

[00015] The present disclosure relates to pharmaceutical compositions comprising these compounds and to their use for the prevention and treatment of a Human Epidermal Growth Factor Receptor-related (HER-) disorder. In certain embodiments, the HER-related disorder is HER2-related disorder. In certain embodiments, the HER-related disorder is HER3-related disorder. Exemplary HER-related disorders include, but are not limited to, cancers such as breast, lung, kidney, brain, ovarian, colon, cervical, endometrial, prostate, liver, thyroid, GI tract, blood and lymphoma and other diseases such as multiple sclerosis.

[00016] The present disclosure relates to pharmaceutical compositions comprising these compounds and to their use for the prevention and treatment of an mTOR-related disorder. Exemplary mTOR-related disorders include, but are not limited to, cancers, such as breast, lung, kidney, brain, ovarian, colon, cervical, endometrial, prostate, liver, thyroid, GI tract, hematological cancers, and lymphoma, and other diseases such as hamartoma syndromes, rheumatoid arthritis, and multiple sclerosis.

[00017] The present disclosure relates to pharmaceutical compositions comprising these compounds and to their use for the prevention and treatment of diseases such as, but not limited to, proliferative diseases, cancer (*e.g.*, hematological cancers, non-solid cancers, and solid tumors), inflammatory diseases, neurodegenerative diseases (*e.g.*, Alzheimer's disease, autism, or autism spectrum disorders (*e.g.* Asperger syndrome or Mendelsohn's Syndrome), metabolic disorders (obesity, diabetes) as well as methods of treating these disorders using compounds described herein as single agents or in combination with one or more additional agents. In some embodiments, the additional agent is a kinase inhibitor. In some embodiments, the additional agent is an mTOR inhibitor (*e.g.*, Sirolimus (rapamycin), Temsirolimus (CCI779), Everolimus (RAD001), AP23573 or other compounds disclosed in U.S. Pat. No. 7,091,213). In some embodiments, the additional agent is a PI3K inhibitor. Exemplary PI3-kinase inhibitors include wortmannin, demethoxyviridin, LY294002, perifosine, CAL101, PX-886, BEZ235, SF1126, INK1117, INK1197, IPI-145, GDC-0941, BKM120, XL147, XL765, palomid 529, GSK1059615, ZSTK474, PWT33597, IC87114, TG100-115, CAL263, PI-103, GNE-477, CUDC-907, GSK 2126458, GDC-0980, PF-46915032, CAL263, SF1126 and PX-886. In some embodiments, the PI3-kinase inhibitor inhibits PI3K- α , PI3K- β , PI3K- γ , and/or PI3K- δ .

[00017a] In another aspect, there is provided a compound as described herein, for use in therapy.

[00017b] In another aspect, there is provided the use of the compound as described herein in the manufacture of a medicament for the treatment of a disorder selected from the group consisting of cancer, an inflammatory disease, a neurodegenerative disease, and a metabolic disorder, wherein the cancer is solid tumor or hematological tumor, wherein the metabolic disorder is obesity or diabetes, and wherein the neurodegenerative disease is Alzheimer's disease, autism, or autism spectrum.

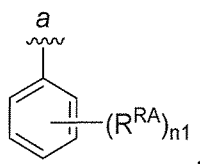
[00018] The present disclosure describes methods for the synthesis of compounds of Formula (I), such as, for example, (4-methylpiperazin-1-yl)(4-(3-

each instance of R^{NZ} is independently hydrogen, optionally substituted C_{1-6} alkyl, or a nitrogen protecting group.

7. The compound of claim 4, wherein Z is $-O-$ or $-NR^{NZ}-$, wherein R^{NZ} is hydrogen, optionally substituted C_{1-6} alkyl, or unsubstituted C_{1-6} alkyl.

8. The compound of claim 1, wherein R^{pa} or R^{pb} is hydrogen or halogen.

9. The compound of claim 1, wherein Ring A is optionally substituted five-membered heteroaryl with two heteroatoms selected from the group consisting of O, S, and N; or wherein Ring A is optionally substituted six-membered heteroaryl with one or two N; or wherein Ring A is of the formula:



wherein

a indicates the point of attachment to the alkyne;

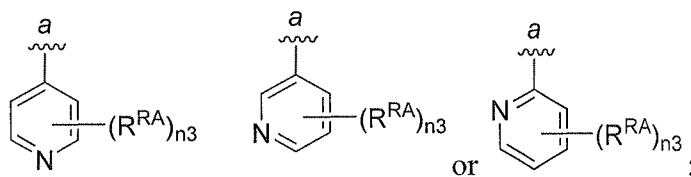
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted acyl, $-CN$, $-OR^{AO}$, or $-N(R^{AN})_2$;

each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group;

each instance of R^{AN} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group; and

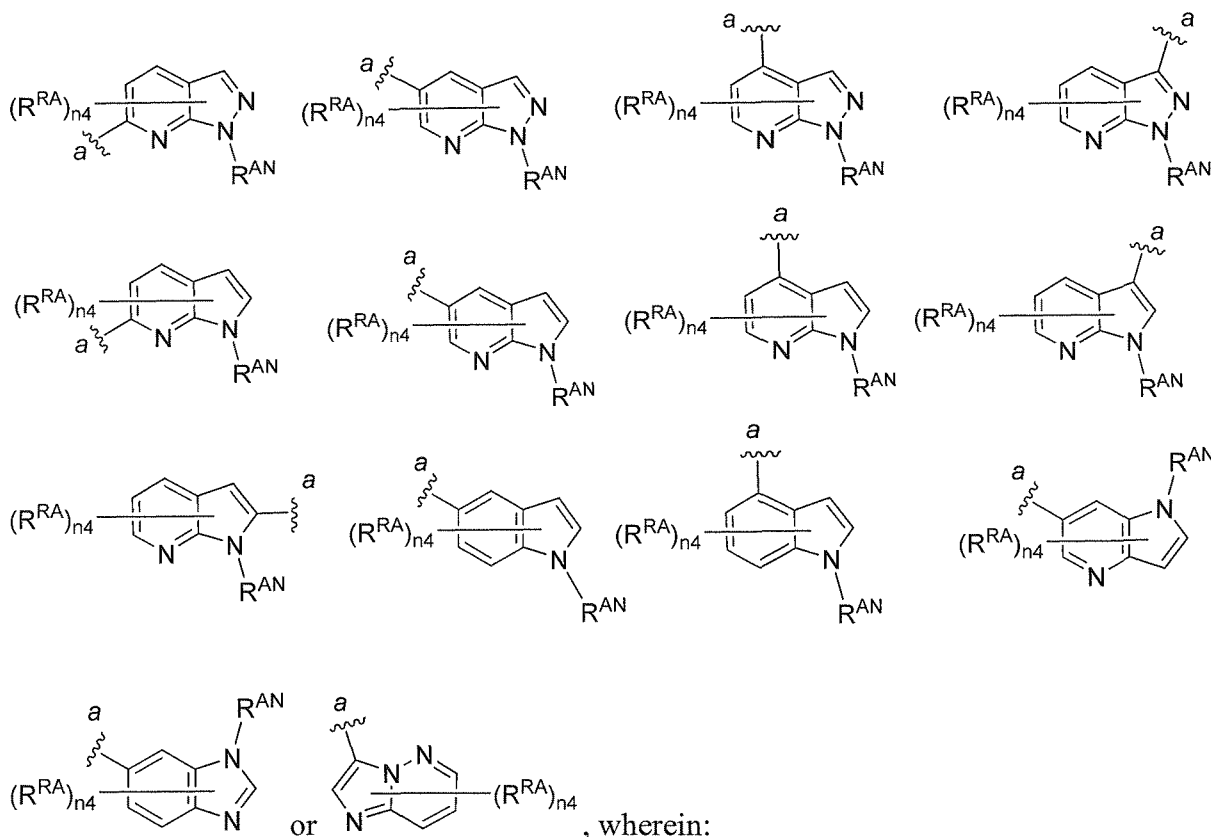
$n1$ is an integer of 1 to 5, inclusive.

10. The compound of claim 9, wherein Ring A is one of the following formulae:



wherein





a indicates the point of attachment to the alkyne;

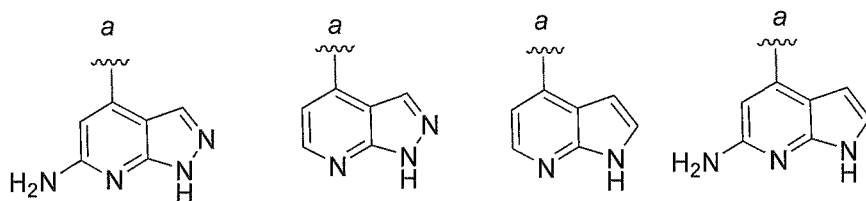
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted acyl, $-CN$, $-OR^{AO}$, or $-N(R^{AN})_2$;

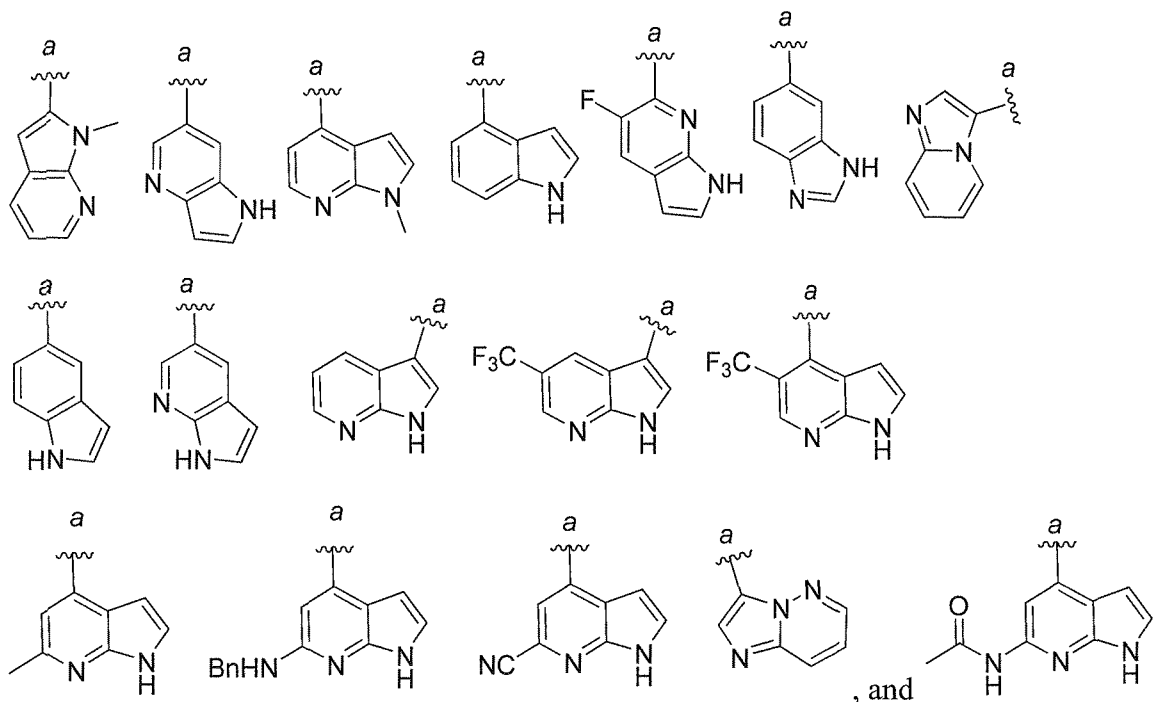
each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group;

R^{AN} is hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group; and

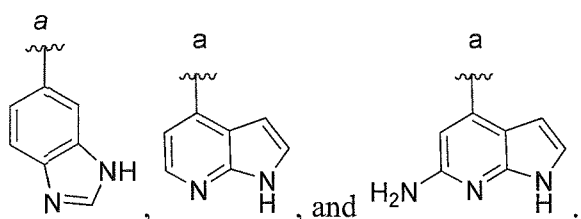
each instance of n_4 is independently an integer of 1 to 5, inclusive.

16. The compound of claim 15, wherein Ring A is selected from the group consisting of optionally substituted groups of the formula:

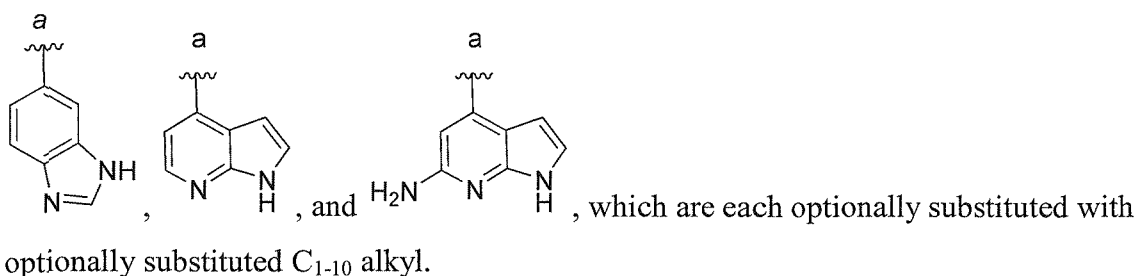




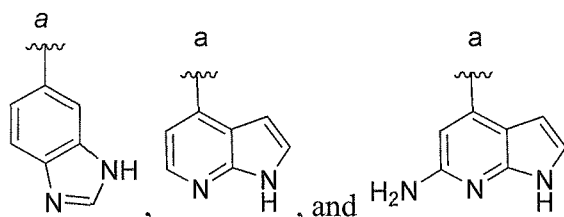
17. The compound of claim 13, wherein Ring A is selected from the group consisting of optionally substituted groups of the formula:



18. The compound of claim 13, wherein Ring A is selected from the group consisting of groups of the formula:



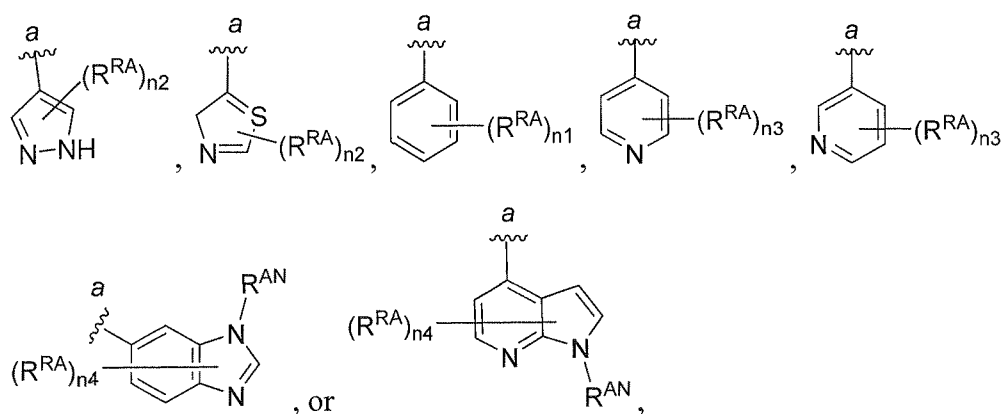
19. The compound of claim 13, wherein Ring A is selected from the group consisting of groups of the formula:


, which are each optionally substituted with optionally substituted methyl, optionally substituted ethyl, or optionally substituted propyl.

20. The compound of claim 4, wherein Z is O and Ring A is optionally substituted 5,6-bicyclic heteroaryl.

21. The compound of claim 4, wherein Ring A is optionally substituted 5-membered monocyclic heteroaryl, 6-membered monocyclic heteroaryl, or 5,6-bicyclic heteroaryl.

22. The compound of claim 21, wherein Ring A is one of the following formulae:



wherein:

a indicates the point of attachment to the alkyne;

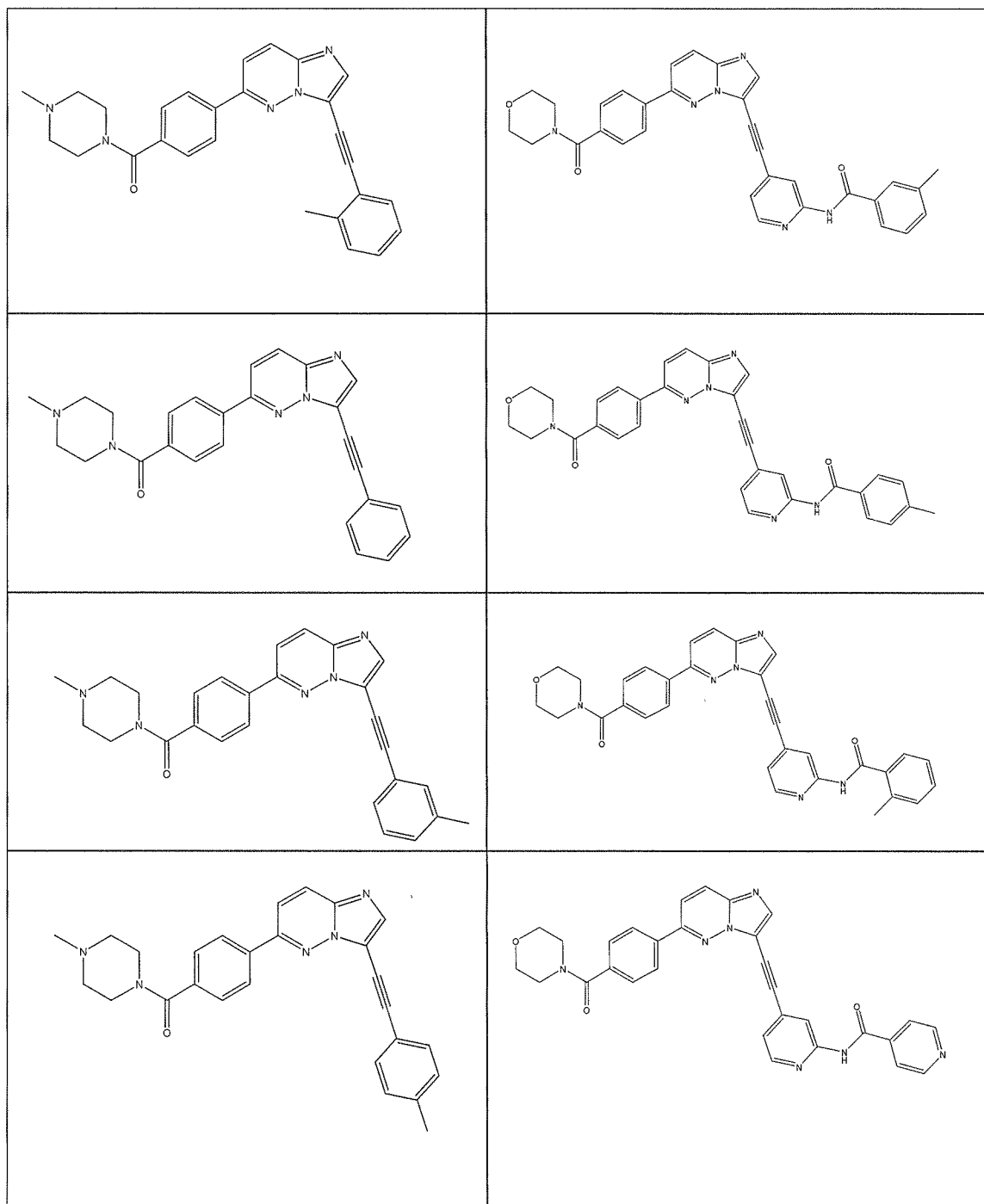
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted acyl, -CN, -OR^{AO}, or -N(R^{AN})₂;

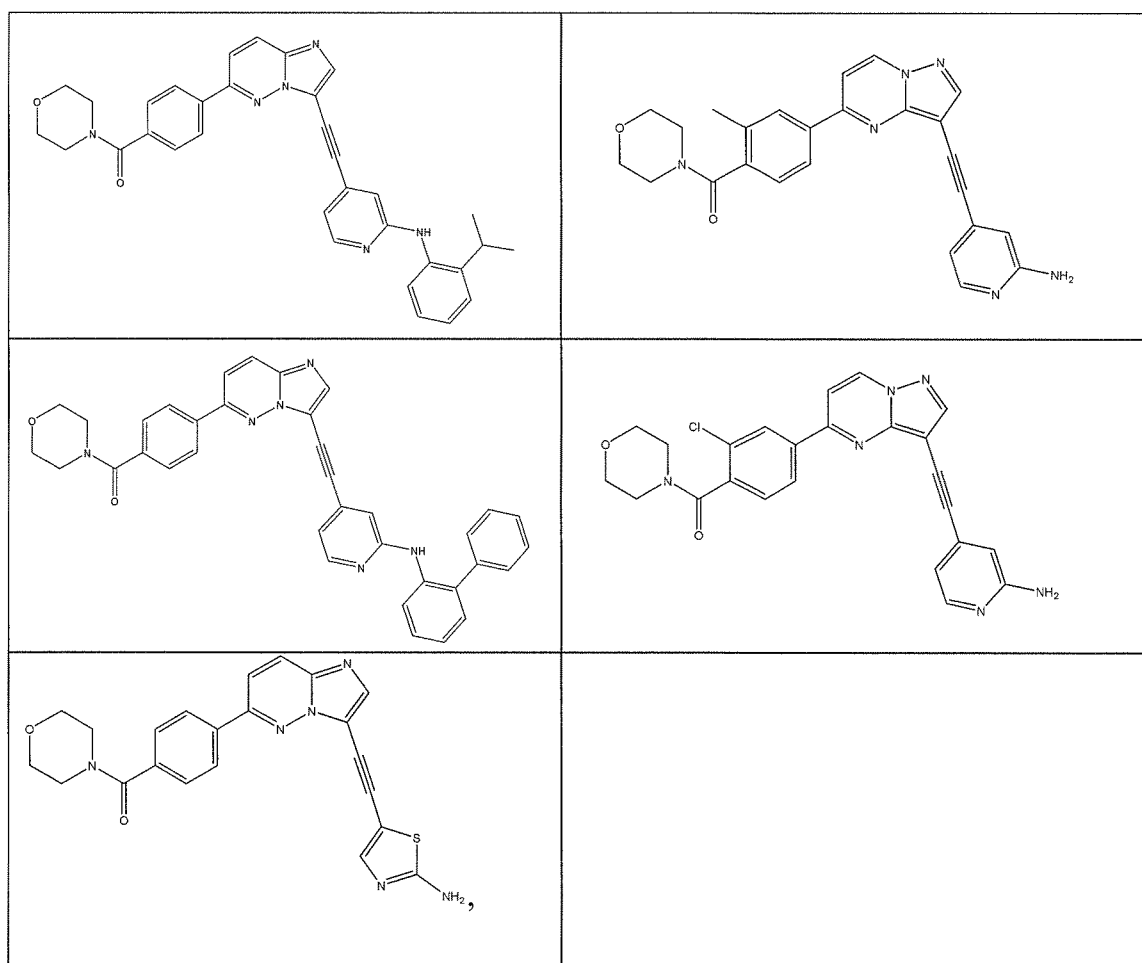
each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group;

R^{AN} is hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group;

each instance of n2 is independently an integer of 1 or 2;
each instance of n3 is independently an integer of 1 to 4, inclusive; and
each instance of n4 is independently an integer of 1 to 5, inclusive.

23. The compound of claim 1, wherein the compound is of the formula:





or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a compound of any one of claims 1 to 23 and a pharmaceutically acceptable excipient, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound.

25. A compound of any one of claims 1 to 23, for use in therapy.

26. Use of the compound of any one of claims 1 to 23 in the manufacture of a medicament for the treatment of a disorder selected from the group consisting of cancer, an inflammatory disease, a neurodegenerative disease, and a metabolic disorder, wherein the cancer is solid tumor or hematological tumor, wherein the metabolic disorder is obesity or diabetes, and wherein the neurodegenerative disease is Alzheimer's disease, autism, or autism spectrum.