METHODS FOR PREPARING PYRIMIDINE DERIVATIVES USEFUL AS PROTEIN KINASE INHBITORS

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CROSS-REFERENCE

[0001] This application claims priority to U.S. Application No. 61/245,769, filed on September 25, 2009. The entire contents of the aforementioned application are incorporated herein.

BACKGROUND OF THE INVENTION

[0002] The search for new therapeutic agents has been greatly aided in recent years by a better understanding of the structure of enzymes and other biomolecules associated with diseases. One important class of enzymes that has been the subject of intensive study is protein kinases.

[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell (see Hardie, G and Hanks, S. *The Protein Kinase Facts Book, I and II*, Academic Press, San Diego, CA: 1995). Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids etc). Sequence motifs have been identified that generally correspond to each of these kinase families (See, for example, Hanks, S.K., Hunter, T., *FASEB J.* **1995**, *9*, 576-596; Knighton et al., *Science* **1991**, *253*, 407-414; Hiles et al, *Cell* **1992**, *70*, 419-429; Kunz et al, Cell **1993**, *73*, 585-596; Garcia-Bustos et al, *EMBO J* **1994**, *13*, 2352-2361).

[0004] In general, protein kinases mediate intracellular signaling by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. These phosphorylation events are ultimately triggered in response to a variety of extracellular and other stimuli. Examples of such stimuli include environmental and chemical stress signals (e.g., shock, heat shock, ultraviolet radiation, bacterial

endotoxin, and H_2O_2), cytokines (e.g., interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-a), and growth factors (e.g., granulocyte macrophage-colony stimulating factor (GM-CSF), and fibroblast growth factor (FGF)). An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, survival and regulation of the cell cycle.

[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, cancer, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cardiovascular diseases, allergies and asthma, Alzheimer's disease and hormone related diseases. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

[0006] The Polo-like kinases (Plk) belong to a family of serine / threonine kinases that are highly conserved across the species, ranging from yeast to man (reviewed in Lowery DM et al., *Oncogene* **2005,** *24*;248-259). The Plk kinases have multiple roles in cell cycle, including control of entry into and progression through mitosis.
Plk1 is the best characterized of the Plk family members. Plk1 is widely expressed and is most abundant in tissues with a high mitotic index. Protein levels of Plk1 rise and peak in mitosis (Hamanaka, R et al., *J Biol Chem* **1995,** *270*, 21086-21091). The reported substrates of Plk1 are all molecules that are known to regulate entry and progression through mitosis, and include CDC25C, cyclin B, p53, APC, BRCA2 and the proteasome. Plk1 is upregulated in multiple cancer types and the expression levels correlate with severity of disease (Macmillan, JC et al., *Ann Surg Oncol* **2001,** *8*, 729-740). Plk1 is an oncogene and can transform NIH-3T3 cells (Smith, MR et al., *Biochem Biophys Res Commun* **1997,** *234*, 397-405). Depletion or inhibition of Plk1 by siRNA, antisense, microinjection of antibodies, or transfection of a dominant negative construct of Plk1 into cells, reduces proliferation and viability of tumour cells in vitro (Guan, R et al., *Cancer Res* **2005,** *65*, 2698-2704; Liu, X et al., Proc Natl Acad Sci U S A **2003,** 100, 5789-5794, Fan, Y et al., *World J Gastroenterol* **2005,** *11*, 4596-4599; Lane, HA et al., *J Cell Biol* **1996,** *135*, 1701-1713). Tumour cells that have been depleted of Plk1 have activated spindle checkpoints and defects in spindle formation, chromosome alignment and separation and cytokinesis. Loss in viability has been reported to be the result of an induction of apoptosis. In contrast, normal cells have been reported to maintain viability on depletion of Plk1. In vivo knock

down of Plk1 by siRNA or the use of dominant negative constructs leads to growth inhibition or regression of tumours in xenograft models.

[0007] Plk2 is mainly expressed during the G1 phase of the cell cycle and is localized to the centrosome in interphase cells. Plk2 knockout mice develop normally, are fertile and have normal survival rates, but are around 20% smaller than wild type mice. Cells from knockout animals progress through the cell cycle more slowly than in normal mice (Ma, S et al., *Mol Cell Biol* **2003,** *23*, 6936-6943). Depletion of Plk2 by siRNA or transfection of kinase inactive mutants into cells blocks centriole duplication. Downregulation of Plk2 also sensitizes tumour cells to taxol and promotes mitotic catastrophe, in part by suppression of the p53 response (Burns TF et al., *Mol Cell Biol* **2003,** *23*, 5556-5571).

[0008] Plk3 is expressed throughout the cell cycle and increases from G1 to mitosis. Expression is upregulated in highly proliferating ovarian tumours and breast cancer and is associated with a worse prognosis (Weichert, W et al., *Br J Cancer* **2004,** *90*, 815-821; Weichert, W et al., *Virchows Arch* **2005,** *446*, 442-450). In addition to regulation of mitosis, Plk3 is believed to be involved in Golgi fragmentation during the cell cycle and in the DNA-damage response. Inhibition of Plk3 by dominant negative expression is reported to promote p53-independent apoptosis after DNA damage and suppresses colony formation by tumour cells (Li, Z et al., *J Biol Chem* **2005,** *280*, 16843-16850.

[0009] Plk4 is structurally more diverse from the other Plk family members. Depletion of this kinase causes apoptosis in cancer cells (Li, J et al., *Neoplasia* **2005,** *7*, 312-323). Plk4 knockout mice arrest at E7.5 with a high fraction of cells in mitosis and partly segregated chromosomes (Hudson, JW et al., *Current Biology* **2001,** *11*, 441-446).

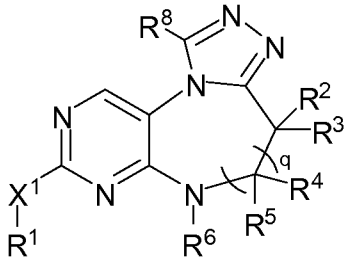
[0010] Molecules of the protein kinase family have been implicated in tumour cell growth, proliferation and survival. Accordingly, there is a great need to develop compounds useful as inhibitors of protein kinases. The evidence implicating the Plk kinases as essential for cell division is strong. Blockade of the cell cycle is a clinically validated approach to inhibiting tumour cell proliferation and viability.

[0011] A number of Plk kinase inhibitors have been reported in the art. See, for example, US 2009/0062292, US 2008/0167289, US 2006/004014, US 6,806,272, US 6,861,422, WO2009/040556, WO 2009/042711, and WO 2006/058876. Considering the potential of these Plk kinase inhibitors for treating one or more of the

aforementioned diseases, it would be desirable to develop new efficient synthetic methods for such inhibitors and for their derivatives.

SUMMARY OF THE INVENTION

[0012] The present invention generally relates to a method of preparing a compound represented by Structural Formula (**I**):



(**I**) ,

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bond, -O-, -NR^7-, -S-, -S(O)-, or -$S(O)_2$-;

R^1 is -H, C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each of said aliphatic, cycloaliphatic, aryl, heteroaryl, and heterocyclyl groups represented by R^1 is optionally and independently substituted with one or more instances of J^1;

each R^2, R^3, R^4, and R^5 is independently -H, halogen, cyano, C_{1-6} aliphatic, or C_{3-10} cycloaliphatic, wherein each of said aliphatic and cycloaliphatic groups represented by R^2, R^3, R^4, and R^5, respectively, is optionally and independently substituted with one or more instances of J^2, J^3, J^4, and J^5, respectively;

optionally, R^2 and R^3, together with the carbon atom to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B;

optionally, R^3 and R^4, together with the carbon atoms to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B;

optionally, R^4 and R^5, together with the carbon atom to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B;

R^6 is -H, C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each of said aliphatic,

cycloaliphatic, aryl, heteroaryl, and heterocyclyl groups represented by R^6 is optionally and independently substituted with one or more instances of J^6;

R^7 is -H, or a C_{1-6} aliphatic or C_{3-8} cycloaliphatic group optionally substituted with one or more instanced of J^A, or, optionally R^7, together with R^1 and the nitrogen atom to which it is attached, forms a 4-7 membered heterocyclic ring that is optionally being substituted with one or more instances of J^B;

R^8 is –H, C_{1-6} aliphatic, or C_{3-8} cycloaliphatic, wherein said aliphatic group is independently and optionally substituted with one or more instances of J^A, and wherein said cycloaliphatic group is independently and optionally substituted with one or more instances of J^B;

each J^1 is independently T or C_{1-6} aliphatic optionally substituted with one or more instances of T;

each of J^2, J^3, J^4, J^5, and J^6 is independently M, or C_{1-6} aliphatic optionally substituted with one or more instances of M;

each T is independently halogen, oxo, $-NO_2$, -CN, Q^1, $-Z^1$-H, or $-Z^2$-Q^2;

each Z^1 is independently a unit consisting of one or more groups independently selected from the group consisting of -NR-, -O-, -S- , -C(O)-, -C(=NR)- , -C(=NOR)-, and $-SO_2N(R)$-;

each Z^2 is independently a unit consisting of one or more groups independently selected from the group consisting of -NR-, -O-, -S- , -C(O)-, -C(=NR)- , -C(=NOR)-, -S(O)-, and $-S(O)_2$-;

each Q^1 is independently C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each Q^1 is independently and optionally substituted with one or more instances of J^Q;

each Q^2 is independently C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocyclyl, or Q^1-Q^1, each of which is optionally and independently substituted with one or more instances of J^Q; or each Q^2, together with R and the nitrogen atom to which it is attached, optionally forms a 4-7 membered heterocyclic ring optionally being substituted with one or more instances of J^B;

each J^Q is independently M or C_{1-6} aliphatic optionally substituted with one or more instances of M;

each M is independently halogen, oxo, $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -COR', $-CO_2R'$, $-CONR'_2$, -OCOR'', $-OCON(R')_2$, -NRCOR', $-NRCO_2R'$, $-NRCON(R')_2$, -S(O)R'', $-SO_2R''$, $-SO_2N(R')_2$, $-NRSO_2R''$, $-NRSO_2N(R')_2$, C_{3-10}

cycloaliphatic, 3-10 membered heterocyclyl, C_{6-10} aryl, or 5-10 membered heteroaryl, wherein each of said cycloaliphatic, heterocyclyl, aryl and heteroaryl groups represented by M is optionally and independently substituted with one or more instances of J^B;

each R is independently -H or C_{1-6} aliphatic, or each R, together with Q^2 and the nitrogen atom to which it is attached, optionally forms a 4-7 membered heterocyclic ring optionally being substituted with one or more instances of J^B;

each R' is independently –H or C_{1-6} aliphatic optionally substituted with one or more instances of J^A; or two R' groups, together with the nitrogen atom to which they are attached, form a 4-7 membered heterocyclic ring optionally being substituted with one or more instances of J^B;

each R" is independently C_{1-4} aliphatic optionally substituted with one or more instances of J^A;

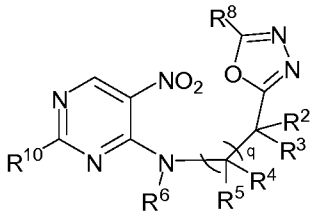
each J^A is independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), C_{3-7} cycloalkyl, and C_{3-7} cyclo(haloalkyl);

each J^B is independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), and C_1-C_4 aliphatic that is optionally substituted with one or more instances of J^A; and

q is 0 or 1.

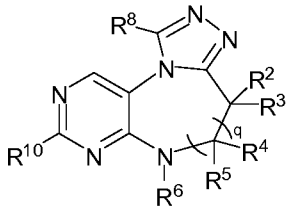
The method comprises the step of:

a) cyclizing a compound represented by Structural Formula **A**:



(A)

under suitable reductive cyclisation conditions to form a compound represented by Structural Formula **B:**



(**B**) ,

wherein R^{10} is LG_1 or $-X^1R^1$, and LG_1 is a suitable leaving group; and

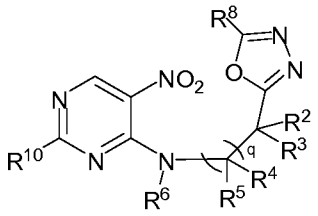
b) optionally, when R^{10} of Structural Formula (**B**) is LG_1, further comprising the step of replacing the $-LG_1$ with $-X^1R^1$ to form the compound represented by Structural Formula (**I**).

[0013] The compounds represented by Structural Formula (**I**) can inhibit protein kinases, such as Plk kinases (e.g., Plk1, Plk2, Plk3 and/or Plk4). See, for example, US 2009/0062292. The present invention can provide efficient synthetic methods with relatively high yields and/or relatively less steps for preparing such compounds that are useful as protein kinases inhibitors, particularly Plk inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

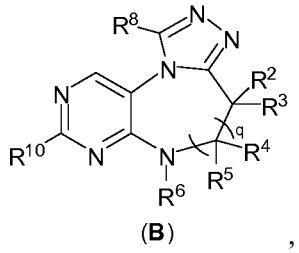
[0014] The methods of the invention employ oxadiazole intermediates for preparing the compounds of Structural Formula (**I**). Certatin aspects of the methods of the invention are depicted below in schemes and preparative examples that follow. Unless otherwise inidcated, all variables in the following schemes are as defined herein.

[0015] The methods of the invention employ the step of: a) cyclisating a compound represented by Structural Formula **A**:



(**A**)

under suitable reductive cyclisation conditions to form a compound represented by Structural Formula **B:**



(**B**) ,

wherein R^{10} is LG_1 or $-X^1R^1$, and LG_1 is a suitable leaving group. If R^{10} is LG_1 in Structural Formula (**B**), the method optionally further includes the step of: b) replacing $-LG_1$ of Structural Formula (**B**) with $-X^1(R^1)$ under suitable conditions to form the compound represented by Structural Formula (**I**).

[0016] Any suitable reductive cyclisation condition known in the art, for example, in WO 2005/121152, WO 2005/068466, and WO 2004/108138, can be employed in the invention. In one embodiment, the reductive cyclisation is performed by the use of Zn powder in acetic acid (Zn/AcOH) or by the use of Fe powder in acetic acid (Fe/AcOH).

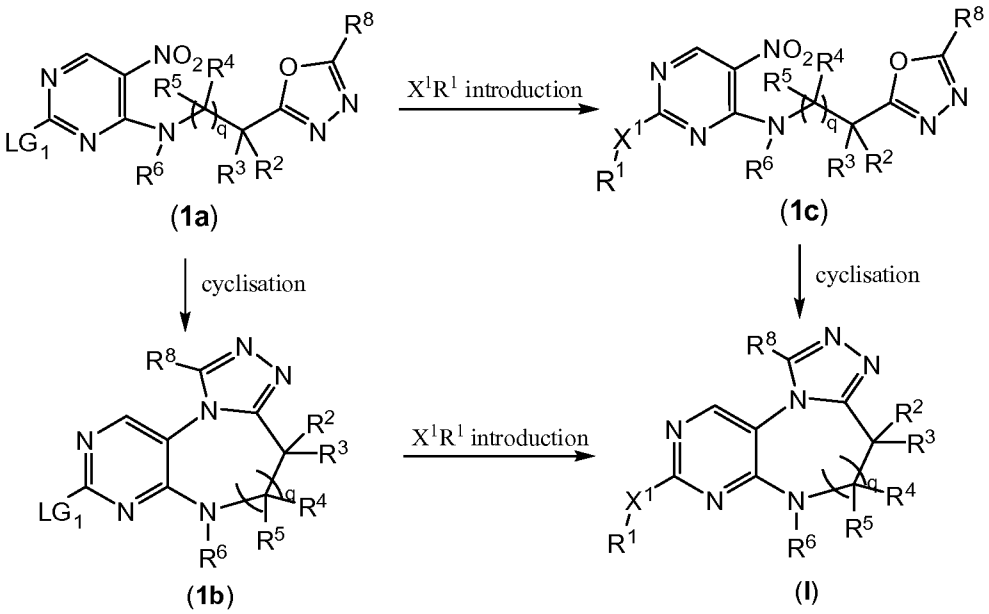
[0017] Any suitable leaving group known in the art can be employed in the invention for LG_1. One suitable example of LG_1 is halogen, such as –Cl, -Br, or -I. Other suitable examples of LG_1 include triflate ($-OSO_2CF_3$), tosylate (O-(p-toluenesulfonyl)), mesylate ($-OSO_2(CH_3)$), lower alkyl sulfones, such as methylsulfone ($-SO_2Me$), etc. In one specific embodiment, LG_1 is -Cl.

[0018] The $-X^1R^1$ moiety of R^{10} can be introduced at any suitable point during the synthesis of a compound of Structural Formula (**I**), for example, prior to or after the reductive cyclisation step a). In one embodiment, the $-X^1R^1$ introduction is performed after the reductive cyclisation step a). In this embodiment, R^{10} in Structural Formulae (**A**) and (**B**) is $-LG_1$ (see Compounds (**1a**) and (**1b**) in Scheme 1). As shown in Scheme 1, Compound (**1a**) undergoes the reductive cyclisation step a) to form Compound (**1b**). The $-LG_1$ leaving group of Compound (**1b**) is then replaced with $-X^1R^1$ after the cyclisation step a).

[0019] In another embodiment, the $-X^1R^1$ introduction is performed prior to the reductive cyclisation step a). For example, as shown in Scheme 1, the $-LG_1$ leaving group of Compound (**1a**) is replaced with $-X^1R^1$ prior to the reductive cyclisation step a) to form Compound (**1c**). Compound (**1c**) then undergoes the reductive cyclisation

step a) to produce a compound represented by Structural Formula (**I**).

Scheme 1



[0020] In yet another embodiment, the -X^1R^1 group can be introduced during the synthesis of the compounds represented by Structural Formula (**A**).

[0021] The -X^1R^1 group can replace –LG_1 in a variety of ways known to one skilled in the art depending upon the values of X^1. For example, if X^1 is –O-, -NR^7- or –S-, then HX^1R^1 can displace –LG_1 in the presence of suitable base or acid, solvent and conditions. Suitable displacement reactions are known to one skilled in the art and can be found in a variety of resources, including "March's Advanced Organic Chemistry." A sulfur linker (wherein X^1 is –S-) can be oxidized under suitable oxidation conditions to form compounds wherein X^1 is –S(O)- or –$S(O)_2$-. Compounds of Structural Formula (**I**), wherein X^1 is a bond and R^1 is bonded to X^1 via a carbon atom, can be formed under suitable cross-coupling conditions. In these cross coupling reactions, one of the starting materials is R^1 bonded to a cross-coupling group. This starting material can react with, for example, the compounds of Structural Formula (**B**) wherein R^{10} –LG_1 under suitable cross coupling conditions to form compounds of Structural Formula (**I**), wherein X^1 is a bond and R^1 is bonded to X^1 *via* a carbon atom.

[0022] The term "cross-coupling reaction", as used herein, refers to a reaction in which a carbon-carbon bond is formed with the aid of a metal catalyst. Usually, one of the carbon atoms is bonded to a functional group (a "cross-coupling group") while

the other carbon atom is bonded to a halogen. Examples of cross coupling reactions include, but are not limited to, Suzuki couplings, Stille couplings, and Negishi couplings.

[0023] The term "cross-coupling group", as used herein, refers to a functional group capable of reacting with another functional group (e.g., halo) in a cross coupling reaction to form a carbon-carbon ("C-C") bond. In some embodiments, the C-C bond is formed between two aromatic groups.

[0024] The term "cross coupling condition", as used herein, refers to the chemical conditions (e.g., temperature, length of time of reaction, volume of solvent required) required in order to enable the cross coupling reaction to occur.

[0025] Examples of cross-coupling groups and their respective cross-coupling conditions include, but are not limited to, boronic acids and boronic esters with Suzuki coupling conditions, $SnBu_3$ (Bu: butyl) with Stille coupling conditions, and ZnX (X: halogen) with Negishi coupling conditions.

[0026] All three of these coupling conditions typically involve the use of a catalyst, a suitable solvent, and optionally a base. Suzuki coupling conditions involve the use of a palladium catalyst and a suitable solvent. Examples of suitable palladium catalysts include, but are not limited to, $PdCl_2(PPh_3)_2$, $Pd(Ph_3)_4$, and $PdCl_2$(dppf) (wherein each Ph is phenyl, and dppf is 1,1'-bis(diphenylphosphino)ferrocene). Suitable bases include, but are not limited to, K_2CO_3 and Na_2CO_3. Suitable solvents include, but are not limited to, tetrahydrofuran, toluene, and ethanol.

[0027] Stille coupling conditions involve the use of a catalyst (usually palladium, but sometimes nickel), a suitable solvent, and other optional reagents. Examples of suitable catalysts include, but are not limited to, $PdCl_2(PPh_3)_2$, $Pd(Ph_3)_4$, and $PdCl_2$(dppf). Suitable solvents include, but are not limited to, tetrahydrofuran, toluene, and dimethylformamide.

[0028] Negishi coupling conditions involve the use of a catalyst (palladium or nickel) and a suitable solvent. Examples of suitable catalysts include, but are not limited to $Pd_2(dba)_3$, $Ni(PPh_3)_2Cl_2$, $PdCl_2(PPh_3)_2$, and $Pd(Ph_3)_4$ (where "dba" is tris(dibenzylideneacetone)dipalladium). Suitable solvents include, but are not limited to, tetrahydrofuran, toluene, and dimethylformamide.

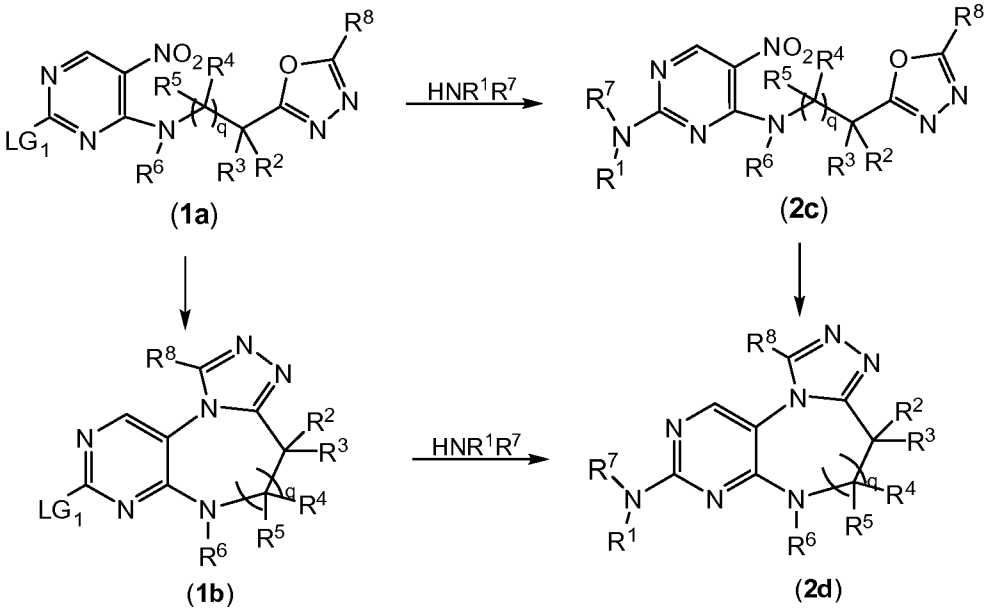
[0029] Suzuki, Stille, and Negishi conditions are known to one skilled in the art

and are described in more detail in a variety of references, including "March's Advanced Organic Chemistry".

[0030] As would be understood by one skilled in the art, cross-coupling groups are formed from coupling group precursors. A coupling group precursor is a reagent or group of reagents used to form a cross-coupling group. Examples include, but are not limited to, bis(pinacolato)diborane for the formation of boronate esters, trimethylborates for the formation of boronic acids, Bu_3SnCl for the formation of stannanes, and $ZnCl_2$ for the formation zincates in Negishi coupling reactions. Examples of suitable coupling group formation conditions include, but are not limited to, making boronic esters via palladium-mediated catalysis; making boronic acids by hydrolyzing boronic esters; making stannanes via a two step process: 1) halogen metal exchange followed by 2) transmetallation with Bu_3SnCl and making zincates via a two step process: 1) halogen metal exchange followed by 2) addition of $ZnCl_2$.

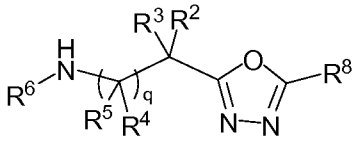
[0031] In some embodiments, X^1 is $-NR^7-$. As shown in Scheme 2, the replacement reaction between the $-LG_1$ group of Compounds (**1a**) and (**1b**) with $-NR^1R^7$ can be done *via*, for example, reacting Compounds (**1a**) and (**1b**) with HNR^1R^7, respectively, to form respective Compounds (**2c**) and (**2d**). In one specific embodiment, the introduction of $-NR^1R^7$ is performed prior to the reductive cyclisation step a). In this embodiment, for example, as showin in Scheme 2, Compound (**1a**) reacts with HNR^1R^7 to form Compound (**2c**). Compound (**2c**) then further undergoes the cyclisation step a) to form compound (**2d**), a compound of Structural Formula (**I**).

Scheme 2



[0032] In another specific embodiment, X^1 is $-NR^7-$; and the $-NR^1R^7$ introduction is performed after the reductive cyclisation step a). In this embodiment, for example, Compound (**1a**) undergoes the reductive cyclisation step a) to form Compound (**1b**). The $-LG_1$ leaving group of Compound (**1b**) is then replaced with $-NR^1R^7$ *via* reacting Compound (**1b**) with HNR^1R^7 to form compound (**2d**), a compound of Structural Formula (**I**).

[0033] The compounds of Structural Formula (**A**) (e.g, Compound (**1a**)) can be prepared by any suitable method known in the art. In one embodiment, a compound of Structural Formula (**A**) can be prepared *via* reacting a compound of Structural Formula (**D**):



(**D**)

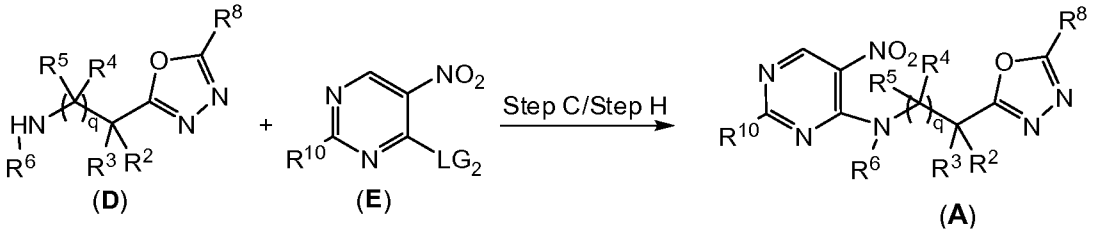
with a compound of Structural Formula (**E**):  under suitable conditions, as shown in Scheme 3. LG_2 in Structural Formula (**E**) is a suitable leaving group.

[0034] Any suitable condition known in the art can be employed for the reaction of the compounds of Structural formula (**D**) and the compounds of Strcutural Formula

(**E**). In Scheme 3, Steps C (when R^6 is –H) and H (R^6 is other then –H), respectively, can go through by the aid of a base, such as potassium carbonate, in a suitable organic solvent system. Suitable solvents for this reaction include DCM (dichloromethane), THF (tetrahydrofuran), petroleum ether, acetone, and mixtures thereof. In one example, a compound of Structural formula (**D**) is suspended in a mixture of DCM (dichloromethane) and THF (tetrahydrofuran), and into this suspension is added a base, such as potassium carbonate. A compound of Strcutural Formula (**E**) is then added into the resulting mixture. In another example, a mixture of a compound of Strcutural Formulae (**D**) and (**E**) is heated in the presence of a base, suhc as potassium carbonate, in a polar organic solvent, such as acetone.

[0035] Any suitable leaving group known in the art can be employed in the invention for LG_2. One suitable example of LG_2 is halogen, such as –Cl, -Br, or -I. Other suitable examples of LG_1 include triflate ($-OSO_2CF_3$), tosylate (O-(p-toluenesulfonyl)), mesylate ($-OSO_2(CH_3)$), lower alkyl sulfones, such as methylsulfone ($-SO_2Me$), etc. In one specific embodiment, LG_2 is -Cl.

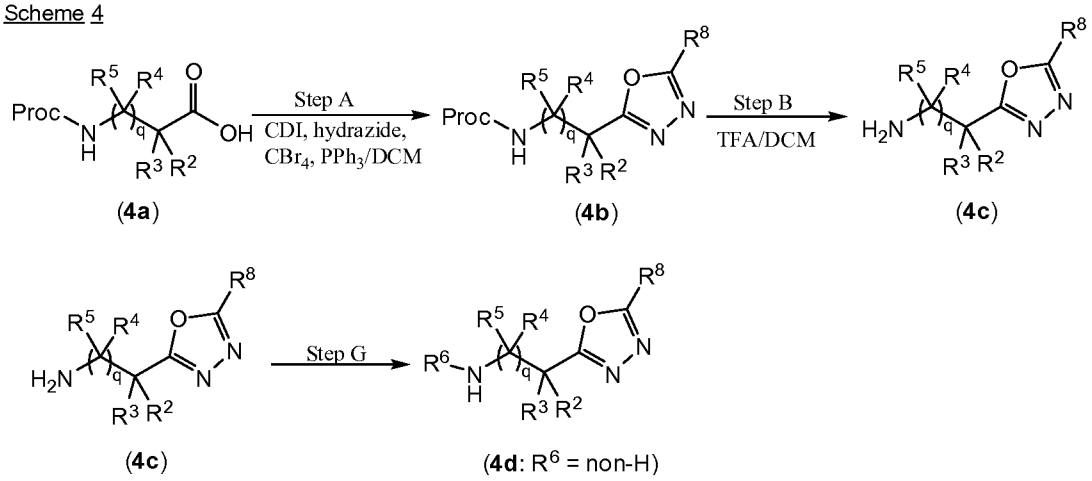
Scheme 3



[0036] The compounds of Structural Formula (**D**) can be prepared by any suitable method known in the art, for example, Barrett, *et al.*, *Bioorganic & Medical Chemistry Letters*, 2004, *14(10)*, 2543-2546. In one embodiment, the compounds of Structural Formula (**D**) are prepared by reacting Compound (**4a**) with a hydrazide (e.g., formohydrazide, acetohydrazide, isobutyrohydrazide, etc.: Step A) followed by de-protection of the amine protecting group "Proc" of Compound (**4b**) (Step B), as shown in Scheme 4. The "Proc" group in each of Compounds (**4a**) and (**4b**) is a suitable amine protecting group. Any suitable amine protecting group known in the art can be employed in the invention. Suitable examples include Carbobenzyloxy (Cbz), *p*-Methoxybenzyl carbonyl (Moz or MeOZ), *tert*-Butyloxycarbonyl (Boc), 9-Fluorenylmethyloxycarbonyl (FMOC), Benzyl (Bn), *p*-Methoxybenzyl (PMB) , 3,4-Dimethoxybenzyl (DMPM), *p*-methoxyphenyl (PMP), Tosyl (Ts), etc. Any suitable condition known in the art, for example, those of Barrett, *et al.*, can be employed for

the hydrazide reaction and the deprotection steps. Exemplary conditions for these steps are depicted in Scheme 4, where CDI is *N,N1*-carbonyldiimidazole, DCM is dichloromethane, and TFA is teterafluoroacetic acid.

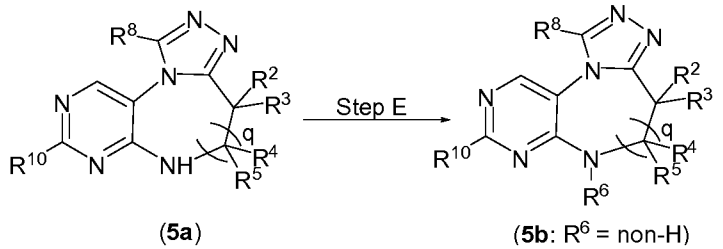
Scheme 4



The compounds of Structural Formula (**D**), wherein R^6 is other than –H, can be prepared by reacting Compound (**4c**) with a suitable reagent known in the art as a source for the non-hydrogen R^6 group (e.g., R^6Br, R^6Cl, $NaBH(OC(O)CH_3)_3$ (for R^6 = cyclopentyl), etc.) to form Compound (**4d**) having non-hydrogen R^6 (Step G in Scheme 5).

[0037] The non-hydrogen R^6 group can generally be introduced during the preparation of the compounds of Structural Formula (**D**) as discussed above. Alternatively, as shown in Scheme 5, the non-hydrogen R^6 group can be introduced after the cyclisation step a) as desired by reacting Compound (**5a**) with a suitable reagent known in the art as a source for the non-hydrogen R^6 group (e.g., R^6Br, R^6Cl, etc.) to form Compound (**5b**):

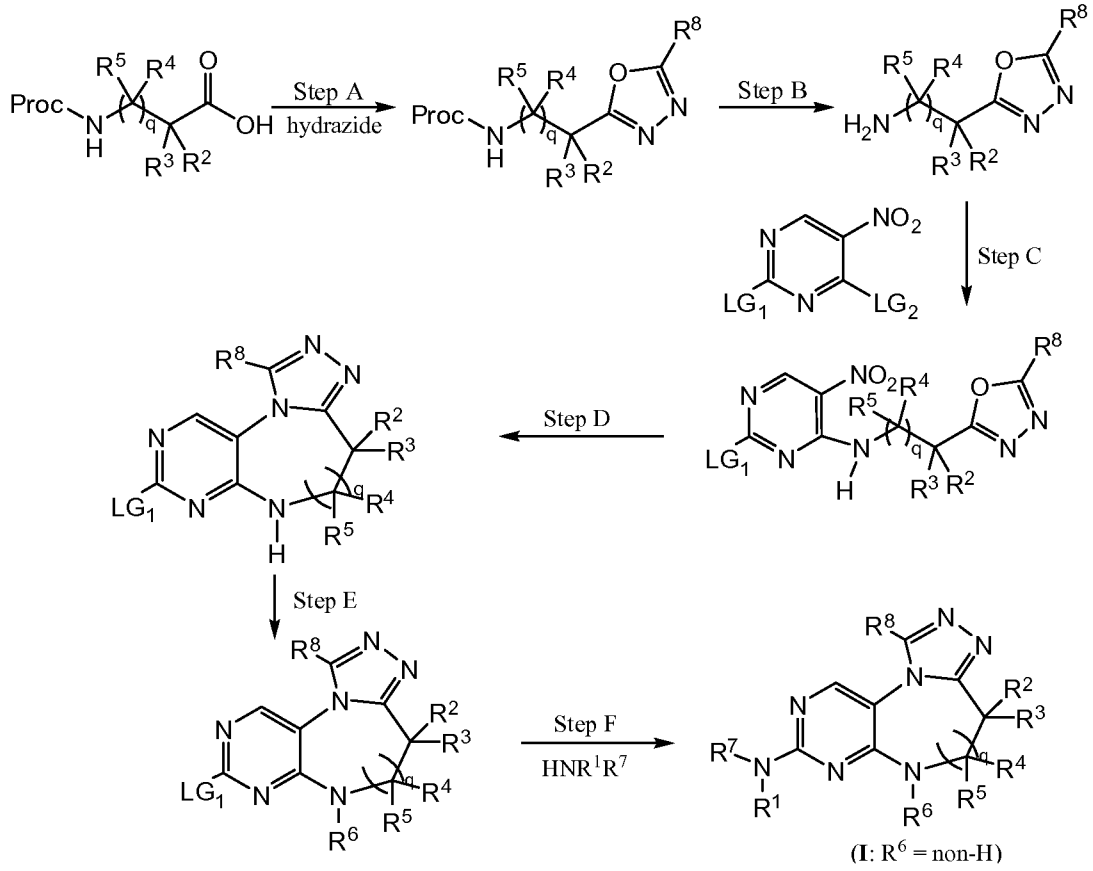
Scheme 5



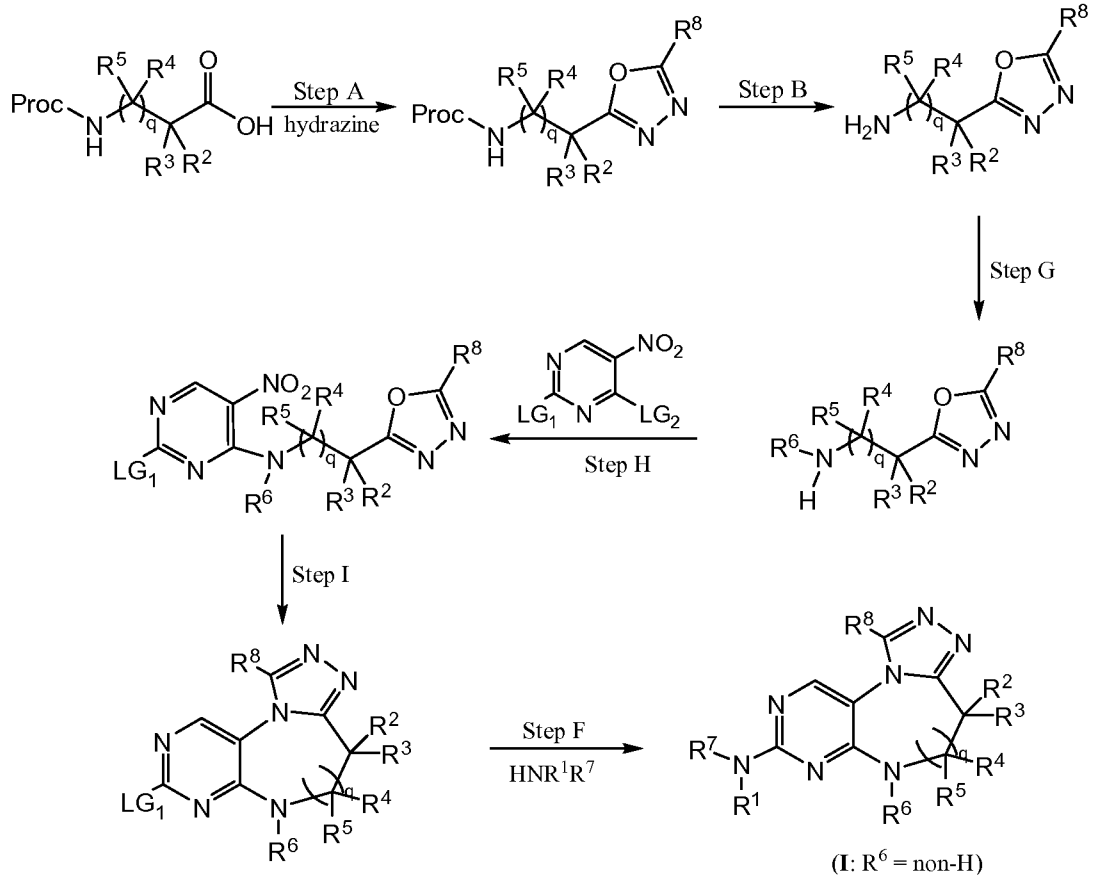
[0038] In one embodiment, the compounds represented by Structural Formula (**I**), wherein X^1 is $–NR^7–$, and R^6 is other than-H, are prepared by the methods of the invention. In one specific embodiment, the methods comprise Steps A-F of Scheme 6. In yet another specific embodiment, the methods comprise Steps A, B, G, H, I and

F of Scheme 7. In yet another specific embodiment, the methods comprise Steps A, B, G, H, J and K of Scheme 8. In Schemes 6, 7 and 8 below, each R^6 is other than –H.

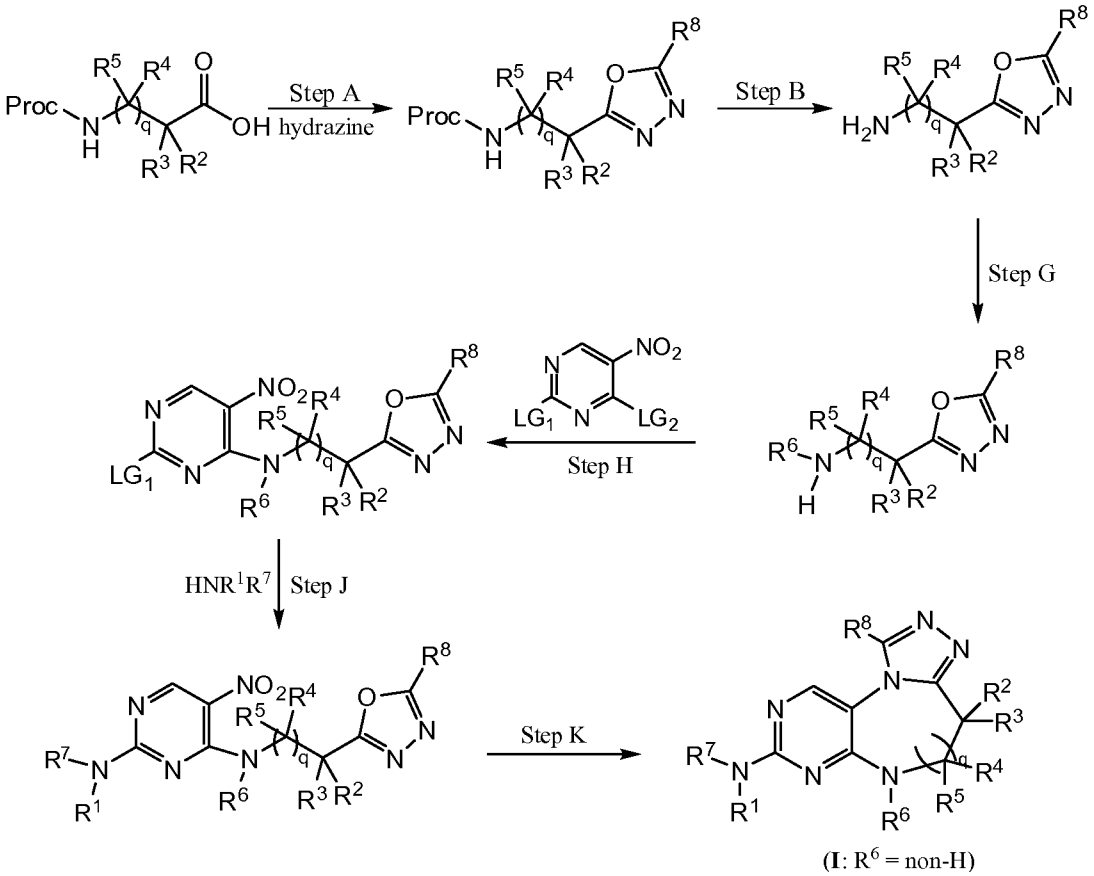
Scheme 6



Scheme 7


Step A
hydrazine
Step B
Step G
Step H
Step I
Step F
HNR1R7
(I: R6 = non-H)

Scheme 8



In each of Schemes 6, 7 and 8: Steps A and B are independently as those described above in Scheme 4 for the synthesis of the compounds of Structural Formula (**D**); Steps C and H are independently as those described above in Scheme 3; Steps D, I and K are independently as described above for the reductive cyclisation step a); Steps G and E are independently as described above for those in Schemes 4 and 5, respectively; and Steps F and J are independently as described above for the amination reaction of Compound (**1b**) with HNR^1R^7 to form Compound (**2d**) in Scheme 2. In yet another specific embodiment, LG_1 and LG_2 are independently halogen, such as –Cl, -Br, or –I, in each of Schemes 6, 7 and 8. In yet another specific embodiment, LG_1 and LG_2 are both -Cl in each of Schemes 6, 7 and 8.

[0039] In one embodiment, the methods of the invention can be employed in preparing the compounds represented by Structural Formula (**I**) or pharmaceutically acceptable salts thereof, wherein values of the variables of Structural Formula (**I**) are as described below.

[0040] The first set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, -NR^7-, -S-, -S(O)-, or -$S(O)_2$-. Specifically, X^1 is -O-, -NR^7-, or -S-. More specifically, X^1 is -NR^7-.

R^1 is -H, C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each of said aliphatic, cycloaliphatic, aryl, heteroaryl, and heterocyclyl groups represented by R^1 is optionally and independently substituted with one or more instances of J^1. Specifically, R^1 is optionally substituted C_{1-6} aliphatic, optionally substituted C_{6-10} aryl, or optionally substituted 5-10 membered heteroaryl. Specifically, R^1 is optionally substituted C_{6-10} aryl or optionally substituted 5-10 membered heteroaryl. More specifically, R^1 is optionally substituted C_{6-10} aryl or optionally substituted 5-6 membered heteroaryl. More specifically, R^1 is optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl. More specifically, R^1 is optionally substituted phenyl.

Each R^2, R^3, R^4, and R^5 is independently -H, halogen, cyano, C_{1-6} aliphatic, or C_{3-10} cycloaliphatic, wherein each of said aliphatic and cycloaliphatic groups represented by R^2, R^3, R^4, and R^5, respectively, is optionally and independently substituted with one or more instances of J^2, J^3, J^4, and J^5, respectively. Optionally, R^2 and R^3, together with the carbon atom to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B. Optionally, R^3 and R^4, together with the carbon atoms to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B. Optionally, R^4 and R^5, together with the carbon atom to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B.

Specifically, each of R^2, R^3, R^4 and R^5 is independently -H, halogen, optionally substituted C_{1-6} aliphatic, or optionally substituted C_{3-7} cycloaliphatic; or optionally R^2 and R^3, R^3 and R^4, and R^4 and R^5, respectively, together with the atom to which they are bound, independently form an optionally substituted C_{3-7} cycloaliphatic ring. Specifically, each of R^2, R^3, R^4, and R^5 is independently -H, halogen, optionally substituted C_{1-6} aliphatic; or optionally R^2 and R^3, together with the carbon atom to which they are attached, form an optionally substituted C_{3-6} cycloalkyl ring. Specifically, each of R^2, R^3, R^4 and R^5 is independently -H, or optionally substituted C_{1-6} alkyl; or optionally R^2 and R^3, together with the atom to which they are bound, form an optionally substituted C_{3-7} cycloalkyl ring. Specifically, each of R^2, R^3, R^4 and R^5 is independently -H, or optionally substituted

C_{1-6} alkyl; or optionally R^2 and R^3, together with the atom to which they are bound, form an optionally substituted C_{3-6} cycloalkyl ring. More specifically, R^2 is –H or C_{1-3} alkyl; R^3 is C_{1-3} alkyl; R^4 is –H or C_{1-3} alkyl; and R^5 is –H or C_{1-3} alkyl. More specifically, R^2 and R^3 together with the atom to which they are bound form a C_{3-7} cycloalkyl ring; R^4 is –H or C_{1-3} alkyl; and R^5 is –H or C_{1-3} alkyl. More specifically, R^2 is –H or C_{1-3} alkyl; R^3 is C_{1-3} alkyl; R^4 is –H; and R^5 is –H. More specifically, R^2 and R^3 together with the atom to which they are bound form a C_{3-7} cycloalkyl ring; R^4 is –H; and R^5 is –H.

R^6 is -H, C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each of said aliphatic, cycloaliphatic, aryl, heteroaryl, and heterocyclyl groups represented by R^6 is optionally and independently substituted with one or more instances of J^6. Specifically, R^6 is –H, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-7} cycloaliphatic, optionally substituted 4-7 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl. Specifically, R^6 is –H, optionally substituted C_{1-6} aliphatic or optionally substituted C_{3-7} cycloaliphatic. Specifically, R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-7} cycloalkyl. Specifically, R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} cycloalkyl. More specifically, R^6 is optionally substituted C_{3-6} cycloalkyl. Even more specifically, R^6 is cyclopentyl.

R^7 is -H, or a C_{1-6} aliphatic or C_{3-8} cycloaliphatic group optionally substituted with one or more instanced of J^A, or, optionally R^7, together with R^1 and the nitrogen atom to which it is attached, forms a 4-7 membered heterocyclic ring that is optionally being substituted with one or more instances of J^B. Specifically, the heterocyclic ring formed with R^1 and R^7 is 5-6 membered. Specifically, R^7 is –H, or optionally substituted C_{1-6} aliphatic. More specifically, R^7 is –H, or C_{1-6} alkyl. Even more specifically, R^7 is –H.

R^8 is –H, C_{1-6} aliphatic, or C_{3-8} cycloaliphatic, wherein said aliphatic group is independently and optionally substituted with one or more instances of J^A, and wherein said cycloaliphatic group is independently and optionally substituted with one or more instances of J^B. Specifically, R^8 is –H, optionally substituted C_{1-6} alkyl, C_{3-7} cycloalkyl, or C_{3-7} cyclo(haloalkyl). Specifically, R^8 is –H or optionally substituted C_{1-6} aliphatic. Specifically, R^8 is –H or optionally substituted C_{1-6} alkyl. Specifically, R^8 is –H, C_{1-6} alkyl or C_{1-6} haloalkyl. Specifically, R^8 is –H or C_{1-6} alkyl.

Each J^1 is independently T or C_{1-6} aliphatic optionally substituted with one or more instances of T.

Each of J^2, J^3, J^4, J^5, and J^6 is independently M, or C_{1-6} aliphatic optionally substituted with one or more instances of M.

Each T is independently halogen, oxo, $-NO_2$, -CN, Q^1, $-Z^1-H$, or $-Z^2-Q^2$. Specifically, each T is halogen, cyano, Q^1, -N(R)H, -OH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$.

More specifically, each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

Each M is independently halogen, oxo, $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -COR', $-CO_2R'$, $-CONR'_2$, -OCOR'', $-OCON(R')_2$, -NRCOR', $-NRCO_2R'$, $-NRCON(R')_2$, -S(O)R'', $-SO_2R''$, $-SO_2N(R')_2$, $-NRSO_2R''$, $-NRSO_2N(R')_2$, C_{3-10} cycloaliphatic, 3-10 membered heterocyclyl, C_{6-10} aryl, or 5-10 membered heteroaryl, wherein each of said cycloaliphatic, heterocyclyl, aryl and heteroaryl groups represented by M is optionally and independently substituted with one or more instances of J^B.

Each Z^1 is independently a unit consisting of one or more groups (e.g., up to four groups) independently selected from the group consisting of -NR-, -O-, -S- , -C(O)-, -C(=NR)-, -C(=NOR)-, and $-SO_2N(R)-$. Specifically, each Z^1 is independently -N(R)-, -O-, $-CO_2-$, -C(O)N(R)-, -OC(O)N(R)-, $-N(R)CO_2-$, -N(R)C(O)N(R)-, $-C(O)N(R)CO_2-$, $-SO_2N(R)-$, or $-N(R)SO_2N(R)-$.

Each Z^2 is independently a unit consisting of one or more groups independently selected from the group consisting of -NR-, -O-, -S- , -C(O)-, -C(=NR)-, -C(=NOR)-, -S(O)-, and $-S(O)_2-$. Specifically, each Z^2 is independently -N(R)-, -O-, $-CO_2-$, -OC(O)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, $-N(R)CO_2-$, -N(R)C(O)N(R)-, $-C(O)N(R)CO_2-$, $-S(O)_2-$, $-SO_2N(R)-$, $-N(R)SO_2-$, or $-N(R)SO_2N(R)-$.

Each Q^1 is independently C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each Q^1 is independently and optionally substituted with one or more instances of J^Q. Specifically, each Q^1 is independently optionally substituted C_{3-7} cycloalkyl, optionally substituted phenyl,

optionally substituted 5-6 membered heteroaryl, or optionally substituted 4-7 membered heterocyclyl. More specifically, each Q^1 is independently optionally substituted C_{3-7} cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl, or optionally substituted 4-7 membered heterocyclyl.

Each Q^2 is independently C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocyclyl, or Q^1-Q^1, each of which is optionally and indepednently substituted with one or more instances of J^Q; or each Q^2, together with R and the nitrogen atom to which is attached, optionally forms a 4-7 membered heterocyclic ring optionally being substituted with one or more instances of J^B. Specifically, each Q^2 is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl, or optionally substituted 4-7 membered heterocyclyl, or each Q^2, together with R and the nitrogen atom to which it is attached, optionally and independently forms an optionally substituted 4-7 membered heterocyclic ring.

Each J^Q is independently M or C_{1-6} aliphatic optionally substituted with one or more instances of M. Specifically, values of J^Q for each of the C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, and 4-7 membered heterocyclyl groups represented by Q^1 independently include halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), –O(C_1-C_4 alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl. Specifically, values of J^Q for the C_{1-6} aliphatic (e.g., C_{1-6} alkyl) represented by Q^2 include halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl). Values of J^Q for each of the cycloalkyl, aryl, heteroaryl, and heterocyclyl groups represented by Q^2 independently include halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), –O(C_1-C_4 alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

Each R is independently -H or C_{1-6} aliphatic, or each R, together with Q^2 and the nitrogen atom to which it is attached, optionally forms a 4-7 membered heterocyclic ring optionally substituted with one or more instances of J^B. Specifically, the C_{1-4} aliphatic group is C_{1-4} alkyl. Specifically, each R is independently –H, -CH_3 or –CH_2CH_3, or each R, together with Q^2 and the nitrogen atom to which it is

attached, optionally forms a 4-7 membered heterocyclic ring optionally substituted with one or more instances of J^B.

Each R' is independently –H or C_{1-6} aliphatic optionally substituted with one or more instances of J^A; or two R' groups, together with the nitrogen atom to which they are attached, form a 4-7 membered heterocyclic ring optionally being substituted with one or more instances of J^B. Specifically, the C_{1-4} aliphatic group is C_{1-4} alkyl.

Each R" is independently C_{1-4} aliphatic optionally substituted with one or more instances of J^A. Specifically, the C_{1-4} aliphatic group is C_{1-4} alkyl.

Each J^A is independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), –$O(C_1-C_4$ alkyl), C_{3-7} cycloalkyl, and C_{3-7} cyclo(haloalkyl).

Each J^B is independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), and C_1-C_4 aliphatic that is optionally substituted with one or more instances of J^A.

[0041] In a second set of variables of Structural Formula (**I**), X^1 is a bond, -O-, $-NR^7$, or -S-; and values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0042] A third set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, $-NR^7$-, or -S-.

R^1 is optionally substituted C_{1-6} aliphatic, optionally substituted C_{6-10} aryl, or optionally substituted 5-10 membered heteroaryl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0043] A fourth set of variables of Structural Formula (**I**) is as follows:

R^7 is –H or optionally substituted C_{1-6} aliphatic.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0044] A fifth set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, $-NR^7$-, or -S-.

R^7 is –H or optionally substituted C_{1-6} aliphatic.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0045] A sixth set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, -NR^7-, or -S-.

R^1 is optionally substituted C_{1-6} aliphatic, optionally substituted C_{6-10} aryl, or optionally substituted 5-10 membered heteroaryl.

R^7 is –H or optionally substituted C_{1-6} aliphatic.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0046] A seventh set of variables of Structural Formula (**I**) is as follows:

R^6 is –H, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-7} cycloaliphatic, optionally substituted 4-7 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0047] An eighth set of variables of Structural Formula (**I**) is as follows:

Values of X^1, R^1 and R^7, wherever applicable, are independently as described above in the second, third, fourth, fifth or sixth set of variables of Structural Formula (**I**).

R^6 is –H, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-7} cycloaliphatic, optionally substituted 4-7 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0048] A ninth set of variables of Structural Formula (**I**) is as follows:

Each of R^2, R^3, R^4 and R^5 is independently -H, halogen, optionally substituted C_{1-6} aliphatic, or optionally substituted C_{3-7} cycloaliphatic; or optionally R^2 and R^3, R^3 and R^4, and R^4 and R^5, respectively, together with the atom to which they are bound, independently form an optionally substituted C_{3-7} cycloaliphatic ring.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0049] A tenth set of variables of Structural Formula (**I**) is as follows:

Values of X^1, R^1, R^6 and R^7, wherever applicable, are independently as described above in the second, third, fourth, fifth, sixth, seventh or eighth set of variables of Structural Formula (**I**).

Each of R^2, R^3, R^4 and R^5 is independently -H, halogen, optionally substituted C_{1-6} aliphatic, or optionally substituted C_{3-7} cycloaliphatic; or optionally R^2 and R^3, R^3 and R^4, and R^4 and R^5, respectively, together with the atom to which they are bound, independently form an optionally substituted C_{3-7} cycloaliphatic ring.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0050] An eleventh set of variables of Structural Formula (**I**) is as follows:

Values of R^1, R^2, R^3, R^4, R^5, R^6 and R^7, wherever applicable, are independently as described above in the second, third, fourth, fifth, sixth, seventh, eighth, or ninth set of variables of Structural Formula (**I**).

R^8 is –H or optionally substituted C_{1-6} aliphatic.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0051] An twelfth set of variables of Structural Formula (**I**) is as follows:

Each Z^1 is independently -N(R)-, -O-, -S-, -CO_2-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -SO_2N(R)-, or -N(R)SO_2N(R)-.

Each Z^2 is independently -N(R)-, -O-, -S-, -CO_2-, -OC(O)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -$S(O)_2$-, -SO_2N(R)-, -N(R)SO_2-, or -N(R)SO_2N(R)-.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0052] A thirteenth set of variables of Structural Formula (**I**) is as follows:

Values of X^1, R^1, R^2, R^3, R^4, R^5, R^6 and R^7, wherever applicable, are independently as described above in the second, third, fourth, fifth, sixth, seventh, eighth, ninth, or tenth set of variables of Structural Formula (**I**).

Each Z^1 is independently -N(R)-, -O-, -S-, -CO_2-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -SO_2N(R)-, or -N(R)SO_2N(R)-.

Each Z^2 is independently -N(R)-, -O-, -S-, -CO_2-, -OC(O)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -$S(O)_2$-, -SO_2N(R)-, -N(R)SO_2-, or -N(R)SO_2N(R)-.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0053] A fourteenth set of variables of Structural Formula (**I**) is as follows:

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, -CO_2H, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, -SO_2N(R)H, -N(R)SO_2N(R)H, -$S(O)_2Q^2$, -N(R)Q^2, -OQ^2, -SQ^2, -CO_2Q^2, -OC(O)Q^2, -C(O)N(R)Q^2, -N(R)C(O)Q^2, -N(R)CO_2Q^2, -OC(O)N(R)Q^2, -C(O)N(R)CO_2Q^2, -N(R)C(O)N(R)Q^2, -SO_2N(R)Q^2, -N(R)SO_2Q^2, or -N(R)SO_2N(R)Q^2. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, -CO_2H, -C(O)N(R)H, -OC(O)N(R)H, -N(R)Q^2, -OQ^2, -CO_2Q^2, -OC(O)Q^2, -C(O)N(R)Q^2, -N(R)C(O)Q^2, -N(R)CO_2Q^2, -OC(O)N(R)Q^2, -C(O)N(R)CO_2Q^2, or -N(R)C(O)N(R)Q^2.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0054] A fifteenth set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, -NR^7-, or -S-.

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group

consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-SQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0055] A sixteenth set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, $-NR^7$-, or -S-.

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), and $-O(C_1-C_4$ alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-SQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

R^7 is –H, or optionally substituted C_{1-6} aliphatic.

Values, including specific values, of the remaining variables are as described

above in the first set of variables of Structural Formula (**I**).

[0056] A seventeenth set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, -NR^7-, or -S-.

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, -CO_2H, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, -SO_2N(R)H, -N(R)SO_2N(R)H, -S(O)$_2Q^2$, -N(R)Q^2, -OQ^2, -SQ^2, -CO_2Q^2, -OC(O)Q^2, -C(O)N(R)Q^2, -N(R)C(O)Q^2, -N(R)CO_2Q^2, -OC(O)N(R)Q^2, -C(O)N(R)CO_2Q^2, -N(R)C(O)N(R)Q^2, -SO_2N(R)Q^2, -N(R)SO_2Q^2, or -N(R)SO_2N(R)Q^2. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, -CO_2H, -C(O)N(R)H, -OC(O)N(R)H, -N(R)Q^2, -OQ^2, -CO_2Q^2, -OC(O)Q^2, -C(O)N(R)Q^2, -N(R)C(O)Q^2, -N(R)CO_2Q^2, -OC(O)N(R)Q^2, -C(O)N(R)CO_2Q^2, or -N(R)C(O)N(R)Q^2.

R^6 is –H, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-7} cycloaliphatic, optionally substituted 4-7 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl.

R^7 is –H, or optionally substituted C_{1-6} aliphatic.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0057] A eighteenth set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, -NR^7-, or -S-.

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently

substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-SQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

Each of R^2, R^3, R^4 and R^5 is independently -H, halogen, optionally substituted C_{1-6} aliphatic, or optionally substituted C_{3-7} cycloaliphatic; or optionally R^2 and R^3, R^3 and R^4, and R^4 and R^5, respectively, together with the atom to which they are bound, independently form an optionally substituted C_{3-7} cycloaliphatic ring.

R^6 is –H, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-7} cycloaliphatic, optionally substituted 3-7 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl.

R^7 is –H, or optionally substituted C_{1-6} aliphatic.

R^8 is –H, or optionally substituted C_{1-6} aliphatic.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0058] An nineteenth set of variables of Structural Formula (**I**) is as follows:

X^1 is a bond, -O-, $-NR^7$-, or -S-.

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), and $-O(C_1-C_4$ alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$,

$-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-SQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

Each of R^2, R^3, R^4 and R^5 is independently -H, halogen, optionally substituted C_{1-6} aliphatic, or optionally substituted C_{3-7} cycloaliphatic; or optionally R^2 and R^3, R^3 and R^4, and R^4 and R^5, respectively, together with the atom to which they are bound, independently form an optionally substituted C_{3-7} cycloaliphatic ring.

R^6 is –H, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-7} cycloaliphatic, optionally substituted 3-7 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl.

R^7 is –H, or C_{1-6} alkyl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0059] A twentieth set of variables of Structural Formula (**I**) is as follows:

Values, including specific values, of X^1, R^1, R^2, R^3, R^4, R^5, and R^6 are independently as described above in any set of fourteenth through nineteenth sets of variables of Structural Formula (**I**).

R^7 is –H.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0060] A twenty first set of variables of Structural Formula (**I**) is as follows:

Values, including specific values, of X^1, R^1, R^2, R^3, R^4, and R^5 are independently as described above in any set of fourteenth through nineteenth sets of variables of Structural Formula (**I**).

R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-7} cycloalkyl.

R^7 is –H or C_{1-6} alkyl. Specifically, R^7 is –H.

Values, including specific values, of the remaining variables are as described

above in the first set of variables of Structural Formula (**I**).

[0061] A twenty second set of variables of Structural Formula (**I**) is as follows:

Values, including specific values, of X^1, R^1, R^2, R^3, R^4, and R^5 are independently as described above in any set of fourteenth through nineteenth sets of variables of Structural Formula (**I**).

R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-7} cycloalkyl.

R^7 is –H, or C_{1-6} alkyl. Specifically, R^7 is –H.

R^8 is –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0062] A twenty third set of variables of Structural Formula (**I**) is as follows:

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), $-CO_2H$, $-CO_2$(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-SQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

Each of R^2, R^3, R^4 and R^5 is independently -H, or optionally substituted C_{1-6} alkyl; or optionally R^2 and R^3, together with the atom to which they are bound, form an optionally substituted C_{3-7} cycloalkyl ring.

R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-7} cycloalkyl.

R^7 is –H, or C_{1-6} alkyl.

R^8 is –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0063] A twenty fourth set of variables of Structural Formula (**I**) is as follows:

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), and $-O(C_1-C_4$ alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, $-CO_2H$, $-C(O)N(R)H$, $-OC(O)N(R)H$, $-N(R)C(O)N(R)H$, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-SQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, $-C(O)N(R)H$, $-OC(O)N(R)H$, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

i) R^2 is –H or C_{1-3} alkyl; R^3 is C_{1-3} alkyl; R^4 is –H or C_{1-3} alkyl; and R^5 is –H or C_{1-3} alkyl; or ii) R^2 and R^3 together with the atom to which they are bound form a C_{3-7} cycloalkyl ring; R^4 is –H or C_{1-3} alkyl; and R^5 is –H or C_{1-3} alkyl.

R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-7} cycloalkyl.

R^7 is –H, or C_{1-6} alkyl.

R^8 is –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0064] A twenty fifth set of variables of Structural Formula (**I**) is as follows:

R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), and $-O(C_1-C_4$ alkyl). Alternatively, R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, $-CO_2H$, $-C(O)N(R)H$, $-OC(O)N(R)H$, $-N(R)C(O)N(R)H$, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-SQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$. Specifically, R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, $-C(O)N(R)H$, $-OC(O)N(R)H$, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

i) R^2 is –H or C_{1-3} alkyl; R^3 is C_{1-3} alkyl; R^4 is –H; and R^5 is –H; or ii) R^2 and R^3 together with the atom to which they are bound form a C_{3-7} cycloalkyl ring; R^4 is –H; and R^5 is –H.

R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-7} cycloalkyl.

R^7 is –H, or C_{1-6} alkyl.

R^8 is –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0065] A twenty sixth set of variables of Structural Formula (**I**) is as follows:

R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, $-CO_2H$, $-C(O)N(R)H$, $-OC(O)N(R)H$, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, or $-N(R)C(O)N(R)Q^2$.

i) R^2 is –H or C_{1-3} alkyl; R^3 is C_{1-3} alkyl; R^4 is –H; and R^5 is –H; or ii) R^2 and R^3 together with the atom to which they are bound form a C_{3-7} cycloalkyl ring; R^4 is –H; and R^5 is –H.

R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-7} cycloalkyl.

R^7 is –H, or C_{1-6} alkyl.

R^8 is –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0066] A twenty seventh set of variables of Structural Formula (**I**) is as follows:

Values, including specific values, of R^1, R^2, R^3, R^4, R^5, and R^6 are independently as described above in the twenty sixth set of variables of Structural Formula (**I**).

R^7 is –H.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0067] A twenty eighth set of variables of Structural Formula (**I**) is as follows:

Values, including specific values, of R^1, R^2, R^3, R^4, and R^5 are independently as described above in the twenty sixth set of variables of Structural Formula (**I**).

R^6 is optionally substituted C_{3-6} cycloalkyl

R^7 is –H.

Values, including specific values, of the remaining variables are as described above in the first set of variables of Structural Formula (**I**).

[0068] A twenty ninth set of variables of Structural Formula (**I**) is as follows:

X^1 is –O-, –NR^7-, or –S-.

Values, including specific values, of the remaining variables of Structural Formula (**I**) are as described above in any set of the first through twenty eighth sets of variables of Structural Formula (**I**).

[0069] A thirtieth set of variables of Structural Formula (**I**) is as follows:

X^1 is –NR^7-.

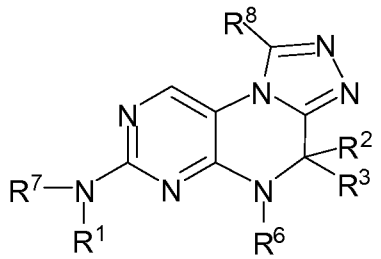
Values, including specific values, of the remaining variables of Structural Formula (**I**) are as described above in any set of the first through twenty eighth sets of variables of Structural Formula (**I**).

[0070] A thirty first set of variables of Structural Formula (**I**) is as follows:

q is 0

Values, including specific values, of the remaining variables of Structural Formula (**I**) are as described above in any set of the first through thirtieth sets of variables of Structural Formula (**I**).

[0071] In another embodiment, the methods of the invention can be employed in preparing the compounds represented by Structural Formula (**II**) or pharmaceutically acceptable salts thereof, wherein values of the variables of Structural Formula (**II**) are as described below:



(**II**)

[0072] In a first set of variables of Structural Formula (**II**), values, including specific values, of variables of Structural Formula (**II**) are independently as described above in any set of the first through twenty sixth sets of variables of Structural Formula (**I**).

[0073] A second set of variables of Structural Formula (**II**) is as follows:

R^6 is –H, C_{1-6} aliphatic, or C_{3-7} cycloaliphatic, wherein each of the C_{1-6} aliphatic and C_{3-7} cycloaliphatic groups is optionally and independently substituted with one or more instances of J^6.

Values, including specific values, of variables of Structural Formula (**II**) are independently as described above in the first set of variables of Structural Formula (**I**).

[0074] A third set of variables of Structural Formula (**II**) is as follows:

R^1 is optionally substituted C_{6-10} aryl or optionally substituted 5-10 membered heteroaryl.

Each Z^1 is independently -N(R)-, -O-, -S-, -CO_2-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -SO_2N(R)-, or -N(R)SO_2N(R)-.

Each Z^2 is independently -N(R)-, -O-, -S-, -CO_2-, -OC(O)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -S(O)-, -$S(O)_2$-, -SO_2N(R)-, -N(R)SO_2-, or -N(R)SO_2N(R)-.

Each Q^1 is independently optionally substituted C_{3-7} cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl, or optionally substituted 4-7 membered heterocyclyl.

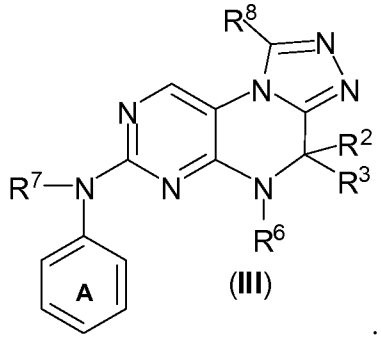
Each of R^2 and R^3 is independently –H, halogen, cyano, or C_{1-6} aliphatic, or optionally R^2 and R^3, together with the carbon atom(s) to which they are bound, independently form a C_{3-7} cycloalkyl ring, wherein each of said aliphatic and cycloalkyl ring is independently and optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl).

R^6 is –H, C_{1-6} aliphatic or C_{3-7} cycloaliphatic, each of which is optionally and independently substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl).

Each of R^7 and R^8 is independently –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables of Structural Formula (**I**) are as described above in the first set of variables of Structural Formula (**I**).

[0075] In another embodiment, the methods of the invention can be employed in preparing the compounds represented by Structural Formula (**III**) or pharmaceutically acceptable salts thereof, wherein values of the variables of Structural Formula (**III**) are as described below:



(III)

[0076] In a first set of variables of Structural Formula (**III**), values, including specific values, of variables of Structural Formula (**III**) are independently as described above in any set of the first through twenty sixth sets of variables of Structural Formula (**I**).

[0077] In a second set of variables of Structural Formula (**III**), values, including specific values, of variables of Structural Formula (**III**) are independently as described above in the second or thrid set of variables of Structural Formula (**II**).

[0078] A third set of variables of Structural Formula (**III**) is as follows:

Phenyl ring **A** is optionally substituted with one or more substitutents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T.

Each T is halogen, cyano, Q^1, -N(R)H, -OH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$.

Q^1 is C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, or 4-7 membered heterocyclyl, each optionally and independently substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

Each Q^2 is independently C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, or 4-7membered heterocyclyl, or each Q^2, together with R, optionally and independently forms an optionally substituted, 4-7 membered heterocyclic ring; wherein said C_{1-6} alkyl represented by Q^2 is optionally substituted with one or more

substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl); and wherein each of said cycloalkyl, aryl, heteroaryl, and heterocyclyl groups represented by Q^2 is optionally and independently substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), –O(C_1-C_4 alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

Each of R^2 and R^3 is independently -H, halogen, optionally substituted C_{1-6} aliphatic; or optionally R^2 and R^3, together with the carbon atom to which they are attached, form an optionally substituted C_{3-6} cycloalkyl ring.

R^6 is optionally substituted –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} cycloalkyl.

Each of R^7 and R^8 is independently –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables of Structural Formula (**I**) are as described above in the first set of variables of Structural Formula (**I**).

[0079] A fourth set of variables of Structural Formula (**III**) is as follows:

Phenyl ring **A** is substituted with one or more substituents independently selected from the group consisting of -C(O)N(R)H, -C(O)N(R)Q^2, -N(R)C(O)Q^2, -CO_2H, -CO_2Q^2, -OC(O)Q^2, -N(R)CO_2Q^2, -OC(O)N(R)Q^2, and -N(R)C(O)N(R)Q^2; and optionally further substituted with one or one or more substituents independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, –O(C_1-C_4 alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

Each Q^2 is independently C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, or 4-7membered heterocyclyl, or each Q^2, together with R, optionally and independently forms an optionally substituted, 4-7 membered heterocyclic ring; wherein said C_{1-6} alkyl represented by Q^2 is optionally substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl); and wherein each of said cycloalkyl, aryl, heteroaryl, and heterocyclyl groups represented by Q^2 is optionally

and independently substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

Each of R^2 and R^3 is independently -H, halogen, optionally substituted C_{1-6} aliphatic; or optionally R^2 and R^3, together with the carbon atom to which they are attached, form an optionally substituted C_{3-6} cycloalkyl ring.

R^6 is optionally substituted –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} cycloalkyl.

Each of R^7 and R^8 is independently –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables of Structural Formula (**I**) are as described above in the first set of variables of Structural Formula (**I**).

[0080] A fifth set of variables of Structural Formula (**III**) is as follows:

Phenyl ring **A** is substituted with $-OC(O)Q^2$, $-C(O)N(R)Q^2$, or $-N(R)C(O)Q^2$, and optionally further substituted with one or one or more substituents independently selected from the group consisting of halogen, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-O(C_1-C_4$ alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

Each Q^2 is independently C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, or 4-7membered heterocyclyl, or each Q^2, together with R, optionally and independently forms an optionally substituted, 4-7 membered heterocyclic ring; wherein said C_{1-6} alkyl represented by Q^2 is optionally substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), and $-O(C_1-C_4$ alkyl); and wherein each of said cycloalkyl, aryl, heteroaryl, and heterocyclyl groups represented by Q^2 is optionally and independently substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

Each of R^2 and R^3 is independently -H, halogen, optionally substituted C_{1-6} aliphatic; or optionally R^2 and R^3, together with the carbon atom to which they are attached, form an optionally substituted C_{3-6} cycloalkyl ring.

R^6 is optionally substituted –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} cycloalkyl.

Each of R^7 and R^8 is independently –H or C_{1-6} alkyl.

Values, including specific values, of the remaining variables of Structural Formula (**I**) are as described above in the first set of variables of Structural Formula (**I**).

[0081] A sixth set of variables of Structural Formula (**III**) is as follows:

R^6 is C_{5-6} cycloalkyl.

Values, including specific values, of the remaining variables of Structural Formula (**III**) are independently as described in the second, third or fourth set of variables of Structural Formula (**III**).

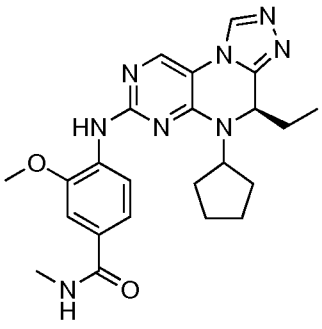
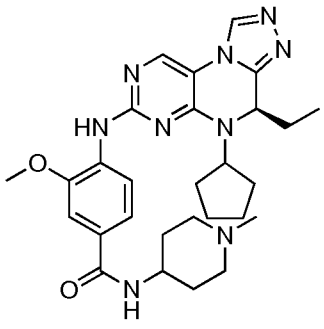
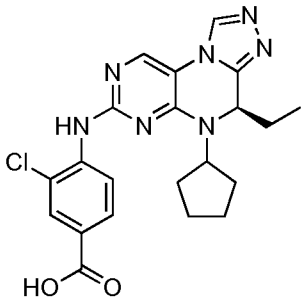
[0082] A seventh set of variables of Structural Formula (**III**) is as follows:

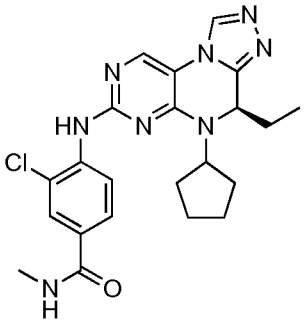
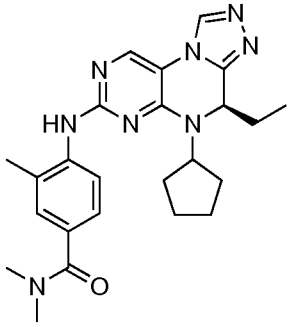
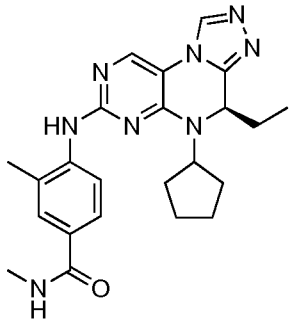
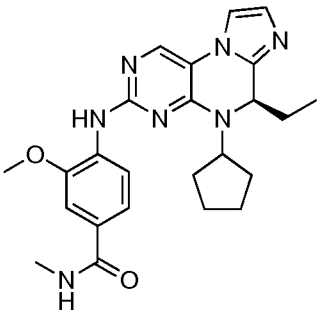
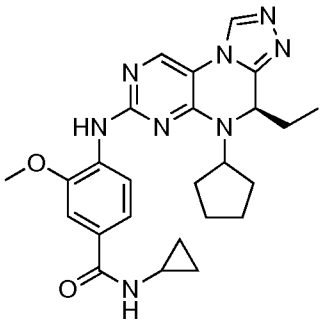
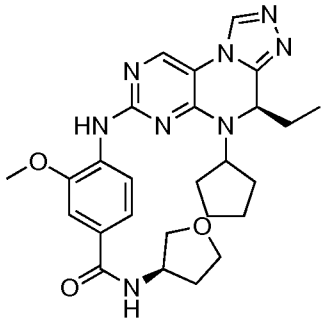
R^2 is –H or C_{1-3} alkyl, and R^3 is C_{1-3} alkyl; or R^2 and R^3 together with the atom to which they are bound form a C_{3-6} cycloalkyl ring.

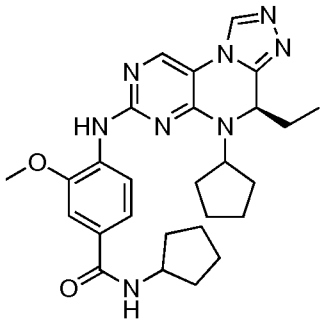
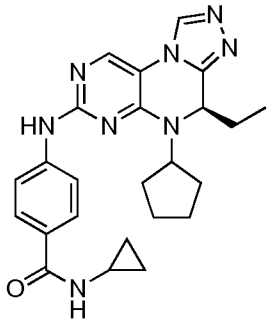
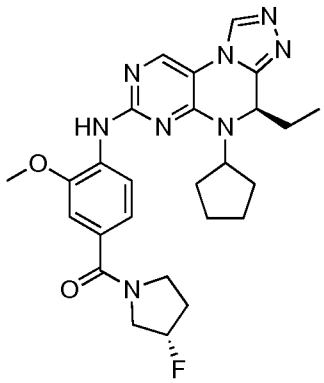
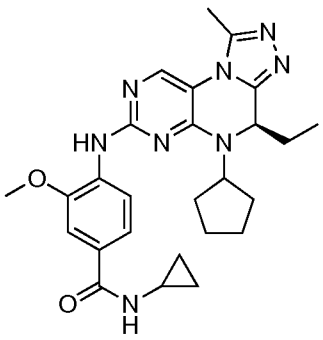
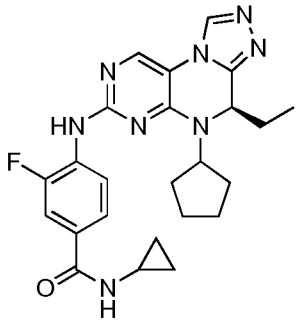
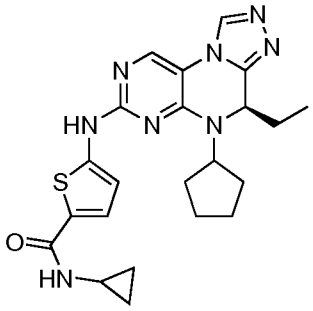
R^6 is C_{5-6} cycloalkyl.

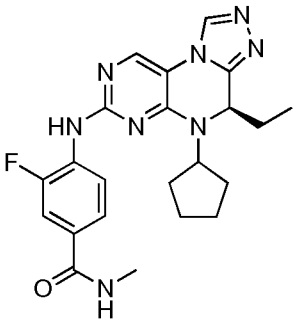
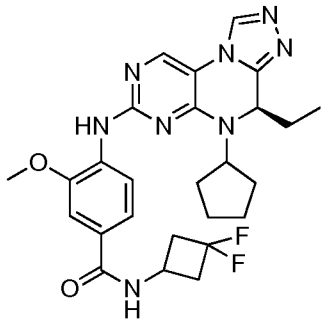
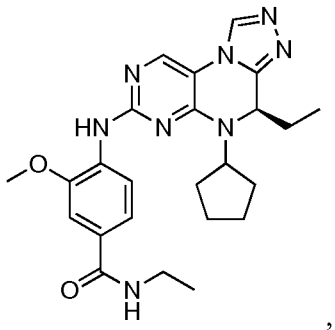
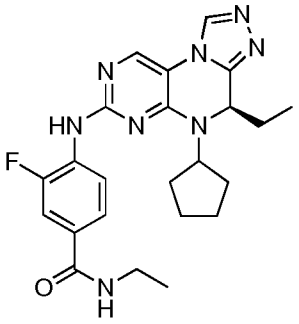
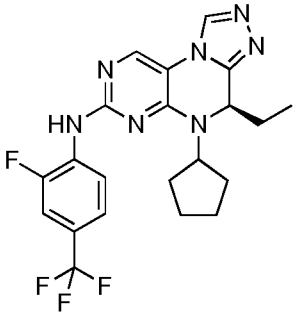
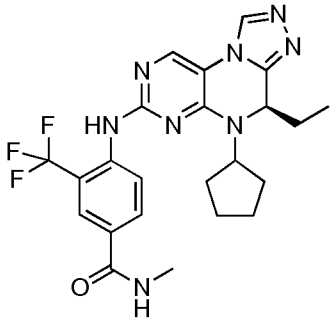
Values, including specific values, of the remaining variables of Structural Formula (**III**) are independently as described in the second, third or fourth set of variables of Structural Formula (**III**).

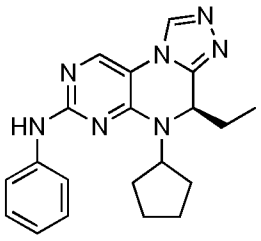
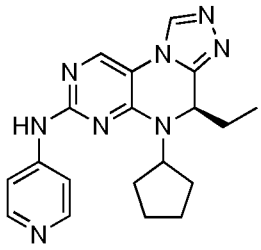
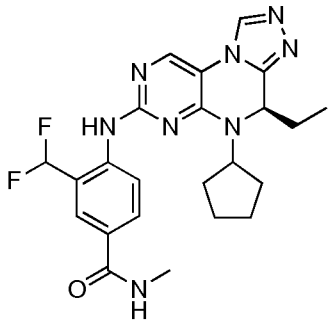
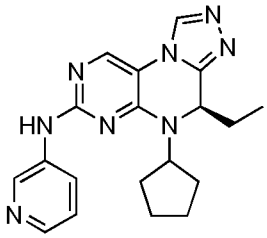
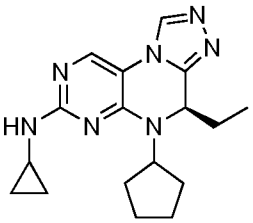
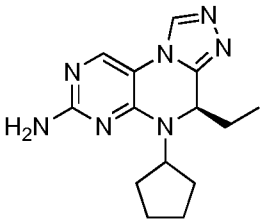
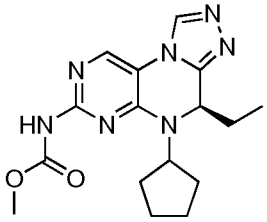
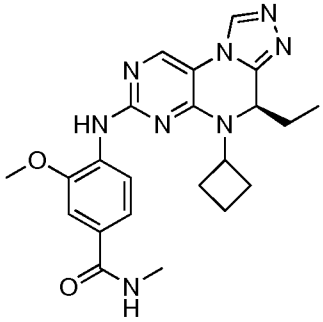
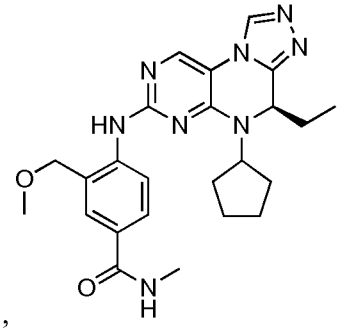
[0083] In yet another embodiment, the methods of the invention can be employed in preparing the compounds represented by any one of the following structural formulae, or pharmaceutically acceptable salts thereof:

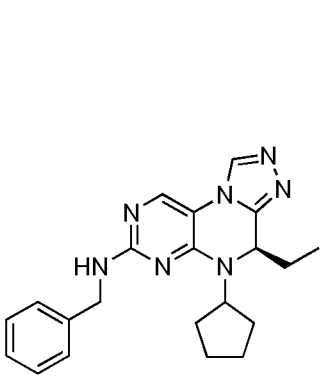
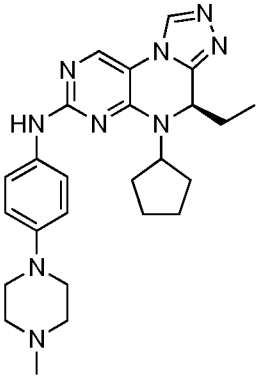
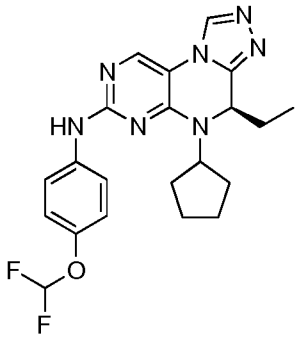
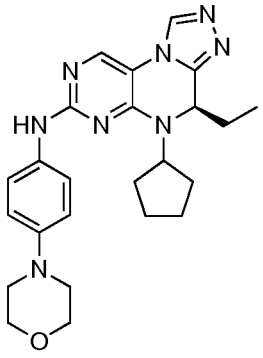
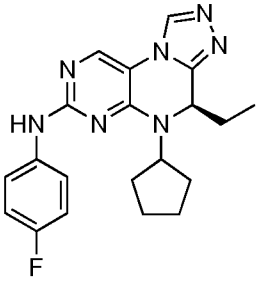
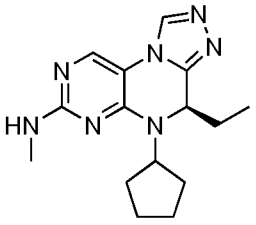
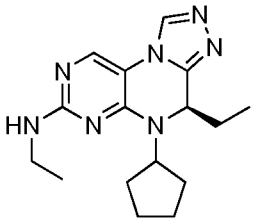
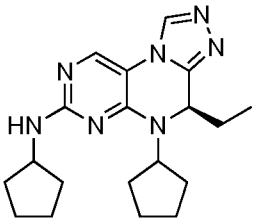
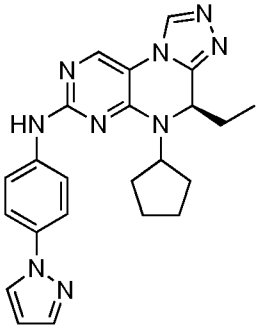
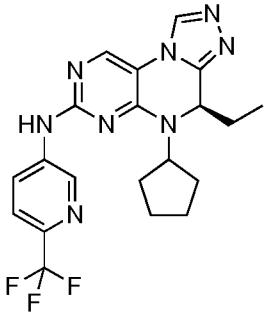
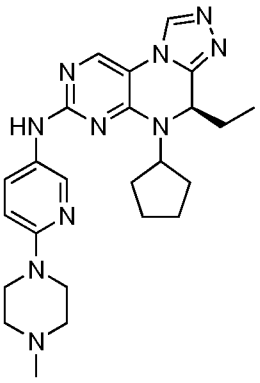
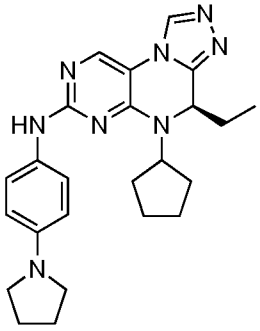

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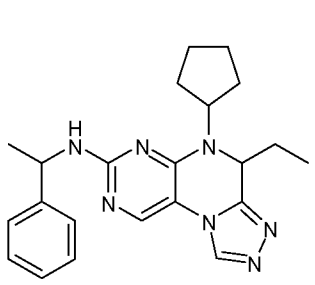
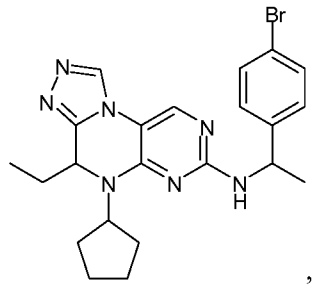
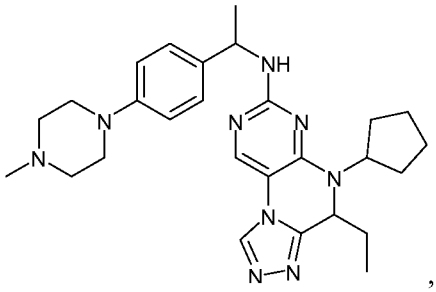
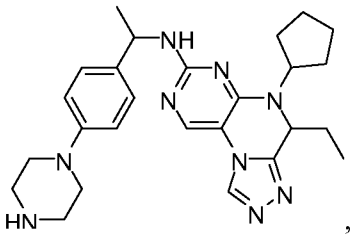
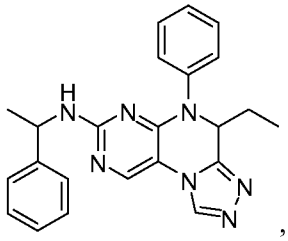
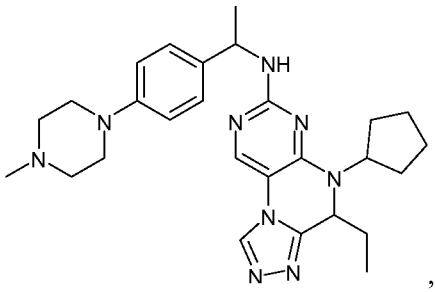
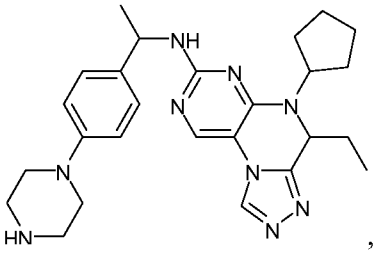
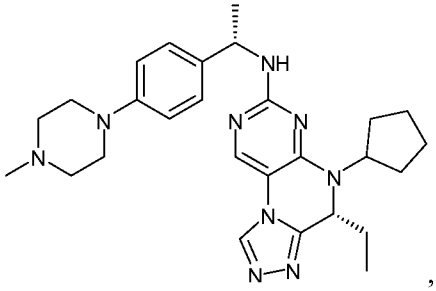

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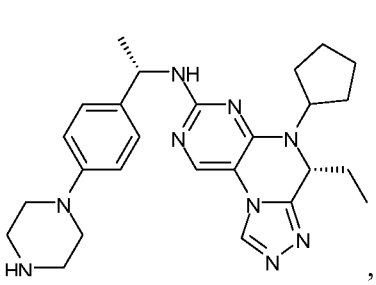
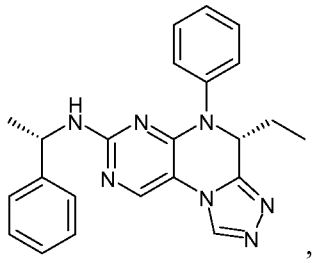
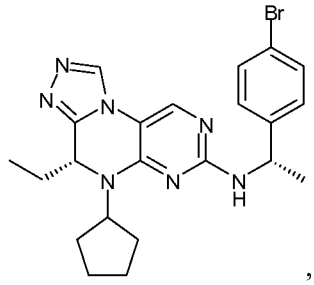
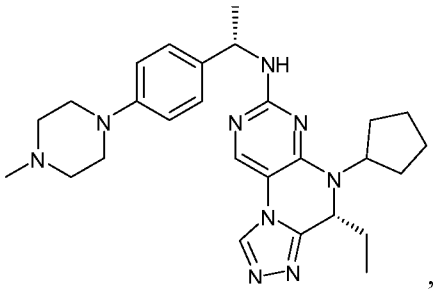
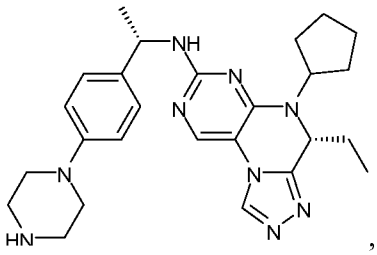
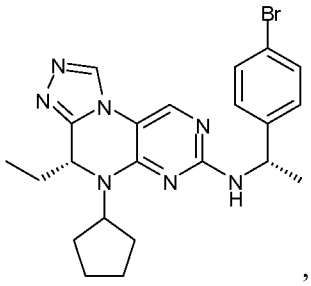
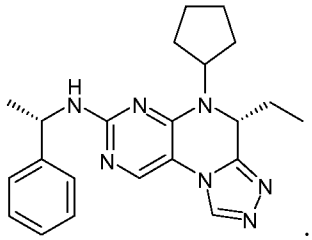

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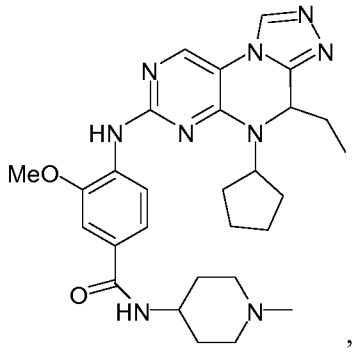
[0084] In yet another embodiment, the methods of the invention can be employed

in preparing the compounds represented by any one of the following structural formulae, or pharmaceutically acceptable salts thereof:


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[0085] In yet another embodiment, the methods of the invention can be employed in preparing the compound represented by the following structural formula:

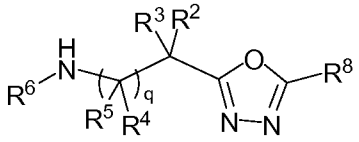

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or a pharmaceutically acceptable salt thereof.

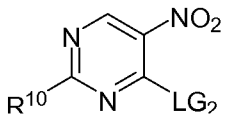
[0086] Additional examples of compounds that can be prepared by the methods of the invention can be found in, for example, US 2009/0062292.

[0087] In some embodiments, the methods of the invention further comprise the

step of reacting a compound of Structural Formula (**D**):

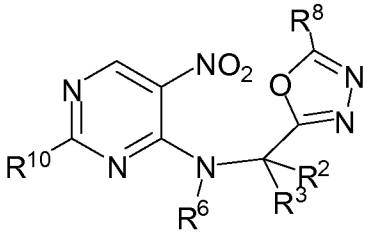


(**D**) with a compound of Structural Formula (**E**):



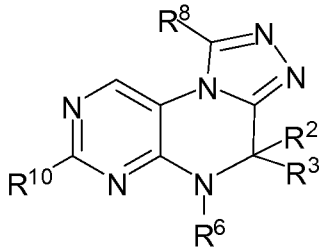
under suitable conditions to form the compound represented by Structural Formula (**A**). Details of this formation of a compound of Structural Formula (**A**) are as described above.

[0088] In some embodiments, the compounds prepared by a method of the invention are represented by Structural Formula (**II**), or pharmaceutically acceptable salts thereof, wherein values of the variables of Structural Formula (**II**) are independently as described above in the first, second, or third set of varaibles of Structural Formula (**II**). In these embodiments, the method comprises: a) cyclizing a compound represented by StructuralFormula (**A1**):



(**A1**)

under suitable reductive cyclisation conditions to form a compound represented by Structural Formula (**B1**):



(**B1**) ,

wherein: R^{10} is LG_1 or $-NR^1R^7$; and LG_1 is a suitable leaving group; and b) optionally, when R^{10} of Structural Formula (**B1**) is LG_1, further comprising the step of replacing $-LG_1$ of Structural Formula (**B1**) with $-NR^1R^7$ under suitable conditions to form the compound represented by Structural Formula (**I**). In one specific aspect of these embodiments, R^{10} of Structural Formula (**A1**) is $-LG_1$, and the method

comprises comprises the step of replacing $-LG_1$ of Structural Formula (**A1**) with $-NR^1R^7$ prior to the cyclisation step a) by reacting the compound represented by Structural Formula (**A1**) with HNR^1R^7 under suitable conditions to form the compound represented by Structural Formula (**A1**) having $-NR^1R^7$ for R^{10}. The compound represented by Structural Formula (**A1**) having $-NR^1R^7$ for R^{10} then undergoes the reductive cyclisation step a) to form a compound represented by Structural Formula (**B**) wherein R^{10} is $-NR^1R^7$, i.e., a compound represented by Structural Formula (**II**).

[0089] It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds described above may involve, at various stages, the addition and removal of one or more protecting groups. The protection and deprotection of functional groups is described in "Protective Groups in Organic Chemistry." edited by J. W. F. McOmie, Plenum Press (1973) and "Protective Groups in Organic Synthesis," 3rd edition, T. W. Greene and P. G. M. Wuts, Wiley Interscience, and "Protecting Groups," 3rd edition, P. J. Kocienski, Thieme (2005)

[0090] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausolito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0091] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as illustrated generally below, or as exemplified by particular classes, subclasses, and species of the compounds described above. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than

one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. When the term "optionally substituted" precedes a list, said term refers to all of the subsequent substitutable groups in that list. If a substituent radical or structure is not identified or defined as "optionally substituted", the substituent radical or structure is unsubstituted. For example, if X is optionally substituted C_1-C_3alkyl or phenyl; X may be either optionally substituted C_1-C_3 alkyl or optionally substituted phenyl. Likewise, if the term "optionally substituted" follows a list, said term also refers to all of the substitutable groups in the prior list unless otherwise indicated. For example: if X is C_1-C_3alkyl or phenyl wherein X is optionally and independently substituted by J^X, then both C_1-C_3alkyl and phenyl may be optionally substituted by J^X. As is apparent to one having ordinary skill in the art, groups such as H, halogen, NO_2, CN, NH_2, OH, or OCF_3 would not be substitutable groups.

[0092] The phrase "up to", as used herein, refers to zero or any integer number that is equal or less than the number following the phrase. For example, "up to 3" means any one of 0, 1, 2, and 3. As described herein, a specified number range of atoms includes any integer therein. For example, a group having from 1-4 atoms could have 1, 2, 3, or 4 atoms.

[0093] Selection of substituents and combinations of substituents envisioned by this invention are those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, specifically, their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week. Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

[0094] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched), or branched, hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation but is non-aromatic. Unless otherwise specified, aliphatic groups contain 1-10 aliphatic carbon atoms. In some

embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. Aliphatic groups may be linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. Specific examples include, but are not limited to, methyl, ethyl, isopropyl, n-propyl, sec-butyl, vinyl, n-butenyl, ethynyl, and tert-butyl and acetylene.

[0095] The term "alkyl" as used herein means a saturated straight or branched chain hydrocarbon. The term "alkenyl" as used herein means a straight or branched chain hydrocarbon comprising one or more double bonds. The term "alkynyl" as used herein means a straight or branched chain hydrocarbon comprising one or more triple bonds. Each of the "alkyl", "alkenyl" or "alkynyl" as used herein can be optionally substituted as set forth below. In some embodiments, the "alkyl" is C_1-C_6 alkyl or C_1-C_4 alkyl. In some embodiments, the "alkenyl" is C_2-C_6 alkenyl or C_2-C_4 alkenyl. In some embodiments, the "alkynyl" is C_2-C_6 alkynyl or C_2-C_4 alkynyl.

[0096] The term "cycloaliphatic" (or "carbocycle" or "carbocyclyl" or "carbocyclic") refers to a non-aromatic carbon only containing ring system which can be saturated or contains one or more units of unsaturation, having three to fourteen ring carbon atoms. In some embodiments, the number of carbon atoms is 3 to 10. In other embodiments, the number of carbon atoms is 4 to 7. In yet other embodiments, the number of carbon atoms is 5 or 6. The term includes monocyclic, bicyclic or polycyclic, fused, spiro or bridged carbocyclic ring systems. The term also includes polycyclic ring systems in which the carbocyclic ring can be "fused" to one or more non-aromatic carbocyclic or heterocyclic rings or one or more aromatic rings or combination thereof, wherein the radical or point of attachment is on the carbocyclic ring. "Fused" bicyclic ring systems comprise two rings which share two adjoining ring atoms. Bridged bicyclic group comprise two rings which share three or four adjacent ring atoms. Spiro bicyclic ring systems share one ring atom. Examples of cycloaliphatic groups include, but are not limited to, cycloalkyl and cycloalkenyl groups. Specific examples include, but are not limited to, cyclohexyl, cyclopropenyl, and cyclobutyl.

[0097] The term "heterocycle" (or "heterocyclyl," or "heterocyclic" or "non-aromatic heterocycle") as used herein refers to a non-aromatic ring system which can be saturated or contain one or more units of unsaturation, having three to fourteen ring atoms in which one or more ring carbons is replaced by a heteroatom such as, N, S, or O and each ring in the system contains 3 to 7 members. In some embodiments, non-aromatic heterocyclic rings comprise up to three heteroatoms selected from N, S and

O within the ring. In other embodiments, non-aromatic heterocyclic rings comprise up to two heteroatoms selected from N, S and O within the ring system. In yet other embodiments, non-aromatic heterocyclic rings comprise up to two heteroatoms selected from N and O within the ring system. The term includes monocyclic, bicyclic or polycyclic fused, spiro or bridged heterocyclic ring systems. The term also includes polycyclic ring systems in which the heterocyclic ring can be fused to one or more non-aromatic carbocyclic or heterocyclic rings or one or more aromatic rings or combination thereof, wherein the radical or point of attachment is on the heterocyclic ring. Examples of heterocycles include, but are not limited to, piperidinyl, piperizinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, azepanyl, diazepanyl, triazepanyl, azocanyl, diazocanyl, triazocanyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, oxazocanyl, oxazepanyl, thiazepanyl, thiazocanyl, benzimidazolonyl, tetrahydrofuranyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiophenyl, morpholino, including, for example, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3-thiazolidinyl, 4-thiazolidinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolanyl, benzodithianyl, 3-(1-alkyl)-benzimidazol-2-onyl, and 1,3-dihydro-imidazol-2-onyl.

[0098] The term “aryl” (or “aryl ring” or “aryl group”) used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, “aryloxyalkyl”, or “heteroaryl” refers to carbocyclic aromatic ring systems. The term “aryl” may be used interchangeably with the terms “aryl ring” or “aryl group”. “Carbocyclic aromatic ring” groups have only carbon ring atoms (typically six to fourteen) and include monocyclic aromatic rings such as phenyl and fused polycyclic aromatic ring systems in which two or more carbocyclic aromatic rings are fused to one another. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term “carbocyclic aromatic ring” or “carbocyclic aromatic”, as it is used herein, is a group in which an aromatic ring is “fused” to one or more non-aromatic rings (carbocyclic or heterocyclic), such as in an indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

[0099] The terms "heteroaryl", "heteroaromatic", "heteroaryl ring", "heteroaryl group", "aromatic heterocycle" or "heteroaromatic group", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refer to heteroaromatic ring groups having five to fourteen members, in which one or more ring carbons is replaced by a heteroatom such as, N, S, or O. In some embodiments, heteroaryl rings comprise up to three heteroatoms selected from N, S and O within the ring. In other embodiments, heteroaryl rings comprise up to two heteroatoms selected from N, S and O within the ring system. In yet other embodiments, heteroaryl rings comprise up to two heteroatoms selected from N and O within the ring system. Heteroaryl rings include monocyclic heteroaromatic rings and polycyclic aromatic rings in which a monocyclic aromatic ring is fused to one or more other aromatic rings. Also included within the scope of the term "heteroaryl", as it is used herein, is a group in which an aromatic ring is "fused" to one or more non-aromatic rings (carbocyclic or heterocyclic), where the radical or point of attachment is on the aromatic ring. Bicyclic 6,5 heteroaromatic ring, as used herein, for example, is a six membered heteroaromatic ring fused to a second five membered ring, wherein the radical or point of attachment is on the six membered ring. Examples of heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl or thiadiazolyl including, for example, 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-pyrazolyl, 4-pyrazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-triazolyl, 5-triazolyl, tetrazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, benzisoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, purinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

[00100] As used herein, "cyclo", "cyclic", "cyclic group" or "cyclic moiety", include mono-, bi-, and tri-cyclic ring systems including cycloaliphatic, heterocycloaliphatic, aryl, or heteroaryl, each of which has been previously defined.

[00101] As used herein, a "bicyclic ring system" includes 8-12 (e.g., 9, 10, or 11)

membered structures that form two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common). Bicyclic ring systems include bicycloaliphatics (e.g., bicycloalkyl or bicycloalkenyl), bicycloheteroaliphatics, bicyclic aryls, and bicyclic heteroaryls.

[00102] As used herein, a "bridged bicyclic ring system" refers to a bicyclic heterocycloalipahtic ring system or bicyclic cycloaliphatic ring system in which the rings are bridged. Examples of bridged bicyclic ring systems include, but are not limited to, adamantanyl, norbornanyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, bicyclo[3.2.3]nonyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.03,7]nonyl. A bridged bicyclic ring system can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkylalkyl)carbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkylalkyl)carbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, alkylsulfanyl, sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[00103] As used herein, "bridge" refers to a bond or an atom or an unbranched chain of atoms connecting two different parts of a molecule. The two atoms that are connected through the bridge (usually but not always, two tertiary carbon atoms) are denotated as "bridgeheads".

[00104] As used herein, the term "spiro" refers to ring systems having one atom (usually a quaternary carbon) as the only common atom between two rings.

[00105] The term "ring atom" is an atom such as C, N, O or S that is in the ring of an aromatic group, cycloalkyl group or non-aromatic heterocyclic ring.

[00106] A "substitutable ring atom" in an aromatic group is a ring carbon or nitrogen atom bonded to a hydrogen atom. The hydrogen can be optionally replaced with a suitable substituent group. Thus, the term "substitutable ring atom" does not include ring nitrogen or carbon atoms which are shared when two rings are fused. In addition, "substitutable ring atom" does not include ring carbon or nitrogen atoms

when the structure depicts that they are already attached to a moiety other than hydrogen.

[00107] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[00108] As used herein an optionally substituted aralkyl can be substituted on both the alkyl and the aryl portion. Unless otherwise indicated as used herein optionally substituted aralkyl is optionally substituted on the aryl portion.

[00109] In some embodiments, an aliphatic group and a heterocyclic ring may independently contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring are selected from those described above, for example, in the definition of J^A and J^B. Other suitable substitutents include those listed as suitable for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2$(alkyl), $=NNHSO_2$(alkyl), or $=NR^*$, wherein each R^* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic. Optional substituents on the aliphatic group of R^* are selected from NH_2, $NH(C_{1-4}$ aliphatic), $N(C_{1-4}$ aliphatic$)_2$, halogen, C_{1-4} aliphatic, OH, $O(C_{1-4}$ aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$ aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R^* is unsubstituted.

[00110] In some embodiments, optional substituents on the nitrogen of a heterocyclic ring include those described above. Examples of such suitable substituents include -OH, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)_2$, $-CO(C_1$-C_4 alkyl), $-CO_2H$, $-CO_2(C_1$-C_4 alkyl), $-O(C_1$-C_4 alkyl), and C_1-C_4 aliphatic that is optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)_2$, $-OCO(C_1$-C_4 alkyl), $-CO(C_1$-C_4 alkyl), $-CO_2H$, $-CO_2(C_1$-C_4 alkyl), $-O(C_1$-C_4 alkyl), C_{3-7} cycloalkyl, and C_{3-7} cyclo(haloalkyl). Other suitable substituents include $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted $-CH_2$(Ph), optionally substituted $-(CH_2)_2$(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered

heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, two independent occurrences of R^+, on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or a 3-8-membered cycloalkyl ring, wherein said heteroaryl or heterocyclyl ring has 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from NH_2, $NH(C_{1-4}$ aliphatic), $N(C_{1-4}$ aliphatic$)_2$, halogen, C_{1-4} aliphatic, OH, $O(C_{1-4}$ aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$ aliphatic), O(halo C_{1-4} aliphatic), or halo(C_{1-4} aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R^+ is unsubstituted.

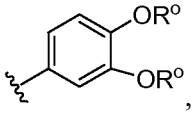
[00111] In some embodiments, an aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are selected from those described above. Specific examples include halogen, -CN, -OH, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)_2$, $-OCO(C_1$-C_4 alkyl), $-CO(C_1$-C_4 alkyl), $-CO_2H$, $-CO_2(C_1$-C_4 alkyl), $-O(C_1$-C_4 alkyl), and C_1-C_4 aliphatic that is optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl$)_2$, $-OCO(C_1$-C_4 alkyl), $-CO(C_1$-C_4 alkyl), $-CO_2H$, $-CO_2(C_1$-C_4 alkyl), $-O(C_1$-C_4 alkyl), C_{3-7} cycloalkyl, and C_{3-7} cyclo(haloalkyl). Other suitable substituents include: halogen; -R°; -OR°; -SR°; 1,2-methylenedioxy; 1,2-ethylenedioxy; phenyl (Ph) optionally substituted with R°; -O(Ph) optionally substituted with R°; $-(CH_2)_{1-2}$(Ph), optionally substituted with R°; -CH=CH(Ph), optionally substituted with R°; $-NO_2$; -CN; $-N(R°)_2$; -NR°C(O)R°; -NR°C(S)R°; -NR°C(O)N(R°)$_2$; -NR°C(S)N(R°)$_2$; -NR°CO_2R°; -NR°NR°C(O)R°; -NR°NR°C(O)N(R°)$_2$; -NR°NR°CO_2R°; -C(O)C(O)R°; -C(O)CH_2C(O)R°; -CO_2R°; -C(O)R°; -C(S)R°; -C(O)N(R°)$_2$; -C(S)N(R°)$_2$; -OC(O)N(R°)$_2$; -OC(O)R°; -C(O)N(OR°) R°; -C(NOR°) R°; -$S(O)_2$R°; -$S(O)_3$R°; -$SO_2N(R°)_2$; -S(O)R°; -NR°$SO_2N(R°)_2$; -NR°SO_2R°; -N(OR°)R°; -C(=NH)-N(R°)$_2$; or $-(CH_2)_{0-2}$NHC(O)R°; wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or $-CH_2$(Ph), or, two independent occurrences of R°, on the same substituent or different substituents, taken together with the atom(s) to which each R° group is bound, form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or

a 3-8-membered cycloalkyl ring, wherein said heteroaryl or heterocyclyl ring has 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group of R° are selected from NH_2, $NH(C_{1-4}$aliphatic), $N(C_{1-4}$aliphatic$)_2$, halogen, C_{1-4}aliphatic, OH, $O(C_{1-4}$aliphatic), NO_2, CN, CO_2H, $CO_2(C_{1-4}$aliphatic), $O(haloC_{1-4}$ aliphatic), or $haloC_{1-4}$aliphatic, CHO, $N(CO)(C_{1-4}$ aliphatic), $C(O)N(C_{1-4}$ aliphatic), wherein each of the foregoing C_{1-4}aliphatic groups of R° is unsubstituted.

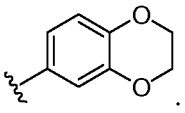
[00112] Non-aromatic nitrogen containing heterocyclic rings that are substituted on a ring nitrogen and attached to the remainder of the molecule at a ring carbon atom are said to be N substituted. For example, an N alkyl piperidinyl group is attached to the remainder of the molecule at the two, three or four position of the piperidinyl ring and substituted at the ring nitrogen with an alkyl group. Non-aromatic nitrogen containing heterocyclic rings such as pyrazinyl that are substituted on a ring nitrogen and attached to the remainder of the molecule at a second ring nitrogen atom are said to be N' substituted-N-heterocycles. For example, an N' acyl N-pyrazinyl group is attached to the remainder of the molecule at one ring nitrogen atom and substituted at the second ring nitrogen atom with an acyl group.

[00113] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[00114] As detailed above, in some embodiments, two independent occurrences of R^o (or R^+, or any other variable similarly defined herein), may be taken together with the atom(s) to which each variable is bound to form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or a 3-8-membered cycloalkyl ring. Exemplary rings that are formed when two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^o)_2$, where both occurrences of R^o are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example

where a phenyl group is substituted with two occurrences of OR^o 

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these two occurrences of R^o are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring: . It will be appreciated that a variety of other rings can be formed when two independent occurrences of R^o (or R^+, or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[00115] As used herein, an "amino" group refers to $-NH_2$.

[00116] The term "hydroxyl"or "hydroxy" or "alcohol moiety" refers to –OH.

[00117] As used herein, an "oxo" refers to =O.

[00118] As used herein, the term "alkoxy", or "alkylthio", as used herein, refers to an alkyl group, as previously defined, attached to the molecule through an oxygen ("alkoxy" e.g., –O–alkyl) or sulfur ("alkylthio" e.g., –S-alkyl) atom.

[00119] As used herein, the terms "halogen", "halo", and "hal" mean F, Cl, Br, or I.

[00120] As used herein, the term "cyano" or "nitrile" refer to –CN or –C≡N.

[00121] The terms "alkoxyalkyl", "alkoxyalkenyl", "alkoxyaliphatic", and "alkoxyalkoxy" mean alkyl, alkenyl, aliphatic or alkoxy, as the case may be, substituted with one or more alkoxy groups.

[00122] The terms "haloalkyl", "haloalkenyl", "haloaliphatic", and "haloalkoxy" mean alkyl, alkenyl, aliphatic or alkoxy, as the case may be, substituted with one or more halogen atoms. This term includes perfluorinated alkyl groups, such as $-CF_3$ and $-CF_2CF_3$.

[00123] The terms "cyanoalkyl", "cyanoalkenyl", "cyanoaliphatic", and "cyanoalkoxy" mean alkyl, alkenyl, aliphatic or alkoxy, as the case may be, substituted with one or more cyano groups. In some embodiments, the cyanoalkyl is (NC)-alkyl-.

[00124] The terms "aminoalkyl", "aminoalkenyl", "aminoaliphatic", and "aminoalkoxy" mean alkyl, alkenyl, aliphatic or alkoxy, as the case may be, substituted with one or more amino groups, wherein the amino group is as defined above.

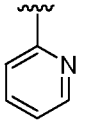
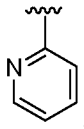
[00125] The terms "hydroxyalkyl", "hydroxyaliphatic", and "hydroxyalkoxy" mean alkyl, aliphatic or alkoxy, as the case may be, substituted with one or more –OH groups.

[00126] The terms "alkoxyalkyl", "alkoxyaliphatic", and "alkoxyalkoxy" mean alkyl, aliphatic or alkoxy, as the case may be, substituted with one or more alkoxy groups. For example, an "alkoxyalkyl" refers to an alkyl group such as (alkyl-O)-alkyl-, wherein alkyl has been defined above.

[00127] The term "protecting group" and "protective group" as used herein, are interchangeable and refer to an agent used to temporarily block one or more desired functional groups in a compound with multiple reactive sites. In certain embodiments, a protecting group has one or more, or specifically all, of the following characteristics: a) is added selectively to a functional group in good yield to give a protected substrate that is b) stable to reactions occurring at one or more of the other reactive sites; and c) is selectively removable in good yield by reagents that do not attack the regenerated, deprotected functional group. As would be understood by one skilled in the art, in some cases, the reagents do not attack other reactive groups in the compound. In other cases, the reagents may also react with other reactive groups in the compound. Examples of protecting groups are detailed in Greene, T. W., Wuts, P. G in "Protective Groups in Organic Synthesis", Third Edition, John Wiley & Sons, New York: 1999 (and other editions of the book), the entire contents of which are hereby incorporated by reference. The term "nitrogen protecting group", as used herein, refers to an agent used to temporarily block one or more desired nitrogen reactive sites in a multifunctional compound. Preferred nitrogen protecting groups also possess the characteristics exemplified for a protecting group above, and certain exemplary nitrogen protecting groups are also detailed in Chapter 7 in Greene, T.W., Wuts, P. G in "Protective Groups in Organic Synthesis", Third Edition, John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference.

[00128] As used herein, the term "displaceable moiety" or "leaving group" refers to a group that is associated with an aliphatic or aromatic group as defined herein and is subject to being displaced by nucleophilic attack by a nucleophile.

[00129] Unless otherwise indicated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, cis-trans, conformational, and rotational) forms of the structure. For example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers are included in this invention, unless only one of the isomers is drawn specifically. As would be understood to one skilled in the art, a substituent can freely

rotate around any rotatable bonds. For example, a substituent drawn as  also represents .

[00130] Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, cis/trans, conformational, and rotational mixtures of the present compounds are within the scope of the invention.

[00131] Unless otherwise indicated, all tautomeric forms of the compounds of the invention are within the scope of the invention.

[00132] Additionally, unless otherwise indicated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays. Such compounds, especially deuterium analogs, can also be therapeutically useful.

[00133] The terms “a bond” and “absent” are used interchangeably to indicate that a group is absent.

[00134] The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound’s identity.

[00135] The compounds described herein can exist in free form, or, where appropriate, as salts. Those salts that are pharmaceutically acceptable are of particular interest since they are useful in administering the compounds described above for medical purposes. Salts that are not pharmaceutically acceptable are useful in manufacturing processes, for isolation and purification purposes, and in some instances, for use in separating stereoisomeric forms of the compounds of the invention or intermediates thereof.

[00136] As used herein, the term "pharmaceutically acceptable salt" refers to salts of a compound, which are, within the scope of sound medical judgment, suitable for use in humans and lower animals without undue side effects, such as, toxicity, irritation, allergic response and the like, and are commensurate with a reasonable

benefit/risk ratio.

[00137] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds described herein include those derived from suitable inorganic and organic acids and bases. These salts can be prepared in situ during the final isolation and purification of the compounds.

[00138] Where the compound described herein contains a basic group, or a sufficiently basic bioisostere, acid addition salts can be prepared by 1) reacting the purified compound in its free-base form with a suitable organic or inorganic acid and 2) isolating the salt thus formed. In practice, acid addition salts might be a more convenient form for use and use of the salt amounts to use of the free basic form.

[00139] Examples of pharmaceutically acceptable, non-toxic 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, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, glycolate, gluconate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[00140] Where the compound described herein contains a carboxy group or a sufficiently acidic bioisostere, base addition salts can be prepared by 1) reacting the purified compound in its acid form with a suitable organic or inorganic base and 2) isolating the salt thus formed. In practice, use of the base addition salt might be more convenient and use of the salt form inherently amounts to use of the free acid form. Salts derived from appropriate bases include alkali metal (e.g., sodium, lithium, and potassium), alkaline earth metal (e.g., magnesium and calcium), ammonium and

$N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[00141] Basic addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminium. The sodium and potassium salts are usually preferred. 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. Suitable inorganic base addition salts are prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide and the like. Suitable amine base addition salts are prepared from amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use. Ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N, N'-dibenzylethylenediamine, chloroprocaine, dietanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, dicyclohexylamine and the like.

[00142] Other acids and bases, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds described herein and their pharmaceutically acceptable acid or base addition salts.

[00143] It should be understood that this invention includes mixtures/combinations of different pharmaceutically acceptable salts and also mixtures/combinations of compounds in free form and pharmaceutically acceptable salts.

[00144] In addition to the compounds described herein, the methods of the invention can be employed for preparing pharmaceutically acceptable solvates (e.g., hydrates) and clathrates of these compounds.

[00145] As used herein, the term "pharmaceutically acceptable solvate," is a solvate formed from the association of one or more pharmaceutically acceptable solvent molecules to one of the compounds described herein. The term solvate includes hydrates (e.g., hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate,

and the like).

[00146] As used herein, the term "hydrate" means a compound described herein or a salt thereof that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

[00147] As used herein, he term "clathrate" means a compound described herein or a salt thereof in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a solvent or water) trapped within.

[00148] In addition to the compounds described herein, the methods of the invention can be employed for preparing pharmaceutically acceptable derivatives or prodrugs of these compounds.

[00149] A "pharmaceutically acceptable derivative or prodrug" includes any pharmaceutically acceptable ester, salt of an ester, or other derivative or salt thereof, of a compound described herein, which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound described herein or an inhibitorily active metabolite or residue thereof. Particularly favoured derivatives or prodrugs are those that increase the bioavailability of the compounds when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

[00150] As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide a compound described herein. Prodrugs may become active upon such reaction under biological conditions, or they may have activity in their unreacted forms. Examples of prodrugs contemplated in this invention include, but are not limited to, analogs or derivatives of compounds of the invention that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of compounds described herein that comprise -NO, -NO_2, -ONO, or -ONO_2 moieties. Prodrugs can typically be prepared using well-known methods, such as those described by BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed).

[00151] A "pharmaceutically acceptable derivative" is an adduct or derivative which, upon administration to a patient in need, is capable of providing, directly or

indirectly, a compound as otherwise described herein, or a metabolite or residue thereof. Examples of pharmaceutically acceptable derivatives include, but are not limited to, esters and salts of such esters.

[00152] Pharmaceutically acceptable prodrugs of the compounds described above include, without limitation, esters, amino acid esters, phosphate esters, metal salts and sulfonate esters.

[00153] The compounds described above are useful as protein kinase inhibitors, such as Plk (Plk1, Plk2, Plk3, and/or Plk4) inhibitors. Thus, these compounds can inhibit the activity of such protein kinase(s) in a patient. Generally, inhibiting such protein kinase activity can treat or prevent a condition selected from autoimmune diseases, inflammatory diseases, proliferative and hyperproliferative diseases, immunologically-mediated diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cardiovascular diseases, hormone related diseases, allergies, asthma, and Alzheimer's disease.

[00154] Particularly, the compounds described above are useful for the treatment of diseases, disorders, and conditions characterized by excessive or abonormal cell proliferation. Such diseases include a proliferative or hyperproliferative disease, and a neurodegenerative disease. Examples of proliferative and hyperproliferative diseases include, without limitation, cancer.

[00155] The term "cancer" includes, but is not limited to, the following cancers: breast; ovary; cervix; prostate; testis, genitourinary tract; esophagus; larynx, glioblastoma; neuroblastoma; stomach; skin, keratoacanthoma; lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma; bone; colon; colorectal; adenoma; pancreas, adenocarcinoma; thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma; seminoma; melanoma; sarcoma; bladder carcinoma; liver carcinoma and biliary passages; kidney carcinoma; myeloid disorders; lymphoid disorders, Hodgkin's, hairy cells; buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx; small intestine; colon-rectum, large intestine, rectum; brain and central nervous system; chronic myeloid leukemia (CML), and leukemia. The term "cancer" includes, but is not limited to, the following cancers: myeloma, lymphoma, or a cancer selected from gastric, renal, or and the following cancers: head and neck, oropharangeal, non-small cell lung cancer (NSCLC), endometrial, hepatocarcinoma, Non-Hodgkins lymphoma, and pulmonary.

[00156] The term "cancer" also includes, but is not limited to, the following cancers: epidermoid Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac:

sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum, Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes

(carcinoma), breast; Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma] hairy cell; lymphoid disorders; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma; medullary thyroid carcinoma, undifferentiated thyroid cancer, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[00157] More particularly, the compounds described above are useful for treating cancer, such as colorectal, thyroid, breast, and lung cancer; and myeloproliferative disorders, such as polycythemia vera, thrombocythemia, myeloid metaplasia with myelofibrosis, chronic myelogenous leukemia, chronic myelomonocytic leukemia, hypereosinophilic syndrome, juvenile myelomonocytic leukemia, and systemic mast cell disease. Specific examples of diseases and conditions where the compounds described herein and their compositions are useful include hematopoietic disorders, in particular, acute-myelogenous leukemia (AML), chronic-myelogenous leukemia (CML), acute-promyelocytic leukemia (APL), and acute lymphocytic leukemia (ALL). Examples of neurodegenerative diseases include, without limitation, Alzheimer's disease.

[00158] The compounds described above can be particularly useful for treating a protein-kinase mediated condition, such as a Plk-mediated disease. The term "protein kinase-mediated condition," as used herein, means any disease or other deleterious condition in which a protein kinase plays a role. Such conditions include, without limitation, autoimmune diseases, inflammatory diseases, proliferative and hyperproliferative diseases, immunologically-mediated diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cardiovascular diseases, hormone related diseases, allergies, asthma, and Alzheimer's disease. The term "Plk-mediated condition", as used herein means any disease or other deleterious condition in which Plk plays a role. Such conditions include, without limitation, a proliferative or hyperproliferative disease, or a neurodegenerative disease.

[00159] As used herein, a "patient" means an animal, preferably a human.

[00160] An "effective amount" of a compound for treating or preventing a protein kinase-mediated disease/condition (e.g., a Plk-mediated disease/condition) is the amount effective in order to treat said disease/condition. The compounds described above may be administered using any amount and any route of administration effective for treating or lessening the severity of said disease. For example, the compounds can be administered in a dosage of between 0.01 - 100 mg/kg body weight/day.

[00161] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of the compound will also depend upon the particular compound in the composition.

[00162] Depending upon the particular protein kinase-mediated conditions to be treated or prevented, additional drugs, which are normally administered to treat or prevent that condition, may be administered together with the protease inhibitors described herein. For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the protein kinase inhibitors of this invention to treat proliferative diseases.

[00163] Those additional agents may be administered separately, as part of a multiple dosage regimen, from the protein kinase inhibitor-containing compound or composition. Alternatively, those agents may be part of a single dosage form, mixed together with the protein kinase inhibitor in a single composition.

[00164] Examples of known chemotherapeutic agents include, but are not limited to, Gleevec™, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives. Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and

immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[00165] As inhibitors of protein kinases, the compounds described above are also useful in biological samples. For example, the compounds are useful in inhibiting protein kinase activity in a biological sample. The term "biological sample", as used herein, means an *in vitro* or an *ex vivo* sample, including, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00166] Inhibition of protein kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, and biological specimen storage.

[00167] The compounds described above are also useful the study of protein kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such protein kinases; and the comparative evaluation of new protein kinase inhibitors. Examples of such uses include, but are not limited to, biological assays such as enzyme assays and cell-based assays.

[00168] The activity of the compounds as protein kinase inhibitors may be assayed *in vitro, in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the kinase activity or ATPase activity of the activated kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase and may be measured either by radiolabelling the inhibitor prior to binding, isolating the inhibitor/kinase complex and determining the amount of radiolabel bound, or by running a competition experiment where new inhibitors are incubated with the kinase bound to known radioligands. Protein kinase inhibition assays are

known in the art. For example, detailed conditions for Plk1, Plk2, Plk3, and Plk4 are set forth in US 2008/0167289 and US 2009/0062292.

[00169] In treating or preventing one or more conditions/diseases described above, the compounds described above can be formulated in pharmaceutically acceptable formulations that optionally further comprise a pharmaceutically acceptable carrier, adjuvant or vehicle.

[00170] As described herein, the pharmaceutically acceptable compositions comprise a compound described above in an effective amount, and additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a therapy (e.g., a prophylactic or therapeutic agent). Side effects are always unwanted, but unwanted effects are not necessarily adverse. An adverse effect from a therapy (e.g., prophylactic or therapeutic agent) might be harmful or uncomfortable or risky.

[00171] A pharmaceutically acceptable carrier may contain inert ingredients which do not unduly inhibit the biological activity of the compounds. The pharmaceutically acceptable carriers should be biocompatible, e.g., non-toxic, non-inflammatory, non-immunogenic or devoid of other undesired reactions or side-effects upon the administration to a subject. Standard pharmaceutical formulation techniques can be employed.

[00172] Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (such as human serum albumin), buffer substances (such as twin 80, phosphates, glycine, sorbic acid, or potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes (such

as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, or zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, methylcellulose, hydroxypropyl methylcellulose, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00173] The compounds described above, and pharmaceutically acceptable compositions thereof can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. The term "parenteral" as used herein includes, but is not limited to, subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Specifically, the compositions are administered orally, intraperitoneally or intravenously.

[00174] Any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions, can be used for the oral administration. In the case of tablets for oral use, carriers commonly used include, but are not limited to, lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00175] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions,

syrups and elixirs. In addition to the active compounds (the compounds described above), the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00176] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00177] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as

well as high molecular weight polethylene glycols and the like.

[00178] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00179] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00180] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00181] Sterile injectable forms may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol.

Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00182] In order to prolong the effect of the active compounds administered, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00183] Compositions for rectal or vaginal administration are specifically suppositories which can be prepared by mixing the active compound with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00184] Dosage forms for topical or transdermal administration include ointments,

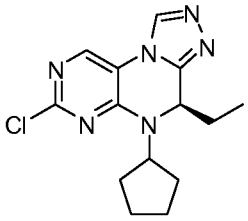
pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body, can also be used. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00185] Alternatively, the compounds described above and pharmaceutically acceptable compositions thereof may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

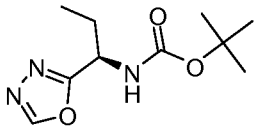
[00186] The compounds described above and pharmaceutically acceptable compositions thereof can be formulated in unit dosage form. The term "unit dosage form" refers to physically discrete units suitable as unitary dosage for subjects undergoing treatment, with each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, optionally in association with a suitable pharmaceutical carrier. The unit dosage form can be for a single daily dose or one of multiple daily doses (e.g., about 1 to 4 or more times per day). When multiple daily doses are used, the unit dosage form can be the same or different for each dose. The amount of the active compound in a unit dosage form will vary depending upon, for example, the host treated, and the particular mode of administration, for example, from 0.01 mg/kg body weight/day to 100 mg/kg body weight/day.

EXEMPLIFICATION

Example 1: Preparation of (R)-7-chloro-5-cyclopentyl-4-ethyl-4,5-dihydro-[1,2,4]triazolo[4,3-f]pteridine:

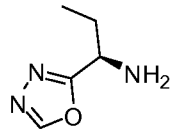


Method A: *tert*-butyl N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]carbamate



[00100] (2R)-2-(tert-butoxycarbonylamino)butanoic acid (5 g, 24.60 mmol) was dissolved in DCM (500 mL) and cooled to 0 °C. CDI (4.188 g, 25.83 mmol) was added and the reaction stirred for 60 minutes. Formic hydrazine (1.477 g, 24.60 mmol) was added and the reaction stirred at 0 °C for 45 minutes then allowed to reach ambient temperature overnight. The reaction was cooled to 0 °C and treated with PS-PPh3 (22.88 g, 49.20 mmol) and CBr4 (16.32 g, 49.20 mmol) The reaction was allowed to warm slowly to ambient temperature over 2 hours, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (25 to 50% EtOAc/Petrol) to give the sub-title compound as a colourless oil(2,30 g, 41%); 1H NMR (400.0 MHz, DMSO) d 0.88 (t, 3H), 1.27 - 1.39 (2 x s, 9H), 1.75-1.87 (m, 2H), 4.71 (dd, 1H), 7.62 (d, 1H), 9.17 (s, 1H) MS ES(+) 228.

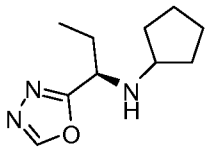
Method B: (1R)-1-(1,3,4-oxadiazol-2-yl)propan-1-amine



[00101] tert-butyl N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]carbamate (2.255 g, 9.923 mmol) was dissolved in DCM (17.76 mL) at 0 °C and TFA (17.76 mL) was added. The reaction was stirred at 0 °C for 4.5 hours then concentrated under high vacuum. The residue was azeotroped with DCM (X2). The resultant oil was dissolved in a mixture of THF (40ml) and DCM (20ml) then treated with MP-carbonate (15 g, 199.9 mmol). The reaction was stirred gently for 1 hour then filtered. The resin was stirred with further portions DCM (2x25ml) and filtered. The combined filtrates were

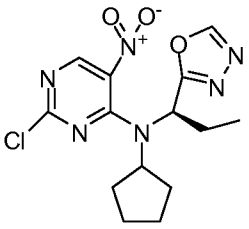
filtered and concentrated to give the sub-title compound as a colourless oil (908mg, 72%); 1H NMR (400.0 MHz, DMSO) d 0.86 (3H, t), 1.61-1.80 (2H, m), 2.23 (2H, br hump), 3.98 (1H, m), 9.15 (1H, s); MS ES (+) 128.

Method C: N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]cyclopentanamine



[00102] (1R)-1-(1,3,4-oxadiazol-2-yl)propan-1-amine (610 mg, 4.798 mmol) in THF (6.972 mL) was treated with cyclopentanone (407.6 mg, 428.6 µL, 4.846 mmol) then acetic acid (288.1 mg, 272.8 µL, 4.798 mmol). The reaction was stirred at ambient temperature for 20 minutes then treated with sodium triacetoxyborohydride (1.485 g, 7.005 mmol). The reaction was stirred at ambient temperature for 5 hours then basified with aqueous NaHCO3. The mixture was extracted with DCM (x10), dried over MgSO4 and concentrated under reduced pressure. The residue was purified by column chromatography (50% EtOAc/petrol) to give the sub-title compound as a colourless solid (694mg, 74%); 1H NMR (400.0 MHz, CDCl3) d 0.81 (3H, t), 1.10-1.87 (10H, m), 2.85 (1H, m), 3.95 (1H, t), 8.33 (1H, s); MS ES (+) 196.

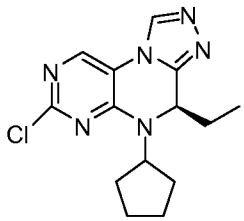
Method D: 2-chloro-N-cyclopentyl-5-nitro-N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]pyrimidin-4-amine



[00103] 17 N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]cyclopentanamine (199 mg, 1.019 mmol) in anhydrous THF (3.980 mL) was treated with NaHCO3 (342.4 mg, 4.076 mmol) then 2,4-dichloro-5-nitro-pyrimidine (197.7 mg, 1.019 mmol) . The reaction was stirred overnight at ambient temperature. The reaction was further stirred at 45 °C for 10 hours, diluted with EtOAc/Brine and extracted EtOAc (x3). The combined organic extracts were dried over MgSO4 and concentrated under reduced pressure. The residue was purified by column chromatography (30%EtOAc/petrol) to give the sub-tilte compound as a pale yellow oil (107mg, 30%); 1H NMR (400.0

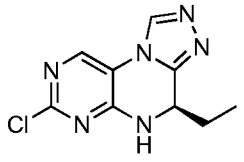
MHz, CDCl3) d 1.03 (3H, t), 1.45-2.80 (10H, m), 3.55 (1H, m), 4.39 (1H, m), 8.31 (1H, s), 8.60 (1H, s); MS ES (+) 353.1.

Method E: (R)-7-chloro-5-cyclopentyl-4-ethyl-4,5-dihydro-[1,2,4]triazolo[4,3-f]pteridine

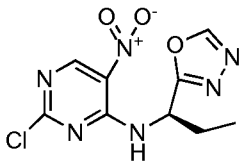


[00104] 2-chloro-N-cyclopentyl-5-nitro-N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]pyrimidin-4-amine (37 mg, 0.1049 mmol) in methanol (1.850 mL) was treated with zinc (116.6 mg, 16.35 µL, 1.783 mmol) and then dropwise acetic acid (245.7 mg, 232.7 µL, 4.091 mmol). The reaction was stirred at ambient temperature for 10 minutes. The reaction was filtered and the residual zinc washed with methanol. The combined filtrates were concentrated and re-dissolved in acetic acid (2 mL) and stirred at 70 °C for 1 hour. The reaction was filtered and precipitate washed with methanol. The filtrates were concentrated to dryness under reduced pressure, taken into 10% MeOH/DCM and passed through a short silica gel column. The residue was trituated with ether and the title compound isolated by filtration as a pale brown solid (21 mg, 66%); 1H NMR (400.0 MHz, DMSO) d 0.75 (3H, t), 1.50-1.64 (2H, m), 1.80-2.08 (8H, m), 4.22-4.33 (1H, m), 5.28-5.35 (1H, m), 8.68 (1H, s), 9.35 (1H, s); MS ES (+) 305.7.

Example 2: Preparation of (R)-7-chloro-4-ethyl-4,5-dihydro-[1,2,4]triazolo[4,3-f]pteridine

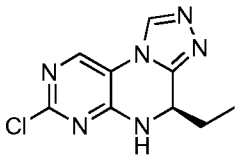


2-chloro-N-cyclopentyl-5-nitro-N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]pyrimidin-4-amine



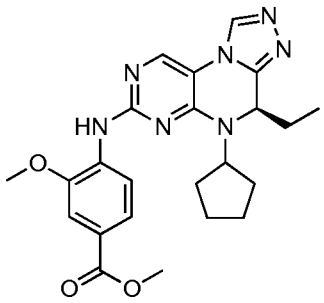
[00105] Prepared by a method similar to Method D, using (1R)-1-(1,3,4-oxadiazol-2-yl)propan-1-amine and 2,4-dichloro-5-nitro-pyrimidine. Title compound was obtained as a white solid (70%); 1H NMR (400.0 MHz, CDCl3) d 1.10 (3H, dt), 2.10-2.33 (2H, m), 5.81 (1H, m), 8.46 (1H, d), 8.82 (1H, d), 9.14 (1H, d); MS ES (+) 285.0, ES (-) 283.0.

(R)-7-chloro-4-ethyl-4,5-dihydro-[1,2,4]triazolo[4,3-f]pteridine

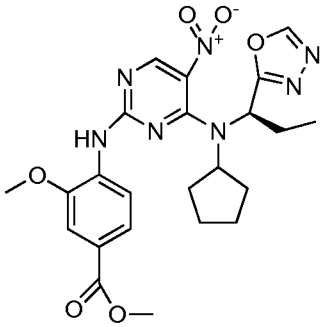


[00106] Prepared by a method similar to Method E, using 2-chloro-N-cyclopentyl-5-nitro-N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]pyrimidin-4-amine. Title compound was obtained as a white solid (70%); 1H NMR (400.0 MHz, DMSO) d 0.85-0.90 (3H, m), 1.92-1.98 (2H, m), 5.12 (1H, m), 8.62 (1H, s), 9.01 (1H, s), 9.23 (1H, s); MS ES (+) 236.9, ES (-) 235.0.

Example 3: Preparation of (*R*)-methyl 4-(5-cyclopentyl-4-ethyl-4,5-dihydro-[1,2,4]triazolo[1,5-*f*]pteridin-7-ylamino)-3-methoxybenzoate

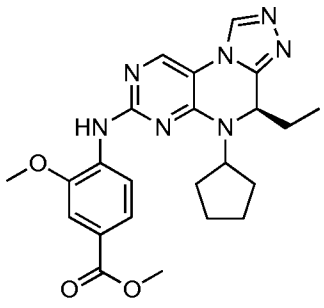


Method F: (*R*)-methyl 4-(4-((1-(1,3,4-oxadiazol-2-yl)propyl)(cyclopentyl)amino)-5-nitropyrimidin-2-ylamino)-3-methoxybenzoate



[00107] 2-chloro-N-cyclopentyl-5-nitro-N-[(1R)-1-(1,3,4-oxadiazol-2-yl)propyl]pyrimidin-4-amine (61.5 mg, 0.1743 mmol) and methyl 4-amino-3-methoxy benzoate (37.9 mg, 0.2092 mmol) in 4-methylpentan-2-ol (600 L) were treated with DIPEA (33.8 mg, 45.6 mL, 0.2614 mmol) and the reaction mixture stirred at 140 °C for 4 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (50% EtOAc/Petrol) to give the sub-title compound as a brown oil (42 mg, 48%); 1H NMR (400.0 MHz, DMSO) d 0.75-0.89 (3H, m), 1.15-1.75 (8H, m), 2.24-2.34 (1H, m), 2.40-2.51 (1H, m), 2.61-2.72 (1H, m), 3.55-3.63 (1H, m), 3.84 (3H, s), 3.89 (3H, s), 7.44 (1H, s), 7.55 -7.65 (2H, m), 7.75-8.03 (1H, br s), 8.12 (1H, s), 8.77 (1H, s); MS ES(+) 498.1.

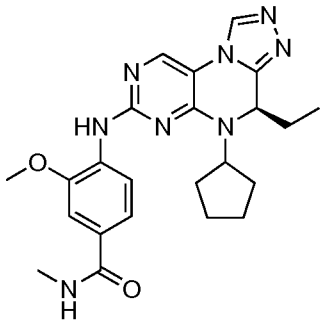
Method G: (*R*)-methyl 4-(5-cyclopentyl-4-ethyl-4,5-dihydro-[1,2,4]triazolo[1,5-*f*]pteridin-7-ylamino)-3-methoxybenzoate



[00108] Zinc (22.1 mg, 0.3377 mmol) was added to a stirred solution of (*R*)-methyl 4-(4-((1-(1,3,4-oxadiazol-2-yl)propyl)(cyclopentyl)amino)-5-nitropyrimidin-2-ylamino)-3-methoxybenzoate (12 mg, 0.02412 mmol) in methanol (1 mL). Glacial acetic acid (56.49 mg, 53.49 L, 0.9407 mmol) was added dropwise and the reaction allowed to stir at ambient temperature for 90 minutes. The solvent was removed *in vacuo* and the residue redissolved in glacial acetic acid (1 mL) and the reaction mixture heated at 70 °C for 2 hours. The reaction mixture was concentrated *in vacuo*

and the residue dissolved in DCM. The organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (10% MeOH/DCM) to give the title compound as a brown solid (7 mg, 65%); 1H NMR (400.0 MHz, DMSO) d 0.76-0.80 (3H, t), 1.20-2.20 (10H, m), 3.91 (3H, s), 3.84 (3H, s), 4.49-4.60 (1H, m), 5.01-5.10 (1H, m), 7.48 (1H, s), 7.63 (1H, s), 7.80 (1H, s), 8.17 (1H, s), 8.38-8.51 (2H, m); MS ES(+) 450.2.

Method H: 4-((*R*)-5-cyclopentyl-4-ethyl-4,5-dihydro-[1,2,4]triazolo[4,3-*f*]pteridin-7-ylamino)-3-methoxy-*N*-methylbenzamide



[00109] To a solution of (*R*)-7-chloro-5-cyclopentyl-4-ethyl-4,5-dihydro-[1,2,4]triazolo[4,3-*f*]pteridine (80mg, 0.263 mmol) in a mixture ethanol/water (1/4, 5 mL) were added 4-amino-3-methoxy-*N*-methylbenzamide (72mg, 0.394 mmol) followed by a catalytic amount of concentrated HCl (0.04mL). The reaction mixture was stirred at 90°C for 24 hours, then cooled to room temperature and basified with saturated aqueous solution of $NaHCO_3$. The mixture was extracted with ethyl acetate, the organic layer was dried (MgSO4) and the residue purified by flash chromatography to give the title compound as a colourless solid (92mg, 78% yield); ^{1}H NMR (DMSO D6) 0.75 (3H, t), 1.43-1.60 (4H, m), 1.80-2.07 (6H, m), 2.80 (3H, d), 3.88 (3H, s), 4.19 (1H, m), 5.38 (1H, m), 7.50 (1H, d), 7.59 (1H, s), 7.83 (1H, d), 8.47 (1H, m), 8.67 (1H, s), 9.31 (1H, s), 9.40 (1H, br s); LC/MS M+1 (obs.) 449.3.

[00110] All references provided herein are incorporated herein in its entirety by reference. As used herein, all abbreviations, symbols and conventions are consistent with those used in the contemporary scientific literature. See, e.g., Janet S. Dodd, ed., *The ACS Style Guide: A Manual for Authors and Editors*, 2nd Ed., Washington, D.C.: American Chemical Society, 1997.

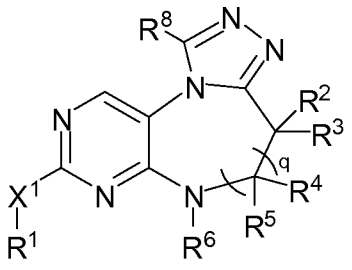
[00111] It is to be understood that while the invention has been described in

conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

CLAIMS

What is claimed is:

1. A method of preparing a compound represented by Structural Formula (**I**):



(**I**) ,

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is a bond, -O-, -NR^7-, -S-, -S(O)-, or -$S(O)_2$-;

R^1 is -H, C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each of said aliphatic, cycloaliphatic, aryl, heteroaryl, and heterocyclyl groups represented by R^1 is optionally and independently substituted with one or more instances of J^1;

each R^2, R^3, R^4, and R^5 is independently -H, halogen, cyano, C_{1-6} aliphatic, or C_{3-10} cycloaliphatic, wherein each of said aliphatic and cycloaliphatic groups represented by R^2, R^3, R^4, and R^5, respectively, is optionally and independently substituted with one or more instances of J^2, J^3, J^4, and J^5, respectively;

optionally, R^2 and R^3, together with the carbon atom to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B;

optionally, R^3 and R^4, together with the carbon atoms to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B;

optionally, R^4 and R^5, together with the carbon atom to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B;

R^6 is -H, C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each of said aliphatic, cycloaliphatic, aryl, heteroaryl, and heterocyclyl groups represented by R^6 is optionally and independently substituted with one or more instances of J^6;

R^7 is -H, or a C_{1-6} aliphatic or C_{3-8} cycloaliphatic group optionally substituted with one or more instanced of J^A, or, optionally R^7, together with R^1 and the nitrogen atom to which it is attached, forms a 4-7 membered heterocyclic ring that is optionally being substituted with one or more instances of J^B;

R^8 is –H, C_{1-6} aliphatic, or C_{3-8} cycloaliphatic, wherein said aliphatic group is independently and optionally substituted with one or more instances of J^A, and wherein said cycloaliphatic group is independently and optionally substituted with one or more instances of J^B;

each J^1 is independently T or C_{1-6} aliphatic optionally substituted with one or more instances of T;

each of J^2, J^3, J^4, J^5, and J^6 is independently M, or C_{1-6} aliphatic optionally substituted with one or more instances of M;

each T is independently halogen, oxo, $-NO_2$, -CN, Q^1, $-Z^1$-H, or $-Z^2$-Q^2;

each Z^1 is independently a unit consisting of one or more groups independently selected from the group consisting of -NR-, -O-, -S- , -C(O)-, -C(=NR)- , -C(=NOR)-, and $-SO_2N(R)$-;

each Z^2 is independently a unit consisting of one or more groups independently selected from the group consisting of -NR-, -O-, -S- , -C(O)-, -C(=NR)- , -C(=NOR)-, -S(O)-, and $-S(O)_2$-;

each Q^1 is independently C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each Q^1 is independently and optionally substituted with one or more instances of J^Q;

each Q^2 is independently C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocyclyl, or Q^1-Q^1, each of which is optionally and indepednently substituted with one or more instances of J^Q; or each Q^2, together with R and the nitrogen atom to which it is attached, optionally forms a 4-7 membered heterocyclic ring optionally substituted with one or more instances of J^B; and

each J^Q is independently M or C_{1-6} aliphatic optionally substituted with one or more instances of M;

each M is independently halogen, oxo, $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -COR', $-CO_2R'$, $-CONR'_2$, -OCOR'', $-OCON(R')_2$, -NRCOR', $-NRCO_2R'$, $-NRCON(R')_2$, -S(O)R'', $-SO_2R''$, $-SO_2N(R')_2$, $-NRSO_2R''$, $-NRSO_2N(R')_2$, C_{3-10} cycloaliphatic, 3-10 membered heterocyclyl, C_{6-10} aryl, or 5-10 membered heteroaryl, wherein each of said cycloaliphatic, heterocyclyl, aryl and heteroaryl groups

represented by M is optionally and independently substituted with one or more instances of J^B;

each R is independently -H or C_{1-6} aliphatic, or each R, together with Q^2 and the nitrogen atom to which it is attached, optionally forms a 4-7 membered heterocyclic ring optionally substituted with one or more instances of J^B;

each R' is independently –H or C_{1-6} aliphatic optionally substituted with one or more instances of J^A; or two R' groups, together with the nitrogen atom to which they are bound, form a 4-7 membered heterocyclic ring optionally substituted with one or more instances of J^B;

each R" is independently C_{1-4} aliphatic optionally substituted with one or more instances of J^A;

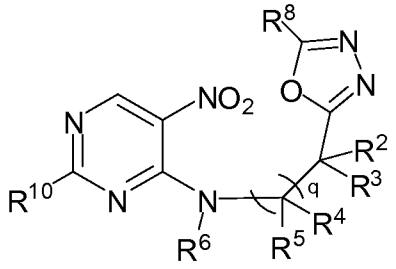
each J^A is independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), C_{3-7} cycloalkyl, and C_{3-7} cyclo(haloalkyl);

each J^B is independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), and C_1-C_4 aliphatic that is optionally substituted with one or more instances of J^A; and

q is 0 or 1;

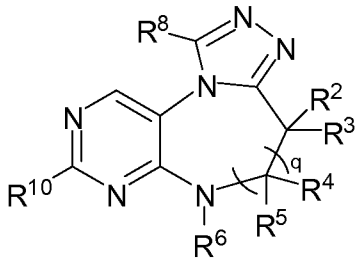
comprising the step of:

a) cyclizing a compound represented by Structural Formula (**A**):



(**A**)

under suitable reductive cyclisation conditions to form a compound represented by Structural Formula (**B**):



(**B**) ,

wherein R^{10} is $-LG_1$ or $-X^1R^1$, and $-LG_1$ is a suitable leaving group; and

b) optionally, when R^{10} of Structural Formula (**B**) is LG_1, further comprising the step of replacing the $-LG_1$ with $-X^1(R^1)$ under suitable conditions to form the compound represented by Structural Formula (**I**).

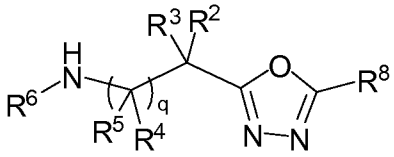
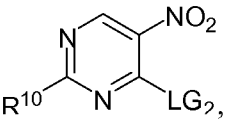
2. The method of any of claim 1, wherein X^1 is a bond, -O-, $-NR^7$-, or -S-.

3. The method of claim 1 or 2, wherein R^1 is optionally substituted C_{1-6} aliphatic, optionally substituted C_{6-10} aryl, or optionally substituted 5-10 membered heteroaryl.

4. The method of any one of claims 1-3, wherein R^7 is –H, or optionally substituted C_{1-6} aliphatic.

5. The method of any one of claims 1-4, wherein R^6 is –H, optionally substituted C_{1-6} aliphatic, optionally substituted C_{3-7} cycloaliphatic, optionally substituted 4-7 membered heterocyclyl, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl.

6. The method of any one of claims 1-5, wherein each of R^2, R^3, R^4 and R^5 is independently -H, halogen, optionally substituted C_{1-6} aliphatic, or optionally substituted C_{3-7} cycloaliphatic; or optionally R^2 and R^3, R^3 and R^4, and R^4 and R^5, respectively, together with the atom to which they are bound, independently form an optionally substituted C_{3-7} cycloaliphatic ring.

7. The method of any one of claims 1-6, further comprising the step of reacting a compound of Structural Formula (**D**):  (**D**) with a compound of Structural Formula (**E**): , wherein LG_2 is a suitable leaving group, under suitable conditions to form the compound of Structural Formula (**A**).

8. The method of claim 7, wherein LG_1 and LG_2 are both independently halogen.

9. The method of claim 8, wherein LG_1 and LG_2 are both -Cl.

10. The method of any one of claims 1-9, wherein:

each Z^1 is independently -N(R)-, -O-, -S-, -CO_2-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -SO_2N(R)-, or -N(R)SO_2N(R)-; and

each Z^2 is independently -N(R)-, -O-, -S-, -CO_2-, -OC(O)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -$S(O)_2$-, -SO_2N(R)-, -N(R)SO_2-, or -N(R)SO_2N(R)-.

11. The method of claim 10, wherein R^1 is C_{1-4} alkyl substituted with Q^1 and optionally further substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl).

12. The method of claim 10, wherein R^1 is C_{6-10} aryl or 5-6 membered heteroaryl, each optionally and independently substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, Q^1, -N(R)H, -OH, -CO_2H, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, -SO_2N(R)H, -N(R)SO_2N(R)H, -$S(O)_2Q^2$, -N(R)Q^2, -OQ^2, -SQ^2, -CO_2Q^2, -OC(O)Q^2,

-C(O)N(R)Q^2, -N(R)C(O)Q^2, -N(R)CO_2Q^2, -OC(O)N(R)Q^2, -C(O)N(R)CO_2Q^2, -N(R)C(O)N(R)Q^2, -SO_2N(R)Q^2, -N(R)SO_2Q^2, or -N(R)SO_2N(R)Q^2.

13. The method of claim 11 or 12, wherein R^7 is –H, or C_{1-6} alkyl.

14. The method of claim 13, wherein R^6 is –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-7} cycloalkyl.

15. The method of claim 13, wherein R^8 is –H or C_{1-6} alkyl.

16. The method of claim 15, wherein each of R^2, R^3, R^4 and R^5 is independently -H, or optionally substituted C_{1-6} alkyl; or optionally R^2 and R^3, together with the atom to which they are bound, form an optionally substituted C_{3-7} cycloalkyl ring.

17. The method of claim 16, wherein:

i) R^2 is –H or C_{1-3} alkyl; R^3 is C_{1-3} alkyl; R^4 is –H or C_{1-3} alkyl; and R^5 is –H or C_{1-3} alkyl; or

ii) R^2 and R^3 together with the atom to which they are bound form a C_{3-7} cycloalkyl ring; R^4 is –H or C_{1-3} alkyl; and R^5 is –H or C_{1-3} alkyl.

18. The method of claim 17, wherein R^4 and R^5 are both -H.

19. The method of any one of claims 12-18, wherein R^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T; and wherein each T is halogen, cyano, -N(R)H, -OH, -CO_2H, -C(O)N(R)H, -OC(O)N(R)H, -N(R)Q^2, -OQ^2, -CO_2Q^2, -OC(O)Q^2, -C(O)N(R)Q^2, -N(R)C(O)Q^2, -N(R)CO_2Q^2, -OC(O)N(R)Q^2, -C(O)N(R)CO_2Q^2, or -N(R)C(O)N(R)Q^2.

20. The compound of claim 19, wherein R^7 is –H.

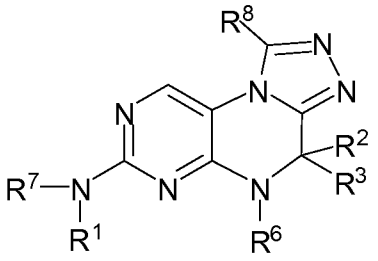
21. The method of claim 20, wherein R^6 is optionally substituted C_{3-6} cycloalkyl.

22. The method of any one of claims 1-20, wherein X^1 is –O-, –NR^7-, or –S-.

23. The method of claim 22, wherein X^1 is –NR^7-.

24. The method of any one of claims 1-22, wherein q is 0.

25. A method of preparing a compound represented by Structural Formula (**II**):



(**II**) ,

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is -H, C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each of said aliphatic, cycloaliphatic, aryl, heteroaryl, and heterocyclyl groups represented by R^1 is optionally and independently substituted with one or more instances of J^1;

each of R^2 and R^3 is independently -H, halogen, cyano, C_{1-6} aliphatic, or C_{3-10} cycloaliphatic, wherein each of said aliphatic and cycloaliphatic groups represented by R^2 and R^3, respectively, is optionally and independently substituted with one or more instances of J^2 and J^3, respectively;

optionally, R^2 and R^3, together with the carbon atom to which they are attached, form a C_{3-7} cycloaliphatic ring that is optionally substituted with one or more instances of J^B;

R^6 is -H, C_{1-6} aliphatic, or C_{3-10} cycloaliphatic, wherein each of said aliphatic and cycloaliphatic groups represented by R^6 is optionally and independently substituted with one or more instances of J^6;

R^7 is –H or C_{1-6} aliphatic optionally substituted with one or more instanced of J^A, or, optionally R^7, together with R^1 and the nitrogen atom to which it is attached, forms a 4-7 membered heterocyclic ring that is optionally being substituted with one or more instances of J^B;

R^8 is –H, C_{1-6} aliphatic, or C_{3-8} cycloaliphatic, wherein said aliphatic group is independently and optionally substituted with one or more instances of J^A, and wherein said cycloaliphatic group is independently and optionally substituted with one or more instances of J^B;

each J^1 is independently T or C_{1-6} aliphatic optionally substituted with one or more instances of T;

each of J^2, J^3, J^4, J^5, and J^6 is independently M, or C_{1-6} aliphatic optionally substituted with one or more instances of M;

each T is independently halogen, oxo, $-NO_2$, -CN, Q^1, $-Z^1-H$, or $-Z^2-Q^2$;

each Z^1 is independently a unit consisting of one or more groups independently selected from the group consisting of -NR-, -O-, -S- , -C(O)-, -C(=NR)- , -C(=NOR)-, and $-SO_2N(R)-$;

each Z^2 is independently a unit consisting of one or more groups independently selected from the group consisting of -NR-, -O-, -S- , -C(O)-, -C(=NR)- , -C(=NOR)-, -S(O)-, and $-S(O)_2-$;

each Q^1 is independently C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, or 3-10 membered heterocyclyl, wherein each Q^1 is independently and optionally substituted with one or more instances of J^Q;

each Q^2 is independently C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl, 3-10 membered heterocyclyl, or Q^1-Q^1, each of which is optionally and indepednently substituted with one or more instances of J^Q; or each Q^2, together with R and the nitrogen atom to which it is attached, optionally forms a 4-7 membered heterocyclic ring optionally substituted with one or more instances of J^B; and

each J^Q is independently M or C_{1-6} aliphatic optionally substituted with one or more instances of M;

each M is independently halogen, oxo, $-NO_2$, -CN, -OR', -SR', $-N(R')_2$, -COR', $-CO_2R'$, $-CONR'_2$, -OCOR'', $-OCON(R')_2$, -NRCOR', $-NRCO_2R'$, $-NRCON(R')_2$, -S(O)R'', $-SO_2R''$, $-SO_2N(R')_2$, $-NRSO_2R''$, $-NRSO_2N(R')_2$, C_{3-10} cycloaliphatic, 3-10 membered heterocyclyl, C_{6-10} aryl, or 5-10 membered heteroaryl, wherein each of said cycloaliphatic, heterocyclyl, aryl and heteroaryl groups represented by M is optionally and independently substituted with one or more instances of J^B;

each R is independently -H or C_{1-6} aliphatic, or each R, together with Q^2 and the nitrogen atom to which it is attached, optionally forms a 4-7 membered heterocyclic ring optionally substituted with one or more instances of J^B;

each R' is independently –H or C_{1-6} aliphatic optionally substituted with one or more instances of J^A; or two R' groups, together with the nitrogen atom to which

they are bound, form a 4-7 membered heterocyclic ring optionally substituted with one or more instances of J^B;

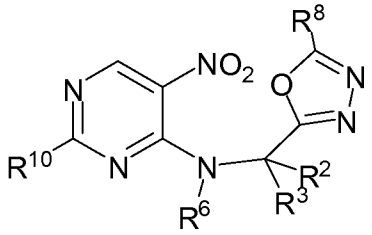
each R" is independently C_{1-4} aliphatic optionally substituted with one or more instances of J^A; and

each J^A is independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), C_{3-7} cycloalkyl, and C_{3-7} cyclo(haloalkyl);

each J^B is independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), and C_1-C_4 aliphatic that is optionally substituted with one or more instances of J^A;

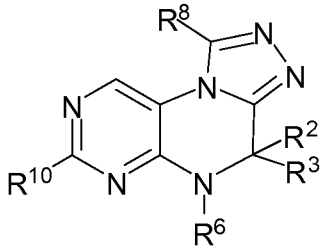
comprising the step of:

a) cyclizing a compound represented by Structural Formula (**A1**):



(**A1**)

under suitable reductive cyclisation conditions to form a compound represented by Structural Formula (**B1**):



(**B1**) ,

wherein: R^{10} is LG_1 or $-NR^1R^7$; and LG_1 is a suitable leaving group; and

b) optionally, when R^{10} of Structural Formula (**B1**) is LG_1, further comprising the step of replacing $-LG_1$ of Structural Formula (**B1**) with $-NR^1R^7$ under suitable conditions to form the compound represented by Structural Formula (**I**).

26. The method of claim 25, wherein:

R^1 is optionally substituted C_{6-10} aryl or optionally substituted 5-10 membered heteroaryl;

each Z^1 is independently -N(R)-, -O-, -S-, -CO_2-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -SO_2N(R)-, or -N(R)SO_2N(R)-;

each Z^2 is independently -N(R)-, -O-, -S-, -CO_2-, -OC(O)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, -N(R)CO_2-, -N(R)C(O)N(R)-, -C(O)N(R)CO_2-, -S(O)-, -$S(O)_2$-, -SO_2N(R)-, -N(R)SO_2-, or -N(R)SO_2N(R)-;

Q^1 is optionally substituted C_{3-7} cycloalkyl, optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl, or optionally substituted 4-7 membered heterocyclyl;

each of R^2 and R^3 is independently –H, halogen, cyano, or C_{1-6} aliphatic, or optionally R^2 and R^3, together with the carbon atom(s) to which they are bound, independently form a C_{3-7} cycloalkyl ring, wherein each of said aliphatic and cycloalkyl ring is independently and optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl);

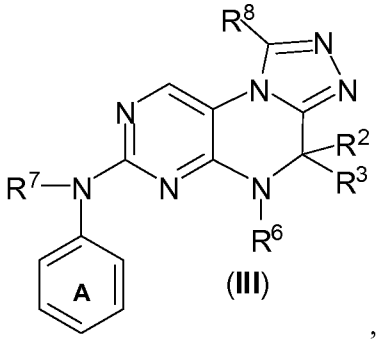
R^6 is –H, C_{1-6} aliphatic or C_{3-7} cycloaliphatic, each of which is optionally and independently substituted with one or more substituents independently selected from the group consisting of halogen, oxo, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OCO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -CO_2H, -CO_2(C_1-C_4 alkyl), and –O(C_1-C_4 alkyl); and

each of R^7 and R^8 is independently –H or C_{1-6} alkyl.

27. The method of claim 25 or 26, when R^{10} of Structural Formula (**A1**) is –LG_1, further comprising the step of replacing the –LG_1 of Structural Formula (**A1**) with -NR^1R^7 prior to the cyclisation step a) by reacting the compound represented by Structural Formula (**A1**) with HNR^1R^7 under suitable conditions.

28. The method of claim 27, wherein LG_1 is –Cl.

29. The method of any one of claims 25-28, wherein the compound produced by the method is represented by Structural Formula (**III**):



(III)

,

or a pharmaceutically acceptable salt thereof, wherein:

phenyl ring **A** is optionally substituted with one or more substitutents independently selected from the group consisting of T and C_{1-6} aliphatic optionally substituted with one or more instances of T;

each T is halogen, cyano, Q^1, -N(R)H, -OH, -SH, $-CO_2H$, -C(O)N(R)H, -OC(O)N(R)H, -N(R)C(O)N(R)H, $-SO_2N(R)H$, $-N(R)SO_2N(R)H$, $-S(O)_2Q^2$, $-N(R)Q^2$, $-OQ^2$, $-SQ^2$, $-CO_2Q^2$, $-OC(O)Q^2$, $-C(O)N(R)Q^2$, $-N(R)C(O)Q^2$, $-N(R)CO_2Q^2$, $-OC(O)N(R)Q^2$, $-C(O)N(R)CO_2Q^2$, $-N(R)C(O)N(R)Q^2$, $-SO_2N(R)Q^2$, $-N(R)SO_2Q^2$, or $-N(R)SO_2N(R)Q^2$;

Q^1 is C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, or 4-7 membered heterocyclyl, each optionally and independently substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl;

each Q^2 is independently C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, 5-6 membered heteroaryl, or 4-7membered heterocyclyl, or each Q^2, together with R, optionally and independently forms an optionally substituted, 4-7 membered heterocyclic ring; wherein said C_{1-6} alkyl represented by Q^2 is optionally substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), and $-O(C_1-C_4$ alkyl); and wherein each of said cycloalkyl, aryl, heteroaryl, and heterocyclyl groups represented by Q^2 is optionally and independently substituted with one or more substitutents independently selected from the group consisting of halogen, oxo, -CN, -OH, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)_2$, $-OCO(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-CO_2H$, $-CO_2(C_1-C_4$ alkyl), $-O(C_1-C_4$ alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl;

each of R^2 and R^3 independently -H, halogen, optionally substituted C_{1-6} aliphatic; or optionally R^2 and R^3, together with the carbon atom to which they are attached, form an optionally substituted C_{3-6} cycloalkyl ring; and

R^6 is optionally substituted –H, optionally substituted C_{1-6} alkyl, or optionally substituted C_{3-6} cycloalkyl.

30. The method of claim 29, wherein R^6 is C_{5-6} cycloalkyl.

31. The method of claim 30, wherein:

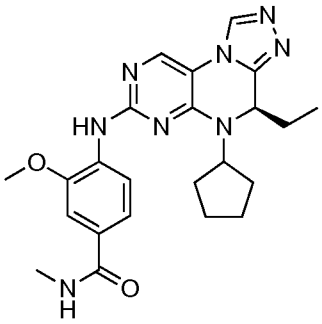
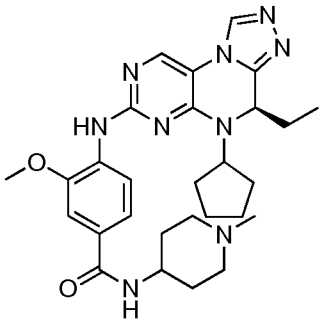
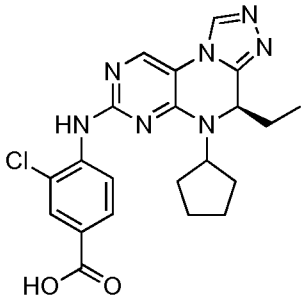
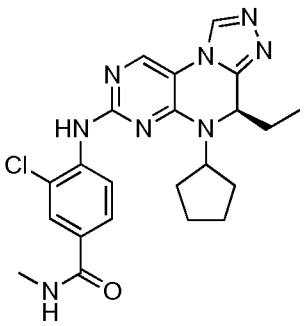
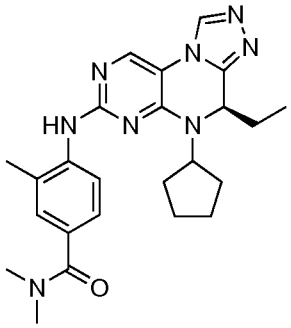
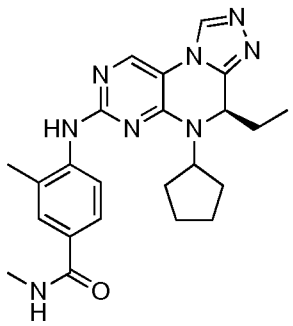
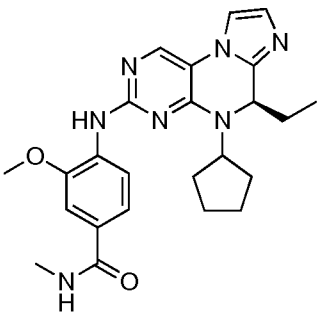
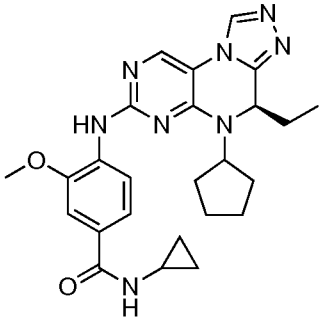
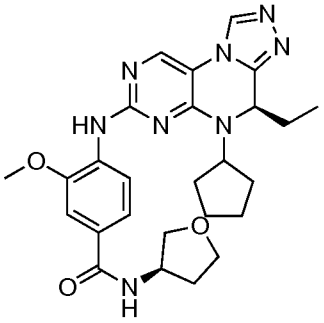
i) R^2 is –H or C_{1-3} alkyl; and R^3 is C_{1-3} alkyl; or

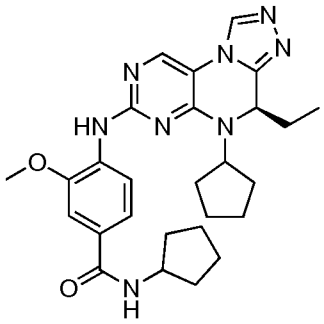
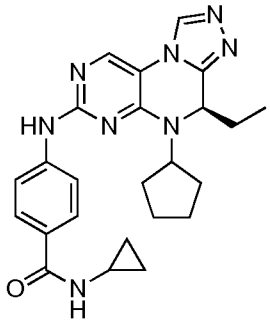
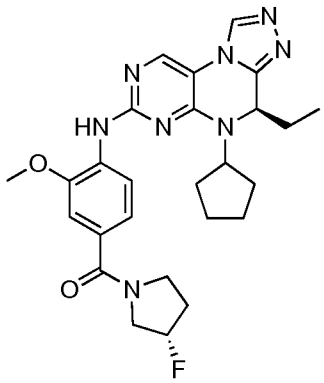
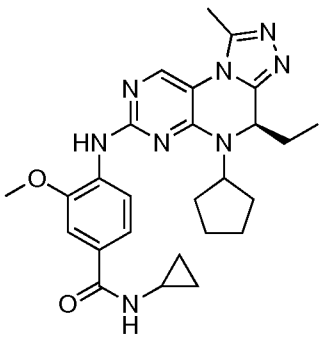
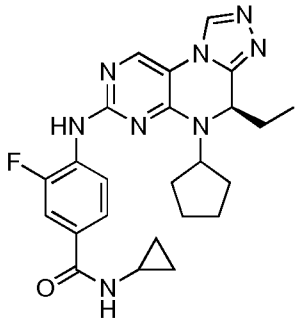
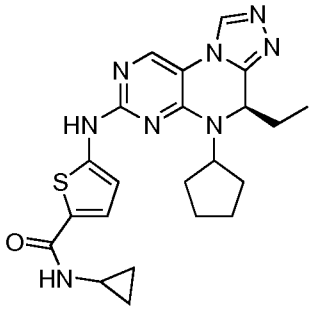
ii) R^2 and R^3 together with the atom to which they are bound form a C_{3-6} cycloalkyl ring.

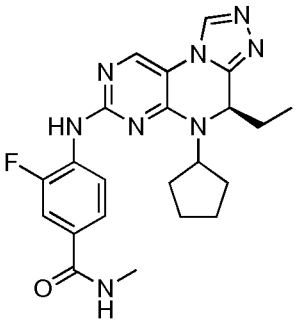
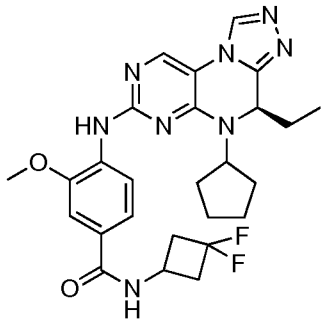
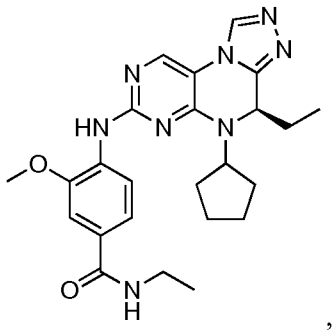
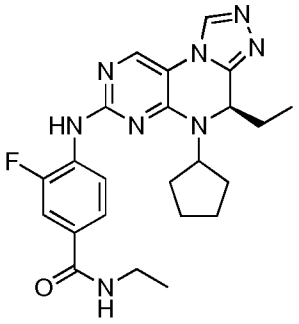
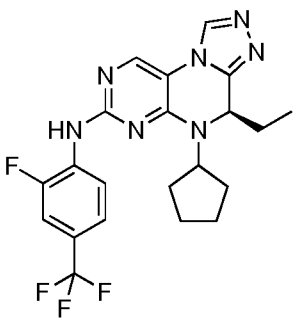
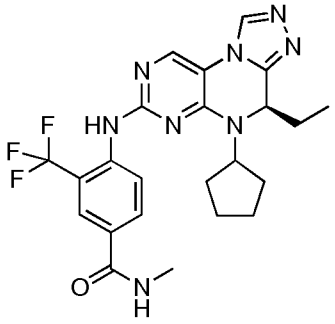
32. The method of any one of claims 29-31, wherein phenyl ring **A** is substituted with one or more substituents independently selected from the group consisting of -C(O)N(R)H, -C(O)N(R)Q^2, -N(R)C(O)Q^2, -CO_2H, -CO_2Q^2, -OC(O)Q^2, -N(R)CO_2Q^2, -OC(O)N(R)Q^2, and -N(R)C(O)N(R)Q^2; and optionally further substituted with one or one or more substituents independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, –O(C_1-C_4 alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

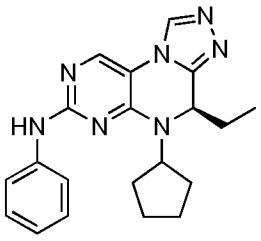
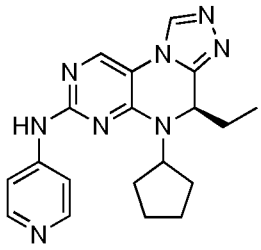
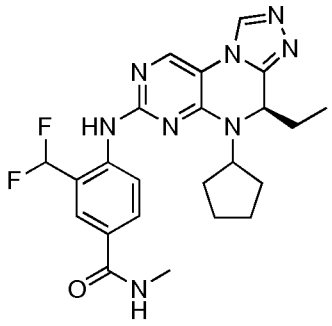
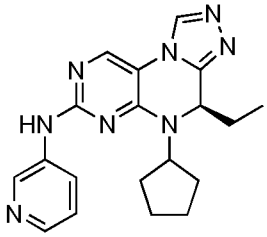
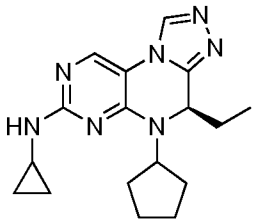
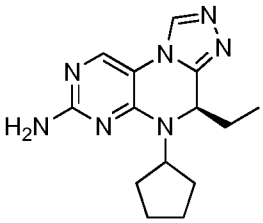
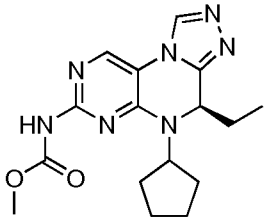
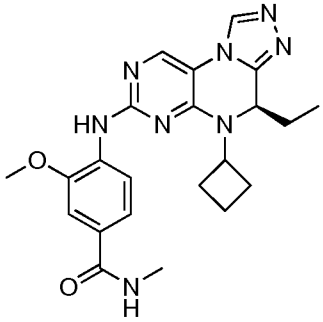
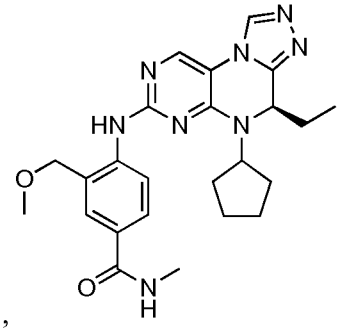
33. The method of claim 32, wherein phenyl ring **A** is substituted with -OC(O)Q^2, -C(O)N(R)Q^2, or -N(R)C(O)Q^2, and optionally further substituted with one or one or more substituents independently selected from the group consisting of halogen, -CN, -OH, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, –O(C_1-C_4 alkyl), C_1-C_4 alkyl, C_1-C_4 haloalkyl; C_1-C_4 cyanoalkyl, C_1-C_4 aminoalkyl, C_1-C_4 hydroxyalkyl, and C_2-C_4 alkoxyalkyl.

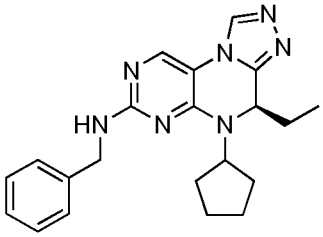
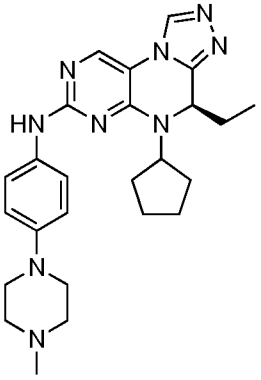
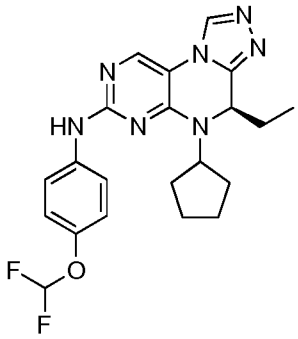
34. The method of claim 1, wherein the compound produced by the method is represented by any one of the following structural formulae, or a pharmaceutically acceptable salt thereof:

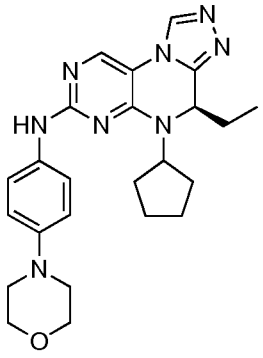
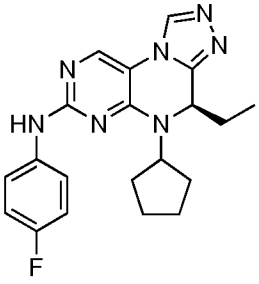
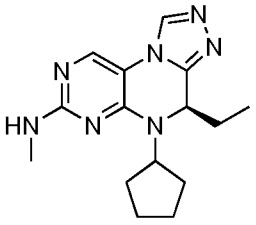

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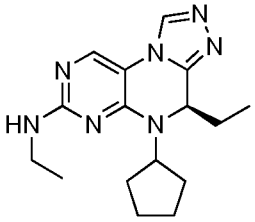
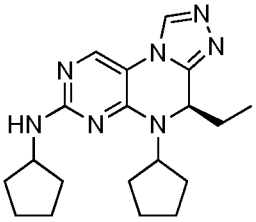
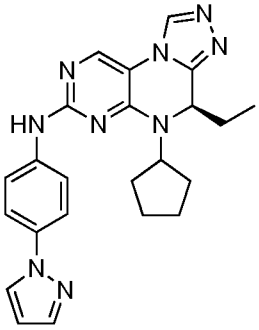

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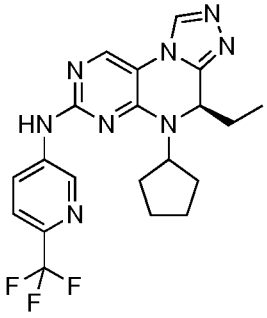
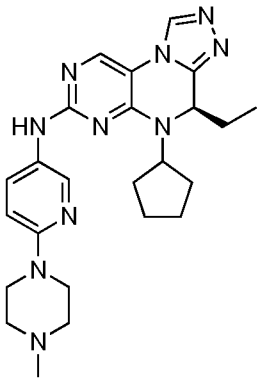
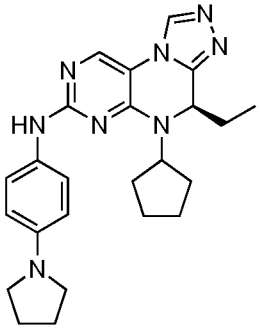

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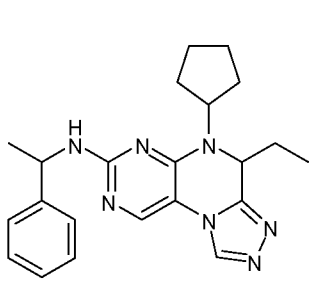
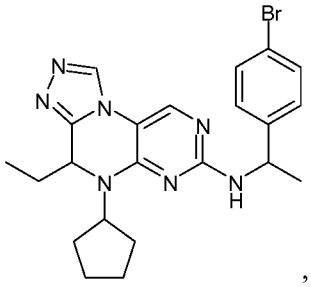
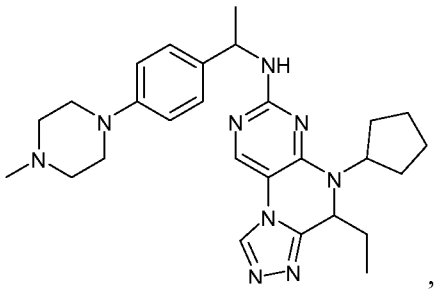
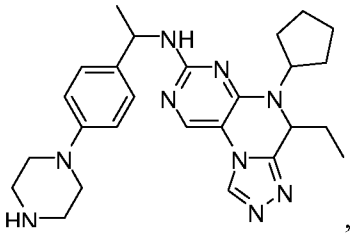
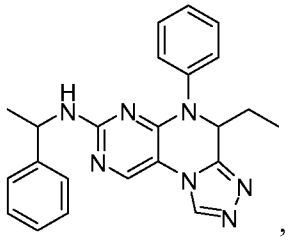
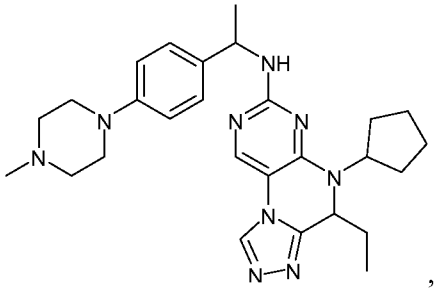
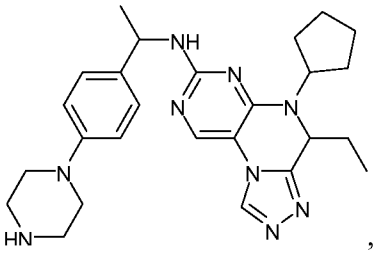
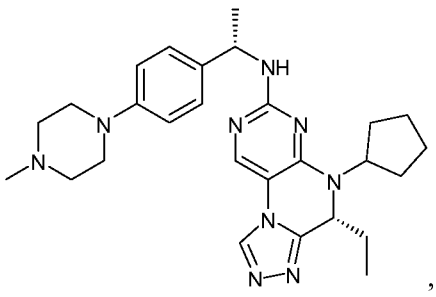

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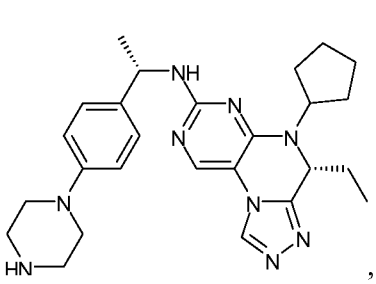
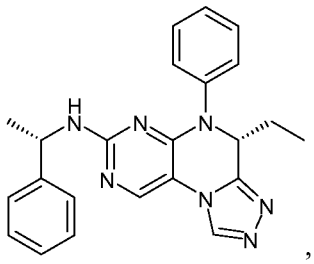
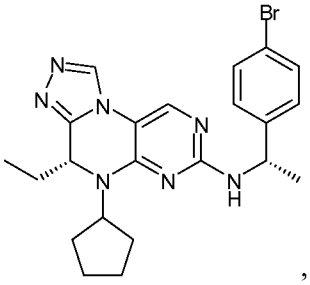
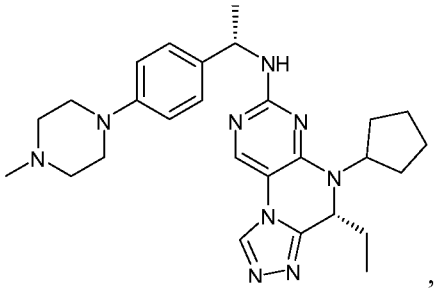
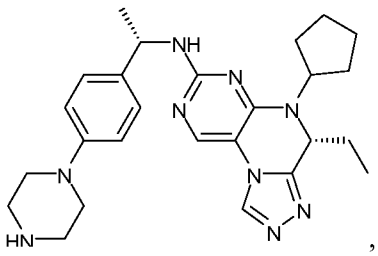
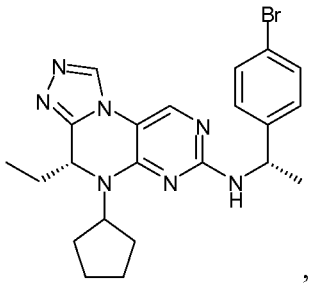
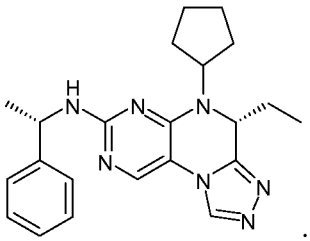

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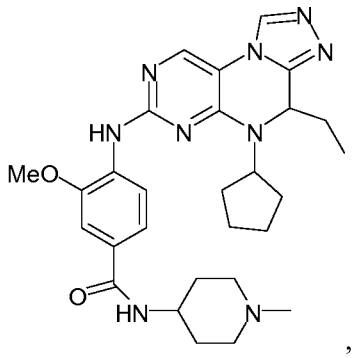

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35. The method of claim 1, wherein the compound produced by the method is represented by any one of the following structural formulae, or a pharmaceutically acceptable salt thereof:


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36. The method of claim 1, wherein the compound produced by the method is represented by the following structural formula:


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or a pharmaceutically acceptable salt thereof.