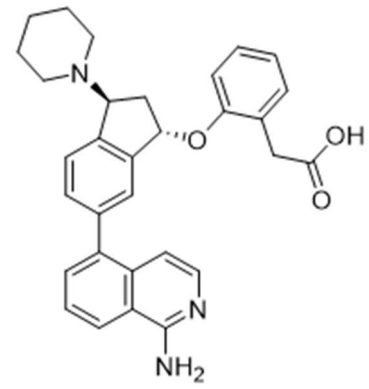
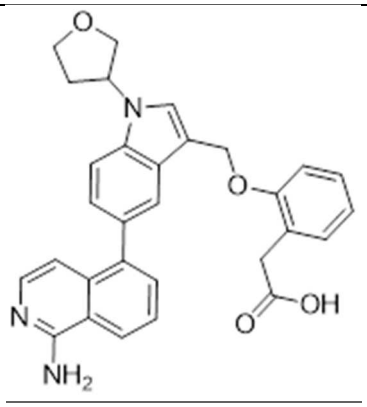
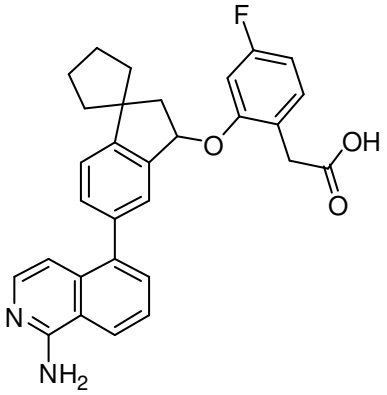
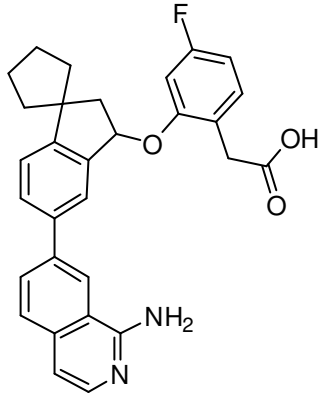
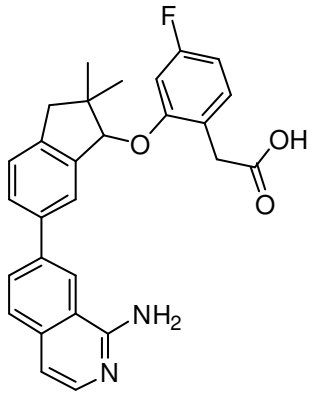
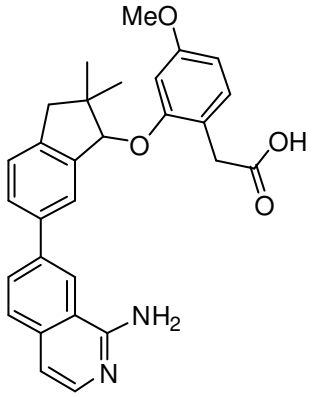
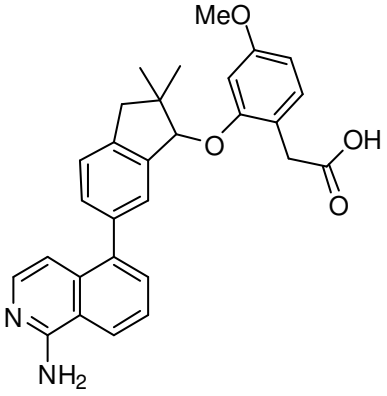
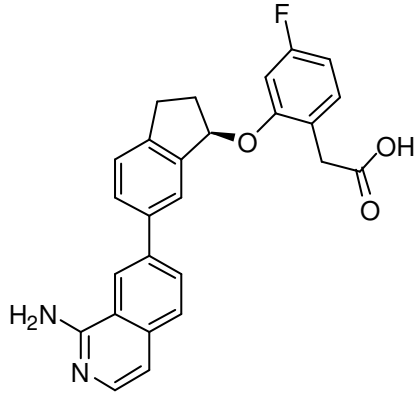
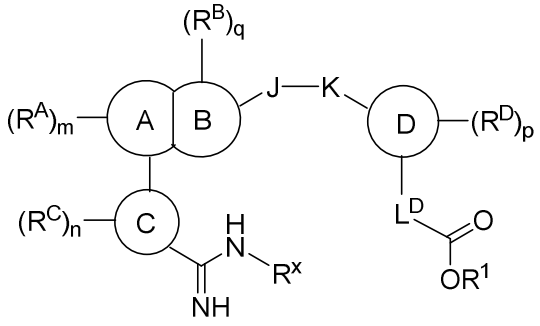
	
	
	
	

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I);

wherein:

ring A is arylene or heteroarylene;

ring B is arylene or heteroarylene;

ring A is fused to ring B at two and only two adjacent positions;

ring C is aryl or heteroaryl;

ring D is aryl or heteroaryl;

J represents $–CH_2–$, –NH–, $–CH_2CH_2–$, –C(O)–, –C≡C–, –O–, –S–, –S(O)–, $–SO_2–$, –N(alkyl)–, –CH(alkyl)–, –CH(aryl)–, $–C(alkyl)_2–$, –CH(cycloalkyl)–, or  ;

K represents a bond, –O–, –NH–, –C(O)–, $–CH_2–$, –S–, –S(O)–, $–SO_2–$, –N(alkyl)–, –CH(alkyl)–, or –CH(cycloalkyl)–;

wherein at least one of J and K is a bond, –C(O)–, $–CH_2–$, $–CH_2CH_2–$, –CH(alkyl)–, or –CH(aryl)–;

L^D represents $–CH_2–$, $–CH_2CH_2–$, $–CF_2–$, –CH(F)–, $–CD_2–$, –CH(D)–, –CH(OH)–, –CH(alkyl)–, –CH(cycloalkyl)–, $–CHNH_2–$, –CH(NH(alkyl))–, –CH(NH(cycloalkyl))–, or a bond;

R^A, independently for each occurrence, represents H, halo, hydroxyl, cyano, amino, alkyl, optionally substituted alkoxy, hydroxyalkyl, optionally substituted aryloxy, (aryloxy)alkyl, (cycloalkyl)alkoxy, (heterocycloalkyl)alkoxy, optionally substituted (heteroaryl)alkoxy, haloalkyl, haloalkoxy,

(hydroxy)haloalkyl, alkoxyalkyl, optionally substituted aminoalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (cycloalkyl)alkenyl, optionally substituted heterocycloalkyl, optionally substituted (heterocycloalkyl)alkyl, –C(O)OH, –C(O)NH_2–, –C(O)N(alkyl)$_2$–, –CH_2C(O)OH, –NO_2, –CH_2NH(optionally substituted alkyl), –CH_2NH(Boc), –CH_2N(Boc)(optionally substituted alkyl), –CH_2NH((cycloalkyl)alkyl), –CH_2N(alkyl)(cycloalkyl), –CH_2N(alkyl)((cycloalkyl)alkyl), –NH(optionally substituted alkyl), –NH(cycloalkyl), –NH((cycloalkyl)alkyl), –NH((heterocycloalkyl)alkyl), –N(alkyl)$_2$, –N(alkyl)((cycloalkyl)alkyl, –N(alkyl)((heterocycloalkyl)alkyl, –NH(heteroarylalkyl), –CH_2O(optionally substituted aryl), –C(O)O(alkyl), –C(O)NH(optionally substituted alkyl), –C(O)NH((cycloalkyl)alkyl), –NHC(O)O(alkyl), or –CH_2N(alkyl)$_2$;

R^B, independently for each occurrence, represents H, oxo, –C(O)O(alkyl), halogen, cyano, amino, –C(O)OH, –CH_2C(O)OH, –C(O)NH_2, –C(O)NH(cycloalkyl), –C(O)NH(alkyl), –C(O)NH(aryl), -C(O)NH(heteroaryl), –C(O)(alkyl), -S(O)$_2$alkyl, alkylaminoalkyl, alkylaminocycloalkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, (hydroxy)haloalkyl, or tosyl, or is optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, spirocycloalkyl, halocycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, spiroheterocycloalkyl, or (heterocycloalkyl)alkyl; or two geminal occurrences of R^B taken together with the atom to which they are attached form an optionally substituted spirocycloalkyl or a spiroheterocycloalkyl;

R^C, independently for each occurrence, represents H, halo, -OH, cyano, or amino, or is optionally substituted alkoxy, haloalkoxy, alkyl, cycloalkyl, heterocycloalkyl, or (heteroaryl)alkoxy;

R^x is H or OH;

R^D, independently for each occurrence, represents H, halo, hydroxyl, cyano, –NH_2, -NH(Ac), -NH(alkyl), -N(alkyl)$_2$, -NH(CO)(alkyl), –CH_2NH_2, -CH_2NHC(O)(alkyl), –C(O)NH_2, –C(O)OH, or –NHC(O)O(alkyl), or is optionally substituted alkyl, alkoxy, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, haloalkoxy, or haloalkyl;

R^1 represents H or optionally substituted alkyl; and

m, n, p, and q are each independently 0, 1, or 2.

2. The compound of claim 1, wherein:

ring A is arylene or heteroarylene;

ring B is arylene or heteroarylene;

ring A is fused to ring B at two and only two adjacent positions;

ring C is aryl or heteroaryl;

ring D is aryl;

J represents $–CH_2–$ or –C(O)–;

K represents –O–, –NH–, or a bond;

L^D represents $–CH_2–$, –CH(OH)–, or a bond;

R^A, independently for each occurrence, represents H, optionally substituted alkoxy, or optionally substituted (heteroaryl)alkoxy;

R^B, independently for each occurrence, represents H, oxo, or is optionally substituted alkyl, aryl, cycloalkyl, (cycloalkyl)alkyl, or heterocycloalkyl;

R^C, independently for each occurrence, represents H, halo, -OH, or alkoxy;

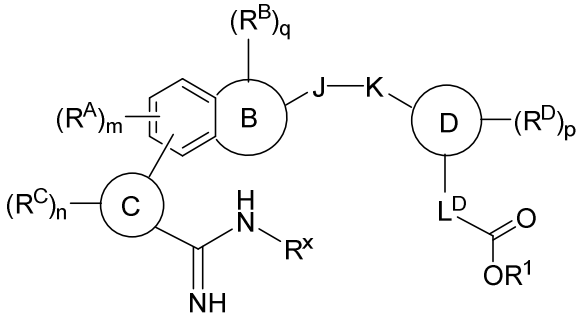
R^x is H or OH;

R^D, independently for each occurrence, represents H, or is optionally substituted alkyl or alkoxy;

R^1 represents H; and

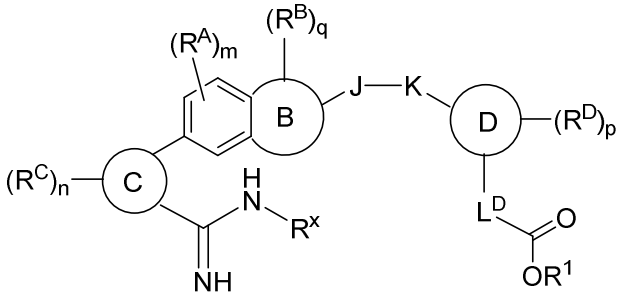
m, n, p, and q are each independently 0, 1, or 2.

3. The compound of claim 1 or 2, having the structure of formula (Ia):



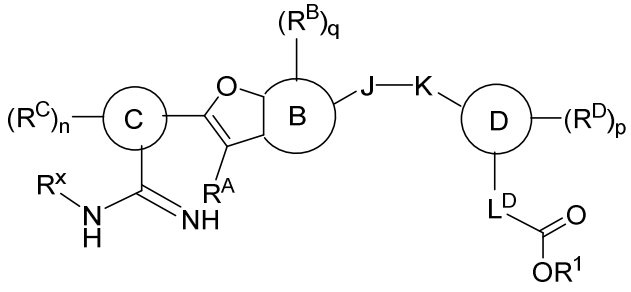
(Ia).

4. The compound of any one of claims 1-3, having the structure of formula (Ia-1):



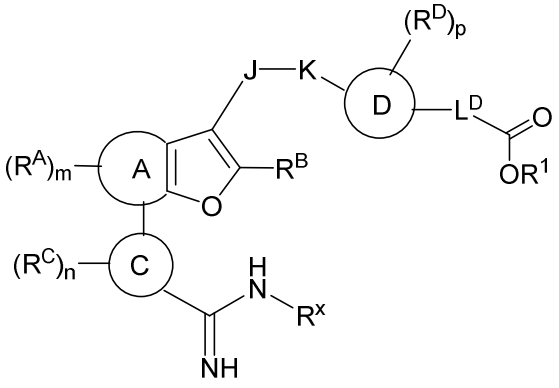
(Ia-1).

5. The compound of claim 1 or 2, having the structure of formula (Ib):



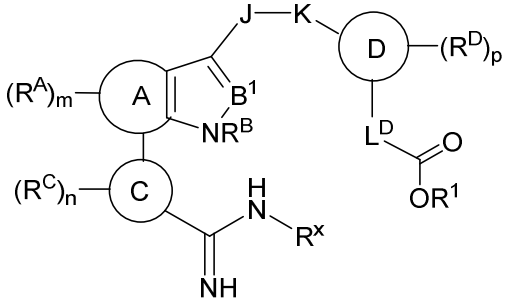
(Ib).

6. The compound of claim 1 or 2, having the structure of formula (Ic):



(Ic).

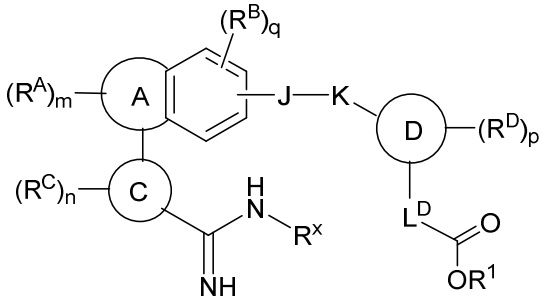
7. The compound of claim 1 or 2, having the structure of formula (Id):



(Id);

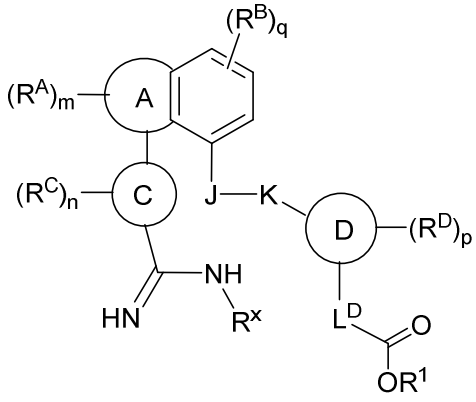
wherein B^1 represents N or CH.

8. The compound of claim 1 or 2, having the structure of formula (Ie):



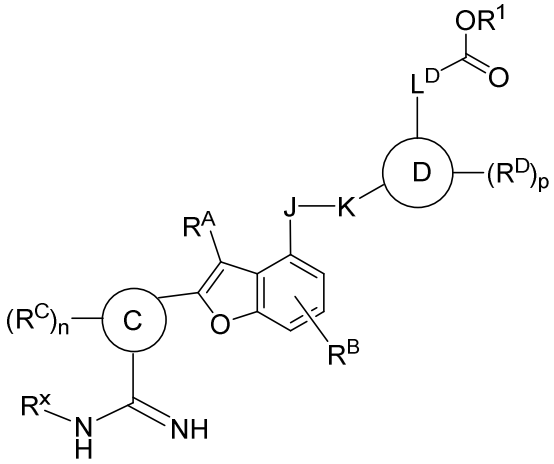
(Ie).

9. The compound of claim 1 or 2, having the structure of formula (If):



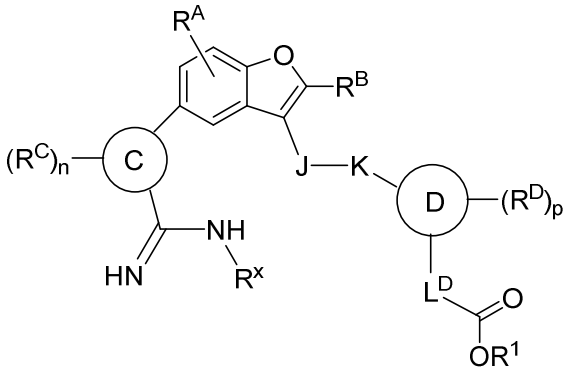
(If).

10. The compound of claim 1 or 2, having the structure of formula (Ig):



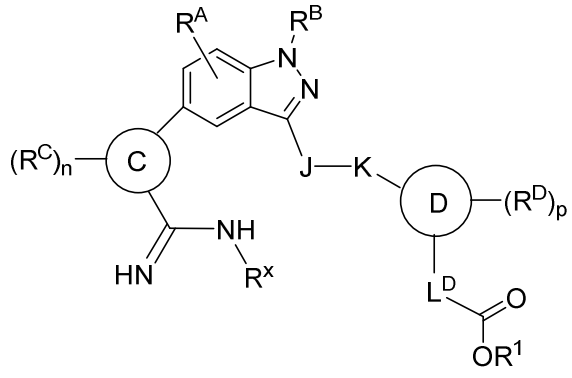
(Ig).

11. The compound of claim 1 or 2, having the structure of formula (Ih):



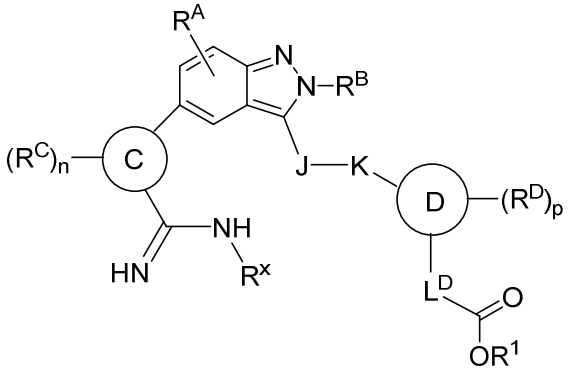
(Ih).

12. The compound of claim 1 or 2, having the structure of formula (Ij):



(Ij).

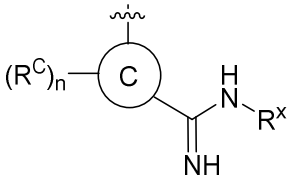
13. The compound of claim 1 or 2, having the structure of formula (Ik):

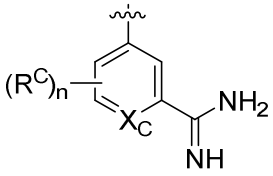


(Ik).

14. The compound of any one of claims 1-13, wherein ring  represents a 6-membered aryl or heteroaryl.

15. The compound of any one of claims 1-14, wherein:

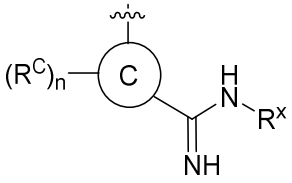


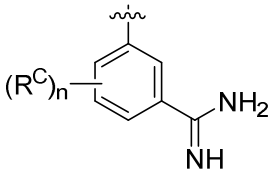
represents 

; and

X_C represents CH or N.

16. The compound of any one of claims 1-15, wherein



represents 

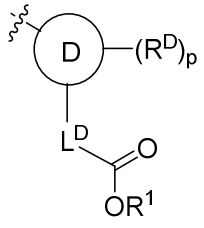
.

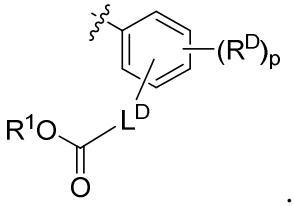
17. The compound of any one of claims 1-16, wherein R^C represents H.

18. The compound of any one of claims 1-16, wherein R^C represents alkoxy (e.g., methoxy).

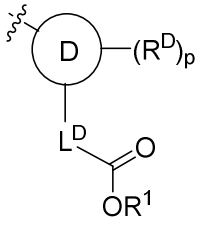
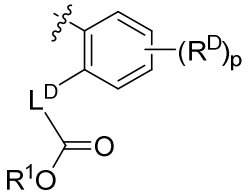
19. The compound of any one of claims 1 and 3-18, wherein J represents $–CH_2–$, –NH–, $–CH_2CH_2–$, –C(O)–, –O–, –S–, –S(O)–, $–SO_2–$, –N(alkyl)–, –CH(alkyl)–, –CH(aryl)–, $–C(alkyl)_2–$, –CH(cycloalkyl)–, or  .

20. The compound of any one of claims 1-19, wherein –J–K– represents $–CH_2$-O– or –C(O)-NH–.

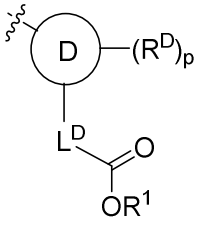
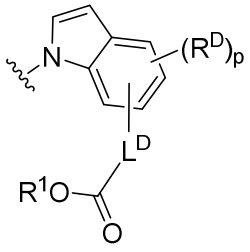
21. The compound of any one of claims 1-20, wherein 

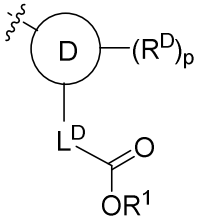
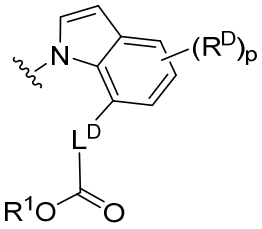
represents 

.

22. The compound of any one of claims 1-21, wherein  represents  .

23. The compound of claim 1, wherein ring  is bicyclic heteroaryl.

24. The compound of claim 23, wherein  represents  .

25. The compound of claim 23, wherein  represents  .

26. The compound of any one of claims 1-25, wherein R^1 is H.

27. The compound of any one of claims 1-26, wherein L^D represents $–CH_2–$ or a bond.

28. The compound of any one of claims 1-27, wherein L^D represents $–CH_2–$.

29. The compound of any one of claims 1-28, wherein R^D, independently for each occurrence, represents H, alkyl, or alkoxy.

30. The compound of any one of claims 1-29, wherein R^D represents H.

31. The compound of any one of claims 1-30, wherein R^B, independently for each occurrence, represents H, alkyl, cycloalkyl, (cycloalkyl)alkyl, or heterocycloalkyl.

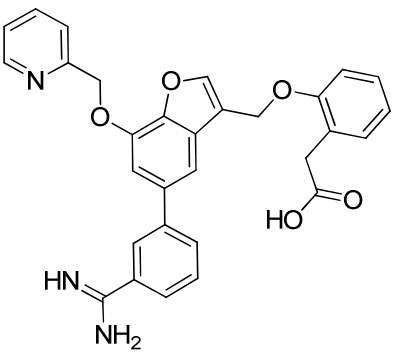
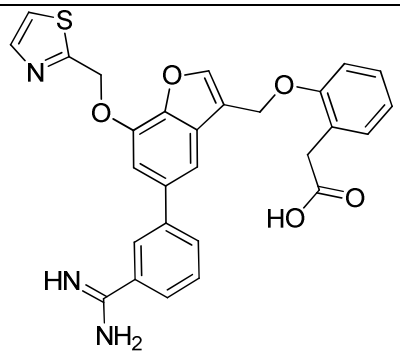
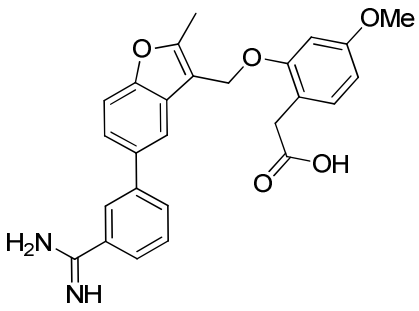
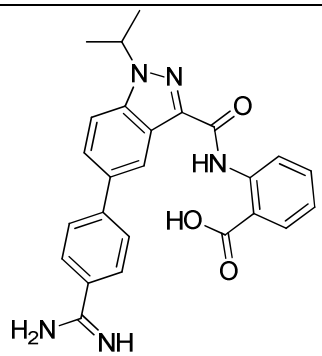
32. The compound of any one of claims 1-31, wherein R^B represents H.

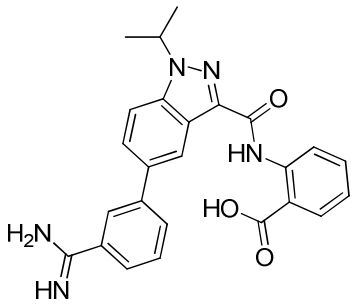
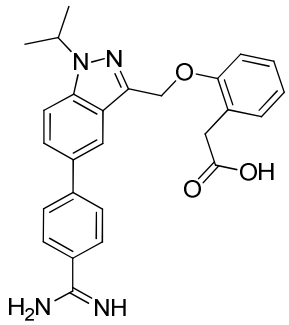
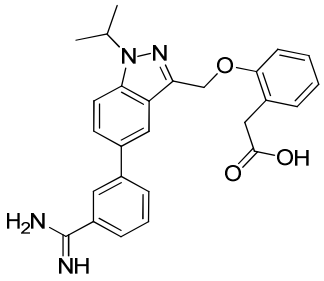
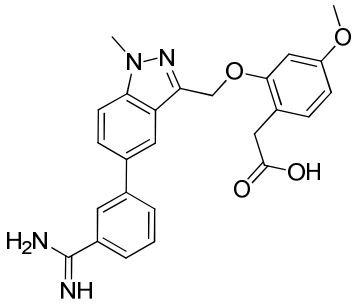
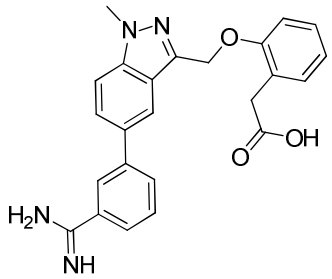
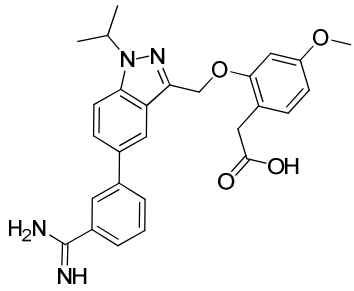
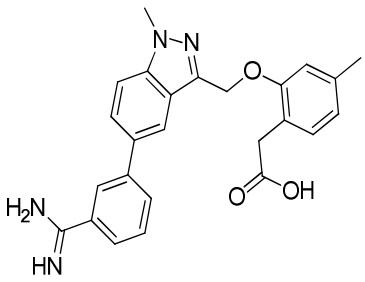
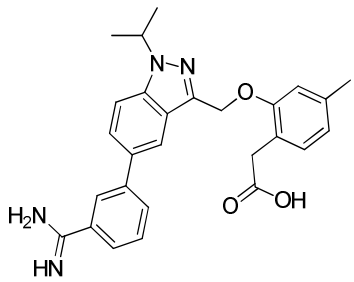
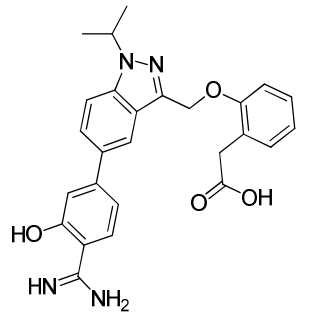
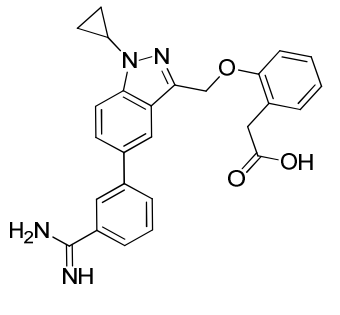
33. The compound of any one of claims 1-31, wherein R^B, independently for each occurrence, represents alkyl or cycloalkyl.

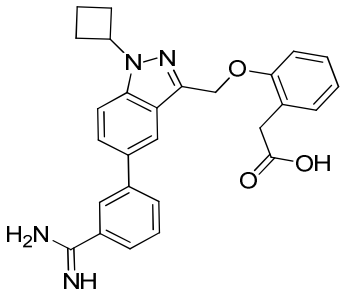
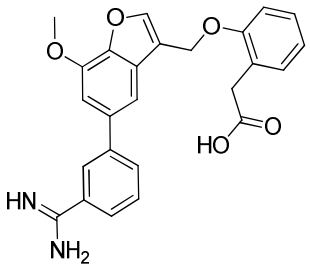
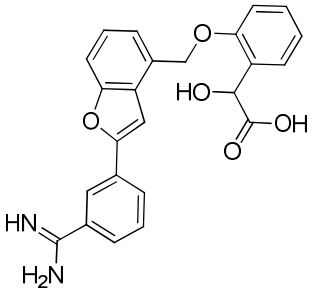
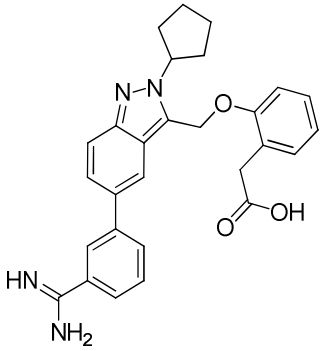
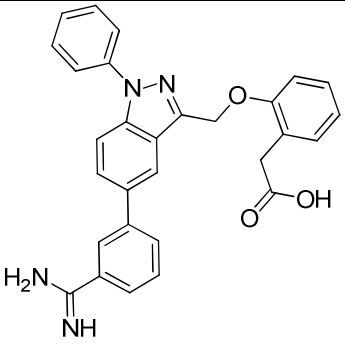
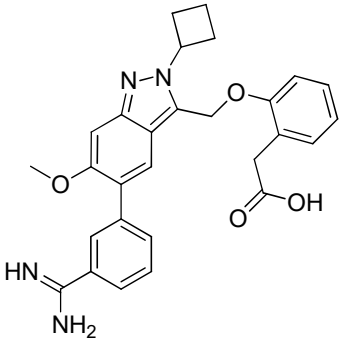
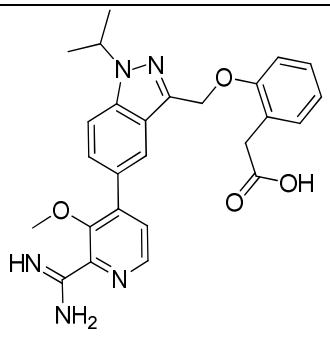
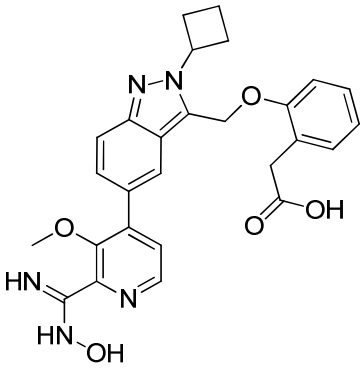
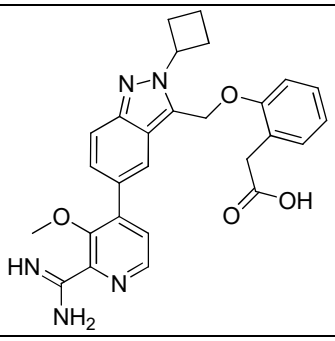
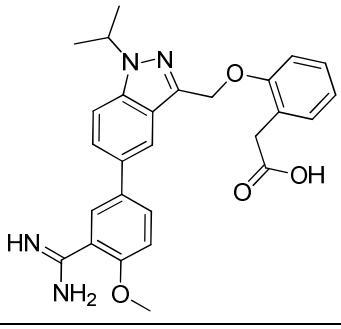
34. The compound of any one of claims 1-33, wherein R^A, independently for each occurrence, represents H, optionally substituted alkoxy, or optionally substituted (heteroaryl)alkoxy.

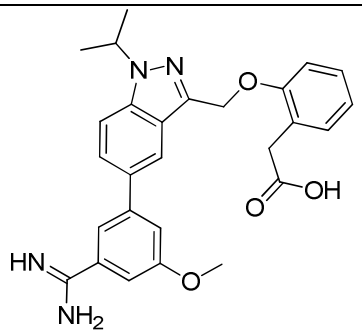
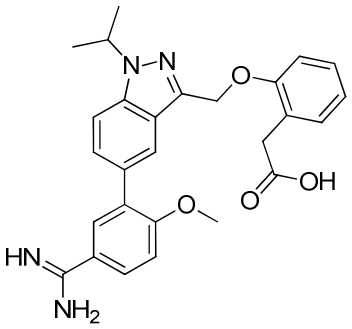
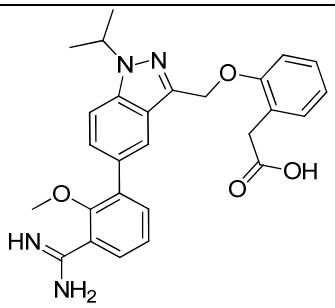
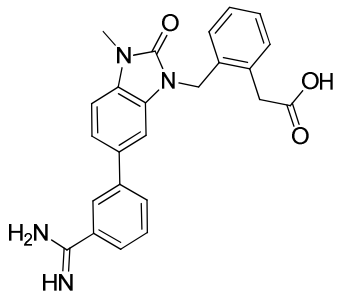
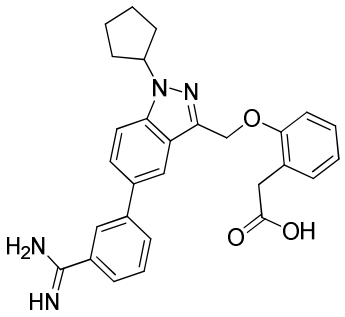
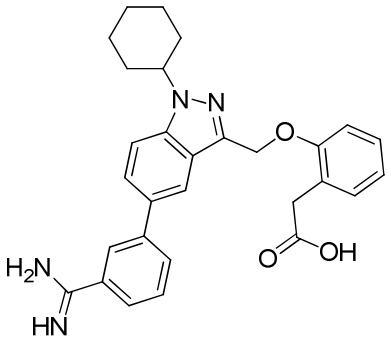
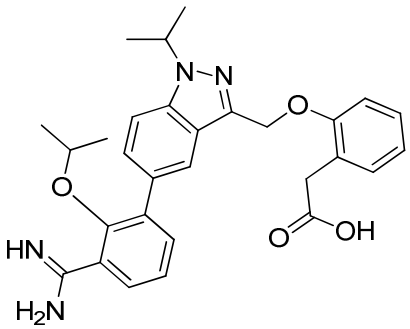
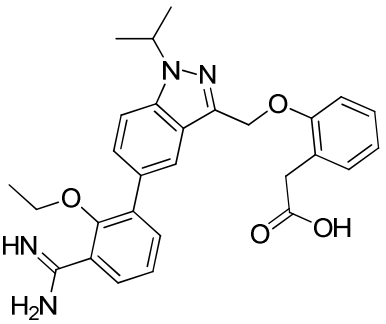
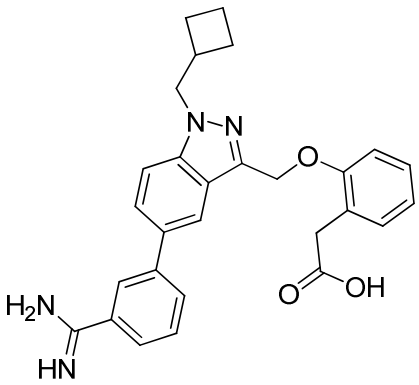
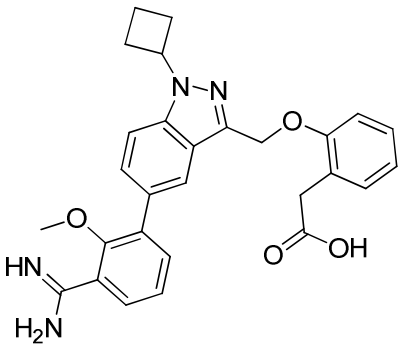
35. The compound of any one of claims 1-34, wherein R^A represents H.

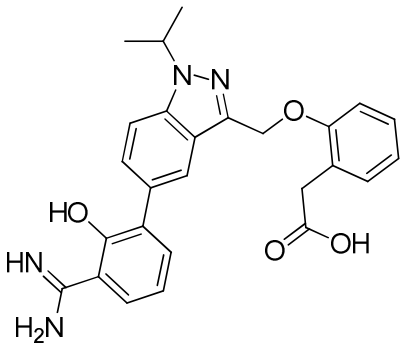
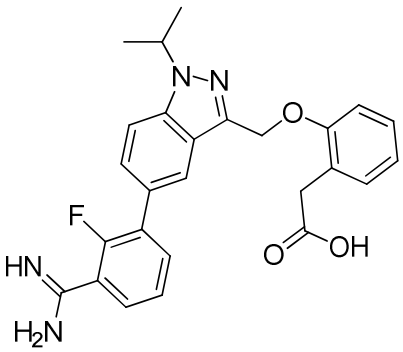
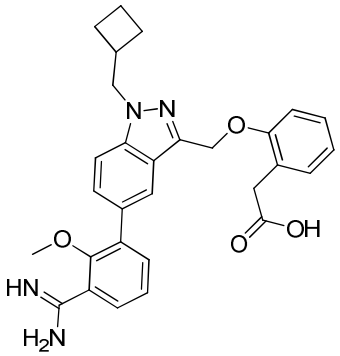
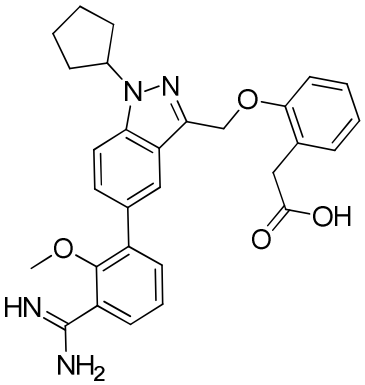
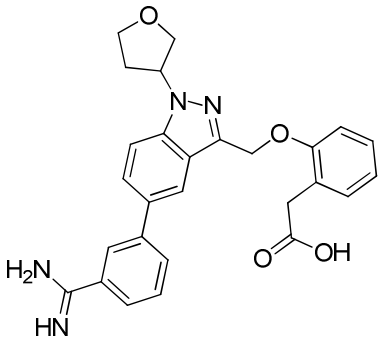
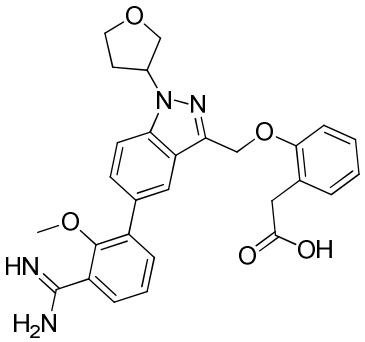
36. The compound of claim 1, selected from the following table:

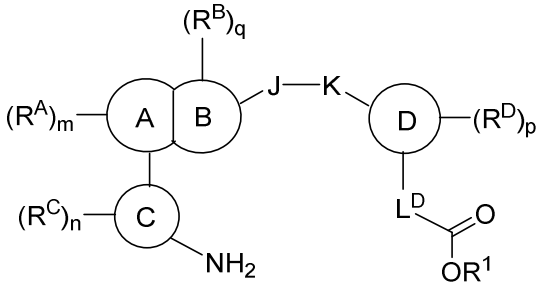
	
	
	
	
	

.

37. A compound of formula (II), or a pharmaceutically acceptable salt thereof:



(II);

wherein:

ring  is arylene or heteroarylene;

ring  is arylene or heteroarylene;

ring  is fused to ring  at two and only two adjacent positions;

ring  is a bicyclic ring system, where the ring attached to ring  is aryl or heteroaryl;

ring  is aryl or heteroaryl;

J represents $–CH_2–$, –NH–, $–CH_2CH_2–$, –C(O)–, –C≡C–, –O–, –S–, –S(O)–, $–SO_2–$, –N(alkyl)–, –CH(alkyl)–, –CH(aryl)–, $–C(alkyl)_2–$, –CH(cycloalkyl)–, or  ;

K represents a bond, –O–, –NH–, –C(O)–, $–CH_2–$, –S–, –S(O)–, $–SO_2–$, –N(alkyl)–, –CH(alkyl)–, or –CH(cycloalkyl)–;

wherein at least one of J and K is a bond, –C(O)–, $–CH_2–$, $–CH_2CH_2–$, –CH(alkyl)–, or –CH(aryl)–;

L^D represents $–CH_2–$, $–CH_2CH_2–$, $–CF_2–$, –CH(F)–, $–CD_2–$, –CH(D)–, –CH(OH)–, –CH(alkyl)–, –CH(cycloalkyl)–, $–CHNH_2–$, –CH(NH(alkyl))–, –CH(NH(cycloalkyl))–, or a bond;

R^A, independently for each occurrence, represents H, halo, hydroxyl, cyano, amino, alkyl, optionally substituted alkoxy, hydroxyalkyl, optionally substituted aryloxy, (aryloxy)alkyl, (cycloalkyl)alkoxy, (heterocycloalkyl)alkoxy, optionally substituted (heteroaryl)alkoxy, haloalkyl, haloalkoxy, (hydroxy)haloalkyl, alkoxyalkyl, optionally substituted aminoalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (cycloalkyl)alkenyl, optionally substituted heterocycloalkyl, optionally substituted (heterocycloalkyl)alkyl, –C(O)OH, $–C(O)NH_2$, $–C(O)N(alkyl)_2–$, $–CH_2C(O)OH$, $–NO_2$, $–CH_2NH$(optionally substituted alkyl), $–CH_2NH(Boc)$, $–CH_2N(Boc)$(optionally substituted alkyl), $–CH_2NH$((cycloalkyl)alkyl), $–CH_2N$(alkyl)(cycloalkyl), $–CH_2N$(alkyl)((cycloalkyl)alkyl), –NH(optionally substituted alkyl), –NH(cycloalkyl), –NH((cycloalkyl)alkyl), –NH((heterocycloalkyl)alkyl), $–N(alkyl)_2$, –N(alkyl)((cycloalkyl)alkyl,

–N(alkyl)((heterocycloalkyl)alkyl, –NH(heteroarylalkyl), –CH_2O(optionally substituted aryl), –C(O)O(alkyl), –C(O)NH(optionally substituted alkyl), –C(O)NH((cycloalkyl)alkyl), –NHC(O)O(alkyl), or –$CH_2N(alkyl)_2$;

R^B, independently for each occurrence, represents H, oxo, –C(O)O(alkyl), halogen, cyano, amino, –C(O)OH, –CH_2C(O)OH, –$C(O)NH_2$, –C(O)NH(cycloalkyl), –C(O)NH(alkyl), –C(O)NH(aryl), -C(O)NH(heteroaryl), –C(O)(alkyl), -$S(O)_2$alkyl, alkylaminoalkyl, alkylaminocycloalkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, (hydroxy)haloalkyl, or tosyl, or is optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, spirocycloalkyl, halocycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, spiroheterocycloalkyl, or (heterocycloalkyl)alkyl; or two geminal occurrences of R^B taken together with the atom to which they are attached form an optionally substituted spirocycloalkyl or a spiroheterocycloalkyl;

R^C, independently for each occurrence, represents H, halo, -OH, cyano, or amino, or is optionally substituted alkoxy, haloalkoxy, alkyl, cycloalkyl, heterocycloalkyl, or (heteroaryl)alkoxy;

R^D, independently for each occurrence, represents H, halo, hydroxyl, cyano, –NH_2, -NH(Ac), -NH(alkyl), -$N(alkyl)_2$, -NH(CO)(alkyl), –CH_2NH_2, -CH_2NHC(O)(alkyl), –$C(O)NH_2$, –C(O)OH, or –NHC(O)O(alkyl), or is optionally substituted alkyl, alkoxy, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, haloalkoxy, or haloalkyl;

R^1 represents H or optionally substituted alkyl; and

m, n, p, and q are each independently 0, 1, or 2.

38. The compound of claim 37, wherein:

ring (A) is arylene or heteroarylene;

ring (B) is arylene or heteroarylene;

ring (A) is fused to ring (B) at two and only two adjacent positions;

ring (C) is a bicyclic ring system, where the ring attached to ring (A) is aryl or heteroaryl;

ring  is aryl;

J represents $–CH_2–$ or –C(O)–;

K represents –O– or –NH–;

L^D represents $–CH_2–$ or –CH(alkyl)–;

R^A, independently for each occurrence, represents H, cyano, alkyl, optionally substituted alkoxy, optionally substituted heteroaryl, optionally substituted aminoalkyl, $-C(O)NH_2$, or –NH((cycloalkyl)alkyl);

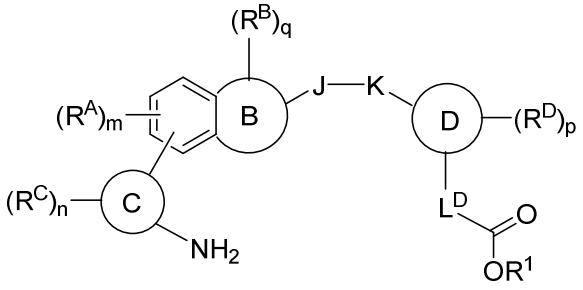
R^B, independently for each occurrence, represents H, oxo, alkoxyalkyl, or haloalkyl, or is optionally substituted alkyl, aryl, cycloalkyl, (cycloalkyl)alkyl, spirocycloalkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl;

R^C, independently for each occurrence, represents H or halo, or is optionally substituted alkoxy or alkyl;

R^D, independently for each occurrence, represents H, halo, cyano, or –C(O)OH, or is optionally substituted alkyl, cycloalkyl, alkoxy, haloalkoxy, or haloalkyl;

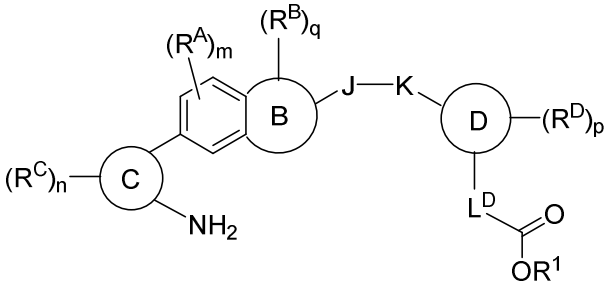
R^1 represents H or optionally substituted alkyl.

39. The compound of claim 37 or 38, having the structure of formula (IIa):



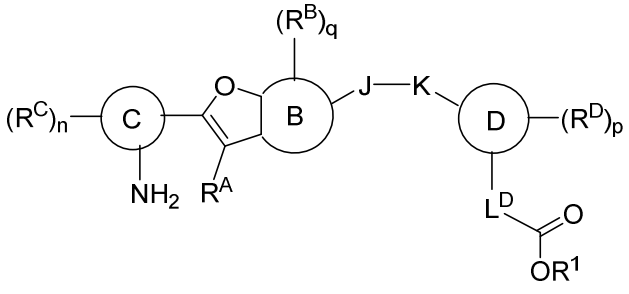
(IIa).

40. The compound of any one of claims 37-39, having the structure of formula (IIa-1):



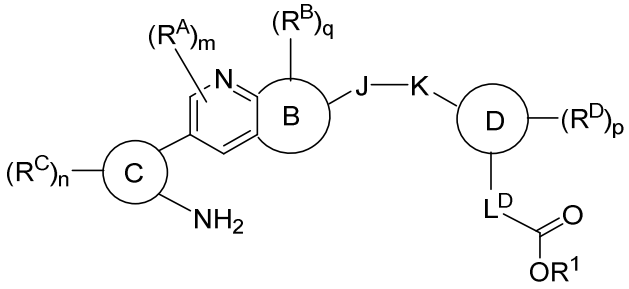
(IIa-1).

41. The compound of claim 37 or 38, having the structure of formula (IIb):



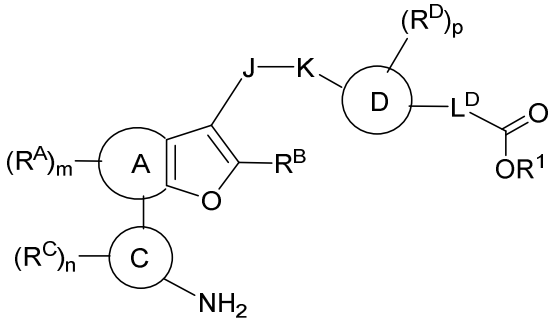
(IIb).

42. The compound of claim 37 or 38, having the structure of formula (IIc):



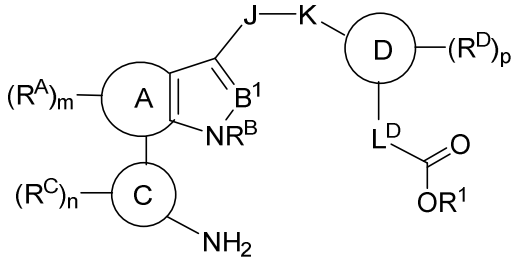
(IIc).

43. The compound of claim 37 or 38, having the structure of formula (IId):



(IId).

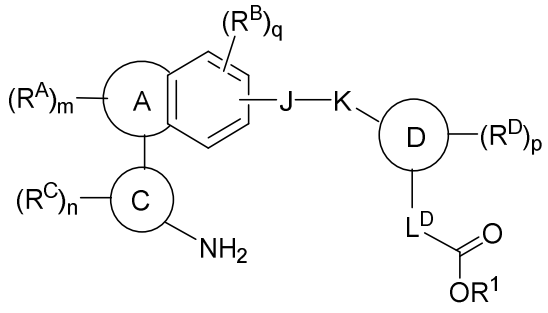
44. The compound of claim 37 or 38, having the structure of formula (IIe):



(IIe);

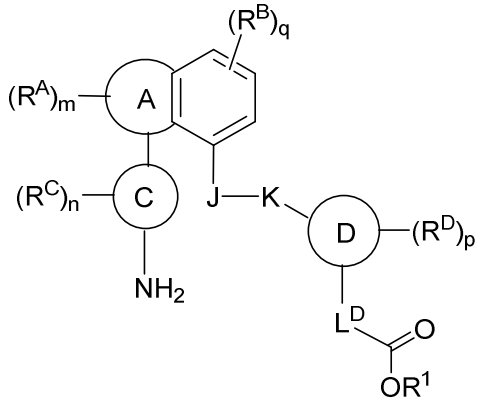
wherein B^1 represents N or CH.

45. The compound of claim 37 or 38, having the structure of formula (IIf):



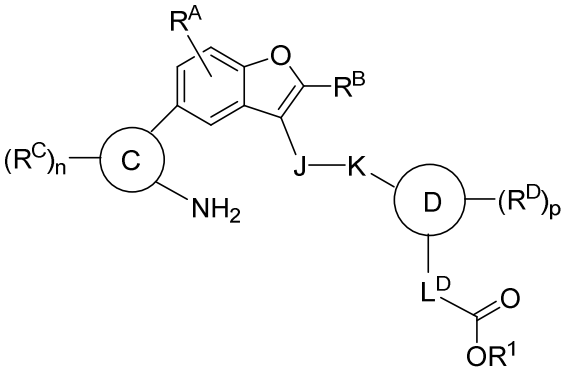
(IIf).

46. The compound of claim 37 or 38, having the structure of formula (IIf-1):



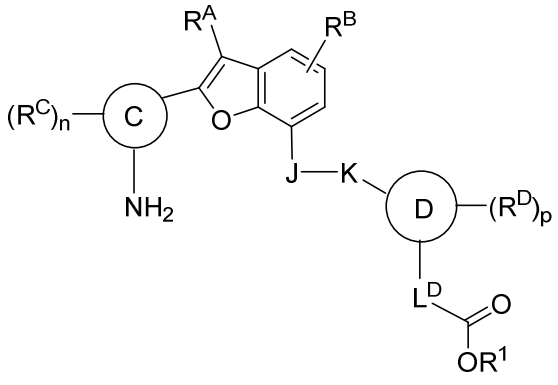
(IIf-1).

47. The compound of claim 37 or 38, having the structure of formula (IIg):



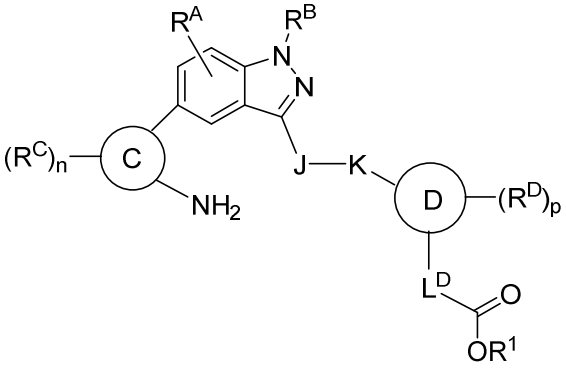
(IIg).

48. The compound of claim 37 or 38, having the structure of formula (IIh):



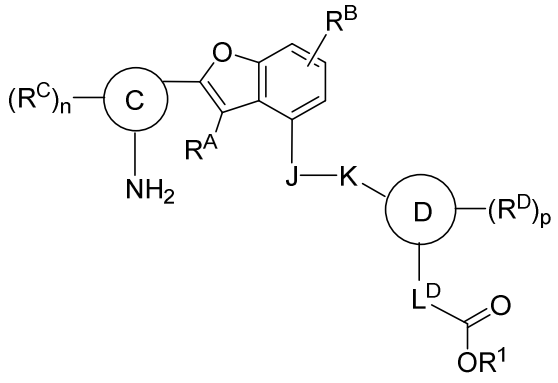
(IIh).

49. The compound of claim 37 or 38, having the structure of formula (IIj):



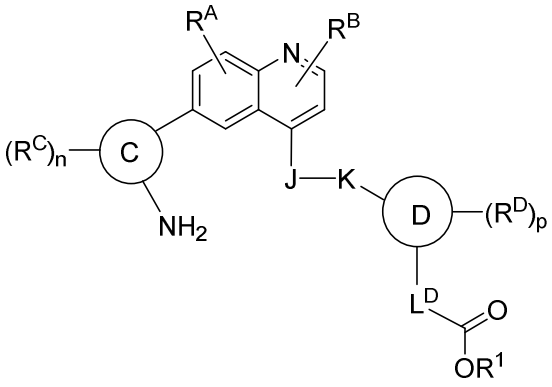
(IIj).

50. The compound of claim 37 or 38, having the structure of formula (IIk):



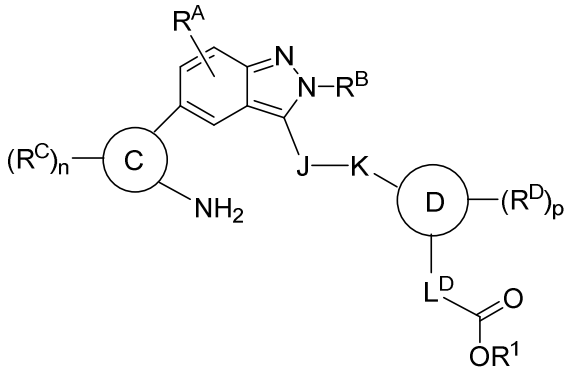
(IIk).

51. The compound of claim 37 or 38, having the structure of formula (IIm):



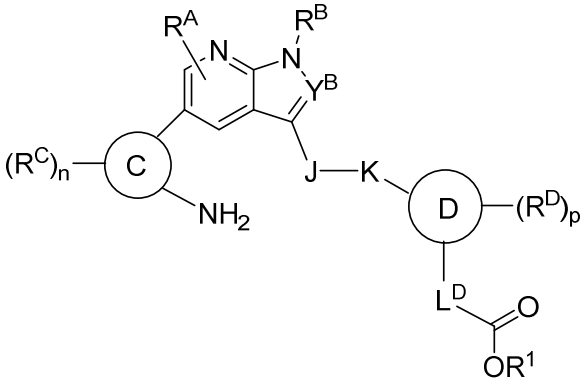
(IIm).

52. The compound of claim 37 or 38, having the structure of formula (IIn):



(IIn).

53. The compound of claim 37 or 38, having the structure of formula (IIo):

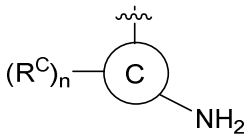
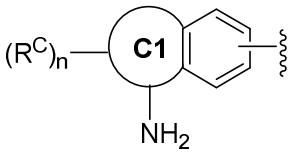


(IIo);

wherein Y^B is H or CH.

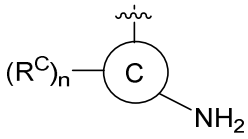
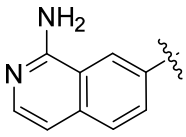
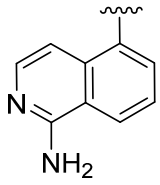
54. The compound of any one of claims 37-53, wherein ring C is a bicyclic ring system, where the ring attached to ring A is aryl.

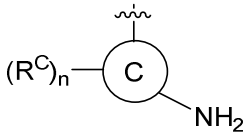
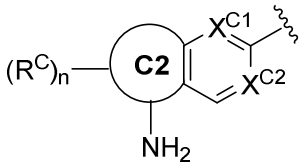
55. The compound of any one of claims 37-53, wherein ring  is a bicyclic ring system, where the ring attached to ring  is heteroaryl.

56. The compound of any one of claims 37-54, wherein  represents  , wherein ring  represents aryl, heteroaryl, or heterocycloalkyl.

57. The compound of claim 56, wherein ring  represents heteroaryl.

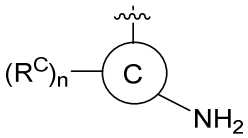
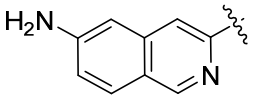
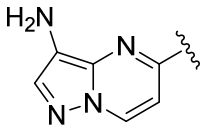
58. The compound of claim 56 or 57, wherein ring  represents a 5- or 6-membered heteroaryl containing at least one nitrogen atom.

59. The compound of any one of claims 37-53 and 56-58, wherein  represents  or  .

60. The compound of any one of claims 37-53 and 55, wherein  represents  , wherein ring  represents aryl, heteroaryl, or heterocycloalkyl; and

X^{C1} and X^{C2} each independently represent CH or N.

61. The compound of claim 60, wherein ring  represents aryl or heteroaryl.

62. The compound of claim 60 or 61, wherein  represents  or  .

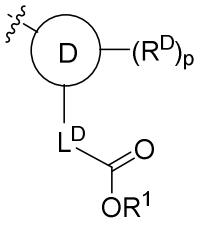
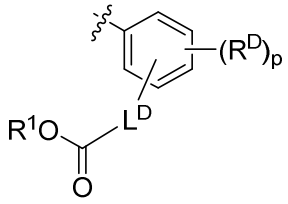
63. The compound of any one of claims 37-58 and 60-61, wherein R^C represents H.

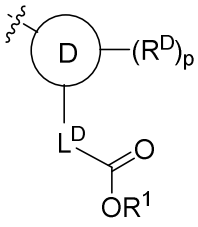
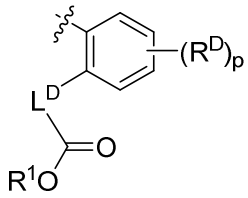
64. The compound of any one of claims 37-58 and 60-61, wherein R^C, independently for each occurrence, represents alkoxy or alkyl.

65. The compound of any one of claims 37 and 39-64, wherein J represents $–CH_2–$, –NH–, $–CH_2CH_2–$, –C(O)–, –O–, –S–, –S(O)–, $–SO_2–$, –N(alkyl)–, –CH(alkyl)–, –CH(aryl)–, $–C(alkyl)_2–$, –CH(cycloalkyl)–, or  .

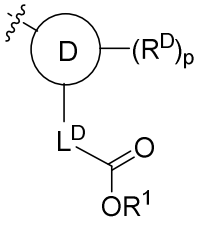
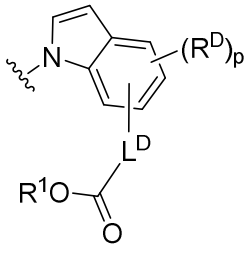
66. The compound of any one of claims 37-65, wherein –J–K– represents $–CH_2$-O– or –C(O)-NH–.

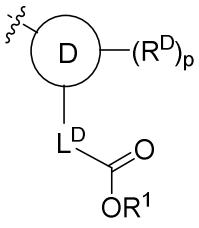
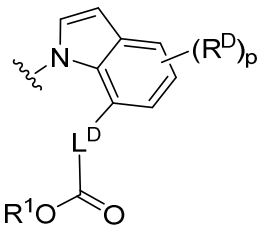
67. The compound of any one of claims 37-66, wherein ring  is aryl.

68. The compound of any one of claims 37-67, wherein  represents  .

69. The compound of any one of claims 37-68, wherein  represents  .

70. The compound of claim 37, wherein ring  is bicyclic heteroaryl.

71. The compound of claim 70, wherein  represents  .

72. The compound of claim 70, wherein  represents  .

73. The compound of any one of claims 37-72, wherein R^1 is H.

74. The compound of any one of claims 37-73, wherein L^D represents $–CH_2–$ or –CH(alkyl)–.

75. The compound of any one of claims 37-74, wherein L^D represents $–CH_2–$.

76. The compound of any one of claims 37-75, wherein R^D, independently for each occurrence, represents H, alkyl, or alkoxy.

77. The compound of any one of claims 37-76, wherein R^D represents H.

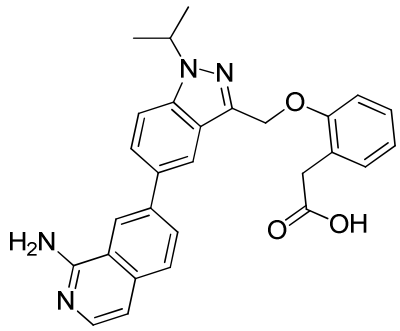
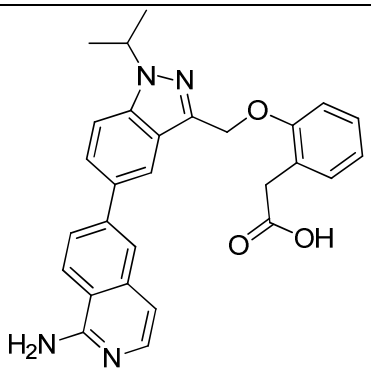
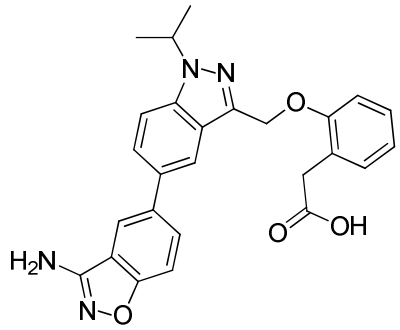
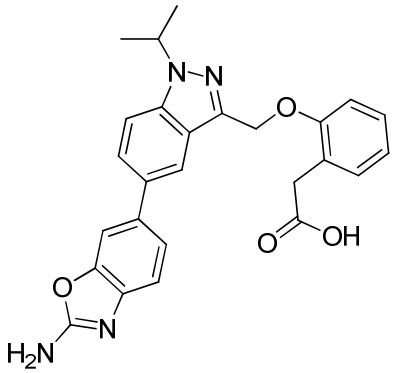
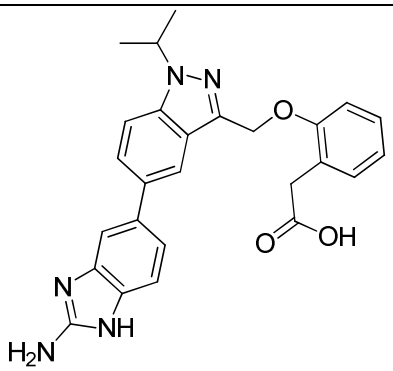
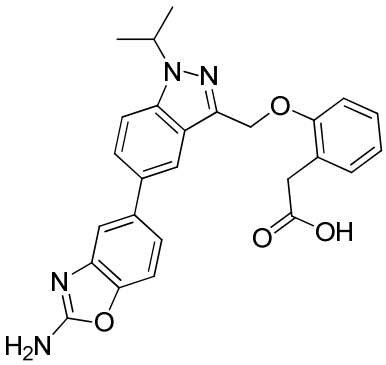
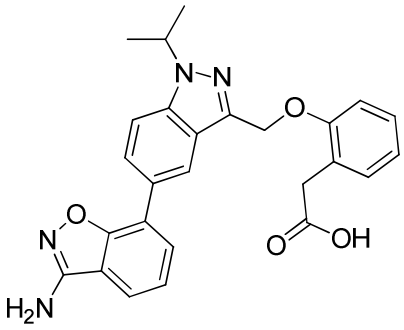
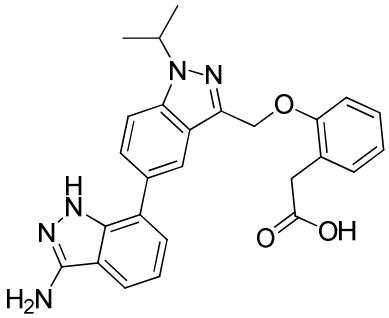
78. The compound of any one of claims 37-77, wherein R^B, independently for each occurrence, represents H, alkoxyalkyl, or haloalkyl, or is optionally substituted alkyl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl.

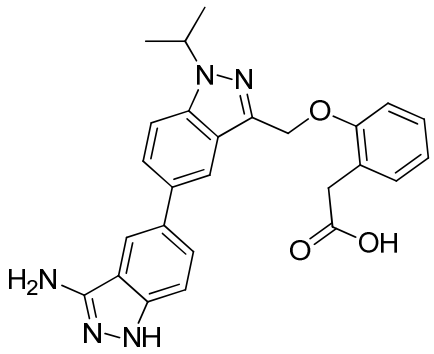
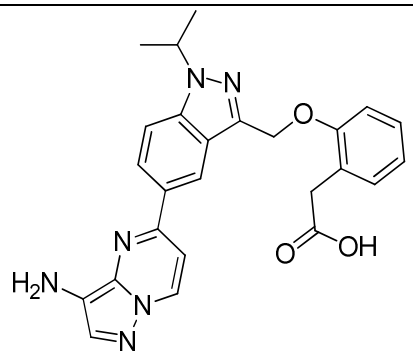
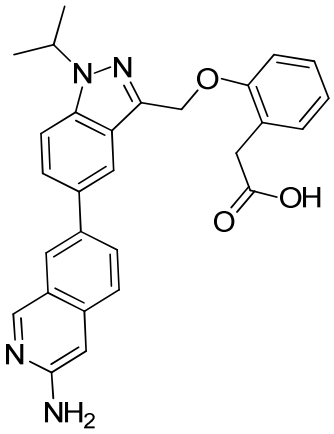
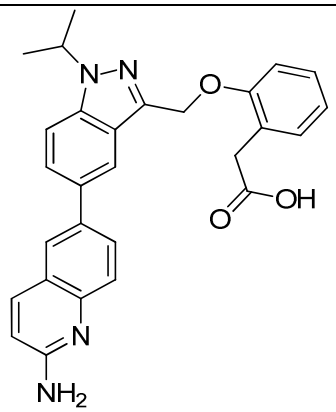
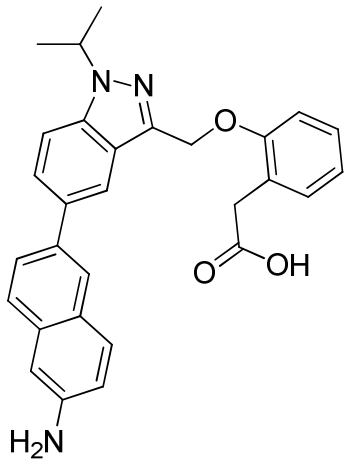
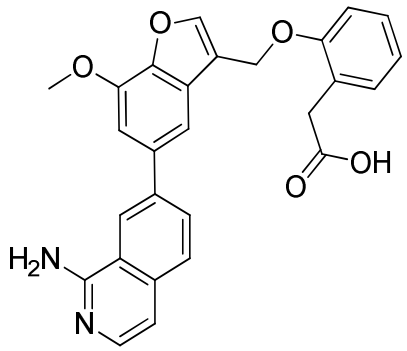
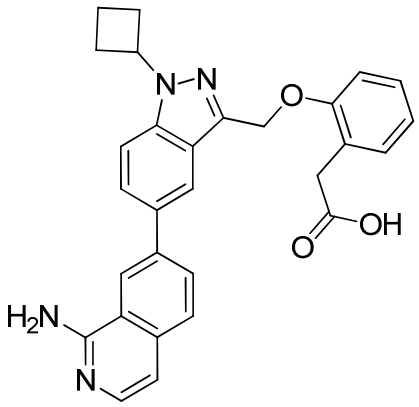
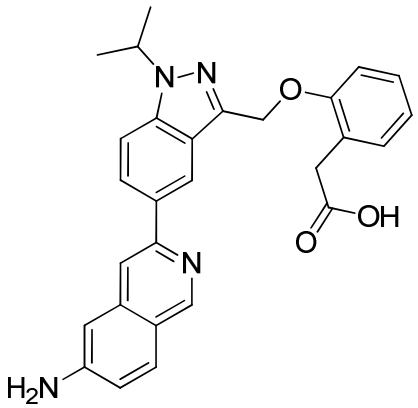
79. The compound of any one of claims 37-78, wherein R^B, independently for each occurrence, represents optionally substituted alkyl, cycloalkyl, or heterocycloalkyl, e.g., heterocycloalkyl substituted with alkyl, hydroxyalkyl, alkoxyalkyl.

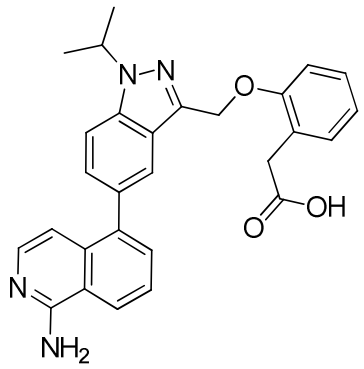
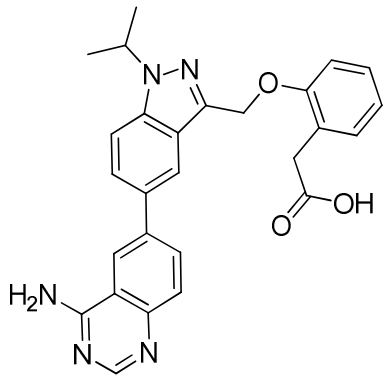
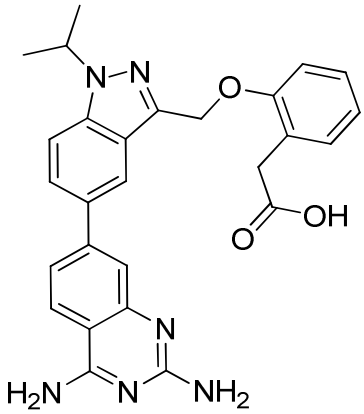
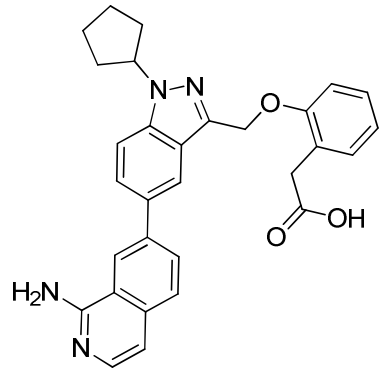
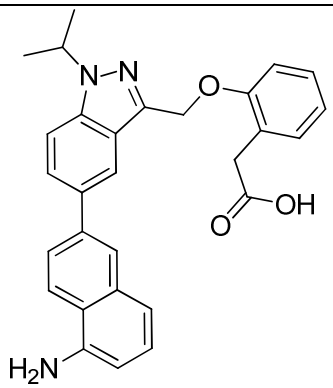
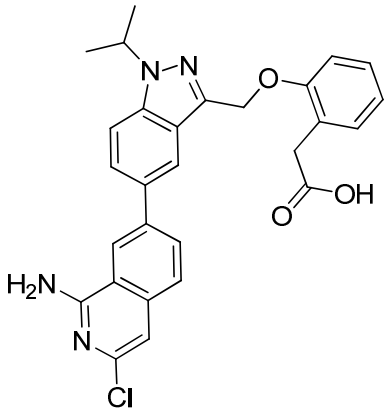
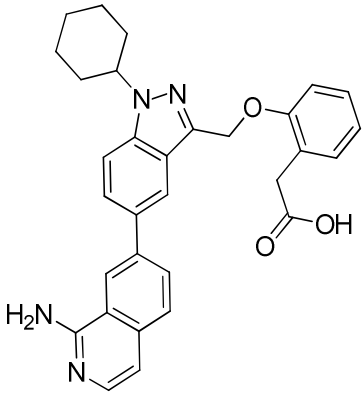
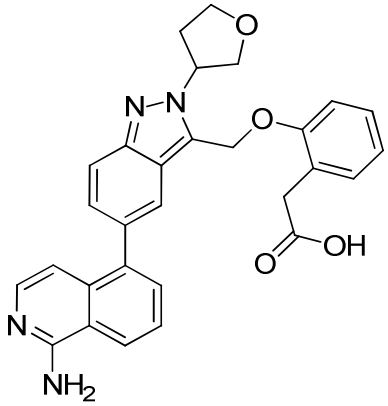
80. The compound of any one of claims 37-79, wherein R^A, independently for each occurrence, represents H, cyano, alkyl, optionally substituted alkoxy, optionally substituted heteroaryl, or –NH((cycloalkyl)alkyl).

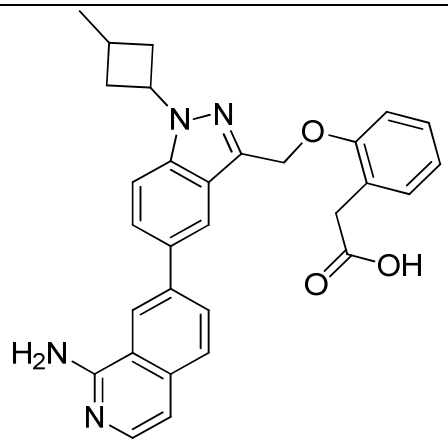
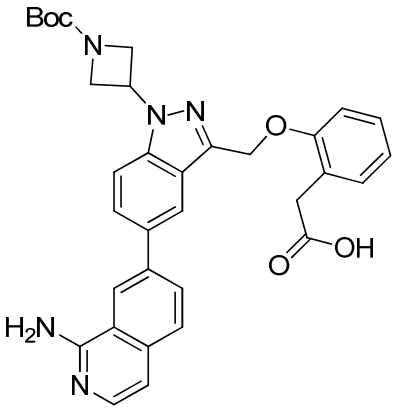
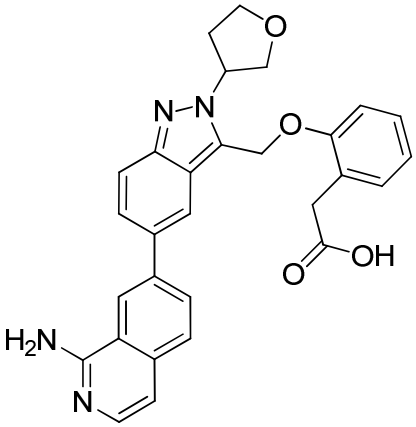
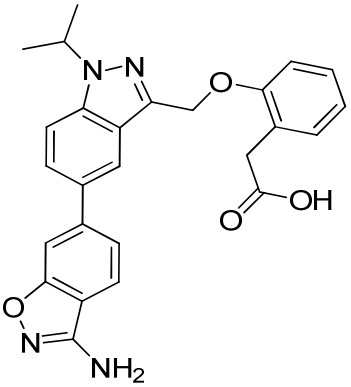
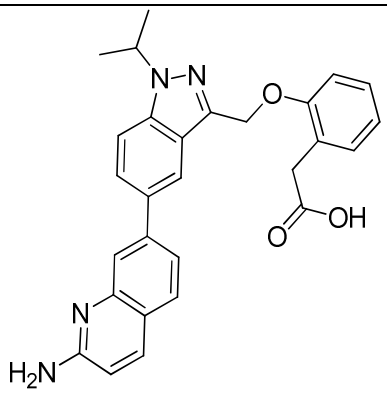
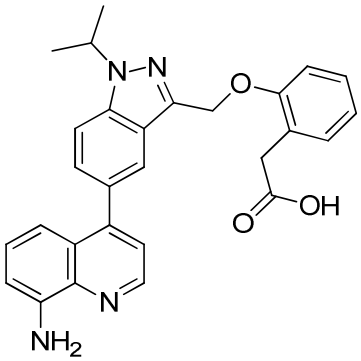
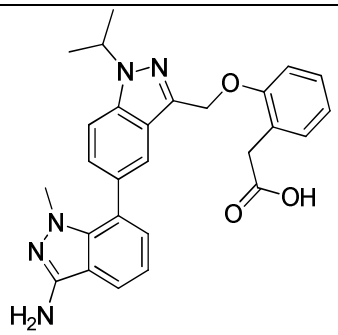
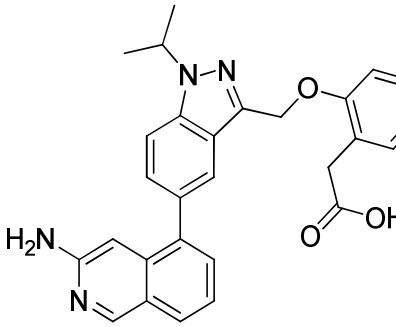
81. The compound of any one of claims 37-80, wherein R^A represents H.

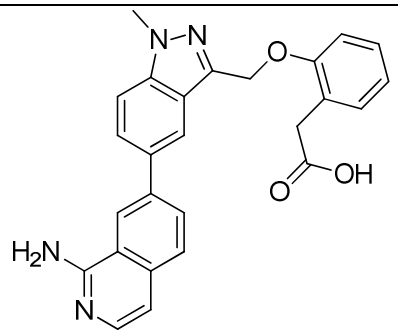
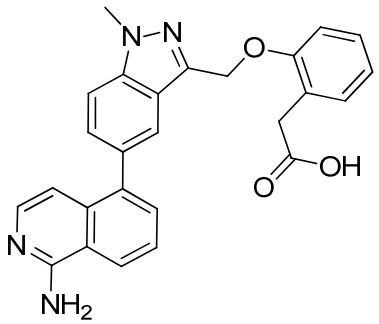
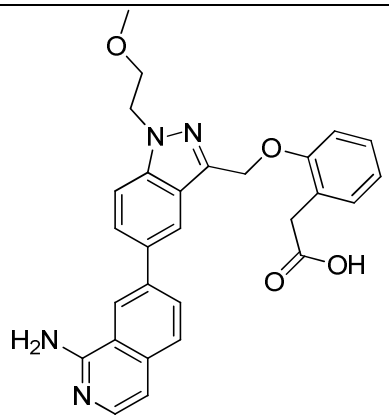
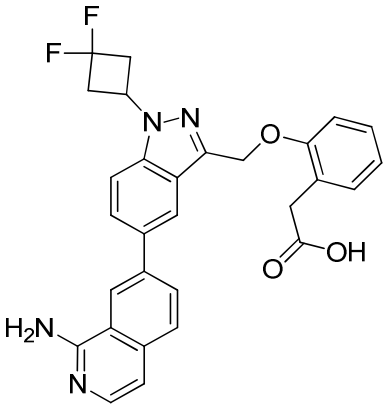
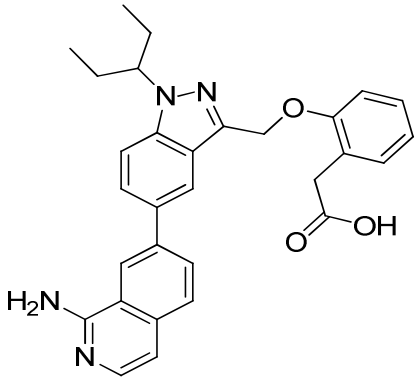
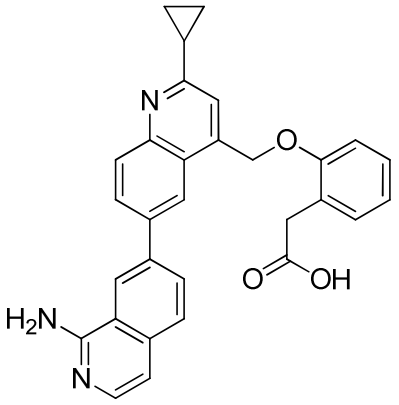
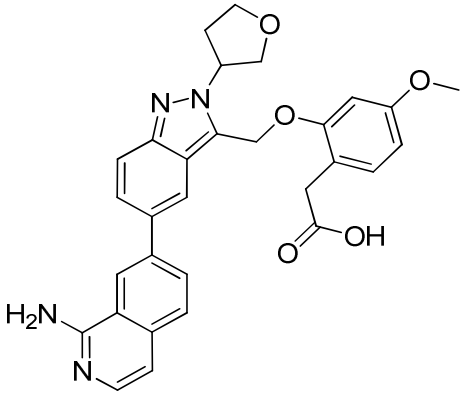
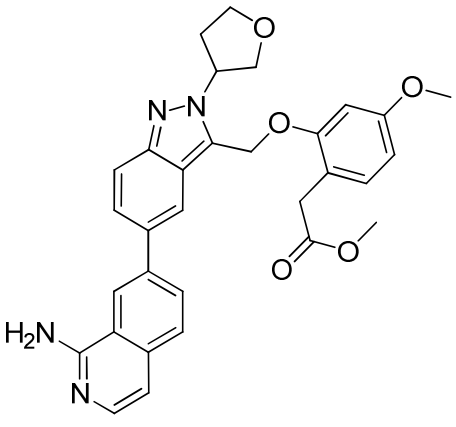
82. The compound of claim 37, selected from the following table:

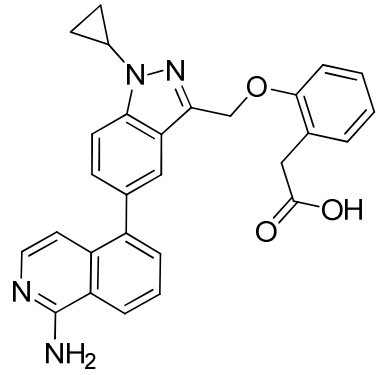
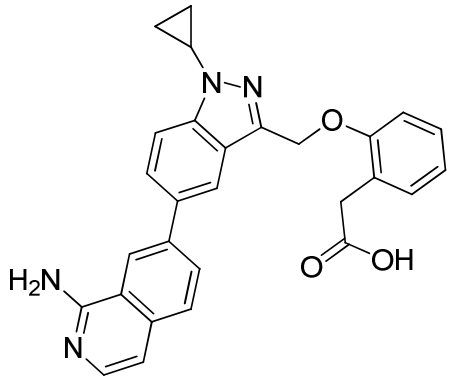
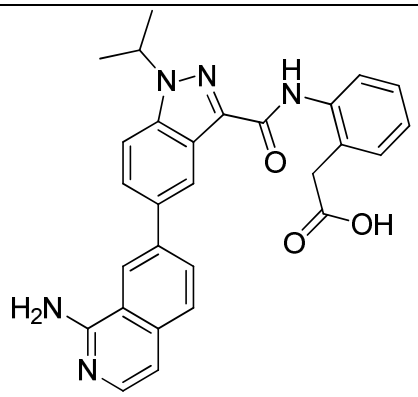
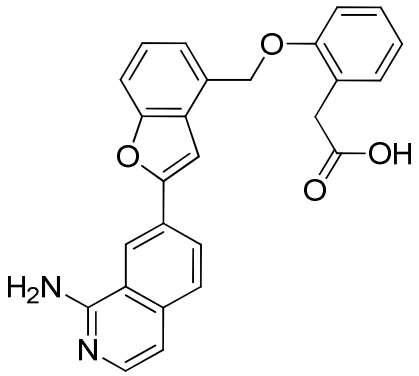
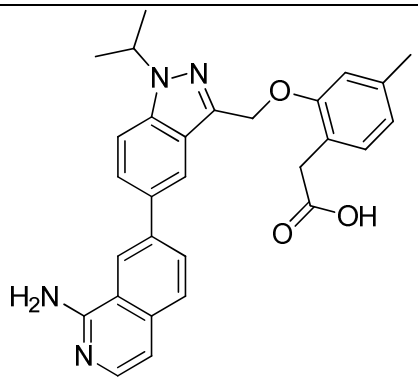
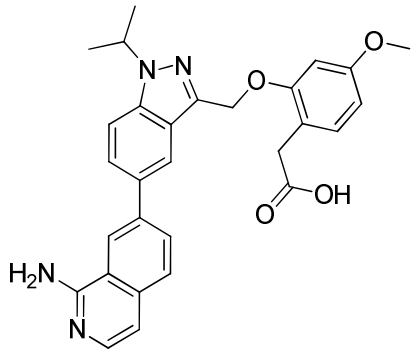
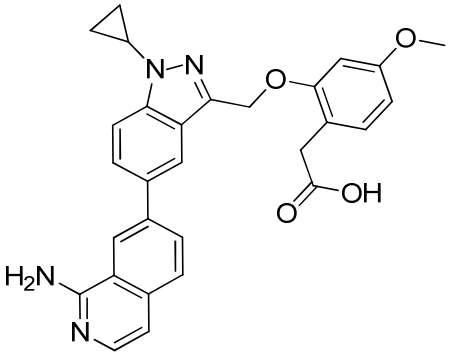
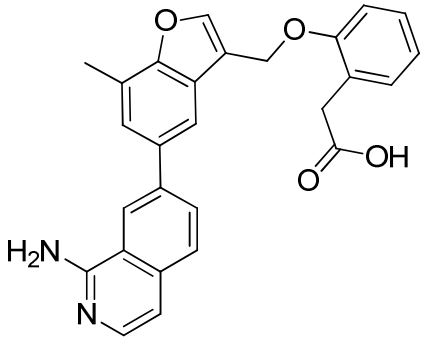
	
	
	
	

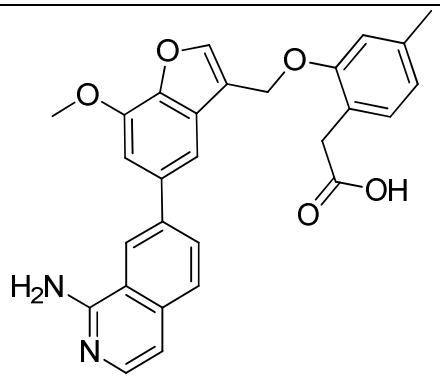
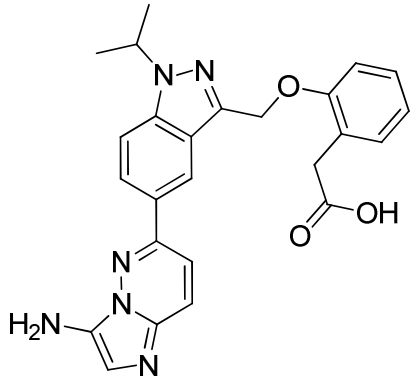
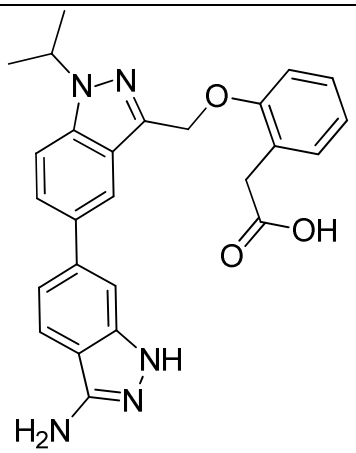
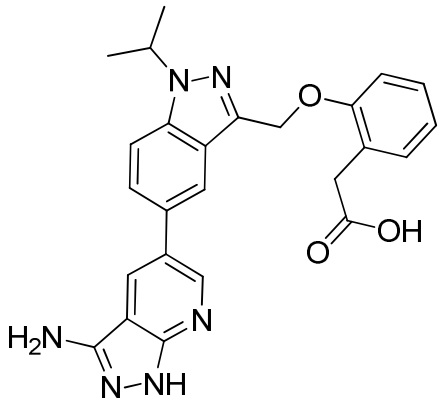
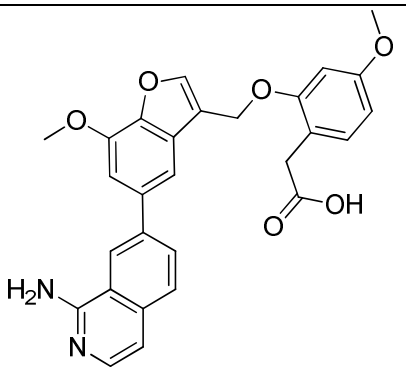
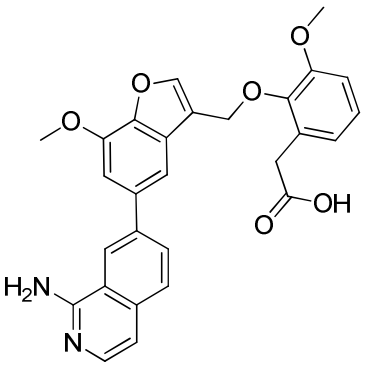
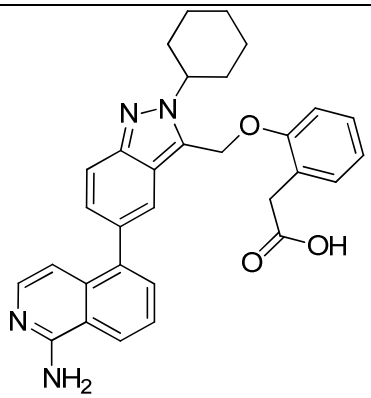
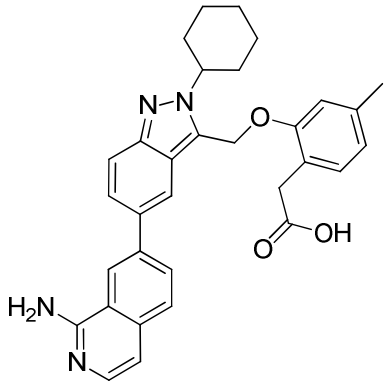
	
	
	
	

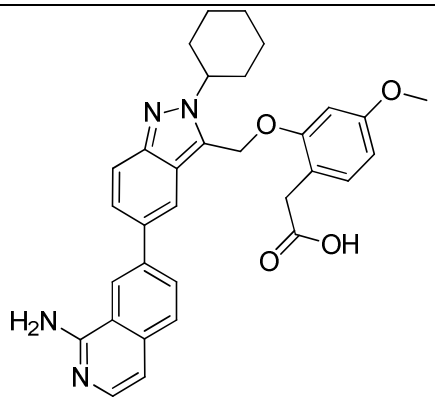
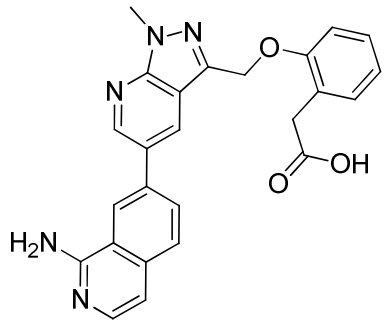
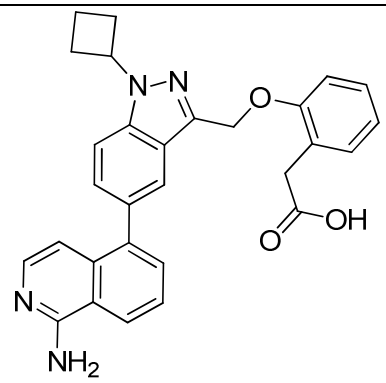
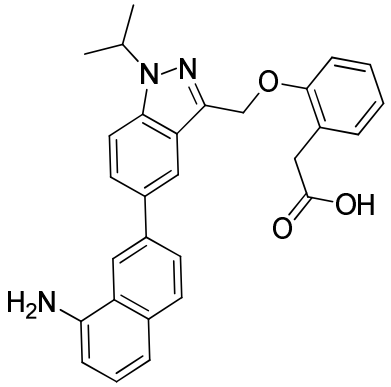
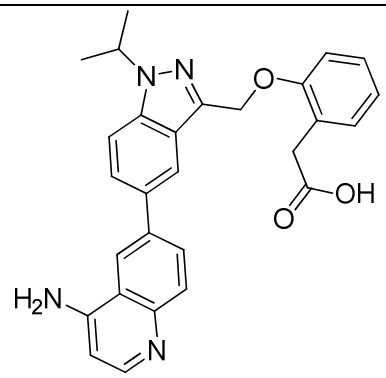
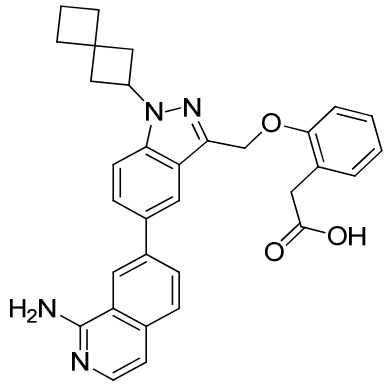
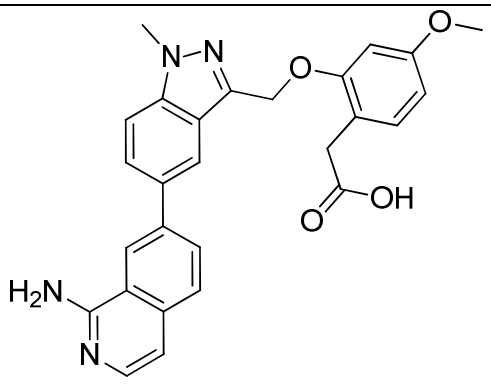
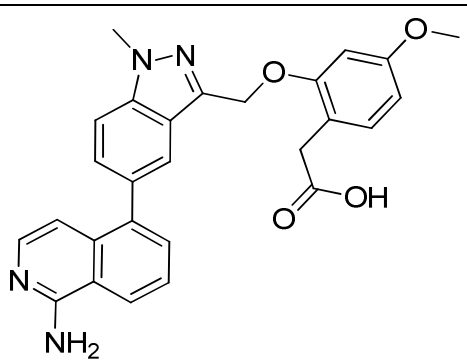
	
	
	
	

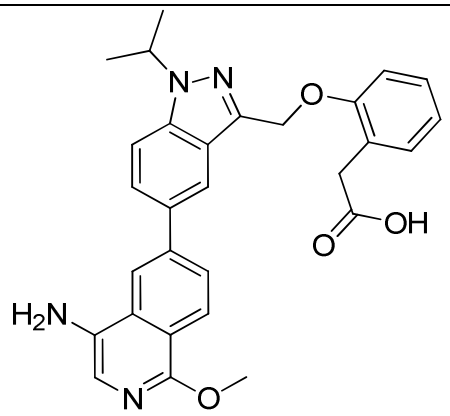
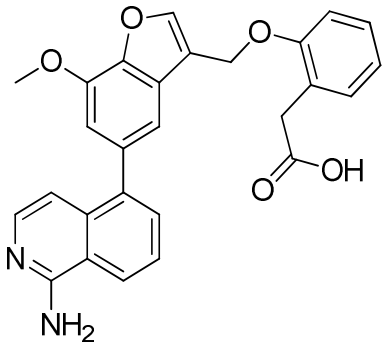
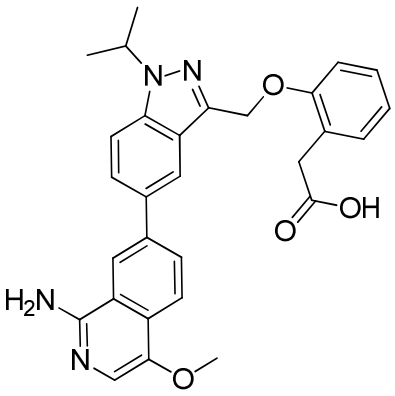
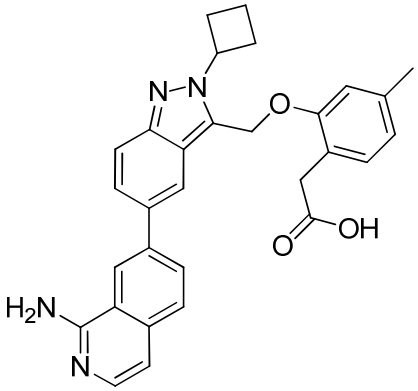
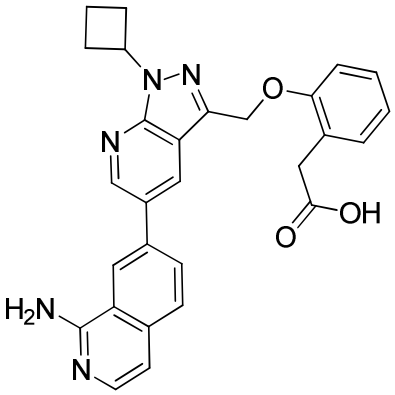
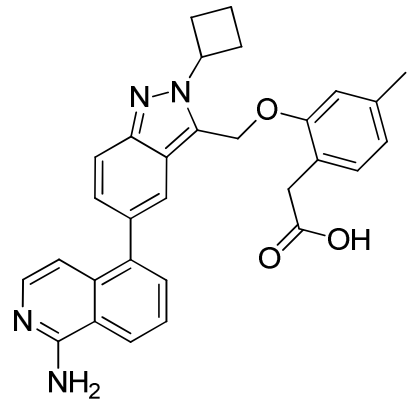
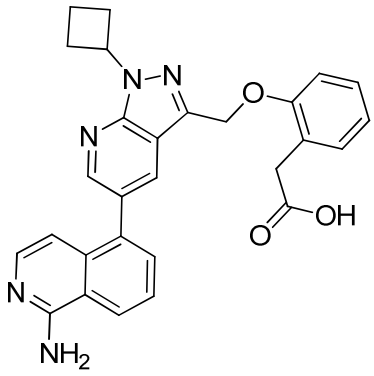
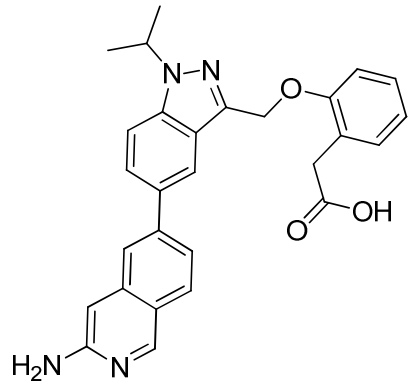
	
	
	
	

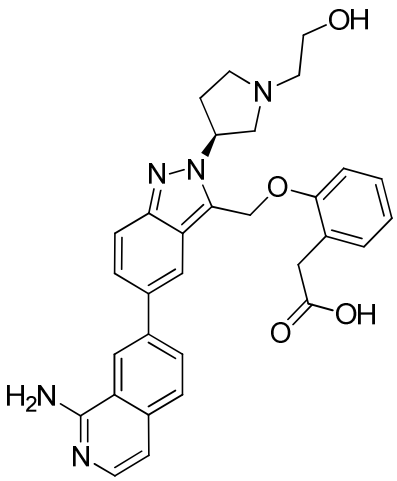
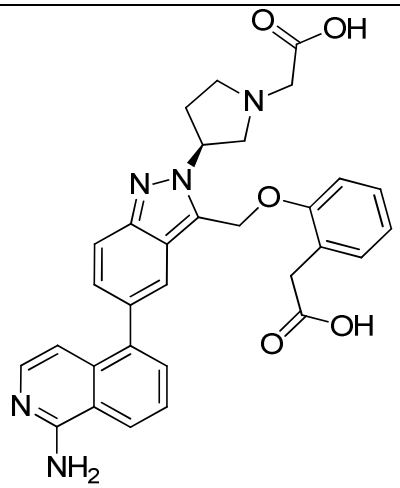
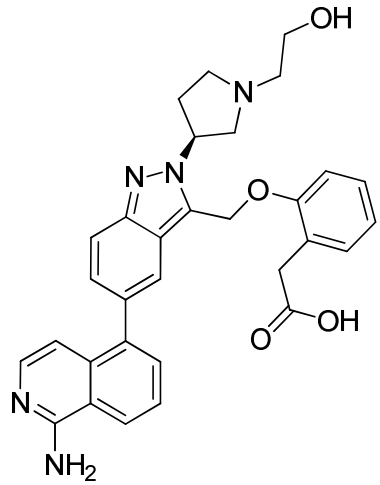
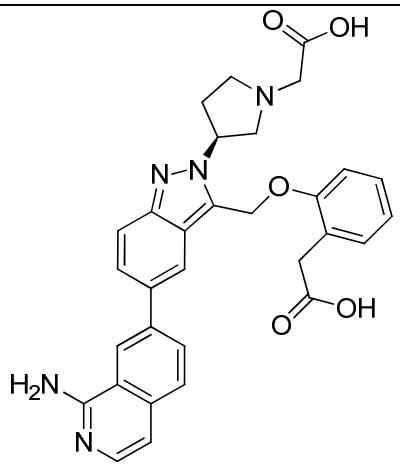
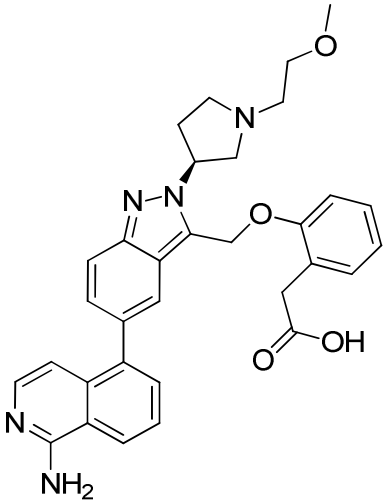
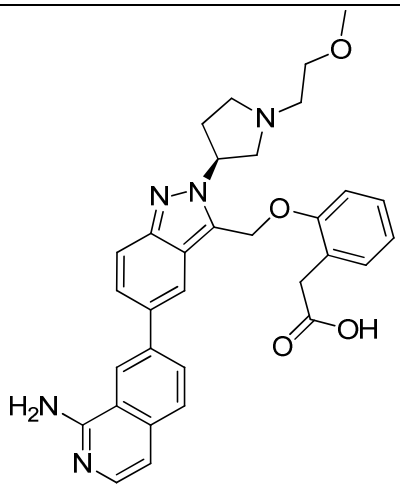
	
	
	
	

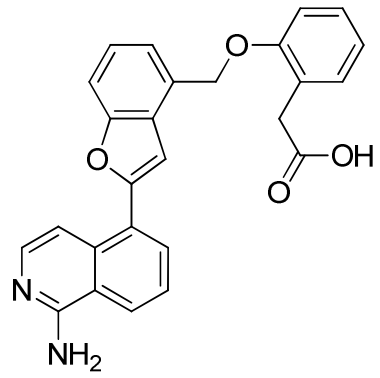
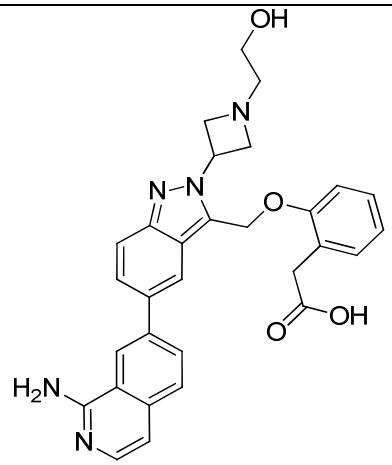
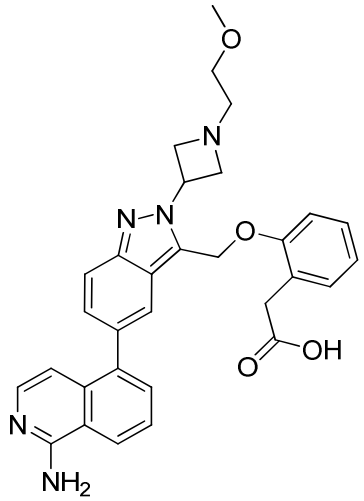
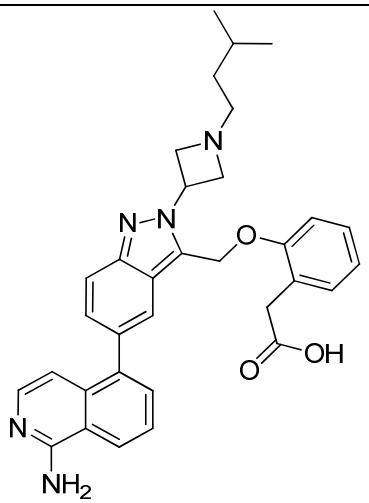
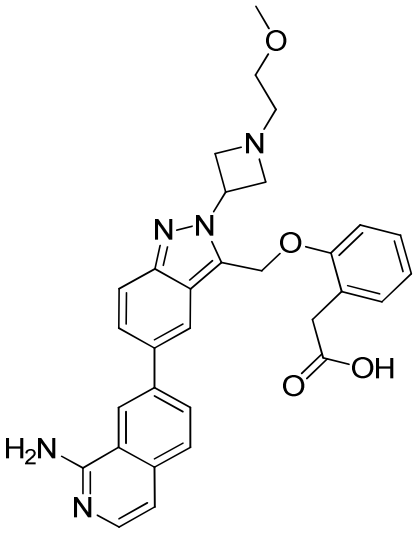
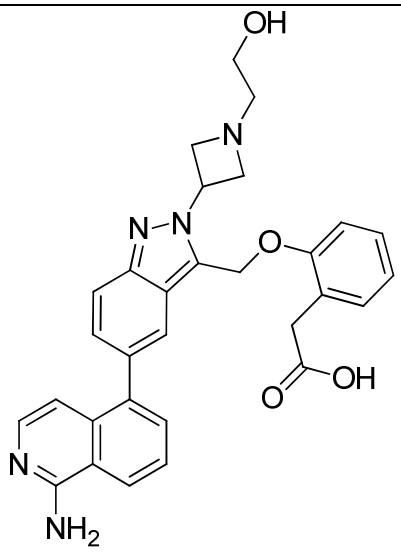
	
	
	
	

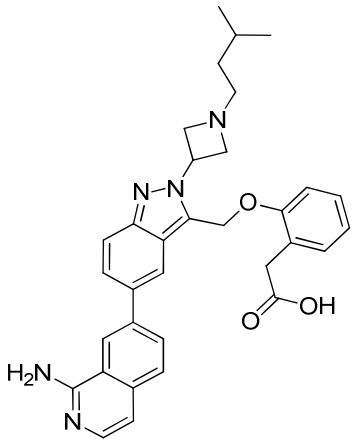
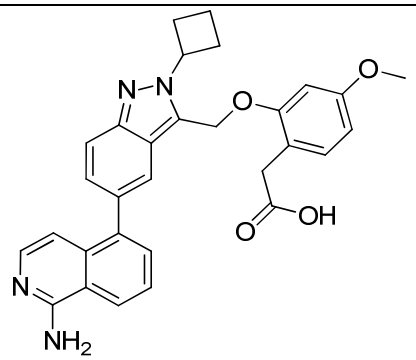
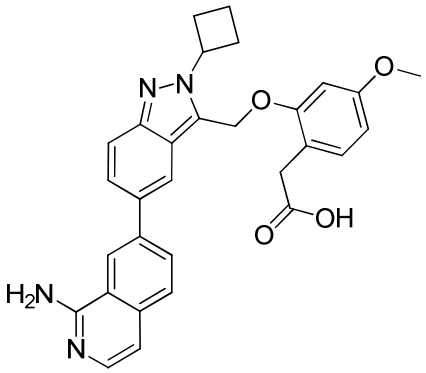
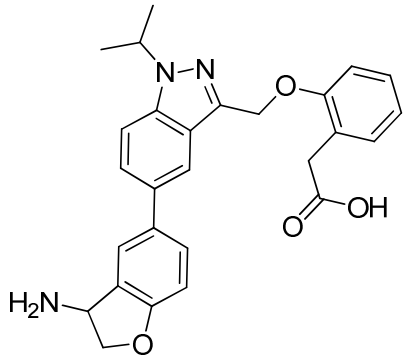
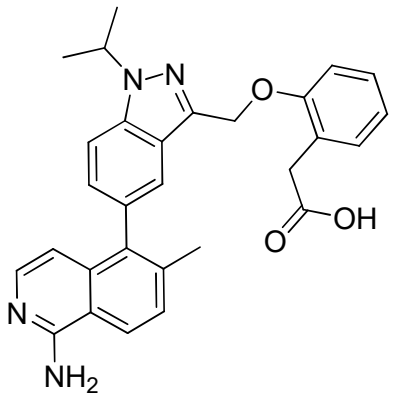
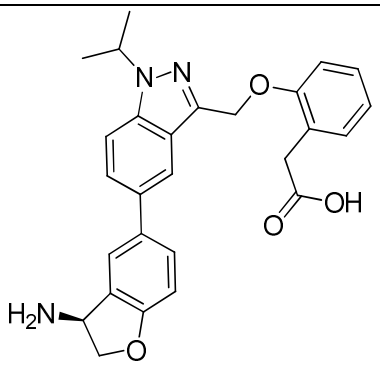
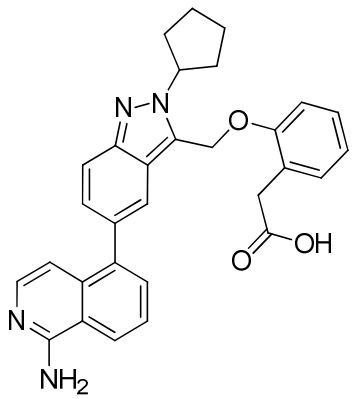
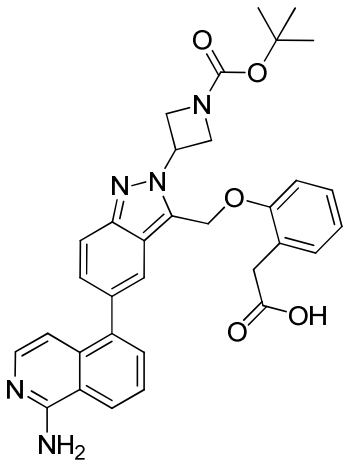
	
	
	
	

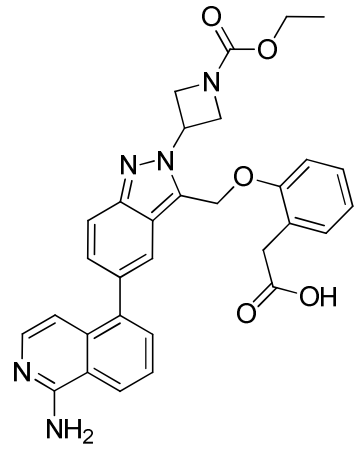
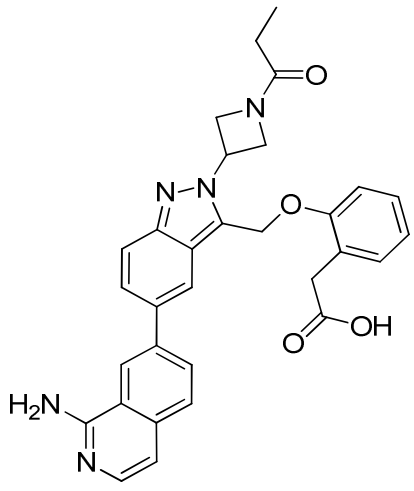
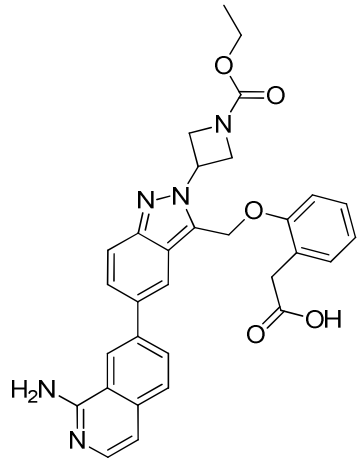
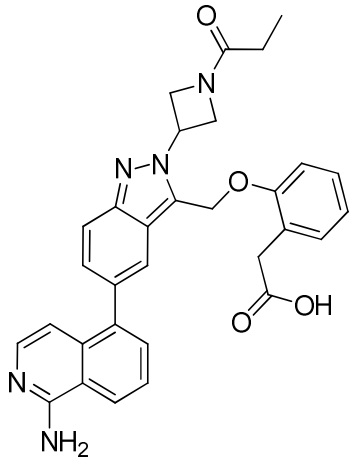
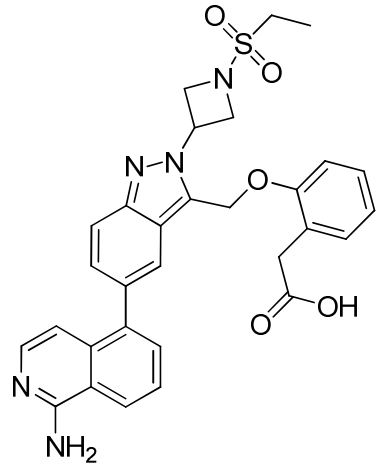
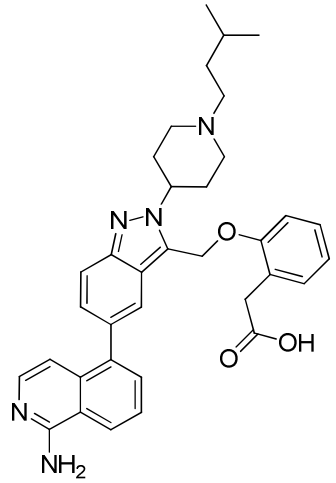
	
	
	
	

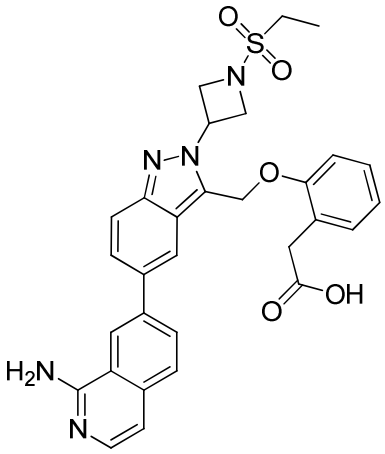
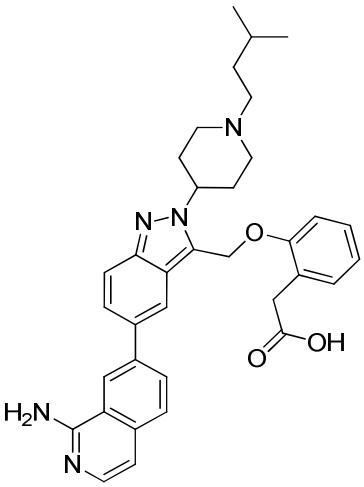
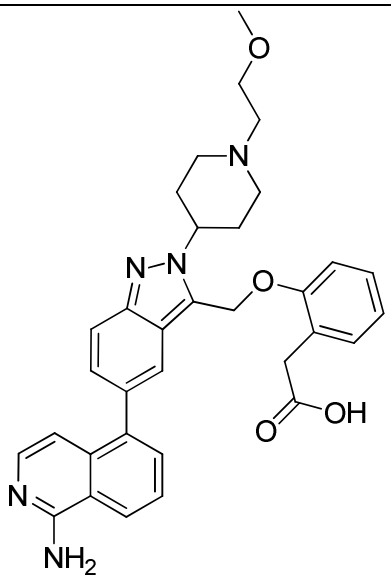
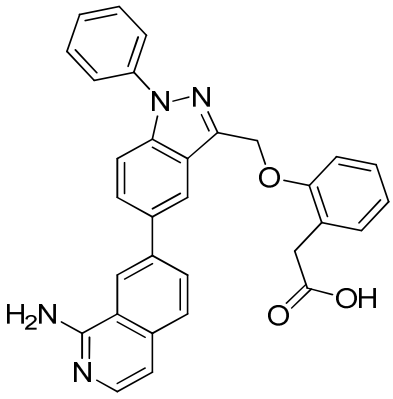
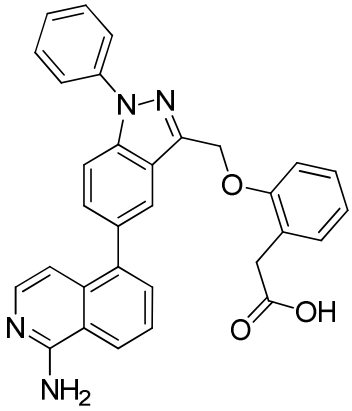
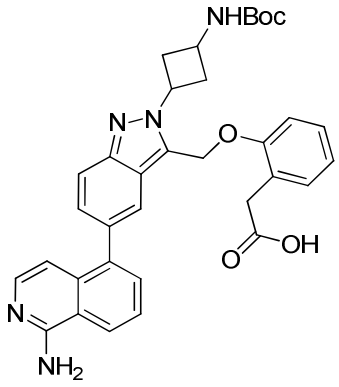
	
	
	
	

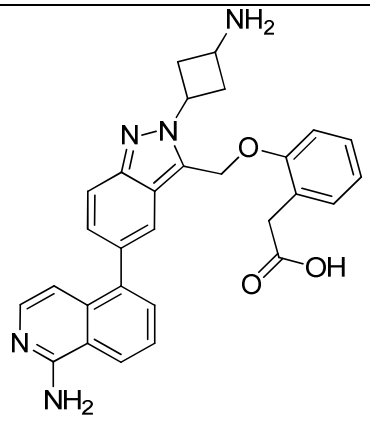
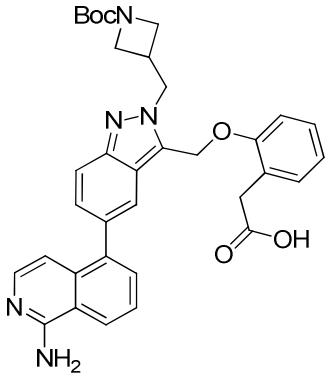
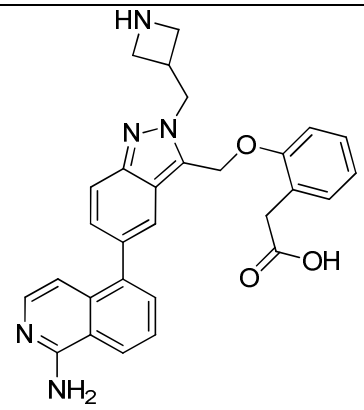
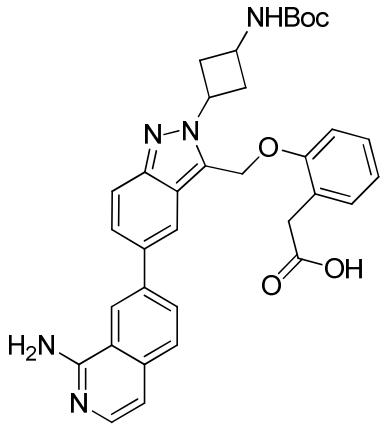
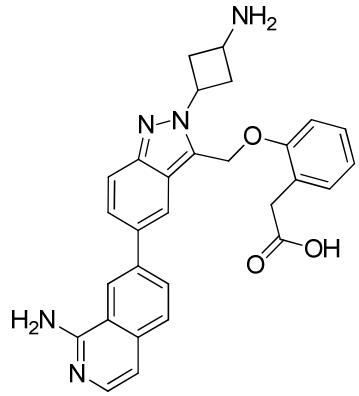
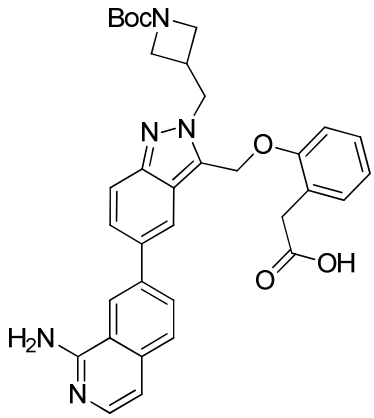
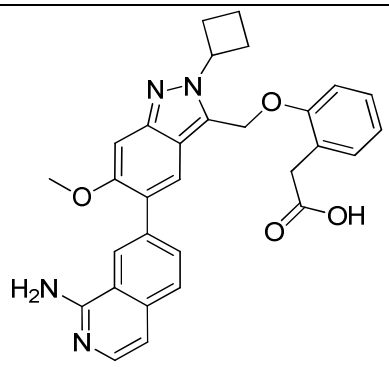
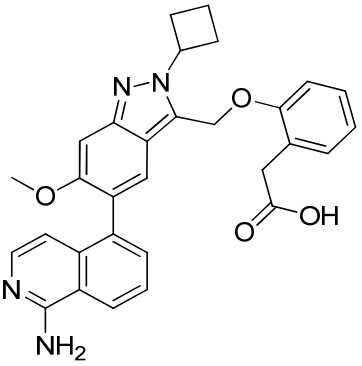
	
	
	

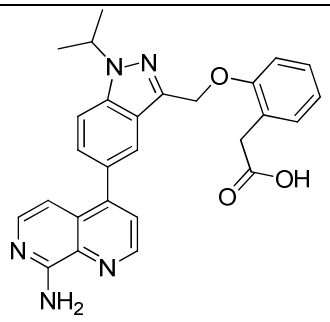
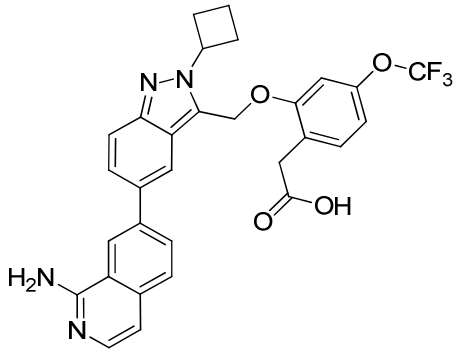
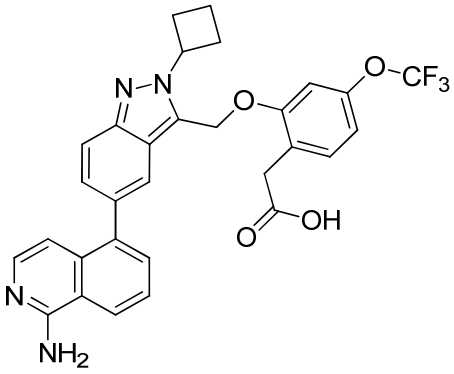
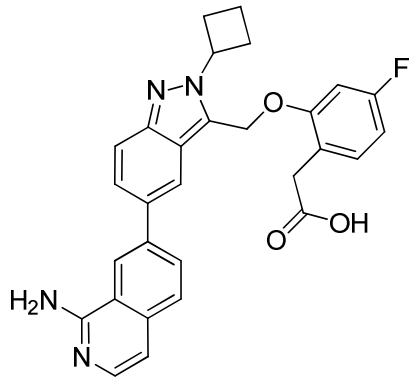
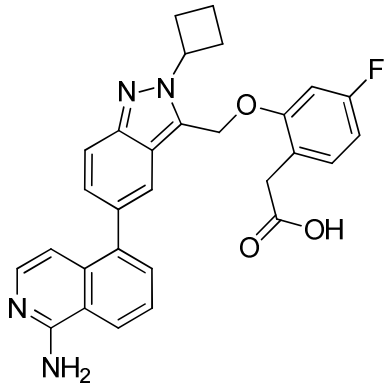
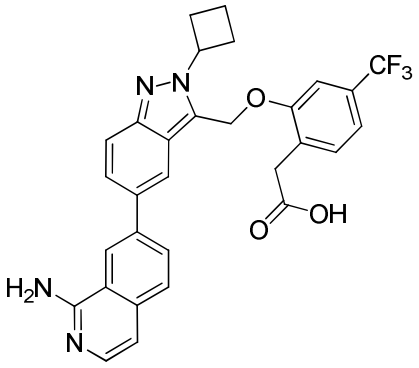
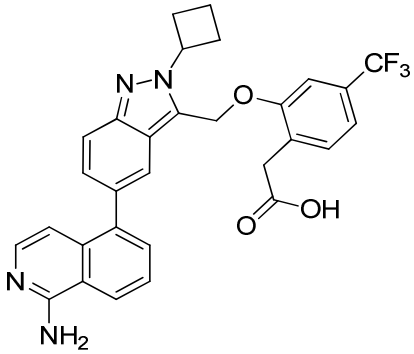
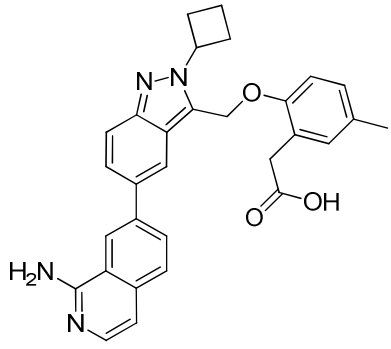
	
	
	

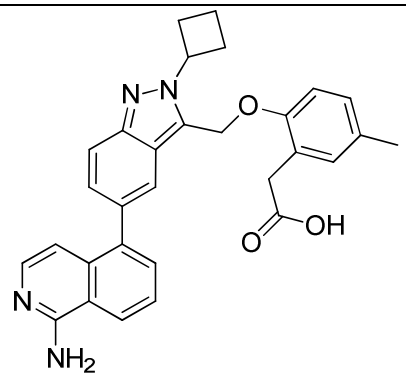
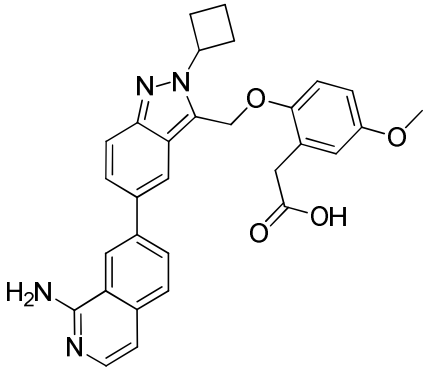
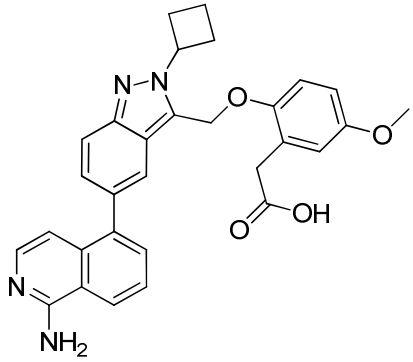
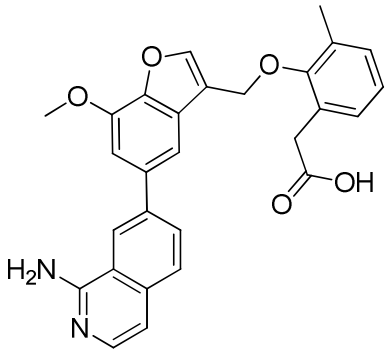
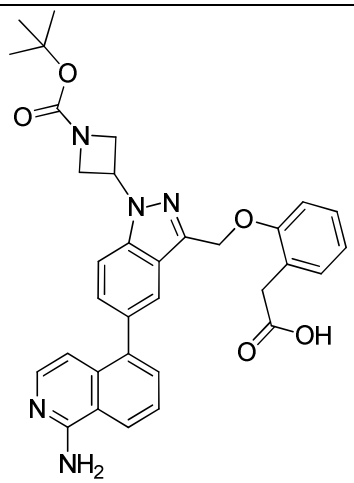
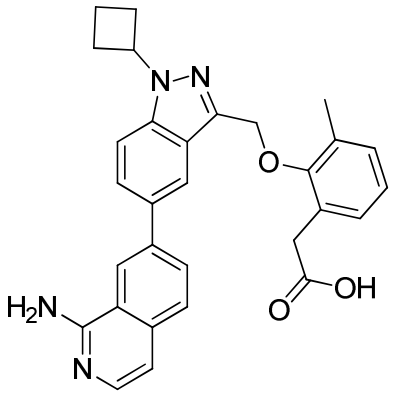
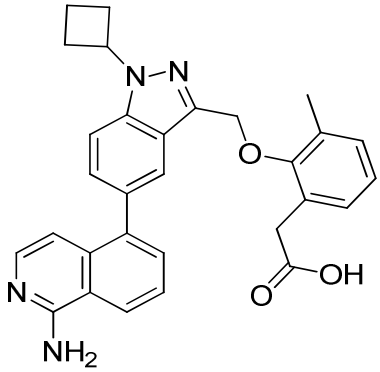
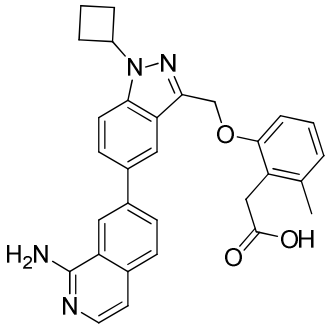
	
	
	
	

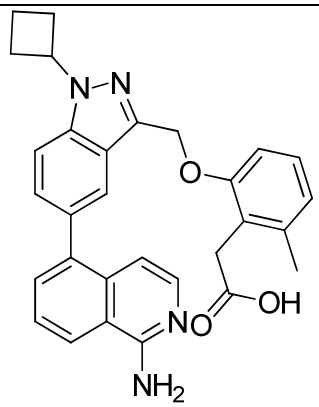
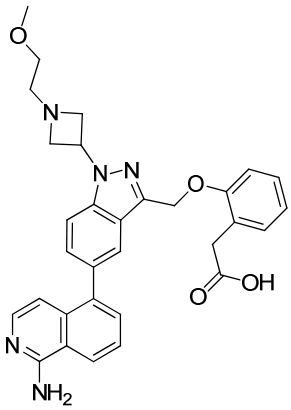
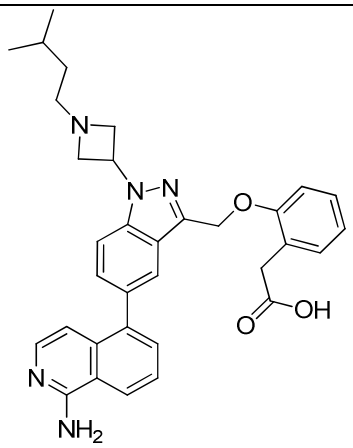
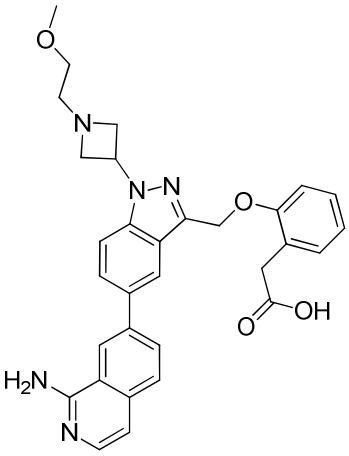
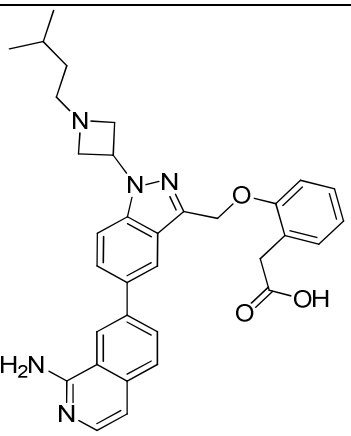
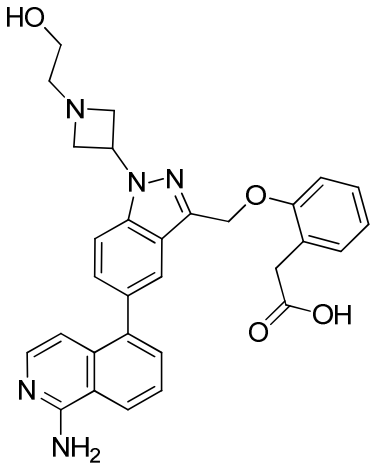
	
	
	

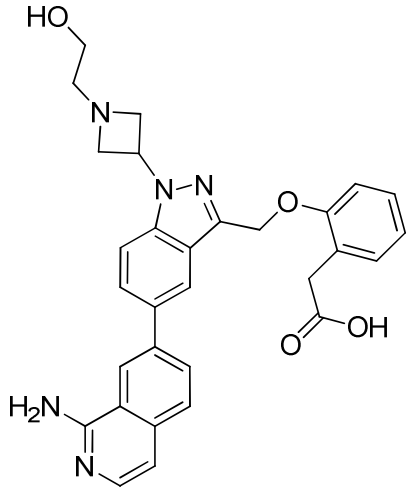
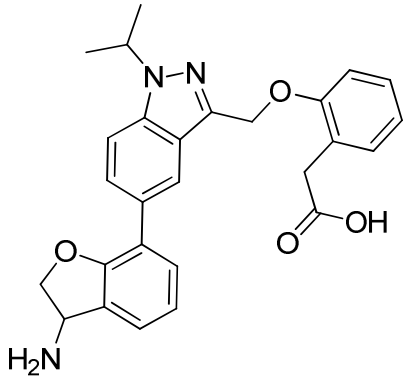
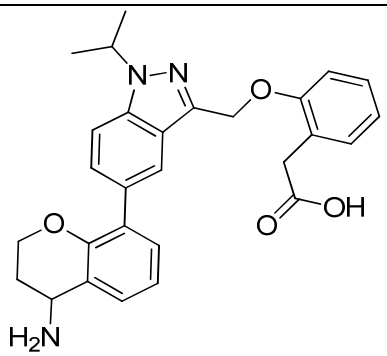
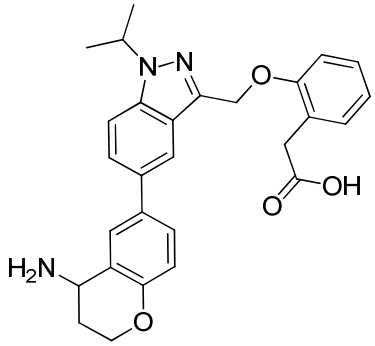
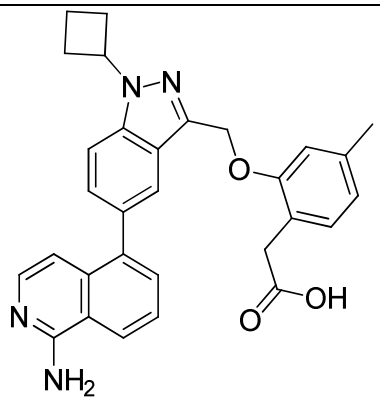
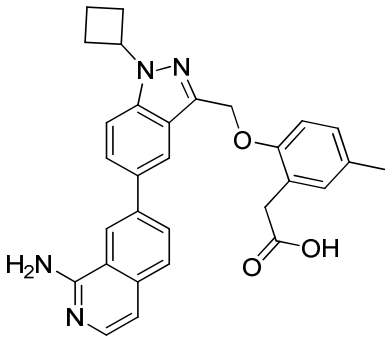
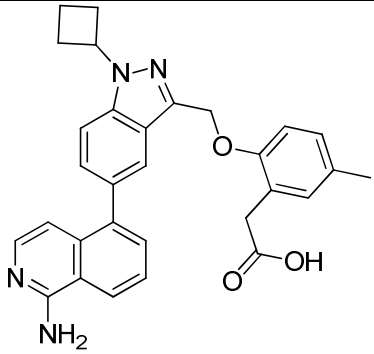
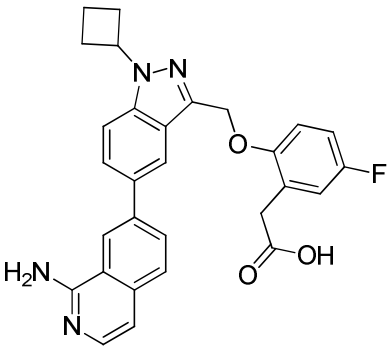
	
	
	

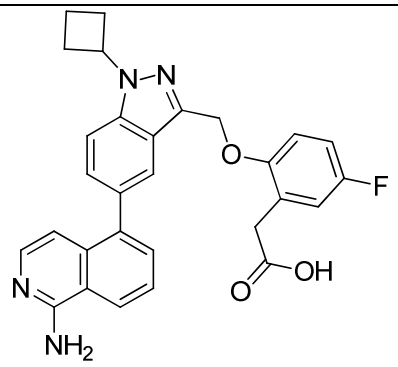
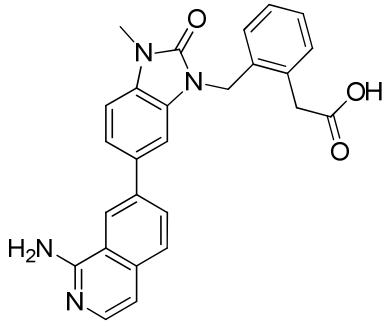
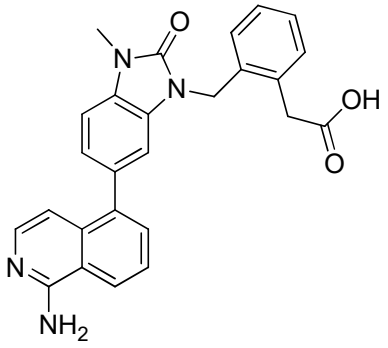
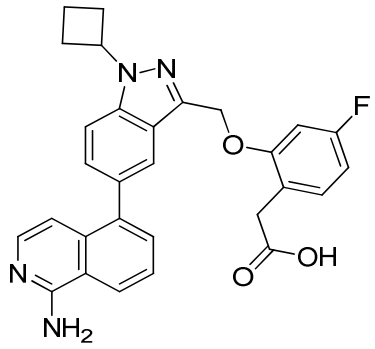
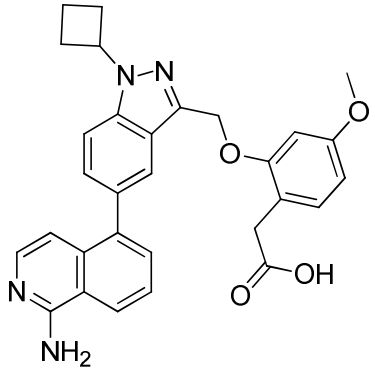
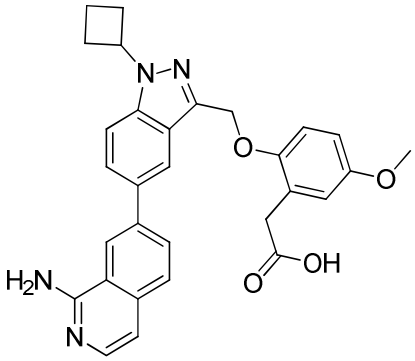
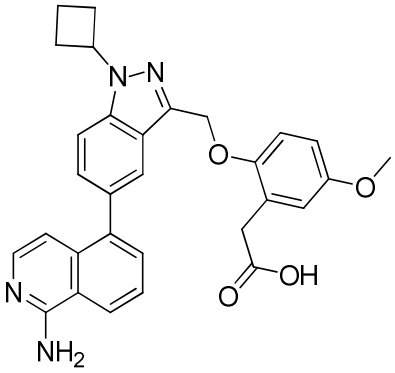
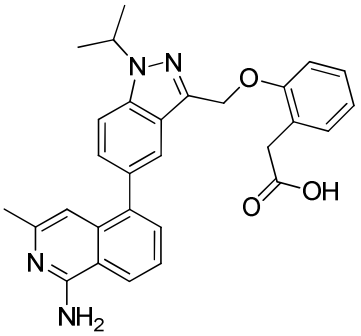
	
	
	
	

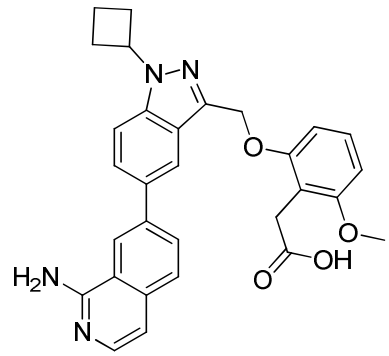
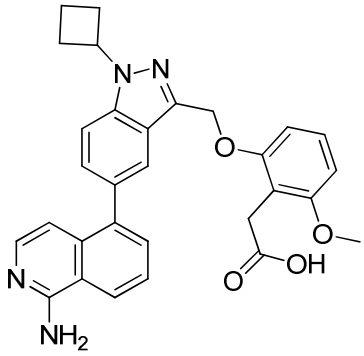
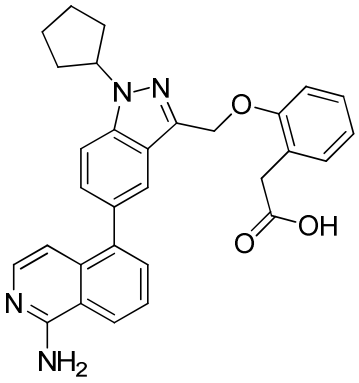
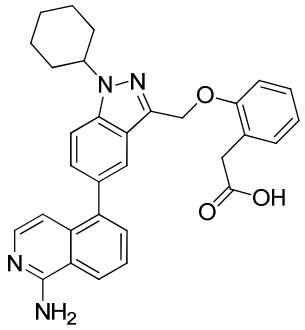
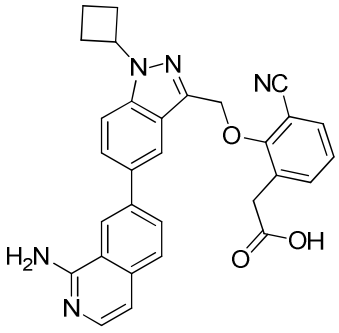
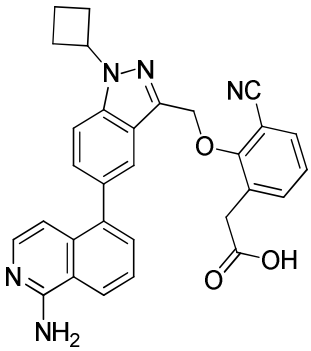
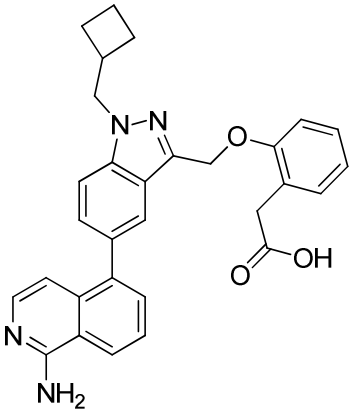
	
	
	
	

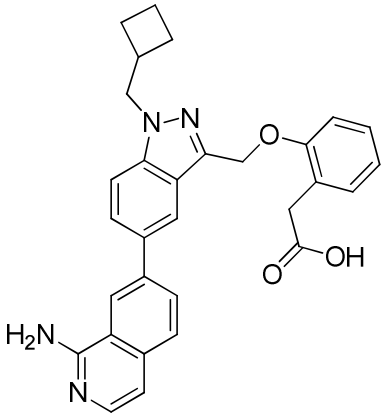
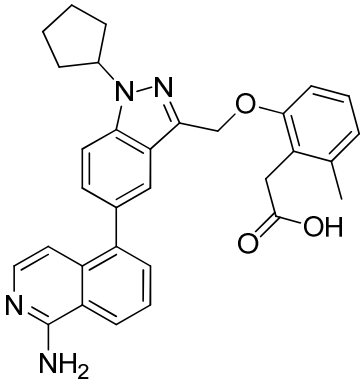
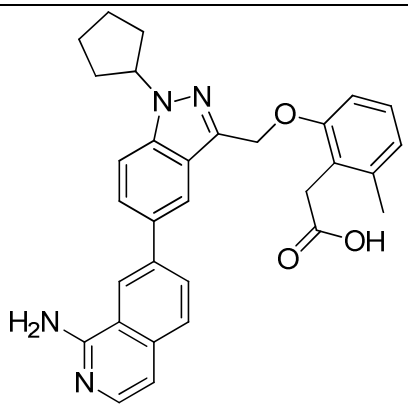
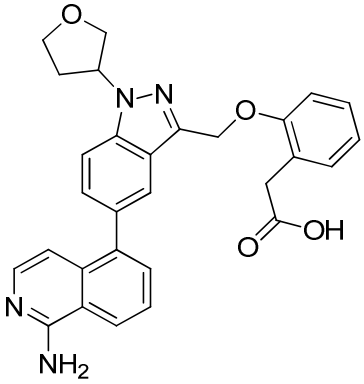
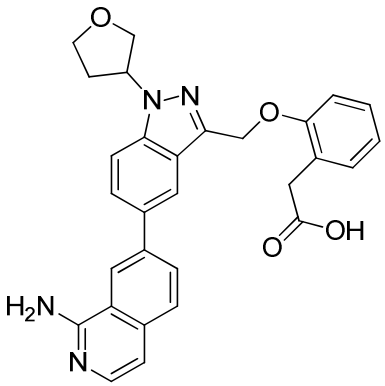
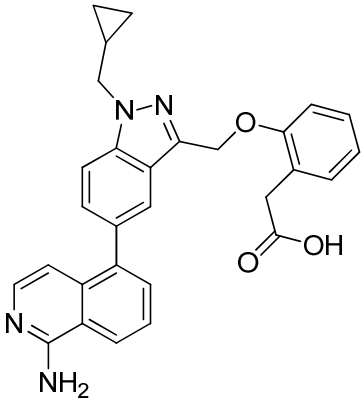
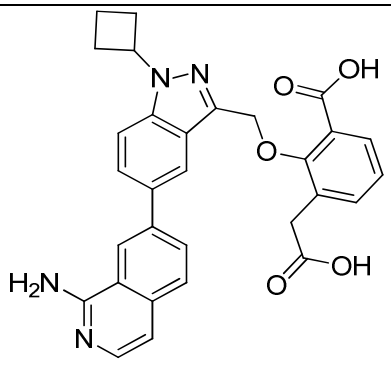
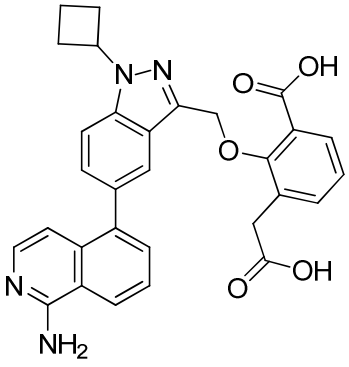
	
	
	
	

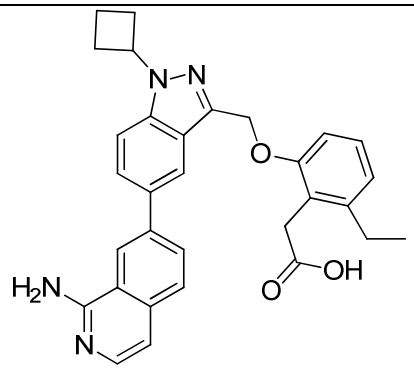
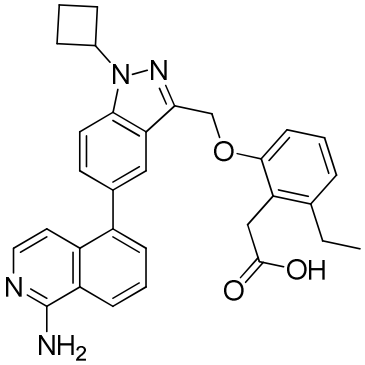
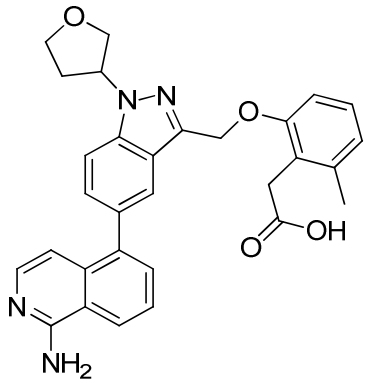
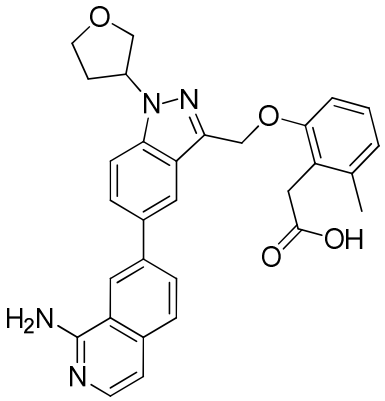
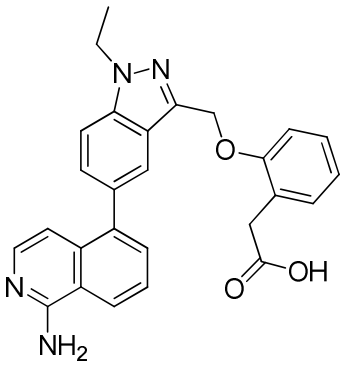
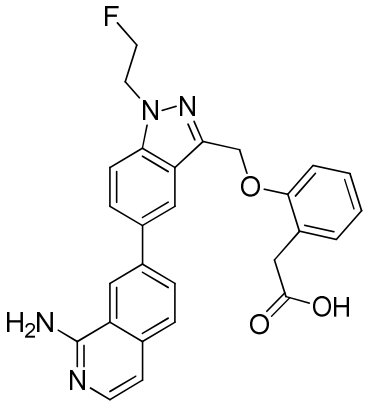
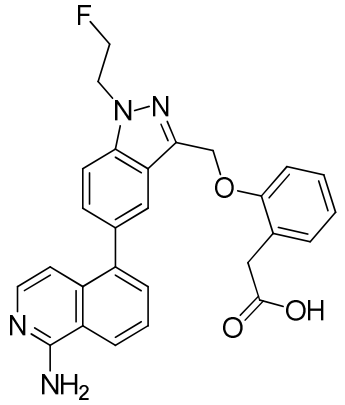
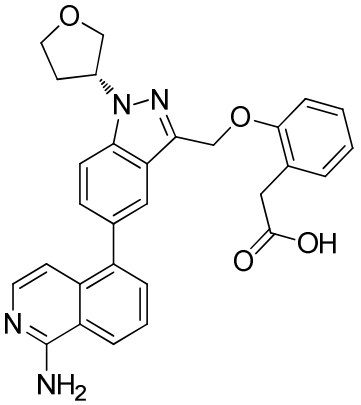
	
	
	

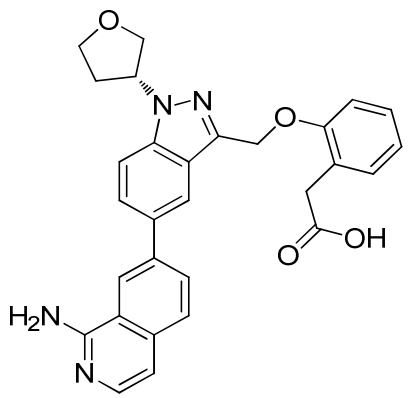
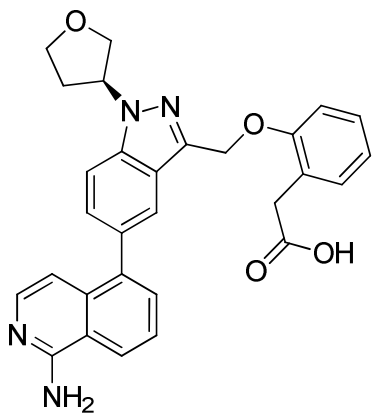
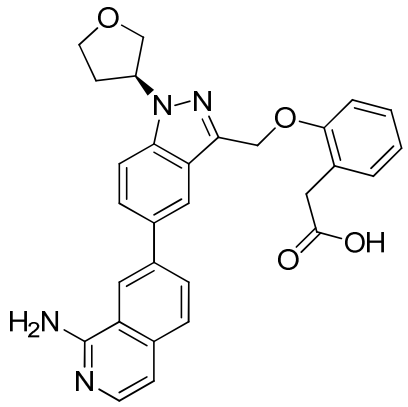
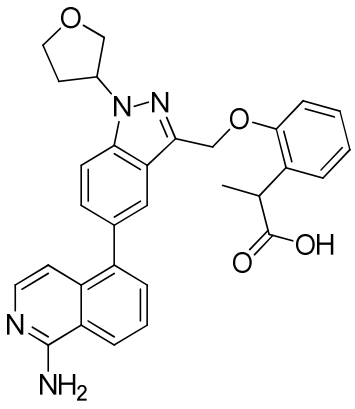
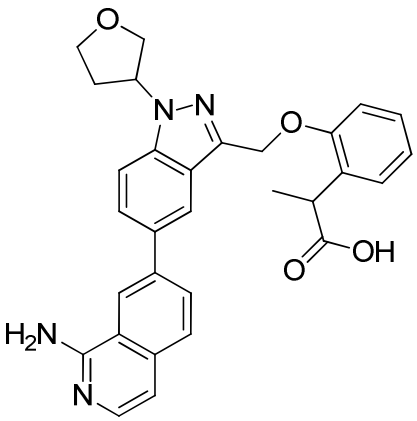
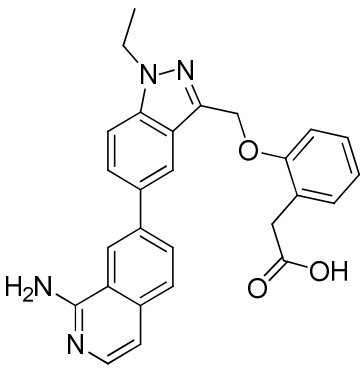
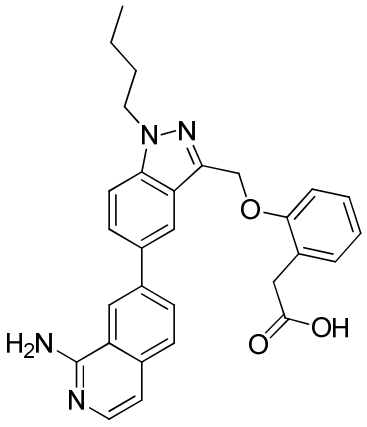
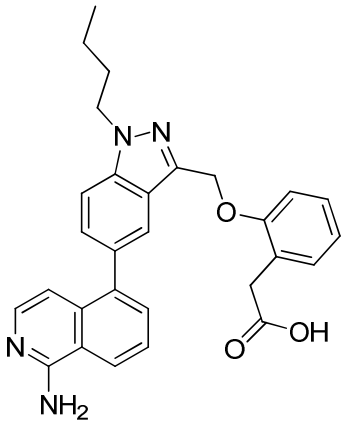
	
	
	
	

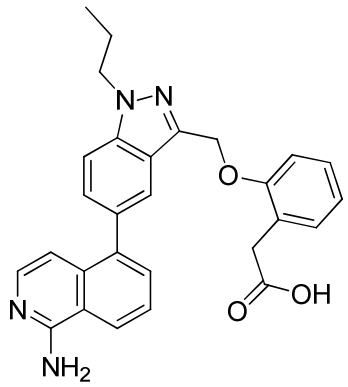
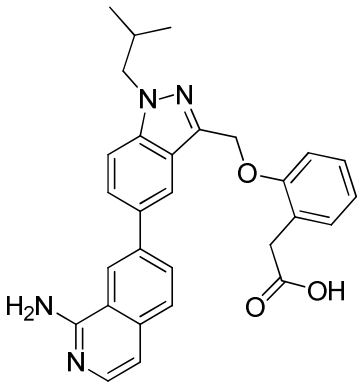
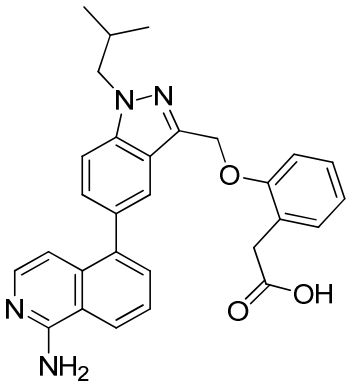
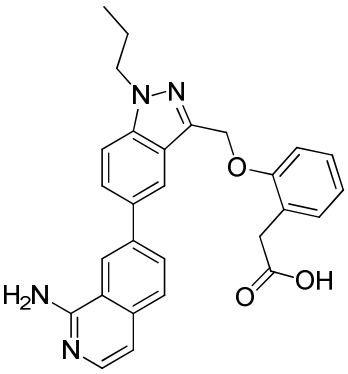
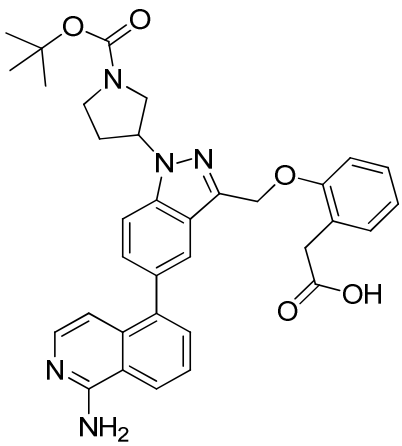
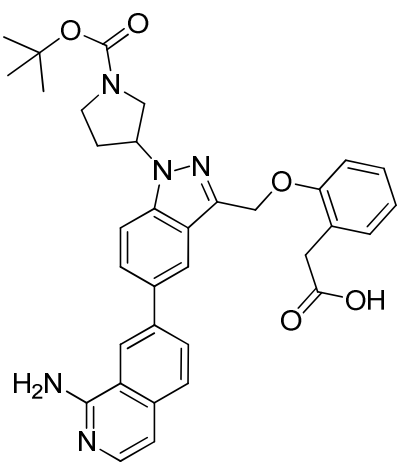
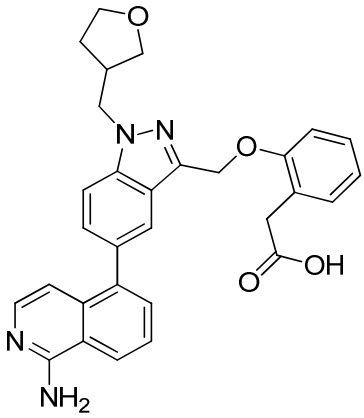
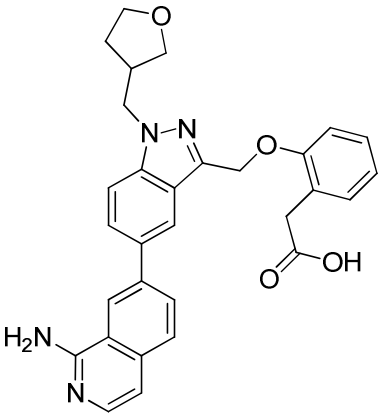
	
	
	
	

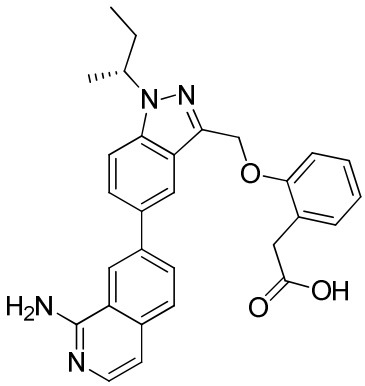
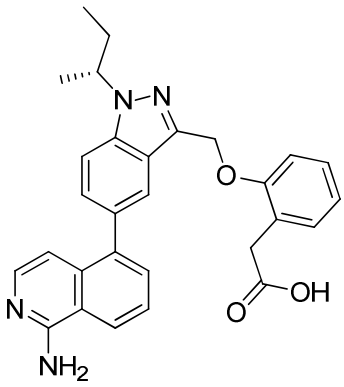
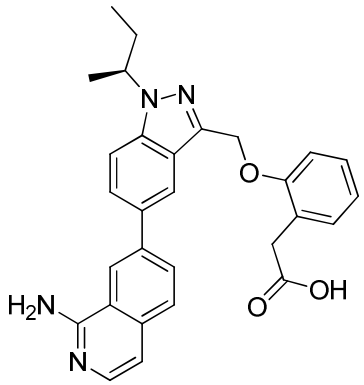
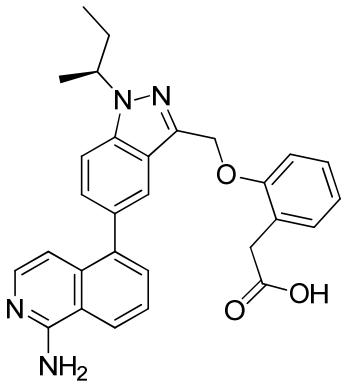
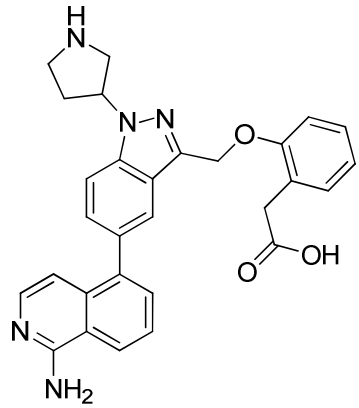
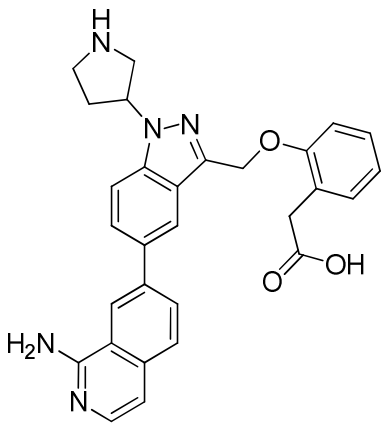
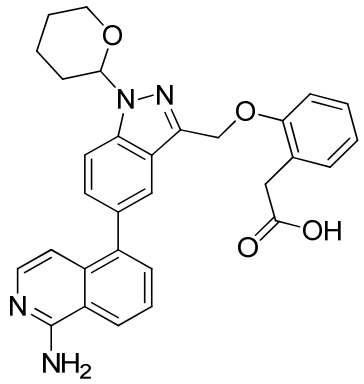
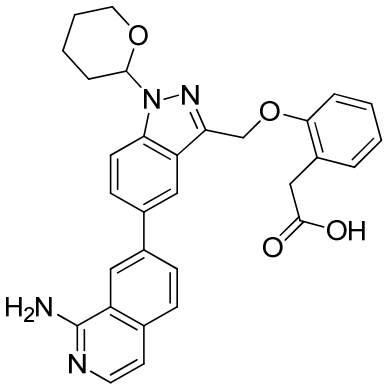
	
	
	
	

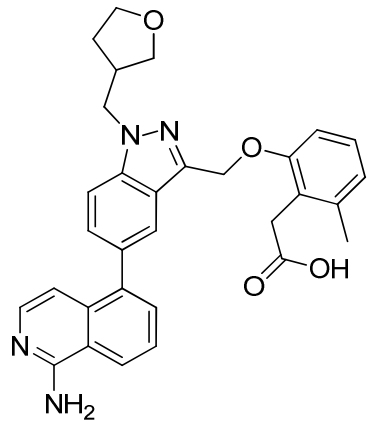
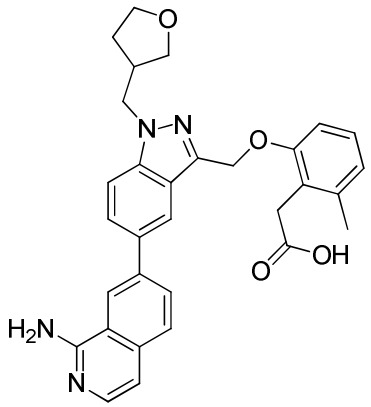
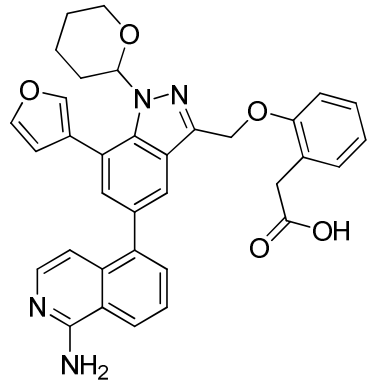
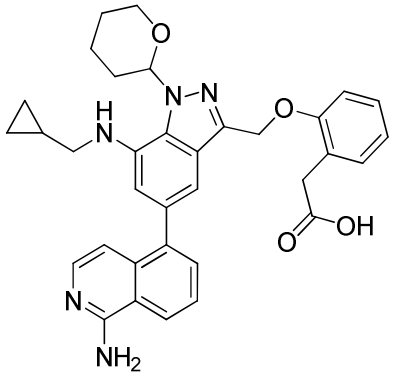
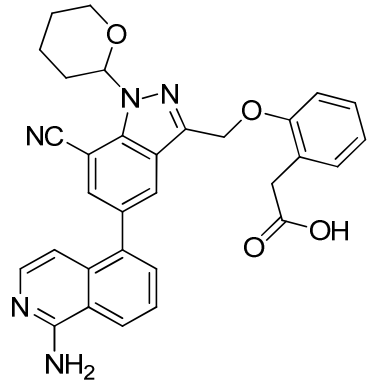
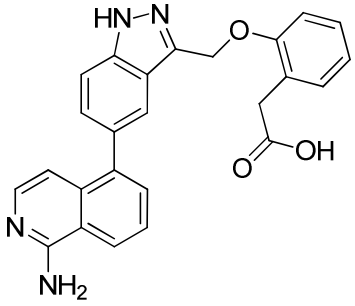
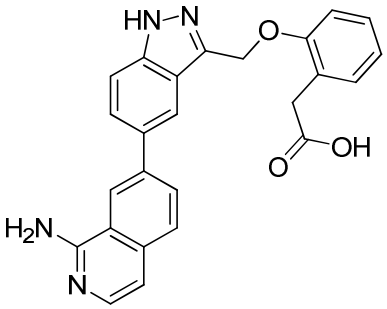
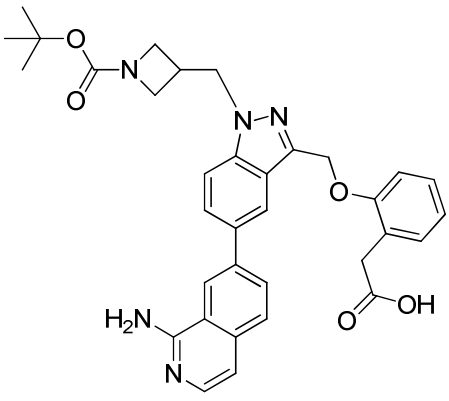
	
	
	
	

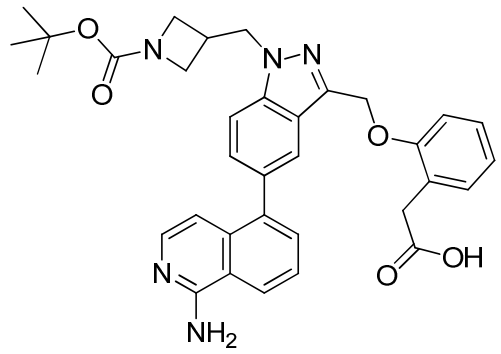
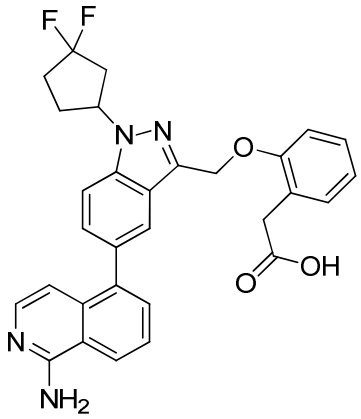
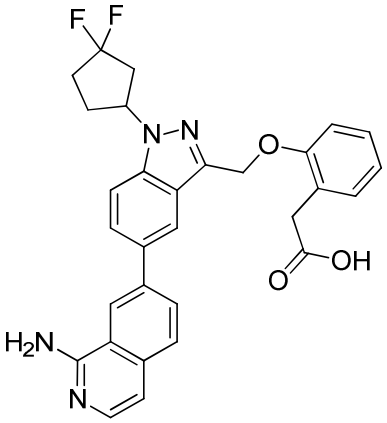
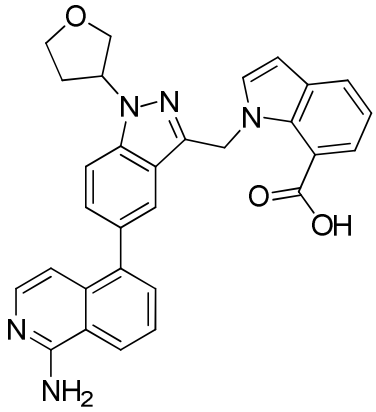
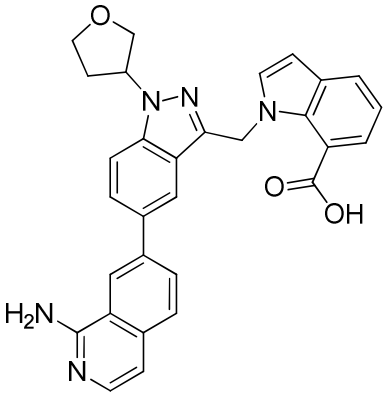
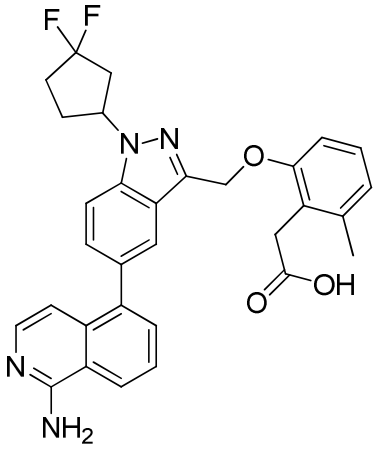
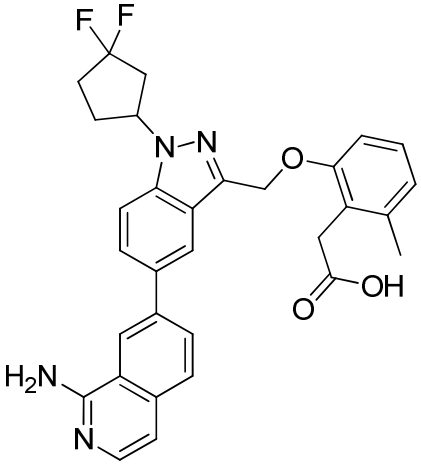
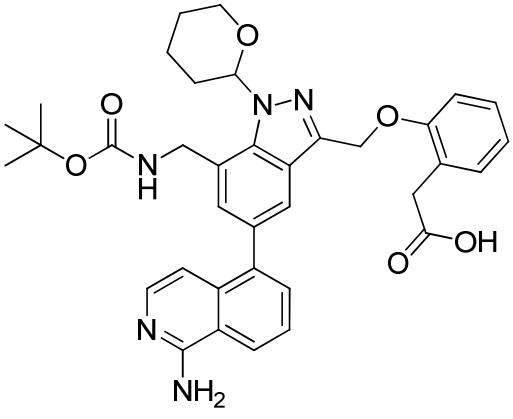
	
	
	
	

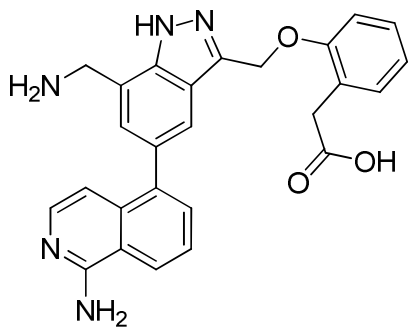
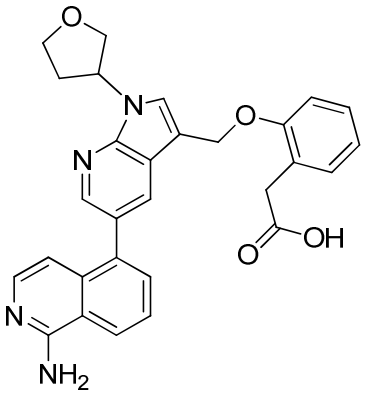
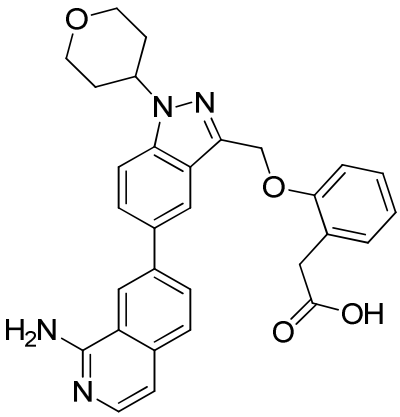
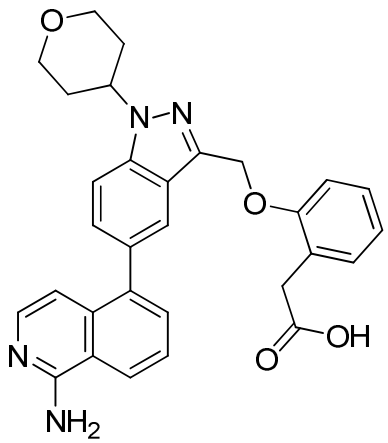
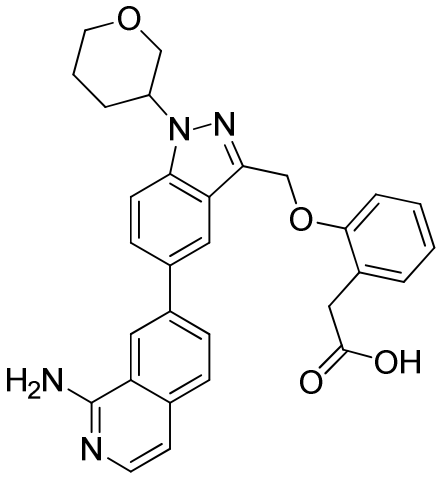
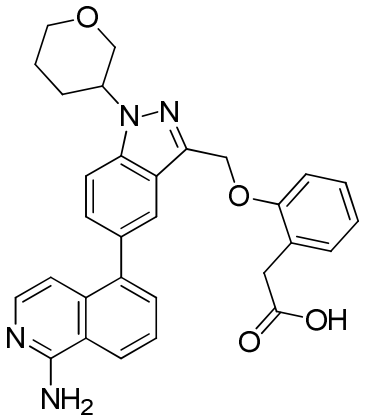
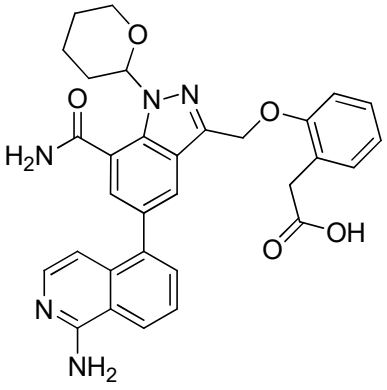
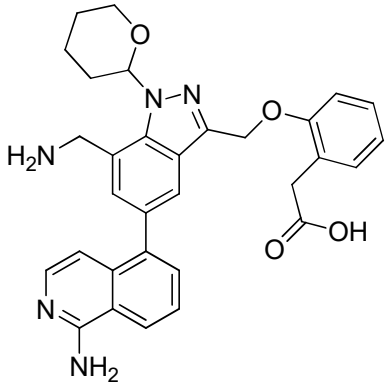
	
	
	
	

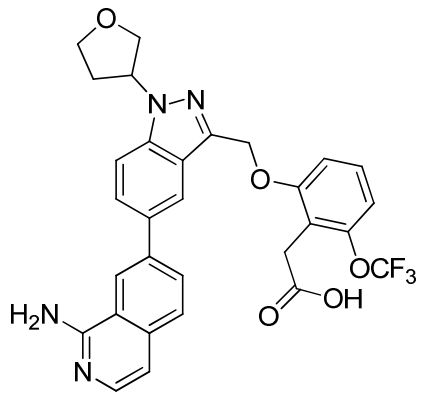
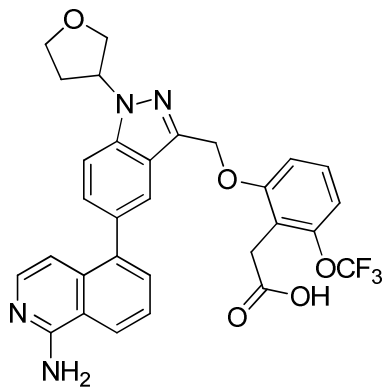
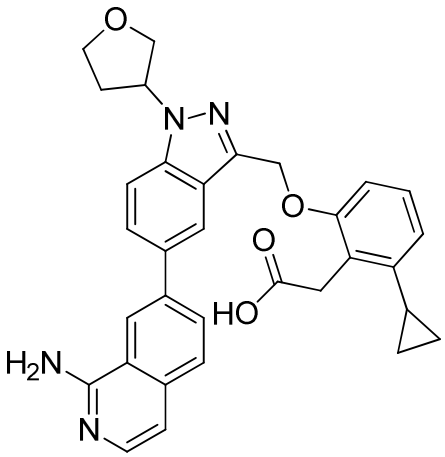
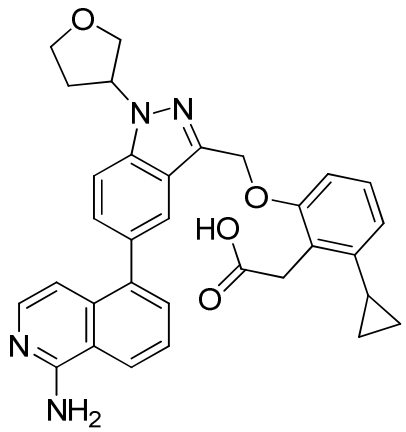
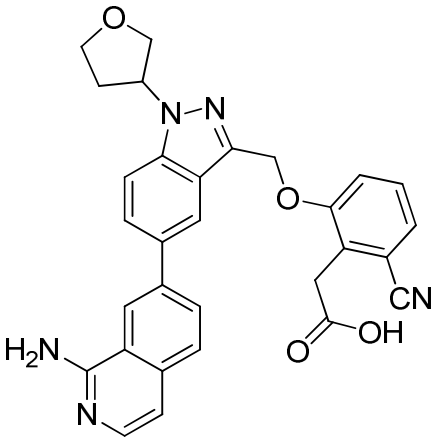
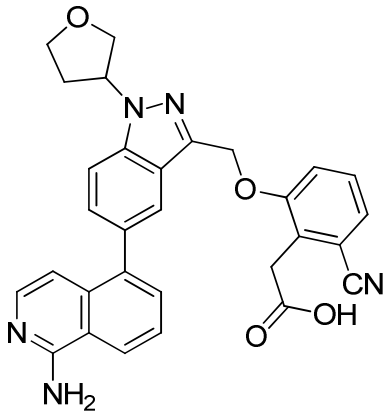
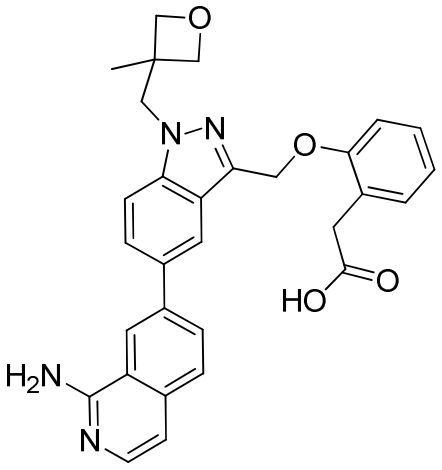
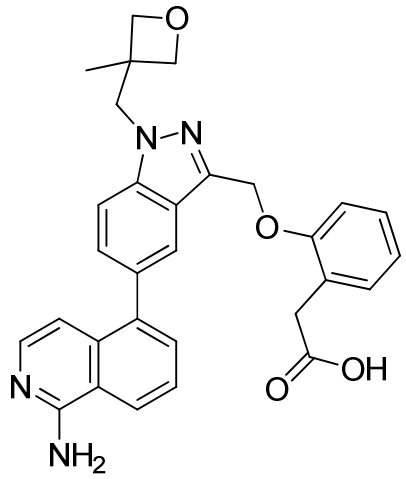
	
	
	
	

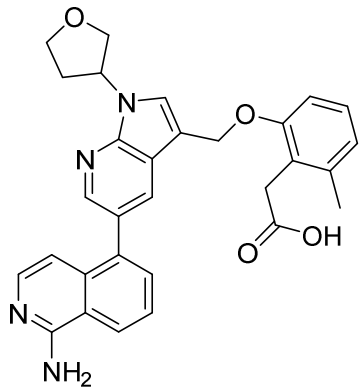
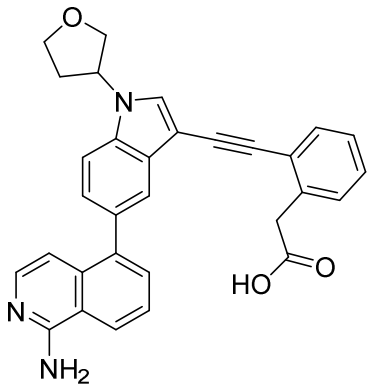
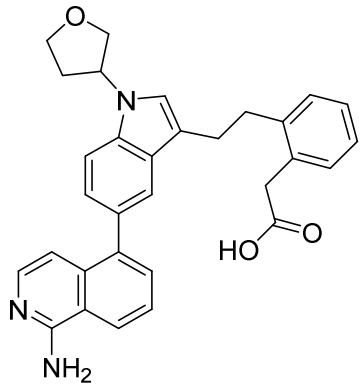
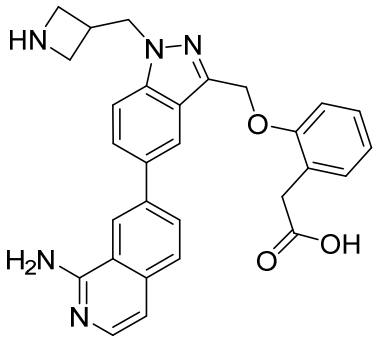
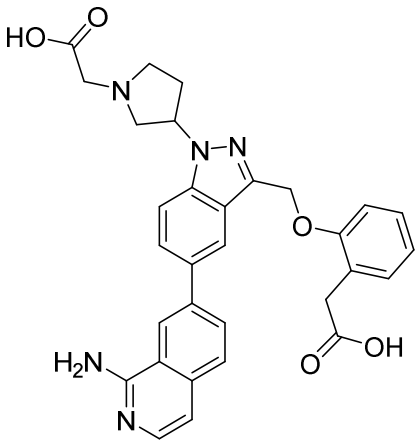
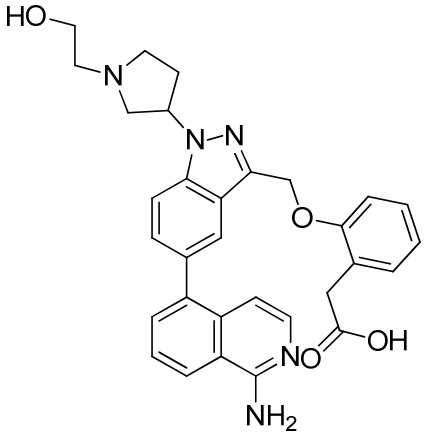
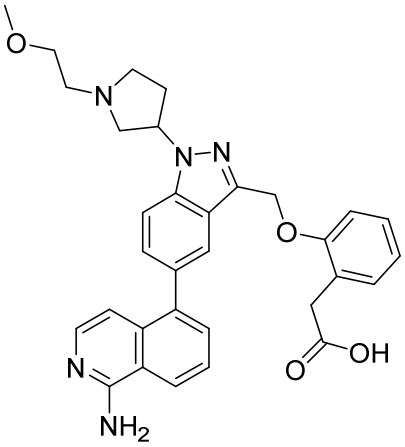
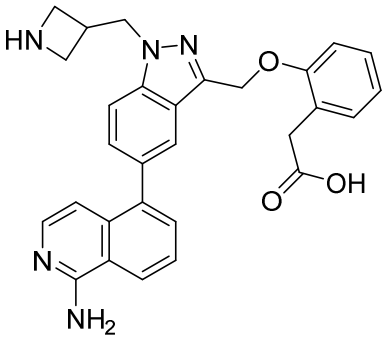
	
	
	
	

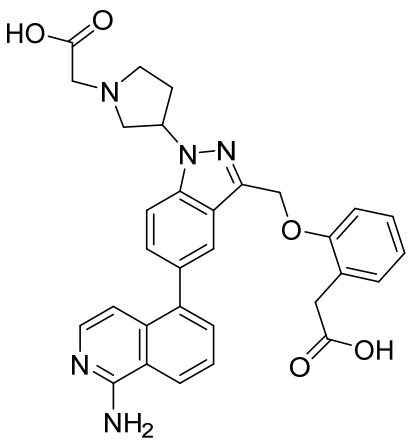
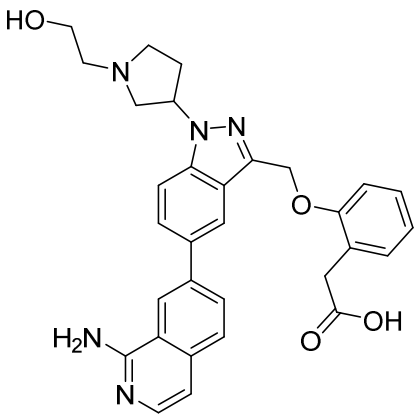
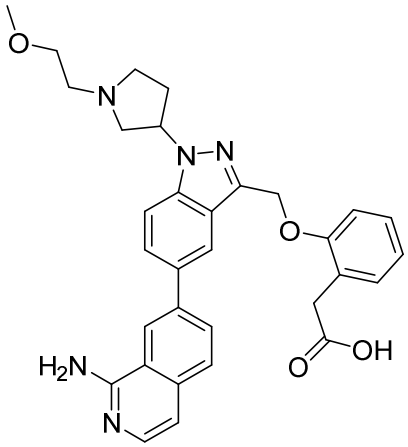
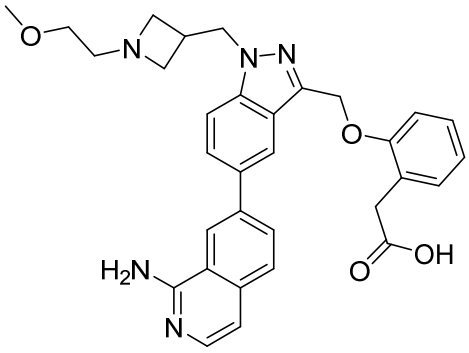
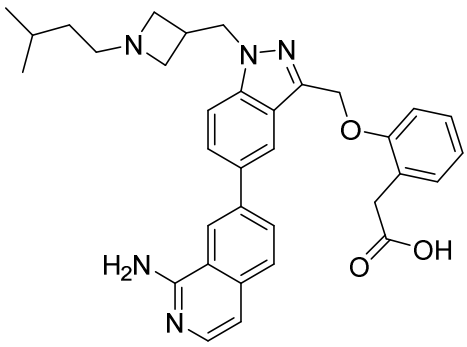
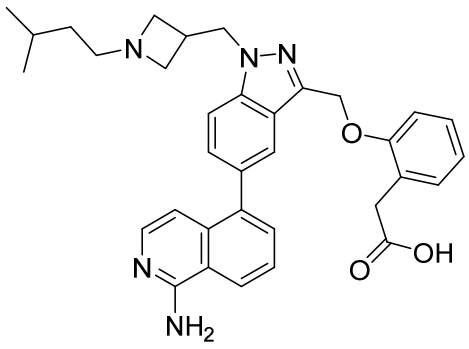
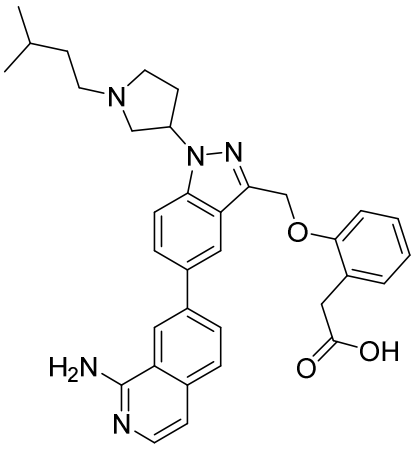
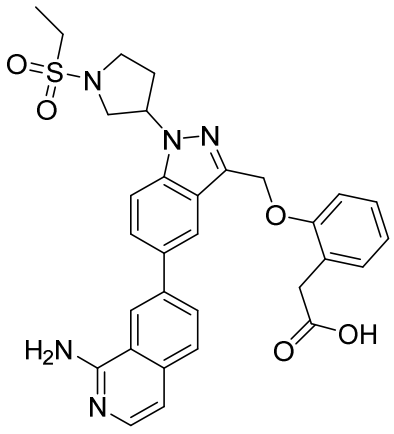
	
	
	
	

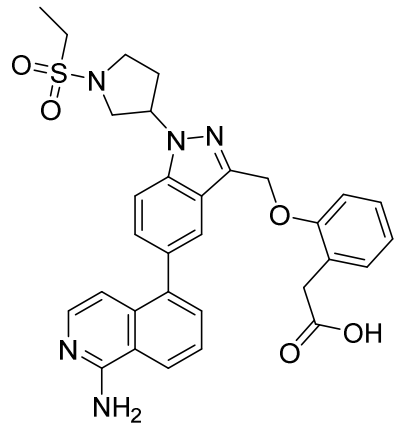
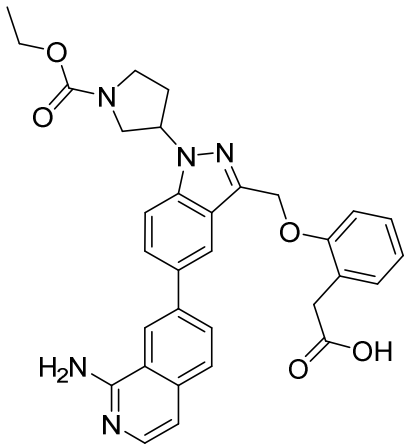
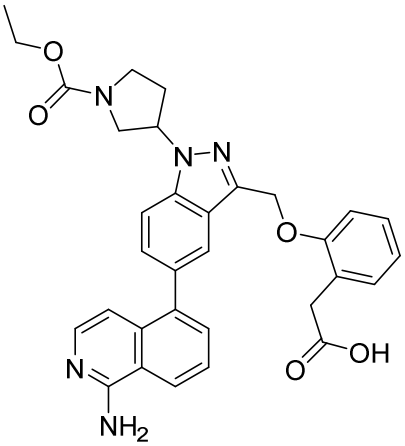
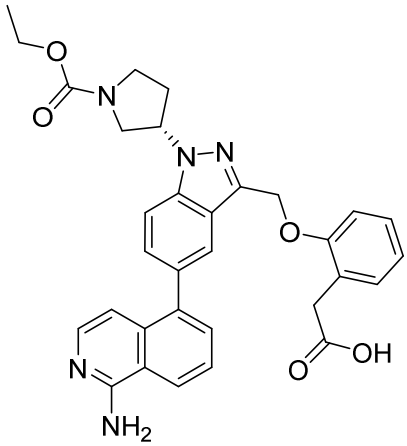
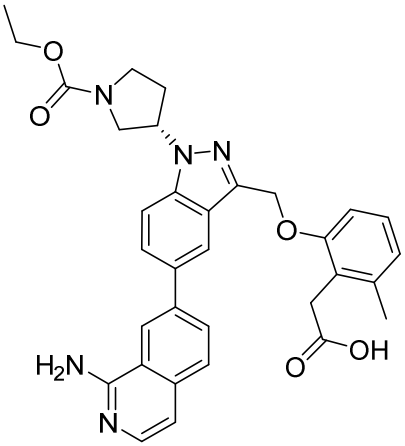
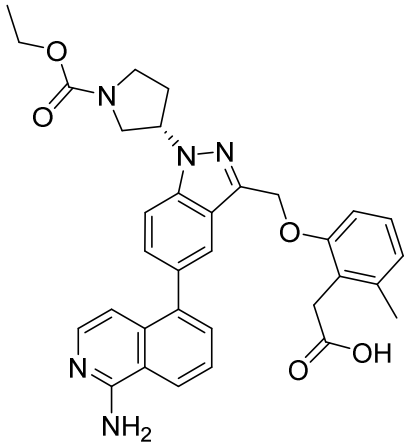
	
	
	
	

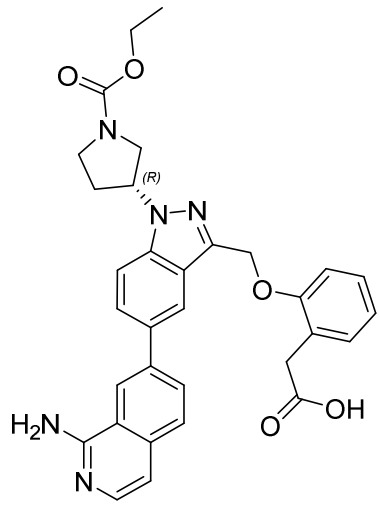
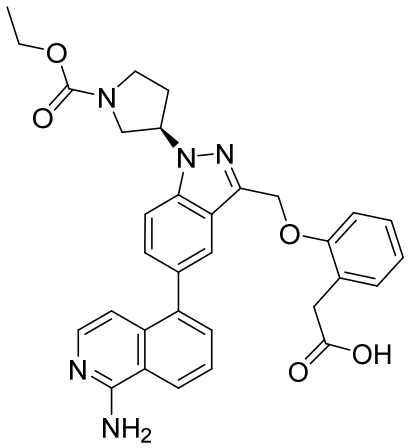
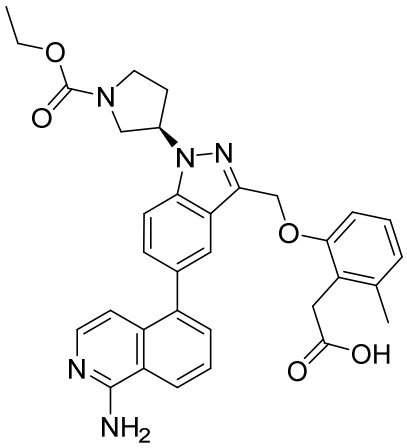
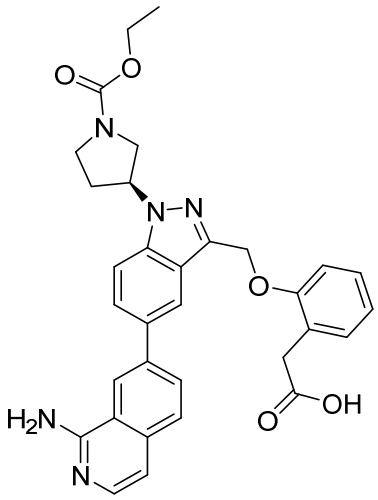
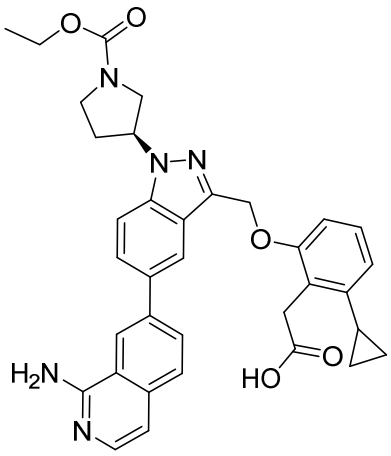
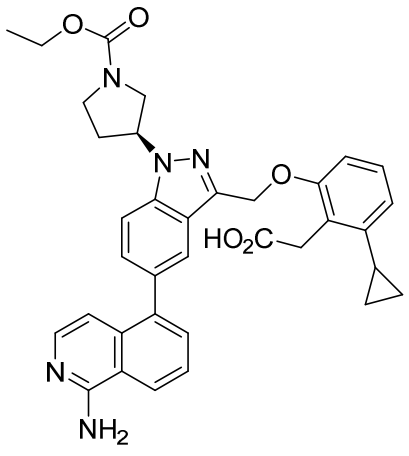
	
	
	
	

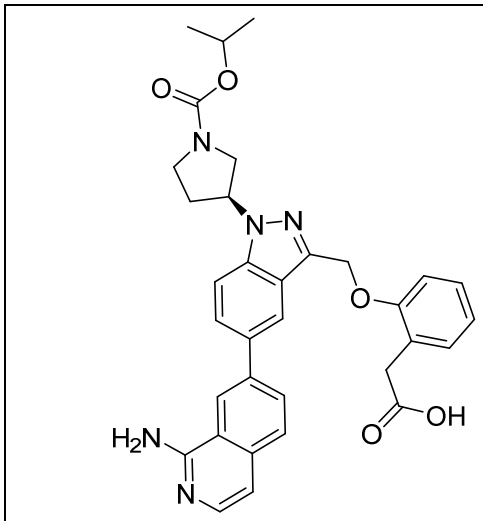
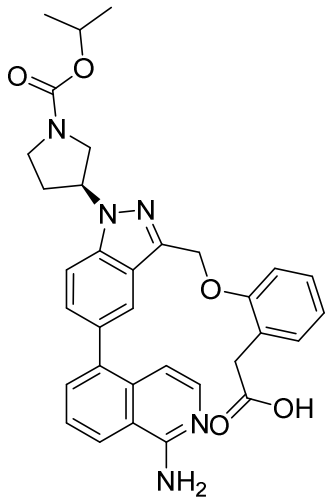
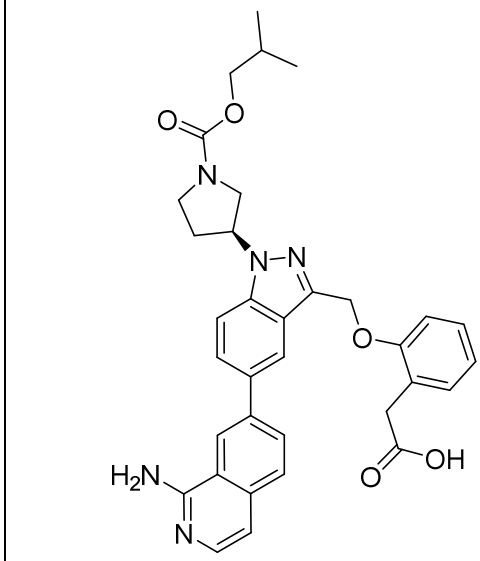
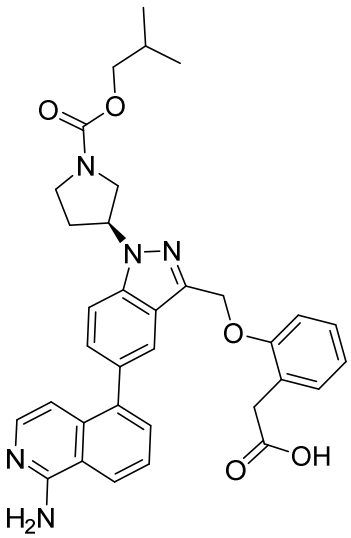
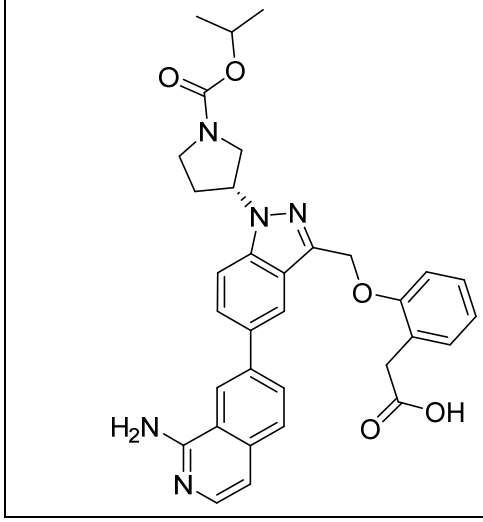
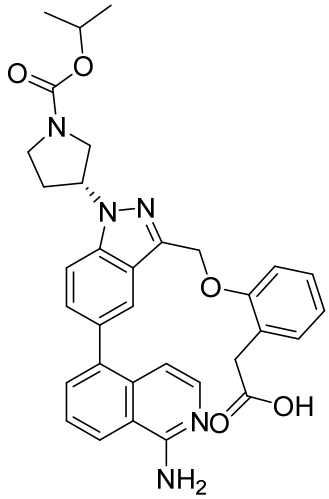
	
	
	
	

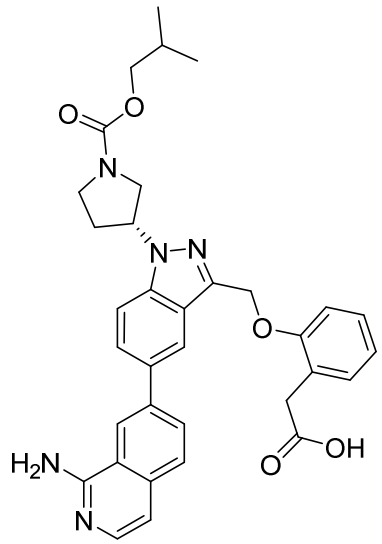
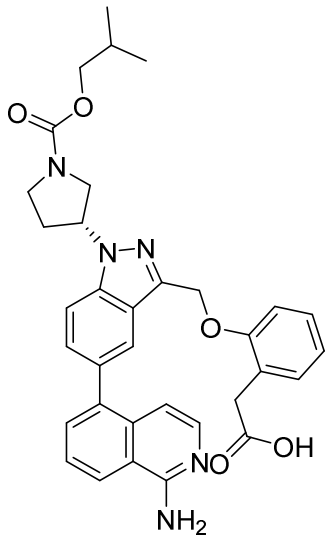
	
	
	
	

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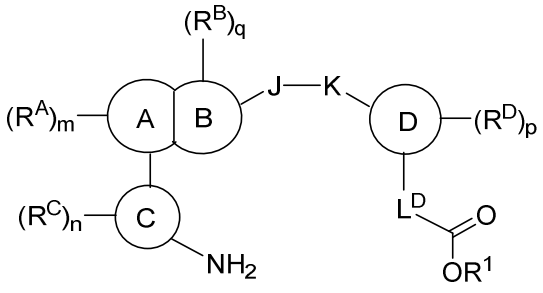
83. A compound of formula (III), or a pharmaceutically acceptable salt thereof:



(III);

wherein:

ring A is arylene or heteroarylene;

ring B is cycloalkylene, heterocycloalkylene, cycloalkenylene, or heterocycloalkenylene;

ring A is fused to ring B at two and only two adjacent positions;

ring C is a bicyclic ring system, where the ring attached to ring A is aryl or heteroaryl;

ring D is aryl or heteroaryl;

J represents –CH_2–, –NH–, –CH_2CH_2–, –C(O)–, –C≡C–, –O–, –S–, –S(O)–, –SO_2–, –N(alkyl)–, –CH(alkyl)–, –CH(aryl)–, –$C(alkyl)_2$–, –CH(cycloalkyl)–, or  ;

K represents a bond, –O–, –NH–, –C(O)–, –CH_2–, –S–, –S(O)–, –SO_2–, –N(alkyl)–, –CH(alkyl)–, or –CH(cycloalkyl)–;

wherein at least one of J and K is a bond, –C(O)–, –CH_2–, –CH_2CH_2–, –CH(alkyl)–, or –CH(aryl)–;

L^D represents –CH_2–, –CH_2CH_2–, –CF_2–, –CH(F)–, –CD_2–, –CH(D)–, –CH(OH)–, –CH(alkyl)–, –CH(cycloalkyl)–, –$CHNH_2$–, –CH(NH(alkyl))–, –CH(NH(cycloalkyl))–, or a bond;

R^A, independently for each occurrence, represents H, halo, hydroxyl, cyano, amino, alkyl, optionally substituted alkoxy, hydroxyalkyl, optionally substituted aryloxy, (aryloxy)alkyl, (cycloalkyl)alkoxy, (heterocycloalkyl)alkoxy, optionally substituted (heteroaryl)alkoxy, haloalkyl, haloalkoxy, (hydroxy)haloalkyl, alkoxyalkyl, optionally substituted aminoalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (cycloalkyl)alkenyl, optionally substituted heterocycloalkyl, optionally substituted (heterocycloalkyl)alkyl, –C(O)OH, –$C(O)NH_2$–, –$C(O)N(alkyl)_2$–, –CH_2C(O)OH, –NO_2, –CH_2NH(optionally substituted alkyl), –CH_2N(Boc), –CH_2N(Boc)(optionally substituted alkyl), –CH_2NH((cycloalkyl)alkyl), –CH_2N(alkyl)(cycloalkyl), –CH_2N(alkyl)((cycloalkyl)alkyl), –NH(optionally substituted alkyl), –NH(cycloalkyl), –NH((cycloalkyl)alkyl), –NH((heterocycloalkyl)alkyl), –$N(alkyl)_2$, –N(alkyl)((cycloalkyl)alkyl, –N(alkyl)((heterocycloalkyl)alkyl, –NH(heteroarylalkyl), –CH_2O(optionally substituted aryl), –C(O)O(alkyl), –C(O)NH(optionally substituted alkyl), –C(O)NH((cycloalkyl)alkyl), –NHC(O)O(alkyl), or –$CH_2N(alkyl)_2$;

R^B, independently for each occurrence, represents H, oxo, –C(O)O(alkyl), halogen, cyano, amino, –C(O)OH, –CH_2C(O)OH, –$C(O)NH_2$, –C(O)NH(cycloalkyl), –C(O)NH(alkyl), –C(O)NH(aryl), -C(O)NH(heteroaryl), –C(O)(alkyl), -$S(O)_2$alkyl, alkylaminoalkyl, alkylaminocycloalkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, (hydroxy)haloalkyl, or tosyl, or is optionally

substituted alkyl, aryl, heteroaryl, cycloalkyl, spirocycloalkyl, halocycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, spiroheterocycloalkyl, or (heterocycloalkyl)alkyl; or two adjacent occurrences of R^B taken together with the intervening atoms form an aromatic ring; or two geminal occurrences of R^B taken together with the atom to which they are attached form an optionally substituted spirocycloalkyl or a spiroheterocycloalkyl;

R^C, independently for each occurrence, represents H, halo, -OH, cyano, or amino, or is optionally substituted alkoxy, haloalkoxy, alkyl, cycloalkyl, heterocycloalkyl, or (heteroaryl)alkoxy;

R^D, independently for each occurrence, represents H, halo, hydroxyl, cyano, $–NH_2$, -NH(Ac), -NH(alkyl), $-N(alkyl)_2$, -NH(CO)(alkyl), $–CH_2NH_2$, $-CH_2NHC(O)(alkyl)$, $–C(O)NH_2$, –C(O)OH, or –NHC(O)O(alkyl), or is optionally substituted alkyl, alkoxy, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, haloalkoxy, or haloalkyl;

R^1 represents H or optionally substituted alkyl; and

m, n, p, and q are each independently 0, 1, or 2.

84. The compound of claim 83, wherein ring  is cycloalkylene or heterocycloalkylene.

85. The compound of claim 83 or 84, wherein:

ring  is arylene;

ring  is cycloalkylene;

ring  is fused to ring  at two and only two adjacent positions;

ring  is a bicyclic ring system, where the ring attached to ring  is aryl;

ring  is aryl;

J represents –O–;

K represents a bond;

L^D represents $–CH_2–$;

R^A, independently for each occurrence, represents H, halo, alkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted cycloalkyl;

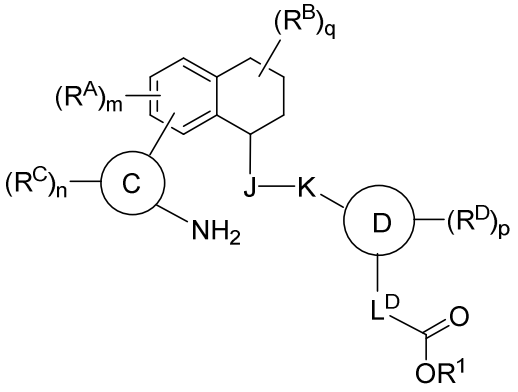
R^B, independently for each occurrence, represents H, or two adjacent occurrences of R^B taken together with the intervening atoms form an aromatic ring; or two geminal occurrences of R^B taken together with the atom to which they are attached form an optionally substituted spirocycloalkyl or a spiroheterocycloalkyl;

R^C represents H;

R^D represents H or optionally substituted alkyl;

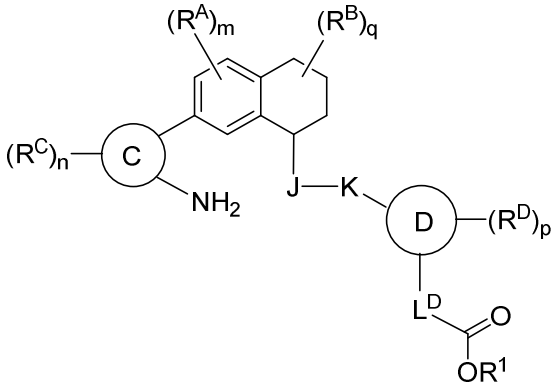
R^1 represents H.

86. The compound of any one of claims 83-85, having the structure of formula (IIIa):



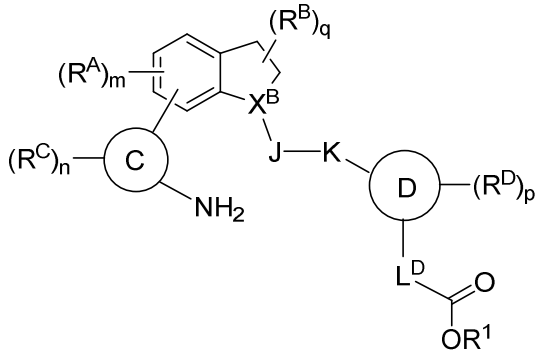
(IIIa).

87. The compound of any one of claims 83-86, having the structure of formula (IIIa-1):



(IIIa-1).

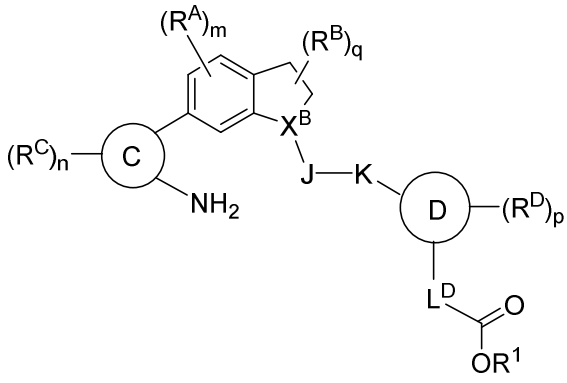
88. The compound of any one of claims 83-85, having the structure of formula (IIIb):



(IIIb);

wherein X^B represents CH or N.

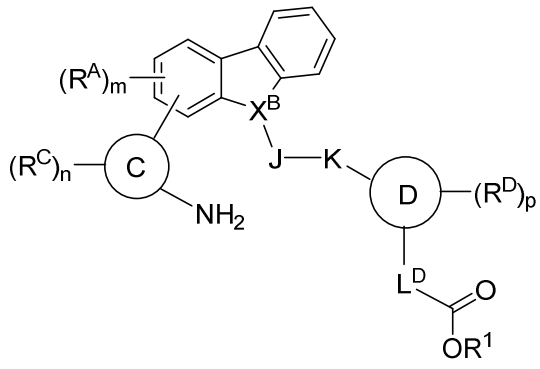
89. The compound of claim 88, having the structure of formula (IIIb-1):



(IIIb-1);

wherein X^B represents CH or N.

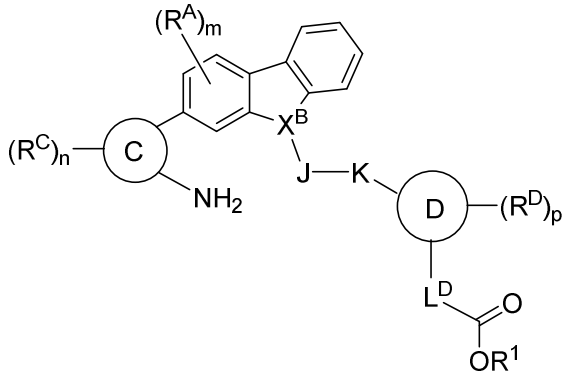
90. The compound of any one of claims 83-85, having the structure of formula (IIIc):



(IIIc);

wherein X^B represents CH or N.

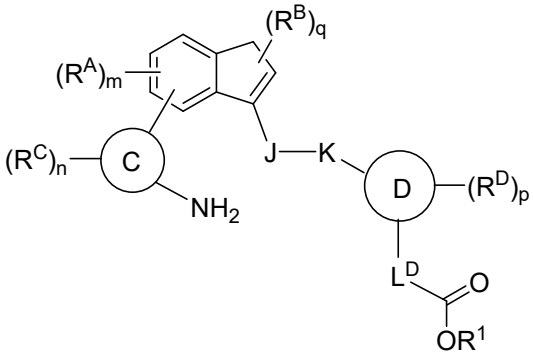
91. The compound of claim 90, having the structure of formula (IIIc-1):



(IIIc-1);

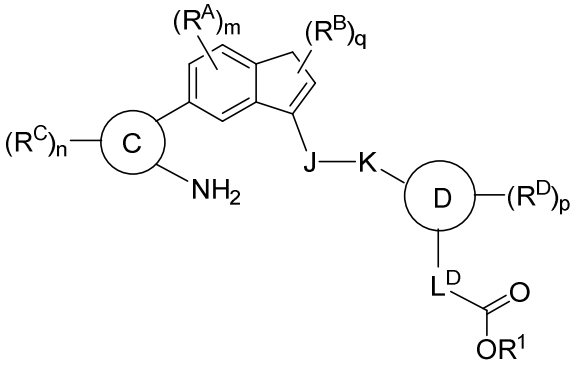
wherein X^B represents CH or N.

92. The compound of any one of claims 83-85, having the structure of formula (IIId):



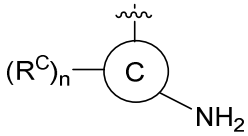
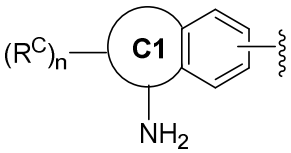
(IIId).

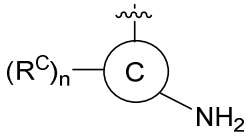
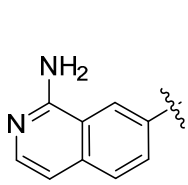
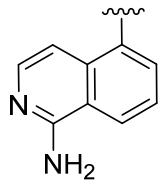
93. The compound of claim 92, having the structure of formula (IIId-1):



(IIId-1).

94. The compound of any one of claims 83-93, wherein ring C is a bicyclic ring system, where the ring attached to ring A is aryl.

95. The compound of any one of claims 83-94, wherein  represents  , wherein ring  represents heteroaryl.

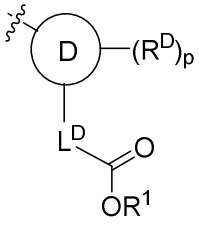
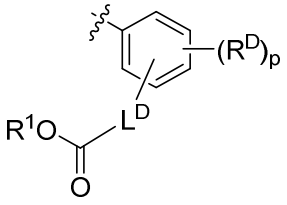
96. The compound of any one of claims 83-95, wherein  represents  or  .

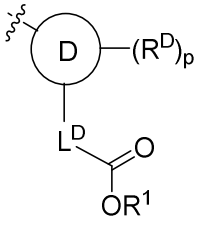
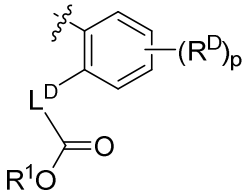
97. The compound of any one of claims 83-96, wherein R^C represents H.

98. The compound of any one of claims 83-84 and 86-97, wherein J represents $–CH_2–$, –NH–, $–CH_2CH_2–$, –C(O)–, –O–, –S–, –S(O)–, $–SO_2–$, –N(alkyl)–, –CH(alkyl)–, –CH(aryl)–, $–C(alkyl)_2–$, –CH(cycloalkyl)–, or  .

99. The compound of any one of claims 83-98, wherein –J–K– represents –O–.

100. The compound of any one of claims 83-99, wherein ring  is aryl.

101. The compound of any one of claims 83-100, wherein  represents  .

102. The compound of any one of claims 83-101, wherein  represents  .

103. The compound of claim 83, wherein ring  is bicyclic heteroaryl.

104. The compound of any one of claims 83-103, wherein R^1 is H.

105. The compound of any one of claims 83-104, wherein L^D represents $–CH_2–$.

106. The compound of any one of claims 83-105, wherein R^D, independently for each occurrence, represents H or alkyl.

107. The compound of any one of claims 83-106, wherein two geminal occurrences of R^B taken together with the atom to which they are attached form an optionally substituted spirocycloalkyl or a spiroheterocycloalkyl.

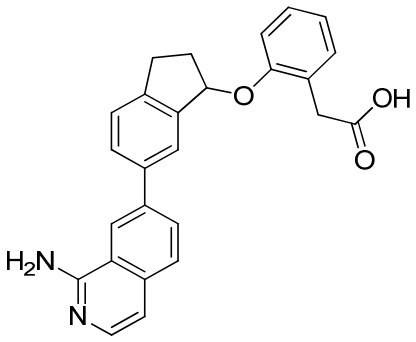
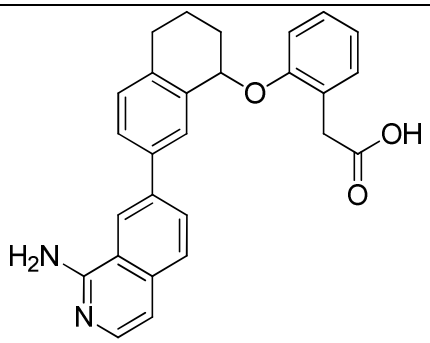
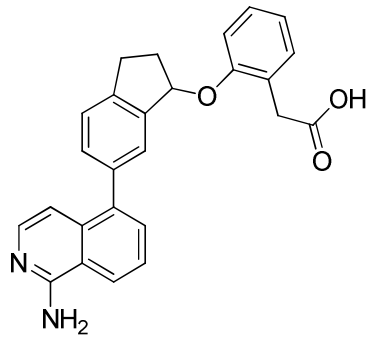
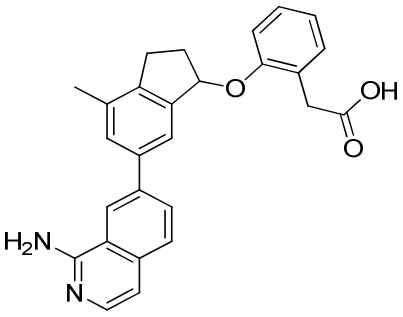
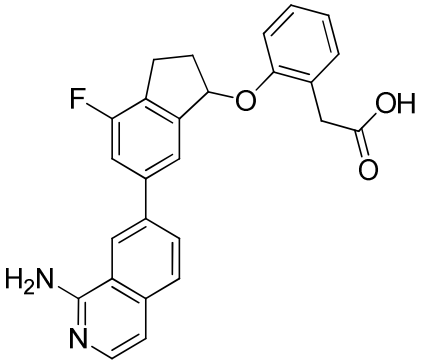
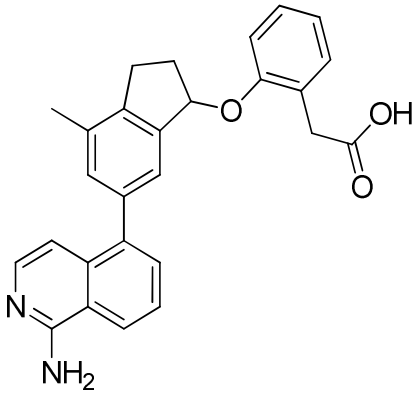
108. The compound of any one of claims 83-107, wherein two geminal occurrences of R^B taken together with the atom to which they are attached form a substituted spiroheterocycloalkyl.

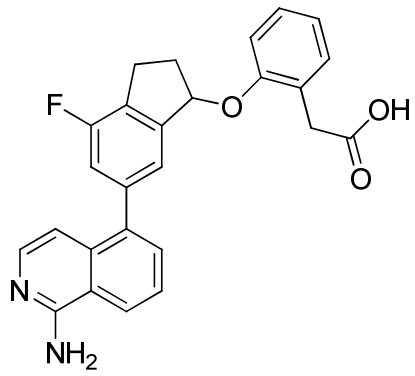
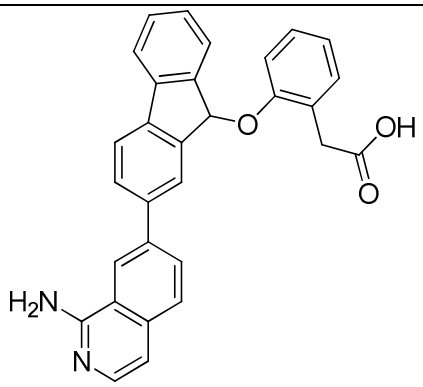
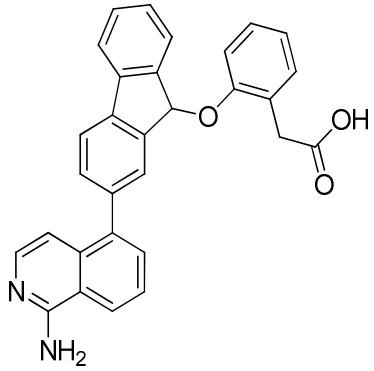
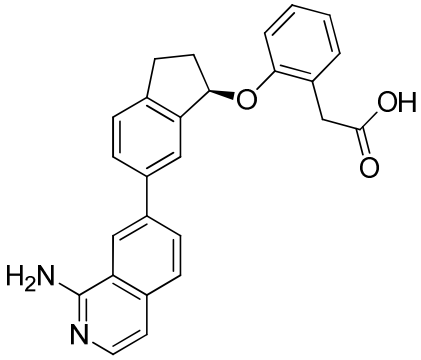
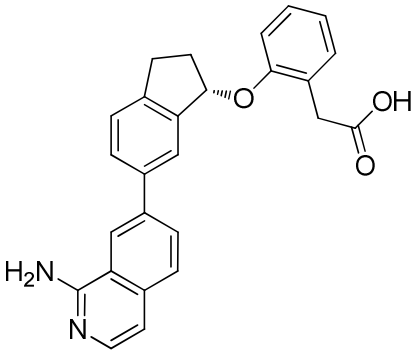
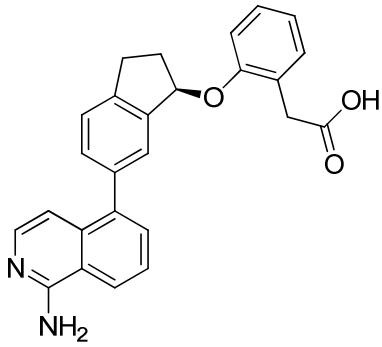
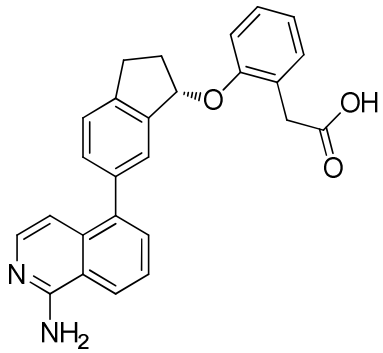
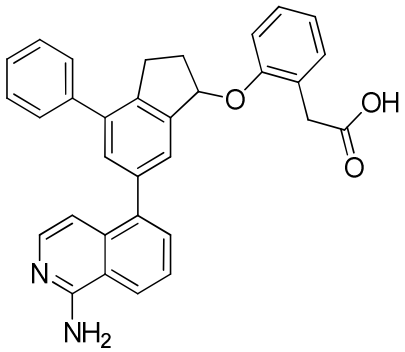
109. The compound of any one of claims 83-108, wherein R^B represents H.

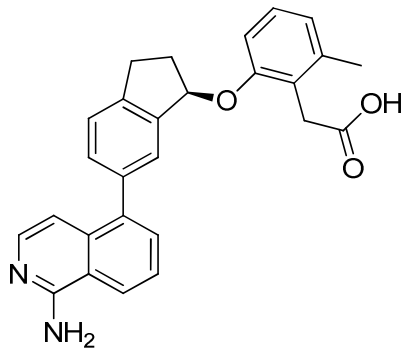
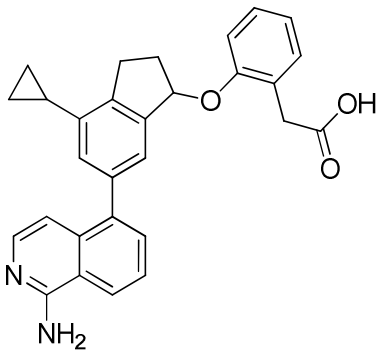
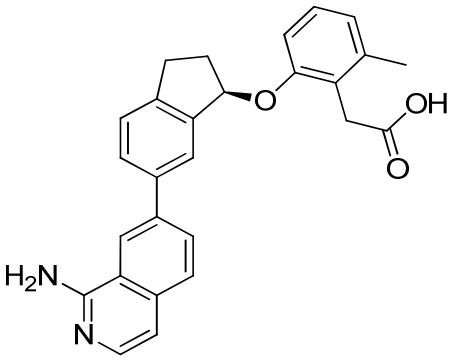
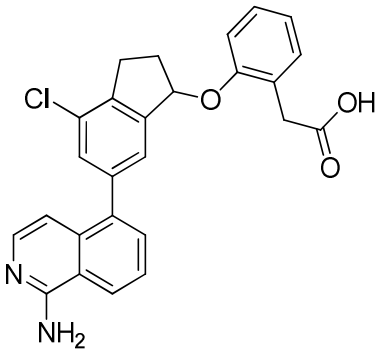
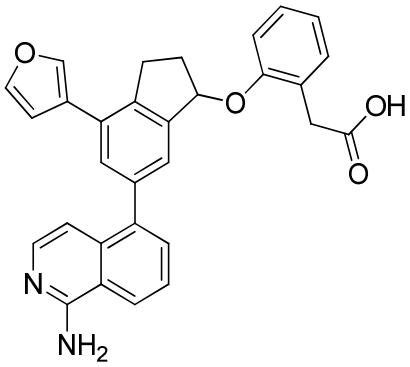
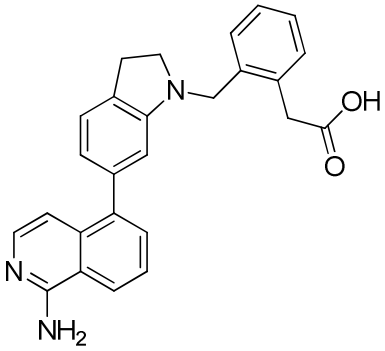
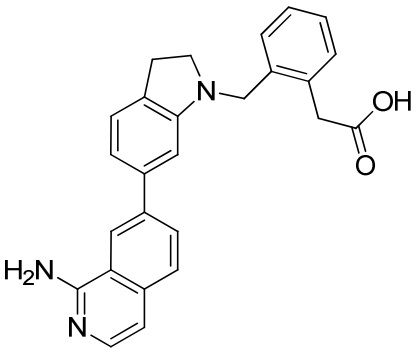
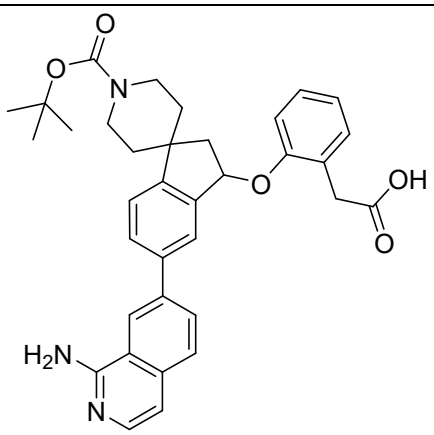
110. The compound of any one of claims 83-109, wherein R^A, independently for each occurrence, represents H, halo, alkyl, aryl, heteroaryl, or cycloalkyl.

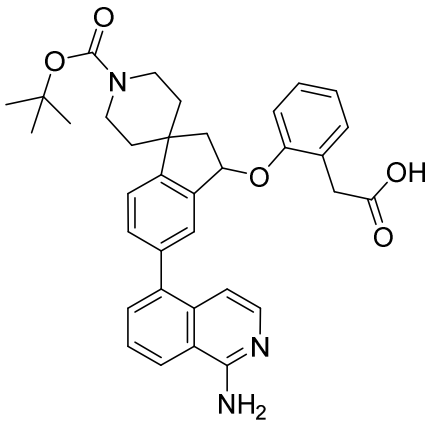
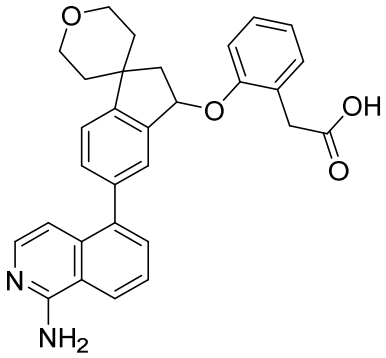
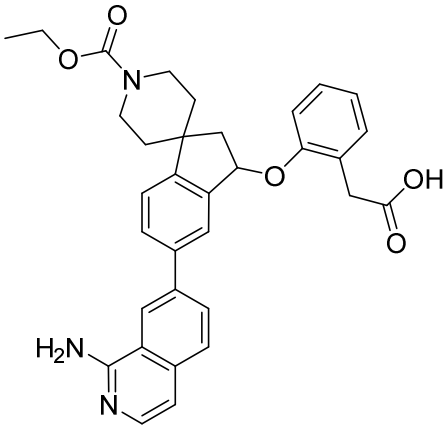
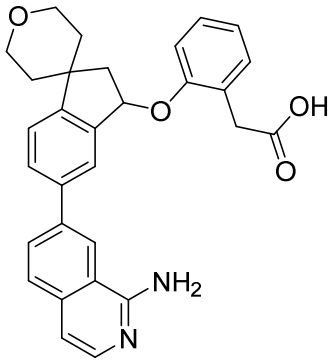
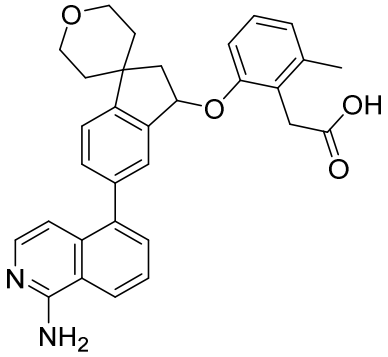
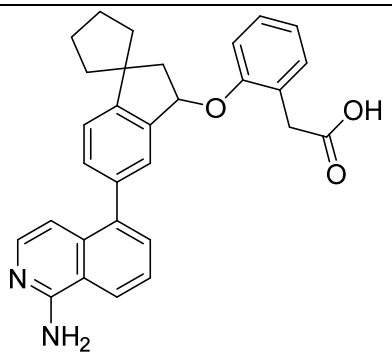
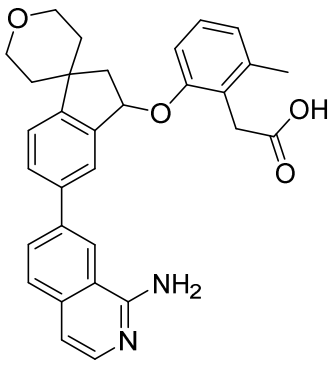
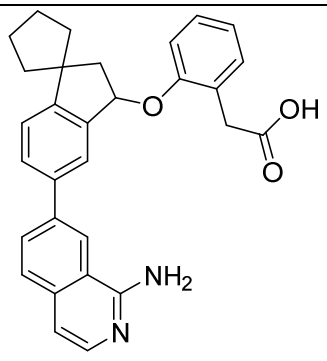
111. The compound of any one of claims 83-110, wherein R^A represents H.

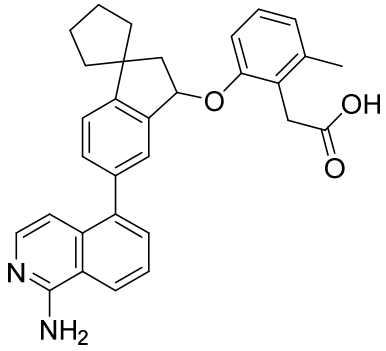
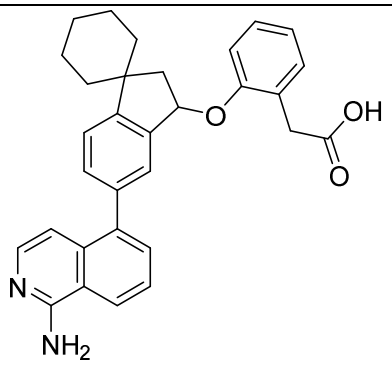
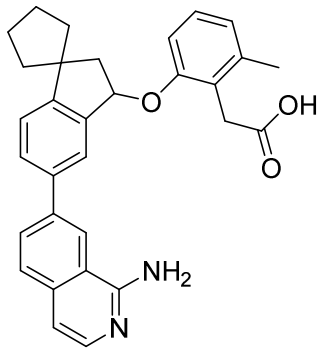
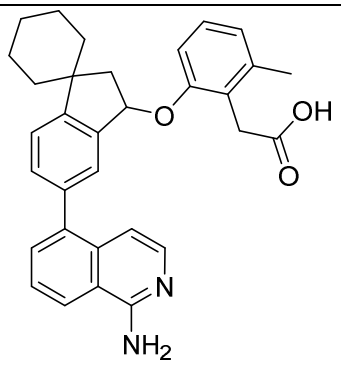
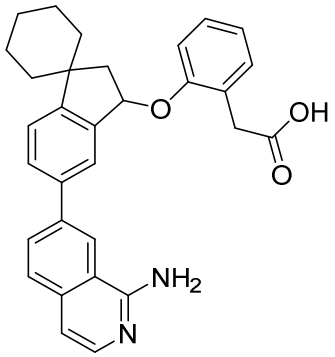
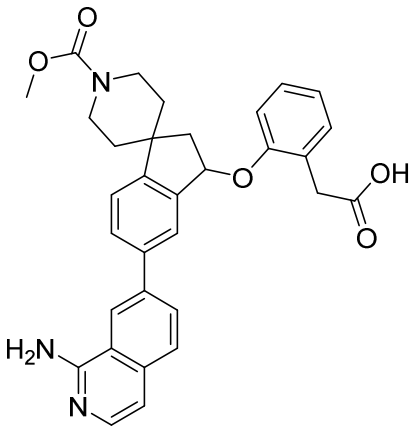
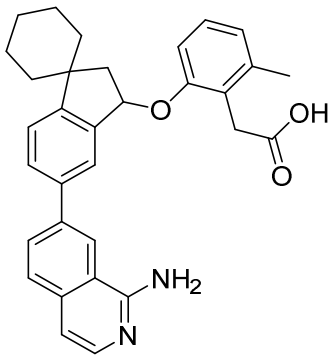
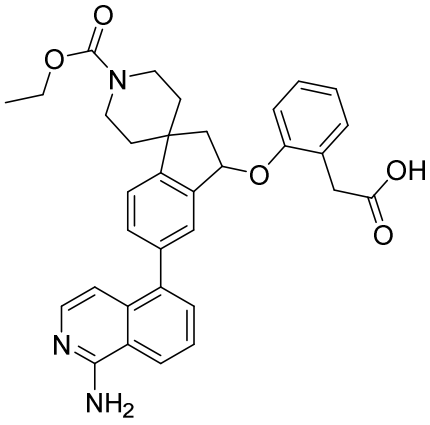
112. The compound of claim 83, selected from the following table:

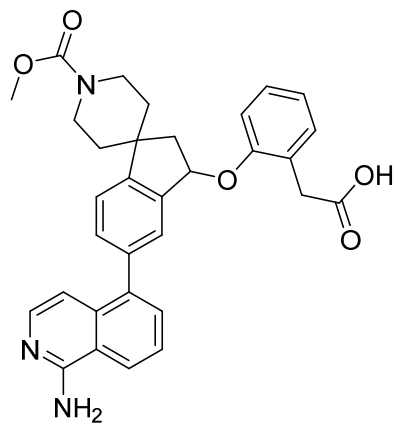
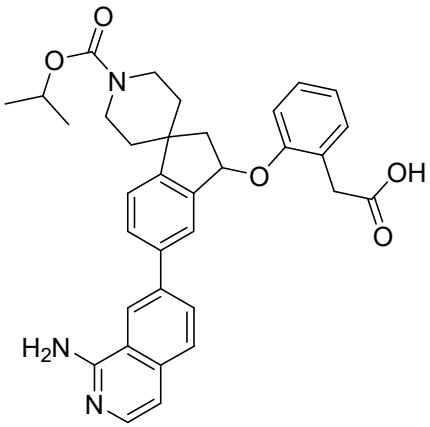
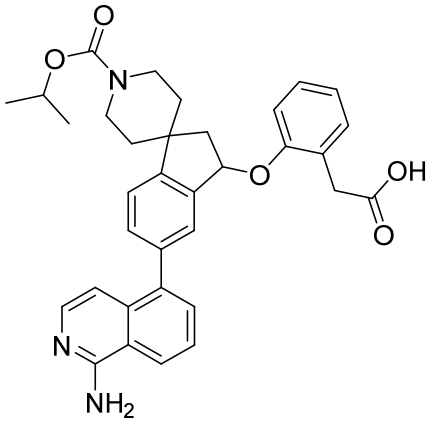
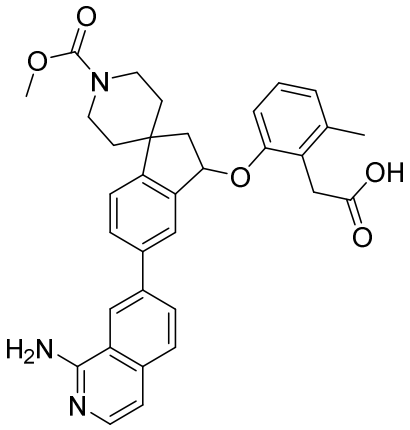
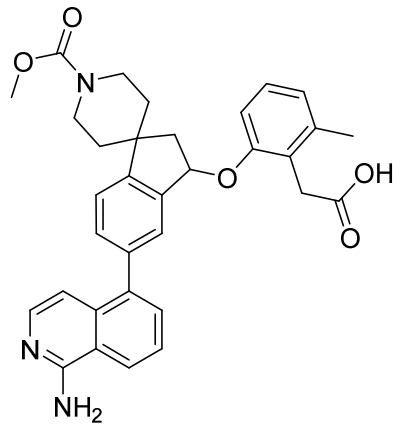
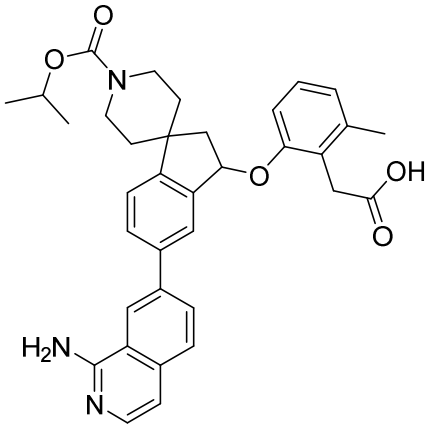
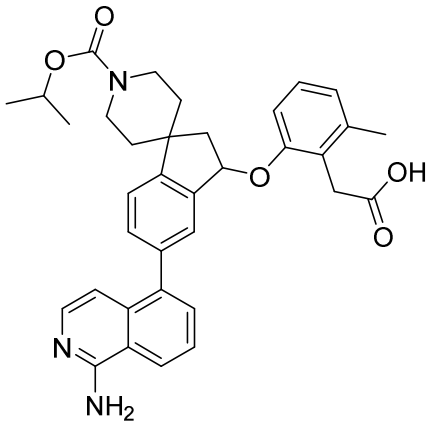
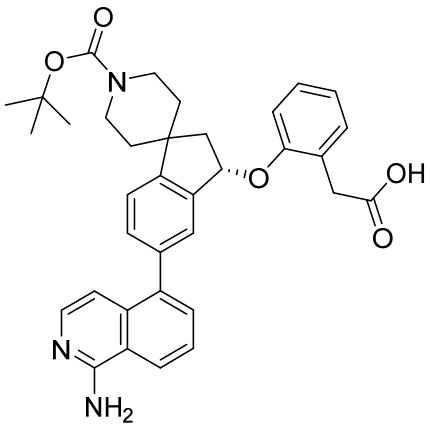
	
	
	

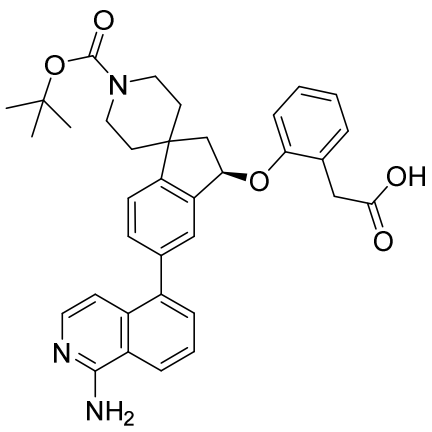
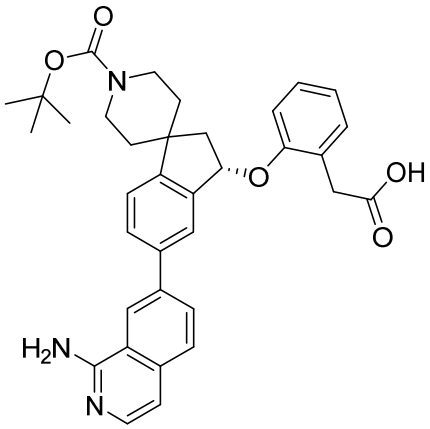
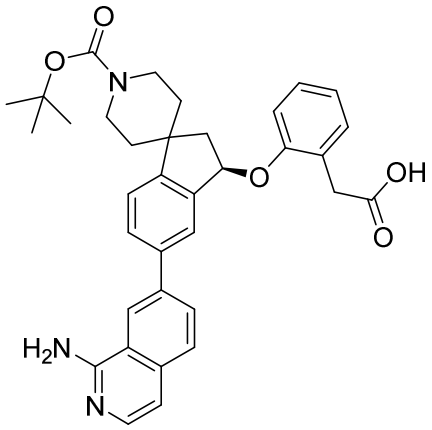
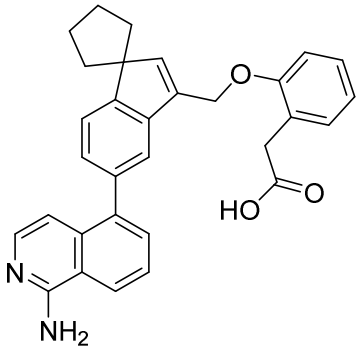
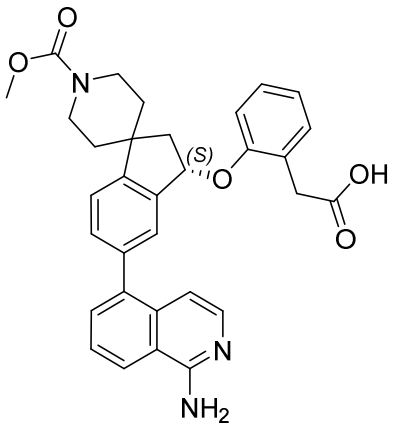
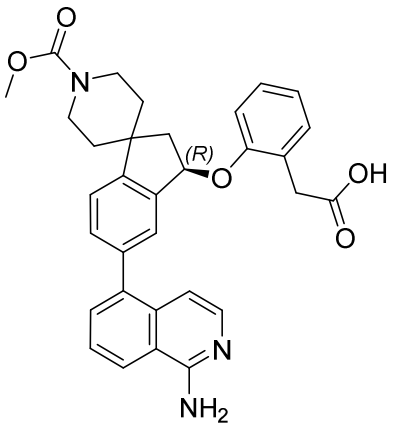
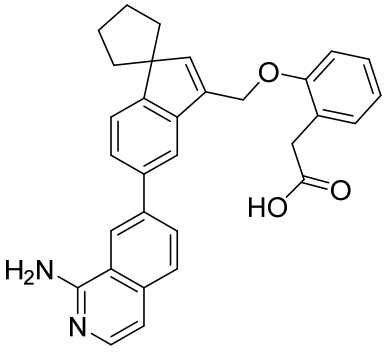
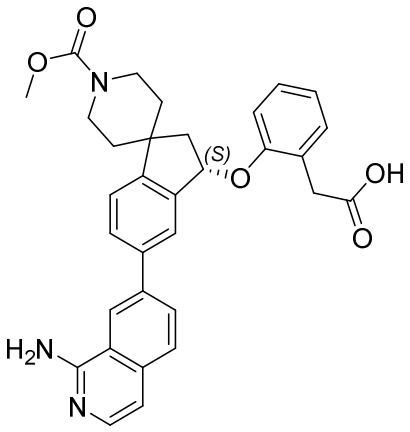
	
	
	
	

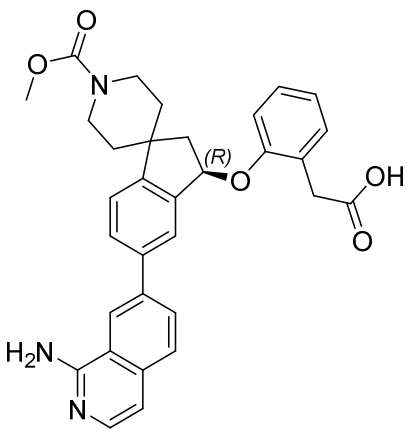
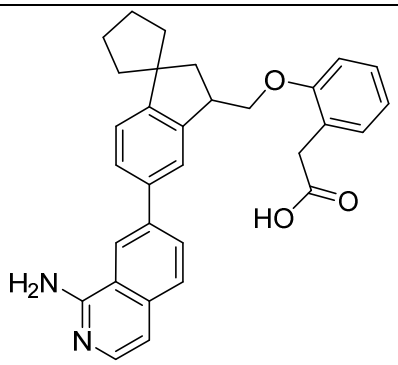
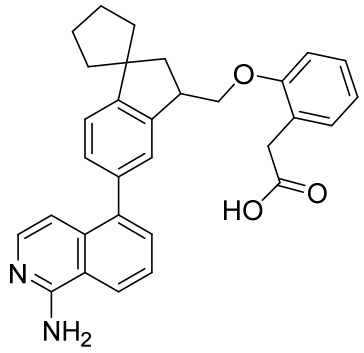
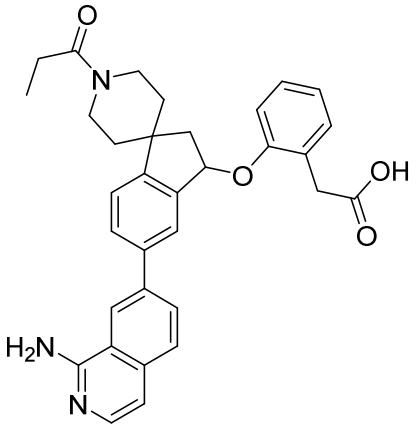
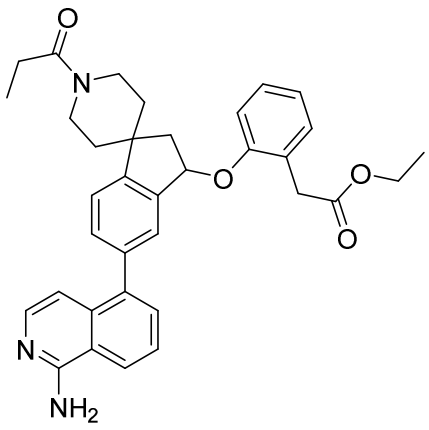
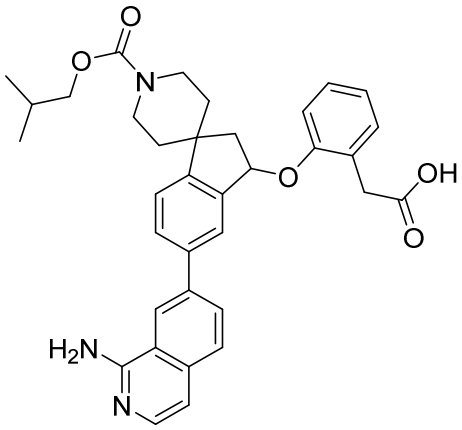
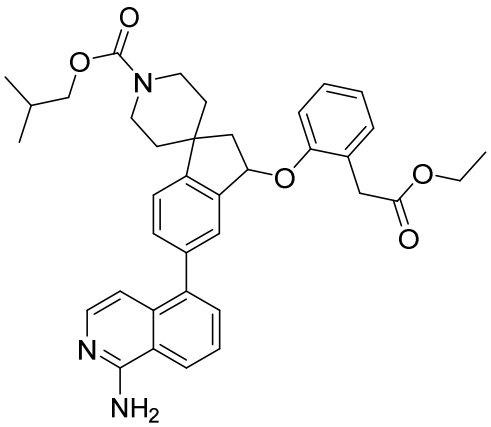
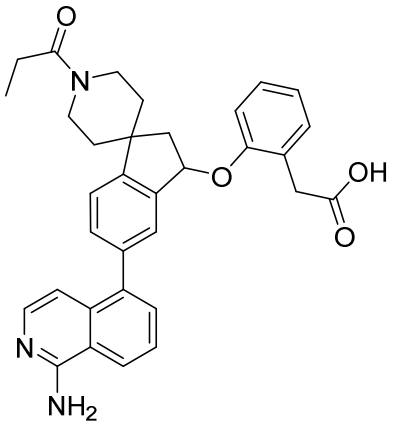
	
	
	
	

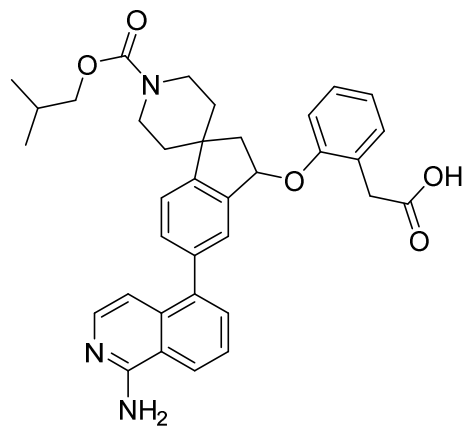
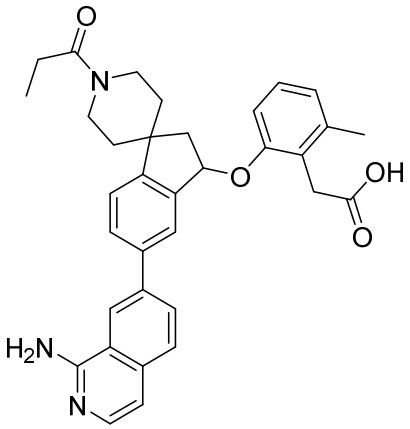
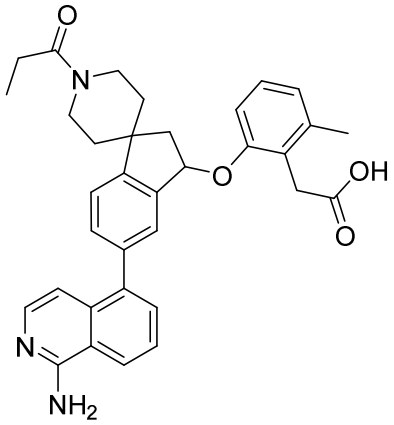
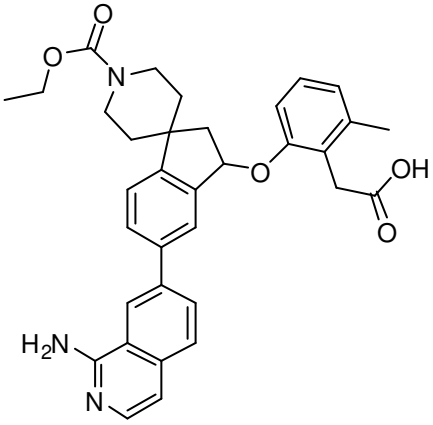
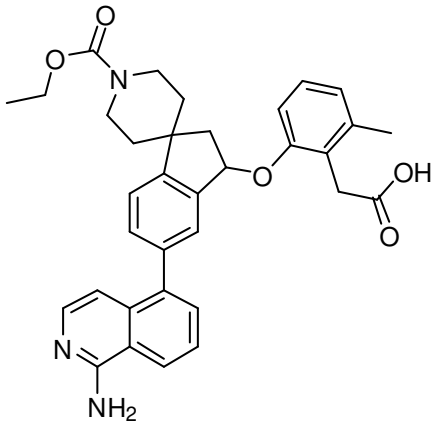
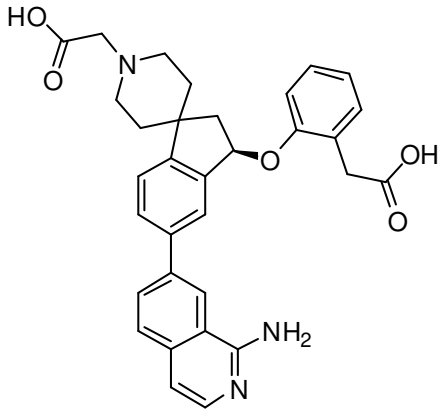
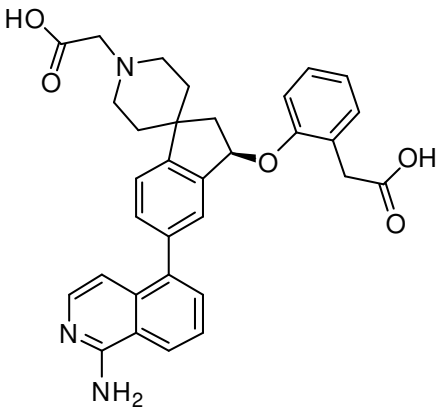
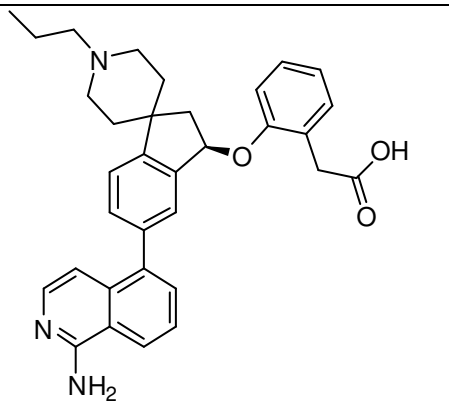
	
	
	
	

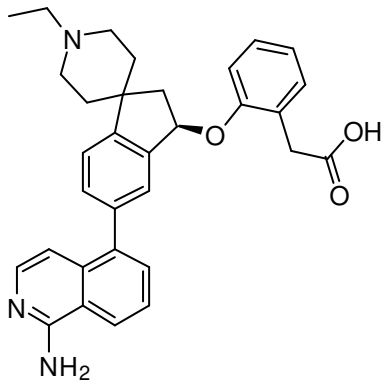
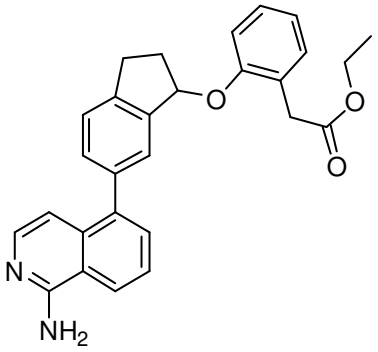
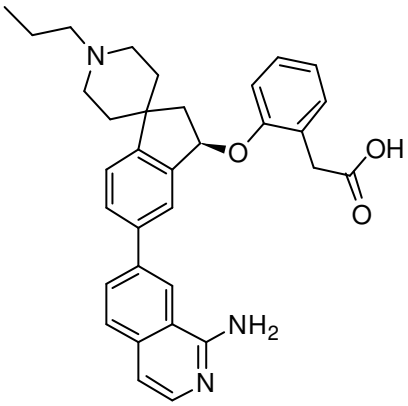
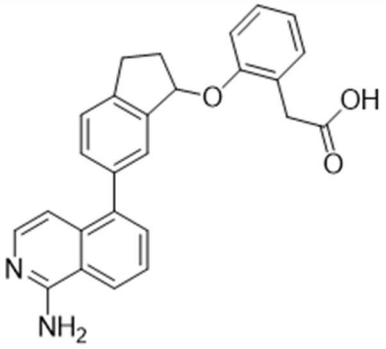
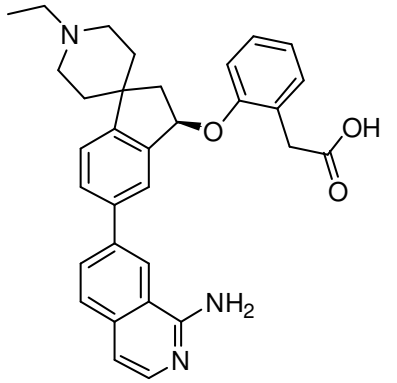
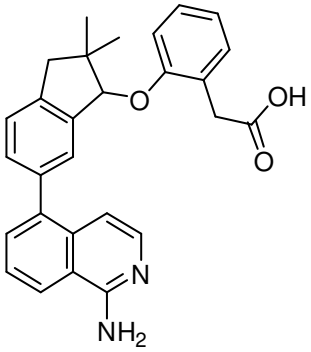
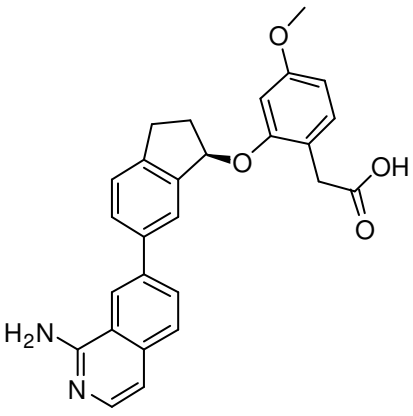
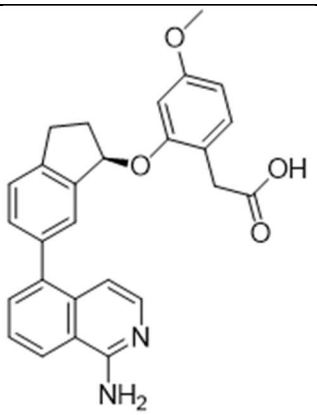
	
	
	
	

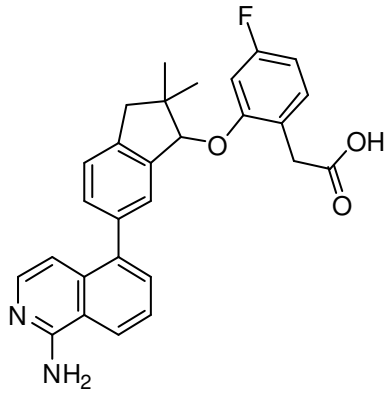
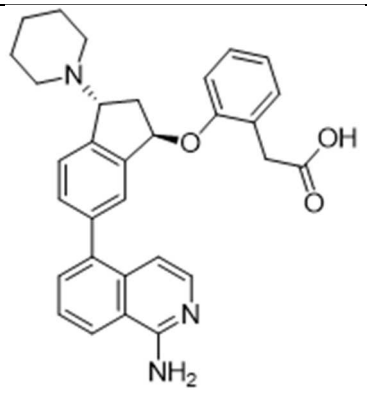
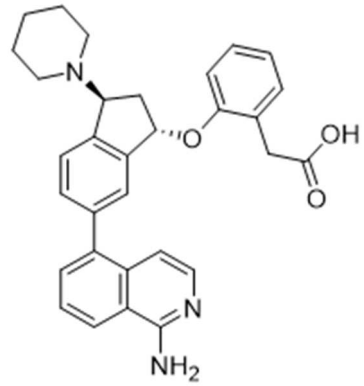
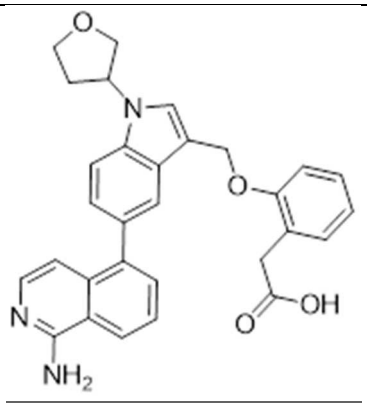
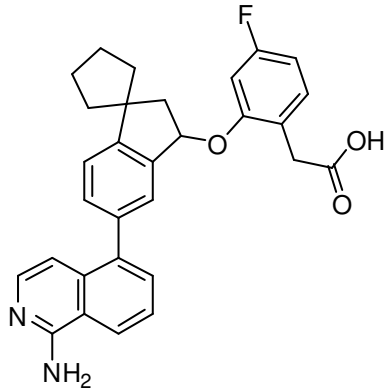
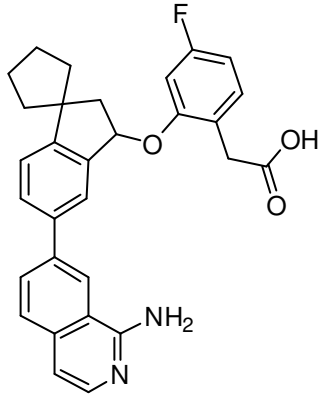
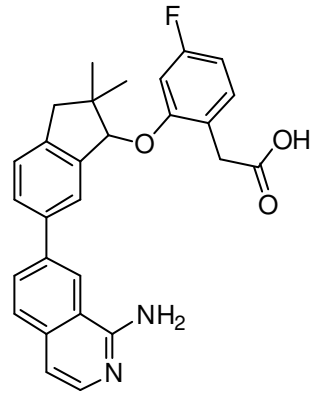
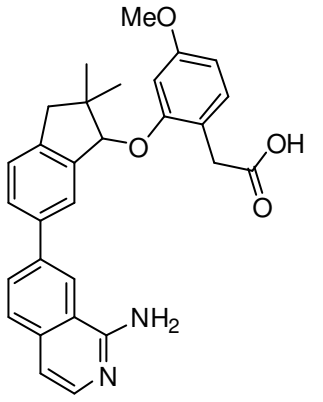
	
	
	
	

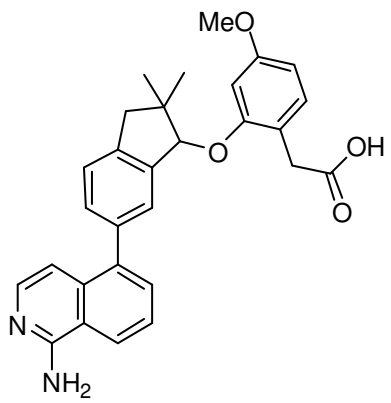
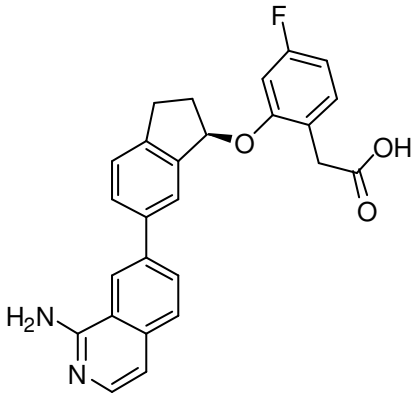
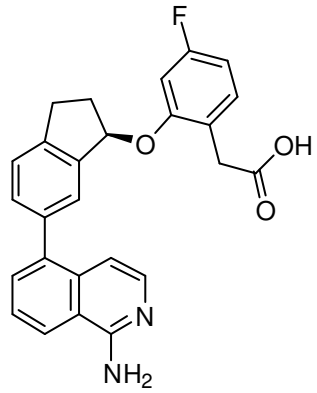
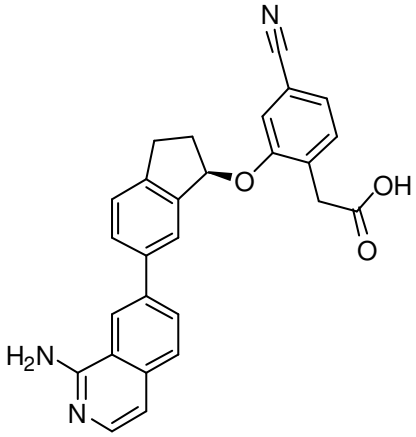
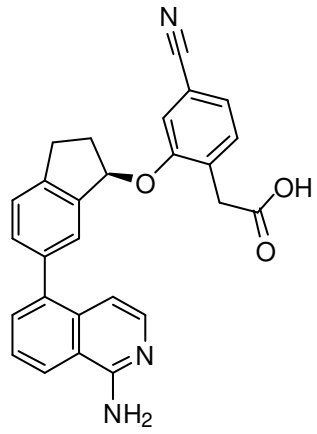
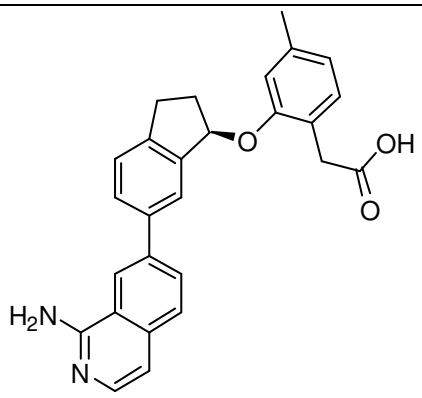
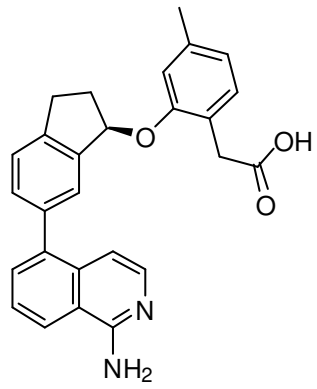
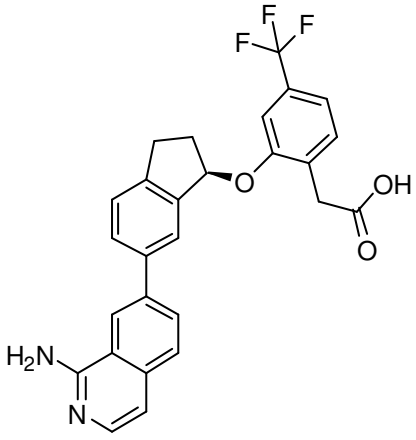
	
	
	
	

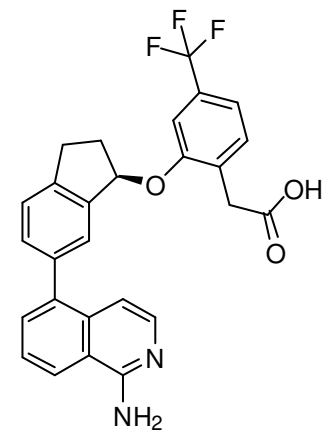
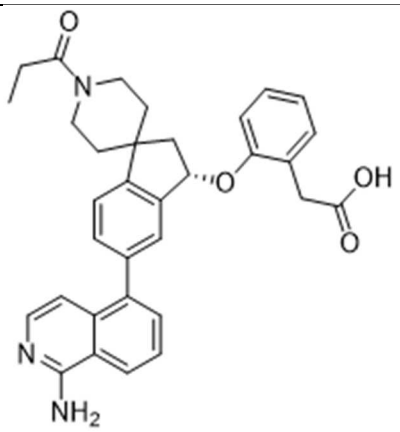
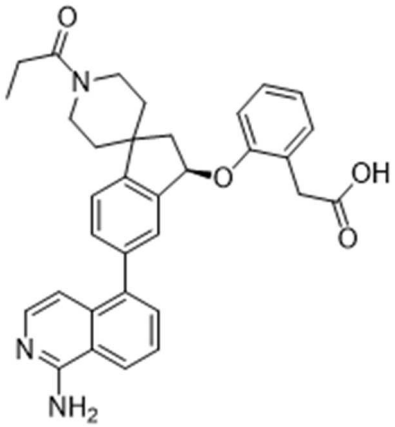
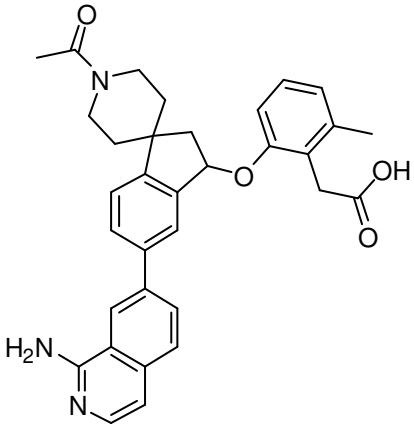
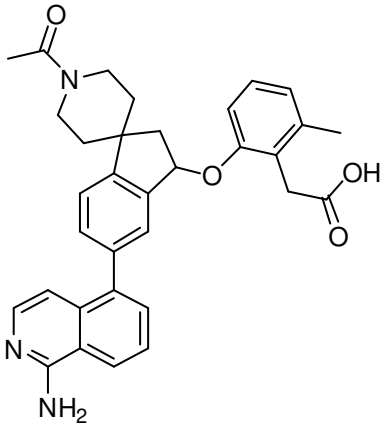
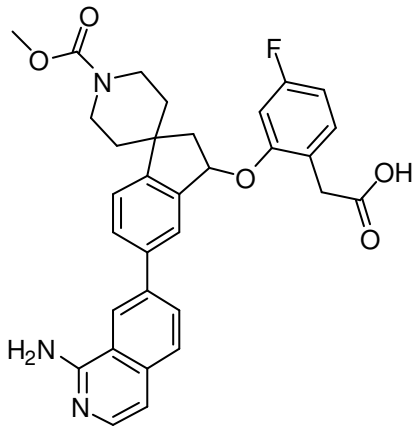
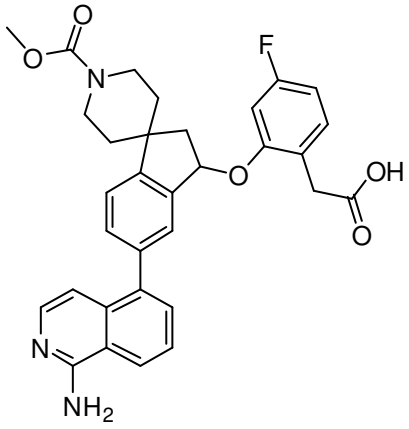
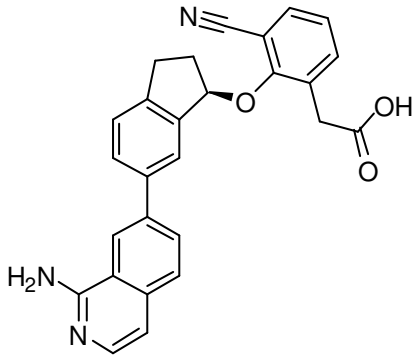
	
	
	
	

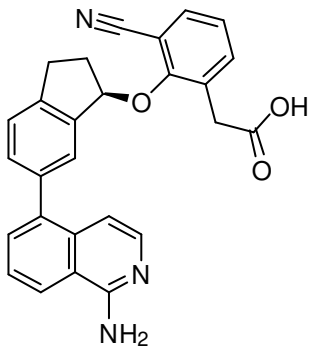
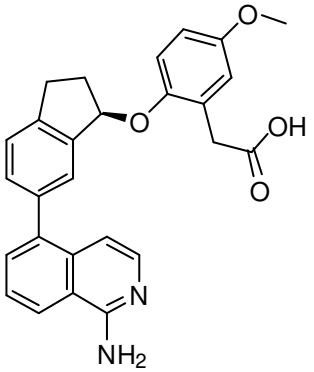
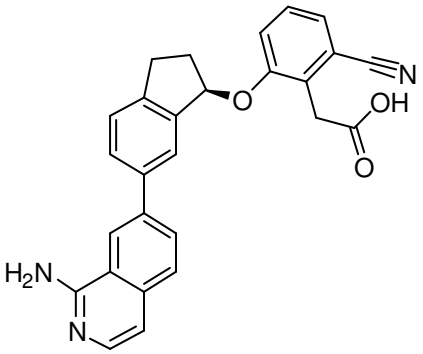
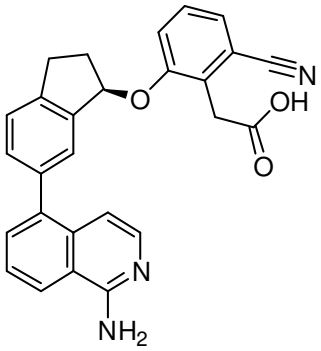
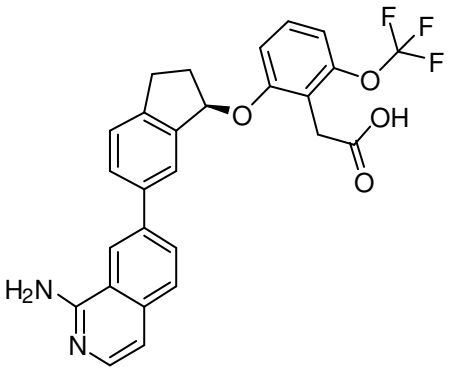
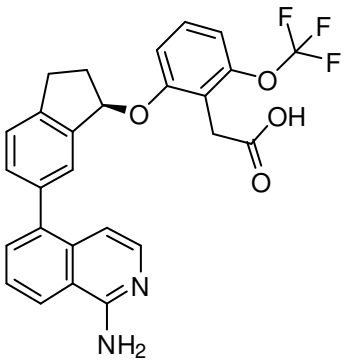
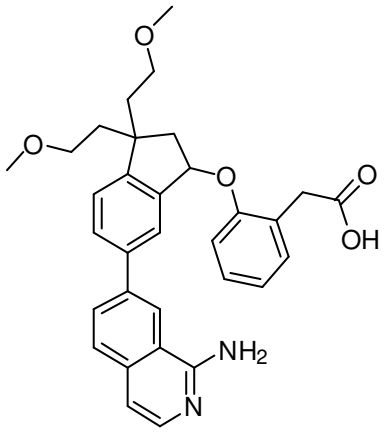
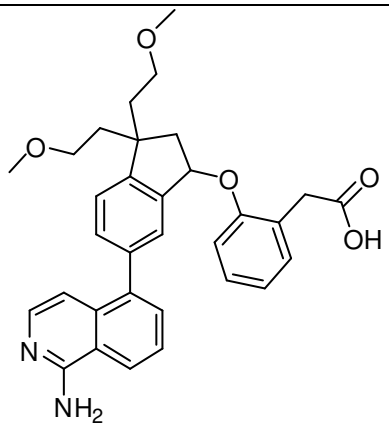
	
	
	
	

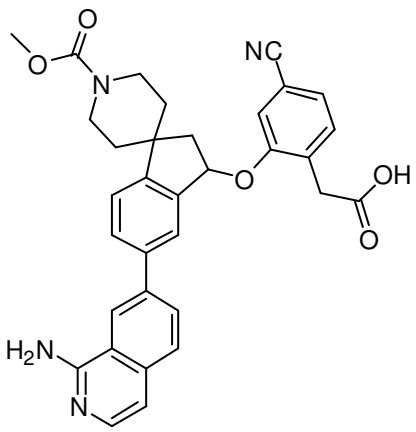
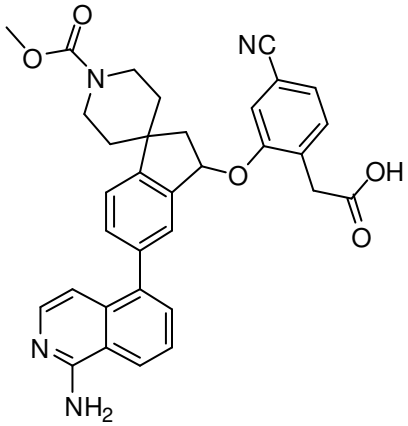
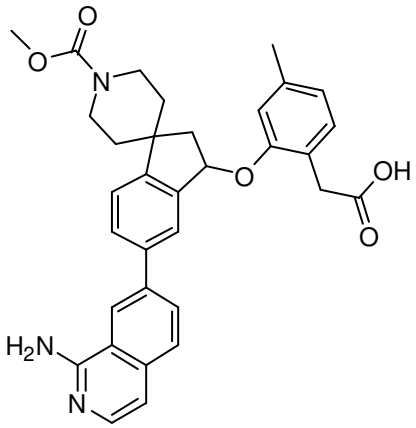
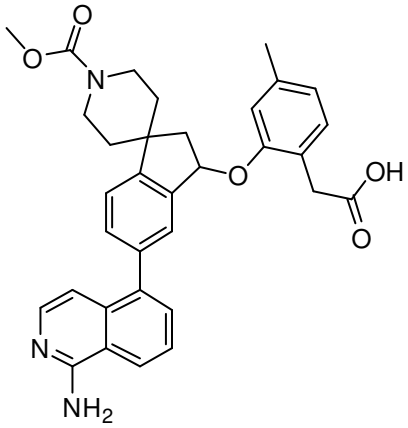
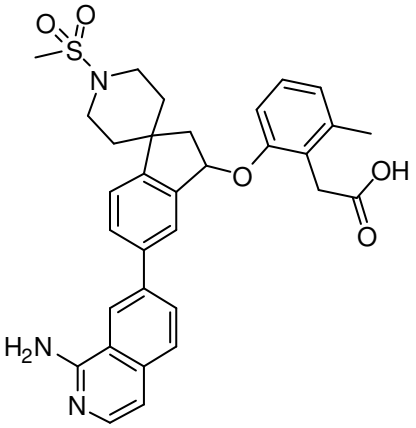
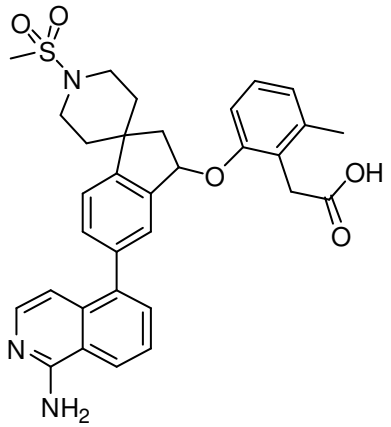
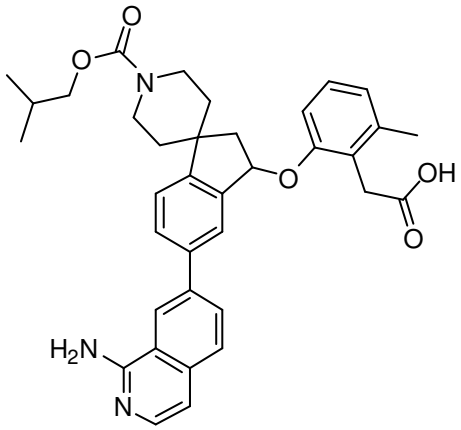
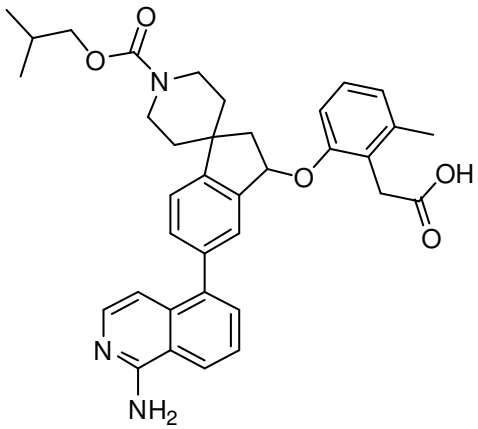
	
	
	
	

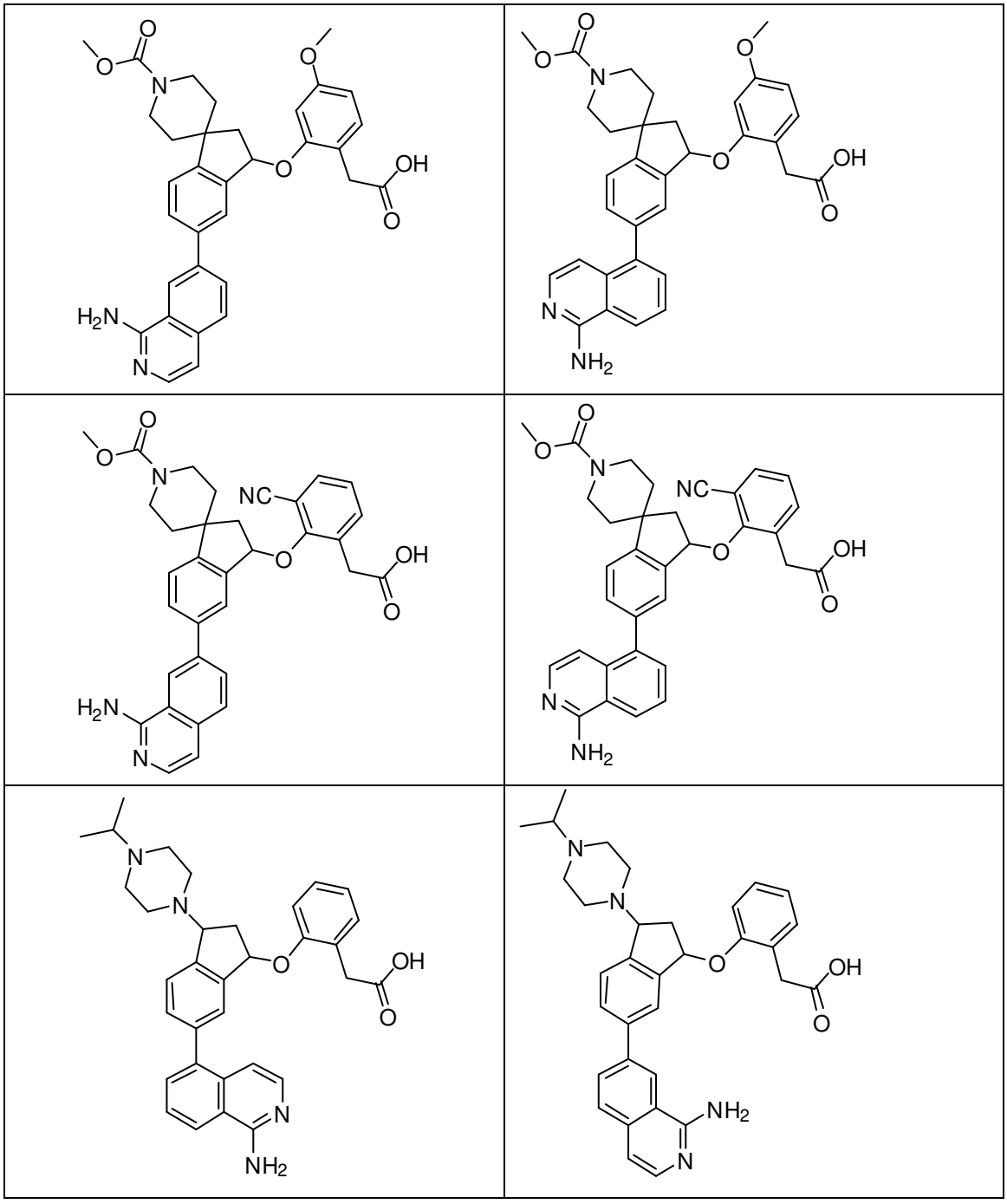
	
	
	
	

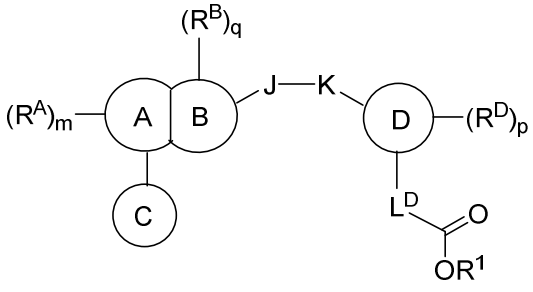
	
	
	
	



.

113. A compound of formula (IV), or a pharmaceutically acceptable salt thereof:



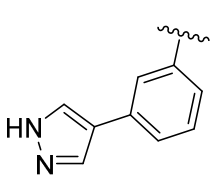
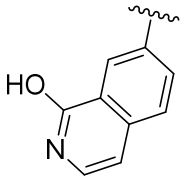
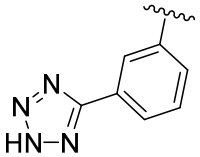
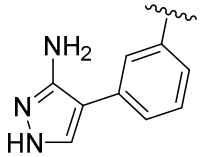
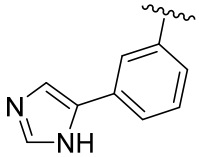
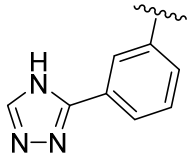
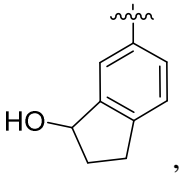
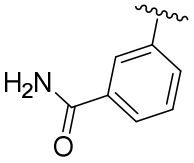
(IV);

wherein:

ring A is arylene or heteroarylene;

ring B is arylene or heteroarylene;

ring A is fused to ring B at two and only two adjacent positions;

ring C is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ;

ring D is aryl or heteroaryl;

J represents –CH_2–, –NH–, –CH_2CH_2–, –C(O)–, –C≡C–, –O–, –S–, –S(O)–, –SO_2–, –N(alkyl)–, –CH(alkyl)–, –CH(aryl)–, –$C(alkyl)_2$–, –CH(cycloalkyl)–, or  ;

K represents a bond, –O–, –NH–, –C(O)–, –CH_2–, –S–, –S(O)–, –SO_2–, –N(alkyl)–, –CH(alkyl)–, or –CH(cycloalkyl)–;

wherein at least one of J and K is a bond, –C(O)–, –CH_2–, –CH_2CH_2–, –CH(alkyl)–, or –CH(aryl)–;

L^D represents $–CH_2–$, $–CH_2CH_2–$, $–CF_2–$, –CH(F)–, $–CD_2–$, –CH(D)–, –CH(OH)–, –CH(alkyl)–, –CH(cycloalkyl)–, $–CHNH_2–$, –CH(NH(alkyl))–, –CH(NH(cycloalkyl))–, or a bond;

R^A, independently for each occurrence, represents H, halo, hydroxyl, cyano, amino, alkyl, optionally substituted alkoxy, hydroxyalkyl, optionally substituted aryloxy, (aryloxy)alkyl, (cycloalkyl)alkoxy, (heterocycloalkyl)alkoxy, optionally substituted (heteroaryl)alkoxy, haloalkyl, haloalkoxy, (hydroxy)haloalkyl, alkoxyalkyl, optionally substituted aminoalkyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted (cycloalkyl)alkenyl, optionally substituted heterocycloalkyl, optionally substituted (heterocycloalkyl)alkyl, –C(O)OH, $–C(O)NH_2–$, $–C(O)N(alkyl)_2–$, $–CH_2C(O)OH$, $–NO_2$, $–CH_2NH$(optionally substituted alkyl), $–CH_2NH$(Boc), $–CH_2N$(Boc)(optionally substituted alkyl), $–CH_2NH$((cycloalkyl)alkyl), $–CH_2N$(alkyl)(cycloalkyl), $–CH_2N$(alkyl)((cycloalkyl)alkyl), –NH(optionally substituted alkyl), –NH(cycloalkyl), –NH((cycloalkyl)alkyl), –NH((heterocycloalkyl)alkyl), $–N(alkyl)_2$, –N(alkyl)((cycloalkyl)alkyl, –N(alkyl)((heterocycloalkyl)alkyl, –NH(heteroarylalkyl), $–CH_2O$(optionally substituted aryl), –C(O)O(alkyl), –C(O)NH(optionally substituted alkyl), –C(O)NH((cycloalkyl)alkyl), –NHC(O)O(alkyl), or $–CH_2N(alkyl)_2$;

R^B, independently for each occurrence, represents H, oxo, –C(O)O(alkyl), halogen, cyano, amino, –C(O)OH, $–CH_2C(O)OH$, $–C(O)NH_2$, –C(O)NH(cycloalkyl), –C(O)NH(alkyl), –C(O)NH(aryl), -C(O)NH(heteroaryl), –C(O)(alkyl), $-S(O)_2$alkyl, alkylaminoalkyl, alkylaminocycloalkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, (hydroxy)haloalkyl, or tosyl, or is optionally substituted alkyl, aryl, heteroaryl, cycloalkyl, spirocycloalkyl, halocycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, spiroheterocycloalkyl, or (heterocycloalkyl)alkyl; or two geminal occurrences of R^B taken together with the atom to which they are attached form an optionally substituted spirocycloalkyl or a spiroheterocycloalkyl;

R^D, independently for each occurrence, represents H, halo, hydroxyl, cyano, $–NH_2$, -NH(Ac), -NH(alkyl), $-N(alkyl)_2$, -NH(CO)(alkyl), $–CH_2NH_2$, $-CH_2NHC(O)$(alkyl), $–C(O)NH_2$, –C(O)OH, or –NHC(O)O(alkyl), or is

optionally substituted alkyl, alkoxy, cycloalkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, haloalkoxy, or haloalkyl;

R^1 represents H or optionally substituted alkyl; and

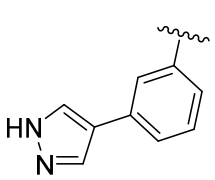
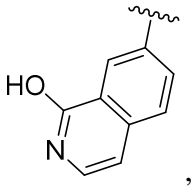
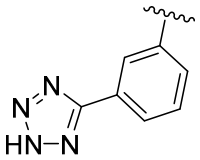
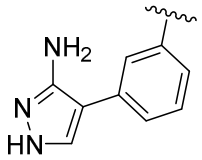
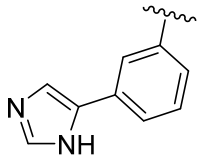
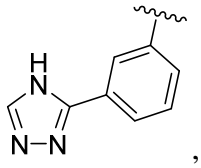
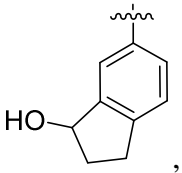
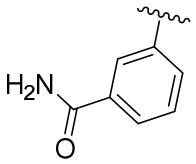
m, p, and q are each independently 0, 1, or 2.

114. The compound of claim 113, wherein:

ring A is arylene;

ring B is heteroarylene;

ring A is fused to ring B at two and only two adjacent positions;

ring C is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ;

ring D is aryl;

J represents $–CH_2–$;

K represents a bond or –O–;

L^D represents $–CH_2–$;

R^A represents H;

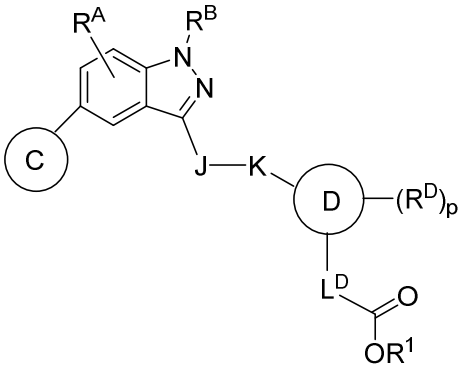
R^B, independently for each occurrence, represents H, oxo, or alkyl;

R^D represents H;

R^1 represents H; and

m, p, and q are each independently 0, 1, or 2.

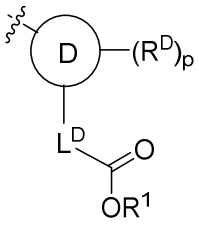
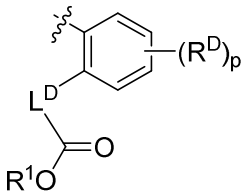
115. The compound of claim 113 or 114, having the structure of formula (IVa):



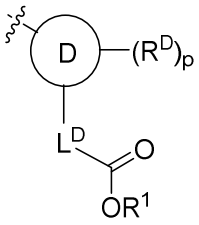
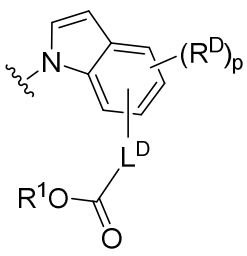
(IVa).

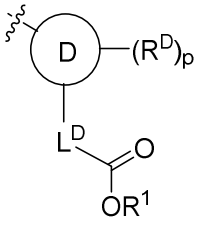
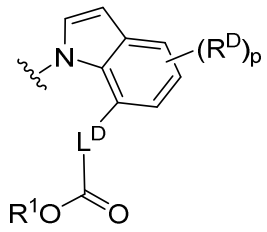
116. The compound of any one of claims 113 or 115, wherein J represents –CH_2–, –NH–, –CH_2CH_2–, –C(O)–, –O–, –S–, –S(O)–, –SO_2–, –N(alkyl)–, –CH(alkyl)–, –CH(aryl)–, –$C(alkyl)_2$–, –CH(cycloalkyl)–, or  .

117. The compound of any one of claims 113-116, wherein –J–K– represents –CH_2-O– or – CH_2–.

118. The compound of any one of claims 113-117, wherein  represents  .

119. The compound of claim 113, wherein ring  is bicyclic heteroaryl.

120. The compound of claim 119, wherein  represents  .

121. The compound of claim 119, wherein  represents  .

122. The compound of any one of claims 113-121, wherein R^1 is H.

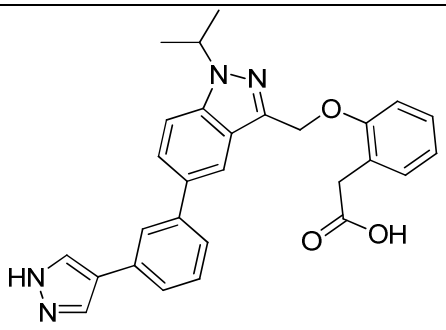
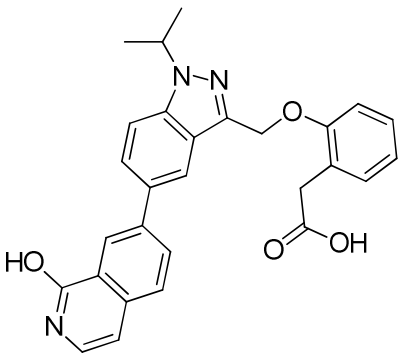
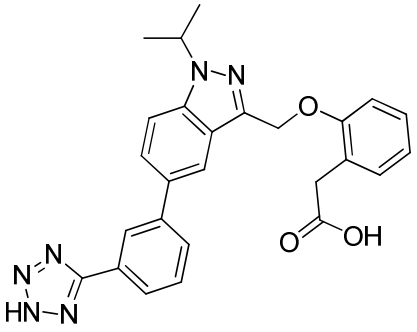
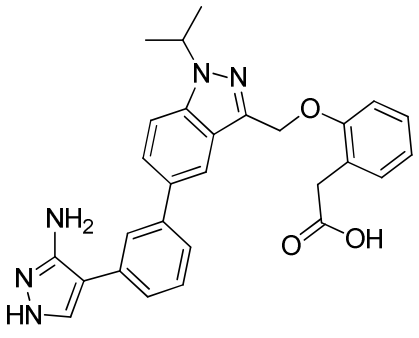
123. The compound of any one of claims 113-122, wherein L^D represents $–CH_2–$.

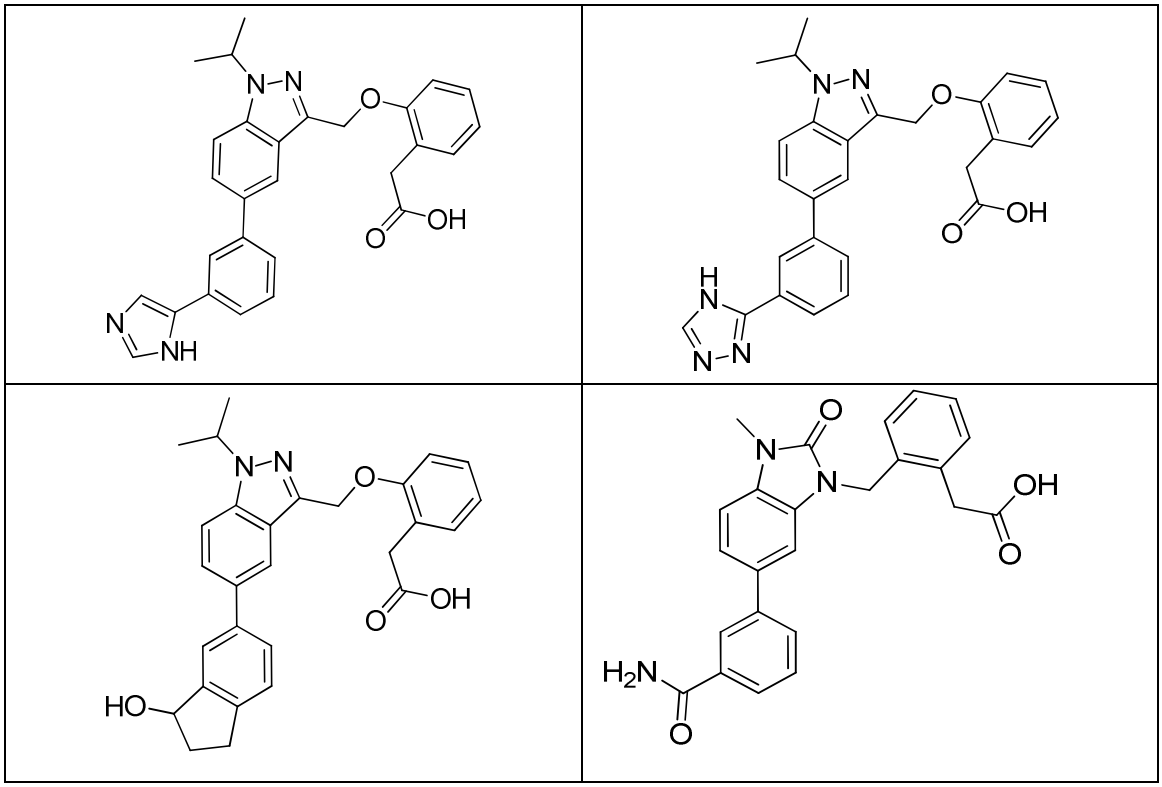
124. The compound of any one of claims 113-123, wherein R^D represents H.

125. The compound of any one of claims 113-124, wherein R^B, independently for each occurrence, represents H, oxo, or alkyl.

126. The compound of any one of claims 113-125, wherein R^A represents H.

127. The compound of claim 113, selected from the following table:



.

128. A pharmaceutical composition, comprising a compound of any one of claims 1-127, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

129. Use of a therapeutically effective amount of a compound of any one of claims 1-127, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease or condition characterized by aberrant kallikrein activity in a subject in need thereof.

130. The use of claim 129, wherein the disease or condition is characterized by aberrant kallikrein-related peptidase 5 (KLK5) activity.

131. The use of claim 129 or 130, wherein the disease or condition is a skin disease.

132. The use of any one of claims 129-131, wherein the disease or condition is Netherton Syndrome.

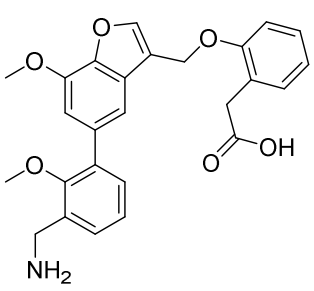
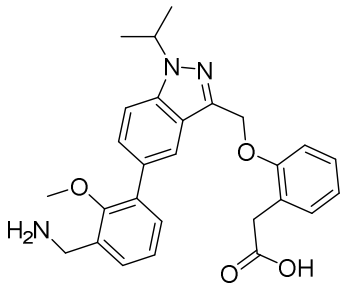
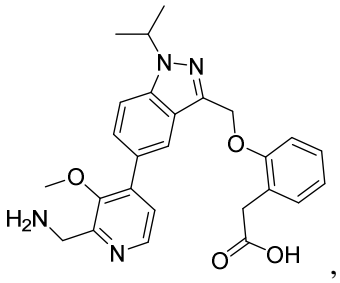
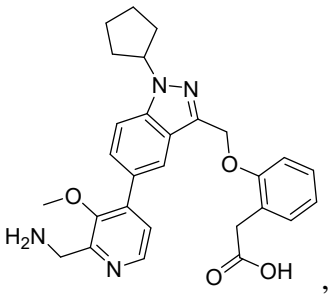
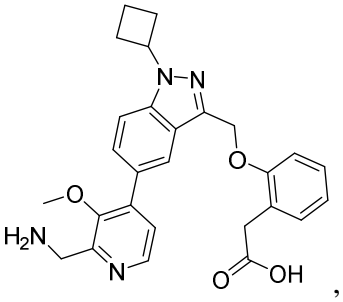
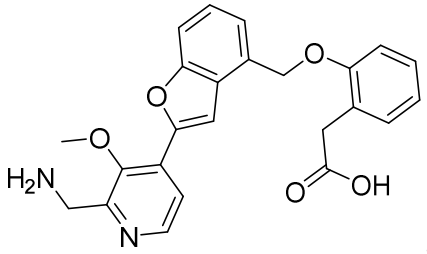
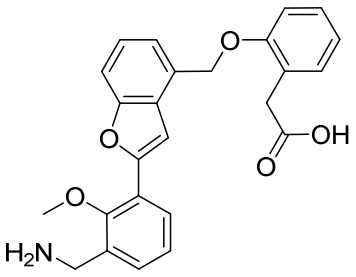
133. The use of claim 131, wherein the skin disease is eczema, atopic eczema, atopic dermatitis, ichthyosiform (scaly) erythroderma (IE), rosacea, or a skin infection.

134. The use of claim 129 or 130, wherein the disease or condition is selected from the group consisting of hypersensitivity of the immune system (atopy), hyper IgE syndrome, allergies (including allergies to food and airborne agents), asthma, allergic asthma, chronic inflammation, rhinitis, conjunctivitis, angioedema, eosinophilia, eosinophilic esophagitis, growth delay, failure to thrive, trichorrhexis invaginata (TI), respiratory tract infections, systemic infections, and gastrointestinal disorders.

135. The use of claim 129 or 130, wherein the disease or condition is cancer.

136. The use of claim 135, wherein the cancer is selected from the group consisting of ovarian cancer, breast cancer, prostate cancer, bladder cancer, cervical cancer, glioblastoma multiforme, and neuroblastoma.

137. Use of a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease or condition characterized by aberrant kallikrein activity in a subject in need thereof; wherein the compound is selected from the group consisting of:


,

,

,

,

,

, and

.

138. The use of claim 137, wherein the disease or condition is characterized by aberrant kallikrein-related peptidase 5 (KLK5) activity.

139. The use of claim 137 or 138, wherein the disease or condition is a skin disease.

140. The use of any one of claims 137-139, wherein the disease or condition is Netherton Syndrome.

141. The use of claim 139, wherein the skin disease is eczema, atopic eczema, atopic dermatitis, ichthyosiform (scaly) erythroderma (IE), rosacea, or a skin infection.

142. The use of claim 137 or 138, wherein the disease or condition is selected from the group consisting of rhinitis, conjunctivitis, angioedema, eosinophilia, eosinophilic esophagitis, growth delay, failure to thrive, trichorrhexis invaginata (TI), respiratory tract infections, systemic infections and gastrointestinal disorders.

143. The use of claim 137 or 138, wherein the disease or condition is selected from the group consisting of hypersensitivity of the immune system (atopy), hyper IgE syndrome, allergies (including allergies to food and airborne agents), asthma, allergic asthma, and chronic inflammation.

144. The use of claim 137 or 138, wherein the disease or condition is cancer.

145. The use of claim 144, wherein the cancer is selected from the group consisting of ovarian cancer, breast cancer, prostate cancer, bladder cancer, cervical cancer, glioblastoma multiforme, and neuroblastoma.

146. A compound of any one of claims 1-127, or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease or condition characterized by aberrant kallikrein activity in a subject in need thereof.