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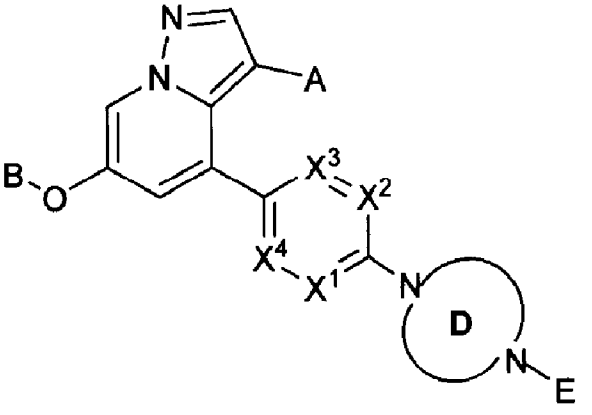
(54) **Titre : COMPOSES SUBSTITUES DE PYRAZOLO[1,5-A]PYRIDINE EN TANT QU'INHIBITEURS DE LA KINASE RET**
(54) **Title: SUBSTITUTED PYRAZOLO[1,5-A]PYRIDINE COMPOUNDS AS RET KINASE INHIBITORS**



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(57) **Abrégé/Abstract:**
Provided herein are compounds of the Formula I and stereoisomers and pharmaceutically acceptable salts or solvates thereof, in which A, B, X^1, X^2, X^3, X^4, Ring D, and E have the meanings given in the specification, which are inhibitors of RET kinase and are

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useful in the treatment and prevention of diseases which can be treated with a RET kinase inhibitor, including RET-associated diseases and disorders.

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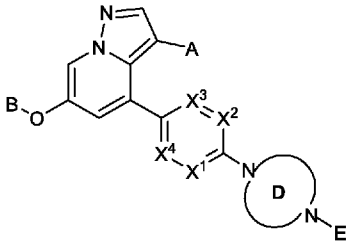

(I)

(57) Abstract: Provided herein are compounds of the Formula I and stereoisomers and pharmaceutically acceptable salts or solvates thereof, in which A, B, X^1, X^2, X^3, X^4, Ring D, and E have the meanings given in the specification, which are inhibitors of RET kinase and are useful in the treatment and prevention of diseases which can be treated with a RET kinase inhibitor, including RET-associated diseases and disorders.

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JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __3___

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SUBSTITUTED PYRAZOLO[1,5-A]PYRIDINE COMPOUNDS AS RET KINASE INHIBITORS

[0001]

BACKGROUND

[0002] The present disclosure relates to novel compounds which exhibit Rearranged during Transfection (RET) kinase inhibition, pharmaceutical compositions comprising the compounds, processes for making the compounds, and the use of the compounds in therapy. More particularly, it relates to substituted pyrazolo[1,5-a]pyridine compounds useful in the treatment and prevention of diseases which can be treated with a RET kinase inhibitor, including RET-associated diseases and disorders.

[0003] RET is a single-pass transmembrane receptor belonging to the tyrosine kinase superfamily that is required for normal development, maturation and maintenance of several tissues and cell types (Mulligan, L. M., *Nature Reviews Cancer*, 2014, 14, 173-186). The extracellular portion of the RET kinase contains four calcium-dependent cadherin-like repeats involved in ligand binding and a juxtamembrane cysteine-rich region necessary for the correct folding of the RET extracellular domain, while the cytoplasmic portion of the receptor includes two tyrosine kinase subdomains.

[0004] RET signaling is mediated by the binding of a group of soluble proteins of the glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs), which also includes neurturin (NTRN), artemin (ARTN) and persephin (PSPN) (Arighi et al., *Cytokine Growth Factor Rev.*, 2005, 16, 441-67). Unlike other receptor tyrosine kinases, RET does not directly bind to GFLs and requires an additional co-receptor: that is, one of four GDNF family receptor-α (GFRα) family members, which are tethered to the cell surface by a glycosylphosphatidylinositol linkage. GFLs and GFRα family members form binary complexes that in turn bind to RET and recruit it into cholesterol-rich membrane subdomains, which are known as lipid rafts, where RET signaling

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occurs.

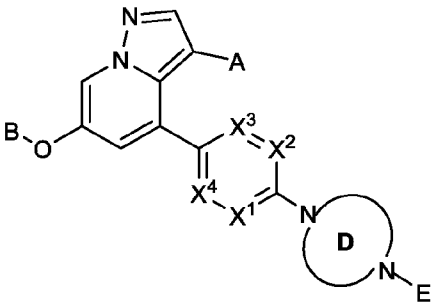
[0005] Upon binding of the ligand-co-receptor complex, RET dimerization and autophosphorylation on intracellular tyrosine residues recruits adaptor and signaling proteins to stimulate multiple downstream pathways. Adaptor protein binding to these docking sites leads to activation of Ras-MAPK and PI3K-Akt/mTOR signaling pathways or to recruitment of the CBL family of ubiquitin ligases that functions in RET downregulation of the RET-mediated functions.

[0006] Aberrant RET expression and/or activity have been demonstrated in different cancers and in gastrointestinal disorders such as irritable bowel syndrome (IBS).

SUMMARY OF THE INVENTION

[0007] It has now been found that substituted pyrazolo[1,5-a]pyridine compounds are inhibitors of RET kinase, and are useful for treating diseases such as proliferative diseases including cancers.

[0008] Accordingly, provided herein is a compound of the Formula **I**:



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[0009] or pharmaceutically acceptable salt or solvate thereof, wherein A, B, X^1, X^2, X^3, X^4, and Ring D are as defined herein.

[0010] Also provided herein is a pharmaceutical composition comprising a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable diluent or carrier.

[0011] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein.

[0012] Also provided herein is a method of treating a RET-associated disease or disorder

in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein.

[0013] Also provided herein is a method of treating cancer and/or inhibiting metastasis associated with a particular cancer in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein.

[0014] Also provided herein is a method of treating irritable bowel syndrome (IBS) and/or pain associated with IBS in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein.

[0015] Also provided is a method of providing supportive care to a cancer patient, including preventing or minimizing gastrointestinal disorders, such as diarrhea, associated with treatment, including chemotherapeutic treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein.

[0016] Also provided herein is a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[0017] Also provided herein is a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer and/or inhibiting metastasis associated with a particular cancer.

[0018] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of irritable bowel syndrome (IBS) or pain associated with IBS.

[0019] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use providing supportive care to a cancer patient, including preventing or minimizing gastrointestinal disorders, such as diarrhea, associated with treatment, including chemotherapeutic treatment.

[0020] Also provided herein is a compound of Formula **I** or a pharmaceutically acceptable

salt or solvate thereof for use in the inhibition of RET kinase activity.

[0021] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein, for use in the treatment of a RET-associated disease or disorder.

[0022] Also provided herein is the use of a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of cancer and/or inhibiting metastasis associated with a particular cancer.

[0023] Also provided herein is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the treatment of irritable bowel syndrome (IBS) or pain associated with IBS.

[0024] Also provided herein is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for providing supportive care to a cancer patient, including preventing or minimizing gastrointestinal disorders, such as diarrhea, associated with treatment, including chemotherapeutic treatment.

[0025] Also provided herein is a use of a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, as defined herein in the manufacture of a medicament for the inhibition of RET kinase activity.

[0026] Also provided herein is the use of a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, as defined herein, in the manufacture of a medicament for the treatment of a RET-associated disease or disorder.

[0027] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising (a) determining if the cancer is associated with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same (e.g., a RET-associated cancer); and (b) if the cancer is determined to be associated with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same (e.g., a RET-associated cancer), administering to the patient a therapeutically effective amount of a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof.

[0028] Also provided herein is a pharmaceutical combination for treating cancer (e.g., a RET-associated cancer, such as a RET-associated cancer having one or more RET inhibitor resistance mutations) in a patient in need thereof, which comprises (a) a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and

(c) optionally at least one pharmaceutically acceptable carrier, wherein the compound of Formula I or the pharmaceutically acceptable salt or solvate thereof and the additional therapeutic are formulated as separate compositions or dosages for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the cancer. Also provided herein is a pharmaceutical composition comprising such a combination. Also provided herein is the use of such a combination for the preparation of a medicament for the treatment of cancer. Also provided herein is a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer a patient in need thereof.

[0029] Also provided herein is a method for reversing or preventing acquired resistance to an anticancer drug, comprising administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, to a patient at risk for developing or having acquired resistance to an anticancer drug. In some embodiments, the patient is administered a dose of the anticancer drug (e.g., at substantially the same time as a dose of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is administered to the patient).

[0030] Also provided herein is a method of delaying and/or preventing development of cancer resistant to an anticancer drug in an individual, comprising administering to the individual an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, before, during, or after administration of an effective amount of the anticancer drug.

[0031] Also provided herein is a method of treating an individual with cancer who has an increased likelihood of developing resistance to an anticancer drug, comprising administering to the individual (a) an effective amount of a compound of Formula I before, during, or after administration of (b) an effective amount of the anticancer drug.

[0032] Also provided are methods of treating an individual with a RET-associated cancer that has one or more RET inhibitor resistance mutations that increase resistance of the cancer to a first RET inhibitor (e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, and/or one or more RET inhibitor resistance mutations listed in Tables 3 and 4), that include administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, before, during, or after administration of another anticancer drug (e.g., a second RET kinase

inhibitor).

[0033] Also provided are methods of treating an individual with a RET-associated cancer that include administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, before, during, or after administration of another anticancer drug (e.g., a first RET kinase inhibitor).

[0034] Also provided herein is a method for treating irritable bowel syndrome (IBS) in a patient in need thereof, the method comprising (a) determining if the IBS is associated with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same; and (b) if the IBS is determined to be associated with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, administering to the patient a therapeutically effective amount of a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof.

[0035] Also provided herein is a pharmaceutical combination for treating irritable bowel syndrome (IBS) in a patient in need thereof, which comprises administering (a) a compound of General Formula **I** or a pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use for the treatment of IBS, wherein the amounts of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the IBS. Also provided herein is a pharmaceutical composition comprising such a combination. Also provided herein is the use of such a combination for the preparation of a medicament for the treatment of the IBS. Also provided herein is a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of the IBS a patient in need thereof.

[0036] Also provided herein is a process for preparing a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0037] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof obtained by a process of preparing the compound as defined herein.

[0038] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other,

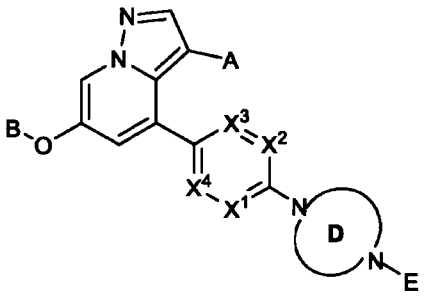
suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting.

In case of conflict, the present specification, including definitions, will control.

[0039[Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

[0040[Provided herein is a compound of the Formula **I**:



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[0041[and pharmaceutically acceptable salts and solvates thereof, wherein:

[0042[X^1, X^2, X^3 and X^4 are independently CH, CF, CCH_3 or N, wherein zero, one or two of X^1, X^2, X^3 and X^4 is N;

[0043[A is H, CN, Cl, CH_3-, CH_3CH_2-, cyclopropyl, -CH_2CN or -$CH(CN)CH_3$;

[0044[B is

[0045[(a) hydrogen,

[0046[(b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

[0047[(c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,

[0048[(d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,

[0049[(e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

[0050[(f) (R^1R^2N)C1-C6 alkyl- wherein said alkyl portion is optionally substituted with OH and wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3

fluoros);

[0051] (g) $hetAr^1C1$-C3 alkyl-, wherein $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;

[0052] (h) (C3-C6 cycloalkyl)C1-C3 alkyl-, wherein said cycloalkyl is optionally substituted with OH,

[0053] (i) $(hetCyc^a)$C1-C3 alkyl-,

[0054] (j) $hetCyc^a$-,

[0055] (k) C3-C6 cycloalkyl-, wherein said cycloalkyl is optionally substituted with OH,

[0056] (l) (C1-C4 alkyl)C(=O)O-C1-C6 alkyl-, wherein each of the C1-C4 alkyl and C1-C6 alkyl portions is optionally and independently substituted with 1-3 fluoros, or

[0057] (m) (R^1R^2N)C(=O)C1-C6 alkyl-, wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

[0058] $hetCyc^a$- is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl-, and fluoro, or wherein $hetCyc^a$ is substituted with oxo;

[0059] Ring D is (i) a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, (ii) a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, (iii) a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, or (iv) a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein each of said rings is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group;

[0060] E is

[0061] (a) hydrogen,

[0062] (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

[0063] (c) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

[0064] (d) (C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with

1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl,

[0065] (e) (hydroxyC2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros,

[0066] (f) (C1-C6 alkoxy)C(=O)-,

[0067] (g) (C3-C6 cycloalkyl)C(=O)-, wherein said cycloalkyl is optionally substituted with one or more substituents independently selected from C1-C6 alkyl, C1-C6 alkoxy, OH, and (C1-C6 alkoxy)C1-C6 alkyl-, or said cycloalkyl is substituted with a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O,

[0068] (h) Ar^1C1-C6 alkyl-,

[0069] (i) Ar^1(C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, C1-C6 alkoxy, R^mR^nN- or R^mR^nN-CH_2-, wherein each R^m and R^n is independently H or C1-C6 alkyl,

[0070] (j) $hetAr^2$C1-C6 alkyl-, wherein said alkyl portion is optionally substituted with 1-3 fluoros,

[0071] (k) $hetAr^2$(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy,

[0072] (l) $hetAr^2$C(=O)-,

[0073] (m) $hetCyc^1$C(=O)-,

[0074] (n) $hetCyc^1$C1-C6 alkyl-,

[0075] (o) $R^3R^4NC(=O)$-,

[0076] (p) $Ar^1N(R^3)C(=O)$-,

[0077] (q) $hetAr^2N(R^3)C(=O)$-,

[0078] (r) (C1-C6 alkyl)SO_2-, wherein the alkyl portion is optionally substituted with 1-3 fluoros,

[0079] (s) Ar^1SO_2-,

[0080] (t) $hetAr^2SO_2$-,

[0081] (u) N-(C1-C6 alkyl)pyridinonyl,

[0082] (v) Ar^1C(=O)-;

[0083] (w) Ar^1O-C(=O)-,

[0084] (x) (C3-C6 cycloalkyl)(C1-C6 alkyl)C(=O)-,

[0085] (y) (C3-C6 cycloalkyl)(C1-C6 alkyl)SO_2-, wherein the alkyl portion is optionally substituted with 1-3 fluoros,

[0086] (z) Ar^1(C1-C6 alkyl)SO_2-,

[0087] (aa) hetCyc^1-O-C(=O)-,

[0088] (bb) hetCyc$^1CH_2C$(=O)-,

[0089] (cc) hetAr^2, or

[0090] (dd) C3-C6 cycloalkyl;

[0091] Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H, C1-C6 alkyl, (R^pR^qN)C1-C6 alkoxy- wherein R^p and R^q are independently H or C1-C6 alkyl, and (hetAr^a)C1-C6 alkyl- wherein hetAr^a is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms, or Ar^1 is a phenyl ring fused to a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

[0092] hetAr^2 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein hetAr^2 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, OH, (C1-C6 alkoxy)C1-C6 alkoxy- and C3-C6 cycloalkyl;

[0093] hetCyc^1 is a 4-6 membered saturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N, O and S wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from C1-C6 alkoxy and halogen;

[0094] R^3 is H or C1-C6 alkyl; and

[0095] R^4 is C1-C6 alkyl.

[0096] For complex chemical names employed herein, the substituent group is named before the group to which it attaches. For example, methoxyethyl comprises an ethyl backbone with a methoxy substituent.

[0097] The term "halogen" means -F (sometimes referred to herein as "fluoro" or "fluoros"), -Cl, -Br and -I.

[0098] The terms "C1-C3 alkyl", "C1-C6 alkyl", "C2-C6 alkyl" and "C3-C6 alkyl" as used herein refer to saturated linear or branched-chain monovalent hydrocarbon radicals of one to three,

one to six, two to six, or three to six carbon atoms, respectively. Examples include, but are not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, isobutyl, sec-butyl, tert-butyl, 2-methyl-2-propyl, pentyl, neopentyl, and hexyl.

[0099] The term "C1-C6 alkoxy" as used herein refers to a saturated linear or branched-chain monovalent alkoxy radical of one to six carbon atoms, wherein the radical is on the oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

[00100] The terms "(C1-C6 alkoxy)C1-C6 alkyl-" and "(C1-C6 alkoxy)C2-C6 alkyl-" as used herein refers to saturated linear or branched-chain monovalent radicals of one to six carbon atoms or two to six carbon atoms, respectively, wherein one of the carbon atoms is substituted with a (C1-C6 alkoxy) group as defined herein. Examples include methoxymethyl (CH_3OCH_2-) and methoxyethyl ($CH_3OCH_2CH_2$-).

[00101] The terms "hydroxyC1-C6 alkyl-" and "hydroxyC2-C6 alkyl-" as used herein refer to a saturated linear or branched-chain monovalent alkyl radicals of one to six or two to six carbon atoms, respectively, wherein one of the carbon atoms is substituted with a hydroxy group.

[00102] The term "dihydroxyC3-C6 alkyl-" as used herein refers to a saturated linear or branched-chain monovalent alkyl radical of three to six carbon atoms, wherein two of the carbon atoms are substituted with a hydroxy group.

[00103] The terms "(R^1R^2N)C1-C6 alkyl-" and "(R^1R^2N)C2-C6 alkyl-" as used herein refers to a C1-C6 alkyl or C2-C6 radical, respectively, as defined herein, wherein one of the carbon atoms is substituted with a R^1R^2N- group, wherein R^1 and R^2 are as defined herein.

[00104] The term "hetAr^1C1-C6 alkyl-" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with a hetAr^1 group, wherein hetAr^1 is as defined herein.

[00105] The term "C3-C6 cycloalkyl" as used herein refers to cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[00106] The terms "(C3-C6 cycloalkyl)C1-C3 alkyl-" and "(C3-C6 cycloalkyl)C1-C6 alkyl-" as used herein refers to a C1-C3 alkyl radical or C1-C6 radical, respectively, as defined herein, wherein one of the carbon atoms is substituted with a C3-C6 cycloalkyl ring as defined herein.

[00107] The term "C3-C6 cycloalkylidene ring" as used herein refers to a divalent carbocyclic ring of three to six carbons. The suffix "ylidine" refers to bivalent radical derived from a saturated hydrocarbon by removal of two hydrogen atoms from the same carbon atom

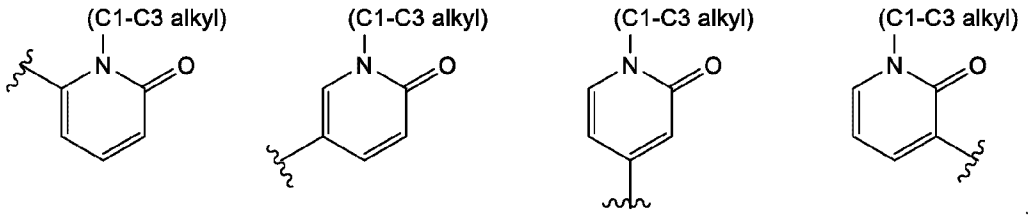
[00108] The term "(hetCyc^a)C1-C3 alkyl-" as used herein refers to a C1-C3 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with a hetCyc^a group, wherein hetCyc^a is as defined herein.

[00109] The term "Ar^{1}C1-C6 alkyl-" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with an Ar^1 group, wherein Ar^1 is as defined herein.

[00110] The terms "hetAr^{2}C1-C6 alkyl-" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with an hetAr^2 group, wherein hetAr^2 is as defined herein.

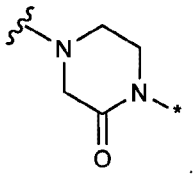
[00111] The term "hetCyc^{1}C1-C6 alkyl-" as used herein refers to a C1-C6 alkyl radical as defined herein, wherein one of the carbon atoms is substituted with a hetCyc^1 group, wherein hetCyc^1 is as defined herein.

[00112] The term "N-(C1-C6 alkyl)pyridinonyl" as used herein refers to a pyridin-2(1H)-one ring wherein the ring nitrogen atom is substituted with a C1-C6 alkyl substituent, and wherein the radical may be on any of the ring carbon atoms other than the carbon bearing the oxo group. Examples include the structures:



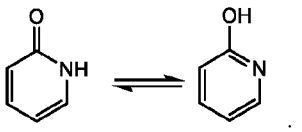
[00113] The term "heterospirocyclic" as used herein refers to a group having two rings joined by a spirocyclic linkage through a carbon atom, wherein each ring has 4 to 6 ring atoms (with one ring carbon atom being common to both rings), and wherein two of the ring atoms are nitrogen atoms.

[00114] The term "oxo" or "oxo group" as used herein means an oxygen that is double bonded to a carbon atom, i.e., =O. For example, in one embodiment when referring to Ring D, a saturated 6 membered heterocyclic ring having two ring nitrogen atoms may be, for example, a piperazinyl ring that is substituted with an oxo group (e.g., a piperazinonyl ring), which may be represented by the structure:



[00115] The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

[00116] The term "tautomer" as used herein refers to compounds whose structures differ markedly in arrangement of atoms, but which exist in easy and rapid equilibrium, and it is to be understood that compounds provided herein may be depicted as different tautomers, and when compounds have tautomeric forms, all tautomeric forms are intended to be within the scope of the invention, and the naming of the compounds does not exclude any tautomer. Exemplary tautomerizations include, but are not limited to, keto-to-enol; amide-to-imide; lactam-to-lactim; enamine-to-imine; and enamine-to-(a different) enamine tautomerizations. A specific example of phenol-keto tautomerization is the interconversion of pyridin-2-ol and pyridin-2(1H)-one tautomers, for example:



[00117] It will be appreciated that certain compounds provided herein may contain one or more centers of asymmetry and may therefore be prepared and isolated in a mixture of isomers such as a racemic mixture, or in an enantiomerically pure form.

[00118] In certain embodiments of Formula **I**, X^1, X^2, X^3 and X^4 are independently CH, CF or CCH_3. In certain embodiments, each of X^1, X^2, X^3 and X^4 is CH.

[00119] In certain embodiments of Formula **I**, X^1, X^2, X^3 and X^4 are independently CH, CF or CCH_3 or N, wherein one of X^1, X^2, X^3 and X^4 is N and the remainder are independently CH, CF or CCH_3. In certain embodiments of Formula **I**, X^1 is N, and X^2, X^3 and X^4 are independently CH or CF. In certain embodiments, X^1 is N, and X^2, X^3 and X^4 are CH. In certain embodiments,

X^1 is N, X^2 is CF, and X^3 and X^4 are CH.

[00120] In certain embodiments of Formula **I**, X^1, X^2, X^3 and X^4 are independently CH, CF or CCH_3 or N, wherein two of X^1, X^2, X^3 and X^4 are N. In certain embodiments of Formula **I**, X^1 and X^3 are N and X^2 and X^4 are independently CH, CF or CCH_3. In one embodiment, X^1 and X^3 are N and X^2 and X^4 are CH. In certain embodiments of Formula **I**, X^1 and X^2 are N and X^1 and X^4 are independently CH or CF. In certain embodiments of Formula **I**, X^1 and X^2 are N and X^1 and X^4 are CH.

[00121] In certain embodiments of Formula **I**, A is H.

[00122] In certain embodiments of Formula **I**, A is Cl.

[00123] In certain embodiments of Formula **I**, A is CN.

[00124] In certain embodiments of Formula **I**, A is CH_3-.

[00125] In certain embodiments of Formula **I**, A is CH_3CH_2-.

[00126] In certain embodiments of Formula **I**, A is cyclopropyl.

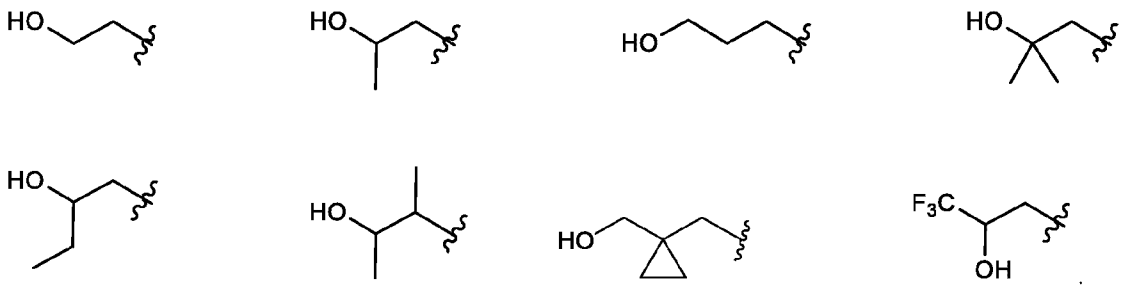
[00127] In certain embodiments of Formula **I**, A is -CH_2CN.

[00128] In certain embodiments of Formula **I**, A is -$CH(CN)CH_3$.

[00129] In certain embodiments of Formula **I**, B is hydrogen.

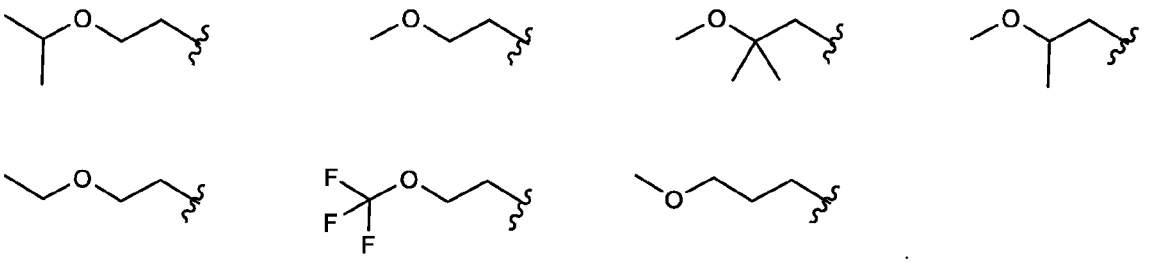
[00130] In certain embodiments of Formula **I**, B is C1-C6 alkyl optionally substituted with 1-3 fluoros. Non-limiting examples include methyl, ethyl, propyl, isopropyl, isobutyl, 2-methylbutyl, 2-ethylbutyl, 2,2-dimethylpropyl, difluoromethyl, 2,2-difluoroethyl, and 2,2,2-trifluoroethyl.

[00131] In certain embodiments of Formula **I**, B is hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring. In certain embodiments of Formula **I**, B is hydroxyC2-C6 alkyl-, wherein the alkyl portion is unsubstituted. Non-limiting examples include the structures:

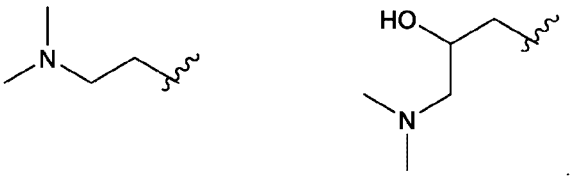


[00132] In certain embodiments of Formula **I**, B is dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In certain embodiments of Formula **I**, B is dihydroxyC3-C6 alkyl-. A non-limiting example includes 2,3-dihydroxypropyl.

[00133] In certain embodiments of Formula **I**, B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In certain embodiments of Formula **I**, B is (C1-C6 alkoxy)C2-C6 alkyl- optionally substituted with 1-3 fluoros. Non-limiting examples include the structures:

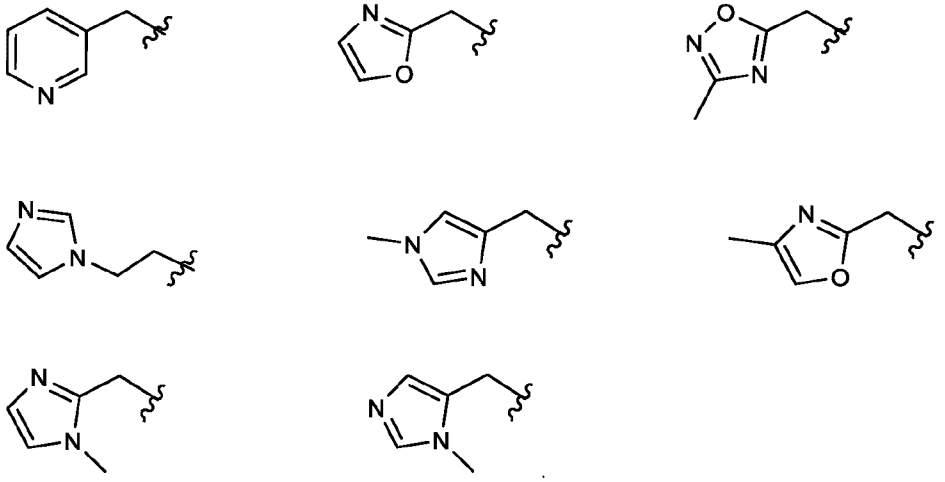


[00134] In certain embodiments of Formula **I**, B is (R^1R^2N)C1-C6 alkyl-,wherein said alkyl portion is optionally substituted with OH and R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros). In certain embodiments of Formula **I**, B is (R^1R^2N)C1-C6 alkyl-, wherein said alkyl portion is optionally substituted with OH and R^1 and R^2 are independently H or C2-C6 alkyl (optionally substituted with 1-3 fluoros). In certain embodiments of Formula **I**, B is (R^1R^2N)C1-C6 alkyl- wherein said alkyl portion is optionally substituted with OH and R^1 and R^2 are independently selected from C1-C6 alkyl substituents. Non-limiting examples when B is (R^1R^2N)C1-C6 alkyl- include the structures

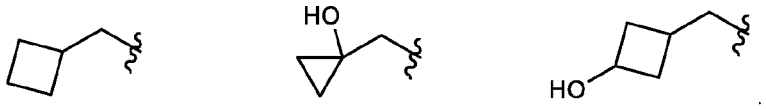


[00135] In certain embodiments of Formula **I**, B is $hetAr^1$C1-C3 alkyl-, wherein $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents. In certain embodiments, $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms

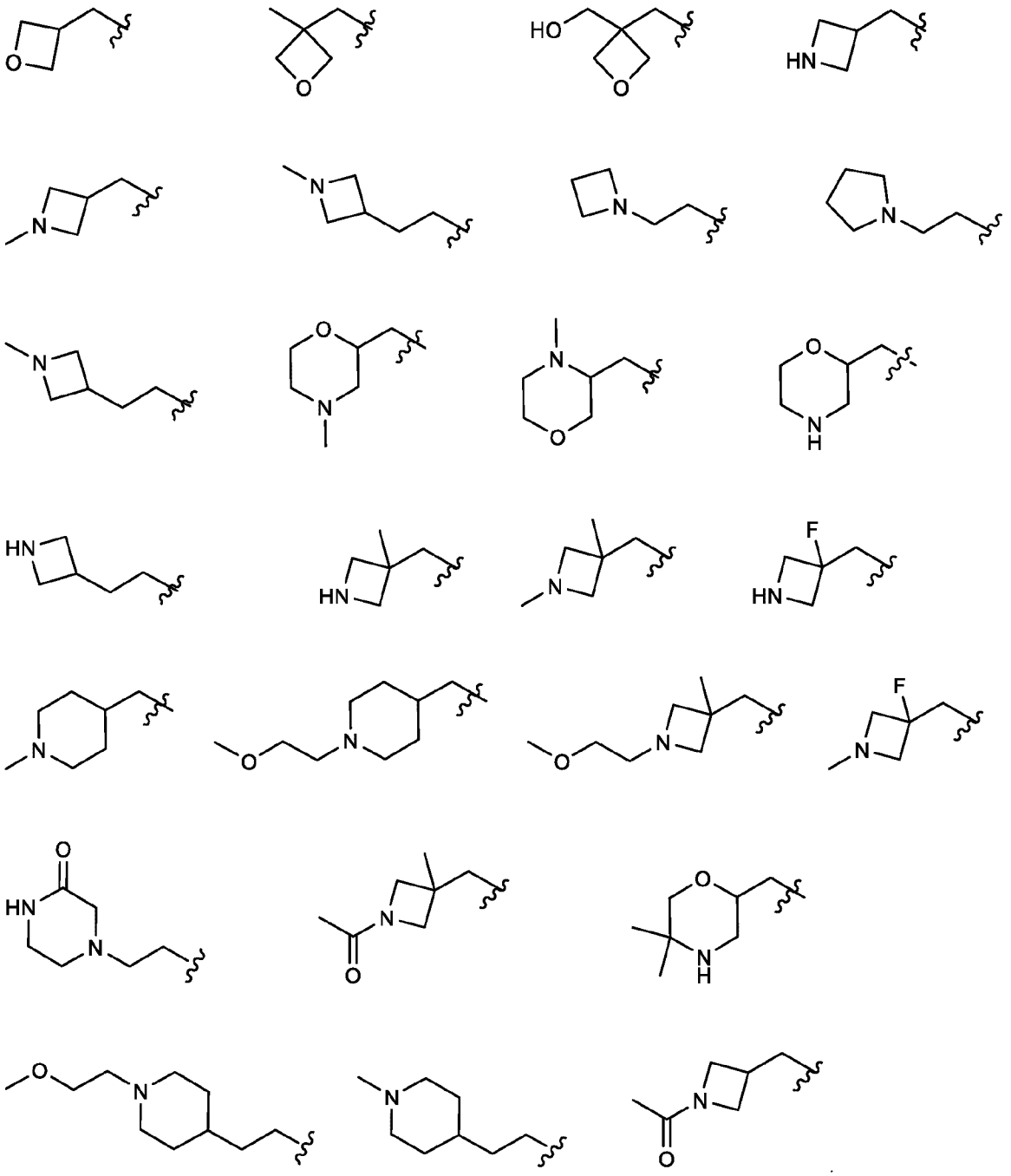
independently selected from N and O and is optionally substituted with C1-C6 alkyl. Non-limiting examples of hetAr^{1}C1-C3 alkyl- include the structures:



[00136] In certain embodiments of Formula **I**, B is (C3-C6 cycloalkyl)C1-C3 alkyl- wherein said cycloalkyl is optionally substituted with OH. Non-limiting examples include the structures:

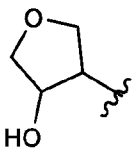
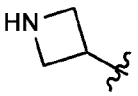
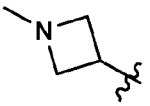
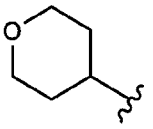
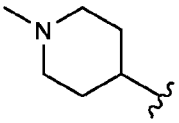


[00137] In certain embodiments of Formula **I**, B is (hetCyc^a)C1-C3 alkyl-, wherein hetCyc^a is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl- and fluoro, or wherein hetCyc^a is substituted with oxo. Non-limiting examples include the structures:

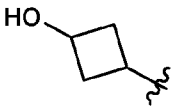


[00138] In certain embodiments of Formula **I**, B is hetCyc[a], wherein hetCyc[a] is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6

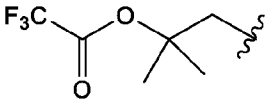
alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl- and fluoro, or wherein hetCyc[a] is substituted with oxo. In certain embodiments, hetCyc[a] is optionally substituted with OH or C1-C6 alkyl (optionally substituted with 1-3 fluoros). Non-limiting examples include the structures:

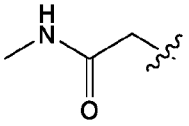
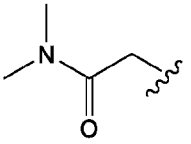
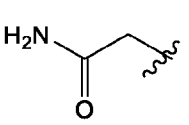
[00139] In certain embodiments of Formula **I**, B is C3-C6 cycloalkyl-, wherein said cycloalkyl is optionally substituted with OH. A non-limiting example is the structure:



[00140] In certain embodiments of Formula **I**, B is (C1-C4 alkyl)C(=O)O-C1-C6 alkyl- optionally substituted with 1-3 fluoros. A non-limiting example is the structure:



[00141] In certain embodiments of Formula **I**, B is (R^1R^2N)C(=O)C1-C6 alkyl- wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros). Non-limiting examples include the structures:

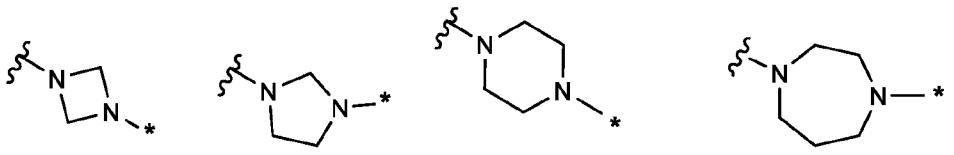




[00142] In one embodiment of Formula **I**, Ring D is a (i) saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, (ii) a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, (iii) a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, or (iv) a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein each of said rings is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group.

[00143] As used herein, the phrase "having two ring nitrogen atoms" when referring to Ring D means that the two ring nitrogen atoms of Ring D are the two ring nitrogen atoms shown in Formula **I,** wherein one of the ring nitrogen atoms is bonded the ring comprising X^1, X^2, X^3 and X^4, and the other ring nitrogen atom is bonded to the E group.

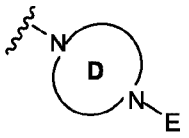
[00144] In one embodiment, Ring D is a (i) saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, (ii) a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, (iii) a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, or (iv) a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein each of said rings is unsubstituted.

[00145] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. As used herein, the phrase "having two ring nitrogen atoms" when Ring D is a saturated monocyclic 4-7 membered heterocyclic ring means that said ring nitrogen atoms are the two nitrogen atoms shown in Ring D of Formula **I**, that is, Ring D may be represented by the structures:

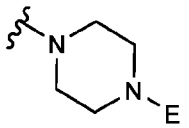


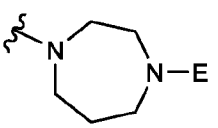
[00146] wherein the wavy line indicates the point of attachment to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to the E group, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment, Ring D is an unsubstituted saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms wherein said ring is substituted with oxo. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms wherein said ring is substituted with a C3-C6 cycloalkylidene ring. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms wherein said ring is substituted with a C3-C6 cyclopropylidine ring. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms wherein said ring is substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms wherein said ring is substituted with C1-C3 alkyl which is optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 7 membered heterocyclic ring having two ring nitrogen atoms, wherein said ring is unsubstituted.

[00147] In one embodiment when Ring D is a saturated 6-7 membered heterocyclic ring having two ring nitrogen atoms, Ring D and E portion of Formula **I**, that is,



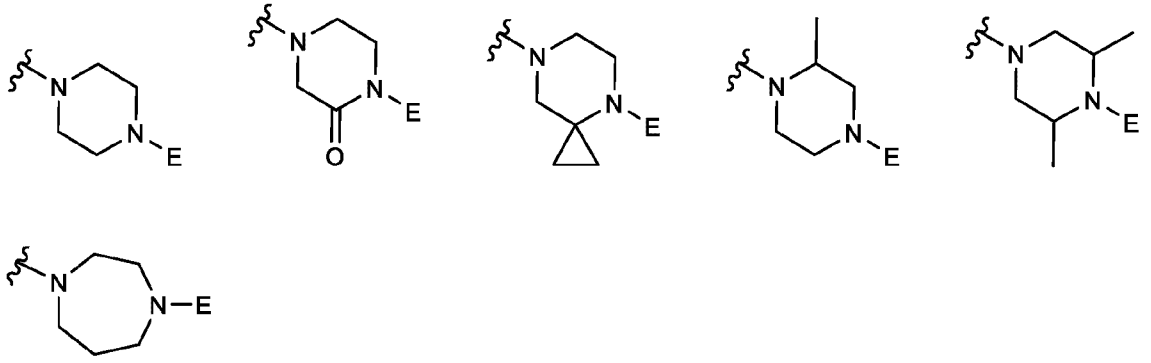
[00148] may be represented by the structures:





[00149] wherein the wavy line indicates the point of attachment to the ring comprising X^1, X^2, X^3 and X^4, wherein Ring D is optionally substituted with (a) one to four groups independently

selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is substituted with oxo. In one embodiment, Ring D is substituted with a C3-C6 cyclopropylidine ring. In one embodiment, Ring D is substituted with oxo. In one embodiment, Ring D is substituted with one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms wherein said ring is substituted with one to four C1-C3 alkyl groups which are optionally substituted with 1-3 fluoros. In one embodiment, Ring D is unsubstituted, or ring D is substituted with one to four independently selected C1-C3 alkyl groups (each of which is optionally substituted with 1- fluoros), or Ring D is substituted with a C3-C6 cyclopropylidine ring, or Ring D is substituted with oxo. In one embodiment, Ring D is a saturated 7 membered heterocyclic ring having two ring nitrogen atoms, wherein said ring is unsubstituted. Examples of saturated 6 and 7 membered heterocyclic D rings include the structures:



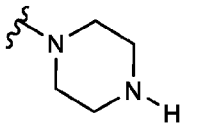
[00150] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is as defined for Formula **I**. In one embodiment, Ring D is a saturated 6-7 membered heterocyclic ring having two ring nitrogen atoms. In one

embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is substituted with oxo. In one embodiment, Ring D is substituted with a cyclopropylidine ring. In one embodiment, Ring D is substituted with one or two C1-C3 alkyl groups, for example one or two methyl groups.

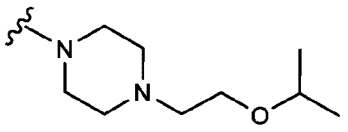
[00151] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (a) hydrogen, (c) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, (d) (C1-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros, (e) (hydroxy C2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros, (f) (C1-C6 alkoxy)C(=O)-, (g) (C3-C6 cycloalkyl)C(=O)- wherein said cycloalkyl is optionally substituted with (C1-C6 alkoxy)C1-C6 alkyl- or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O, (h) Ar^1C1-C6 alkyl-, (i) Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy, (j) $hetAr^2$C1-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros, (k) $hetAr^2$(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy, (l) $hetAr^2$C(=O)-, (m) $hetCyc^1$C(=O)-, (n) $hetCyc^1$C1-C6 alkyl- (o) R^3R^4NC(=O)-, or (cc) $hetAr^2$, wherein Ar^1, $hetAr^2$, $hetCyc^1$, R^3 and R^4 are as defined for Formula I. In one embodiment, Ring D is a saturated 6-7 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is a saturated 7 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D a saturated 6-7 membered heterocyclic ring, wherein Ring D is unsubstituted. In one embodiment, Ring D is a saturated 6 membered ring. In one embodiment, Ring D is substituted with oxo. In one embodiment, Ring D is substituted with a cyclopropylidine ring. In one embodiment, Ring D is substituted with one or two C1-C3 alkyl groups, for example one or two methyl groups.

[00152] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6

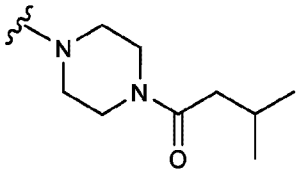
cycloalkylidene ring, or (c) an oxo group, and E is hydrogen. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. A non-limiting example is the structure:



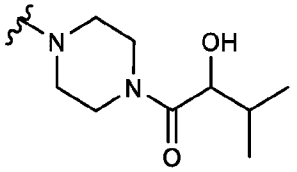
[00153] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. A non-limiting example is the structure:



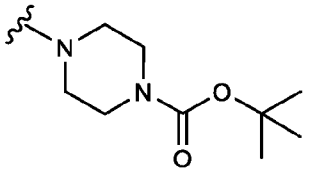
[00154] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. A non-limiting example is the structure:



[00155] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (hydroxy C2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. A non-limiting example is the structure:

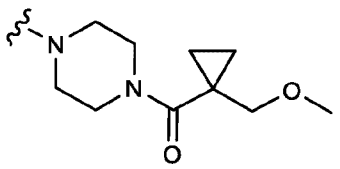


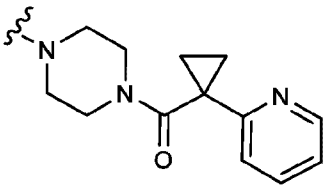
[00156] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkoxy)C(=O)-. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. A non-limiting example is the structure:



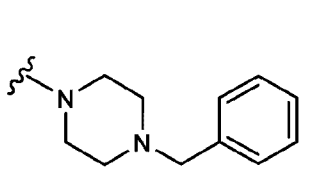
[00157] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C3-C6 cycloalkyl)C(=O)- wherein said cycloalkyl is optionally substituted with (C1-C6 alkoxy)C1-C6 alkyl- or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O, for example pyridinyl. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. Non-limiting examples include

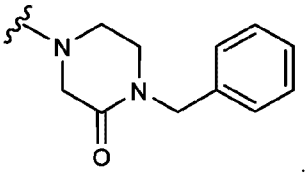
the structures:





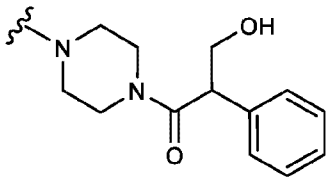
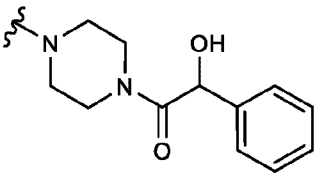
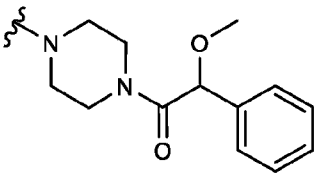
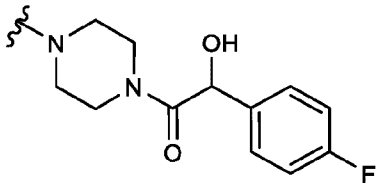
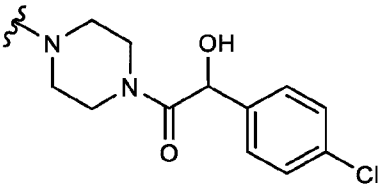
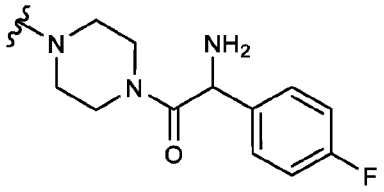
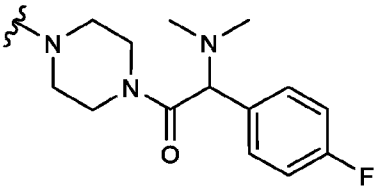
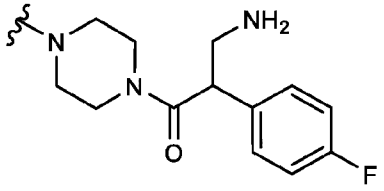
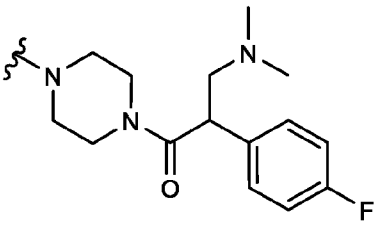
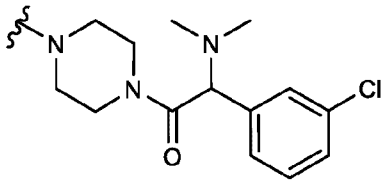
[00158] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is Ar^1C1-C6 alkyl-, wherein Ar^1 is as defined for Formula **I**. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is substituted with oxo. In one embodiment, Ar^1 is unsubstituted. Non-limiting examples include the structures:

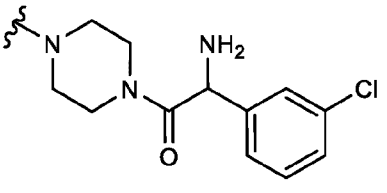


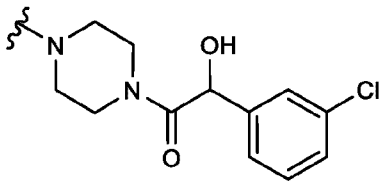


[00159] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl, C1-C6 alkoxy, R^mR^nN- or R^mR^nN-CH_2-, wherein each R^m and R^n is independently H or C1-C6 alkyl, and Ar^1 is as defined for Formula **I**. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. In one embodiment, Ar^1 is unsubstituted or substituted with one or more halogens. Non-limiting examples include the

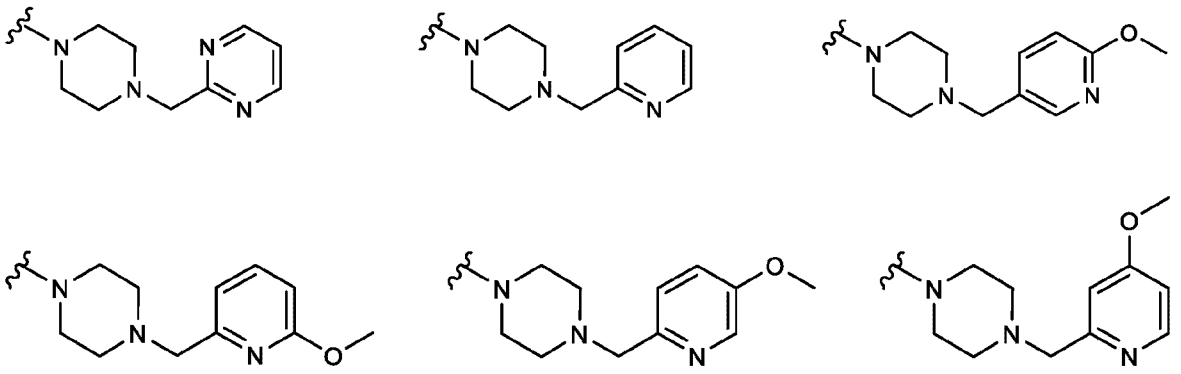
structures:

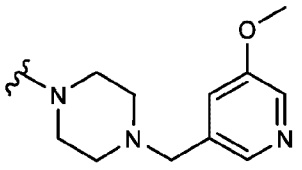
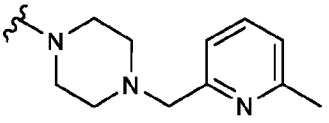
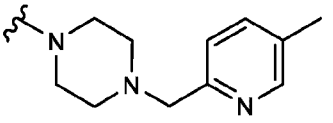
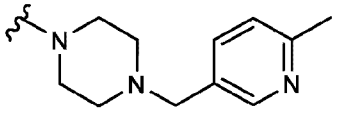
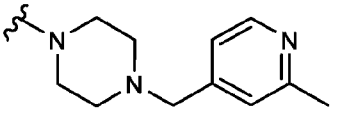
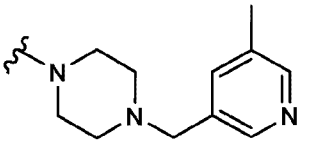
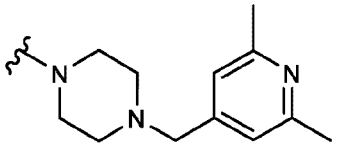
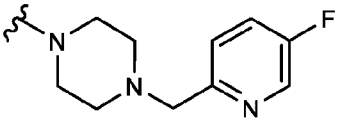
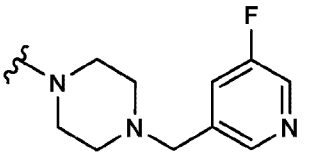
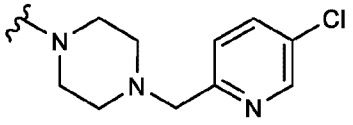
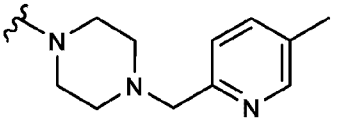
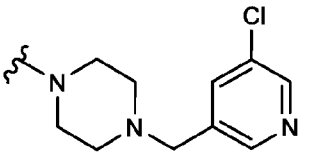
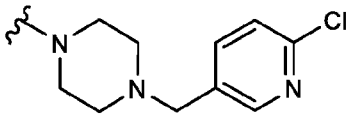
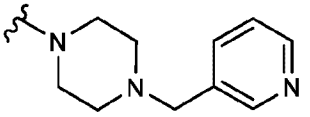
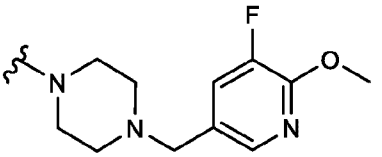
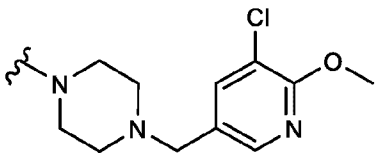
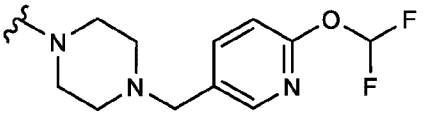
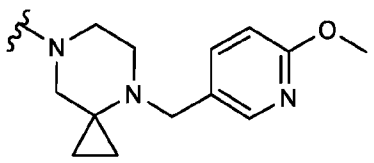
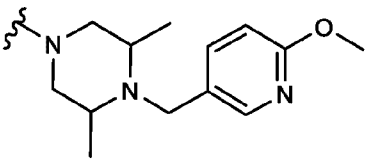











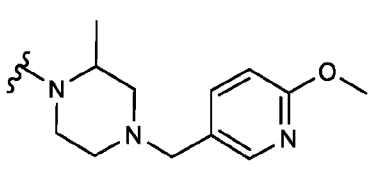
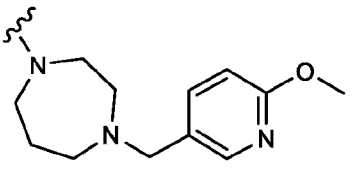
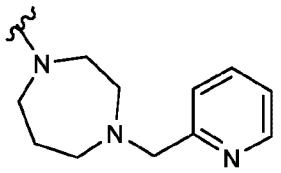
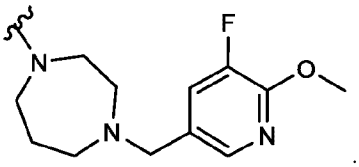




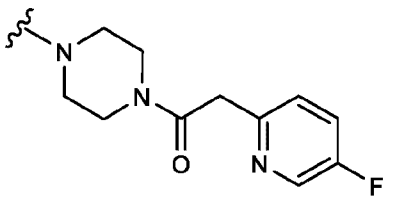
[00160] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2$C1-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros, and wherein $hetAr^2$ is as defined for Formula **I**. In one embodiment, Ring D is a saturated 6-7 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is substituted with a cyclopropylidine ring. In one embodiment, $hetAr^2$ is a 5-6 membered heterocyclic ring having 1-2 ring nitrogen atoms. In one embodiment, $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, $hetAr^2$ is a 6 membered heteroaryl ring having 1-2 ring nitrogen atoms and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). Non-limiting examples include the structures:



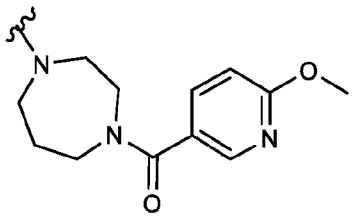





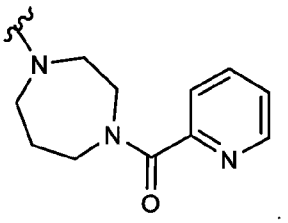
[00161] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2$(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl or C1-C6 alkoxy, and wherein $hetAr^2$ is as defined for Formula **I**. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. In one embodiment, the alkyl portion of $hetAr^2$(C1-C6 alkyl)C(=O)- is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heterocyclic ring having 1-2 ring nitrogen atoms. In one embodiment, $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, $hetAr^2$ is a 6 membered ring having 1-2 ring nitrogen atoms and is optionally substituted with one or more halogens. A non-limiting example includes the structure:



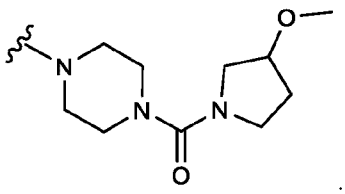
[00162] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having

two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2C(=O)$- wherein $hetAr^2$ is as defined for Formula **I**. In one embodiment, Ring D is a saturated 6-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is unsubstituted. In one embodiment, Ring D is a saturated 7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heterocyclic ring having 1-2 ring nitrogen atoms. In one embodiment, $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, $hetAr^2$ is a 6 membered ring having 1-2 ring nitrogen atoms and is optionally substituted with C1-C6 alkoxy. Non-limiting examples includes the structures:

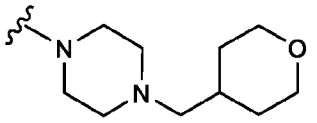




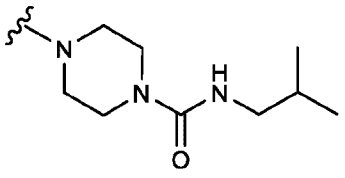
[00163] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetCyc^1C(=O)$- wherein $hetCyc^1$ is as defined for Formula **I**. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. In one embodiment $hetCyc^1$ is a 4-6 membered saturated heterocyclic ring having a ring nitrogen atom, wherein said heterocyclic ring is optionally substituted with one or more independently selected C1-C6 alkoxy substituents. A non-limiting example includes the structure:



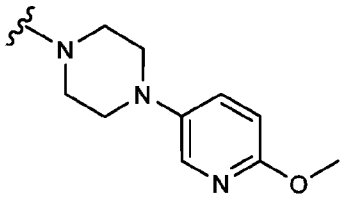
[00164] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is hetCyc^{1}C1-C6 alkyl- wherein hetCyc^1 is as defined for Formula **I**. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. In one embodiment hetCyc^1 is a 4-6 membered saturated heterocyclic ring having a ring oxygen atom. In one embodiment, hetCyc^1 is unsubstituted. A non-limiting example includes the structure:



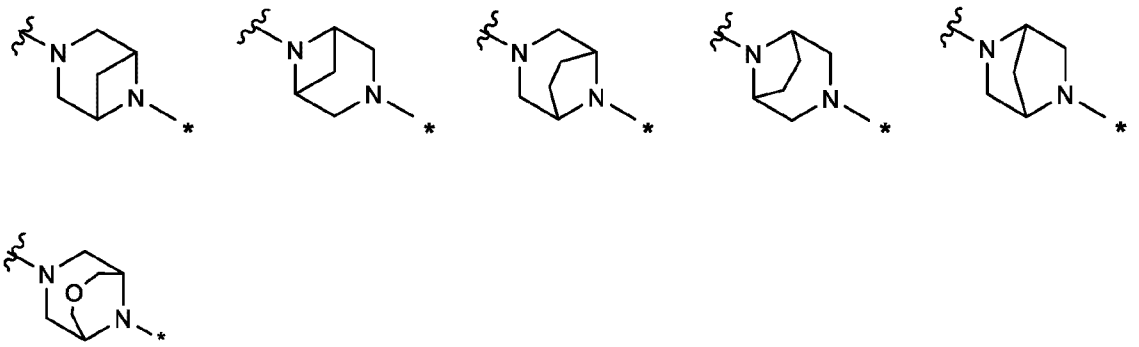
[00165] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $R^3R^4NC(=O)$- wherein R^3 and R^4 are as defined for Formula **I**. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms. In one embodiment, said Ring D is unsubstituted. A non-limiting example includes the structure:



[00166] In one embodiment, Ring D is a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2$, wherein $hetAr^2$ is as defined for Formula I. In one embodiment, Ring D is a saturated 6 membered heterocyclic ring having two ring nitrogen atoms, wherein Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heterocyclic ring having 1-2 ring nitrogen atoms. In one embodiment, $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, $hetAr^2$ is a 6 membered ring having 1-2 ring nitrogen atoms and is optionally substituted with C1-C6 alkoxy. A non-limiting example includes the structure:

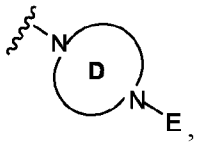


[00167] In one embodiment of Formula **I**, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. As used herein, the phrase "having two ring nitrogen atoms" when Ring D is a saturated 7-8 membered bridged heterocyclic ring means that said ring nitrogen atoms are the two nitrogen atoms shown in Ring D of Formula **I**, wherein one of the ring nitrogen atoms is bonded the ring comprising X^1, X^2, X^3 and X^4, and the other ring nitrogen atom is bonded to the E group as shown in Formula **I**. Non-limiting examples when Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen include the following structures:

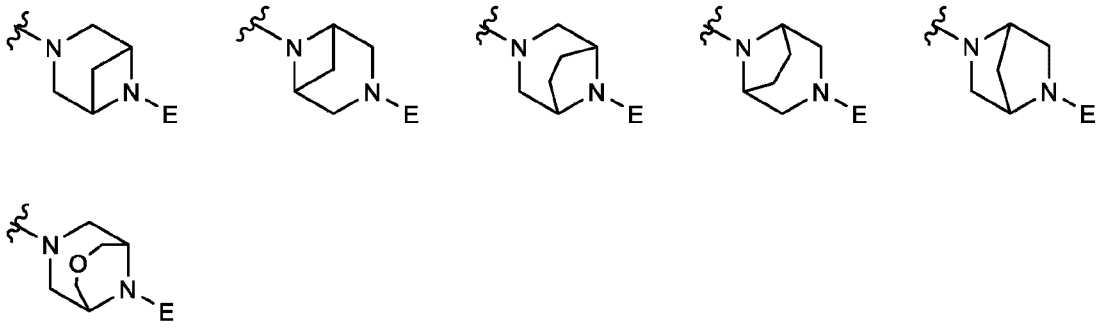


[00168] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment, Ring D is unsubstituted.

[00169] In one embodiment when Ring D is a saturated 7-9 membered bridged heterocyclic ring having 2-3 ring heteroatoms independently selected from N and O, Ring D and E portion of Formula **I**, that is



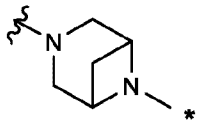
[00170] may be represented by the non-limiting structures:



[00171] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring

D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment, Ring D is unsubstituted.

[00172] In one embodiment, Ring D is a saturated 7 membered bridged heterocyclic ring having two ring nitrogen atoms represented by the structure:

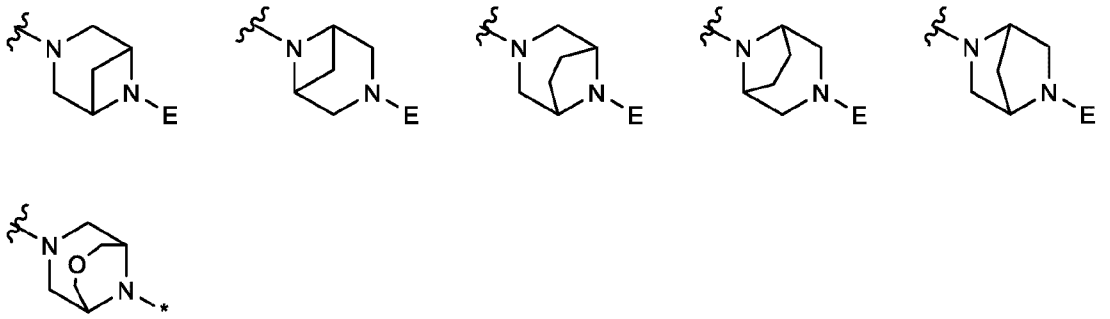


[00173] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment, Ring D is unsubstituted.

[00174] In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is as defined for Formula **I**. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted.

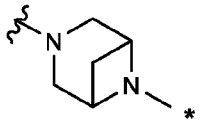
[00175] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is selected from the group consisting of (a) hydrogen, (b) C1-C6 alkyl, (c) (C1-C6 alkoxy)C1-C6 alkyl-, (d) (C1-C6 alkyl)C(=O)-, (e) (hydroxyC2-C6 alkyl)C(=O)-, (f) (C1-C6 alkoxy)C(=O)-, (g) (C3-C6 cycloalkyl)C(=O)-, (h)

Ar^1C1-C6 alkyl-, (i) Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl or C1-C6 alkoxy, (j) $hetAr^2$C1-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros, (k) $hetAr^2$(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy, (l) $hetAr^2$C(=O)-, (m) $hetCyc^1$C(=O)-, (o) R^3R^4NC(=O)-, (p) Ar^1R^3NC(=O)-, (q) $hetAr^2$N(R^3)C(=O)-, (r) (C1-C6 alkyl)SO_2-, (t) $hetAr^2SO_2$-. (u) N-(C1-C6 alkyl)pyridinonyl, (v) Ar^1C(=O)-, (w) Ar^1O-C(=O)-, (x) (C3-C6 cycloalkyl)CH_2C(=O)-, (y) (C3-C6 cycloalkyl)(C1-C6 alkyl)SO_2-, (z) Ar^1(C1-C6 alkyl)SO_2-, (aa) $hetCyc^1$-O-C(=O)-, (bb) $hetCyc^1$-CH_2-C(=O)-, and (cc) $hetAr^2$, wherein Ar^1, $hetAr^2$, R^3 and $hetCyc^1$ are as defined for Formula I. In one embodiment, Ring D is selected from the structures



[00176] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E.

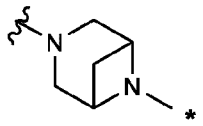
[00177] In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms represented by the structure:



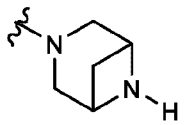
[00178] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, and E is selected from the group consisting of (a) hydrogen, (b) C1-C6 alkyl, (c) (C1-C6 alkoxy)C1-C6 alkyl-, (d) (C1-C6 alkyl)C(=O)-, (e) (hydroxyC2-C6 alkyl)C(=O)-, (f) (C1-C6 alkoxy)C(=O)-, (g) (C3-C6 cycloalkyl)C(=O)-, (h) Ar^1C1-C6 alkyl-, (i) Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl or C1-C6 alkoxy, (j) $hetAr^2$C1-C6

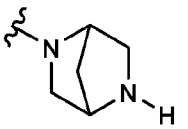
alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros, (k) $hetAr^2$(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy, (l) $hetAr^2C(=O)$-, (m) $hetCyc^1C(=O)$-, (o) $R^3R^4NC(=O)$-, (p) $Ar^1N(R^3)C(=O)$-, (q) $hetAr^2N(R^3)C(=O)$-, (r) (C1-C6 alkyl)SO_2-, (t) $hetAr^2SO_2$-, (u) N-(C1-C6 alkyl)pyridinonyl, (v) $Ar^1C(=O)$-, (w) Ar^1O-C(=O)-, (x) (C3-C6 cycloalkyl)$CH_2C(=O)$-, (y) (C3-C6 cycloalkyl)(C1-C6 alkyl)SO_2-, (z) Ar^1(C1-C6 alkyl)SO_2-, (aa) $hetCyc^1$-O-C(=O)-, (bb) $hetCyc^1$-CH_2-C(=O)-, and (cc) $hetAr^2$, wherein Ar^1, $hetAr^2$, R^3 and $hetCyc^1$ are as defined for Formula I. In one embodiment, said Ring D is unsubstituted.

[00179] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is H. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



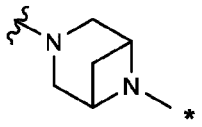
[00180] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:



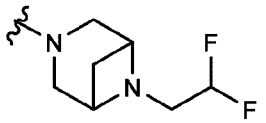


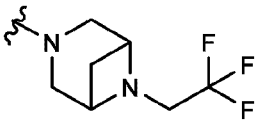
[00181] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6

cycloalkylidene ring, or (c) an oxo group, and E is C1-C6 alkyl optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

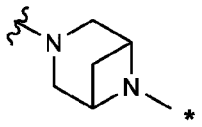


[00182] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

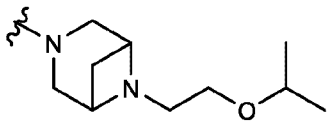




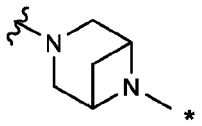
[00183] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



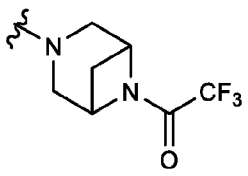
[00184] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example includes the structure:

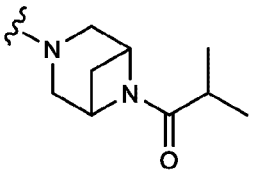


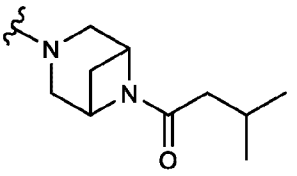
[00185] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

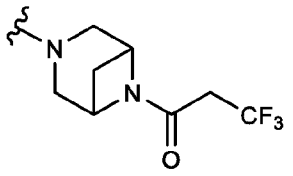


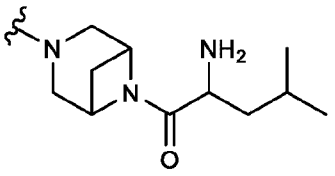
[00186] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

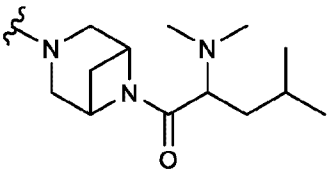


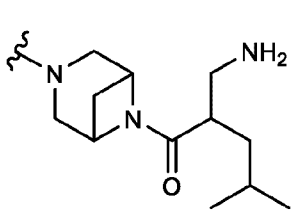
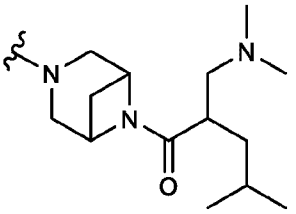




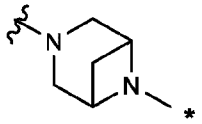




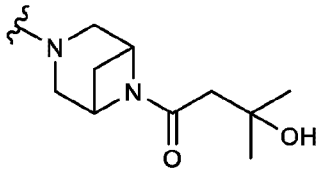


[00187] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (hydroxyC2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

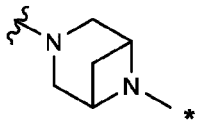
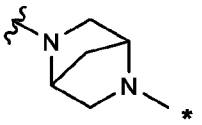


[00188] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example includes the structure:

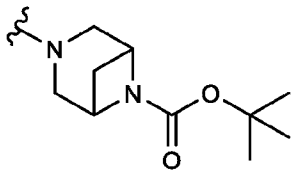
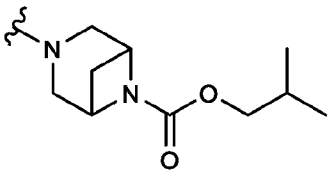
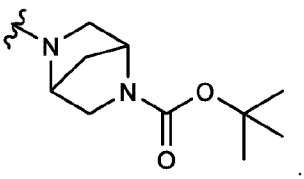


[00189] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b a C3-C6

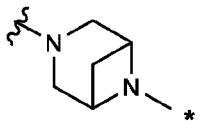
cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkoxy)C(=O)-. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structures:

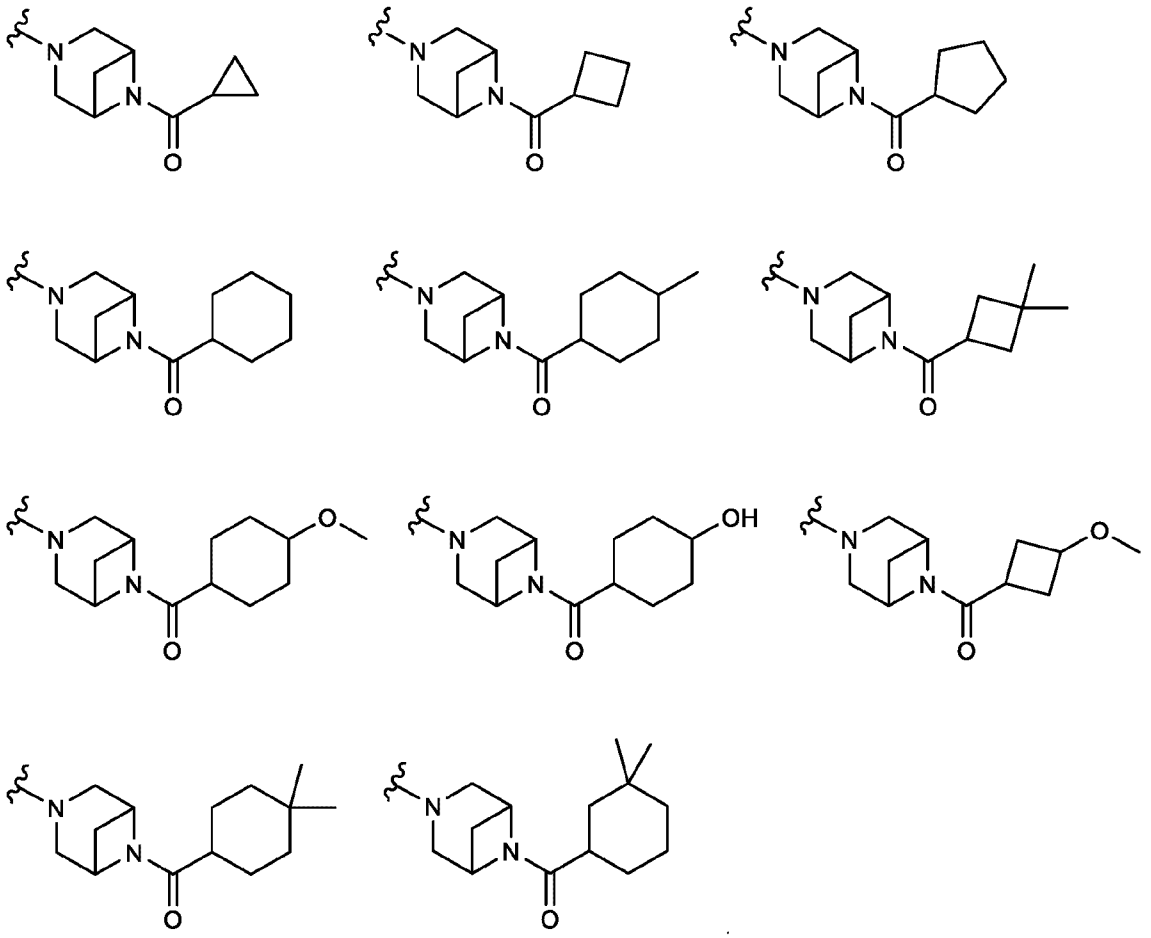
[00190] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

[00191] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is C3-C6 cycloalkyl)C(=O)- wherein said cycloalkyl is optionally substituted with one or more substituents independently selected from C1-C6 alkyl, C1-C6 alkoxy, OH, and (C1-C6 alkoxy)C1-C6 alkyl-, or said cycloalkyl is substituted with a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O. In one embodiment, E is C3-C6 cycloalkyl)C(=O)- wherein said cycloalkyl is optionally substituted with one or more substituents independently selected from C1-C6 alkyl, C1-C6 alkoxy, OH, and (C1-C6 alkoxy)C1-C6 alkyl-. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

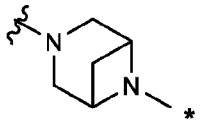


[00192] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

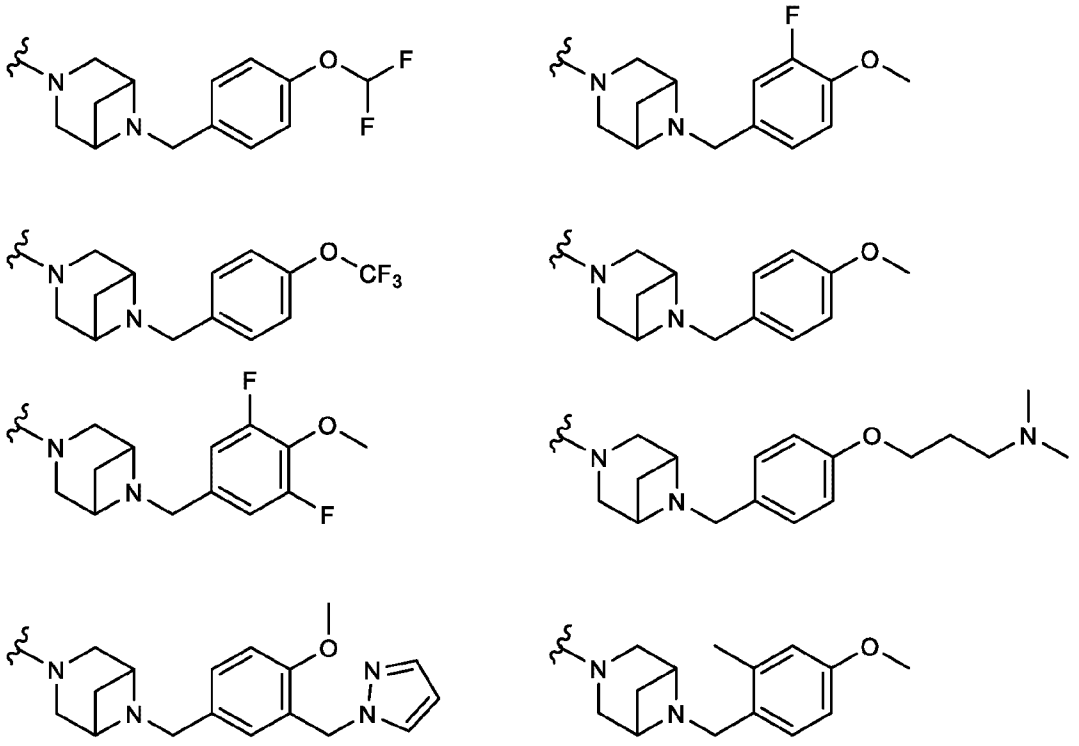


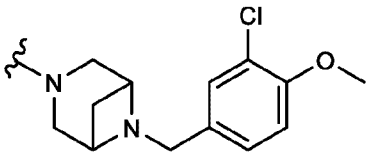
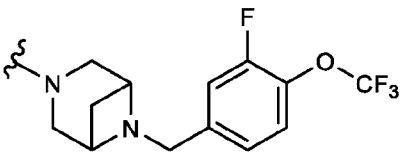
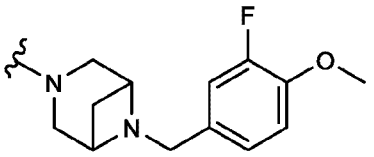
[00193] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3

fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is Ar^1C1-C6 alkyl-, wherein Ar^1 is as defined for Formula I. In one embodiment, E is Ar^1C1-C6 alkyl- wherein Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (R^pR^qN)C1-C6 alkoxy- wherein R^p and R^q are independently H or C1-C6 alkyl, and (hetAr^a)C1-C6 alkyl- wherein hetAr^a is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

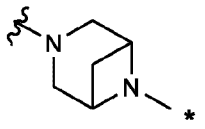


[00194] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Nonlimiting examples include the structures:

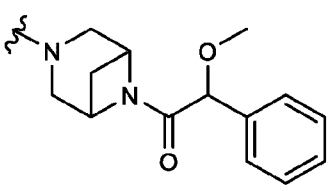
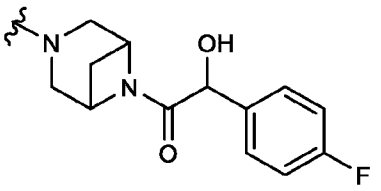
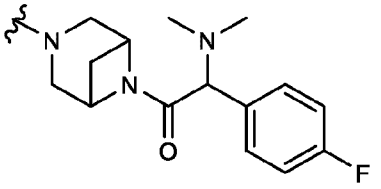
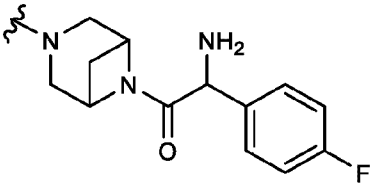
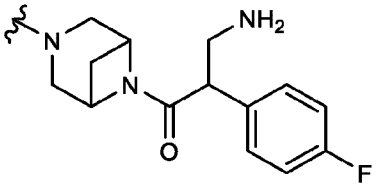
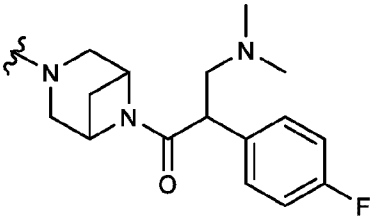


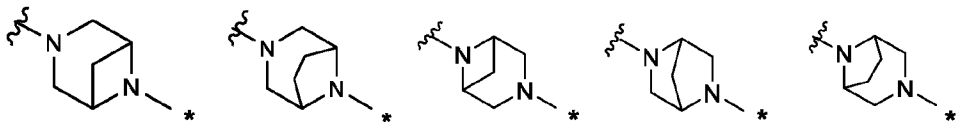
[00195] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl, C1-C6 alkoxy, R^mR^nN- or R^mR^nN-CH_2-, wherein each R^m and R^n is independently H or C1-C6 alkyl, and Ar^1 is as defined for Formula **I**. In one embodiment, Ar^1 is phenyl which is unsubstituted or substituted with one or more halogens. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



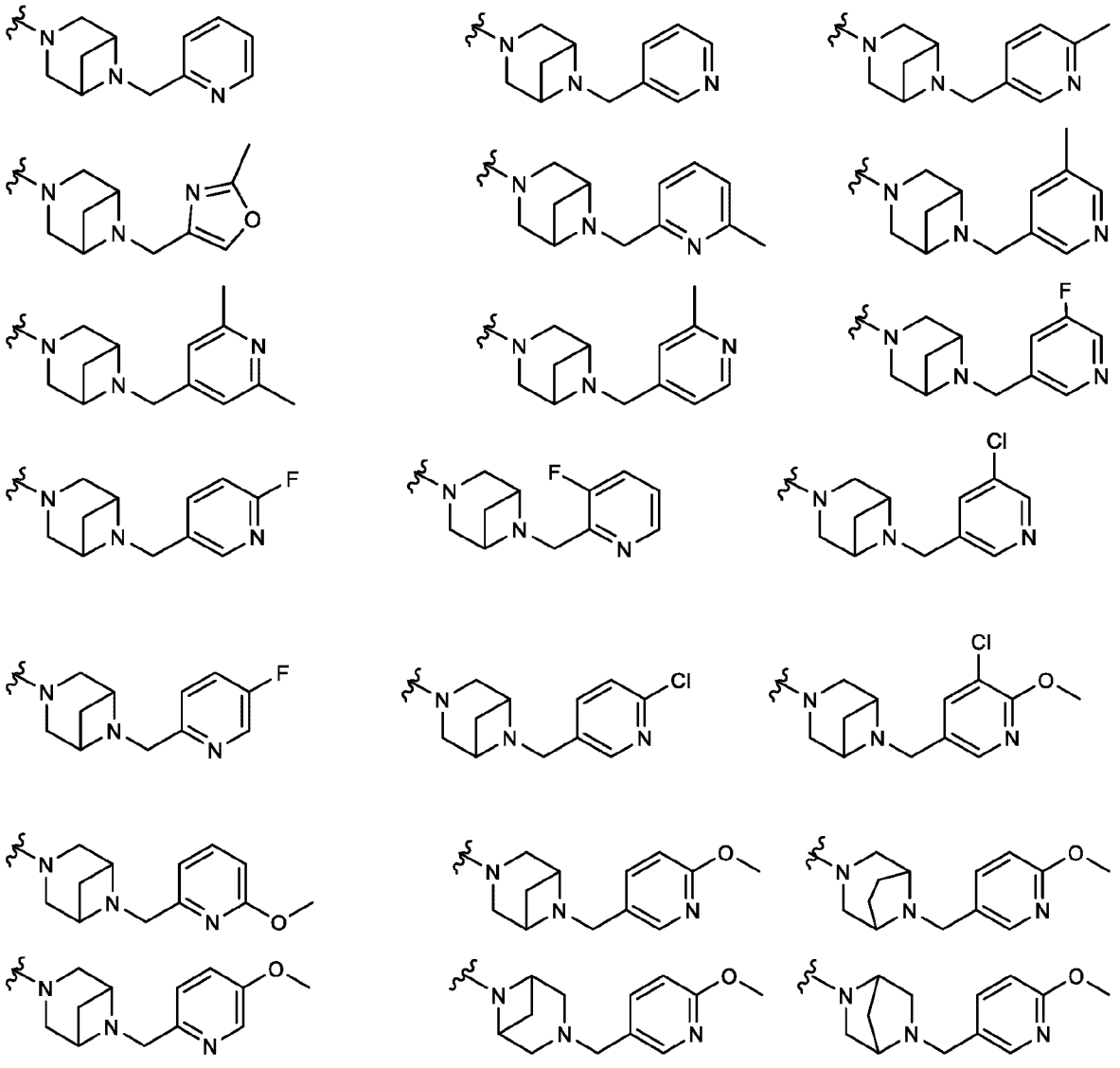
[00196] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

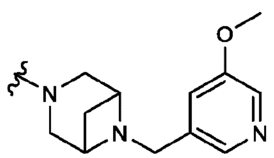
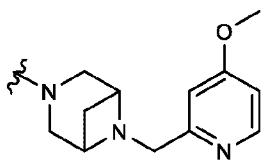
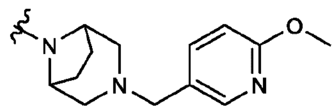
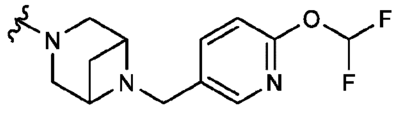
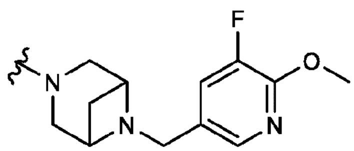
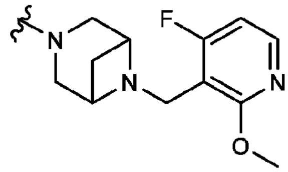
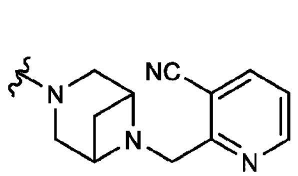
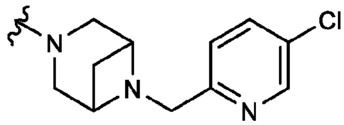
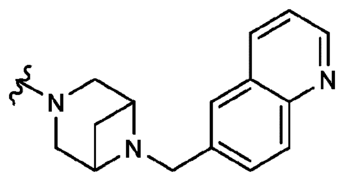
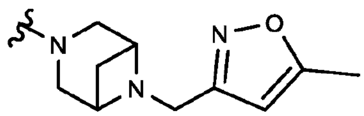
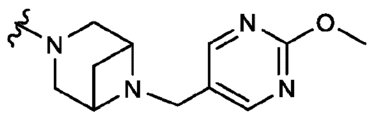
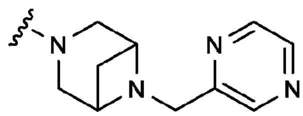
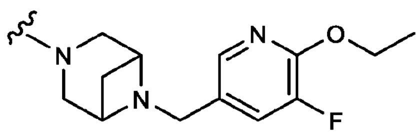
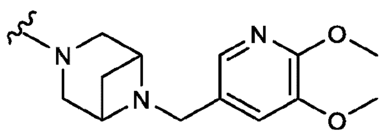
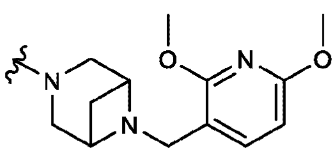
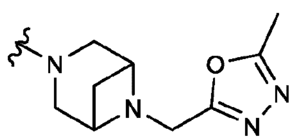
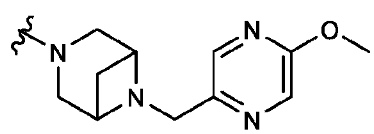
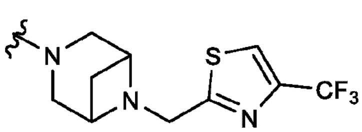
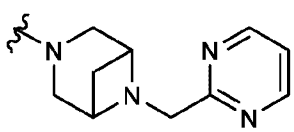
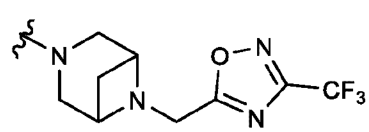
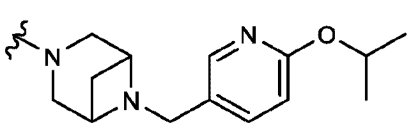
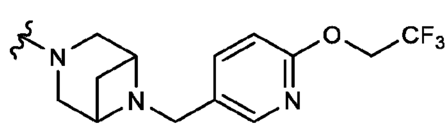







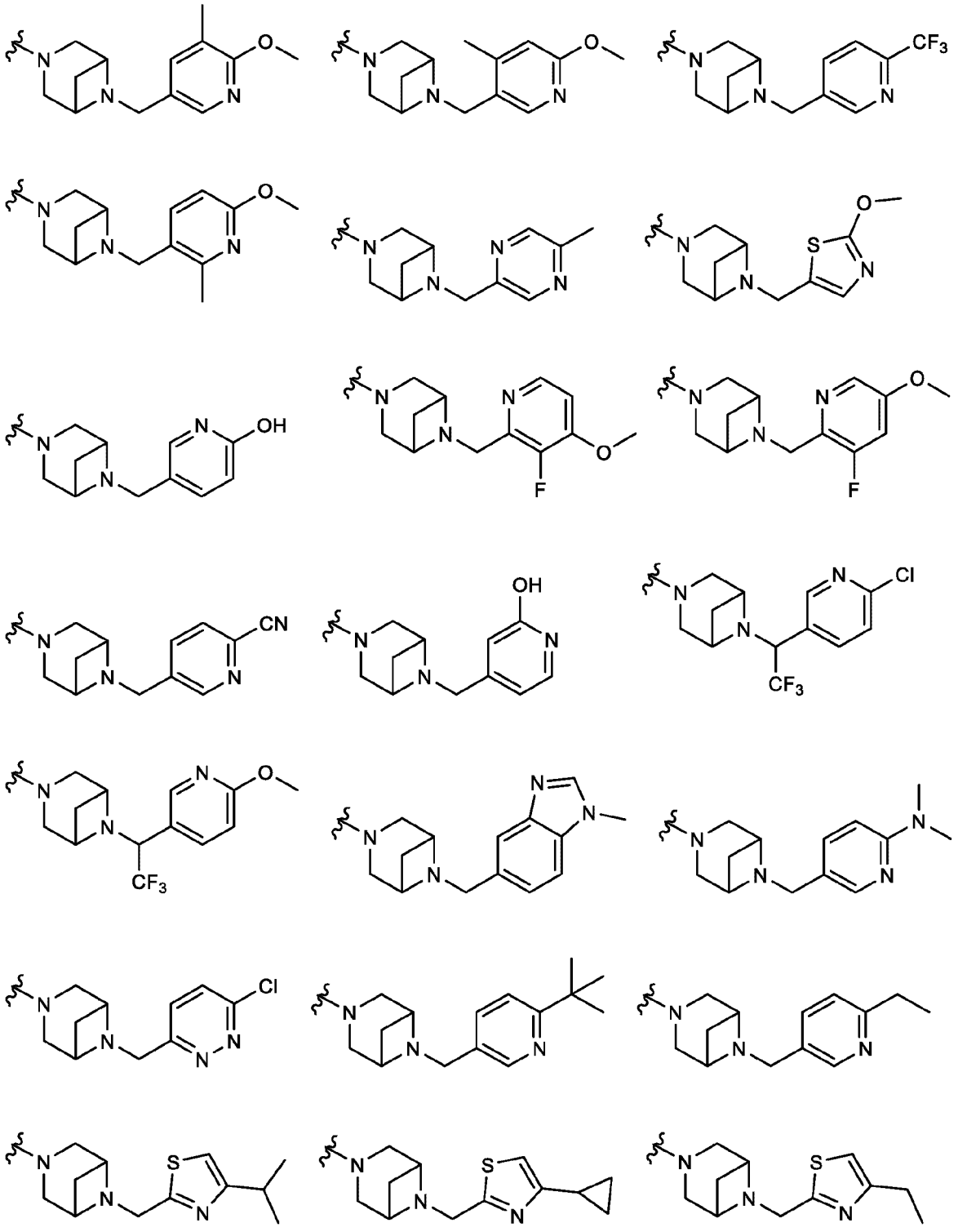
[00197] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2C1$-C6 alkyl-, wherein said alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I**. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S, or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), OH, C3-C6 cycloalkyl, and R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structures:

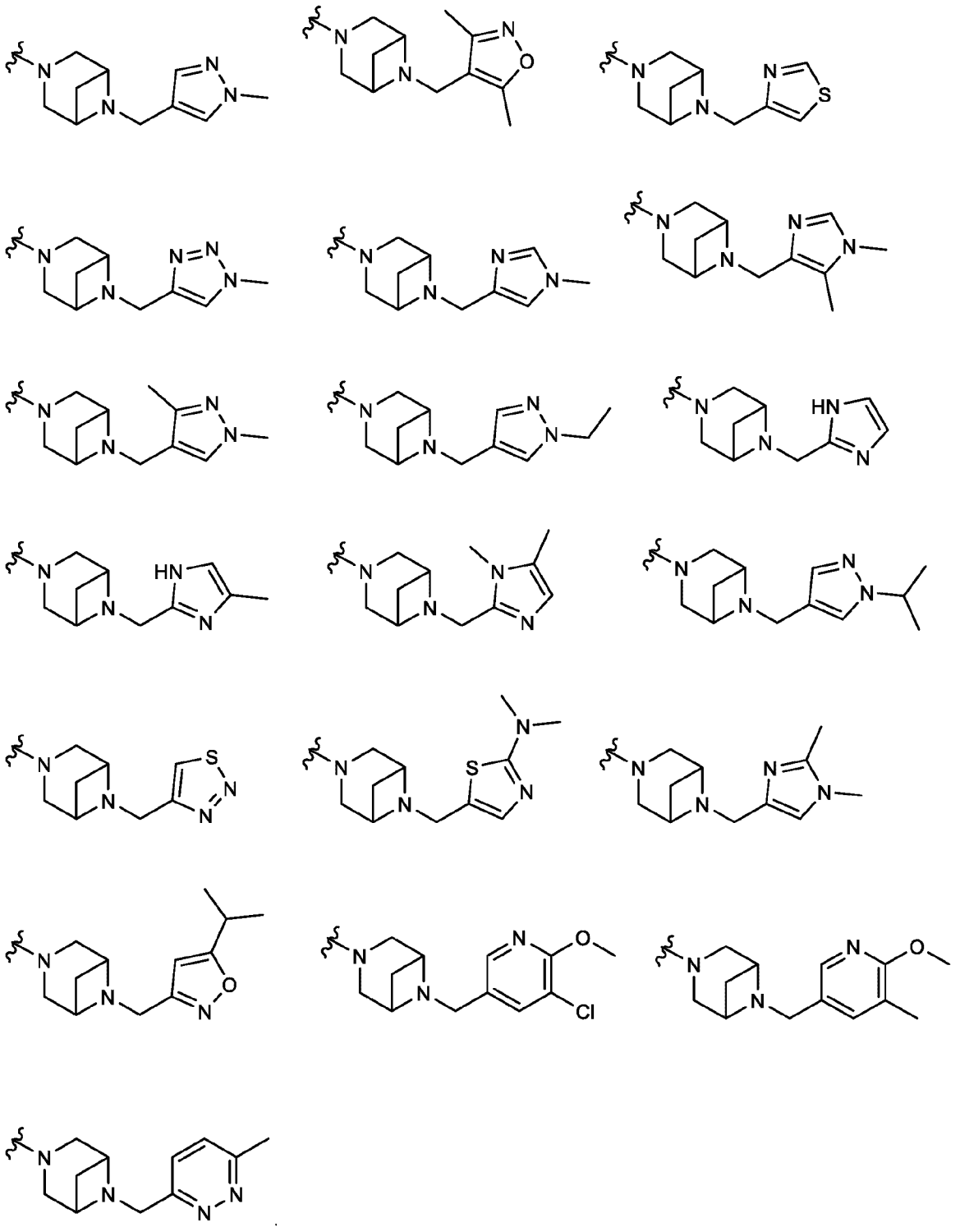


[00198] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:



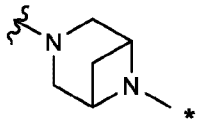

























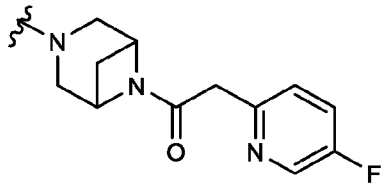


[00199] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged

heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2$(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy and $hetAr^2$ is as defined for Formula **I**. In one embodiment the alkyl portion is unsubstituted. In one embodiment $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms and is optionally substituted with one or more halogens. In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

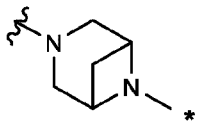
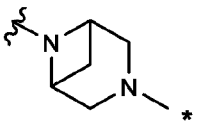
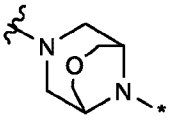


[00200] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example is the structure:

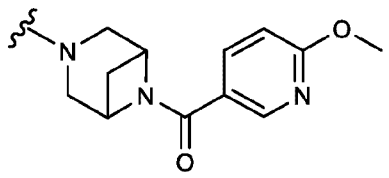
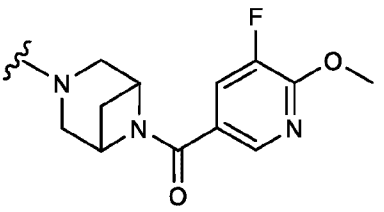
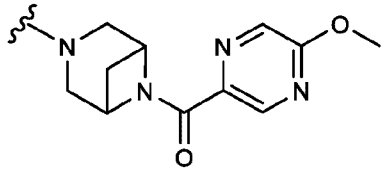
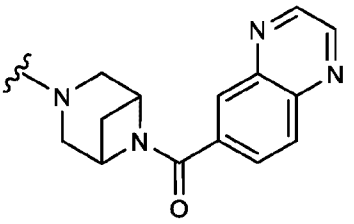
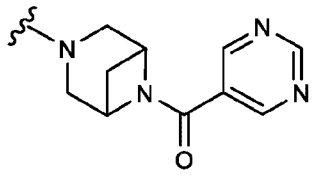
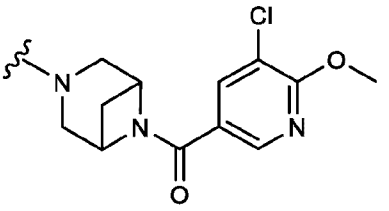
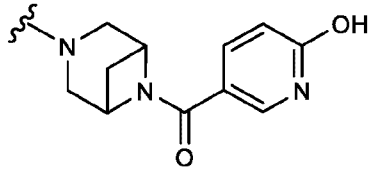
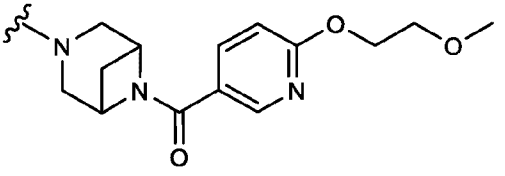


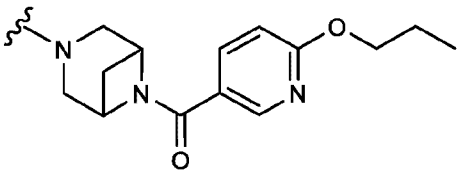
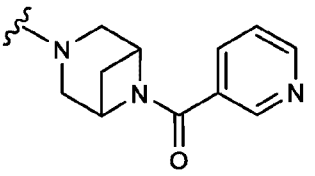
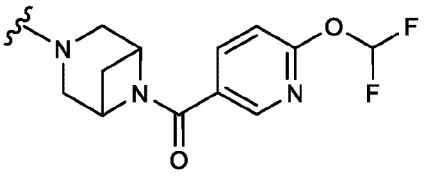
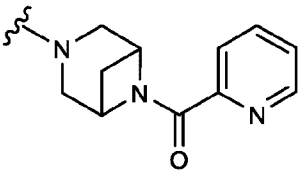
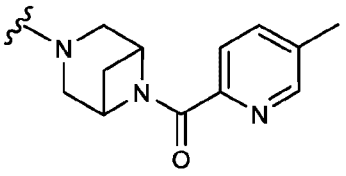
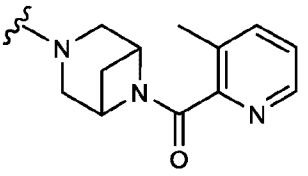
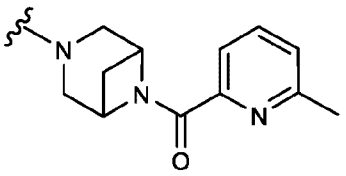
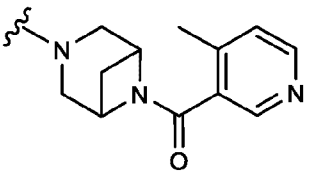
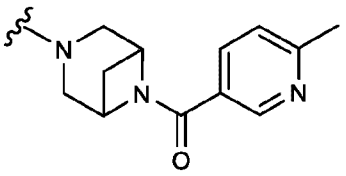
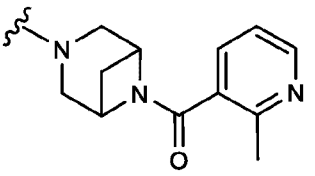
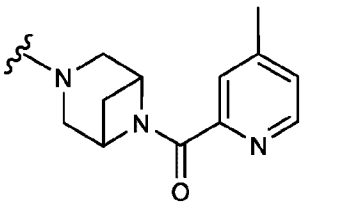
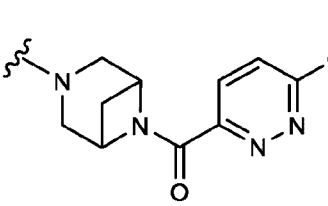
[00201] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2$C(=O)- wherein $hetAr^2$ is as defined for Formula **I**. In one embodiment $hetAr^2$ is a 6-membered heteroaryl ring having 1-2 ring nitrogen atoms and is optionally substituted with one or more substituents independently selected from halogen, C1-C6 alkoxy (optionally substituted with 1-3 fluoros) and (C1-C6 alkoxy)C1-C6

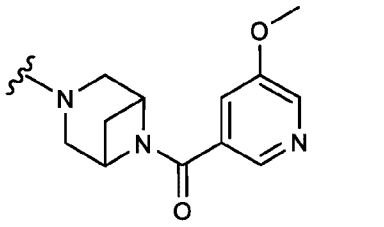
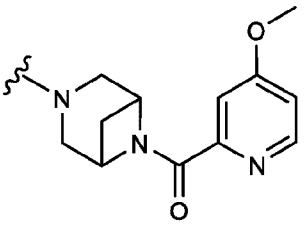
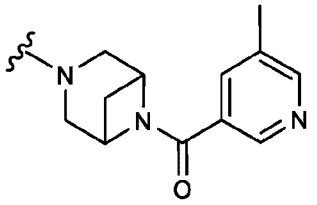
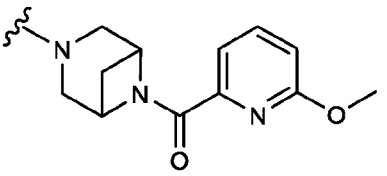
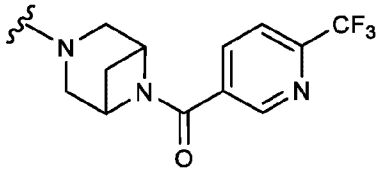
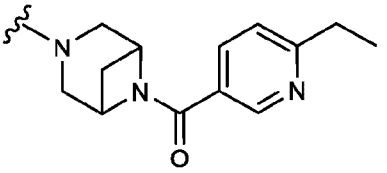
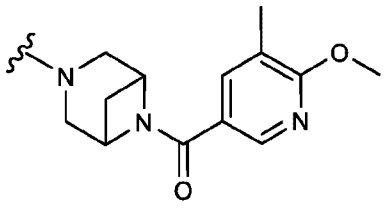
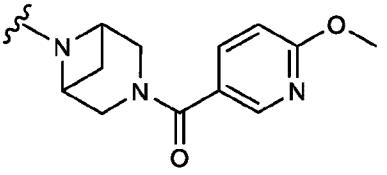
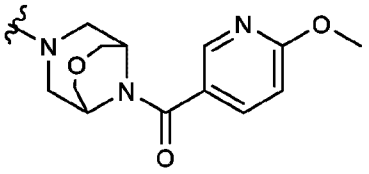
alkoxy-. In one embodiment, Ring D is represented by the structures:

[00202] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

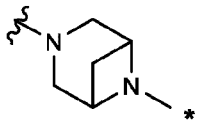









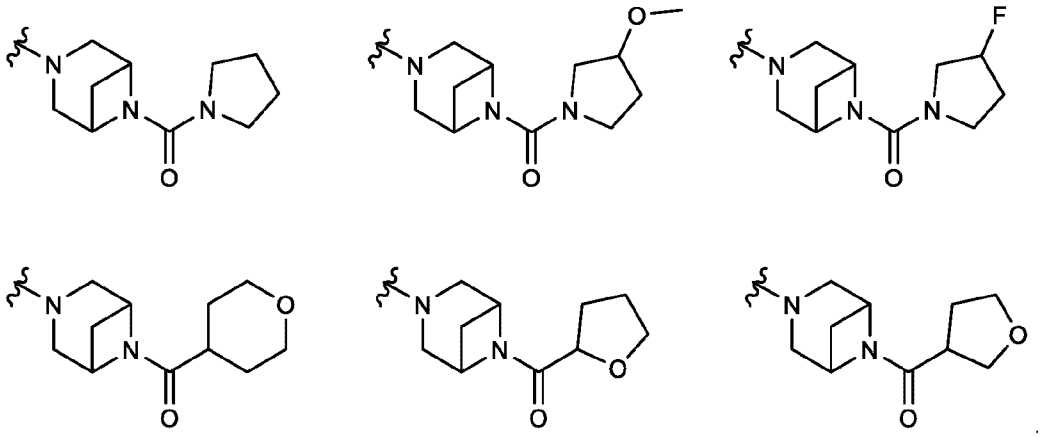










[00203] In one embodiment of Formula **I**, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetCyc^1C(=O)$-, wherein $hetCyc^1$ is as defined

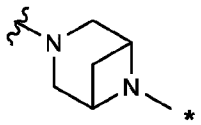
for Formula I. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



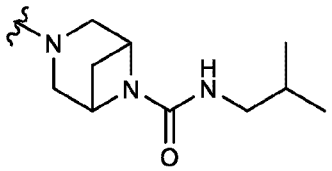
[00204] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:



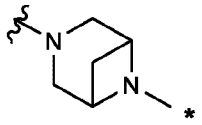
[00205] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $R^3R^4NC(=O)$-, wherein R^3 is H or C1-C6 alkyl and R^4 is C1-C6 alkyl. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



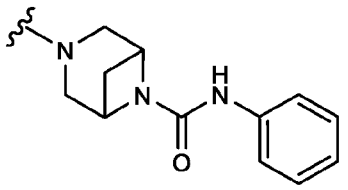
[00206] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example includes the structure:

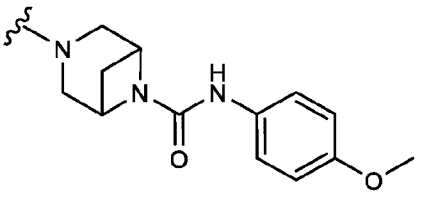


[00207] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $Ar^1N(R^3)C(=O)$- wherein Ar^1 and R^3 are as defined for Formula **I**. In one embodiment, Ar^1 is unsubstituted or substituted with C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

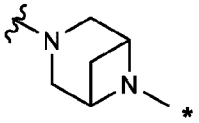


[00208] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

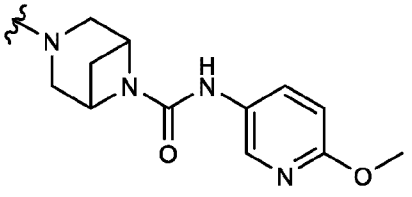




[00209] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2N(R^3)C(=O)$-, wherein $hetAr^2$ and R^3 are as defined for Formula I. In one embodiment, $hetAr^2$ is unsubstituted or substituted with C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

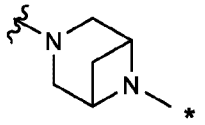


[00210] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example is the structure:

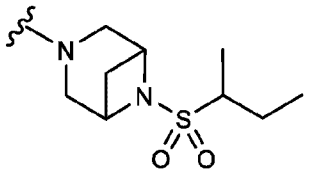


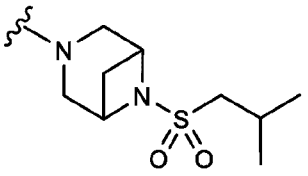
[00211] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3

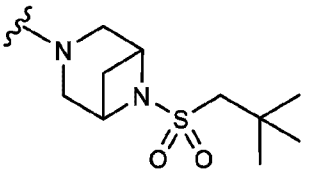
fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkyl)SO_2- wherein the alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is represented by the structure:

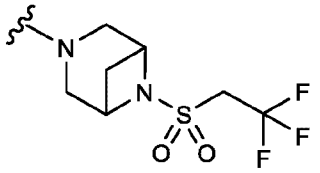


[00212] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

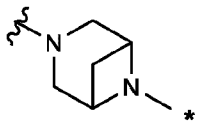




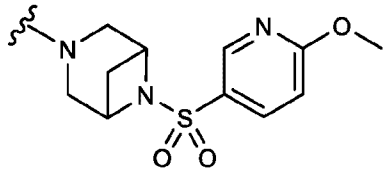




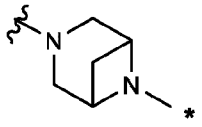
[00213] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is hetAr^2SO_2- wherein hetAr^2 is as defined for Formula I. In one embodiment, hetAr^2 is unsubstituted or substituted with C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



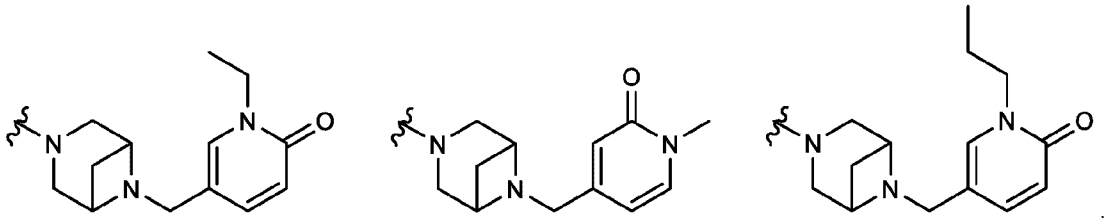
[00214] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example is the structure:



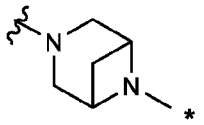
[00215] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is N-(C1-C6 alkyl)pyridinonyl. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



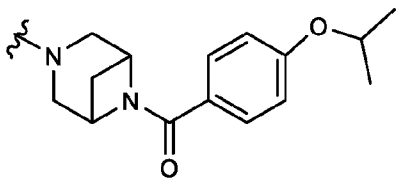
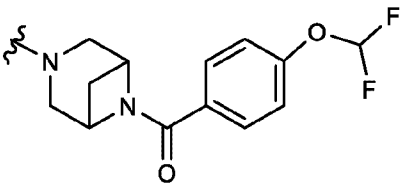
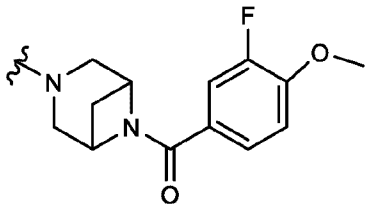
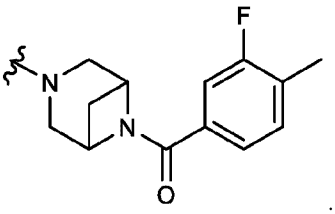
[00216] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:



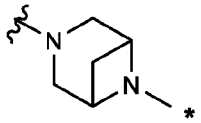
[00217] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $Ar^1C(=O)$- wherein Ar^1 is as defined for Formula I. In one embodiment, Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros), or Ar^1 is a phenyl ring fused to a 5-6 membered heterocyclic ring having two ring oxygen atoms. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



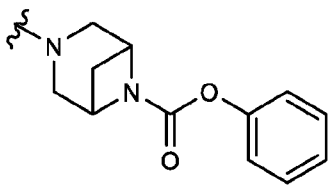
[00218] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

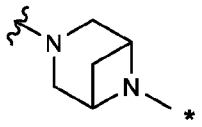
[00219] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is Ar^1O-C(=O)- wherein Ar^1 is as defined for Formula I. In one embodiment, Ar^1 is unsubstituted. In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



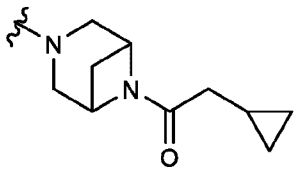
[00220] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. A non-limiting example includes the structure:



[00221] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is C3-C6 cycloalkyl)$CH_2C(=O)$-, wherein the alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

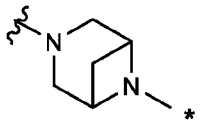


[00222] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example includes the structure:

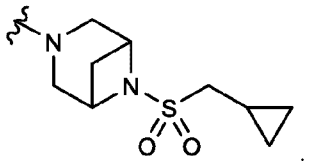


[00223] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C3-C6 cycloalkyl)(C1-C3 alkyl)SO_2-, wherein the alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one

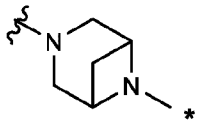
embodiment, Ring D is represented by the structure:



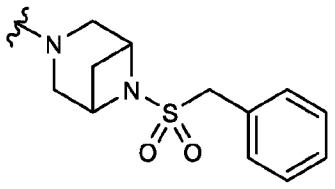
[00224] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example includes the structure:



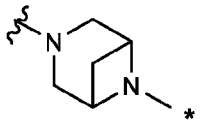
[00225] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is Ar^1(C1-C6 alkyl)SO_2- wherein Ar^1 is as defined for Formula I. In one embodiment, Ar^1 is unsubstituted. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure



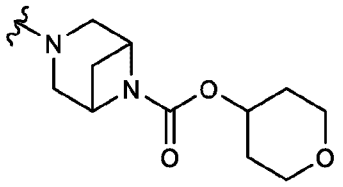
[00226] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example includes the structure:

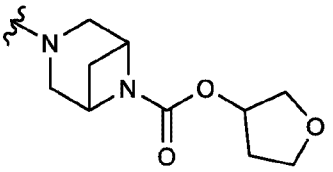


[00227] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetCyc^1$-O-C(=O)-, wherein $hetCyc^1$ is as defined for Formula I. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:



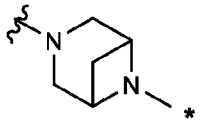
[00228] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:



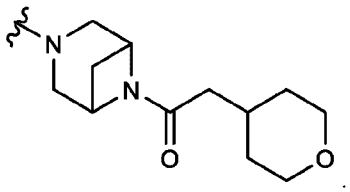


[00229] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3

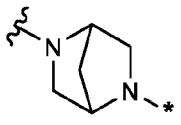
fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetCyc^1$-CH_2-C(=O)-, wherein $hetCyc^1$ is as defined for Formula I. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structure:

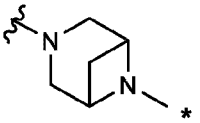


[00230] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A non-limiting example includes the structure:

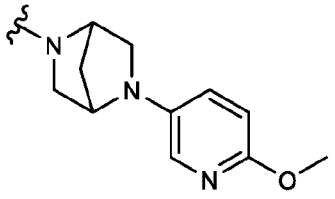
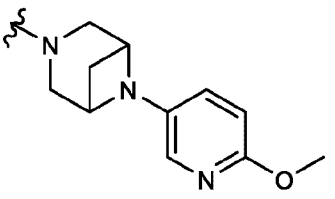


[00231] In one embodiment of Formula **I**, Ring D is a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2$, wherein $hetAr^2$ is as defined for Formula I. In one embodiment, $hetAr^2$ is a 6 membered ring having 1-2 ring nitrogen atoms and is optionally substituted with C1-C6 alkoxy. In one embodiment, Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms. In one embodiment, Ring D is represented by the structures:

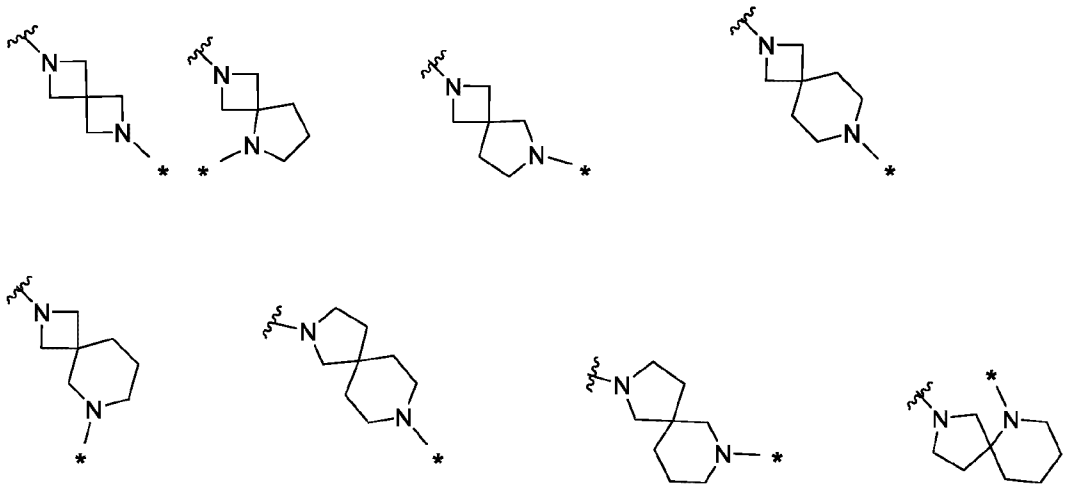


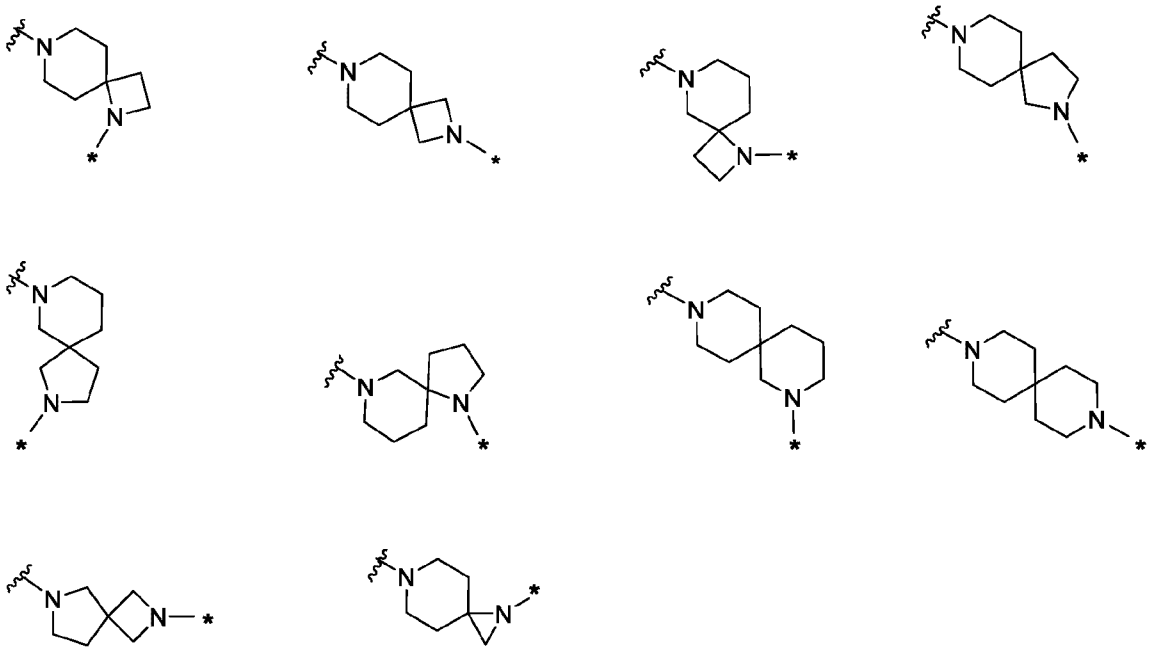


[00232] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. Non-limiting examples include the structures:

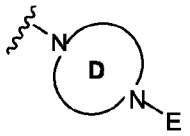
[00233] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. As used herein, the phrase "having two ring nitrogen atoms" when Ring D is a saturated 7-11 membered heterospirocyclic ring means that said ring nitrogen atoms are the two nitrogen atoms shown in Ring D of Formula **I**, wherein one of the ring nitrogen atoms is bonded the ring comprising X^1, X^2, X^3 and X^4, and the other ring nitrogen atom is bonded to the E group as shown in Formula **I**. Non-limiting examples when Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms include the structures:



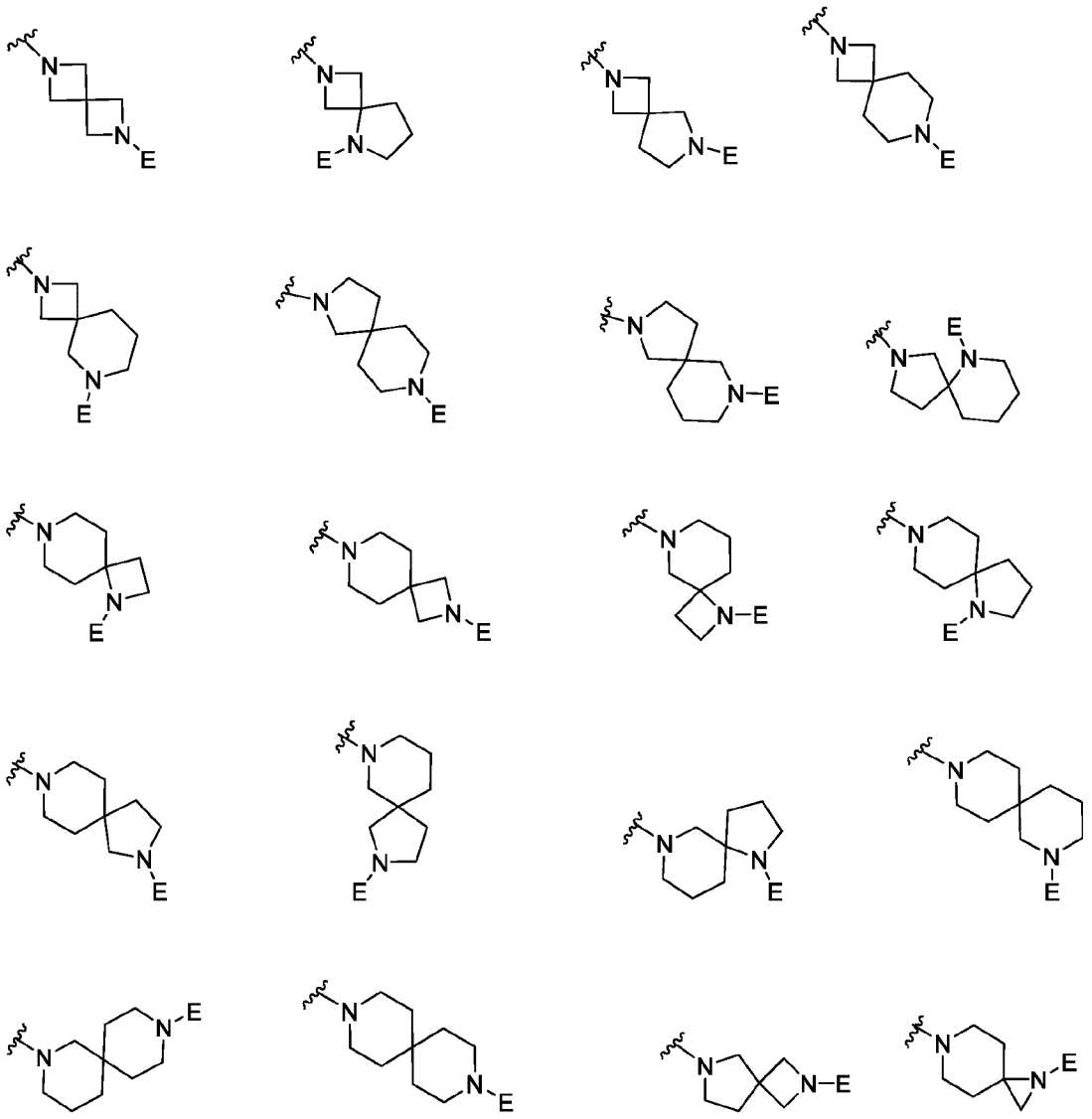


[00234] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein each of said rings is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment, Ring D is unsubstituted.

[00235] In one embodiment when Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, Ring D and E portion of Formula **I**, that is

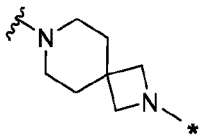


[00236] may be represented by the non-limiting structures:



[00237] wherein the wavy line indicates the point of attachment of Ring D to the ring containing X^1, X^2, X^3 and X^4, wherein each of said rings is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is as defined for Formula **I**. In one embodiment, Ring D is unsubstituted.

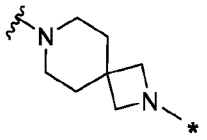
[00238] In one embodiment, Ring D is represented by the structure:



[00239] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment, said Ring D is unsubstituted.

[00240] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is selected from the group consisting of (a) hydrogen, (b) C1-C6 alkyl optionally substituted with 1-3 fluoros, (d) (C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl, (f) (C1-C6 alkoxy)C(=O)-, (l) $hetAr^2C(=O)$-, (o) $R^3R^4NC(=O)$-, (s) Ar^1SO_2-, (t) $hetAr^2SO_2$-, (v) $Ar^1C(=O)$-, (cc) $hetAr^2$, and (dd) C3-C6 cycloalkyl, wherein $hetAr^2$, Ar^1, R^3 and R^4 are as defined for Formula **I**. In one embodiment, said Ring D is unsubstituted.

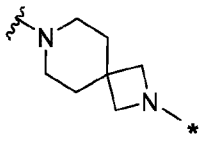
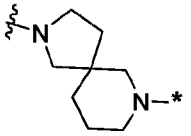
[00241] In one embodiment, Ring D is a saturated 9 membered heterospirocyclic ring having two ring nitrogen atoms represented by the structure:



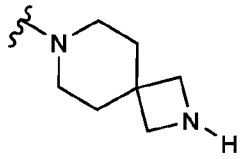
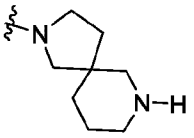
[00242] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is

selected from the group consisting of (a) hydrogen, (d) (C1-C6 alkoxy)C(=O)- and (o) $R^3R^4NC(=O)$-. In one embodiment, said Ring D is unsubstituted

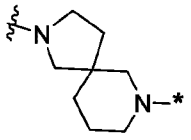
[00243] In one embodiment, In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is hydrogen. In one embodiment, said Ring D is represented by the structures:

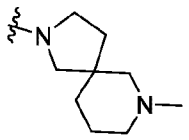
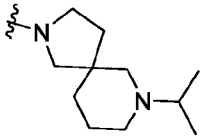
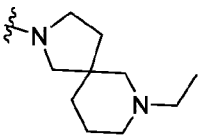
[00244] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, said Ring D is unsubstituted. Non-limiting examples includes the structures:

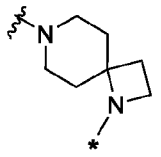
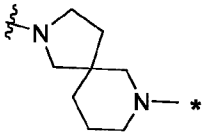
[00245] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (b) C1-C6 alkyl optionally substituted with 1-3 fluoros. In one embodiment, said Ring D is represented by the structure:



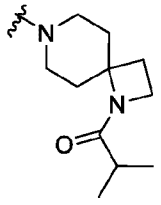
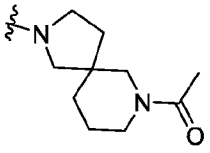
[00246] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, said Ring D is unsubstituted. Non-limiting examples includes the structures:

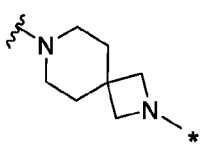
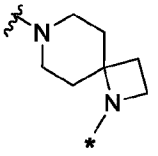
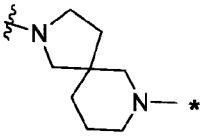
[00247] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl. In one embodiment, said Ring D is represented by the structures:

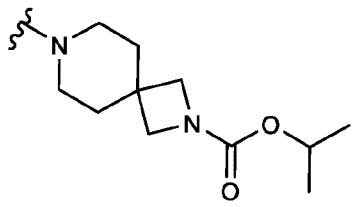
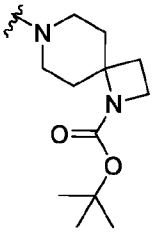
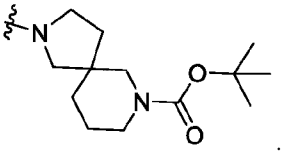
[00248] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, said Ring D is unsubstituted. Non-limiting examples includes the structures:

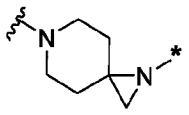
[00249] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkoxy)C(=O)-. In one embodiment, said Ring D is represented by the structures:

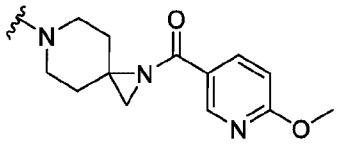
[00250] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, said Ring D is unsubstituted. Non-limiting examples include the structures:

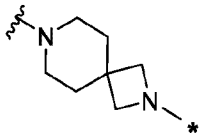
[00251] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2C(=O)$-, wherein $hetAr^2$ is as defined for Formula I. In one embodiment, $hetAr^2$ is a 5-6 membered heterocyclic ring having 1-2 ring nitrogen atoms. In one embodiment, $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, $hetAr^2$ is a 6 membered ring having 1-2 ring nitrogen atoms and is optionally substituted with C1-C6 alkoxy. In one embodiment, Ring D is unsubstituted. In one embodiment, Ring D is represented by the structure:



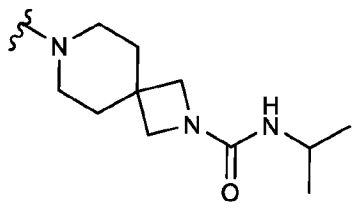
[00252] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. A non-limiting example includes the structure:



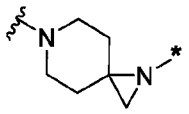
[00253] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $R^3R^4NC(=O)$- wherein R^3 and R^4 are as defined for Formula **I**. In one embodiment, R^3 is H and R^4 is C1-C6 alkyl. In one embodiment, said Ring D is represented by the structure:



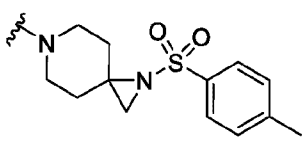
[00254] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, said Ring D is unsubstituted. A non-limiting example includes the structure:

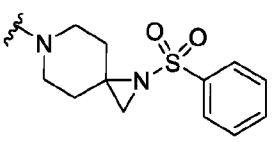


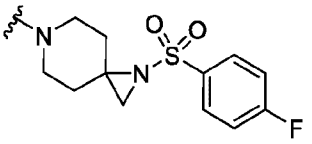
[00255] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is Ar^1SO_2-, wherein Ar^1 is as defined for Formula I. In one embodiment, Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, said Ring D is unsubstituted. In one embodiment, said Ring D is represented by the structure

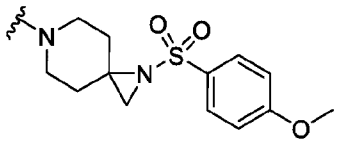


[00256] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. Non-limiting examples include the structures:



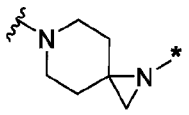




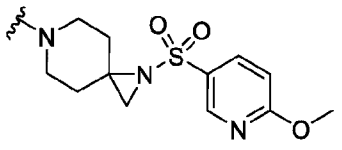


[00257] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6

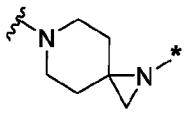
cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2SO_2$-, wherein $hetAr^2$ is as defined for Formula I. In one embodiment, $hetAr^2$ is a 5-6 membered heterocyclic ring having 1-2 ring nitrogen atoms. In one embodiment, $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, $hetAr^2$ is a 6 membered ring having 1-2 ring nitrogen atoms and is optionally substituted with C1-C6 alkoxy. In one embodiment, said Ring D is unsubstituted. In one embodiment, said Ring D is represented by the structure:



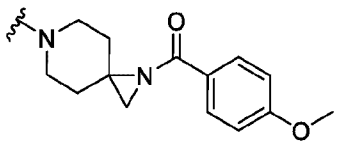
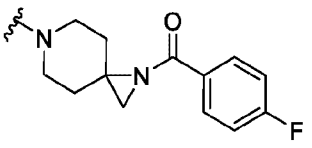
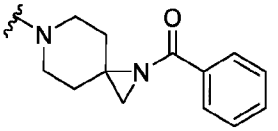
[00258] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. A non-limiting example includes the structure:



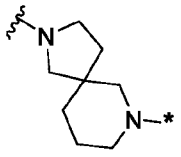
[00259] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $Ar^1C(=O)$-, wherein Ar^1 is as defined for Formula I. In one embodiment, Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, said Ring D is unsubstituted. In one embodiment, said Ring D is represented by the structure:



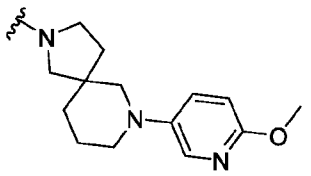
[00260] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. Non-limiting examples include the structures:

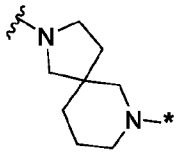
[00261] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is $hetAr^2$, wherein $hetAr^2$ is as defined for Formula I. In one embodiment, $hetAr^2$ is a 5-6 membered heterocyclic ring having 1-2 ring nitrogen atoms. In one embodiment, $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, $hetAr^2$ is a 6 membered ring having 1-2 ring nitrogen atoms and is optionally substituted with C1-C6 alkoxy. In one embodiment, said Ring D is unsubstituted. In one embodiment, said Ring D is represented by the structure:



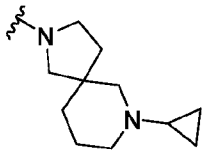
[00262] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. A non-limiting example includes the structure:



[00263] In one embodiment, Ring D is a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is C3-C6 cycloalkyl. In one embodiment, said Ring D is unsubstituted. In one embodiment, said Ring D is represented by the structure:

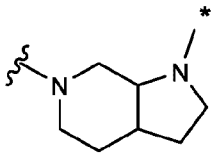


[00264] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. A non-limiting example includes the structure:



[00265] In one embodiment, Ring D is a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally

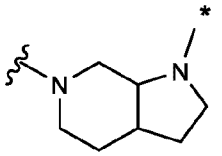
substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. As used herein, the phrase "having two ring nitrogen atoms" when Ring D is a saturated 9-10 membered bicyclic fused heterocyclic ring means that said ring nitrogen atoms are the two nitrogen atoms shown in Ring D of Formula **I**, wherein one of the ring nitrogen atoms is bonded the ring comprising X^1, X^2, X^3 and X^4, and the other ring nitrogen atom is bonded to the E group as shown in Formula **I**. Fused ring include 5,5, 5,6, 6,5 and 6,6 fused ring systems. In one embodiment, said Ring D is represented by the structure:



[00266] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment, said Ring D is unsubstituted.

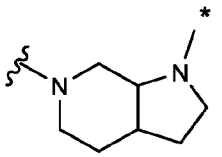
[00267] In one embodiment, Ring D is a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is as defined for Formula **I**.

[00268] In one embodiment, Ring D is a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is hydrogen or (C1-C6 alkoxy)C(=O)-. In one embodiment, Ring D is represented by the structure:

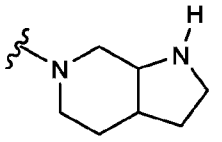


[00269] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted.

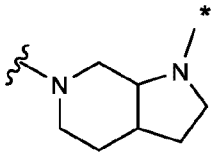
[00270] In one embodiment, Ring D is a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is hydrogen. In one embodiment, Ring D is represented by the structure:



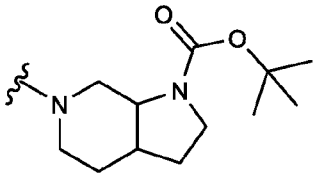
[00271] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, Ring D is unsubstituted. A nonlimiting example is the structure:



[00272] In one embodiment, Ring D is a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group, and E is (C1-C6 alkoxy)C(=O)-. In one embodiment, Ring D is represented by the structure:



[00273] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E. In one embodiment, said Ring D is unsubstituted. A nonlimiting example is the structure:



[00274] In one embodiment, Formula **I** includes compounds of Formula **I-A**, wherein:

[00275] X^1, X^2, X^3 and X^4 are independently CH, CF or N, wherein zero, one or two of X^1, X^2, X^3 and X^4 is N;

[00276] A is H, CN, Cl, CH_3-, CH_3CH_2-, cyclopropyl, -CH_2CN or -$CH(CN)CH_3$;

[00277] B is

[00278] (a) hydrogen,

[00279] (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

[00280] (c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,

[00281] (d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,

[00282] (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

[00283] (f) (R^1R^2N)C1-C6 alkyl- wherein said alkyl portion is optionally substituted with OH and wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

[00284] (g) hetAr^1C1-C3 alkyl-, wherein hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;

[00285] (h) (C3-C6 cycloalkyl)C1-C3 alkyl-, wherein said cycloalkyl is optionally

substituted with OH,

[00286] (i) (hetCyc[a])C1-C3 alkyl-,

[00287] (j) hetCyc[a]-,

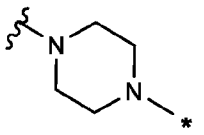
[00288] (k) C3-C6 cycloalkyl-, wherein said cycloalkyl is optionally substituted with OH,

[00289] (l) (C1-C4 alkyl)C(=O)O-C1-C6 alkyl-, wherein each of the C1-C4 alkyl and C1-C6 alkyl portions is optionally and independently substituted with 1-3 fluoros, or

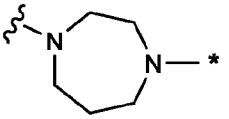
[00290] (m) (R^1R^2N)C(=O)C1-C6 alkyl-, wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

[00291] hetCyc[a]- is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl-, and fluoro, or wherein hetCyc[a] is substituted with oxo;

[00292] Ring D is



or



[00293] wherein the wavy line indicates the point of attachment to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to the E group, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group;

[00294] E is

[00295] (a) hydrogen,

[00296] (c) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

[00297] (d) (C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl,

[00298] (e) (hydroxy C2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros,

[00299] (f) (C1-C6 alkoxy)C(=O)-,

[00300] (g) (C3-C6 cycloalkyl)C(=O)- wherein said cycloalkyl is optionally substituted with one or more substituents independently selected from C1-C6 alkyl, C1-C6 alkoxy, OH, and

(C1-C6 alkoxy)C1-C6 alkyl-, or said cycloalkyl is substituted with a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O,

[00301] (h) Ar^1C1-C6 alkyl-,

[00302] (i) Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, C1-C6 alkoxy, R^mR^nN- or R^mR^nN-CH_2-, wherein each R^m and R^n is independently H or C1-C6 alkyl,

[00303] (j) hetAr^2C1-C6 alkyl- wherein said alkyl portion is optionally substituted with 1-3 fluoros,

[00304] (k) hetAr^2(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl or C1-C6 alkoxy,

[00305] (l) hetAr^2C(=O)-,

[00306] (m) hetCyc^1C(=O)-,

[00307] (n) hetCyc^1C1-C6 alkyl-,

[00308] (o) R^3R^4NC(=O)-, or

[00309] (cc) hetAr^2;

[00310] Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, (R^pR^qN)C1-C6 alkoxy- wherein R^p and R^q are independently H or C1-C6 alkyl, and (hetAr^a)C1-C6 alkyl- wherein hetAr^a is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms, or Ar^1 is a phenyl ring fused to a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

[00311] hetAr^2 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein hetAr^2 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, OH, (C1-C6 alkoxy)C1-C6 alkoxy- and C3-C6 cycloalkyl;

[00312] hetCyc^1 is a 4-6 membered saturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N, O and S wherein said heterocyclic ring is optionally substituted

with one or more substituents independently selected from C1-C6 alkoxy and halogen; and

[00313] R^4 is C1-C6 alkyl.

[00314] In one embodiment of Formula **I-A**, Ring D is unsubstituted.

[00315] In one embodiment of Formula **I-A**, X^1 is N; X^2, X^3 and X^4 are CH.

[00316] In one embodiment of Formula **I-A,** A is CN.

[00317] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; and A is CN.

[00318] In one embodiment of Formula **I-A**, B is C1-C6 alkyl optionally substituted with 1-3 fluoros.

[00319] In one embodiment of Formula **I-A**, B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring.

[00320] In one embodiment of Formula **I-A**, B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In one embodiment of Formula **I-A**, B is (C1-C6 alkoxy)C2-C6 alkyl- optionally substituted with 1-3 fluoros.

[00321] In one embodiment of Formula **I-A**, B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment, the alkyl portion is unsubstituted.

[00322] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring.

[00323] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In one embodiment, B is (C1-C6 alkoxy)C2-C6 alkyl- optionally substituted with 1-3 fluoros.

[00324] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment, the alkyl portion of the B group is unsubstituted.

[00325] In one embodiment of Formula **I-A**, E is Ar^1C1-C6 alkyl-, $hetAr^2$C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or Ar^1(C1-C6 alkyl)C(=O)-, wherein Ar^1 and $hetAr^2$ are as defined for Formula **I-A**.

[00326] In one embodiment of Formula **I-A**, E is Ar^1C1-C6 alkyl-, $hetAr^2$C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or Ar^1(C1-C6 alkyl)C(=O)-, wherein Ar^1 is an unsubstituted phenyl and $hetAr^2$ is a 5-6 membered heterocyclic ring having 1-2 ring nitrogen atoms and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment of Formula **I-A,** $hetAr^2$ is a 6 membered heterocyclic ring having 1-2 ring nitrogen atoms and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros).

[00327] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and E is Ar^1C1-C6 alkyl-, $hetAr^2$C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or Ar^1(C1-C6 alkyl)C(=O)-, wherein Ar^1 and $hetAr^2$ are as defined for Formula **I-A**.

[00328] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; and E is Ar^1C1-C6 alkyl-, $hetAr^2$C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or Ar^1(C1-C6 alkyl)C(=O)-, wherein Ar^1 and $hetAr^2$ are as defined for Formula **I-A**.

[00329] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; and E is Ar^1C1-C6 alkyl- wherein Ar^1 is as defined for Formula **I-A**.

[00330] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; and E is $hetAr^2$C1-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-A**.

[00331] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; or E is Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy and Ar^1 is as defined for Formula **I-A**.

[00332] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and E is Ar^1C1-C6 alkyl-, $hetAr^2$C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or Ar^1(C1-C6 alkyl)C(=O)-, wherein Ar^1 and $hetAr^2$ are as defined for Formula **I-A**. In one embodiment, the alkyl portion of the B group is unsubstituted.

[00333] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and E is Ar^1C1-C6 alkyl- wherein Ar^1 is as defined for Formula **I-A**. In one embodiment, the alkyl portion of the B group is unsubstituted.

[00334] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and E is $hetAr^2$C1-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-A**. In one embodiment, the alkyl portion of the B group is unsubstituted.

[00335] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^1 is N; X^2, X^3 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and E is Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy and Ar^1 is as defined for Formula **I-A**. In one embodiment, Ar^1 is an unsubstituted phenyl. In one embodiment, B is hydroxyC2-C6 alkyl- wherein the alkyl portion is unsubstituted.

[00336] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^2 is N; X^1, X^3 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros, (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, or ($hetCyc^a$)C1-C3 alkyl-; and E is Ar^1C1-C6 alkyl- or Ar^1(C1-C6 alkyl)C(=O)-, wherein the alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy and $hetCyc^a$ and Ar^1 are as defined for Formula **I-A**.

[00337] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^2 is N; X^1, X^3 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; and E is Ar^1(C1-C6 alkyl)C(=O)-, wherein the alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy and Ar^1 is as defined for Formula **I-A**.

[00338] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^2 is N; X^1, X^3 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; and E is Ar^1C1-C6 alkyl- and Ar^1 is as defined for Formula **I-A**.

[00339] In one embodiment of Formula **I-A**, Ring D is unsubstituted; X^2 is N; X^1, X^3 and X^4 are CH; A is CN; B is (hetCyc^a)C1-C3 alkyl-; and E is Ar^1C1-C6 alkyl- and hetCyc^a and Ar^1 are as defined for Formula **I-A**.

[00340] In one embodiment, Formula **I** includes compounds of Formula **I-B**, wherein:

[00341] X^1, X^2, X^3 and X^4 are independently CH, CF or N, wherein zero, one or two of X^1, X^2, X^3 and X^4 is N;

[00342] A is H, CN, Cl, CH_3-, CH_3CH_2-, cyclopropyl, -CH_2CN or -$CH(CN)CH_3$;

[00343] B is

[00344] (a) hydrogen,

[00345] (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

[00346] (c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,

[00347] (d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,

[00348] (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

[00349] (f) (R^1R^2N)C1-C6 alkyl- wherein said alkyl portion is optionally substituted with OH and wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

[00350] (g) hetAr^1C1-C3 alkyl-, wherein hetAr^1 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;

[00351] (h) (C3-C6 cycloalkyl)C1-C3 alkyl-, wherein said cycloalkyl is optionally substituted with OH,

[00352] (i) (hetCyc^a)C1-C3 alkyl-,

[00353] (j) hetCyc[a]-,

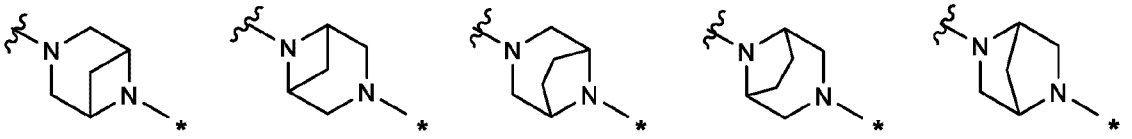
[00354] (k) C3-C6 cycloalkyl-, wherein said cycloalkyl is optionally substituted with OH,

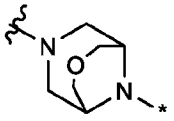
[00355] (l) (C1-C4 alkyl)C(=O)O-C1-C6 alkyl-, wherein each of the C1-C4 alkyl and C1-C6 alkyl portions is optionally and independently substituted with 1-3 fluoros, or

[00356] (m) (R^1R^2N)C(=O)C1-C6 alkyl-, wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

[00357] hetCyc[a]- is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl-, and fluoro, or wherein hetCyc[a] is substituted with oxo;

[00358] Ring D is



or 

[00359] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group;

[00360] E is

[00361] (a) hydrogen,

[00362] (b) C1-C6 alkyl,

[00363] (c) (C1-C6 alkoxy)C1-C6 alkyl-,

[00364] (d) (C1-C6 alkyl)C(=O)-,

[00365] (e) (hydroxyC2-C6 alkyl)C(=O)-,

[00366] (f) (C1-C6 alkoxy)C(=O)-,

[00367] (g) (C3-C6 cycloalkyl)C(=O)-,

[00368] (h) Ar^1C1-C6 alkyl-,

[00369] (i) Ar^1(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, C1-C6 alkoxy, R^mR^nN- or R^mR^nN-CH_2-, wherein each R^m and R^n is independently H or C1-C6 alkyl,

[00370] (j) $hetAr^2$C1-C6 alkyl- wherein said alkyl portion is optionally substituted with 1-3 fluoros,

[00371] (k) $hetAr^2$(C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy,

[00372] (l) $hetAr^2$C(=O)-,

[00373] (m) $hetCyc^1$C(=O)-,

[00374] (o) R^3R^4NC(=O)-,

[00375] (p) Ar^1R^3NC(=O)-,

[00376] (q) $hetAr^2$N(R^3)C(=O)-,

[00377] (r) (C1-C6 alkyl)SO_2- wherein the alkyl portion is optionally substituted with 1-3 fluoros,

[00378] (t) $hetAr^2SO_2$-,

[00379] (u) N-(C1-C6 alkyl)pyridinonyl,

[00380] (v) Ar^1C(=O)-,

[00381] (w) Ar^1O-C(=O)-,

[00382] (x) (C3-C6 cycloalkyl)CH_2C(=O)-,

[00383] (y) (C3-C6 cycloalkyl)(C1-C6 alkyl)SO_2-,

[00384] (z) Ar^1(C1-C6 alkyl)SO_2-,

[00385] (aa) $hetCyc^1$-O-C(=O)-,

[00386] (bb) $hetCyc^1$-CH_2-C(=O)-, or

[00387] (cc) $hetAr^2$;

[00388] Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, (R^pR^qN)C1-C6 alkoxy- wherein R^p and R^q are independently H or C1-C6 alkyl, and ($hetAr^a$)C1-C6 alkyl- wherein $hetAr^a$ is a 5-6 membered heteroaryl ring having

1-2 ring nitrogen atoms, or Ar^1 is a phenyl ring fused to a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

[00389] $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, OH, (C1-C6 alkoxy)C1-C6 alkoxy- and C3-C6 cycloalkyl;

[00390] $hetCyc^1$ is a 4-6 membered saturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N, O and S wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from C1-C6 alkoxy and halogen;

[00391] R^3 is H or C1-C6 alkyl; and

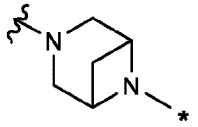
[00392] R^4 is C1-C6 alkyl.

[00393] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH.

[00394] In one embodiment of Formula **I-B**, X^1 and X^3 are N; and X^2 and X^4 are CH.

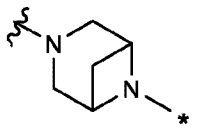
[00395] In one embodiment of Formula **I-B**, A is CN.

[00396] In one embodiment of Formula **I-B**, Ring D is



[00397] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group.

[00398] In one embodiment of Formula **I-B**, Ring D is



[00399] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is unsubstituted.

[00400] In one embodiment of Formula **I-B**, B is C1-C6 alkyl optionally substituted with 1-3 fluoros; (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; hydroxyC2-C6 alkyl wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; $hetAr^1$C1-C3 alkyl-; or ($hetCyc^a$)C1-C3 alkyl-; wherein $hetAr^1$ and $hetCyc^a$ are as defined for Formula I-**B**.

[00401] In one embodiment of Formula **I-B**, B is C1-C6 alkyl optionally substituted with 1-3 fluoros. In one embodiment of Formula **I-B**, B is C1-C6 alkyl.

[00402] In one embodiment of Formula **I-B**, B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring.

[00403] In one embodiment of Formula **I-B**, B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In one embodiment of Formula **I-B**, B is (C1-C6 alkoxy)C2-C6 alkyl- optionally substituted with 1-3 fluoros.

[00404] In one embodiment of Formula **I-B**, B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment, the alkyl portion of the B group is unsubstituted.

[00405] In one embodiment of Formula **I-B**, B is $hetAr^1$C1-C3 alkyl-, wherein $hetAr^1$ is as defined for Formula I-**B**.

[00406] In one embodiment of Formula **I-B**, B is ($hetCyc^a$)C1-C3 alkyl-; wherein $hetCyc^a$ is as defined for Formula I-B.

[00407] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; and B is C1-C6 alkyl optionally substituted with 1-3 fluoros. In one embodiment of Formula **I-B**, B is C1-C6 alkyl.

[00408] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; and B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

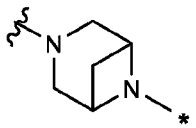
[00409] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; and B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00410] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; and B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment, the alkyl portion of the B group is unsubstituted. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00411] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; and B is $hetAr^1$C1-C3 alkyl-, wherein $hetAr^1$ is as defined for Formula I-B. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH

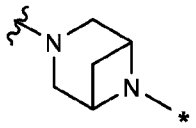
[00412] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; and B is (hetCyc[a])C1-C3 alkyl-; wherein hetCyc[a] is as defined for Formula I-B. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00413] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; and Ring D is



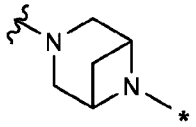
[00414] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment of Formula **I-B**, said Ring D is unsubstituted. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00415] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and Ring D is



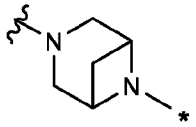
[00416] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment of Formula **I-B**, said Ring D is unsubstituted. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00417] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and Ring D is



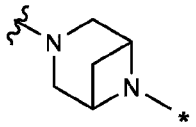
[00418] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00419] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is $hetAr^1$C1-C3 alkyl-, wherein $hetAr^1$ is as defined for Formula I-B; and Ring D is



[00420] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment of Formula **I-B**, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

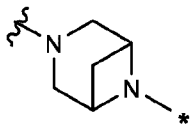
[00421] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (hetCyc^a)C1-C3 alkyl-; wherein hetCyc^a is as defined for Formula I-B; and Ring D is



[00422] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group. In one embodiment of Formula **I-B**, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

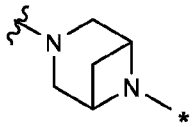
[00423] In one embodiment of Formula **I-B**, E is hetAr^{2}C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, hetAr^{2}C(=O)-, Ar^{1}R^{3}NC(=O)-, or (C1-C6 alkyl)SO_2-, wherein hetAr^2, Ar^1, and R^3 are as defined for Formula **I-B**. In one embodiment, hetAr^2 is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros).

[00424] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; Ring D is



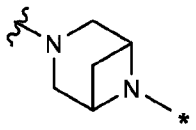
[00425] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, $hetAr^2C(=O)$-, $Ar^1R^3NC(=O)$- or (C1-C6 alkyl)SO_2- wherein $hetAr^2$, Ar^1 and R^3 are as defined for Formula **I-B**. In one embodiment of Formula **I-B**, said Ring D is unsubstituted. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00426] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; Ring D is



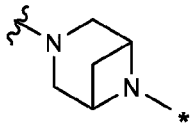
[00427] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros. In one embodiment of Formula **I-B**, said Ring D is unsubstituted. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00428] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; Ring D is



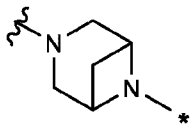
[00429] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2C(=O)$-, wherein $hetAr^2$ is as defined for Formula **I-B**. In one embodiment of Formula **I-B**, said Ring D is unsubstituted. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00430] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; Ring D is



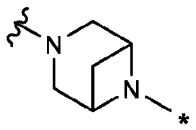
[00431] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $Ar^1R^3NC(=O)$- wherein Ar^1 is as defined for Formula **I-B**. In one embodiment of Formula **I-B**, said Ring D is unsubstituted. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00432] In one embodiment of Formula **I-B**, X^1 is N; X^2, X^3 and X^4 are CH, or X^1 and X^3 are N; and X^2 and X^4 are CH; A is CN; B is C1-C6 alkyl optionally substituted with 1-3 fluoros; Ring D is



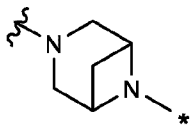
[00433] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is (C1-C6 alkyl)SO_2-. In one embodiment of Formula **I-B**, said Ring D is unsubstituted. In one embodiment, X^1 is N; X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00434] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



[00435] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, $hetAr^2C(=O)$-, $Ar^1R^3NC(=O)$- or (C1-C6 alkyl)SO_2- wherein $hetAr^2$, Ar^1 and R^3 are as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

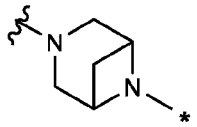
[00436] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; Ring D is



[00437] wherein the wavy line indicates the point of attachment of Ring D to the ring

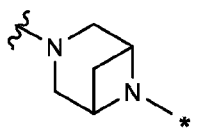
comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, $hetAr^2C(=O)$-, $Ar^1R^3NC(=O)$- or (C1-C6 alkyl)SO_2- wherein $hetAr^2$, Ar^1 and R^3 and are as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00438] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



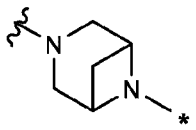
[00439] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, $hetAr^2C(=O)$-, $Ar^1R^3NC(=O)$- or (C1-C6 alkyl)SO_2- wherein $hetAr^2$, Ar^1 and R^3 and are as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00440] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is $hetAr^1$C1-C3 alkyl-, wherein $hetAr^1$ is as defined for Formula I-B; Ring D is



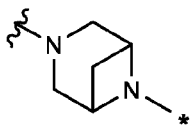
[00441] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, $hetAr^2C(=O)$-, $Ar^1R^3NC(=O)$- or (C1-C6 alkyl)SO_2- wherein $hetAr^2$, Ar^1 and R^3 and are as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00442] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is ($hetCyc^a$)C1-C3 alkyl-, wherein $hetCyc^a$ is as defined for Formula I-B; Ring D is



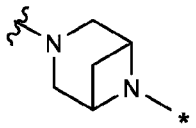
[00443] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, $hetAr^2C(=O)$-, $Ar^1R^3NC(=O)$- or (C1-C6 alkyl)SO_2- wherein $hetAr^2$, Ar^1 and R^3 and are as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00444] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



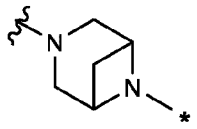
[00445] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl, wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00446] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



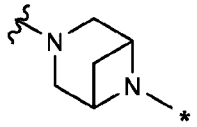
[00447] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C(=O)-, wherein $hetAr^2$ is as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00448] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



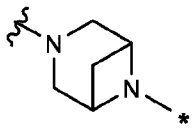
[00449] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $Ar^1R^3NC(=O)$- wherein Ar^1 and R^3 are as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00450] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



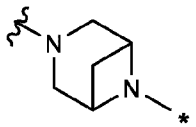
[00451] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is (C1-C6 alkyl)SO_2-. In one embodiment said Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00452] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; Ring D is



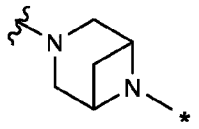
[00453] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, $hetAr^2C(=O)$-, $Ar^1R^3NC(=O)$- or (C1-C6 alkyl)SO_2- wherein $hetAr^2$, Ar^1 and R^3 are as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00454] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; Ring D is



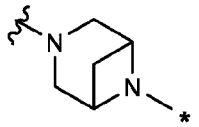
[00455] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl, wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00456] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; Ring D is



[00457] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2C(=O)$-, wherein $hetAr^2$ is as defined for Formula **I-B.** In one embodiment said Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

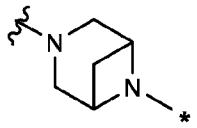
[00458] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; Ring D is



[00459] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $Ar^1R^3NC(=O)$- wherein Ar^1 and R^3 are as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1

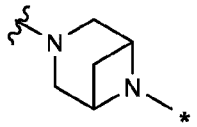
and X^3 are N; and X^2 and X^4 are CH.

[00460] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; Ring D is



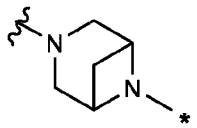
[00461] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is (C1-C6 alkyl)SO_2-. In one embodiment Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00462] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl-; Ring D is



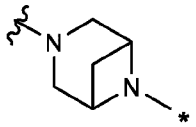
[00463] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $hetAr^2$C1-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, or $hetAr^2$C(=O), wherein $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C1-C6 alkoxy (optionally substituted with 1-3 fluoros) and $hetAr^2$ is as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00464] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl-; Ring D is



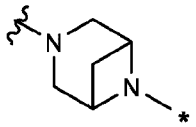
[00465] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $hetAr^2C1$-C6 alkyl wherein the alkyl portion is optionally substituted with 1-3 fluoros, wherein $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C1-C6 alkoxy (optionally substituted with 1-3 fluoros) and $hetAr^2$ is as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00466] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl-; Ring D is



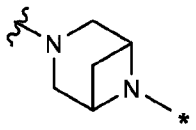
[00467] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $hetAr^2C(=O)$, wherein $hetAr^2$ is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C1-C6 alkoxy (optionally substituted with 1-3 fluoros) and $hetAr^2$ is as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00468] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



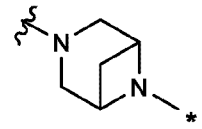
[00469] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $Ar^1N(R^3)C(=O)$ and Ar^1 and R^3 are as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00470] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



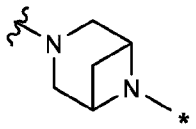
[00471] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $hetAr^2C1$-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or $hetAr^2C(=O)$-, and $hetAr^2$ is as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00472] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



[00473] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $hetAr^2C1$-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

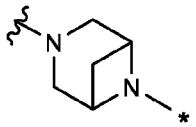
[00474] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



[00475] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $hetAr^2C(=O)$- and $hetAr^2$ is as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

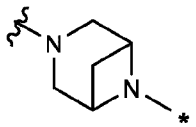
[00476] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is

optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



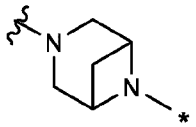
[00477] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $hetAr^2C1$-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00478] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; Ring D is



[00479] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E; and E is $hetAr^2C1$-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-B**. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

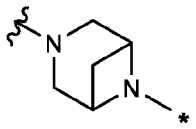
[00480] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is $hetAr^1C1$-C3 alkyl-, wherein $hetAr^1$ is as defined for Formula I-B; Ring D is



[00481] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is

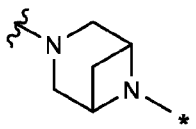
$hetAr^2C1$-C6 alkyl, wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00482] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is $hetAr^1C1$-C3 alkyl-, wherein $hetAr^1$ is as defined for Formula I-B; Ring D is



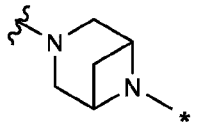
[00483] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2C(=O)$-, wherein $hetAr^2$ is as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00484] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is $hetAr^1C1$-C3 alkyl-, wherein $hetAr^1$ is as defined for Formula I-B; Ring D is



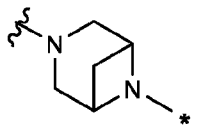
[00485] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $Ar^1R^3NC(=O)$- wherein Ar^1 and R^3 are as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00486] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is $hetAr^1$C1-C3 alkyl-, wherein $hetAr^1$ is as defined for Formula I-B; Ring D is



[00487] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is (C1-C6 alkyl)SO_2-. In one embodiment, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

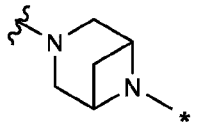
[00488] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is ($hetCyc^a$)C1-C3 alkyl-, wherein $hetCyc^a$ is as defined for Formula I-B; Ring D is



[00489] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally

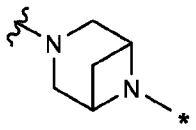
substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C1-C6 alkyl, wherein the alkyl portion is optionally substituted with 1-3 fluoros and $hetAr^2$ is as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00490] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (hetCyc^a)C1-C3 alkyl-, wherein hetCyc^a is as defined for Formula I-B; Ring D is



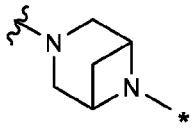
[00491] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $hetAr^2$C(=O)-, wherein $hetAr^2$ is as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C1-C6 alkyl (optionally substituted with 1-3 fluoros), and C1-C6 alkoxy (optionally substituted with 1-3 fluoros). In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00492] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (hetCyc^a)C1-C3 alkyl-, wherein hetCyc^a is as defined for Formula I-B; Ring D is



[00493] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is $Ar^1R^3NC(=O)$- wherein Ar^1 and R^3 are as defined for Formula **I-B.** In one embodiment, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00494] In one embodiment of Formula **I-B**, X^1 is N, and X^2, X^3 and X^4 are CH; or X^1 and X^3 are N, and X^2 and X^4 are CH; A is CN; B is (hetCyc^a)C1-C3 alkyl-, wherein hetCyc^a is as defined for Formula I-B; Ring D is



[00495] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E, wherein Ring D is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group; and E is (C1-C6 alkyl)SO_2-. In one embodiment, Ring D is unsubstituted. In one embodiment, X^1 is N; and X^2, X^3 and X^4 are CH. In one embodiment, X^1 and X^3 are N; and X^2 and X^4 are CH.

[00496] In one embodiment, Formula **I** includes compounds of Formula **I-C** wherein:

[00497] X^1, X^2, X^3 and X^4 are independently CH, CF or N, wherein zero, one or two of X^1, X^2, X^3 and X^4 is N;

[00498] A is H, CN, Cl, CH_3-, CH_3CH_2-, cyclopropyl, -CH_2CN or -$CH(CN)CH_3$;

[00499] B is

[00500] (a) hydrogen,

[00501] (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

[00502] (c) hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,

[00503] (d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,

[00504] (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

[00505] (f) (R^1R^2N)C1-C6 alkyl- wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

[00506] (g) $hetAr^1$C1-C3 alkyl-, wherein $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;

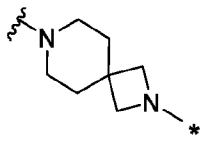
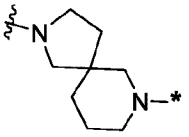
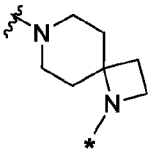
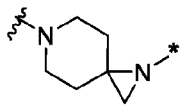
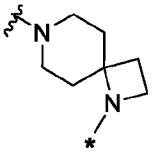
[00507] (h) (C3-C6 cycloalkyl)C1-C3 alkyl-,

[00508] (i) ($hetCyc^a$)C1-C3 alkyl-, or

[00509] (j) $hetCyc^a$;

[00510] $hetCyc^a$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and is optionally substituted with OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros) or hydroxyC1-C6 alkyl-;

[00511] Ring D is

[00512] wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E;

[00513] E is

[00514] (a) hydrogen,

[00515] (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

[00516] (d) (C1-C6 alkyl)C(=O)- wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl,

[00517] (f) (C1-C6 alkoxy)C(=O),

[00518] (l) $hetAr^2C(=O)$-,

[00519] (o) $R^3R^4NC(=O)$-,

[00520] (s) Ar^1SO_2-,

[00521] (t) $hetAr^2SO_2$-,

[00522] (v) $Ar^1C(=O)$-,

[00523] (cc) $hetAr^2$, or

[00524] (dd) C3-C6 cycloalkyl;

[00525] R^3 is H or C1-C6 alkyl; and

[00526] R^4 is C1-C6 alkyl.

[00527] In one embodiment of Formula **I-C**, X^1 is N; X^2, X^3 and X^4 are CH.

[00528] In one embodiment of Formula **I-C,** A is CN.

[00529] In one embodiment of Formula **I-C**, X^1 is N; X^2, X^3 and X^4 are CH; and A is CN.

[00530] In one embodiment of Formula **I-C**, B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, or hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring.

[00531] In one embodiment of Formula **I-C**, B is (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros. In one embodiment of Formula **I-C**, B is (C1-C6 alkoxy)C2-C6 alkyl- optionally substituted with 1-3 fluoros.

[00532] In one embodiment of Formula **I-C**, B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring. In one embodiment, the alkyl portion of the B group is unsubstituted.

[00533] In one embodiment of Formula **I-C**, X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is (C1-C6 alkoxy)C1-C6 alkyl optionally substituted with 1-3 fluoros.

[00534] In one embodiment of Formula **I-C**, X^2 is N; X^1, X^3 and X^4 are CH; A is CN; B is hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring; and E is (C1-C6 alkoxy)C(=O)-.

[00535] In one embodiment of Formula **I-C**, X^1 is N; X^2, X^3 and X^4 are CH; A is CN; and B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6

cycloalkylidene ring. In one embodiment, the alkyl portion of the B group is unsubstituted.

[00536] The compounds of Formula **I** include pharmaceutically acceptable salts thereof. In addition, the compounds of Formula **I** also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula **I** and/or for separating enantiomers of compounds of Formula **I**. Non-limiting examples of pharmaceutically acceptable salts of compounds of Formula **I** include monohydrochloride, dihydrochloride, trifluoroacetic acid, and di-trifluoroacetic acid salts. In one embodiment, compounds of Formula I include trifluoroacetic acid and dihydrochloride salts.

[00537] It will further be appreciated that the compounds of Formula **I** or their salts may be isolated in the form of solvates, and accordingly that any such solvate is included within the scope of the present invention. For example, compounds of Formula **I** and salts thereof can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like.

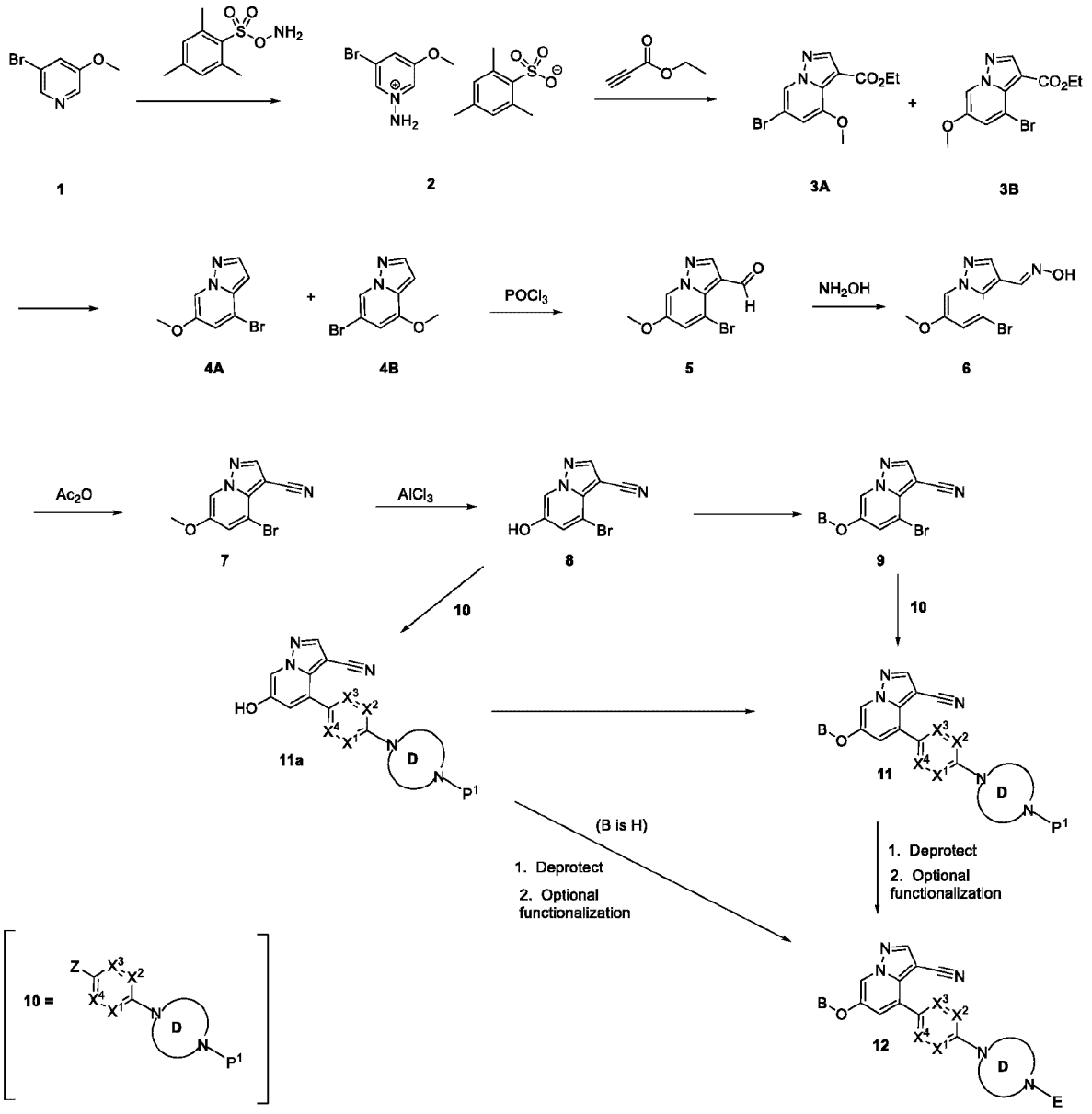
[00538] In one embodiment, the compounds of Formula **I** include the compounds of Examples 1-561 and stereoisomers and pharmaceutically acceptable salts and solvates thereof. In one embodiment, the compounds of Examples 1-561 are in the free base form. In one embodiment, the compounds of Examples 1-561 are dihydrochloride, and trifluoroacetic acid salts.

[00539] The term "pharmaceutically acceptable" indicates that the compound, or salt or composition thereof is compatible chemically and/or toxicologically with the other ingredients comprising a formulation and/or the patient being treated therewith.

[00540] Compounds provided herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. That is, an atom, in particular when mentioned in relation to a compound according to Formula **I**, comprises all isotopes and isotopic mixtures of that atom, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, when hydrogen is mentioned, it is understood to refer to ^{1}H, ^{2}H, ^{3}H or mixtures thereof; when carbon is mentioned, it is understood to refer to ^{11}C, ^{12}C, ^{13}C, ^{14}C or mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{13}N, ^{14}N, ^{15}N or mixtures thereof; when oxygen is mentioned, it is understood to refer to ^{14}O, ^{15}O, ^{16}O, ^{17}O, ^{18}O or mixtures thereof; and when fluoro is mentioned, it is understood to refer to ^{18}F, ^{19}F or mixtures thereof. The compounds provided herein therefore also

comprise compounds with one or more isotopes of one or more atoms, and mixtures thereof, including radioactive compounds, wherein one or more non-radioactive atoms has been replaced by one of its radioactive enriched isotopes. Radiolabeled compounds are useful as therapeutic agents, e.g., cancer therapeutic agents, research reagents, e.g., assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds provided herein, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[00541] For illustrative purposes, Schemes 1-6 show general methods for preparing the compounds provided herein as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.



SCHEME 1

[00542] Scheme 1 shows a general scheme for the synthesis of compound **12** wherein A is CN, and B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**.

[00543] Compound **2** is obtained by treating 3-bromo-5-methoxypyridine (compound 1), which is commercially available, with O-(mesitylsulfonyl)hydroxylamine. The O-mesitylsulfonylhydroxylamine may be prepared as described in Mendiola, J., et al., Org. Process Res. Dev. 2009, 13(2), 263-267. Compound **2** may be reacted with ethyl propiolate to provide a mixture of compounds **3A** and **3B**, which typically are obtained in a ratio of approximately 2:1 to

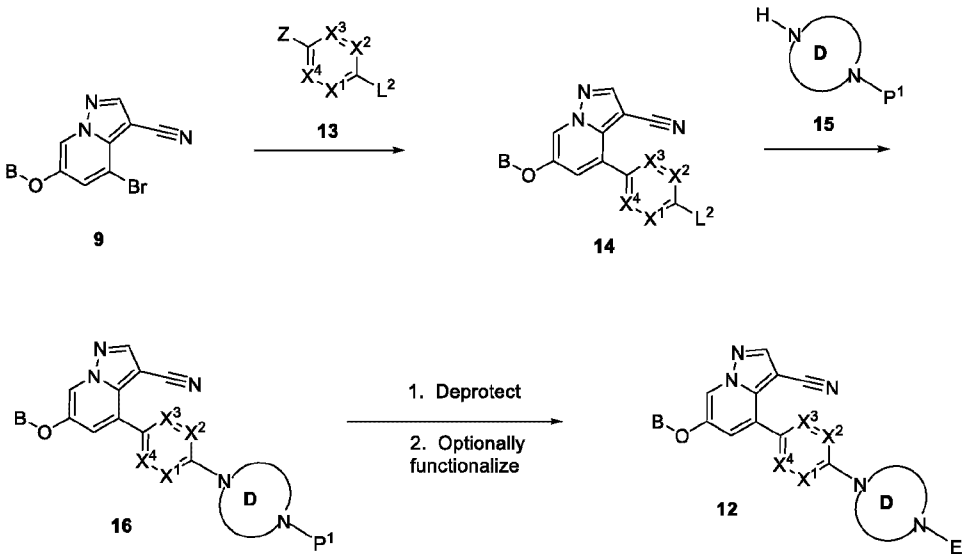
9:1, respectively. The mixture of compounds **3A** and **3B** may be treated with 48% HBr at elevated temperatures, followed by recrystallization or chromatography purifications, to isolate compound **4A** as the minor isomer and compound **4B** as the major isomer. After isolation, compound **4A** may be treated with $POCl_3$ to provide compound **5**. The formyl group may be converted to an oxime group using NH_2OH to provide compound **6**. The oxime group may be converted to a nitrile group using acetic anhydride to provide compound **7**. The methoxy group of compound **7** may be converted to a hydroxy group by treating compound **7** with aluminum trichloride to provide compound **8**.

[00544] To prepare compound **12** wherein B is hydrogen, compound **12** may be prepared by coupling compound **8** with the corresponding boronic ester compound **10** (wherein Ring D, X^1, X^2, X^3 and X^4 are as defined for Formula **I**; P^1 is an amino protecting group; Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) to provide compound **11a** using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures). The protecting group P^1 on Ring D of compound **11a** may be removed under standard conditions (for example, a Boc group may be removed by treating compound **11a** to acidic conditions, e.g., HCl) to provide compound **12** wherein B is hydrogen and E is hydrogen. Alternatively, the deprotected Ring D may be functionalized (i.e., reacted or treated with an appropriate reagent) to introduce the E group under standard conditions such as described below to provide compound **12** wherein B is hydrogen and E is as defined for Formula **I** except that E is not hydrogen.

[00545] Alternatively, to prepare compound **12** wherein B is as defined for Formula **I** other than hydrogen, compound **11a** may be reacted with a reagent such as C1-C6 alkyl-OH optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-OH, dihydroxyC3-C6 alkyl-OH, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-OH wherein R^1 and R^2 are as defined for Formula **I**, $hetAr^1$C1-C3 alkyl-OH, (C3-C6 cycloalkyl)C1-C3 alkyl-OH, $(hetCyc^a)$C1-C3alkyl-OH, or $hetCyc^a$-OH, wherein $hetAr^1$ and $hetCyc^a$ are defined for Formula **I**, and wherein each of said reagents ins optionally substituted with a protecting group, under Mitsunobu reaction conditions (e.g., PPh_3 and diisopropyl azodicarboxylate) to provide

compound **11**. Compound **12** may then be prepared from compound **11** as described above, followed by removal of the protecting group on B if present.

[00546] As an alternative process for preparing compound **12** wherein B is as defined for Formula **I** other than hydrogen, compound **9** may be prepared by reacting compound **8** with reagent such as C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X, dihydroxyC3-C6 alkyl-X, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X wherein R^1 and R^2 are as defined for Formula **I**, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, ($hetCyc^a$)C1-C3 alkyl-X, or $hetCyc^a$-X, wherein $hetAr^1$ and $hetCyc^a$ are defined for Formula **I** and X is a leaving atom or group (such as a halide or triflate), in the presence of a suitable base (e.g., a metal alkali carbonate, such as potassium carbonate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if the B group has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound 9 may be prepared by reacting compound **8** with C1-C6 alkyl-X wherein said alkyl is optionally substituted with 1-3 fluoros and X is a halogen such as Br or Cl, or a leaving group such as triflate. Compound **11** may then be prepared by coupling compound **9** with the corresponding boronic ester compound **10** using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures). Compound **12** may then be prepared from compound **11** as described above, followed by removal of the protecting group on B if present.



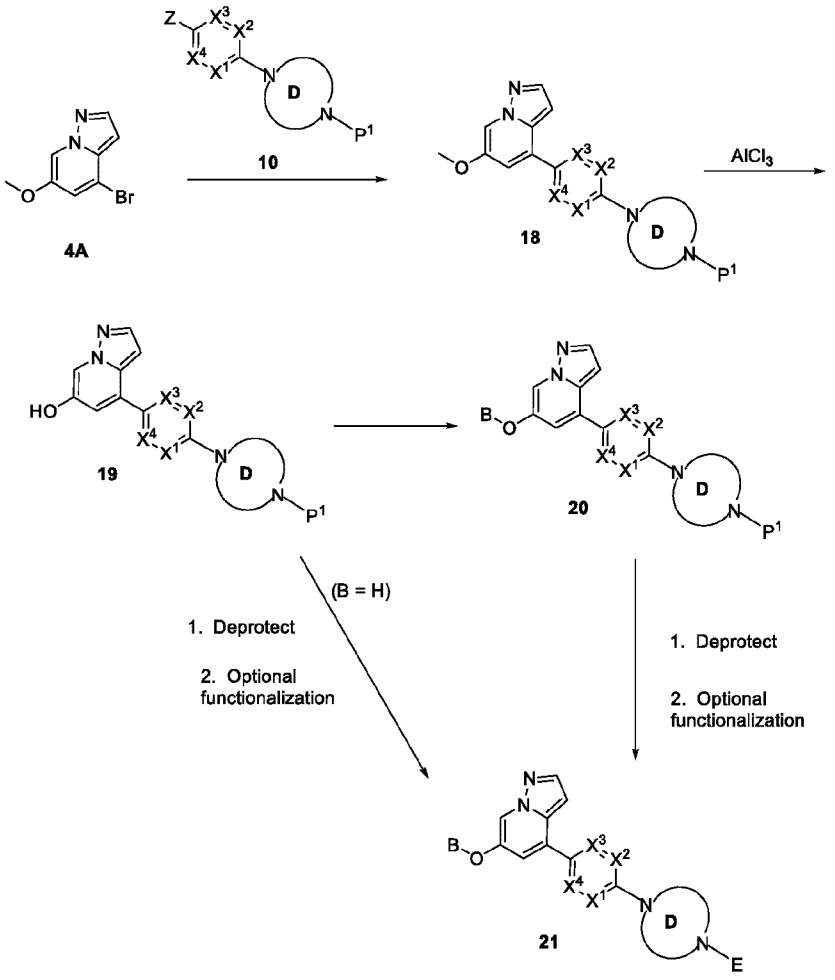
SCHEME 2

[00547] Scheme 2 shows another general scheme for the synthesis of compound **12** wherein A is CN, and B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**.

[00548] Compound **9** (prepared, e.g., as described in Scheme 1) in which B is as defined for Formula **I**, may be coupled with the corresponding boronic ester **13** (wherein X^1, X^2, X^3 and X^4 are as defined for Formula **I**; L^2 is a leaving group such as a triflate or halide); Z is -B(OR^x)(OR^y) and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)), using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures) to provide compound **14**. Compound **16** may be prepared by coupling compound **14** with compound **15** wherein Ring D is as defined for Formula I and P^1 is an amino protecting group, under appropriate S_NAr conditions (for example, optionally in the presence of a base such as K_2CO_3 and at elevated temperature).

[00549] The protecting group P^1 on Ring D ring of compound **16** may be removed under standard conditions (for example, a Boc group may be removed by treating compound **1** to acidic conditions, e.g., HCl) to provide compound **12** wherein E is H. Alternatively, the deprotected Ring D may be functionalized (i.e., reacted or treated with an appropriate reagent) to introduce the E

group under standard conditions such as described below to provide compound **12** wherein E is as defined for Formula **I** except that E is not H.



SCHEME 3

[00550] Scheme 3 shows a general scheme for the synthesis of Compound **21** wherein A is H, and B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**.

[00551] Compound **18** may be prepared by coupling compound **4A** (prepared e.g., as described in Scheme 1) with the corresponding boronic ester compound **10** (wherein Ring D, X^1, X^2, X^3 and X^4 are as defined for Formula **I**; P^1 is an amino protecting group; Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are

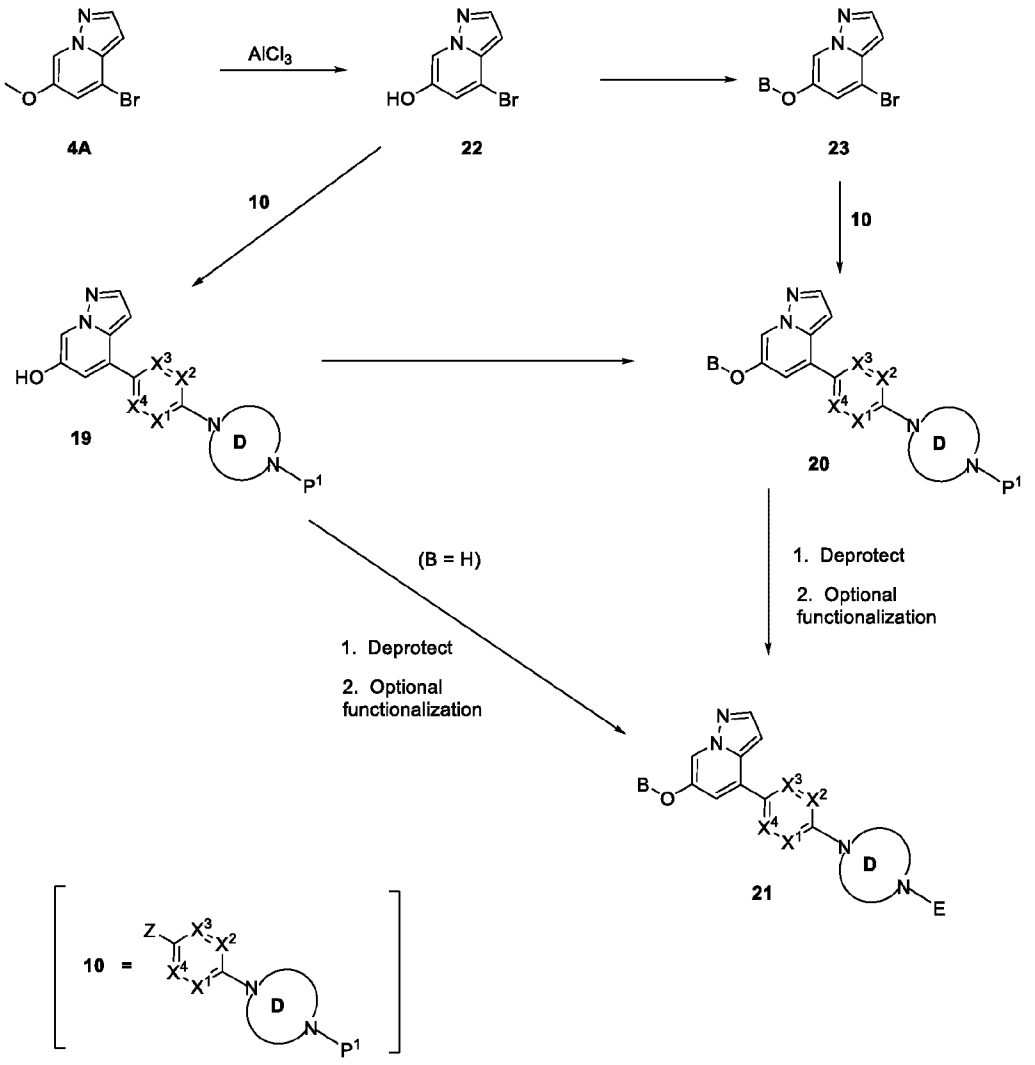
connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures. Compound **19** may be prepared by treating compound **18** with aluminum trichloride.

[00552] To prepare compound **21** wherein B is as defined for Formula **I** other than hydrogen, compound **20** may be prepared by reacting compound **19** with reagent such as C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X, dihydroxyC3-C6 alkyl-X, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X wherein R^1 and R^2 are as defined for Formula **I**, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, (hetCyc[a])C1-C3alkyl-X or hetCyc[a]-X, wherein $hetAr^1$ and hetCyc[a] are as defined for Formula **I** and X is a leaving atom or group (such as a halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if the B group has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound may be prepared by reacting compound **19** with a C1-C6 alkyl-X wherein said alkyl is optionally substituted with 1-3 fluoros and X is a halogen such as Br or Cl, or a leaving group such as triflate. The protecting group P^1 on Ring D ring of compound **20** may be removed under standard conditions (for example, a Boc group may be removed by treating compound **20** to acidic conditions, e.g., HCl) to provide compound **21** wherein E is H. Alternatively, the deprotected Ring D of compound **21** may be functionalized (i.e., reacted or treated with an appropriate reagent) to introduce the E group under standard conditions such as described below to provide compound **21** wherein E is as defined for Formula **I** except that E is not H.

[00553] Alternatively, to prepare compound **21** wherein B is as defined for Formula **I** other than hydrogen, compound **19** may be reacted with a reagent such as C1-C6 alkyl-OH optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-OH, dihydroxyC3-C6 alkyl-OH, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-OH wherein R^1 and R^2 are as defined for Formula **I**, $hetAr^1$C1-C3 alkyl-OH, (C3-C6 cycloalkyl)C1-C3 alkyl-OH, (hetCyc[a])C1-C3alkyl-OH, or hetCyc[a]-OH, wherein $hetAr^1$ and hetCyc[a] are defined for Formula **I**, wherein each of said reagents is optionally substituted with a protecting group, under Mitsunobu reaction conditions (e.g., PPh_3 and diisopropyl azodicarboxylate) to provide compound

20. Compound **21** may then be prepared from compound **20** as described above, followed by removal of the protecting group on B if present.

[00554] When group B is hydrogen, compound **21** may be prepared from compound **19** according to the deprotection and optional functionalization steps described herein.



SCHEME 4

[00555] Scheme 4 shows an alternative general scheme for the synthesis of Compound **21** wherein A is H, and B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**.

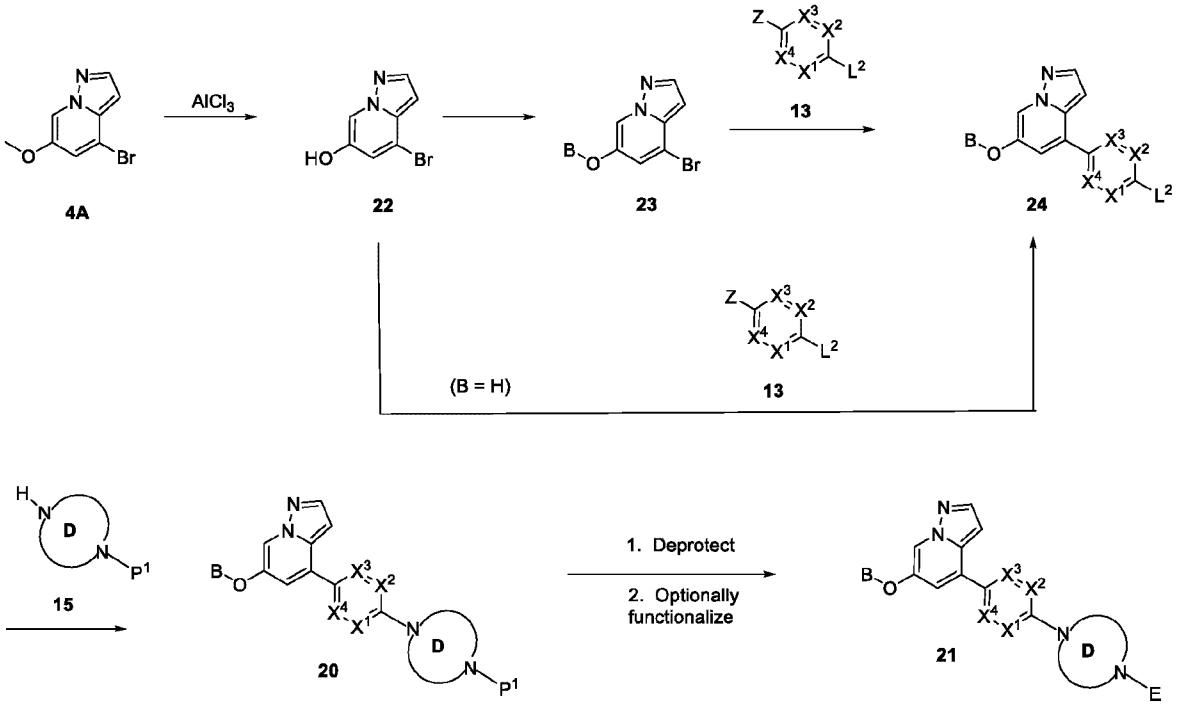
[00556] Compound **22** may be prepared by treating compound **4A** (prepared e.g., as described in Scheme 1) with aluminum trichloride.

[00557] To prepare compound **21** wherein B is hydrogen, compound **19** may be prepared by coupling compound **22** with the corresponding boronic ester compound **10** (wherein Ring D, X^1, X^2, X^3 and X^4 are as defined for Formula **I**; P^1 is an amino protecting group; Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures). Compound **21** may be prepared from compound **19** according to the process described for Scheme 3.

[00558] Alternatively, to prepare compound **21** wherein B is as defined for Formula **I** other than hydrogen, compound **23** may be prepared by reacting compound **22** with reagent such as C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X, dihydroxyC3-C6 alkyl-X, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X wherein R^1 and R^2 are as defined for Formula **I**, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, $(hetCyc^a)$C1-C3 alkyl-X or $hetCyc^a$-X, wherein $hetAr^1$ and $hetCyc^a$ are defined for Formula **I** and X is a leaving atom or group (such as a halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if the B group has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound **23** may be prepared by reacting compound **22** with a C1-C6 alkyl-X wherein said alkyl is optionally substituted with 1-3 fluoros and X is a halogen such as Br or Cl, or a leaving group such as triflate. Compound **20** may be prepared by coupling compound **23** with compound **10** as described in Scheme 3. Compound **21** may be prepared from compound **20** according to the process described for Scheme 3.

[00559] Alternatively, to prepare compound **21** wherein B is as defined for Formula **I** other than hydrogen, compound **19** may be reacted with a reagent such as C1-C6 alkyl-OH optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-OH, dihydroxyC3-C6 alkyl-OH, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-OH wherein R^1 and R^2 are as defined for Formula **I**, $hetAr^1$C1-C3 alkyl-OH, (C3-C6 cycloalkyl)C1-C3 alkyl-

OH, (hetCyc[a])C1-C3alkyl-OH, or hetCyc[a]-OH, wherein hetAr[1] and hetCyc[a] are defined for Formula **I**, wherein each of said reagents is optionally substituted with a protecting group, under Mitsunobu reaction conditions (e.g., PPh_3 and diisopropyl azodicarboxylate) to provide compound **20**. Compound **21** may then be prepared from compound **20** as described for Scheme 3, followed by removal of the protecting group on B if present.



SCHEME 5

[00560] Scheme 5 shows an alternative general scheme for the synthesis of Compound **21** wherein A is H, and B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**.

[00561] Compound **22** may be prepared by treating compound **4A** (prepared e.g., as described in Scheme 1) with aluminum trichloride.

[00562] To prepare compound **21** wherein B is as defined for Formula **I** other than hydrogen, compound **23** may be prepared by reacting compound **22** with reagent such as C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X, dihydroxyC3-C6 alkyl-X, (C1-C6

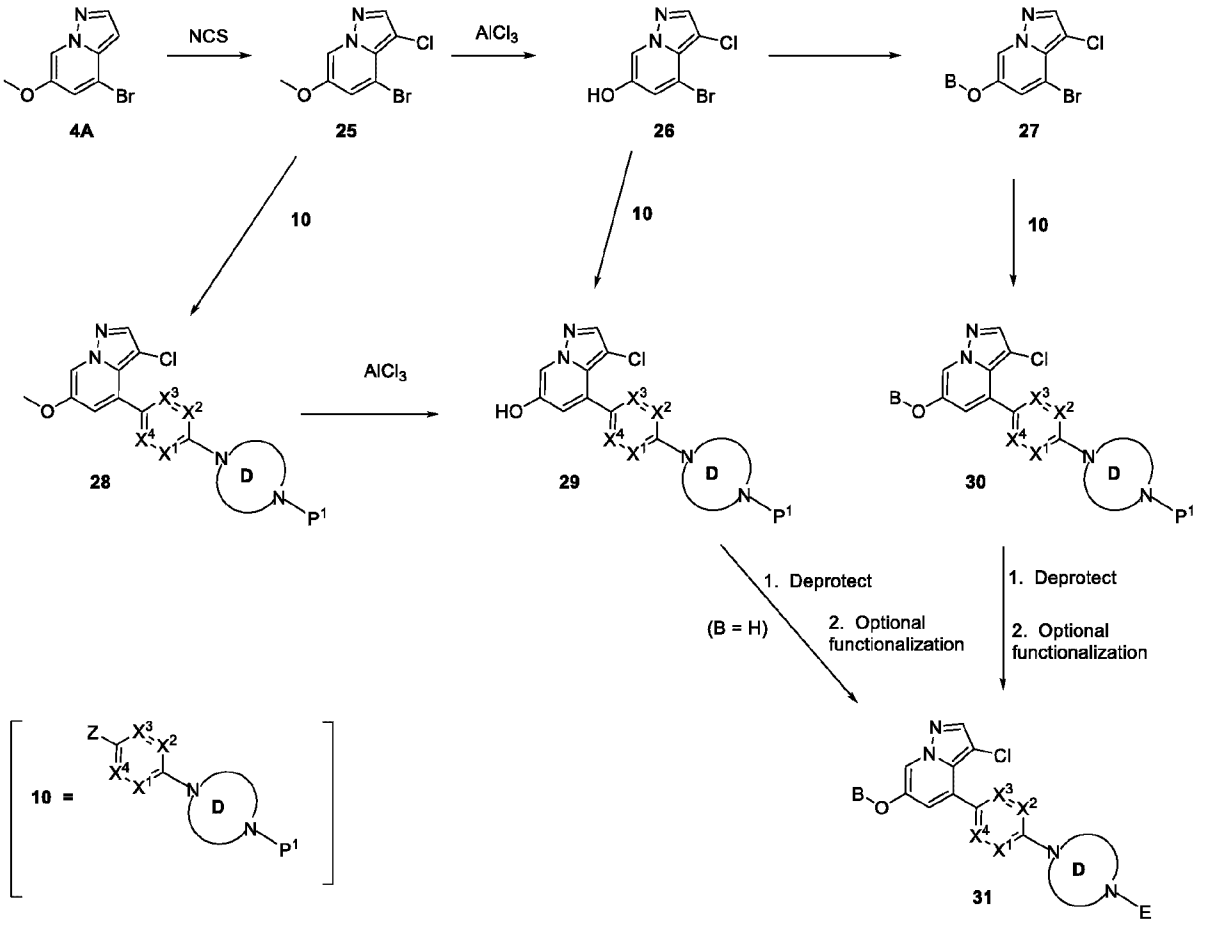
alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X wherein R^1 and R^2 are as defined for Formula **I**, $hetAr^1$C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X , ($hetCyc^a$)C1-C3 alkyl-X or $hetCyc^a$-X, wherein $hetAr^1$ and $hetCyc^a$ are defined for Formula **I** and X is a leaving atom or group (such as a halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if the B group has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound may be prepared by reacting compound **22** with a C1-C6 alkyl-X wherein said alkyl is optionally substituted with 1-3 fluoros and X is a halogen such as Br or Cl, or a leaving group such as triflate.

[00563] Compound **24** may be prepared by reacting compound **23** with the boronic ester **13** (wherein X^1, X^2, X^3 and X^4 are as defined for Formula **I**; L^2 is a leaving group such as a triflate or halide); Z is -B(OR^x)(OR^y) and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures).

[00564] To prepare compound **21** wherein B is hydrogen, compound **24** may be prepared by reacting compound **22** directly with compound **13** as described above.

[00565] Compound **20** may be prepared by coupling compound **24** with compound **15** wherein P^1 is an amino protecting group under appropriate S_NAr conditions (for example, optionally in the presence of a base such as K_2CO_3 and at elevated temperature).

[00566] Compound **21** may be prepared from compound **20** according to the process described for Scheme 3.



SCHEME 6

[00567] Scheme 6 shows a general scheme for the synthesis of Compound **31** wherein A is Cl, and B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**.

[00568] Compound **25** may be prepared by treating compound 4A (prepared e.g., as described in Scheme 1) with aluminum trichloride.

[00569] Compound **26** may be prepared by treating compound **25** with aluminum trichloride.

[00570] To prepare compound **31** wherein B is as defined for Formula **I** other than hydrogen, compound **27** may be prepared by reacting compound **26** with reagent such as C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X, dihydroxyC3-C6 alkyl-X, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X wherein R^1

and R^2 are as defined for Formula **I**, hetAr^{1}C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, (hetCyc^a)C1-C3 alkyl-X or hetCyc^a-X, wherein hetAr^1 and hetCyc^a are defined for Formula **I** and X is a leaving atom or group (such as a halide or triflate), wherein each of said reagents is optionally substituted with a protecting group (e.g., a t-butyldimethylsilyl group if the B group has one or two additional hydroxy groups). For example, when B is C1-C6 alkyl optionally substituted with 1-3 fluoros, compound may be prepared by reacting compound **26** with a C1-C6 alkyl-X wherein said alkyl is optionally substituted with 1-3 fluoros and X is a halogen such as Br or Cl, or a leaving group such as triflate.

[00571] Compounds **28** (wherein group B is methyl), **29** (wherein group B is hydrogen) and **30** (wherein group B is other than hydrogen) may be prepared by coupling compounds **25**, **26** and **27**, respectively, with the corresponding boronic ester compound **10** (wherein Ring D, X^1, X^2, X^3 and X^4 are as defined for Formula **I**; P^1 is an amino protecting group; Z is -B(OR^x)(OR^y) and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from (C1-C3 alkyl)) using appropriate palladium-catalyzed cross-coupling reaction conditions, e.g., Suzuki coupling reaction conditions (for example, a palladium catalyst and optionally a ligand in the presence of an inorganic base, for example, $Pd(PPh_3)_4$ and Na_2CO_3 in dioxane at elevated temperatures).

[00572] The protecting group P^1 on Ring D of compound **29** or **30** may be removed under standard conditions (for example, a Boc group may be removed by treating compound **29** or **30** to acidic conditions, e.g., HCl) to provide compound **31** wherein E is H. Alternatively, the deprotected Ring D may be functionalized (i.e., reacted or treated with an appropriate reagent) to include the E group under standard conditions such as described below to provide compound **31** wherein E is as defined for Formula **I** except that E is not H.

[00573] Ring D of compounds **12**, **21** and **31** described in Schemes 1-6 may be functionalized (i.e., reacted or treated with an appropriate reagent) to include an E group, wherein E is any of the E groups defined for Formula **I** with the exception of hydrogen, using standard chemistry well known to persons skilled in the art. As used herein, the term "functionalized" refers to a process step in which a compound of Formula **12, 21** or **31** wherein E is hydrogen is reacted or treated with an appropriate reagent to provide a compound of Formula **12, 21** or **31** wherein E is as defined for Formula **I** other than hydrogen.

[00574] For example, a compound of Formula **I** wherein E is (C1-C6 alkyl)C(=O)- optionally substituted with one to three fluoros; (hydroxy C2-C6 alkyl)C(=O)- optionally substituted with one to three fluoros; (C1-C6 alkoxy)C(=O)-; (C3-C6 cycloalkyl)C(=O)- (wherein said cycloalkyl is optionally substituted with (C1-C6 alkoxy)C1-C6 alkyl or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O); Ar^1(C1-C6 alkyl)C(=O)- (wherein the alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, or C1-C6 alkoxy); $hetAr^2$(C1-C6 alkyl)C(=O)- (wherein the alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl, or C1-C6 alkoxy); or $hetCyc^1$(C1-C6 alkyl)C(=O)-, may be obtained by treating compound **12** having a deprotected Ring D (i.e., compound **12** wherein E is hydrogen) with a corresponding carboxylic acid using conventional amide bond formation conditions, for example by treating the corresponding carboxylic acid with an activating agent (e.g., HATU), followed by addition of the compound **12** having a deprotected Ring D (i.e., wherein E is H) in the presence of a base (e.g., an amine base such as DIEA) in an appropriate solvent (such as DMA) to provide a functionalized compound **12** (i.e., in this instance compound **12** wherein E is (C1-C6 alkyl)C(=O)- optionally substituted with one to three fluoros; (hydroxy C2-C6 alkyl)C(=O)- optionally substituted with one to three fluoros; (C1-C6 alkoxy)C(=O)-; (C3-C6 cycloalkyl)C(=O)- (wherein said cycloalkyl is optionally substituted with (C1-C6 alkoxy)C1-C6 alkyl- or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O); Ar^1(C1-C6 alkyl)C(=O)- (wherein the alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, or C1-C6 alkoxy); $hetAr^2$(C1-C6 alkyl)C(=O)- (wherein the alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, or C1-C6 alkoxy); or $hetCyc^1$(C1-C6 alkyl)C(=O)-). The same chemistry may be utilized with compounds **21** and **31** to prepare functionalized compounds **21** and **31** (i.e., in this instance compounds **21** and **31**, respectively, wherein E is (C1-C6 alkyl)C(=O)- optionally substituted with one to three fluoros; (hydroxy C2-C6 alkyl)C(=O)- optionally substituted with one to three fluoros; (C1-C6 alkoxy)C(=O)-; (C3-C6 cycloalkyl)C(=O)- (wherein said cycloalkyl is optionally substituted with (C1-C6 alkoxy)C1-C6 alkyl- or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O); Ar^1(C1-C6 alkyl)C(=O)- (wherein the alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, or C1-C6 alkoxy); $hetAr^2$(C1-C6 alkyl)C(=O)- (wherein the alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, or (C1-C6)alkoxy); or $hetCyc^1$(C1-C6 alkyl)C(=O)-).

[00575] As another example, a compound of Formula **I** wherein E is hetCyc^{1}C(=O)- or R^{3}R^{4}NC(=O)- may be prepared by first activating the deprotected ring nitrogen in Ring D of compound **12** (i.e., wherein E is H) with triphosgene in the presence of DIEA and in a solvent such as DCM, followed by addition of an amine reagent having the formula hetCyc^1-H or R^{3}R^{4}NH (wherein hetCyc^1-H is a saturated 4-6 membered heterocycle having 1-2 ring heteroatoms independently selected from N, O and S wherein the ring has at least one ring N atom and the "-H" indicates that the hydrogen is on the ring nitrogen atom, wherein said heterocycle is optionally substituted with one or more independently selected C1-C6 alkoxy substituents) to provide a functionalized compound **12** (i.e., in this instance compound **12** wherein E is hetCyc^{1}C(=O)- or R^{3}R^{4}NC(=O)-). The same chemistry may be utilized with compounds **21** and **31** to prepare functionalized compounds **21** and **31** (i.e., in this instance compound **21** and **31**, respectively, wherein E is hetCyc^{1}C(=O)- or R^{3}R^{4}NC(=O)-).

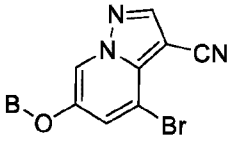
[00576] As another example, a compound of Formula **I** wherein E is C1-C6 alkyl optionally substituted with one to three fluoros, (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, Ar^{1}C1-C6 alkyl-, hetAr^{2}C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or hetCyc^{1}C1-C6 alkyl-, may be prepared by treating deprotected compound **12** (i.e., wherein E is H) with a corresponding reagent having the formula C1-C6 alkyl-X optionally substituted with one to three fluoros, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, Ar^{1}C1-C6 alkyl-X, hetAr^{2}C1-C6 alkyl-X, or hetCyc^{1}C1-C6 alkyl-X wherein X is Br or Cl, in the presence of a base such as DIEA in a solvent at ambient or elevated temperatures) to provide a functionalized compound **12** (i.e., in this instance compound **12** wherein E is C1-C6 alkyl optionally substituted with one to three fluoros, (C1-C6 alkoxy)C1-C6 alkyl optionally substituted with 1-3 fluoros, Ar^{1}C1-C6 alkyl-, hetAr^{2}C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or hetCyc^{1}C1-C6 alkyl-). The same chemistry may be utilized with compounds **21** and **31** to prepare functionalized compounds **21** and **31** (i.e., in this instance in this instance compound **21** and **31**, respectively, wherein E is C1-C6 alkyl optionally substituted with one to three fluoros, (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros, Ar^{1}C1-C6 alkyl-, hetAr^{2}C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or hetCyc^{1}C1-C6 alkyl-).

[00577] As another example, a compound of Formula **I** wherein E is C1-C6 alkyl optionally substituted with one to three fluoros; (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3

fluoros; Ar^1C1-C6 alkyl-, $hetAr^2$C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or $hetCyc^1$C1-C6 alkyl-), may be prepared by treating deprotected compound **12** (i.e., wherein E is H), with corresponding aldehyde, e.g., (C1-C5 alkyl(C=O)H optionally substituted with one to three fluoros; (C1-C6 alkoxy)(C1-C5 alkyl)C(=O)H optionally substituted with one to three fluoros; Ar^1(C1-C5 alkyl)C(=O)H; $hetAr^2$(C1-C5 alkyl)C(=O)H; or $hetCyc^1$(C1-C5 alkyl)-C(=O)H, in the presence of a reducing agent, e.g., $NaBH(AcO)_3$ to provide a functionalized compound **12** (i.e., in this instance compound **12** wherein E is C1-C6 alkyl optionally substituted with one to three fluoros; (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; Ar^1C1-C6 alkyl-, $hetAr^2$C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or $hetCyc^1$C1-C6 alkyl-). The same chemistry may be utilized with compounds **21** and **31** to prepare functionalized compounds **21** and **31** (i.e., in this instance in this instance compounds **21** and **31**, respectively, wherein E is C1-C6 alkyl optionally substituted with one to three fluoros; (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros; Ar^1C1-C6 alkyl-, $hetAr^2$C1-C6 alkyl- wherein the alkyl portion is optionally substituted with 1-3 fluoros, or $hetCyc^1$C1-C6 alkyl-).

[00578] Accordingly, also provided herein is a process for preparing of a compound of Formula **I** or a pharmaceutically acceptable salt thereof as defined herein which comprises:

[00579] (a) for a compound of Formula **I** wherein E is H, A is CN, $-CH_2CN$ or $-CH(CN)CH_3$ and B, X^1, X^2, X^3, X^4, and Ring D are as defined for Formula **I**, coupling a corresponding compound **9** having the formula



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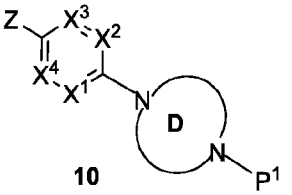
[00580] wherein B is as defined for Formula **I**, with a corresponding boronic ester of the formula **10**



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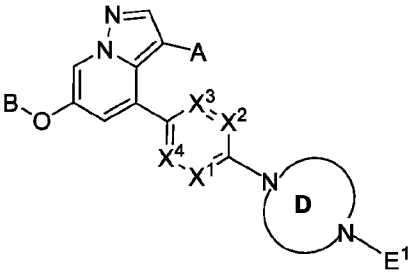
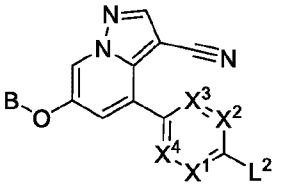
[00581] wherein P^1 is an amino protecting group, Z is $-B(OR^x)(OR^y)$ wherein R^x and R^y are H or C1-C6 alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from C1-C3 alkyl, and X^1, X^2, X^3 and X^4 are as defined for Formula **I**, in the presence of a palladium catalyst and optionally a ligand and in the presence of a base, followed by removal of the protecting group; or

[00582] (b) for a compound of Formula **I** wherein A, B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I** with the exception that E is not hydrogen, functionalizing a corresponding compound of the formula



[00583] wherein A, Ring D, B, X^1, X^2, X^3 and X^4 are as defined for Formula **I** and E^1 is hydrogen; or

[00584] (c) for a compound of Formula **I** wherein A is CN, and Ring D, B, X^1, X^2, X^3, X^4 and E are as defined for Formula **I**, reacting a corresponding compound of the formula **14**



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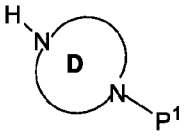
[00585] wherein B, X^1, X^2, X^3 and X^4 are as defined for Formula **I** and L^2 is a leaving group or atom, with a compound of the formula **15**



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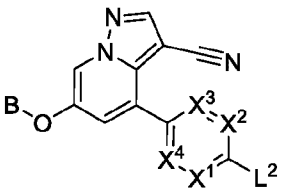
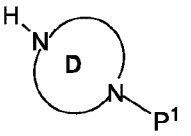
[00586] wherein P^1 is an amino protecting group, followed by removing the protecting group P^1 and optionally functionalizing Ring D; or

[00587] (d) for a compound of Formula **I** wherein E is H, A is CN, and B, X^1, X^2, X^3, X^4, and Ring D are as defined for Formula **I**, coupling a compound of formula **14**



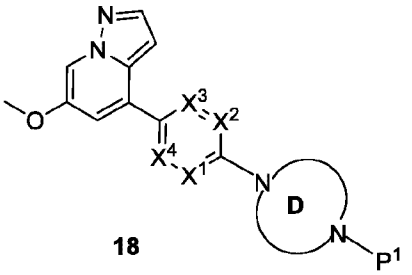
14

[00588] wherein L^2 is a leaving group or atom and B, X^1, X^2, X^3, and X^4 are as defined for Formula **I**, with a compound of formula **15**



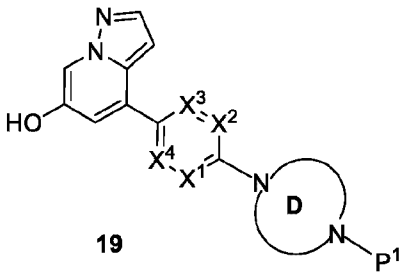
[00589] wherein P^1 is an amino protecting group, followed by removing the protecting group P^1; or

[00590] (e) for a compound of Formula **I** wherein A is H, B is H, and X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**, treating a compound of formula **18**



18

[00591] wherein P^1 is an amino protecting group and X^1, X^2, X^3, X^4, Ring D are as defined for Formula **I**, with aluminum trichloride to provide compound **19**



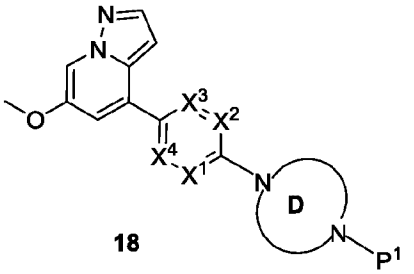
19

[00592] wherein Ring D, X^1, X^2, X^3, and X^4 are as defined for Formula **I** and P^1 is an amino protecting group;

[00593] followed by removal of the protecting group P^1 and optionally functionalizing Ring D; or

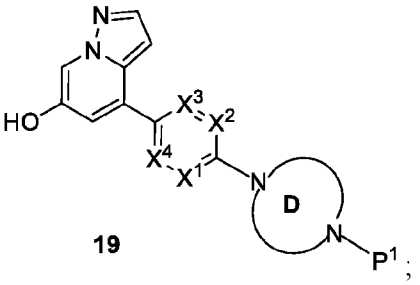
[00594] (f) for a compound of Formula **I** wherein A is H, B is C1-C6 alkyl optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl, dihydroxyC3-C6 alkyl, (C1-C6 alkoxy)C1-C6 alkyl optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl, ($hetAr^1$)C1-C3 alkyl, (C3-C6 cycloalkyl)C1-C3 alkyl, ($hetCyc^a$)C1-C3 alkyl, or $hetCyc^a$, wherein R^1, R^2, $hetAr^1$, $hetCyc^a$, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I,**

[00595] (i) treating a compound of formula **18**



18

[00596] wherein P^1 is an amino protecting group and X^1, X^2, X^3, X^4 and Ring D are as defined for Formula **I**, with aluminum trichloride to provide compound **19**

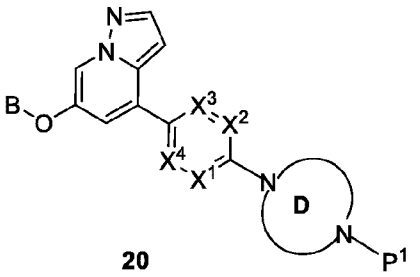


19;

[00597] wherein Ring D is as defined for Formula **I,** P^1 is an amino protecting group, and X^1, X^2, X^3, and X^4 are as defined for Formula **I**;

[00598] (ii) reacting compound **19** with C1-C6 alkyl-X optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl-X wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring, dihydroxyC3-C6 alkyl-X, (C1-C6 alkoxy)C1-C6 alkyl-X optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl-X, ($hetAr^1$)C1-C3 alkyl-X, (C3-C6 cycloalkyl)C1-C3 alkyl-X, ($hetCyc^a$)C1-C3 alkyl-X, or $hetCyc^a$-X, wherein R^1, R^2, $hetAr^1$ and

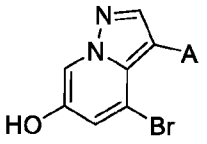
hetCyc[a] are as defined for Formula **I** and X is a leaving atom or group such as a halide or a triflate, in the presence of a base, to provide compound **20**



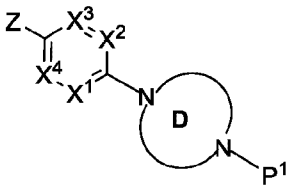
20

[00599] wherein Ring D is as defined for D of Formula **I,** P^1 is an amino protecting group, X^1, X^2, X^3, and X^4 are as defined for Formula **I** and B is C1-C6 alkyl optionally substituted with 1-3 fluoros, hydroxyC2-C6 alkyl, dihydroxyC3-C6 alkyl, (C1-C6 alkoxy)C1-C6 alkyl optionally substituted with 1-3 fluoros, (R^1R^2N)C1-C6 alkyl, ($hetAr^1$)C1-C3 alkyl, (C3-C6 cycloalkyl)C1-C3 alkyl, (hetCyc[a])C1-C3 alkyl, or hetCyc[a], wherein R^1, R^2, $hetAr^1$, hetCyc[a] are as defined for Formula I, followed by removal of the protecting group P^1 and optionally functionalizing Ring D; or

[00600] (g) for a compound of Formula **I** wherein A is H or Cl, B is H, and X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**, treating a compound of formula

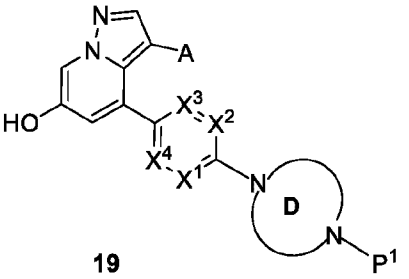


[00601] wherein A is H or Cl with a corresponding boronic ester of formula **10**



10

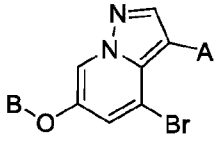
[00602] wherein Ring D, X^1, X^2, X^3 and X^4 are as defined for Formula **I**; P^1 is an amino protecting group; Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from C1-C3 alkyl, to provide a compound of formula **19**



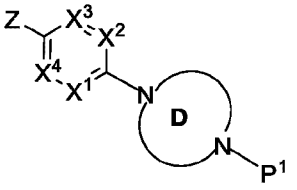
19

[00603] wherein Ring D, X^1, X^2, X^3, and X^4 are as defined for Formula **I**, P^1 is an amino protecting group and A is H or Cl, followed by removal of the protecting group P^1 and optionally functionalizing Ring D; or

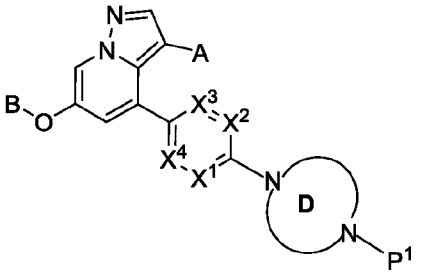
[00604] (h) for a compound of Formula **I** wherein A is H or Cl, and B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**, coupling a compound of the formula



[00605] wherein A is H or Cl, and B is as defined for Formula **I**, with a corresponding boronic ester of formula **10**

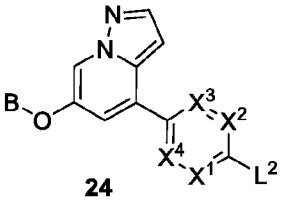


[00606] wherein Ring D, X^1, X^2, X^3 and X^4 are as defined for Formula **I**; P^1 is an amino protecting group, and Z is $-B(OR^x)(OR^y)$ and R^z and R^y are H or (1-6C)alkyl, or R^x and R^y together with the atoms to which they are connected form a 5-6 membered ring optionally substituted with 1-4 substituents selected from C1-C3 alkyl, in the presence of a palladium catalyst and optionally a ligand and in the presence of a base, to provide a compound of the formula



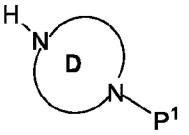
[00607] wherein Ring D, X^1, X^2, X^3, X^4 and B are as defined for Formula **I**; A is H or Cl; and P^1 is an amino protecting group, followed by removal of the protecting group P^1 and optionally functionalizing Ring D;

[00608] (i) for a compound of Formula **I** wherein A is H, and B, X^1, X^2, X^3, X^4, Ring D and E are as defined for Formula **I**, coupling a compound of formula **24**

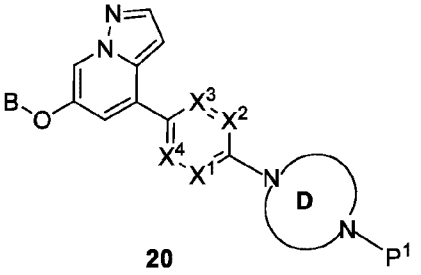


24

[00609] wherein L^2 is a leaving group and B, X^1, X^2, X^3, and X^4 are as defined for Formula **I**, with a compound of formula **15**



[00610] wherein P^1 is an amino protecting group and Ring D is as defined for Formula **I**, to provide a compound of formula **20**



20

[00611] wherein P^1 is an amino protecting group, and Ring D, X^1, X^2, X^3, X^4, and B are as defined for Formula **I,** followed by removal of the protecting group P^1 and optionally functionalizing Ring D; and

[00612] removing any additional protecting groups if present and optionally forming a pharmaceutically acceptable salt thereof.

[00613] The term "amino protecting group" as used herein refers to a derivative of the groups commonly employed to block or protect an amino group while reactions are carried out on other functional groups on the compound. Examples of suitable protecting groups for use in any of the processes described herein include carbamates, amides, alkyl and aryl groups, imines, as well as many N-heteroatom derivatives which can be removed to regenerate the desired amine group. Non-limiting examples of amino protecting groups are acetyl, trifluoroacetyl, t-butyloxycarbonyl ("Boc"), benzyloxycarbonyl ("CBz") and 9-fluorenylmethyleneoxycarbonyl ("Fmoc"). Further examples of these groups, and other protecting groups, are found in T. W. Greene, et al., Greene's Protective Groups in Organic Synthesis. New York: Wiley Interscience, 2006.

[00614] Hydroxy groups may be protected with any convenient hydroxy protecting group, for example as described in T. W. Greene, et al., Greene's Protective Groups in Organic Synthesis. New York: Wiley Interscience, 2006. Examples include benzyl, trityl, silyl ethers, and the like.

[00615] Nitrogen atoms in compounds described in any of the above methods may be protected with any convenient nitrogen protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2nd ed. New York; John Wiley & Sons, Inc., 1991. Examples of nitrogen protecting groups include acyl and alkoxycarbonyl groups, such as t-butoxycarbonyl (BOC), phenoxycarbonyl, and [2-(trimethylsilyl)ethoxy]methyl (SEM).

[00616] The ability of test compounds to act as RET inhibitors may be demonstrated by the assay described in Example A. IC_{50} values are shown in **Table 5**.

[00617] In some embodiments, the compounds provided herein exhibit potent and selective RET inhibition. For example, the compounds provided herein exhibit nanomolar potency against wild type RET and select RET mutants, including the KIF5B-RET fusion and V804M gatekeeper mutation, with minimal activity against related kinases.

[00618] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt or solvate thereof, selectively target a RET kinase. For example, a compound of

Formula I or a pharmaceutically acceptable salt or solvate thereof, can selectively target a RET kinase over another kinase or non-kinase target.

[00619] In some embodiments, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, exhibits at least a 30-fold selectivity for a RET kinase over another kinase. For example, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, exhibits at least a 40-fold selectivity; at least a 50-fold selectivity; at least a 60-fold selectivity; at least a 70-fold selectivity; at least a 80-fold selectivity; at least a 90-fold selectivity; at least 100-fold selectivity; at least 200-fold selectivity; at least 300-fold selectivity; at least 400-fold selectivity; at least 500-fold selectivity; at least 600-fold selectivity; at least 700-fold selectivity; at least 800-fold selectivity; at least 900-fold selectivity; or at least 1000-fold selectivity for a RET kinase over another kinase. In some embodiments, selectivity for a RET kinase over another kinase is measured in a cellular assay (e.g., a cellular assay as provided herein).

[00620] In some embodiments, the compounds provided herein can exhibit selectivity for a RET kinase over a KDR kinase (e.g., VEGFR2). In some embodiments, the selectivity for a RET kinase over a KDR kinase is observed without loss of gatekeeper mutant potency. In some embodiments, the selectivity over a KDR kinase is at least 10-fold (e.g., at least a 40-fold selectivity; at least a 50-fold selectivity; at least a 60-fold selectivity; at least a 70-fold selectivity; at least a 80-fold selectivity; at least a 90-fold selectivity; at least 100-fold selectivity; at least 150-fold selectivity; at least 200-fold selectivity; at least 250-fold selectivity; at least 300-fold selectivity; at least 350-fold selectivity; or at least 400-fold selectivity) as compared to the inhibition of KIF5B-RET (i.e. the compounds were more potent against KIF5B-RET than KDR). In some embodiments, the selectivity for a RET kinase over a KDR kinase is about 30-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 100-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 150-fold. In some embodiments, the selectivity for a RET kinase over a KDR kinase is at least 400-fold. Without being bound by any theory, potent KDR kinase inhibition is believed to be a common feature among multikinase inhibitors (MKIs) that target RET and may be the source of the dose-limiting toxicities observed with such compounds.

[00621] In some embodiments, inhibition of V804M was similar to that observed for wild-type RET. For example, inhibition of V804M was within about 2-fold (e.g., about 5-fold, about 7-fold, about 10-fold) of inhibition of wild-type RET (i.e. the compounds were similarly potent

against wild-type RET and V804M). In some embodiments, selectivity for a wildtype or V804M RET kinase over another kinase is measured in an enzyme assay (e.g., an enzyme assay as provided herein). In some embodiments, the compounds provided herein exhibit selective cytotoxicity to RET-mutant cells.

[00622] In some embodiments, the compounds provided herein exhibit brain and/or central nervous system (CNS) penetrance. Such compounds are capable of crossing the blood brain barrier and inhibiting a RET kinase in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in a therapeutically effective amount. For example, treatment of a patient with cancer (e.g., a RET-associated cancer such as a RET-associated brain or CNS cancer) can include administration (e.g., oral administration) of the compound to the patient. In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor.

[00623] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt or solvate thereof, exhibit one or more of high GI absorption, low clearance, and low potential for drug-drug interactions.

[00624] Compounds of Formula I are useful for treating diseases and disorders which can be treated with a RET kinase inhibitor, such as RET-associated diseases and disorders, e.g., proliferative disorders such as cancers, including hematological cancers and solid tumors, and gastrointestinal disorders such as IBS.

[00625] As used herein, terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[00626] As used herein, the terms "subject," "individual," or "patient," are used interchangeably, refers to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the patient is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the

subject has been identified or diagnosed as having a cancer with a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (a RET-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved assay or kit). The subject can be a subject with a tumor(s) that is positive for a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a dysregulation of a RET gene, a RET protein, or expression or activity, or a level of the same (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a RET-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the patient is a pediatric patient.

[00627] The term "pediatric patient" as used herein refers to a patient under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson *Textbook of Pediatrics*, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. *Rudolph's Pediatrics*, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR. *Pediatric Medicine*, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age

to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

[00628] In certain embodiments, compounds of Formula I are useful for preventing diseases and disorders as defined herein (for example, autoimmune diseases, inflammatory diseases, and cancer). The term "preventing" as used herein means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

[00629] The term "RET-associated disease or disorder" as used herein refers to diseases or disorders associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein), or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a RET gene, a RET kinase, a RET kinase domain, or the expression or activity or level of any of the same described herein). Non-limiting examples of a RET-associated disease or disorder include, for example, cancer and gastrointestinal disorders such as irritable bowel syndrome (IBS).

[00630] The term "RET-associated cancer" as used herein refers to cancers associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein), or expression or activity, or level of any of the same. Non-limiting examples of a RET-associated cancer are described herein.

[00631] The phrase "dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same" refers to a genetic mutation (e.g., a RET gene translocation that results in the expression of a fusion protein, a deletion in a RET gene that results in the expression of a RET protein that includes a deletion of at least one amino acid as compared to the wild-type RET protein, a mutation in a RET gene that results in the expression of a RET protein with one or more point mutations, or an alternative spliced version of a RET mRNA that results in a RET protein having a deletion of at least one amino acid in the RET protein as compared to the wild-type RET protein) or a RET gene amplification that results in overexpression of a RET protein or an autocrine activity resulting from the overexpression of a RET gene in a cell that results in a pathogenic increase in the activity of a kinase domain of a RET protein (e.g., a constitutively active kinase domain of a RET protein) in a cell. As another example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same,

can be a mutation in a RET gene that encodes a RET protein that is constitutively active or has increased activity as compared to a protein encoded by a RET gene that does not include the mutation. For example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of RET that includes a functional kinase domain, and a second portion of a partner protein (i.e., that is not RET). In some examples, dysregulation of a RET gene, a RET protein, or expression or activity or level of any of the same can be a result of a gene translocation of one RET gene with another non-RET gene. Non-limiting examples of fusion proteins are described in Table 1. Non-limiting examples of RET kinase protein point mutations/insertions/deletions are described in Table 2. Additional examples of RET kinase protein mutations (e.g., point mutations) are RET inhibitor resistance mutations. Non-limiting examples of RET inhibitor resistance mutations are described in Tables 3 and 4.

[00632] The term "wildtype" or "wild-type" describes a nucleic acid (e.g., a RET gene or a RET mRNA) or protein (e.g., a RET protein) that is found in a subject that does not have a RET-associated disease, e.g., a RET-associated cancer (and optionally also does not have an increased risk of developing a RET-associated disease and/or is not suspected of having a RET-associated disease), or is found in a cell or tissue from a subject that does not have a RET-associated disease, e.g., a RET-associated cancer (and optionally also does not have an increased risk of developing a RET-associated disease and/or is not suspected of having a RET-associated disease).

[00633] The term "regulatory agency" refers to a country's agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[00634] Provided herein is a method of treating cancer (e.g., a RET-associated cancer) in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. For example, provided herein are methods for treating a RET-associated cancer in a patient in need of such treatment, the method comprising a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression

or activity or level of any of the same includes one or more fusion proteins. Non-limiting examples of RET gene fusion proteins are described in Table 1. In some embodiments, the fusion protein is KIF5B-RET. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET kinase protein point mutations/insertions. Non-limiting examples of RET kinase protein point mutations/insertions/deletions are described in Table 2. In some embodiments, the RET kinase protein point mutations/insertions/deletions are selected from the group consisting of M918T, M918V, C634W, V804L, and V804M. In some embodiments, a compound of Formula I is selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt or solvate thereof.

[00635] In some embodiments of any of the methods or uses described herein, the cancer (e.g., RET-associated cancer) is a hematological cancer. In some embodiments of any of the methods or uses described herein, the cancer (e.g., RET-associated cancer) is a solid tumor. In some embodiments of any of the methods or uses described herein, the cancer (e.g., RET-associated cancer) is lung cancer (e.g., small cell lung carcinoma or non-small cell lung carcinoma), thyroid cancer (e.g., papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, or refractory differentiated thyroid cancer), thyroid ademona, endocrine gland neoplasms, lung adenocarcinoma, bronchioles lung cell carcinoma, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, mammary cancer, mammary carcinoma, mammary neoplasm, colorectal cancer (e.g., metastatic colorectal cancer), papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, inflammatory myofibroblastic tumor, or cervical cancer. In some embodiments of any of the methods or uses described herein, the cancer (e.g., RET-associated cancer) is selected from the group of: acute lymphoblastic leukemia (ALL), acute

myeloid leukemia (AML), cancer in adolescents, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumor, Burkitt lymphoma, carcinoid tumor, unknown primary carcinoma, cardiac tumors, cervical cancer, childhood cancers, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasms, neoplasms by site, neoplasms, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, bile duct cancer, ductal carcinoma in situ, embryonal tumors, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic disease, glioma, hairy cell tumor, hairy cell leukemia, head and neck cancer, thoracic neoplasms, head and neck neoplasms, CNS tumor, primary CNS tumor, heart cancer, hepatocellular cancer, histiocytosis, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma of bone, osteocarcinoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, neoplasms by site, neoplasms, myelogenous leukemia, myeloid leukemia, multiple myeloma, myeloproliferative neoplasms, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer, lung neoplasm, pulmonary cancer, pulmonary neoplasms, respiratory tract neoplasms, bronchogenic carcinoma, bronchial neoplasms, oral cancer, oral cavity cancer, lip cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromosytoma, pituitary cancer, plasma cell neoplasm, pleuropulmonary blastoma, pregnancy and breast cancer, primary central nervous system lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, colon cancer, colonic neoplasms, renal cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Sezary syndrome,

skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach cancer, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, unknown primary carcinoma, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms' tumor.

[00636] In some embodiments, a hematological cancer (e.g., hematological cancers that are RET-associated cancers) is selected from the group consisting of leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocyctic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM). Additional examples of hematological cancers include myeloproliferative disorders (MPD) such as polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic primary myelofibrosis (IMF/IPF/PMF). In one embodiment, the hematological cancer (e.g., the hematological cancer that is a RET-associated cancer) is AML or CMML.

[00637] In some embodiments, the cancer (e.g., the RET-associated cancer) is a solid tumor. Examples of solid tumors (e.g., solid tumors that are RET-associated cancers) include, for example, thyroid cancer (e.g., papillary thyroid carcinoma, medullary thyroid carcinoma), lung cancer (e.g., lung adenocarcinoma, small-cell lung carcinoma), pancreatic cancer, pancreatic ductal carcinoma, breast cancer, colon cancer, colorectal cancer, prostate cancer, renal cell carcinoma, head and neck tumors, neuroblastoma, and melanoma. See, for example, Nature Reviews Cancer, 2014, 14, 173-186.

[00638] In some embodiments, the cancer is selected from the group consisting of lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric

mucosa, and cervical cancer.

[00639] In some embodiments, the patient is a human.

[00640] Compounds of Formula I and pharmaceutically acceptable salts and solvates thereof are also useful for treating a RET-associated cancer.

[00641] Accordingly, also provided herein is a method for treating a patient diagnosed with or identified as having a RET-associated cancer, e.g., any of the exemplary RET-associated cancers disclosed herein, comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein.

[00642] Dysregulation of a RET kinase, a RET gene, or the expression or activity or level of any (e.g., one or more) of the same can contribute to tumorigenesis. For example, a dysregulation of a RET kinase, a RET gene, or expression or activity or level of any of the same can be a translocation, overexpression, activation, amplification, or mutation of a RET kinase, a RET gene, or a RET kinase domain. Translocation can include translocations involving the RET kinase domain, mutations can include mutations involving the RET ligand-binding site, and amplification can be of a RET gene. Other dysregulations can include RET mRNA splice variants and RET autocrine/paracrine signaling, which can also contribute to tumorigenesis.

[00643] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes overexpression of wild-type RET kinase (e.g., leading to autocrine activation). In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, includes overexpression, activation, amplification, or mutation in a chromosomal segment comprising the RET gene or a portion thereof, including, for example, the kinase domain portion, or a portion capable of exhibiting kinase activity.

[00644] In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, includes one or more chromosome translocations or inversions resulting in a RET gene fusion. In some embodiments, the dysregulation of a RET gene, a RET kinase protein, or expression or activity or level of any of the same, is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from a non-RET partner protein, and includes a minimum of a functional RET kinase domain.

[00645] Non-limiting examples of RET fusion proteins are shown in **Table 1**.

[00646] **Table 1. Exemplary RET Fusion Partners and Cancers**

Fusion Partner	Non-limiting Exemplary RET-Associated Cancer(s)
BCR	Chronic Myelomonocytic Leukemia (CMML)
CLIP1	Adenocarcinoma
KIF5B	NSCLC, Ovarian Cancer, Spitzoid Neoplasms; Lung Adenocarcinoma[3, 4, 14, 28]; Adenosquamous Carcinomas[15]
CCDC6 (also called PTC1, D10S170, or H4)	NSCLC, Colon Cancer, Papillary Thyroid Cancer; Adenocarcinomas; Lung Adenocarcinoma; Metastatic Colorectal Cancer[5]; Adenosquamous Carcinomas[15], Breast Cancer[30]
PTC1ex9 (a novel CCDC6 rearrangement)	Metastatic papillary thyroid cancer[2]
NCOA4 (also called PTC3, ELE1, and RFG)	Papillary Thyroid Cancer[21], NSCLC, Colon Cancer, Salivary Gland Cancer, Metastatic Colorectal Cancer[5]; Lung Adenocarcinoma[15]; Adenosquamous Carcinomas[15] Diffuse Sclerosing Variant of Papillary Thyroid Cancer[16], Breast Cancer[30], Acinic Cell Carcinoma[32], Mammary Analog Secretory Carcinoma[33]
TRIM33 (also called PTC7 and RFG7)	NSCLC, Papillary Thyroid Cancer
ERC1 (also called ELKS)	Papillary Thyroid Cancer, Breast Cancer
FGFR1OP	CMML, Primary Myelofibrosis with

Fusion Partner	Non-limiting Exemplary RET-Associated Cancer(s)
	secondary Acute Myeloid Leukemia
MBD1(also known as PCM1)	Papillary Thyroid Cancer
RAB61P2	Papillary Thyroid Cancer
PRKAR1A (also called PTC2)	Papillary Thyroid Cancer
TRIM24 (also called PTC6)	Papillary Thyroid Cancer
KTN1 (also called PTC8)	Papillary Thyroid Cancer
GOLGA5 (also called PTC5)	Papillary Thyroid Cancer, Spitzoid Neoplasms
HOOK3	Papillary Thyroid Cancer
KIAA1468 (also called PTC9 and RFG9)	Papillary Thyroid Cancer, Lung Adenocarcinoma[8, 12]
TRIM27 (also called RFP)	Papillary Thyroid Cancer
AKAP13	Papillary Thyroid Cancer
FKBP15	Papillary Thyroid Cancer
SPECC1L	Papillary Thyroid Cancer; Thyroid Gland Carcinoma
TBL1XR1	Papillary Thyroid Cancer; Thyroid Gland Carcinoma
CEP55	Diffuse Gastric Cancer[7]
CUX1	Lung Adenocarcinoma
ACBD5	Papillary Thyroid Carcinoma
MYH13	Medullary Thyroid Carcinoma[1]
Uncharacterized	Inflammatory Myofibroblastic Tumor[6]
PIBF1	Bronchiolus Lung Cell Carcinoma[9]
KIAA1217 (also called SKT)	Papillary Thyroid Cancer[10, 13] Lung Adenocarcinoma[14] NSCLC[14]
MPRIP	NSCLC[11]
HRH4-RET	Thyroid cancer and/or paillary thyroid carcinoma[17]

Fusion Partner	Non-limiting Exemplary RET-Associated Cancer(s)
Ria-RET	Thyroid cancer and/or papillary thyroid carcinoma[17]
RFG8	Papillary thyroid carcinoma[18]
FOXP4	Lung adenocarcinoma[19]
MYH10	Infantile myofibromatosis[20]
HTIF1	Various[22]
TIF1G	Various[22]
H4L	Various[22]
PTC4 (a novel NCO4/ELE1 rearrangement)	Papillary thyroid cancer[23]
FRMD4A	NSCLC[24]
SQSTM1	Papillary thyroid carcinoma[25]
AFAP1L2	Papillary thyroid carcinoma[25]
AFAP1	NSCLC[31]
PPFIBP2	Papillary thyroid carcinoma[25]
EML4	Papillary thyroid cancer[26]
PARD3	NSCLC[27]
UVELD	Papillary thyroid cancer[29]
RASGEF1A	Breast cancer[30]
TEL	*In vitro*[34]
RUFY1	Colorectal Cancer[35]
OLFM4	Small-Bowel Cancer[36]
UEVLD	Papillary Thyroid Carcinoma[37]
DLG5	Non-Anaplastic Thyroid (NAT) Cancer[38]
RRBP1	Colon Cancer[39]

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[00647] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes one or more deletions (e.g., deletion of an amino acid at position 4), insertions, or point mutation(s) in a RET kinase. In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes a deletion of one or more residues from the RET kinase, resulting in constitutive activity of the RET kinase domain.

[00648] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type RET kinase (see, for example, the point mutations listed in **Table 2**).

[00649] Table 2. Activating RET Kinase Protein Point Mutations/Insertions/Deletions

Exemplary RET Point Mutations
Amino acid position 2
Amino acid position 3
Amino acid position 4
Amino acid position 5
Amino acid position 6

Exemplary RET Point Mutations
Amino acid position 7
Amino acid position 8
Amino acid position 11
Amino acid position 12
Amino acid position 13
Amino acid position 20
Amino acid position 32 (e.g., S32L)
Amino acid position 34 (e.g., D34S)
Amino acid position 40 (e.g., L40P)
Amino acid position 56 (e.g., L56M)[30]
Amino acid position 64 (e.g., P64L)
Amino acid position 67 (e.g., R67H)
Amino acid position 114 (e.g., R114H)
Amino acid position 136 (e.g., glutamic acid to stop codon)
Amino acid position 145 (e.g., V145G)
Amino acid position 180 (e.g., arginine to stop codon)
Amino acid position 200
Amino acid position 292 (e.g., V292M)
Amino acid position 294
Amino acid position 321 (e.g., G321R)
Amino acid position 330 (e.g., R330Q)
Amino acid position 338 (e.g., T338I)
Amino acid position 360 (e.g., R360W)
Amino acid position 373 (e.g., alanine to frameshift)
Amino acid position 393 (e.g., F393L)
Amino acid position 423 (e.g., G423R)[27]
Amino acid position 432
Amino acid position 446 (e.g., G446R)[28]
Δ Amino acid residues 505-506 (6-Base Pair In-Frame Germline Deletion in Exon 7)[3]
Amino acid position 510 (e.g., A510V)
Amino acid position 511 (e.g., E511K)
Amino acid position 513 (e.g., G513D)[7*]
Amino acid position 515 (e.g., C515S, C515W[4])
Amino acid position 525 (e.g., R525W)[7*]
Amino acid position 531 (e.g., C531R, or 9 base pair duplication[2])
Amino acid position 532 (e.g., duplication)[2]
Amino acid position 533 (e.g., G533C, G533S)
Amino acid position 550 (e.g., G550E)
Amino acid position 591 (e.g., V591I)
Amino acid position 593 (e.g., G593E)
Amino acid position 595 (e.g., E595D and E595A)[18]

Exemplary RET Point Mutations
Amino acid position 600 (e.g., R600Q)
Amino acid position 602 (e.g., I602V)[6]
Amino acid position 603 (e.g., K603Q, K603E[2])
Amino acid position 606 (e.g., Y606C)
Amino acid position 609 (e.g., C609Y, C609S, C609G, C609R, C609F, C609W, C609C[32])
Amino acid position 611 (e.g., C611R, C611S, C611G, C611Y, C611F, C611W)
Amino acid position 616 (e.g., E616Q)[23]
Amino acid position 618 (e.g., C618S, C618Y, C618R, C618Y, C618G, C618F, C618W)
Amino acid position 619 (e.g., F619F)
Amino acid position 620 (e.g., C620S, C620W, C620R, C620G, C620L, C620Y, C620F)
Amino acid position 623 (e.g., E623K)
Amino acid position 624 (e.g., D624N)
Amino acid position 630 (e.g., C630A, C630R, C630S, C630Y, C630F, C630W)
Amino acid position 631 (e.g., D631N, D631Y, D631A, D631G, D631V, D631E,)
Amino acid position 632 (e.g., E632K, E632G[5, 11])
Δ Amino acid residues 632-633 (6-Base Pair In-Frame Germline Deletion in Exon 11)[9]
Amino acid position 633 (e.g., 9 base pair duplication[2])
Amino acid position 634 (e.g., C634W, C634Y, C634S, C634R, C634F, C634G, C634L, C634A, or C634T, or an insertion ELCR[2], or a 12 base pair duplication[2]) (e.g., causing MTC)
Amino acid position 635 (e.g., R635G)
Amino acid position 636 (e.g., T636P[2], T636M[4])
Amino acid position 640 (e.g., A640G)
Amino acid position 641 (e.g., A641S, A641T[8])
Amino acid position 648 (e.g., V648I)
Amino acid position 649 (e.g., S649L)[28]
Amino acid position 664 (e.g., A664D)
Amino acid position 665 (e.g., H665Q)
Amino acid position 666 (e.g., K666E, K666M, K666N, K666R)
Amino acid position 675 (T675T, silent nucleotide change)[18]
Amino acid position 686 (e.g., S686N)
Amino acid position 689 (e.g., S689T)[18]
Amino acid position 691 (e.g., G691S)
Amino acid position 694 (e.g., R694Q)

Exemplary RET Point Mutations
Amino acid position 700 (e.g., M700L)
Amino acid position 706 (e.g., V706M, V706A)
Amino acid position 713 splice variant (e.g., E713K)[6]
Amino acid position 732 (e.g., E732K)[20]
Amino acid position 736 (e.g., G736R)[6]
Amino acid position 748 (e.g., G748C)
Amino acid position 750 (e.g., A750P)
Amino acid position 765 (e.g., S765P)
Amino acid position 766 (e.g., P766S, P766M[6])
Amino acid position 768 (e.g., E768Q, E768D)
Amino acid position 769 (e.g., L769L)
Amino acid position 770 (e.g., R770Q)
Amino acid position 771 (e.g., D771N)
Amino acid position 777 (e.g., N777S)
Amino acid position 778 (e.g., V778I)
Amino acid position 781 (e.g., Q781R)
Amino acid position 788 (e.g., I788I[32])
Amino acid position 790 (e.g., L790F)
Amino acid position 791 (e.g., Y791F, Y791N[24])
Amino acid position 802
Amino acid position 804 (e.g., V804L[15, 16], V804M[15, 16], V804E[12]) (e.g., causing MTC)
Amino acid position 805 (e.g., E805K)
Amino acid position 804/805 (e.g., V804M/E805K)[17]
Amino acid position 806 (e.g., Y806F, Y806S[12], Y806G, Y806C[2, 12, 14], Y806E[14], Y806H[12], Y806N[12], Y806Y[32])
Amino acid position 810 (e.g., G810R[12], G810S[12], G810A[13])
Amino acid position 818 (e.g., E818K)
Amino acid position 819 (e.g., S819I)
Amino acid position 823 (e.g., G823E)
Amino acid position 826 (e.g., Y826M, Y826S)[10]
Amino acid position 833 (e.g., R833C)
Amino acid position 836 (e.g., S836S)[19]
Amino acid position 841 (e.g., P841L, P841P)
Amino acid position 843 (e.g., E843D)
Amino acid position 844 (e.g., R844W, R844Q, R844L)
Amino acid position 848 (e.g., M848T)
Amino acid position 852 (e.g., I852M)
Amino acid position 865 (e.g., L865V)[12]
Amino acid position 870 (e.g., L870F)[12]

Exemplary RET Point Mutations
Amino acid position 873 (e.g., R873W)
Amino acid position 876 (e.g., A876V)
Amino acid position 881 (e.g., L881V)
Amino acid position 882
Amino acid position 883 (e.g., A883F, A883S, A883T)
Amino acid position 884 (e.g., E884K)
Amino acid position 886 (e.g., R886W)
Amino acid position 891 (e.g., S891A, S891S[32])
Amino acid position 897 (e.g., R897Q)
Amino acid position 898 (e.g., D898V)
Amino acid position 900 (e.g., Y900F)[22]
Amino acid position 901 (e.g., E901K)
Amino acid position 904 (e.g., S904F, S904S, S904C[2])
Amino acid position 905 (e.g., Y905F)[22]
Amino acid position 907 (e.g., K907E, K907M)
Amino acid position 908 (e.g., R908K)
Amino acid position 911 (e.g., G911D)
Amino acid position 912 (e.g., R912P, R912Q)
Amino acid position 918 (e.g., M918T[2], M918V, M918L[6]) (e.g., causing MTC)
Amino acid position 919 (e.g., A919V)
Amino acid position 921 (e.g., E921K)
Amino acid position 922 (e.g., S922P, S922Y)
Amino acid position 930 (e.g., T930M)
Amino acid position 961 (e.g., F961L)
Amino acid position 972 (e.g., R972G)
Amino acid position 981 (e.g., Y981F)[22]
Amino acid position 982 (e.g., R982C)
Amino acid position 1009 (e.g., M1009V)
Amino acid position 1015 (e.g., Y1015F)[22]
Amino acid position 1017 (e.g., D1017N)
Amino acid position 1041 (e.g., V1041G)
Amino acid position 1064 (e.g., M1064T)
Amino acid position 1096 (e.g., Y1096F)[21]
RET+3[1]
(In-Frame Deletion in Exons 6 and 11)[25]
(3bp In-Frame Deletion in Exon 15)[26]
Nucleotide position 2136+2 (e.g., 2136+2T>G)[29]
(del632-636 ins6)[31]
Amino acid positions 791 and 852 (e.g., Y791F + I852M)[31]
Amino acid positions 634 and 852 (e.g., C634R + I852M)[31]

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[00650] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type RET kinase (see, for example, the point mutations listed in **Table 2a**).

[00651] Table 2a Exemplary activating RET Kinase Protein Point Mutations/Insertions/Deletions

Exemplary RET Point Mutations
Amino acid position 20
Amino acid position 32 (e.g., S32L)
Amino acid position 34 (e.g., D34S)
Amino acid position 40 (e.g., L40P)
Amino acid position 64 (e.g., P64L)
Amino acid position 67 (e.g., R67H)

Exemplary RET Point Mutations
Amino acid position 114 (e.g., R114H)
Amino acid position 145 (e.g., V145G)
Amino acid position 200
Amino acid position 292 (e.g., V292M)
Amino acid position 294
Amino acid position 321 (e.g., G321R)
Amino acid position 330 (e.g., R330Q)
Amino acid position 338 (e.g., T338I)
Amino acid position 360 (e.g., R360W)
Amino acid position 393 (e.g., F393L)
Amino acid position 432
Δ Amino acid residues 505-506 (6-Base Pair In-Frame Germline Deletion in Exon 7)
Amino acid position 510 (e.g., A510V)
Amino acid position 511 (e.g., E511K)
Amino acid position 513 (e.g., G513D)
Amino acid position 515 (e.g., C515S, C515W[4])
Amino acid position 525 (e.g., R525W)
Amino acid position 531 (e.g., C531R, or 9 base pair duplication)
Amino acid position 532 (e.g., duplication)
Amino acid position 533 (e.g., G533C, G533S)
Amino acid position 550 (e.g., G550E)
Amino acid position 591 (e.g., V591I)
Amino acid position 593 (e.g., G593E)
Amino acid position 595 (e.g., E595D and E595A)
Amino acid position 600 (e.g., R600Q)
Amino acid position 602 (e.g., I602V)
Amino acid position 603 (e.g., K603Q, K603E)
Amino acid position 606 (e.g., Y606C)
Amino acid position 609 (e.g., C609Y, C609S, C609G, C609R, C609F, C609W)
Amino acid position 611 (e.g., C611R, C611S, C611G, C611Y, C611F, C611W)
Amino acid position 616 (e.g., E616Q)
Amino acid position 618 (e.g., C618S, C618Y, C618R, C618G, C618F, C618W)
Amino acid position 620 (e.g., C620S, C620W, C620R, C620G, C620L, C620Y, C620F)
Amino acid position 623 (e.g., E623K)
Amino acid position 624 (e.g., D624N)
Amino acid position 630 (e.g., C630A, C630R, C630S, C630Y, C630F, C630W)

Exemplary RET Point Mutations
Amino acid position 631 (e.g., D631N, D631Y, D631A, D631G, D631V, D631E,)
Amino acid position 632 (e.g., E632K, E632G)
Δ Amino acid residues 632-633 (6-Base Pair In-Frame Germline Deletion in Exon 11)
Amino acid position 633 (e.g., 9 base pair duplication)
Amino acid position 634 (e.g., C634W, C634Y, C634S, C634R, C634F, C634G, C634L, C634A, or C634T, or an insertion ELCR, or a 12 base pair duplication) (e.g., causing MTC)
Amino acid position 635 (e.g., R635G)
Amino acid position 636 (e.g., T636P, T636M)
Amino acid position 640 (e.g., A640G)
Amino acid position 641 (e.g., A641S, A641T)
Amino acid position 648 (e.g., V648I)
Amino acid position 649 (e.g., S649L)
Amino acid position 664 (e.g., A664D)
Amino acid position 665 (e.g., H665Q)
Amino acid position 666 (e.g., K666E, K666M, K666N, K666R)
Amino acid position 686 (e.g., S686N)
Amino acid position 689 (e.g., S689T)
Amino acid position 691 (e.g., G691S)
Amino acid position 694 (e.g., R694Q)
Amino acid position 700 (e.g., M700L)
Amino acid position 706 (e.g., V706M, V706A)
Amino acid position 713 splice variant (e.g., E713K)
Amino acid position 732 (e.g., E732K)
Amino acid position 736 (e.g., G736R)
Amino acid position 748 (e.g., G748C)
Amino acid position 750 (e.g., A750P)
Amino acid position 765 (e.g., S765P)
Amino acid position 766 (e.g., P766S, P766M)
Amino acid position 768 (e.g., E768Q, E768D)
Amino acid position 769 (e.g., L769L)
Amino acid position 770 (e.g., R770Q)
Amino acid position 771 (e.g., D771N)
Amino acid position 777 (e.g., N777S)
Amino acid position 778 (e.g., V778I)
Amino acid position 781 (e.g., Q781R)
Amino acid position 790 (e.g., L790F)
Amino acid position 791 (e.g., Y791F, Y791N)
Amino acid position 802

Exemplary RET Point Mutations
Amino acid position 804 (e.g., V804L, V804M, V804E) (e.g., causing MTC)
Amino acid position 805 (e.g., E805K)
Amino acid position 804/805 (e.g., V804M/E805K)
Amino acid position 806 (e.g., Y806F, Y806S, Y806G, Y806C, Y806E, Y806H, Y806N)
Amino acid position 810 (e.g., G810R, G810S, G810A)
Amino acid position 818 (e.g., E818K)
Amino acid position 819 (e.g., S819I)
Amino acid position 823 (e.g., G823E)
Amino acid position 826 (e.g., Y826M, Y826S)
Amino acid position 833 (e.g., R833C)
Amino acid position 836 (e.g., S836S)
Amino acid position 841 (e.g., P841L, P841P)
Amino acid position 843 (e.g., E843D)
Amino acid position 844 (e.g., R844W, R844Q, R844L)
Amino acid position 848 (e.g., M848T)
Amino acid position 852 (e.g., I852M)
Amino acid position 865 (e.g., L865V)
Amino acid position 870 (e.g., L870F)
Amino acid position 873 (e.g., R873W)
Amino acid position 876 (e.g., A876V)
Amino acid position 881 (e.g., L881V)
Amino acid position 882
Amino acid position 883 (e.g., A883F, A883S, A883T)
Amino acid position 884 (e.g., E884K)
Amino acid position 886 (e.g., R886W)
Amino acid position 891 (e.g., S891A)
Amino acid position 897 (e.g., R897Q)
Amino acid position 898 (e.g., D898V)
Amino acid position 900 (e.g., Y900F)
Amino acid position 901 (e.g., E901K)
Amino acid position 904 (e.g., S904F, S904S, S904C)
Amino acid position 907 (e.g., K907E, K907M)
Amino acid position 908 (e.g., R908K)
Amino acid position 911 (e.g., G911D)
Amino acid position 912 (e.g., R912P, R912Q)
Amino acid position 918 (e.g., M918T, M918V, M918L) (e.g., causing MTC)
Amino acid position 919 (e.g., A919V)
Amino acid position 921 (e.g., E921K)
Amino acid position 922 (e.g., S922P, S922Y)

Exemplary RET Point Mutations
Amino acid position 930 (e.g., T930M)
Amino acid position 961 (e.g., F961L)
Amino acid position 972 (e.g., R972G)
Amino acid position 982 (e.g., R982C)
Amino acid position 1009 (e.g., M1009V)
Amino acid position 1015 (e.g., Y1015F)
Amino acid position 1017 (e.g., D1017N)
Amino acid position 1041 (e.g., V1041G)
Amino acid position 1064 (e.g., M1064T)
Amino acid position 1096 (e.g., Y1096F)
RET+3
(In-Frame Deletion in Exons 6 and 11)
(3bp In-Frame Deletion in Exon 15)

[00652] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes a splice variation in a RET mRNA which results in an expressed protein that is an alternatively spliced variant of RET having at least one residue deleted (as compared to the wild-type RET kinase) resulting in a constitutive activity of a RET kinase domain.

[00653] A "RET kinase inhibitor" as defined herein includes any compound exhibiting RET inhibition activity. In some embodiments, a RET kinase inhibitor is selective for a RET kinase. Exemplary RET kinase inhibitors can exhibit inhibition activity (IC_{50}) against a RET kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a RET kinase inhibitors can exhibit inhibition activity (IC_{50}) against a RET kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

[00654] As used herein, a "first RET kinase inhibitor" or "first RET inhibitor" is a RET kinase inhibitor as defined herein, but which does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as defined herein. As used herein, a "second RET kinase inhibitor" or a "second RET inhibitor" is a RET kinase inhibitor as defined herein, but which does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as defined herein. When both a first and a second RET inhibitor are present in a method provided herein, the first and second RET kinase inhibitor are different.

[00655] In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions or insertions or deletions in a RET gene that results in the production of a RET kinase that has one or more amino acids inserted or removed, as compared to the wild-type RET kinase. In some cases, the resulting RET kinase is more resistant to inhibition of its phosphotransferase activity by one or more first RET kinase inhibitor(s), as compared to a wildtype RET kinase or a RET kinase not including the same mutation. Such mutations, optionally, do not decrease the sensitivity of the cancer cell or tumor having the RET kinase to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof (e.g., as compared to a cancer cell or a tumor that does not include the particular RET inhibitor resistance mutation). In such embodiments, a RET inhibitor resistance mutation can result in a RET kinase that has one or more of an increased V_{max}, a decreased K_m for ATP, and an increased K_D for a first RET kinase inhibitor, when in the presence of a first RET kinase inhibitor, as compared to a wildtype RET kinase or a RET kinase not having the same mutation in the presence of the same first RET kinase inhibitor.

[00656] In other embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, includes at least one point mutation in a RET gene that results in the production of a RET kinase that has one or more amino acid substitutions as compared to the wild-type RET kinase, and which has increased resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as compared to a wildtype RET kinase or a RET kinase not including the same mutation. In such embodiments, a RET inhibitor resistance mutation can result in a RET kinase that has one or more of an increased V_{max}, a decreased K_m, and a decreased K_D in the presence of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as compared to a wildtype RET kinase or a RET kinase not having the same mutation in the presence of the same compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[00657] Examples of RET inhibitor resistance mutations can, e.g., include point mutations, insertions, or deletions in and near the ATP binding site in the tertiary structure of RET kinase, including but not limited to the gatekeeper residue, P-loop residues, residues in or near the DFG motif, and ATP cleft solvent front amino acid residues. Additional examples of these types of mutations include changes in residues that may affect enzyme activity and/or drug binding

including but are not limited to residues in the activation loop, residues near or interacting with the activation loop, residues contributing to active or inactive enzyme conformations, changes including mutations, deletions, and insertions in the loop proceeding the C-helix and in the C-helix. Specific residues or residue regions that may be changed (and are RET inhibitor resistance mutations) include but are not limited to those listed in Table 3 based on the human wildtype RET protein sequence (e.g., SEQ ID NO: 1). Additional examples of RET inhibitor resistance mutation positions are shown in Table 4. Changes to these residues may include single or multiple amino acid changes, insertions within or flanking the sequences, and deletions within or flanking the sequences.

[00658] Exemplary Sequence of Mature Human RET Protein (SEQ ID NO: 1)

MAKATSGAAG LRLLLLLLLP LLGKVALGLY FSRDAYWEKL YVDQAAGTPL LYVHALRDAP EEVPSFRLGQ
HLYGTYRTRL HENNWICIQE DTGLLYLNRS LDHSSWEKLS VRNRGFPLLT VYLKVFLSPT SLREGECQWP
GCARVYFSFF NTSFPACSSL KPRELCFPET RPSFRIRENR PPGTFHQFRL LPVQFLCPNI SVAYRLLEGE
GLPFRCAPDS LEVSTRWALD REQREKYELV AVCTVHAGAR EEVVMVPFPV TVYDEDDSAP TFPAGVDTAS
AVVEFKRKED TVVATLRVFD ADVVPASGEL VRRYTSTLLP GDTWAQQTFR VEHWPNETSV QANGSFVRAT
VHDYRLVLNR NLSISENRTM QLAVLVNDSD FQGPGAGVLL LHFNVSVLPV SLHLPSTYSL SVSRRARRFA
QIGKVCVENC QAFSGINVQY KLHSSGANCS TLGVVTSAED TSGILFVNDT KALRRPKCAE LHYMVVATDQ
QTSRQAQAQL LVTVEGSYVA EEAGCPLSCA VSKRRLECEE CGGLGSPTGR CEWRQGDGKG ITRNFSTCSP
STKTCPDGHC DVVETQDINI CPQDCLRGSI VGGHEPGEPR GIKAGYGTCN CFPEEEKCFC EPEDIQDPLC
DELCRTVIAA AVLFSFIVSV LLSAFCIHCY HKFAHKPPIS SAEMTFRRPA QAFPVSYSSS GARRPSLDSM
ENQVSVDAFK ILEDPKWEFP RKNLVLGKTL GEGEFGKVVK ATAFHLKGRA GYTTVAVKML KENASPSELR
DLLSEFNVLK QVNHPHVIKL YGACSQDGPL LLIVEYAKYG SLRGFLRESR KVGPGYLGSG GSRNSSSLDH
PDERALTMGD LISFAWQISQ GMQYLAEMKL VHRDLAARNI LVAEGRKMKI SDFGLSRDVY EEDSYVKRSQ
GRIPVKWMAI ESLFDHIYTT QSDVWSFGVL LWEIVTLGGN PYPGIPPERL FNLLKTGHRM ERPDNCSEEM
YRLMLQCWKQ EPDKRPVFAD ISKDLEKMMV KRRDYLDLAA STPSDSLIYD DGLSEEETPL VDCNNAPLPR
ALPSTWIENK LYGMSDPNWP GESPVPLTRA DGTNTGFPRY PNDSVYANWM LSPSAAKLMD TFDS

[00659] In some embodiments, compounds of Formula I and pharmaceutically acceptable salts and solvates are useful in treating patients that develop cancers with RET inhibitor resistance mutations (e.g., that result in an increased resistance to a first RET inhibitor, e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E, and/or one or more RET inhibitor resistance mutations listed in Tables 3 and 4) by either dosing in combination or as a follow-up therapy to existing drug treatments (e.g., other RET kinase inhibitors; e.g., first and/or second RET kinase inhibitors). Exemplary first and second RET kinase inhibitors are described herein. In some embodiments, a first or second RET kinase inhibitor can be selected from the group consisting of

cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864.

[00660] In some embodiments, compounds of Formula I or pharmaceutically acceptable salts and solvates thereof are useful for treating a cancer that has been identified as having one or more RET inhibitor resistance mutations (that result in an increased resistance to a first or second RET inhibitor, e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E). Non-limiting examples of RET inhibitor resistance mutations are listed in Tables 3 and 4.

Table 3. RET Inhibitor Resistance Mutations

Exemplary RET Resistance Mutations
Amino acid position 732 (e.g., E732K)[7]
Amino acid position 788 (e.g., I788N)[8]
Amino acid position 804 (e.g., V804M[1, 2], V804L[1, 2], V804E[6])
Amino acid position 804/805 (e.g., V804M/E805K)[3]
Amino acid position 806 (e.g., Y806C[4, 6], Y806E[4], Y806S[6], Y806H[6], Y806N[6])
Amino acid position 810 (e.g., G810A[5], G810R[6], G810S[6])
Amino acid position 865 (e.g., L865V[6])
Amino acid position 870 (e.g., L870F[6])

[1] Yoon et al., *J. Med. Chem.* 59(1):358-73, 2016.

[2] U.S. Patent No. 8,629,135.

[3] Cranston, et al., *Cancer Res.* 66(20):10179-87, 2006.

[4] Carlomagno, et al., *Endocr. Rel. Cancer* 16(1):233-41, 2009.

[5] Huang et al., Mol. Cancer Ther., 2016 Aug 5. pii: molcanther.0258.2016. [Epub ahead of print].

[6] PCT Patent Application Publication No. WO 2016/127074.

[7] Nadezda et al., Summer Undergraduate Research Programs (SURP) Student Abstracts, University of Oklahoma Health Sciences Center, 2016.

[8] Plenker et al., *Sci. Transl. Med.*, 9(394), doi: 10.1126/scitranslmed.aah6144, 2017.

Table 4. Additional Exemplary Amino Acid Positions of RET Inhibitor Resistance Mutations

RET Amino Acid and Position	**Exemplary Mutation**	**Mechanistic Resistance Rationale**
L730	P	Steric hindrance and/or active conformational effect

G731	V	Steric hindrance and/or active conformational effect
E732	K	Steric hindrance and/or active conformational effect
G733	V	Steric hindrance and/or active conformational effect
E734	K	Steric hindrance and/or active conformational effect
L760	M	Active conformational effect
K761	E	Active conformational effect
E762	K	Active conformational effect
N763	D	Active conformational effect
A764	V	Active conformational effect
S765	N	Active conformational effect
P766	A	Active conformational effect
S767	C	Active conformational effect
E768	K	Active conformational effect
L779	M	Steric hindrance and/or active conformational effect
I788	M	Steric hindrance and/or active conformational effect
M868	R	Steric hindrance and/or active conformational effect
K869	E	Steric hindrance and/or active conformational effect
L870	Q	Steric hindrance and/or active conformational effect
V871	M	Steric hindrance and/or active conformational effect
H872	R	Steric hindrance and/or active conformational effect
R873	P	Steric hindrance and/or active conformational effect
D874	Y	Steric hindrance and/or active conformational effect
L881	R	Steric hindrance and/or active conformational effect
L895	M	Active conformational effect
S896	N	Active conformational effect
R897	C	Active conformational effect
D898	Y	Active conformational effect
V899	G	Active conformational effect
Y900	D	Active conformational effect
E901	K	Active conformational effect

E902	K	Active conformational effect
D903	Y	Active conformational effect
S904	C	Active conformational effect
Y905	D	Active conformational effect
V906	M	Active conformational effect
K907	E	Active conformational effect
R908	P	Active conformational effect
S909	C	Active conformational effect
Q910	R	Active conformational effect
G911	C	Active conformational effect
R912	P	Active conformational effect

[00661] The oncogenic role of RET was firstly described in papillary thyroid carcinoma (PTC) (Grieco et al., *Cell*, 1990, 60, 557-63), which arises from follicular thyroid cells and is the most common thyroid malignancy. Approximately 20-30% of PTC harbor somatic chromosomal rearrangements (translocations or inversions) linking the promoter and the 5' portions of constitutively expressed, unrelated genes to the RET tyrosine kinase domain (Greco et al., Q. *J. Nucl. Med. Mol. Imaging*, 2009, 53, 440-54), therefore driving its ectopic expression in thyroid cells. Fusion proteins generated by such rearrangements are termed "RET/PTC" proteins. For example, RET/PTC 1 is a fusion between CCDD6 and RET that is commonly found in papillary thyroid carcinomas. Similarly, both RET/PTC3 and RET/PTC4 are fusions of ELE1 and RET that are commonly found in papillary thyroid carcinomas, although the fusion events resulting RET/PTC3 and RET/PTC4 lead to different proteins with different molecular weights (see e.g., Fugazzola et al., *Oncogene*, 13(5):1093-7, 1996). Some RET fusions associated with PTC are not referred to as "RET/PTC", but instead are referred to as the the fusion protein inself. For example, fusion between RET and both ELKS and PCM1 are found in PTCs, but the fusion proteins are referred to as ELKS-RET and PCM1-RET (see e.g., Romei and Elisei, *Front. Endocrinol. (Lausanne)*, 3:54, doi: 10.3389/fendo.2012.00054, 2012). The role of RET-PTC rearrangements in the pathogenesis of PTC has been confirmed in transgenic mice (Santoro et al., *Oncogene*, 1996, 12, 1821-6). To date, a variety of fusion partners have been identified, from PTC and other cancer types, all providing a protein/protein interaction domain that induces ligand-independent RET

dimerization and constitutive kinase activity (see, e.g., Table 1). Recently, a 10.6 Mb pericentric inversion in chromosome 10, where RET gene maps, has been identified in about 2% of lung adenocarcinoma patients, generating different variants of the chimeric gene KIF5B-RET (Ju et al., *Genome Res.*, 2012, 22, 436-45; Kohno et al., 2012, *Nature Med.*, 18, 375-7; Takeuchi et al., *Nature Med.*, 2012, 18, 378-81; Lipson et al., 2012, *Nature Med.*, 18, 382-4). The fusion transcripts are highly expressed and all the resulting chimeric proteins contain the N-terminal portion of the coiled-coil region of KIF5B, which mediates homodimerization, and the entire RET kinase domain. None of RET positive patients harbor other known oncogenic alterations (such as EGFR or K-Ras mutation, ALK translocation), supporting the possibility that KIF5B-RET fusion could be a driver mutation of lung adenocarcinoma. The oncogenic potential of KIF5B-RET has been confirmed by transfecting the fusion gene into cultured cell lines: similarly to what has been observed with RET-PTC fusion proteins, KIF5B-RET is constitutively phosphorylated and induces NIH-3T3 transformation and IL-3 independent growth of BA-F3 cells. However, other RET fusion proteins have been identified in lung adenocarcinoma patients, such as the CCDC6-RET fusion protein, which has been found to play a key role in the proliferation of the human lung adenocarcinoma cell line LC-2/ad (*Journal of Thoracic Oncology*, 2012, 7(12):1872-1876). RET inhibitors have been shown to be useful in treating lung cancers involving RET rearrangements (Drilon, A.E. et al. *J Clin Oncol* 33, 2015 (suppl; abstr 8007)). RET fusion proteins have also been identified in patients having colorectal cancer (Song Eun-Kee, et al. *International Journal of Cancer*, 2015, 136: 1967-1975).

[00662] Besides rearrangements of the RET sequence, gain of function point mutations of RET proto-oncogene are also driving oncogenic events, as shown in medullary thyroid carcinoma (MTC), which arises from parafollicular calcitonin-producing cells (de Groot, et al., *Endocrine Rev.*, 2006, 27, 535-60; Wells and Santoro, *Clin. Cancer Res.*, 2009, 15, 7119-7122). Around 25% of MTC are associated with multiple endocrine neoplasia type 2 (MEN2), a group of inherited cancer syndromes affecting neuroendocrine organs caused by germline activating point mutations of RET. In MEN2 subtypes (MEN2A, MEN2B and Familial MTC/FMTC) RET gene mutations have a strong phenotype-genotype correlation defining different MTC aggressiveness and clinical manifestations of the disease. In MEN2A syndrome mutations involve one of the six cysteine residues (mainly C634) located in the cysteine-rich extracellular region, leading to ligand-independent homodimerization and constitutive RET activation. Patients develop MTC at a young

age (onset at 5-25 years) and may also develop pheochromocytoma (50%) and hyperparathyroidism. MEN2B is mainly caused by M918T mutation, which is located in the kinase domain. This mutation constitutively activates RET in its monomeric state and alters substrate recognition by the kinase. MEN2B syndrome is characterized by an early onset (< 1 year) and very aggressive form of MTC, pheochromocytoma (50% of patients) and ganglioneuromas. In FMTC the only disease manifestation is MTC, usually occurring at an adult age. Many different mutations have been detected, spanning the entire RET gene. The remaining 75% of MTC cases are sporadic and about 50% of them harbor RET somatic mutations: the most frequent mutation is M918T that, as in MEN2B, is associated with the most aggressive phenotype. Somatic point mutations of RET have also been described in other tumors such as colorectal cancer (Wood et al., *Science*, 2007, 318, 1108-13) and small cell lung carcinoma (*Jpn. J. Cancer Res.*, 1995, 86, 1127-30).

[00663] RET signaling components have been found to be expressed in primary breast tumors and to functionally interact with estrogen receptor-cc pathway in breast tumor cell lines (Boulay et al., *Cancer Res.* 2008, 68, 3743-51; Plaza-Menacho et al., *Oncogene*, 2010, 29, 4648-57), while RET expression and activation by GDNF family ligands could play an important role in perineural invasion by different types of cancer cells (Ito et al., *Surgery*, 2005, 138, 788-94; Gil et al., J. Natl. Cancer Inst., 2010, 102, 107-18; Iwahashi et al., Cancer, 2002, 94, 167-74).

[00664] RET is also expressed in 30-70% of invasive breast cancers, with expression being relatively more frequent in estrogen receptor-positive tumors (Plaza-Menacho, I., et al., *Oncogene*, 2010, 29, 4648-4657; Esseghir, S., et al., *Cancer Res.*, 2007, 67, 11732-11741; Morandi, A., et al., *Cancer Res.*, 2013, 73, 3783-3795; Gattelli, A., *EMBO Mol. Med.*, 2013, 5, 1335-1350).

[00665] The identification of RET rearrangements has been reported in a subset of (patient-derived xenograft) PDX established from colorectal cancer. Although the frequency of such events in colorectal cancer patients remains to be defined, these data suggest a role of RET as a target in this indication (Gozgit et al., AACR Annual Meeting 2014). Studies have shown that the RET promoter is frequently methylated in colorectal cancers, and heterozygous missense mutations, which are predicted to reduce RET expression, are identified in 5-10% of cases, which suggests that RET might have some features of a tumor suppressor in sporadic colon cancers (Luo, Y., et al., *Oncogene*, 2013, 32, 2037-2047; Sjoblom, T., et al., *Science*, 2006, 268-274; Cancer Genome Atlas Network, *Nature*, 2012, 487, 330-337).

[00666] An increasing number of tumor types are now being shown to express substantial

levels of wild-type RET kinase that could have implications for tumor progression and spread. RET is expressed in 50-65% of pancreatic ductal carcinomas, and expression is more frequent in metastatic and higher grade tumors (Ito, Y, et al., *Surgery*, 2005, 138, 788-794; Zeng, Q., et al., *J. Int. Med. Res.* 2008, 36, 656-664).

[00667] In neoplasms of hematopoietic lineages, RET is expressed in acute myeloid leukemia (AML) with monocytic differentiation, as well as in CMML (Gattei, V. et al., *Blood*, 1997, 89, 2925-2937; Gattei, V., et al., *Ann. Hematol*, 1998, 77, 207-210; Camos, M., *Cancer Res.* 2006, 66, 6947-6954). Recent studies have identified rare chromosomal rearrangements that involve RET in patients with chronic myelomonocytic leukemia (CMML). CMML is frequently associated with rearrangements of several tyrosine kinases, which result in the expression of chimeric cytosolic oncoproteins that lead to activation of RAS pathways (Kohlmann, A., et al., *J. Clin. Oncol.* 2010, 28, 2858-2865). In the case of RET, gene fusions that link RET with BCR (BCR-RET) or with fibroblast growth factor receptor 1 oncogene partner (FGFR1OP-RET) were transforming in early hematopoietic progenitor cells and could shift maturation of these cells towards monocytic paths, probably through the initiation of RET-mediated RAS signaling (Ballerini, P., et al., *Leukemia*, 2012, 26, 2384-2389).

[00668] RET expression has also been shown to occur in several other tumor types, including prostate cancer, small-cell lung carcinoma, melanoma, renal cell carcinoma, and head and neck tumors (Narita, N., et al., *Oncogene*, 2009, 28, 3058-3068; Mulligan, L. M., et al., *Genes Chromosomes Cancer*, 1998, 21, 326-332; Flavin, R., et al., *Urol. Oncol.*, 2012, 30, 900-905; Dawson, D. M., *J Natl Cancer Inst*, 1998, 90, 519-523).

[00669] In neuroblastoma, RET expression and activation by GFLs has roles in tumor cell differentiation, potentially collaborating with other neurotrophic factor receptors to down regulate N-Myc, the expression of which is a marker of poor prognosis (Hofstra, R. M., W., et al., *Hum. Genet.* 1996, 97, 362-364; Petersen, S. and Bogenmann, E., *Oncogene*, 2004, 23, 213-225; Brodeur, G. M., *Nature Ref. Cancer*, 2003, 3, 203-216).

[00670] Multitargeted inhibitors which cross react with RET are known (Borrello, M.G., et al., *Expert Opin. Ther. Targets*, 2013, 17(4), 403-419; International Patent Application Nos. WO 2014/141187, WO 2014/184069, and WO 2015/079251).

[00671] Accordingly, provided herein are methods for treating a patient diagnosed with (or identified as having) a cancer that include administering to the patient a therapeutically effective

amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Also provided herein are methods for treating a patient identified or diagnosed as having a RET-associated cancer that include administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. In some embodiments, the patient that has been identified or diagnosed as having a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is a RET-associated cancer. For example, the RET-associated cancer can be a cancer that includes one or more RET inhibitor resistance mutations.

[00672] Also provided are methods for treating cancer in a patient in need thereof, the method comprising: (a) determining if the cancer in the patient is a RET-associated cancer; and (b) if the cancer is determined to be a RET-associated cancer, administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or immunotherapy). In some embodiments, the subject was previously treated with a first RET inhibitor or previously treated with another anticancer treatment, e.g., resection of the tumor or radiation therapy. In some embodiments, the patient is determined to have a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is a RET-associated cancer. For example, the RET-associated cancer can be a cancer that includes one or more RET inhibitor resistance mutations.

[00673] Also provided are methods of treating a patient that include performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and administering (e.g.,

specifically or selectively administering) a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof to the patient determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or immunotherapy). In some embodiments of these methods, the subject was previously treated with a first RET inhibitor or previously treated with another anticancer treatment, e.g., resection of a tumor or radiation therapy. In some embodiments, the patient is a patient suspected of having a RET-associated cancer, a patient presenting with one or more symptoms of a RET-associated cancer, or a patient having an elevated risk of developing a RET-associated cancer. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. Additional, non-limiting assays that may be used in these methods are described herein. Additional assays are also known in the art. In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[00674] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof for use in treating a RET-associated cancer in a patient identified or diagnosed as having a RET-associated cancer through a step of performing an assay (e.g., an in vitro assay) on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, where the presence of a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, identifies that the patient has a RET-associated cancer. Also provided is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a RET-associated cancer in a patient identified or diagnosed as having a RET-associated cancer through a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same where the presence of dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, identifies that the patient has a RET-associated cancer. Some embodiments of any of the methods

or uses described herein further include recording in the patient's clinical record (e.g., a computer readable medium) that the patient is determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, through the performance of the assay, should be administered a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[00675] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of a cancer in a patient in need thereof or a patient identified or diagnosed as having a RET-associated cancer. Also provided is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a cancer in a patient identified or diagnosed as having a RET-associated cancer. In some embodiments, the cancer is a RET-associated cancer, for example, a RET-associated cancer having one or more RET inhibitor resistance mutations. In some embodiments, a patient is identified or diagnosed as having a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the sample. As provided herein, a RET-associated cancer includes those described herein and known in the art.

[00676] In some embodiments of any of the methods or uses described herein, the patient has been identified or diagnosed as having a cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient has a tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient can be a patient with a tumor(s) that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient can be a patient whose tumors have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein,

the patient is suspected of having a RET-associated cancer (e.g., a cancer having one or more RET inhibitor resistance mutations). In some embodiments, provided herein are methods for treating a RET-associated cancer in a patient in need of such treatment, the method comprising a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more fusion proteins. Non-limiting examples of RET gene fusion proteins are described in Table 1. In some embodiments, the fusion protein is KIF5B-RET. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET kinase protein point mutations/insertions/deletions. Non-limiting examples of RET kinase protein point mutations/insertions/deletions are described in Table 2. In some embodiments, the RET kinase protein point mutations/insertions/deletions are selected from the group consisting of M918T, M918V, C634W, V804L, and V804M. In some embodiments, the dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations. Non-limiting examples of RET inhibitor resistance mutations are described in Tables 3 and 4. In some embodiments, the RET inhibitor resistance mutation is V804M. In some embodiments, the cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a tumor positive for one or more RET inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

[00677] In some embodiments of any of the methods or uses described herein, the patient has a clinical record indicating that the patient has a tumor that has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same (e.g., a tumor having one or more RET inhibitor resistance mutations). In some embodiments, the clinical record indicates that the patient should be treated with one or more of the compounds of Formula I or a pharmaceutically acceptable salts or solvates thereof or compositions provided herein. In some embodiments, the

cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a cancer having one or more RET inhibitor resistance mutations. In some embodiments, the cancer with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor that is positive for a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is a tumor positive for one or more RET inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

[00678] Also provided are methods of treating a patient that include administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to a patient having a clinical record that indicates that the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. Also provided is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a RET-associated cancer in a patient having a clinical record that indicates that the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. Some embodiments of these methods and uses can further include: a step of performing an on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and recording the information in a patient's clinical file (e.g., a computer readable medium) that the patient has been identified to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the dysregulation of a RET gene, RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[00679] Also provided herein is a method of treating a subject. The method includes performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a RET gene, a RET protein, or expression or level of any of the same. The method also includes administering to a subject determined to have a dysregulation of a RET gene, a RET

protein, or expression or activity, or level of any of the same a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the dysregulation in a RET gene, a RET kinase protein, or expression or activity of the same is a gene or chromosome translocation that results in the expression of a RET fusion protein (e.g., any of the RET fusion proteins described herein). In some embodiments, the RET fusion can be selected from a KIF5B-RET fusion and a CCDC6-RET fusion. In some embodiments, the dysregulation in a RET gene, a RET kinase protein, or expression or activity or level of any of the same is one or more point mutation in the RET gene (e.g., any of the one or more of the RET point mutations described herein). The one or more point mutations in a RET gene can result, e.g., in the translation of a RET protein having one or more of the following amino acid substitutions: M918T, M918V, C634W, V804L, and V804M. In some embodiments, the dysregulation in a RET gene, a RET kinase protein, or expression or activity or level of any of the same is one or more RET inhibitor resistance mutations (e.g., any combination of the one or more RET inhibitor resistance mutations described herein). Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second RET inhibitor a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or immunotherapy).

[00680] In some embodiments, the compounds provided herein exhibit brain and/or central nervous system (CNS) penetrance. Such compounds are capable of crossing the blood brain barrier and inhibiting a RET kinase in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in a therapeutically effective amount. For example, treatment of a patient with cancer (e.g., a RET-associated cancer such as a RET-associated brain or CNS cancer) can include administration (e.g., oral administration) of the compound to the patient. In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor. For example, the compounds can be used in the treatment of one or more of gliomas such as glioblastoma (also known as glioblastoma multiforme), astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas, meningiomas, medulloblastomas, gangliogliomas, schwannomas (neurilemmomas), and craniopharyngiomas (see, for example, the tumors listed in Louis, D.N. et al. *Acta Neuropathol* 131(6), 803-820 (June 2016)). In some embodiments, the brain tumor is a primary brain tumor. In some embodiments, the patient has previously been treated with

another anticancer agent, e.g., another RET inhibitor (e.g., a compound that is not a compound of General Formula I) or a multi-kinase inhibitor. In some embodiments, the brain tumor is a metastatic brain tumor. In some embodiments, the patient has previously been treated with another anticancer agent, e.g., another RET inhibitor (e.g., a compound that is not a compound of General Formula I) or a multi-kinase inhibitor.

[00681] Also provided are methods (e.g., in vitro methods) of selecting a treatment for a patient identified or diagnosed as having a RET-associated cancer. Some embodiments can further include administering the selected treatment to the patient identified or diagnosed as having a RET-associated cancer. For example, the selected treatment can include administration of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Some embodiments can further include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and identifying and diagnosing a patient determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, as having a RET-associated cancer. In some embodiments, the cancer is a RET-associated cancer having one or more RET inhibitor resistance mutations. In some embodiments, the patient has been identified or diagnosed as having a RET-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient. In some embodiments, the RET-associated cancers is a cancer described herein or known in the art. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes the next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit.

[00682] Also provided herein are methods of selecting a treatment for a patient, wherein the methods include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same (e.g., one or more RET inhibitor resistance mutations), and identifying or diagnosing a patient determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, as having a RET-associated cancer. Some embodiments further include administering the selected treatment to the patient identified or

diagnosed as having a RET-associated cancer. For example, the selected treatment can include administration of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to the patient identified or diagnosed as having a RET-associated cancer. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes the next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit.

[00683] Also provided are methods of selecting a patient for treatment, wherein the methods include selecting, identifying, or diagnosing a patient having a RET-associated cancer, and selecting the patient for treatment including administration of a therapeutically-effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, identifying or diagnosing a patient as having a RET-associated cancer can include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and identifying or diagnosing a patient determined to have a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, as having a RET-associated cancer. In some embodiments, the method of selecting a treatment can be used as a part of a clinical study that includes administration of various treatments of a RET-associated cancer. In some embodiments, a RET-associated cancer is a cancer having one or more RET inhibitor resistance mutations. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes the next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the dysregulation of the RET gene, the RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations.

[00684] In some embodiments of any of the methods or uses described herein, an assay used to determine whether the patient has a dysregulation of a RET gene, or a RET kinase, or expression or activity or level of any of the same, using a sample from a patient can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one

labelled antibody or antigen-binding fragment thereof. Assays can utilize other detection methods known in the art for detecting dysregulation of a RET gene, a RET kinase, or expression or activity or levels of any of the same (see, e.g., the references cited herein). In some embodiments, the dysregulation of the RET gene, the RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations. In some embodiments, the sample is a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from the patient. In some embodiments, the patient is a patient suspected of having a RET-associated cancer, a patient having one or more symptoms of a RET-associated cancer, and/or a patient that has an increased risk of developing a RET-associated cancer)

[00685] In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment or therapy in addition to compositions provided herein may be, for example, surgery, radiotherapy, and chemotherapeutic agents, such as kinase inhibitors, signal transduction inhibitors and/or monoclonal antibodies. Compounds of Formula I therefore may also be useful as adjuvants to cancer treatment, that is, they can be used in combination with one or more additional therapies or therapeutic agents, for example a chemotherapeutic agent that works by the same or by a different mechanism of action.

[00686] In some embodiments of any the methods described herein, the compound of Formula I (or a pharmaceutically acceptable salt or solvate thereof) is administered in combination with a therapeutically effective amount of at least one additional therapeutic agent selected from one or more additional therapies or therapeutic (e.g., chemotherapeutic) agents.

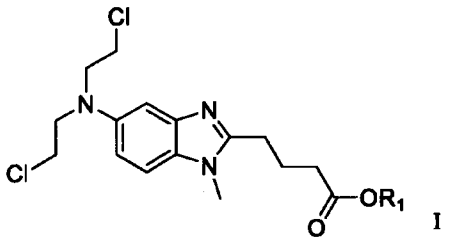
[00687] Non-limiting examples of additional therapeutic agents include: other RET-targeted therapeutic agents (i.e. a first or second RET kinase inhibitor), receptor tyrosine kinase-targeted therapeutic agents, signal transduction pathway inhibitors, checkpoint inhibitors, modulators of the apoptosis pathway (e.g. obataclax); cytotoxic chemotherapeutics, angiogenesis-targeted therapies, immune-targeted agents, including immunotherapy, and radiotherapy.

[00688] In some embodiments, the other RET-targeted therapeutic is a multikinase inhibitor exhibiting RET inhibition activity. In some embodiments, the other RET-targeted therapeutic inhibitor is selective for a RET kinase. Exemplary RET kinase inhibitors can exhibit inhibition activity (IC_{50}) against a RET kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than

about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a RET kinase inhibitors can exhibit inhibition activity (IC_{50}) against a RET kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

[00689] Non-limiting examples of RET-targeted therapeutic agents include alectinib, apatinib, cabozantinib (XL-184), dovitinib, lenvatinib, motesanib, nintedanib, ponatinib, regorafenib, sitravatinib (MGCD516), sunitinib, sorafenib, vatalanib, vandetanib, AUY-922 (5-(2,4-Dihydroxy-5-isopropyl-phenyl)-N-ethyl-4-[4-(morpholinomethyl)phenyl]isoxazole-3-carboxamide), BLU6864, BLU-667, DCC-2157, GSK3179106, NVP-AST487 (1-[4-[(4-ethylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]-3-[4-[6-(methylamino)pyrimidin-4-yl]oxyphenyl]urea), PZ-1, RPI-1 (1,3-dihydro-5,6-dimethoxy-3-[(4-hydroxyphenyl)methylene]-H-indol-2-one), RXDX-105 (1-(3-((6,7-dimethoxyquinazolin-4-yl)oxy)phenyl)-3-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)urea), SPP86 (1-Isopropyl-3-(phenylethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine), and TG101209 (N-(1,1-dimethylethyl)-3-[[5-methyl-2-[[4-(4-methyl-1-piperazinyl)phenyl]amino]-4-pyrimidinyl]amino]-benzenesulfonamide).

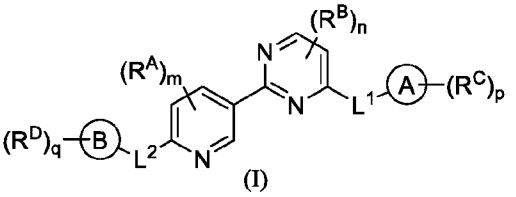
[00690] Additional examples of other RET kinase inhibitors include those described in U.S. Patent Nos. 9,150,517 and 9,149,464, and International Publication No. WO 2014075035. For example, in some embodiments the other RET inhibitor is a compound of formula I:



I

wherein R_1 is C_6-C_{24}alkyl or polyethylene glycol; or a pharmaceutically acceptable salt form thereof. In some embodiments, the other RET inhibitor is 4-{5-[bis-(chloroethyl)-amino]-1-methyl-1H-benzimidazol-2-yl}butyric acid dodecyl ester.

[00691] Additional examples of other RET kinase inhibitors include those described in International Publication No. WO 2016127074. For example, in some embodiments, the other RET inhibitor is a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein:



(I)

wherein Rings A and B are each independently selected from aryl, heteroaryl, cycloalkyl and heterocyclyl;

each L^1 and L^2 is independently selected from a bond, -(C1-C6 alkylene)-, -(C2-C6alkenylene)-, -(C2-C6 alkynylene)-, -(C1-C6 haloalkylene)-, -(C1-C6 heteroalkylene)-, -C(O)-, -O-, -S-, -S(O), -$S(O)_2$-, -$N(R^1)$-, -O-(C1-C6 alkylene)-, -(C1-C6 alkylene)-O-, -$N(R^1)$-C(O)-, -$C(O)N(R^1)$-, -(C1-C6 alkylene)-$N(R^1)$-, -$N(R^1)$-(C1-C6 alkylene)-, -$N(R^1)$-C(O)-(C1-C6 alkylene)-, -(C1-C6 alkylene)-$N(R^1)$-C(O)-, -C(O)-$N(R^1)$-(C1-C6 alkylene)-, -(C1-C6 alkylene)-C(O)-$N(R^1)$-, -$N(R^1)$-$S(O)_2$-, -$S(O)_2$-$N(R^1)$-, -$N(R^1)$-$S(O)_2$-(C1-C6 alkylene)-, and-$S(O)_2$-$N(R^1)$-(C1-C6 alkylene)-; wherein each alkylene, alkenylene, alkynylene, haloalkylene, and heteroalkylene is independently substituted with 0-5 occurrences of R';

each R^A and R^B is independently selected from C1-C6 alkyl, C1-C6 alkoxy, halo, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C1-C6 heteroalkyl, and -$N(R^1)(R^1)$; wherein each alkyl, alkoxy, haloalkyl, hydroxyalkyl, and hydroxyalkyl is independently substituted with 0-5 occurrences of Ra;

each R^C and R^D is independently selected from C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 alkoxy, halo, C1-C6 heteroalkyl, C1-C6 haloalkyl, C1-C6 haloalkoxy, C1-C6 hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, heterocyclylalkyl, nitro, cyano, -$C(O)R^1$, -$OC(O)R^1$, -$C(O)OR^1$, -(C1-C6 alkylene)-$C(O)R^1$, -SR^1,-$S(O)_2R^1$, -$S(O)_2$-$N(R^1)(R^1)$, -(C1-C6 alkylene)-$S(O)_2R^1$, -(C1-C6 alkylene)-$S(O)_2$-$N(R^1)(R^1)$, -$N(R^1)(R^1)$ -C(O)-$N(R^1)(R^1)$-$N(R^1)$-$C(O)R^1$, -$N(R^1)$-$C(O)OR^1$, -(C1-C6 alkylene)-$N(R^1)$-$C(O)R^1$, -$N(R^1)S(O)_2R^1$, and -$P(O)(R^1)(R^1)$; wherein each of alkyl, alkenyl, alkynyl, alkoxy, heteroalkyl, haloalkyl, haloalkoxy, hydroxyalkyl, cycloalkyl, aryl, heteroaryl, aryloxy, aralkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^a; or 2 R^C or 2 R^D together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^a;

each R^1 is independently selected from hydrogen, hydroxyl, halo, thiol, C1-C6 alkyl, C1-C6 thioalkyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, C1-C6 heteroalkyl,

cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of alkyl, thioalkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^b, or 2 R^1 together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring independently substituted with 0-5 occurrences of R^b;

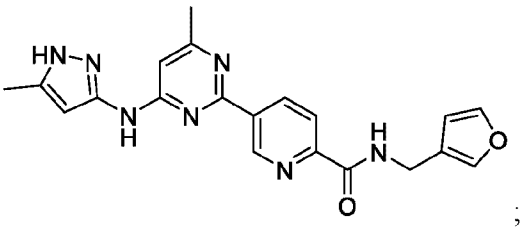
each R^a and R^b is independently C1-C6 alkyl, halo, hydroxyl, C1-C6 haloalkyl, C1-C6 heteroalkyl, C1-C6 hydroxyalkyl, C1-C6 alkoxy, cycloalkyl, heterocyclyl, or cyano, wherein each of alkyl, haloalkyl, heteroalkyl, hydroxyalkyl, alkoxy, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R';

each R' is C1-C6 alkyl, C1-C6 heteroalkyl, halo, hydroxyl, C1-C6 haloalkyl, C1-C6 hydroxyalkyl, cycloalkyl or cyano; or 2 R', together with the atom(s) to which they are attached form a cycloalkyl or heterocyclyl ring;

m is 0, 1, 2, or 3;

n is 0, 1, or 2; and

p and q are each independently 0, 1, 2, 3, or 4. For example, a RET inhibitor can be selected from the group consisting of: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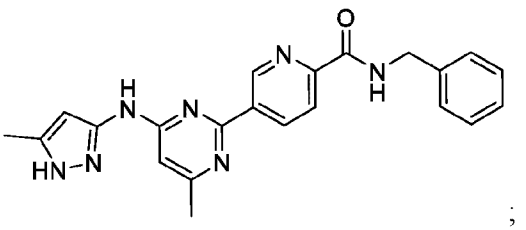
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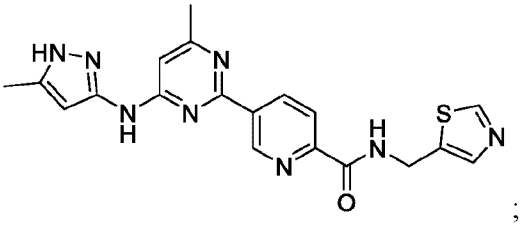
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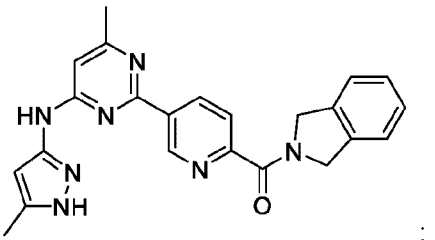
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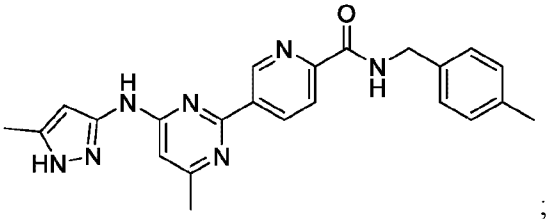
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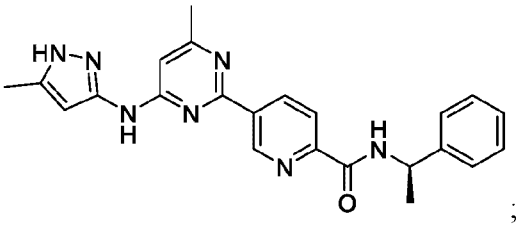
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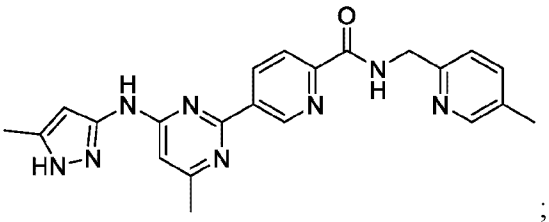
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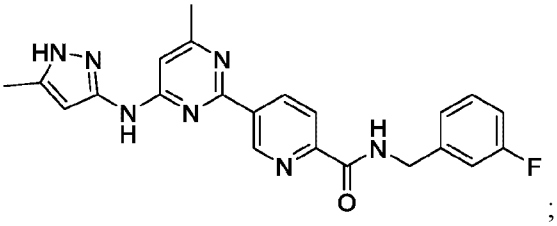
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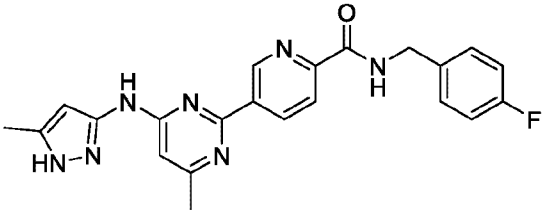
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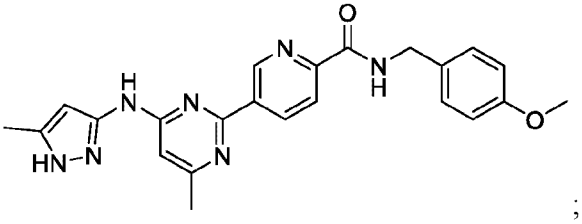
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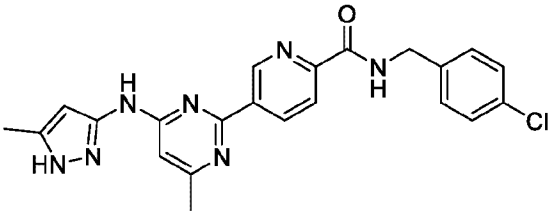
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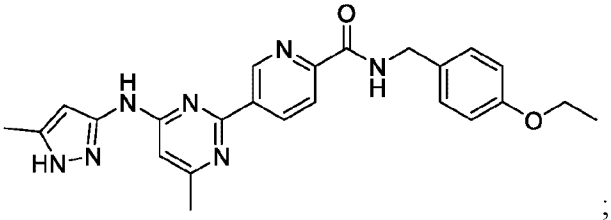
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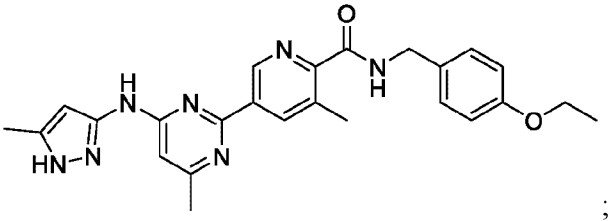
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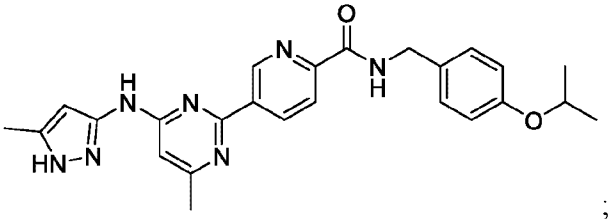
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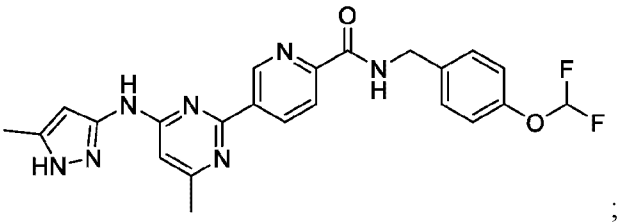
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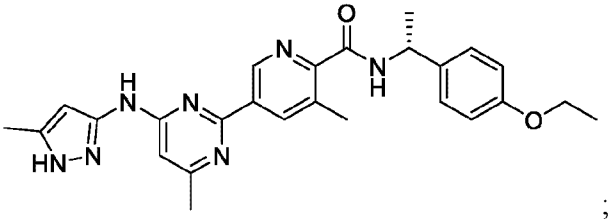
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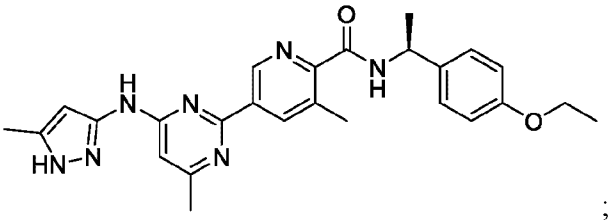
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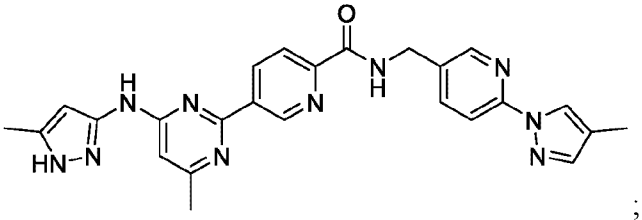
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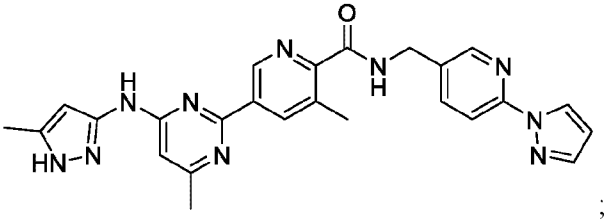
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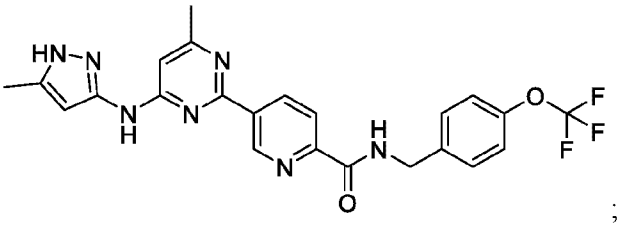
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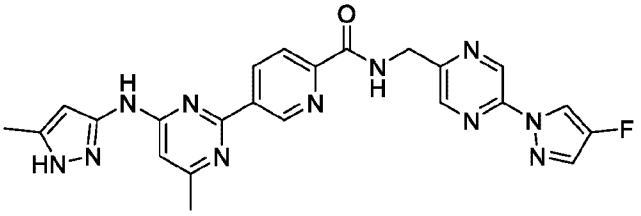
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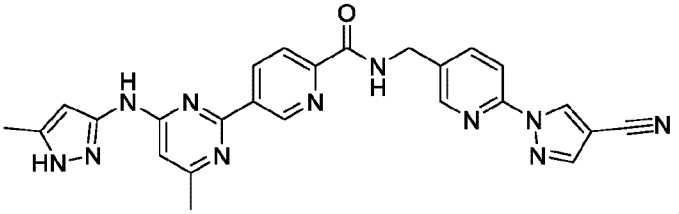
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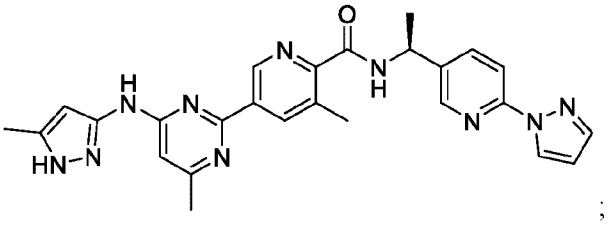
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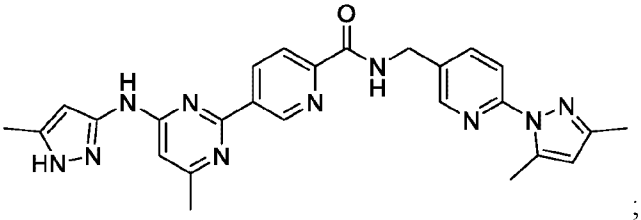
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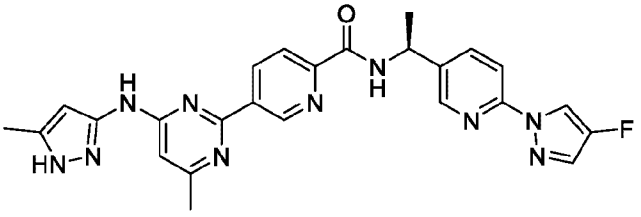
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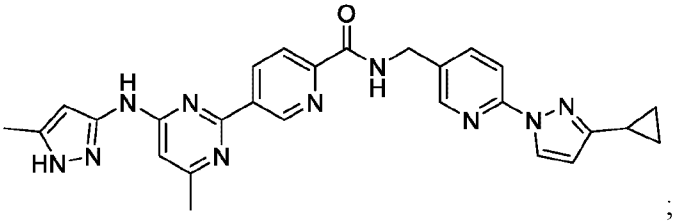
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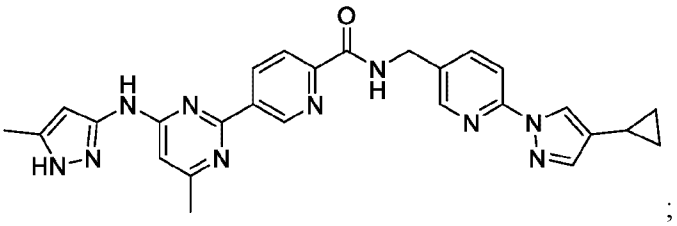
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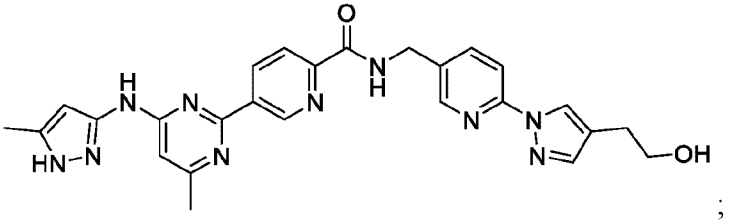
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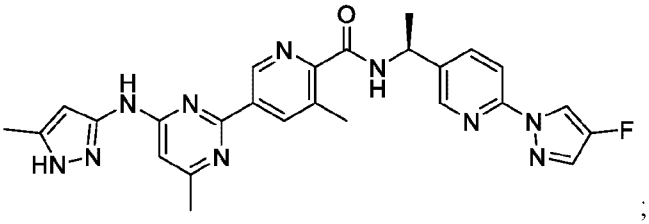
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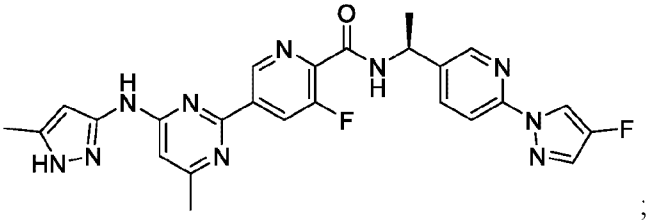
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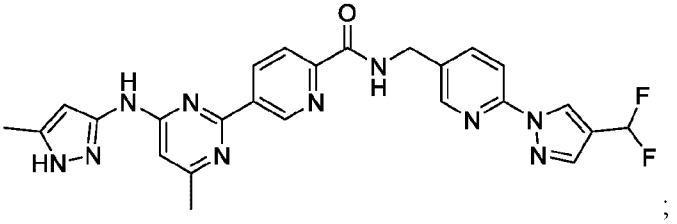
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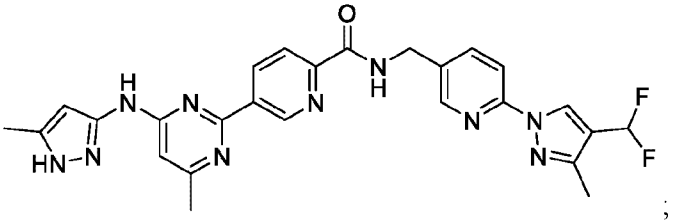
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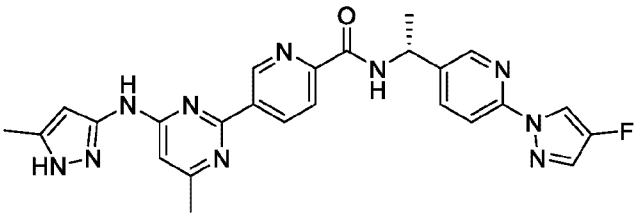
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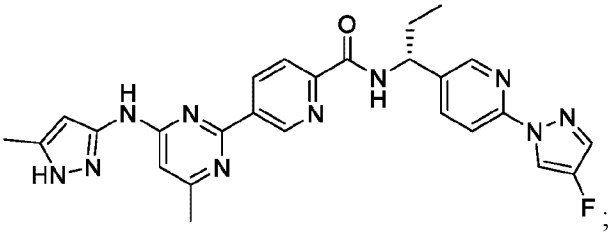
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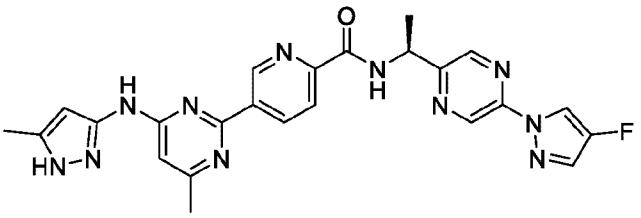
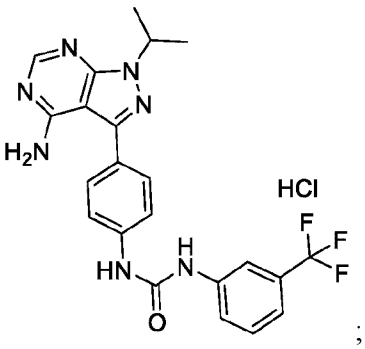

, or a pharmaceutically acceptable salt thereof.

[00692] In some embodiments, a RET inhibitor is selected from the group consisting of: ABT-348 (N-[4-[4-Amino-7-[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]thieno[3,2-c]pyridin-3-yl]phenyl]-N'-(3-fluorophenyl)urea); AD-57, which has the structure:


; AD-80 (1-(4-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)phenyl)-3-(2-fluoro-5-(trifluoromethyl)phenyl)urea); ALW-II-41-27 (N-(5-((4-((4-

ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)carbamoyl)-2-methylphenyl)-5-(thiophen-2-yl)nicotinamide); Amuvatinib (MP470) (N-(benzo[d][1,3]dioxol-5-ylmethyl)-4-(benzofuro[3,2-d]pyrimidin-4-yl)piperazine-1-carbothioamide); BPR1J373 (a derivative of 5-phenylthhiazol-2-ylamine-pyriminide); CLM3; doramapimod (BIRB-796) (1-(3-(tert-butyl)-1-(p-tolyl)-1H-pyrazol-5-yl)-3-(4-(2-morpholinoethoxy)naphthalen-1-yl)urea); DS-5010; famitinib (5-[2-(diethylamino)ethyl]-2-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-3-methyl-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-4-one); fedratinib (SAR 302503, TG101348) (N-(tert-butyl)-3-((5-methyl-2-((4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)pyrimidin-4-yl)amino)benzenesulfonamide); GSK3179106; GSK3352589; HG-6-63-01 ((E)-3-(2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)vinyl)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide); NVP-BBT594 (5-((6-acetamidopyrimidin-4-yl)oxy)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)indoline-1-carboxamide); PP2 (4-amino-5-(4-chlorophenyl)-7-(dimethylethyl)pyrazolo[3,4-d]pyrimidine); PP242 (2-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1H-indol-5-ol); quizartinib (AC220) (1-(5-(tert-butyl)isoxazol-3-yl)-3-(4-(7-(2-morpholinoethoxy)benzo[d]imidazo[2,1-b]thiazol-2-yl)phenyl)urea); semaxanib (SU5416, VEGFR2 Kinase Inhibitor III) ((Z)-3-((3,5-dimethyl-1H-pyrrol-2-yl)methylene)indolin-2-one); SU4984 (3-[4-(1-formylpiperazin-4-yl)benzylidenyl]-2-indolinone); Withaferin A ((4β,5β,6β,22R)-4,27-Dihydroxy-5,6:22,26-diepoxyergosta-2,24-diene-1,26-dione); XL-999 ((Z)-5-((1-ethylpiperidin-4-yl)amino)-3-((3-fluorophenyl)(5-methyl-1H-imidazol-2-yl)methylene)indolin-2-one); XMD15-44 (N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(pyridin-3-ylethynyl)benzamide); Y078-DM1 (antibody drug conjugate composed of a RET antibody (Y078) linked to a derivative of the cytotoxic agent maytansine); and Y078-DM1 (antibody drug conjugate composed of a RET antibody (Y078) linked to a derivative of the cytotoxic agent maytansine).

[00693] Further examples of RET inhibitors include: N-(2-fluoro-5-trifluoromethylphenyl)-N'-{4'-[(2"-benzamido)pyridin-4"-ylamino]phenyl}urea; 1-isopropyl-3-(phenylethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine; 3-((6,7-dimethoxyquinazolin-4-yl)amino)-4-fluoro-2-methylphenol; N-(5-(tert-butyl)isoxazol-3-yl)-2-(4-(imidazo[1,2-a]pyridin-6-yl)phenyl)acetamide; N-(5-(tert-butyl)isoxazol-3-yl)-2-(3-(imidazo[1,2-b]pyridazin-6-yloxy)phenyl)acetamide; 2-amino-6-{[2-(4-chlorophenyl)-2-oxoethyl]sulfanyl}-4-(3-thienyl)pyridine-3,5-dicarbonitrile; and 3-arylureidobenzylidene-indolin-2-ones.

[00694] Yet other therapeutic agents include RET inhibitors such as those described, for example, in U.S. Patent Nos. 7,504,509; 8,299,057; 8,399,442; 8,067,434; 8,937,071; 9,006,256; and 9,035,063; U.S. Publication Nos. 2014/0121239; 20160176865; 2011/0053934; 2011/0301157; 2010/0324065; 2009/0227556; 2009/0130229; 2009/0099167; 2005/0209195; International Publication Nos. WO 2016/037578; WO 2016/038519; WO 2016/038552; WO 2014/184069; WO 2014/072220; WO 2012/053606; WO 2009/017838; WO 2008/031551; WO 2007/136103; WO 2007/087245; WO 2007/057399; WO 2005/051366; WO 2005/062795; and WO 2005/044835; and *J. Med.Chem.* 2012, 55 (10), 4872-4876.

[00695] Non-limiting examples of receptor tyrosine kinase (e.g., Trk) targeted therapeutic agents, include afatinib, cabozantinib, cetuximab, crizotinib, dabrafenib, entrectinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, pazopanib, panitumumab, pertuzumab, sunitinib, trastuzumab, l-((3S,4R)-4-(3-fluorophenyl)-l-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(2- methylpyrimidin-5-yl)-l -phenyl- lH-pyrazol-5-yl)urea, AG 879, AR-772, AR-786, AR-256, AR-618, AZ-23, AZ623, DS-6051, Gö 6976, GNF-5837, GTx-186, GW 441756, LOXO-101, MGCD516, PLX7486, RXDX101, TPX-0005, and TSR-011. Additional Trk targeted therapeutic agents include those described in U.S. Patent No. 8,450,322; 8,513,263; 8,933,084; 8,791,123; 8,946,226; 8,450,322; 8,299,057; and 8,912,194; U.S. Publication No. 2016/0137654; 2015/0166564; 2015/0051222; 2015/0283132; and 2015/0306086; International Publication No. WO 2010/033941; WO 2010/048314; WO 2016/077841; WO 2011/146336; WO 2011/006074; WO 2010/033941; WO 2012/158413; WO 2014078454; WO 2014078417; WO 2014078408; WO 2014078378; WO 2014078372; WO 2014078331; WO 2014078328; WO 2014078325; WO 2014078323; WO 2014078322; WO 2015175788; WO 2009/013126; WO 2013/174876; WO 2015/124697; WO 2010/058006; WO 2015/017533; WO 2015/112806; WO 2013/183578; and WO 2013/074518.

[00696] Further examples of Trk inhibitors can be found in U.S. Patent No. 8,637,516, International Publication No. WO 2012/034091, U.S. Patent No. 9,102,671, International Publication No. WO 2012/116217, U.S. Publication No. 2010/0297115, International Publication No. WO 2009/053442, U.S. Patent No. 8,642,035, International Publication No. WO 2009092049, U.S. Patent No. 8,691,221, International Publication No. WO2006131952.

Exemplary Trk inhibitors include GNF-4256,

described in *Cancer Chemother. Pharmacol.* 75(1):131-141, 2015; and GNF-5837 (N-[3-[[2,3-dihydro-2-oxo-3-(1H-pyrrol-2-ylmethylene)-1H-indol-6-yl]amino]-4-methylphenyl]-N′-[2-fluoro-5-(trifluoromethyl)phenyl]-urea), described in *ACS Med. Chem. Lett.* 3(2):140-145, 2012.

[00697] Additional examples of Trk inhibitors include those disclosed in U.S. Publication No. 2010/0152219, U.S. Patent No. 8,114,989, and International Publication No. WO 2006/123113. Exemplary Trk inhibitors include AZ623, described in *Cancer* 117(6):1321-1391, 2011; AZD6918, described in *Cancer Biol. Ther.* 16(3):477-483, 2015; AZ64, described in *Cancer Chemother. Pharmacol.* 70:477-486, 2012; AZ-23 ((S)-5-Chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine), described in *Mol. Cancer Ther.* 8:1818-1827, 2009; and AZD7451.

[00698] A Trk inhibitor can include those described in U.S. Patent Nos. 7,615,383; 7,384,632; 6,153,189; 6,027,927; 6,025,166; 5,910,574; 5,877,016; and 5,844,092.

[00699] Further examples of Trk inhibitors include CEP-751, described in *Int. J. Cancer* 72:672-679, 1997; CT327, described in *Acta Derm. Venereol.* 95:542-548, 2015; compounds described in International Publication No. WO 2012/034095; compounds described in U.S. Patent No. 8,673,347 and International Publication No. WO 2007/022999; compounds described in U.S. Patent No. 8,338,417; compounds described in International Publication No. WO 2016/027754; compounds described in U.S. Patent No. 9,242,977; compounds described in U.S. Publication No. 2016/0000783; sunitinib (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide), as described in *PLoS One* 9:e95628, 2014; compounds described in International Publication No. WO 2011/133637; compounds described in U.S. Patent No. 8,637,256; compounds described in *Expert. Opin. Ther. Pat.* 24(7):731-744, 2014; compounds described in *Expert Opin. Ther. Pat.* 19(3):305-319, 2009; (R)-2-phenylpyrrolidine substituted imidazopyridazines, e.g., GNF-8625, (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-[2,4'-bipyridin]-2'-yl)piperidin-4-ol as described in ACS Med. Chem. Lett. 6(5):562-567, 2015; GTx-186 and others, as described in *PLoS One* 8(12):e83380, 2013; K252a ((9S-(9α,10β,12α))-2,3,9,10,11,12-hexahydro-10-hydroxy-10-(methoxycarbonyl)-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-

i][1,6]benzodiazocin-1-one), as described in *Mol. Cell Biochem.* 339(1-2):201-213, 2010; 4-aminopyrazolylpyrimidines, e.g., AZ-23 (((S)-5-chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine)), as described in *J. Med. Chem.* 51(15):4672-4684, 2008; PHA-739358 (danusertib), as described in *Mol. Cancer Ther.* 6:3158, 2007; Gö 6976 (5,6,7,13-tetrahydro-13-methyl-5-oxo-12H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-12-propanenitrile), as described in *J. Neurochem.* 72:919-924, 1999; GW441756 ((3Z)-3-[(1-methylindol-3-yl)methylidene]-1H-pyrrolo[3,2-b]pyridin-2-one), as described in *IJAE* 115:117, 2010; milciclib (PHA-848125AC), described in *J. Carcinog.* 12:22, 2013; AG-879 ((2E)-3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-cyano-2-propenethioamide); altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); cabozantinib (N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); lestaurtinib ((5S,6S,8R)-6-Hydroxy-6-(hydroxymethyl)-5-methyl-7,8,14,15-tetrahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[b,h]cycloocta[jkl]cyclopenta[e]-as-indacen-13(6H)-one); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); ONO-5390556; regorafenib (4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate); and VSR-902A.

[00700[The ability of a Trk inhibitor to act as a TrkA, TrkB, and/or Trk C inhibitor may be tested using the assays described in Examples A and B in U.S. Patent No. 8,513,263.

[00701[In some embodiments, signal transduction pathway inhibitors include Ras-Raf-MEK-ERK pathway inhibitors (e.g., binimetinib, selumetinib, encorafinib, sorafenib, trametinib, and vemurafenib), PI3K-Akt-mTOR-S6K pathway inhibitors (e.g. everolimus, rapamycin, perifosine, temsirolimus), and other kinase inhibitors, such as baricitinib, brigatinib, capmatinib, danusertib, ibrutinib, milciclib, quercetin, regorafenib, ruxolitinib, semaxanib, AP32788, BLU285, BLU554, INCB39110, INCB40093, INCB50465, INCB52793, INCB54828, MGCD265, NMS-088, NMS-1286937, PF 477736 ((R)-amino-N-[5,6-dihydro-2-(1-methyl-1H-

pyrazol-4-yl)-6-oxo-1Hpyrrolo[4,3,2-ef][2,3]benzodiazepin-8-yl]-cyclohexaneacetamide), PLX3397, PLX7486, PLX8394, PLX9486, PRN1008, PRN1371, RXDX103, RXDX106, RXDX108, and TG101209 (N-tert-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4- ylamino)benzenesulfonamide).

[00702] Non-limiting examples of checkpoint inhibitors include ipilimumab, tremelimumab, nivolumab, pidilizumab, MPDL3208A, MEDI4736, MSB0010718C, BMS-936559, BMS-956559, BMS-935559 (MDX-1105), AMP-224, and pembrolizumab.

[00703] In some embodiments, cytotoxic chemotherapeutics are selected from arsenic trioxide, bleomycin, cabazitaxel, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine, irinotecan, lomustine, methotrexate, mitomycin C, oxaliplatin, paclitaxel, pemetrexed, temozolomide, and vincristine.

[00704] Non-limiting examples of angiogenesis-targeted therapies include aflibercept and bevacizumab.

[00705] The term "immunotherapy" refers to an agent that modulates the immune system. In some embodiments, an immunotherapy can increase the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can decrease the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can recruit and/or enhance the activity of an immune cell.

[00706] In some embodiments, the immunotherapy is a cellular immunotherapy (e.g., adoptive T-cell therapy, dendritic cell therapy, natural killer cell therapy). In some embodiments, the cellular immunotherapy is sipuleucel-T (APC8015; Provenge™; Plosker (2011) Drugs 71(1): 101-108). In some embodiments, the cellular immunotherapy includes cells that express a chimeric antigen receptor (CAR). In some embodiments, the cellular immunotherapy is a CAR-T cell therapy. In some embodiments, the CAR-T cell therapy is tisagenlecleucel (Kymriah™).

[00707] In some embodiments, the immunotherapy is an antibody therapy (e.g., a monoclonal antibody, a conjugated antibody). In some embodiments, the antibody therapy is bevacizumab (Mvasti™, Avastin®), trastuzumab (Herceptin®), avelumab (Bavencio®), rituximab (MabThera™, Rituxan®), edrecolomab (Panorex), daratumuab (Darzalex®), olaratumab (Lartruvo™), ofatumumab (Arzerra®), alemtuzumab (Campath®), cetuximab (Erbitux®), oregovomab, pembrolizumab (Keytruda®), dinutiximab (Unituxin®), obinutuzumab

(Gazyva®), tremelimumab (CP-675,206), ramucirumab (Cyramza®), ublituximab (TG-1101), panitumumab (Vectibix®), elotuzumab (Empliciti™), avelumab (Bavencio®), necitumumab (Portrazza™), cirmtuzumab (UC-961), ibritumomab (Zevalin®), isatuximab (SAR650984), nimotuzumab, fresolimumab (GC1008), lirilumab (INN), mogamulizumab (Poteligeo®), ficlatuzumab (AV-299), denosumab (Xgeva®), ganitumab, urelumab, pidilizumab or amatuximab.

[00708] In some embodiments, the immunotherapy is an antibody-drug conjugate. In some embodiments, the antibody-drug conjugate is gemtuzumab ozogamicin (Mylotarg™), inotuzumab ozogamicin (Besponsa®), brentuximab vedotin (Adcetris®), ado-trastuzumab emtansine (TDM-1; Kadcyla®), mirvetuximab soravtansine (IMGN853) or anetumab ravtansine

[00709] In some embodiments, the immunotherapy includes blinatumomab (AMG103; Blincyto®) or midostaurin (Rydapt).

[00710] In some embodiments, the immunotherapy includes a toxin. In some embodiments, the immunotherapy is denileukin diftitox (Ontak®).

[00711]

[00712] In some embodiments, the immunotherapy is a cytokine therapy. In some embodiments, the cytokine therapy is an interleukin 2 (IL-2) therapy, an interferon alpha (IFNα) therapy, a granulocyte colony stimulating factor (G-CSF) therapy, an interleukin 12 (IL-12) therapy, an interleukin 15 (IL-15) therapy, an interleukin 7 (IL-7) therapy or an erythropoietin-alpha (EPO) therapy. In some embodiments, the IL-2 therapy is aldesleukin (Proleukin®). In some embodiments, the IFNα therapy is IntronA® (Roferon-A®). In some embodiments, the G-CSF therapy is filgrastim (Neupogen®).

[00713] In some embodiments, the immunotherapy is an immune checkpoint inhibitor. In some embodiments, the immunotherapy includes one or more immune checkpoint inhibitors. In some embodiments, the immune checkpoint inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the CTLA-4 inhibitor is ipilimumab (Yervoy®) or tremelimumab (CP-675,206). In some embodiments, the PD-1 inhibitor is pembrolizumab (Keytruda®) or nivolumab (Opdivo®). In some embodiments, the PD-L1 inhibitor is atezolizumab (Tecentriq®), avelumab (Bavencio®) or durvalumab (Imfinzi™).

[00714] In some embodiments, the immunotherapy is mRNA-based immunotherapy. In some embodiments, the mRNA-based immunotherapy is CV9104 (see, e.g., Rausch et al. (2014) Human

Vaccin Immunother 10(11): 3146-52; and Kubler et al. (2015) J. Immunother Cancer 3:26).

[00715] In some embodiments, the immunotherapy is bacillus Calmette-Guerin (BCG) therapy.

[00716] In some embodiments, the immunotherapy is an oncolytic virus therapy. In some embodiments, the oncolytic virus therapy is talimogene alherparepvec (T-VEC; Imlygic®).

[00717] In some embodiments, the immunotherapy is a cancer vaccine. In some embodiments, the cancer vaccine is a human papillomavirus (HPV) vaccine. In some embodiments, the HPV vaccine is Gardasil®, Gardasil9® or Cervarix®. In some embodiments, the cancer vaccine is a hepatitis B virus (HBV) vaccine. In some embodiments, the HBV vaccine is Engerix-B®, Recombivax HB® or GI-13020 (Tarmogen®). In some embodiments, the cancer vaccine is Twinrix® or Pediarix®. In some embodiments, the cancer vaccine is BiovaxID®, Oncophage®, GVAX, ADXS11-001, ALVAC-CEA, PROSTVAC®, Rindopepimut®, CimaVax-EGF, lapuleucel-T (APC8024; Neuvenge™), GRNVAC1, GRNVAC2, GRN-1201, hepcortespenlisimut-L (Hepko-V5), DCVAX®, SCIB1, BMT CTN 1401, PrCa VBIR, PANVAC, ProstAtak®, DPX-Survivac, or viagenpumatucel-L (HS-110).

[00718] In some embodiments, the immunotherapy is a peptide vaccine. In some embodiments, the peptide vaccine is nelipepimut-S (E75) (NeuVax™), IMA901, or SurVaxM (SVN53-67). In some embodiments, the cancer vaccine is an immunogenic personal neoantigen vaccine (see, e.g., Ott et al. (2017) Nature 547: 217-221; Sahin et al. (2017) Nature 547: 222-226). In some embodiments, the cancer vaccine is RGSH4K, or NEO-PV-01. In some embodiments, the cancer vaccine is a DNA-based vaccine. In some embodiments, the DNA-based vaccine is a mammaglobin-A DNA vaccine (see, e.g., Kim et al. (2016) OncoImmunology 5(2): e1069940).

[00719] In some embodiments, immune-targeted agents are selected from aldesleukin, interferon alfa-2b, ipilimumab, lambrolizumab, nivolumab, prednisone, and sipuleucel-T.

[00720] Non-limiting examples of radiotherapy include radioiodide therapy, external-beam radiation, and radium 223 therapy.

[00721] Additional kinase inhibitors include those described in, for example, U.S. Patent No. 7,514,446; 7,863,289; 8,026,247; 8,501,756; 8,552,002; 8,815,901; 8,912,204; 9,260,437; 9,273,051; U.S. Publication No. US 2015/0018336; International Publication No. WO 2007/002325; WO 2007/002433; WO 2008/080001; WO 2008/079906; WO 2008/079903; WO 2008/079909; WO 2008/080015; WO 2009/007748; WO 2009/012283; WO 2009/143018; WO 2009/143024; WO WO 2009/014637; 2009/152083; WO 2010/111527; WO 2012/109075; WO

2014/194127; WO 2015/112806; WO 2007/110344; WO 2009/071480; WO 2009/118411; WO 2010/031816; WO 2010/145998; WO 2011/092120; WO 2012/101032; WO 2012/139930; WO 2012/143248; WO 2012/152763; WO 2013/014039; WO 2013/102059; WO 2013/050448; WO 2013/050446; WO 2014/019908; WO 2014/072220; WO 2014/184069; and WO 2016/075224.

[00722] Further examples of kinase inhibitors include those described in, for example, WO 2016/081450; WO 2016/022569; WO 2016/011141; WO 2016/011144; WO 2016/011147; WO 2015/191667; WO 2012/101029; WO 2012/113774; WO 2015/191666; WO 2015/161277; WO 2015/161274; WO 2015/108992; WO 2015/061572; WO 2015/058129; WO 2015/057873; WO 2015/017528; WO/2015/017533; WO 2014/160521; and WO 2014/011900.

[00723] Accordingly, also provided herein is a method of treating cancer, comprising administering to a patient in need thereof a pharmaceutical combination for treating cancer which comprises (a) a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and the additional therapeutic agent are together effective in treating the cancer.

[00724] In some embodiments, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same.

[00725] These additional therapeutic agents may be administered with one or more doses of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or pharmaceutical composition thereof, as part of the same or separate dosage forms, via the same or different routes of administration, and/or on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

[00726] Also provided herein is (i) a pharmaceutical combination for treating a cancer in a patient in need thereof, which comprises (a) a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) at least one additional therapeutic agent (e.g., any of the exemplary additional therapeutic agents described herein or known in the art), and (c) optionally

at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I or pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the cancer; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of cancer; and (iv) a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer in a patient in need thereof. In one embodiment the patient is a human. In some embodiments, the cancer is a RET-associated cancer. For example, a RET-associated cancer having one or more RET inhibitor resistance mutations.

[00727] The term "pharmaceutical combination", as used herein, refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and at least one additional therapeutic agent (e.g., a chemotherapeutic agent), are both administered to a patient simultaneously in the form of a single composition or dosage. The term "non-fixed combination" means that a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and at least one additional therapeutic agent (e.g., chemotherapeutic agent) are formulated as separate compositions or dosages such that they may be administered to a patient in need thereof simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the patient. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients

[00728] Accordingly, also provided herein is a method of treating a cancer, comprising administering to a patient in need thereof a pharmaceutical combination for treating cancer which comprises (a) a compound of Formula I or pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula **I** or pharmaceutically acceptable salt or solvate thereof and the additional therapeutic agent are together effective in treating the cancer. In one embodiment, the compound of Formula **I** or pharmaceutically acceptable salt or solvate thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In one embodiment, the

compound of Formula I or pharmaceutically acceptable salt or solvate thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order, in jointly therapeutically effective amounts, e.g. in daily or intermittently dosages. In one embodiment, the compound of Formula I or pharmaceutically acceptable salt or solvate thereof, and the additional therapeutic agent are administered simultaneously as a combined dosage. In some embodiments, the cancer is a RET-associated cancer. For example, a RET-associated cancer having one or more RET inhibitor resistance mutations.

[00729] Also provided herein is a method of treating a disease or disorder mediated by RET in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. In some embodiments, the disease or disorder mediated by RET is a dysregulation of RET gene, a RET kinase, or expression or activity or level of any of the same. For example the dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same includes one or more RET inhibitor resistance mutations. A disease or disorder mediated by RET can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of RET, including overexpression and/or abnormal activity levels. In one embodiment, the disease is cancer (e.g., a RET-associated cancer). In one embodiment, the cancer is any of the cancers or RET-associated cancers described herein.

[00730] Although the genetic basis of tumorigenesis may vary between different cancer types, the cellular and molecular mechanisms required for metastasis appear to be similar for all solid tumor types. During a metastatic cascade, the cancer cells lose growth inhibitory responses, undergo alterations in adhesiveness and produce enzymes that can degrade extracellular matrix components. This leads to detachment of tumor cells from the original tumor, infiltration into the circulation through newly formed vasculature, migration and extravasation of the tumor cells at favorable distant sites where they may form colonies. A number of genes have been identified as being promoters or suppressors of metastasis. For example, overexpression of glial cell-derived neurotrophic factor (GDNF) and its RET receptor tyrosine kinase have been correlated with cancer proliferation and metastasis. See, e.g., Zeng, Q. et al. *J. Int. Med. Res.* (2008) 36(4): 656-64.

[00731] Accordingly, also provided herein are methods for inhibiting, preventing, aiding in the prevention, or decreasing the symptoms of metastasis of a cancer in a patient in need thereof,

the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. Such methods can be used in the treatment of one or more of the cancers described herein. See, e.g., US Publication No. 2013/0029925; International Publication No. WO 2014/083567; and US Patent No. 8,568,998. In some embodiments, the cancer is a RET-associated cancer. In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is used in combination with an additional therapy or another therapeutic agent, including a chemotherapeutic agent, such as a kinase inhibitor. For example, a first or second RET kinase inhibitor.

[00732] The term "metastasis" is an art known term and means the formation of an additional tumor (e.g., a solid tumor) at a site distant from a primary tumor in a subject or patient, where the additional tumor includes the same or similar cancer cells as the primary tumor.

[00733] Also provided are methods of decreasing the risk of developing a metastasis or an additional metastasis in a patient having a RET-associated cancer that include: selecting, identifying, or diagnosing a patient as having a RET-associated cancer, and administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to the patient selected, identified, or diagnosed as having a RET-associated cancer. Also provided are methods of decreasing the risk of developing a metastasis or an additional metastasis in a patient having a RET-associated cancer that includes administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvent thereof to a patient having a RET-associated cancer. The decrease in the risk of developing a metastasis or an additional metastasis in a patient having a RET-associated cancer can be compared to the risk of developing a metastasis or an additional metastasis in the patient prior to treatment, or as compared to a patient or a population of patients having a similar or the same RET-associated cancer that has received no treatment or a different treatment. In some embodiments, the RET-associated cancer is a RET-associated cancer having one or more RET inhibitor resistance mutations.

[00734] The phrase "risk of developing a metastasis" means the risk that a subject or patient having a primary tumor will develop an additional tumor (e.g., a solid tumor) at a site distant from a primary tumor in a subject or patient over a set period of time, where the additional tumor includes the same or similar cancer cells as the primary tumor. Methods for reducing the risk of

developing a metastasis in a subject or patient having a cancer are described herein.

[00735] The phrase "risk of developing additional metastases" means the risk that a subject or patient having a primary tumor and one or more additional tumors at sites distant from the primary tumor (where the one or more additional tumors include the same or similar cancer cells as the primary tumor) will develop one or more further tumors distant from the primary tumor, where the further tumors include the same or similar cancer cells as the primary tumor. Methods for reducing the risk of developing additional metastasis are described herein.

[00736] As used herein, a "first RET kinase inhibitor" or "first RET inhibitor" is a RET kinase inhibitor as defined herein, but which does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as defined herein. As used herein, a "second RET kinase inhibitor" or a "second RET inhibitor" is a RET kinase inhibitor as defined herein, but which does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as defined herein. When both a first and a second RET inhibitor are present in a method provided herein, the first and second RET kinase inhibitor are different.

[00737] In some embodiments, the presence of one or more RET inhibitor resistance mutations in a tumor causes the tumor to be more resistant to treatment with a first RET inhibitor. Methods useful when a RET inhibitor resistance mutation causes the tumor to be more resistant to treatment with a first RET inhibitor are described below. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and administering to the identified subject a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is administered in combination with the first RET inhibitor. Also provided are methods of treating a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations that include administering to the subject a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is administered in combination with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance

mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E.

[00738] For example, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first RET inhibitor, wherein the first RET inhibitor is selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a compound of Formula I, or a pharmaceutically acceptable salt of solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the first RET inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first RET inhibitor, wherein the first RET inhibitor is selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a compound of Formula I selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi)

Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the first RET inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions/deletions of Table 2 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first RET inhibitor, wherein the first RET inhibitor is selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4; and (d) administering a compound of Formula I selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the first RET inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first RET inhibitor, wherein the first RET inhibitor is selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib,

sunitinib, foretinib, BLU667, and BLU6864. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has the RET inhibitor resistance mutation V804M; and (d) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof selected from the group consisting of a compound of Formula I selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the first RET inhibitor of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00739] As another example, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a second RET inhibitor, wherein the second RET inhibitor is selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided

herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering a second RET inhibitor, wherein the second RET inhibitor is selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions/deletions of Table 2 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360;

xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4; and (d) administering a second RET inhibitor, wherein the second RET inhibitor is selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has the RET inhibitor resistance mutation V804M; and (d) administering a second RET inhibitor, wherein the second RET inhibitor is selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor

resistance mutation; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation.

[00740] Also, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has at least one RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject as a monotherapy

or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has at least one RET inhibitor resistance mutation. In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 1 and/or one or more RET kinase protein point mutations/insertions/deletions of Table 2 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof selected from the group consisting of a compound of Formula I selected from i) Example No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation of Tables 3 or 4; and (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has at least one RET inhibitor resistance mutation. In some embodiments, a second RET inhibitor selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864 is administered in step (d). In some embodiments, provided herein are methods for treating a RET-associated cancer in a subject in need of such treatment, the method comprising (a) detecting the fusion protein KIF5B-RET in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from i) Example

No. 1-20; ii) Example No. 21-40; iii) Example No. 41-60; iv) Example No. 61-80; v) Example No. 81-100; vi) Example No. 101-120; vii) Example No. 121-140; viii) Example No. 141-160; ix) Example No. 161-180; x) Example No. 181-200; xi) Example No. 201-220; xii) Example No. 221-240; xiii) Example No. 241-260; xiv) Example No. 261-280; xv) Example No. 281-300; xvi) Example No. 301-320; xvii) Example No. 321-340; xviii) Example No. 341-360; xix) Example No. 361-380; xx) Example No. 381-400; xxi) Example No. 401-420; xxii) Example No. 421-440; xxiii) Example No. 441-460; xxiii) Example No. 461-480; xxiv) Example No. 481-500; xxv) Example No. 501-520; xxvi) Example No. 521-540; or xxvii) Example No. 541-561, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has the RET inhibitor resistance mutation V804M; and (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second RET inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt thereof, or immunotherapy) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has at least one RET inhibitor resistance mutation. In some embodiments, a second RET inhibitor selected from the group consisting of cabozantinib, vandetanib, alectinib, sorafenib, lenvatinib, ponatinib, dovitinib, sunitinib, foretinib, BLU667, and BLU6864 is administered in step (d).

[00741] Also provided are methods of selecting a treatment for a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and selecting a treatment that includes administration of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a first RET inhibitor. In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is administered in combination with the first RET inhibitor. Also provided are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that includes administration of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations. Also provided are methods of selecting a subject having a cancer for a treatment that does not include a first RET inhibitor as a monotherapy that include:

identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and selecting the identified subject for a treatment that includes a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Also provided are methods of selecting a subject having a cancer for a treatment that does not include a first RET inhibitor as a monotherapy that include: selecting a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations for a treatment that includes administration of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. In some embodiments, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E.

[00742] Also provided are methods of determining the likelihood that a subject having a cancer (e.g., a RET-associated cancer) will have a positive response to treatment with a first RET inhibitor as a monotherapy that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that a subject having a cancer cell that has one or more RET inhibitor resistance mutations has a decreased likelihood of having a positive response (i.e. an increased likelihood of having a negative response) to treatment with a first RET inhibitor as a monotherapy. Also provided are methods of determining the likelihood that a subject having a cancer (e.g., a RET-associated cancer) will have a positive response to treatment with a first RET inhibitor as a monotherapy that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that a subject not having a cancer cell that has one or more RET inhibitor resistance mutations has an increased likelihood of having a positive response to treatment with a first RET inhibitor as a monotherapy as compared to a subject having a cancer cell that has one or more RET inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a first RET inhibitor as a monotherapy in a subject having cancer that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that treatment with a first RET inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more RET inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a first RET inhibitor as a monotherapy in a subject having cancer that include: determining that treatment with a first RET inhibitor as a

monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more RET inhibitor resistance mutations. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E.

[00743] Also provided are methods of treating a subject having a cancer that include: (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (c) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (d) administering additional doses of the first RET inhibitor of step (a) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the first RET inhibitor of step (a), the subject can also be administered another anticancer agent (e.g., a second RET inhibitor or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or immunotherapy). In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of step (c), another RET inhibitor can be the first RET inhibitor administered in step (a). In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E.

[00744] Also provided are methods of treating a subject having a cancer that include: (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one

RET inhibitor resistance mutation; and (c) administering a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (d) administering additional doses of the first RET inhibitor step (a) to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the first RET inhibitor of step (a), the subject can also be administered another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, the additional anticancer agent is an immunotherapy.

[00745] Also provided are methods of treating a subject having a cancer (e.g., a RET-associated cancer) that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor, has one or more RET inhibitor resistance mutations; and (b) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (c) administering additional doses of the first RET inhibitor previously administered to the subject if the subject has cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the first RET inhibitor previously administered to the subject, the subject can also be administered another anticancer agent (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or immunotherapy). In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino

acid position 804, e.g., V804M, V804L, or V804E. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of step (b), another anticancer agent can be the first RET inhibitor administered in step (a).

[00746] Also provided are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor has one or more RET inhibitor resistance mutations; and (b) administering a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (c) administering additional doses of the first RET inhibitor previously administered to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the first RET inhibitor previously administered to the subject, the subject can also be administered another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of (b), another anticancer agent can be the first RET inhibitor administered in step (a).

[00747] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (c) selecting a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more RET

inhibitor resistance mutations; or (d) selecting additional doses of the first RET inhibitor of step (a) for the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, when additional doses of the first RET inhibitor of step (a) are selected for the subject, the method can further include selecting doses of another anticancer agent for the subject. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of step (c), another RET inhibitor can be the first RET inhibitor administered in step (a).

[00748] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) administering one or more doses of a first RET inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one RET inhibitor resistance mutation; and (c) selecting a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent if the subject has a cancer cell that has one or more RET inhibitor resistance mutations; or (d) selecting additional doses of the first RET inhibitor of step (a) for the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, when additional doses of the first RET inhibitor of step (a) are selected for the subject, the method can further include selecting doses of another anticancer agent for the subject. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof).

In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the first RET inhibitor administered in step (a).

[00749] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor has one or more RET inhibitor resistance mutations; (b) selecting a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (c) selecting additional doses of the first RET inhibitor previously administered to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, when additional doses of the first RET inhibitor previously administered to the subject are selected for the subject, the method can further include selecting doses of another anticancer agent (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof) for the subject. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments of step (c), another RET inhibitor can be the first RET inhibitor administered in step (a).

[00750] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first RET inhibitor has one or more RET inhibitor resistance mutations; (b) selecting a second RET inhibitor as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has at least one RET inhibitor resistance mutation; or (c) selecting additional doses of the first RET inhibitor previously administered to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, when additional doses of the first

RET inhibitor previously administered to the subject are selected for the subject, the method can further include selecting doses of another anticancer agent (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or an immunotherapy) for the subject. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the first RET inhibitor administered in step (a).

[00751] Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a first RET inhibitor that include: determining whether a cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and identifying a subject having a cell that has one or more RET inhibitor resistance mutations, as having an increased likelihood of developing a cancer that has some resistance to the first RET inhibitor. Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a first RET inhibitor that include: identifying a subject having a cell that has one or more RET inhibitor resistance mutations, as having an increased likelihood of developing a cancer that has some resistance to the first RET inhibitor. Also provided are methods of determining the presence of a cancer that has some resistance to a first RET inhibitor that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that the subject having a cancer cell that has one or more RET inhibitor resistance mutations has a cancer that has some resistance to the first RET inhibitor. Also provided are methods of determining the presence of a cancer that has some resistance to a first RET inhibitor in a subject that include: determining that a subject having a cancer cell that has one or more RET inhibitor resistance mutations, has a cancer that has some resistance to the first RET inhibitor. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first RET inhibitor. In

some embodiments, the one or more RET inhibitor resistance mutations include one or more RET inhibitor resistance mutations listed in Tables 3 and 4. For example, the one or more RET inhibitor resistance mutations can include a substitution at amino acid position 804, e.g., V804M, V804L, or V804E.

[00752] In some embodiments of any of the methods described herein, a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a first RET inhibitor can be any of the RET inhibitor resistance mutations listed in Table 3 or 4 (e.g., a substitution at amino acid position 804, e.g., V804M, V804L, or V804E).

[00753] In some embodiments, the presence of one or more RET inhibitor resistance mutations in a tumor causes the tumor to be more resistant to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Methods useful when a RET inhibitor resistance mutation causes the tumor to be more resistant to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof are described below. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and administering to the identified subject a treatment that does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy (e.g., a second RET kinase inhibitor). Also provided are methods of treating a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations that include administering to the subject a treatment that does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy (e.g., a second RET kinase inhibitor). In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[00754] Also provided are methods of selecting a treatment for a subject having a cancer that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and selecting a treatment that does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy for the identified subject (e.g., a second RET kinase inhibitor). Also provided are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy (e.g., a second

RET kinase inhibitor) for a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations. Also provided are methods of selecting a subject having a cancer for a treatment that does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy (e.g., a second RET kinase inhibitor) that include: identifying a subject having a cancer cell that has one or more RET inhibitor resistance mutations; and selecting the identified subject for a treatment that does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy (e.g., a second RET kinase inhibitor). Also provided are methods of selecting a subject having a cancer for a treatment that does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy (e.g., a second RET kinase inhibitor) that include: selecting a subject identified as having a cancer cell that has one or more RET inhibitor resistance mutations for a treatment that does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[00755] Also provided are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that the subject having the cancer cell that has one or more RET inhibitor resistance mutations has a decreased likelihood of having a positive response to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy. Also provided are methods of determining the likelihood that a subject having cancer will have a positive response to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy that include: determining that a subject having a cancer cell that has one or more RET inhibitor resistance mutations has a decreased likelihood of having a positive response to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy. Also provided are methods of predicting the efficacy of treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy in a subject having cancer that include: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and

determining that treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more RET inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy in a subject having cancer that include: determining that treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more RET inhibitor resistance mutations. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[00756] Also provided are methods of treating a subject having a cancer that include: (a) administering one or more doses of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and (c) administering a second RET inhibitor or a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to a subject having a cancer cell that has one or more RET inhibitor resistance mutations; or (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (a) to a subject having a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (a), the subject can also be administered another anticancer agent or a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof administered in step (a).

[00757] Also provided are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, has one or more RET inhibitor resistance mutations; (b) administering a second RET inhibitor or a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to a subject having a cancer cell that has one or more RET inhibitor resistance mutations; or (c) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof previously administered to a subject having a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where the subject is administered additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (a), the subject can also be administered another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof administered in step (a).

[00758] Also provided are methods of selecting a treatment for a subject having a cancer that include: (a) administering one or more doses of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and (c) selecting a second RET inhibitor or a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has a RET inhibitor resistance mutation; or (d) selecting additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (a) for the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where additional doses of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (a) are selected for the subject, the method can also include further selecting another

anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof administered in step (a).

[00759] Also provided are methods of selecting a treatment for a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, has one or more RET inhibitor resistance mutations; (b) selecting a second RET inhibitor or a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has a RET inhibitor resistance mutation; or (c) selecting additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof previously administered to the subject if the subject has a cancer cell that does not have a RET inhibitor resistance mutation. In some embodiments, where additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (a) are selected for the subject, the method can also include further selecting another anticancer agent. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the additional anticancer agent is any anticancer agent known in the art. For example, the additional anticancer agent is another RET inhibitor (e.g., a second RET inhibitor). In some embodiments, the additional anticancer agent is an immunotherapy. In some embodiments, another RET can be the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof administered in step (a).

[00760] Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof that include: determining whether a cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and identifying the subject if the subject has a cell that has one or more RET inhibitor resistance mutations as having an increased likelihood of

developing a cancer that has some resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof that include: identifying a subject having a cell that has one or more RET inhibitor resistance mutations as having an increased likelihood of developing a cancer that has some resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Also provided are methods of determining the presence of a cancer that has some resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof that includes: determining whether a cancer cell in a sample obtained from the subject has one or more RET inhibitor resistance mutations; and determining that the subject having the cancer cell that has one or more RET inhibitor resistance mutations has a cancer that has some resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Also provided are methods of determining the presence of a cancer that has some resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof in a subject that include: determining that a subject having a cancer cell that has one or more RET inhibitor resistance mutations has a cancer that has some resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the one or more RET inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[00761] In some embodiments of any of the methods described herein, a RET inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, can be any of the RET inhibitor resistance mutations listed in Table 3 or 4.

[00762] Methods of determining the level of resistance of a cancer cell or a tumor to a RET inhibitor (e.g., any of the RET inhibitors described herein or known in the art) can be determined using methods known in the art. For example, the level of resistance of a cancer cell to a RET inhibitor can be assessed by determining the IC_{50} of a RET inhibitor (e.g., any of the RET inhibitors described herein or known in the art) on the viability of a cancer cell. In other examples, the level of resistance of a cancer cell to a RET inhibitor can be assessed by determining the growth rate of the cancer cell in the presence of a RET inhibitor (e.g., any of the RET inhibitors described herein). In other examples, the level of resistance of a tumor to a RET inhibitor can be assessed by

determining the mass or size of one or more tumors in a subject over time during treatment with a RET inhibitor (e.g., any of the RET inhibitors described herein). In other examples, the level of resistance of a cancer cell or a tumor to a RET inhibitor can be indirectly assessed by determining the activity of a RET kinase including one or more of the RET inhibitor resistance mutations (i.e., the same RET kinase expressed in a cancer cell or a tumor in a subject). The level of resistance of a cancer cell or tumor having one or more RET inhibitor resistance mutations to a RET inhibitor is relative to the level of resistance in a cancer cell or tumor that does not have a RET inhibitor resistance mutation (e.g., a cancer cell or tumor that does not have the same RET inhibitor resistance mutations, a cancer cell or a tumor that does not have any RET inhibitor resistance mutations, or a cancer cell or a tumor that expresses a wildtype RET protein). For example, the determined level of resistance of a cancer cell or a tumor having one or more RET inhibitor resistance mutations can be greater than about 1%, greater than about 2%, greater than about 3% ,greater than about 4%, greater than about 5%, greater than about 6%, greater than about 7%, greater than about 8%, greater than about 9%, greater than about 10%, greater than about 11%, greater than about 12%, greater than about 13%, greater than about 14%, greater than about 15%, greater than about 20%, greater than about 25%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, greater than about 150%, greater than about 160%, greater than about 170%, greater than about 180%, greater than about 190%, greater than about 200%, greater than about 210%, greater than about 220%, greater than about 230%, greater than about 240%, greater than about 250%, greater than about 260%, greater than about 270%, greater than about 280%, greater than about 290%, or greater than about 300% of the level of resistance in a cancer cell or tumor that does not have a RET inhibitor resistance mutation (e.g., a cancer cell or tumor that does not have the same RET inhibitor resistance mutations, a cancer cell or a tumor that does not have any RET inhibitor resistance mutations, or a cancer cell or a tumor that expresses a wildtype RET protein).

[00763] RET is thought to play an important role in the development and survival of afferent nociceptors in the skin and gut. RET kinase knock-out mice lack enteric neurons and have other nervous system anomalies suggesting that a functional RET kinase protein product is necessary during development (Taraviras, S. et al., *Development*, 1999, 126:2785-2797). Moreover

population studies of patients with Hirschsprung's disease characterized by colonic obstruction due to lack of normal colonic enervation have a higher proportion of both familial and sporadic loss of function RET mutations (Butler Tjaden N., et al., *Transl. Res.*, 2013, 162: 1-15). Irritable bowel syndrome (IBS) is a common illness affecting 10-20% of individuals in developed countries and is characterized by abnormal bowel habits, bloating and visceral hypersensitivity (Camilleri, M., *N. Engl. J. Med.*, 2012, 367: 1626-1635). While the etiology of IBS is unknown it is thought to result from either a disorder between the brain and gastrointestinal tract, a disturbance in the gut microbiome or increased inflammation. The resulting gastrointestinal changes affect normal bowel transit resulting in either diarrhea or constipation. Furthermore in many IBS patients the sensitization of the peripheral nervous system results in visceral hypersensitivity or allodynia (Keszthelyi, D., *Eur. J. Pain*, 2012, 16: 1444-1454). See, e.g., U.S. Publication No. 2015/0099762.

[00764] Accordingly, provided herein are methods for treating a patient diagnosed with (or identified as having) an irritable bowel syndrome (IBS) including diarrhea-predominant, constipation- predominant or alternating stool pattern, functional bloating, functional constipation, functional diarrhea, unspecified functional bowel disorder, functional abdominal pain syndrome, chronic idiopathic constipation, functional esophageal disorders, functional gastroduodenal disorders, functional anorectal pain, and inflammatory bowel disease that include administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[00765] Also provided herein are methods for treating a patient identified or diagnosed as having a RET-associated irritable bowel syndrome (IBS) (e.g., a patient that has been identified or diagnosed as having a RET-associated irritable bowel syndrome (IBS) through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient) that include administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[00766] Also provided herein are methods for treating pain associated with IBS that include administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is administered in combination with another therapeutic agent useful for treating one or more symptoms of IBS.

[00767] Also provided are methods for treating an irritable bowel syndrome (IBS) in a patient in need thereof, the method comprising: (a) determining if the irritable bowel syndrome (IBS) in the patient is a RET-associated IBS (e.g., using a regulatory-agency approved, e.g., FDA-approved, kit for identifying dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient, or by performing any of the non-limiting examples of assays described herein); and (b) if the IBS is determined to be a RET-associated IBS, administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[00768] In some embodiments, the compounds of the present invention are useful for treating irritable bowel syndrome (IBS) in combination with one or more additional therapeutic agents or therapies effective in treating the irritable bowel syndrome that work by the same or a different mechanism of action. The at least one additional therapeutic agent may be administered with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as part of the same or separate dosage forms, via the same or different routes of administration, and on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

[00769] Non-limiting examples of additional therapeutics for the treatment of irritable bowel syndrome (IBS) include probiotics, fiber supplements (e.g., psyllium, methylcellulose), anti-diarrheal medications (e.g., loperamide), bile acid binders (e.g., cholestyramine, colestipol, colesevelam), anticholinergic and antispasmodic medications (e.g., hyoscyamine, dicyclomine), antidepressant medications (e.g., tricyclic antidepressant such as imipramine or notriptyline or a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine or paroxetine), antibiotics (e.g., rifaximin), alosetron, and lubiprostone.

[00770] Accordingly, also provided herein are methods of treating irritable bowel syndrome (IBS), comprising administering to a patient in need thereof a pharmaceutical combination for treating IBS which comprises (a) a compound of Formula **I** or pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of IBS, wherein the amounts of the compound of Formula I or pharmaceutically acceptable salt or solvate thereof and the additional therapeutic agent are together effective in treating the IBS. In one embodiment, the compound of Formula I or pharmaceutically acceptable salt or solvate

thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In one embodiment, the compound of Formula **I** or pharmaceutically acceptable salt or solvate thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order, in jointly therapeutically effective amounts, e.g. in daily or intermittently dosages. In one embodiment, compound of Formula **I** or pharmaceutically acceptable salt or solvate thereof, and the additional therapeutic agent are administered simultaneously as a combined dosage.

[00771] Also provided herein is (i) a pharmaceutical combination for treating irritable bowel syndrome in a patient in need thereof, which comprises (a) a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) at least one additional therapeutic agent (e.g., any of the exemplary additional therapeutic agents described herein for treating irritable bowel syndrome or known in the art), and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of irritable bowel syndrome, wherein the amounts of the compound of Formula I or pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the irritable bowel syndrome; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of irritable bowel syndrome; and (iv) a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of irritable bowel syndrome in a patient in need thereof. In one embodiment the patient is a human.

[00772] The term "pharmaceutical combination", as used herein, refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and at least one additional therapeutic agent (e.g., an agent effective in treating irritable bowel syndrome), are both administered to a patient simultaneously in the form of a single composition or dosage. The term "non-fixed combination" means that a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and at least one additional therapeutic agent (e.g., an agent effective in treating irritable bowel syndrome) are formulated as separate compositions or dosages, such that they may be administered to a patient in need thereof simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the patient.

In one embodiment, the compound of Formula I and the additional therapeutic agent are formulated as separate unit dosage forms, wherein the separate dosages forms are suitable for either sequential or simultaneous administration. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients.

[00773] In some embodiments, a compound provided herein can be used as an agent for supportive care for a patient undergoing cancer treatment. For example, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, can be useful to reduce one or more symptoms associated with treatment with one or more cancer therapies such as diarrheal or constipations complications and/or abdominal pain. See, for example, U.S. Publication No. 2015/0099762 and Hoffman, J.M. et al. *Gastroenterology* (2012) 142:844-854. Accordingly, a compound, or a pharmaceutically acceptable salt thereof, or composition provided herein can be administered to a patient to address one or more complications associated with cancer treatment (e.g., gastrointestinal complications such as diarrhea, constipation, or abdominal pain).

[00774] In some embodiments, a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, can be administered to a patient undergoing cancer treatment (e.g., a patient experiencing an adverse event associated with cancer treatment such as an immune-related adverse event or a gastrointestinal complication including diarrhea, constipation, and abdominal pain). For example, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be used in the treatment of colitis or IBS associated with administration of a checkpoint inhibitor; see, e.g., Postow, M.A. et al. *Journal of Clinical Oncology* (2015) 33: 1974-1982. In some such embodiments, a compound provided herein, or a pharmaceutically acceptable salt thereof, can be formulated to exhibit low bioavailability and/or be targeted for delivery in the gastrointestinal tract. See, for example, US Patent No. 6,531,152.

[00775] Also provided is a method for inhibiting RET kinase activity in a cell, comprising contacting the cell with a compound of Formula I. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo. In one embodiment, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to a subject having a cell having RET kinase activity. In some embodiments, the cell is a cancer cell. In one embodiment, the cancer cell is any cancer as described herein. In some embodiments, the cancer cell is a RET-associated cancer cell. In some embodiments, the cell is a gastrointestinal cell.

[00776] Also provided is a method for inhibiting RET kinase activity in a mammalian cell, comprising contacting the cell with a compound of Formula I. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo. In one embodiment, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to a mammal having a cell having RET kinase activity. In some embodiments, the mammalian cell is a mammalian cancer cell. In one embodiment, the mammalian cancer cell is any cancer as described herein. In some embodiments, the mammalian cancer cell is a RET-associated cancer cell. In some embodiments, the mammalian cell is a gastrointestinal cell.

[00777] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" a RET kinase with a compound provided herein includes the administration of a compound provided herein to an individual or patient, such as a human, having a RET kinase, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the RET kinase.

[00778] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein

[00779] The phrase "effective amount" means an amount of compound that, when administered to a patient in need of such treatment, is sufficient to (i) treat a RET kinase-associated disease or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a compound of Formula I that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the patient in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

[00780] When employed as pharmaceuticals, the compounds of Formula I can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated.

Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Oral administration can include a dosage form formulated for once-daily or twice-daily (BID) administration. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable

[00781] Also provided herein are pharmaceutical compositions which contain, as the active ingredient, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. In one embodiment, the composition is formulated for oral administration. In one embodiment, the composition is formulated as a tablet or capsule.

[00782] The compositions comprising a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other patients, each unit containing a predetermined quantity of active material (i.e., a compound for Formula I as provided herein) calculated to produce the

desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[00783] In some embodiments, the compositions provided herein contain from about 5 mg to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 mg to about 10 mg, about 10 mg to about 15 mg, about 15 mg to about 20 mg, about 20 mg to about 25 mg, about 25 mg to about 30 mg, about 30 mg to about 35 mg, about 35 mg to about 40 mg, about 40 mg to about 45 mg, or about 45 mg to about 50 mg of the active ingredient.

[00784] In some embodiments, the compositions provided herein contain from about 50 mg to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 mg to about 100 mg, about 100 mg to about 150 mg, about 150 mg to about 200 mg, about 200 mg to about 250 mg, about 250 mg to about 300 mg, about 350 mg to about 400 mg, or about 450 mg to about 500 mg of the active ingredient.

[00785] In some embodiments, the compositions provided herein contain from about 500 mg to about 1,000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 mg to about 550 mg, about 550 mg to about 600 mg, about 600 mg to about 650 mg, about 650 mg to about 700 mg, about 700 mg to about 750 mg, about 750 mg to about 800 mg, about 800 mg to about 850 mg, about 850 mg to about 900 mg, about 900 mg to about 950 mg, or about 950 mg to about 1,000 mg of the active ingredient.

[00786] The active compound may be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[00787] In some embodiments, the compounds provided herein can be administered in an amount ranging from about 1 mg/kg to about 100 mg/kg. In some embodiments, the compound provided herein can be administered in an amount of about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 50 mg/kg, about 10 mg/kg to about 40 mg/kg, about 15 mg/kg to about 45 mg/kg, about 20 mg/kg to about 60 mg/kg, or about 40 mg/kg to about 70 mg/kg. For example, about 5

mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, or about 100 mg/kg. In some embodiments, such administration can be once-daily or twice-daily (BID) administration.

[00788] Provided herein are pharmaceutical kits useful, for example, in the treatment of RET-associated diseases or disorders, such as cancer or irritable bowel syndrome (IBS), which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

[00789] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

[00790] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

Examples

[00791] The following examples illustrate the invention.

Biological Examples

Example A

RET Enzyme Assay

[00792] Compounds of Formula I were screened for their ability to inhibit wildtype and V804M mutant RET kinase using CisBio's HTRF® KinEASE™-TK assay technology. Briefly, N-terminal GST tagged recombinant human RET cytoplasmic domain (aa 658-end) from Eurofins (0.25 nM RET; Catalog No. 14-570M) or N-terminal GST tagged recombinant human V804M

mutant RET cytoplasmic domain (aa 658-end) from Millipore (0.25 nM enzyme; Catalog No. 14-760) was incubated with 250 nM TK-substrate biotin (CisBio, part of Catalog No. 62TK0PEC) and 1 mM ATP along with test compound in a buffer consisting of 25 mM HEPES pH 7.4, 10 mM $MgCl_2$, 0.01% Triton X-100, and 2% DMSO in a volume of 8 µL. Compounds were typically prepared in a threefold serial dilution in DMSO and added to the assay to give the appropriate final concentration. After a 30-minute incubation at 22 °C, the reaction was quenched by adding 8 µL of quench solution containing 31.25 nM Sa-XL665 and 1X TK-ab-Cryptate in HTRF detection buffer (all from CisBio, part of Cat. No. 62TK0PEC). After a 1 hour incubation at 22°C, the extent of reaction was determined using a PerkinElmer EnVision multimode plate reader via HTRF dual wavelength detection, and the percent of control (POC) was calculated using a ratiometric emission factor. 100 POC was determined using no test compounds and 0 POC was determined using pre-quenched control reactions. The POC values were fit to a 4 parameter logistic curve, and the IC_{50} is defined as the concentration of inhibitor at which the POC equals 50 for the fitted curve. The IC_{50} values for the compounds tested in this assay are provided in Table 5.

[00793] **Example B**

[00794] RET cell assay

[00795] The cellular potency of a compound inhibiting RET kinase was determined in HEK-293 cells expressing a Kif5b-RET fusion protein. Briefly, HEK-293 cells expressing a Kif5b-RET fusion protein were plated at 50K cells /well in 96 well poly-D-Lysine coated plates the day prior to the assay. The cells were incubated for 1 hour with test compound in DMEM (Dulbecco's Modified Eagle Medium) at a final DMSO concentration of 0.5%. Compounds were typically prepared in a three fold serial dilution in DMSO and added to the assay to give the appropriate final concentration. After 1 hour the media was removed, the cells were fixed with 3.8% formaldehyde for 20 min, washed with PBS, and permeabilized for 10 min with 100% methanol. The plates were then washed with PBS-0.05% Tween20, and blocked with LI-COR Blocking solution (LI-COR catalog # 927-40000) for 1 hour. Plates were washed with PBS-0.05% Tween20, then incubated with anti-phospho-RET(Tyr1062) (Santa Cruz catalog #sc-20252-R) antibody and anti-GAPDH (Millipore catalog # MAB374) antibody for 2 hours. The plates were washed with PBS-0.05%Tween20, and incubated with anti-rabbit 680 (Molecular Probes catalog No. A21109) and anti-mouse 800 (LI-COR catalog No. 926-32210) secondary antibodies for 1 hour. All antibodies were diluted in LI-COR Block containing 0.05% Tween. The plates were

washed with PBS-0.05% Tween20, 100 μL PBS was added to each well, and the plates were read on a LI-COR Aerius fluorescent plate reader. The phospho-RET signal was normalized to the GAPDH signal. 100 POC (percent of control) was determined using no test compounds and 0 POC was determined using 1 μM of a control inhibitor. The POC values were fit to a 4 parameter logistic curve. The IC_{50} value is the point where the curve crosses 50 POC. The IC_{50} values for the compounds tested in this assay are provided in Table 5.

[00796] Example C

[00797] RET G810R mutant assay

[00798] The potency of a compound inhibiting G810R mutant RET kinase was determined using CisBio's HTRF Kinease-TK assay technology. The assays contained G810R mutant RET produced at Array Biopharma, Inc. (1 nM enzyme – p1982 Lot. No. 160713. The kinase was incubated with 250 nM TK-substrate biotin (CisBio, part of Catalog # 62TK0PEC) and 1 mM ATP along with test compound in a buffer consisting of 25 mM HEPES, pH 7.4, 10 mM $MgCl_2$, 0.01% Triton X-100, and 2% DMSO in a volume of 8 μL. Compounds were typically prepared as a three-fold serial dilution in DMSO and added to the assay to give the appropriate final concentration. After a 60-min incubation at 22 °C, the reaction was quenched by adding 8 μL of quench solution containing 31.25 nM Sa-XL665 and 1x TK-Ab-Cryptate in HTRF detection buffer (all from CisBio, part of cat # 62TK0PEC). After a 1-h incubation at 22 °C, the extent of reaction was determined using a PerkinElmer EnVision multimode plate reader via HTRF dual wavelength detection, and the percent of control (POC) was calculated using a ratiometric emission factor. One hundred POC was determined using no test compounds, and 0 POC was determined using pre-quenched control reactions. A 4-parameter logistic curve was fit to the POC values as a function of the concentration of compound, and the IC_{50} value was the point where the best-fit curve crossed 50 POC.

[00799] **Table 5. IC_{50}'s of compounds tested in the assay of Examples A, B and C**

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
1	24.0	145.2	1074.2	N/A
2	32.1	176.2	70.3	202.3
3	16.1	90.2	37.8	N/A
4	92.1	10000.0	437.2	N/A
5	15.4	66.9	30.8	N/A
6	16.8	61.8	22.4	N/A
7	25.2	141.4	23.3	N/A
8	66.2	315.7	95.2	N/A
9	14.9	95.8	32.6	N/A
10	110.1	492.8	N/A	N/A
11	42.5	143.1	89.7	N/A
12	9.5	46.6	24.0	N/A
13	19.2	95.6	38.6	N/A
14	165.4	1135.1	N/A	N/A
15	264.0	1839.1	N/A	N/A
16	14.1	45.0	133.9	N/A
17	18.1	62.8	11.8	N/A
18	11.7	116.4	37.4	N/A
19	11.4	40.0	40.6	N/A
20	30.9	127.7	39.4	N/A
21	20.2	94.2	14.5	255.1
22	50.3	239.1	100.2	N/A
23	39.9	463.1	111.5	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
24	31.0	241.5	99.7	611.3
25	258.8	1693.0	N/A	N/A
26	4048.1	5174.2	N/A	N/A
27	3545.8	10000.0	N/A	N/A
28	1314.8	10000.0	N/A	N/A
29	345.1	2124.0	N/A	N/A
30	433.8	4733.4	N/A	N/A
31	13.5	88.2	26.5	N/A
32	69.6	409.7	85.6	N/A
33	9.9	88.1	21.1	N/A
34	19.7	138.2	19.9	N/A
35	209.8	1263.8	N/A	N/A
36	62.4	534.0	120.0	N/A
37	80.4	963.4	160.5	N/A
38	353.4	3915.7	N/A	N/A
39	15.1	97.2	23.5	N/A
40	63.2	802.4	193.7	N/A
41	25.2	208.7	54.1	N/A
42	33.0	188.5	107.8	N/A
43	25.9	59.1	1991.1	N/A
44	54.5	396.5	175.0	N/A
45	138.2	901.3	N/A	N/A
46	60.8	735.8	88.6	N/A
47	29.5	239.7	50.5	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
48	22.1	44.3	5.4	182.4
49	12.5	101.3	24.1	N/A
50	12.6	60.7	18.9	N/A
51	14.0	62.0	46.6	N/A
52	15.4	80.6	59.8	N/A
53	15.6	181.0	54.8	N/A
54	16.6	84.4	40.8	N/A
55	17.2	89.1	202.1	N/A
56	20.3	222.0	99.6	N/A
57	22.3	131.0	92.1	N/A
58	23.2	225.2	68.0	N/A
59	24.3	147.6	95.0	N/A
60	32.4	220.9	125.1	N/A
61	34.6	254.8	129.3	N/A
62	38.1	253.9	133.7	N/A
63	18.5	67.1	12.9	550.1
64	73.1	644.9	241.3	N/A
65	208.7	1451.6	N/A	N/A
66	54.6	250.1	157.2	N/A
67	6588.9	10000.0	N/A	N/A
68	166.2	1329.1	N/A	N/A
69	222.7	678.9	N/A	N/A
70	469.9	3978.2	N/A	N/A
71	56.4	341.5	165.7	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
72	36.3	271.3	89.0	N/A
73	107.8	601.8	N/A	N/A
74	76.3	492.4	287.0	N/A
75	128.2	768.6	N/A	N/A
76	133.0	656.6	N/A	N/A
77	277.0	1133.2	N/A	N/A
78	180.1	920.8	N/A	N/A
79	241.6	968.2	N/A	N/A
80	1212.3	5647.2	N/A	N/A
81	728.9	4512.1	N/A	N/A
82	2656.5	8939.1	N/A	N/A
83	72.7	410.3	382.8	N/A
84	124.1	748.4	N/A	N/A
85	209.6	1003.6	N/A	N/A
86	120.8	696.6	N/A	N/A
87	215.6	1075.5	N/A	N/A
88	34.3	151.2	30.0	N/A
89	261.7	1190.6	N/A	N/A
90	454.6	1712.2	N/A	N/A
91	163.3	764.6	N/A	N/A
92	32.2	152.5	35.9	N/A
93	157.5	771.8	N/A	N/A
94	88.1	702.5	370.6	N/A
95	136.6	952.6	N/A	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
96	62.8	593.9	271.5	N/A
97	39.1	255.9	90.1	487.0
98	21.4	152.1	269.8	N/A
99	20.0	125.2	20.7	N/A
100	14.1	91.3	43.4	N/A
101	60.4	465.3	346.3	N/A
102	69.0	535.9	149.7	N/A
103	95.2	786.8	224.0	N/A
104	476.6	3574.3	N/A	N/A
105	45.4	237.2	138.3	N/A
106	33.3	360.8	58.5	N/A
107	47.2	457.7	67.4	N/A
108	54.6	543.1	102.95	N/A
108	25.2	N/A	91.7	N/A
110	8.1	18.5	4.5	90.0
111	16.4	74.9	10.5	N/A
112	25.7	162.9	40.4	N/A
113	614.9	4754.7	N/A	N/A
114	109.9	843.6	N/A	N/A
115	15.0	70.5	16.6	54.3
116	103.8	1255.1	221.8	N/A
117	51.6	322.0	135.9	N/A
118	19.2	103.8	32.8	N/A
119	32.1	147.9	48.3	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
120	37.3	275.1	72.3	N/A
121	34.3	181.8	20.3	N/A
122	80.4	790.4	213.8	N/A
123	36.8	276.9	50.0	N/A
124	152.6	1075.5	294.6	N/A
125	27.5	310.4	69.2	N/A
126	91.5	708.9	181.3	N/A
127	41.9	228.5	201.5	N/A
128	10.2	24.0	2.5	575.7
129	21.6	179.2	24.1	N/A
130	30.9	183.7	20.1	N/A
131	41.5	422.5	113.5	N/A
132	256.3	1332.2	593.3	N/A
133	124.4	914.8	N/A	N/A
134	33.1	398.3	109.7	N/A
135	77.0	756.1	173.9	N/A
136	13.1	26.1	3.9	386.6
137	43.7	252.0	27.1	N/A
138	41.9	360.9	87.7	N/A
139	237.5	1733.1	N/A	N/A
140	23.5	219.7	96.2	N/A
141	85.5	651.3	159.0	N/A
142	51.0	319.0	59.1	N/A
143	36.3	276.0	46.5	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
144	39.3	220.6	37.4	N/A
145	55.1	560.5	115.5	N/A
146	113.7	712.2	N/A	N/A
147	84.2	867.7	256.2	N/A
148	144.5	1206.0	N/A	N/A
149	49.4	328.1	100.8	N/A
150	432.5	5390.5	N/A	N/A
151	490.4	5556.6	N/A	N/A
152	122.8	1986.9	N/A	N/A
153	36.7	283.5	69.7	N/A
154	26.2	180.3	26.8	N/A
155	28.0	146.1	45.0	N/A
156	31.9	157.6	20.5	N/A
157	35.0	346.0	72.3	N/A
158	100.6	703.4	130.9	N/A
159	270.8	1356.1	N/A	N/A
160	34.8	397.3	86.6	N/A
161	86.3	634.0	119.6	N/A
162	67.0	562.6	246.7	N/A
163	14.0	24.1	4.2	530.7
164	18.6	154.0	22.1	N/A
165	25.3	123.1	21.6	N/A
166	29.3	84.2	22.6	N/A
167	35.3	320.9	89.5	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
168	50.4	212.9	50.8	N/A
169	63.0	299.4	109.3	N/A
170	68.6	426.2	146.2	N/A
171	144.4	912.1	N/A	N/A
172	268.6	1788.4	N/A	N/A
173	46.9	244.2	44.8	N/A
174	13.3	52.2	6.8	847.2
175	19.9	37.9	2.9	N/A
176	24.5	74.5	10.1	N/A
177	134.4	839.7	N/A	N/A
178	28.4	79.8	12.2	N/A
179	32.1	110.8	25.4	N/A
180	23.2	63.2	15.7	N/A
181	91.0	674.8	165.4	N/A
182	634.3	3688.8	N/A	N/A
183	15.1	34.1	6.4	472.6
184	21.6	82.5	17.0	3097.4
185	27.0	185.2	36.6	N/A
186	20.2	149.0	36.9	N/A
187	56.2	499.6	254.5	N/A
188	69.2	692.5	160.5	N/A
189	82.7	789.6	211.3	N/A
190	443.6	5301.9	N/A	N/A
191	37.3	207.3	111.6	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
192	12.3	282.3	44.7	N/A
193	38.3	372.5	38.6	N/A
194	57.8	610.2	106.8	N/A
195	30.5	178.1	73.6	N/A
196	78.1	567.2	238.3	N/A
197	149.4	1533.8	N/A	N/A
198	59.1	356.1	193.0	N/A
199	50.3	449.9	91.5	N/A
200	461.7	5324.1	N/A	N/A
201	59.0	273.6	90.0	N/A
202	278.2	2284.8	N/A	N/A
203	253.6	3034.5	N/A	N/A
204	103.7	581.8	131.7	N/A
205	18.2	89.0	11.7	N/A
206	61.3	519.1	78.0	N/A
207	27.4	123.0	18.8	N/A
208	33.3	234.5	40.4	N/A
209	41.3	288.1	39.7	N/A
210	34.5	196.7	57.2	786.7
211	113.5	901.6	N/A	N/A
212	222.7	2022.5	N/A	N/A
213	25.2	253.7	78.3	N/A
214	54.4	338.0	148.8	N/A
215	108.5	753.1	N/A	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
216	29.1	211.8	73.3	N/A
217	27.0	189.9	68.4	N/A
218	85.6	499.9	194.1	N/A
219	77.8	423.7	92.3	N/A
220	101.8	661.0	181.7	N/A
221	54.9	293.0	55.0	N/A
222	40.8	273.9	40.9	N/A
223	57.1	438.6	62.1	N/A
224	125.7	1033.3	N/A	N/A
225	56.7	447.9	101.7	N/A
226	36.3	382.8	95.6	N/A
227	49.8	379.7	76.3	N/A
228	45.3	388.9	76.4	N/A
229	100.0	946.3	124.3	N/A
230	908.8	9120.4	N/A	N/A
231	398.9	2999.9	N/A	N/A
232	41.9	223.7	60.0	N/A
233	194.3	1040.2	N/A	N/A
234	533.5	4156.4	N/A	N/A
235	306.4	3651.1	N/A	N/A
236	348.3	3801.2	N/A	N/A
237	37.7	213.2	28.7	N/A
238	42.4	347.8	87.5	N/A
239	48.9	498.9	125.6	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
240	62.4	566.0	137.0	N/A
241	69.6	560.0	142.1	N/A
242	30.5	161.4	21.3	N/A
243	46.3	150.4	70.2	N/A
244	107.4	476.9	N/A	N/A
245	543.5	10000.0	N/A	N/A
246	413.8	7839.8	N/A	N/A
247	49.6	324.3	33.8	N/A
248	21.8	42.0	7.3	N/A
249	10.6	37.3	8.1	N/A
250	19.8	62.6	10.5	N/A
251	35.0	222.7	22.1	1828.5
252	29.9	59.0	10.9	3738.7
253	51.3	1141.8	85.5	N/A
254	14.8	85.7	36.8	104.5
255	14.4	128.3	22.2	80.1
256	39.3	512.3	445.1	N/A
257	483.3	6165.2	N/A	N/A
258	660.5	1914.1	N/A	N/A
259	74.9	930.5	251.5	N/A
260	240.5	3455.9	N/A	N/A
261	30.7	61.4	10.7	58.7
262	92.8	549.5	58.9	872.3
263	93.2	1133.3	173.0	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
264	117.2	1326.1	N/A	938.2
265	156.5	1451.0	N/A	N/A
266	643.9	3333.3	N/A	N/A
267	121.7	1293.1	N/A	N/A
268	2835.2	8899.5	N/A	N/A
269	3789.0	10000.0	N/A	N/A
270	271.5	2977.8	1667.0	N/A
271	514.0	4965.8	N/A	N/A
272	69.8	982.3	673.4	N/A
273	109.4	1109.1	N/A	N/A
274	223.4	1756.1	N/A	N/A
275	965.2	9236.5	N/A	N/A
276	63.2	274.7	64.3	N/A
277	9.7	80.8	76.6	N/A
278	35.6	237.8	47.3	N/A
279	64.9	704.7	136.8	N/A
280	10.2	90.4	9.0	N/A
281	9.4	19.3	5.4	N/A
282	20.0	49.1	8.1	N/A
283	31.9	107.5	8.1	N/A
284	13.8	55.5	13.3	N/A
285	13.1	84.9	24.1	N/A
286	28.9	150.9	27.7	N/A
287	17.9	121.9	30.1	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
288	26.5	215.5	47.3	N/A
289	36.8	209.1	54.8	N/A
290	52.2	393.1	84.6	N/A
291	43.4	547.9	86.2	N/A
292	43.8	177.8	99.8	N/A
293	47.7	487.0	129.3	N/A
294	59.3	430.5	134.2	N/A
295	53.4	181.3	195.8	N/A
296	83.7	448.4	300.8	N/A
297	102.3	1091.2	787.6	N/A
298	33.9	234.8	31.4	N/A
299	33.5	302.0	29.5	N/A
300	31.0	257.6	50.2	N/A
301	24.0	181.0	113.1	N/A
302	65.1	504.4	158.5	N/A
303	75.0	605.4	264.1	N/A
304	100.2	652.5	383.3	N/A
305	108.1	680.5	N/A	N/A
306	125.4	881.5	N/A	N/A
307	229.0	1552.5	N/A	N/A
308	255.8	2199.0	N/A	N/A
309	140.5	1056.1	N/A	N/A
310	319.2	3631.3	N/A	N/A
311	117.4	215.0	N/A	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
312	20.8	287.9	26.1	N/A
313	13.7	132.1	9.2	N/A
314	28.9	308.4	36.1	N/A
315	9.6	23.2	4.9	N/A
316	31.9	221.4	38.2	N/A
317	20.7	196.6	44.3	N/A
318	69.5	345.6	142.7	N/A
319	53.5	674.9	166.2	N/A
320	88.8	701.8	1667.0	N/A
321	94.7	757.0	1667.0	N/A
322	223.4	1490.6	N/A	N/A
323	9.9	21.6	4.0	N/A
324	11.4	15.5	10.9	N/A
325	24.2	103.6	27.8	N/A
326	41.1	368.2	78.8	N/A
327	94.7	517.6	314.1	N/A
328	82.4	586.8	444.5	N/A
329	106.7	337.0	N/A	N/A
330	45.4	372.1	93.2	N/A
331	9.4	30.8	10.3	N/A
332	14.6	75.5	24.4	N/A
333	29.4	218.1	33.2	N/A
334	38.5	251.0	46.0	N/A
335	39.4	218.5	47.1	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
336	45.3	334.8	164.0	N/A
337	12.6	30.0	4.6	N/A
338	33.6	568.2	70.4	N/A
339	51.7	756.7	236.9	N/A
340	65.1	582.7	769.3	N/A
341	79.2	397.2	1667.0	N/A
342	63.8	309.7	1667.0	N/A
343	55.3	329.9	970.1	N/A
344	65.6	552.2	175.1	N/A
345	26.8	140.5	37.5	N/A
346	35.2	172.7	45.9	N/A
347	77.9	832.3	161.1	N/A
348	183.9	1196.6	N/A	N/A
349	55.7	348.7	260.8	N/A
350	77.2	225.7	96.1	N/A
351	313.9	2730.6	N/A	N/A
352	2379.9	10000.0	N/A	N/A
353	89.3	570.5	128.6	N/A
354	3347.1	10000.0	N/A	N/A
355	405.4	5472.6	N/A	N/A
356	242.1	2291.9	N/A	N/A
357	154.1	2082.0	N/A	N/A
358	50.3	710.0	150.6	N/A
359	60.7	1477.2	100.2	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
360	190.6	2393.4	N/A	N/A
361	62.5	288.0	102.7	N/A
362	170.0	732.6	N/A	N/A
363	31.7	88.9	24.8	N/A
364	257.3	1895.7	N/A	N/A
365	47.8	187.1	61.0	N/A
366	22.3	47.5	19.3	N/A
367	109.1	1098.7	N/A	N/A
368	19.8	47.2	30.3	N/A
369	16.2	36.9	12.1	N/A
370	19.4	56.5	13.5	N/A
371	28.9	147.3	35.7	N/A
372	33.9	78.7	35.7	N/A
373	277.5	2974.6	N/A	N/A
374	581.6	6256.9	N/A	N/A
375	113.1	1561.6	N/A	N/A
376	164.8	2788.1	N/A	N/A
377	69.9	977.2	149.0	N/A
378	110.3	1374.6	N/A	N/A
379	474.9	4809.7	N/A	N/A
380	127.5	1994.2	N/A	N/A
381	147.5	1714.8	N/A	N/A
382	31.2	134.0	28.9	N/A
383	32.8	257.8	55.3	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
384	77.4	598.8	381.7	N/A
385	59.5	401.8	112.0	N/A
386	193.8	2911.9	N/A	N/A
387	355.0	4202.6	N/A	N/A
388	72.6	551.6	223.5	N/A
389	44.3	236.7	50.2	N/A
390	69.2	621.2	231.1	N/A
391	459.9	5367.8	N/A	N/A
392	170.9	3419.8	N/A	N/A
393	706.7	7376.4	N/A	N/A
394	111.6	887.1	N/A	N/A
395	365.2	2494.9	N/A	N/A
396	110.9	1859.9	N/A	N/A
397	75.6	668.0	51.9	N/A
398	197.0	3411.4	N/A	N/A
399	86.8	1309.2	129.2	N/A
400	110.0	1427.0	N/A	N/A
401	94.9	1249.8	261.5	N/A
402	114.1	1349.6	N/A	N/A
403	50.3	738.7	105.0	N/A
404	293.8	6841.7	N/A	N/A
405	48.2	331.7	70.0	N/A
406	46.5	299.7	46.2	N/A
408	159.2	3136.0	N/A	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
409	502.1	5012.6	N/A	N/A
410	69.6	1038.4	1667.0	N/A
411	264.3	2912.5	1667.0	N/A
412	184.1	2524.7	N/A	N/A
413	388.6	3712.7	N/A	N/A
414	298.0	3136.0	990.0	N/A
415	61.6	767.8	146.5	N/A
416	14.1	48.3	9.3	N/A
417	109.3	974.6	N/A	N/A
418	340.4	3890.4	N/A	N/A
419	402.4	5308.7	N/A	N/A
420	280.2	4516.5	N/A	N/A
421	135.3	685.8	N/A	N/A
422	27.4	101.6	256.9	N/A
423	15.0	82.9	13.7	N/A
424	102.3	736.4	N/A	N/A
425	21.2	162.0	49.7	3238.7
426	24.5	157.0	23.5	1489.0
427	38.7	448.8	51.1	3764.4
428	24.1	135.4	33.4	1742.5
429	38.5	452.6	34.2	5466.1
430	45.1	333.2	25.1	4137.1
431	4.5	12.3	2.4	N/A
432	29.5	155.5	20.8	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
433	14.2	28.4	3.3	246.8
434	9.3	18.1	2.8	N/A
435	9.5	25.0	6.5	N/A
436	34.3	117.9	11.5	351.1
437	19.0	138.8	11.1	278.0
438	10.4	53.4	5.2	104.8
439	22.6	47.0	5.7	128.1
440	13.2	32.6	36.4	N/A
441	45.3	433.6	63.2	N/A
442	13.8	21.5	2.0	100.6
443	6.5	11.9	0.8	N/A
444	7.8	16.1	3.6	68.5
445	8.2	24.0	2.5	N/A
446	9.5	44.7	10.0	119.7
447	18.2	32.1	2.7	213.4
448	9.6	20.4	94.5	N/A
449	11.9	28.7	2.9	400.8
450	11.4	31.3	12.6	112.7
451	8.3	14.7	7.6	52.4
452	12.4	28.4	2.9	281.7
453	9.2	29.3	227.2	N/A
454	16.3	47.9	8.2	1938.2
455	23.2	53.3	5.5	904.7
456	14.7	30.0	6.7	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
457	22.4	35.4	2.8	521.9
458	59.0	210.4	29.7	4116.7
459	10.6	56.1	15.5	123.0
460	12.9	27.4	2.3	207.5
461	5.6	16.4	90.8	N/A
462	9.0	11.9	17.5	84.8
463	22.8	158.5	256.1	N/A
464	38.8	252.8	61.3	N/A
465	48.5	289.1	103.2	N/A
466	9.7	46.4	19.3	N/A
467	13.5	31.8	10.2	N/A
468	4.8	10.2	6.0	N/A
469	12.0	27.3	17.6	N/A
470	5.5	10.4	4.0	41.0
471	18.3	29.5	10.6	175.3
472	14.5	77.0	30.1	N/A
473	17.4	58.4	8.2	642.2
474	33.7	88.3	22.1	N/A
475	20.0	50.0	3.4	252.5
476	20.0	55.1	21.3	N/A
477	35.4	95.0	28.9	N/A
478	18.3	39.9	3.2	208.3
479	12.6	51.4	10.4	242.0
480	7.4	29.3	8.3	N/A

Ex#	RET Enzyme (wild type) IC_{50} (nM)	RET enzyme (V804M) IC_{50} (nM)	KIF5B-RET pTYR1062 Cell IC_{50} (nM)	RET enzyme (G810R) IC_{50} (nM)
481	28.4	65.4	18.8	N/A
482	9.1	22.9	25.9	N/A
483	19.4	28.3	6.8	159.2
484	38.2	75.2	14.4	814.4
485	289.6	4217.1	N/A	N/A
486	21.7	162.4	101.8	N/A
487	64.7	632.9	134.6	N/A
488	80.7	321.9	144.4	N/A
489	12.5	35.9	2.7	614.5
490	28.2	67.5	13.2	N/A
491	19.7	75.5	38.0	N/A
492	86.1	518.8	122.8	N/A
493	15.3	74.6	35.2	N/A
494	76.8	269.4	195.4	N/A
495	20.6	139.9	37.5	N/A
496	30.1	114.1	34.8	N/A
497	23.5	115.9	29.3	N/A
498	41.4	48.9	57.3	N/A
499	42.5	70.2	49.5	N/A
500	170.3	325.4	N/A	N/A
501	102.4	298.9	100.7	N/A
502	487.6	931.3	N/A	N/A
503	692.5	6084.2	N/A	N/A

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __3___

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

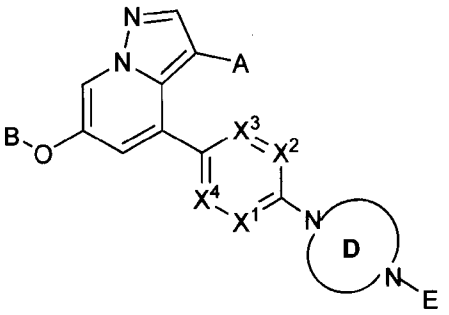
THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __3___

NOTE: For additional volumes please contact the Canadian Patent Office.

What is claimed is:

1. A compound of the Formula **I**:



I

and pharmaceutically acceptable salts and solvates thereof, wherein:

X^1, X^2, X^3 and X^4 are independently CH, CF, CCH_3 or N, wherein zero, one or two of X^1, X^2, X^3 and X^4 is N;

A is H, CN, Cl, CH_3-, CH_3CH_2-, cyclopropyl, $-CH_2CN$ or $-CH(CN)CH_3$;

B is

(a) hydrogen,

(b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

(c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,

(d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,

(e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

(f) (R^1R^2N)C1-C6 alkyl-, wherein said alkyl portion is optionally substituted with OH and wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

(g) $hetAr^1$C1-C3 alkyl-, wherein $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently N, O or S and is optionally substituted with one or more independently C1-C6 alkyl substituents;

(h) (C3-C6 cycloalkyl)C1-C3 alkyl-, wherein said cycloalkyl is optionally substituted with OH,

(i) ($hetCyc^a$)C1-C3 alkyl-,

(j) $hetCyc^a$-;

(k) C3-C6 cycloalkyl-, wherein said cycloalkyl is optionally substituted with OH,

(l) (C1-C4 alkyl)C(=O)O-C1-C6 alkyl-, wherein each of the C1-C4 alkyl and C1-C6 alkyl portions

is optionally and independently substituted with 1-3 fluoros, or

(m) $(R^1R^2N)C(=O)C1$-C6 alkyl-, wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

$hetCyc^a$- is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently N or O and optionally substituted with one or more substituents independently OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl- or fluoro, or wherein $hetCyc^a$ is substituted with oxo;

Ring D is (i) a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, (ii) a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, (iii) a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, or (iv) a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein each of said rings is optionally substituted with (a) one to four groups independently halogen, OH, or C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group;

E is

(a) hydrogen,

(b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

(c) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

(d) (C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl,

(e) (hydroxyC2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros,

(f) (C1-C6 alkoxy)C(=O)-,

(g) (C3-C6 cycloalkyl)C(=O)-, wherein said cycloalkyl is optionally substituted with one or more substituents independently C1-C6 alkyl, C1-C6 alkoxy, OH, or (C1-C6 alkoxy)C1-C6 alkyl-, or said cycloalkyl is substituted with a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently N or O,

(h) Ar^1C1-C6 alkyl-,

(i) Ar^1(C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, C1-C6 alkoxy, R^mR^nN- or R^mR^nN-CH_2- wherein each R^m and R^n is independently H or C1-C6 alkyl,

(j) $hetAr^2C1$-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros,

(k) $hetAr^2$(C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy,

(l) $hetAr^2C(=O)$-,

(m) $hetCyc^1C(=O)$-,

(n) $hetCyc^1$C1-C6 alkyl-,

(o) $R^3R^4NC(=O)$-,

(p) $Ar^1N(R^3)C(=O)$-,

(q) $hetAr^2N(R^3)C(=O)$-,

(r) (C1-C6 alkyl)SO_2-, wherein the alkyl portion is optionally substituted with 1-3 fluoros,

(s) Ar^1SO_2-,

(t) $hetAr^2SO_2$-,

(u) N-(C1-C6 alkyl)pyridinonyl,

(v) $Ar^1C(=O)$-,

(w) Ar^1O-C(=O)-,

(x) (C3-C6 cycloalkyl)(C1-C6 alkyl)C(=O)-,

(y) (C3-C6 cycloalkyl)(C1-C6 alkyl)SO_2-, wherein the alkyl portion is optionally substituted with 1-3 fluoros,

(z) Ar^1(C1-C6 alkyl)SO_2-,

(aa) $hetCyc^1$-O-C(=O)-,

(bb) $hetCyc^1CH_2C(=O)$-,

(cc) $hetAr^2$, or

(dd) C3-C6 cycloalkyl;

Ar^1 is phenyl optionally substituted with one or more substituents independently halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, (R^pR^qN)C1-C6 alkoxy- wherein R^p and R^q are independently H or C1-C6 alkyl, or $(hetAr^a)$C1-C6 alkyl- wherein $hetAr^a$ is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms, or Ar^1 is a phenyl ring fused to a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently N or O;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently N, O or S or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein $hetAr^2$ is optionally substituted with one or more substituents independently halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, OH, (C1-C6 alkoxy)C1-C6 alkoxy- or C3-C6 cycloalkyl;

$hetCyc^1$ is a 4-6 membered saturated heterocyclic ring having 1-2 ring heteroatoms independently N, O or S wherein said heterocyclic ring is optionally substituted with one or more substituents

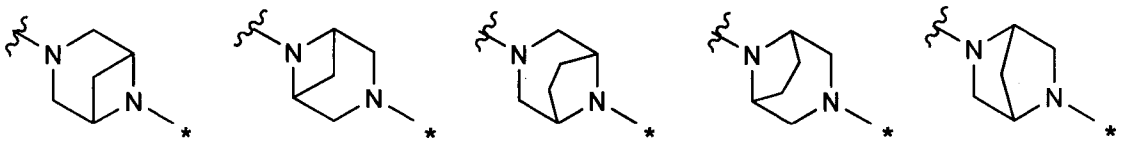
independently C1-C6 alkoxy or halogen;

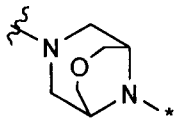
R^3 is H or C1-C6 alkyl; and

R^4 is C1-C6 alkyl.

2. A compound according to claim 1, wherein Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently halogen, OH, or C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group.

3. A compound according to claim 2, wherein Ring D is

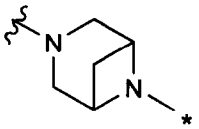




or

wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1, X^2, X^3 and X^4, and the asterisk indicates the point of attachment to E.

4. A compound according to claim 3, wherein Ring D is



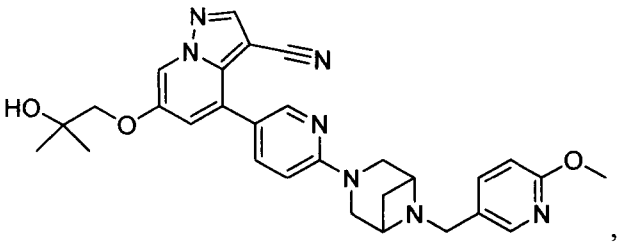
5. A compound according to any one of claims 1-4, wherein B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring.

6. A compound according to any one of claims 1-4, wherein B is (hetCyc[a])C1-C3 alkyl-.

7. A compound according to any one of claims 1-6, wherein X^1 is N, and X^2, X^3 and X^4 are CH.

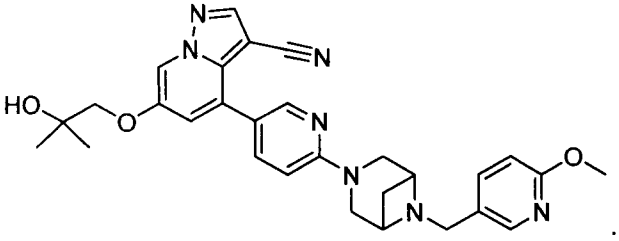
8. A compound according to any one of claims 1-7, wherein A is CN.

9. A compound which is



, or a pharmaceutically acceptable salt thereof.

10. The compound of claim 9, which is



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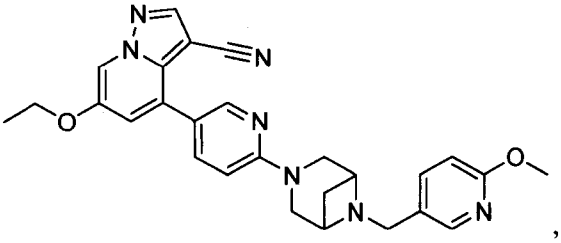
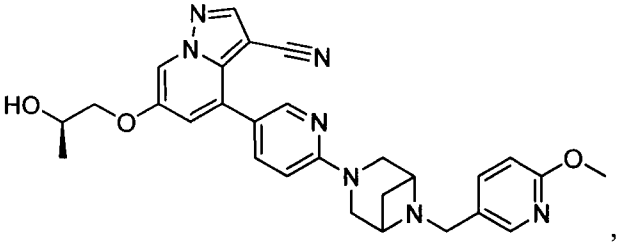
11. A compound which is



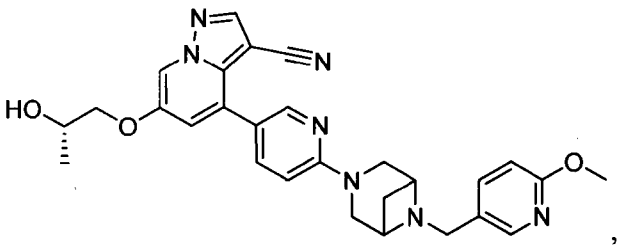
, or a pharmaceutically acceptable salt thereof.

12. A compound which is



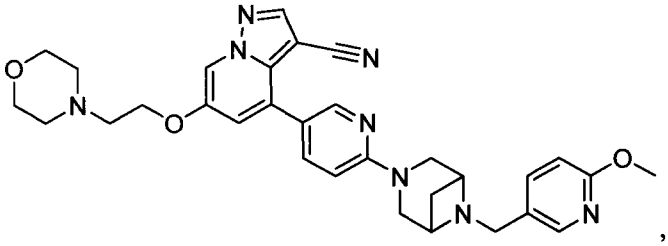
, or a pharmaceutically acceptable salt thereof.

13. A compound which is



, or a pharmaceutically acceptable salt thereof.

14. A compound which is



, or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition, comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-14, in admixture with a pharmaceutically acceptable diluent or carrier.

16. A pharmaceutical composition, comprising a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 8-14 in admixture with a pharmaceutically acceptable diluent or carrier.

17. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancer.

18. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, for treating cancer.

19. Use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a RET-associated cancer in a patient.

20. The use of a compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, for treating a RET-associated cancer in a patient.

21. The use of claim 19 or 20, wherein the RET-associated cancer is a cancer having a dysregulation in a RET gene, a RET kinase protein, or expression or activity or level of any of the same.

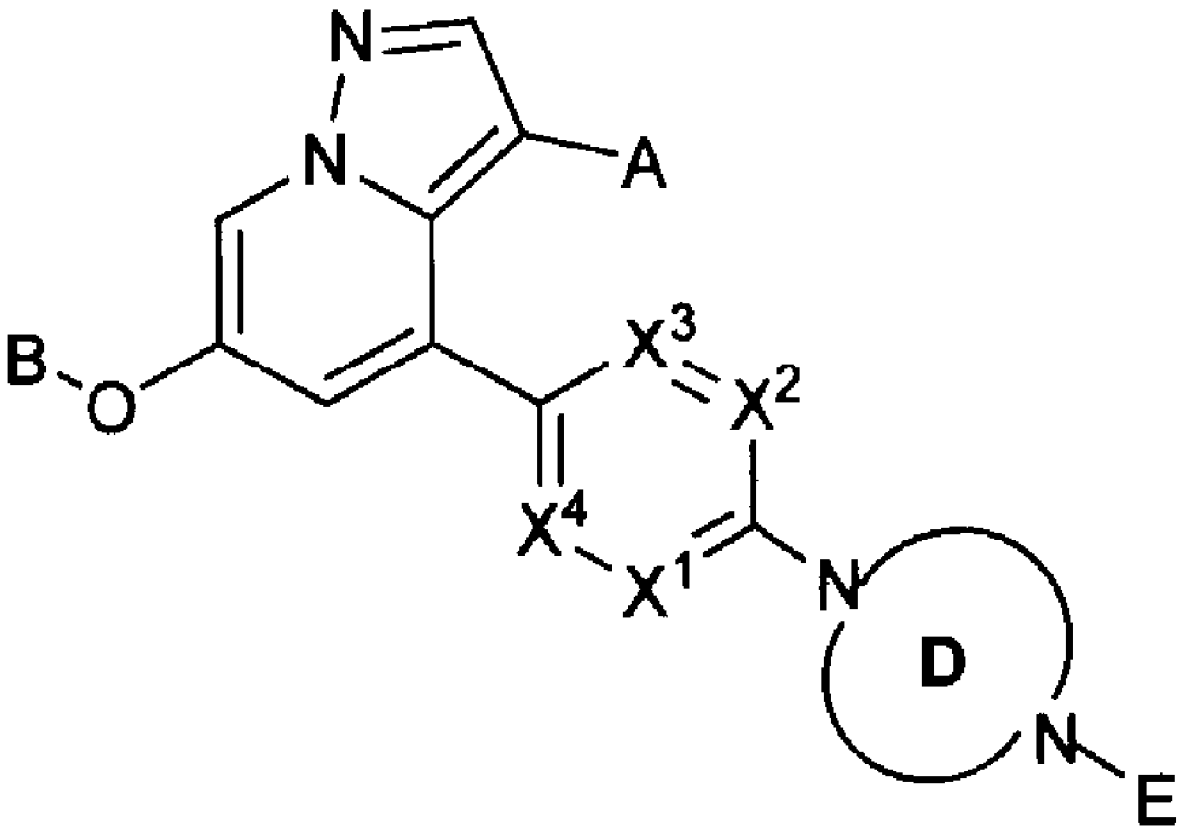
22. The use of any one of claims 19-21, wherein the RET-associated cancer is: lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, or cervical cancer.

23. The use of claim 22, wherein the lung cancer is RET fusion lung cancer or the cancer is medullary thyroid cancer.

24. The use of claim 22, wherein the lung cancer is small cell lung carcinoma, non-small cell lung cancer, bronchioles lung cell carcinoma, or lung adenocarcinoma.

25. The use of any one of claims 17, 19, 21, 22, 23 and 24, wherein the medicament is formulated for oral administration.

26. The use of any one of claims 18, 20, 21, 22, 23 and 24 for oral administration.



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