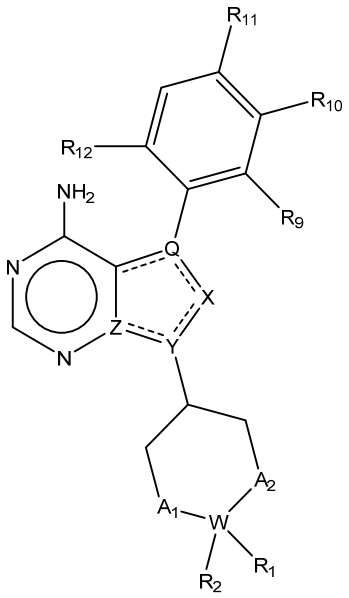
Claims

1. A compound of Formula (I):



(I)

wherein

each Q, Y and Z are independently selected from N and C, and X is N or C-R^a;

provided that at least one of Q, X, Y and Z is N, and

each dashed bond is independently a single or double bond such that the bicycle they form is a heteroaryl;

R_1 is selected from alkyl, alkenyl, alkynyl, amino, acylamino, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, and heteroaralkyl;

either

a) W is N, R_2 is absent, and A_1 and A_2 are each CH_2;

b) W is C, R_2 is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, and amino, and A_1 and A_2 are each independently selected from CH_2 and O; or

c) W is C, and R_1 and R_2 are taken together to form a =CH_2-amido, cycloalkyl, and heterocyclyl, and A_1 and A_2 are each independently selected from CH_2 and O;

R^a is selected from H, halo, CN and alkyl;

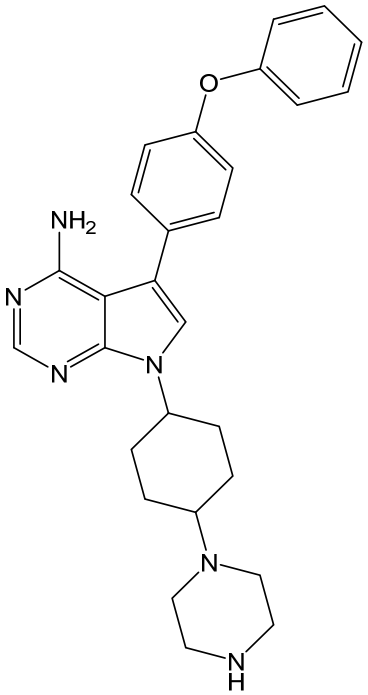
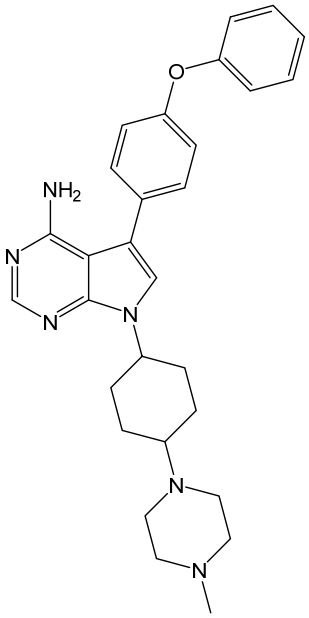
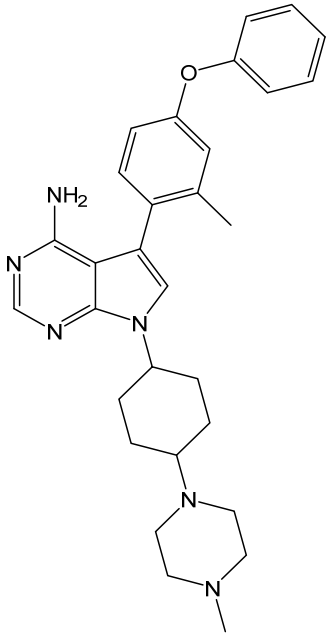
R_9 is selected from H, halo, alkyl, alkoxy, hydroxy, acyloxy, and amino;

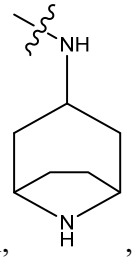
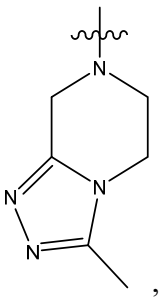
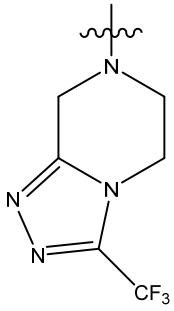
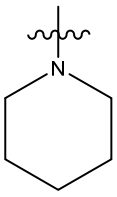
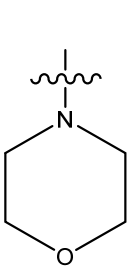
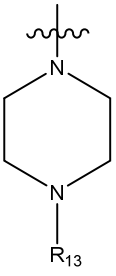
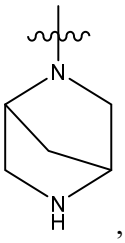
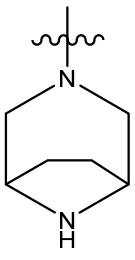
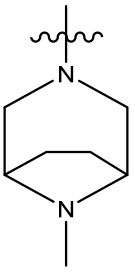
R_{10} is H or alkoxy;

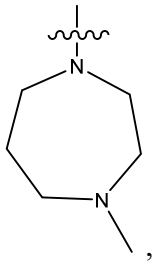
R_{11} is aryloxy, heteroaryloxy, arylalkyl, alkoxycarbonyl, ureido or -C(O)-aryl; and

R_{12} is selected from H, halo, CN, alkyl, alkoxy, hydroxy, and acyloxy;

provided that the compound of Formula (I) is not



or

; and

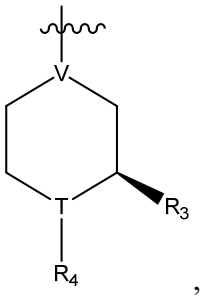
if W is C, R_2, R_9 and R_{12} are each hydrogen, and R_{11} is unsubstituted phenyloxy, then R_1 is not -$NHCH_2OH$, -$NHCH_2COOH$, -$NHCH_2CONH_2$, -$NHCH_2CH_2NH_2$, -$NH(CH_2)_2N(Me)_2$, -$NHCH_2$-pyridinyl, -NHCO-pyridyl, -C(O)OEt, -NH-tetrahydropyran, -$NHCH_2$pyrrolidinyl, -$NH(CH_2)_3$imidazolyl, -NHpyrrolidinonyl, , , , , , , , , , or



,

wherein R_{13} is selected from H, ethyl, isopropyl, t-butyl, -CH_2OCH_3, -CH_2CH_2OH and -$CH_2CH_2OCH_3$; and

if W is N, R_9 and R_{12} are each hydrogen, and R_{11} is unsubstituted phenyloxy, then R_1 is not piperidinyl.

2. The compound of any one of claims 1-5, wherein R_1 is 

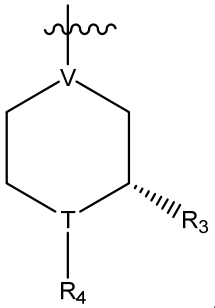
,

V is N or CH;

T is N or CH;

R_3 is alkyl; and

R_4 is H or alkyl.

3. The compound of any one of claims 1-5, wherein R_1 is 

,

V is N or CH;

T is N or CH;

R_3 is alkyl; and

R_4 is H or alkyl.

4. The compound of any one of claims 1-3, wherein

Q is C, X is C-R^a, R^a is H, Y is N and Z is C;

Q is C, X is C-R^a, R^a is halo, Y is N and Z is C;

Q is C, X is N, Y is C and Z is N;

Q is C, X is N, Y is N and Z is C;

Q is N, X is C-R^a, R^a is H, Y is C and Z is C;

Q is C, X is C-R^a, R^a is H, Y is C and Z is N; or

Q is C, X is C-R^a, R^a is H, Y is N and Z is C.

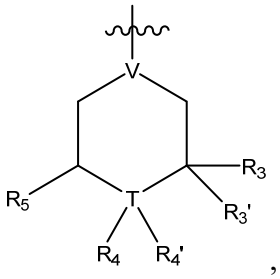
5. The compound of any one of claims 1-4, wherein A_1 and A_2 are both CH_2.

6. The compound of any one of claims 1-4, wherein A_1 and A_2 are both O.

7. The compound of claim 1, wherein R_2 is selected from H, hydroxy and amino.

8. The compound of any one of claims 1-7, wherein R_1 is selected from alkyl, amino, cycloalkyl, heterocyclyl, heterocyclylalkyl, and heteroaryl.

9. The compound of any one of claims 1-8, wherein R_1 is selected from



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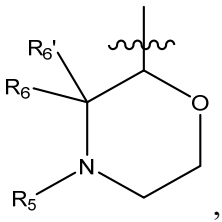

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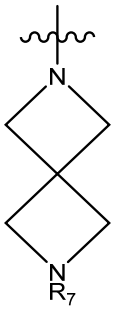

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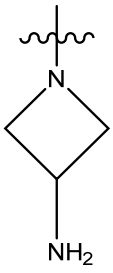

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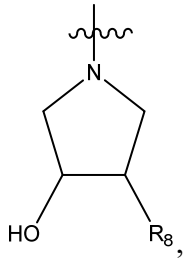

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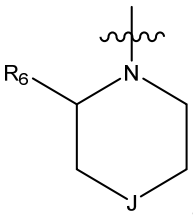

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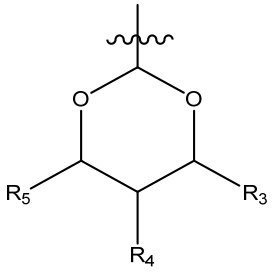

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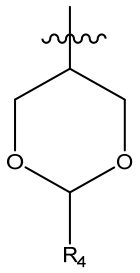


;

V is N or CH;

either T is N and R_4' is absent, or T is C;

J is selected from sulfonyl, C(H)sulfonamido, and >P(=O)-alkyl;

R_3 is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, amino, amido, cycloalkyl, heterocyclyl, carboxy, and alkoxycarbonyl;

R_3' is H or alkyl, or

R_3 and R_3' taken together with the carbon atom to which they are attached form a cycloalkyl;

R_4 is selected from H, halo, CN, alkyl, alkoxy, acyloxy, amino, and amido;

R_4' is H or alkyl;

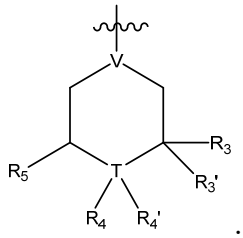
R_5 is H or alkyl;

R_6 and R_6' are each H;

R_6 and R_6' together with the carbon atom to which they are attached form an oxo;

R_7 is H or alkyl; and

R_8 is H, hydroxy, acyloxy, or amino.

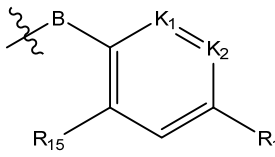
10. The compound of claim 9, wherein R_1 is 

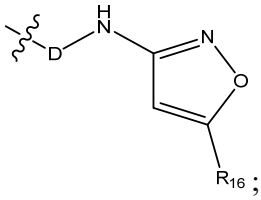
.

11. The compound of any one of claim 9-10, wherein R_3 is selected from H, alkyl, amino, cycloalkyl, heterocyclyl, carboxy, and alkoxycarbonyl.

12. The compound of any one of claims 9-11, wherein R_9 is selected from halo, alkyl, alkoxy, hydroxy, acyloxy, and amino.

13. The compound of any one of claims 9-12, wherein

R_{11} is selected from amido, 

, and 

;

B is selected from -O-, CH_2, CHOH, NH, N(C_{1-6}alkyl) and carbonyl;

K_1 and K_2 are independently selected from N and CR_{13};

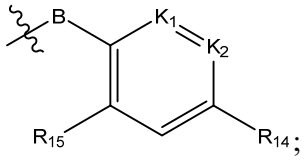
D is selected from -CH_2-C(O)-, -NH-C(O)-, N(C_{1-6}alkyl)-C(O), and -$CH_2S(O)_2$-;

R_{13} is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, alkoxycarbonyl, amino, amido, and alkoxycarbonyl;

R_{14} is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, alkoxycarbonyl, amino, amido, and alkoxycarbonyl;

R_{15} is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, alkoxycarbonyl, amino, amido, and alkoxycarbonyl; and

R_{16} is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, amino, amido, and alkoxycarbonyl.

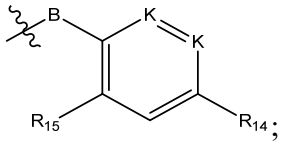
14. The compound of claim 13, wherein R_{11} is ;

B is O;

K_1 and K_2 are each CH;

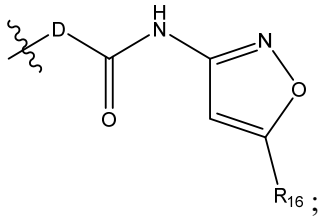
R_{14} is H; and

R_{15} is H.

15. The compound of claim 13, wherein R_{11} is ;

K_1 and K_2 are each N; and

R_{14} and R_{15} are each H.

16. The compound of claim 13, wherein R_{11} is ;

D is NH; and

R_{16} is alkyl.

.17. Use of a compound of formula (I) according to any one of claims 1-16 in the manufacture of a medicament for treating acute myeloid leukemia, wherein the compound of formula (I) is to be administered conjointly with a BCL-2 inhibitor.

18. The use of claim 17, wherein the subject has FLT3-ITD+ acute myeloid leukemia.

19. The use of any one of claims 17-18, wherein the compound of formula (I) is a HCK inhibitor.

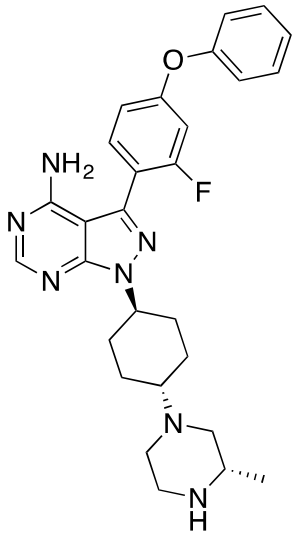
20. The use of any one of claims 17-19, wherein the medicament is for conjoint administration with a FLT3-ITD inhibitor.

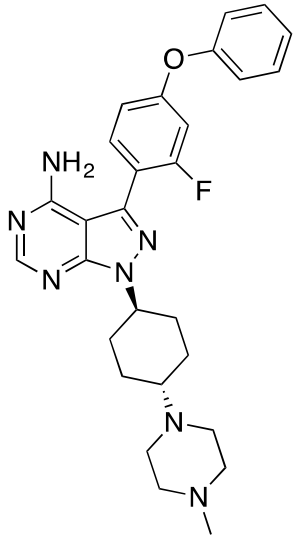
21. The use of claim 19, wherein the HCK inhibitor is a dual HCK/FLT3-ITD inhibitor.

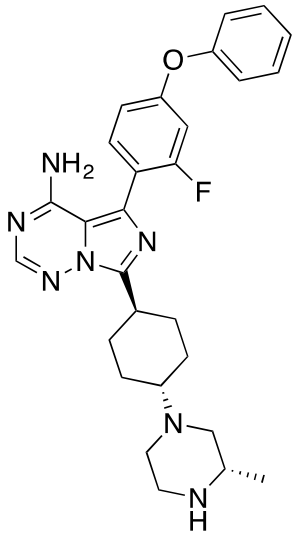
22. The use of claim 20wherein the FLT3-ITD inhibitor is selected from AC220, sorafenib, PKC412, CEP-701, UNC2025, MLN518, KW-2449 and AMG-925, sunitinib, SU5614, AC2206, crenolanib, and PLX3397.

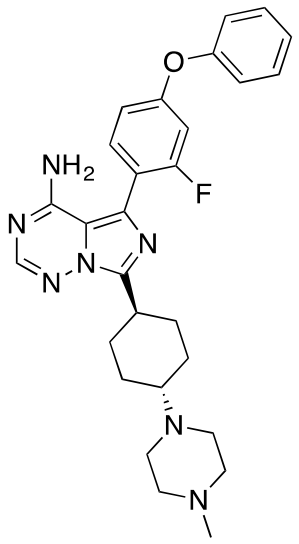
23. The use of any one of claims 17-22, wherein the BCL-2 inhibitor is selected from AT-101, TW-37, TM-1206, gossypolic acid, gossypolonic acid, apogossypol, apogossypolone, A385358, ABT-737, ABT-263, ABT-199, WEHI-539, BXI-61, BXI-72, obatoclax, JY-1-106, and SAHB peptides.

24. The use of claim 23, wherein the BCL-2 inhibitor is ABT-199.

25. The use of claim 19, wherein the HCK inhibitor is  and the BCL-2 inhibitor is ABT-199.

26. The use of claim 19, wherein the HCK inhibitor is  and the BCL-2 inhibitor is ABT-199.

27. The use of claim 19, wherein the HCK inhibitor is  and the BCL-2 inhibitor is ABT-199.

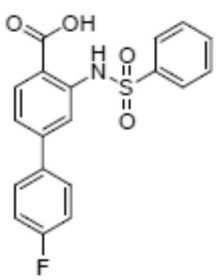
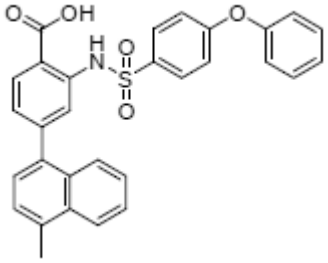
28. The use of claim 19, wherein the HCK inhibitor is  and the BCL-2 inhibitor is ABT-199.

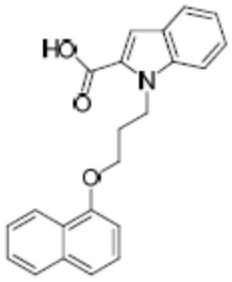
29. The use of any one of claims 17-28, wherein the medicament isfor conjoint administration with an anti-apoptosis agent.

30. The use of claim 29, wherein the anti-apoptosis agent is tretinoin, GGTI 298 TFA salt, BTSA1, AT406, SM-406, elesclomol, STA-4783, Ganetespib, STA-9090, NQDI-1, or zoledronic acid.

31. The use of any one of claims 17-30, wherein the medicament is for conjoint administration with an Mcl-1 inhibitor.

32. The use of claim 31, wherein the Mcl-1 inhibitor is

 ,  ,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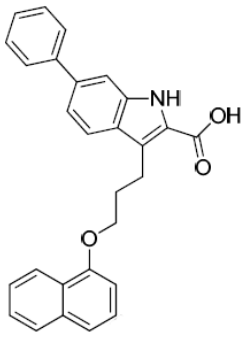
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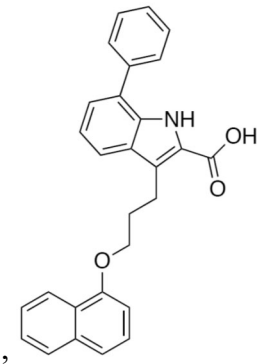
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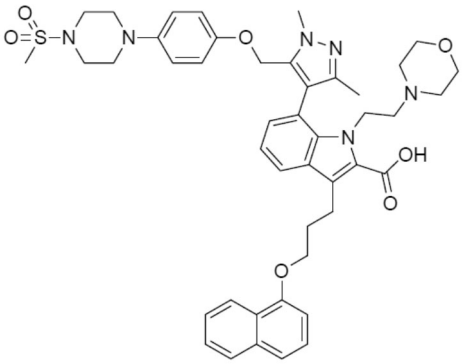
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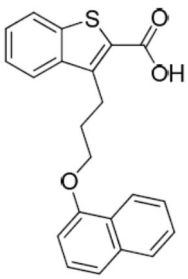
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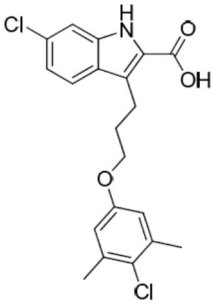
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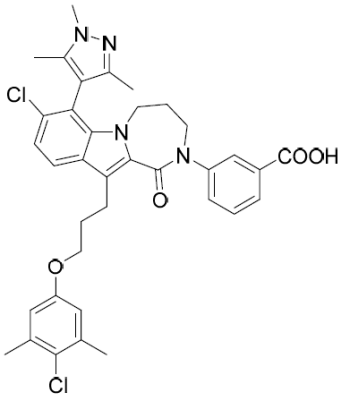
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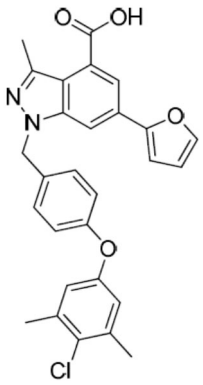
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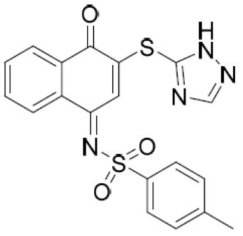
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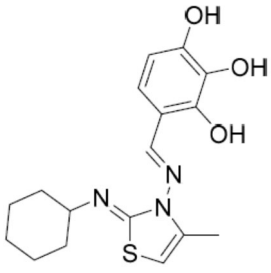
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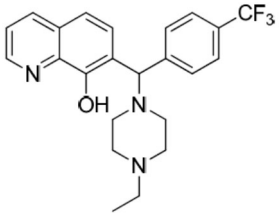
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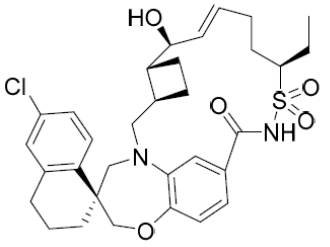
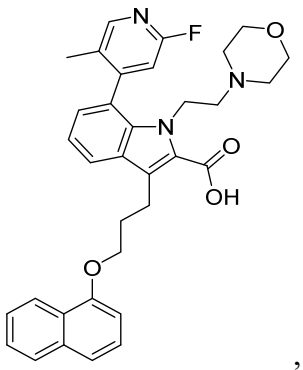
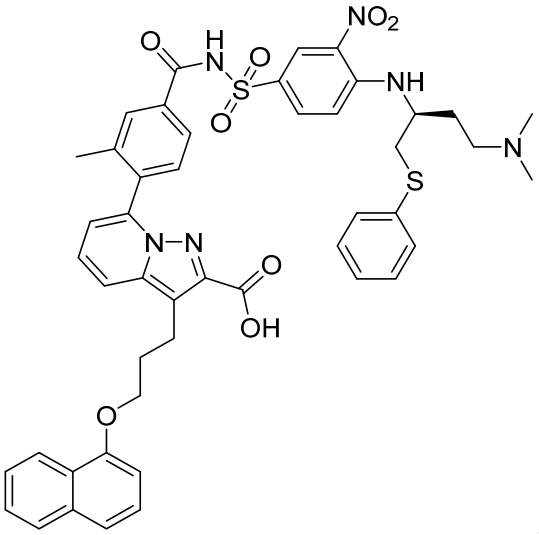
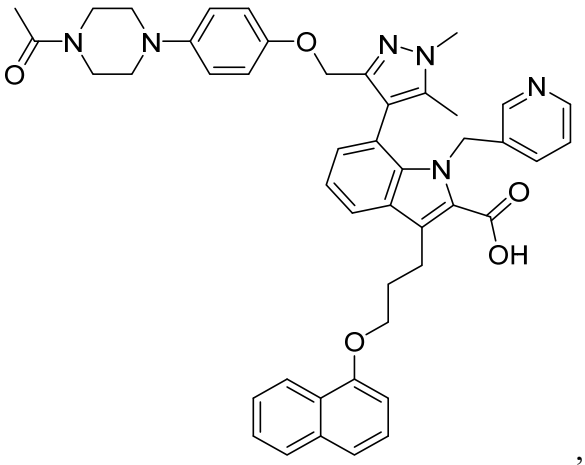
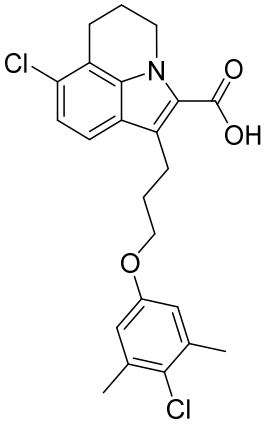
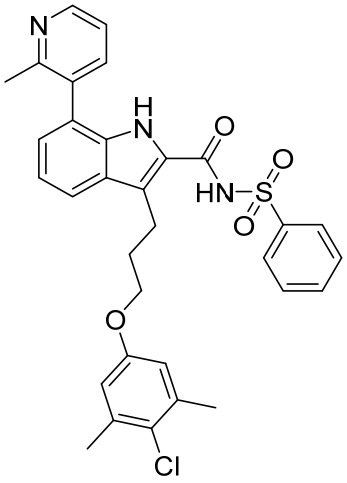
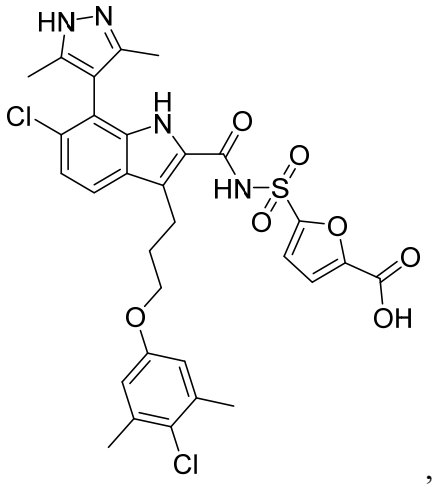

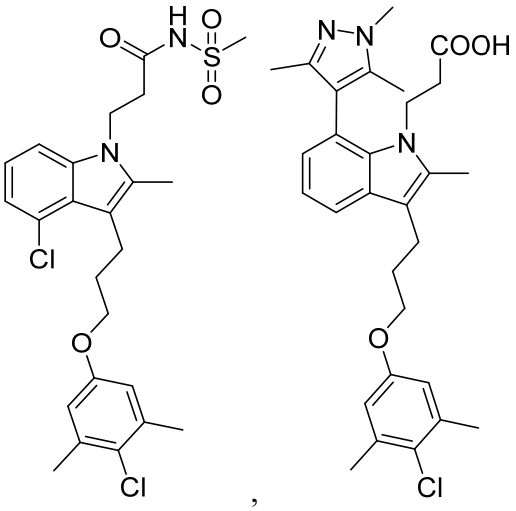
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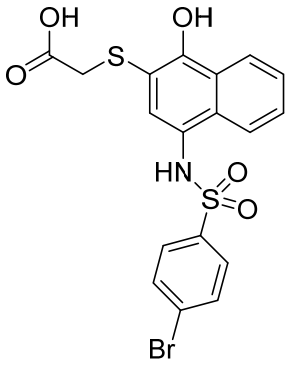
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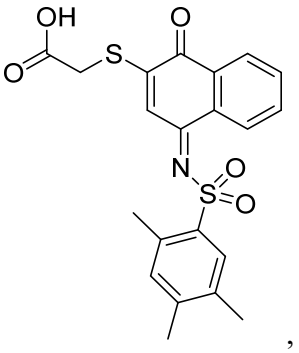
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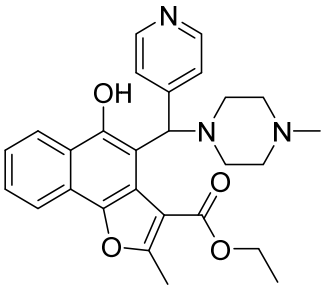
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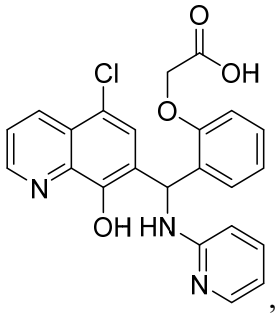
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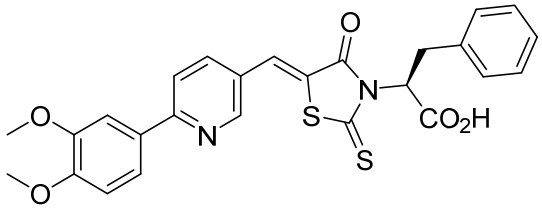
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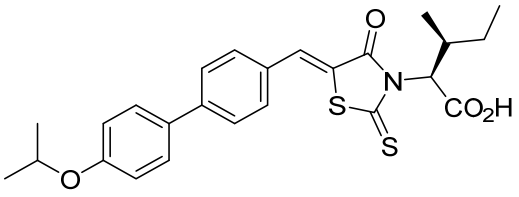
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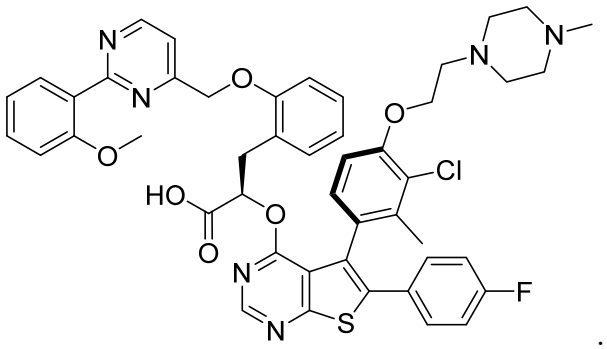
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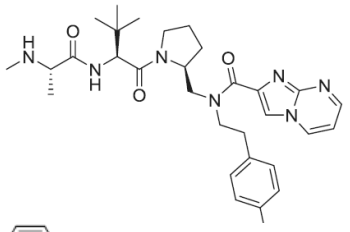
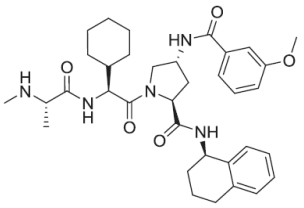
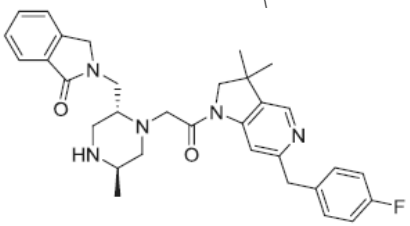
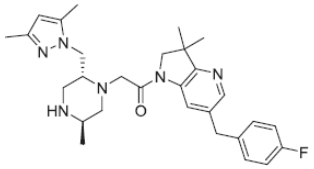
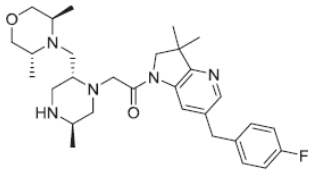
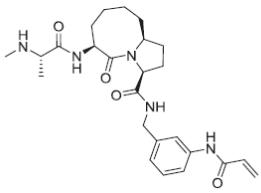
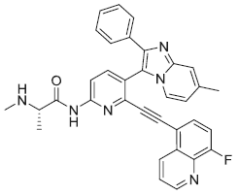
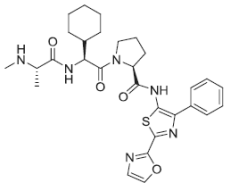
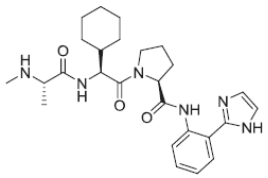
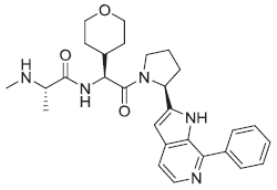
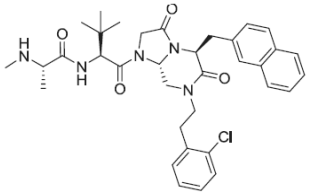
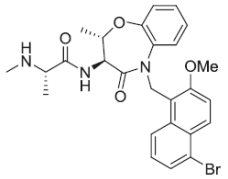
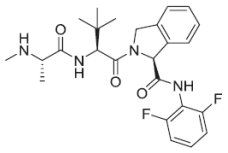
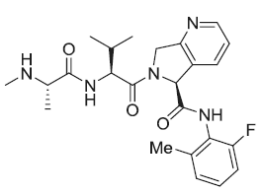
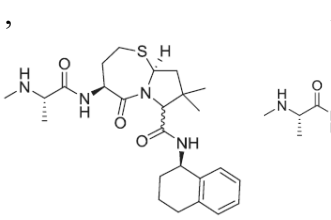
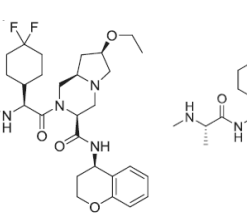
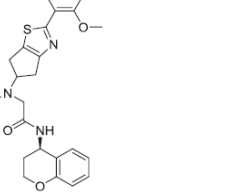
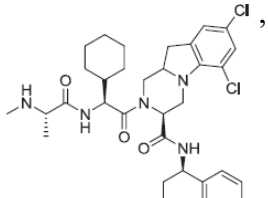
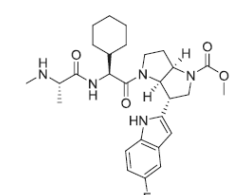
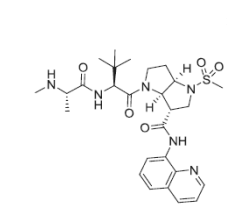
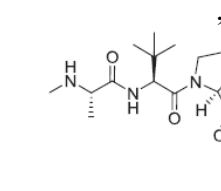
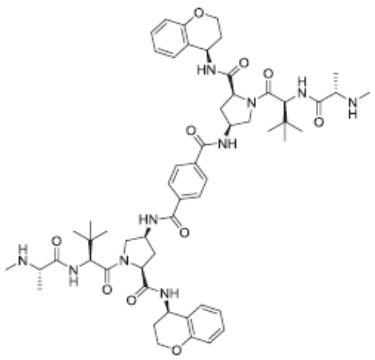
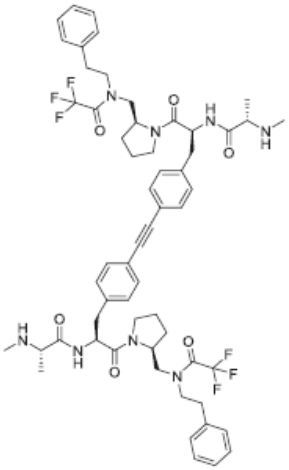
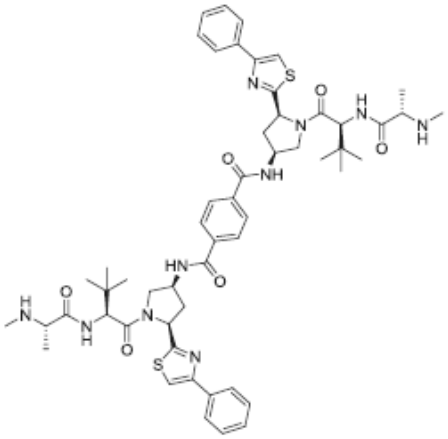
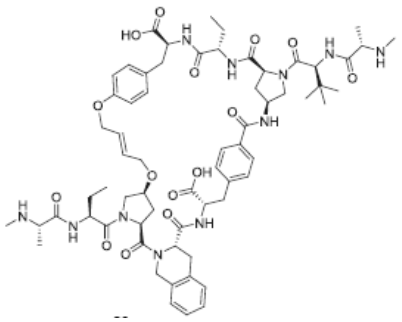
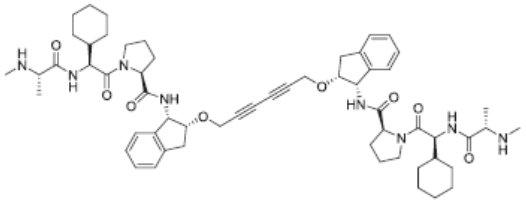
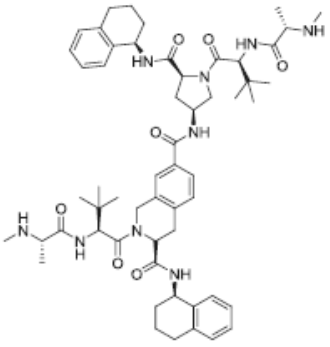
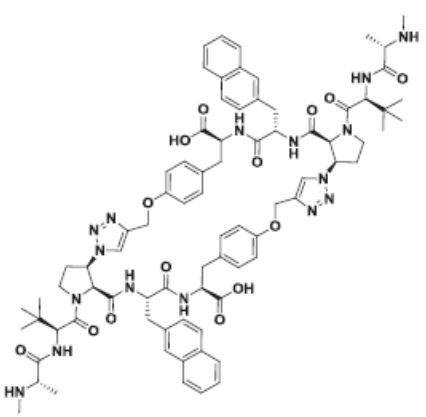
33. The use of any one of claims 17-33, wherein the medicament is for conjoint administration with an IAP antagonist.

34. The use of claim 33, wherein the IAP antagonist is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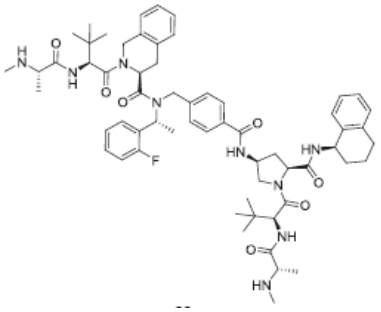
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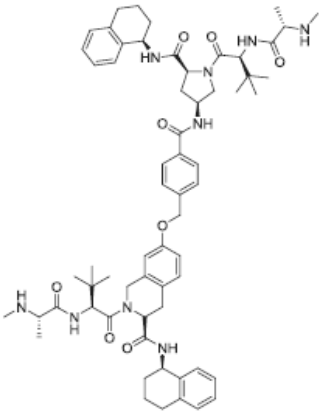
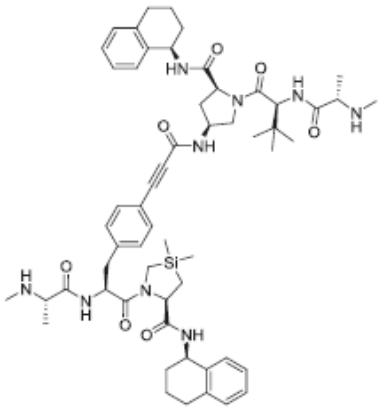
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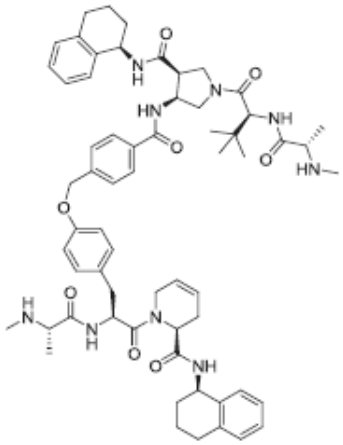
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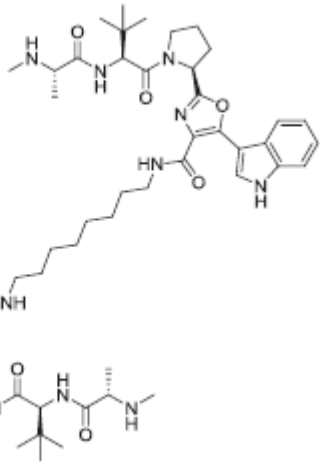
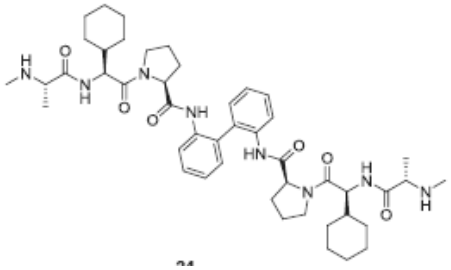
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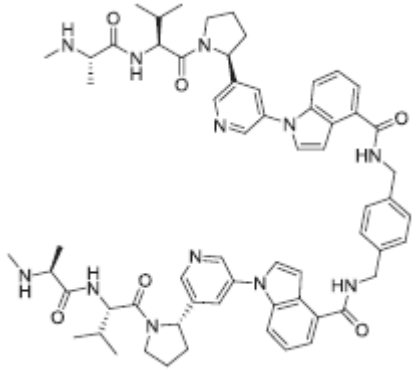
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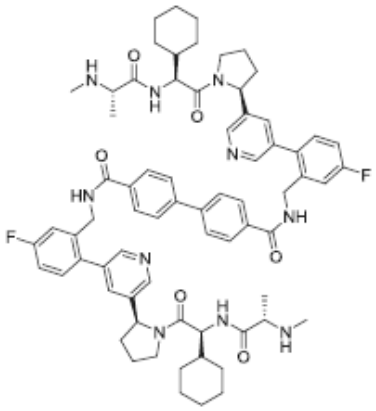
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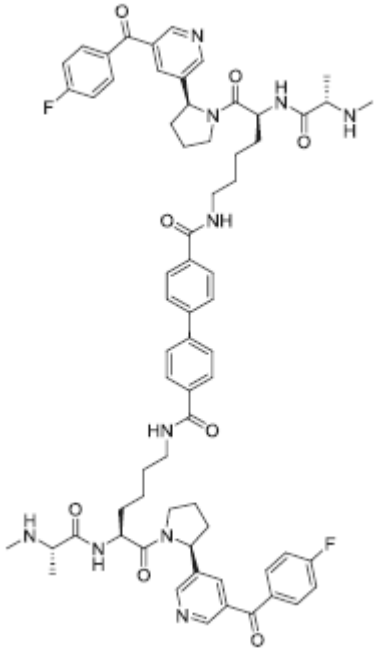
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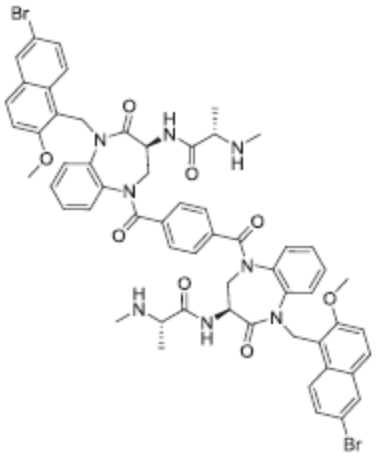
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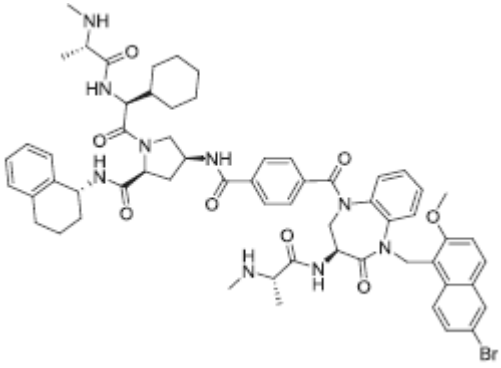
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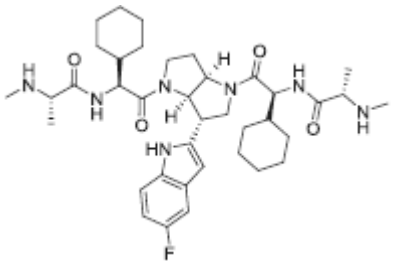
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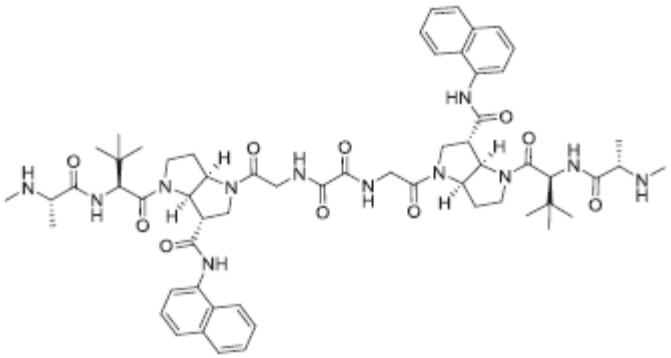
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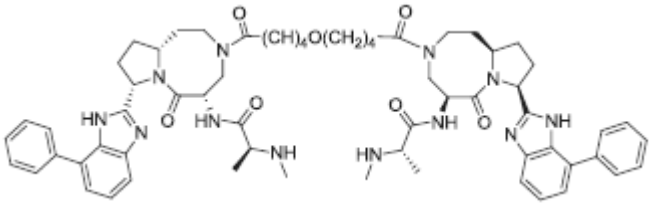
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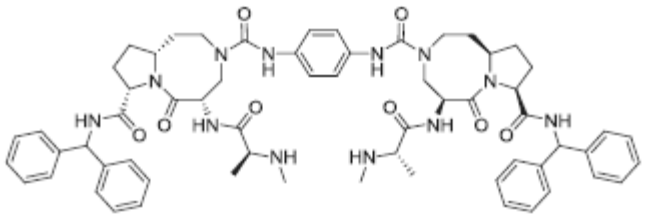
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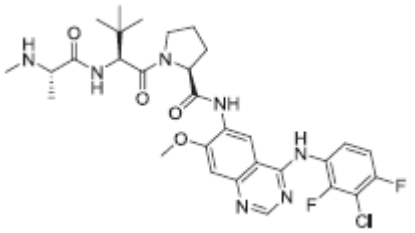
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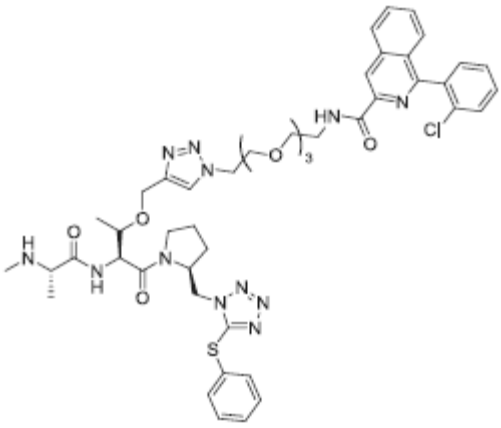
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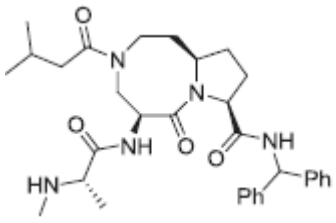
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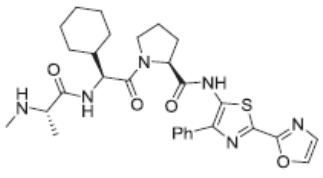
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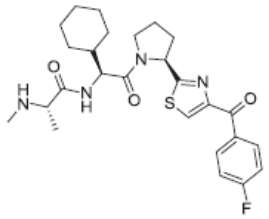
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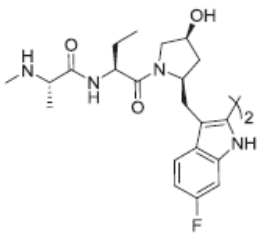

, AT-406/Debio 1143, GDC-0917/CUDC-427, LCL161, or TL-32711.

35. The use of any one of claims 17-34, wherein the medicament is for conjoint administration with with a cell-cycle inhibitor.

36. The use of claim 35, wherein the cell cycle inhibitor is selected from palbociclib, ribociclib, abemaciclib, flavopiridol, AT9283, alisertib, and MK-1775.

37. A compound of formula (I) according to any one of claims 1-15 for use in treating treating acute myeloid leukemia conjointly with a BCL-2 inhibitor.

38. The compound for use of claim 37, wherein the subject has FLT3-ITD+ acute myeloid leukemia.

39. The compound for use of any one of claims 37-38, wherein the compound of formula (I) is a HCK inhibitor.

40. The compound for use of any one of claims 36-37, wherein the compound of formula (I) is for conjoint administration with a FLT3-ITD inhibitor.

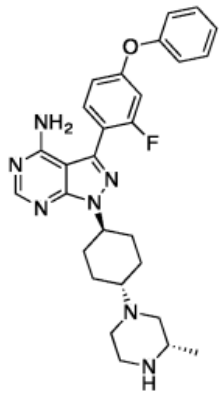
41. The compound for use of claim 39, wherein the HCK inhibitor is a dual HCK/FLT3-ITD inhibitor.

42. The compound for use of claim 40, wherein the FLT3-ITD inhibitor is selected from AC220, sorafenib, PKC412, CEP-701, UNC2025, MLN518, KW-2449 and AMG-925, sunitinib, SU5614, AC2206, crenolanib, and PLX3397.

43. The compound for use of any one of claims 37-42, wherein the BCL-2 inhibitor is selected from AT-101, TW-37, TM-1206, gossypolic acid, gossypolonic acid, apogossypol, apogossypolone, A385358, ABT-737, ABT-263, ABT-199, WEHI-539, BXI-61, BXI-72, obatoclax, JY-1-106, and SAHB peptides.

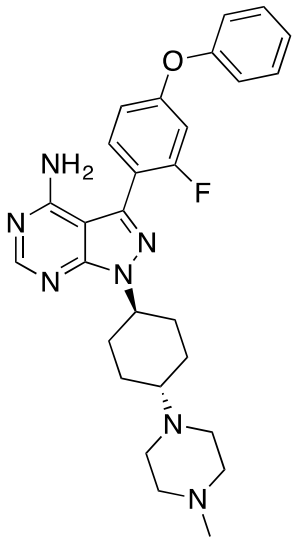
44. The compound for use of claim 43, wherein the BCL-2 inhibitor is ABT-199.

45. The compound for use of claim 39, wherein the HCK inhibitor is



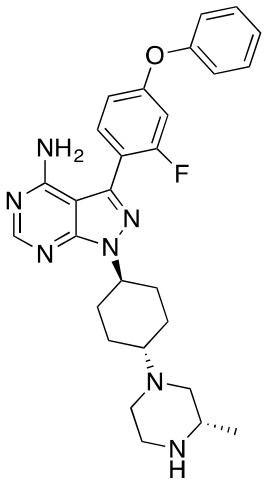
and the BCL-2 inhibitor is ABT-199.

46. The compound for use of claim 39, wherein the HCK inhibitor is



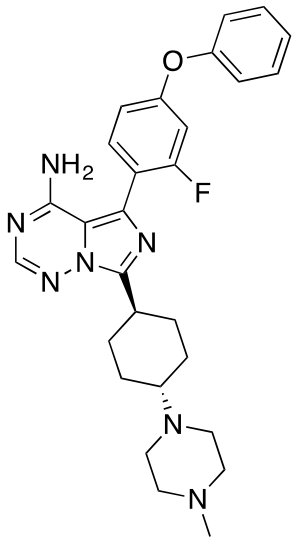
and the BCL-2 inhibitor is ABT-199.

47. The compound for use of claim 39, wherein the HCK inhibitor is



and the BCL-2 inhibitor is ABT-199.

48. The compound for use of claim 39, wherein the HCK inhibitor is

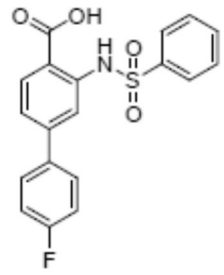
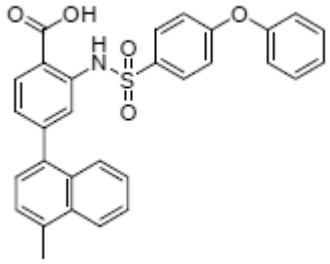
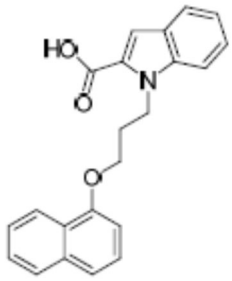
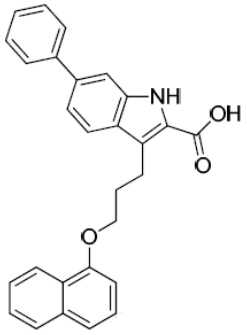
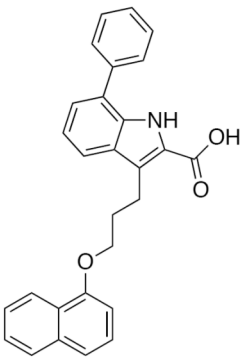
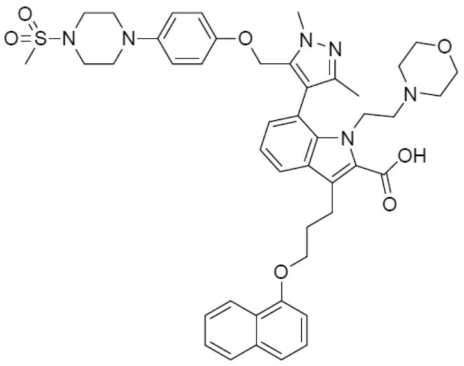
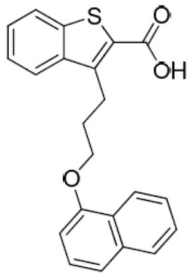
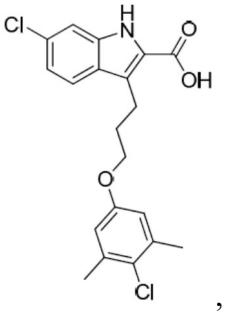
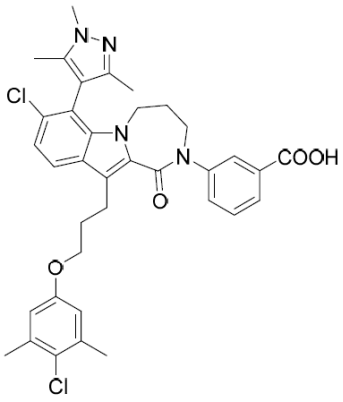
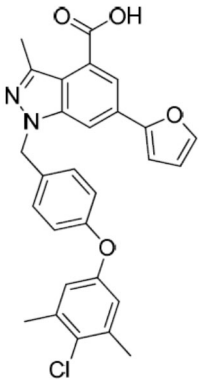
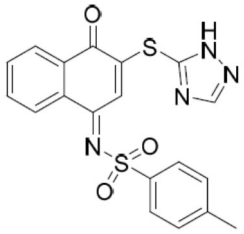


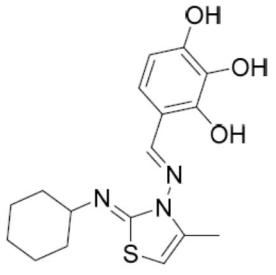
and the BCL-2 inhibitor is ABT-199.

49. The compound for use of any one of claims 37-48, wherein the HCK inhibitor, and/or FLT3-ITD inhibitor, and/or the BCL-2 inhibitor is for conjoint administration with an anti-apoptosis agent.

50. The compound for use of claim 49, wherein the anti-apoptosis agent is tretinoin, GGTI 298 TFA salt, BTSA1, AT406, SM-406, elesclomol, STA-4783, Ganetespib, STA-9090, NQDI-1, or zoledronic acid.

51. The compound for use of any one of claims 37-50, wherein the HCK inhibitor, and/or FLT3-ITD inhibitor, and/or the BCL-2 inhibitor is for conjoint administration with an Mcl-1 inhibitor.

52. The compound for use of claim 51, wherein the Mcl-1 inhibitor is , , , , , , , , , , .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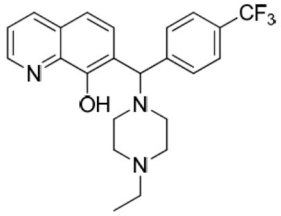
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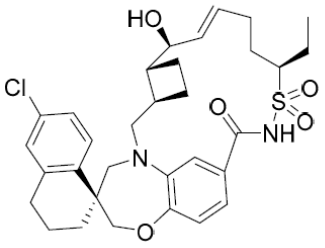
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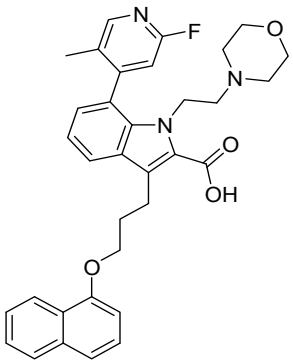
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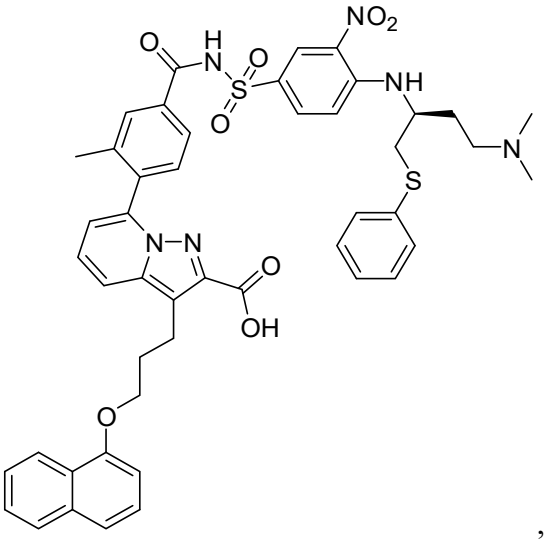
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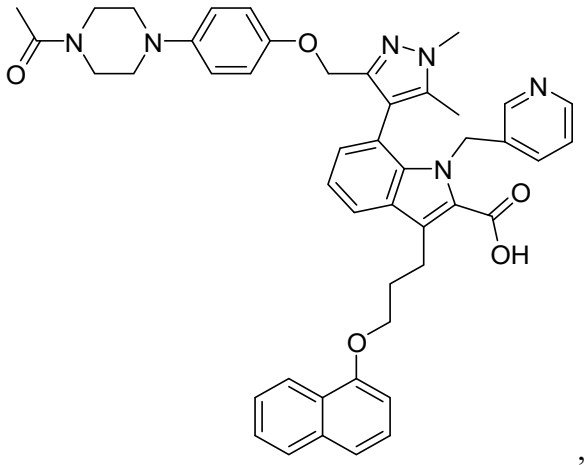
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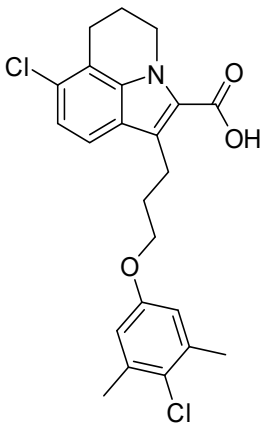
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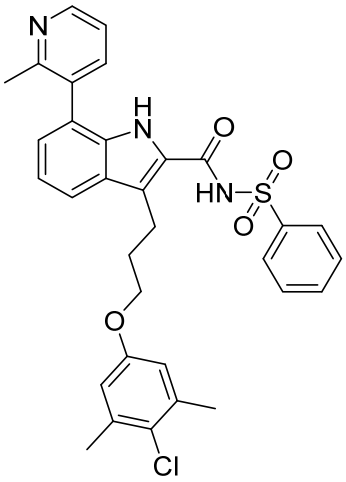
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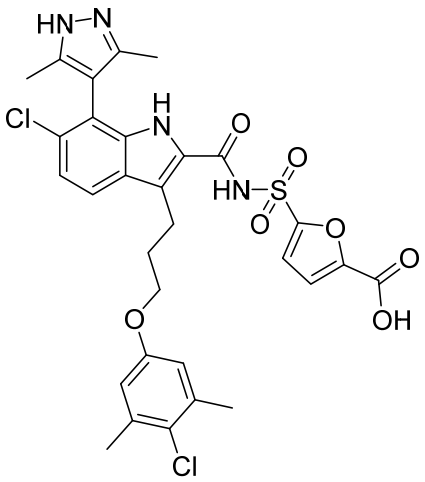
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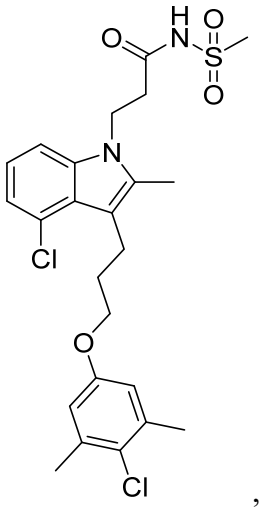
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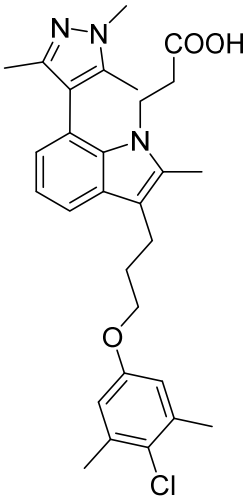
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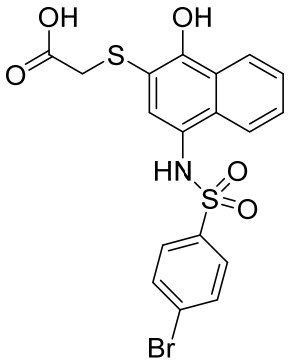
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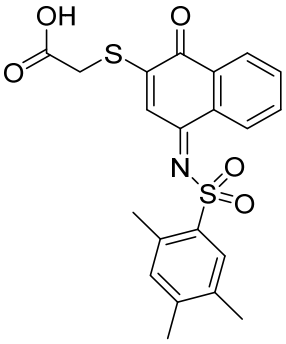
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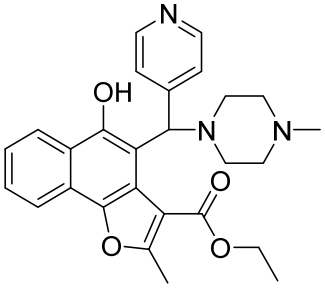
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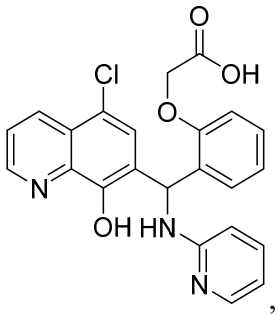
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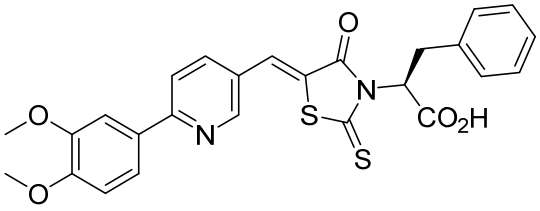
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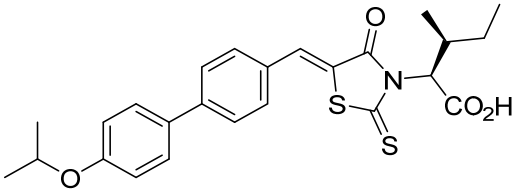
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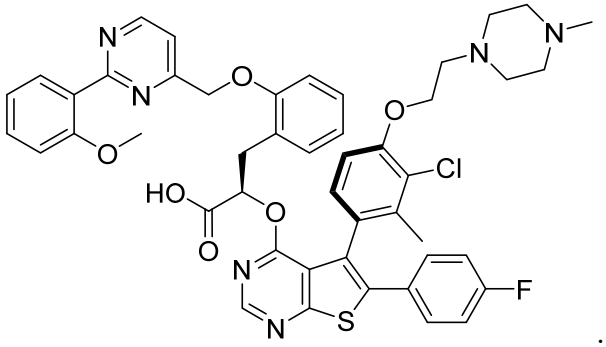
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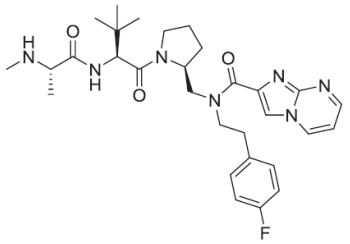
53. The compound for use of any one of claims 37-52, wherein the HCK inhibitor, and/or FLT3-ITD inhibitor, and/or the BCL-2 inhibitor is for conjoint administration with an IAP antagonist.

54. The compound for use of claim 53, wherein the IAP antagonist is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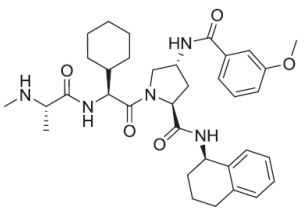
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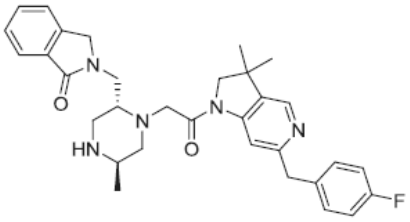
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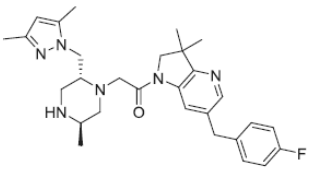
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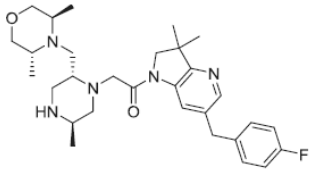
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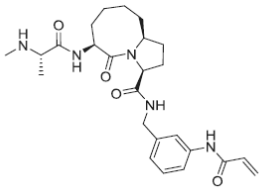
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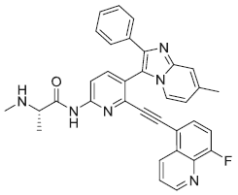
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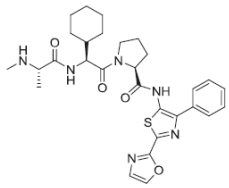
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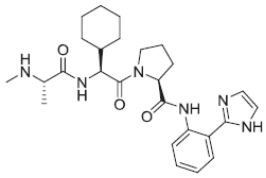
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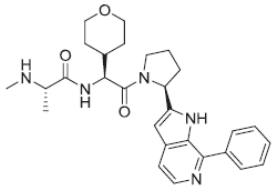
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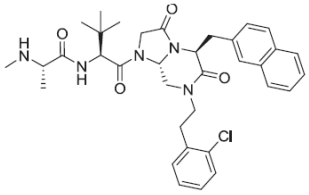
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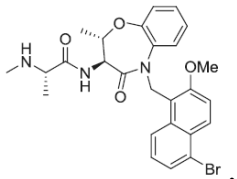
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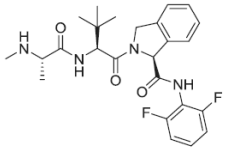
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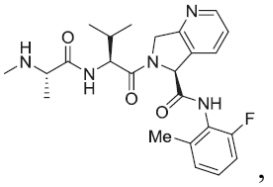
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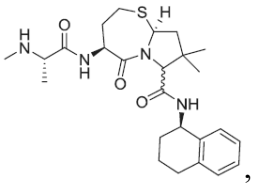
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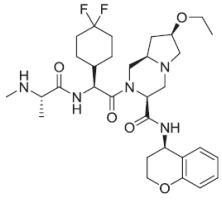
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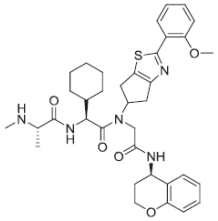
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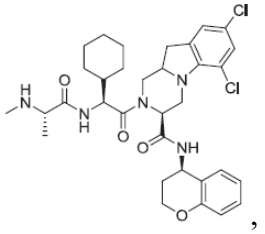
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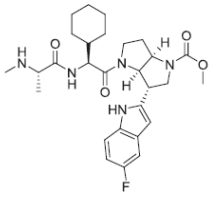
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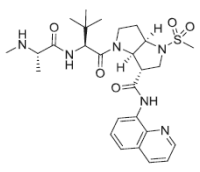
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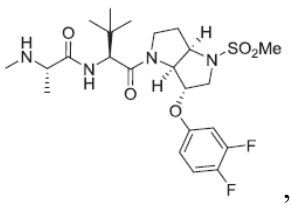
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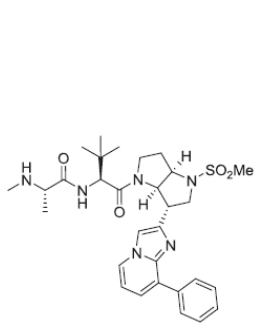
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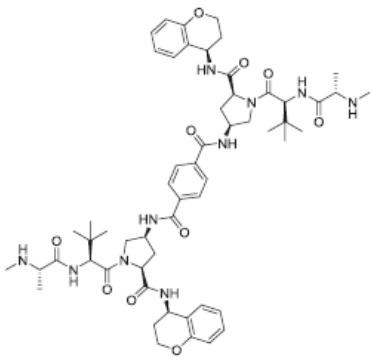
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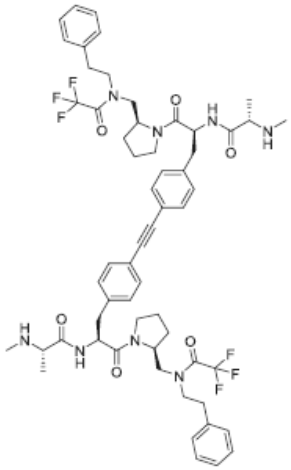
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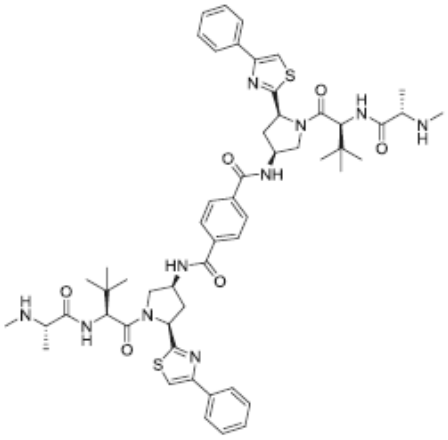
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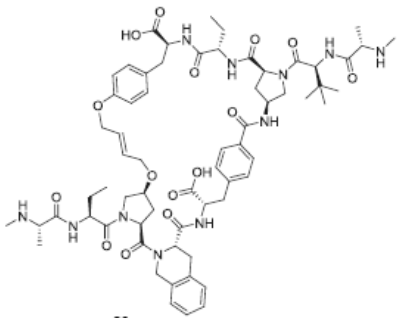
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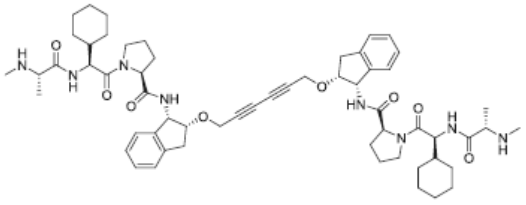
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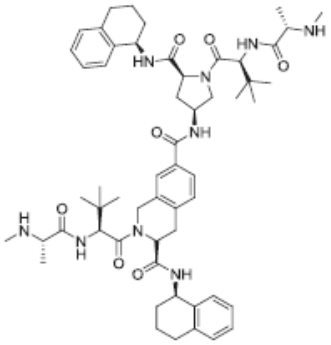
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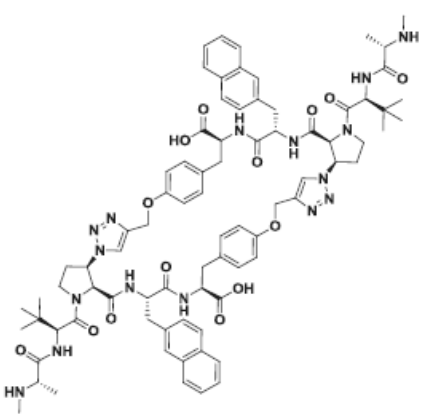
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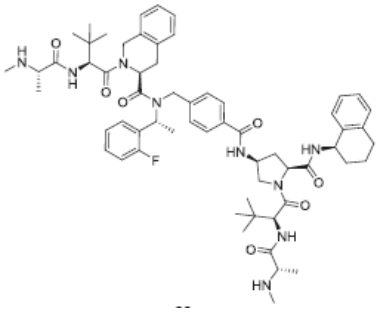
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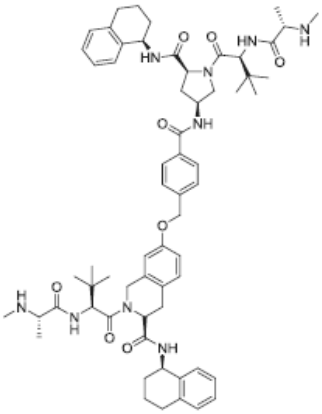
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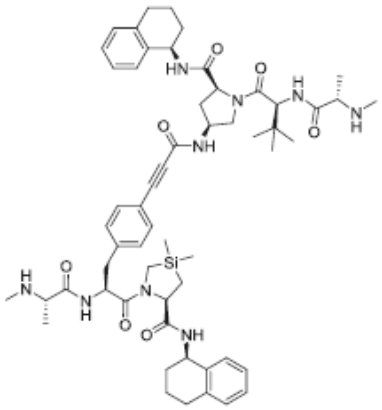
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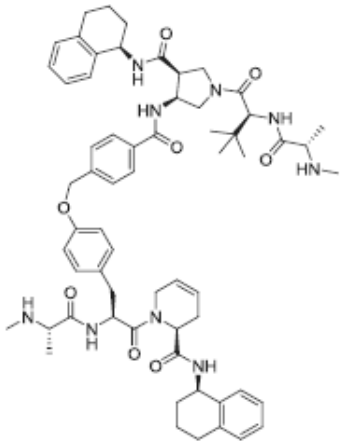
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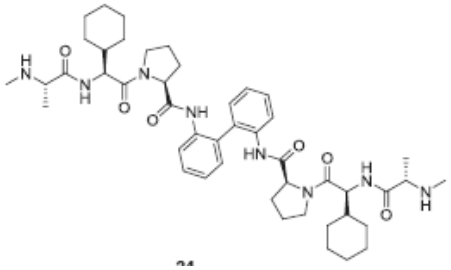
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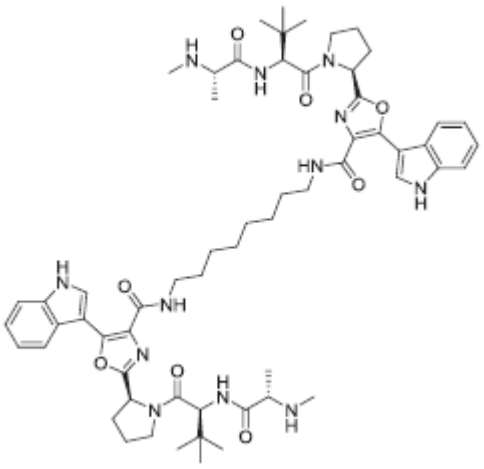
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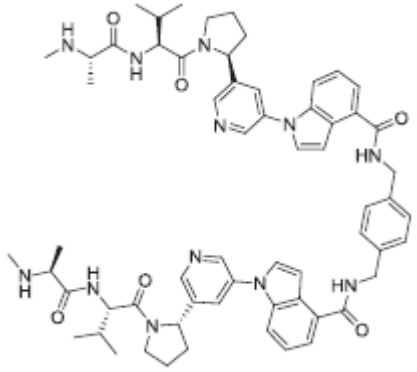
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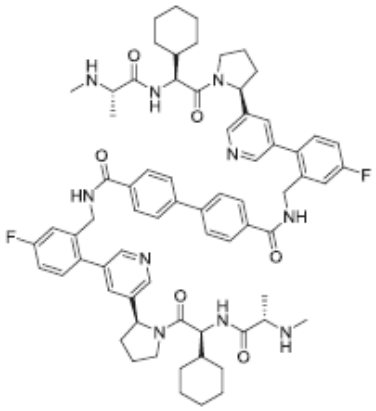
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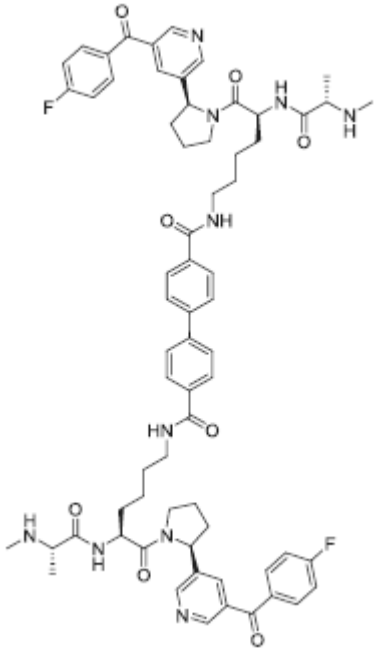
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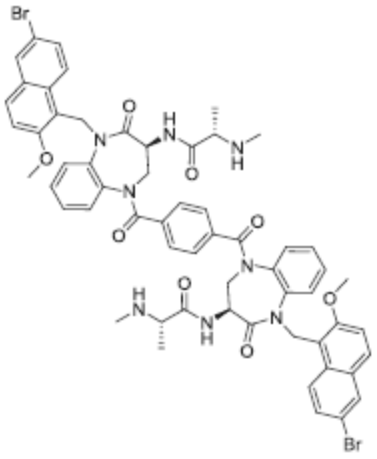
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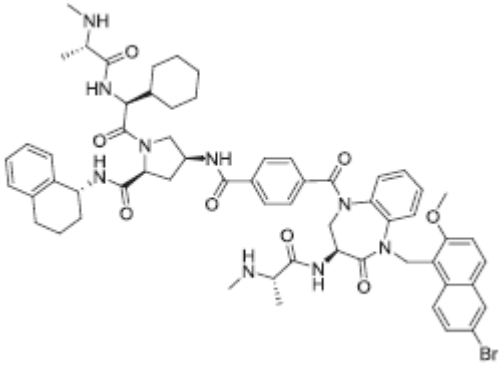
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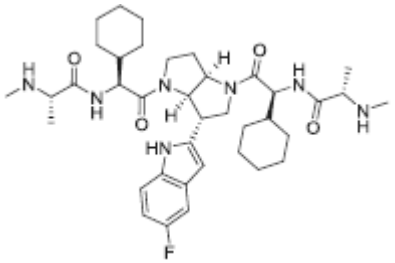
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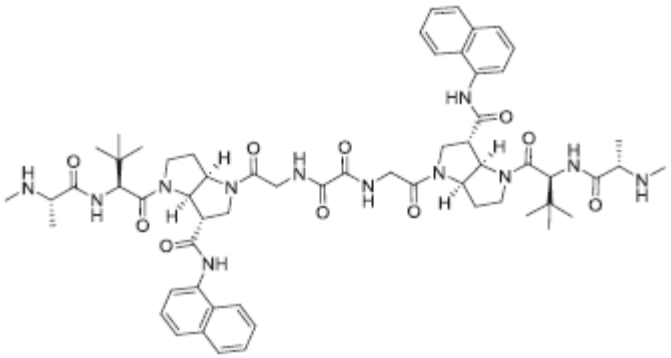
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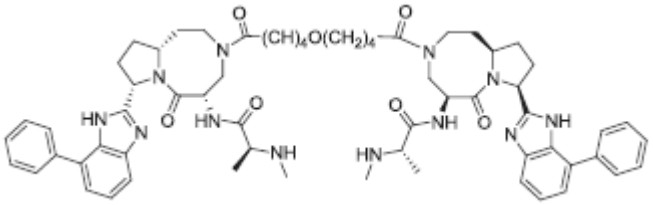
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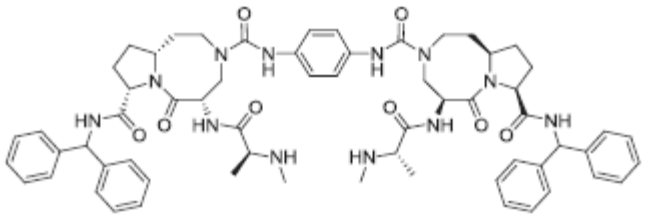
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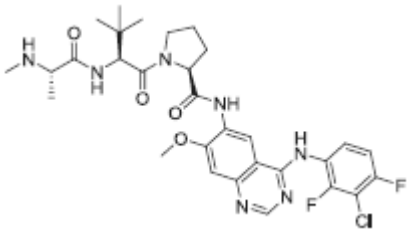
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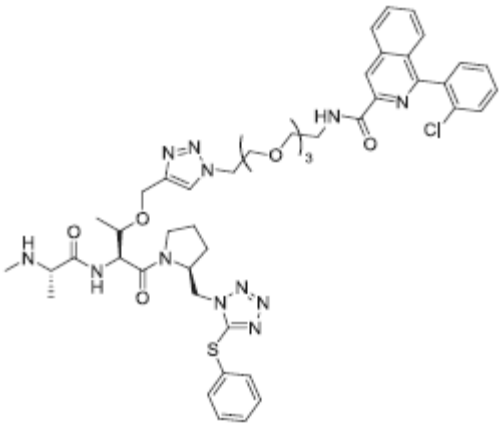
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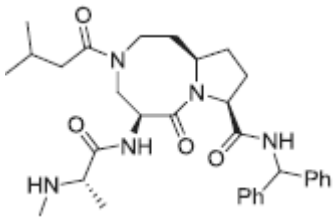
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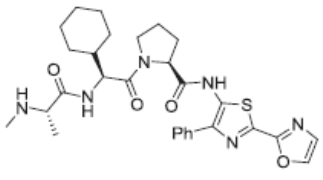
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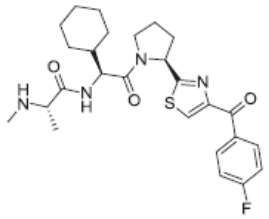
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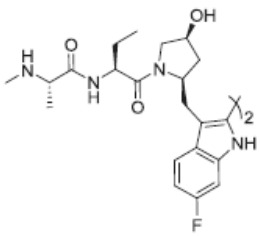
, AT-406/Debio 1143, GDC-0917/CUDC-427, LCL161, or TL-32711.

55. The compound for use of any one of claims 37-34, wherein the HCK inhibitor, and/or FLT3-ITD inhibitor, and/or the BCL-2 inhibitor is for conjoint administration with a cell-cycle inhibitor.

56. The compound for use of claim 55, wherein the cell-cycle inhibitor is selected from palbociclib, ribociclib, abemaciclib, flavopiridol, AT9283, alisertib, and MK-1775.