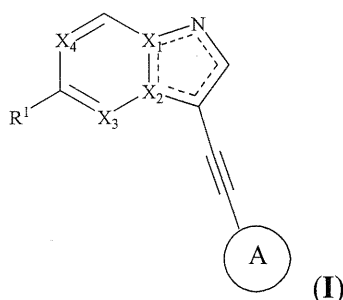


Akcakanat, A.; Singh, G.; Luyimbazi, D.; Zheng, Y.; Kim, D.; Gonzalez-Angulo, A.; Meric-Bernstam, F. *Mol.Cancer Ther.* 2008, 7, 1782-1788; Berkel, H. J.; Turbat-Herrera, E. A.; Shi, R.; De Benedetti, A. *Cancer Epidemiol.Biomarkers Prev.* 2001, 10, 663-666; Wendel, H. G.; De Stanchina, E.; Fridman, J. S.; Malina, A.; Ray, S.; Kogan, S.; Cordon-Cardo, C.; Pelletier, J.; Lowe, S. W. *Nature* 2004, 428, 332-337; De Benedetti, A.; Graff, J. R. *Oncogene* 2004, 23, 3189-3199).

SUMMARY OF THE INVENTION

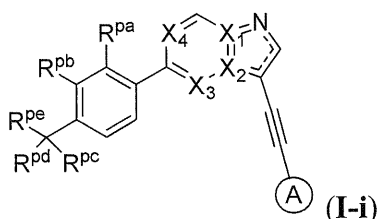
[0009] ~~In one aspect, the~~ The present invention ~~disclosure~~ relates to compounds that act as kinase inhibitors, in particular as inhibitors of the MAP kinase interacting kinases 1 and 2 (MNK1 and MNK2). These compounds may be useful in the treatment of various disease associated with kinase activity such as proliferative disorders (*e.g.*, cancer), autoimmune disorders, inflammatory disorders, metabolic disorders, and neurological disorders.

[00010] In certain embodiments, a compound of the present ~~invention~~ disclosure is of Formula (I):



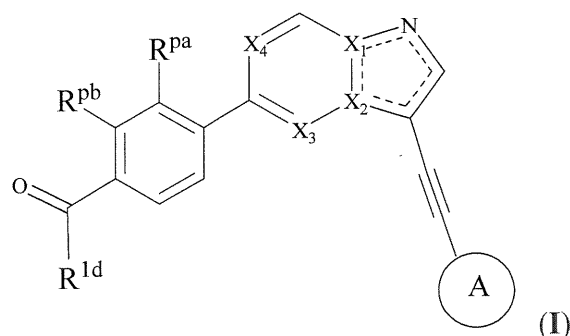
or a pharmaceutically acceptable form (such as pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, and prodrugs thereof thereof, wherein R¹, Ring A, X₁, X₂, X₃, and X₄ are as described herein. In certain embodiments, the pharmaceutical acceptable form is pharmaceutically acceptable salt. These compound are useful in treating proliferative diseases (*e.g.* cancer including hematological cancers and solid tumors), inflammatory diseases, neurodegenerative diseases (*e.g.* Alzheimer's disease, autism, or autism spectrum disorders (*e.g.* Asperger syndrome or Mendelsohnn's Syndrome), and metabolic disorders (*e.g.* obesity, diabetes).

[00011] In certain embodiments, the provided compound is of formula



wherein R^{pa} , R^{pb} , R^{pc} , R^{pd} , R^{pe} , Ring A, X_1 , X_2 , X_3 , and X_4 are as described herein.

[00011a] In one aspect, there is provided a compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein

X_1 and X_2 are independently N or C;

X_3 and X_4 are independently N or CR^2 ;

provided that at least two of X_1 , X_2 , X_3 , and X_4 are N;

----- is a single or double bond, as valency allows;

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

R^{ld} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$;

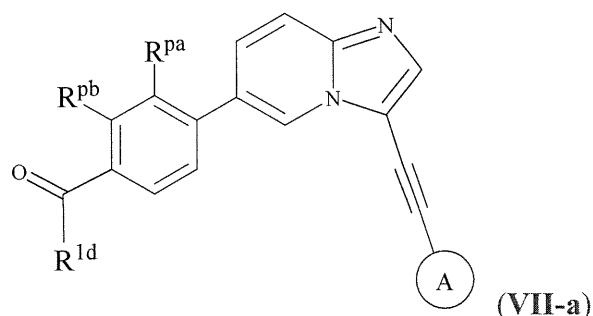
each instance of R^2 is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, $-OR^A$, or $-N(R^B)_2$,

Ring A is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6-bicyclic heteroaryl;

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group.

[00011b] In another aspect, there is provided a compound of Formula (VII-a):



or a pharmaceutically acceptable salt thereof,

wherein

R^{1d} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$;

wherein

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group;

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group; and

Ring A is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6-bicyclic heteroaryl.

[00011c] In another aspect, there is provided a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable excipient, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound.

[00012] ~~In another aspect, the~~ The present invention disclosure relates to pharmaceutical compositions comprising an inventive compound, and optionally a pharmaceutically acceptable excipient, and to their use for treating diseases associated with aberrant MNK1 or MNK2 activity or dysregulation of the MNK1 or MNK2 pathway, where MNK1 and

MNK2 play a role (MNK overexpression, eIF4E overexpression, P38 MAPK kinase pathway). Exemplary MNK-related disorders include, but are not limited to, metabolic diseases such as obesity, as well as related disorders such as eating disorder, cachexia, diabetes mellitus, hypertension, coronary heart disease, hypercholesterolemia, dyslipidemia, osteoarthritis, gallstones, and sleep apnea, neurodegenerative disorders such as Alzheimer's disease, autism, or autism spectrum disorders (e.g. Asperger syndrome or Mendelsohn's Syndrome), and cancer such as breast, prostate, hematological malignancies (e.g., CML, AML, lymphomas), head and neck, colon, bladder, prostatic adenocarcinoma, lung, cervical, and lymphomas.

[00013] ~~In another aspect, the~~ The present invention disclosure relates to pharmaceutical compositions comprising an inventive compound, and optionally a pharmaceutically acceptable excipient, and to their use for the prevention and treatment of a PI3-kinase (PI3K)-related disorder. In certain embodiments, the PI3K-related disorder is PI3K α -related disorder. In certain embodiments, the PI3K-related disorder is PI3K β -related disorder. In certain embodiments, the PI3K-related disorder is PI3K γ -related disorder. In certain embodiments, the PI3K-related disorder is PI3K δ -related disorder. Exemplary PI3K-related disorders include, but are not limited to, cancers such as ovarian cancer, cervical cancer, breast cancer, colon cancer, rectal cancer, endometrial cancer, stomach cancer, liver cancer, lung cancer, thyroid cancer, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and glioblastomas.

[00014] ~~In another aspect, the~~ The present invention disclosure relates to pharmaceutical compositions comprising these compounds and to their use for the prevention and treatment of a Janus kinase (JAK)-related disorder. In certain embodiments, the JAK-related disorder is JAK1-related disorder. In certain embodiments, the JAK-related disorder is JAK2-related disorder. In certain embodiments, the JAK-related disorder is JAK3-related disorder. Exemplary JAK-related disorders include, but are not limited to, psoriasis, rheumatoid arthritis, and cancers such as prostate, colon, ovarian and breast cancers, melanoma, leukemia and other hematological malignancies.

[00015] ~~In another aspect, the~~ The present invention-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] ~~In another aspect, the~~ The present invention-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] ~~In another aspect, the~~ The present invention-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 the treatment of a disease comprising a MNK-related disorder, an mTOR-related disorder, a

PI3K-related disorder, a HER-related disorder, or a JAK-related disorder, wherein the PI3K-related disorder is a PIK3 α -related disorder, PIK3 β -related disorder, PIK3 γ -related disorder, or PIK3 δ -related disorder; wherein the HER-related disorder is a HER2-related disorder or a HER3-related disorder; wherein the JAK-related disorder is a JAK1-related disorder, a JAK2-related disorder, or a JAK3-related disorder; and wherein the MNK-related disorder is MNK1-related disorder or MNK2-related disorder;

_____ and optionally wherein the disorder is cancer, an inflammatory disease, a neurodegenerative disease, or 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.

[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 disease comprising a MNK-related disorder, an mTOR-related disorder, a PI3K-related disorder, a HER-related disorder, or a JAK-related disorder, wherein the PI3K-related disorder is a PIK3 α -related disorder, PIK3 β -related disorder, PIK3 γ -related disorder, or PIK3 δ -related disorder; wherein the HER-related disorder is a HER2-related disorder or a HER3-related disorder; wherein the JAK-related disorder is a JAK1-related disorder, a JAK2-related disorder, or a JAK3-related disorder; and wherein the MNK-related disorder is MNK1-related disorder or MNK2-related disorder;

_____ and optionally wherein the disorder is cancer, an inflammatory disease, a neurodegenerative disease, or 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] In yet another aspect, the ~~The present invention disclosure~~ describes methods for the synthesis of compounds of Formula (I), such as, for example, (4-methylpiperazin-1-yl)(4-(3-

(phenylethynyl)imidazo[1,2-a]pyrazin-6-yl)phenyl)methanone and 4-methyl-2-((6-(4-(piperazine-1-carbonyl)phenyl)imidazo[1,2-a]pyrazin-3-yl)ethynyl)benzonitrile.

[00019] ~~In another aspect, the~~ The present invention disclosure provides kits comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. The provided kits may be useful for the treatment of 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)), and metabolic disorders (e.g., obesity, diabetes). In certain embodiments, the kits described herein further include instructions for administering the compound as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. The kits may also include packaging information describing the use or prescribing information for the subject or a health care professional. Such information may be required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). The kit may also optionally include a device for administration of the compound or composition, for example, a syringe for parenteral administration.

BRIEF DESCRIPTION OF THE DRAWING

[00020] *Figure 1* illustrates the cellular pathways that lead to eIF4E activation and phosphorylation by MNK1/2 (PNAS, 2010, 107(32): 13975-6).

DEFINITIONS

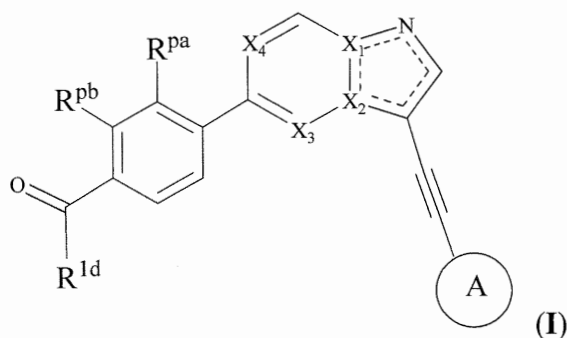
Chemical definitions

[00021] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein.

Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

CLAIMS

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein

X_1 and X_2 are independently N or C;

X_3 and X_4 are independently N or CR^2 ;

provided that at least two of X_1 , X_2 , X_3 , and X_4 are N;

----- is a single or double bond, as valency allows;

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

R^{ld} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$;

each instance of R^2 is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, $-OR^A$, or $-N(R^B)_2$,

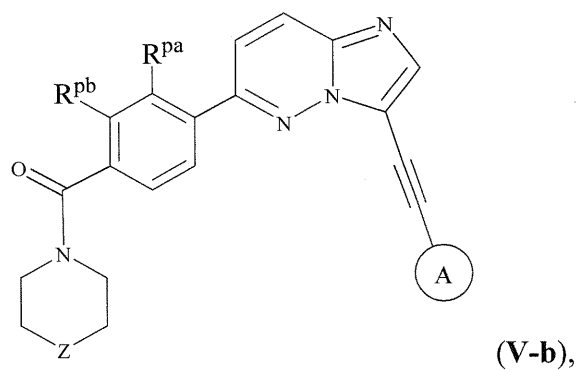
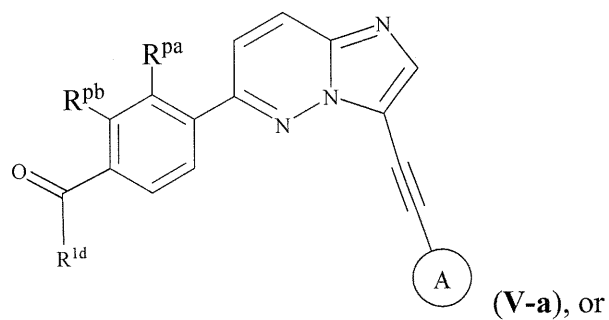
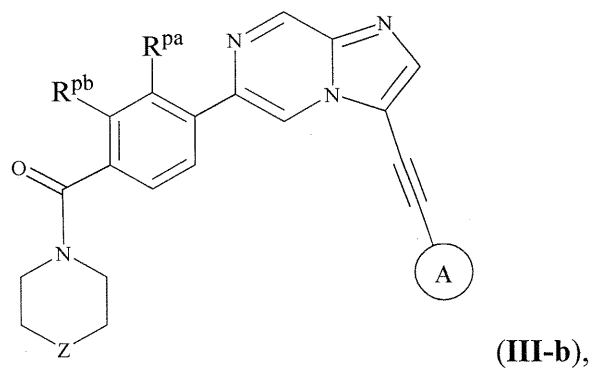
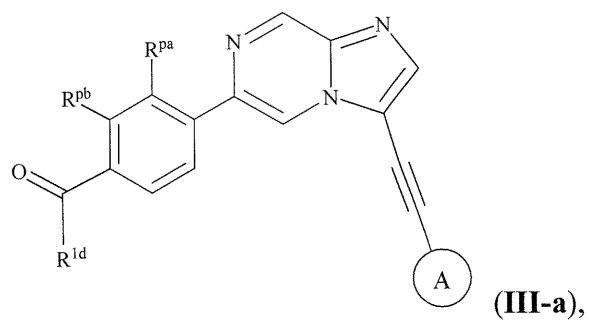
Ring A is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6-bicyclic heteroaryl;

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted

heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group.

2. The compound of claim 1, wherein the compound is of Formula (III-a), (III-b), (V-a), or (V-b):



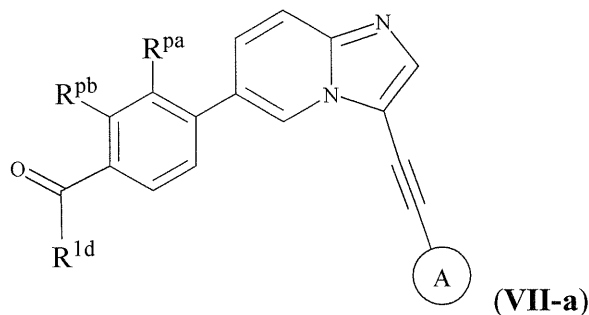
wherein

Z is $-O-$ or $-NR^{NZ}-$; and

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

or a pharmaceutically acceptable salt thereof.

3. A compound of Formula (VII-a):



or a pharmaceutically acceptable salt thereof,

wherein

R^{ld} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$;

wherein

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

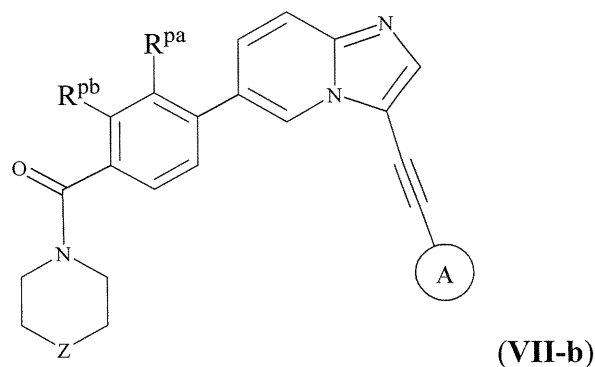
R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group;

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group; and

Ring A is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6-bicyclic heteroaryl.

4. The compound of claim 3, wherein the compound is of Formula (VII-b):



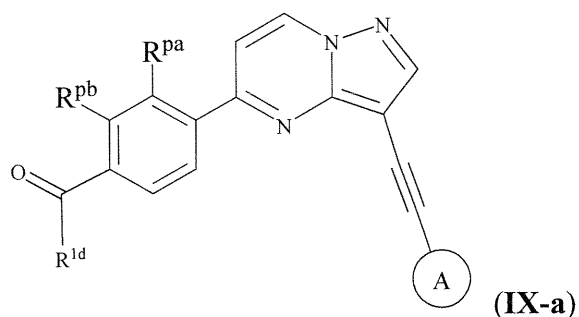
or a pharmaceutically acceptable salt thereof,

wherein

Z is $-O-$ or $-NR^{NZ}-$; and

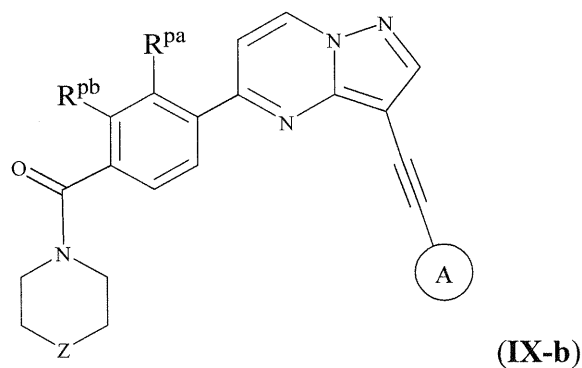
each instance of R^{NZ} is independently hydrogen, optionally substituted C_{1-6} alkyl, or a nitrogen protecting group.

5. The compound of claim 1, wherein the compound is of Formula (IX-a):



or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5, wherein the compound is of Formula (IX-b):



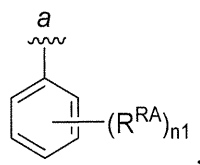
or a pharmaceutically acceptable salt thereof,

wherein

Z is $-O-$ or $-NR^{NZ}-$; and

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

7. The compound of claim 3, 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;

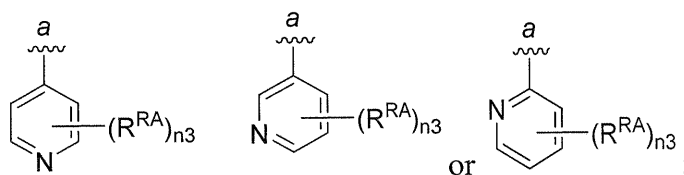
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted acyl, $-CN$, $-OR^{AO}$, or $-N(R^{AN})_2$;

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

α 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 $-N(R^{AN})_2$;

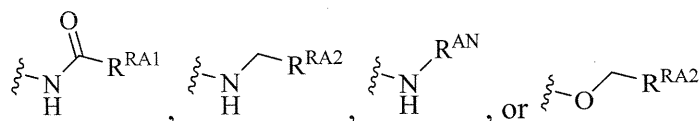
each instance of R^{AO} is independently hydrogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

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

each instance of n_3 is independently an integer of 1 to 4, inclusive.

11. The compound of claim 10, wherein R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, or $-N(CH_3)R^{AN}$, wherein R^{AN} is optionally substituted C_{1-6} alkyl, or unsubstituted C_{1-6} alkyl.

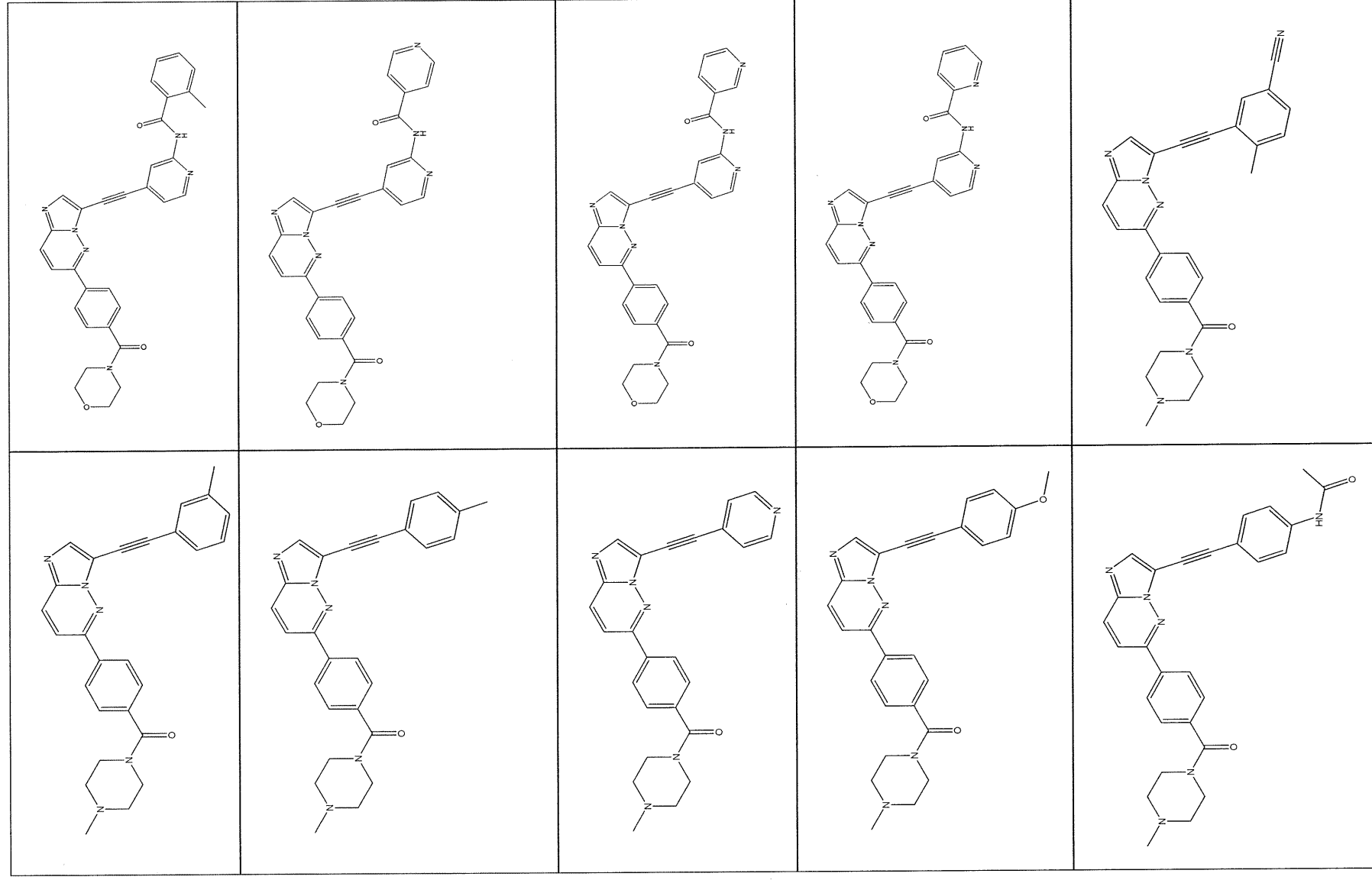
12. The compound of claim 10, wherein R^{RA} is of one of the following formulae:

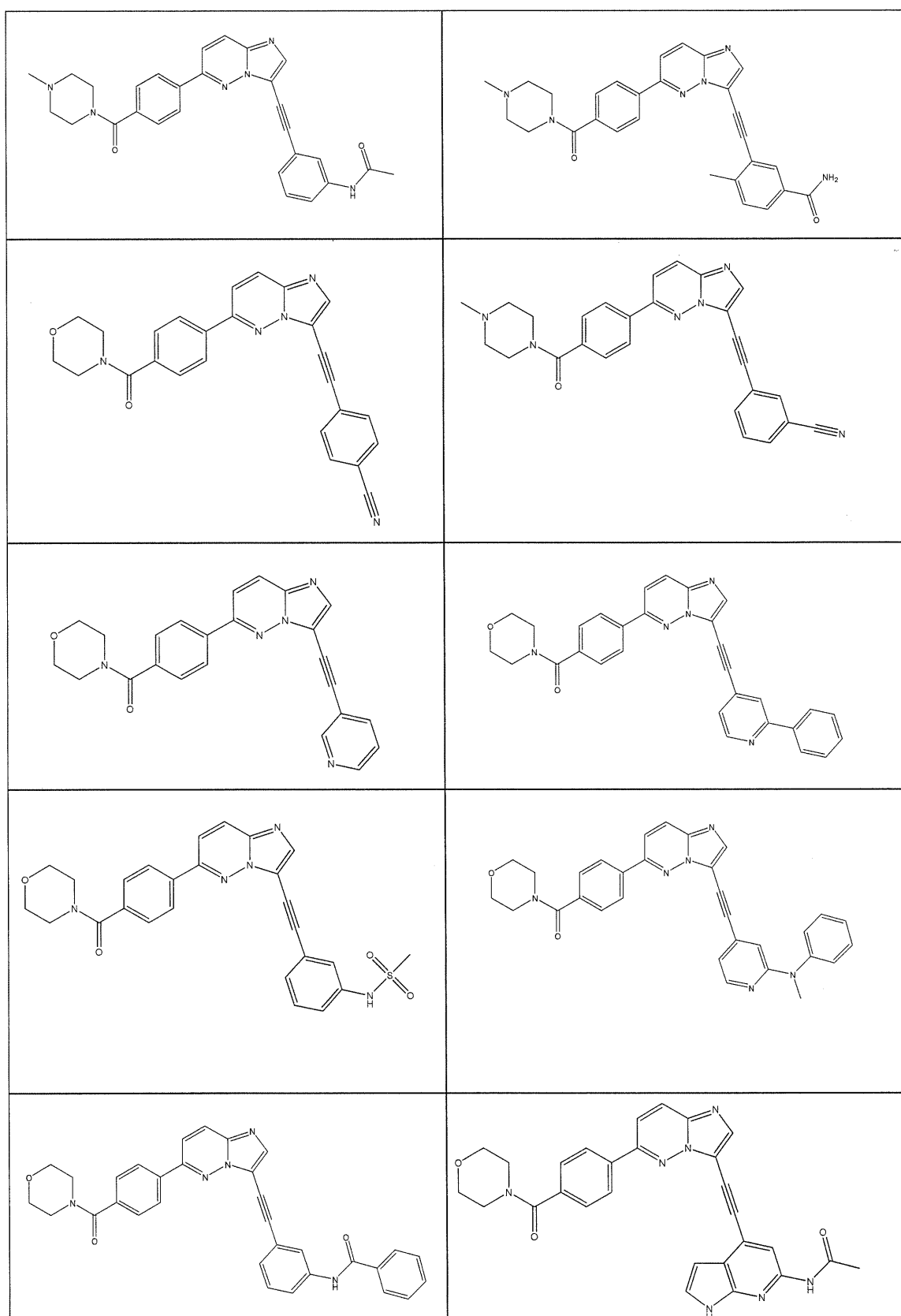


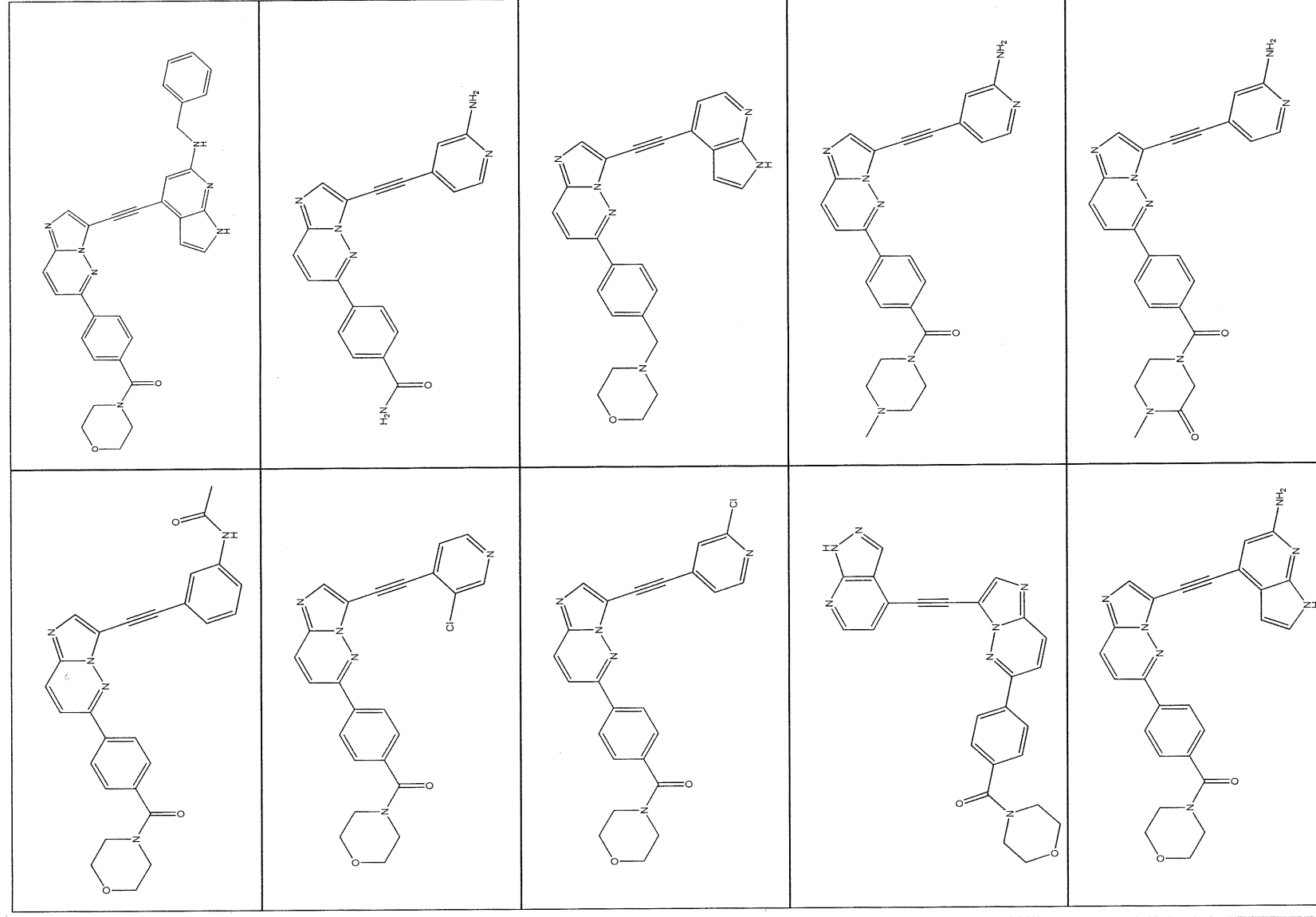
wherein

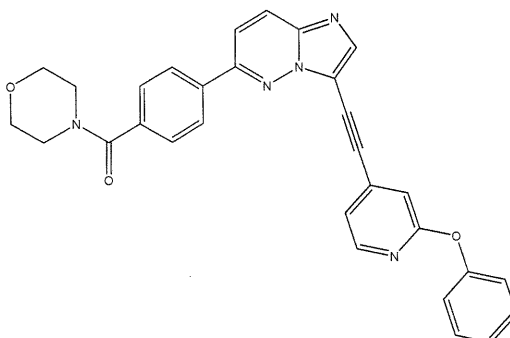
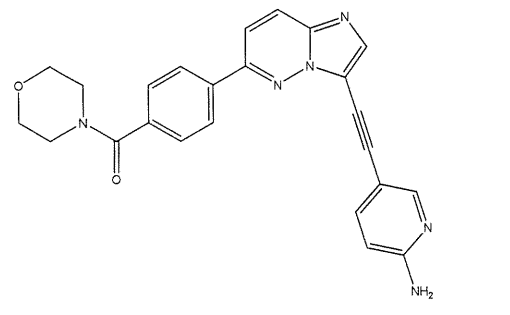
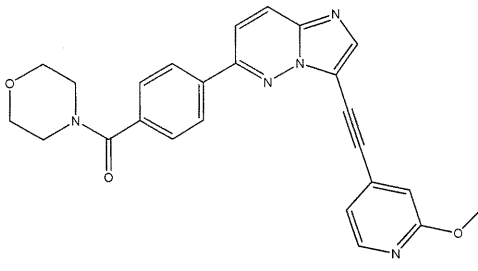
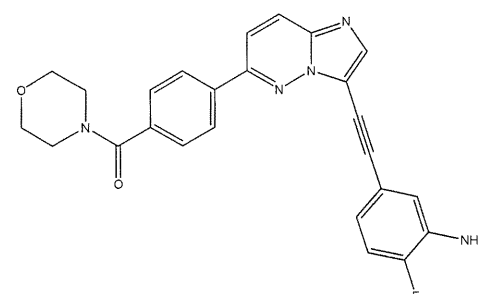
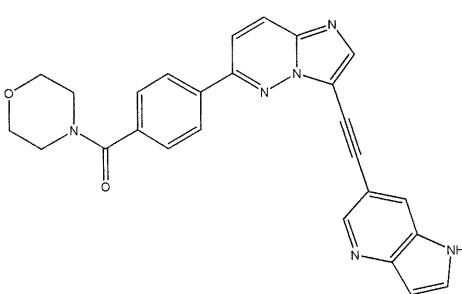
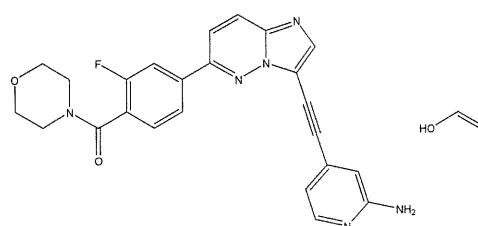
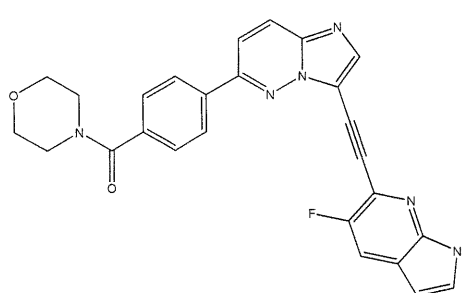
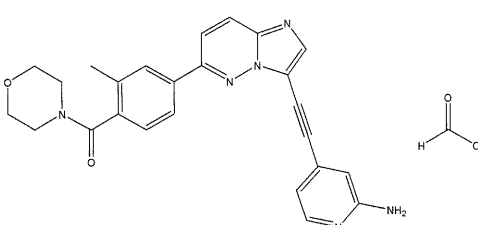
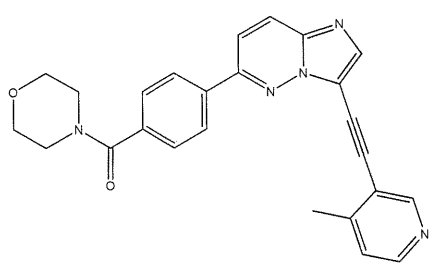
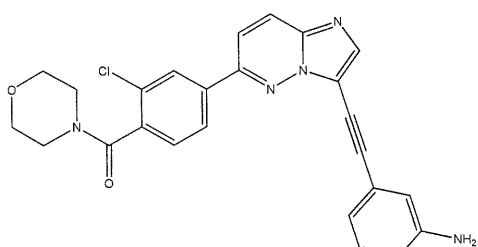
R^{RA1} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, $-OR^A$, or $-N(R^B)_2$; and

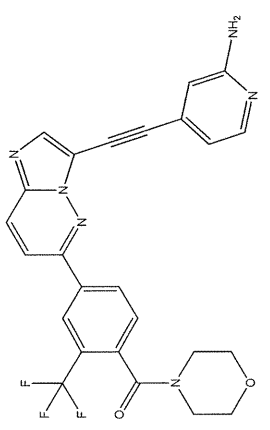
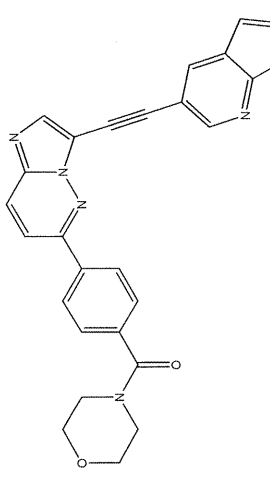
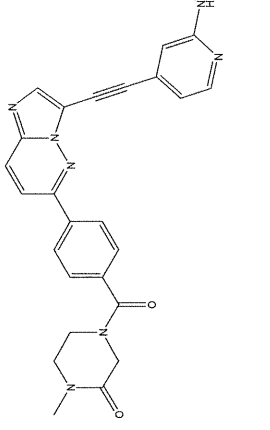
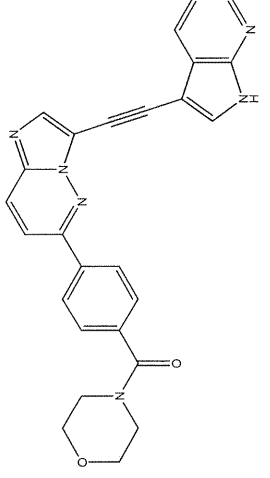
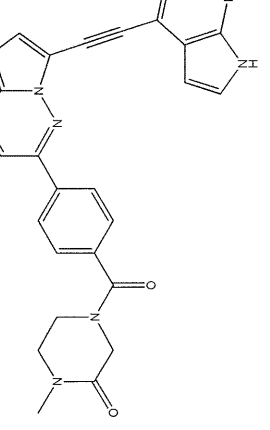
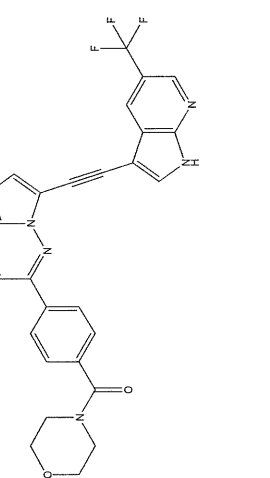
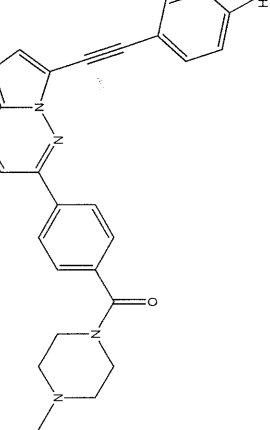
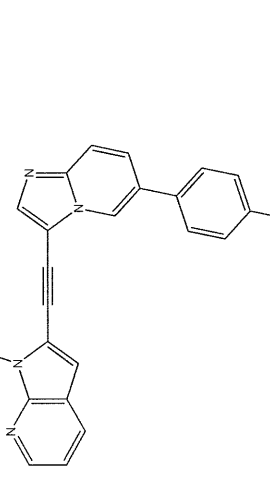
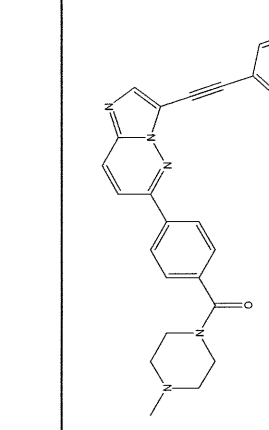
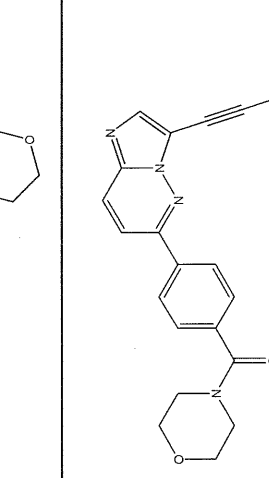
each instance of R^{RA2} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heterocyclyl, or optionally substituted five- or six-membered heteroaryl; or wherein R^{RA} is one of the following formulae: hydrogen, $-Ph$, $-OH$, $-NH_2$, $-OCH_3$, $-OPh$, $-Cl$, $-CF_3$, $-CH_3$,

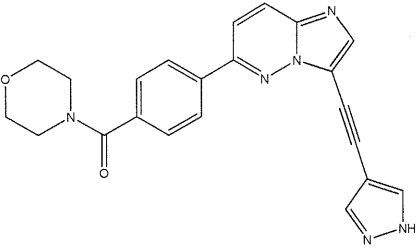
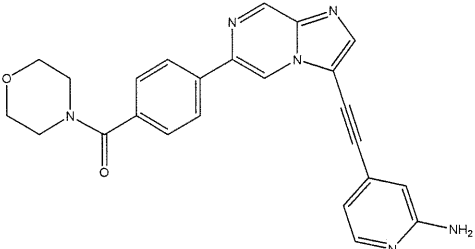
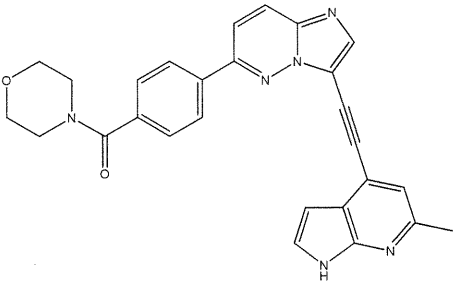
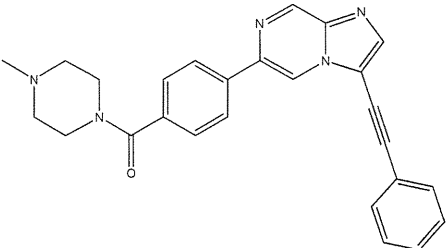
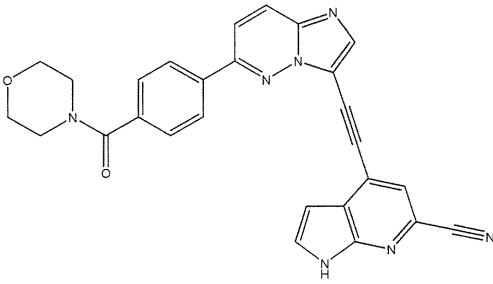
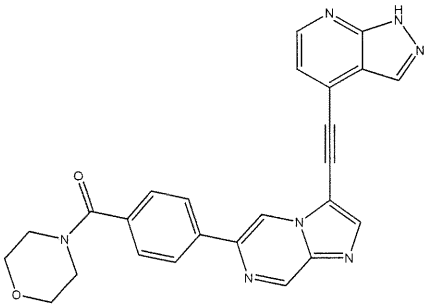
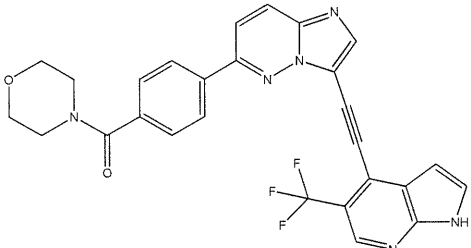
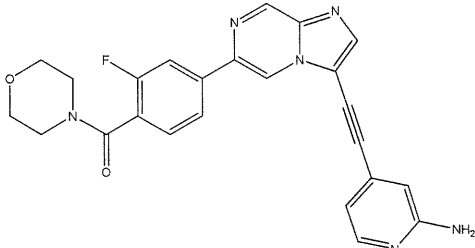
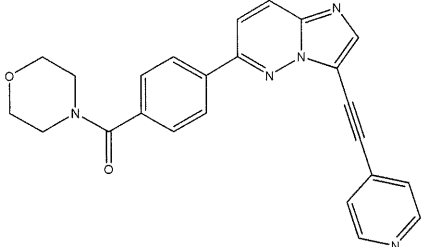
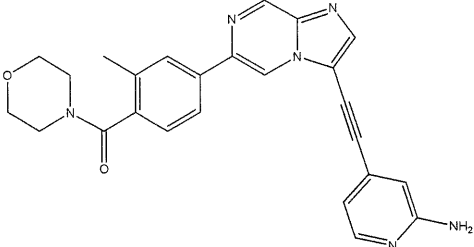


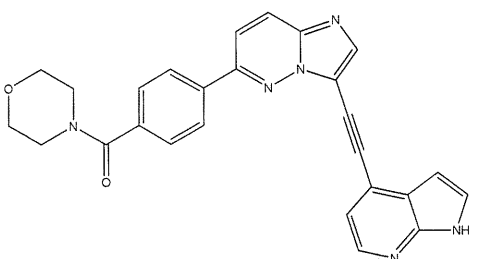
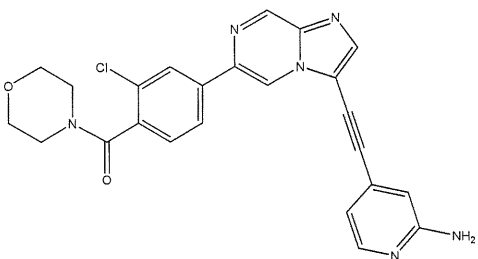
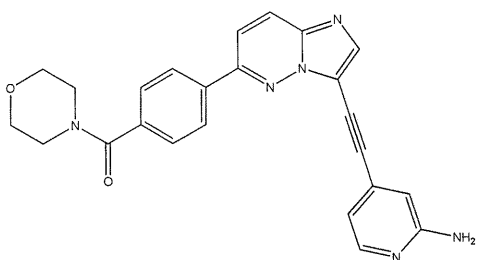
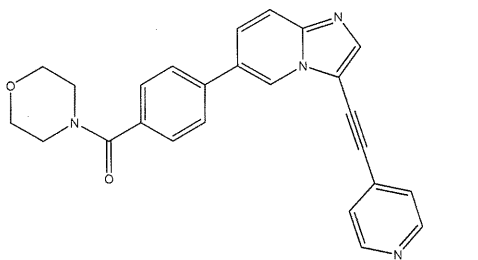
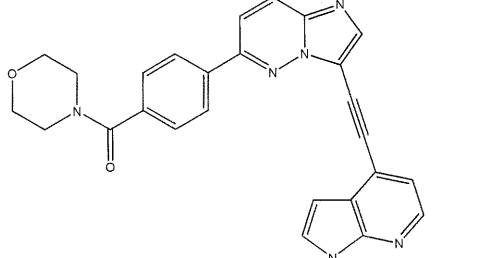
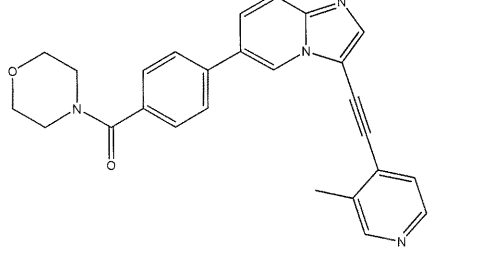
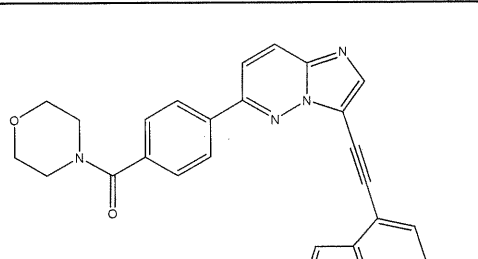
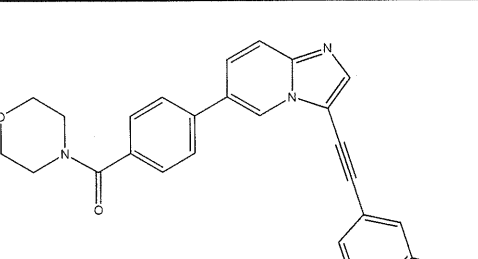
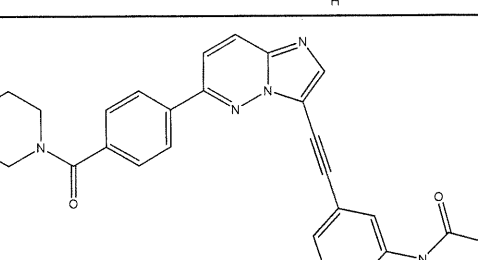
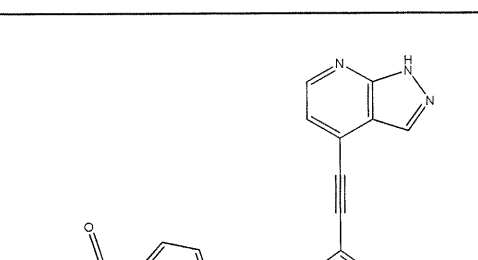


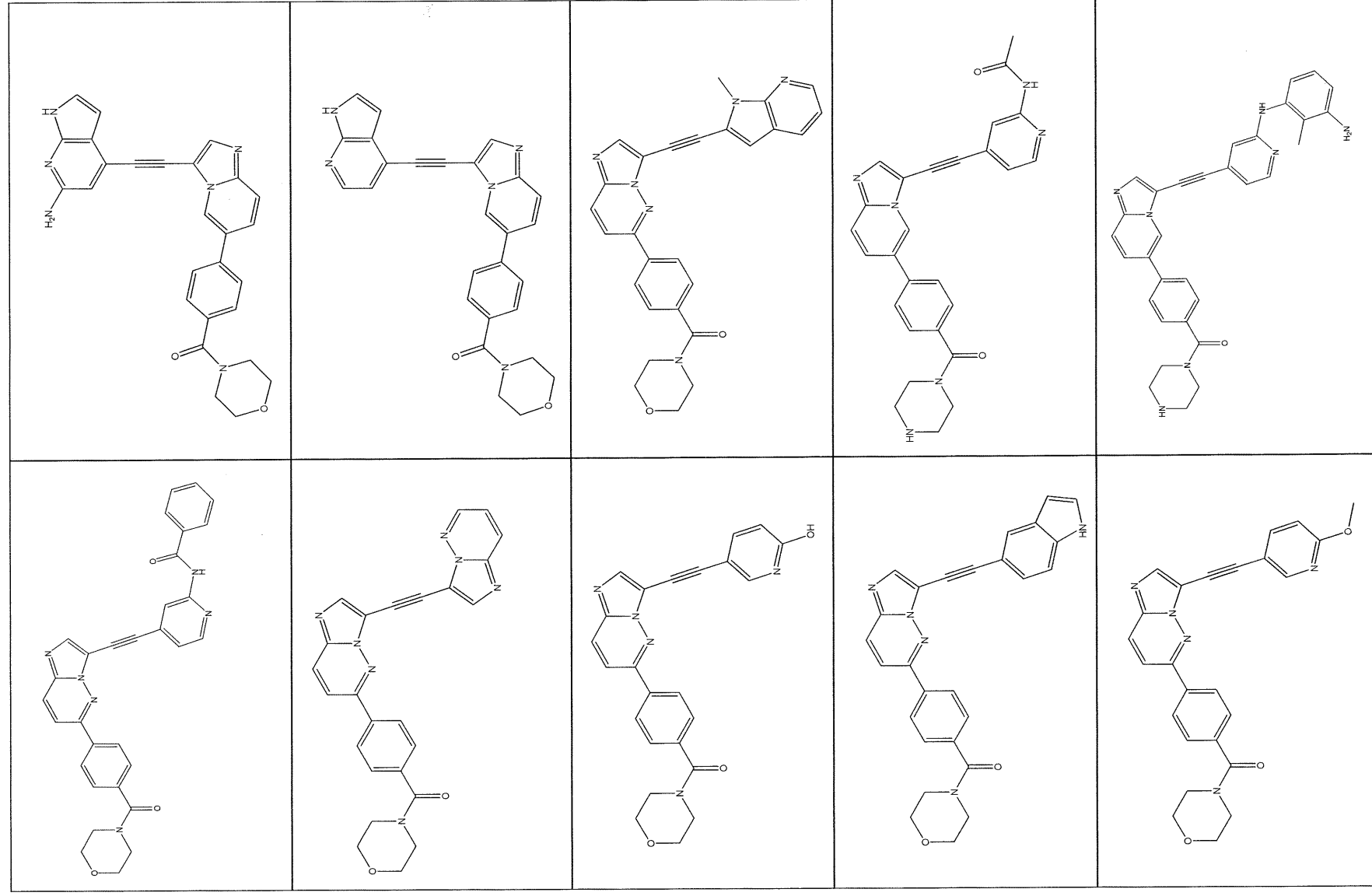


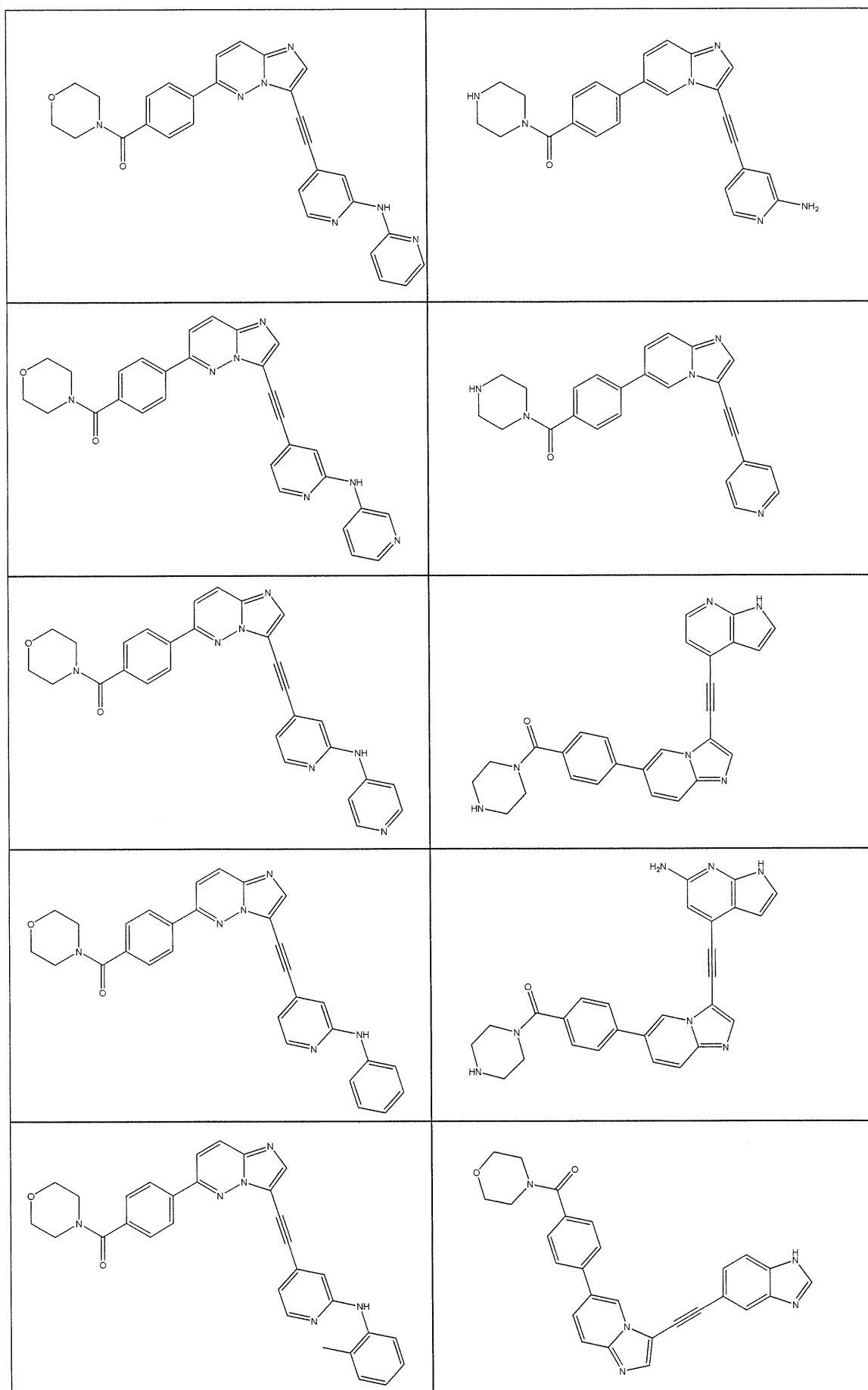
	
	
	
	
	

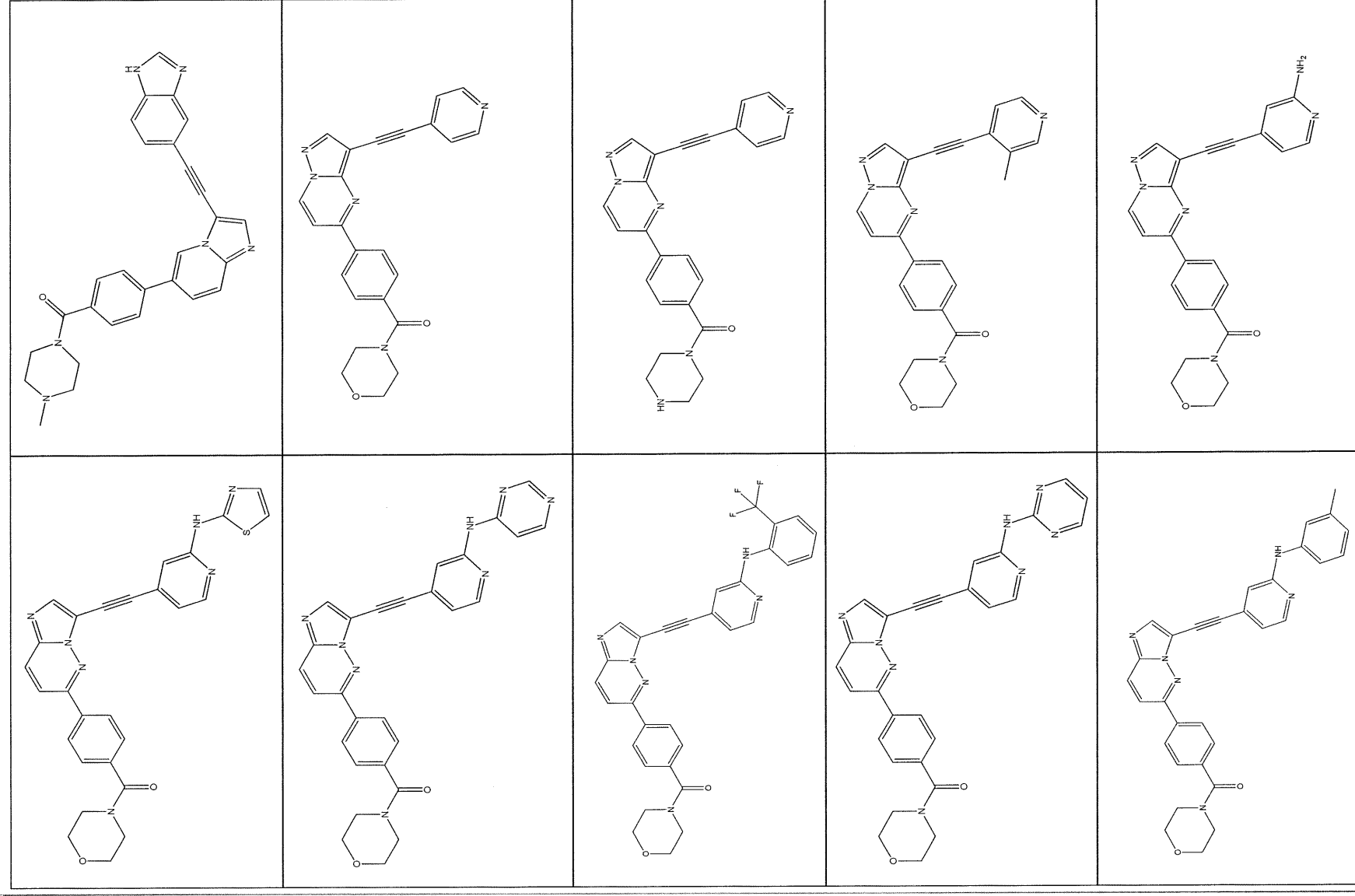
	
	
	
	
	

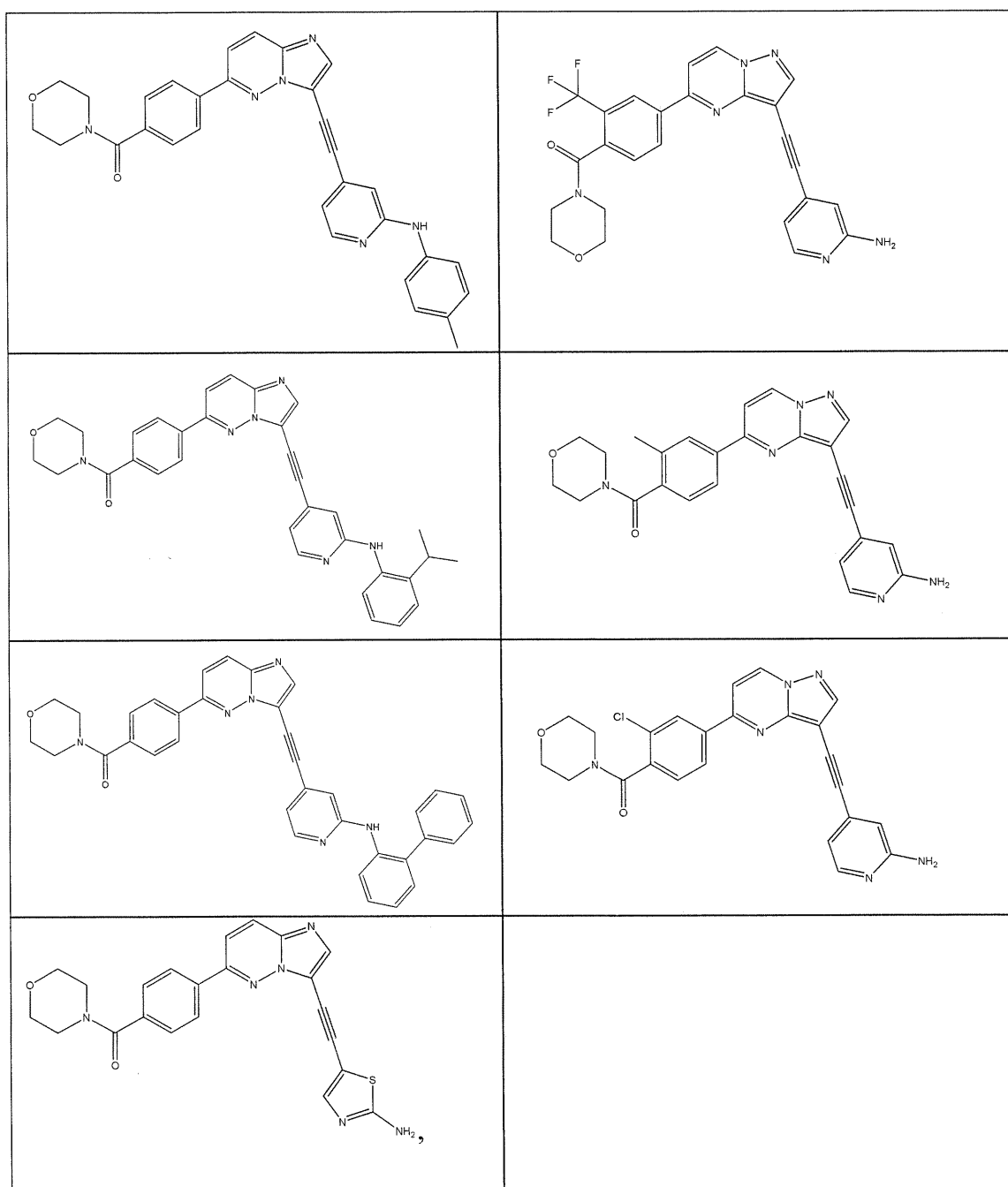
	
	
	
	
	









or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound.

15. A compound of claim 1, for use in the treatment of a disease comprising a MNK-related disorder, an mTOR-related disorder, a PI3K-related disorder, a HER-related disorder, or a JAK-related disorder, wherein the PI3K-related disorder is a PIK3 α -related disorder, PIK3 β -related disorder, PIK3 γ -related disorder, or PIK3 δ -related disorder;

wherein the HER-related disorder is a HER2-related disorder or a HER3-related disorder; wherein the JAK-related disorder is a JAK1-related disorder, a JAK2-related disorder, or a JAK3-related disorder; and wherein the MNK-related disorder is MNK1-related disorder or MNK2-related disorder;

and optionally wherein the disorder is cancer, an inflammatory disease, a neurodegenerative disease, or 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.

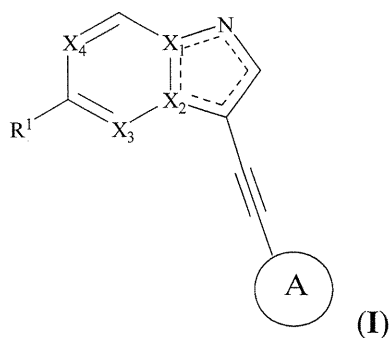
16. Use of the compound of claim 1 in the manufacture of a medicament for the treatment of a disease comprising a MNK-related disorder, an mTOR-related disorder, a PI3K-related disorder, a HER-related disorder, or a JAK-related disorder, wherein the PI3K-related disorder is a PIK3 α -related disorder, PIK3 β -related disorder, PIK3 γ -related disorder, or PIK3 δ -related disorder; wherein the HER-related disorder is a HER2-related disorder or a HER3-related disorder; wherein the JAK-related disorder is a JAK1-related disorder, a JAK2-related disorder, or a JAK3-related disorder; and wherein the MNK-related disorder is MNK1-related disorder or MNK2-related disorder;

and optionally wherein the disorder is cancer, an inflammatory disease, a neurodegenerative disease, or 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.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein

X_1 and X_2 are independently N or C;

X_3 and X_4 are independently N or CR^2 ;

provided that at least two of X_1 , X_2 , X_3 , and X_4 are N;

----- is a single or double bond, as valency allows;

R^1 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted six-membered heteroaryl, optionally substituted six-membered heterocyclyl, optionally substituted C_{3-6} carbocyclalkyl, optionally substituted arylalkyl, optionally substituted five- or six-membered heteroarylalkyl, optionally substituted five- or six-membered heterocyclalkyl, -CN, $-OR^A$, or $-N(R^B)_2$;

each instance of R^2 is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, $-OR^A$, or $-N(R^B)_2$,

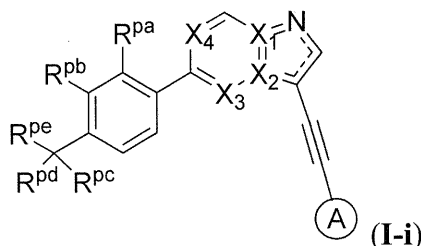
Ring A is optionally substituted phenyl, optionally substituted five-membered heteroaryl, optionally substituted six-membered heteroaryl, or optionally substituted 5,6-bicyclic heteroaryl;

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted

heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group.

2. A compound of claim 1 of Formula (I-i):



or a pharmaceutically acceptable salt thereof,

wherein

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each of R^{pc} and R^{pd} is independently hydrogen, , halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

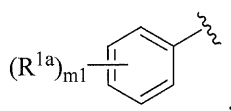
or R^{pc} and R^{pd} are joined to form $=O$; and

R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group.

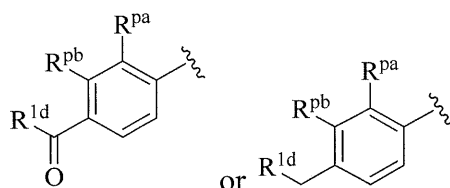
3. A compound of claim 1, wherein R^1 is optionally substituted phenyl of the formula:



wherein

each instance of R^{1a} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heteroaryl, optionally substituted five- or six-membered heterocyclyl, optionally substituted acyl, $-CN$, $-OR^A$, or $-N(R^B)_2$; and
 $m1$ is an integer of 1 to 5, inclusive.

4. A compound of claim 3, wherein R^1 is of the formula:



wherein

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

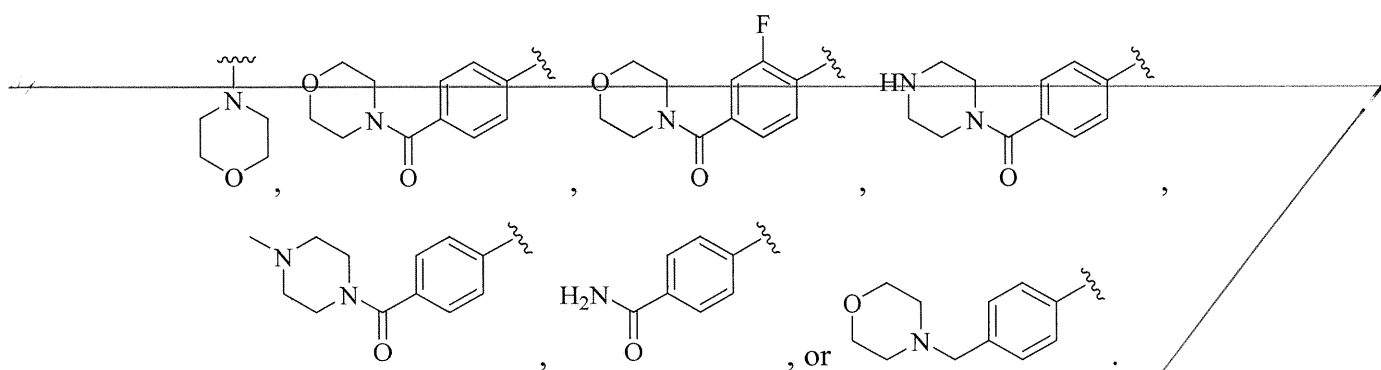
each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

or R^{pc} and R^{pd} are joined to form $=O$; and

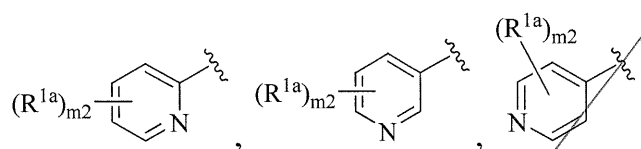
R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and
each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group;
and each instance of R^{1d} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$.

5. A compound of claim 4, wherein R^1 is one of the following formulae:



6. A compound of claim 1, wherein R^1 is one of the following formulae:



wherein

each instance of R^{1a} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted acyl, $-CN$, $-OR^A$, or $-N(R^B)_2$;

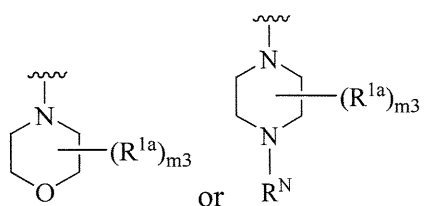
each instance of m_2 is independently an integer of 1 to 4, inclusive;

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group.

7. A compound of claim 1, wherein R^1 is optionally substituted six-membered heterocyclyl.

8. A compound of claim 7, wherein R^1 is one of the following formulae:

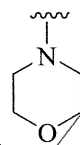


wherein

each instance of R^{1a} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted acyl, -CN, -OR^A, or -N(R^B)₂;

each instance of m_3 is independently an integer of 1 to 8, inclusive; and

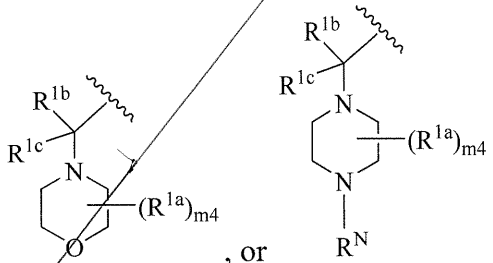
R^N is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group.



9. A compound of claim 8, wherein R^1 is of the formula .

10. A compound of claim 1, wherein R^1 is optionally substituted six-membered heterocyclalkyl.

11. A compound of claim 10, wherein R^1 is one of the following formulae:



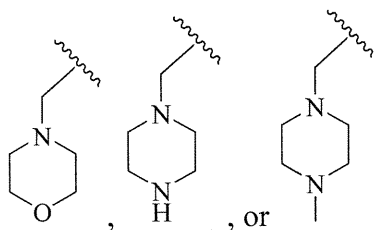
wherein

each instance of R^{1a} , R^{1b} , and R^{1c} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted acyl, -CN, -OR^A, or -N(R^B)₂;

each instance of m_4 is independently an integer of 1 to 8, inclusive, as valency permits; and

R^N is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group.

12. A compound of claim 11, wherein R^1 is one of the following formulae:

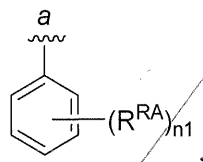


13. A compound of claim 1, wherein R^1 is hydrogen.

14. A compound of claim 1, wherein R^1 is $-N(R^B)_2$.

15. A compound of claim 14, wherein R^1 is $-N(CH_3)_2$ or $-NHAc$.

16. The compound of claim 1 or 2, wherein Ring A is of the formula:



wherein

a indicates the point of attachment to the alkyne;

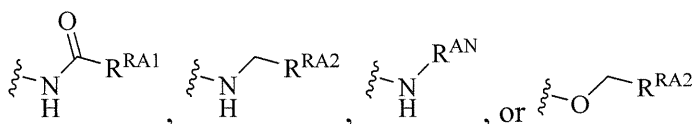
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted acyl, $-CN$, $-OR^{AO}$, or $-N(R^{AN})_2$;

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.

17. The compound of claim 16, wherein R^{RA} is one of the following formulae:

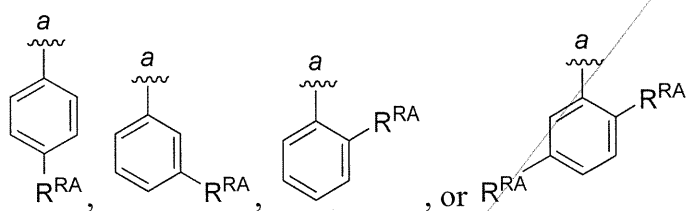


wherein

R^{RA1} is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^{RA2} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heterocyclyl, or optionally substituted five- or six-membered heteroaryl,

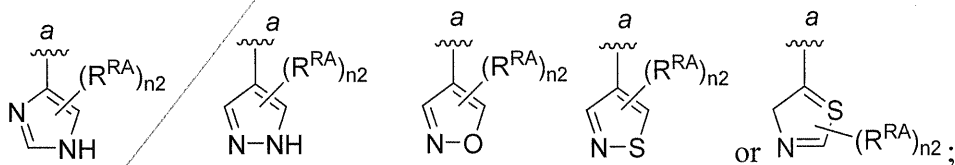
18. The compound of claim 16, wherein Ring A is of one of following formulae:



wherein each instance of R^{RA} is independently hydrogen, $-CN$, $-CH_3$, $-OCH_3$, $-NHAc$, $-NHC(=O)Ph$, $-NHSO_2CH_3$, $-C(=O)NH_2$.

19. The compound of claim 1 or 2, wherein Ring A is optionally substituted five-membered heteroaryl with two heteroatoms selected from the group consisting of O, S, and N.

20. The compound of claim 19, wherein Ring A is one of the following formulae:



wherein

a indicates the point of attachment to the alkyne;

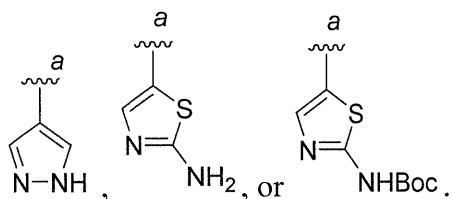
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted acyl, $-CN$, $-OR^{AO}$, or $-N(R^{AN})_2$;

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; and

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

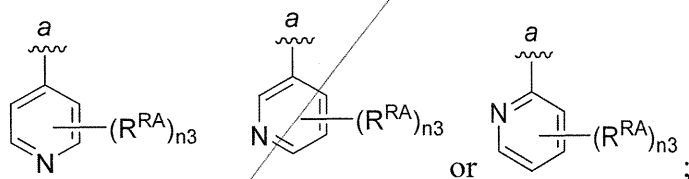
each instance of n_2 is independently an integer of 1 or 2.

21. The compound of claim 20, wherein Ring A is of the formula:



22. The compound of any one of claims 1-2, wherein Ring A is optionally substituted six-membered heteroaryl with one or two N.

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



wherein

a indicates the point of attachment to the alkyne;

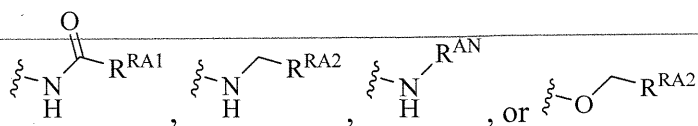
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted acyl, $-CN$, $-OR^{AO}$, or $-N(R^{AN})_2$;

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; and

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

each instance of n_3 is independently an integer of 1 to 4, inclusive.

24. The compound of claim 23, wherein R^{RA} is one of the following formulae:

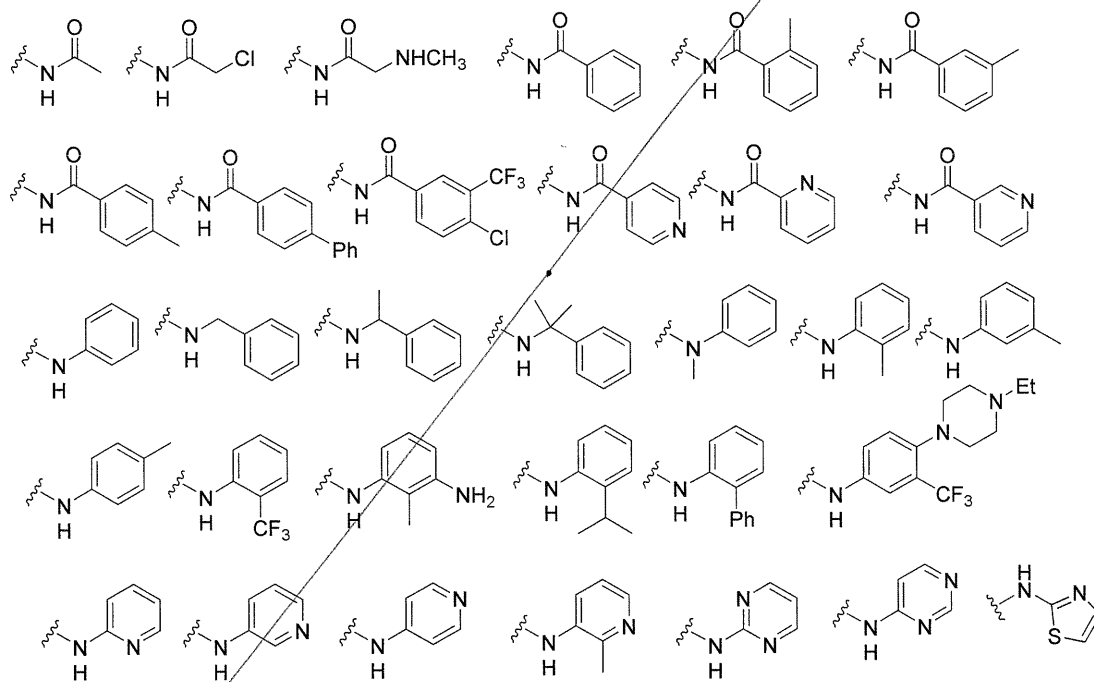


wherein

R^{RA1} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heterocyclyl, optionally substituted five- or six-membered heteroaryl, $-\text{OR}^{\text{A}}$, or $-\text{N}(\text{R}^{\text{B}})_2$; and

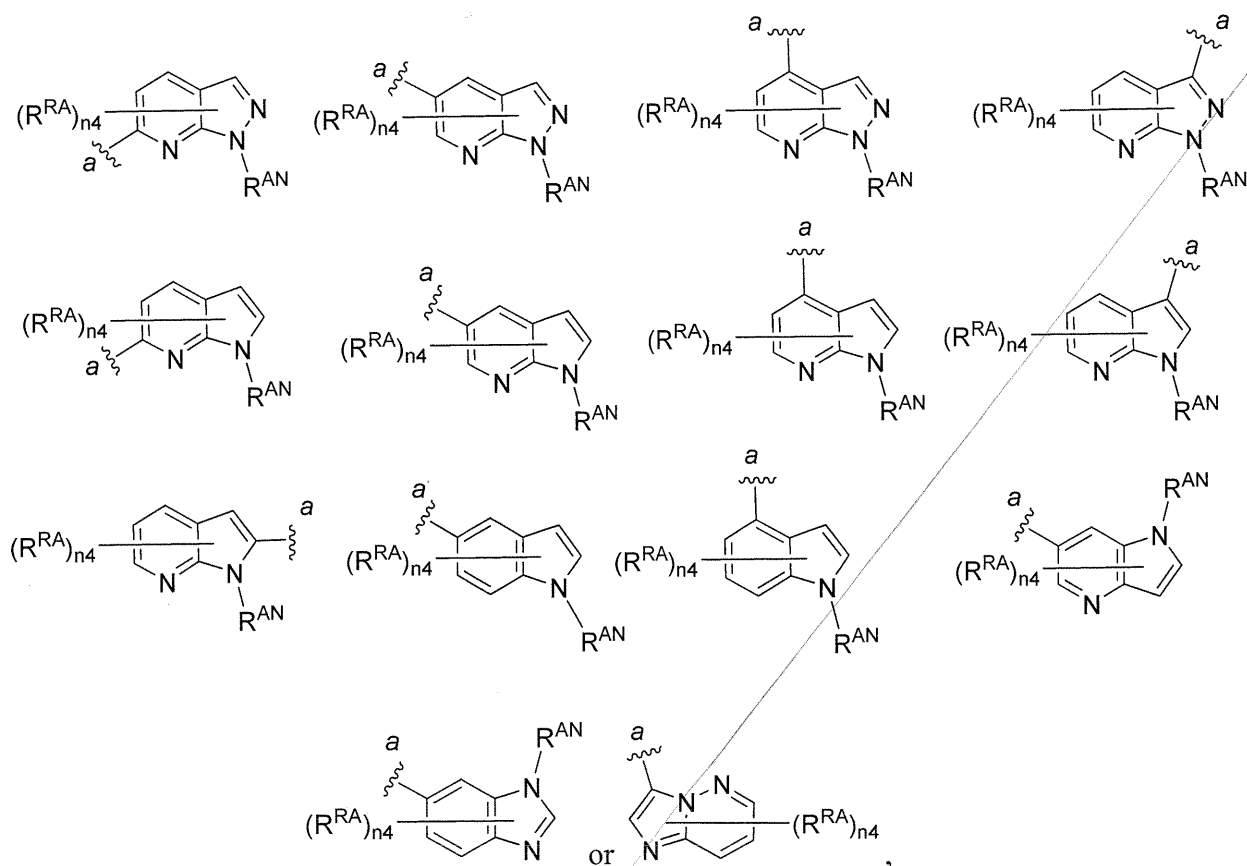
each instance of R^{RA2} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heterocyclyl, or optionally substituted five- or six-membered heteroaryl.

25. The compound of claim 23 or 24, wherein R^{RA} is one of the following formulae:
hydrogen, -Ph, -OH, $-\text{NH}_2$, $-\text{OCH}_3$, $-\text{OPh}$, $-\text{Cl}$, $-\text{CF}_3$, $-\text{CH}_3$,



26. The compound of any one of claims 1-2, wherein Ring A is optionally substituted 5,6-bicyclic heteroaryl with one, two, or three N.

27. The compound of claim 26, wherein Ring A is one of the following formulae:



wherein

a indicates the point of attachment to the alkyne;

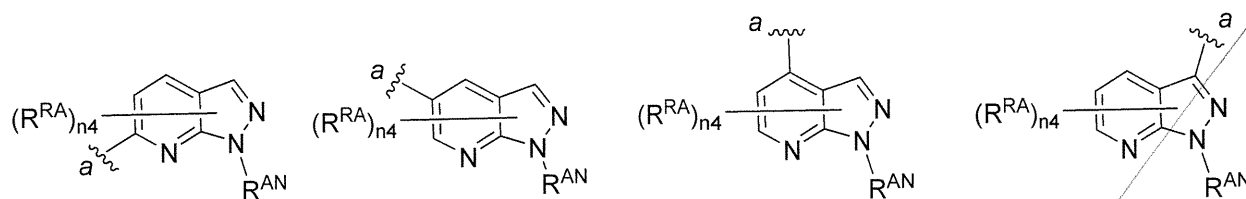
each instance of R^{RA} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted acyl, $-CN$, $-OR^{AO}$, or $-N(R^{AN})_2$;

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; and

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

each instance of $n4$ is independently an integer of 1 to 5, inclusive.

28. The compound of claim 27, wherein Ring A is of one of the following formulae:

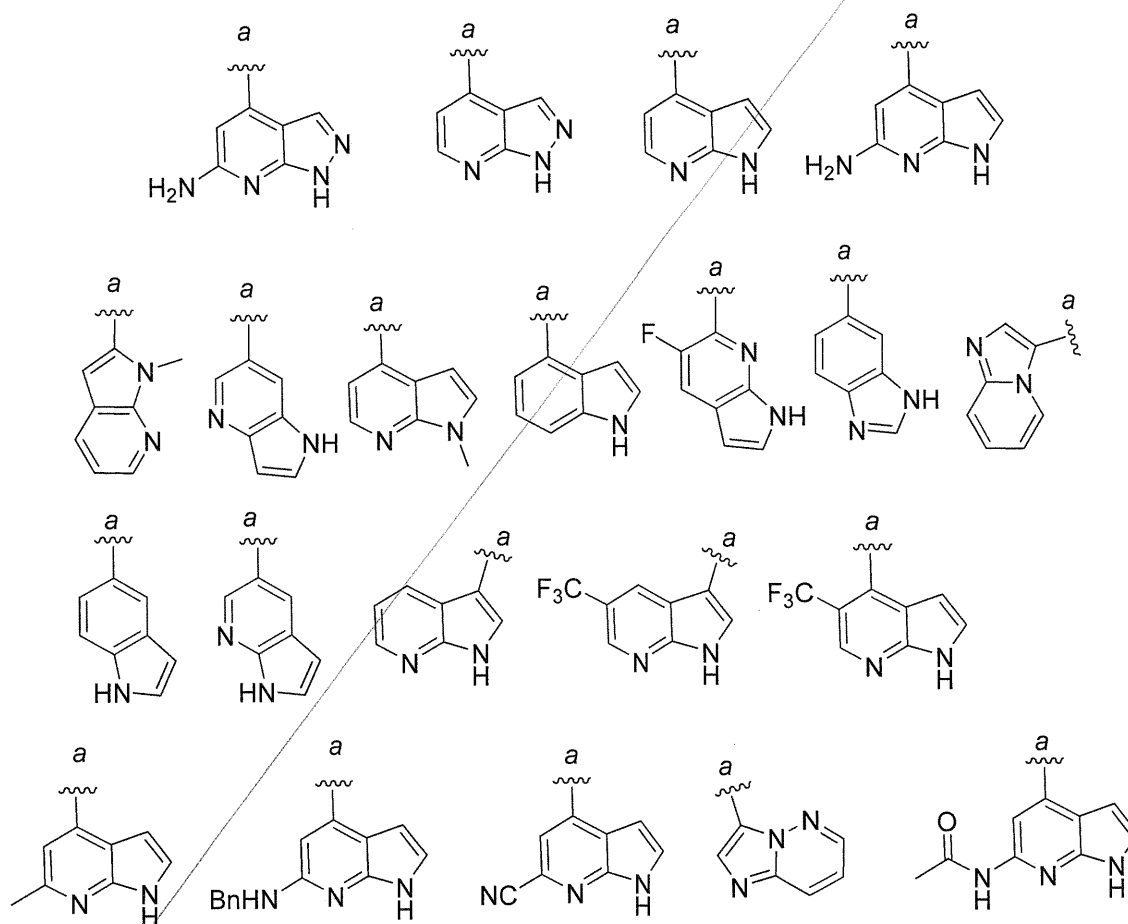


wherein

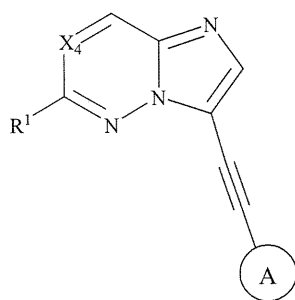
R^{RA} is CN, $-CF_3$, $-CH_3$, $-NHAc$, or $-NH_2$; and

each instance of n_4 is 1.

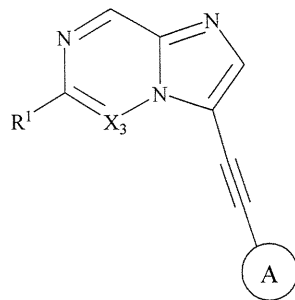
29. The compound of claim 27, wherein Ring A is one of the following formulae:



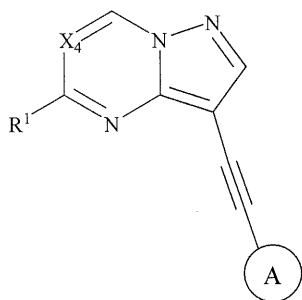
30. The compound of claim 1 having one of the following formulae:



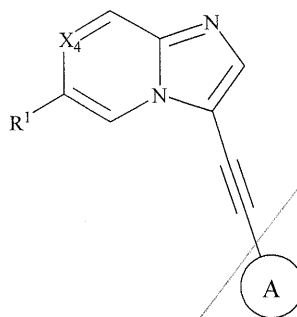
(I-a),



(I-b),



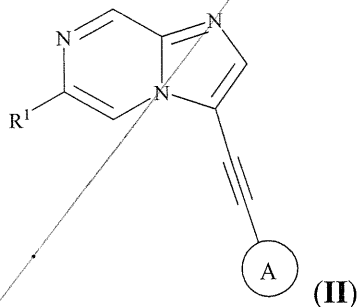
(I-c),



(I-d),

or a pharmaceutically acceptable salt thereof.

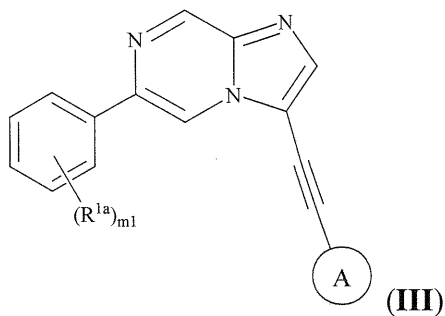
31. The compound of claim 1 of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

32. The compound of claim 31 of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof,

wherein

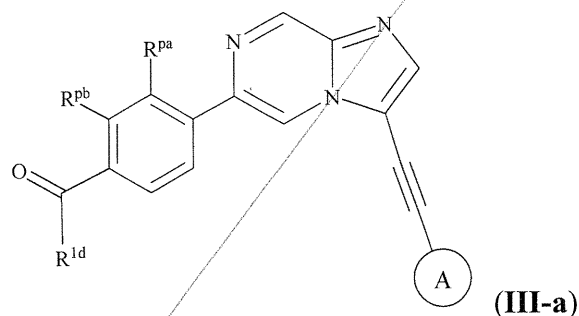
each instance of R^{1a} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heteroaryl, optionally substituted five- or six-membered heterocyclyl, optionally substituted acyl, $-CN$, $-OR^A$, or $-N(R^B)_2$;

$m1$ is an integer of 1 to 5, inclusive;

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

each instance of R^B 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.

33. The compound of claim 32 of Formula (III-a):



or a pharmaceutically acceptable salt thereof,

wherein

R^{pa} is hydrogen, halogen, CN , optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN , $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

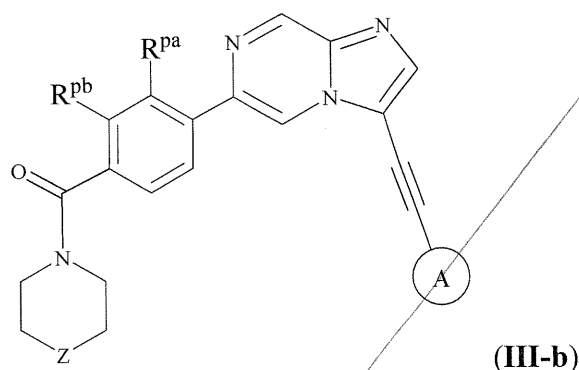
each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN , $-OR^A$, or optionally substituted C_{1-6} alkyl;

or R^{pc} and R^{pd} are joined to form $=O$; and

R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group; and R^{1d} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$.

34. The compound of claim 32 of Formula (III-b):



or a pharmaceutically acceptable salt thereof,
wherein

Z is $-O-$ or $-NR^{NZ}-$;

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

wherein

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

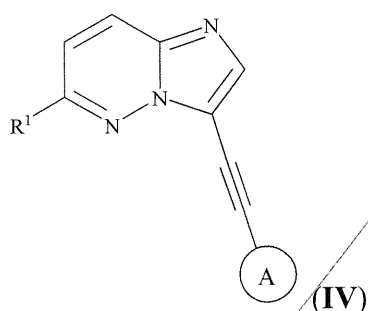
or R^{pc} and R^{pd} are joined to form $=O$; and

R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

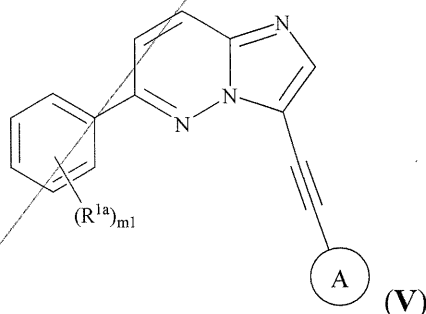
each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group.

35. The compound of claim 1 of Formula (IV):



or a pharmaceutically acceptable salt thereof.

36. The compound of claim 35 of Formula (V):



or a pharmaceutically acceptable salt thereof,
wherein

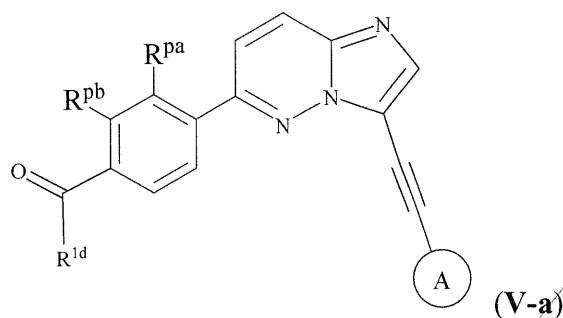
each instance of R^{1a} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heteroaryl, optionally substituted five- or six-membered heterocyclyl, optionally substituted acyl, $-\text{CN}$, $-\text{OR}^A$, or $-\text{N}(\text{R}^B)_2$;

$m1$ is an integer of 1 to 5, inclusive;

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

each instance of R^B 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.

37. The compound of claim 36 of Formula (V-a):



or a pharmaceutically acceptable salt thereof,

wherein

R^{ld} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$;

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

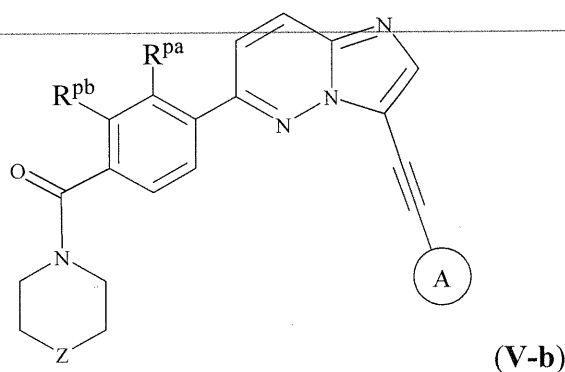
or R^{pc} and R^{pd} are joined to form $=O$; and

R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group.

38. The compound of claim 36 of Formula (V-b):



or a pharmaceutically acceptable salt thereof,

wherein

Z is $-O-$ or $-NR^{NZ}-$;

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

wherein

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

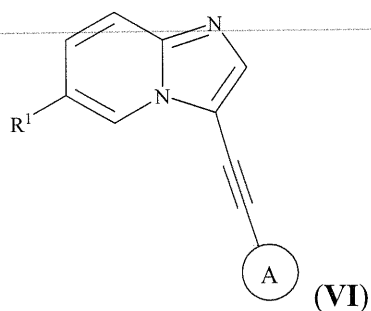
or R^{pc} and R^{pd} are joined to form $=O$; and

R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

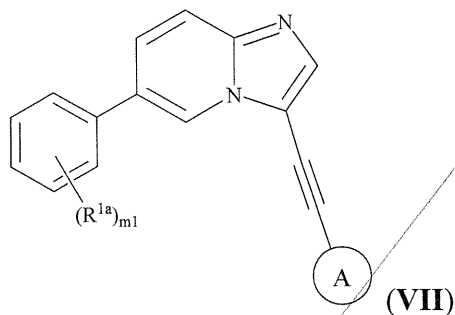
each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group.

39. The compound of claim 1 of Formula (VI):



or a pharmaceutically acceptable salt thereof.

40. The compound of claim 39 of Formula (VII):



or a pharmaceutically acceptable salt thereof,
wherein

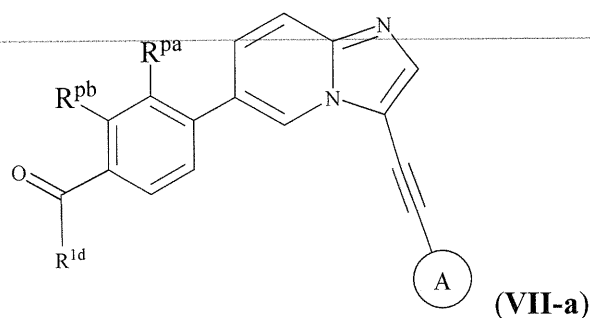
each instance of R^{1a} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heteroaryl, optionally substituted five- or six-membered heterocyclyl, optionally substituted acyl, $-CN$, $-OR^A$, or $-N(R^B)_2$;

m_1 is an integer of 1 to 5, inclusive;

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

each instance of R^B 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.

41. The compound of claim 40 of Formula (VII-a):



or a pharmaceutically acceptable salt thereof,

wherein

R^{ld} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$;

wherein

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

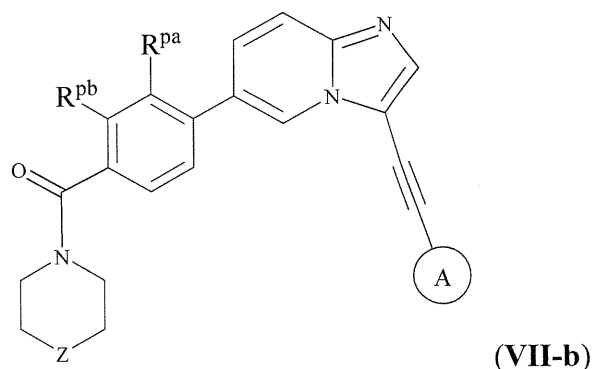
or R^{pc} and R^{pd} are joined to form $=O$; and

R^{pc} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group.

42. The compound of claim 40 of Formula (VII-b):



or a pharmaceutically acceptable salt thereof,

wherein

Z is $-O-$ or $-NR^{NZ}-$;

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

wherein

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

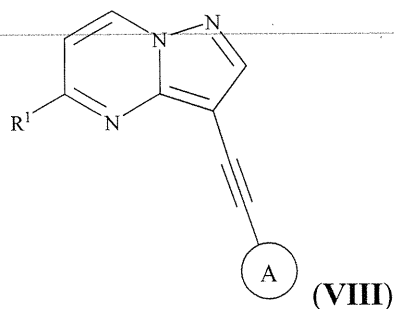
or R^{pc} and R^{pd} are joined to form $=O$; and

R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

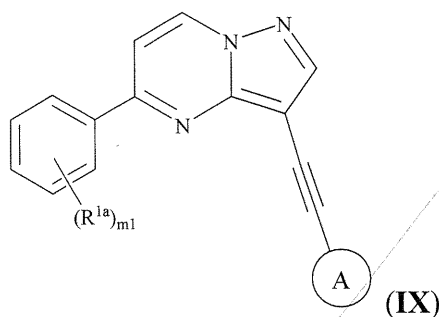
each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group.

43. The compound of claim 1 of Formula (VIII):



or a pharmaceutically acceptable salt thereof.

44. The compound of claim 43 of Formula (IX):



or a pharmaceutically acceptable salt thereof,
wherein

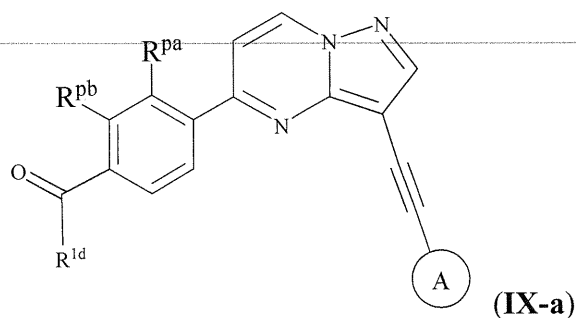
each instance of R^{1a} is independently hydrogen, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted phenyl, optionally substituted five- or six-membered heteroaryl, optionally substituted five- or six-membered heterocyclyl, optionally substituted acyl, $-CN$, $-OR^A$, or $-N(R^B)_2$;

m_1 is an integer of 1 to 5, inclusive;

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

each instance of R^B 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.

45. The compound of claim 44 of Formula (IX-a):



or a pharmaceutically acceptable salt thereof,

wherein

R^{ld} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$;

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

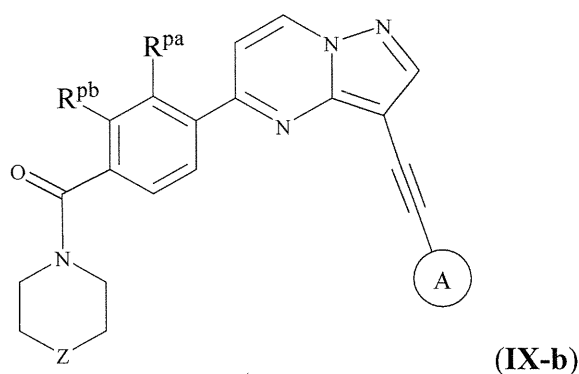
or R^{pc} and R^{pd} are joined to form $=O$; and

R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group.

46. The compound of claim 44 of Formula (IX-b):



or a pharmaceutically acceptable salt thereof,

wherein

Z is $-O-$ or $-NR^{NZ}-$;

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

R^{pa} is hydrogen, halogen, CN, optionally substituted C_{1-6} alkyl, $-OR^A$, $-N(R^B)_2$, $-NH-CO-R^C$;

R^C is optionally substituted C_{1-6} alkyl;

R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

each of R^{pc} and R^{pd} is independently hydrogen, halogen, CN, $-OR^A$, or optionally substituted C_{1-6} alkyl;

or R^{pc} and R^{pd} are joined to form $=O$; and

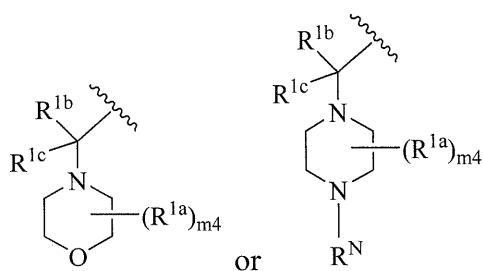
R^{pe} is optionally substituted six-membered heterocyclyl, $-OR^A$, or $-N(R^B)_2$; and

each instance of R^A is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or an oxygen protecting group; and

each instance of R^B is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteraryl, optionally substituted acyl, or a nitrogen protecting group.

47. The compound of any one of claims 34, 38, 42 and 46, wherein Z is $-O-$, $-NH-$, $-NMe-$ or $-Net-$.

48. The compound of any one of claims 31, 35, 39 and 43, wherein R^1 is of the formula:



wherein

each instance of R^{1a} , R^{1b} , and R^{1c} is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted acyl, -CN, -OR^A, or -N(R^B)₂;

each instance of m_4 is independently an integer of 1 to 8, inclusive, as valency permits;

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

each instance of R^B and R^N 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.

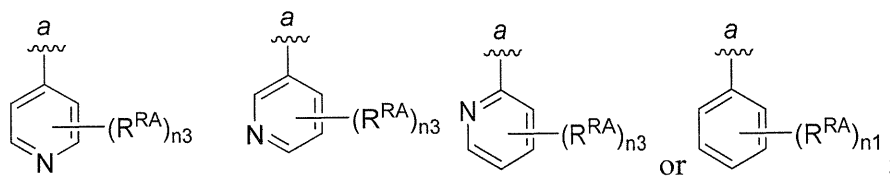
49. The compound of claim 48, wherein R^N is H.

50. The compound of claim 48, wherein R^N is Me.

51. The compound of claim 48, wherein R^N is Et.

52. The compound of any one of claims 48-51, wherein R^{1b} and R^{1c} are both hydrogen.

53. The compound of any one of claims 30-52, 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; and

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

each instance of n_3 is independently an integer of 1 to 4, inclusive.

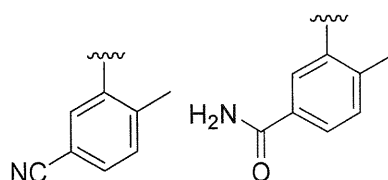
54. The compound of claim 53, wherein

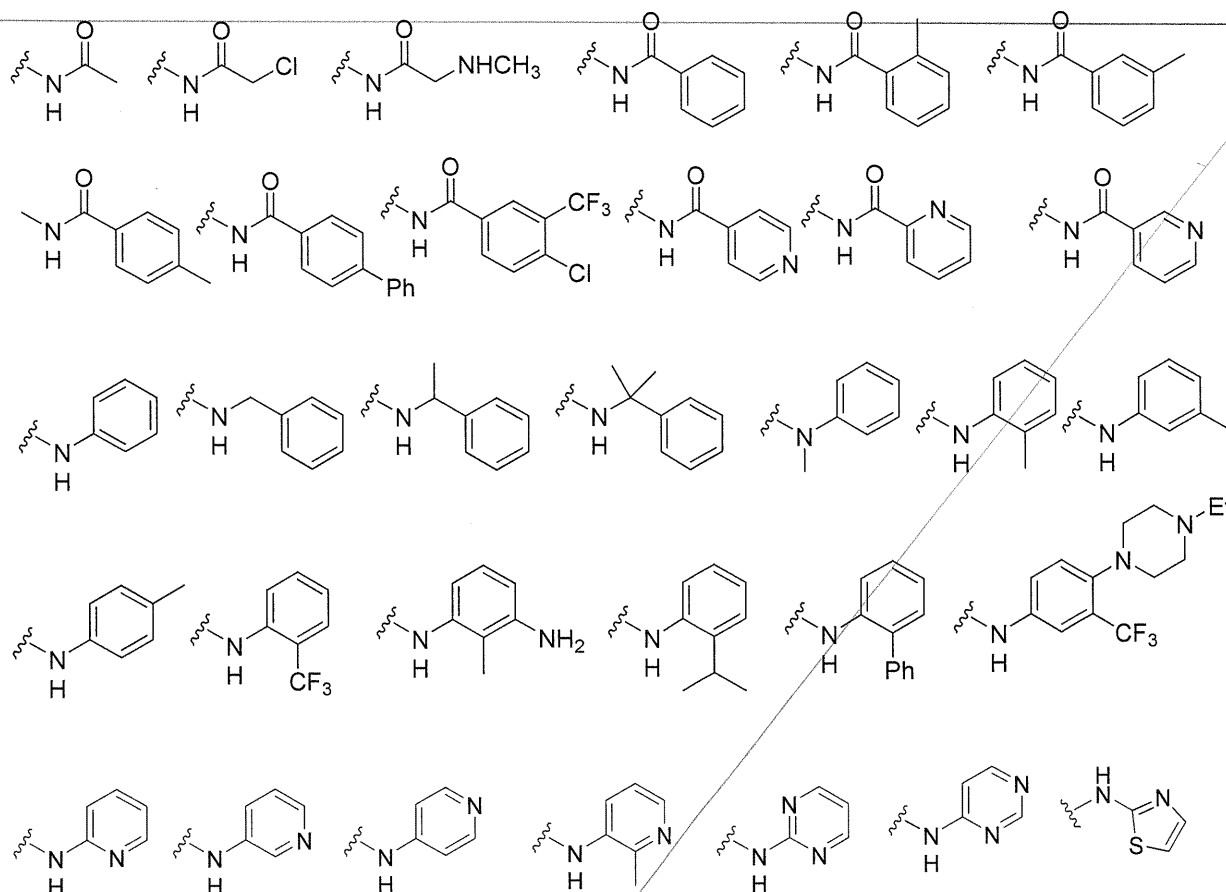
each instance of R^{RA} is independently hydrogen, $-CN$, or optionally substituted C_{1-6} alkyl; and

each instance of n_3 is independently 1 or 2.

55. The compound of any one of claims 30-54, wherein Ring A is of one of the following formulae:

$-CN$, $-Cl$, $-CF_3$, $-CH_3$, $-Ph$, $-OH$, $-OCH_3$, $-OPh$, $-NH_2$, $-NHAc$, $-NHSO_2CH_3$,





56. The compound of claim 1, wherein the compound is one of the compounds in Table 1.
57. A pharmaceutical composition comprising a compound of any one of claims 1-56 and a pharmaceutically acceptable excipient.
58. The pharmaceutical composition of claim 57 comprising a therapeutically effective amount of the compound.
59. Use of a compound of any one of claims 1-56, or a pharmaceutical composition of claim 57 or 58 for treatment of a MNK-related disorder.
60. Use of a compound or pharmaceutical composition of claim 59, wherein the MNK-related disorder is MNK1-related disorder.

61. Use of a compound or pharmaceutical composition of claim 59, wherein the MNK-related disorder is MNK2-related disorder.
62. Use of a compound of any one of claims 1-56 or a pharmaceutical composition of claim 57 or 58 for treatment of an mTOR-related disorder.
63. Use of a compound of any one of claims 1-56 or a pharmaceutical composition of claim 57 or 58 for treatment of a PI3K-related disorder.
64. Use of a compound or pharmaceutical composition of claim 63, wherein the PI3K-related disorder is PIK3 α -related disorder.
65. Use of a compound or pharmaceutical composition of claim 63, wherein the PI3K-related disorder is PIK3 β -related disorder.
66. Use of a compound or pharmaceutical composition of claim 63, wherein the PI3K-related disorder is PIK3 γ -related disorder.
67. Use of a compound or pharmaceutical composition of claim 63, wherein the PI3K-related disorder is PIK3 δ -related disorder.
68. Use of a compound of any one of claims 1-56 or a pharmaceutical composition of claim 57 or 58 for treatment of a HER-related disorder.
69. Use of a compound or pharmaceutical composition of claim 68, wherein the HER-related disorder is a HER2-related disorder.
70. Use of a compound or pharmaceutical composition of claim 68, wherein the HER-related disorder is a HER3-related disorder
71. Use of a compound of any one of 1-56 or a pharmaceutical composition of claim 57 or 58 for treatment of a JAK-related disorder.

72. Use of a compound or pharmaceutical composition of claim 71, wherein the JAK-related disorder is a JAK1-related disorder.

73. Use of a compound or pharmaceutical composition of claim 71, wherein the JAK-related disorder is a JAK2-related disorder.

74. Use of a compound or pharmaceutical composition of claim 71, wherein the JAK-related disorder is a JAK3-related disorder.

75. Use of a compound or pharmaceutical composition of claim 59, wherein the compound is used in combination with another therapeutic agent.

76. Use of a compound or pharmaceutical composition of claim 75, wherein the therapeutic agent is a kinase inhibitor.

77. Use of a compound or composition of claim 76, wherein the kinase inhibitor is a JAK inhibitor.

78. Use of a compound or composition of claim 77, wherein the JAK inhibitor is a JAK1 inhibitor.

79. Use of a compound or composition of claim 77, wherein the JAK inhibitor is a JAK2 inhibitor.

80. Use of a compound or composition of claim 77, wherein the JAK inhibitor is a JAK3 inhibitor.

81. Use of a compound or composition of claim 76, wherein the kinase inhibitor is a PI3K inhibitor.

82. Use of a compound or composition of claim 81, wherein the PI3K inhibitor is a PI3K α -related inhibitor.

83. Use of a compound or composition of claim 81, wherein the PI3K inhibitor is a PI3K β -related inhibitor.

84. Use of a compound or composition of claim 81, wherein the PI3K inhibitor is a PI3K γ -related inhibitor.

85. Use of a compound or composition of claim 81, wherein the PI3K inhibitor is a PI3K δ -related inhibitor.

86. Use of a compound or composition of claim 75, wherein the therapeutic agent is an mTOR inhibitor.

87. Use of a compound or composition of claim 75, wherein the therapeutic agent is a HER inhibitor.

88. Use of a compound or composition of claim 87, wherein the HER inhibitor is a HER2 inhibitor.

89. Use of a compound or composition of claim 87, wherein the HER inhibitor is a HER3 inhibitor.

90. Use of a compound or composition of any one of claims 59-89, wherein the disorder is cancer, an inflammatory disease, a neurodegenerative disease, or a metabolic disorder.

91. Use of a compound of claim 90, wherein the disorder is cancer.

92. Use of a compound of claim 90, wherein the disorder is solid tumor.

93. Use of a compound of claim 90, wherein the disorder is hematological tumor.

94. Use of a compound of claim 90, wherein the disorder is a metabolic disorder.

95. Use of a compound of claim 94, wherein the metabolic disorder is obesity.

96. Use of a compound of claim 94, wherein the metabolic disorder is diabetes.
97. Use of a compound of claim 90, wherein the disorder is an inflammatory disease.
98. Use of a compound of claim 90, wherein the disorder is a neurodegenerative disease.
99. Use of a compound of claim 90, wherein the neurodegenerative disease is Alzheimer's disease.
100. Use of a compound of claim 90, wherein the neurodegenerative disease is autism or autism spectrum.
101. Use of a compound or composition of any one of claims 59-100, wherein the compound or composition is administered at a dosage level sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg to a subject in need thereof.
102. A method of treating a MNK-related disorder in a subject comprising administering an effective amount of a compound of any one of claims 1-56, or a pharmaceutical composition of claim 57 or 58 to the subject.
103. A method of treating an mTOR-related disorder in a subject comprising administering an effective amount of a compound of any one of claims 1-56, or a pharmaceutical composition of claim 57 or 58 to the subject.
104. A method of treating a HER-related disorder in a subject comprising administering an effective amount of a compound of any one of claims 1-56, or a pharmaceutical composition of claim 57 or 58 to the subject.
105. The method of claim 104, wherein the HER-related disorder is a HER2-related disorder.

106. The method of claim 105, wherein the HER-related disorder is a HER3-related disorder.

107. A method of treating a PI3K-related disorder in a subject, comprising administering an effective amount of a compound of any one of claims 1-56, or a pharmaceutical composition of claim 57 or 58 to the subject.

108. The method of claim 107, wherein the PI3K-related disorder is a PI3K α -related disorder.

109. The method of claim 107, wherein the PI3K-related disorder is a PI3K β -related disorder.

110. The method of claim 107, wherein the PI3K-related disorder is a PI3K γ -related disorder.

111. The method of claim 107, wherein the PI3K-related disorder is a PI3K δ -related disorder.

112. A method of treating a JAK-related disorder in a subject, comprising administering an effective amount of a compound of any one of claims 1-56, or a pharmaceutical composition of claim 57 or 58 to the subject.

113. The method of claim 112, wherein the JAK -related disorder is a JAK1-related disorder.

114. The method of claim 112, wherein the JAK -related disorder is a JAK2-related disorder.

115. The method of claim 112, wherein the JAK -related disorder is a JAK3-related disorder.

116. A kit comprising a compound of any one of claims 1-56, or a pharmaceutical composition of claim 57 or 58; and instructions for administering the compound or the composition to a subject.