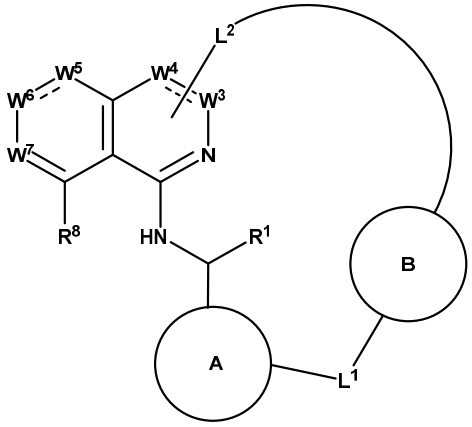
CLAIMS

WHAT IS CLAIMED IS:

1. Use of a small molecule SOS1 inhibitor in the manufacture of a medicament for the treatment of Philadelphia chromosome-positive (Ph+) blood cancer in a subject in need thereof, wherein the subject is identified as having a genetic aberration in *BCR-ABL*, and wherein the SOS1 inhibitor is a compound of Formula (I-1):



(I-1),

or a pharmaceutically acceptable salt or solvate thereof, wherein:



is selected from C_{5-7} carbocycle and 5- to 7-membered heterocycle, each of which is optionally substituted with one or more R^{11};



is absent or selected from C_{3-8} carbocycle and 3- to 8-membered heterocycle, each of which is optionally substituted with one or more R^{11a};

L^1 is selected from a bond, C_{1-6} alkylene, and C_{1-6} haloalkylene;

L^2 is selected from C_{5-25} alkylene, C_{5-25} alkenylene, C_{5-25} alkynylene, 5- to 25-membered heteroalkylene, and 5- to 25-membered heteroalkenylene, each of which is optionally substituted with one or more R^{11b}, wherein L^2 is covalently bound to one of W^3, W^4, W^5, W^6, or W^7;

W^3 is selected from $N(R^{3b})$, N, $C(R^3)$, and C(O);

W^4 is selected from $N(R^{4b})$, N, $C(R^4)$, and C(O);

W^5 is selected from $N(R^{5b})$, N, and $C(R^5)$;

W^6 is selected from $C(R^6)$ and C(O);

W^7 is $C(R^7)$;

R^1 is C_{1-3} alkyl optionally substituted with one or more R^{11c};

R^8 is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{20};

R^3, R^4, R^5, R^6, and R^7 are each independently selected from a bond to L^2, hydrogen, halogen, -CN, C_{1-6}

alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{20};

R^{3b}, R^{4b}, and R^{5b} are each independently selected from a bond to L^2, hydrogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{12}$, $-SR^{12}$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, and $-CH_2S(O)_2N(R^{12})(R^{13})$, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle and 3- to 10-membered heterocycle is independently optionally substituted with one, two, or three R^{20};

R^{11} and R^{11a} are each independently selected at each occurrence from halogen, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-CH_2N(R^{12})S(O)_2(R^{13})$, and $-P(O)(R^{17})(R^{17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{20};

R^{11b} is independently selected at each occurrence from halogen, oxo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, 3- to 10-membered heterocycle, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})(R^{13})$, $-C(O)OR^{12}$, $-OC(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)OR^{15}$, $-N(R^{14})S(O)_2R^{15}$, $-C(O)R^{15}$, $-S(O)R^{15}$, $-OC(O)R^{15}$, $-C(O)N(R^{12})(R^{13})$, $-C(O)C(O)N(R^{12})(R^{13})$, $-N(R^{14})C(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2N(R^{12})(R^{13})$, $-S(=O)(=NH)N(R^{12})(R^{13})$, $-CH_2C(O)N(R^{12})(R^{13})$, $-CH_2N(R^{14})C(O)R^{15}$, $-CH_2S(O)_2R^{15}$, $-CH_2S(O)_2N(R^{12})(R^{13})$, $-CH_2N(R^{12})S(O)_2(R^{13})$, and $-P(O)(R^{17})(R^{17a})$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{20};

R^{11c} is independently selected at each occurrence from halogen, $-OR^{12}$, and $-N(R^{12})(R^{13})$;

R^{12} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{20};

R^{13} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl; or R^{12} and R^{13}, together with the nitrogen atom to which they are attached, form a 3- to 10-membered heterocycle optionally substituted with one, two, or three R^{20};

R^{14} is independently selected at each occurrence from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^{15} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three R^{20};

R^{17} and R^{17a} are each independently selected at each occurrence from C_{1-6} alkyl and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl and C_{3-6} cycloalkyl are optionally substituted with one, two or three R^{20}; or R^{17} and R^{17a}, together with the phosphorous atom to which they are attached, form a 3- to 10-membered heterocycle;

R^{20} is independently selected at each occurrence from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-}

$_6$ alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, -CH_2-(3- to 10-membered heterocycle), -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, -$OCH_2C(O)OR^{22}$, and -$OC(O)R^{25}$, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, -CH_2-(C_{3-10} carbocycle), 3- to 10-membered heterocycle, and -CH_2-(3- to 10-membered heterocycle) are optionally substituted with one, two, or three groups independently selected from halogen, oxo, =NH, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, -OR^{21}, -SR^{21}, -$N(R^{22})(R^{23})$, -$C(O)OR^{22}$, -$C(O)N(R^{22})(R^{23})$, -$C(O)C(O)N(R^{22})(R^{23})$, -$OC(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)N(R^{22})(R^{23})$, -$N(R^{24})C(O)OR^{25}$, -$N(R^{24})C(O)R^{25}$, -$N(R^{24})S(O)_2R^{25}$, -$C(O)R^{25}$, -$S(O)_2R^{25}$, -$S(O)_2N(R^{22})(R^{23})$, and -$OC(O)R^{25}$;

R^{21} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{22} is independently selected at each occurrence from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{3-10} carbocycle and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen and C_{1-6} alkyl;

R^{23} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{24} is independently selected at each occurrence from H and C_{1-6} alkyl;

R^{25} is independently selected at each occurrence from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle, wherein C_{1-6} alkyl, C_{3-10} carbocycle, and 3- to 10-membered heterocycle are optionally substituted with one, two, or three groups independently selected from halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-10} carbocycle, and 3- to 10-membered heterocycle; and

------ indicates a single or double bond such that all valences are satisfied.

2. The use of claim 1, wherein the genetic aberration is a mutation in *BCR-ABL* associated with resistance to a tyrosine kinase inhibitor against BCR-ABL tyrosine kinase (TKI).

3. The use of claim 1, wherein the genetic aberration is characterized by a mutation in BCR-ABL selected from the group consisting of T315I, F359V, Y253H, E255K, M351T, G250E, F359I, and H396R.

4. The use of any one of claims 1 to 3, wherein the Ph+ blood cancer is selected from the group consisting of chronic myelogenous leukemia (CML), Ph+ acute lymphoblastic leukemia (Ph+ALL), and Ph+ lymphoblastic lymphoma (Ph+LBL).

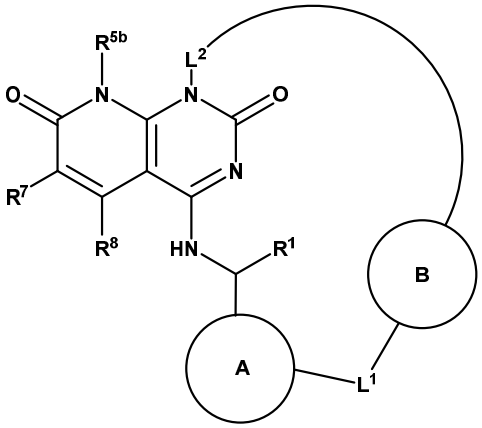
5. The use of any one of claims 1 to 4, wherein the treatment further comprises an additional agent or additional therapy.

6. The use of claim 5, wherein the additional agent is selected from the group consisting of dasatinib, nilotinib, bosutinib, radotinib, flumatinib, ponatinib, olverembatinib, and asciminib.

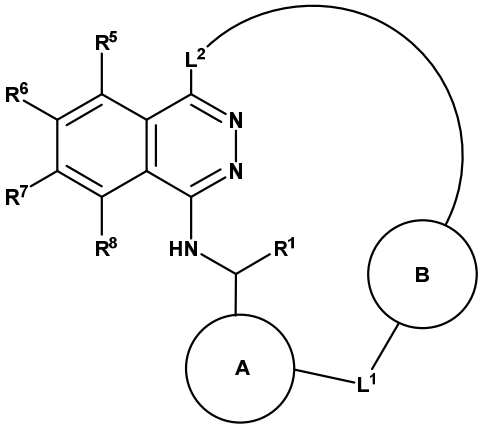
7. The use of any one of claims 1 to 6, wherein the subject has previously been treated with a tyrosine kinase inhibitor against BCR-ABL tyrosine kinase (TKI).

8. The use of any one of claims 1 to 7, wherein the compound of Formula (I-1) is a compound of Formula (I-

B1) or (I-B2):



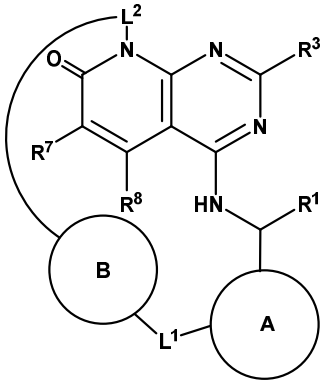
(I-B1) or



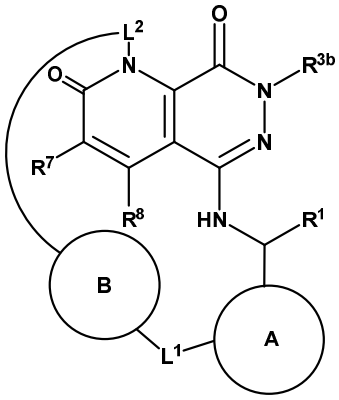
(I-B2),

or a pharmaceutically acceptable salt or solvate thereof.

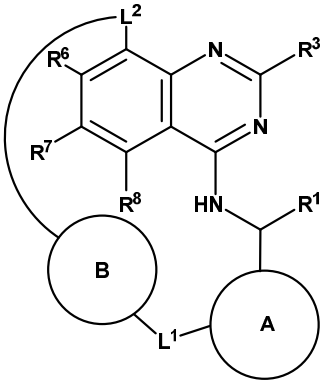
9. The use of any one of claims 1 to 7, wherein the compound of Formula (I-1) is a compound of Formula (I-C1), (I-C2), or (I-C3):



(I-C1),



(I-C2), or



(I-C3),

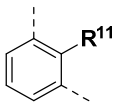
or a pharmaceutically acceptable salt or solvate thereof.

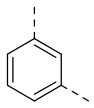
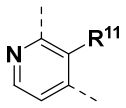
10. The use of any one of claims 1 to 9, wherein R^1 is $-CH_3$, R^3 is selected from hydrogen, -CN, $-OR^{12}$, and $-CH_3$, and R^8 is hydrogen.

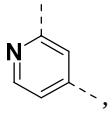
11. The use of any one of claims 1 to 10, wherein R^6 is selected from hydrogen, $-OR^{12}$, and C_{1-6} alkyl optionally substituted with one, two, or three R^{20}, and wherein R^{12} is selected from C_{1-6} alkyl.

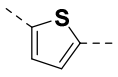
12. The use of any one of claims 1 to 11, wherein R^7 is selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and $-N(R^{12})(R^{13})$, wherein C_{1-6} alkyl, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl are optionally substituted with one, two, or three R^{20}.

13. The use of any one of claims 1 to 12, wherein 

is selected from 

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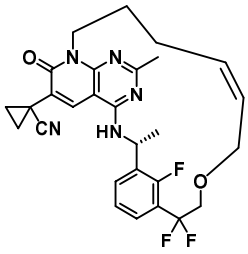
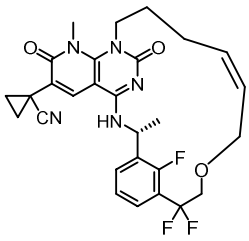
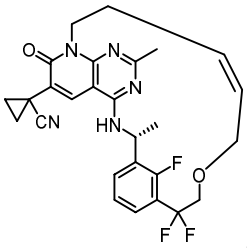
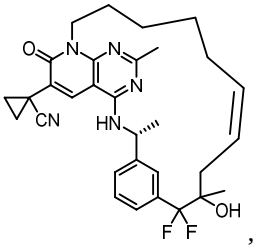
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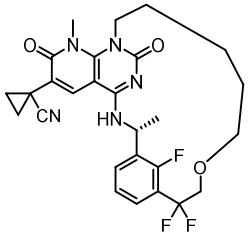
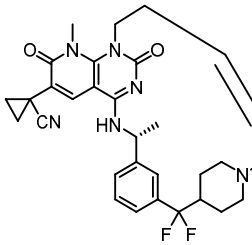
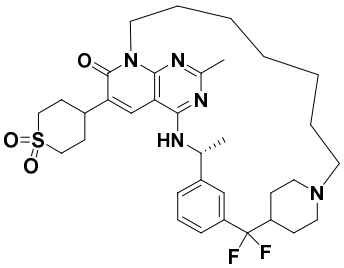
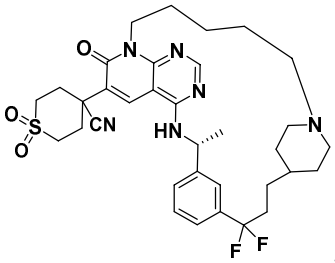
, and R^{11} is independently selected from fluorine and $-CH_3$.

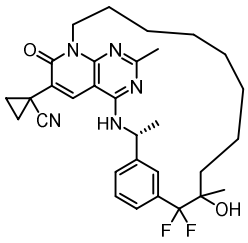
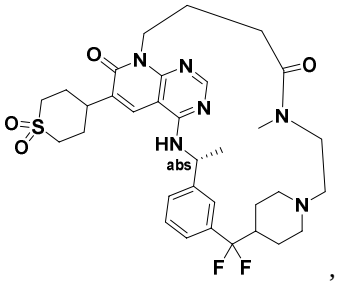
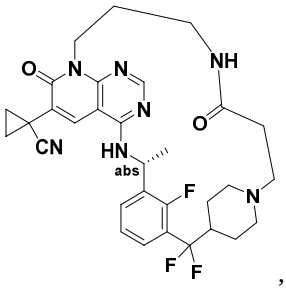
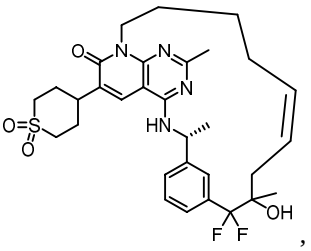
14. The use of any one of claims 1 to 13, wherein L^1 is C_{1-3} haloalkylene; L^2 is selected from C_{6-15} alkylene, C_{6-15} alkenylene, C_{6-15} alkynylene, 6- to 15-membered heteroalkylene, and 6- to 15-membered heteroalkenylene,

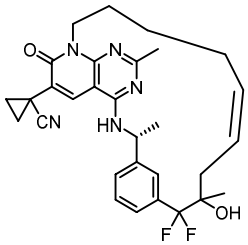
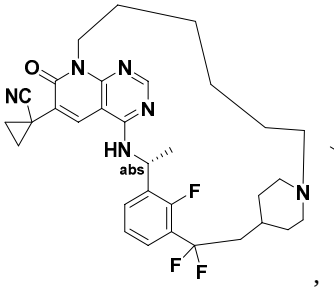
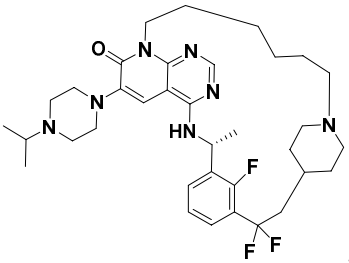
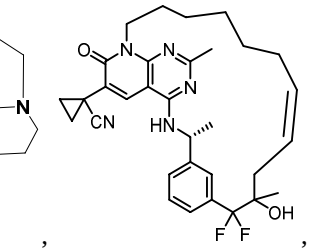
each of which is optionally substituted with one or more R^{11b}; and  is selected from absent, phenyl, and 4- to 8-membered heterocycle, wherein the phenyl and 4- to 8-membered heterocycle are optionally substituted with one or more R^{11a}.

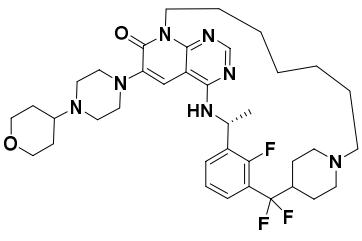
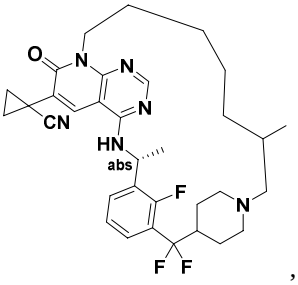
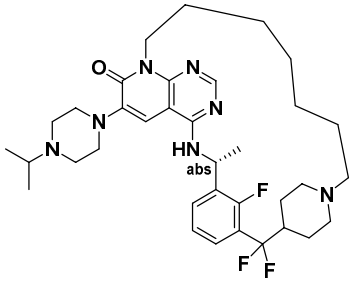
15. The use of any one of claims 1 to 7, wherein the compound of Formula (I-1) is selected from

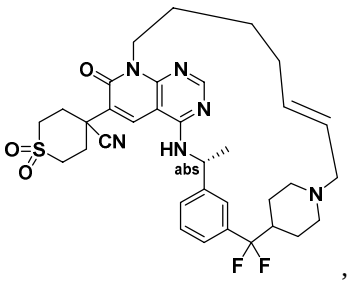
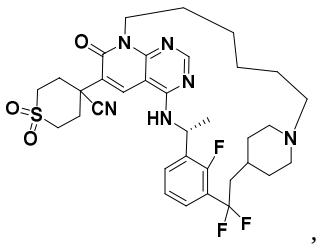
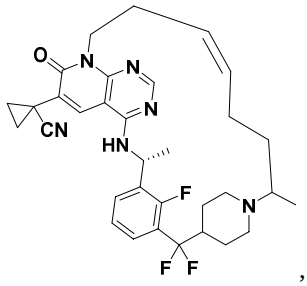
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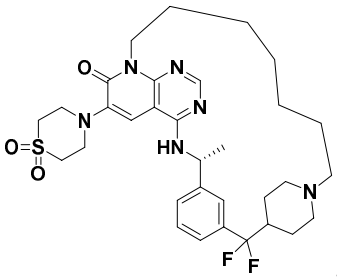
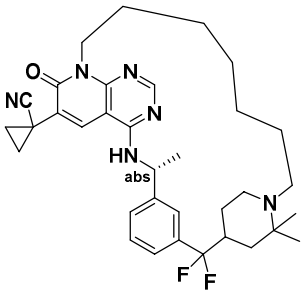
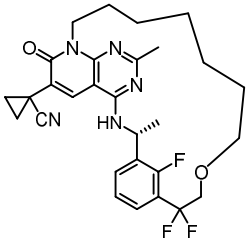
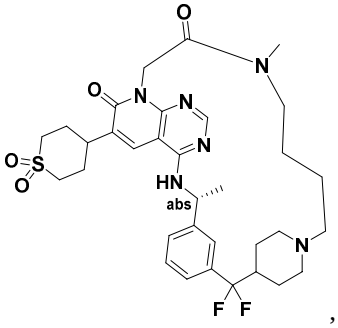
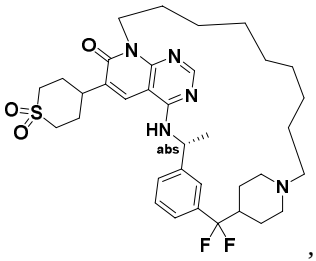
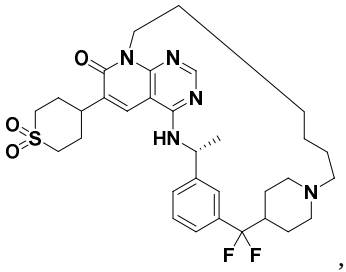
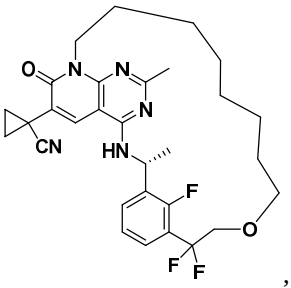
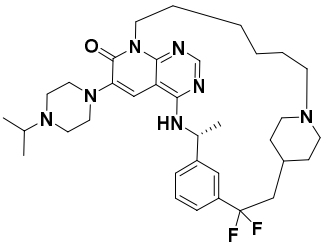
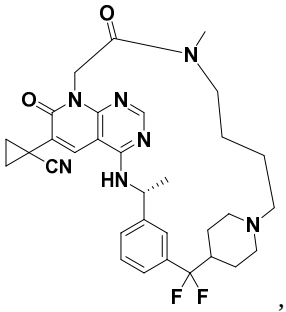
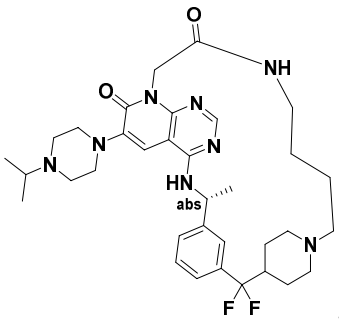
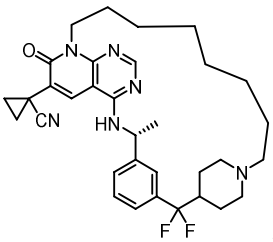
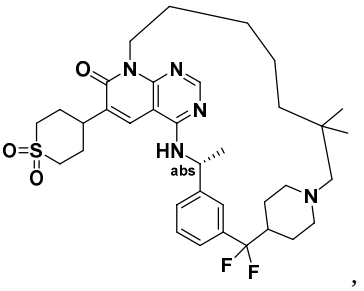
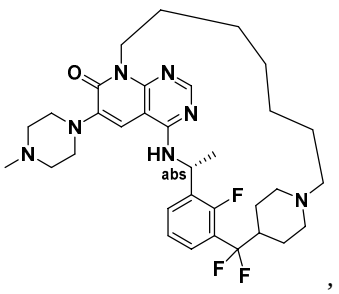
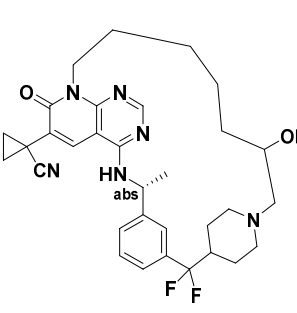
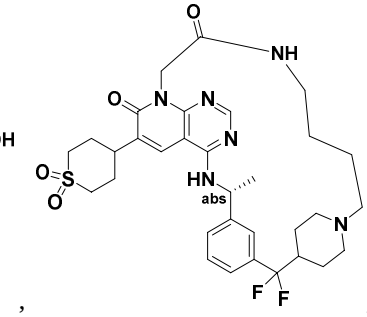
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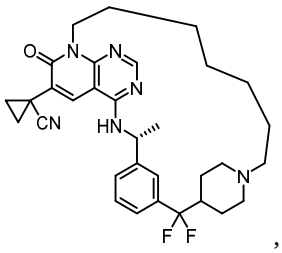
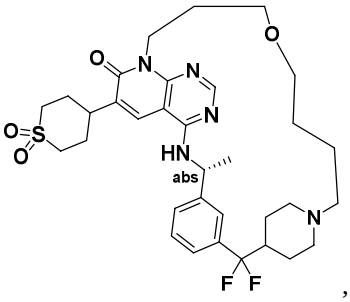
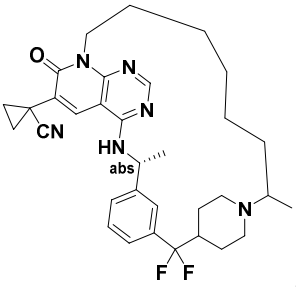
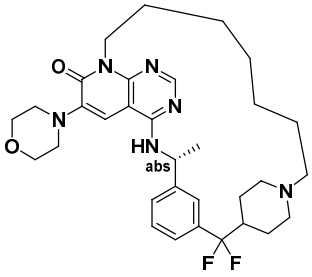
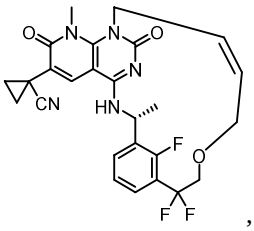
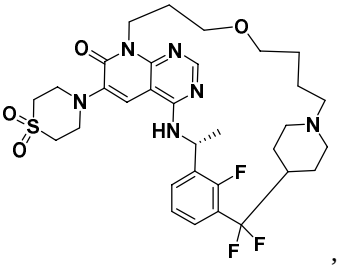
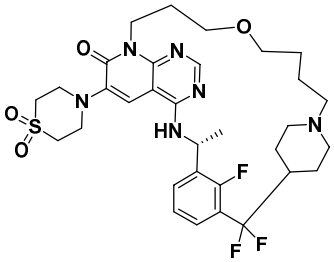
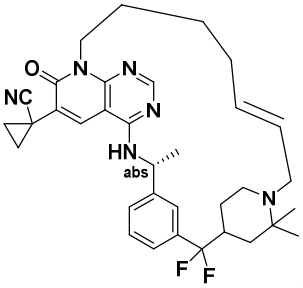
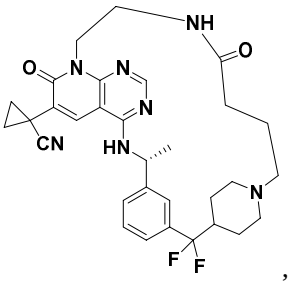
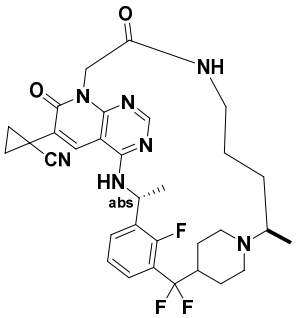
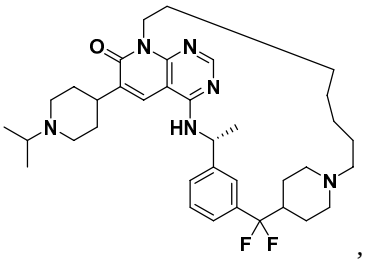
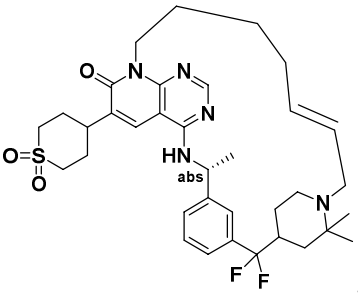
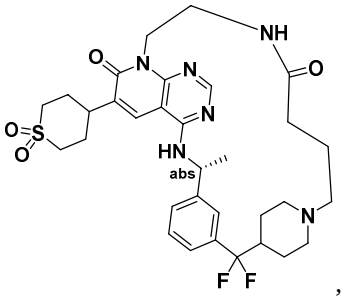
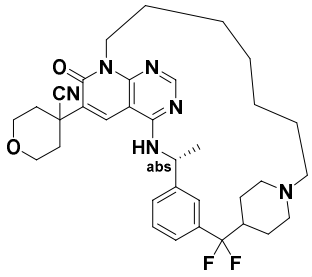
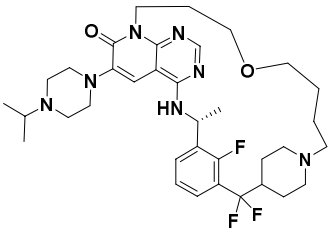
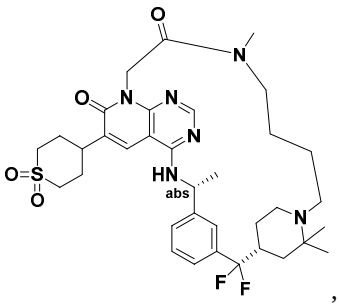
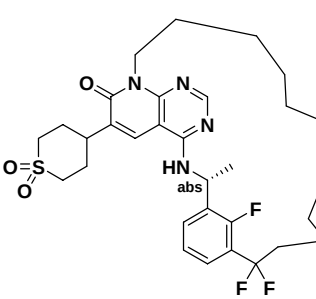

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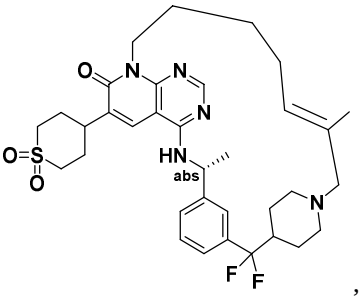
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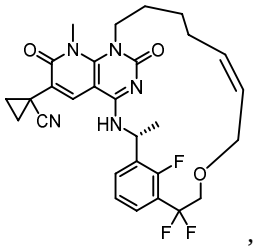
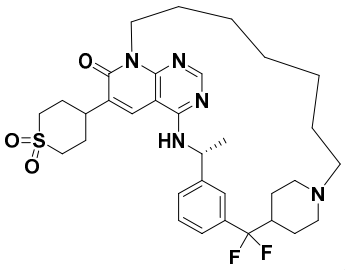
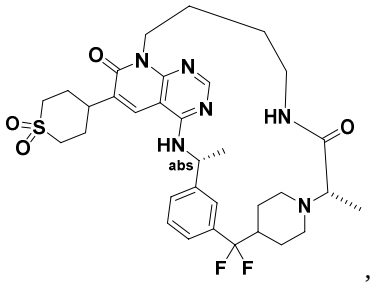
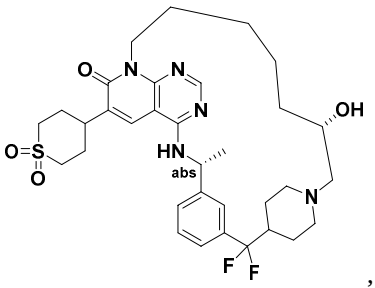
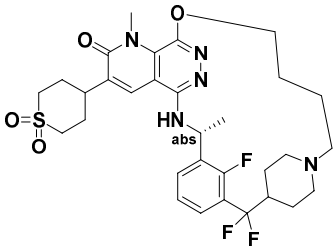
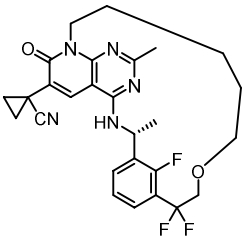
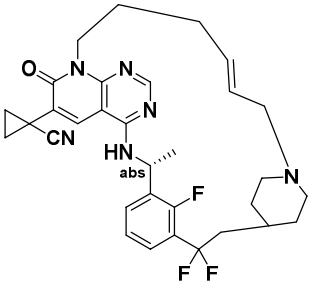
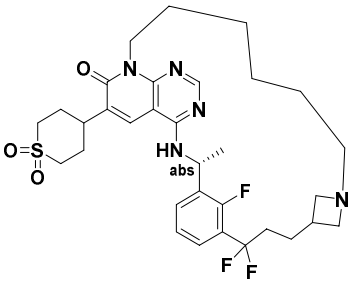
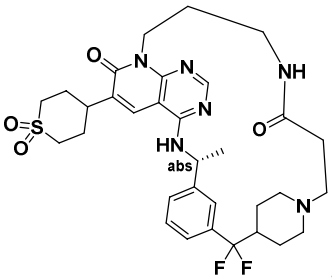
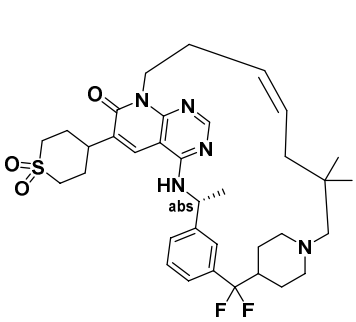
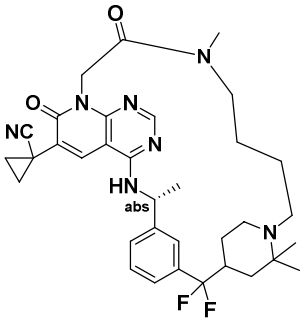
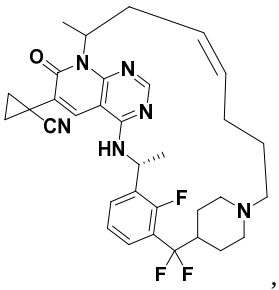
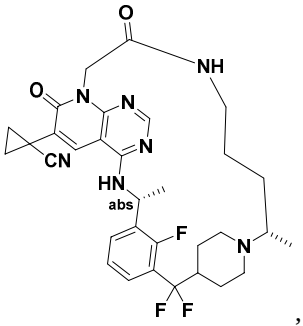
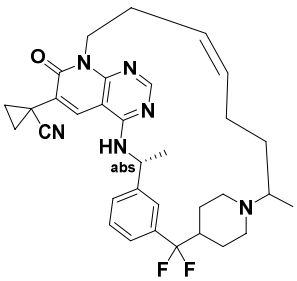
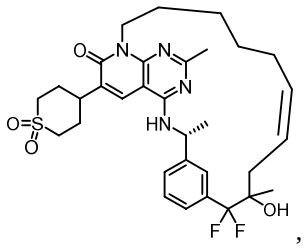
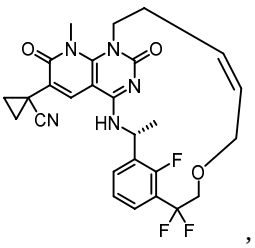
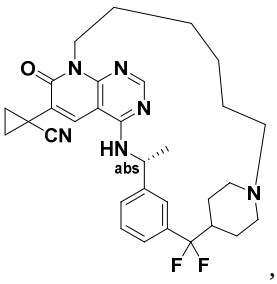
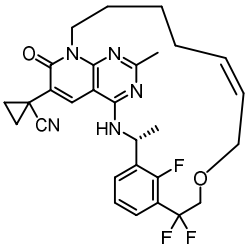
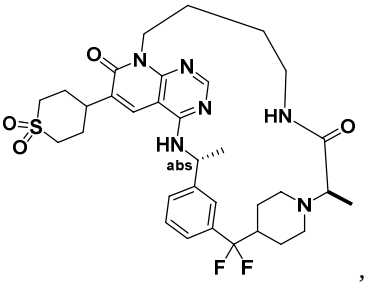
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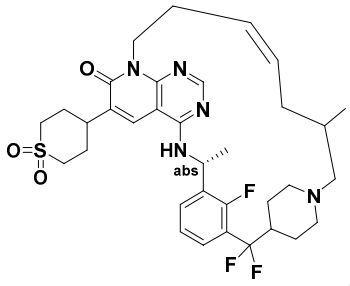
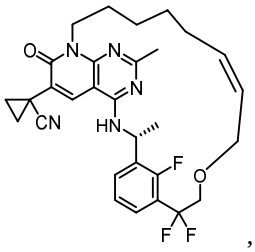
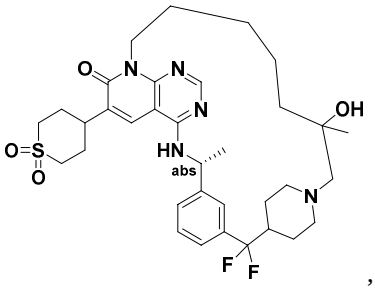
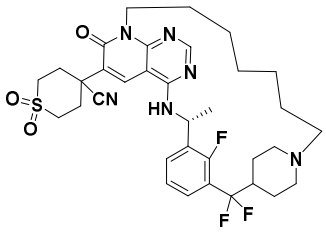
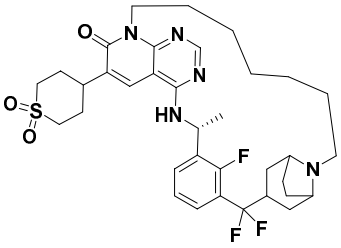
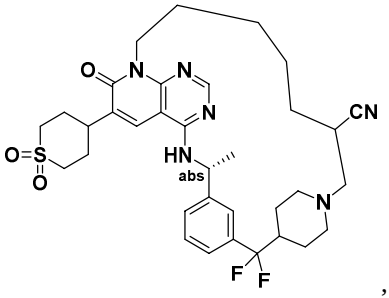
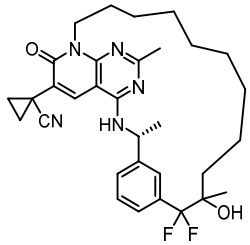
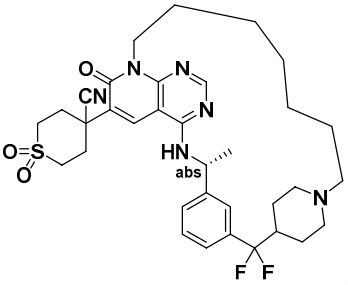
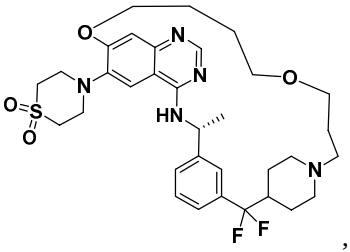
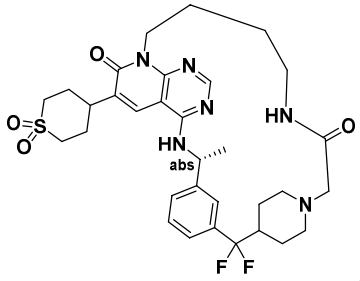
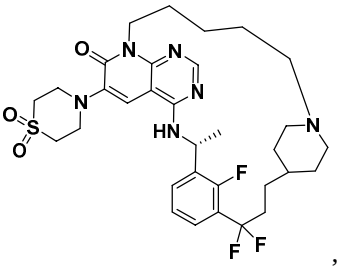
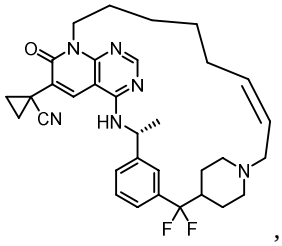
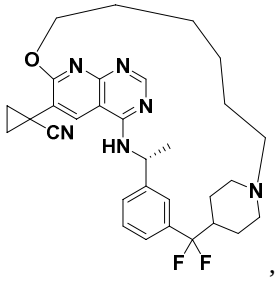
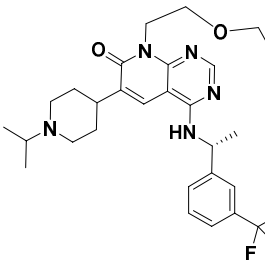
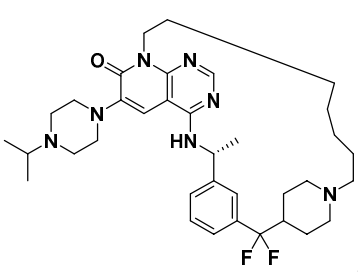
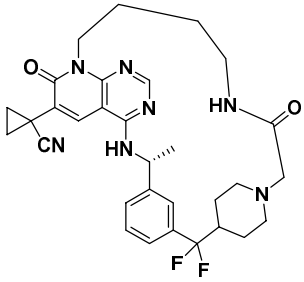
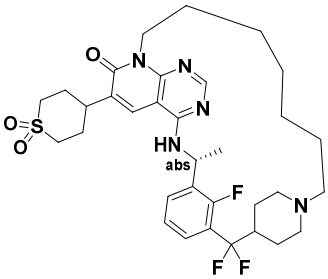
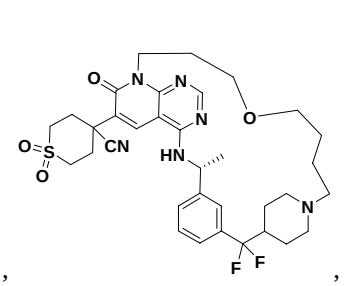

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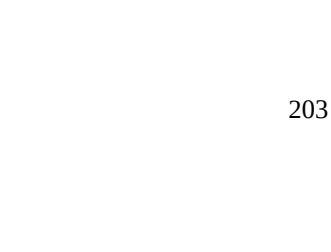
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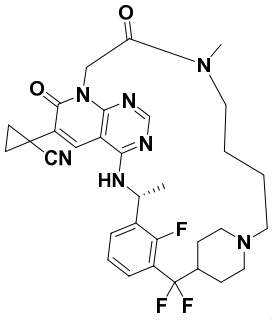
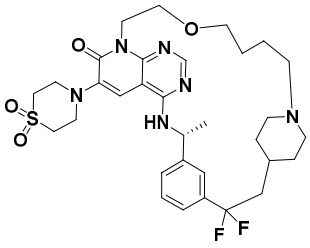
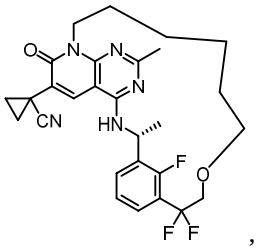
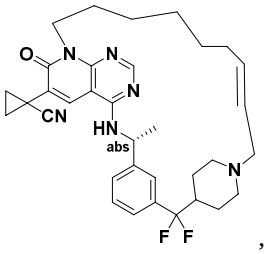
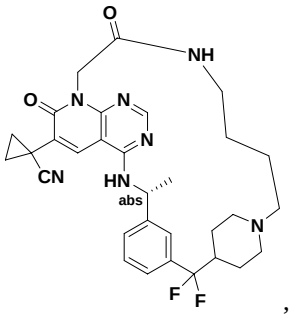
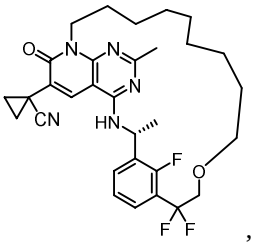
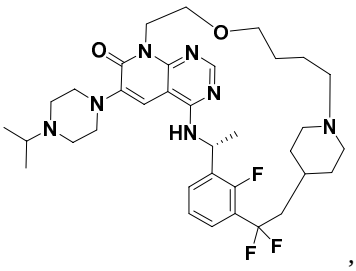
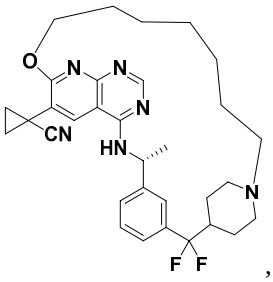
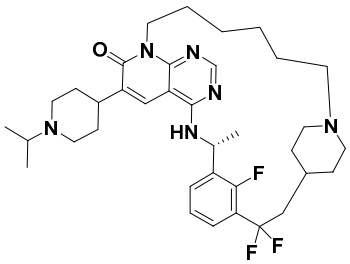
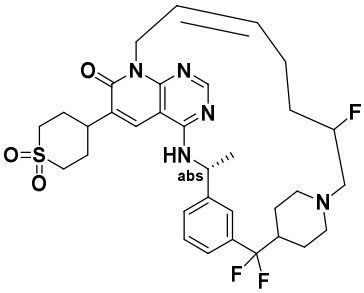
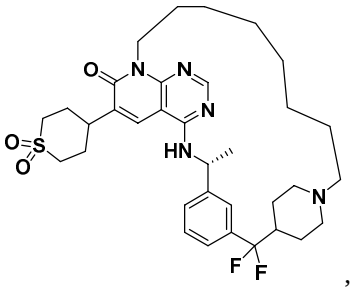
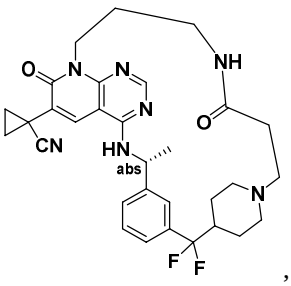
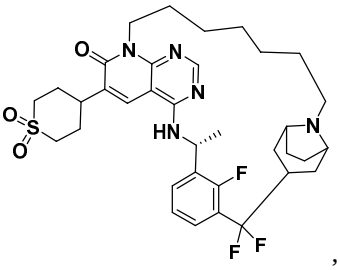
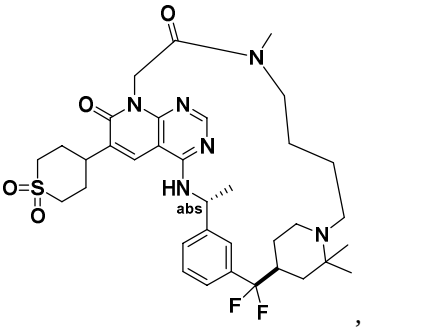
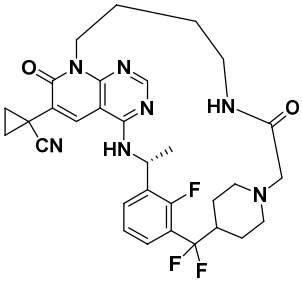
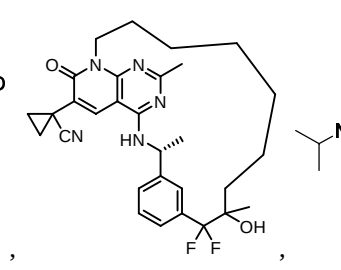
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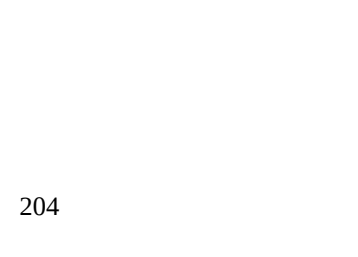
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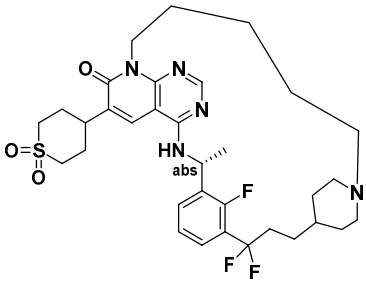
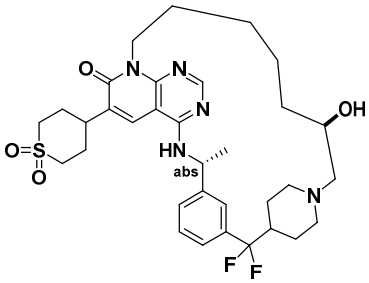
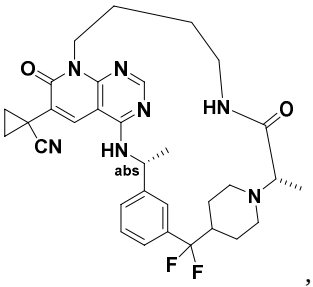
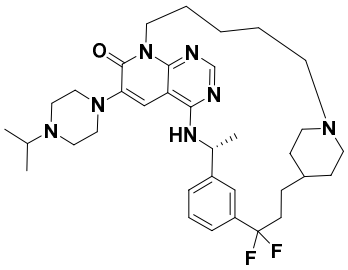
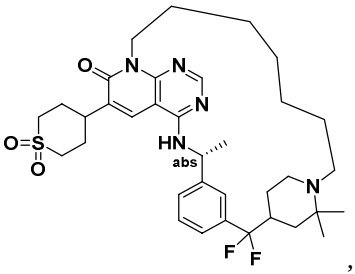
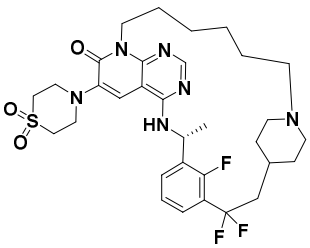
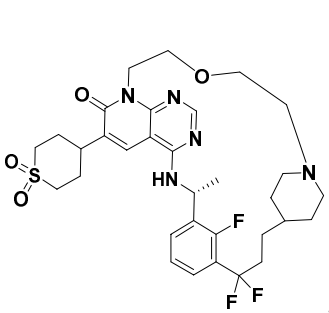
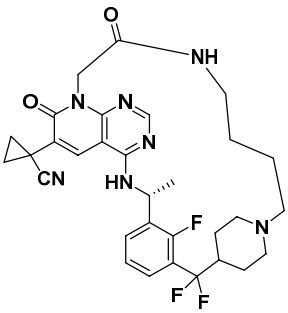
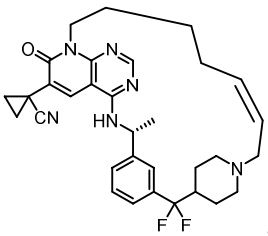
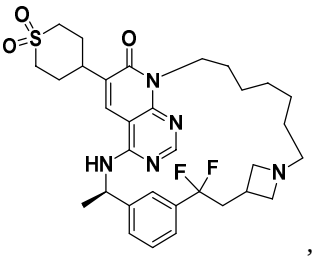
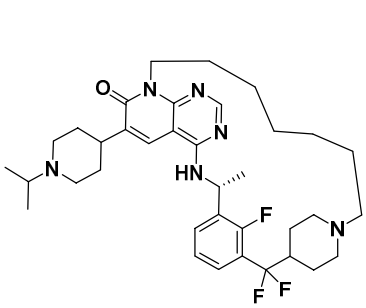
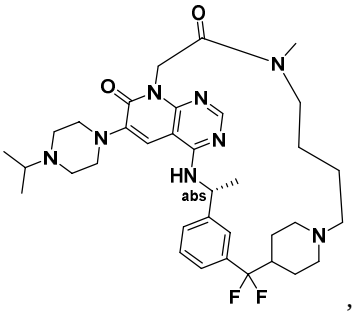
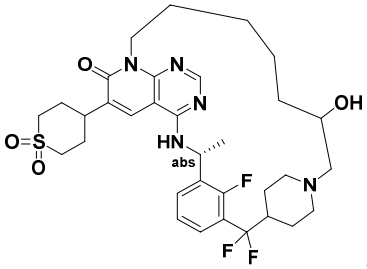
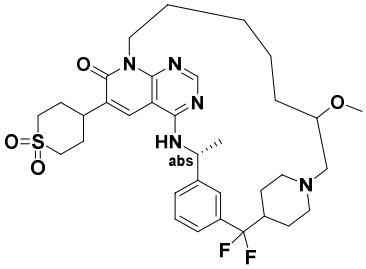
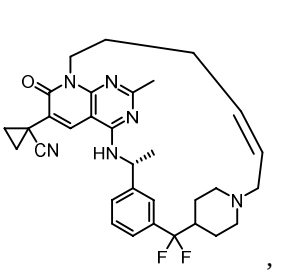
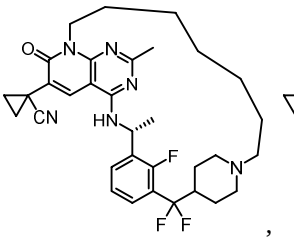
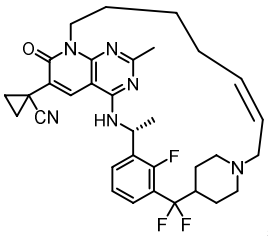
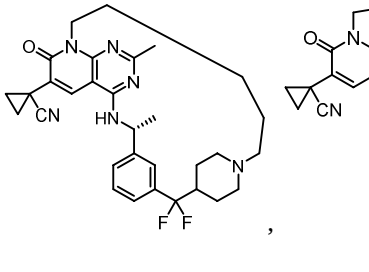
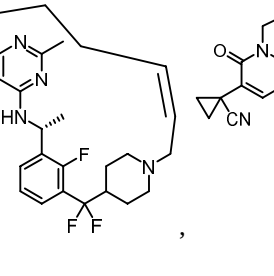
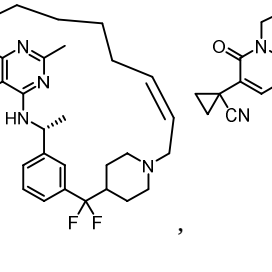
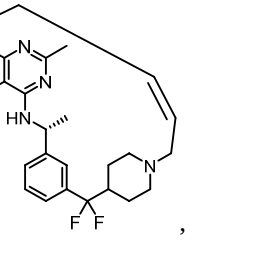
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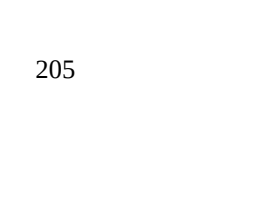
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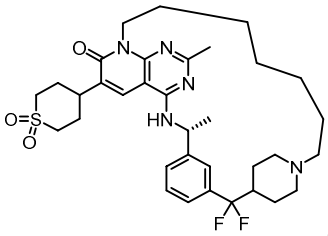
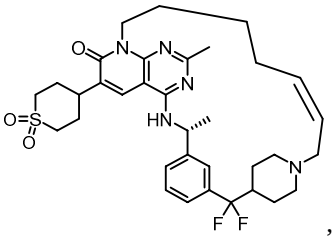
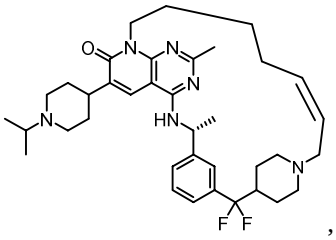
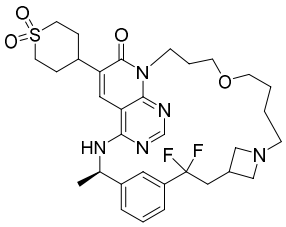
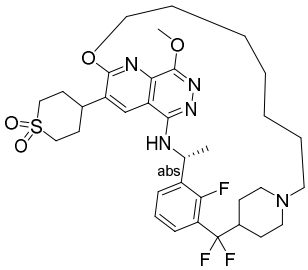
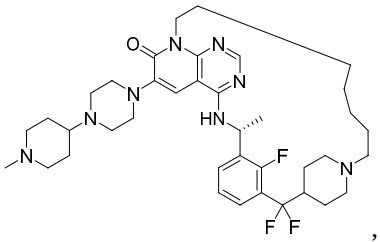
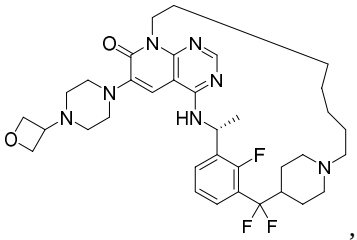
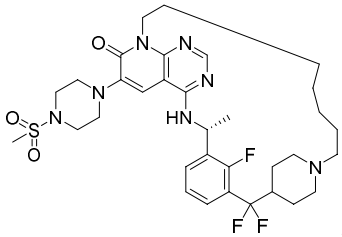
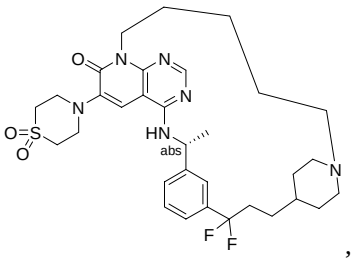
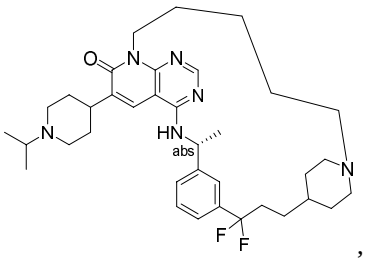
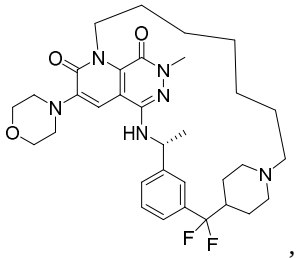
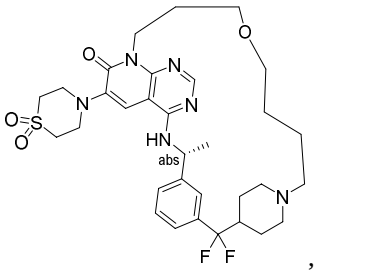
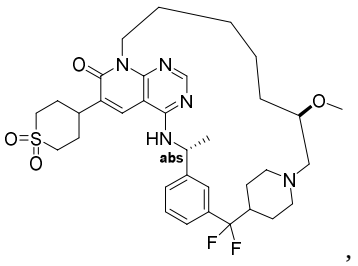
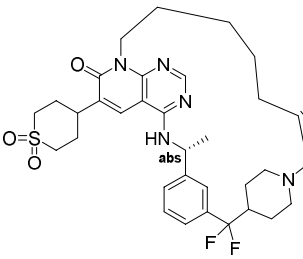
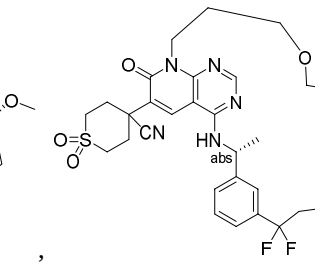
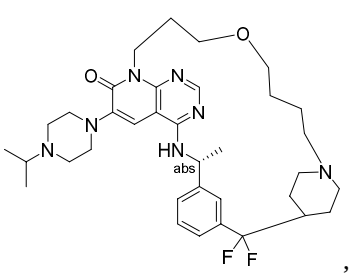
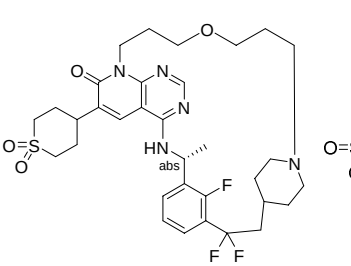
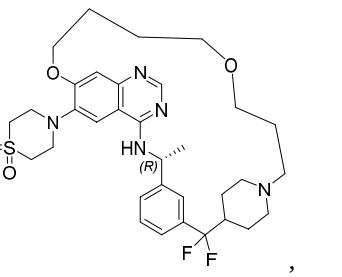
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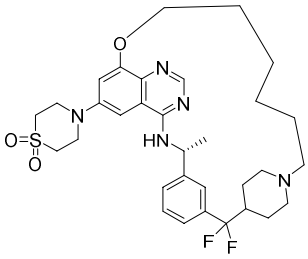
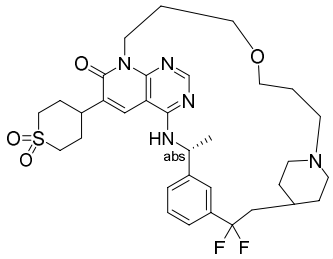
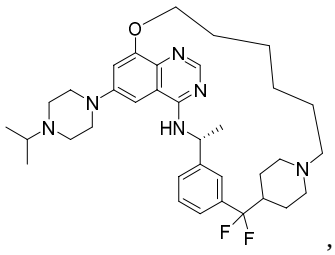
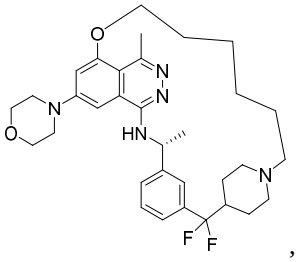
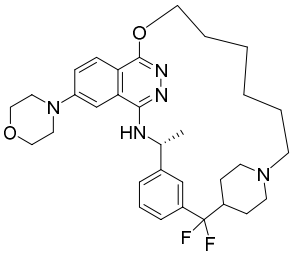
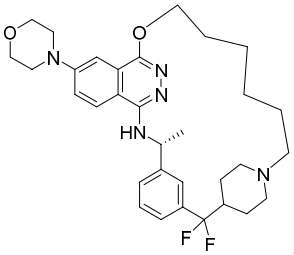
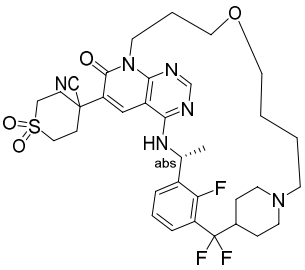
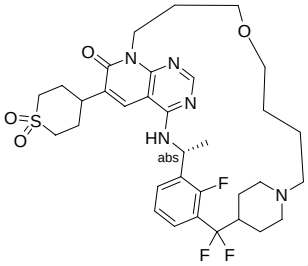
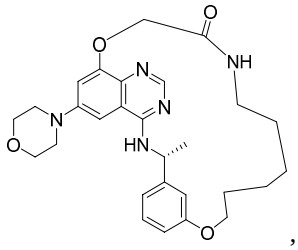
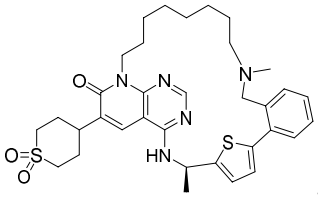
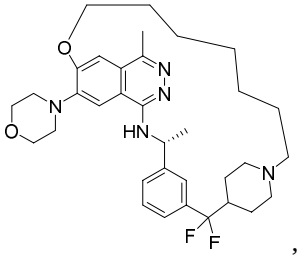
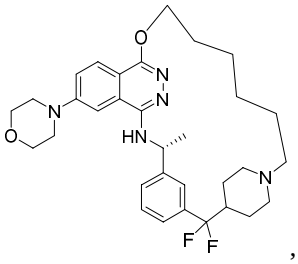
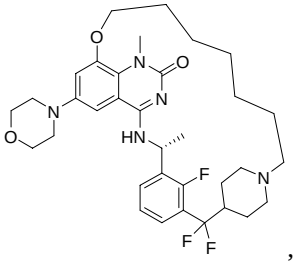
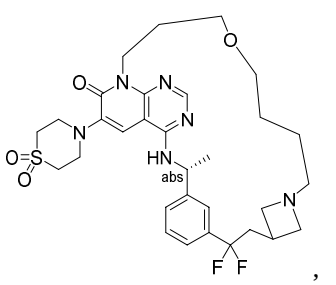
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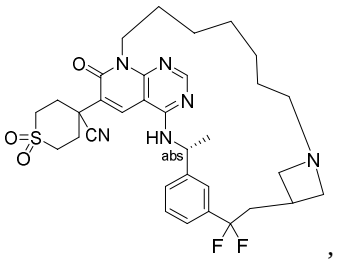
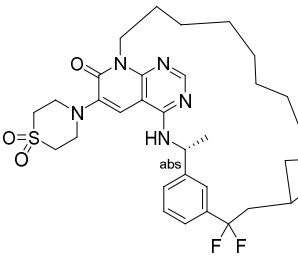
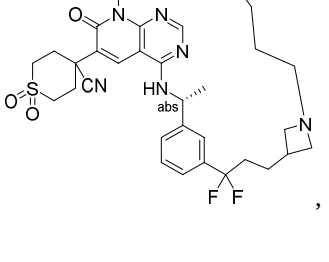
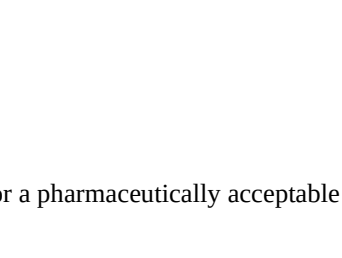
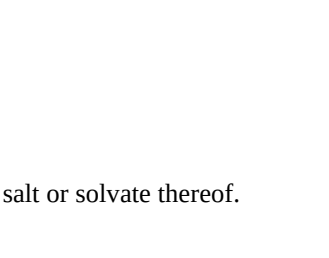

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