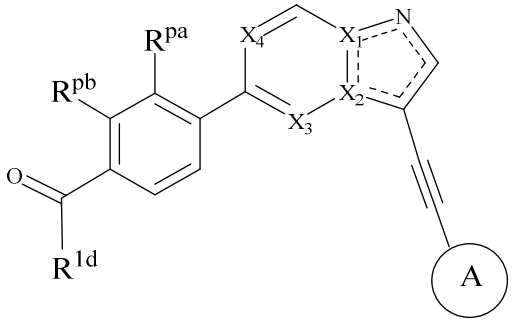
[00011b] In some embodiments, there is provided a compound of Formula (**I**):



(**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^{1d} 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,

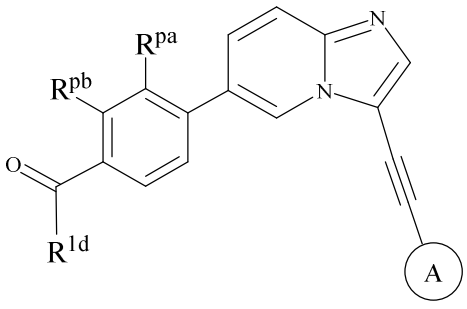
Ring A is phenyl, five-membered heteroaryl, six-membered heteroaryl or 5,6-bicyclic heteroaryl, each optionally substituted with one or more R^{RA};

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.

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



(**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;

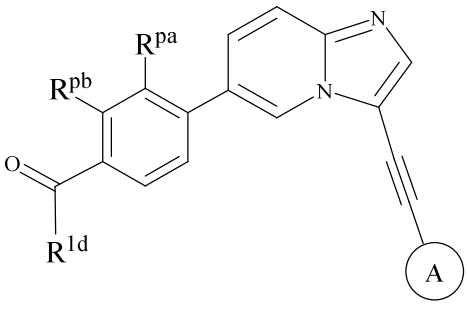
R^{pb} is independently hydrogen, halogen, CN, $-OR^A$, $-N(R^B)_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, or optionally substituted heteroaryl;

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 heteroaryl, 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.

[00011d] In some embodiments, there is provided a compound of Formula (**VII-a**):



(**VII-a**)

or a pharmaceutically acceptable salt thereof,

wherein

R^{1d} 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 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 Mendelsohnn's Syndrome), and cancer such as breast, protate, 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 excipeient, 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.

EQUIVALENTS AND SCOPE

[000405] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[000406] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[000407] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of

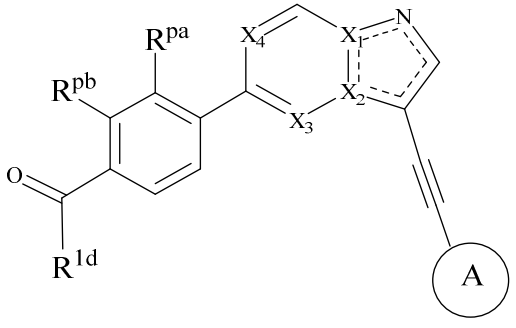
the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[000407a] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

[000408] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

1. A compound of Formula (**I**):



(**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^{1d} 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,

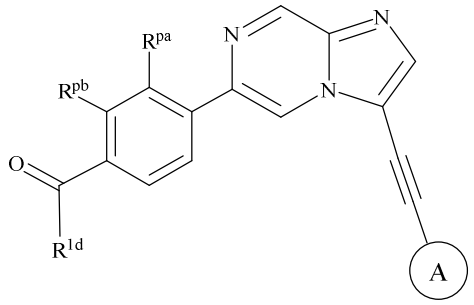
Ring A is phenyl, five-membered heteroaryl, six-membered heteroaryl or 5,6-bicyclic heteroaryl, each optionally substituted with one or more R^{RA};

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;

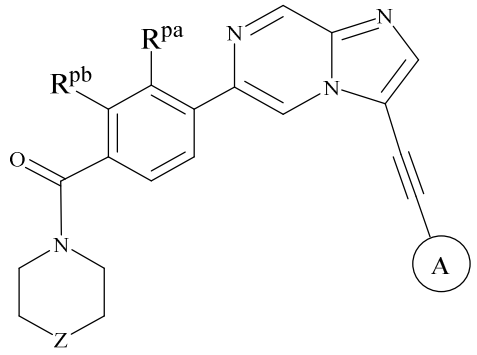
each instance of R^{AO} is independently hydrogen, C_{1-6} alkyl, or aryl;

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.

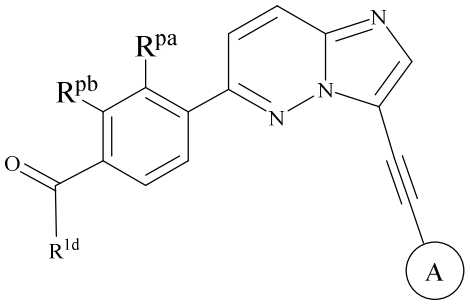
2. The compound of claim 1, wherein the compound is of Formula (**III-a**), (**III-b**), (**V-a**), or (**V-b**):



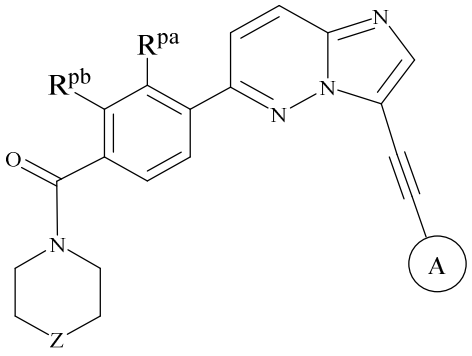
(**III-a**),



(**III-b**),



(**V-a**), or



(**V-b**),

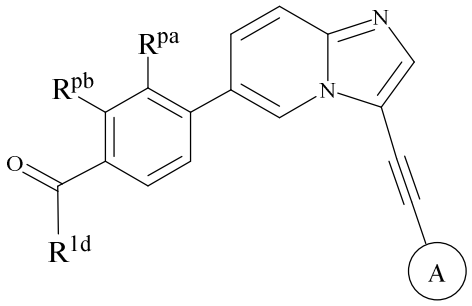
wherein

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**):



(**VII-a**)

or a pharmaceutically acceptable salt thereof,

wherein

R^{1d} 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;

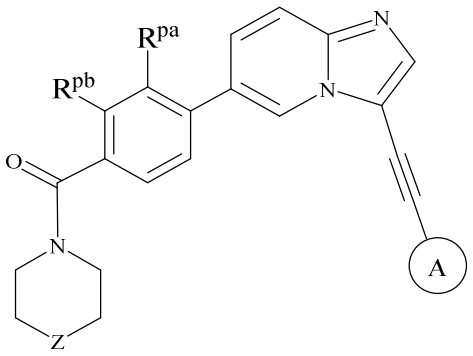
Ring A is phenyl, five-membered heteroaryl, six-membered heteroaryl, or 5,6-bicyclic heteroaryl, each optionally substituted with one or more R^{RA};

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**):



(**VII-b**)

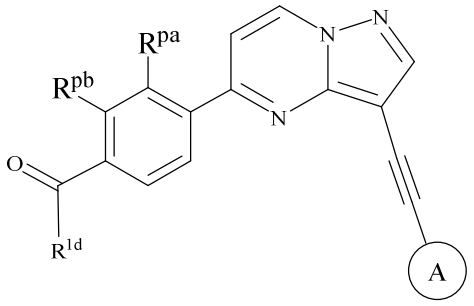
or a pharmaceutically acceptable salt thereof,

wherein

Z is –O– or –NR^{NZ}-; and

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

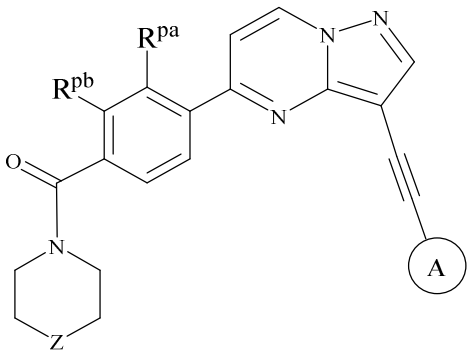
5. The compound of claim 1, wherein the compound is of Formula (**IX-a**):



(**IX-a**)

or a pharmaceutically acceptable salt thereof.

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



(**IX-b**)

or a pharmaceutically acceptable salt thereof,

wherein

Z is –O– or –NR^{NZ}–; and

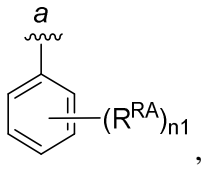
each instance of R^{NZ} is independently hydrogen, or C_{1-6} alkyl.

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:



,

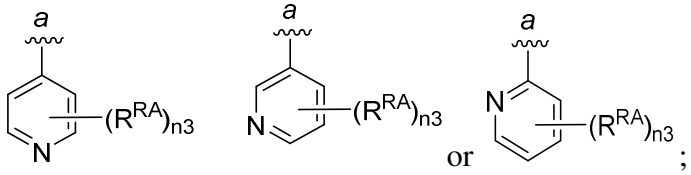
wherein

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:



or ;

wherein

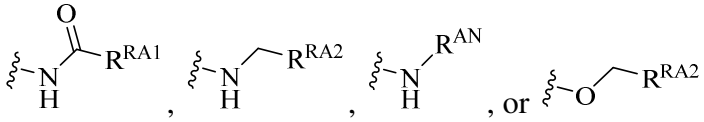
a indicates the point of attachment to the alkyne;

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:



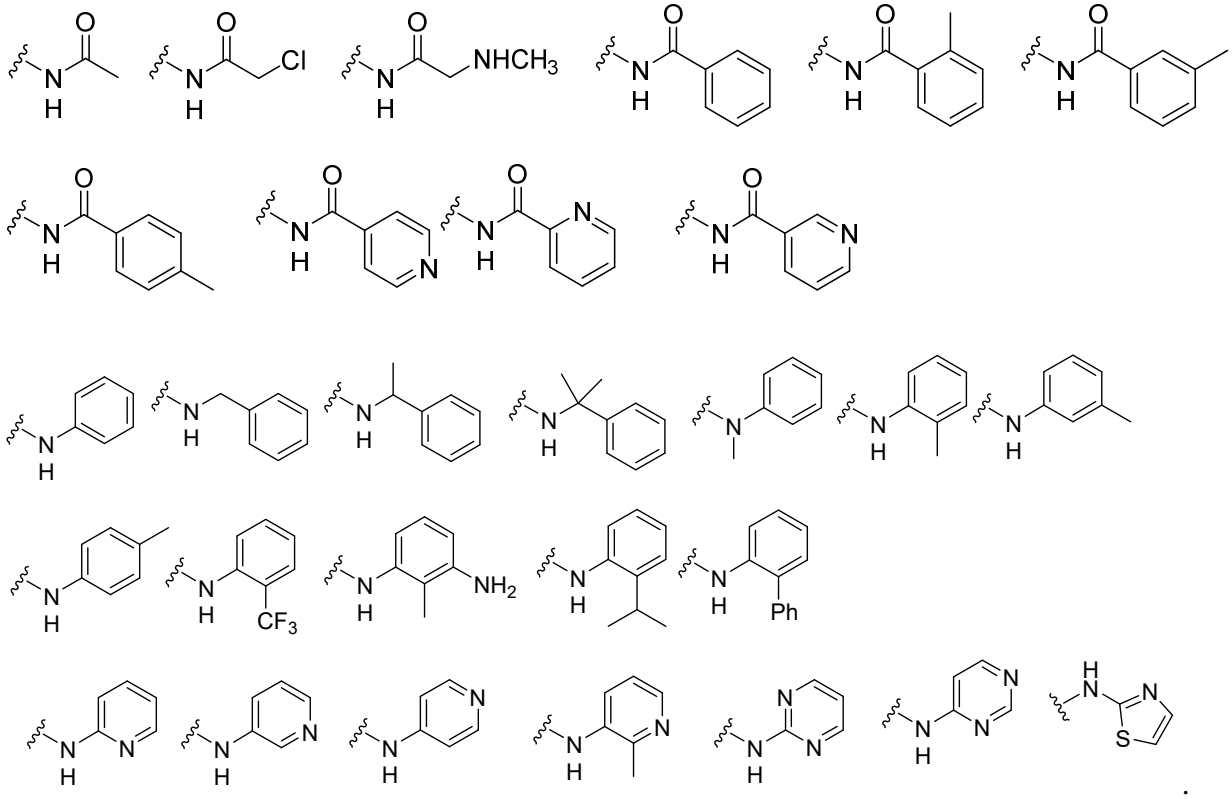
, , , or

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;

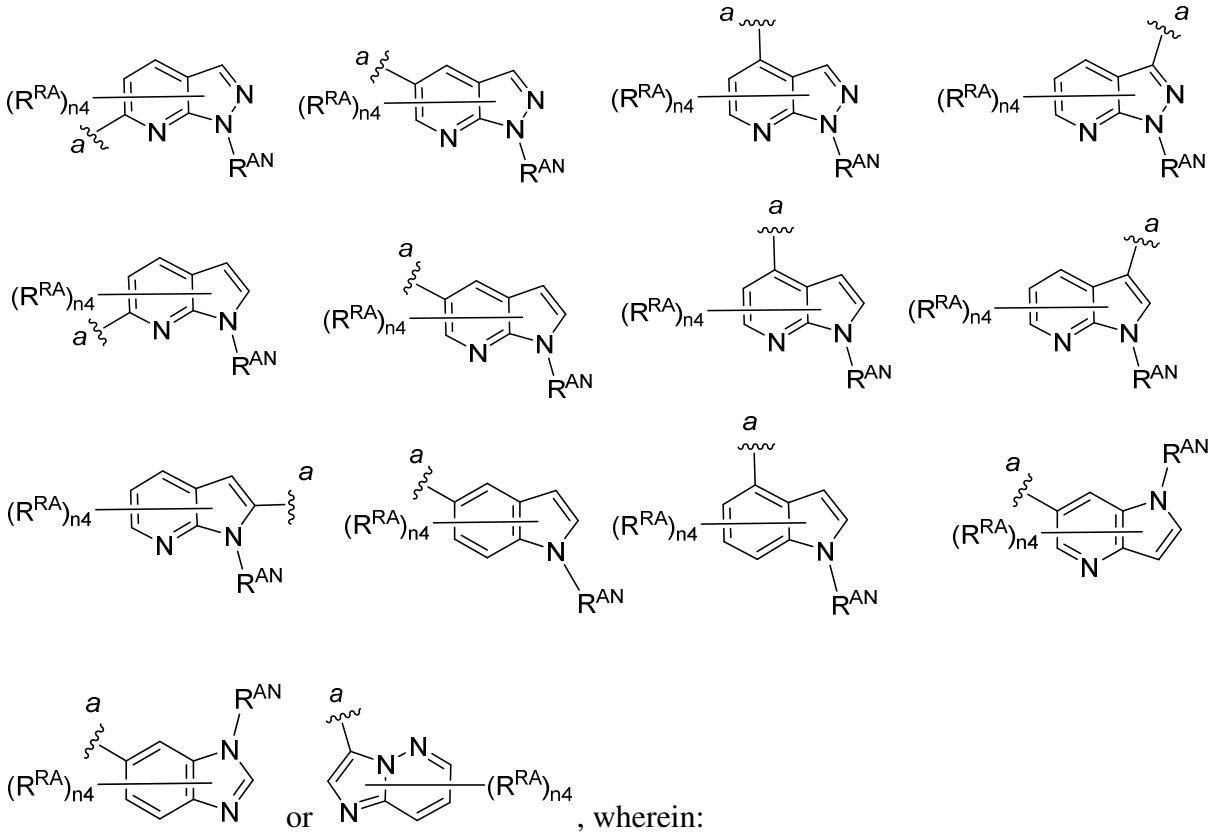
or wherein R^{RA} is one of the following formulae: hydrogen, -Ph, -OH, $-NH_2$, $-OCH_3$, -OPh, -Cl, $-CF_3$, $-CH_3$,



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. The compound of claim 12, wherein Ring A is one of the following formulae:



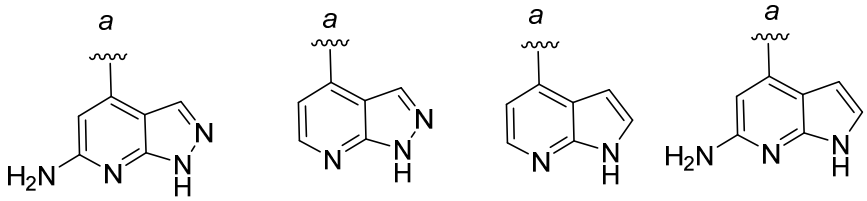
, wherein:

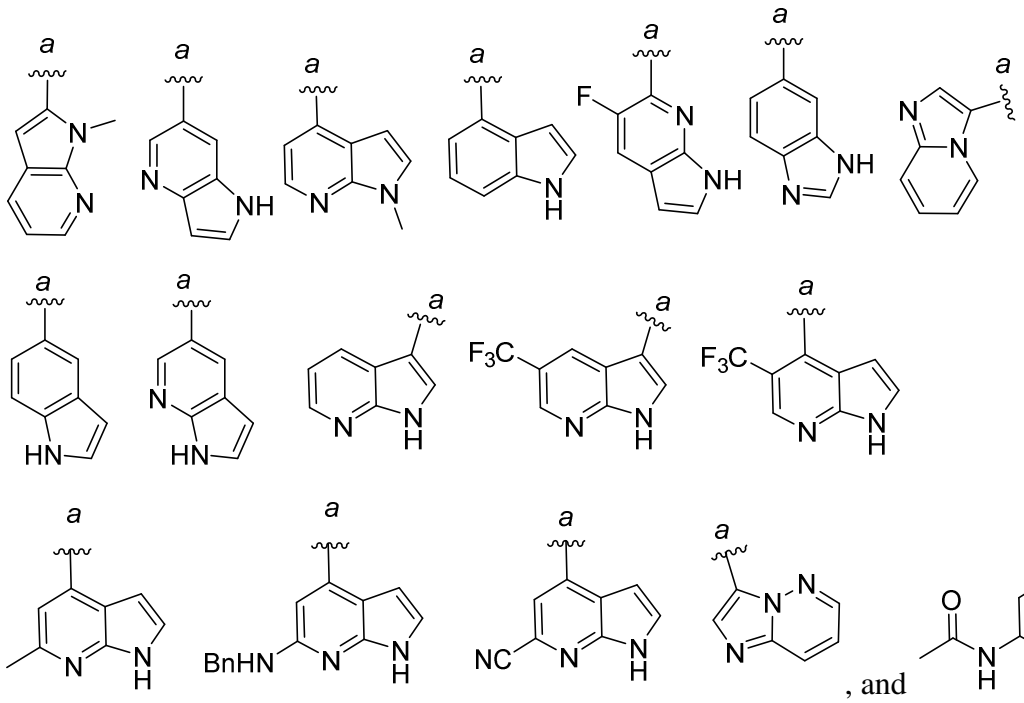
a indicates the point of attachment to the alkyne;

R^{RA} and R^{AN} and as defined in claim 3; and

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

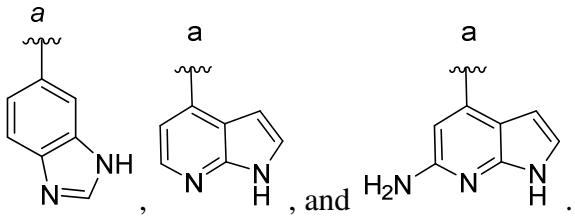
15. The compound of claims 13 or 14, wherein Ring A is selected from the group consisting of optionally substituted groups of the formula:





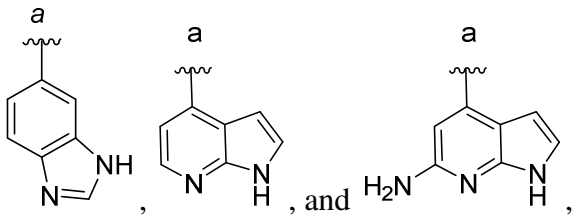
, and .

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



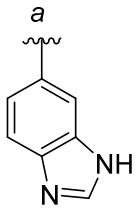
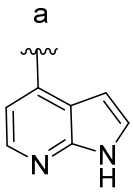
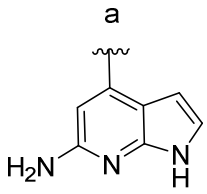
, , and .

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



, , and , which are each optionally substituted with $C_{1\text{-}6}$ alkyl optionally substituted with one to three halogen.

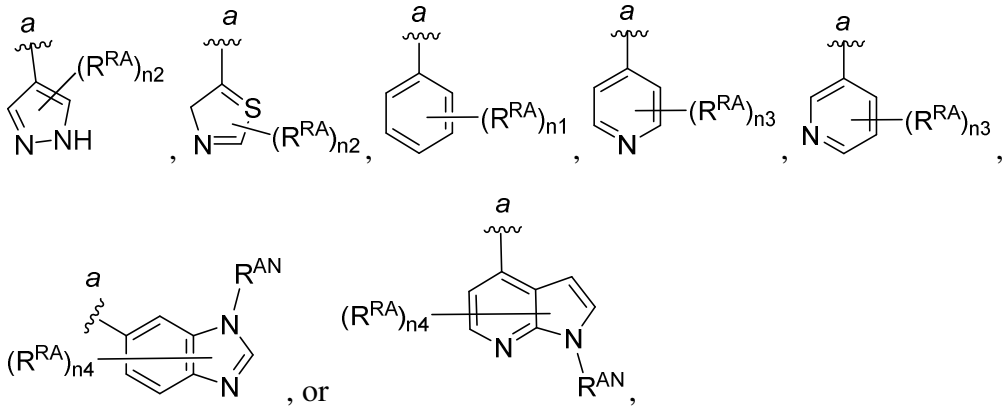
18. The compound of claim 12, wherein Ring A is selected from the group consisting of groups of the formula:



, and  , which are each optionally substituted with methyl, ethyl, or propyl, each optionally substituted with one to three halogen.

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. The compound of claim 4, wherein Ring A is one of the following formulae:



wherein:

a indicates the point of attachment to the alkyne;

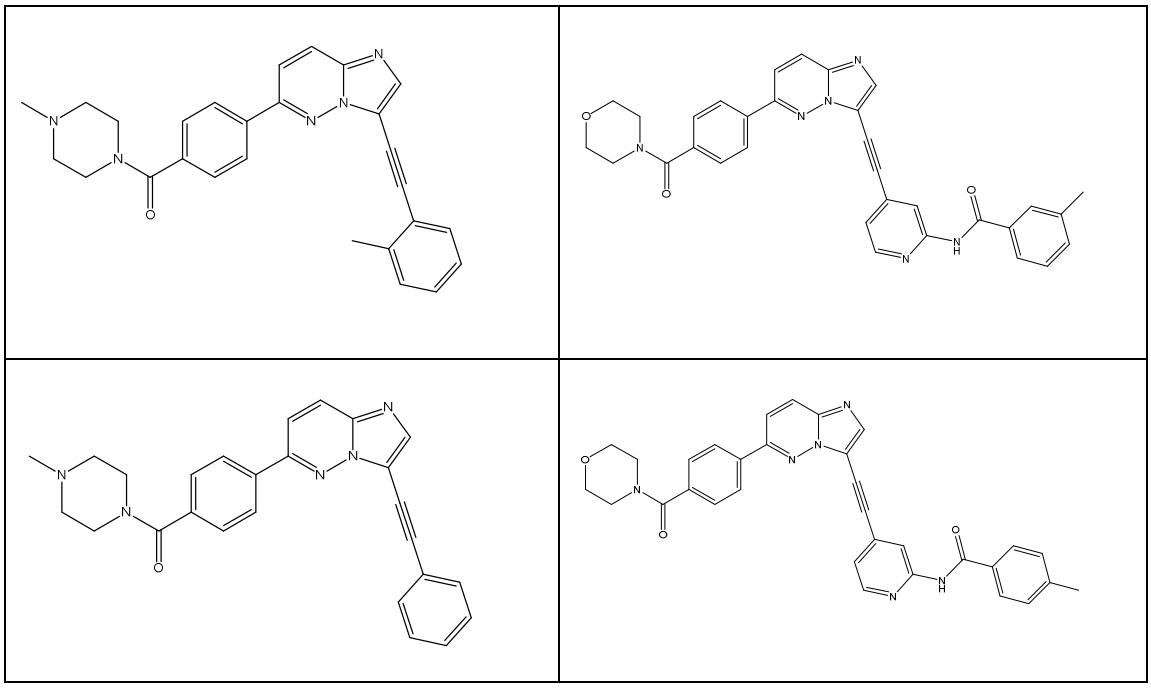
R^{RA} and R^{AN} are as defined in claim 3;

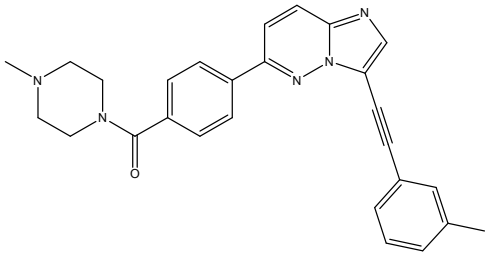
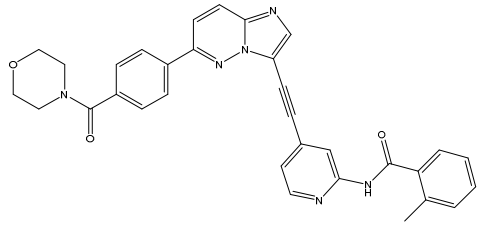
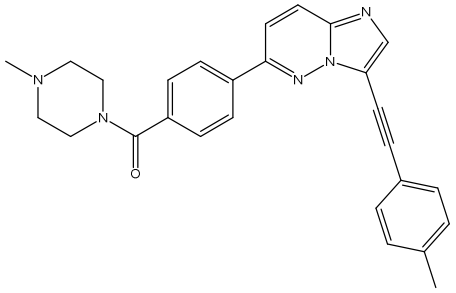
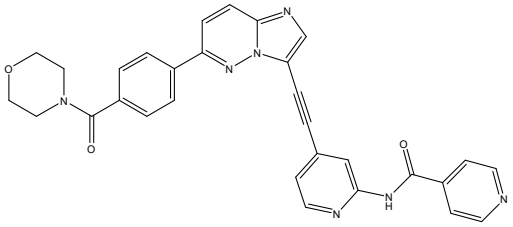
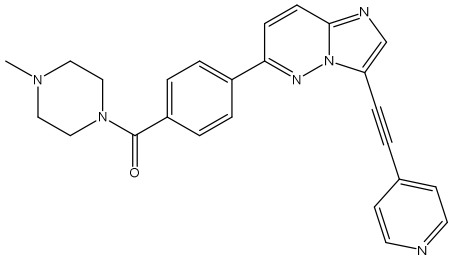
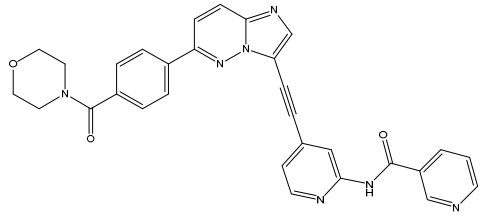
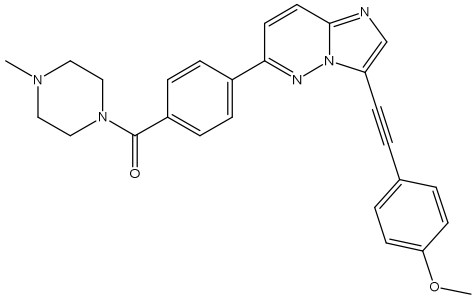
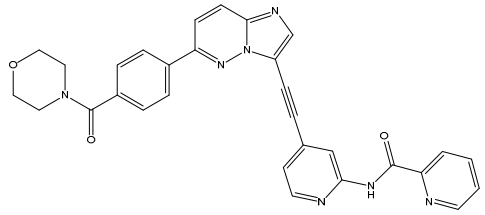
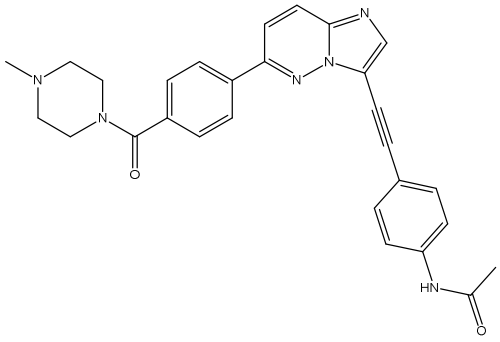
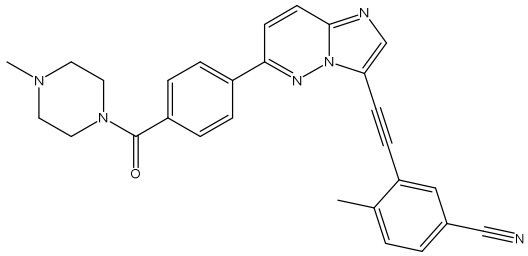
each instance of n2 is independently an integer of 1 or 2;

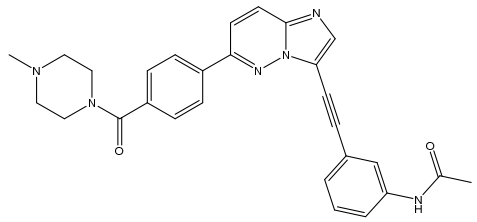
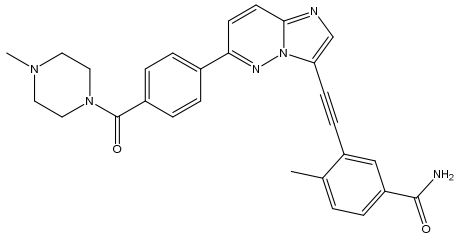
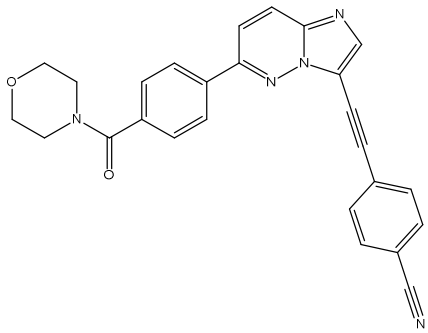
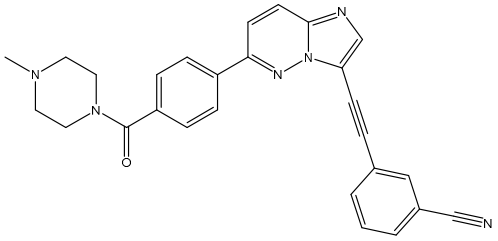
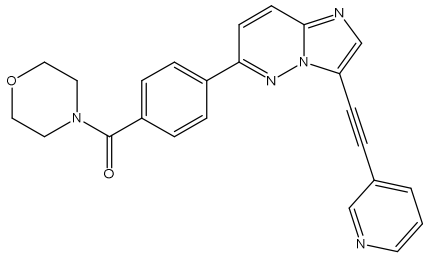
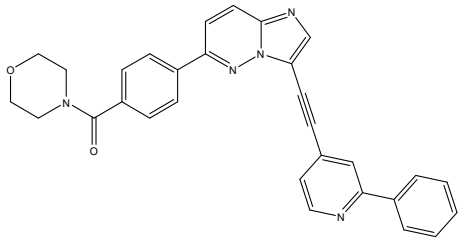
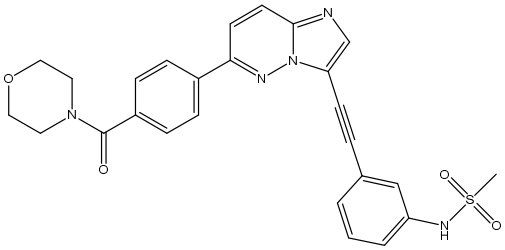
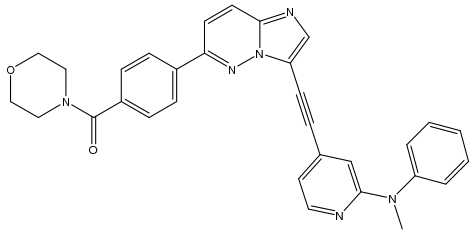
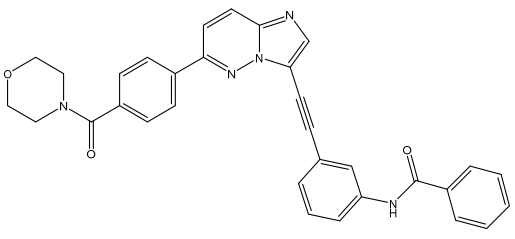
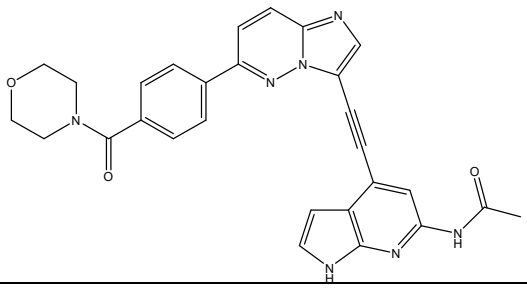
each instance of n3 is independently an integer of 1 to 4, inclusive; and

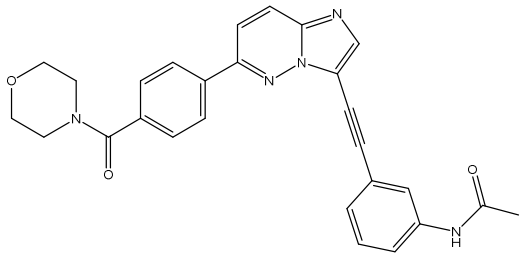
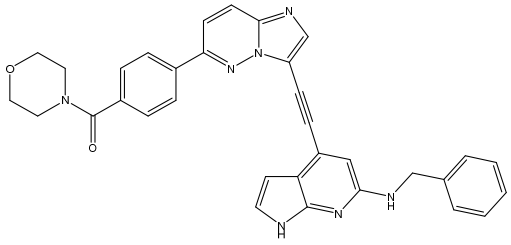
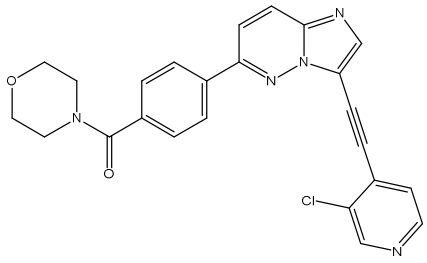
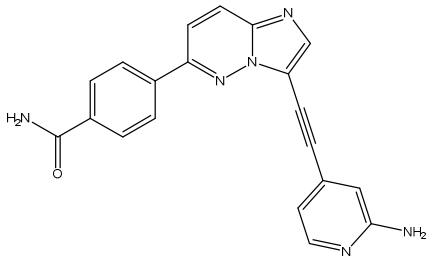
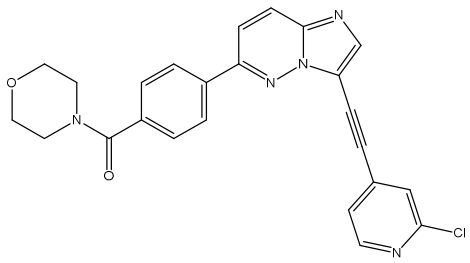
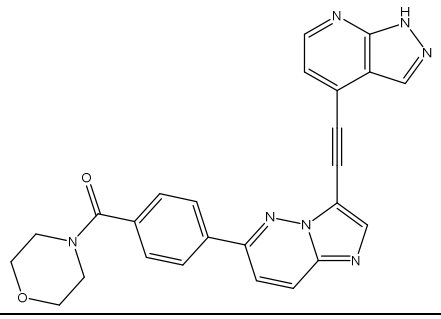
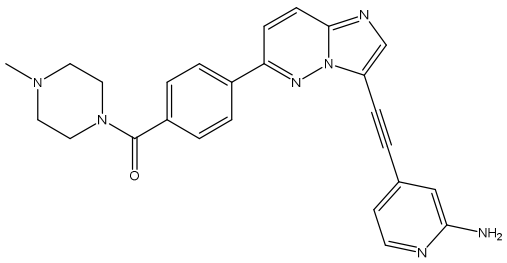
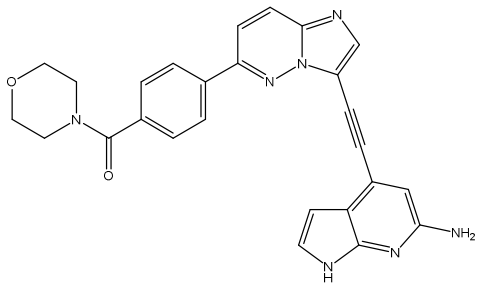
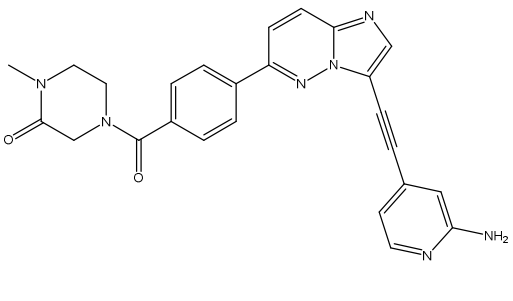
each instance of n4 is independently an integer of 1 to 5, inclusive.

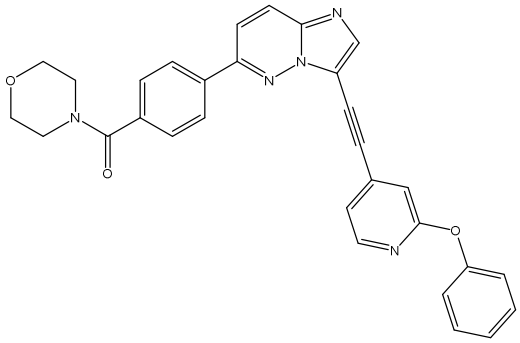
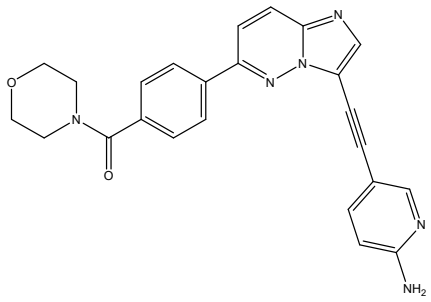
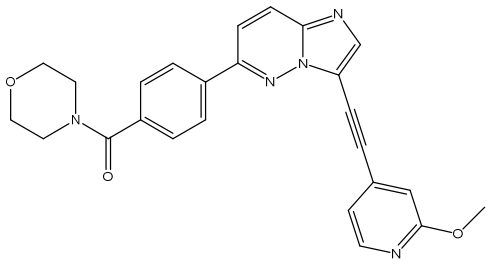
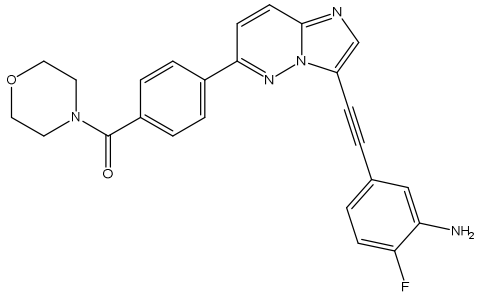
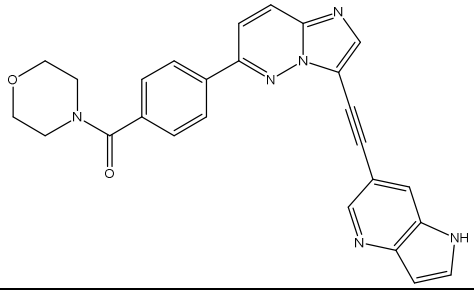
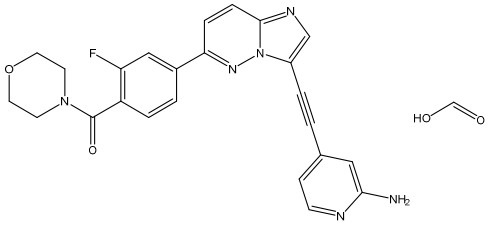
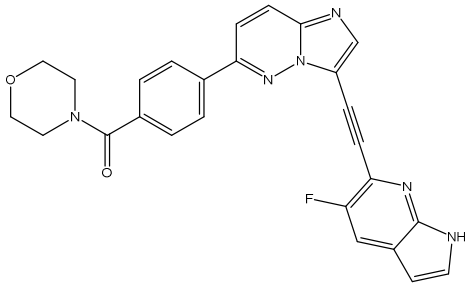
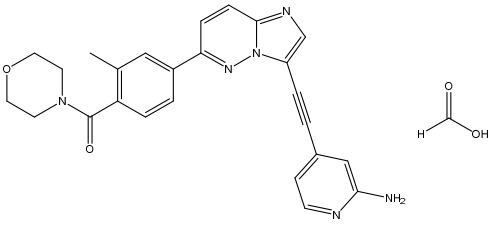
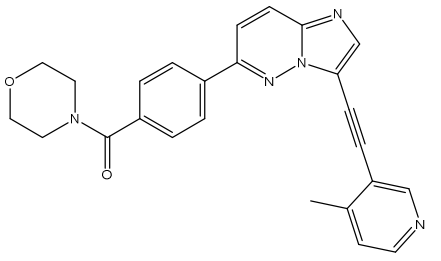
22. A compound of the formula:

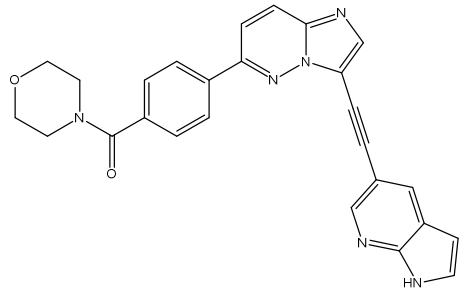
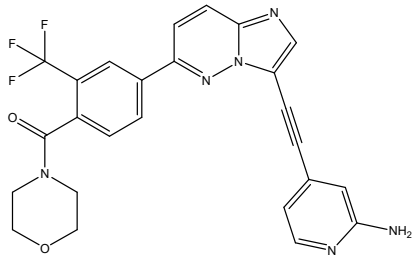
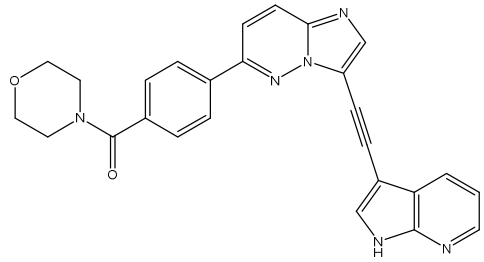
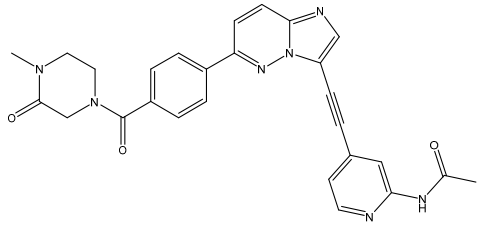
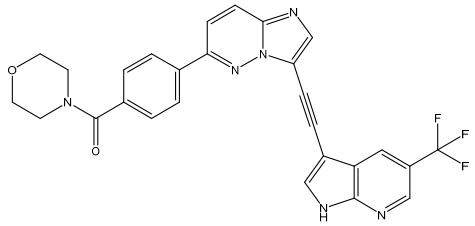
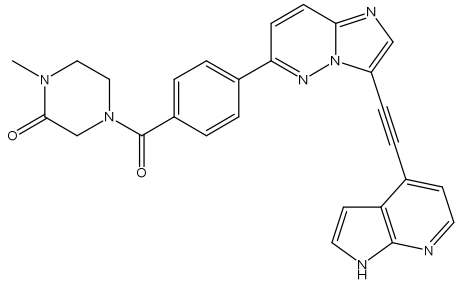
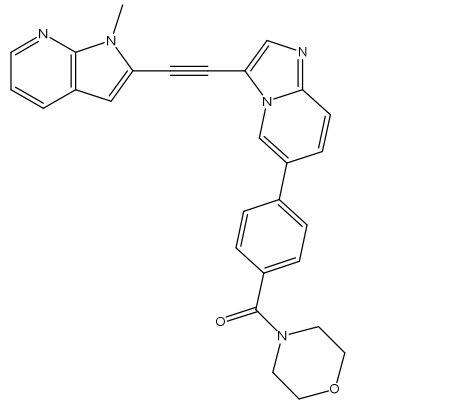
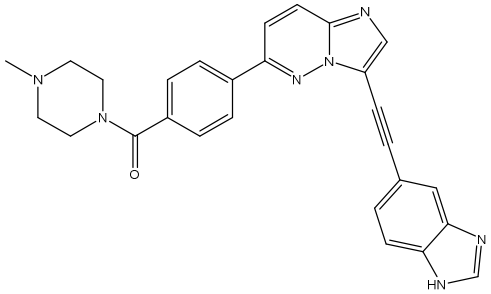
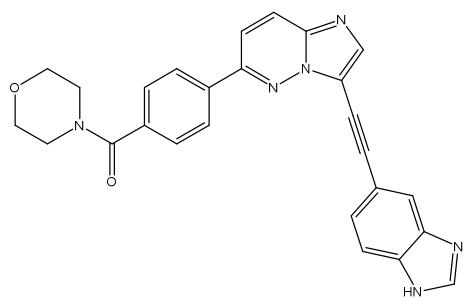
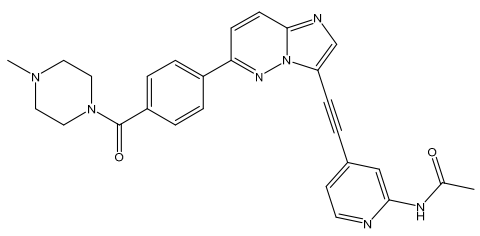


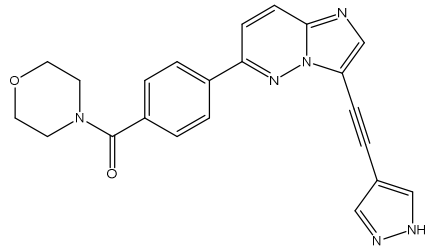
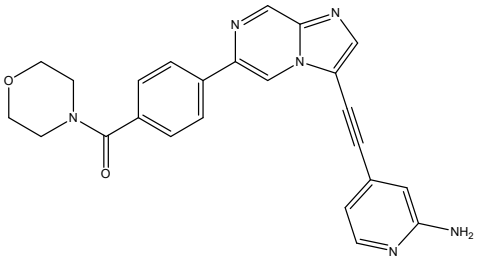
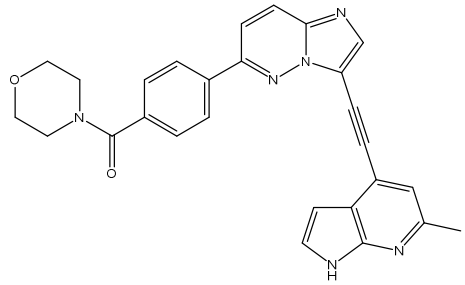
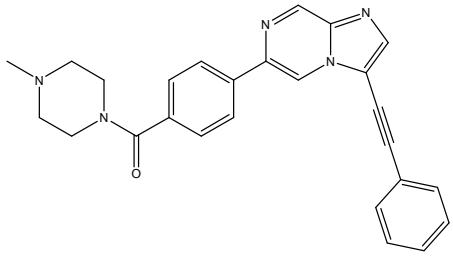
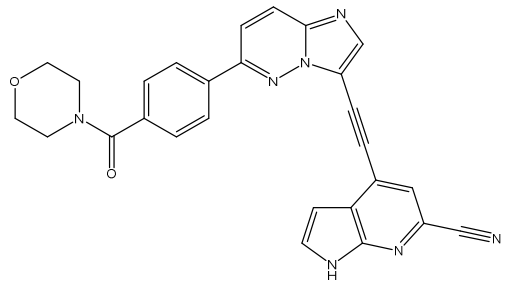
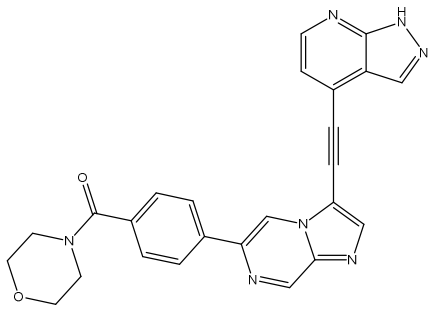
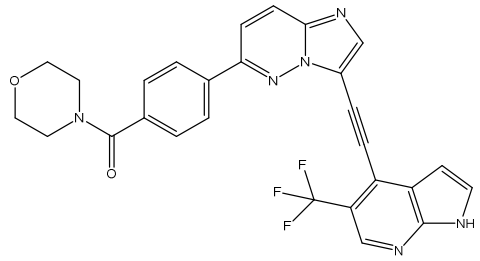
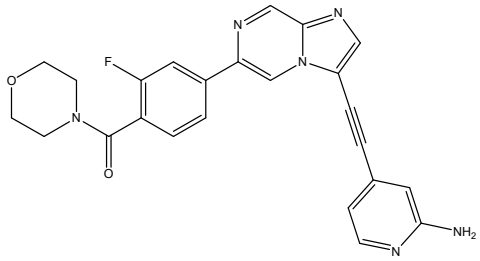
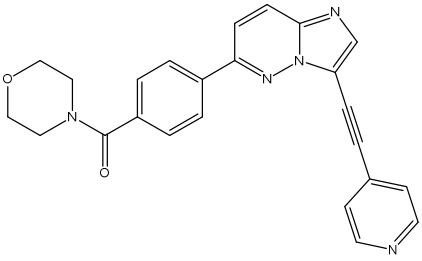
	
	
	
	
	

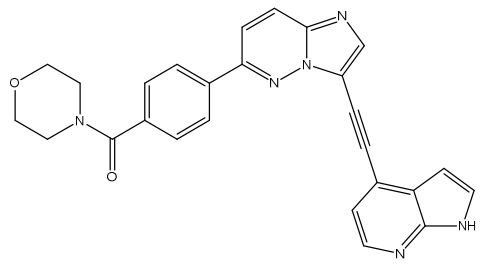
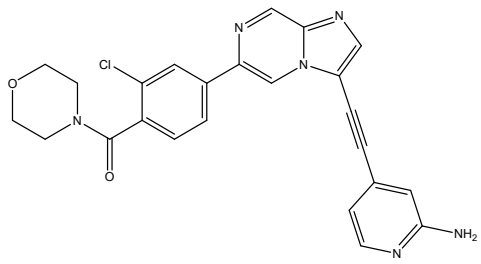
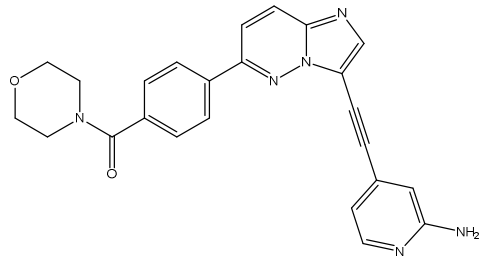
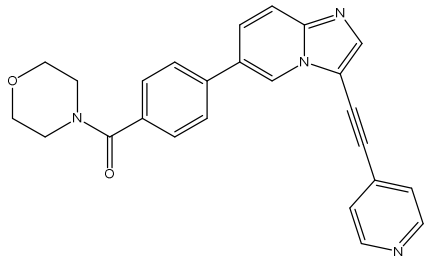
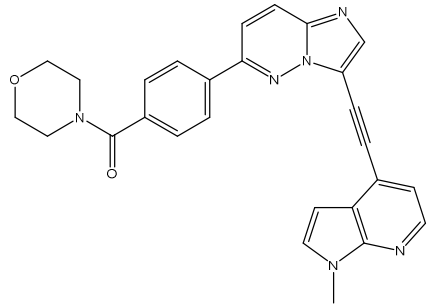
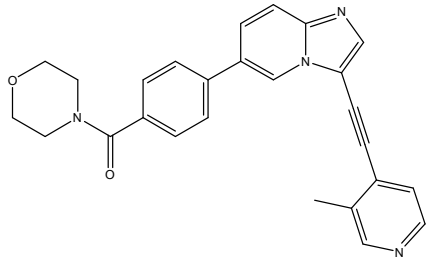
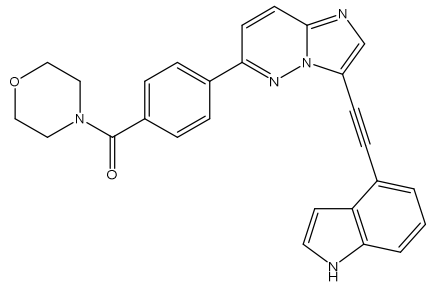
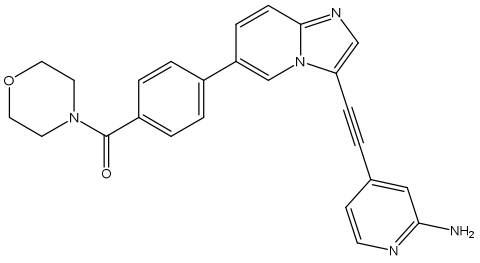
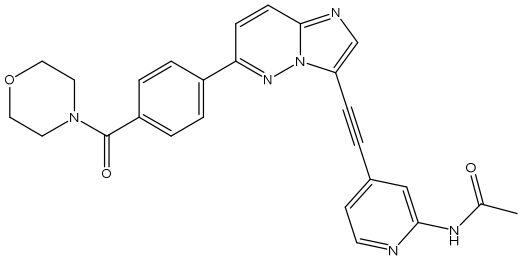
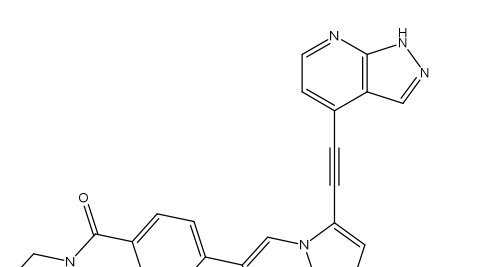
	
	
	
	
	

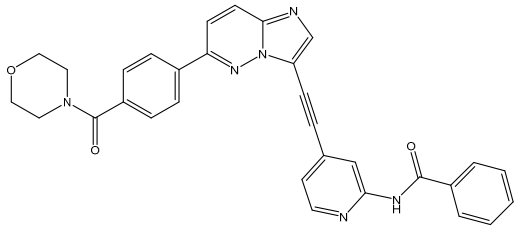
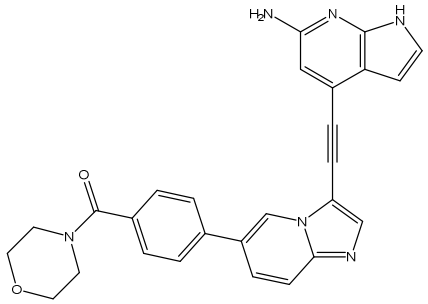
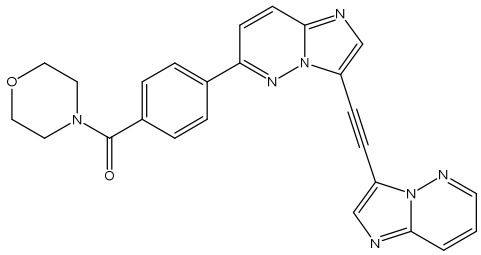
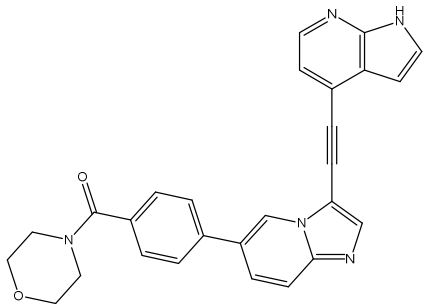
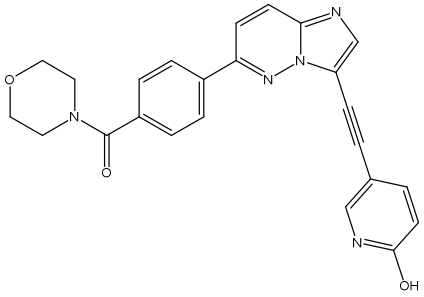
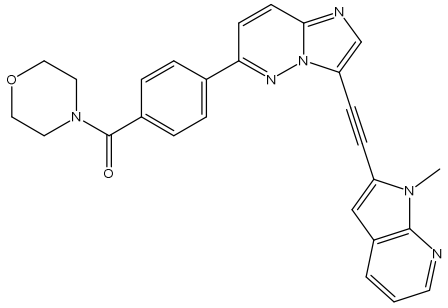
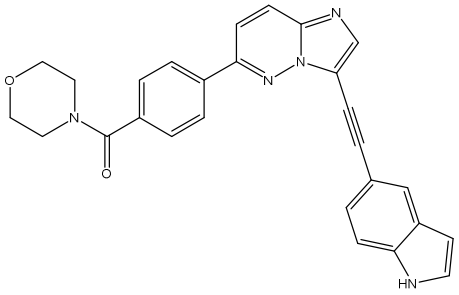
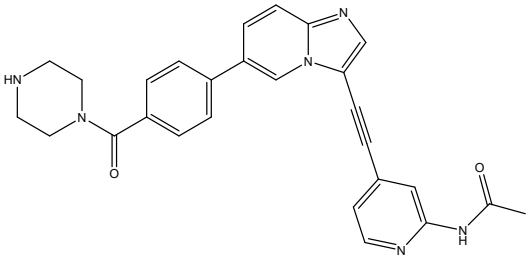
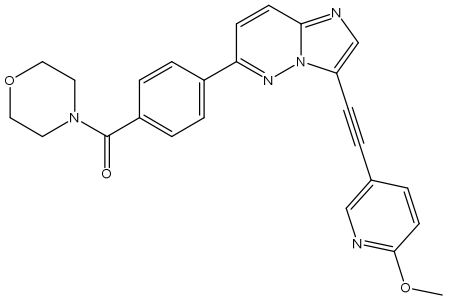
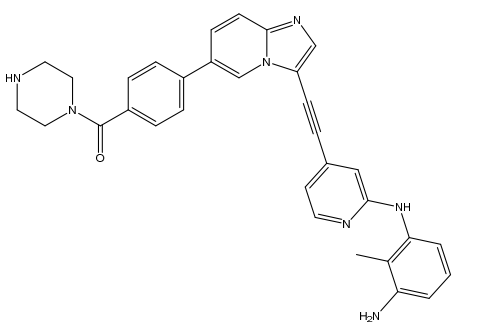
	
	
	
	
	

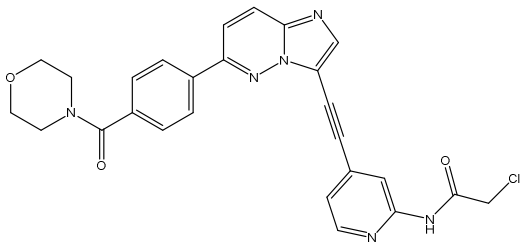
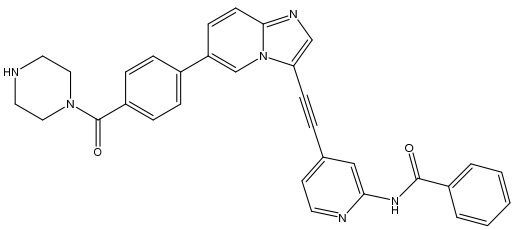
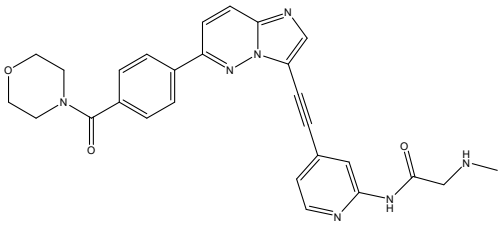
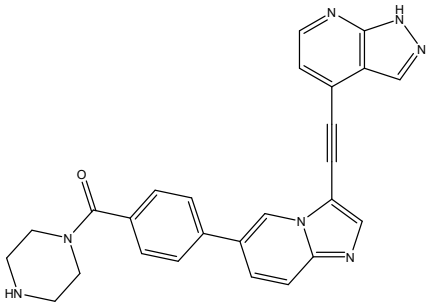
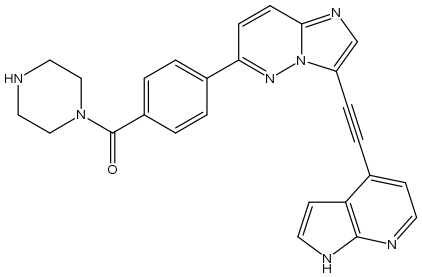
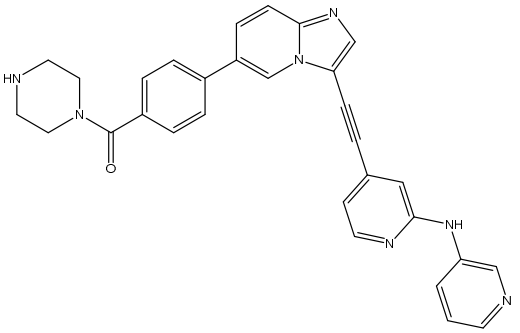
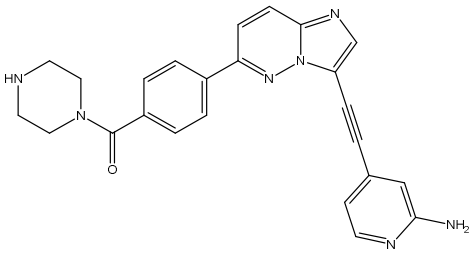
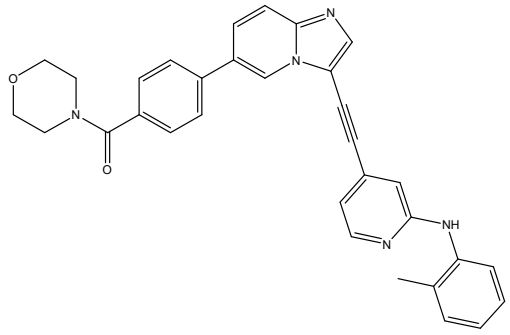
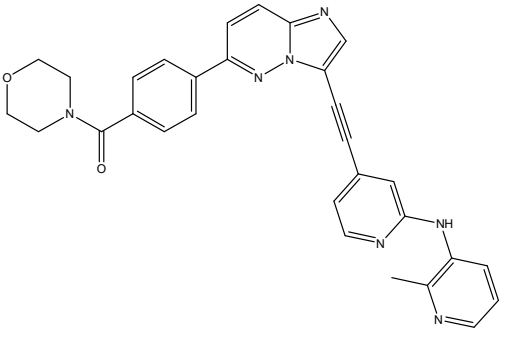
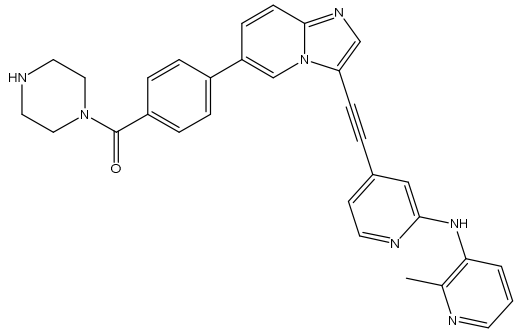
	
	
	
	
	

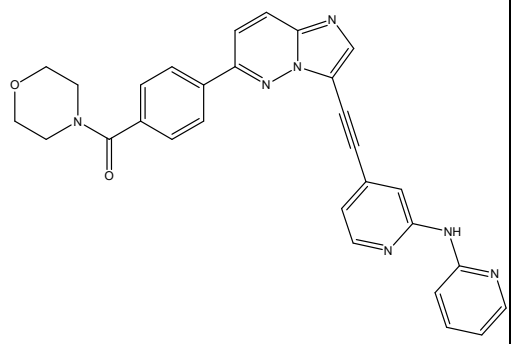
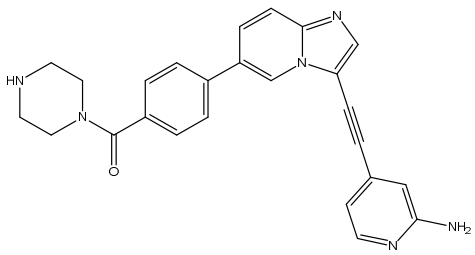
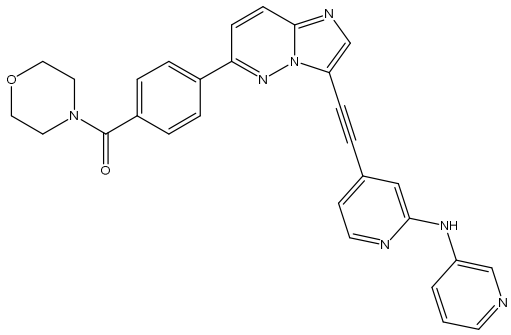
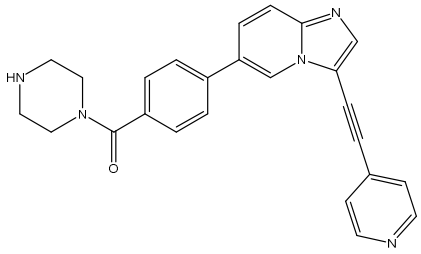
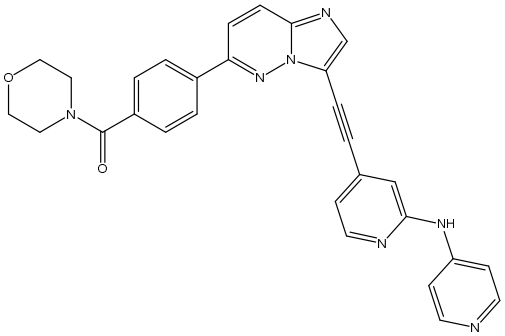
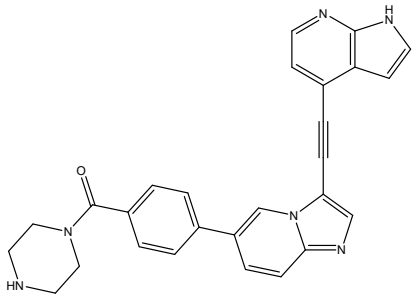
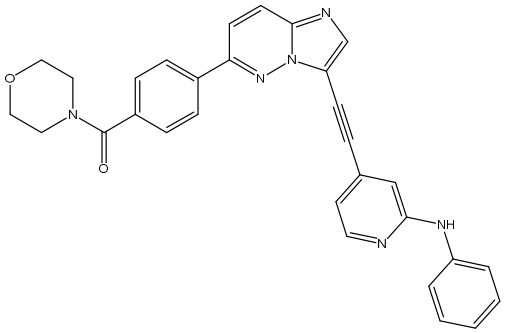
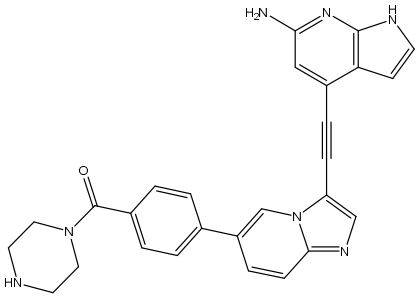
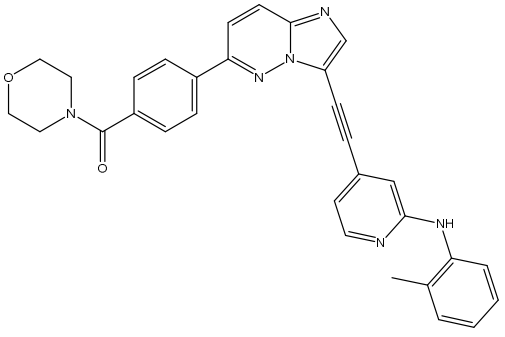
	
	
	
	
	

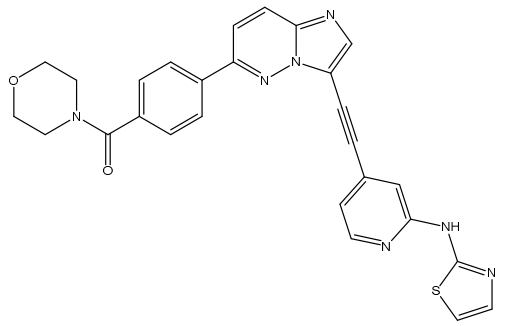
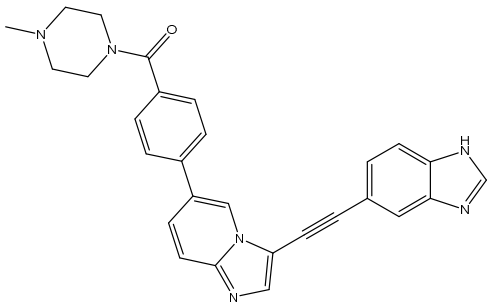
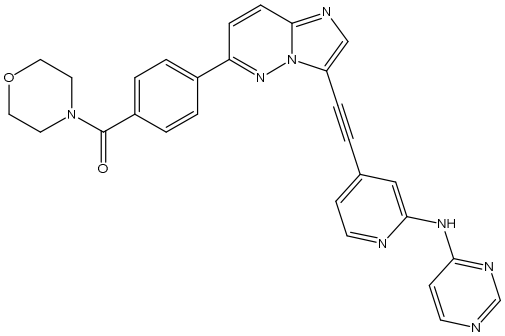
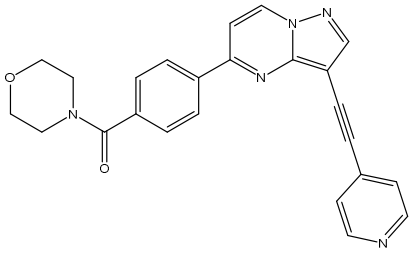
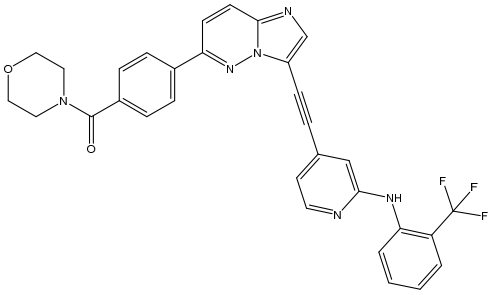
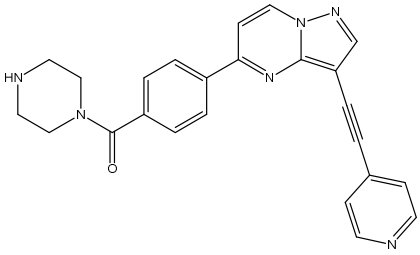
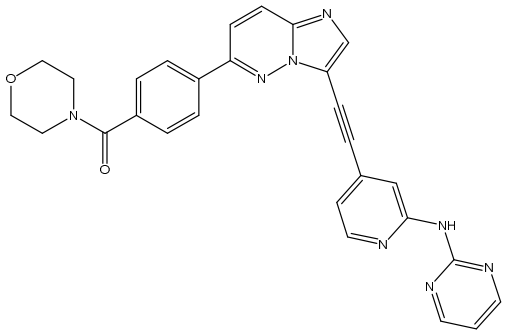
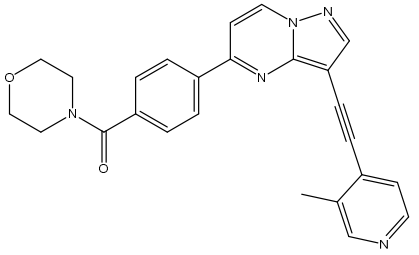
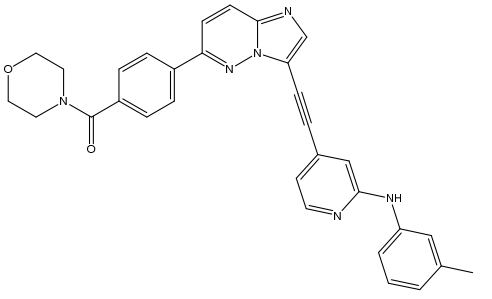
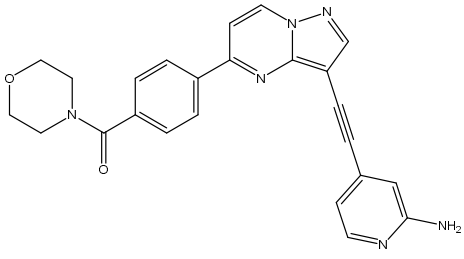
	
	
	
	
	

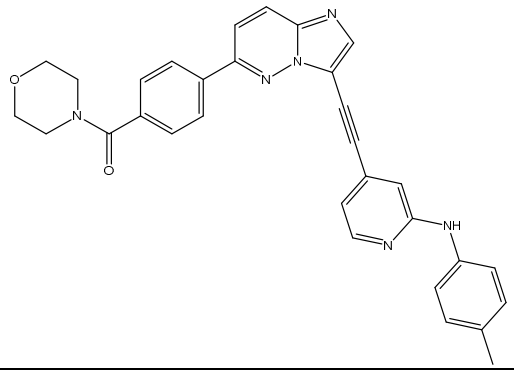
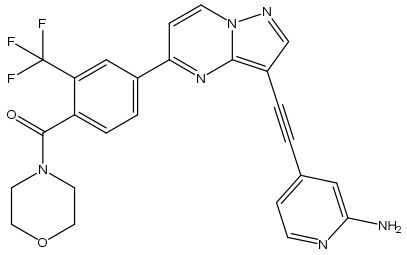
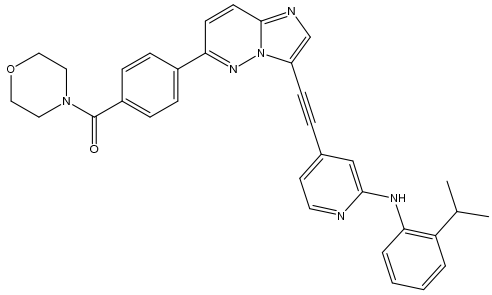
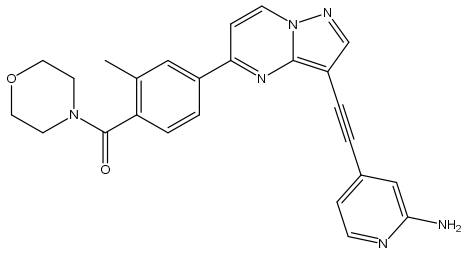
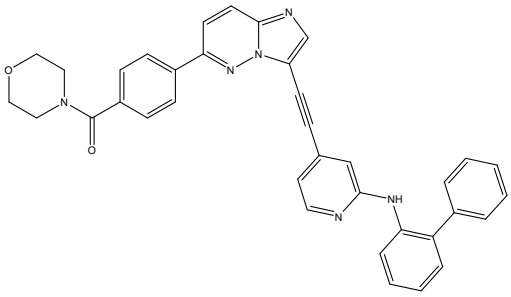
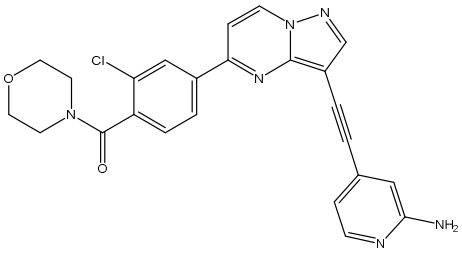
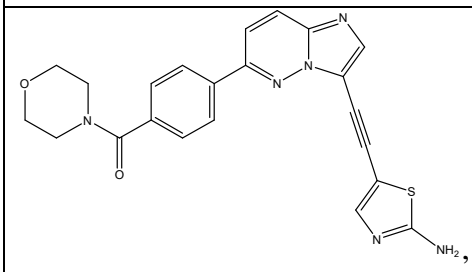
	
	
	
	
	

or a pharmaceutically acceptable salt thereof.

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.