4890. Resistance to FLT3 inhibitors has been reported in the clinic through secondary mutations in *FLT3* including mutations in the tyrosine kinase domain in prior ITD-only mutant tumors (Heidel *et al.*, 2006, Blood 107(1):293-300, Smith *et al.*, 2012, Nature 485(7397):260-263).

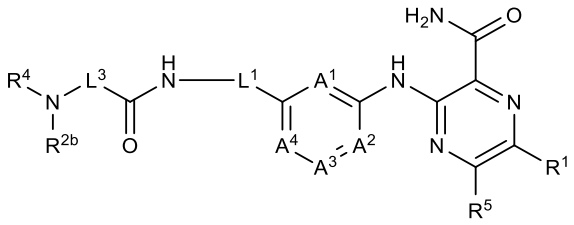
[0011] Despite research in this area, there is still a need to deliver effective compounds for the inhibition of FLT3. Therefore, the object of the present invention is to provide inhibitors of FLT3, pharmaceutical compositions thereof, and methods for the inhibition of FLT3. Also of key importance is to develop inhibitors that will overcome the known resistance mechanisms of co-mutations of ITD that re-awaken the autophosphorylation capabilities of FLT3.

SUMMARY

[0012] Described herein are inhibitors of FLT3. Also described herein are specific heterocyclic inhibitors of FLT3. In some examples, the inhibitors of FLT3 are covalent inhibitors. In some examples, the inhibitors of FLT3 are non-covalent inhibitors.

[0013] Described herein are methods for synthesizing such covalent inhibitors, methods for using such covalent inhibitors in the treatment of diseases (including diseases wherein inhibition of FLT3 provides therapeutic benefit to a patient having the disease). Further described are pharmaceutical compositions that comprise an inhibitor of FLT3 and one or more pharmaceutically acceptable carriers, excipients, or diluents. Also, described herein are compounds and methods of use thereof to inhibit FLT3. In certain examples, the compounds and pharmaceutical compositions described herein are used for the treatment of hematological malignancies, including but not limited to, acute myeloid leukemia.

[0014] In some examples, provided herein are compounds according to Formula (P6-I) having the structure:



(P6-I)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

wherein: each A^1, A^2, A^3, and A^4 is independently –C(R^7)=, or -N=; provided no more than two of A^1, A^2, A^3, and A^4 is N;

each L^1 and L^3 is independently substituted or unsubstituted C_1-C_4 alkylene;

R^1 is H, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl;

R^{2b} is independently H or C_1-C_4 alkyl;

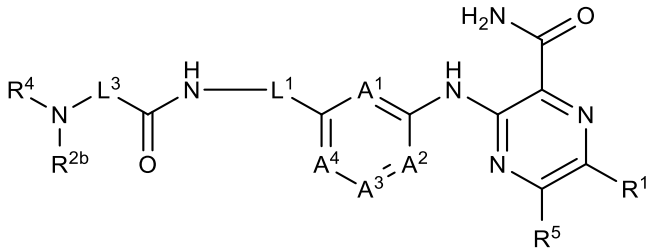
R^4 is i) -C(O)-C(R^{6a})=C(R^{6b})(R^{6c}), ii) -S(O)-C(R^{6a})=C(R^{6b})(R^{6c}), iii) -$S(O)_2$-C(R^{6a})=C(R^{6b})(R^{6c}), or iv) substituted or unsubstituted epoxide;

R^5 is H, Cy, CN, halo, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted haloalkoxy, substituted or unsubstituted alkylamino;

Cy is substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl;
each R^{6a} and R^{6b} is independently H, halo, CN, or C_{1-6} alkyl; or R^{6a} and R^{6b} are joined together to form a bond; R^{6c} is H, halo, CN, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is unsubstituted or substituted with one or more groups selected from substituted or unsubstituted amino, substitured or unsubstituted hydroxy, and substituted or unsubstituted heterocycloalkyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each R^7 is independently H, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkoxy, or substituted or unsubstituted heterocycloalkyl.

[0014a] In one aspect, provided herein is a compound according to Formula (P6-I):



(P6-I)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

wherein: each A^1, A^2, A^3, and A^4 is independently –C(R^7)=, or -N=; provided no more than two of A^1, A^2, A^3, and A^4 is N;

each L^1 and L^3 is independently substituted or unsubstituted C_1-C_4 alkylene; and the substituents on each of alkylene are independently selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

R^1 is H, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl, having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and the substituents on each of alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl and heterocycloalkyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

R^{2b} is independently H or C_1-C_4 alkyl;

R^4 is i) -C(O)-C(R^{6a})=C(R^{6b})(R^{6c}), ii) -S(O)-C(R^{6a})=C(R^{6b})(R^{6c}), or iii) -$S(O)_2$-C(R^{6a})=C(R^{6b})(R^{6c});

R^5 is H, Cy, CN, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylamino;

each of Cy, alkyl, alkoxy, and alkylamino is unsubstituted or substituted with

one or more halo, CN, C_{1-4} alkyl, hydroxy, amino, alkylamino, dialkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or C_{1-4} alkoxy;

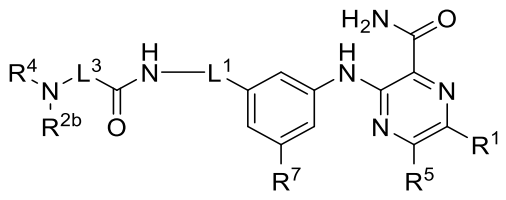
and the substituents on each of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

Cy is cycloalkyl, or heterocycloalkyl;

each R^{6a} and R^{6b} is independently H, halo, CN, or C_{1-6} alkyl; or R^{6a} and R^{6b} are joined together to form a bond; R^{6c} is H, halo, CN, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is unsubstituted or substituted with one or more groups selected from substituted or unsubstituted amino, hydroxy, substituted or unsubstituted C_{1-6} alkoxy, and substituted or unsubstituted heterocycloalkyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and the substituents on each of amino, alkoxy and heterocycloalkyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

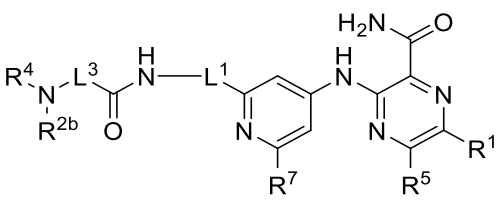
each R^7 is independently H, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkoxy, or substituted or unsubstituted heterocycloalkyl, having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and the substituents on each of alkyl, alkoxy and heterocycloalkyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy.

[0015] In some examples, provided herein is a compound according to Formula (P6-IIa) or (P6-IIb):



(P6-IIa)

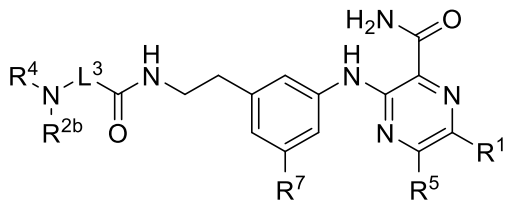
or



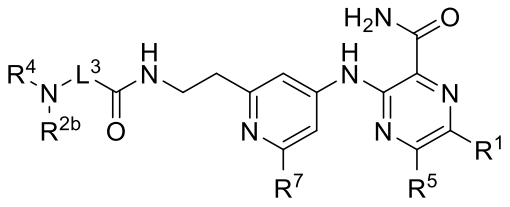
(P6-IIb)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

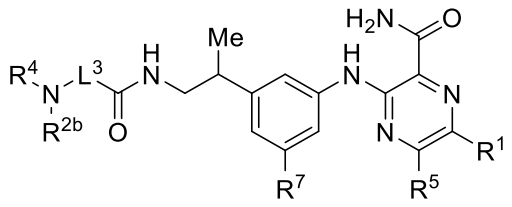
[0016] In some examples, provided herein is a compound according to Formula (P6-IIIa), (P6-IIIb), (P6-IIIc) or (P6-IIId):



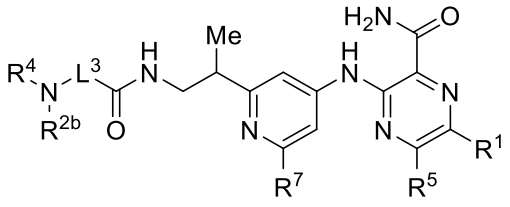
or



(P6-IIIa) (P6-IIIb)



or



(P6-IIIc) (P6-IIId)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[0017] In some examples, with respect to the compounds of any of the formulas described herein, R^5 is H, Cy, CN, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylamino; Cy is cycloalkyl, or heterocycloalkyl; each of Cy, alkyl, alkoxy, and alkylamino is unsubstituted or substituted with one or more halo, CN, C_{1-4} alkyl, hydroxy, amino, alkylamino, or dialkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or C_{1-4} alkoxy.

[0018] In some examples, with respect to the compounds of any of the formulas described herein, R^5 is is Me, Et, n-Pr, i-Pr, i-Bu, cyclopropyl, N,N-dimethyl, N-ethyl-N-methyl, N-isopropylamino, N-isopropyl-N-methylamino, methoxy, ethoxy, or i-propyloxy.

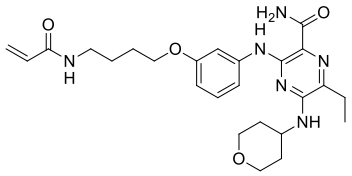
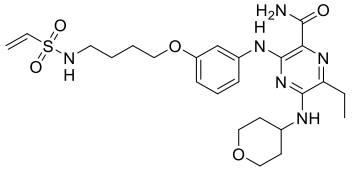
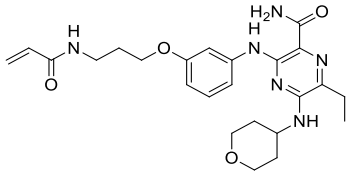
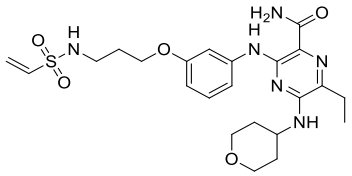
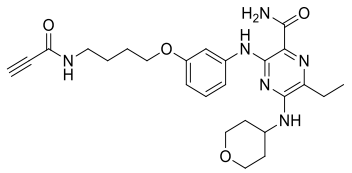
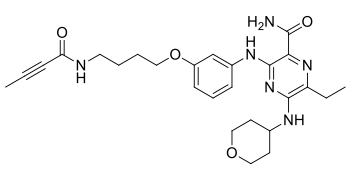
[0019] In some examples, with respect to the compounds of any of the formulas described herein, R^4 is -C(O)-B-C(R^{6a})=C(R^{6b})-C(O)-R^{6c}, -S(O)-B-C(R^{6a})=C(R^{6b})-C(O)-R^{6c},

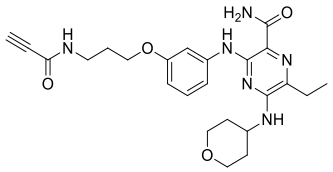
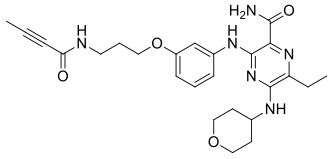
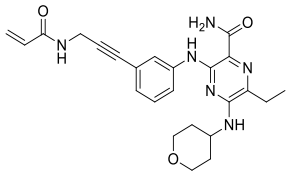
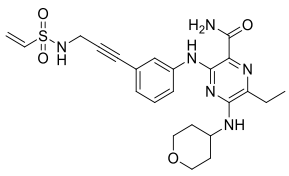
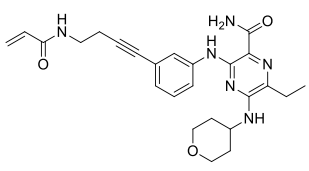
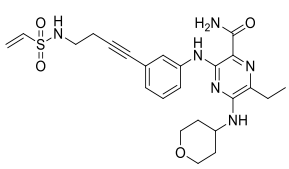
-$S(O)_2$-B-C(R^{6a})=C(R^{6b}) -C(O)-R^{6c}, -B-C(R^{6a})=C(R^{6b})-C(O)-R^{6c}, -B-C(R^{6a})=C(R^{6b})-S(O)-R^{6c}, -B-C(R^{6a})=C(R^{6b})-$S(O)_2$-R^{6c}, -B-C(R^{6a})=C(R^{6b})-P(O)-$R^{6a}R^{6b}$; or -B-C(R^{6a})=C(R^{6b})-P(O)-$OR^{6a}OR^{6b}$; B is substituted or unsubstituted C_{1-4} alkylene, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl; and R^{6c} is substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted heterocycloalkyl, having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some examples, R^4 is -CH_2-CH=CH-C(O)-N(CH_3)$_2$. In some examples, R^4 is -CH_2-C≡CH-C(O)-N(CH_3)$_2$.

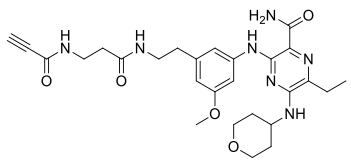
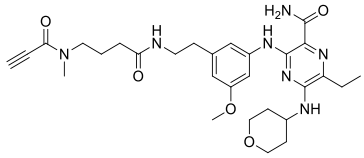
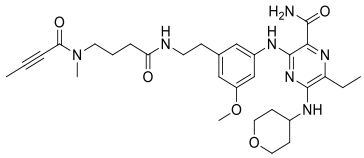
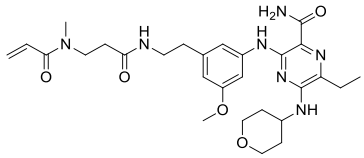
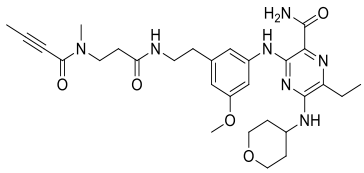
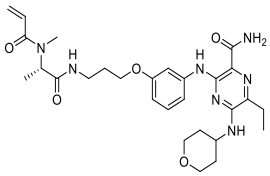
[0020] In certain examples, the compound is capable of covalently bonding FLT3. In certain examples, the compound comprises a functional group, e.g. at R^4, capable of covalently bonding FLT3. In certain examples, the compound comprises a linker that facilitates covalently bonding

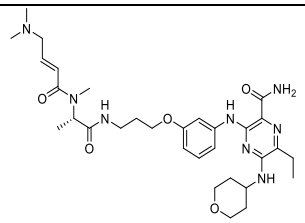
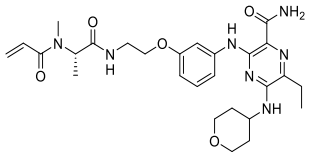
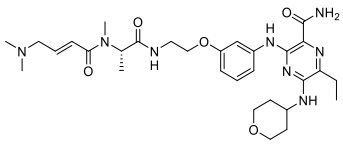
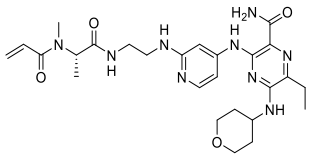
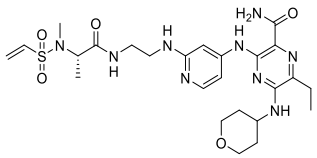
FLT3. While not intending to be bound by any theory of operation, it is believed that the right side (to the right of L1) of the structure P6-I forms a functional group capable of binding a binding pocket of FLT3. The linker of the compounds provided herein provides sufficient length and composition to provide covalent bonding of R^4 to a site on FLT3, for instance Cys12. In certain examples, the linker comprises L^1. In certain examples, the linker comprises L^3. In certain examples, the linker comprises L^1 and L^3. In certain examples, the linker is -L^1-N(H)-C(O)-L^3-. In certain examples, the linker facilitates covalent binding that distinguishes the compounds over compounds known to those of skill, which have linkers of lengths or compositions, or both, insufficient to facilitate sufficient, or any, covalent binding of FLT3.

[0021] In certain examples, the compound is not any of Compounds 1-41, or any salt thereof.

Cpd	Structure
1	
2	
3	
4	
5	
6	

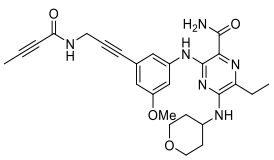
Cpd	Structure
7	
8	
9	
10	
11	
12	

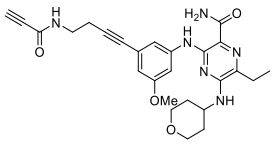
Cpd	Structure
31	
32	
33	
34	
35	
36	

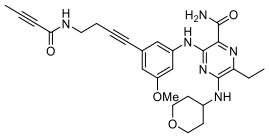
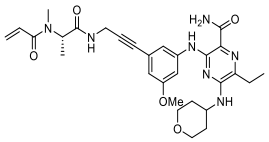
Cpd	Structure
37	
38	
39	
40	
41	

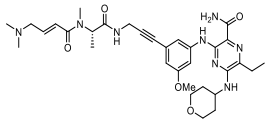
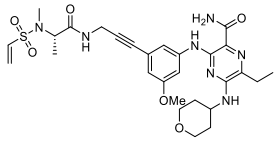
.

[0022] In certain examples, the compound is not any of Compounds 14-P19, or any salt thereof:

Cpd	Structure
P-14	

Cpd	Structure
P-15	

Cpd	Structure
P-16	
P-17	

Cpd	Structure
P-18	
P-19	

[0023] Any combination of the groups described above for the various variables is contemplated herein. It is understood that substituents and substitution patterns on the compounds provided herein can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those set forth herein.

[0024] In some examples, provided herein are pharmaceutical compositions, which comprise a therapeutically effective amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof. In another aspect, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound herein; or a pharmaceutically acceptable stereoisomer, salt, solvate, or prodrug thereof; and a pharmaceutically acceptable excipient. In certain examples, pharmaceutical compositions provided herein further include a pharmaceutically acceptable carrier, excipient and/or diluent.

[0025] Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically effective derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of diseases, disorders or conditions that are modulated or otherwise affected by FLT3 activity, in which FLT3 activity is implicated, or are characterized by a mutation in the *FLT3* gene, are provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the diseases, disorders or conditions disclosed herein.

[0026] In certain examples, provided herein is a pharmaceutical composition comprising: i) a pharmaceutically acceptable carrier, diluent, and/or excipient; and ii) one or more compounds provided herein.

[0027] In some examples, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a compound selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) and a pharmaceutically acceptable carrier, excipient, or diluent. In some examples, the pharmaceutical composition comprising the

compound selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) is formulated for a route of administration selected from oral administration, parenteral administration, buccal administration, nasal administration, topical administration, and rectal administration.

[0028] In some examples, provided herein are methods for preventing, treating or ameliorating in a mammal a disease or condition that is related to the aberrant activity of FLT3, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof. In other examples, provided herein are methods for preventing, treating or ameliorating in a mammal a disease or condition that is related to a mutation of the *FLT3* gene, which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof. In certain examples, the *FLT3* mutation is an internal tandem mutation (*FLT3*-ITD). In certain examples, the *FLT3* mutation is a point mutation in the tyrosine kinase domain (*FLT3*-TKD).

[0029] In some examples, the disease or condition is a hematologic malignancy, including, but not limited to leukemia, lymphoma, or multiple myeloma. In certain examples, the disease or condition is a leukemia, including, but not limited to, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), prolymphocytic leukemia (PLL), large granular lymphocytic (LGL), hairy cell leukemia (HCL), mast-cell leukemia (MCL) or myelodysplastic syndrome (MDS).

[0030] In certain examples, the disease or condition is acute myeloid leukemia (AML). In certain examples, the AML is *FLT3* mutation-positive. In certain examples, the AML is newly diagnosed. In certain examples, the AML is *FLT3* mutation-positive and newly diagnosed. In certain examples, the AML is relapsed or refractory. In certain examples, the AML is relapsed or refractory and is *FLT3* mutation-positive. In certain examples, the patient has an *NPM1* mutation.

[0031] In certain examples, the disease or condition is a lymphoma, including, but not limited to, non-Hodgkin's lymphoma or Hodgkin's lymphoma. In certain examples, the disease or condition is multiple myeloma.

[0032] In some examples, provided herein are compounds selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically salt thereof for use in therapy. In some examples, provided herein are compounds selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in the treatment of a disease or condition related to the aberrant activity of a FLT3 *in vivo.* In some examples, provided herein are compounds

selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in therapy. In some examples, provided herein are compounds selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in the treatment of a disease or condition related to a mutation in the *FLT3* gene *in vivo.* In some examples, provided herein are compounds selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for therapy. In some examples, provided herein are compounds selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for the treatment of a disease or condition related to the aberrant activity of FLT3 or related to a mutation of the *FLT3* gene. Useful diseases and conditions are described herein.

[0033] In some examples, provided herein are pharmaceutical compositions comprising a compound selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in therapy. In some examples, provided herein are pharmaceutical compositions comprising a compound selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in the treatment of a disease or condition related to the aberrant activity of FLT3 or related to a mutation of the *FLT3* gene. In some examples, provided herein are pharmaceutical compositions comprising a compound selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for therapy. In some examples, provided herein are pharmaceutical compositions comprising a compound selected from Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for the treatment of a disease or condition related to the aberrant activity of FLT3 or related to a mutation of the *FLT3* gene *in vivo.* Useful diseases and conditions are described herein.

[0033a] In another aspect, provided herein is a compound, a pharmaceutically acceptable stereoisomer, or a salt thereof, as provided herein, or a pharmaceutical composition as provided herein, for use in therapy.

[0033b] In another aspect, provided herein is a compound, a pharmaceutically acceptable stereoisomer, or a salt thereof, as provided herein, or a pharmaceutical composition as provided herein, for use in the treatment of a proliferative disease or condition.

[0034] In any of the aforementioned examples are some examples in which administration is enteral, parenteral, or both, and wherein (a) an effective amount of a provided compound is systemically administered to the mammal; (b) an effective amount of a provided compound is administered orally to the mammal; (c) an effective amount of a provided compound is intravenously administered to the mammal; (d) an effective amount of a provided compound is administered by inhalation; (e) an effective amount of a provided compound is administered by nasal administration; or (f) an effective amount of a provided compound is administered by injection to the mammal; (g) an effective amount of a provided compound is administered topically (dermal) to the mammal; (h) an effective amount of a provided compound is administered by ophthalmic administration; or (i) an effective amount of a provided compound is administered rectally to the mammal.

[0035] In any of the aforementioned examples are some examples comprising single administrations of an effective amount of a provided compound including some examples in which (i) a provided compound is administered once; (ii) a provided compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[0036] In any of the aforementioned examples are some examples comprising multiple administrations of an effective amount of a provided compound, including some examples in which (i) a provided compound is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) a provided compound is administered to the mammal every 8 hours. In some examples, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. The length of the drug holiday can vary from 2 days to 1 year.

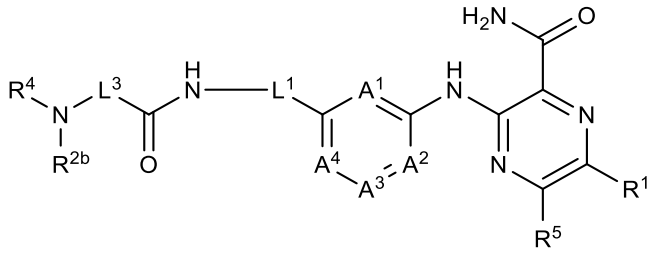
[0037] In any of the aforementioned examples involving the treatment of proliferative disorders, including cancer, for example, a hematological cancer, are some examples comprising administering at least one additional agent selected from the group consisting of alemtuzumab, azacitine, bortezomib, decitabine, everolimus, malademetan, palbociclib, ponatinib, venetoclax, and vorinostat. In other examples, the treatment of proliferative disorders, including cancer, for example, a hematological cancer, comprise the administration of at least one additional active agent selected from arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, Paclitaxel™, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues), interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase irreversible inhibitors such as irinotecan or topotecan, tyrosine kinase irreversible inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

[0038] In certain examples, provided herein are articles of manufacture including packaging material, a compound or composition thereof provided herein within the packaging material, and a label that indicates that the compound or composition is administered to treat a disease or condition.

[0039] In some examples, the compounds of Formula (P2-I), Formula (P4-I) – (P4-Vb), Formula (P5-I') – (P5-Vd), and Formula (P6-I) - (P6-IIId) are covalent inhibitors of FLT3 activity. In certain examples, such covalent inhibitors have an IC_{50} below 10 microM in enzyme assay. In some examples, a FLT3 inhibitor has an IC_{50} of less than 1 microM, and in some examples, less than 0.25 microM or even less than 0.025 microM.

WHAT IS CLAIMED IS:

1. A compound according to Formula (P6-I):



(P6-I)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

wherein: each A^1, A^2, A^3, and A^4 is independently –C(R^7)=, or -N=; provided no more than two of A^1, A^2, A^3, and A^4 is N;

each L^1 and L^3 is independently substituted or unsubstituted C_1-C_4 alkylene; and the substituents on each of alkylene are independently selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

R^1 is H, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, or substituted or unsubstituted heterocycloalkyl, having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and the substituents on each of alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl and heterocycloalkyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

R^{2b} is independently H or C_1-C_4 alkyl;

R^4 is i) -C(O)-C(R^{6a})=C(R^{6b})(R^{6c}), ii) -S(O)-C(R^{6a})=C(R^{6b})(R^{6c}), or iii) -$S(O)_2$-C(R^{6a})=C(R^{6b})(R^{6c});

R^5 is H, Cy, CN, halo, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkylamino;

each of Cy, alkyl, alkoxy, and alkylamino is unsubstituted or substituted with

one or more halo, CN, C_{1-4} alkyl, hydroxy, amino, alkylamino, dialkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or C_{1-4} alkoxy;

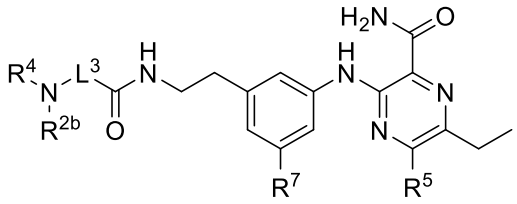
and the substituents on each of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

Cy is cycloalkyl, or heterocycloalkyl;

each R^{6a} and R^{6b} is independently H, halo, CN, or C_{1-6} alkyl; or R^{6a} and R^{6b} are joined together to form a bond; R^{6c} is H, halo, CN, or C_{1-6} alkyl, wherein the C_{1-6} alkyl is unsubstituted or substituted with one or more groups selected from substituted or unsubstituted amino, hydroxy, substituted or unsubstituted C_{1-6} alkoxy, and substituted or unsubstituted heterocycloalkyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and the substituents on each of amino, alkoxy and heterocycloalkyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

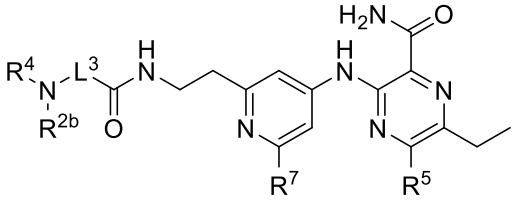
each R^7 is independently H, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted alkoxy, or substituted or unsubstituted heterocycloalkyl, having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and the substituents on each of alkyl, alkoxy and heterocycloalkyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy.

2. The compound according to claim 1, wherein the compound is according to Formula (P6-IVa), (P6-IVb), (P6-IVc) or (P6-IVd):

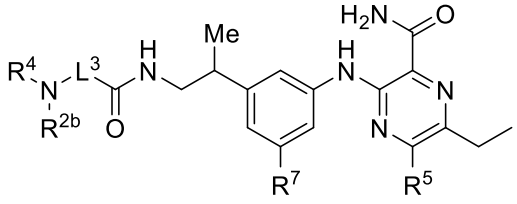


(P6-IVa)

or

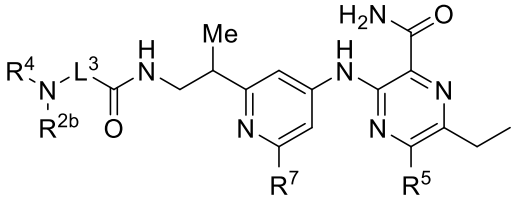


(P6-IVb)



(P6-IVc)

or

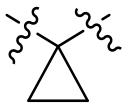


(P6-IVd)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or claim 2, wherein:

- L^3 is i) $-CH_2-$, or -C(Me)H-, or

ii) $-C(Me)_2-$, $-CH_2-CH_2-$, -C(Me)H-CH_2-, $-CH_2$-C(Me)H-, or  ; and/or

- R^{2b} is H, or Me; and/or

- R^7 is H, F, Me, Et, Cl, CF_3, or OMe.

4. The compound according to any one of claims 1-3, wherein R^5 is:

i) Cy, unsubstituted or substituted with one or more halo, CN, C_{1-4} alkyl, hydroxy, amino, alkylamino, dialkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or C_{1-4} alkoxy; and the substituents on each of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy; and Cy is cycloalkyl, or heterocycloalkyl;

ii) unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, or unsubstituted or substituted alkylamino; each of alkyl, alkoxy, and alkylamino is unsubstituted or substituted with one or more halo, CN, C_{1-4} alkyl, hydroxy, amino, alkylamino, dialkylamino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or C_{1-4} alkoxy; and the substituents on each of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy;

iii) Me, Et, i-Pr, n-Pr, n-Bu, i-Bu, t-Bu, sec-Bu, substituted or unsubstituted cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted cyclohexyl, Cl, F, CN, CF_3, OMe, OEt, O-i-Pr, -OCF3, N,N-dimethylamino, N,N-diethylamino, N,N-diisopropylamino, N-ethyl-N-methylamino, N-iso-propyl-N-methylamino, N-iso-propyl-N-ethylamino, N-isopropylamino, N-ethylamino, N-methylamino, N-n-propylamino, substituted or unsubstituted 1-azetidinyl, substituted or unsubstituted 1-pyrrolidinyl, substituted or unsubstituted 1-piperidinyl, or substituted or unsubstituted 1-morpholinyl; and the substituents on each of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy; or

iv) Me, Et, n-Pr, i-Pr, i-Bu, cyclopropyl, N,N-dimethyl, N-ethyl-N-methyl, N-isopropylamino, N-isopropyl-N-methylamino, methoxy, ethoxy, or i-propyloxy.

5. The compound according to any one of the preceding claims, wherein:

a) R^4 is -C(O)-C(R^{6a})=C(R^{6b})(R^{6c}); optionally wherein:

i) each of R^{6a}, R^{6b}, and R^{6c} is H;

ii) each of R^{6a} and R^{6b} is H; and R^{6c} is alkyl substituted with amino, alkylamino or dialkylamino;

iii) R^{6a} and R^{6b} form a bond; and R^{6c} is H or substituted or unsubstituted alkyl; and the substituents on alkyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, and heterocycloalkyl, having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

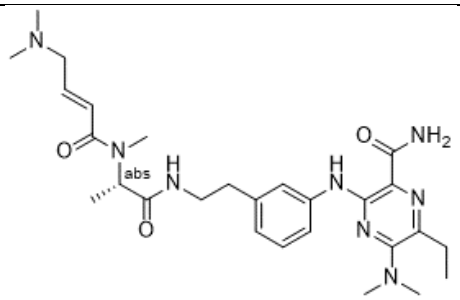
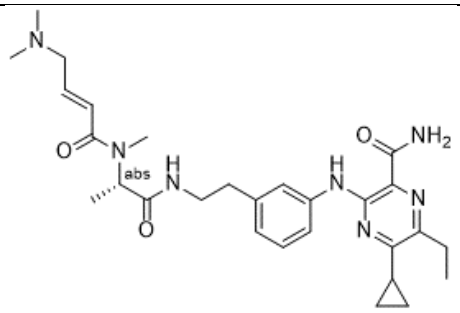
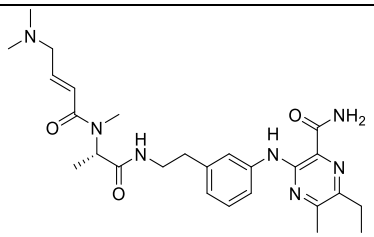
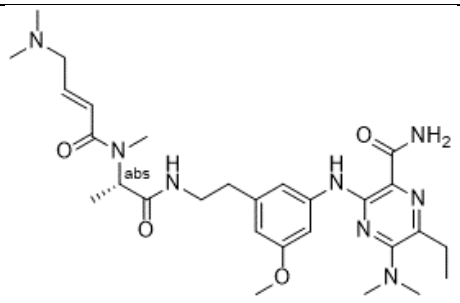
iv) R^{6a} and R^{6b} form a bond; and R^{6c} is Me;

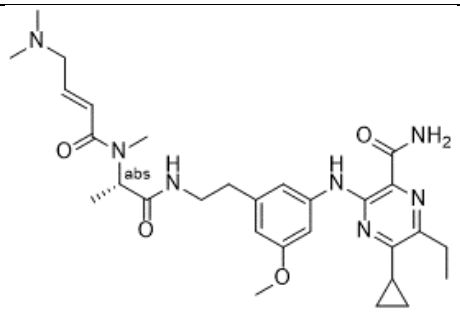
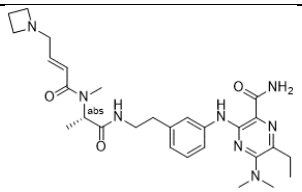
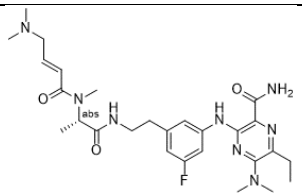
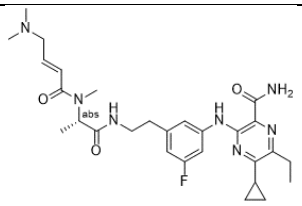
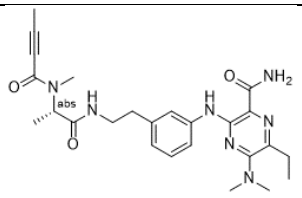
v) each of R^{6a} and R^{6b} is H; and R^{6c} is -$(CH_2)_q$-heterocycloalkyl; and q is 1, optionally wherein heterocycloalkyl is substituted or unsubstituted azetidin-1-yl, substituted or unsubstituted pyrrolidin-1-yl, substituted or unsubstituted piperidin-1-yl, substituted or unsubstituted morpholin-1yl, or substituted or unsubstituted azepin-1-yl; and the substituents on each of azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, and azepinyl are selected from one or more halo, CN, C_{1-4} alkyl, hydroxy, and C_{1-4} alkoxy; or

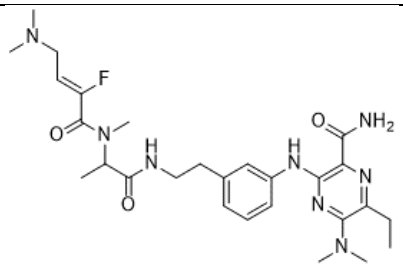
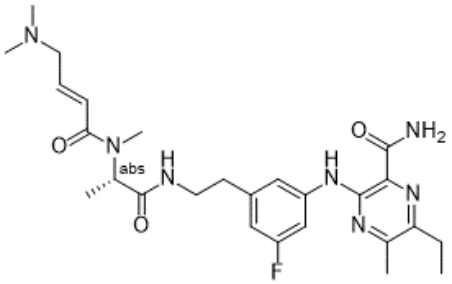
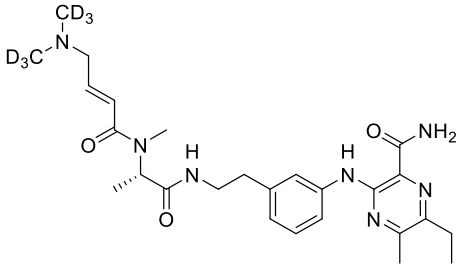
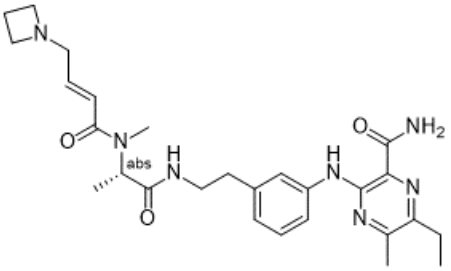
vi) each of R^{6a} and R^{6b} is H or Me; and R^{6c} is –CH_2-azetidin-1-yl, –CH_2-pyrrolidin-1-yl, or –CH_2-piperidin-1-yl; or

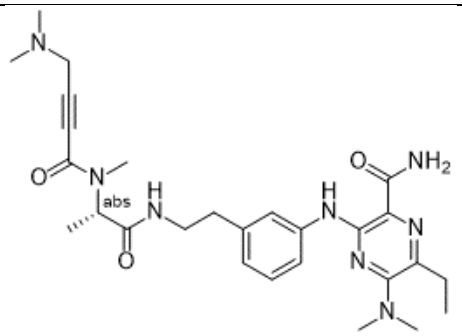
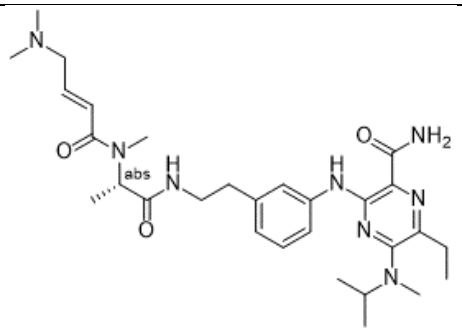
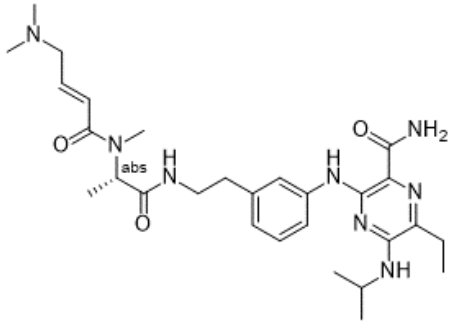
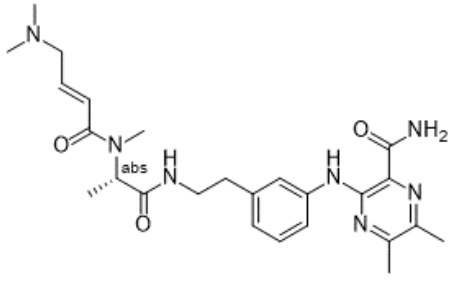
b) R^4 is -C(O)-CH=CH_2, -C(O)-CH=CH-CH_2-NHMe, -C(O)-CH=CH-CH_2-NMe_2, -C(O)-CH=CH-CH_2-azetidin-1-yl, -C(O)-CH=CH-CH_2-(3-fluoroazetidin-1-yl), -C(O)-CH=CH-CH_2-(3,3-difluoroazetidin-1-yl), -C(O)-C≡CH, -C(O)-C≡C-Me, or -C(O)-C≡C-CH_2-NMe_2.

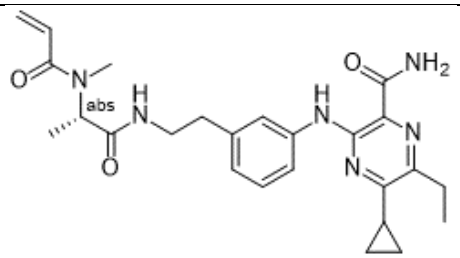
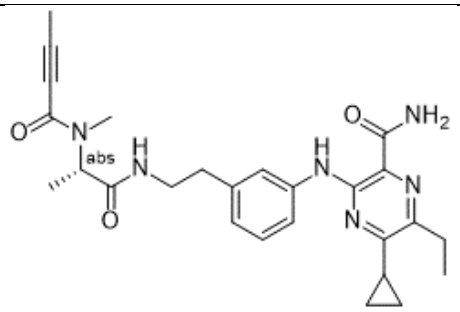
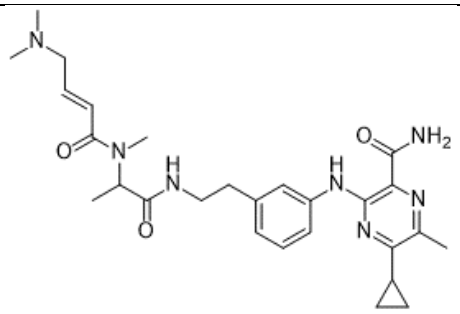
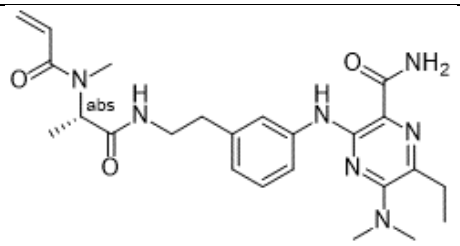
6. The compound according to claim 1, wherein the compound is selected from any one of the compounds listed in the following Table, or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof:

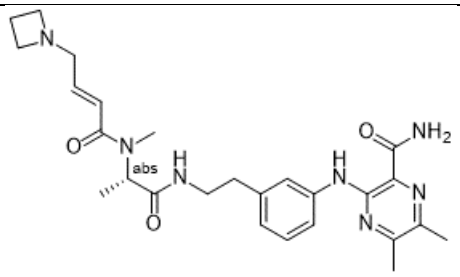
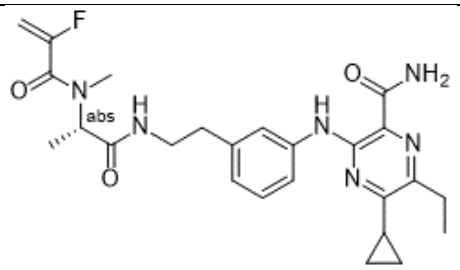
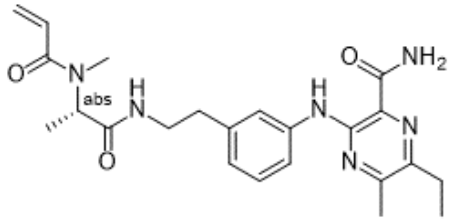
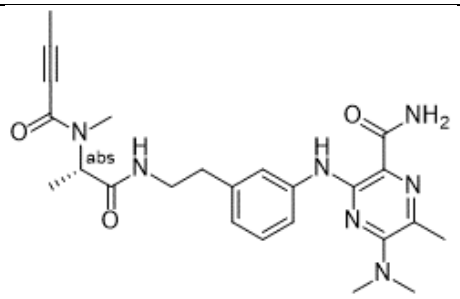
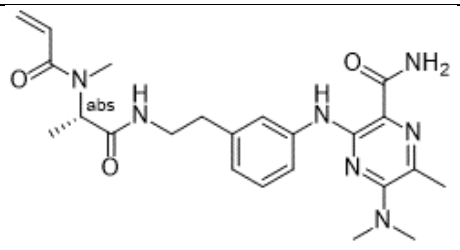
Compd ID	Structure
137	
138	
142A	
143	

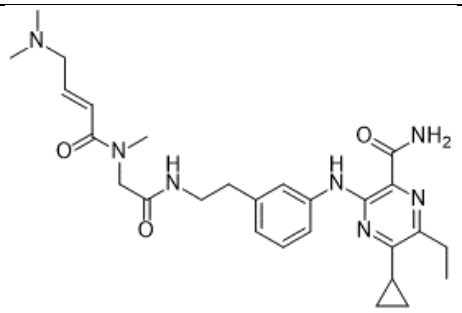
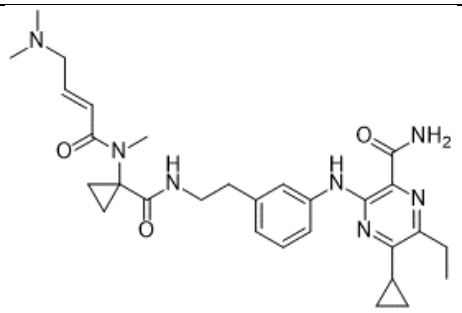
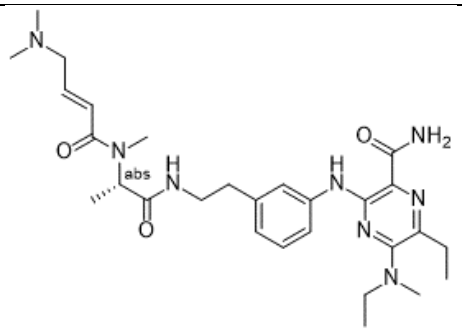
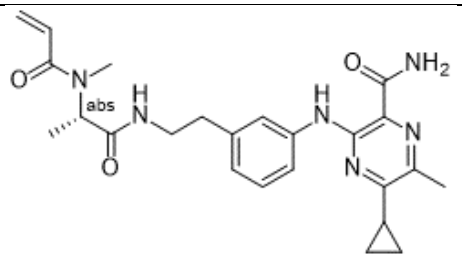
Compd ID	Structure
144	
156	
158	
159	
160	

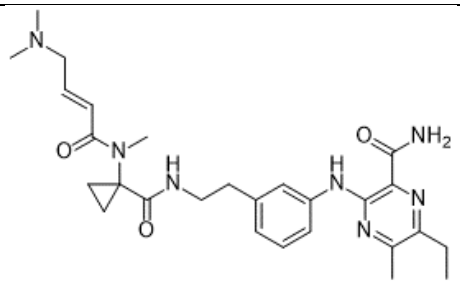
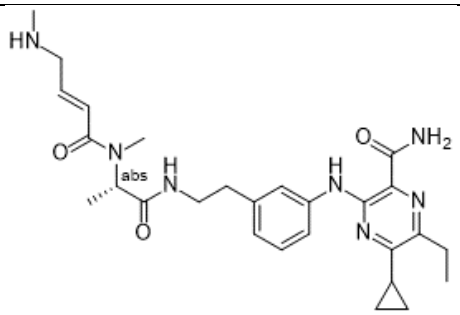
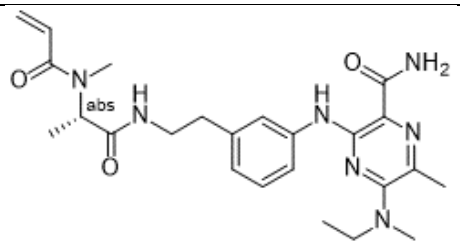
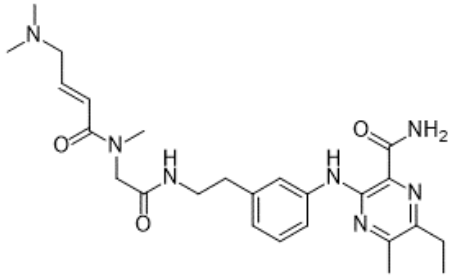
Compd ID	Structure
162	
163	
164	
202	

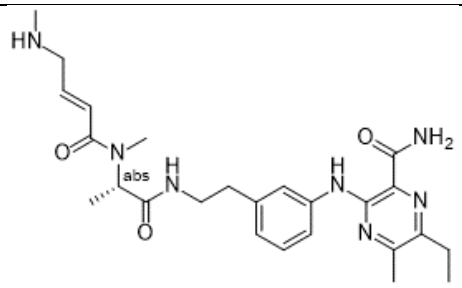
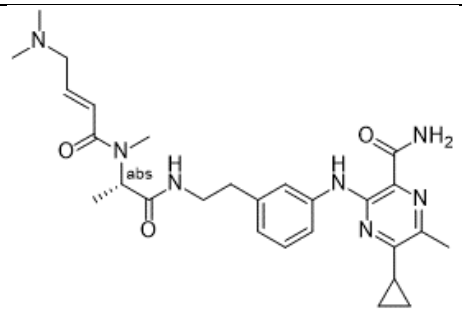
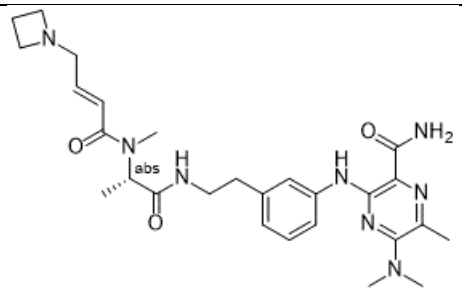
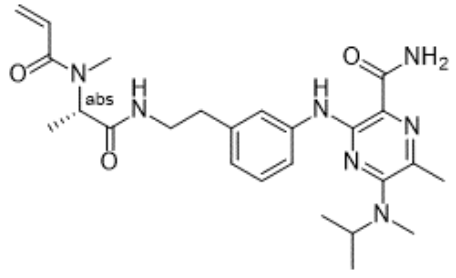
Compd ID	Structure
203	
204	
205	
207	

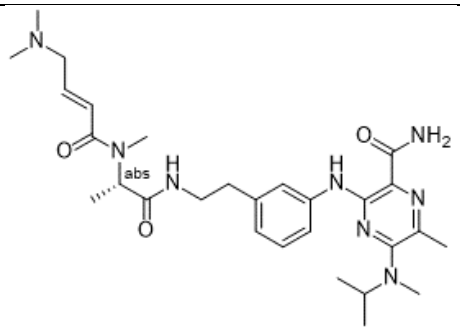
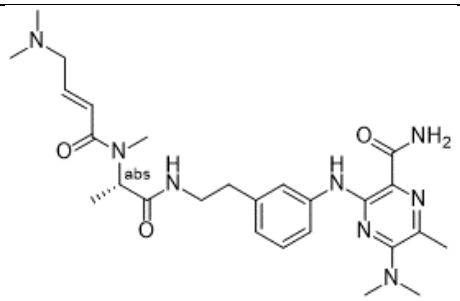
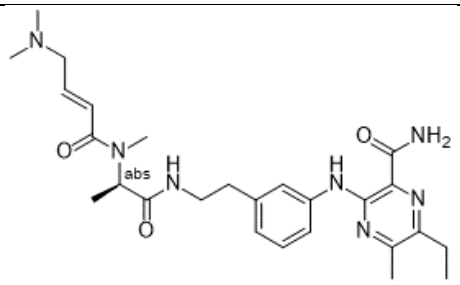
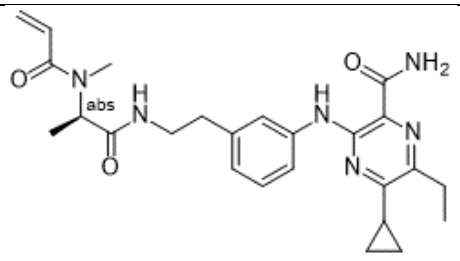
Compd ID	Structure
208	
209	
211	
213	

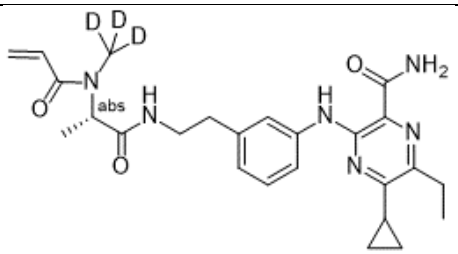
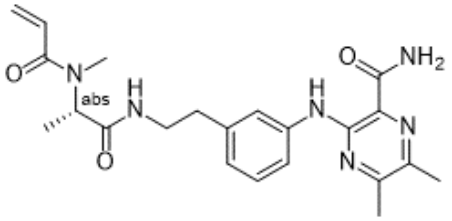
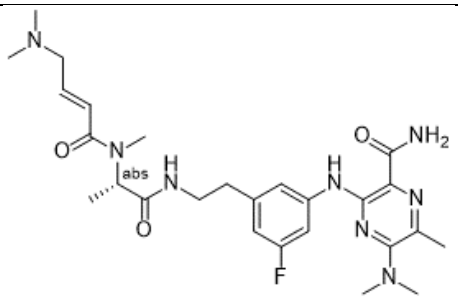
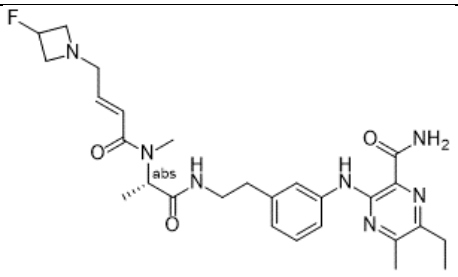
Compd ID	Structure
214	
215	
216	
217	
218	

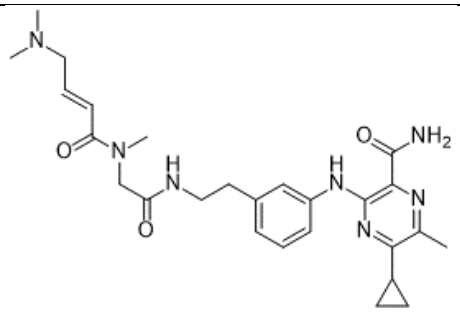
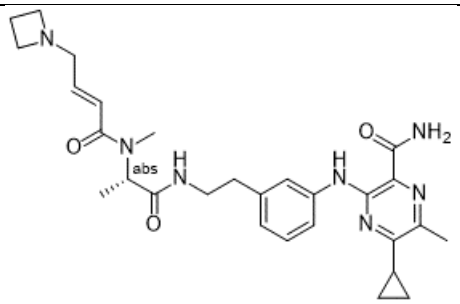
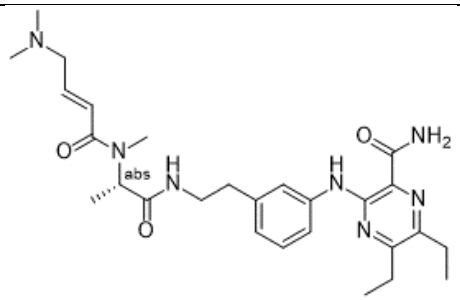
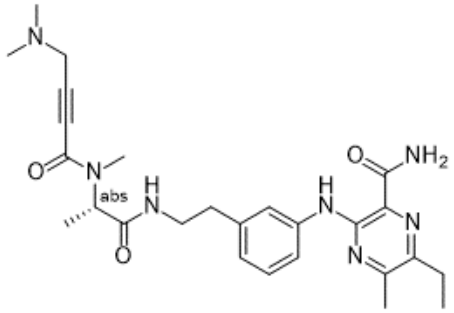
Compd ID	Structure
219	
220	
221	
222	

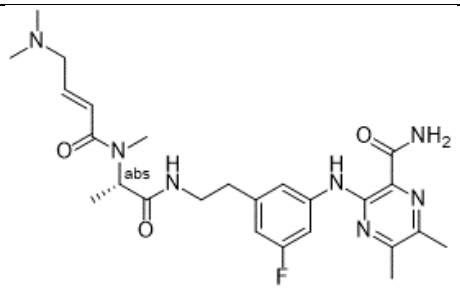
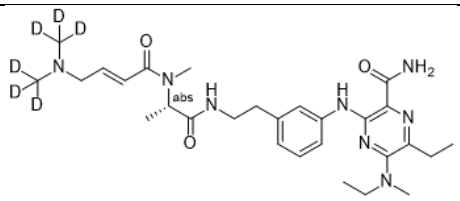
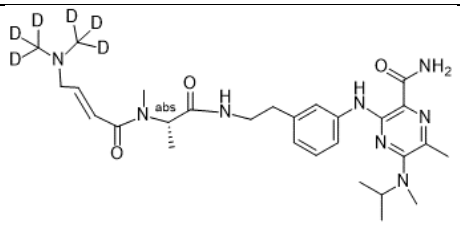
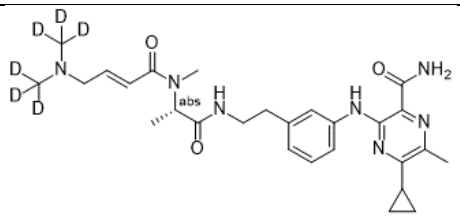
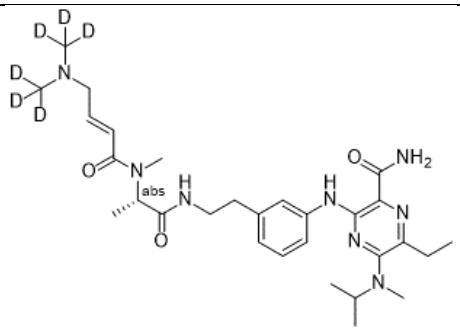
Compd ID	Structure
223	
224	
225	
226	

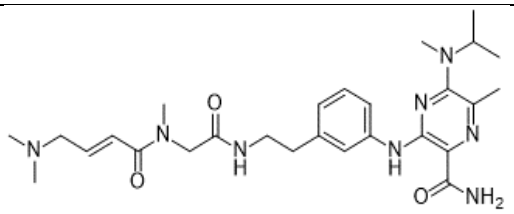
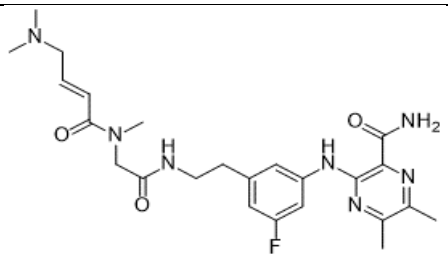
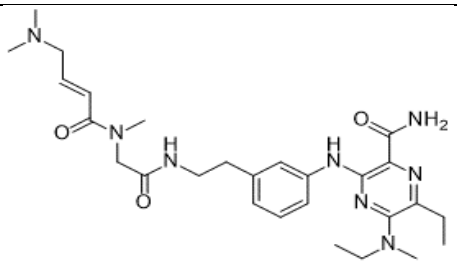
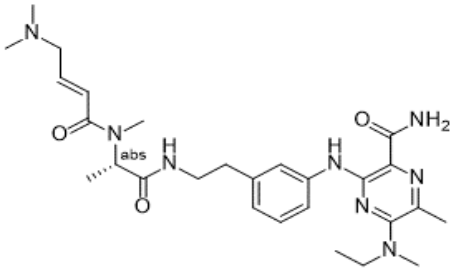
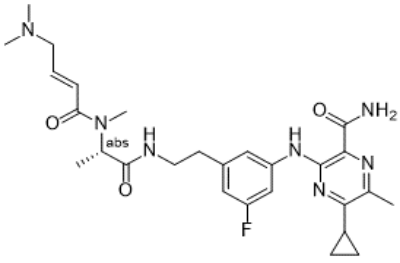
Compd ID	Structure
227	
228	
230	
231	

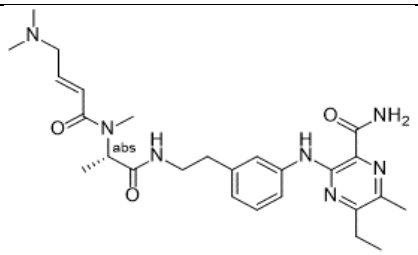
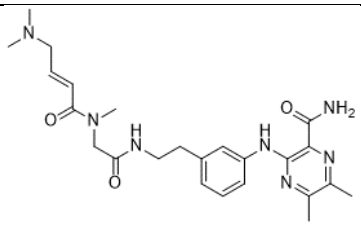
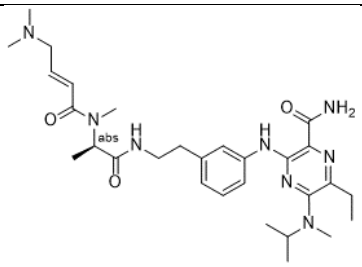
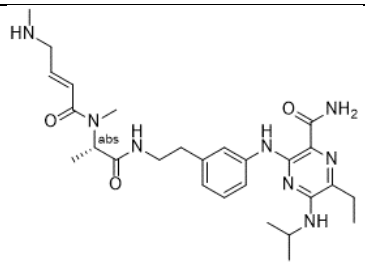
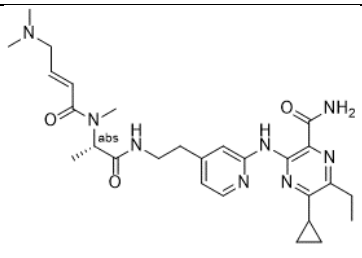
Compd ID	Structure
232	
233	
234	
236	

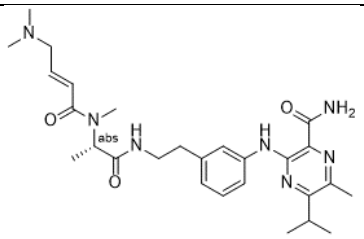
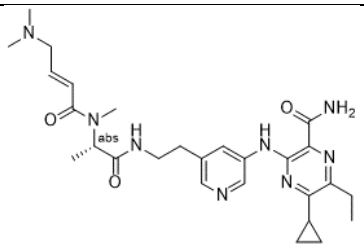
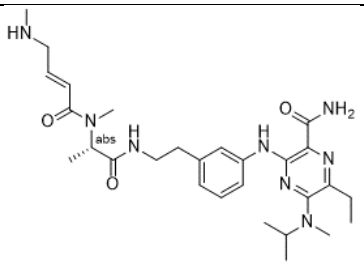
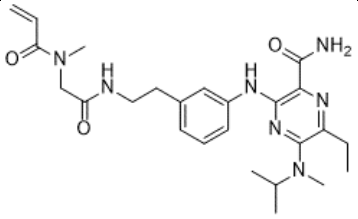
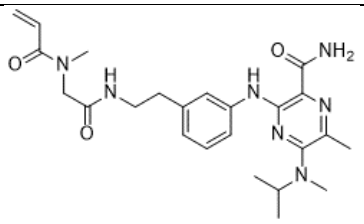
Compd ID	Structure
237	
238	
239	
240	

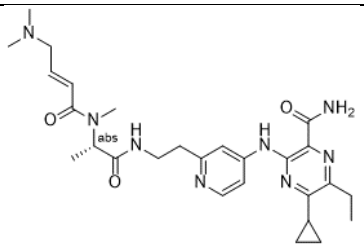
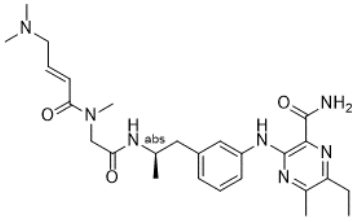
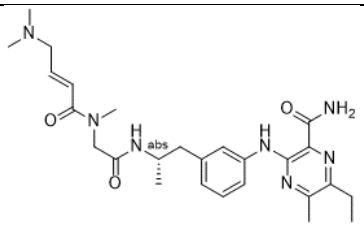
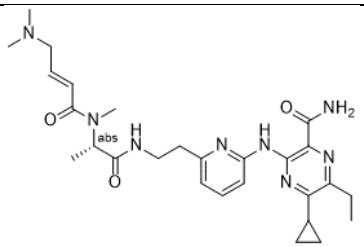
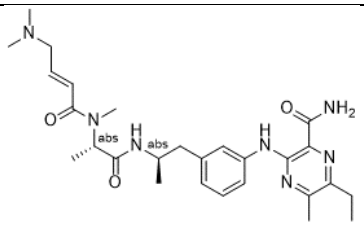
Compd ID	Structure
241	
242	
243	
244	

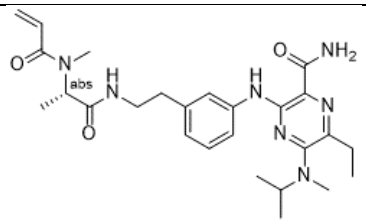
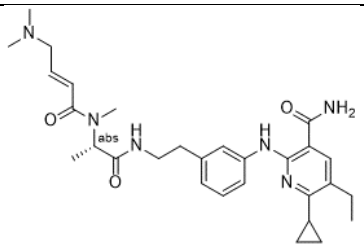
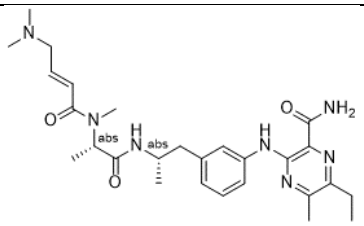
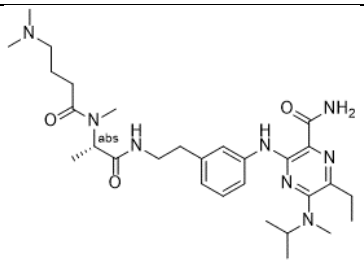
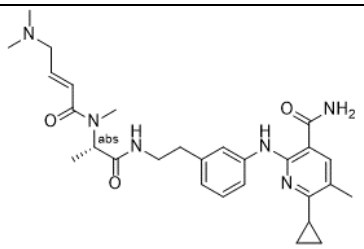
Compd ID	Structure
245	
246	
247	
248	
249	

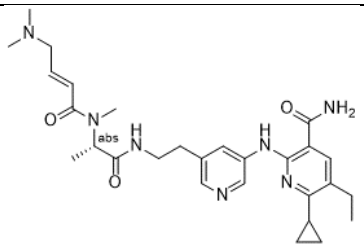
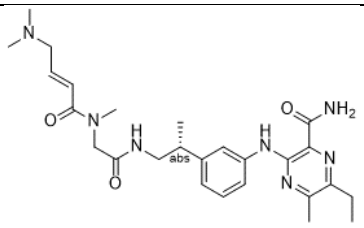
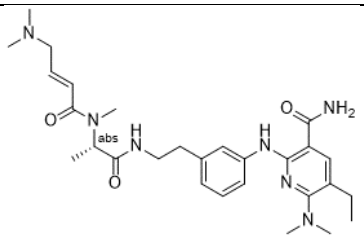
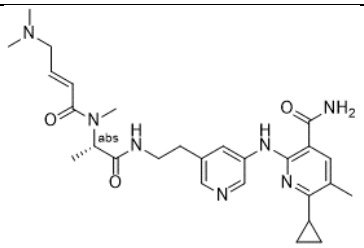
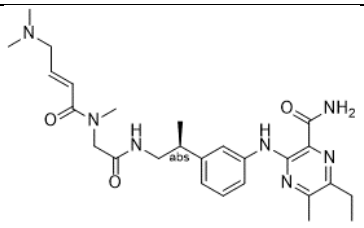
Compd ID	Structure
250	
251	
252	
253	
254	

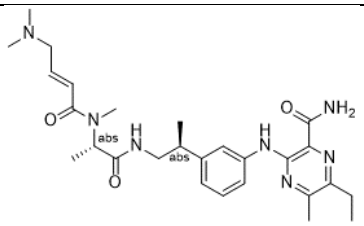
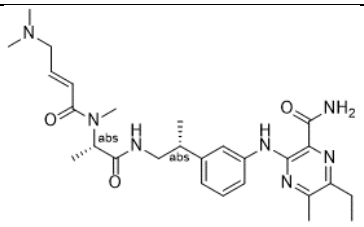
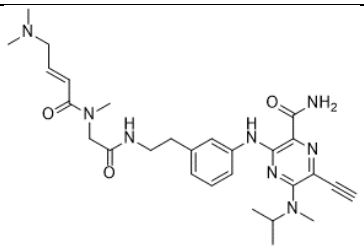
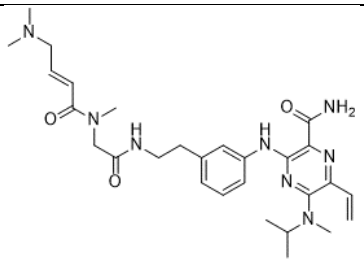
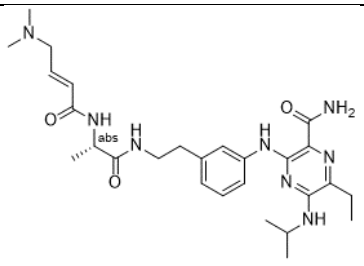
Compd ID	Structure
255	
301	
302	
303	
304	

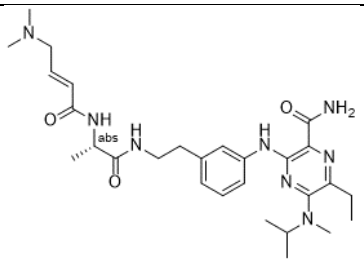
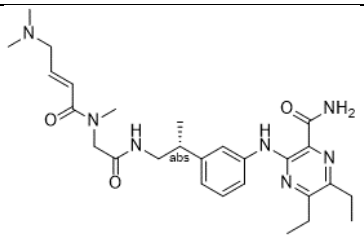
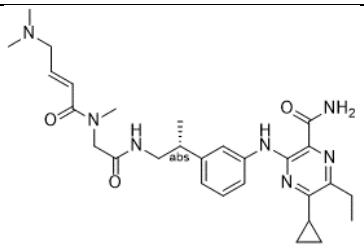
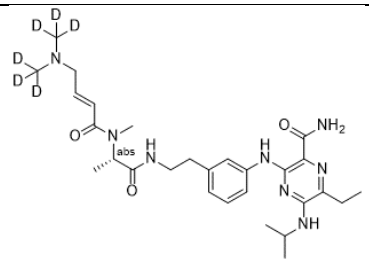
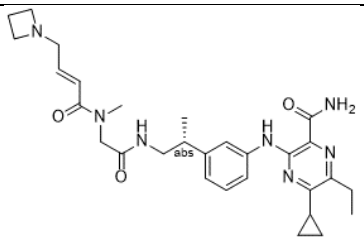
Compd ID	Structure
305	
306	
307	
308	
309	

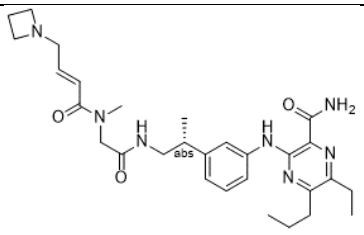
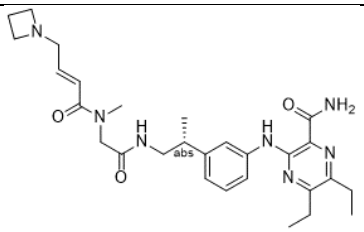
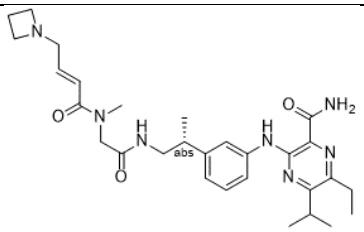
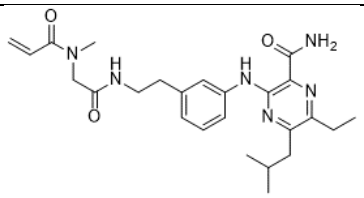
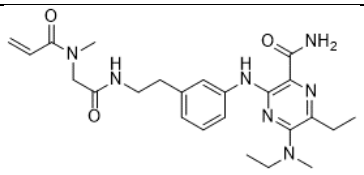
Compd ID	Structure
310	
311	
312	
313	
314	

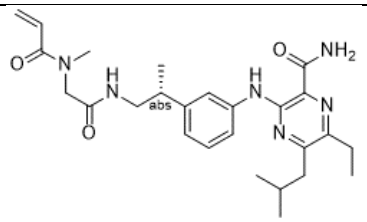
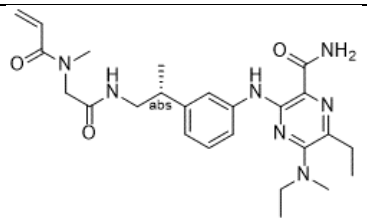
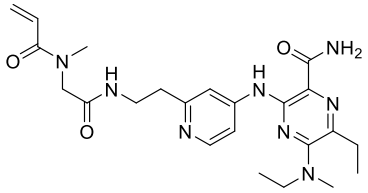
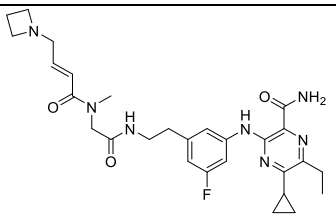
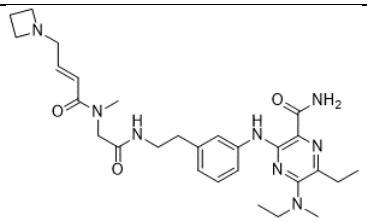
Compd ID	Structure
315	
316	
317	
318	
319	

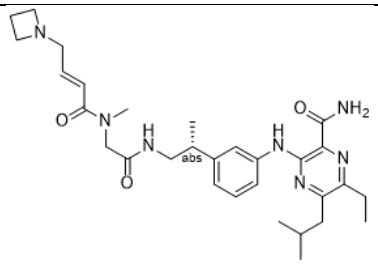
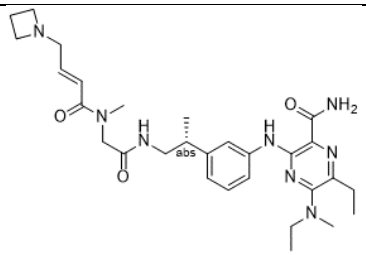
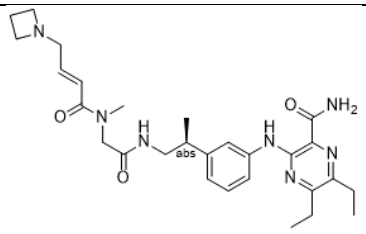
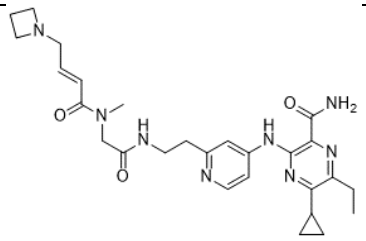
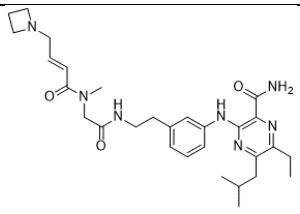
Compd ID	Structure
320	
321	
322	
323	
324	

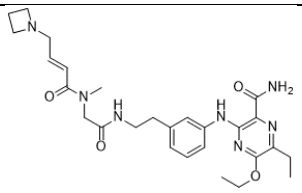
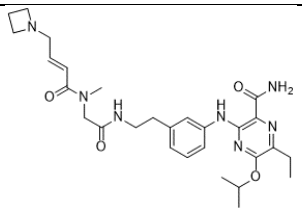
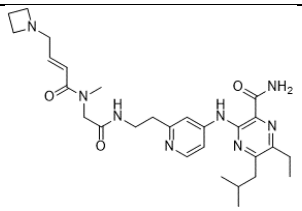
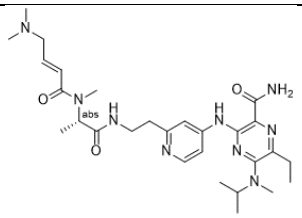
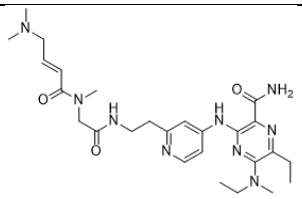
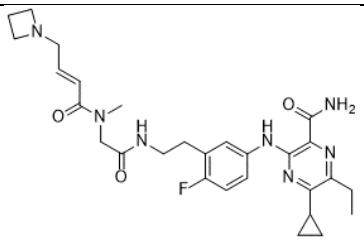
Compd ID	Structure
325	
326	
327	
328	
501	

Compd ID	Structure
502	
503	
504	
505	
506	

Compd ID	Structure
507	
508	
509	
510	
511	

Compd ID	Structure
512	
513	
515	
516	
516A	

Compd ID	Structure
517	
518	
519	
520	
601	

Compd ID	Structure
602	
603	
604	
605	
606	
607	

.

7. The compound according to claim 6, wherein the compound is selected from

i) Compound ID 204, 252, 310, 509, 511, and 516A; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof;

ii) Compound ID 308, 315, 506, 507, 508, 513, 512, 513, 517, and 520; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof; or

iii) Compound ID 506, and 516; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

8. The compound according to claim 6, wherein the compound is Compound ID 204; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

9. The compound according to claim 6, wherein the compound is Compound ID 516A; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

10. The compound according to claim 6, wherein the compound is Compound ID 252; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

11. The compound according to claim 6, wherein the compound is Compound ID 506; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

12. The compound according to claim 6, wherein the compound is Compound ID 511; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

13. The compound according to claim 6, wherein the compound is Compound ID 516; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

14. The compound according to claim 6, wherein the compound is Compound ID 517; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

15. The compound according to claim 6, wherein the compound is Compound ID 520; or a pharmaceutically acceptable stereoisomer, salt, or solvate thereof.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of the preceding claims; or a pharmaceutically acceptable stereoisomer, salt, solvate, or prodrug thereof; and a pharmaceutically acceptable excipient.

17. A compound, a pharmaceutically acceptable stereoisomer, or a salt thereof, according to any one of claims 1 to 15, or a pharmaceutical composition according to claim 16, for use in therapy.

18. A compound, a pharmaceutically acceptable stereoisomer, or a salt thereof, according to any one of claims 1 to 15, or a pharmaceutical composition according to claim 16, for use in the treatment of a proliferative disease or condition.

19. The compound or composition for use according to claim 18, wherein the proliferative disease or condition is cancer.

20. The compound or composition for use according to claim 18, wherein the cancer is i) a hematological malignancy; or ii) a hematological malignancy; and the hematological malignancy is acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), prolymphocytic leukemia (PLL), large granular lymphocytic (LGL), hairy cell leukemia (HCL), mast-cell leukemia (MCL) or myelodysplastic syndrome (MDS).