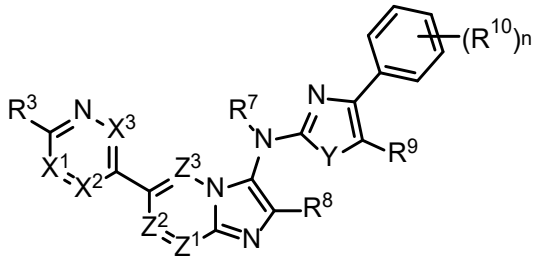
CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or isomer thereof,

wherein:

X^1, X^2, and X^3 are independently selected from C-R^1 and N;

Z^1, Z^2, and Z^3 are independently selected from C-R^1 and N;

each R^1 is independently selected from -H, -halogen, optionally substituted -(C_1-C_6)alkyl and optionally substituted -(C_1-C_6)alkoxy;

Y is selected from S, O, and N-R^2, wherein R^2 is selected from -H, and optionally substituted -(C_1-C_6)alkyl;

R^3 is selected from optionally substituted R^4-C(O)-(C_1-C_3)alkyl-, R^4C(O)-, optionally substituted monocyclic or bicyclic carbocycle, optionally substituted monocyclic or bicyclic heterocycle, R^5R^6HC-, and R^5R^6N-;

R^4 is selected from H_2N-, HO-, R^5R^6N-, optionally substituted (C_1-C_{10})alkyl-, optionally substituted (C_1-C_{10})alkoxy-, optionally substituted monocyclic or bicyclic carbocycle, optionally substituted monocyclic or bicyclic heterocycle, optionally substituted cycloalkyl-(C_1-C_6)alkylene-, and optionally substituted heterocycle-(C_1-C_6)alkylene-;

R^5 and R^6 are independently selected from H-, H_2N-, HO-, optionally substituted (C_1-C_{10})alkyl-, optionally substituted monocyclic or bicyclic carbocycle, optionally substituted monocyclic or bicyclic heterocycle, optionally substituted R^4C(O)-(C_1-C_{10})alkyl-, R^4C(O)-, R^4-, and substituted amino; or R^5 and R^6 together with the nitrogen or carbon atom to which they are attached are cyclically linked to form an optionally substituted carbocycle or an optionally substituted heterocycle;

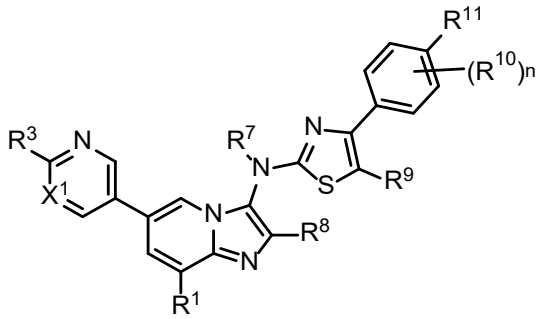
R^7 is selected from H-, and optionally substituted (C_1-C_6)alkyl-;

R^8 is selected from -H, -halogen, and optionally substituted -(C_1-C_6)alkyl;

R^9 and each R^{10} are independently selected from -H, -halogen, -CN, -OH, optionally substituted -(C_1-C_6)alkoxy, -NH_2, substituted amino, optionally substituted -(C_1-C_6)alkyl-NH_2 and optionally substituted -(C_1-C_6)alkyl; and

n is 0, 1, 2, 3, 4, or 5.

2. The compound of claim 1, wherein the compound is of formula (Ia):



(Ia)

wherein:

R^1 is selected from -H, -halogen, optionally substituted -(C_1-C_6)alkyl and optionally substituted -(C_1-C_6)alkoxy;

R^3 is selected from $R^4C(O)$-, $R^4C(O)CH_2$-, R^5R^6N-, and R^5R^6HC-;

R^{11} is -H, -halogen, -CN, -OH, optionally substituted -(C_1-C_6)alkoxy, -NH_2, -NR^5R^6, -CH_2NH_2 and optionally substituted -(C_1-C_6)alkyl; and

n is 0, 1, 2, or 3.

3. The compound of claim 2, wherein X^1 is N.

4. The compound of claim 2, wherein X^1 is C-H.

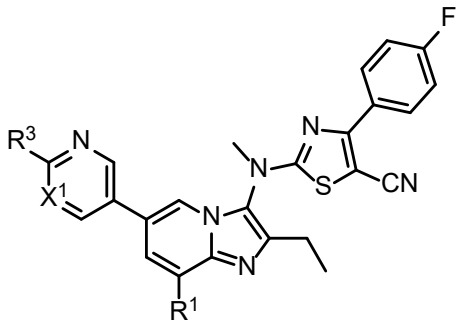
5. The compound of any one of claims 1 to 4, wherein R^7 is optionally substituted (C_1-C_6)alkyl-.

6. The compound of any one of claims 1 to 5, wherein R^8 is optionally substituted -(C_1-C_6)alkyl.

7. The compound of any one of claims 1 to 6, wherein R^9 is -CN.

8. The compound of claim 2, wherein R^{11} is -halogen.

9. The compound of any one of claims 1 to 8, wherein the compound is of formula (Ib):



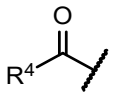
(Ib)

wherein:

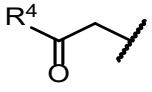
X^1 is C-H or N; and

R^1 is -H, -halogen, or optionally substituted -(C_1-C_6)alkyl and optionally substituted -(C_1-C_6)alkoxy.

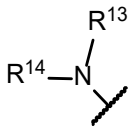
10. The compound of any one of claims 1 to 9, wherein:

a) R^3 is 

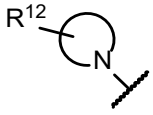
;

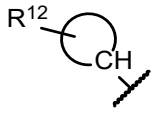
b) R^3 is 

;

c) R^3 is 

;

d) R^3 is  that is an optionally substituted monocyclic or bicyclic (C_2-C_9)heterocycle-; or

e) R^3 is  that is an optionally substituted monocyclic or bicyclic (C_3-C_8)carbocycle-, or an optionally substituted monocyclic or bicyclic (C_2-C_9)heterocycle-;

wherein:

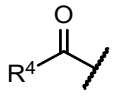
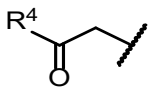
R^4 is selected from HO-, H_2N-, $R^{15}R^{16}N$-, optionally substituted (C_1-C_5)alkyl-, optionally substituted monocyclic or bicyclic carbocycle, and optionally substituted monocyclic or bicyclic heterocycle;

R^{12} is selected from -H, -NH_2, -OH, -$CH_2C(O)R^4$, -$C(O)R^4$, -$CHR^{15}R^{16}$, -$NR^{15}R^{16}$, optionally substituted -(C_1-C_5)alkyl, optionally substituted monocyclic or bicyclic -(C_3-C_8)carbocycle, and an optionally substituted monocyclic or bicyclic -(C_2-C_9)heterocycle; and

R^{13} and R^{14} are independently selected from -H, -$CH_2C(O)R^{17}$, -CH_2R^{17}, -$C(O)R^{17}$, -$R^{18}C(O)R^{17}$, -$CH_2R^{18}C(O)R^{17}$, optionally substituted -(C_1-C_5)alkyl, optionally substituted monocyclic or bicyclic -(C_3-C_8)carbocycle, and an optionally substituted monocyclic or bicyclic -(C_2-C_9)heterocycle, wherein R^{17} and R^{18} are independently selected from optionally substituted -(C_1-C_5)alkyl, optionally substituted monocyclic or bicyclic -(C_3-C_8)carbocycle, and an optionally substituted monocyclic or bicyclic -(C_2-C_9)heterocycle; and

R^{15} and R^{16} are independently selected from H-, optionally substituted (C_2-C_5)heterocycloalkyl-C(O)-, optionally substituted (C_3-C_6) cycloalkyl-C(O)-, optionally substituted (C_1-C_5)alkyl-, optionally substituted 3- to 10-membered saturated monocyclic heterocycle or carbocycle, and optionally substituted 3- to 10-membered saturated bicyclic heterocycle or carbocycle, wherein the optional substituents are selected from hydroxy, $HOCH_2$-, cyano, halogen, substituted amino, and (C_1-C_5)alkyl; or R^{15} and R^{16} are cyclically linked to form a 3- to 6-membered monocyclic saturated heterocycle, optionally substituted with hydroxy, $HOCH_2$-, cyano, halogen, substituted amino, or (C_1-C_5)alkyl.

11. The compound of claim 10, wherein:

R^3 is  or  ,

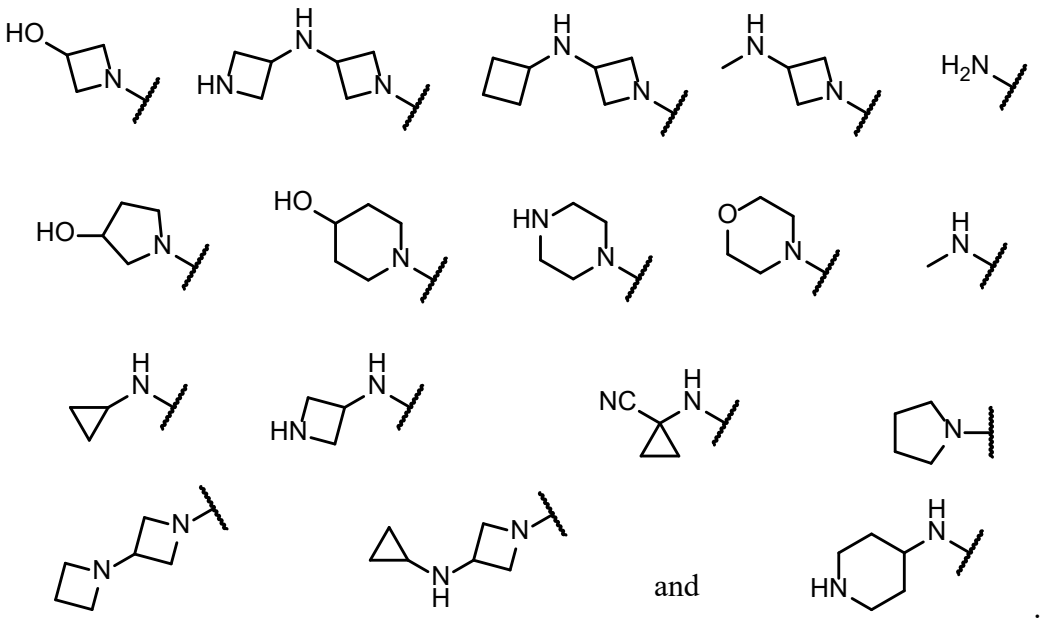
R^4 is selected from R^{32}, $R^{32}HN$-, $R^{32}N(R^{33})$-,and $R^{32}HN$-R^{36}-;

R^{32} and R^{33} are independently selected from H-, optionally substituted (C_1-C_3)alkyl, optionally substituted cycloalkyl, and optionally substituted saturated heterocycle;

R^{36} is selected from optionally substituted (C_1-C_3)alkyl, optionally substituted cycloalkyl, and optionally substituted saturated heterocycle; and

the optional substituents of the R^{32}, R^{33} and R^{36} groups are independently selected from -CN, -OH, -CH_2OH, -(C_1-C_3)alkyl, -(C_1-C_3)alkoxy, -(C_3-C_6)cycloalkyl, (C_2-C_5)heterocycloalkyl, and -$N(R^{37})R^{38}$, wherein R^{37} and R^{38} are independently selected from H, (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, and (C_2-C_5)heterocycloalkyl.

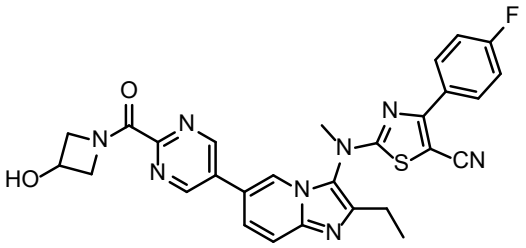
12. The compound of claim 11, wherein R^4 is selected from:



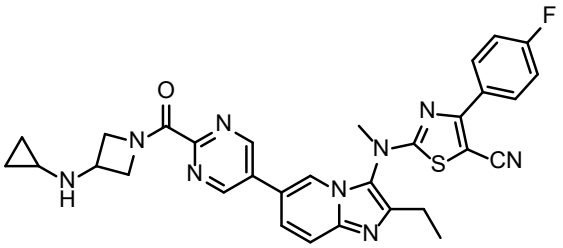
and

.

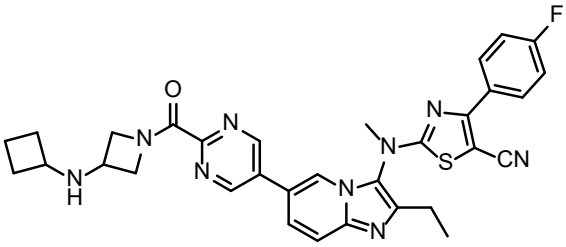
13. The compound of claim 12, wherein the compound is selected from:



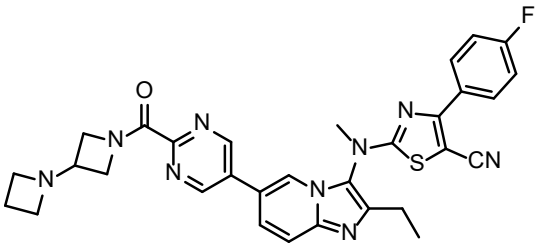
Compound 11



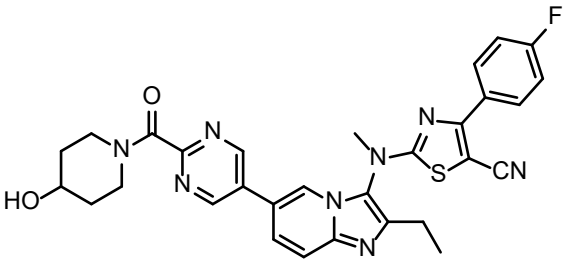
Compound 12



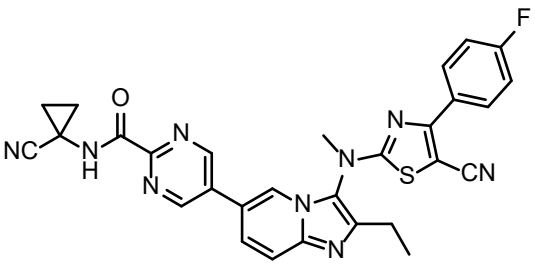
Compound 13



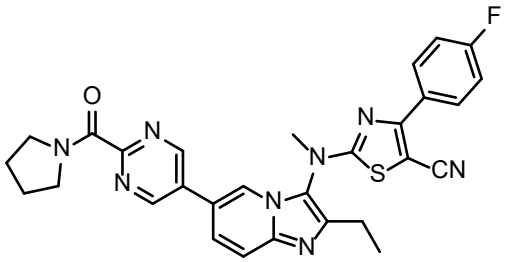
Compound 14



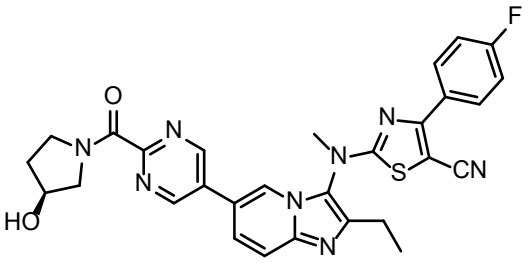
Compound 15



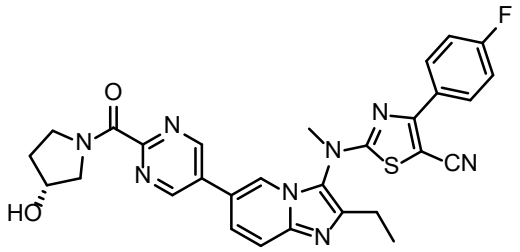
Compound 16



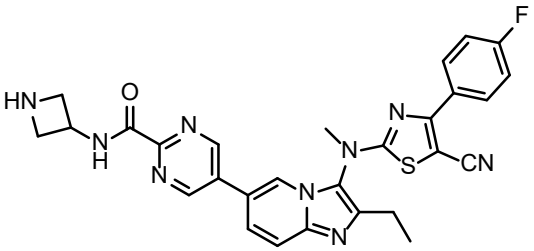
Compound 47



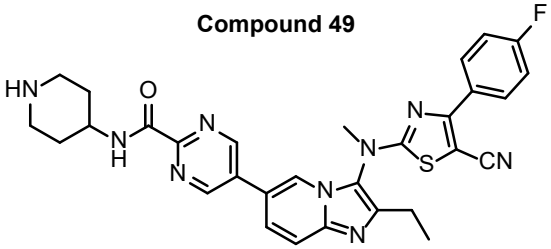
Compound 48



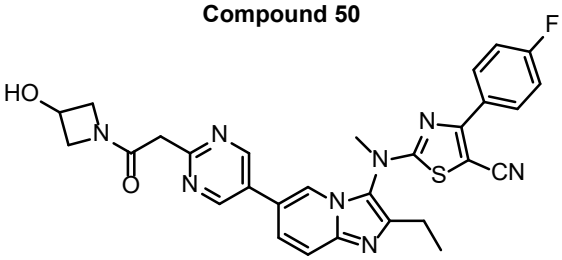
Compound 49



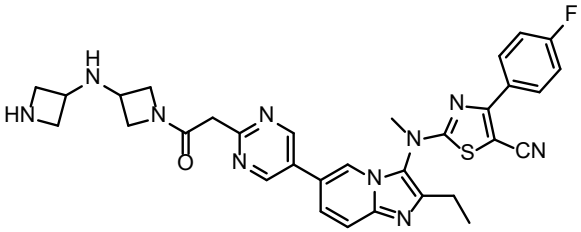
Compound 50



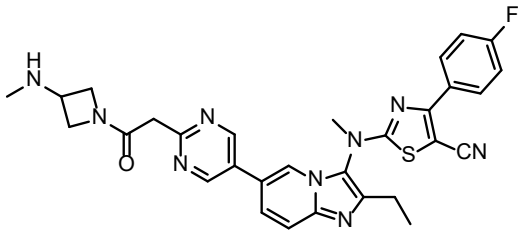
Compound 51



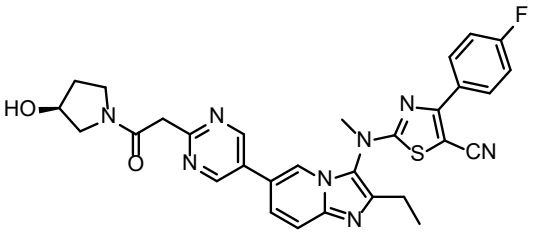
Compound 52



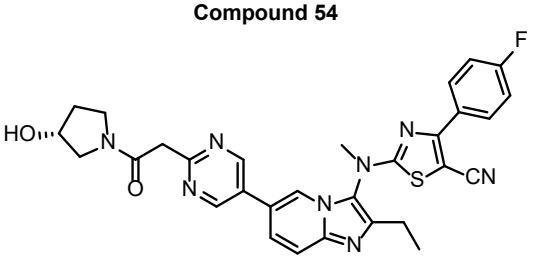
Compound 53



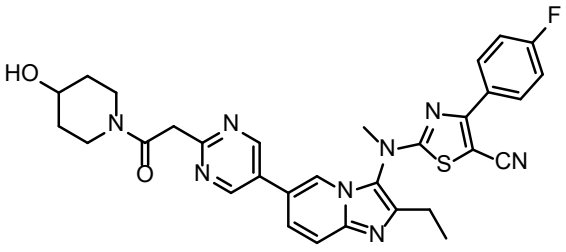
Compound 54



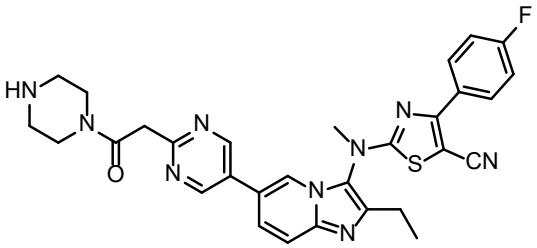
Compound 55



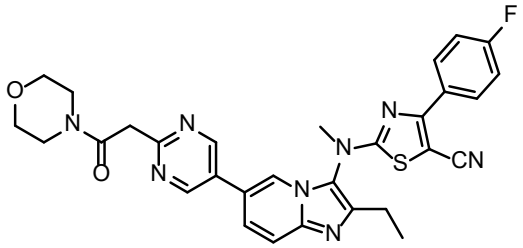
Compound 56



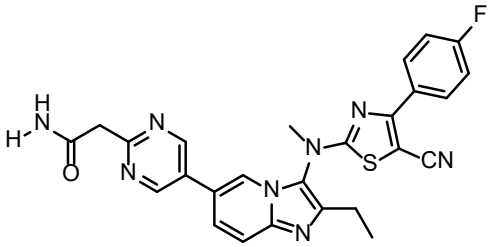
Compound 57



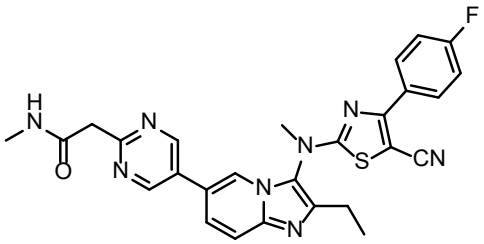
Compound 58



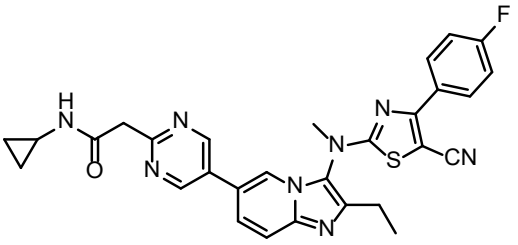
Compound 59



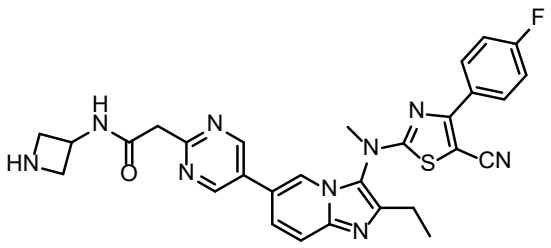
Compound 60



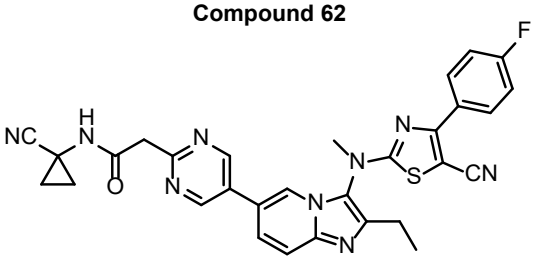
Compound 61



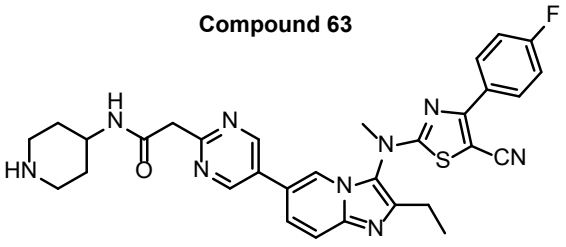
Compound 62



Compound 63

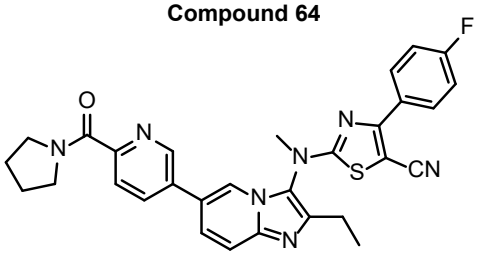


Compound 64



Compound 65

and



Compound 87

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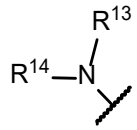
14. The compound of claim 10, wherein:



R^3 is

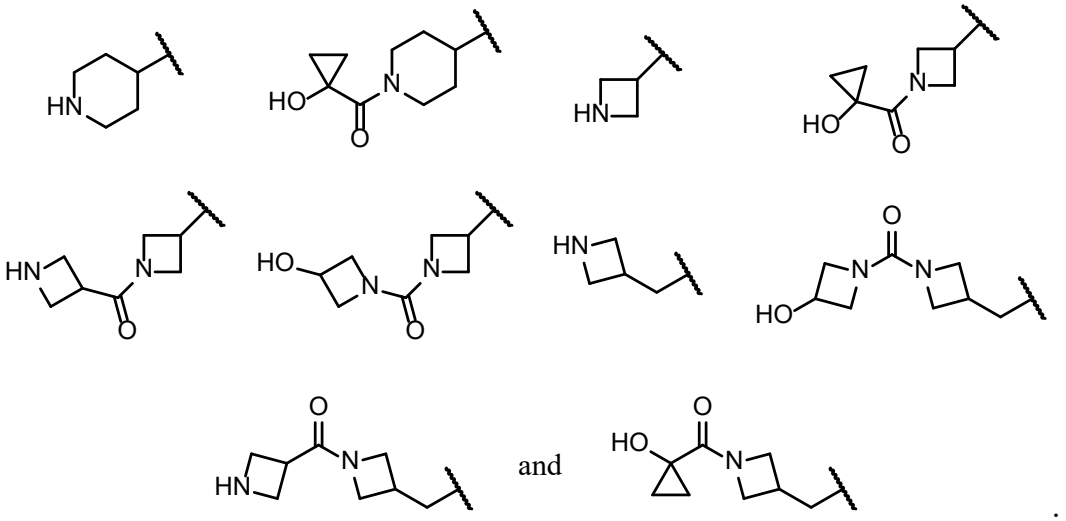
R^{14} is selected from R^{34}-, $R^{34}CH_2$-, $R^{34}C(O)R^{35}$-, and $R^{34}C(O)R^{35}CH_2$-;

each R^{34} and R^{35} are independently selected from optionally substituted -(C_1-C_3)alkyl, optionally substituted cycloalkyl, and optionally substituted saturated heterocycle;

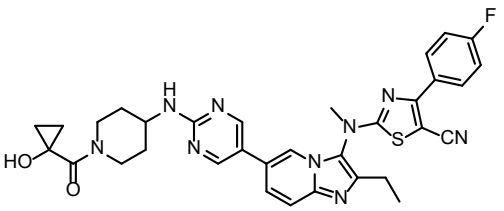
the optional substituents of the R^{34} and R^{35} groups are independently selected from -CN, -OH, -CH_2OH, -(C_1-C_3)alkyl, -(C_1-C_3)alkoxy, and -(C_1-C_3)alkyl; and

R^{13} is -H.

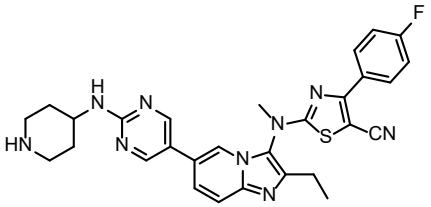
15. The compound of claim 14, wherein R^{14} is selected from:



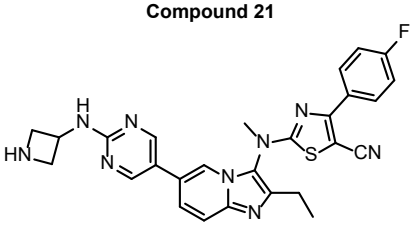
16. The compound of claim 15, wherein the compound is selected from:



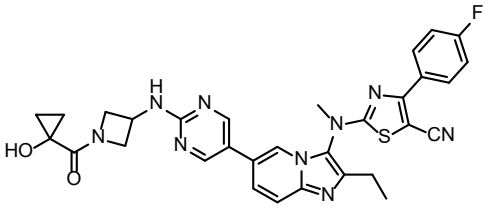
Compound 21



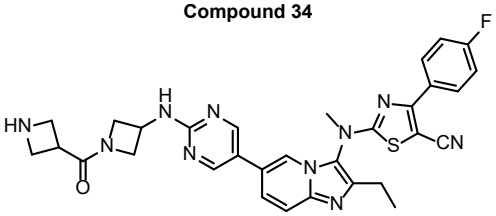
Compound 22



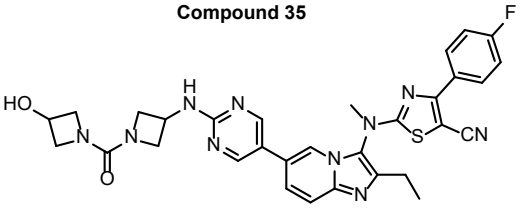
Compound 34



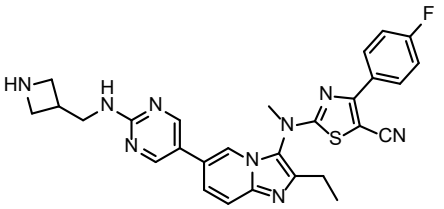
Compound 35



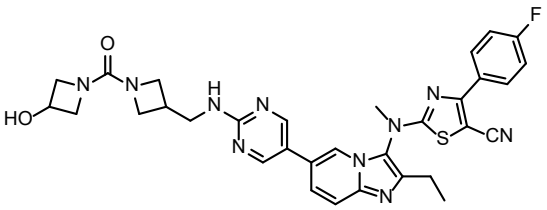
Compound 36



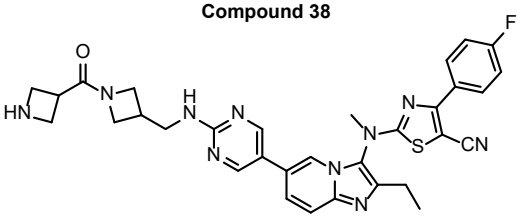
Compound 37



Compound 38

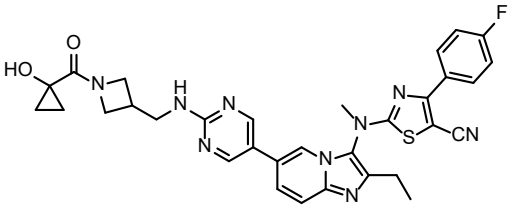


Compound 39



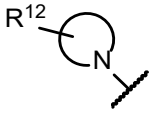
Compound 40

and



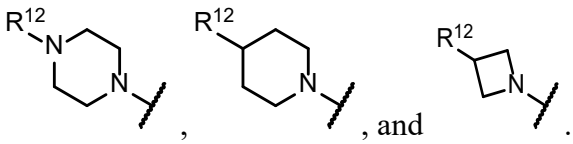
Compound 41

17. The compound of claim 10, wherein R^3 is



.

18. The compound of claim 17, wherein R^3 is selected from:



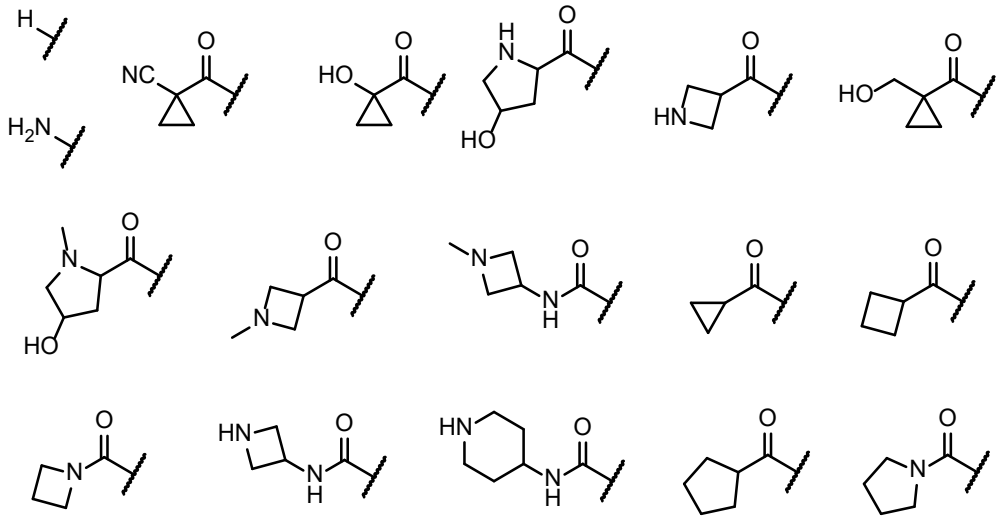
19. The compound of claim 17 or 18, wherein:

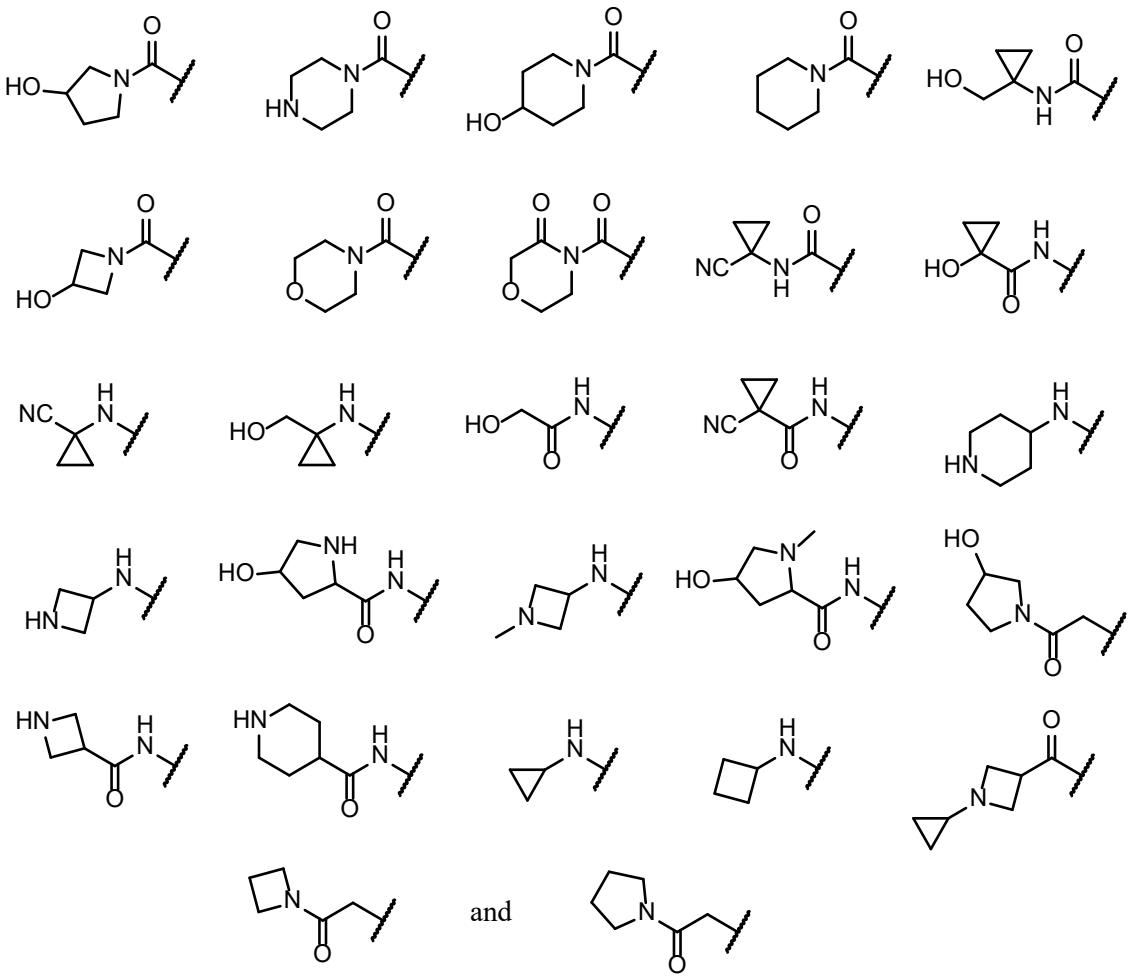
R^{12} is selected from H-, H_2N-, R^{31}-C(O)-, R^{31}-$C(O)CH_2$-, R^{31}-NHC(O)-, R^{31}-C(O)NH-, R^{31}-NH-, R^{31}-$N(CH_3)C(O)$-, R^{31}-$C(O)N(CH_3)$-, R^{31}-$N(CH_3)$-, and R^{31}-O- ;

R^{31} is selected from optionally substituted cycloalkyl, and optionally substituted saturated heterocycle; and

the optional substituents of the R^{31} group are selected from NC-, HO-, $HOCH_2$-, (C_1-C_3)alkyl-, (C_1-C_3)alkoxy-, substituted (C_1-C_3)alkyl-, (C_3-C_6)cycloalkyl-, and (C_2-C_5)heterocycloalkyl-.

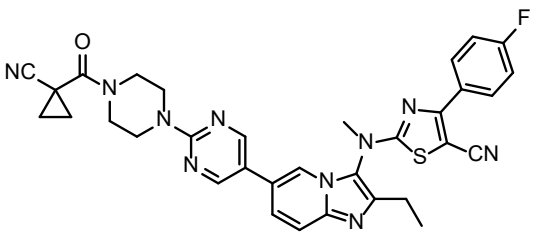
20. The compound of any one of claims 17 to 19, wherein R^{12} is selected from:



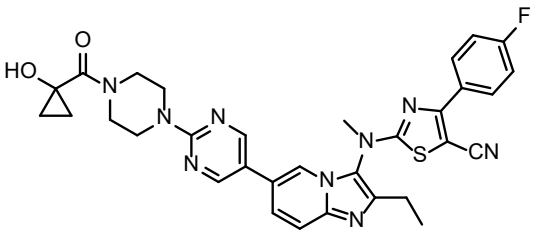


and

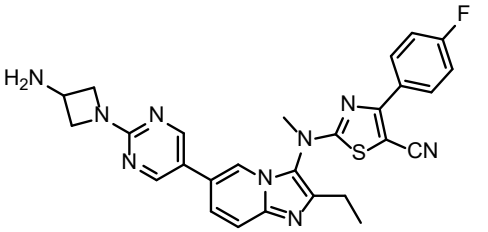
21. The compound of any one of claims 17 to 20, wherein the compound is selected from:



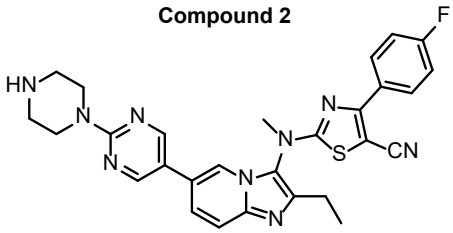
Compound 1



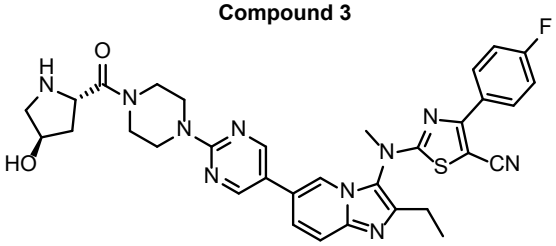
Compound 2



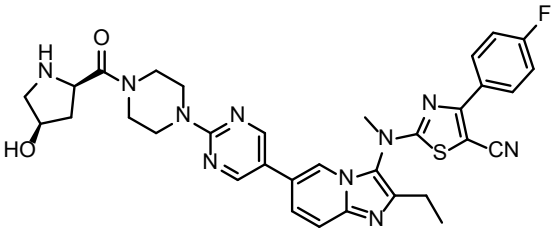
Compound 3



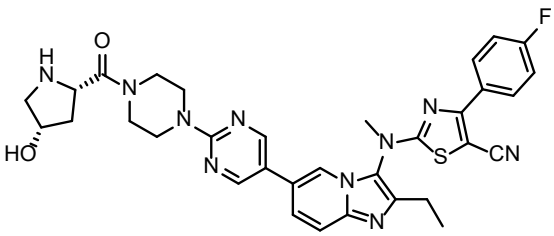
Compound 4



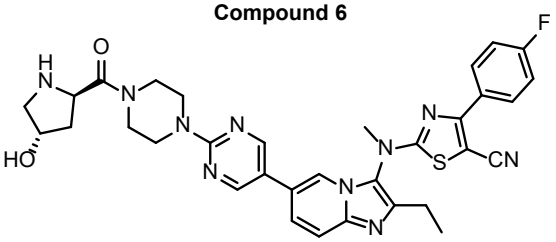
Compound 5



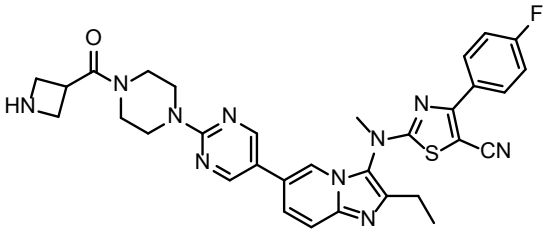
Compound 6



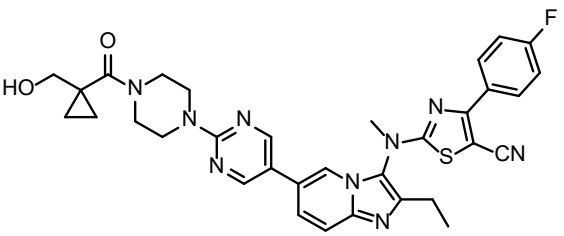
Compound 7



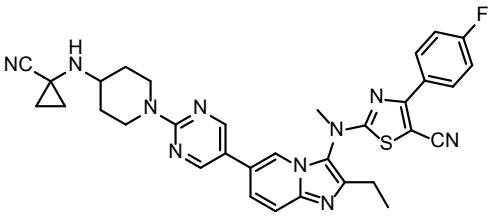
Compound 8



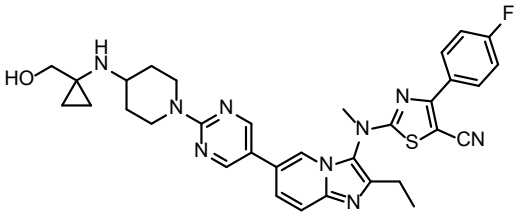
Compound 9



Compound 10



Compound 17



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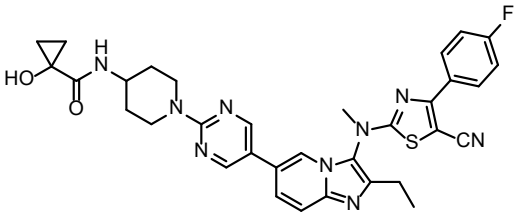
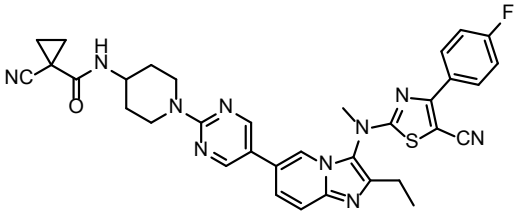
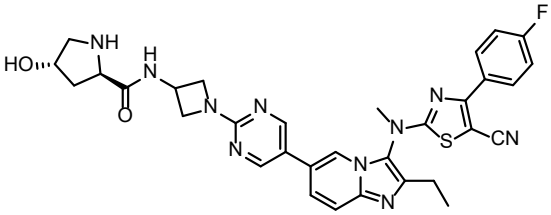


Compound 19



Compound 20



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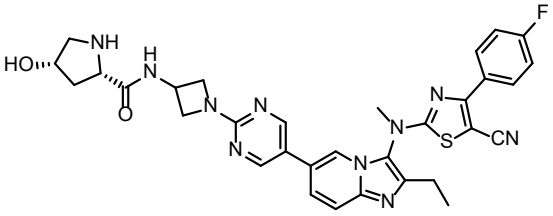

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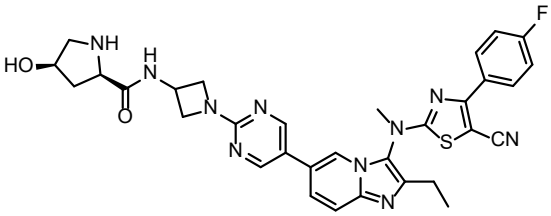

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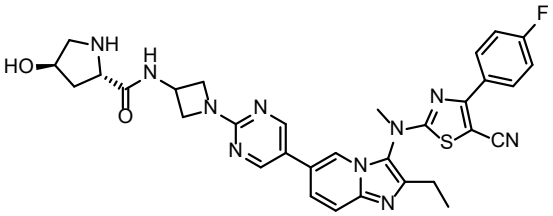

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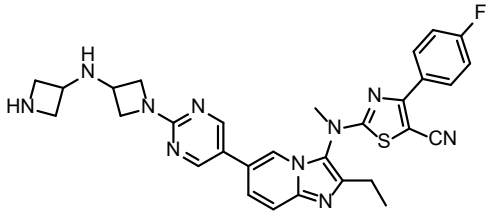

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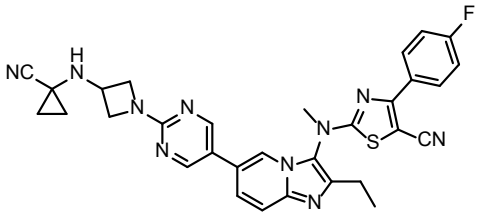

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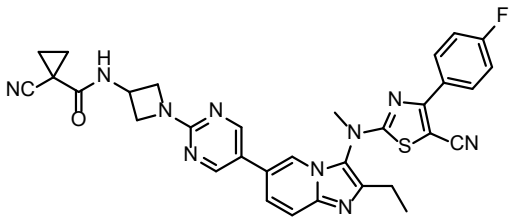

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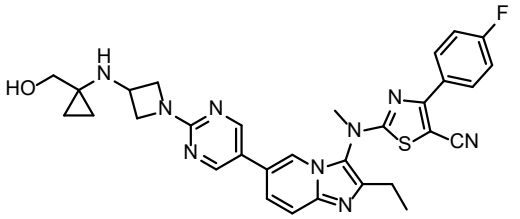

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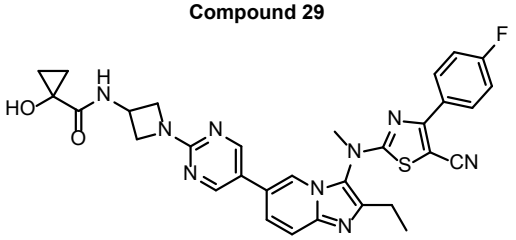

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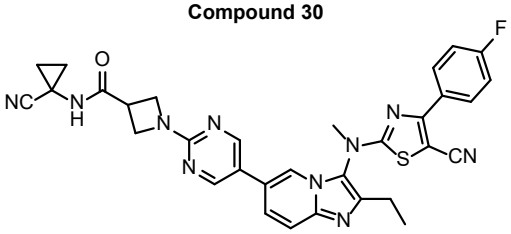

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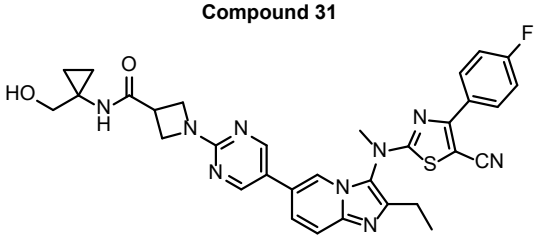

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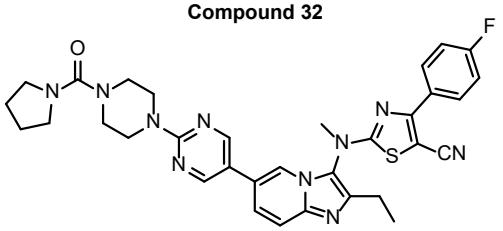

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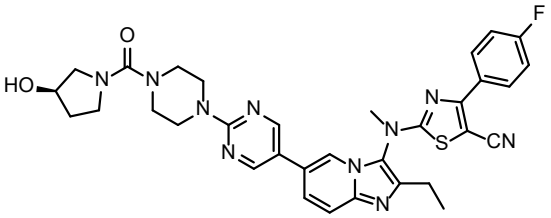

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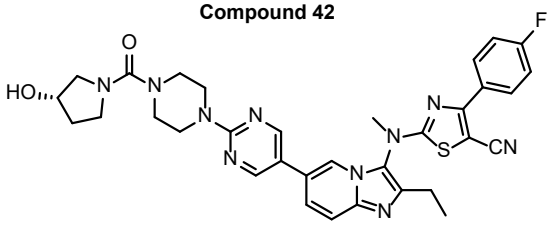

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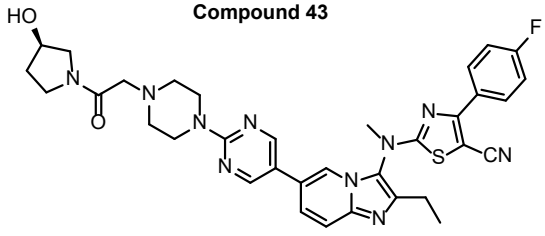

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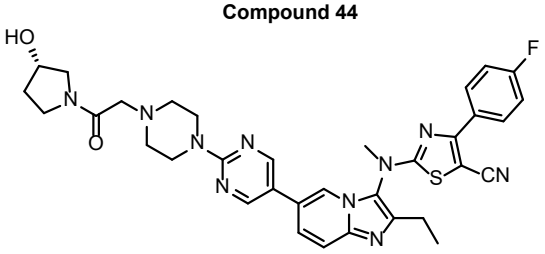

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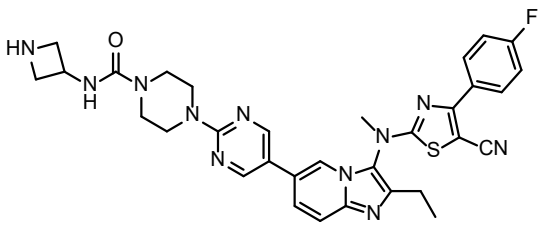

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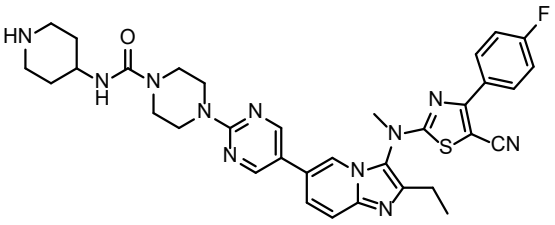

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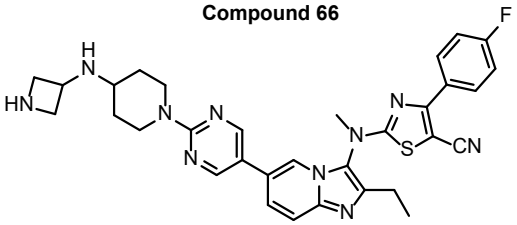

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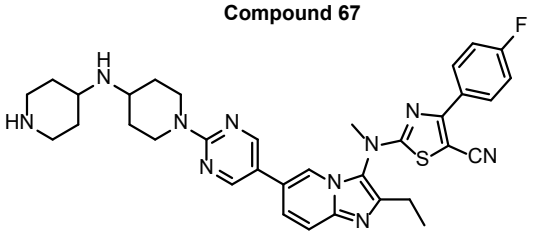

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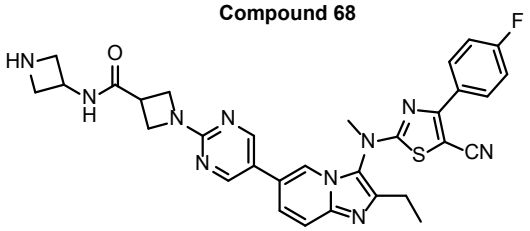

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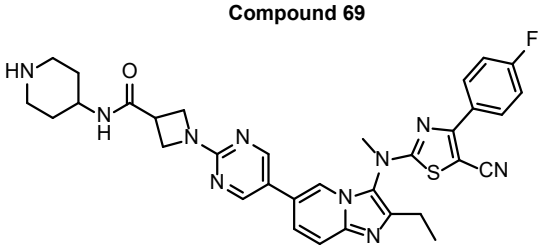
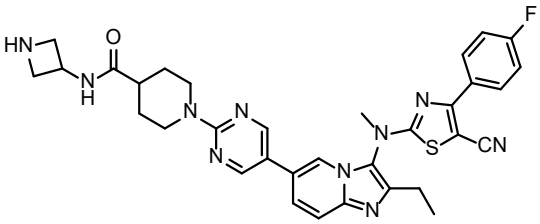
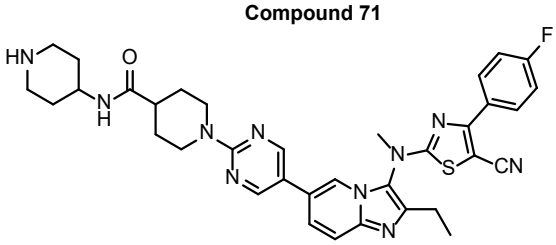


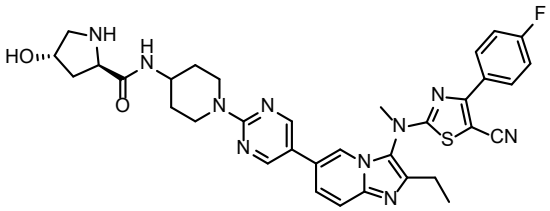
Compound 71



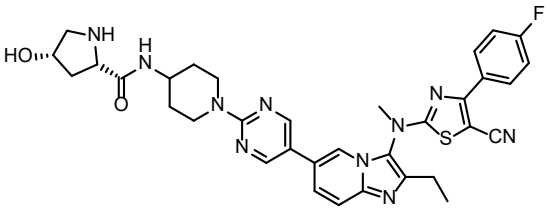
Compound 72



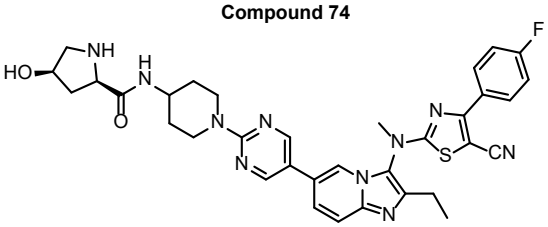
Compound 73



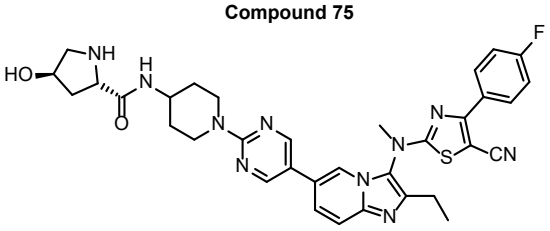
Compound 74



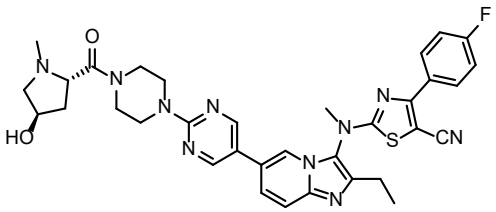
Compound 75



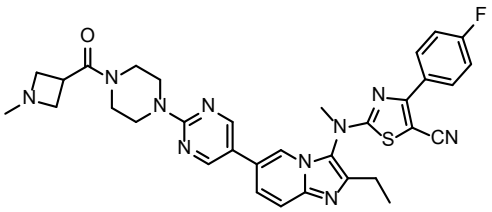
Compound 76



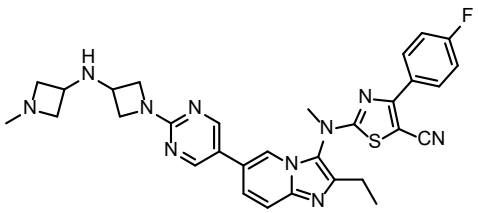
Compound 77



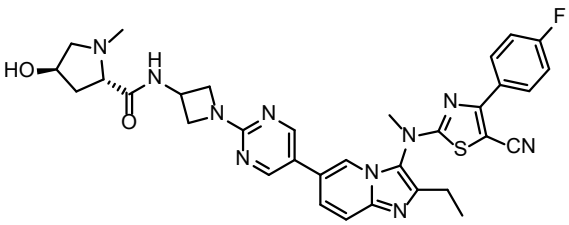
Compound 78



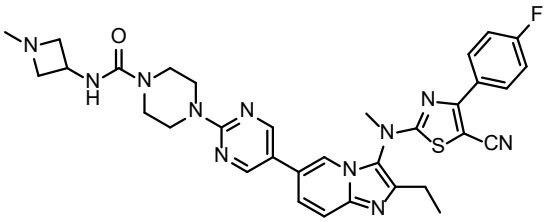
Compound 79



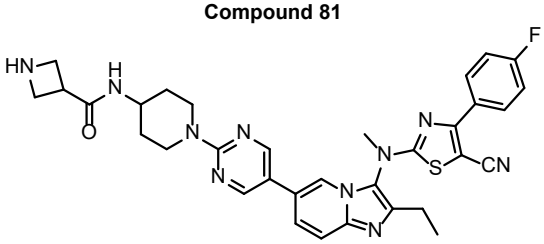
Compound 80



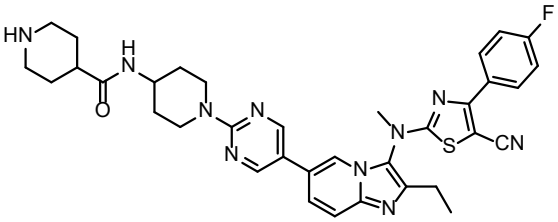
Compound 81



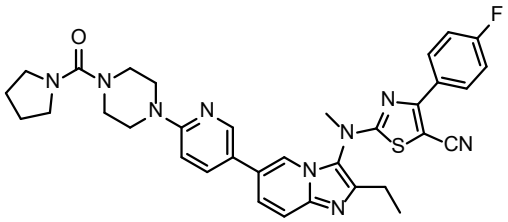
Compound 82



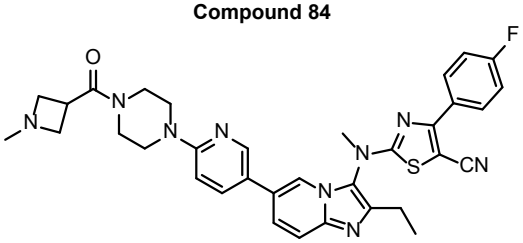
Compound 83



Compound 84



Compound 85



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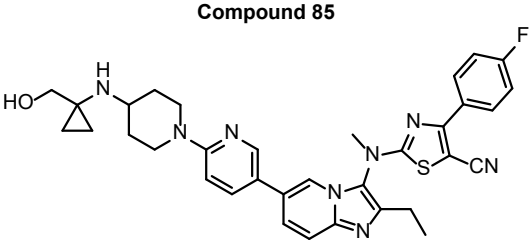
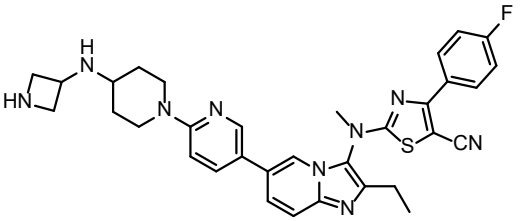


Compound 88



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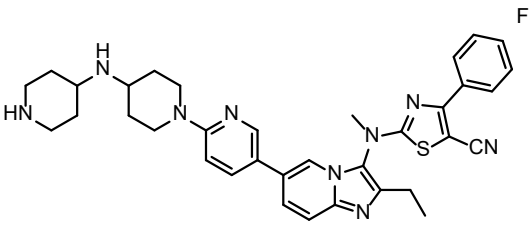
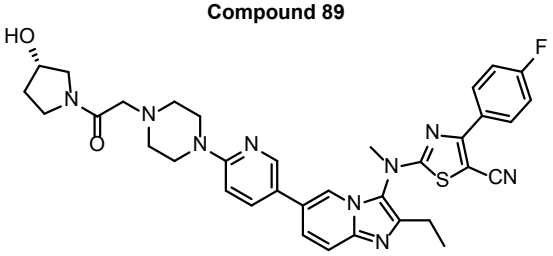


Compound 90



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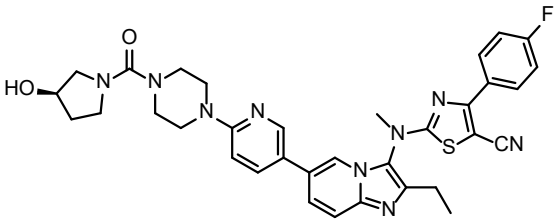
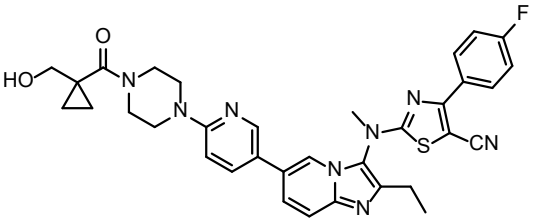
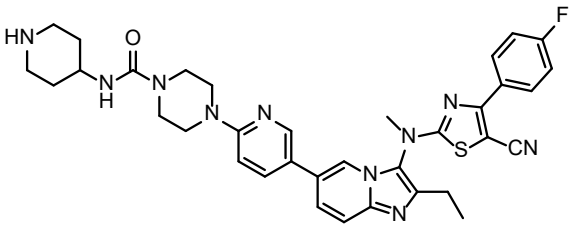


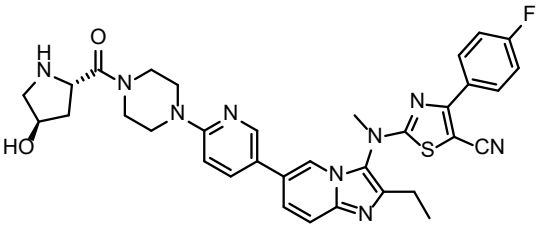
Compound 92



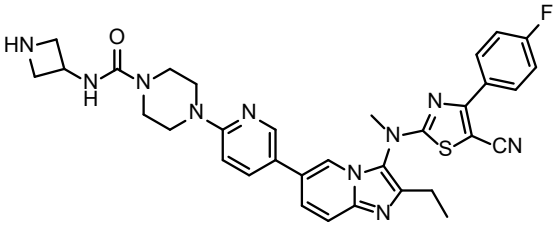
Compound 93



Compound 94



Compound 95



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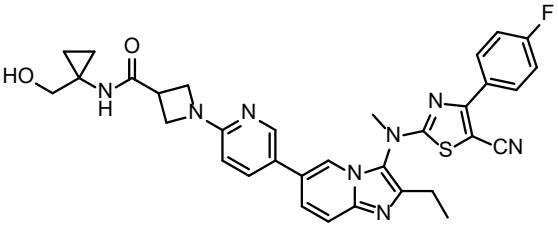
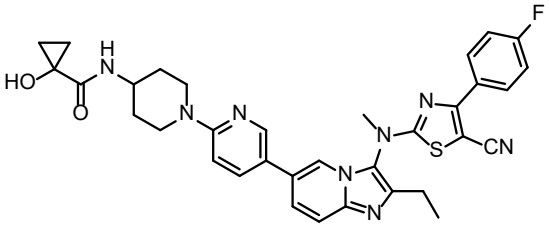


Compound 97



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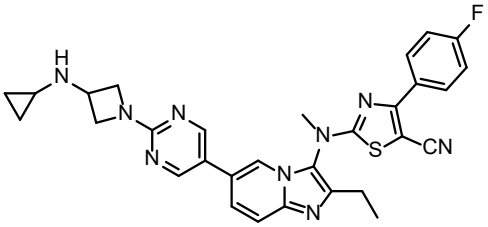
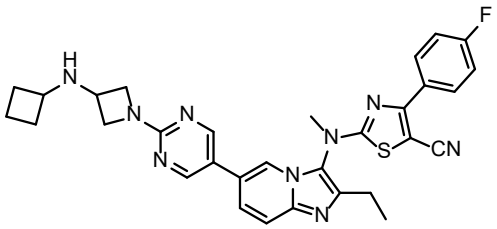
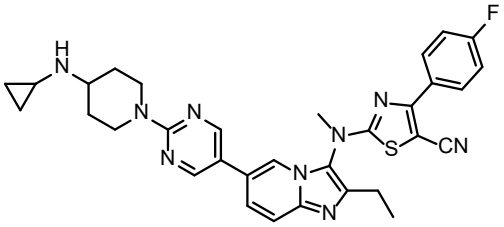


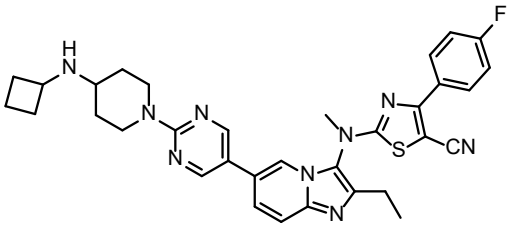
Compound 105



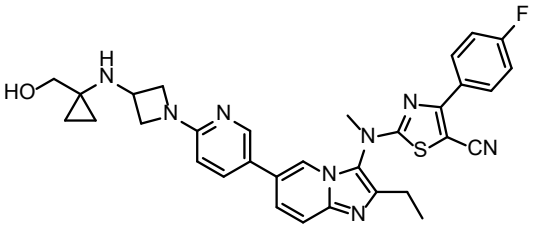
Compound 106



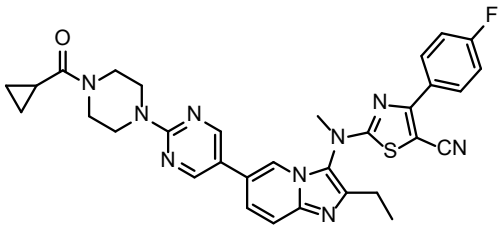
Compound 107



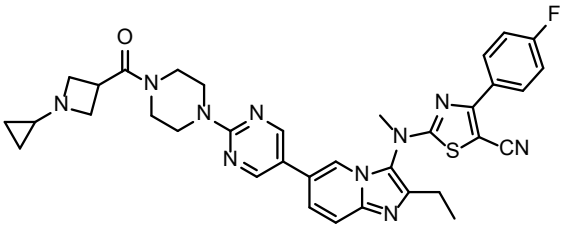
Compound 108



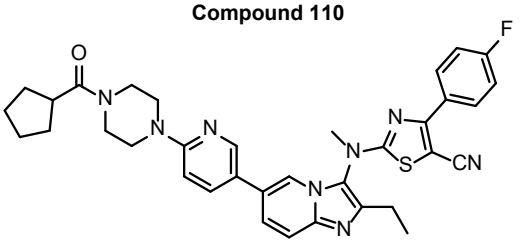
Compound 109



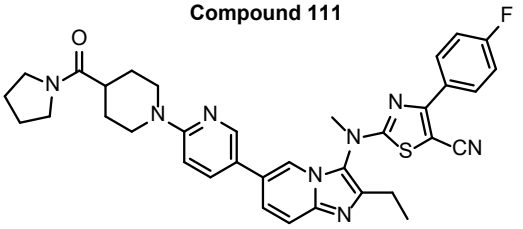
Compound 110



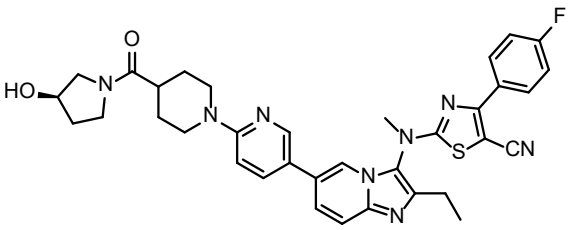
Compound 111



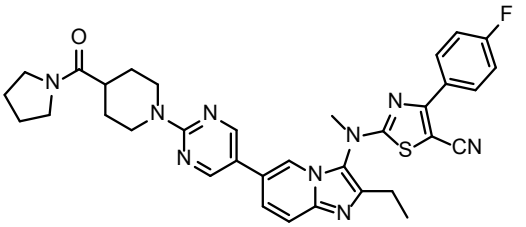
Compound 112



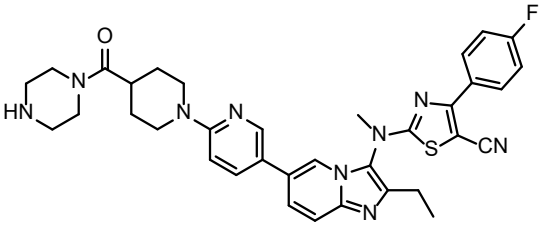
Compound 113



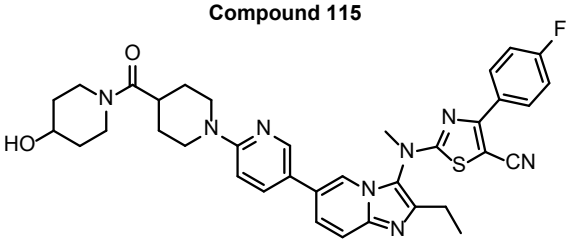
Compound 114



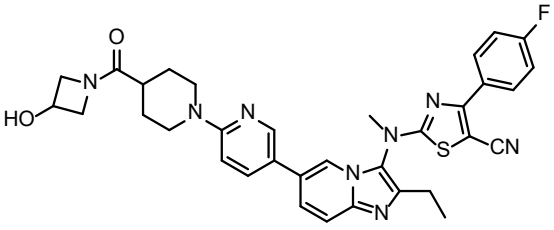
Compound 115



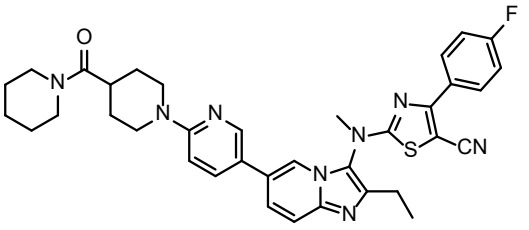
Compound 118



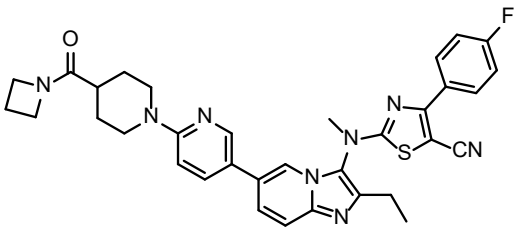
Compound 119



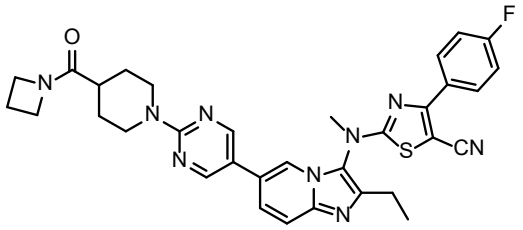
Compound 120



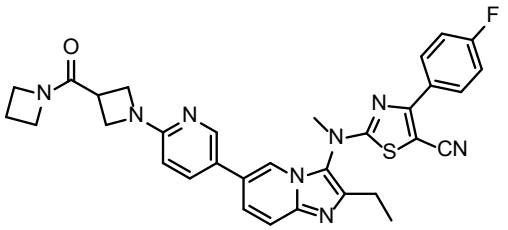
Compound 121



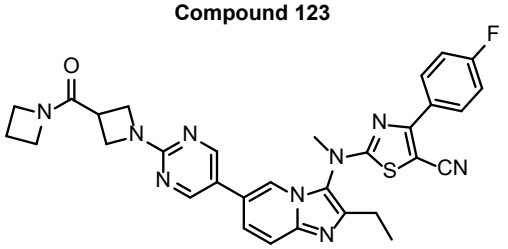
Compound 122



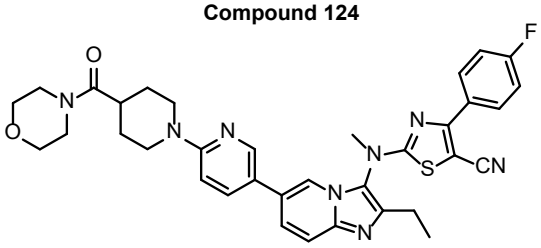
Compound 123



Compound 124

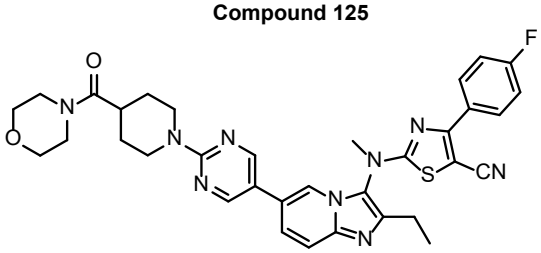


Compound 125



Compound 126

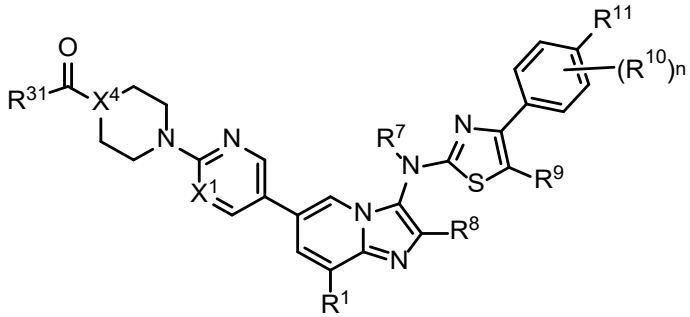
and



Compound 127

.

22. The compound of claim 1, wherein the compound is of formula (Ie):



(Ie)

wherein:

X^1 and X^4 are independently N or C-R^1;

R^1 is selected from H, halogen, optionally substituted -(C_1-C_6)alkyl, and optionally substituted -(C_1-C_6)alkoxy; and

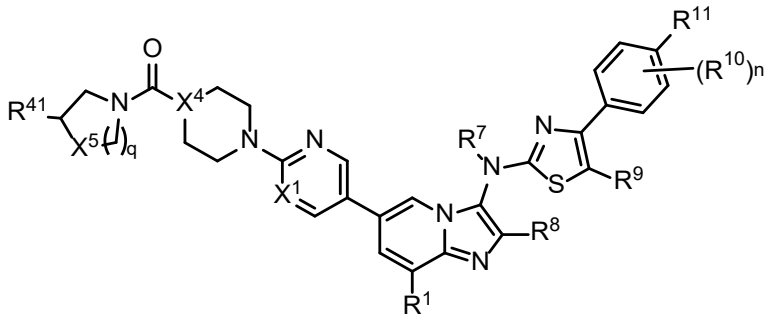
R^{31} is selected from optionally substituted (C_2-C_5)heterocycloalkyl, and optionally substituted (C_3-C_7)cycloalkyl-;

R^{11} is -H, -halogen, -CN, -OH, optionally substituted -(C_1-C_6)alkoxy, -NH_2, -NR^5R^6, -CH_2NH_2 and optionally substituted -(C_1-C_6)alkyl; and

n is 0, 1, 2, or 3.

23. The compound of claim 22, wherein the optional substituents of the R^{31} group are selected from NC-, HO-, $HOCH_2$-, (C_1-C_3)alkyl- (e.g., H_3C-), (C_1-C_3)alkoxy-, substituted (C_1-C_3)alkyl-, and (C_3-C_6)cycloalkyl- (e.g., cyclopropyl).

24. The compound of claim 22 or 23, wherein the compound is of formula (If):



(If)

wherein:

X^1 and X^4 are independently N or CH;

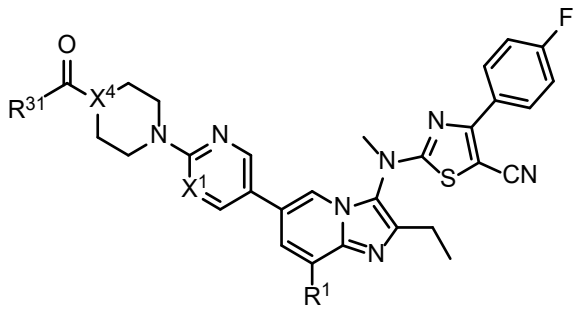
R^{41} is H-, or HO-; and

q is 0, 1 or 2; wherein

when q is 0 or 1, X^5 is CH_2; and

when q is 2, X^5 is NH, O, or CH(OH).

25. The compound of claim 17 or 22, wherein the compound is of formula (Ic):



(Ic)

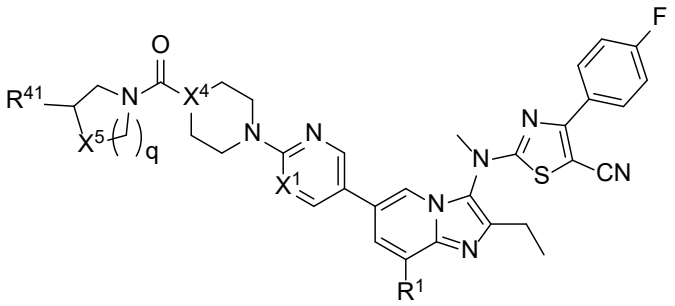
wherein:

X^1 and X^4 are independently N or C-R^1;

R^1 is selected from H, halogen, optionally substituted -(C_1-C_6)alkyl, and optionally substituted -(C_1-C_6)alkoxy; and

R^{31} is selected from optionally substituted (C_2-C_5)heterocycloalkyl, and optionally substituted (C_3-C_7)cycloalkyl-.

26. The compound of claim 25, wherein the compound is of formula (Id):



(Id)

wherein:

X^1 and X^4 are independently N or CH;

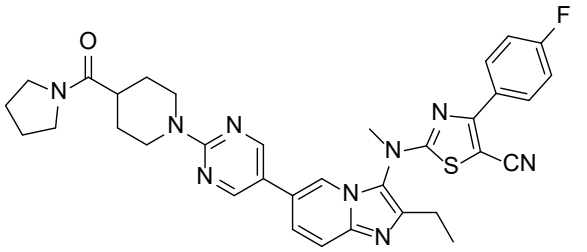
R^{41} is H-, or HO-; and

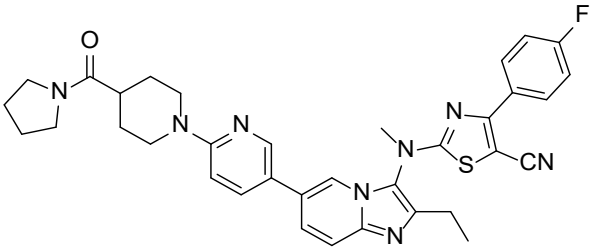
q is 0, 1 or 2; wherein

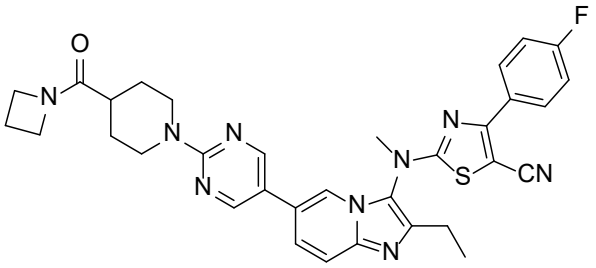
when q is 0 or 1, X^5 is CH_2; and

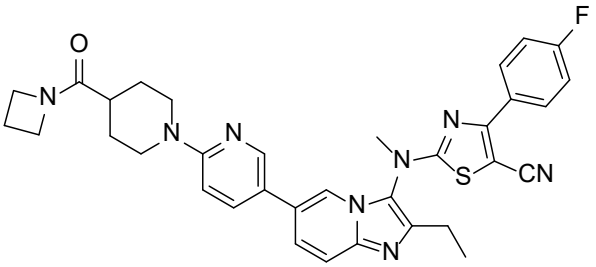
when q is 2, X^5 is NH, O, or CH(OH).

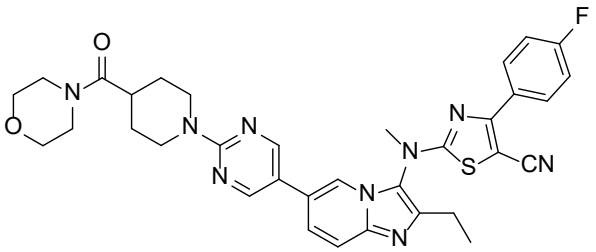
27. The compound of claim 26, wherein the compound is selected from:

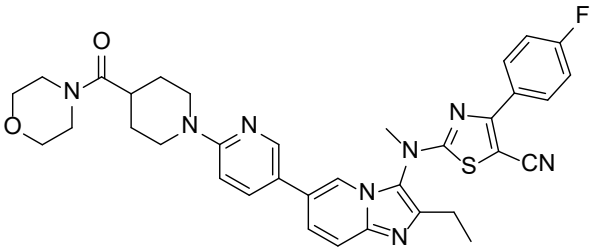




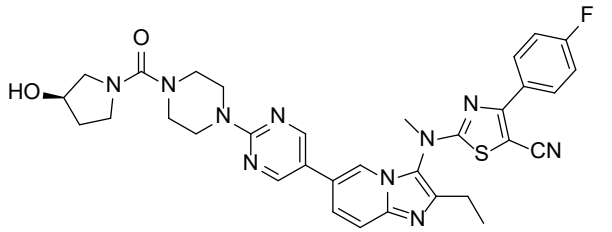


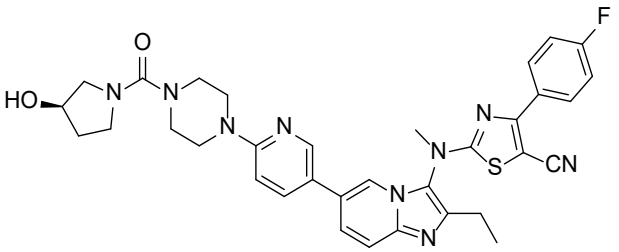


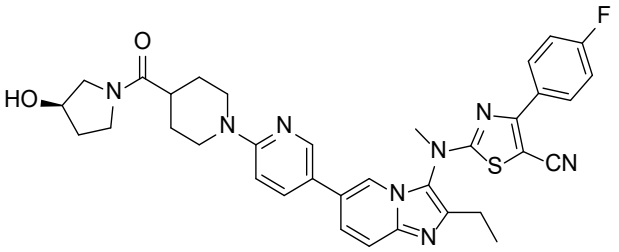


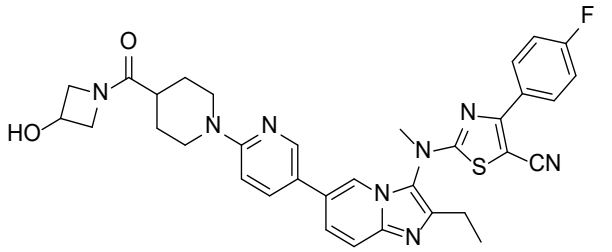


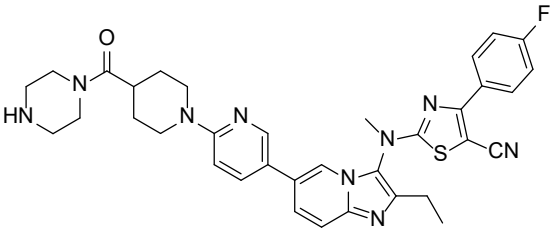
5



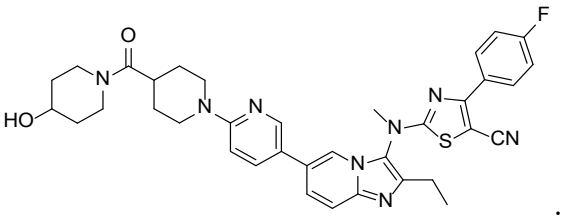






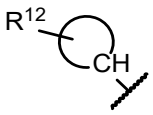


and

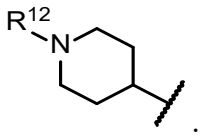


.

28. The compound of claim 10, wherein R^3 is



29. The compound of claim 28, wherein R^3 is



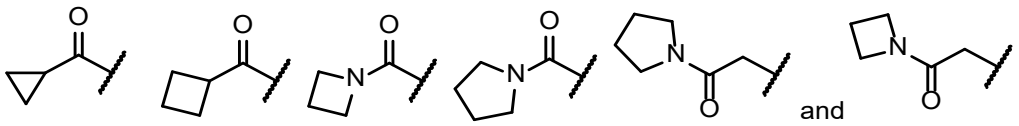
30. The compound of claim 28 or 29, wherein:

R^{12} is selected from H-, R^{31}-C(O)-, R^{31}-C(O)CH_2-, R^{31}-NHC(O)-, R^{31}-C(O)NH-, R^{31}-N(CH_3)C(O)-, and R^{31}-C(O)N(CH_3) -;

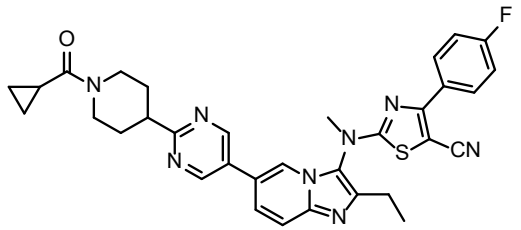
R^{31} is selected from optionally substituted (C_1-C_3)alkyl-, optionally substituted cycloalkyl-, and optionally substituted saturated heterocycle; and

the optional substituents of the R^{31} group are selected from NC-, HO-, $HOCH_2$-, (C_1-C_3)alkyl-, (C_1-C_3)alkoxy- and substituted (C_1-C_3)alkyl-.

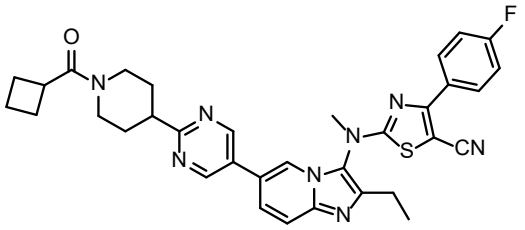
31. The compound of claim 28, wherein R^{12} is selected from:



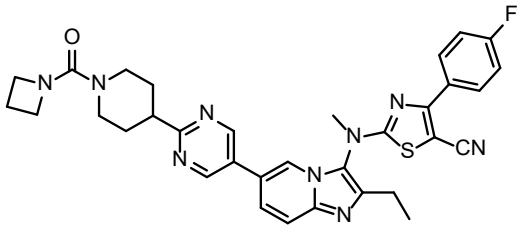
32. The compound of claim 28, wherein the compound is selected from:



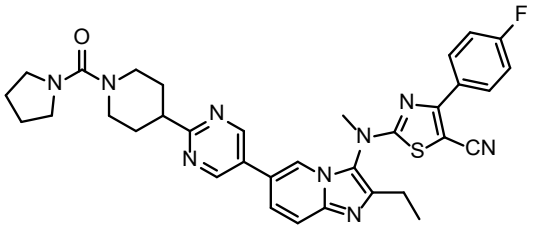
Compound 99



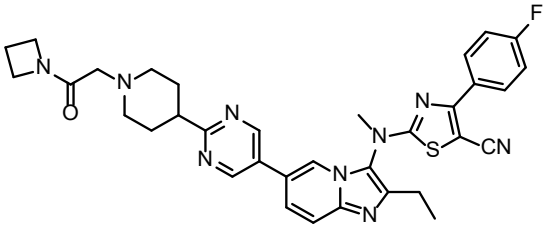
Compound 100



Compound 101

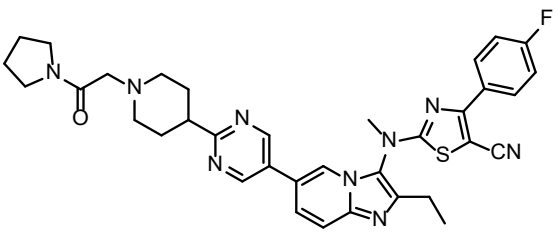


Compound 102



Comopund 103

and



Compound 104

.

33. A pharmaceutical composition comprising:

a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 32; and

a pharmaceutically acceptable excipient.

34. Use of the compound or a pharmaceutically acceptable salt or isomer thereof according to any one of claims 1 to 32 in the manufacture of a medicament for inhibiting autotaxin (ATX).

35. An *in vitro* method of inhibiting autotaxin, the method comprising contacting a biological system comprising autotaxin with an effective amount of a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 32 to inhibit autotaxin.

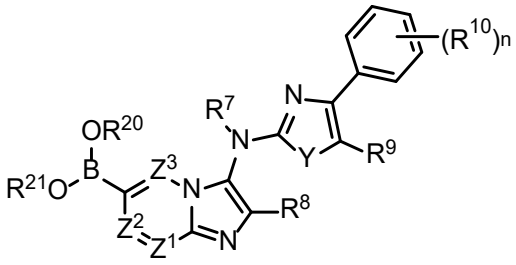
36. A compound for use in inhibiting autotaxin (ATX) or treating an ATX-related indication, wherein the compound is a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 32, or a pharmaceutical composition is according to claim 33.

37. Use of the compound or a pharmaceutically acceptable salt or isomer thereof according to any one of claims 1 to 32 in the manufacture of a medicament for treating an ATX-related indication.

38. The use of claim 37, wherein the ATX-related indication is selected from an inflammatory disease, autoimmune disease, proliferative disease, cancer, and fibrosis.

39. The use of claim 38, wherein the fibrosis occurs in the liver.

40. A compound of formula (II):



(II)

or a pharmaceutically acceptable salt or isomer thereof,

wherein:

Z^1, Z^2, and Z^3 are independently selected from C-R^1 and N;

R^{20} and R^{21} are each independently selected from H, and optionally substituted -(C_1-C_6)alkyl; or R^{20} and R^{21} together with the boron atom to which they are attached from an optionally substituted heterocycle;

each R^1 is independently selected from -H, -halogen, optionally substituted -(C_1-C_6)alkyl and optionally substituted -(C_1-C_6)alkoxy;

Y is selected from S, O, and N-R^2, wherein R^2 is selected from -H, and optionally substituted -(C_1-C_6)alkyl;

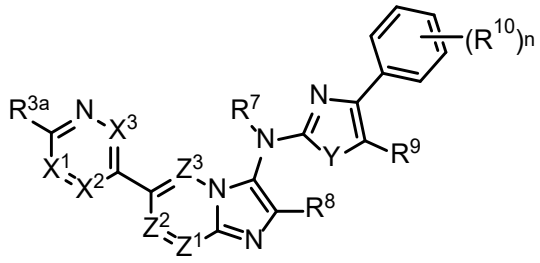
R^7 is selected from H-, and optionally substituted (C_1-C_6)alkyl-;

R^8 is selected from -H, -halogen, and optionally substituted -(C_1-C_6)alkyl;

R^9 and each R^{10} are independently selected from -H, -halogen, -CN, -OH, optionally substituted -(C_1-C_6)alkoxy, -NH_2, substituted amino, optionally substituted -(C_1-C_6)alkyl-NH_2 and optionally substituted -(C_1-C_6)alkyl; and

n is 0, 1, 2, 3, 4, or 5.

41. A compound of formula (III):



(III)

or a pharmaceutically acceptable salt or isomer thereof,

wherein:

X^1, X^2, and X^3 are independently selected from C-R^1 and N;

Z^1, Z^2, and Z^3 are independently selected from C-R^1 and N;

each R^1 is independently selected from -H, -halogen, optionally substituted -(C_1-C_6)alkyl and optionally substituted -(C_1-C_6)alkoxy;

Y is selected from S, O, and N-R^2, wherein R^2 is selected from -H, and optionally substituted -(C_1-C_6)alkyl;

R^{3a} is selected from optionally substituted R^4-C(O)-(C_1-C_3)alkyl-, R^4C(O)-, halogen, optionally substituted monocyclic or bicyclic carbocycle, optionally substituted monocyclic or bicyclic heterocycle, R^5R^6HC-, and R^5R^6N-;

R^4 is selected from H_2N-, HO-, R^5R^6N-, optionally substituted (C_1-C_{10})alkyl-, optionally substituted (C_1-C_{10})alkoxy-, optionally substituted monocyclic or bicyclic carbocycle, optionally substituted monocyclic or bicyclic heterocycle, optionally

substituted cycloalkyl-(C_1-C_6)alkylene-, and optionally substituted heterocycle-(C_1-C_6)alkylene-;

R^5 and R^6 are independently selected from H-, H_2N-, HO-, optionally substituted (C_1-C_{10})alkyl-, optionally substituted monocyclic or bicyclic carbocycle, optionally substituted monocyclic or bicyclic heterocycle, optionally substituted $R^4C(O)$-(C_1-C_{10})alkyl-, $R^4C(O)$-, R^4-, and substituted amino;

or R^5 and R^6 together with the nitrogen or carbon atom to which they are attached are cyclically linked to form an optionally substituted carbocycle or an optionally substituted heterocycle;

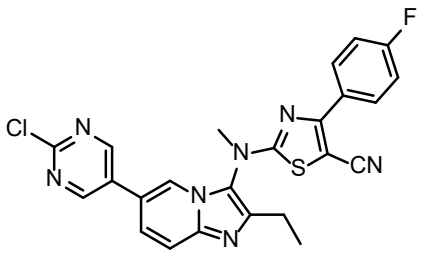
R^7 is selected from H-, and optionally substituted (C_1-C_6)alkyl-;

R^8 is selected from -H, -halogen, and optionally substituted -(C_1-C_6)alkyl;

R^9 and each R^{10} are independently selected from -H, -halogen, -CN, -OH, optionally substituted -(C_1-C_6)alkoxy, -NH_2, substituted amino, optionally substituted -(C_1-C_6)alkyl-NH_2 and optionally substituted -(C_1-C_6)alkyl; and

n is 0, 1, 2, 3, 4, or 5.

42. The compound of claim 41, wherein the compound is:



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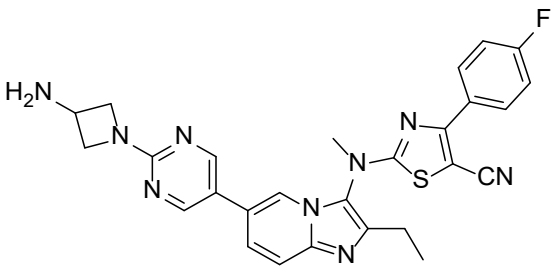

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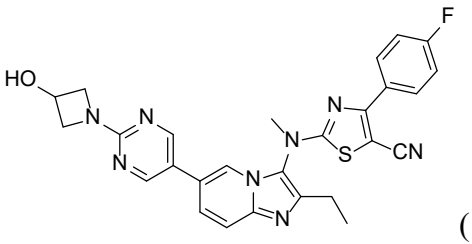

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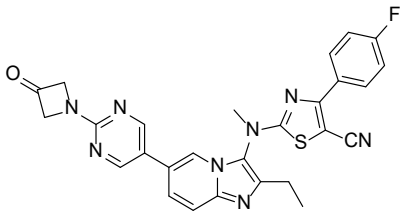

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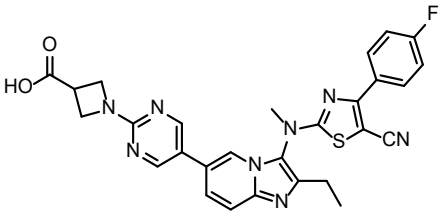

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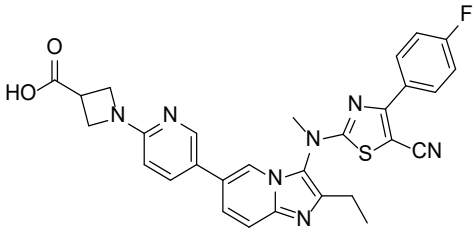

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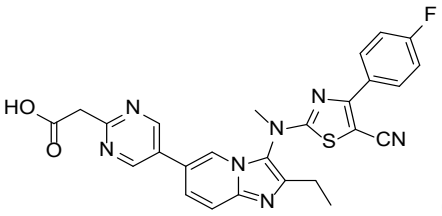

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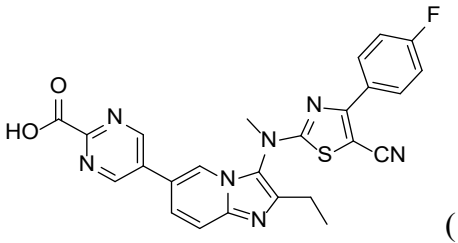

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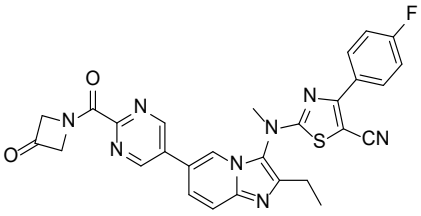

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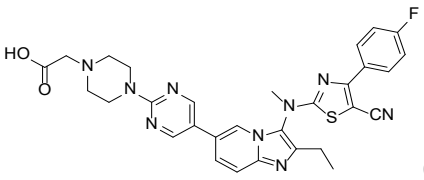

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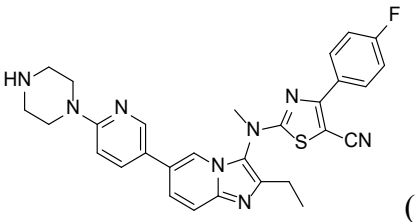

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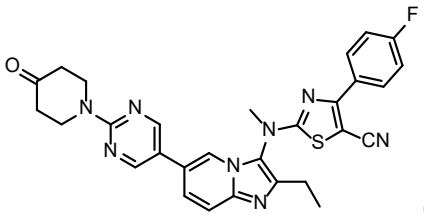

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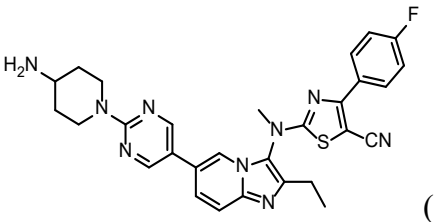
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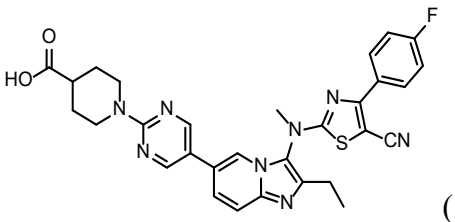
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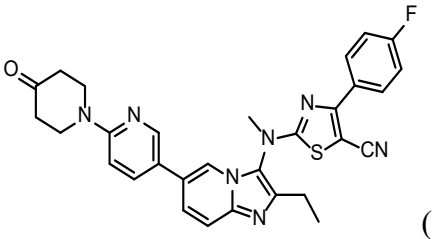
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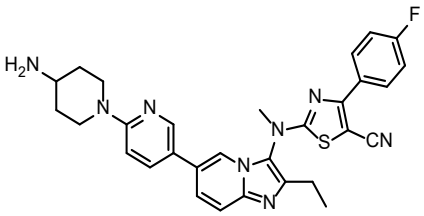
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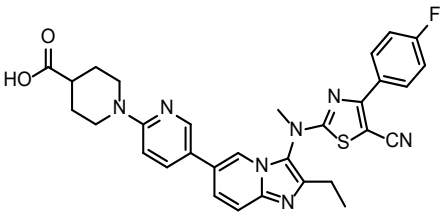
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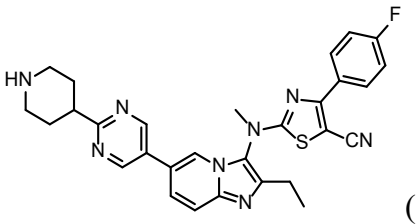
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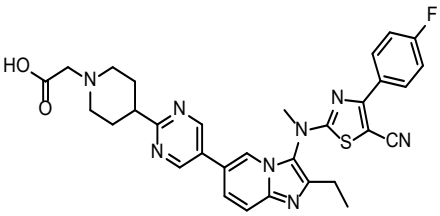
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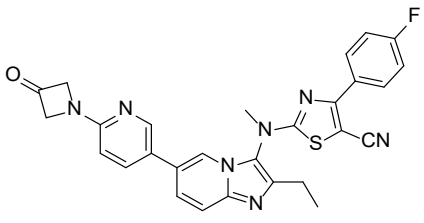
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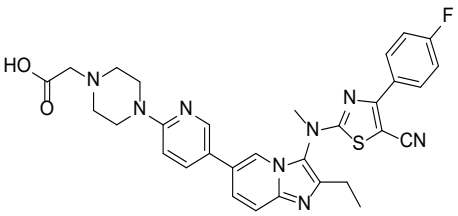
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