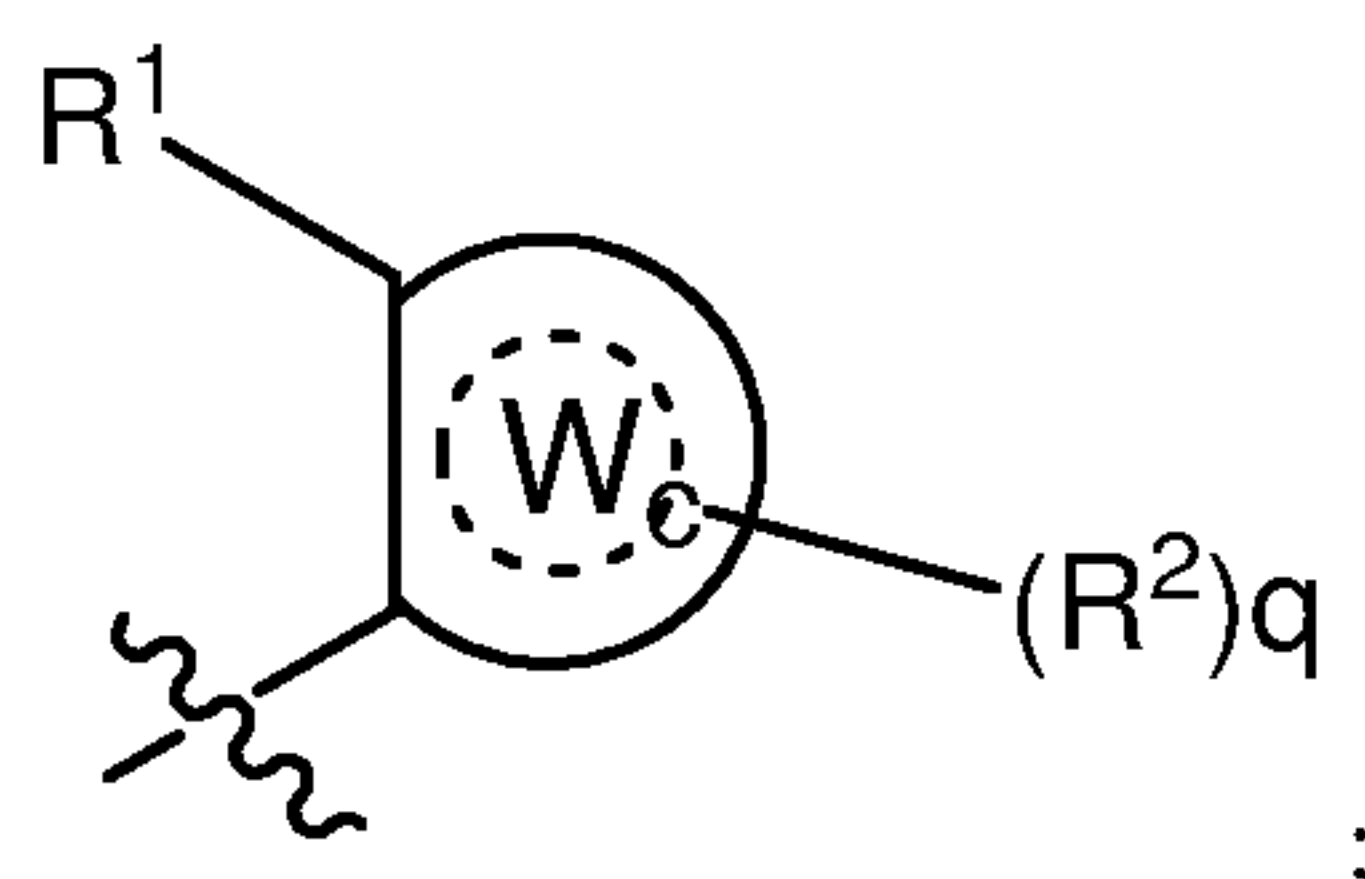
[0034] In certain aspects, a compound is provided of formulae I or Ib wherein B is a moiety of Formula II:



Formula II

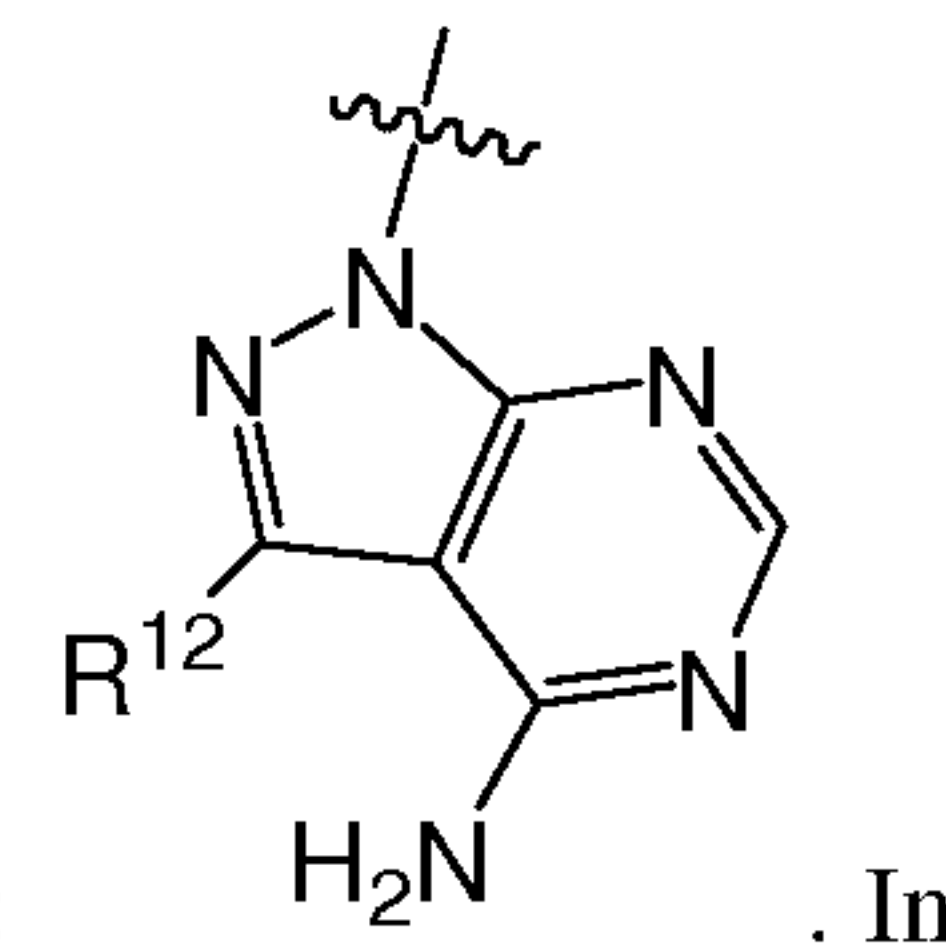
wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; q is an integer of 0 or 1; R^1 is hydrogen, alkyl, or halo; R^2 is alkyl or halo; and R^3 is a 5-membered heteroaryl, 6-membered heteroaryl, or fused 5/6-bicyclic heteroaryl group.

[0035] In certain aspects, a compound is provided of formulae I or Ib wherein B is a moiety of formula:

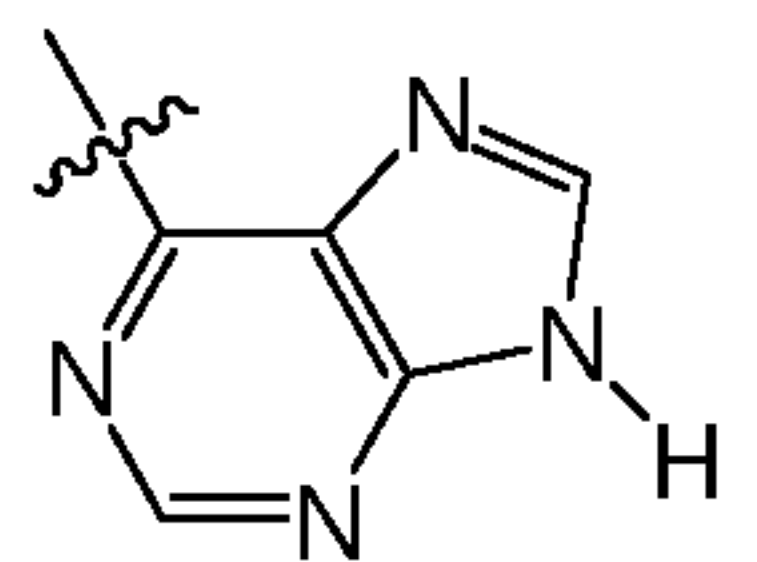


Formula II

wherein W_c is aryl or cycloalkyl. In various embodiments, R^3 contains one or two nitrogen atoms, with the proviso that non-nitrogen heteroatoms can be excluded. In various embodiments, R^3 is a substituted or unsubstituted group selected from phenyl, pyridine, pyrazole, piperazine, imidazole and pyrrolidine. For example, the R^3 group can be substituted with a C_1 - C_6 alkyl group or a halogen.

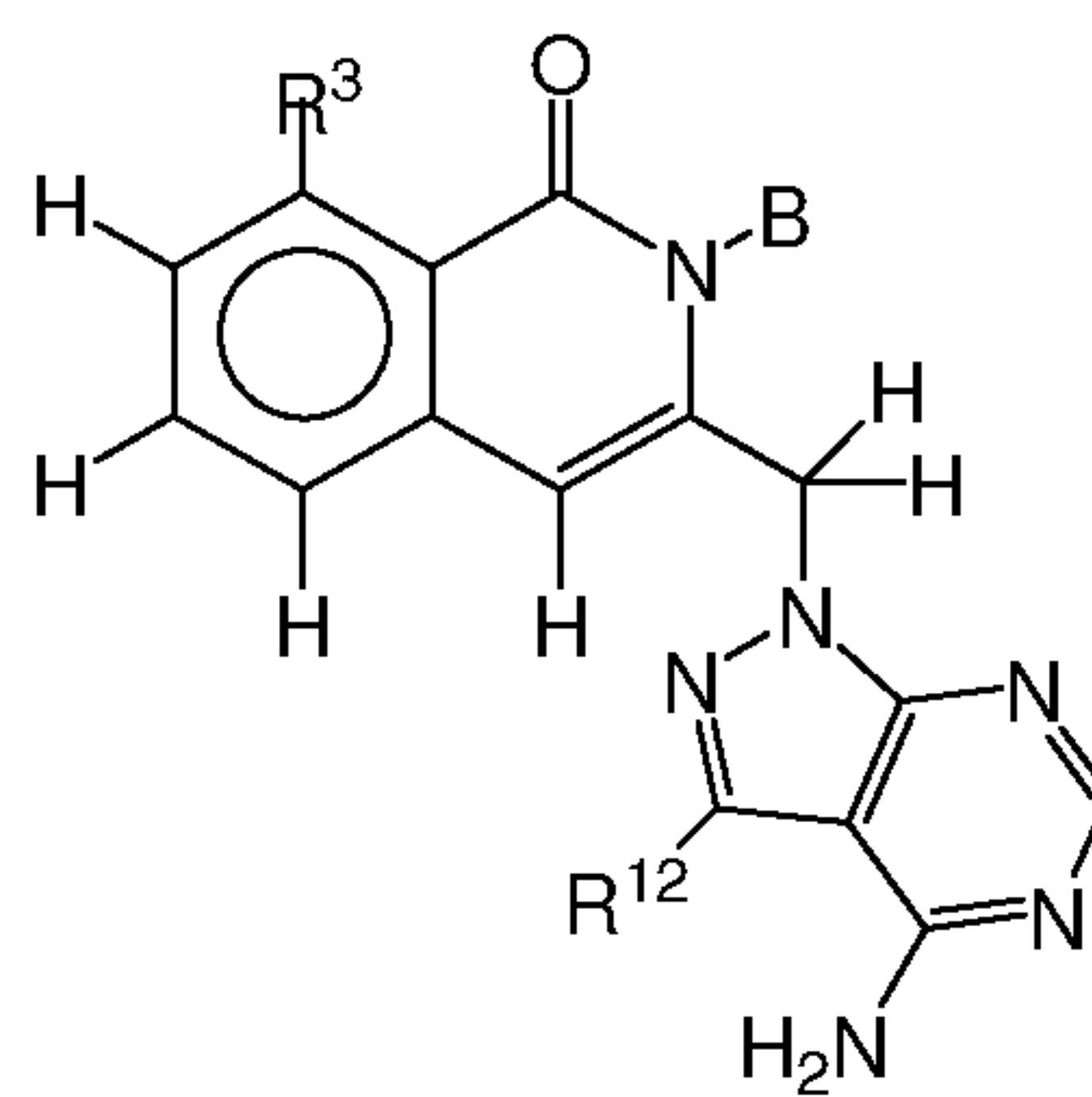


[0036] In some embodiments of the compound of Formula I, Y is absent and W_d is:



other embodiments, Y is present and W_d is:

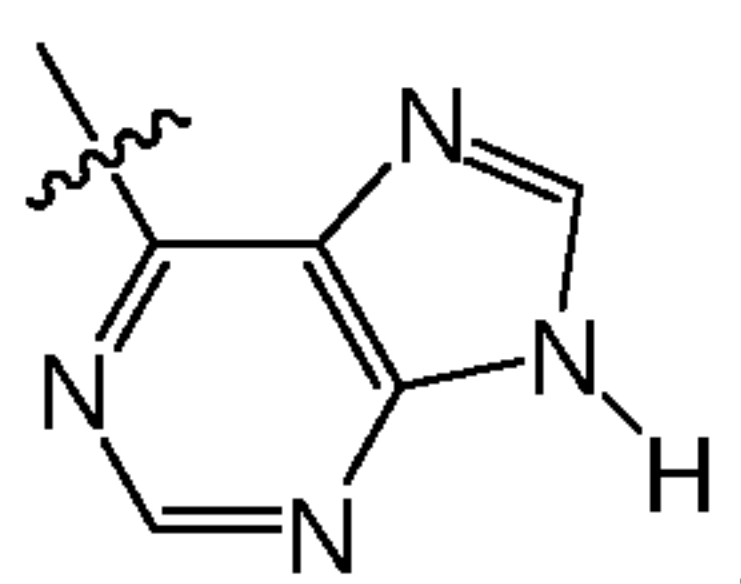
[0037] In some embodiments, a compound is provided wherein the compound has a structure of Formula IV-A:



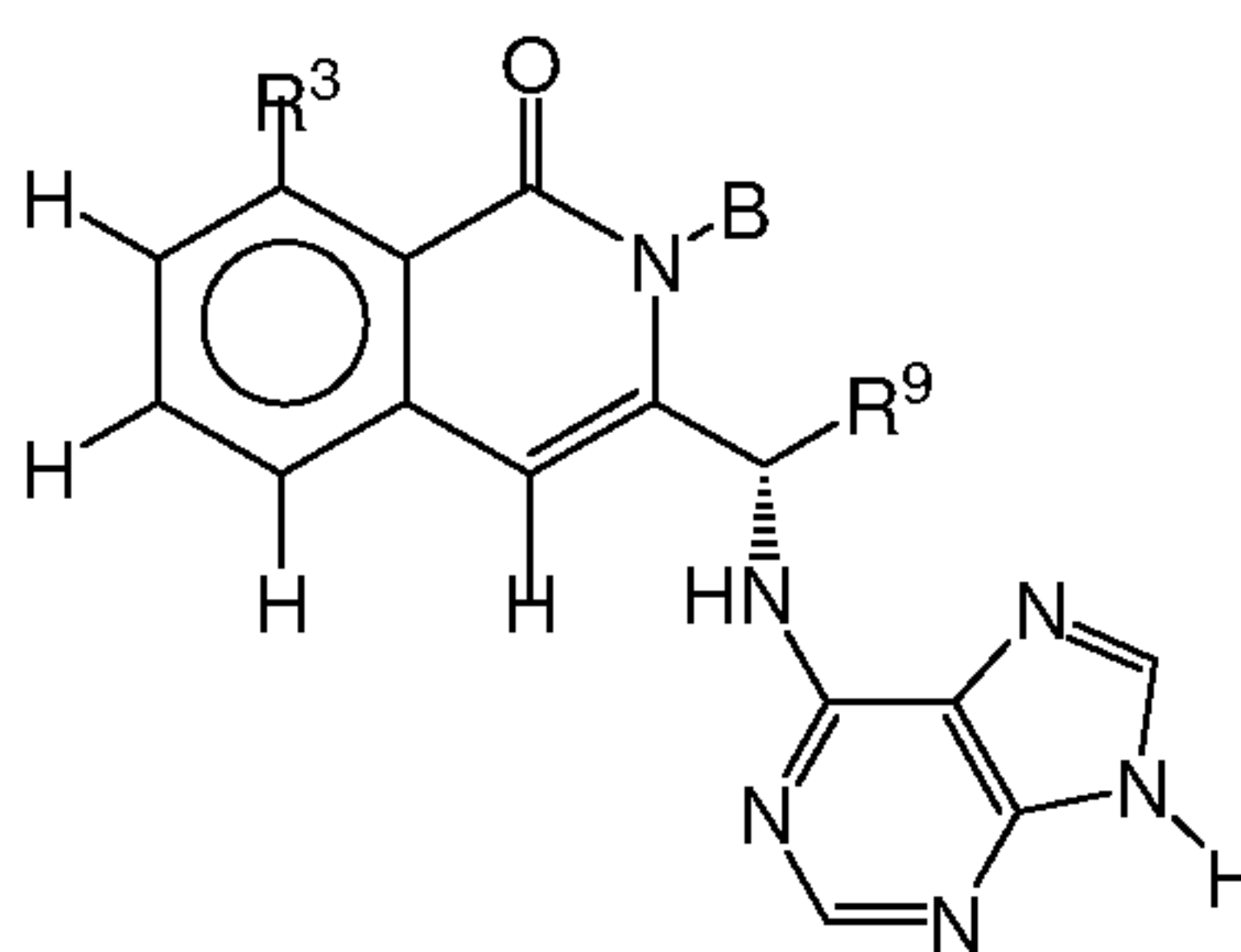
Formula IV-A

In certain embodiments, R^{12} is monocyclic heteroaryl, bicyclic heteroaryl, or nonaromatic heterocyclyl. For example, R^{12} can be a substituted benzoxazole. In certain embodiments, R^3 is a substituted or unsubstituted group selected from pyridine, pyrazole, piperazine, and pyrrolidine. The R^3 group can be substituted with a C_1 - C_6 alkyl group or a halogen.

[0038] In some embodiments, a compound of any of the above formulae is provided wherein X is $-(CH(R^9))_z-$, wherein R^9 is methyl and $z = 1$; and W_d is



Accordingly, in some embodiments, the compound has one stereocenter, wherein said stereocenter can be in an (S)-stereochemical configuration or an (R)-stereochemical configuration. In some embodiments, a compound is provided wherein the compound has a structure of Formula V-A2:

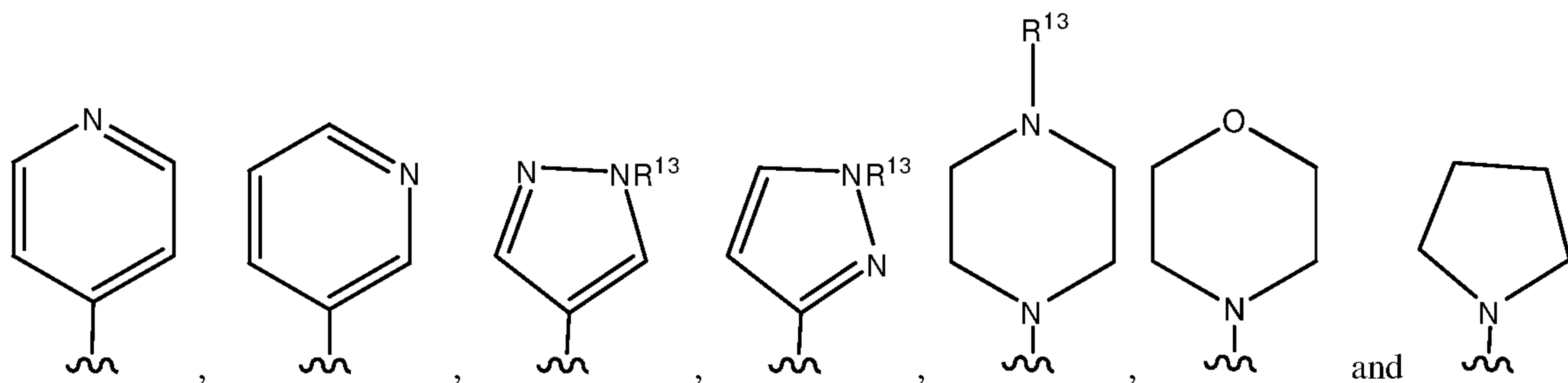


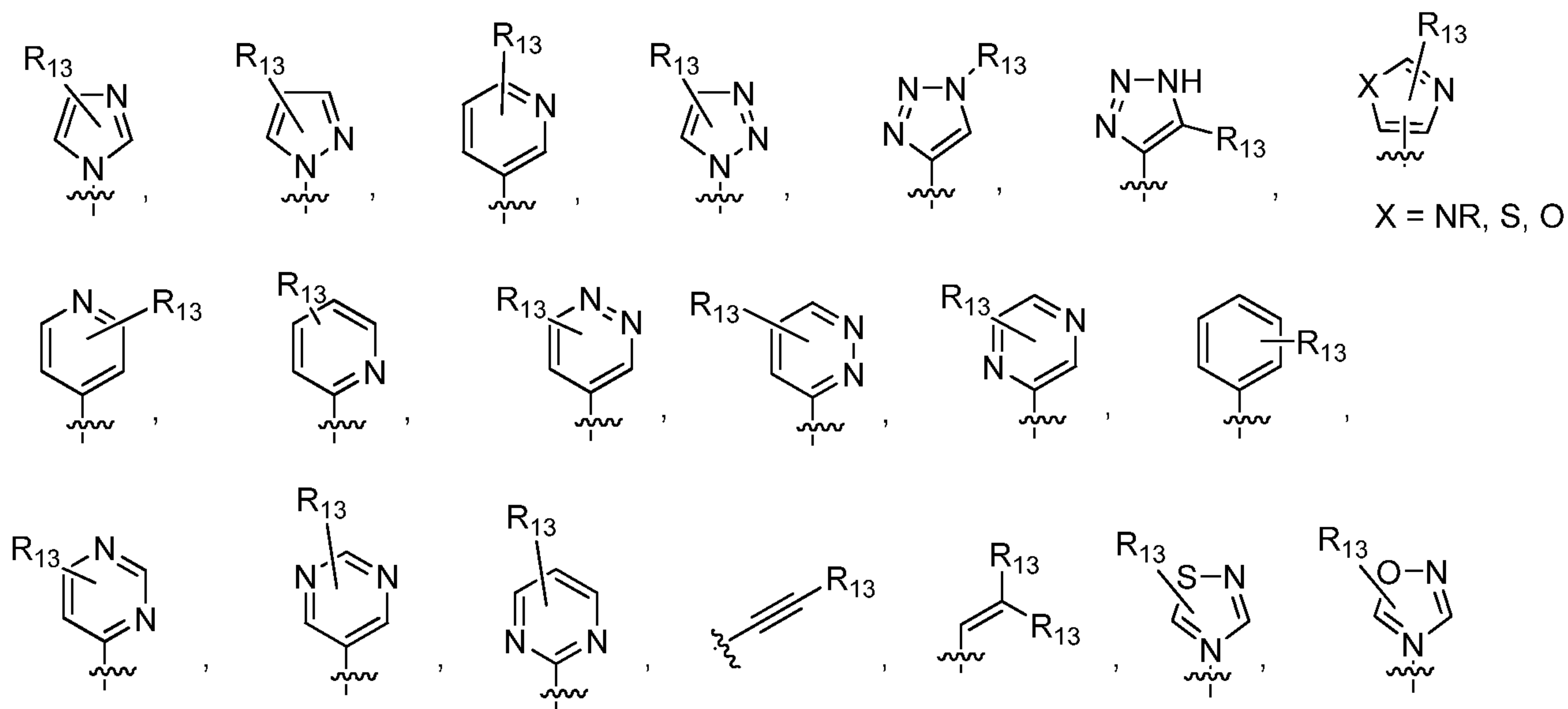
Formula V-A2 .

[0039] In certain embodiments, a compound described herein (*e.g.*, a compound of Formula V-A2) is present in a racemic mixture (*e.g.*, less than about 10% enantiomeric excess of either the R or S stereoisomer). In some embodiments, a compound described herein (*e.g.*, a compound of Formula V-A2) is present in an enantiomeric excess of the R stereoisomer (*e.g.*, about 10%, 50%, 75%, 85%, 90%, 95%, 97%, 99% or greater). In some embodiments, a compound described herein (*e.g.*, a compound of Formula V-A2) is present in an enantiomeric excess of the S stereoisomer (*e.g.*, about 10%, 50%, 75%, 85%, 90%, 95%, 97%, 99% or greater).

[0040] In certain embodiments, R^3 is phenyl, pyridine, pyrazole, piperazine, imidazole or pyrrolidine, substituted with 0, 1, 2, or 3 occurrences of R^{13} . In some embodiments, R^{13} is C_1 - C_6 alkyl (*e.g.*, methyl). In some embodiments, R^{13} is halogen (*e.g.*, fluoro).

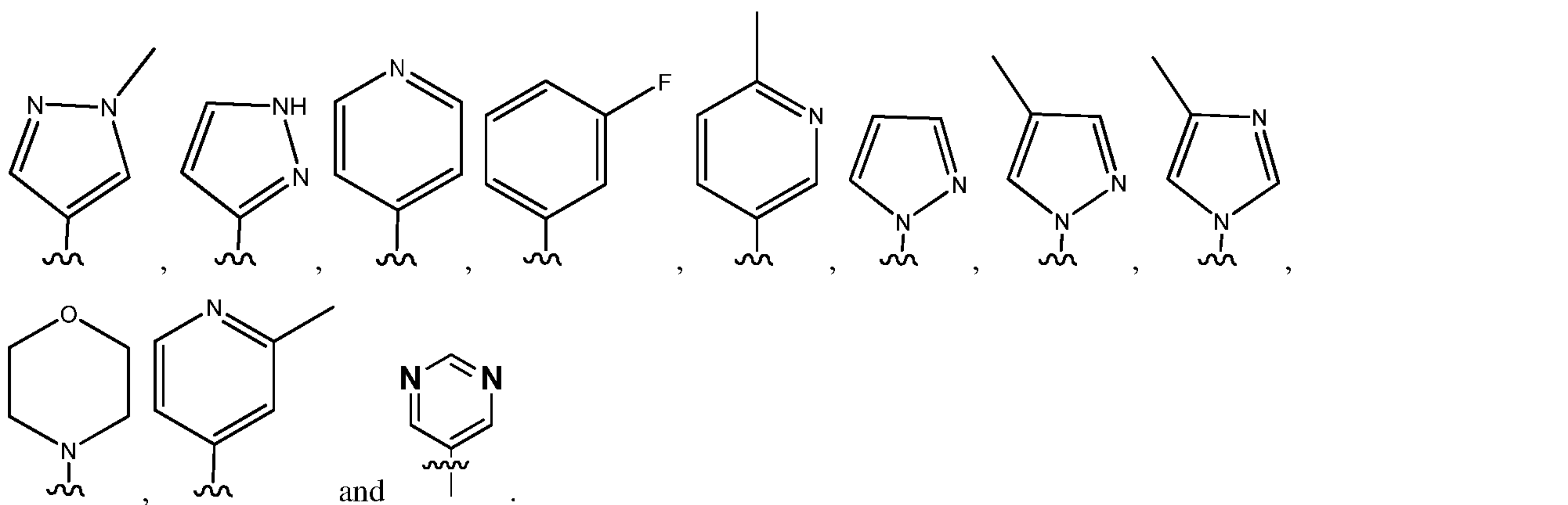
[0041] In some embodiments, a compound is provided wherein R^3 is selected from a 5-membered heteroaryl selected from pyrrole, a furan, a thiazole, a triazole, a tetrazole and a thiophene group; a 5-membered nonaromatic heterocycle selected from pyrrolidine, a tetrahydrofuran, and a tetrahydrothiophene group; a 6-membered heteroaryl selected from pyridine, pyrazine, pyrimidine, and pyridazine; a 6-membered nonaromatic heterocycle selected from piperidine, tetrahydropyran, and thiane; and a fused 5/6-bicyclic heteroaryl selected from indole, isoindole, benzofuran, isobenzofuran, benzothiophene, benzothiazole, benzimidazole, indazole, benzoxazole, benzisoxazole, and purine; each of which can be substituted with 0, 1, 2, or 3 occurrences of R^{13} . In certain embodiments, R^3 is selected from pyridine, pyrazole, piperazine, and pyrrolidine; each of which can be substituted with 0, 1, 2, or 3 occurrences of R^{13} . In some embodiments, R^3 can be substituted with R^{13} , which is C_1 - C_6 alkyl (*e.g.*, methyl) or a halogen (*e.g.*, fluoro). In some embodiments, a compound is provided wherein R^3 is selected from



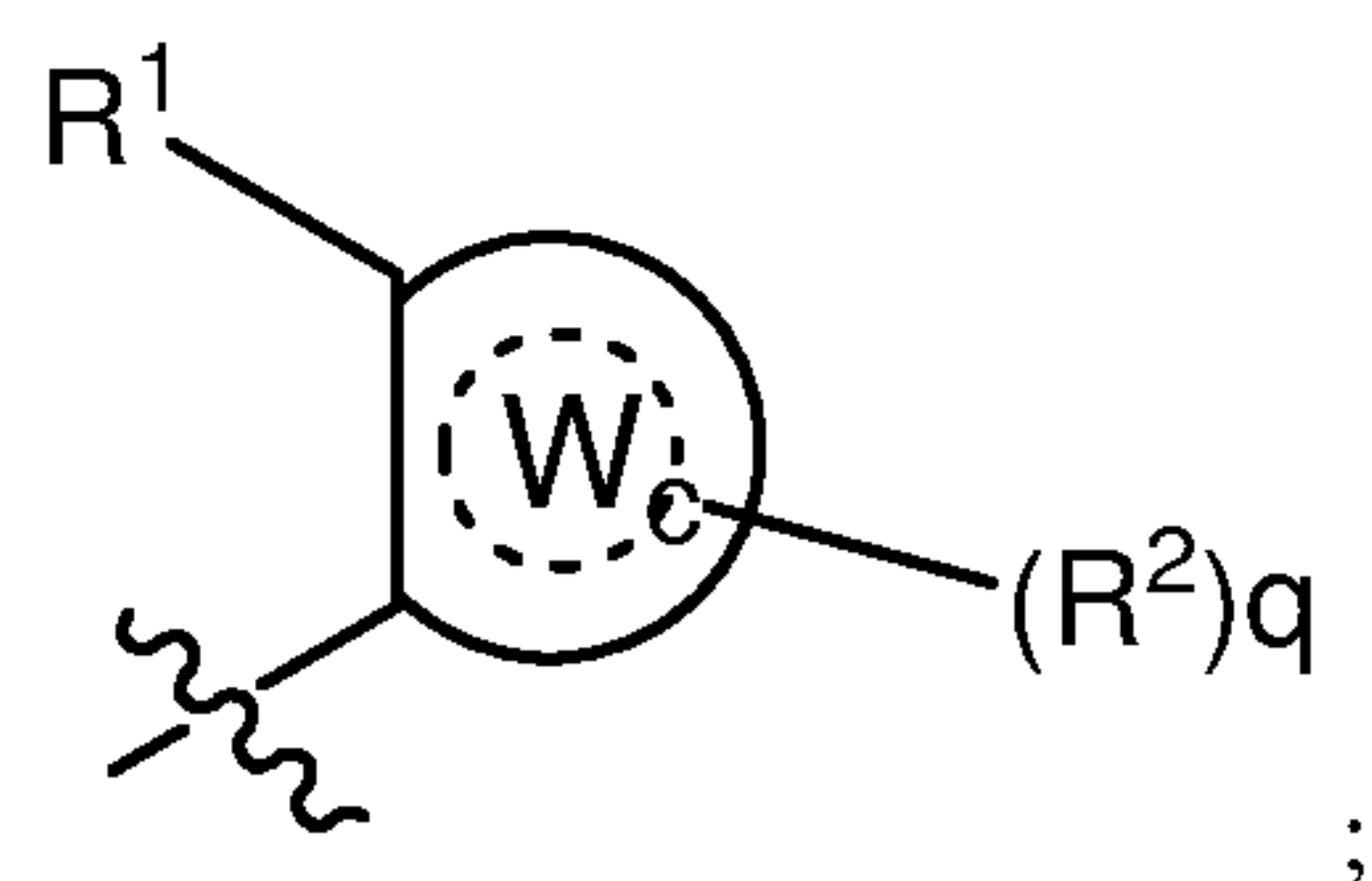


wherein R^{13} is H C_1 - C_6 alkyl (*e.g.*, methyl) or halo (*e.g.*, fluoro). In some embodiments, R^{13} is C_1 - C_6 alkyl (*e.g.*, methyl). In some embodiments, R^{13} is halo (*e.g.*, fluoro).

[0042] In some embodiments, R^3 is selected from:

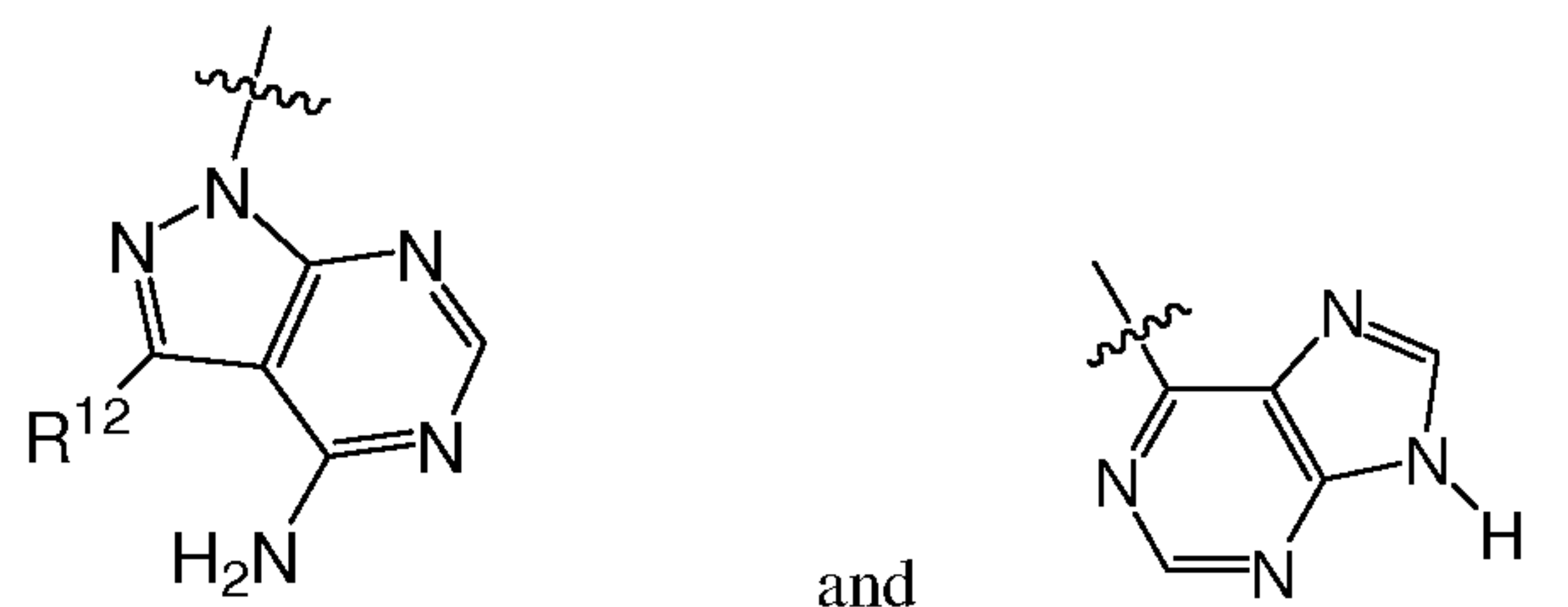


[0043] In certain embodiments, B is a moiety of Formula II:



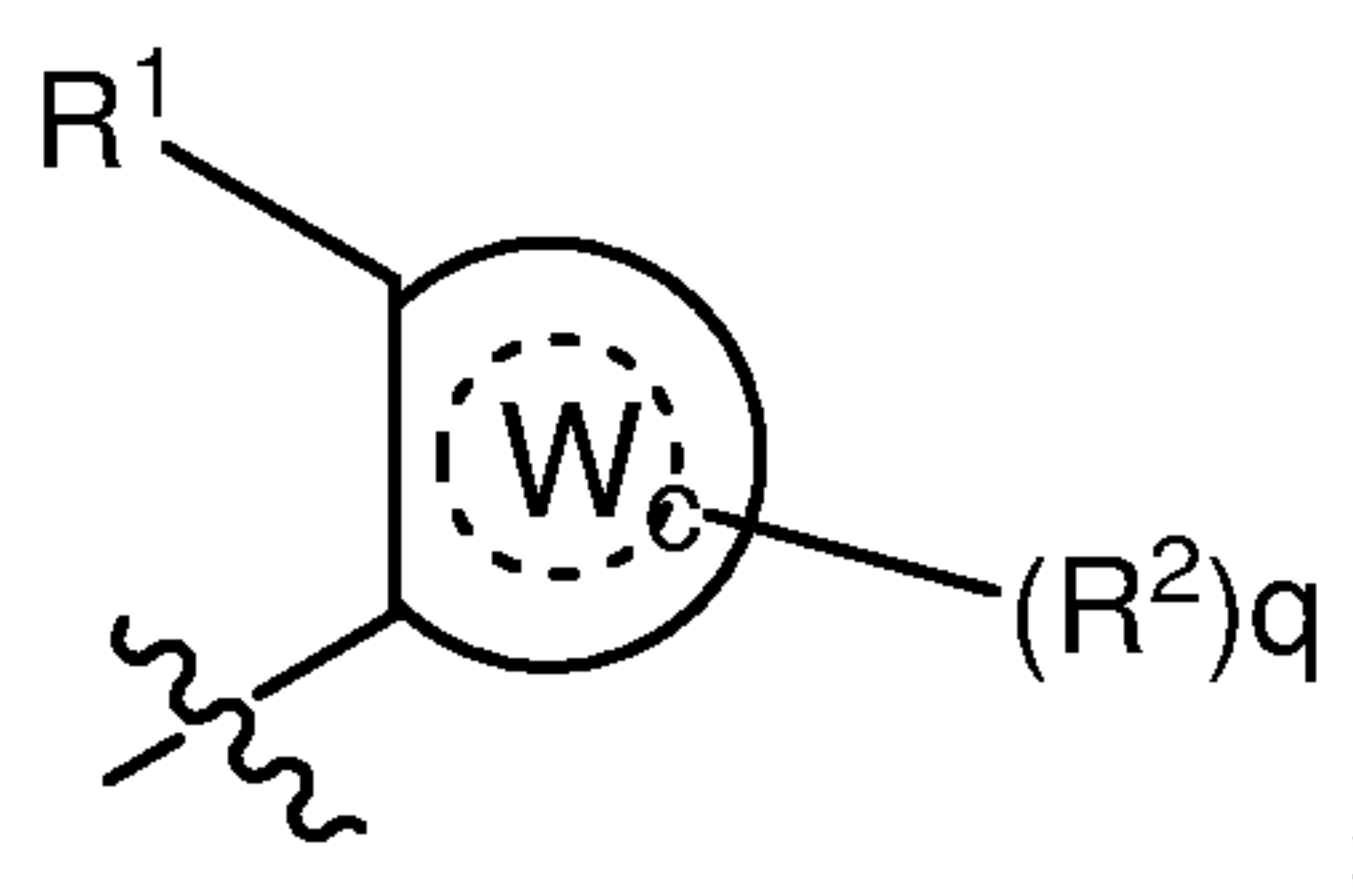
Formula II

wherein W_c is aryl or cycloalkyl. In certain embodiments, W_d is selected from



wherein R^3 can be selected from pyridine, pyrazole, piperazine, and pyrrolidine; each of which can be substituted with 0, 1, 2, or 3 occurrences of R^{13} ;

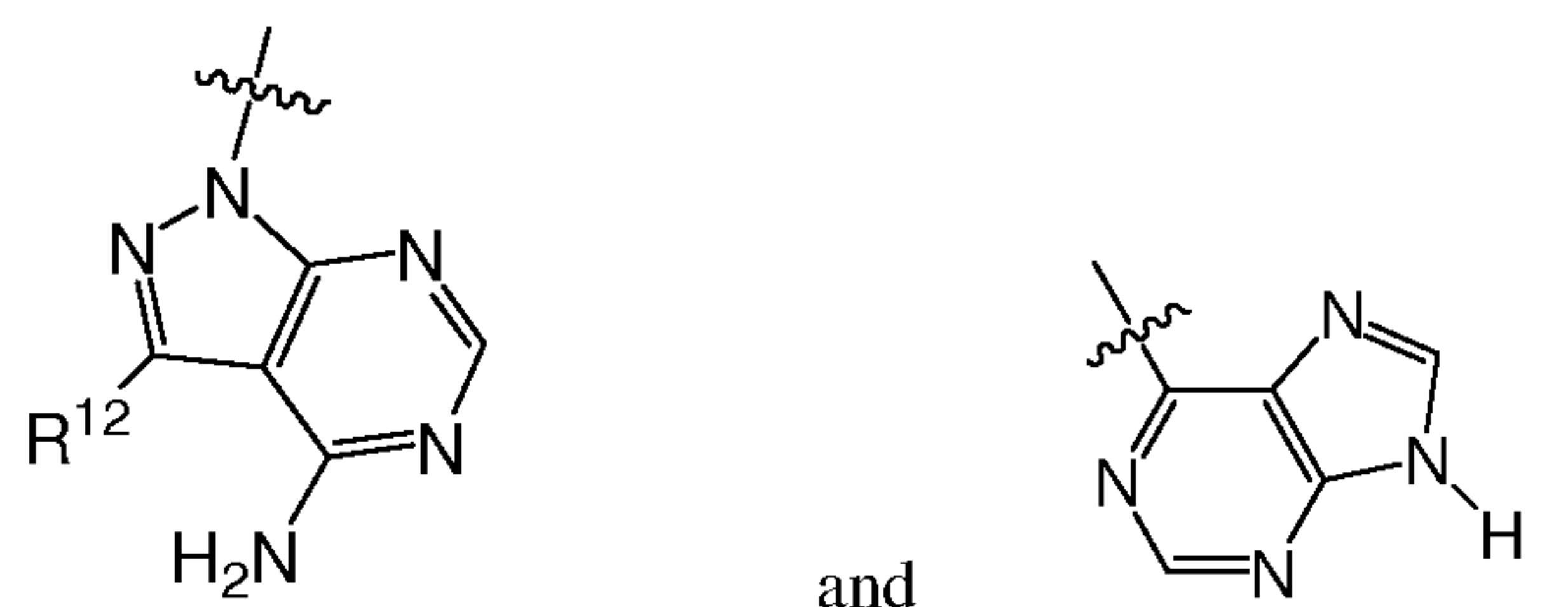
B can be a moiety of Formula II:



Formula II

wherein W_c is aryl or cycloalkyl; and

W_d is selected from



[0044] In certain embodiments, R^{13} is C_1 - C_6 alkyl (*e.g.*, methyl) or a halogen (*e.g.*, fluoro).

[0045] In certain embodiments, a compound as disclosed herein selectively modulates phosphatidyl inositol-3 kinase (PI3 kinase) delta isoform. In certain embodiments, the compound selectively inhibits the delta isoform over the beta isoform. By way of non-limiting example, the ratio of selectivity can be greater than a factor of about 10, greater than a factor of about 50, greater than a factor of about 100, greater than a factor of about 200, greater than a factor of about 400, greater than a factor of about 600, greater than a factor of about 800, greater than a factor of about 1000, greater than a factor of about 1500, greater than a factor of about 2000, greater than a factor of about 5000, greater than a factor of about 10,000, or greater than a factor of about 20,000, where selectivity can be measured by IC_{50} , among other means. In certain embodiments, the PI3 kinase delta isoform IC_{50} activity of a compound as disclosed herein can be less than about 1000 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM.

[0046] In certain embodiments, provided herein is a composition (*e.g.*, a pharmaceutical composition) comprising a compound as described herein and a pharmaceutically acceptable excipient. In some embodiments, provided herein is a method of inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase), comprising contacting the PI3 kinase with an effective amount of a compound or pharmaceutical composition as described herein. In certain embodiments, a method is provided for inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) wherein said PI3 kinase is present in a cell. The inhibition can take place in a subject suffering from a disorder selected from cancer, bone

disorder, inflammatory disease, immune disease, nervous system disease, metabolic disease, respiratory disease, thrombosis, and cardiac disease. In certain embodiments, a second therapeutic agent is administered to the subject.

[0047] In certain embodiments, a method is provided of selectively inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) delta isoform over PI3 kinase beta isoform wherein the inhibition takes place in a cell. Non-limiting examples of the methods disclosed herein can comprise contacting PI3 kinase delta isoform with an effective amount of a compound or pharmaceutical composition as disclosed herein. In an embodiment, such contact can occur in a cell.

[0048] In certain embodiments, a method is provided of selectively inhibiting a phosphatidyl inositol-3 kinase (PI3 kinase) delta isoform over PI3 kinase beta isoform wherein the inhibition takes place in a subject suffering from a disorder selected from cancer, bone disorder, inflammatory disease, immune disease, nervous system disease, metabolic disease, respiratory disease, thrombosis, and cardiac disease, said method comprising administering an effective amount of a compound or pharmaceutical composition to said subject. In certain embodiments, provided herein is a method of treating a subject suffering from a disorder associated with phosphatidyl inositol-3 kinase (PI3 kinase), said method comprising selectively modulating the phosphatidyl inositol-3 kinase (PI3 kinase) delta isoform over PI3 kinase beta isoform by administering an amount of a compound or pharmaceutical composition to said subject, wherein said amount is sufficient for selective modulation of PI3 kinase delta isoform over PI3 kinase beta isoform.

INCORPORATION BY REFERENCE

[0049] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

DETAILED DESCRIPTION

[0050] While specific embodiments of the present disclosure have been discussed, the specification is illustrative and not restrictive. Many variations of this disclosure will become apparent to those skilled in the art upon review of this specification. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[0051] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range can vary from, for example, but not limited to, between 0.1% and 15% of the stated number or numerical range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by the present disclosure.

[0052] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this specification pertains.

[0053] As used in the specification and claims, the singular form “a”, “an” and “the” includes plural references unless the context clearly dictates otherwise.

[0054] As used herein, “agent” or “biologically active agent” refers to a biological, pharmaceutical, or chemical compound or other moiety. Non-limiting examples include simple or complex organic or inorganic molecules, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, an antibody fragment, a vitamin, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound, and metabolites thereof. Various compounds can be synthesized, for example, small molecules and oligomers (*e.g.*, oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide compounds for screening, such as plant or animal extracts, and the like. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of this disclosure.

[0055] The term “agonist” as used herein refers to a compound or agent having the ability to initiate or enhance a biological function of a target protein or polypeptide, such as increasing the activity or expression of the target protein or polypeptide. Accordingly, the term “agonist” is defined in the context of the biological role of the target protein or polypeptide. While some agonists herein specifically interact with (*e.g.*, bind to) the target, compounds and/or agents that initiate or enhance a biological activity of the target protein or polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

[0056] The terms “antagonist” and “inhibitor” are used interchangeably, and they refer to a compound or agent having the ability to inhibit a biological function of a target protein or polypeptide, such as by inhibiting the activity or expression of the target protein or polypeptide. Accordingly, the terms “antagonist” and “inhibitors” are defined in the context of the biological role of the target protein or polypeptide. While some antagonists herein specifically interact with (*e.g.*, bind to) the target, compounds that inhibit a biological activity of the target protein or polypeptide by interacting with other members of the signal transduction pathway of which the target protein or polypeptide is a member are also specifically included within this definition. Non-limiting examples of biological activity inhibited by an antagonist include those associated with the development, growth, or spread of a tumor, or an undesired immune response as manifested in autoimmune disease.

[0057] An “anti-cancer agent”, “anti-tumor agent” or “chemotherapeutic agent” refers to any agent useful in the treatment of a neoplastic condition. One class of anti-cancer agents comprises chemotherapeutic agents. “Chemotherapy” means the administration of one or more chemotherapeutic drugs and/or other agents to a cancer patient by various methods, including intravenous, oral, intramuscular, intraperitoneal, intravesical, subcutaneous, transdermal, buccal, or inhalation or in the form of a suppository.

[0058] The term “cell proliferation” refers to a phenomenon by which the cell number has changed as a result of division. This term also encompasses cell growth by which the cell morphology has changed (*e.g.*, increased in size) consistent with a proliferative signal.

[0059] The term “co-administration,” “administered in combination with,” and their grammatical equivalents, as used herein, encompasses administration of two or more agents to subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which both agents are present.

[0060] The term “effective amount” or “therapeutically effective amount” refers to that amount of a compound or pharmaceutical composition described herein that is sufficient to effect the intended application including, but not limited to, disease treatment, as illustrated below. The therapeutically effective amount can vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated, *e.g.*, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, *e.g.*, reduction of platelet adhesion and/or cell migration. The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0061] As used herein, the terms “treatment”, “treating”, “palliating” and “ameliorating” are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including, but not limited to, therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disorder. For prophylactic benefit, the pharmaceutical compositions can be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0062] A “therapeutic effect,” as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0063] In certain embodiments, the pharmaceutically acceptable form thereof is a pharmaceutically acceptable salt. As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate,

pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N+(C_{1-4}alkyl)^4-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0064] In certain embodiments, the pharmaceutically acceptable form thereof is a prodrug. As used herein, the term “prodrug” refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis (*e.g.*, hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.*, Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., “Pro-drugs as Novel Delivery Systems,” *A.C.S. Symposium Series*, Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it enhances absorption from the digestive tract, or it can enhance drug stability for long-term storage.

[0065] The term “prodrug” is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a subject. Prodrugs of an active compound, as described herein, can be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like.

[0066] For example, if a disclosed compound or a pharmaceutically acceptable form of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as $(C_1-C_8)alkyl$, $(C_2-C_{12})alkanoyloxymethyl$, 1-(alkanoyloxy)ethyl having from

4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl.

[0067] Similarly, if a disclosed compound or a pharmaceutically acceptable form of the compound contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0068] If a disclosed compound or a pharmaceutically acceptable form of the compound incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇)cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, —C(OH)C(O)OY¹ wherein Y¹ is H, (C₁-C₆)alkyl or benzyl, -C(OY²)Y³ wherein Y² is (C₁-C₄) alkyl and Y³ is (C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-N— or di-N,N—(C₁-C₆)alkylaminoalkyl, —C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N— or di-N,N—(C₁-C₆)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

[0069] In certain embodiments, the pharmaceutically acceptable form thereof is a tautomer. As used herein, the term “tautomer” includes two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or vice versa). “Tautomerization” includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. “Prototropic tautomerization” or “proton-shift tautomerization” involves the migration of a proton accompanied by changes in bond order. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible (*e.g.*, in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent. Exemplary tautomerizations include, but are not limited to, keto-to-enol; amide-to-imide; lactam-to-lactim; enamine-to-imine; and enamine-to-(a different) enamine tautomerizations. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[0070] In certain embodiments, the pharmaceutically acceptable form thereof is an isomer. “Isomers” are different compounds that have the same molecular formula. “Stereoisomers” are isomers that differ only in the way the atoms are arranged in space. As used herein, the term “isomer” includes any and all geometric isomers and stereoisomers. For example, “isomers” include cis- and trans-isomers, E- and Z- isomers, R- and S-enantiomers, diastereomers, (d)-isomers, (l)-isomers, racemic mixtures thereof, and other mixtures thereof, as falling within the

scope of this disclosure. “Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A mixture of a pair of enantiomers in any proportion can be known as a “racemic” mixture. The term “(±)” is used to designate a racemic mixture where appropriate. “Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer, the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0071] The “enantiomeric excess” or “% enantiomeric excess” of a composition can be calculated using the equation shown below. In the example shown below, a composition contains 90% of one enantiomer, *e.g.*, the S enantiomer, and 10% of the other enantiomer, *e.g.*, the R enantiomer.

$$ee = (90-10)/100 = 80\%.$$

Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. Some of the compositions described herein contain an enantiomeric excess of at least about 50%, 75%, 90%, 95%, or 99% of Compound 1 (the S-enantiomer). In other words, the compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer.

[0072] For instance, an isomer/enantiomer can, in some embodiments, be provided substantially free of the corresponding enantiomer, and can also be referred to as “optically enriched.” “Optically-enriched,” as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound provided herein is made up of at least about 90% by weight of one enantiomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of one enantiomer. Enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC), the formation and crystallization of chiral salts, or prepared by asymmetric syntheses. *See*, for example, *Enantiomers, Racemates and Resolutions* (Jacques, Ed., Wiley Interscience, New York, 1981); Wilen et al., *Tetrahedron* 33:2725 (1977); *Stereochemistry of Carbon Compounds* (E.L. Eliel, Ed., McGraw-Hill, NY, 1962); and *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0073] “Pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic

compositions as disclosed herein is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

[0074] “Signal transduction” is a process during which stimulatory or inhibitory signals are transmitted into and within a cell to elicit an intracellular response. A modulator of a signal transduction pathway refers to a compound which modulates the activity of one or more cellular proteins mapped to the same specific signal transduction pathway. A modulator can augment (agonist) or suppress (antagonist) the activity of a signaling molecule.

[0075] The term “selective inhibition” or “selectively inhibit” as applied to a biologically active agent refers to the agent’s ability to selectively reduce the target signaling activity as compared to off-target signaling activity, via direct or indirect interaction with the target. For example, a compound that selectively inhibits one isoform of PI3K over another isoform of PI3K has an activity of at least 2X against a first isoform relative to the compound’s activity against the second isoform (*e.g.*, at least 3X, 5X, 10X, 20X, 50X, or 100X).

[0076] The term “B-ALL” as used herein refers to B-cell Acute Lymphoblastic Leukemia.

[0077] “Subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)) and/or other primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, and/or turkeys.

[0078] “Radiation therapy” means exposing a patient, using routine methods and compositions known to the practitioner, to radiation emitters such as, but not limited to, alpha-particle emitting radionuclides (*e.g.*, actinium and thorium radionuclides), low linear energy transfer (LET) radiation emitters (*i.e.*, beta emitters), conversion electron emitters (*e.g.*, strontium-89 and samarium-153-EDTMP, or high-energy radiation, including without limitation x-rays, gamma rays, and neutrons).

[0079] The term “*in vivo*” refers to an event that takes place in a subject’s body.

[0080] The term “*in vitro*” refers to an event that takes place outside of a subject’s body. For example, an *in vitro* assay encompasses any assay conducted outside of a subject. *In vitro* assays encompass cell-based assays in which cells, alive or dead, are employed. *In vitro* assays also encompass a cell-free assay in which no intact cells are employed.

[0081] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ¹³C- or ¹⁴C-enriched carbon are within the scope of this disclosure.

[0082] The disclosure also embraces isotopically labeled compounds which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, respectively. Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ³H and ¹⁴C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ³H) and carbon-14 (*i.e.*, ¹⁴C) isotopes can allow for ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ²H) can afford certain therapeutic advantages resulting from greater metabolic stability

(*e.g.*, increased in vivo half-life or reduced dosage requirements). Isotopically labeled disclosed compounds can generally be prepared by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. In some embodiments, provided herein are compounds that can also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. All isotopic variations of the compounds as disclosed herein, whether radioactive or not, are encompassed within the scope of the present disclosure.

[0083] The following abbreviations and terms have the indicated meanings throughout:

PI3K = Phosphoinositide 3-kinase; PI = phosphatidylinositol; PDK = Phosphoinositide Dependent Kinase; DNA-PK = Deoxyribose Nucleic Acid Dependent Protein Kinase; PTEN = Phosphatase and Tensin homolog deleted on chromosome Ten; PIKK = Phosphoinositide Kinase Like Kinase; AIDS = Acquired Immuno Deficiency Syndrome; HIV = Human Immunodeficiency Virus; MeI = Methyl Iodide; POCl₃ = Phosphorous Oxychloride; KCNS = Potassium Isothiocyanate; TLC = Thin Layer Chromatography; MeOH = Methanol; and CHCl₃ = Chloroform.

[0084] “Alkyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C₁-C₁₀ alkyl). Whenever it appears herein, a numerical range such as “1 to 10” refers to each integer in the given range; *e.g.*, “1 to 10 carbon atoms” means that the alkyl group can consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, it is a C₁-C₆ alkyl group. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, iso-butyl, sec-butyl isobutyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl, decyl, and the like. The alkyl is attached to the rest of the molecule by a single bond, for example, methyl (Me), ethyl (Et), *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, and the like. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where *t* is 1 or 2), -S(O)_tOR^a (where *t* is 1 or 2), -S(O)_tN(R^a)₂ (where *t* is 1 or 2), or PO₃(R^a)₂ where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0085] “Alkylaryl” refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively. The “alkylaryl” is bonded to the parent molecular structure through the alkyl group.

[0086] “Alkylheteroaryl” refers to an -(alkyl)heteroaryl radical where heteroaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively. The “alkylheteroaryl” is bonded to the parent molecular structure through the alkyl group.

[0087] “Alkylheterocycloalkyl” refers to an -(alkyl) heterocycl radical where alkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively. The “alkylheterocycloalkyl” is bonded to the parent molecular structure through the alkyl group.

[0088] “Alkenyl” refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (*i.e.*, C₂-C₁₀ alkenyl). Whenever it appears herein, a numerical range such as “2 to 10” refers to each integer in the given range; *e.g.*, “2 to 10 carbon atoms” means that the alkenyl group can consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to five carbon atoms (*e.g.*, C₂-C₅ alkenyl). The alkenyl is attached to the parent molecular structure by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)^C(O)OR^a, -N(R^a)^C(O)R^a, -N(R^a)^C(O)N(R^a)₂, N(R^a)^C(NR^a)N(R^a)₂, -N(R^a)^S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocycl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0089] “Alkenyl-cycloalkyl” refers to an -(alkenyl)cycloalkyl radical where alkenyl and cyclo alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively. The “alkenyl-cycloalkyl” is bonded to the parent molecular structure through the alkenyl group.

[0090] “Alkynyl” refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (*i.e.*, C₂-C₁₀ alkynyl). Whenever it appears herein, a numerical range such as “2 to 10” refers to each integer in the given range; *e.g.*, “2 to 10 carbon atoms” means that the alkynyl group can consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to five carbon atoms (*e.g.*, C₂-C₅ alkynyl). The alkynyl is attached to the parent molecular structure by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocycl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0091] “Alkynyl-cycloalkyl” refers to refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively. The “alkynyl-cycloalkyl” is bonded to the parent molecular structure through the alkenyl group.

[0092] “Carboxaldehyde” refers to a -(C=O)H radical.

[0093] “Carboxyl” refers to a -(C=O)OH radical.

[0094] “Cyano” refers to a -CN radical.

[0095] “Cycloalkyl” refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (*i.e.*, C₃-C₁₀ cycloalkyl). Whenever it appears herein, a numerical range such as “3 to 10” refers to each integer in the given range; *e.g.*, “3 to 10 carbon atoms” means that the cycloalkyl group can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, etc., up to and including 10 carbon atoms. In some embodiments, it is a C₃-C₈ cycloalkyl radical. In some embodiments, it is a C₃-C₅ cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. The term “cycloalkyl” also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)C(O)N(R^a)₂, N(R^a)C(NR^a)N(R^a)₂, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[0096] “Cycloalkyl-alkenyl” refers to a -(cycloalkyl)alkenyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively. The “cycloalkyl-alkenyl” is bonded to the parent molecular structure through the cycloalkyl group.

[0097] “Cycloalkyl-heterocycloalkyl” refers to a -(cycloalkyl) heterocycyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively. The “cycloalkyl-heterocycloalkyl” is bonded to the parent molecular structure through the cycloalkyl group.

[0098] “Cycloalkyl-heteroaryl” refers to a -(cycloalkyl) heteroaryl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and cycloalkyl respectively. The “cycloalkyl-heteroaryl” is bonded to the parent molecular structure through the cycloalkyl group.

[0099] The term “alkoxy” refers to the group -O-alkyl, including from 1 to 10 carbon atoms of a straight, branched, cyclic configuration and combinations thereof, attached to the parent molecular structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. “Lower alkoxy” refers to alkoxy groups containing one to six carbons. In some embodiments, C₁-C₄ alkyl is an alkyl group which encompasses both straight and branched chain alkyls of from 1 to 4 carbon atoms.

[00100] The term “substituted alkoxy” refers to alkoxy wherein the alkyl constituent is substituted (*i.e.*, -O-(substituted alkyl)). Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy group is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -OC(O)N(R^a)₂,

$-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00101] The term “alkoxycarbonyl” refers to a group of the formula (alkoxy)(C=O)- attached to the parent molecular structure through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a C_1 - C_6 alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. “Lower alkoxycarbonyl” refers to an alkoxycarbonyl group wherein the alkyl portion of the alkoxy group is a lower alkyl group. In some embodiments, C_1 - C_4 alkoxy, is an alkoxy group which encompasses both straight and branched chain alkoxy groups of from 1 to 4 carbon atoms.

[00102] The term “substituted alkoxycarbonyl” refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent molecular structure through the carbonyl functionality. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxycarbonyl group is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, SR^a , $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00103] “Acyl” refers to $R-C(O)-$ groups such as (alkyl)- $C(O)-$, (aryl)- $C(O)-$, (heteroaryl)- $C(O)-$, (heteroalkyl)- $C(O)-$, and (heterocycloalkyl)- $C(O)-$, wherein the group is attached to the parent molecular structure through the carbonyl functionality. In some embodiments, it is a C_1 - C_{10} acyl radical which refers to the total number of chain or ring atoms of the alkyl, aryl, heteroaryl or heterocycloalkyl portion of the alkyl group plus the carbonyl carbon of acyl, *i.e.*, a C_4 -acyl has three other ring or chain atoms plus carbonyl. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the “ R ” of an acyloxy group is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, SR^a , $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00104] “Acyloxy” refers to a $R(C=O)O-$ radical wherein “ R ” is alkyl, aryl, heteroaryl, heteroalkyl, or heterocycloalkyl, which are as described herein. In some embodiments, it is a C_1 - C_4 acyloxy radical which refers to the total number of chain or ring atoms of the alkyl, aryl, heteroaryl or heterocycloalkyl portion of the acyloxy group plus the carbonyl carbon of acyl, *i.e.*, a C_4 -acyloxy has three other ring or chain atoms plus carbonyl. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the “ R ” of an acyloxy group is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl,

arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00105] “Amino” or “amine” refers to a $-N(R^a)_2$ radical group, where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a $-N(R^a)_2$ group has two R^a other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, $-N(R^a)_2$ is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl and each of these moieties can be optionally substituted as defined herein.

[00106] The term “substituted amino” also refers to N-oxides of the groups $-N^+(H)(R^a)O^-$, and $-N^+(R^a)(R^a)O^-$, R^a as described above, where the N-oxide is bonded to the parent molecular structure through the N atom. N-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid. The person skilled in the art is familiar with reaction conditions for carrying out the N-oxidation.

[00107] “Amide” or “amido” refers to a chemical moiety with formula $-C(O)N(R)_2$ or $-NRC(O)R$, where R is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety can itself be optionally substituted. In some embodiments it is a C_1 - C_4 amido or amide radical, which includes the amide carbonyl in the total number of carbons in the radical. The R_2 of $-N(R)_2$ of the amide can optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6-, or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide can be an amino acid or a peptide molecule attached to a compound of Formula (I), thereby forming a prodrug. Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be transformed into an amide group. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

[00108] “Aromatic” or “aryl” refers to a radical with six to ten ring atoms (*e.g.*, C_6 - C_{10} aromatic or C_6 - C_{10} aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals

whose names end in “-yl” by removal of one hydrogen atom from the carbon atom with the free valence are named by adding “-idene” to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as “6 to 10” refers to each integer in the given range; *e.g.*, “6 to 10 ring atoms” means that the aryl group can consist of 6 ring atoms, 7 ring atoms, etc., up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety can be optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where *t* is 1 or 2), $-S(O)_tOR^a$ (where *t* is 1 or 2), $-S(O)_tN(R^a)_2$ (where *t* is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00109] “Aralkyl” or “arylalkyl” refers to an (aryl)alkyl— radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively. The “aralkyl/arylalkyl” is bonded to the parent molecular structure through the alkyl group.

[00110] As used herein, a “covalent bond” or “direct bond” refers to a single bond joining two groups.

[00111] “Ester” refers to a chemical radical of formula $-COOR$, where *R* is selected from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). Any amine, hydroxy, or carboxyl side chain on the compounds described herein can be esterified. The procedures and specific groups to make such esters are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety. Unless stated otherwise specifically in the specification, an ester group can be optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where *t* is 1 or 2), $-S(O)_tOR^a$ (where *t* is 1 or 2), $-S(O)_tN(R^a)_2$ (where *t* is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00112] “Fluoroalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical can be optionally substituted as defined above for an alkyl group.

[00113] “Halo”, “halide”, or, alternatively, “halogen” means fluoro, chloro, bromo or iodo. The terms “haloalkyl,” “haloalkenyl,” “haloalkynyl” and “haloalkoxy” include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms “fluoroalkyl” and “fluoroalkoxy” include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

[00114] “Heteroalkyl” “heteroalkenyl” and “heteroalkynyl” include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range can be given, *e.g.*, C₁-C₄ heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. For example, a -CH₂OCH₂CH₃ radical is referred to as a “C₄” heteroalkyl, which includes the heteroatom center in the atom chain length description. Connection to the rest of the parent molecular structure can be through either a heteroatom or a carbon in the heteroalkyl chain. A heteroalkyl group can be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00115] “Heteroalkylaryl” refers to an -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl respectively. The “heteroalkylaryl” is bonded to the parent molecular structure through a carbon atom of the heteroalkyl group.

[00116] “Heteroalkylheteroaryl” refers to an -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl respectively. The “heteroalkylheteroaryl” is bonded to the parent molecular structure through a carbon atom of the heteroalkyl group.

[00117] “Heteroalkylheterocycloalkyl” refers to an -(heteroalkyl)heterocycloalkyl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl respectively. The “heteroalkylheterocycloalkyl” is bonded to the parent molecular structure through a carbon atom of the heteroalkyl group.

[00118] “Heteroalkylcycloalkyl” refers to an -(heteroalkyl) cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl respectively. The “heteroalkylcycloalkyl” is bonded to the parent molecular structure through a carbon atom of the heteroalkyl group.

[00119] “Heteroaryl” or, alternatively, “heteroaromatic” refers to a 5- to 18-membered aromatic radical (*e.g.*, C₅-C₁₃ heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as “5 to 18” refers to each integer in the given range; *e.g.*, “5 to 18 ring atoms” means that the heteroaryl group can consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in “-yl” by removal of one hydrogen atom from the atom with the free valence are named by adding “-idene” to the name of the corresponding univalent radical, *e.g.*, a pyridyl group with two points of attachment is a pyridylidene. An N-containing “heteroaromatic” or “heteroaryl” moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group can be fused or non-fused. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the parent molecular structure through any atom of the ring(s).

Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolynyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolynyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolynyl, isoindolynyl, isoquinolyl, indolizynyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolynyl, isoquinolynyl, tetrahydroquinolynyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (*i.e.*, thienyl). Unless stated otherwise specifically in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -N(R^a)₂, -C(O)R^a, -C(O)OR^a, -C(O)N(R^a)₂, -N(R^a)C(O)OR^a, -N(R^a)C(O)R^a, -N(R^a)S(O)_tR^a (where t is 1 or 2), -S(O)_tOR^a (where t is 1 or 2), -S(O)_tN(R^a)₂ (where t is 1 or 2), or PO₃(R^a)₂, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00120] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as pyridinyl N-oxides.

[00121] “Heterocyclyl” refers to any 3- to 18-membered aromatic radical monocyclic or polycyclic moiety comprising at least one heteroatom selected from nitrogen, oxygen and sulfur. As used herein, heterocyclyl moieties can be aromatic or nonaromatic. A heterocyclyl group can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as “3 to 18” refers to each integer in the given range; *e.g.*, “5 to 18 ring atoms” means that the heterocyclyl group can consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heterocyclyl radicals whose names end in “-yl” by removal of one hydrogen atom from the atom with the free valence are named by adding “-idene” to the name of the corresponding univalent radical, *e.g.*, a piperidine group with two points of attachment is a piperidylidene. An N-containing heterocyclyl moiety refers to an non-aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heterocyclyl group can be fused or non-fused. The heteroatom(s) in the heterocyclyl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the parent molecular structure through any atom of the ring(s). Unless stated otherwise, heterocyclyl moieties are

optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thio, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocycl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl.

[00122] “Heteroarylalkyl” refers to an $-(\text{heteroaryl})$ alkyl radical where heteroaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroaryl and alkyl respectively. The “heteroarylalkyl” is bonded to the parent molecular structure through any atom atom of the heteroaryl group.

[00123] “Heterocycloalkyl” refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Whenever it appears herein, a numerical range such as “3 to 18” refers to each integer in the given range; *e.g.*, “3 to 18 ring atoms” means that the heterocycloalkyl group can consist of 3 ring atoms, 4 ring atoms, etc., up to and including 18 ring atoms. In some embodiments, it is a C_5-C_{10} heterocycloalkyl. In some embodiments, it is a C_4-C_{10} heterocycloalkyl. In some embodiments, it is a C_3-C_{10} heterocycloalkyl. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical can be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl can be attached to the parent molecular group through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyran, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently include: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thio, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocycl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroarylalkyl.

[00124] “Heterocycloalkyl” also includes bicyclic ring systems wherein one non-aromatic ring, such as a ring having 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually having 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not aromatic.

[00125] “Moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00126] “Nitro” refers to the $-NO_2$ radical.

[00127] “Oxa” refers to the -O- radical.

[00128] “Oxo” refers to the =O radical.

[00129] A “leaving group or atom” is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable non-limiting examples of such groups unless otherwise specified include halogen atoms, mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

[00130] “Protecting group” has the meaning conventionally associated with it in organic synthesis, *i.e.*, a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and such that the group can readily be removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T.H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, New York (1999). For example, a hydroxy protected form is where at least one of the hydroxy groups present in a compound is protected with a hydroxy protecting group. Likewise, amines and other reactive groups can similarly be protected.

[00131] “Substituted” means that the referenced group can be substituted with one or more additional group(s) individually and independently selected from acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Di-substituted amino groups encompass those which form a ring together with the nitrogen of the amino group, such as for instance, morpholino. The substituents themselves can be substituted, for example, a cycloalkyl substituent can have a halide substituted at one or more ring carbons, and the like. The protecting groups that can form the protective derivatives of the above substituents are known to those of skill in the art and can be found in references such as Greene and Wuts, above.

[00132] “Sulfanyl” refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl), and -S-(optionally substituted heterocycloalkyl).

[00133] “Sulfinyl” refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted amino), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl), and -S(O)-(optionally substituted heterocycloalkyl).

[00134] “Sulfonyl” refers to the groups: -S(O₂)-H, -S(O₂)-(optionally substituted alkyl), -S(O₂)-(optionally substituted amino), -S(O₂)-(optionally substituted aryl), -S(O₂)-(optionally substituted heteroaryl), and -S(O₂)-(optionally substituted heterocycloalkyl).

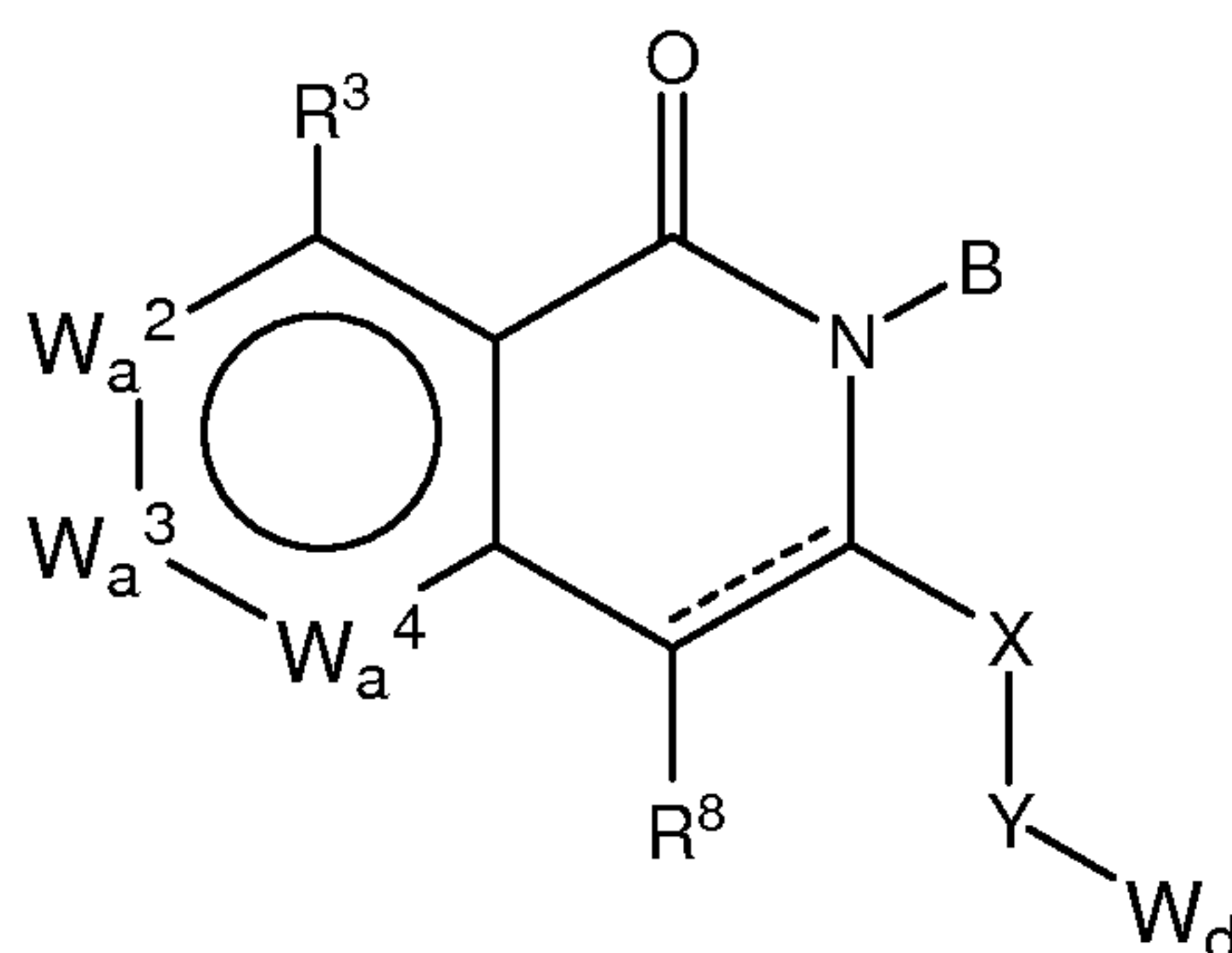
[00135] “Sulfonamidyl” or “sulfonamido” refers to a -S(=O)₂-NRR or -N(R)-S(=O)₂- radical, where each R is selected independently from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heterocycloalkyl (bonded through a ring carbon). The R groups in -NRR of the -S(=O)₂-NRR radical can be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6-, or 7-membered ring. In some embodiments, it is a C₁-C₁₀ sulfonamido, wherein each R in sulfonamido contains 1 carbon, 2 carbons, 3 carbons, or 4 carbons total. A sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, and heteroaryl respectively

[00136] “Sulfoxyl” refers to a -S(=O)₂OH radical.

[00137] “Sulfonate” refers to a $-S(=O)_2-OR$ radical, where R is selected from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, and heteroaryl respectively.

[00138] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, *e.g.*, $-CH_2O-$ is equivalent to $-OCH_2-$.

[00139] In one aspect, provided herein is a compound of Formula I:

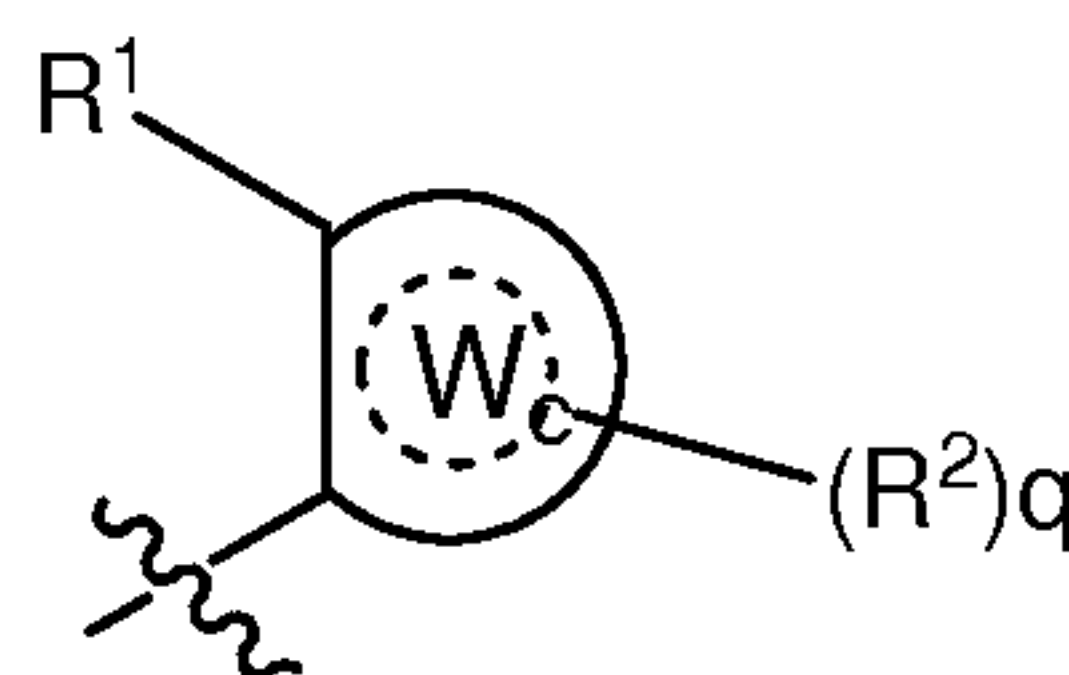


Formula I

or pharmaceutically acceptable forms thereof, wherein,

W_a^2 is CR^5 or N; W_a^3 is CR^6 or N; W_a^4 is CR^7 or N; wherein no more than two adjacent ring atoms selected from W_a^2 , W_a^3 , and W_a^4 are heteroatoms;

B is hydrogen, alkyl, amino, heteroalkyl, or a moiety of formula II:



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

q is an integer of 0, 1, 2, 3, or 4;

X is absent or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3, or 4;

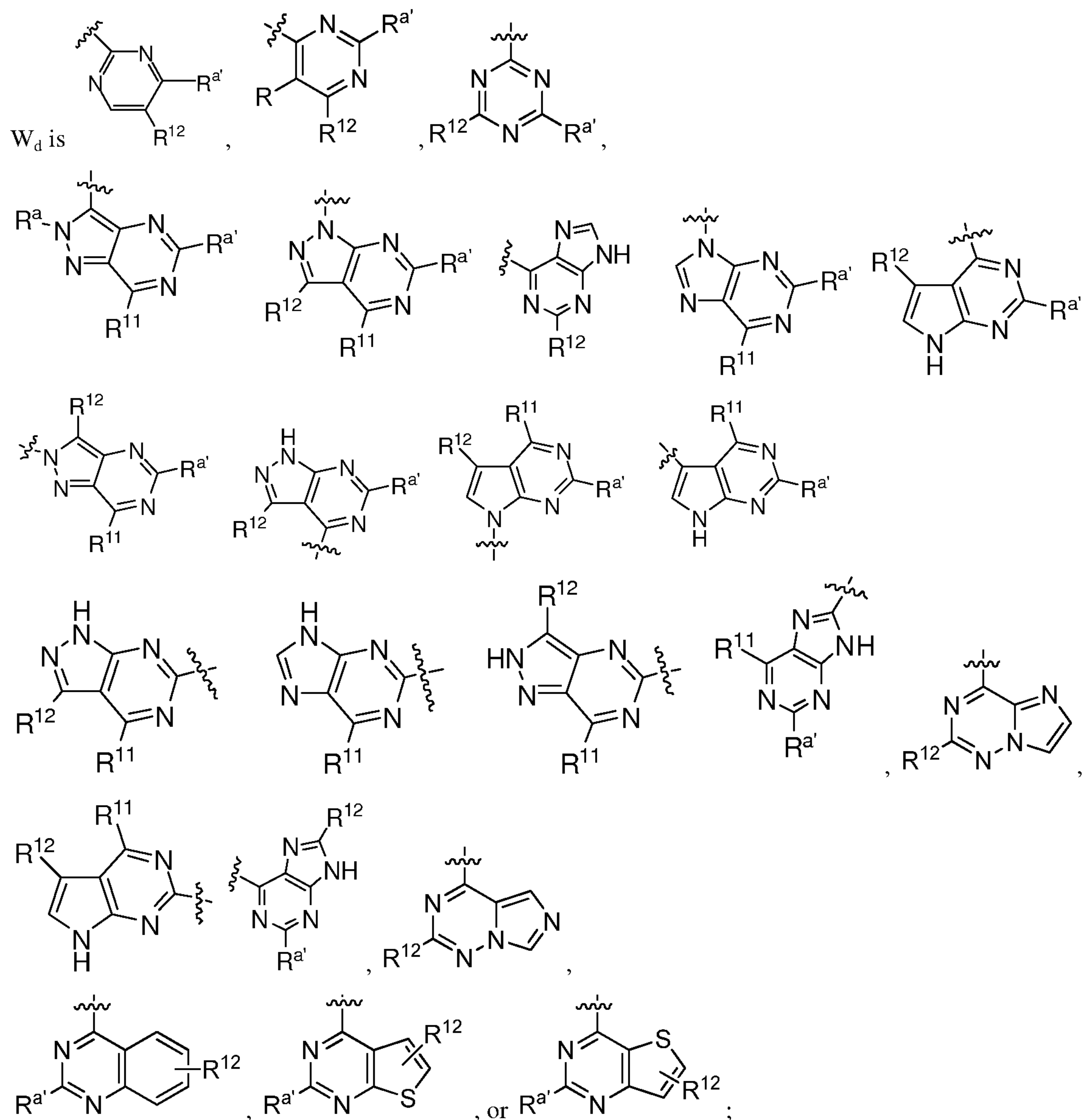
Y is absent, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)(CH(R^9))_z-$, $-N(R^9)-$, $N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$, or $-N(R^9)C(R^9)_2-$, and z is an integer of 1, 2, 3, or 4;

R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

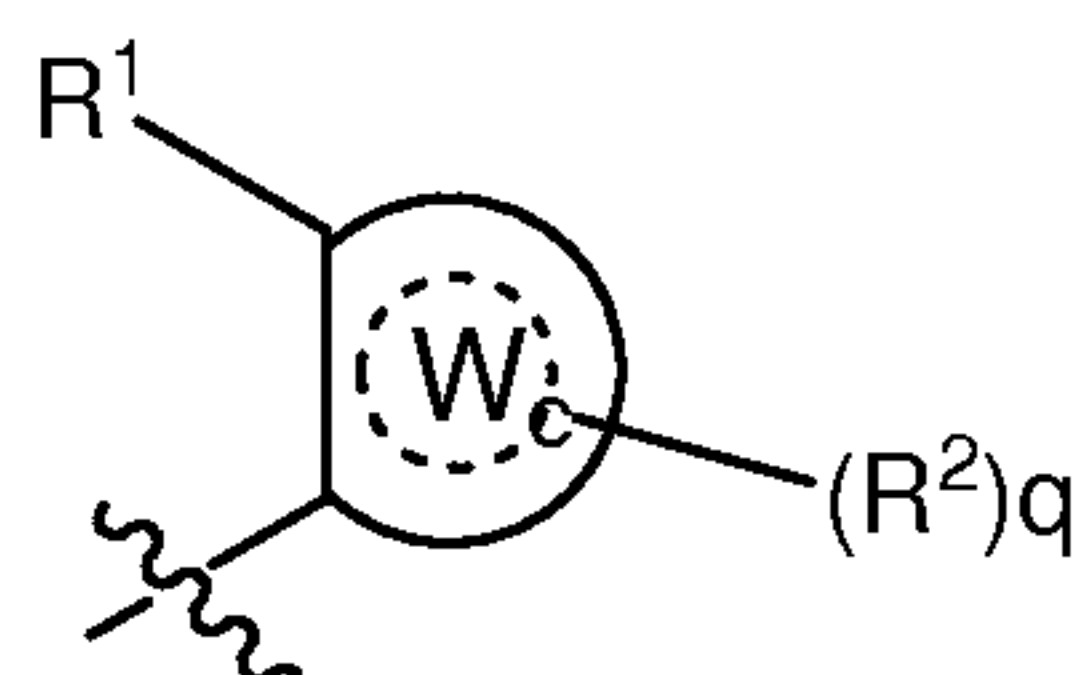
each R^2 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

R^3 is cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclalkyl, alkenyl, or alkynyl, or R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C_1-C_6 alkyl group to an aryl, heteroaryl or heterocyclyl, or R^3 and R^5 are taken together with the carbons to which they are attached form a 5- or 6-membered ring; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{13} ;

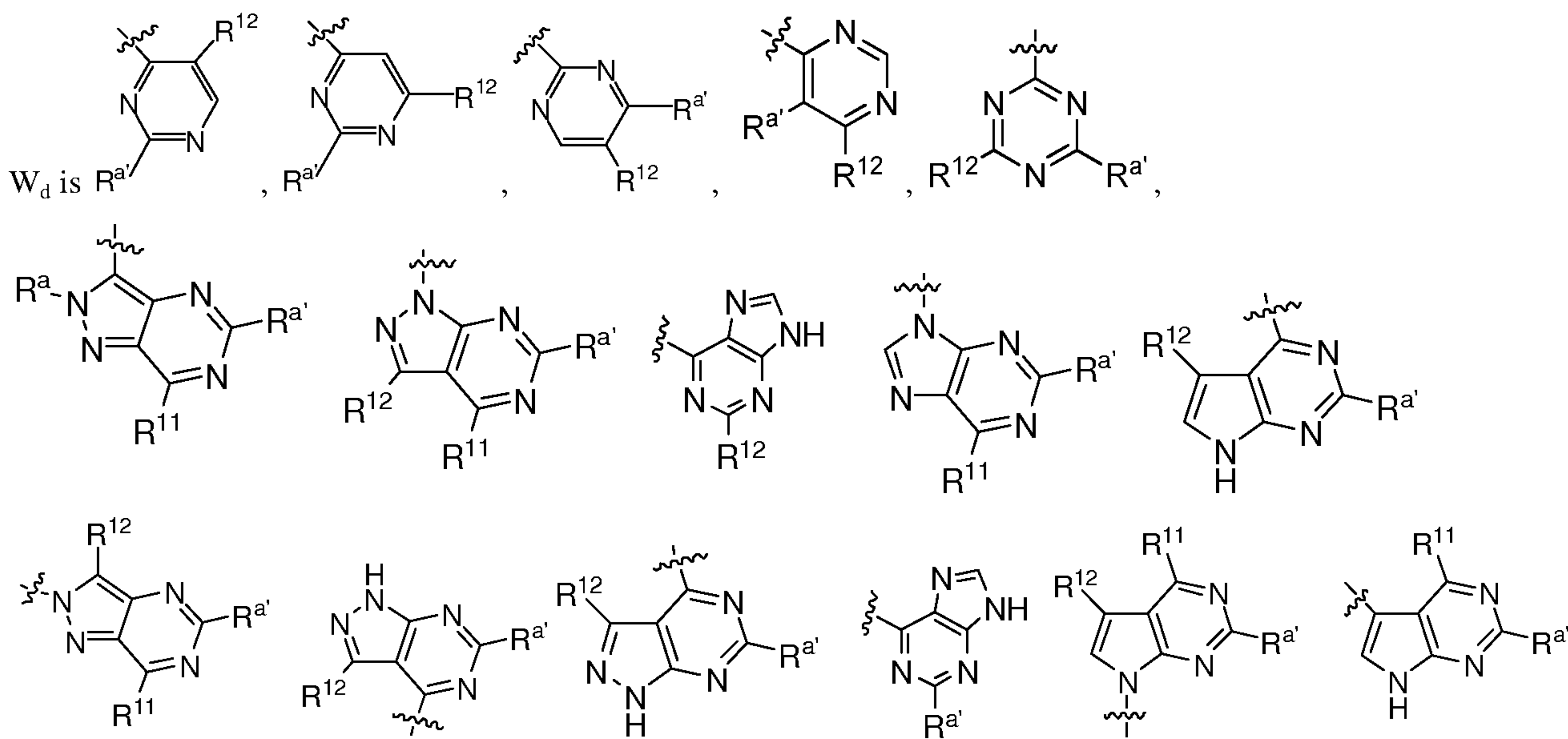
R^5 , R^6 , R^7 , and R^8 are independently hydrogen, halo, cyano, alkyl or amino;
each R^9 is independently hydrogen, alkyl, or heterocycloalkyl;

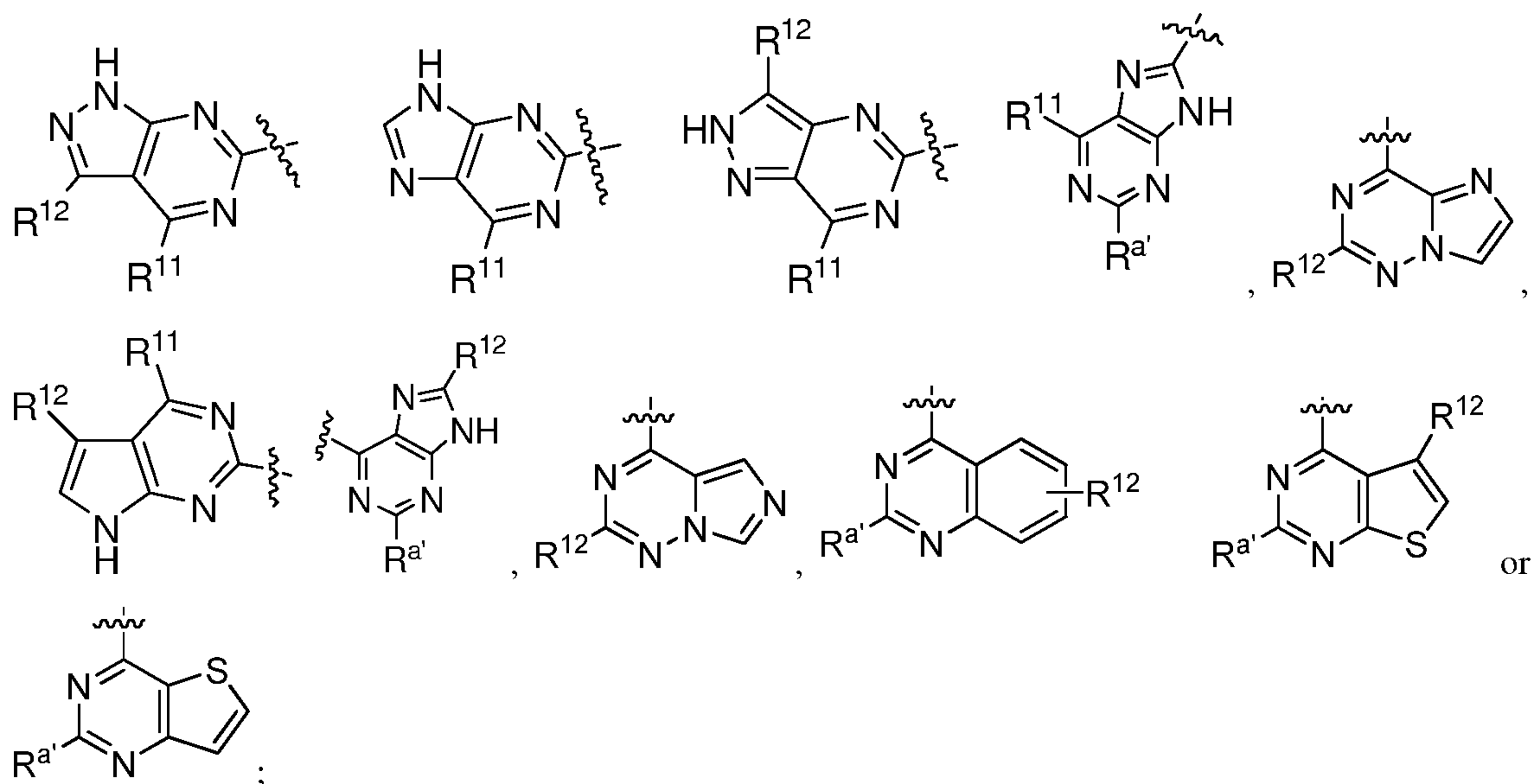


[00140] In some embodiments, W_a^2 is CR^5 or N; W_a^3 is CR^6 or N; W_a^4 is CR^7 or N wherein no more than two adjacent ring atoms selected from W_a^2 , W_a^3 , and W_a^4 are heteroatoms; B is hydrogen, alkyl, amino, heteroalkyl, or a moiety of the following formula:



wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4; X is absent or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3, or 4; and Y is absent, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)(CHR^9)_z-$, $-N(R^9)-$, $N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$, or $-N(R^9)C(R^9)_2$, and z is an integer of 1, 2, 3, or 4. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro; each R^2 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate; and R^3 is cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclalkyl, alkenyl, or alkynyl, or R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C_1-C_6 alkyl group to an aryl, heteroaryl or heterocyclyl, or R^3 and R^5 are taken together with the carbons to which they are attached form a 5- or 6-membered ring; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{13} . In some embodiments, R^5 , R^6 , R^7 , and R^8 are independently hydrogen, halo, cyano, alkyl or amino; and each R^9 is independently hydrogen, alkyl, or heterocycloalkyl;

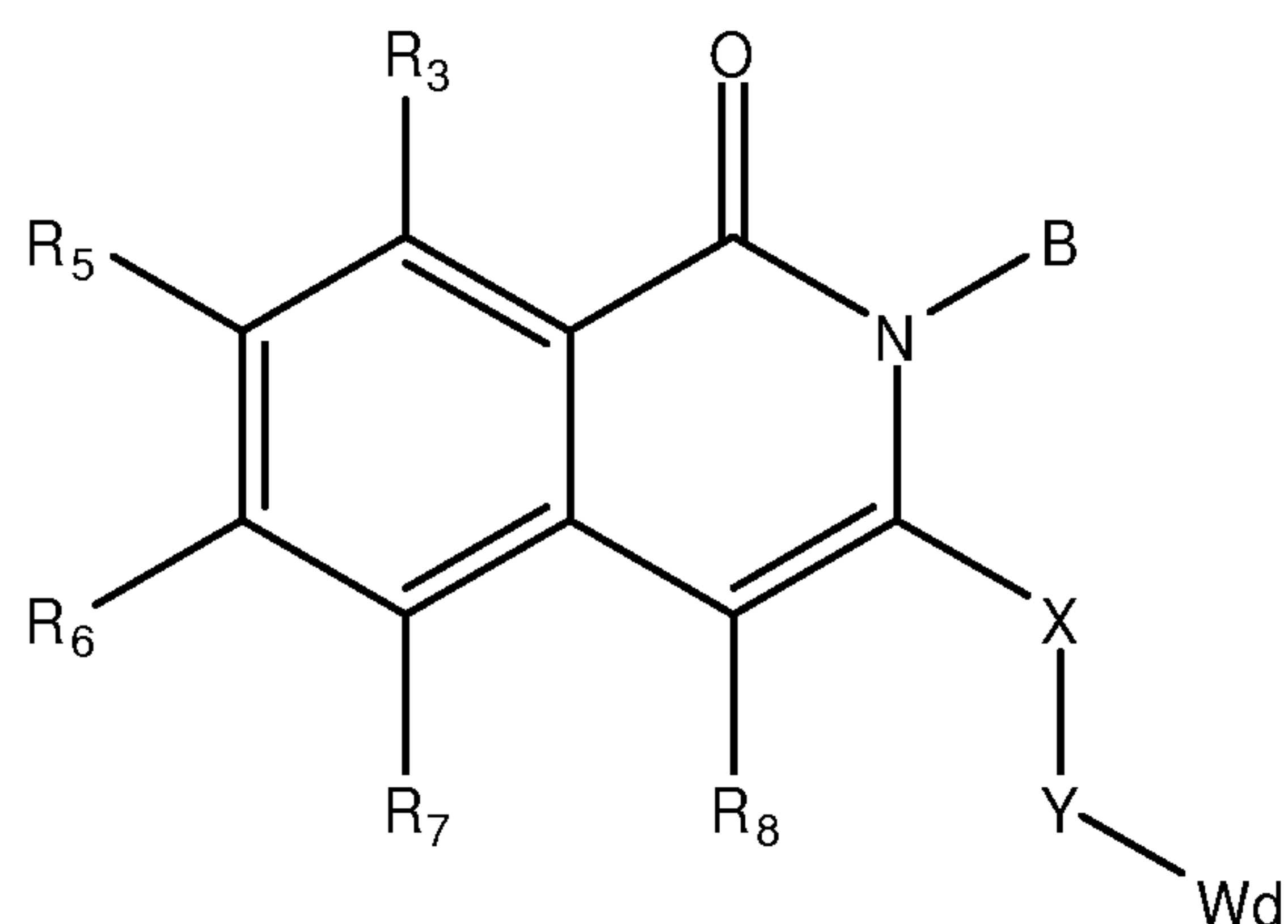




R^{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, alkoxy, phosphate, urea, or carbonate; R^{12} is hydrogen, alkyl, haloalkyl, alkynyl, alkenyl, halo, $-C(O)NH_2$, aryl, heteroaryl, nonaromatic heterocyclyl, or cycloalkyl; $R^{a'}$ is hydrogen, alkyl, $-NH_2$, cyano, or halogen; and each R^{13} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or halogen.

[00141]

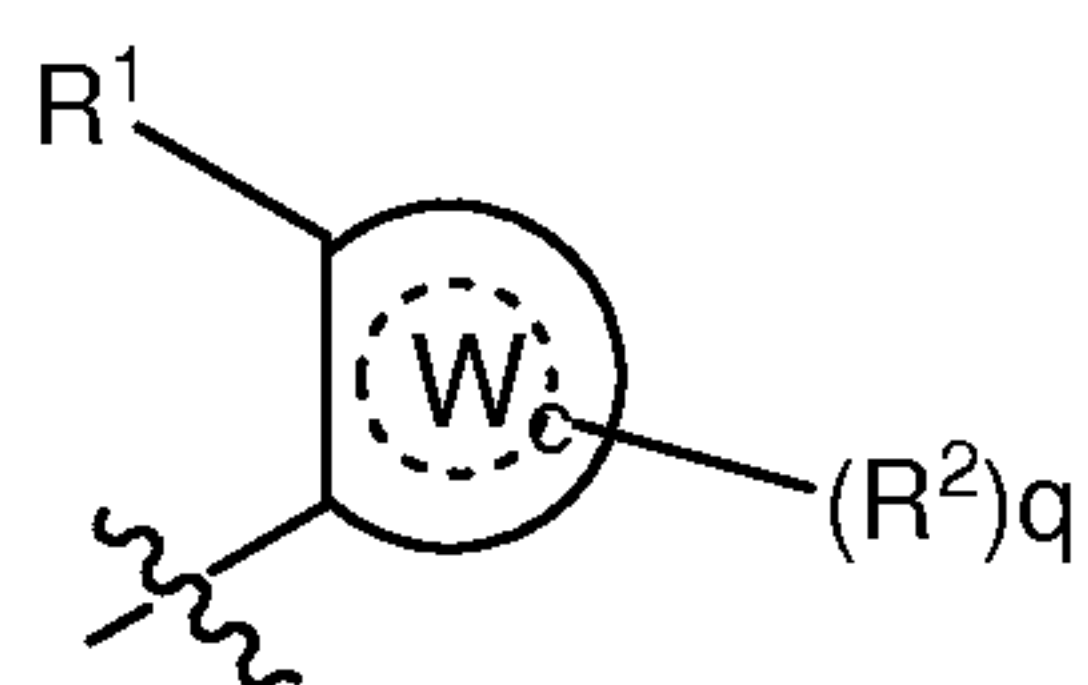
In another aspect, provided herein are compounds of Formula Ib:



Formula Ib

or pharmaceutically acceptable forms thereof, wherein

B is hydrogen, alkyl, amino, heteroalkyl, or a moiety of Formula II:



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

q is an integer of 0, 1, 2, 3, or 4;

X is absent or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3, or 4;

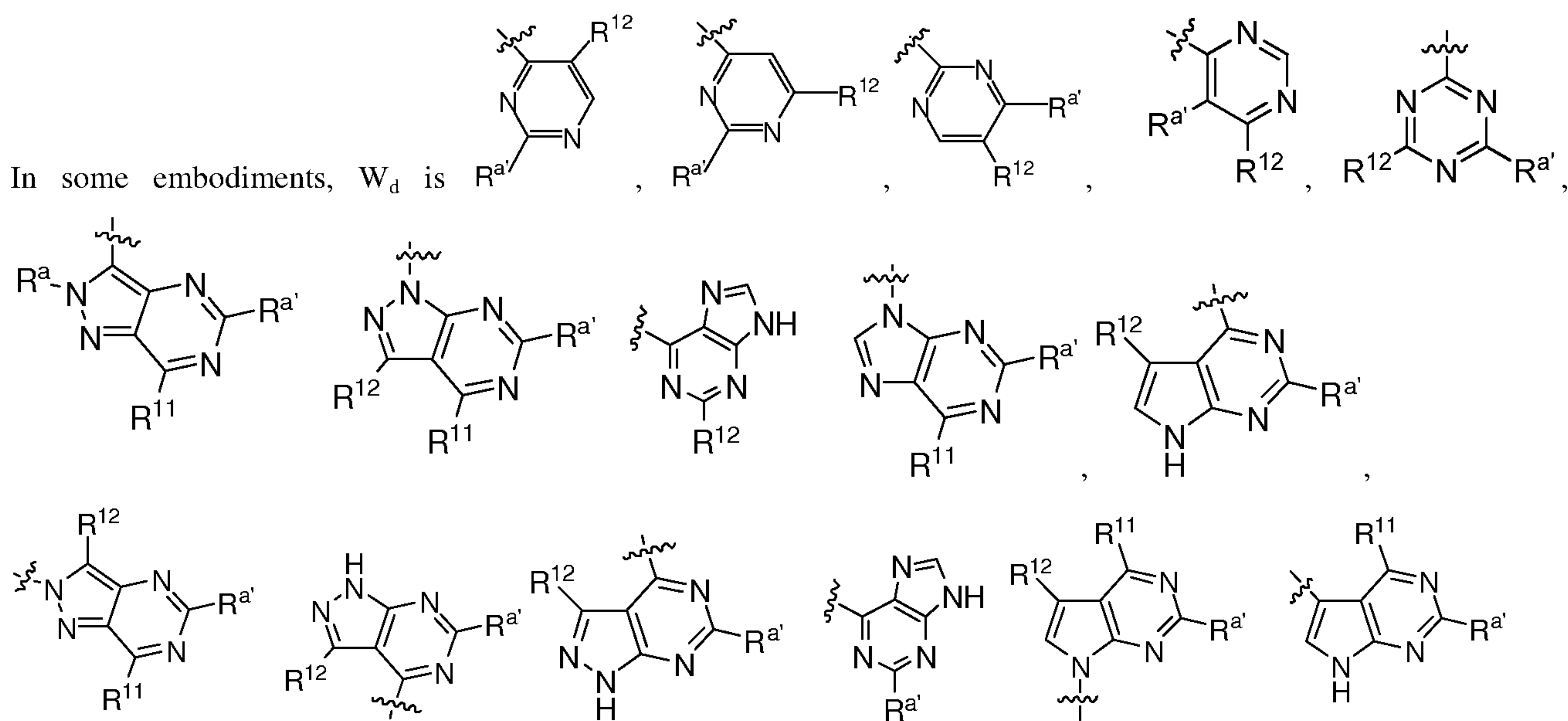
Y is absent, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)(CH(R^9))_z-$, $-N(R^9)-$, $N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$, or $-N(R^9)C(R^9)_2-$, and z is an integer of 1, 2, 3, or 4;

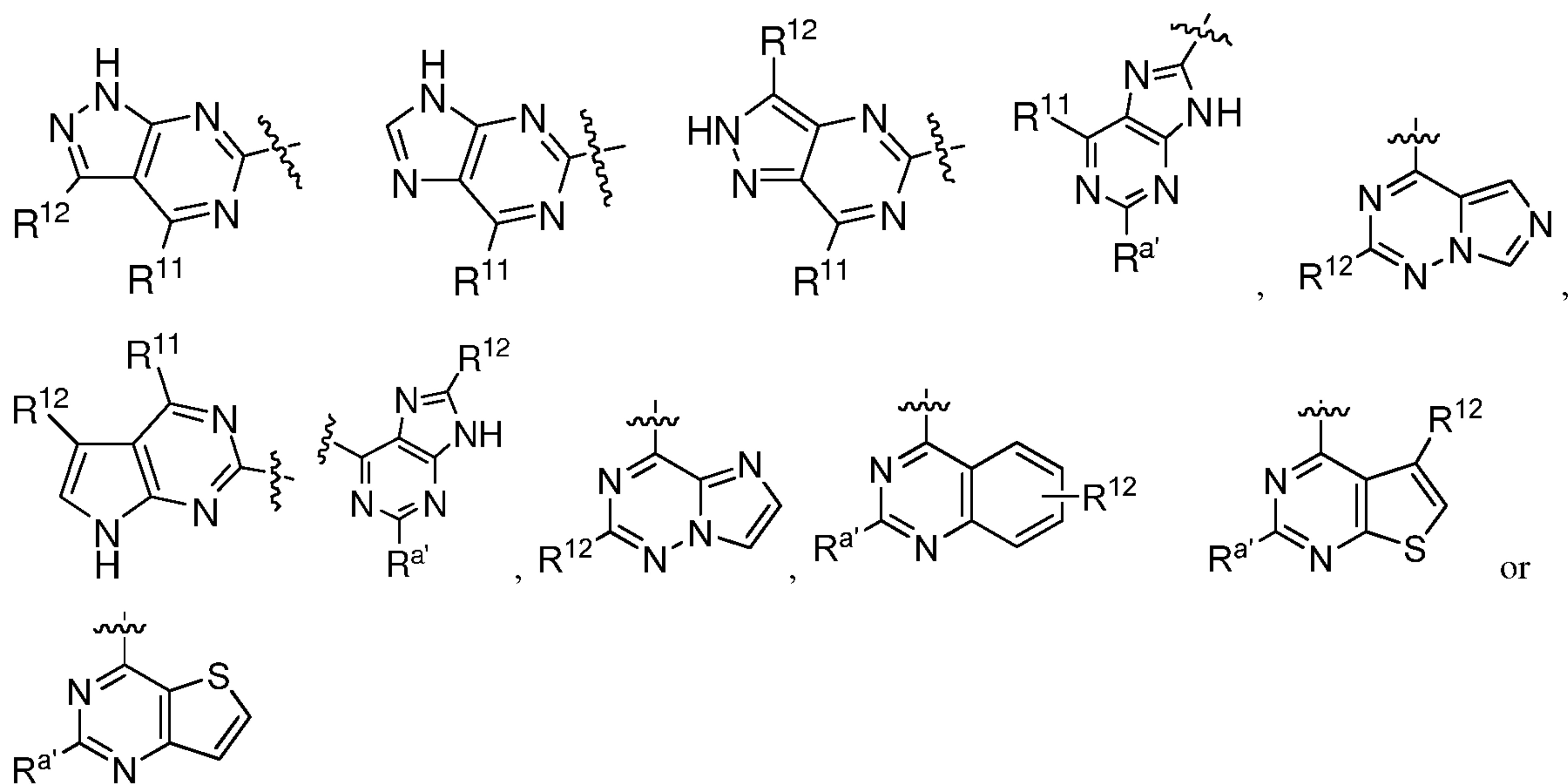
R^{12} is hydrogen, alkyl, haloalkyl, alkynyl, alkenyl, halo, $-C(O)NH_2$, aryl, heteroaryl, nonaromatic heterocyclyl, or cycloalkyl,

$R^{a'}$ is hydrogen, alkyl, $-NH_2$, cyano or halogen; and

each R^{13} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or halogen.

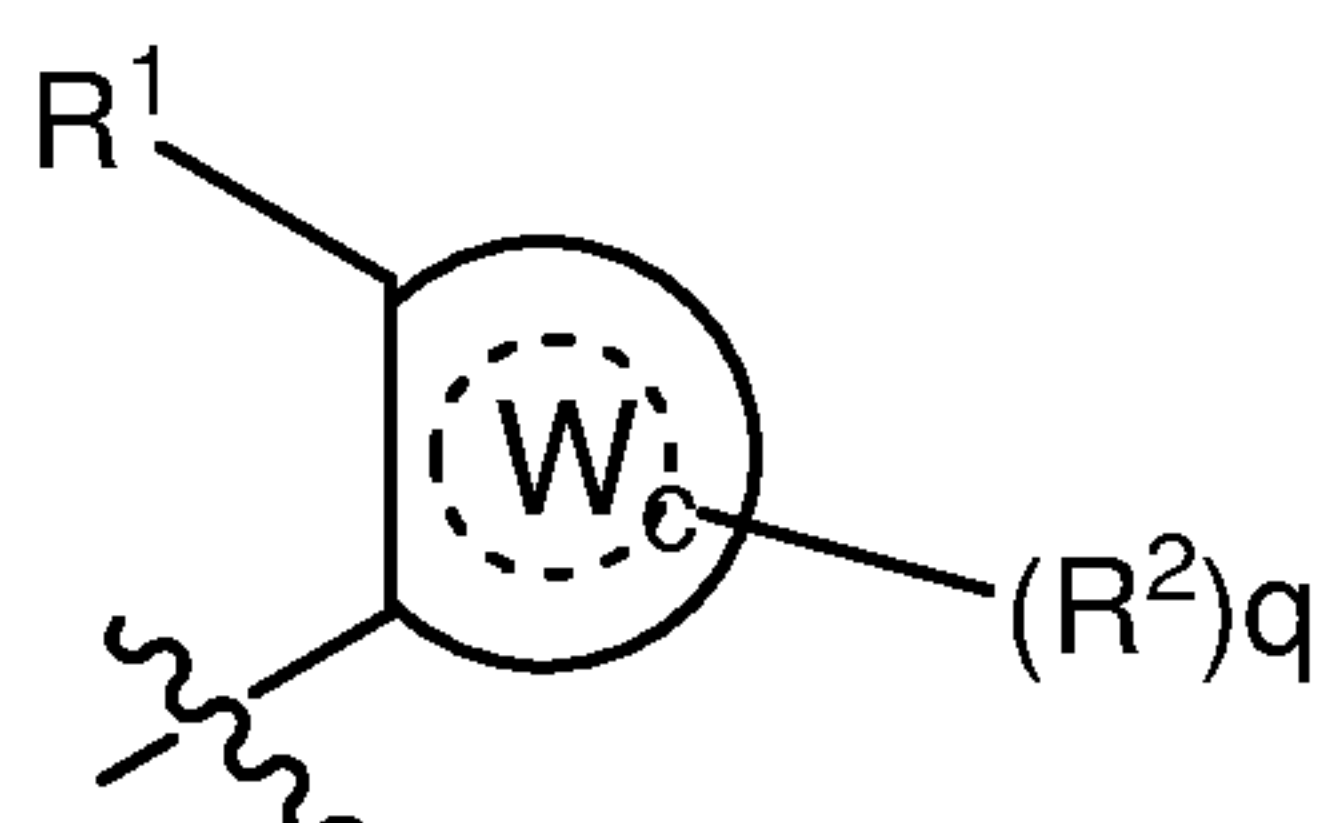
[00142] In some embodiments of Formula II, W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; q is an integer of 0, 1, 2, 3, or 4; X is absent or $-(CH(R^9))_z$, and z is an integer of 1, 2, 3, or 4; Y is absent, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)(CHR^9)_z$, $-N(R^9)-$, $N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$, or $-N(R^9)C(R^9)_2-$, and z is an integer of 1, 2, 3, or 4. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro; each R^2 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate; R^3 is cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, alkenyl, or alkynyl, or R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C_1 - C_6 alkyl group to an aryl, heteroaryl or heterocyclyl or R^3 and R^5 are taken together with the carbons to which they are attached form a 5- or 6-membered ring; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{13} ; R^5 , R^6 , R^7 , and R^8 are independently hydrogen, halo, cyano, alkyl or amino; and each R^9 is independently hydrogen, alkyl, or heterocycloalkyl.





R¹¹ is hydrogen, alkyl, halo, amino, amido, hydroxy, alkoxy, phosphate, urea, or carbonate; R¹² is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, nonaromatic heterocyclyl, or cycloalkyl; R^{a'} is hydrogen, alkyl, -NH₂, cyano or halogen; and each R¹³ is independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy or halogen.

[00143] In certain embodiments, R³ is selected from a 5-membered heteroaryl; a 5-membered nonaromatic heterocycle; a 6-membered aryl; a 6-membered heteroaryl; a 6-membered nonaromatic heterocycle; a fused 5/6-bicyclic heteroaryl; a fused 5/6-bicyclic nonaromatic heterocycle; a C₁-C₆ alkyl group substituted with a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered aryl or heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R³ is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C₁-C₆ alkyl group to a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered aryl or heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R³ is a C₁-C₆ alkyl group substituted with a fused polycyclic group, wherein the polycyclic group has greater than two rings and is carbocyclic or heterocyclic; C₁-C₆ alkyl group substituted with a bridged cycloalkyl or bridged heterocyclic group. In some embodiments, R³ is a C₁-C₆ alkyl group substituted with a spirocyclic cycloalkyl or spirocyclic heterocyclic group. In some embodiments, R³ is a branched C₄-C₁₂ alkyl group, wherein said branched alkyl group contains at least one terminal t-butyl group. In compounds of Formula I-B, W_a² is CR⁵ or N; W_a³ is CR⁶ or N; W_a⁴ is CR⁷ or N wherein no more than two adjacent ring atoms selected from W_a², W_a³, and W_a⁴ are heteroatoms; and B is hydrogen, alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II:



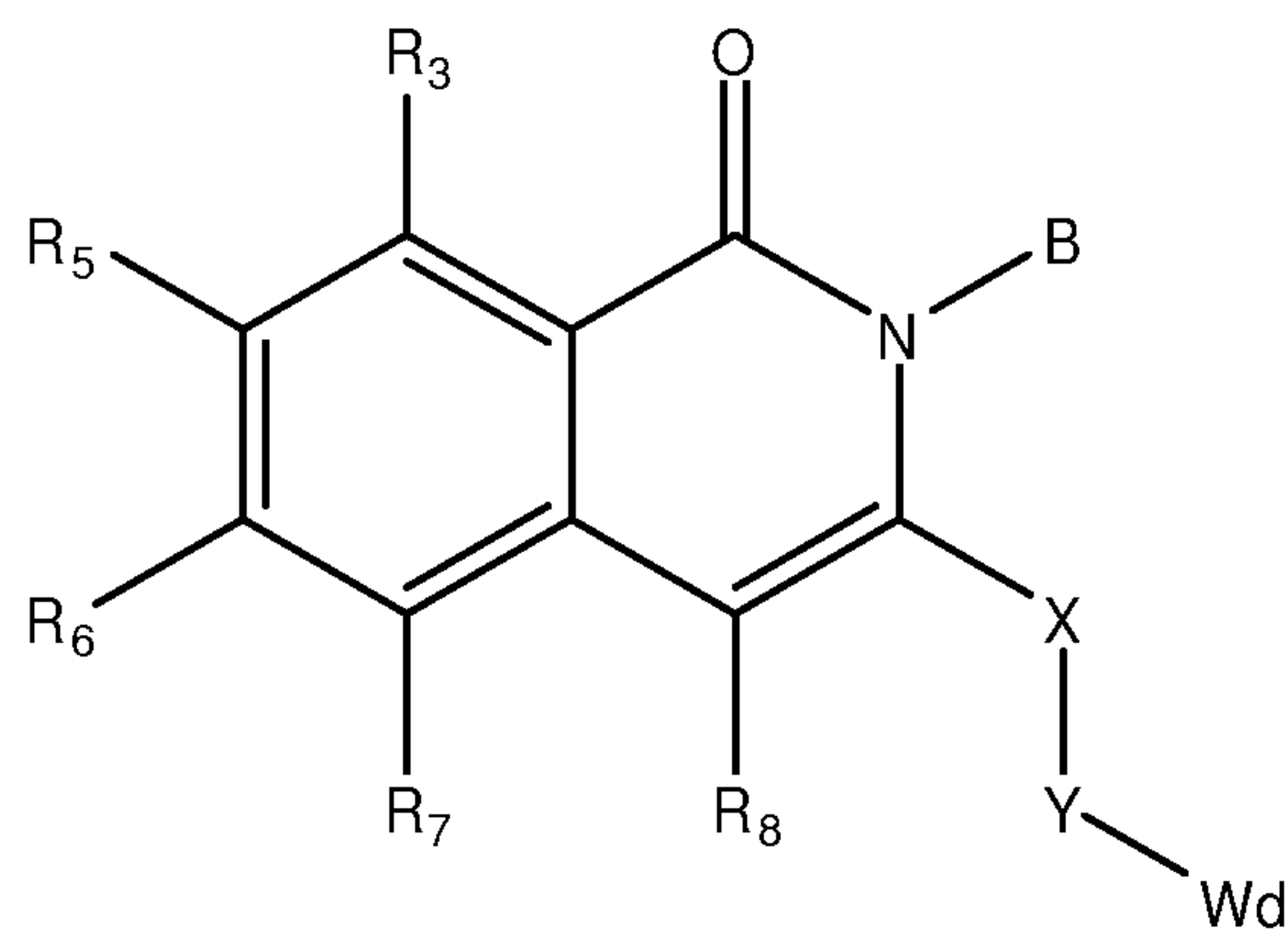
Formula II.

[00144] In some embodiments of the compounds of Formula II, W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4. In some embodiments, X is absent or is -(CH(R⁹))_z-, and each instance of z is independently an integer of 1, 2, 3, or 4. In some embodiments, Y is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -N(R⁹)-,

-C(=O)-(CHR⁹)_z-, -C(=O)-, -N(R⁹)-C(=O)-, or -N(R⁹)-C(=O)NH-, -N(R⁹)C(R⁹)₂-, or -C(=O)-(CHR⁹)_z-; wherein when W_b⁵ is N, no more than one of X or Y is absent. In some embodiments, R¹ is hydrogen, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate. In some embodiments, each R² is independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate. In some embodiments, R³ is cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, alkenyl, or alkynyl, or R³ is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C₁-C₆ alkyl group to an aryl, heteroaryl or heterocyclyl or R³ and R⁵ are taken together with the carbons to which they are attached form a 5- or 6-membered ring; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R¹³. In certain embodiments, R³ is selected from a 5-membered heteroaryl; a 5-membered nonaromatic heterocycle; a 6-membered aryl; a 6-membered heteroaryl; a 6-membered nonaromatic heterocycle; a fused 5/6-bicyclic heteroaryl; a fused 5/6-bicyclic nonaromatic heterocycle; a C₁-C₆ alkyl group substituted with a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered aryl or heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R³ is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C₁-C₆ alkyl group to a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered aryl or heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R³ is a C₁-C₆ alkyl group substituted with a fused polycyclic group, wherein the polycyclic group has greater than two rings and is carbocyclic or heterocyclic; C₁-C₆ alkyl group substituted with a bridged cycloalkyl or bridged heterocyclic group. In some embodiments, R³ is a C₁-C₆ alkyl group substituted with a spirocyclic cycloalkyl or spirocyclic heterocyclic group. In some embodiments, R³ is a branched C₄-C₁₂ alkyl group, wherein said branched alkyl group contains at least one terminal t-butyl group.

[00145]

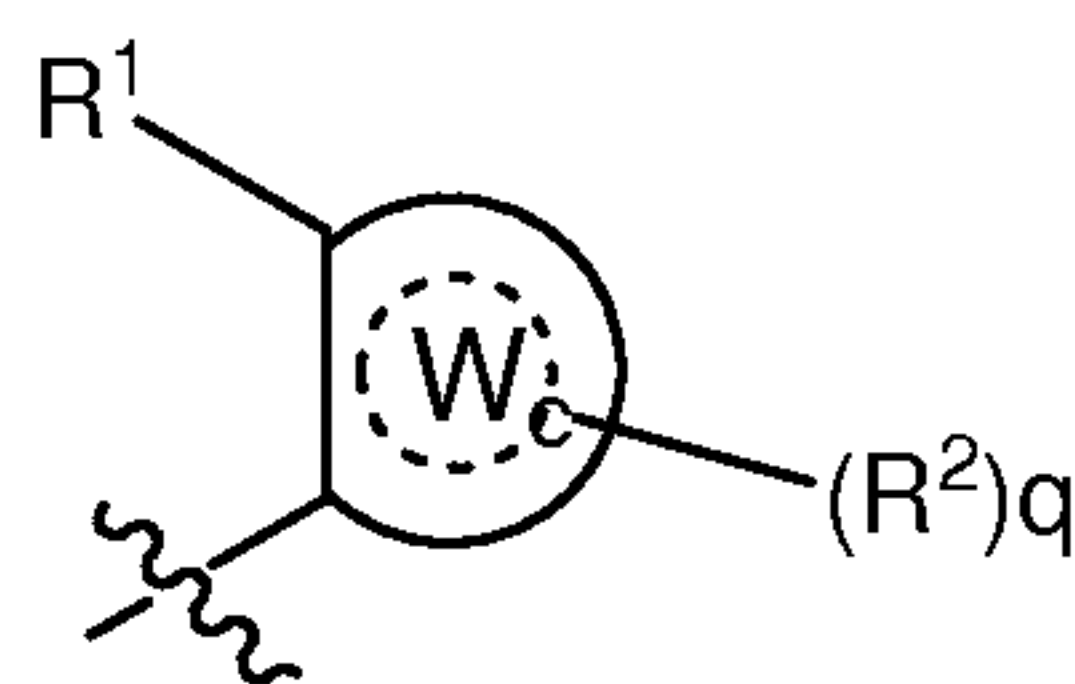
In another aspect, provided herein are compounds of Formula I-C:



Formula IC

or pharmaceutically acceptable forms thereof, wherein

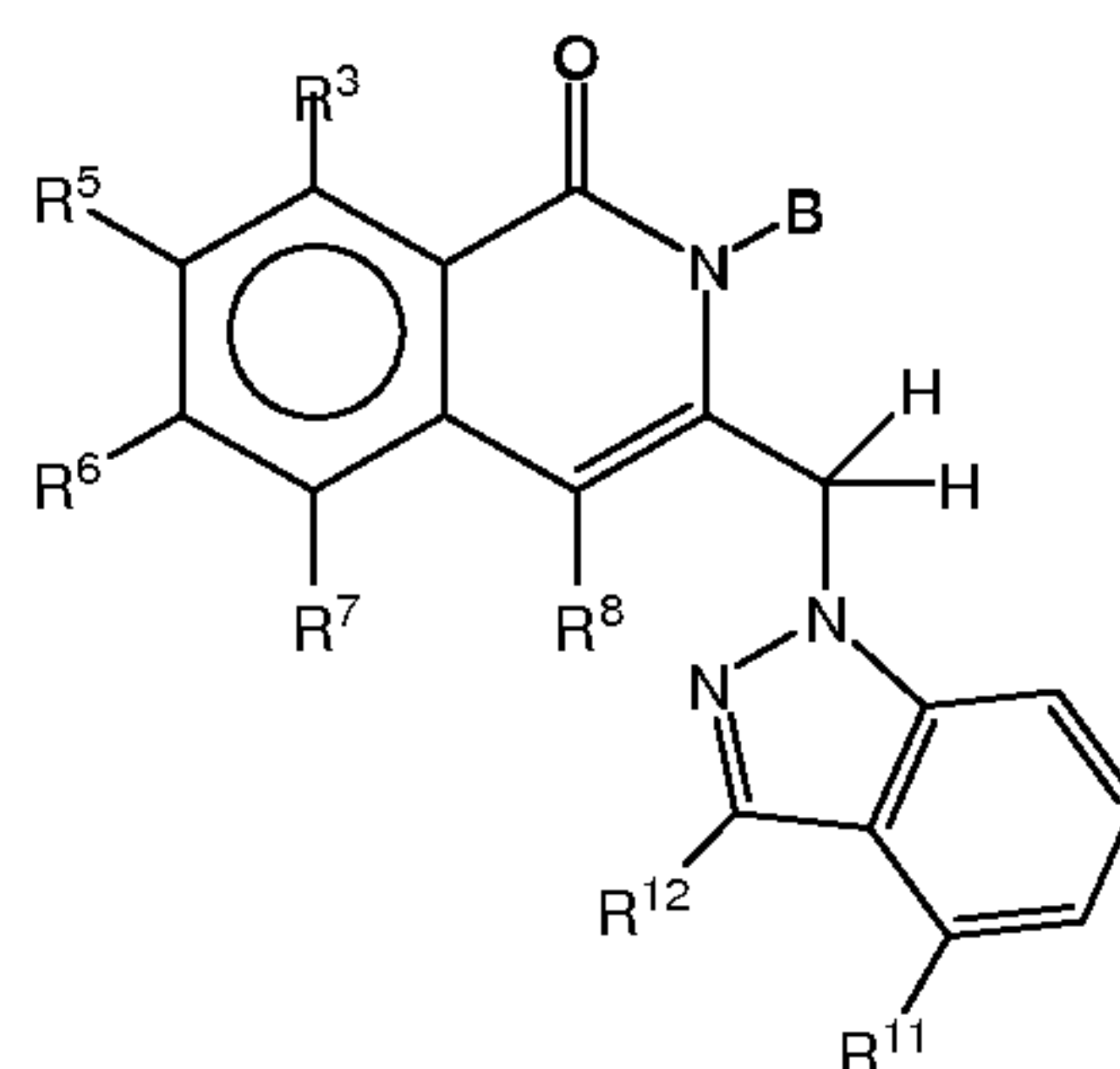
B is alkyl, amino, heteroalkyl, cycloalkyl, heterocycloalkyl, or a moiety of Formula II:



Formula II

[00146] In some embodiments of Formula II, W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and q is an integer of 0, 1, 2, 3, or 4; X is absent or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3, or 4; Y is absent, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)(CHR^9)_z-$, $-N(R^9)-$, $N(R^9)-C(=O)-$, $-N(R^9)-C(=O)NH-$, or $-N(R^9)C(R^9)_2-$, and z is an integer of 1, 2, 3, or 4. In some embodiments, R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro; each R^2 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate; R^3 is alkyl, alkenyl, or alkynyl; 5-membered heteroaryl; a 5-membered nonaromatic heterocycle; a 6-membered aryl; a 6-membered heteroaryl; a 6-membered nonaromatic heterocycle; a fused 5/6-bicyclic heteroaryl; a fused 5/6-bicyclic nonaromatic heterocycle; a C_1 - C_6 alkyl group substituted with a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered aryl or heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C_1 - C_6 alkyl group to a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered aryl or heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In some embodiments, R^3 is a C_1 - C_6 alkyl group substituted with a fused polycyclic group, wherein the polycyclic group has greater than two rings and is carbocyclic or heterocyclic; C_1 - C_6 alkyl group substituted with a bridged cycloalkyl or bridged heterocyclic group. In some embodiments, R^3 is a C_1 - C_6 alkyl group substituted with a spirocyclic cycloalkyl or spirocyclic heterocyclic group. In some embodiments, R^3 is a branched C_4 - C_{12} alkyl group, wherein said branched alkyl group contains at least one terminal t-butyl group; R^5 , R^6 , R^7 , and R^8 are independently hydrogen, halo, cyano, alkyl or amino group; and each R^9 is independently hydrogen, alkyl, or heterocycloalkyl. In some embodiments, R^{11} is hydrogen, alkyl, halo, amino, amido, hydroxy, alkoxy, phosphate, urea, or carbonate; R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, nonaromatic heterocycle, or cycloalkyl; R^a is hydrogen, alkyl, $-NH_2$, cyano or halogen; and each R^{13} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or halogen. In certain embodiments, R^3 and R^5 taken together with the carbons to which they are attached can form a 5- or 6-membered ring. In some embodiments of compounds of Formula I-C, R^3 is C_2 - C_{10} alkyl, alkenyl or alkynyl, unsubstituted or substituted with alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$ where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

[00147] In some embodiments, the compound of Formula I is a compound having a structure of Formula IV:

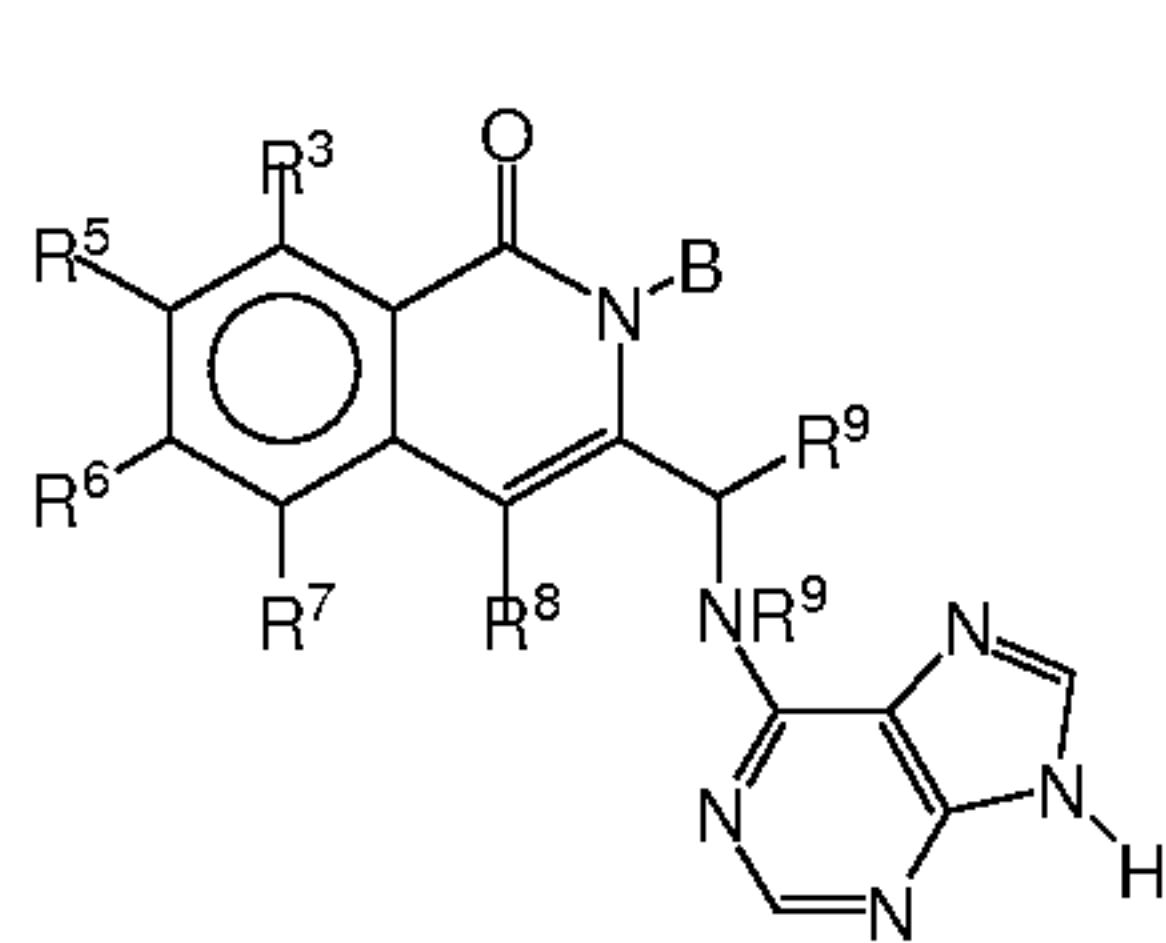


Formula IV

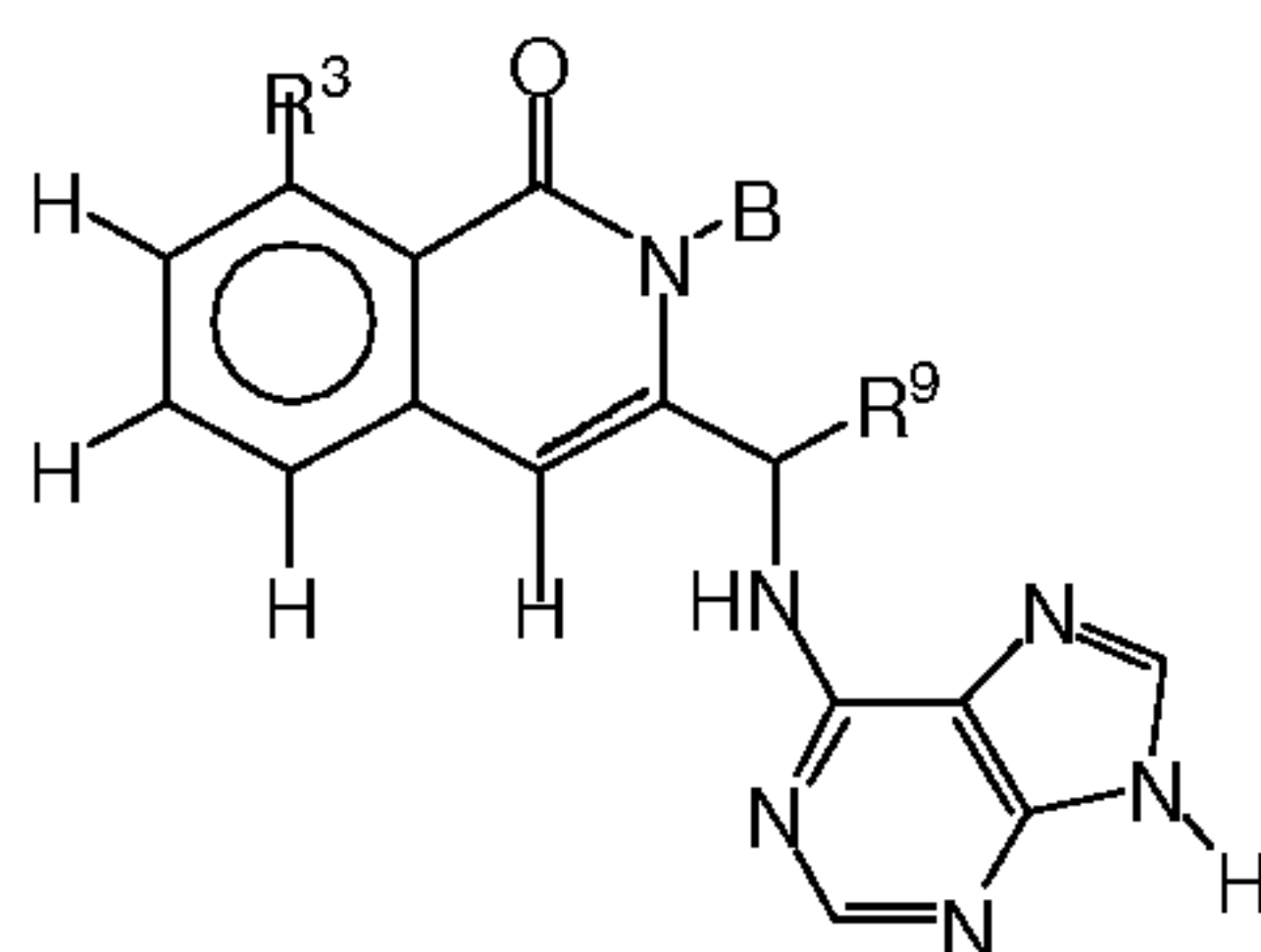
or pharmaceutically acceptable forms thereof.

[00148] In some embodiments of the compound of Formula IV, R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In another embodiment, R^{11} is amino and R^{12} is alkyl, alkenyl, heteroaryl, aryl, or heterocycloalkyl. In some embodiments, R^{11} is amino and R^{12} is cyano, amino, carboxylic acid, alkoxy carbonyl, or amido.

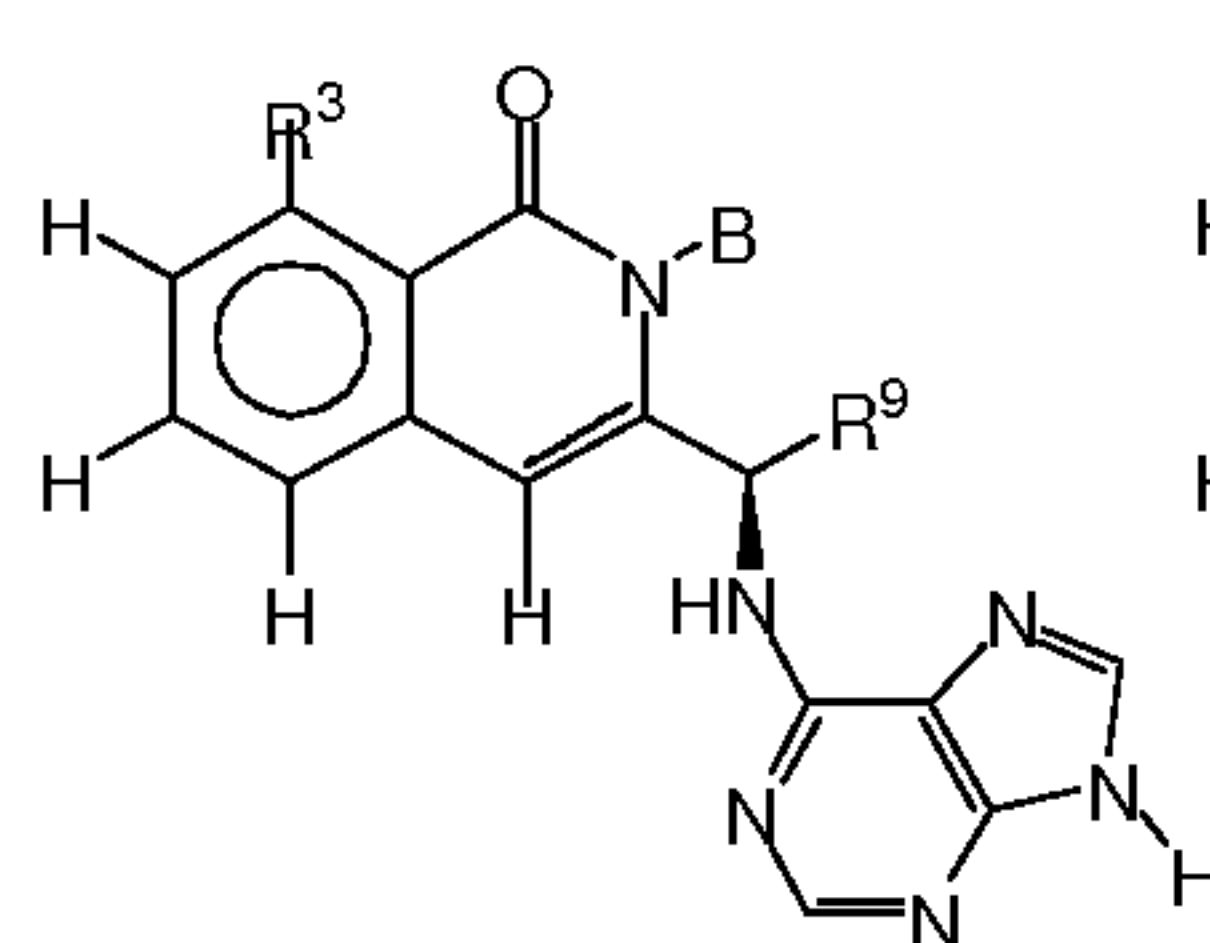
[00149] The disclosure also provides compounds of Formula I having a structure of any of Formulae V, V-A, V-A1, V-A2, V-B, VI, VI-A, VII-A, VII-A1, VII-A2, VIII-A, VIII-A1, VIII-A2, IX-A, IX-A1, IX-A2, X-A, X-A1, X-A2, XI-A, XI-A1, XI-A2, XII-A, XII-A1, XII-A2, XIII-A, XIII-A1, XIII-A2, XIV-A, XIV-A1, XIV-A2, XV-A, XV-A1, XV-A2, XVI-A, XVI-A1, XVI-A2, XVII-A, XVII-A1, XVII-A2, XVIII-A, XVIII-A1, XVIII-A2, XIX-A, XIX-A2, XIX-A3, XX-A, XX-A2, XX-A3, XXI-A, XXI-A2, XXI-A3, XXII-A, XXII-A2 and XXII-A3:



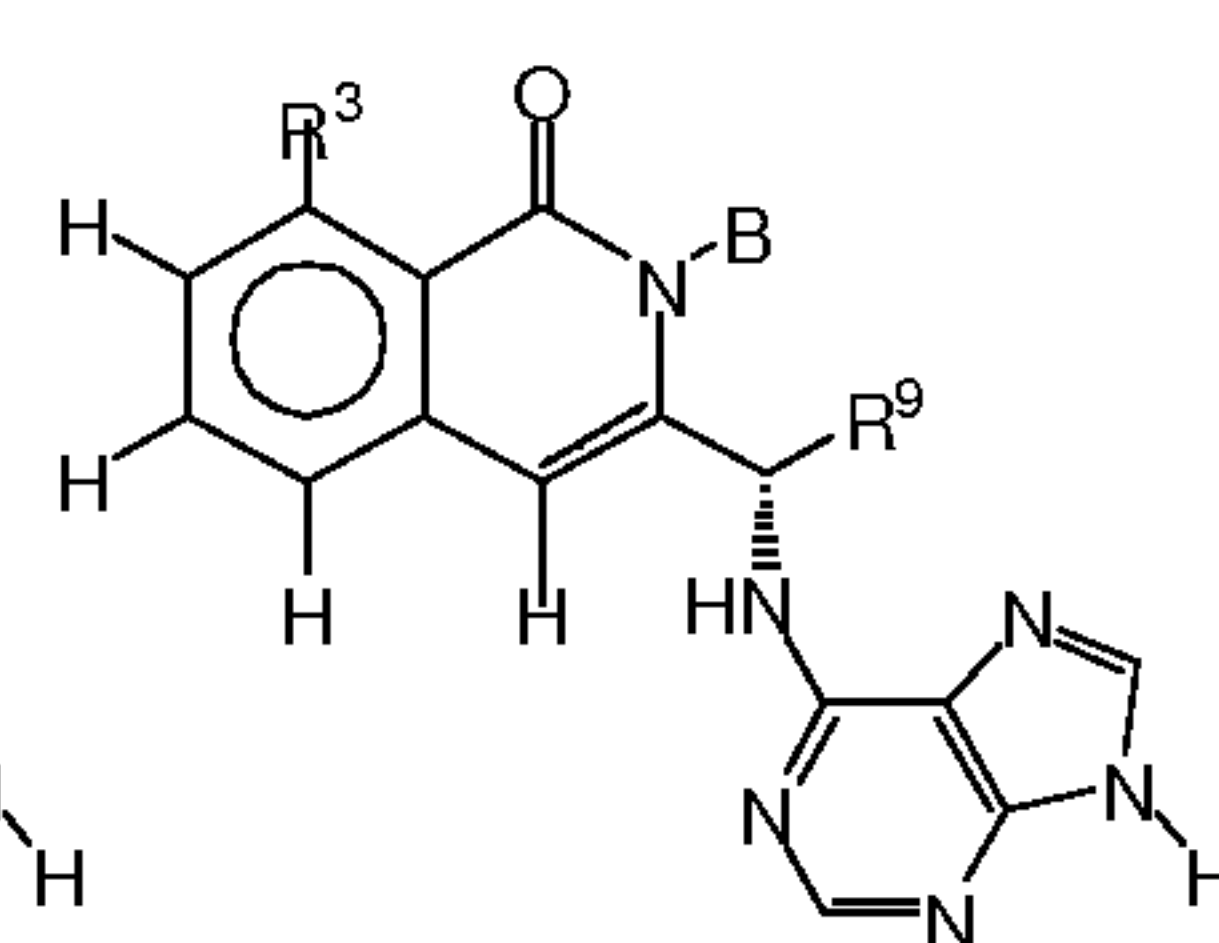
Formula V



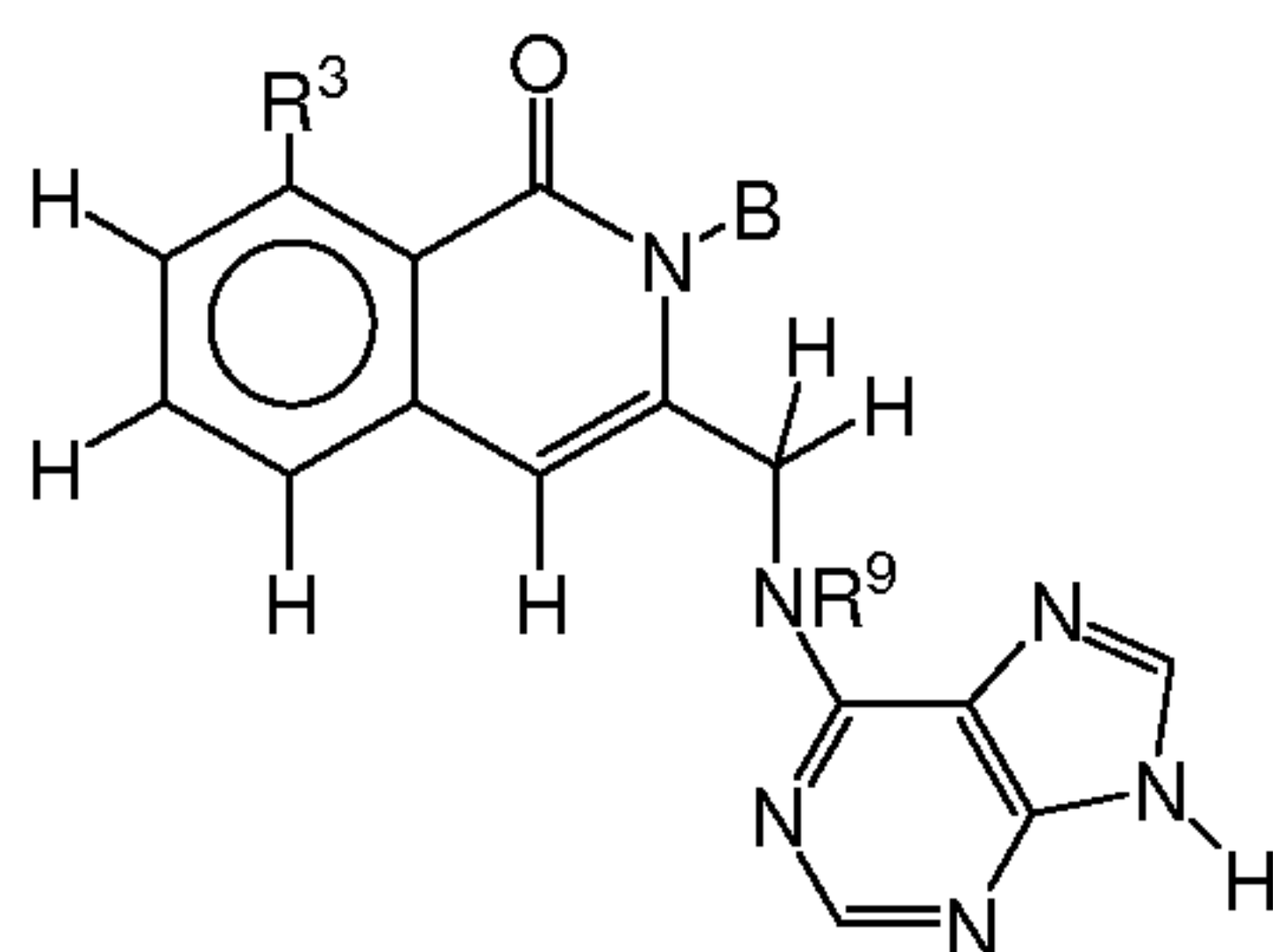
Formula V-A



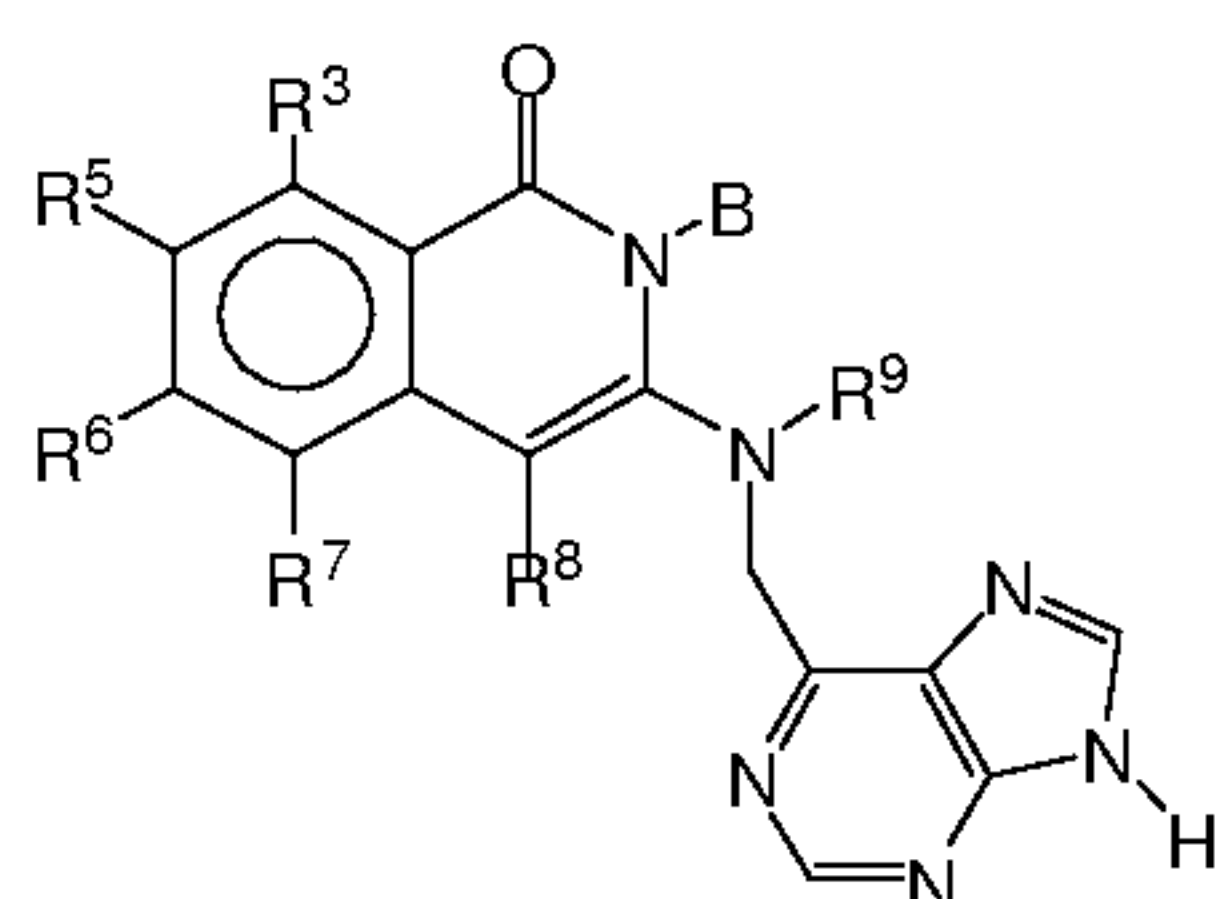
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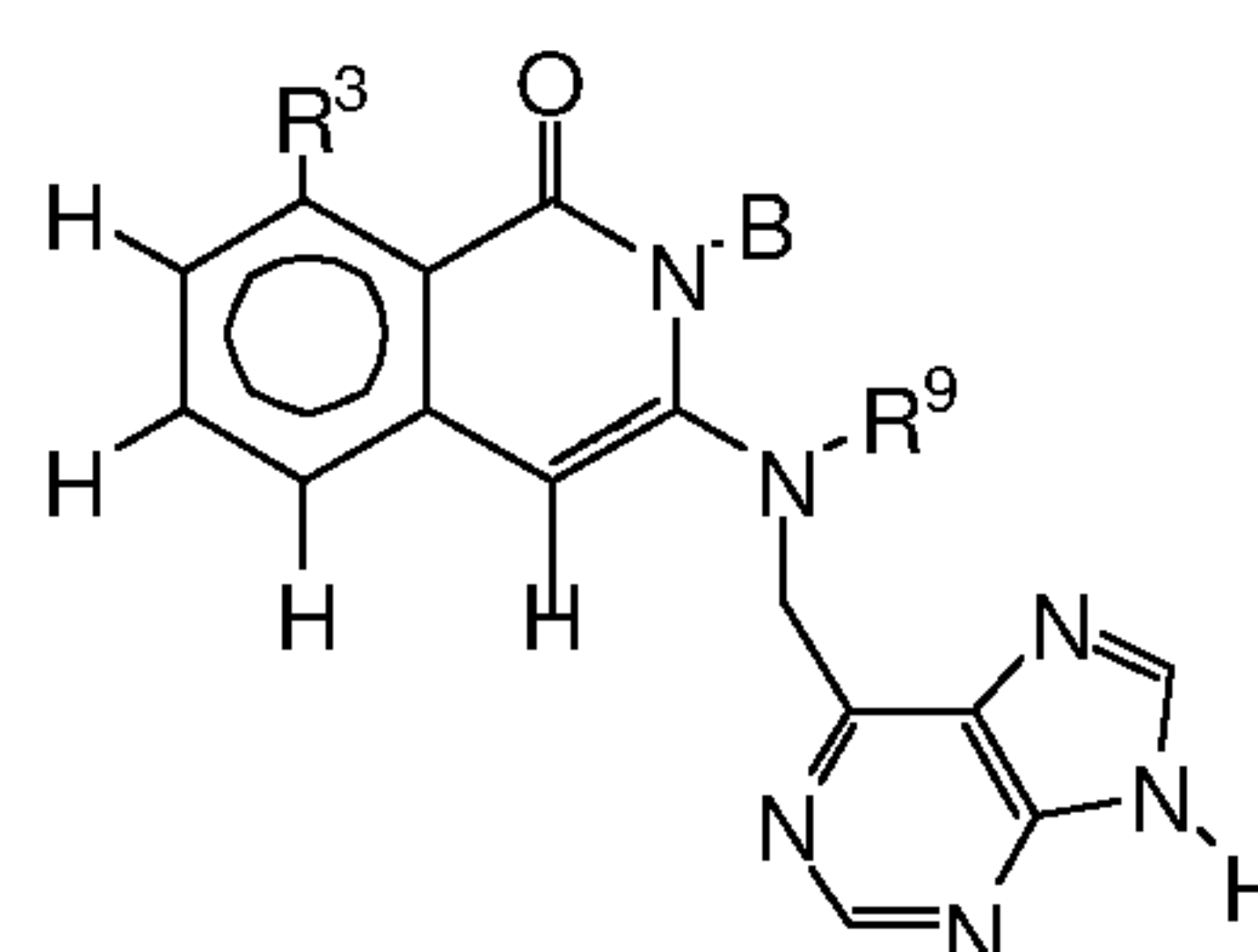
Formula V-A2



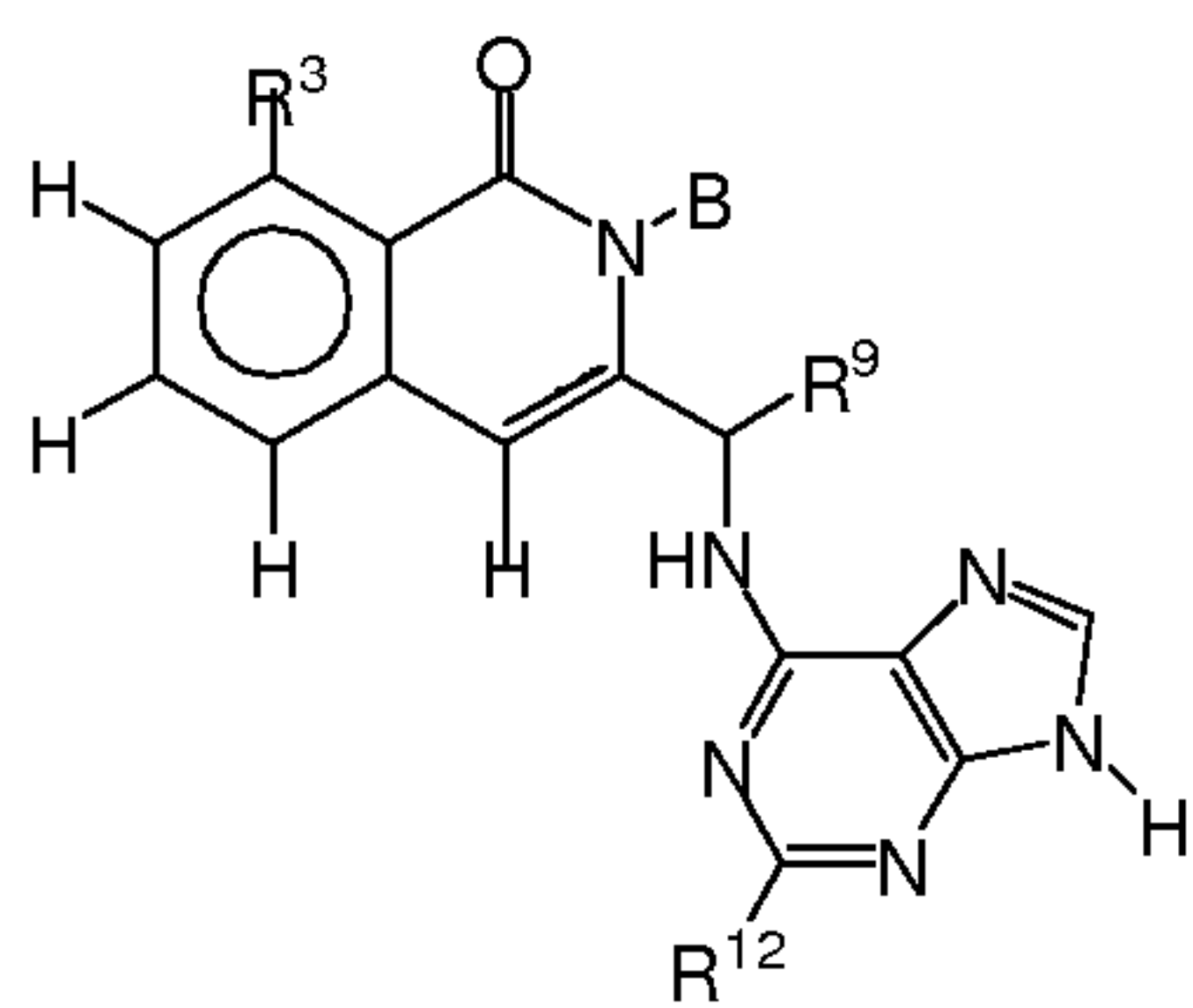
Formula V-B



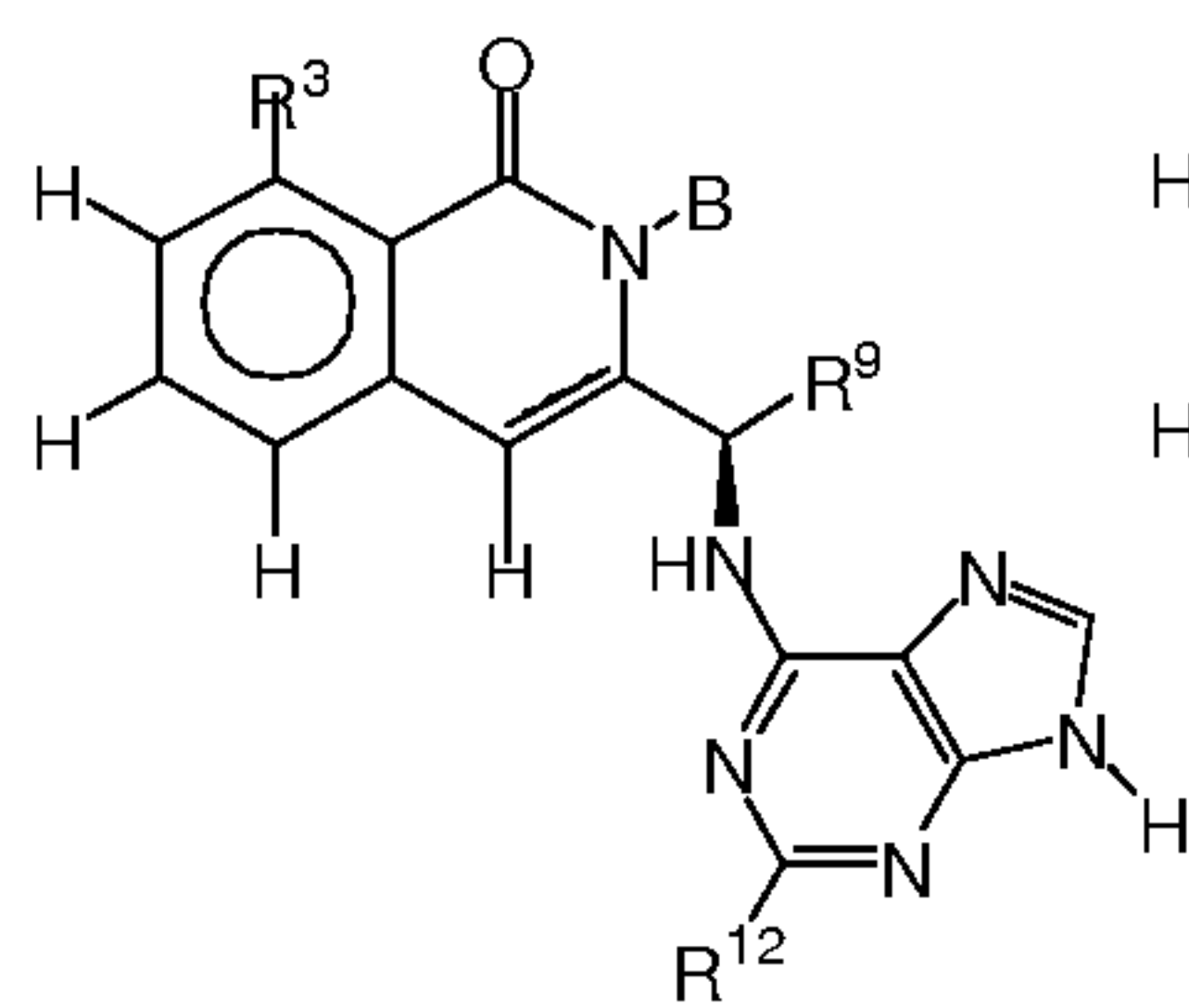
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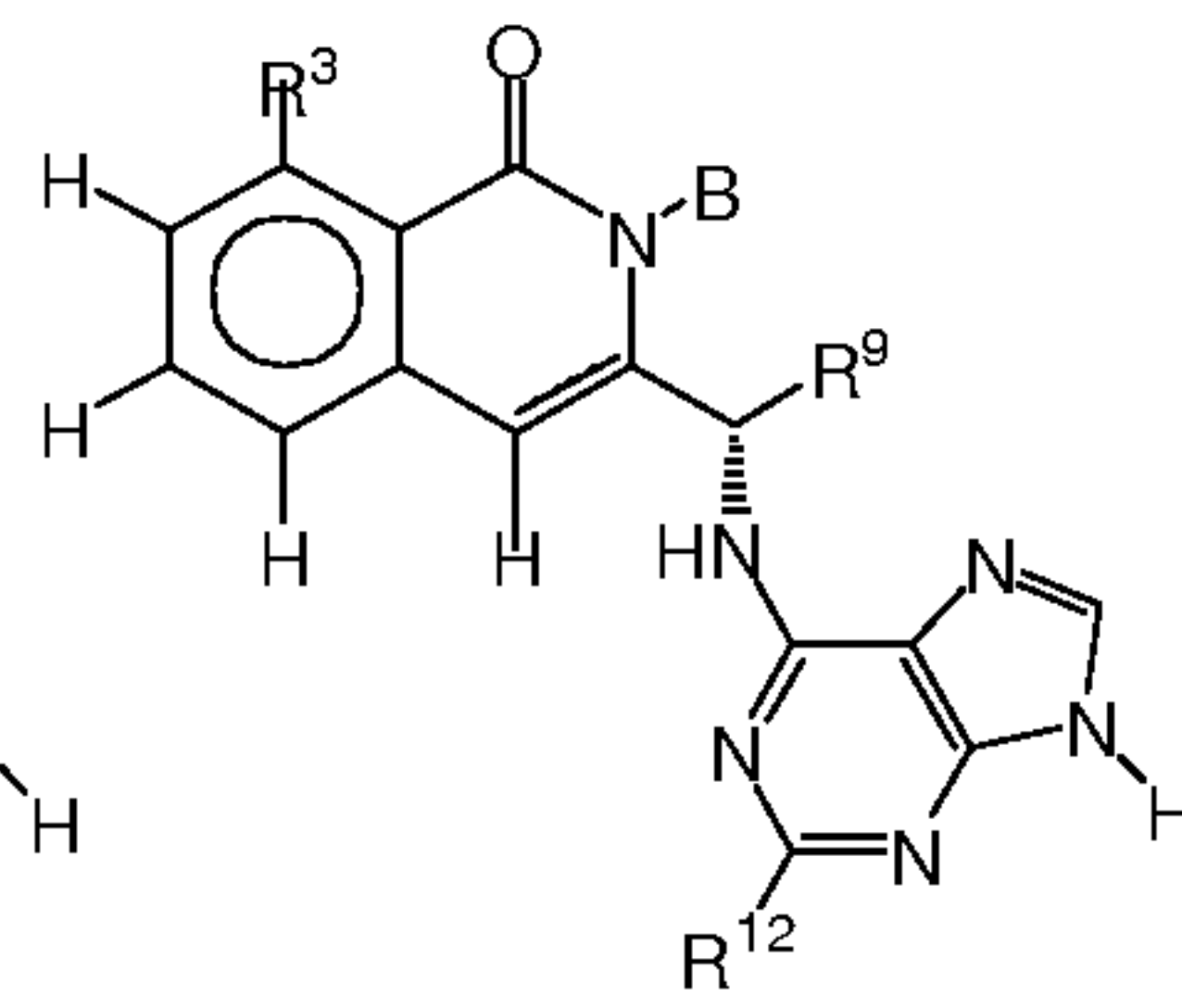
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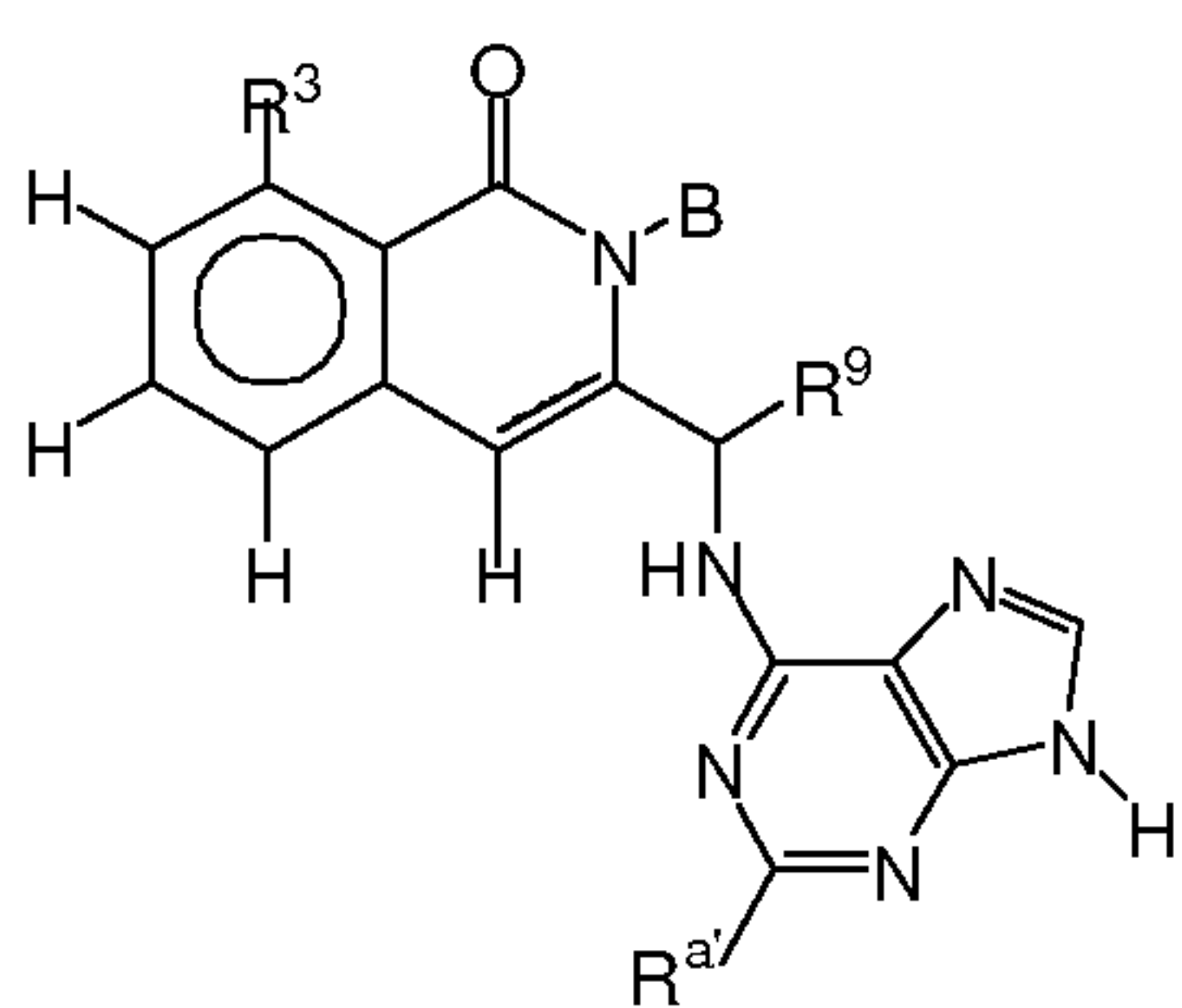
Formula VII-A



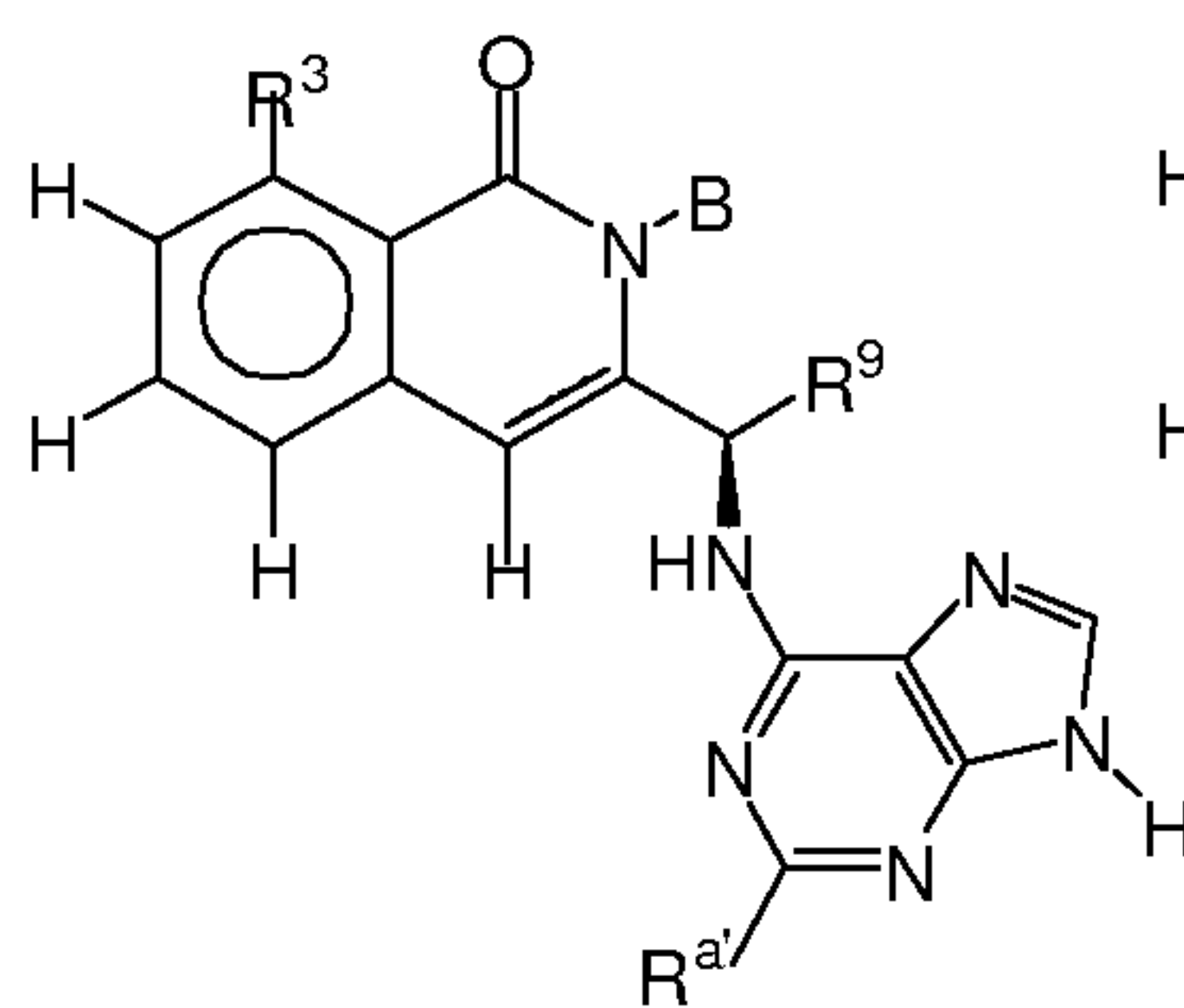
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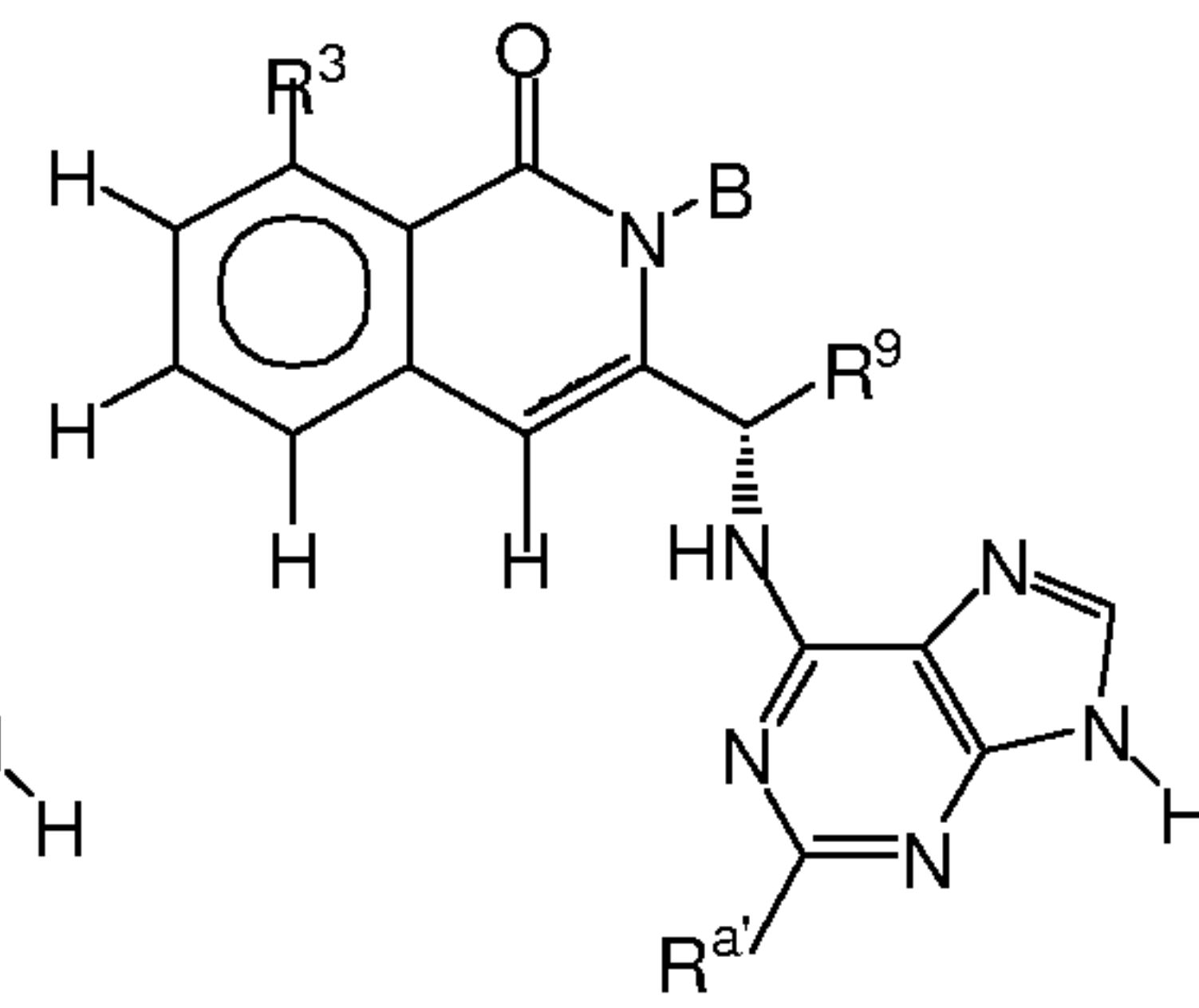
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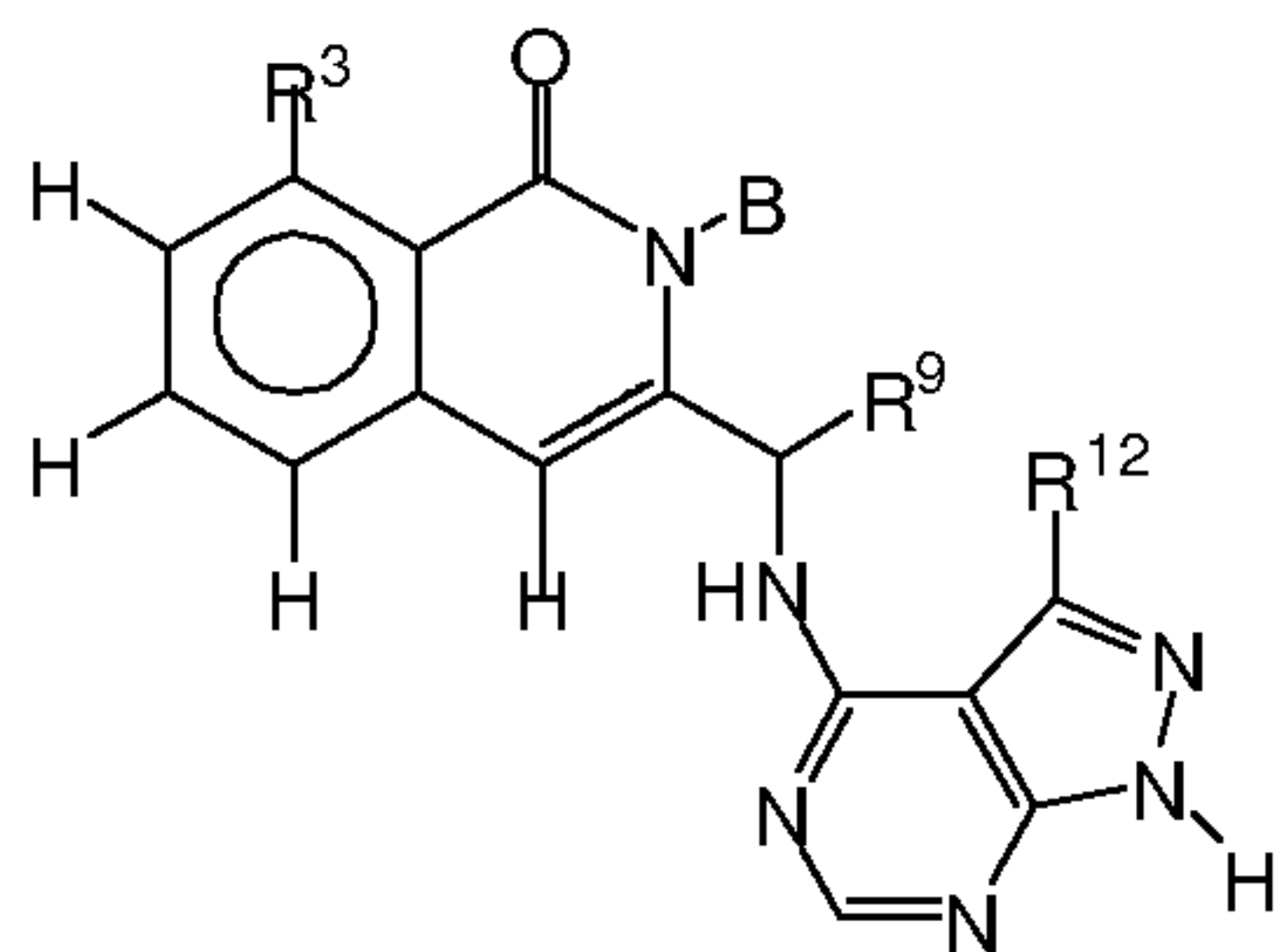
Formula VIII-A



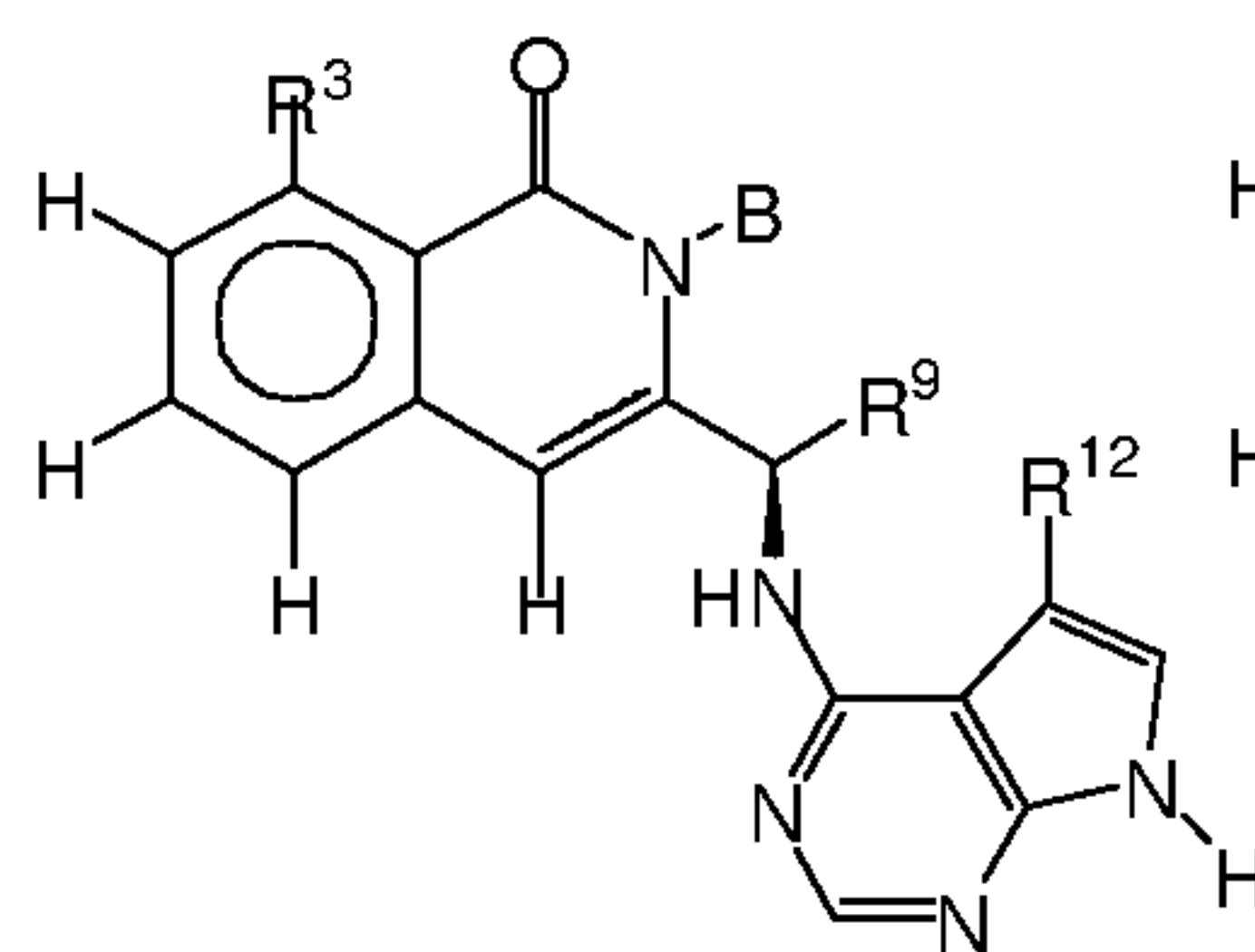
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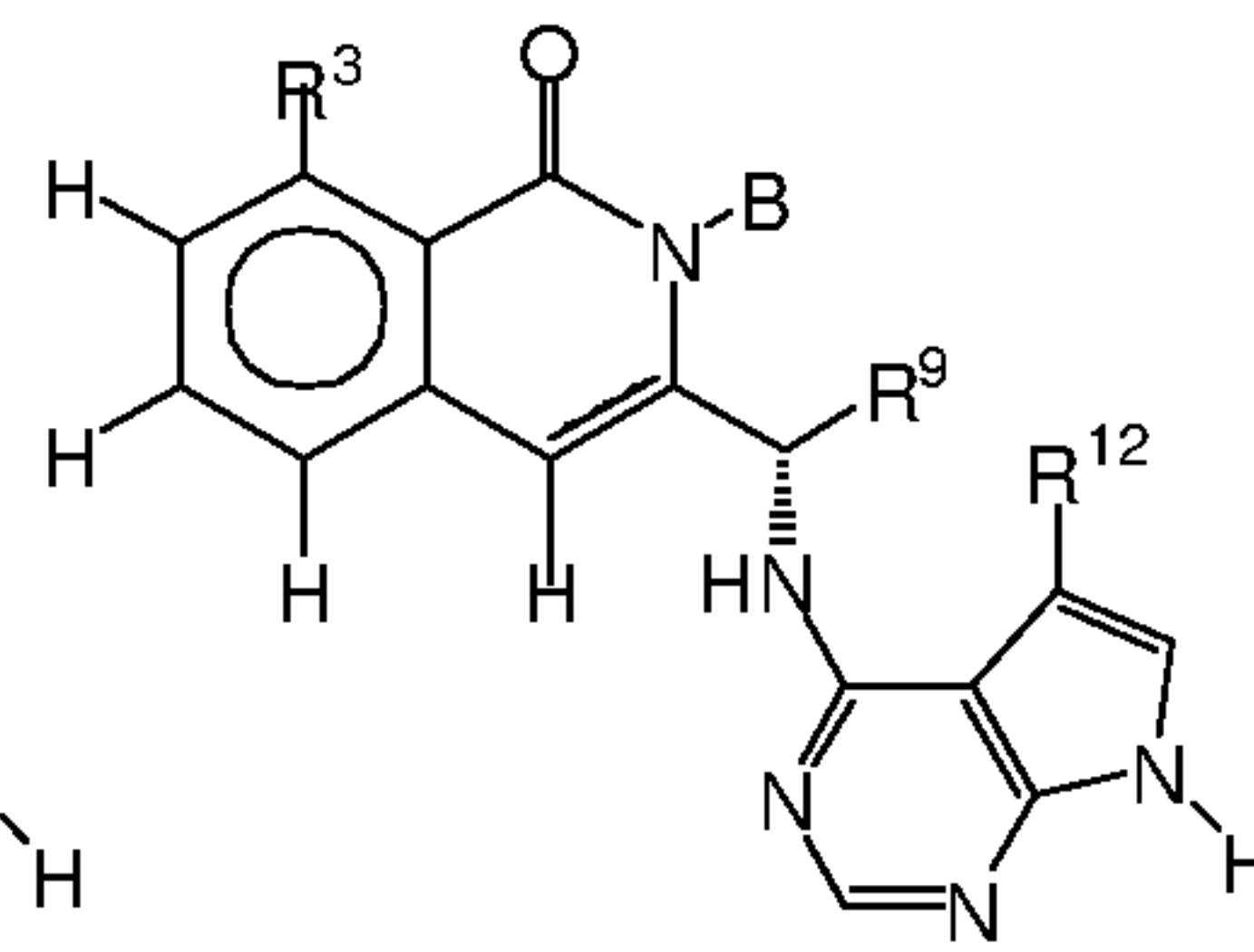
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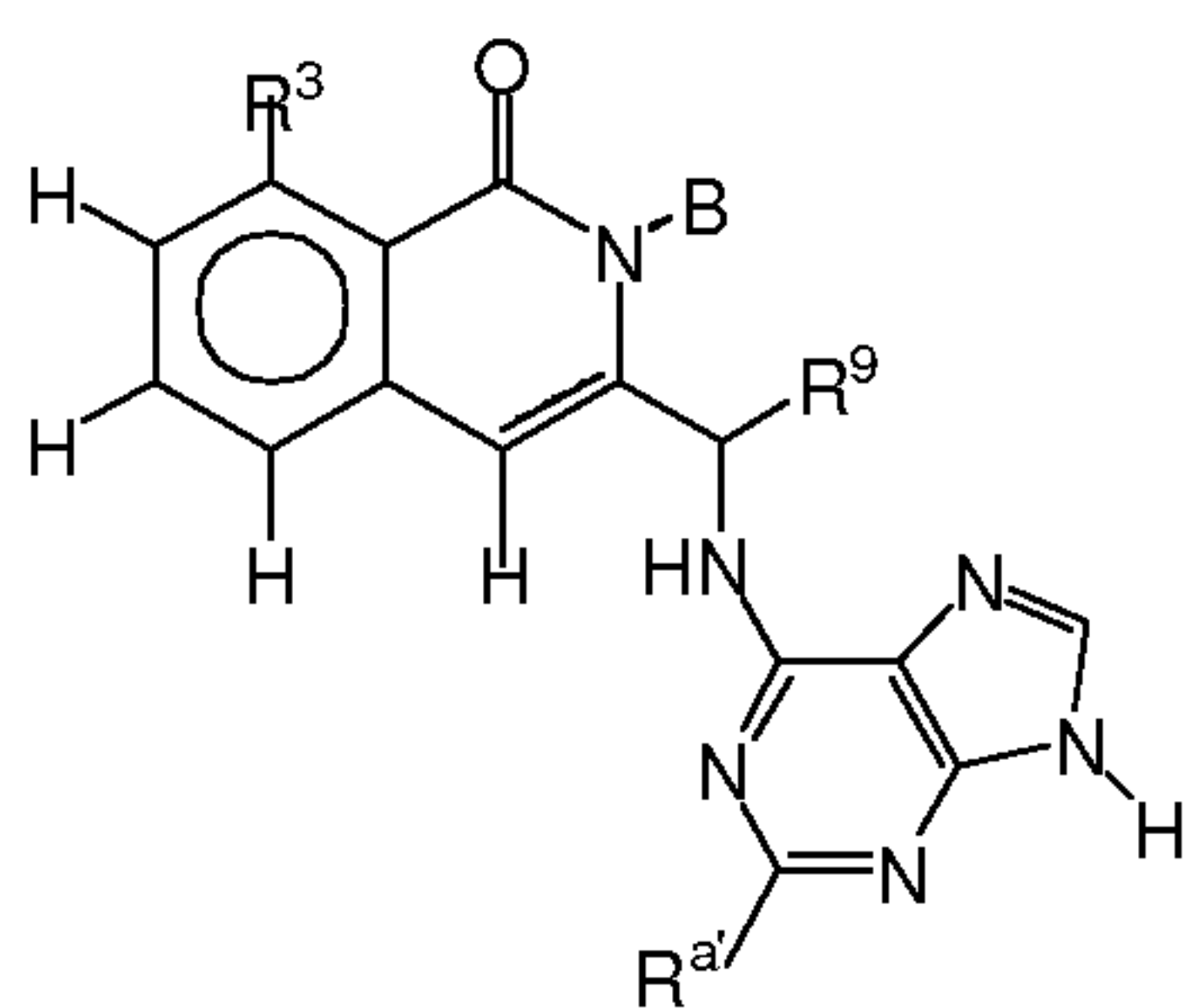
Formula IX-A



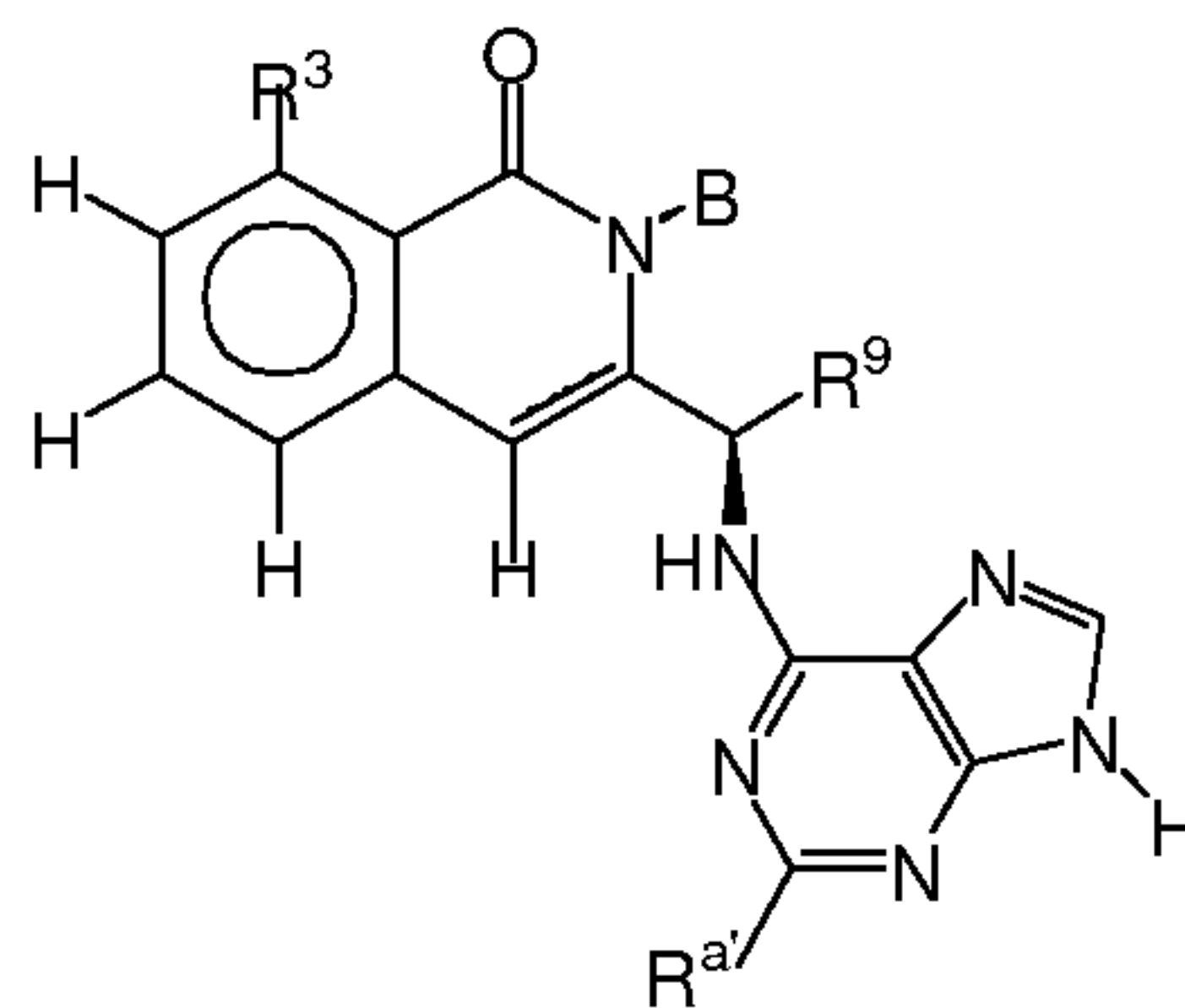
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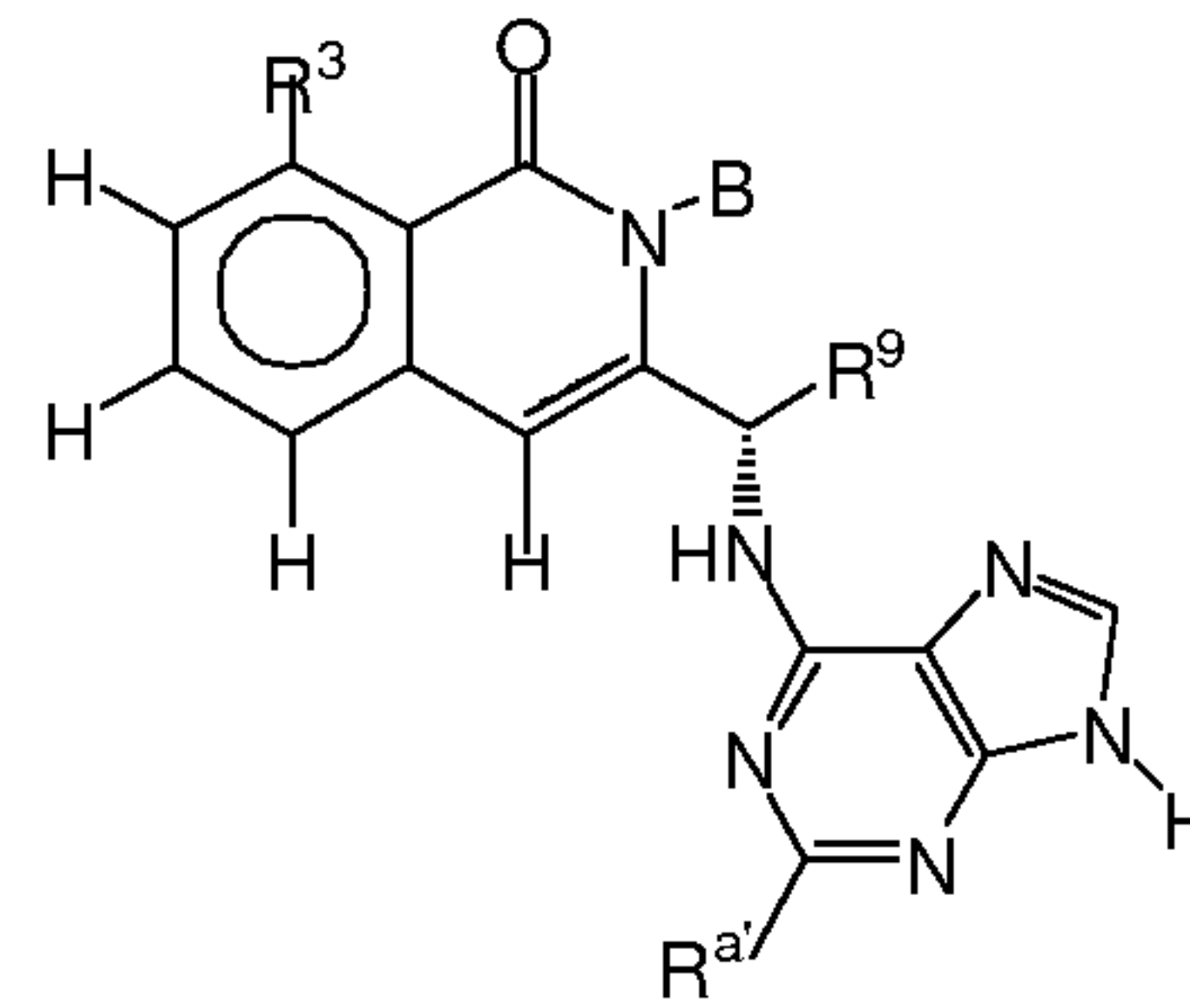
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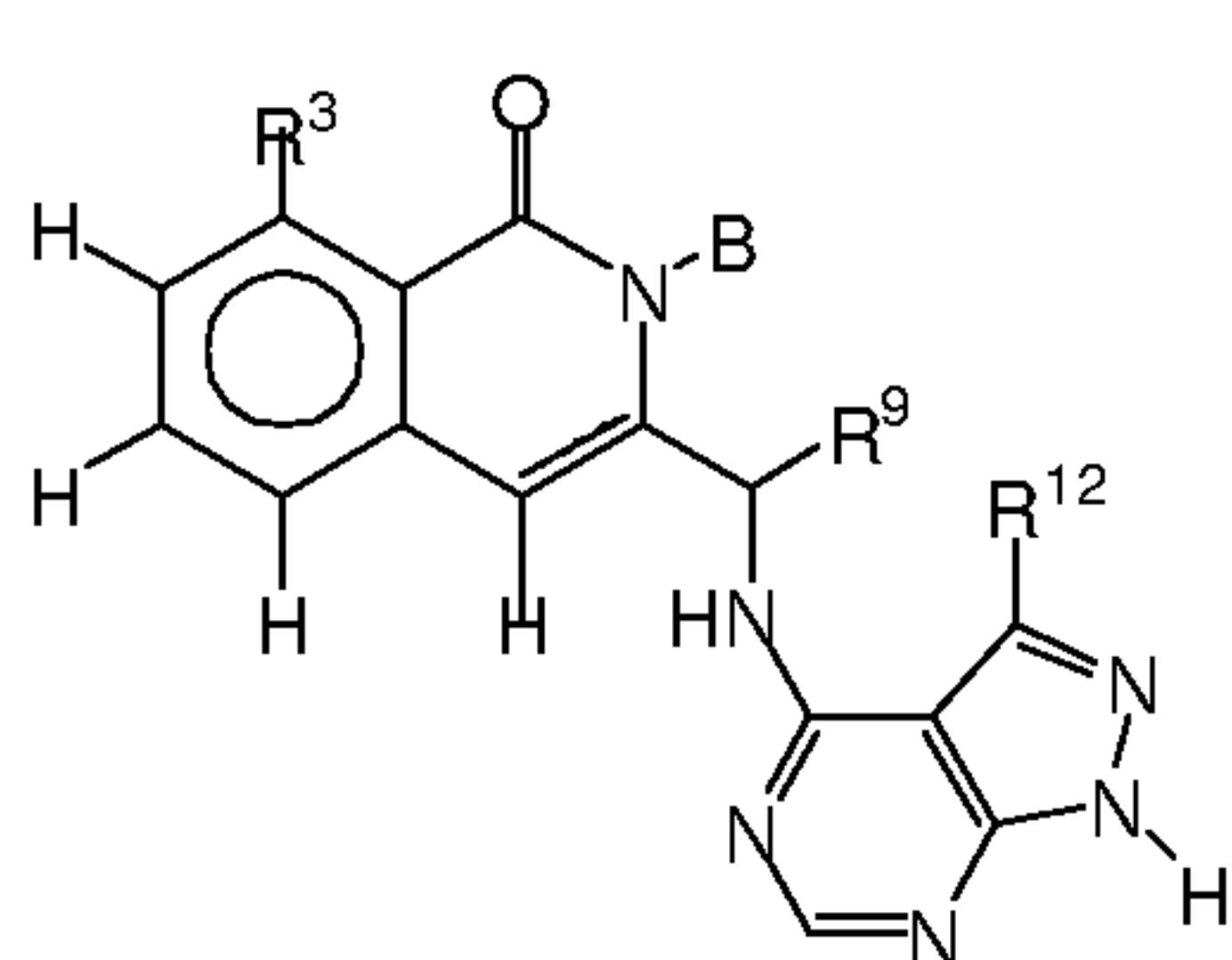
Formula X-A



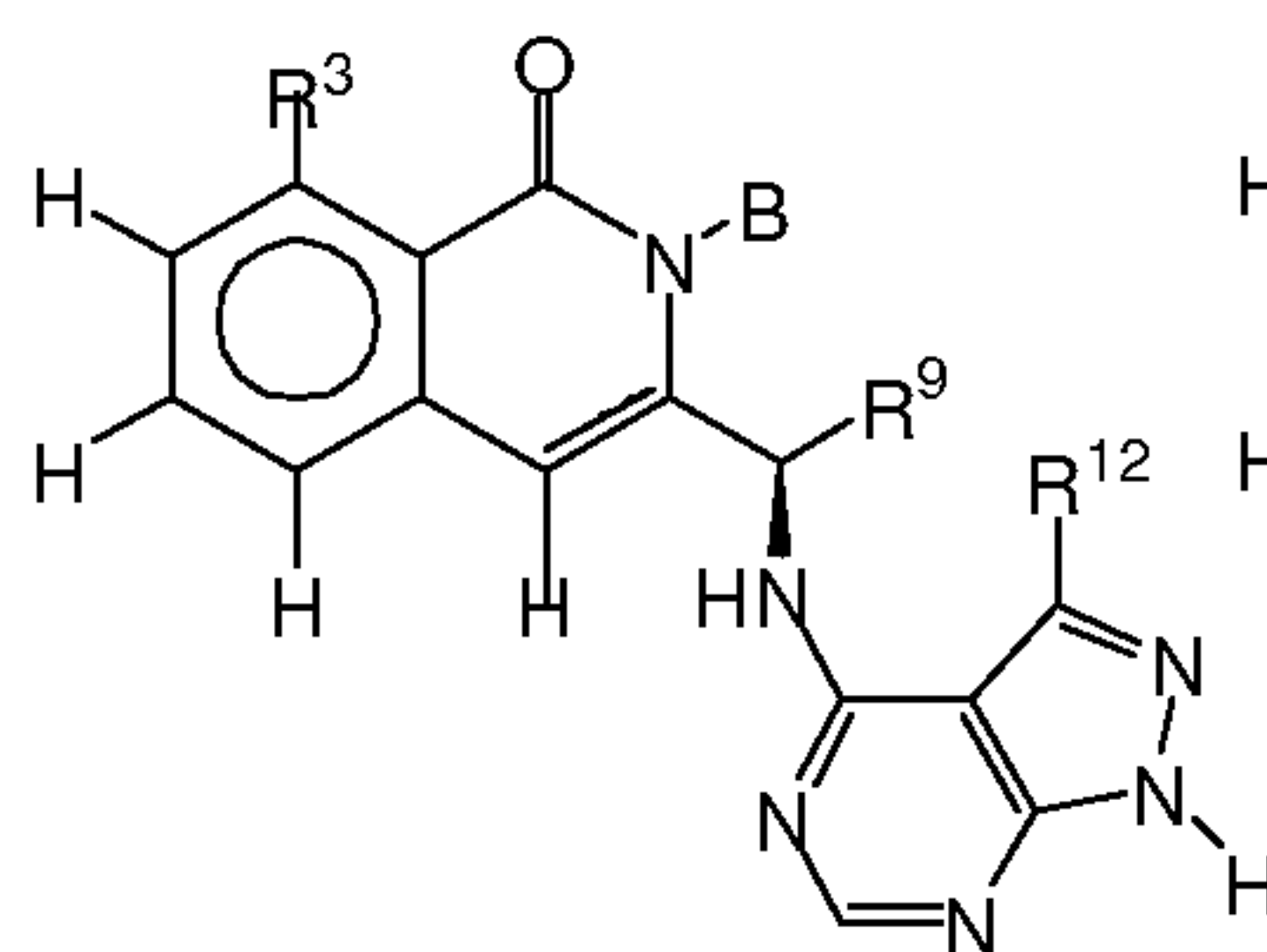
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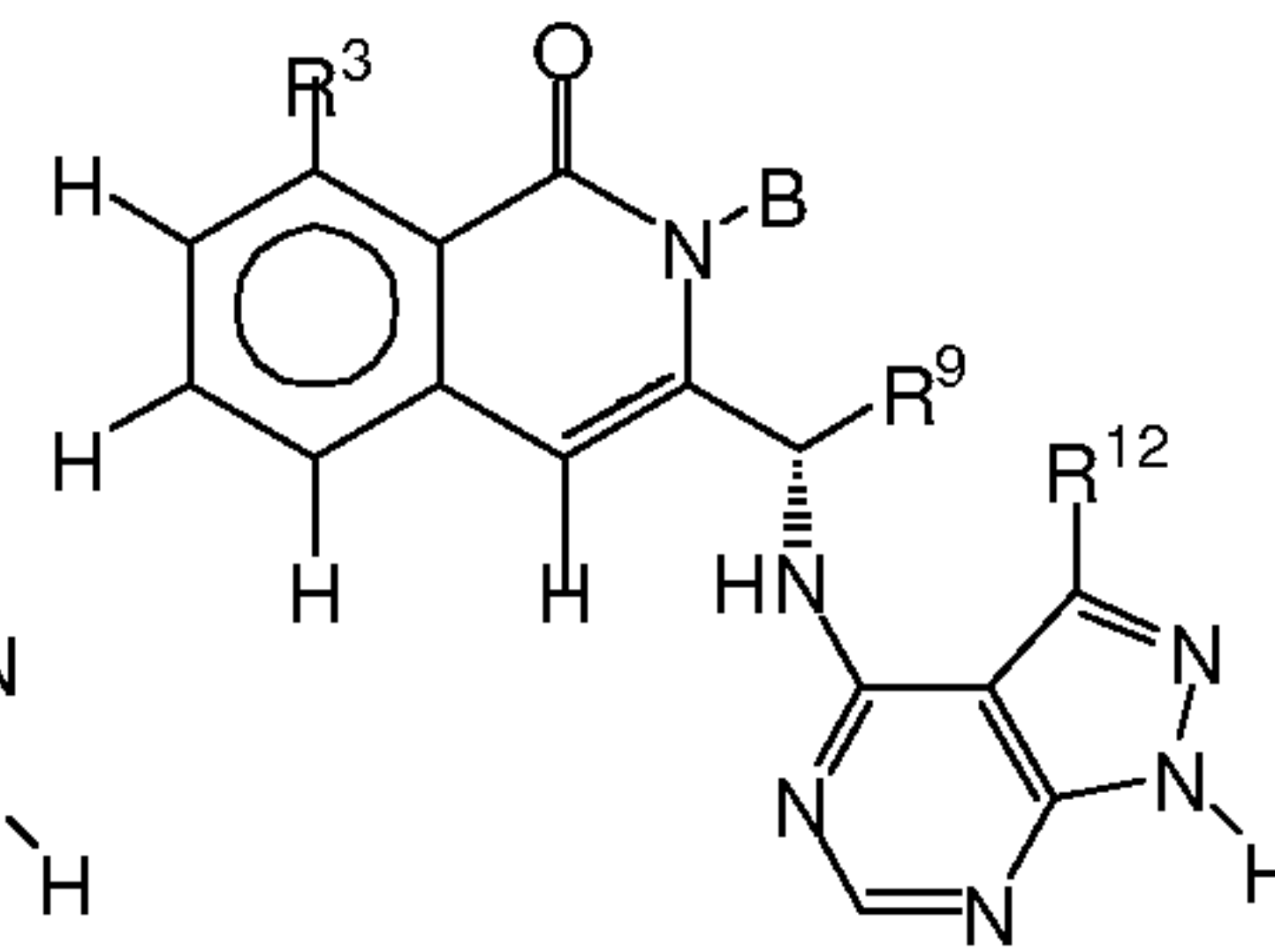
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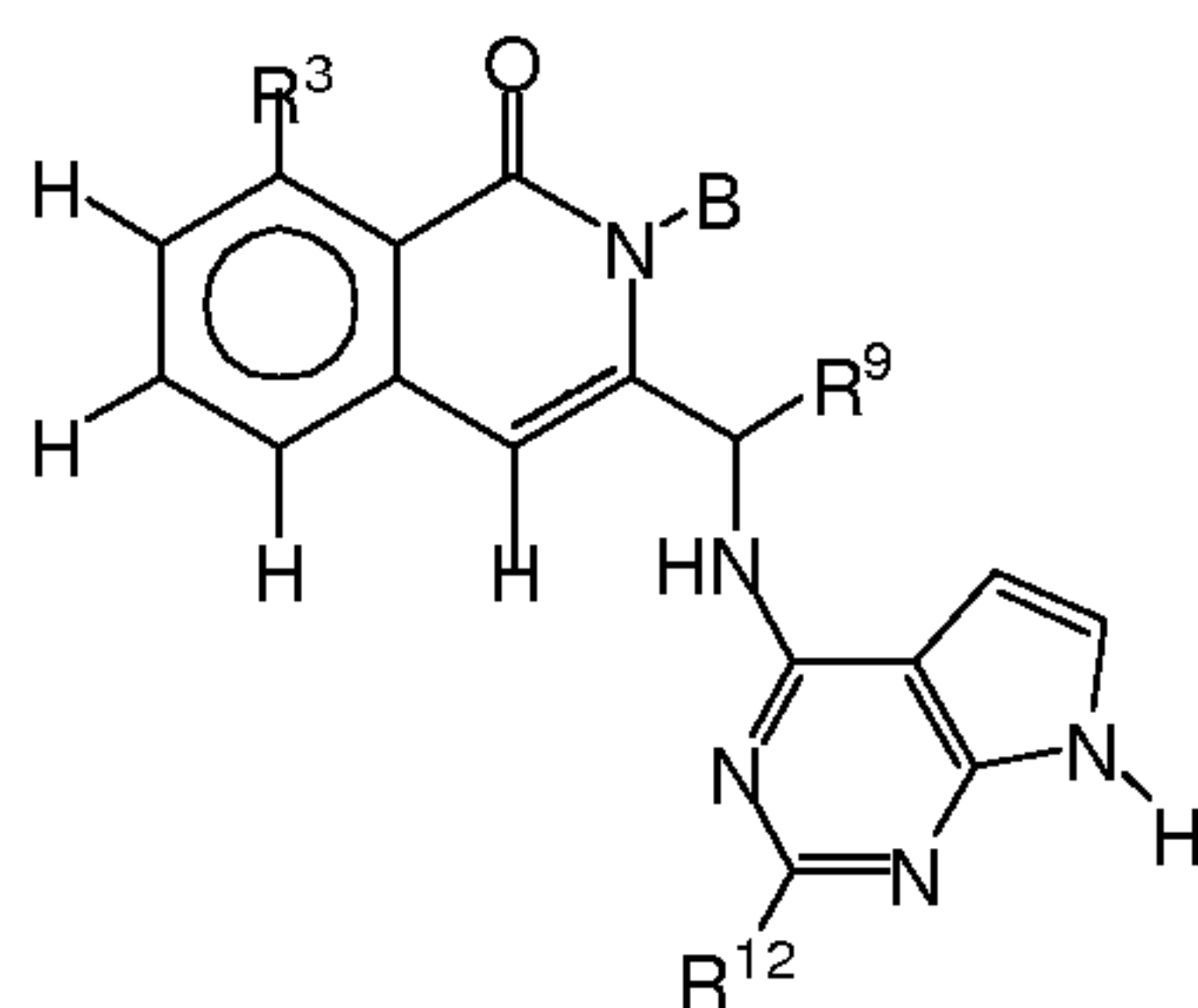
Formula XI-A



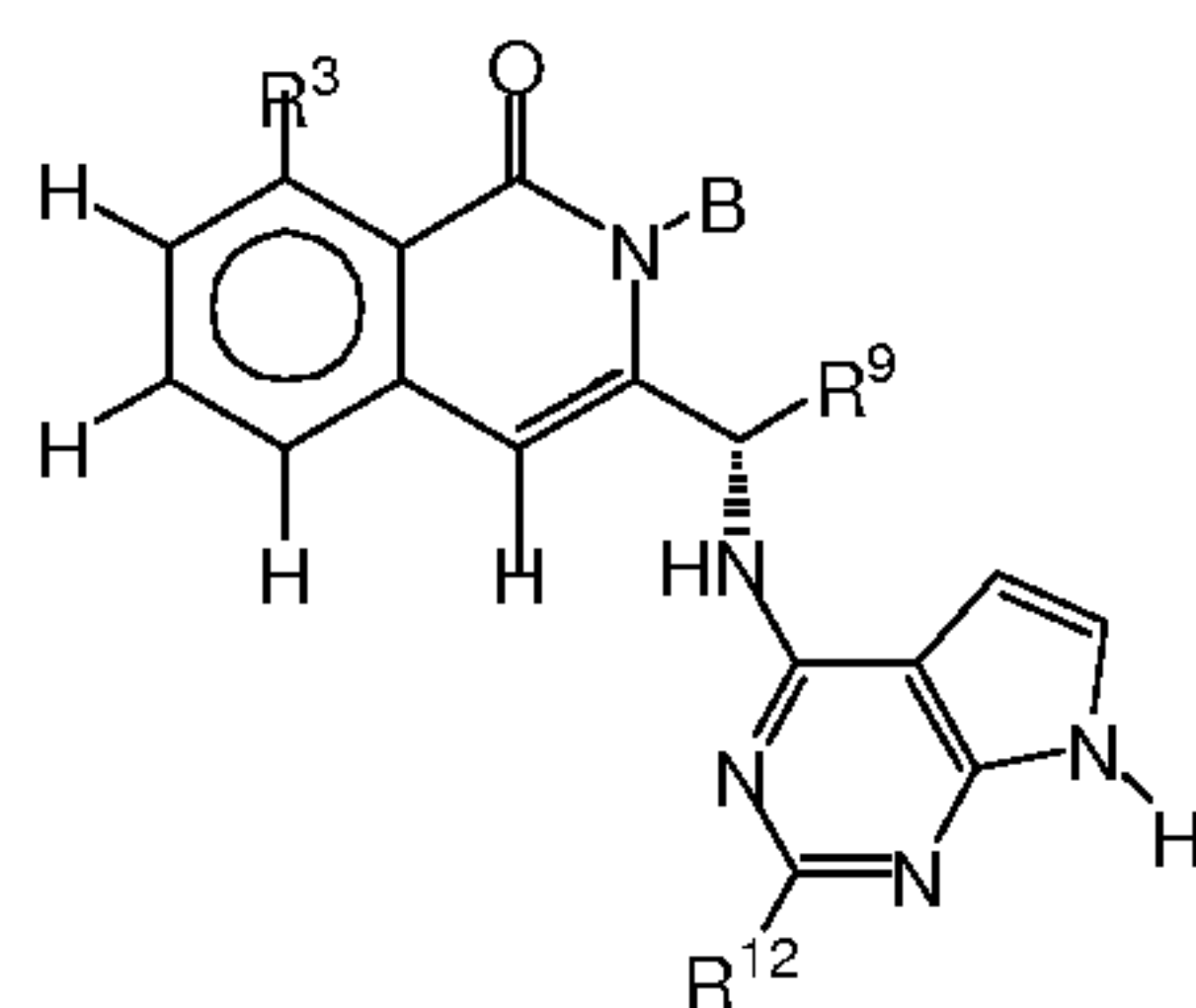
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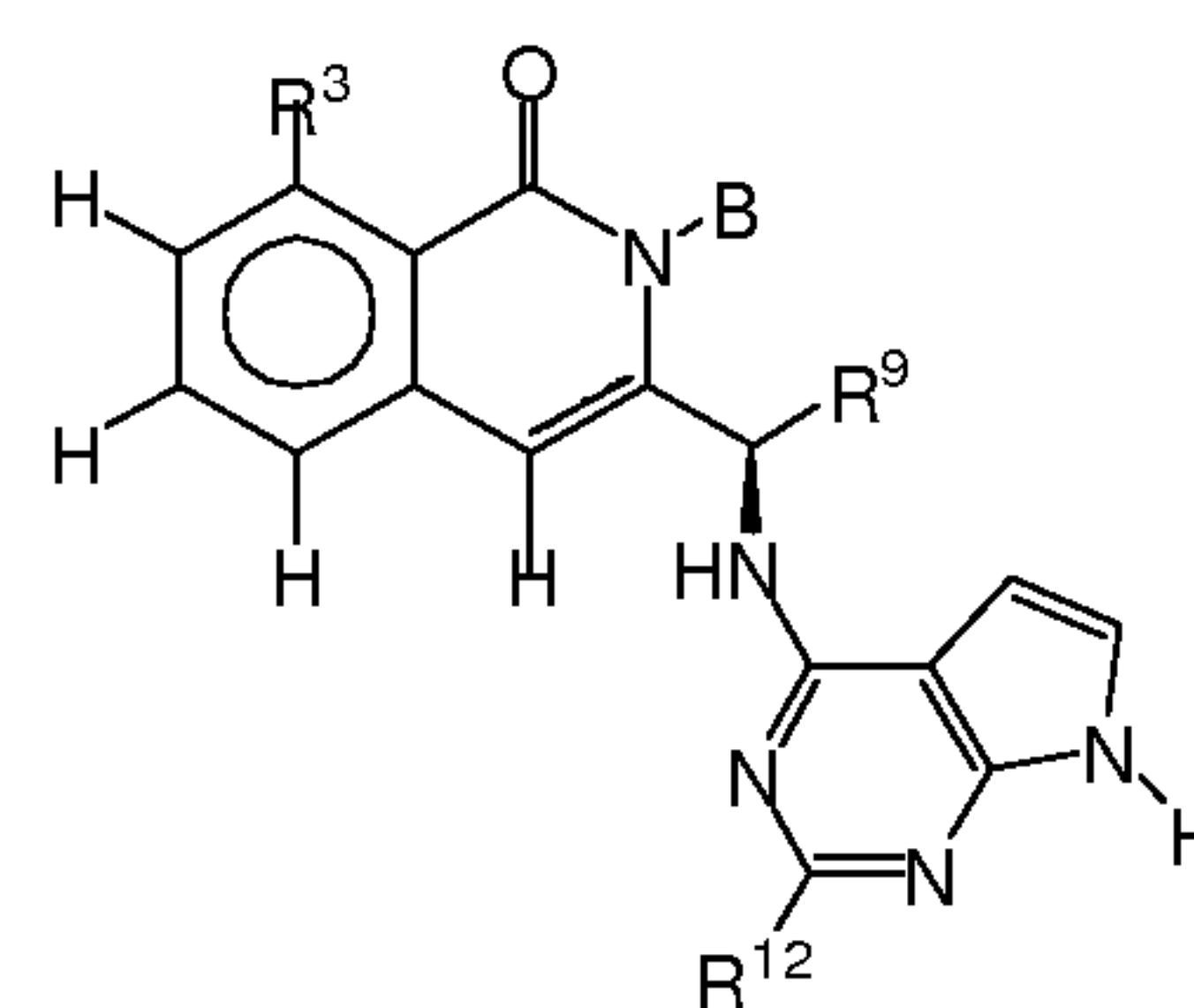
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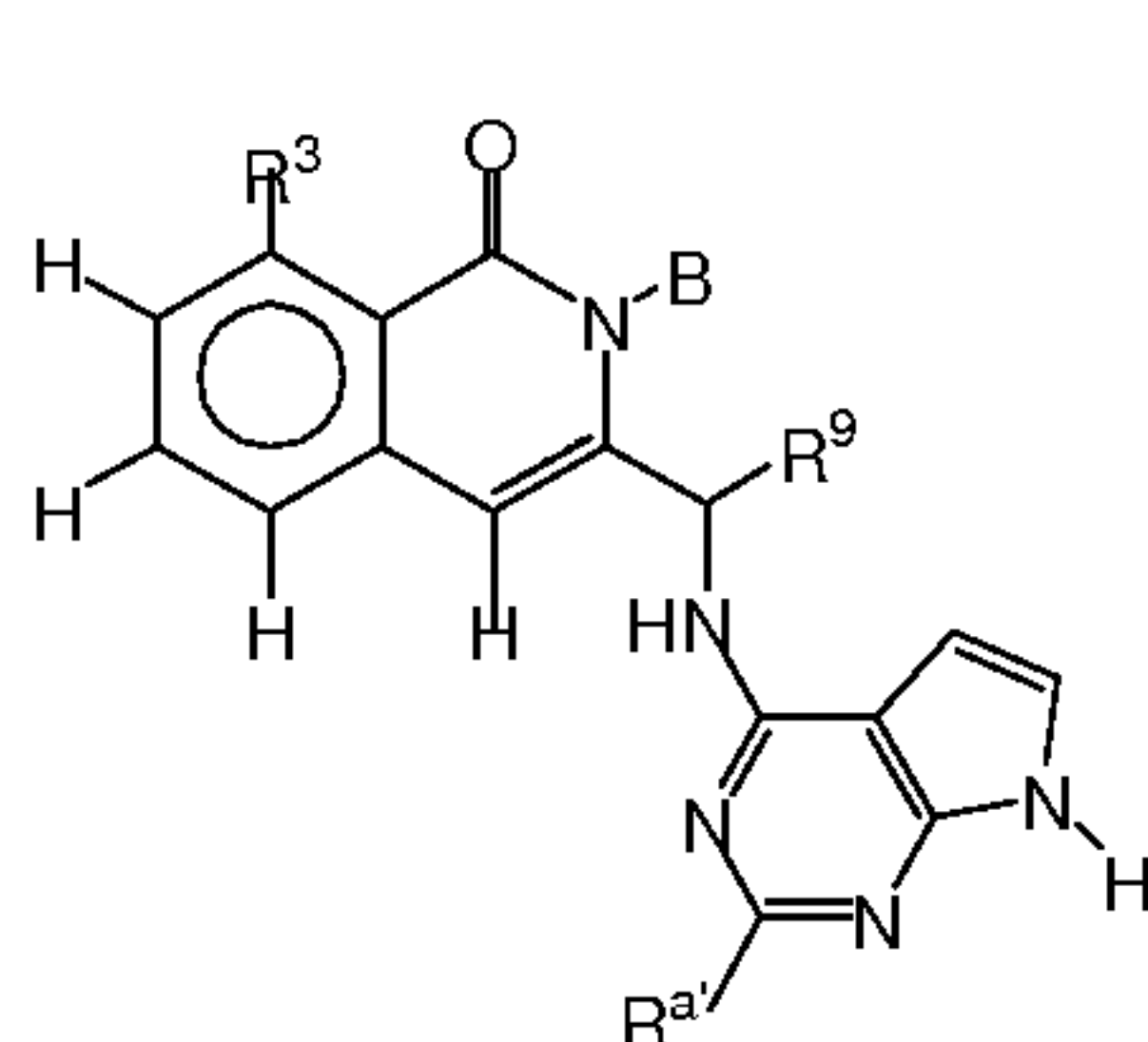
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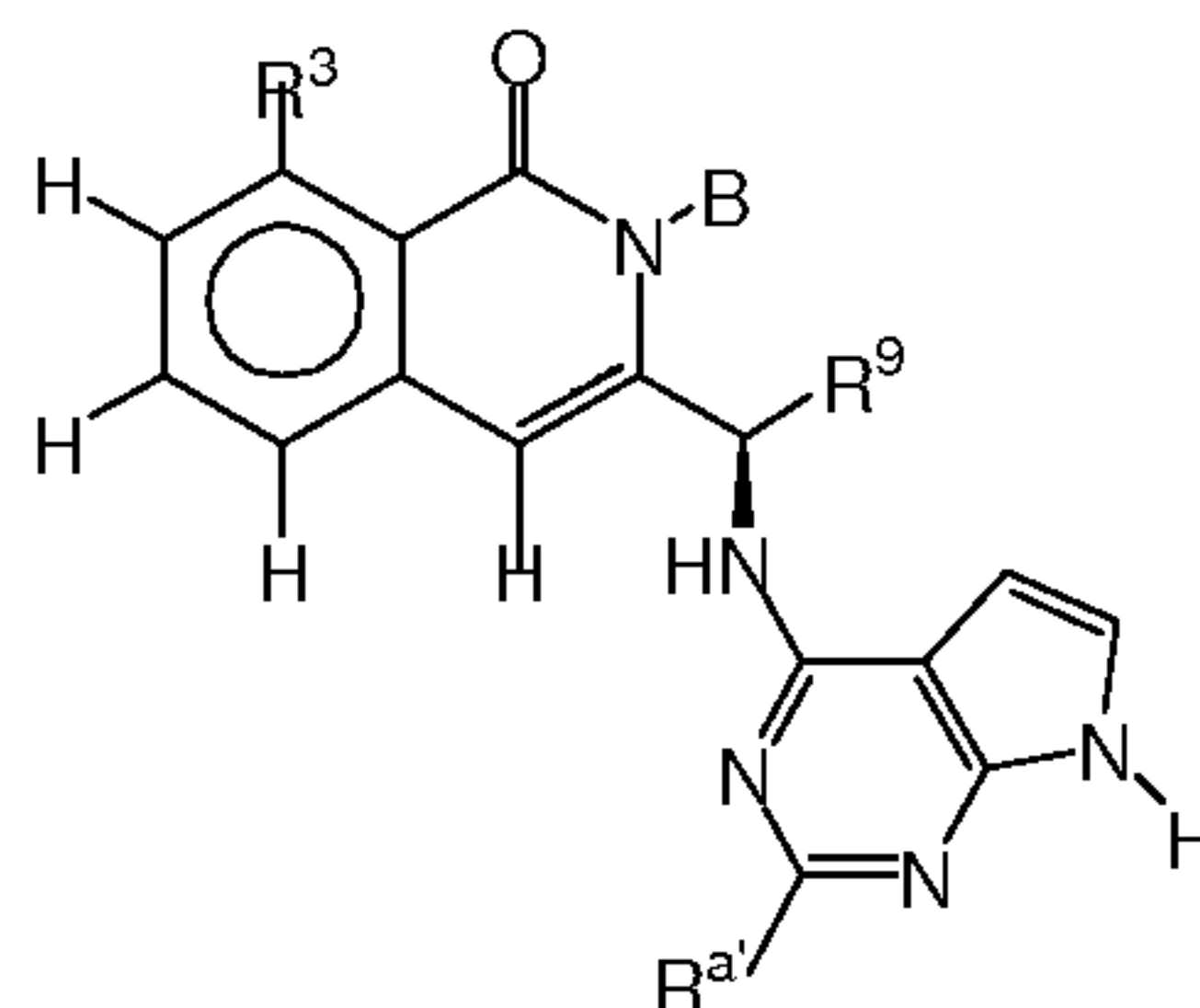
Formula XII-A1



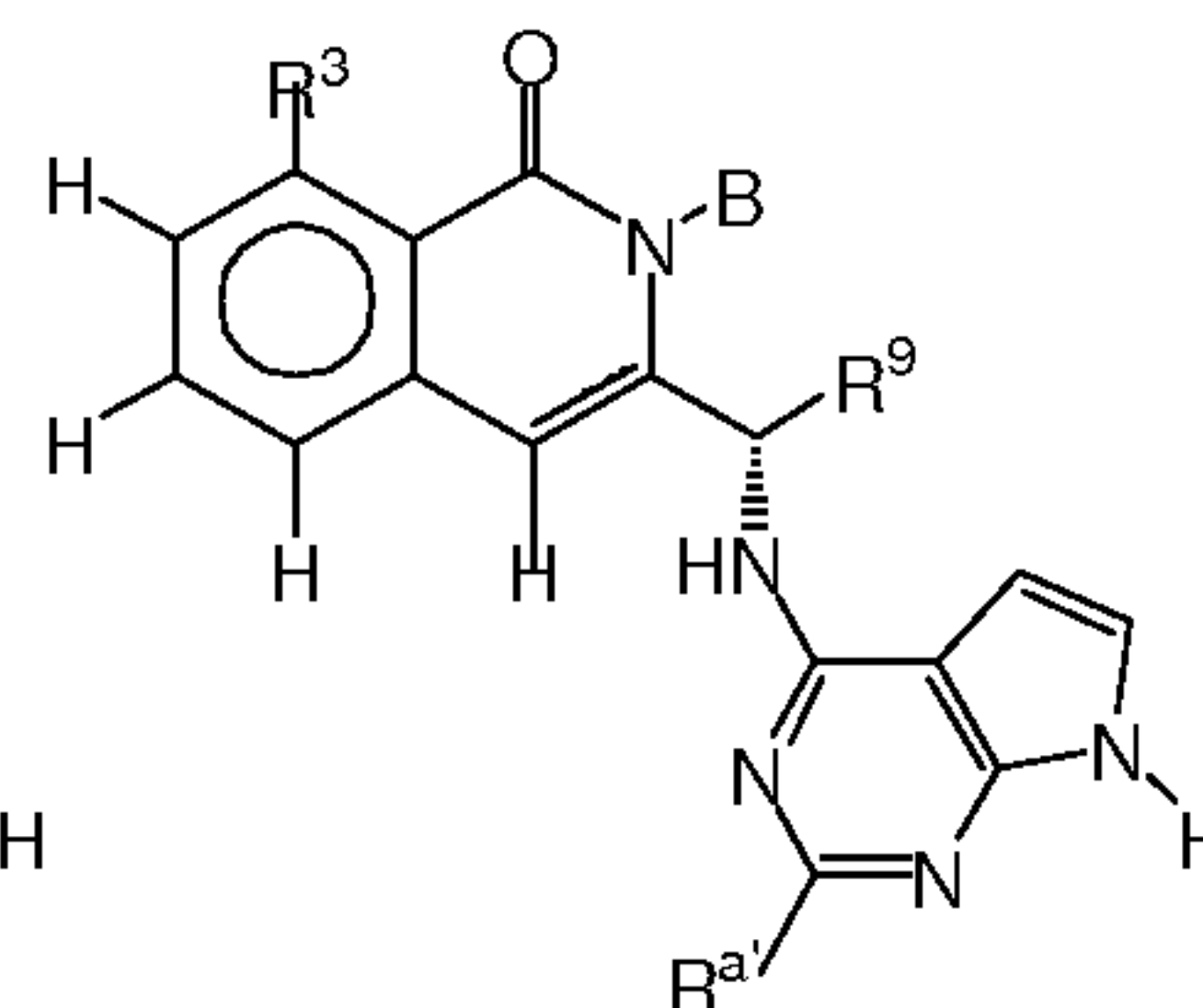
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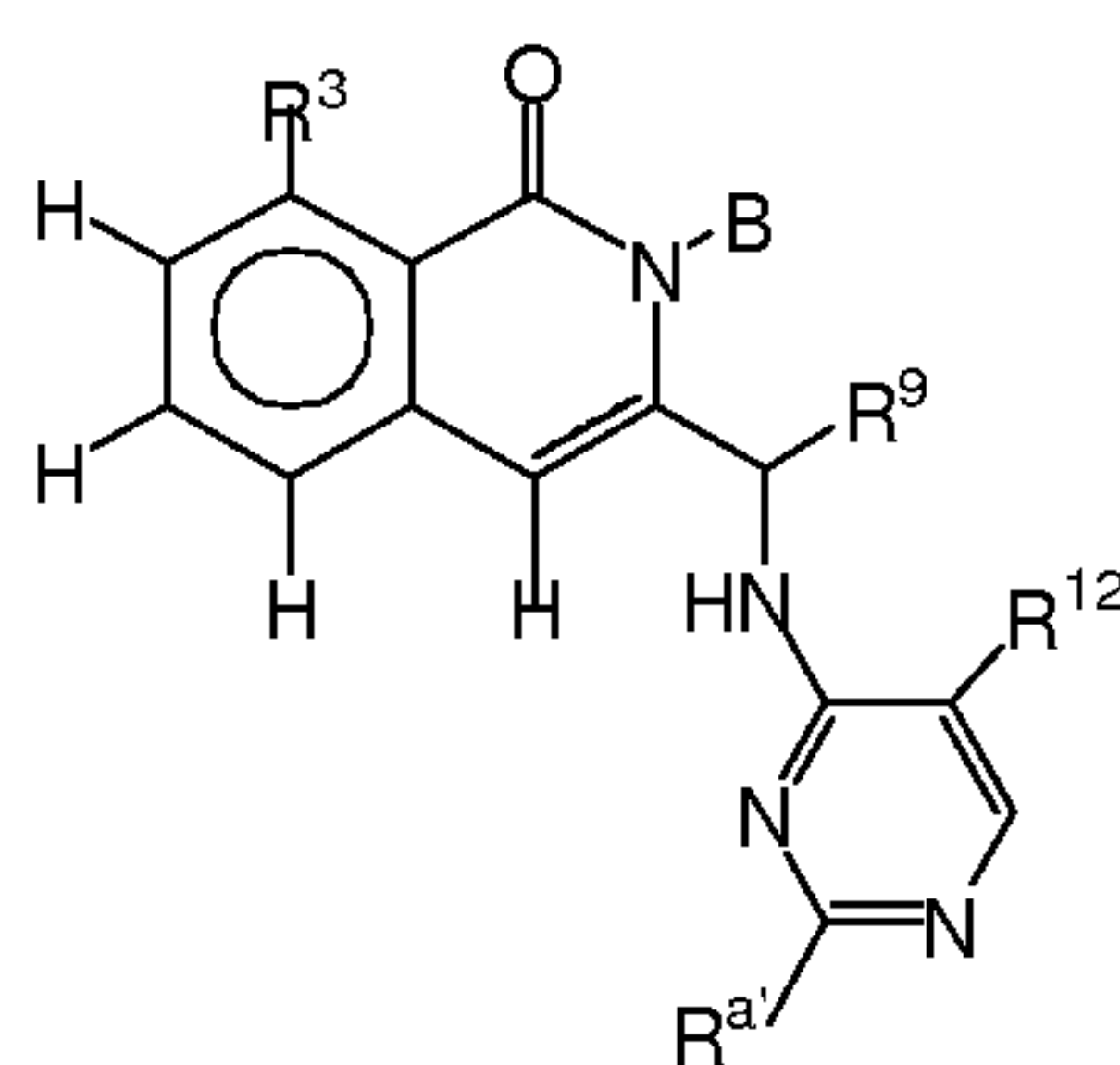
Formula XIII-A



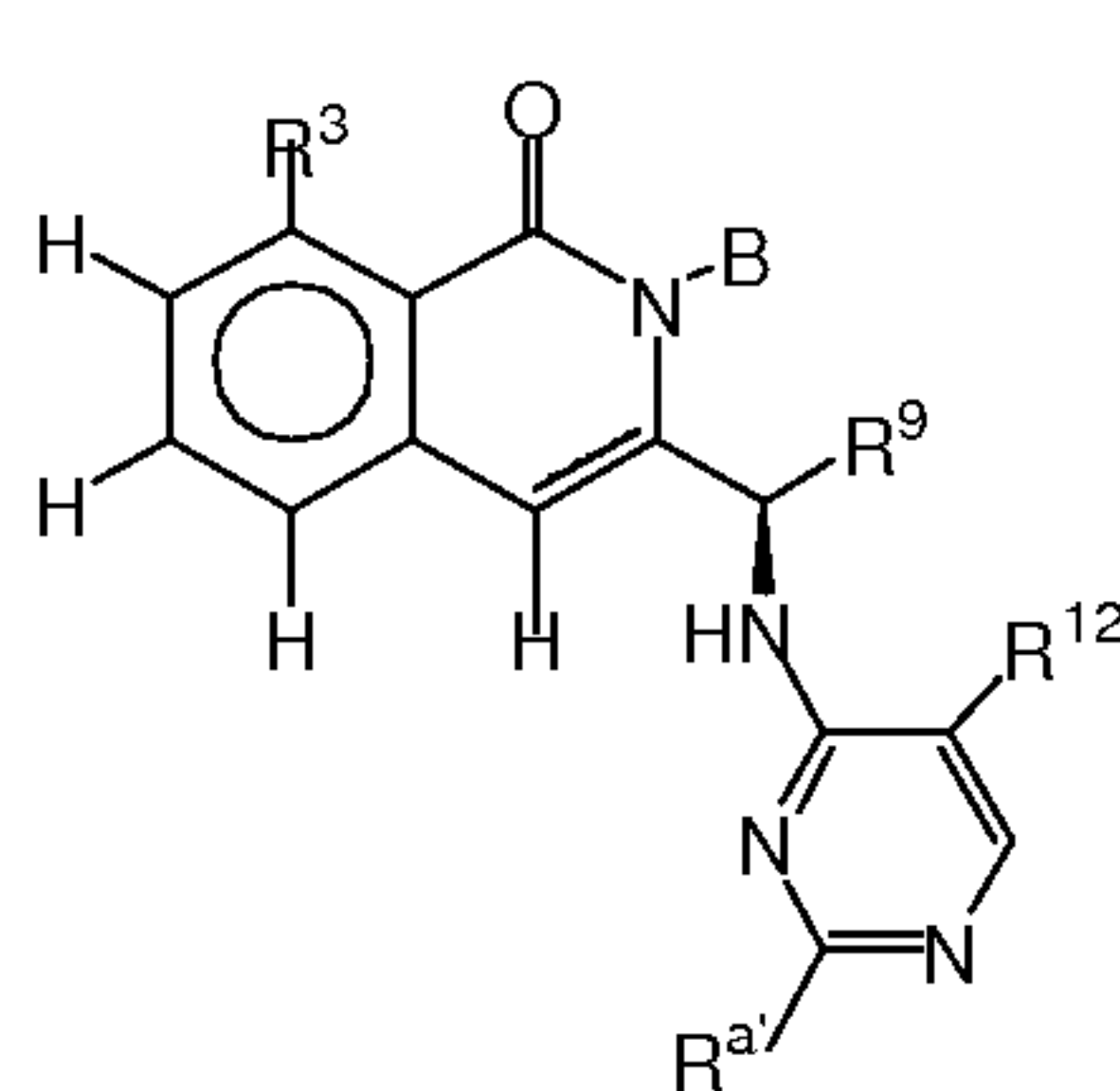
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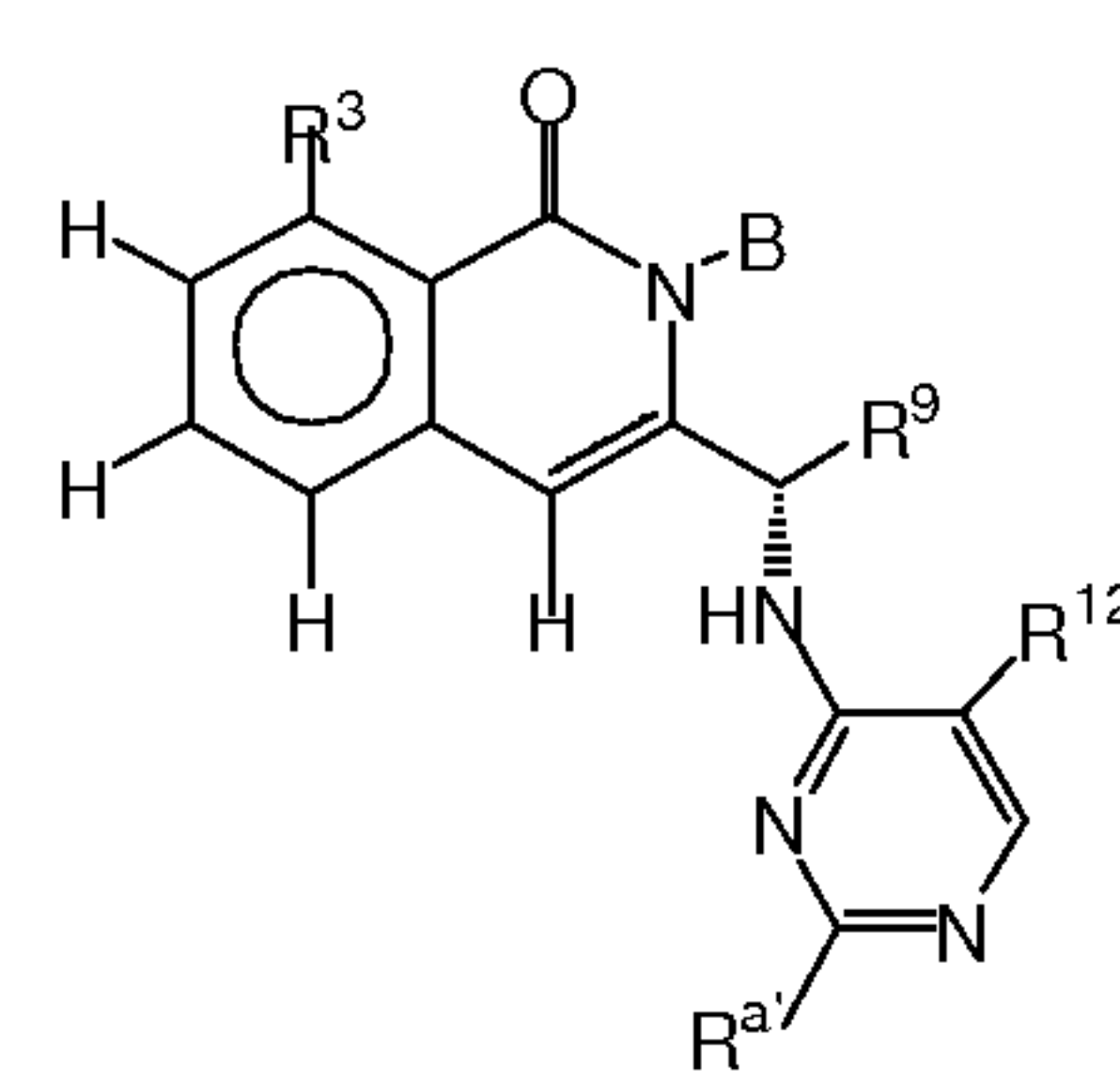
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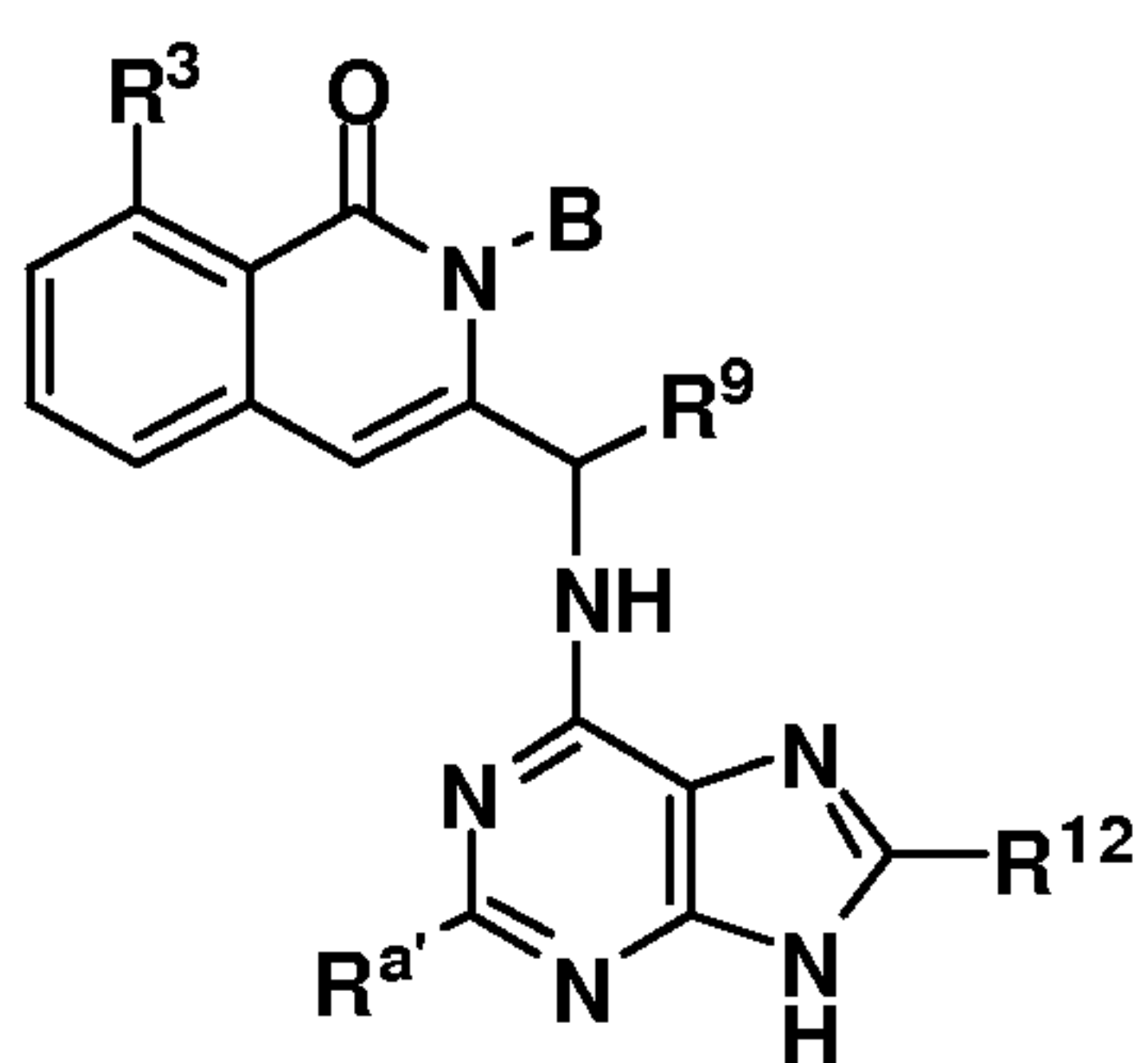
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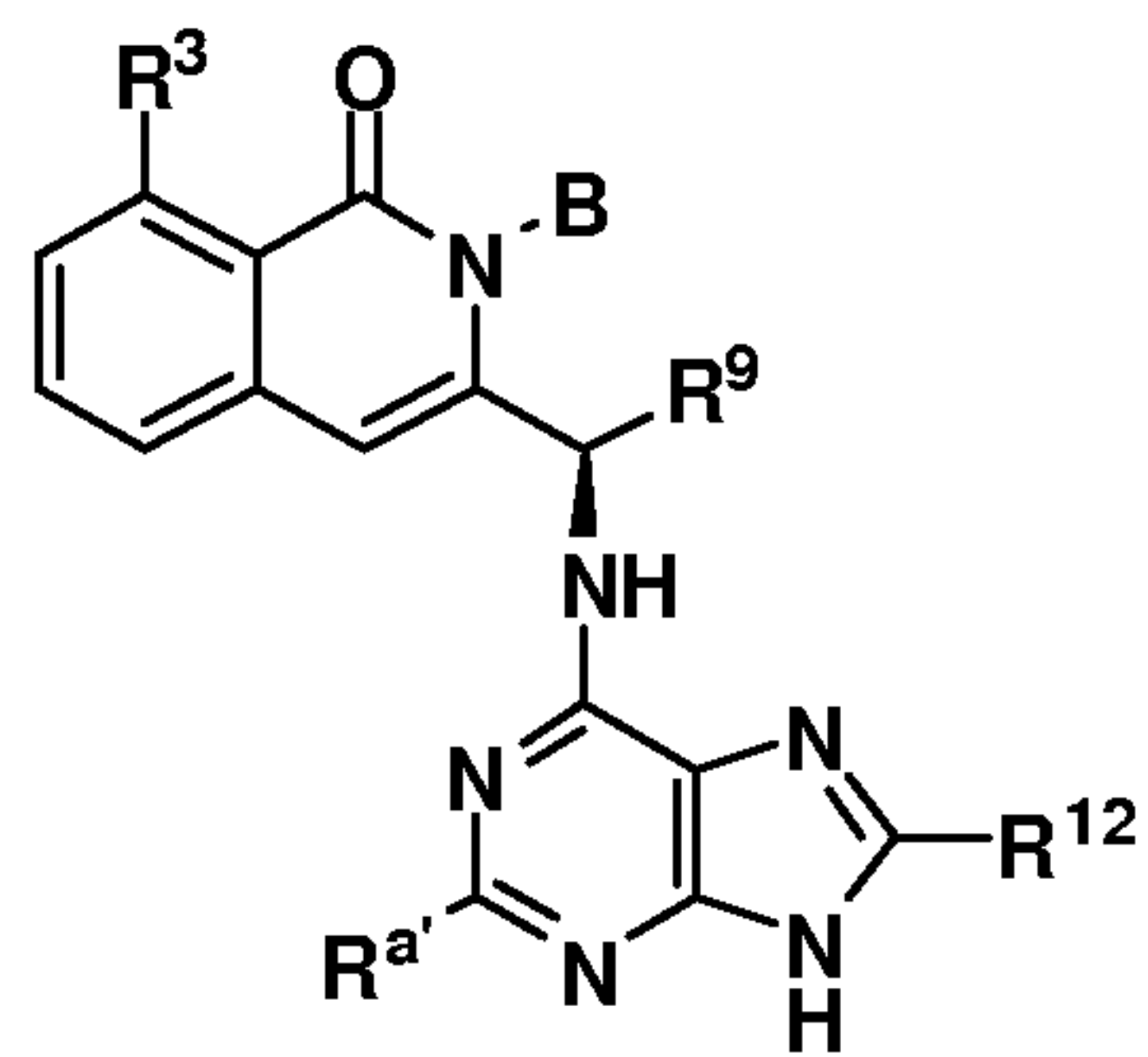
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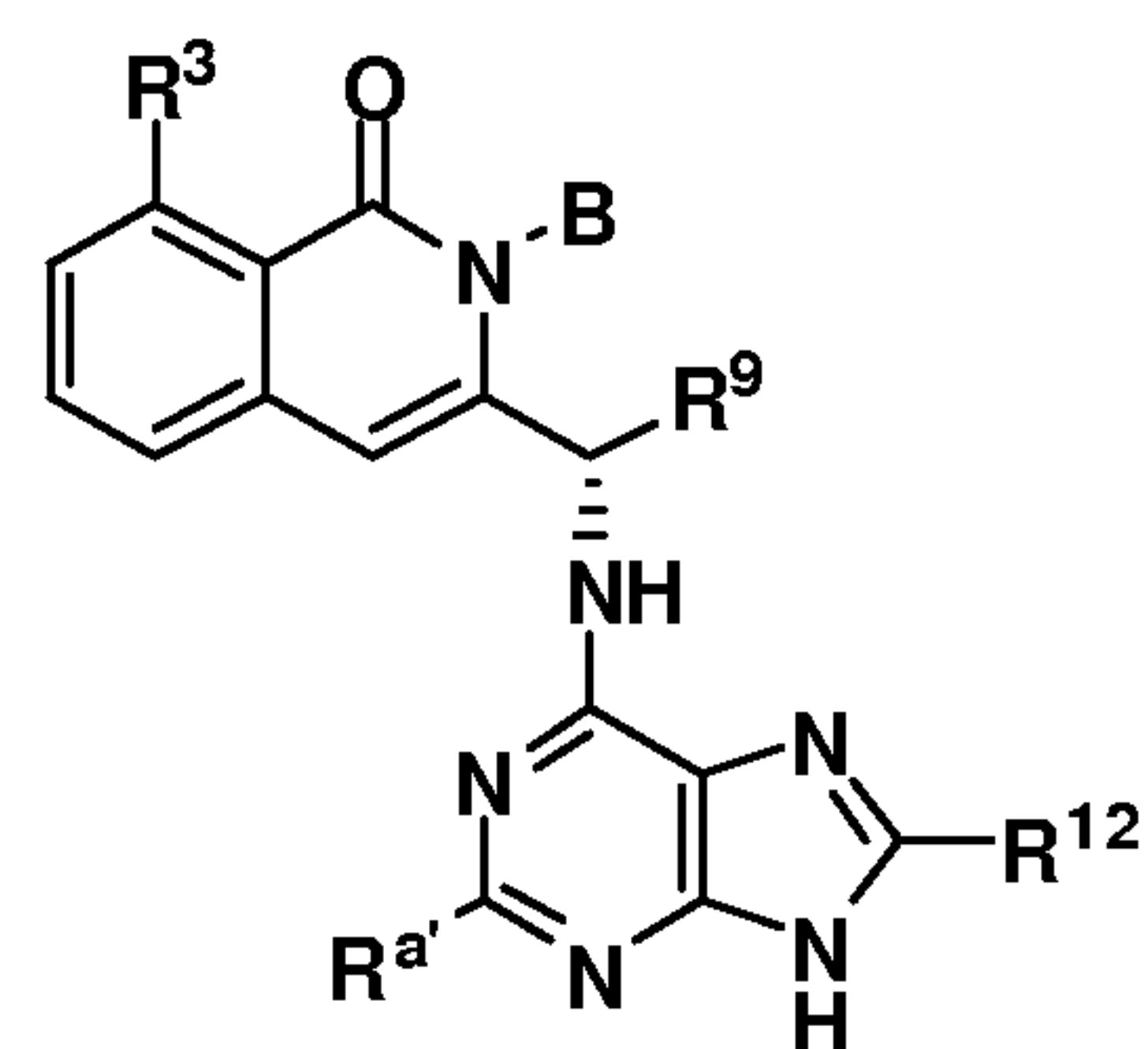
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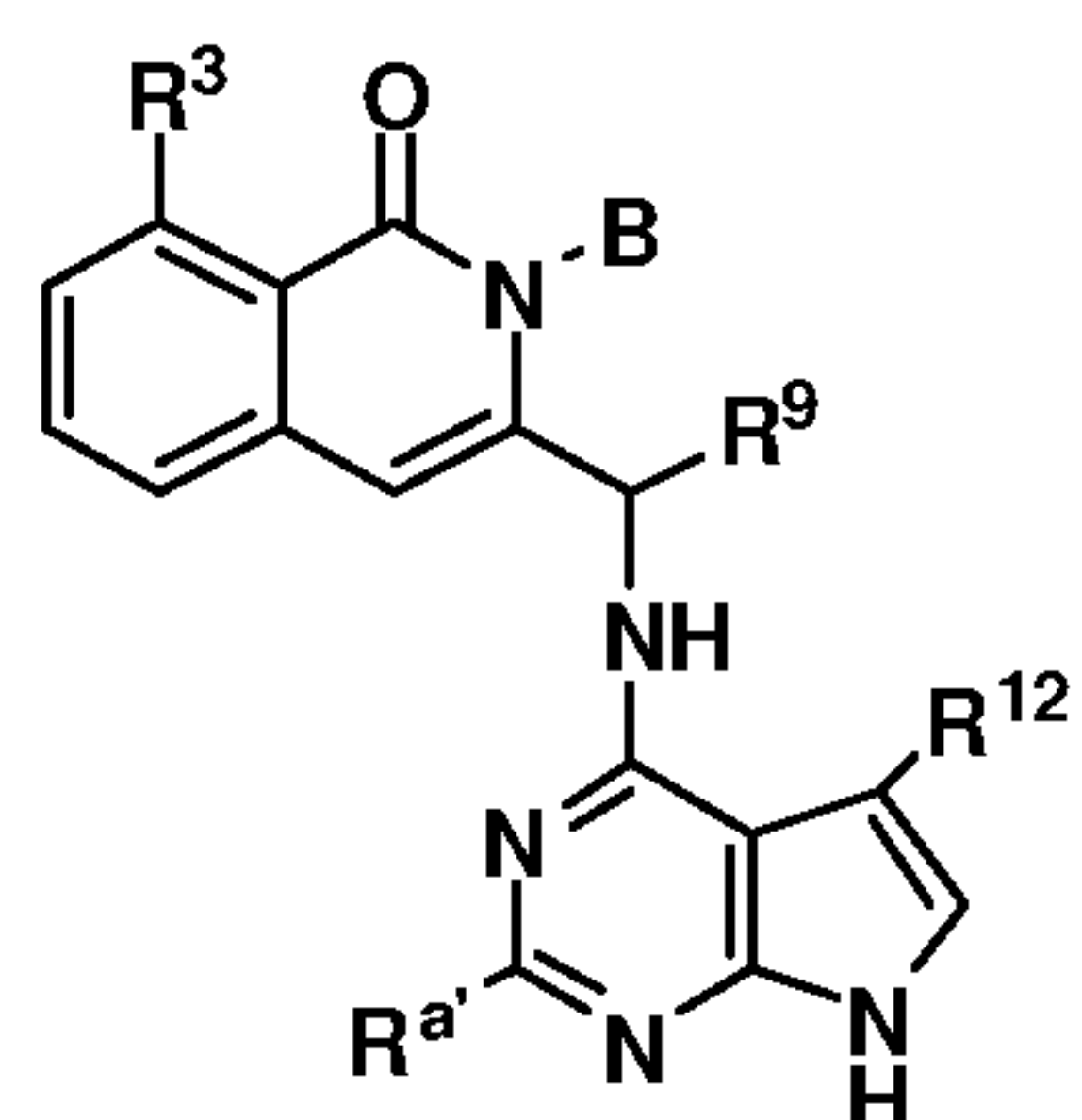
Formula XV-A



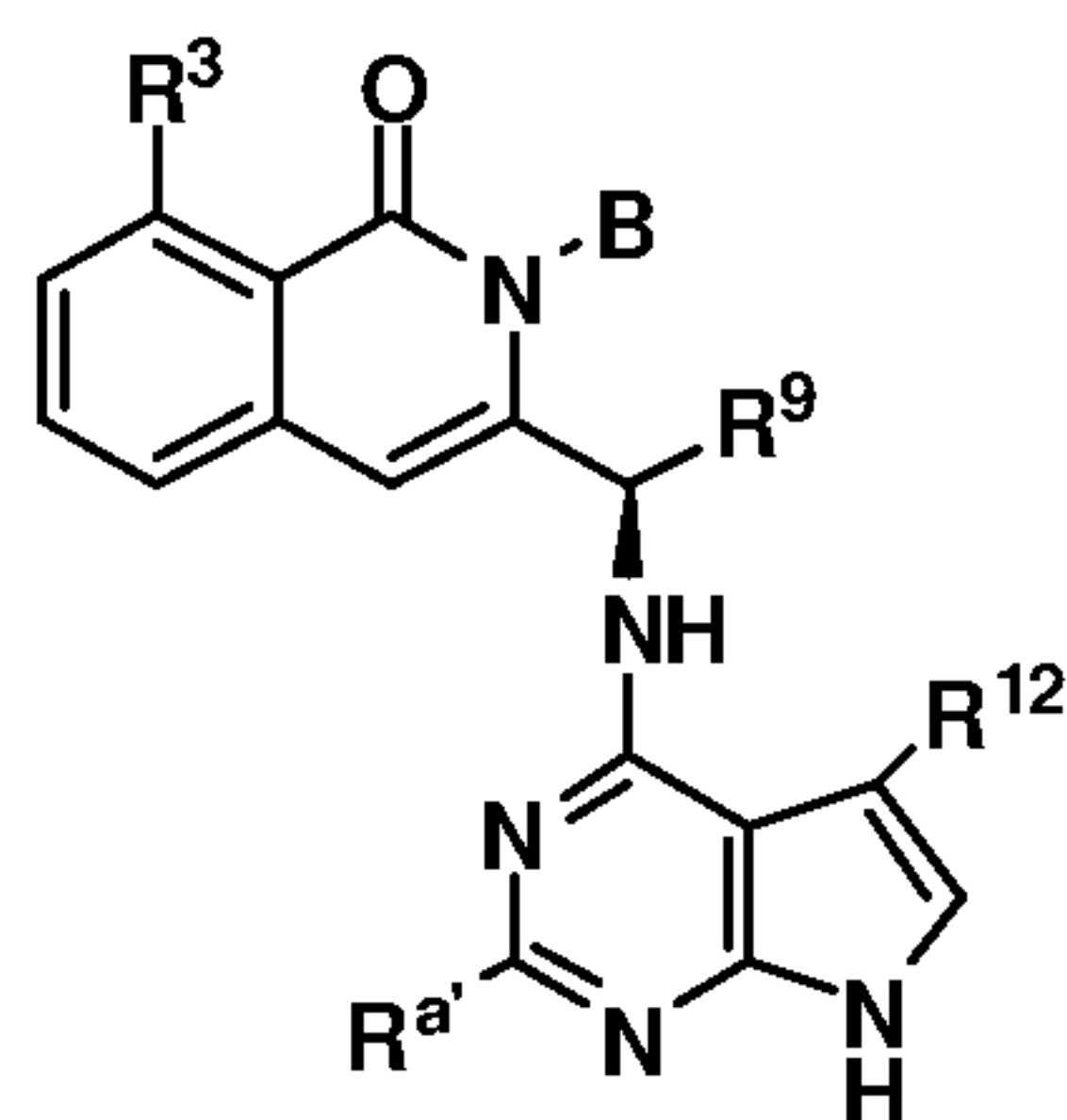
Formula XV-A1



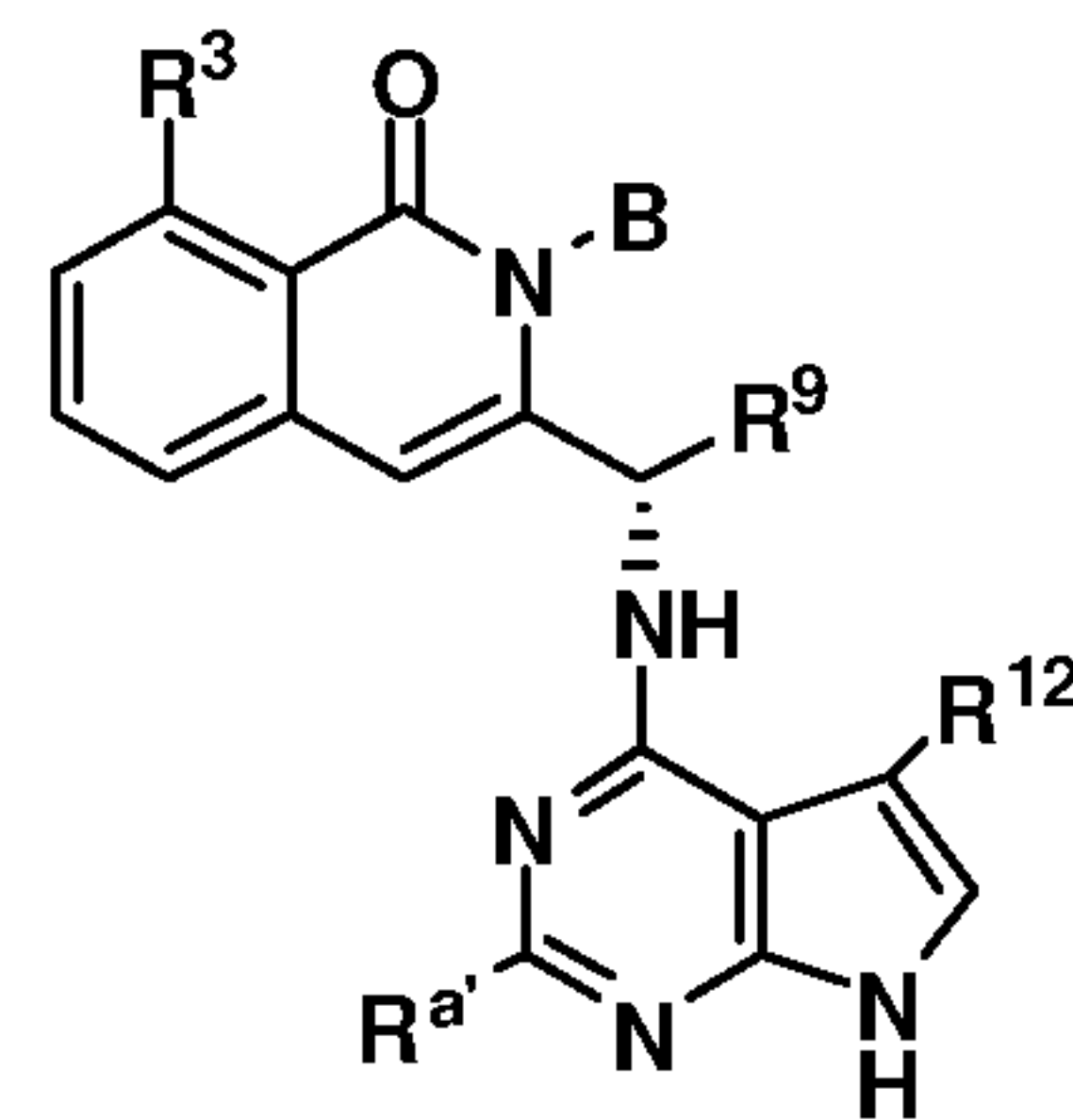
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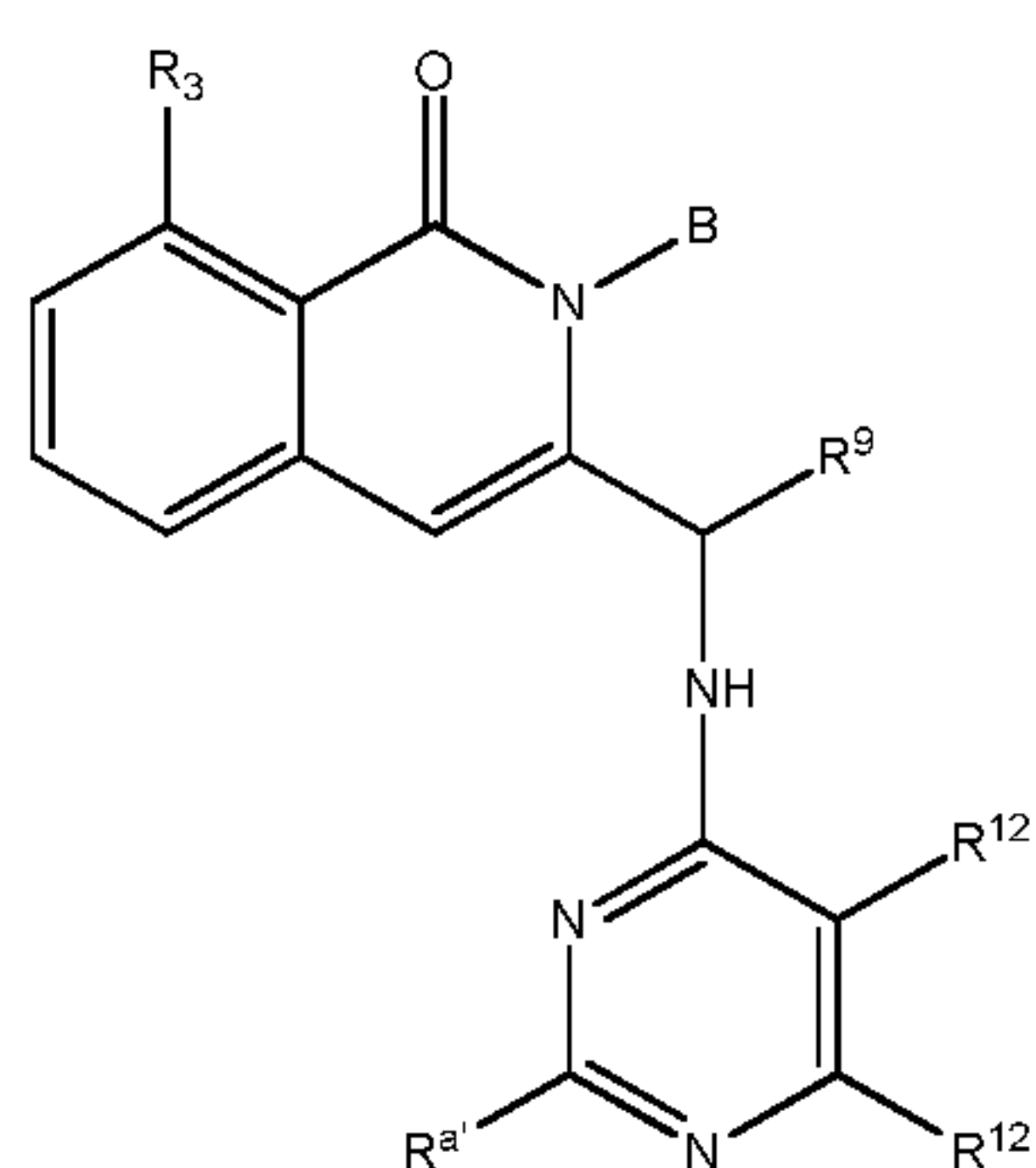
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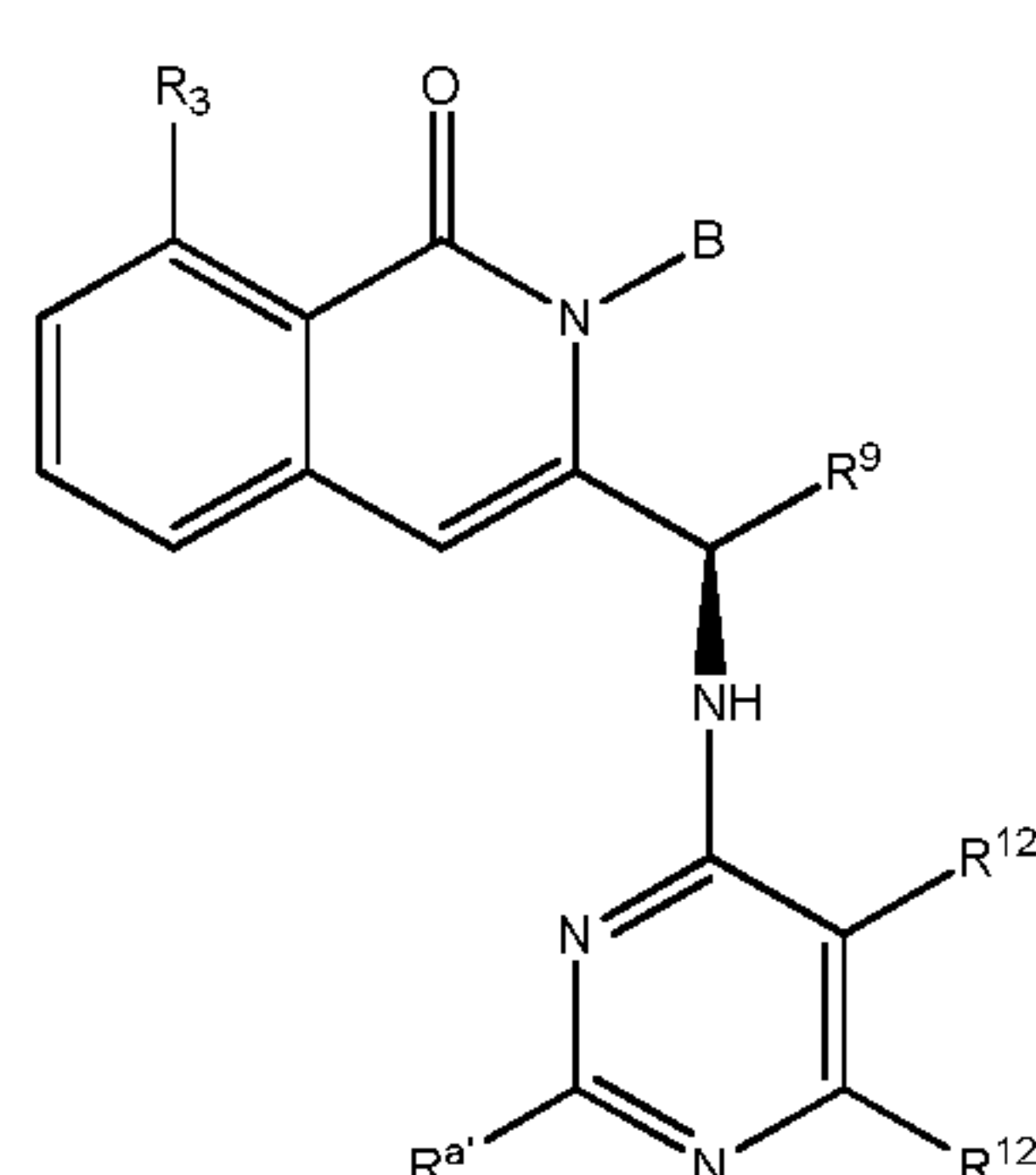
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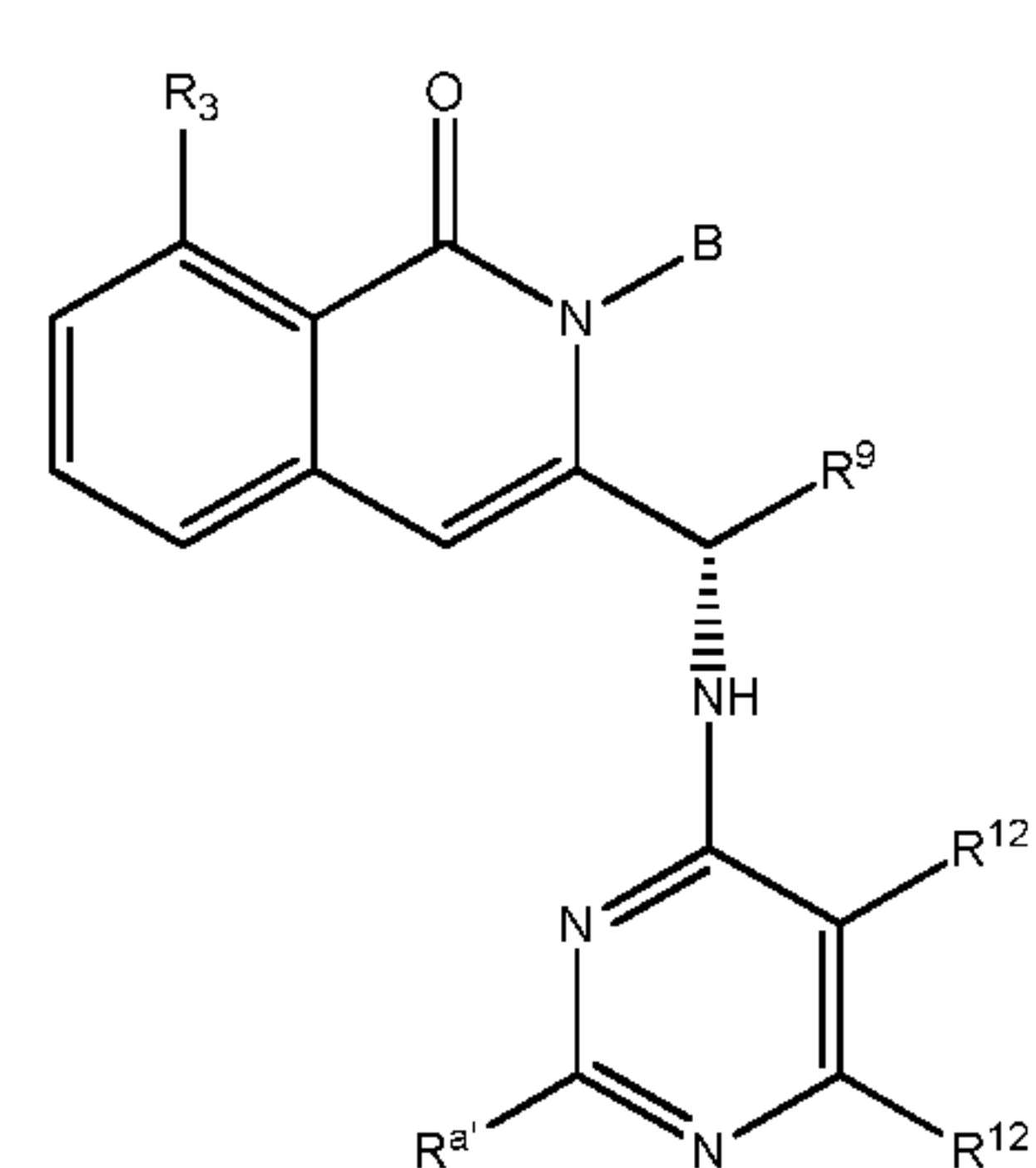
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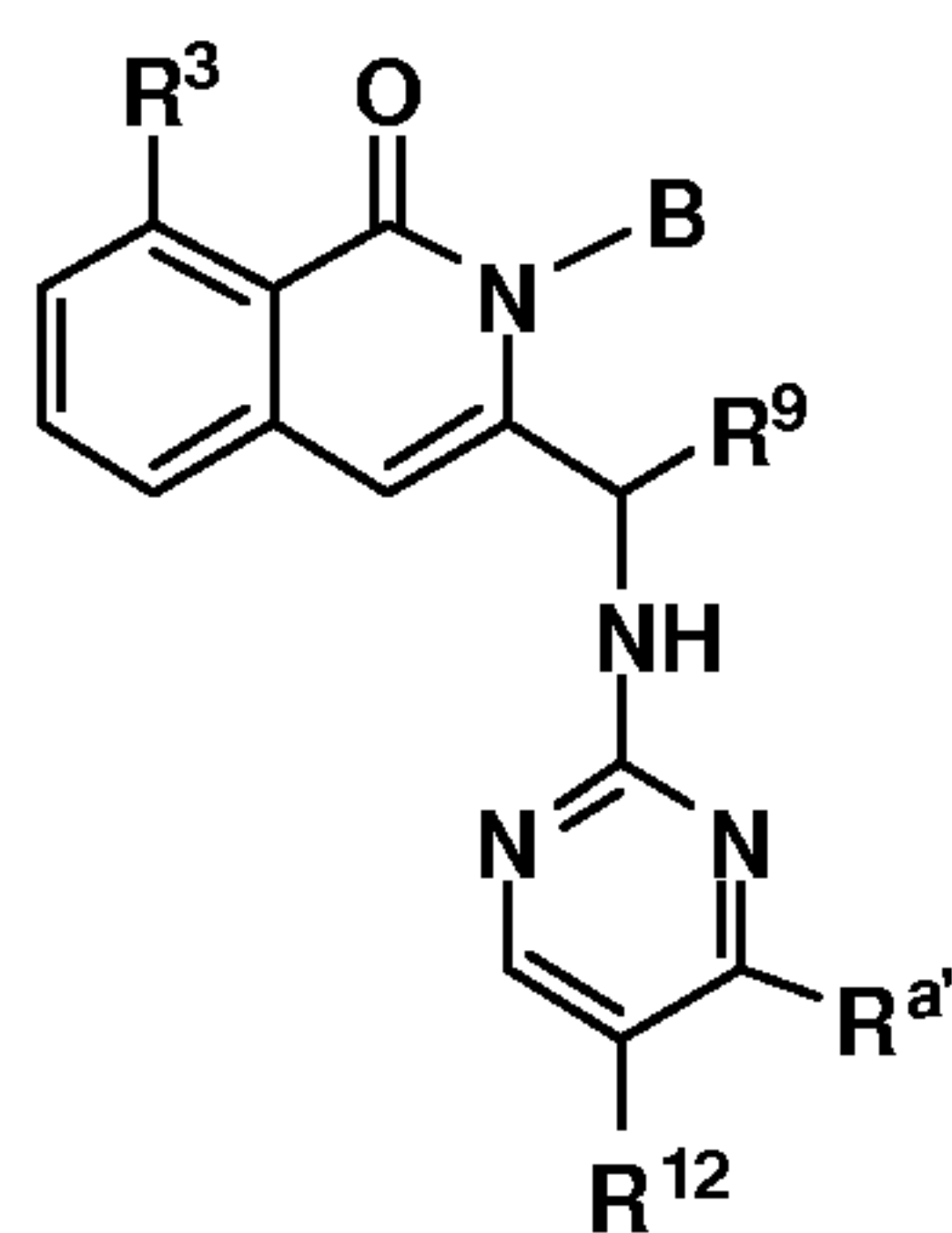
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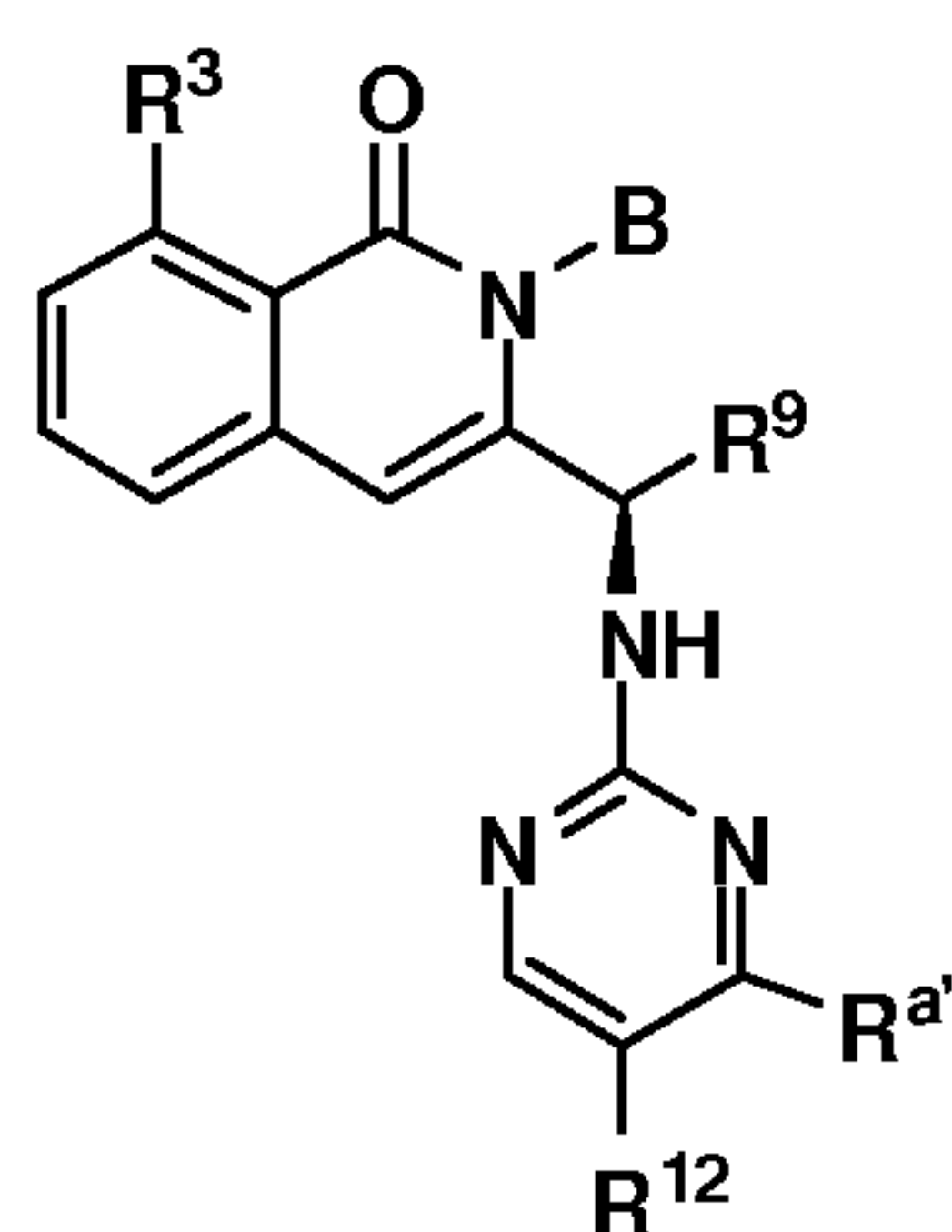
Formula XVII-A1



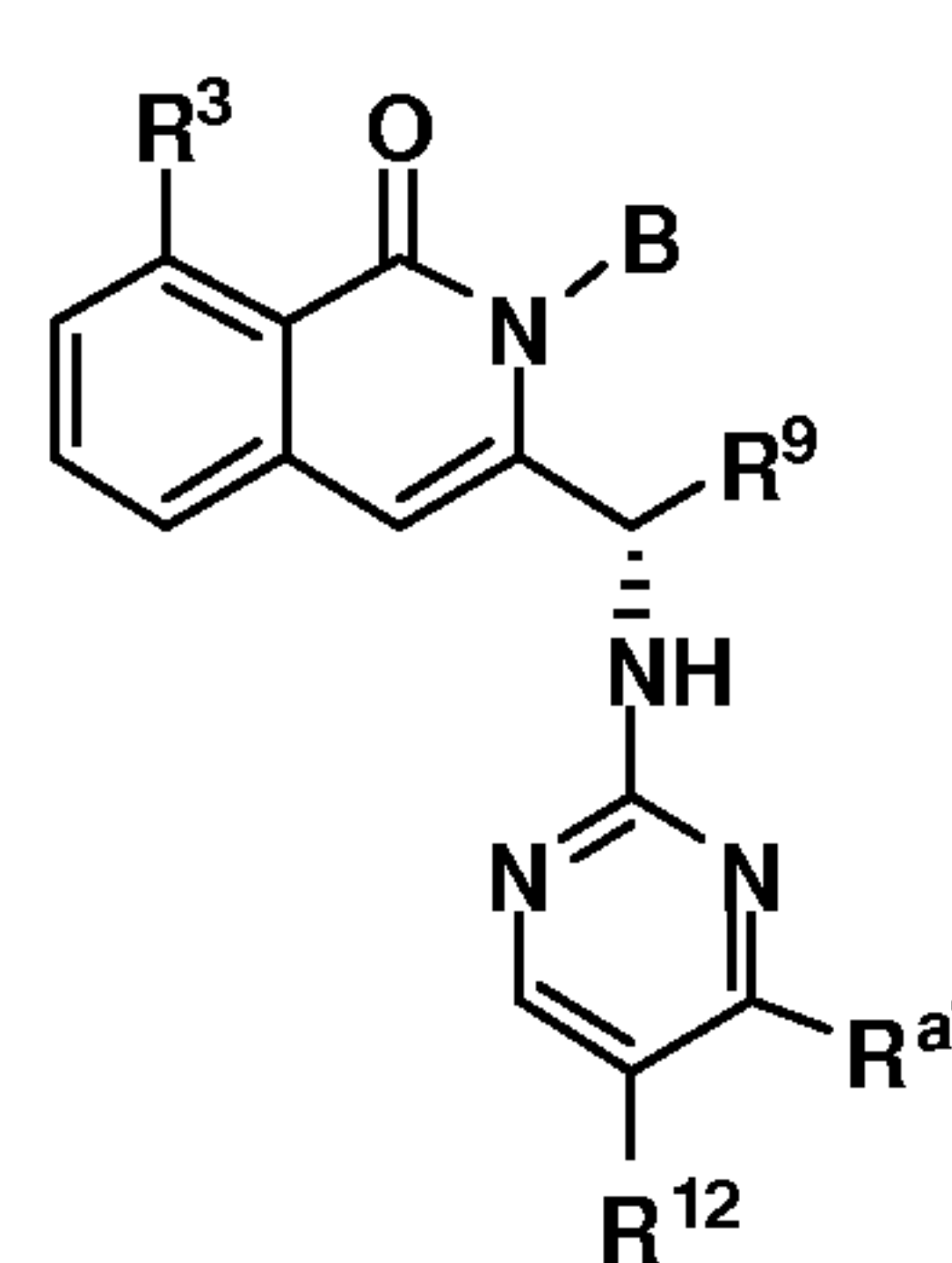
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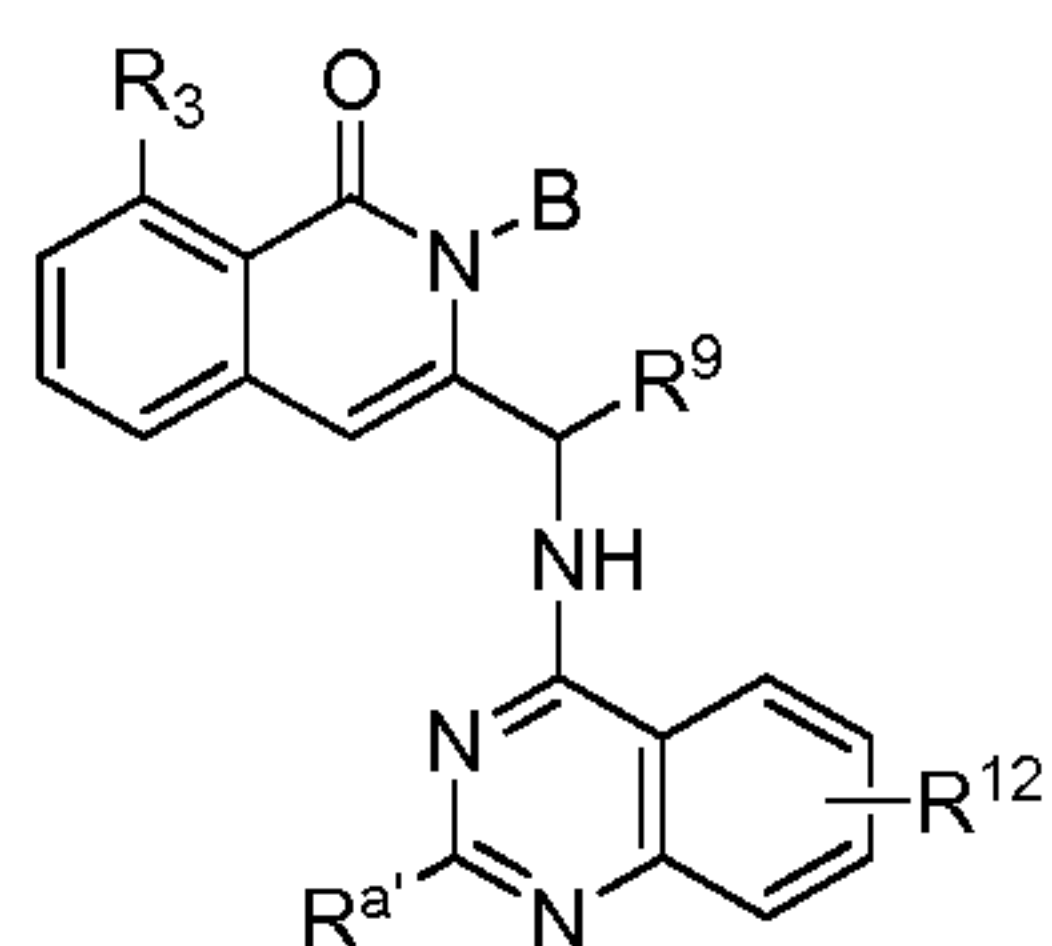
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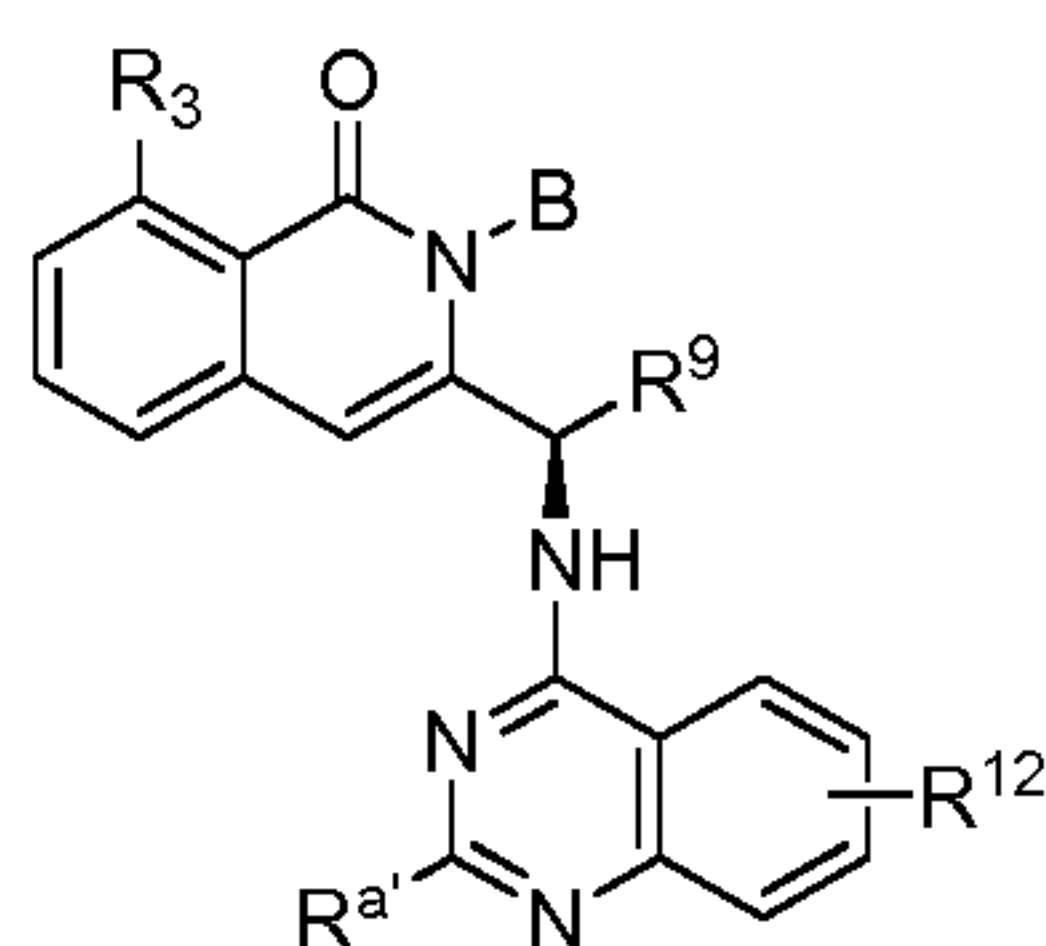
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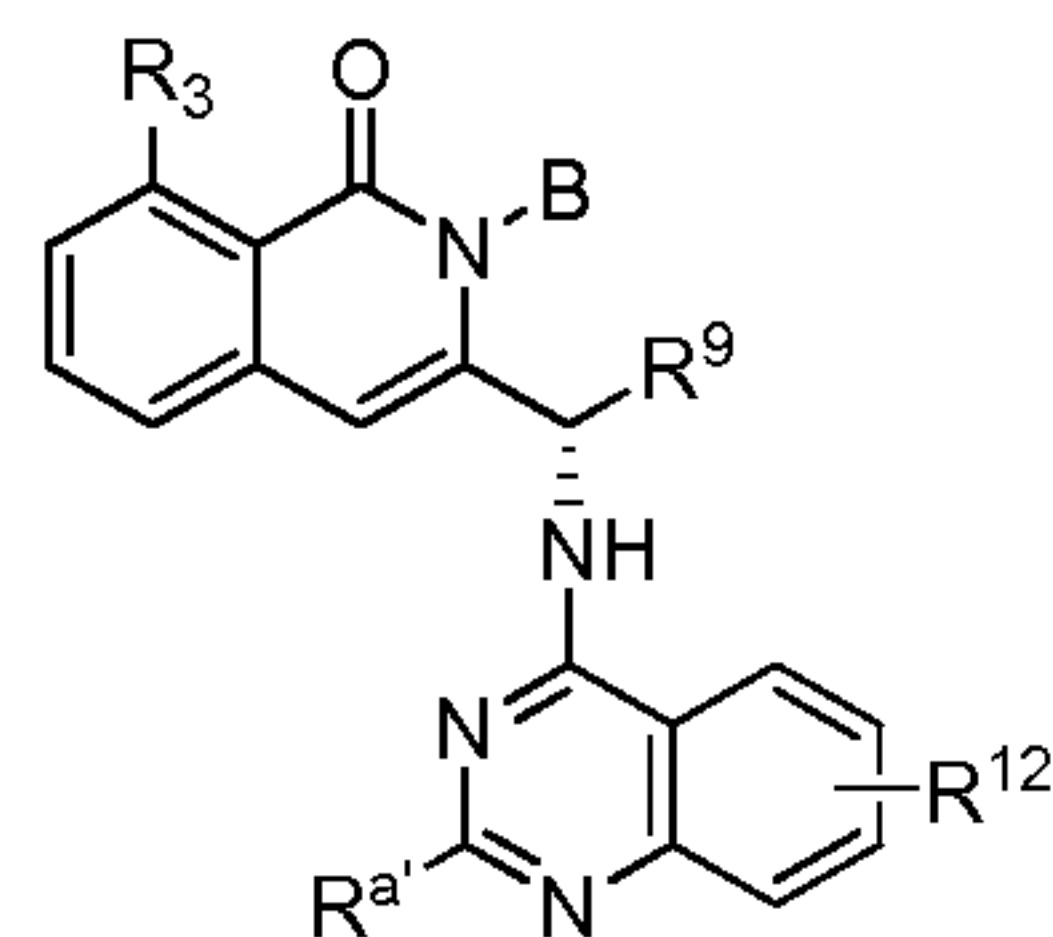
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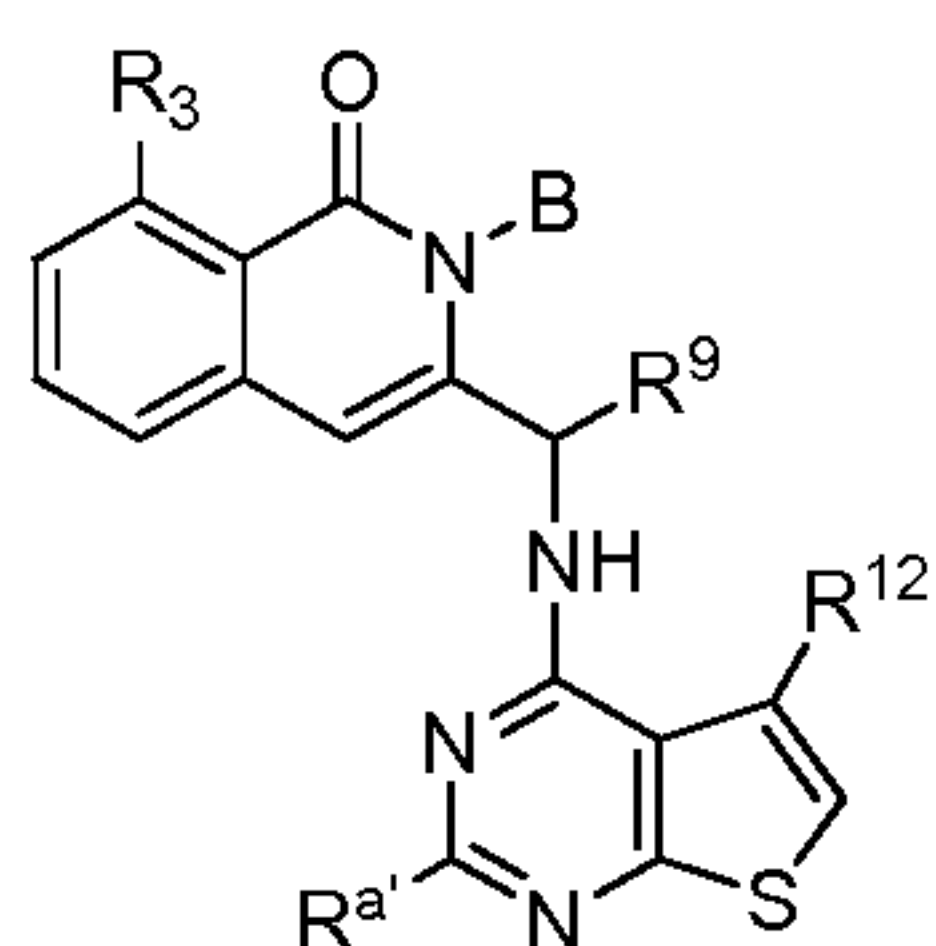
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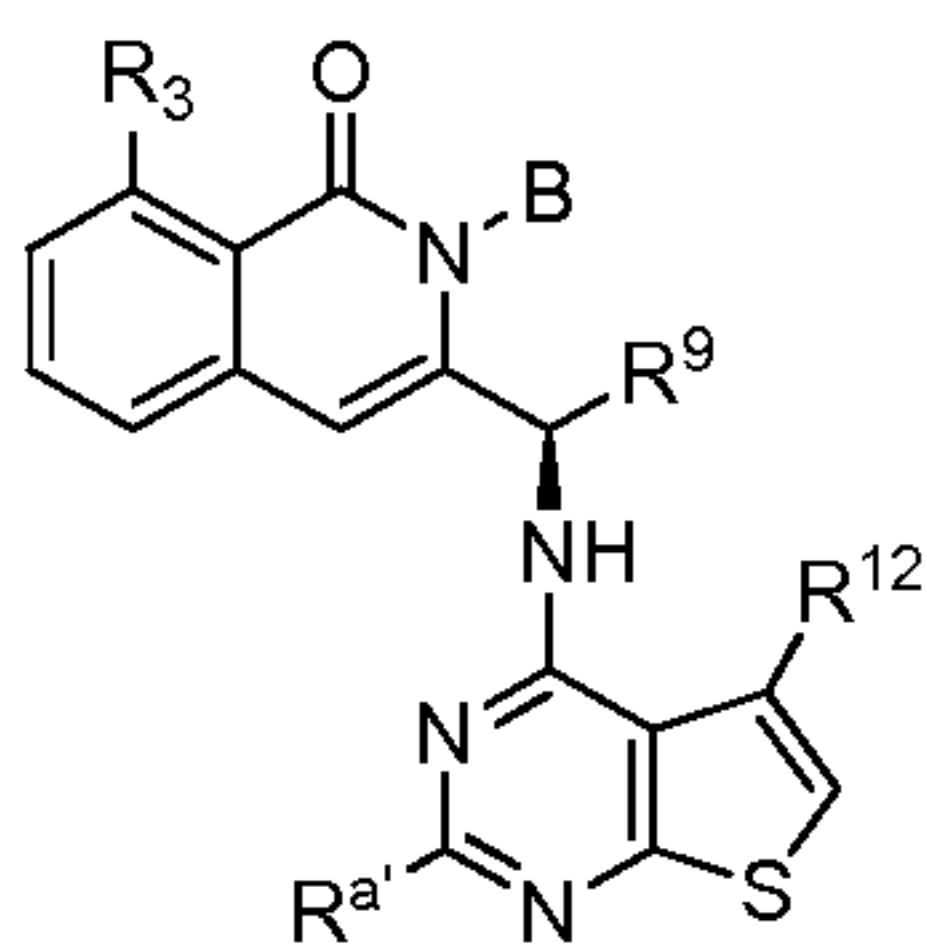
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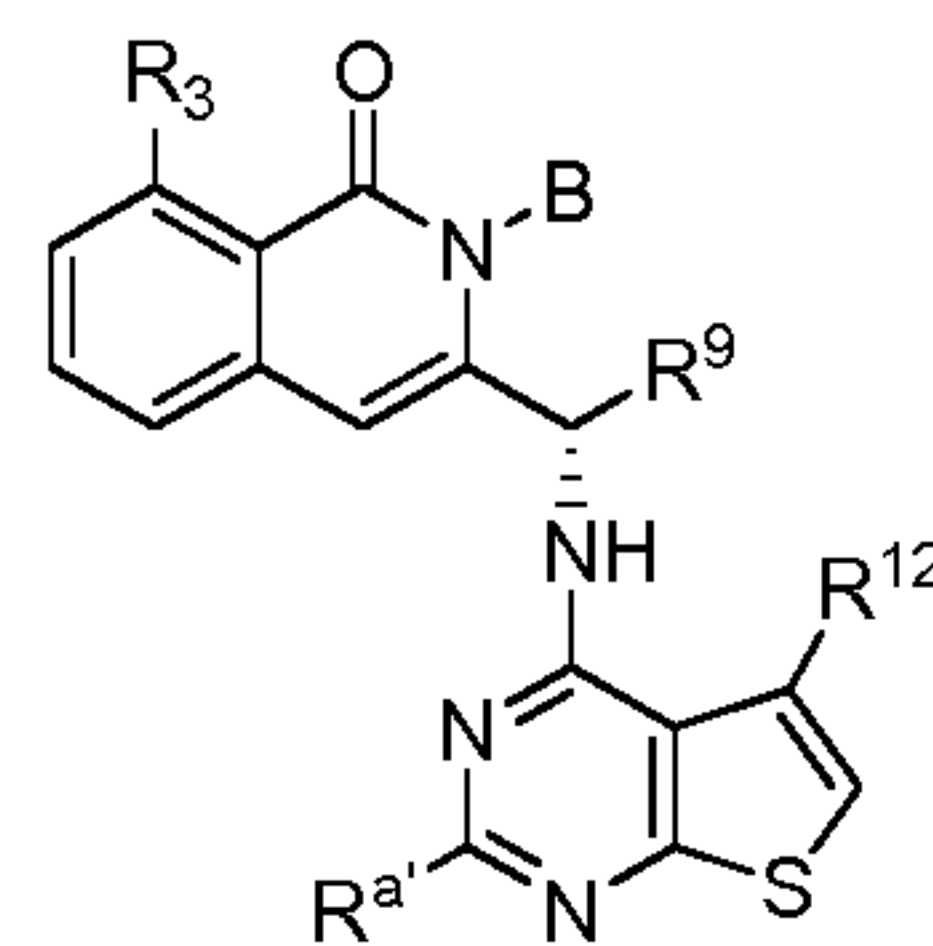
Formula XIX-A3



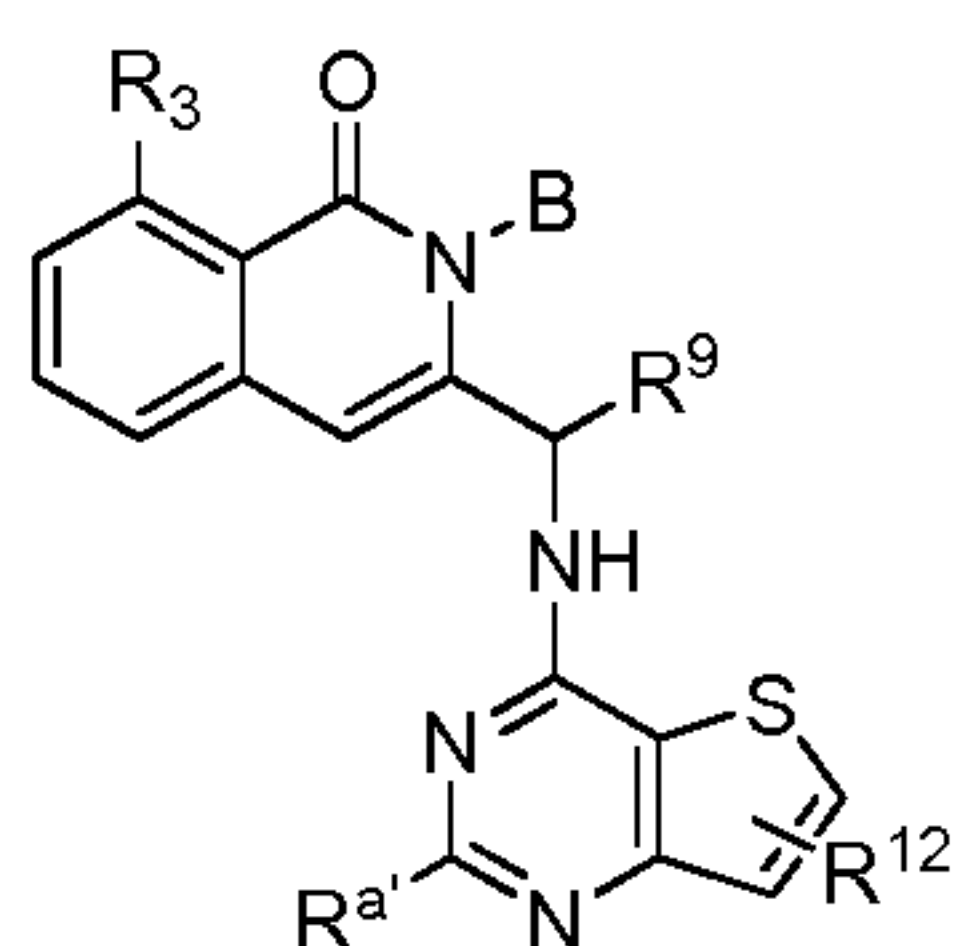
Formula XX-A



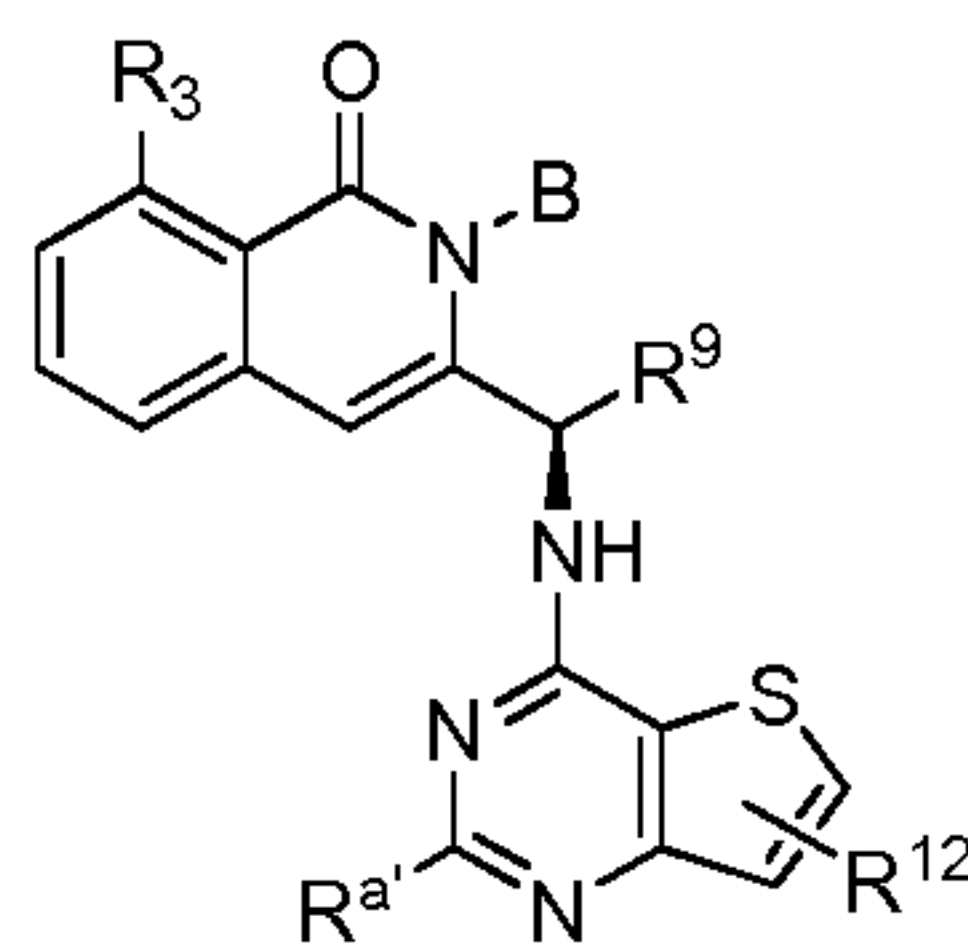
Formula XX-A2



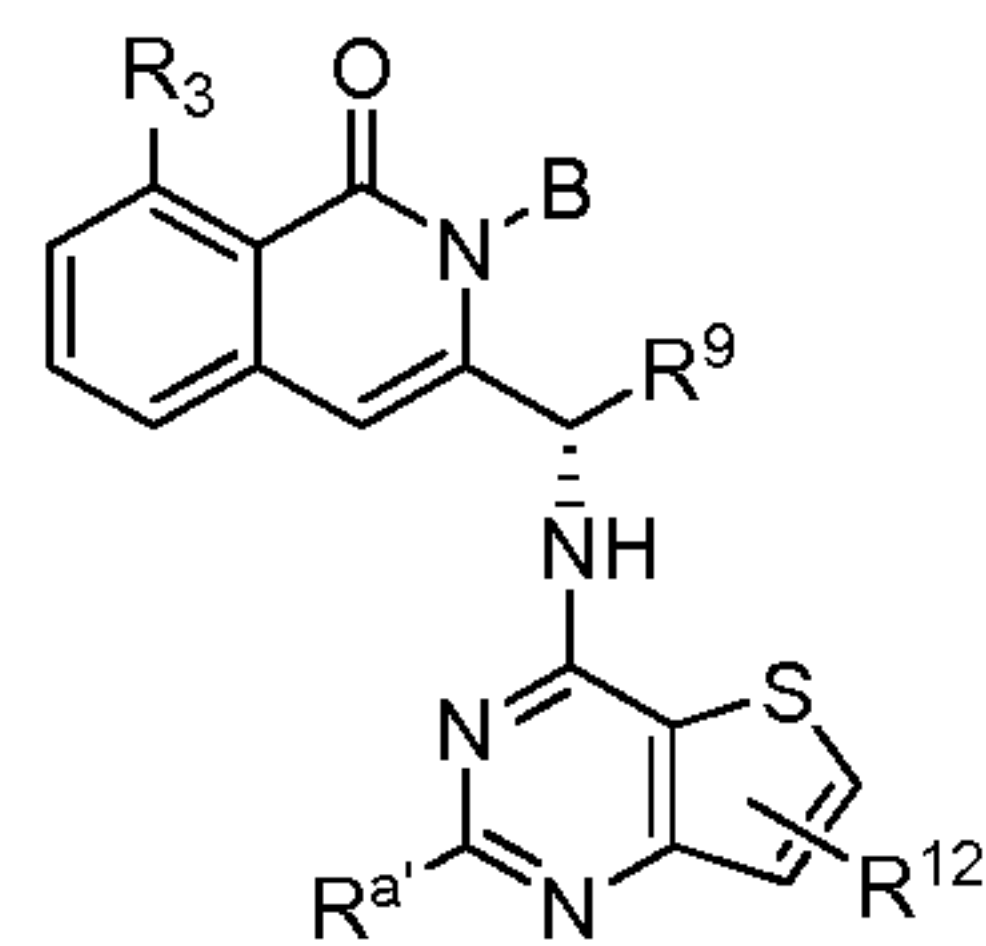
Formula XX-A3



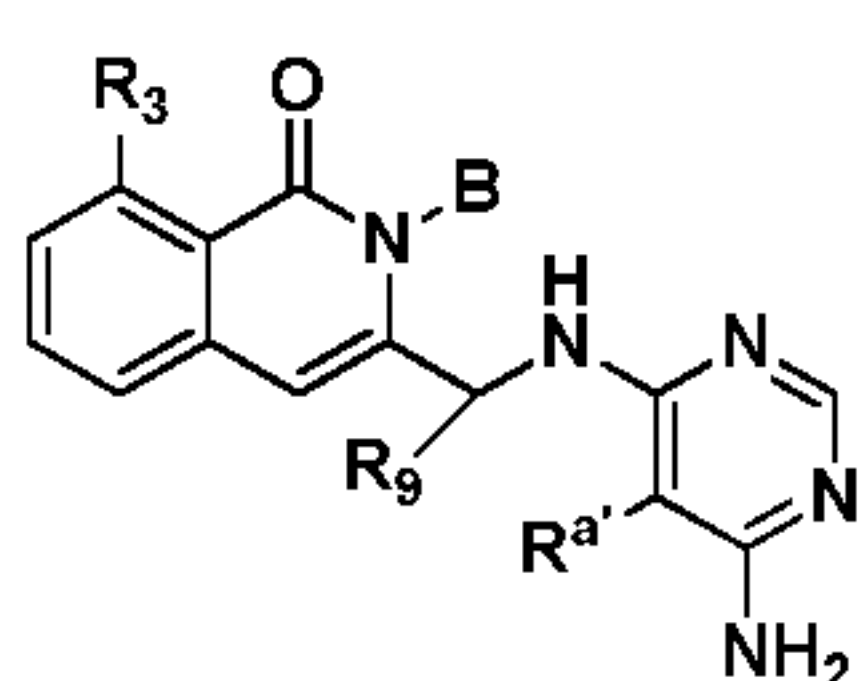
Formula XXI-A



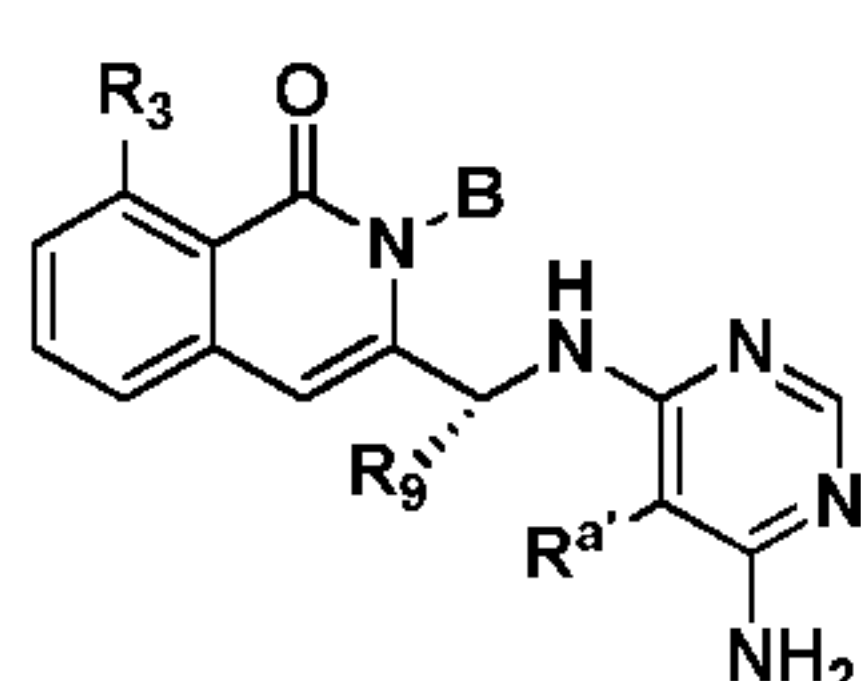
Formula XXI-A2



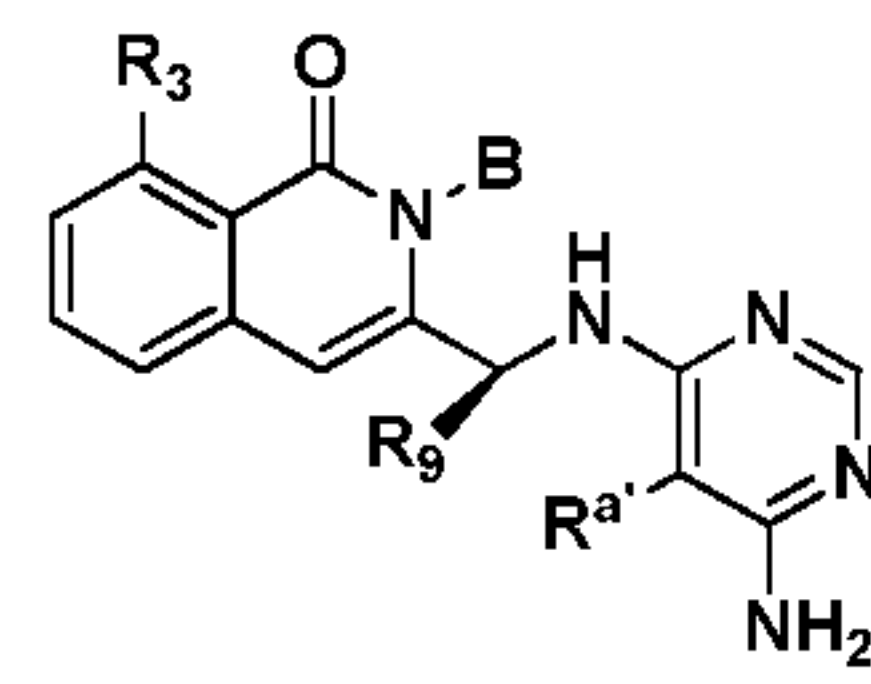
Formula XXI-A3



Formula XXII-A



Formula XXII-A2

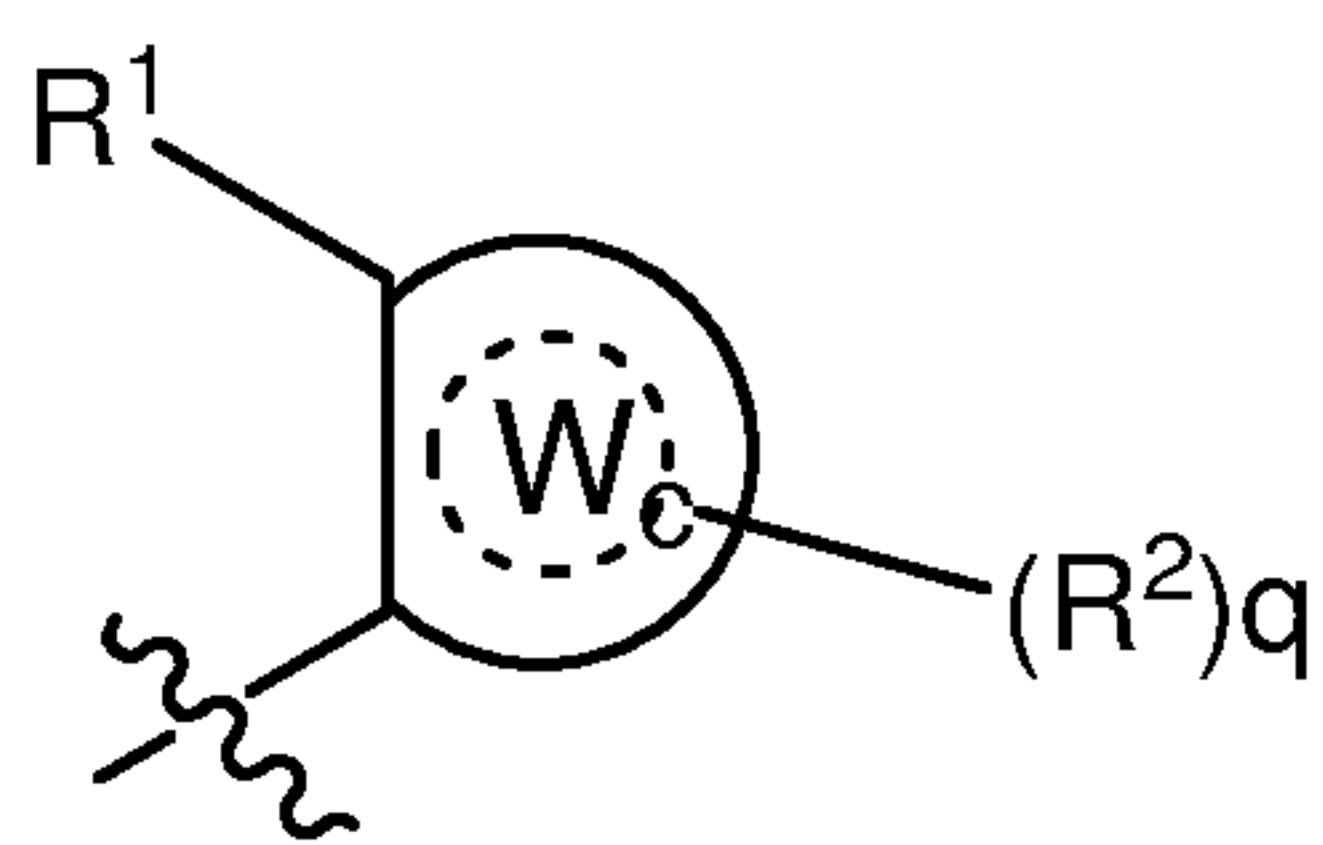


Formula XXII-A3

[00150] Any of the disclosed elements and their substituents for the compounds of Formula I can be used in any combination.

[00151] In some embodiments, B is unsubstituted or substituted alkyl, including but not limited to $-(CH_2)_2-NR^aR^a$, wherein each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, or NR^aR^a are combined together to form a cyclic moiety, which includes but is not limited to piperidinyl, piperazinyl, and morpholinyl. In some embodiments, B is unsubstituted or substituted amino. In some embodiments, B is unsubstituted or substituted heteroalkyl.

[00152] In some embodiments, B is a moiety of Formula II:

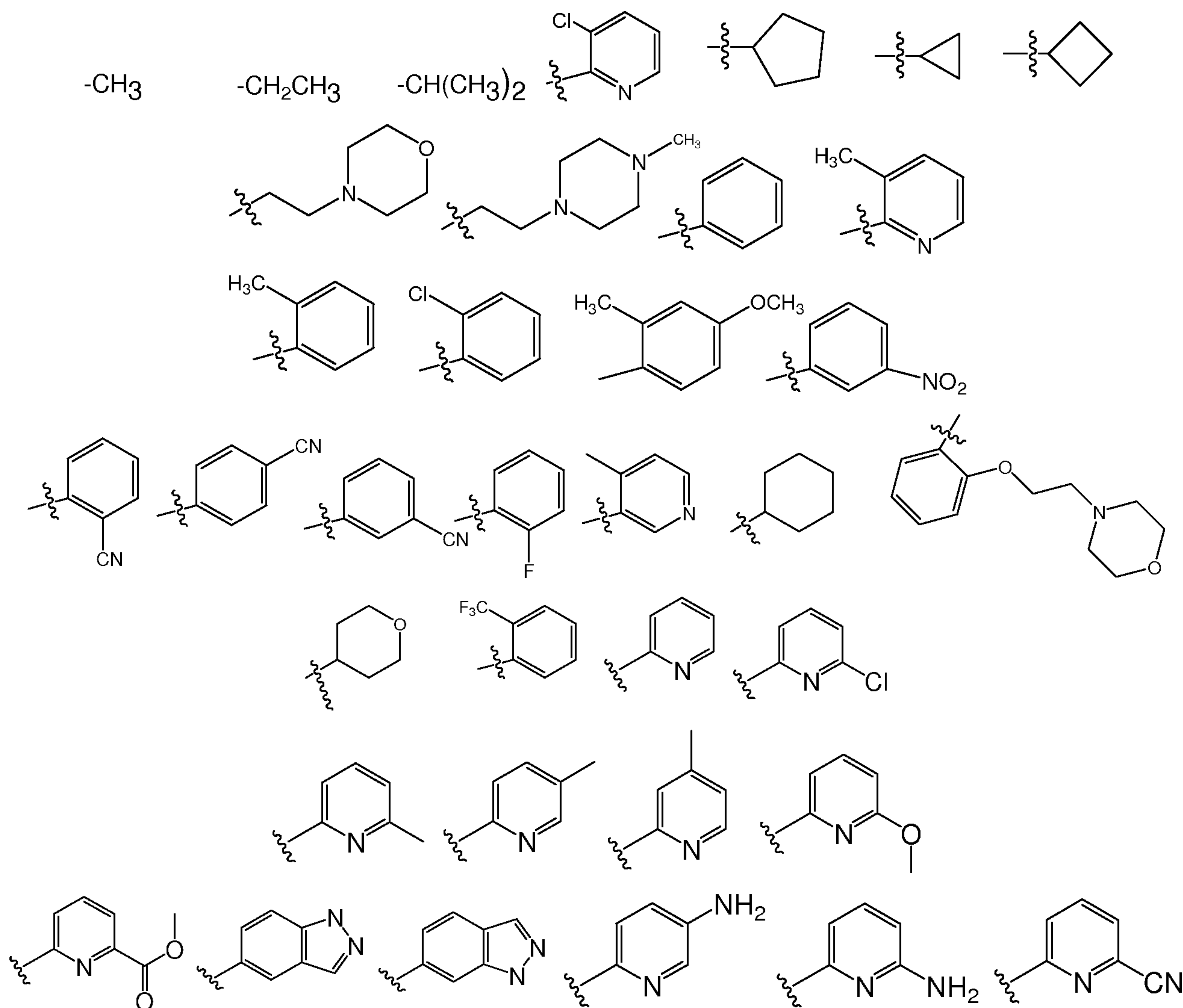


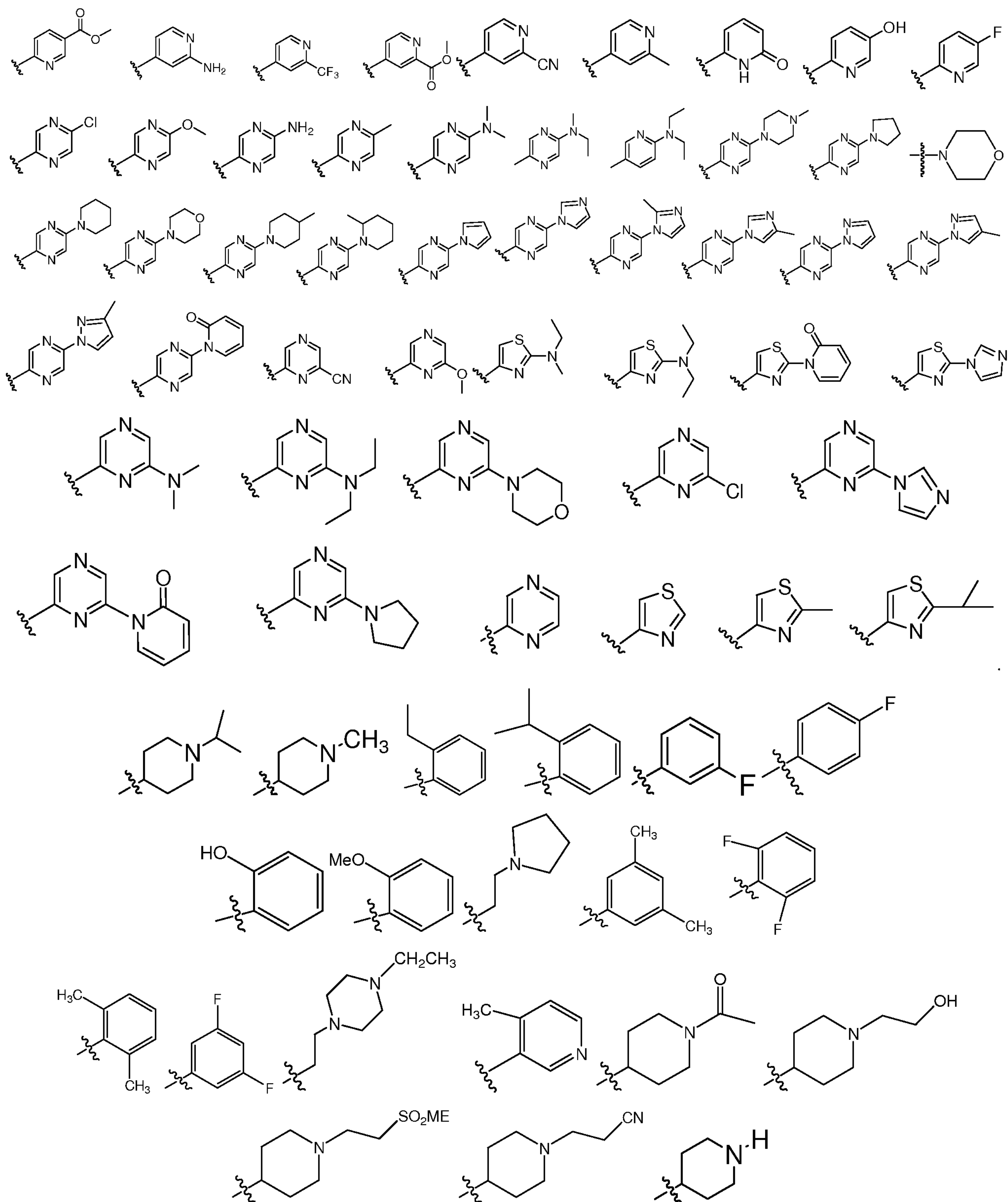
Formula II

and wherein W_c is selected from unsubstituted or substituted aryl, substituted phenyl, unsubstituted or substituted heteroaryl including, but not limited to, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrimidin-4-yl, pyrimidin-2-yl, pyrimidin-5-yl, or pyrazin-2-yl, unsubstituted or substituted monocyclic heteroaryl, unsubstituted or substituted bicyclic heteroaryl, a heteroaryl comprising two heteroatoms as ring atoms, unsubstituted or substituted heteroaryl comprising a nitrogen ring atom, a heteroaryl comprising two nitrogen ring atoms, a heteroaryl comprising a nitrogen and a sulfur as ring atoms, unsubstituted or substituted heterocycloalkyl including, but not limited to, morpholinyl, tetrahydropyranyl, piperazinyl, and piperidinyl, or unsubstituted or substituted cycloalkyl including, but not limited, and cyclopentyl and cyclohexyl.

[00153]

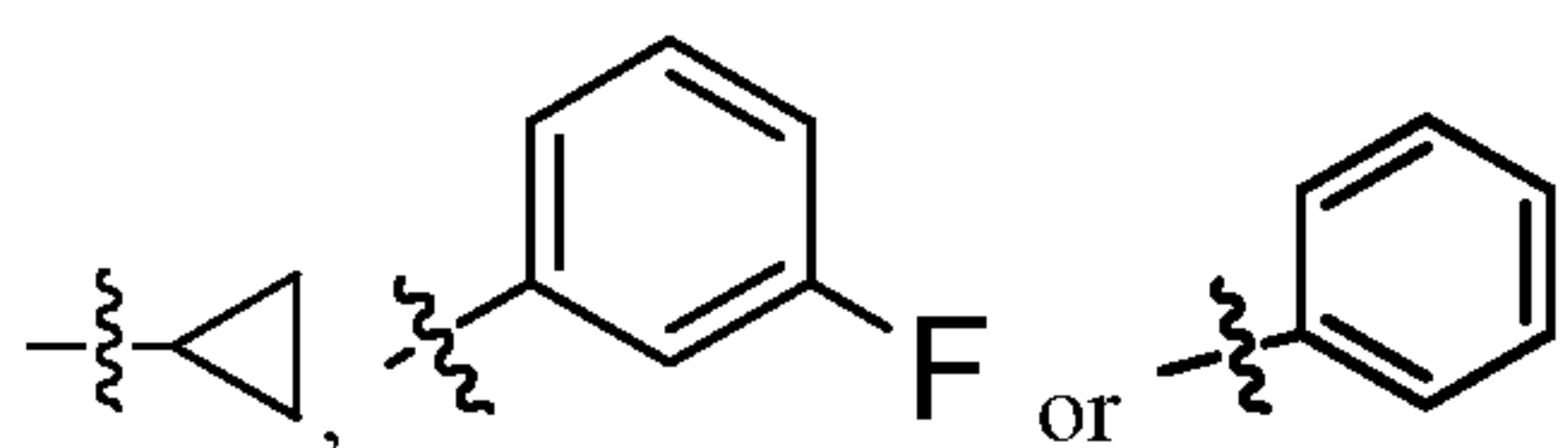
In some embodiments, B is one of the following moieties:





[00154]

In some embodiments, B is one of the following moieties:



[00155] In some embodiments, B is substituted by one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, or sulfonamido, can itself be substituted.

[00156] In some embodiments, R^1 is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted heteroalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, and unsubstituted or substituted heterocycloalkyl. In some embodiments, R^1 is unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroaryl, or unsubstituted or substituted heteroarylalkyl. In some embodiments, R^1 is unsubstituted or substituted alkoxy, unsubstituted or substituted amido, or unsubstituted or substituted amino. In some embodiments, R^1 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, or unsubstituted or substituted sulfonamido. In some embodiments, R^1 is halo which includes -Cl, -F, -I, and -Br. In some embodiments, R^1 is selected from cyano, hydroxy, nitro, unsubstituted or substituted phosphate, unsubstituted or substituted urea, and carbonate.

[00157] In some embodiments, when R^1 is alkyl, R^1 is methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, *sec*-butyl, pentyl, hexyl or heptyl.

[00158] In some embodiments, when R^1 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, or hydroxy, R^1 is substituted by phosphate, unsubstituted urea, substituted urea, carbonic acid, or carbonate.

[00159] In some embodiments, when R^1 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido, R^1 is substituted by one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

[00160] In some embodiments, q is an integer of 0. In some embodiments, q is an integer of 1. In some embodiments, q is an integer of 2. In some embodiments, q is an integer of 3. In some embodiments, q is an integer of 4.

[00161] In some embodiments, R^2 is selected from unsubstituted or substituted alkyl, unsubstituted or substituted heteroalkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, and unsubstituted or substituted heterocycloalkyl. In some embodiments, R^2 is unsubstituted or substituted aryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroaryl, or unsubstituted or substituted heteroarylalkyl. In some embodiments, R^2 is unsubstituted or substituted alkoxy, unsubstituted or substituted amido, or unsubstituted or substituted amino. In some embodiments, R^2 is unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, or unsubstituted or substituted sulfonamido. In some embodiments, R^2 is halo, which is -I, -F, -Cl, or -Br. In some embodiments, R^2 is selected from cyano, hydroxy, nitro, a carbonic acid, and a carbonate. In some embodiments, R^2 is unsubstituted or substituted

phosphate. In some embodiments, R^2 is unsubstituted or substituted urea. In some embodiments, when R^2 is alkyl, R^2 is methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, *sec*-butyl, pentyl, hexyl or heptyl.

[00162] In some embodiments, when R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, or hydroxy, it is substituted by phosphate, substituted by urea, or substituted by carbonate.

[00163] In some embodiments, when R^2 is alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido, R^2 is substituted by one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

[00164] In some embodiments, R^3 is a 5-membered heteroaryl group. Such groups include, for example, pyrrole, furan, thiophene, triazole, oxazole, pyrazole, and isoxazole. In other embodiments, R^3 is a 5-membered nonaromatic heterocycle, including, but not limited to, oxazoline and oxazolidinone. In still other embodiments, R^3 is a 6-membered heteroaryl group such as pyridine, pyrazine, pyrimidine and pyridazine. In another embodiment, R^3 is a 6-membered nonaromatic heterocycle, including moieties such as morpholino or piperidino. In other embodiments, R^3 is a fused 5/6-bicyclic heteroaryl, for example benzothiazole, benzoxazole, benzisoxazole, indazole, benzimidazole, benzothiophene, indole, isoindole, purine, or pyrazolopyrimidine. In yet other embodiments, R^3 is a fused 5/6-bicyclic nonaromatic heterocycle.

[00165] In some embodiments, R^3 is a C_1 - C_6 alkyl group substituted with a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle. In other embodiments, R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C_1 - C_6 alkyl group to a 5-membered heteroaryl, a 5-membered nonaromatic heterocycle, a 6-membered heteroaryl, a 6-membered nonaromatic heterocycle, a fused 5/6-bicyclic heteroaryl, or a fused 5/6-bicyclic nonaromatic heterocycle.

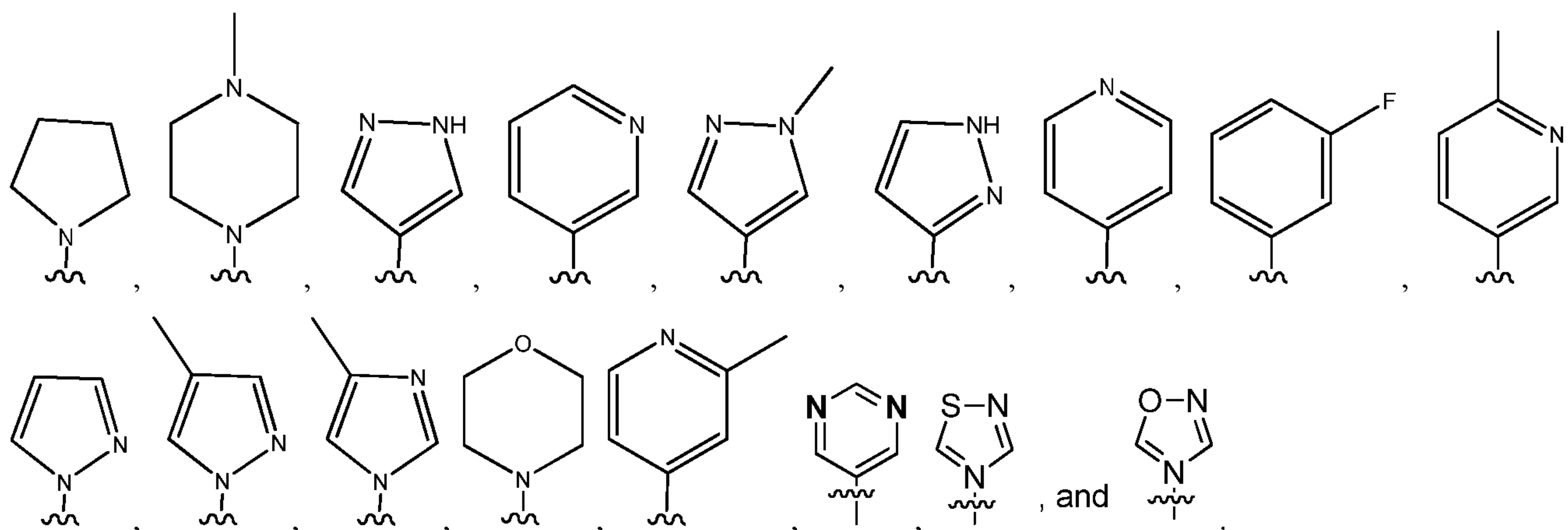
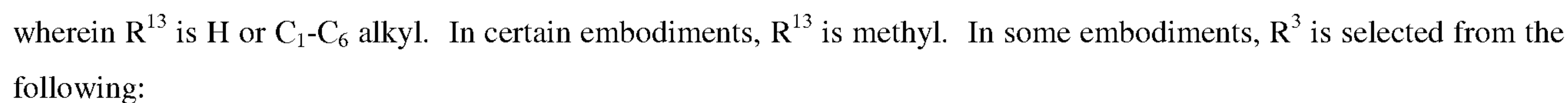
[00166] In other embodiments, R^3 is a C_1 - C_6 alkyl group substituted with a fused polycyclic group, wherein the polycyclic group has greater than two rings and is carbocyclic or heterocyclic; C_1 - C_6 alkyl group substituted with a bridged cycloalkyl or bridged heterocyclic group; C_1 - C_6 alkyl group substituted with a spirocyclic cycloalkyl or spirocyclic heterocyclic group; or branched C_4 - C_{12} alkyl group, wherein said branched alkyl group contains at least one terminal *t*-butyl group.

[00167] Each of the embodiments named above for R^3 is unsubstituted or optionally additionally substituted with an alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro group.

[00168] In certain embodiments, R^3 is a substituted or unsubstituted group selected from pyridine, pyrazole, piperazine, and pyrrolidine, wherein the substituent can be a C_1 - C_6 alkyl group or a halogen.

[00169] In some embodiments, a compound is provided wherein R^3 is selected from a 5-membered heteroaryl selected from pyrrole, a furan, and a thiophene group; 5-membered nonaromatic heterocycle selected from a pyrrolidine, a tetrahydrofuran, and a tetrahydrothiophene group; 6-membered heteroaryl selected from pyridine, pyrazine, pyrimidine, and pyridazine; 6-membered nonaromatic heterocycle selected from piperidine, tetrahydropyran,

[00170] In some embodiments, a compound is provided wherein R³ is selected from



[00171] In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently hydrogen, unsubstituted or substituted alkyl (including, but not limited to, unsubstituted or substituted C_1 - C_4 alkyl). In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted alkenyl including, but not limited to, unsubstituted or substituted C_2 - C_5 alkenyl. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted alkynyl including, but not limited to, unsubstituted or substituted C_2 - C_5 alkynyl. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted cycloalkyl including, but not limited to, unsubstituted or substituted C_3 - C_5 cycloalkyl. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted heterocycloalkyl. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted heteroalkyl including, but not limited to, unsubstituted or substituted C_1 - C_4 heteroalkyl. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted alkoxy including, but not limited to, unsubstituted or substituted C_1 - C_4 alkoxy. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted amido including, but not limited to, unsubstituted or substituted C_1 - C_4 amido. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted amino. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently unsubstituted or substituted acyl, unsubstituted or substituted acyloxy, unsubstituted or substituted C_1 - C_4 acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted sulfonamido, or unsubstituted or substituted C_1 - C_4 sulfonamido. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently halo, which is -I, -F, -Cl, or -Br. In some embodiments, R^5 , R^6 , R^7 , and R^8 are each independently selected from cyano, hydroxy, and nitro. In some other embodiments, R^5 , R^6 , R^7 , and R^8 are each independently -CH₃, -CH₂CH₃, n-propyl, isopropyl, -OCH₃, -OCH₂CH₃, or -CF₃.

[00172] In some embodiments, when R^5 , R^6 , R^7 , and R^8 are each independently alkyl, alkenyl, alkynyl, cycloalkyl, heteroalkyl, acyl, alkoxy, amido, amino, acyloxy, alkoxycarbonyl, or sulfonamido, R^5 , R^6 , R^7 , and R^8 are each independently optionally substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

[00173] In some embodiments, R^5 , R^6 , R^7 , and R^8 are H.

[00174] In some embodiments, X is absent. In some embodiments, X is $-(CH(R^9))_z$, and z is an integer of 1, 2, 3 or 4.

[00175] In some embodiments, R^9 is unsubstituted or substituted alkyl including, but not limited to, unsubstituted or substituted C_1 - C_{10} alkyl. In some embodiments, R^9 is unsubstituted or substituted cycloalkyl including but not limited to unsubstituted or substituted C_3 - C_7 cycloalkyl. In some embodiments, R^9 is ethyl, methyl or hydrogen. In some embodiments, R^9 is unsubstituted or substituted heterocycloalkyl including, but not limited to, unsubstituted or substituted C_2 - C_{10} heteroalkyl. In some embodiments, R^9 is unsubstituted or substituted heteroalkyl including, but not limited to, unsubstituted or substituted C_2 - C_{10} heteroalkyl.

[00176] In some embodiments, provided herein is a compound of Formula I (e.g., a compound of formula (I), (Ia), (Ib) or (Ic)) wherein R^9 is hydrogen, and X is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH(CH₃)-, or -CH(CH₂CH₃)-. In other embodiments, X is $-(CH(R^9))_z$, R^9 is alkyl, or heterocycloalkyl, and z is an integer of 1. When X is -CH(R⁹)- and R^9 is alkyl, or heterocycloalkyl, then the compound can adopt either an (S)- or (R)-stereochemical configuration with respect to carbon X. In some embodiments, the compound is a racemic mixture of (S)- and (R)- isomers with

respect to carbon X. In other embodiments, provided herein is a mixture of compounds of Formula I wherein individual compounds of the mixture exist predominately in an (S)- or (R)- isomeric configuration. For example, the compound mixture has an (S)-enantiomeric excess of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more at the X carbon. In other embodiments, the compound mixture has an (S)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00177] In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5% or more at the X carbon. In some other embodiments, the compound mixture has an (R)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5% or more.

[00178] In other embodiments, the compound mixture contains identical chemical entities except for their stereochemical orientations, namely (S)- or (R)- isomers. For instance, in the compounds of Formula I, when X is -CH(R⁹)-, and R⁹ is not hydrogen, then the -CH(R⁹)- is in an (S)- or (R)- stereochemical orientation for each of the identical chemical entities. In some embodiments, the mixture of identical chemical entities of Formula I is a racemic mixture of (S)- and (R)- isomers at the carbon represented by X. In another embodiment, the mixture of the identical chemical entities (except for their stereochemical orientations), contain predominately (S)-isomers or predominately (R)-isomers. For example, the (S)- isomers in the mixture of identical chemical entities are present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5% ,or more, relative to the (R)- isomers. In some embodiments, the (S)- isomers in the mixture of identical chemical entities are present at an (S)-enantiomeric excess of greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%, greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5% or more.

[00179] In another embodiment, the (R)- isomers in the mixture of identical chemical entities (except for their stereochemical orientations), are present at about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, or more, relative to the (S)- isomers. In some embodiments, the (R)- isomers in the mixture of identical chemical entities (except for their stereochemical orientations), are present at a (R)- enantiomeric excess greater than about 55% to about 99.5%, greater than about about 60% to about 99.5%, greater than about 65% to about 99.5%, greater than about 70% to about 99.5%,

greater than about 75% to about 99.5%, greater than about 80% to about 99.5%, greater than about 85% to about 99.5%, greater than about 90% to about 99.5%, greater than about 95% to about 99.5%, greater than about 96% to about 99.5%, greater than about 97% to about 99.5%, greater than about 98% to greater than about 99.5%, greater than about 99% to about 99.5%, or more.

[00180] In some embodiments, the compound of Formula I, X is $-\text{CH}(\text{R}^9)-$, R^9 is methyl or ethyl, and the compound is the (S)- isomer.

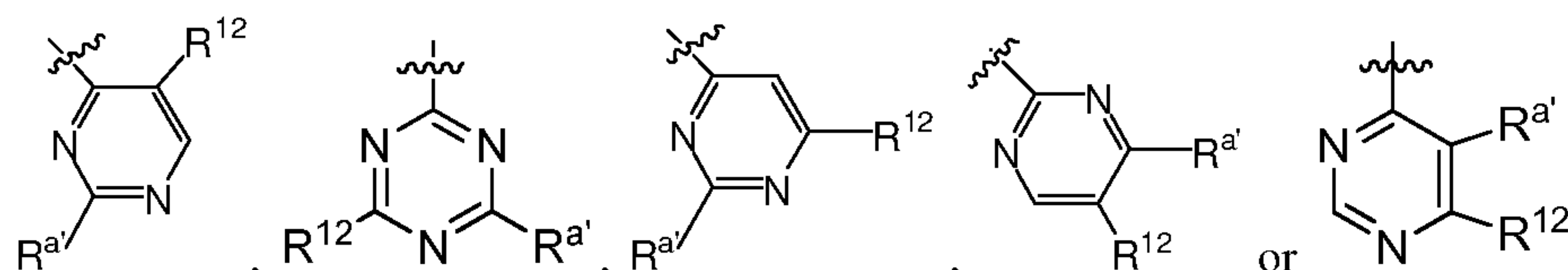
[00181] In some embodiments of the compound of Formula I, Y is absent. In some embodiments, Y is $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{=O})-$, $-\text{S}(\text{=O})_2-$, $-\text{C}(\text{=O})-$, $-\text{N}(\text{R}^9)(\text{C}=\text{O})-$, $-\text{N}(\text{R}^9)(\text{C}=\text{O})\text{NH}-$, $-\text{N}(\text{R}^9)\text{C}(\text{R}^9)_2-$ (such as $-\text{N}(\text{R}^9)\text{CH}_2-$, specifically $-\text{N}(\text{CH}_3)\text{CH}_2-$, $\text{N}(\text{CH}(\text{CH}_3)_2)\text{CH}_2-$ or $\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2-$), $-\text{N}(\text{R}^9)-$, $-\text{N}(\text{CH}_3)-$, $-\text{N}(\text{CH}_2\text{CH}_3)-$, or $-\text{N}(\text{CH}(\text{CH}_3)_2)-$. In some embodiments, Y is $-\text{C}(\text{=O})-(\text{CHR}^9)_z-$ and z is an integer of 1, 2, 3, or 4.

[00182] In some embodiments, at least one of X and Y is present. In some embodiments of the compound of Formula I, $-\text{XY}-$ is $-\text{CH}_2-$, $-\text{CH}_2-\text{N}(\text{CH}_3)-$, $-\text{CH}_2-\text{N}(\text{CH}_2\text{CH}_3)-$, $-\text{CH}(\text{CH}_3)-\text{NH}-$, (S) $-\text{CH}(\text{CH}_3)-\text{NH}-$, or (R) $-\text{CH}(\text{CH}_3)-\text{NH}-$. In other embodiments, X-Y is $-\text{N}(\text{CH}_3)\text{CH}_2-$, $\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2-$, $-\text{N}(\text{CH}(\text{CH}_3)_2)\text{CH}_2-$, or $-\text{NHCH}_2-$. In some embodiments, other compounds of Formula I are provided wherein when X-Y is X is $-(\text{CH}(\text{R}^9))_z\text{N}(\text{R}^9)-$, z is an integer of 1, 2, 3 or 4, and $-\text{N}(\text{R}^9)-$ is not $-\text{NH}-$, then $-\text{XY}-$ is not connected to purinyl.

[00183] In some embodiments, W_d in a formula disclosed herein (including but not limited to I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI and VI-A), is selected from unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl.

[00184] In various embodiments, W_d is unsubstituted or substituted monocyclic heteroaryl (including, but not limited to, pyrimidinyl, pyrrolyl, pyrazinyl, triazinyl, or pyridazinyl) or unsubstituted or substituted bicyclic heteroaryl.

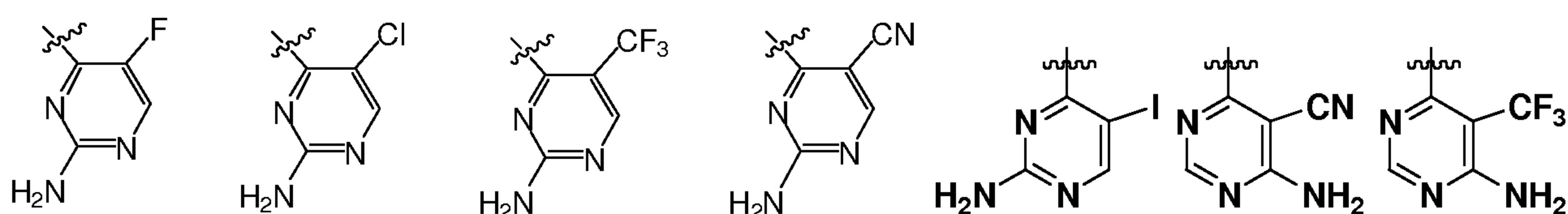
[00185] In some embodiments, W_d is a monocyclic heteroaryl of the following formula:

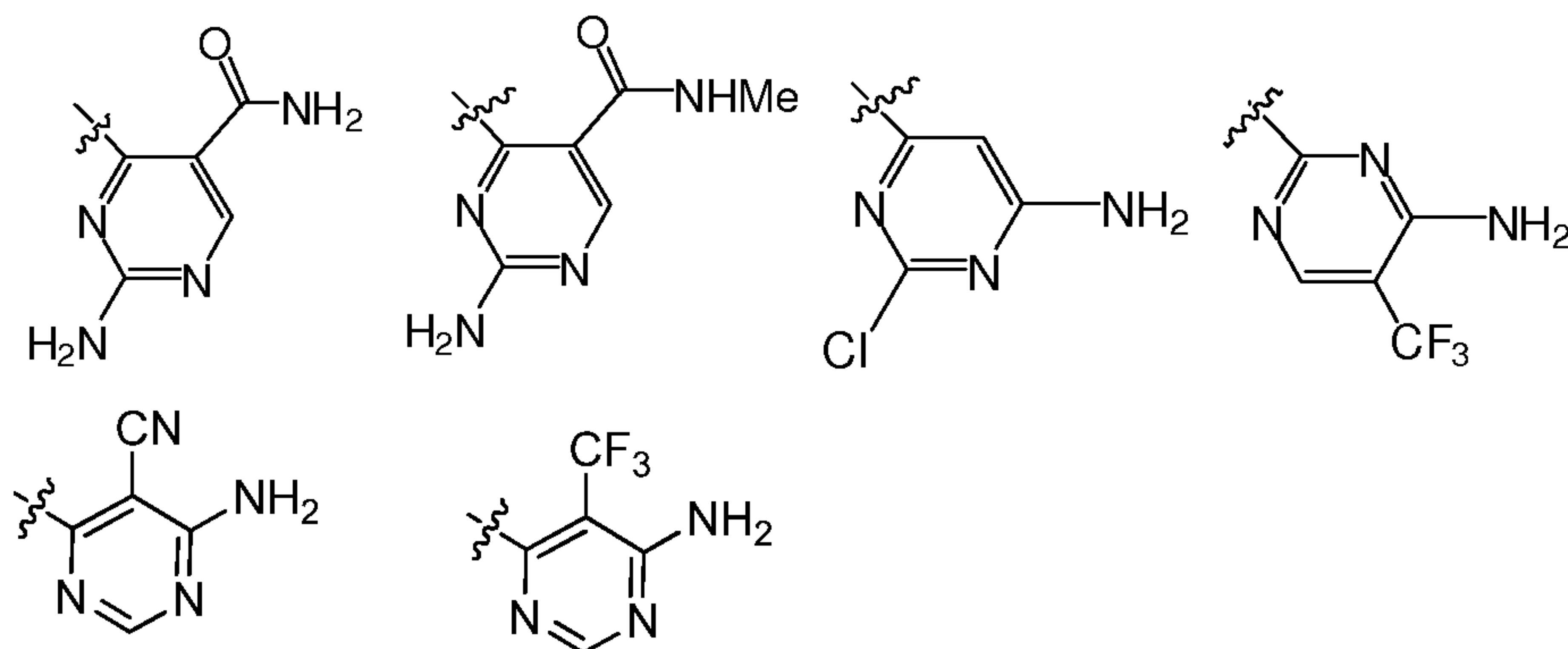


wherein R^a' is hydrogen, halo, phosphate, urea, a carbonate, unsubstituted or substituted amino, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroalkyl, or unsubstituted or substituted heterocycloalkyl; and

R^{12} is hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted cyano, unsubstituted or substituted alkynyl, unsubstituted or substituted alkenyl, halo, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted amino, carboxylic acid, unsubstituted or substituted alkoxy carbonyl, unsubstituted or substituted amido, unsubstituted or substituted acyl, or unsubstituted or substituted sulfonamido.

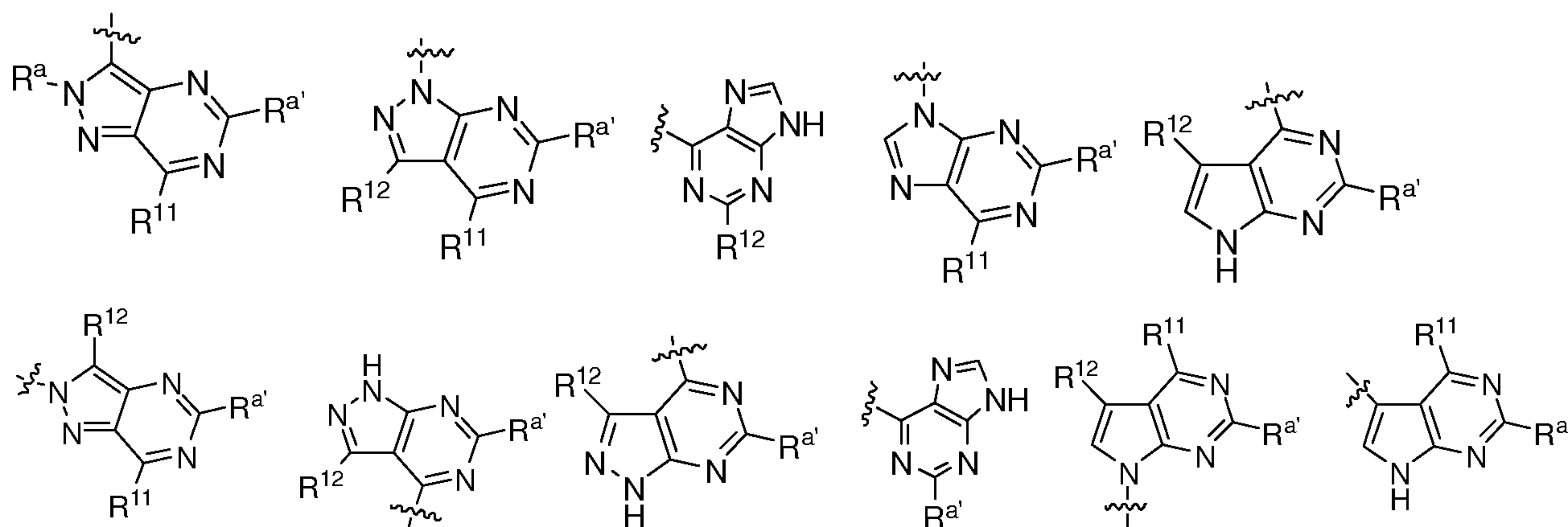
[00186] Provided herein are monocyclic heteroaryl W_d including, but not limited to, one of the following formulae:

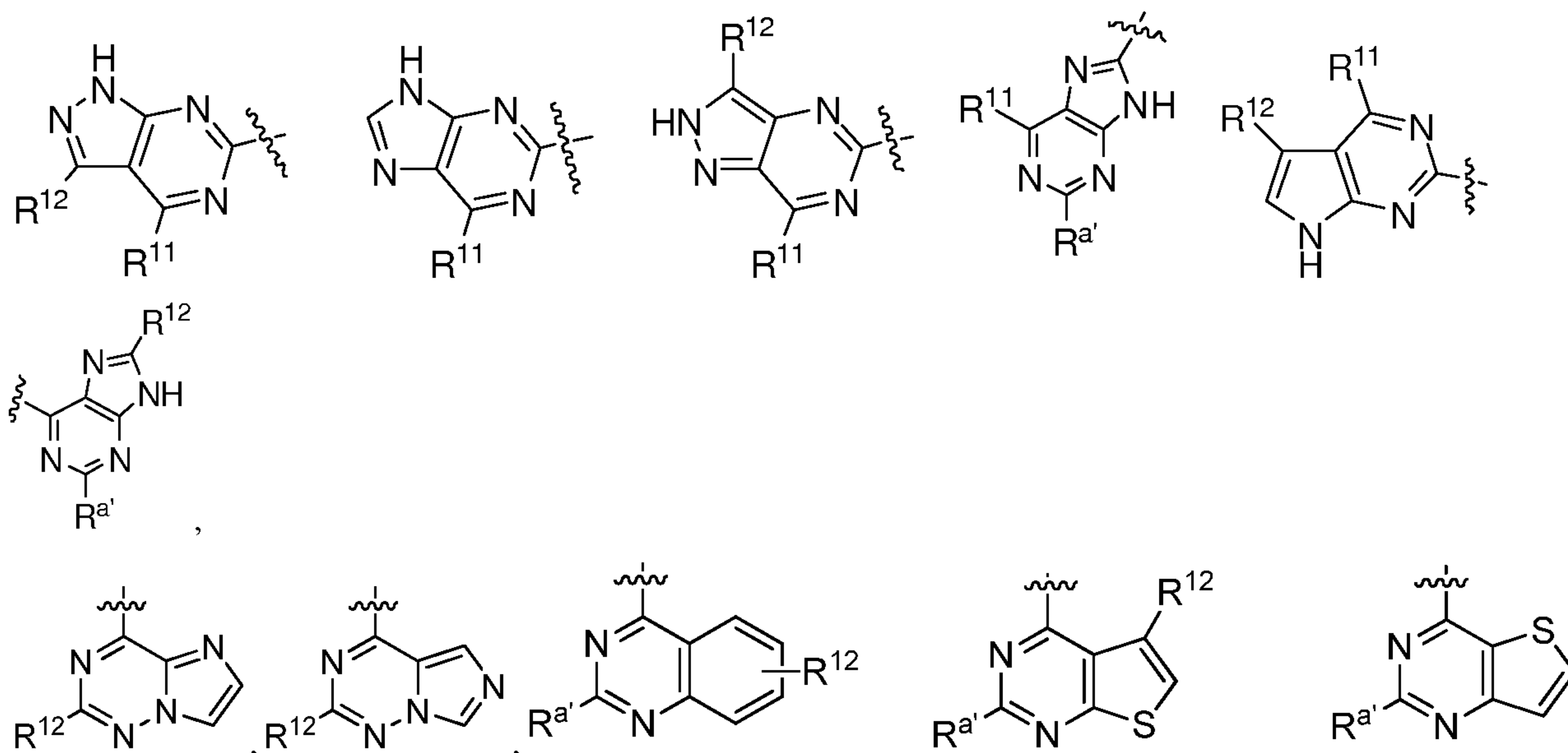




[00187] In some embodiments, W_d in a formula disclosed herein (including but not limited to I, I-1, IV, IV-A, V, V-A, V-A2, V-B, VI and VI-A), is a bicyclic heteroaryl having at least one heteroatom, *e.g.*, a bicyclic heteroaryl having at least one nitrogen ring atom. In some embodiments, W_d is a bicyclic heteroaryl having at least two heteroatoms, *e.g.*, a bicyclic heteroaryl having at least two nitrogen ring atoms. In some embodiments, W_d is a bicyclic heteroaryl having two heteroatoms in the ring which is connected to XY. In some embodiments, W_d is a bicyclic heteroaryl having two nitrogen ring atoms in the ring to which XY is connected. In some embodiments, W_d is a bicyclic heteroaryl having four heteroatoms, *e.g.*, a bicyclic heteroaryl having four nitrogen ring atoms. In some embodiments, W_d is unsubstituted or substituted 4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl, unsubstituted or substituted 7-amino-2-methyl-2H-pyrazolo[4,3-d]pyrimidin-3-yl, unsubstituted or substituted 6-methylenyl-9H-purin-6-yl, or unsubstituted or substituted 6-amino-9H-purin-9-yl.

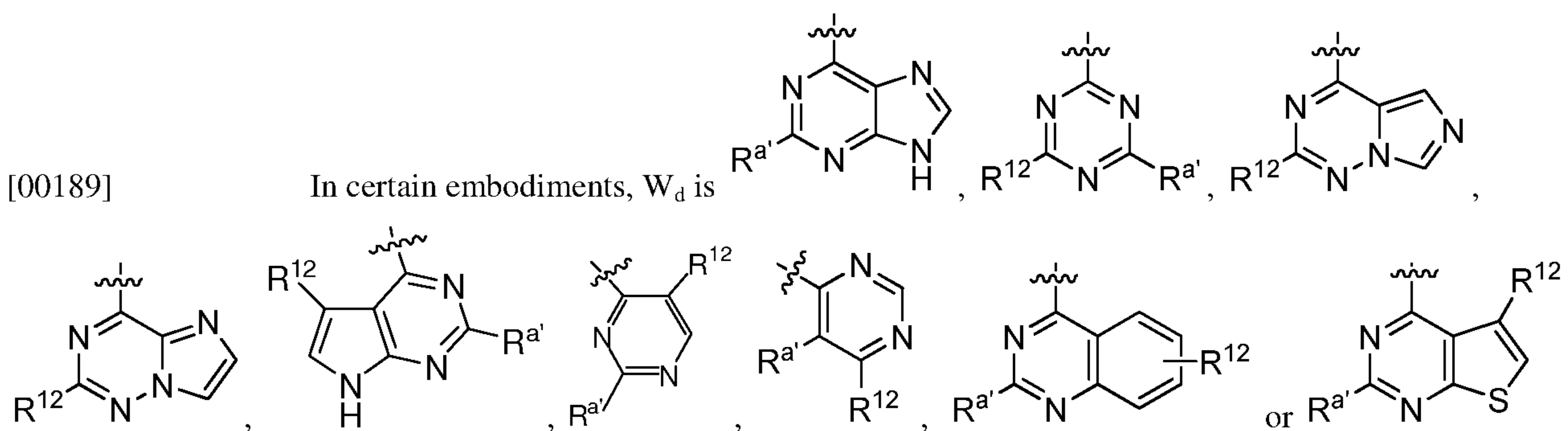
[00188] In some embodiments W_d is one of the following:





wherein R^a is hydrogen, halo, phosphate, urea, a carbonate, unsubstituted or substituted amino, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heteroalkyl, or unsubstituted or substituted heterocycloalkyl; R^{11} is hydrogen, unsubstituted or substituted alkyl, halo (which includes -I, -F, -Cl, or -Br), unsubstituted or substituted amino, unsubstituted or substituted amido, hydroxy, or unsubstituted or substituted alkoxy, phosphate, unsubstituted or substituted urea, or carbonate; and R^{12} is H, unsubstituted or substituted alkyl, unsubstituted or substituted cyano, unsubstituted or substituted alkynyl, unsubstituted or substituted alkenyl, halo, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocycloalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted amino, carboxylic acid, unsubstituted or substituted alkoxy, unsubstituted or substituted amido, unsubstituted or substituted acyl, or unsubstituted or substituted sulfonamido.

[00189]

In certain embodiments, W_d is

wherein R^a and R^{12} are as defined herein.

[00190]

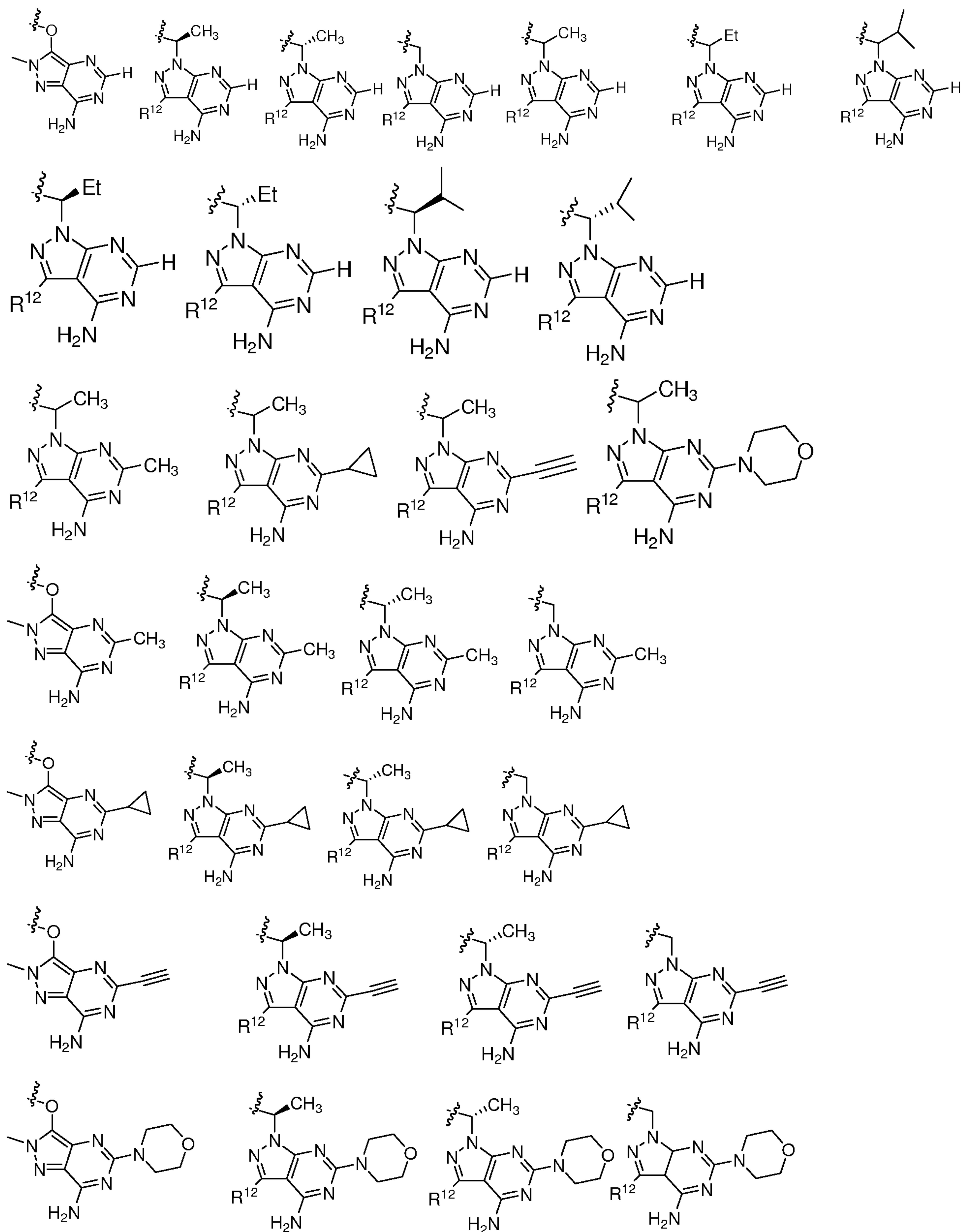
In some embodiments of W_d of the compounds of Formula I, when R^a is alkyl, alkynyl, cycloalkyl, heteroalkyl, or heterocycloalkyl, it is substituted by phosphate, urea, or carbonate.

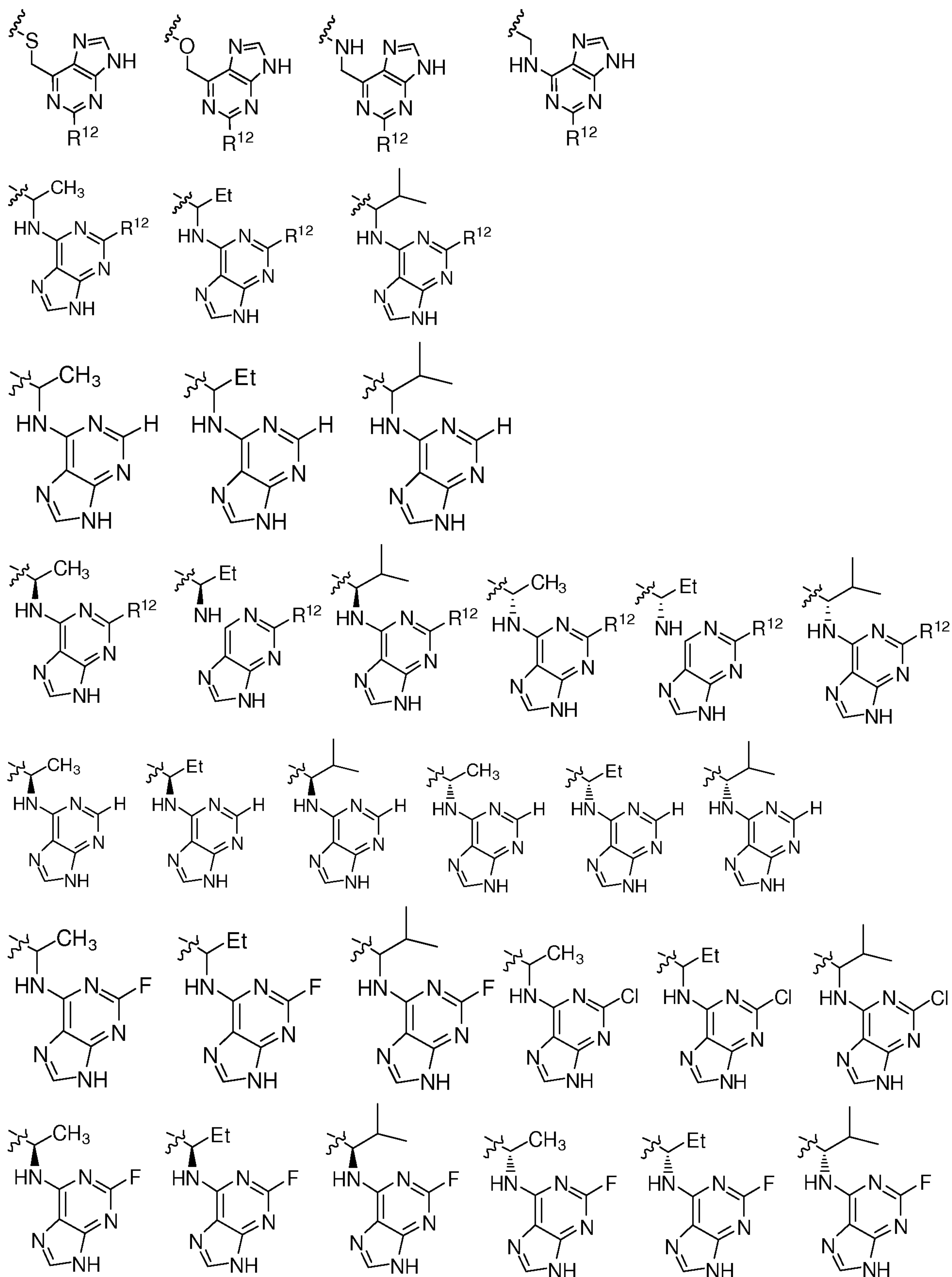
[00191]

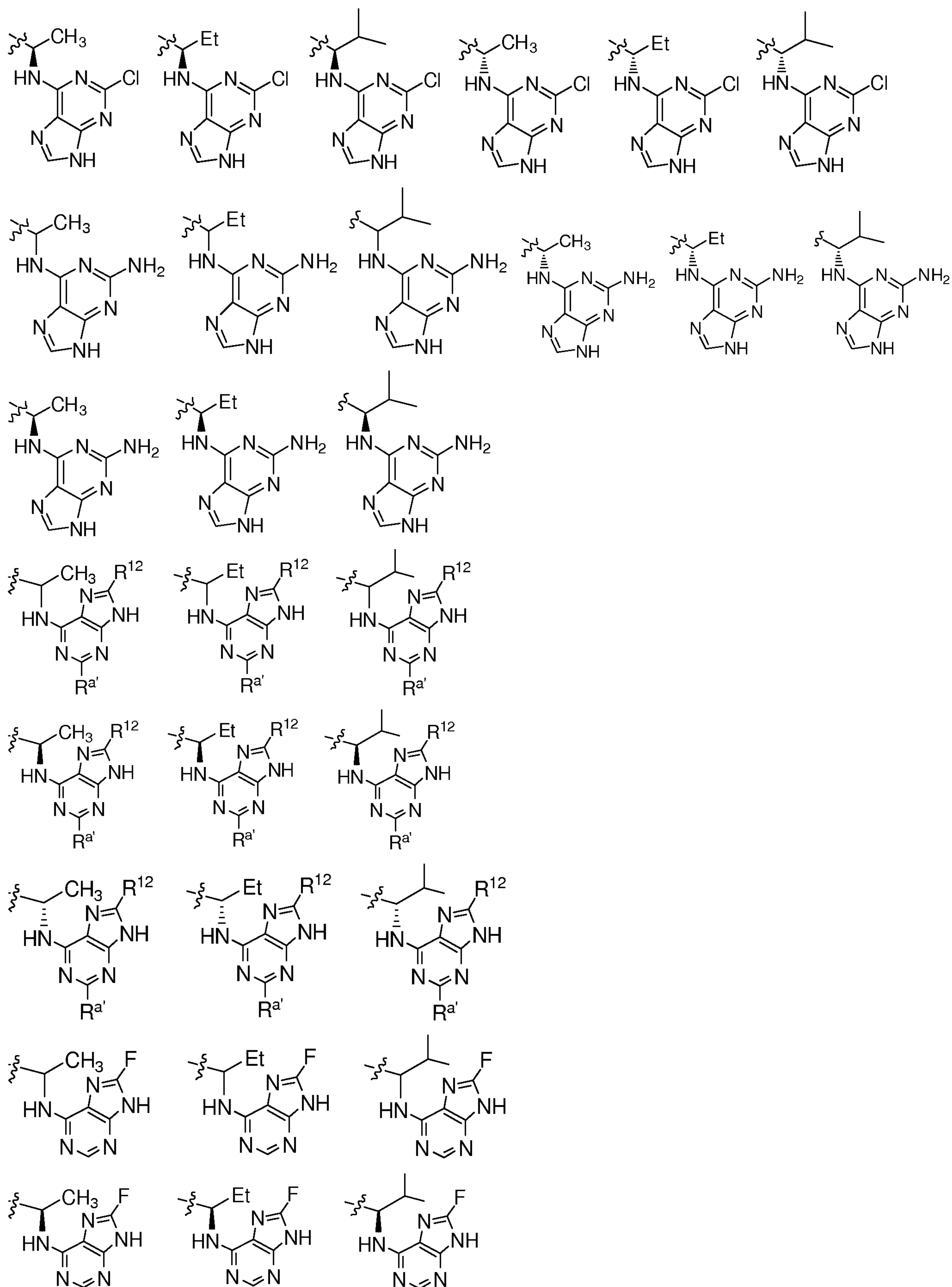
In some embodiments of W_d of the compounds of Formula I, when R^{11} is alkyl, amino, amido, hydroxy, or alkoxy, it is substituted by phosphate, urea, or carbonate.

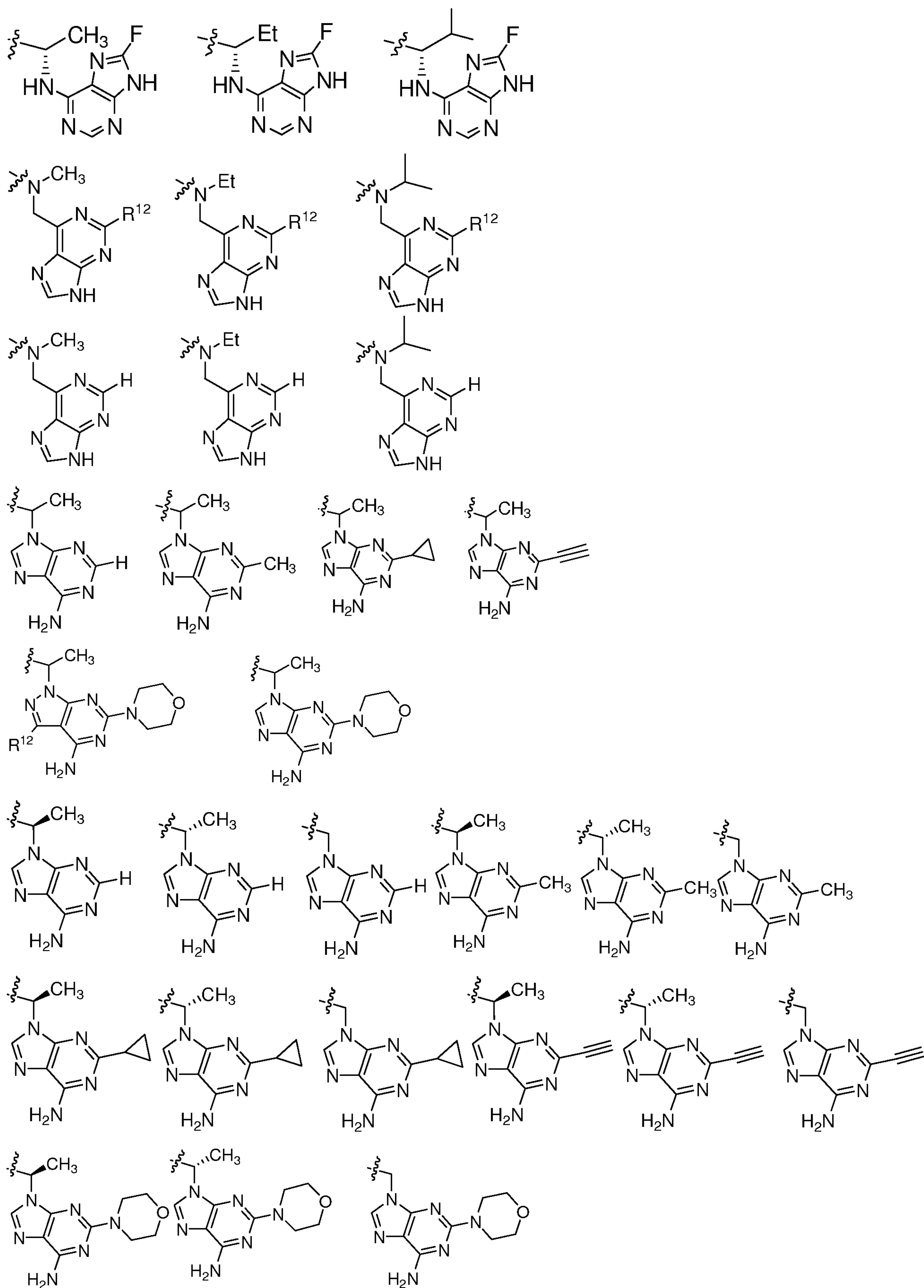
[00192]

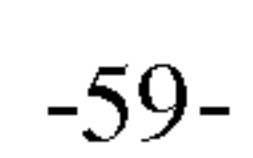
In some embodiments of the compound of Formula I, -X-Y- W_d is one of the following moieties:

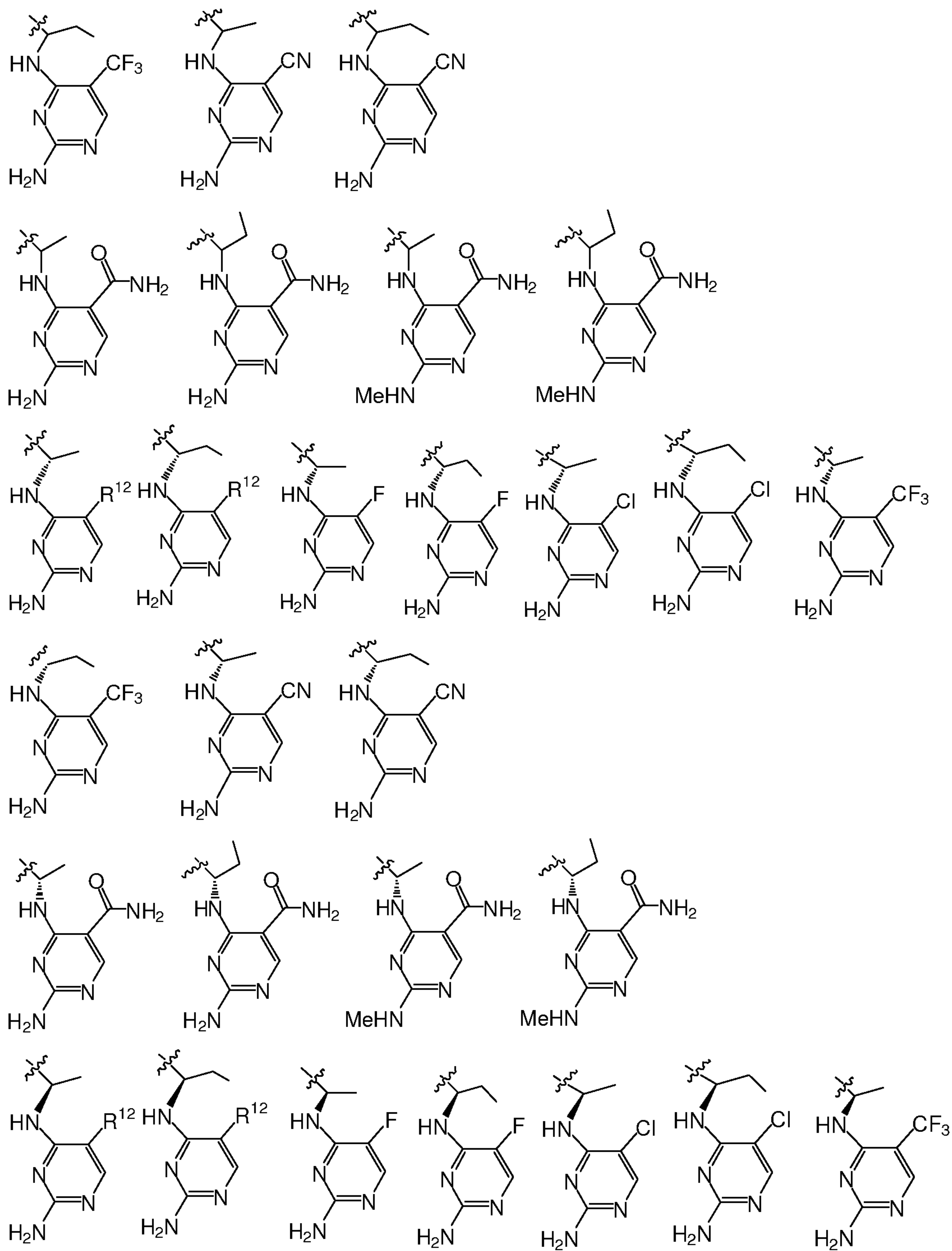


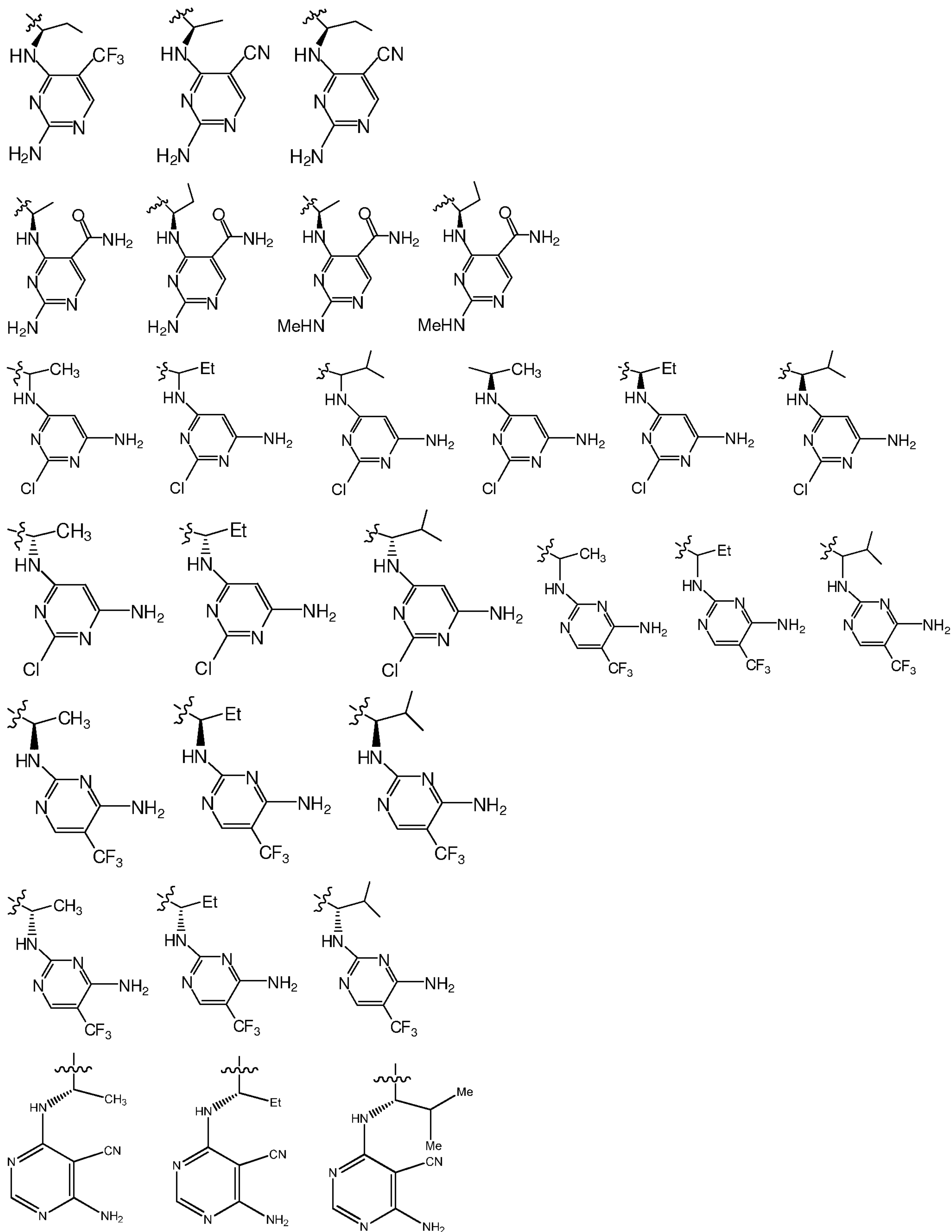












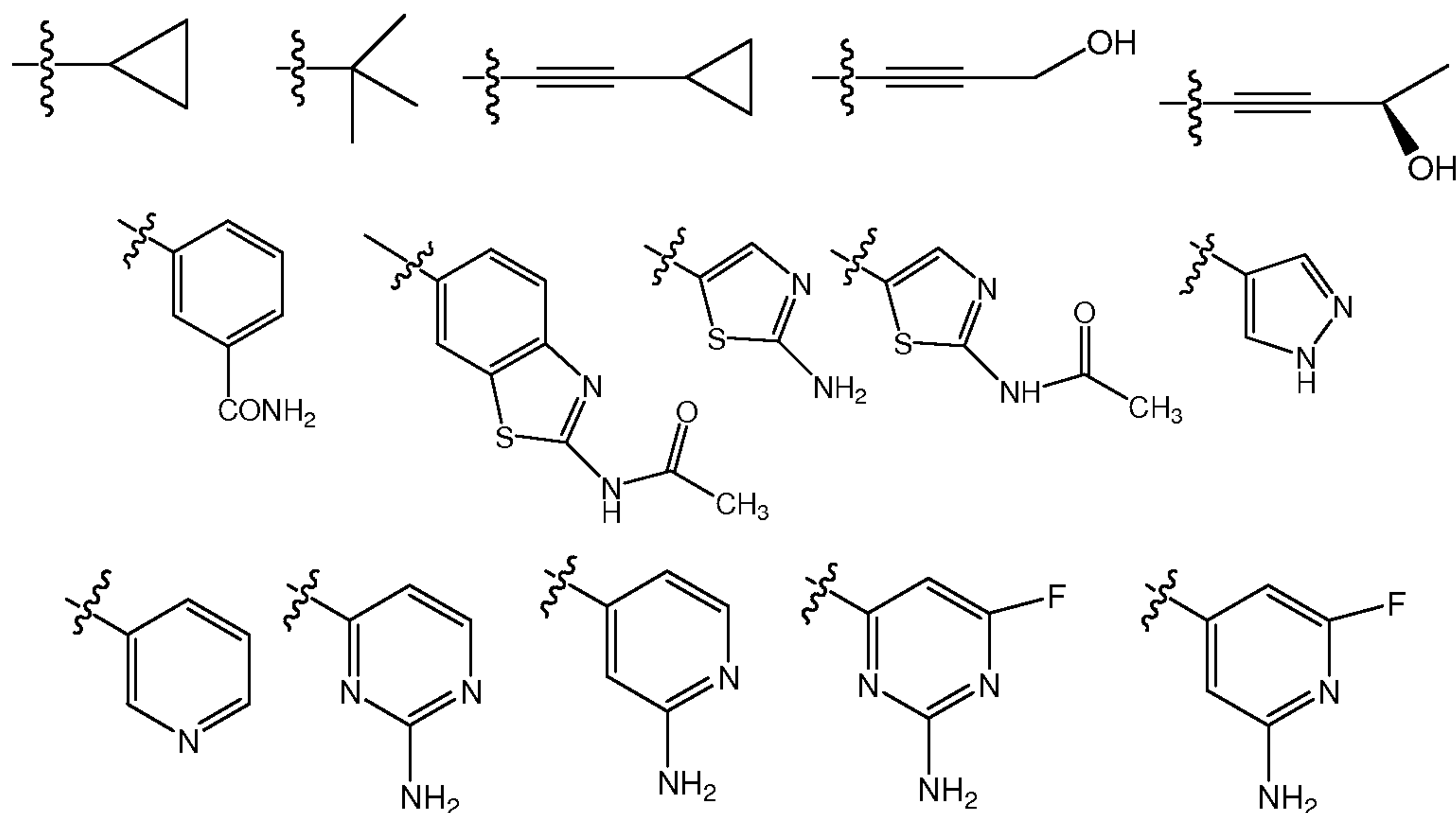
[00193] In some embodiments of the compound of Formula I, R^{12} is selected from hydrogen, cyano, halo, unsubstituted or substituted alkyl, unsubstituted or substituted alkynyl, and unsubstituted or substituted alkenyl. In some

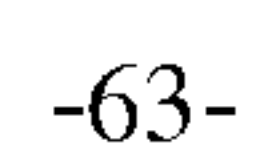
embodiments, R^{12} is unsubstituted or substituted aryl. In some embodiments, R^{12} is unsubstituted or substituted heteroaryl, which includes, but is not limited to, heteroaryl having a five membered ring, heteroaryl having a six membered ring, heteroaryl with at least one nitrogen ring atom, heteroaryl with two nitrogen ring atoms, monocyclic heteroaryl, and bicyclic heteroaryl. In some embodiments, R^{12} is unsubstituted or substituted heterocycloalkyl, which includes, but is not limited to, heterocycloalkyl with one nitrogen ring atom, heterocycloalkyl with one oxygen ring atom, heterocycloalkyl with one sulfur ring atom, 5 membered heterocycloalkyl, 6 membered heterocycloalkyl, saturated heterocycloalkyl, unsaturated heterocycloalkyl, heterocycloalkyl having an unsaturated moiety connected to the heterocycloalkyl ring, heterocycloalkyl substituted by oxo, and heterocycloalkyl substituted by two oxo. In some embodiments, R^{12} is unsubstituted or substituted cycloalkyl, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkyl substituted by one oxo, or cycloalkyl having an unsaturated moiety connected to the cycloalkyl ring. In some embodiments, R^{12} is unsubstituted or substituted amido, carboxylic acid, unsubstituted or substituted acyloxy, unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted acyl, or unsubstituted or substituted sulfonamido.

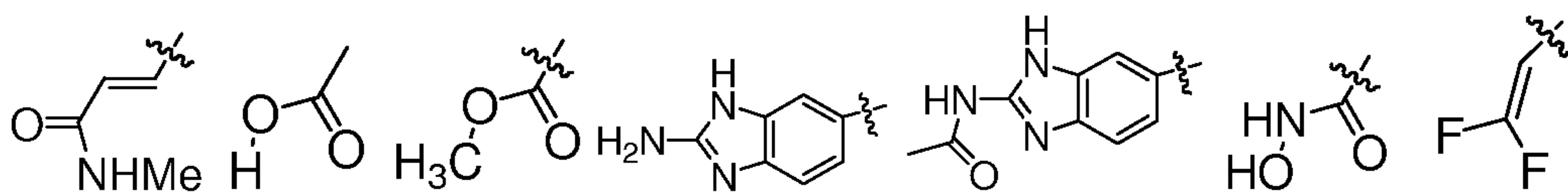
[00194] In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, it is substituted with phosphate. In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, it is substituted with urea. In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, it is substituted with carbonate.

[00195] In some embodiments, when R^{12} is alkyl, alkynyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, alkoxycarbonyl, amido, acyloxy, acyl, or sulfonamido, it is substituted with one or more of alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy or nitro, each of which alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, or sulfonamido can itself be substituted.

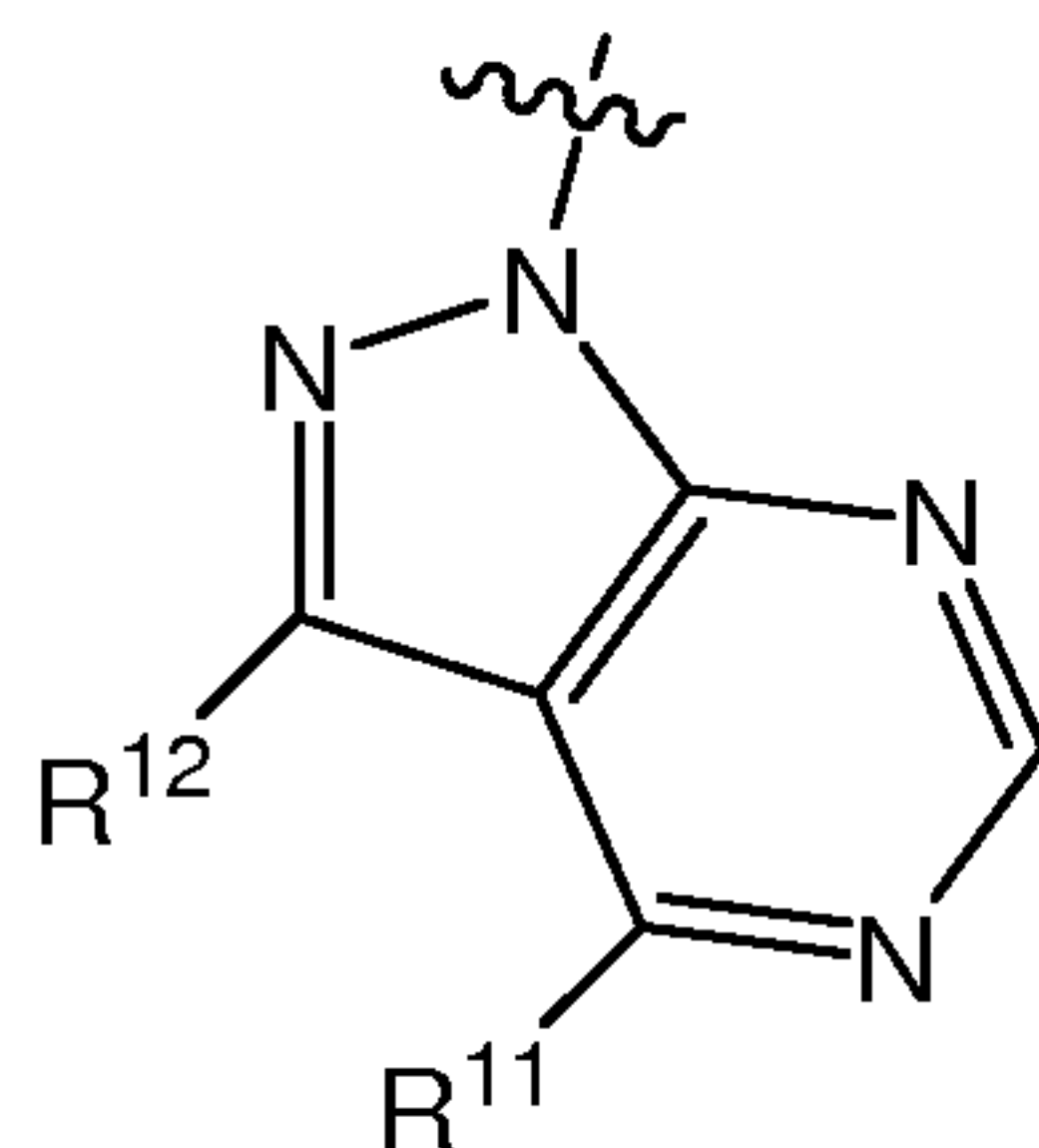
[00196] In some embodiments, R^{12} of W_d is one of the following moieties:







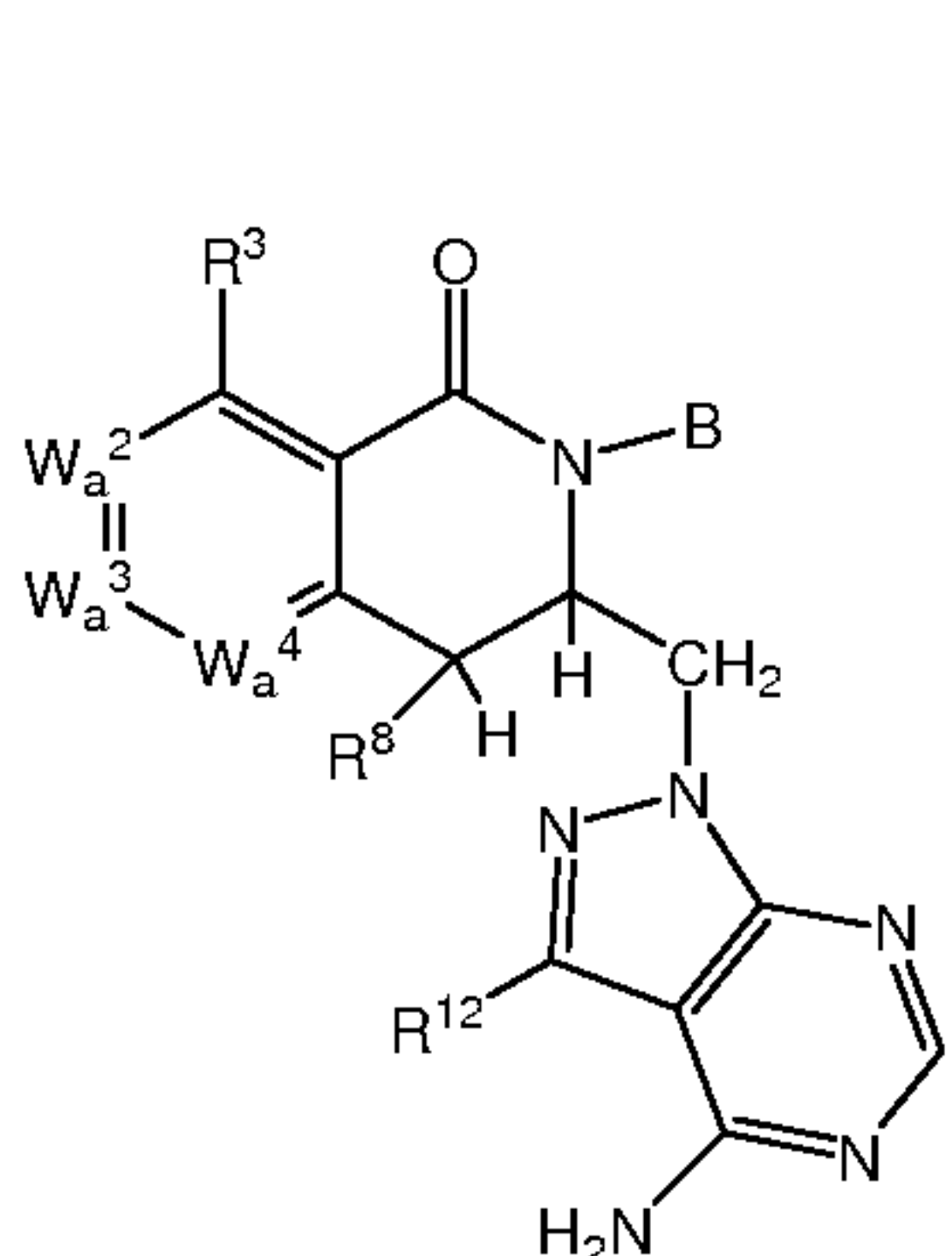
[00197] In some embodiments, W_d is a pyrazolopyrimidine of Formula III:



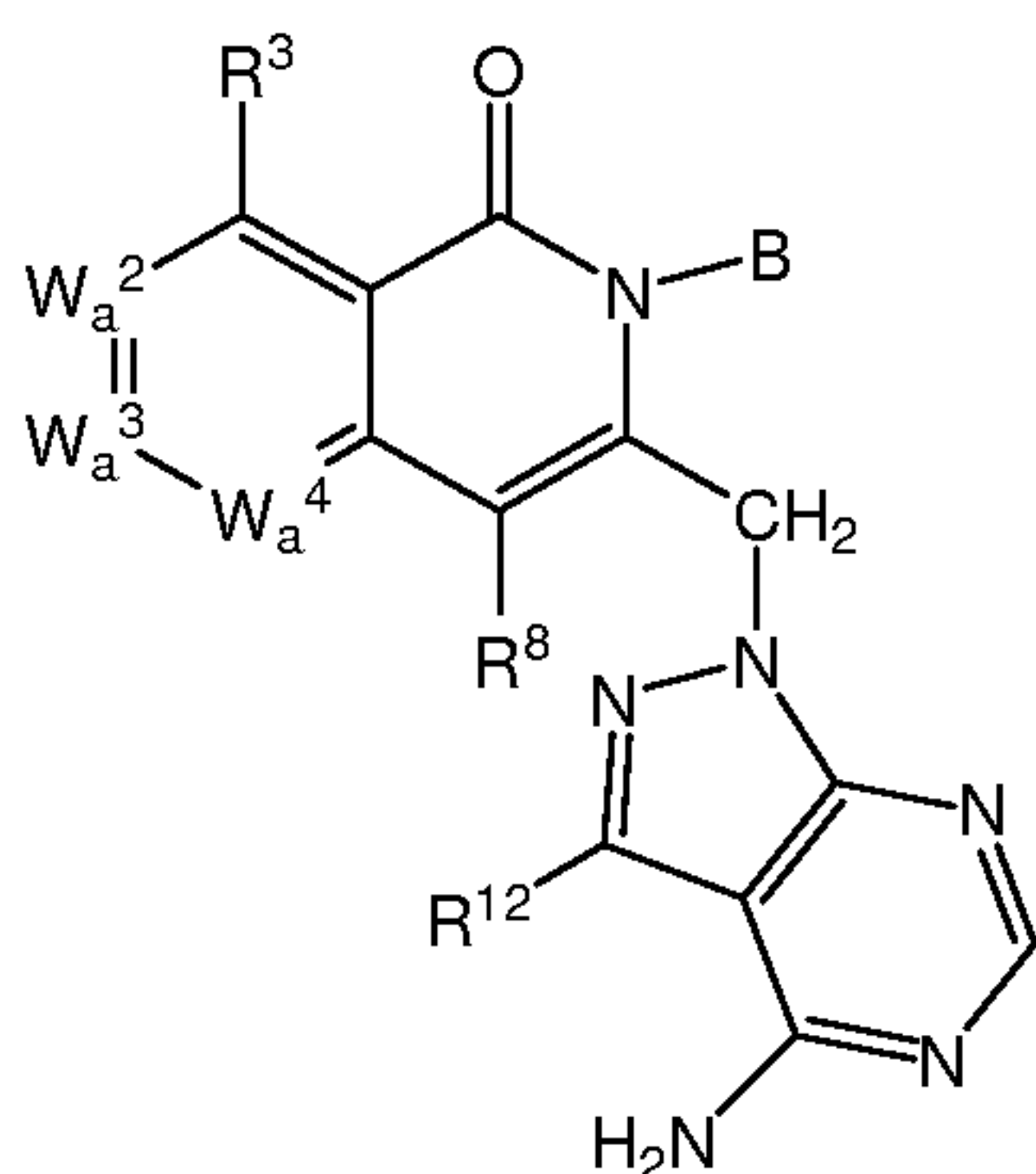
Formula III

wherein R^{11} is H, alkyl, halo, amino, amido, hydroxy, or alkoxy, and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In some embodiments, R^{11} is amino and R^{12} is H, alkyl, alkynyl, alkenyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In some embodiments, R^{11} is amino and R^{12} is alkyl, halo, aryl, heteroaryl, heterocycloalkyl, or cycloalkyl. In some embodiments, R^{11} is amino and R^{12} is monocyclic heteroaryl. In some embodiments, R^{11} is amino and R^{12} is bicyclic heteroaryl. In some embodiments, R^{11} is amino and R^{12} is cyano, amino, carboxylic acid, acyloxy, alkoxy, carbonyl, or amido.

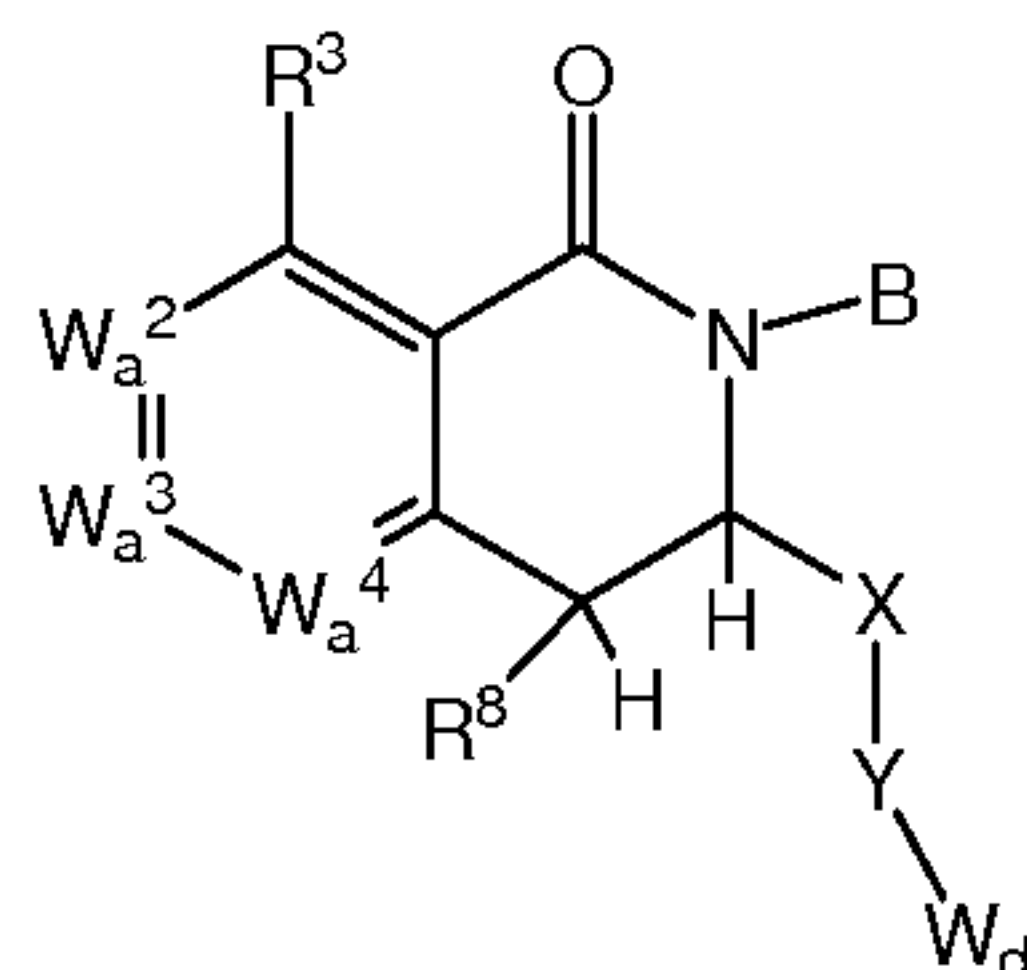
[00198] In some embodiments, the compound of Formula I is a compound which has a structure selected from Formula XXIII-A, XXIII-B, XXIV-A, XXIV-B, XXV, XXVI, XXVI-A, XXVII, XXVII-A, XXVII-B, XXVII-C, XXVII-C1, XXVII-C2, XXVII-D, and XXVII-E:



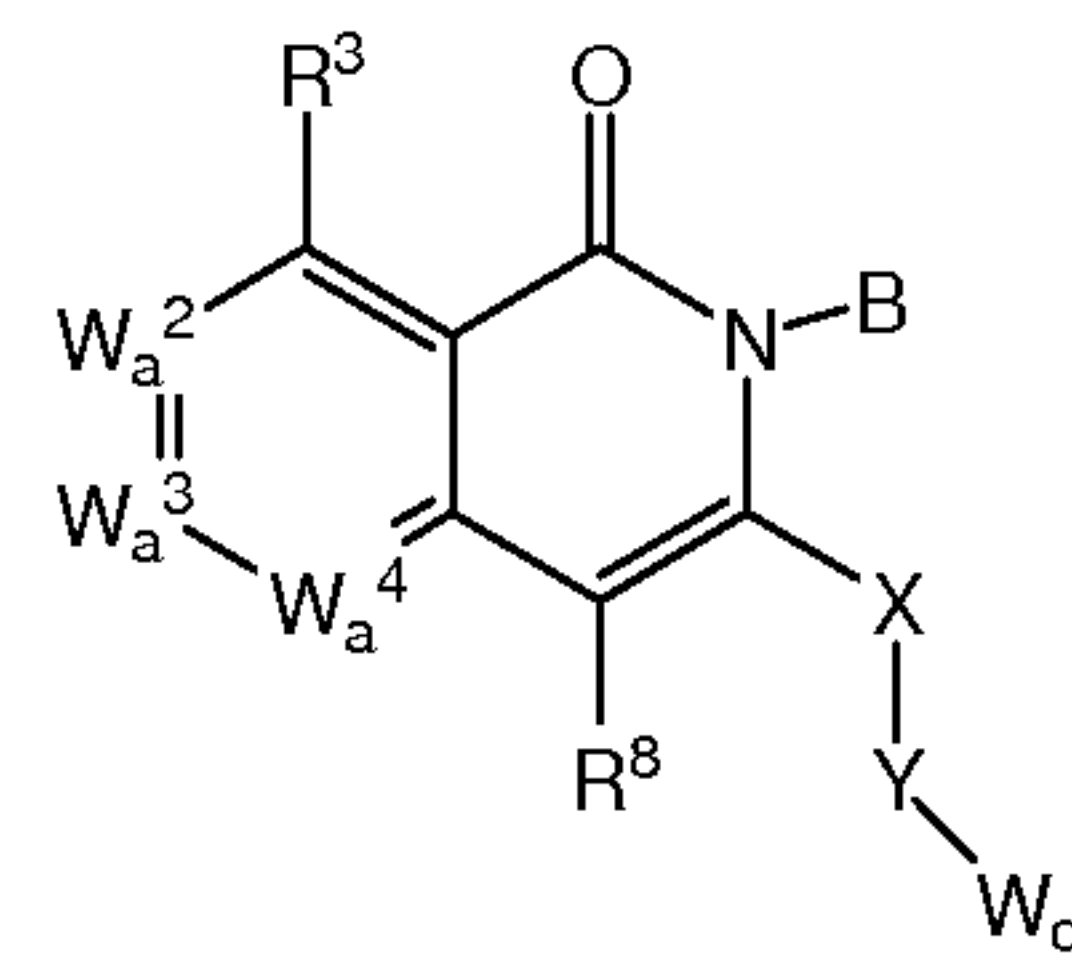
Formula XXIII-A



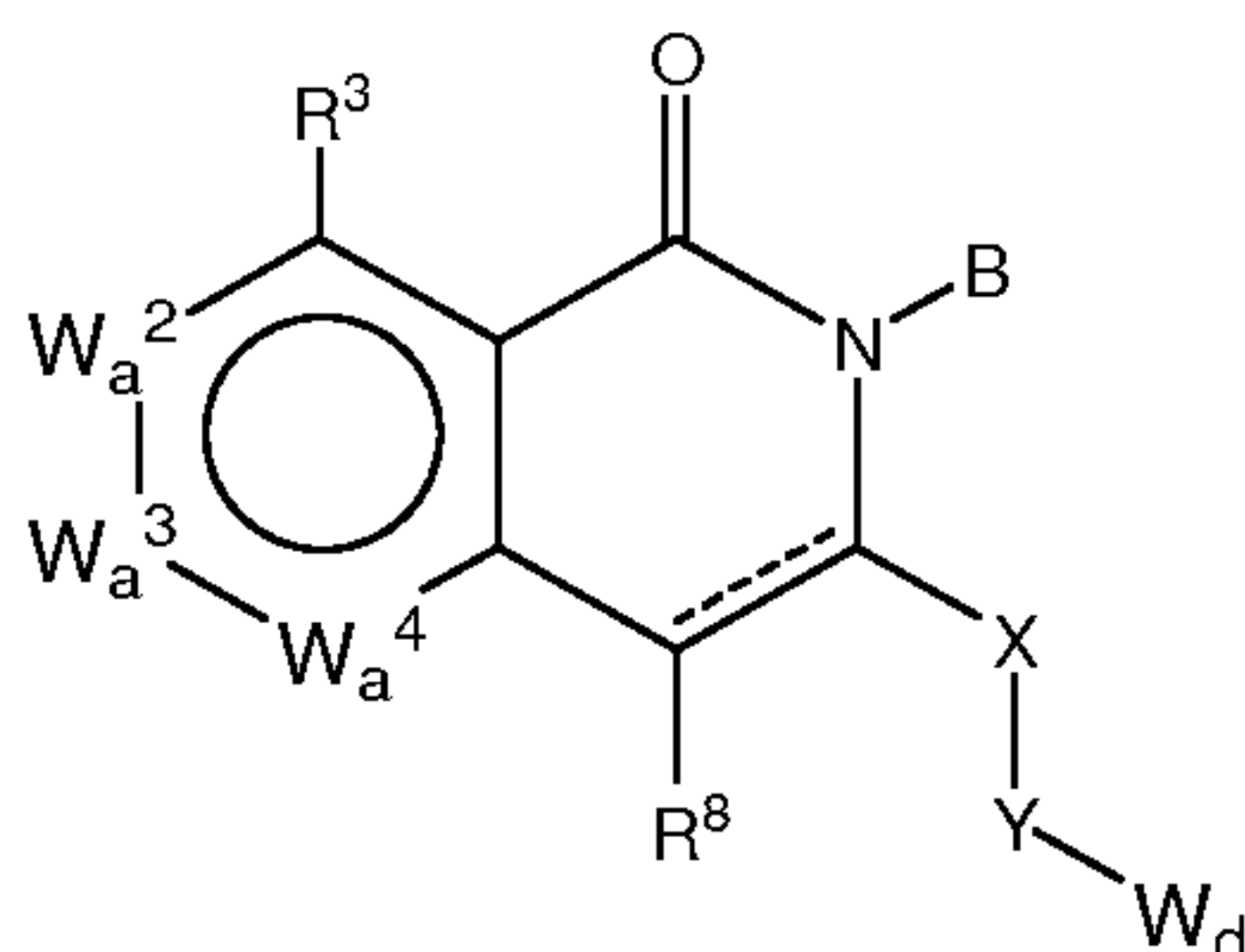
Formula XXIII-B



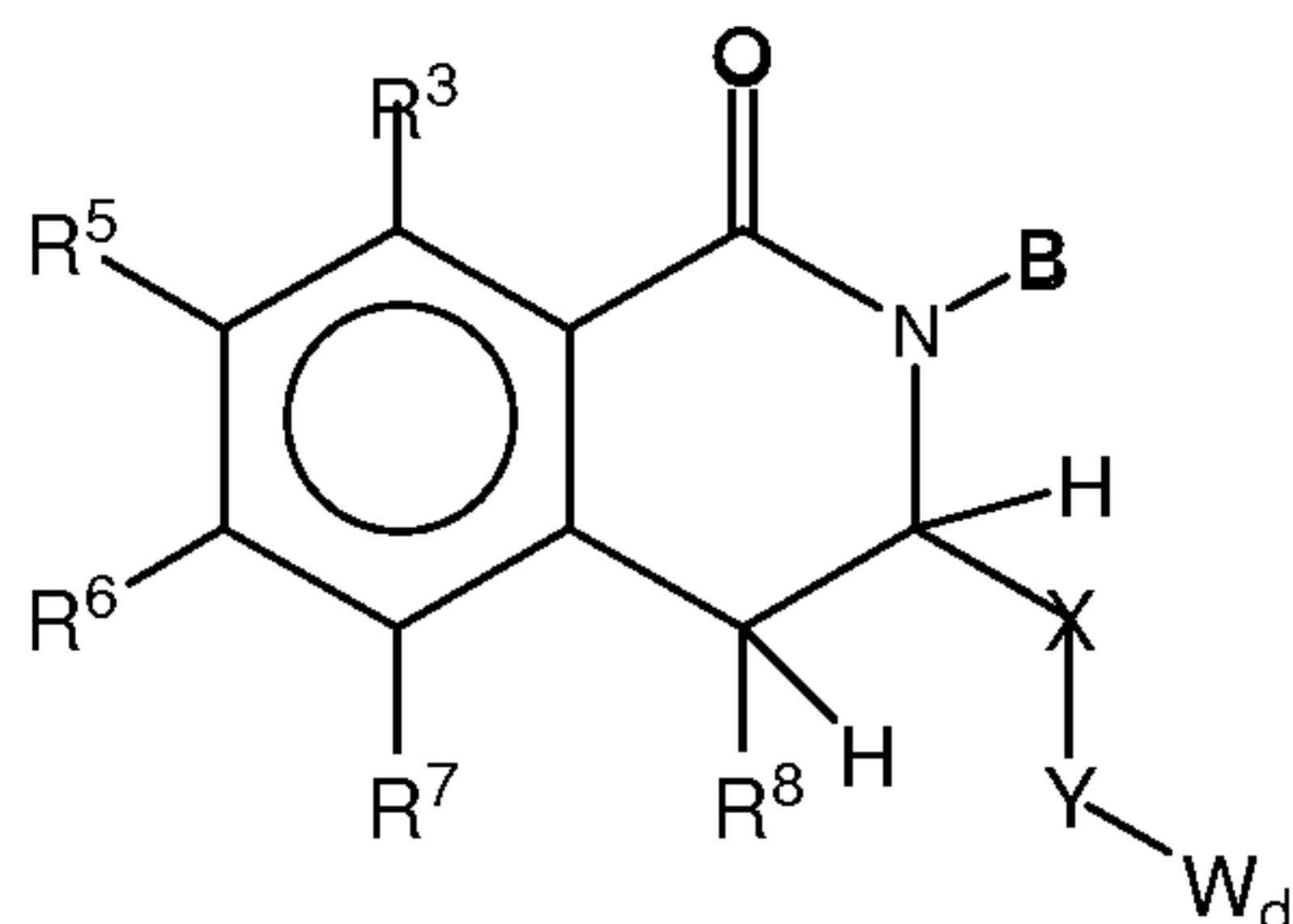
Formula XXIV-A



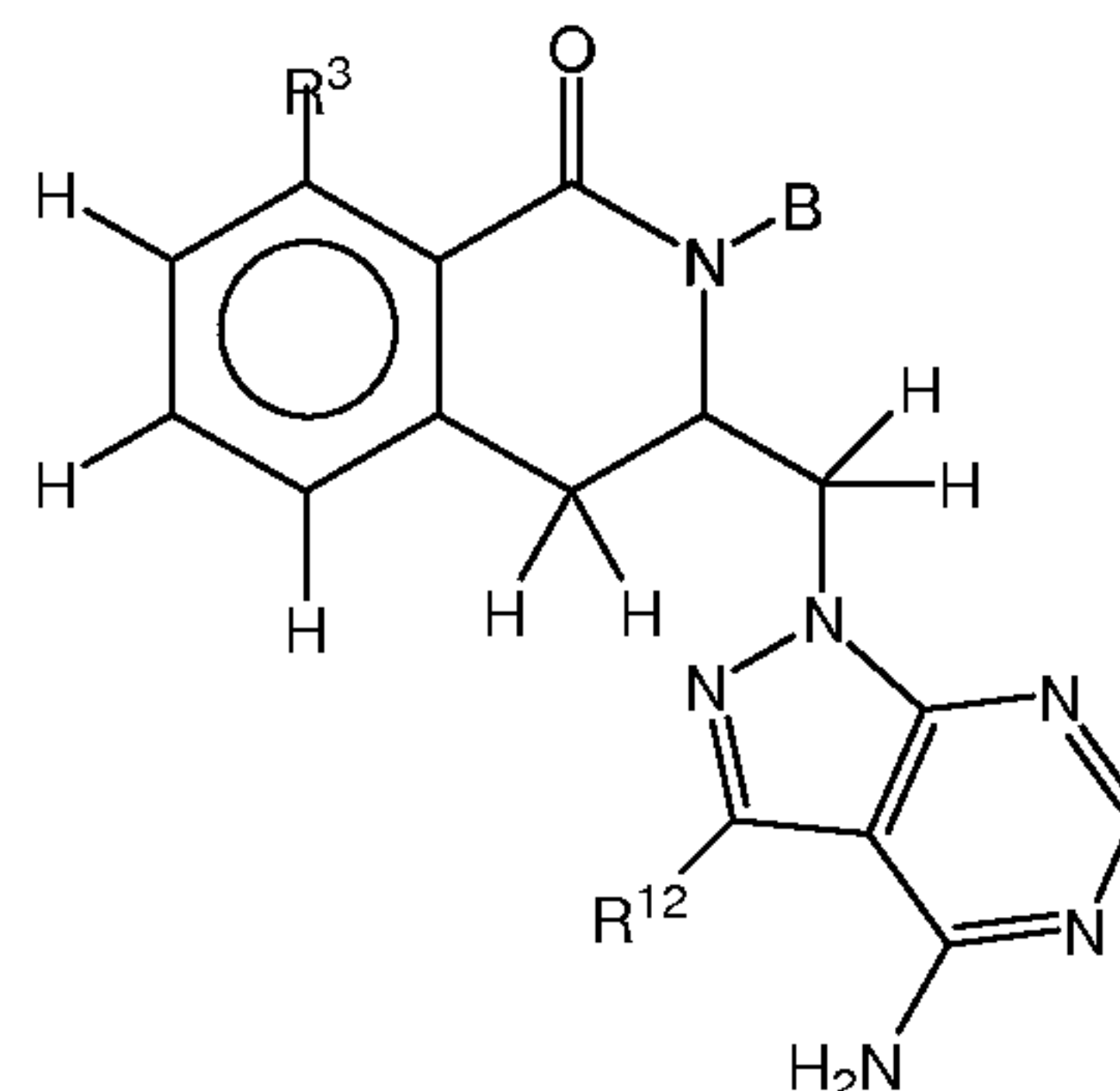
Formula XXIV-B



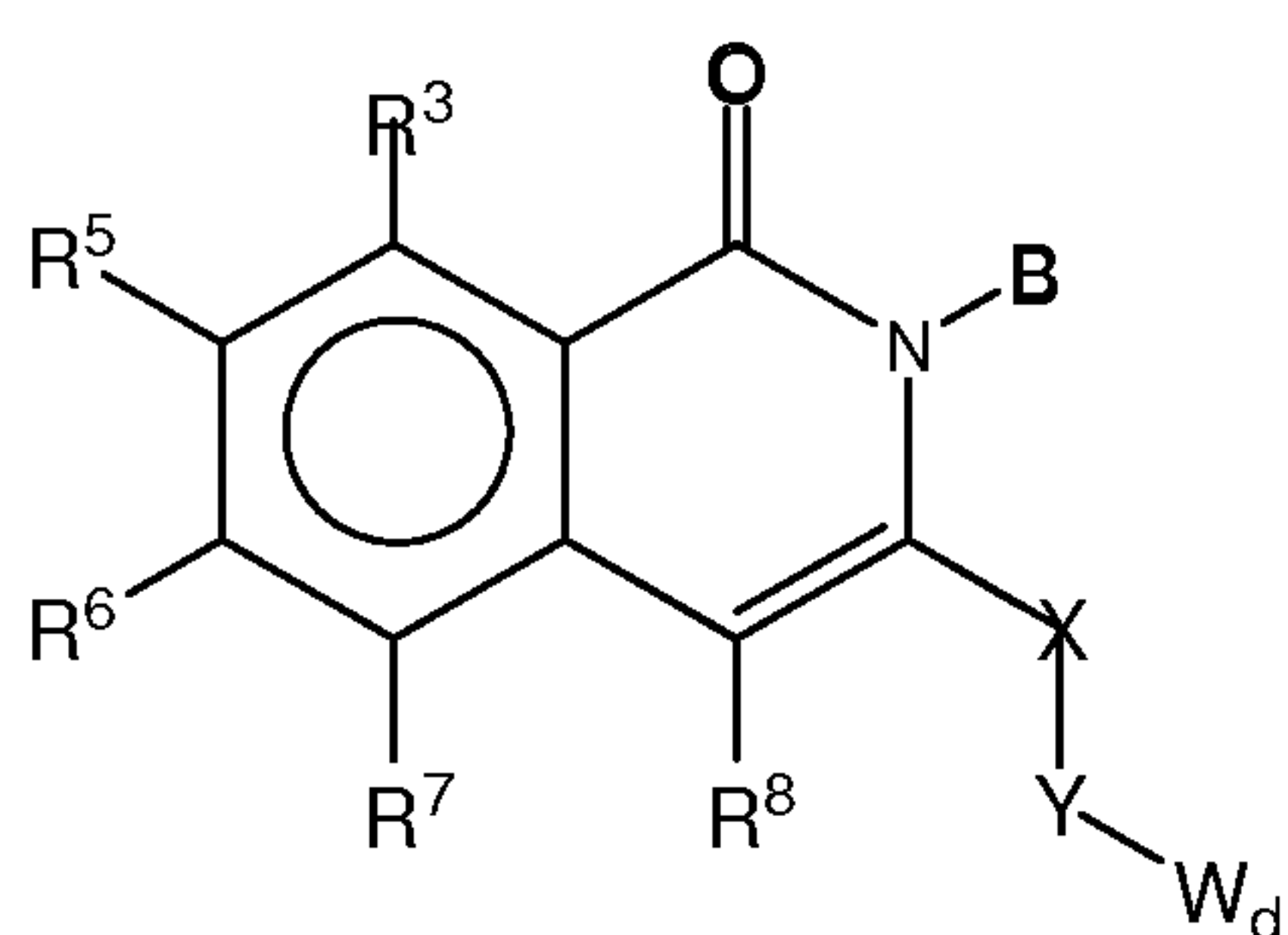
Formula XXV



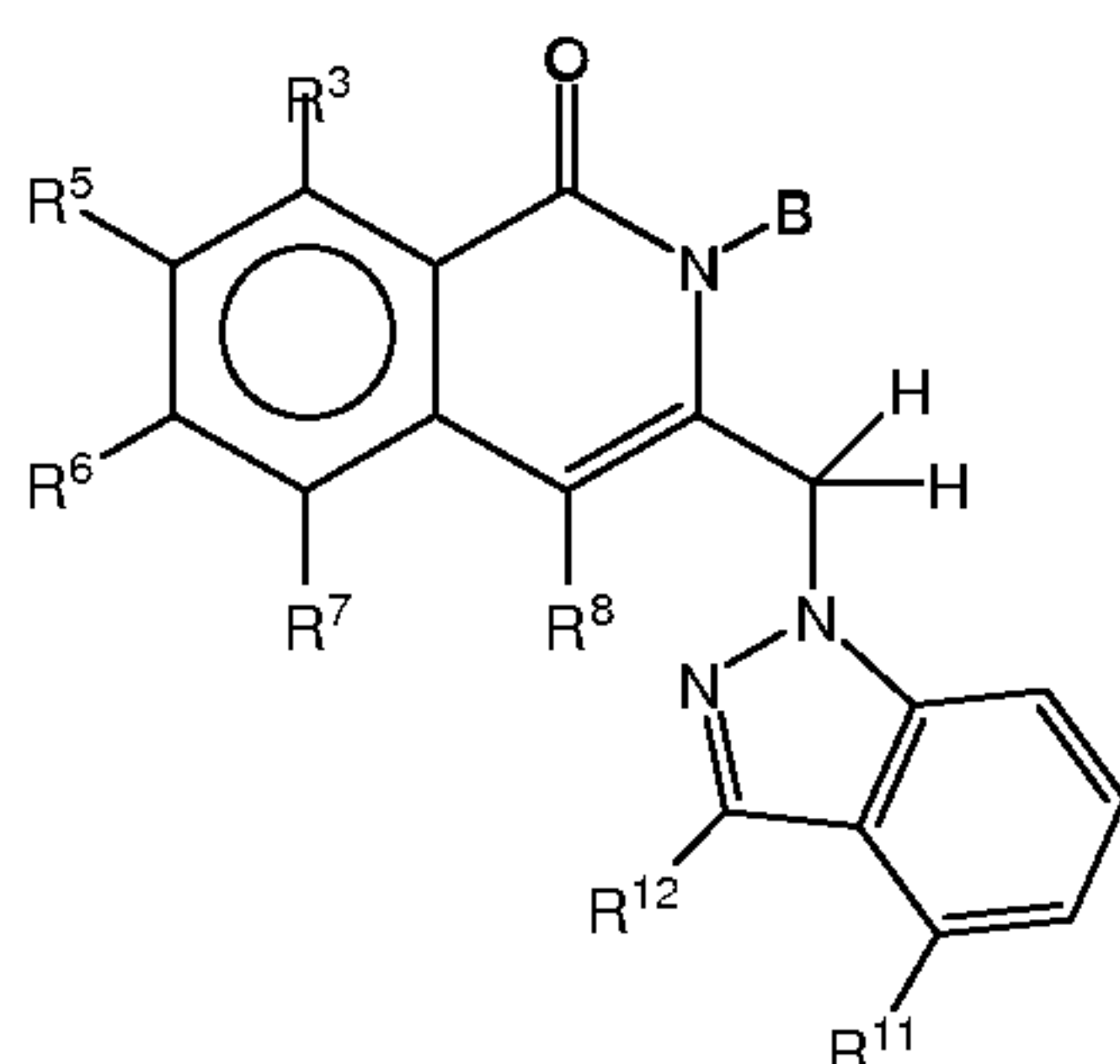
Formula XXVI



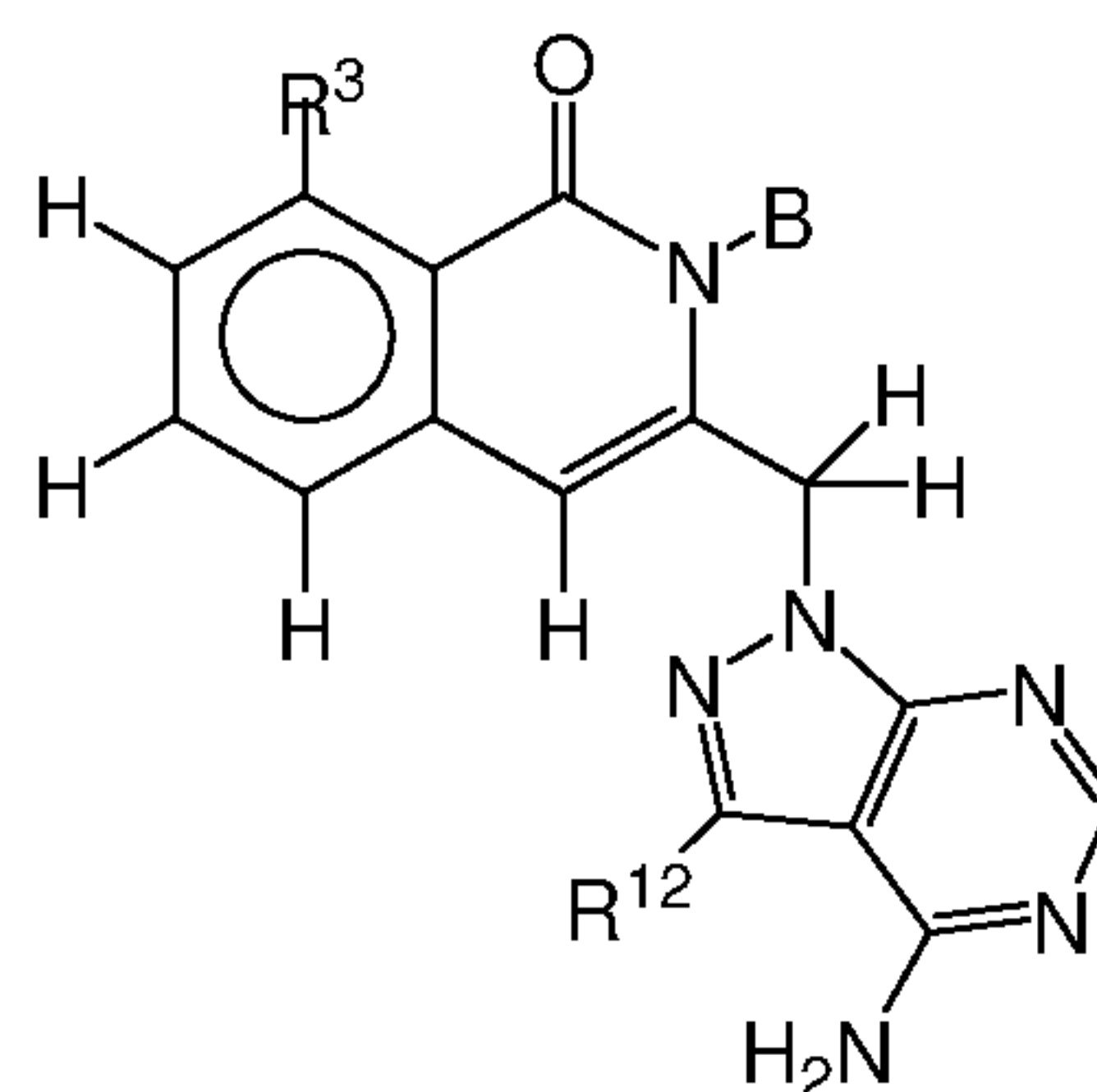
Formula XXVI-A



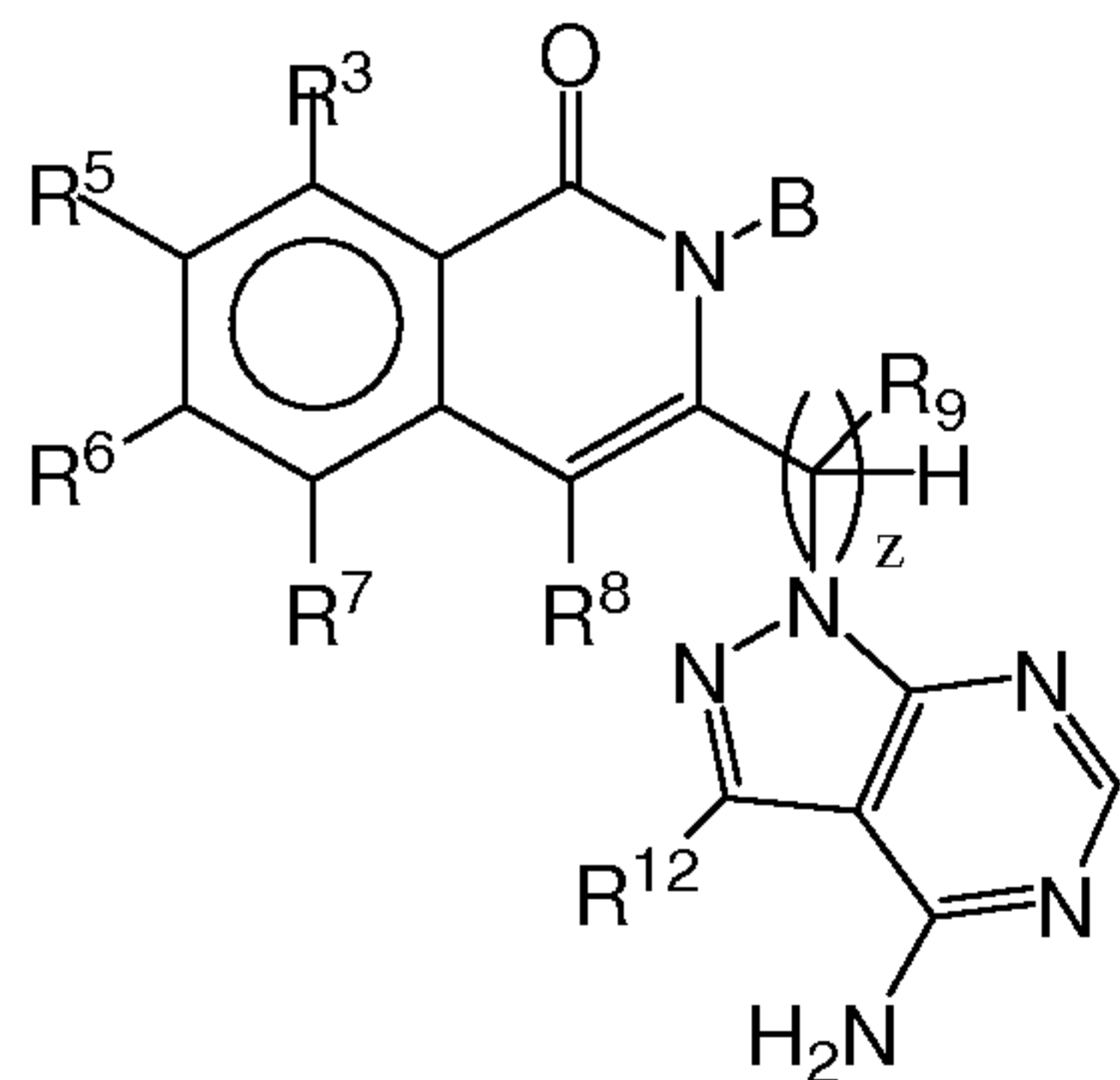
Formula XXVII



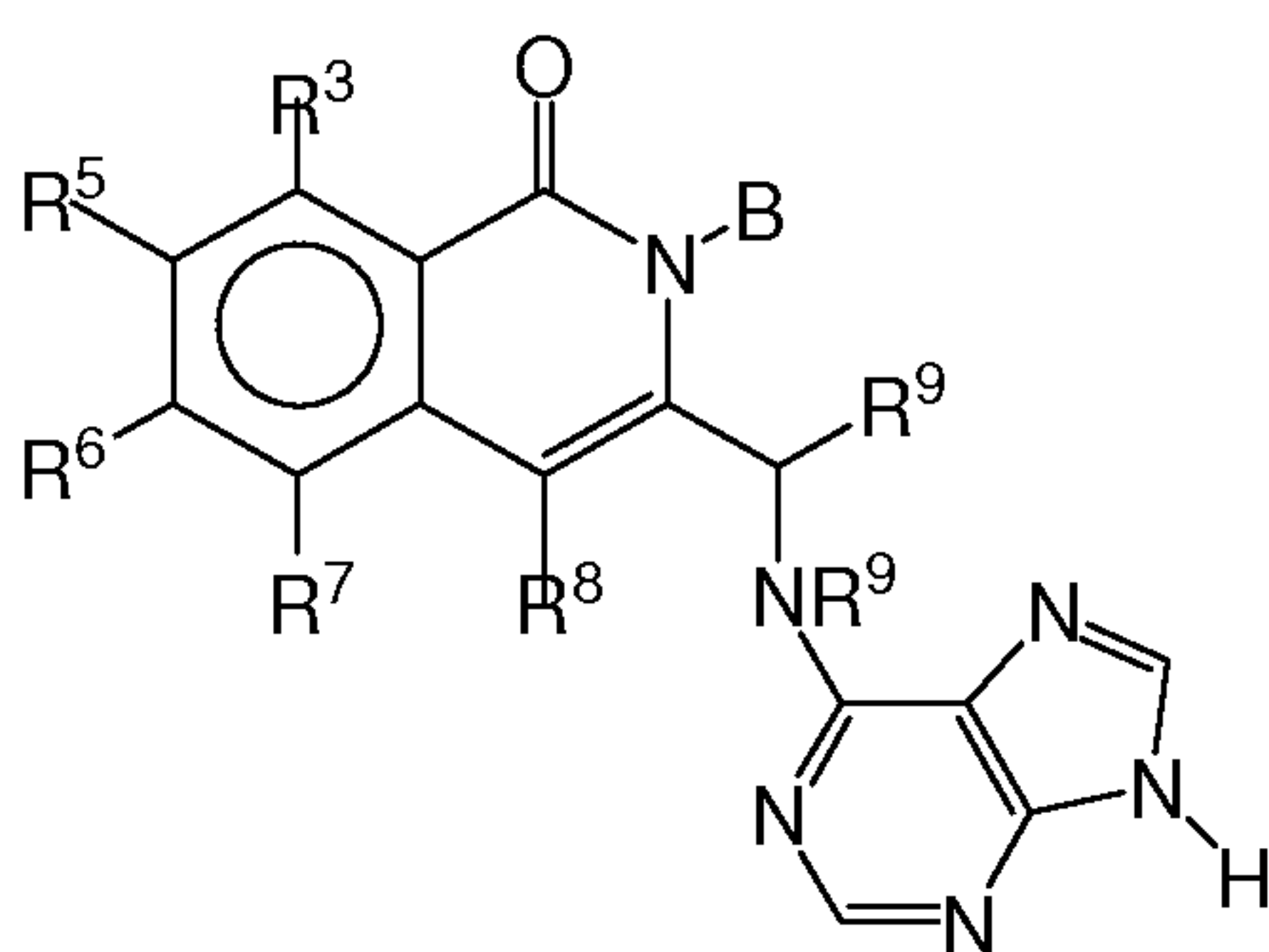
Formula XXVII-A



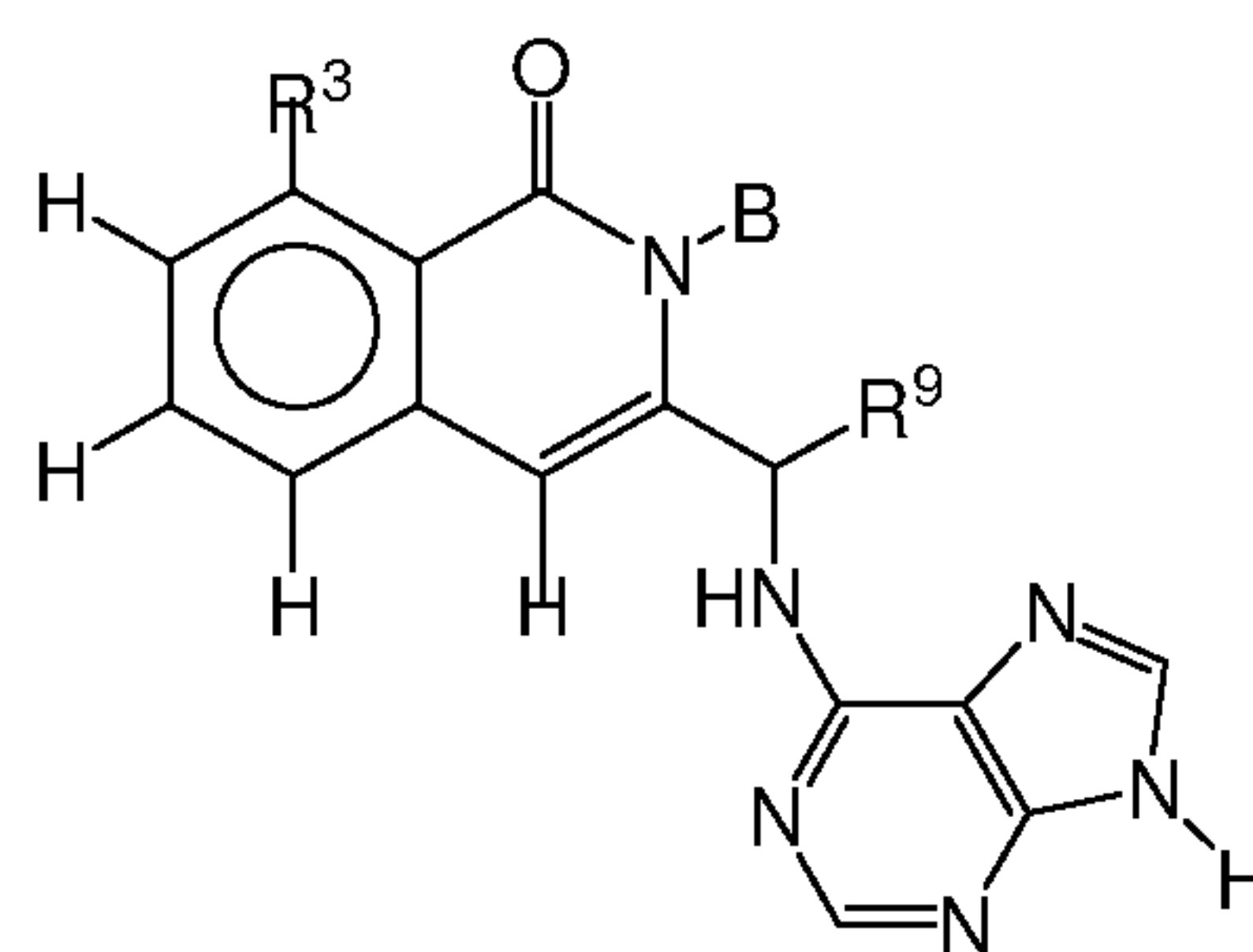
Formula XXVII-A1



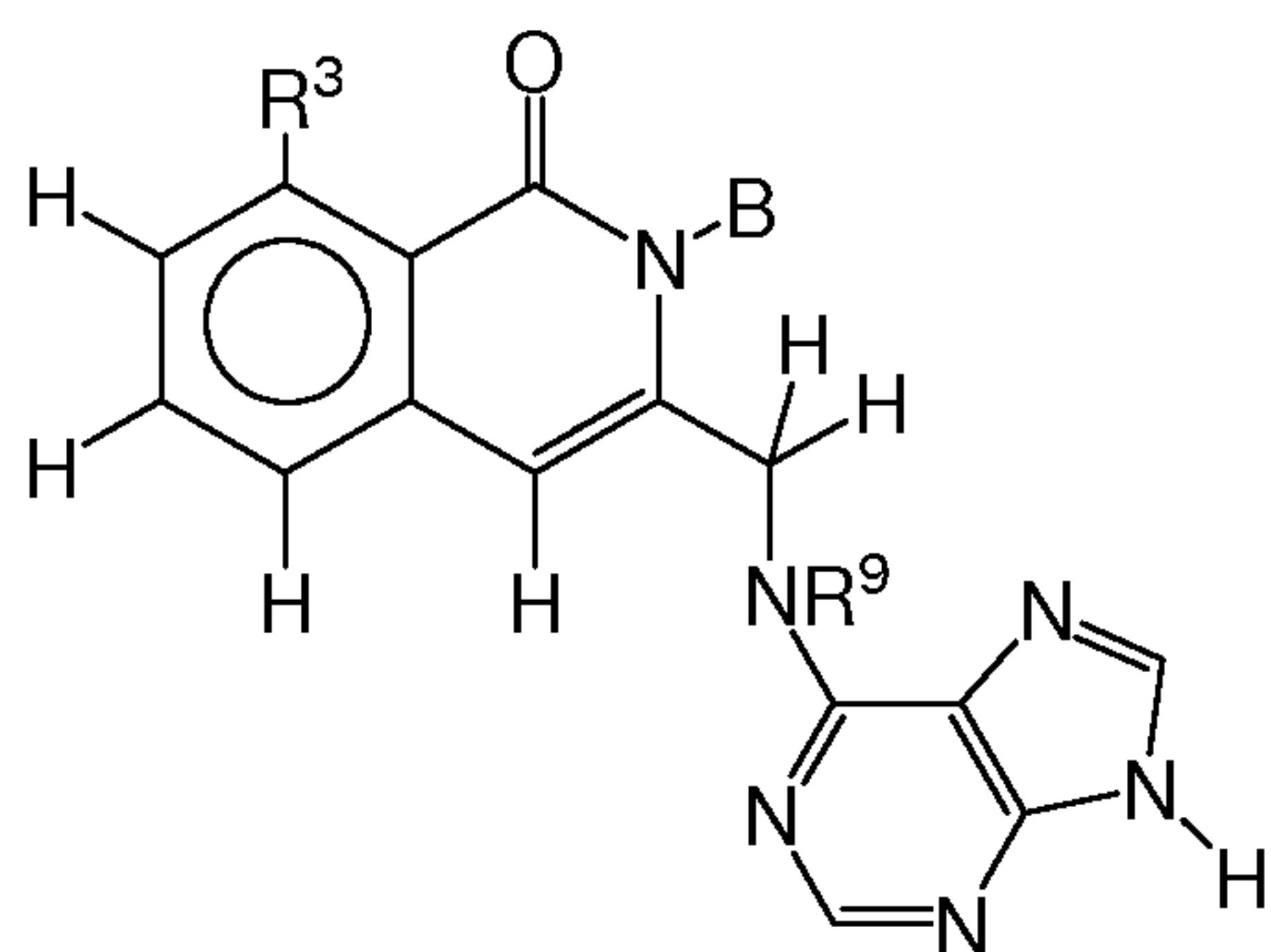
Formula XXVII-B



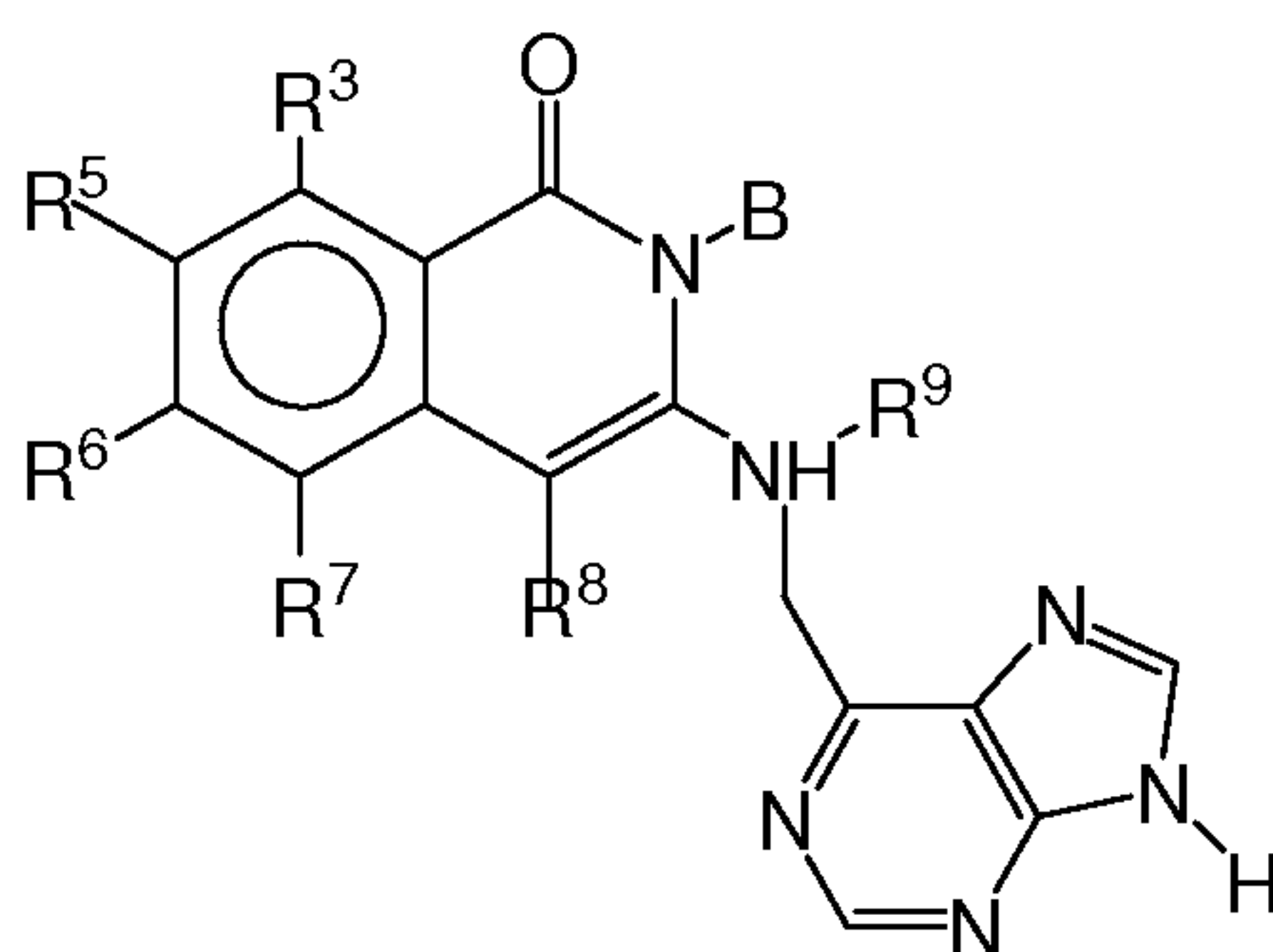
Formula XXVII-C



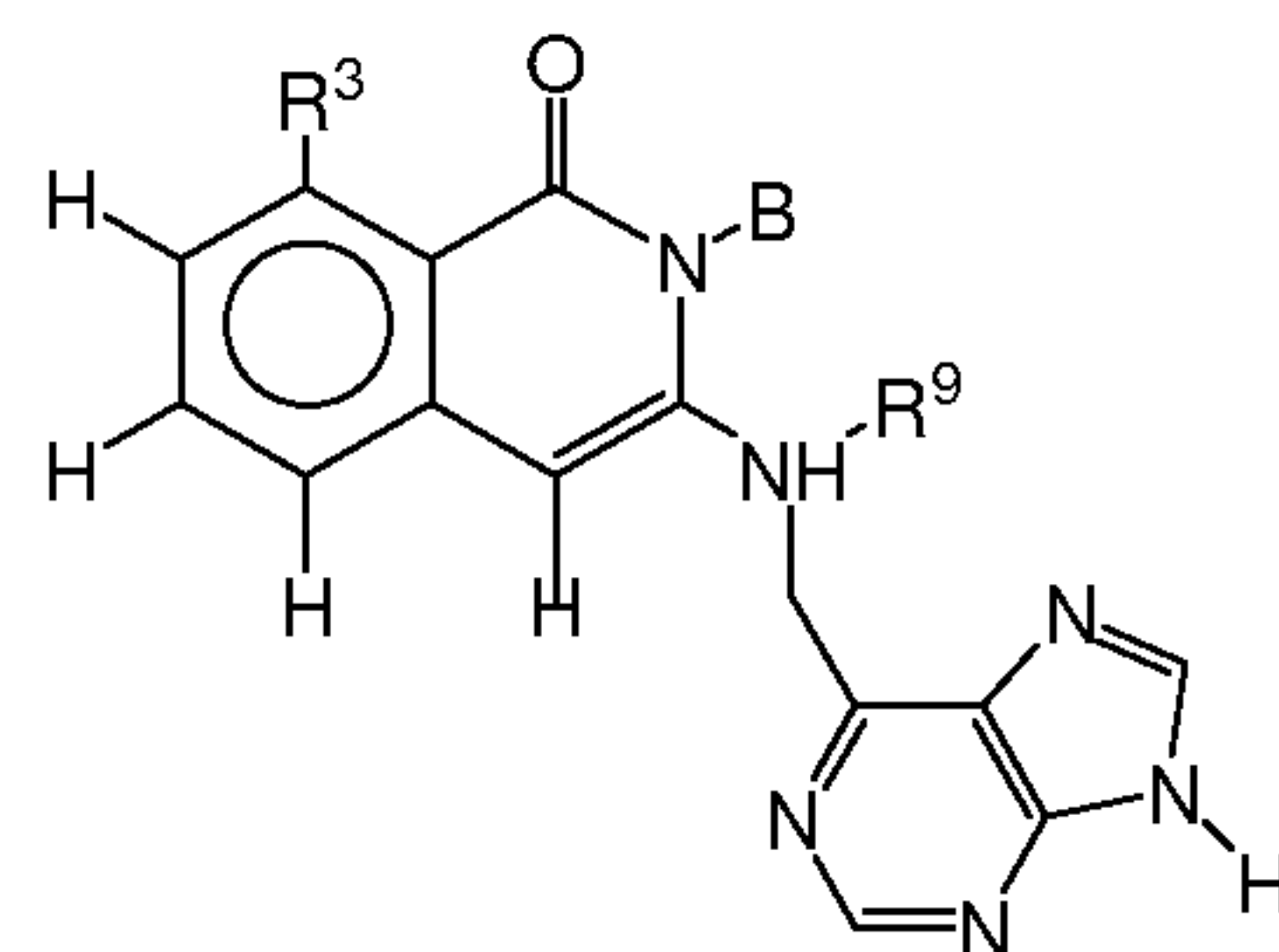
Formula XXVII-C1



Formula XXVII-C2

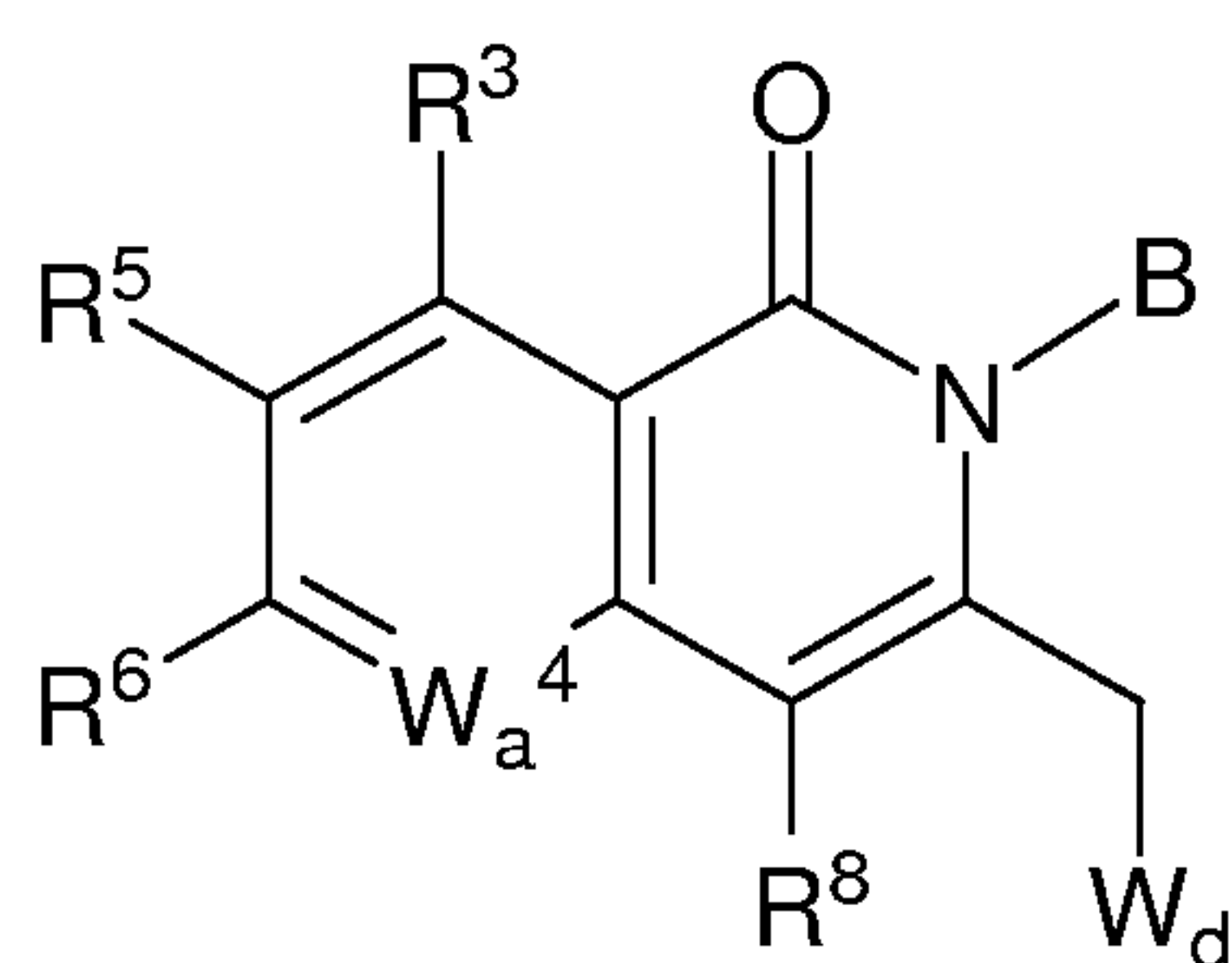


Formula XXVII-D

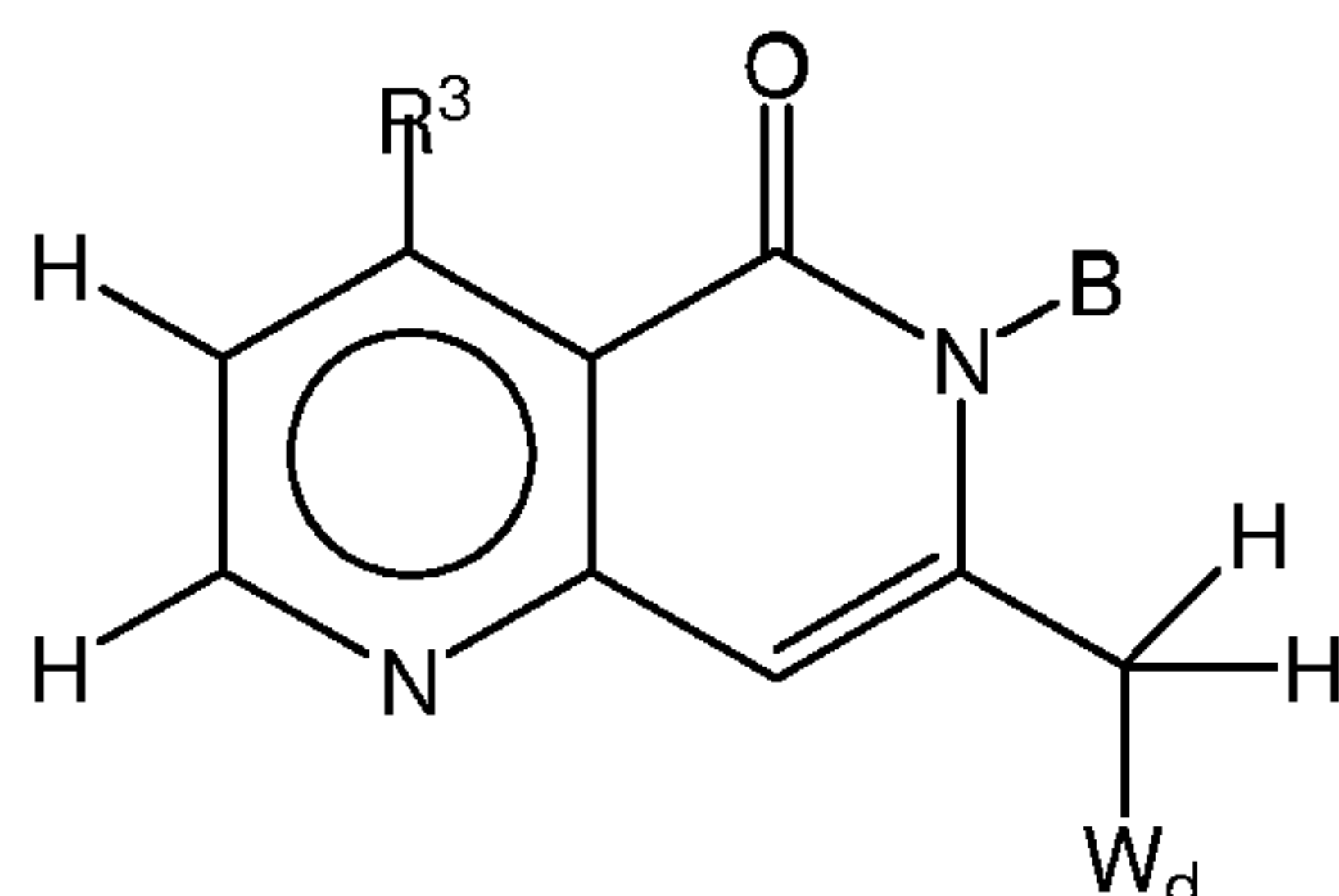


Formula XXVII-D

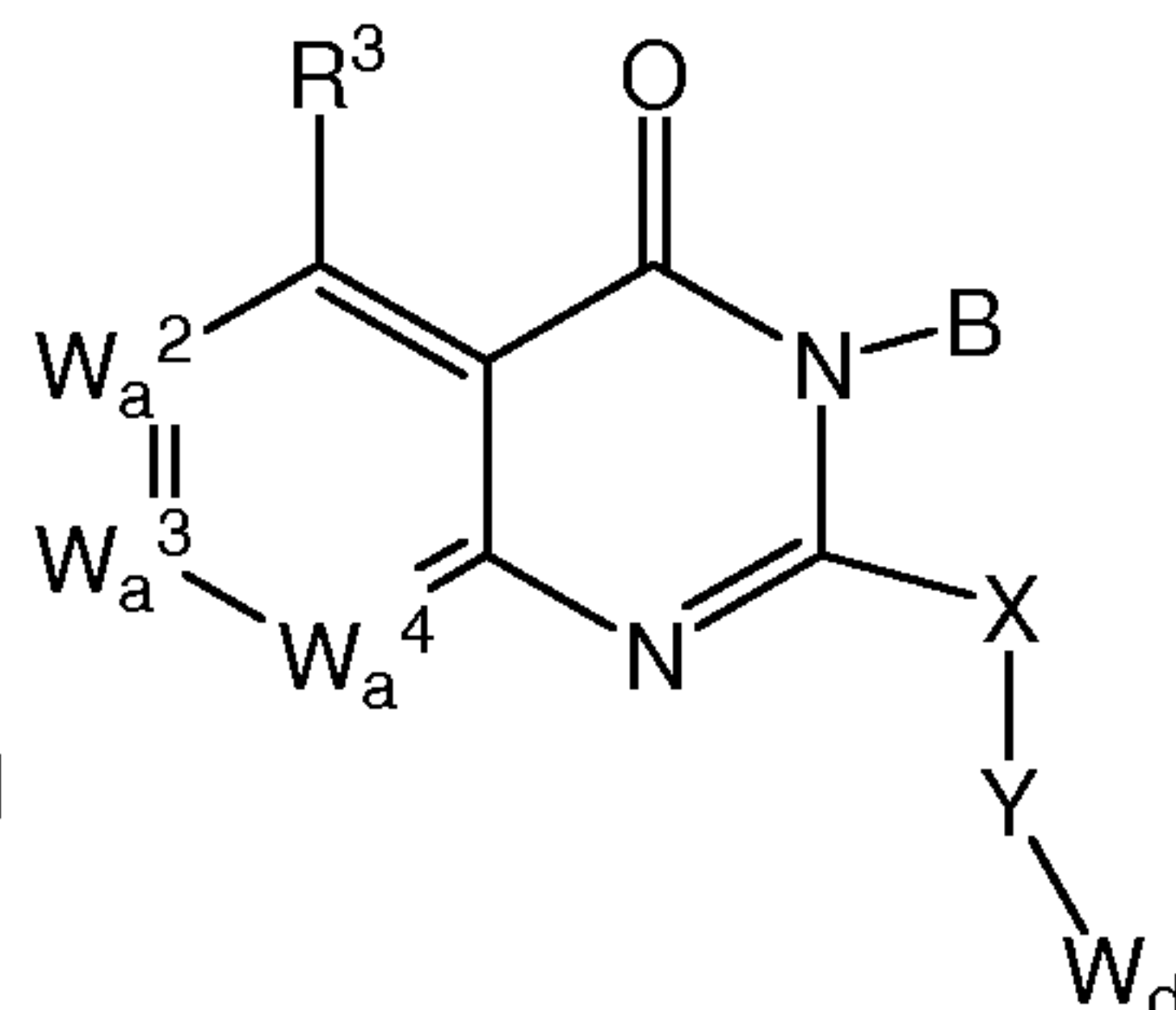
[00199] In another embodiment, the compound of Formula I is a compound which has a structure selected from Formula XXVIII, XXVIII-A, XXIX, XXIX-A, and XXIX-A1:



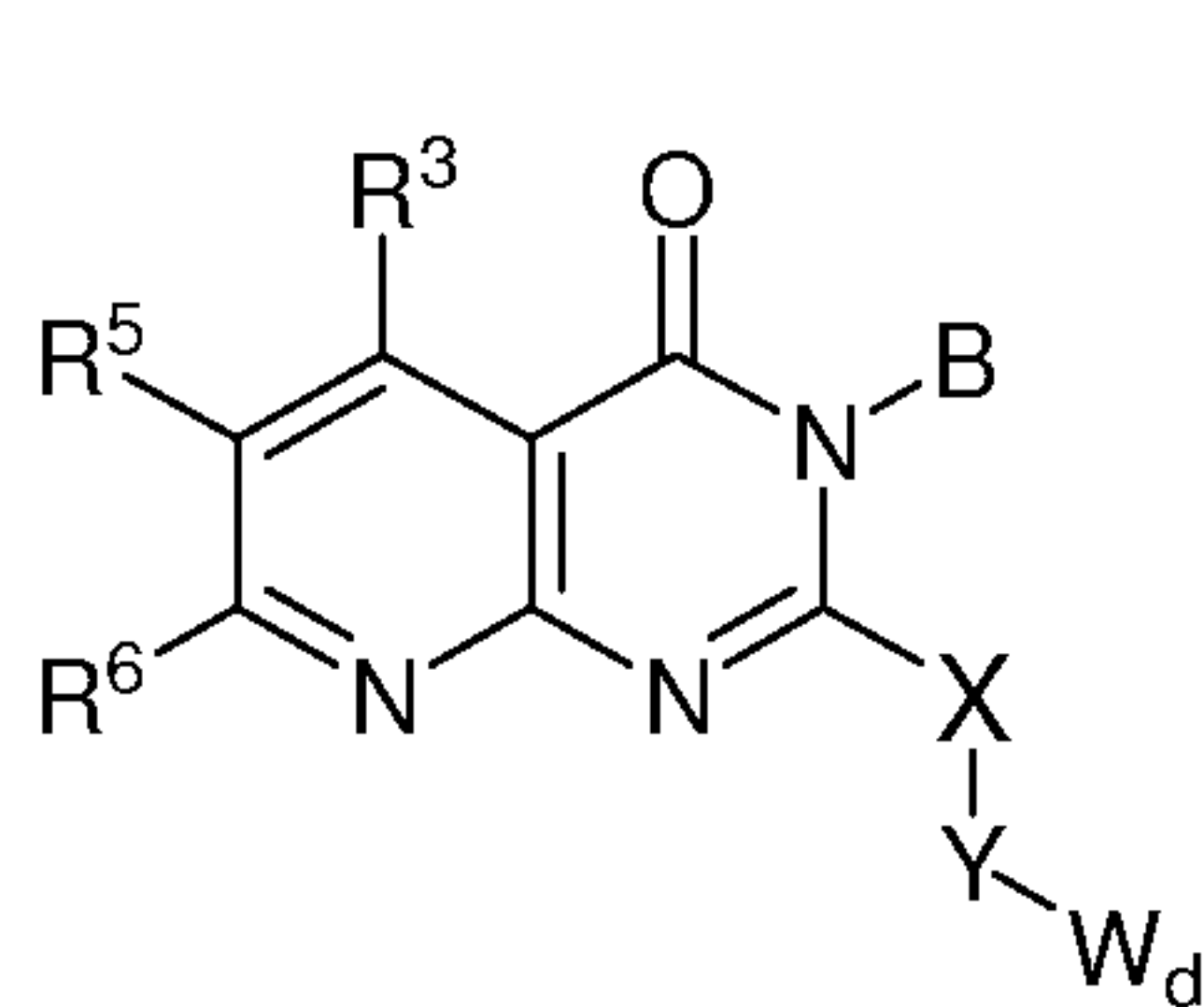
Formula XXVIII



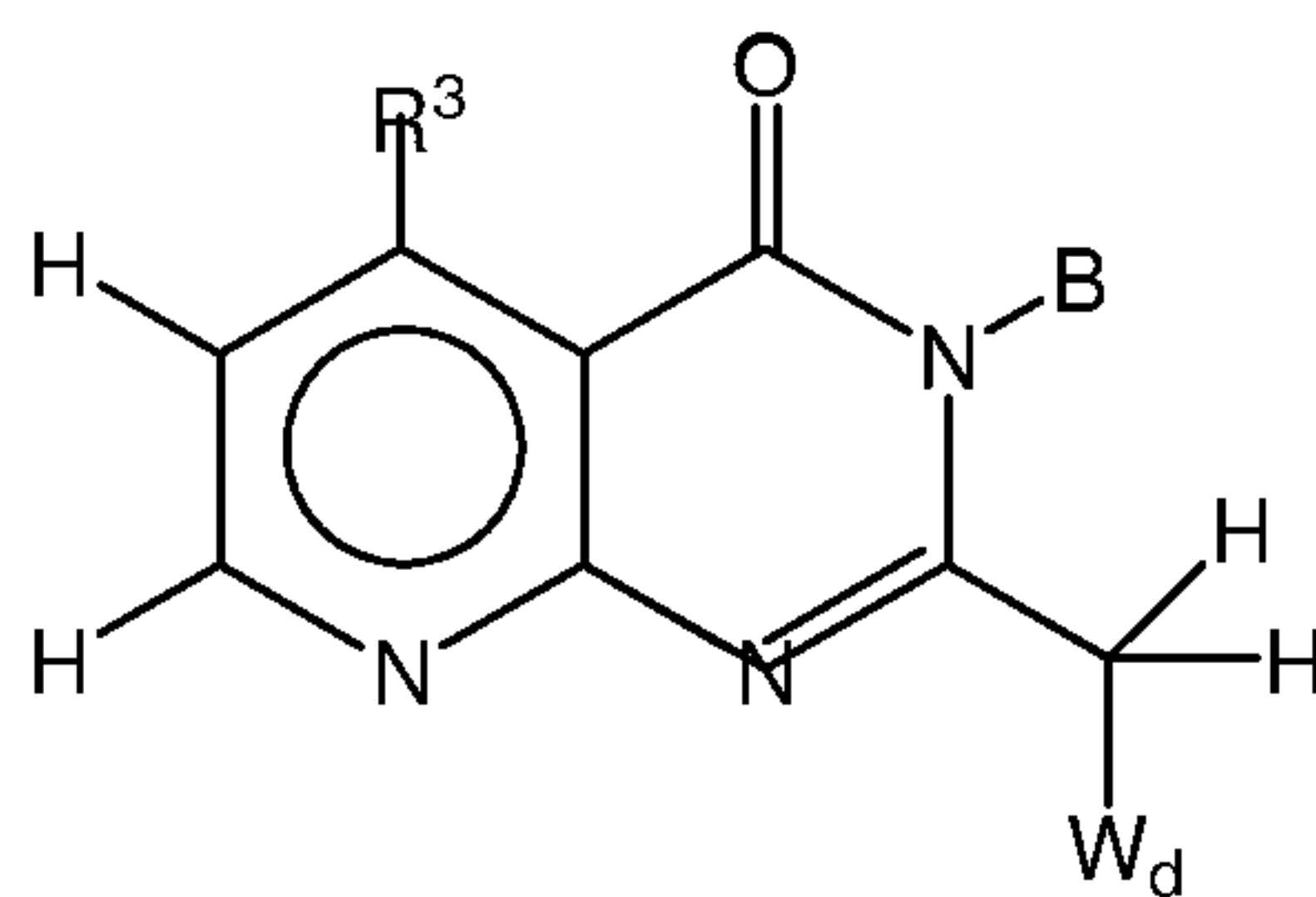
Formula XXVIII-A



Formula XXIX

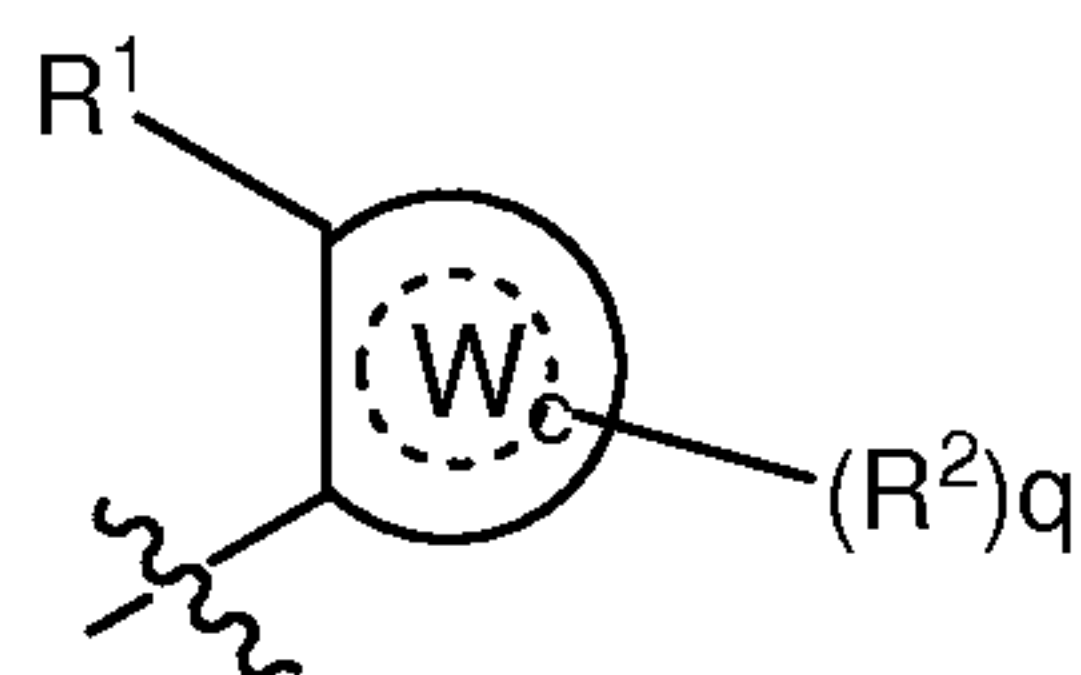


Formula XXIX-A



Formula XXIX-A1

[00200] In one aspect, for compounds described herein, R_3 is H, CH_3 , CF_3 , Cl, F, aryl, or heteroaryl; B is alkyl or a moiety of Formula II:

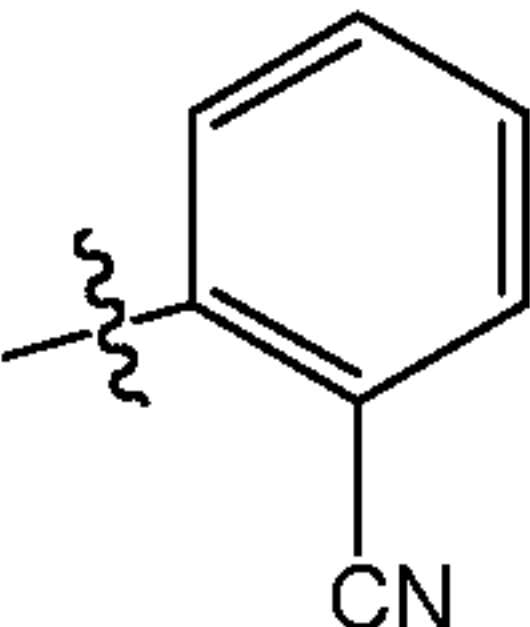
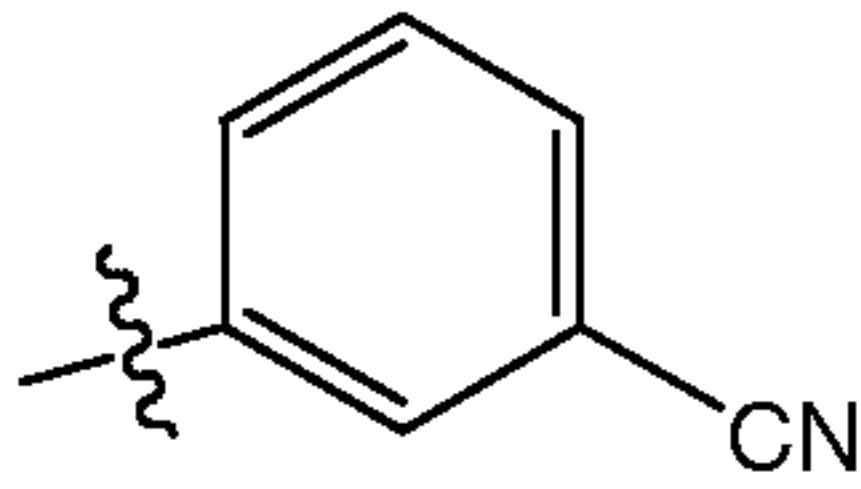
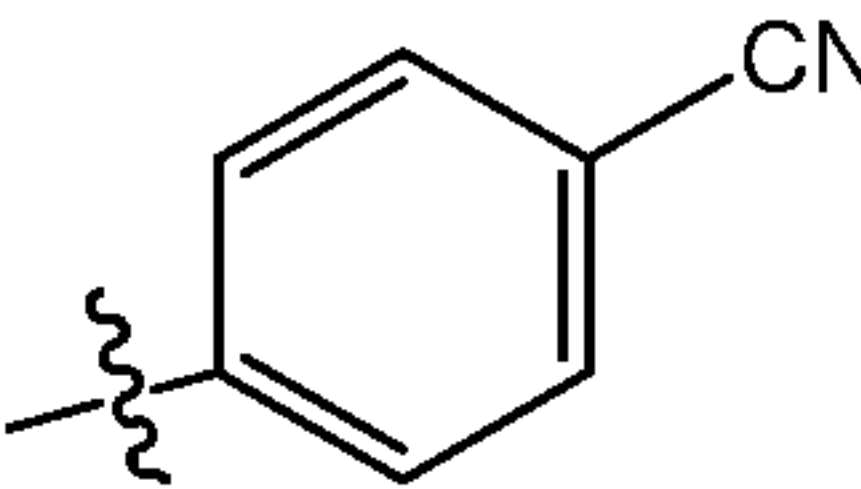
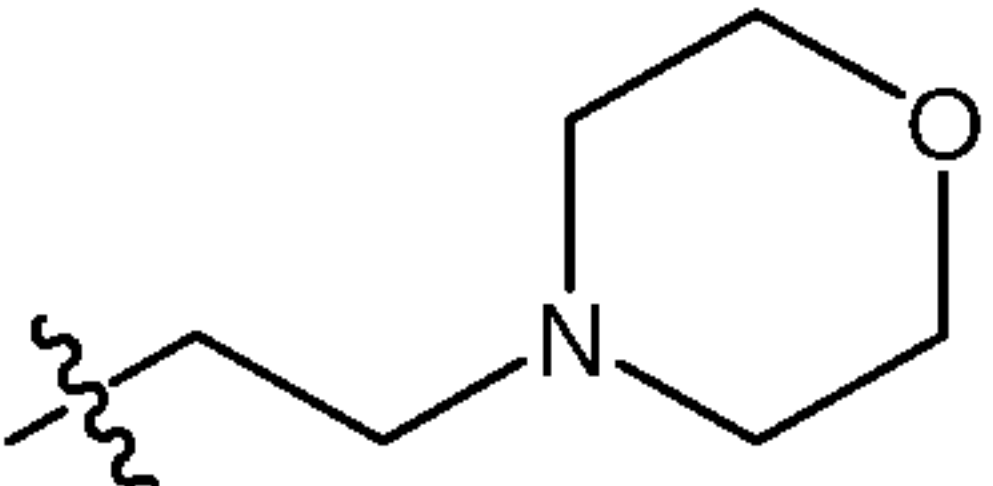
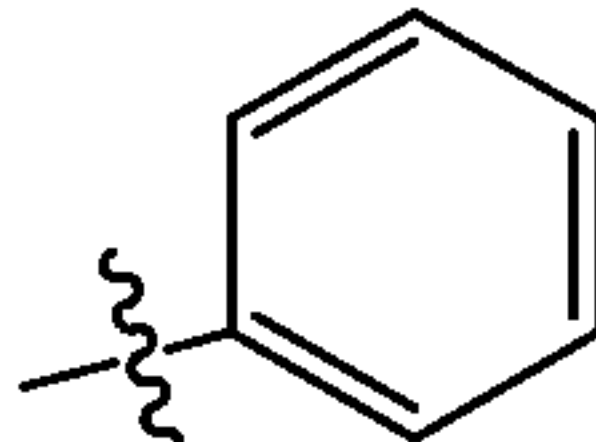
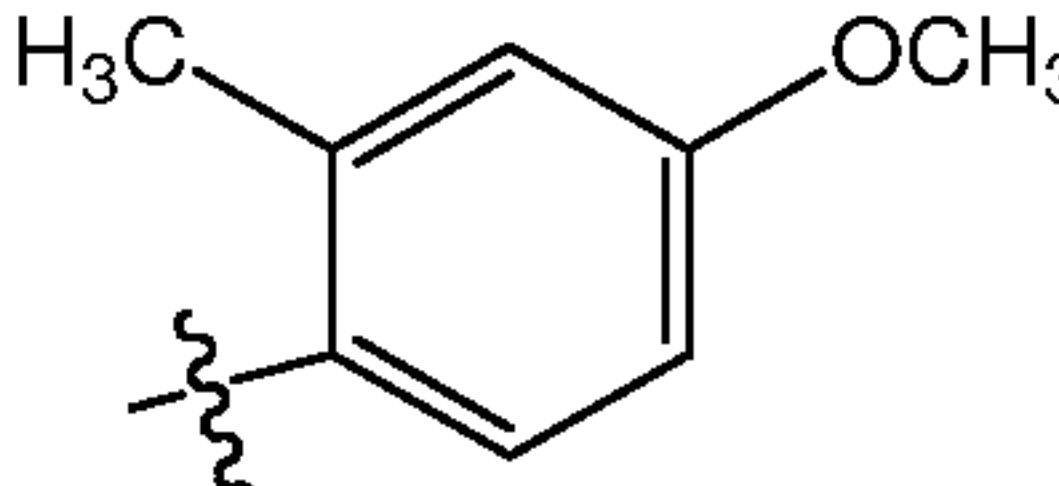
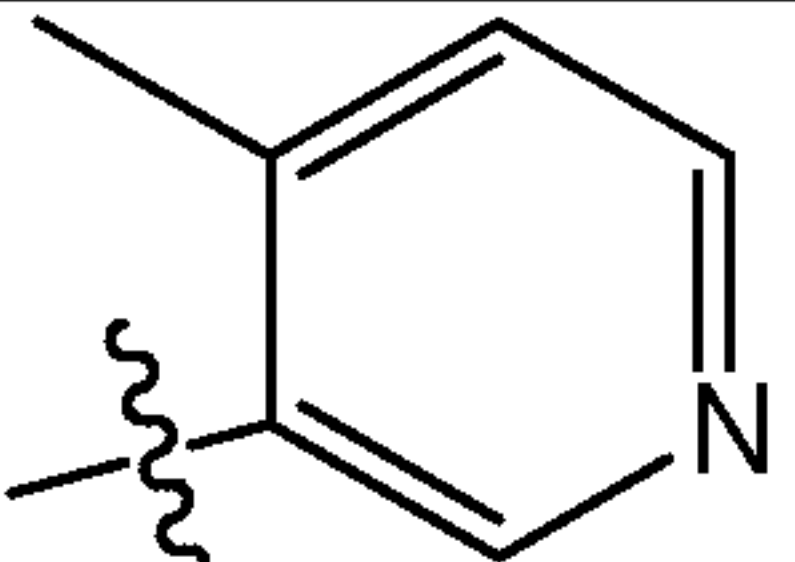
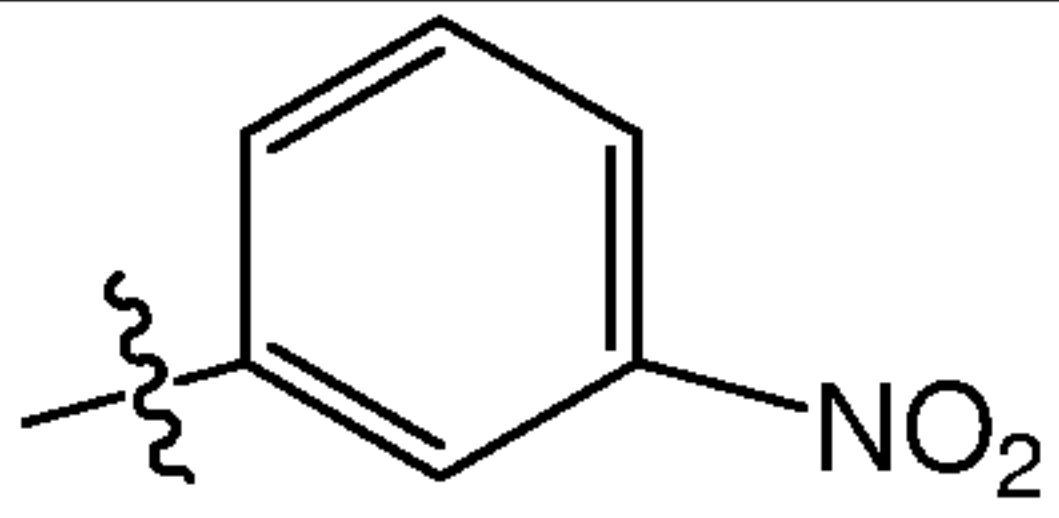
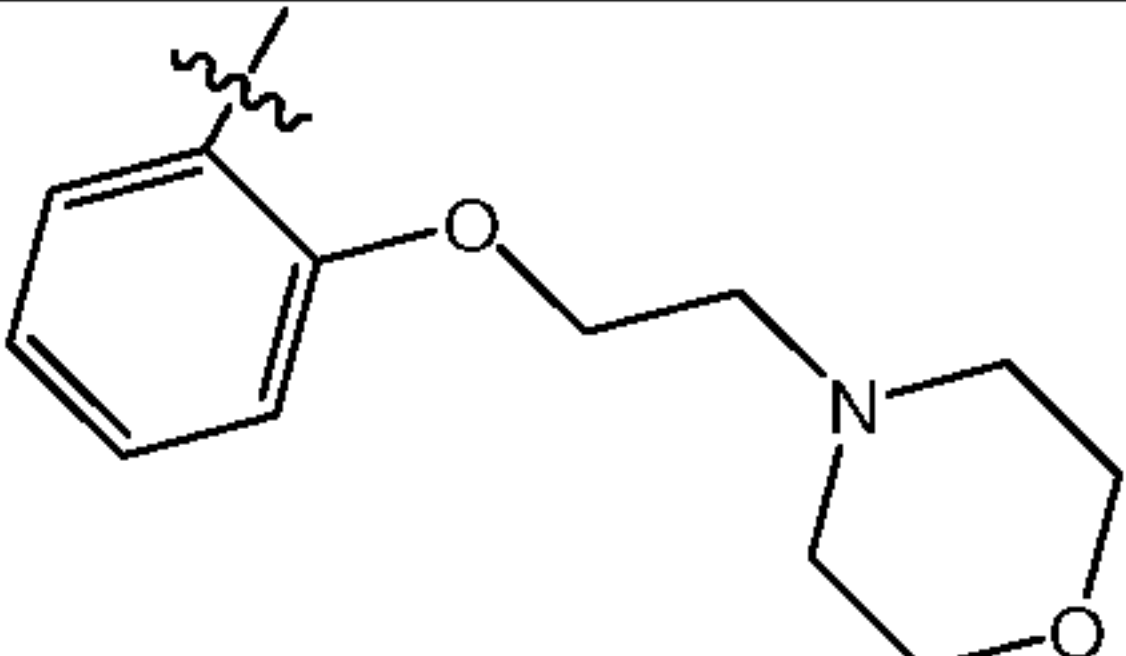
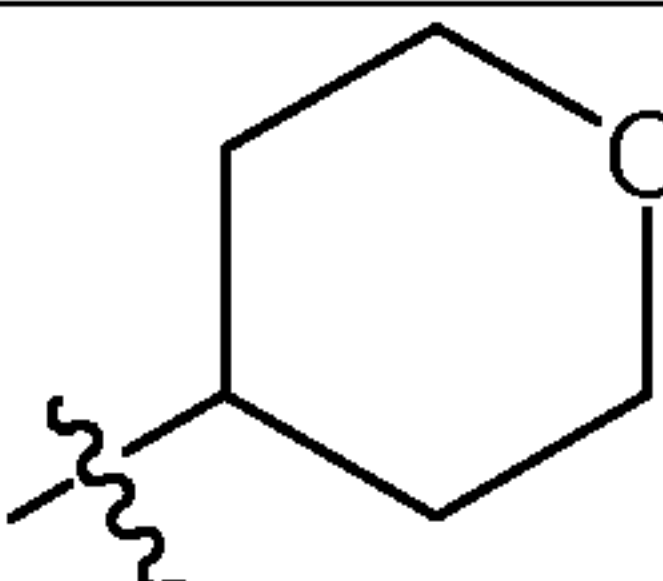
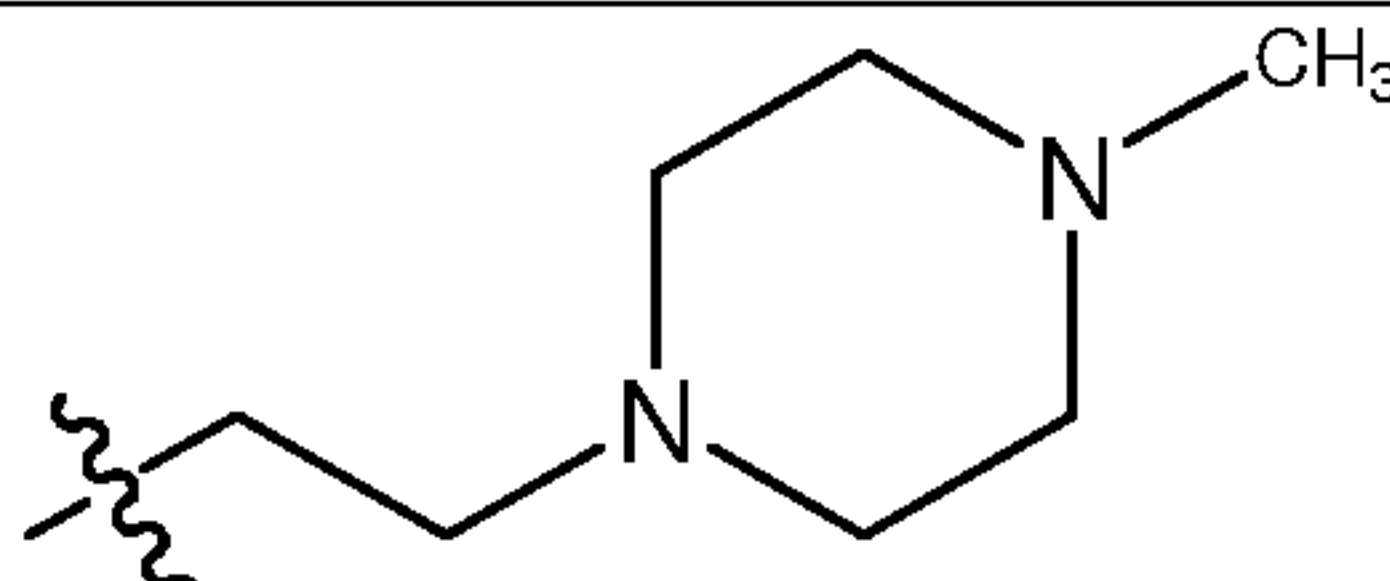
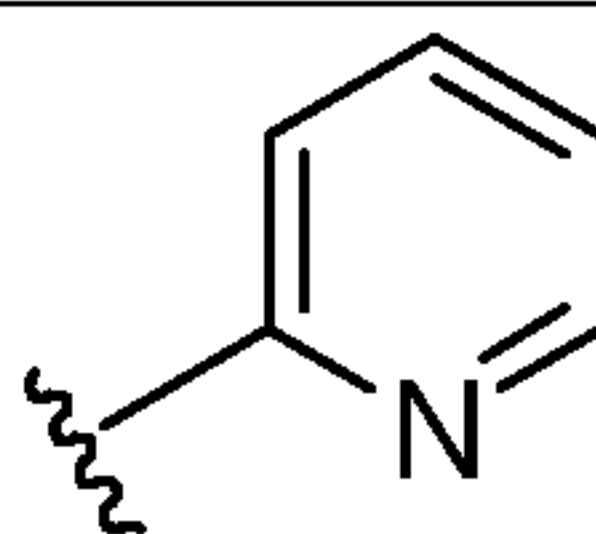
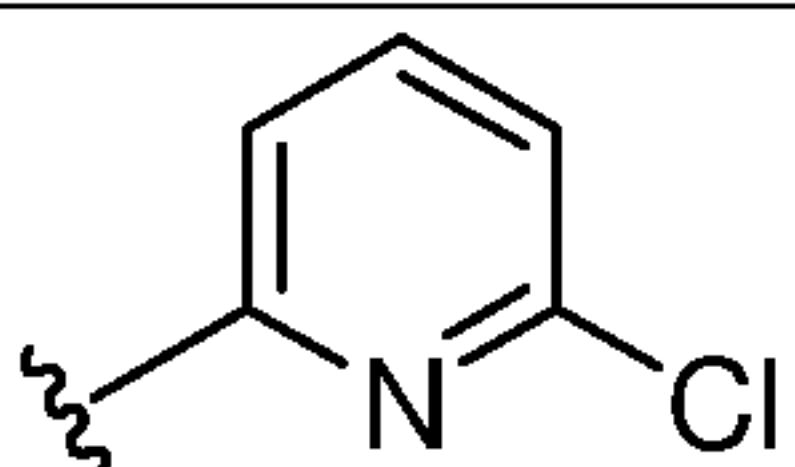
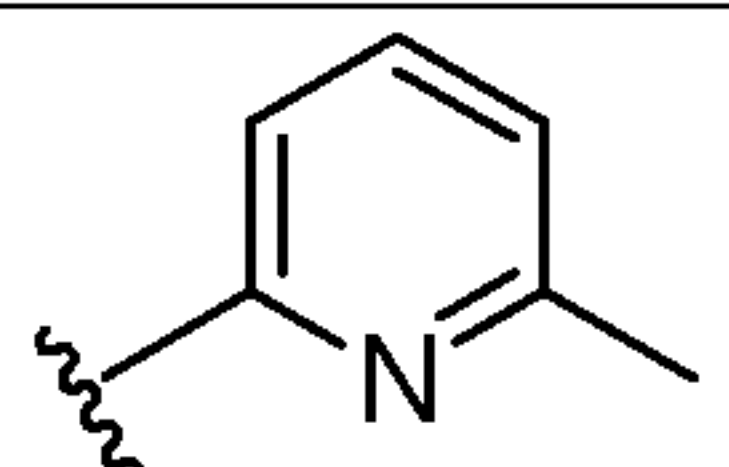
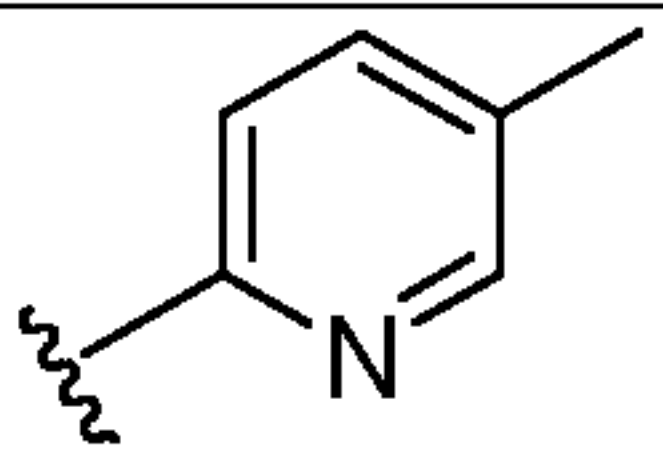
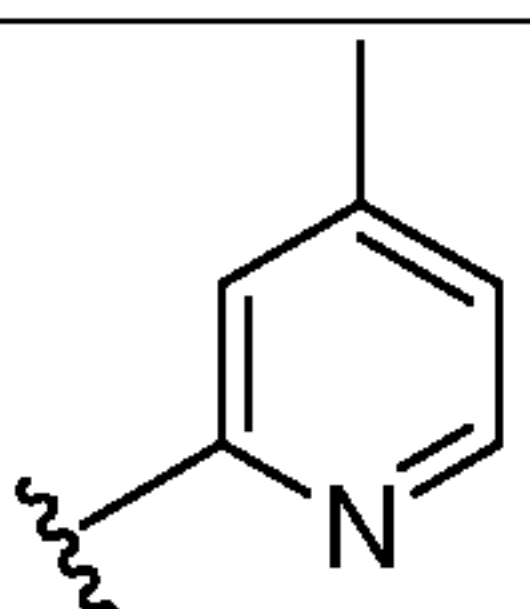
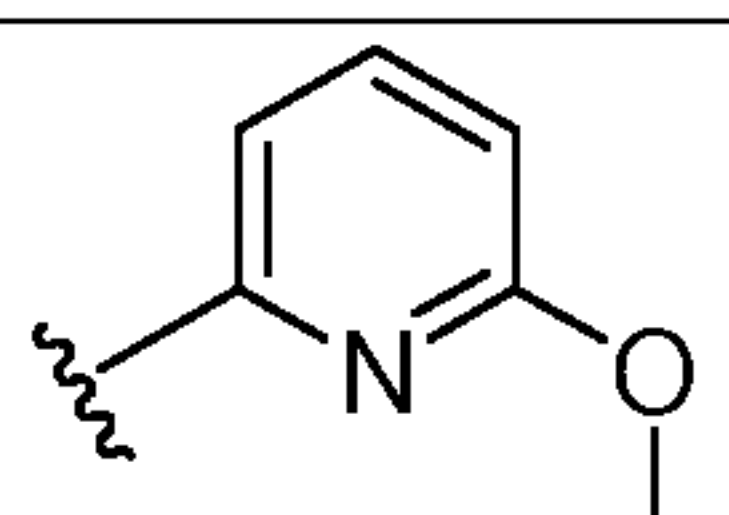
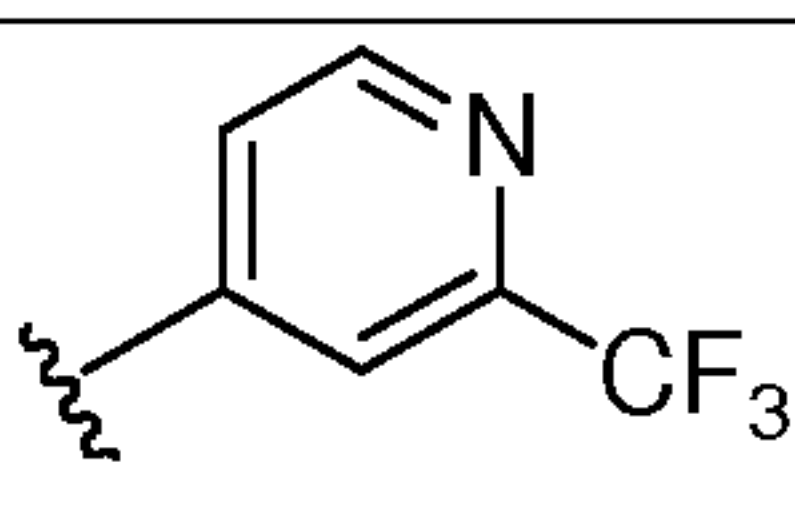
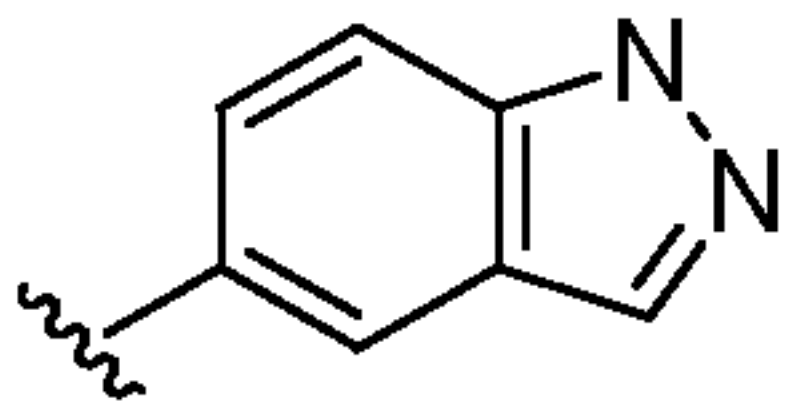
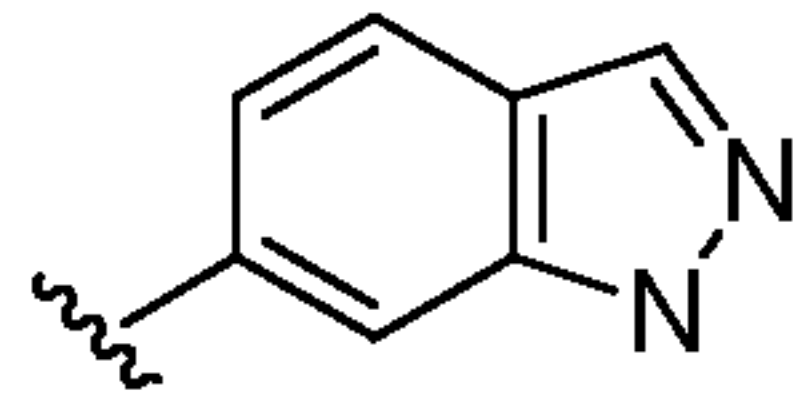
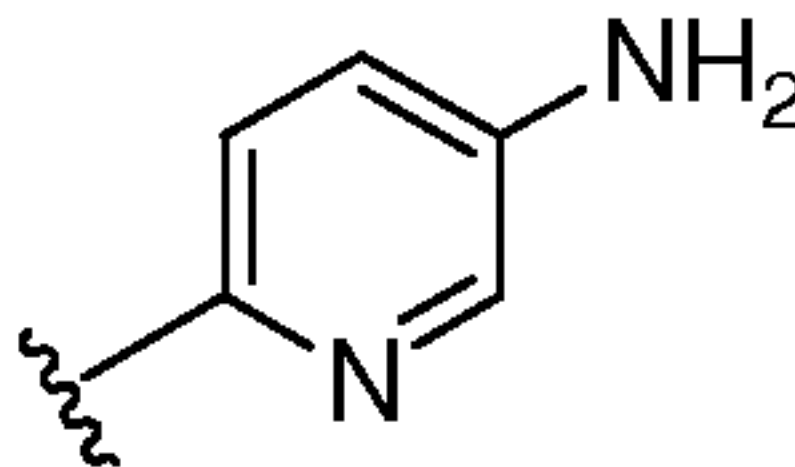
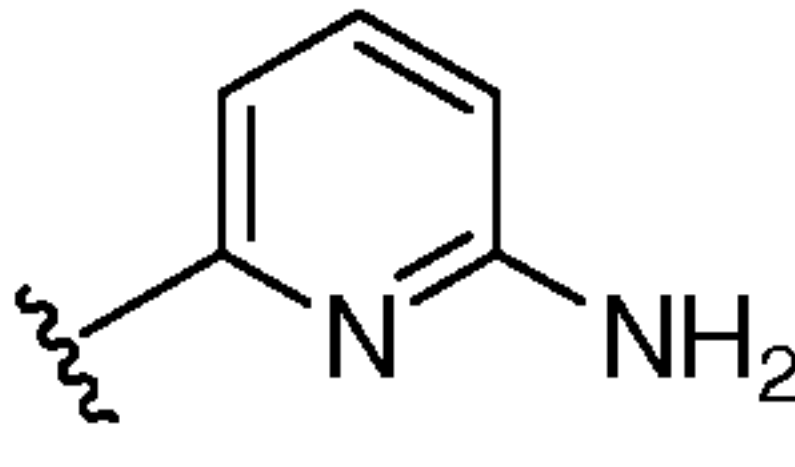
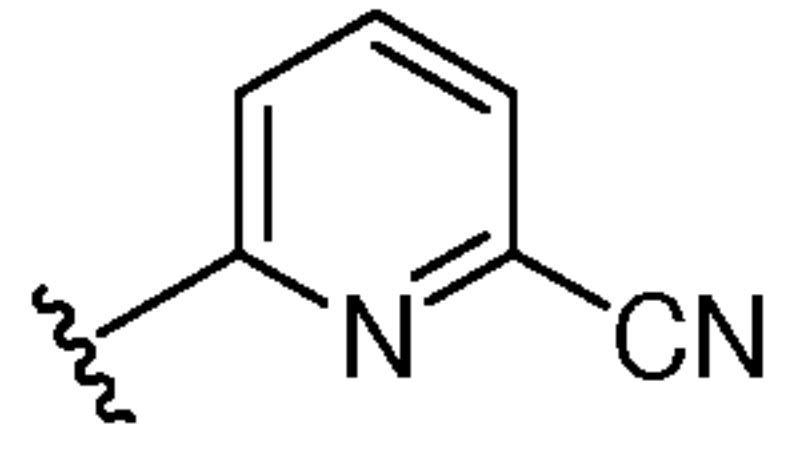
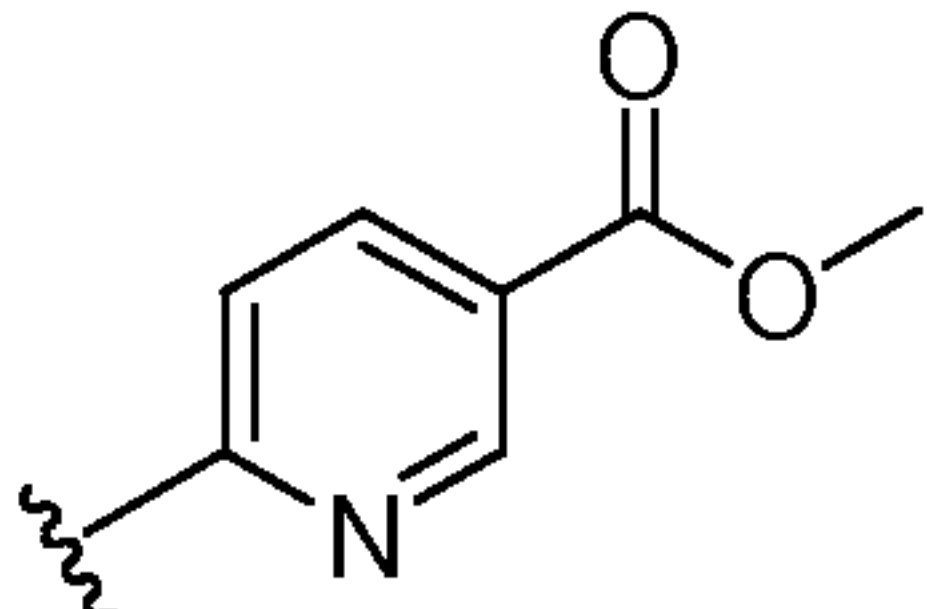
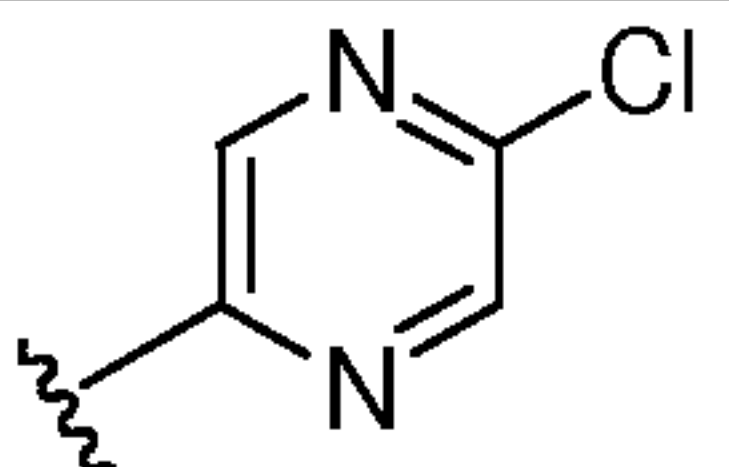
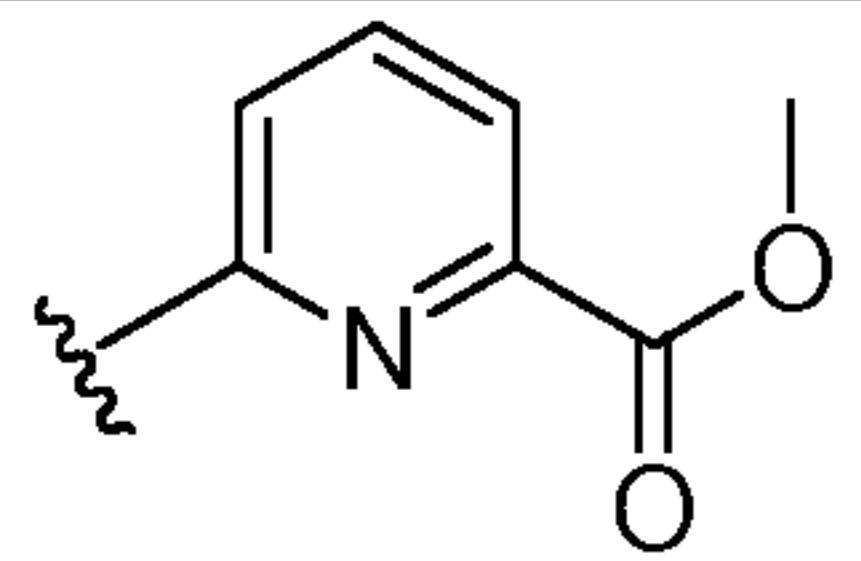
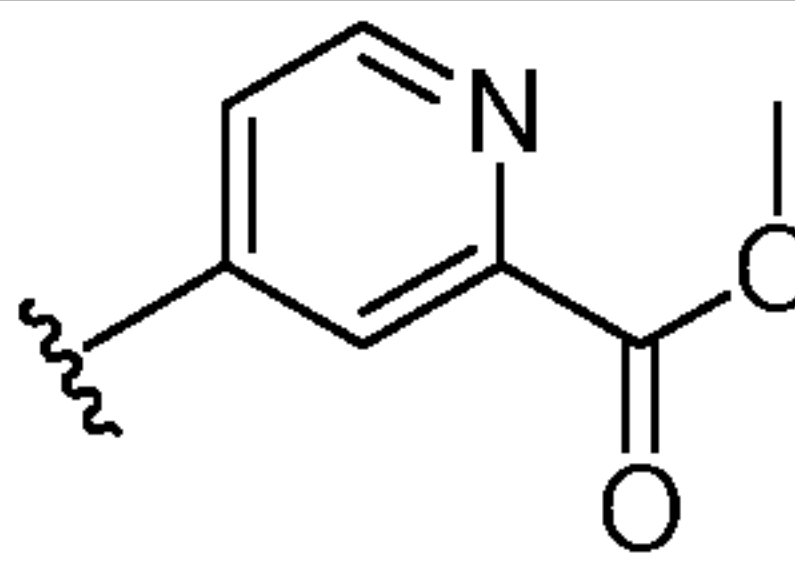
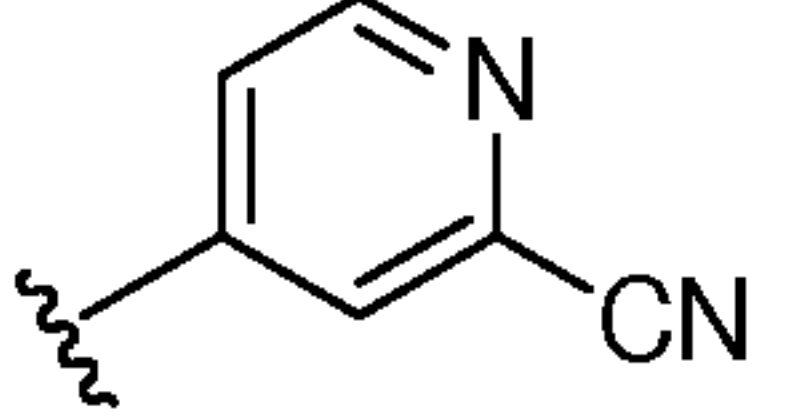
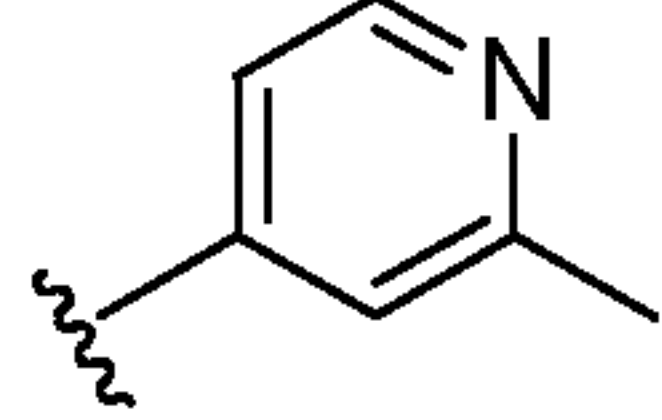
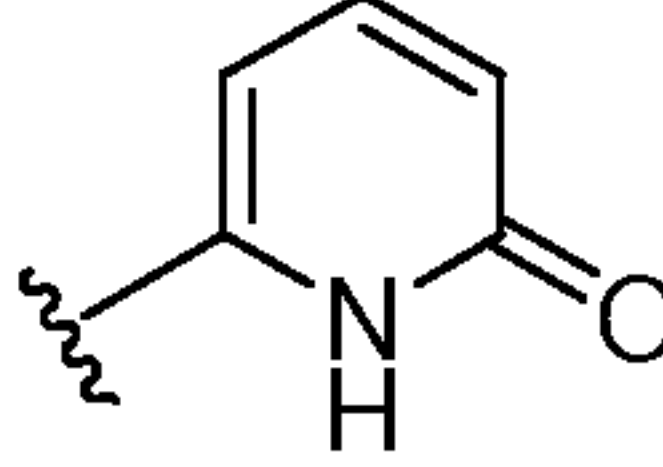
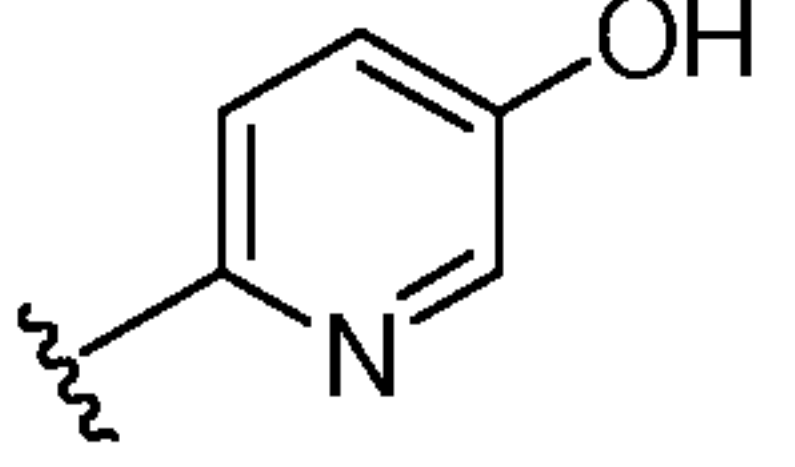
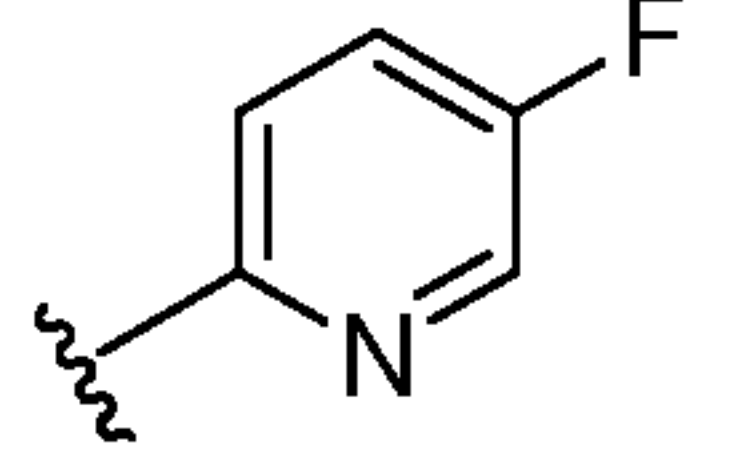
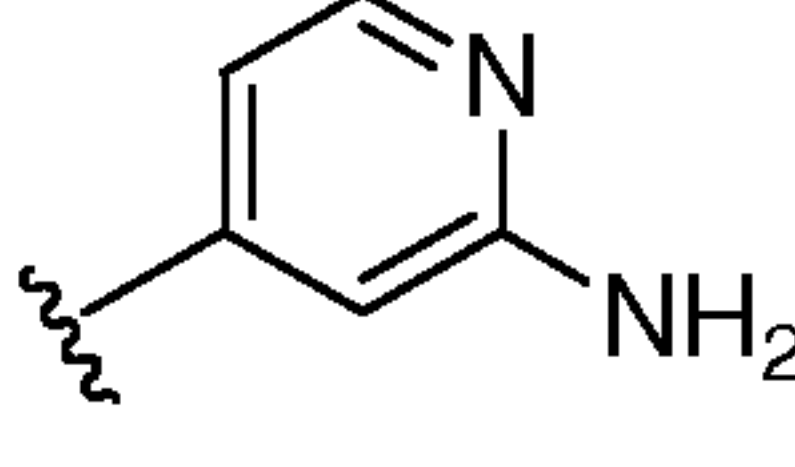
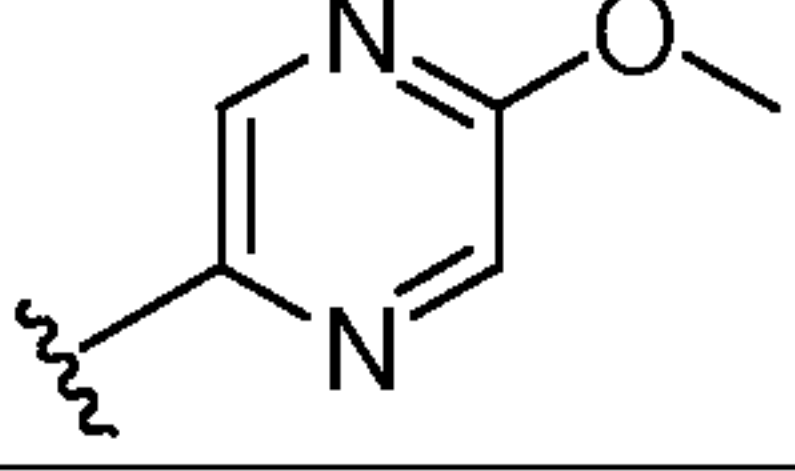
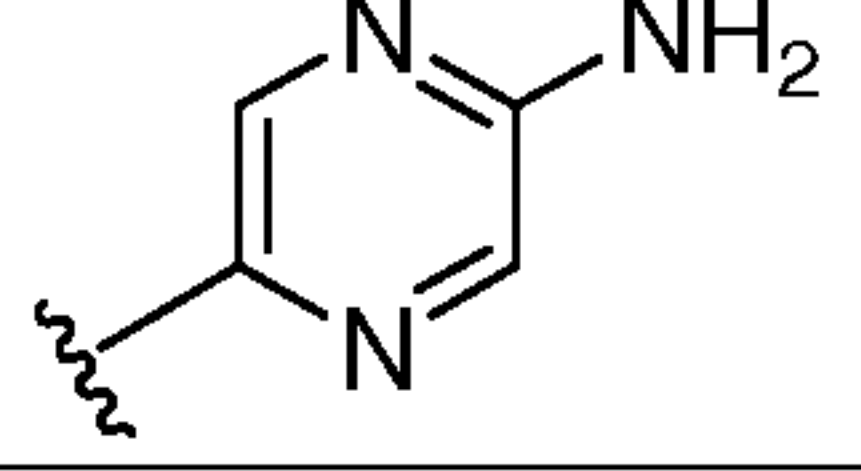
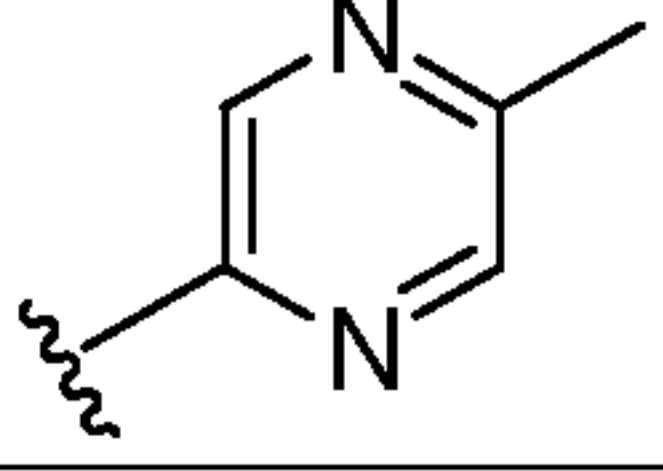


Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl; R^1 is H, $-\text{F}$, $-\text{Cl}$, $-\text{CN}$, $-\text{CH}_3$, isopropyl, $-\text{CF}_3$, $-\text{OCH}_3$, nitro, or phosphate; R^2 is halo, hydroxy, cyano, nitro, or phosphate; q is an integer of 0, 1, 2, 3, or 4; R^5 , R^6 , R^7 , and R^8 are H; X is absent or $(\text{CH}_2)_z$; z is 1; Y is absent, $-\text{N}(\text{R}^9)-$, or $-\text{N}(\text{R}^9)\text{CH}(\text{R}^9)-$; R^9 is hydrogen, C_1 - C_{10} alkyl, C_3 - C_7 cycloalkyl, or C_2 - C_{10} heteroalkyl; and W_d is pyrazolopyrimidine or purine.

Table 1. Illustrative B moieties of compounds of Formula I include, but are not limited to:

Sub-class #	B	Sub-class #	B	Sub-class #	B
B-1		B-2		B-3	$-\text{CH}(\text{CH}_3)_2$
B-4		B-5		B-6	
B-7		B-8		B-9	
B-10		B-11		B-12	
B-13		B-14		B-15	

B-16		B-17		B-18	
B-19		B-20		B-21	
B-22		B-23		B-24	
B-25		B-26		B-27	
B-28		B-29		B-30	
B-31		B-32		B-33	
B-34		B-35		B-36	
B-37		B-38		B-39	
B-40		B-41		B-42	
B-43		B-44		B-45	
B-46		B-47		B-48	
B-49		B-50		B-51	

B-52		B-53		B-54	
B-55		B-56		B-57	
B-58		B-59		B-60	
B-61		B-62		B-63	
B-64		B-65		B-66	
B-67		B-68		B-69	
B-70		B-71		B-72	
B-73		B-74		B-75	
B-76		B-77		B-78	
B-79		B-80		B-81	
B-82		B-83		B-84	
B-85		B-86		B-87	-CH ₃

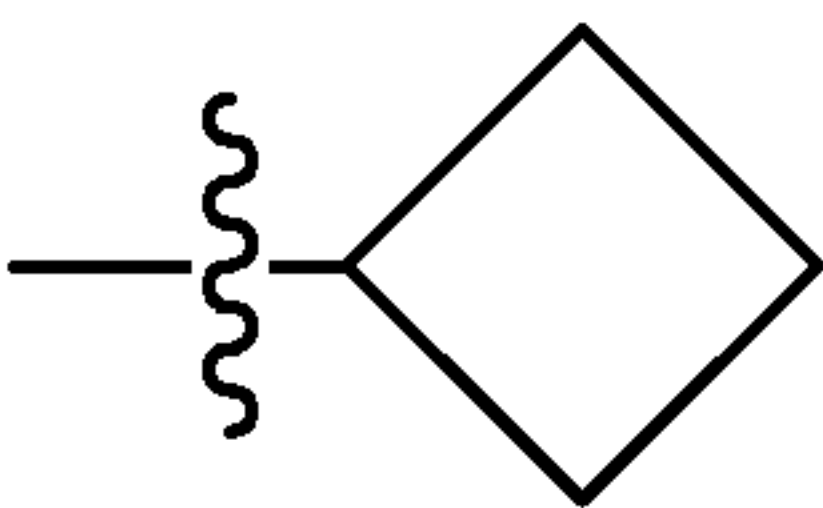
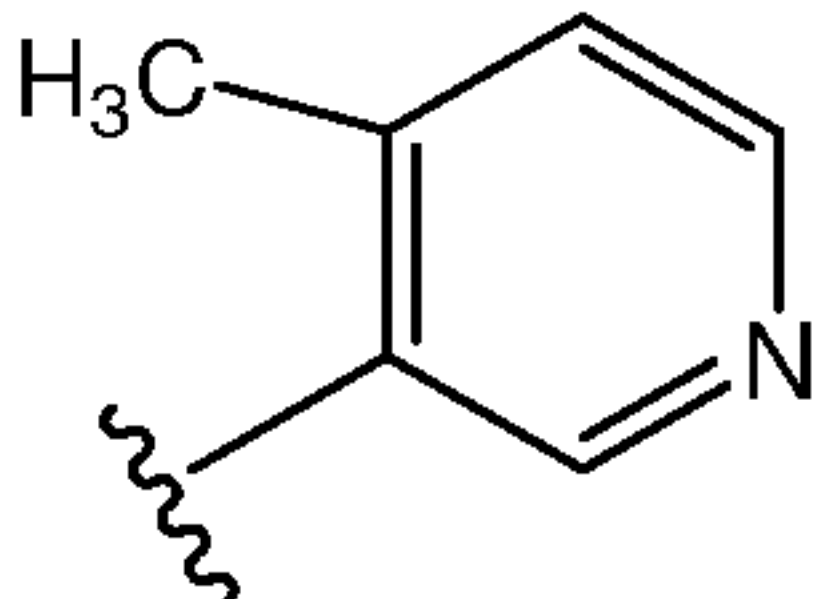
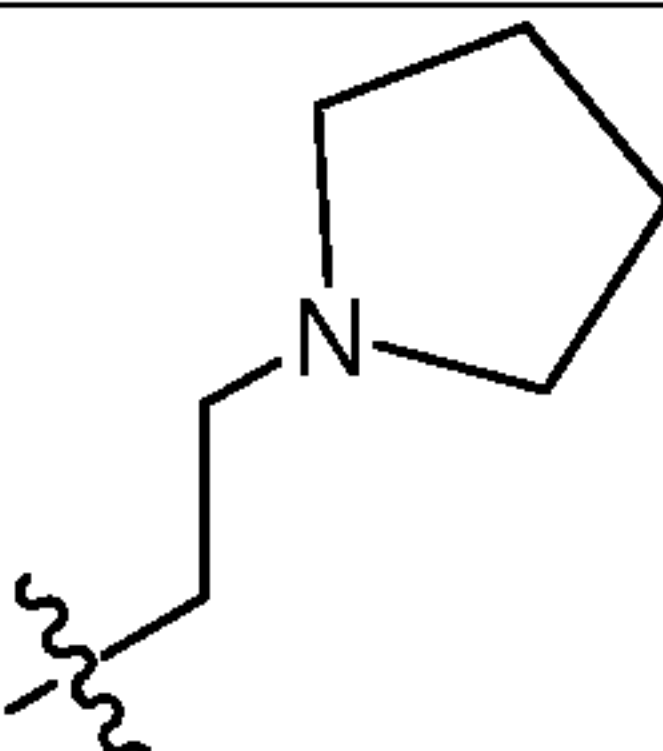
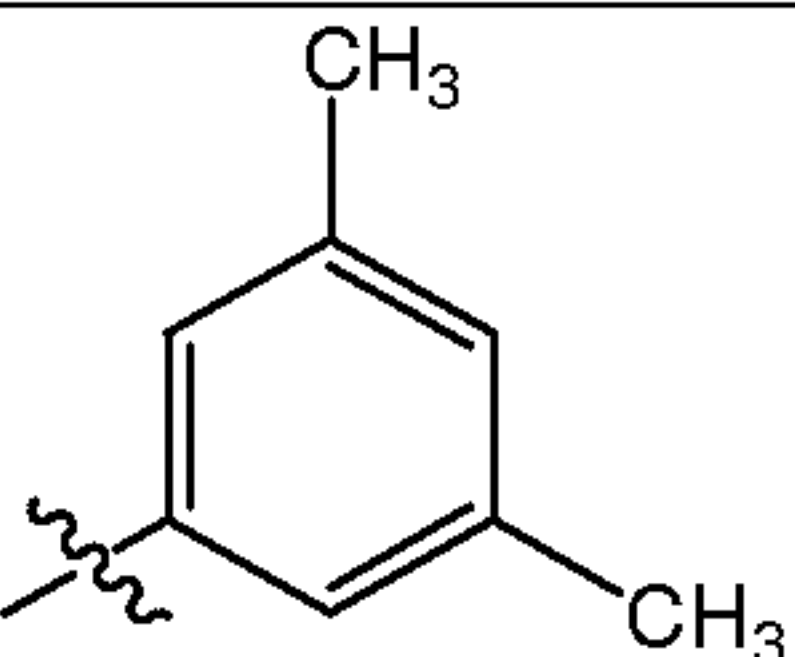
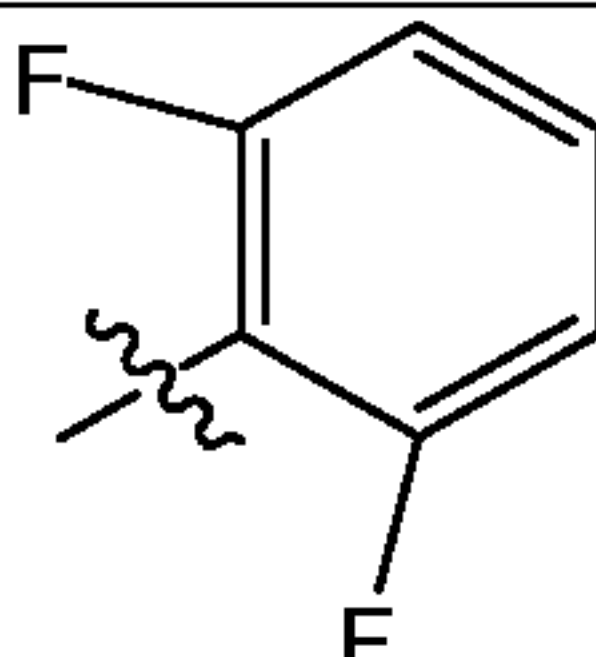
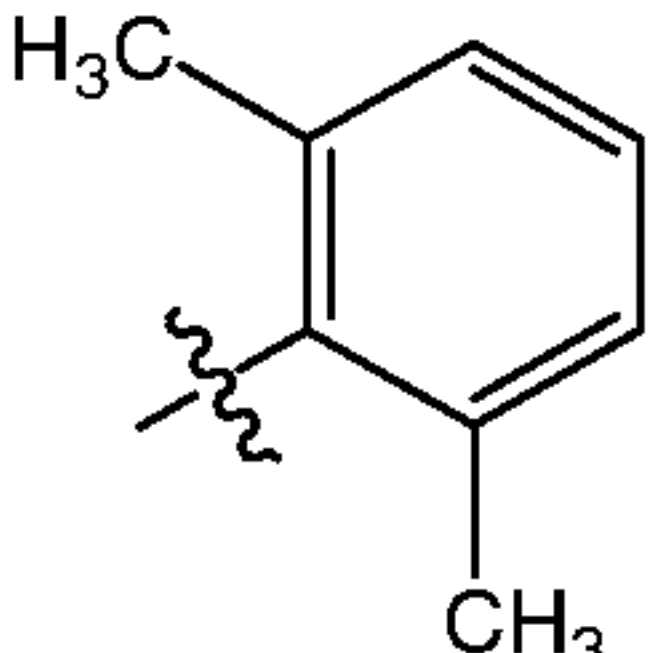
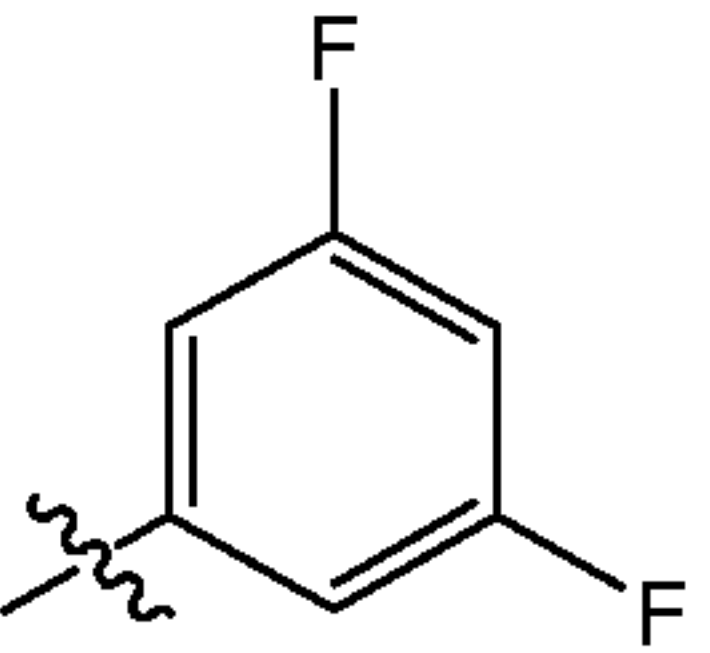
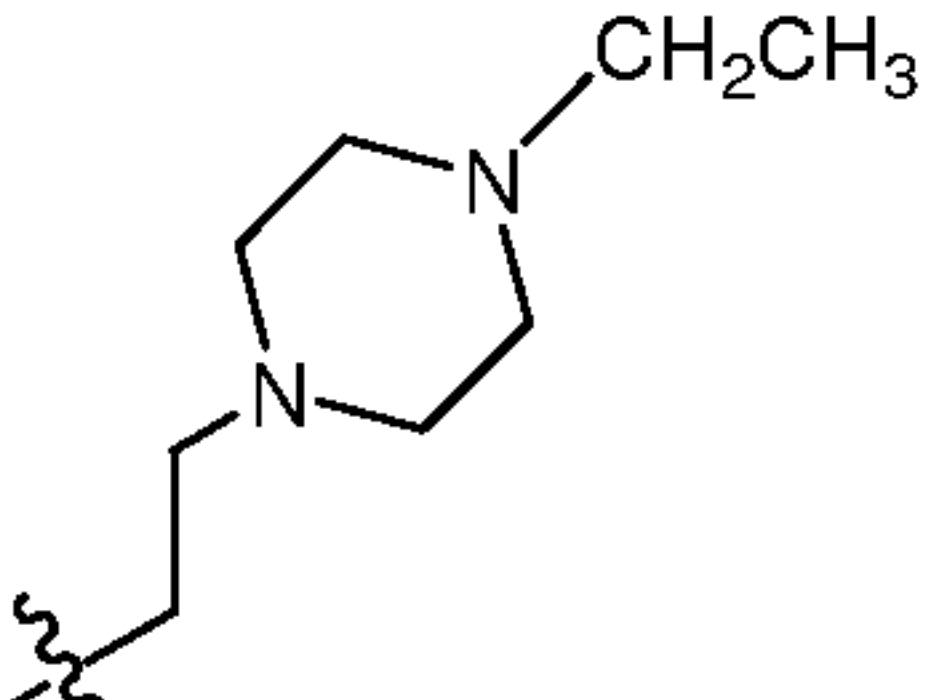
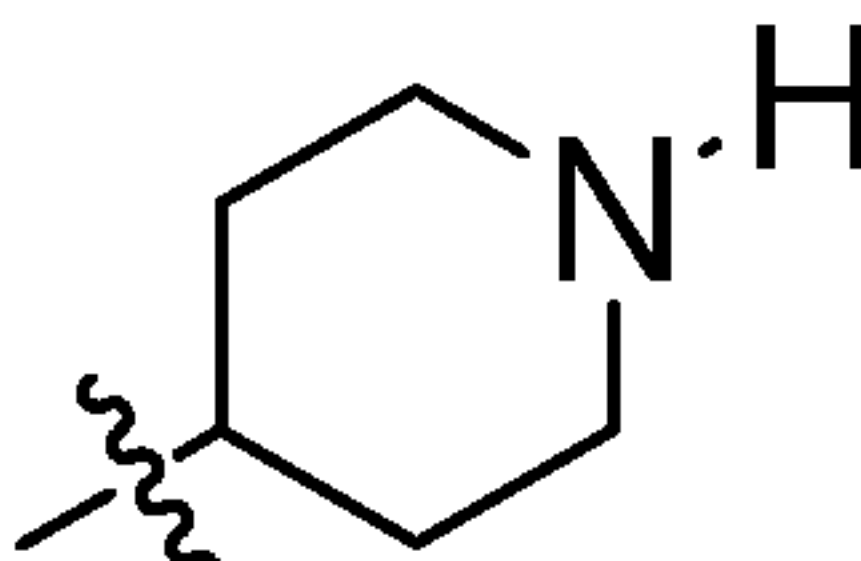
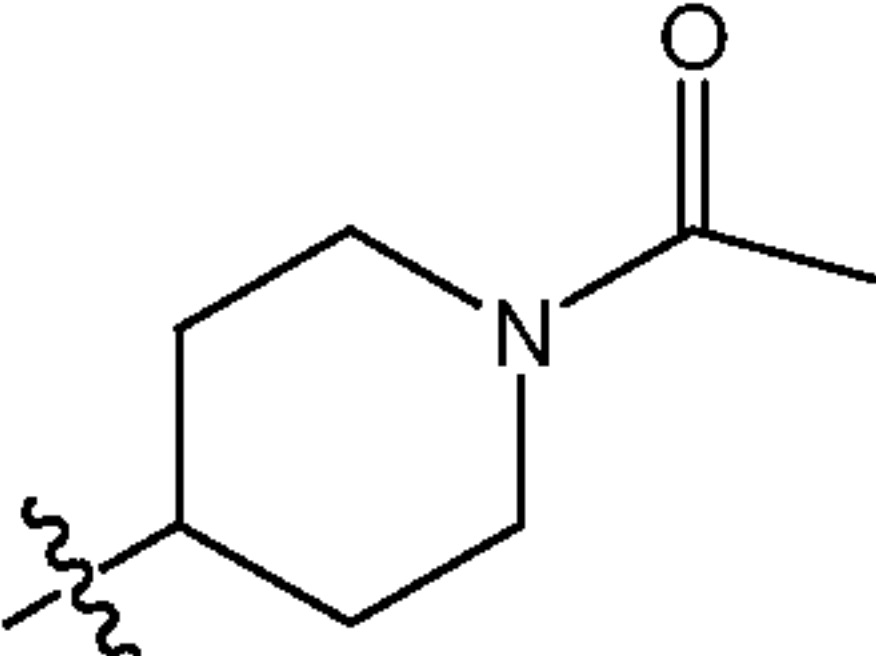
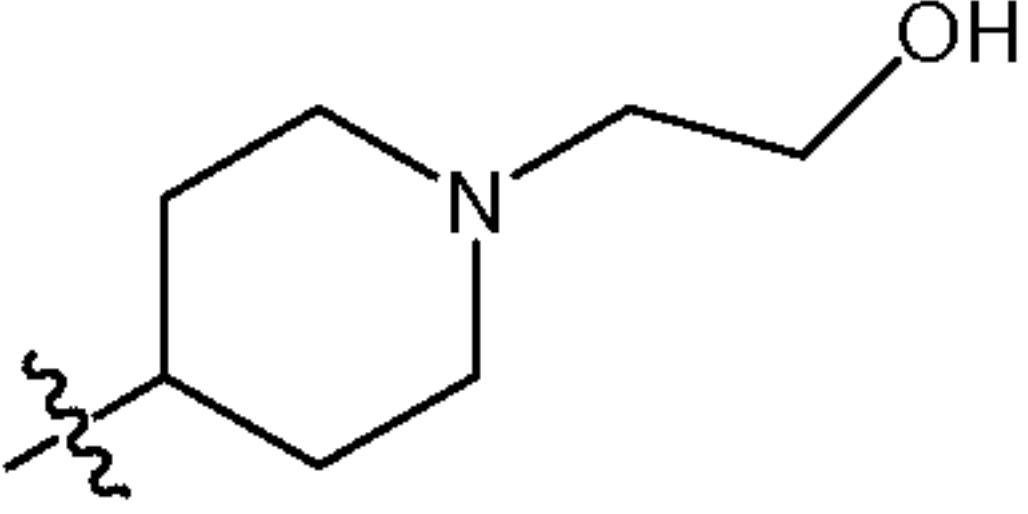
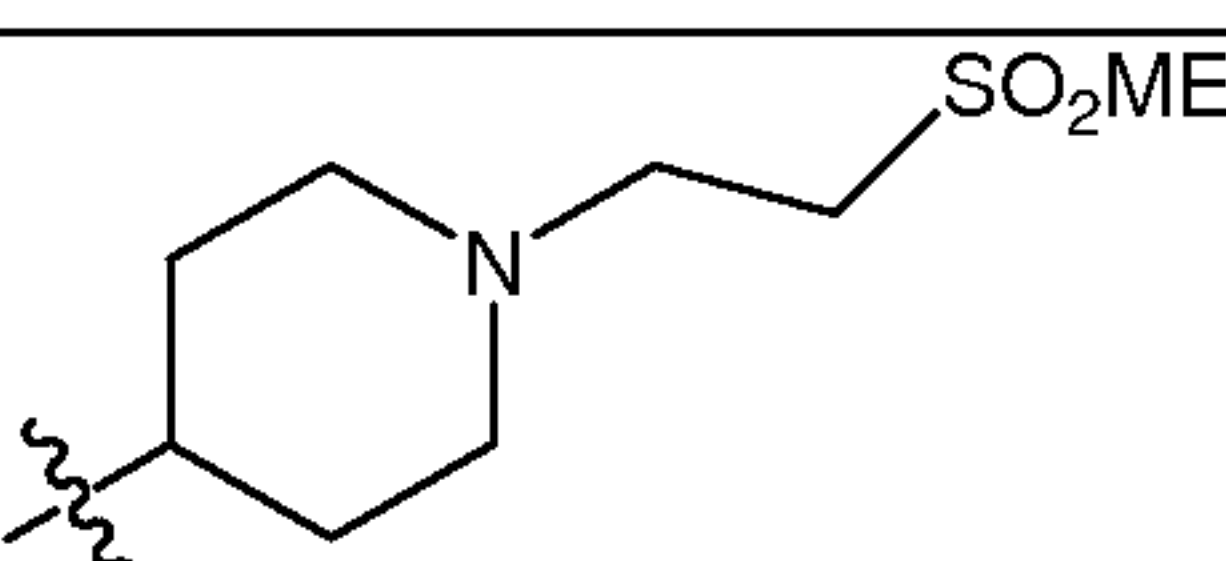
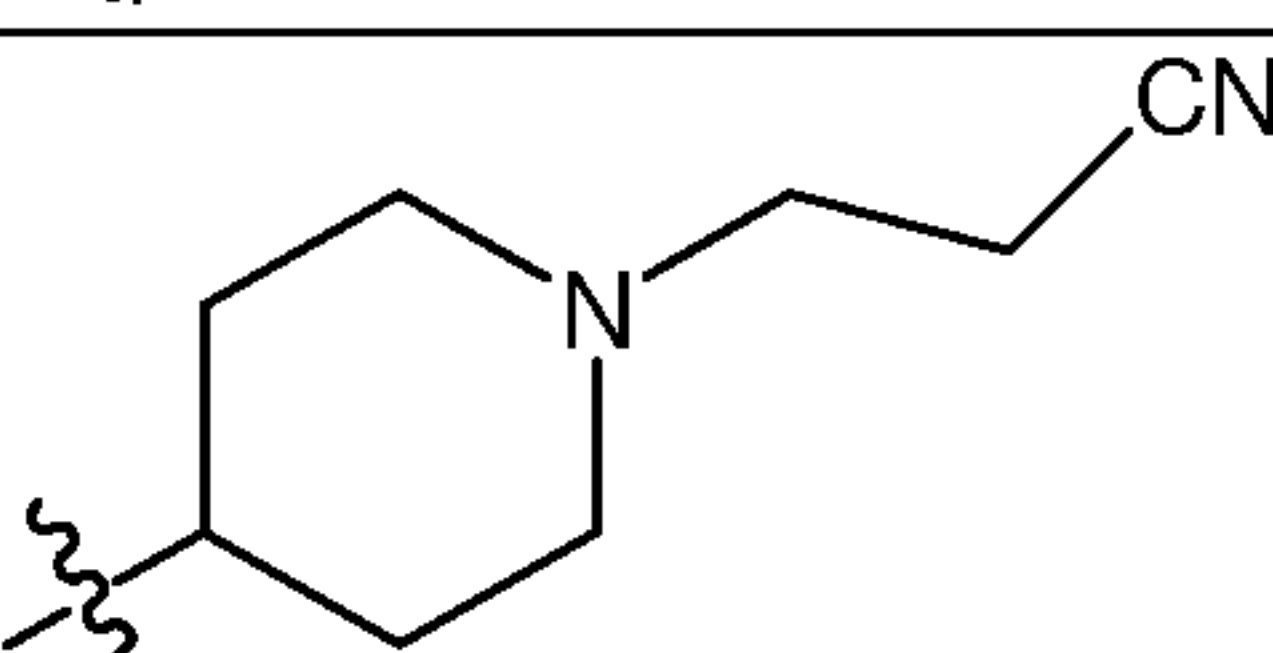
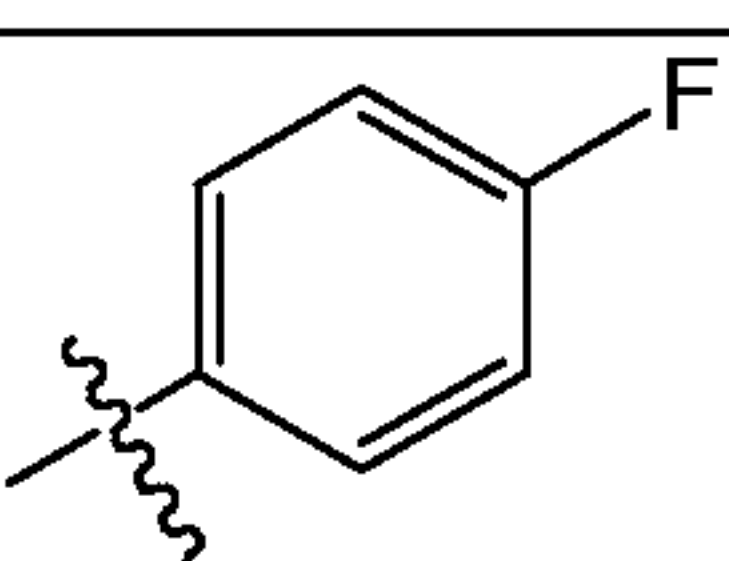
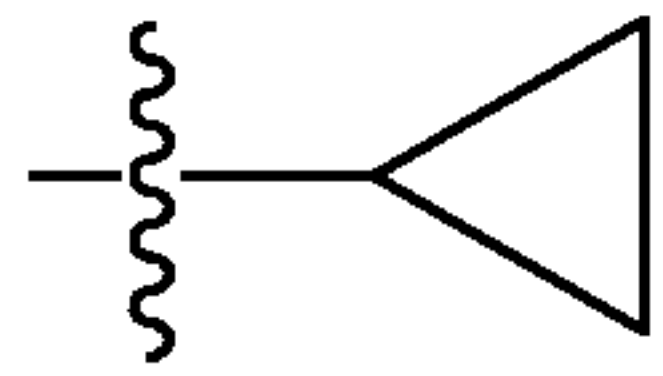
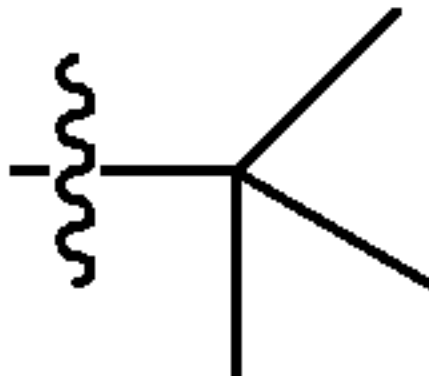
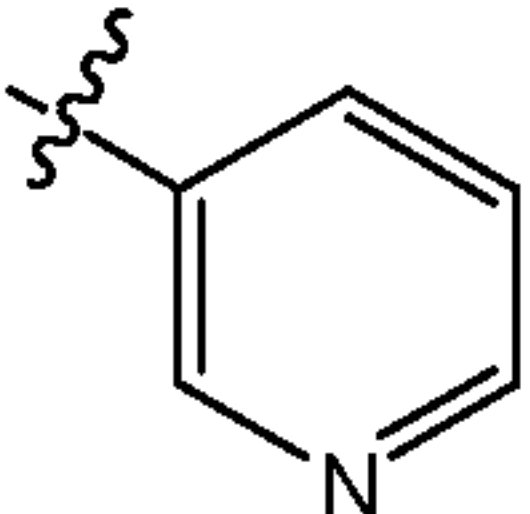
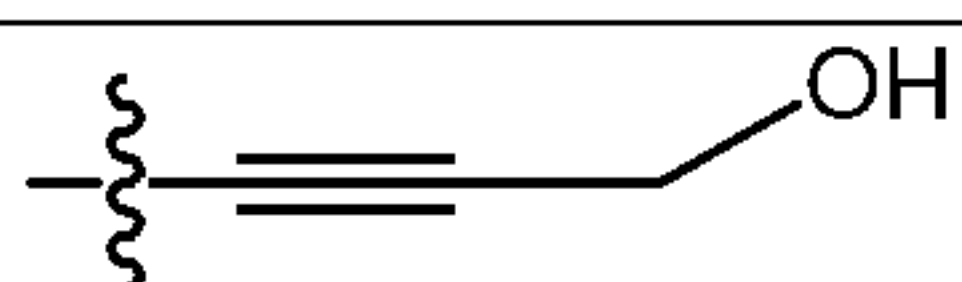
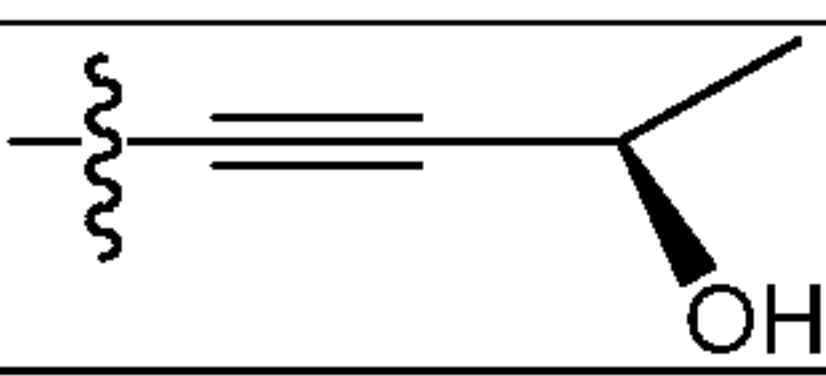
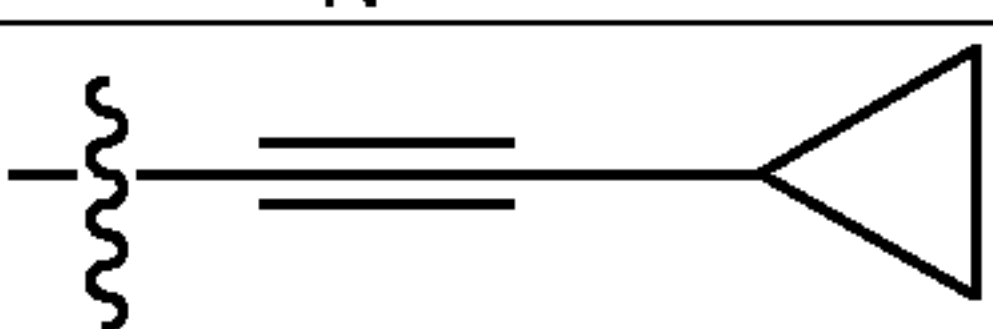
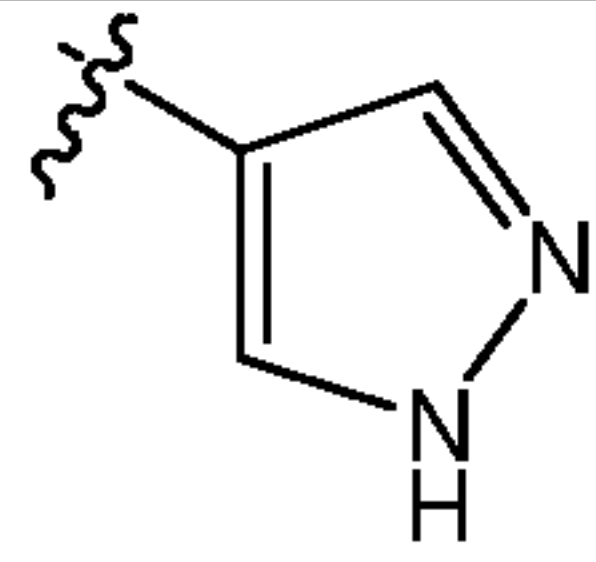
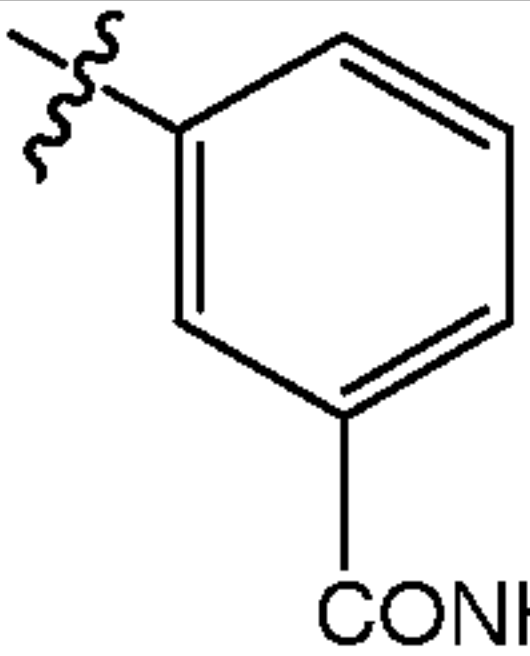
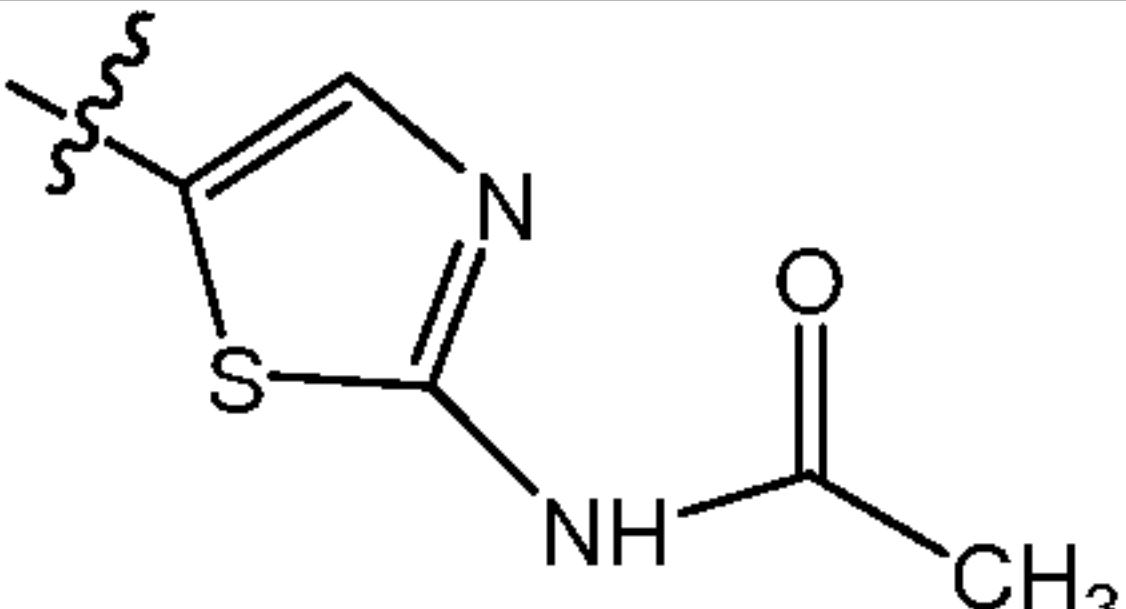
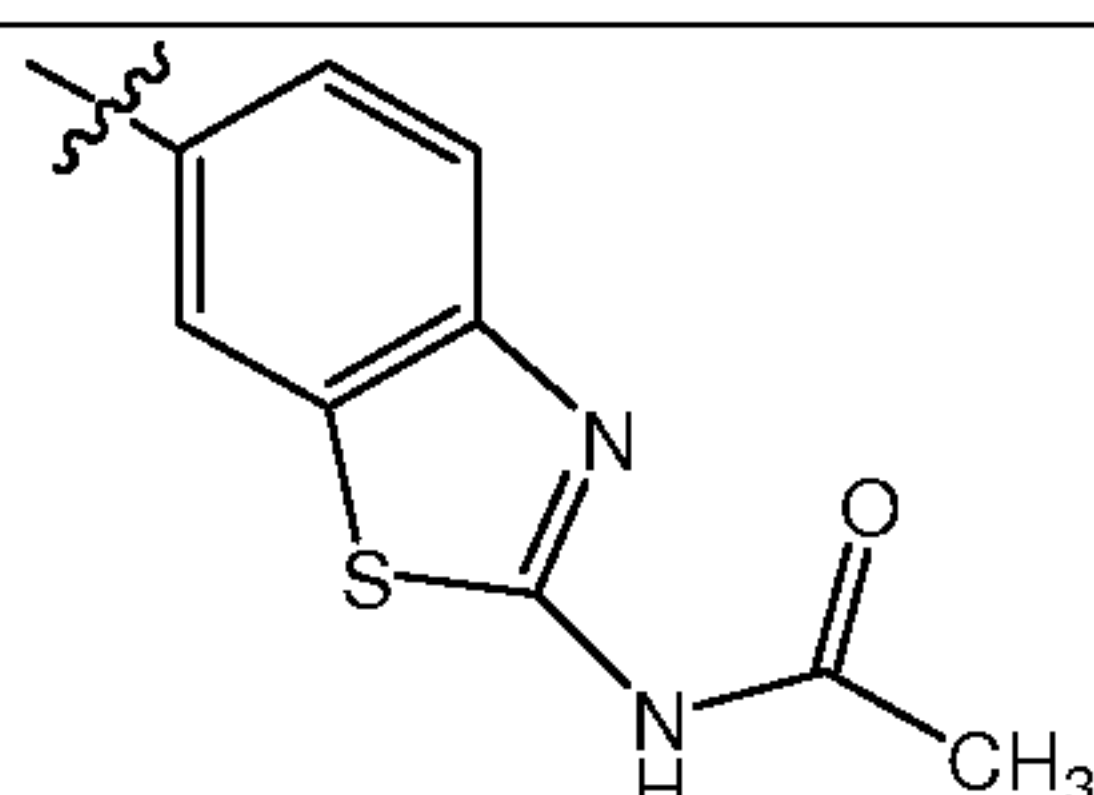
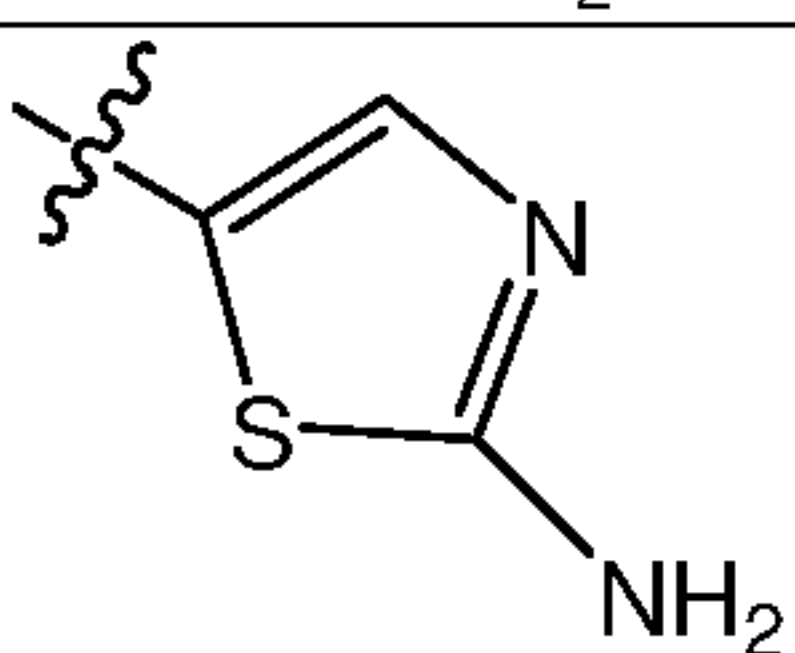
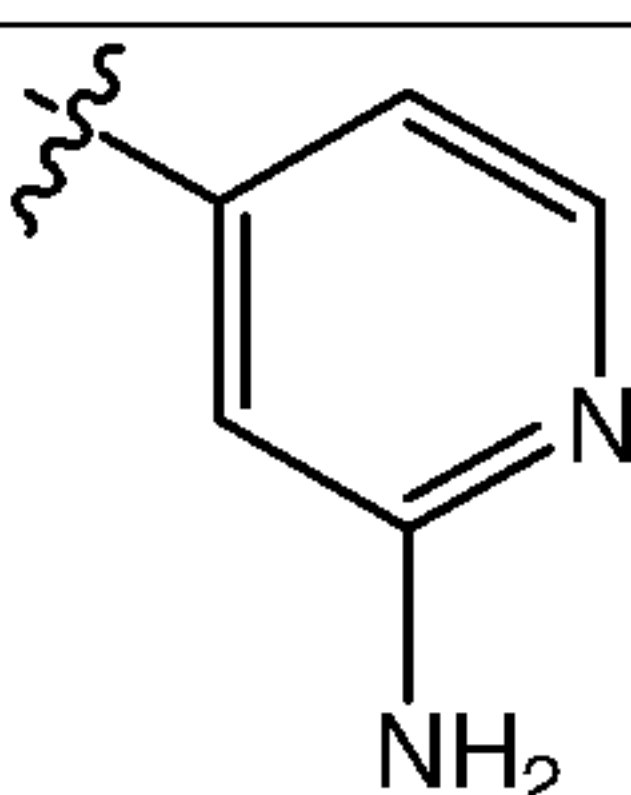
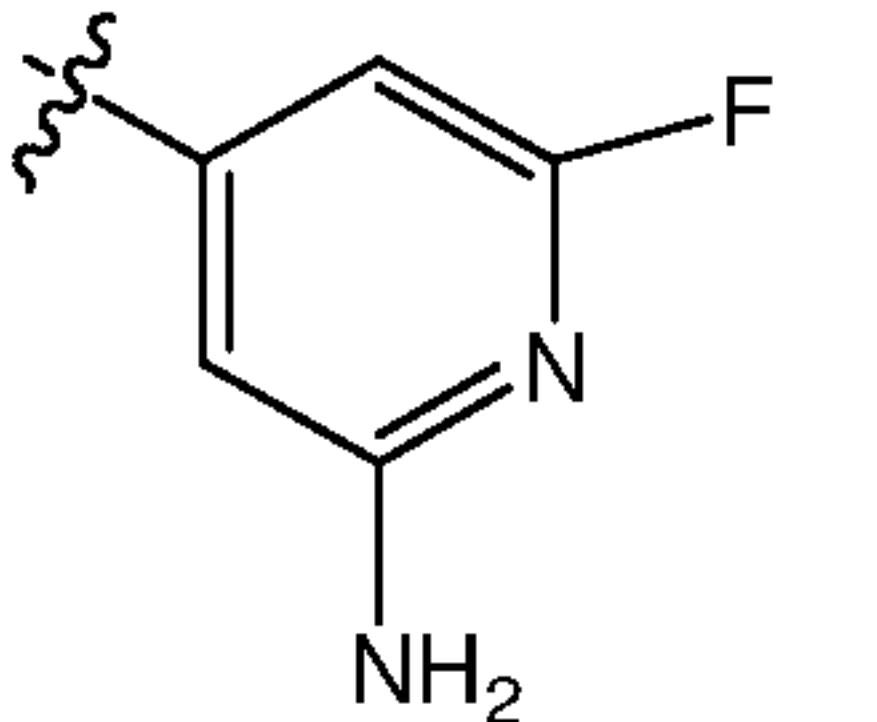
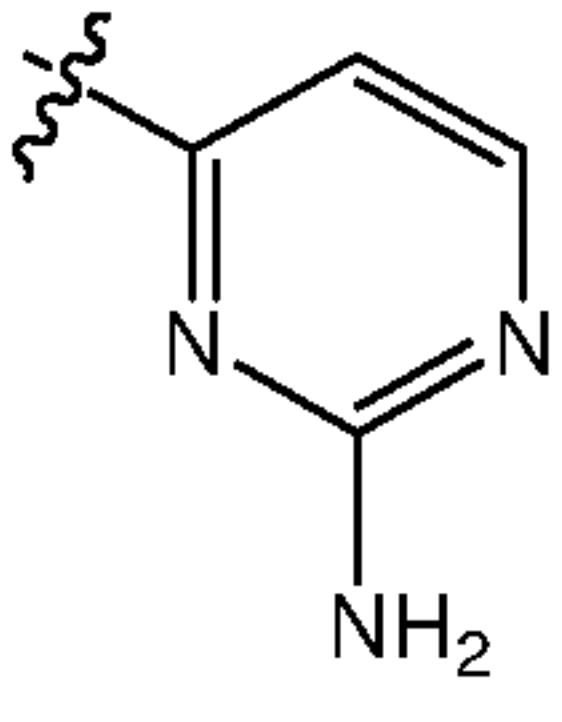
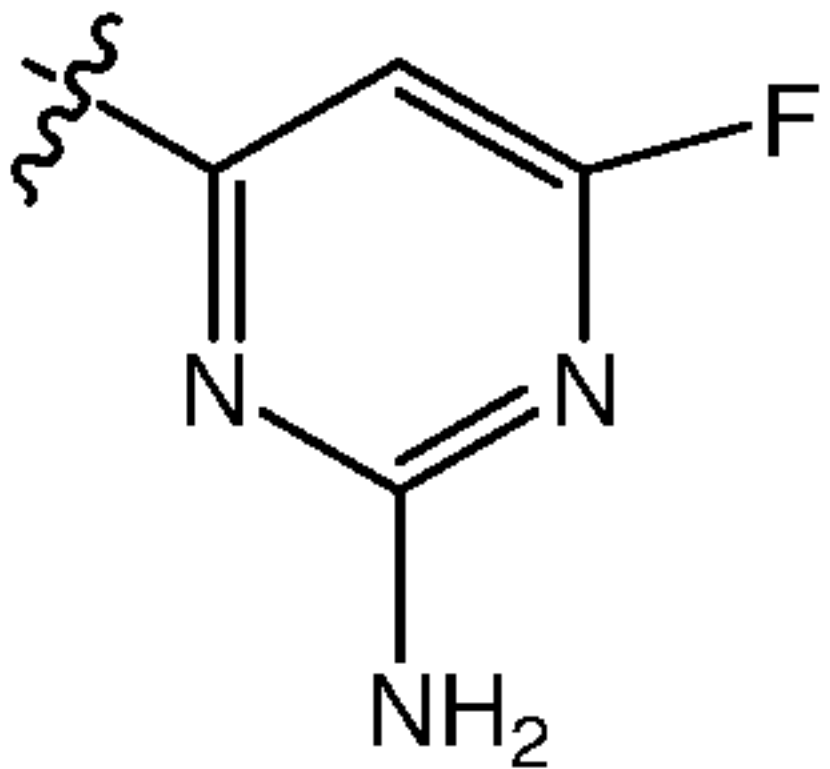
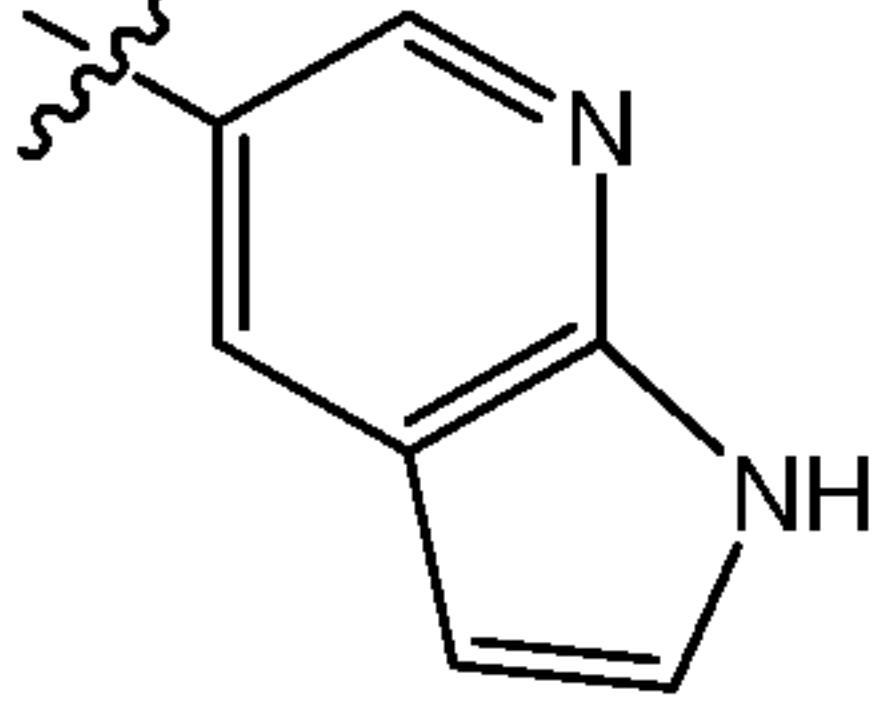
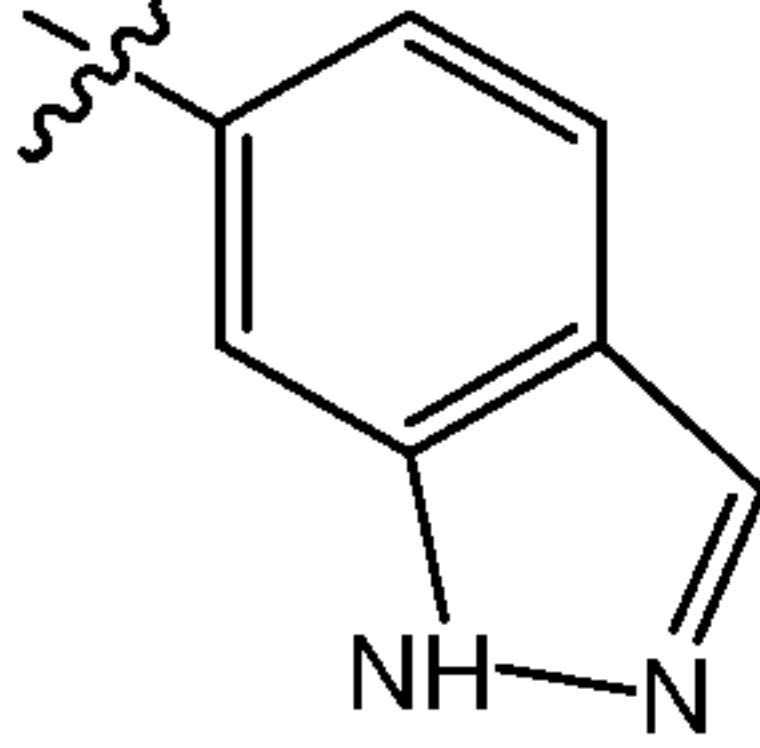
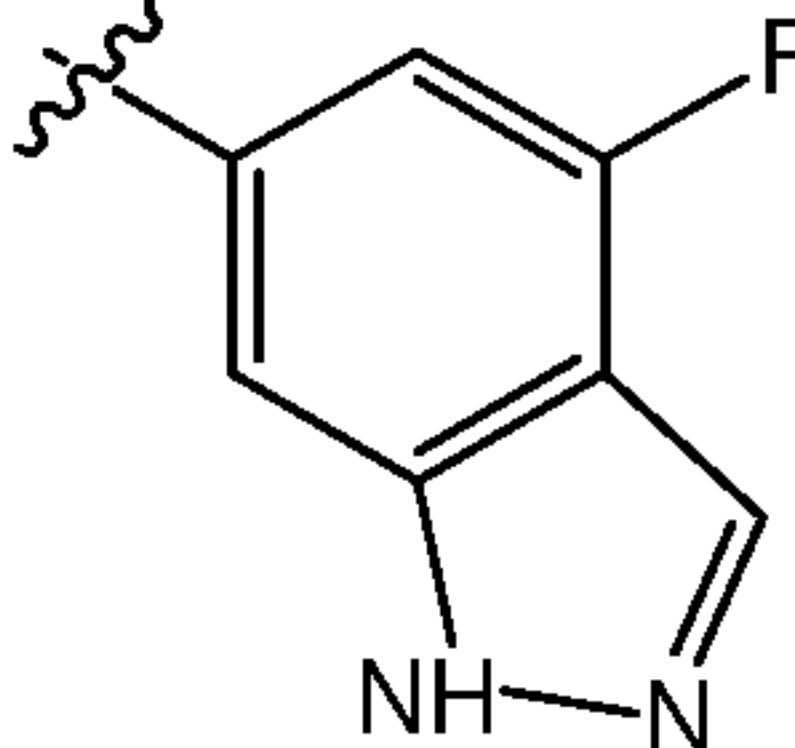
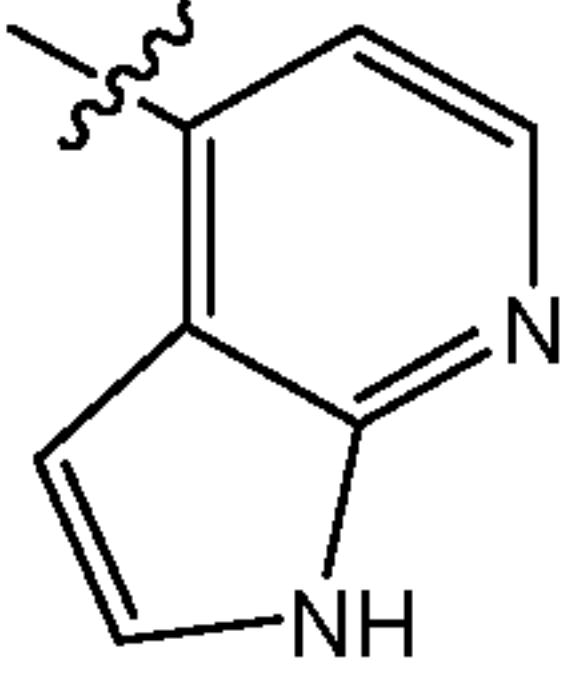
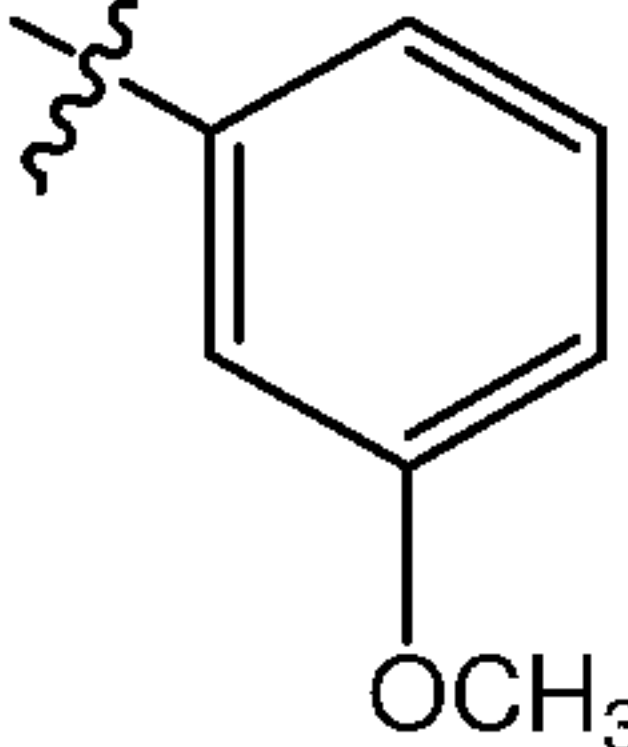
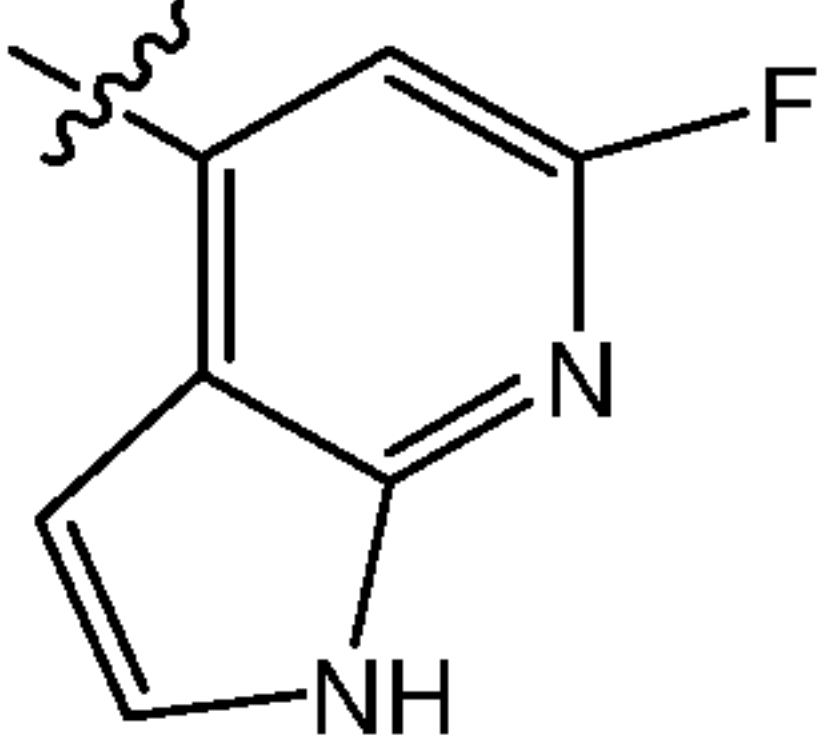
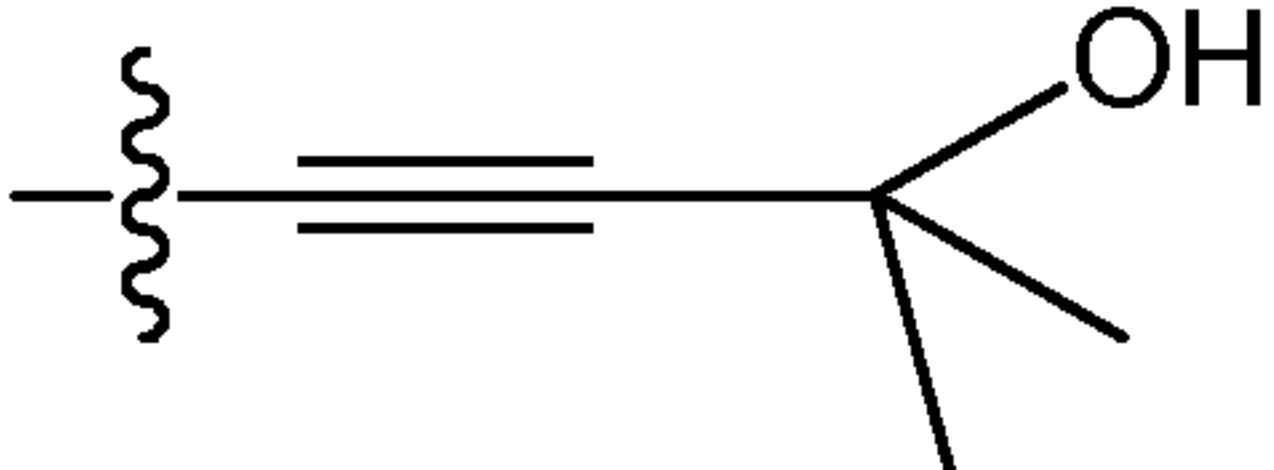
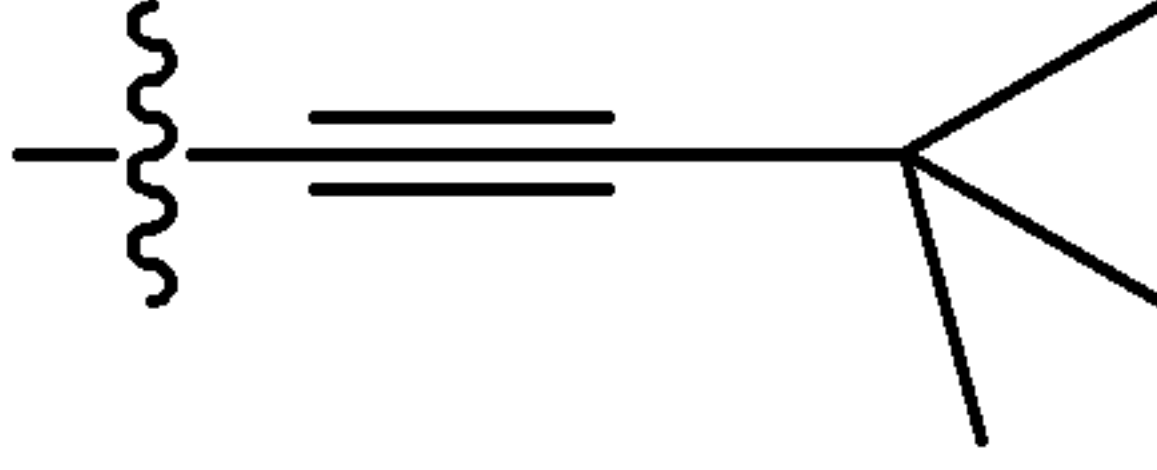
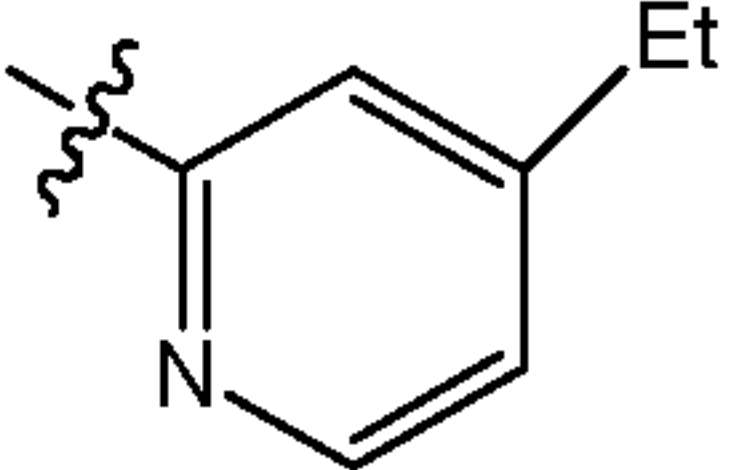
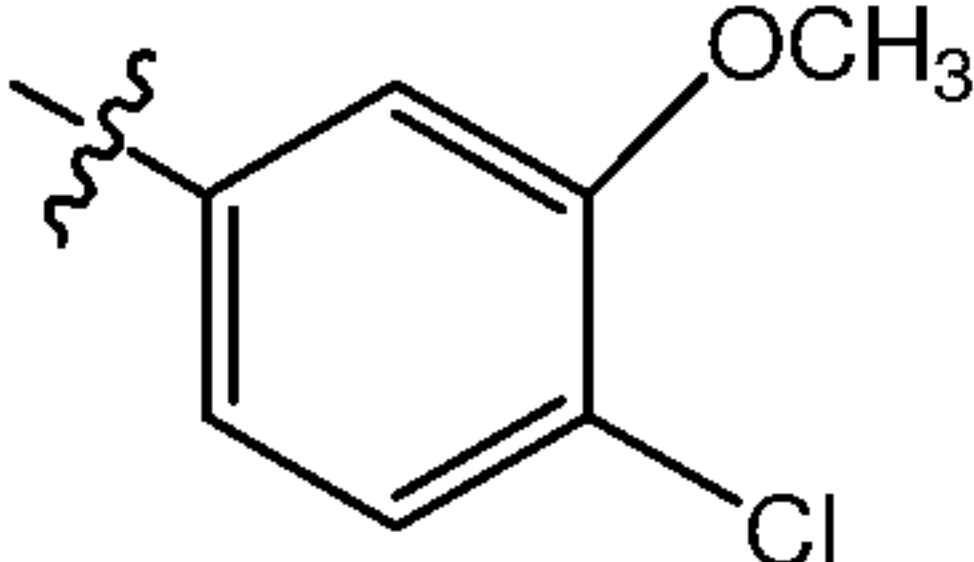
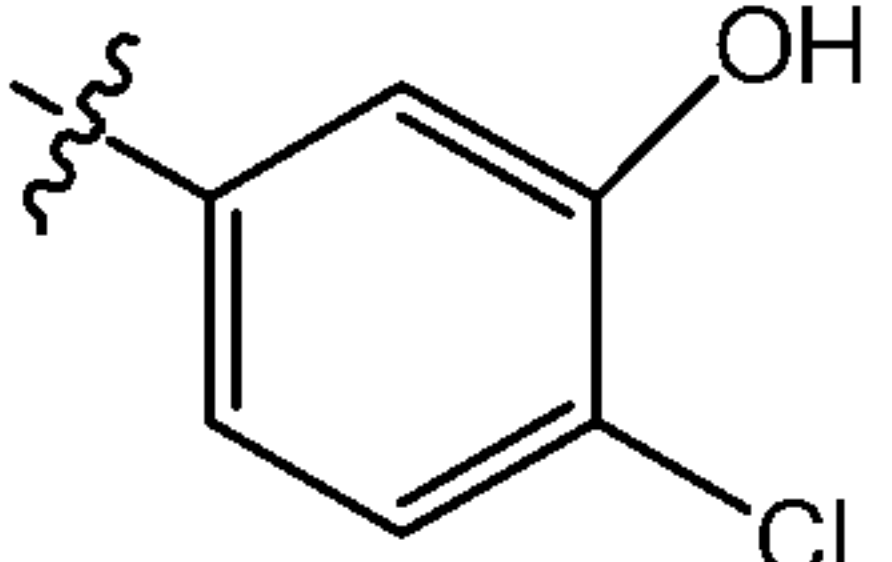
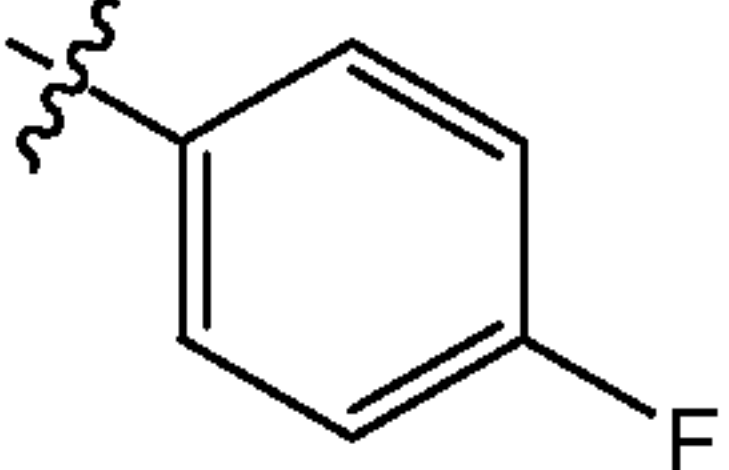
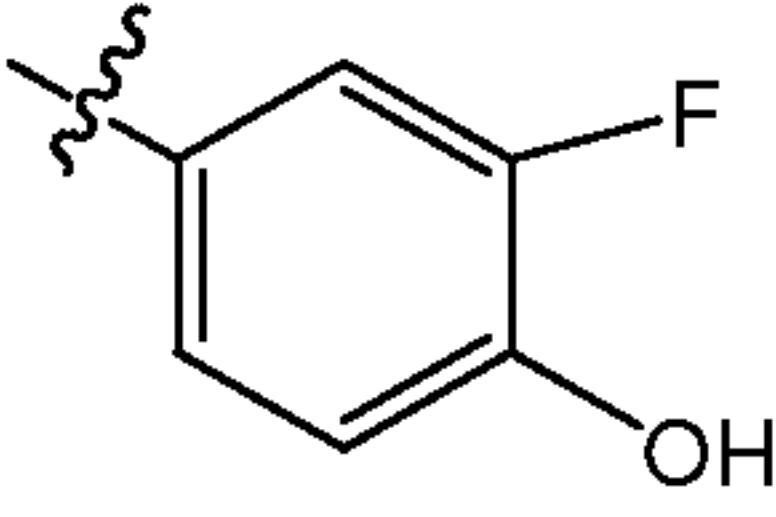
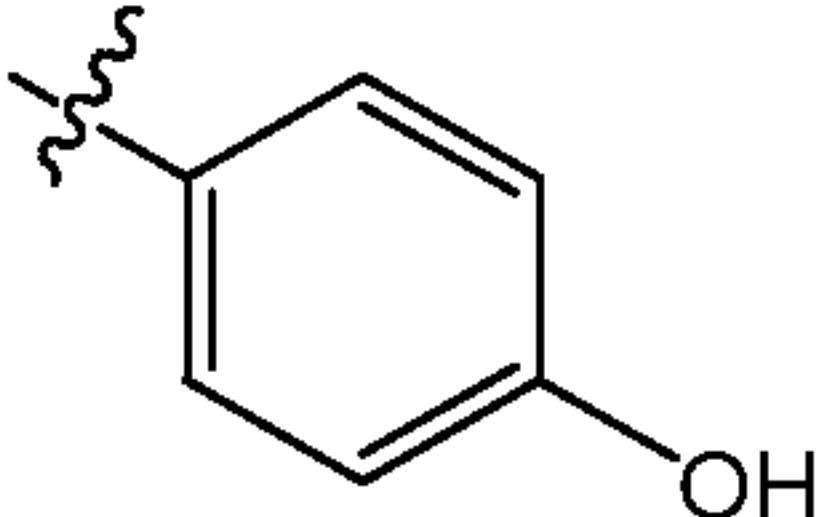
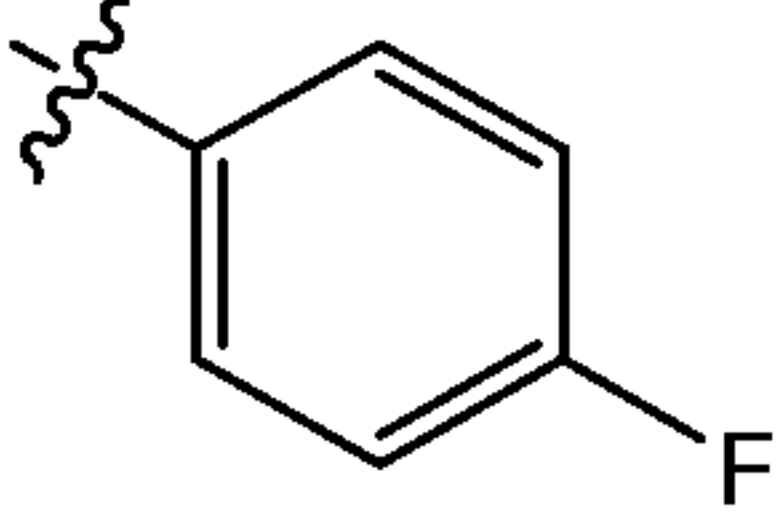
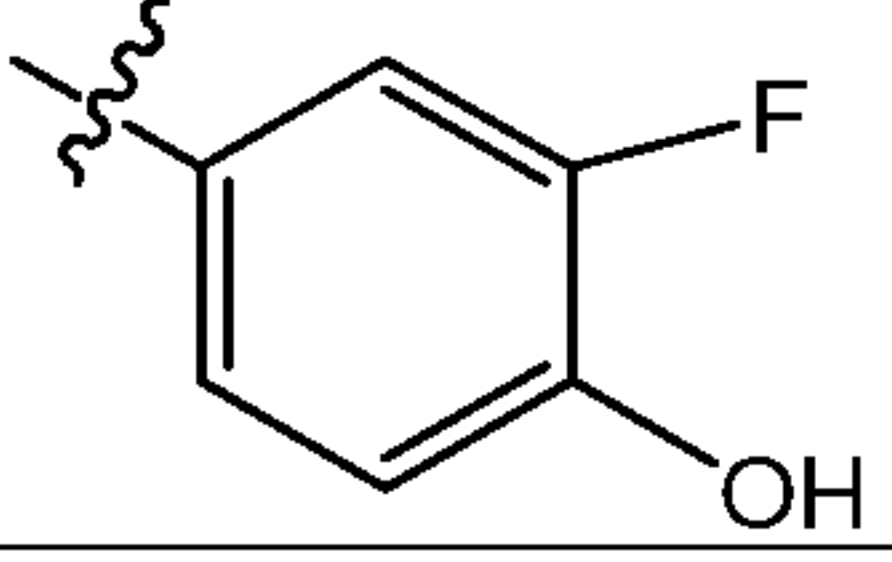
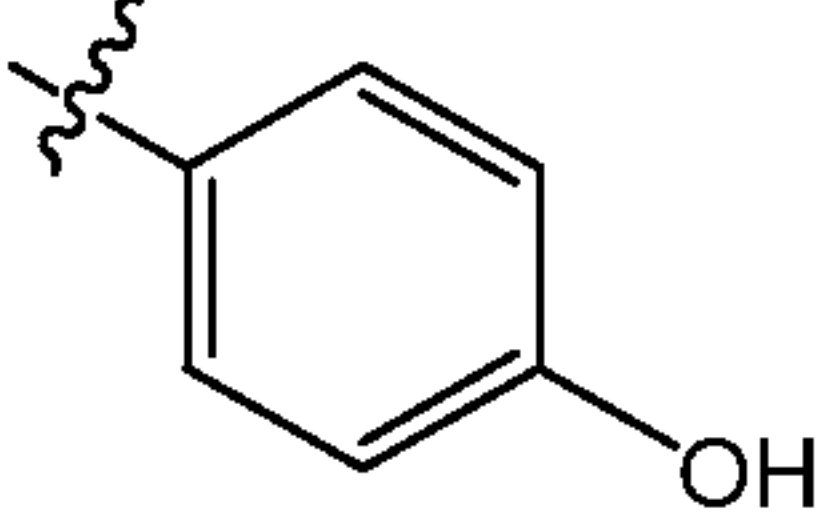
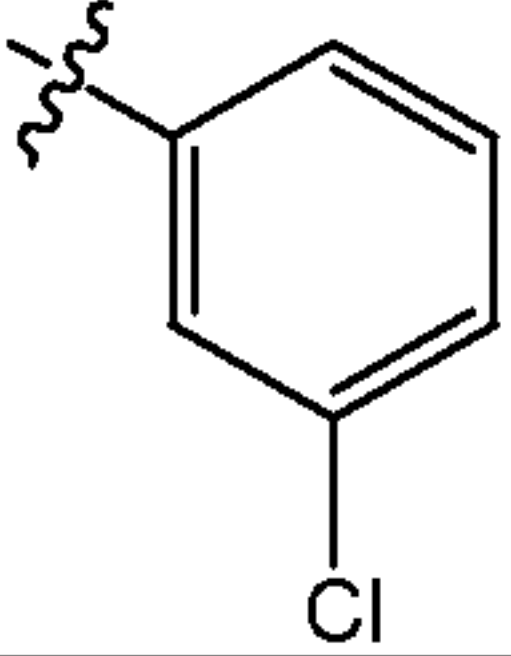
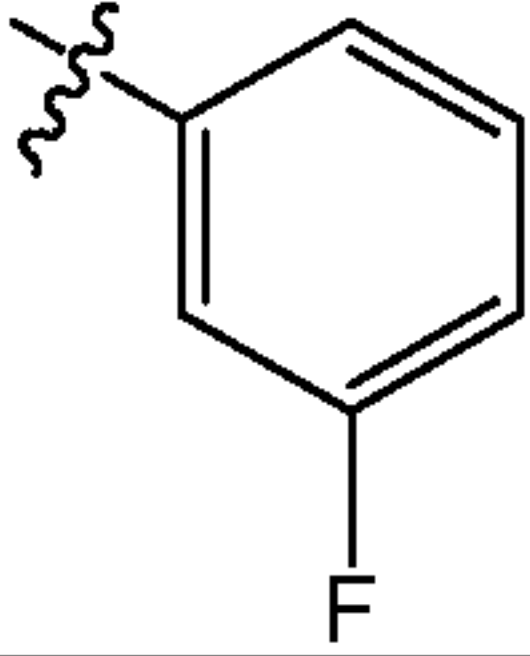
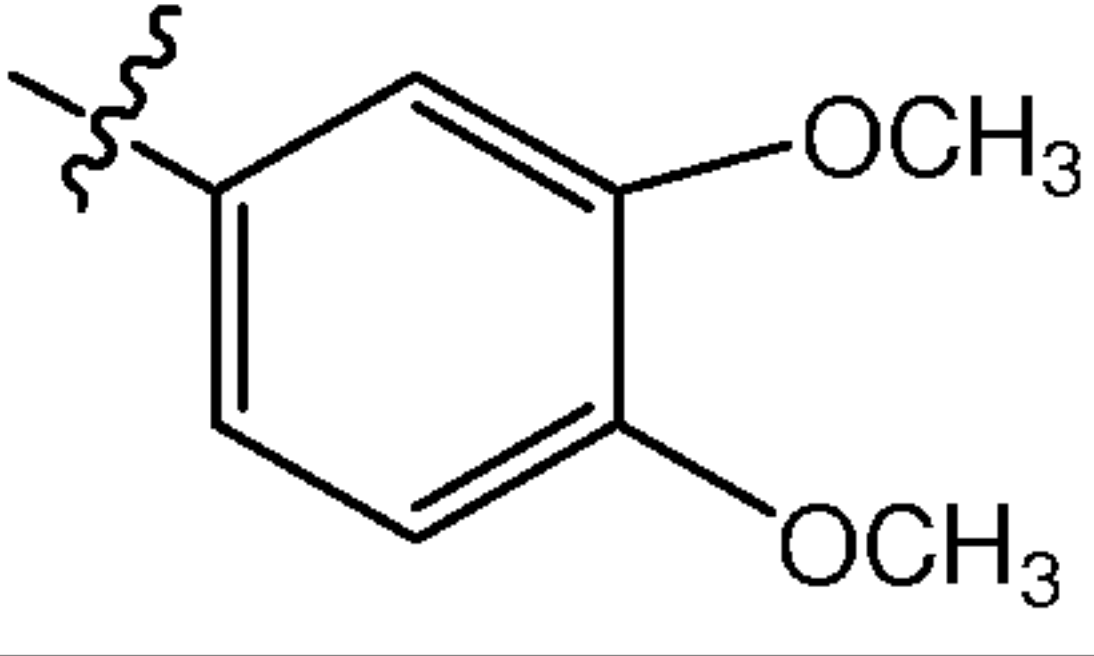
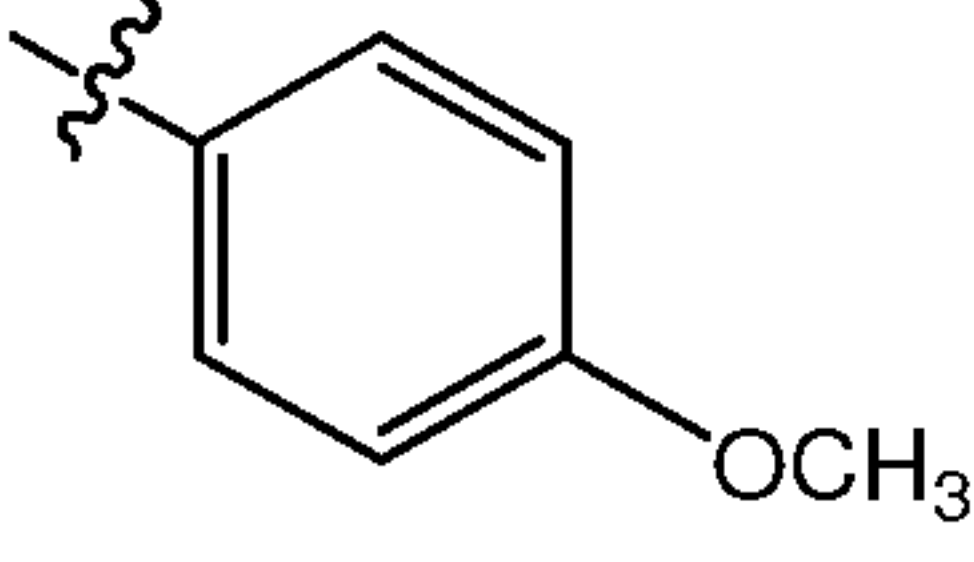
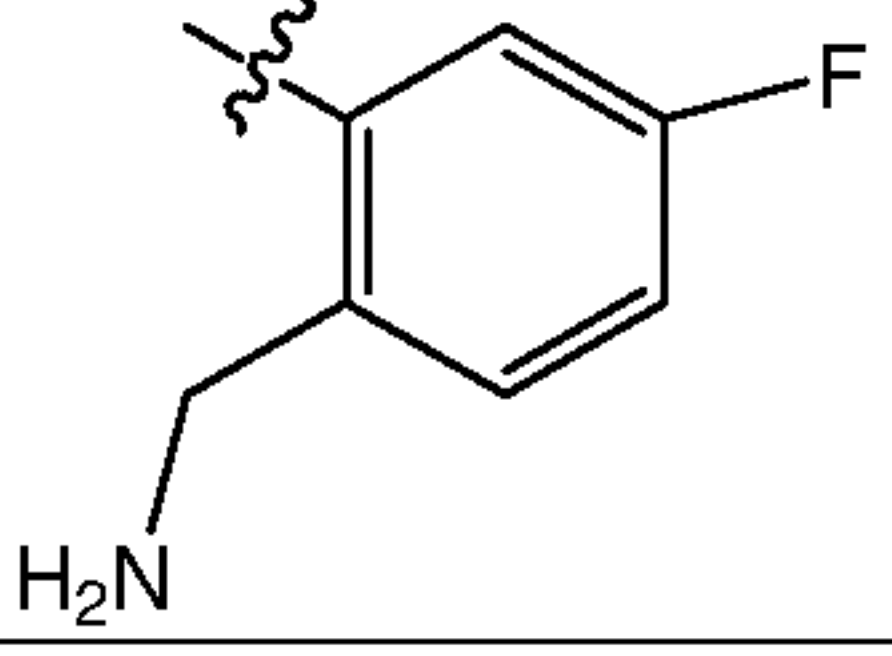
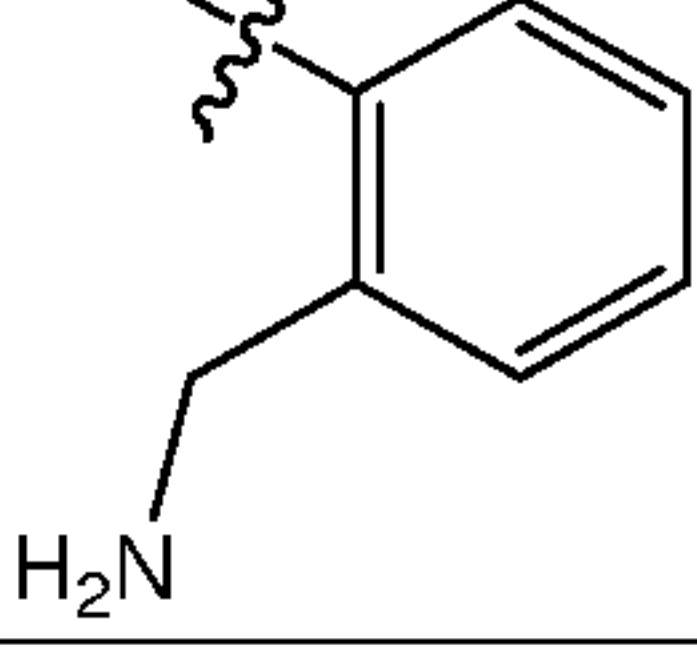
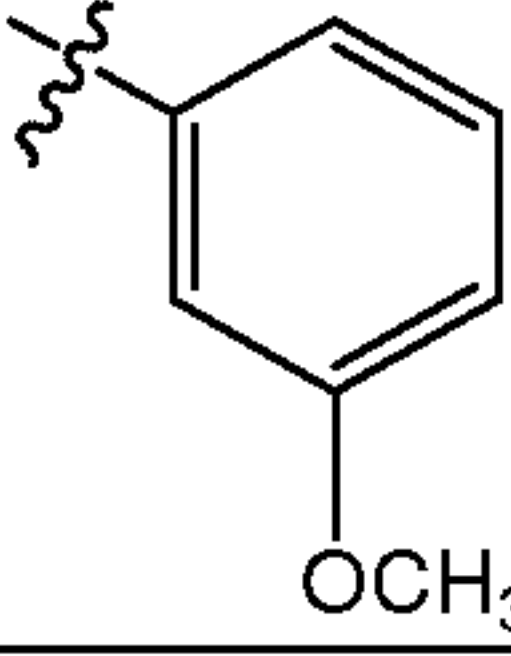
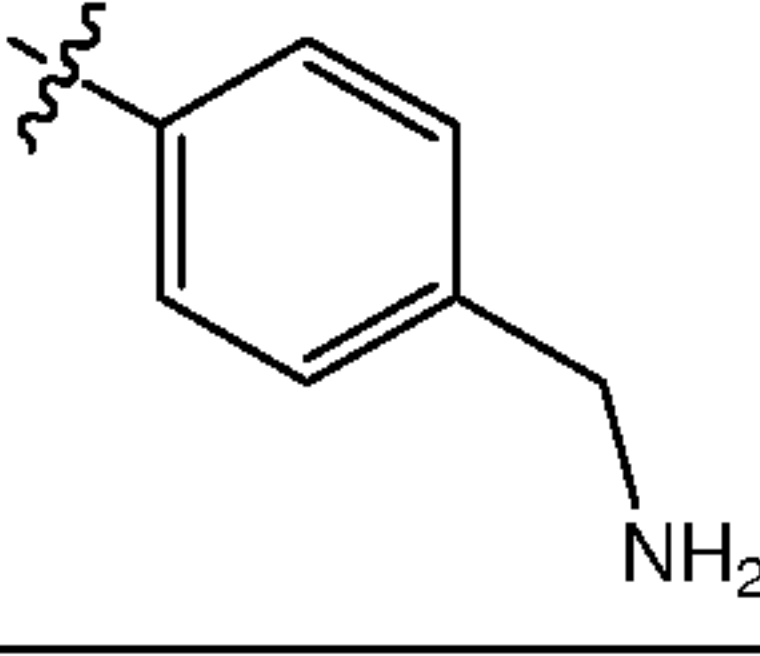
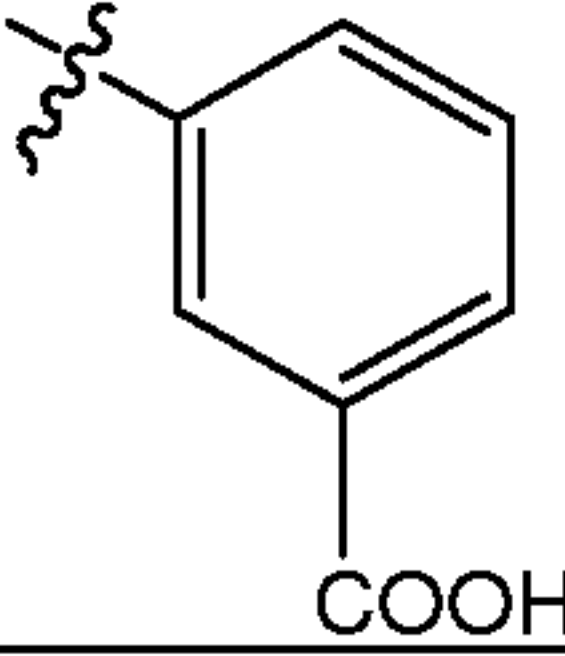
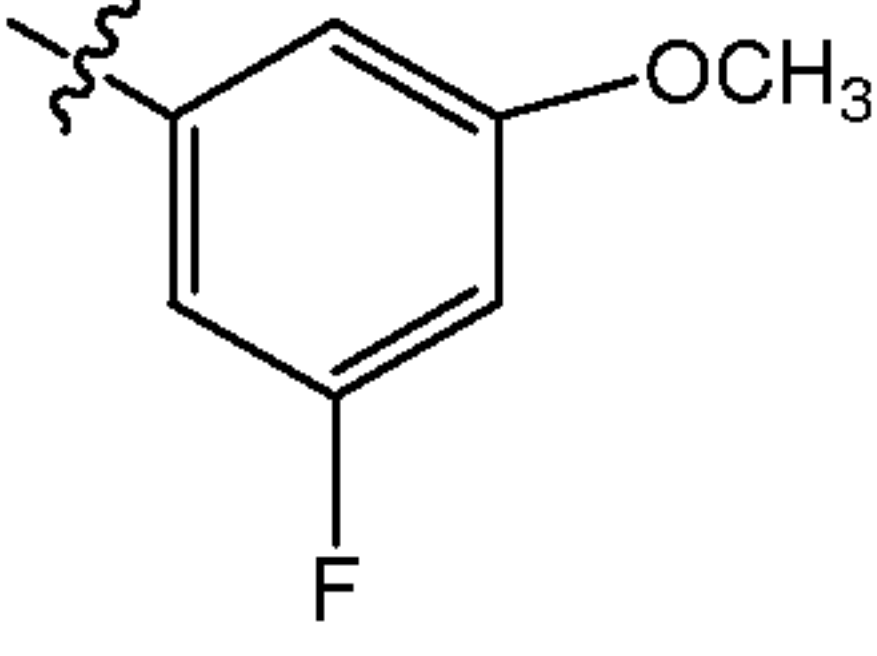
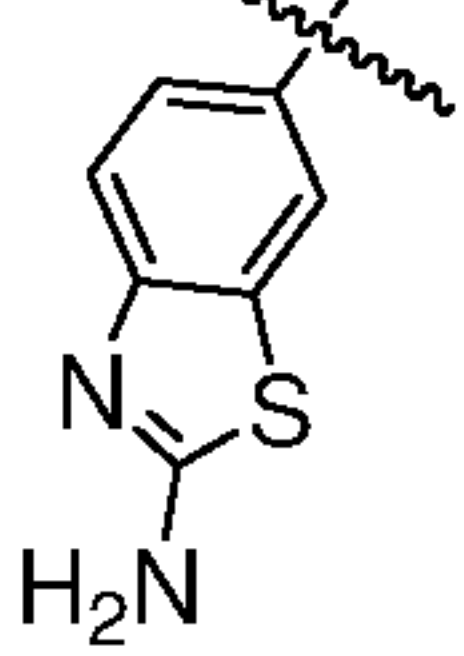
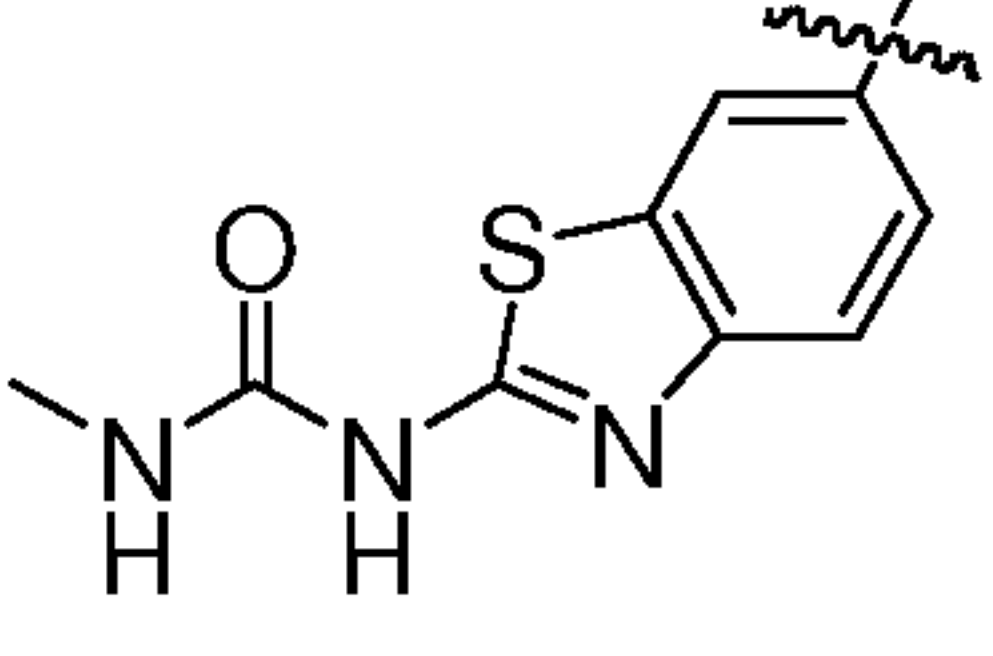
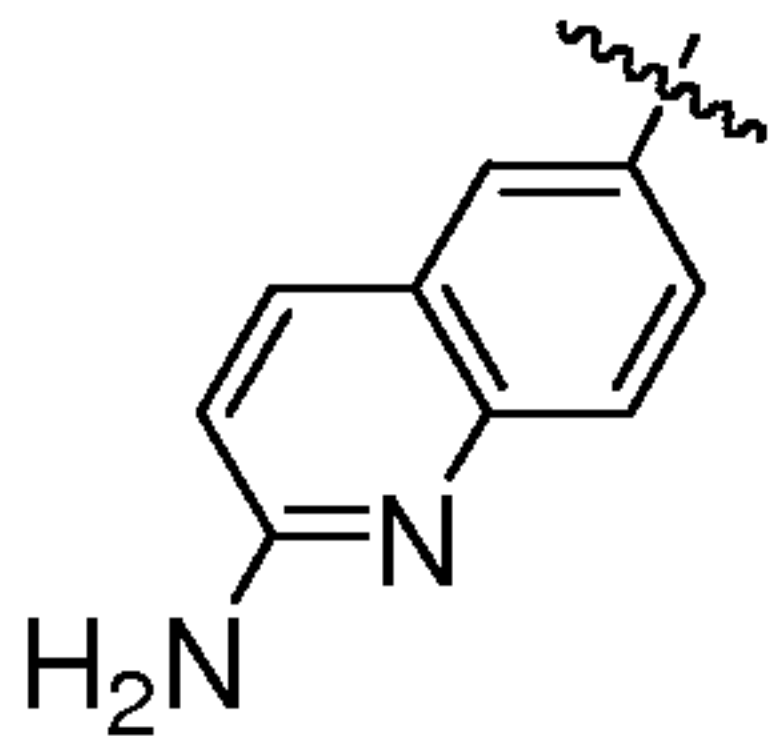
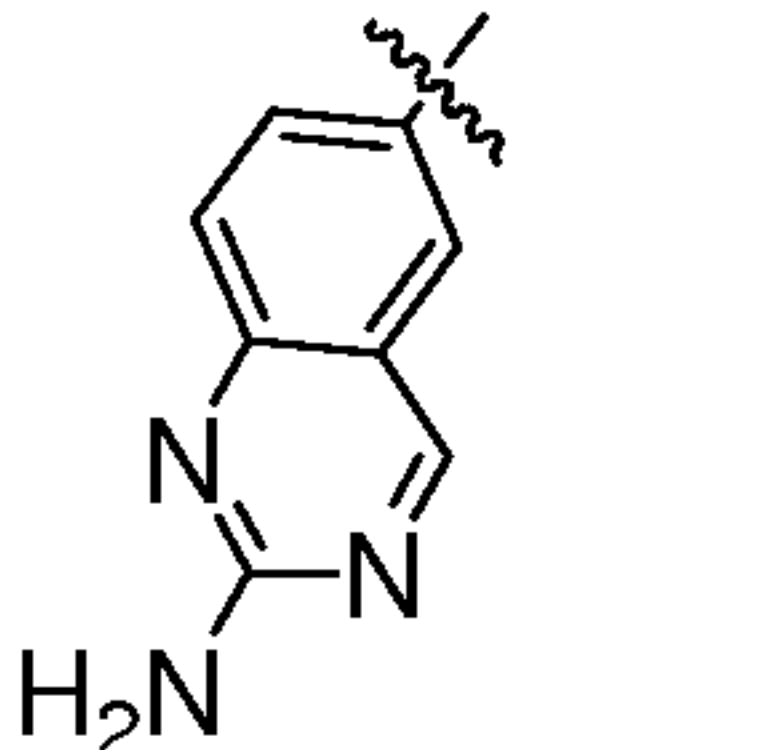
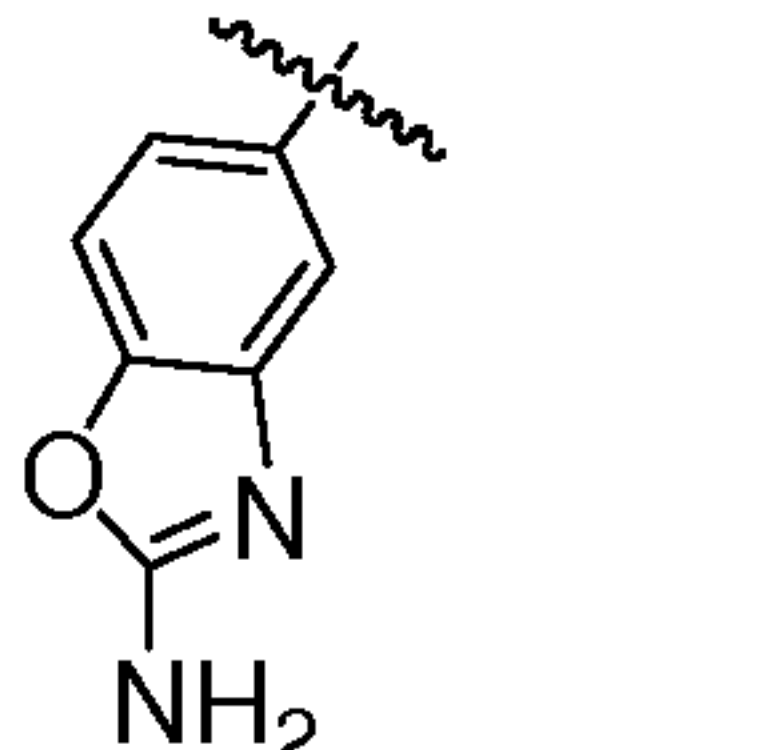
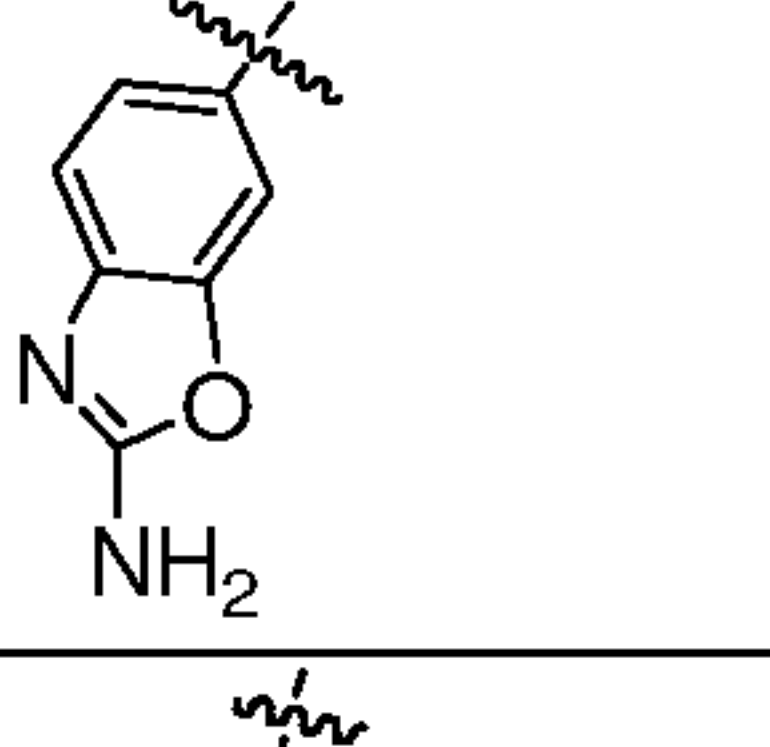
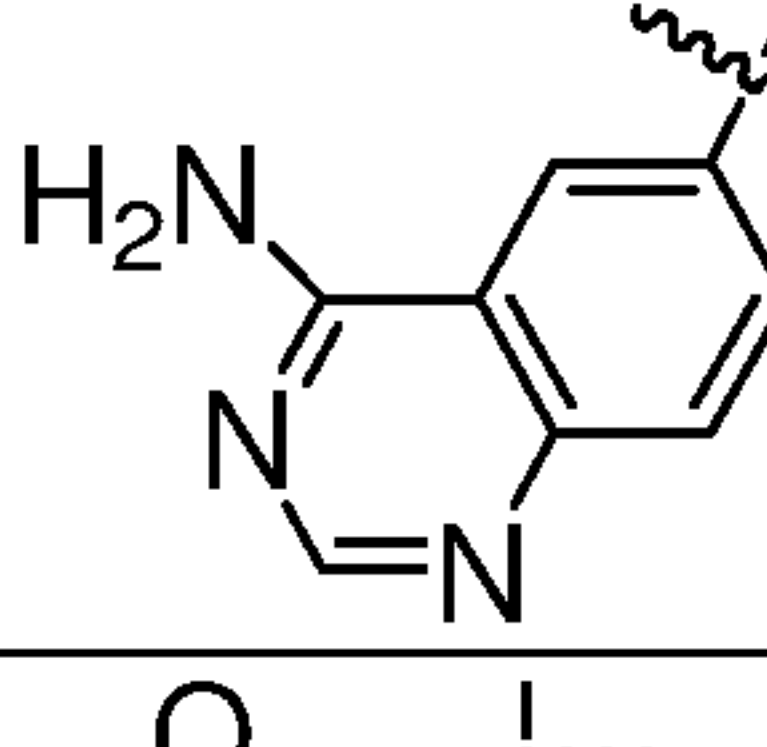
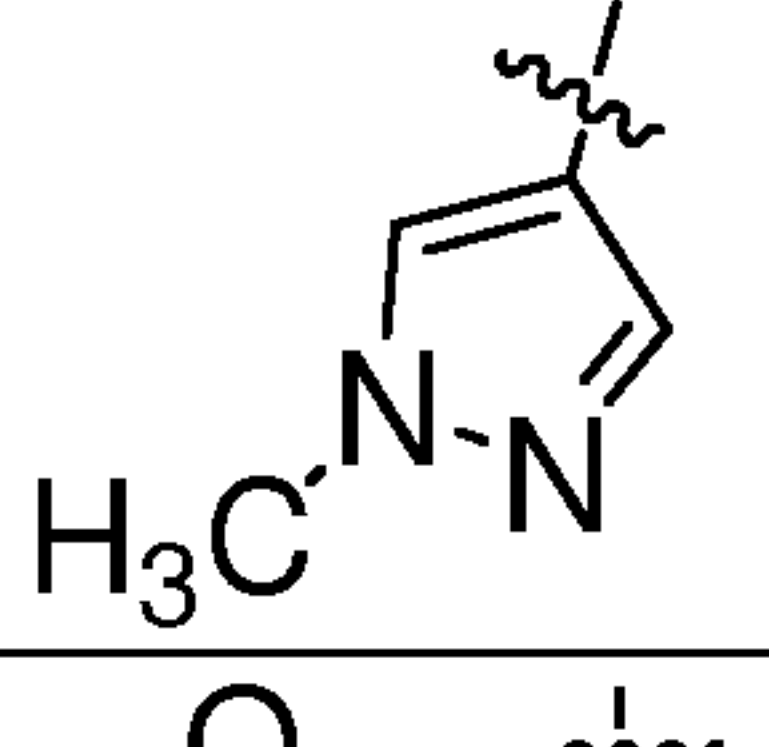
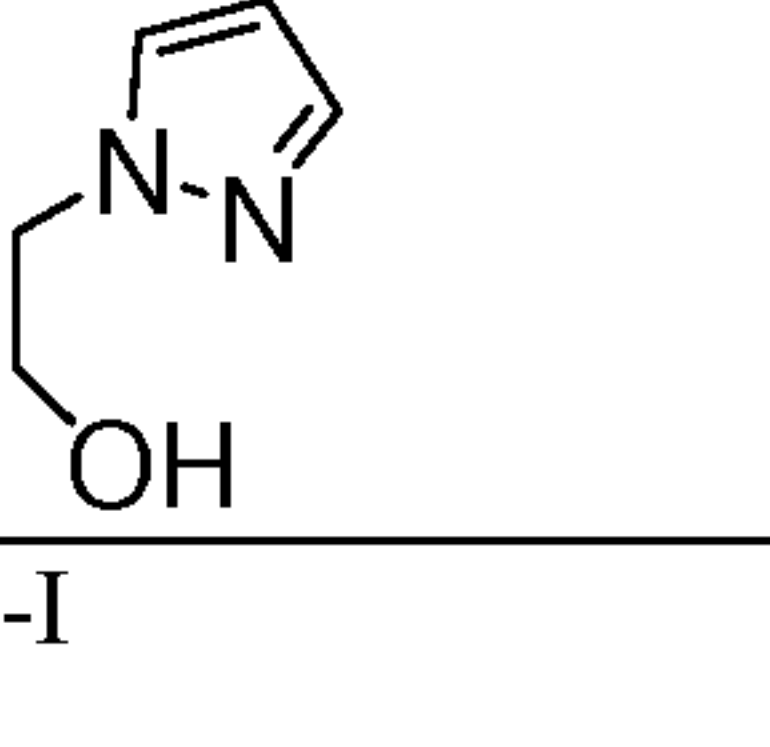
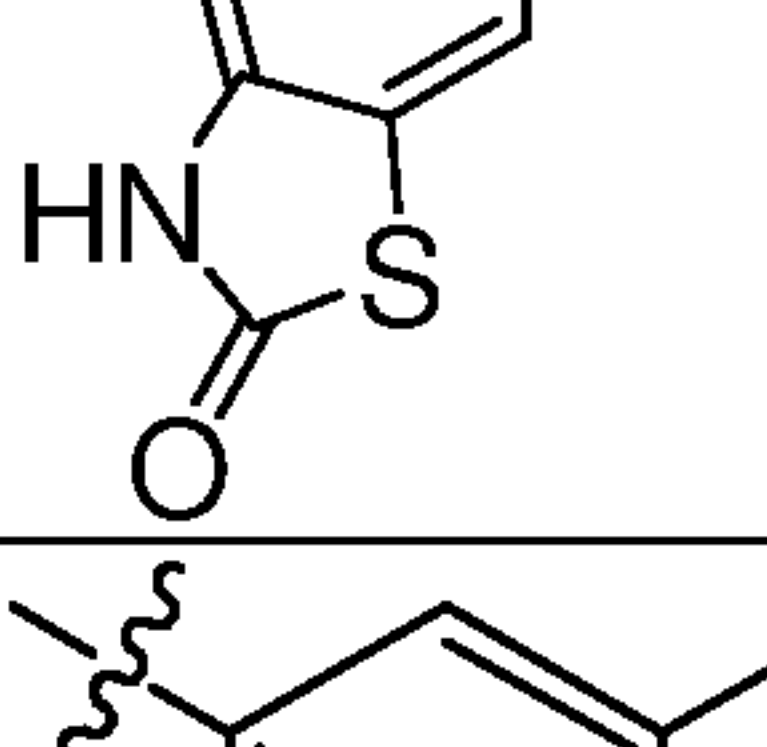
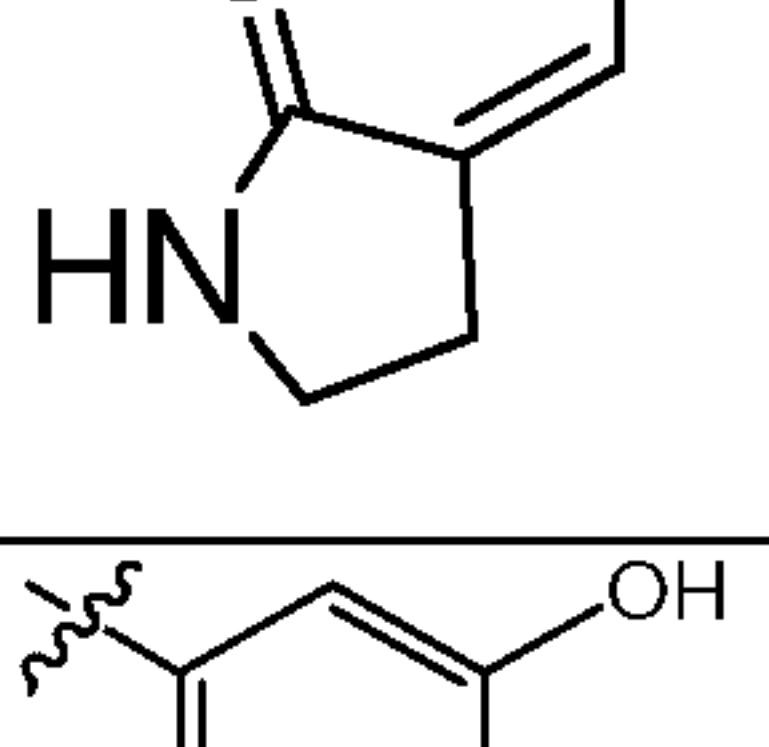
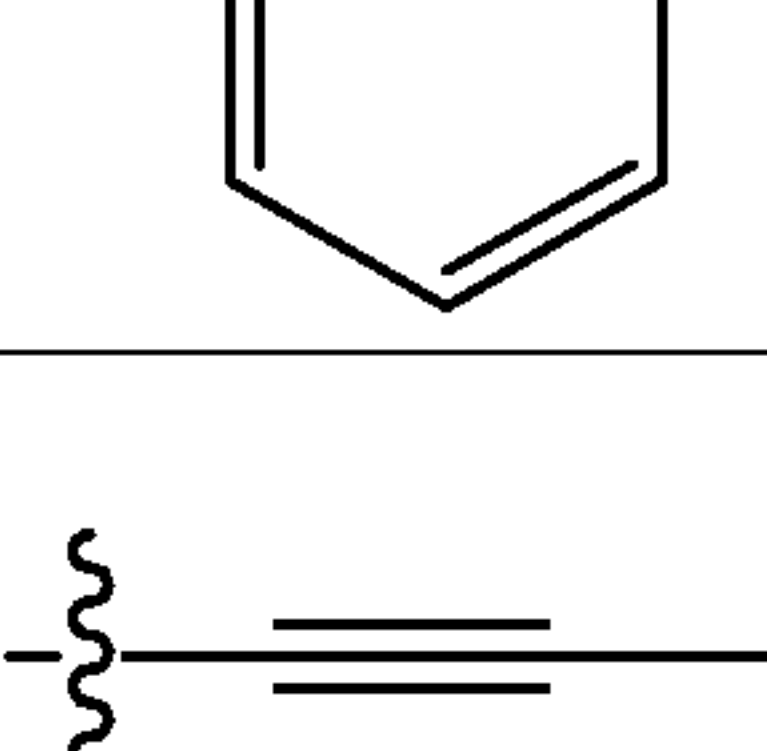
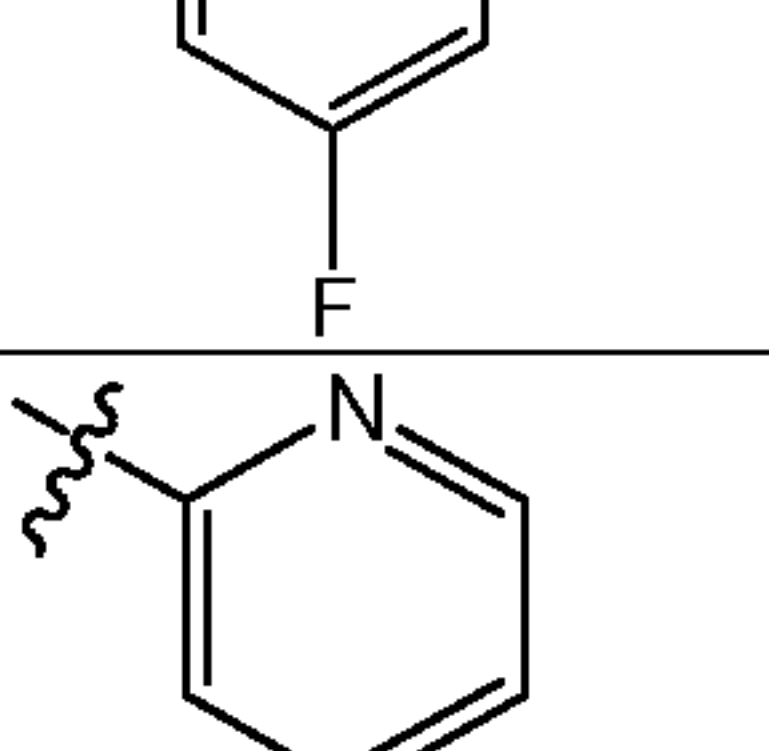
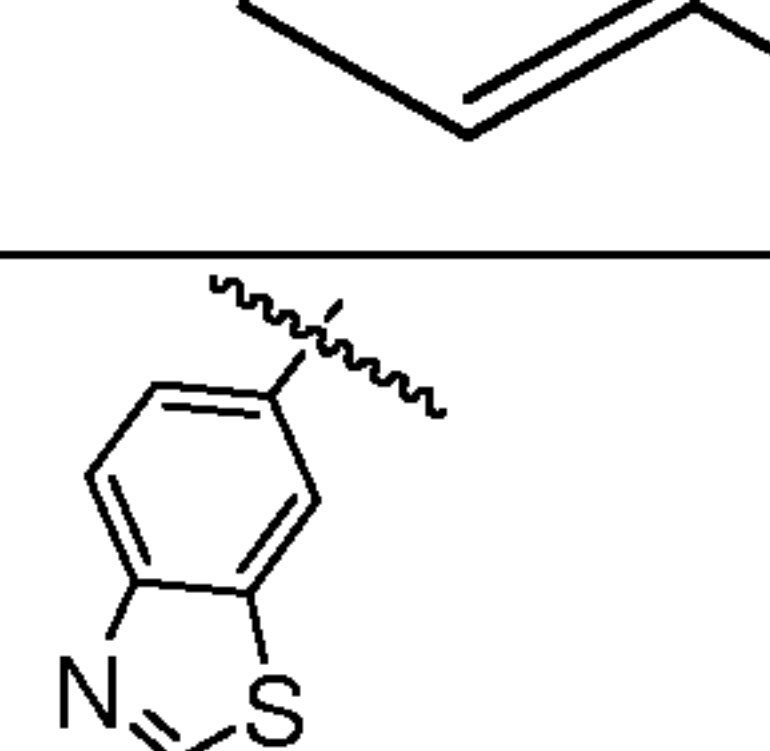
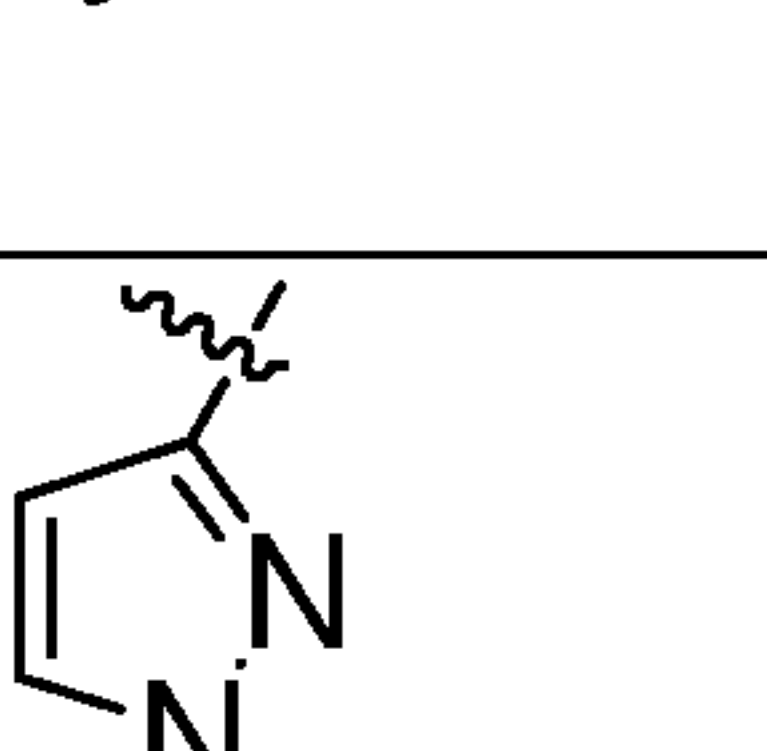
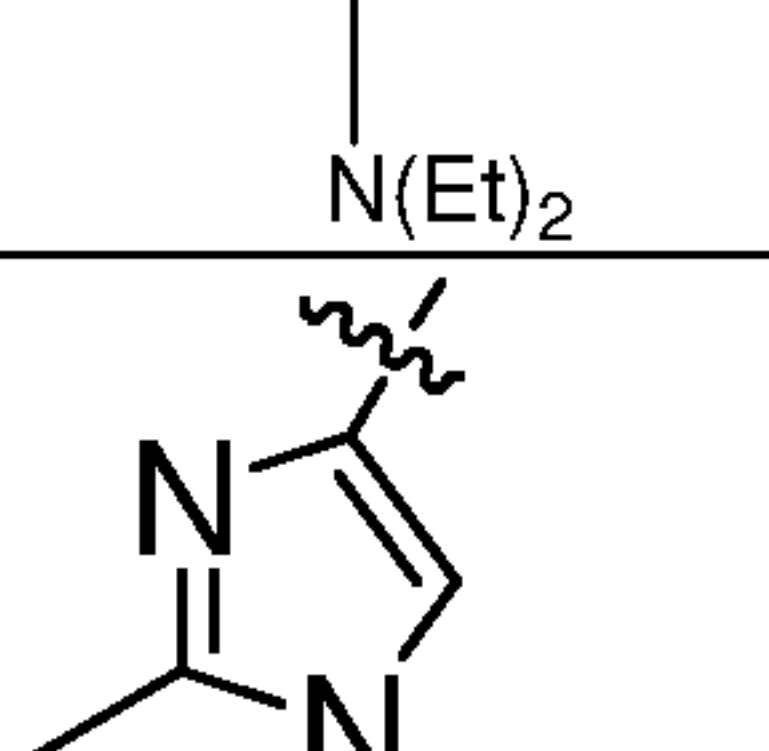
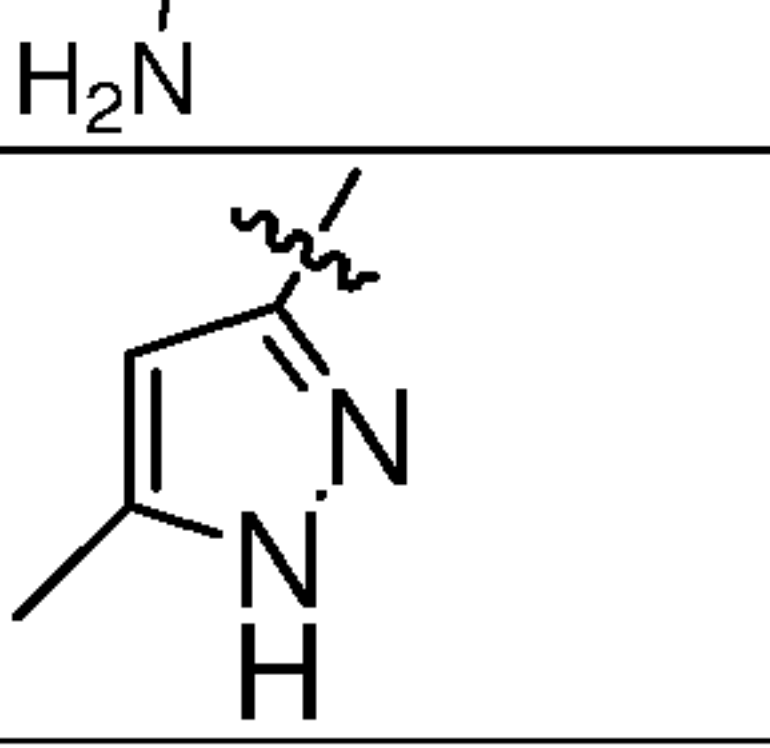
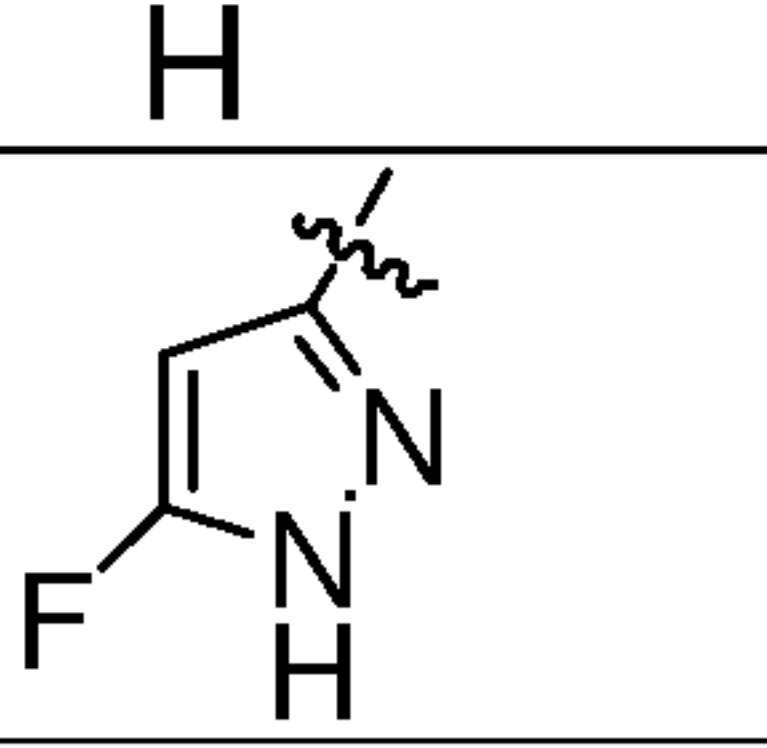
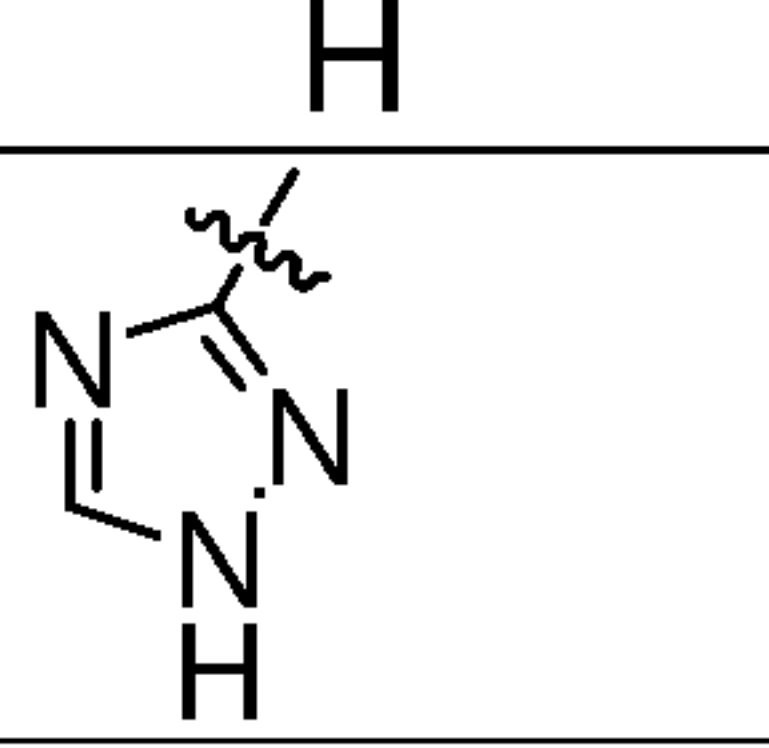
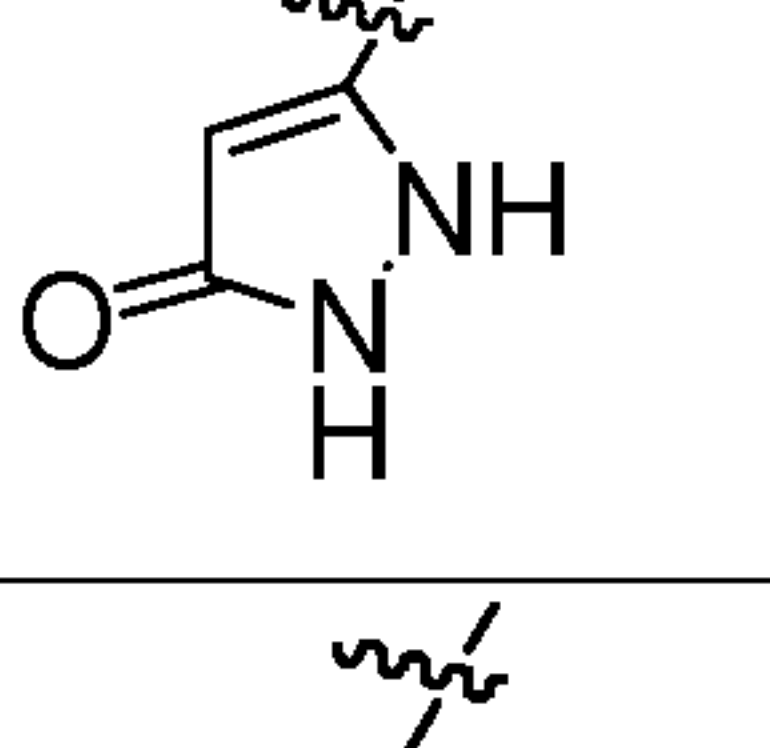
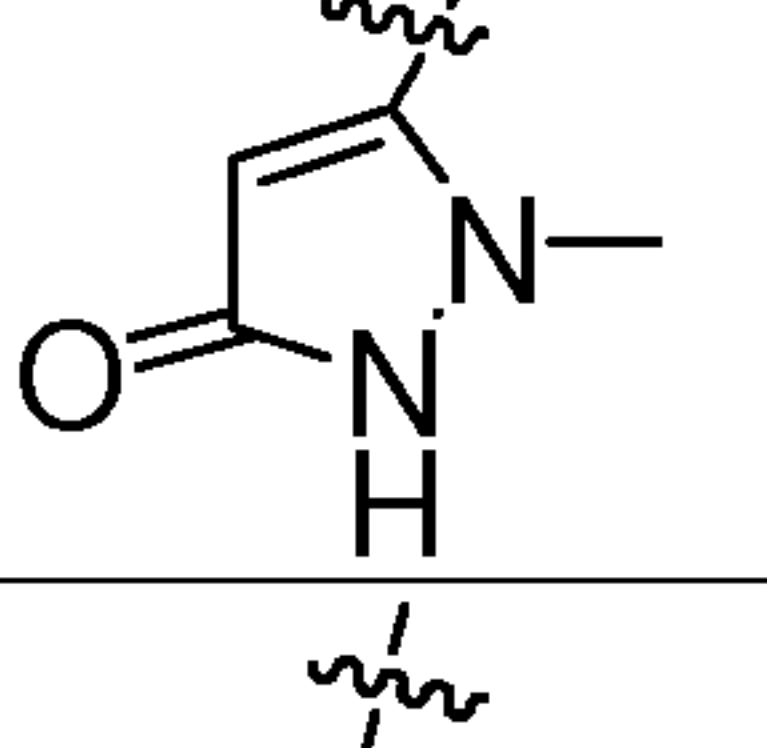
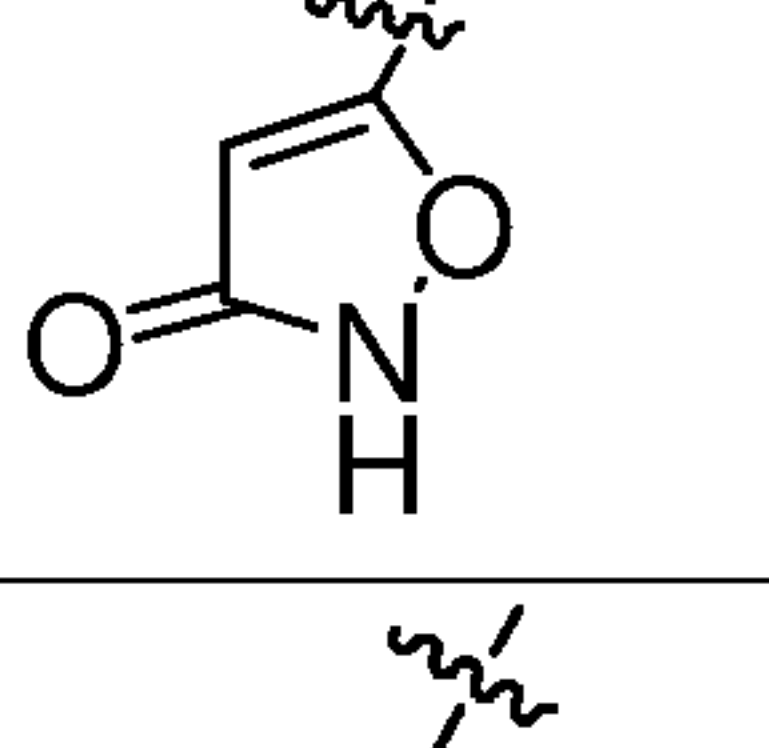
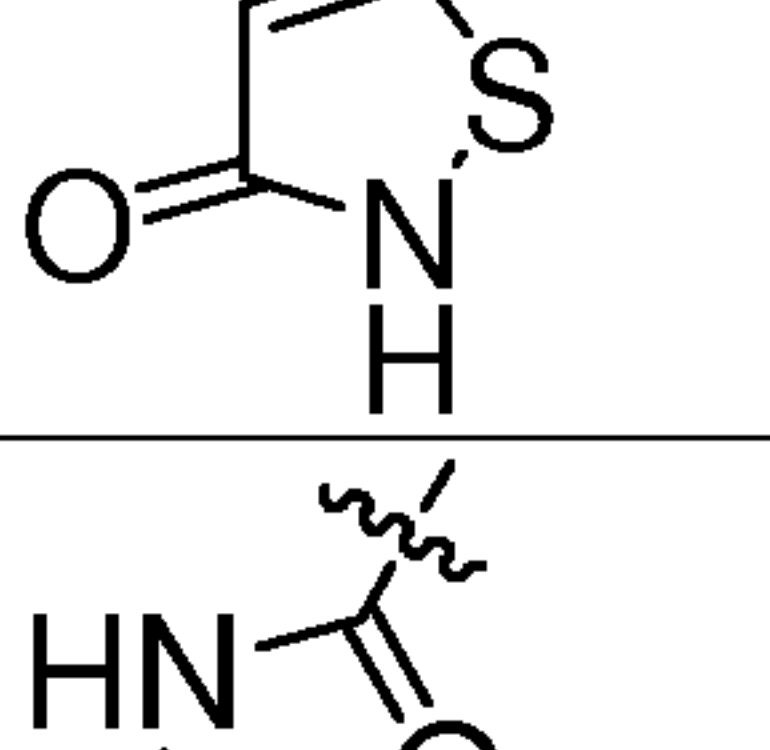
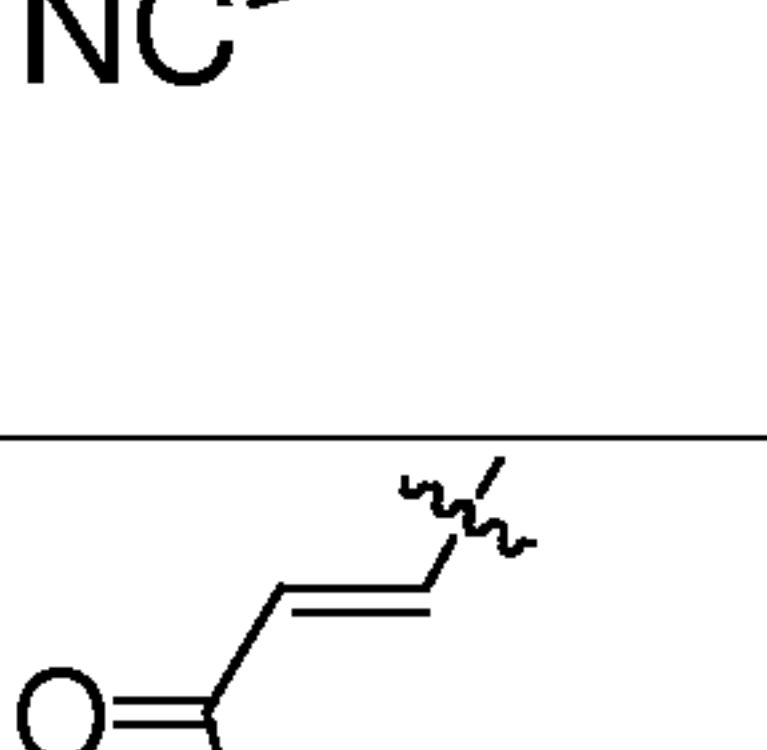
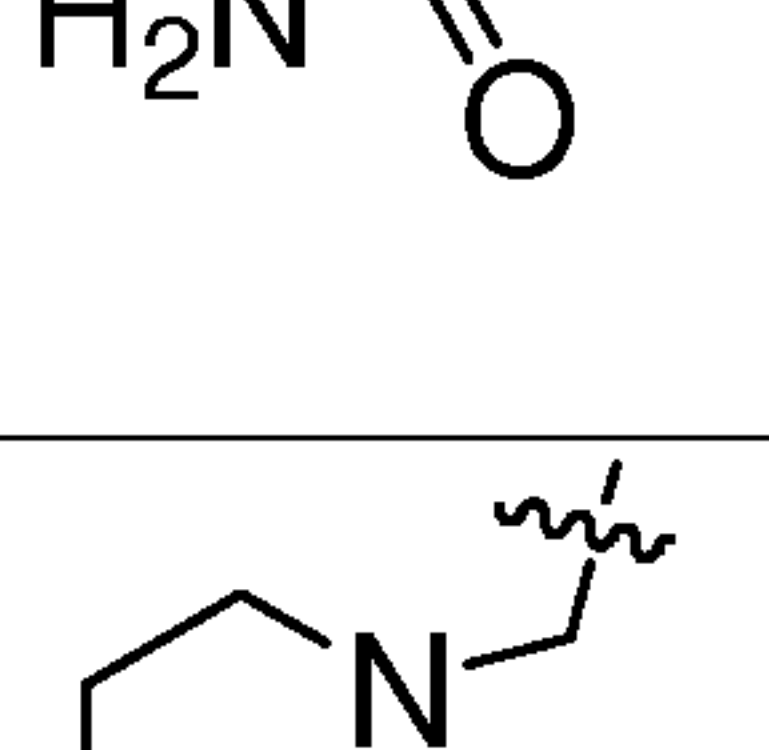
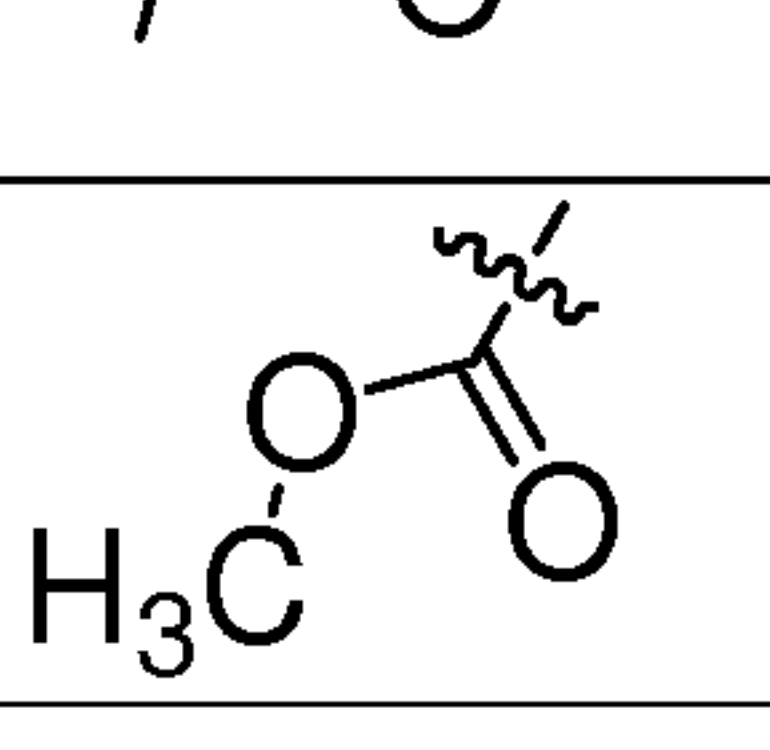
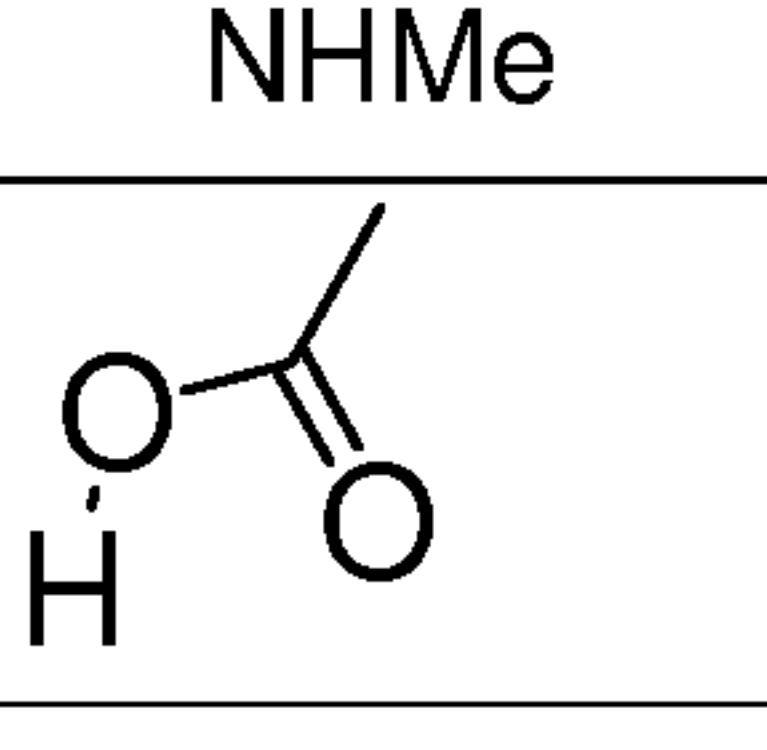
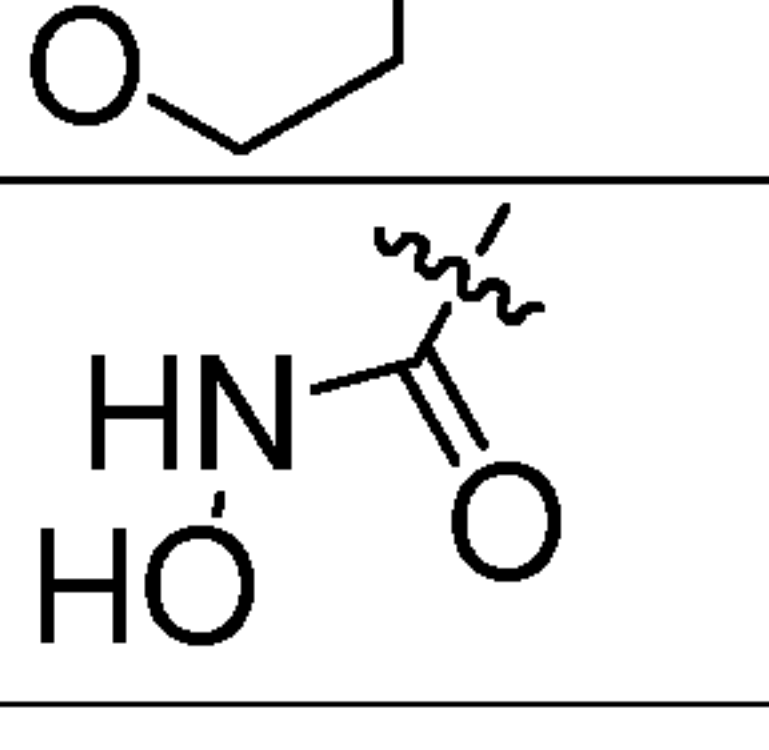
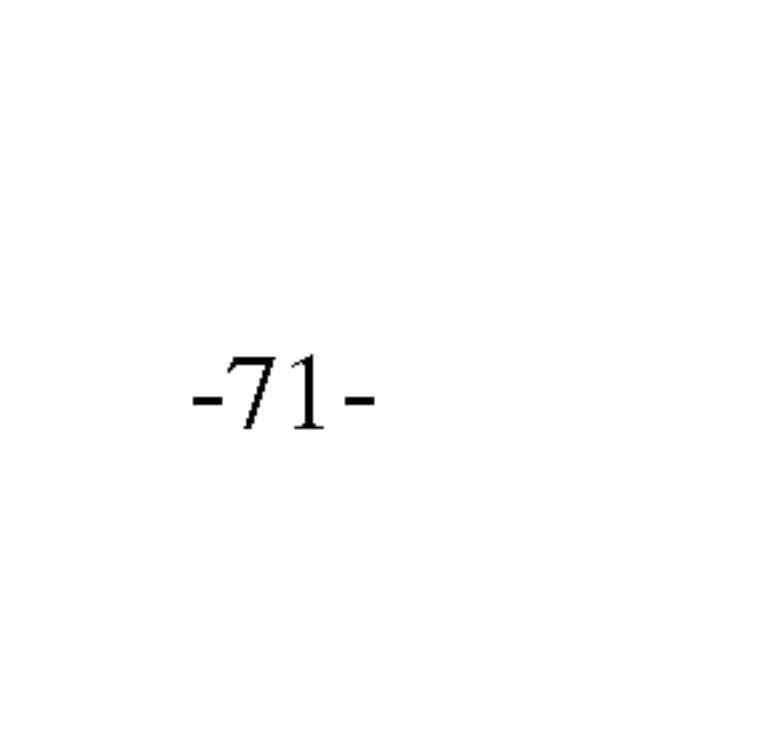
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B-91		B-92		B-93	
B-94		B-95		B-96	
B-97		B-98		B-99	
B-100		B-101		B-102	

Table 2. Illustrative R^{12} moieties of compounds of Formula I include, but are not limited to:

Sub-class #	R^{12}	Sub-class #	R^{12}	Sub-class #	R^{12}
12-1	$-\text{CN}$	12-2	$-\text{Br}$	12-3	$-\text{Cl}$
12-4	$-\text{CH}_2\text{CH}_3$	12-5	$-\text{CH}_3$	12-6	$-\text{CH}(\text{CH}_3)_2$
12-7		12-8		12-9	
12-10		12-11		12-12	
12-13		12-14		12-15	
12-16		12-17		12-18	

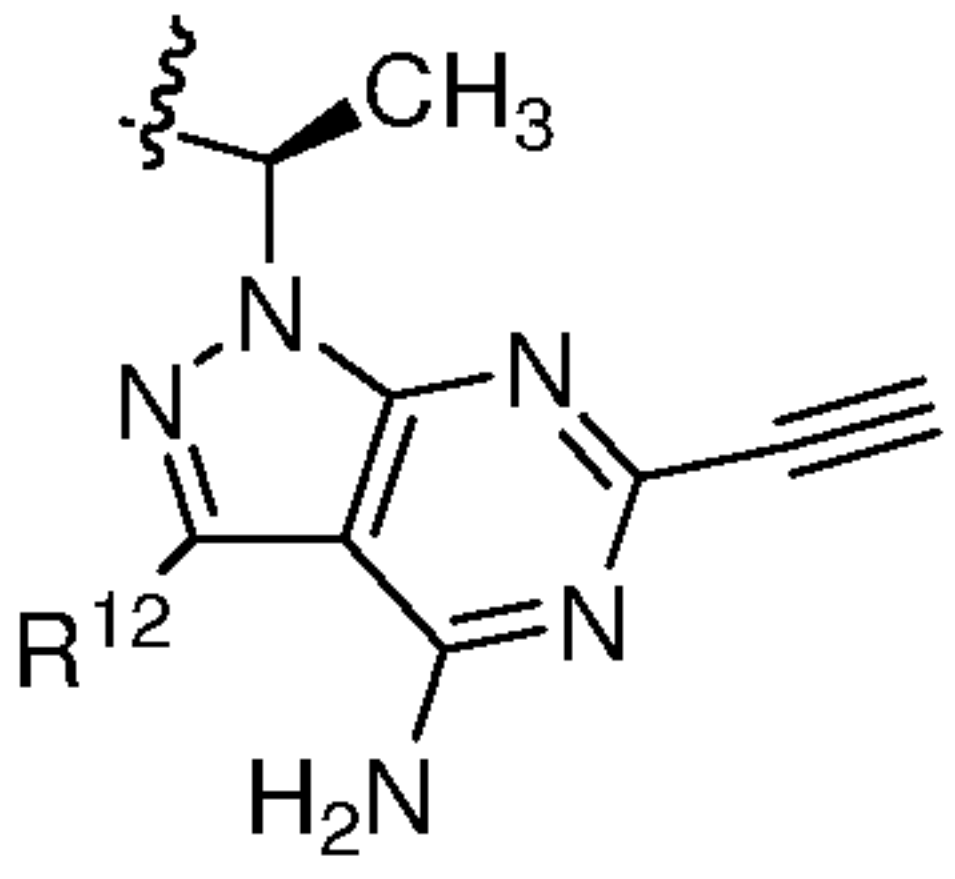
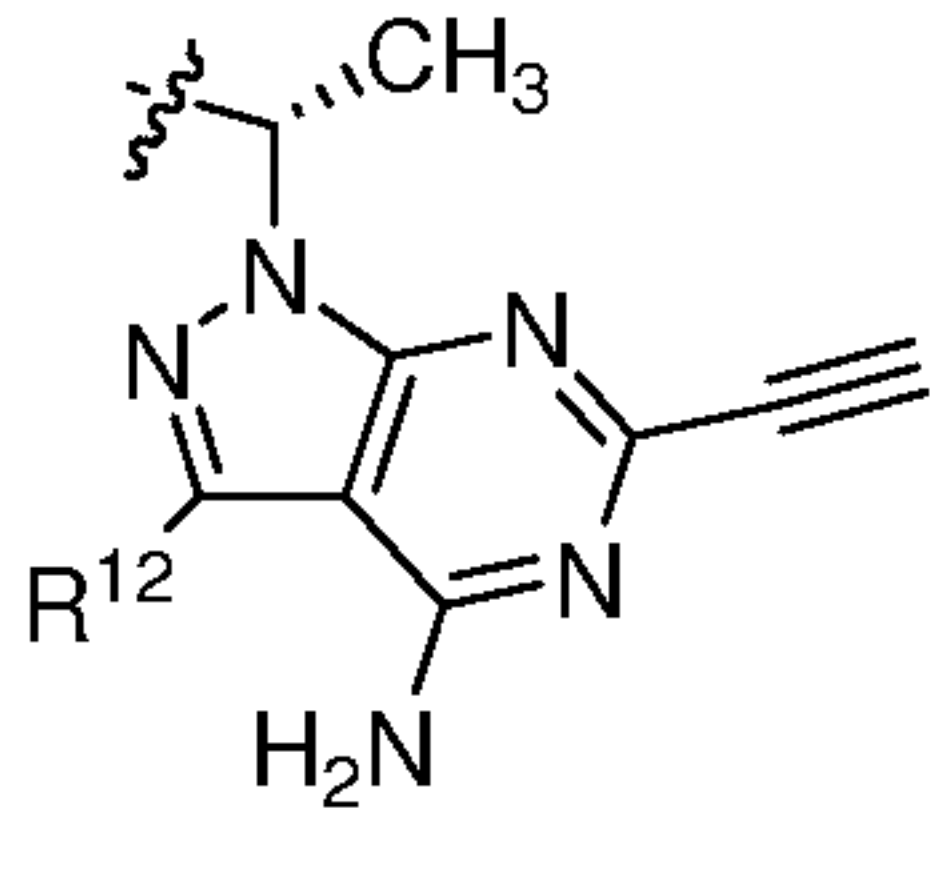
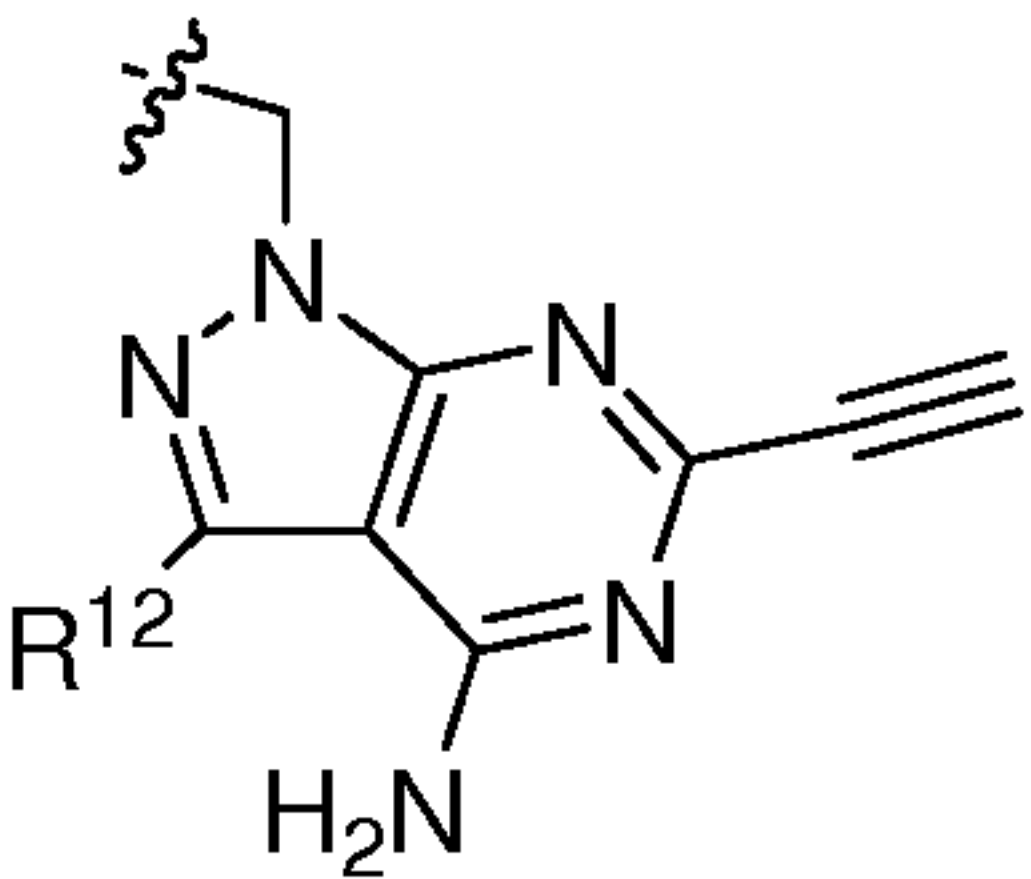
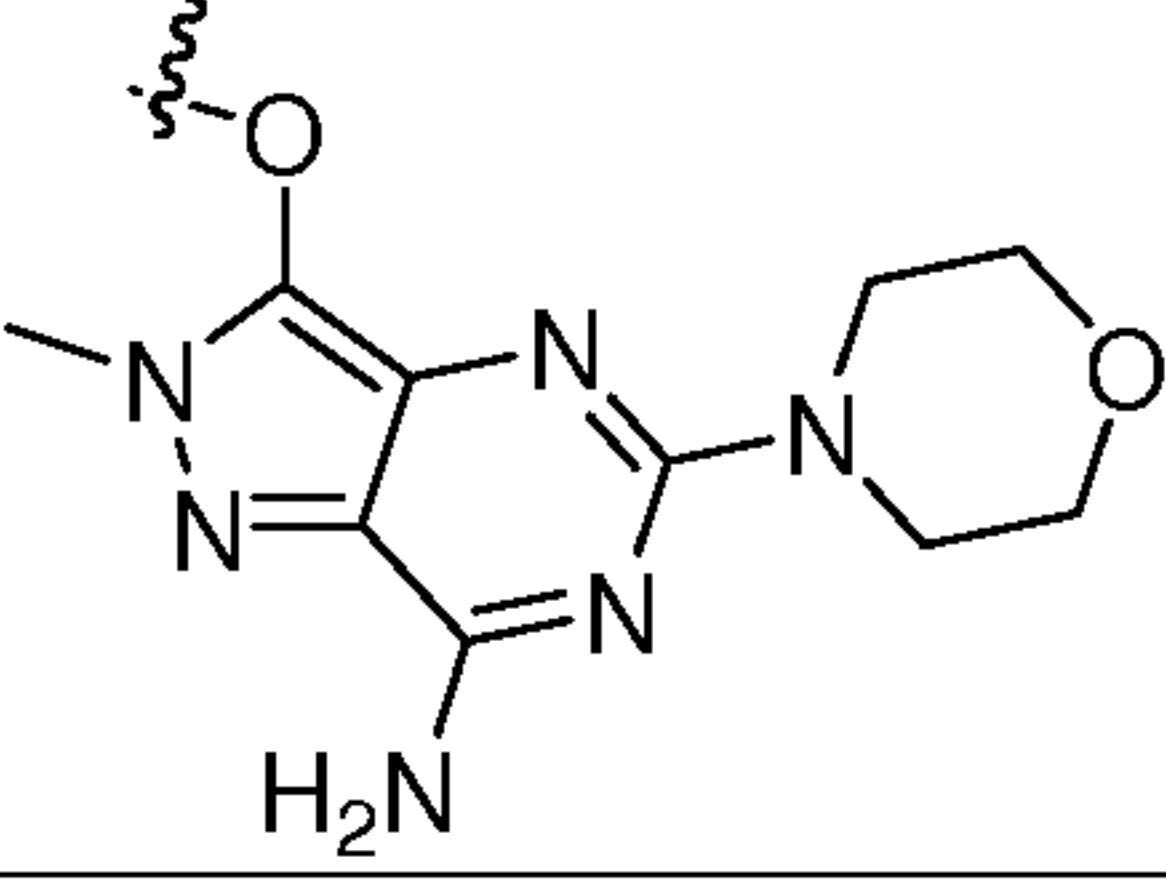
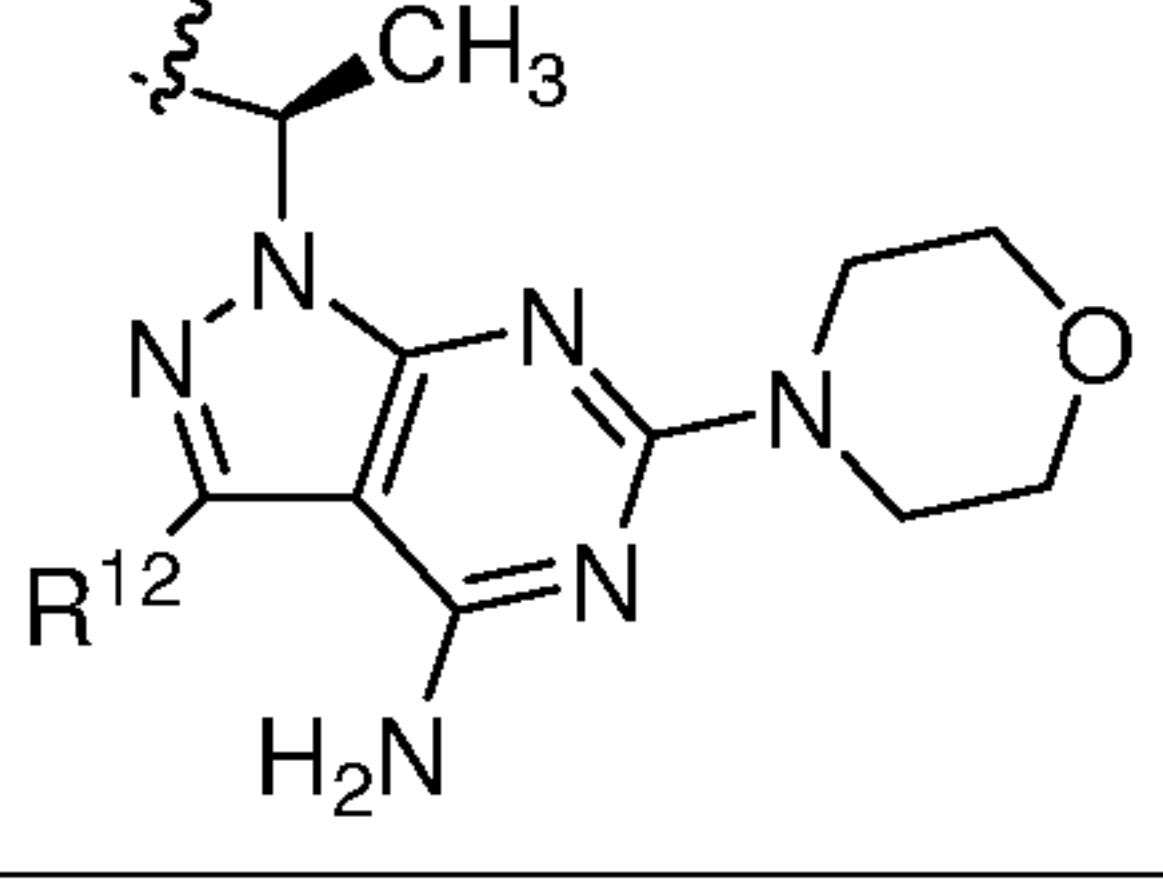
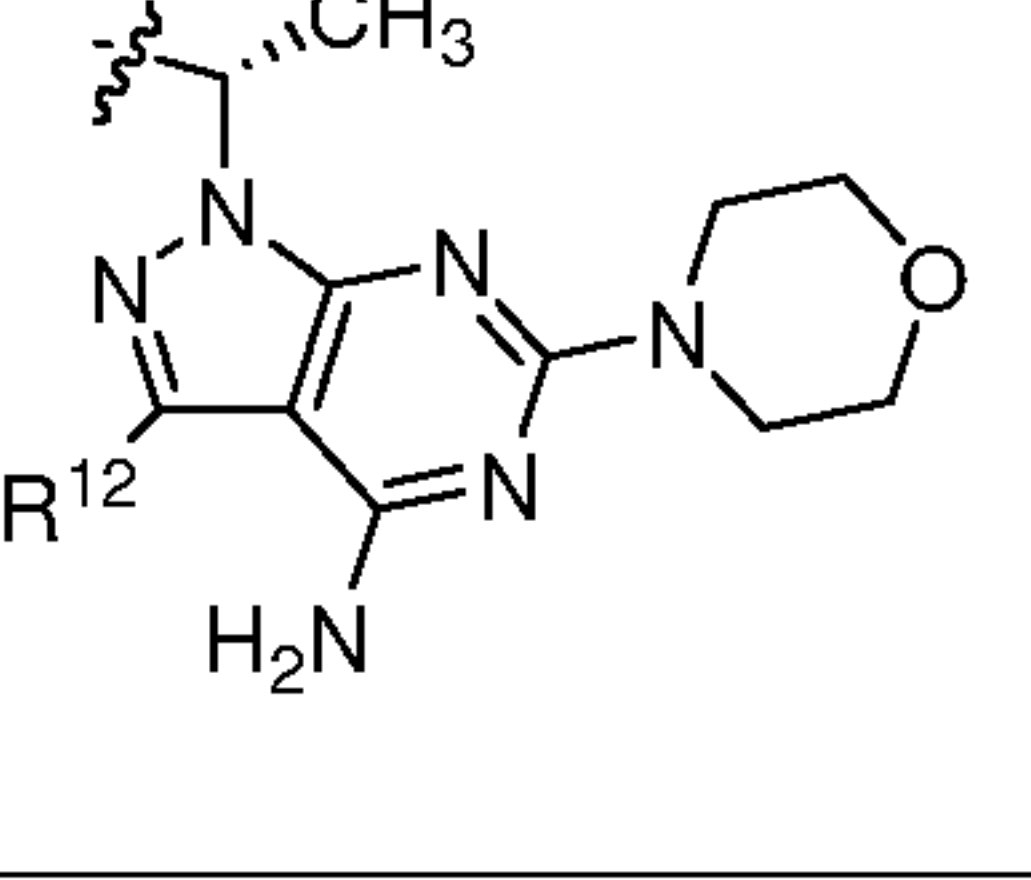
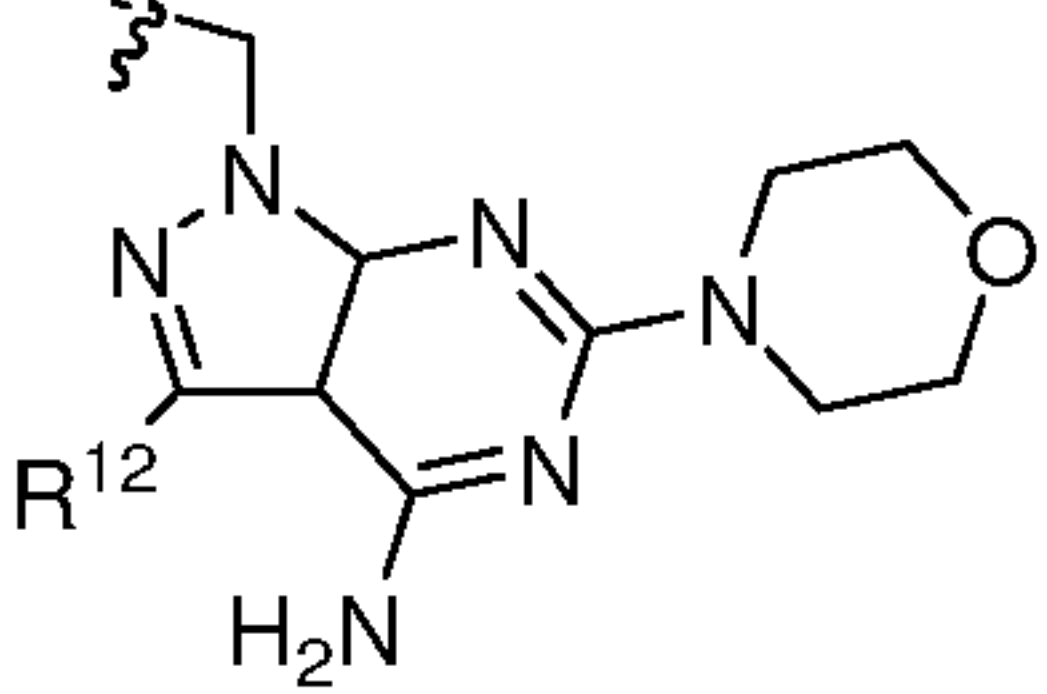
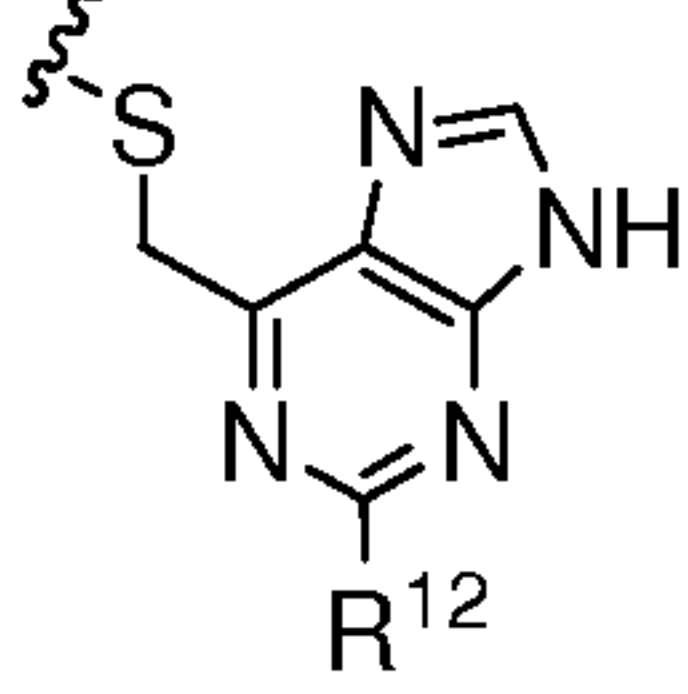
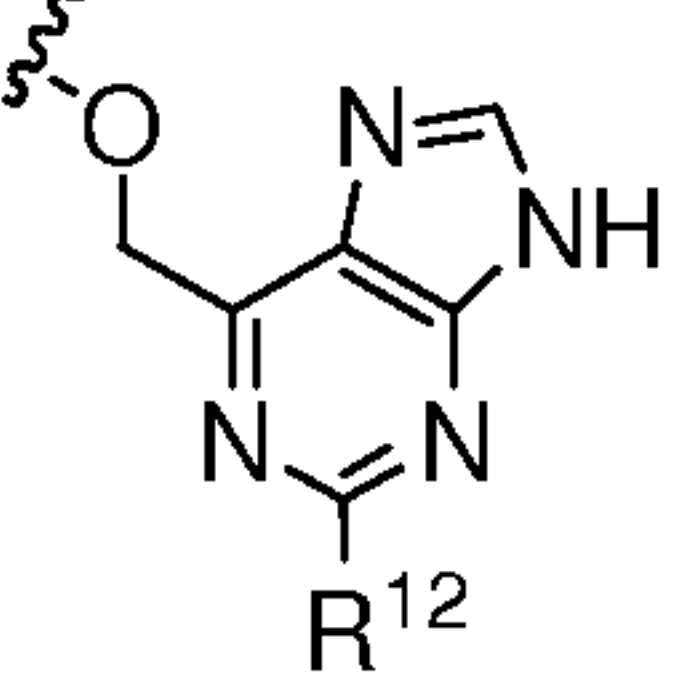
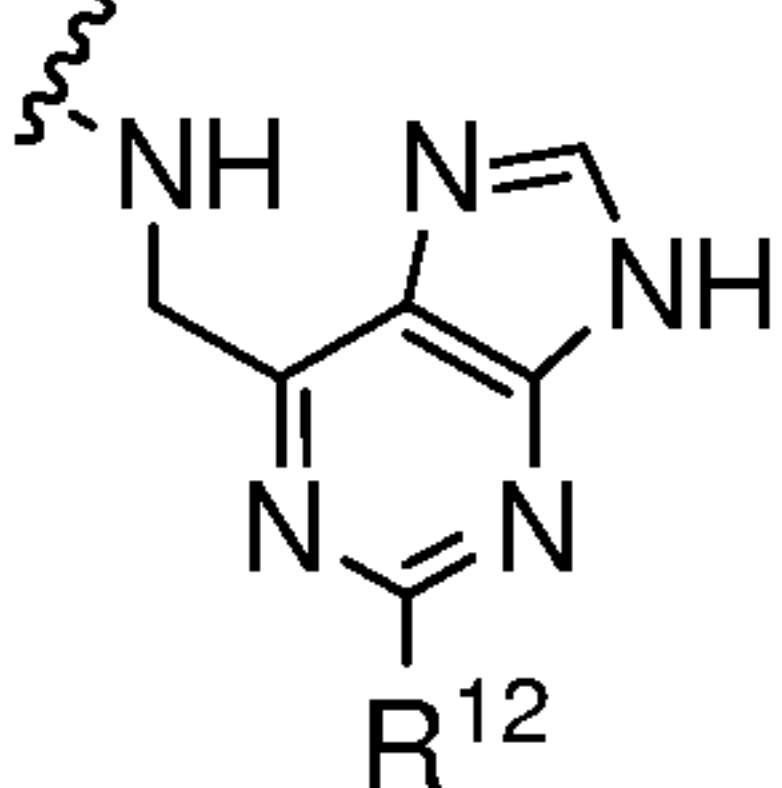
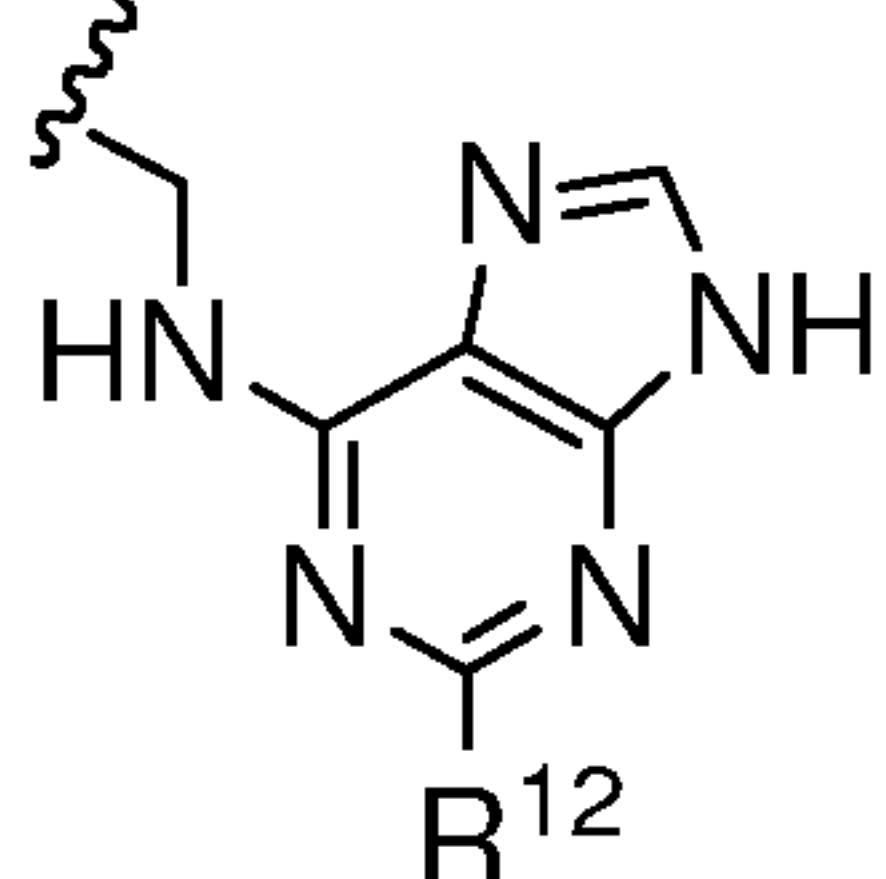
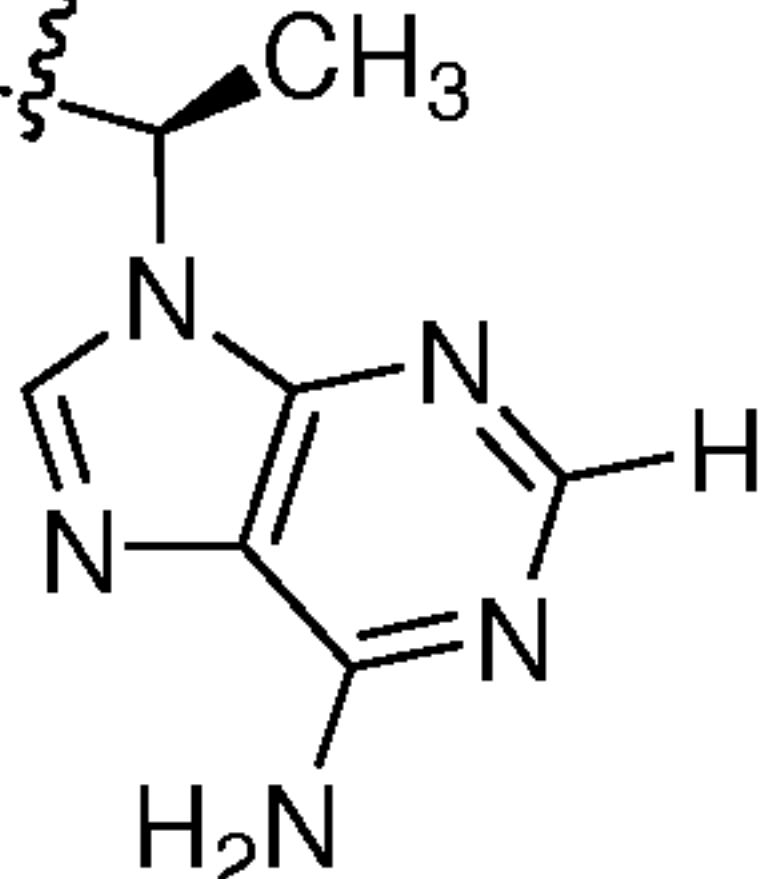
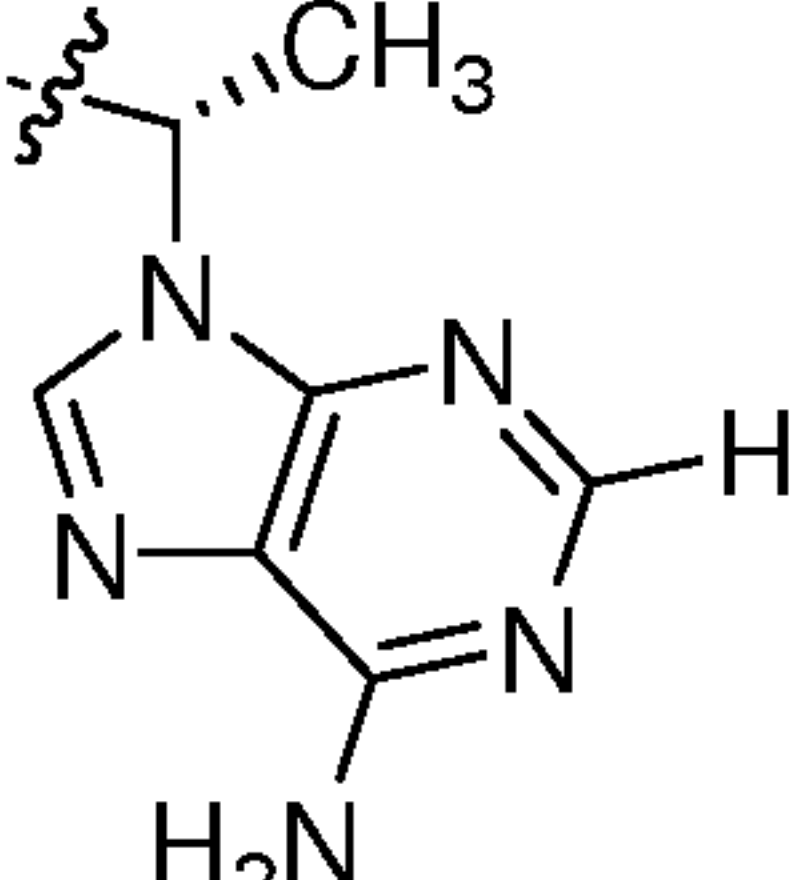
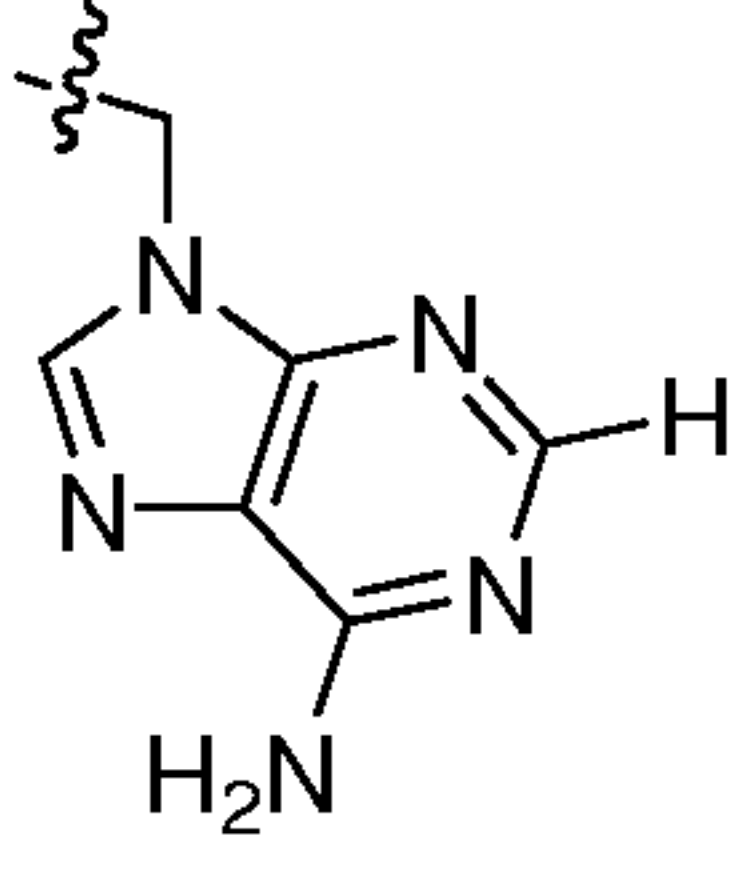
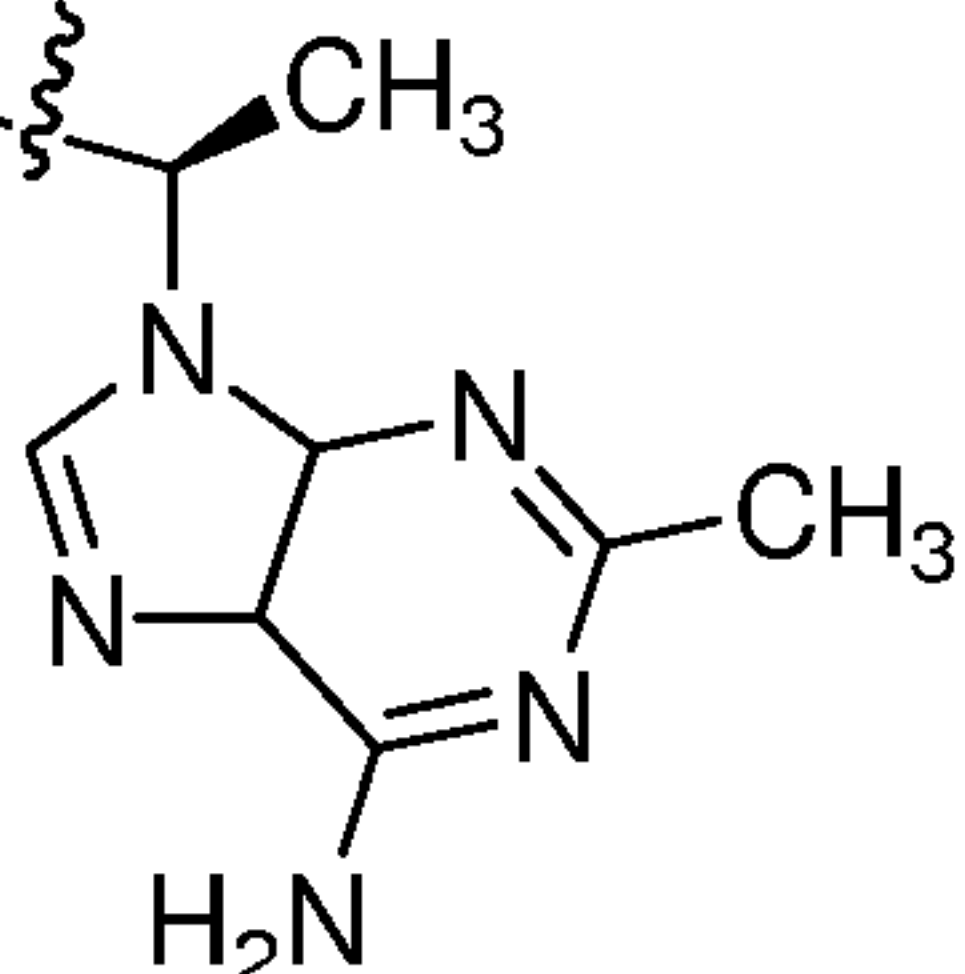
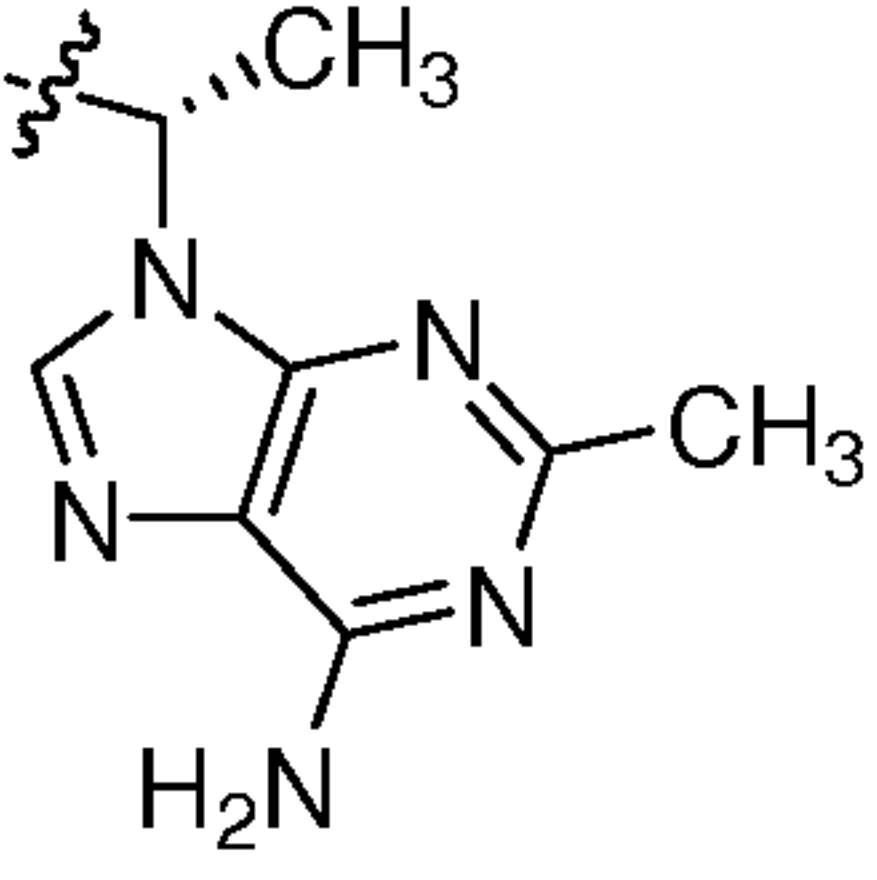
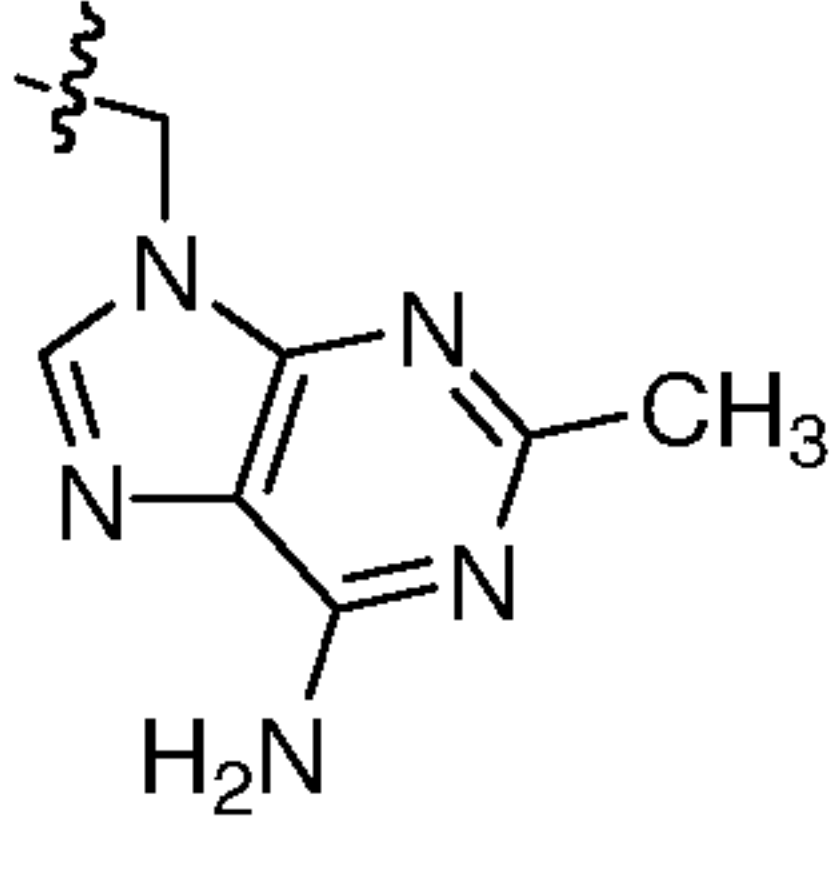
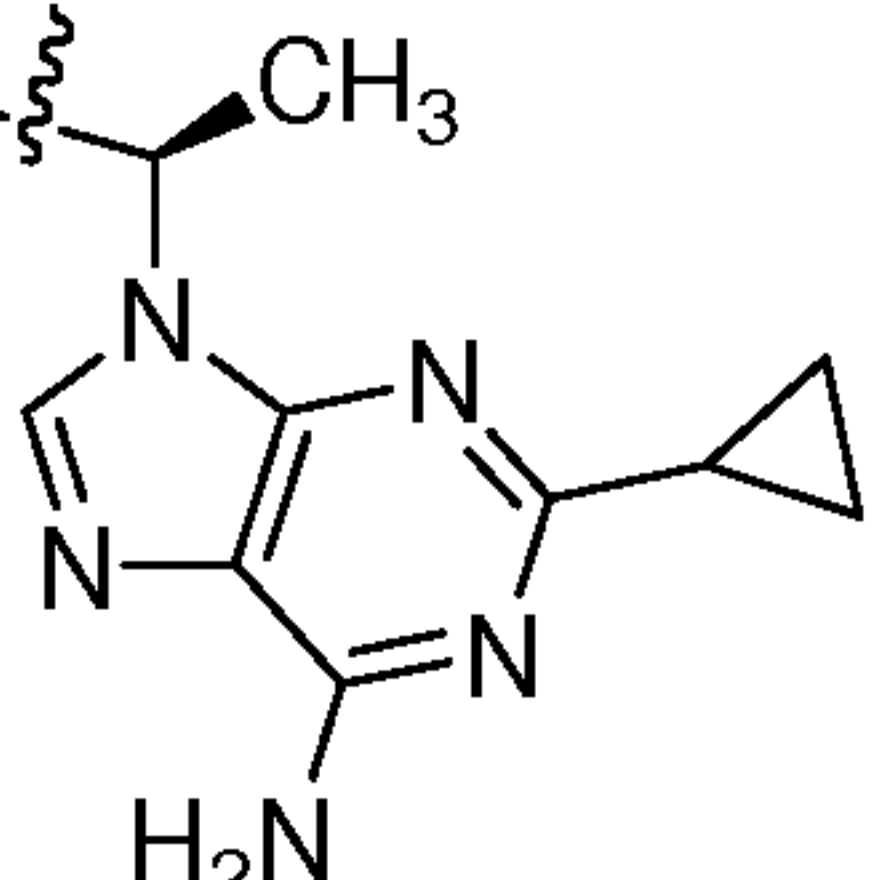
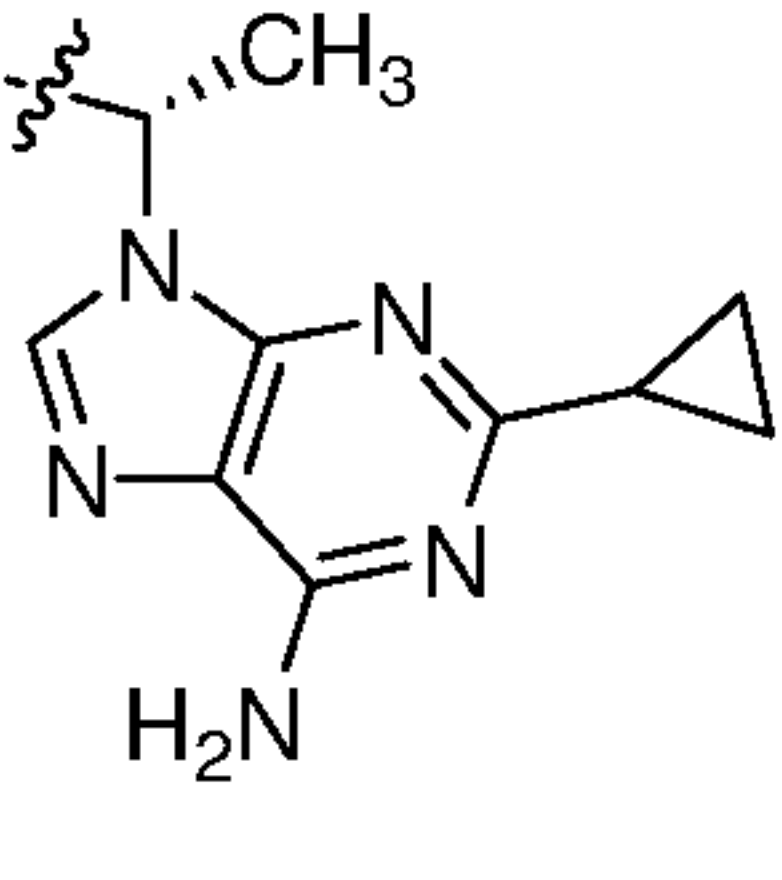
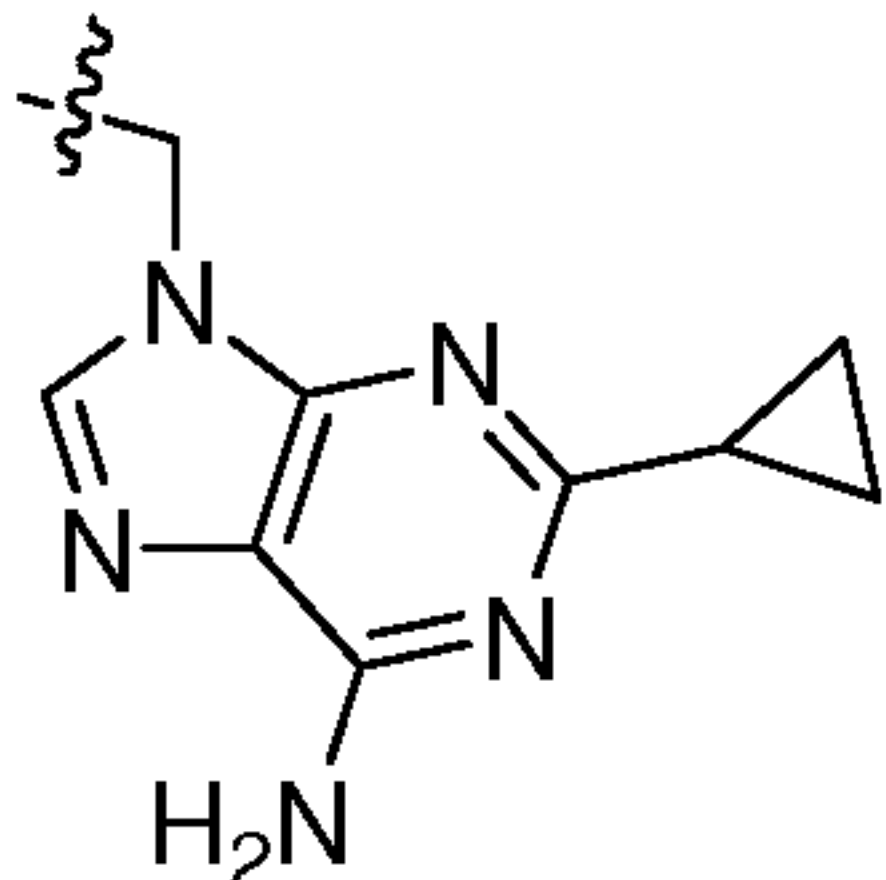
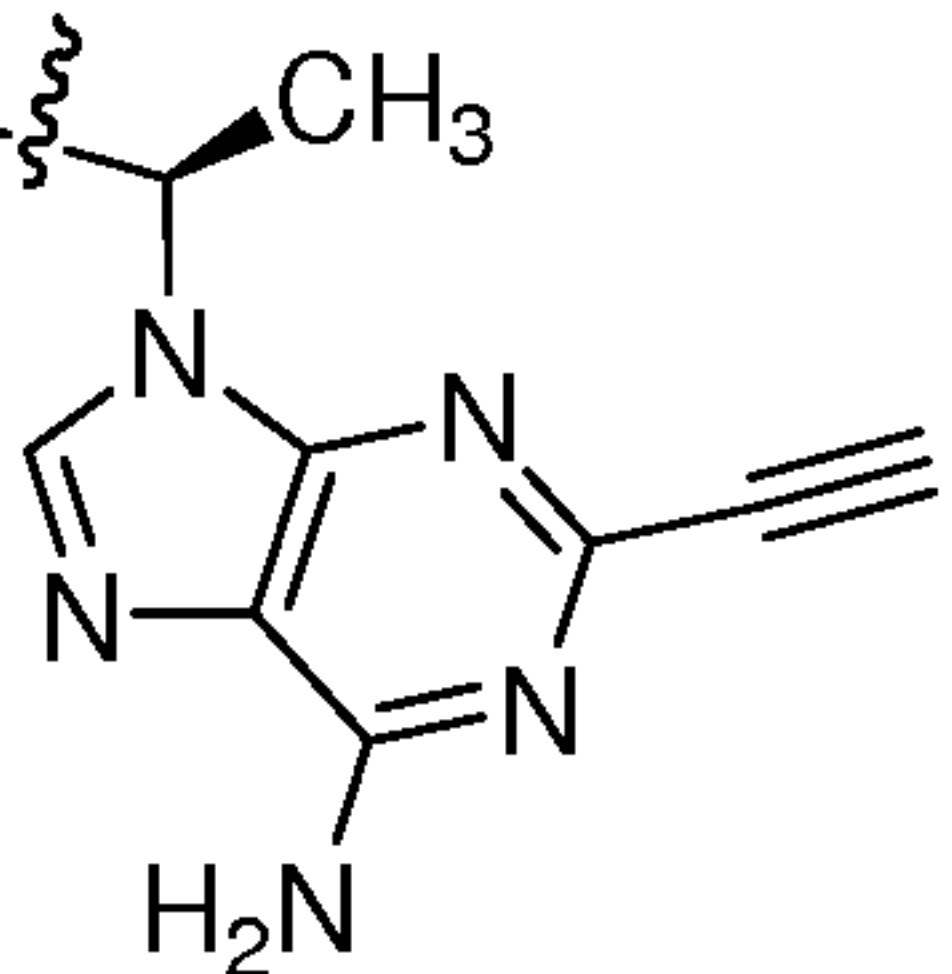
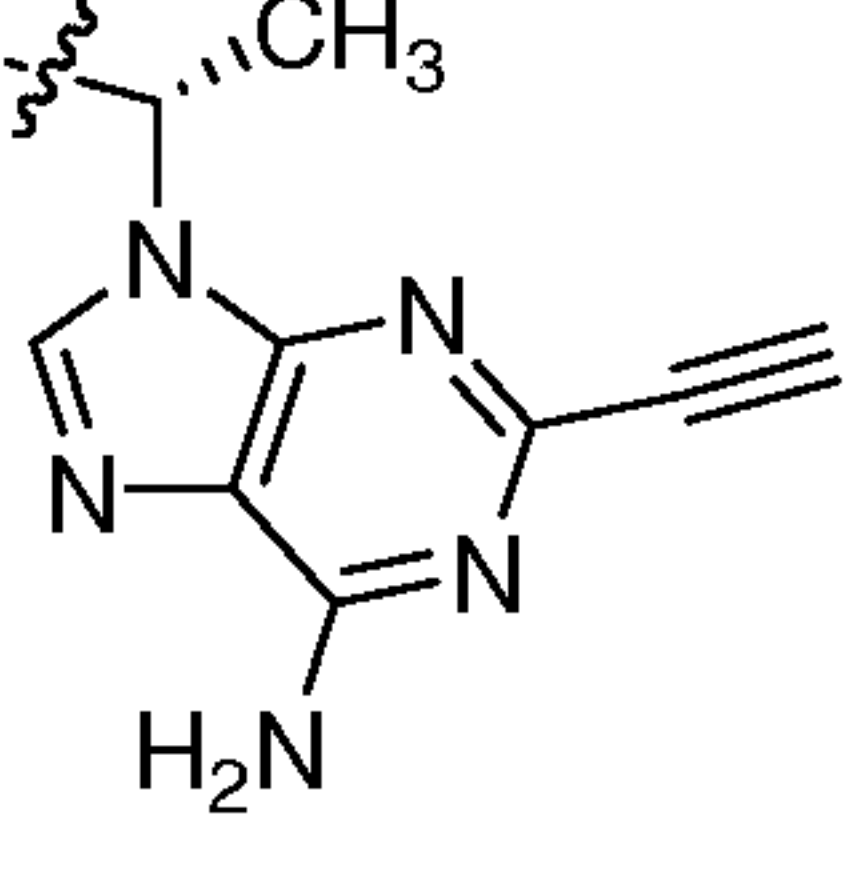
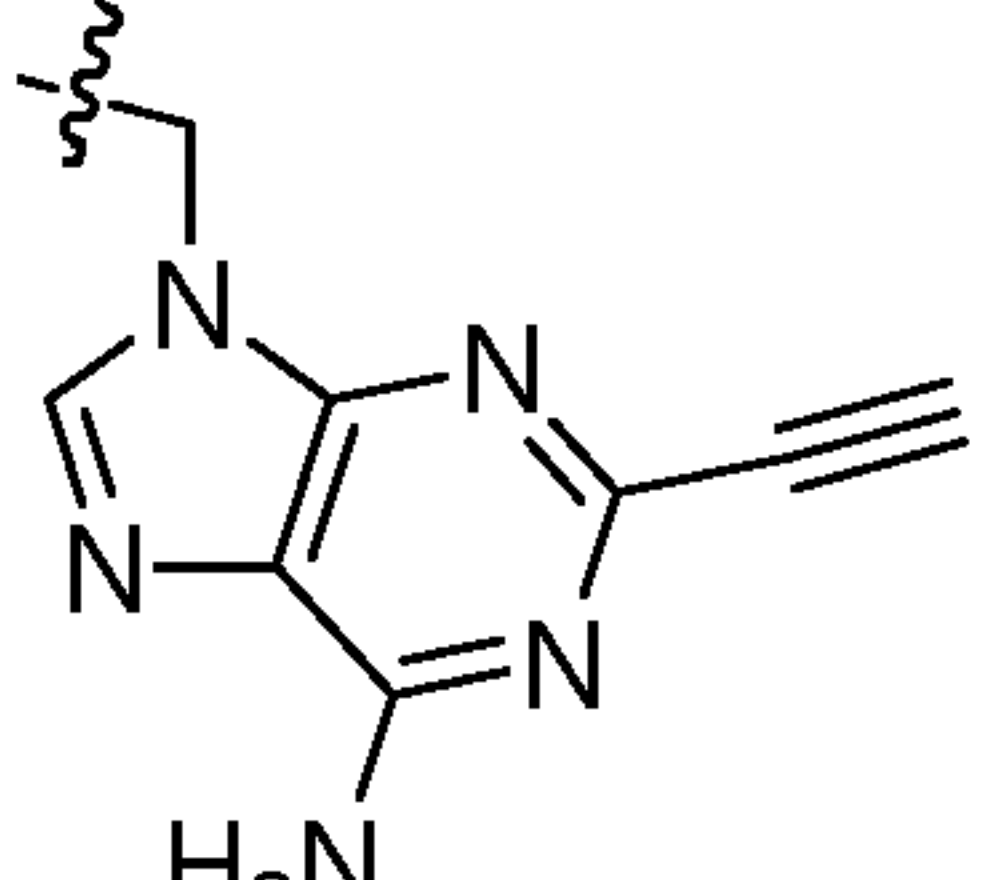
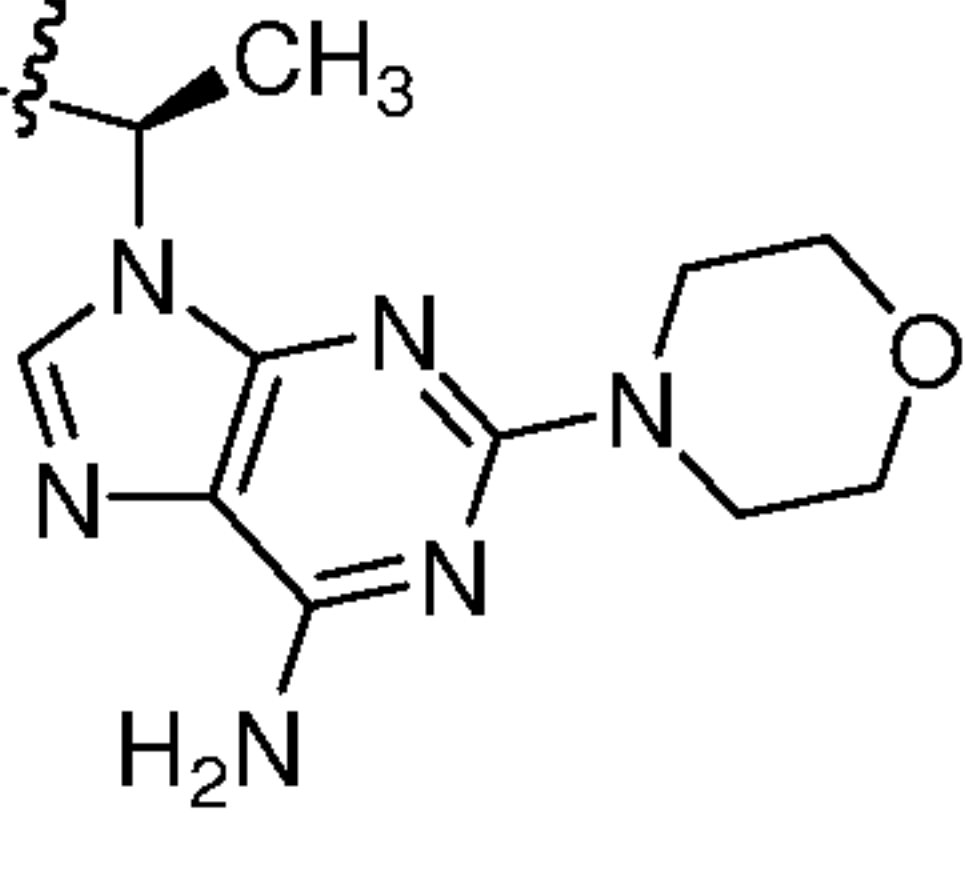
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12-22		12-23		12-24	
12-25		12-26		12-27	
12-28		12-29		12-30	
12-31		12-32		12-33	
12-34		12-35	-H	12-36	
12-37		12-38		12-39	
12-40		12-41		12-42	
12-43		12-44		12-45	
12-46		12-47		12-48	
12-49		12-50		12-51	

12-52		12-53		12-54	
12-55		12-56		12-57	
12-58		12-59		12-60	
12-61	-I	12-62		12-63	
12-64		12-65		12-66	
12-67		12-68		12-69	
12-70		12-71		12-72	
12-73		12-74		12-75	
12-76		12-77		12-78	
12-79		12-80		12-81	
12-82		12-83		12-84	

12-85		12-86		12-87	
12-88		12-89		12-90	
12-91		12-92		12-93	
12-94		12-95		12-96	

Table 3. Illustrative X-Y-W_d of compounds of Formula I include, but are not limited to:

Sub-class #	X-Y-W _d	Sub-class #	X-Y-W _d	Sub-class #	X-Y-W _d
1		2		3	
4		5		6	
7		8		9	
10		11		12	

13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	

37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55					

[00201] In some embodiments, one or more subject compounds bind specifically to a PI3 kinase.

[00202] In some embodiments, the IC_{50} of a subject compound for p110 α , p110 β , p110 γ , or p110 δ is less than about 1 μ M, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5nM. In some embodiments, the IC_{50} of a subject compound for mTor is less than about 1 μ M, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5 nM. In some other

embodiments, one or more subject compounds exhibit dual binding specificity and are capable of inhibiting a PI3 kinase (*e.g.*, a class I PI3 kinase) as well as a protein kinase (*e.g.*, mTor) with an IC_{50} value less than about 1 μ M, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than 1 nM or even less than about 0.5 nM. One or more subject compounds are capable of inhibiting tyrosine kinases including, for example, DNA-dependent protein kinase DNA-dependent protein kinase (Pubmed protein accession number (PPAN) AAA79184), Abl tyrosine kinase (CAA52387), Bcr-Abl, hemopoietic cell kinase (PPAN CAI19695), Src (PPAN CAA24495), vascular endothelial growth factor receptor 2 (PPAN ABB82619), vascular endothelial growth factor receptor-2 (PPAN ABB82619), epidermal growth factor receptor (PPAN AG43241), EPH receptor B4 (PPAN EAL23820), stem cell factor receptor (PPAN AAF22141), Tyrosine-protein kinase receptor TIE-2 (PPAN Q02858), fms-related tyrosine kinase 3 (PPAN NP_004110), platelet-derived growth factor receptor alpha (PPAN NP_990080), RET (PPAN CAA73131), and functional mutants thereof. In some embodiments, the tyrosine kinase is Abl, Bcr-Abl, EGFR, or Flt-3, and any other kinases listed in the Tables herein.

[00203] In some embodiments, non-limiting exemplary compounds exhibit one or more functional characteristics disclosed herein. For example, one or more subject compounds bind specifically to a PI3 kinase. In some embodiments, the IC_{50} of a subject compound for p110 α , p110 β , p110 γ , or p110 δ is less than about 1 μ M, less than about 100 nM, less than about 50 nM, less than about 10 nM, less than about 1 nM, less than about 0.5 nM, less than about 100 pM, or less than about 50 pM.

[00204] In some embodiments, one or more of the subject compound can selectively inhibit one or more members of type I or class I phosphatidylinositol 3-kinases (PI3-kinase) with an IC_{50} value of about 100 nM, 50 nM, 10 nM, 5 nM, 100 pM, 10 pM or 1 pM, or less as measured in an *in vitro* kinase assay.

[00205] In some embodiments, one or more of the subject compounds can selectively inhibit one or two members of type I or class I phosphatidylinositol 3-kinases (PI3-kinase) such as PI3-kinase α , PI3-kinase β , PI3-kinase γ , and PI3-kinase δ . In some aspects, some of the subject compounds selectively inhibit PI3-kinase δ as compared to all other type I PI3-kinases. In other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase γ as compared to the rest of the type I PI3-kinases. In yet other aspects, some of the subject compounds selectively inhibit PI3-kinase α and PI3-kinase β as compared to the rest of the type I PI3-kinases. In still yet some other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase α as compared to the rest of the type I PI3-kinases. In still yet some other aspects, some of the subject compounds selectively inhibit PI3-kinase δ and PI3-kinase β as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase δ and PI3-kinase α as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase α and PI3-kinase γ as compared to the rest of the type I PI3-kinases, or selectively inhibit PI3-kinase γ and PI3-kinase β as compared to the rest of the type I PI3-kinases.

[00206] In yet another aspect, an inhibitor that selectively inhibits one or more members of type I PI3-kinases, or an inhibitor that selectively inhibits one or more type I PI3-kinase mediated signaling pathways, alternatively can be understood to refer to a compound that exhibits a 50% inhibitory concentration (IC_{50}) with respect to a given type I PI3-kinase, that is at least about 10-fold, at least about 20-fold, at least about 50-fold, at least about 100-fold, at least about 1000-fold, at least about 10,000-fold, or lower, than the inhibitor's IC_{50} with respect to the rest of the other type I PI3-kinases. In one embodiment, an inhibitor selectively inhibits PI3-kinase δ as compared to PI3-kinase β with at least about 10-fold lower IC_{50} for PI3-kinase δ . In certain embodiments, the IC_{50} for PI3-kinase δ is below about 100 nM,

while the IC_{50} for PI3-kinase β is above about 1000 nM. In certain embodiments, the IC_{50} for PI3-kinase δ is below about 50 nM, while the IC_{50} for PI3-kinase β is above about 5000 nM. In certain embodiments, the IC_{50} for PI3-kinase δ is below about 10 nM, while the IC_{50} for PI3-kinase β is above about 1000 nM, above about 5,000 nM, or above about 10,000 nM.

Pharmaceutical Compositions

[00207] In some embodiments, provided herein are pharmaceutical compositions comprising one or more compounds as disclosed herein and one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition comprises a compound as disclosed herein and one or more pharmaceutically acceptable excipients.

[00208] In some embodiments, provided herein are pharmaceutical compositions for treating diseases or conditions related to an undesirable, over-active, harmful or deleterious immune response in a subject. Such undesirable immune response can be associated with or result in, *e.g.*, asthma, emphysema, bronchitis, psoriasis, allergy, anaphylaxis, auto-immune diseases, rheumatoid arthritis, graft versus host disease, and lupus erythematosus. The pharmaceutical compositions can be used to treat other respiratory diseases including, but not limited to, diseases affecting the lobes of the lung, pleural cavity, bronchial tubes, trachea, upper respiratory tract, or the nerves and muscle responsible for breathing.

[00209] In some embodiments, provided herein are pharmaceutical compositions for the treatment of multiorgan failure. Also provided herein are pharmaceutical compositions for the treatment of liver diseases (including diabetes), gall bladder disease (including gallstones), pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) or pain in a subject.

[00210] In some embodiments, provided herein are pharmaceutical compositions for the prevention of blastocyte implantation in a subject.

[00211] In some embodiments, provided herein are pharmaceutical compositions for treating a disease related to vasculogenesis or angiogenesis in a subject which can manifest as tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as bullous pemphigoid (BP), psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00212] In some embodiments, provided herein are pharmaceutical compositions for the treatment of disorders involving platelet aggregation or platelet adhesion, including but not limited to Idiopathic thrombocytopenic purpura, Bernard-Soulier syndrome, Glanzmann's thrombasthenia, Scott's syndrome, von Willebrand disease, Hermansky-Pudlak Syndrome, and Gray platelet syndrome.

[00213] In some embodiments, pharmaceutical compositions are provided for treating a disease which is skeletal muscle atrophy, skeletal or muscle hypertrophy. In some embodiments, provided herein are pharmaceutical compositions for the treatment of disorders that include, but are not limited to, cancers as discussed herein, transplantation-related disorders (*e.g.*, lowering rejection rates, graft-versus-host disease, etc.), muscular sclerosis (MS), allergic disorders (*e.g.*, arthritis, allergic encephalomyelitis) and other immunosuppressive-related disorders, metabolic disorders (*e.g.*, diabetes), reducing intimal thickening following vascular injury, and misfolded protein disorders (*e.g.*,

Alzheimer's Disease, Gaucher's Disease, Parkinson's Disease, Huntington's Disease, cystic fibrosis, macular degeneration, retinitis pigmentosa, and prion disorders) (as mTOR inhibition can alleviate the effects of misfolded protein aggregates). The disorders also include hamartoma syndromes, such as tuberous sclerosis and Cowden Disease (also termed Cowden syndrome and multiple hamartoma syndrome)

[00214] In some embodiments, the disclosure provides a pharmaceutical composition for treating ophthalmic disorders. The pharmaceutical composition is formulated for ocular administration and it contains an effective amount of a compound as disclosed herein and a pharmaceutical excipient suitable for ocular administration. Pharmaceutical compositions suitable for ocular administration can be presented as discrete dosage forms, such as drops or sprays each containing a predetermined amount of an active ingredient a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Eye drops can be prepared by dissolving the active ingredient in a sterile aqueous solution such as physiological saline, buffering solution, etc., or by combining powder compositions to be dissolved before use. Other vehicles can be chosen, as is known in the art, including, but not limited to: balance salt solution, saline solution, water soluble polyethers such as polyethylene glycol, polyvinyls, such as polyvinyl alcohol and povidone, cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose, petroleum derivatives such as mineral oil and white petrolatum, animal fats such as lanolin, polymers of acrylic acid such as carboxypolymethylene gel, vegetable fats such as peanut oil and polysaccharides such as dextrans, and glycosaminoglycans such as sodium hyaluronate. In some embodiments, additives ordinarily used in the eye drops can be added. Such additives include isotonicizing agents (*e.g.*, sodium chloride, etc.), buffer agent (*e.g.*, boric acid, sodium monohydrogen phosphate, sodium dihydrogen phosphate, etc.), preservatives (*e.g.*, benzalkonium chloride, benzethonium chloride, chlorobutanol, etc.), thickeners (*e.g.*, saccharide such as lactose, mannitol, maltose, etc.; *e.g.*, hyaluronic acid or its salt such as sodium hyaluronate, potassium hyaluronate, etc.; *e.g.*, mucopolysaccharide such as chondroitin sulfate, etc.; *e.g.*, sodium polyacrylate, carboxyvinyl polymer, crosslinked polyacrylate, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art).

[00215] The subject pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a compound as disclosed herein as the active ingredient, or a pharmaceutically acceptable form, salt, ester, prodrug or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable form, such as a salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[00216] The subject pharmaceutical compositions can be administered alone or in combination with one or more other agents, which are also typically administered in the form of pharmaceutical compositions. In some embodiments, the subject compounds and other agent(s) can be mixed into a preparation or both components can be formulated into separate preparations to use them in combination separately or at the same time.

[00217] In some embodiments, the concentration of one or more of the compounds provided in the disclosed pharmaceutical compositions is less than about 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%,

0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v or v/v.

[00218] In some embodiments, the concentration of one or more of the compounds as disclosed herein is greater than about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25%, 19%, 18.75%, 18.50%, 18.25%, 18%, 17.75%, 17.50%, 17.25%, 17%, 16.75%, 16.50%, 16.25%, 16%, 15.75%, 15.50%, 15.25%, 15%, 14.75%, 14.50%, 14.25%, 14%, 13.75%, 13.50%, 13.25%, 13%, 12.75%, 12.50%, 12.25%, 12%, 11.75%, 11.50%, 11.25%, 11%, 10.75%, 10.50%, 10.25%, 10%, 9.75%, 9.50%, 9.25%, 9%, 8.75%, 8.50%, 8.25%, 8%, 7.75%, 7.50%, 7.25%, 7%, 6.75%, 6.50%, 6.25%, 6%, 5.75%, 5.50%, 5.25%, 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 1.25%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v.

[00219] In some embodiments, the concentration of one or more of the compounds as disclosed herein is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v. v/v.

[00220] In some embodiments, the concentration of one or more of the compounds as disclosed herein is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[00221] In some embodiments, the amount of one or more of the compounds as disclosed herein is equal to or less than about 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

[00222] In some embodiments, the amount of one or more of the compounds as disclosed herein is more than about 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g,

0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5g, 7 g, 7.5g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

[00223] In some embodiments, the amount of one or more of the compounds as disclosed herein is in the range of about 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

[00224] The compounds as disclosed herein are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.01 to 1000 mg, from about 0.5 to 100 mg, from about 1 to 50 mg per day, and from about 5 to 40 mg per day are examples of dosages that can be used. An exemplary dosage is about 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[00225] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

[00226] Pharmaceutical compositions for oral administration: In some embodiments, provided herein are pharmaceutical compositions for oral administration containing a compound as disclosed herein, and a pharmaceutical excipient suitable for oral administration.

[00227] In some embodiments, provided herein are solid pharmaceutical compositions for oral administration containing: (i) an effective amount of a disclosed compound; optionally (ii) an effective amount of a second agent; and (iii) a pharmaceutical excipient suitable for oral administration. In some embodiments, the pharmaceutical composition further contains: (iv) an effective amount of a third agent.

[00228] In some embodiments, the pharmaceutical composition can be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00229] The present disclosure further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water can be added (*e.g.*, about 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. For example, pharmaceutical compositions and dosage forms which contain

lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition can be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous pharmaceutical compositions can be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[00230] An active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the pharmaceutical compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. In some embodiments, tablets can be coated by standard aqueous or nonaqueous techniques.

[00231] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00232] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00233] Disintegrants can be used in the pharmaceutical compositions as provided herein to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant can produce tablets which can disintegrate in the bottle. Too little may be insufficient for disintegration to occur and can thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) can be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used can vary based upon the type of formulation and mode of administration, and can be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, can be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums or mixtures thereof.

[00234] Lubricants which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol,

polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00235] When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient therein can be combined with various sweetening or flavoring agents, coloring matter or dyes and, for example, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00236] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00237] Surfactant which can be used to form pharmaceutical compositions and dosage forms include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants can be employed, a mixture of lipophilic surfactants can be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant can be employed.

[00238] A suitable hydrophilic surfactant can generally have an HLB value of at least about 10, while suitable lipophilic surfactants can generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.*, hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00239] Hydrophilic surfactants can be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00240] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of

alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00241] Ionic surfactants can be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, choly sarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00242] Hydrophilic non-ionic surfactants can include, but are not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol can be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00243] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00244] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and

di-glycerides; hydrophobic transesterification products of a polyol with at least one member of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, non-limiting examples of lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00245] In one embodiment, the pharmaceutical composition can include a solubilizer to ensure good solubilization and/or dissolution of a compound as provided herein and to minimize precipitation of the compound. This can be especially important for pharmaceutical compositions for non-oral use, *e.g.*, pharmaceutical compositions for injection. A solubilizer can also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the pharmaceutical composition as a stable or homogeneous solution or dispersion.

[00246] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ϵ -caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ϵ -caprolactone and isomers thereof, δ -valerolactone and isomers thereof, β -butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monoctanoin, diethylene glycol monoethyl ether, and water.

[00247] Mixtures of solubilizers can also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcitol, propylene glycol, and dimethyl isosorbide. In some embodiments, solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00248] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer can be limited to a bioacceptable amount, which can be readily determined by one of skill in the art. In some circumstances, it can be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the pharmaceutical composition to a subject using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of about 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer can also be used, such as about 5%, 2%, 1% or even less. Typically, the solubilizer can be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00249] The pharmaceutical composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents,

buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00250] In addition, an acid or a base can be incorporated into the pharmaceutical composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Examples can include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00251] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

[00252] Pharmaceutical compositions for injection. In some embodiments, provided herein are pharmaceutical compositions for injection containing a compound as disclosed herein and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the pharmaceutical compositions are as described herein.

[00253] The forms in which the disclosed pharmaceutical compositions can be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00254] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils can also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[00255] Sterile injectable solutions are prepared by incorporating a compound as disclosed herein in the required amount in the appropriate solvent with various other ingredients as enumerated above, as appropriate, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into

a sterile vehicle which contains the basic dispersion medium and the appropriate other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional ingredient from a previously sterile-filtered solution thereof.

[00256] Pharmaceutical compositions for topical (*e.g.*, transdermal) delivery. In some embodiments, provided herein are pharmaceutical compositions for transdermal delivery containing a compound as disclosed herein and a pharmaceutical excipient suitable for transdermal delivery.

[00257] Pharmaceutical compositions provided herein can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation can provide more immediate exposure of the active ingredient to the chosen area.

[00258] The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (*e.g.*, urea), glycols (*e.g.*, propylene glycol), alcohols (*e.g.*, ethanol), fatty acids (*e.g.*, oleic acid), surfactants (*e.g.*, isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (*e.g.*, menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00259] Another exemplary formulation for use in the disclosed methods employs transdermal delivery devices ("patches"). Such transdermal patches can be used to provide continuous or discontinuous infusion of a compound as provided herein in controlled amounts, either with or without another agent.

[00260] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches can be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[00261] Pharmaceutical compositions for inhalation. Pharmaceutical compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid pharmaceutical compositions can contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the pharmaceutical compositions are administered by the oral or nasal respiratory route for local or systemic effect. Pharmaceutical compositions in pharmaceutically acceptable solvents can be nebulized by use of inert gases. Nebulized solutions can be inhaled directly from the nebulizing device or the nebulizing device can be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder pharmaceutical compositions can be administered, *e.g.*, orally or nasally, from devices that deliver the formulation in an appropriate manner.

[00262] Pharmaceutical compositions can also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art.

See, *e.g.*, Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingstone, New York, 1990; Katzung, ed., *Basic and Clinical Pharmacology*, Ninth Edition, McGraw Hill, 20037ybg; Goodman and Gilman, eds., *The Pharmacological Basis of Therapeutics*, Tenth Edition, McGraw Hill, 2001; *Remingtons Pharmaceutical Sciences*, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, *The Extra Pharmacopoeia*, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety.

[00263] Administration of the compounds or pharmaceutical compositions as disclosed herein can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (*e.g.*, transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. Compounds can also be administered intraadiposally or intrathecally.

[00264] The amount of the compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage can be in the range of about 0.001 to about 100 mg per kg body weight per day, such as from about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range can be more than adequate, while in other cases still larger doses can be employed without causing any harmful side effect, *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

[00265] In some embodiments, a compound as provided herein is administered in a single dose. Typically, such administration will be by injection, *e.g.*, intravenous injection, in order to introduce the agent quickly. However, other routes can be used as appropriate. A single dose of a compound as provided herein can also be used for treatment of an acute condition.

[00266] In some embodiments, a compound as provided herein is administered in multiple doses. Dosing can be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing can be about once a month, once every two weeks, once a week, or once every other day. In another embodiment, a compound as disclosed herein and another agent are administered together about once per day to about 6 times per day. In another embodiment, the administration of a compound as provided herein and an agent continues for less than about 7 days. In yet another embodiment, the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00267] Administration of the agents as disclosed herein can continue as long as necessary. In some embodiments, an agent as disclosed herein is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, an agent as disclosed herein is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, an agent as disclosed herein is administered chronically on an ongoing basis, *e.g.*, for the treatment of chronic effects.

[00268] An effective amount of a compound as disclosed herein can be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal,

intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[00269] The pharmaceutical compositions provided herein can also be delivered via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. Such a method of administration can, for example, aid in the prevention or amelioration of restenosis following procedures such as balloon angioplasty. Without being bound by theory, compounds as disclosed herein can slow or inhibit the migration and proliferation of smooth muscle cells in the arterial wall which contribute to restenosis. A compound as disclosed herein can be administered, for example, by local delivery from the struts of a stent, from a stent graft, from grafts, or from the cover or sheath of a stent. In some embodiments, a compound as disclosed herein is admixed with a matrix. Such a matrix can be a polymeric matrix, and can serve to bond the compound to the stent. Polymeric matrices suitable for such use, include, for example, lactone-based polyesters or copolyesters such as polylactide, polycaprolactone, glycolide, polyorthoesters, polyanhydrides, polyaminoacids, polysaccharides, polyphosphazenes, poly (ether-ester) copolymers (*e.g.*, PEO-PLLA); polydimethylsiloxane, poly(ethylene-vinylacetate), acrylate-based polymers or copolymers (*e.g.*, polyhydroxyethyl methacrylate, polyvinyl pyrrolidone), fluorinated polymers such as polytetrafluoroethylene and cellulose esters. Suitable matrices can be nondegrading or can degrade with time, releasing the compound or compounds. Compounds as disclosed herein can be applied to the surface of the stent by various methods such as dip/spin coating, spray coating, dip-coating, and/or brush-coating. The compounds can be applied in a solvent and the solvent can be allowed to evaporate, thus forming a layer of compound onto the stent. Alternatively, the compound can be located in the body of the stent or graft, for example in microchannels or micropores. When implanted, the compound diffuses out of the body of the stent to contact the arterial wall. Such stents can be prepared by dipping a stent manufactured to contain such micropores or microchannels into a solution of the compound as disclosed herein in a suitable solvent, followed by evaporation of the solvent. Excess drug on the surface of the stent can be removed via an additional brief solvent wash. In yet other embodiments, compounds as disclosed herein can be covalently linked to a stent or graft. A covalent linker can be used which degrades *in vivo*, leading to the release of the compound as disclosed herein. Any bio-labile linkage can be used for such a purpose, such as ester, amide or anhydride linkages. Compounds provided herein can additionally be administered intravascularly from a balloon used during angioplasty. Extravascular administration of the compounds via the pericard or via adventitial application of formulations provided herein can also be performed to decrease restenosis.

[00270] A variety of stent devices which can be used as described are disclosed, for example, in the following references, all of which are hereby incorporated by reference: U.S. Pat. No. 5451233; U.S. Pat. No. 5040548; U.S. Pat. No. 5061273; U.S. Pat. No. 5496346; U.S. Pat. No. 5292331; U.S. Pat. No. 5674278; U.S. Pat. No. 3657744; U.S. Pat. No. 4739762; U.S. Pat. No. 5195984; U.S. Pat. No. 5292331; U.S. Pat. No. 5674278; U.S. Pat. No. 5879382; U.S. Pat. No. 6344053.

[00271] The compounds provided herein can be administered in dosages. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. Dosing for a compound provided herein can be found by routine experimentation in light of the instant disclosure.

[00272] When a compound provided herein, is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound provided herein unit dose forms of the agent and the compound provided herein can be adjusted accordingly.

[00273] The subject pharmaceutical composition can, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, or suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition can be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound as provided herein as an active ingredient. In addition, it can include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

[00274] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00275] In some embodiments, provided herein are kits. The kits include a compound or compounds as described herein, in suitable packaging, and written material that can include instructions for use, discussion of clinical studies, listing of side effects, and the like. Such kits can also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the pharmaceutical composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information can be based on the results of various studies, for example, studies using experimental animals involving *in vivo* models and studies based on human clinical trials. The kit can further contain another agent. In some embodiments, the compound as disclosed herein and the agent are provided as separate pharmaceutical compositions in separate containers within the kit. In some embodiments, the compound as disclosed herein and the agent are provided as a single pharmaceutical composition within a container in the kit. Suitable packaging and additional articles for use (*e.g.*, measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and can be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits can also, in some embodiments, be marketed directly to the consumer.

[00276] Phosphoinositide 3-kinases (PI3Ks) are members of a conserved family of lipid kinases that regulate numerous cell functions, including proliferation, differentiation, cell survival and metabolism. Several classes of PI3Ks exist in mammalian cells, including Class IA subgroup (*e.g.*, PI3K- α , β , δ), which are generally activated by receptor tyrosine kinases (RTKs); Class IB (*e.g.*, PI3K- γ), which is activated by G-protein coupled receptors, among others. PI3Ks exert their biological activities via a “PI3K-mediated signaling pathway” that includes several components that directly and/or indirectly transduce a signal triggered by a PI3K, including the generation of secondary messenger phosphatidylinositol, 3, 4, 5-triphosphate (PIP3) at the plasma membrane, activation of heterotrimeric G protein signaling, and generation of further second messengers such as cAMP, DAG, and IP3, all of which leads to an extensive cascade of protein kinase activation (reviewed in Vanhaesebroeck, B. *et al.* (2001) *Annu Rev Biochem.* 70:535-602). For example, PI3K- δ is activated by cellular receptors through interaction between the PI3K regulatory subunit (p85) SH2 domains, or through direct interaction with RAS. PIP3 produced by PI3K activates effector pathways downstream

through interaction with plextrin homology (PH) domain containing enzymes (*e.g.*, PDK-1 and AKT [PKB]). (Fung-Leung WP. (2011) *Cell Signal*. 23(4):603-8). Unlike PI3K- δ , PI3K- γ is not a Class 1A PI3K, and is not associated with a regulatory subunit of the P85 family, but rather with a regulatory subunit in the p101 family. PI3K- γ is associated with G-protein coupled receptors (GPCRs), and is responsible for the very rapid induction of PIP3, and can be also activated by RAS.

[00277] As used herein, a “PI3K-mediated disorder” refers to a disease or condition involving aberrant PI3K-mediated signaling pathway. In one embodiment, provided herein is a method of treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition as disclosed herein. In some embodiments, provided herein is a method of treating a PI3K- δ or PI3K- γ mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound or a pharmaceutical composition as disclosed herein. In some embodiments, provided herein is a method for inhibiting at least one of PI3K- δ or PI3K- γ , the method comprising contacting a cell expressing PI3K *in vitro* or *in vivo* with an effective amount of the compound or composition disclosed herein. PI3Ks have been associated with a wide range of conditions, including immunity, cancer and thrombosis (reviewed in Vanhaesebroeck, B. *et al.* (2010) *Current Topics in Microbiology and Immunology*, DOI 10.1007/82_2010_65). For example, Class I PI3Ks, particularly PI3K γ and PI3K δ isoforms, are highly expressed in leukocytes and have been associated with adaptive and innate immunity; thus, these PI3Ks are believed to be important mediators in inflammatory disorders and hematologic malignancies (reviewed in Harris, SJ *et al.* (2009) *Curr Opin Investig Drugs* 10(11):1151-62; Rommel C. *et al.* (2007) *Nat Rev Immunol* 7(3):191-201; Durand CA *et al.* (2009) *J Immunol*. 183(9):5673-84; Dil N, Marshall AJ. (2009) *Mol Immunol*. 46(10):1970-8; Al-Alwan MM *et al.* (2007) *J Immunol*. 178(4):2328-35; Zhang TT, *et al.* (2008) *J Allergy Clin Immunol*. 2008;122(4):811-819.e2; Srinivasan L, *et al.* (2009) *Cell* 139(3):573-86).

[00278] Numerous publications support roles of PI3K- δ , PI3K- γ , and PI3K- β in the differentiation, maintenance, and activation of immune and malignant cells, as described in more detail below.

[00279] The importance of PI3K- δ in the development and function of B-cells is supported from inhibitor studies and genetic models. PI3K- δ is an important mediator of B-cell receptor (BCR) signaling, and is upstream of AKT, calcium flux, PLC γ , MAP kinase, P70S6k, and FOXO3a activation. PI3K- δ is also important in IL4R, S1P, and CXCR5 signaling, and has been shown to modulate responses to toll-like receptors 4 and 9. Inhibitors of PI3K- δ have shown the importance of PI3K- δ in B-cell development (Marginal zone and B1 cells), B-cell activation, chemotaxis, migration and homing to lymphoid tissue, and in the control of immunoglobulin class switching leading to the production of IgE. Clayton E *et al.* (2002) *J Exp Med*. 196(6):753-63; Bilancio A, *et al.* (2006) *Blood* 107(2):642-50; Okkenhaug K. *et al.* (2002) *Science* 297(5583):1031-4; Al-Alwan MM *et al.* (2007) *J Immunol*. 178(4):2328-35; Zhang TT, *et al.* (2008) *J Allergy Clin Immunol*. 2008;122(4):811-819.e2; Srinivasan L, *et al.* (2009) *Cell* 139(3):573-86)

[00280] In T-cells, PI3K- δ has been demonstrated to have a role in T-cell receptor and cytokine signaling, and is upstream of AKT, PLC γ , and GSK3b. In PI3K- δ deletion or kinase-dead knock-in mice, or in inhibitor studies, T-cell defects including proliferation, activation, and differentiation have been observed, leading to reduced T helper cell 2 (TH2) response, memory T-cell specific defects (DTH reduction), defects in antigen dependent cellular trafficking, and defects in chemotaxis/migration to chemokines (*e.g.*, S1P, CCR7, CD62L). (Garçon F. *et al.* (2008) *Blood* 111(3):1464-71; Okkenhaug K *et al.* (2006). *J Immunol*. 177(8):5122-8; Soond DR, *et al.* (2010) *Blood* 115(11):2203-13; Reif K, (2004). *J Immunol*. 2004;173(4):2236-40; Ji H. *et al.* (2007) *Blood* 110(8):2940-7; Webb LM, *et al.* (2005) *J Immunol*.

175(5):2783-7; Liu D, *et al.* (2010) *J Immunol.* 184(6):3098-105; Haylock-Jacobs S, *et al.* (2011) *J Autoimmun.* 2011;36(3-4):278-87; Jarmin SJ, *et al.* (2008) *J Clin Invest.* 118(3):1154-64).

[00281] In neutrophils, PI3K- δ along with PI3K- γ , and PI3K- β , contribute to the responses to immune complexes, FCgRII signaling, including migration and neutrophil respiratory burst. Human neutrophils undergo rapid induction of PIP3 in response to formyl peptide receptor (FMLP) or complement component C5a (C5a) in a PI3K- γ dependent manner, followed by a longer PIP3 production period that is PI3K- δ dependent, and is essential for respiratory burst. The response to immune complexes is contributed by PI3K- δ , PI3K- γ , and PI3K- β , and is an important mediator of tissue damage in models of autoimmune disease (Randis TM *et al.* (2008) *Eur J Immunol.* 38(5):1215-24; Pinho V, (2007) *J Immunol.* 179(11):7891-8; Sadhu C. *et al.* (2003) *J Immunol.* 170(5):2647-54 ; Condliffe AM *et al.* (2005) *Blood* 106(4):1432-40).

[00282] In macrophages collected from patients with chronic obstructive pulmonary disease (COPD), glucocorticoid responsiveness can be restored by treatment of the cells with inhibitors of PI3K- δ . Macrophages also rely on PI3K- δ and PI3K- γ for responses to immune complexes through the arthus reaction (FCgR and C5a signaling) (Randis TM, *et al.* (2008) *Eur J Immunol.* 38(5):1215-24 ; Marwick JA *et al.* (2009) *Am J Respir Crit Care Med.* 179(7):542-8; Konrad S, *et al.* (2008) *J Biol Chem.* 283(48):33296-303).

[00283] In mast cells, stem cell factor- (SCF) and IL3-dependent proliferation, differentiation and function are PI3K- δ dependent, as is chemotaxis. The allergen/IgE crosslinking of FCgR1 resulting in cytokine release and degranulation of the mast cells is severely inhibited by treatment with PI3K- δ inhibitors, suggesting a role for PI3K- δ in allergic disease (Ali K *et al.* (2004) *Nature* 431(7011):1007-11; Lee KS, *et al.* (2006) *FASEB J.* 20(3):455-65; Kim MS, *et al.* (2008) *Trends Immunol.* 29(10):493-501).

[00284] Natural killer (NK) cells are dependent on both PI3K- δ and PI3K- γ for efficient migration towards chemokines including CXCL10, CCL3, S1P and CXCL12, or in response to LPS in the peritoneum (Guo H, *et al.* (2008) *J Exp Med.* 205(10):2419-35; Tassi I, *et al.* (2007) *Immunity* 27(2):214-27; Saudemont A, (2009) *Proc Natl Acad Sci U S A.* 106(14):5795-800; Kim N, *et al.* (2007) *Blood* 110(9):3202-8).

[00285] The roles of PI3K- δ , PI3K- γ , and PI3K- β in the differentiation, maintenance, and activation of immune cells support a role for these enzymes in inflammatory disorders ranging from autoimmune diseases (*e.g.*, rheumatoid arthritis, multiple sclerosis) to allergic inflammatory disorders, such as asthma and COPD. Extensive evidence is available in experimental animal models, or can be evaluated using art-recognized animal models. In an embodiment, described herein is a method of treating inflammatory disorders ranging from autoimmune diseases (*e.g.*, rheumatoid arthritis, multiple sclerosis) to allergic inflammatory disorders, such as asthma and COPD using a compound described herein.

[00286] For example, inhibitors of PI3K δ and/or γ have been shown to have anti-inflammatory activity in several autoimmune animal models for rheumatoid arthritis (Williams, O. *et al.* (2010) *Chem Biol*, 17(2):123-34; WO 2009/088986; WO2009/088880; WO 2011/008302). PI3K δ is expressed in the RA synovial tissue (especially in the synovial lining which contains fibroblast-like synoviocytes (FLS), and selective PI3K δ inhibitors have been shown to be effective in inhibiting synoviocyte growth and survival (Bartok *et al.* (2010) *Arthritis Rheum* 62 Suppl 10:362). Several PI3K δ and γ inhibitors have been shown to ameliorate arthritic symptoms (*e.g.*, swelling of joints, reduction of serum-induced collagen levels, reduction of joint pathology and/or inflammation), in art-recognized models for RA, such as collagen-induced arthritis and adjuvant induced arthritis (WO 2009/088986; WO2009/088880; WO 2011/008302).

[00287] The role of PI3K- δ has also been shown in models of T-cell dependent response, including the DTH model. In the murine experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis, the PI3K-g/d-double mutant mice are resistant. PI3K- δ inhibitors have also been shown to block EAE disease induction and development of TH-17 cells both in vitro and in vivo (Haylock-Jacobs, S. *et al.* (2011) *J. Autoimmunity* 36(3-4):278-87).

[00288] Systemic lupus erythematosus (SLE) is a complex disease that at different stages requires memory T-cells, B-cell polyclonal expansion and differentiation into plasma cells, and the innate immune response to endogenous damage associated molecular pattern molecules (DAMPs), and the inflammatory responses to immune complexes through the complement system as well as the F_C receptors. The role of PI3K- δ and PI3K- γ together in these pathways and cell types suggest that blockade with an inhibitor would be effective in these diseases. A role for PI3K in lupus is also predicted by two genetic models of lupus. The deletion of phosphatase and tensin homolog (PTEN) leads to a lupus-like phenotype, as does a transgenic activation of Class1A PI3Ks, which includes PI3K- δ . The deletion of PI3K- γ in the transgenically activated class 1A lupus model is protective, and treatment with a PI3K- γ selective inhibitor in the murine MLR/*lpr* model of lupus improves symptoms (Barber, DF *et al.* (2006) *J. Immunol.* 176(1): 589-93).

[00289] In allergic disease, PI3K- δ has been shown by genetic models and by inhibitor treatment to be essential for mast-cell activation in a passive cutaneous anaphylaxis assay (Ali K *et al.* (2008) *J Immunol.* 180(4):2538-44; Ali K, (2004) *Nature* 431(7011):1007-11). In a pulmonary measure of response to immune complexes (Arthus reaction) a PI3K- δ knockout is resistant, showing a defect in macrophage activation and C5a production. Knockout studies and studies with inhibitors for both PI3K- δ and PI3K- γ support a role for both of these enzymes in the ovalbumin induced allergic airway inflammation and hyper-responsiveness model (Lee KS *et al.* (2006) *FASEB J.* 20(3):455-65). Reductions of infiltration of eosinophils, neutrophils, and lymphocytes as well as TH2 cytokines (IL4, IL5, and IL13) were seen with both PI3K- δ specific and dual PI3K- δ and PI3K- γ inhibitors in the Ova induced asthma model (Lee KS *et al.* (2006) *J Allergy Clin Immunol* 118(2):403-9).

[00290] PI3K- δ and PI3K- γ inhibition can be used in treating COPD. In the smoked mouse model of COPD, the PI3K- δ knockout does not develop smoke induced glucocorticoid resistance, while wild-type and PI3K- γ knockout mice do. An inhaled formulation of dual PI3K- δ and PI3K- γ inhibitor blocked inflammation in a LPS or smoke COPD models as measured by neutrophilia and glucocorticoid resistance (Doukas J, *et al.* (2009) *J Pharmacol Exp Ther.* 328(3):758-65).

[00291] Class I PI3Ks, particularly PI3K δ and PI3K γ isoforms, are also associated with cancers (reviewed, *e.g.*, in Vogt, PK *et al.* (2010) *Curr Top Microbiol Immunol.* 347:79-104; Fresno Vara, JA *et al.* (2004) *Cancer Treat Rev.* 30(2):193-204; Zhao, L and Vogt, PK. (2008) *Oncogene* 27(41):5486-96). Inhibitors of PI3K, *e.g.*, PI3K δ and/or γ , have been shown to have anti-cancer activity (*e.g.*, Courtney, KD *et al.* (2010) *J Clin Oncol.* 28(6):1075-1083); Markman, B *et al.* (2010) *Ann Oncol.* 21(4):683-91; Kong, D and Yamori, T (2009) *Curr Med Chem.* 16(22):2839-54; Jimeno, A *et al.* (2009) *J Clin Oncol.* 27:156s (suppl; abstr 3542); Flinn, IW *et al.* (2009) *J Clin Oncol.* 27:156s (suppl; abstr 3543); Shapiro, G *et al.* (2009) *J Clin Oncol.* 27:146s (suppl; abstr 3500); Wagner, AJ *et al.* (2009) *J Clin Oncol.* 27:146s (suppl; abstr 3501); Vogt, PK *et al.* (2006) *Virology* 344(1):131-8; Ward, S *et al.* (2003) *Chem Biol.* 10(3):207-13; WO 2011/041399; US 2010/0029693; US 2010/0305096; US 2010/0305084). In an embodiment, described herein is a method of treating cancer.

[00292] Types of cancer that can be treated with an inhibitor of PI3K (particularly, PI3K δ and/or γ) include, *e.g.*, leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia (*e.g.*, Salmena, L *et*

al. (2008) *Cell* 133:403-414; Chapuis, N et al. (2010) *Clin Cancer Res.* 16(22):5424-35; Khwaja, A (2010) *Curr Top Microbiol Immunol.* 347:169-88); lymphoma, *e.g.*, non-Hodgkin's lymphoma (*e.g.*, Salmena, L et al. (2008) *Cell* 133:403-414); lung cancer, *e.g.*, non-small cell lung cancer, small cell lung cancer (*e.g.*, Herrera, VA et al. (2011) *Anticancer Res.* 31(3):849-54); melanoma (*e.g.*, Haluska, F et al. (2007) *Semin Oncol.* 34(6):546-54); prostate cancer (*e.g.*, Sarker, D et al. (2009) *Clin Cancer Res.* 15(15):4799-805); glioblastoma (*e.g.*, Chen, JS et al. (2008) *Mol Cancer Ther.* 7:841-850); endometrial cancer (*e.g.*, Bansal, N et al. (2009) *Cancer Control.* 16(1):8-13); pancreatic cancer (*e.g.*, Furukawa, T (2008) *J Gastroenterol.* 43(12):905-11); renal cell carcinoma (*e.g.*, Porta, C and Figlin, RA (2009) *J Urol.* 182(6):2569-77); colorectal cancer (*e.g.*, Saif, MW and Chu, E (2010) *Cancer J.* 16(3):196-201); breast cancer (*e.g.*, Torbett, NE et al. (2008) *Biochem J.* 415:97-100); thyroid cancer (*e.g.*, Brzezianska, E and Pastuszak-Lewandoska, D (2011) *Front Biosci.* 16:422-39); and ovarian cancer (*e.g.*, Mazzeo, M and Brogini, M (2010) *Curr Med Chem.* 17(36):4433-47).

[00293] Numerous publications support a role of PI3K- δ and PI3K- γ in treating hematological cancers. PI3K- δ and PI3K- γ are highly expressed in the heme compartment, and some solid tumors, including prostate, breast and glioblastomas (Chen J.S. *et al.* (2008) *Mol Cancer Ther.* 7(4):841-50; Ikeda H. *et al.* (2010) *Blood* 116(9):1460-8). In hematological cancers including acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL), overexpression and constitutive activation of PI3K- δ supports the model that PI3K- δ inhibition would be therapeutic Billottet C, et al. (2006) *Oncogene* 25(50):6648-59; Billottet C, et al. (2009) *Cancer Res.* 69(3):1027-36; Meadows, SA, 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Ikeda H, et al. (2010) *Blood* 116(9):1460-8; Herman SE *et al.* (2010) *Blood* 116(12):2078-88; Herman SE *et al.* (2011). *Blood* 117(16):4323-7. In an embodiment, described herein is a method of treating hematological cancers including, but not limited to acute myeloid leukemia (AML), multiple myeloma (MM), and chronic lymphocytic leukemia (CLL).

[00294] A PI3K- δ inhibitor (CAL-101) has been evaluated in a phase 1 trial in patients with haematological malignancies, and showed activity in CLL in patients with poor prognostic characteristics. In CLL, inhibition of PI3K- δ not only affects tumor cells directly, but it also affects the ability of the tumor cells to interact with their microenvironment. This microenvironment includes contact with and factors from stromal cells, T-cells, nurse like cells, as well as other tumor cells. CAL-101 suppresses the expression of stromal and T-cell derived factors including CCL3, CCL4, and CXCL13, as well as the CLL tumor cells' ability to respond to these factors. CAL-101 treatment in CLL patients induces rapid lymph node reduction and redistribution of lymphocytes into the circulation, and affects tonic survival signals through the BCR, leading to reduced cell viability, and an increase in apoptosis. Single agent CAL-101 treatment was also active in mantle cell lymphoma and refractory non Hodgkin's lymphoma (Furman, RR, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Hoellenriegel, J, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Webb, HK, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Meadows, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Kahl, B, et al. 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Lannutti BJ, et al. (2011) *Blood* 117(2):591-4).

[00295] PI3K- δ inhibitors have shown activity against PI3K- δ positive gliomas *in vitro* (Kashishian A, *et al.* Poster presented at: The American Association of Cancer Research 102nd Annual Meeting; 2011 Apr 2-6; Orlando, FL). PI3K- β is the PI3K isoform that is most commonly activated in tumors where the PTEN tumor suppressor is mutated

(Ward S, et al. (2003) *Chem Biol.* 10(3):207-13). In this subset of tumors, treatment with the PI3K- δ inhibitor either alone or in combination with a cytotoxic agent can be effective.

[00296] Another mechanism for PI3K- δ inhibitors to have an affect in solid tumors involves the tumor cells' interaction with their micro-environment. PI3K- δ , PI3K- γ , and PI3K- β are expressed in the immune cells that infiltrate tumors, including tumor infiltrating lymphocytes, macrophages, and neutrophils. PI3K- δ inhibitors can modify the function of these tumor-associated immune cells and how they respond to signals from the stroma, the tumor, and each other, and in this way affect tumor cells and metastasis (Hoellenriegel, J, *et al.* 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL).

[00297] PI3K- δ is also expressed in endothelial cells. It has been shown that tumors in mice treated with PI3K- δ selective inhibitors are killed more readily by radiation therapy. In this same study, capillary network formation is impaired by the PI3K inhibitor, and it is postulated that this defect contributes to the greater killing with radiation. PI3K- δ inhibitors can affect the way in which tumors interact with their microenvironment, including stromal cells, immune cells, and endothelial cells and be therapeutic either on its own or in conjunction with another therapy (Meadows, SA, *et al.* Paper presented at: 52nd Annual ASH Meeting and Exposition; 2010 Dec 4-7; Orlando, FL; Geng L, et al. (2004) *Cancer Res.* 64(14):4893-9).

[00298] In some embodiments, provided herein are methods of using the compounds or pharmaceutical compositions to treat disease conditions, including but not limited to diseases associated with malfunctioning of one or more types of PI3 kinase. A detailed description of conditions and disorders mediated by p110 δ kinase activity is set forth in Sadu et al., WO 01/81346, which is incorporated herein by reference in its entirety for all purposes.

[00299] The treatment methods provided herein comprise administering to the subject a therapeutically effective amount of a compound as disclosed herein.

[00300] In some embodiments, the disclosure relates to a method of treating a hyperproliferative disorder in a subject that comprises administering to said subject a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable form, salt, ester, prodrug or derivative thereof. In some embodiments, said method relates to the treatment of cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS-related (*e.g.*, Lymphoma and Kaposi's Sarcoma) or viral-induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (*e. g.*, psoriasis), restenosis, or prostate (*e. g.*, benign prostatic hypertrophy (BPH)).

[00301] In one embodiment, provided herein is a method of treating an inflammation disorder, including autoimmune diseases in a subject. The method comprises administering to said subject a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable form, salt, ester, prodrug or derivative thereof. Examples of autoimmune diseases includes but is not limited to acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, coeliac disease, Crohn's disease, Diabetes mellitus (type 1), Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's disease, lupus erythematosus, multiple sclerosis, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, Ord's thyroiditis, oemphigus, polyarthritis, primary biliary cirrhosis, psoriasis, rheumatoid arthritis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis (also known as "giant cell

arteritis”), warm autoimmune hemolytic anemia, Wegener’s granulomatosis, alopecia universalis, Chagas disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, and vulvodynia. Other disorders include bone-resorption disorders and thrombosis.

[00302] In some embodiments, provided herein are methods for treating disorders or conditions in which the δ isoform of PI3K is implicated to a greater extent than other PI3K isoforms such as PI3K α and/or β . Selective inhibition of PI3K- δ and/or PI3K- γ can provide advantages over using less selective compounds which inhibit PI3K α and/or β , such as an improved side effects profile or lessened reduction in the ability to reduce a bacterial, viral, and/or fungal infection.

[00303] In certain embodiments, a method of treating inflammatory or autoimmune diseases is provided comprising administering to a subject (*e.g.*, a mammal) a therapeutically effective amount of one or more compounds as disclosed herein that selectively inhibit PI3K- δ and/or PI3K- γ as compared to all other type I PI3 kinases. Such selective inhibition of PI3K- δ and/or PI3K- γ can be advantageous for treating any of the diseases or conditions described herein. For example, selective inhibition of PI3K- δ can inhibit inflammatory responses associated with inflammatory diseases, autoimmune disease, or diseases related to an undesirable immune response including but not limited to asthma, emphysema, allergy, dermatitis, rheumatoid arthritis, psoriasis, lupus erythematosus, or graft versus host disease. Selective inhibition of PI3K- δ can further provide for a reduction in the inflammatory or undesirable immune response without a concomitant reduction in the ability to reduce a bacterial, viral, and/or fungal infection. Selective inhibition of both PI3K- δ and PI3K- γ can be advantageous for inhibiting the inflammatory response in the subject to a greater degree than that would be provided for by inhibitors that selectively inhibit PI3K - δ or PI3K- γ alone. In one aspect, one or more of the subject methods are effective in reducing antigen specific antibody production *in vivo* by about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more. In another aspect, one or more of the subject methods are effective in reducing antigen specific IgG3 and/or IgGM production *in vivo* by about 2-fold, 3-fold, 4-fold, 5-fold, 7.5-fold, 10-fold, 25-fold, 50-fold, 100-fold, 250-fold, 500-fold, 750-fold, or about 1000-fold or more.

[00304] In one aspect, one of more of the subject methods are effective in ameliorating symptoms associated with rheumatoid arthritis including but not limited to a reduction in the swelling of joints, a reduction in serum anti-collagen levels, and/or a reduction in joint pathology such as bone resorption, cartilage damage, pannus, and/or inflammation. In another aspect, the subject methods are effective in reducing ankle inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, 60%, or about 75% to 90%. In another aspect, the subject methods are effective in reducing knee inflammation by at least about 2%, 5%, 10%, 15%, 20%, 25%, 30%, 50%, 60%, or about 75% to 90% or more. In still another aspect, the subject methods are effective in reducing serum anti-type II collagen levels by at least about 10%, 12%, 15%, 20%, 24%, 25%, 30%, 35%, 50%, 60%, 75%, 80%, 86%, 87%, or about 90% or more. In another aspect, the subject methods are effective in reducing ankle histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 90% or more. In still another aspect, the subject methods are effective in reducing knee histopathology scores by about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 90% or more.

[00305] In other embodiments, provided herein are methods of using the compounds or pharmaceutical compositions to treat respiratory diseases including but not limited to diseases affecting the lobes of lung, pleural cavity,

bronchial tubes, trachea, upper respiratory tract, or the nerves and muscle for breathing. For example, methods are provided to treat obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) is an umbrella term for a group of respiratory tract diseases that are characterized by airflow obstruction or limitation. Conditions included in this umbrella term include, but are not limited to: chronic bronchitis, emphysema, and bronchiectasis.

[00306] In another embodiment, the compounds described herein are used for the treatment of asthma. Also, the compounds or pharmaceutical compositions described herein can be used for the treatment of endotoxemia and sepsis. In one embodiment, the compounds or pharmaceutical compositions described herein are used to for the treatment of rheumatoid arthritis (RA). In yet another embodiment, the compounds or pharmaceutical compositions described herein is used for the treatment of contact or atopic dermatitis. Contact dermatitis includes irritant dermatitis, phototoxic dermatitis, allergic dermatitis, photoallergic dermatitis, contact urticaria, systemic contact-type dermatitis and the like. Irritant dermatitis can occur when too much of a substance is used on the skin of when the skin is sensitive to certain substance. Atopic dermatitis, sometimes called eczema, is a kind of dermatitis, an atopic skin disease.

[00307] In some embodiments, the disclosure provides a method of treating diseases related to vasculogenesis or angiogenesis in a subject that comprises administering to said subject a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable form, salt, ester, prodrug, or derivative thereof. In some embodiments, said method is for treating a disease selected from tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00308] Patients that can be treated with compounds as disclosed herein, or pharmaceutically acceptable form, salt, ester, prodrug or derivative of said compounds, according to the methods as disclosed herein include, for example, but not limited to, patients that have been diagnosed as having psoriasis; restenosis; atherosclerosis; BPH; breast cancer such as a ductal carcinoma in duct tissue in a mammary gland, medullary carcinomas, colloid carcinomas, tubular carcinomas, and inflammatory breast cancer; ovarian cancer, including epithelial ovarian tumors such as adenocarcinoma in the ovary and an adenocarcinoma that has migrated from the ovary into the abdominal cavity; uterine cancer; cervical cancer such as adenocarcinoma in the cervix epithelial including squamous cell carcinoma and adenocarcinomas; prostate cancer, such as a prostate cancer selected from the following: an adenocarcinoma or an adenocarinoma that has migrated to the bone; pancreatic cancer such as epithelioid carcinoma in the pancreatic duct tissue and an adenocarcinoma in a pancreatic duct; bladder cancer such as a transitional cell carcinoma in urinary bladder, urothelial carcinomas (transitional cell carcinomas), tumors in the urothelial cells that line the bladder, squamous cell carcinomas, adenocarcinomas, and small cell cancers; leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, myeloproliferative disorders, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), mastocytosis, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), and myelodysplastic syndrome (MDS); bone cancer; lung cancer such as non-small cell lung cancer (NSCLC), which is divided into squamous cell carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas, and small cell lung cancer; skin cancer such as basal cell carcinoma, melanoma, squamous cell carcinoma and actinic keratosis, which is a skin condition that sometimes develops into squamous cell carcinoma; eye retinoblastoma; cutaneous or intraocular (eye) melanoma;

primary liver cancer (cancer that begins in the liver); kidney cancer; thyroid cancer such as papillary, follicular, medullary and anaplastic; AIDS-related lymphoma such as diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma and small non-cleaved cell lymphoma; Kaposi's Sarcoma; viral-induced cancers including hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma; human lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/lymphoma; and human papilloma virus (HPV) and cervical cancer; central nervous system cancers (CNS) such as primary brain tumor, which includes gliomas (astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme), Oligodendroglioma, Ependymoma, Meningioma, Lymphoma, Schwannoma, and Medulloblastoma; peripheral nervous system (PNS) cancers such as acoustic neuromas and malignant peripheral nerve sheath tumor (MPNST) including neurofibromas and schwannomas, malignant fibrous cytoma, malignant fibrous histiocytoma, malignant meningioma, malignant mesothelioma, and malignant mixed Müllerian tumor; oral cavity and oropharyngeal cancer such as, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and oropharyngeal cancer; stomach cancer such as lymphomas, gastric stromal tumors, and carcinoid tumors; testicular cancer such as germ cell tumors (GCTs), which include seminomas and nonseminomas, and gonadal stromal tumors, which include Leydig cell tumors and Sertoli cell tumors; thymus cancer such as thymomas, thymic carcinomas, Hodgkin disease, non-Hodgkin lymphomas carcinoids or carcinoid tumors; rectal cancer; and colon cancer.

[00309] In some embodiments, the disclosure relates to a method of treating diabetes in a subject that comprises administering to said subject a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable form, salt, ester, prodrug or derivative thereof.

[00310] In addition, the compounds described herein can be used to treat acne.

[00311] In addition, the compounds described herein can be used for the treatment of arteriosclerosis, including atherosclerosis. Arteriosclerosis is a general term describing any hardening of medium or large arteries. Atherosclerosis is a hardening of an artery specifically due to an atheromatous plaque.

[00312] Further, the compounds described herein can be used for the treatment of glomerulonephritis. Glomerulonephritis is a primary or secondary autoimmune renal disease characterized by inflammation of the glomeruli. It can be asymptomatic, or present with hematuria and/or proteinuria. There are many recognized types, divided in acute, subacute or chronic glomerulonephritis. Causes are infectious (bacterial, viral or parasitic pathogens), autoimmune or paraneoplastic.

[00313] Additionally, the compounds described herein can be used for the treatment of bursitis, lupus, acute disseminated encephalomyelitis (ADEM), Addison's disease, antiphospholipid antibody syndrome (APS), aplastic anemia, autoimmune hepatitis, coeliac disease, crohn's disease, diabetes mellitus (type 1), goodpasture's syndrome, graves' disease, guillain-barré syndrome (GBS), hashimoto's disease, inflammatory bowel disease, lupus erythematosus, myasthenia gravis, opsoclonus myoclonus syndrome (OMS), optic neuritis, ord's thyroiditis,osteoarthritis, uveoretinitis, pemphigus, polyarthritis, primary biliary cirrhosis, reiter's syndrome, takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, wegener's granulomatosis, alopecia universalis, chagas' disease, chronic fatigue syndrome, dysautonomia, endometriosis, hidradenitis suppurativa, interstitial cystitis, neuromyotonia, sarcoidosis, scleroderma, ulcerative colitis, vitiligo, vulvodynia, appendicitis, arteritis, arthritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, cholecystitis, chorioamnionitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, hepatitis, hidradenitis, ileitis, iritis, laryngitis, mastitis, meningitis, myelitis,

myocarditis, myositis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, or vulvitis.

[00314] In some embodiments, provided herein is a method of treating a cardiovascular disease in a subject that comprises administering to said subject a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable form, salt, ester, prodrug or derivative thereof. Examples of cardiovascular conditions include, but are not limited to, atherosclerosis, restenosis, vascular occlusion and carotid obstructive disease.

[00315] In another aspect, provided herein are methods of disrupting the function of a leukocyte or disrupting a function of an osteoclast. The method includes contacting the leukocyte or the osteoclast with a function disrupting amount of a compound as disclosed herein.

[00316] In another aspect, methods are provided for treating ophthalmic disease by administering one or more of the subject compounds or pharmaceutical compositions to the eye of a subject.

[00317] Methods are further provided for administering the compounds provided herein include via eye drop, intraocular injection, intravitreal injection, topically, or through the use of a drug eluting device, microcapsule, implant, or microfluidic device. In some cases, the compounds as disclosed herein are administered with a carrier or excipient that increases the intraocular penetrance of the compound such as an oil and water emulsion with colloid particles having an oily core surrounded by an interfacial film. It is contemplated that all local routes to the eye can be used including topical, subconjunctival, periocular, retrobulbar, subtenon, intracameral, intravitreal, intraocular, subretinal, juxtasceral and suprachoroidal administration. Systemic or parenteral administration can be feasible including but not limited to intravenous, subcutaneous, and oral delivery. An exemplary method of administration will be intravitreal or subtenon injection of solutions or suspensions, or intravitreal or subtenon placement of bioerodible or non-bioerodible devices, or by topical ocular administration of solutions or suspensions, or posterior juxtasceral administration of a gel or cream formulation.

[00318] In some cases, the colloid particles include at least one cationic agent and at least one non-ionic surfactant such as a poloxamer, tyloxapol, a polysorbate, a polyoxyethylene castor oil derivative, a sorbitan ester, or a polyoxyl stearate. In some cases, the cationic agent is an alkylamine, a tertiary alkyl amine, a quaternary ammonium compound, a cationic lipid, an amino alcohol, a biguanidine salt, a cationic compound or a mixture thereof. In some cases, the cationic agent is a biguanidine salt such as chlorhexidine, polyaminopropyl biguanidine, phenformin, alkylbiguanidine, or a mixture thereof. In some cases, the quaternary ammonium compound is a benzalkonium halide, lauralkonium halide, cetrimide, hexadecyltrimethylammonium halide, tetradecyltrimethylammonium halide, dodecyltrimethylammonium halide, cetrimonium halide, benzethonium halide, behenalkonium halide, cetalkonium halide, cetethyldimonium halide, cetylpyridinium halide, benzododecinium halide, chlorallyl methenamine halide, myristylalkonium halide, stearylalkonium halide or a mixture of two or more thereof. In some cases, cationic agent is a benzalkonium chloride, lauralkonium chloride, benzododecinium bromide, benzethonium chloride, hexadecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, dodecyltrimethylammonium bromide or a mixture of two or more thereof. In some cases, the oil phase is mineral oil and light mineral oil, medium chain triglycerides (MCT), coconut oil; hydrogenated oils comprising hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenate castor oil or hydrogenated soybean oil; polyoxyethylene hydrogenated castor oil derivatives comprising polyoxyl-40 hydrogenated castor oil, polyoxyl-60 hydrogenated castor oil or polyoxyl-100 hydrogenated castor oil.

[00319] In some embodiments, provided herein are methods of modulating a PI3K kinase activity by contacting the kinase with an effective amount of a compound as disclosed herein. Modulation can be inhibiting or activating kinase activity. In some embodiments, provided herein are methods of inhibiting kinase activity by contacting the kinase with an effective amount of a compound as disclosed herein in solution. In some embodiments, provided herein are methods of inhibiting the kinase activity by contacting a cell, tissue, organ that express the kinase of interest. In some embodiments, provided herein are methods of inhibiting kinase activity in a subject by administering into the subject an effective amount of a compound as disclosed herein. In some embodiments, the percentage of inhibiting exceeds about 25%, 30%, 40%, 50%, 60%, 70%, 80%, or 90%.

[00320] In some embodiments, the kinase is a lipid kinase or a protein kinase. In some embodiments, the kinase is selected from a PI3 kinase including different isoforms such as PI3 kinase α , PI3 kinase β , PI3 kinase γ , PI3 kinase δ ; DNA-PK; mTor; Abl, VEGFR, Ephrin receptor B4 (EphB4); TEK receptor tyrosine kinase (TIE2); FMS-related tyrosine kinase 3 (FLT-3); Platelet derived growth factor receptor (PDGFR); RET; ATM; ATR; hSmg-1; Hck; Src; Epidermal growth factor receptor (EGFR); KIT; Insulin Receptor (IR) and IGFR.

[00321] In some embodiments, disclosed herein are methods of modulating PI3 kinase activity by contacting a PI3 kinase with an amount of a compound as disclosed herein sufficient to modulate the activity of the PI3 kinase. Modulate can be inhibiting or activating PI3 kinase activity. In some embodiments, provided herein are methods of inhibiting PI3 kinase activity by contacting a PI3 kinase with an amount of a compound as disclosed herein sufficient to inhibit the activity of the PI3 kinase. In some embodiments, provided herein are methods of inhibiting PI3 kinase activity. Such inhibition can take place in solution, in a cell expressing one or more PI3 kinases, in a tissue comprising a cell expressing one or more PI3 kinases, or in an organism expressing one or more PI3 kinases. In some embodiments, provided herein are methods of inhibiting PI3 kinase activity in a subject (including mammals such as humans) by contacting said subject with an amount of a compound as disclosed herein sufficient to inhibit the activity of the PI3 kinase in said subject.

[00322] In some embodiments, provided herein are methods for combination therapies in which an agent known to modulate other pathways, or other components of the same pathway, or even overlapping sets of target enzymes are used in combination with a compound as disclosed herein, or a pharmaceutically acceptable form, salt, ester, prodrug or derivative thereof. In one aspect, such therapy includes, but is not limited to, the combination of the subject compound with chemotherapeutic agents, therapeutic antibodies, and radiation treatment, to provide a synergistic or additive therapeutic effect.

[00323] In one aspect, the compounds or pharmaceutical compositions as disclosed herein can present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Such combination can reduce the undesired effect of high level of IgE associated with the use of one or more PI3K δ inhibitors, if such effect occurs. This can be particularly useful in treatment of autoimmune and inflammatory disorders (AIID) such as rheumatoid arthritis. Additionally, the administration of PI3K δ or PI3K δ/γ inhibitors as disclosed herein in combination with inhibitors of mTOR can also exhibit synergy through enhanced inhibition of the PI3K pathway.

[00324] In a separate but related aspect, provided herein is a combination treatment of a disease associated with PI3K δ comprising administering to a PI3K δ inhibitor and an agent that inhibits IgE production or activity. Other exemplary PI3K δ inhibitors are applicable for this combination and they are described, *e.g.*, US Patent No. 6,800,620.

Such combination treatment is particularly useful for treating autoimmune and inflammatory diseases (AIID) including but not limited to rheumatoid arthritis.

[00325] Agents that inhibit IgE production are known in the art and they include, but are not limited to, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (*i.e.*, rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as for example Omalizumab and TNX-901.

[00326] For treatment of autoimmune diseases, the subject compounds or pharmaceutical compositions can be used in combination with commonly prescribed drugs including but not limited to Enbrel[®], Remicade[®], Humira[®], Avonex[®], and Rebif[®]. For treatment of respiratory diseases, the subject compounds or pharmaceutical compositions can be administered in combination with commonly prescribed drugs including but not limited to Xolair[®], Advair[®], Singulair[®], and Spiriva[®].

[00327] The compounds as disclosed herein can be formulated or administered in conjunction with other agents that act to relieve the symptoms of inflammatory conditions such as encephalomyelitis, asthma, and the other diseases described herein. These agents include non-steroidal anti-inflammatory drugs (NSAIDs), *e.g.*, acetylsalicylic acid; ibuprofen; naproxen; indomethacin; nabumetone; tolmetin; etc. Corticosteroids are used to reduce inflammation and suppress activity of the immune system. An exemplary drug of this type is Prednisone. Chloroquine (Aralen) or hydroxychloroquine (Plaquenil) can also be used in some individuals with lupus. They can be prescribed for skin and joint symptoms of lupus. Azathioprine (Imuran) and cyclophosphamide (Cytoxan) suppress inflammation and tend to suppress the immune system. Other agents, *e.g.*, methotrexate and cyclosporin are used to control the symptoms of lupus. Anticoagulants are employed to prevent blood from clotting rapidly. They range from aspirin at very low dose which prevents platelets from sticking, to heparin/coumadin.

[00328] In another aspect, provided herein is a pharmaceutical composition for inhibiting abnormal cell growth in a subject which comprises an amount of a compound as disclosed herein, or a pharmaceutically acceptable form, salt, ester, prodrug or derivative thereof, in combination with an amount of an anti-cancer agent (*e.g.*, a chemotherapeutic agent). Many chemotherapeutics are presently known in the art and can be used in combination with the compounds as disclosed herein.

[00329] In some embodiments, the chemotherapeutic is selected from mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens. Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec[®] (Imatinib Mesylate), Velcade[®] (bortezomib), Casodex (bicalutamide), Iressa[®], and Adriamycin as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN[™]); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such

as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabacin, carminomycin, carzinophilin, CasodexTM, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiolestanol, mepitiolestanol, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguanzone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.RTM; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, *e.g.*, paclitaxel (TAXOLTM, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERETM, Rhone-Poulenc Rorer, Antony, France) and ABRAAXANE[®] (paclitaxel protein-bound particles); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable forms, salts, acids or derivatives of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen (NolvadexTM), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO). Where desired, the compounds or pharmaceutical composition as disclosed herein can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin[®], Avastin[®], Erbitux[®], Rituxan[®], Taxol[®], Arimidex[®], Taxotere[®], ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126, and Zosuquidar.

[00330] In some embodiments, the chemotherapeutic is selected from hedgehog inhibitors including, but not limited to IPI-926 (*See* U.S. Patent 7,812,164). Other suitable hedgehog inhibitors include, for example, those described and disclosed in U.S. Patent 7,230,004, U.S. Patent Application Publication No. 2008/0293754, U.S. Patent Application Publication No. 2008/0287420, and U.S. Patent Application Publication No. 2008/0293755, the entire disclosures of which are incorporated by reference herein. Examples of other suitable hedgehog inhibitors include those described in U.S. Patent Application Publication Nos. US 2002/0006931, US 2007/0021493 and US 2007/0060546, and International Application Publication Nos. WO 2001/19800, WO 2001/26644, WO 2001/27135, WO 2001/49279, WO 2001/74344, WO 2003/011219, WO 2003/088970, WO 2004/020599, WO 2005/013800, WO 2005/033288, WO 2005/032343, WO 2005/042700, WO 2006/028958, WO 2006/050351, WO 2006/078283, WO 2007/054623, WO 2007/059157, WO 2007/120827, WO 2007/131201, WO 2008/070357, WO 2008/110611, WO 2008/112913, and WO 2008/131354. Additional examples of hedgehog inhibitors include, but are not limited to, GDC-0449 (also known as RG3616 or vismodegib) described in, *e.g.*, Von Hoff D. *et al.*, *N. Engl. J. Med.* 2009; 361(12):1164-72; Robarge K.D. *et al.*, *Bioorg Med Chem Lett.* 2009; 19(19):5576-81; Yauch, R. L. *et al.* (2009) *Science* 326: 572-574; *Sciencexpress*: 1-3 (10.1126/science.1179386); Rudin, C. *et al.* (2009) *New England J of Medicine* 361-366 (10.1056/nejma0902903); BMS-833923 (also known as XL139) described in, *e.g.*, in Siu L. *et al.*, *J. Clin. Oncol.* 2010; 28:15s (suppl; abstr 2501); and National Institute of Health Clinical Trial Identifier No. NCT00670189; LDE-225 described, *e.g.*, in Pan S. *et al.*, *ACS Med. Chem. Lett.*, 2010; 1(3): 130-134; LEQ-506 described, *e.g.*, in National Institute of Health Clinical Trial Identifier No. NCT01106508; PF-04449913 described, *e.g.*, in National Institute of Health Clinical Trial Identifier No. NCT00953758; Hedgehog pathway antagonists disclosed in U.S. Patent Application Publication No. 2010/0286114; SMOi2-17 described, *e.g.*, U.S. Patent Application Publication No. 2010/0093625; SANT-1 and SANT-2 described, *e.g.*, in Rominger C.M. *et al.*, *J. Pharmacol. Exp. Ther.* 2009; 329(3):995-1005; 1-piperazinyl-4-arylphthalazines or analogues thereof, described in Lucas B.S. *et al.*, *Bioorg. Med. Chem. Lett.* 2010; 20(12):3618-22.

[00331] In some embodiments, the chemotherapeutic is selected from HSP90 inhibitors. The HSP90 inhibitor can be a geldanamycin derivative, *e.g.*, a benzoquinone or hydroquinone ansamycin HSP90 inhibitor (*e.g.*, IPI-493 and/or IPI-504). Non-limiting examples of HSP90 inhibitors include IPI-493, IPI-504, 17-AAG (also known as tanespimycin or CNF-1010), BIIB-021 (CNF-2024), BIIB-028, AUY-922 (also known as VER-49009), SNX-5422, STA-9090, AT-13387, XL-888, MPC-3100, CU-0305, 17-DMAG, CNF-1010, Macbecin (*e.g.*, Macbecin I, Macbecin II), CCT-018159, CCT-129397, PU-H71, or PF-04928473 (SNX-2112).

[00332] In some embodiments, the chemotherapeutic is selected from PI3K inhibitors (*e.g.*, including those PI3K inhibitors disclosed herein and those PI3K inhibitors not disclosed herein). In some embodiment, the PI3K inhibitor is an inhibitor of delta and gamma isoforms of PI3K. In some embodiments, the PI3K inhibitor is an inhibitor of alpha isoforms of PI3K. In other embodiments, the PI3K inhibitor is an inhibitor of one or more alpha, beta, delta and gamma isoforms of PI3K. Exemplary PI3K inhibitors that can be used in combination are described in, *e.g.*, WO 2010/036380; WO 2010/006086, WO 09/114870, WO 05/113556. Additional PI3K inhibitors that can be used in combination with the pharmaceutical compositions, include but are not limited to, GSK 2126458, GDC-0980, GDC-0941, Sanofi XL147, XL756, XL147, PF-46915032, BKM 120, CAL-101, CAL 263, SF1126, PX-886, and a dual PI3K inhibitor (*e.g.*, Novartis BEZ235). In one embodiment, the PI3K inhibitor is an isoquinolinone. In one embodiment, the PI3K inhibitor is IPI-145 or a derivative thereof. In other embodiments, the PI3K inhibitor is INK1117 or a derivative thereof.

[00333] In some embodiments, provided herein is a method for using the compounds or pharmaceutical composition in combination with radiation therapy in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the subject. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound as disclosed herein in this combination therapy can be determined as described herein.

[00334] Radiation therapy can be administered through one of several methods, or a combination of methods, including without limitation external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy and permanent or temporary interstitial brachytherapy. The term "brachytherapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended without limitation to include exposure to radioactive isotopes (*e.g.*, At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner as disclosed herein include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), *e.g.*, a solution of I-125 or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

[00335] Without being limited by any theory, the compounds as disclosed herein can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, provided herein is a method for sensitizing abnormal cells in a subject to treatment with radiation which comprises administering to the subject an amount of a compound as disclosed herein or pharmaceutically acceptable forms, salt, ester, prodrug, or derivative thereof, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound, form, salt in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

[00336] The compounds or pharmaceutical compositions as disclosed herein can be used in combination with an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, glycolysis inhibitors, or autophagy inhibitors.

[00337] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound as disclosed herein and pharmaceutical compositions described herein. Anti-angiogenesis agents include, for example, rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include CELEBREXTM (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931, 788 (published July 28, 1999), WO 90/05719 (published May 31,

1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. In some embodiments, MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. Other embodiments include those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (*i.e.*, MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some non-limiting examples of MMP inhibitors are AG-3340, RO 32-3555, and RS 13-0830.

[00338] Autophagy inhibitors include, but are not limited to, chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), can also be used.

[00339] In some embodiments, disclosed herein is a method of and/or a pharmaceutical composition for treating a cardiovascular disease in a subject which comprises an amount of a compound as disclosed herein, or a pharmaceutically acceptable form, salt, ester, prodrug or derivative thereof, or an isotopically-labeled derivative thereof, and an amount of one or more therapeutic agents use for the treatment of cardiovascular diseases.

[00340] Exemplary agents for use in cardiovascular disease applications are anti-thrombotic agents, *e.g.*, prostacyclin and salicylates, thrombolytic agents, *e.g.*, streptokinase, urokinase, tissue plasminogen activator (TPA) and anisoylated plasminogen-streptokinase activator complex (APSAC), anti-platelets agents, *e.g.*, acetyl-salicylic acid (ASA) and clopidogrel, vasodilating agents, *e.g.*, nitrates, calcium channel blocking drugs, anti-proliferative agents, *e.g.*, colchicine and alkylating agents, intercalating agents, growth modulating factors such as interleukins, transformation growth factor-beta and congeners of platelet derived growth factor, monoclonal antibodies directed against growth factors, anti-inflammatory agents, both steroidal and non-steroidal, and other agents that can modulate vessel tone, function, arteriosclerosis, and the healing response to vessel or organ injury post intervention. Antibiotics can also be included in combinations or coatings. Moreover, a coating can be used to effect therapeutic delivery focally within the vessel wall. By incorporation of the active agent in a swellable polymer, the active agent will be released upon swelling of the polymer.

[00341] The compounds described herein can be formulated or administered in conjunction with liquid or solid tissue barriers also known as lubricants. Examples of tissue barriers include, but are not limited to, polysaccharides, polyglycans, seprafilm, interceed and hyaluronic acid.

[00342] Medicaments which can be administered in conjunction with the compounds described herein include any suitable drugs usefully delivered by inhalation for example, analgesics, *e.g.*, codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, *e.g.*, diltiazem; antiallergics, *e.g.* cromoglycate, ketotifen or nedocromil; anti-infectives, *e.g.*, cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidine; antihistamines, *e.g.*, methapyrilene; anti-inflammatories, *e.g.*, beclomethasone, flunisolide, budesonide, tipredane,

triamcinolone acetonide or fluticasone; antitussives, *e.g.*, noscapine; bronchodilators, *e.g.*, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutalin, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]-amino]methyl]benzenemethanol; diuretics, *e.g.*, amiloride; anticholinergics *e.g.*, ipratropium, atropine or oxitropium; hormones, *e.g.*, cortisone, hydrocortisone or prednisolone; xanthines *e.g.*, aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, *e.g.*, insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments can be used in the form of salts (*e.g.*, as alkali metal or amine salts or as acid addition salts) or as esters (*e.g.*, lower alkyl esters) to optimize the activity and/or stability of the medicament.

[00343] Other exemplary therapeutic agents useful for a combination therapy include, but are not limited to, agents as described above, radiation therapy, hormone antagonists, hormones and their releasing factors, thyroid and antithyroid drugs, estrogens and progestins, androgens, adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones, insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas, agents affecting calcification and bone turnover: calcium, phosphate, parathyroid hormone, vitamin D, calcitonin, vitamins such as water-soluble vitamins, vitamin B complex, ascorbic acid, fat-soluble vitamins, vitamins A, K, and E, growth factors, cytokines, chemokines, muscarinic receptor agonists and antagonists; anticholinesterase agents; agents acting at the neuromuscular junction and/or autonomic ganglia; catecholamines, sympathomimetic drugs, and adrenergic receptor agonists or antagonists; and 5-hydroxytryptamine (5-HT, serotonin) receptor agonists and antagonists.

[00344] Therapeutic agents can also include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β -adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

[00345] Additional therapeutic agents contemplated herein include diuretics, vasopressin, agents affecting the renal conservation of water, rennin, angiotensin, agents useful in the treatment of myocardial ischemia, anti-hypertensive agents, angiotensin converting enzyme inhibitors, β -adrenergic receptor antagonists, agents for the treatment of hypercholesterolemia, and agents for the treatment of dyslipidemia.

[00346] Other therapeutic agents contemplated herein include drugs used for control of gastric acidity, agents for the treatment of peptic ulcers, agents for the treatment of gastroesophageal reflux disease, prokinetic agents, antiemetics, agents used in irritable bowel syndrome, agents used for diarrhea, agents used for constipation, agents used for inflammatory bowel disease, agents used for biliary disease, agents used for pancreatic disease. Therapeutic agents include, but are not limited to, those used to treat protozoan infections, drugs used to treat Malaria, Amebiasis, Giardiasis, Trichomoniasis, Trypanosomiasis, and/or Leishmaniasis, and/or drugs used in the chemotherapy of helminthiasis. Other therapeutic agents include, but are not limited to, antimicrobial agents, sulfonamides,

trimethoprim-sulfamethoxazole quinolones, and agents for urinary tract infections, penicillins, cephalosporins, and other, β -Lactam antibiotics, an agent containing an aminoglycoside, protein synthesis inhibitors, drugs used in the chemotherapy of tuberculosis, mycobacterium avium complex disease, and leprosy, antifungal agents, antiviral agents including nonretroviral agents and antiretroviral agents.

[00347] Examples of therapeutic antibodies that can be combined with a subject compound include but are not limited to anti-receptor tyrosine kinase antibodies (cetuximab, panitumumab, trastuzumab), anti CD20 antibodies (rituximab, tositumomab), and other antibodies such as alemtuzumab, bevacizumab, and gemtuzumab.

[00348] Moreover, therapeutic agents used for immunomodulation, such as immunomodulators, immunosuppressive agents, tolerogens, and immunostimulants are contemplated by the methods herein. In addition, therapeutic agents acting on the blood and the blood-forming organs, hematopoietic agents, growth factors, minerals, and vitamins, anticoagulant, thrombolytic, and antiplatelet drugs.

[00349] For treating renal carcinoma, one can combine a compound as disclosed herein with sorafenib and/or avastin. For treating an endometrial disorder, one can combine a compound as disclosed herein with doxorubicin, taxotere (taxol), and/or cisplatin (carboplatin). For treating ovarian cancer, one can combine a compound as disclosed herein with cisplatin (carboplatin), taxotere, doxorubicin, topotecan, and/or tamoxifen. For treating breast cancer, one can combine a compound as disclosed herein with taxotere (taxol), gemcitabine (capecitabine), tamoxifen, letrozole, tarceva, lapatinib, PD0325901, avastin, herceptin, OSI-906, and/or OSI-930. For treating lung cancer, one can combine a compound as disclosed herein with taxotere (taxol), gemcitabine, cisplatin, pemetrexed, Tarceva, PD0325901, and/or avastin.

[00350] Further therapeutic agents that can be combined with a subject compound can be found in Goodman and Gilman's *"The Pharmacological Basis of Therapeutics"* Tenth Edition edited by Hardman, Limbird and Gilman or the Physician's Desk Reference, both of which are incorporated herein by reference in their entirety.

[00351] The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments, the compounds as disclosed herein will be co-administered with other agents as described above. When used in combination therapy, the compounds described herein can be administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described above can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound as disclosed herein and any of the agents described above can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound as disclosed herein can be administered just followed by and any of the agents described above, or vice versa. In the separate administration protocol, a compound as disclosed herein and any of the agents described above can be administered a few minutes apart, or a few hours apart, or a few days apart.

[00352] Administration of the compounds as disclosed herein can be effected by any method that enables delivery of the compounds to the site of action. An effective amount of a compound as disclosed herein can be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously,

intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

[00353] When a compound as disclosed herein is administered in a pharmaceutical composition that comprises one or more agents, and the agent has a shorter half-life than the compound as disclosed herein, unit dose forms of the agent and the compound as disclosed herein can be adjusted accordingly.

[00354] The examples and preparations provided below further illustrate and exemplify the compounds as disclosed herein and methods of preparing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers can be obtained by methods known to those skilled in the art.

EXAMPLES

Biological Activity Assessment

[00355] The activity of the compounds as described herein can be determined by the following procedure, as well as the procedures described in the examples below. The activity of the kinase is assessed by measuring the incorporation of γ - ^{33}P -phosphate from γ - ^{33}P -ATP onto N-terminal His tagged substrate, which is expressed in *E. coli* and is purified by conventional methods, in the presence of the kinase. The assay is carried out in 96-well polypropylene plate. The incubation mixture (100, μL) comprises of 25 mM Hepes, pH 7.4, 10 mM MgCl_2 , 5 mM β -glycerolphosphate, 100 μM Na-orthovanadate, 5 mM DTT, 5 nM kinase, and 1 μM substrate. Inhibitors are suspended in DMSO, and all reactions, including controls are performed at a final concentration of 1% DMSO. Reactions are initiated by the addition of 10 μM ATP (with 0.5 μCi γ - ^{33}P -ATP/well) and incubated at ambient temperature for 45 minutes. Equal volume of 25% TCA is added to stop the reaction and precipitate the proteins. Precipitated proteins are trapped onto glass fiber B filterplates, and excess labeled ATP washed off using a Tomtec MACH III harvester. Plates are allowed to air-dry prior to adding 30 μL /well of Packard Microscint 20, and plates are counted using a Packard TopCount.

Chemical Examples

[00356] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques well known in the art.

[00357] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from $-10\text{ }^\circ\text{C}$ to $200\text{ }^\circ\text{C}$. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, *e.g.*, taking place at about atmospheric pressure within a temperature range of about $-10\text{ }^\circ\text{C}$ to about $110\text{ }^\circ\text{C}$ over a period that is, for example, about 1 to about 24 hours; reactions left to run overnight in some embodiments can average a period of about 16 hours.

[00358] The terms “solvent,” “organic solvent,” or “inert solvent” each mean a solvent inert under the conditions of the reaction being described in conjunction therewith including, for example, benzene, toluene, acetonitrile, tetrahydrofuran (“THF”), dimethylformamide (“DMF”), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, N-methylpyrrolidone (“NMP”), pyridine and the like. Unless specified to the

contrary, the solvents used in the reactions described herein are inert organic solvents. Unless specified to the contrary, for each gram of the limiting reagent, one cc (or mL) of solvent constitutes a volume equivalent.

[00359] Isolation and purification of the chemical entities and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures are given by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can also be used.

[00360] When desired, the (R)- and (S)-isomers of the non-limiting exemplary compounds, if present, can be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which can be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which can be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, a specific enantiomer can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

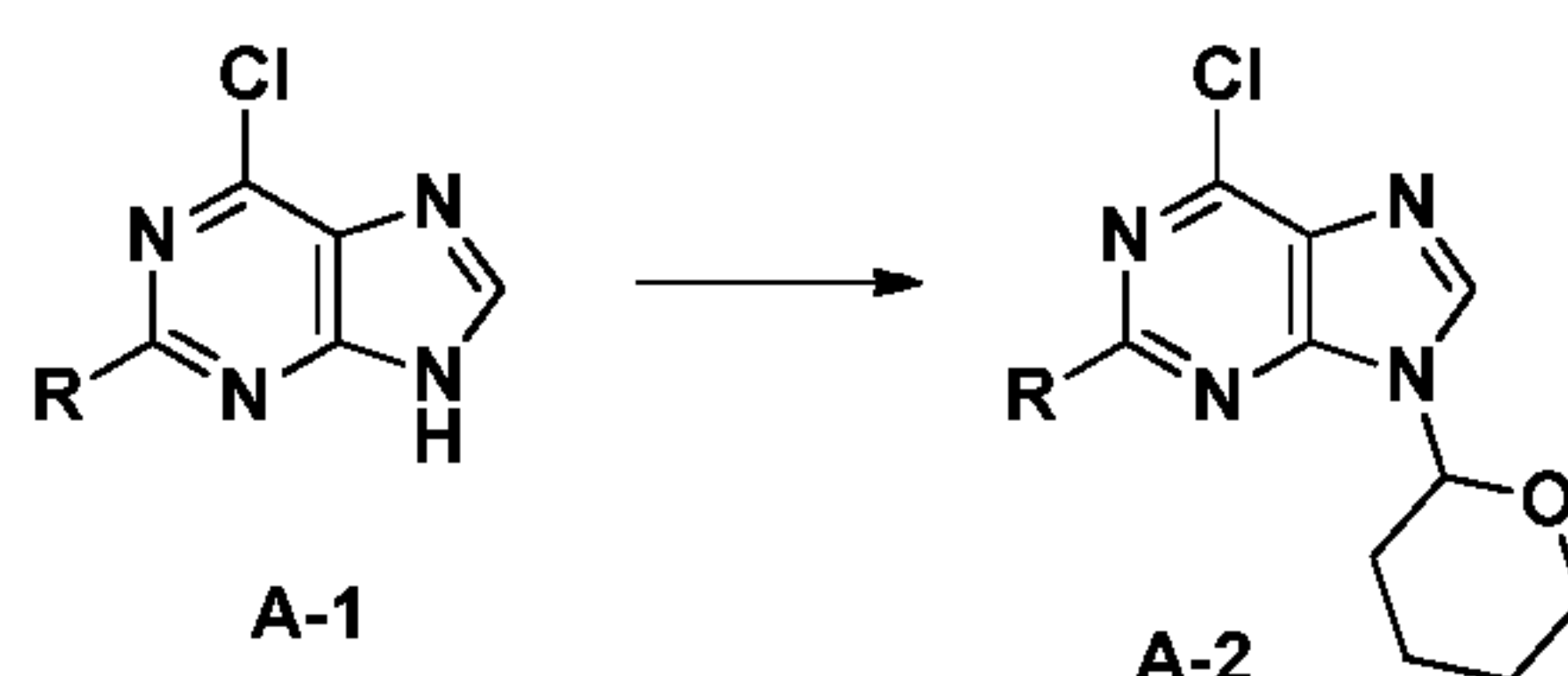
[00361] The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts. Also, the compounds described herein can be optionally contacted with a pharmaceutically acceptable base to form the corresponding basic addition salts.

[00362] In some embodiments, disclosed compounds can generally be synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing these chemical entities are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available, *e.g.*, from Aldrich Chemical Company (Milwaukee, WI) or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

[00363] The discussion below is offered to illustrate certain of the diverse methods available for use in making the disclosed compounds and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds provided herein.

General Synthetic Methods

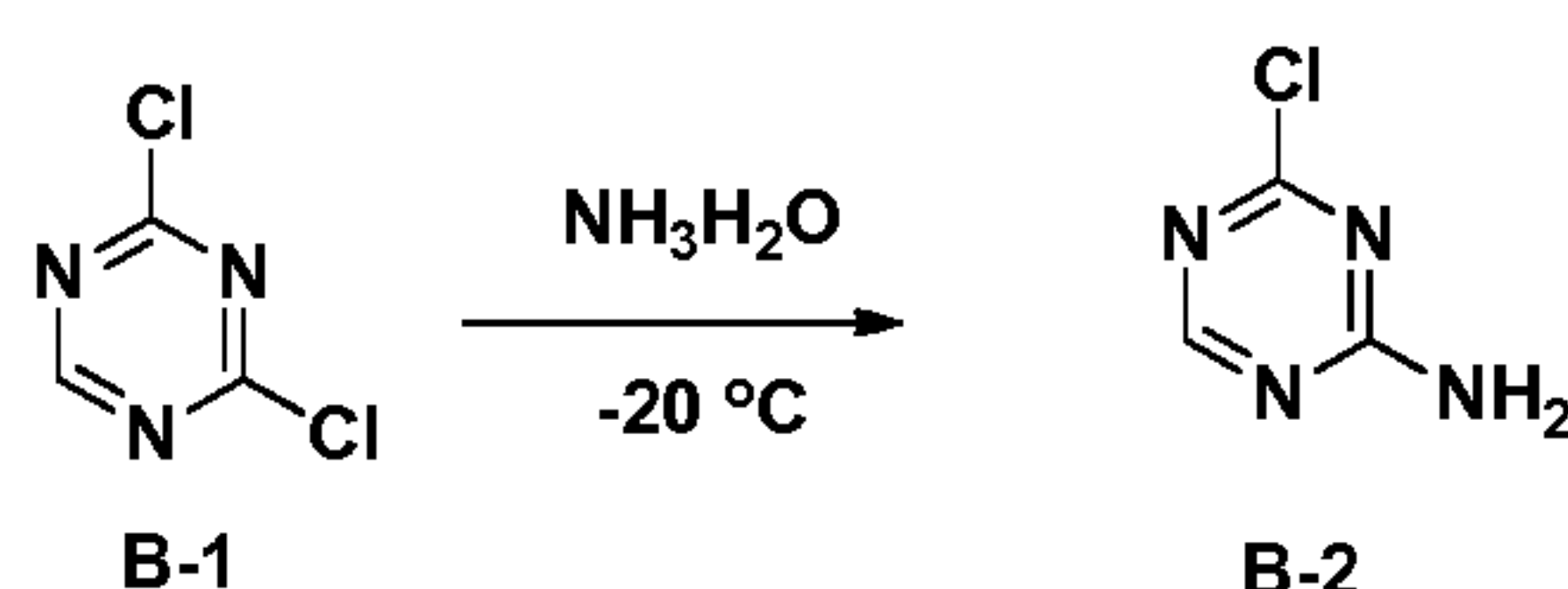
General method for the synthesis of Cl-W_d heterocycles:



Method A

General conditions for the preparation of 6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purines:

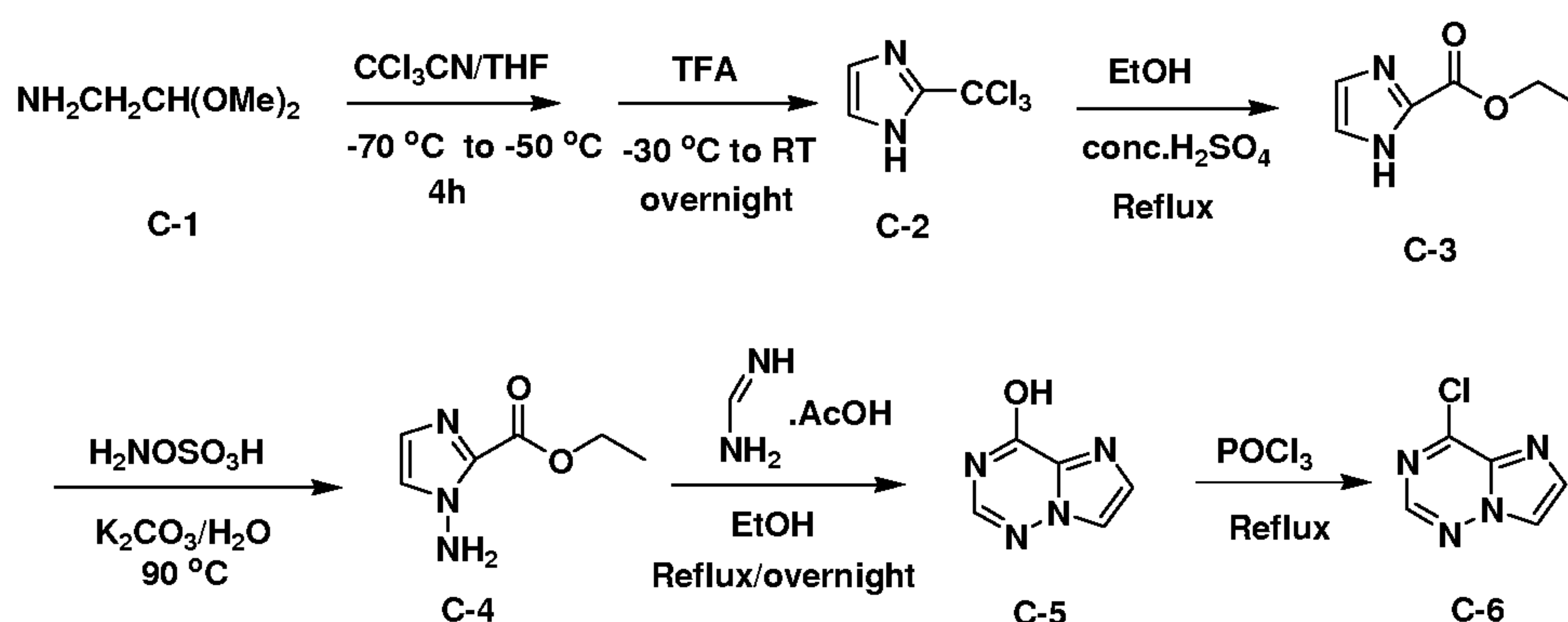
[00364] To a solution of a given 6-chloro-9H-purine (**A-1**) (1.29 mol, 1 eq) and TsOH (0.02 mol, 0.015 eq) in ethyl acetate (1000 mL), 3,4-dihydro-2H-pyran (1.94 mol, 1.5 eq) is added and the resulting mixture is stirred at reflux for 2 h. The reaction mixture is allowed to cool to RT, aqueous Na₂CO₃ solution (3%, 500 mL) is added and the resulting mixture is stirred for 10 min. The organic layer is separated, washed with water (500 mL x 2) and brine (500 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate is concentrated *in vacuo*. The product is dissolved in ethyl acetate (50 mL), and then n-heptane (500 mL) is added. The resulting mixture is stirred at RT for 1 h. The precipitate is collected by filtration, rinsed with heptane (100 mL) and dried *in vacuo* to afford the product 6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (**A-2**) as a yellowish solid.



Method B

General conditions for the preparation of 4-chloro-1,3,5-triazin-2-amine:

[00365] 2,4-Dichloro-1,3,5-triazine (**B-1**) (500 mg, 3.3 mmol, 1.0 eq) is dissolved in concentrated ammonium hydroxide (100 mL, 700 mmol, 212 eq) at -20 °C and the resulting mixture is stirred at this temperature for 10 min. The mixture is then filtered, rinsed with water (5 mL x 3) and dried *in vacuo* to afford the product, 4-chloro-1,3,5-triazin-2-amine (**B-2**) as a solid.



Method C

General conditions for the preparation of 4-chloroimidazo[1,2-f][1,2,4]triazine:

[00366] To a stirred solution of trichloroacetonitrile (28.8 g, 200 mmol, 1 eq) in anhydrous THF (70 mL) at -60 °C under an argon atmosphere, 2,2-dimethoxyethanamine (**C-1**) (21.8 mL, 200 mmol, 1.0 eq) is added dropwise over 5 min. The resulting mixture is allowed to warm to RT and stirred at RT for 4 h. The mixture is concentrated *in vacuo* and the residue is added in portions to a stirred solution of trifluoroacetic acid (100 mL) at -30 °C under argon.

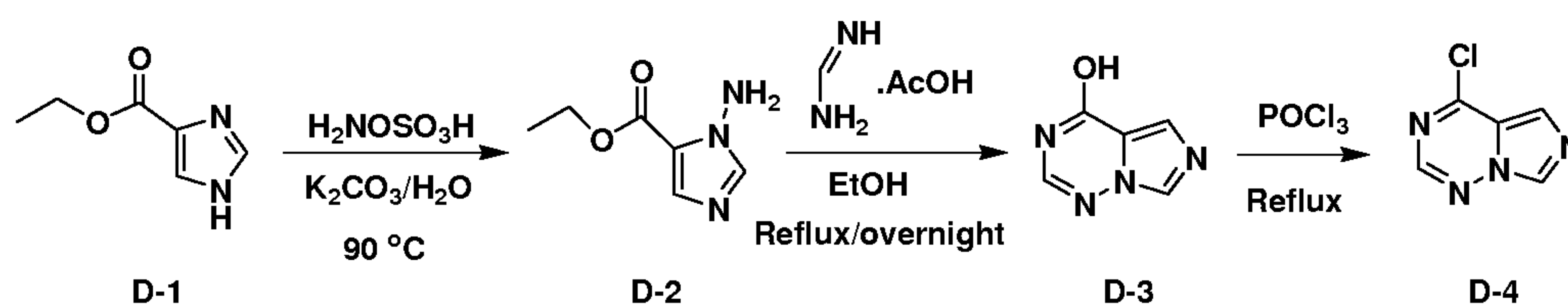
The resulting mixture is then stirred from -30 °C to RT overnight. The reaction mixture is concentrated *in vacuo* to afford the product, 2-(trichloromethyl)-1H-imidazole (**C-2**). The product is used in the next step without further purification.

[00367] The above-obtained residue (**C-2**) is dissolved in EtOH (300 mL). To this solution, conc. H₂SO₄ (98%, 30 mL, 522 mmol, 2.76 eq) is added dropwise while keeping the reaction temperature below 25 °C. The resulting mixture is stirred at reflux for 7 h and then stirred at RT overnight. The mixture is concentrated *in vacuo* to remove EtOH. The resulting suspension is diluted with ice-water (200 mL) and neutralized with concentrated ammonium hydroxide to adjust the pH to 5-6 while keeping the temperature below 5 °C. The solid is collected by filtration, rinsed with water (10 mL x 3), and dried *in vacuo* to afford a first portion of the product. The filtrate is extracted with ethyl acetate (200 mL x 2). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo*. The resulting residue is combined with the first portion of product and then recrystallized in isopropyl ether to afford the product, ethyl 1H-imidazole-2-carboxylate (**C-3**).

[00368] To a stirred solution of hydroxylamine-o-sulfonic acid (26.64 g, 235.8 mmol, 3.0 eq) in H₂O (17 mL) at 0 °C, ethyl 1H-imidazole-2-carboxylate (**C-3**) (11.0 g, 78.6 mmol, 1.0 eq) is added and the resulting mixture is stirred at 90 °C for 30 min. The mixture is cooled to RT and K₂CO₃ (3.6 g, 26.2 mmol, 1.0 eq) is added in portions. The resulting mixture is stirred at RT overnight, filtered and rinsed with H₂O (10 mL x 3). The filtrate is extracted with ethyl acetate (50 mL x 5). The combined organic layer is washed with brine, dried over Na₂SO₄ and filtered. The filtrate is evaporated *in vacuo* and the residue is purified by flash column chromatography on silica gel (1% MeOH-DCM) to afford the product, ethyl 1-amino-1H-imidazole-2-carboxylate (**C-4**) as a colorless oil.

[00369] A mixture of ethyl 1-amino-1H-imidazole-2-carboxylate (**C-4**) (800 mg, 5.16 mmol, 1.0 eq) and formamidine acetate (2.68 g, 25.78 mmol, 5.0 eq) in EtOH (100 mL) is stirred at reflux overnight. The resulting mixture is cooled to RT. The solid is collected by filtration, rinsed with EtOH (3 x 2 mL) and petroleum ether (2 mL x 3), and then dried *in vacuo* to afford the product, imidazo[1,2-f][1,2,4]triazin-4-ol (**C-5**).

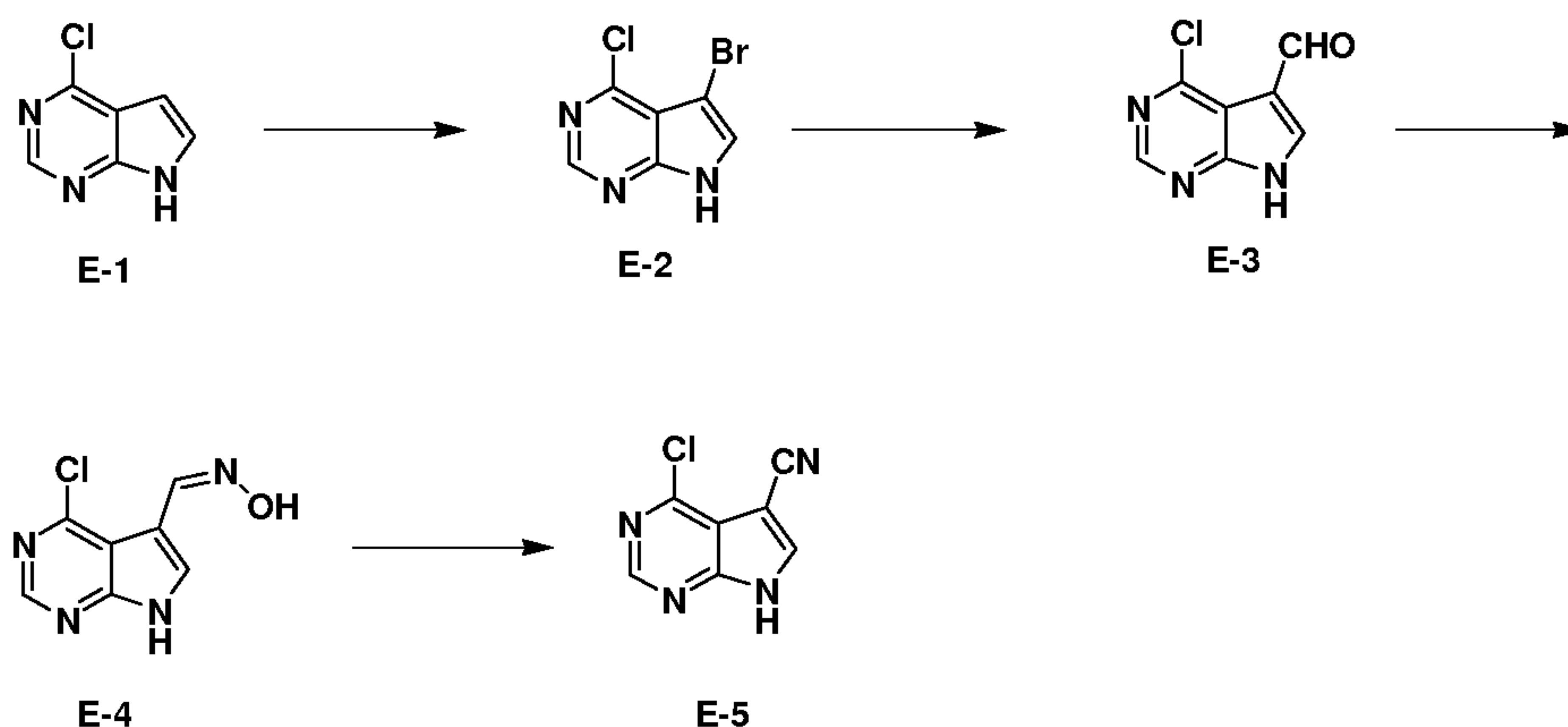
[00370] Imidazo[1,2-f][1,2,4]triazin-4-ol (**C-5**) (400 mg, 2.94 mmol, 1.0 eq) is dissolved in POCl₃ (10 mL, 109.2 mmol, 37.1 eq) and the resulting mixture is stirred at reflux for 2 h. The mixture is concentrated *in vacuo* to remove POCl₃. The residue is poured into ice water (30 mL) and neutralized with saturated aqueous NaHCO₃ solution to adjust the pH to 6-7 while keeping the temperature below 5 °C. The mixture is extracted with ethyl acetate (30 mL x 4). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (16% ethyl acetate in petro ether) to afford the product, 4-chloroimidazo[1,2-f][1,2,4] triazine (**C-6**).



Method D

General conditions for the preparation of 4-chloroimidazo[1,5-f][1,2,4]triazine:

[00371] 4-Chloroimidazo[1,5-f][1,2,4]triazine (**D-4**) is prepared from commercially available material (**D-1**) through a three-step sequence in analogous fashion to the synthesis of 4-chloroimidazo[1,2-f][1,2,4] triazine (**C-6**) from compound (**C-3B**) in Method C.

**Method E**

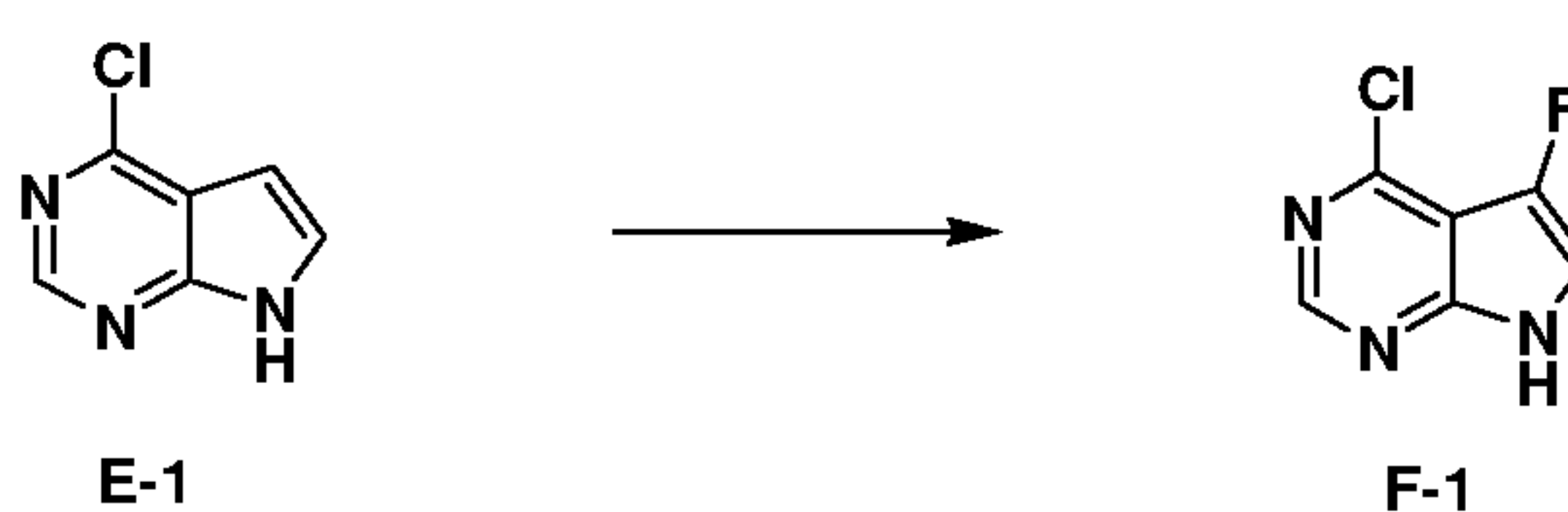
General method for the synthesis of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile:

[00372] To a suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**E-1**) (3.99 g, 26.0 mmol, 1.0 eq) in dry DCM (150 mL) under argon, N-bromosuccinimide (6.02 g, 33.8 mmol, 1.3 eq) is added and the resulting mixture is stirred at RT for 3 h. The reaction mixture is diluted with MeOH (30 mL) and then concentrated *in vacuo* to yield a slight brown solid. The residue is triturated with H₂O (150 mL). The solid is collected by filtration and then re-crystallized in MeOH to afford the product, 5-bromo-4-chloro-7H-pyrrolo[2,3-d] pyrimidine (**E-2**).

[00373] To a solution of 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**E-2**) (2.33 g, 10.0 mmol, 1.0 eq) in anhydrous THF (100 mL) at -78 °C under argon, n-BuLi solution (2.5 M in THF, 8.8 mL, 22.0 mmol, 2.2 eq) is added dropwise (over 10 min). The resulting mixture is stirred at -78 °C for 1h and then DMF (2.0 g, 11.0 mmol, 1.1 eq) is added dropwise (over 10 min). The mixture is stirred at -78 °C for an additional 30 min and then stirred at RT overnight. The reaction mixture is quenched with H₂O (50 mL) and then concentrated *in vacuo*. The residue is triturated with saturated aqueous NH₄Cl solution. The solid is collected by filtration, rinsed with ethyl acetate, and dried *in vacuo* to afford the product, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (**E-3**).

[00374] To a suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (**E-3**) (1.17 g, 6.47 mmol, 1.0 eq) and hydroxylamine hydrochloride (0.54 g, 7.77 mmol, 1.2 eq) in EtOH (25 mL), aqueous NaOH solution (0.31 g, 7.77 mmol, 1.2 eq) in H₂O (4 mL) is added dropwise. The resulting mixture is stirred at RT for 30 min and then is diluted with a sufficient amount of EtOH to allow stirring for additional 30 min. The solid is collected by filtration, rinsed with H₂O and dried *in vacuo* to afford the product, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde oxime (**E-4**) as a mixture of isomers.

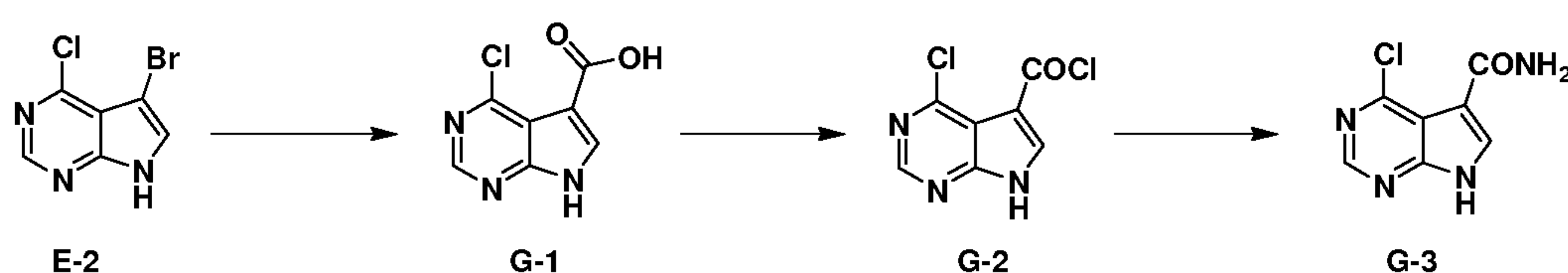
[00375] To a suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde oxime (**E-4**) (865 mg, 4.40 mmol, 1.0 eq) in DCM (20 mL), thionyl chloride (3.1 mL, 43.7 mmol, 10.0 eq) is added and the resulting mixture is stirred at RT overnight. The reaction mixture is concentrated *in vacuo*. The residue is suspended in water (60 mL) and saturated aqueous NaHCO₃ is added to adjust the pH to 4. The solid is collected by filtration, rinsed with water followed by ethyl acetate to afford a first portion of product. The filtrate is then extracted with ethyl acetate (50 mL × 3). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue is combined with the first portion of product. The product is then re-crystallized in ethyl acetate/hexanes (1:1) and dried *in vacuo* to afford the final product, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (**E-5**) as a pale solid.



Method F

General method for the synthesis of 4-chloro-5-fluoro-7H-pyrrolo[2,3-d]pyrimidine:

[00376] 4-Chloro-7H-pyrrolo[2,3-d]pyrimidine (**E-1**) (5.01 g, 32.6 mmol, 1 eq) and Selectfluor (17.32 g, 48.9 mmol, 1.5 eq) are dissolved in a mixture of dry acetonitrile (250 mL) and AcOH (50 mL). The resulting mixture is stirred at 70 °C under argon for 16 h. The mixture is concentrated *in vacuo*. The residue is dissolved in a mixture of DCM-ethyl acetate (1:1, 50 mL) and filtered through celite. The filtrate is concentrated *in vacuo* and the residue is purified by flash chromatography on silica gel (0-0.7% MeOH-DCM) to afford the product, 4-chloro-5-fluoro-7H-pyrrolo[2,3-d]pyrimidine (**F-1**) as a pink solid.

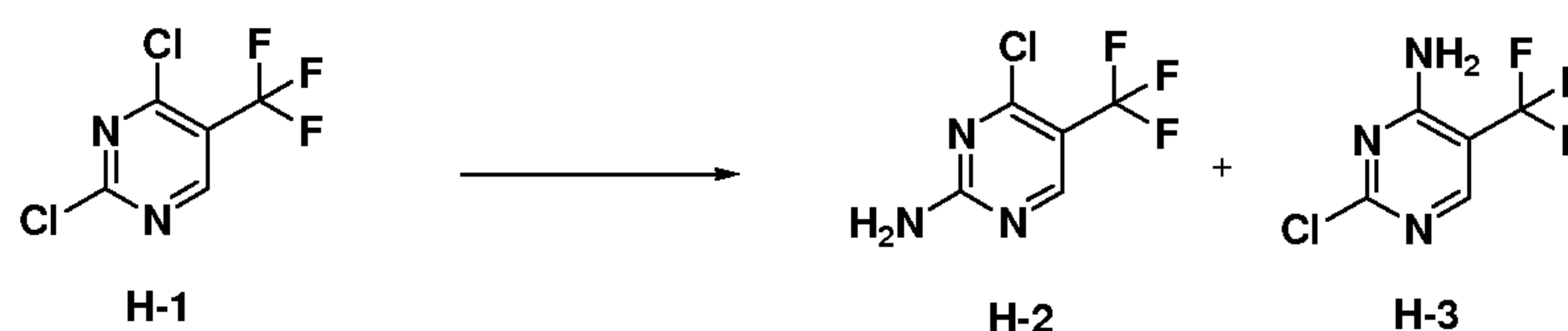


Method G

General method for the synthesis of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide:

[00377] To a mixture of 5-bromo-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**E-2**) (6.24 g, 26.8 mmol, 1.0 eq) in anhydrous THF (100 mL) at 78 °C under argon, n-BuLi solution (2.5 M in THF, 23.6 mL, 59.0 mmol, 2.2 eq) is added dropwise (over 30 min). The reaction mixture is then stirred at -78 °C for 1 h and then dry ice (300 g) is added in portions under an argon atmosphere. The resulting mixture is allowed to warm to RT and then stirred at RT overnight. The reaction mixture is then diluted with H₂O (200 mL) and extracted with ethyl acetate (50 mL × 4). The aqueous layer is acidified with con. HCl to adjust the pH to 3-4. The precipitate is then collected by filtration, rinsed with H₂O (30 mL) and dried *in vacuo* to afford the product, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylic acid (**G-1**).

[00378] To a stirred suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylic acid (**G-1**) (3.11 g, 15.7 mmol, 1.0 eq) and a catalytic amount of DMF in a mixture of DCM (40 mL) and THF (40 mL) at RT, oxalyl dichloride (2.0 mL, 23.5 mmol, 1.5 eq) is added dropwise. The resulting mixture is stirred for 2 h and then concentrated *in vacuo*. The residue (**G2**) is dissolved in DCM (50 mL) and the resulting solution is added dropwise to saturated aqueous ammonium hydroxide (200 mL) at RT. The resulting mixture is stirred for 30 min and then filtered. The filter cake is then rinsed with H₂O (30 mL × 2). The filtrate is acidified with con. HCl to adjust the pH to 4-5. The solid is collected by filtration, rinsed with water and dried *in vacuo* to afford the product, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide (**G-3**).

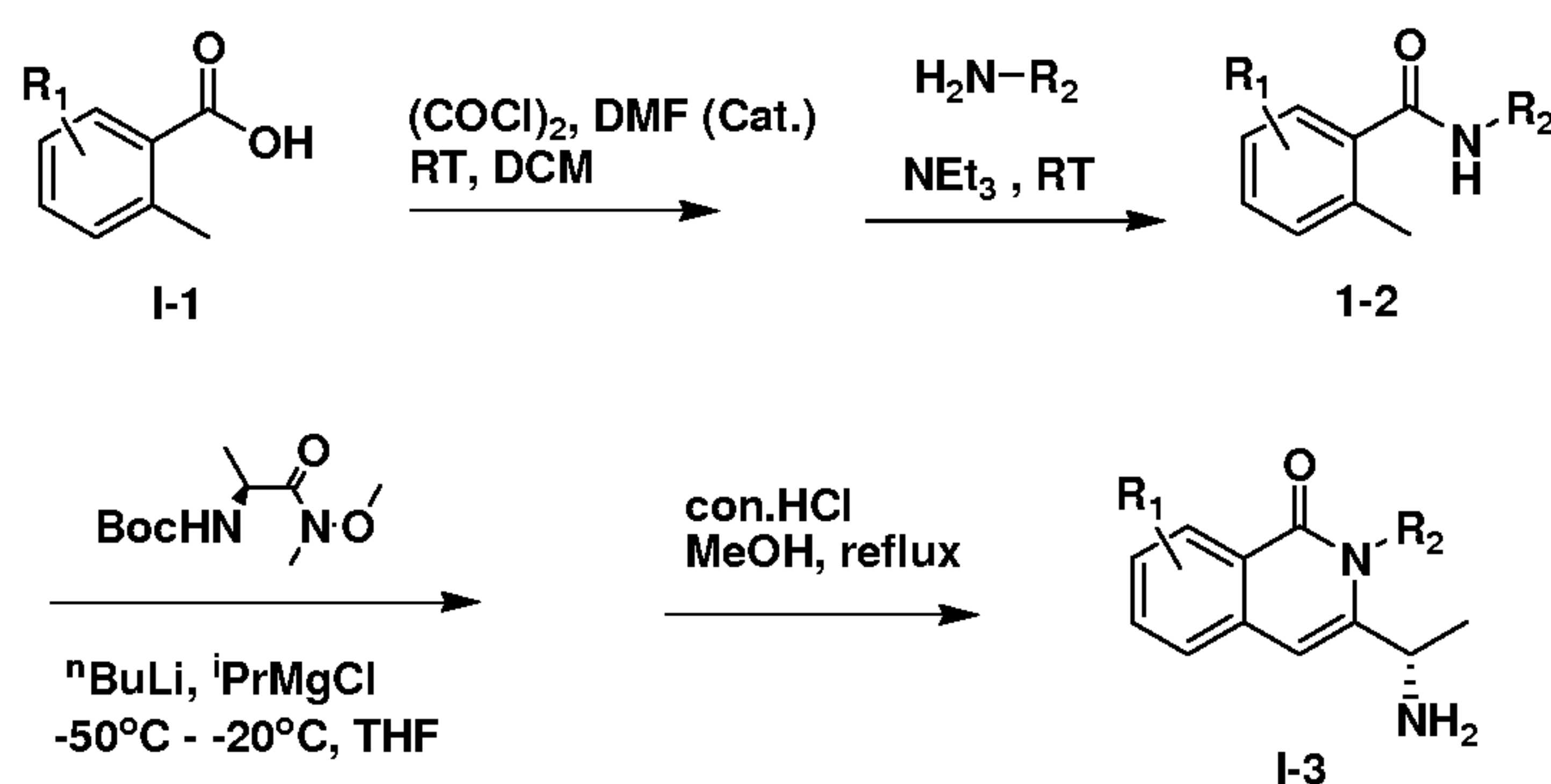


Method H

General method for the synthesis of 4-chloro-5-(trifluoromethyl)pyrimidin-2-amine:

[00379] Ammonia in methanol (7N solution, 15 mL) is added dropwise to the stirred neat 2,4-dichloro-5-(trifluoromethyl)pyrimidine (**H-1**) (5.0 g, 23.04 mmol) under argon, and the resulting mixture is stirred at RT for 2 h. The reaction mixture is quenched with water and then extracted with ethyl acetate (200 mL × 2). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash chromatography on silica gel (0-20% ethyl acetate-hexanes) to afford the product, 4-chloro-5-(trifluoromethyl)pyrimidin-2-amine (**H-2**) as a white solid. The regional-isomer, 2-chloro-5-(trifluoromethyl)pyrimidin-4-amine (**H-3**) can also be isolated as a white solid.

General method for the synthesis of amine cores:



Method I

General conditions for the preparation of (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones:

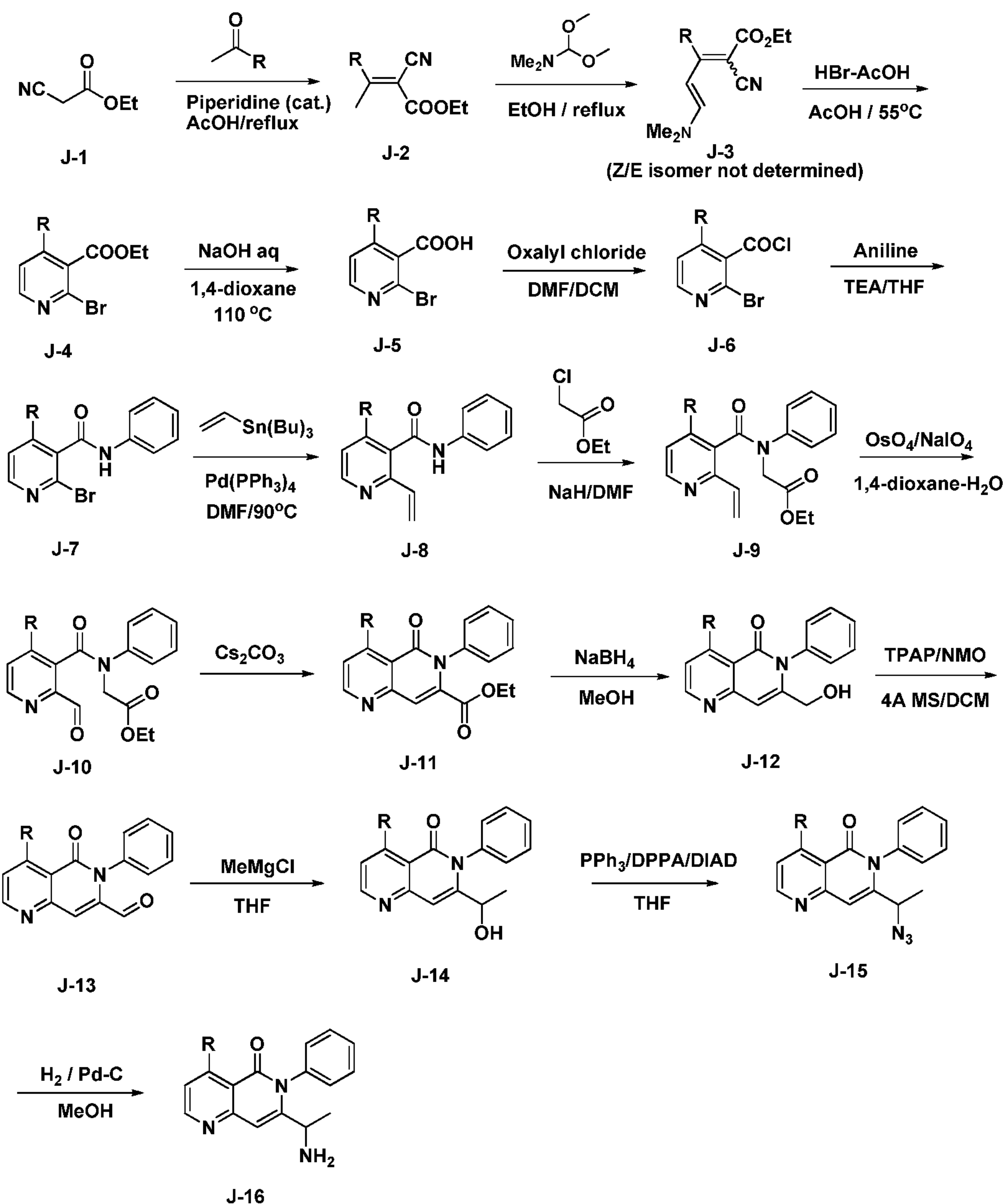
[00380] To a stirred mixture of a given o-methylbenzoic acid (**I-1**) (1.5 mol, 1 eq) and DMF (2 mL) in DCM (1275 mL) at RT, oxalyl chloride (1.65 mol, 1.1 eq) is added over 5 min and the resulting mixture is stirred at RT

for 2 h. The mixture is then concentrated *in vacuo*. The residue is dissolved in DCM (150 mL) and the resulting solution (solution A) is used directly in the next step.

[00381] To a stirred mixture of aniline (1.58 mol, 1.05 eq) and triethylamine (3.15 mol, 2.1 eq) in DCM (1350 mL), the above solution A (150 mL) is added dropwise while the reaction temperature is maintained between 25 °C to 40 °C by an ice-water bath. The resulting mixture is stirred at RT for 2 h and then water (1000 mL) was added. The organic layers are separated and washed with water (1000 mL x 2), dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo*. The product is suspended in n-heptanes (1000 mL) and stirred at RT for 30 min. The precipitate is collected by filtration, rinsed with heptanes (500 mL) and further dried *in vacuo* to afford the amide (**I-2**) as a yellow solid.

[00382] To a stirred mixture of amide (**I-2**) (173 mmol, 1 eq) in anhydrous THF (250 mL) at -30 °C under an argon atmosphere, a solution of n-butyllithium in hexanes (432 mol, 2.5 eq) is added dropwise over 30 min while keeping inner temperature between -30 °C and -10 °C. The resulting mixture is then stirred at -30 °C for 30 min.

[00383] To a stirred mixture of (S)-tert-butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (260 mmol, 1.5 eq) in anhydrous THF (250 mL) at -30 °C under an argon atmosphere, a solution of isopropylmagnesium chloride in THF (286 mmol, 1.65 eq) is added dropwise over 30 min while keeping inner temperature between -30 °C and -10 °C. The resulting mixture is stirred at -30 °C for 30 min. This solution is then slowly added to above reaction mixture while keeping inner temperature between -30 °C and -10 °C. The resulting mixture is stirred at -15 °C for 1 h. The reaction mixture is quenched with water (50 mL) and then acidified with conc. HCl at -10 °C - 0 °C to adjust the pH to 1-3. The mixture is allowed to warm to RT and concentrated *in vacuo*. The residue is dissolved in MeOH (480 mL), and then conc. HCl (240 mL) is added quickly at RT. The resulting mixture is stirred at reflux for 1 h. The reaction mixture is concentrated *in vacuo* to reduce the volume to about 450 mL. The residue is extracted with a 2:1 mixture of heptane and ethyl acetate (500 mL x 2). The aqueous layer is basified with concentrated ammonium hydroxide to adjust the pH value to 9-10 while keeping the inner temperature between -10 °C and 0 °C. The mixture is then extracted with DCM (300 mL x 3), washed with brine, dried over MgSO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue is dissolved in MeOH (1200 mL) at RT. To this solution, D- (-) - tartaric acid (21g, 140 mmol, 0.8 eq) is added in one portion at RT. After stirring at RT for 30 min, white solid precipitates out and the mixture is slurried at RT for 10 h. The solid is collected by filtration and rinsed with MeOH (50 mL x 3). The collected solid is suspended in water (500 mL) and then neutralized with concentrated ammonium hydroxide solution at RT to adjust the pH to 9-10. The mixture is extracted with DCM (200 mL x 3). The combined organic layers are washed with brine, dried over MgSO₄ and filtered. The filtrate is concentrated *in vacuo* to afford (S)-3-(1-aminoethyl)-isoquinolin-1(2H)-ones (**I-3**).



Method J

General conditions for the preparation of 7-(1-aminoethyl-6-phenyl-1,6-naphthyridin-5(6H)-ones:

[00384] To a mixture of ethyl 2-cyanoacetate (**J-1**) (45.2 g, 400 mmol) and a given ketone (800 mmol) in glacial acetic acid (50 mL), piperidine (2 mL, 20 mmol) is added and the resulting mixture is stirred at reflux for 24 h. The reaction mixture is allowed to cool to RT, and then concentrated *in vacuo*. The residue is diluted with water (200 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layers are washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (0-2% EA/PE) to afford the product (**J-2**) as a white solid.

[00385] To a solution of (**J-2**) (285 mol) in absolute EtOH (300 mL), N,N-dimethylformamide dimethyl acetal (37.3 g, 313 mmol) is added dropwise and the resulting mixture is stirred at reflux 6 h. The mixture is allowed to

cool to RT, and concentrated *in vacuo* to afford the product (**J-3**) in as a yellow solid. This material is used in the next step without further purification.

[00386] Dienoate (**J-3**) (148 mmol) is dissolved in AcOH (120 mL) and the mixture is stirred at 40 °C. A solution of 45% HBr-AcOH (120 mL) is added dropwise, and then the mixture is stirred at 55 °C for 2 h. The mixture is allowed to cool to RT, poured onto ice, neutralized with solid Na₂CO₃, and extracted with ethyl acetate (150 mL x 3). The combined organic layers are washed with brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by flash column chromatography on silica gel (5-20% EA/PE) to afford the product (**J-4**) as a yellow oil.

[00387] To a solution of 4-substituted ethyl 2-bromolnicotinate (**J-4**) (52 mmol) in 1,4-dioxane (15 mL), a solution of NaOH (8.0 g, 200 mmol) in H₂O (15 mL) is added and the resulting mixture is stirred at reflux for 12 h. The mixture is allowed to cool to RT, diluted with H₂O, and washed with ethyl acetate (30 mL x 3). The aqueous layer is acidified with concentrated hydrochloric acid to pH to 1, and then extracted with ethyl acetate (50 mL x 3). The combined organic layers are washed with brine (25 mL), dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford the product nicotinic acid (**J-5**) as a white solid.

[00388] To a solution of (**J-5**) (60 mmol) and DMF (3 drops) in CH₂Cl₂ (150 mL), oxalyl chloride (11.4 g, 90 mmol) is added dropwise and the resulting mixture is stirred at RT for 2 h. The reaction mixture is concentrated *in vacuo* to afford the nicotinoyl chloride (**J-6**) as a yellow oil.

[00389] To a solution of nicotinoyl chloride (**J-6**) (23.26 mmol) in anhydrous THF (70 mL) at 0 °C, aniline (25.59 mmol) and triethylamine (3.6 mL, 25.59 mmol) is added slowly. The resulting mixture is stirred at RT for 1 h. The reaction mixture is quenched with water and extracted with ethyl acetate. The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford the amide (**J-7**) as a tan solid.

[00390] To a solution of nicotinamide (**J-7**) (6.77 g, 23.25 mmol) and tributyl(vinyl)tin (10.2 mL, 34.88 mmol) in DMF (250 mL) under argon, Pd(PPh₃)₄ (1.07 g, 0.93 mmol) is added and the resulting mixture is stirred at 90 °C for 1 h. The mixture is allowed to cool to RT, quenched with water and extracted with ethyl acetate (100 mL x 2). The organic layer is washed with brine, dried over Na₂SO₄, and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by ISCO (silica gel cartridge, 0-60% EA/Hexanes) to afford the vinylnicotinamide (**J-8**) as a red solid.

[00391] To a solution of 2-vinylnicotinamide (**J-8**) (30.21 mmol) in anhydrous DMF (100 mL) at RT, sodium hydride (60% in mineral oil, 6.04 g, 151.08 mmol) is slowly added in portions. The resulting mixture is stirred at RT for 45 min. To this mixture, ethyl chloroacetate (16 mL, 151.08 mmol) is added dropwise and the resulting

mixture is stirred for 2 h. The reaction is quenched with water and extracted with ethyl acetate. The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford (**J-9**).

To a solution of (**J-9**) (17.36 mmol) in 1,4-dioxane-H₂O (3:1, 150 mL) at RT, osmium tetroxide (4% wt in H₂O, 2.72 mL, 0.35 mmol) is added and the resulting mixture is stirred at RT for 30 min. To this mixture, sodium periodate (14.85 g, 69.44 mmol) is added and the resulting mixture is stirred at RT for 16 h. The mixture is filtered through celite and the filtrate is extracted with ethyl acetate (2 x 100 mL). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford the product (**J-10**) as a tan/yellow solid.

[00392] To a solution of (**J-10**) (17.35 mmol) in EtOH-ethyl acetate (3:1, 200 mL) is added cesium carbonate (6.22 g, 19.09 mmol) and the resulting mixture is stirred at 50 °C for 2 h. The mixture is allowed to cool to RT and filtered through celite. The filtrate is concentrated *in vacuo* and the residue is partitioned between water and ethyl acetate. The organic layer is washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by ISCO (silica gel cartridge, 0-50% EA/Hex) to afford the product (**J-11**) as an off white solid.

[00393] To a solution of (**J-11**) (6.97 mmol) in anhydrous MeOH (40 mL), sodium borohydride (2.62 g, 69.34 mmol) is added in two portions. The mixture is stirred at RT for 16 h, quenched with water and extracted with ethyl acetate. The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford product (**J-12**).

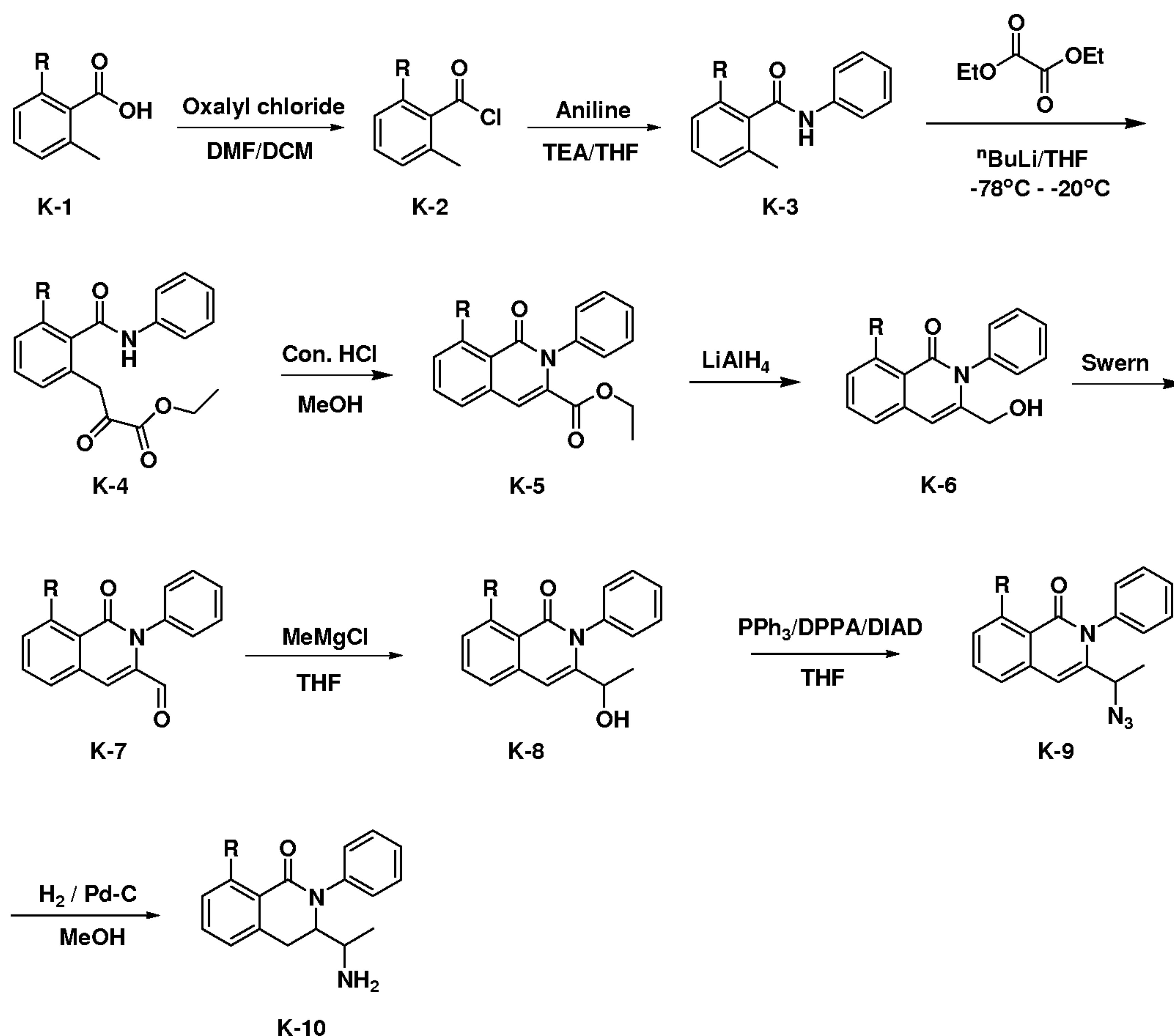
[00394] To a solution of (**J-12**) (13.61 mmol) in anhydrous DCM (50 mL) at RT, 4Å molecular sieves (powder, 3.62 g), NMO (1.59 g, 13.6 mmol) and TPAP (tetrapropylammonium perruthenate) (119.5 mg, 0.34 mmol) are added sequentially. The resulting mixture is stirred at RT for 16 h (overnight). The mixture is filtered through a celite/silica gel pad and the filtrate is concentrated *in vacuo* to afford the product (**J-13**).

[00395] To a solution of (**J-13**) (6.80 mmol) in anhydrous THF (100 mL) at -78 °C under argon, methylmagnesium chloride solution (3.0 M in THF, 6.8 mL, 20.41 mmol) is added dropwise and the resulting mixture was stirred from -78 °C to RT for 2 h. An additional amount of methylmagnesium chloride solution (2 mL) is added to bring reaction to completion. The reaction mixture is quenched with water (150 mL) and extracted with ethyl acetate (200 mL x 2). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by ISCO (silica gel cartridge, 0-10% MeOH-DCM) to afford the product (**J-14**) as a white solid.

[00396] To a solution of (**J-14**) (4.28 mmol) in anhydrous THF (25 mL) at 0 °C under argon, triphenyl phosphine (2.24 g, 8.56 mmol) is added and the resulting mixture was stirred for 5 min. To this mixture, diphenyl phosphoryl azide (2.31 mL, 10.7 mmol) is added followed by slow addition of diisopropyl azodicarboxylate (1.69 mL, 8.56 mmol) over 20 min period of time. The resulting mixture is stirred from 0 °C to RT for 2 h. The mixture is then partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over Na₂SO₄ and filtered. The

filtrate is concentrated *in vacuo* and the residue is purified by ISCO (silica gel cartridge, 0-70% EA/Hex) to afford the product, (**J-15**) as a white solid.

[00397] A mixture of (**J-15**) (3.08 mmol) and palladium (10% weight on carbon, 190 mg, 20% of starting material by weight) in anhydrous MeOH (25 mL) are degassed and flushed with hydrogen (three cycles). The reaction mixture is stirred under a hydrogen atmosphere (hydrogen balloon) at RT for 30 min. The mixture is then filtered through celite over a Buchner funnel and rinsed with ethyl acetate. The filtrate is concentrated *in vacuo* to afford the product (**J-16**) as an off-white solid.



Method K

General conditions for the preparation of 3-(1-aminoethyl)-2-phenyl-3,4-dihydroisoquinolin-1(2H)-ones:

[00398] A mixture of benzoic acid (**K-1**) (400 mmol), oxalyl chloride (101 g, 800 mmol) and DMF (0.2 ml) in DCM (400 mL) is stirred at RT for 2 h. The mixture is concentrated *in vacuo* to afford the acid chloride (**K-2**) as a yellow oil. The product obtained is used directly in the next step without purification.

[00399] A mixture of aniline (420 mmol) and triethylamine (71 g, 700 mmol) in DCM (300 mL) is stirred at RT for 10 min. To this mixture, acid chloride (**K-2**) (64 g, 400 mmol) is added dropwise, and the resulting mixture is stirred at RT for 30 min. The reaction mixture is poured into water (300 mL) and extracted with DCM (200 mL x 3), dried over anhydrous Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford the product. The product is

suspended in isopropyl ether (300 mL), stirred at reflux for 30min, and then cooled to 0 - 5°C. The precipitate is collected by filtration and further dried *in vacuo* to afford the product amide (**K-3**) as a yellow solid.

[00400] To a stirred solution of amide (**K-3**) (0.1 mol, 1.0 eq) in anhydrous THF (225 mL) at -78 °C under an argon atmosphere, a solution of n-butyllithium in hexanes (120 mL, 2.5 M, 0.3 mol, 3 eq) is added dropwise over 1 h period of time while keeping inner temperature between -78 °C to -50 °C. The resulting mixture is stirred at -70 °C for 1 h, and then diethyl oxalate (17.5 g, 0.12 mol, 1.2 eq) is quickly added (with an increase in temperature to -20 °C upon addition). The mixture is stirred at -50 °C for 10 min, and then quenched with water (100 mL). The inorganic salt is removed by filtration, and the filtrate is extracted with ethyl acetate (100 mL x 2). The combined organic layers are washed with brine (100 mL), dried over MgSO₄ and filtered. The filtrate is concentrated *in vacuo* to afford the product as a semi-solid. The product is slurried in isopropyl ether (100 mL) at RT for 10 min. The solid is collected by filtration and further dried *in vacuo* to afford the product (**K-4**) as a white solid. The product obtained is used directly in the next step.

[00401] Compound (**K-4**) (88 mmol, 1eq) is dissolved in HCl/MeOH (10 M, 100 mL, 10 mL/ 1 g of **K-4**), and the resulting mixture is stirred at reflux for 1 h. The reaction mixture is concentrated *in vacuo*, and the residue is slurried in ethyl acetate (100 mL) at RT for 30 min. The solid is collected by filtration, rinsed with ethyl acetate (50 mL x 3), and further dried *in vacuo* to afford the product (**K-5**) as a white solid.

[00402] To a stirred suspension of lithium aluminum hydride (15.6 g, 410 mmol) in anhydrous THF (500 mL) at -78 °C under a nitrogen atmosphere, (**K-5**) (137 mmol) is slowly added over a 10 min period of time. The resulting mixture is allowed to warm to -30 °C and stirred for 30 min (TLC shows the completion of the reaction). Then the mixture is cooled to -78 °C, and quenched carefully with water (100 mL). The mixture is allowed to warm to RT, filtered through silica gel (20 g), and the filtrate is concentrated *in vacuo*. The product is poured into H₂O (200 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layers are washed with brine (100 mL), dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo*. The product is suspended in ethyl acetate (30 mL) and stirred for 10 min. The solid is collected by filtration and further dried *in vacuo* to afford the product (**K-6**) as a white solid.

[00403] To a stirred solution of oxalyl chloride (2.0 M in DCM, 12.8 mL) in anhydrous DCM (100 mL) at -78 °C under argon, DMSO (4.82 mL, 68 mmol) is slowly added and the resulting mixture is stirred at -78 °C for 50 min. To this reaction mixture, a solution of (**K-6**) (17 mmol) in DCM (50 mL) is added slowly. The resulting mixture is stirred at -78 °C for 1 h and then triethylamine (11.8 mL, 85 mmol) is added. The mixture is stirred from -78 °C to RT for 1 h and quenched with water (100 mL). The organic layer is separated and the aqueous layer is extracted with DCM (50 mL x 2). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford the product, (**K-7**).

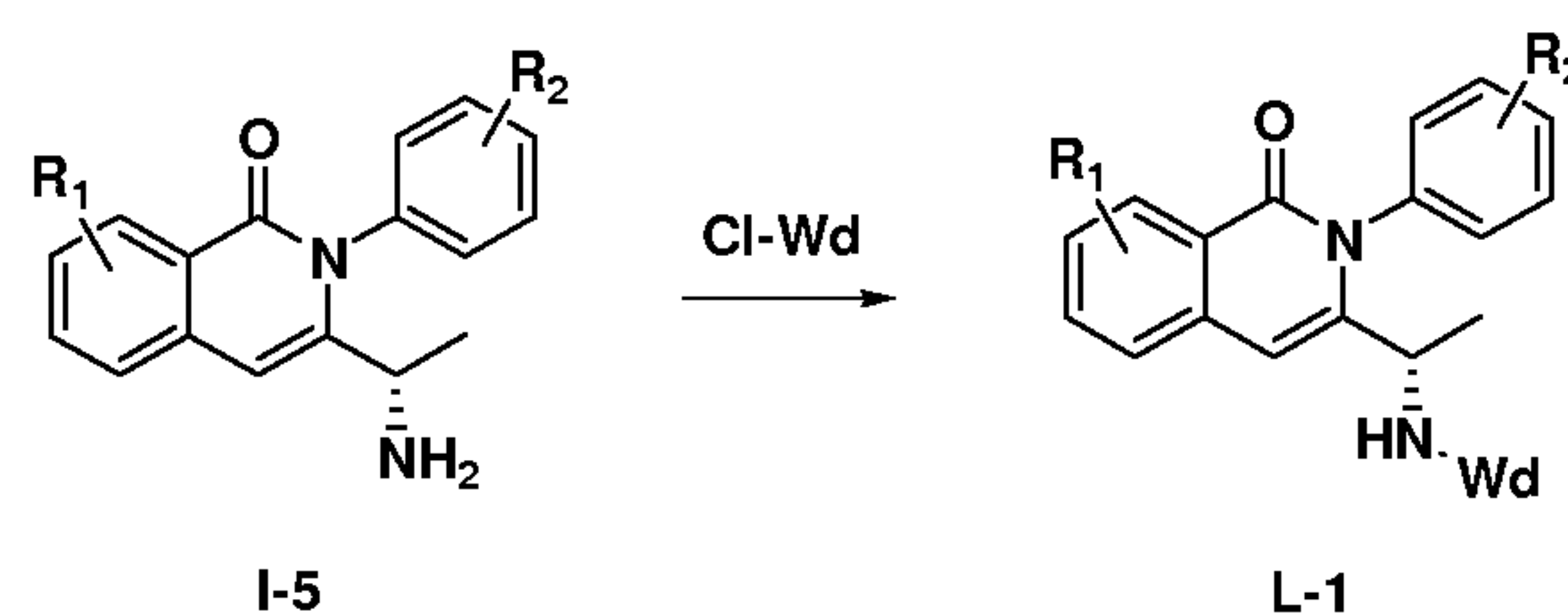
[00404] To a solution of (**K-7**) (17.0 mmol) in anhydrous THF (120 mL) at -78 °C under argon, methylmagnesium chloride solution (3.0 M in THF, 14.9 mL, 44.2 mmol) is added dropwise and the resulting mixture is stirred at -78 °C for 3 h. The mixture is quenched with saturated NH₄Cl aqueous solution (50 mL) and extracted with

ethyl acetate (200 mL x 2). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue was triturated with 20% ethyl acetate-hexanes to afford the product (**K-8**) as a yellowish solid.

[00405] To a solution of (**K-8**) (7.88 mmol) in anhydrous THF (60 mL) at 0 °C under argon, triphenyl phosphine (3.1 g, 11.81 mmol) is added and the resulting mixture was stirred for 5 min. To this mixture, diphenyl phosphoryl azide (3.41 mL, 15.76 mmol) is added followed by slow addition of diisopropyl azodicarboxylate (2.32 mL, 11.81 mmol) over 20 min. The resulting mixture is stirred from 0 °C to RT for 5 h. The mixture is then partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* and the residue is purified by ISCO (silica gel cartridge, 0-100% ethyl acetate/hexanes) to afford the product azide (**K-9**).

[00406] A mixture of azide (**K-9**) (1.1 mmol) and palladium (10% weight on carbon, 100 mg, 30% of starting material by weight) in anhydrous methanol (20 mL) is degassed and flushed with hydrogen (three cycles). The reaction mixture is stirred under a hydrogen atmosphere (hydrogen balloon) at RT for 24 h. The mixture is filtered through celite over a Buchner funnel and rinsed with ethyl acetate. The filtrate is concentrated *in vacuo* to afford the amine (**K-10**) as a yellow solid.

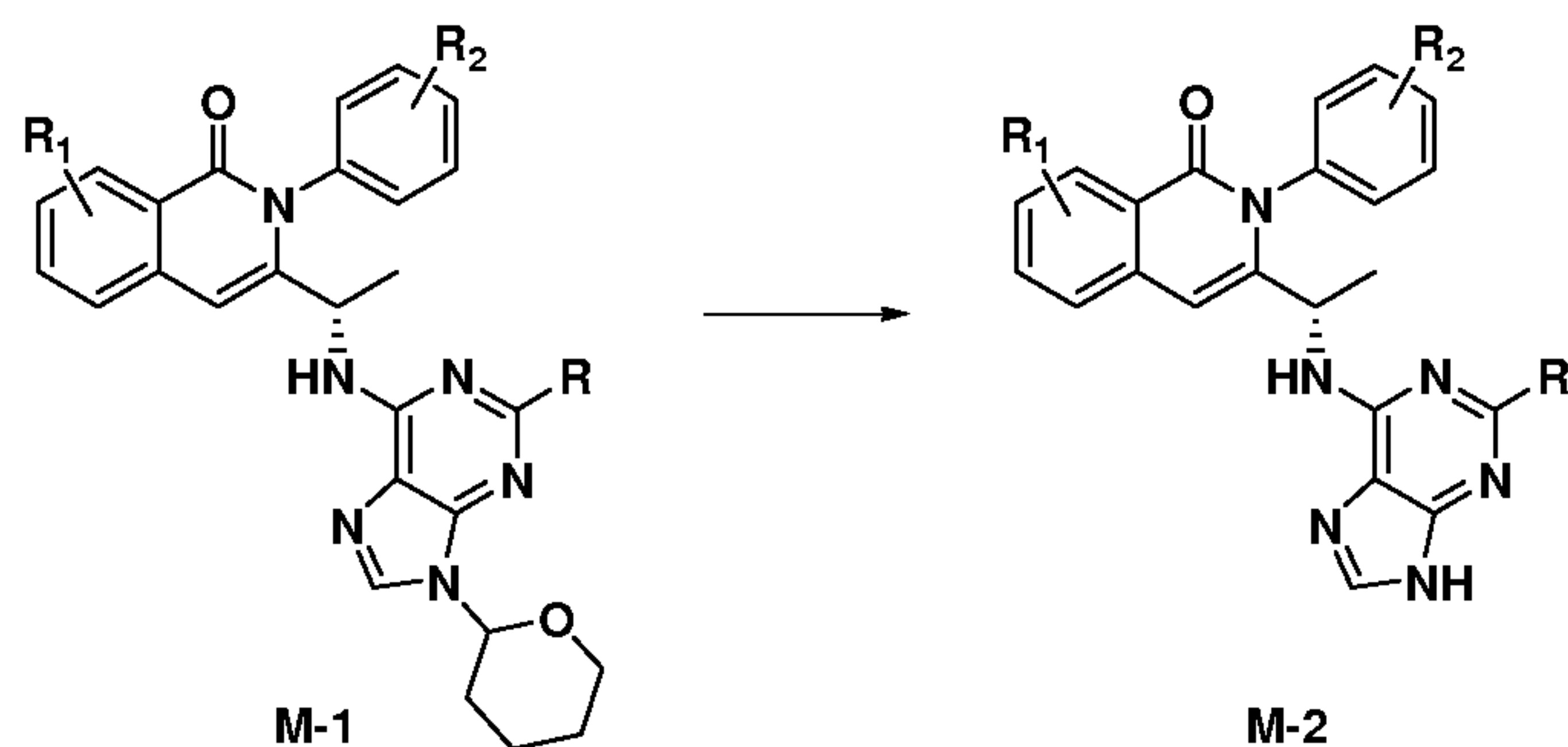
General method for the capping of amine cores with Cl-W_d:



Method L

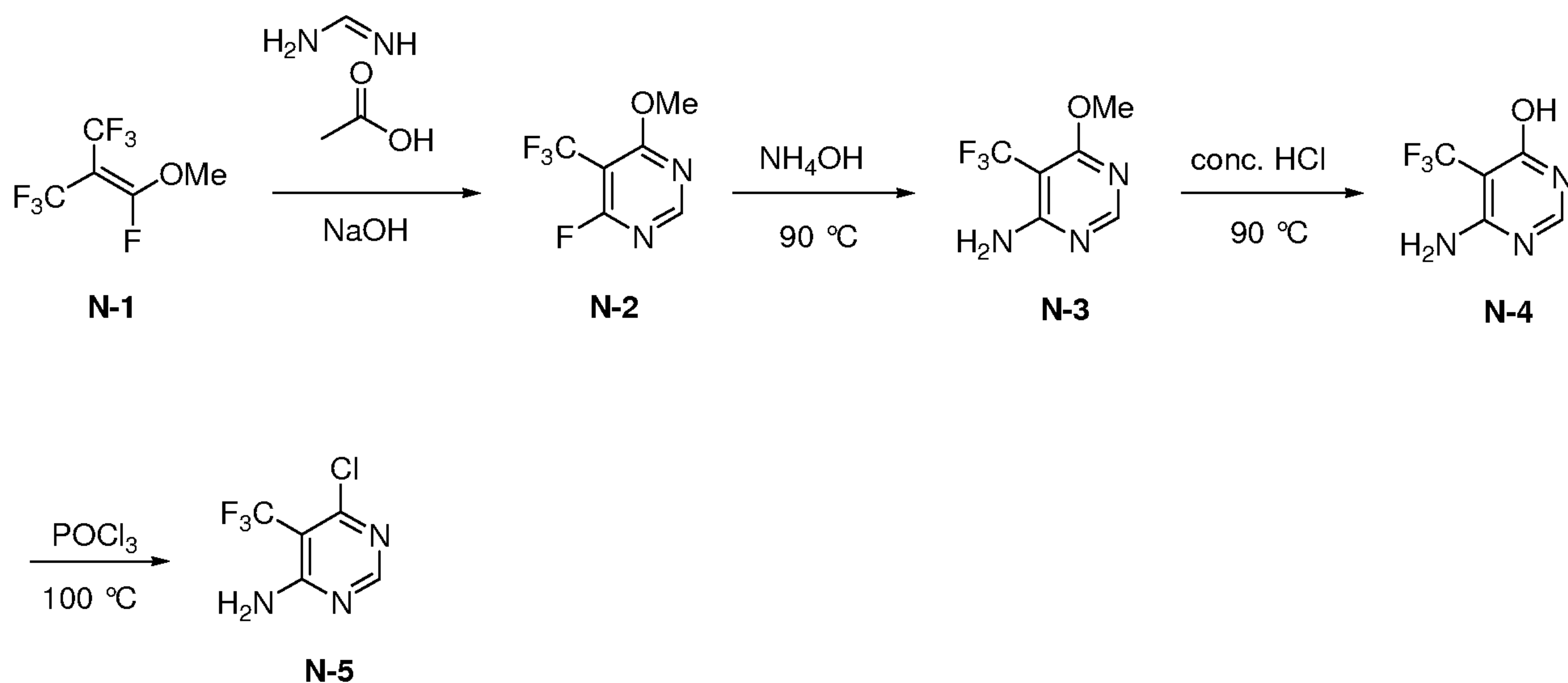
[00407] An (S)-3-(1-Aminoethyl)-isoquinolin-1(2H)-one (**I-5**) (115 mmol, 1.0 eq), **Cl-W_d** (173 mmol, 1.5 eq) and triethylamine (344 mmol, 3.0 eq) are dissolved in n-BuOH (350 mL) and the mixture is stirred at reflux for 16 h. The reaction mixture is cooled to RT and concentrated *in vacuo*. The residue is slurried in a mixture of H₂O (200 mL) and ethyl acetate (100 mL) and stirred at RT for 30 min. The solid is then collected by filtration, rinsed with ethyl acetate (25 mL) and dried *in vacuo* to afford the product (**L-1**).

[00408] General method for the elaboration of W_d heterocycles:



Method M

[00409] A mixture of tetrahydro-2H-pyran-intermediate (**M-1**) in ethanol (4 vol)/water (2 vol) followed by addition of conc. HCl solution (2 vol) is stirred at RT for 1 h. The resulting mixture is diluted with cold water, neutralized with saturated aqueous NaHCO₃ to adjust the pH to 8-9 and then extracted with DCM (20 vol x 3). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo*. The resultant residue is suspended in petroleum ether with ultrasonic vibration for 5 min. The solid is collected by filtration and dried *in vacuo* to afford the product (**M-2**).



Method N

[00410] General method for the synthesis of 6-chloro-5-(trifluoromethyl)pyrimidin-4-amine:

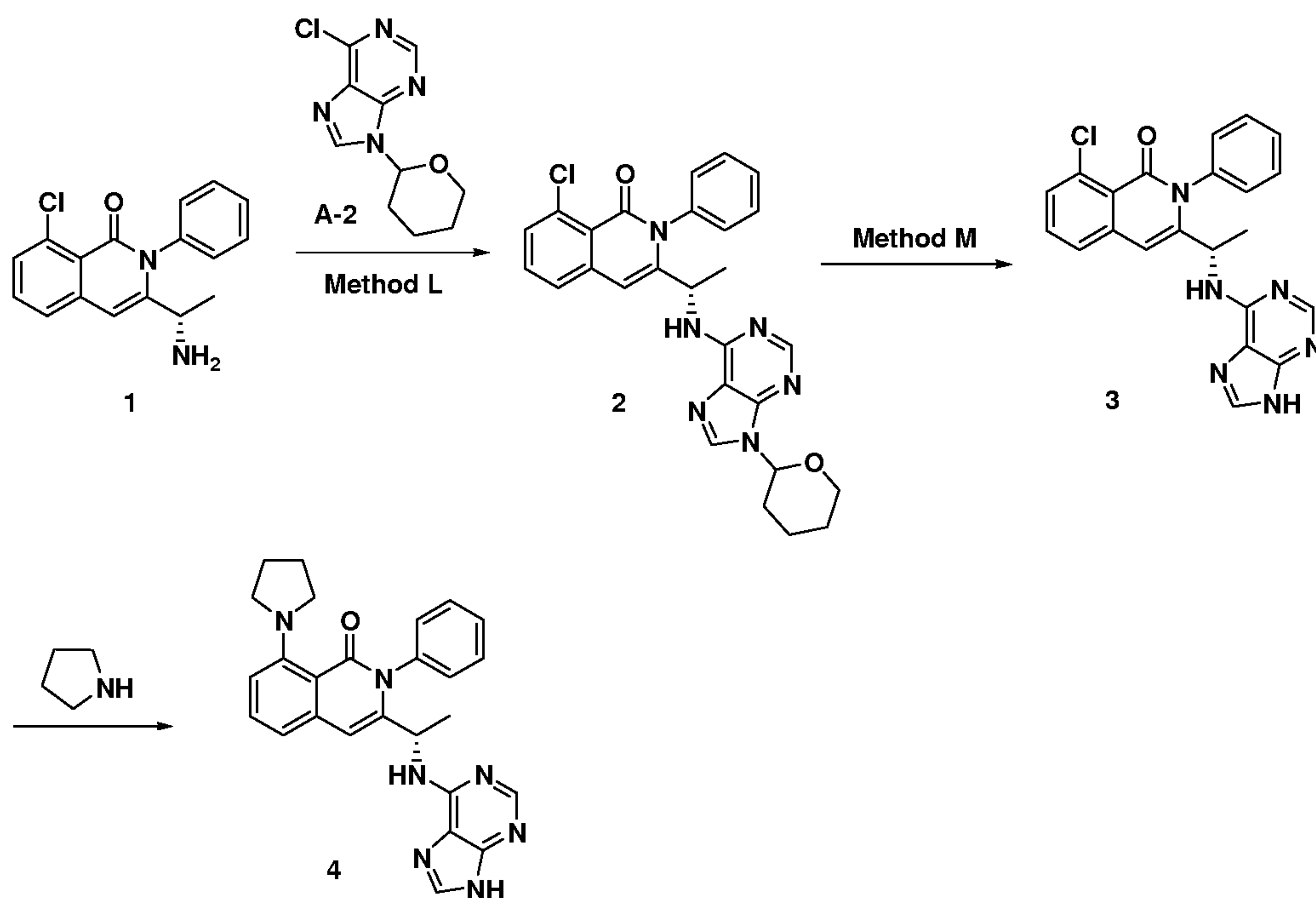
[00411] To a rapidly stirred mixture of 1,1,1,3-tetrafluoro-2-(trifluoromethyl)-4-oxapent-2-ene (**N-1**) (10.0 g, 47.15 mmol) and formamidine acetate (7.37 g, 70.73 mmol) in a mixture of water (50 mL) and dichloromethane (50 mL) at 0 °C, a solution of sodium hydroxide (7.54 g, 189 mmol) in water (40 mL) is added dropwise and the resulting mixture is stirred for 30 min after complete addition. The dichloromethane layer is separated, washed with 1M aqueous HCl solution and water, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford 4-fluoro-6-methoxy-5-(trifluoromethyl)pyrimidine (**N-2**) as a yellow solid. The product is used directly in the next step without further purification.

[00412] To a solution of 4-fluoro-6-methoxy-5-(trifluoromethyl)pyrimidine (**N-2**) (1.10 g, 5.61 mmol) in n-butanol (4 mL) in a pressure vessel, ammonium hydroxide (5 mL) is added and the resulting mixture is stirred at 90 °C for 1 h. The mixture is allowed to cool to RT, quenched with water, and extracted with ethyl acetate (100 mL x 2). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford the product 6-methoxy-5-(trifluoromethyl)pyrimidin-4-amine (**N-3**) as an off-white solid. The product is used directly in the next step without further purification.

[00413] To a solution of 6-methoxy-5-(trifluoromethyl)pyrimidin-4-amine (**N-3**) (420 mg, 2.18 mmol) in 1,4-dioxane (10 mL), concentrated HCl (1.81 mL, 21.8 mmol) is added and the resulting mixture is stirred at 90 °C for 3 h. The mixture is allowed to cool to RT and then concentrated *in vacuo* to afford the product, 6-amino-5-(trifluoromethyl)pyrimidin-4-ol (**N-4**) as yellowish solid.

[00414] The mixture of 6-amino-5-(trifluoromethyl)pyrimidin-4-ol (**N-4**) (300 mg, 1.66 mmol) in POCl₃ (8 mL) in a pressure vessel is stirred at 100 °C for 1 h. The mixture is allowed to cool to RT and concentrated *in vacuo*. The residue is taken up in water (20 mL), basified with saturated NaHCO₃ aqueous solution to pH = 9 and then extracted with DCM (30 mL x3). The combined organic layers are washed with brine, dried over Na₂SO₄ and filtered. The filtrate is concentrated *in vacuo* to afford the desired product, 6-chloro-5-(trifluoromethyl)pyrimidin-4-amine (**N-5**) as a yellow solid.

Example 1

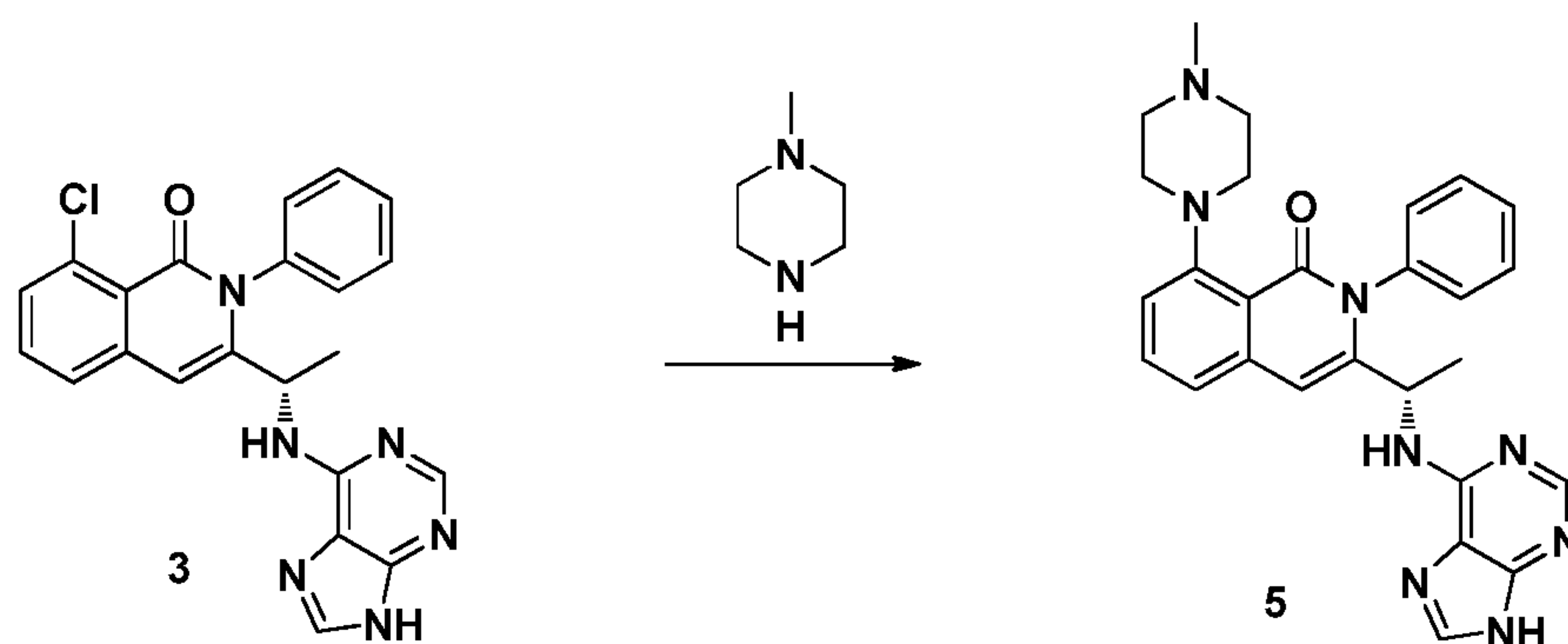


[00415] Isoquinolinone **4** was prepared from compound **1** through a 3-step sequence. Compound **1** was prepared using Method I and was then converted to **2** by coupling with **A-2** according to Method L. Compound **2** was

converted to compound **3** according to Method M. Compound **4** was then prepared according to the following procedure:

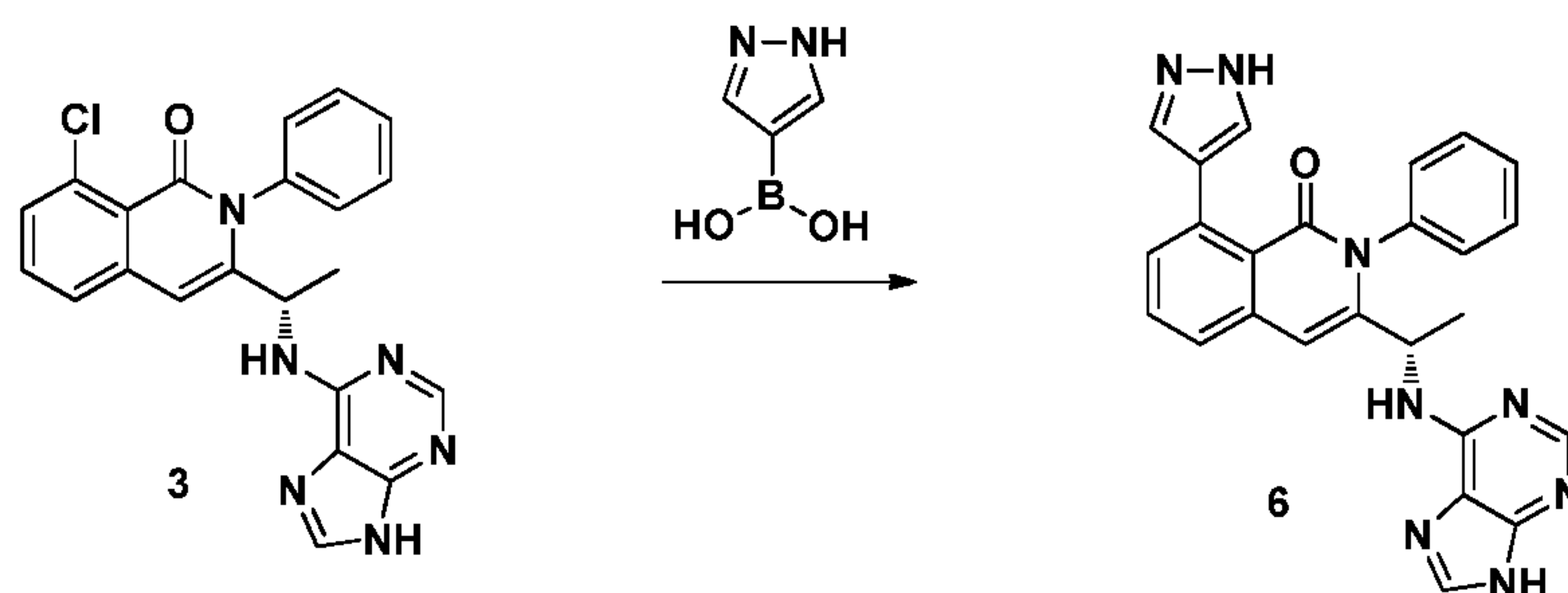
[00416] To a solution of (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (**3**) (100 mg, 0.24 mmol) in 1,4-dioxane (3 mL) in a sealed tube, pyrrolidine (1.25 mL, excess amount) was added and the resulting mixture was stirred at 135 °C for 17 h. The mixture was allowed to cool to RT, partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-10% MeOH-DCM) to afford the product, (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-2-phenyl-8-(pyrrolidin-1-yl)isoquinolin-1(2H)-one (**4**) as an off-white solid. ESI-MS *m/z*: 452.2 [M+H]⁺.

Example 2



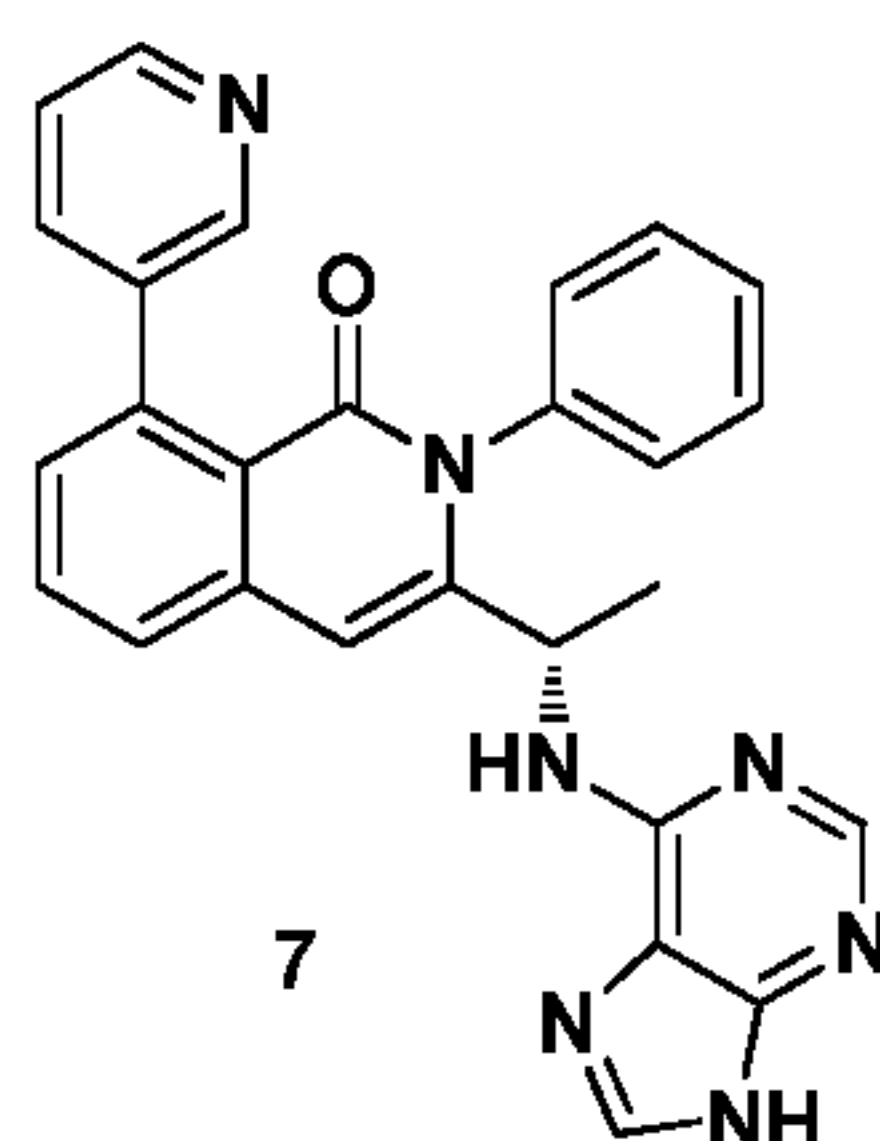
[00417] Isoquinolinone **5** was prepared from compound **3** according to the following procedure:

[00418] (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (**3**) (200 mg, 0.48 mmol) and 1-methylpiperazine (0.267 mL, 2.4 mmol) were dissolved in anhydrous NMP (8 mL) and the resulting solution was degassed and back-filled with argon (two cycles). To this mixture, Na₂CO₃ (102 mg, 0.96 mmol), Pd(OAc)₂ (11 mg, 0.048 mmol) and di-(1-adamantyl)-n-butylphosphine (52 mg, 0.144 mmol) were added sequentially. The resulting mixture was degassed and back-filled with argon (two cycles) and then stirred at 160 °C under argon for 16 h. The reaction mixture was allowed to cool to RT and then partitioned between water and ethyl acetate. The organic layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-10% MeOH-DCM with 0.1% TEA) to afford the product, (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-8-(4-methylpiperazin-1-yl)-2-phenylisoquinolin-1(2H)-one (**5**) as a yellowish solid. ESI-MS *m/z*: 481.2 [M+H]⁺.

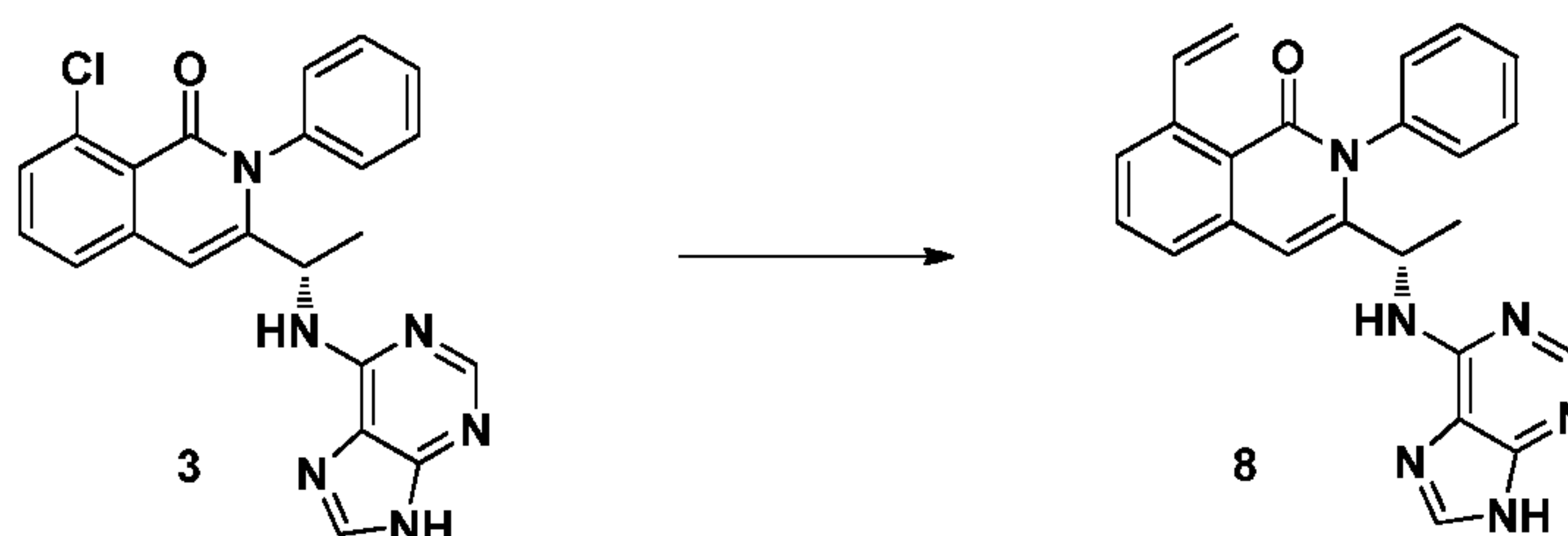
Example 3

[00419] Isoquinolinone **6** was prepared from compound **3** by coupling with 1H-pyrazole-4-boronic acid using the following procedure:

[00420] (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (**3**) (200 mg, 0.48 mmol) and 1H-pyrazole-4-boronic acid (108 mg, 0.96 mmol) were dissolved in anhydrous NMP (8 mL) and the resulting solution was degassed and back-filled with argon (two cycles). To this mixture, Na₂CO₃ (152 mg, 1.44 mmol), Pd(OAc)₂ (22 mg, 0.096 mmol) and di-(1-adamantyl)-n-butylphosphine (104 mg, 0.288 mmol) were added sequentially. The resulting mixture was degassed and back-filled with argon (two cycles) and then stirred at 160 °C under argon for 3 h. The reaction mixture was allowed to cool to RT and then partitioned between water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was triturated with Et₂O to afford the product, (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-2-phenyl-8-(1H-pyrazol-3-yl)isoquinolin-1(2H)-one (**6**) as a yellowish solid. ESI-MS *m/z*: 449.2 [M+H]⁺.

Example 4

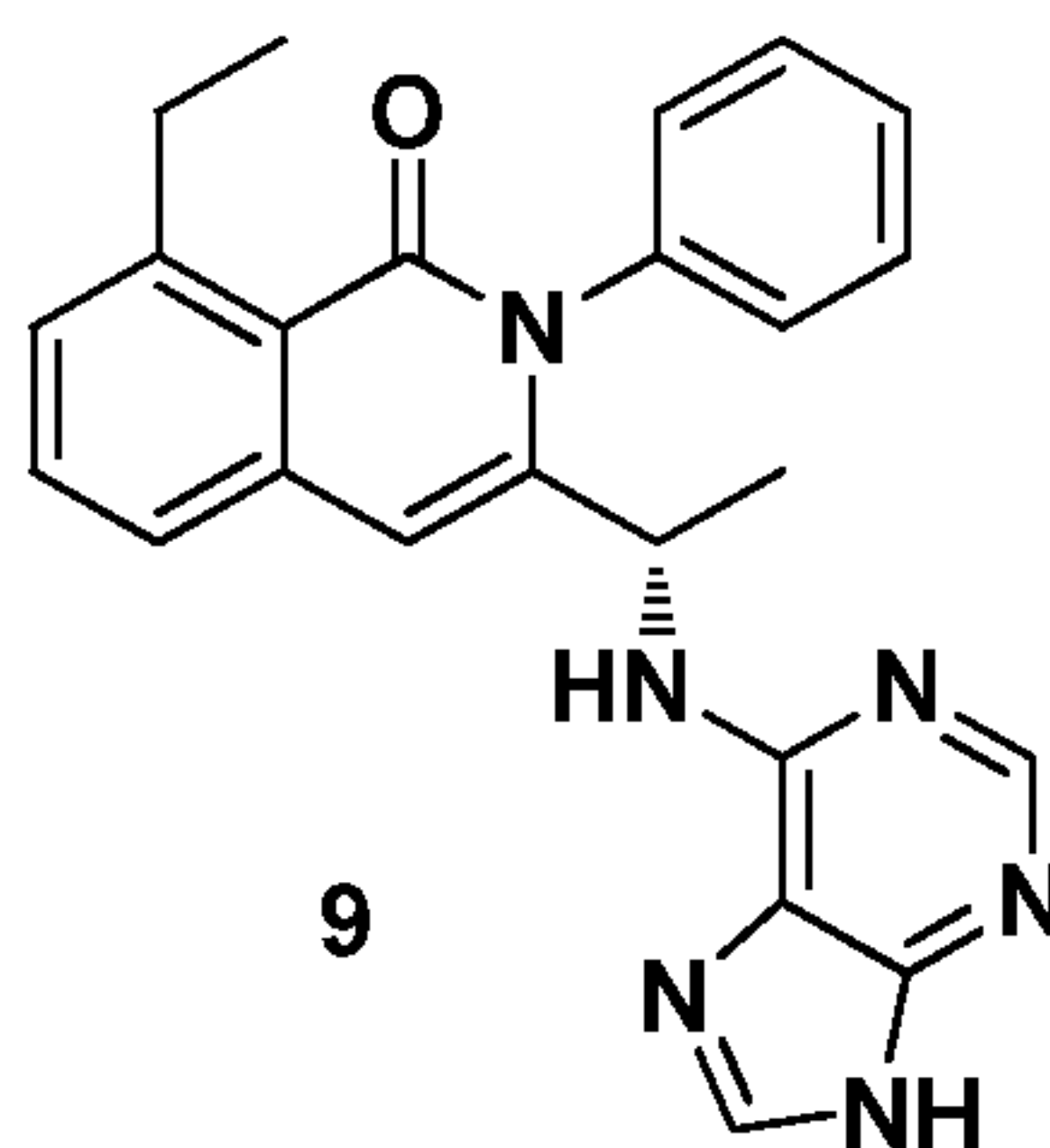
[00421] Isoquinolinone **7** was prepared from compound **3** in analogous fashion to compound **6** in Example 3 except that pyridin-3-ylboronic acid was used in place of 1H-pyrazole-4-boronic acid. ESI-MS *m/z*: 460.2 [M+H]⁺.

Example 5

[00422] Isoquinolinone **8** was prepared from compound **3** according to the following procedure:

[00423] (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (**3**) (417 mg, 1.0 mmol) and tributyl(vinyl)tin (0.58 mL, 2.0 mmol) were dissolved in anhydrous NMP (10 mL) and the resulting solution was degassed and back-filled with argon (two cycles). To this mixture, Na₂CO₃ (212 mg, 2.0 mmol), Pd(OAc)₂ (45 mg, 0.2 mmol) and di-(1-adamantyl)-n-butylphosphine (215 mg, 0.6 mmol) were added sequentially. The resulting mixture was degassed and back-filled with argon (two cycles) and then stirred at 160 °C under argon for 1 h. The reaction mixture was allowed to cool to RT and then partitioned between water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-10% MeOH-DCM) to afford the product, (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-2-phenyl-8-vinylisoquinolin-1(2H)-one (**8**) as an off-white solid. ESI-MS *m/z*: 409.2 [M+H]⁺.

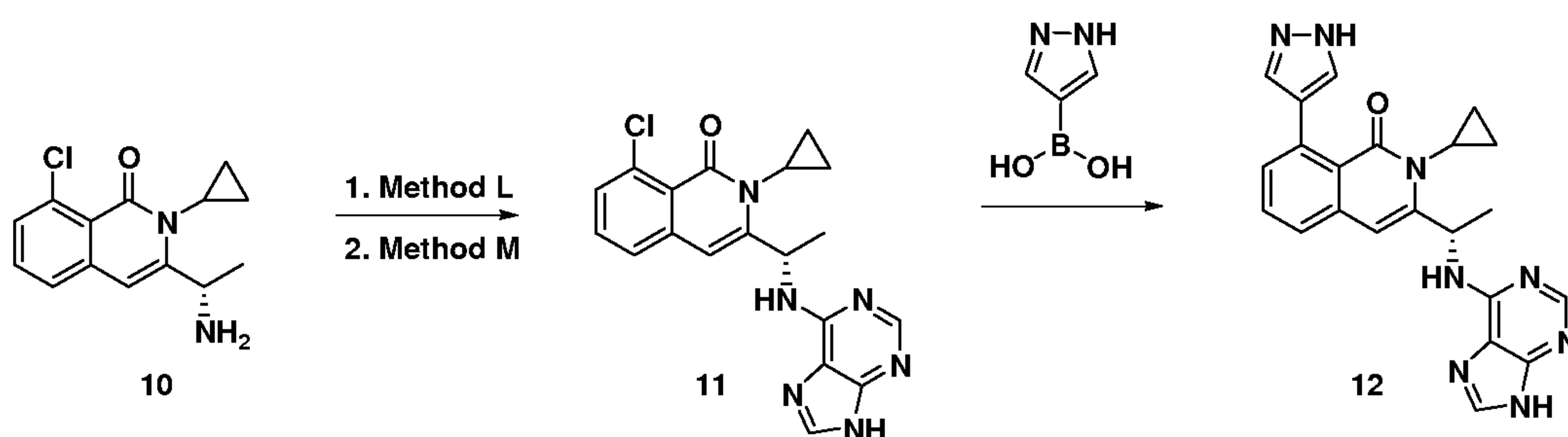
Example 6



[00424] Isoquinolinone **9** was prepared from compound **8** according to the following procedure:

[00425] A mixture of (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-2-phenyl-8-vinylisoquinolin-1(2H)-one (**8**) (120 mg, 0.29 mmol) and palladium (10% weight on carbon, 24 mg) in anhydrous MeOH (25 mL) was degassed and flushed with hydrogen (three cycles). The reaction mixture was stirred under a hydrogen atmosphere (hydrogen balloon) at RT for 1 h. The mixture was filtered through Celite and rinsed with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-10% MeOH-DCM) to afford the product, (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-8-ethyl-2-phenylisoquinolin-1(2H)-one (**9**). ESI-MS *m/z*: 411.2 [M+H]⁺.

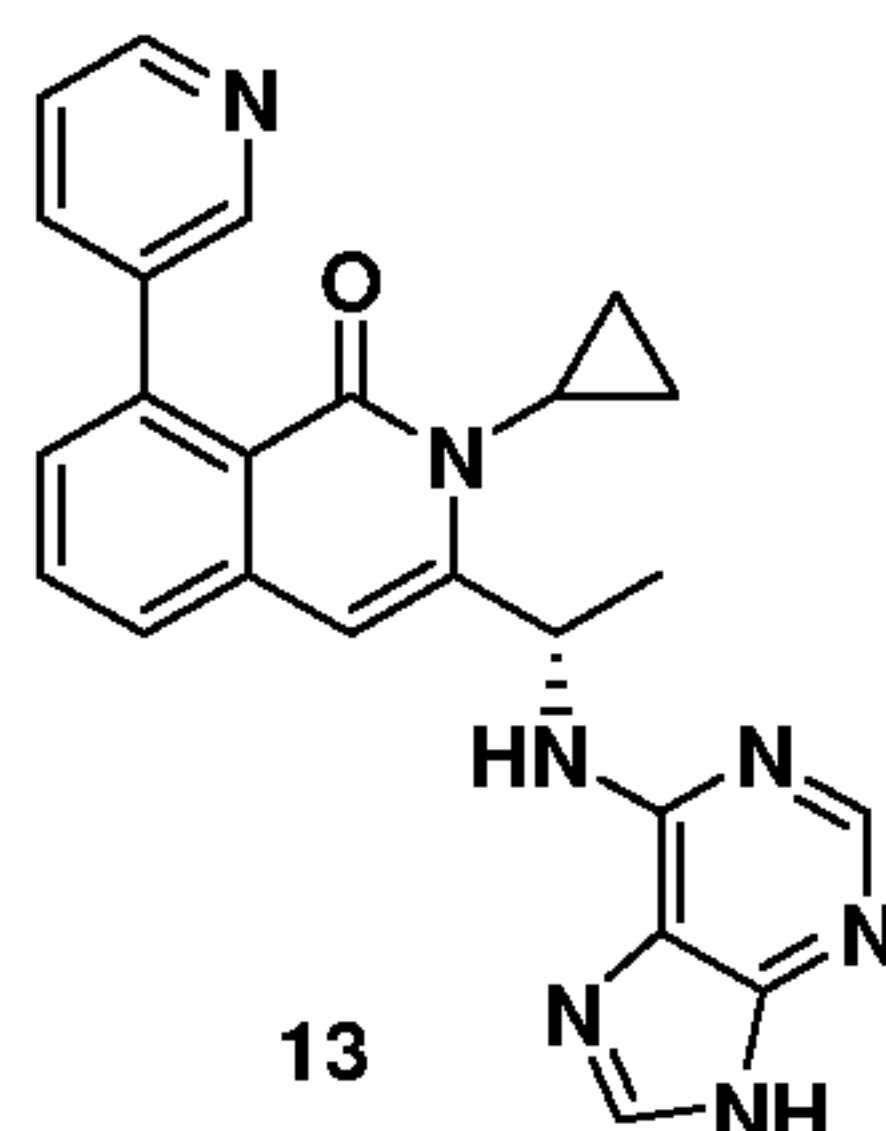
Example 7



[00426] Isoquinoline **12** was prepared in 3 steps according to the following procedures. Amine **10** was prepared using Method I. The amine was then converted to **11** according to Method L followed by Method M.

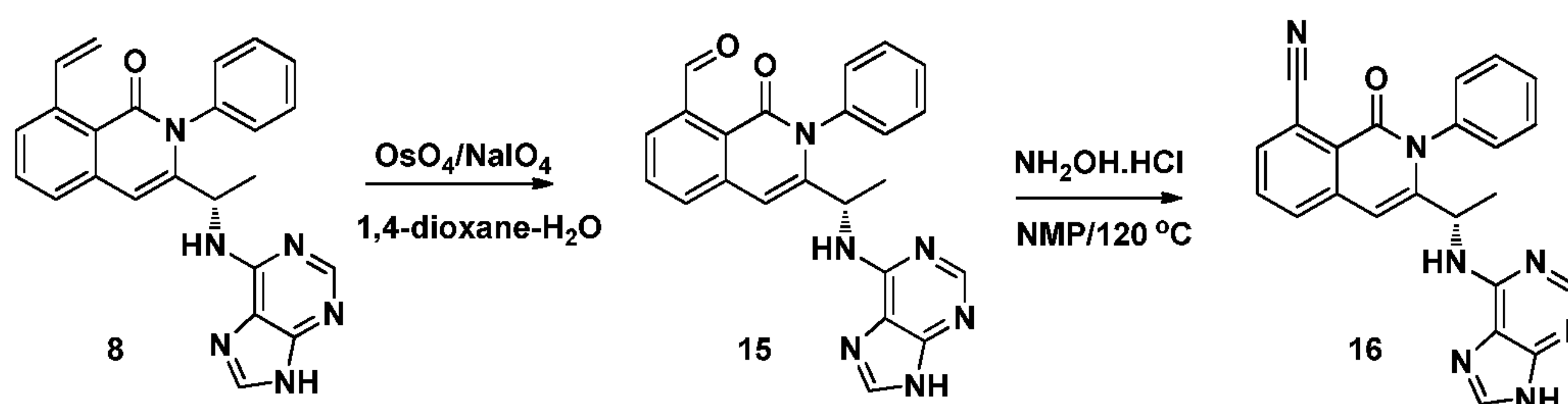
Compound **11** was then converted to compound **12** in analogous fashion to compound **6** in Example 3. ESI-MS m/z : 413.2 $[M+H]^+$.

Example 8



[00427] Isoquinolinone **13** was prepared from compound **11** in analogous fashion to compound **12** in Example 7 except that pyridin-3-ylboronic acid was used in place of 1H-pyrazole-4-boronic acid. ESI-MS m/z : 424.2 $[M+H]^+$.

Example 9



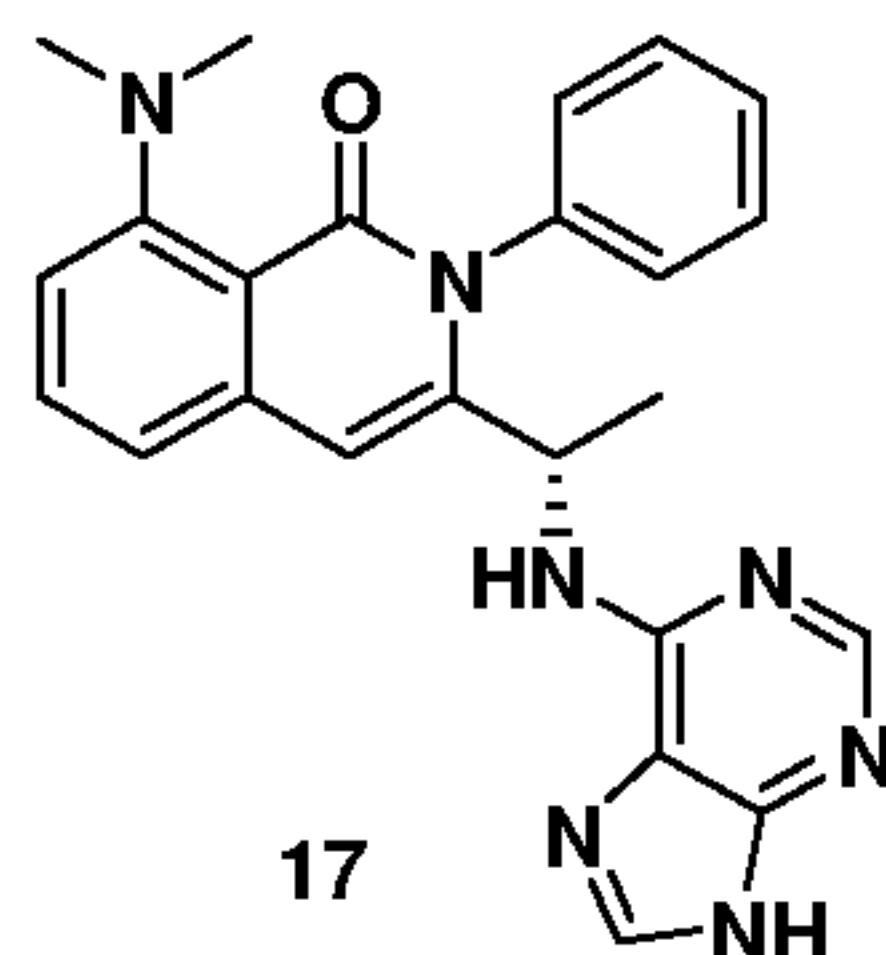
[00428] Isoquinoline **16** was prepared from compound **8** according to the following procedure:

[00429] To a solution of ethyl 2-(4-methyl-N-phenyl-2-vinylnicotinamido)acetate (**8**) (767 mg, 1.88 mmol) in 1,4-dioxane- H_2O (3:1, 20 mL) at RT, osmium tetroxide (2.5% wt in H_2O , 0.5 mL, 0.05 mmol) was added and the resulting mixture was stirred at RT for 30 min. To this mixture, sodium periodate (1.21 g, 5.53 mmol) was added and the resulting mixture was stirred at RT for 30 h. The mixture was filtered through celite and the filtrate was extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the product, (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-1-oxo-2-phenyl-1,2-dihydroisoquinoline-8-carbaldehyde (**15**) (730 mg, 95% yield) as a yellowish solid. ESI-MS m/z : 411.2 $[M+H]^+$.

[00430] To a solution of (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-1-oxo-2-phenyl-1,2-dihydroisoquinoline-8-carbaldehyde (**15**) (50 mg, 0.12 mmol) in anhydrous 1-methyl-2-pyrrolidinone (3 mL), hydroxylamine hydrochloride (17 mg, 0.24 mmol) was added and the resulting mixture was stirred at 120 °C for 16 h. The mixture was allowed to cool to RT, partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-10%

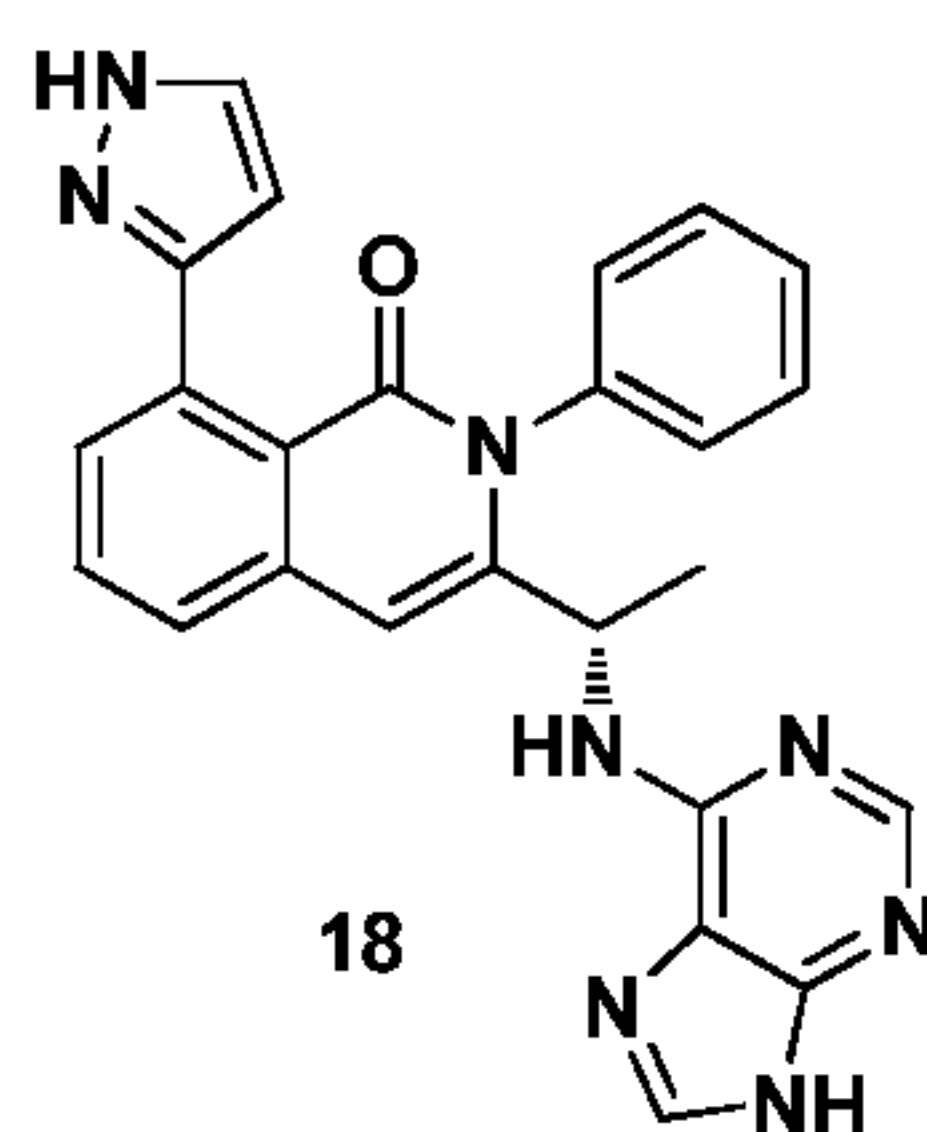
MeOH-DCM) to afford the product, (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-1-oxo-2-phenyl-1,2-dihydroisoquinoline-8-carbonitrile (**16**) (14 mg, 28% yield) as a white solid. ESI-MS m/z : 408.2 $[M+H]^+$.

Example 10



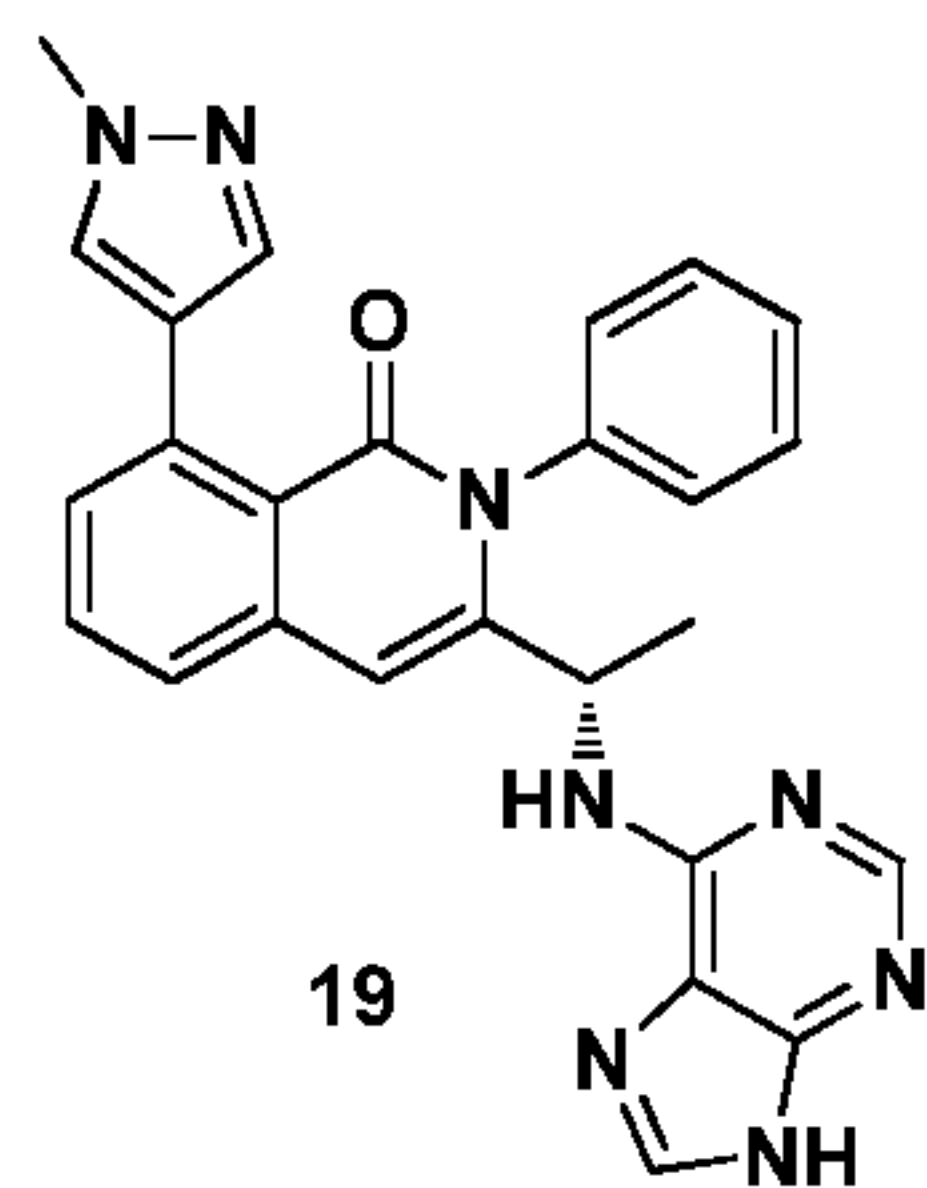
[00431] Isoquinolinone **17** was prepared in analogous fashion to compound **5** in Example 2 except that dimethylamine THF solution was used in place of 1-methylpiperazine. ESI-MS m/z : 426.20 $[M+H]^+$.

Example 11

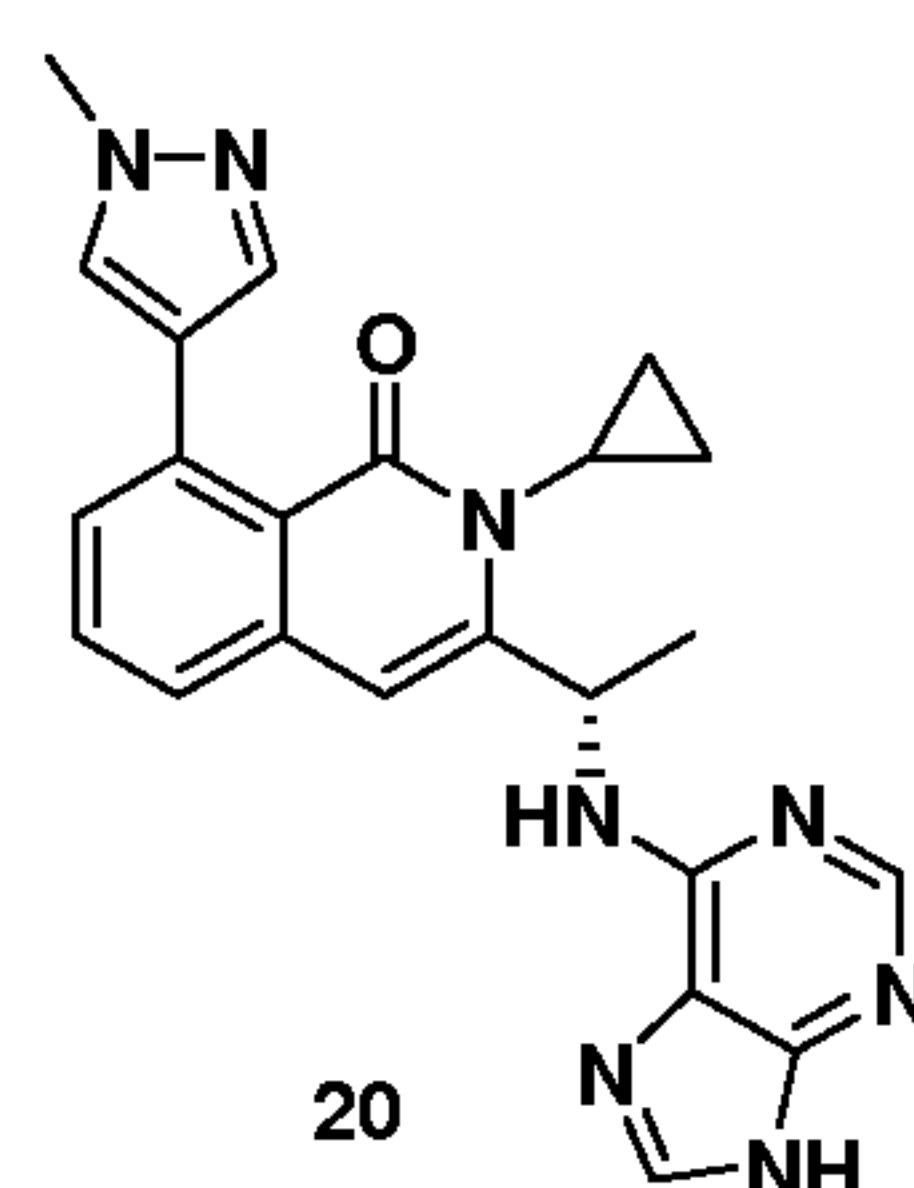


[00432] Isoquinolinone **18** was prepared from compound **3** in analogous fashion to compound **6** in Example 3 except that 1H-pyrazol-3-boronic acid was used in place of 1H-pyrazole-4-boronic acid. ESI-MS m/z : 449.2 $[M+H]^+$.

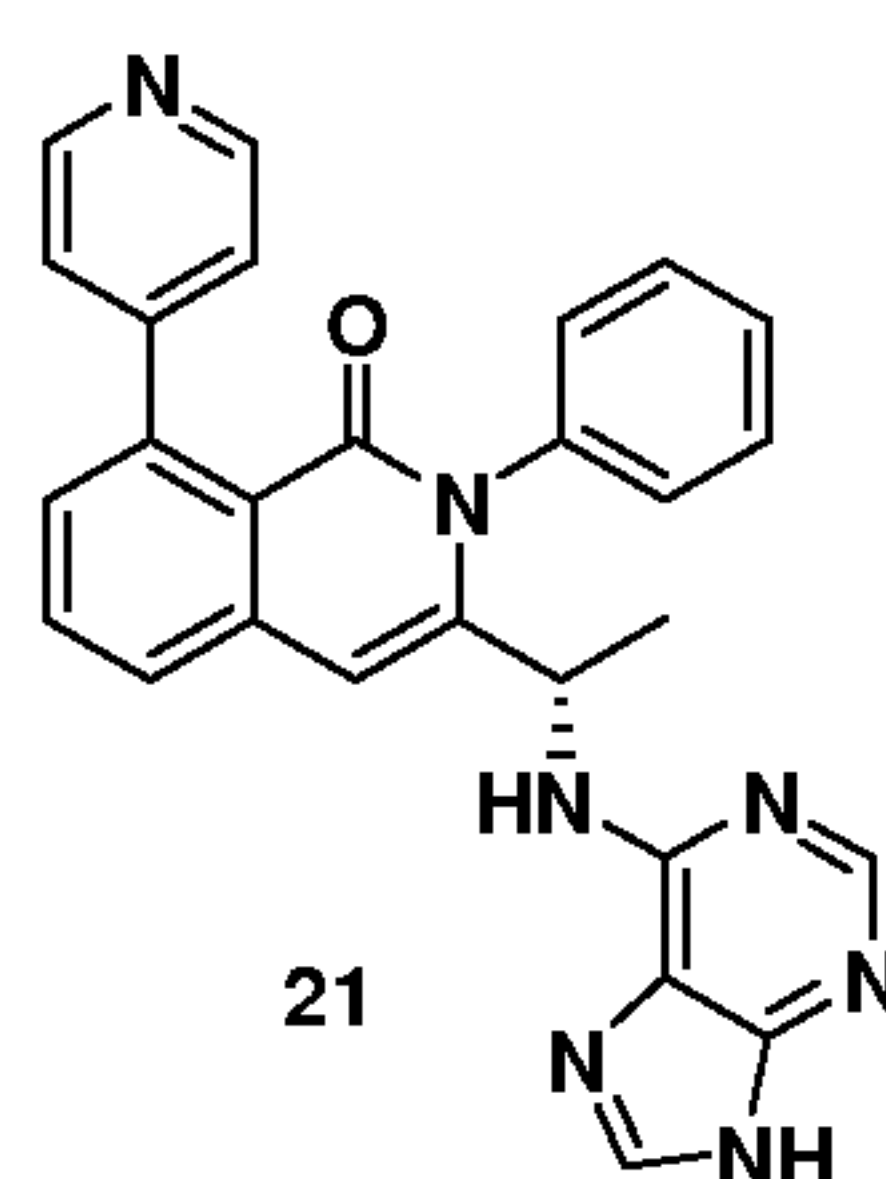
Example 12



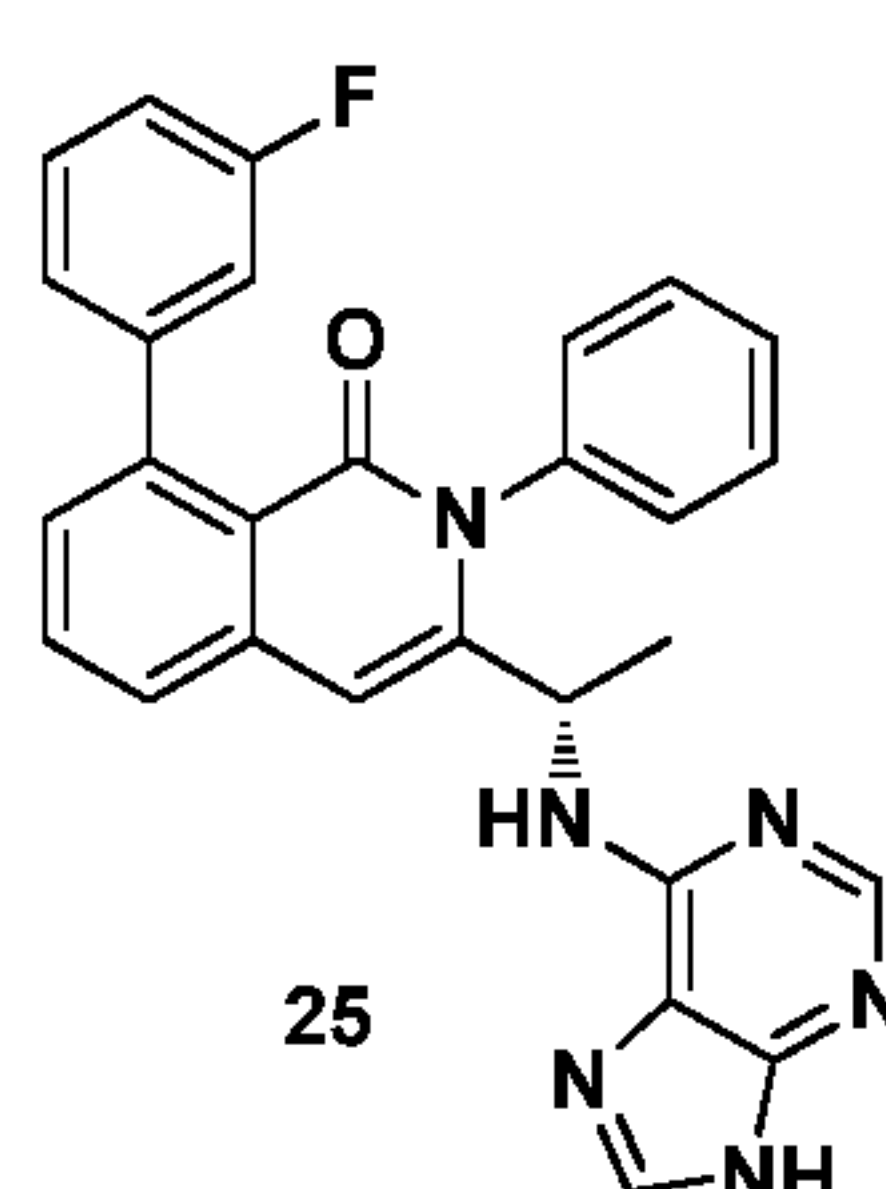
[00433] Isoquinolinone **19** was prepared from compound **3** in analogous fashion to compound **6** in Example 3 except that (1-methyl-1H-pyrazol-4-yl)boronic acid was used in place of 1H-pyrazole-4-boronic acid. ESI-MS m/z : 463.2 $[M+H]^+$.

Example 13

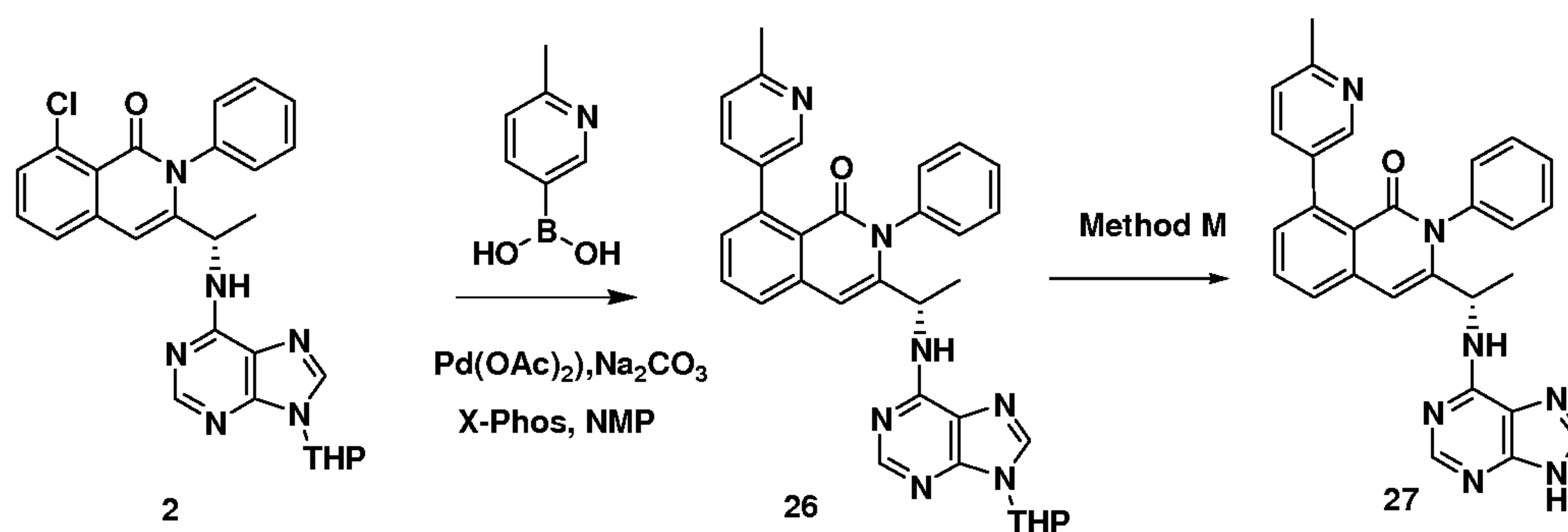
[00434] Isoquinolinone **20** was prepared from compound **11** in analogous fashion to compound **12** in Example 7 except that (1-methyl-1H-pyrazol-4-yl)boronic acid was used in place of 1H-pyrazole-4-boronic acid. ESI-MS m/z : 427.2 $[M+H]^+$.

Example 14

[00435] Isoquinolinone **21** was prepared from compound **3** in analogous fashion to compound **6** in Example 3 except that pyridine-4-boronic acid was used in place of 1H-pyrazole-4-boronic acid. ESI-MS m/z : 458.2 $[M+H]^+$.

Example 15

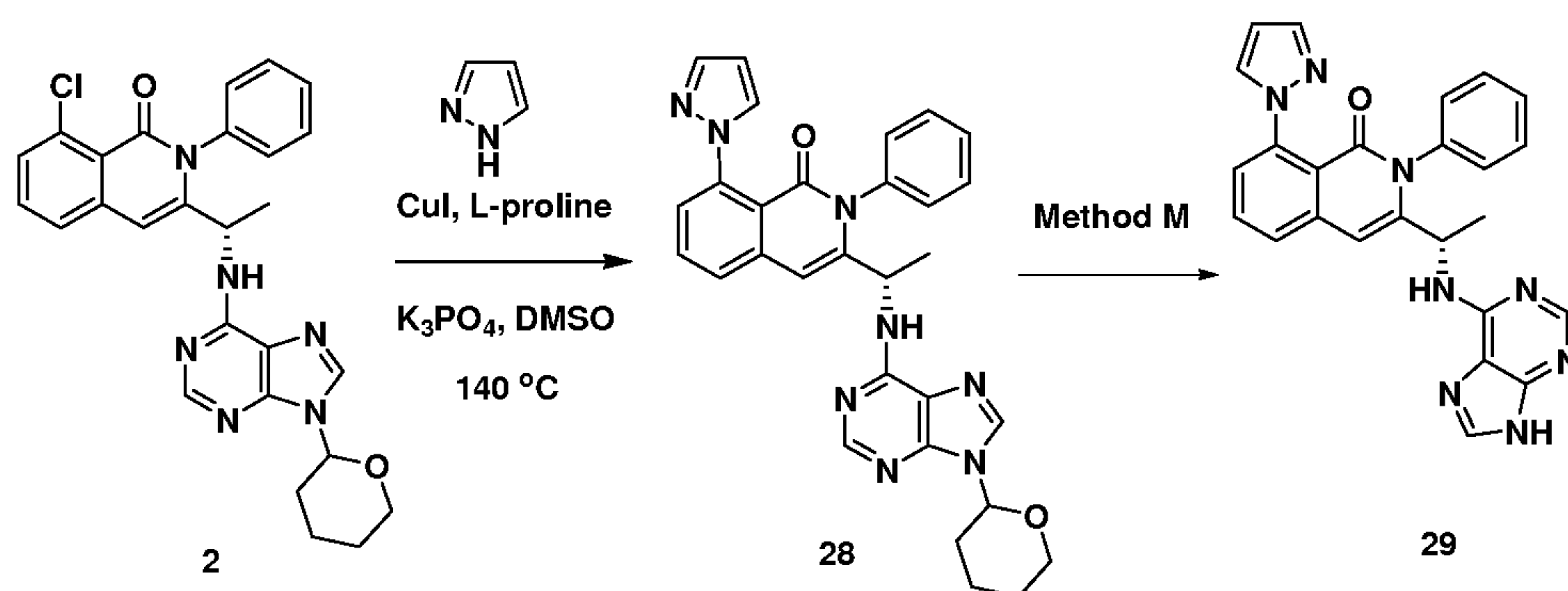
[00436] Isoquinolinone **25** was prepared from compound **3** in analogous fashion to compound **6** in Example 3 except that (3-fluorophenyl)boronic acid was used in place of 1H-pyrazole-4-boronic acid. ESI-MS m/z : 477.2 $[M+H]^+$.

Example 16

[00437] Isoquinolinone **27** was prepared from compound **2** in 2 steps:

[00438] Compound **2** was converted to compound **26** according to the following Suzuki coupling procedure. 8-Chloro-2-phenyl-3-((S)-1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino) ethyl)isoquinolin-1(2H)-one (**2**) (100 mg, 0.2 mmol, 1.0 eq), 6-methylpyridin-3-ylboronic acid (56 mg, 0.41 mmol, 2.0 eq), Pd(OAc)₂ (9 mg, 0.04 mmol, 0.2 eq), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (58 mg, 0.12 mmol, 0.6 eq) and Na₂CO₃ (64 mg, 0.6 mmol, 3.0 eq) were dissolved in 1-methyl-2-pyrrolidinone (10 mL). The resulting mixture was degassed and back-filled with argon three times, and then stirred at 160 °C under an argon atmosphere for 1.5 h. The reaction was complete based on TLC analysis. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1:30 MeOH-DCM) to afford the product, 8-(6-methylpyridin-3-yl)-2-phenyl-3-((S)-1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl) isoquinolin-1(2H)-one (**26**); ESI-MS *m/z* : 558.30 [M+H]⁺.

[00439] Compound **26** was then converted to the product **27** using Method M. ESI-MS *m/z*: 474.20 [M+H]⁺.

Example 17

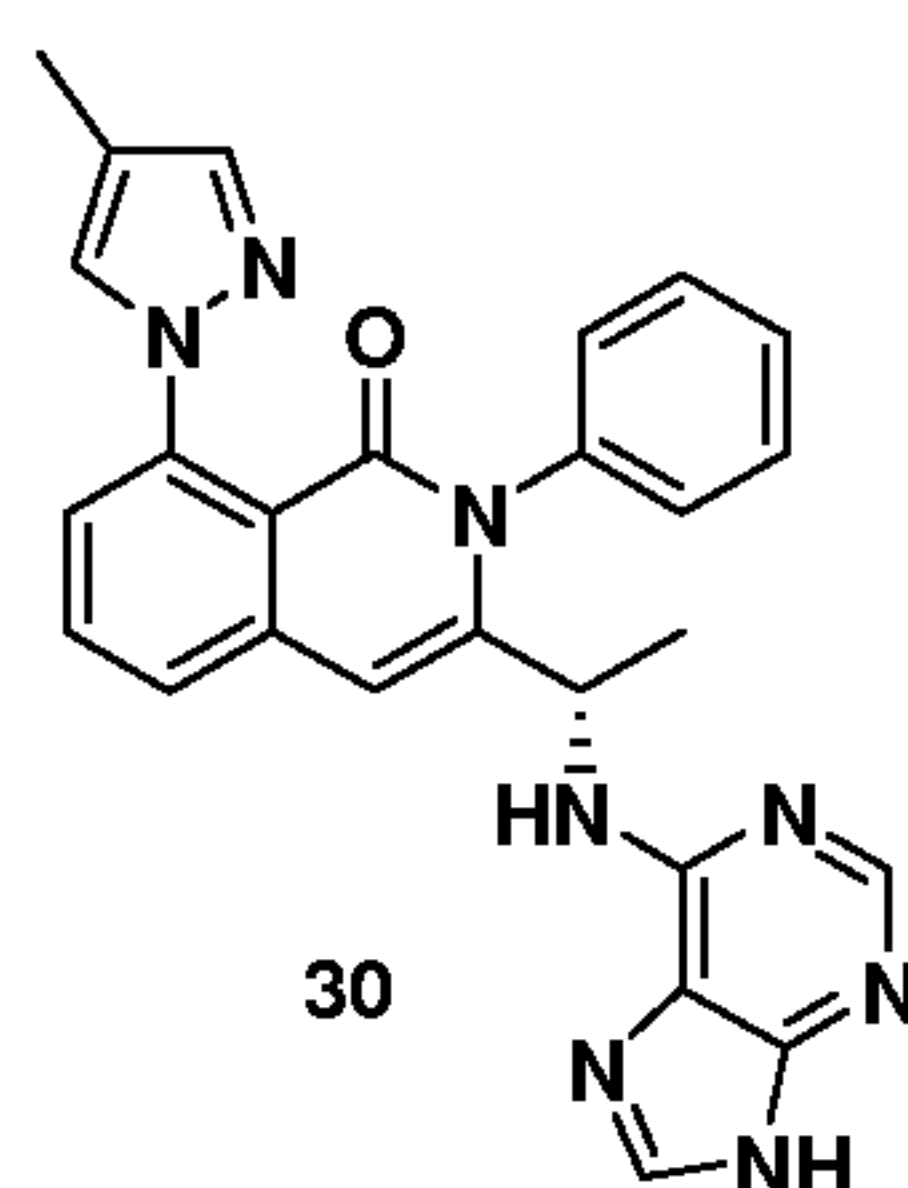
[00440] Isoquinolinone **29** was prepared from compound **2** in 2 steps:

[00441] Compound **2** first was converted to compound **28** using the following Buchwald-Hartwig coupling procedure: A mixture of 8-chloro-2-phenyl-3-((S)-1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino) ethyl) isoquinolin-1(2H)-one (**2**) (300 mg, 0.6 mmol, 1.0 eq), pyrazole (61 mg, 0.9 mmol, 1.5 eq), L-proline (14 mg, 0.12 mmol, 0.2 eq), copper(I) iodide (12 mg, 0.06 mmol, 0.1 eq), and potassium phosphate (318 mg, 1.5 mmol, 2.5 eq) was

suspended in DMSO (10 mL). The resulting mixture was degassed and back-filled with argon three times and stirred at 140 °C under an argon atmosphere overnight. After the reaction mixture was cooled to RT, it was diluted with water (50 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo*. The resultant residue was purified by flash column chromatography on silica gel (1% MeOH-DCM) to afford the product, 2-phenyl-8-(1H-pyrazol-1-yl)-3-((S)-1-(9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-ylamino)ethyl)isoquinolin-1(2H)-one (**28**). ESI-MS *m/z*: 533.30 [M+H]⁺.

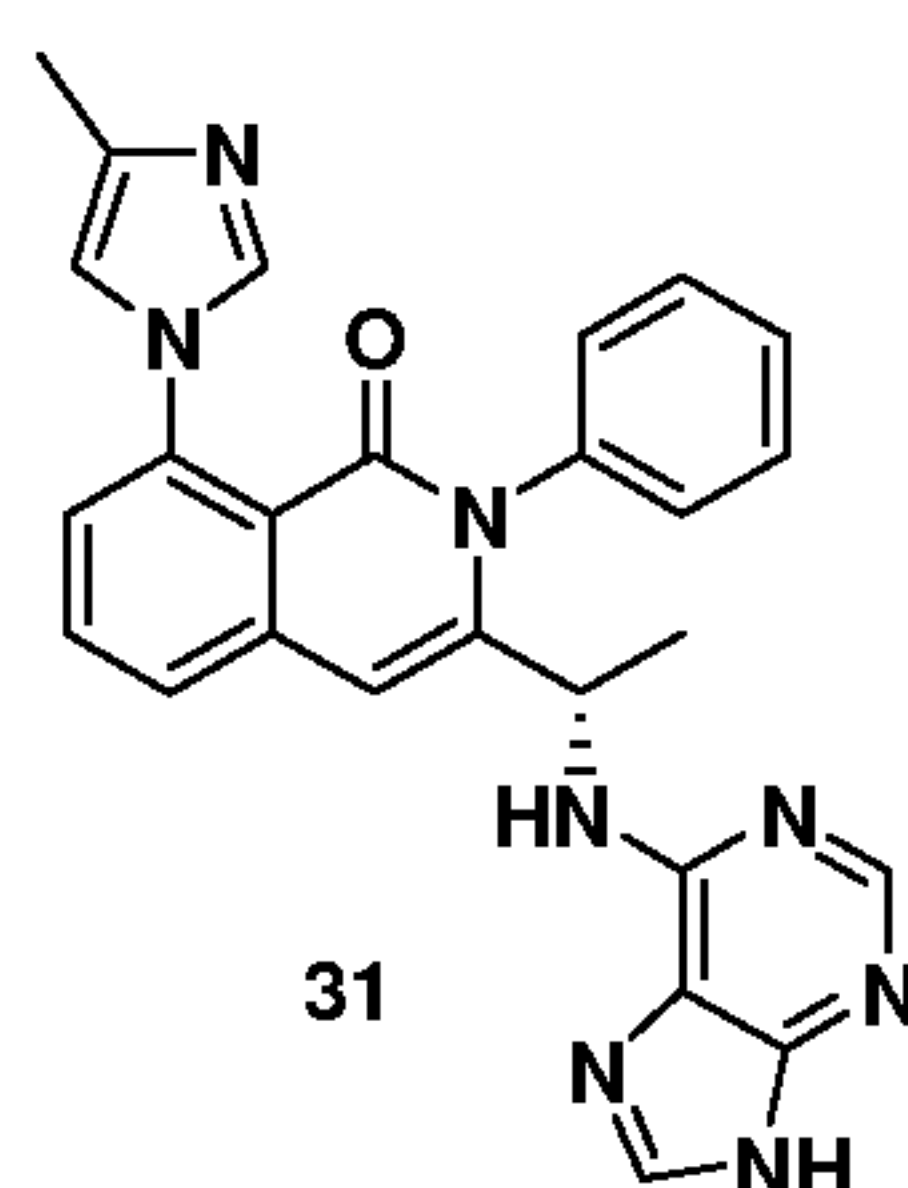
[00442] Compound **28** was then converted to compound **29** using Method M. ESI-MS *m/z*: 449.25 [M+H]⁺.

Example 18



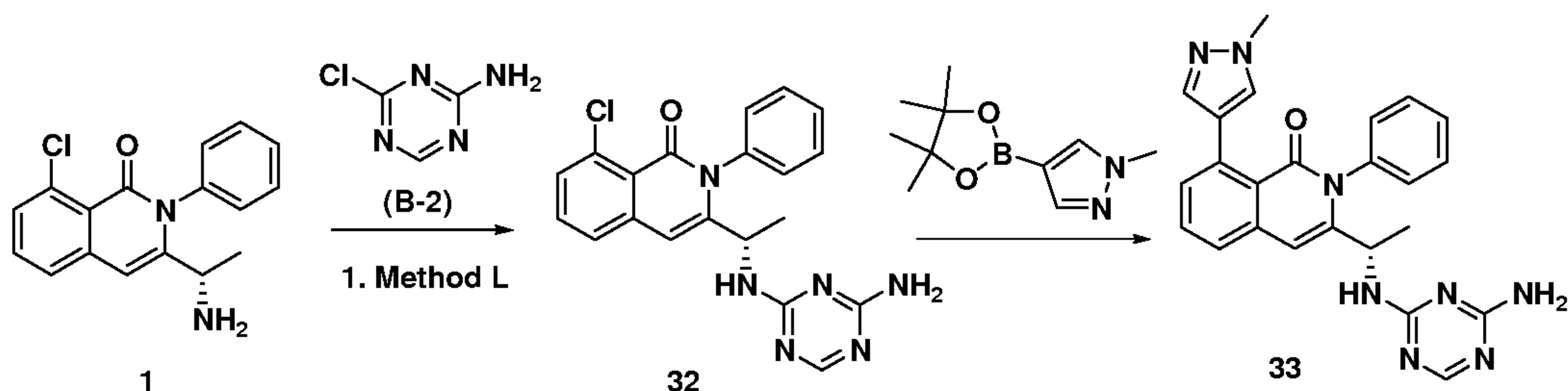
[00443] Isoquinolinone **30** was prepared from compound **2** in analogous fashion to compound **29** in Example 17 except that 4-methyl-1H-pyrazole was used in place of 1H-pyrazole. ESI-MS *m/z*: 463.25 [M+H]⁺.

Example 19



[00444] Isoquinolinone **31** was prepared from compound **2** in analogous fashion to compound **29** in Example 17 except that 4-methyl-1H-imidazole was used in place of 1H-pyrazole. ESI-MS *m/z*: 463.20 [M + H]⁺.

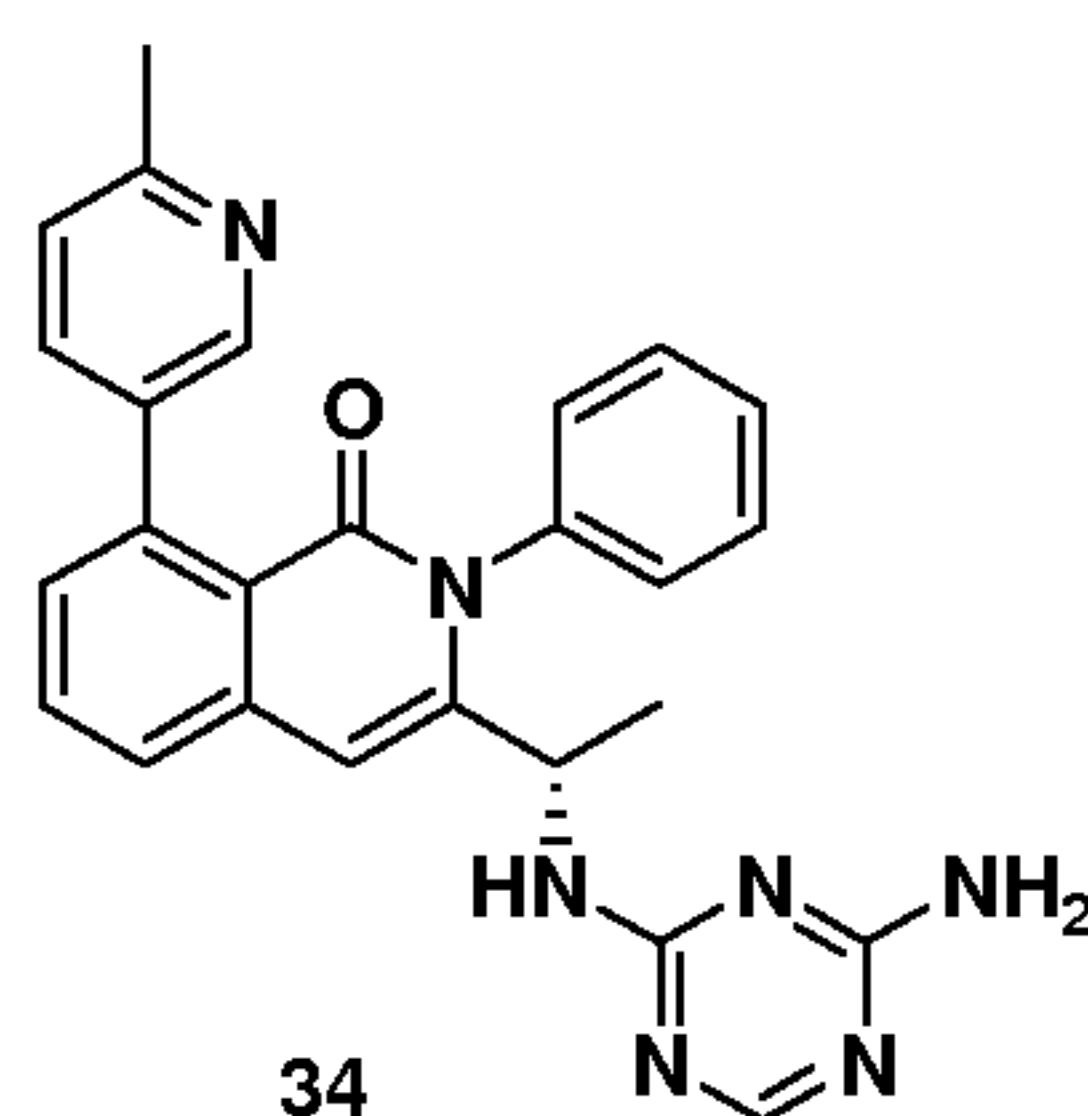
Example 20



[00445] Isoquinolinone **33** was prepared from compound **1** in 2 steps. Compound **1** was converted to compound **32** using Method L (intermediate **B-2** was prepared by Method B). Compound **32** was then converted to **33** according to the following procedure:

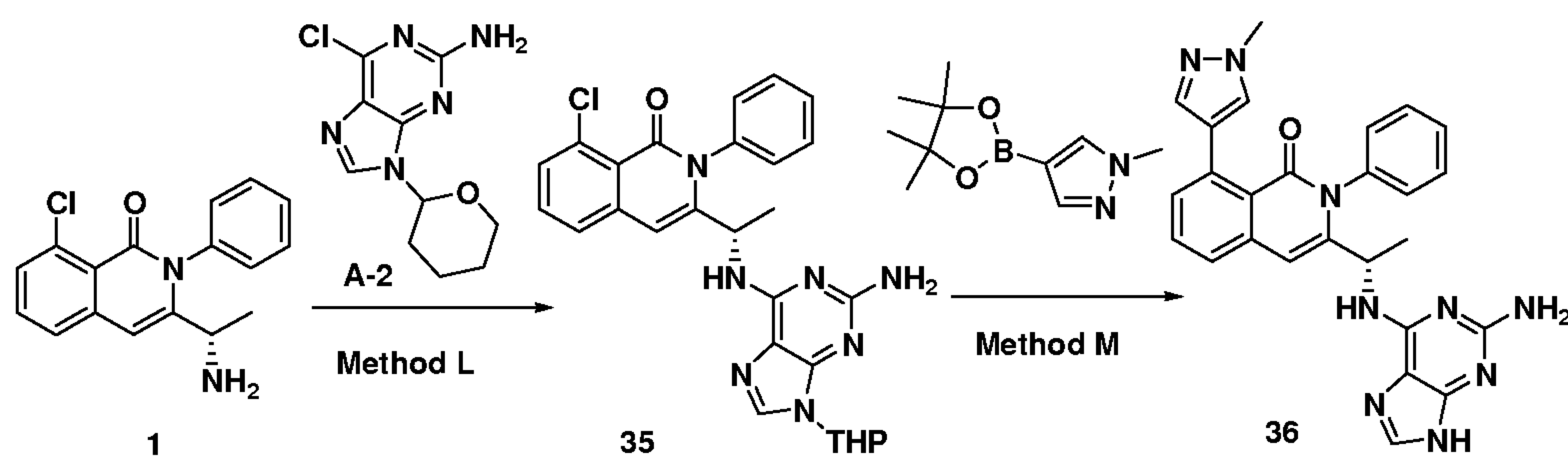
[00446] (S)-3-(1-(4-Amino-1,3,5-triazin-2-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (**32**) (100 mg, 0.26 mmol, 1.0 eq), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (106 mg, 0.51 mmol, 2 eq), PdCl₂(dppf) (16 mg, 0.02 mmol, 0.08 eq), and Na₂CO₃ (81 mg, 0.765 mmol, 3.0 eq) were suspended in a mixture of N,N-dimethylacetamide (20 mL) and water (1 mL). The resulting mixture was degassed and back-filled with argon three times and stirred at 120 °C under an argon atmosphere for 16 h. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (1-4 % MeOH-DCM) to afford the product, 3-((S)-1-(4-amino-1,3,5-triazin-2-ylamino)ethyl)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenylisoquinolin-1(2H)-one (**33**). ESI-MS *m/z*: 439.25 [M + H]⁺.

Example 21

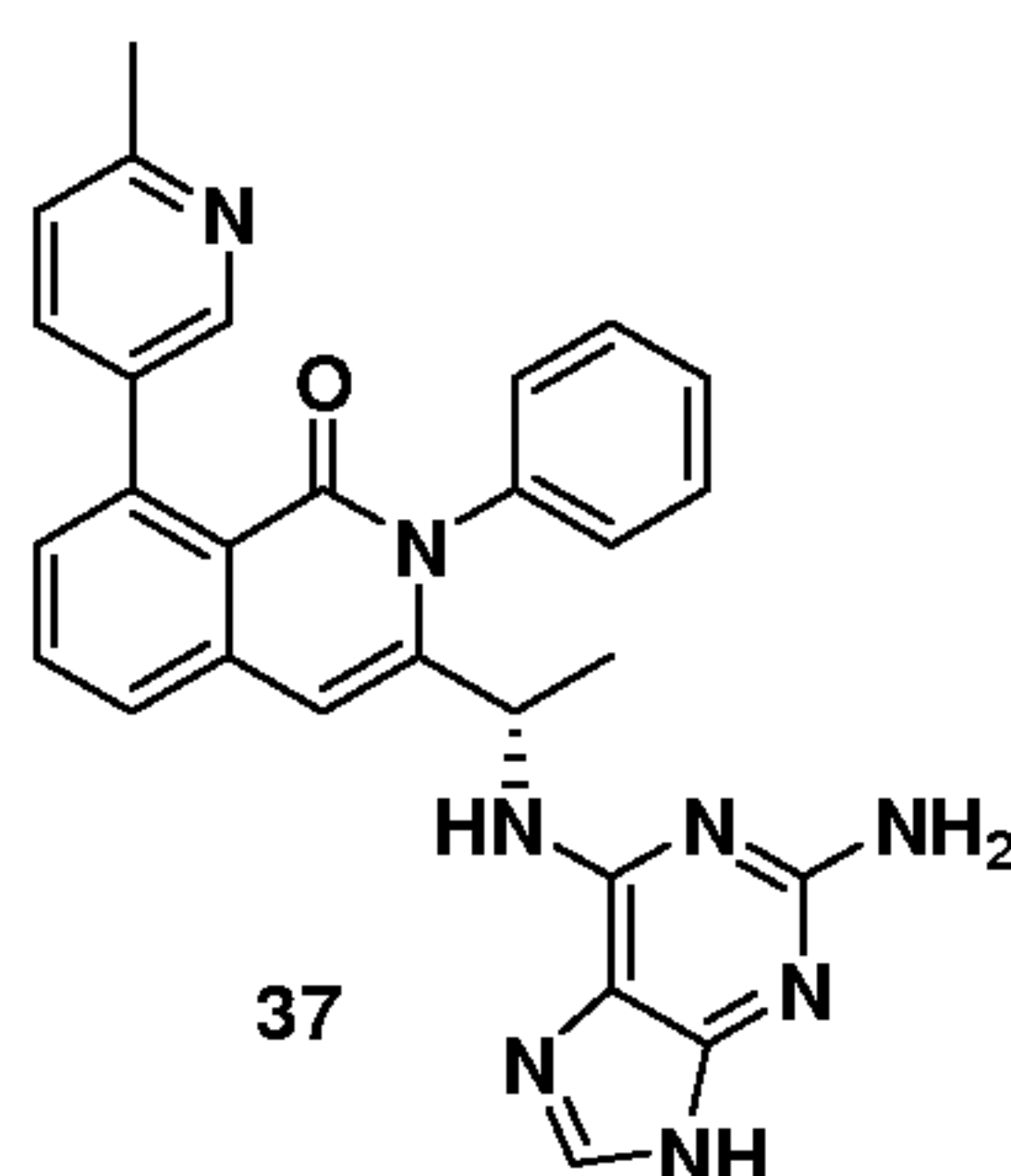


[00447] Isoquinolinone **34** was prepared from compound **32** in analogous fashion to compound **33** in Example 20 except that 6-methylpyridin-3-ylboronic acid was used in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. ESI-MS *m/z*: 450.25 [M + H]⁺.

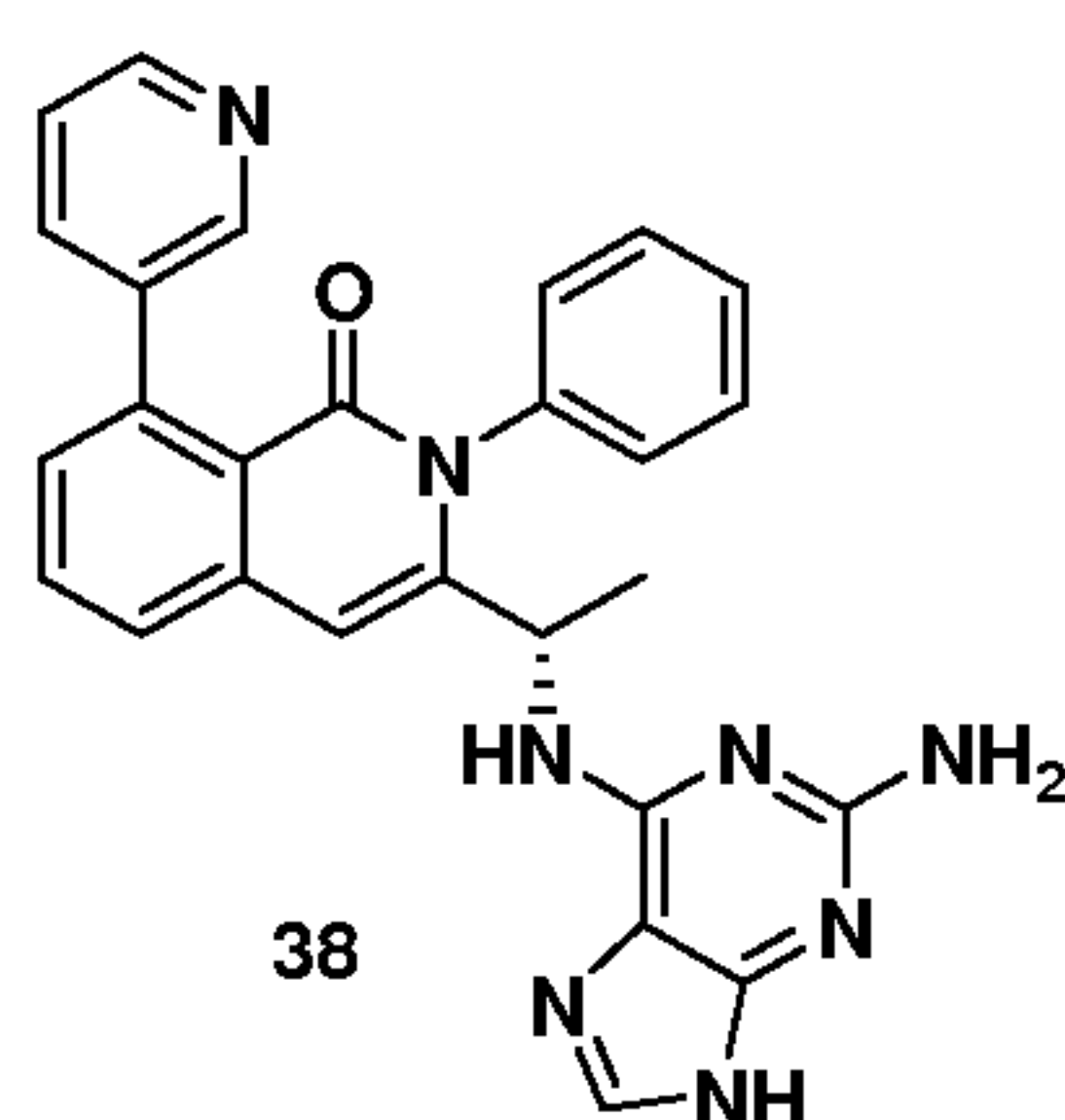
Example 22



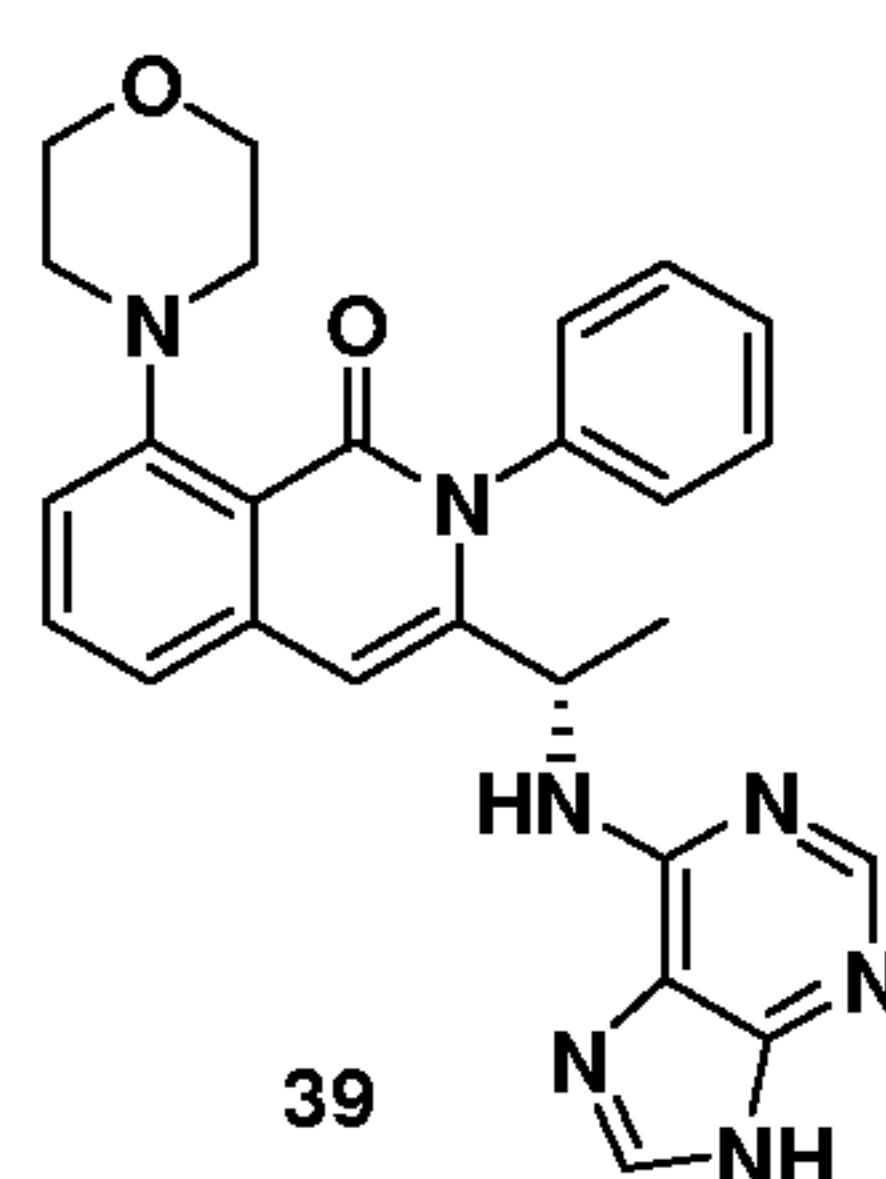
[00448] Isoquinolinone **36** was prepared from compound **1** in 3 steps. Compound **1** was first converted to compound **35** using Method L. Compound **35** was then coupled to 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using the analogous procedures for compound **33** in Example 20 after which it was converted to compound **36** using Method M. ESI-MS *m/z*: 478.2 [M + H]⁺.

Example 23

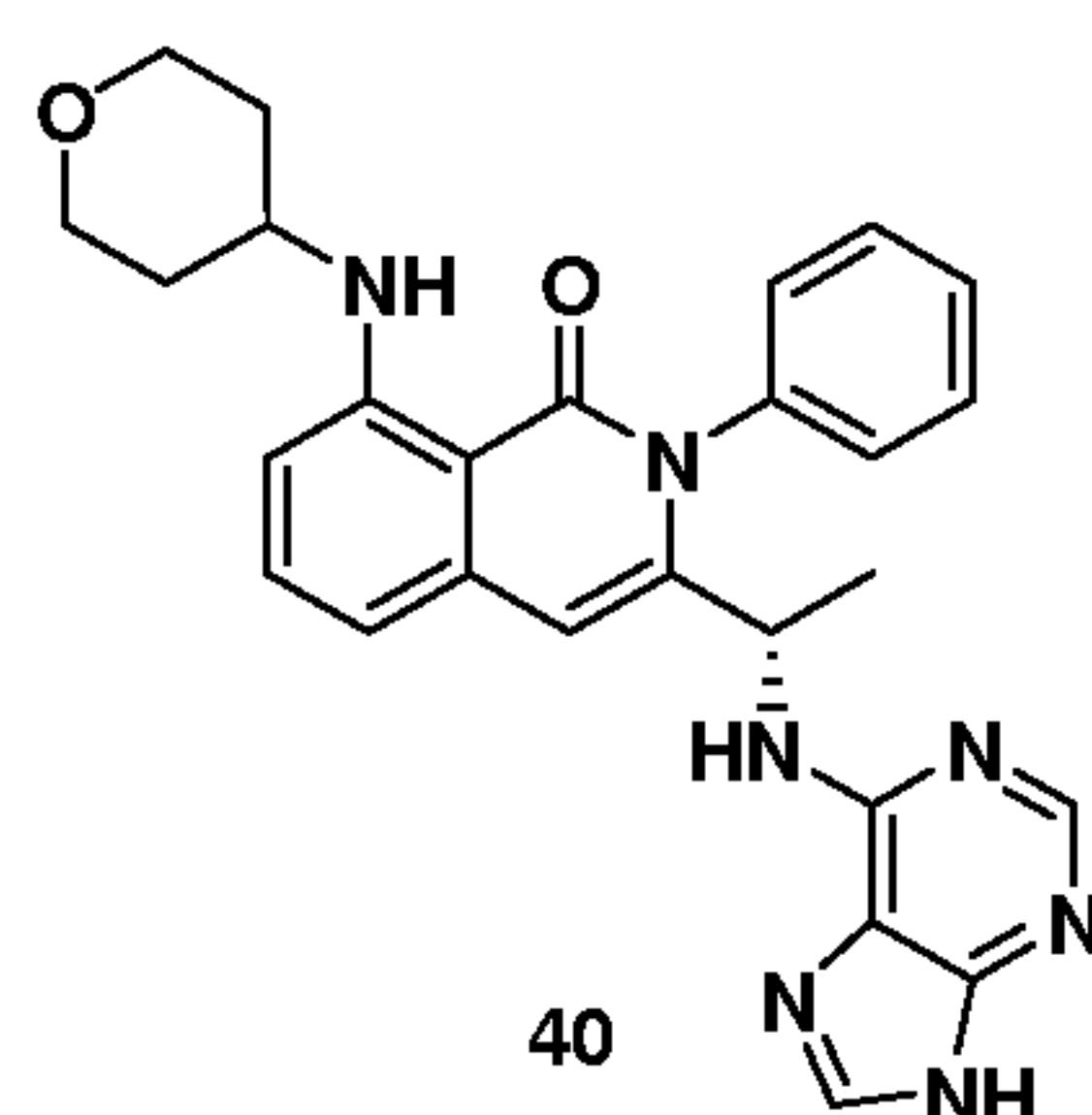
[00449] Isoquinolinone **37** was prepared from compound **35** in analogous fashion to compound **36** in Example 22 except that 6-methylpyridin-3-ylboronic acid was used in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. ESI-MS m/z : 487.2 $[M-H]^-$.

Example 24

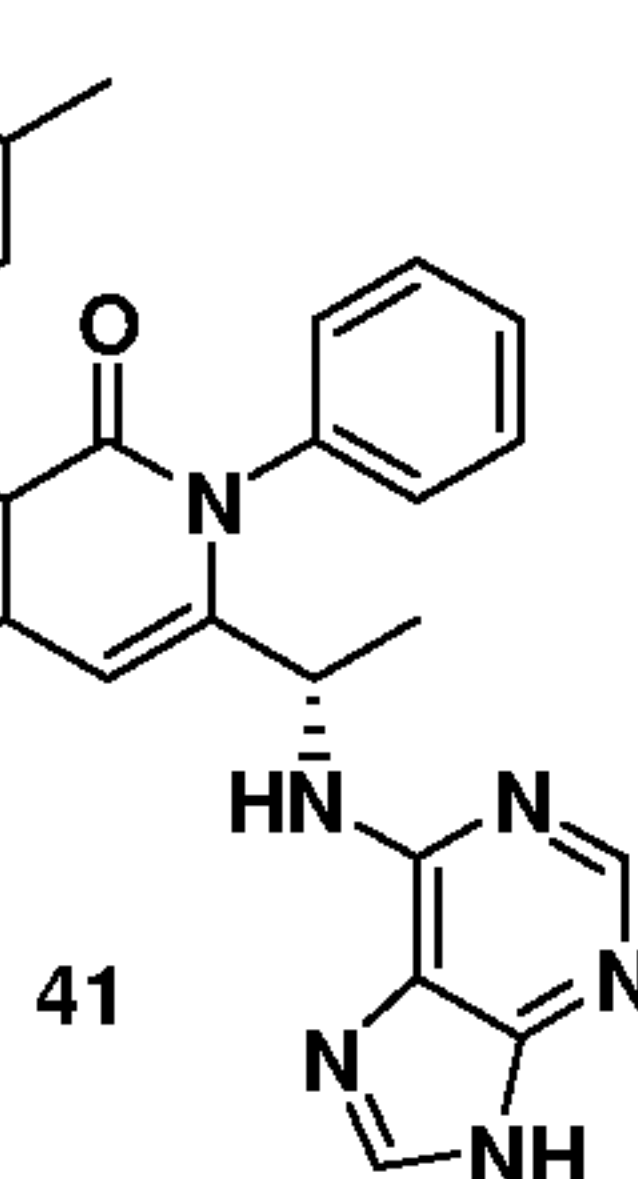
[00450] Isoquinolinone **38** was prepared from compound **35** in analogous fashion to compound **36** in Example 22 except that pyridin-3-ylboronic acid was used in place of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. ESI-MS m/z : 475.30 $[M+H]^+$.

Example 25

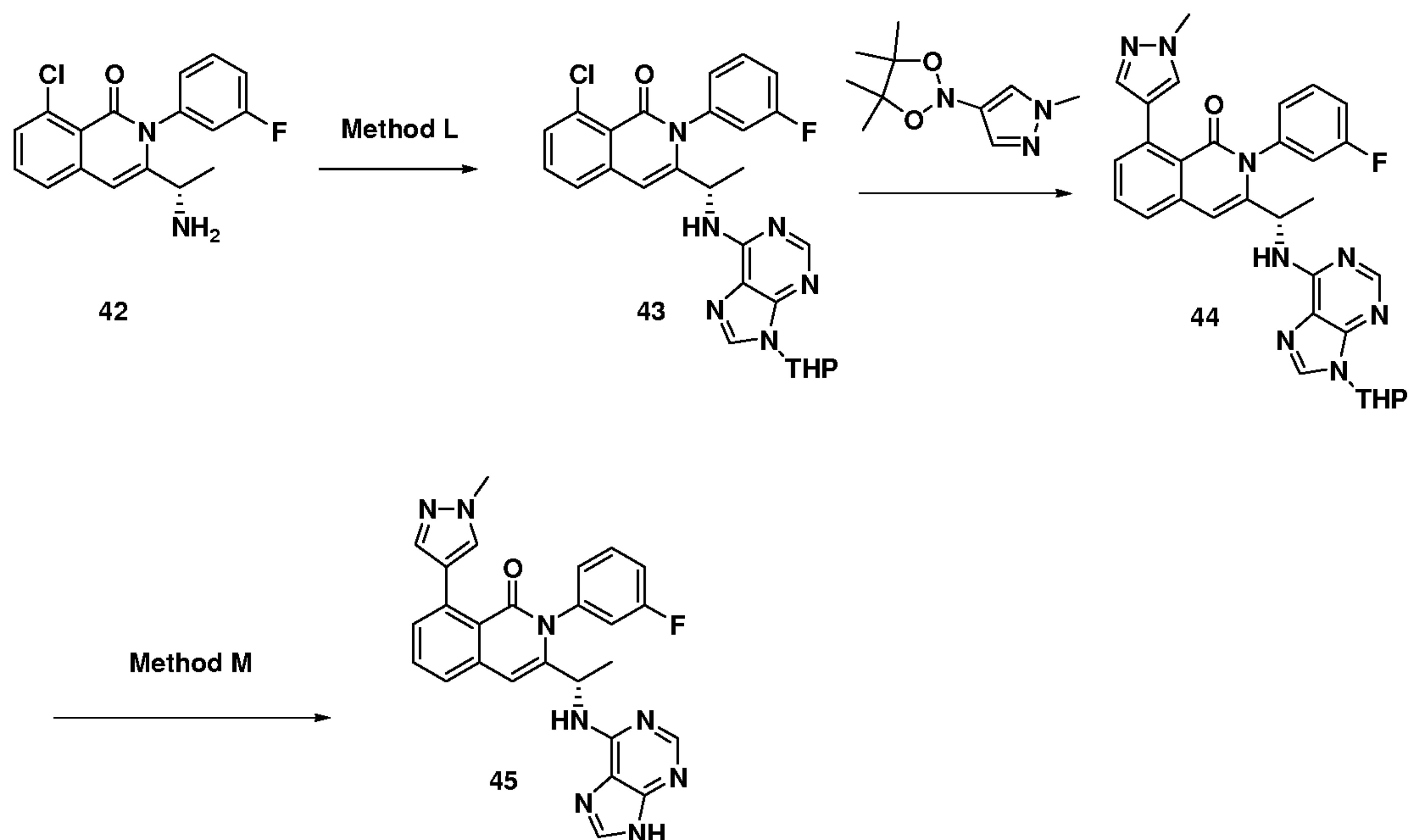
[00451] Isoquinolinone **39** was prepared in analogous fashion to compound **4** in Example 1 except that morpholine was used in place of pyrrolidine. ESI-MS m/z : 468.0 $[M+H]^+$.

Example 26

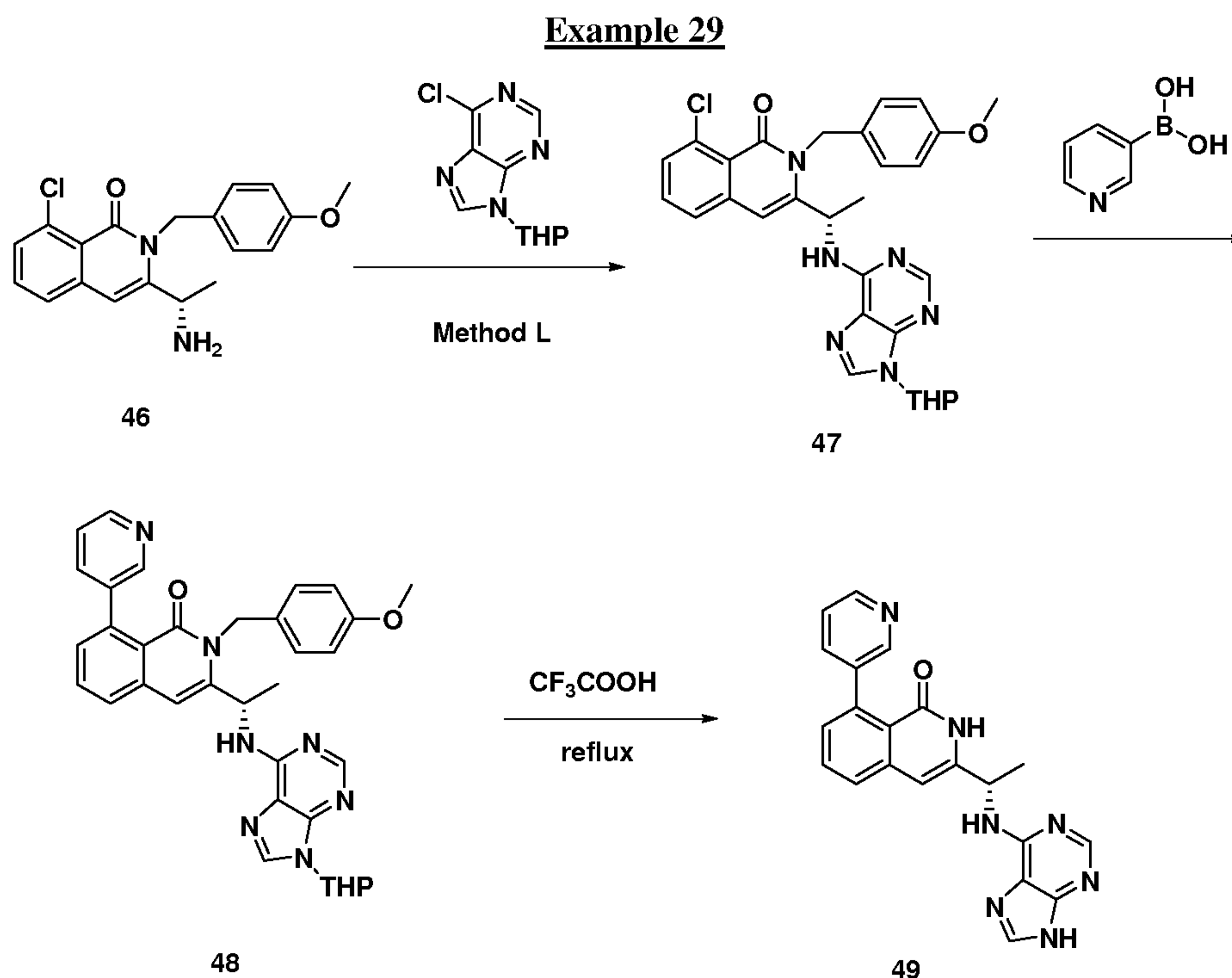
[00452] Isoquinolinone **40** was prepared in analogous fashion to compound **4** in Example 1 except that tetrahydro-2H-pyran-4-amine was used in place of pyrrolidine. ESI-MS m/z : 482.2 $[M+H]^+$.

Example 27

[00453] Isoquinolinone **41** was prepared from compound **2** in analogous fashion to compound **27** in Example 16 except that 2-methylpyridin-4-ylboronic acid was used in place of 6-methylpyridin-3-ylboronic acid. ESI-MS m/z : 474.30 $[M+H]^+$.

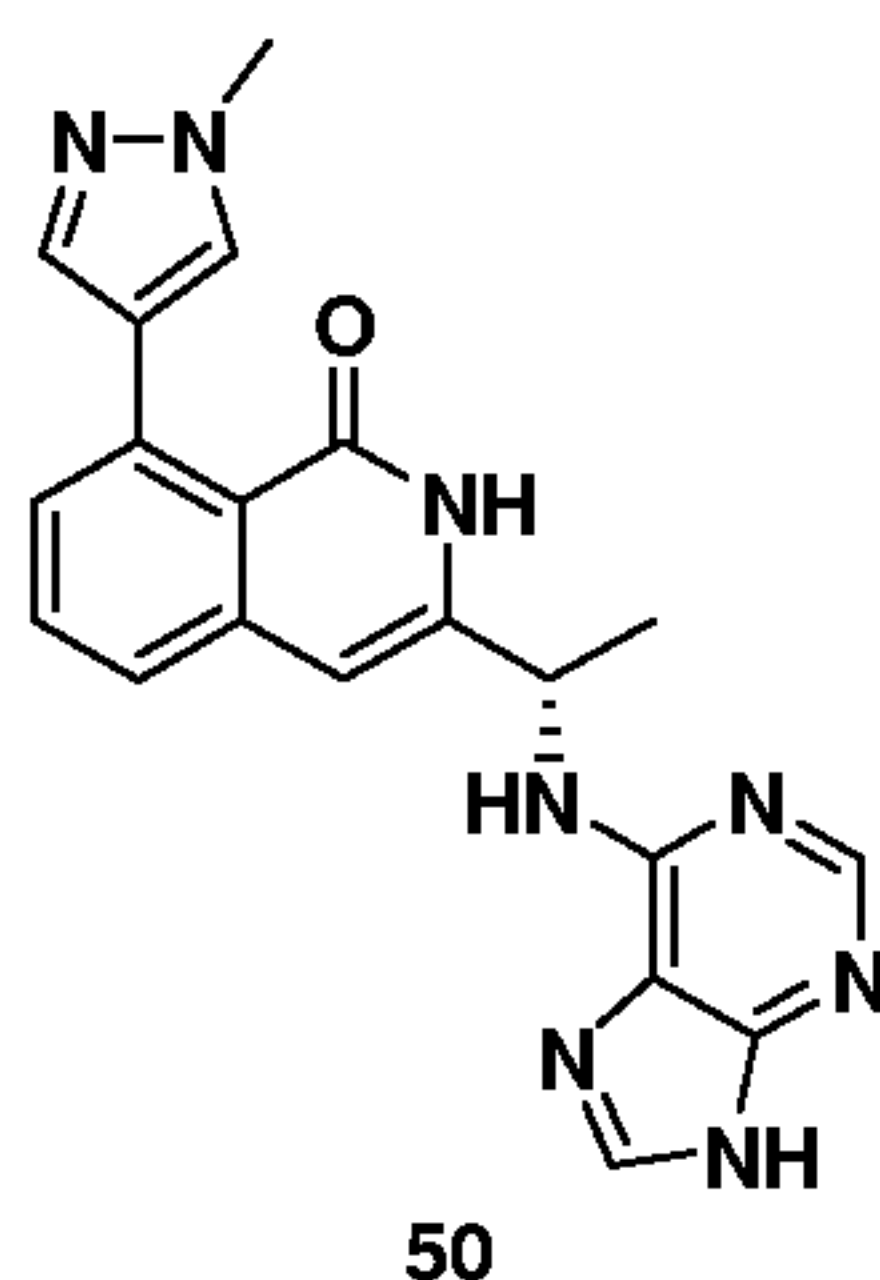
Example 28

[00454] Isoquinolinone **45** was prepared according to the following sequences: Amine **42** was prepared by Method I and converted to compound **43** using Method L. The compound **44** was then obtained in analogous fashion to compound **27** in Example 16. Compound **44** was then converted to compound **45** using Method M. ESI-MS m/z : 481.45 (M+H)⁺.

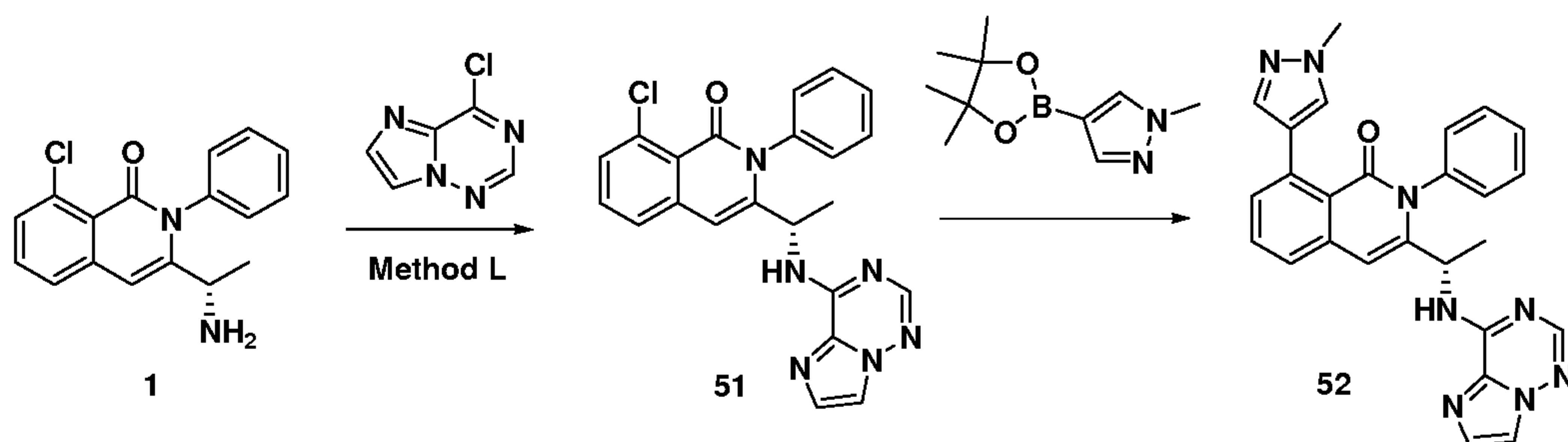


Isoquinoline **49** was prepared according to the following sequences: Amine **46** was prepared by Method I and converted to compound **47** using Method L. Compound **48** was then coupled to pyridin-3-ylboronic using the analogous procedure in Example 20 after which it was converted to the compound **49** according to the following procedure:

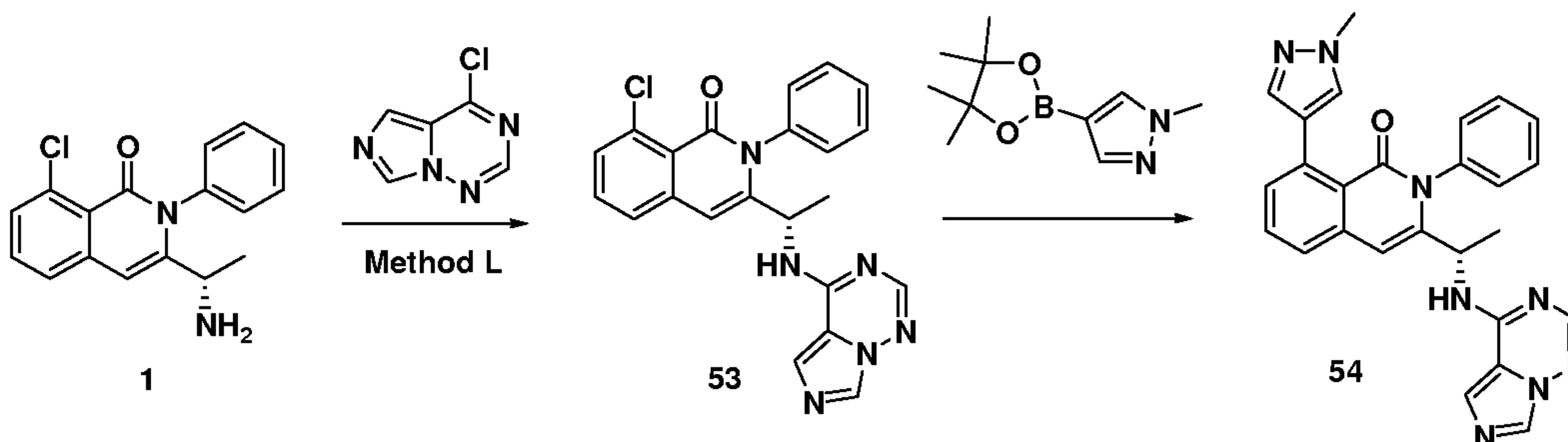
[00455] Compound **48** (290 mg, 0.49 mmol) was dissolved in trifluoroacetic acid (20 mL) and the resulting mixture was stirred at reflux for 48 h. The mixture was allowed to cool RT and then concentrated *in vacuo* to remove the excess amount of trifluoroacetic acid. The residue was diluted with water (50 mL), neutralized with aqueous Na₂CO₃ solution to adjust the PH to 8 and then extracted with DCM (100 mL x 3). The combined organic layer was dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated to dryness *in vacuo* and the residue was purified by flash chromatography on silica gel (gradient of 1-20% methanol/methylene chloride) to give the product **49** (80 mg, 42.6% yield) as an off-white solid. ESI-MS m/z : 384.2 [M+H]⁺.

Example 30

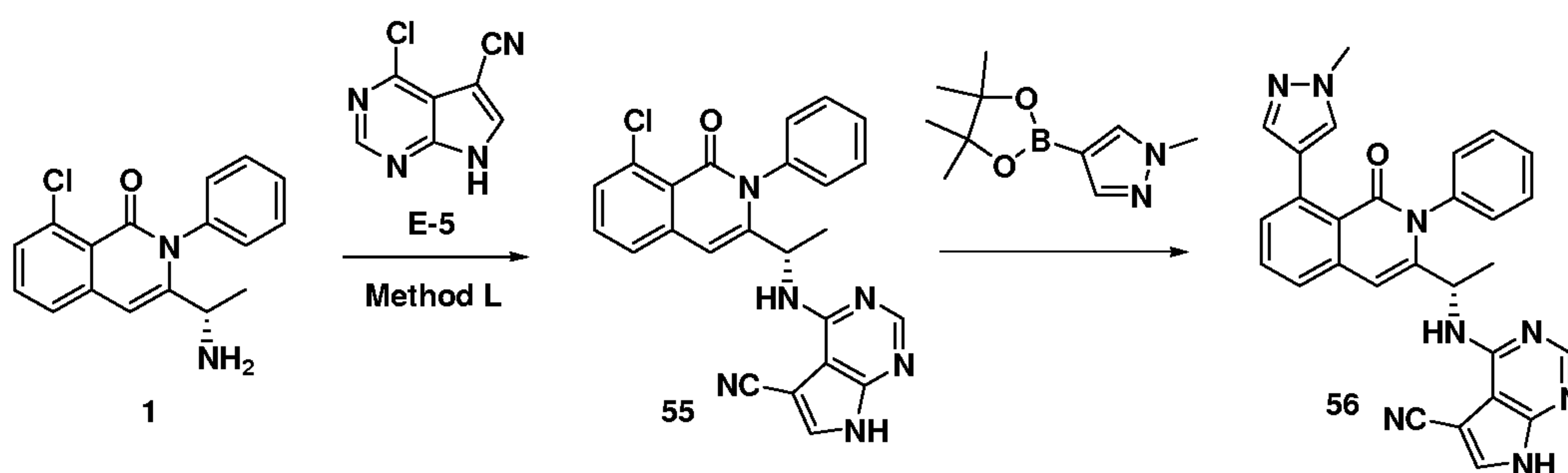
[00456] Compound **50** was prepared in analogous fashion to compound **49** in Example 29 except that 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of 3-pyridylboronic acid. . ESI-MS m/z : 387.2 $[M+H]^+$.

Example 31

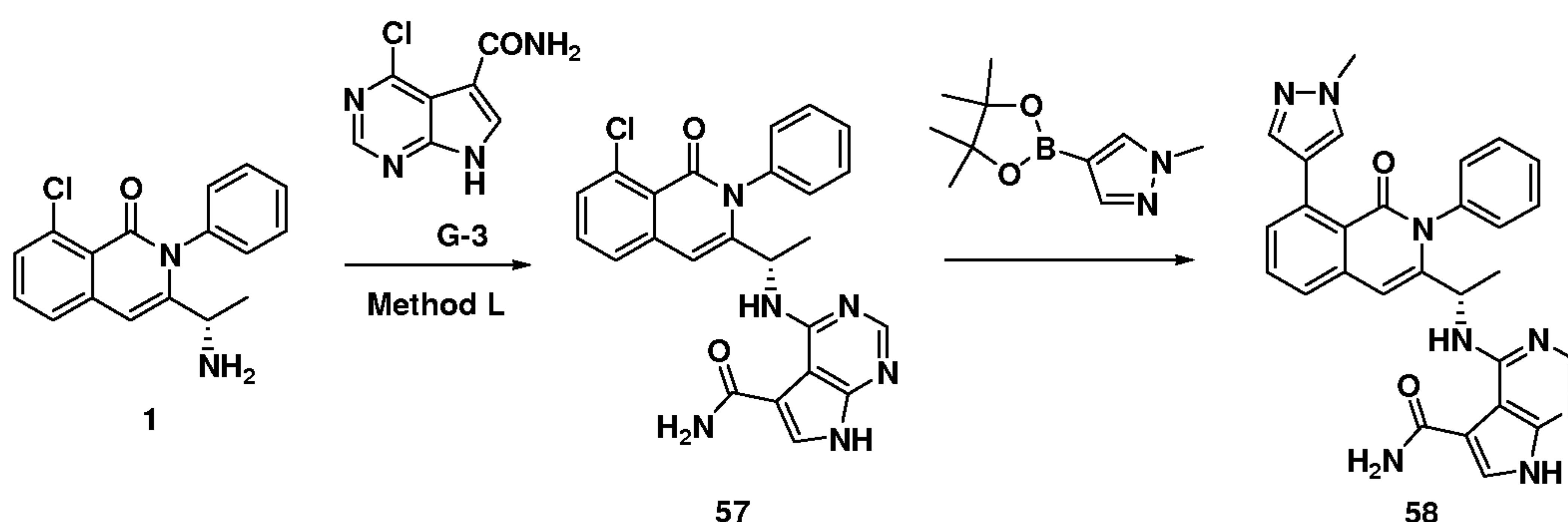
[00457] Isoquinolinone **52** was prepared from compound **1** in 2 steps. Compound **1** was converted to compound **51** using Method L. Compound **51** was then coupled to 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using the analogous conditions from Example 20 to provide compound **52**. ESI-MS m/z : 463.4 $[M+H]^+$.

Example 32

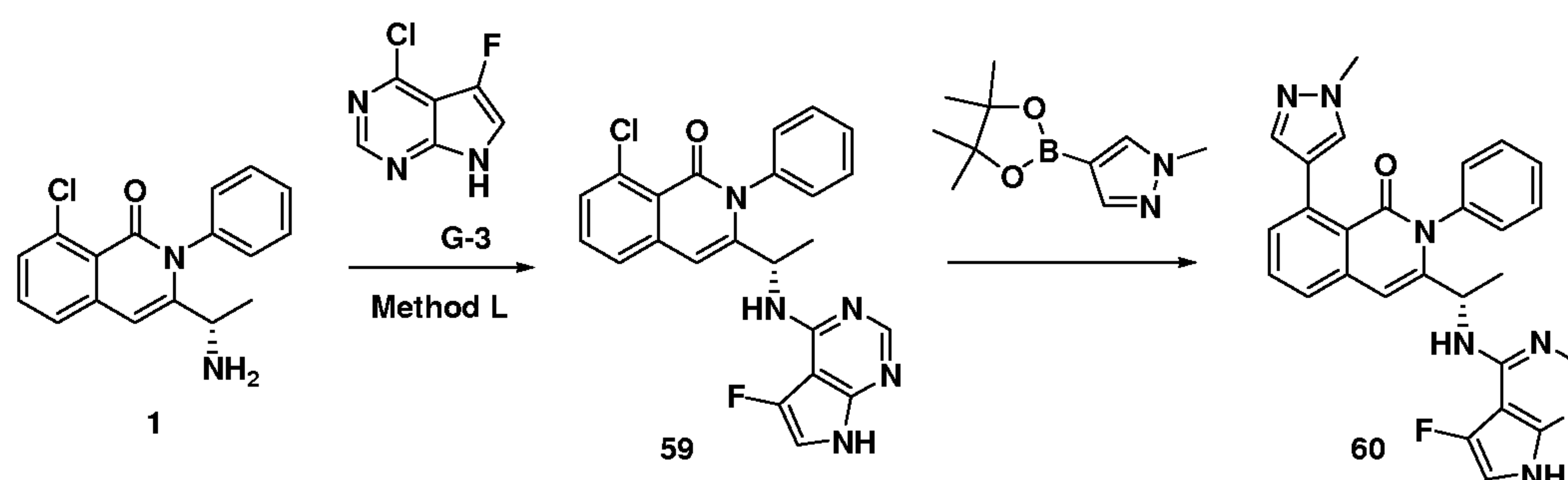
[00458] Isoquinolinone **54** was prepared from compound **1** in 2 steps. Compound **1** was converted to compound **53** using Method L. Compound **53** was then coupled to 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using the analogous conditions from Example 20 to provide compound **54**. ESI-MS m/z : 463.35 $[M+H]^+$.

Example 33

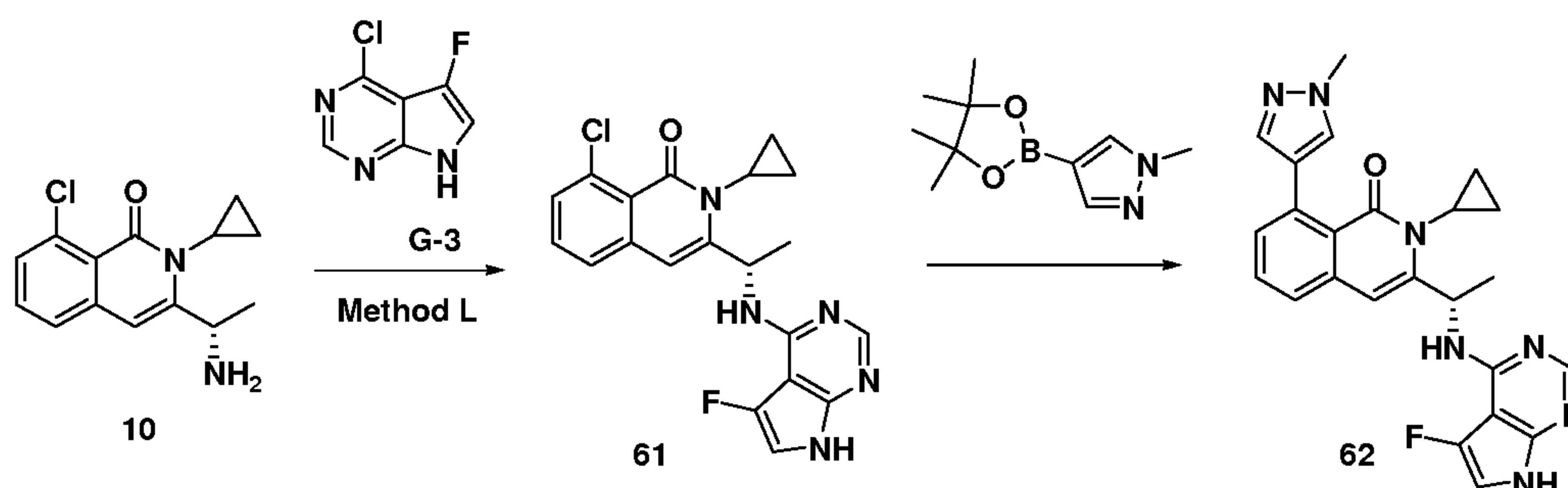
[00459] Isoquinolinone **56** was prepared from compound **1** in 2 steps. Compound **1** was converted to compound **55** using Method L. Compound **55** was then coupled to 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using the analogous conditions from Example 20 to provide compound **56**. ESI-MS m/z : 487.2 $[M+H]^+$.

Example 34

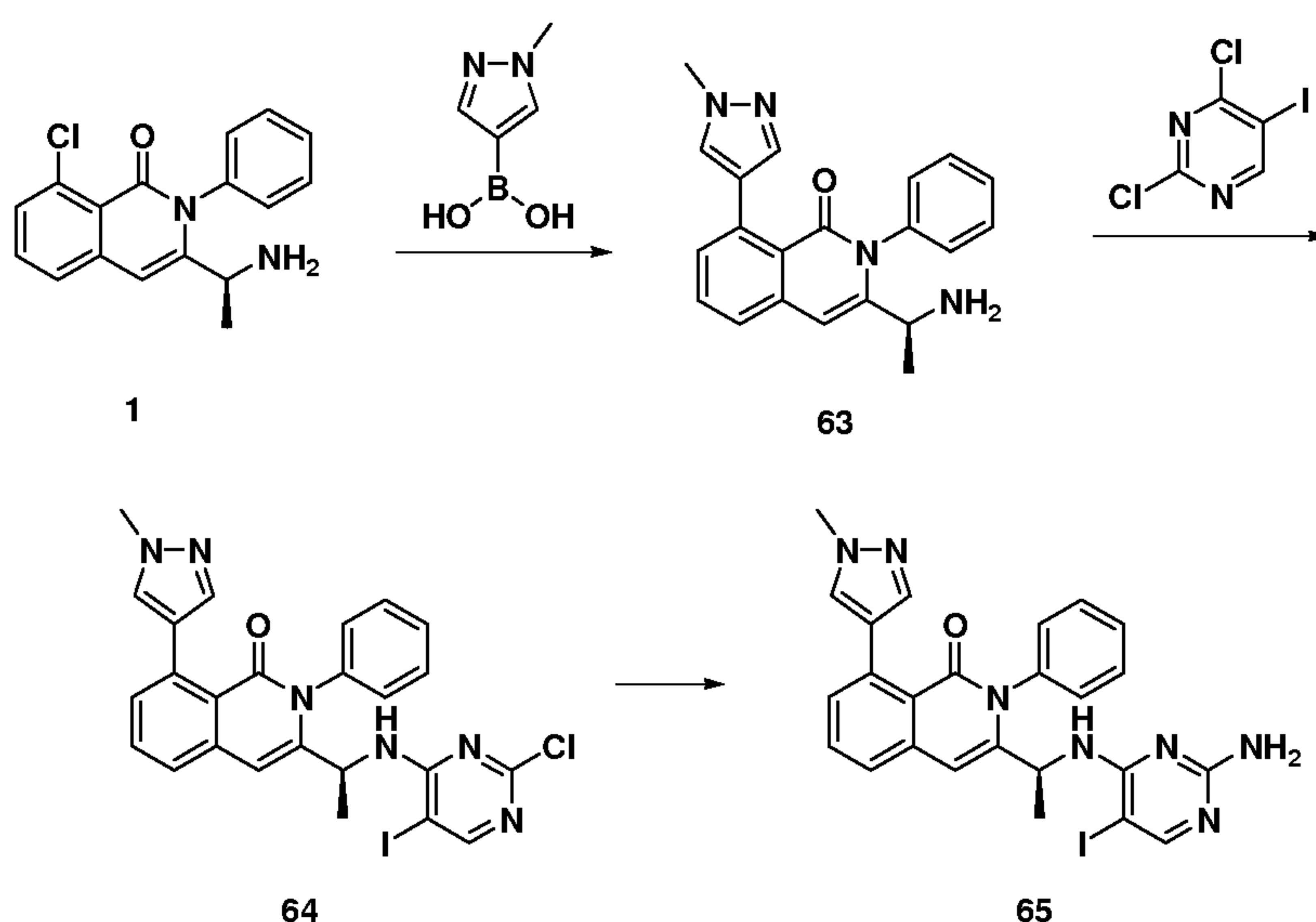
[00460] Isoquinolinone **58** was prepared from compound **1** in 2 steps. Compound **1** was converted to compound **57** using Method L. Compound **57** was then coupled to 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using the analogous conditions from Example 20 to provide compound **58**. ESI-MS m/z : 505.2 $[M+H]^+$.

Example 35

[00461] Isoquinolinone **60** was prepared from compound **1** in 2 steps. Compound **1** was converted to compound **59** using Method L. Compound **59** was then coupled to 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using the analogous conditions from Example 20 to provide compound **60**. ESI-MS m/z : 480.2 $[M+H]^+$.

Example 36

[00462] Isoquinolinone **62** was prepared from compound **10** in 2 steps. Compound **10** was converted to compound **61** using Method L. Compound **61** was then coupled to 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole using the analogous conditions from Example 20 to provide compound **62**. ESI-MS m/z : 444.2 $[M+H]^+$.

Example 37

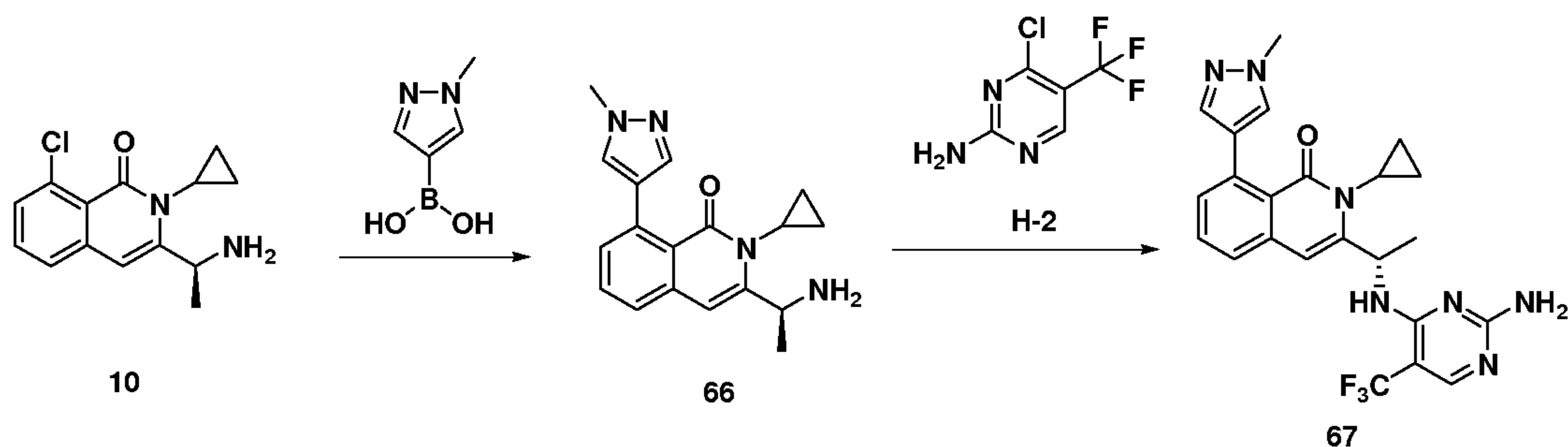
[00463] To a mixture of (S)-3-(1-aminoethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (**1**) (1.0 g, 3.35 mmol) and 1-methyl-1H-pyrazole-4-boronic acid (815 mg, 5.02 mmol) in anhydrous DMA (10 mL) in a sealed tube, $\text{PdCl}_2(\text{dppf})$ (219 mg, 0.27 mmol) and aqueous Na_2CO_3 solution (1 M, 10.0 mL, 10.0 mmol) were added and the resulting mixture was stirred at 120 °C for 3 h. The reaction mixture was allowed to cool to RT, quenched with water, and then extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-8% MeOH-DCM) to afford the product, (S)-3-(1-aminoethyl)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenylisoquinolin-1(2H)-one (**63**) (990 mg, 85% yield) as a pink/magenta solid. ESI-MS m/z : 345.2 $[M+H]^+$.

[00464] (S)-3-(1-Aminoethyl)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenylisoquinolin-1(2H)-one (**63**) (570 mg, 1.66 mmol), 2,4-dichloro-5-iodopyrimidine (455 mg, 1.66 mmol) and DIEA (0.27 mL, 1.66 mmol) were dissolved

in n-butanol (12 mL) in a sealed tube, and the resulting mixture was stirred at 100 °C for 16 h. The mixture was allowed to cool to RT, quenched with water and extracted with ethyl acetate (150 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* to afford the product (S)-3-(1-((2-chloro-5-iodopyrimidin-4-yl)amino)ethyl)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenylisoquinolin-1(2H)-one (64) as an oil. The product obtained was used in the next step without purification. ESI-MS *m/z*: 583.0 [M+H]⁺.

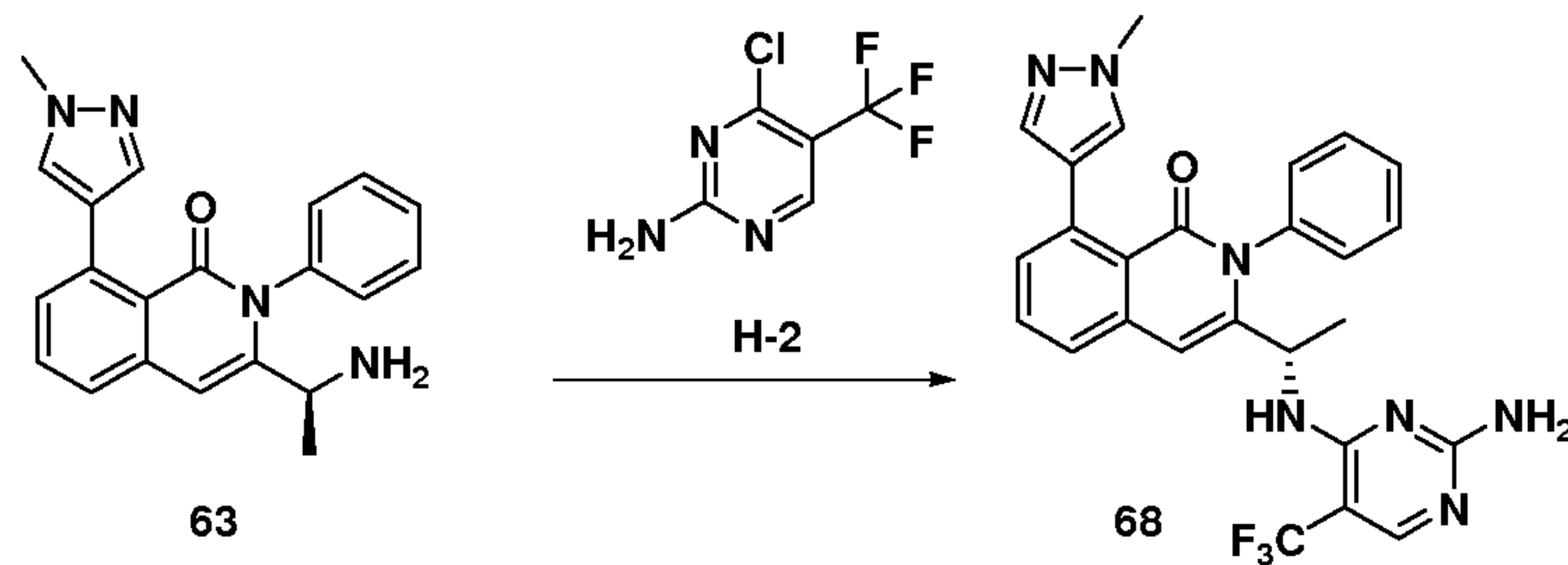
[00465] To a solution of (S)-3-(1-((2-chloro-5-iodopyrimidin-4-yl)amino)ethyl)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenylisoquinolin-1(2H)-one (64) (964 mg, 1.65 mmol) in anhydrous 1,4-dioxane (5 mL) in a sealed tube, ammonium hydroxide (6 mL) was added and the resulting mixture was stirred at 110 °C for 16 h. An additional amount of ammonium hydroxide (3 mL) was added to the reaction mixture and stirring was continued for 16 h. The mixture was allowed to cool to RT, quenched with water and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-8% MeOH-DCM) to afford the product, (S)-3-(1-((2-amino-5-iodopyrimidin-4-yl)amino)ethyl)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenylisoquinolin-1(2H)-one (65) (532 mg, 57% yield) as a light tan solid. ESI-MS *m/z*: 564.0 [M+H]⁺.

Example 38

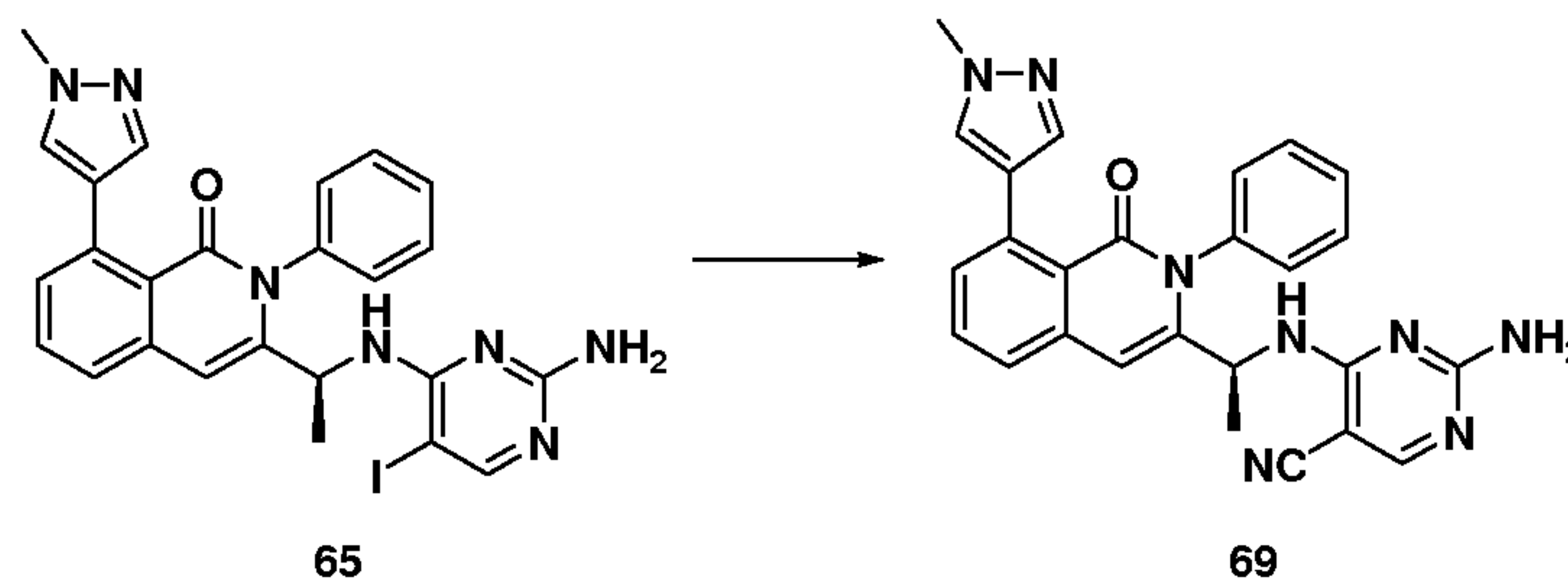


[00466] Compound 67 was prepared in 2 steps from amine 10. Compound 66 was prepared using analogous Suzuki coupling procedures as in the conversion of 1 to 63 in Example 37. Compound 66 was then converted to 67 using the same conditions in Example 37 except that H-2 was used in place of 2,4-dichloro-5-iodopyrimidine. ESI-MS *m/z*: 470.2 [M+H]⁺.

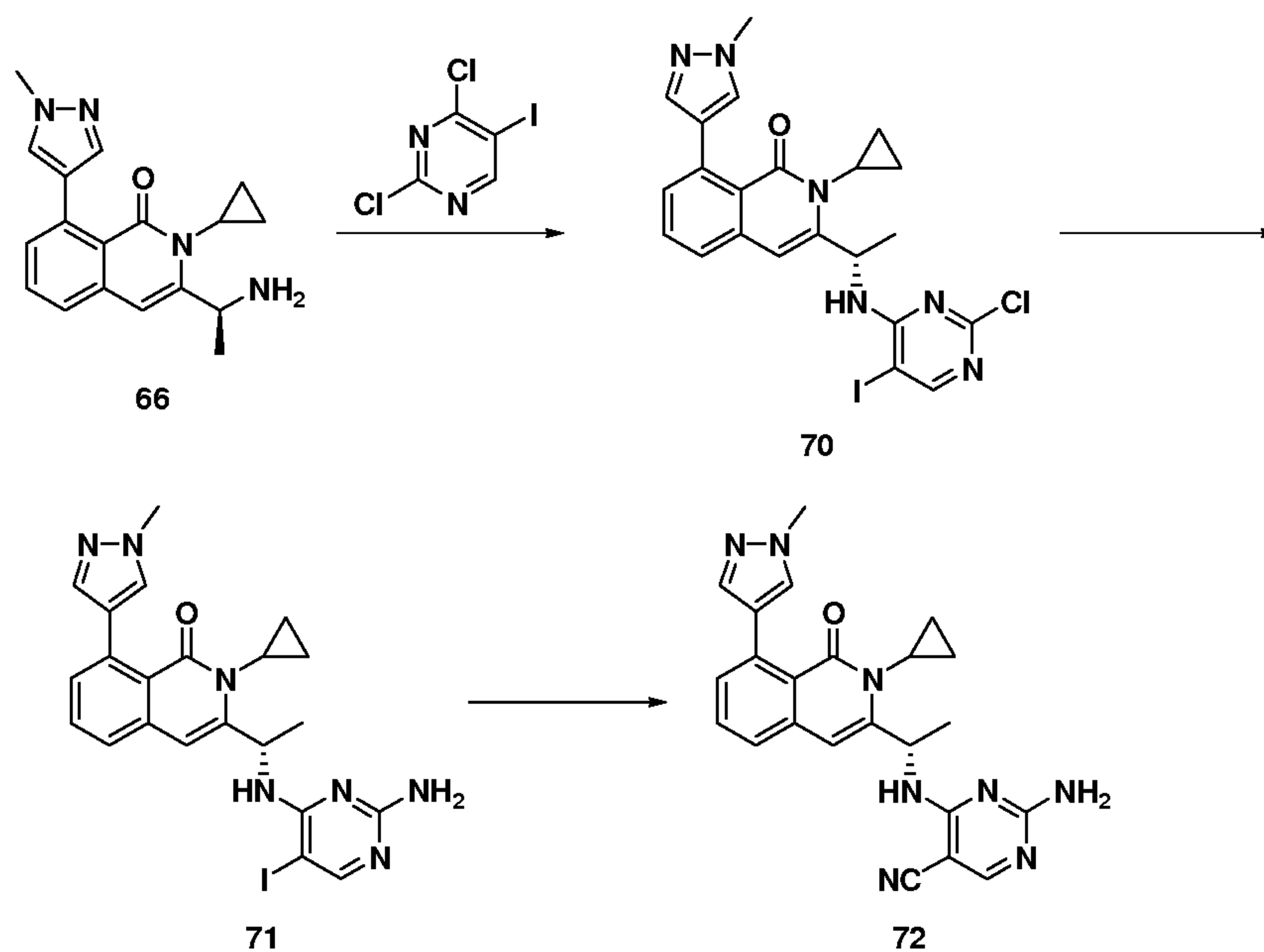
Example 39



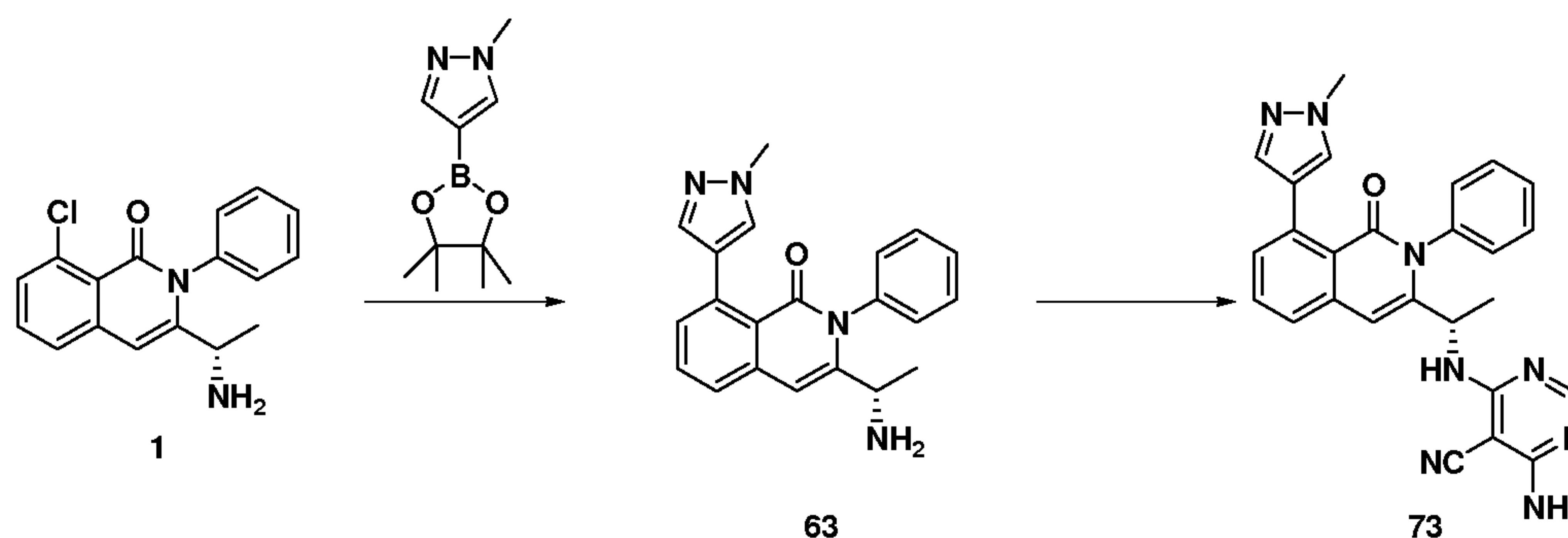
[00467] Compound 68 was prepared in analogous fashion to compound 64 in Example 37 except that H-2 was used in place of 2,4-dichloro-5-iodopyrimidine. ESI-MS *m/z*: 506.2 [M+H]⁺.

Example 40

[00468] To a solution of (S)-3-(1-((2-amino-5-iodopyrimidin-4-yl)amino)ethyl)-8-(1-methyl-1H-pyrazol-4-yl)-2-phenylisoquinolin-1(2H)-one (**65**) (240 mg, 0.43 mmol) in anhydrous acetonitrile (12 mL) in a sealed tube, sodium cyanide (209 mg, 4.26 mmol), tetrakis(triphenylphosphine) palladium(0) (246 mg, 0.21 mmol), and copper iodide (57 mg, 0.30 mmol) were added and the resulting mixture was stirred at 80 °C for 16 h. The mixture was allowed to cool to RT, quenched with water and extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by ISCO (silica gel cartridge, 0-10% MeOH-DCM) to afford the product, (S)-2-amino-4-((1-(8-(1-methyl-1H-pyrazol-4-yl)-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)amino)pyrimidine-5-carbonitrile (**69**) (60 mg, 30% yield). ESI-MS *m/z*: 463.2 [M+H]⁺.

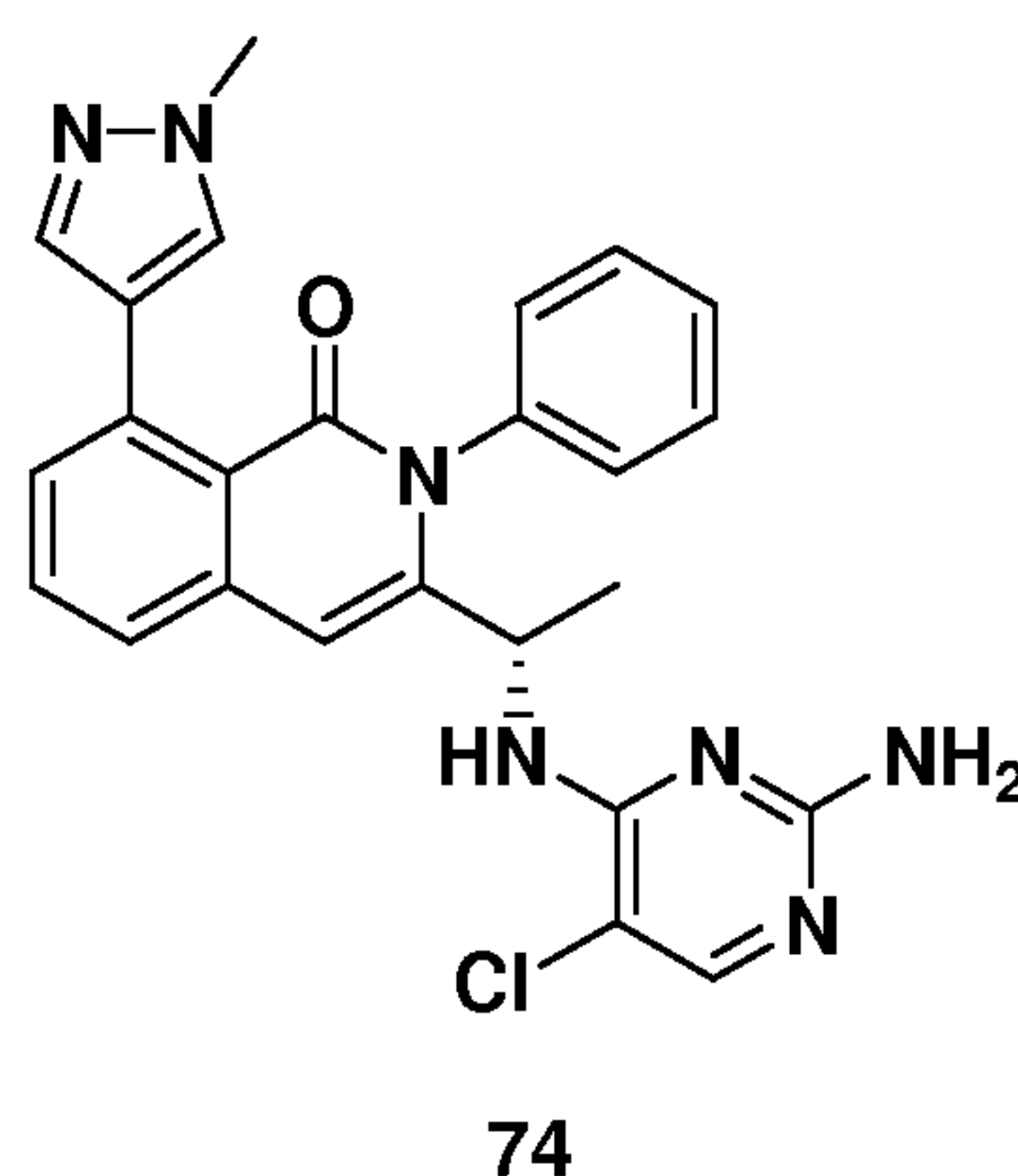
Example 41

[00469] Compound **72** was prepared in 3 steps from compound **66**. Compound **66** was converted to **70** and then **71** using the analogous procedures in Example 37. Compound **71** was then converted to the product **72** using the procedure in Example 40. ESI-MS *m/z*: 427.2 [M+H]⁺.

Example 42

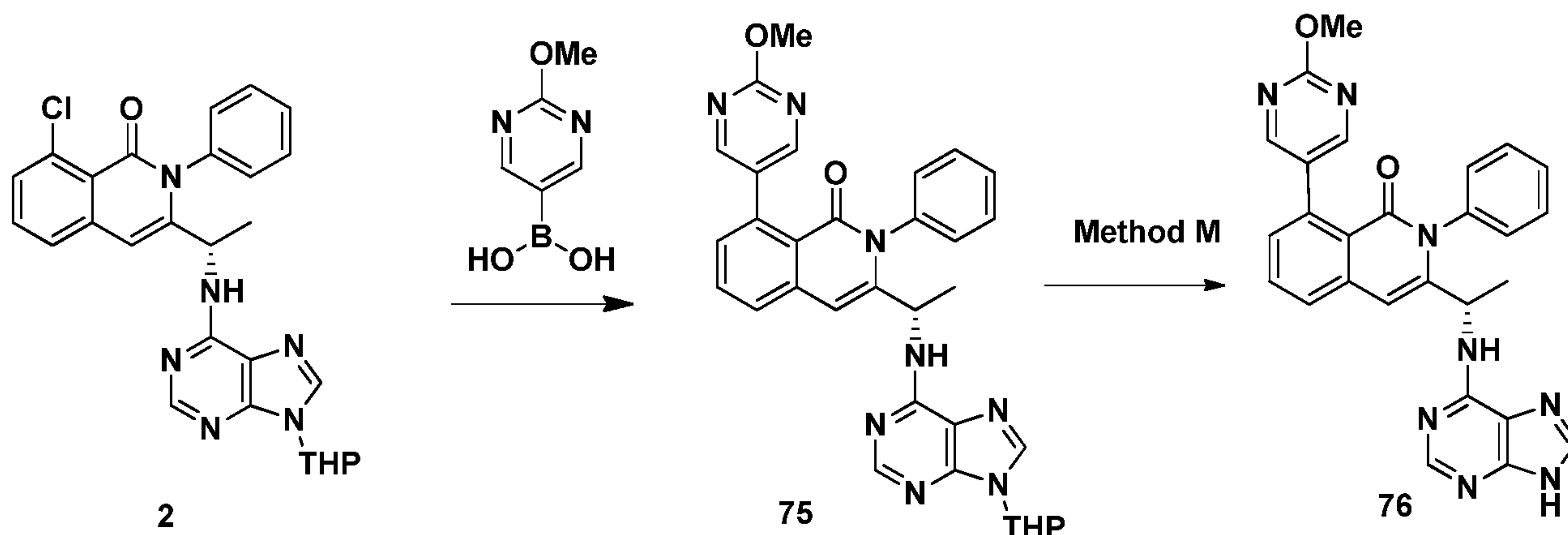
[00470] Compound **73** was prepared in two steps from compound **1** according to the following procedures: Compound **1** (860 mg, 2.9 mmol, 1 eq.), 1-methylpyrazole-4-boronic acid pinacol ester (1.8 g, 3 eq.), sodium carbonate (1.6 g, 5 eq.), palladium diacetate (100 mg, 0.15 eq.) and RuPhos (400 mg, 0.30 eq) were combined in a 20 mL septum-sealed microwave reaction tube with stir bar. The tube was purged with vacuum and refilled with dry argon three times, then charged with 1,4-dioxane (16 mL) and water (4 mL), and subjected to microwave heating at 125 °C for 3h. The reaction mixture was then purified using flash silica gel chromatography (30g of silica gel packed using a solution of 1% triethylamine in methylene chloride, mobile phase was a gradient of 1-4% methanol:methylene chloride) NMR analysis revealed this material to be a mixture of the amine **63** and 2.6 eq. of pinacol; this mixture was taken forward without further purification.

[00471] A 15 mL thick-walled tube with o-ring seal and stir bar was charged with amine intermediate **Z** (53% by mass, 300 mg, 0.46 mmol, 1 eq.), n-butanol (5 mL), diisopropylethylamine (160 uL, 2 eq.), and 4-chloro-5-cyano-6-aminopyrimidine (110 mg, 1.5 eq., commercially available from Ark Pharm, Inc.), capped tightly, and heated in a 120 °C bath during 3d. The solvent was removed *in vacuo*, the residue taken up in DCM and treated with silica gel, and concentrated. The compound was initially purified using flash silica gel chromatography (gradient of 0-5% methanol:methylene chloride). A sample of this material was further purified by partitioning between diethyl ether and 5% acetic acid in water, discarding the ether layer, and extracting the aqueous three times with methylene chloride. The combine organic layers were dried over sodium sulfate to provide compound **73** in 31% yield. . ESI-MS *m/z*: 463.26 [M+H]⁺.

Example 43

[00472] Compound **74** was prepared in analogous fashion to compound **72** in Example 41 except that 2,4,5-trichloropyrimidine was used in place of 2,4-dichloro-5-iodopyrimidine. ESI-MS m/z : 472.2 $[M+H]^+$.

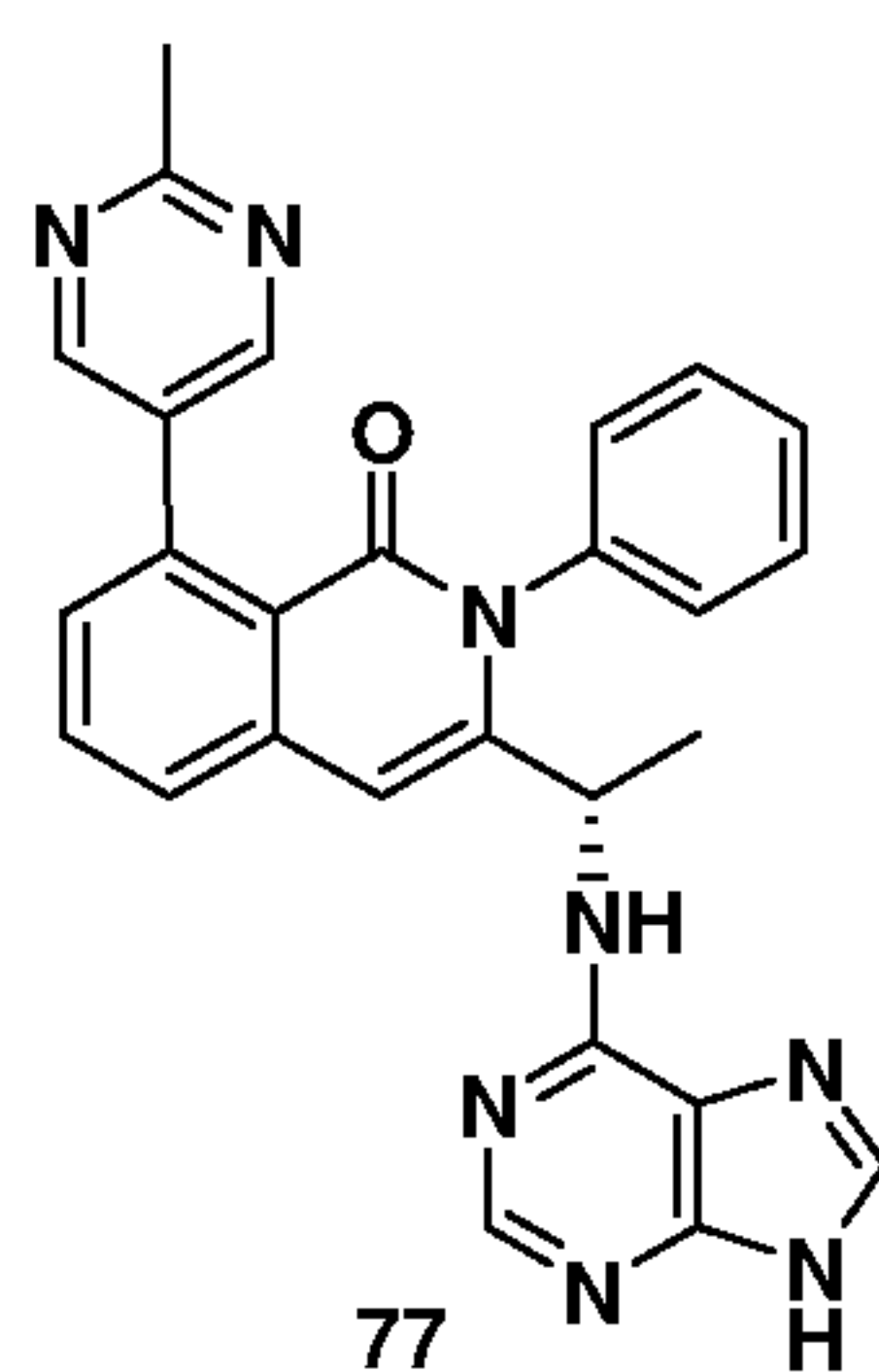
Example 44



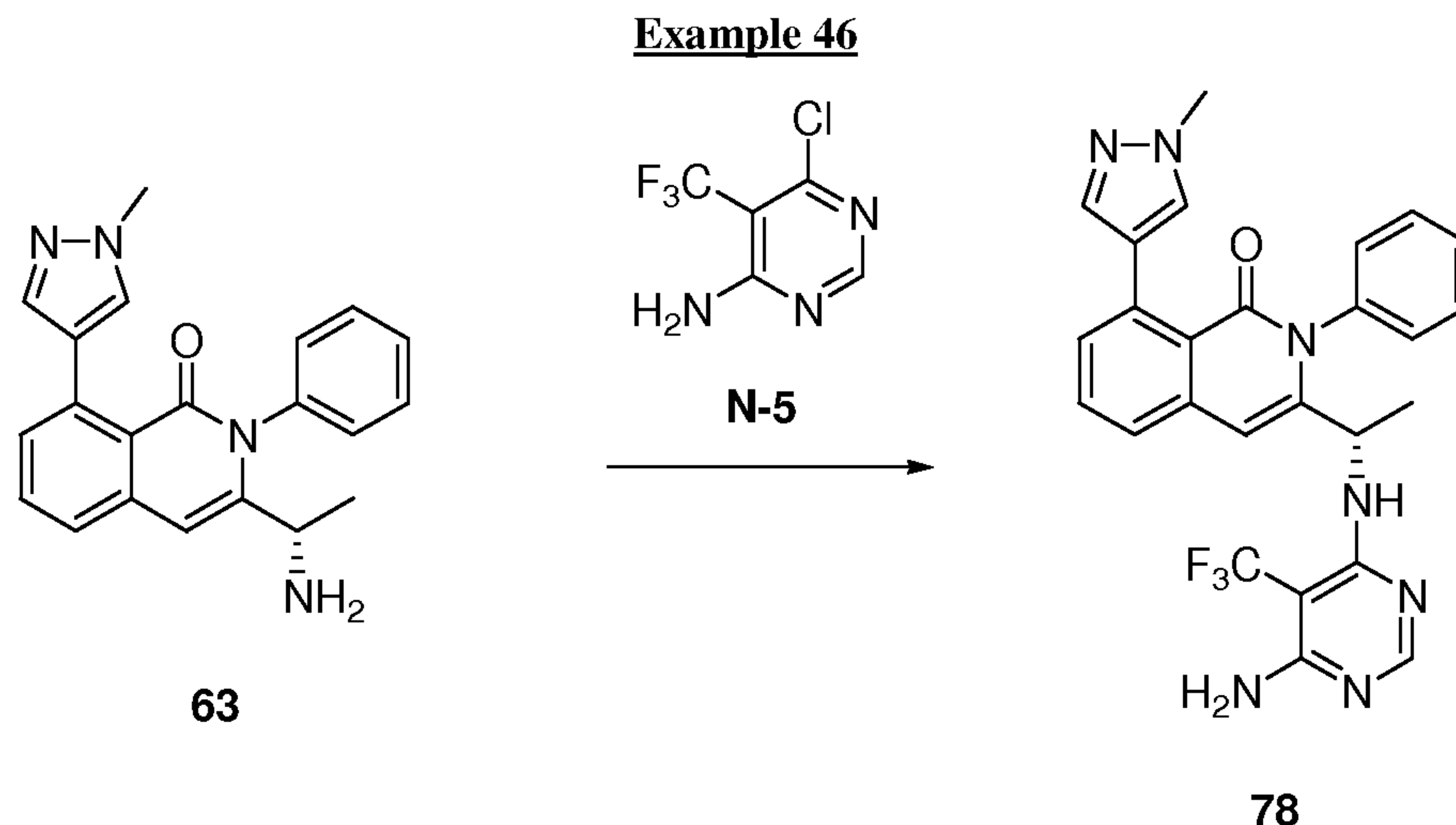
[00473] Compound **76** was prepared from compound **2** in two steps: A 2mL thick-walled microwave-reaction tube with stir bar was charged with compound **2** (120 mg, 0.24 mmol, 1 eq.), 2-methoxypyrimidine-5-boronic acid (74 mg, 2 eq.), sodium carbonate (130 mg, 5 eq.), palladium diacetate (8 mg, 0.15 eq.) and RuPhos (34 mg, 0.30 eq.), then capped with a septum and purged three time with vacuum, refilling with dry argon. 1,4-Dioxane (1.6 mL) and water (0.4 mL) were added and the reaction subjected to microwave heating at 125 °C during 3h, at which time LC/MS showed complete consumption of the starting chloride. The reaction mixture was diluted with DCM, treated with silica gel (0.5 g) and concentrated, then purified by flash chromatography, eluting 15g silica gel (gradient 1-4% methanol/methylene chloride) to provide 140 mg of compound **75** as an off-white powder. ESI-MS m/z 575.36 $[M+H]^+$.

[00474] Compound **75** was then converted to compound **76** using Method M. ESI-MS m/z : 491.22 $[M+H]^+$.

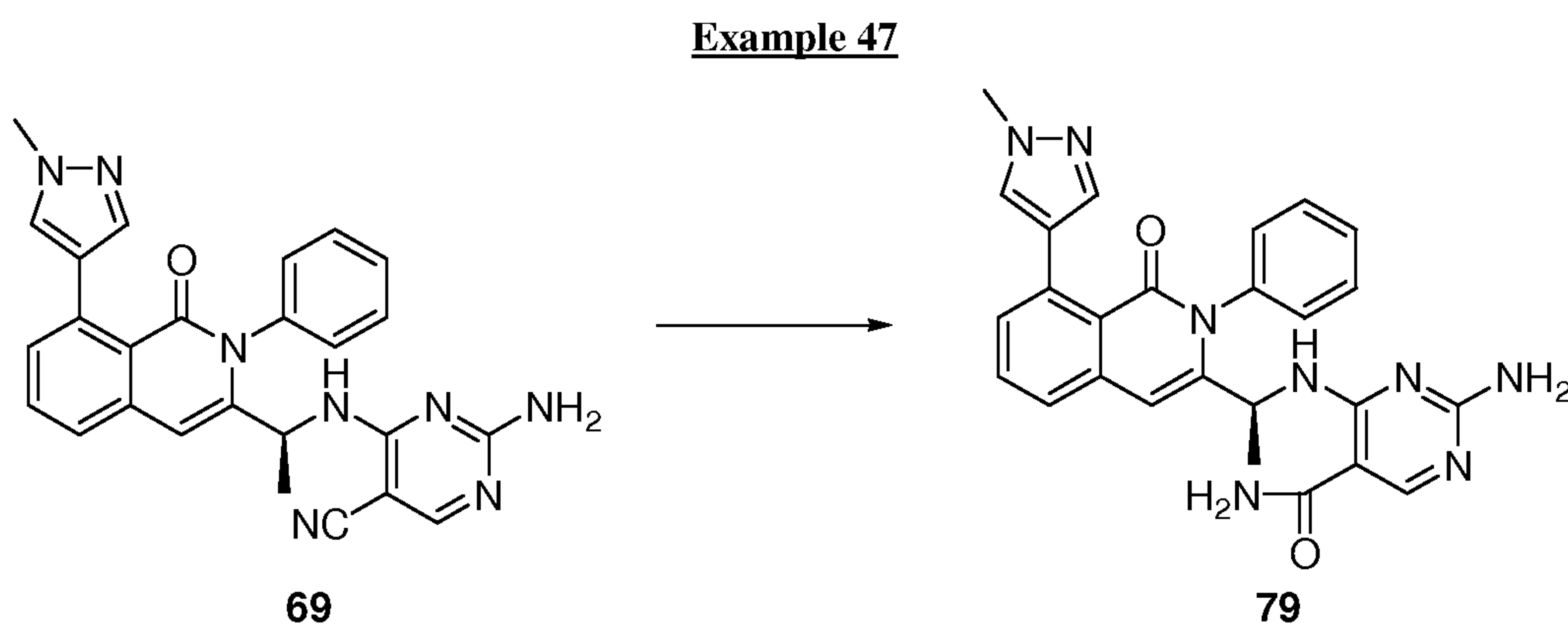
Example 45



[00475] Compound **77** was prepared in analogous fashion to compound **75** in Example 44 except that 2-methylpyrimidin-5-ylboronic acid was used in place of 2-methoxypyrimidin-5-ylboronic acid. ESI-MS m/z 475.21 [M+H]⁺



[00476] Compound **78** was prepared in analogous fashion to compound **64** in Example 37 except that **N-5** was used in place of 2,4-dichloro-5-iodopyrimidine and isopropanol was used in place of n-butanol. ESI-MS m/z : 506.2 [M+H]⁺.



[00477] Compound **79** was prepared from **69** according to the following procedure:

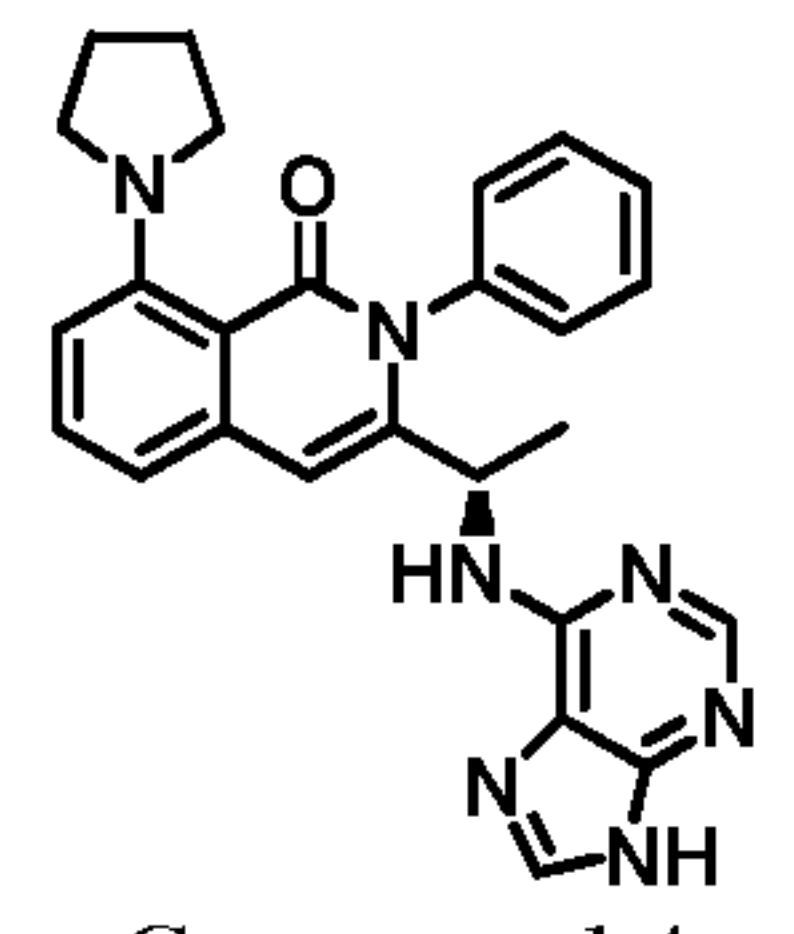
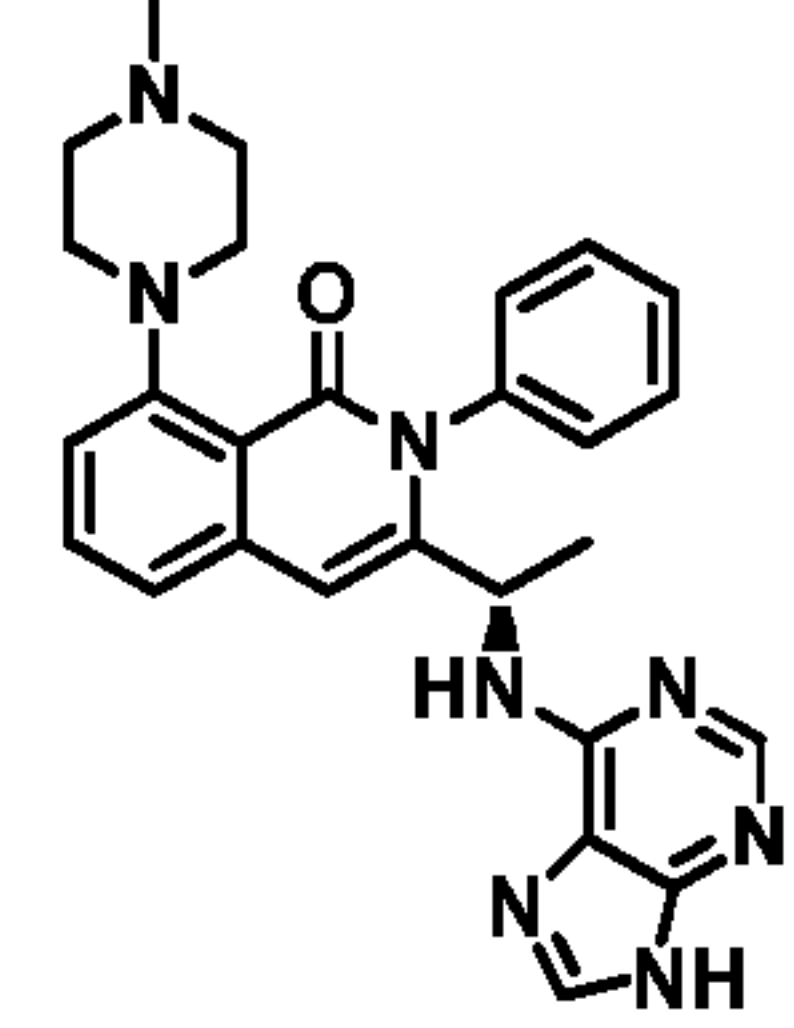
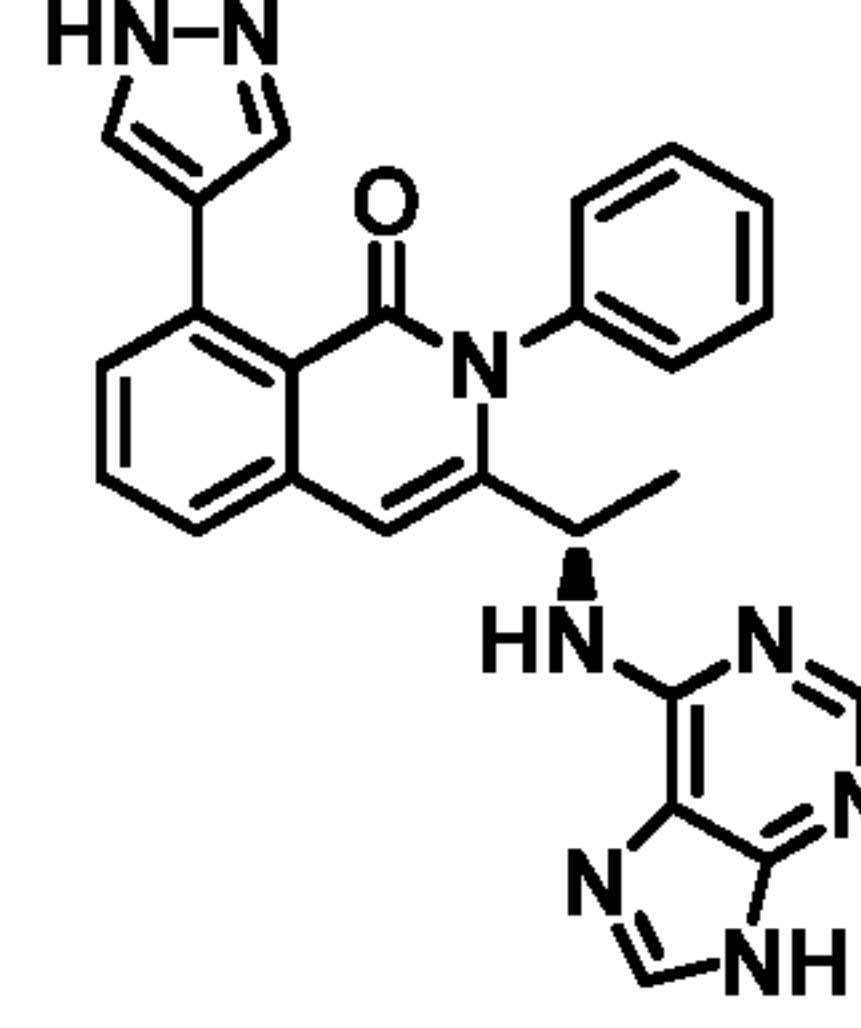
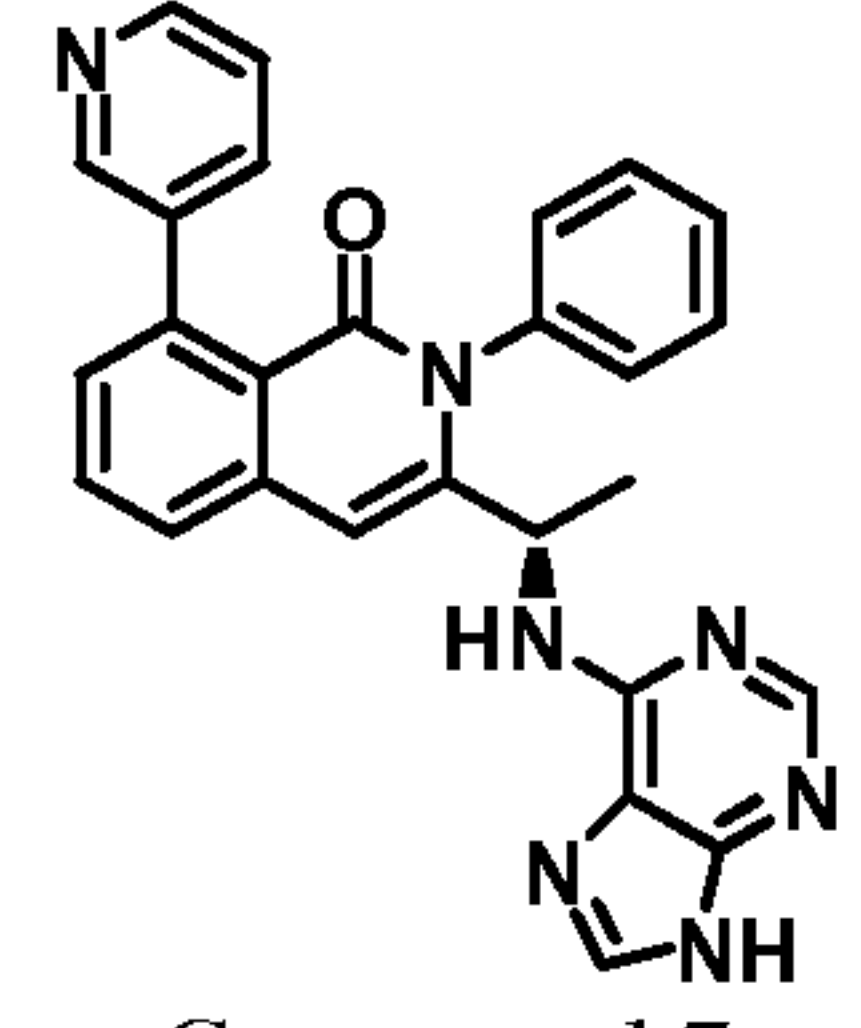
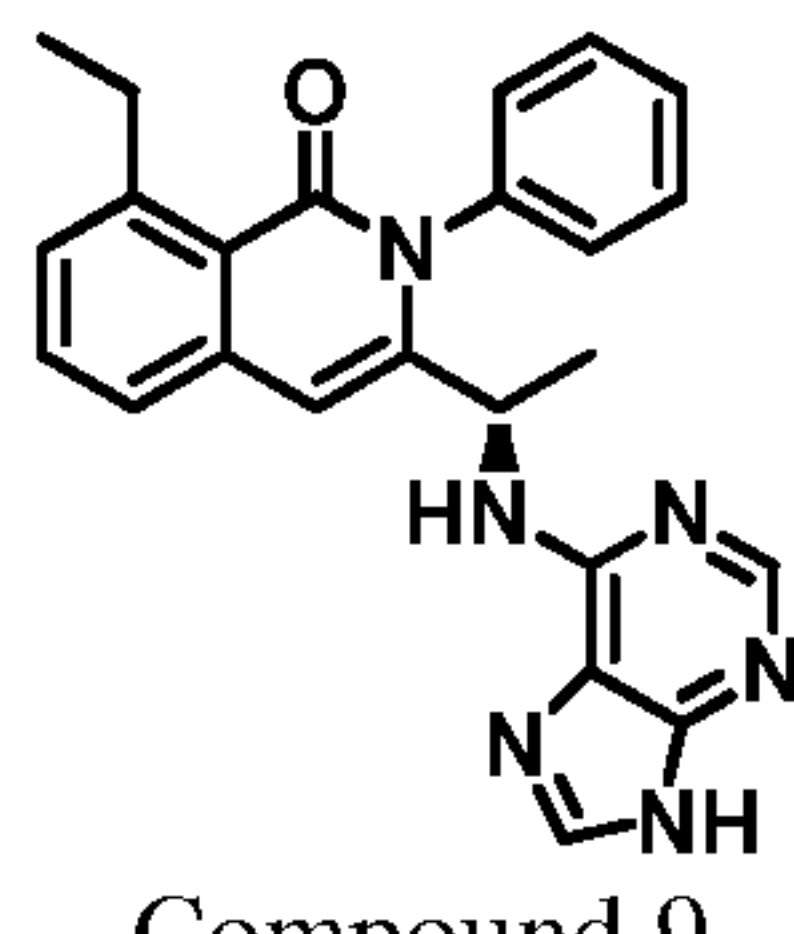
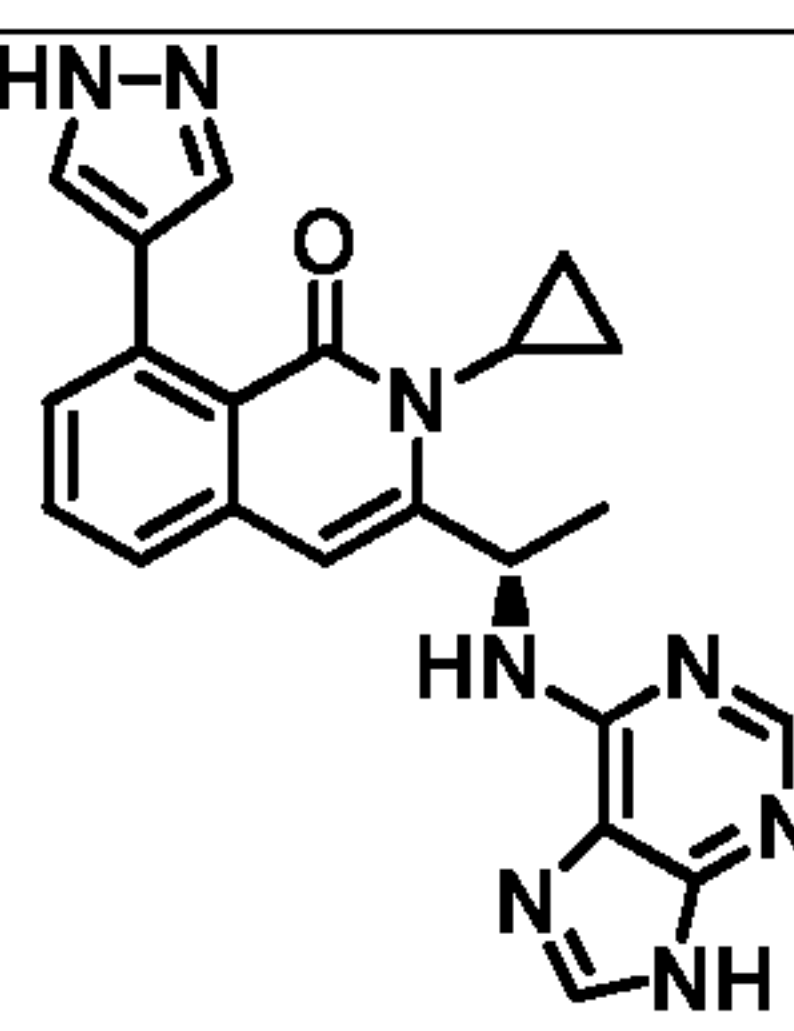
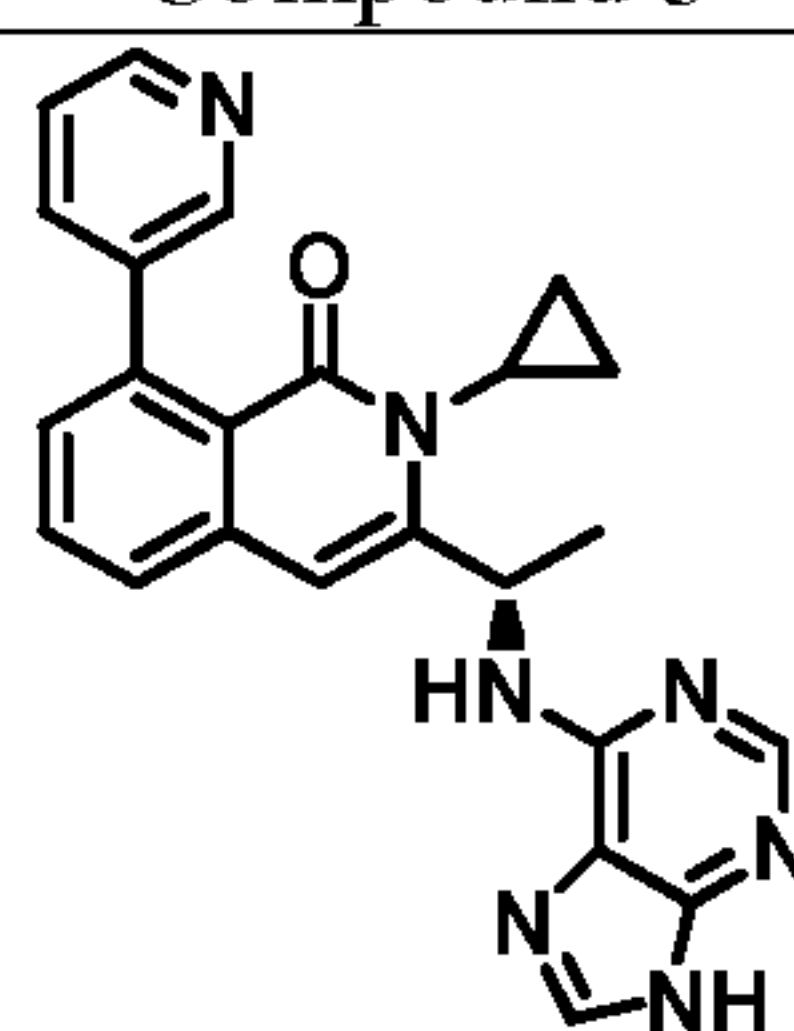
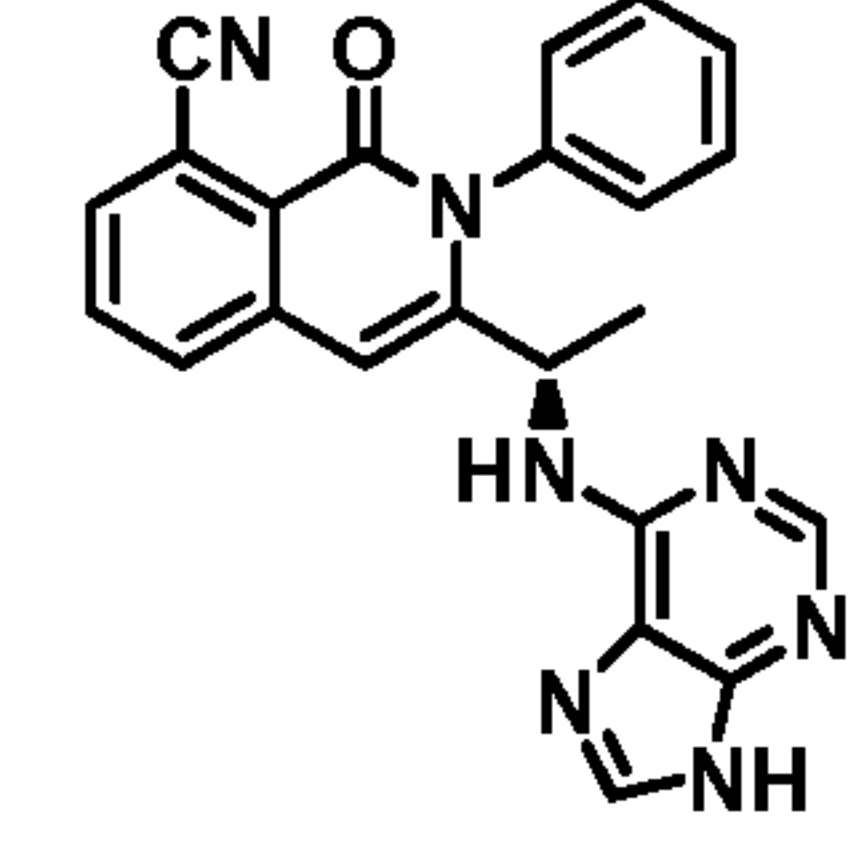
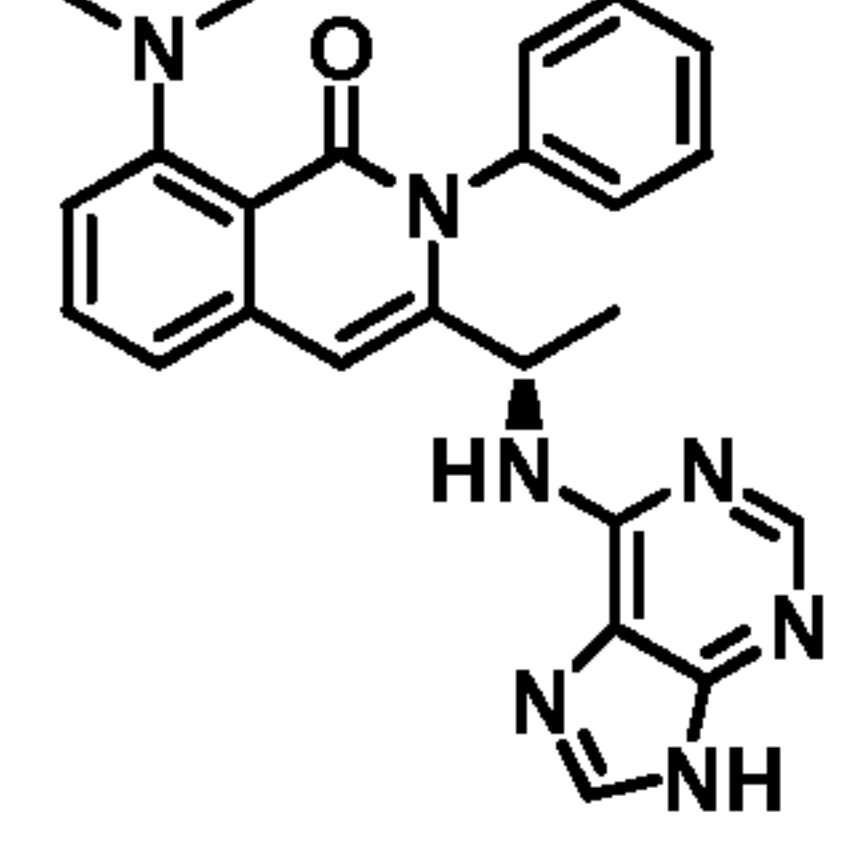
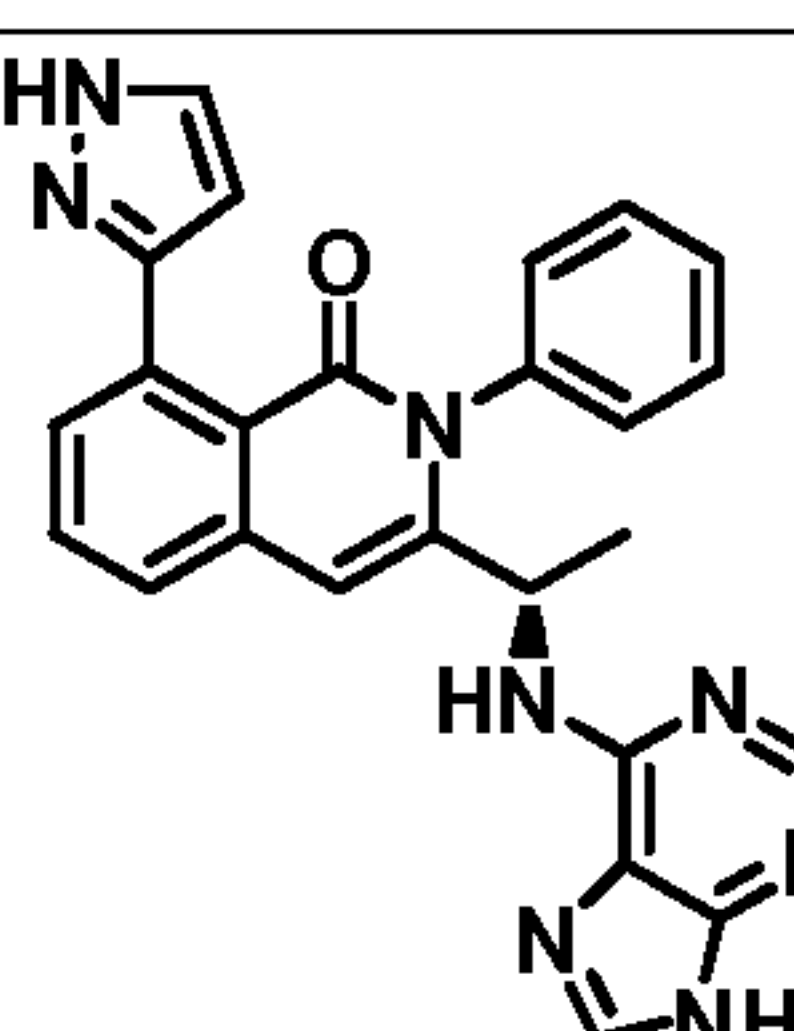
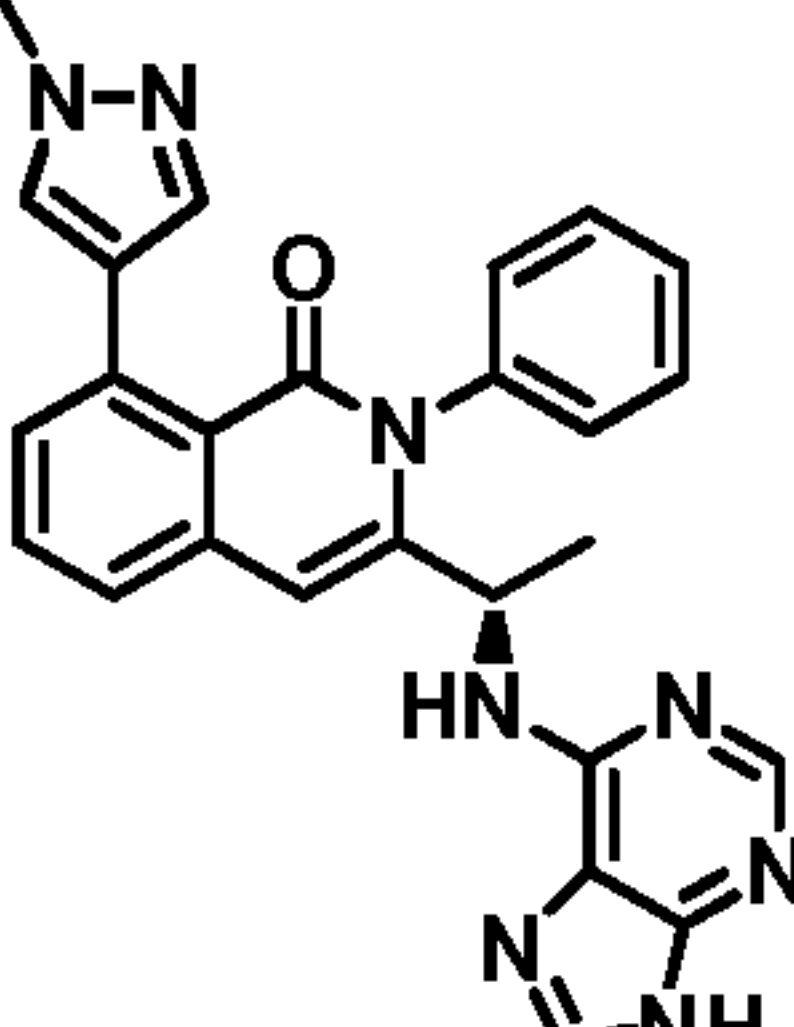
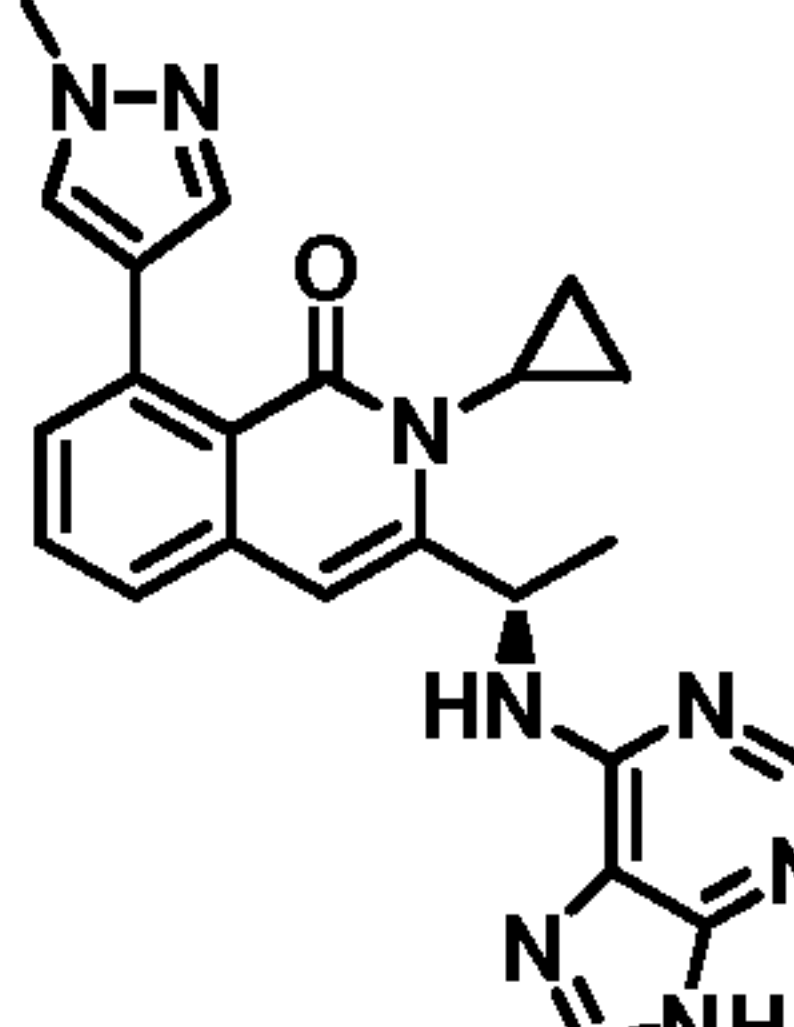
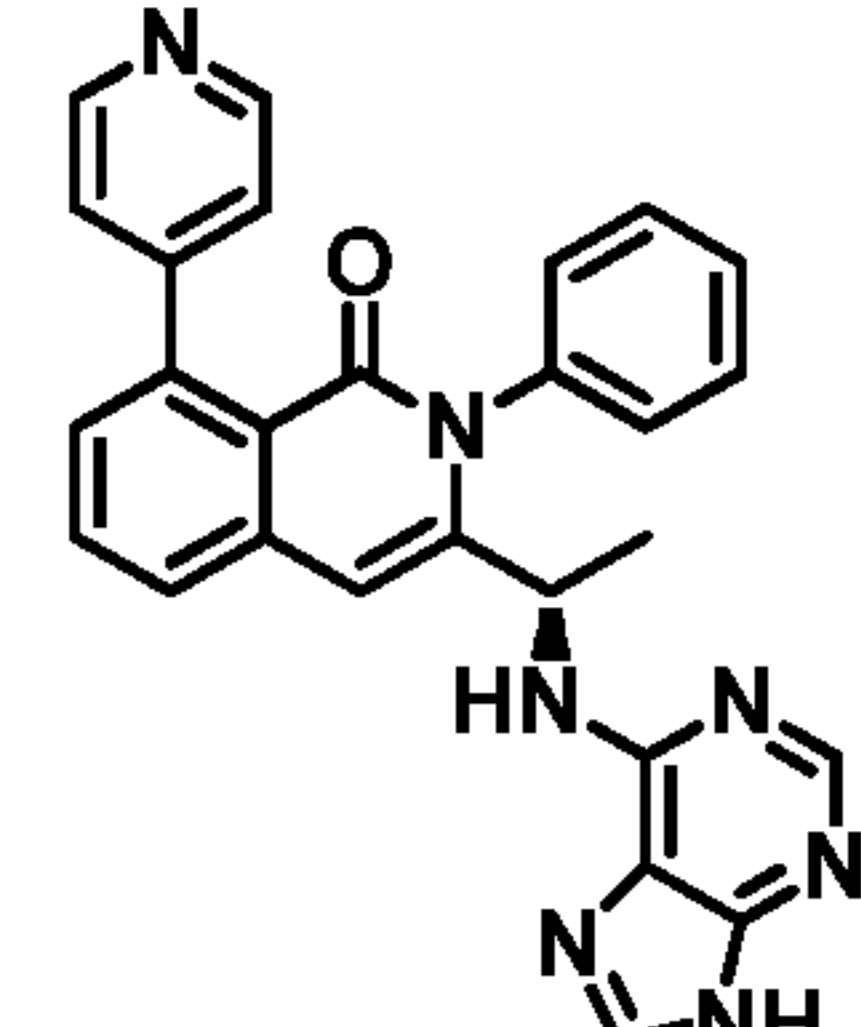
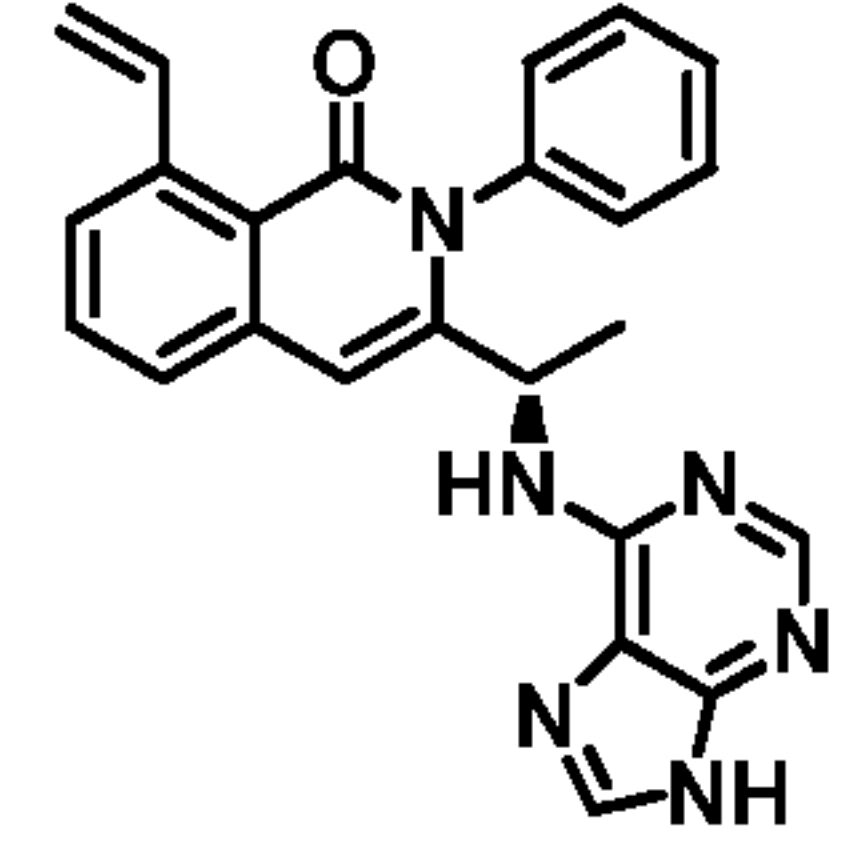
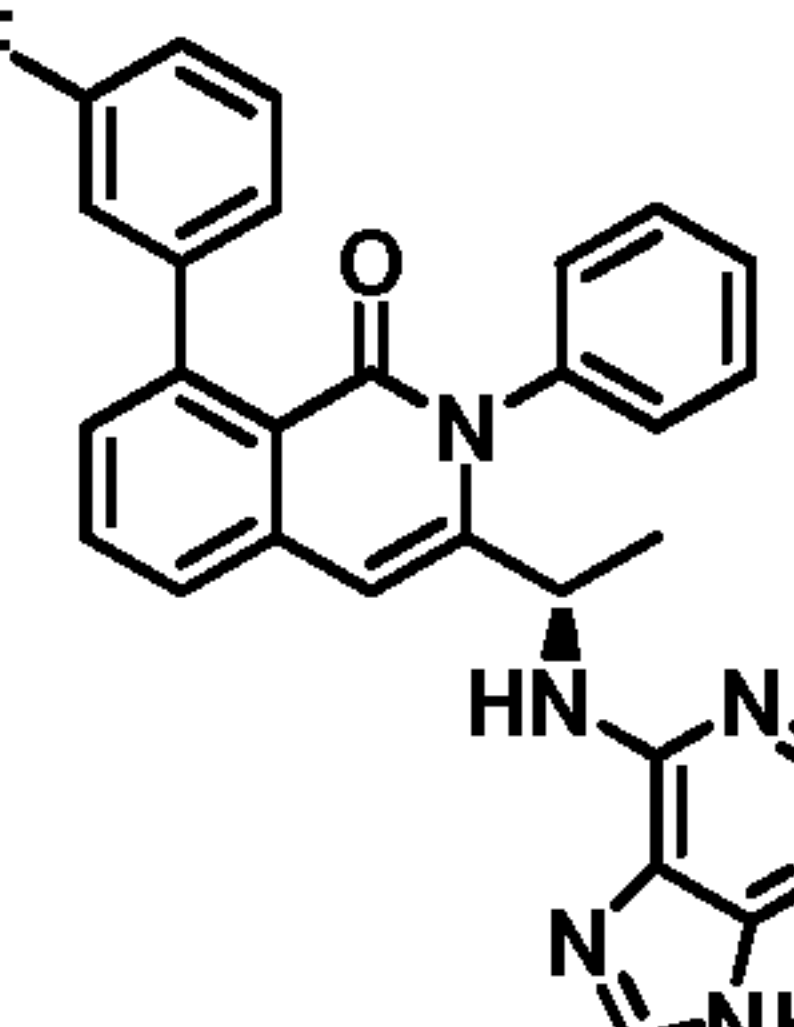
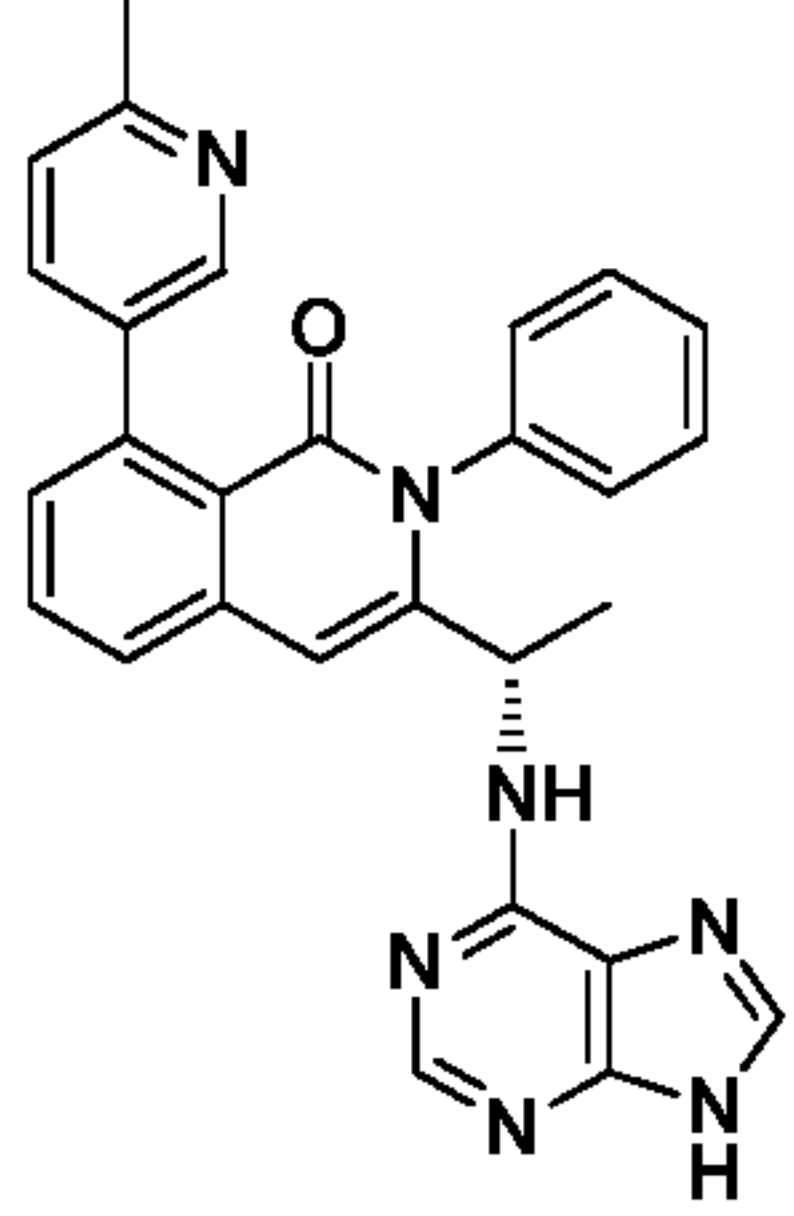
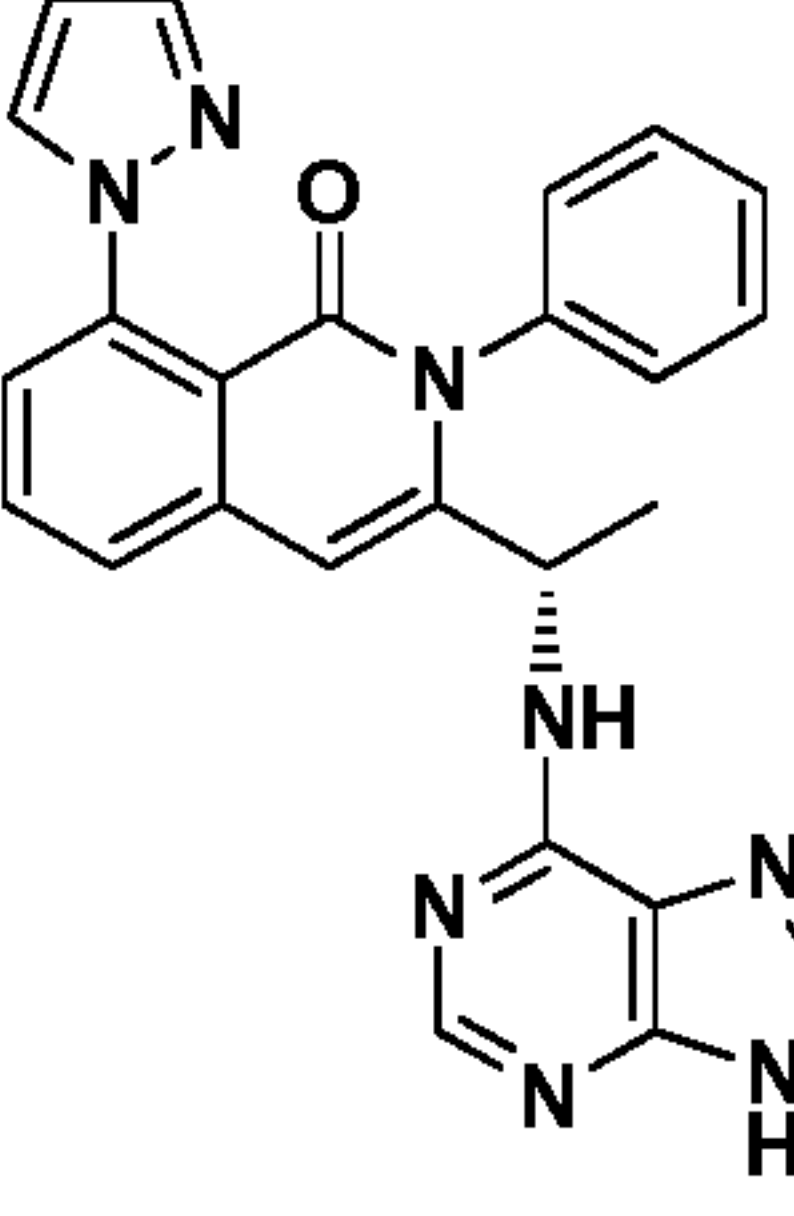
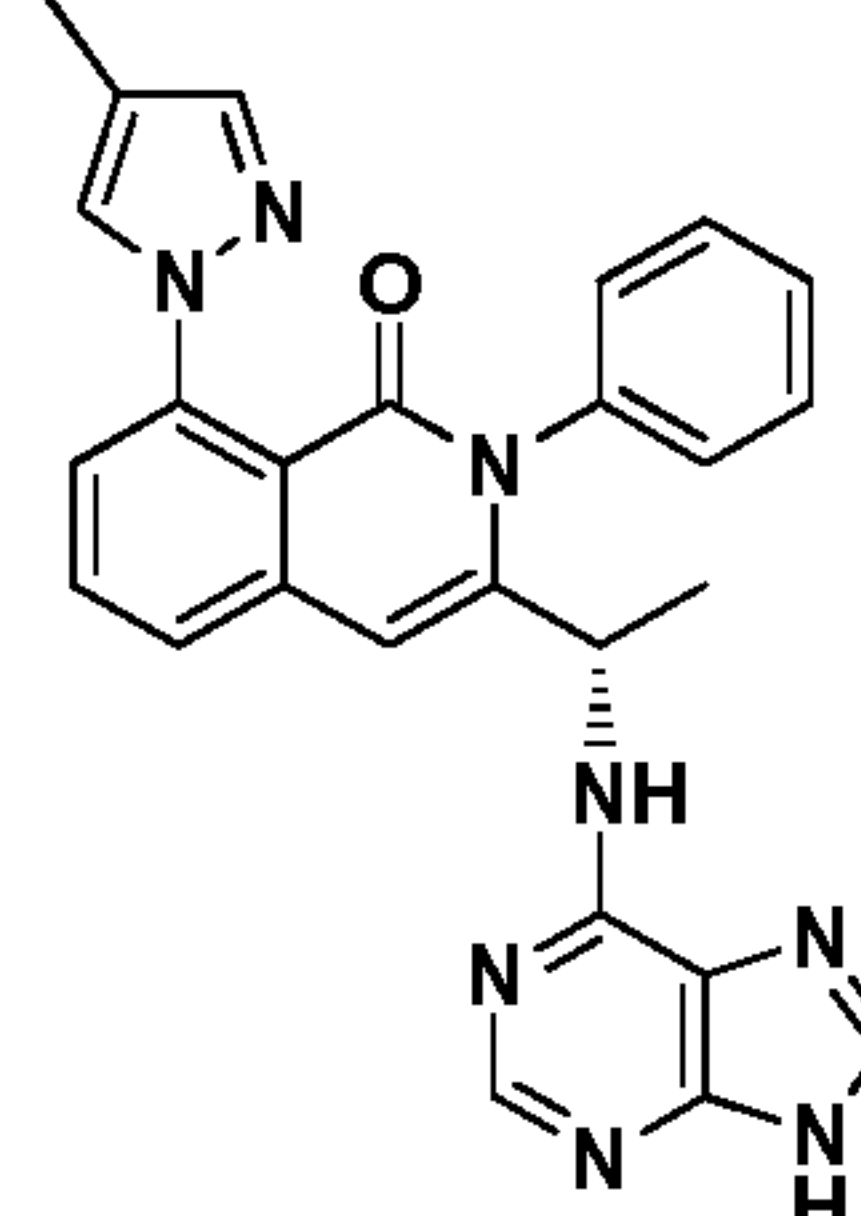
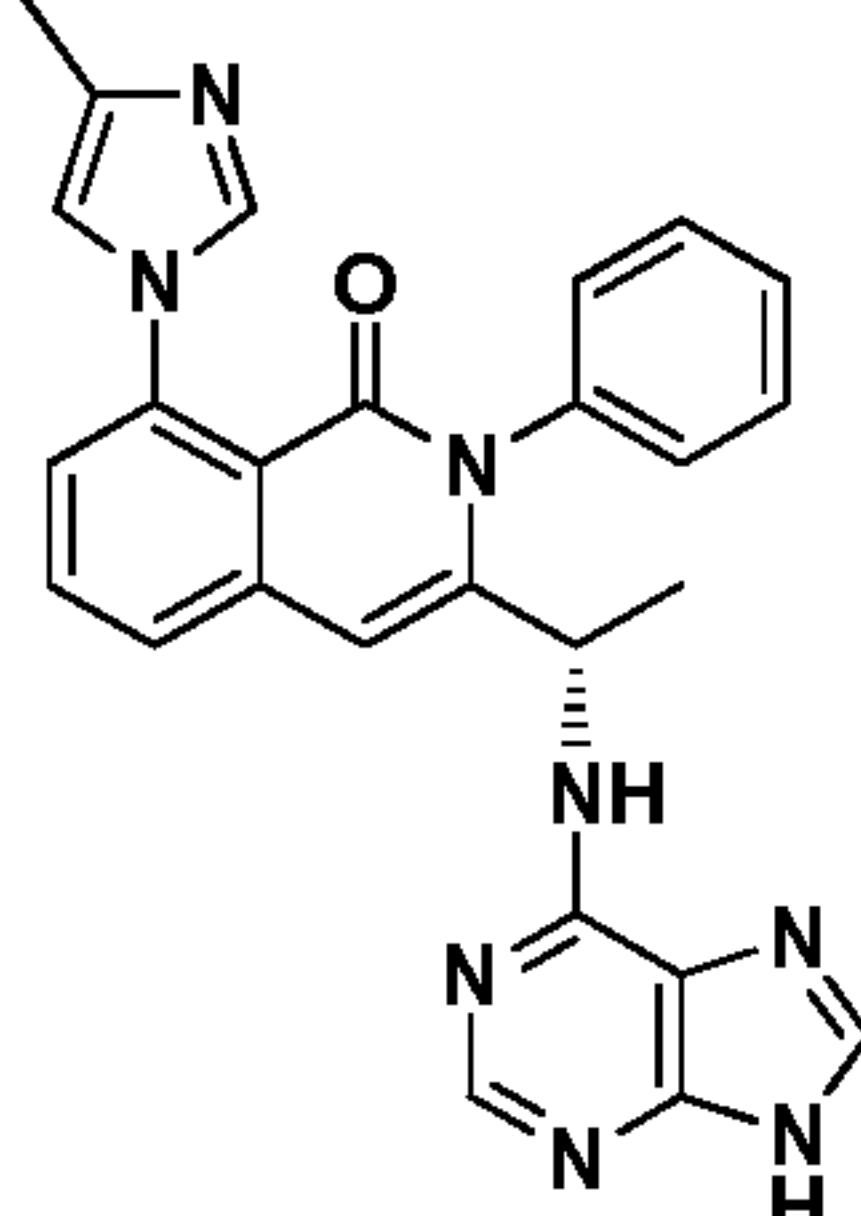
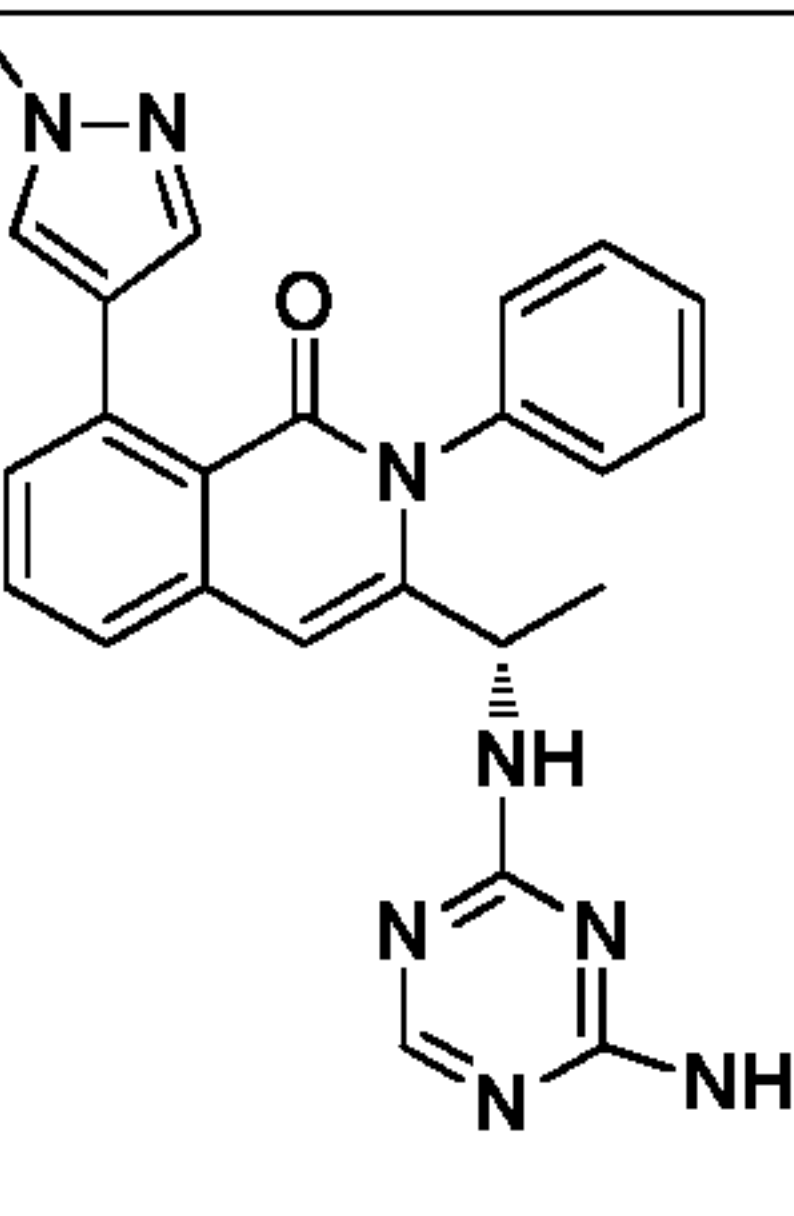
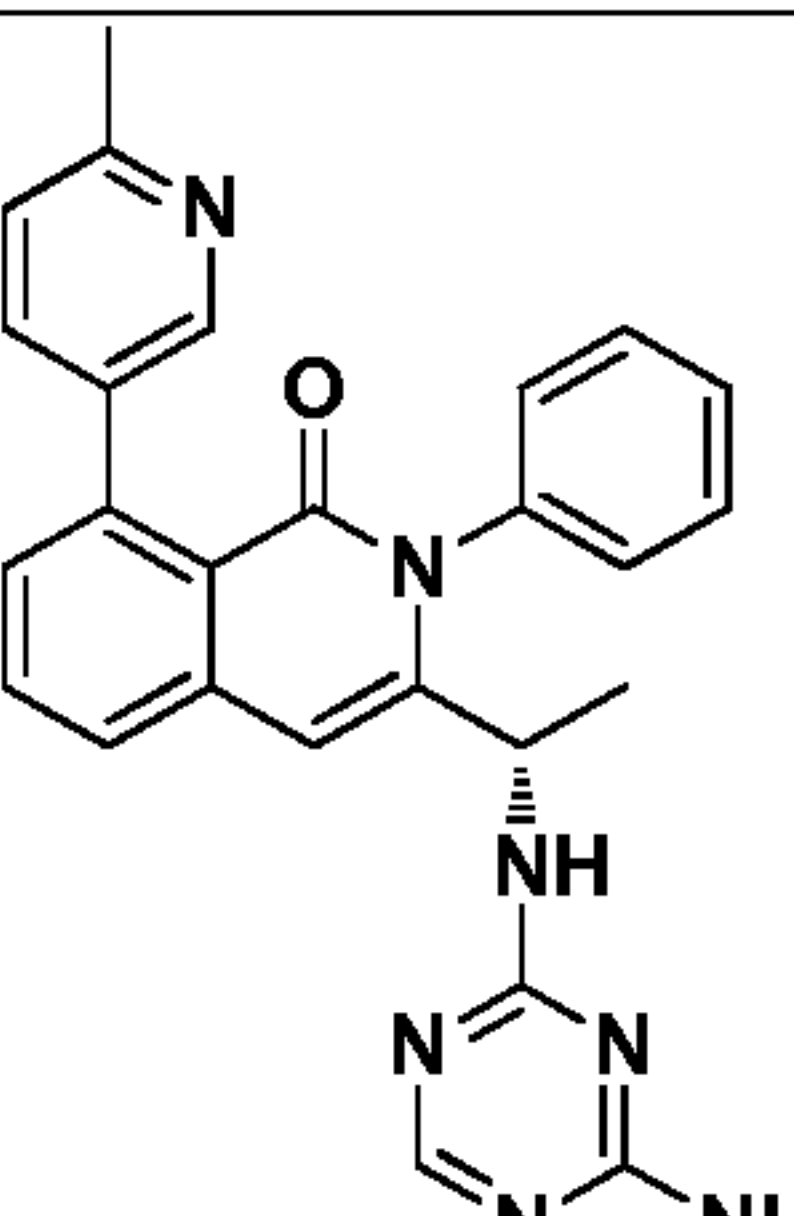
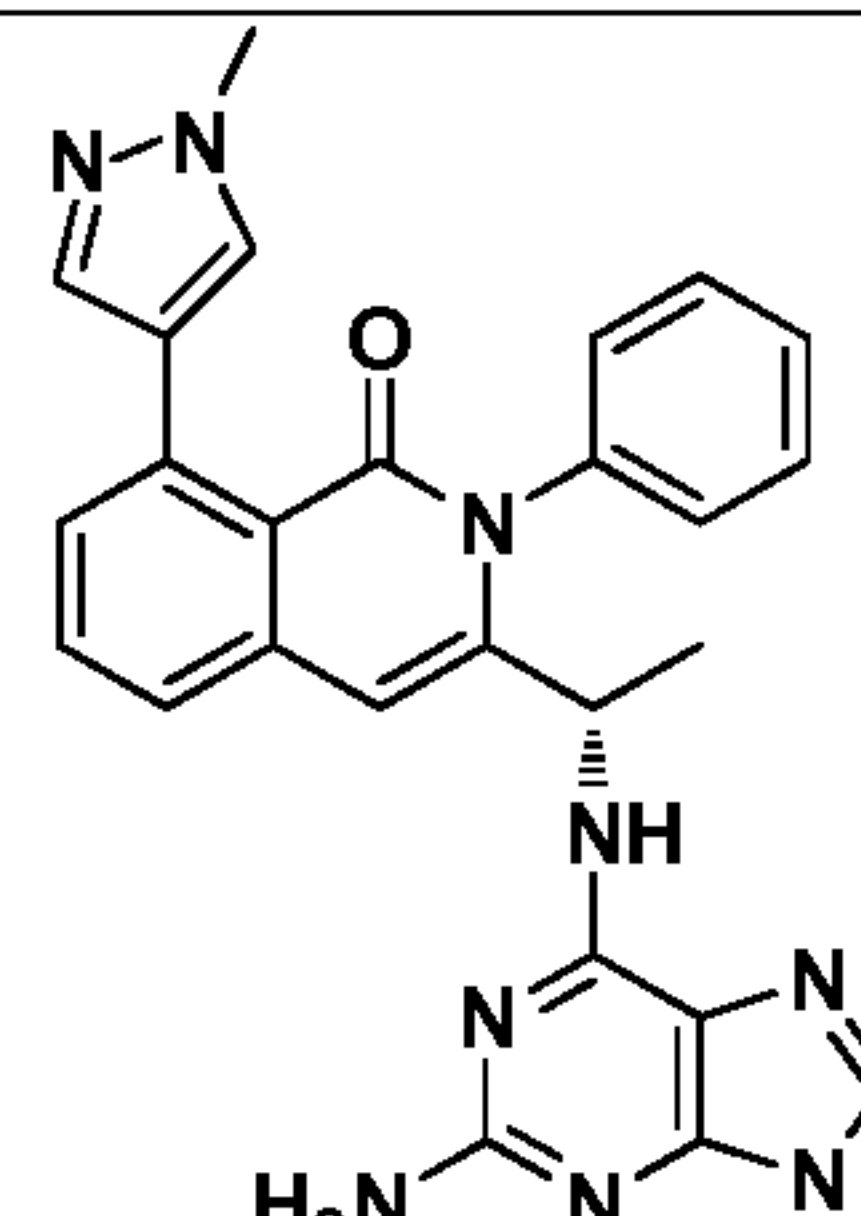
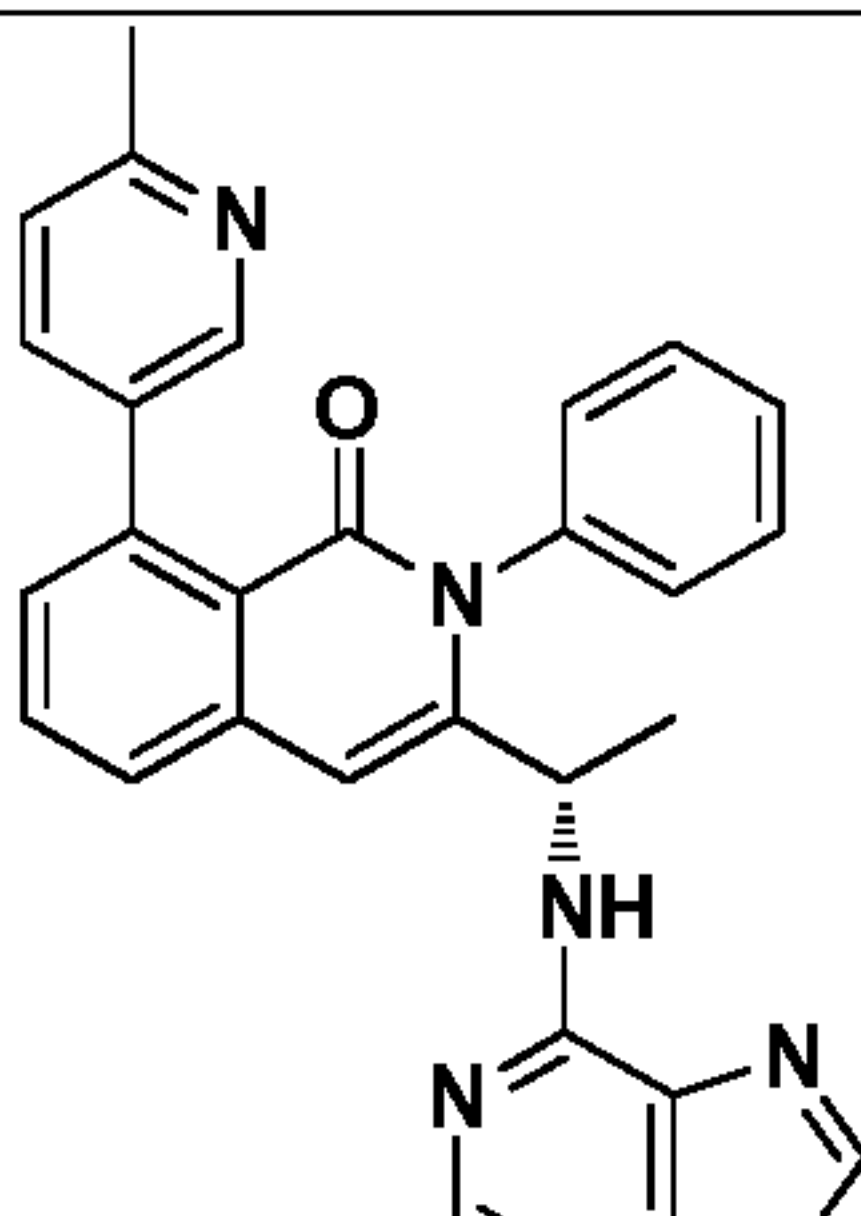
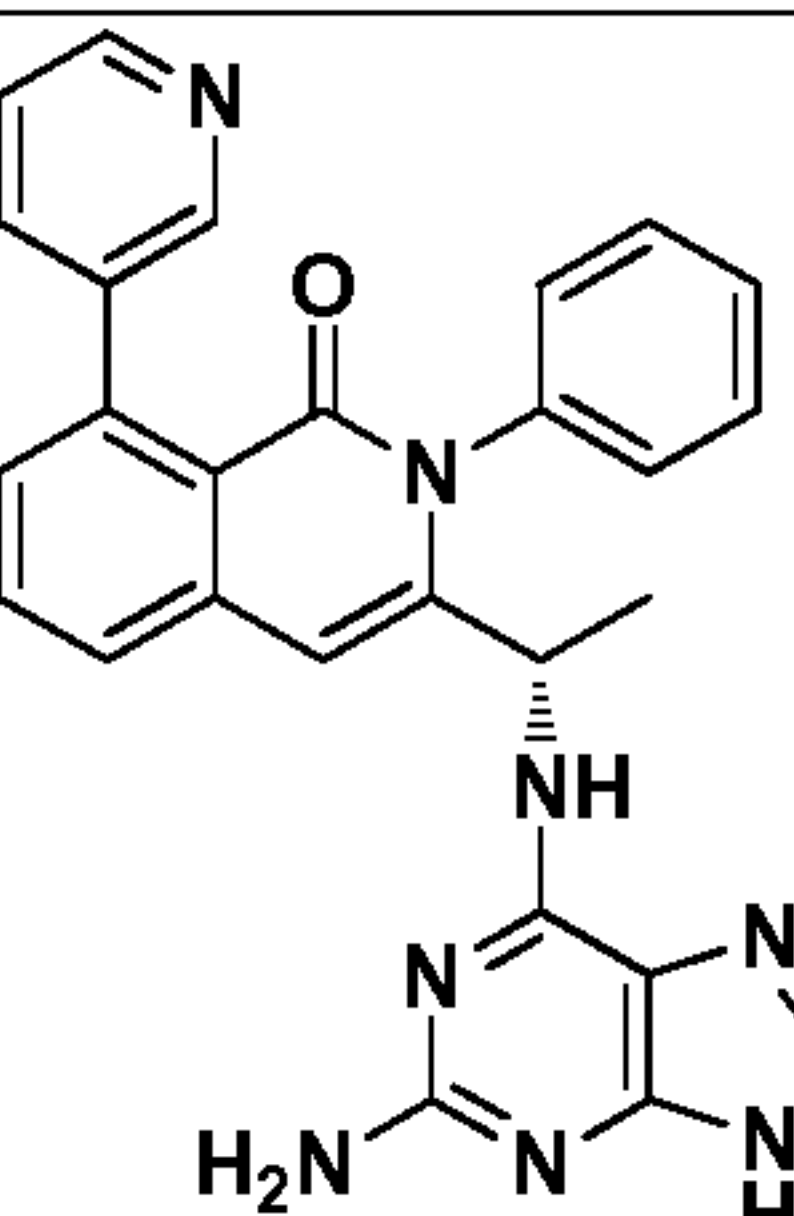
[00478] To a solution of (S)-2-amino-4-((1-(8-(1-methyl-1H-pyrazol-4-yl)-1-oxo-2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)amino)pyrimidine-5-carbonitrile (**69**) (30.4 mg, 0.066 mmol) in anhydrous toluene (1 mL), acetaldoxime (10 μ L, 0.13 mmol), palladium acetate (2 mg, 0.0066 mmol) and triphenyl phosphine (4 mg, 0.013 mmol) were added and the resulting mixture was stirred at 80 °C for 2 h. Additional amounts of acetaldoxime (10 μ L, 0.13 mmol), palladium acetate (2 mg, 0.0066 mmol) and triphenyl phosphine (4 mg, 0.013 mmol) were added and stirring was continued at 80 °C for 2 h. The mixture was allowed to cool to RT, quenched with water (30 mL), and then extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo and the residue was purified by ISCO column chromatography (silica gel cartridge, 0-8.5% MeOH-DCM) to afford the desired product, (S)-2-amino-4-((1-(8-(1-methyl-1H-pyrazol-4-yl)-1-oxo-

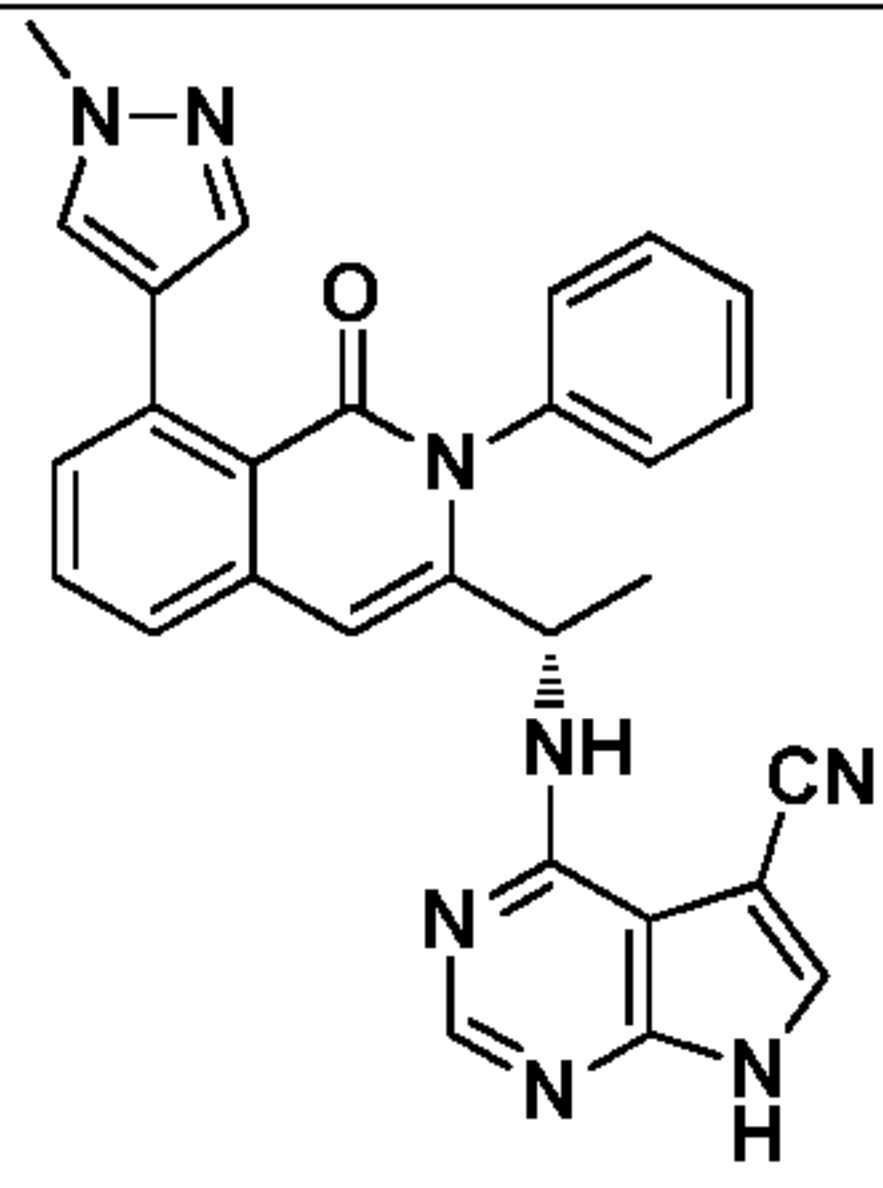
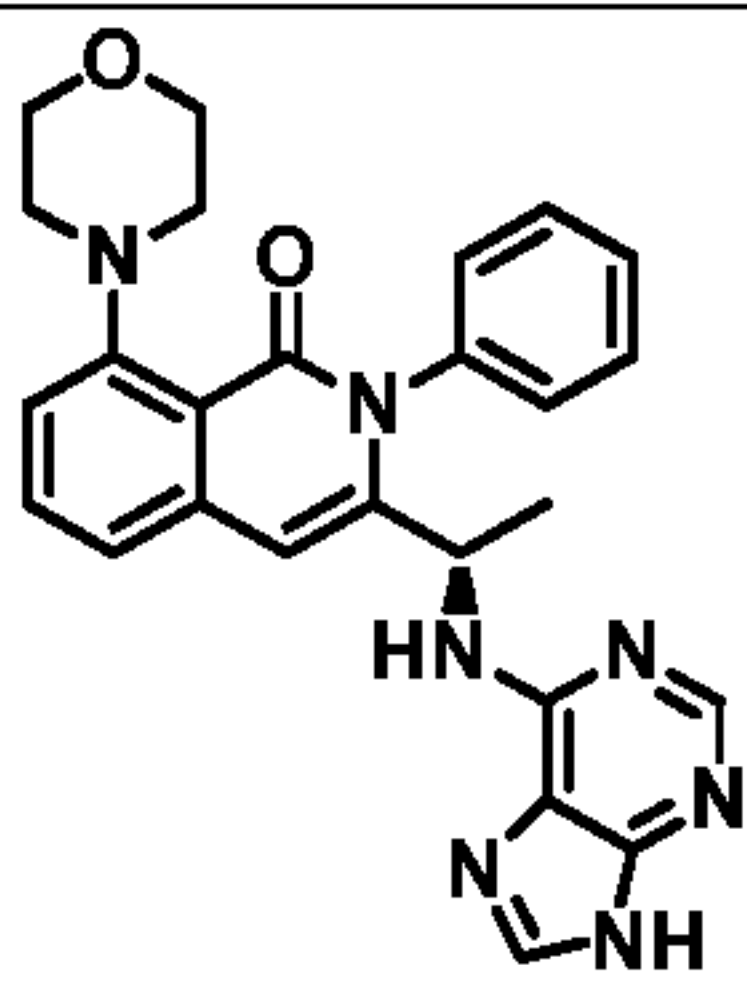
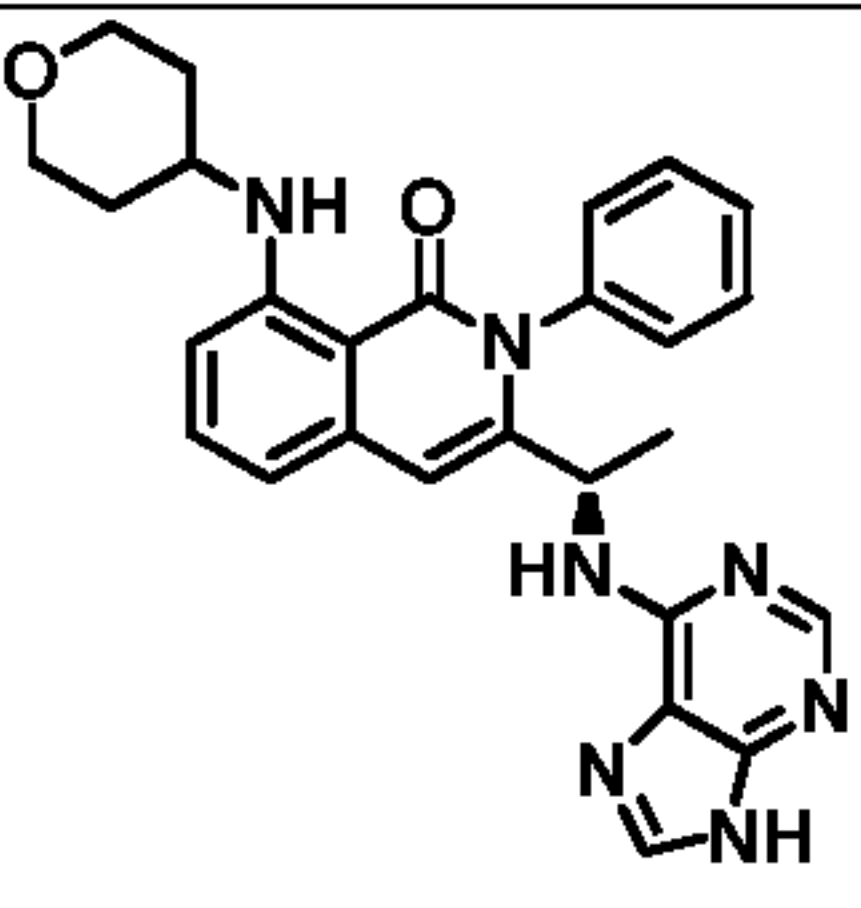
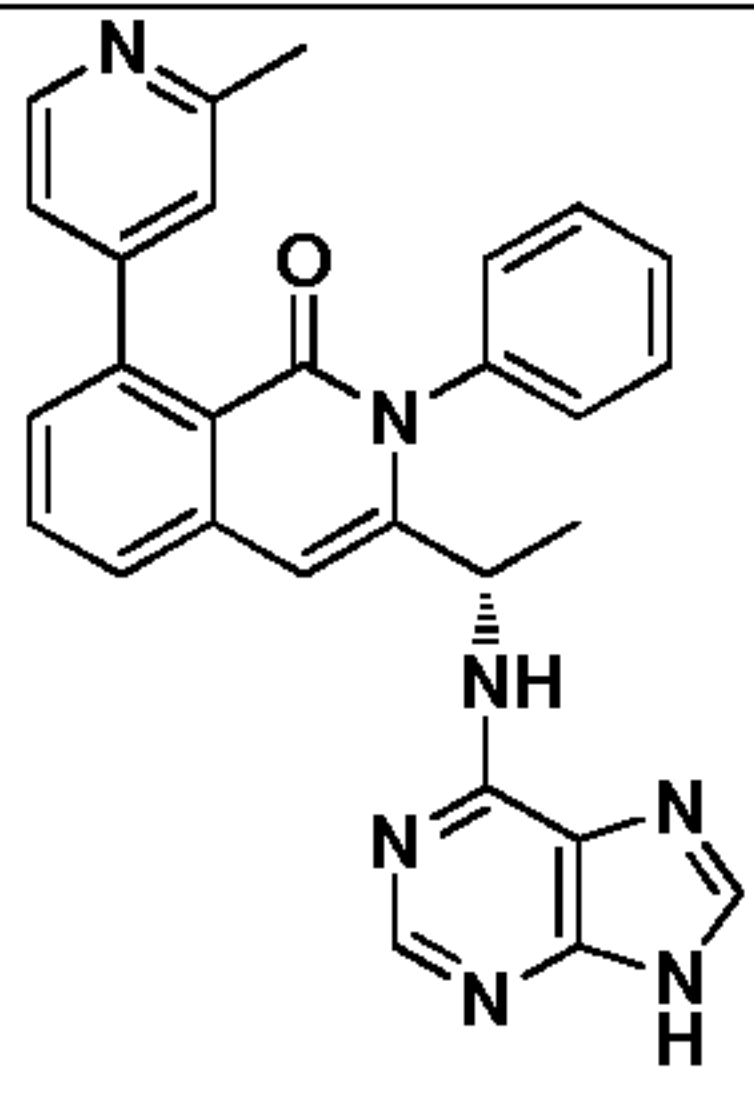
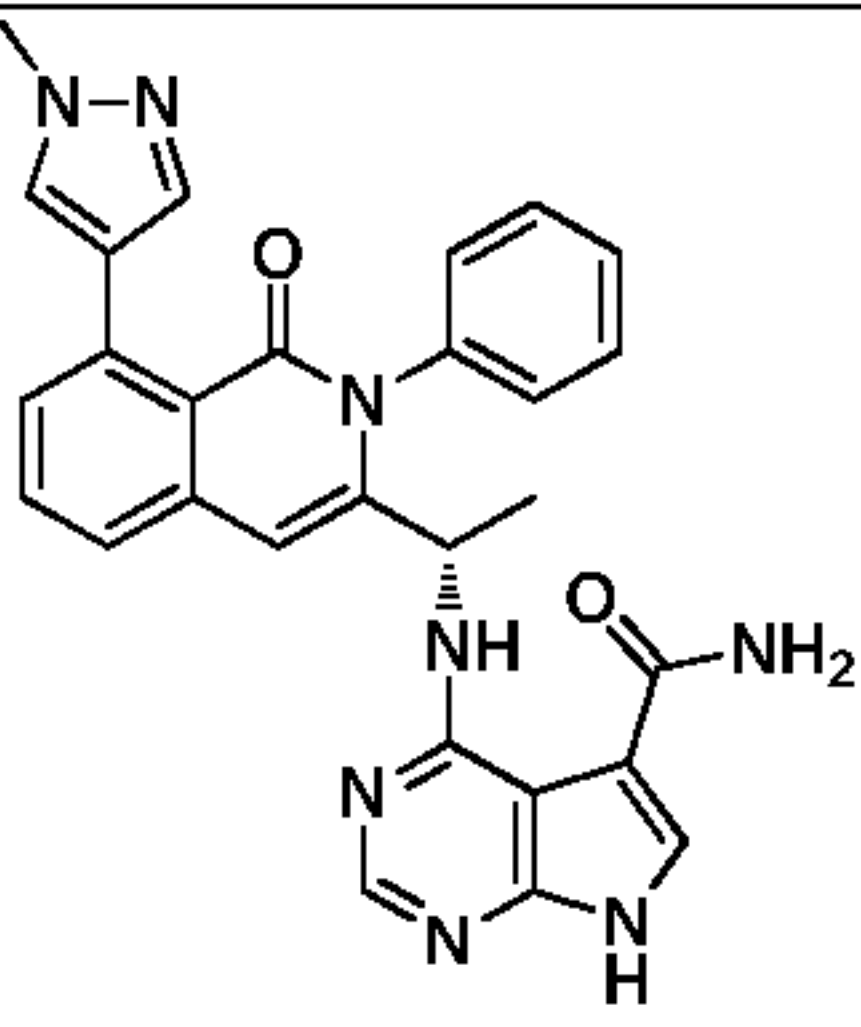
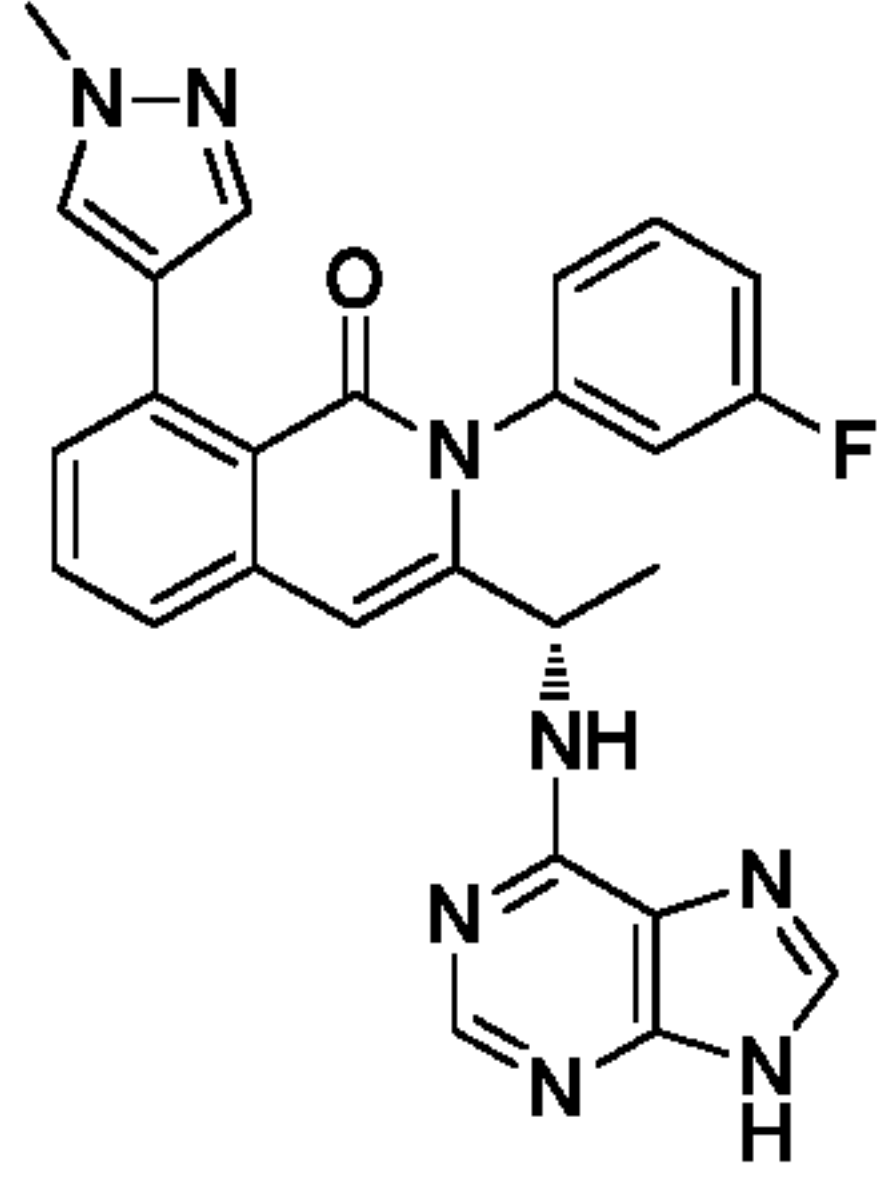
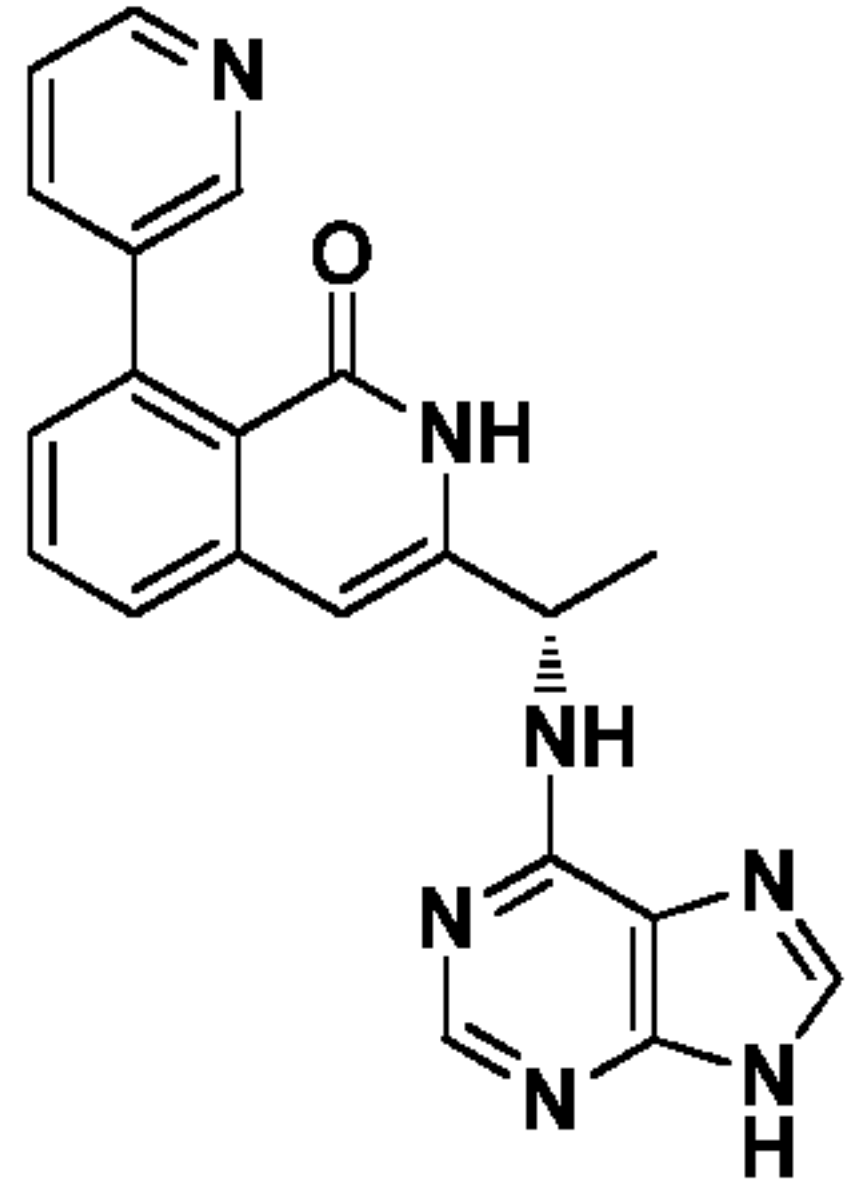
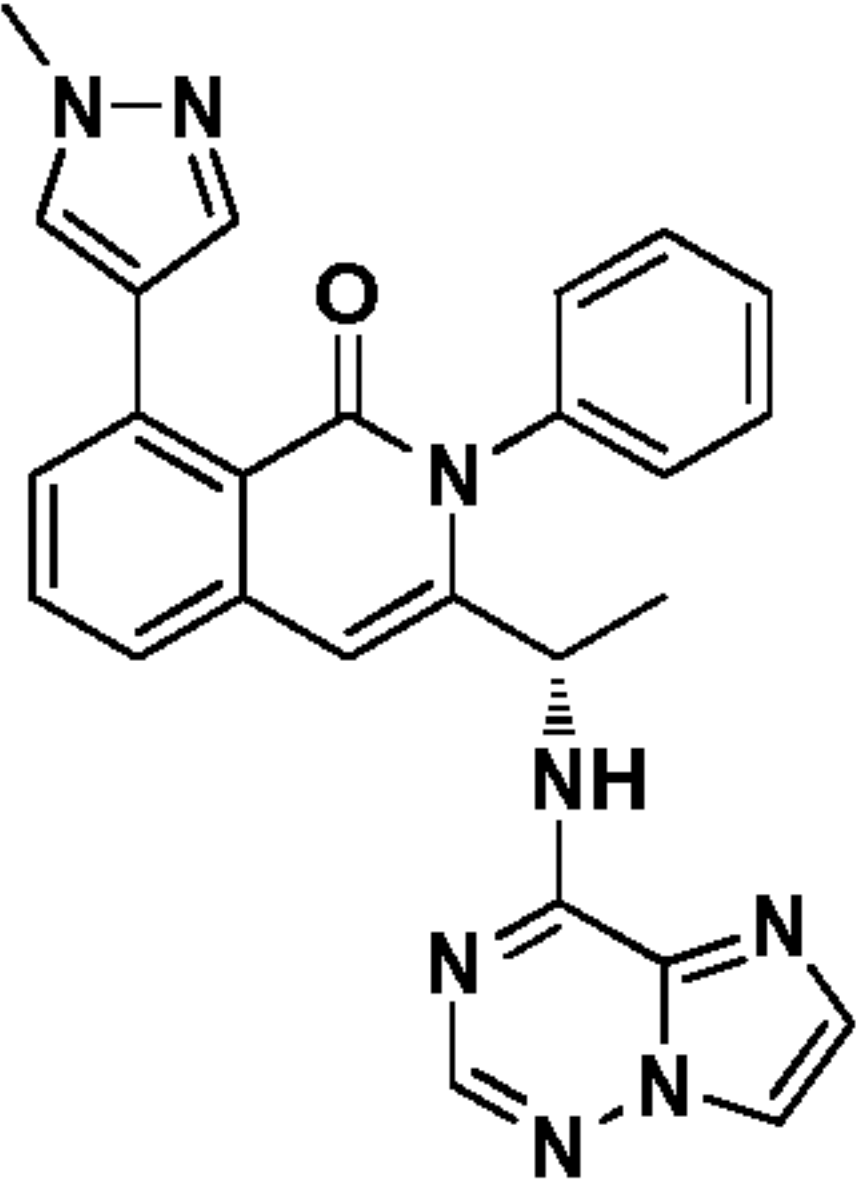
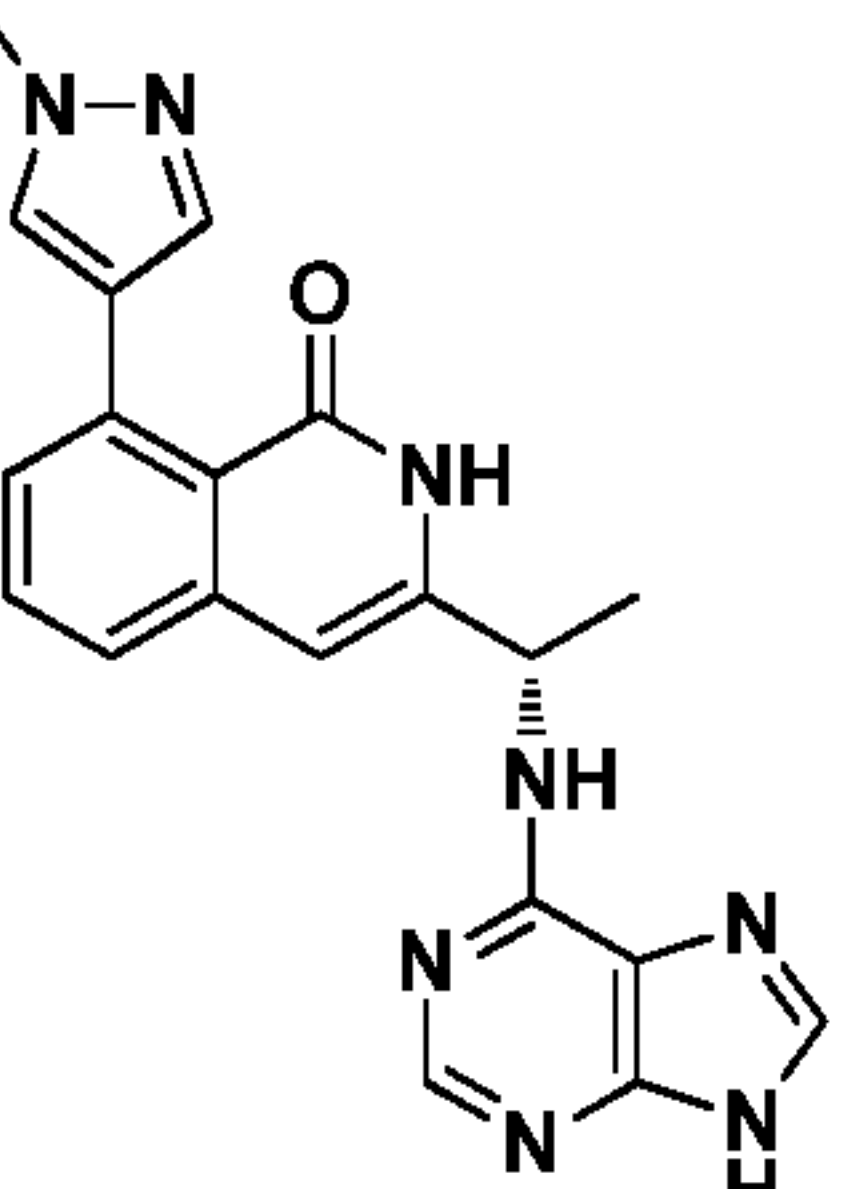
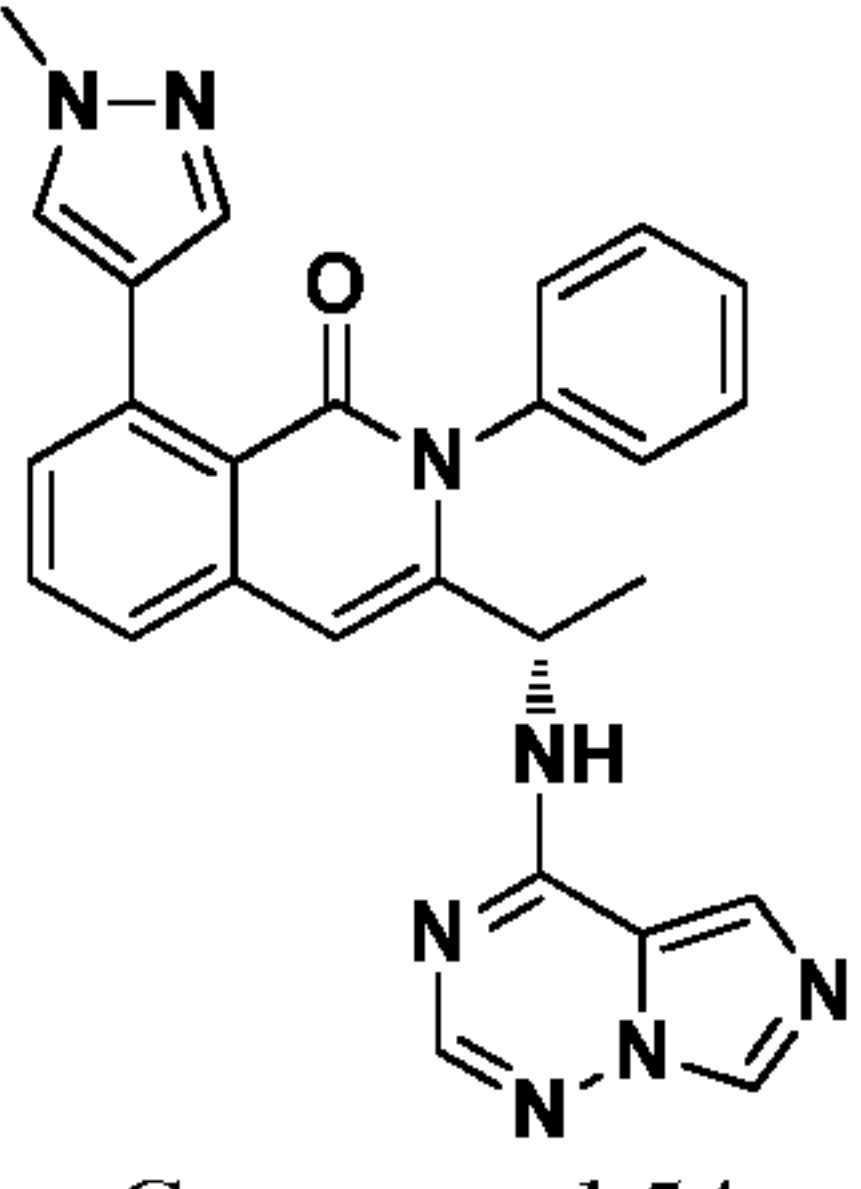
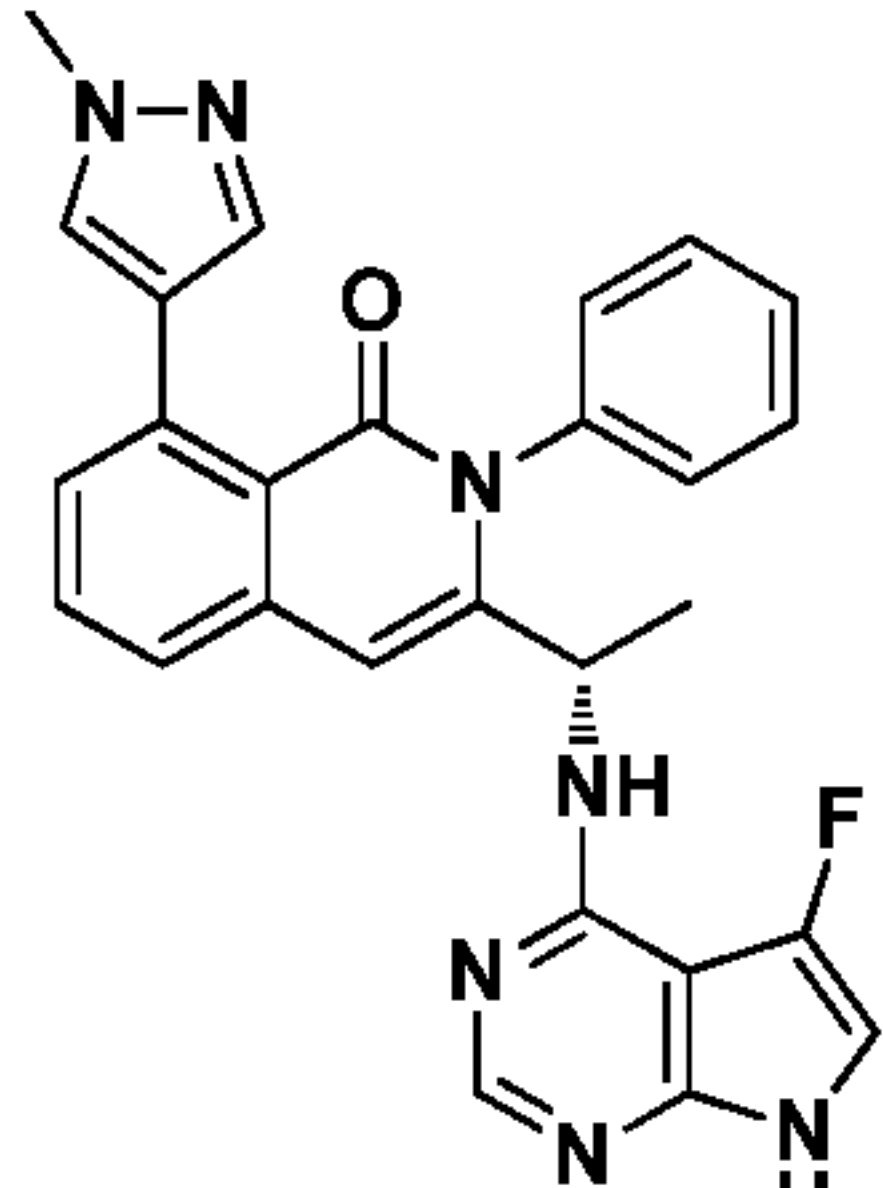
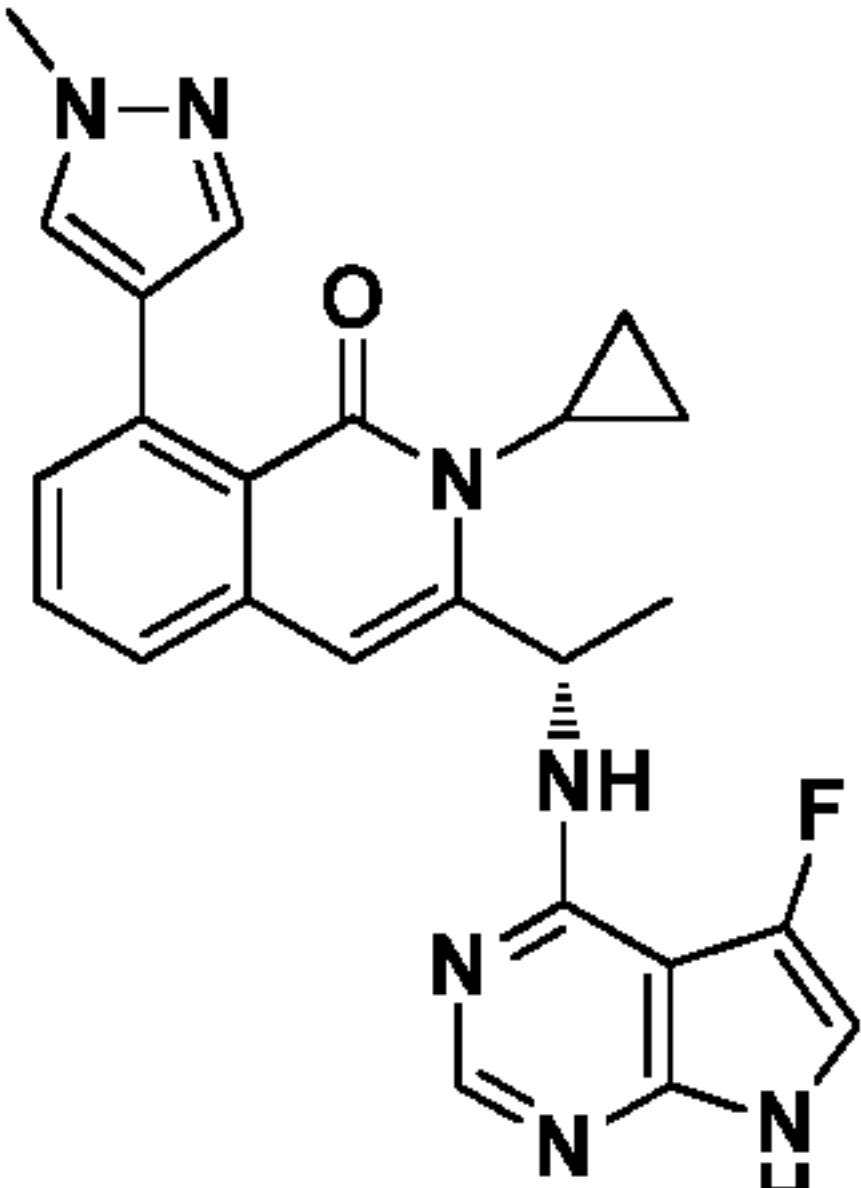
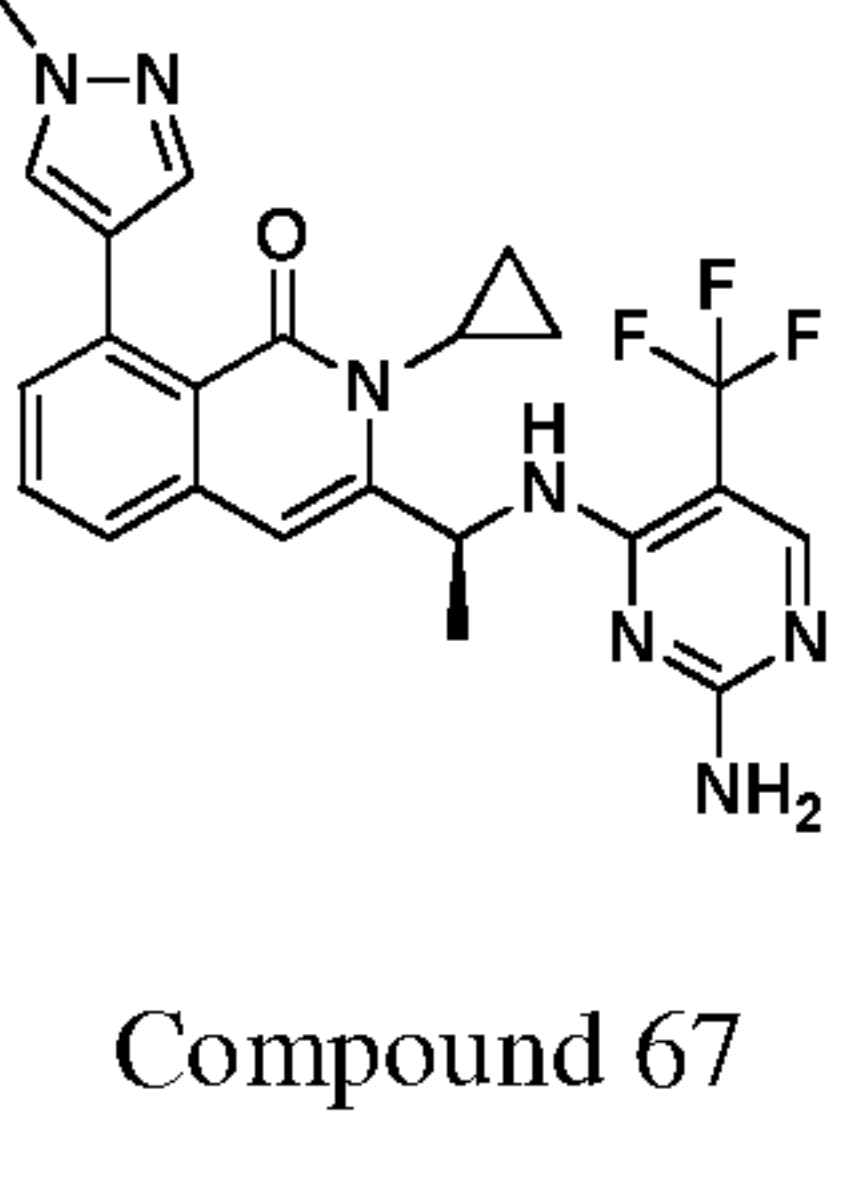
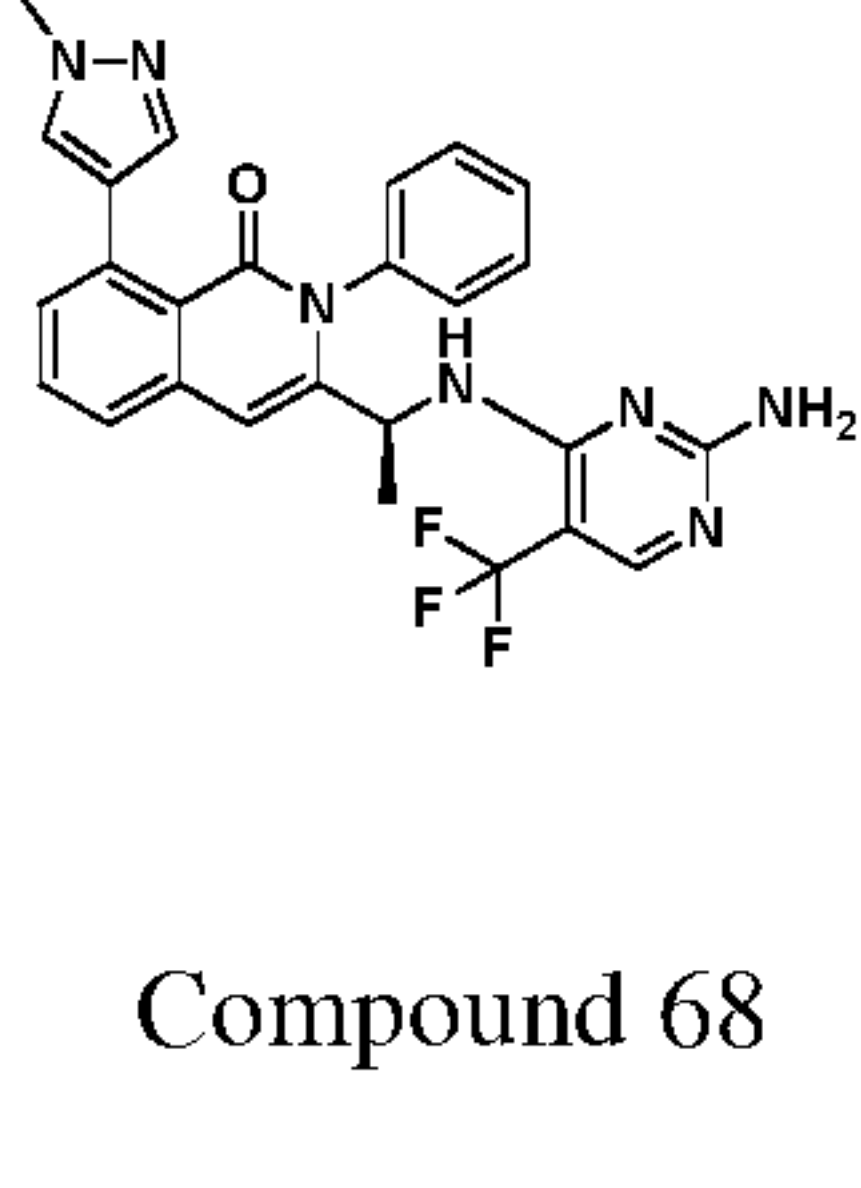
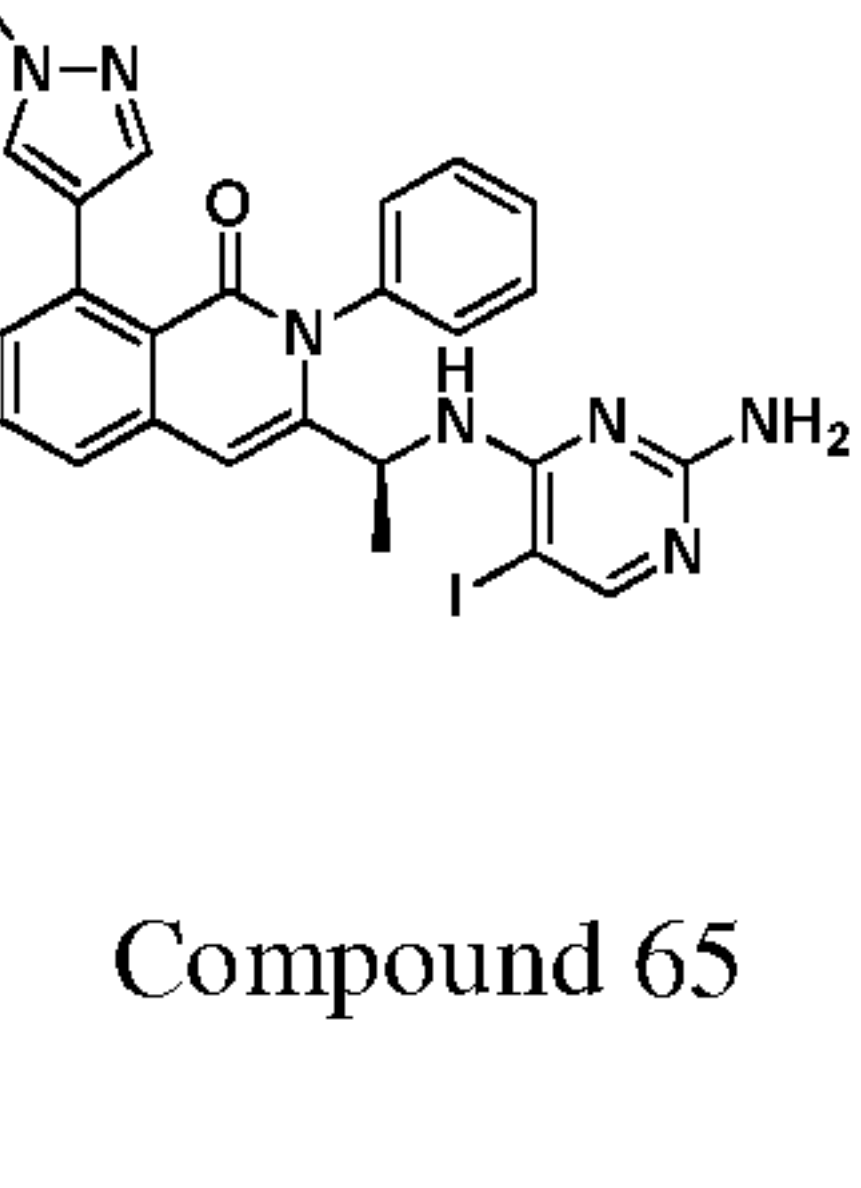
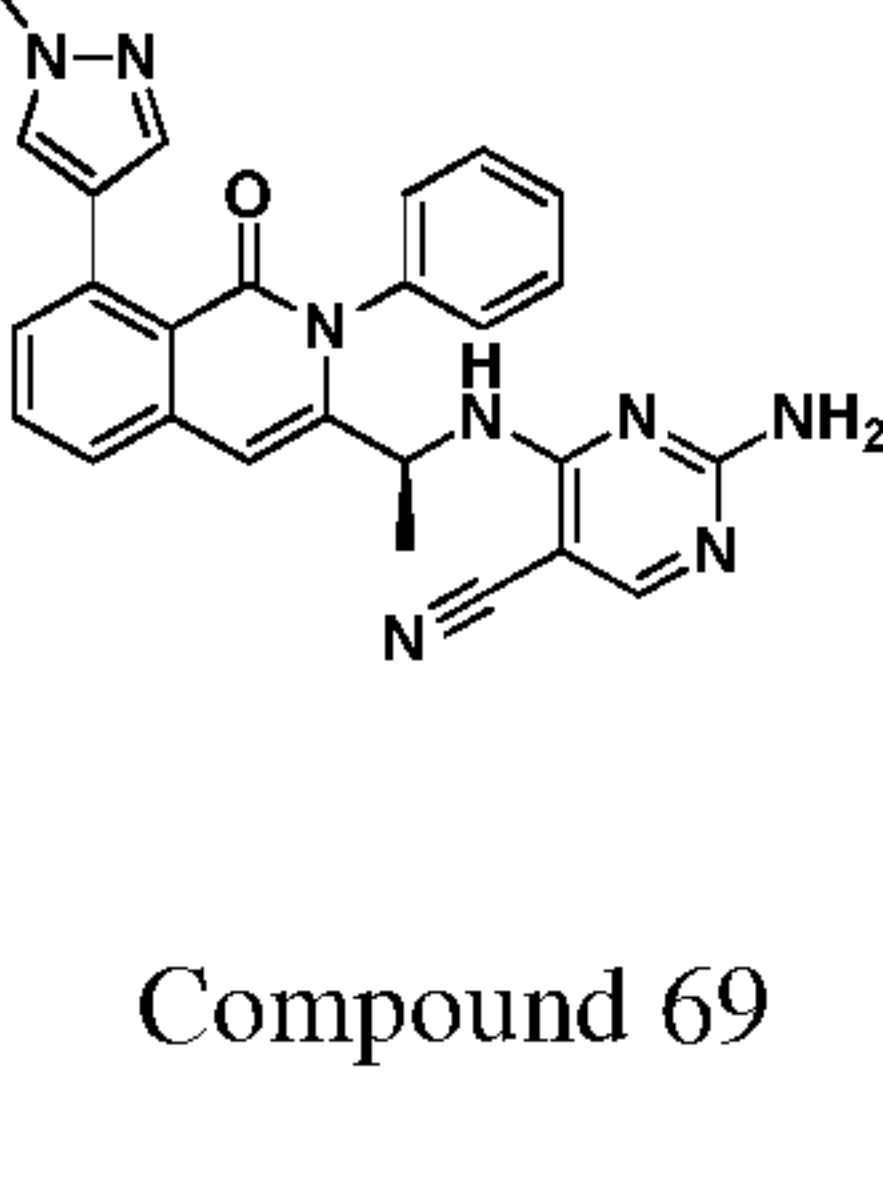
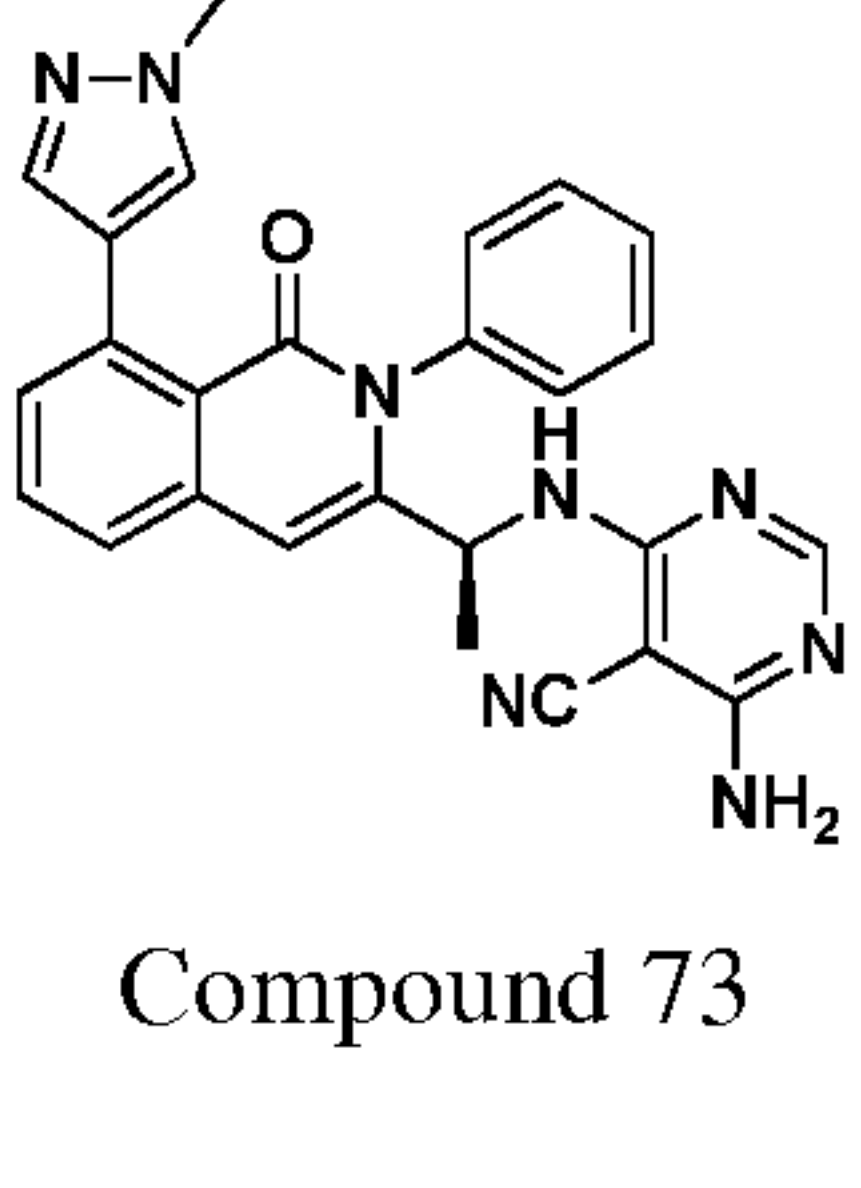
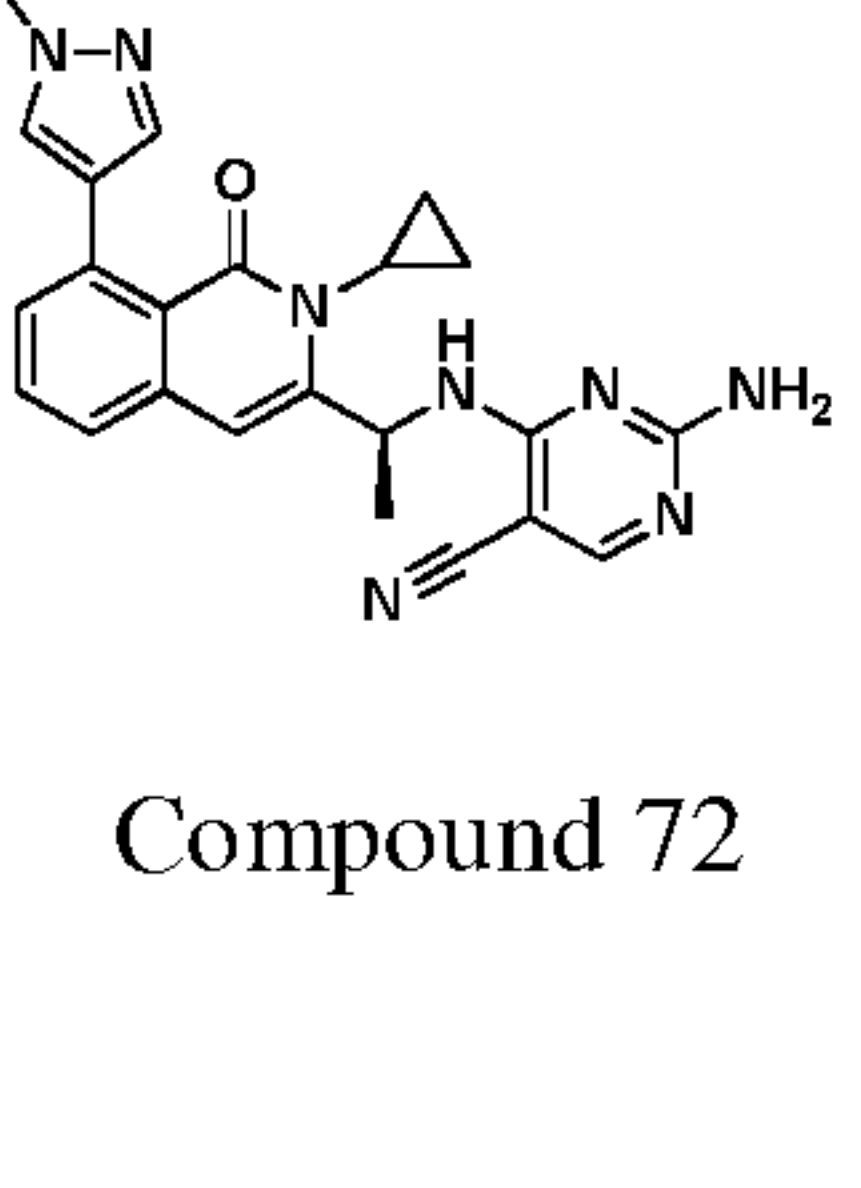
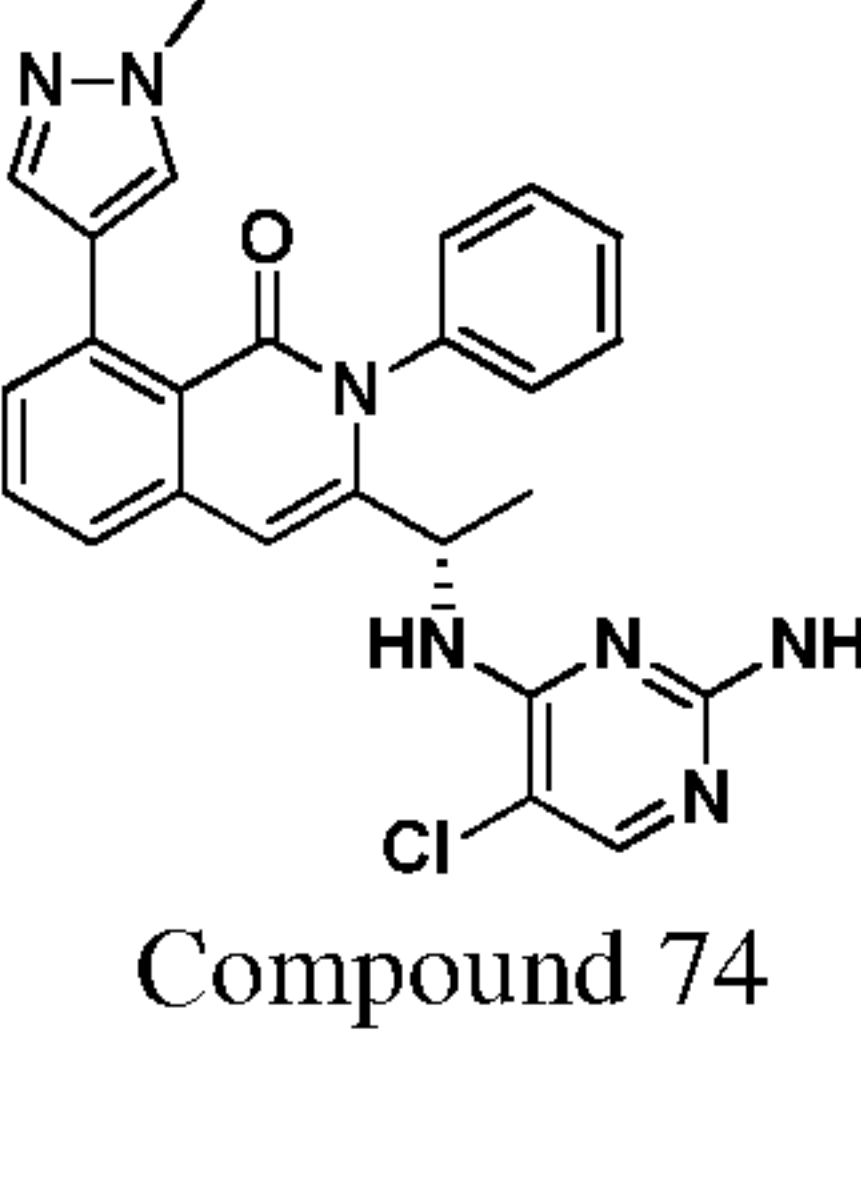
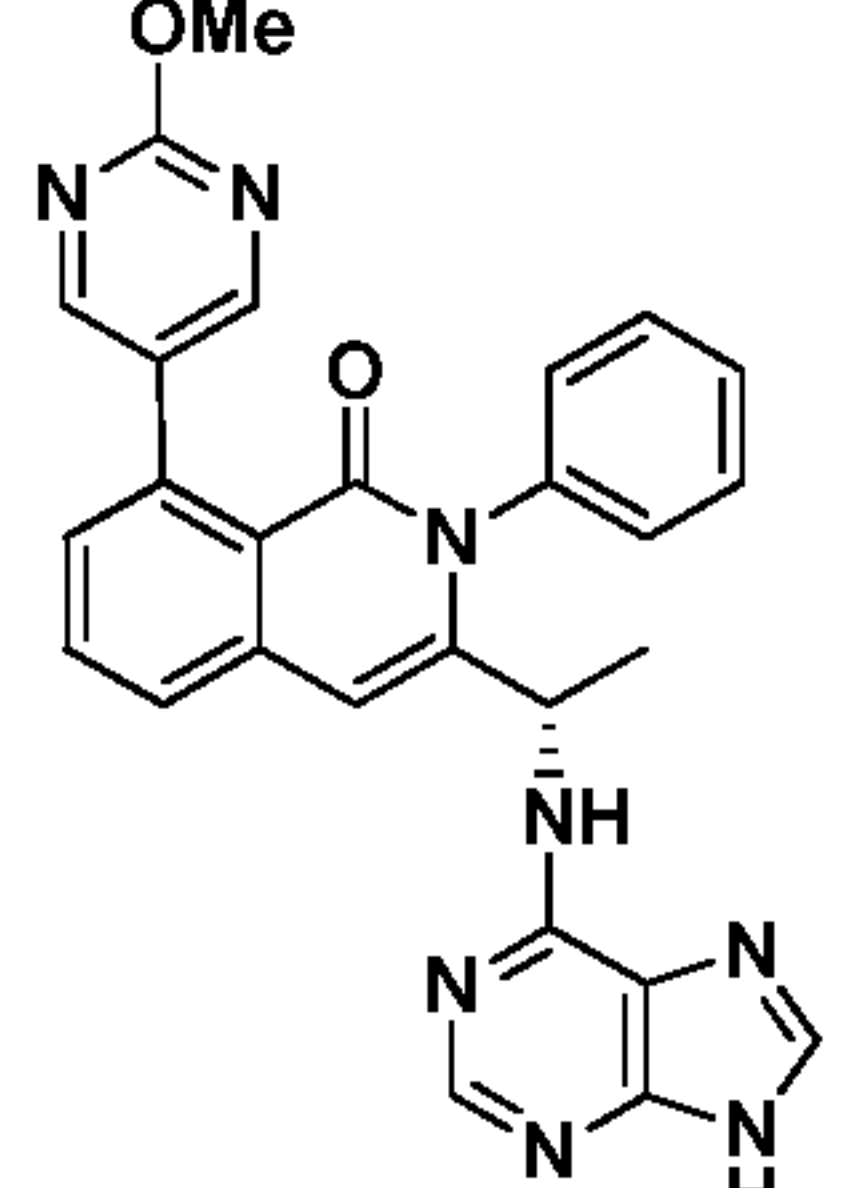
2-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)amino)pyrimidine-5-carboxamide (**79**) as a white solid. ESI-MS m/z: 481.2 [M+H]⁺.

Table 4. *In Vitro* IC₅₀ data for selected compounds.

IC ₅₀ (nM)	+ (greater than 10 microMolar)	++ (less than 10 microMolar)	+++ (less than 1 microMolar)	++++ (less than 100 nM)
PI3K δ	Compound No.	Compound No. 4, 17, 50, 54,	Compound No. 5, 29, 30, 34, 39, 40	Compound No. 6, 7, 9, 12, 13, 16, 18, 19, 20, 21, 8, 25, 27, 31, 33, 36, 37, 38, 56, 41, 58, 45, 49, 52, 62, 67, 68, 65, 69, 72, 73, 74, 76
PI3K γ	Compound No. 5, 50, 54	Compound No. 4, 17, 29, 30, 31, 33, 34, 40, 76	Compound No. 6, 20, 39, 49, 52, 62, 74	Compound No. 7, 9, 12, 13, 16, 18, 19, 21, 8, 25, 27, 36, 37, 38, 56, 41, 58, 45, 67, 68, 65, 69, 72, 73
PI3K α	Compound No. 4, 5, 16, 17, 18, 19, 29, 30, 31, 33, 34, 39, 40, 49, 50, 54, 67, 68, 65, 69, 74	Compound No. 6, 7, 9, 13, 20, 21, 8, 25, 27, 58, 45, 52, 62, 72, 73, 76	Compound No. 12, 349, 36, 37, 38, 56, 41	Compound No.
PI3K β	Compound No. 4, 5, 6, 17, 18, 19, 27, 29, 30, 31, 33, 34, 39, 40, 45, 49, 52, 50, 54, 67, 68, 65, 69, 73, 74, 76	Compound No. 7, 9, 16, 20, 21, 8, 25, 36, 37, 38, 56, 41, 58, 62	Compound No. 12, 13, 349	Compound No. 72
B cell proliferation EC ₅₀ (nM)	Compound No.	Compound No.	Compound No. 4, 29, 30, 34	Compound No. 5, 6, 7, 9, 12, 13, 16, 17, 18, 19, 20, 21, 8, 25, 27, 31, 33, 36, 37, 56, 41, 45, 49, 52, 62, 67, 68

Table 5. Structures of the Compounds for the IC₅₀ results described in Table 4.

Structure				
 Compound 4	 Compound 5	 Compound 6	 Compound 7	 Compound 9
 Compound 12	 Compound 13	 Compound 16	 Compound 17	 Compound 18
 Compound 19	 Compound 20	 Compound 21	 Compound 8	 Compound 25
 Compound 27	 Compound 29	 Compound 30	 Compound 31	
 Compound 33	 Compound 34	 Compound 36	 Compound 37	 Compound 38

Structure				
				
Compound 56	Compound 39	Compound 40	Compound 41	Compound 58
				
Compound 45	Compound 49	Compound 52	Compound 50	Compound 54
				
Compound 60	Compound 62	Compound 67	Compound 68	Compound 65
				
Compound 69	Compound 73	Compound 72	Compound 74	Compound 76

Example 48: Expression and Inhibition Assays of p110 α /p85 α , p110 β /p85 α , p110 δ /p85 α , and p110 γ : Class I PI3-Ks can be either purchased (p110 α /p85 α , p110 β /p85 α , p110 δ /p85 α from Upstate, and p110 γ from Sigma) or expressed as previously described (Knight et al., 2004). IC₅₀ values are measured using either a standard TLC assay for lipid

kinase activity (described below) or a high-throughput membrane capture assay. Kinase reactions are performed by preparing a reaction mixture containing kinase, inhibitor (2% DMSO final concentration), buffer (25 mM HEPES, pH 7.4, 10 mM MgCl₂), and freshly sonicated phosphatidylinositol (100 µg/ml). Reactions are initiated by the addition of ATP containing 10 µCi of γ-³²P-ATP to a final concentration of 10 or 100 µM and allowed to proceed for 5 minutes at room temperature. For TLC analysis, reactions are then terminated by the addition of 105 µl 1N HCl followed by 160 µl CHCl₃:MeOH (1:1). The biphasic mixture is vortexed, briefly centrifuged, and the organic phase is transferred to a new tube using a gel loading pipette tip precoated with CHCl₃. This extract is spotted on TLC plates and developed for 3 – 4 hours in a 65:35 solution of n-propanol:1M acetic acid. The TLC plates are then dried, exposed to a phosphorimager screen (Storm, Amersham), and quantitated. For each compound, kinase activity is measured at 10 – 12 inhibitor concentrations representing two-fold dilutions from the highest concentration tested (typically, 200 µM). For compounds showing significant activity, IC₅₀ determinations are repeated two to four times, and the reported value is the average of these independent measurements.

[00479] Other commercial kits or systems for assaying PI3-K activities are available. The commercially available kits or systems can be used to screen for inhibitors and/or agonists of PI3-Ks including, but not limited to, PI 3-Kinase α, β, δ, and γ. An exemplary system is PI 3-Kinase (human) HTRF™ Assay from Upstate. The assay can be carried out according to the procedures suggested by the manufacturer. Briefly, the assay is a time resolved FRET assay that indirectly measures PIP3 product formed by the activity of a PI3-K. The kinase reaction is performed in a microtiter plate (*e.g.*, a 384 well microtiter plate). The total reaction volume is approximately 20 µl per well. In the first step, each well receives 2 µl of test compound in 20% dimethylsulphoxide resulting in a 2% DMSO final concentration. Next, approximately 14.5 µl of a kinase/PIP2 mixture (diluted in 1X reaction buffer) is added per well for a final concentration of 0.25-0.3 µg/ml kinase and 10 µM PIP2. The plate is sealed and incubated for 15 minutes at room temperature. To start the reaction, 3.5 µl of ATP (diluted in 1X reaction buffer) is added per well for a final concentration of 10 µM ATP. The plate is sealed and incubated for 1 hour at room temperature. The reaction is stopped by adding 5 µl of Stop Solution per well and then 5 µl of Detection Mix is added per well. The plate is sealed, incubated for 1 hour at room temperature, and then read on an appropriate plate reader. Data is analyzed and IC₅₀s are generated using GraphPad Prism 5.

Example 49: Expression and Inhibition Assays of Abl

[00480] The cross-activity or lack thereof of one or more compounds as disclosed herein against Abl kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be assayed in triplicate against recombinant full-length Abl or Abl (T315I) (Upstate) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 200 µM ATP (2.5 µCi of γ-³²P-ATP), and 0.5 mg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK is used as phosphoacceptor (200 µM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 50: Expression and Inhibition Assays of Hck

[00481] The cross-activity or lack thereof of one or more compounds as disclosed herein against Hck kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be assayed in triplicate against recombinant full-length Hck in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 200 µM ATP (2.5 µCi of γ-³²P-ATP), and 0.5 mg/mL BSA. The optimized Src family kinase

peptide substrate EIYGEFKKK is used as phosphoacceptor (200 μ M). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 51: Expression and Inhibition Assays of Insulin Receptor (IR)

[00482] The cross-activity or lack thereof of one or more compounds as disclosed herein against IR receptor kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be assayed in triplicate against recombinant insulin receptor kinase domain (Upstate) in an assay containing 25 mM HEPES, pH 7.4, 10 mM $MgCl_2$, 10 mM $MnCl_2$, 200 μ M ATP (2.5 μ Ci of γ - ^{32}P -ATP), and 0.5 mg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 52: Expression and Inhibition Assays of Src

[00483] The cross-activity or lack thereof of one or more compounds as disclosed herein against Src kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be assayed in triplicate against recombinant full-length Src or Src (T338I) in an assay containing 25 mM HEPES, pH 7.4, 10 mM $MgCl_2$, 200 μ M ATP (2.5 μ Ci of γ - ^{32}P -ATP), and 0.5 mg/mL BSA. The optimized Src family kinase peptide substrate EIYGEFKKK is used as phosphoacceptor (200 μ M). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets were dried and the transferred radioactivity quantitated by phosphorimaging.

Example 53: Expression and Inhibition Assays of DNA-PK (DNAK)

[00484] The cross-activity or lack thereof of one or more compounds as disclosed herein against DNAK kinase can be measured according to any procedures known in the art. DNA-PK can be purchased from Promega and assayed using the DNA-PK Assay System (Promega) according to the manufacturer's instructions.

Example 54: Expression and Inhibition Assays mTOR

[00485] The cross-activity or lack thereof of one or more compounds as disclosed herein against mTor can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant mTOR (Invitrogen) in an assay containing 50 mM HEPES, pH 7.5, 1mM EGTA, 10 mM $MgCl_2$, 2.5 mM, 0.01% Tween, 10 μ M ATP (2.5 μ Ci of μ - ^{32}P -ATP), and 3 μ g/mL BSA. Rat recombinant PHAS-1/4EBP1 (Calbiochem; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

[00486] Other kits or systems for assaying mTOR activity are commercially available. For instance, one can use Invitrogen's LanthaScreen™ Kinase assay to test the inhibitors of mTOR disclosed herein. This assay is a time resolved FRET platform that measures the phosphorylation of GFP labeled 4EBP1 by mTOR kinase. The kinase reaction is performed in a white 384 well microtiter plate. The total reaction volume is 20 μ l per well and the reaction buffer composition is 50 mM HEPES pH 7.5, 0.01% Polysorbate 20, 1 mM EGTA, 10 mM $MnCl_2$, and 2 mM DTT. In the first step, each well receives 2 μ l of test compound in 20% dimethylsulphoxide resulting in a 2% DMSO final concentration. Next, 8 μ l of mTOR diluted in reaction buffer is added per well for a 60 ng/ml final concentration. To start the reaction, 10 μ l of an ATP/GFP-4EBP1 mixture (diluted in reaction buffer) is added per well for a final

concentration of 10 μ M ATP and 0.5 μ M GFP-4EBP1. The plate is sealed and incubated for 1 hour at room temperature. The reaction is stopped by adding 10 μ l per well of a Tb-anti-pT46 4EBP1 antibody/EDTA mixture (diluted in TR-FRET buffer) for a final concentration of 1.3 nM antibody and 6.7 mM EDTA. The plate is sealed, incubated for 1 hour at room temperature, and then read on a plate reader set up for Lanthascreen™ TR-FRET. Data is analyzed and IC₅₀s are generated using GraphPad Prism 5.

Example 55: Expression and Inhibition Assays of Vascular endothelial growth receptor

[00487] The cross-activity or lack thereof of one or more compounds as disclosed herein against VEGF receptor can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant KDR receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 0.1% BME, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 56: Expression and Inhibition Assays of Ephrin receptor B4 (EphB4)

[00488] The cross-activity or lack thereof of one or more compounds as disclosed herein against EphB4 can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant Ephrin receptor B4 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 0.1% BME, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 57: Expression and Inhibition Assays of Epidermal growth factor receptor (EGFR)

[00489] The cross-activity or lack thereof of one or more compounds as disclosed herein against EGFR kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant EGF receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 0.1% BME, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 58: Expression and Inhibition Assays of KIT Assay

[00490] The cross-activity or lack thereof of one or more compounds as disclosed herein against KIT kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant KIT kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 1mM DTT, 10mM MnCl₂, 10 μ M ATP (2.5 μ Ci of μ -32P-ATP), and 3 μ g/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 59: Expression and Inhibition Assays of RET

[00491] The cross-activity or lack thereof of one or more compounds as disclosed herein against RET kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant RET kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 2.5mM DTT, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 60: Expression and Inhibition Assays of Platelet derived growth factor receptor (PDGFR)

[00492] The cross-activity or lack thereof of one or more compounds as disclosed herein against PDGFR kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant PDG receptor kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 2.5 mM DTT, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 61: Expression and Inhibition Assays of FMS-related tyrosine kinase 3 (FLT-3)

[00493] The cross-activity or lack thereof of one or more compounds as disclosed herein against FLT-3 kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant FLT-3 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 2.5 mM DTT, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. The optimized Abl peptide substrate EAIYAAPFAKKK is used as phosphoacceptor (200 μM). Reactions are terminated by spotting onto phosphocellulose sheets, which are washed with 0.5% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 62: Expression and Inhibition Assays of TEK receptor tyrosine kinase (TIE2)

[00494] The cross-activity or lack thereof of one or more compounds as disclosed herein against TIE2 kinase can be measured according to any procedures known in the art or methods disclosed below. The compounds described herein can be tested against recombinant TIE2 kinase domain (Invitrogen) in an assay containing 25 mM HEPES, pH 7.4, 10 mM MgCl₂, 2mM DTT, 10 mM MnCl₂, 10 μM ATP (2.5 μCi of μ-32P-ATP), and 3 μg/mL BSA. Poly E-Y (Sigma; 2 mg/mL) is used as a substrate. Reactions are terminated by spotting onto nitrocellulose, which is washed with 1M NaCl/1% phosphoric acid (approximately 6 times, 5-10 minutes each). Sheets are dried and the transferred radioactivity quantitated by phosphorimaging.

Example 63: B Cell Activation and Proliferation Assay

[00495] The ability of one or more subject compounds to inhibit B cell activation and proliferation is determined according to standard procedures known in the art. For example, an in vitro cellular proliferation assay is established that measures the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Balb/c splenic B cells are purified over a Ficoll-Paque™ PLUS gradient followed by magnetic cell separation using a MACS B cell Isolation Kit (Miletenyi). Cells are plated in 90 μl at 50,000 cells/well in B Cell Media (RPMI + 10% FBS + Penn/Strep + 50 μM bME + 5 mM HEPES). A compound disclosed herein is diluted in B Cell Media and added in a 10 μl volume. Plates are incubated for 30 min at 37 °C and 5% CO₂ (0.2% DMSO final

concentration). A 50 μ l B cell stimulation cocktail is then added containing either 10 μ g/ml LPS or 5 μ g/ml F(ab')₂ Donkey anti-mouse IgM plus 2ng/ml recombinant mouse IL4 in B Cell Media. Plates are incubated for 72 hours at 37 °C and 5% CO₂. A volume of 15 μ L of Alamar Blue reagent is added to each well and plates are incubated for 5 hours at 37 °C and 5% CO₂. Alamar Blue fluoresce is read at 560Ex/590Em, and IC₅₀ or EC₅₀ values are calculated using GraphPad Prism 5.

Example 64: Tumor Cell Line Proliferation Assay

[00496] The ability of one or more subject compounds to inhibit tumor cell line proliferation can be determined according to standard procedures known in the art. For instance, an *in vitro* cellular proliferation assay can be performed to measure the metabolic activity of live cells. The assay is performed in a 96 well microtiter plate using Alamar Blue reduction. Human tumor cell lines are obtained from ATCC (*e.g.*, MCF7, U-87 MG, MDA-MB-468, PC-3), grown to confluency in T75 flasks, trypsinized with 0.25% trypsin, washed one time with Tumor Cell Media (DMEM + 10%FBS), and plated in 90 μ l at 5,000 cells/well in Tumor Cell Media. A compound disclosed herein is diluted in Tumor Cell Media and added in a 10ul volume. Plates are incubated for 72 hours at 37 °C and 5% CO₂. A volume of 10 μ L of Alamar Blue reagent is added to each well and plates are incubated for 3 hours at 37 °C and 5% CO₂. Alamar Blue fluoresce is read at 560Ex/590Em, and IC₅₀ values are calculated using GraphPad Prism 5.

Example 65: Antitumor Activity in Vivo

[00497] The compounds described herein can be evaluated in a panel of human and murine tumor models.

Paclitaxel-refractory Tumor Models

1. Clinically-derived Ovarian Carcinoma Model.

[00498] This tumor model is established from a tumor biopsy of an ovarian cancer patient. Tumor biopsy is taken from the patient. The compounds described herein are administered to nude mice bearing staged tumors using an every 2 days x 5 schedule.

2. A2780Tax Human Ovarian Carcinoma Xenograft (Mutated Tubulin).

[00499] A2780Tax is a paclitaxel-resistant human ovarian carcinoma model. It is derived from the sensitive parent A2780 line by co-incubation of cells with paclitaxel and verapamil, an MDR-reversal agent. Its resistance mechanism has been shown to be non-MDR related and is attributed to a mutation in the gene encoding the beta-tubulin protein. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

3. HCT116/VM46 Human Colon Carcinoma Xenograft (Multi-Drug Resistant).

[00500] HCT116/VM46 is an MDR-resistant colon carcinoma developed from the sensitive HCT116 parent line. *In vivo*, grown in nude mice, HCT116/VM46 has consistently demonstrated high resistance to paclitaxel. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

4. M5076 Murine Sarcoma Model

[00501] M5076 is a mouse fibrosarcoma that is inherently refractory to paclitaxel *in vivo*. The compounds described herein can be administered to mice bearing staged tumors on an every 2 days x 5 schedule.

[00502] One or more compounds as disclosed herein can be used in combination other therapeutic agents *in vivo* in the multidrug resistant human colon carcinoma xenografts HCT/VM46 or any other model known in the art including those described herein.

Example 66: Microsome stability assay

[00503] The stability of one or more subject compounds is determined according to standard procedures known in the art. For example, stability of one or more subject compounds is established by an *in vitro* assay. For example, an *in vitro* microsome stability assay is established that measures stability of one or more subject compounds when reacting with mouse, rat or human microsomes from liver. The microsome reaction with compounds is performed in 1.5 mL Eppendorf tube. Each tube contains 0.1 μ L of 10.0 mg/ml NADPH; 75 μ L of 20.0 mg/ml mouse, rat or human liver microsome; 0.4 μ L of 0.2 M phosphate buffer, and 425 μ L of ddH₂O. Negative control (without NADPH) tube contains 75 μ L of 20.0 mg/ml mouse, rat or human liver microsome; 0.4 μ L of 0.2 M phosphate buffer, and 525 μ L of ddH₂O. The reaction is started by adding 1.0 μ L of 10.0 mM tested compound. The reaction tubes are incubated at 37°C. 100 μ L sample is collected into new Eppendorf tube containing 300 μ L cold methanol at 0, 5, 10, 15, 30 and 60 minutes of reaction. Samples are centrifuged at 15,000 rpm to remove protein. Supernatant of centrifuged sample is transferred to new tube. Concentration of stable compound after reaction with microsome in the supernatant is measured by Liquid Chromatography/Mass Spectrometry (LC-MS).

Example 67: Plasma stability assay

[00504] The stability of one or more subject compounds in plasma is determined according to standard procedures known in the art. *See, e.g., Rapid Commun. Mass Spectrom.*, **10**: 1019-1026. The following procedure is an HPLC-MS/MS assay using human plasma; other species including monkey, dog, rat, and mouse are also available. Frozen, heparinized human plasma is thawed in a cold water bath and spun for 10 minutes at 2000 rpm at 4 °C prior to use. A subject compound is added from a 400 μ M stock solution to an aliquot of pre-warmed plasma to give a final assay volume of 400 μ L (or 800 μ L for half-life determination), containing 5 μ M test compound and 0.5 % DMSO. Reactions are incubated, with shaking, for 0 minutes and 60 minutes at 37 °C, or for 0, 15, 30, 45 and 60 minutes at 37 C for half life determination. Reactions are stopped by transferring 50 μ L of the incubation mixture to 200 μ L of ice-cold acetonitrile and mixed by shaking for 5 minutes. The samples are centrifuged at 6000 x g for 15 minutes at 4°C and 120 μ L of supernatant removed into clean tubes. The samples are then evaporated to dryness and submitted for analysis by HPLC-MS/MS.

[00505] In one embodiment, one or more control or reference compounds (5 μ M) are tested simultaneously with the test compounds: one compound, propoxycaine, with low plasma stability and another compound, propantheline, with intermediate plasma stability.

Samples are reconstituted in acetonitrile/methanol/water (1/1/2, v/v/v) and analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 60 minutes relative to the amount remaining at time zero, expressed as percent, is reported as plasma stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 68: Chemical Stability

[00506] The chemical stability of one or more subject compounds is determined according to standard procedures known in the art. The following details an exemplary procedure for ascertaining chemical stability of a subject compound. The default buffer used for the chemical stability assay is phosphate-buffered saline (PBS) at pH 7.4; other suitable buffers can be used. A subject compound is added from a 100 μ M stock solution to an aliquot of

PBS (in duplicate) to give a final assay volume of 400 μ L, containing 5 μ M test compound and 1% DMSO (for half-life determination a total sample volume of 700 μ L is prepared). Reactions are incubated, with shaking, for 24 hours at 37°C; for half-life determination samples are incubated for 0, 2, 4, 6, and 24 hours. Reactions are stopped by adding immediately 100 μ L of the incubation mixture to 100 μ L of acetonitrile and vortexing for 5 minutes. The samples are then stored at -20°C until analysis by HPLC-MS/MS. Where desired, a control compound or a reference compound such as chlorambucil (5 μ M) is tested simultaneously with a subject compound of interest, as this compound is largely hydrolyzed over the course of 24 hours. Samples are analyzed via (RP)HPLC-MS/MS using selected reaction monitoring (SRM). The HPLC conditions consist of a binary LC pump with autosampler, a mixed-mode, C12, 2 x 20 mm column, and a gradient program. Peak areas corresponding to the analytes are recorded by HPLC-MS/MS. The ratio of the parent compound remaining after 24 hours relative to the amount remaining at time zero, expressed as percent, is reported as chemical stability. In case of half-life determination, the half-life is estimated from the slope of the initial linear range of the logarithmic curve of compound remaining (%) vs. time, assuming first order kinetics.

Example 69: Akt Kinase Assay

[00507] Cells comprising components of the Akt/mTOR pathway, including but not limited to L6 myoblasts, B-ALL cells, B-cells, T-cells, leukemia cells, bone marrow cells, p190 transduced cells, philadelphia chromosome positive cells (Ph+), and mouse embryonic fibroblasts, are typically grown in cell growth media such as DMEM supplemented with fetal bovine serum and/or antibiotics, and grown to confluency.

[00508] In order to compare the effect of one or more compounds disclosed herein on Akt activation, said cells are serum starved overnight and incubated with one or more compounds disclosed herein or about 0.1% DMSO for approximately 1 minute to about 1 hour prior to stimulation with insulin (*e.g.*, 100 nM) for about 1 minute to about 1 hour. Cells are lysed by scraping into ice cold lysis buffer containing detergents such as sodium dodecyl sulfate and protease inhibitors (*e.g.*, PMSF). After contacting cells with lysis buffer, the solution is briefly sonicated, cleared by centrifugation, resolved by SDS-PAGE, transferred to nitrocellulose or PVDF and immunoblotted using antibodies to phospho- Akt S473, phospho- Akt T308, Akt, and β -actin (Cell Signaling Technologies).

[00509] The results demonstrate that one or more compounds of the present disclosure inhibit insulin stimulated phosphorylation of Akt at S473. Alternatively, some compounds disclosed herein additionally inhibit insulin stimulated phosphorylation of Akt at T308. Such class of compounds can inhibit Akt more effectively than rapamycin and can be indicative of mTORC2 inhibitors or inhibitors of upstream kinases such as PI3K or Akt.

Example 70: Kinase Signaling in Blood

[00510] PI3K/ Akt /mTor signaling is measured in blood cells using the phosflow method (*Methods Enzymol.* (2007) 434:131-54). This method is by nature a single cell assay so that cellular heterogeneity can be detected rather than population averages. This allows concurrent distinction of signaling states in different populations defined by other markers. Phosflow is also highly quantitative. To test the effects of one or more compounds disclosed herein, unfractionated splenocytes, or peripheral blood mononuclear cells are stimulated with anti-CD3 to initiate T-cell receptor signaling. The cells are then fixed and stained for surface markers and intracellular phosphoproteins. Inhibitors disclosed herein inhibit anti-CD3 mediated phosphorylation of Akt -S473 and S6, whereas rapamycin inhibits S6 phosphorylation and enhances Akt phosphorylation under the conditions tested.

[00511] Similarly, aliquots of whole blood are incubated for 15 minutes with vehicle (*e.g.*, 0.1% DMSO) or kinase inhibitors at various concentrations, before addition of stimuli to crosslink the T cell receptor (TCR) (anti-CD3

with secondary antibody) or the B cell receptor (BCR) using anti-kappa light chain antibody (Fab'2 fragments). After approximately 5 and 15 minutes, samples are fixed (*e.g.*, with cold 4% paraformaldehyde) and used for phosflow. Surface staining is used to distinguish T and B cells using antibodies directed to cell surface markers that are known to the art. The level of phosphorylation of kinase substrates such as Akt and S6 are then measured by incubating the fixed cells with labeled antibodies specific to the phosphorylated isoforms of these proteins. The population of cells are then analyzed by flow cytometry.

Example 71: Colony Formation Assay

[00512] Murine bone marrow cells freshly transformed with a p190 BCR-Abl retrovirus (herein referred to as p190 transduced cells) are plated in the presence of various drug combinations in M3630 methylcellulose media for about 7 days with recombinant human IL-7 in about 30% serum, and the number of colonies formed is counted by visual examination under a microscope.

[00513] Alternatively, human peripheral blood mononuclear cells are obtained from Philadelphia chromosome positive (Ph+) and negative (Ph-) patients upon initial diagnosis or relapse. Live cells are isolated and enriched for CD19+ CD34+ B cell progenitors. After overnight liquid culture, cells are plated in methocult GF+ H4435, Stem Cell Technologies) supplemented with cytokines (IL-3, IL-6, IL-7, G-CSF, GM-CSF, CF, Flt3 ligand, and erythropoietin) and various concentrations of known chemotherapeutic agents in combination with either compounds of the present disclosure. Colonies are counted by microscopy 12-14 days later. This method can be used to test for evidence of additive or synergistic activity.

Example 72: *In Vivo* Effect of Kinase Inhibitors on Leukemic Cells

[00514] Female recipient mice are lethally irradiated from a γ source in two doses about 4 hr apart, with approximately 5Gy each. About 1 hr after the second radiation dose, mice are injected i.v. with about 1×10^6 leukemic cells (*e.g.*, Ph+ human or murine cells, or p190 transduced bone marrow cells). These cells are administered together with a radioprotective dose of about 5×10^6 normal bone marrow cells from 3-5 week old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs are harvested for analysis. Kinase inhibitor treatment begins about 10 days after leukemic cell injection and continues daily until the mice become sick or a maximum of approximately 35 days post-transplant. Inhibitors are given by oral lavage.

[00515] Peripheral blood cells are collected approximately on day 10 (pre-treatment) and upon euthanization (post treatment), contacted with labeled anti-hCD4 antibodies and counted by flow cytometry. This method can be used to demonstrate that the synergistic effect of one or more compounds disclosed herein in combination with known chemotherapeutic agents can reduce leukemic blood cell counts as compared to treatment with known chemotherapeutic agents (*e.g.*, Gleevec) alone under the conditions tested.

Example 73: Treatment of Lupus Disease Model Mice

[00516] Mice lacking the inhibitory receptor Fc γ RIIb that opposes PI3K signaling in B cells develop lupus with high penetrance. Fc γ RIIb knockout mice (R2KO, Jackson Labs) are considered a valid model of the human disease as some lupus patients show decreased expression or function of Fc γ RIIb (S. Bolland and J.V. Ravtech 2000. *Immunity* 12:277-285).

[00517] The R2KO mice develop lupus-like disease with anti-nuclear antibodies, glomerulonephritis and proteinuria within about 4-6 months of age. For these experiments, the rapamycin analogue RAD001 (available from

LC Laboratories) is used as a benchmark compound, and administered orally. This compound has been shown to ameliorate lupus symptoms in the B6.Sle1z.Sle3z model (T. Wu et al. *J. Clin Invest.* 117:2186-2196).

[00518] Lupus disease model mice such as R2KO, BXSB or MLR/lpr are treated at about 2 months old, approximately for about two months. Mice are given doses of: vehicle, RAD001 at about 10 mg/kg, or compounds disclosed herein at approximately 1 mg/kg to about 500 mg/kg. Blood and urine samples are obtained at approximately throughout the testing period, and tested for antinuclear antibodies (in dilutions of serum) or protein concentration (in urine). Serum is also tested for anti-ssDNA and anti-dsDNA antibodies by ELISA. Animals are euthanized at day 60 and tissues harvested for measuring spleen weight and kidney disease. Glomerulonephritis is assessed in kidney sections stained with H&E. Other animals are studied for about two months after cessation of treatment, using the same endpoints.

[00519] This established art model can be employed to demonstrate that the kinase inhibitors disclosed herein can suppress or delay the onset of lupus symptoms in lupus disease model mice.

Example 74: Murine Bone Marrow Transplant Assay

[00520] Female recipient mice are lethally irradiated from a γ ray source. About 1hr after the radiation dose, mice are injected with about 1×10^6 leukemic cells from early passage p190 transduced cultures (*e.g.*, as described in *Cancer Genet Cytogenet.* 2005 Aug;161(1):51-6). These cells are administered together with a radioprotective dose of approximately 5×10^6 normal bone marrow cells from 3-5wk old donor mice. Recipients are given antibiotics in the water and monitored daily. Mice who become sick after about 14 days are euthanized and lymphoid organs harvested for flow cytometry and/or magnetic enrichment. Treatment begins on approximately day 10 and continues daily until mice become sick, or after a maximum of about 35 days post-transplant. Drugs are given by oral gavage (p.o.). In a pilot experiment a dose of chemotherapeutic that is not curative but delays leukemia onset by about one week or less is identified; controls are vehicle-treated or treated with chemotherapeutic agent, previously shown to delay but not cure leukemogenesis in this model (*e.g.*, imatinib at about 70mg/kg twice daily). For the first phase p190 cells that express eGFP are used, and postmortem analysis is limited to enumeration of the percentage of leukemic cells in bone marrow, spleen and lymph node (LN) by flow cytometry. In the second phase, p190 cells that express a tailless form of human CD4 are used and the postmortem analysis includes magnetic sorting of hCD4+ cells from spleen followed by immunoblot analysis of key signaling endpoints: p Akt -T308 and S473; pS6 and p4EBP-1. As controls for immunoblot detection, sorted cells are incubated in the presence or absence of kinase inhibitors of the present disclosure inhibitors before lysis. Optionally, “phosflow” is used to detect p Akt -S473 and pS6-S235/236 in hCD4-gated cells without prior sorting. These signaling studies are particularly useful if, for example, drug-treated mice have not developed clinical leukemia at the 35 day time point. Kaplan-Meier plots of survival are generated and statistical analysis done according to methods known in the art. Results from p190 cells are analyzed separated as well as cumulatively.

[00521] Samples of peripheral blood (100-200 μ l) are obtained weekly from all mice, starting on day 10 immediately prior to commencing treatment. Plasma is used for measuring drug concentrations, and cells are analyzed for leukemia markers (eGFP or hCD4) and signaling biomarkers as described herein.

[00522] This general assay known in the art can be used to demonstrate that effective therapeutic doses of the compounds disclosed herein can be used for inhibiting the proliferation of leukemic cells.

Example 75: Cell Culture of Epithelial Cells of Ocular Origin

[00523] Ocular epithelial cells are obtained within 5 days postmortem post-mortem from corneas preserved under cold storage conditions in Optisol (Bausch and Lomb, Irvine, CA) or from corneal biopsy from living donors. The tissue is washed with phosphate-buffered saline and incubated in Dispase II (Roche Diagnostics, Basel, Switzerland) at 37°C for 30 minutes, and the epithelial surface is gently scraped to separate the epithelium from the underlying stroma. The separated epithelium is then incubated and pipetted in trypsin- ethylenediaminetetraacetic acid to obtain a single cell suspension. The trypsin is then neutralized with corneal epithelium culture medium. Corneal epithelium culture medium is composed of Dulbecco modified Eagle medium:F12 basal media in a 2:1 ratio containing 10% irradiated fetal bovine serum, hydrocortisone 0.4 µg/mL, cholera toxin 0.1 nmol, recombinant human insulin 5 µg/mL, and epidermal growth factor 10 ng/mL, and the antimicrobials penicillin (100 IU/mL), streptomycin (100 µg/mL), and amphotericin B (0.25 µg/mL). Cells are maintained by sub-culturing at a 1:4 ratio after reaching 80% confluency. Ocular epithelial cells are screened for inhibition of proliferation or toxicity by contacting a test compound with the cells and assaying for viability using the commercially available MTT assay (Promega).

Example 76: Cell Culture of Endothelial Cells of Ocular Origin

[00524] All tissues are maintained at 4°C in storage medium (Optisol; Chiron Vision, Irvine, CA) for less than 10 days before study. The tissue is rinsed three times with DMEM containing 50 mg/mL gentamicin and 1.25 mg/mL amphotericin B. The central cornea is removed by a trephine of 8-mm diameter. Afterward, the Descemet's membrane and corneal endothelial cells are stripped from the posterior surface of the peripheral corneoscleral tissue under a dissecting microscope and digested at 37°C for 1.5 to 16 hours with 2 mg/mL collagenase A in supplemented hormonal epithelial medium (SHEM), which is made of an equal volume of HEPES-buffered DMEM and Ham's F12 supplemented with 5% FBS, 0.5% dimethyl sulfoxide, 2 ng/mL mouse EGF, 5 µg/mL insulin, 5 µg/mL transferrin, 5 ng/mL selenium, 0.5 µg/mL hydrocortisone, 1 nM cholera toxin, 50 µg/mL gentamicin, and 1.25 µg/mL amphotericin B. After digestion, HCECs formed aggregates, which are collected by centrifugation at 2000 rpm for 3 minutes to remove the digestion solution. As a control, Descemet's membrane strips are also digested in 10 mg/mL Dispase II in SHEM and trypsin/EDTA for up to 3 hours.

[00525] Preservation of Isolated HCEC Aggregates: The resultant aggregates of HCECs are preserved in KSFM with complete supplement (storage medium 1), DMEM/F12 with KSFM supplements (storage medium 2), or DMEM/F12 with SHEM supplements without FBS (storage medium 3). All these media are serum free, one of the major differences among them is the calcium concentration, which is 0.09 mM in storage medium 1, but is 1.05 mM in storage media 2 and 3. HCEC aggregates are stored in a tissue culture incubator at 37°C for up to 3 weeks. Cell viability is determined (Live and Dead assay; Invitrogen) and also evaluated by subculturing them in SHEM.

[00526] Preservation of Isolated HCEC Aggregates: The resultant HCEC aggregates, either immediately after digestion or after a period of preservation in a storage medium, are then cultured in SHEM with or without additional growth factors such as 40 ng/mL bFGF, 0.1 mg/mL BPE, and 20 ng/mL NGF on a plastic dish under 37°C and 5% CO₂. The media are changed every 2 to 3 days. Some HCEC aggregates are pretreated with trypsin/EDTA at 37°C for 10 minutes to dissociate endothelial cells before the aforementioned cultivation.

[00527] Immunostaining: HCEC aggregates are embedded in OCT and subjected to frozen sectioning. Cryosections of 4 µm are air-dried at room temperature (RT) for 30 minutes, and fixed in cold acetone for 10 minutes at -20°C. Sections used for immunostaining are rehydrated in PBS, and incubated in 0.2% Triton X-100 for 10 minutes. After three rinses with PBS for 5 minutes each and preincubation with 2% BSA to block nonspecific staining, the

sections are incubated with anti-laminin 5, type IV collagen, perlecan, ZO-1, and connexin 43 (all at 1:100) antibodies for 1 hour. After three washes with PBS for 15 minutes, the sections are incubated with a FITC-conjugated secondary antibody (goat anti-rabbit or anti-mouse IgG at 1:100) for 45 minutes. After three additional PBS washes, each for 10 minutes, they are counterstained with propidium iodide (1:1000) or Hoechst 33342 (10 µg/mL), then mounted with an antifade solution and analyzed with a fluorescence microscope. HCECs cultured in 24-well plates or chamber slides are fixed in 4% paraformaldehyde for 15 minutes at RT and stained with anti-ZO-1 and connexin 43 antibodies as just described. For immunohistochemical staining of Ki67, endogenous peroxidase activity is blocked by 0.6% hydrogen peroxide for 10 minutes. Nonspecific staining is blocked by 1% normal goat serum for 30 minutes. Cells are then incubated with anti-Ki67 antibody (1:100) for 1 hour. After three washes with PBS for 15 minutes, cells are incubated with biotinylated rabbit anti-mouse IgG (1:100) for 30 minutes, followed by incubation with ABC reagent for 30 minutes. The reaction product is developed with DAB for 5 minutes and examined by light microscope.

[00528] Cell-Viability and TUNEL Assays: Cell-viability and terminal deoxynucleotidyl transferase-mediated FITC-linked dUTP nick-end DNA labeling (TUNEL) assays are used to determine living and apoptotic cells, respectively. HCEC aggregates are incubated with cell-viability assay reagents for 15 minutes at RT. Live cells are distinguished by green fluorescence staining of the cell cytoplasm, and dead cells are stained with red fluorescence in the nuclei. The TUNEL assay is performed according to the manufacturer's instructions. Briefly, cross-sections of HCEC aggregates are fixed in 4% paraformaldehyde for 20 minutes at RT and permeabilized with 1% Triton X-100. Samples are then incubated for 60 minutes at 37°C with exogenous TdT and fluorescein-conjugated dUTP, for repair of nicked 3'-hydroxyl DNA ends. Cells are treated with DNase I as the positive control, whereas negative control cells are incubated with a buffer lacking the rTdT enzyme. The apoptotic nuclei are labeled with green fluorescence.

Example 77: Cell Culture of Retinal Cells

[00529] Eyes are cut in half along their equator and the neural retina is dissected from the anterior part of the eye in buffered saline solution, according to standard methods known in the art. Briefly, the retina, ciliary body, and vitreous are dissected away from the anterior half of the eye in one piece, and the retina is gently detached from the clear vitreous. Each retina is dissociated with papain (Worthington Biochemical Corporation, Lakewood, N.J.), followed by inactivation with fetal bovine serum (FBS) and addition of 134 Kunitz units/ml of DNaseI. The enzymatically dissociated cells are triturated and collected by centrifugation, resuspended in Dulbecco's modified Eagle's medium (DMEM)/F12 medium (Gibco BRL, Invitrogen Life Technologies, Carlsbad, Calif.) containing 25 µg/ml of insulin, 100 µg/ml of transferrin, 60 µM putrescine, 30 nM selenium, 20 nM progesterone, 100 U/ml of penicillin, 100 µg/ml of streptomycin, 0.05 M Hepes, and 10% FBS. Dissociated primary retina 1 cells are plated onto Poly-D-lysine- and Matrigel- (BD, Franklin Lakes, N.J.) coated glass coverslips that are placed in 24-well tissue culture plates (Falcon Tissue Culture Plates, Fisher Scientific, Pittsburgh, Pa.). Cells are maintained in culture for 5 days to one month in 0.5 ml of media (as above, except with only 1% FBS) at 37 °C and 5% CO₂.

[00530] Immunocytochemistry Analysis: The retinal neuronal cells are cultured for 1, 3, 6, and 8 weeks in the presence and absence of test compounds as disclosed herein, and the cells are analyzed by immunohistochemistry at each time point. Immunocytochemistry analysis is performed according to standard techniques known in the art. Rod photoreceptors are identified by labeling with a rhodopsin-specific antibody (mouse monoclonal, diluted 1:500; Chemicon, Temecula, Calif.). An antibody to mid-weight neurofilament (NFM rabbit polyclonal, diluted 1:10,000, Chemicon) is used to identify ganglion cells; an antibody to β3-tubulin (G7121 mouse monoclonal, diluted 1:1000,

Promega, Madison, Wis.) is used to generally identify interneurons and ganglion cells, and antibodies to calbindin (AB1778 rabbit polyclonal, diluted 1:250, Chemicon) and calretinin (AB5054 rabbit polyclonal, diluted 1:5000, Chemicon) are used to identify subpopulations of calbindin- and calretinin-expressing interneurons in the inner nuclear layer. Briefly, the retina I cell cultures are fixed with 4% paraformaldehyde (Polysciences, Inc, Warrington, Pa.) and/or ethanol, rinsed in Dulbecco's phosphate buffered saline (DPBS), and incubated with primary antibody for 1 hour at 37° C. The cells are then rinsed with DPBS, incubated with a secondary antibody (Alexa 488- or Alexa 568-conjugated secondary antibodies (Molecular Probes, Eugene, Oreg.)), and rinsed with DPBS. Nuclei are stained with 4',6-diamidino-2-phenylindole (DAPI, Molecular Probes), and the cultures are rinsed with DPBS before removing the glass coverslips and mounting them with Fluoromount-G (Southern Biotech, Birmingham, Ala.) on glass slides for viewing and analysis.

Example 78: Matrigel Plug Angiogenesis Assay

[00531] Matrigel containing test compounds are injected subcutaneously or intraocularly, where it solidifies to form a plug. The plug is recovered after 7–21 days in the animal and examined histologically to determine the extent to which blood vessels have entered it. Angiogenesis is measured by quantification of the vessels in histologic sections. Alternatively, fluorescence measurement of plasma volume is performed using fluorescein isothiocyanate (FITC)-labeled dextran 150. The results are expected to indicate one or more compounds disclosed herein that inhibit angiogenesis and are thus expected to be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 79: Corneal Angiogenesis Assay

[00532] A pocket is made in the cornea, and a plug containing an angiogenesis inducing formulation (*e.g.*, VEGF, FGF, or tumor cells), when introduced into this pocket, elicits the ingrowth of new vessels from the peripheral limbal vasculature. Slow-release materials such as ELVAX (ethylene vinyl copolymer) or Hydron are used to introduce angiogenesis inducing substances into the corneal pocket. Alternatively, a sponge material is used.

[00533] The effect of putative inhibitors on the locally induced (*e.g.*, sponge implant) angiogenic reaction in the cornea (*e.g.*, by FGF, VEGF, or tumor cells). The test compound is administered orally, systemically, or directly to the eye. Systemic administration is by bolus injection or, more effectively, by use of a sustained- release method such as implantation of osmotic pumps loaded with the test inhibitor. Administration to the eye is by any of the methods described herein including but not limited to eye drops, topical administration of a cream, emulsion, or gel, intravitreal injection.

[00534] The vascular response is monitored by direct observation throughout the course of the experiment using a stereomicroscope in mice. Definitive visualization of the corneal vasculature is achieved by administration of fluorochrome-labeled high-molecular weight dextran. Quantification is performed by measuring the area of vessel penetration, the progress of vessels toward the angiogenic stimulus over time, or in the case of fluorescence, histogram analysis or pixel counts above a specific (background) threshold.

[00535] The results can indicate one or more compounds disclosed herein inhibit angiogenesis and thus can be useful in treating ocular disorders related to aberrant angiogenesis and/or vascular permeability.

Example 80: Microtiter-plate Angiogenesis Assay

[00536] The assay plate is prepared by placing a collagen plug in the bottom of each well with 5-10 cell spheroids per collagen plug each spheroid containing 400-500 cells. Each collagen plug is covered with 1100 µl of

storage medium per well and stored for future use (1-3 days at 37°C, 5% CO₂). The plate is sealed with sealing. Test compounds are dissolved in 200 µl assay medium with at least one well including a VEGF positive control and at least one well without VEGF or test compound as a negative control. The assay plate is removed from the incubator and storage medium is carefully pipeted away. Assay medium containing the test compounds are pipeted onto the collagen plug. The plug is placed in a humidified incubator for (37°C, 5% CO₂) 24-48 hours. Angiogenesis is quantified by counting the number of sprouts, measuring average sprout length, or determining cumulative sprout length. The assay can be preserved for later analysis by removing the assay medium, adding 1ml of 10% paraformaldehyde in Hanks BSS per well, and storing at 4°C. The results are expected to identify compounds that inhibit angiogenesis in various cell types tested, including cells of ocular origin.

Example 81: Combination use of PI3Kδ inhibitors and agents that inhibit IgE production or activity

[00537] The compounds as disclosed herein can present synergistic or additive efficacy when administered in combination with agents that inhibit IgE production or activity. Agents that inhibit IgE production include, for example, one or more of TEI-9874, 2-(4-(6-cyclohexyloxy-2-naphtyloxy)phenylacetamide)benzoic acid, rapamycin, rapamycin analogs (*i.e.*, rapalogs), TORC1 inhibitors, TORC2 inhibitors, and any other compounds that inhibit mTORC1 and mTORC2. Agents that inhibit IgE activity include, for example, anti-IgE antibodies such as Omalizumab and TNX-901.

[00538] One or more of the subject compounds capable of inhibiting PI3Kδ can be efficacious in treatment of autoimmune and inflammatory disorders (AIID), for example, rheumatoid arthritis. If any of the compounds causes an undesired level of IgE production, one can choose to administer it in combination with an agent that inhibits IgE production or IgE activity. Additionally, the administration of PI3Kδ or PI3Kδ/γ inhibitors as disclosed herein in combination with inhibitors of mTOR can also exhibit synergy through enhanced inhibition of the PI3K pathway. Various *in vivo* and *in vitro* models can be used to establish the effect of such combination treatment on AIID including but not limited to (a) *in vitro* B-cell antibody production assay, (b) *in vivo* TNP assay, and (c) rodent collagen induced arthritis model.

(a) B-cell Assay

[00539] Mice are euthanized, and the spleens are removed and dispersed through a nylon mesh to generate a single-cell suspension. The splenocytes are washed (following removal of erythrocytes by osmotic shock) and incubated with anti-CD43 and anti-Mac-1 antibody-conjugated microbeads (Miltenyi Biotec). The bead-bound cells are separated from unbound cells using a magnetic cell sorter. The magnetized column retains the unwanted cells and the resting B cells are collected in the flow-through. Purified B-cells are stimulated with lipopolysaccharide or an anti-CD40 antibody and interleukin 4. Stimulated B-cells are treated with vehicle alone or with PI3Kδ inhibitors as disclosed herein with and without mTOR inhibitors such as rapamycin, rapalogs, or mTORC1/C2 inhibitors. The results are expected to show that in the presence of mTOR inhibitors (*e.g.*, rapamycin) alone, there is little to no substantial effect on IgG and IgE response. However, in the presence of PI3Kδ and mTOR inhibitors, the B-cells are expected to exhibit a decreased IgG response as compared to the B-cells treated with vehicle alone, and the B-cells are expected to exhibit a decreased IgE response as compared to the response from B-cells treated with PI3Kδ inhibitors alone.

(b) TNP Assay

[00540] Mice are immunized with TNP-Ficoll or TNP-KHL and treated with: vehicle, a PI3Kδ inhibitor, an mTOR inhibitor, for example rapamycin, or a PI3Kδ inhibitor in combination with an mTOR inhibitor such as

rapamycin. Antigen-specific serum IgE is measured by ELISA using TNP-BSA coated plates and isotype specific labeled antibodies. It is expected that mice treated with an mTOR inhibitor alone exhibit little or no substantial effect on antigen specific IgG3 response and no statistically significant elevation in IgE response as compared to the vehicle control. It is also expected that mice treated with both PI3K δ inhibitor and mTOR inhibitor exhibit a reduction in antigen specific IgG3 response as compared to the mice treated with vehicle alone. Additionally, the mice treated with both PI3K δ inhibitor and mTOR inhibitor exhibit a decrease in IgE response as compared to the mice treated with PI3K δ inhibitor alone.

(c) Rat Collagen Induced Arthritis Model

[00541] Female Lewis rats are anesthetized and given collagen injections prepared and administered as described previously on day 0. On day 6, animals are anesthetized and given a second collagen injection. Caliper measurements of normal (pre-disease) right and left ankle joints are performed on day 9. On days 10-11, arthritis typically occurs and rats are randomized into treatment groups. Randomization is performed after ankle joint swelling is obviously established and there is good evidence of bilateral disease.

[00542] After an animal is selected for enrollment in the study, treatment is initiated. Animals are given vehicle, PI3K δ inhibitor, or PI3K δ inhibitor in combination with rapamycin. Dosing is administered on days 1-6. Rats are weighed on days 1-7 following establishment of arthritis and caliper measurements of ankles taken every day. Final body weights are taken on day 7 and animals are euthanized.

[00543] The combination treatment using a compound as disclosed herein and rapamycin can provide greater efficacy than treatment with PI3K δ inhibitor alone.

Example 82: Delayed Type Hypersensitivity Model

[00544] DTH was induced by sensitizing 60 BALB/c male mice on day 0 and day 1 with a solution of 0.05% 2,4 dinitrofluorobenzene (DNFB) in a 4:1 acetone/olive oil mixture. Mice were gently restrained while 20 μ L of solution was applied to the hind foot pads of each mouse. The hind foot pads of the mice were used as they represent an anatomical site that can be easily isolated and immobilized without anesthesia. On day 5, mice were administered a single dose of vehicle, IPI-145 at 10, 3, 1, or 0.3 mg/kg, or dexamethasone at a dose of 5 mg/kg by oral gavage. Thirty minutes later mice were anaesthetized, and a solution of 0.25% DNFB in a 4:1 acetone/olive oil solution was applied to the left inner and outer ear surface. This application resulted in the induction of swelling to the left ear and under these conditions, all animals responded to this treatment with ear swelling. A vehicle control solution of 4:1 acetone/olive oil was applied to the right inner and outer ear. Twenty four hours later, mice were anaesthetized, and measurements of the left and right ear were taken using a digital micrometer. The difference between the two ears was recorded as the amount of swelling induced by the challenge of DNFB. Drug treatment groups were compared to vehicle control to generate the percent reduction in ear swelling. Dexamethasone is routinely used as a positive control as it has broad anti-inflammatory activity.

Example 83: Peptidoglycan-Polysaccharide rat Arthritic Model

(a) Systemic arthritis model

[00545] All injections are performed under anesthesia. 60 female Lewis rats (150-170) are anesthetized by inhalation isoflurane using a small animal anesthesia machine. The animals are placed in the induction chamber until anesthetized by delivery of 4-5% isoflurane in O₂ and then held in that state using a nose cone on the procedure table. Maintenance level of isoflurane is at 1-2%. Animals are injected intraperitoneally (i.p.) with a single injection of purified

PG-PS 10S Group A, D58 strain (concentration 25ug/g of bodyweight) suspended in sterile 0.85% saline. Each animal receives a total volume of 500 microliters administered in the lower left quadrant of the abdomen using a 1 milliliter syringe with a 23 gauge needle. Placement of the needle is critical to avoid injecting the PG-PS 10S into either the stomach or caecum. Animals are under continuous observation until fully recovered from anesthesia and moving about the cage. An acute response of a sharp increase in ankle measurement, typically 20% above baseline measurement can peak in 3-5 days post injection. Treatment with test compounds can be PO, SC, IV or IP. Rats are dosed no more than two times in a 24 hour time span. Treatment can begin on day 0 or any day after that through day 30. The animals are weighed on days 0, 1, 2, 3, 4, 5, 6, 7 and beginning again on day 12 – 30 or until the study is terminated. Paw/ankle diameter is measured with a digital caliper on the left and right side on day 0 prior to injection and again on day 1, 2, 3, 4, 5, 6 and 7. On day 12, measurements begin again and continue on through day 30. At this time, animals can be anesthetized with isoflurane, as described above, and terminal blood samples can be obtained by tail vein draws for the evaluation of the compound blood levels, clinical chemistry or hematology parameters. Animals are then euthanized with carbon dioxide overdose. A thoracotomy can be conducted as a means of death verification.

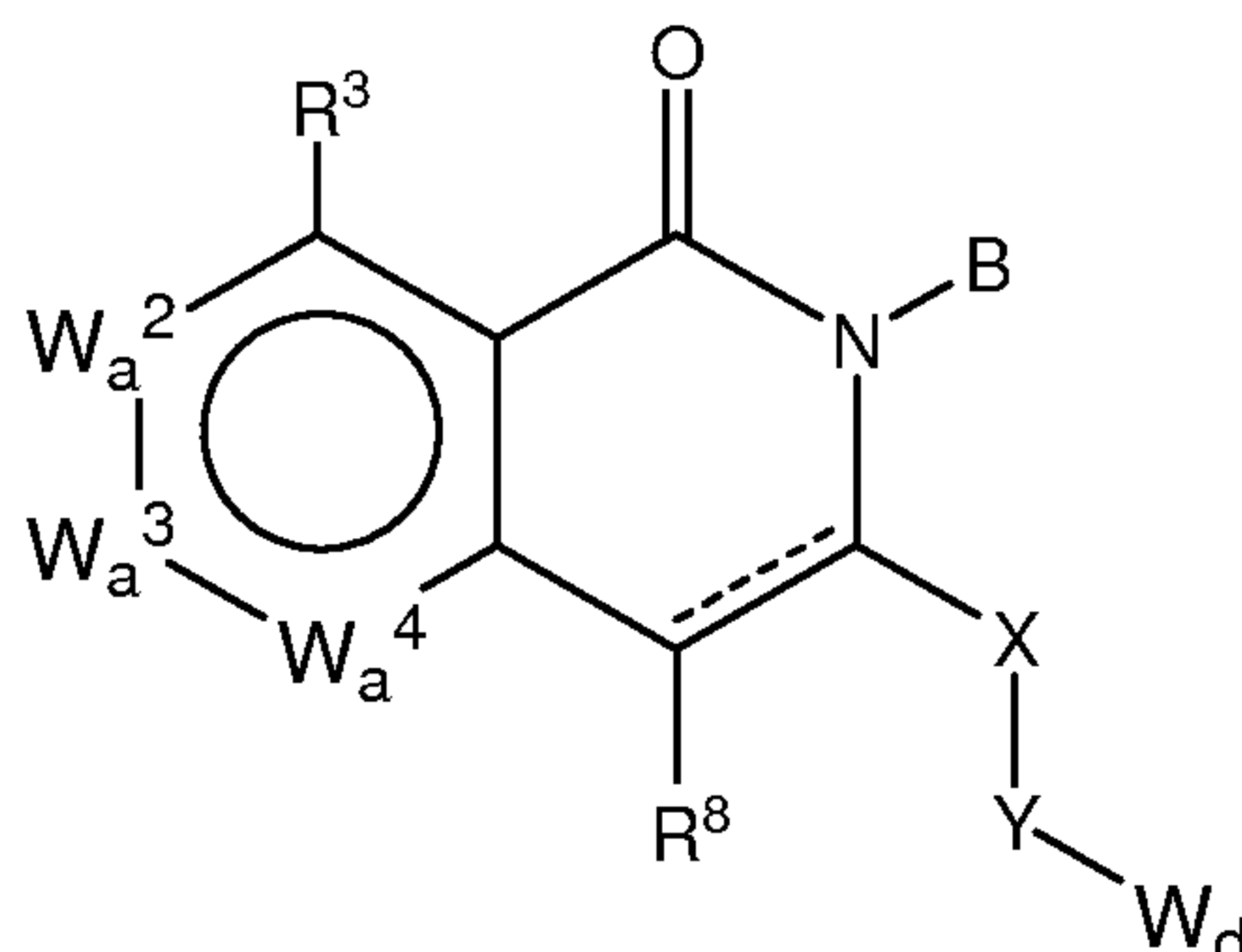
(b) Monoarticular arthritis model

[00546] All injections are performed under anesthesia. 60 female Lewis rats (150-170) are anesthetized by inhalation isoflurane using a small animal anesthesia machine. The animals are placed in the induction chamber until anesthetized by delivery of 4-5% isoflurane in O₂ and then held in that state using a nose cone on the procedure table. Maintenance level of isoflurane is at 1-2%. Animals are injected intra-articular (i.a.) with a single injection of purified PG-PS 100P Group A, D58 strain (concentration 500ug/mL) suspended in sterile 0.85% saline. Each rat receives a total volume of 10 microliters administered into the tibiotalar joint space using a 1 milliliter syringe with a 27 gauge needle. Animals are under continuous observation until fully recovered from anesthesia and moving about the cage. Animals that respond 2-3 days later with a sharp increase in ankle measurement, typically 20% above baseline measurement on the initial i.a. injection, are included in the study. On day 14, all responders are anesthetized again using the procedure previously described. Animals receive an intravenous (I.V.) injection of PG-PS (concentration 250uL/mL). Each rat receives a total volume of 400 microliters administered slowly into the lateral tail vein using a 1 milliliter syringe with a 27 gauge needle. Baseline ankle measurements are measured prior to IV injection and continue through the course of inflammation or out to day 10. Treatment with test compounds will be PO, SC, IV or IP. Rats are dosed no more than two times in a 24 hour time span. Treatment can begin on day 0 or any day after that through day 24. The animals are weighed on days 0, 1, 2, 3, 4, 5, and beginning again on day 14 – 24 or until the study is terminated. Paw/ankle diameter is measured with a digital caliper on the left and right side on day 0 prior to injection and again on day 1, 2, 3, 4, 5, and beginning again on day 14 – 24 or until the study is terminated. At this time, animals can be anesthetized with isoflurane, as described above, and terminal blood samples can be obtained by tail vein draws for the evaluation of the compound blood levels, clinical chemistry or hematology parameters. Animals are then euthanized with carbon dioxide overdose. A thoracotomy can be conducted as a means of death verification.

CLAIMS

WHAT IS CLAIMED IS:

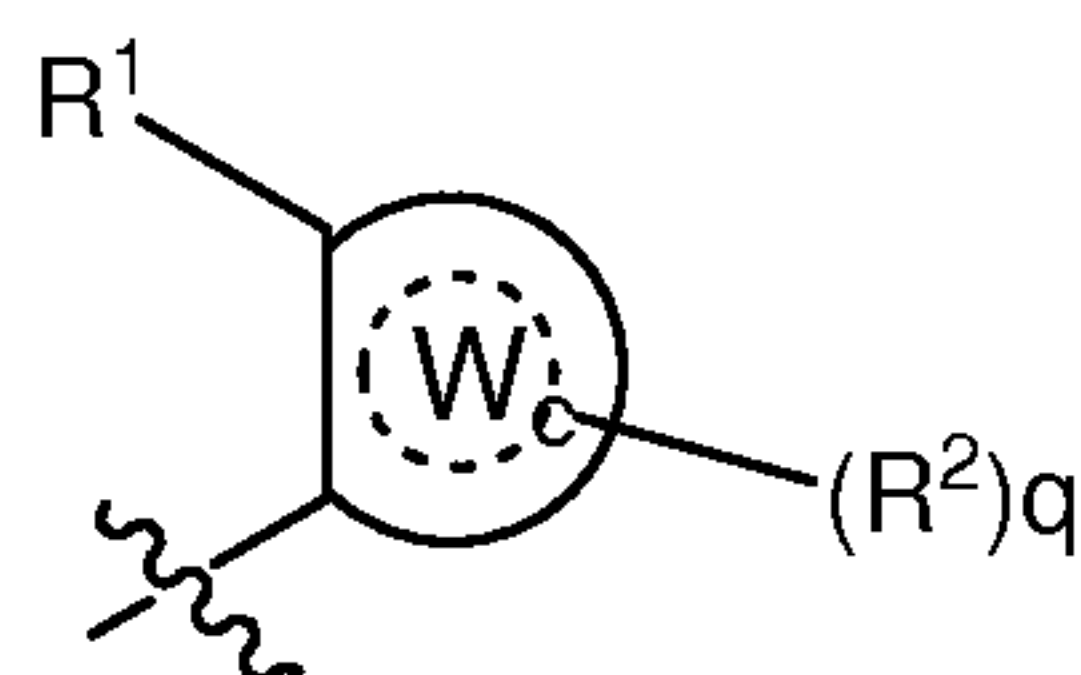
1. A compound of formula (I):



Formula I

W_a^2 is CR^5 or N; W_a^3 is CR^6 or N; W_a^4 is CR^7 or N; wherein no more than two adjacent ring atoms selected from W_a^2 , W_a^3 , and W_a^4 are heteroatoms;

B is hydrogen, alkyl, amino, heteroalkyl, or a moiety of formula II:



Formula II

wherein W_c is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl, and

q is an integer of 0, 1, 2, 3, or 4;

X is absent or $-(CH(R^9))_z-$, and z is an integer of 1, 2, 3, or 4;

Y is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -C(=O)-, -C(=O)(CHR⁹)_z-, -N(R⁹)-, N(R⁹)-C(=O)-, -N(R⁹)-C(=O)NH-, or -N(R⁹)C(R⁹)₂-, and z is an integer of 1, 2, 3, or 4;

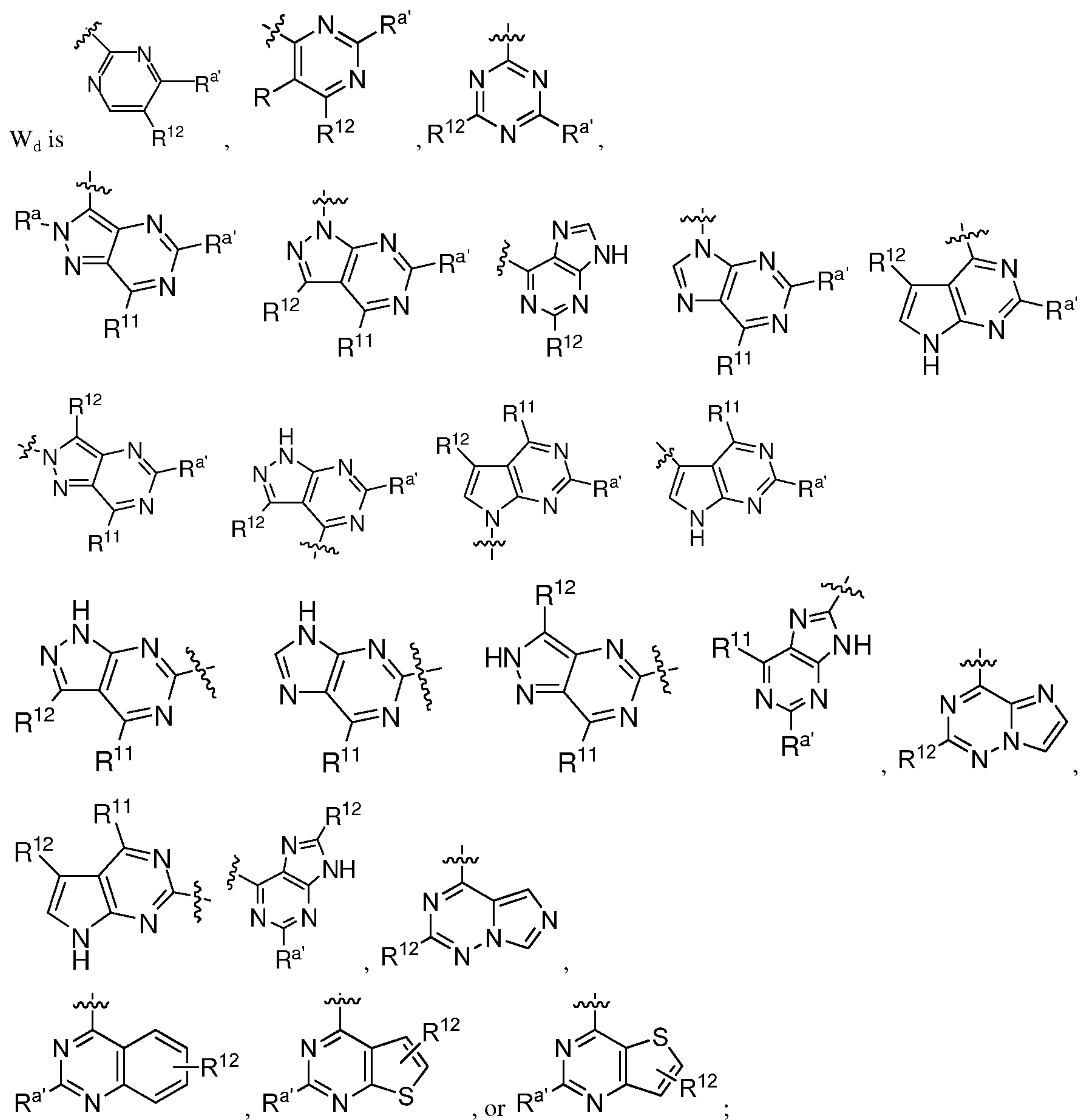
R^1 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, amido, alkoxycarbonyl, sulfonamido, halo, cyano, or nitro;

each R^2 is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, sulfonamido, halo, cyano, hydroxy, nitro, phosphate, urea, or carbonate;

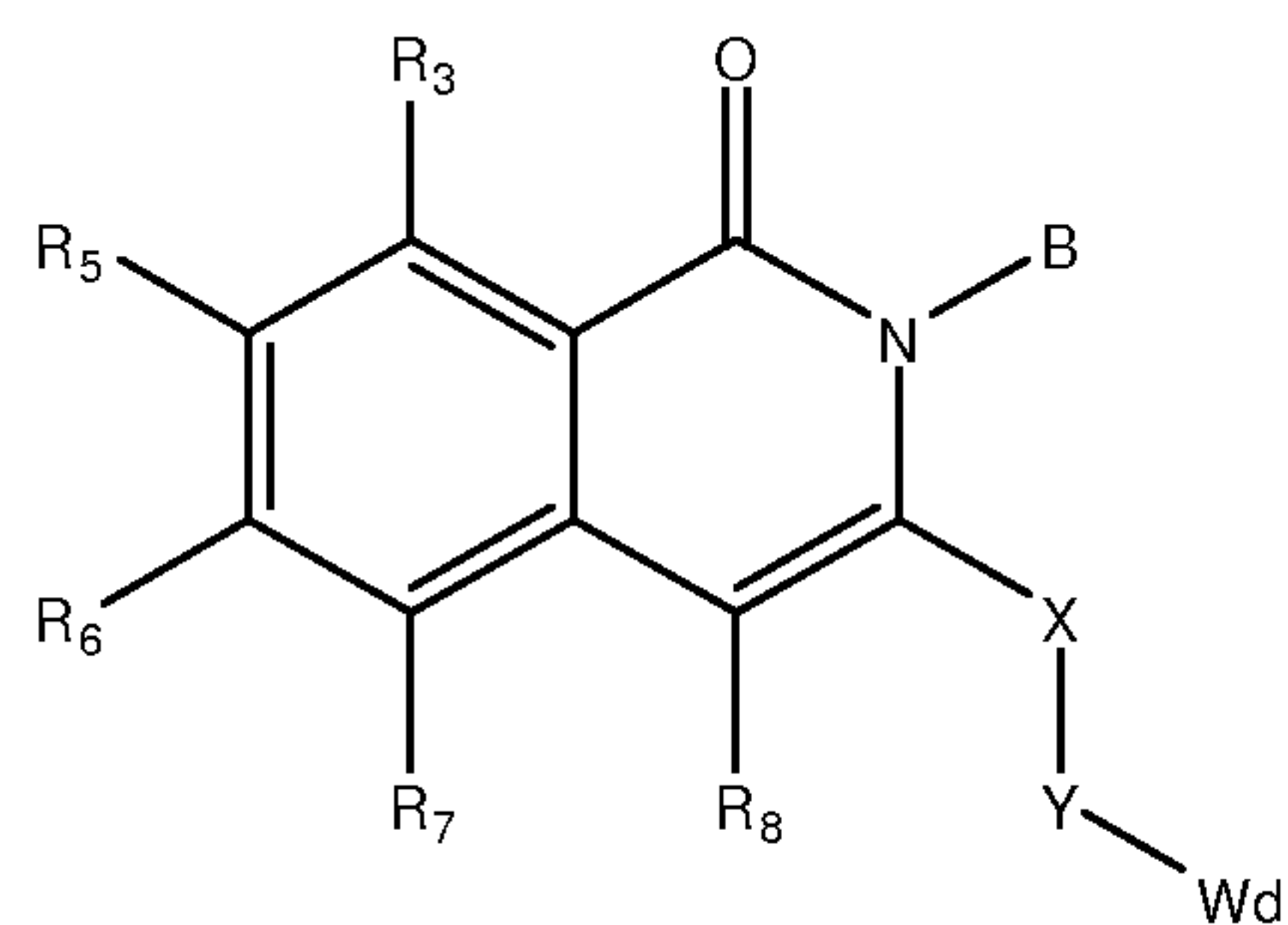
R^3 is cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroaralkyl, heterocyclylalkyl, alkenyl, or alkynyl, or R^3 is a heteroatom selected from N, S, and O, wherein the heteroatom has a covalent bond either directly or through a C₁-C₆ alkyl group to an aryl, heteroaryl or heterocyclyl, or R^3 and R^5 are taken together with the carbons to which they are attached form a 5- or 6-membered ring; wherein each of the above substituents can be substituted with 0, 1, 2, or 3 R^{13} ;

R^5 , R^6 , R^7 , and R^8 are independently hydrogen, halo, cyano, alkyl or amino;

each R^9 is independently hydrogen, alkyl, or heterocycloalkyl;

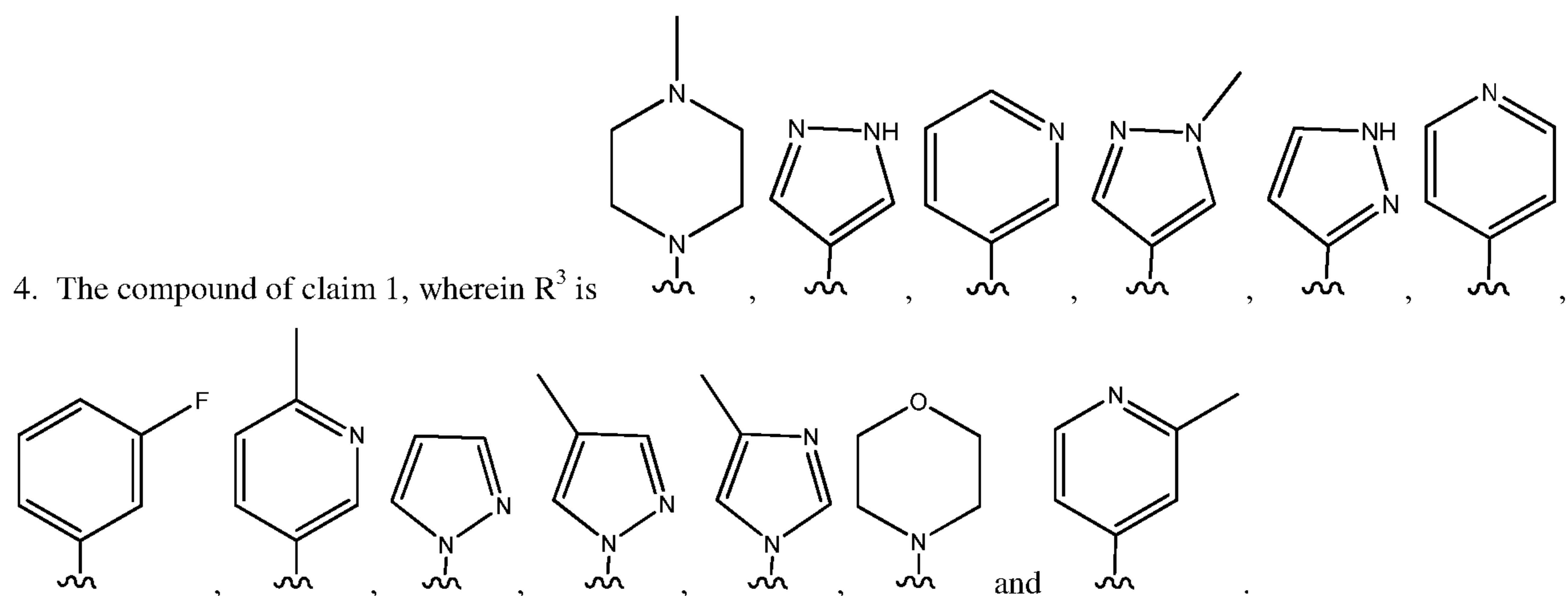


2. The compound of claim 1, wherein the compound of formula (I) is a compound of formula (Ib):

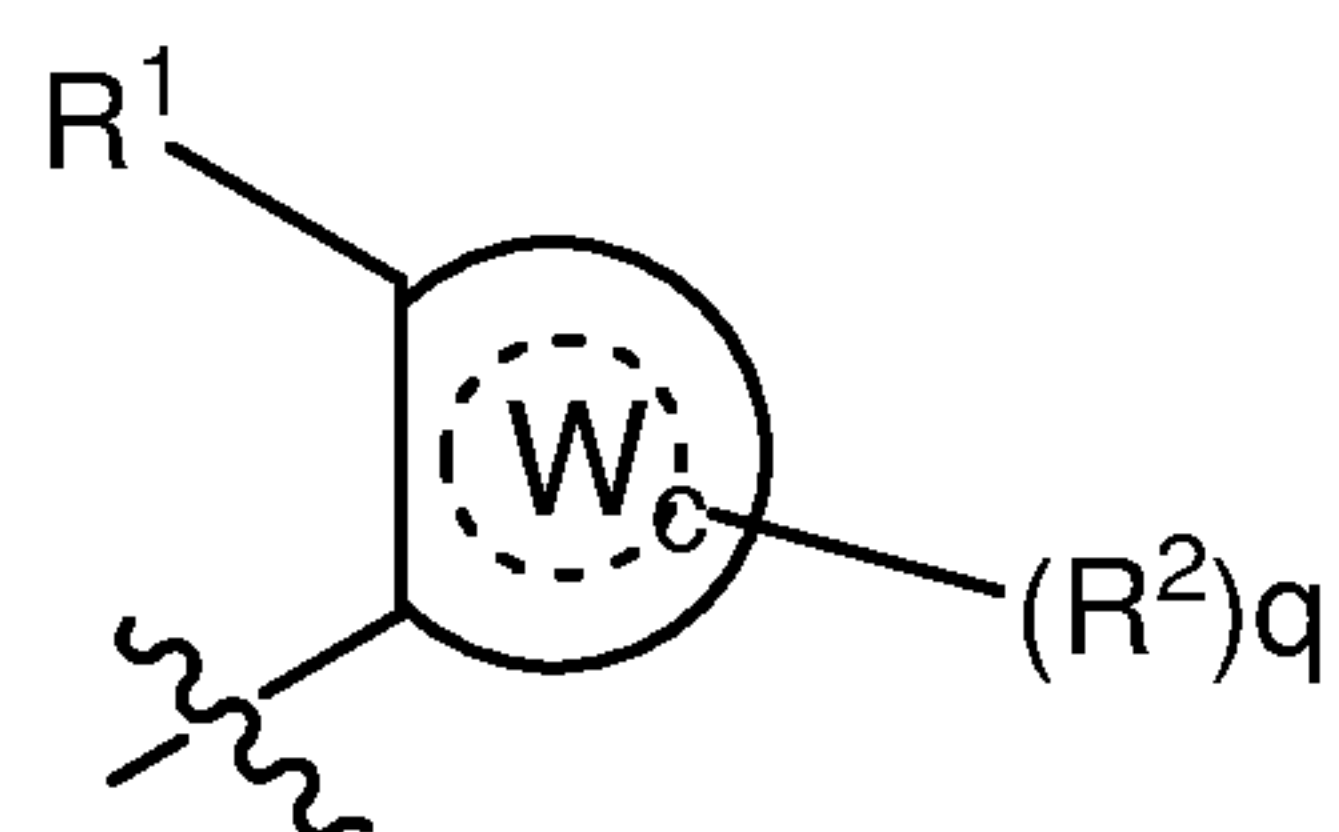


Formula (Ib).

3. The compound of claim 1, wherein R^3 is a 5-membered heteroaryl; a 5-membered nonaromatic heterocycle; a 6-membered aryl; a 6-membered heteroaryl or a 6-membered nonaromatic heterocycle.



5. The compound of claim 1, wherein B is a moiety of Formula II:



Formula II.

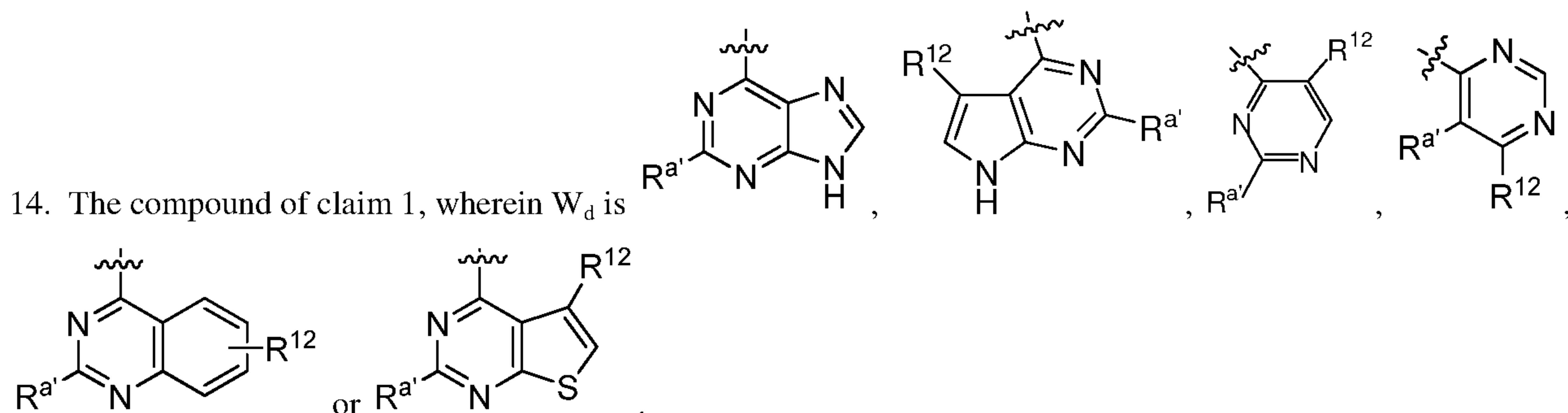
6. The compound of claim 5, wherein W_c is 6-membered aryl or cycloalkyl.
7. The compound of claim 6, wherein q is 0 or 1.
8. The compound of claim 7, wherein R^1 is hydrogen, alkyl, alkoxy, amido, halo, cyano, or nitro.
9. The compound of claim 7, wherein q is 1 and R^2 is alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, amino, halo, cyano, hydroxy or nitro.

10. The compound of claim 1, wherein Y is -O-, -S(=O)₂-, -C(=O)-, -N(R⁹)- or N(R⁹)-C(=O)-.

11. The compound of claim 1, wherein X is -(CH(R⁹))_z-.

12. The compound of claim 11, wherein z is 1, 2 or 3.

13. The compound of claim 11, wherein R⁹ is hydrogen or alkyl.



15. The compound of claim 1, wherein R⁶ is hydrogen, halo, cyano or alkyl.

16. The compound of claim 1, wherein R⁷ is hydrogen, halo, cyano or alkyl.

17. The compound of claim 1, wherein R⁸ is hydrogen, halo, cyano or alkyl.

18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17 and one or more pharmaceutically acceptable excipients.

19. A method of treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 17 or a pharmaceutically composition according to claim 18 to said subject.

20. The method of claim 19, wherein the disorder is cancer, an inflammatory disease or an auto-immune disease.

21. Use of a compound according to any one of claims 1 to 17 or a pharmaceutical composition according to claim 18 in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.