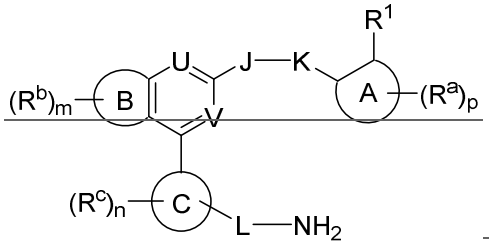
CLAIMS

What is claimed is:

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



(I);

wherein:

ring A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring B is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

ring C is aryl or heteroaryl;

R^a, independently for each occurrence, is halogen, cyano, hydroxy, $-NH_2$, -NH(Ac), -NH(alkyl), -NH(cycloalkyl), -NH(heterocycloalkyl), -NH(aryl), -NH(heteroaryl), $-N(alkyl)_2$, -NHC(O)(alkyl), $-CH(alkyl)NH_2$, $-CH(hydroxyalkyl)NH_2$, $-CH(haloalkyl)NH_2$, $-CH(cycloalkyl)NH_2$, $-CH(heterocycloalkyl)NH_2$, $-CH(aryl)NH_2$, $-CH(heteroaryl)NH_2$, $-CH_2NHC(O)(alkyl)$, $-C(O)NH_2$, -C(O)(alkyl), $-SO_2NH_2$, $-SO_2(cycloalkyl)$, $-SO_2(heterocycloalkyl)$, $-SO_2(alkyl)$, $-SO_2(aryl)$, or $-SO_2(heteroaryl)$; or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

R^b, independently for each occurrence, is halogen, cyano, $-CH_2(OCH_2CH_2)_qOCH_3$, -alkylene-(branched or unbranched polyethylene glycol), -alkylene-O-(branched or unbranched polyethylene glycol), or $-NR^jR^k$; or is selected from the group consisting of substituted or unsubstituted alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl,

(heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, (heteroarylalkoxy)alkyl, (arylalkoxy)alkyl, (aryloxy)alkyl, ((cycloalkyl)alkoxy)alkyl, ((heterocycloalkyl)alkoxy)alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkylene-NR^jR^k, tosyl, SO_2(alkyl), SO_2(cycloalkyl), CO(alkyl), CO(aryl), CO(heteroaryl), CO(cycloalkyl), CO(heterocycloalkyl), CONH(alkyl), CONH(arylalkyl), -CONH(heteroarylalkyl), -$CON(alkyl)_2$, -CONH(heterocycloalkyl), and CONH(cycloalkyl);

R^e, independently for each occurrence, is selected from the group consisting of halogen, OH, NR^jR^k, alkoxy, alkyl, cycloalkyl, and heterocycloalkyl;

R^L is selected from the group consisting of NH_2, COOH, CH_2COOH, -CH(NH(CO)(alkyl))COOH, -CH(NH(CO)(arylalkyl))COOH, CH(NH(CO)(cycloalkyl))COOH, CH(NH(CO)(aryl substituted cycloalkyl))COOH, CH(NH(CO)(heteroaryl substituted cycloalkyl))COOH, CH(S(alkyl))COOH, -CO(NH)CH_2(substituted or unsubstituted aryl), -CO(NH)CH_2(substituted or unsubstituted heteroaryl), -CO(NH)(substituted or unsubstituted aryl), CO(NH)(substituted or unsubstituted heteroaryl), and -CH_2(tetrazolyl);

n is 0, 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

q is an integer from 1-20;

J is C(O), NH, CH_2, O, S, S(O), SO_2, N(alkyl), CH(alkyl), CH(cycloalkyl), -N((C(O)O)arylalkyl), -N((C(O)O)heteroarylalkyl), or -N(C(O)arylalkyl);

K is C(O), NH, CH_2, O, S, S(O), SO_2, N(alkyl), CH(alkyl), CH(cycloalkyl), -N((C(O)O)arylalkyl), -N((C(O)O)heteroarylalkyl), or -N(C(O)arylalkyl);

wherein at least one of J and K is C(O), CH_2, or CH(alkyl);

L is selected from the group consisting of a bond, CH_2, CH_2CH_2, CHR^2, CF_2, CFR^2, C(O), $C(=NR^L)$, $C(=CHR^L)$, $S(O)_2$, and S(O);

wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^e taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, cycloalkyl, hydroxyalkyl, or haloalkyl;

R^j and R^k are each independently H or are selected from the group consisting of substituted or unsubstituted alkyl, aminoalkyl, (heterocycloalkyl)alkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -CO(aryl), -CO(arylalkyl), -CO(heteroarylalkyl), and -CO((heterocycloalkyl)alkyl);

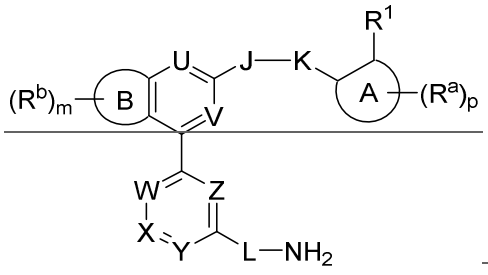
U is N or CR^3;

R^3 is H, halogen, alkyl, cycloalkyl, aryl, heteroaryl, alkoxy, haloalkyl, -CN, $-CONH_2$, $-CO_2H$, $-CH_2CO_2H$, $-NH_2$, hydroxyalkyl, aminoalkyl, -OH, -NH(alkyl), $-N(alkyl)_2$, thioalkyl, or -S(alkyl);

V is N, CH, C(halogen), or C(alkyl); and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

2. The compound of formula (I), having the structure of formula (Ia):



(Ia);

wherein:

W is N, CH, or CR^e;

X is N, CH, or CR^e;

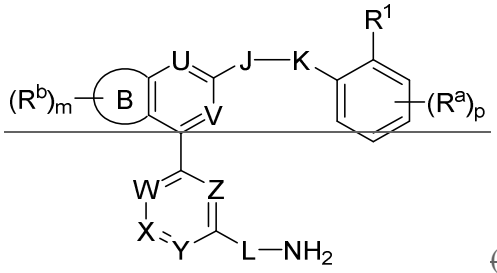
Y is N, CH, or CR^e; and

Z is N, CH, or CR^e.

3. The compound of claim 1 or 2, wherein ring A is napthyl, indenyl, cyclopentyl, pyrrolidinyl, phenyl, benzofuranyl, thiophenyl, or pyridinyl.

4. The compound of claim 3, wherein ring A is phenyl, thiophenyl, or pyridinyl.

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



(Ib).

6. The compound of any one of claims 1-5, wherein p is 1.

7. The compound of claim 6, wherein R^a is halogen, cyano, hydroxy, NH_2, NH(Ac), NH(alkyl), $N(alkyl)_2$, NHC(O)(alkyl), $CH_2NHC(O)(alkyl)$, $C(O)NH_2$, or C(O)(alkyl); or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl.

8. The compound of claim 6, wherein R^a is halogen, cyano, NH_2, NH(Ac), $C(O)CH_3$, $C(O)NH_2$, or hydroxymethyl; or substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, or aminoalkyl.

9. The compound of claim 6, wherein R^a is halogen, NH(Ac), or $C(O)CH_3$; or substituted or unsubstituted aryl, heteroaryl, cycloalkyl, alkoxy, alkyl, or aminoalkyl.

10. The compound of claim 7, wherein R^a is alkyl, cycloalkyl, or halogen.

11. The compound of any one of claims 1-5, wherein p is 0.

12. The compound of any one of claims 1-11, wherein R^1 is CH_2COOH.

13. The compound of any one of claims 1-11, wherein R^1 is $CO(NH)CH_2$(substituted or unsubstituted aryl).

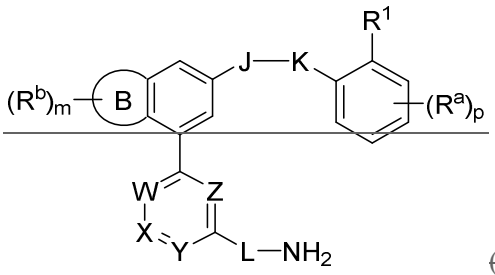
14. The compound of any one of claims 1-13, wherein J-K is selected from the group consisting of C(O)-NH, NH-C(O), and CH_2O.

15. The compound of any one of claims 1-14, wherein J-K is CH_2O.

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

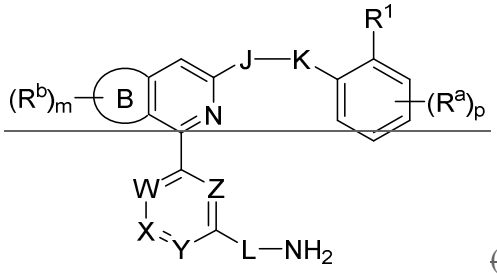
17. The compound of any one of claims 1-16, wherein V is CH.

18. The compound of any one of claims 1-15, having the structure of formula (Ic):



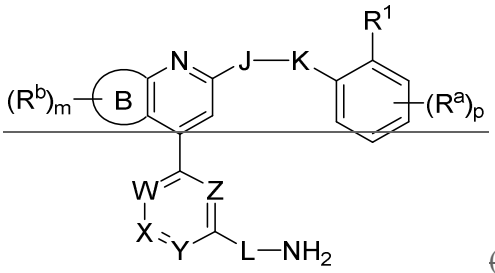
(Ic).

19. The compound of any one of claims 1-15, having the structure of formula (Id):



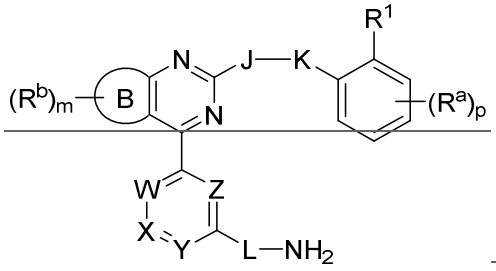
(Id).

20. The compound of any one of claims 1-15, having the structure of formula (Ie):



(Ie).

21. The compound of any one of claims 1-15, having the structure of formula (If):



(If).

22. The compound of any one of claims 1-21, wherein ring  is heteroaryl.

23. The compound of claim 22, wherein ring  is furyl, oxazolyl, isoxazolyl, thiophenyl, pyrrolyl, pyrazolyl, or imidazolyl.

24. The compound of claim 23, wherein ring  is furyl, thiophenyl, or pyrrolyl.

25. The compound of claim 24, wherein ring  is furyl.

26. The compound of any one of claims 1-25, wherein m is 0.

27. The compound of any one of claims 1-25, wherein m is 1.

28. The compound of claim 25, wherein R^b, independently for each occurrence, is halogen, cyano, $-CH_2(OCH_2CH_2)_qOCH_3$, or $-NR^jR^k$; or is selected from the group consisting of substituted or unsubstituted alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, (heteroarylalkoxy)alkyl, (arylalkoxy)alkyl, (aryloxy)alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkylene-NR^jR^k, tosyl, $-SO_2$(alkyl), $-SO_2$(cycloalkyl), -CO(alkyl), -CO(cycloalkyl), -CONH(alkyl), -CONH(arylalkyl), $-CON(alkyl)_2$, and -CONH(cycloalkyl).

29. The compound of claim 27, wherein R^b is halogen; or is selected from the group consisting of substituted or unsubstituted alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, and (cycloalkyl)alkyl.

30. The compound of claim 27, wherein R^b is substituted or unsubstituted -alkylene-NR^jR^k.

31. The compound of any one of claims 1-25, wherein m is 2.

32. The compound of claim 31, wherein each R^b is alkyl.

33. The compound of any one of claims 1-32, wherein each of W, X, Y, and Z is CH.

34. The compound of any one of claims 1-32, wherein at least one of W, X, Y, and Z is CR^e.

35. The compound of claim 34, wherein Z is CR^e.

36. The compound of claim 34 or 35, wherein Y is CR^e.

37. The compound of any one of claims 34-36, wherein R^e is selected from the group consisting of halogen, -OH, $-NR^jR^k$, alkoxy, and alkyl.

38. The compound of any one of claims 34-36, wherein R^e is halogen, e.g., fluoride.

39. The compound of any one of claims 1-32 and 34, wherein at least one of W, X, Y, and Z is N.

40. The compound of claim 39, wherein Z is N.

41. The compound of claim 39, wherein Y is N.

42. The compound of any one of claims 1-41, wherein L is $-CH_2-$.

43. The compound of claim 1, wherein:

ring  is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring  is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

ring  is aryl or heteroaryl;

R^a, independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, $-NH_2$, -NH(Ac), -NH(alkyl), $-N(alkyl)_2$, $-NHC(O)(alkyl)$, $-CH_2NHC(O)(alkyl)$, $-C(O)NH_2$, -C(O)(alkyl), optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

R^b, independently for each occurrence, is selected from the group consisting of halogen, cyano, $-NR^jR^k$, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -alkylene-NR^jR^k, tosyl, $-SO_2(alkyl)$, $-SO_2(cycloalkyl)$, -CO(alkyl), -CO(cycloalkyl), -CONH(alkyl), $-CON(alkyl)_2$, and -CONH(cycloalkyl);

R^c, independently for each occurrence, is selected from the group consisting of halogen, -OH, $-NR^jR^k$, alkoxy, and alkyl;

R^1 is selected from the group consisting of NH_2, CH_2COOH, $CH(NH(CO)(alkyl))COOH$, $CH(NH(CO)(arylalkyl))COOH$, $CH(NH(CO)(cycloalkyl))COOH$, $CH(NH(CO)(aryl\ substituted\ cycloalkyl))COOH$, $CO(NH)CH_2aryl$, $CO(NH)CH_2heteroaryl$, $CO(NH)aryl$, and $CO(NH)heteroaryl$;

n is 0, 1, or 2;

m is 0, 1, or 2;

p is 0, 1, or 2;

J is C(O), NH, CH_2, O, S, S(O), SO_2, N(alkyl), or CH(alkyl);

K is C(O), NH, O, CH_2, S, S(O), SO_2, N(alkyl), or CH(alkyl);

wherein at least one of J and K is C(O), CH_2, or CH(alkyl);

L is selected from the group consisting of a bond, CH_2, CH_2CH_2, CHR^2, CF_2, CFR^2, C(O), $C(=NR^L)$, and $C(=CHR^L)$;

wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^e taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, hydroxyalkyl, or haloalkyl;

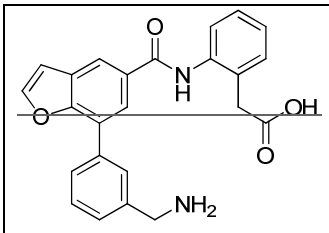
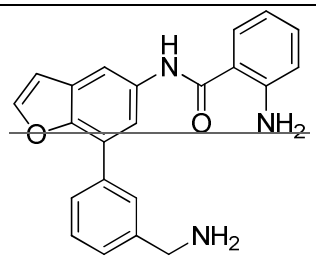
R^j and R^k are each independently selected from the group consisting of H, alkyl, aminoalkyl, (heterocycloalkyl)alkyl, and heterocycloalkyl;

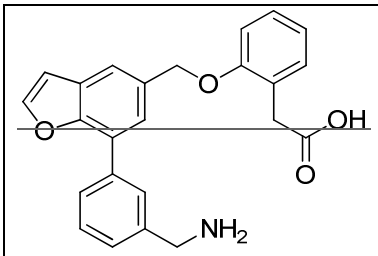
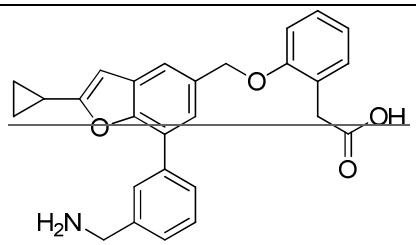
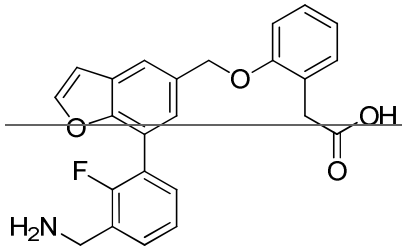
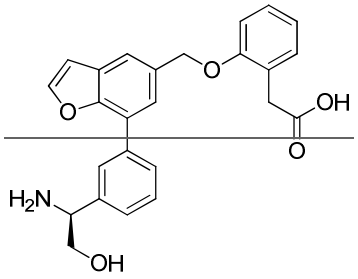
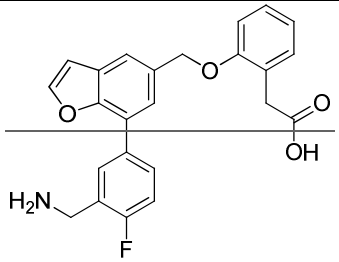
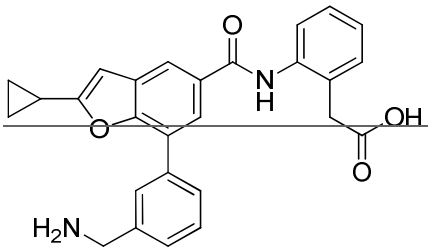
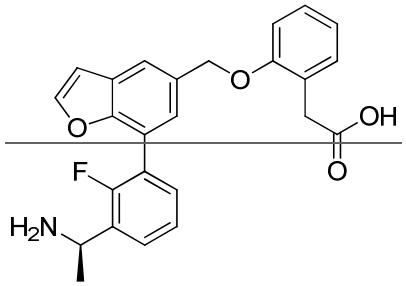
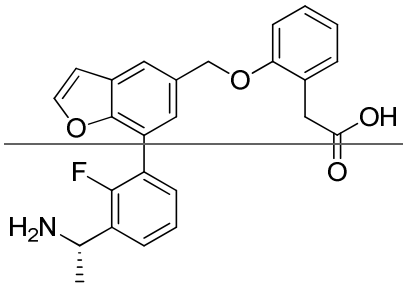
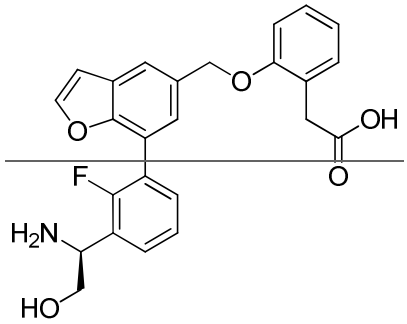
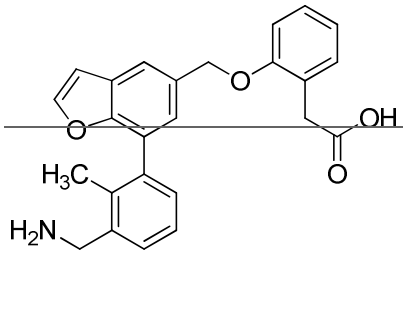
U is N or CR^3;

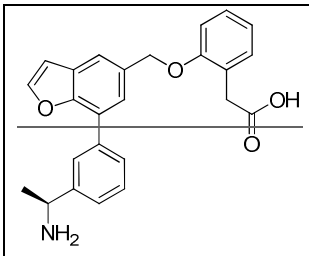
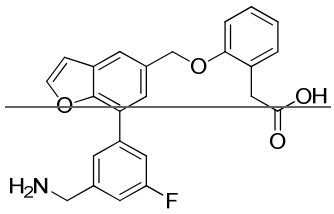
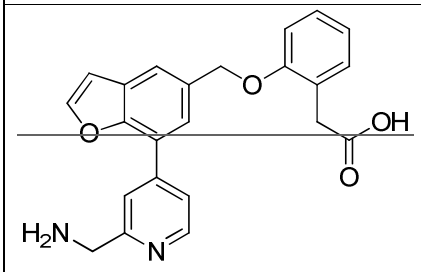
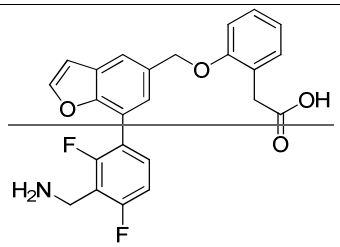
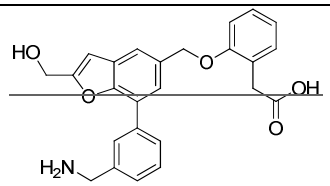
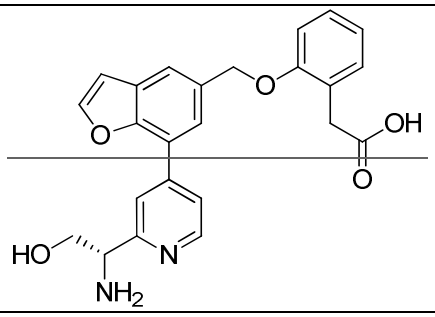
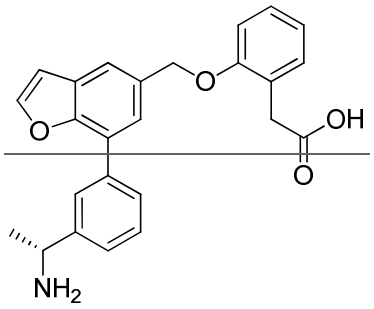
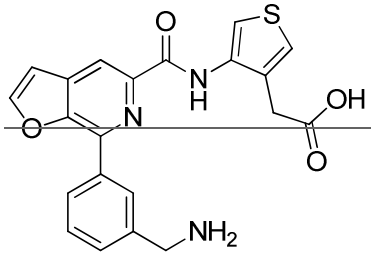
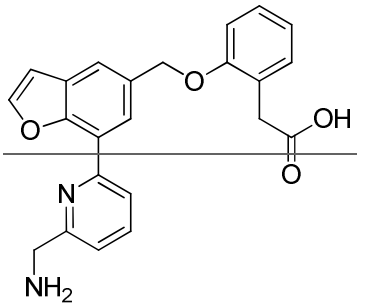
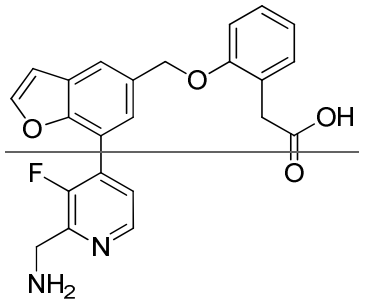
R^3 is H, halogen, alkyl, alkoxy, or haloalkyl; and

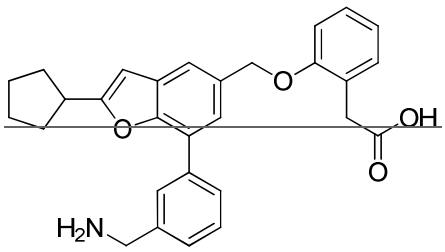
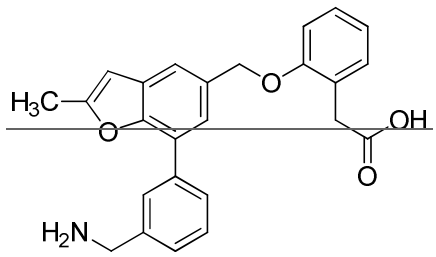
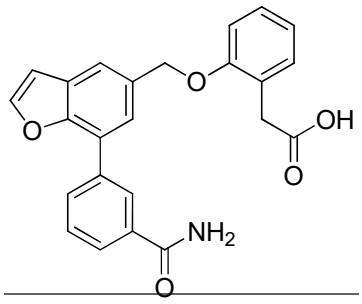
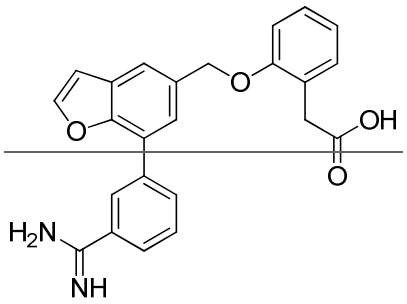
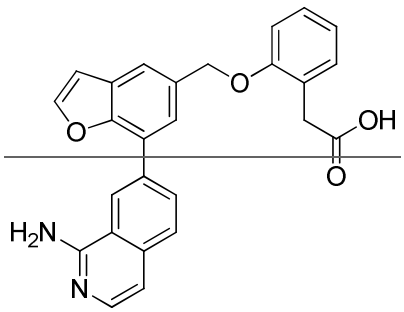
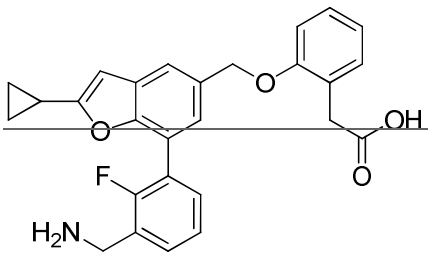
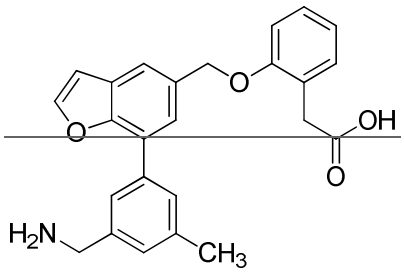
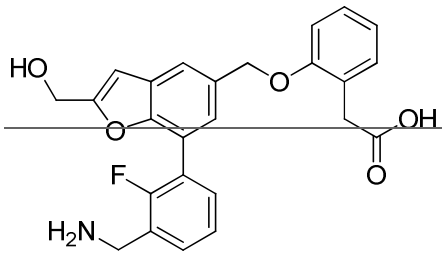
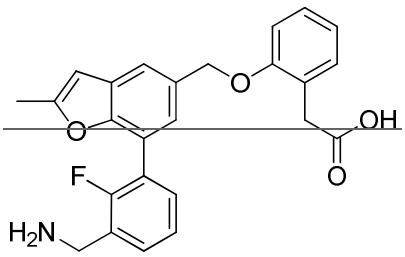
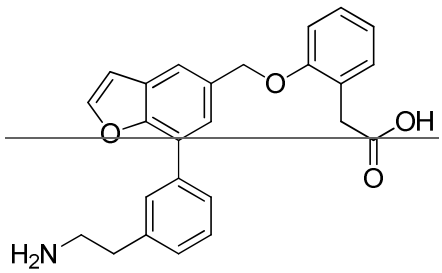
V is N or CH.

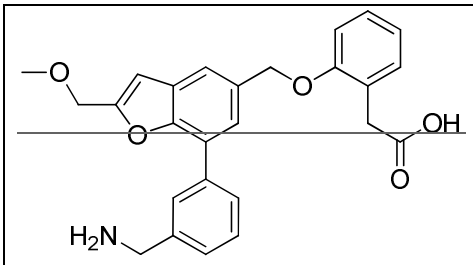
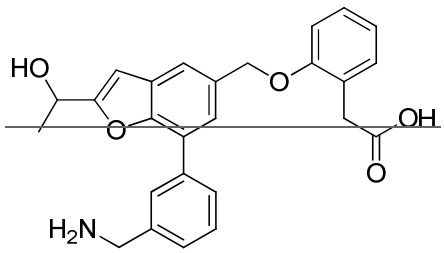
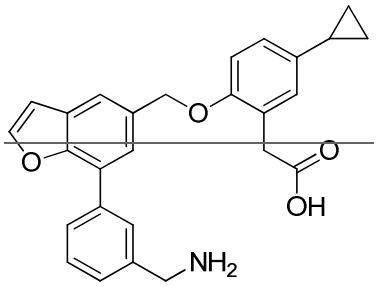
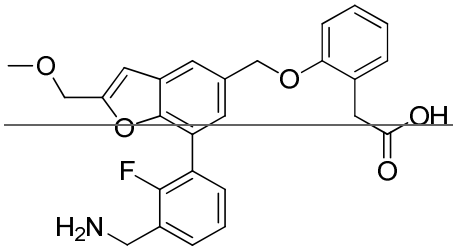
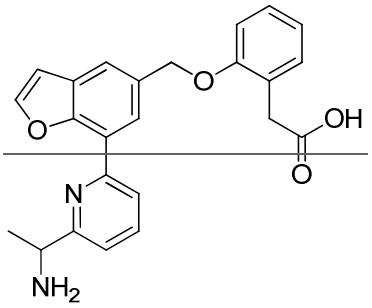
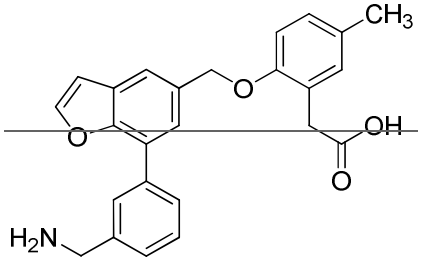
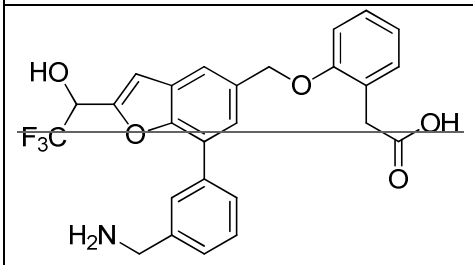
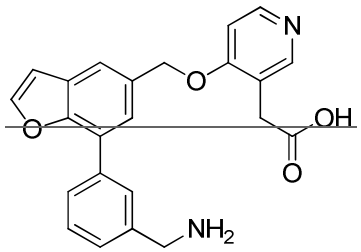
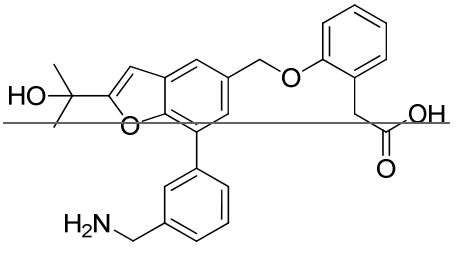
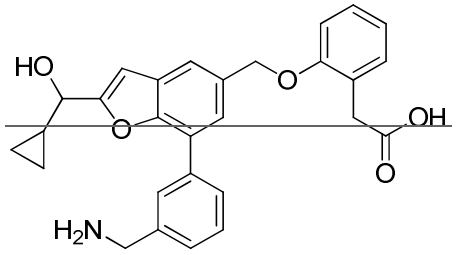
44. The compound of claim 1, selected from the following table:

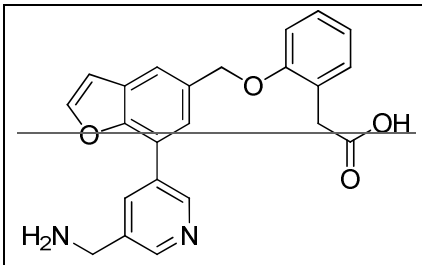
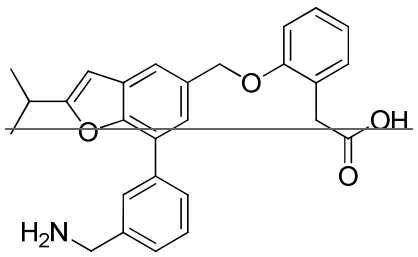
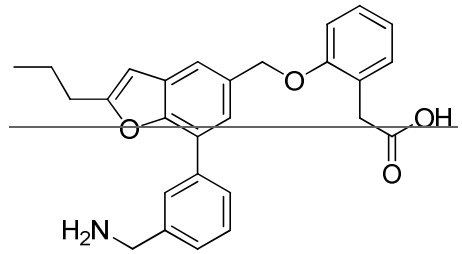
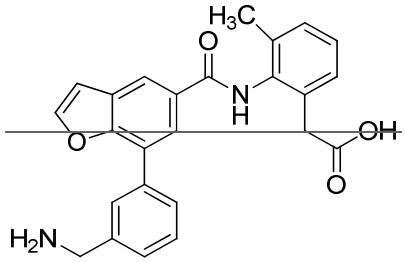
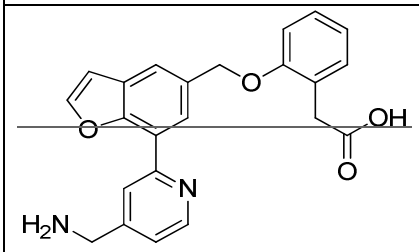
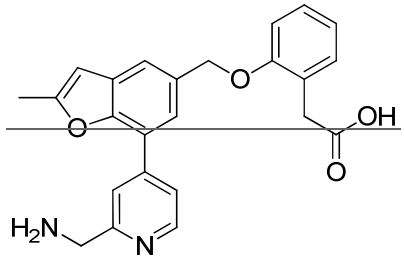
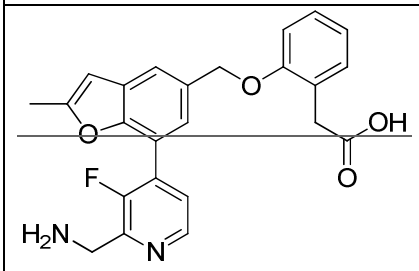
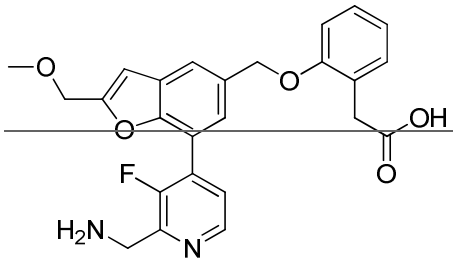
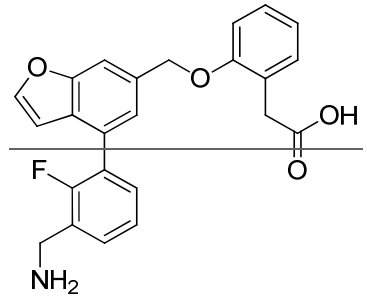
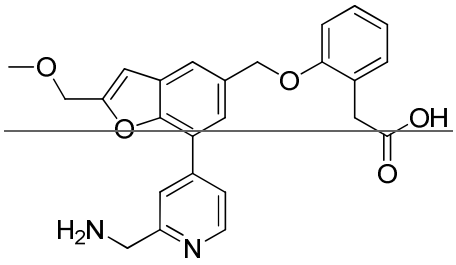
	

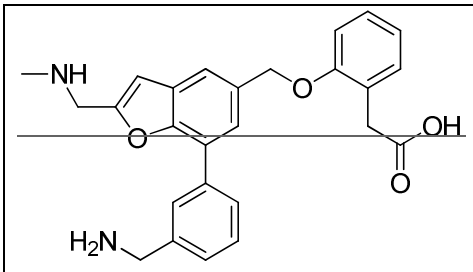
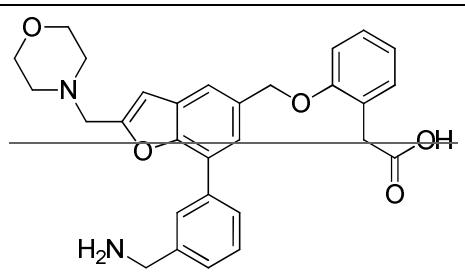
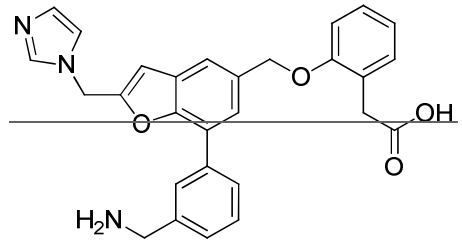
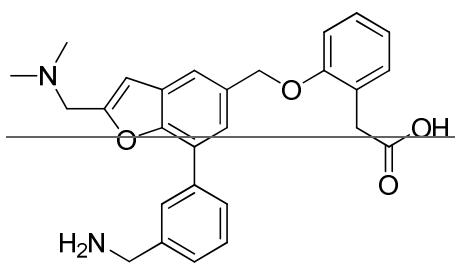
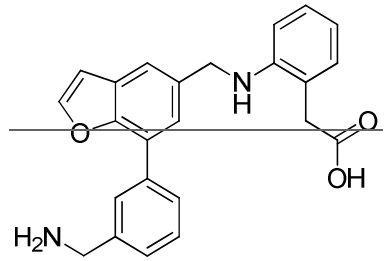
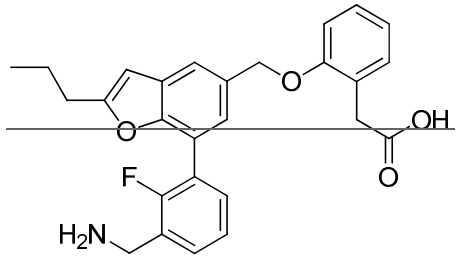
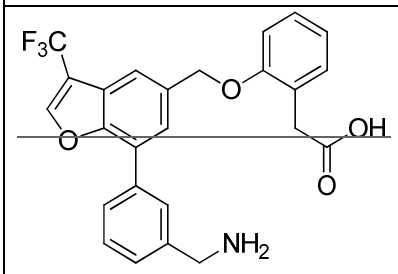
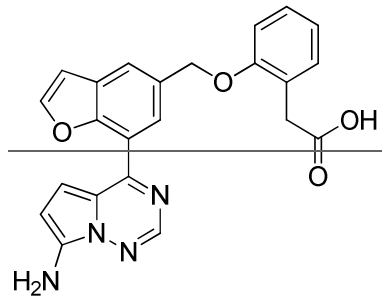
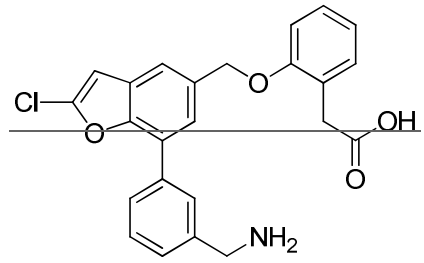
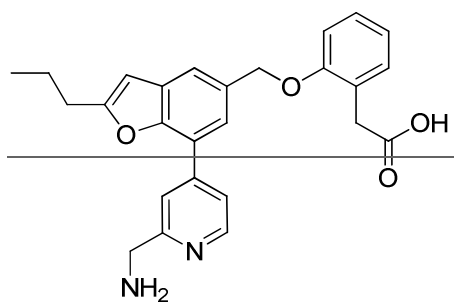
	
	
	
	
	

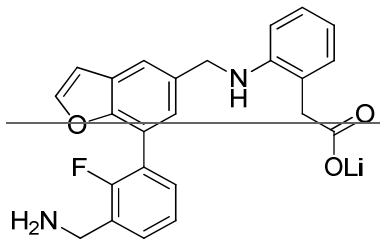
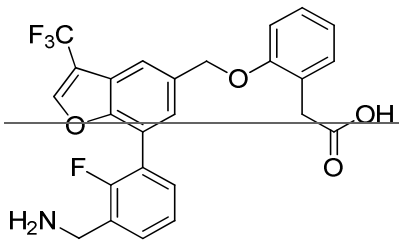
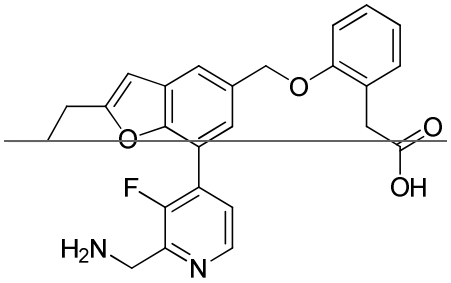
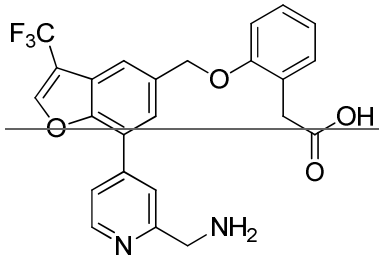
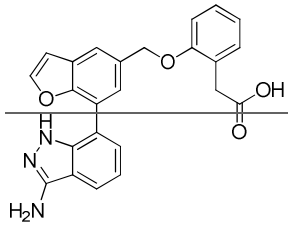
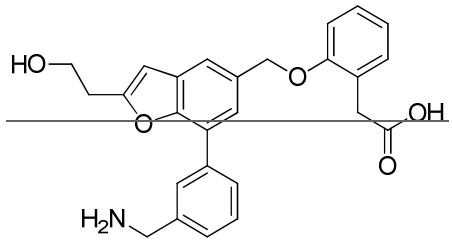
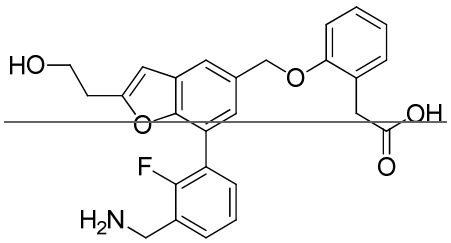
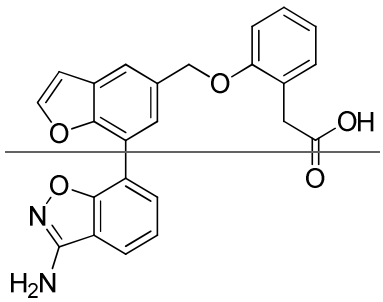
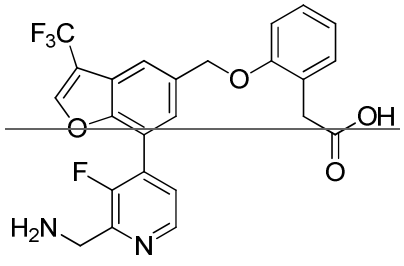
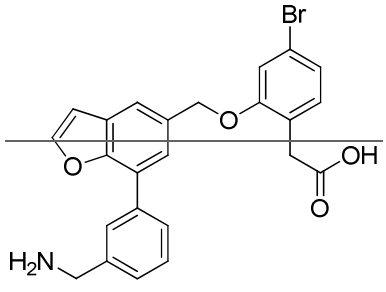
	
	
	
	
	

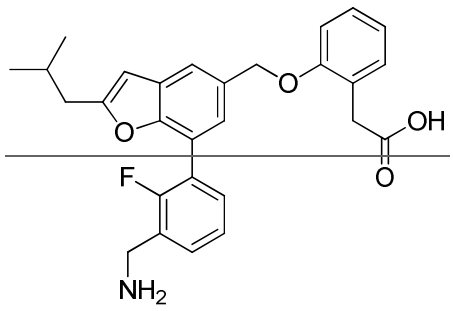
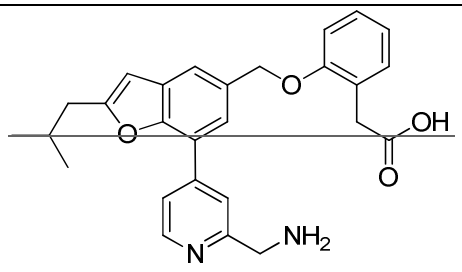
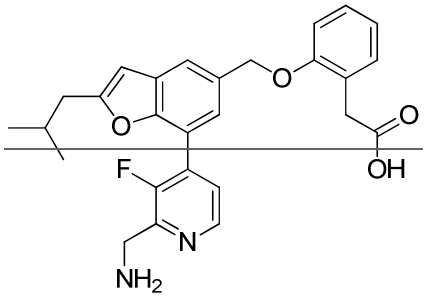
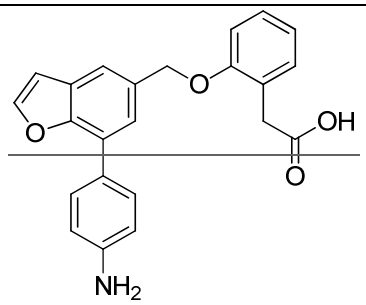
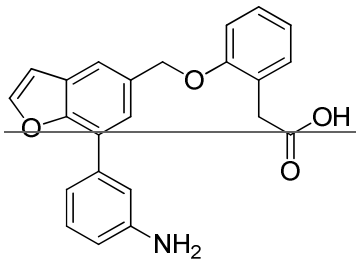
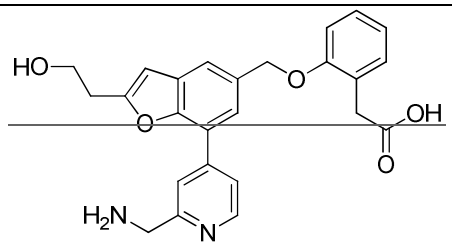
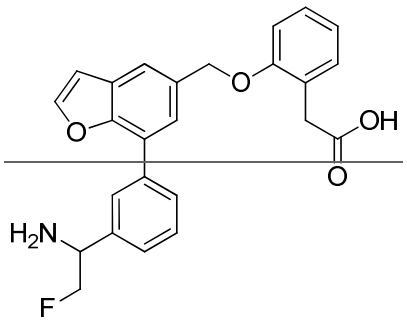
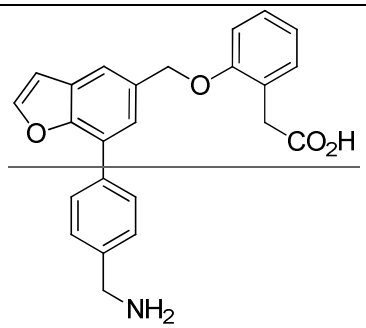
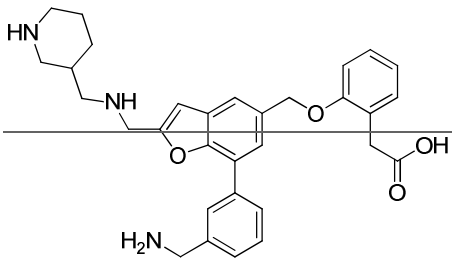
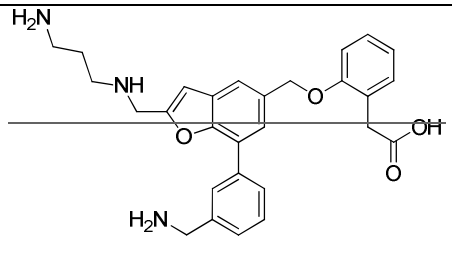
	
	
	
	
	

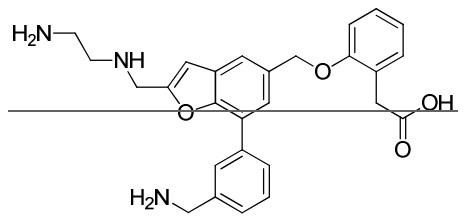
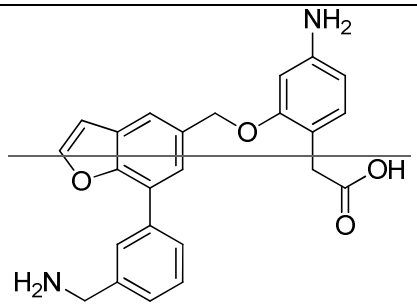
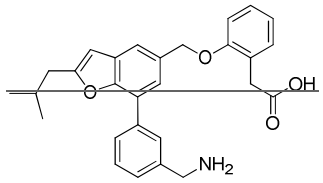
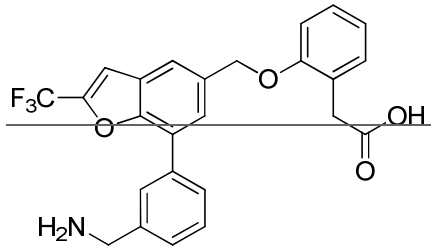
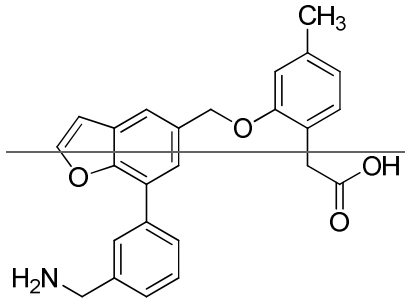
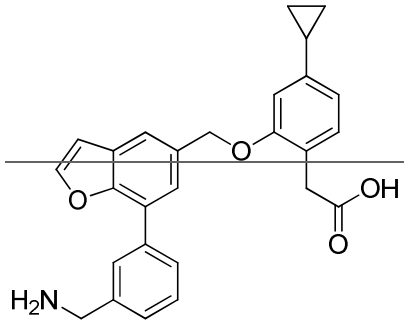
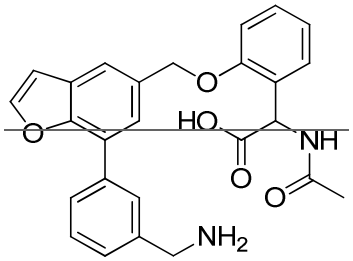
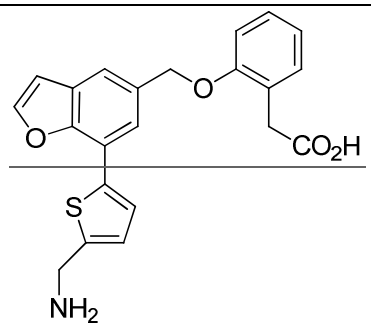
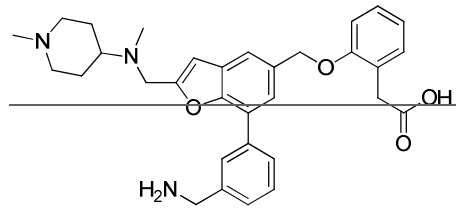
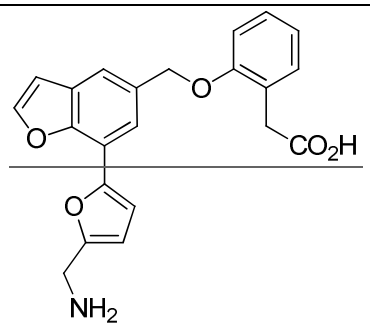
	
	
	
	
	

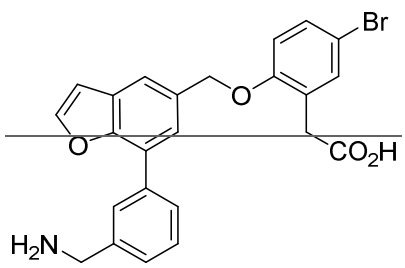
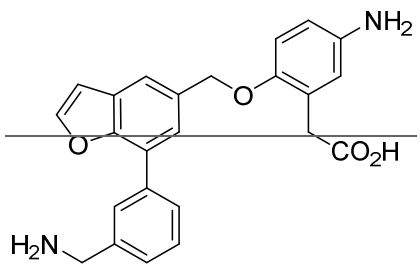
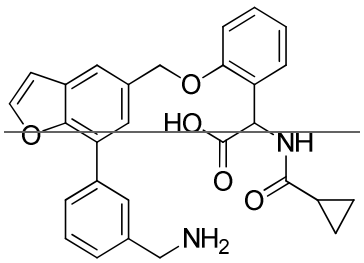
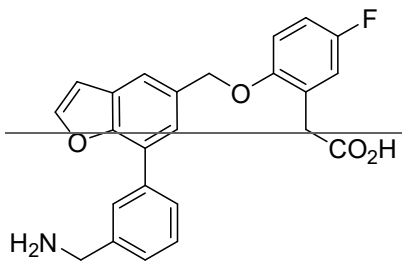
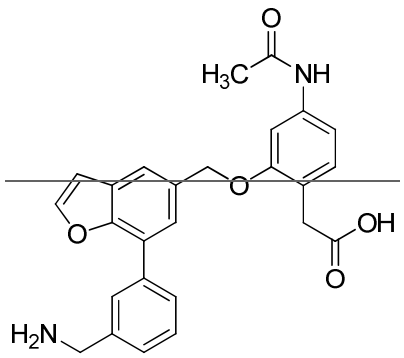
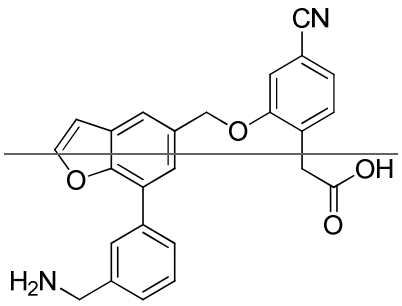
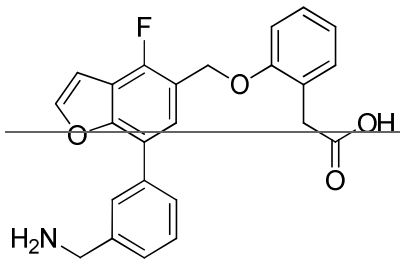
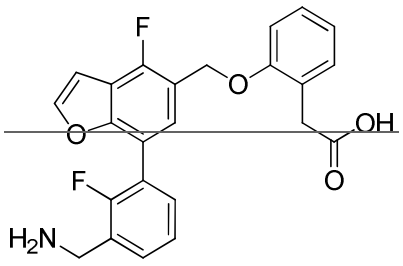
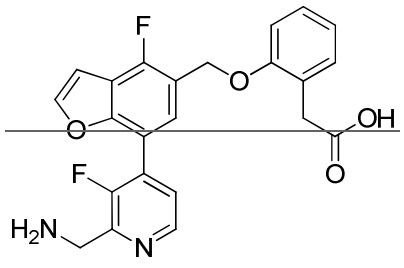
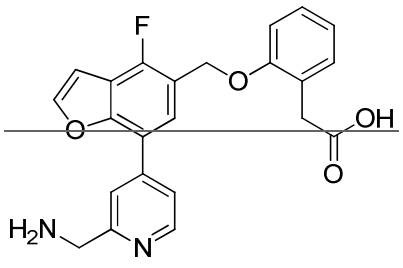
	
	
	
	
	

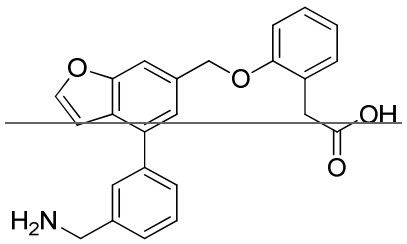
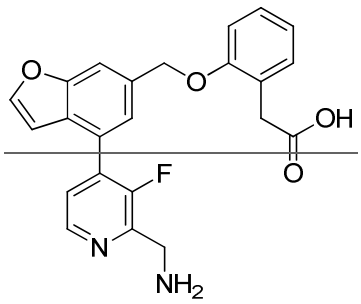
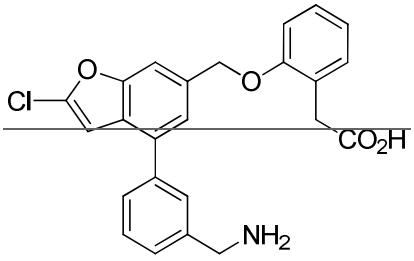
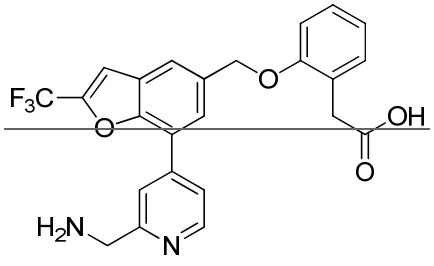
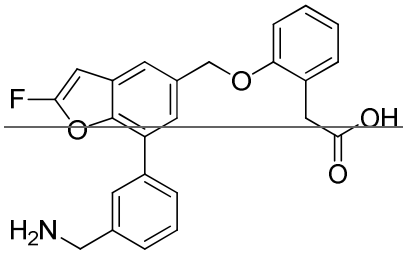
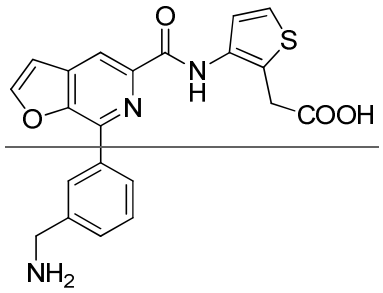
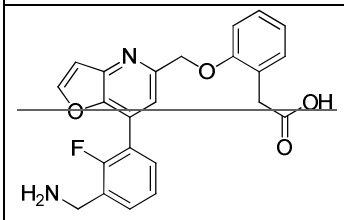
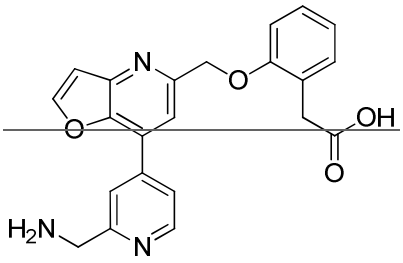
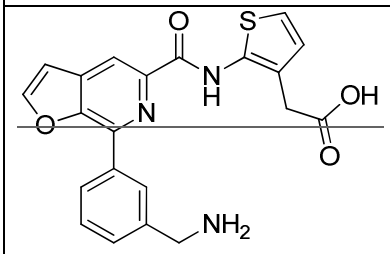
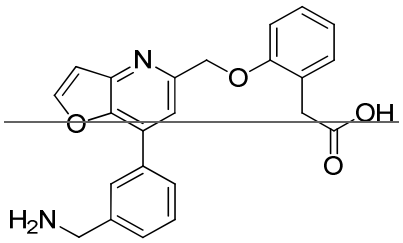
	
	
	
	
	

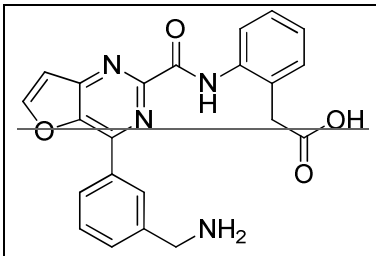
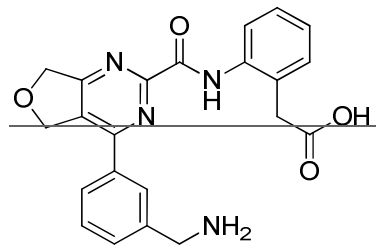
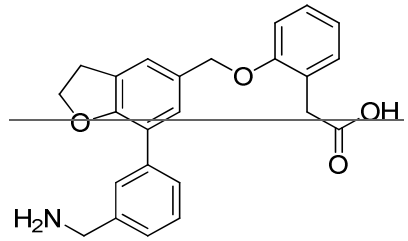
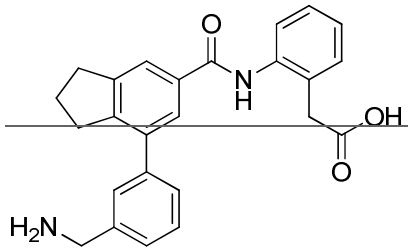
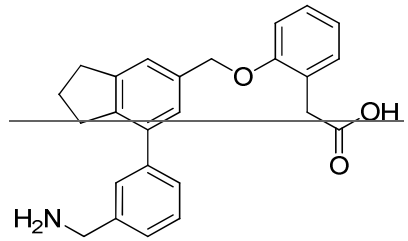
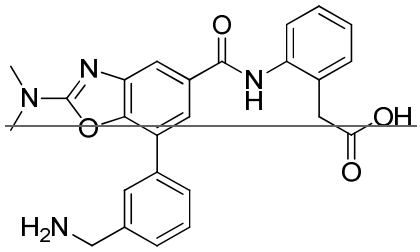
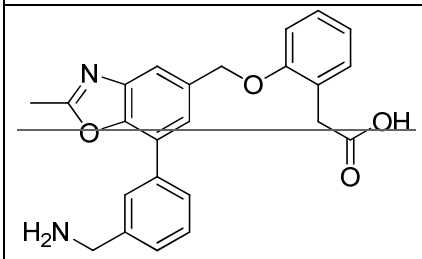
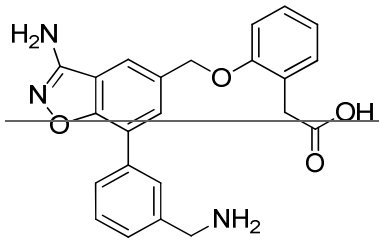
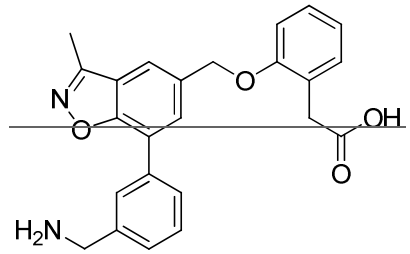
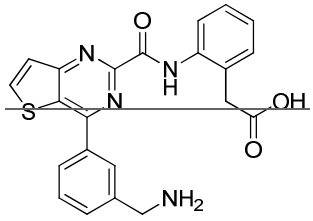
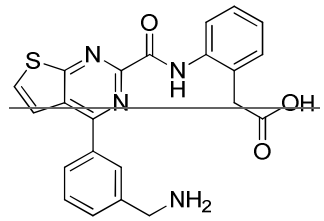
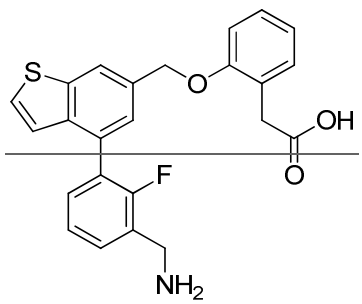
	
	
	
	
	

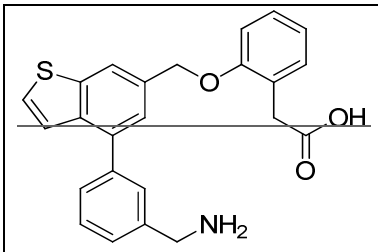
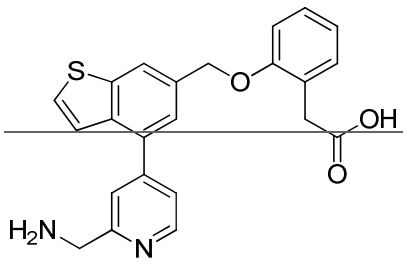
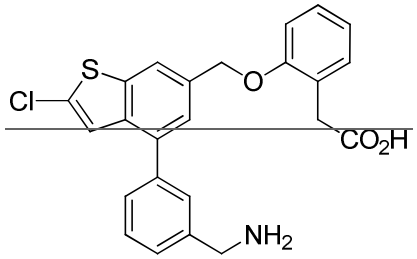
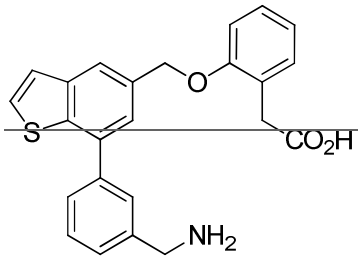
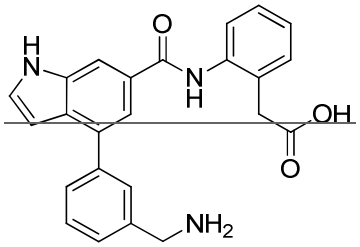
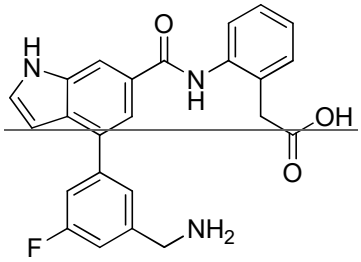
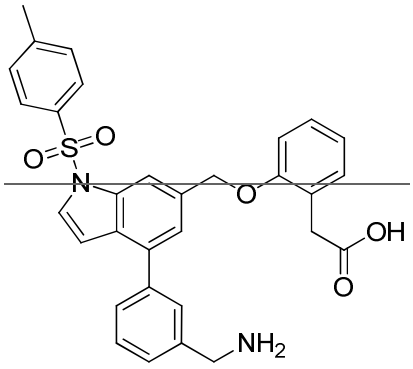
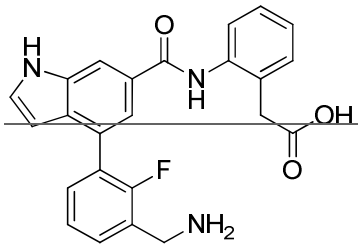
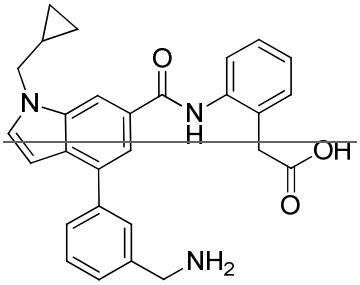
	
	
	
	
	

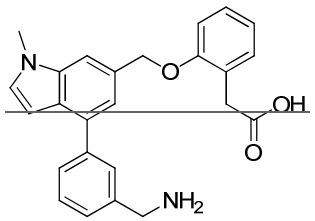
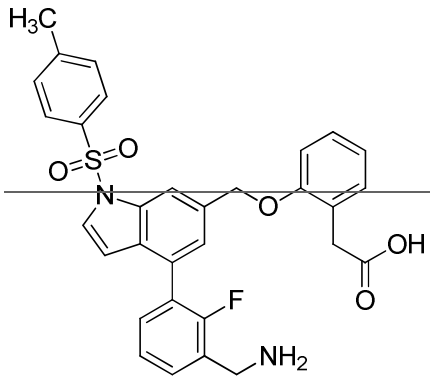
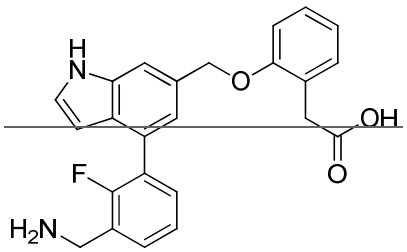
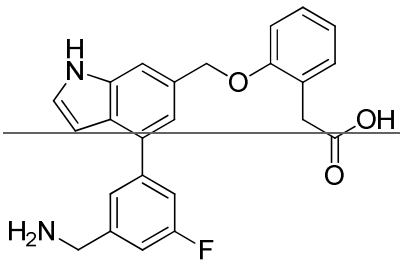
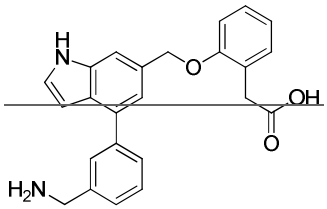
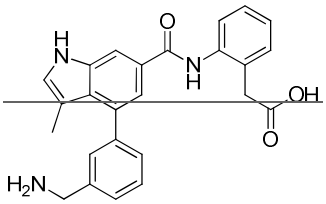
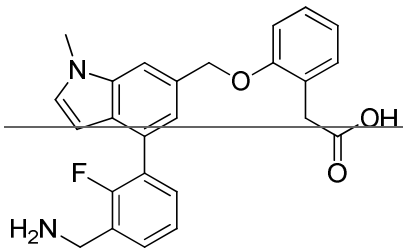
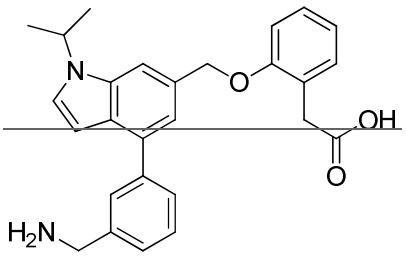
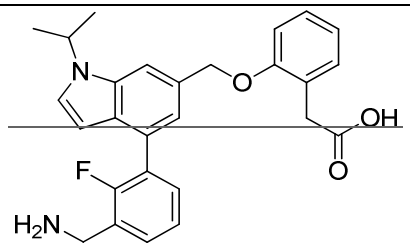
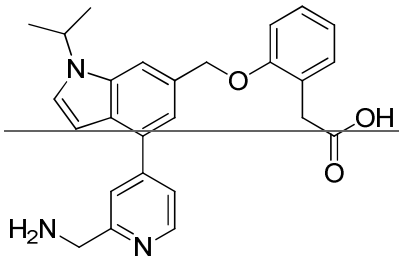
	
	
	
	
	

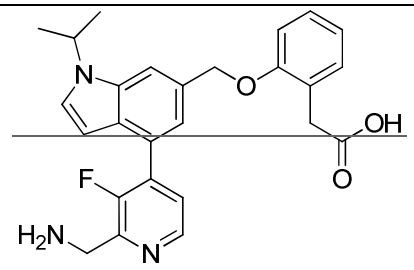
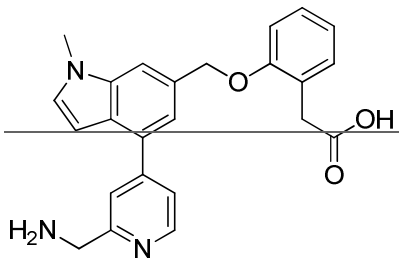
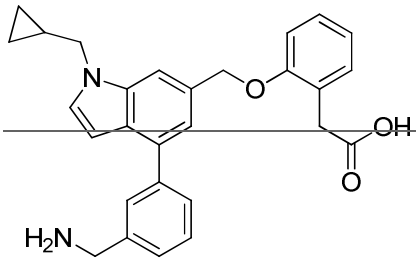
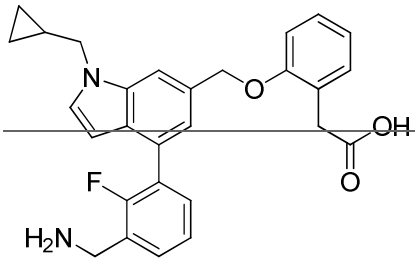
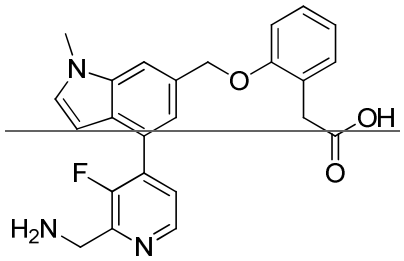
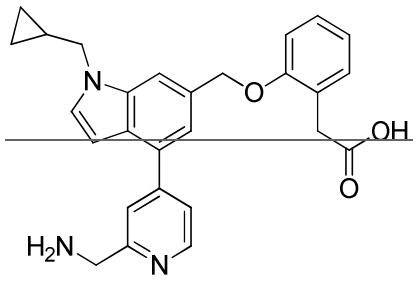
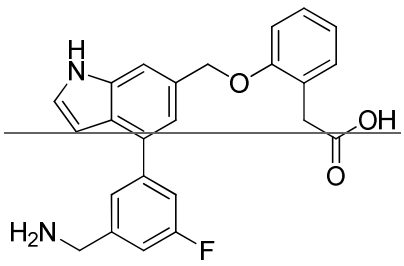
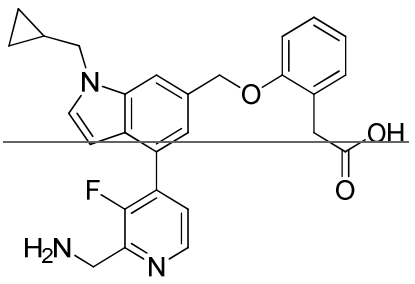
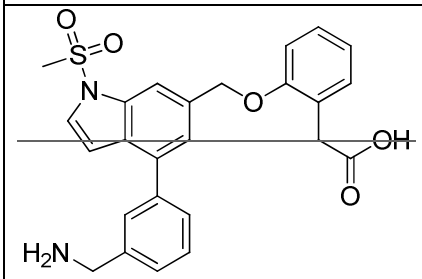
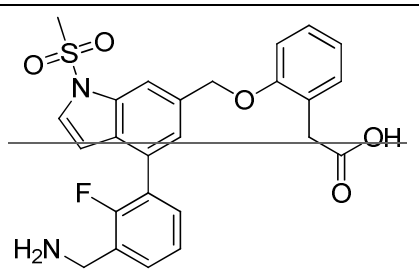
	
	
	
	
	

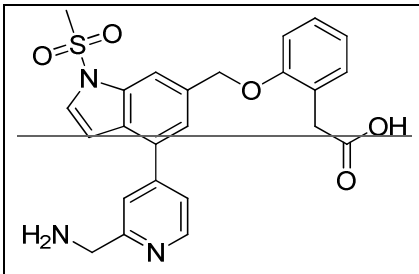
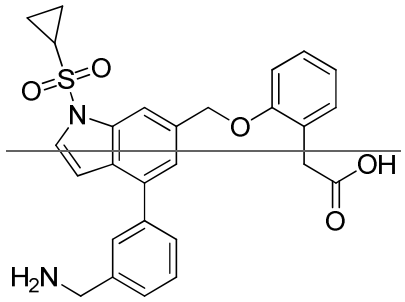
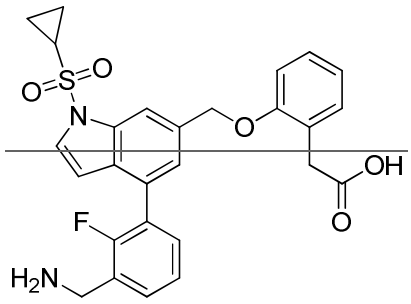
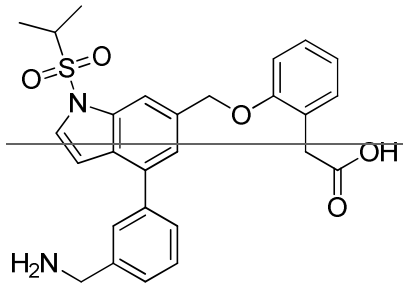
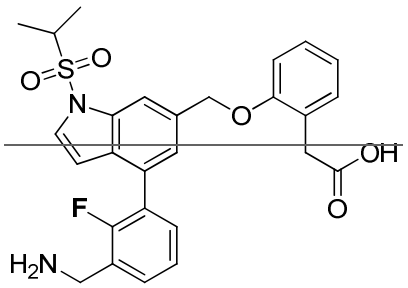
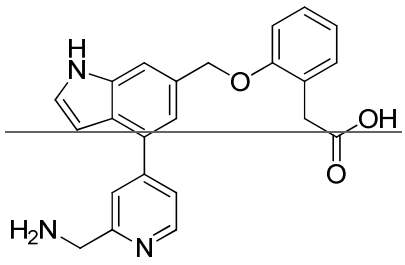
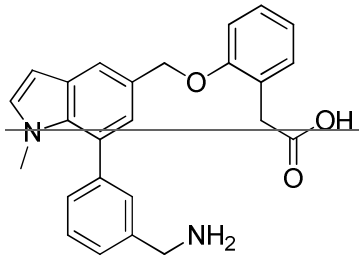
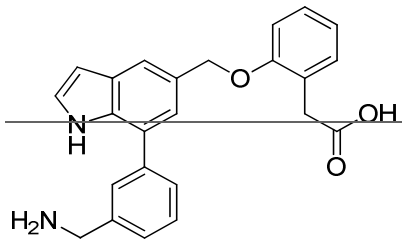
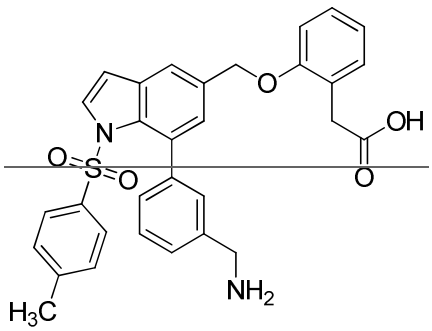
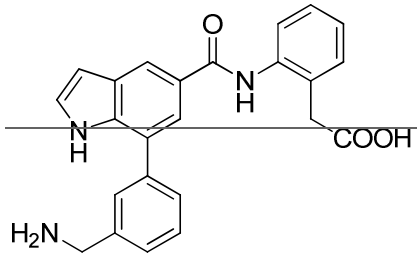
	
	
	
	
	

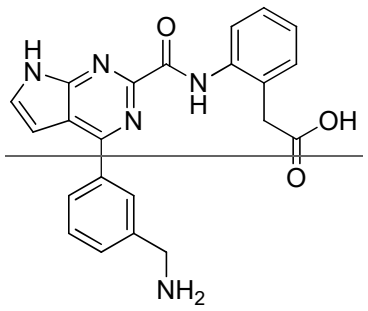
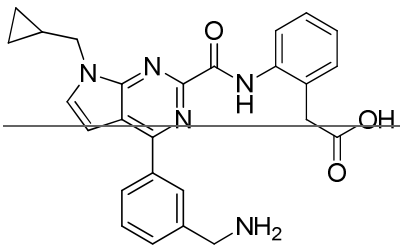
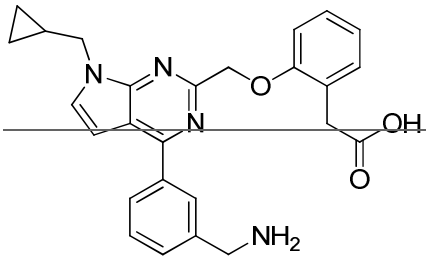
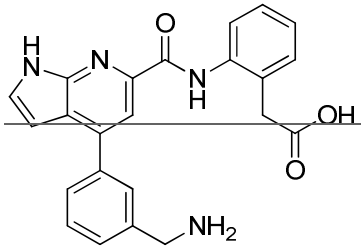
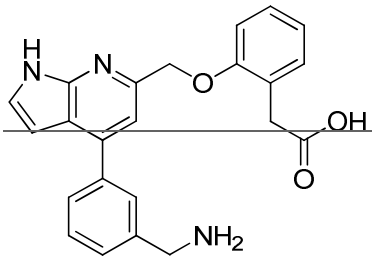
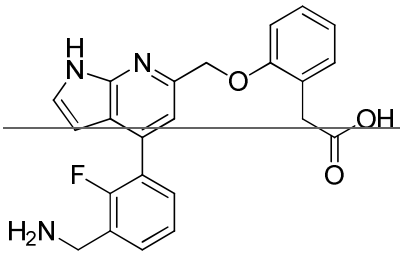
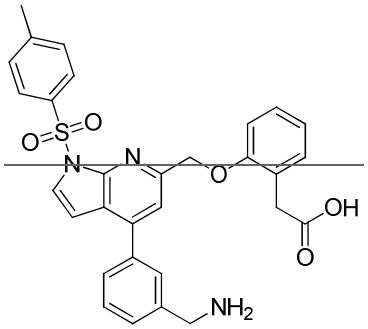
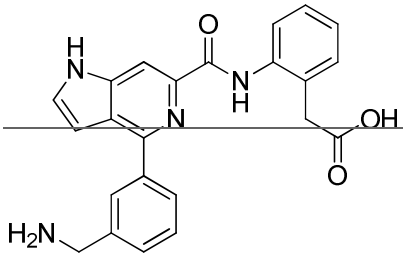
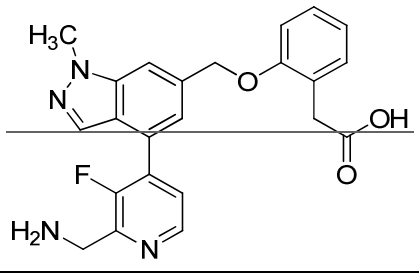
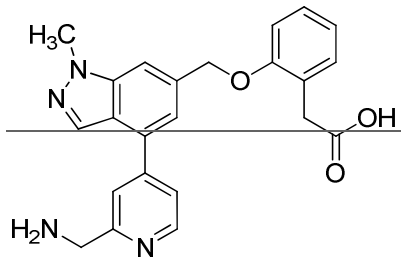
	
	
	
	
	
	

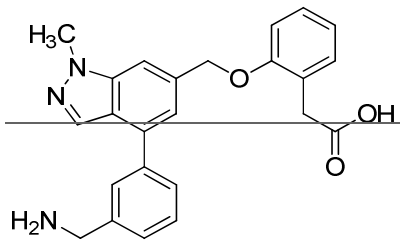
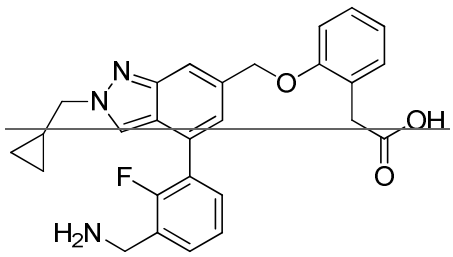
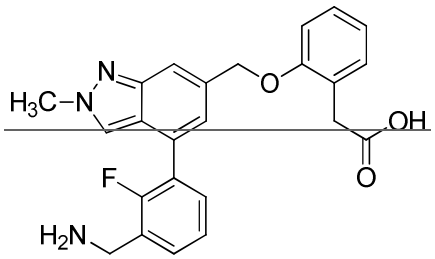
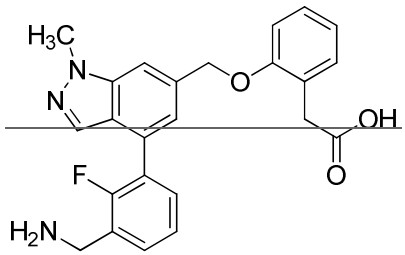
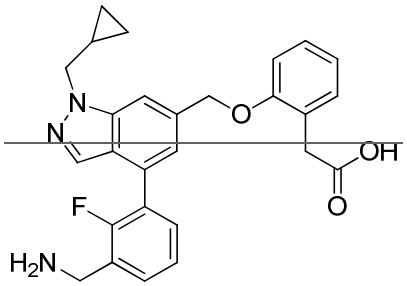
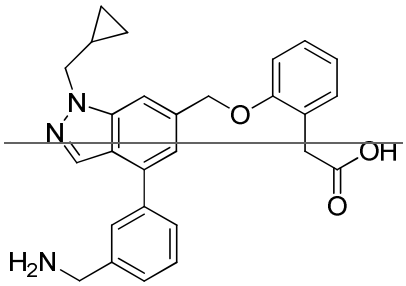
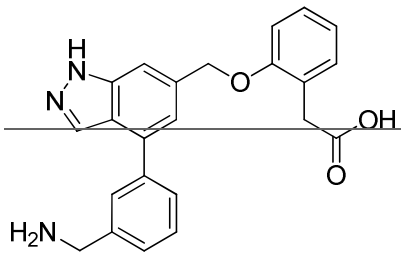
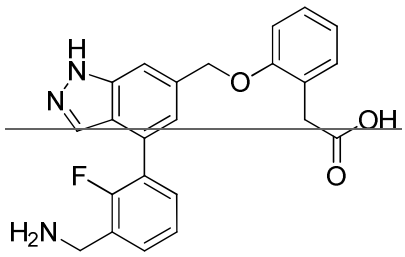
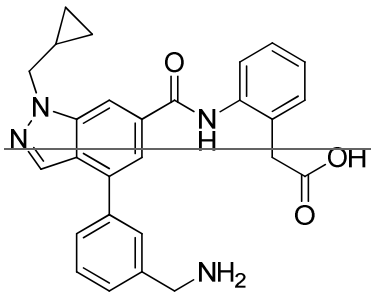
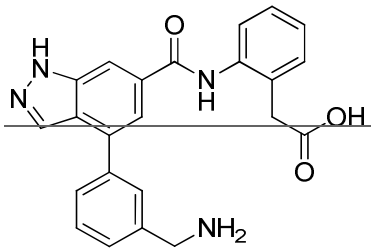
	
	
	
	
	

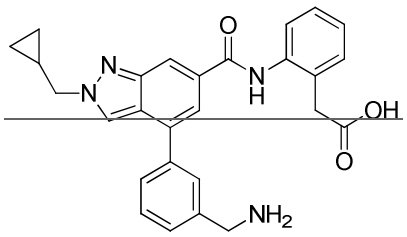
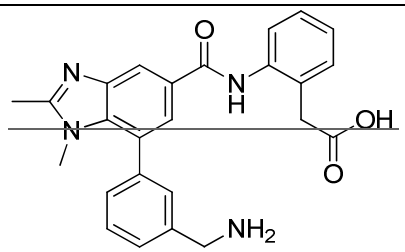
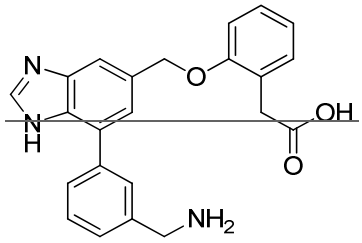
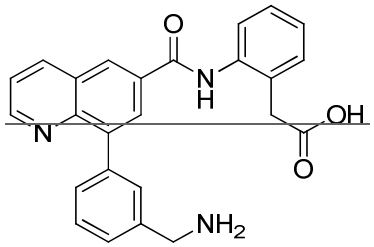
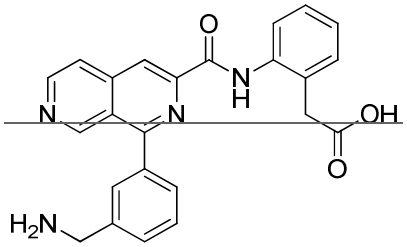
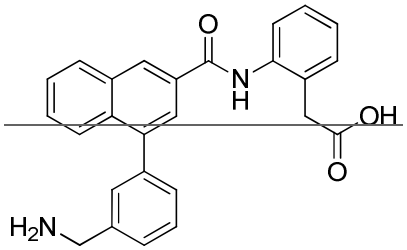
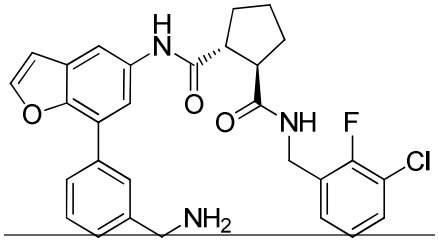
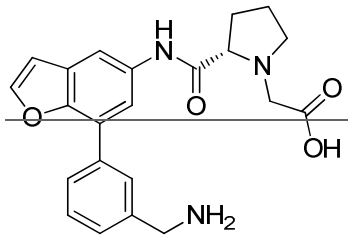
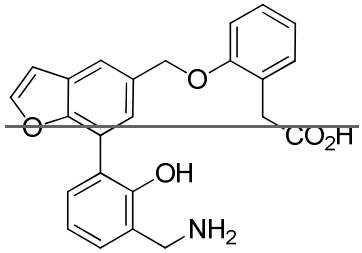
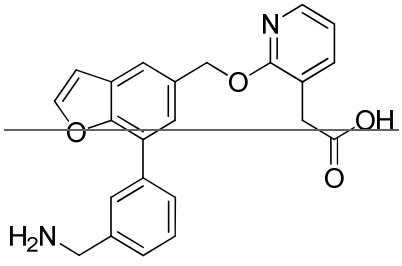
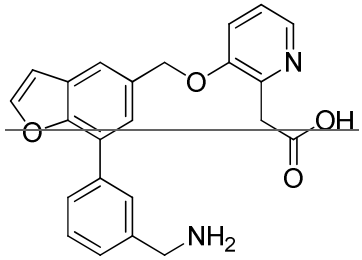
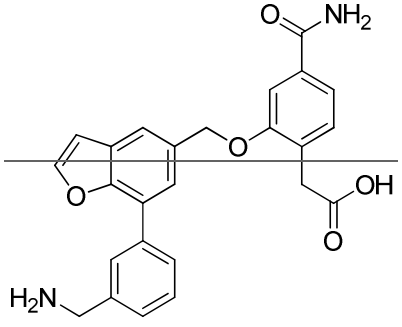
	
	
	
	
	

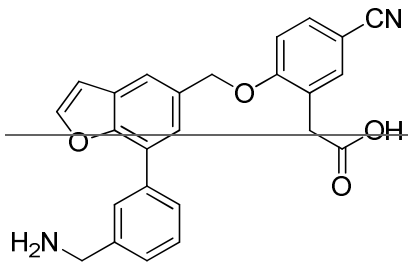
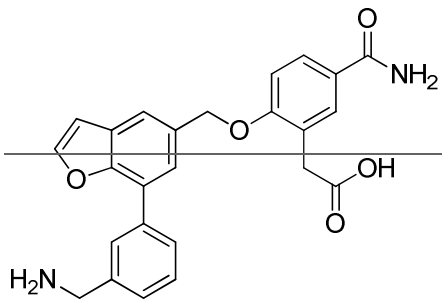
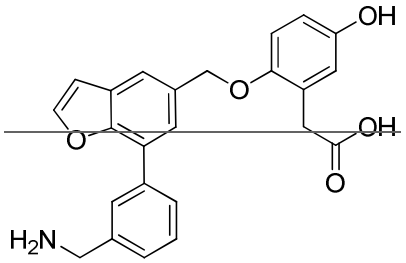
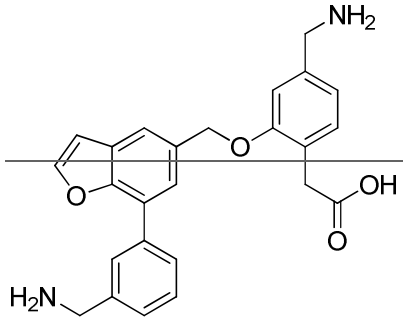
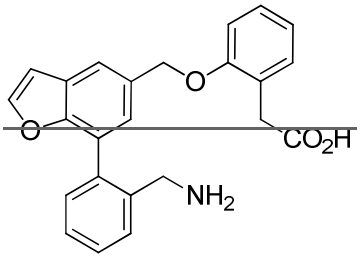
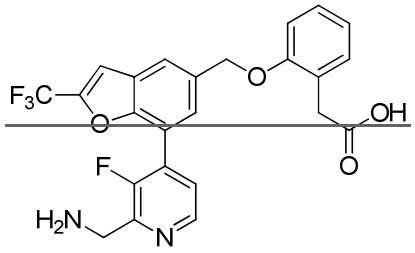
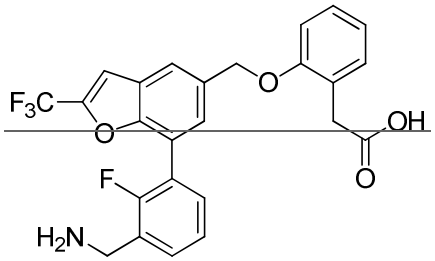
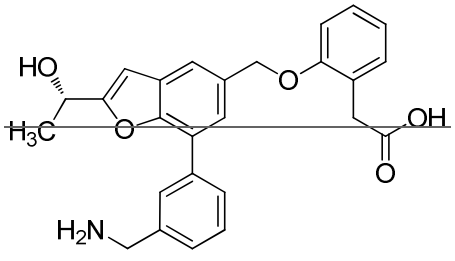
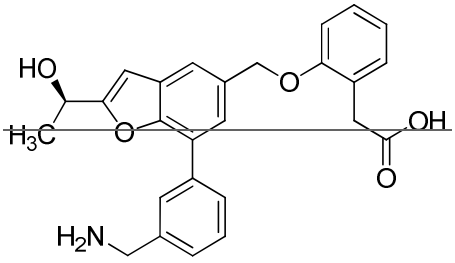
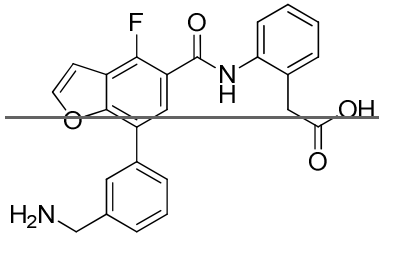
	
	
	
	
	

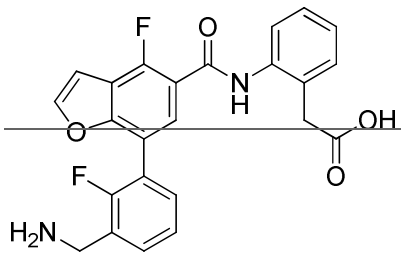
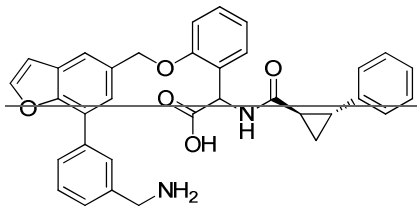
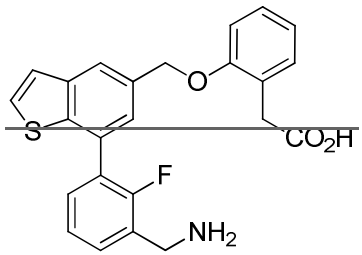
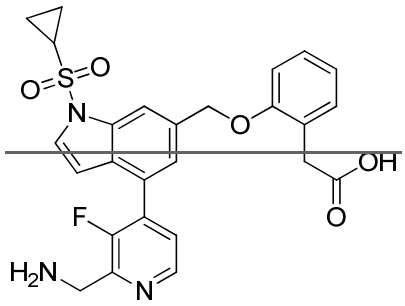
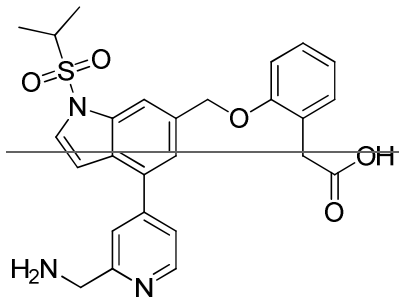
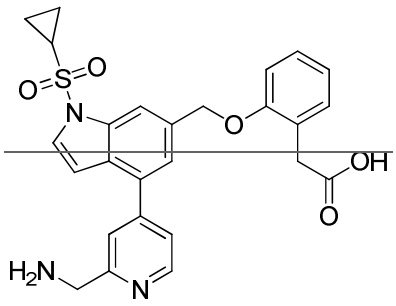
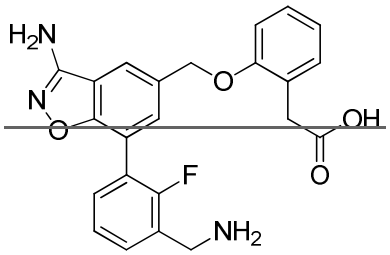
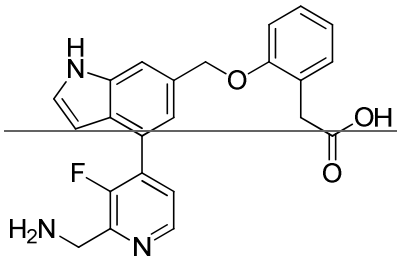
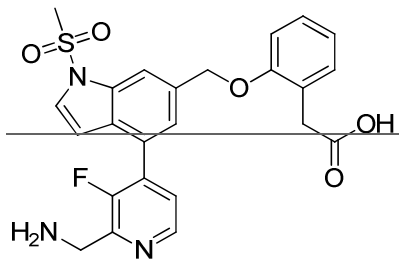
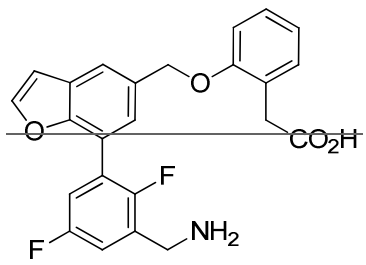
	
	
	
	
	

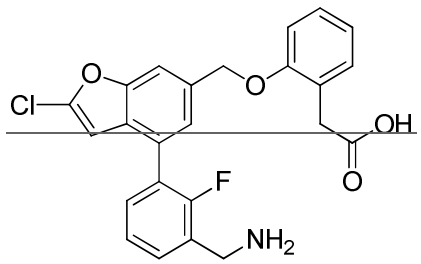
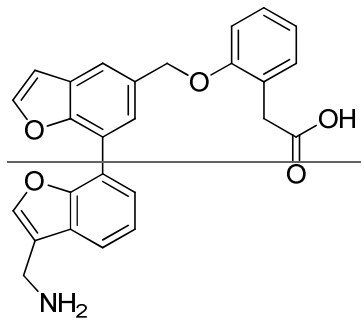
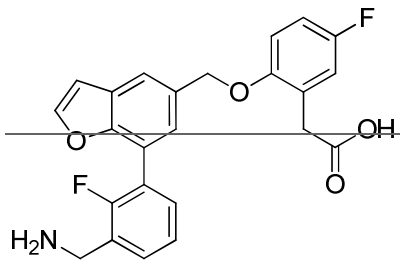
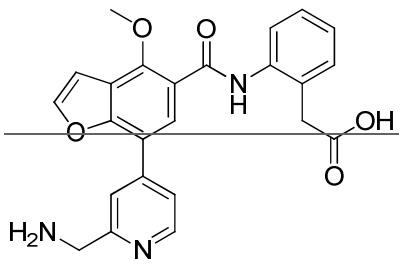
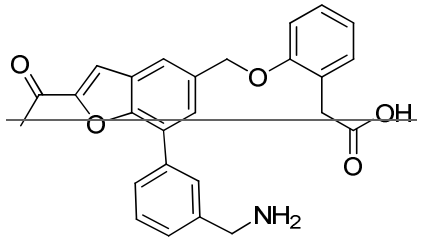
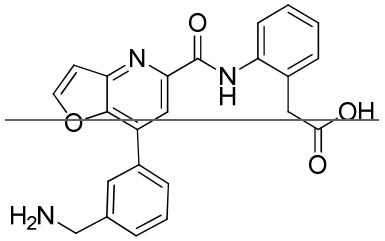
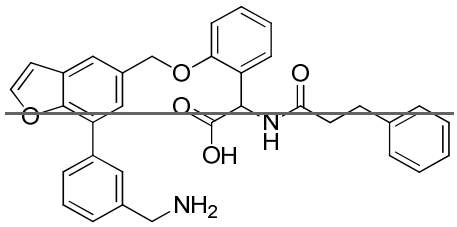
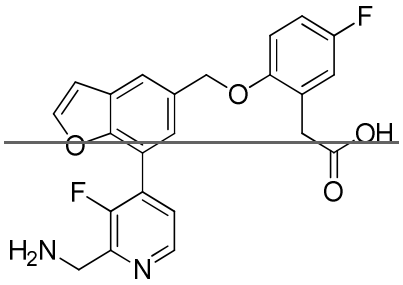
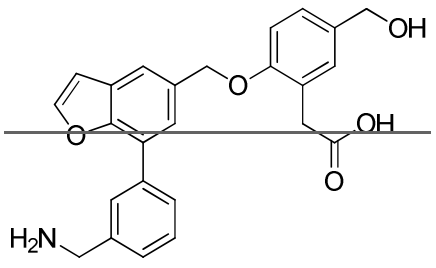
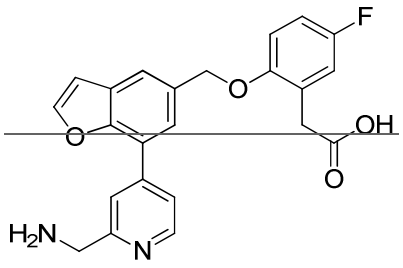
	
	
	
	
	

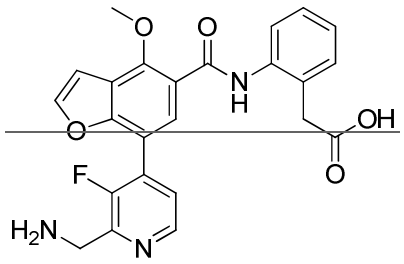
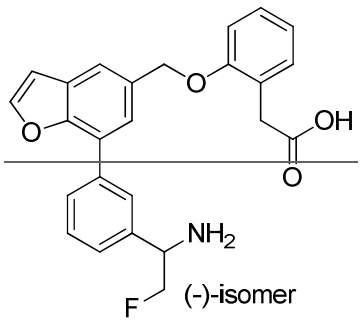
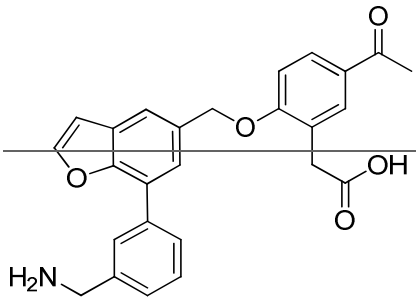
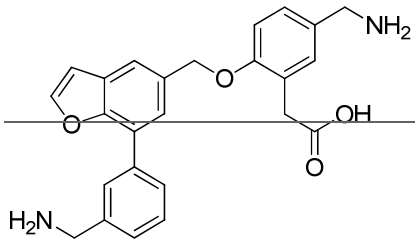
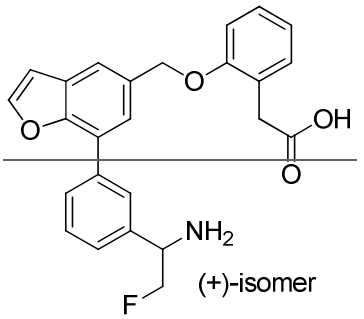
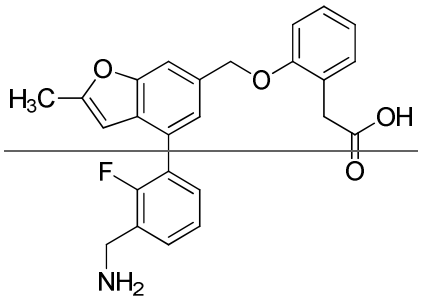
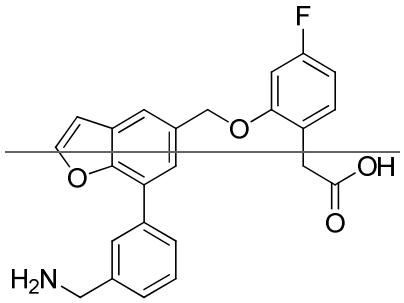
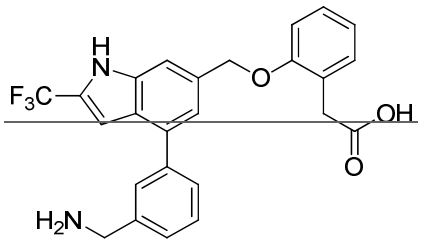
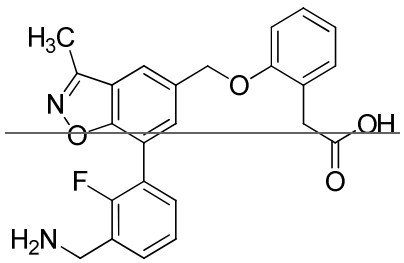
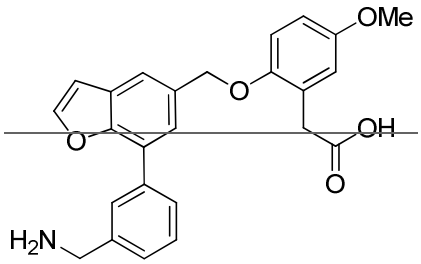
	
	
	
	
	

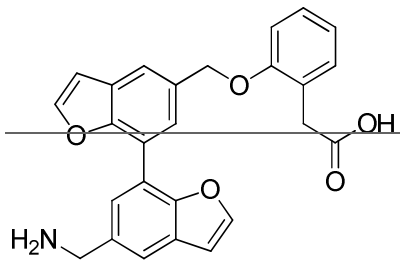
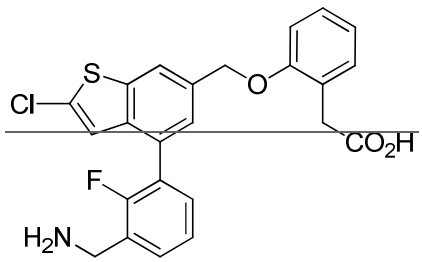
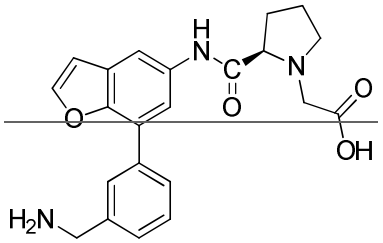
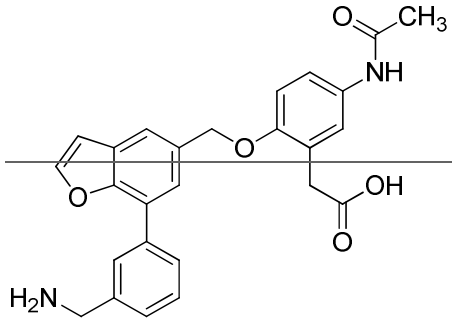
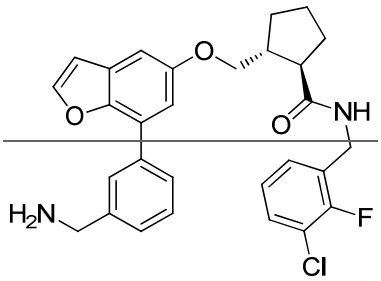
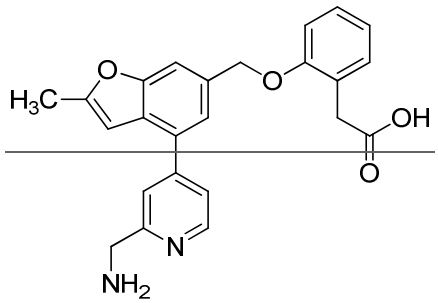
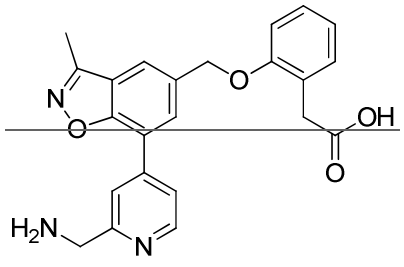
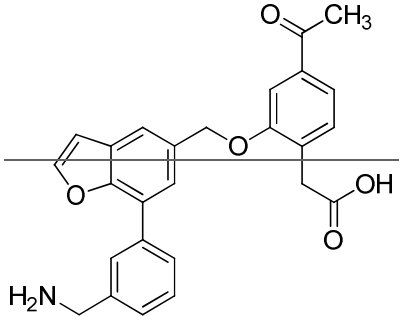
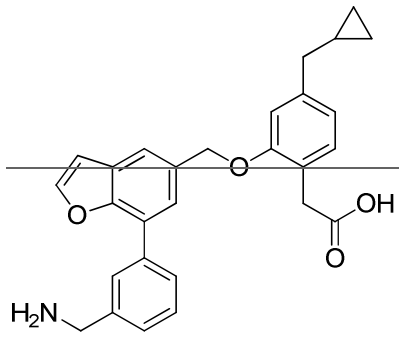
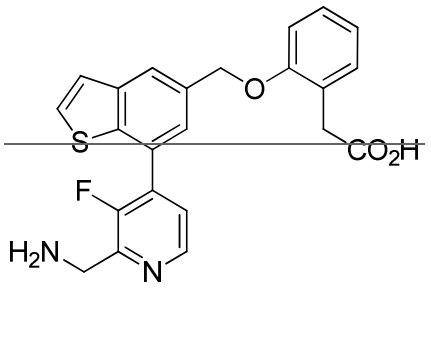
	
	
	
	
	
	

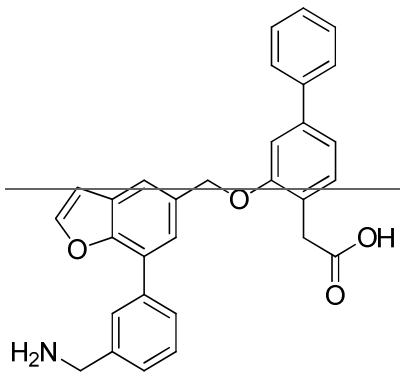
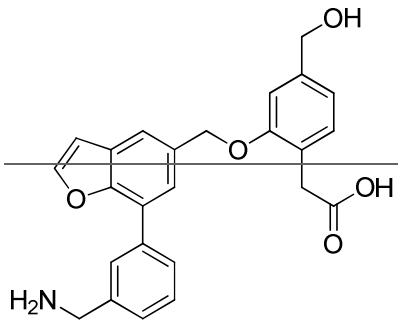
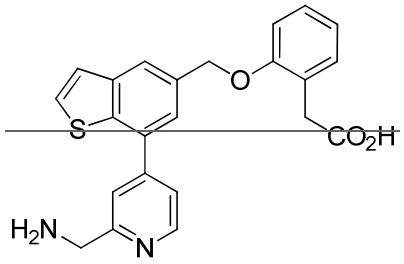
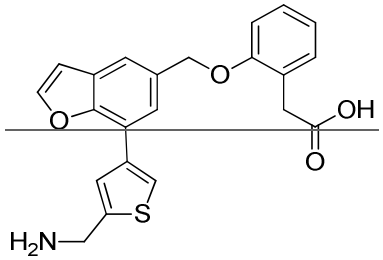
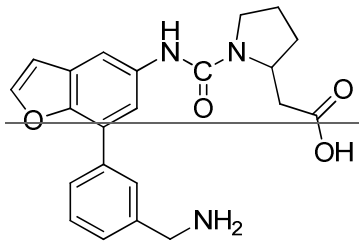
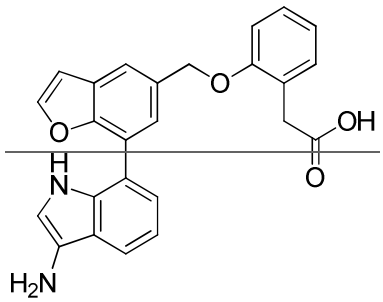
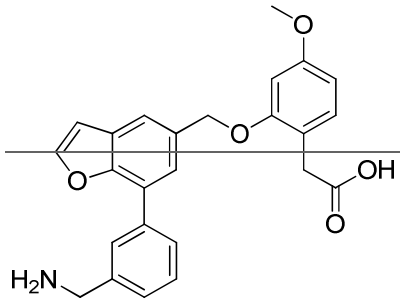
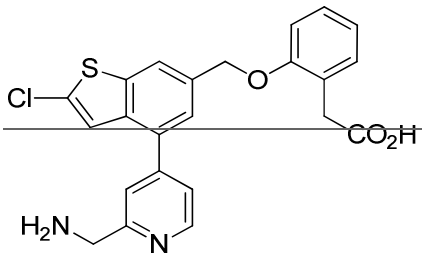
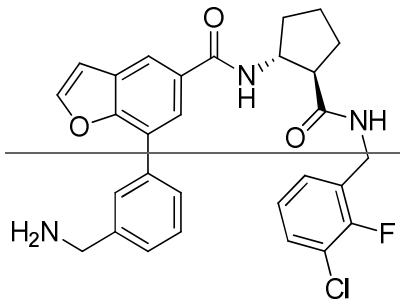
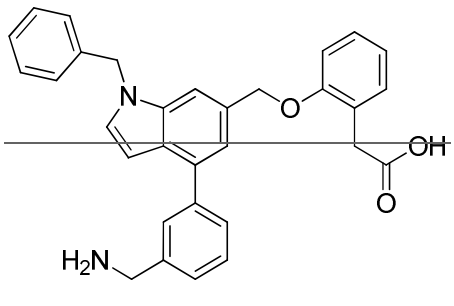
	
	
	
	
	

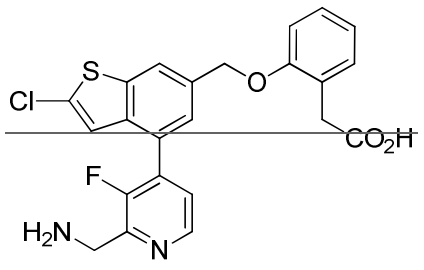
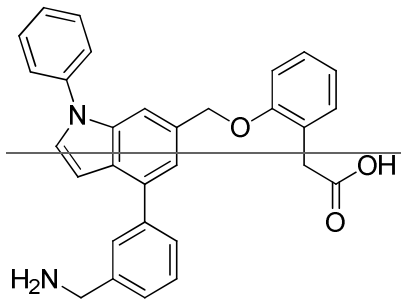
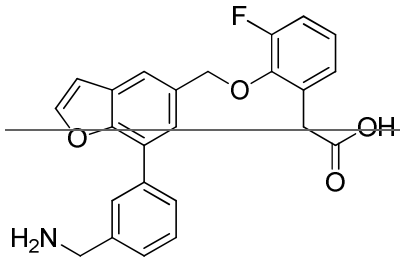
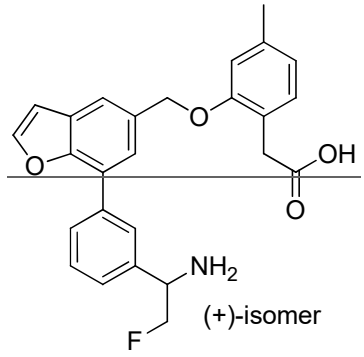
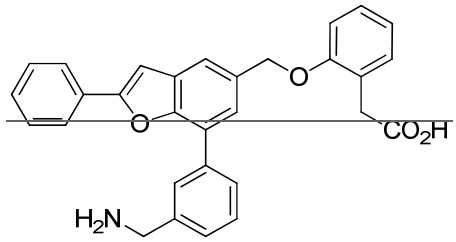
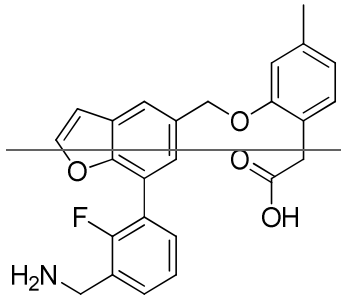
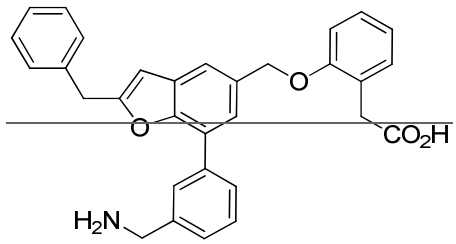
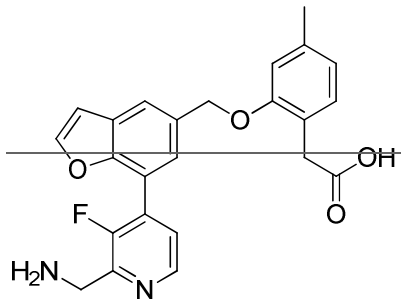
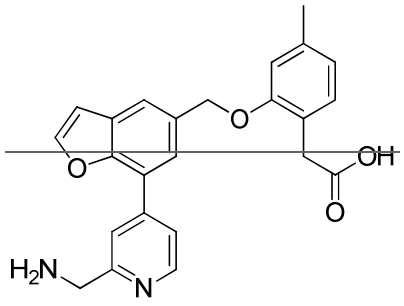
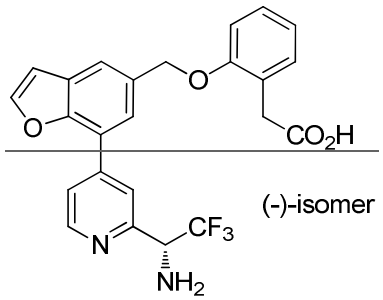
	
	
	
	
	

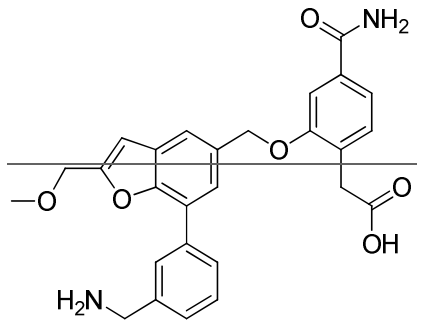
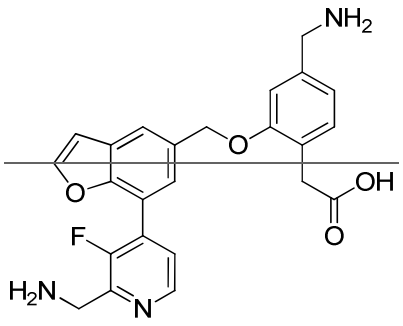
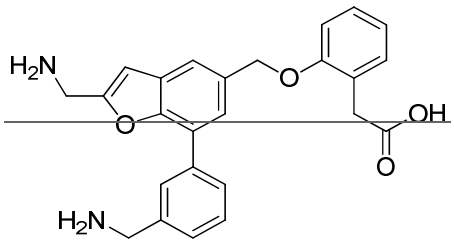
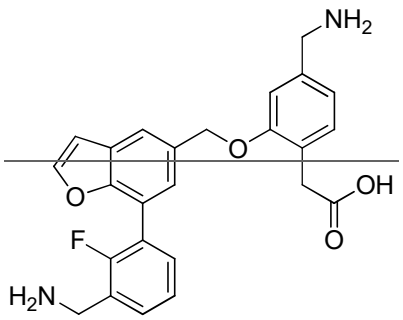
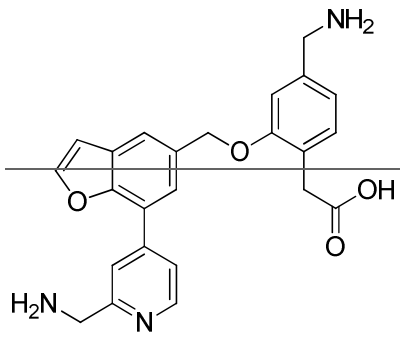
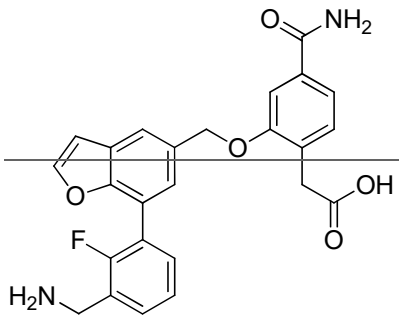
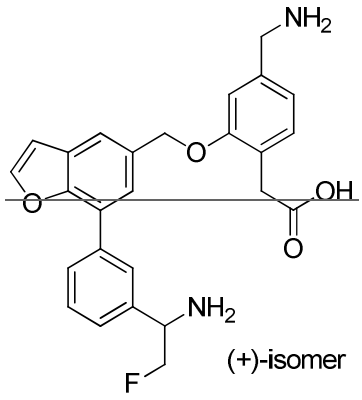
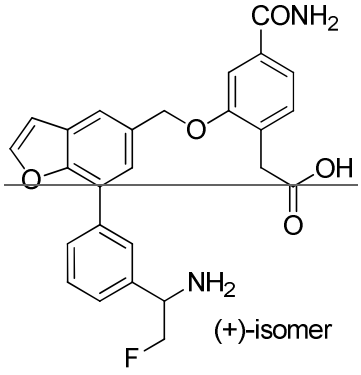
	
	
	
	
	

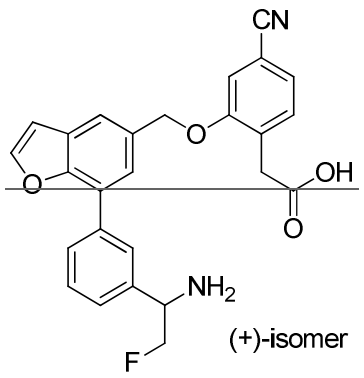
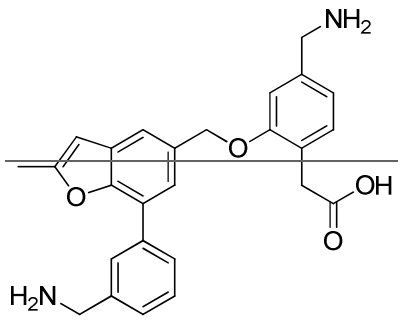
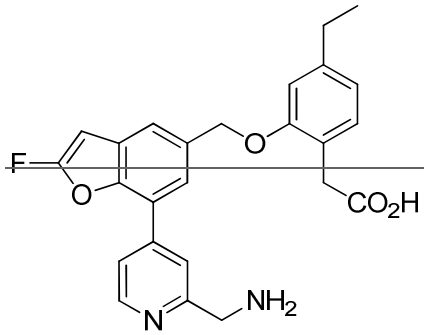
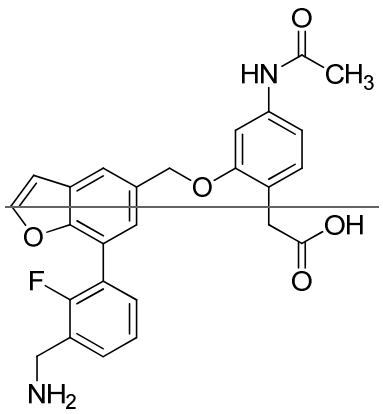
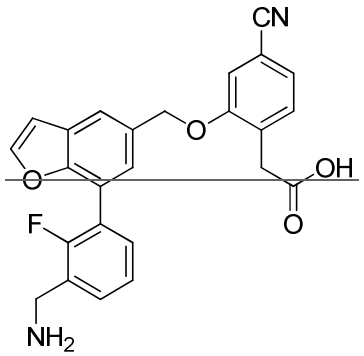
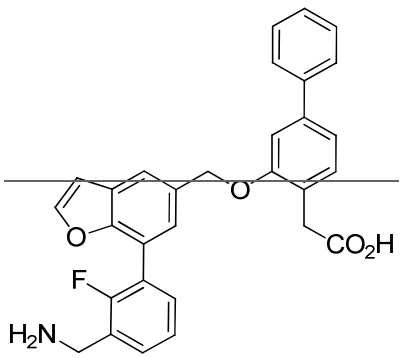
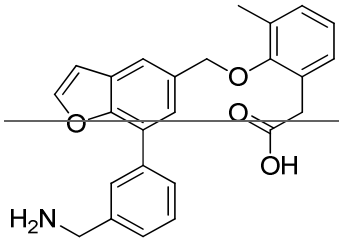
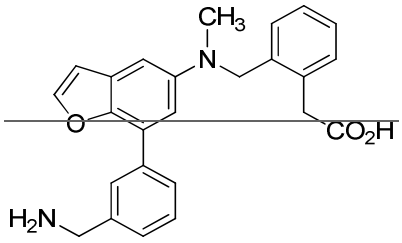
	(-)-isomer
	
(+)-isomer	
	
	

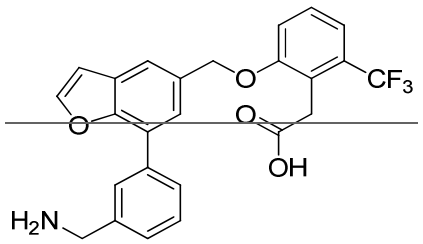
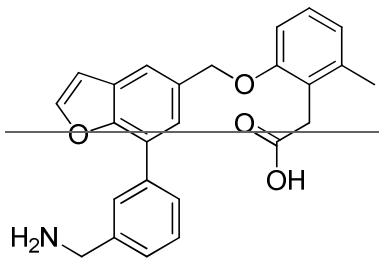
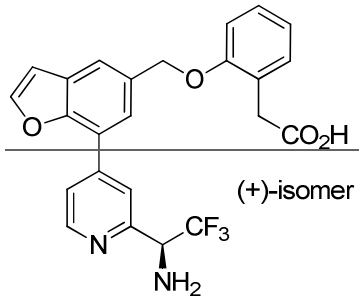
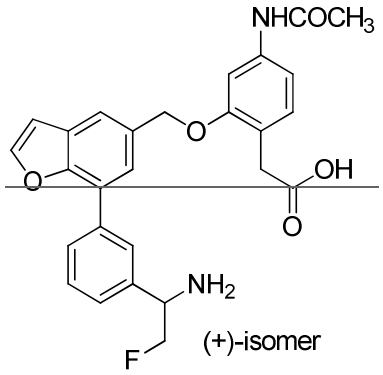
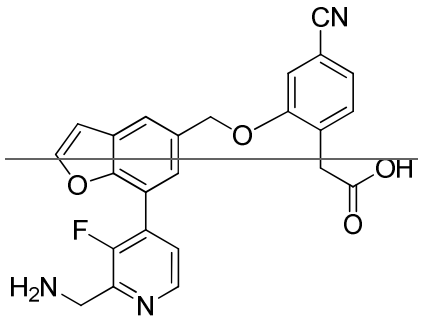
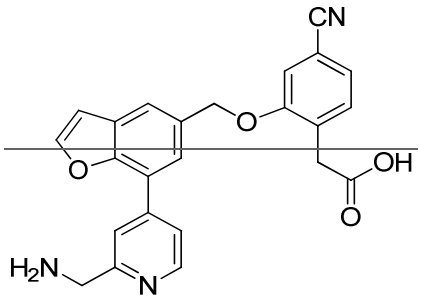
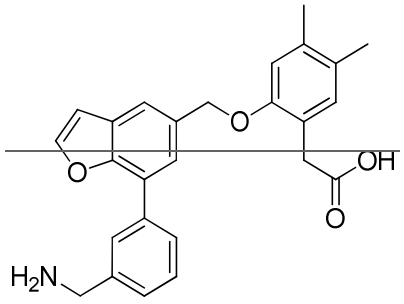
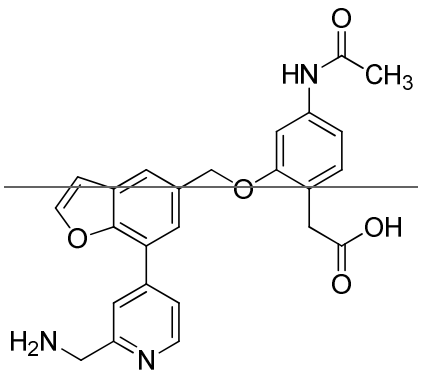
	
	
	
	
	

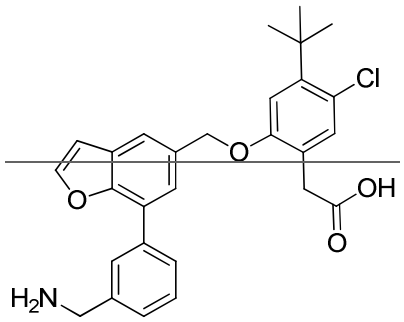
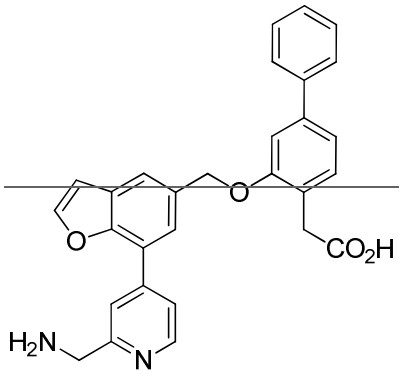
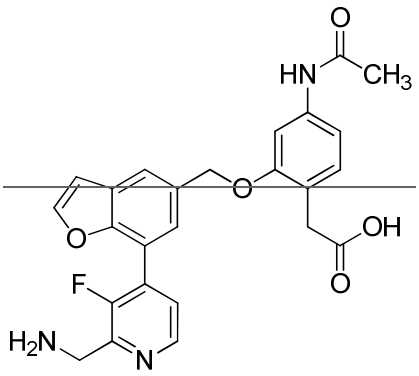
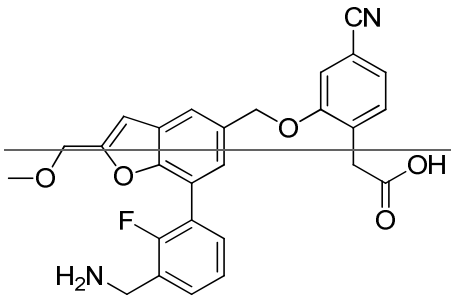
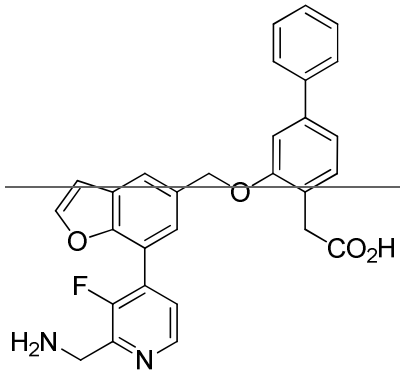
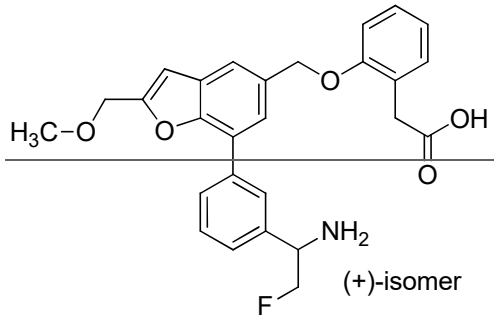
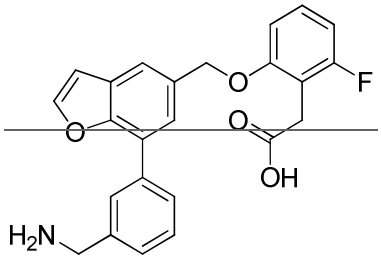
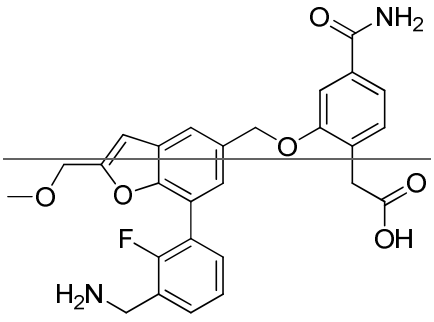
	
	
	
	
	

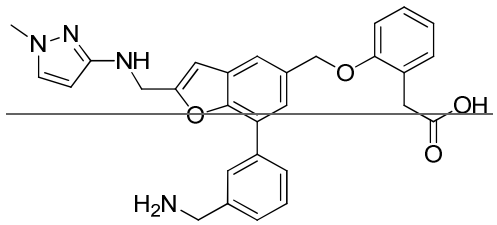
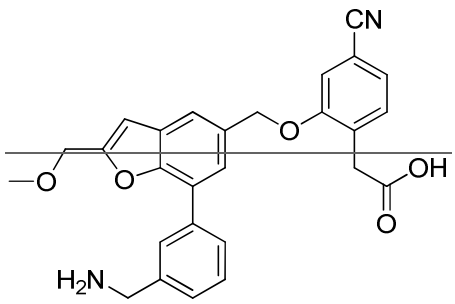
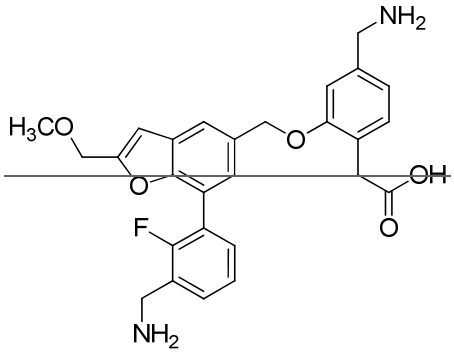
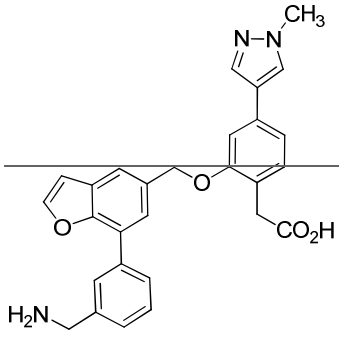
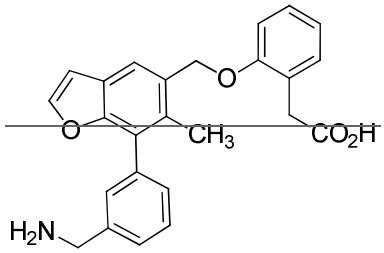
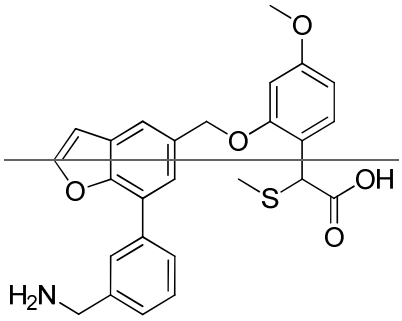
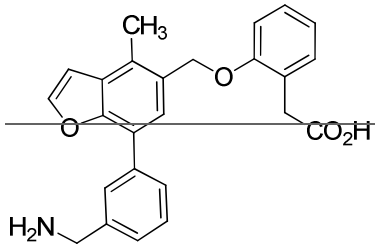
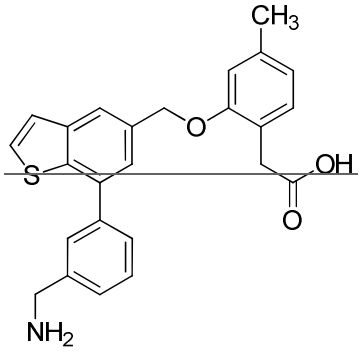
	
	 (+)-isomer
	
	
	 (-)-isomer

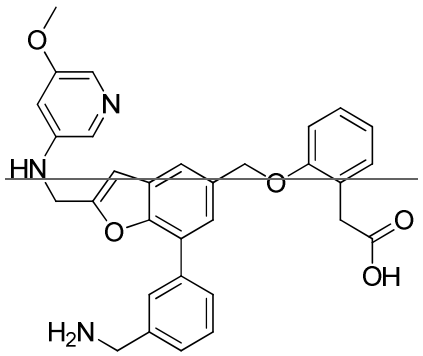
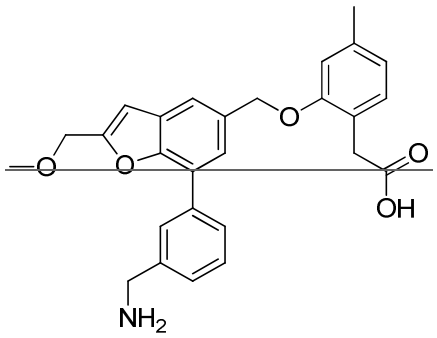
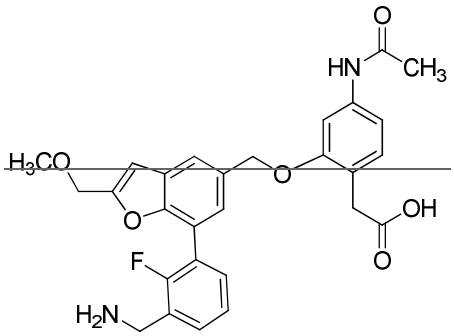
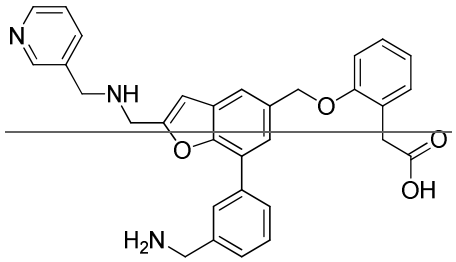
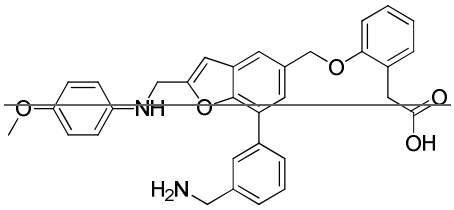
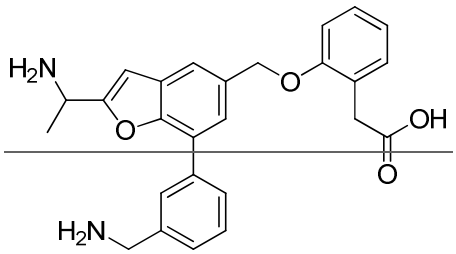
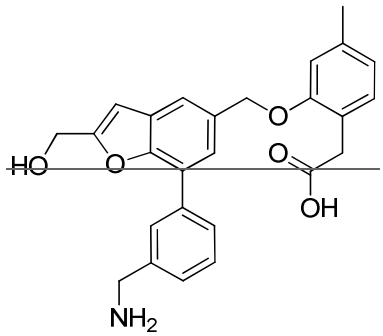
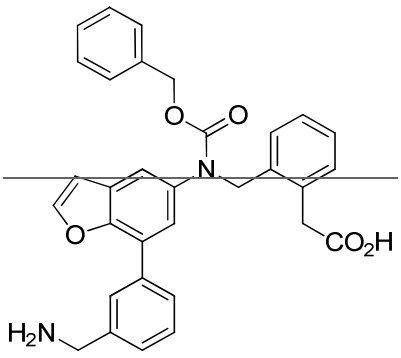
	
	
	
 (+)-isomer	 (+)-isomer

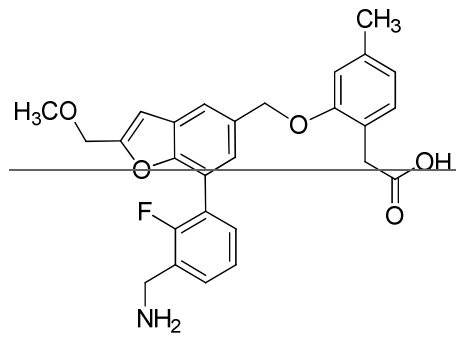
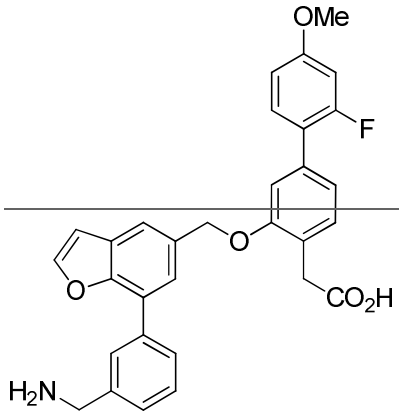
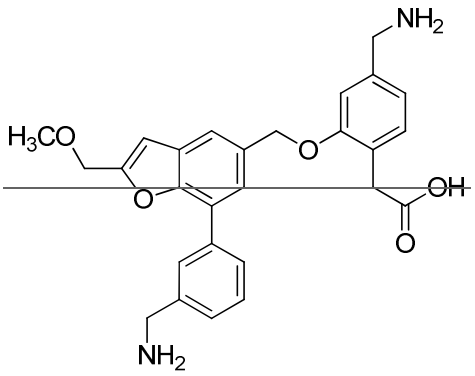
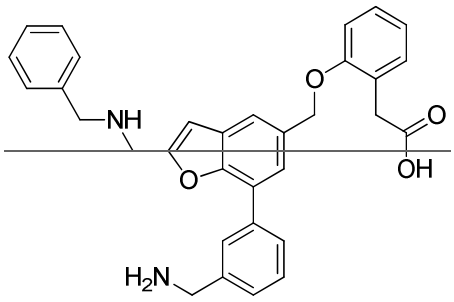
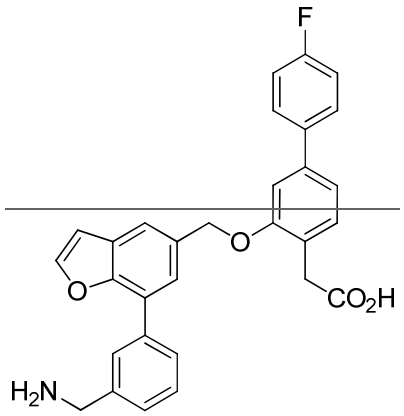
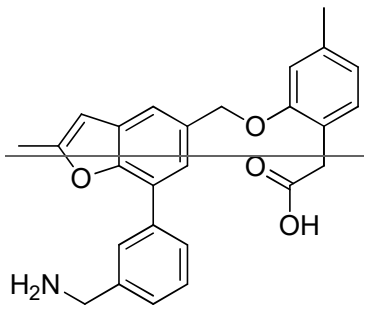
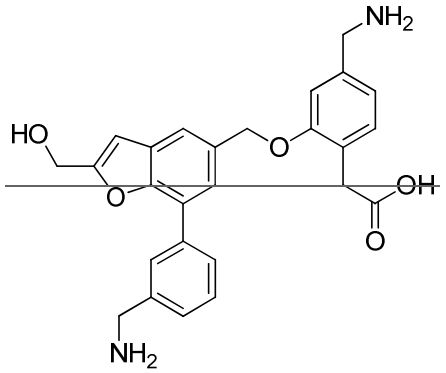
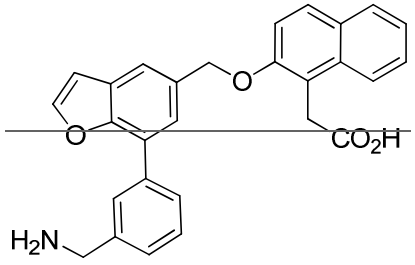
 (+)-isomer	
	
	
	

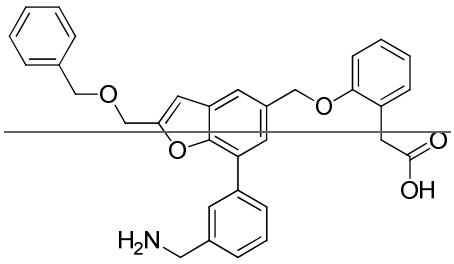
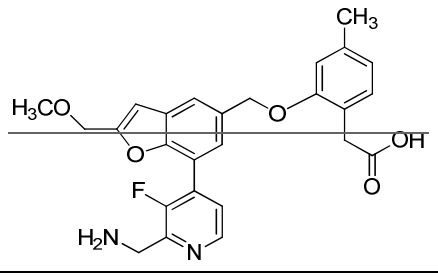
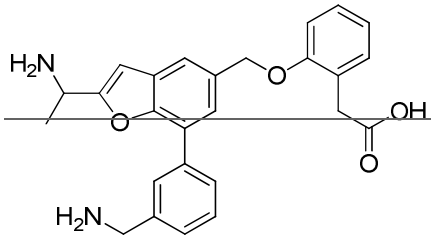
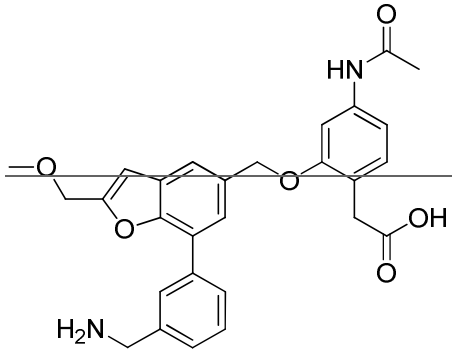
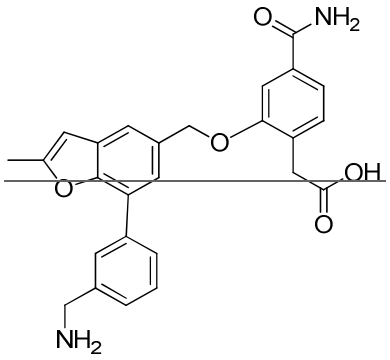
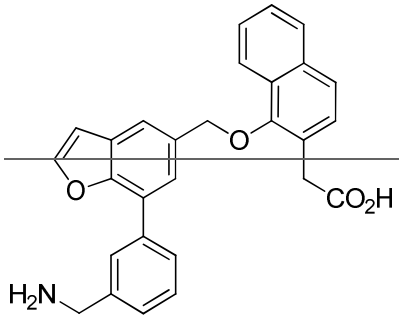
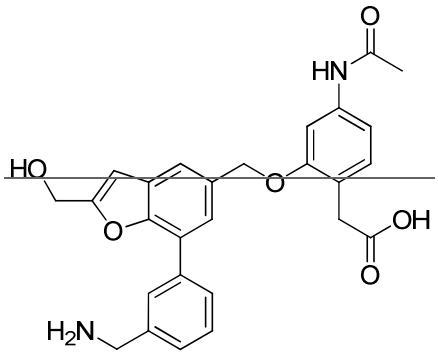
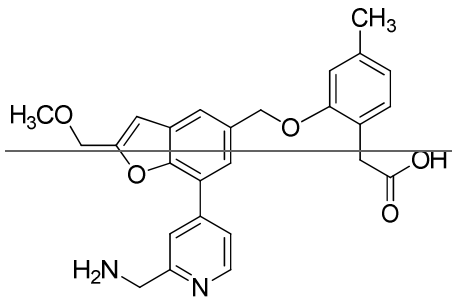
	
	
	
	

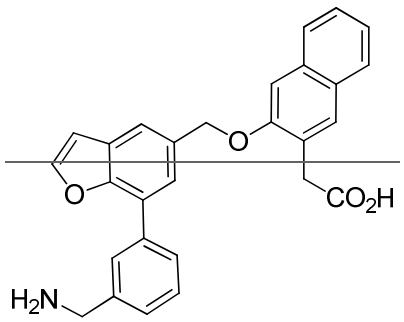
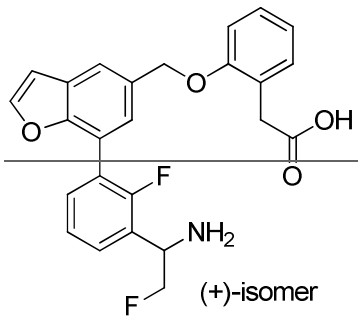
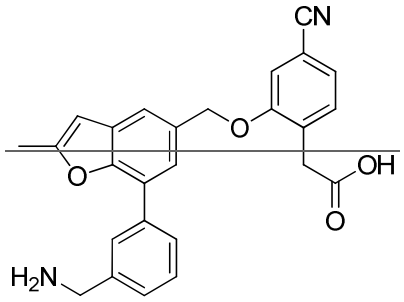
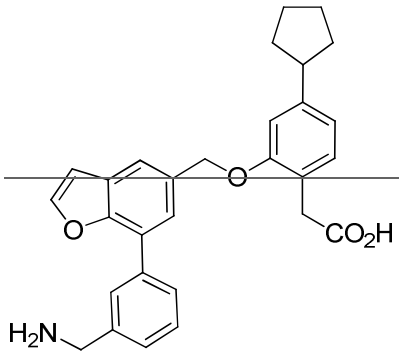
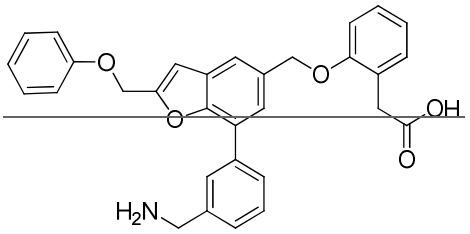
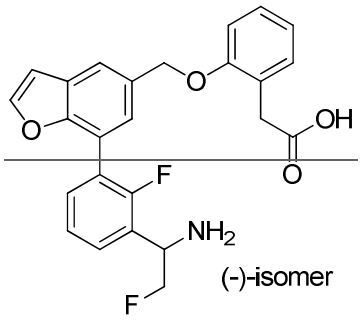
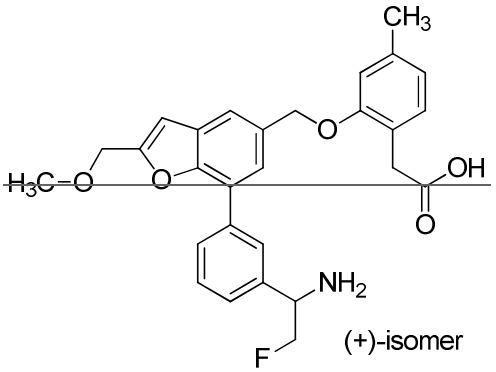
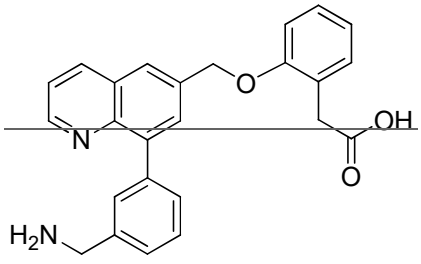
	
	
	 (+)-isomer
	

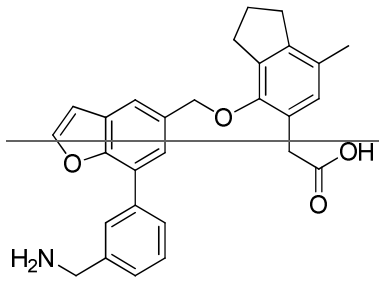
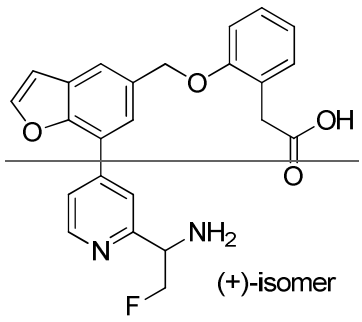
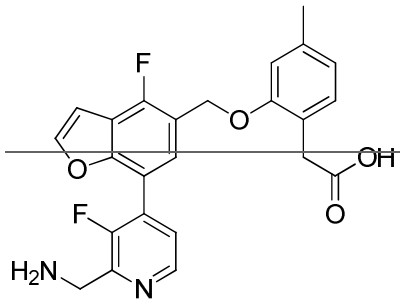
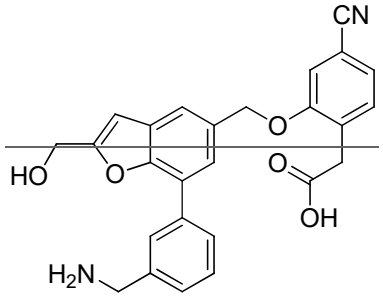
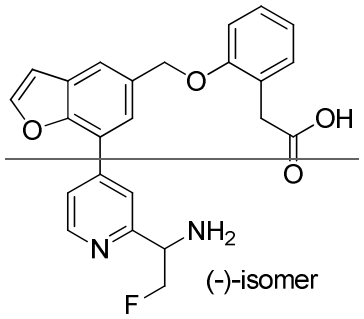
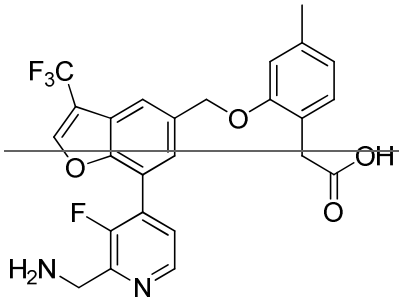
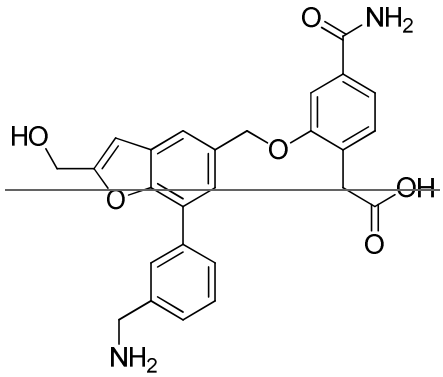
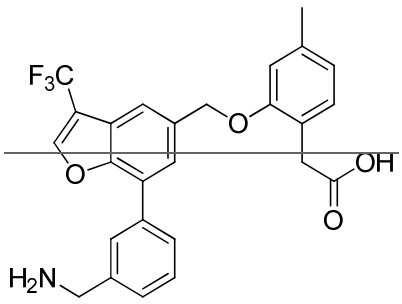
	
	
	
	

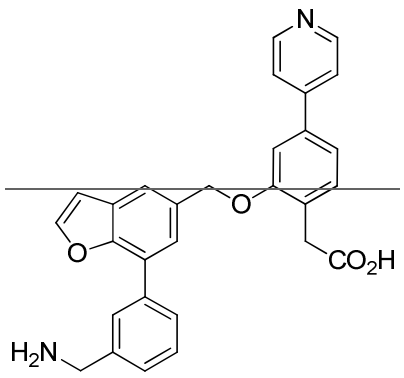
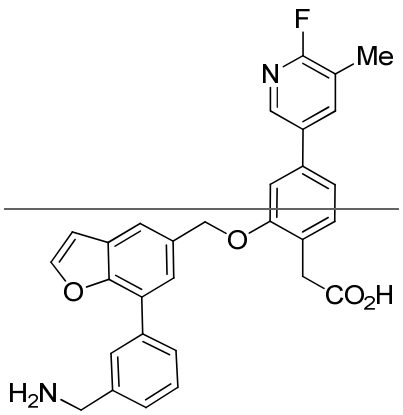
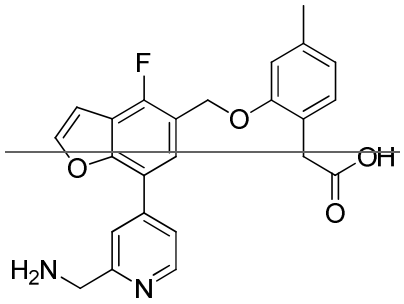
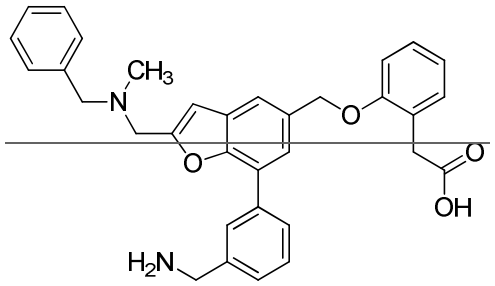
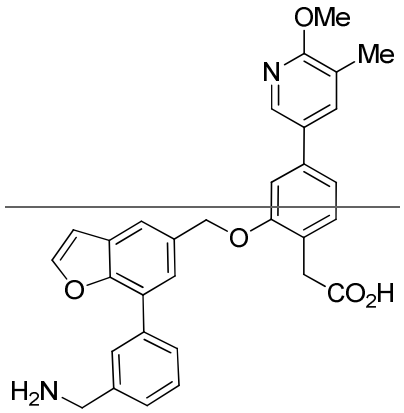
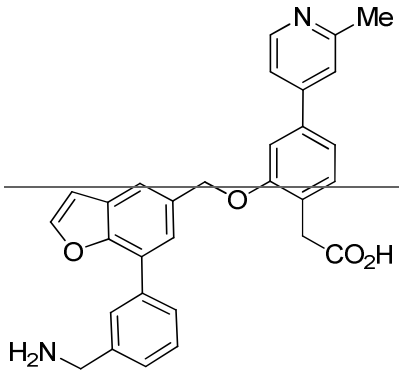
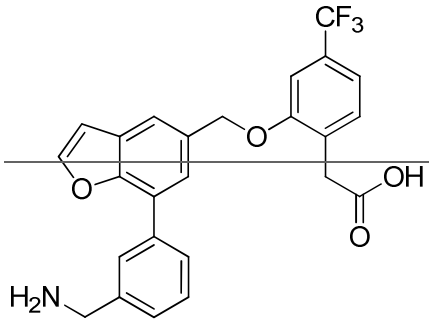
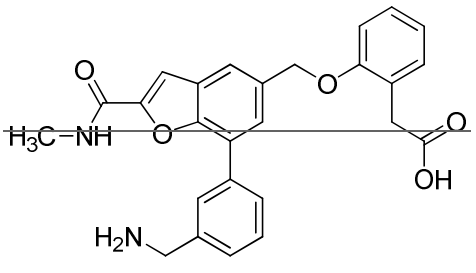
	
	
	 (-)-isomer
	

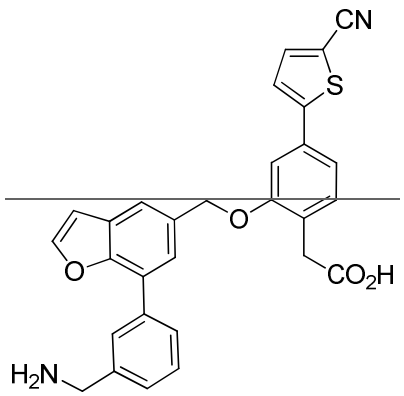
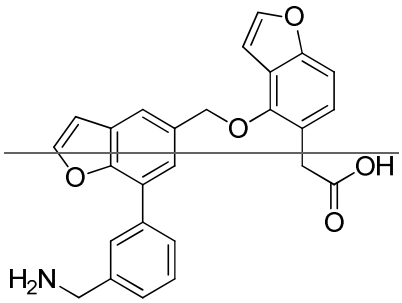
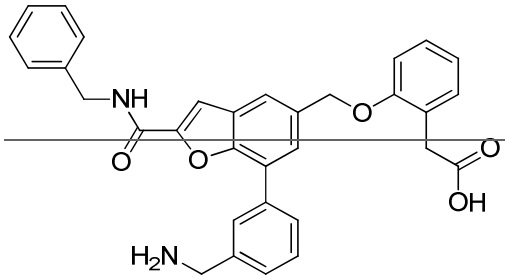
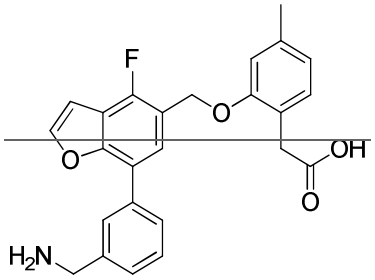
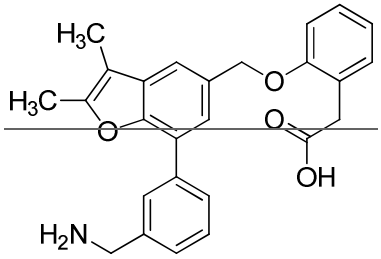
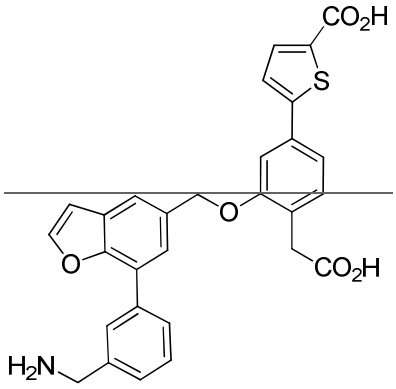
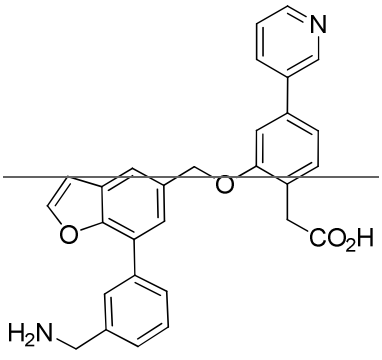
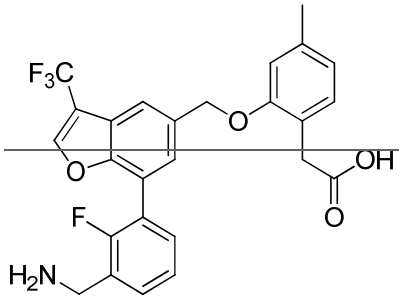
	
	
	
	

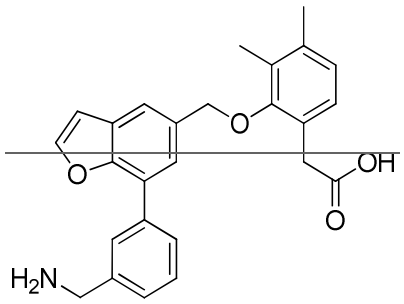
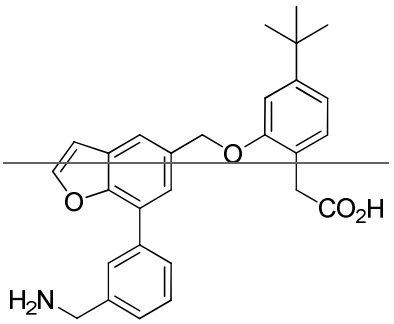
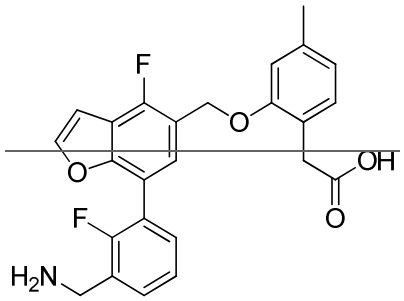
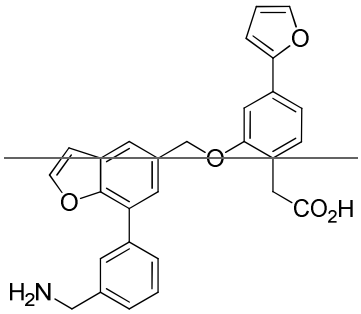
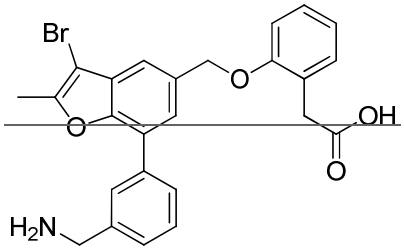
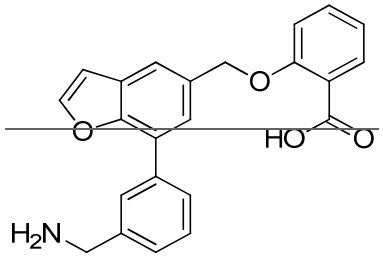
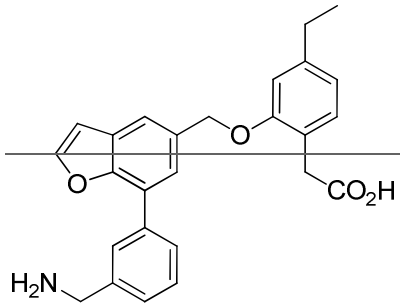
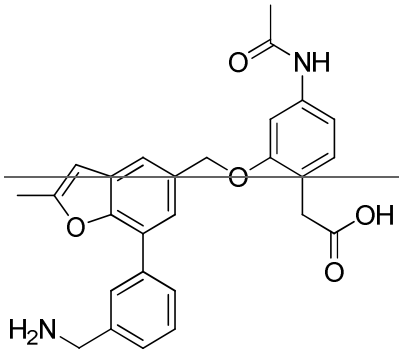
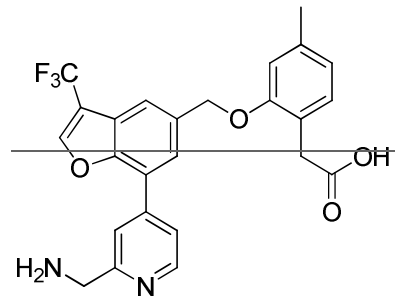
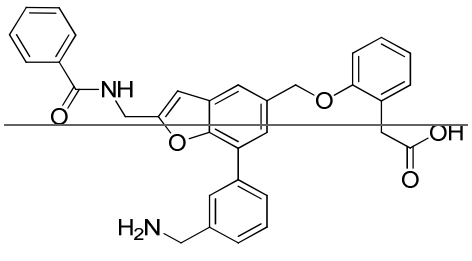
	
	
	
	

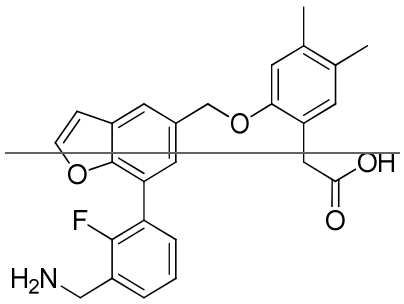
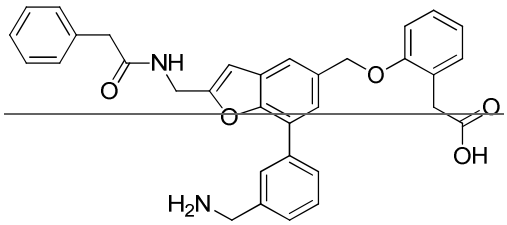
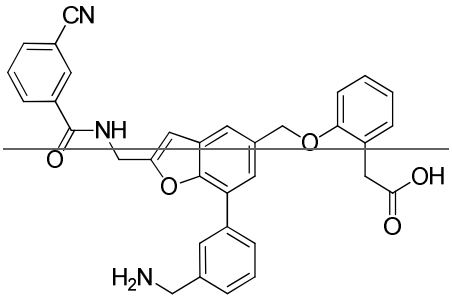
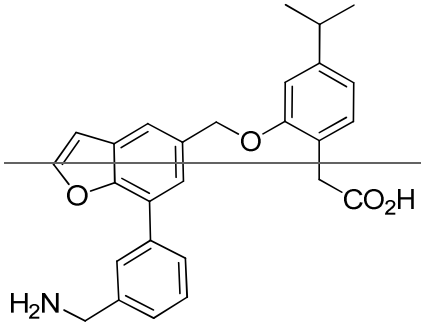
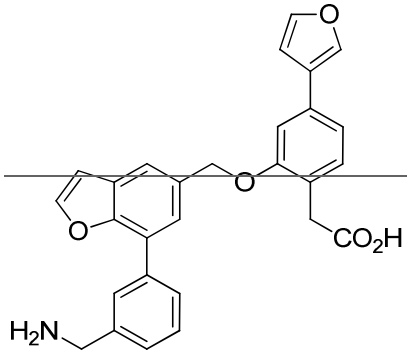
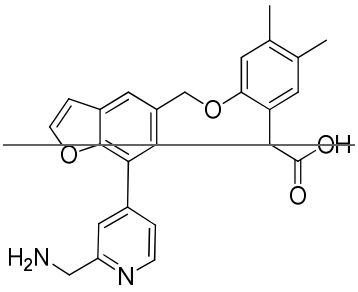
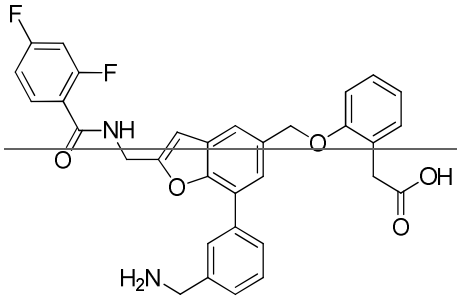
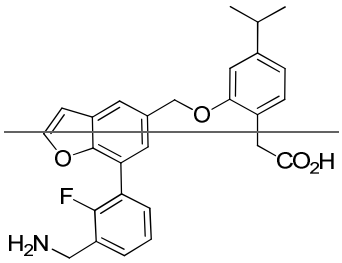
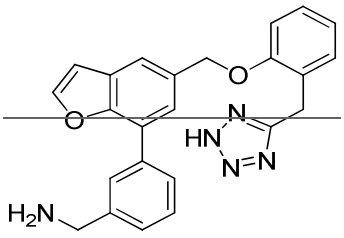
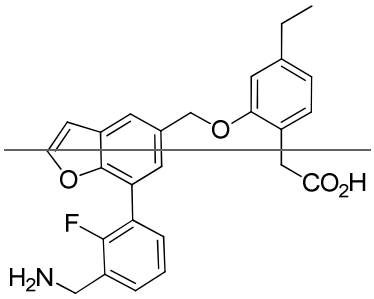
	(+)-isomer
	
	(-)-isomer
(+)-isomer	

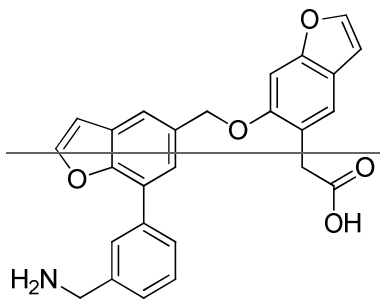
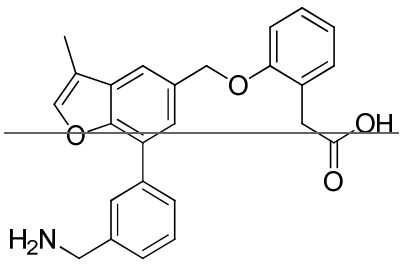
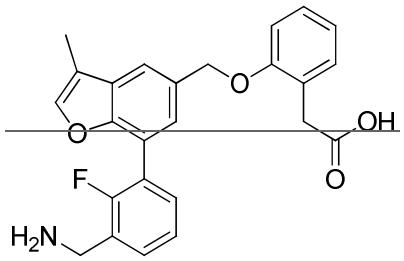
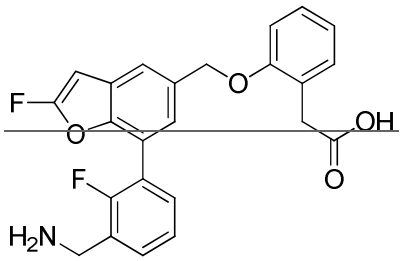
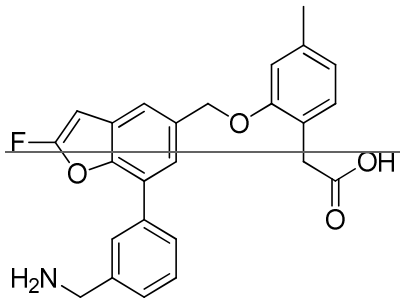
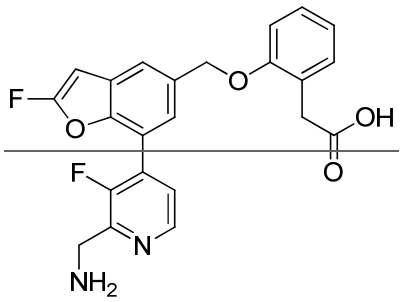
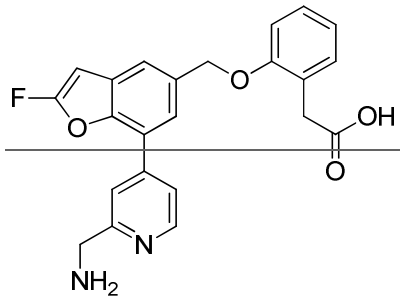
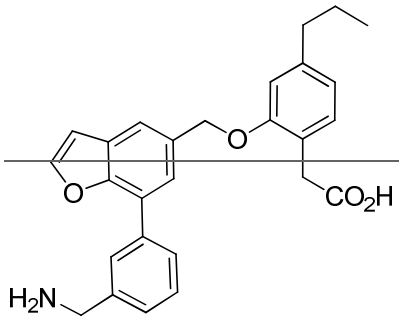
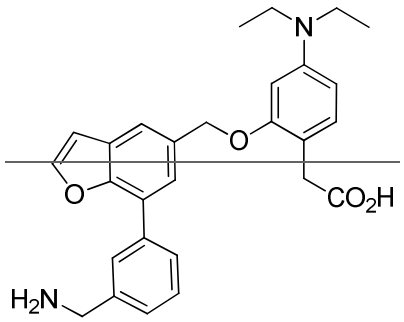
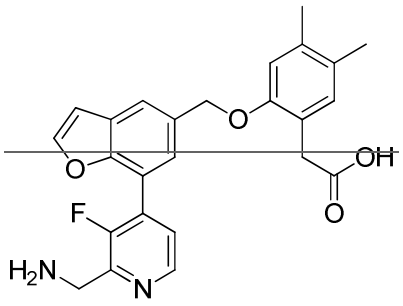
	 (+)-isomer
	
 (-)-isomer	
	

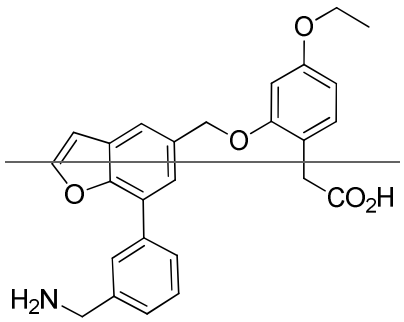
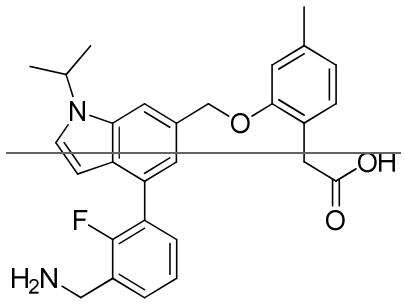
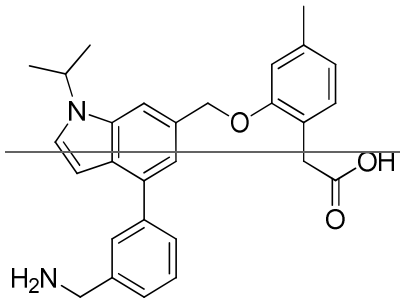
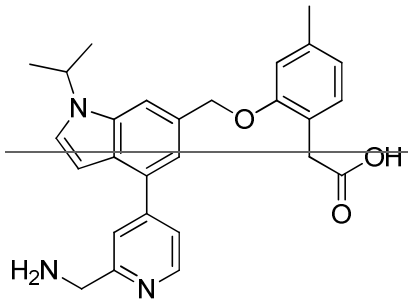
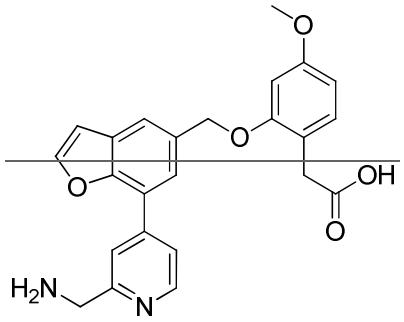
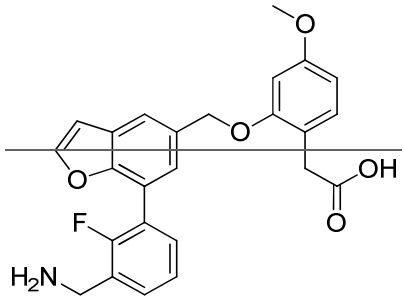
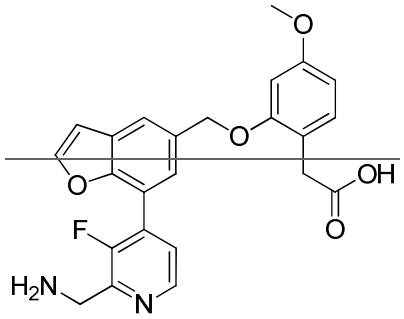
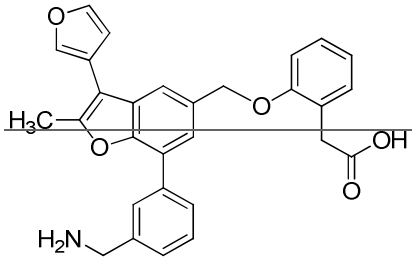
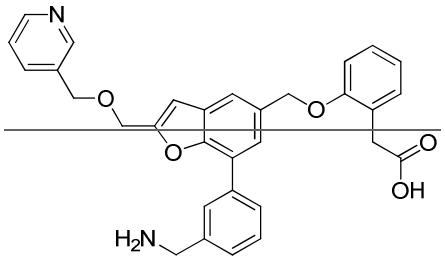
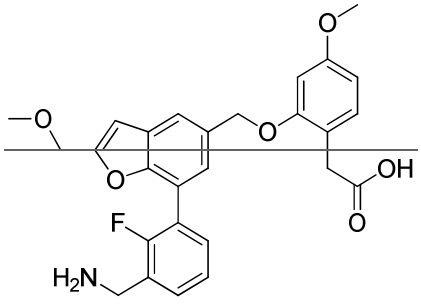
	
	
	
	

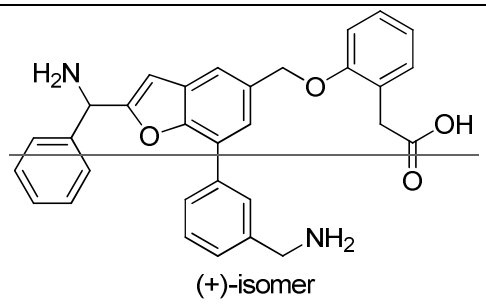
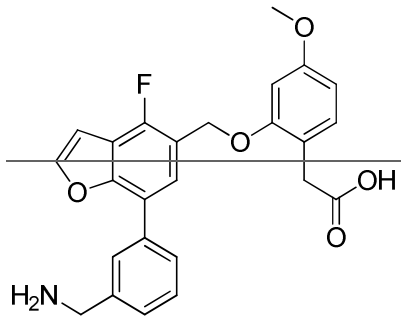
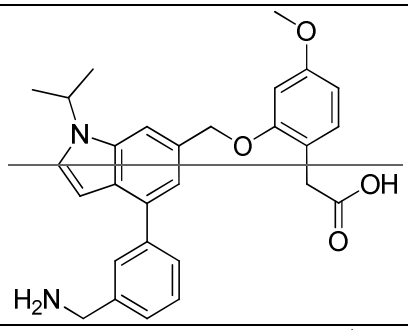
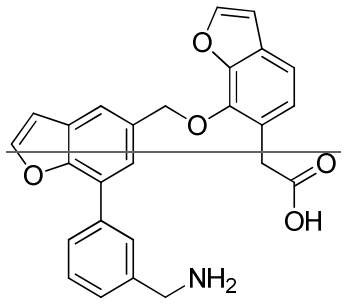
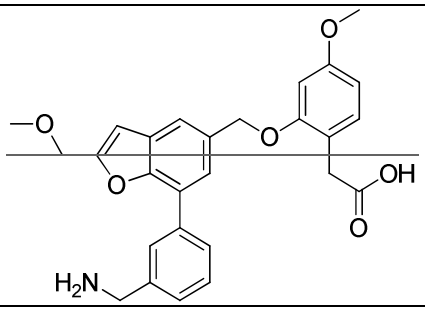
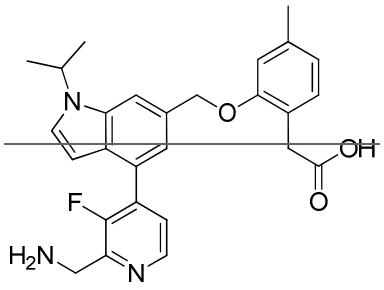
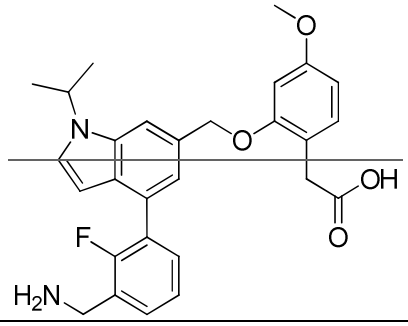
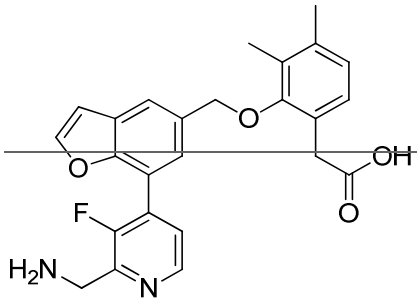
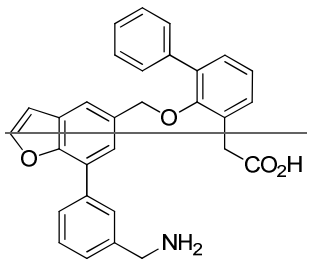
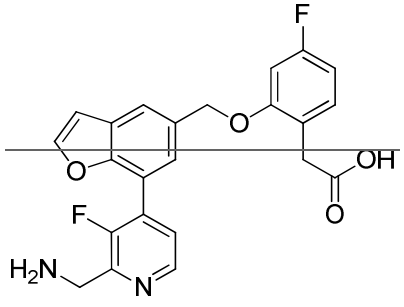
	
	
	
	

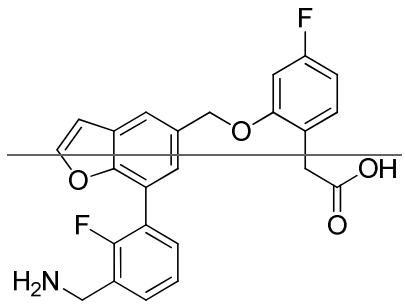
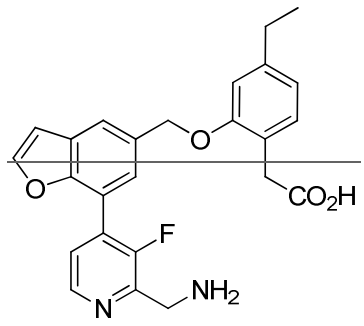
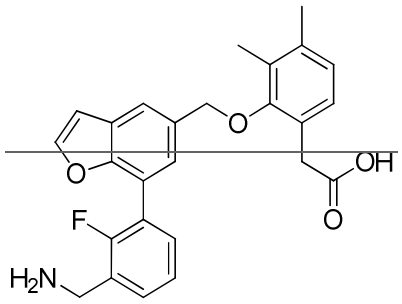
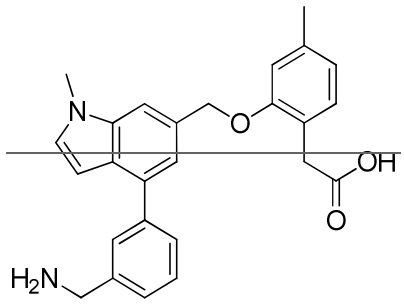
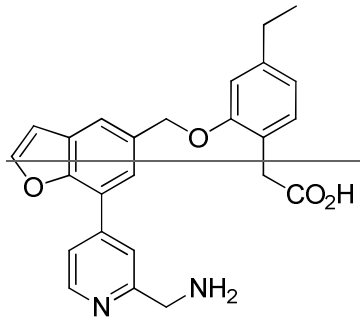
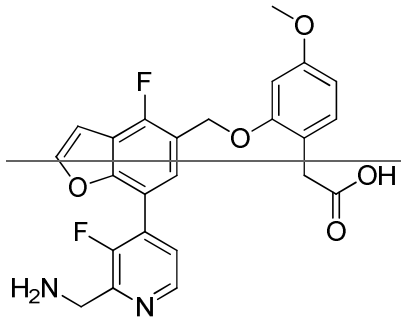
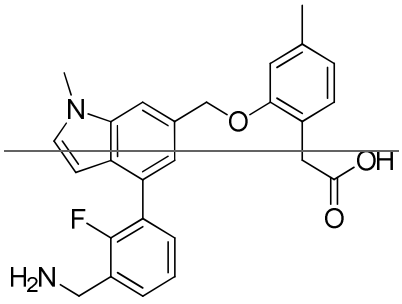
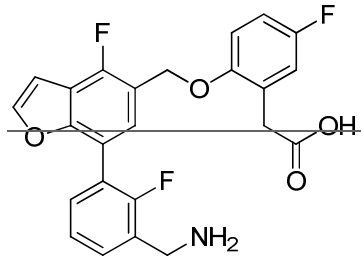
	
	
	
	
	

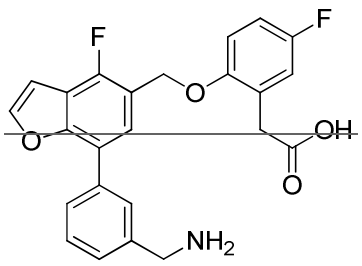
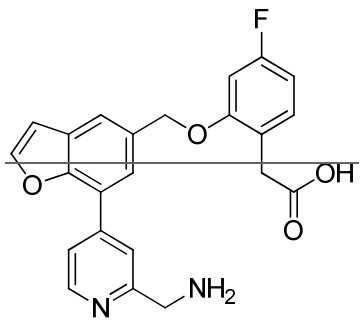
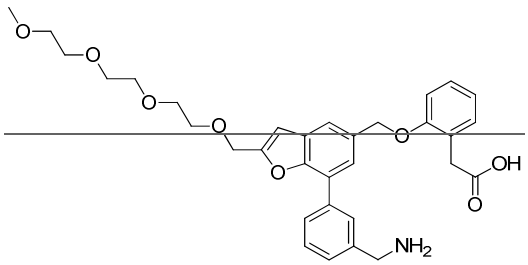
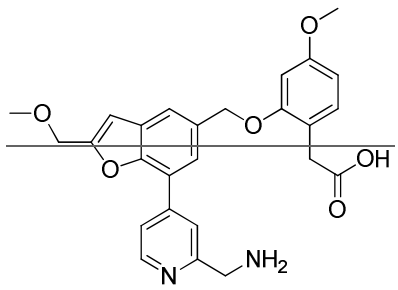
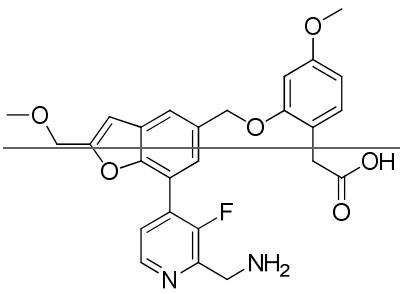
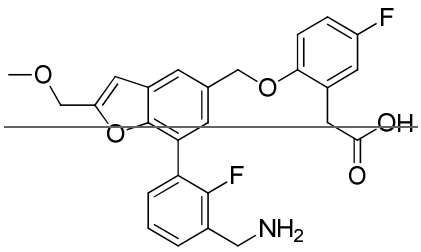
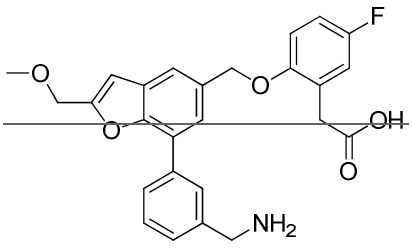
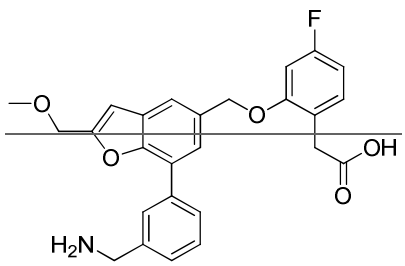
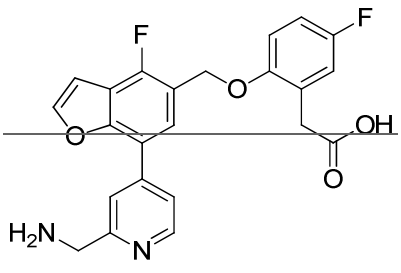
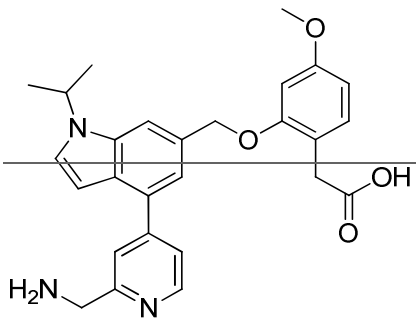
	
	
	
	
	

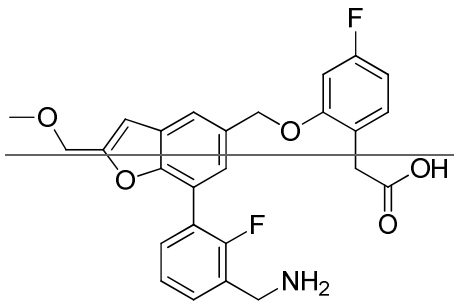
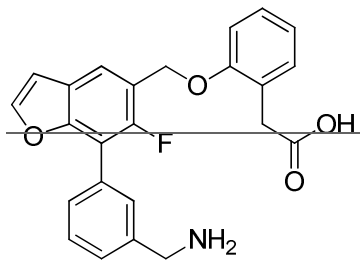
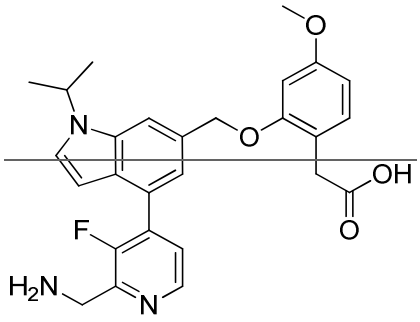
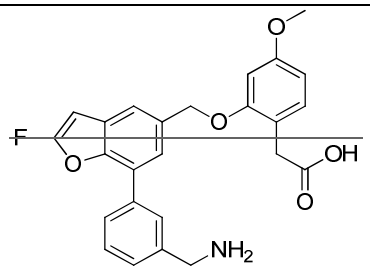
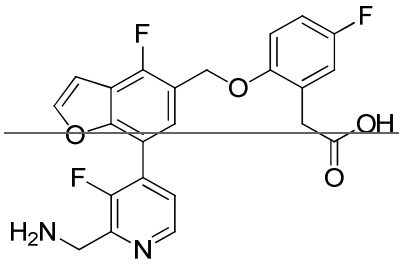
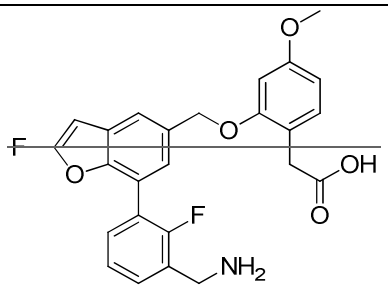
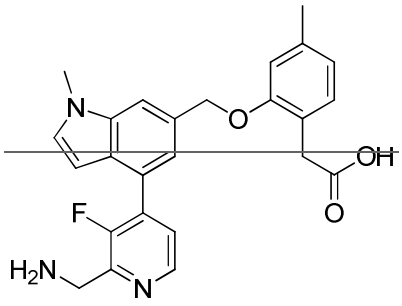
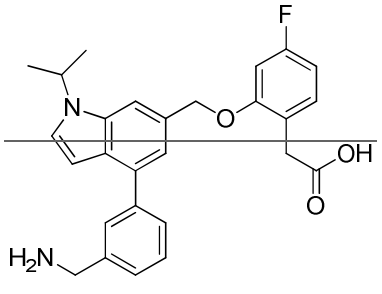
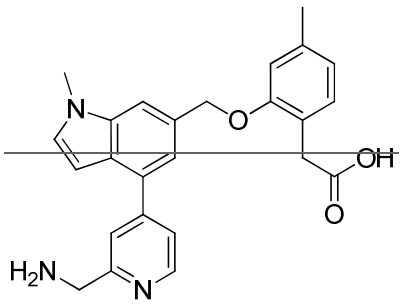
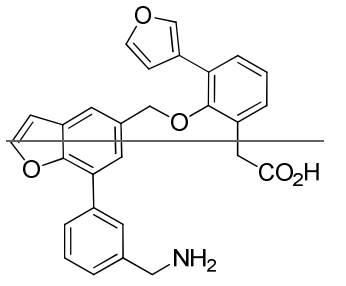
	
	
	
	
	

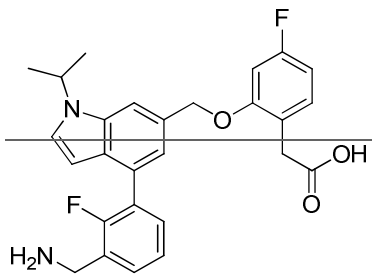
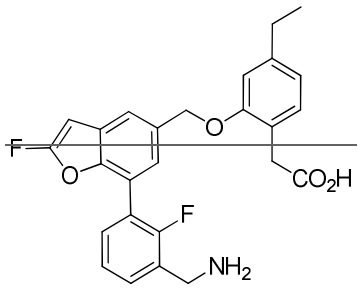
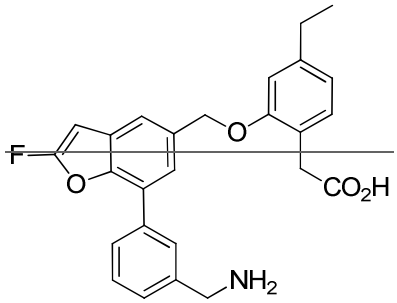
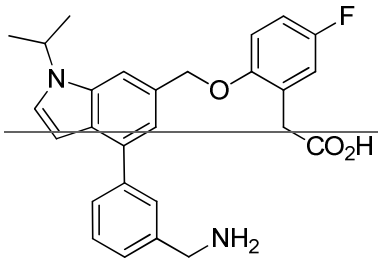
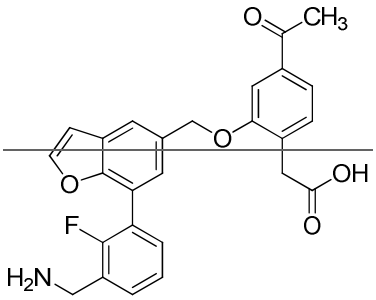
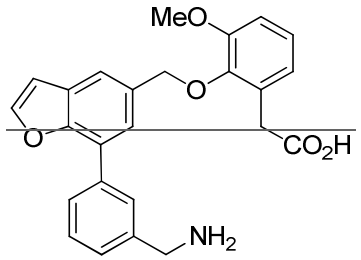
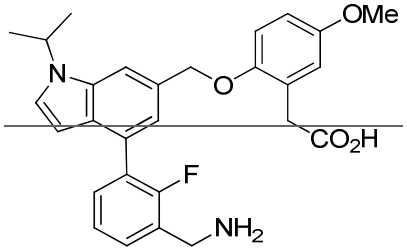
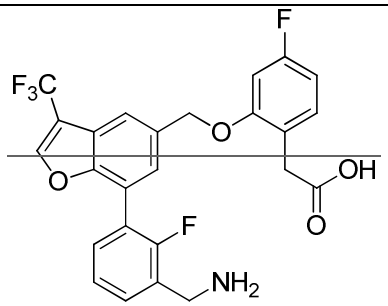
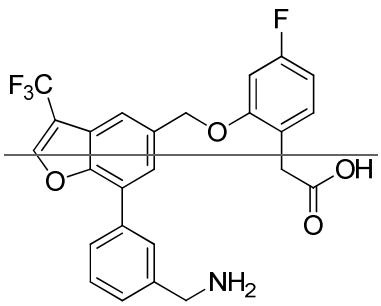
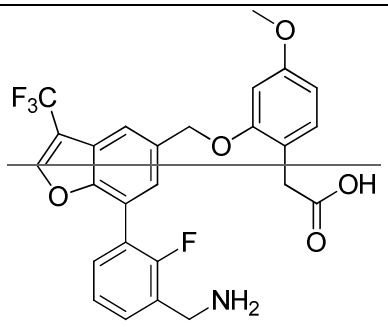
	
	
	
	
	

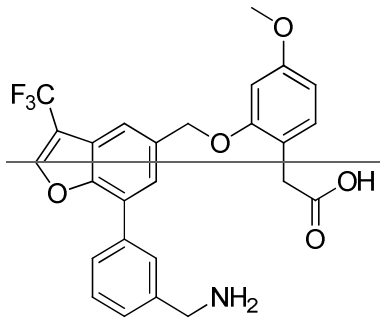
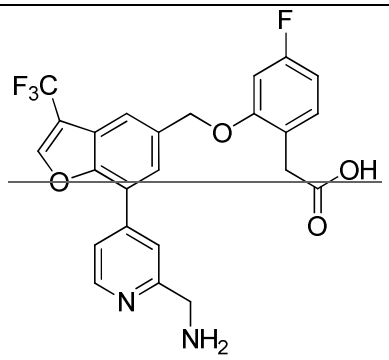
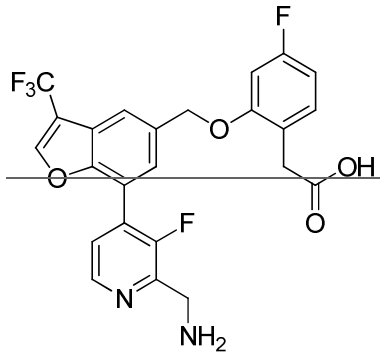
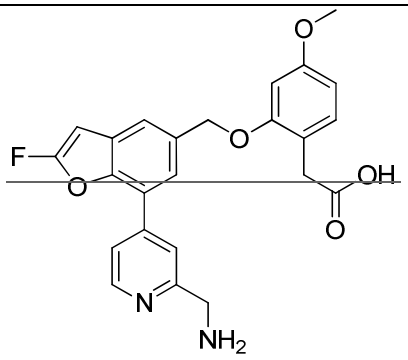
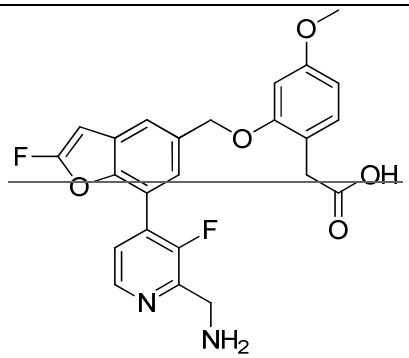
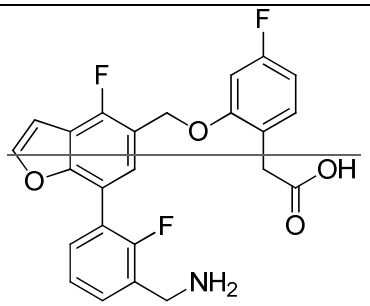
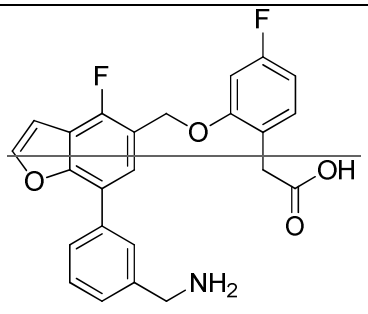
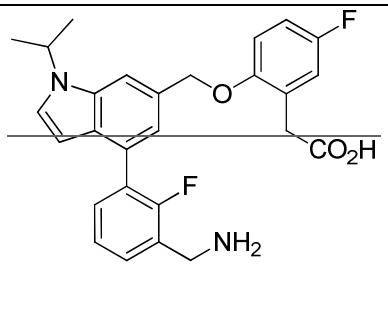
 (+)-isomer	
	
	
	
	

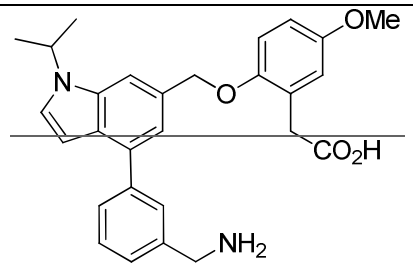
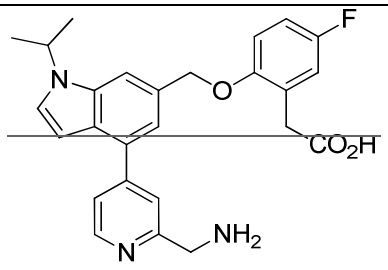
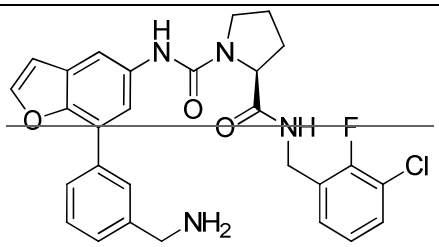
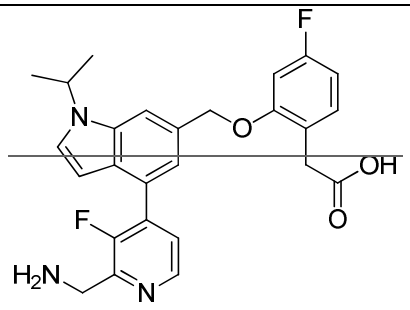
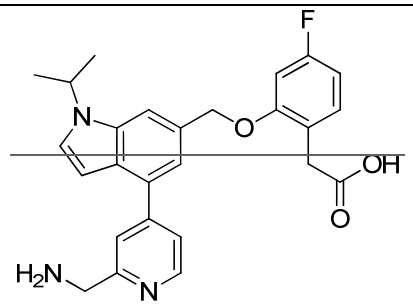
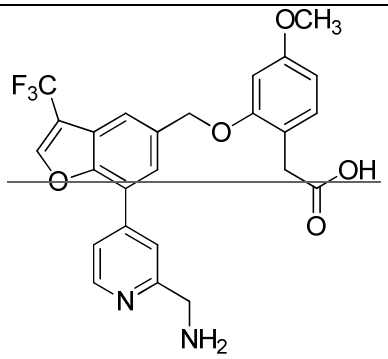
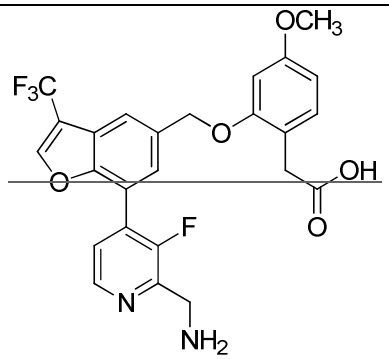
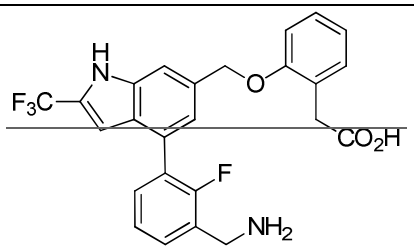
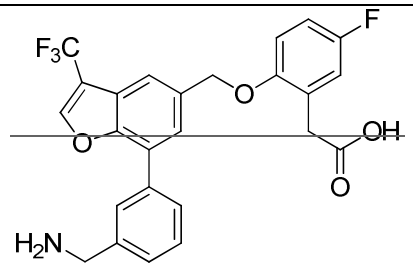
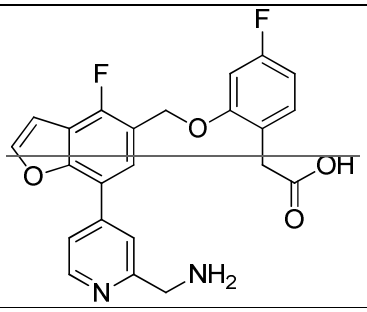
	
	
	
	

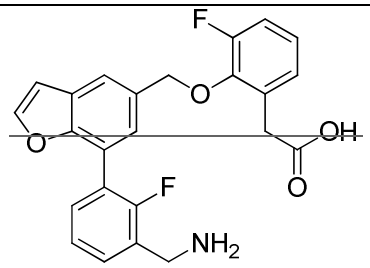
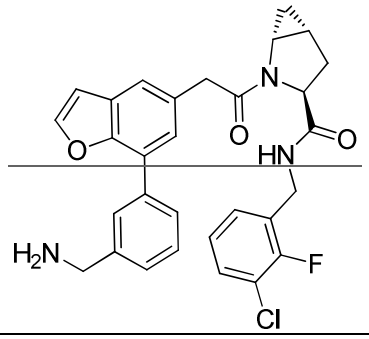
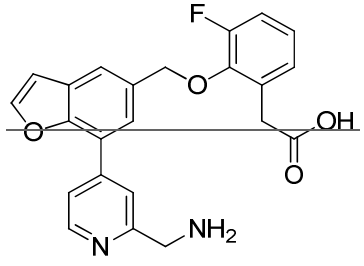
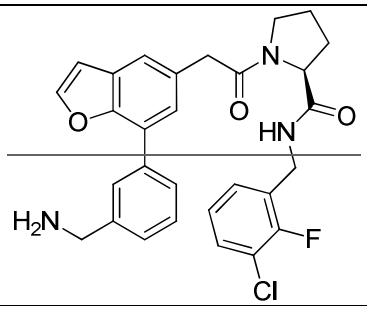
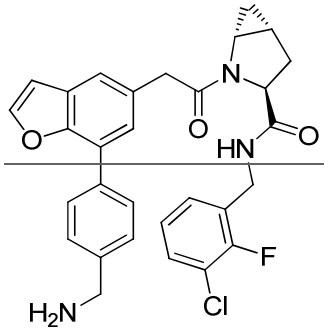
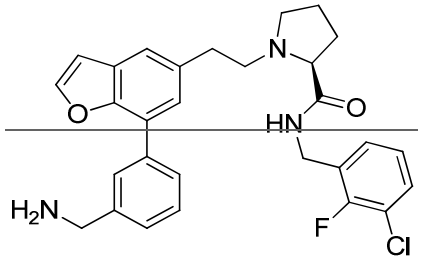
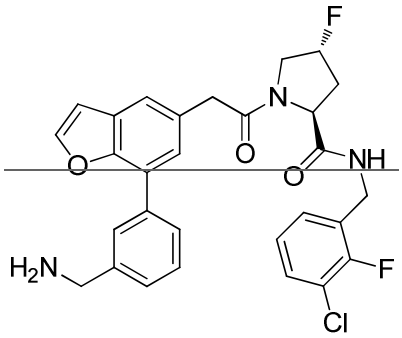
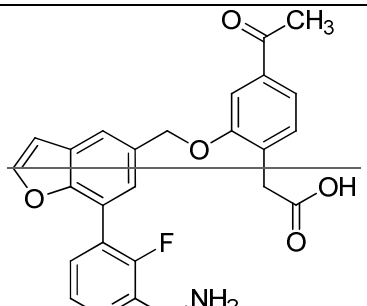
	
	
	
	
	

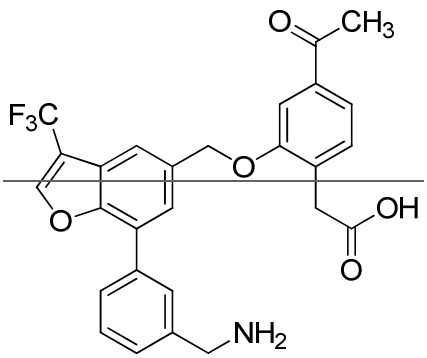
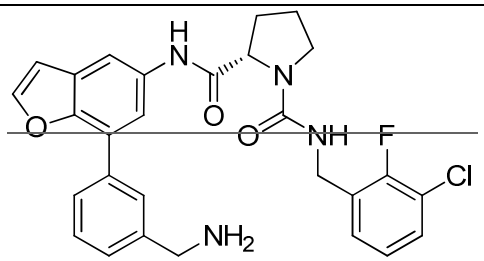
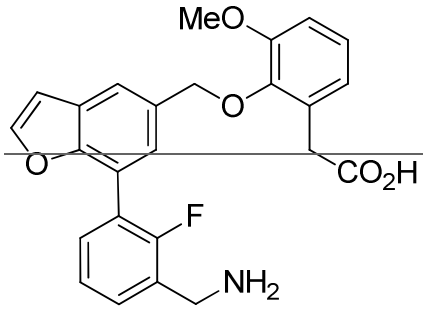
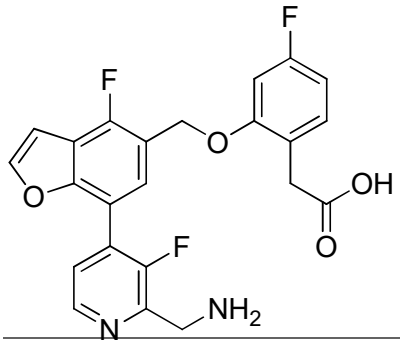
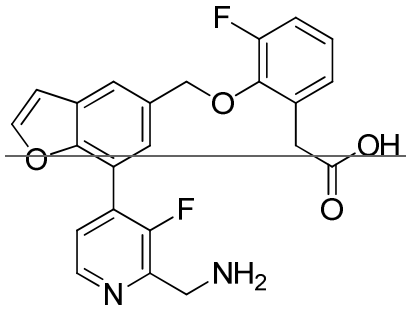
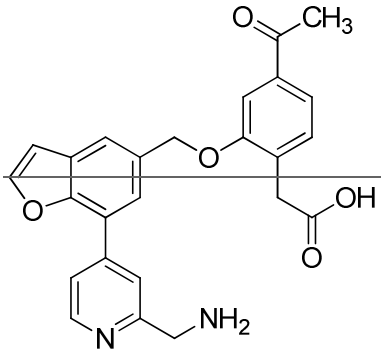
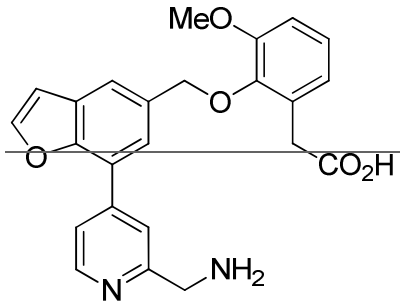
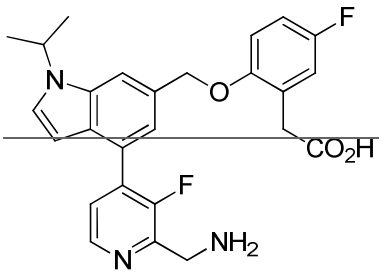
	
	
	
	
	

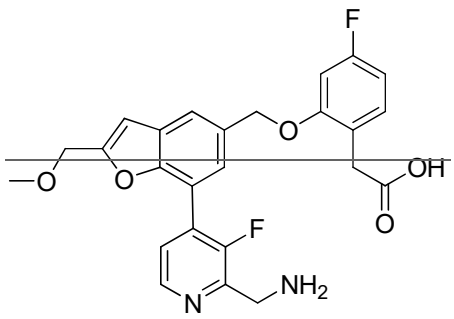
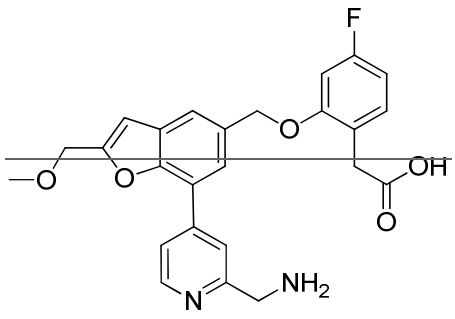
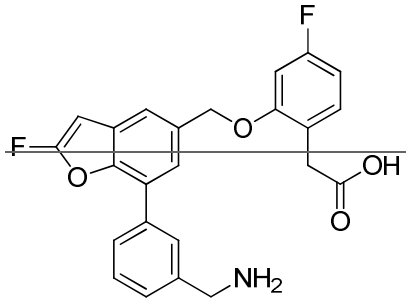
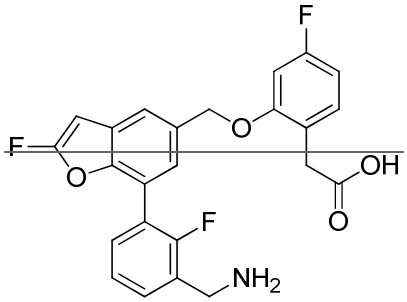
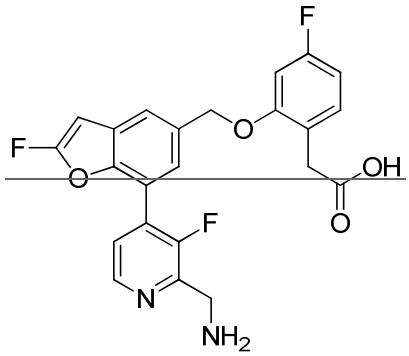
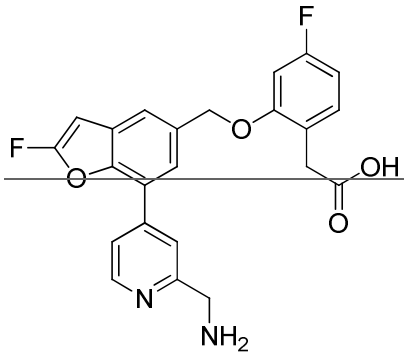
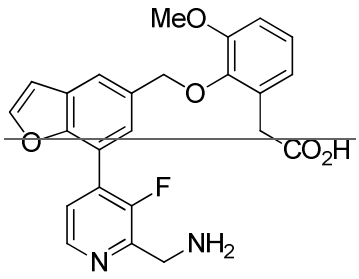
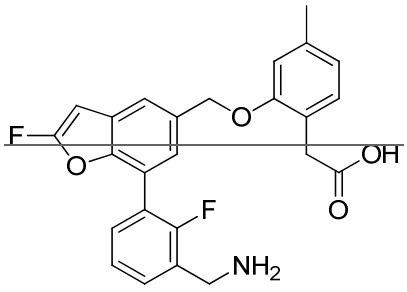
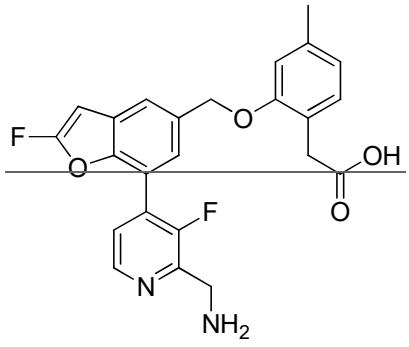
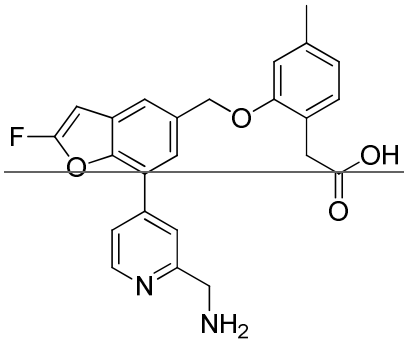
	
	
	
	
	

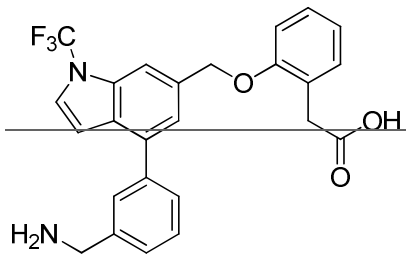
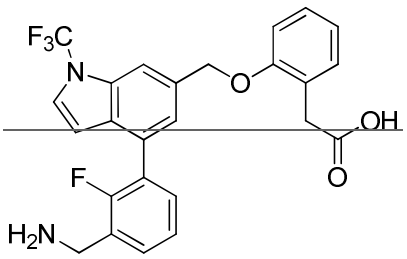
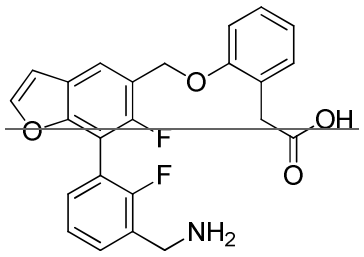
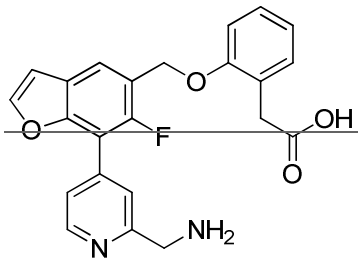
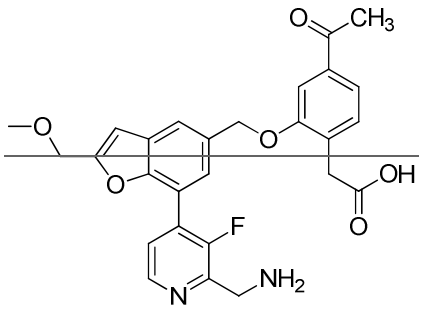
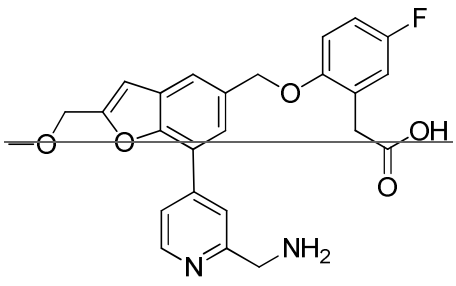
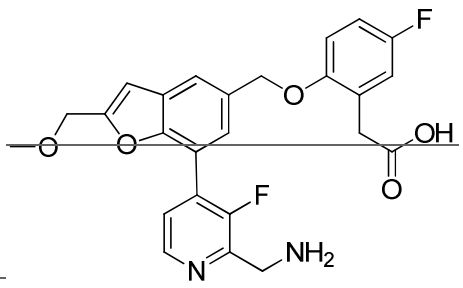
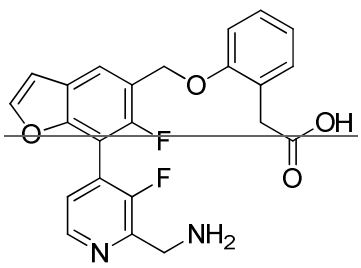
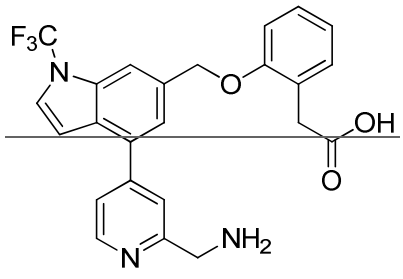
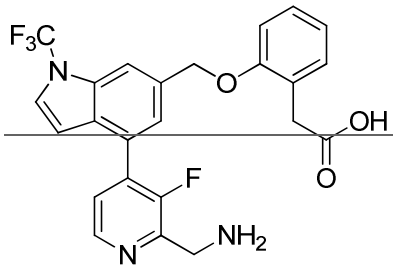
	
	
	
	

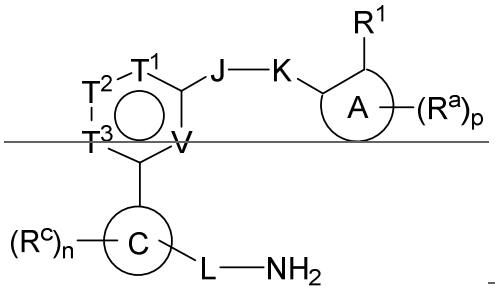
	
	
	
	

45. ~~A compound of formula (II-g), or a pharmaceutically acceptable salt or prodrug thereof:~~



(II-g);

wherein:

ring A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring C is aryl or heteroaryl;

R^a, independently for each occurrence, is halogen, cyano, hydroxy, $-NH_2$, -NH(Ac), -NH(alkyl), -NH(cycloalkyl), -NH(heterocycloalkyl), -NH(aryl), -NH(heteroaryl), -N(alkyl)$_2$, -NHC(O)(alkyl), -CH(alkyl)NH_2, -CH(hydroxyalkyl)NH_2, -CH(haloalkyl)NH_2, -CH(cycloalkyl)NH_2, -CH(heterocycloalkyl)NH_2, -CH(aryl)NH_2, -CH(heteroaryl)NH_2, $-CH_2NHC(O)$(alkyl), -C(O)NH_2, -C(O)(alkyl), $-SO_2NH_2$, $-SO_2$(cycloalkyl), $-SO_2$(heterocycloalkyl), $-SO_2$(alkyl), $-SO_2$(aryl), or $-SO_2$(heteroaryl); or is selected from the group consisting of substituted or unsubstituted aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T^1 is N, CH, NR^{T1}, or CR^{T1};

T^2 is NR^{T2} or CR^{T2};

T^3 is N, CH, NR^{T3}, or CR^{T3};

wherein:

(a) T^1 is CR^{T1} or NR^{T1}, wherein R^{T1} and R^{T2}, taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T^3 is N or CH; or

(b) T^3 is CR^{T3} or NR^{T3}; wherein R^{T3} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T^1 is N or CH; and

at least one of (a) T^2 is NR^{T2}, (b) T^3 is N, or (c) T^1 is NR^{T1};

R^1 is selected from the group consisting of $-NH_2$, $-COOH$, $-CH_2COOH$, $-CH(NH(CO)(alkyl))COOH$, $-CH(NH(CO)(arylalkyl))COOH$, $-CH(NH(CO)(cycloalkyl))COOH$, $-CH(NH(CO)$(aryl substituted cycloalkyl))$COOH$, $-CH(NH(CO)$(heteroaryl substituted cycloalkyl))$COOH$, $-CH(S(alkyl))COOH$, $-CO(NH)CH_2$(substituted or unsubstituted aryl), $-CO(NH)CH_2$(substituted or unsubstituted heteroaryl), $-CO(NH)$(substituted or unsubstituted aryl), $-CO(NH)$(substituted or unsubstituted heteroaryl), and $-CH_2$(tetrazolyl);

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

J is $-C(O)-$, $-NH-$, $-CH_2-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, $-CH(alkyl)-$, $-CH(cycloalkyl)-$, $-N((C(O)O)arylalkyl)-$, $-N((C(O)O)heteroarylalkyl)-$, or $-N(C(O)arylalkyl)-$;

K is $-C(O)-$, $-NH-$, $-CH_2-$, $-O-$, $-S-$, $-S(O)-$, $-SO_2-$, $-N(alkyl)-$, $-CH(alkyl)-$, $-CH(cycloalkyl)-$, $-N((C(O)O)arylalkyl)-$, $-N((C(O)O)heteroarylalkyl)-$, or $-N(C(O)arylalkyl)-$;

R^e, independently for each occurrence, is selected from the group consisting of halogen, OH, $-NR^jR^k$, alkoxy, alkyl, cycloalkyl, and heterocycloalkyl;

L is selected from the group consisting of a bond, $-CH_2-$, $-CH_2CH_2-$, $-CHR^2-$, $-CF_2-$, $-CFR^2-$, $-C(O)-$, $-C(=NR^L)-$, $-C(=CHR^L)-$, $-S(O)_2-$, and $-S(O)-$;

wherein R^L is H or alkyl;

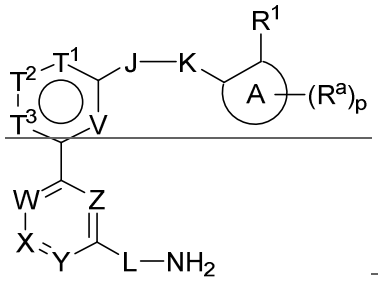
or wherein R^L and an occurrence of R^e taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, cycloalkyl, hydroxyalkyl, or haloalkyl;

V is N or CH; and

the stereochemical configuration at any chiral center is *R*, *S*, or a mixture of *R* and *S*.

46. The compound of claim 45, having the structure of formula (II):



(II);

wherein:

ring A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^a, independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, NH_2, NH(Ac), NH(alkyl), $N(alkyl)_2$, NHC(O)(alkyl), $CH_2NHC(O)(alkyl)$, $C(O)NH_2$, C(O)(alkyl), optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T^1 is N, CH, NR^{T1}, or CR^{T1};

T^2 is NR^{T2} or CR^{T2};

T^3 is N, CH, NR^{T3}, or CR^{T3};

wherein:

(a) T^1 is CR^{T1} or NR^{T1}, wherein R^{T1} and R^{T2}, taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T^3 is N or CH; or

(b) T^3 is CR^{T3} or NR^{T3}; wherein R^{T3} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T^1 is N or CH; and

at least one of (a) T^2 is NR^{T2}, (b) T^3 is N, or (c) T^1 is NR^{T1};

R^1 is selected from the group consisting of NH_2, CH_2COOH, CH(NH(CO)(alkyl))COOH, CH(NH(CO)(cycloalkyl))COOH, $CO(NH)CH_2$aryl, $CO(NH)CH_2$heteroaryl, CO(NH)aryl, and CO(NH)heteroaryl;

p is 0, 1, or 2;

J is C(O), NH, CH_2, O, S, S(O), SO_2, N(alkyl), or CH(alkyl);

K is C(O), NH, O, CH_2, S, S(O), SO_2, N(alkyl), or CH(alkyl);

wherein at least one of J and K is C(O), CH_2, or CH(alkyl);

W is N, CH, or CR^e;

X is N, CH, or CR^e;

Y is N, CH, or CR^e;

Z is N, CH, or CR^e;

R^e, independently for each occurrence, is selected from the group consisting of halogen, OH, NR^jR^k, alkoxy, and alkyl;

L is selected from the group consisting of a bond, CH_2, CH_2CH_2, CHR^2, CF_2, CFR^2, C(O), $C(=NR^L)$, and $C(=CHR^L)$;

wherein R^L is H or alkyl;

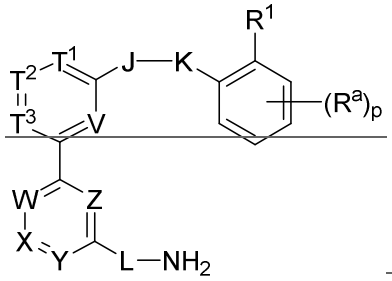
or wherein R^L and an occurrence of R^e taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, hydroxyalkyl, or haloalkyl; and

V is N or CH.

47. The compound of claim 45 or 46, wherein ring  is phenyl, thiophenyl, furyl, pyrazole, or pyridinyl.

48. The compound of claim 45 or 46, having the structure of formula (IIa):



(IIa).

49. The compound of any one of claims 45-48, wherein p is 1.

50. The compound of claim 49, wherein R^a is alkyl or alkoxy.

51. The compound of any one of claims 45-48, wherein p is 0.

~~52. The compound of any one of claims 45-51, wherein R^1 is CH_2COOH.~~

~~53. The compound of any one of claims 45-52, wherein J-K is selected from the group consisting of C(O)-NH, NH-C(O), and CH_2O.~~

~~54. The compound of claim 53, wherein J-K is CH_2O.~~

~~55. The compound of any one of claims 45-54, wherein V is CH.~~

~~56. The compound of any one of claims 45-55, wherein each of W, X, Y, and Z is CH.~~

~~57. The compound of any one of claims 45-55, wherein at least one of W, X, Y, and Z is CR^e.~~

~~58. The compound of claim 57, wherein Z is CR^e.~~

~~59. The compound of claim 57 or 58, wherein Y is CR^e.~~

~~60. The compound of any one of claims 57-59, wherein R^e is halogen, e.g., fluoride.~~

~~61. The compound of any one of claims 45-55 and 57, wherein at least one of W, X, Y, and Z is N.~~

~~62. The compound of claim 61 wherein Z is N.~~

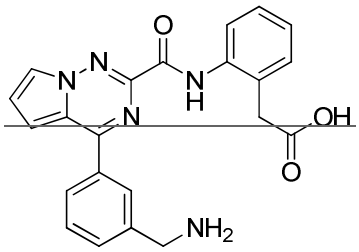
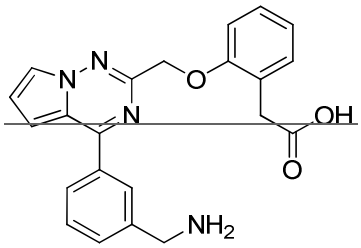
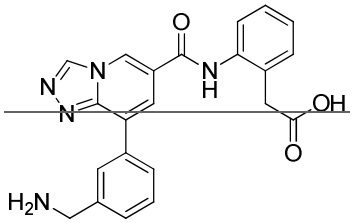
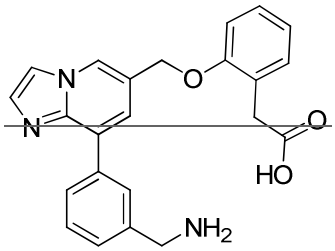
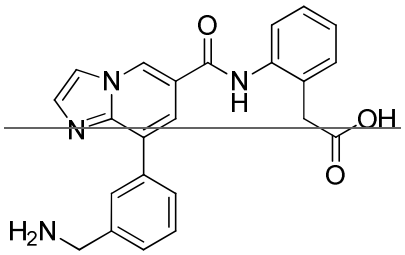
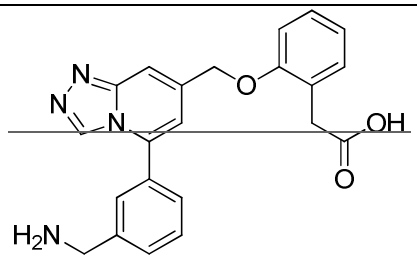
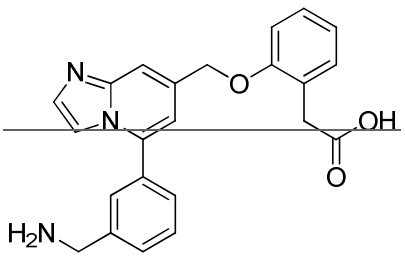
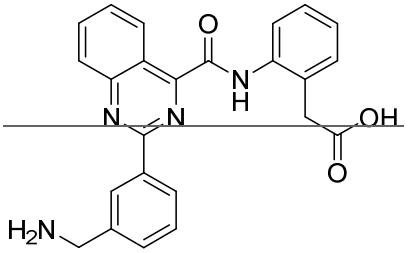
~~63. The compound of claim 61, wherein Y is N.~~

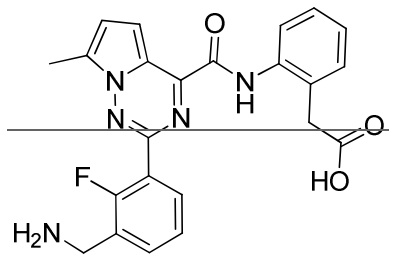
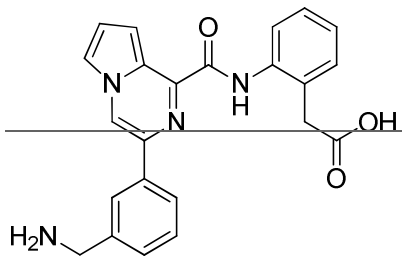
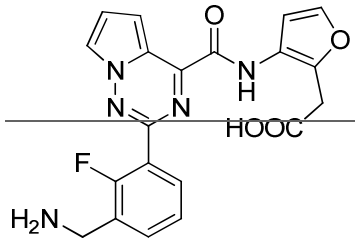
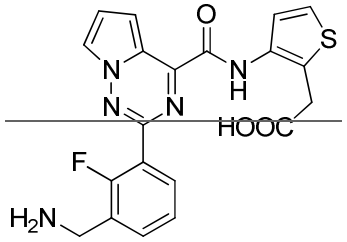
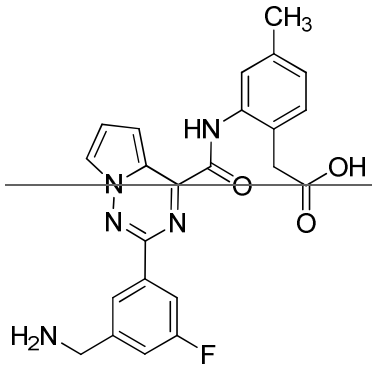
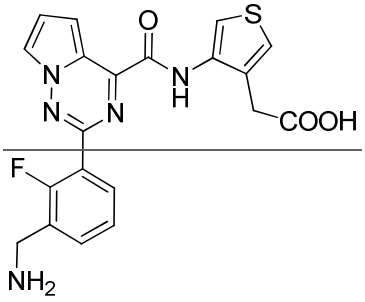
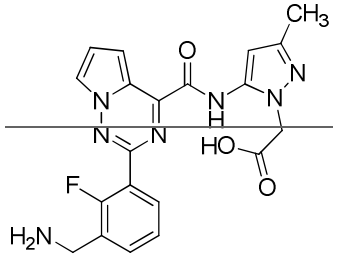
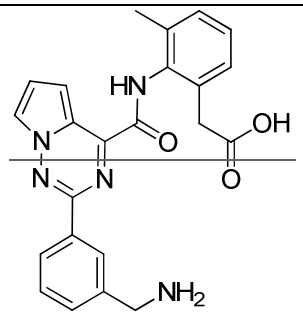
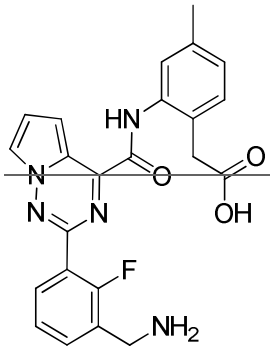
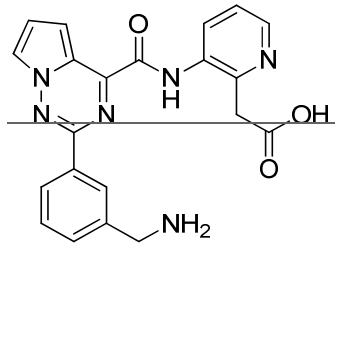
~~64. The compound of any one of claims 45-63, wherein L is CH_2.~~

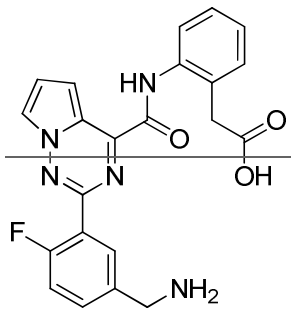
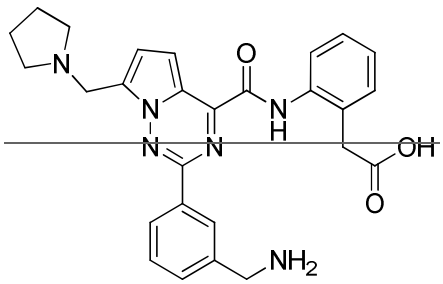
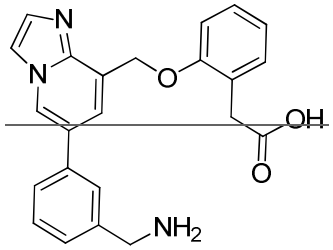
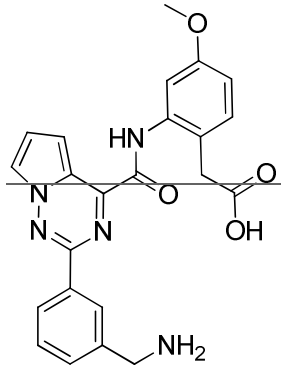
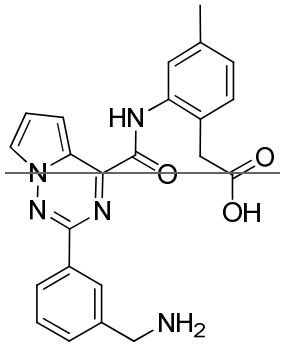
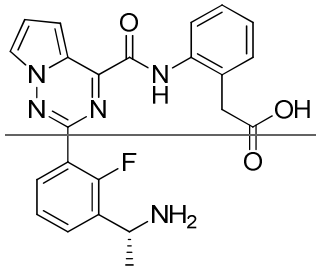
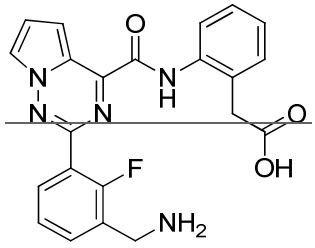
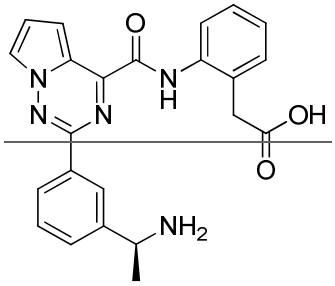
65. The compound of any one of claims 45-64, wherein T^1 is CR^{T1}; and R^{T1} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring, such as pyrrole, imidazole, or 1,2,4-triazole.

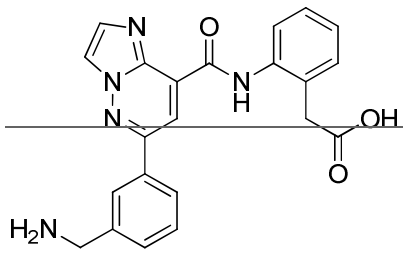
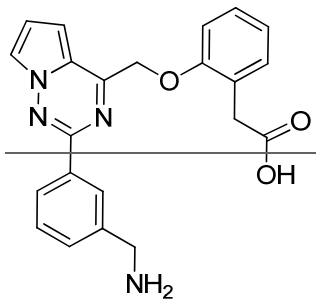
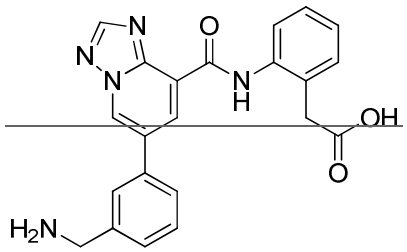
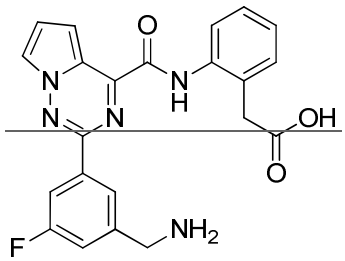
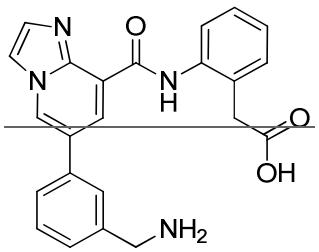
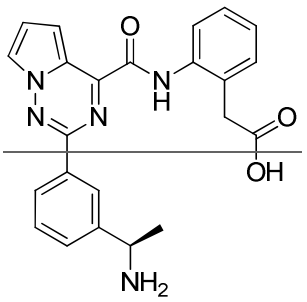
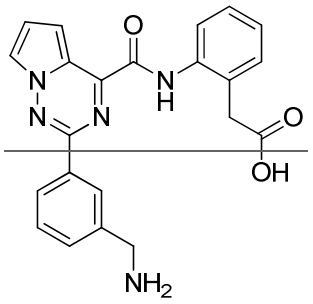
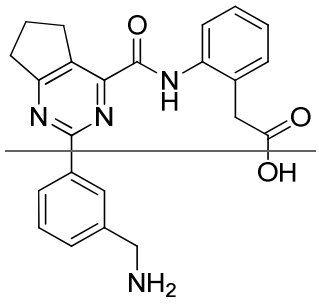
66. The compound of any one of claims 45-64, wherein T^3 is CR^{T3}; and R^{T3} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring, such as pyrrole, imidazole, 1,2,4-triazole, or pyridine.

67. The compound of claim 45 or 46, selected from the following table:

68. ~~A pharmaceutical composition, comprising a compound of any one of claims 1-67, or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically acceptable carrier.~~

69. ~~A method of treating or preventing a disease or condition characterized by aberrant complement system activity, comprising administering to a subject in need thereof a~~

~~therapeutically effective amount of a compound of any one of claims 1-67, or a pharmaceutically acceptable salt or prodrug thereof.~~

~~70. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is an immunological disorder.~~

~~71. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a disease of the central nervous system.~~

~~72. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a neurodegenerative disease or neurological disease.~~

~~73. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a renal disease.~~

~~74. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a cardiovascular disease.~~

~~75. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is selected from the group consisting of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, organ transplant rejection, myasthenia gravis, neuromyelitis optica, membranoproliferative glomerulonephritis, dense-deposit disease, cold agglutinin disease, and catastrophic antiphospholipid syndrome.~~

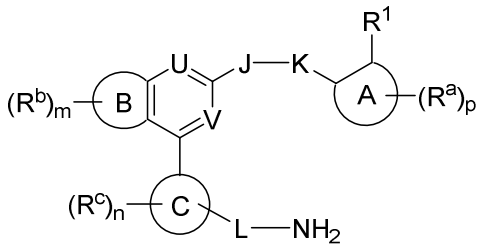
~~76. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is selected from the group consisting of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), warm autoimmune hemolytic anemia, IgA nephropathy, C3 glomerulonephritis, and focal segmental glomerulosclerosis.~~

~~77. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is a hematological disorder.~~

~~78. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is an ocular disorder or an eye disorder.~~

~~79. The method of claim 69, wherein the disease or condition characterized by aberrant complement system activity is macular degeneration, age-related macular degeneration (AMD), macular edema, diabetic macular edema, choroidal neovascularization (CNV), uveitis, Behcet's uveitis, proliferative diabetic retinopathy, non-proliferative diabetic retinopathy, glaucoma, hypertensive retinopathy, a corneal neovascularization disease, post-corneal transplant rejection, a corneal dystrophic disease, an autoimmune dry eye disease, Stevens-Johnson syndrome, Sjogren's syndrome, an environmental dry eye disease, Fuchs' endothelial dystrophy, retinal vein occlusion, or post-operative inflammation.~~

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



(I);

wherein:

ring A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

ring B is aryl, heteroaryl, heterocycloalkyl, or cycloalkyl;

ring C is aryl or heteroaryl;

R^a, independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, $-NH_2$, -NH(Ac), -NH(alkyl), $-N(alkyl)_2$,

-NHC(O)(alkyl), -CH_2NHC(O)(alkyl), -C(O)NH_2, -C(O)(alkyl), optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

R^b, independently for each occurrence, is selected from the group consisting of halogen, cyano, -NR^jR^k, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, (hydroxy)haloalkyl, hydroxy(cycloalkyl)alkyl, (cycloalkyl)alkyl, (heterocycloalkyl)alkyl, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -alkylene-NR^jR^k, tosyl, -SO_2(alkyl), -SO_2(cycloalkyl), -CO(alkyl), -CO(cycloalkyl), -CONH(alkyl), -CON(alkyl)$_2$, and -CONH(cycloalkyl);

R^c, independently for each occurrence, is selected from the group consisting of halogen, -OH, -NR^jR^k, alkoxy, and alkyl;

R^1 is selected from the group consisting of -NH_2, -CH_2COOH, -CH(NH(CO)(alkyl))COOH, -CH(NH(CO)(arylalkyl))COOH, -CH(NH(CO)(cycloalkyl))COOH, -CH(NH(CO)(aryl substituted cycloalkyl))COOH, -CO(NH)CH_2aryl, -CO(NH)CH_2heteroaryl, -CO(NH)aryl, and -CO(NH)heteroaryl;

n is 0, 1, or 2;

m is 0, 1, or 2;

p is 0, 1, or 2;

J is –C(O)–, –NH–, –CH_2–, –O–, –S–, –S(O)–, –SO_2–, –N(alkyl)–, or –CH(alkyl)–;

K is –C(O)–, –NH–, –O–, –CH_2–, –S–, –S(O)–, –SO_2–, –N(alkyl)–, or –CH(alkyl)–;

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

L is selected from the group consisting of a bond, –CH_2–, –CH_2CH_2–, –CHR^2–, –CF_2–, –CFR^2–, –C(O)–, –C(=NR^L)–, and –C(=CHR^L)–;

wherein R^L is H or alkyl;

or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, hydroxyalkyl, or haloalkyl;

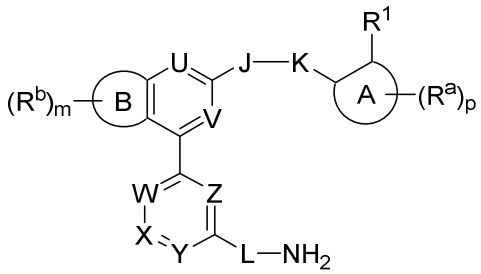
R^j and R^k are each independently selected from the group consisting of H, alkyl, aminoalkyl, (heterocycloalkyl)alkyl, and heterocycloalkyl;

U is N or CR^3;

R^3 is H, halogen, alkyl, alkoxy, or haloalkyl; and

V is N or CH.

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



(Ia);

wherein:

W is N, CH, or CR^c;

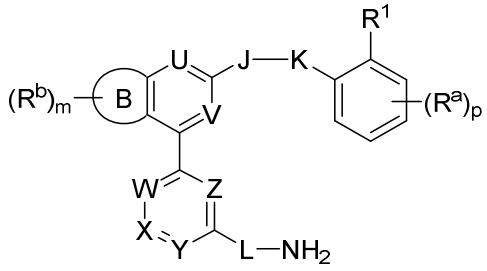
X is N, CH, or CR^c;

Y is N, CH, or CR^c; and

Z is N, CH, or CR^c.

3. The compound of claim 1 or 2, wherein ring A is phenyl, thiophenyl, or pyridinyl.

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



(Ib).

5. The compound of any one of claims 1-4, wherein p is 1.

6. The compound of claim 5, wherein R^a is alkyl, cycloalkyl, or halogen.

7. The compound of any one of claims 1-4, wherein p is 0.

8. The compound of any one of claims 1-7, wherein R^1 is $-CH_2COOH$.

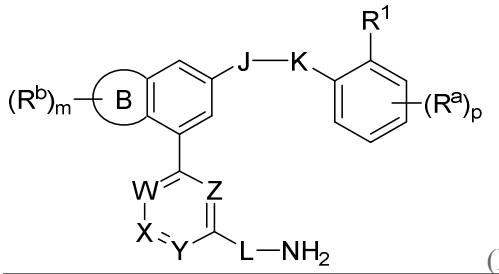
9. The compound of any one of claims 1-8, wherein –J–K– is selected from the group consisting of –C(O)-NH–, –NH-C(O)–, and $–CH_2O–$.

10. The compound of any one of claims 1-9, wherein –J–K– is $–CH_2O–$.

11. The compound of any one of claims 1-10, wherein U is CH.

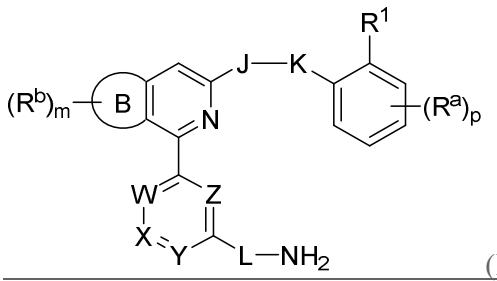
12. The compound of any one of claims 1-11, wherein V is CH.

13. The compound of any one of claims 2-12, having the structure of formula (Ic):



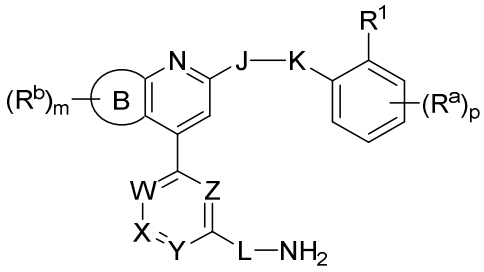
(Ic).

14. The compound of any one of claims 2-10, having the structure of formula (Id):



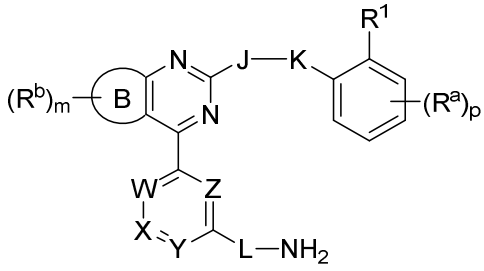
(Id).

15. The compound of any one of claims 2-10, having the structure of formula (Ie):



(Ie).

16. The compound of any one of claims 2-10, having the structure of formula (If):



(If).

17. The compound of any one of claims 1-16, wherein m is 0.

18. The compound of any one of claims 1-16, wherein m is 1.

19. The compound of claim 18, wherein R^b is selected from the group consisting of alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, halogen, and (cycloalkyl)alkyl.

20. The compound of any one of claims 1-16, wherein m is 2.

21. The compound of claim 20, wherein each R^b is alkyl.

22. The compound of any one of claims 2-21, wherein each of W, X, Y, and Z is CH.

23. The compound of any one of claims 2-21, wherein at least one of W, X, Y, and Z is CR^c.

24. The compound of claim 23, wherein Z is CR^c.

25. The compound of claim 23 or 24, wherein Y is CR^c.

26. The compound of any one of claims 23-25, wherein R^c is halogen, e.g., fluoride.

27. The compound of any one of claims 2-21 and 23, wherein at least one of W, X, Y, and Z is N.

28. The compound of claim 27, wherein Z is N.

29. The compound of claim 27, wherein Y is N.

30. The compound of any one of claims 1-29, wherein L is $–CH_2–$.

31. The compound of any one of claims 1-30 or a pharmaceutically acceptable salt or prodrug thereof, wherein ring 

is heteroaryl.

32. The compound of claim 31 or a pharmaceutically acceptable salt or prodrug thereof, wherein ring 

is furyl, oxazolyl, isoxazolyl, thiophenyl, pyrrolyl, pyrazolyl, or imidazolyl.

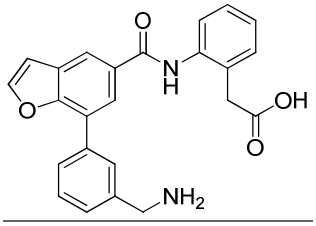
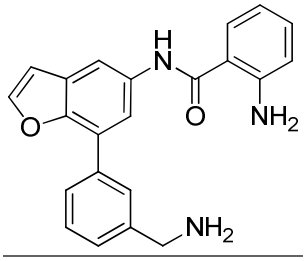
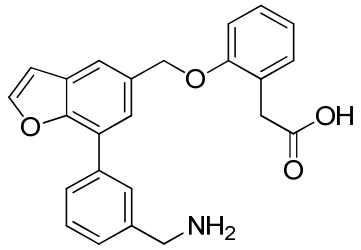
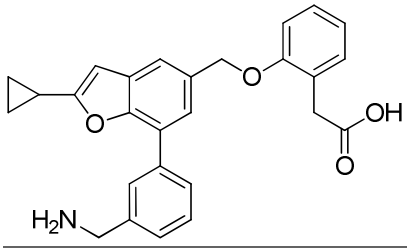
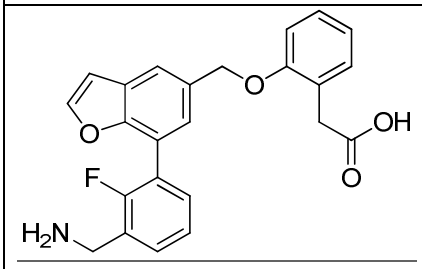
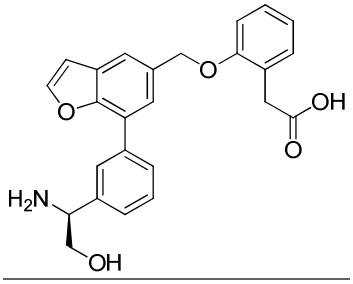
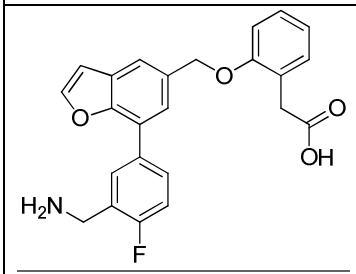
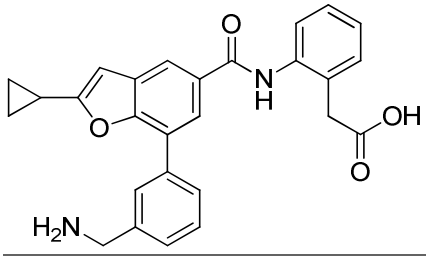
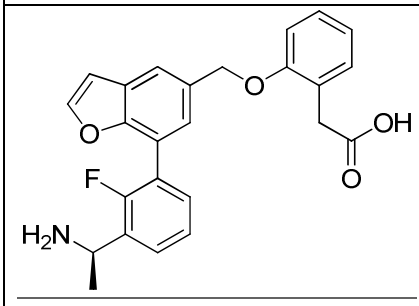
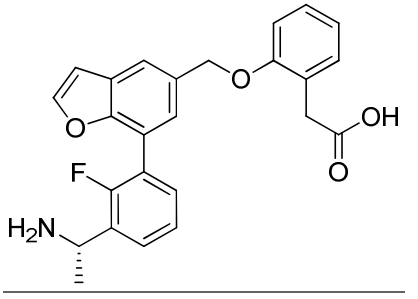
33. The compound of claim 32 or a pharmaceutically acceptable salt or prodrug thereof, wherein ring 

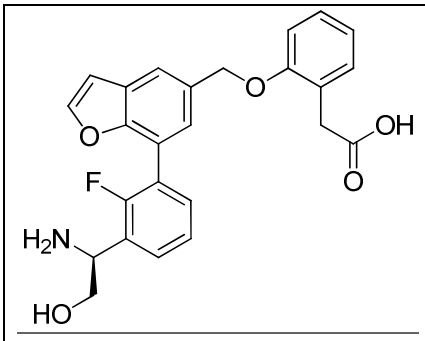
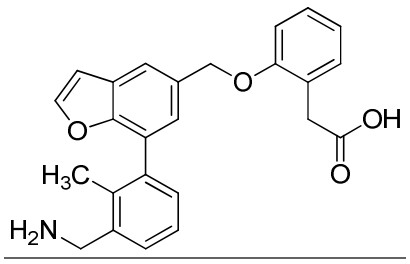
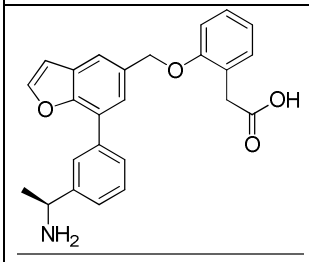
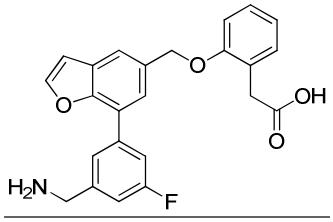
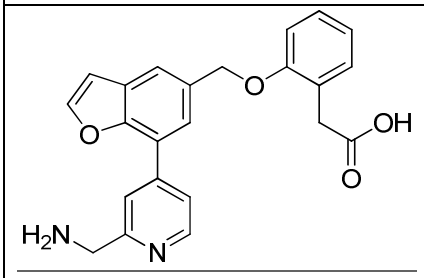
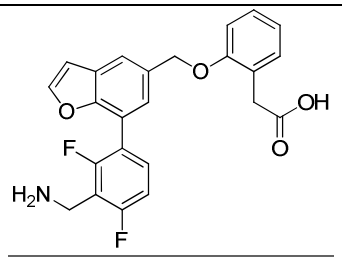
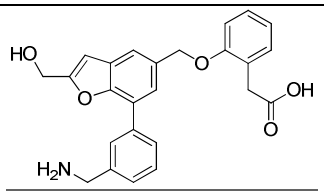
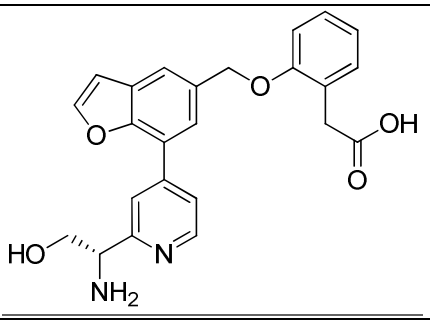
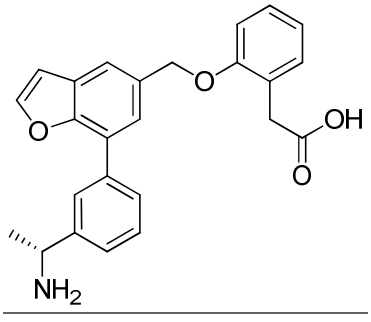
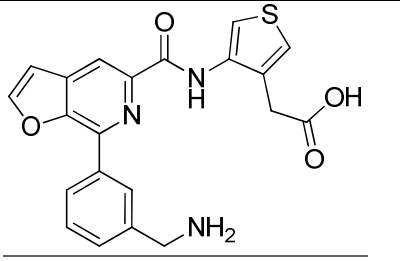
is furyl.

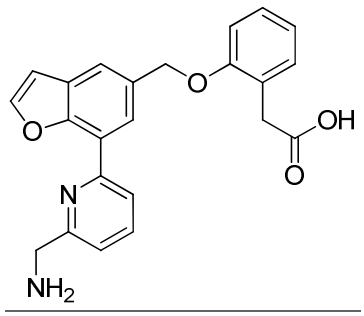
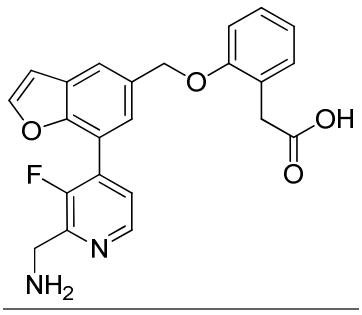
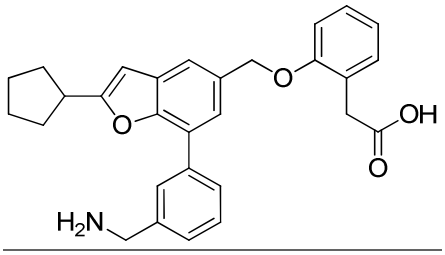
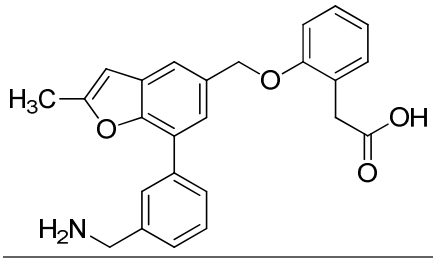
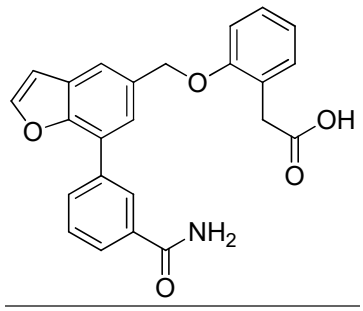
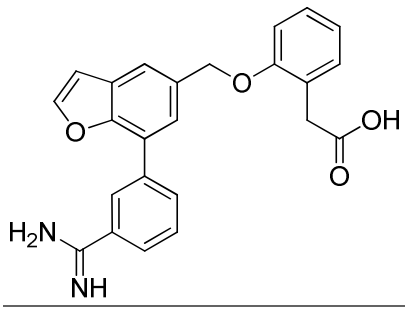
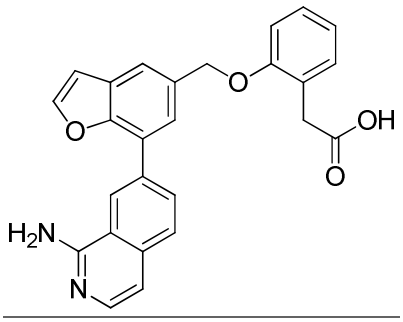
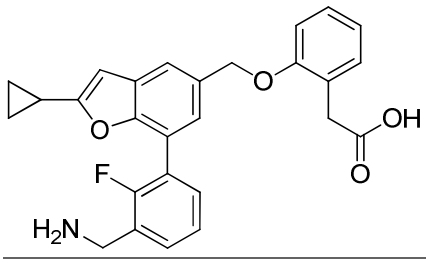
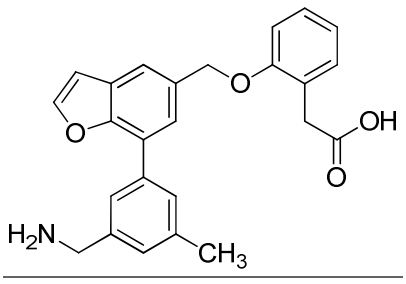
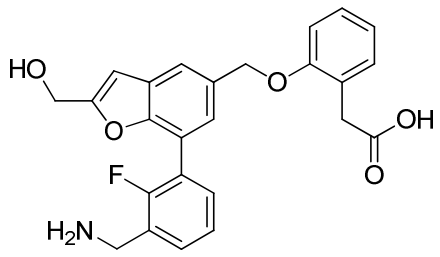
34. The compound of claim 32 or a pharmaceutically acceptable salt or prodrug thereof, wherein ring 

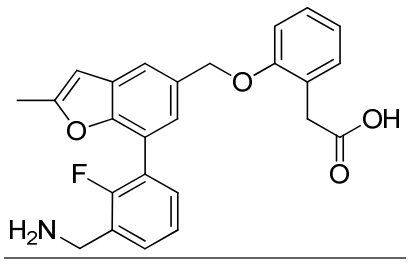
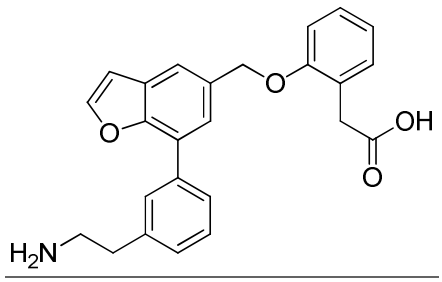
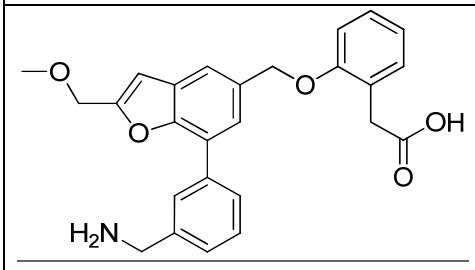
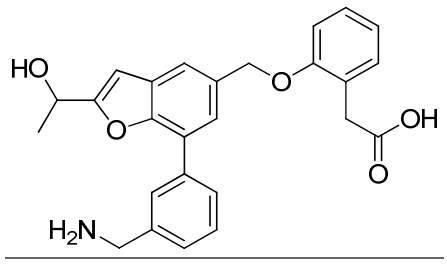
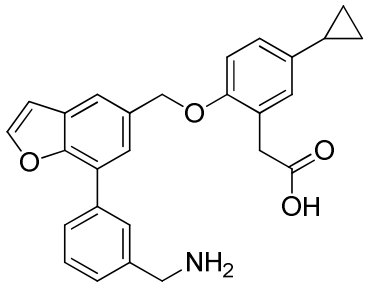
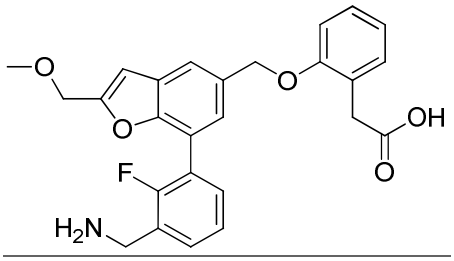
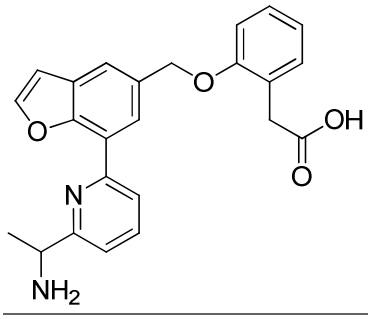
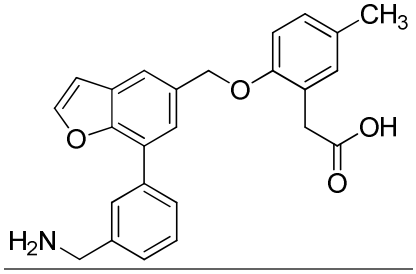
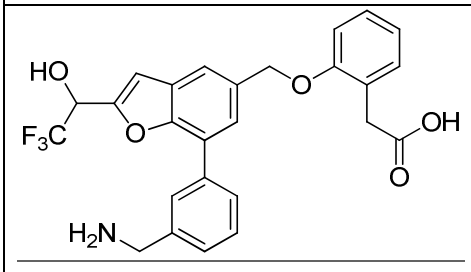
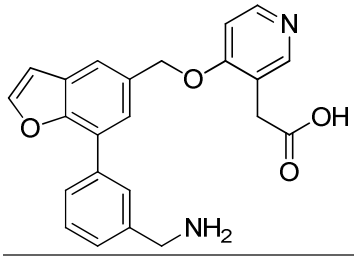
is pyrrolyl.

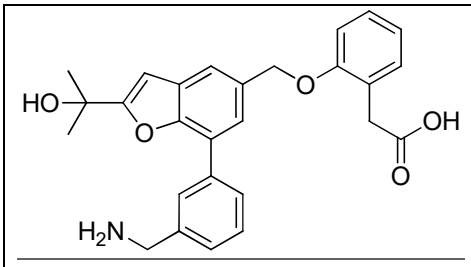
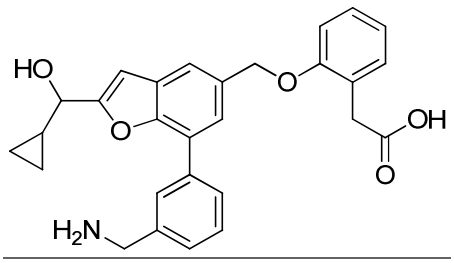
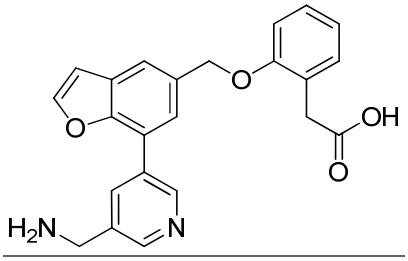
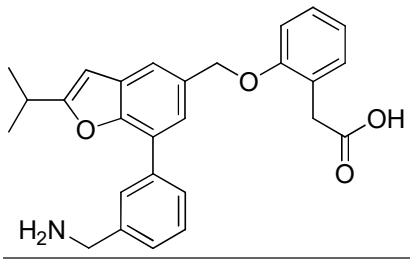
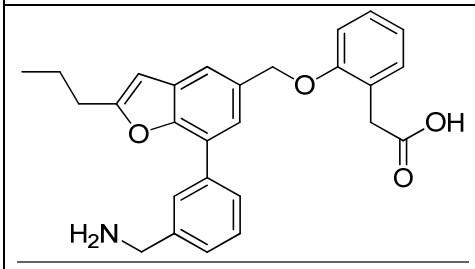
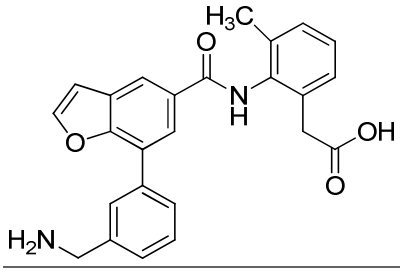
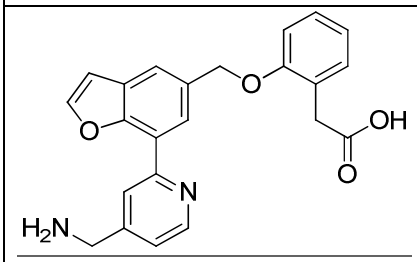
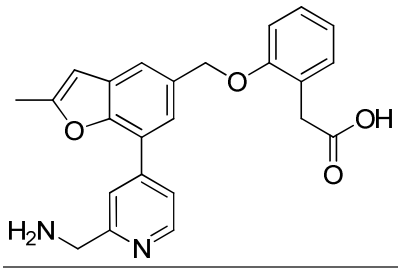
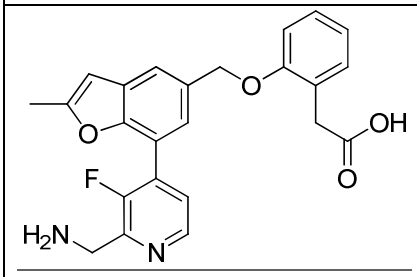
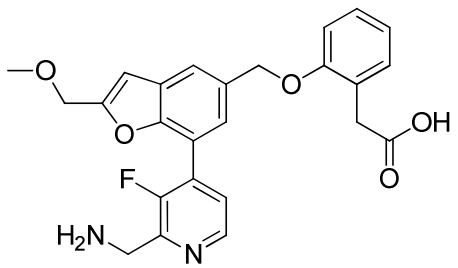
35. The compound of claim 1, selected from the following table:

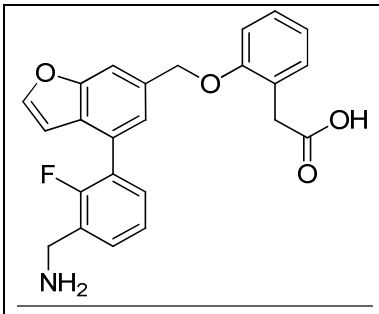
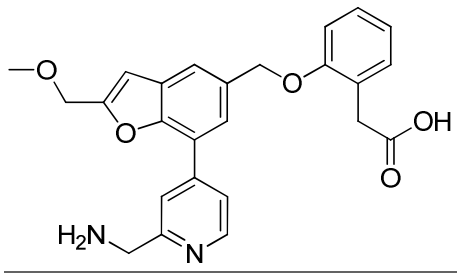
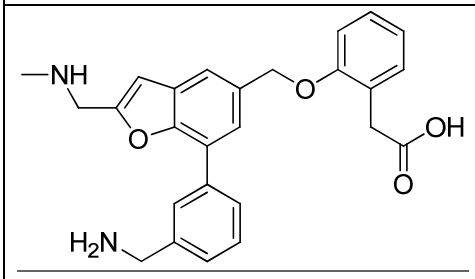
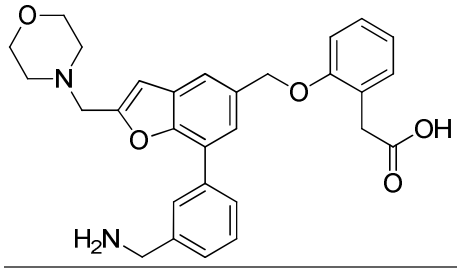
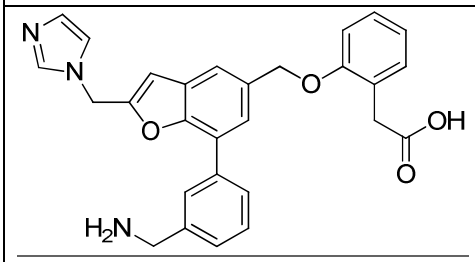
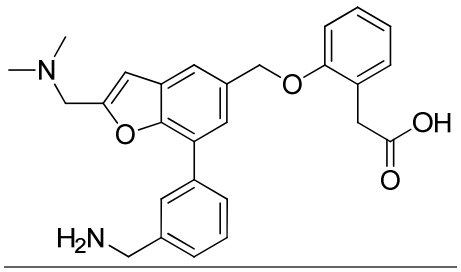
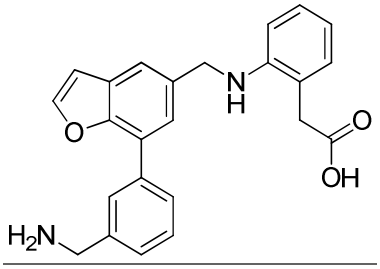
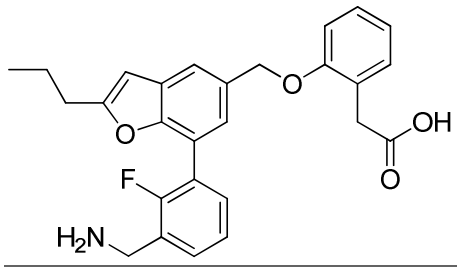
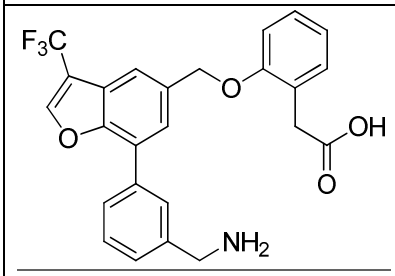
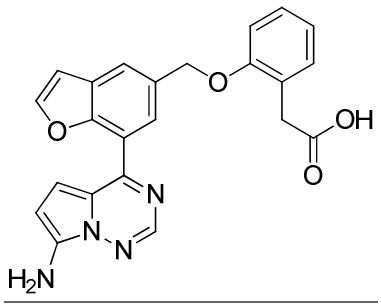
	
	
	
	
	

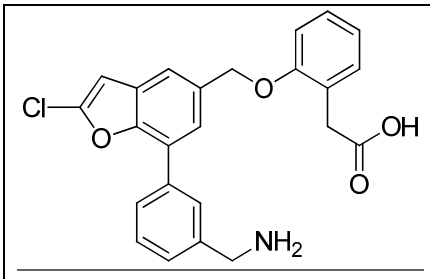
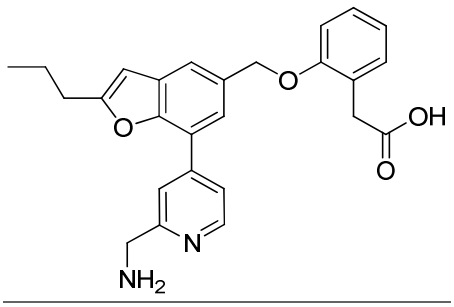
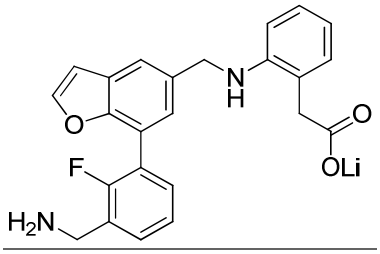
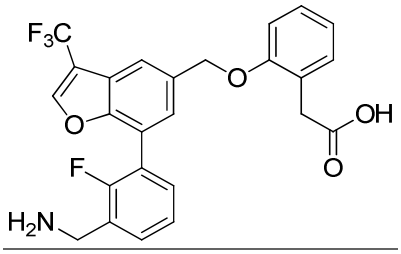
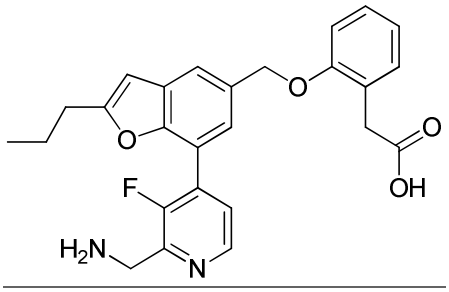
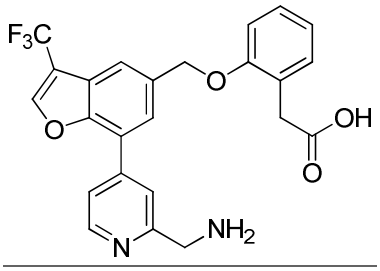
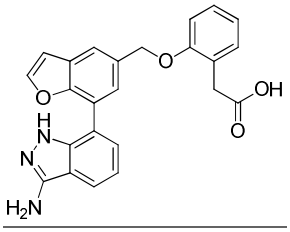
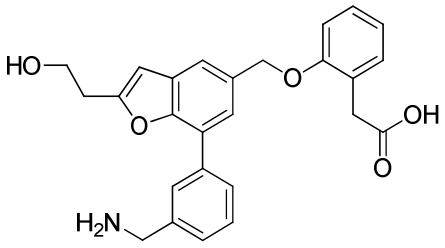
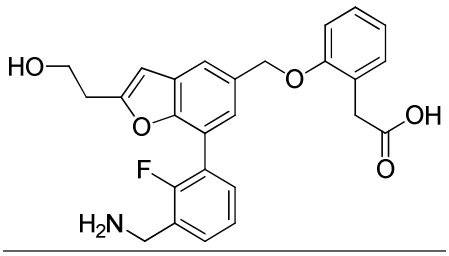
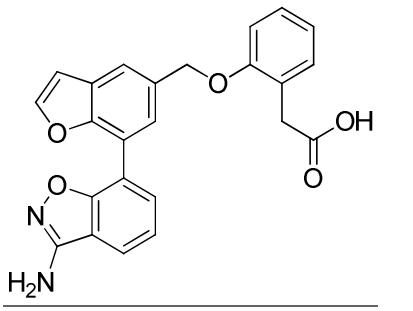
	
	
	
	
	

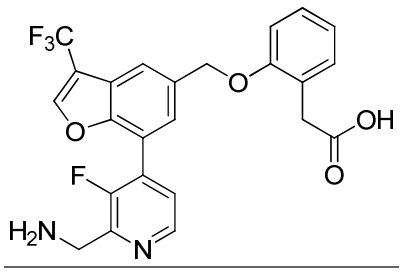
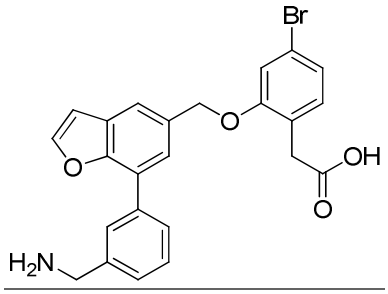
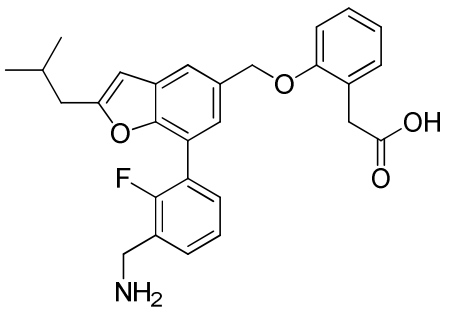
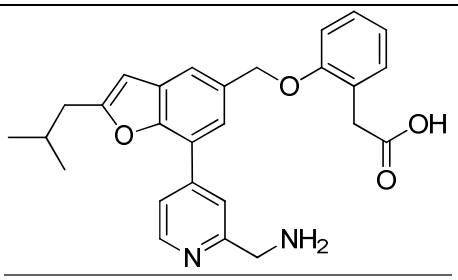
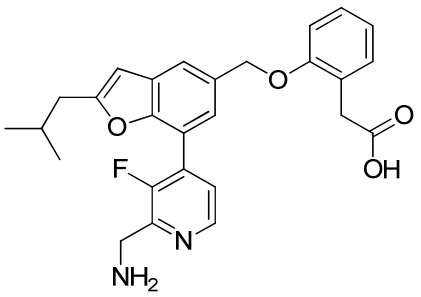
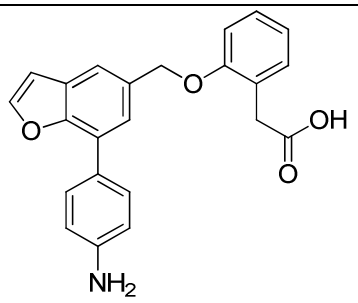
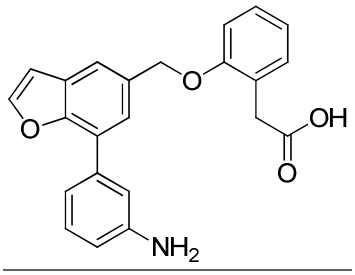
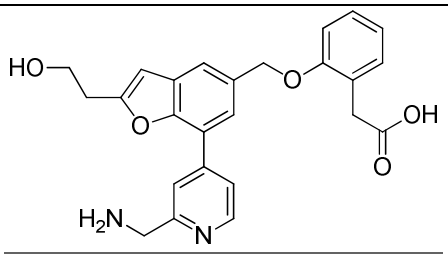
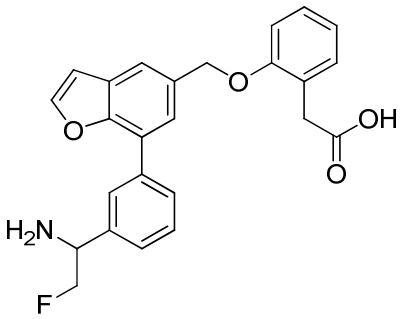
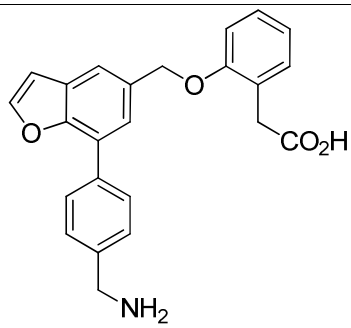
	
	
	
	
	

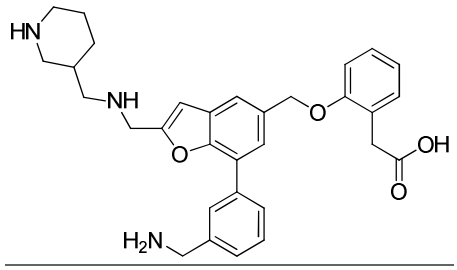
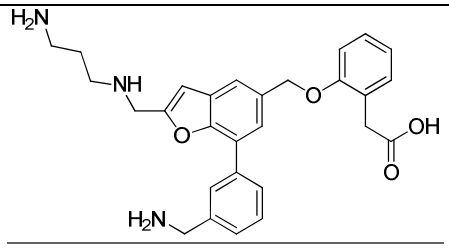
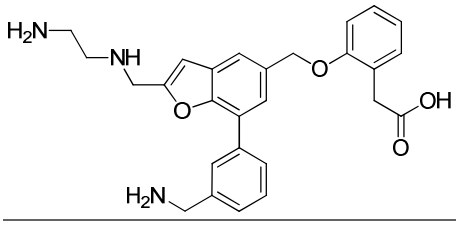
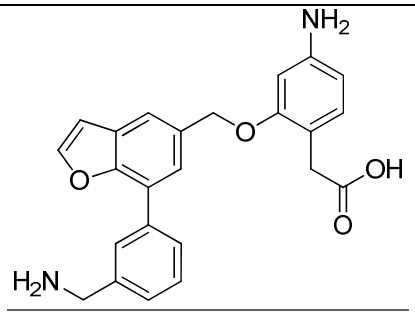
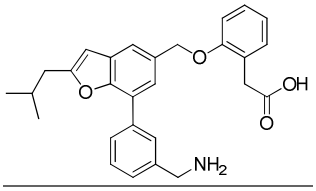
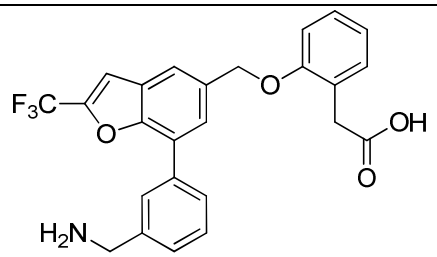
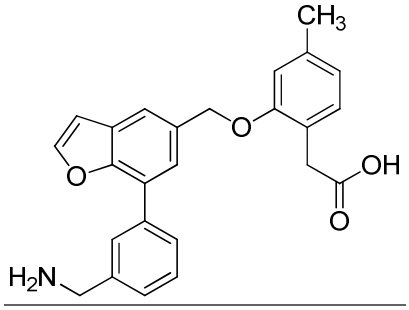
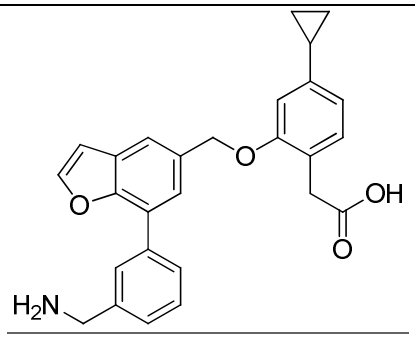
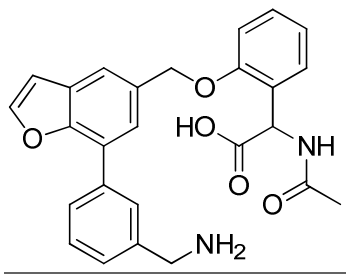
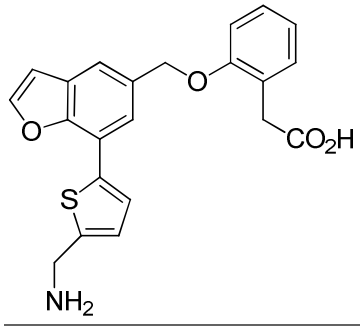
	
	
	
	
	

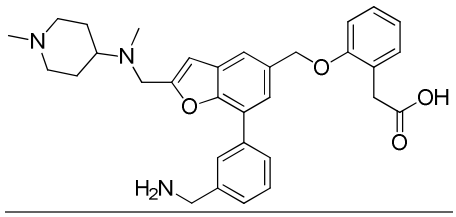
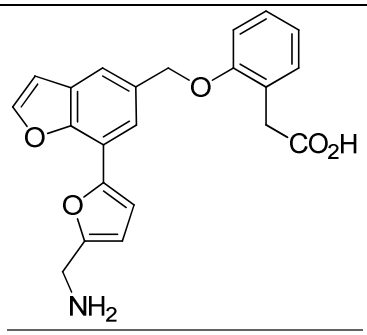
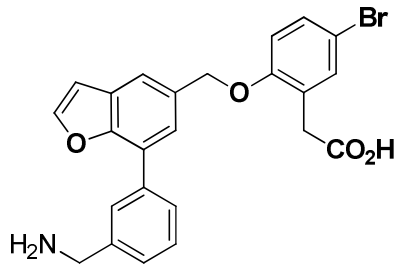
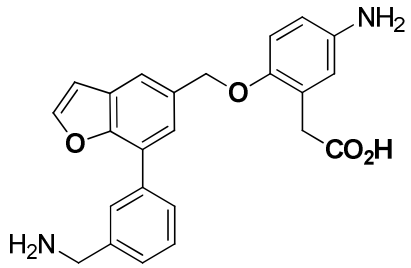
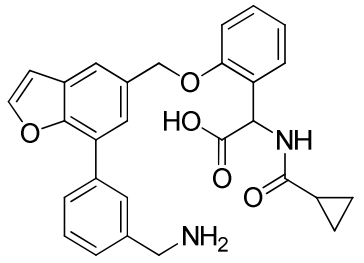
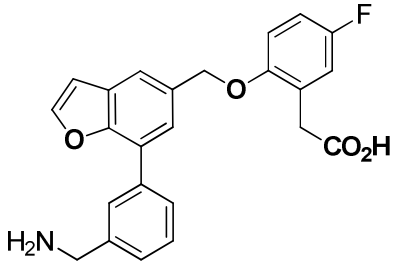
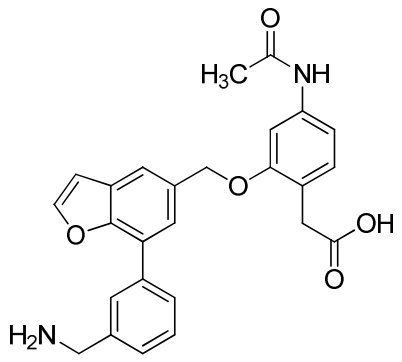
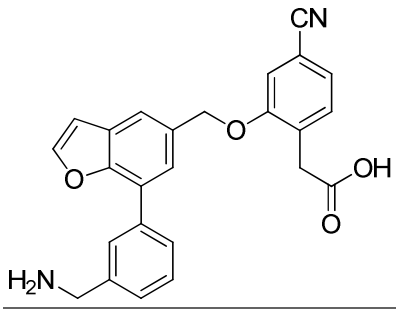
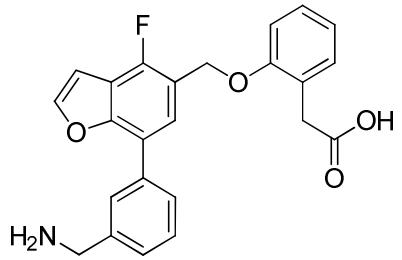
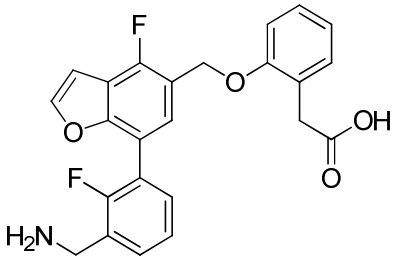
	
	
	
	
	

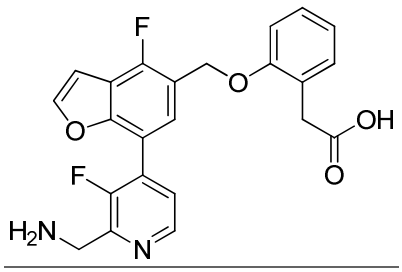
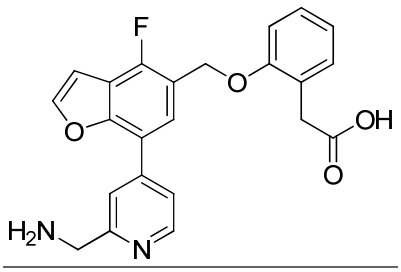
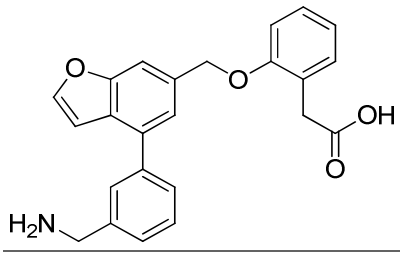
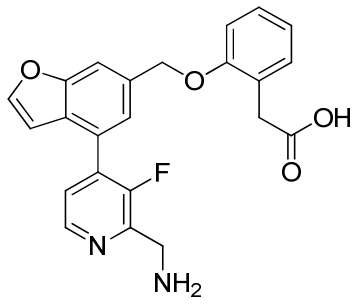
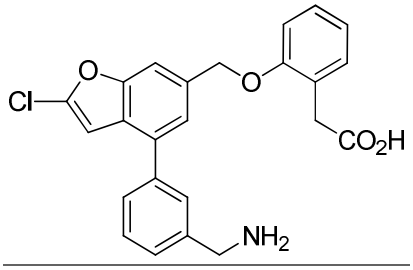
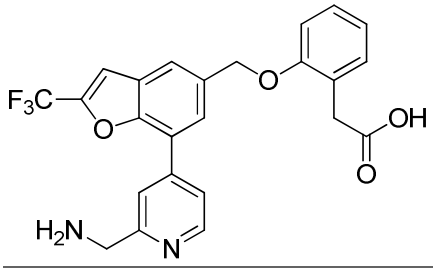
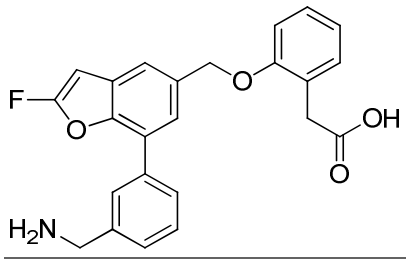
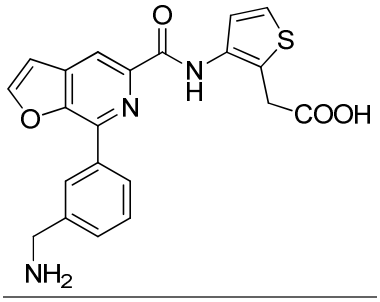
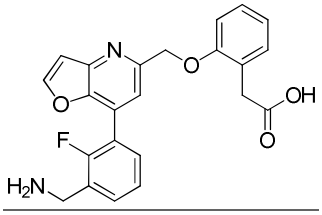
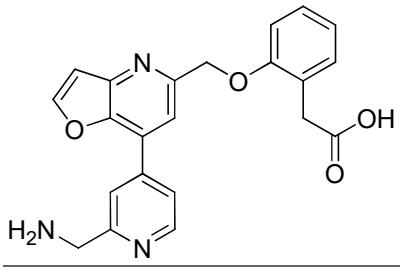
	
	
	
	
	

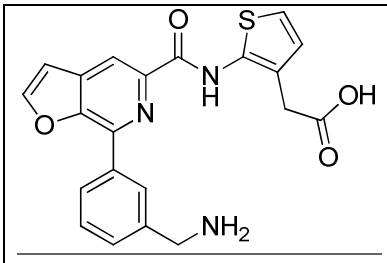
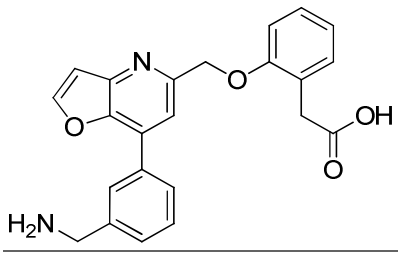
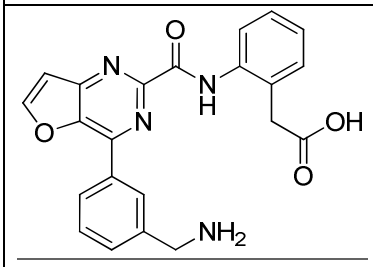
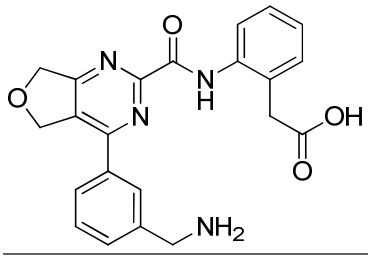
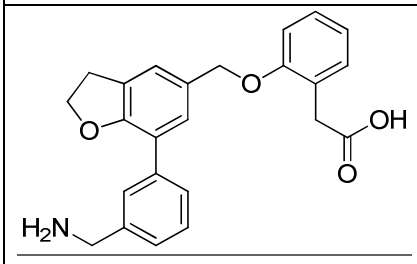
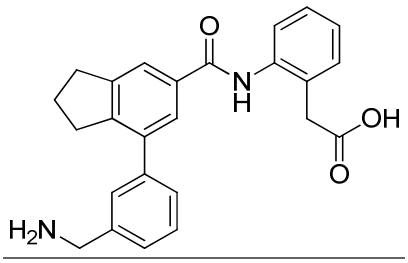
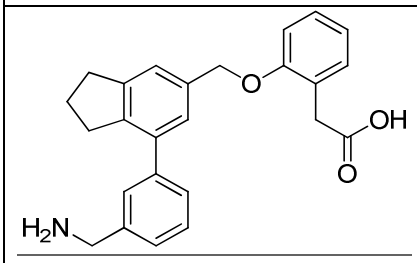
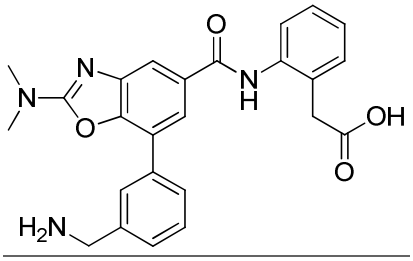
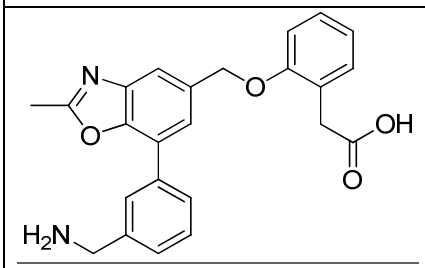
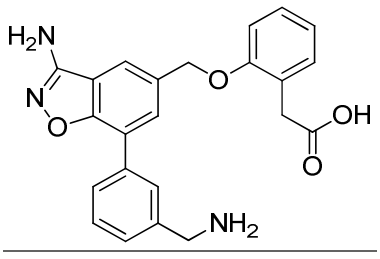
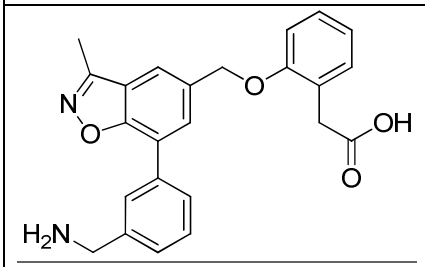
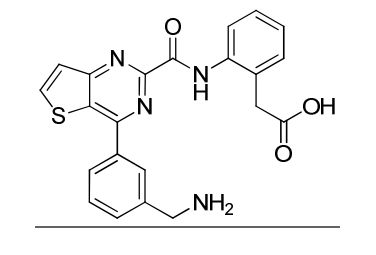
	
	
	
	
	

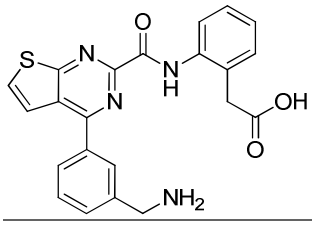
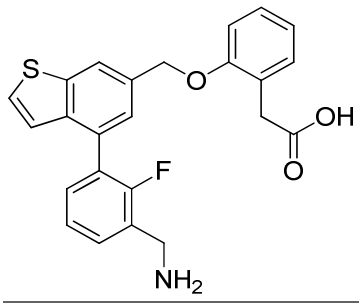
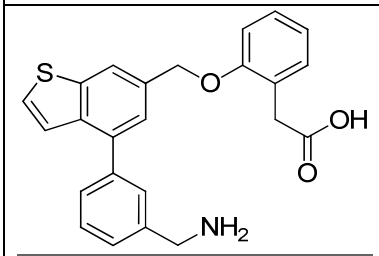
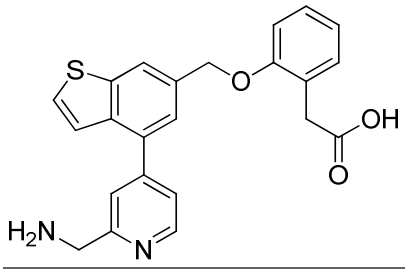
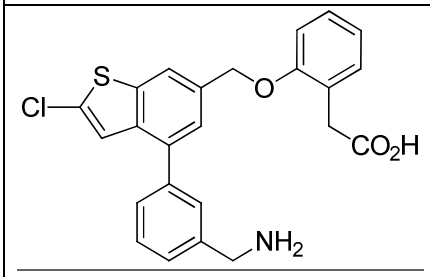
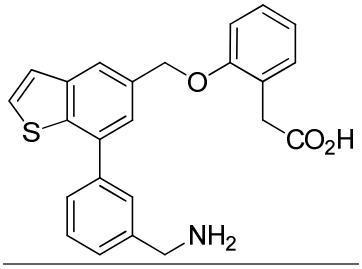
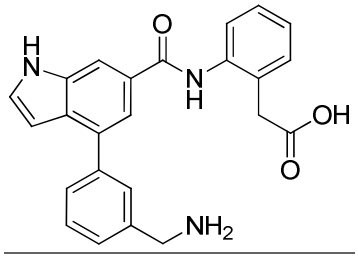
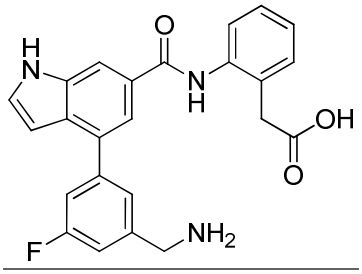
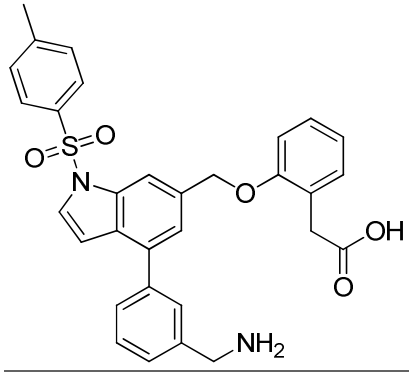
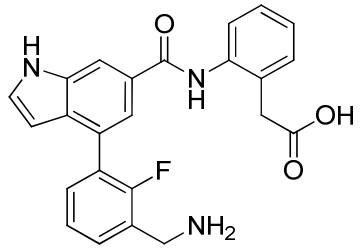
	
	
	
	
	

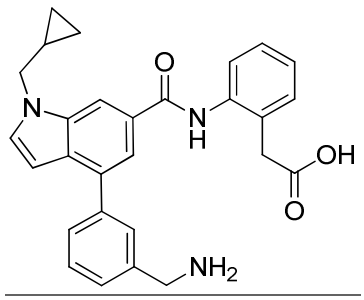
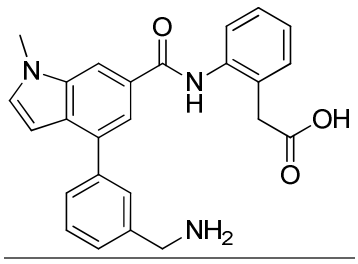
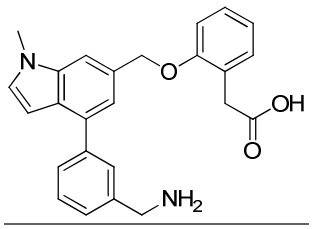
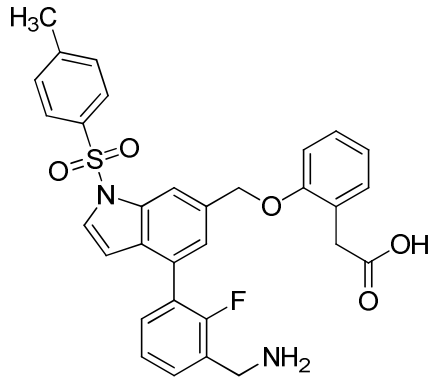
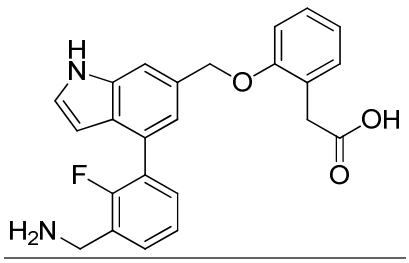
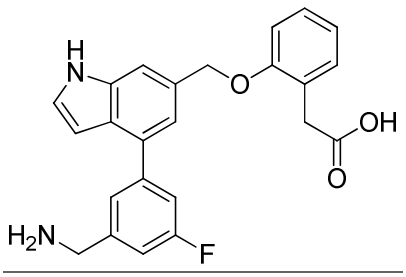
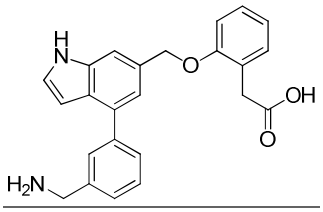
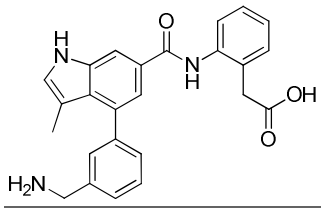
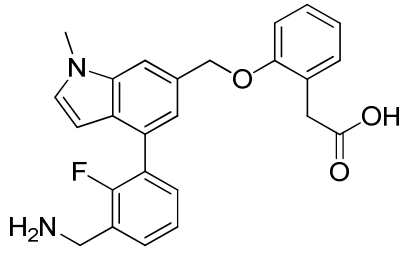
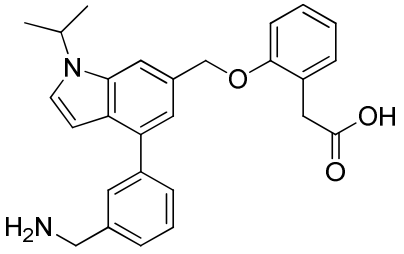
	
	
	
	
	

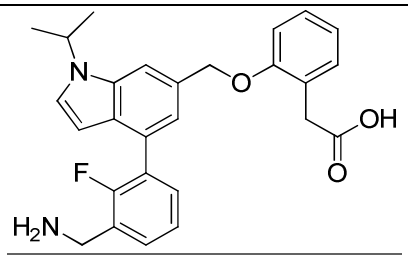
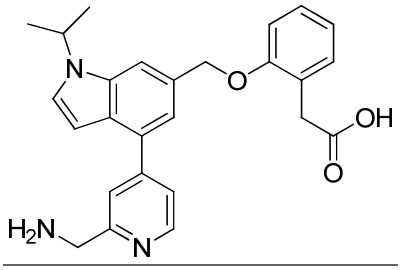
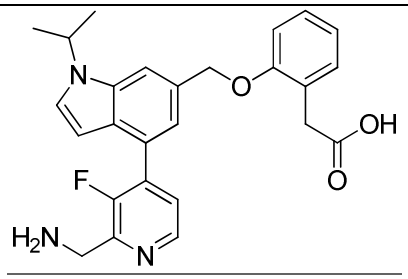
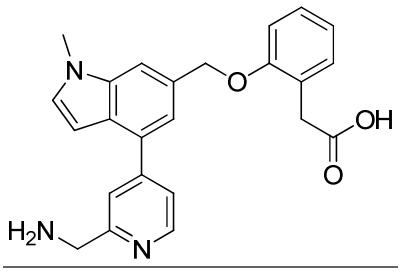
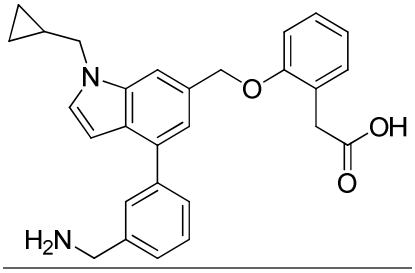
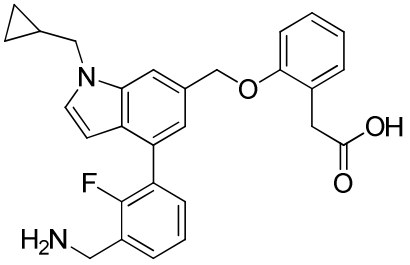
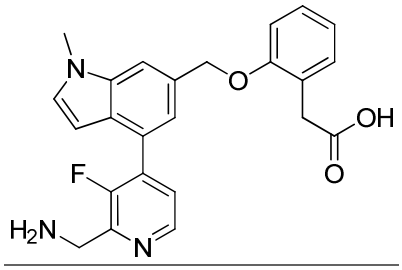
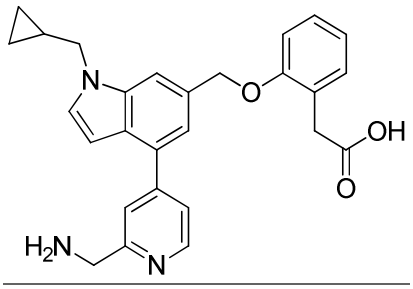
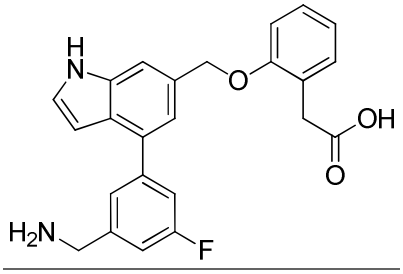
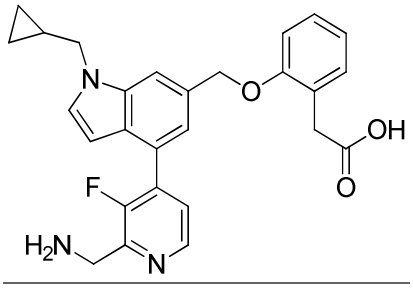
	
	
	
	
	

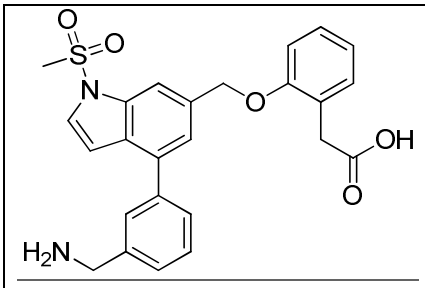
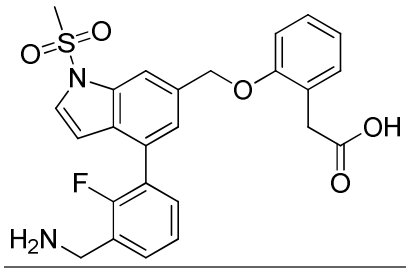
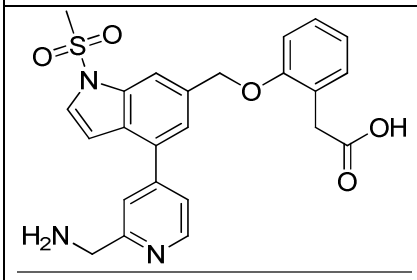
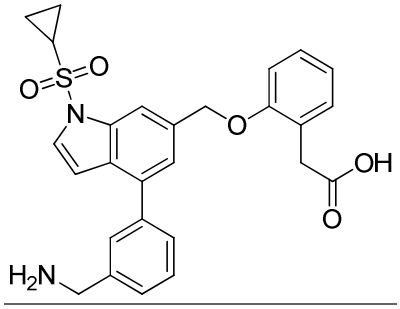
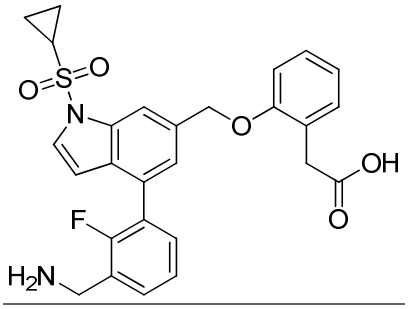
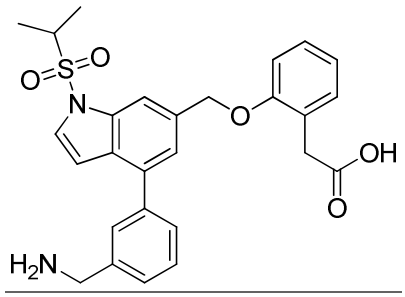
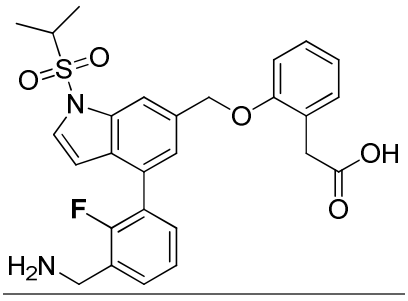
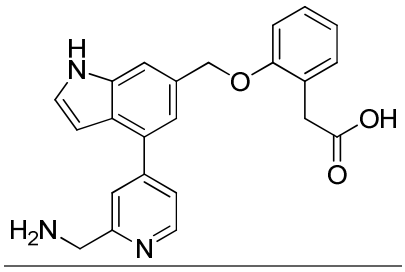
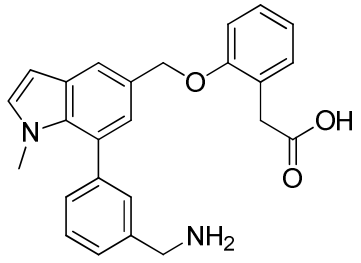
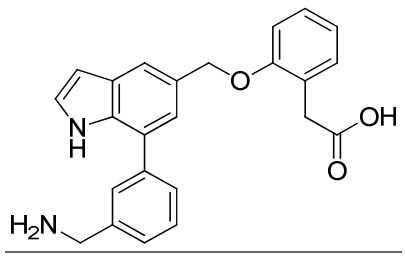
	
	
	
	
	

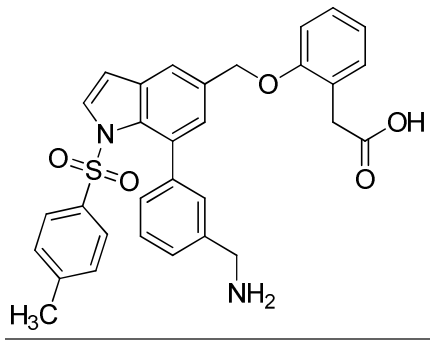
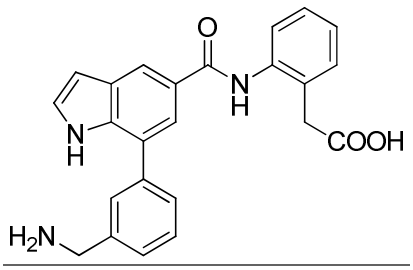
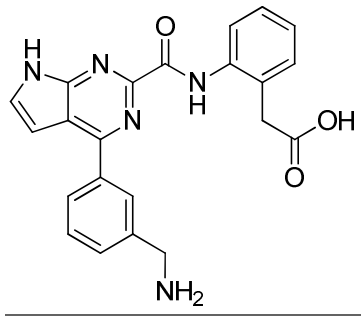
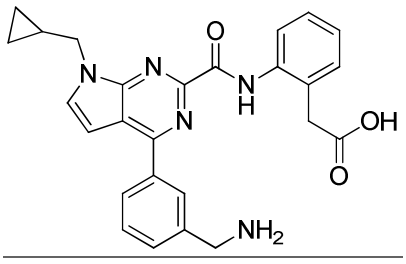
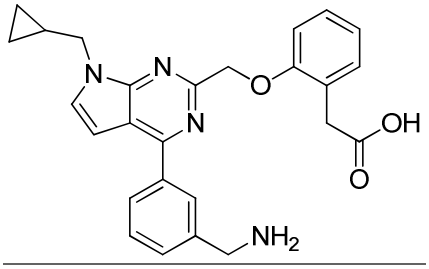
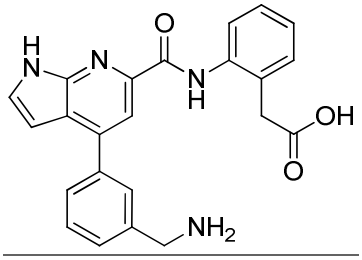
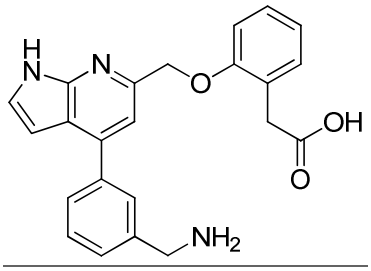
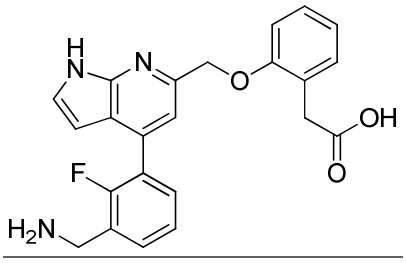
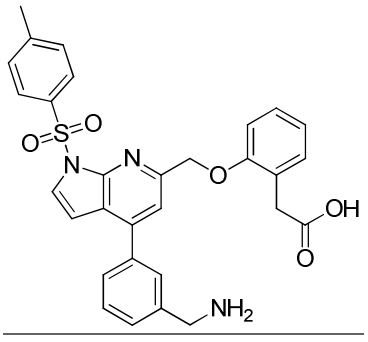
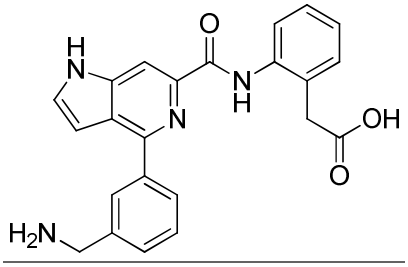
	
	
	
	
	
	

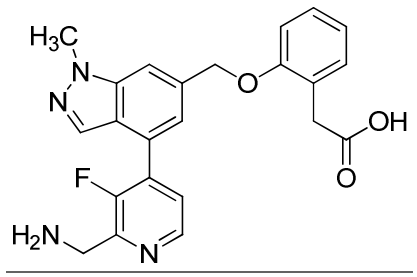
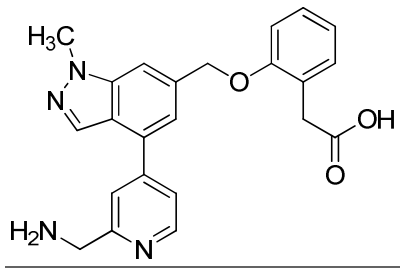
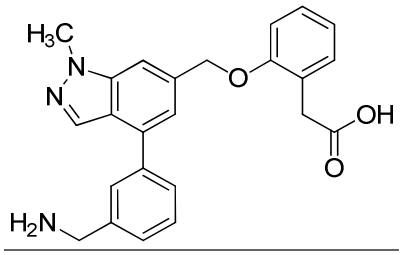
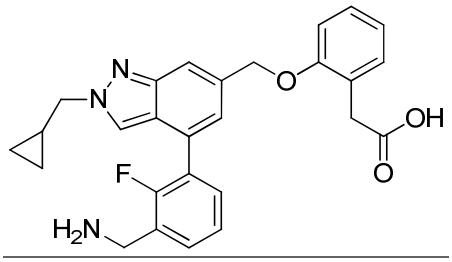
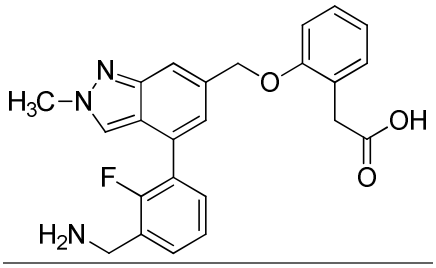
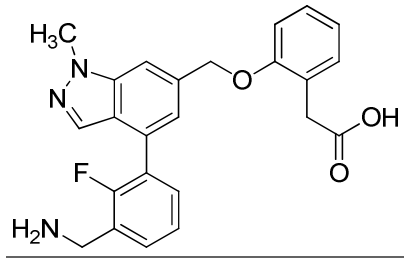
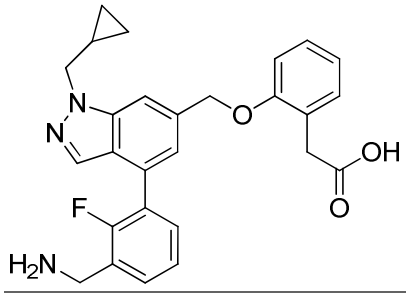
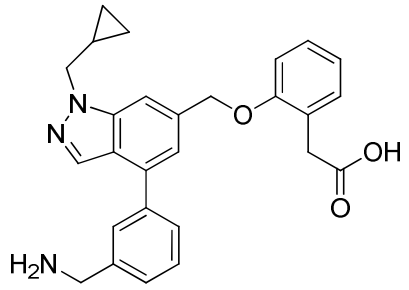
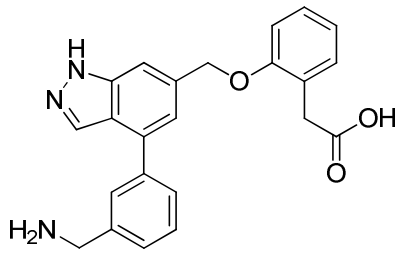
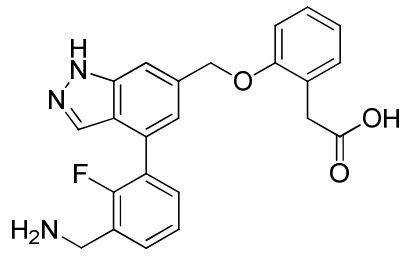
	
	
	
	
	

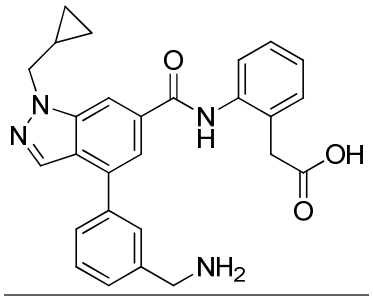
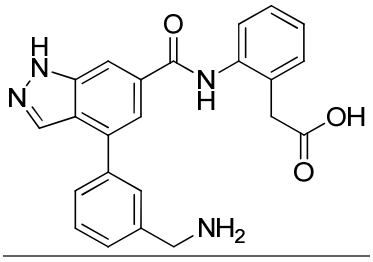
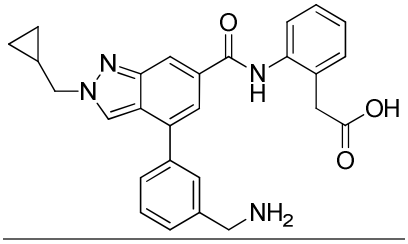
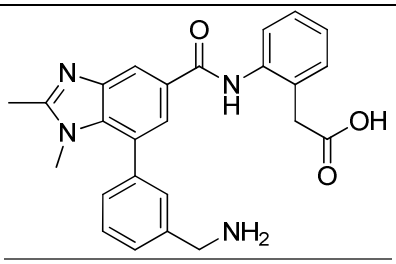
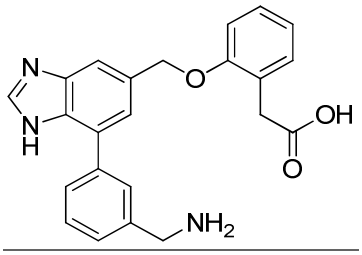
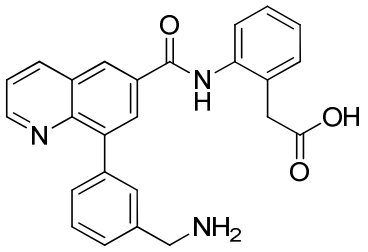
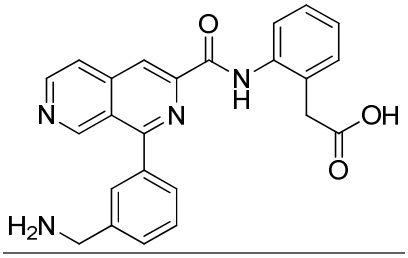
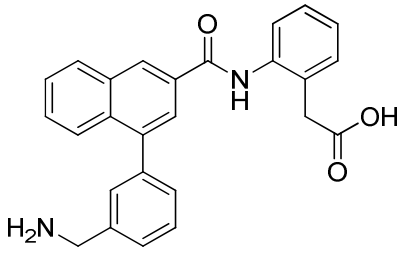
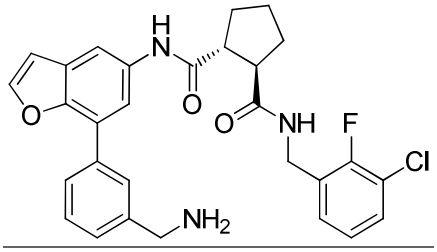
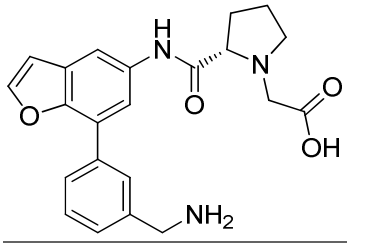
	
	
	
	
	

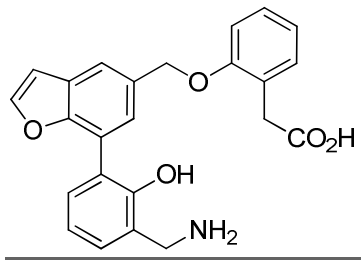
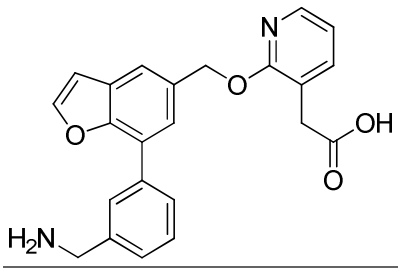
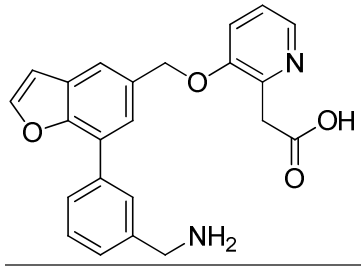
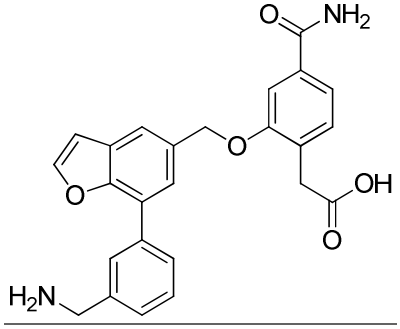
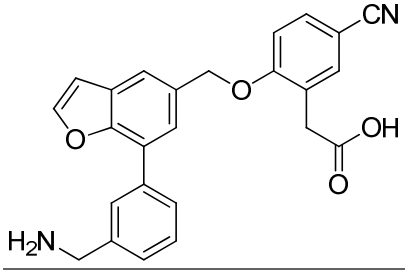
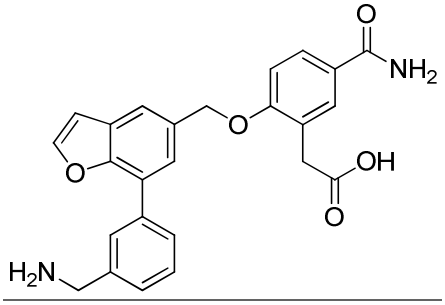
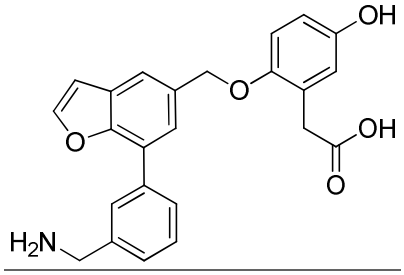
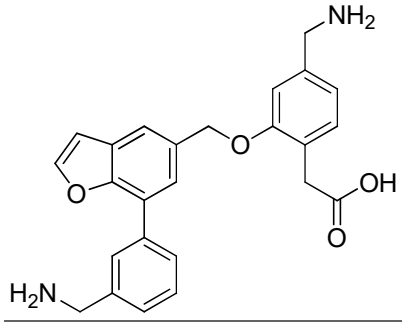
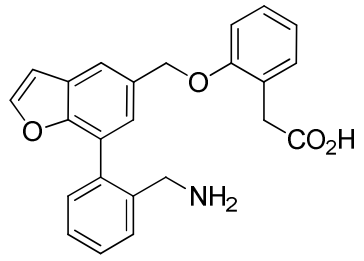
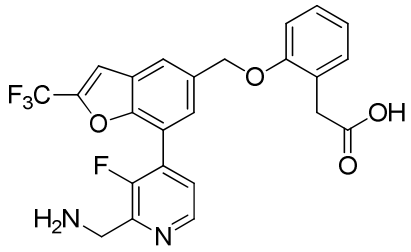
	
	
	
	
	

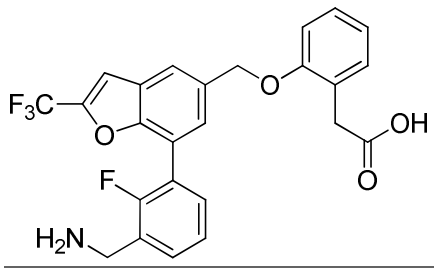
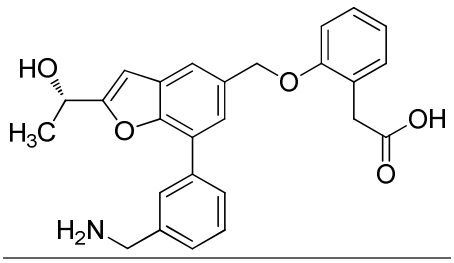
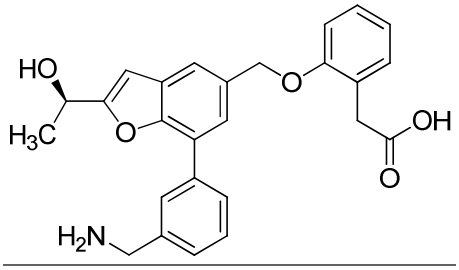
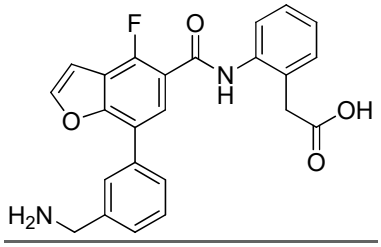
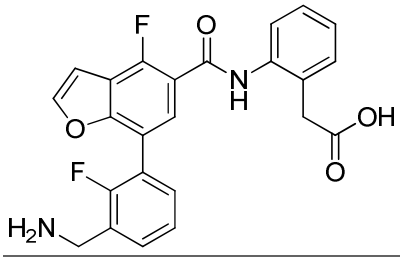
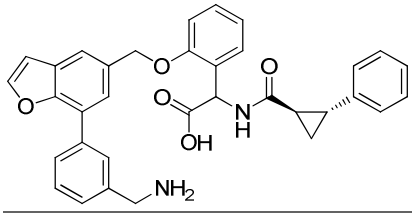
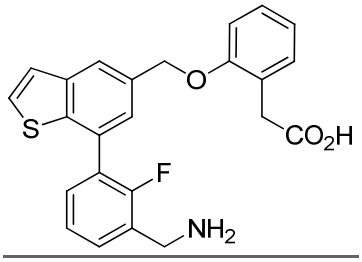
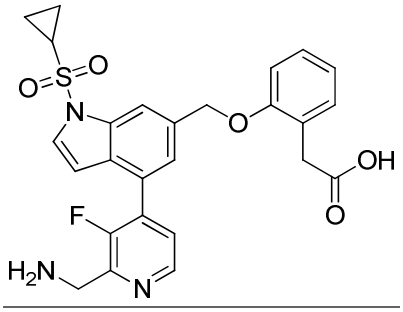
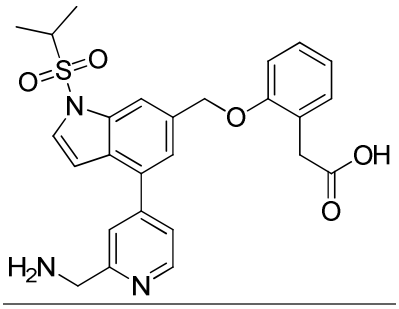
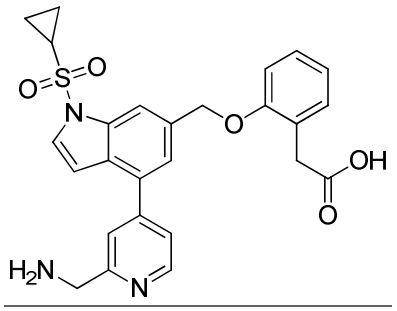
	
	
	
	
	

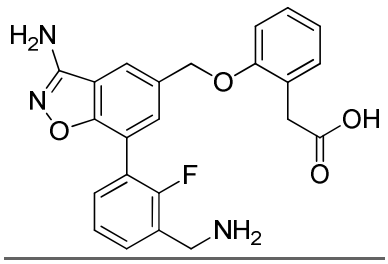
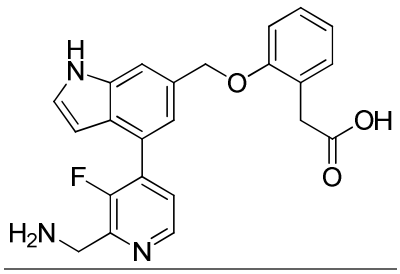
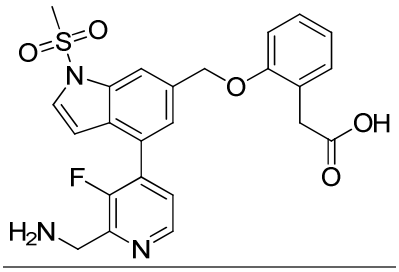
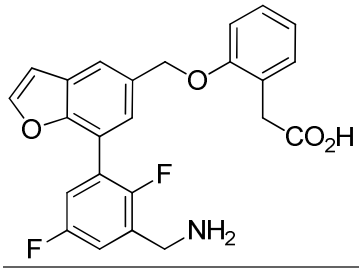
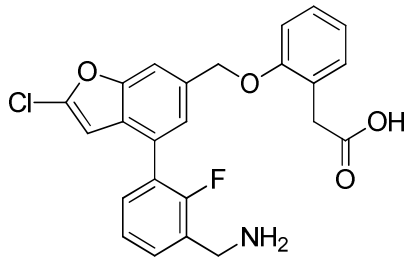
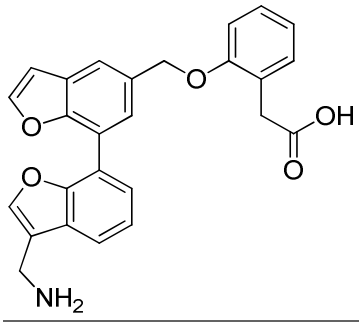
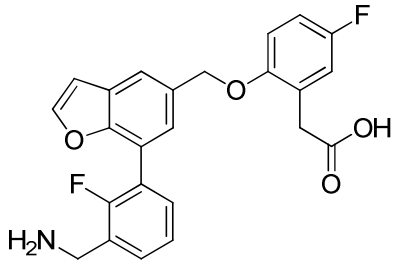
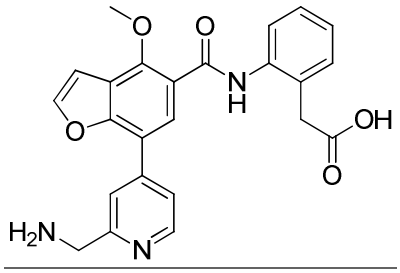
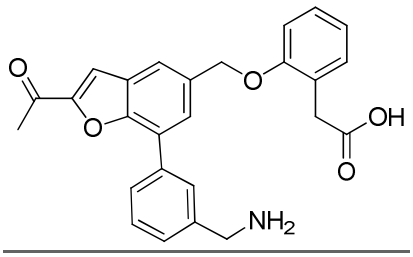
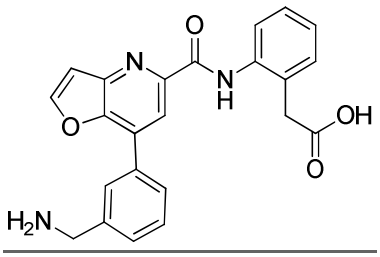
	
	
	
	
	

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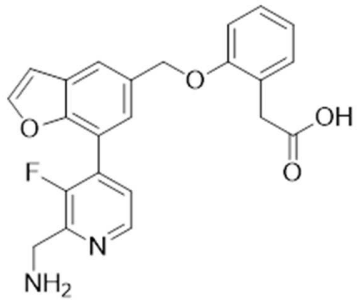
36. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:



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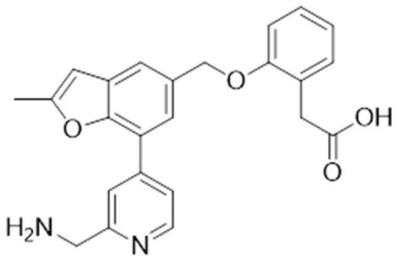

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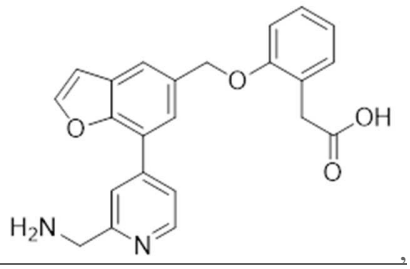

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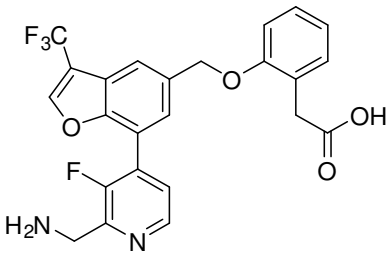

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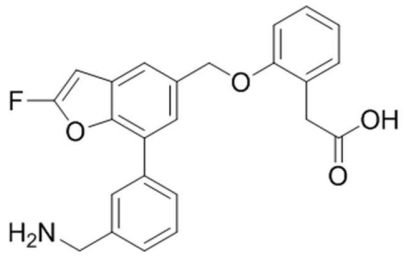
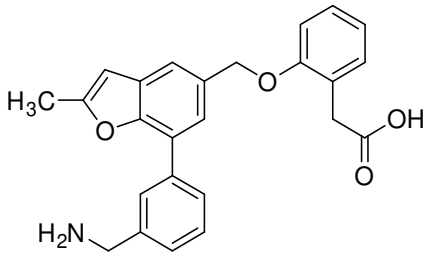
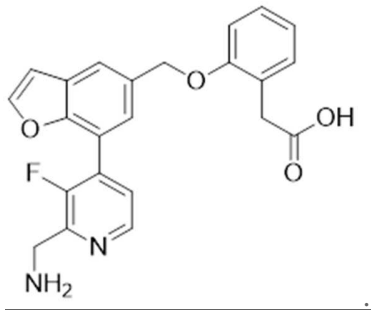


, and


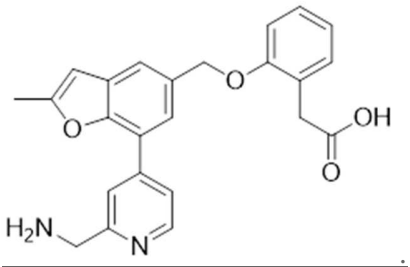
.

37. The compound of claim 36, or a pharmaceutically acceptable salt thereof, having the following formula:



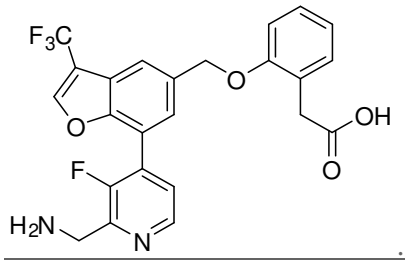
.

38. The compound of claim 36, or a pharmaceutically acceptable salt thereof, having the following formula:



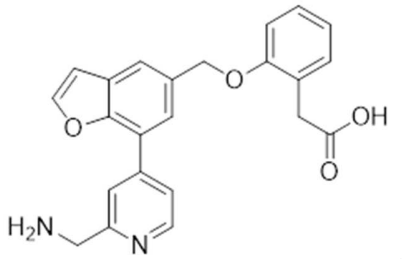
.

39. The compound of claim 36, or a pharmaceutically acceptable salt thereof, having the following formula:



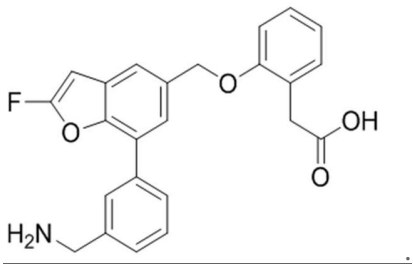
.

40. The compound of claim 36, or a pharmaceutically acceptable salt thereof, having the following formula:



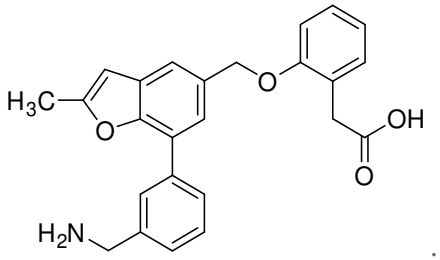
.

41. The compound of claim 36, or a pharmaceutically acceptable salt thereof, having the following formula:



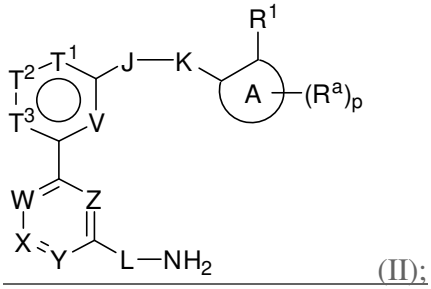
.

42. The compound of claim 36, or a pharmaceutically acceptable salt thereof, having the following formula:



.

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



(II);

wherein:

ring A is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

R^a, independently for each occurrence, is selected from the group consisting of halogen, cyano, hydroxy, $-NH_2$, -NH(Ac), -NH(alkyl), $-N(alkyl)_2$, $-NHC(O)(alkyl)$, $-CH_2NHC(O)(alkyl)$, $-C(O)NH_2$, -C(O)(alkyl), optionally substituted aryl, optionally substituted heteroaryl, cycloalkyl, alkoxy, alkyl, (cycloalkyl)alkyl, hydroxyalkyl, aminoalkyl, and haloalkyl;

T^1 is N, CH, NR^{T1}, or CR^{T1};

T^2 is NR^{T2} or CR^{T2};

T^3 is N, CH, NR^{T3}, or CR^{T3};

wherein:

(a) T^1 is CR^{T1} or NR^{T1}, wherein R^{T1} and R^{T2}, taken together with the intervening atoms, form an optionally substituted cycloalkyl, aryl, or heteroaryl ring; and

T^3 is N or CH; or

(b) T^3 is CR^{T3} or NR^{T3}; wherein R^{T3} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring; and

T^1 is N or CH; and

at least one of (a) T^2 is NR^{T2}, (b) T^3 is N, or (c) T^1 is NR^{T1};

R^1 is selected from the group consisting of $-NH_2$, $-CH_2COOH$, -CH(NH(CO)(alkyl))COOH, -CH(NH(CO)(cycloalkyl))COOH, $-CO(NH)CH_2$aryl, $-CO(NH)CH_2$heteroaryl, -CO(NH)aryl, and -CO(NH)heteroaryl;

p is 0, 1, or 2;

J is $–C(O)–$, $–NH–$, $–CH_2–$, $–O–$, $–S–$, $–S(O)–$, $–SO_2–$, $–N(alkyl)–$, or $–CH(alkyl)–$;

K is $–C(O)–$, $–NH–$, $–O–$, $–CH_2–$, $–S–$, $–S(O)–$, $–SO_2–$, $–N(alkyl)–$, or $–CH(alkyl)–$;

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

W is N, CH, or CR^c;

X is N, CH, or CR^c;

Y is N, CH, or CR^c;

Z is N, CH, or CR^c;

R^c, independently for each occurrence, is selected from the group consisting of halogen, -OH, $-NR^jR^k$, alkoxy, and alkyl;

L is selected from the group consisting of a bond, $–CH_2–$, $–CH_2CH_2–$, $–CHR^2–$, $–CF_2–$, $–CFR^2–$, –C(O)–, $–C(=NR^L)–$, and $–C(=CHR^L)–$;

wherein R^L is H or alkyl;

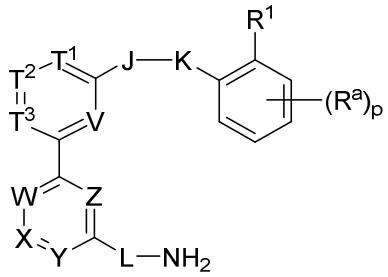
or wherein R^L and an occurrence of R^c taken together with the intervening atoms form a substituted or unsubstituted heteroaryl ring;

R^2 is alkyl, hydroxyalkyl, or haloalkyl;

V is N or CH.

44. The compound of claim 43, wherein ring A is phenyl, thiophenyl, furyl, pyrazole, or pyridinyl.

45. The compound of claim 43 or 44, having the structure of formula (IIa):



(IIa).

46. The compound of any one of claims 43-45, wherein p is 0.

47. The compound of any one of claims 43-46, wherein R^1 is $-CH_2COOH$.

48. The compound of any one of claims 43-47, wherein –J–K– is selected from the group consisting of –C(O)-NH–, –NH-C(O)–, and $–CH_2O–$.

49. The compound of any one of claims 43-48, wherein each of W, X, Y, and Z is CH.

50. The compound of any one of claims 43-48, wherein at least one of W, X, Y, and Z is CR^c, e.g., Z is CR^c.

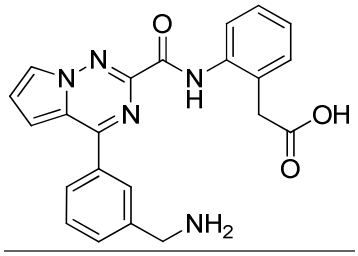
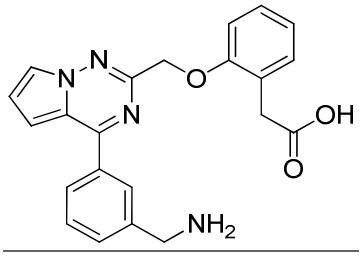
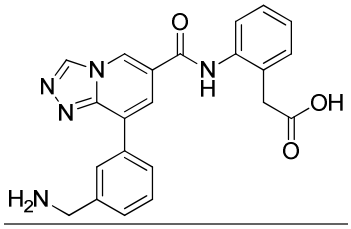
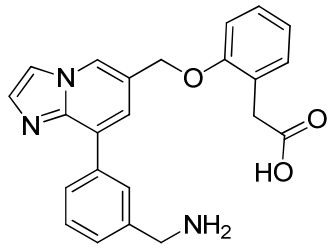
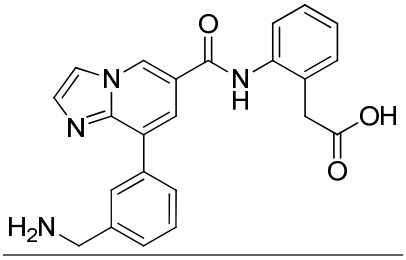
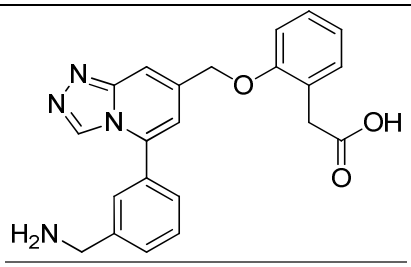
51. The compound of claim 50, wherein R^c is halogen, e.g., fluoride.

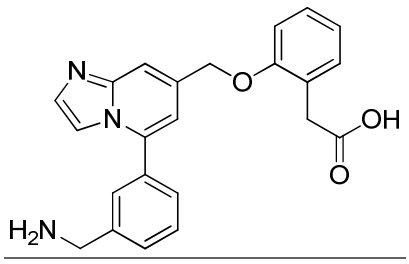
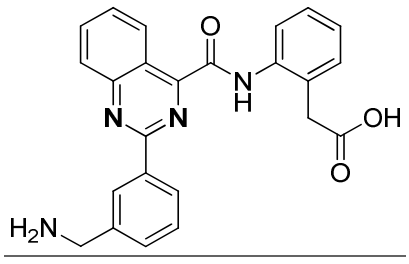
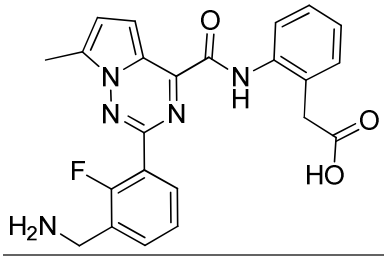
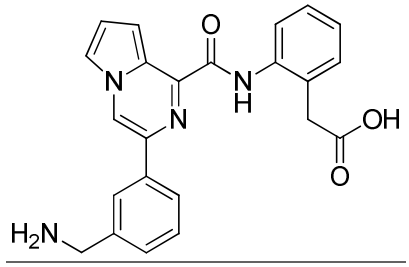
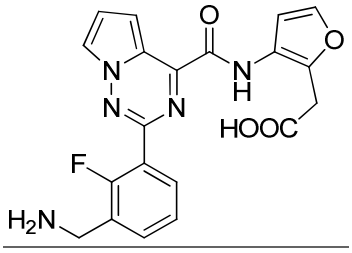
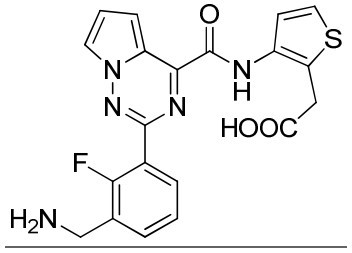
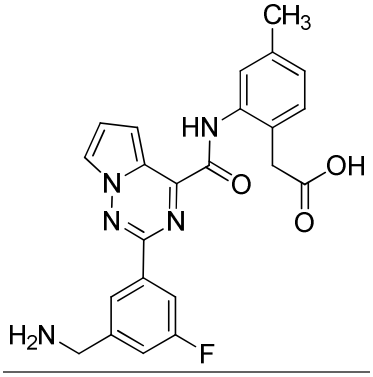
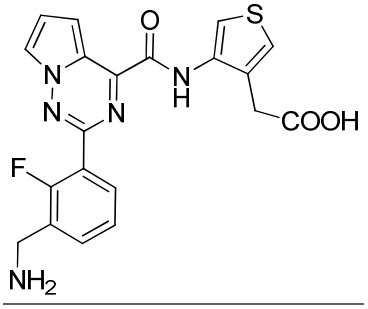
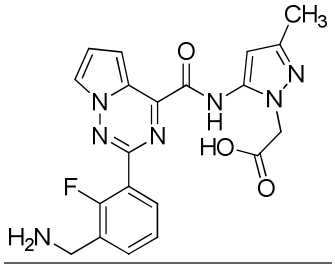
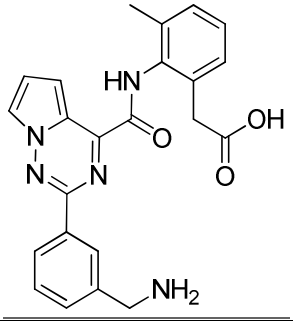
52. The compound of any one of claims 43-51, wherein L is $–CH_2–$.

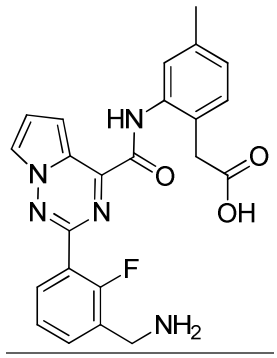
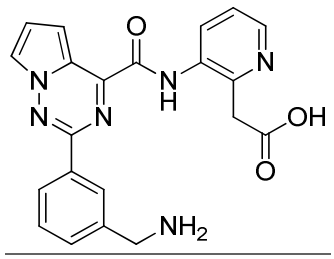
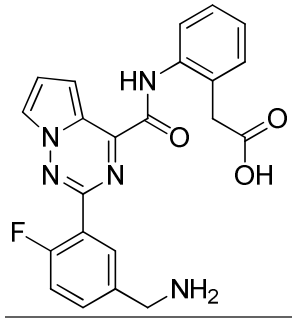
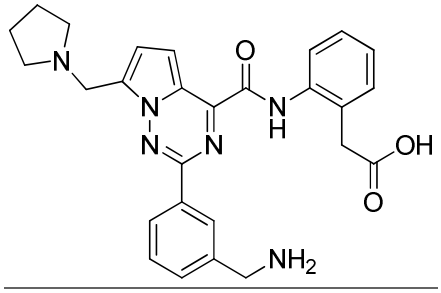
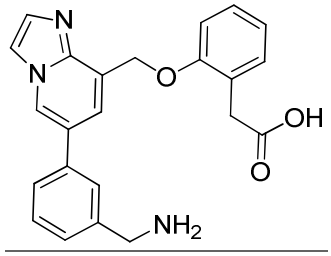
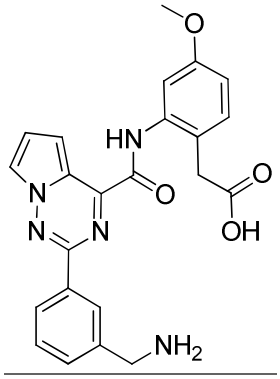
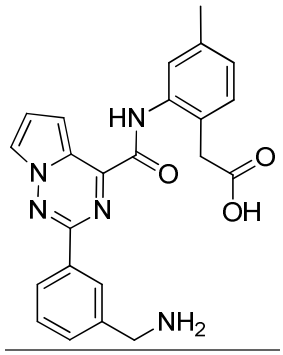
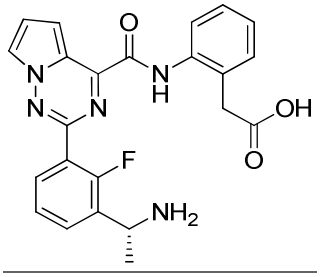
53. The compound of any one of claims 43-52, wherein T^1 is CR^{T1}; and R^{T1} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring, such as pyrrole, imidazole, or 1,2,4-triazole.

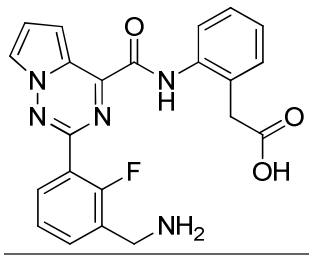
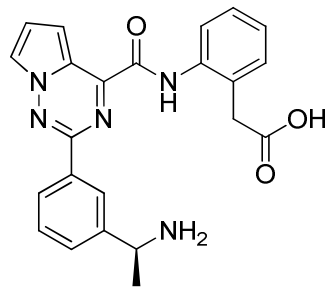
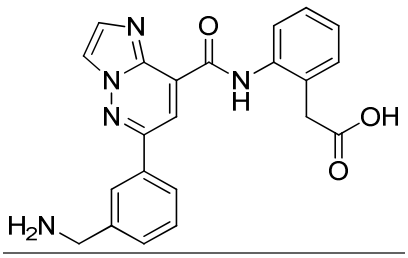
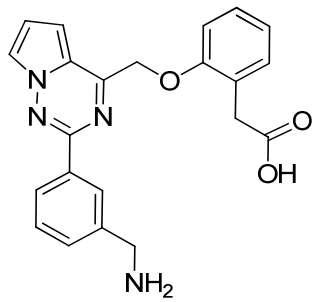
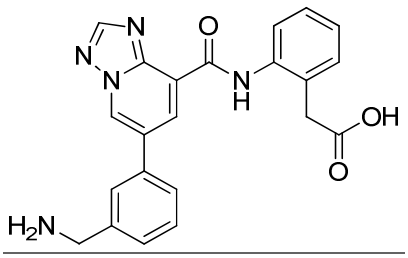
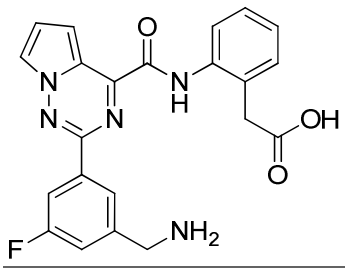
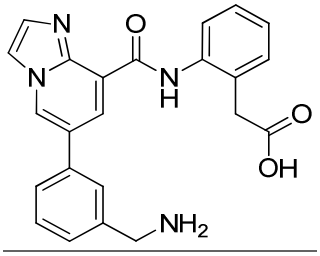
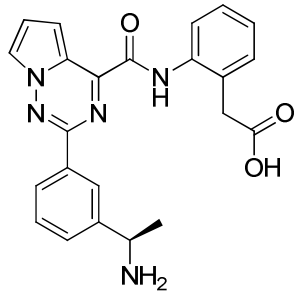
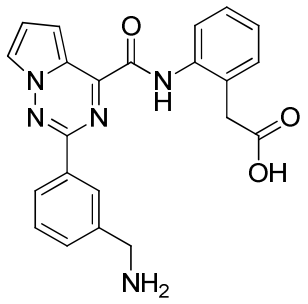
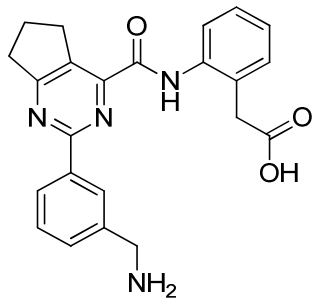
54. The compound of any one of claims 43-52, wherein T^3 is CR^{T3}; and R^{T3} and R^{T2}, taken together with the intervening atoms, form an optionally substituted heteroaryl ring, such as pyrrole, imidazole, 1,2,4-triazole, or pyridine.

55. The compound of claim 43, selected from the following table:

56. A pharmaceutical composition, comprising a compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

57. Use of a compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a disease or condition characterized by aberrant complement system activity.

58. The use of claim 57, wherein the disease or condition characterized by aberrant complement system activity is an immunological disorder.

59. The use of claim 57, wherein the disease or condition characterized by aberrant complement system activity is a disease of the central nervous system.

60. The use of claim 57, wherein the disease or condition characterized by aberrant complement system activity is a neurodegenerative disease or neurological disease.

61. The use of claim 57, wherein the disease or condition characterized by aberrant complement system activity is a renal disease.

62. The use of claim 57, wherein the disease or condition characterized by aberrant complement system activity is a cardiovascular disease.

63. The use of claim 57, wherein the disease or condition characterized by aberrant complement system activity is selected from the group consisting of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, organ transplant rejection, myasthenia gravis, neuromyelitis optica, membranoproliferative glomerulonephritis, dense-deposit disease, cold agglutinin disease, catastrophic antiphospholipid syndrome, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), IgA nephropathy, age-related macular degeneration (AMD), systemic

lupus erythematosus, warm autoimmune hemolytic anemia, and focal segmental glomerulosclerosis.

64. The use of claim 57, wherein the disease or condition characterized by aberrant complement system activity is paroxysmal nocturnal hemoglobinuria.

65. A compound of any one of claims 1-55, or a pharmaceutically acceptable salt or prodrug thereof, for use in therapy.