

or a pharmaceutically acceptable salt thereof,
wherein

R^{ld} is six-membered heterocyclyl with at least two heteroatoms independently selected from N or O optionally substituted with one or more substituents selected from the group consisting of acyl and C_{1-6} alkyl;
wherein

R^{pa} is hydrogen or halogen,;

R^{pb} is independently hydrogen, halogen or C_{1-6} alkyl optionally substituted with one or more halogen;

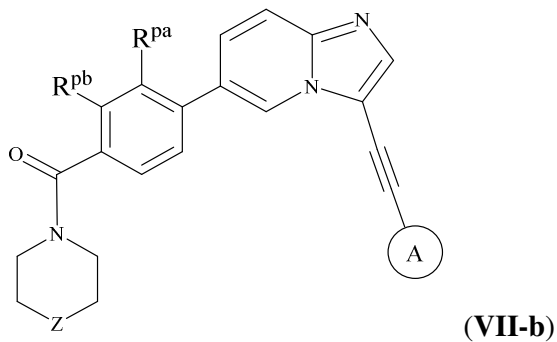
Ring A is phenyl, five-membered heteroaryl, six-membered heteroaryl, or 5,6-bicyclic heteroaryl, each optionally substituted with one or more R^{RA} ;

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

each instance of R^{AO} is independently hydrogen, C_{1-6} alkyl, or aryl;

each instance of R^{AN} is independently hydrogen, C_{1-6} alkyl, aryl(C_{1-6} alkyl), heteroaryl, (C_{1-6} alkyl)heteroaryl, acyl, C_{1-6} alkylacyl, halo(C_{1-6} alkyl)acyl, amino(C_{1-6} alkyl)acyl, (C_{1-6} alkyl)amino(C_{1-6} alkyl)acyl, arylacyl, (C_{1-6} alkyl)arylacyl, heteroarylacyl, methylsulfonyl or aryl optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, halo(C_{1-6} alkyl), dihalo(C_{1-6} alkyl), trihalo(C_{1-6} alkyl), amino and phenyl.

[00011e] In some embodiments, there is disclosed a compound of Formula (VII-b):

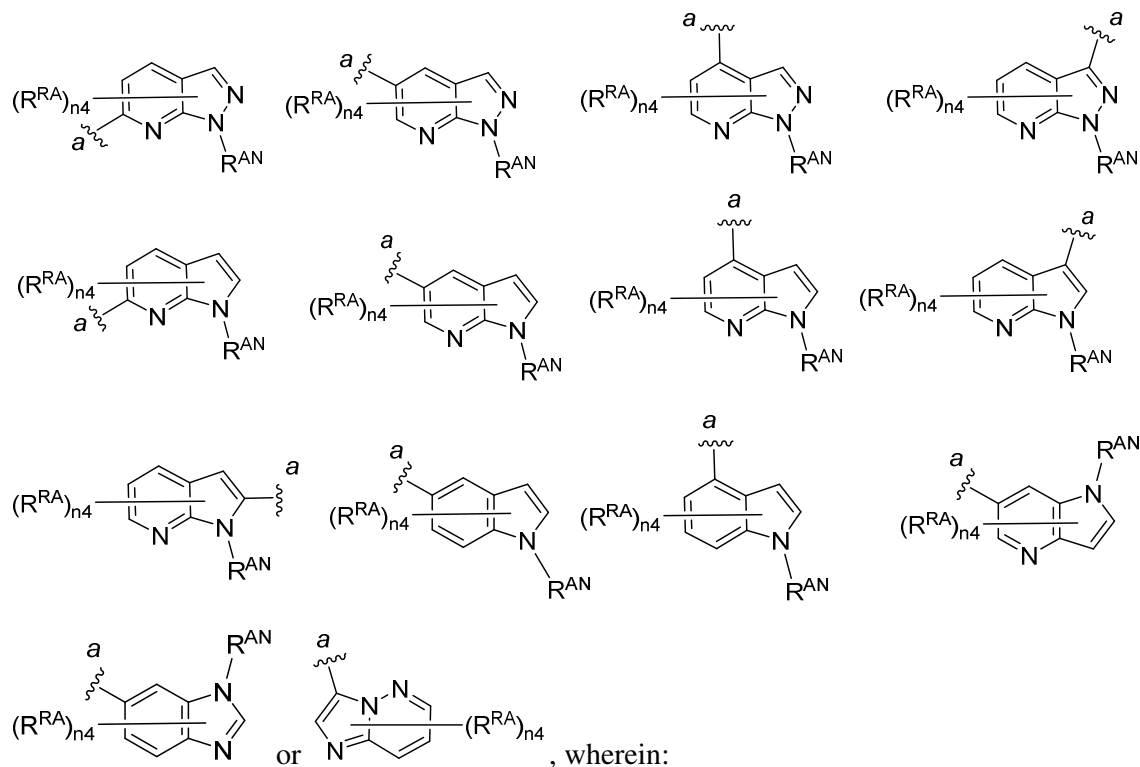


or a pharmaceutically acceptable salt thereof,
wherein

R^{pa} is hydrogen or halogen;

R^{pb} is independently hydrogen, halogen or C_{1-6} alkyl optionally substituted with one or more halogen;

wherein Ring A is one of the following formulae:



a indicates the point of attachment to the alkyne;

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

each instance of R^{RA} is independently hydrogen, halogen, acyl, aminoacyl, $-CN$, $-OR^{AO}$,

$N(R^{AN})_2$, phenyl or C_{1-6} alkyl optionally substituted with one to three halogen;

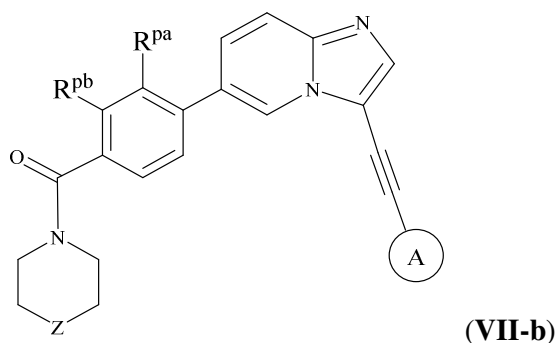
each instance of R^{AO} is independently hydrogen, C_{1-6} alkyl, or aryl;

each instance of R^{AN} is independently hydrogen, C_{1-6} alkyl, aryl(C_{1-6} alkyl), heteroaryl, (C_{1-6} alkyl)heteroaryl, acyl, C_{1-6} alkylacyl, halo(C_{1-6} alkyl)acyl, amino(C_{1-6} alkyl)acyl, (C_{1-6} alkyl)amino(C_{1-6} alkyl)acyl, arylacyl, (C_{1-6} alkyl)arylacyl, heteroarylacyl, methylsulfonyl or aryl optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, halo(C_{1-6} alkyl), dihalo(C_{1-6} alkyl), trihalo(C_{1-6} alkyl), amino and phenyl;

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

each instance of R^{NZ} is independently hydrogen, or C_{1-6} alkyl.

[00011f] In some embodiments, there is disclosed a compound of Formula (VII-b):



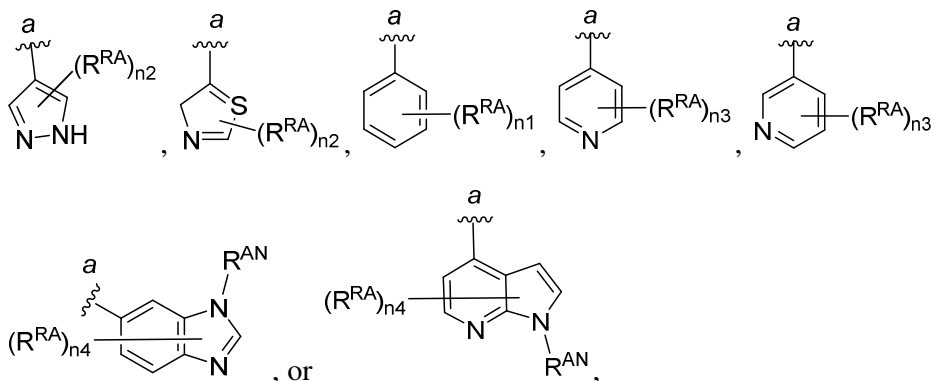
or a pharmaceutically acceptable salt thereof,

wherein

R^{pa} is hydrogen or halogen;

R^{pb} is independently hydrogen, halogen or C_{1-6} alkyl optionally substituted with one or more halogen;

wherein Ring A is one of the following formulae:



wherein:

a indicates the point of attachment to the alkyne;

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

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

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

each instance of R^{RA} is independently hydrogen, halogen, acyl, aminoacyl, -CN, -OR^{AO},

$N(R^{AN})_2$, phenyl or C_{1-6} alkyl optionally substituted with one to three halogen;

each instance of R^{AO} is independently hydrogen, C_{1-6} alkyl, or aryl;

each instance of R^{AN} is independently hydrogen, C_{1-6} alkyl, aryl(C_{1-6} alkyl), heteroaryl, (C_{1-6} alkyl)heteroaryl, acyl, C_{1-6} alkylacyl, halo(C_{1-6} alkyl)acyl, amino(C_{1-6} alkyl)acyl, (C_{1-6} alkyl)amino(C_{1-6} alkyl)acyl, arylacyl, (C_{1-6} alkyl)arylacyl, heteroarylacyl, methylsulfonyl or

aryl optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, halo(C₁₋₆ alkyl), dihalo(C₁₋₆ alkyl), trihalo(C₁₋₆ alkyl), amino and phenyl; wherein Z is -O- or -NR^{NZ}-; and each instance of R^{NZ} is independently hydrogen, or C₁₋₆ alkyl.

[00011g] 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] The present 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.

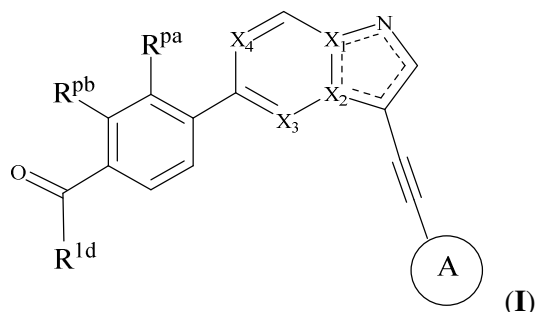
[00013] The present disclosure relates to pharmaceutical compositions comprising an inventive compound, and optionally a pharmaceutically acceptable excipient, and to their use for the prevention and treatment of a PI3-kinase (PI3K)-related disorder. In certain embodiments, the PI3K-related disorder 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] The present 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.

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 or halogen;

R^{pb} is independently hydrogen, halogen or C_{1-6} alkyl optionally substituted with one or more halogen;

R^{ld} is six-membered heterocyclyl with at least two heteroatoms independently selected from N or O optionally substituted with one or more substituents selected from the group consisting of acyl and C_{1-6} alkyl;

each instance of R^2 is independently hydrogen, halogen or C_{1-6} alkyl,

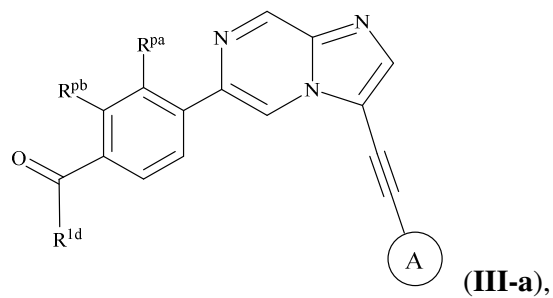
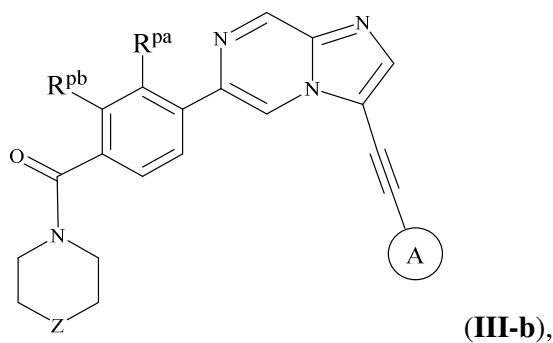
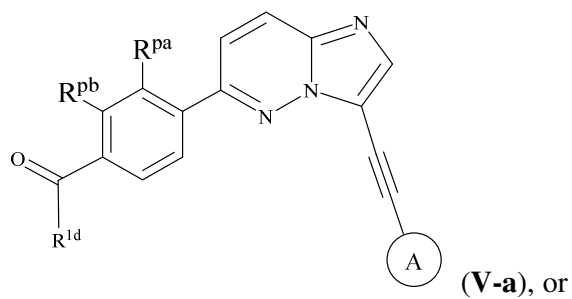
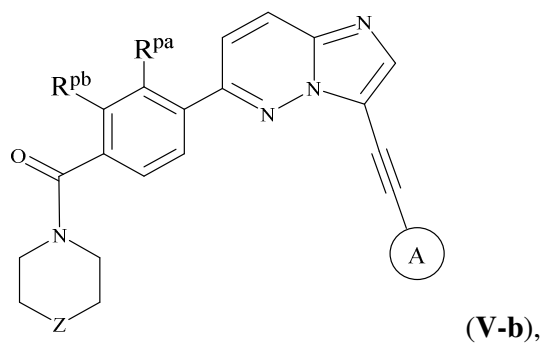
Ring A is phenyl, five-membered heteroaryl, six-membered heteroaryl or 5,6-bicyclic heteroaryl, each optionally substituted with one or more R^{RA} ;

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

each instance of R^{AO} is independently hydrogen, C_{1-6} alkyl, or aryl;

each instance of R^{AN} is independently hydrogen, C_{1-6} alkyl, aryl(C_{1-6} alkyl), heteroaryl, (C_{1-6} alkyl)heteroaryl, acyl, C_{1-6} alkylacyl, halo(C_{1-6} alkyl)acyl, amino(C_{1-6} alkyl)acyl, (C_{1-6} alkyl)amino(C_{1-6} alkyl)acyl, arylacyl, (C_{1-6} alkyl)arylacyl, heteroarylacyl, methylsulfonyl or aryl optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, halo(C_{1-6} alkyl), dihalo(C_{1-6} alkyl), trihalo(C_{1-6} alkyl), amino and phenyl.

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



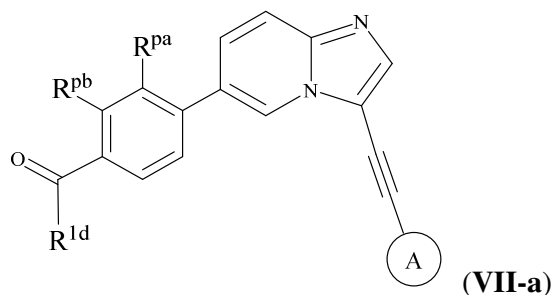
wherein

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

each instance of R^{NZ} is independently hydrogen, or C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof,

wherein

R^{ld} is six-membered heterocyclyl with at least two heteroatoms independently selected from N or O optionally substituted with one or more substituents selected from the group consisting of acyl and C_{1-6} alkyl;

wherein

R^{pa} is hydrogen or halogen,;

R^{pb} is independently hydrogen, halogen or C_{1-6} alkyl optionally substituted with one or more halogen;

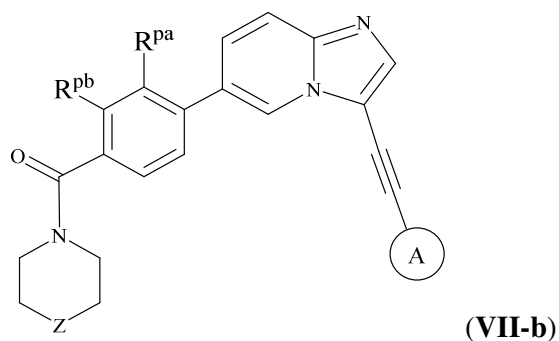
Ring A is phenyl, five-membered heteroaryl, six-membered heteroaryl, or 5,6-bicyclic heteroaryl, each optionally substituted with one or more R^{RA} ;

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

each instance of R^{AO} is independently hydrogen, C_{1-6} alkyl, or aryl;

each instance of R^{AN} is independently hydrogen, C_{1-6} alkyl, aryl(C_{1-6} alkyl), heteroaryl, (C_{1-6} alkyl)heteroaryl, acyl, C_{1-6} alkylacyl, halo(C_{1-6} alkyl)acyl, amino(C_{1-6} alkyl)acyl, (C_{1-6} alkyl)amino(C_{1-6} alkyl)acyl, arylacyl, (C_{1-6} alkyl)arylacyl, heteroarylacyl, methylsulfonyl or aryl optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, halo(C_{1-6} alkyl), dihalo(C_{1-6} alkyl), trihalo(C_{1-6} alkyl), amino and phenyl.

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



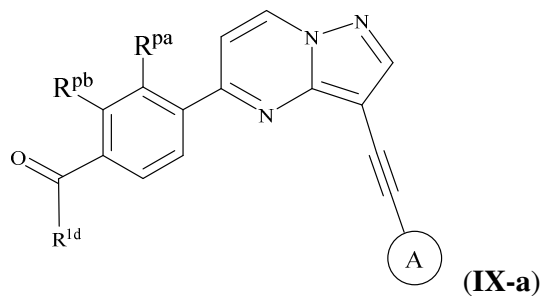
or a pharmaceutically acceptable salt thereof,

wherein

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

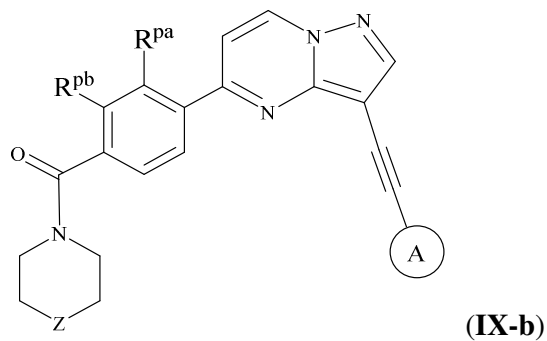
each instance of R^{NZ} is independently hydrogen, or C_{1-6} alkyl.

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):



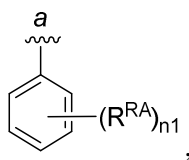
or a pharmaceutically acceptable salt thereof,

wherein

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

each instance of R^{NZ} is independently hydrogen, or C_{1-6} alkyl.

7. The compound of claim 1, wherein R^{pa} or R^{pb} is hydrogen or halogen.
8. The compound of claim 1, wherein Ring A is five-membered heteroaryl with two heteroatoms selected from the group consisting of O, S, and N optionally substituted with one or more R^{RA} ; or
 wherein Ring A is six-membered heteroaryl with one or two N optionally substituted with one or more R^{RA} ; or
 wherein Ring A is of the formula:



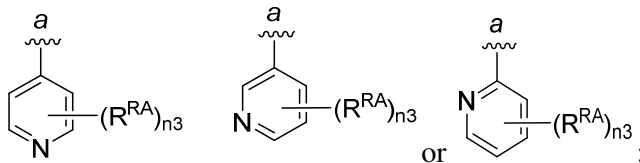
wherein

a indicates the point of attachment to the alkyne;

R^{RA} is as defined in claim 1; and

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

9. The compound of claim 8, wherein Ring A is one of the following formulae:



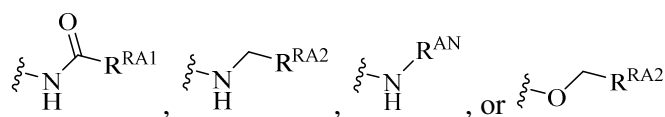
wherein

a indicates the point of attachment to the alkyne;

R^{RA} is as defined in claim 1; and

each instance of $n3$ is independently an integer of 1 to 4, inclusive.

10. The compound of claim 9, wherein R^{RA} is $-N(R^{AN})_2$, $-NHR^{AN}$, or $-N(CH_3)R^{AN}$, wherein R^{AN} is aryl(C_{1-6} alkyl), or C_{1-6} alkyl.
11. The compound of claim 9, wherein R^{RA} is of one of the following formulae:

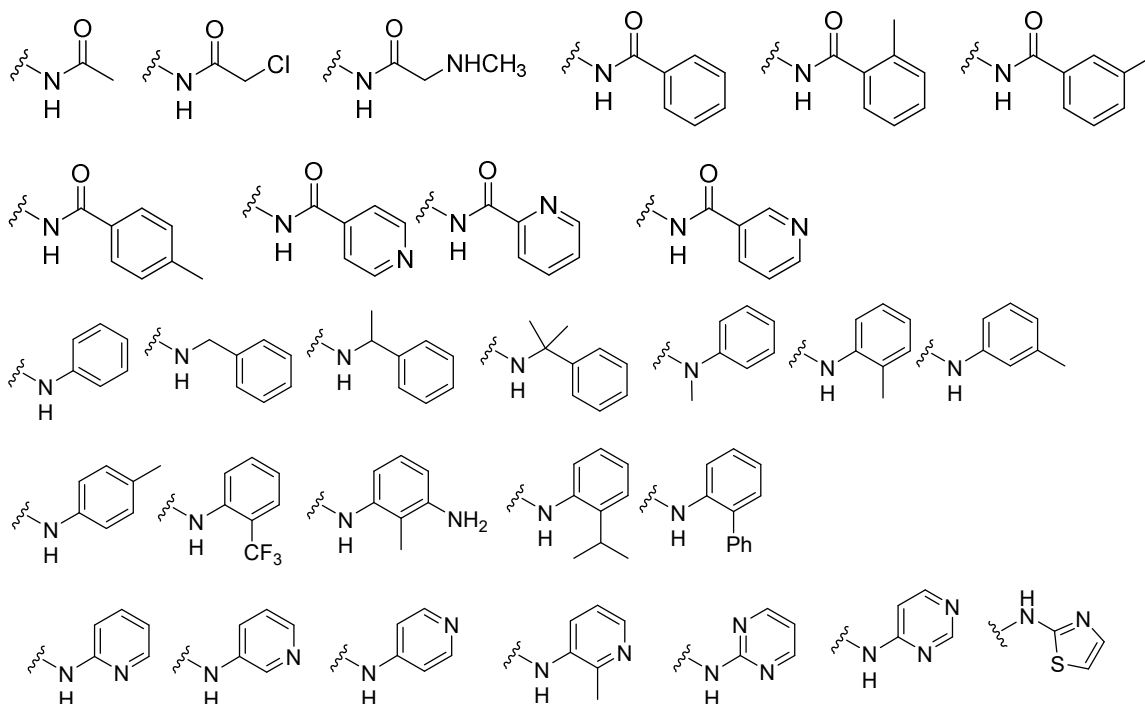


wherein

R^{RA1} is independently C_{1-6} alkyl, halo(C_{1-6} alkyl), amino(C_{1-6} alkyl), (C_{1-6} alkyl)amino(C_{1-6} alkyl), phenyl, (C_{1-6} alkyl)phenyl, five- or six-membered heteroaryl; and

each instance of R^{RA2} is independently C_{1-6} alkyl, or phenyl;

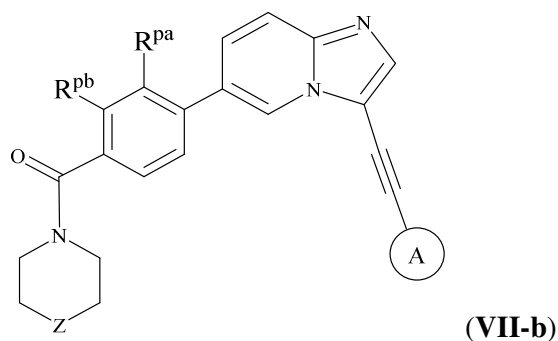
or wherein R^{RA} is one of the following formulae: hydrogen, -Ph, -OH, -NH₂, -OCH₃, -OPh, -Cl, -CF₃, -CH₃,



12. The compound of claim 4, wherein Ring A is 5,6-bicyclic heteroaryl optionally substituted with one or more R^{RA} .

13. The compound of claim 12, wherein Ring A is 5,6-bicyclic heteroaryl with one, two, or three N atoms optionally substituted with one or more R^{RA} .

14. A compound of Formula (VII-b):



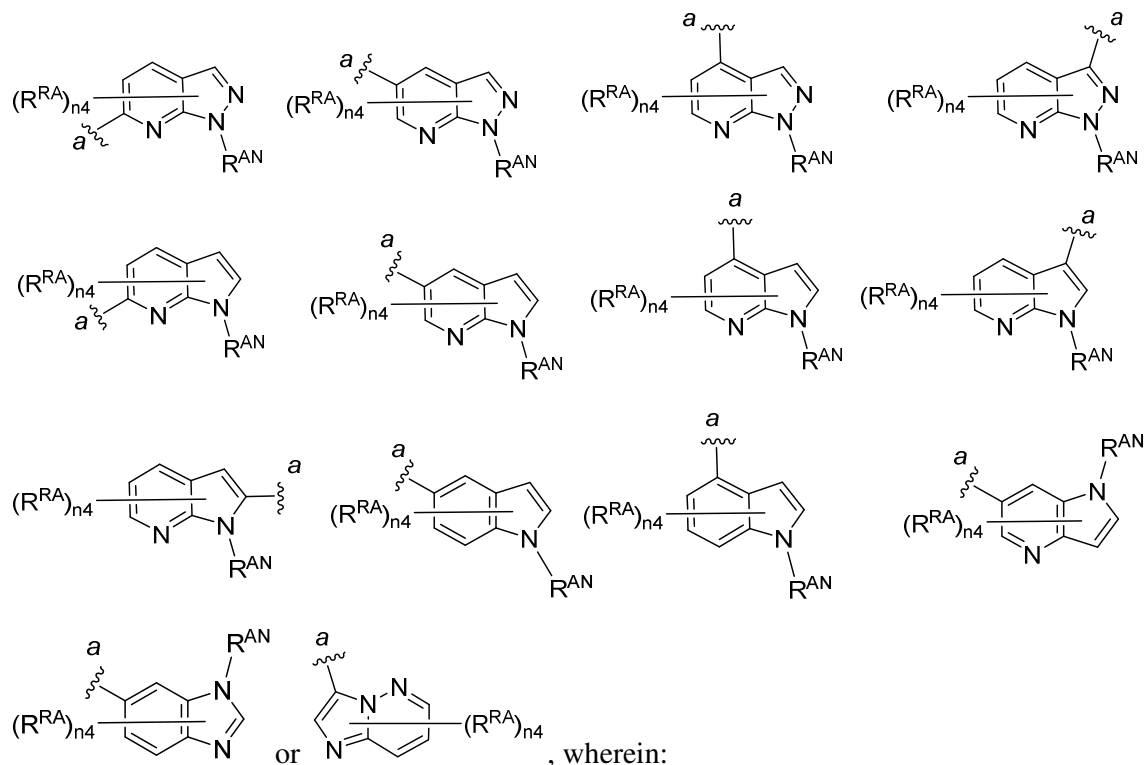
or a pharmaceutically acceptable salt thereof,

wherein

R^{pa} is hydrogen or halogen;

R^{pb} is independently hydrogen, halogen or C_{1-6} alkyl optionally substituted with one or more halogen;

wherein Ring A is one of the following formulae:



a indicates the point of attachment to the alkyne;

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

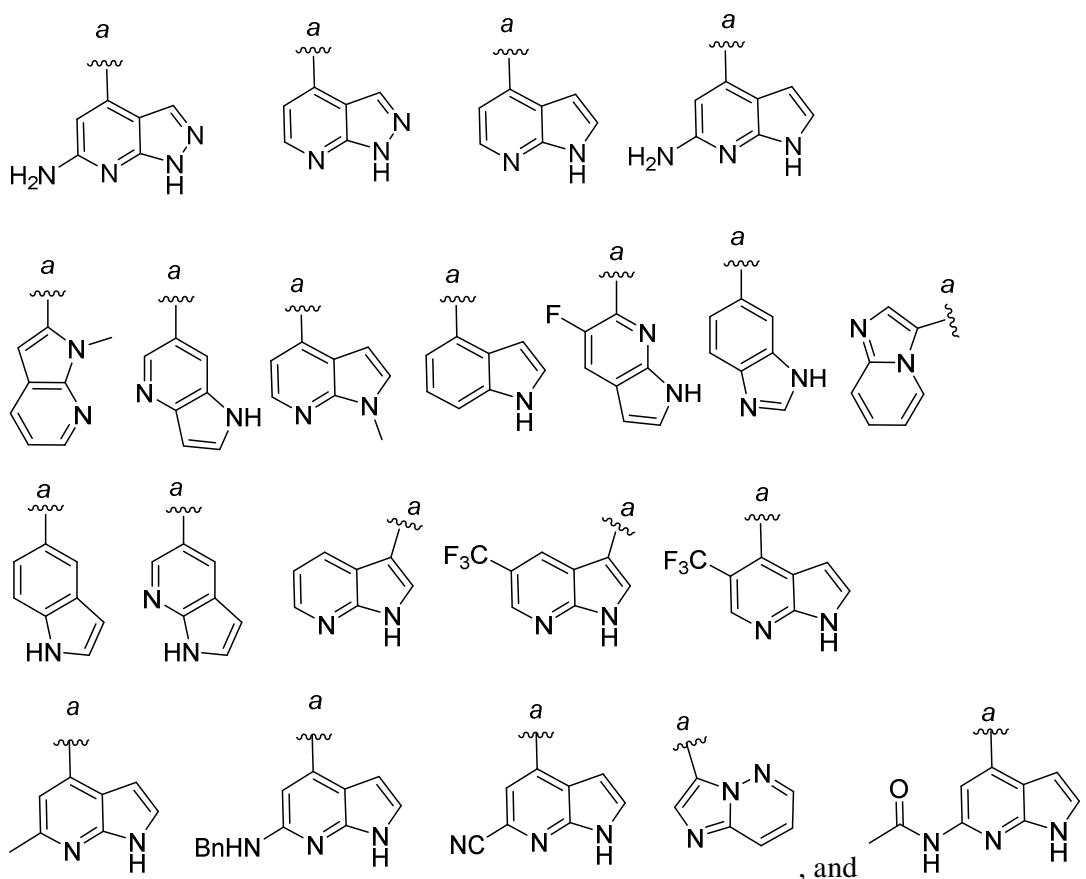
each instance of R^{RA} is independently hydrogen, halogen, acyl, aminoacyl, $-CN$, $-OR^{AO}$,

$N(R^{AN})_2$, phenyl or C_{1-6} alkyl optionally substituted with one to three halogen;

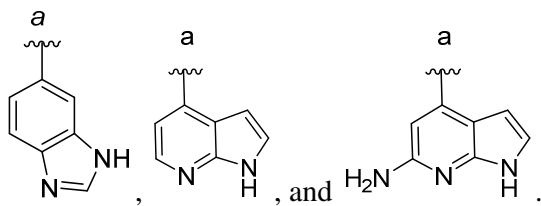
each instance of R^{AO} is independently hydrogen, C_{1-6} alkyl, or aryl;

each instance of R^{AN} is independently hydrogen, C_{1-6} alkyl, aryl(C_{1-6} alkyl), heteroaryl, (C_{1-6} alkyl)heteroaryl, acyl, C_{1-6} alkylacyl, halo(C_{1-6} alkyl)acyl, amino(C_{1-6} alkyl)acyl, (C_{1-6} alkyl)amino(C_{1-6} alkyl)acyl, arylacyl, (C_{1-6} alkyl)arylacyl, heteroarylacyl, methylsulfonyl or aryl optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, halo(C_{1-6} alkyl), dihalo(C_{1-6} alkyl), trihalo(C_{1-6} alkyl), amino and phenyl; wherein Z is $-O-$ or $-NR^{NZ}-$; and each instance of R^{NZ} is independently hydrogen, or C_{1-6} alkyl.

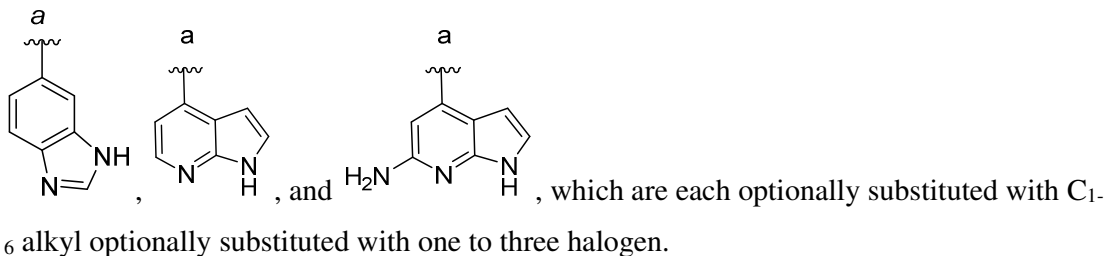
15. The compound of claims 13 or 14, wherein Ring A is selected from the group consisting of optionally substituted groups of the formula:



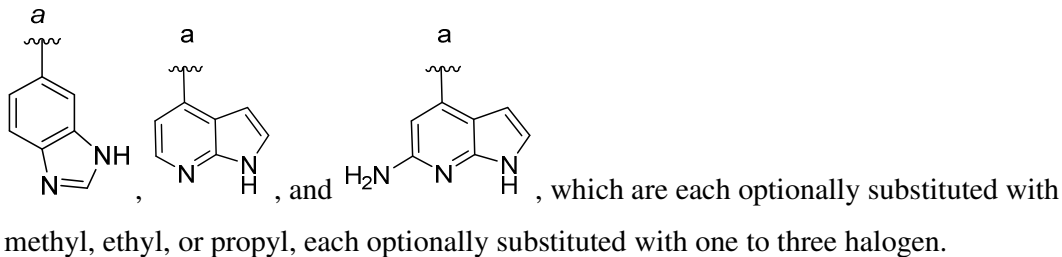
16. The compound of claim 12, wherein Ring A is selected from the group consisting of optionally substituted groups of the formula:



17. The compound of claim 12, wherein Ring A is selected from the group consisting of groups of the formula:



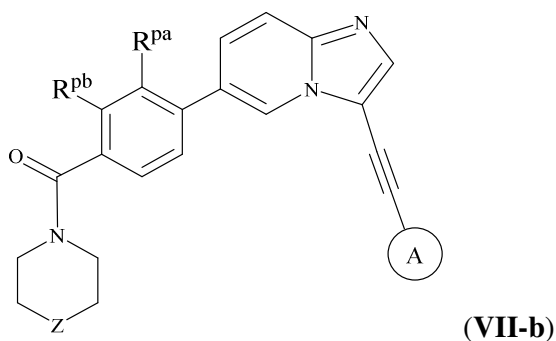
18. The compound of claim 12, wherein Ring A is selected from the group consisting of groups of the formula:



19. The compound of claim 4, wherein Z is O and Ring A is 5,6-bicyclic heteroaryl optionally substituted with one or more R^{RA} .

20. The compound of claim 4, wherein Ring A is 5-membered monocyclic heteroaryl optionally substituted with one or more R^{RA} , 6-membered monocyclic heteroaryl, or 5,6-bicyclic heteroaryl.

21. A compound of Formula (VII-b):



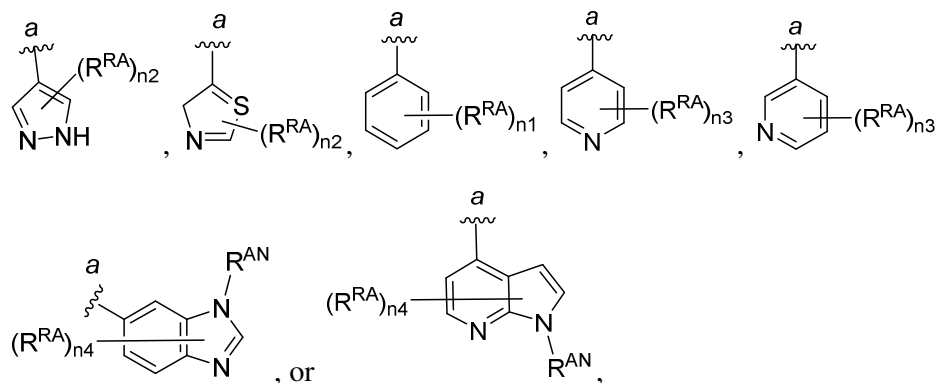
or a pharmaceutically acceptable salt thereof,

wherein

R^{pa} is hydrogen or halogen;

R^{pb} is independently hydrogen, halogen or C₁₋₆ alkyl optionally substituted with one or more halogen;

wherein Ring A is one of the following formulae:



wherein:

a indicates the point of attachment to the alkyne;

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

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

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

each instance of R^A is independently hydrogen, halogen, acyl, aminoacyl, -CN, -OR^{AO},

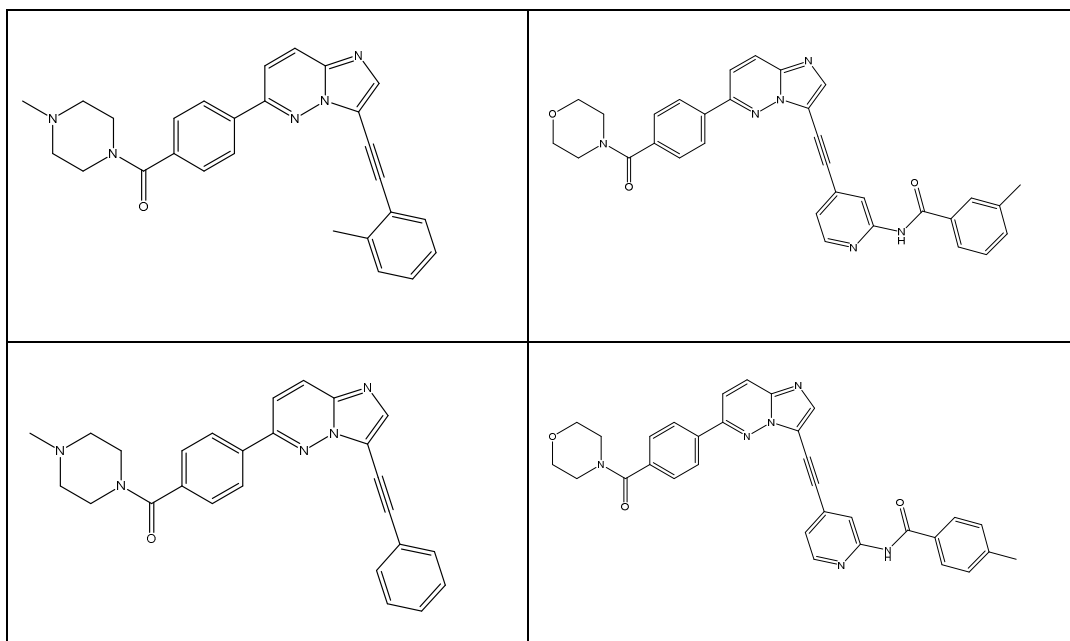
$N(R^{AN})_2$, phenyl or C_{1-6} alkyl optionally substituted with one to three halogen;

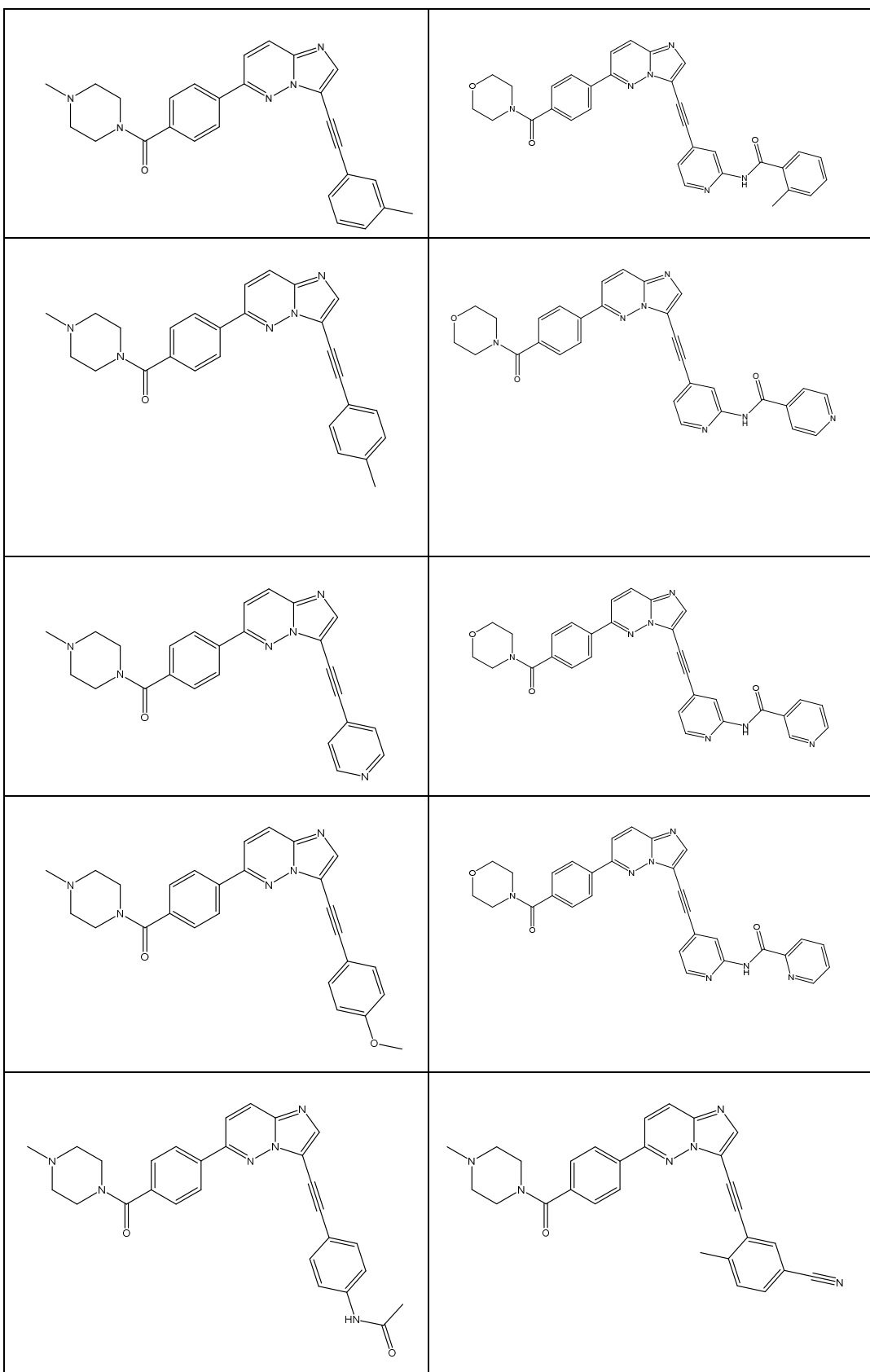
each instance of R^{AO} is independently hydrogen, C₁₋₆ alkyl, or aryl;

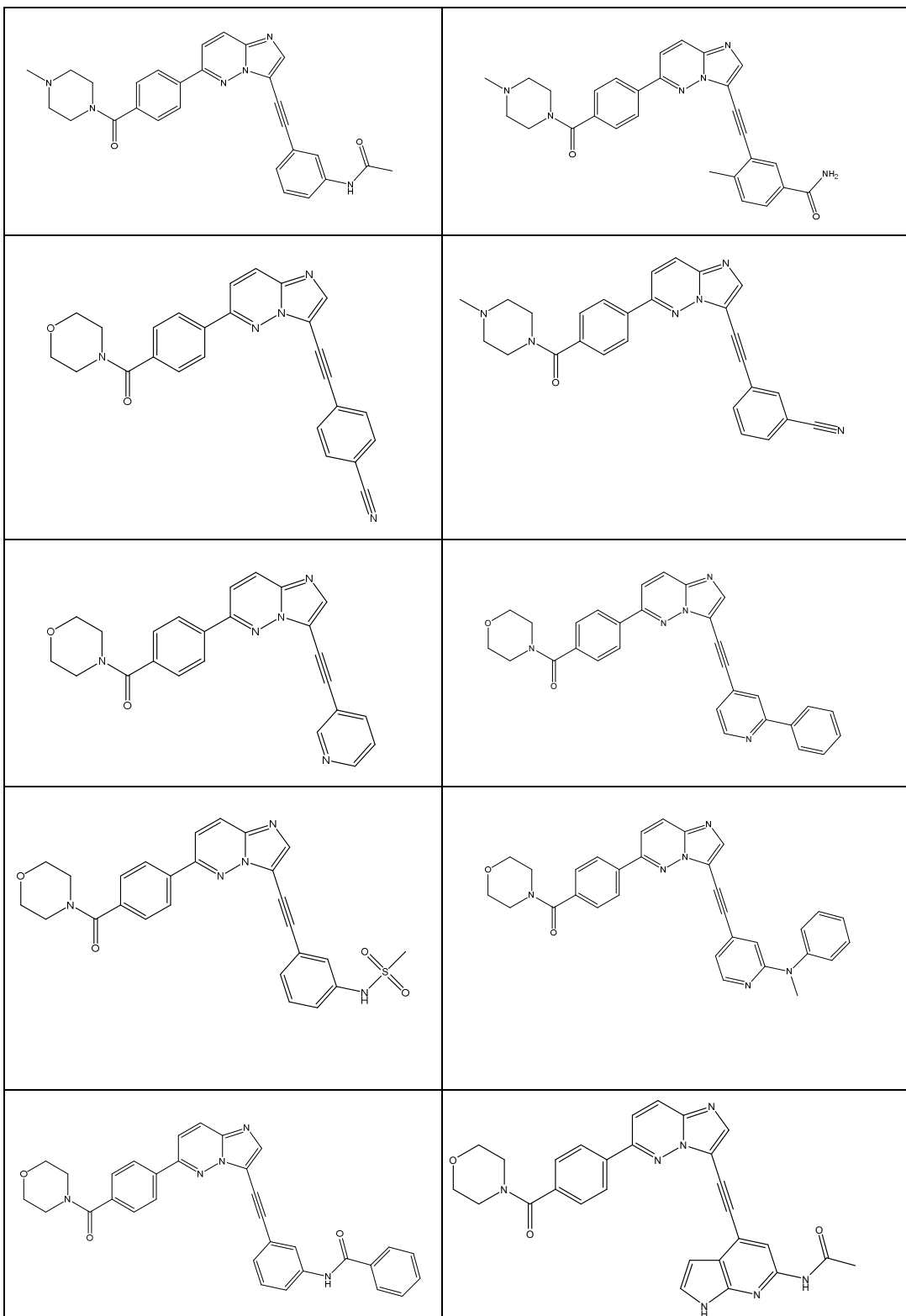
each instance of R^{AN} is independently hydrogen, C₁₋₆ alkyl, aryl(C₁₋₆ alkyl), heteroaryl, (C₁₋₆ alkyl)heteroaryl, acyl, C₁₋₆ alkylacyl, halo(C₁₋₆ alkyl)acyl, amino(C₁₋₆ alkyl)acyl, (C₁₋₆ alkyl)amino(C₁₋₆ alkyl)acyl, arylacyl, (C₁₋₆ alkyl)arylacyl, heteroarylacyl, methylsulfonyl or

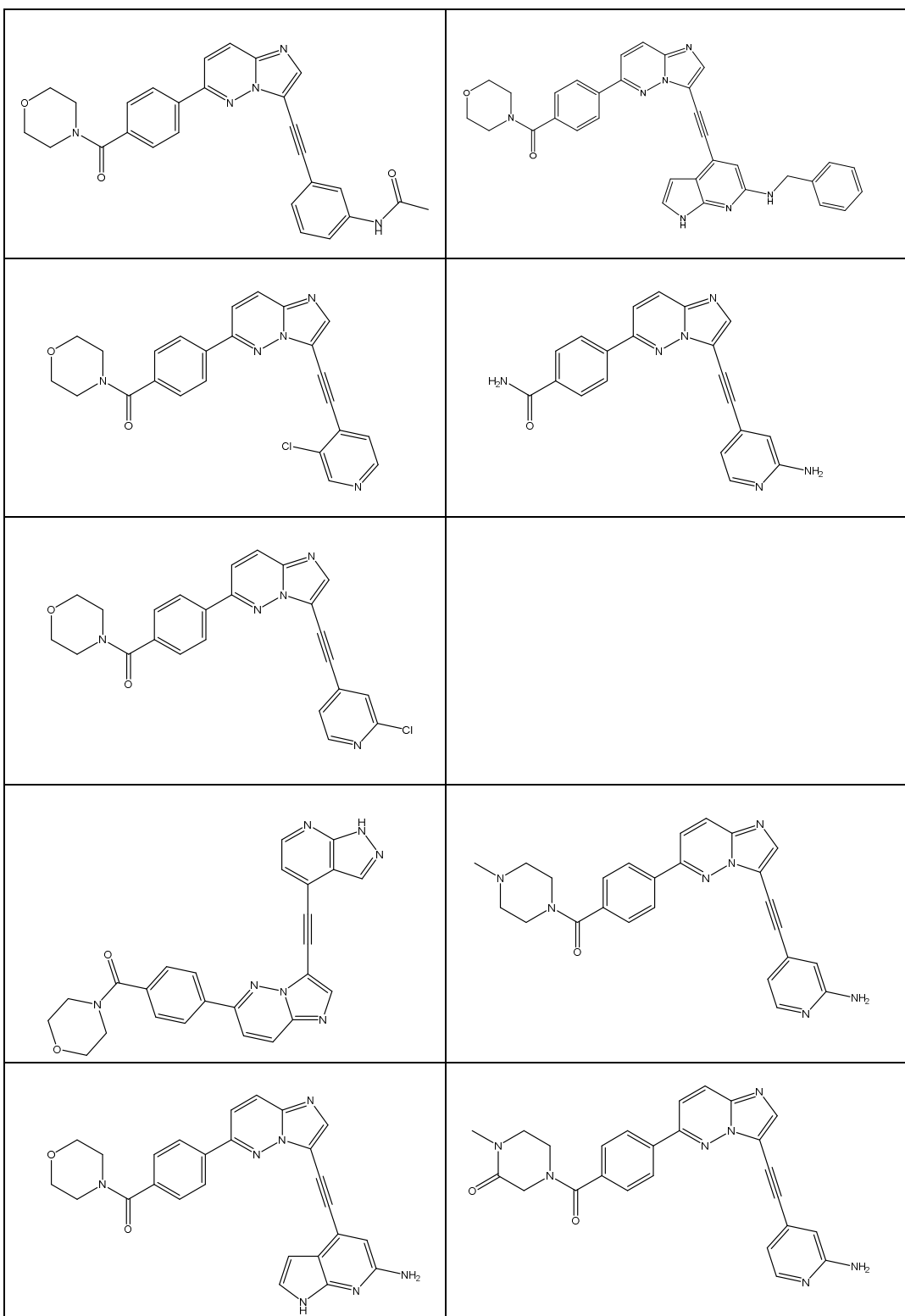
aryl optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, halo(C₁₋₆ alkyl), dihalo(C₁₋₆ alkyl), trihalo(C₁₋₆ alkyl), amino and phenyl;
 wherein Z is -O- or -NR^{NZ}-; and
 each instance of R^{NZ} is independently hydrogen, or C₁₋₆ alkyl.

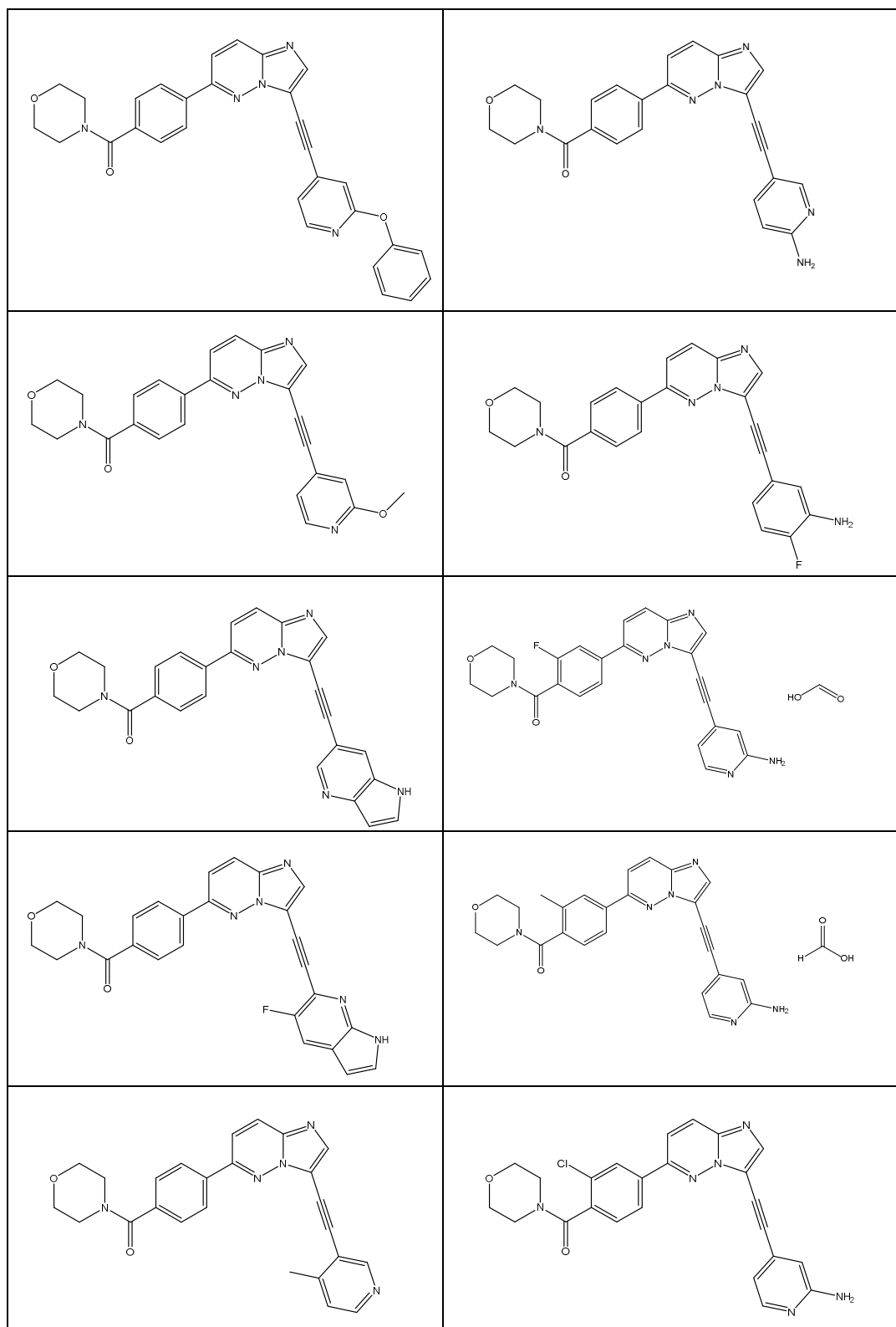
22. A compound of the formula:

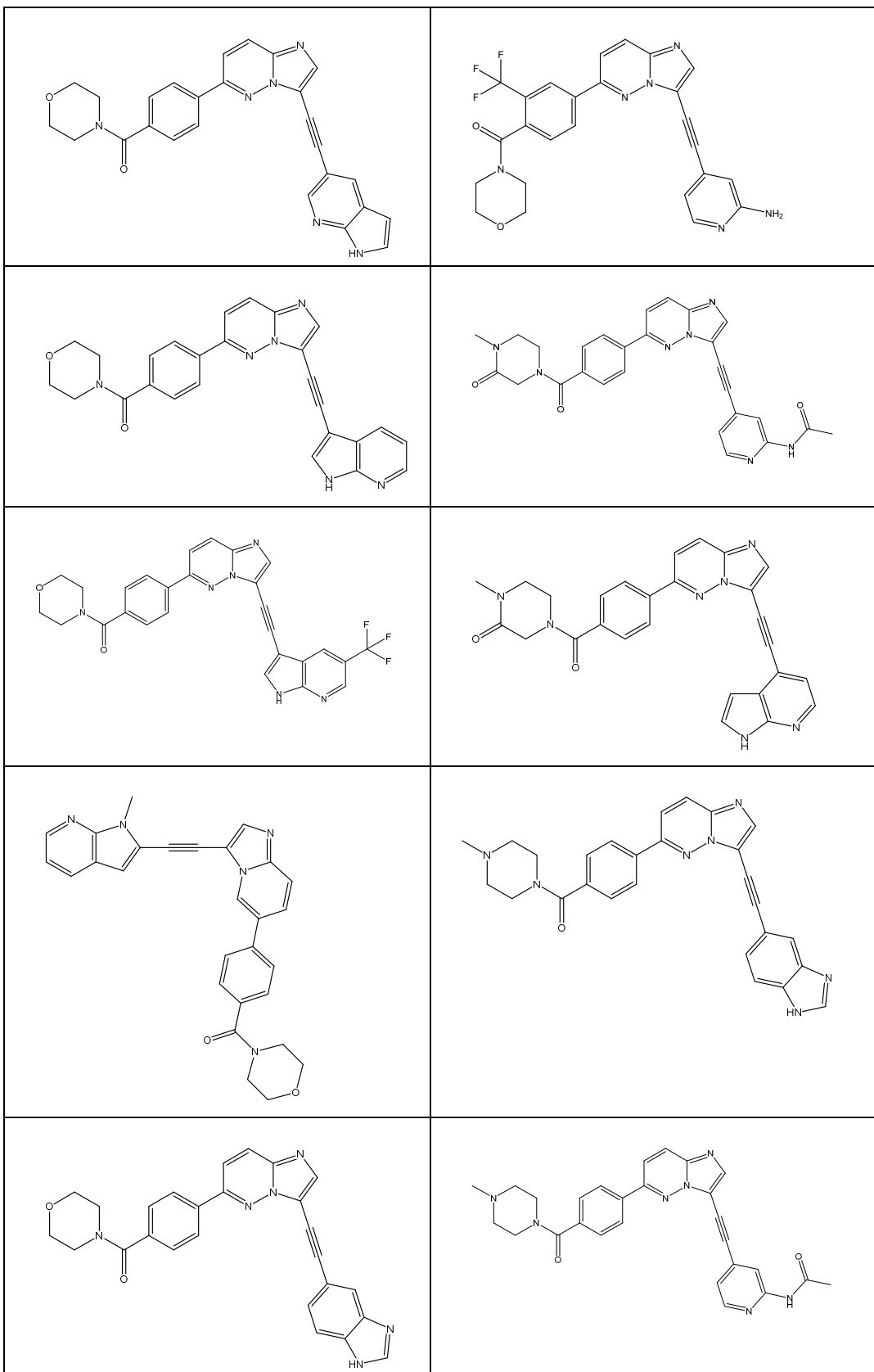


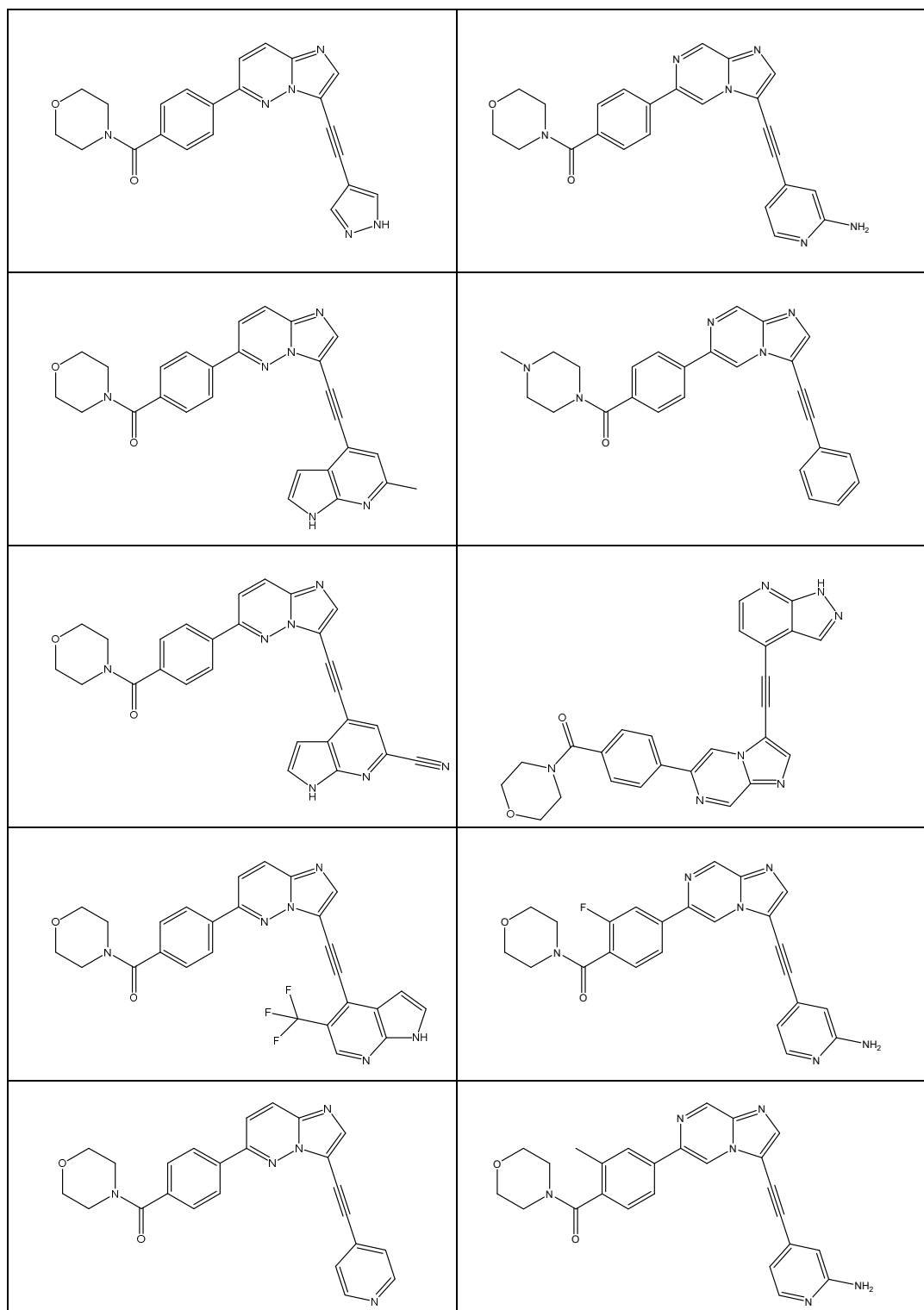


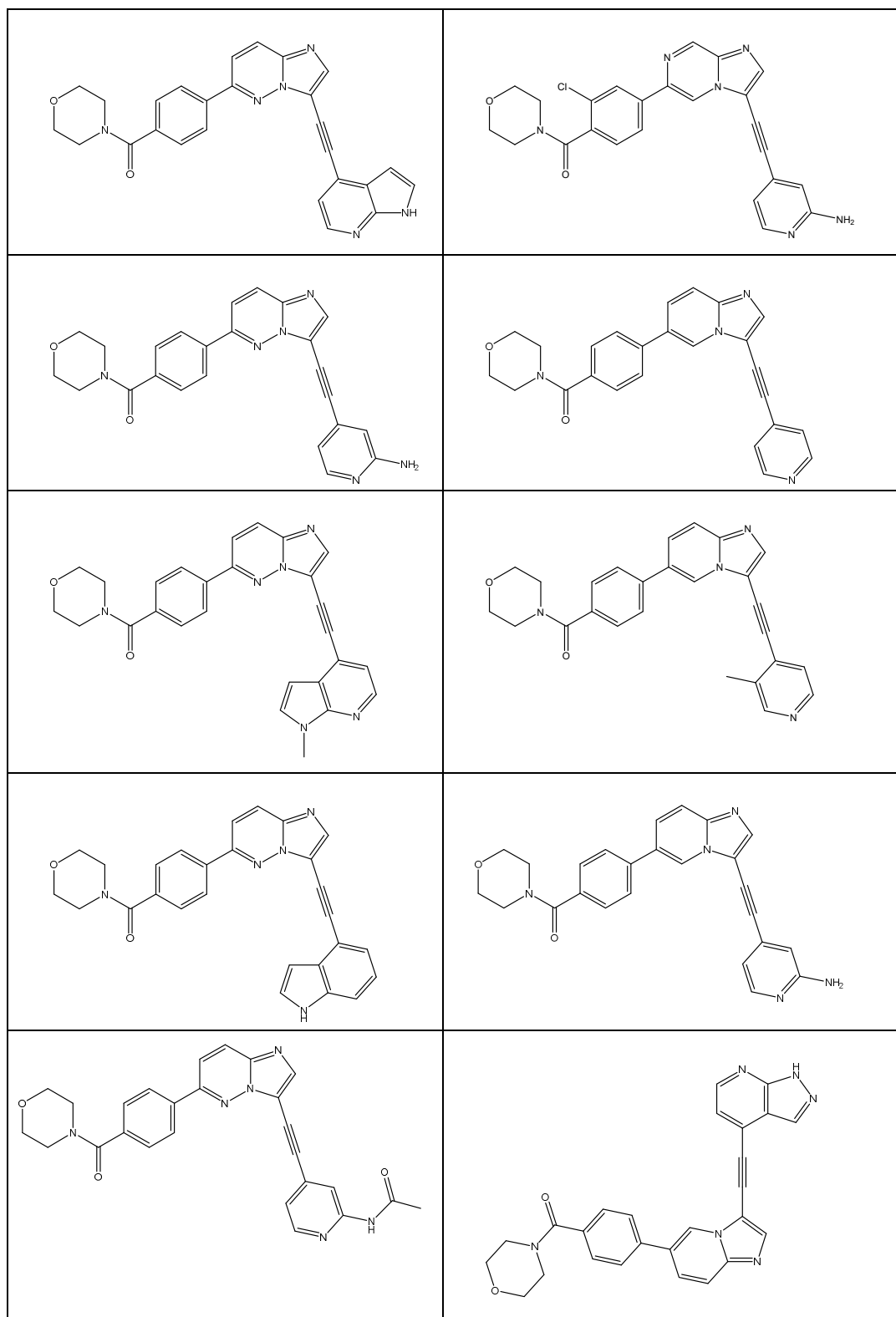


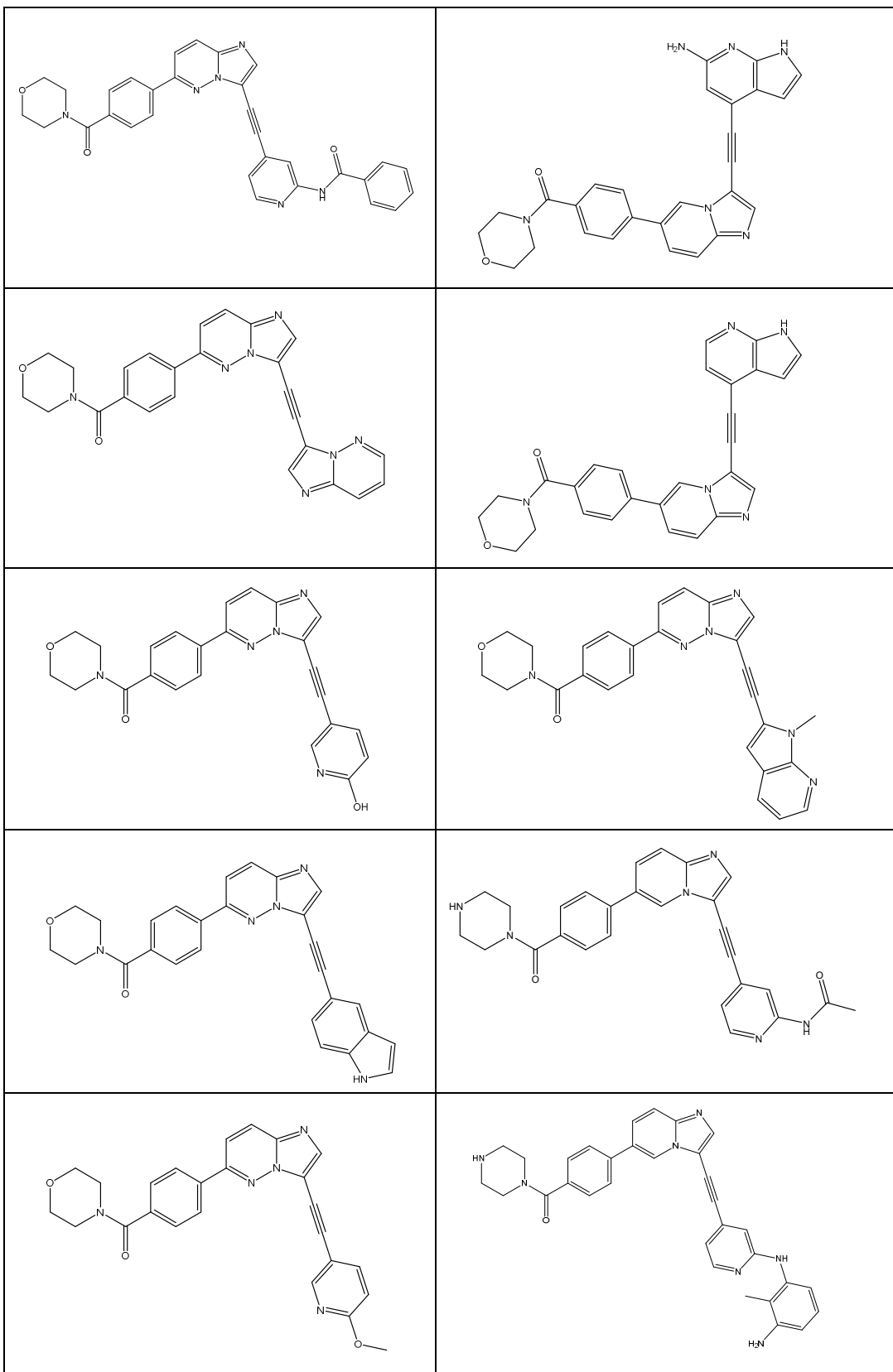


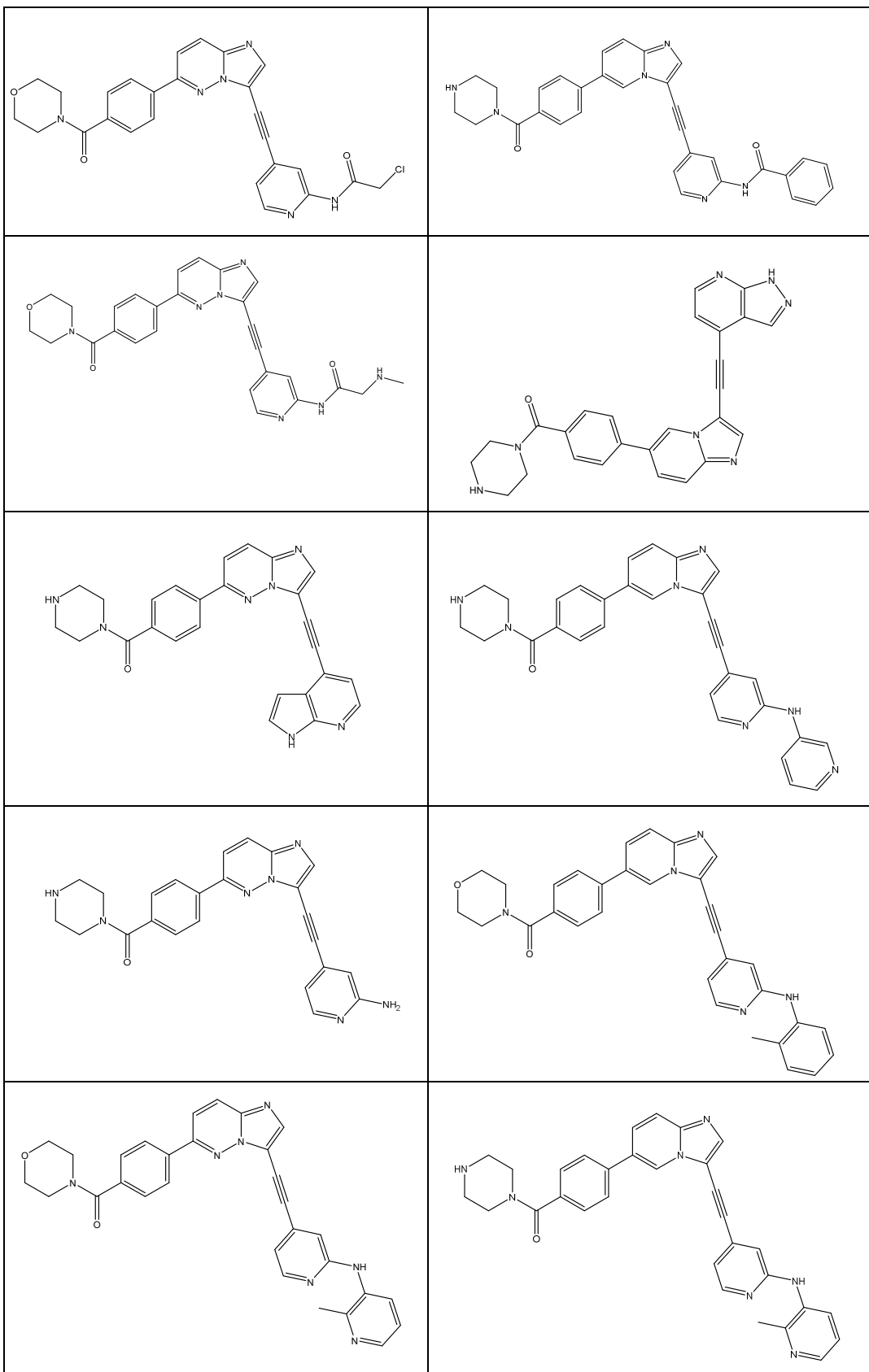


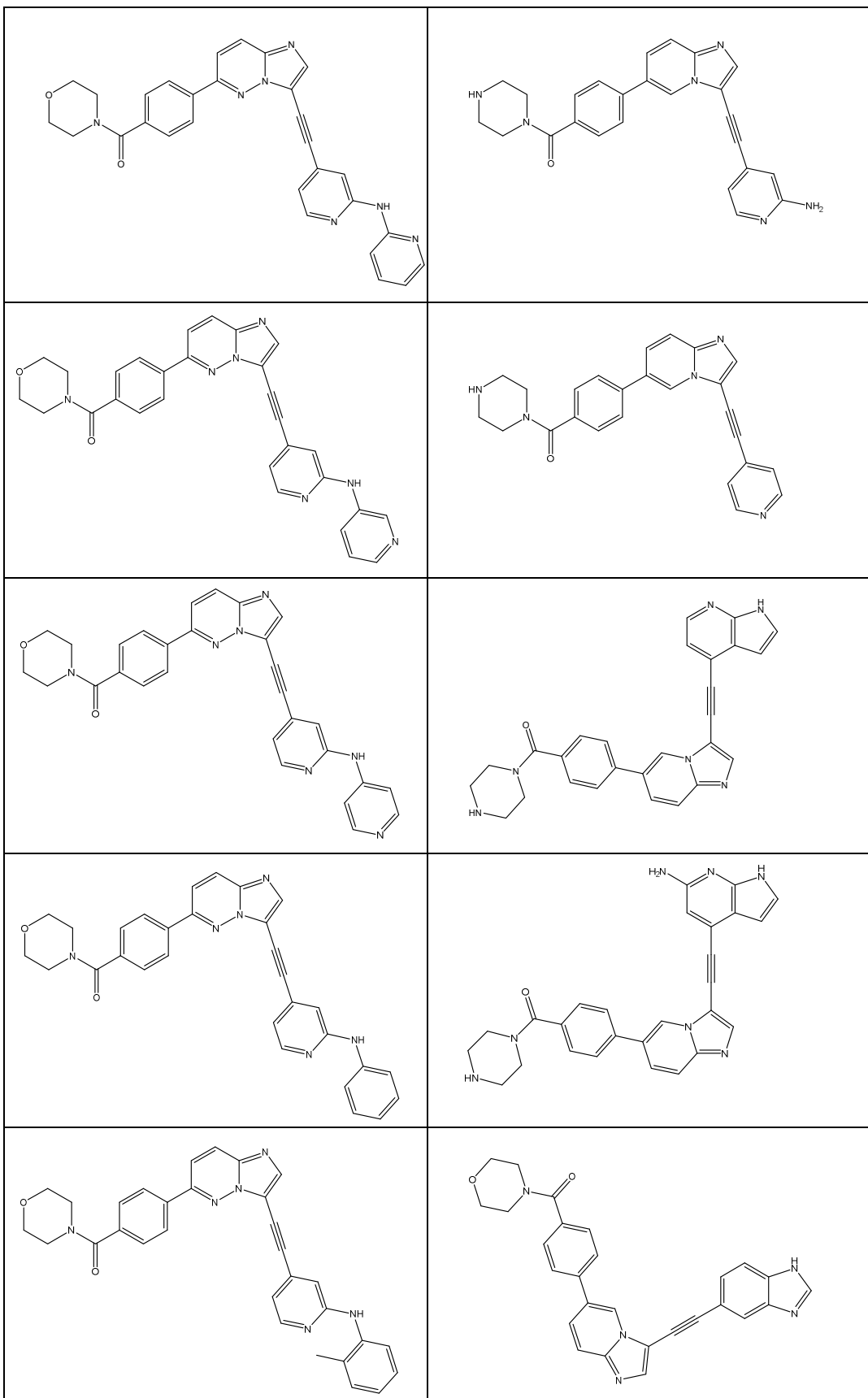


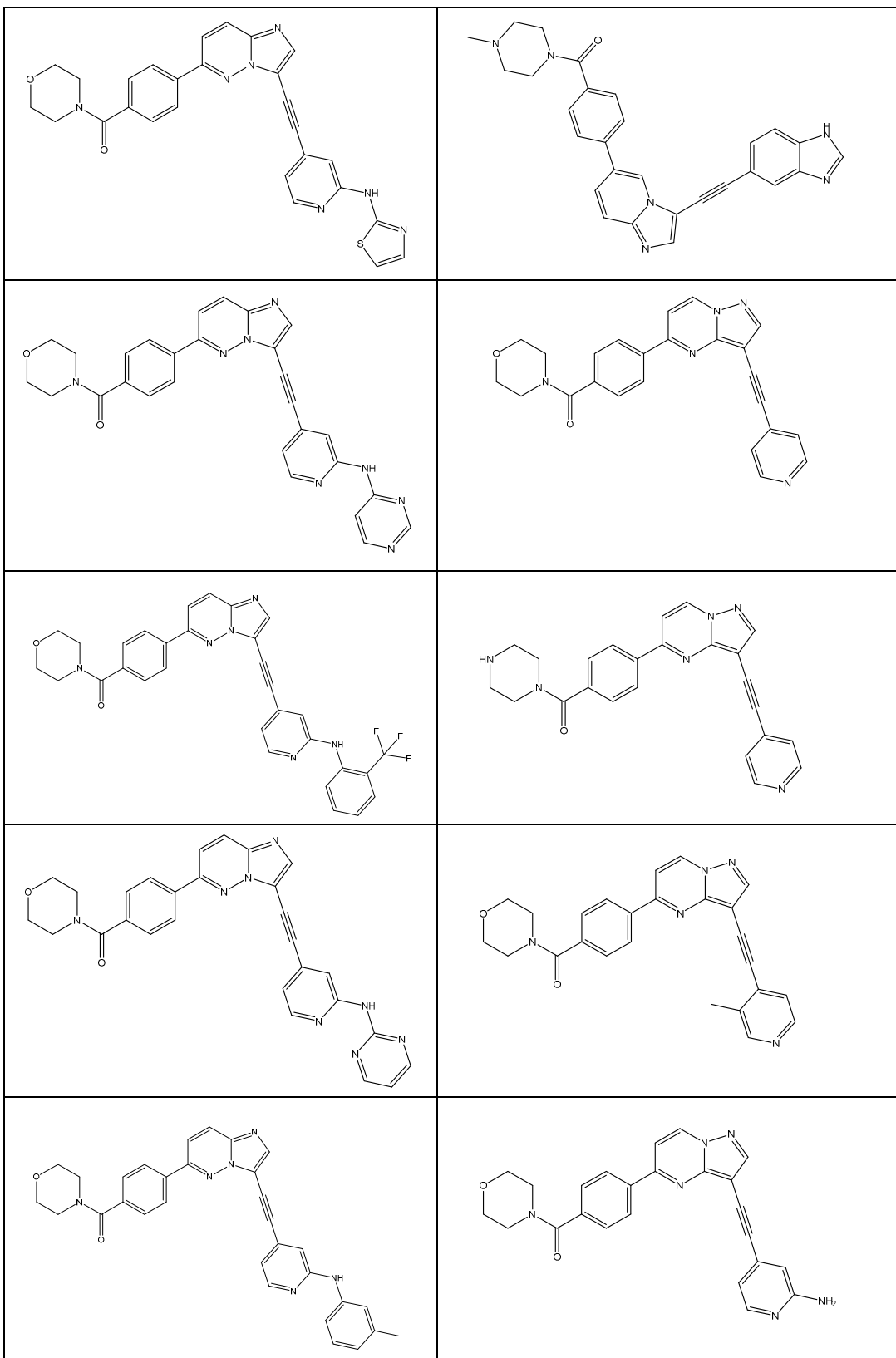


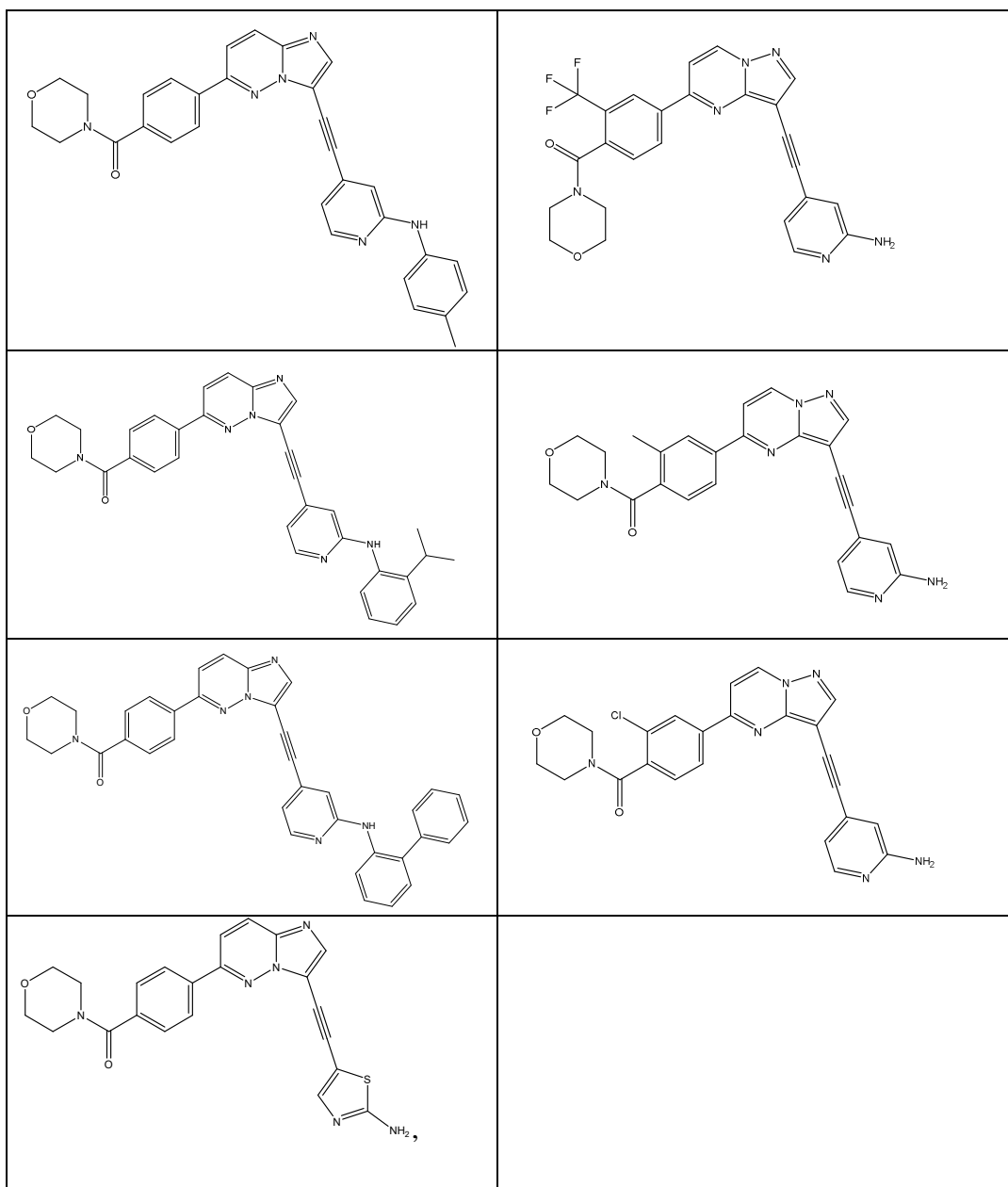












or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a compound of any one of claims 1 to 22 and a pharmaceutically acceptable excipient, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound.

24. A compound of any one of claims 1 to 22, for use in therapy.

25. Use of the compound of any one of claims 1 to 22 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.