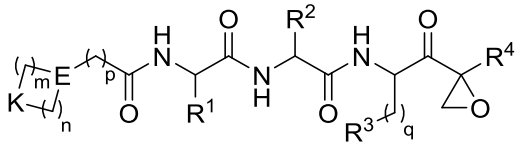
Claims

1. A compound of Formula (X):


(X)

,

wherein:

m and n each independently are 0, 1 or 2, and m + n = 2, 3, or 4;

p is 0 or 1;

q is 0, 1, or 2;

K is selected from the group consisting of CR^5R^6, NR^7, $N(C=O)OR^7$, —NH—(C=O)—, O, S, SO, and SO_2;

E is N or CR^7;

R^1 is selected from the group consisting of H, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, $C_{3\text{-}6}$cycloalkyl, and 3-6 membered heterocycloalkyl, wherein R^1 is optionally substituted with one or more substituents selected from the group consisting of halo, OR^7, SR^7, $N(R^7)_2$, CN, and $(C=O)N(R^7)_2$;

R^2 is $C_{1\text{-}2}$alkylene—G or (C=O)—G; wherein G is selected from the group consisting of aryl, heteroaryl, and pyridinone, with the proviso that when R^2 is CH_2phenyl, the phenyl is substituted with one or more substituents selected from the group consisting of OR^7, halo, $C_{1\text{-}3}$alkyl, OCF_3, SO_2R^7, $(C=O)N(R^7)_2$, CN, and $SO_2N(R^7)_2$;

R^3 is selected from the group consisting of $C_{3\text{-}7}$cycloalkyl, $C_{3\text{-}7}$cycloalkenyl, a 3-7 membered heterocycloalkyl, and a 3-7 membered heterocycloalkenyl, wherein R^3 is optionally substituted with one or more substituents selected from the group consisting of halo, =O, OR^7, SR^7, $N(R^7)_2$, $O(C=O)N(R^7)_2$, and $C_{1\text{-}6}$alkyl;

R^4 is H or $C_{1\text{-}3}$alkyl;

R^5 and R^6 are each independently selected from the group consisting of H, OH, halo, $C_{1\text{-}3}$alkyl, and CF_3, or R^5 and R^6 together with the carbon to which they are attached form C=O or  , wherein W is O or NR^7, and r is 1, 2 or 3; and

each R^7 is independently H or $C_{1\text{-}6}$alkyl,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein m is 0.

3. The compound of claim 1, wherein m is 1.

4. The compound of claim 1, wherein m is 2.

5. The compound of any one of claims 1 to 4, wherein n is 2.

6. The compound of claim 1, 3, or 4, wherein n is 1.

7. The compound of claim 1 or 4, wherein n is 0.

8. The compound of any one of claim 1 to 7, wherein p is 0.

9. The compound of any one of claim 1 to 7, wherein p is 1.

10. The compound of any one of claim 1 to 9, wherein q is 0.

11. The compound of any one of claim 1 to 9, wherein q is 1.

12. The compound of any one of claim 1 to 9, wherein q is 2.

13. The compound of any one of claims 1 to 12, wherein K is CR^5R^6.

14. The compound of claim 13, wherein K is selected from the group consisting of CH(OH), C(CH3)(OH), C=O, CH2, CF2, CH(Cl), CH(CF3),  , and COH(CH3).

15. The compound of any one of claims 1 to 12, wherein K is NR^7.

16. The compound of claim 15, wherein K is NCH_3 or NCH_2CH_3.

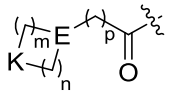
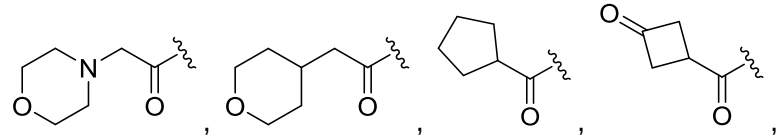
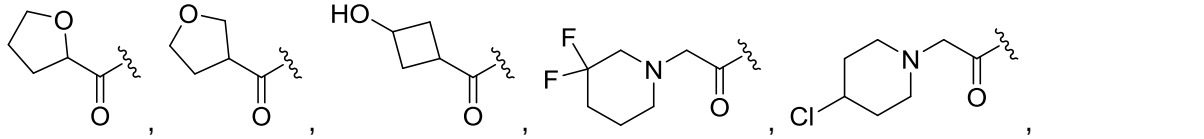
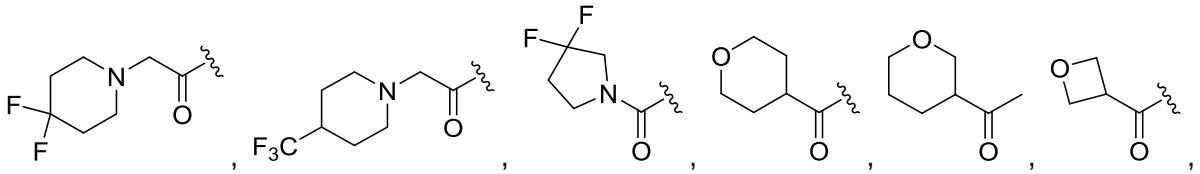
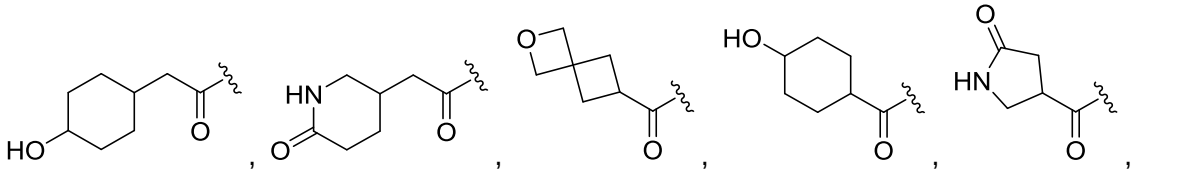
17. The compound of any one of claims 1 to 12, wherein K is $N(C=O)OR^7$, -NH-(C=O)-, S, SO, or SO_2.

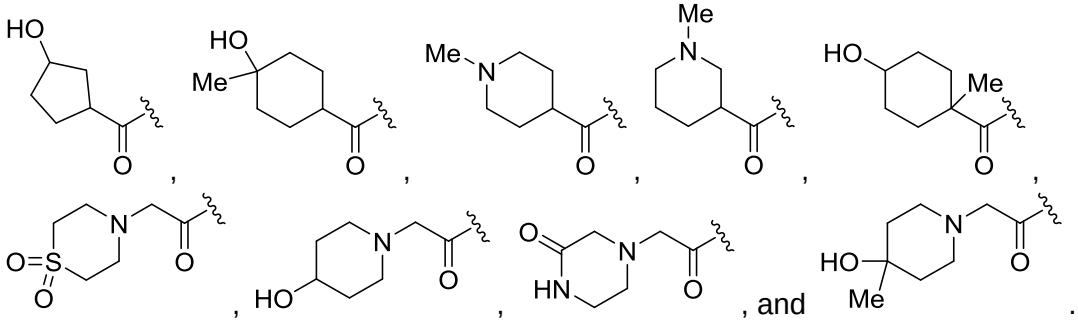
18. The compound of any one of claims 1 to 12, wherein K is O.

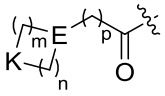
19. The compound of any one of claims 1 to 18, wherein E is N.

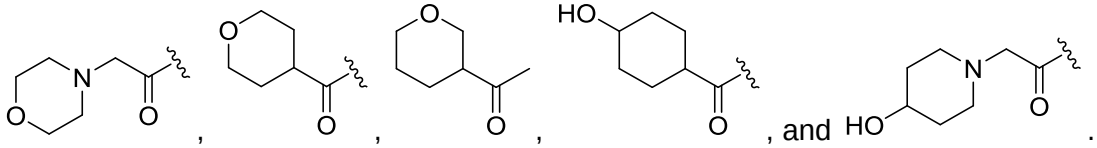
20. The compound of any one of claims 1 to 18, wherein E is CR^7.

21. The compound of claim 20, wherein E is CH or $C(CH_3)$.

22. The compound of any one of claims 1 to 21, wherein  is selected from the group consisting of:  ,  ,  ,  .



23. The compound of any one of claims 1 to 22, wherein  is selected from the group consisting of:



24. The compound of any one of claims 1 to 23, wherein R^1 is $C_{1\text{-}6}$alkyl.

25. The compound of claim 24, wherein R^1 is $C_{1\text{-}3}$alkyl.

26. The compound of any one of claims 1 to 23, wherein R^1 is CH_3, CH_2OH, CF_3, $CH(OH)CH_3$, CH_2CN, or CH_2CH_3.

27. The compound of claim 26, wherein R^1 is CH_3, CH_2OH, $CH(OH)CH_3$, CH_2CN.

28. The compound of any one of claims 1 to 23, wherein R^1 is $C_{2\text{-}6}$alkenyl or $C_{2\text{-}6}$alkynyl.

29. The compound of claim 28, wherein R^1 is CH_2CCH.

30. The compound of any one of claims 1 to 23, wherein R^1 is $C_{3\text{-}6}$cycloalkyl.

31. The compound of claim 30, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

32. The compound of any one of claims 1 to 23, wherein R^1 is a 3-6 membered heterocycloalkyl.

33. The compound of claim 32, wherein R^1 is an oxetanyl, tetrahydrofuranyl, or piperadinyl.

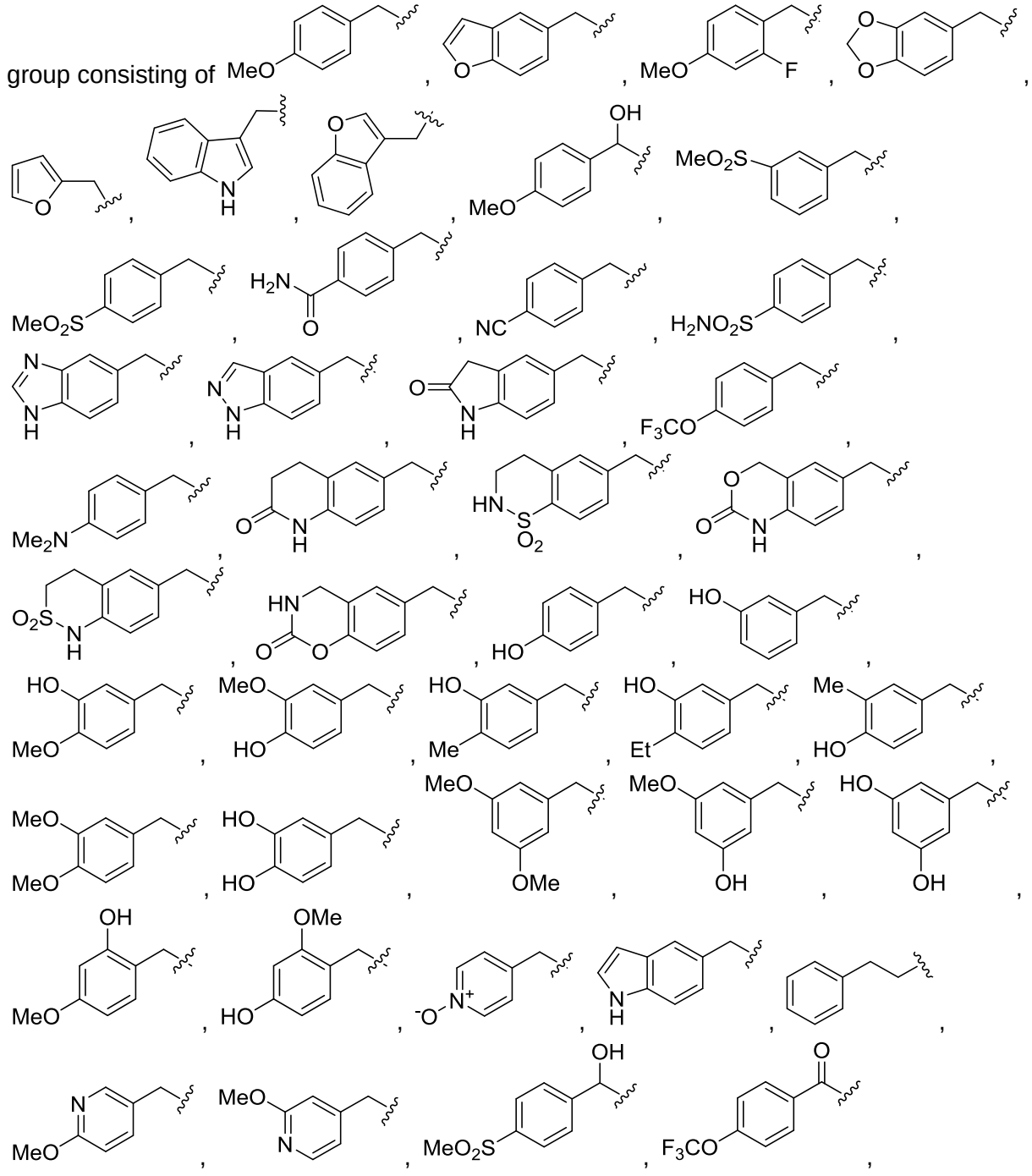
34. The compound of any one of claims 1 to 33, wherein R^2 is $C_{1\text{-}2}$alkylene-heteroaryl.

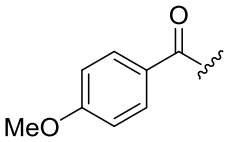
35. The compound of claim 34, wherein R^2 is CH_2-heteroaryl.

36. The compound of any one of claims 1 to 33, wherein R^2 is C_{1-2}alkylene-pyridinone.

37. The compound of any one of claims 1 to 33, wherein R^2 is C_{1-2}alkylene-aryl.

38. The compound of claim 37, wherein R^2 is CH_2-aryl.

39. The compound of any one of claims 1 to 37, wherein R^2 is selected from the group consisting of 



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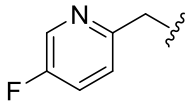

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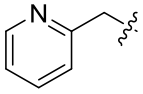

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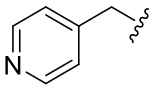

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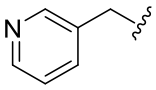

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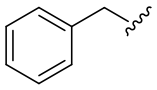
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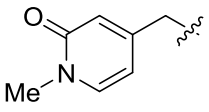

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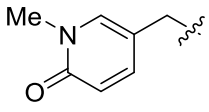

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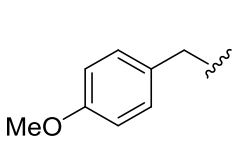
40. The compound of any one of claims 1 to 33, wherein R^2 is selected from the group consisting of:


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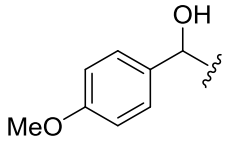

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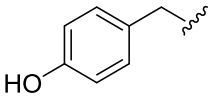

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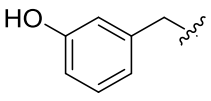

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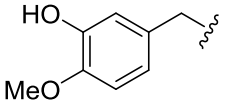

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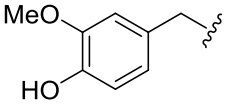

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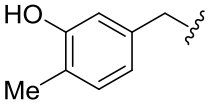

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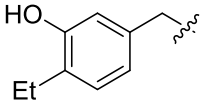

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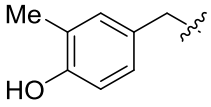

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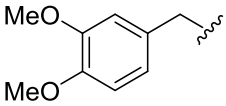

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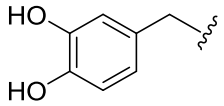

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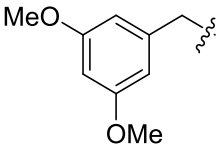

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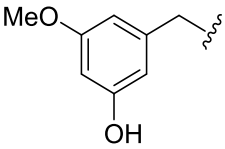

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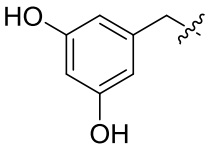

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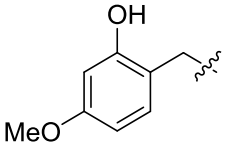

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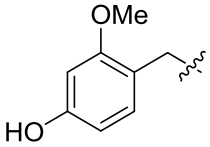

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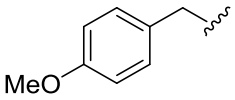
41. The compound of claim 40, wherein R^2 is selected from the group consisting of:


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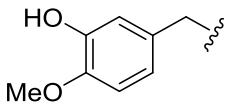

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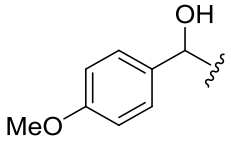

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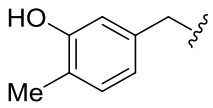

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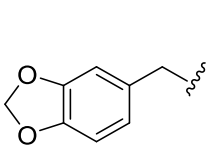
42. The compound of any one of claims 1 to 33, wherein R^2 is selected from the group consisting of


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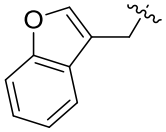

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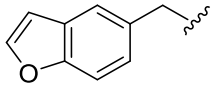

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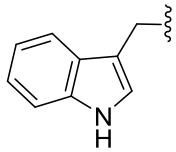

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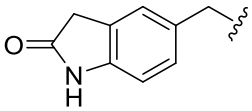

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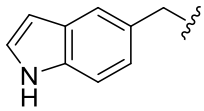

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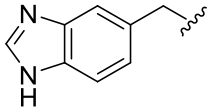

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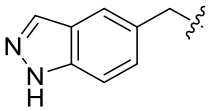

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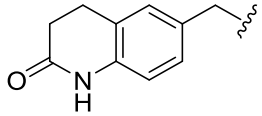

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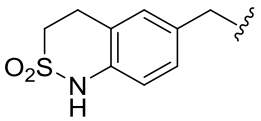

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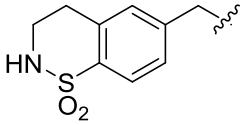

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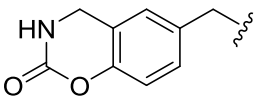

, and

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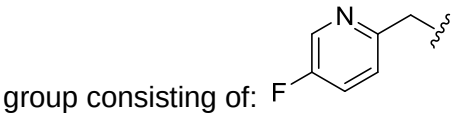
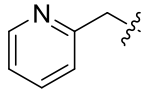
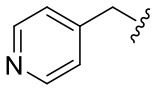
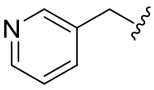
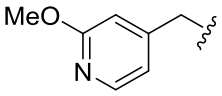
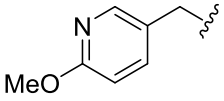
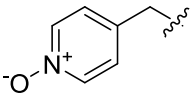
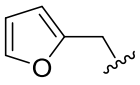
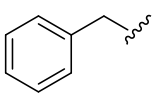
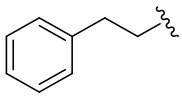
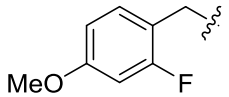
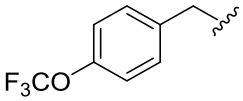
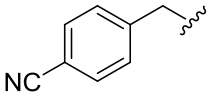
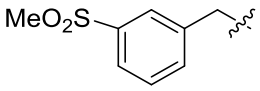
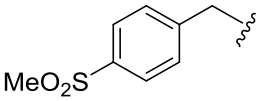
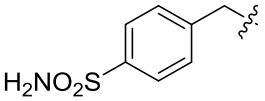
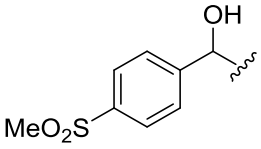
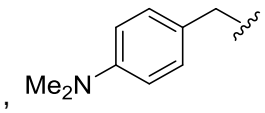
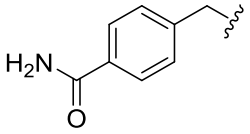
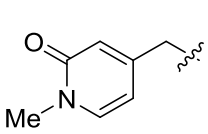
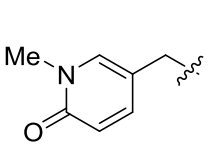
43. The compound of any one of claims 1 to 33, wherein R^2 is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  , and  .

44. The compound of any one of claims 1 to 33, wherein R^2 is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

45. The compound of any one of claims 1 to 44, wherein R^3 is $C_{3\text{-}7}$cycloalkyl.

46. The compound of claim 45, wherein the $C_{3\text{-}7}$cycloalkyl is substituted with at least one substituent selected from the group consisting of OH, F, Me, NH_2, and $O(CO)NH_2$.

47. The compound of claim 45, wherein R^3 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

48. The compound of claim 47, wherein R^3 is cyclopentyl or cyclohexyl.

49. The compound of any one of claims 1 to 44, wherein R^3 is $C_{3\text{-}7}$cycloalkenyl.

50. The compound of claim 49, wherein the $C_{3\text{-}7}$cycloalkenyl is substituted with at least one substituent selected from the group consisting of OH and Me.

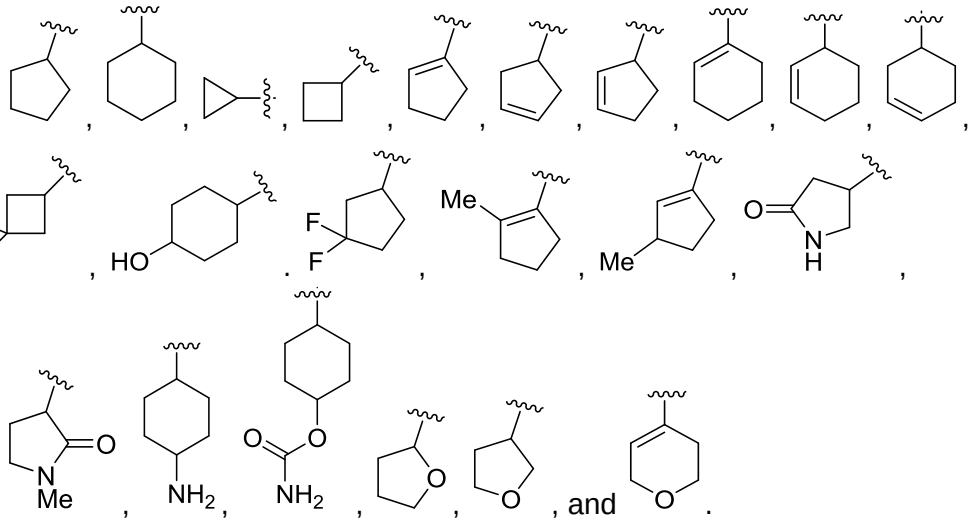
51. The compound of claim 49, wherein R^3 is cyclopentenyl or cyclohexenyl.

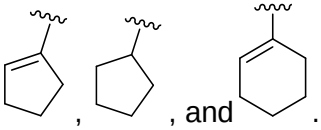
52. The compound of any one of claims 1 to 44, wherein R^3 is a 3-7 membered heterocycloalkyl.

53. The compound of claim 52, wherein R^3 is tetrohydrofuranyl, tetrahydropyranyl, pyrrolindinyl, or pyrrolidinonyl.

54. The compound of any one of claims 1 to 44, wherein R^3 is a 3-7 membered heterocycloalkenyl.

55. The compound of claim 54, wherein R^3 is a dihydropyranyl or dihydrofuranyl.

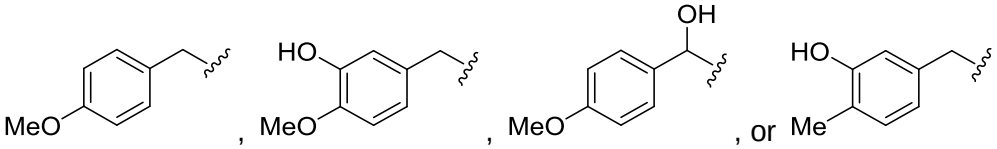
56. The compound of any one of claims 1 to 44, wherein R^3 is selected from the group consisting of:  .

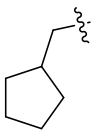
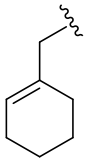
57. The compound of any one of claims 1 to 44, wherein R^3 is selected from the group consisting of  .

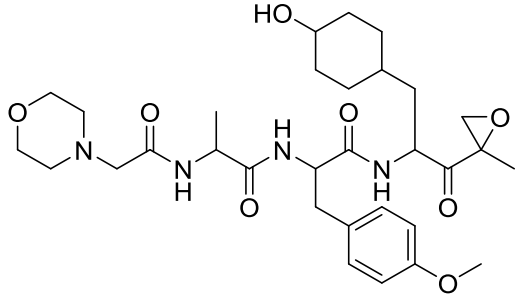
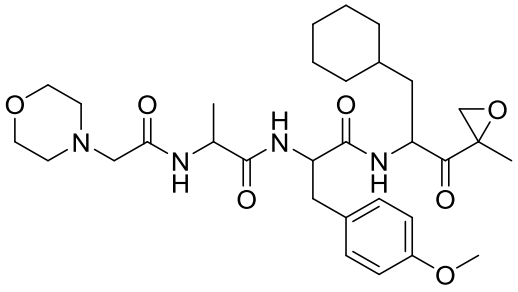
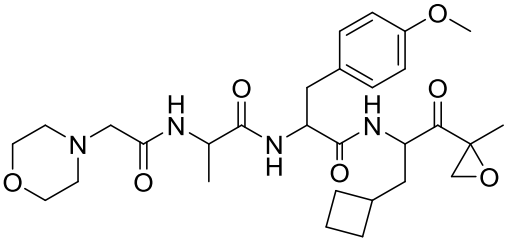
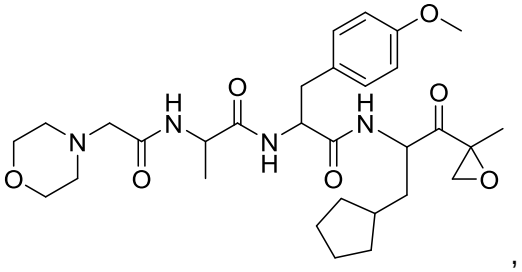
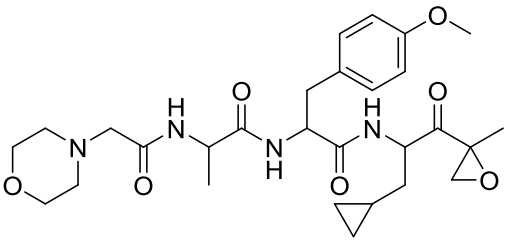
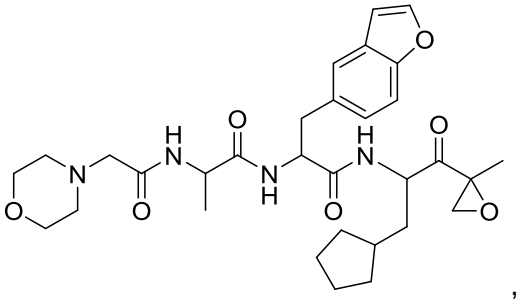
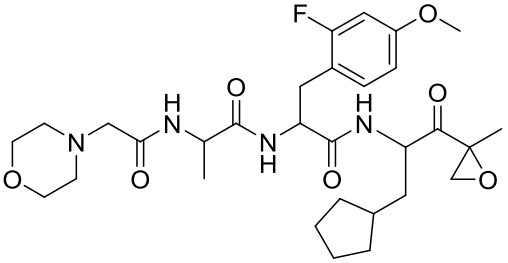
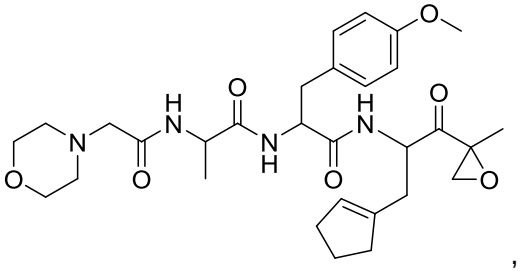
58. The compound of any one of claims 1 to 57, wherein R^4 is $C_{1\text{-}3}$alkyl.

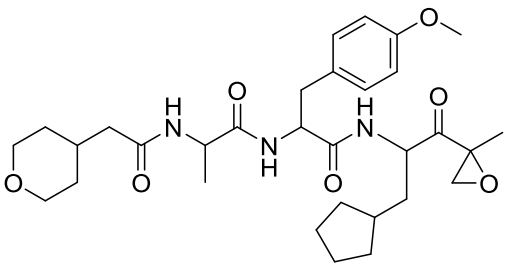
59. The compound of claim 58, wherein R^4 is methyl.

60. The compound of any one of claims 1 to 57, wherein R^4 is H.

61. The compound of claim 1, wherein:
m and n are each independently 2;
p is 1;
q is 1;
K is CR^5R^6 or O;
E is N or CR^7;
R^1 is CH_3, CH_2OH, $CH(OH)CH_3$, or CH_2CN;
R^2 is  ;

R^3 is  ,  , or  ;
R^4 is methyl;
R^5 is H;
R^6 is OH; and
R^7 is H.

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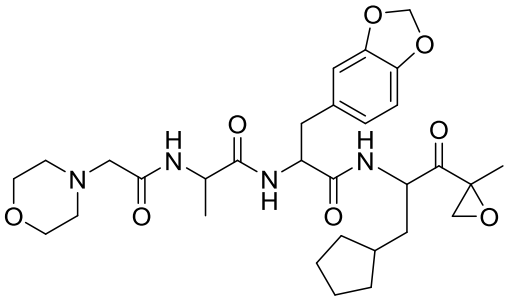
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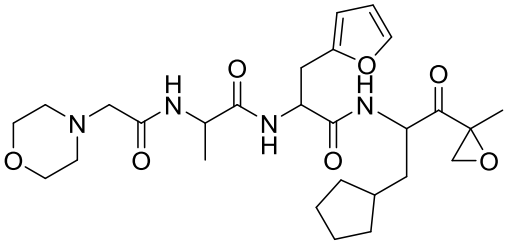
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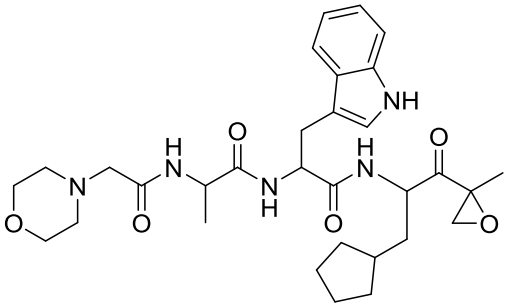
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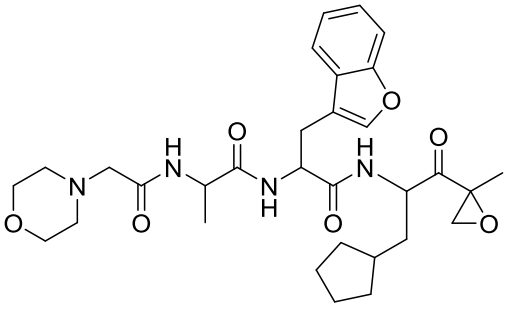
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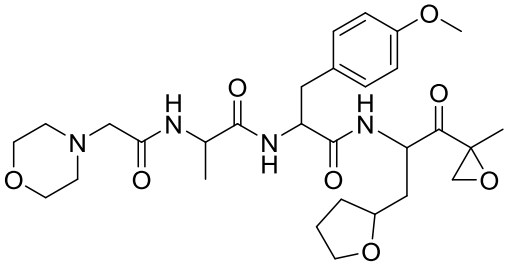
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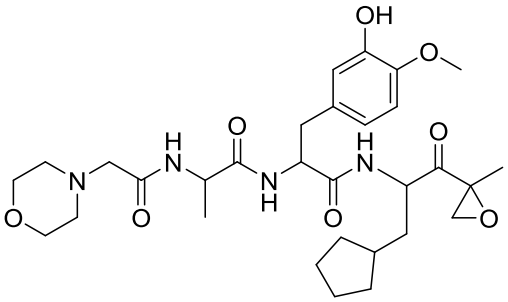
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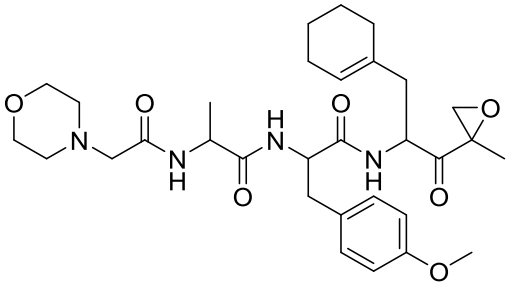
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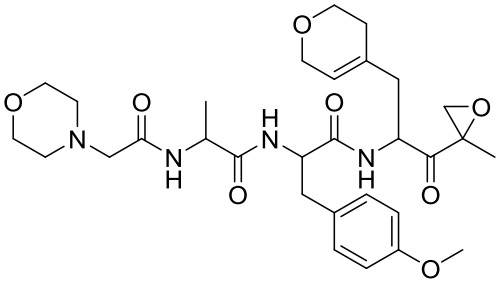
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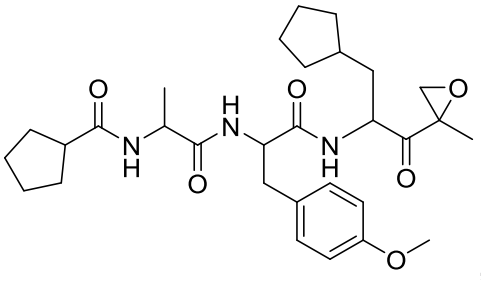
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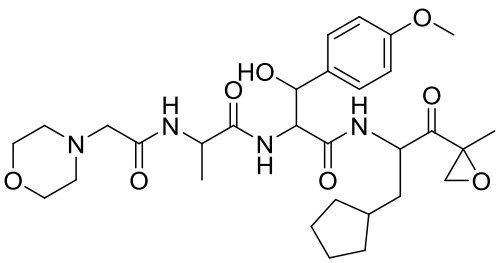
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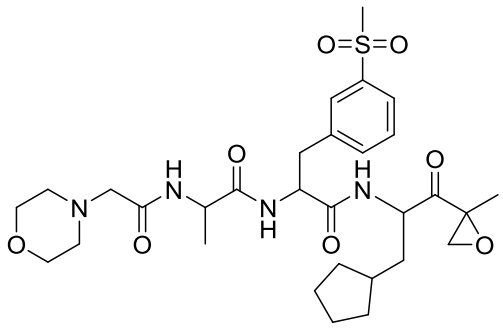
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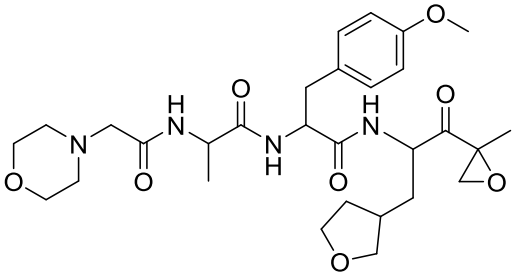
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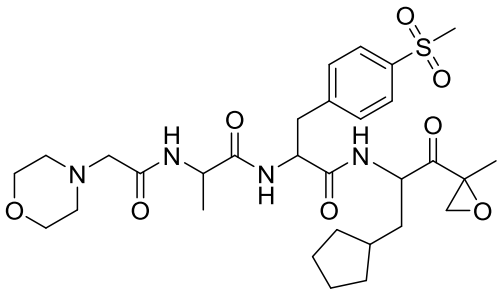
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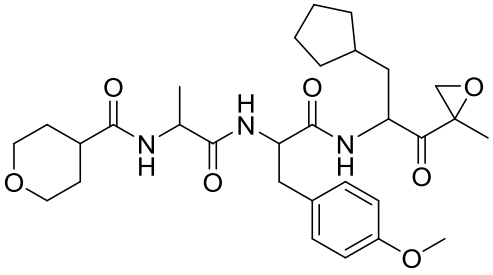
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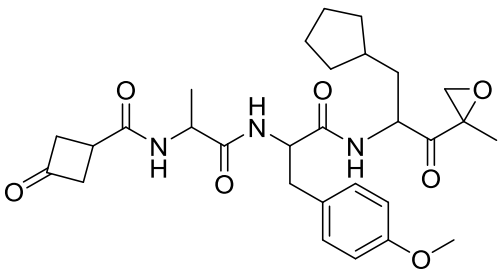
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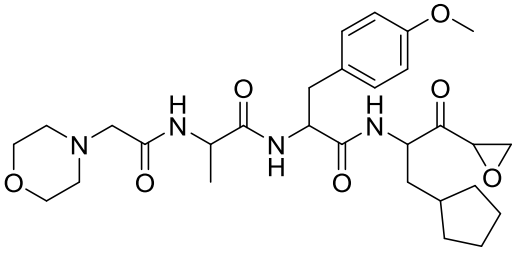
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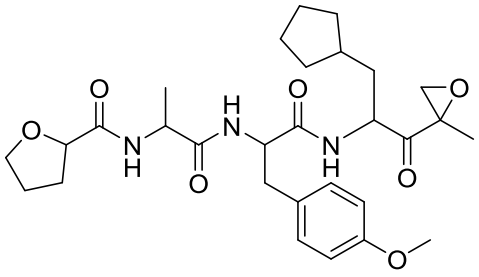
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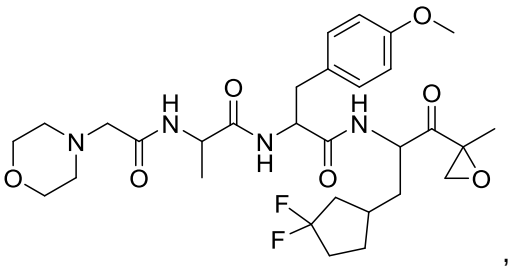
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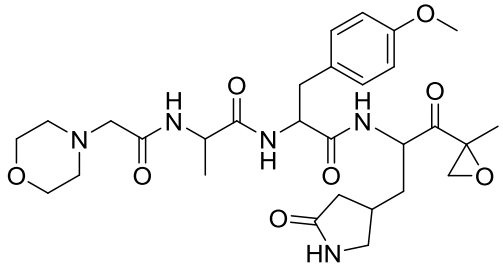
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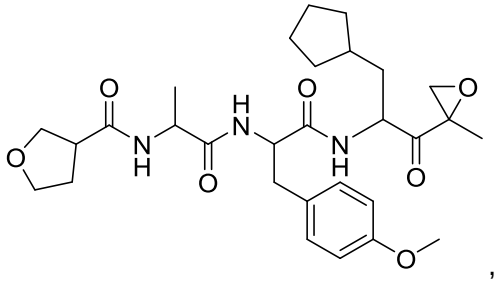
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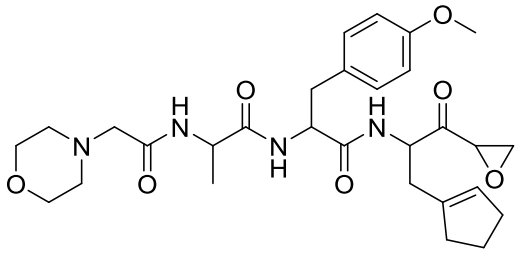
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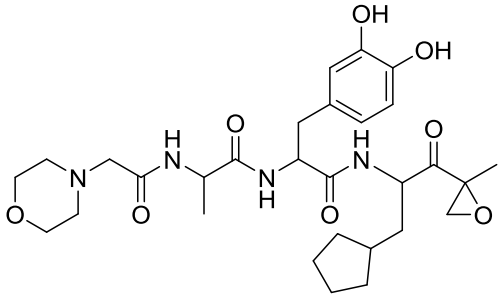
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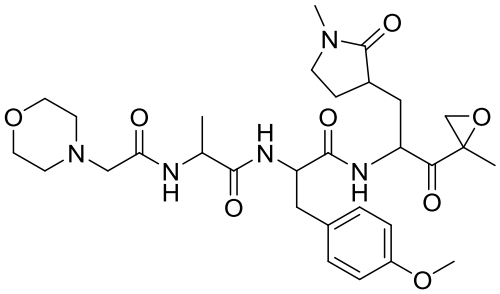
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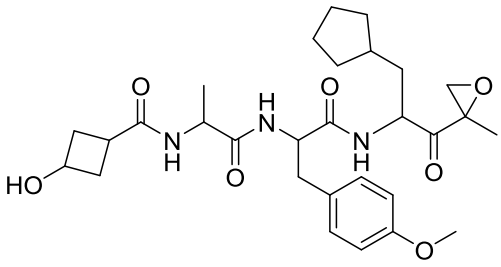
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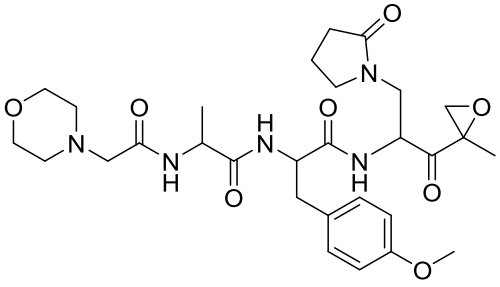
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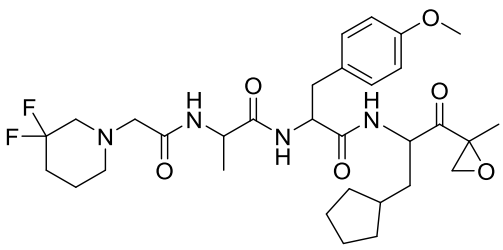
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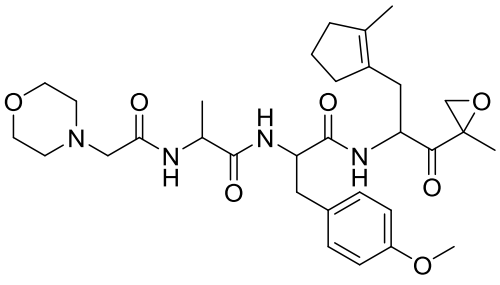
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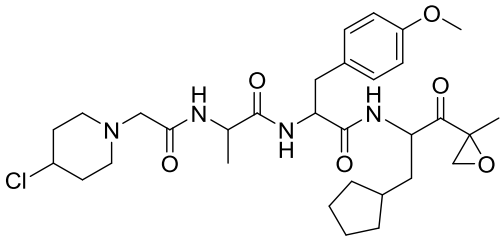
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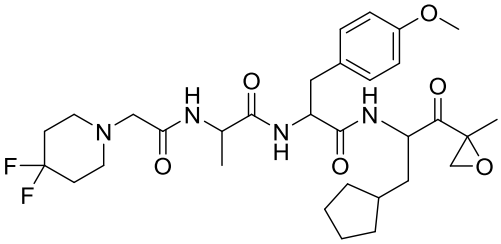
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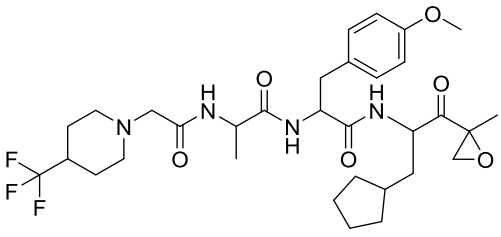
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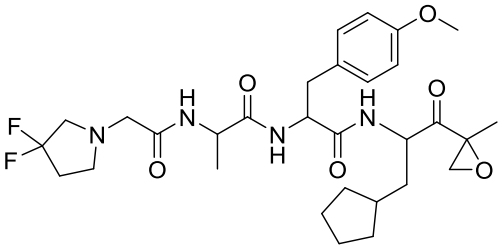
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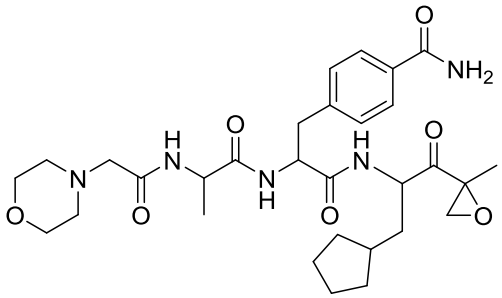
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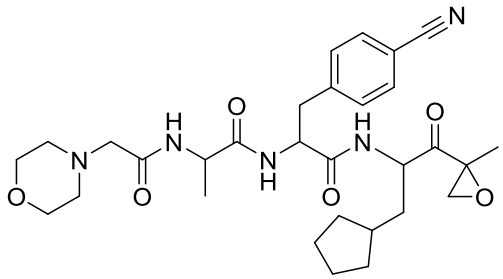
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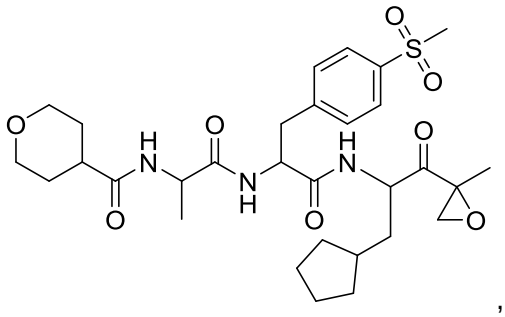
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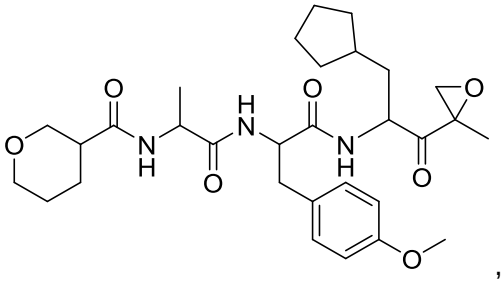
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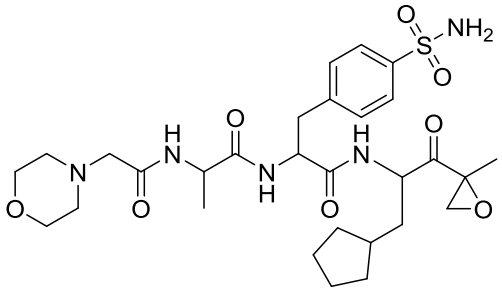
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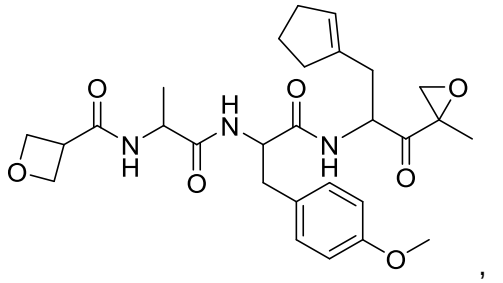
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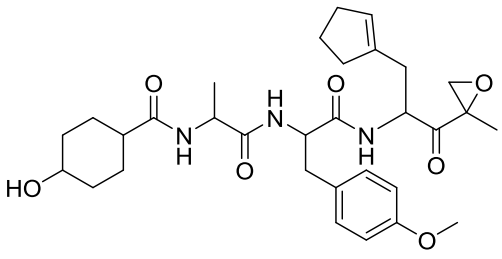
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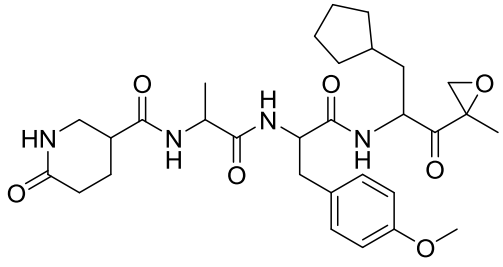
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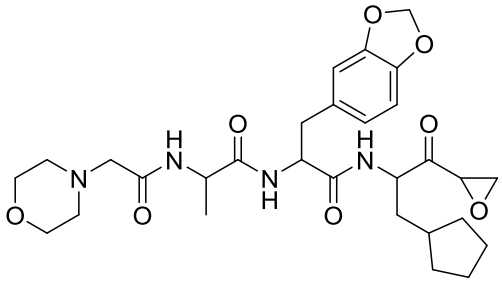
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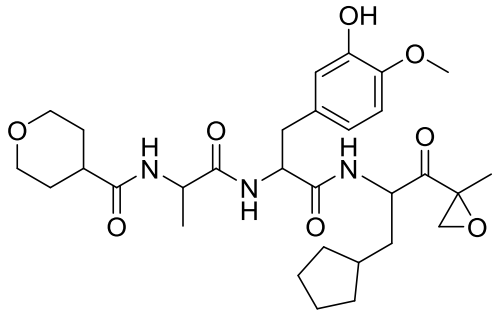
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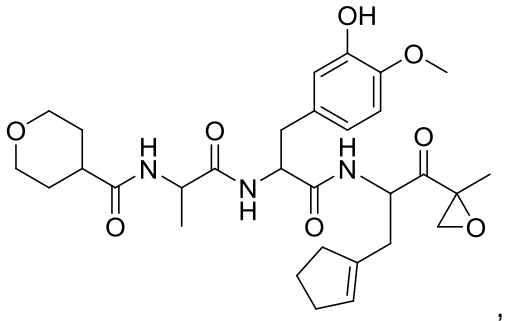
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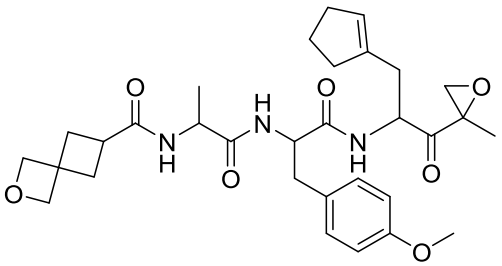
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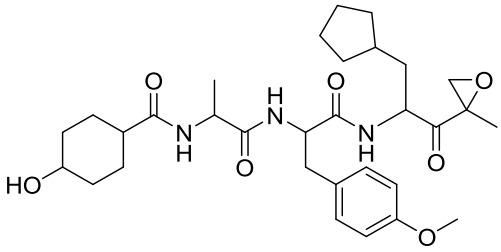
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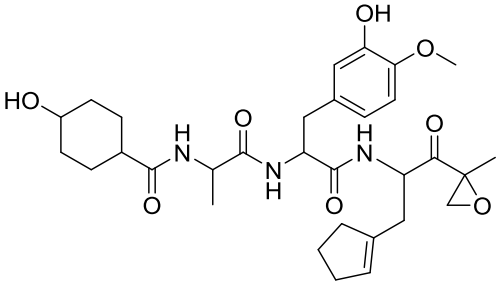
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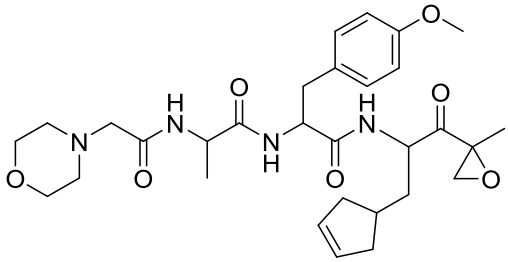
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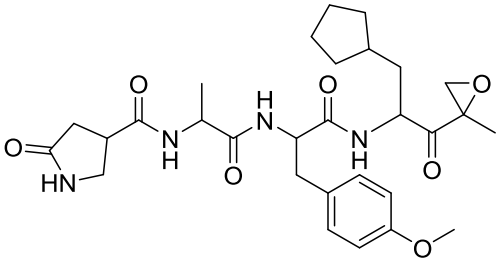
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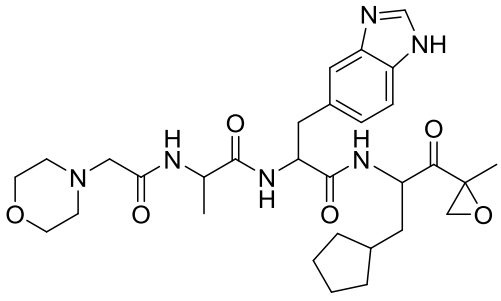
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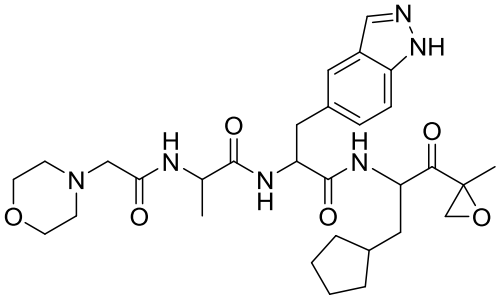
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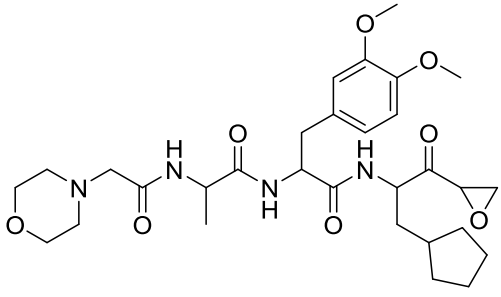
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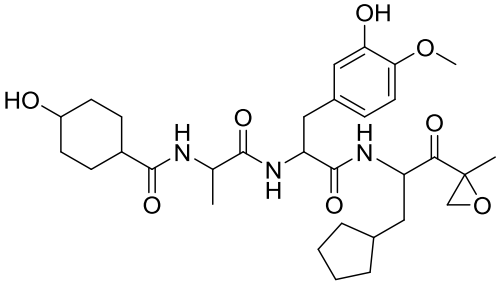
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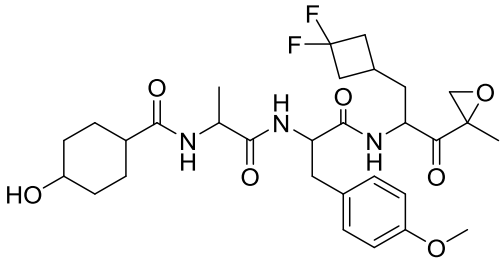
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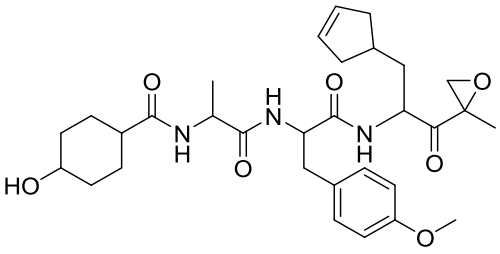
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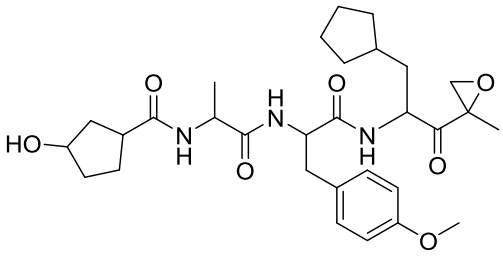
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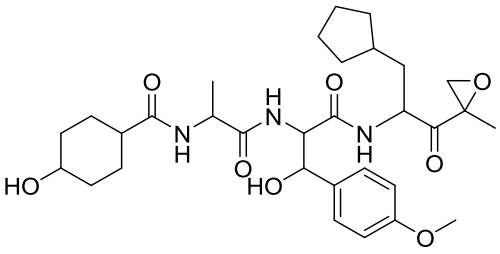
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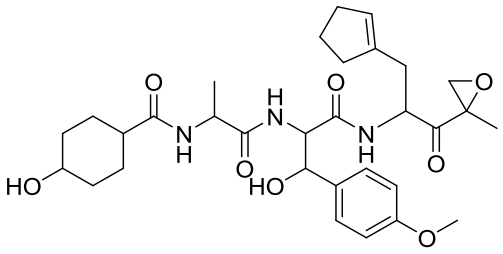
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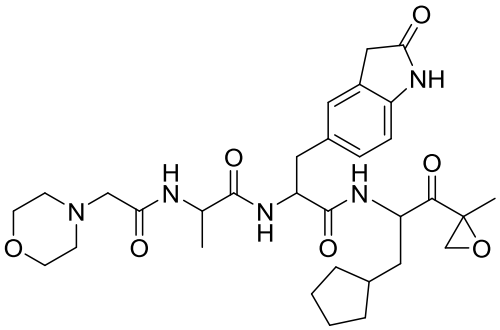
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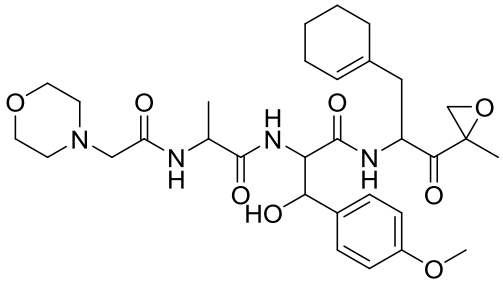
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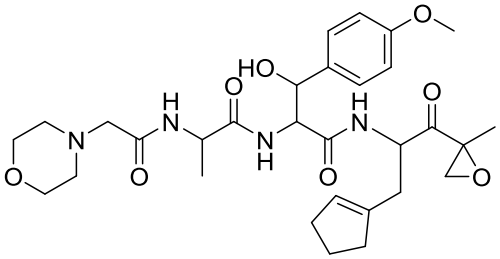
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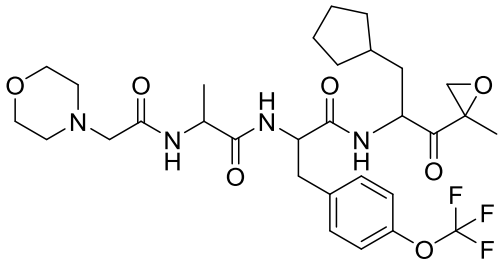
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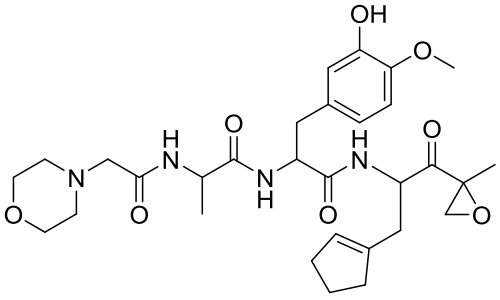
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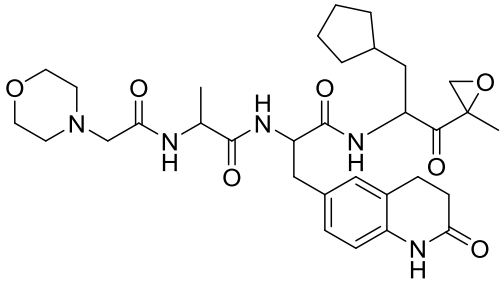
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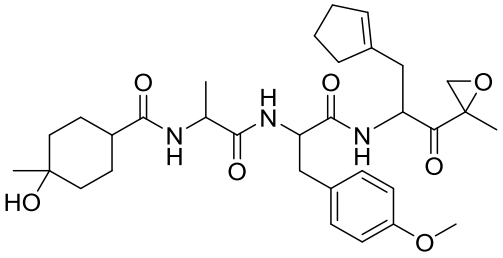
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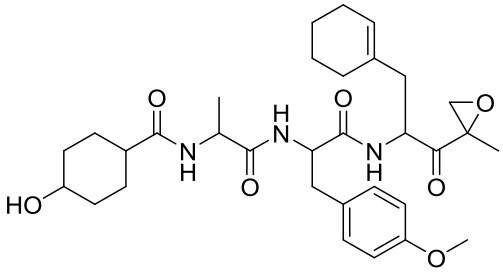
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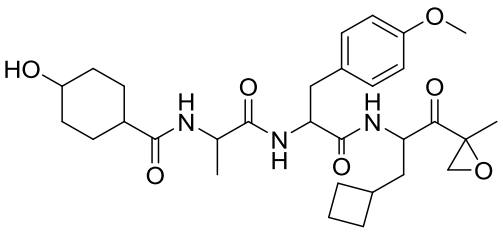
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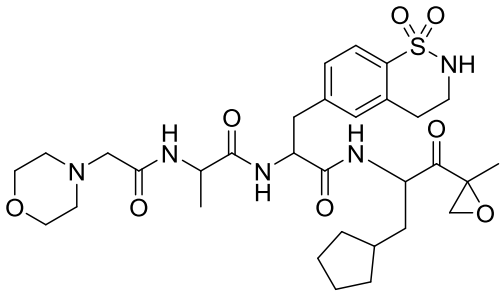
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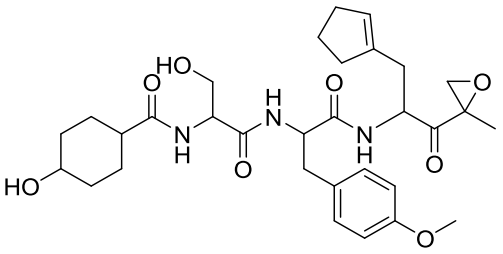
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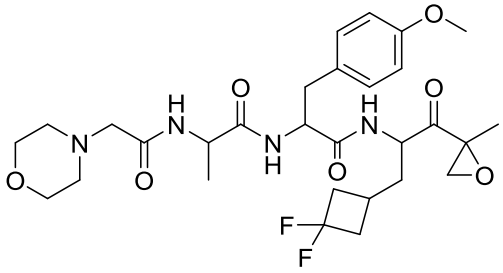
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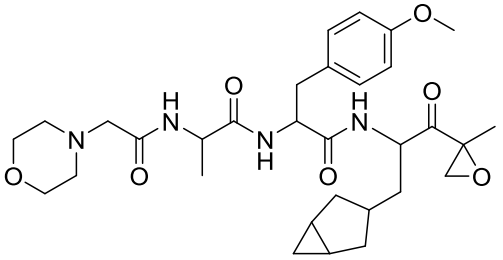
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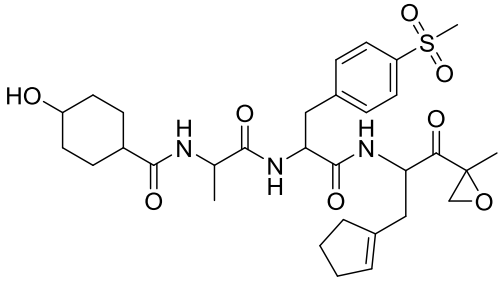
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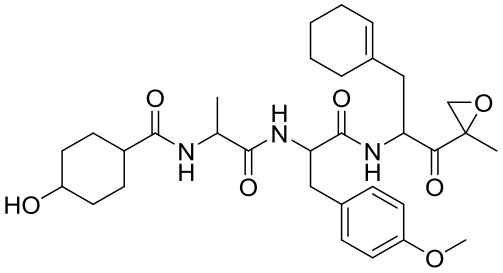
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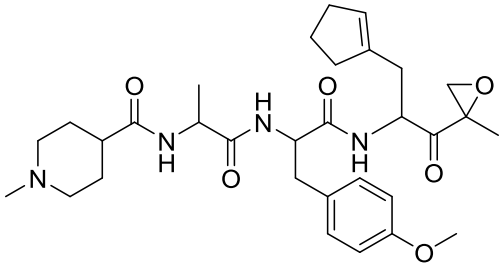
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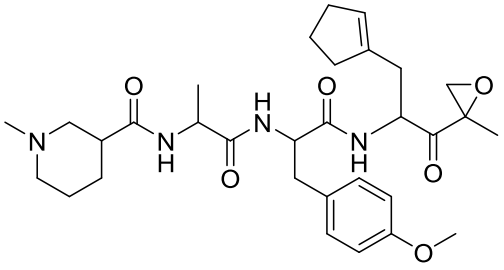
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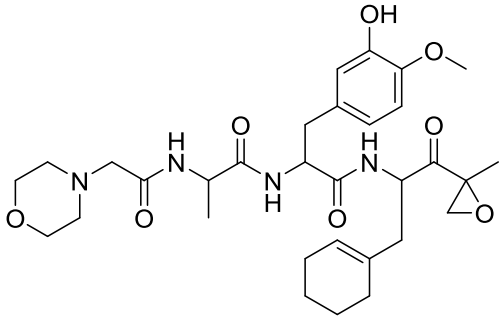
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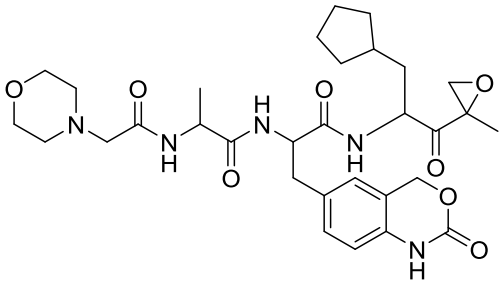
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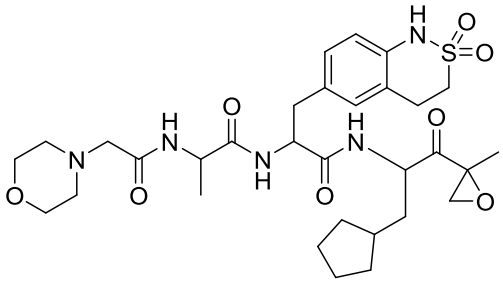
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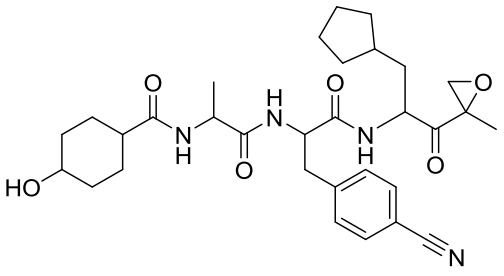
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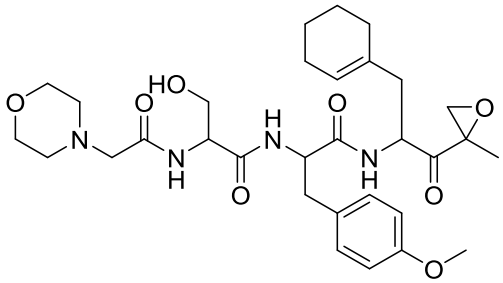
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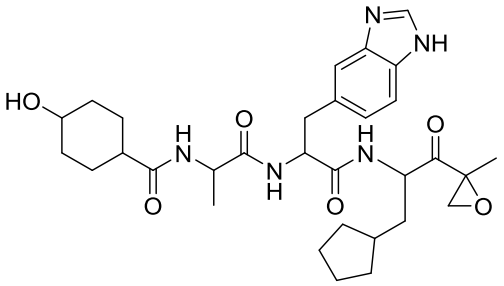
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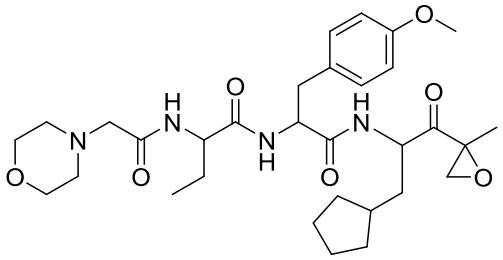
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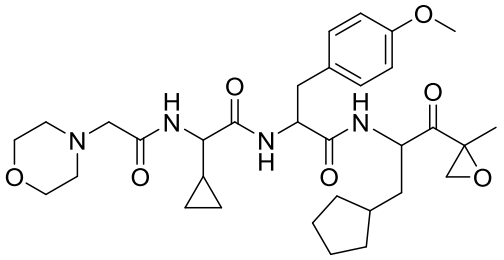
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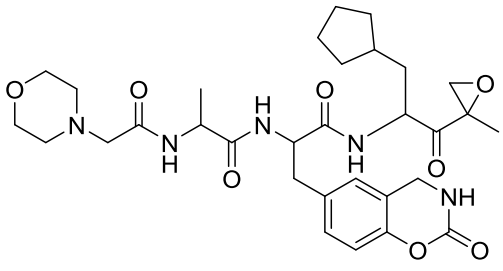
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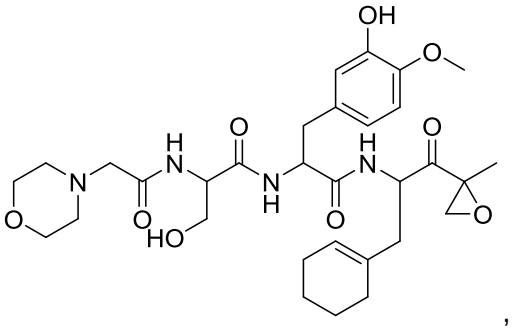
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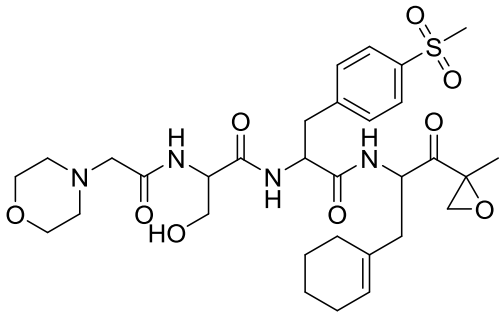
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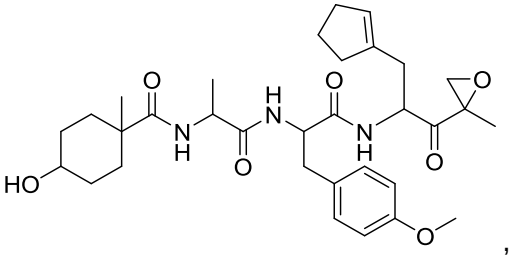
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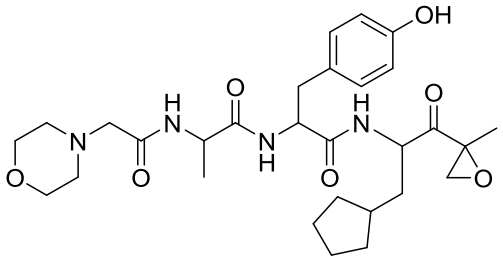
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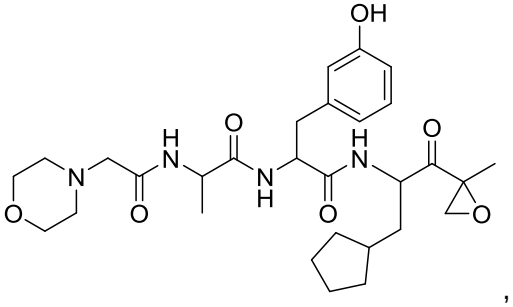
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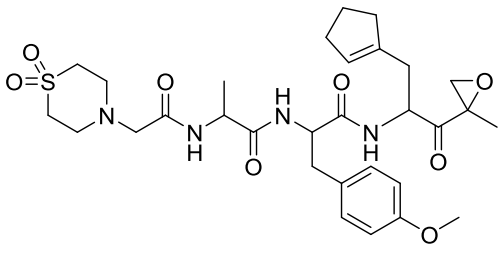
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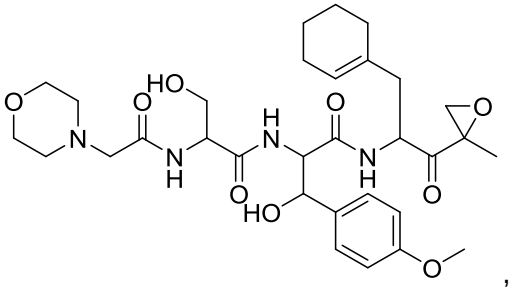
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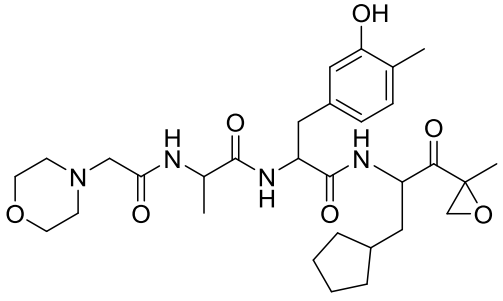
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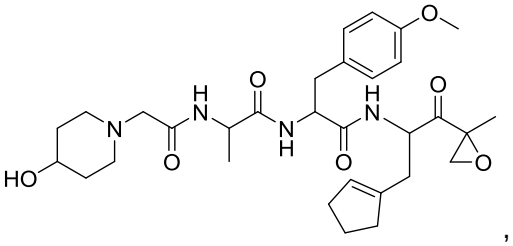
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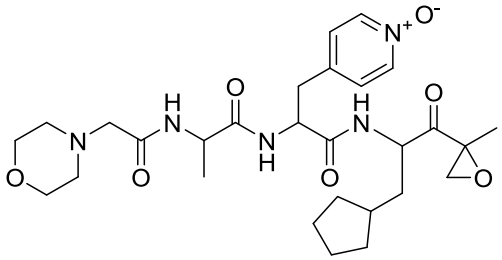
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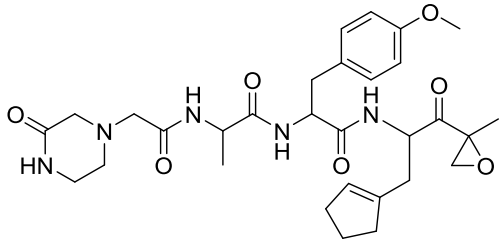
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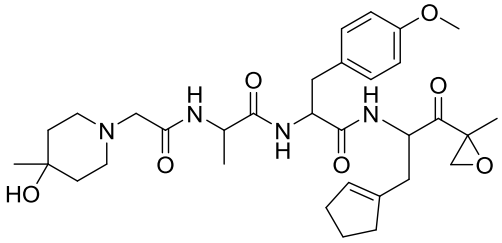
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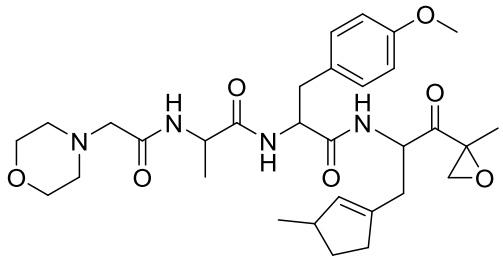
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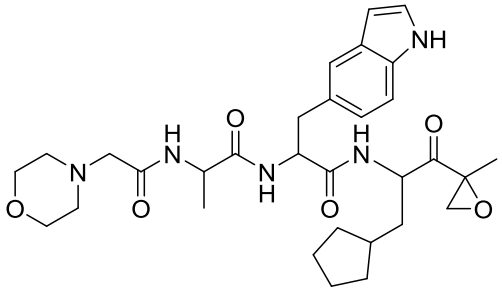
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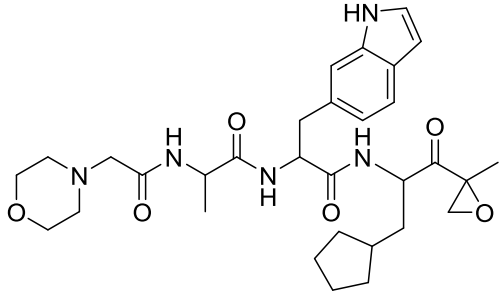
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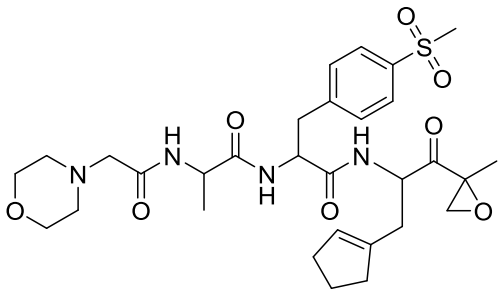
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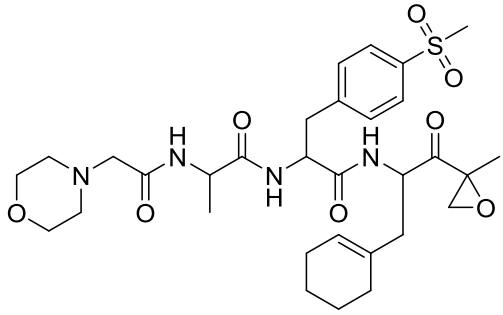
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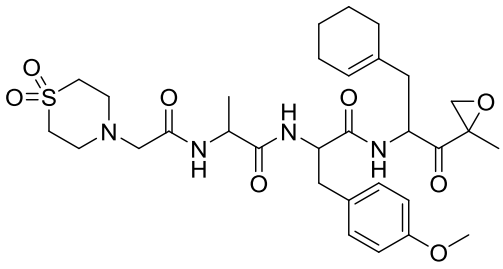
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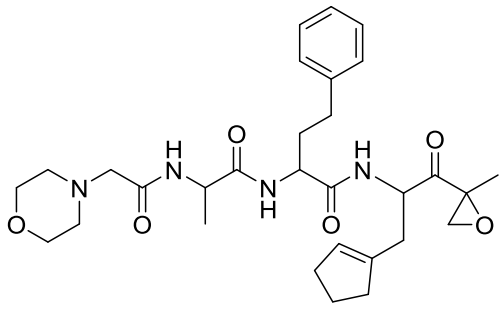
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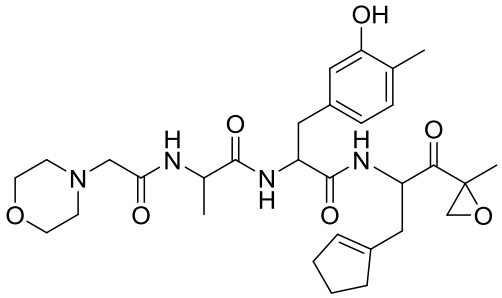
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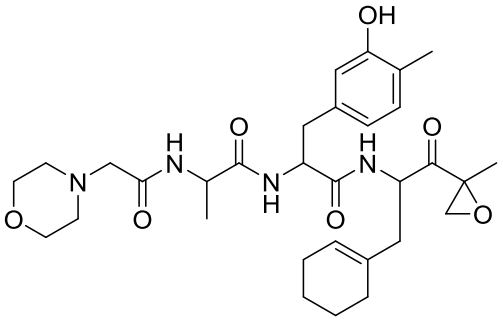
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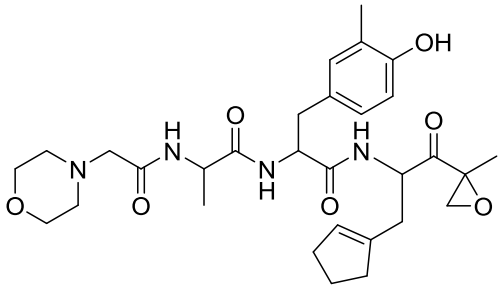
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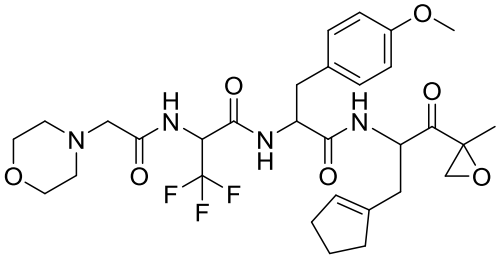
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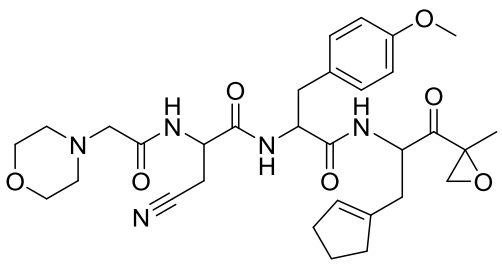
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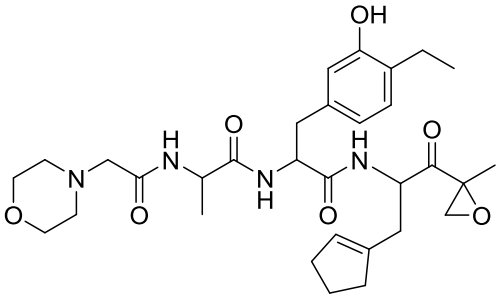
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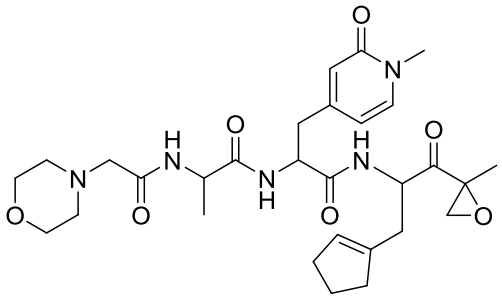
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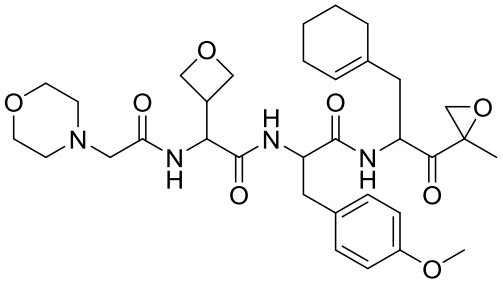
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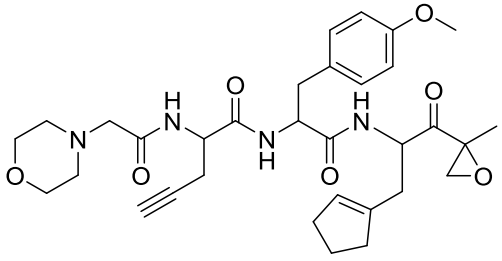
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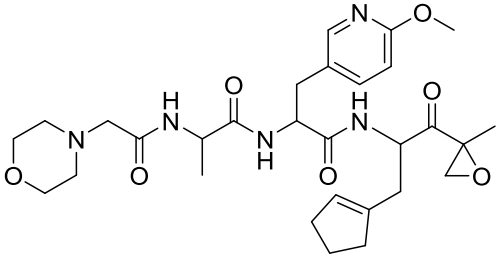
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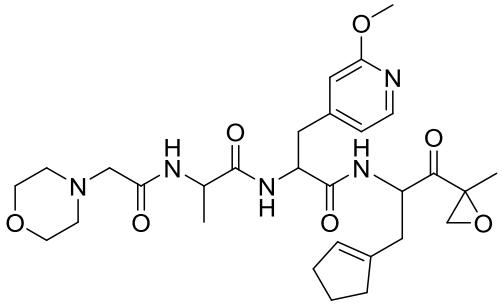
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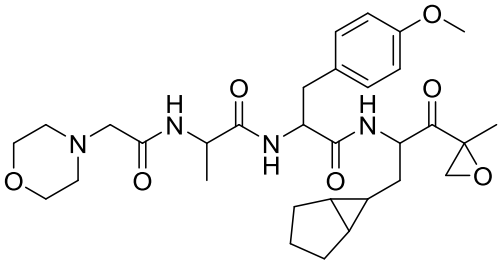
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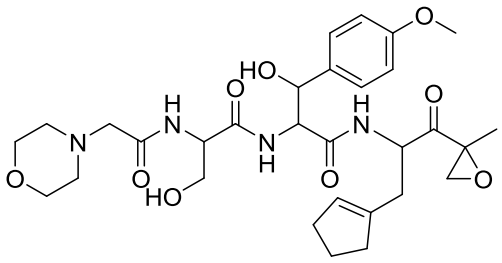
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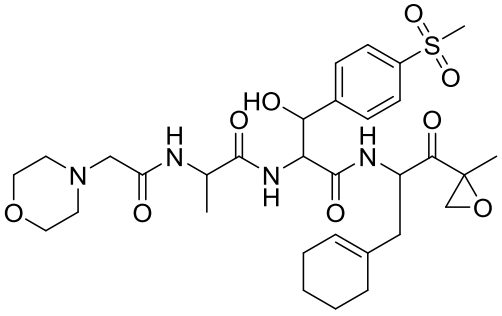
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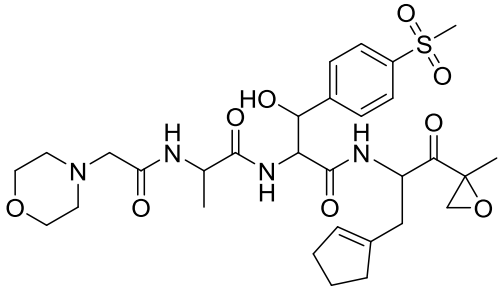
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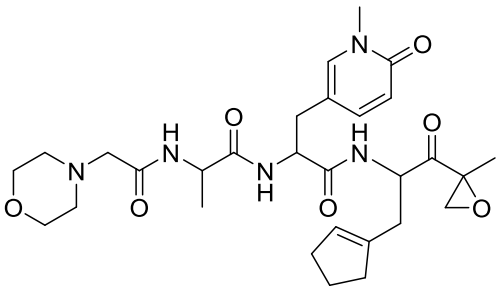
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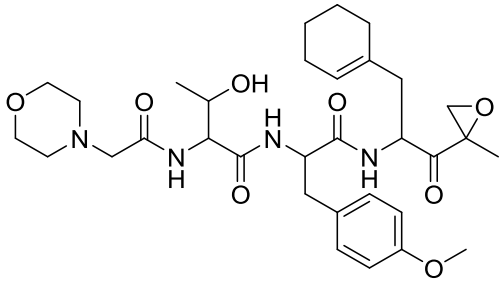
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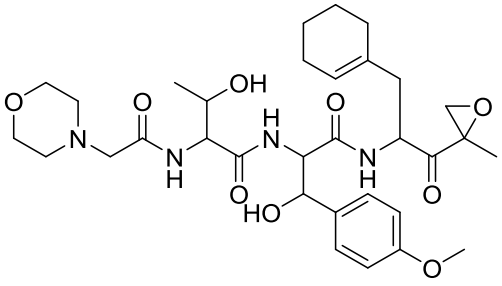
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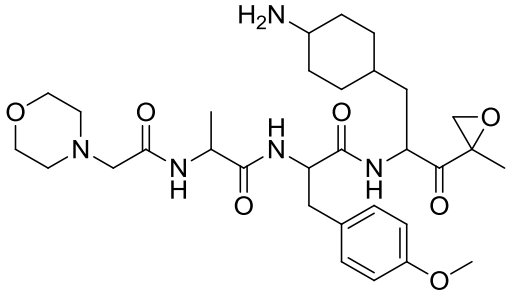
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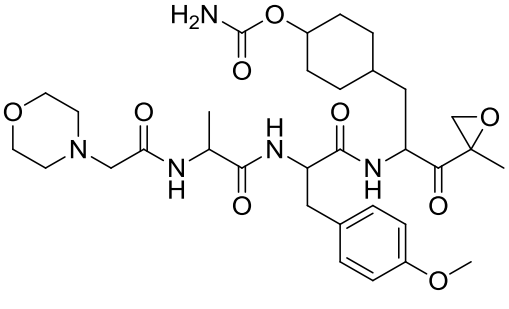
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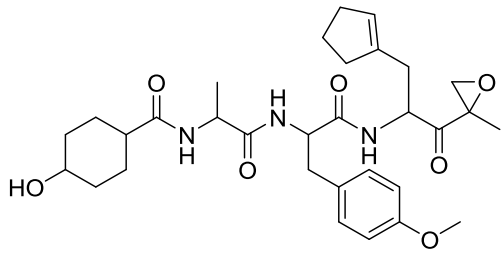
or a pharmaceutically acceptable salt thereof.

63. The compound of claim 62 having a structure selected from the group consisting of: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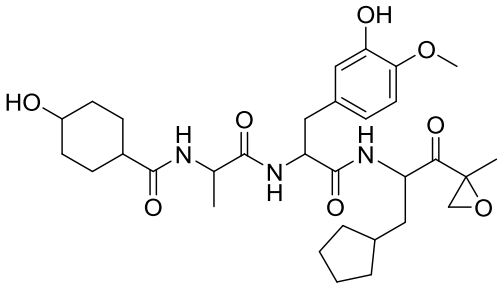
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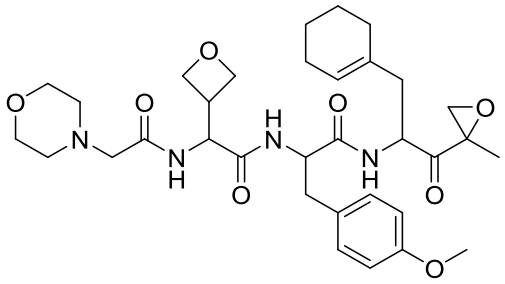
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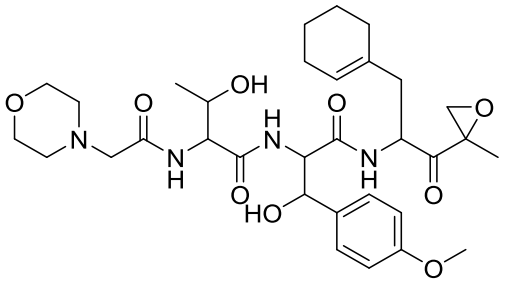
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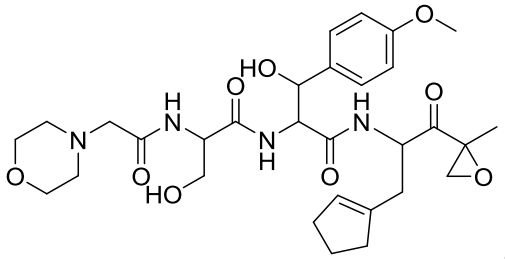
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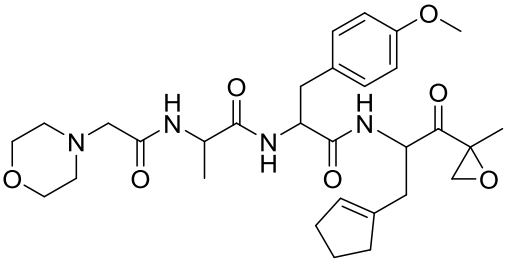
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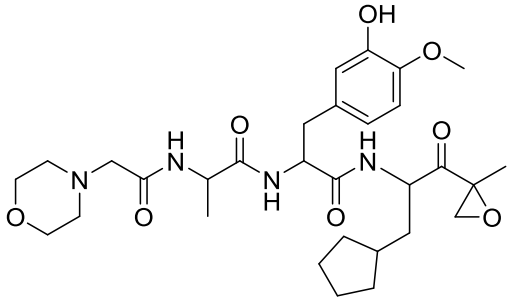
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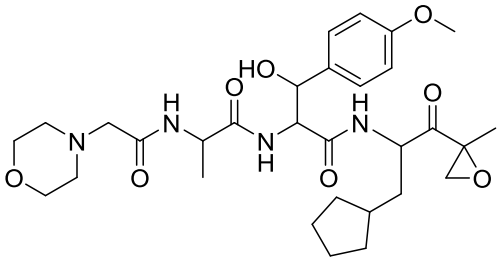
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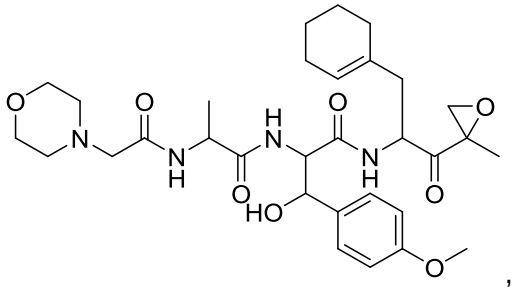
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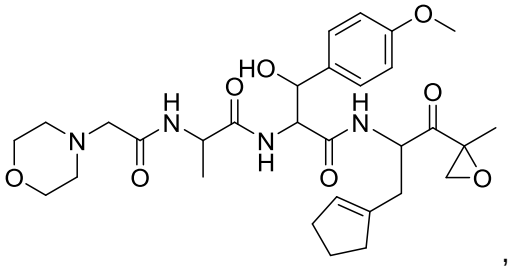
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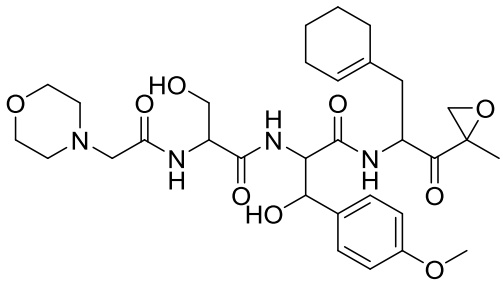
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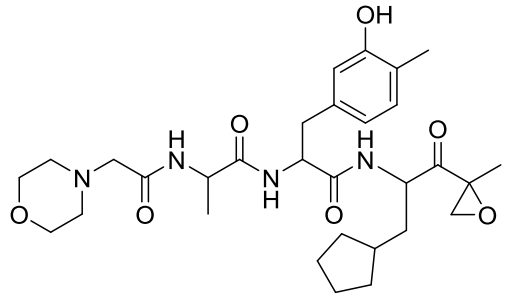
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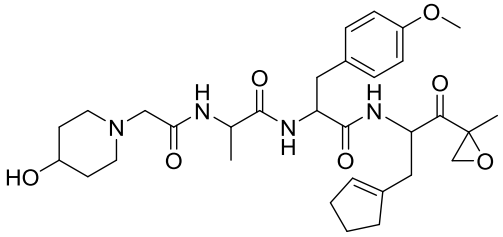
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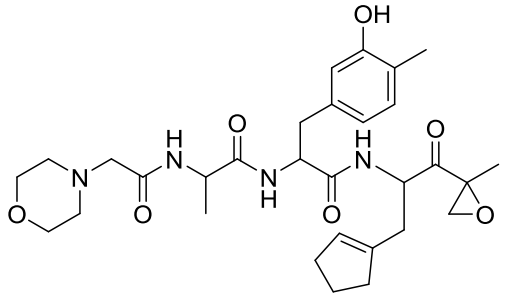
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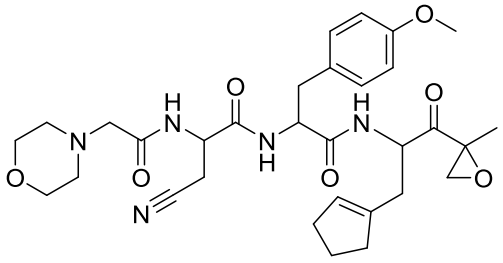
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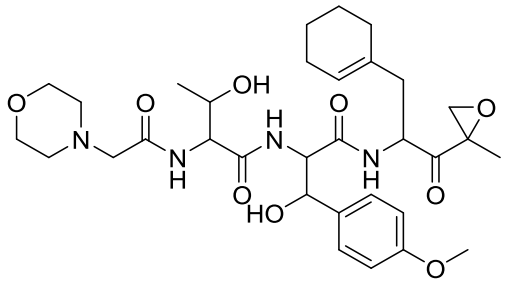
or a pharmaceutically acceptable salt thereof.

64. The compound of claim 62 having a structure selected from the group consisting of: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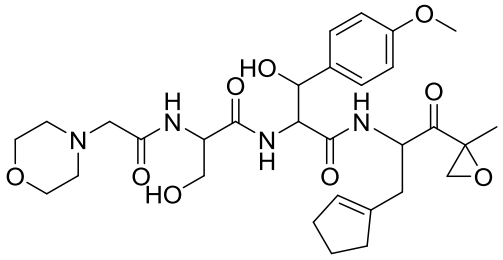
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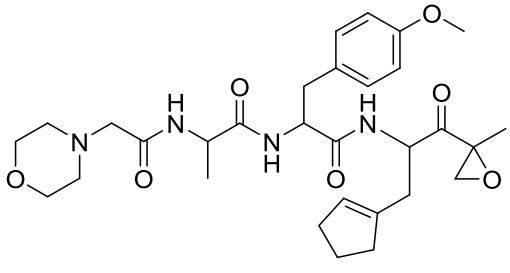
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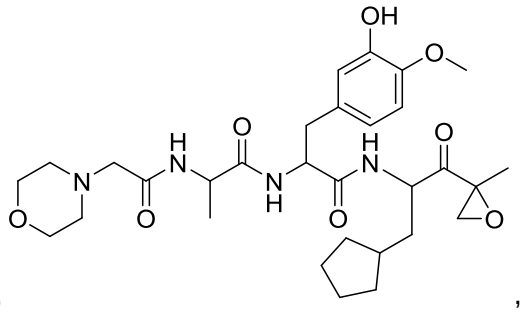
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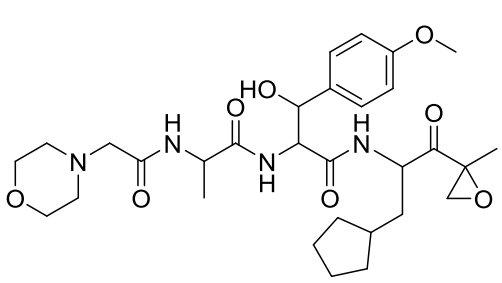
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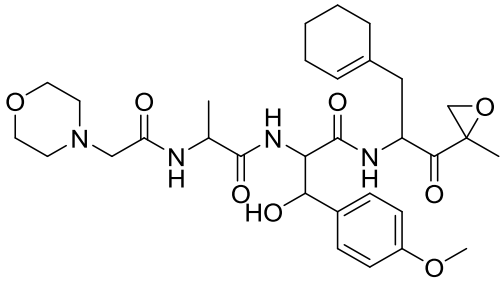
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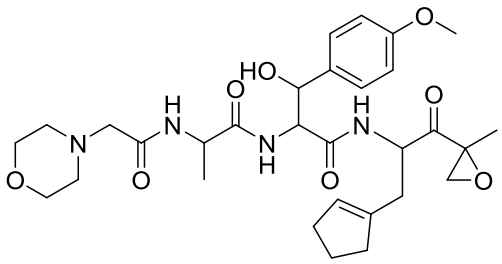
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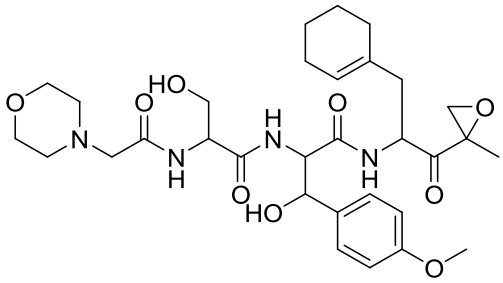
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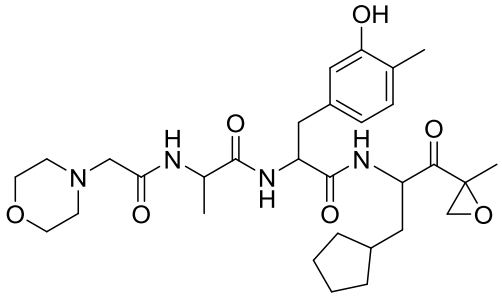
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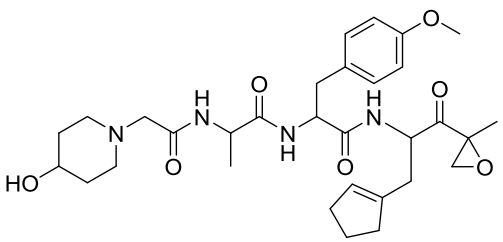
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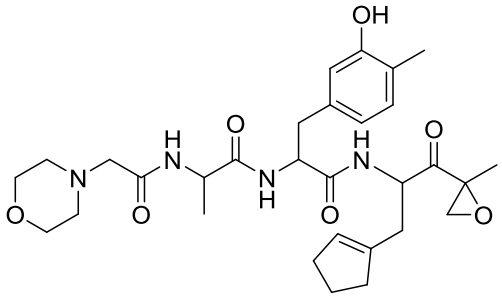
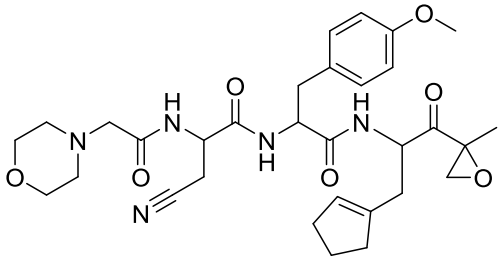
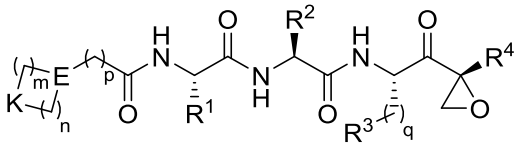


, and
or a pharmaceutically acceptable salt thereof.

65. The compound of any one of claims 1 to 64, wherein the compound has a stereochemical configuration :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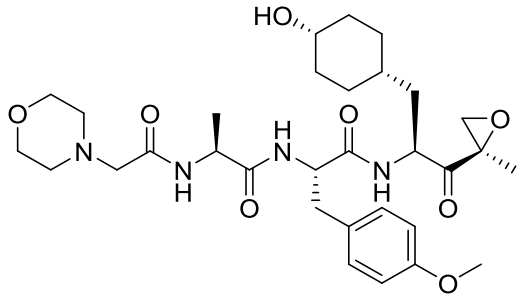
66. The compound of claim 1 having a structure selected from the group consisting of: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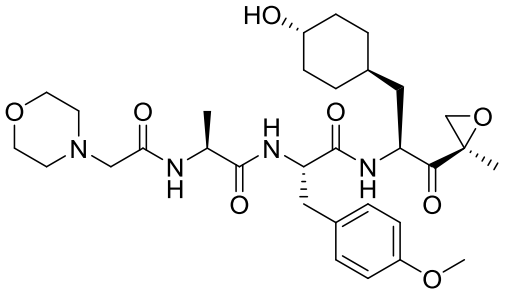
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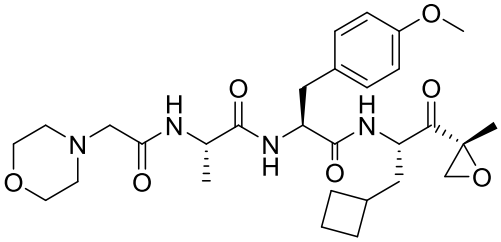
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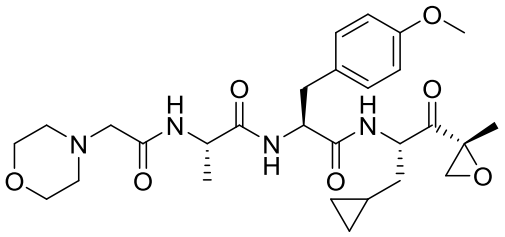
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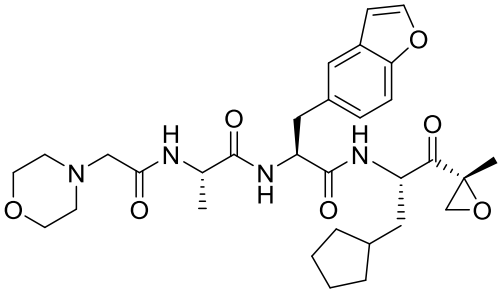
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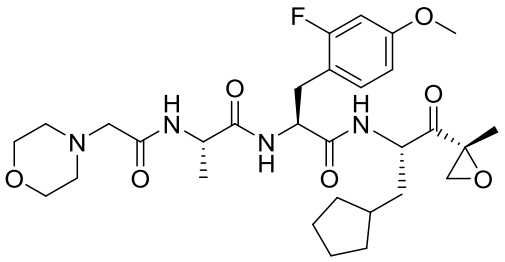
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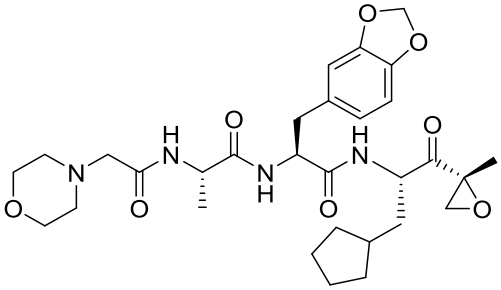
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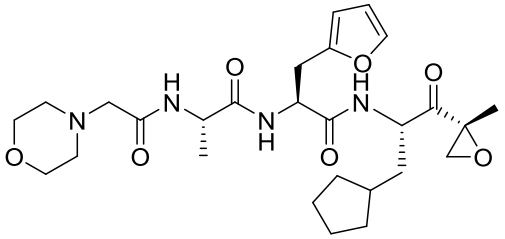
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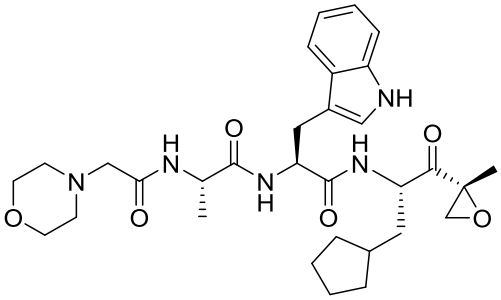
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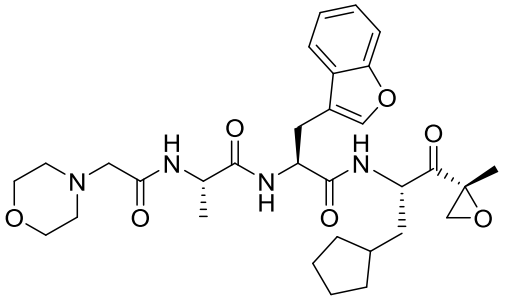
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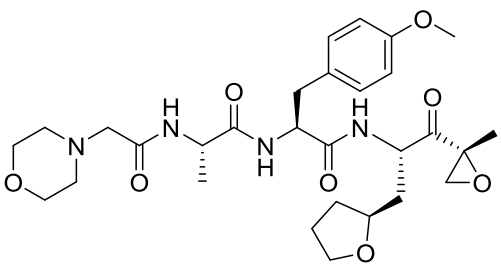
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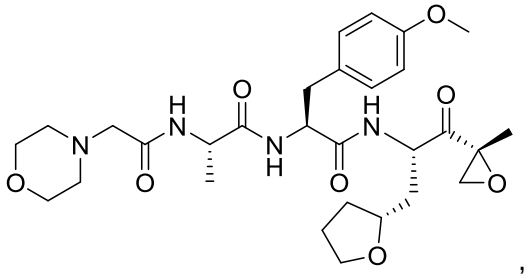
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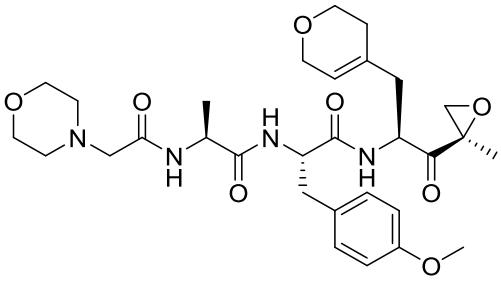
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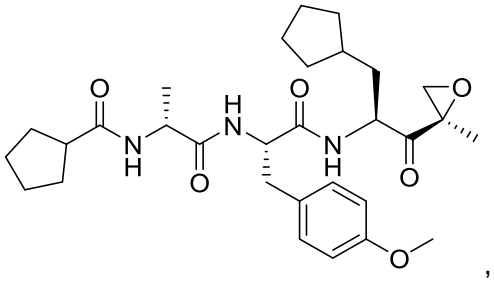
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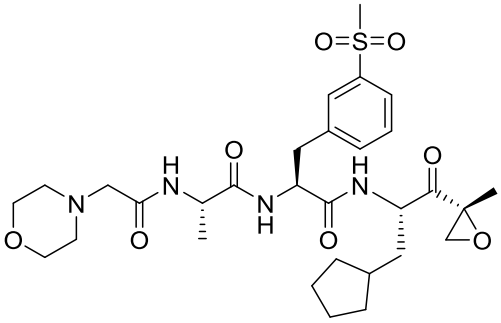
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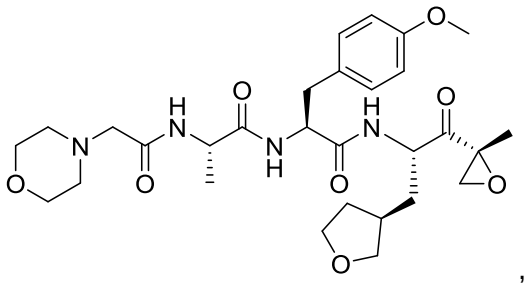
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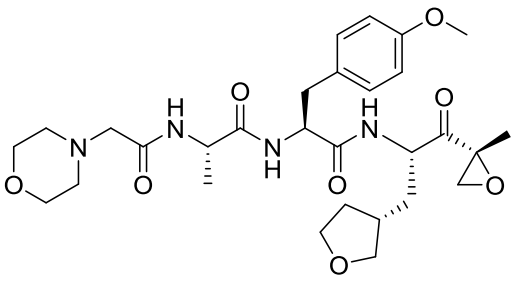
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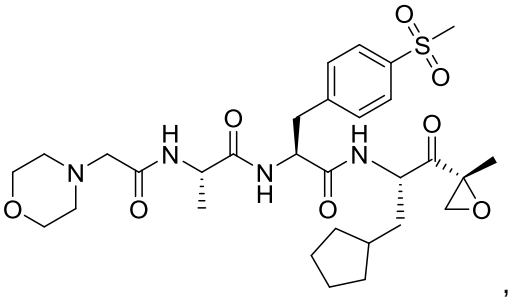
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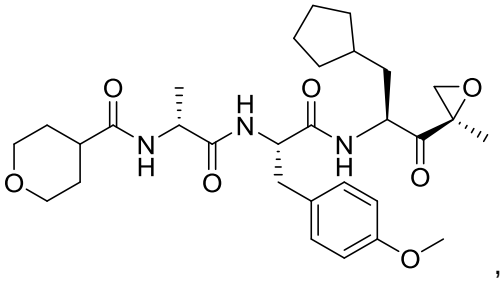
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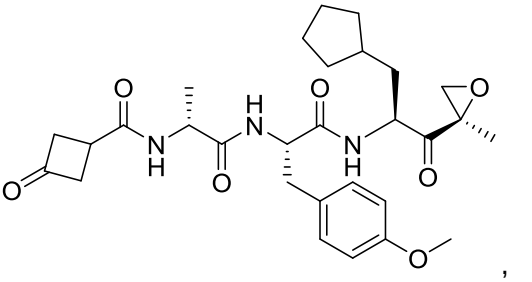

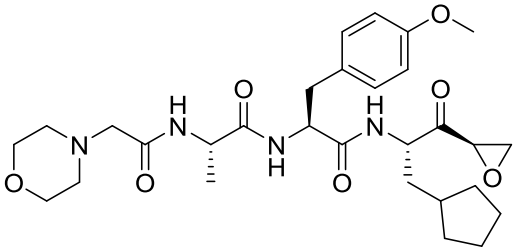
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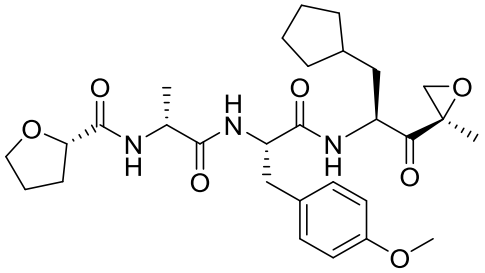
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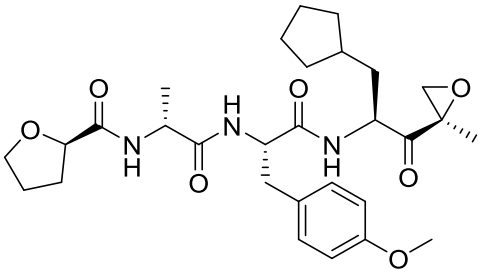
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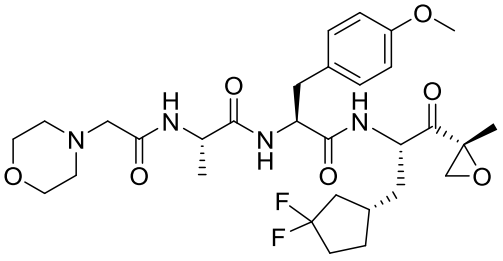
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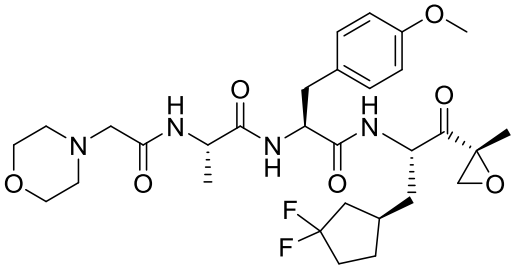
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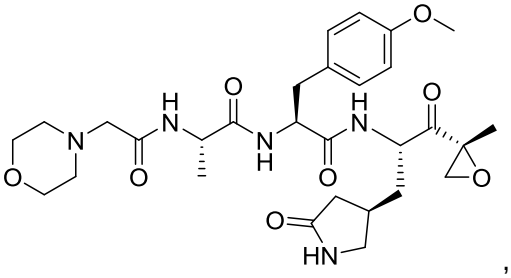
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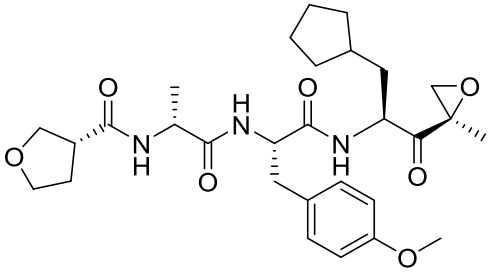
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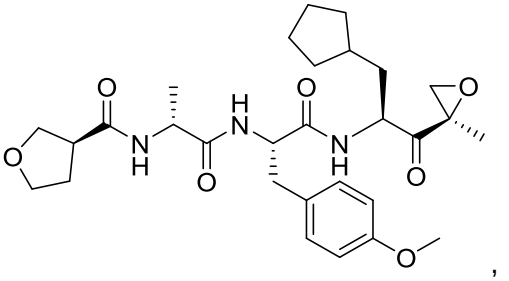
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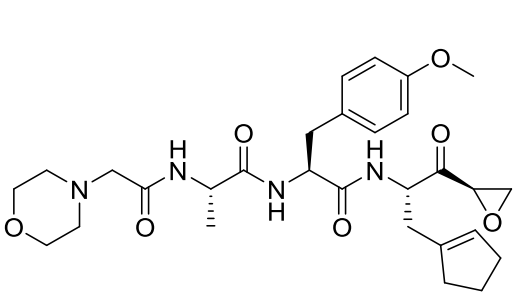
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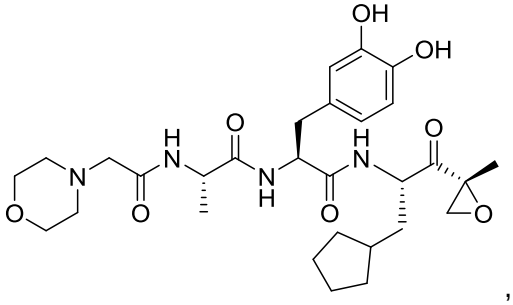
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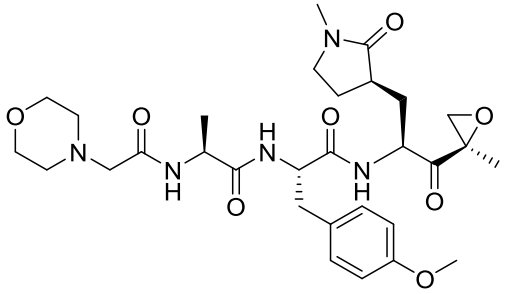
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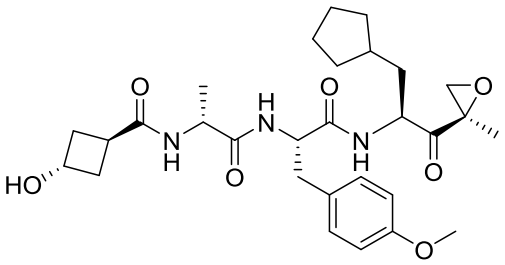
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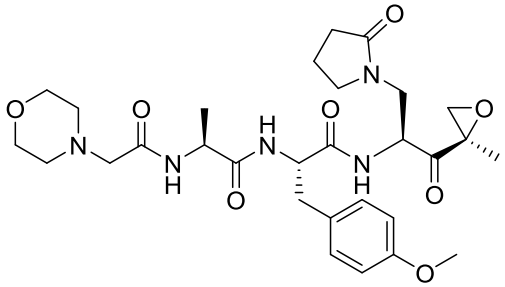
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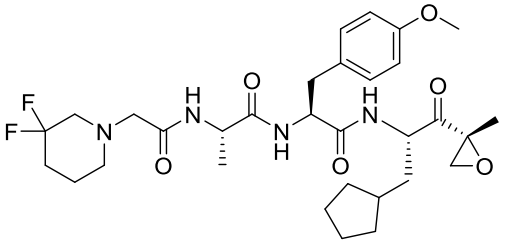
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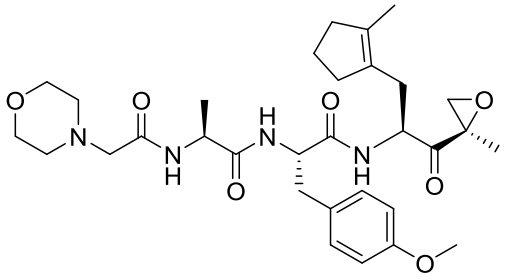
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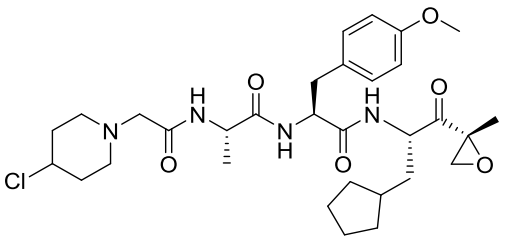
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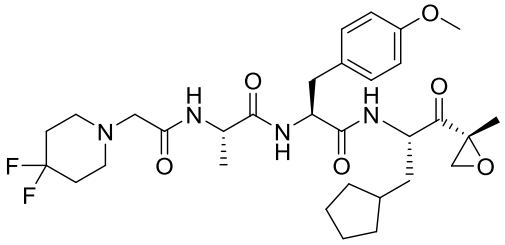
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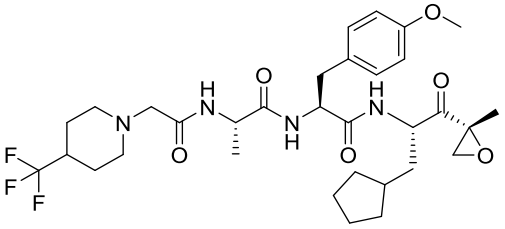
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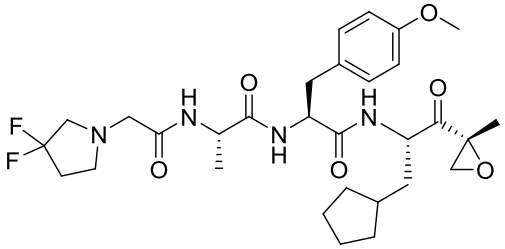
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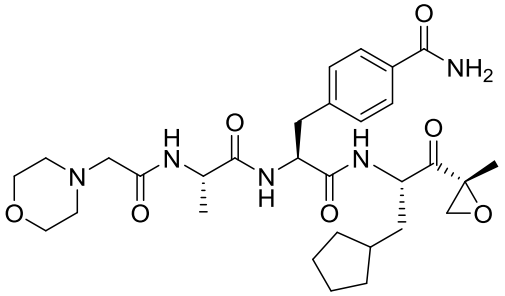
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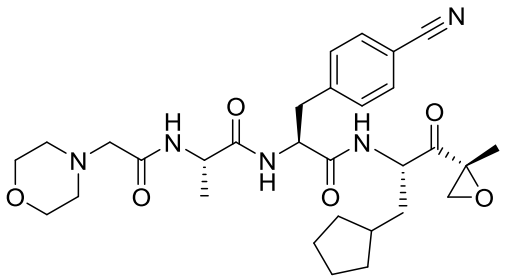
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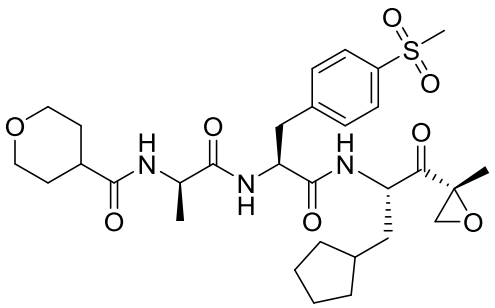
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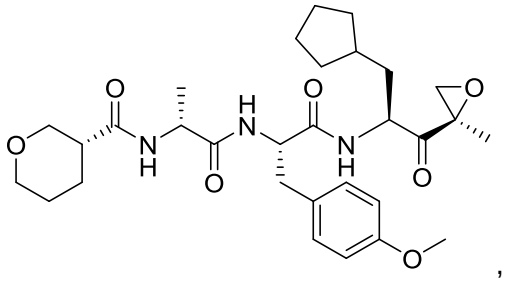
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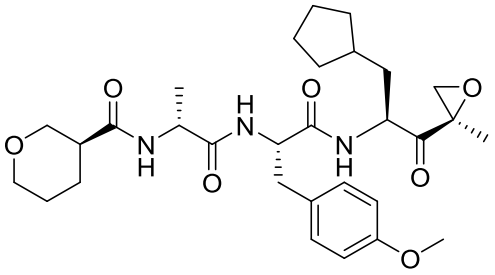
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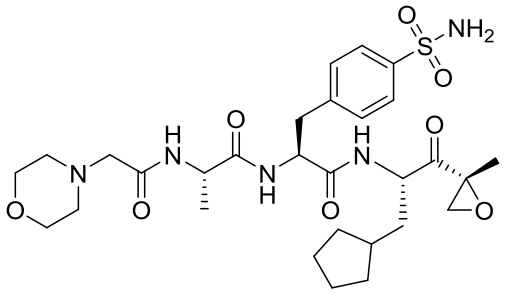
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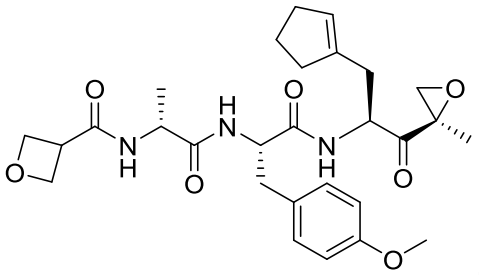
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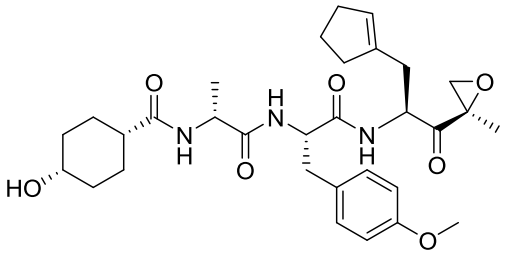
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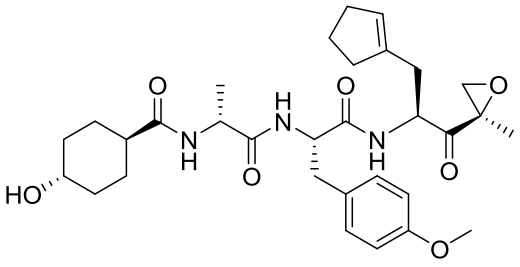
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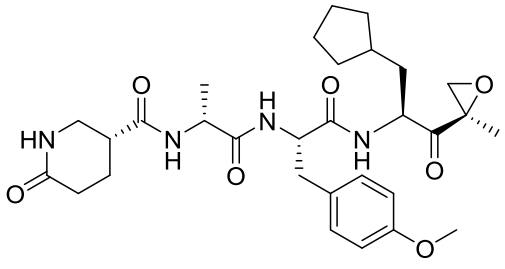
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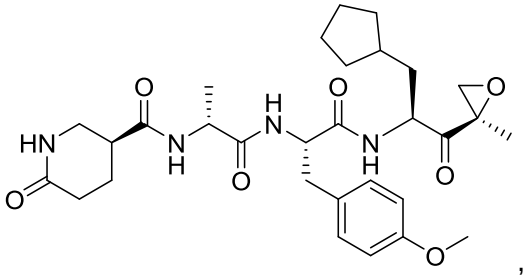
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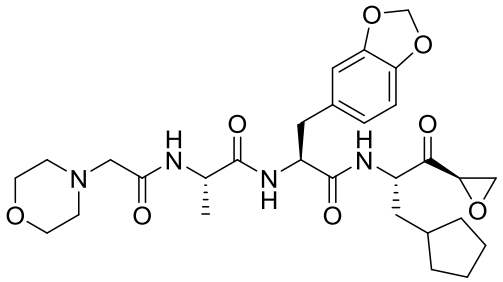
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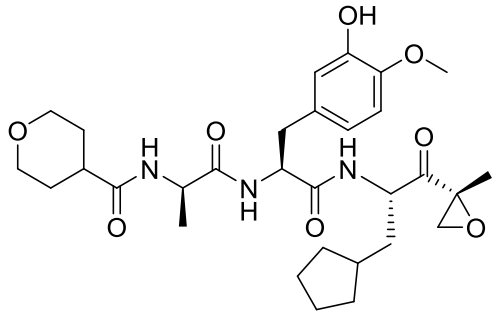
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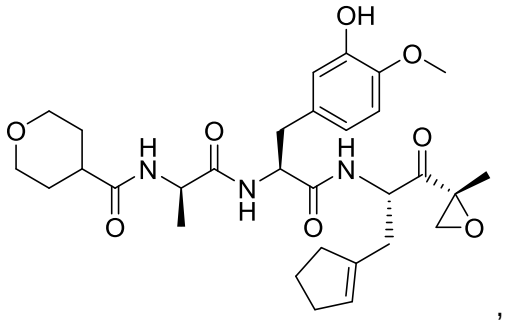
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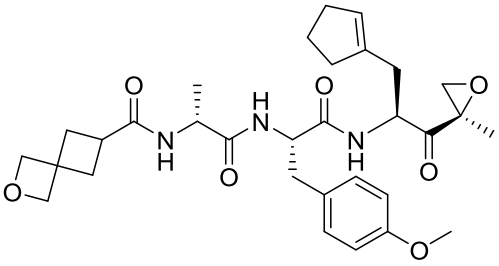
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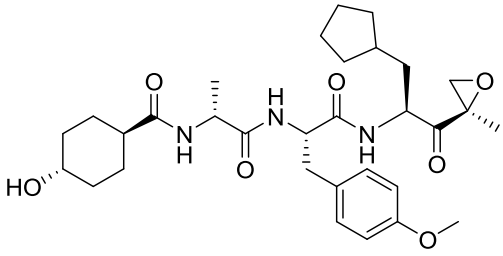
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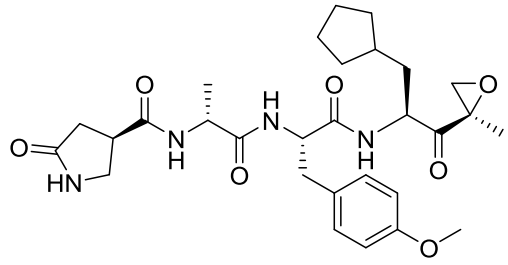
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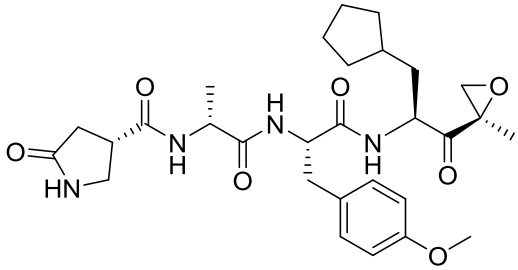
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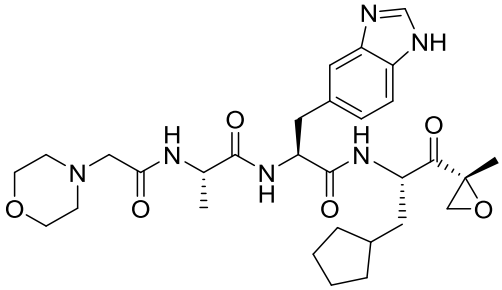
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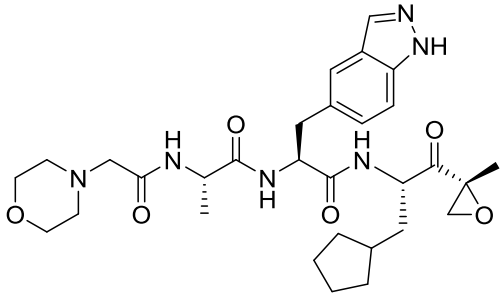
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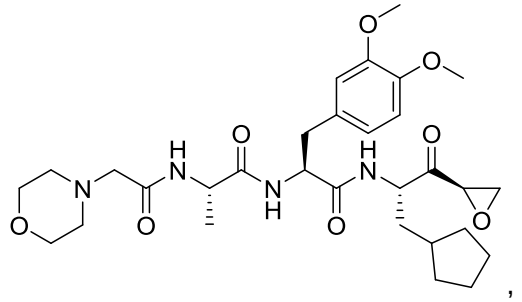
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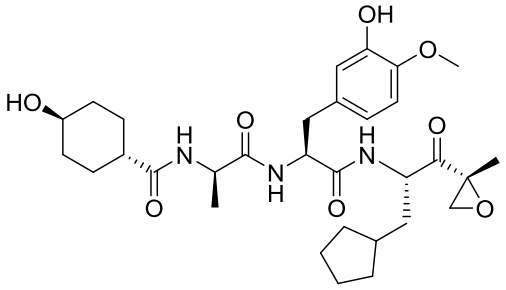
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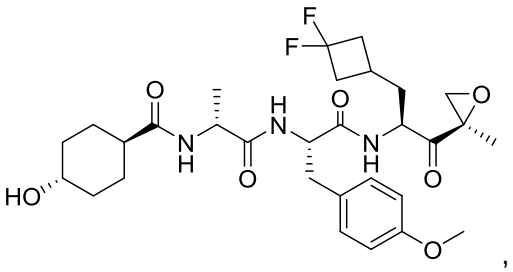
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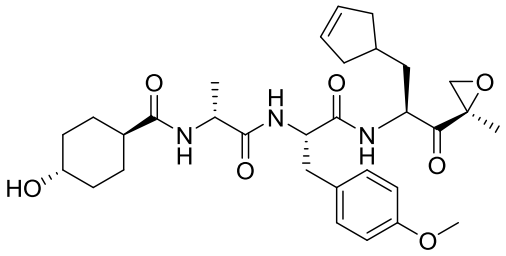
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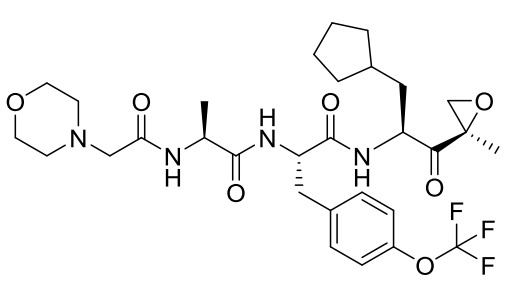
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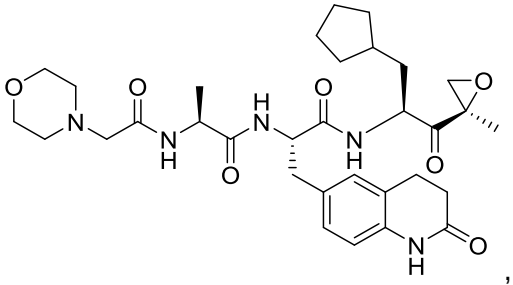
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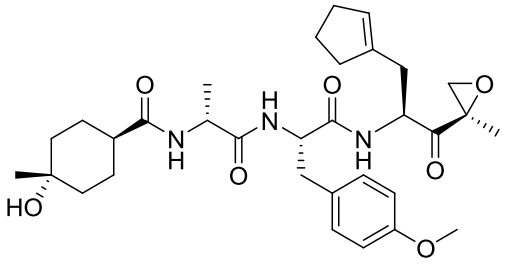
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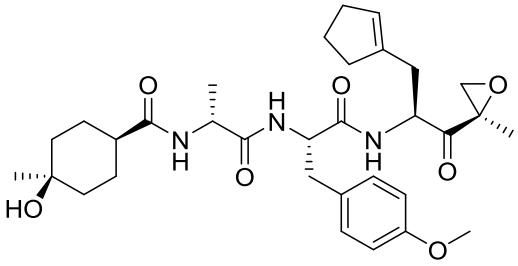
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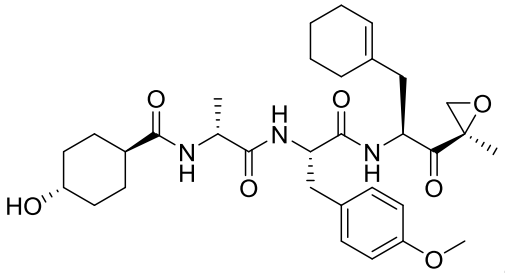
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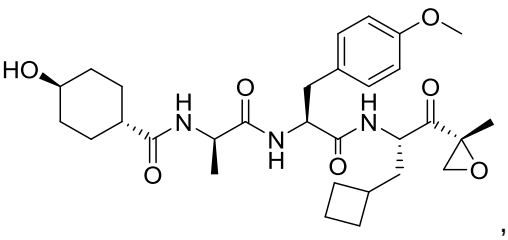
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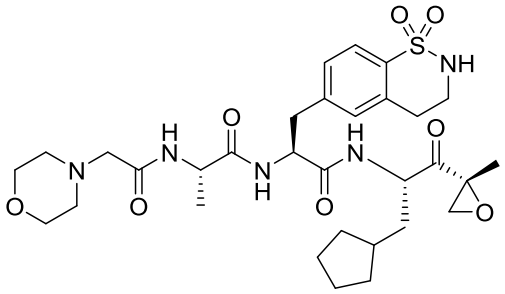
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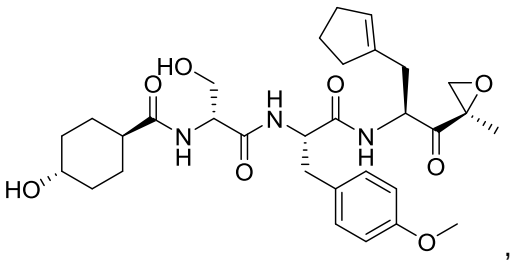
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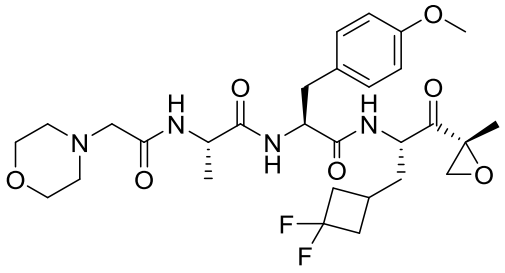
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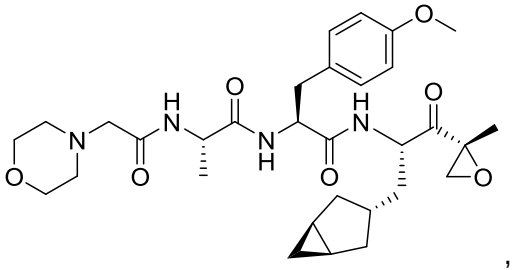
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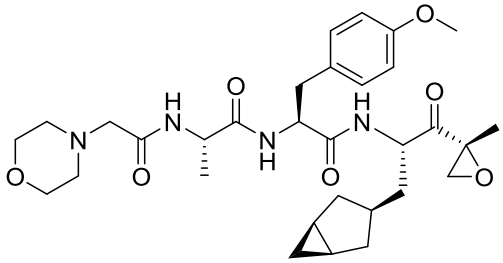
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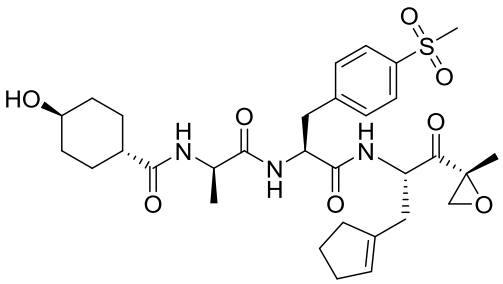
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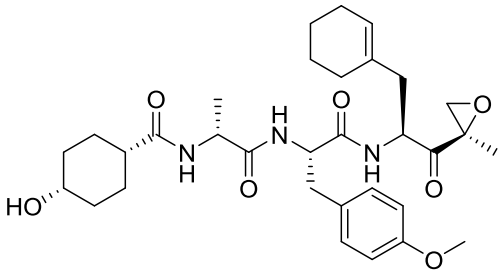
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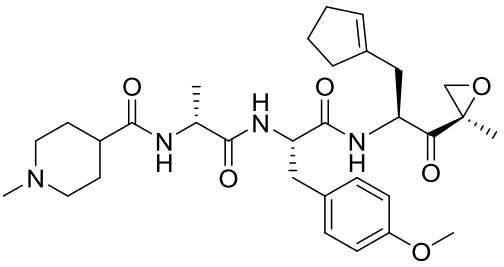
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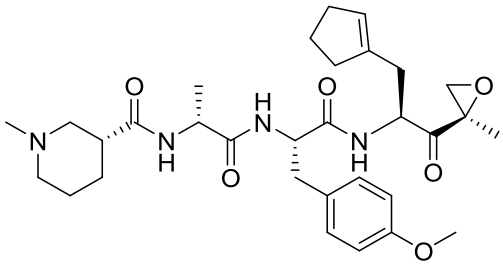
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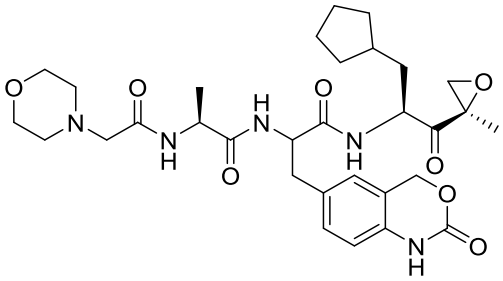
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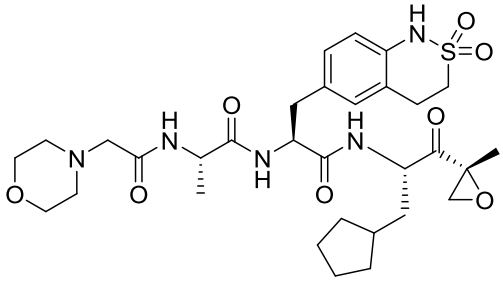
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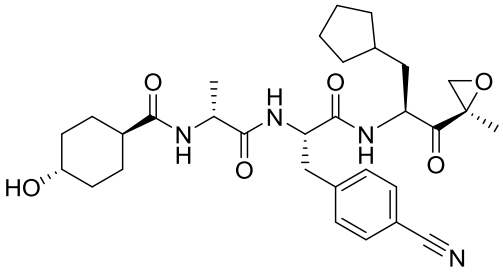
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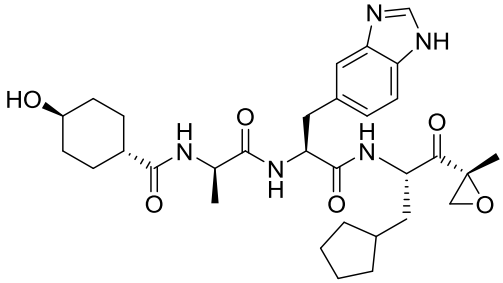
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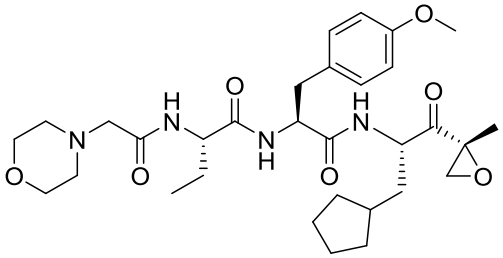

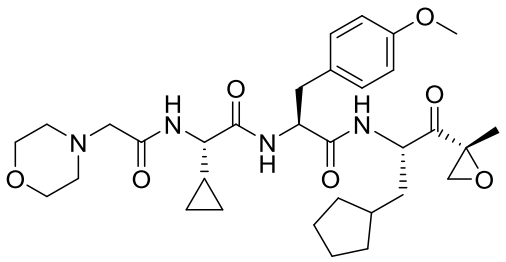
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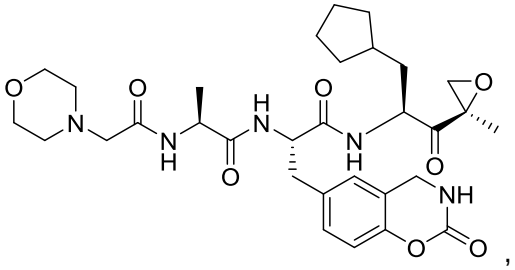
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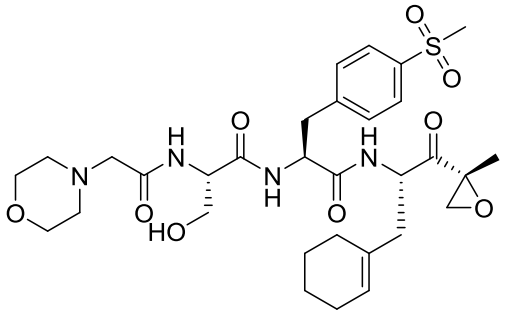
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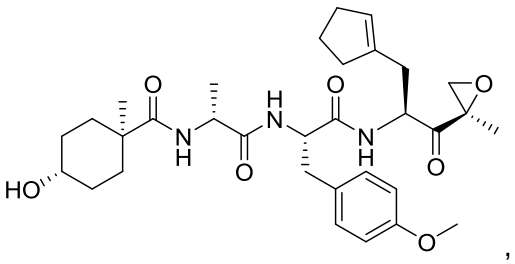
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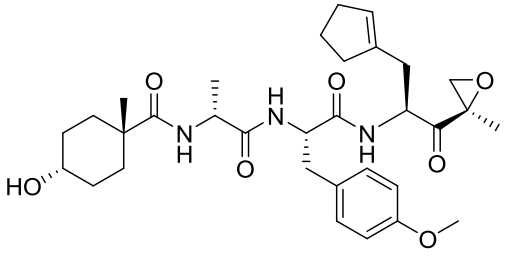
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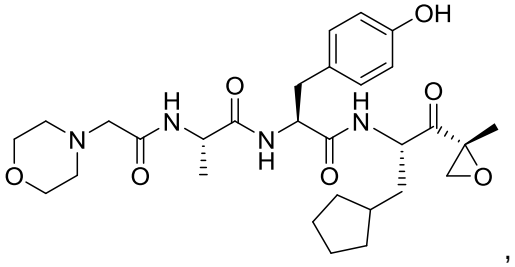
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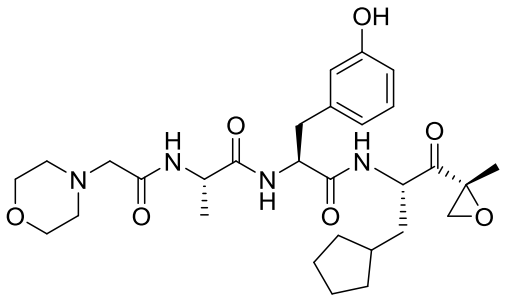
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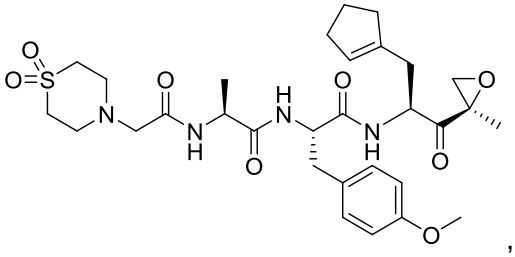
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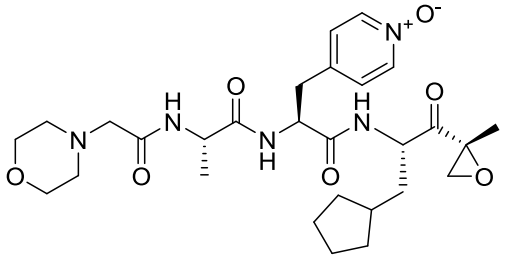
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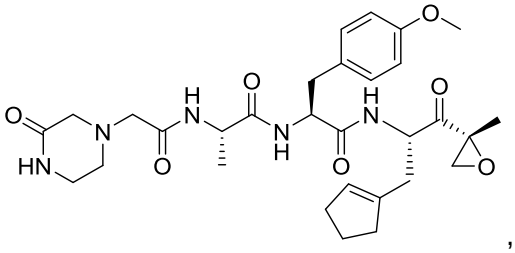
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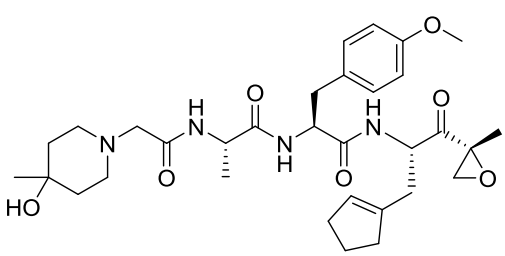
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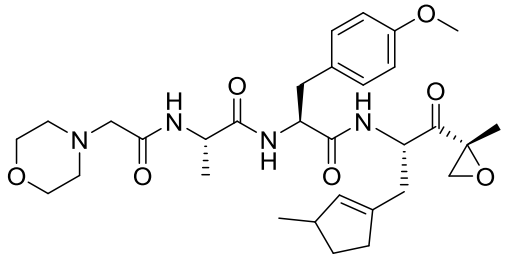
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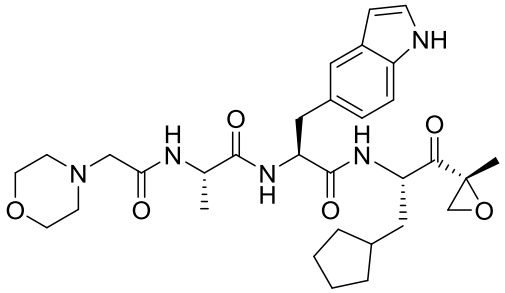
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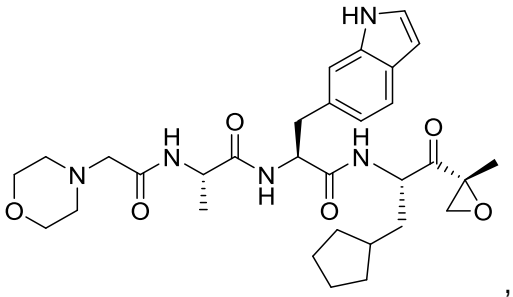
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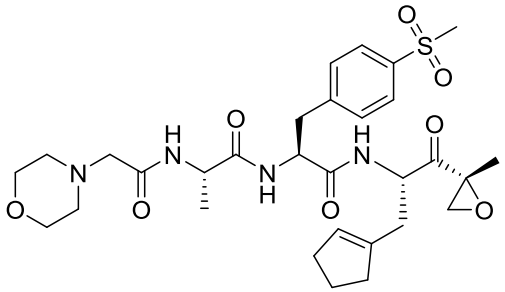
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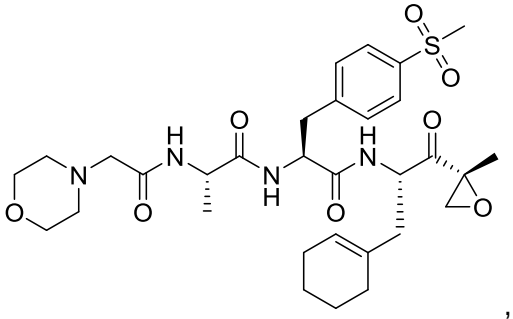
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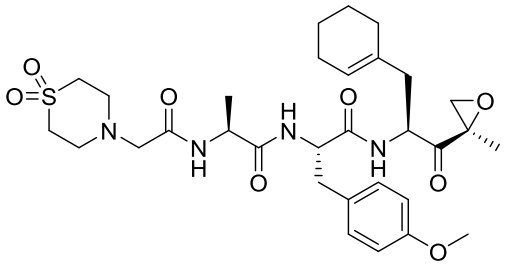
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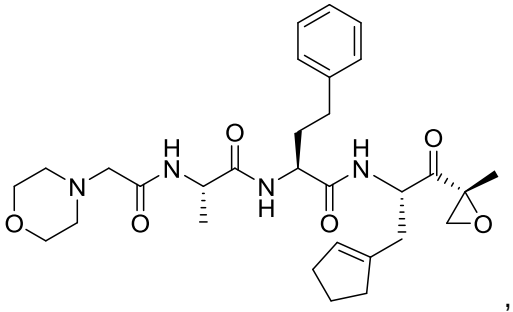
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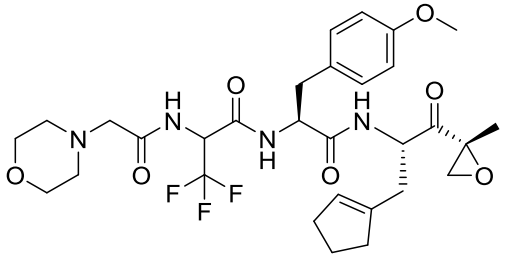
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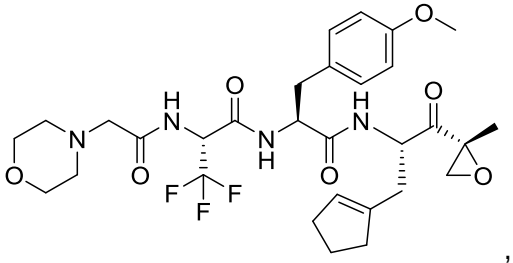
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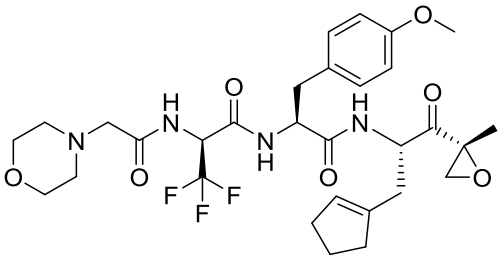
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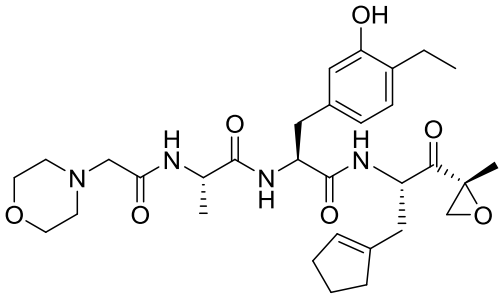
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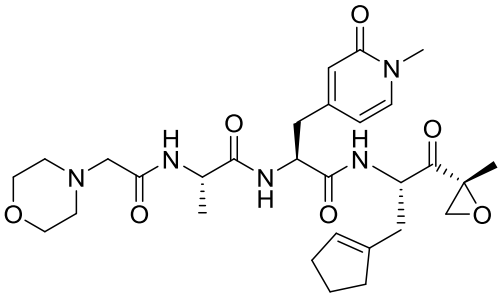
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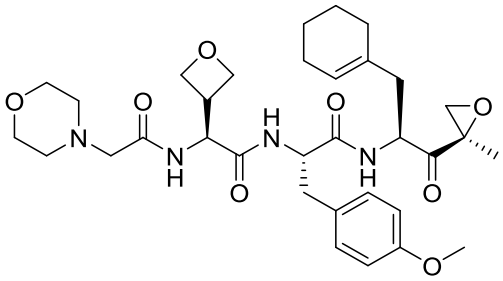
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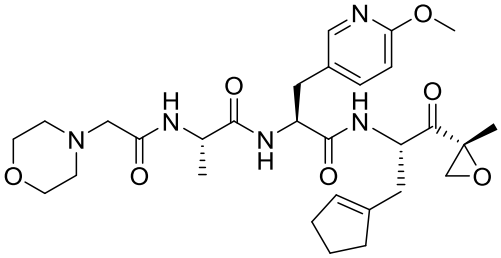
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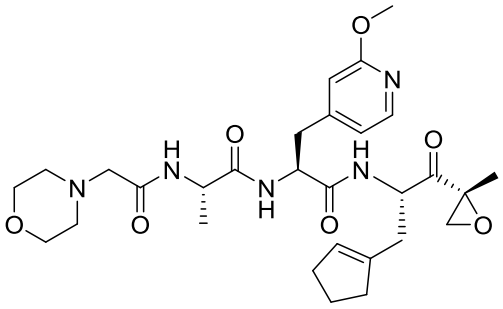
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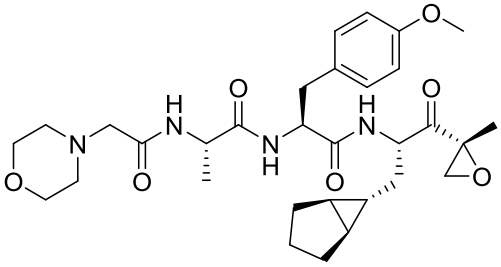
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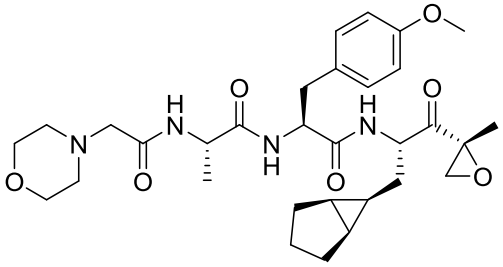
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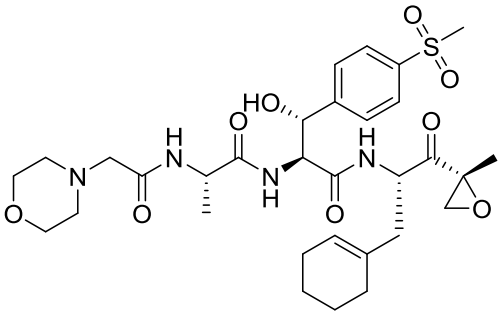
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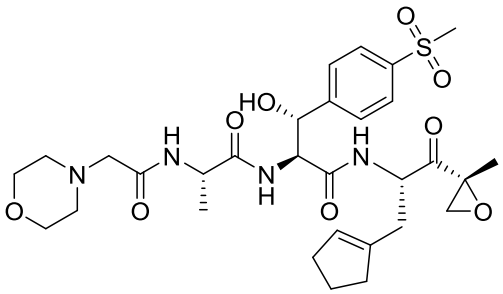
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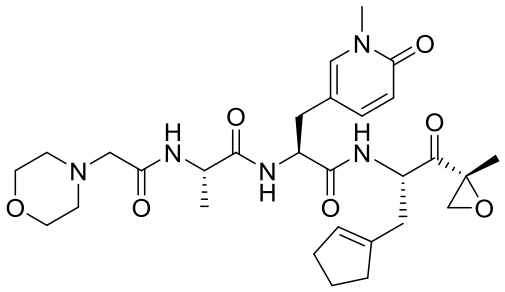
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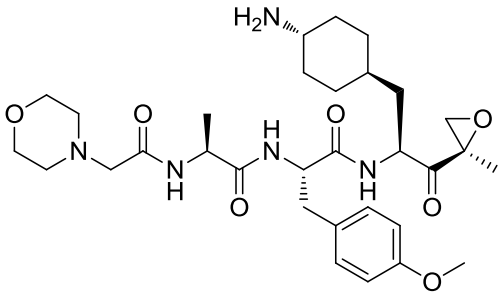
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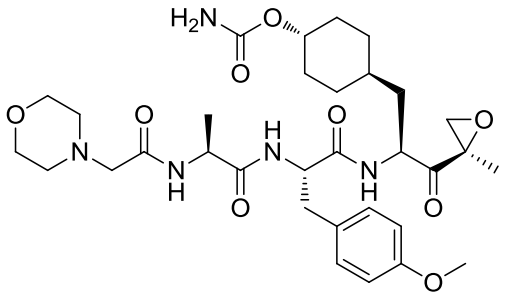
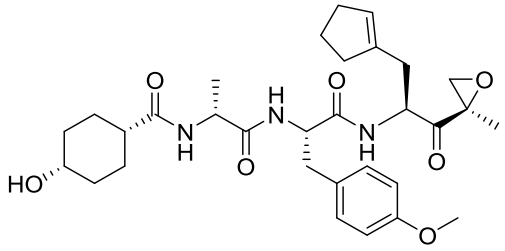

, or a pharmaceutically acceptable salt thereof.

67. The compound of claim 66 having a structure selected from the group consisting of:

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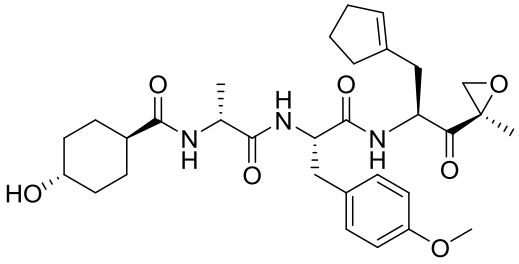
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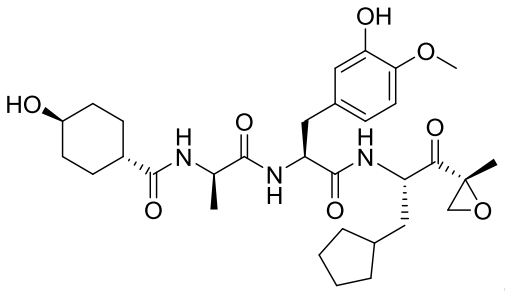
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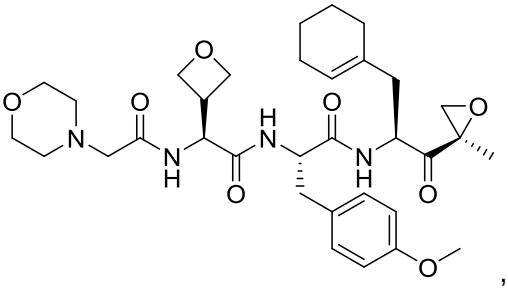
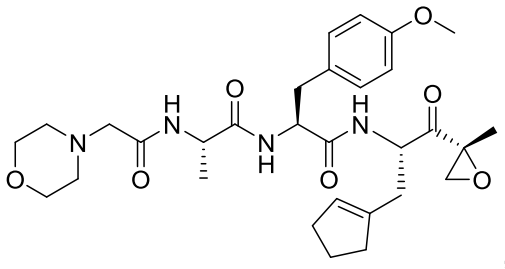

, or a pharmaceutically acceptable salt thereof.

68. A compound having a structure selected from the group consisting of:

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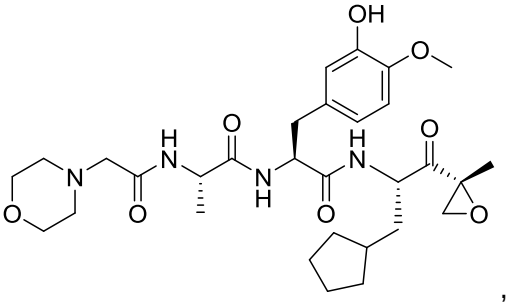
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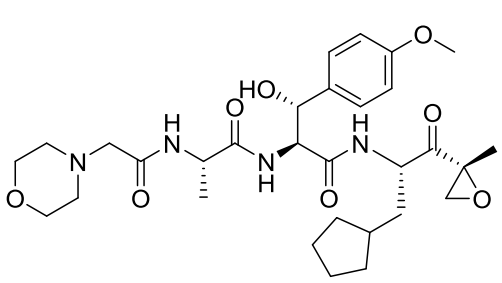
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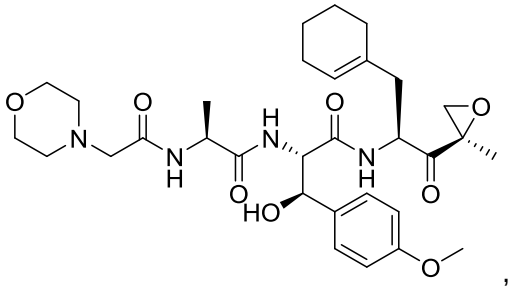
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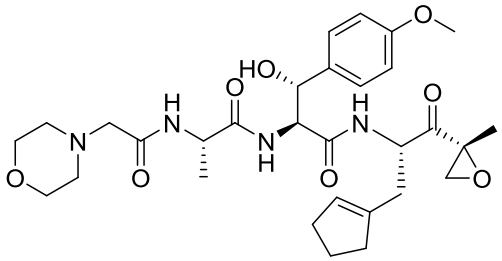
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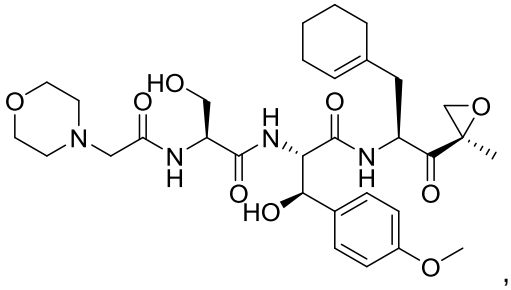
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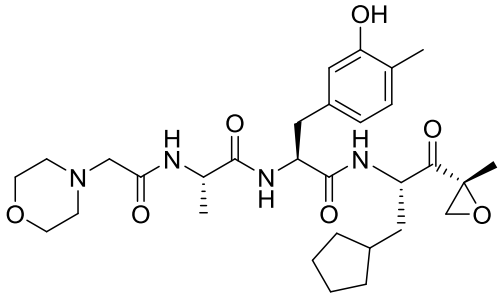
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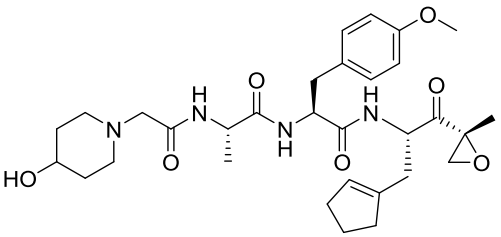
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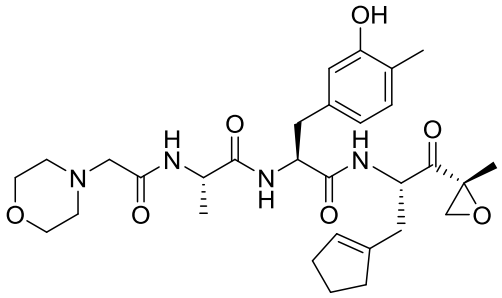
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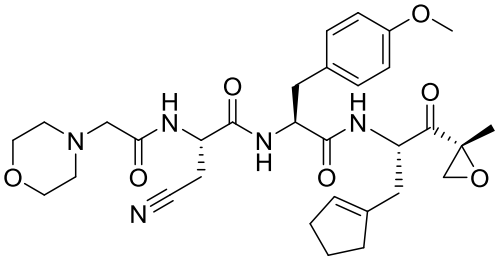
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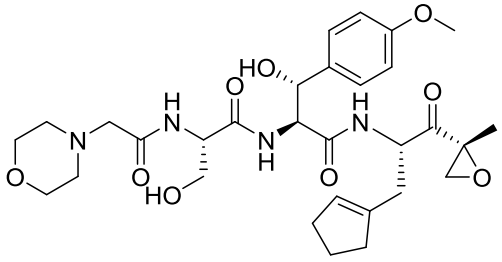
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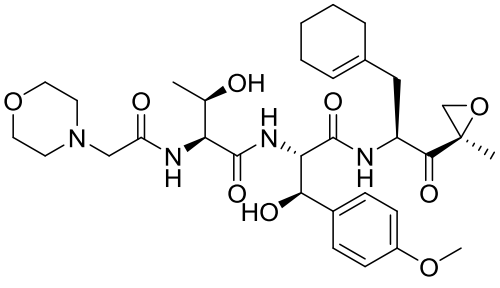

, or a pharmaceutically acceptable salt thereof.

69. A pharmaceutical composition comprising the compound of any one of claims 1 to 79, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

70. A method of inhibiting the immunoproteasome of a cell comprising contacting the cell *in vitro* with a compound of any one of claims 1 to 68 or the composition of claim 69 in an effective amount to inhibit the immunoproteasome in the cell.

71. The method of claim 70, wherein the compound inhibits β5i (LMP7).

72. The method of claim 71, wherein the compound further inhibits one or both of LMP2 and MECL-1.

73. A therapeutically effective amount of the compound of any one of claims 1 to 68 or the composition of claim 69 for use in the treatment of an immune-related disease.

74. The use of a therapeutically effective amount of the compound of any one of claims 1 to 68 or the composition of claim 69 in the manufacture of a medicament for the treatment of an immune-related disease.

75. A therapeutically effective amount of the compound of any one of claims 1 to 68 or the composition of claim 69 for use in the treatment of inflammation, wherein the compound or the composition is to be administered to a subject in need thereof.

76. The use of a therapeutically effective amount of the compound of any one of claims 1 to 68 or the composition of claim 69 in the manufacture of a medicament for the treatment of inflammation.

77. A therapeutically effective amount of the compound of any one of claims 1 to 68 or the composition of claim 69 for use in the treatment of infection, wherein the compound or the composition is to be administered to a subject in need thereof.

78. The use of a therapeutically effective amount of the compound of any one of claims 1 to 68 or the composition of claim 69 in the manufacture of a medicament for the treatment of infection.

79. A therapeutically effective amount of the compound of any one of claims 1 to 68 or the composition of claim 69 for use in the treatment of a neurodegenerative disease associated with abberant immunoproteasome activity.

80. The use of a therapeutically effective amount of the compound of any one of claims 1 to 68 or the composition of claim 69 in the manufacture of a medicament for the treatment of neurodegenerative disease.

81. The use of a compound of any one of claims 1 to 68 or the composition of claim 69 in the manufacture of a medicament able to inhibit the immunoproteasome of a cell for the treatment of an autoimmune disease wherein the autoimmune disease is psoriasis, dermatitis, systemic scleroderma, sclerosis, Crohn's disease, ulcerative colitis; respiratory distress syndrome, meningitis; encephalitis; uveitis; colitis; glomerulonephritis; eczema, asthma, chronic inflammation; atherosclerosis; leukocyte adhesion deficiency; rheumatoid arthritis; systemic lupus erythematosus (SLE); diabetes mellitus; multiple sclerosis; Reynaud's syndrome; autoimmune thyroiditis; allergic encephalomyelitis; Sjorgen's syndrome; juvenile onset diabetes; tuberculosis, sarcoidosis, polymyositis, granulomatosis and vasculitis; pernicious anemia (Addison's disease); diseases involving leukocyte diapedesis; central nervous system (CNS)

inflammatory disorder; multiple organ injury syndrome; hemolytic anemia; myasthenia gravis; antigen-antibody complex mediated diseases; anti-glomerular basement membrane disease; antiphospholipid syndrome; allergic neuritis; Graves' disease; Lambert-Eaton myasthenic syndrome; pemphigoid bullous; pemphigus; autoimmune polyendocrinopathies; Reiter's disease; stiff-man syndrome; Beheet disease; giant cell arteritis; immune complex nephritis; IgA nephropathy; IgM polyneuropathies; immune thrombocytopenic purpura (ITP) or autoimmune thrombocytopenia.

82. The use of claim 81, wherein the compound inhibits β5i (LMP7).

83. The use of claim 82, wherein the compound further inhibits one or both of LMP2 and MECL-1.

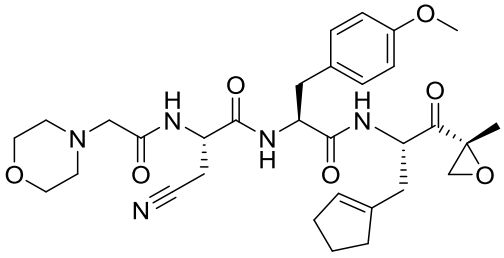
84. The use of any one of claims 81 to 83, wherein the composition is formulated for oral administration, parenteral administration, administration via injection, administration via inhalation, transdermal administration, or transmucosal administration to a subject.

85. The use of claim 84, wherein the subject is a mammal.

86. The use of claim 85, wherein the subject is human.

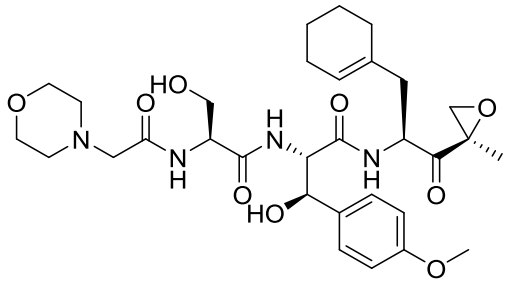
87. A compound of any one of claims 1 to 68 or the composition of claim 69 for use in the treatment of an autoimmune disease inhibiting the immunoproteasome in a cell.

88. The compound of claim 1 having a structure of



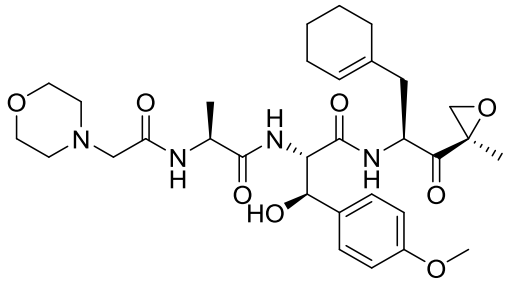
or a pharmaceutically acceptable salt thereof.

89. The compound of claim 1 having a structure of



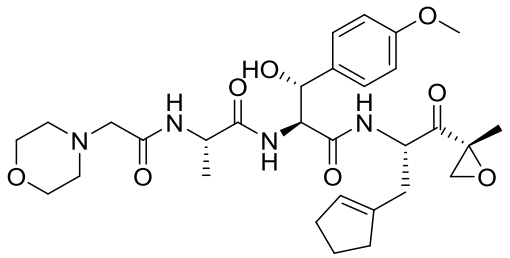
or a pharmaceutically acceptable salt thereof.

90. The compound of claim 1 having a structure of



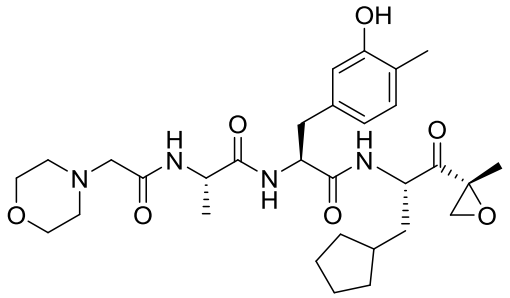
or a pharmaceutically acceptable salt thereof.

91. The compound of claim 1 having a structure of



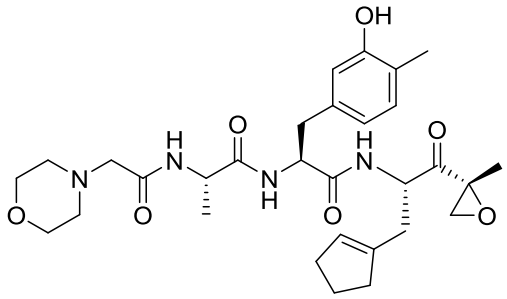
or a pharmaceutically acceptable salt thereof.

92. The compound of claim 1 having a structure of



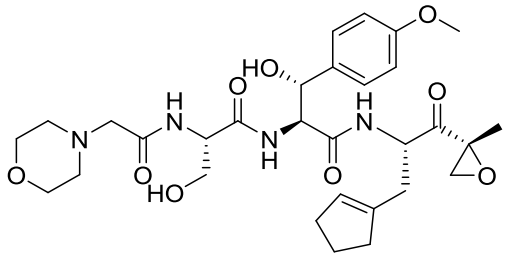
or a pharmaceutically acceptable salt thereof.

93. The compound of claim 1 having a structure of



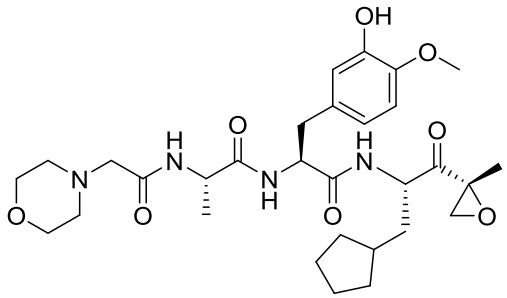
or a pharmaceutically acceptable salt thereof.

94. The compound of claim 1 having a structure of



or a pharmaceutically acceptable salt thereof.

95. The compound of claim 1 having a structure of



or a pharmaceutically acceptable salt thereof.