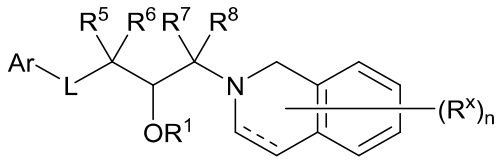
Claims

1. A compound of Formula (**I**):



I

or a pharmaceutically acceptable salt thereof,

wherein

------ represents a single or double bond;

R^1 is hydrogen, R^z, or –C(O)R^z, wherein R^z is optionally substituted C_{1-6} alkyl;

L is –N(R)C(O)–, –C(O)N(R)–, –N(R)C(O)N(R)–,–N(R)C(O)O–, or –OC(O)N(R)–;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

Ar is a monocyclic or bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits;

each R^y is independently selected from the group consisting of halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, or -$SO_2N(R^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^5, R^6, R^7, and R^8 are independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, -OR', and -$N(R'')_2$;

R' is hydrogen or optionally substituted aliphatic;

each R" is independently hydrogen or optionally substituted aliphatic, or two R" are taken together with their intervening atoms to form a heterocyclic ring; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

wherein, and unless otherwise specified,

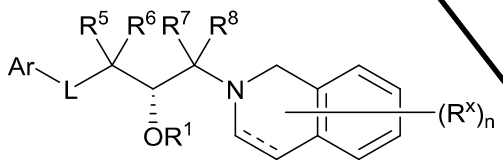
heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

carbocyclyl or carbocyclic refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms and zero heteroatoms in the non–aromatic ring system;

aryl refers to a radical of a monocyclic or polycyclic aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur.

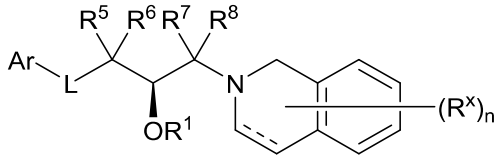
2. The compound of claim 1, wherein the compound is of Formula (**I-a**):



I-a

or a pharmaceutically acceptable salt thereof.

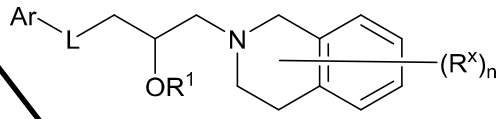
3. The compound of claim 1, wherein the compound is of Formula (**I-b**):



I-b

or a pharmaceutically acceptable salt thereof.

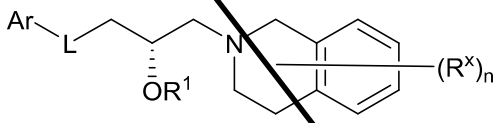
4. The compound of claim 1, wherein the compound is of Formula (**I'**):



I'

or a pharmaceutically acceptable salt thereof.

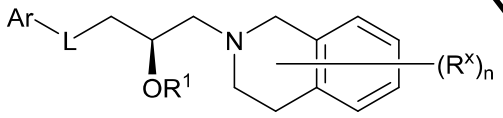
5. The compound of claim 4, wherein the compound is of Formula (**I'-a**):



I'-a

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 4, wherein the compound is of Formula (**I'-b**):



I'-b

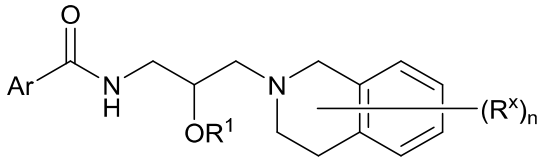
or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, wherein L is –C(O)N(R)–.

8. The compound of any one of claims 1-6, wherein L is –NHC(O)NH-.

9. The compound of any one of claims 1-6, wherein L is –OC(O)NH-.

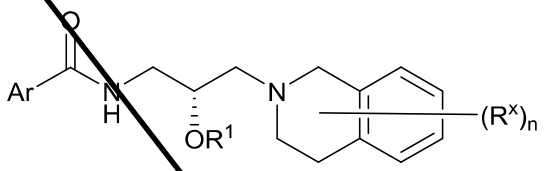
10. The compound of claim 1, wherein the compound is of Formula (**II**):



II

or a pharmaceutically acceptable salt thereof.

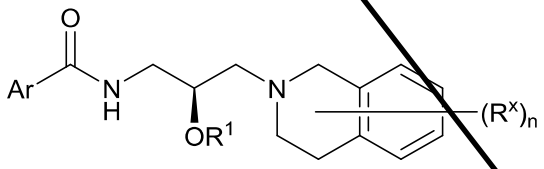
11. The compound of claim 10, wherein the compound is of Formula (**II-a**):



II-a

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 10, wherein the compound is of Formula (**II-b**):



II-b

or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1-12, wherein R^1 is hydrogen.

14. The compound of any one of claims 1-13, wherein n is 0.

15. The compound of any one of claims 1-13, wherein n is 1.

16. The compound of any one of claims 1-13, wherein n is 2.

17. The compound of any one of claims 1-16, wherein Ar is phenyl.

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

19. The compound of claim 18, wherein Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

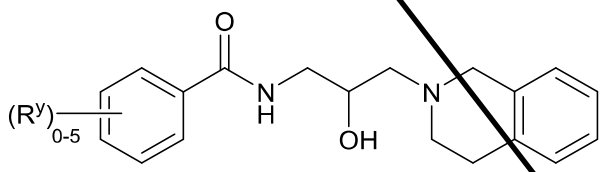
20. The compound of claim 19, wherein Ar is pyridyl.

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

22. The compound of any one of claims 1-20, wherein Ar is substituted with 1 or 2 R^y groups.

23. The compound of claim 22, wherein Ar is substituted with one R^y group.

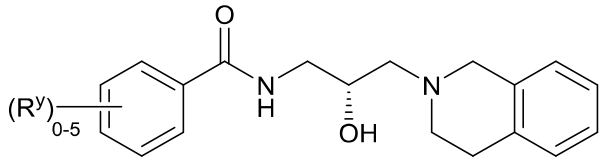
24. The compound of claim 1, wherein the compound is of Formula (**III**):



III

or a pharmaceutically acceptable salt thereof.

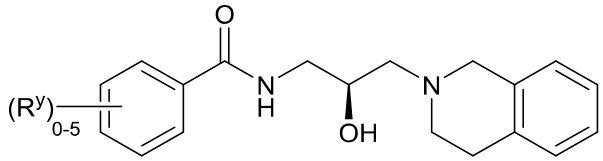
25. The compound of claim 24, wherein the compound is of Formula (**III-a**):



III-a

or a pharmaceutically acceptable salt thereof.

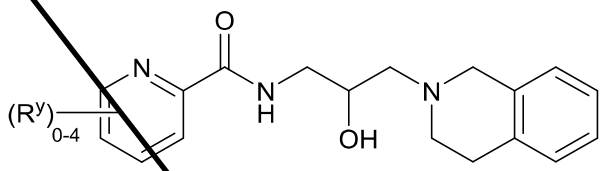
26. The compound of claim 24, wherein the compound is of Formula (**III-b**):



III-b

or a pharmaceutically acceptable salt thereof.

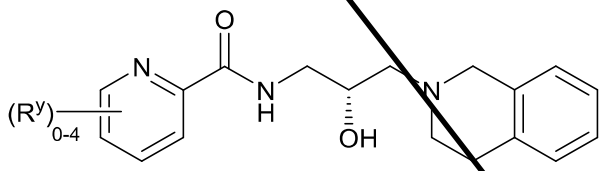
27. The compound of claim 1, wherein the compound is of Formula (**IV**):



IV

or a pharmaceutically acceptable salt thereof.

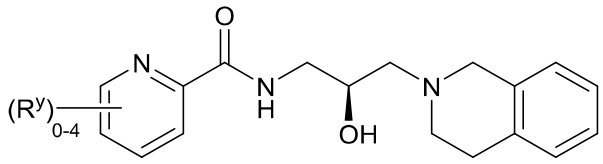
28. The compound of claim 1, wherein the compound is of Formula (**IV-a**):



IV-a

or a pharmaceutically acceptable salt thereof.

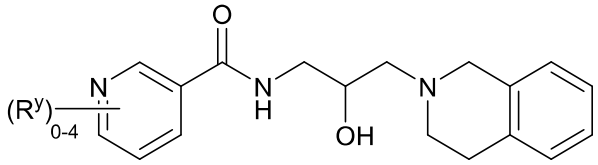
29. The compound of claim 1, wherein the compound is of Formula (**IV-b**):



IV-b

or a pharmaceutically acceptable salt thereof.

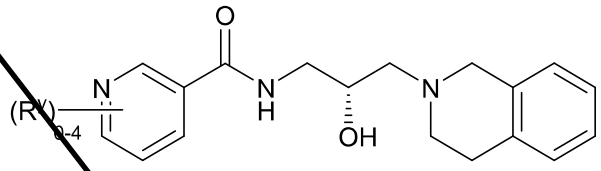
30. The compound of claim 1, wherein the compound is of Formula (**V**):



V

or a pharmaceutically acceptable salt thereof.

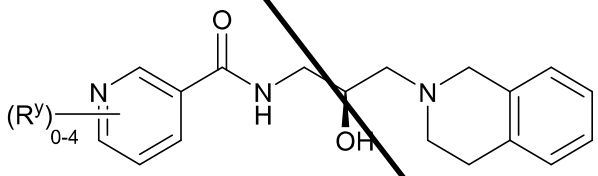
31. The compound of claim 1, wherein the compound is of Formula (**V-a**):



V-a

or a pharmaceutically acceptable salt thereof.

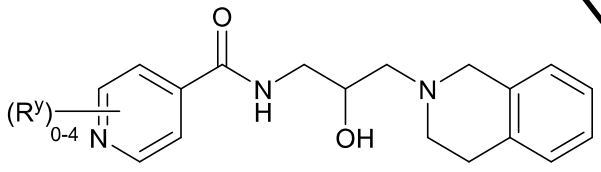
32. The compound of claim 1, wherein the compound is of Formula (**V-b**):



V-b

or a pharmaceutically acceptable salt thereof.

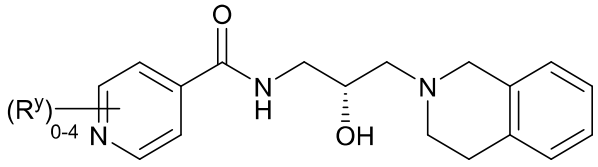
33. The compound of claim 1, wherein the compound is of Formula (**VI**):



VI

or a pharmaceutically acceptable salt thereof.

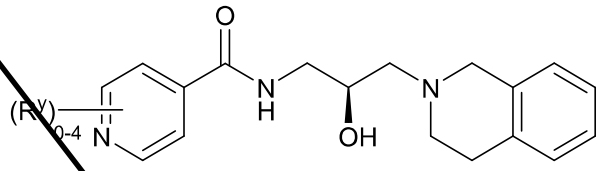
34. The compound of claim 1, wherein the compound is of Formula (**VI-a**):



VI-a

or a pharmaceutically acceptable salt thereof.

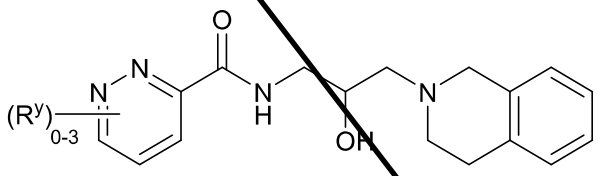
35. The compound of claim 1, wherein the compound is of Formula (**VI-b**):



VI-b

or a pharmaceutically acceptable salt thereof.

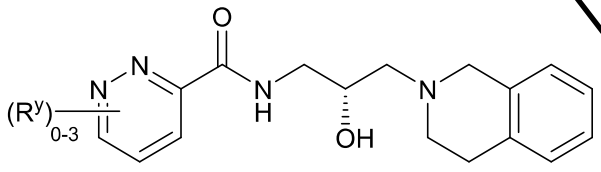
36. The compound of claim 1, wherein the compound is of Formula (**VII**):



VII

or a pharmaceutically acceptable salt thereof.

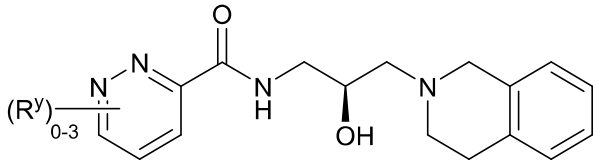
37. The compound of claim 1, wherein the compound is of Formula (**VII-a**):



VII-a

or a pharmaceutically acceptable salt thereof.

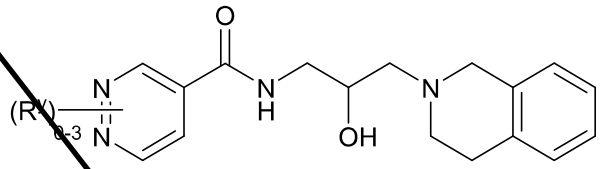
38. The compound of claim 1, wherein the compound is of Formula (**VII-b**):



VII-b

or a pharmaceutically acceptable salt thereof.

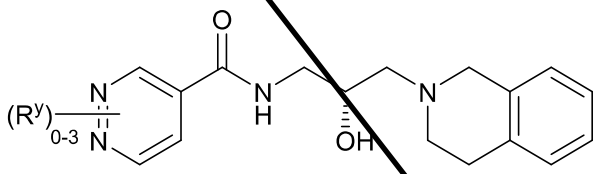
39. The compound of claim 1, wherein the compound is of Formula (**VIII**):



VIII

or a pharmaceutically acceptable salt thereof.

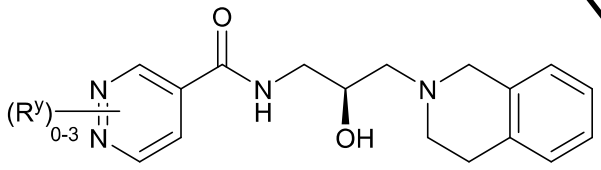
40. The compound of claim 1, wherein the compound is of Formula (**VIII-a**):



VIII-a

or a pharmaceutically acceptable salt thereof.

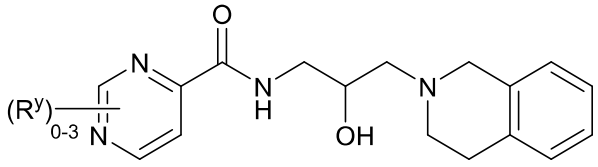
41. The compound of claim 1, wherein the compound is of Formula (**VIII-b**):



VIII-b

or a pharmaceutically acceptable salt thereof.

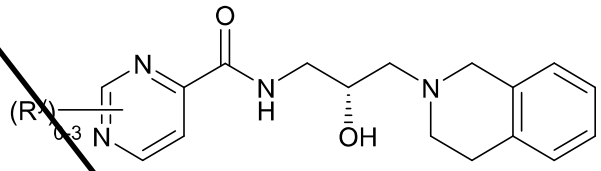
42. The compound of claim 1, wherein the compound is of Formula (**IX**):



IX

or a pharmaceutically acceptable salt thereof.

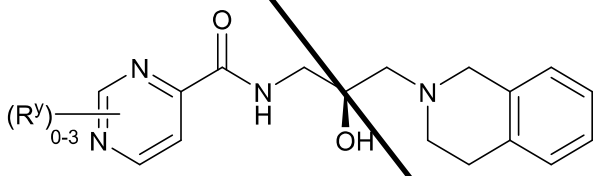
43. The compound of claim 1, wherein the compound is of Formula (**IX-a**):



IX-a

or a pharmaceutically acceptable salt thereof.

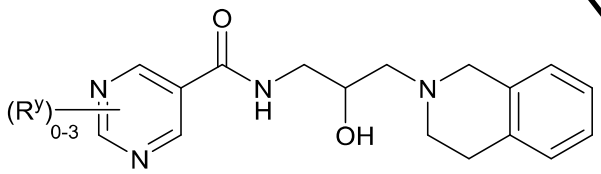
44. The compound of claim 1, wherein the compound is of Formula (**IX-b**):



IX-b

or a pharmaceutically acceptable salt thereof.

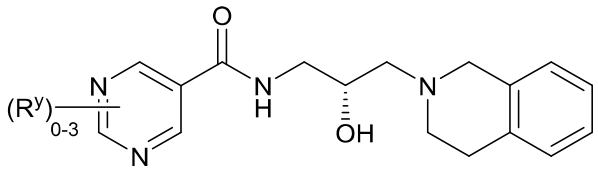
45. The compound of claim 1, wherein the compound is of Formula (**X**):



X

or a pharmaceutically acceptable salt thereof.

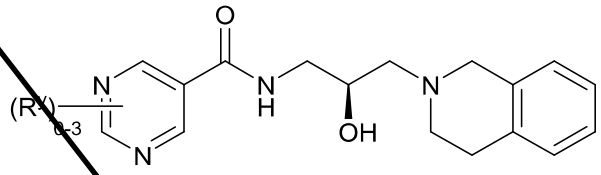
46. The compound of claim 1, wherein the compound is of Formula (**X-a**):



X-a

or a pharmaceutically acceptable salt thereof.

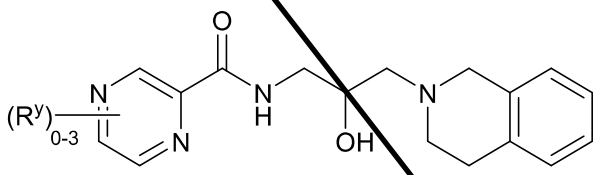
47. The compound of claim 1, wherein the compound is of Formula (**X-b**):



X-b

or a pharmaceutically acceptable salt thereof.

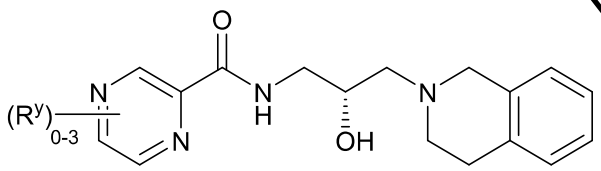
48. The compound of claim 1, wherein the compound is of Formula (**XI**):



XI

or a pharmaceutically acceptable salt thereof.

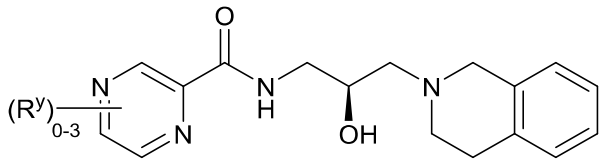
49. The compound of claim 1, wherein the compound is of Formula (**XI-a**):



XI-a

or a pharmaceutically acceptable salt thereof.

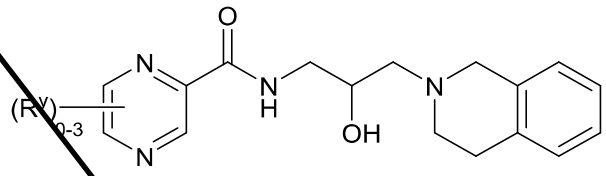
50. The compound of claim 1, wherein the compound is of Formula (**XI-b**):



XI-b

or a pharmaceutically acceptable salt thereof.

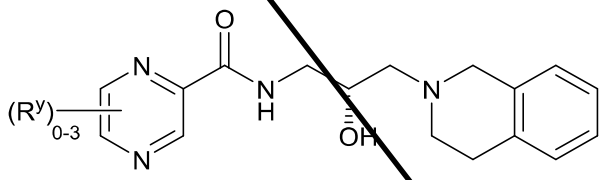
51. The compound of claim 1, wherein the compound is of Formula (**XII**):



XII

or a pharmaceutically acceptable salt thereof.

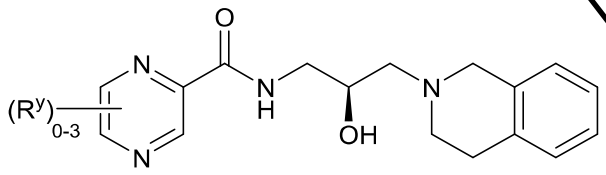
52. The compound of claim 1, wherein the compound is of Formula (**XII-a**):



XII-a

or a pharmaceutically acceptable salt thereof.

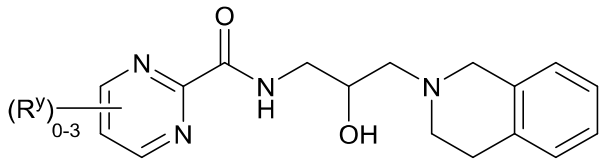
53. The compound of claim 1, wherein the compound is of Formula (**XII-b**):



XII-b

or a pharmaceutically acceptable salt thereof.

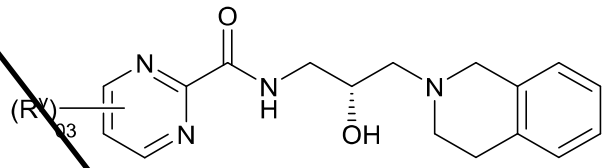
54. The compound of claim 1, wherein the compound is of Formula (**XIII**):



XIII

or a pharmaceutically acceptable salt thereof.

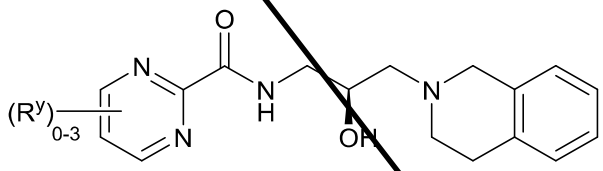
55. The compound of claim 1, wherein the compound is of Formula (**XIII-a**):



XIII-a

or a pharmaceutically acceptable salt thereof.

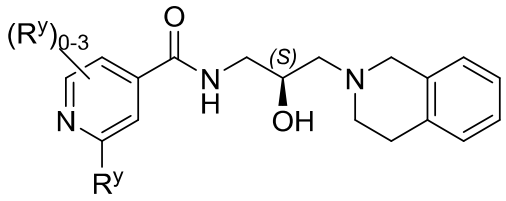
56. The compound of claim 1, wherein the compound is of Formula (**XIII-b**):



XIII-b

or a pharmaceutically acceptable salt thereof.

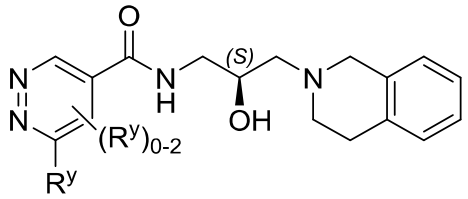
57. The compound of claim 1, wherein the compound is of Formula (**XV**):



XV

or a pharmaceutically acceptable salt thereof.

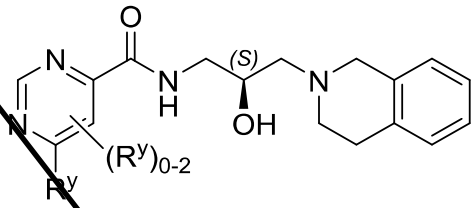
58. The compound of claim 1, wherein the compound is of Formula (**XVI**):



XVI

or a pharmaceutically acceptable salt thereof.

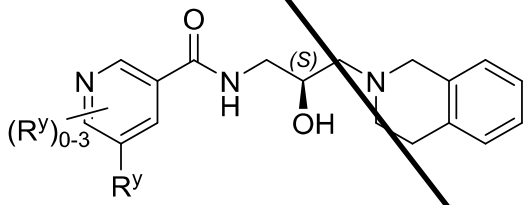
59. The compound of claim 1, wherein the compound is of Formula (**XVII**):



XVII

or a pharmaceutically acceptable salt thereof.

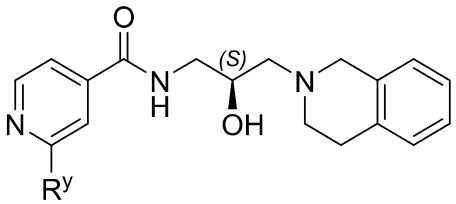
60. The compound of claim 1, wherein the compound is of Formula (**XVIII**):



XVIII

or a pharmaceutically acceptable salt thereof.

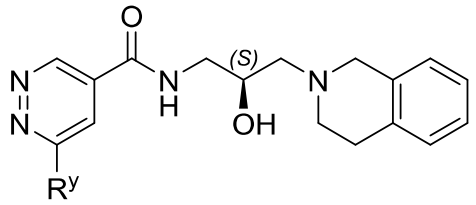
61. The compound of claim 1, wherein the compound is of Formula (**XV-a**):



XV-a

or a pharmaceutically acceptable salt thereof.

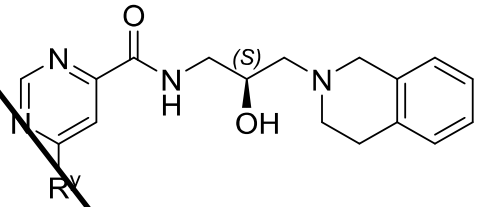
62. The compound of claim 1, wherein the compound is of Formula (**XVI-a**):



XVI-a

or a pharmaceutically acceptable salt thereof.

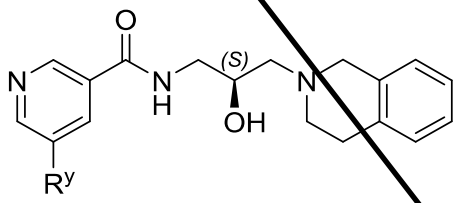
63. The compound of claim 1, wherein the compound is of Formula (**XVII-a**):



XVII-a

or a pharmaceutically acceptable salt thereof.

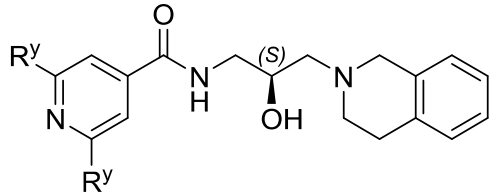
64. The compound of claim 1, wherein the compound is of Formula (**XVIII-a**):



XVIII-a

or a pharmaceutically acceptable salt thereof.

65. The compound of claim 1, wherein the compound is of Formula (**XV-b**):



XV-b

or a pharmaceutically acceptable salt thereof.

66. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is heteroaryl or heterocyclyl.

67. The compound of claim 66, wherein at least one R^y is 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

68. The compound of claim 67, wherein at least one R^y is a 6-membered heteroaryl having 1-3 nitrogens.

69. The compound of claim 68, wherein at least one R^y is pyridyl.

70. The compound of claim 67, wherein at least one R^y is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

71. The compound of claim 70, wherein at least one R^y is optionally substituted pyrazole.

72. The compound of claim 70, wherein at least one R^y is pyrrole.

73. The compound of claim 66, wherein at least one R^y is a 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

74. The compound of claim 73, wherein at least one R^y is a 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur.

75. The compound of claim 74, wherein at least one R^y is optionally substituted pyrrolidine.

76. The compound of claim 73, wherein at least one R^y is a 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

77. The compound of claim 76, wherein at least one R^y is optionally substituted piperazine.

78. The compound of claim 76, wherein at least one R^y is morpholine.

79. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is optionally substituted aliphatic.

80. The compound of claim 79, wherein at least one R^y is optionally substituted C_{1-6} alkyl.

81. The compound of claim 80, wherein at least one R^y is C_{1-6} alkyl substituted with an aryl, heteroaryl, or heterocyclyl.

82. The compound of claim 81, wherein at least one R^y is $-CH_2$-aryl, $-CH_2$-heteroaryl, or $-CH_2$-heterocyclyl.

83. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is $-N(R^B)_2$.

84. The compound of claim 83, wherein one R^B is optionally substituted heterocyclyl, and the other R^B is C_{1-4} alkyl.

85. The compound of claim 83, wherein one R^B is optionally substituted heteroaryl, and the other R^B is C_{1-4} alkyl.

86. The compound of claim 83, wherein one R^B is optionally substituted cycloalkyl, and the other R^B is C_{1-4} alkyl.

87. The compound of claim 83, wherein at least one R^y is $-NHR^B$.

88. The compound of claim 87, wherein R^B is optionally substituted heterocyclyl.

89. The compound of claim 87, wherein R^B is optionally substituted heteroaryl.

90. The compound of claim 87, wherein R^B is optionally substituted cycloalkyl.

91. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is -$SO_2N(R^B)_2$.

92. The compound of claim 91, wherein at least one R^y is –SO_2NHR^B.

93. The compound of claim 92, wherein at least one R^y is –SO_2NH_2.

94. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is -$C(O)N(R^B)_2$.

95. The compound of claim 94, wherein at least one R^y is –$C(O)NHR^B$.

96. The compound of claim 95, wherein at least one R^y is –$C(O)NH_2$.

97. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is -$NR^BC(O)R^A$.

98. The compound of claim 97, wherein at least one R^y is –$NHC(O)R^A$.

99. The compound of claim 98, wherein at least one R^y is –$NHC(O)CH_3$.

100. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is -$NR^BSO_2R^A$.

101. The compound of claim 100, wherein at least one R^y is –$NHSO_2R^A$.

102. The compound of claim 101, wherein at least one R^y is –$NHSO_2CH_3$.

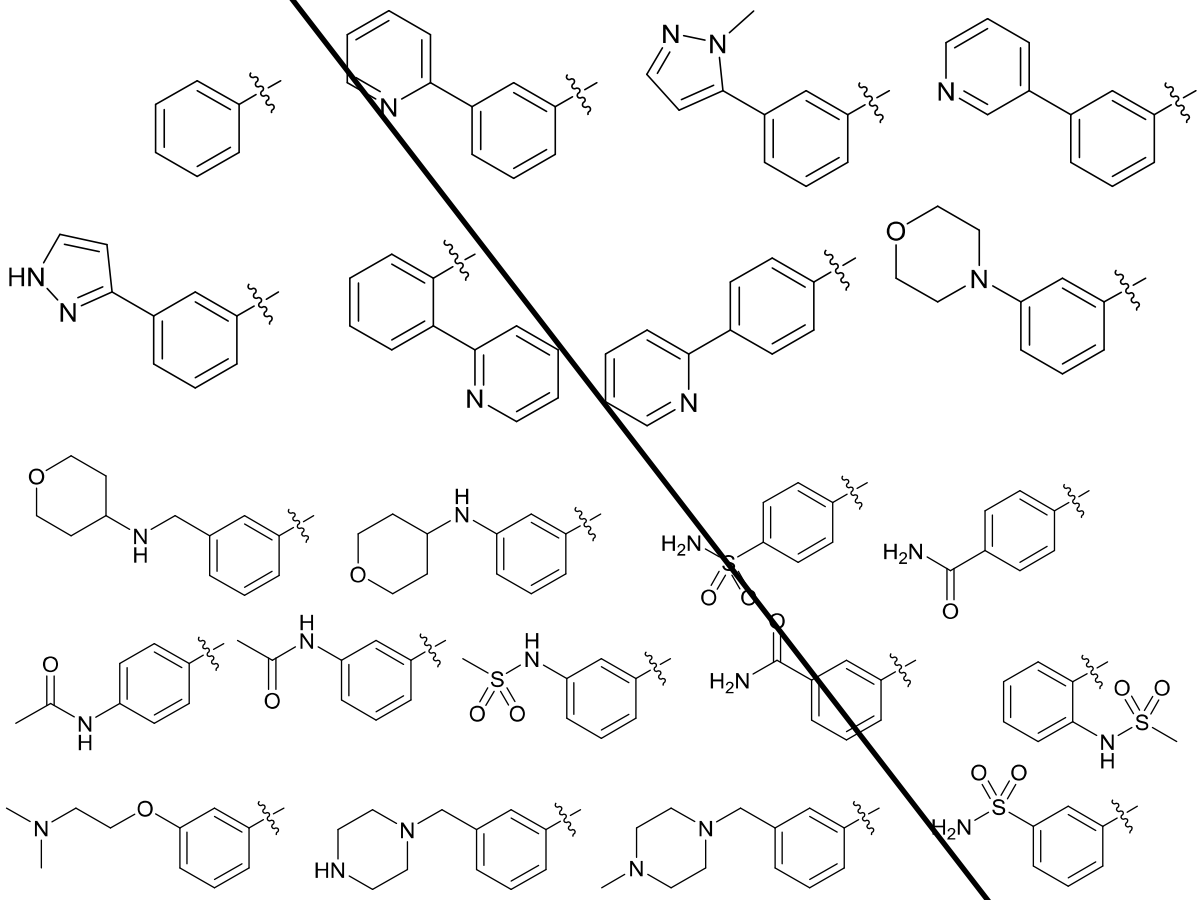
103. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is –OR^A.

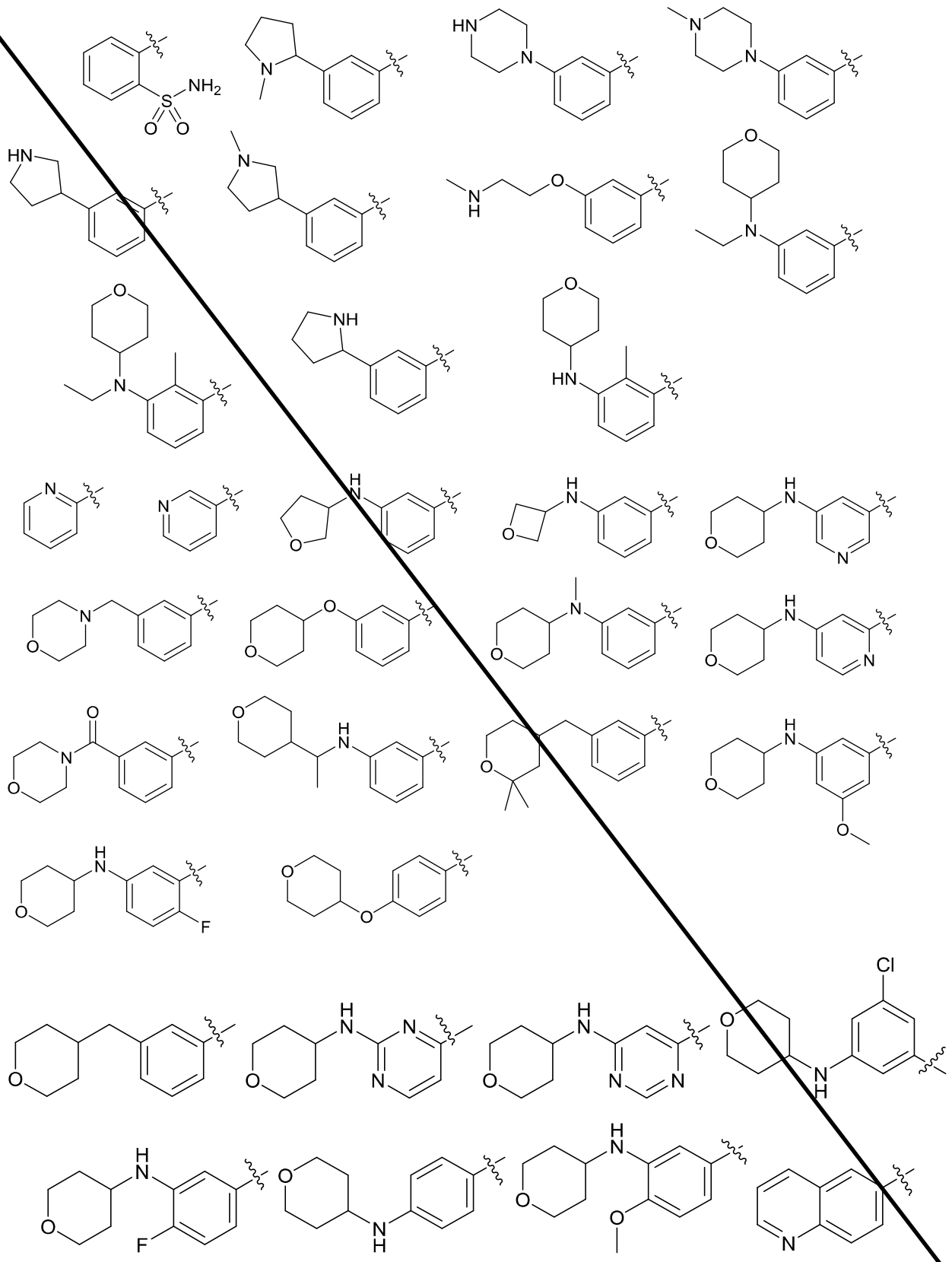
104. The compound of claim 103, wherein R^A is optionally substituted heterocyclyl.

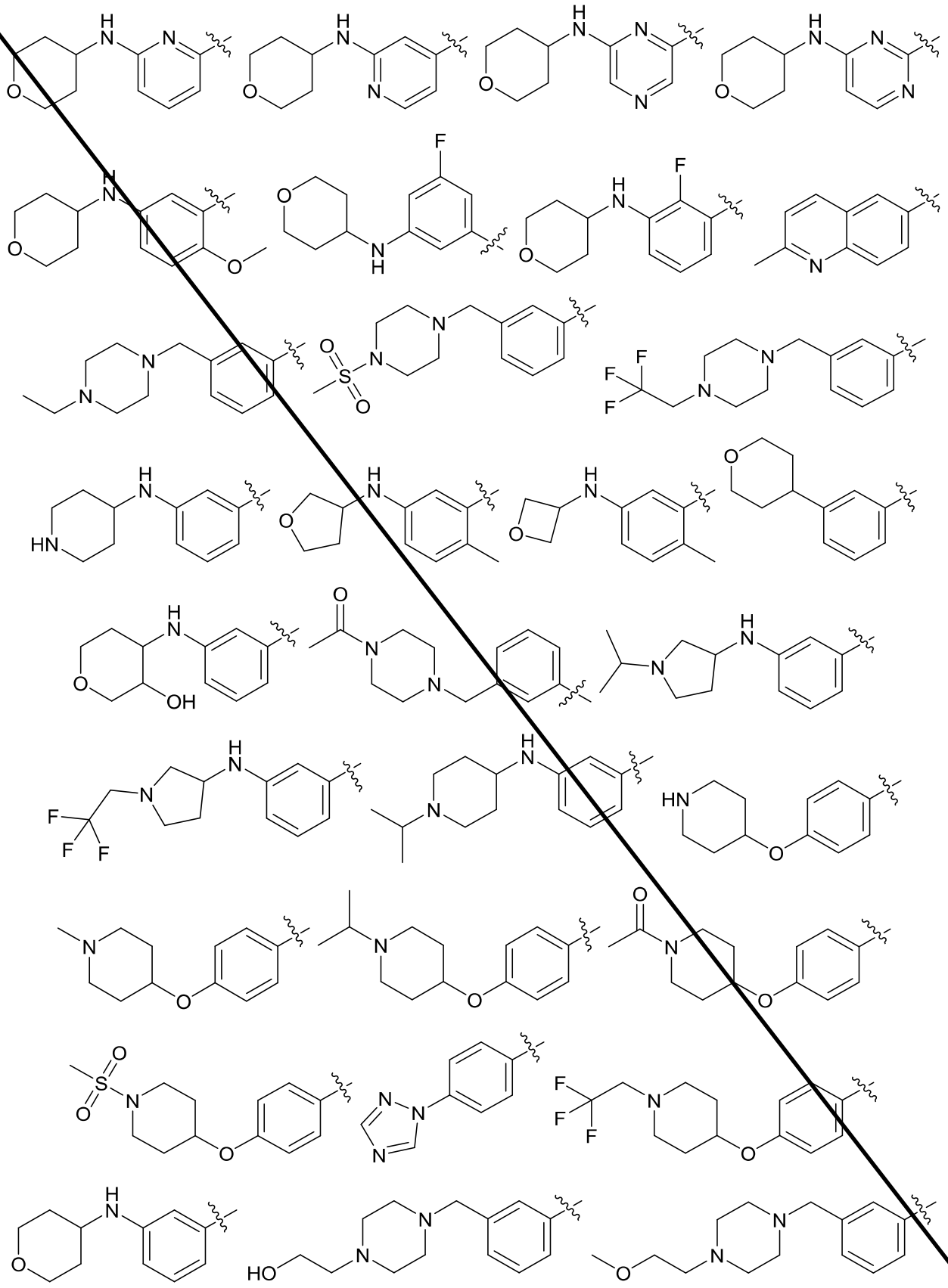
105. The compound of claim 103, wherein R^A is optionally substituted heteroaryl.

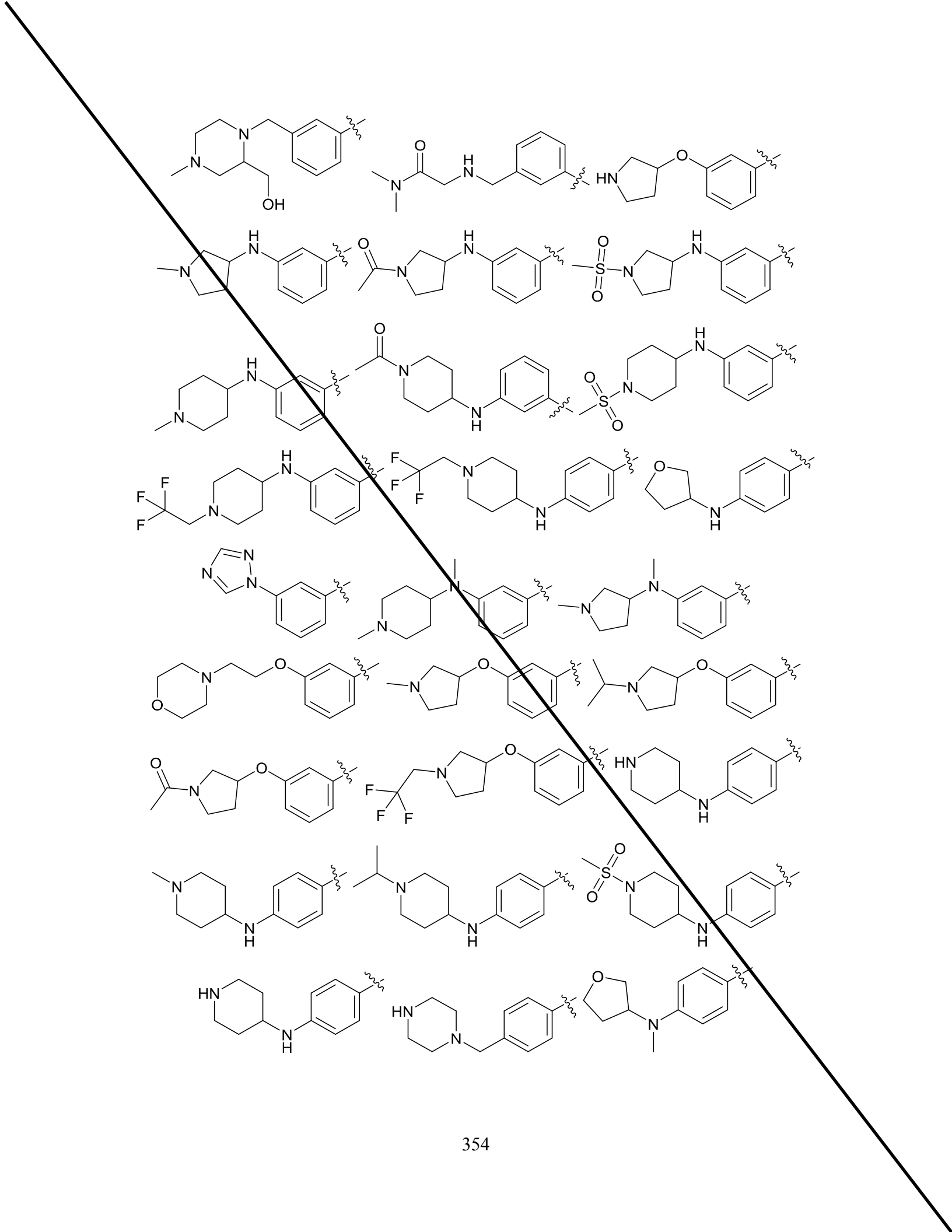
106. The compound of claim 103, wherein R^A is optionally substituted cycloalkyl.

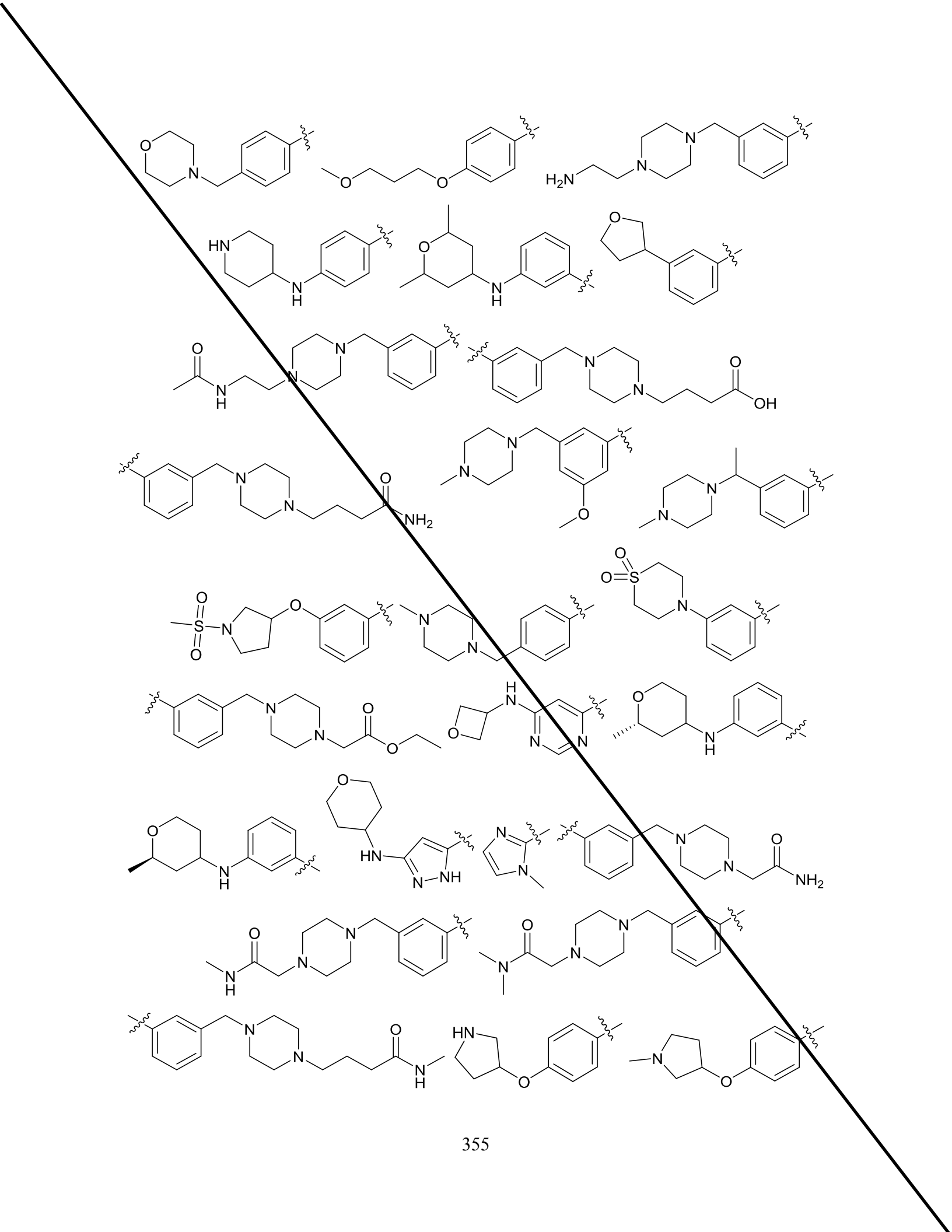
107. The compound of any one of claims 1-16, wherein Ar is selected from the group consisting of:

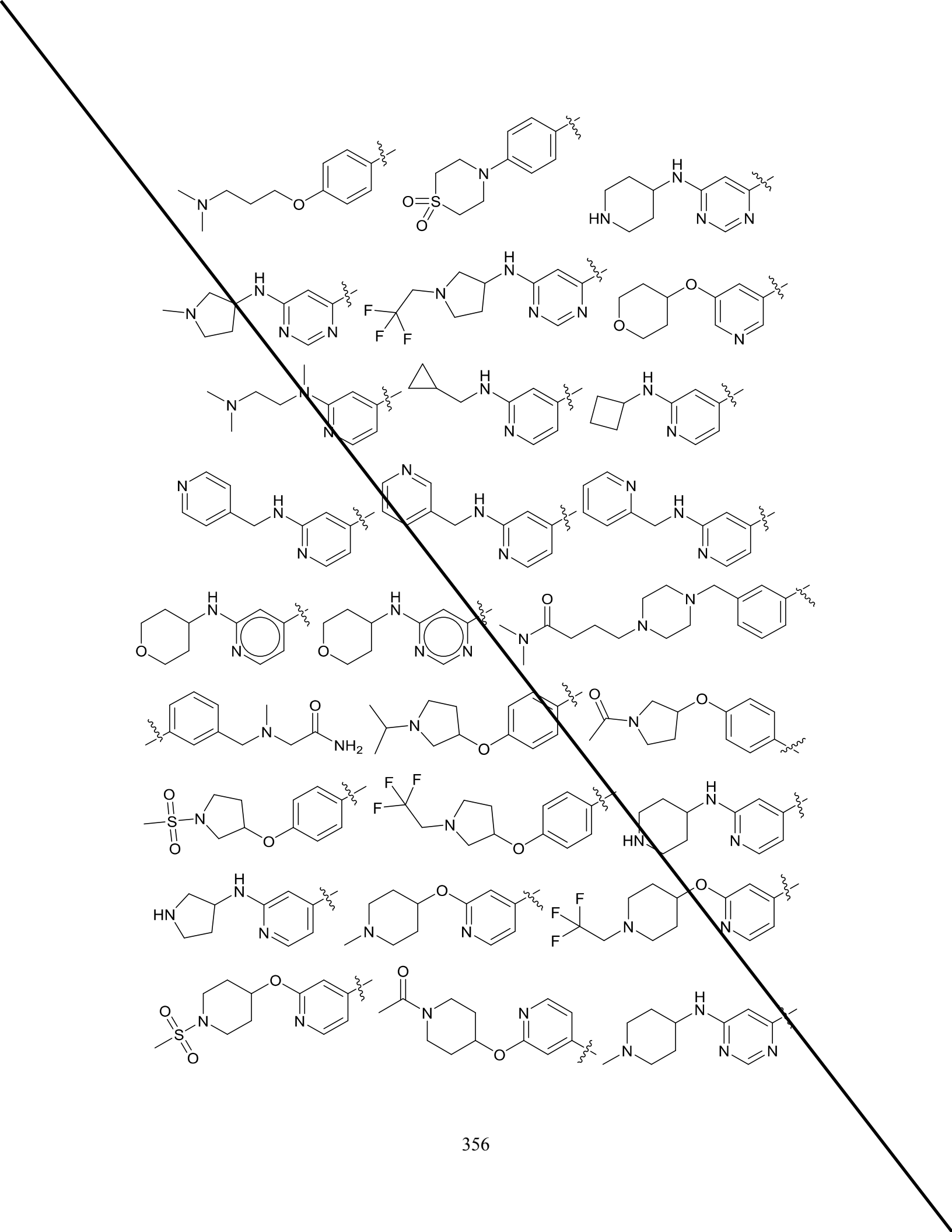


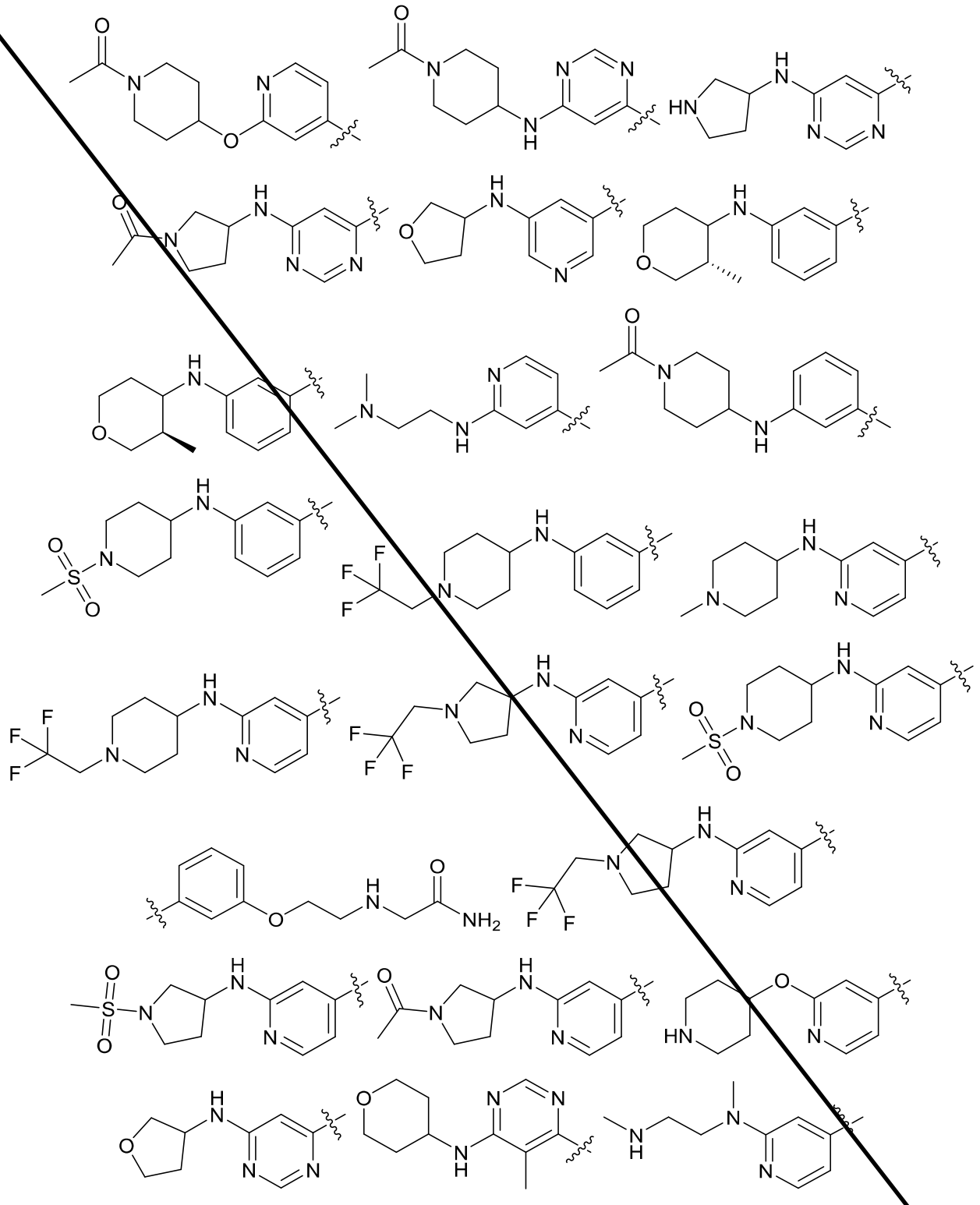


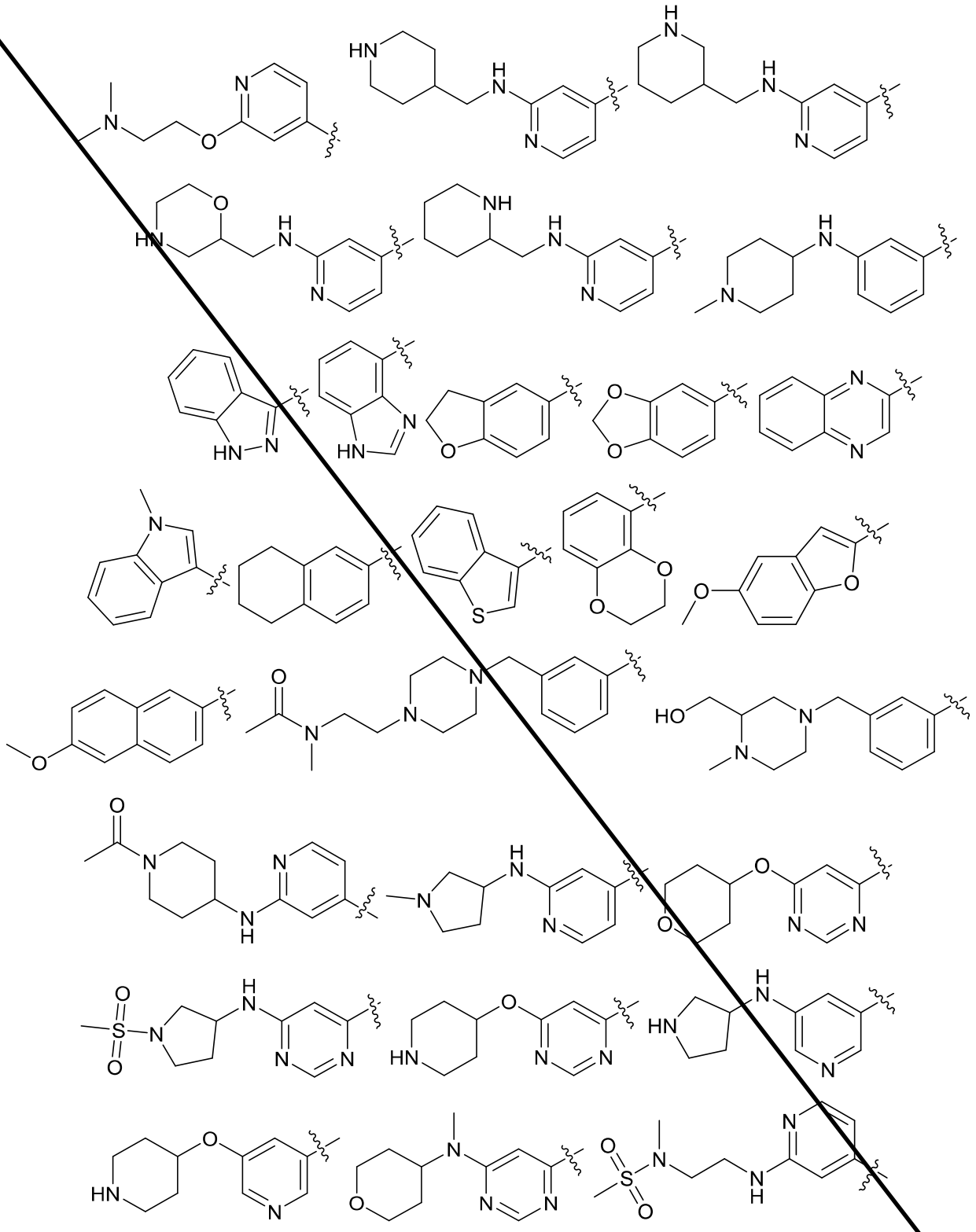


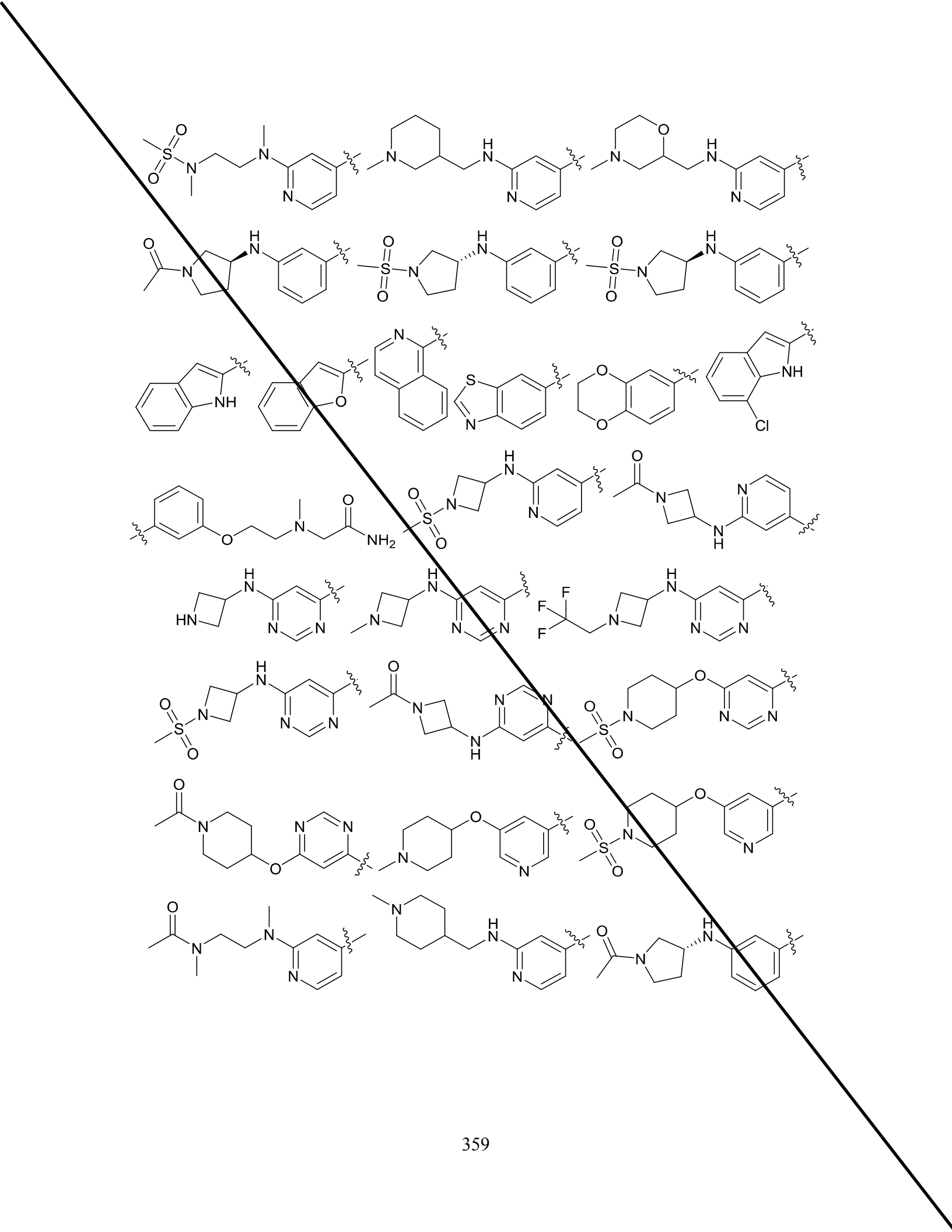


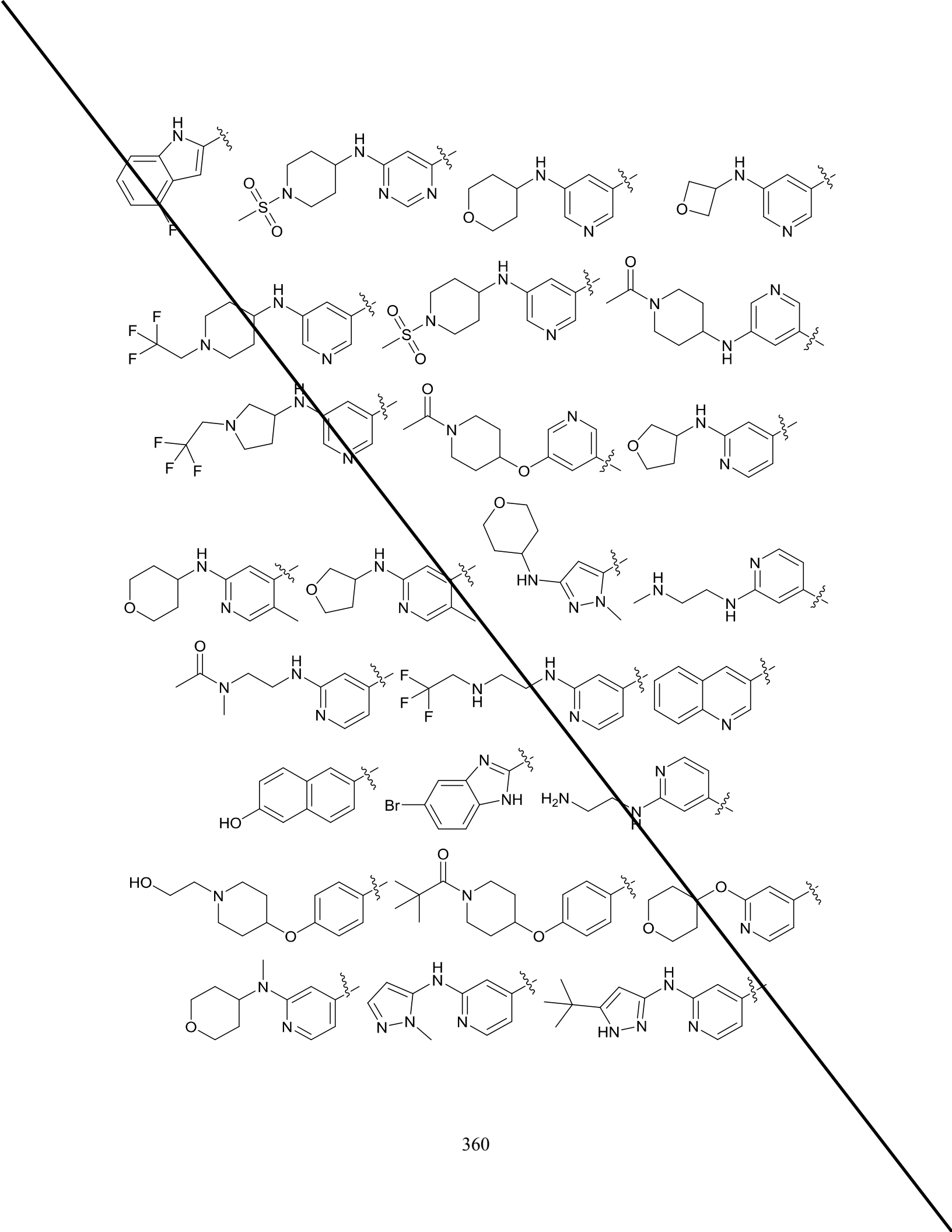


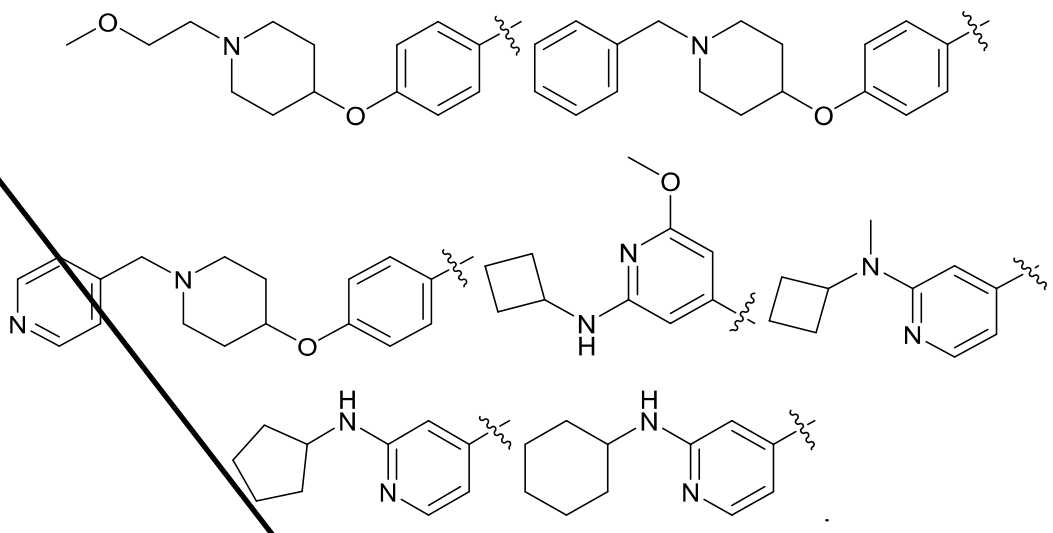




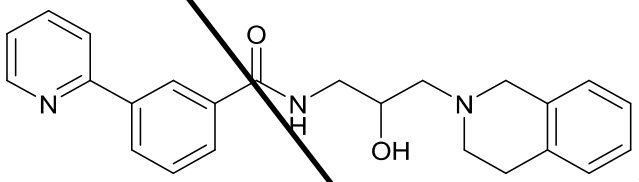


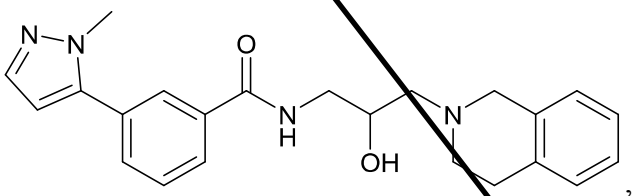


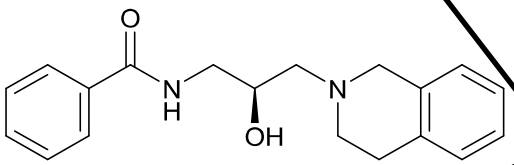


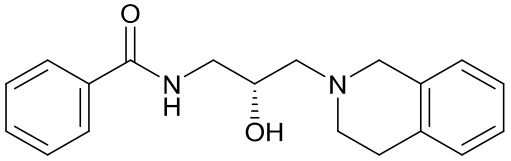


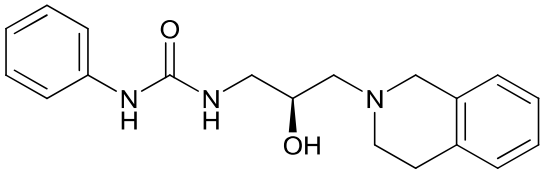
108. The compound of claim 1, wherein the compound is selected from the group consisting of:

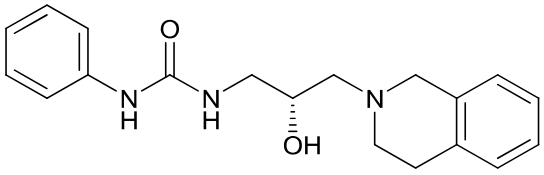








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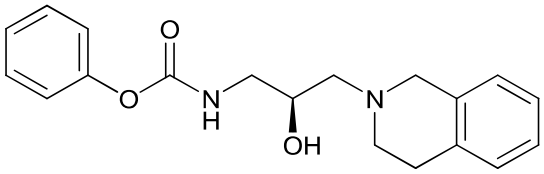
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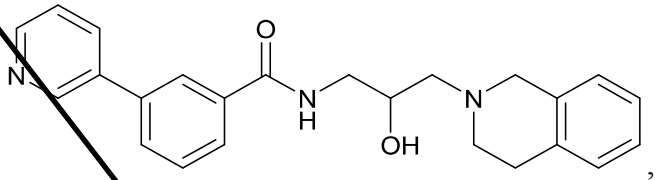
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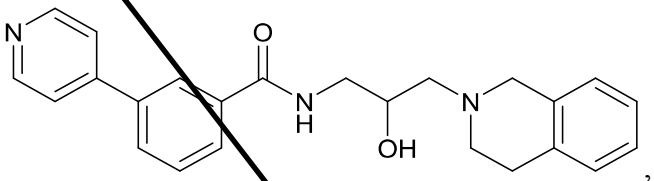
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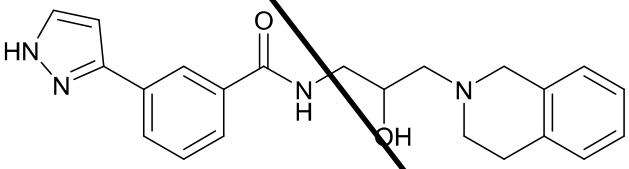
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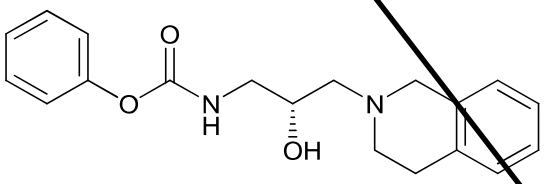
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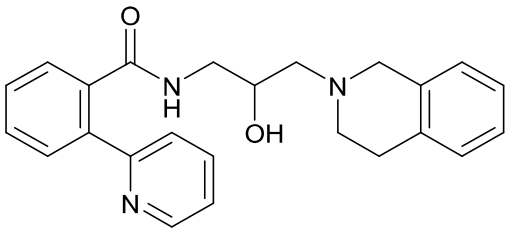
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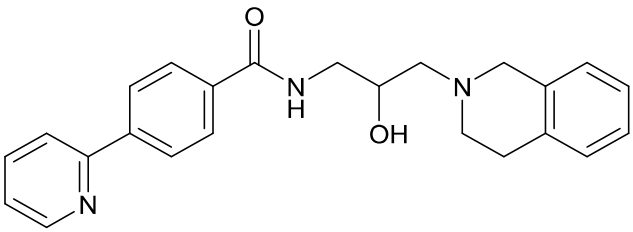
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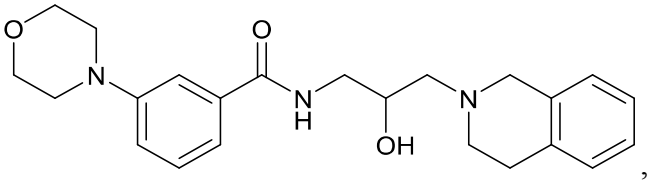
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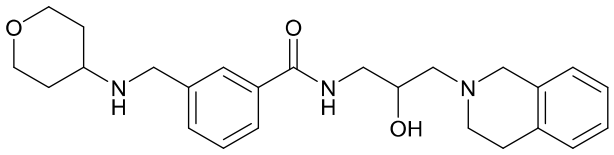
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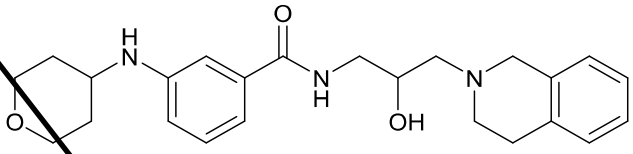
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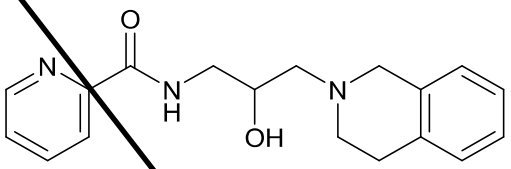
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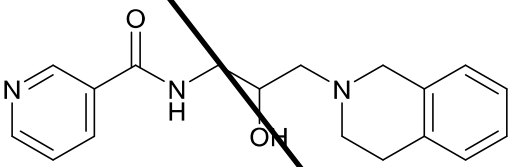
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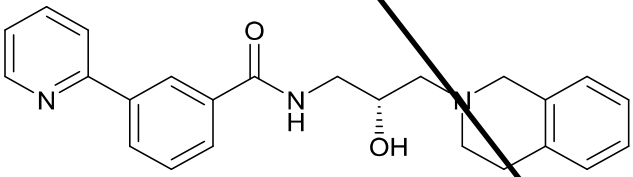
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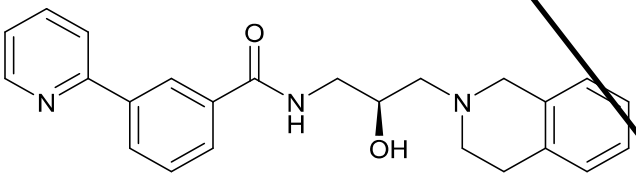
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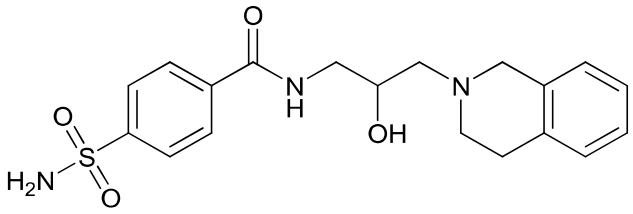
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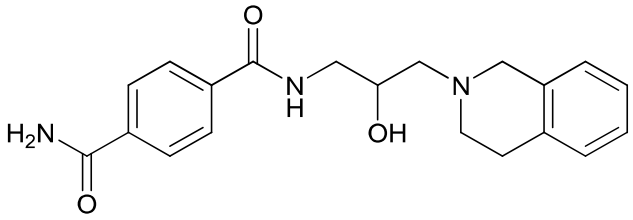
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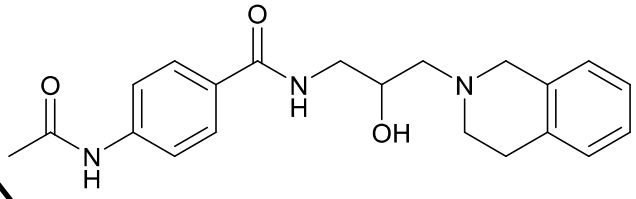
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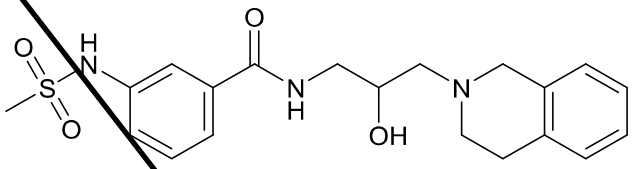
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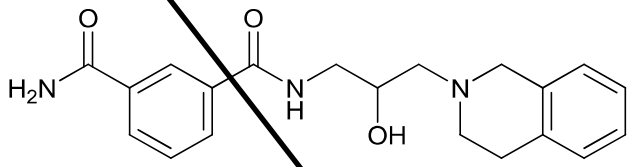
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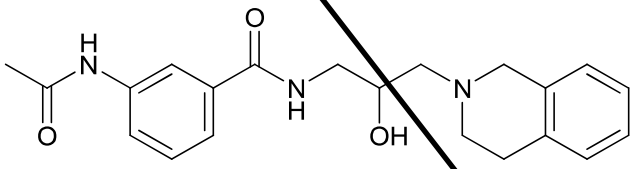
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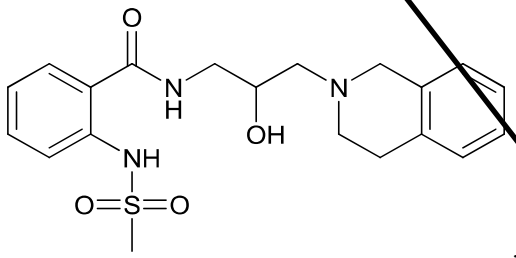
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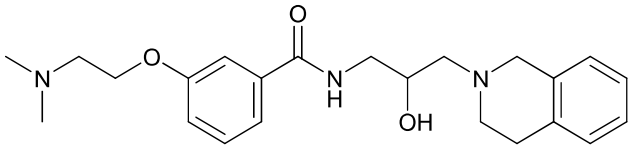
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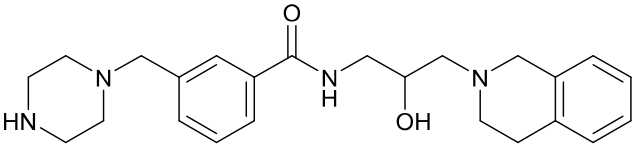
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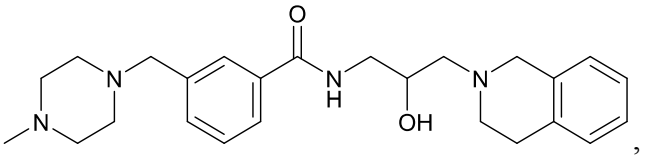
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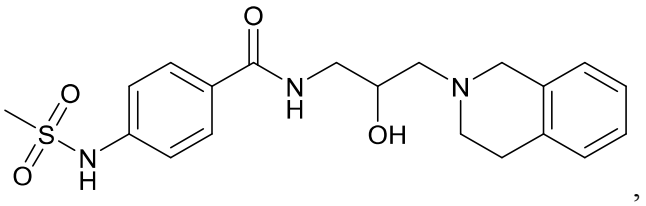
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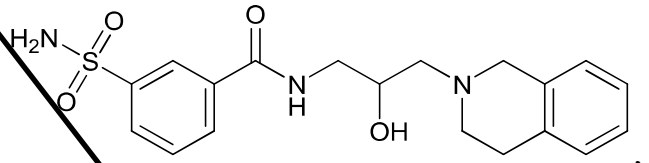
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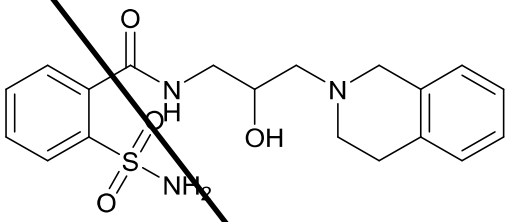
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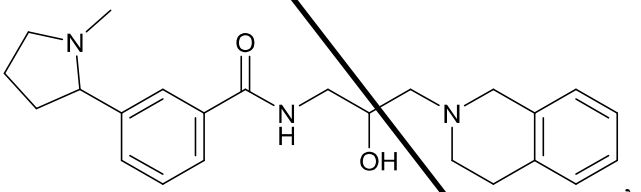
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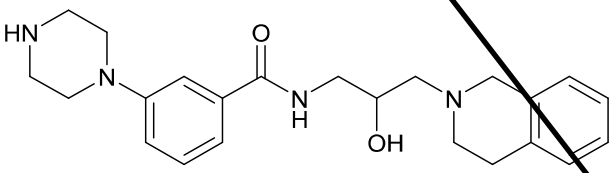
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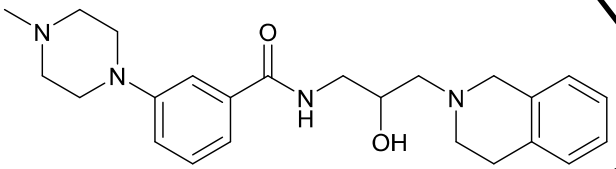
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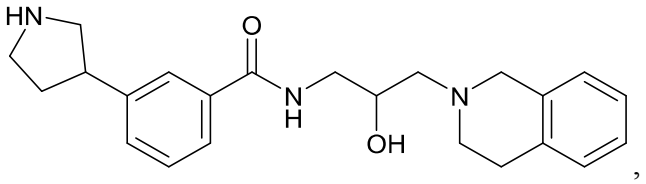
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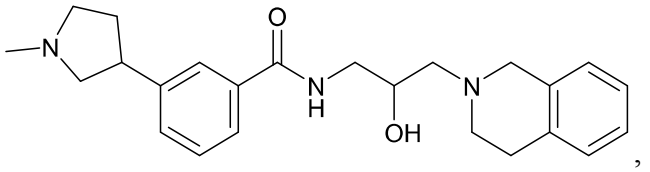
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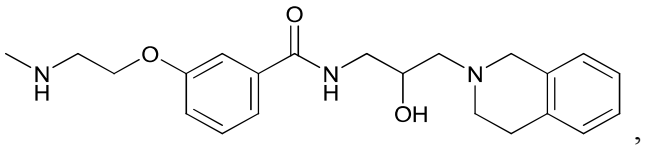
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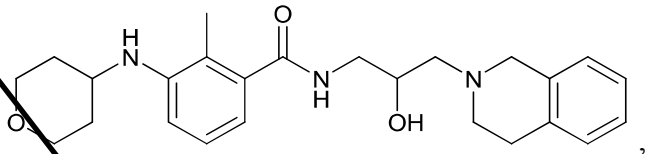
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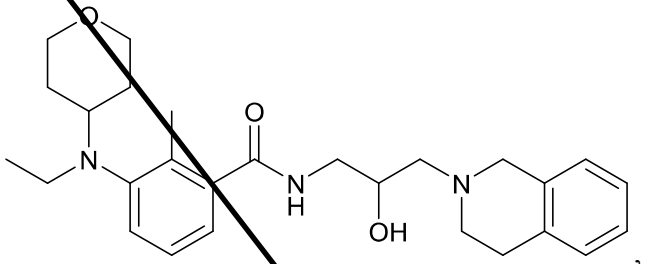
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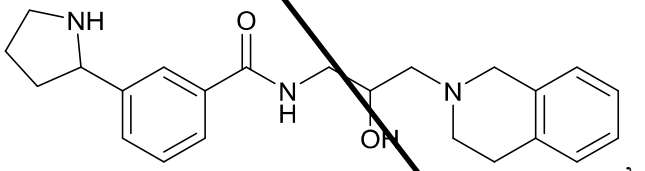
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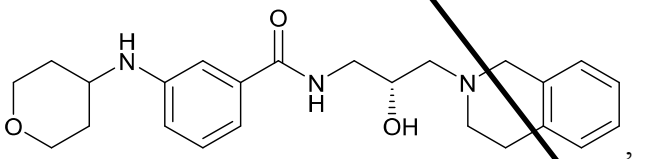
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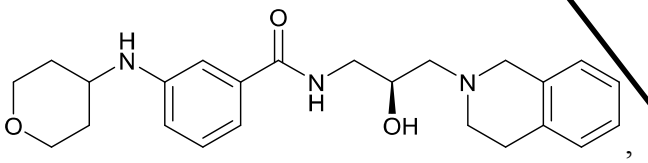
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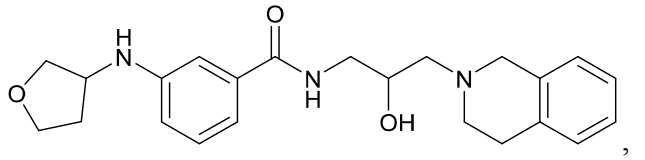
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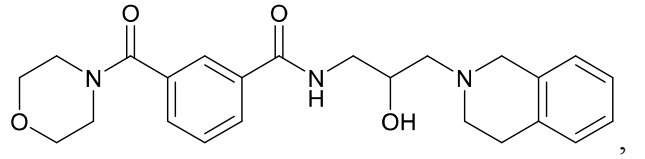
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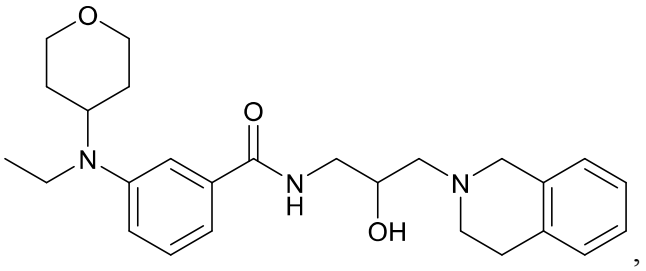
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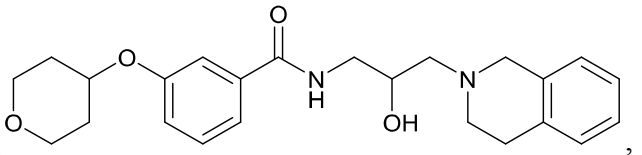
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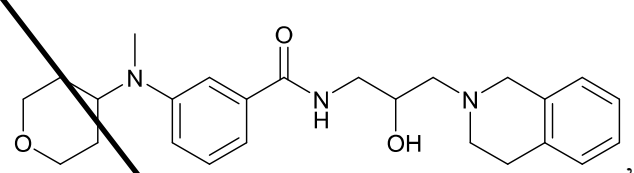
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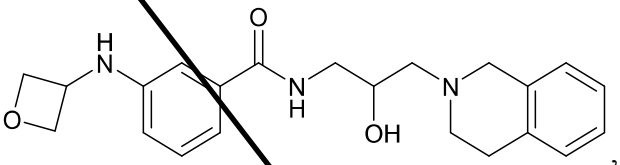
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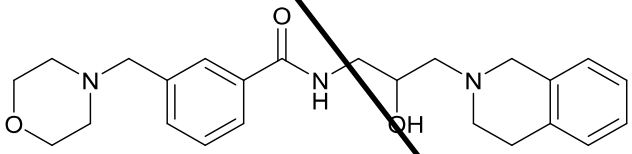
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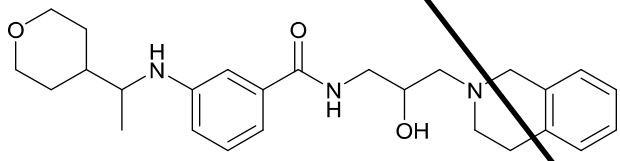
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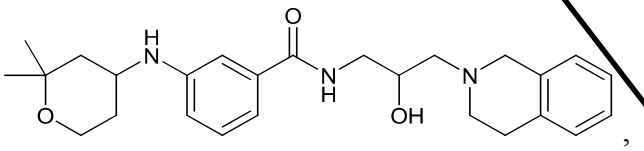
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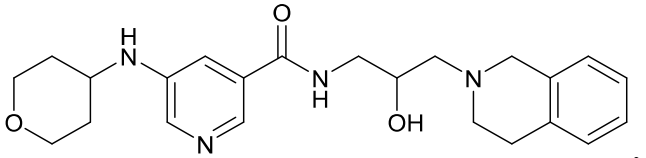
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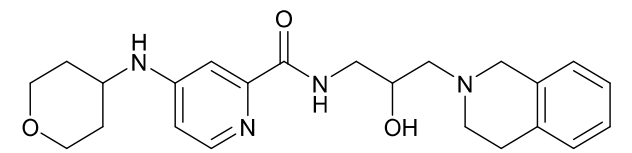
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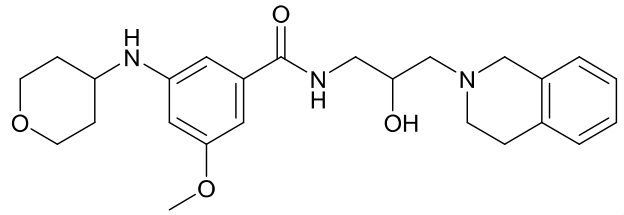
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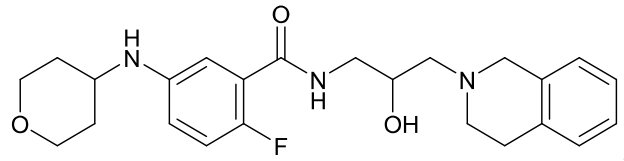
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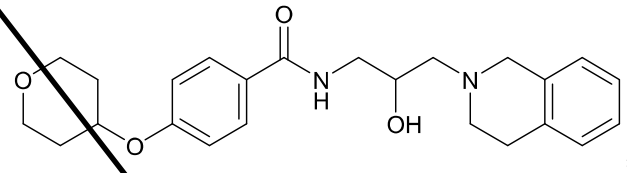
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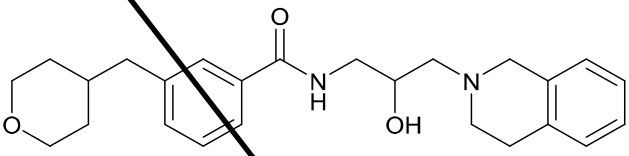
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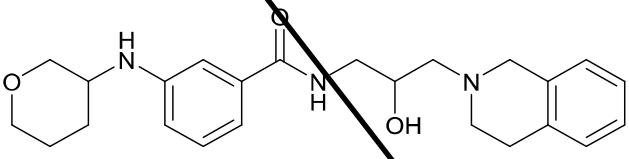
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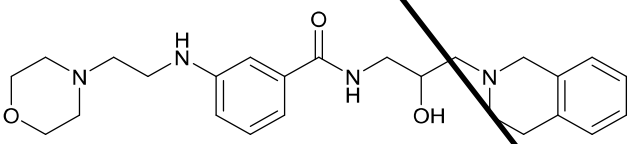
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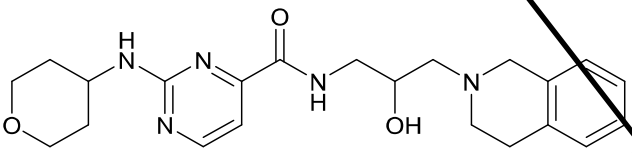
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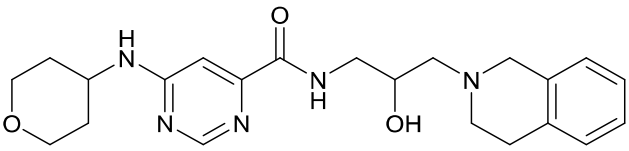
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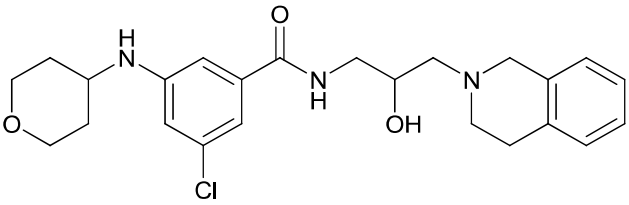
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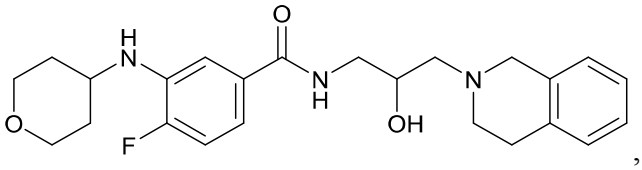
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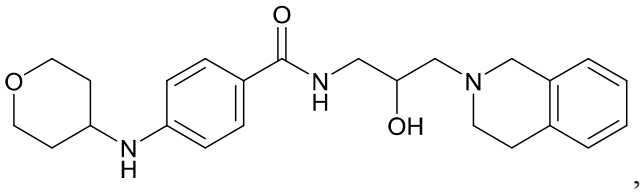
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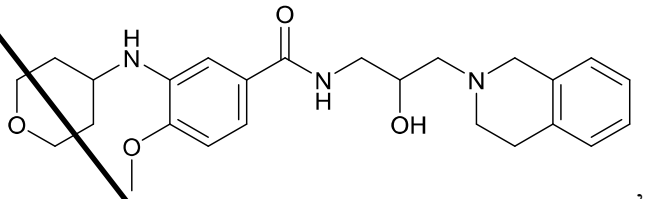
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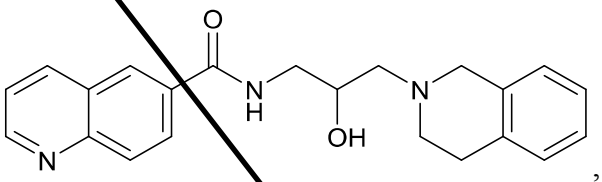
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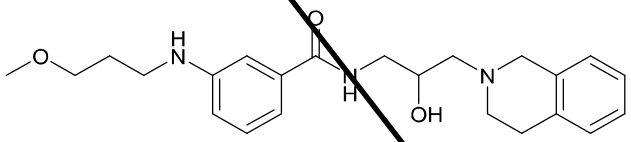
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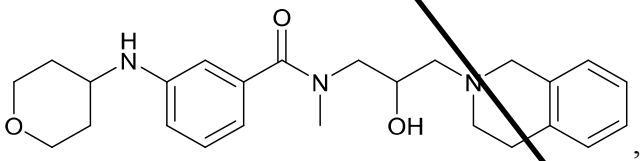
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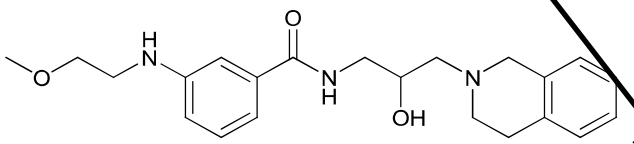
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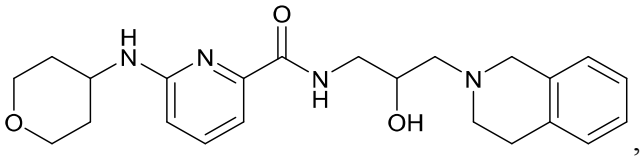
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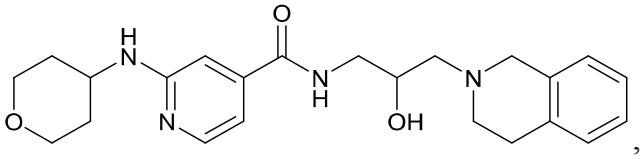
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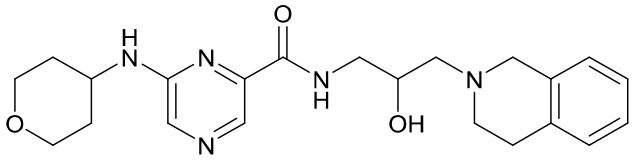
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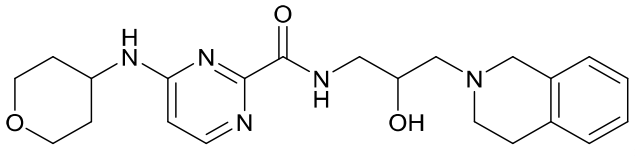
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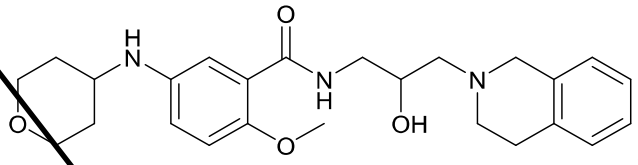
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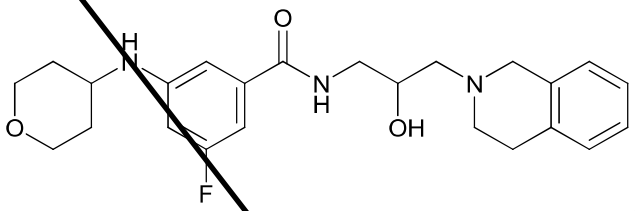
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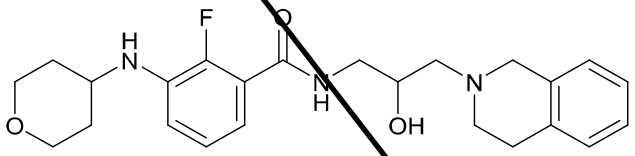
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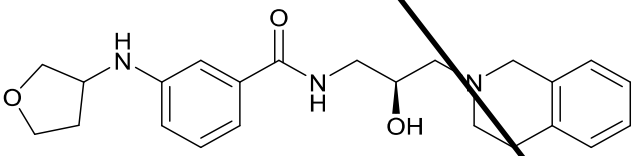
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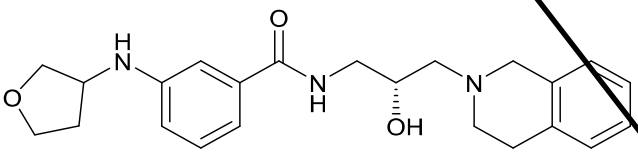
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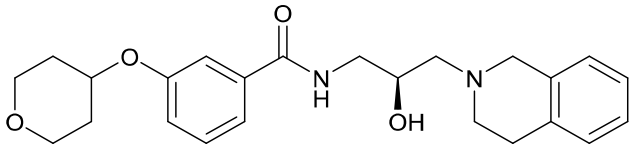
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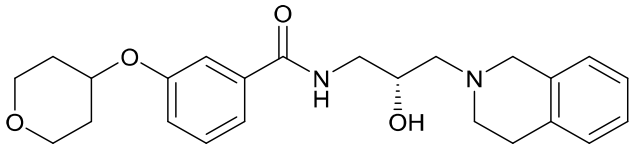
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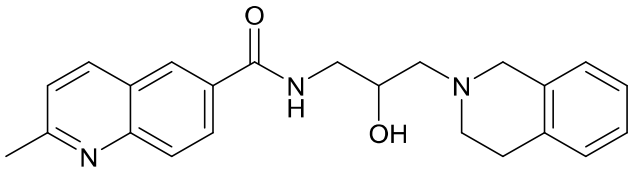
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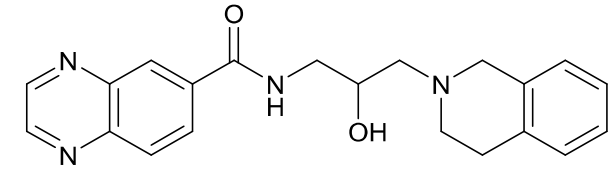
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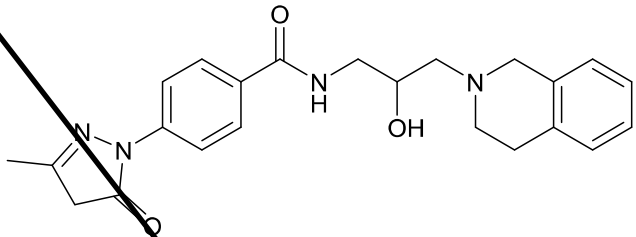
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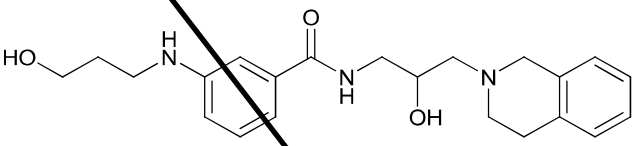
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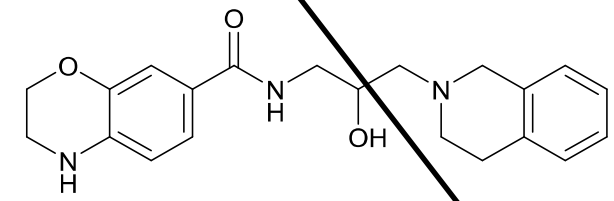
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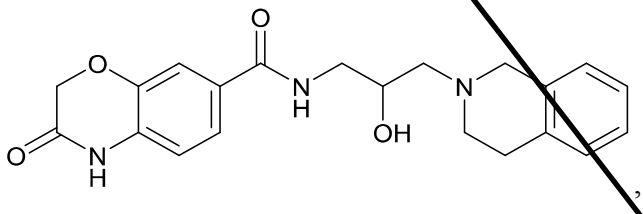
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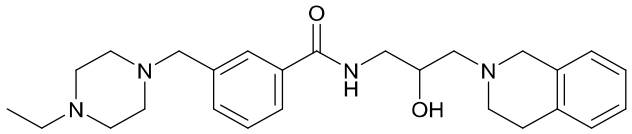
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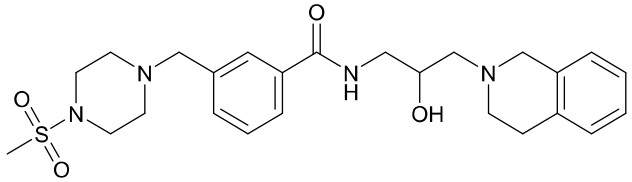
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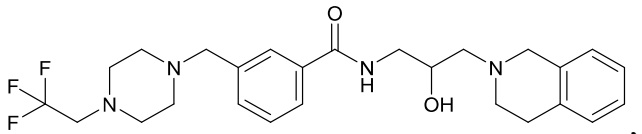
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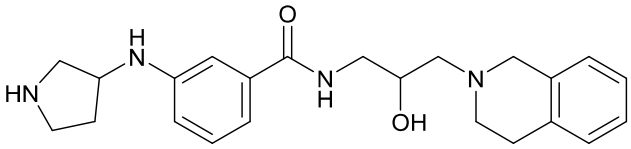
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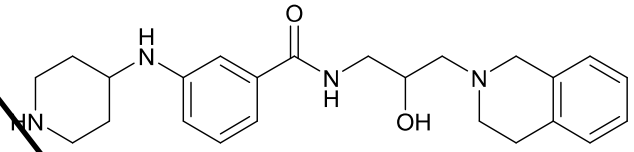
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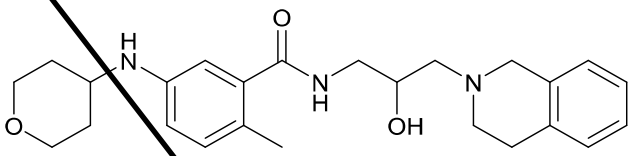
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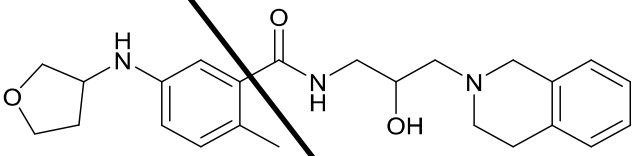
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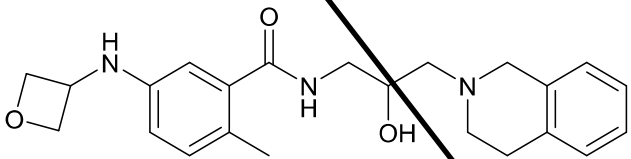
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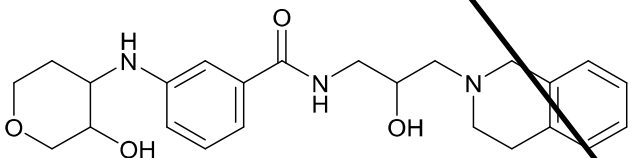
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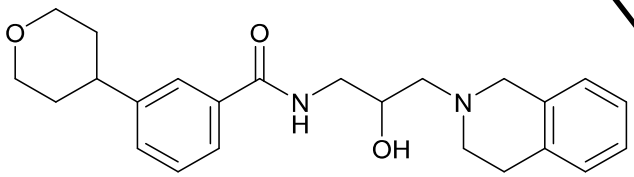
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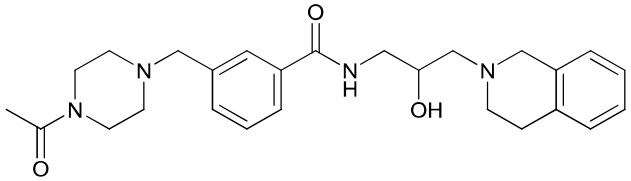
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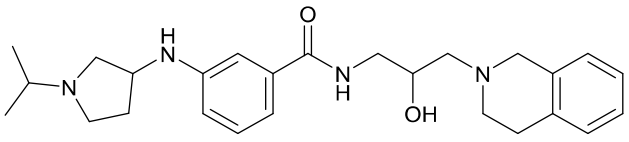
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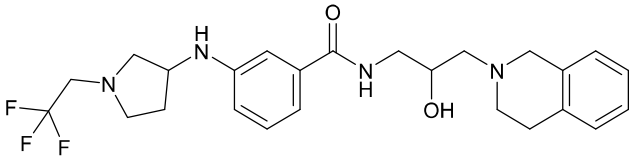
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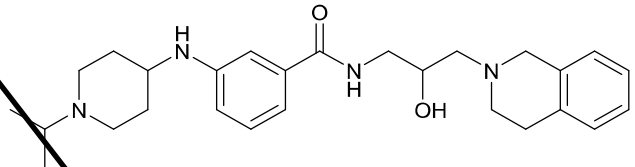
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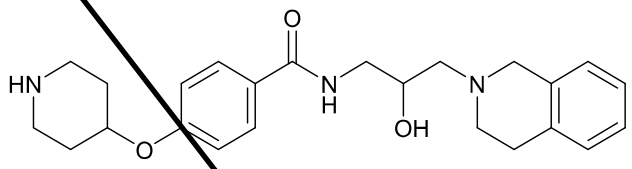
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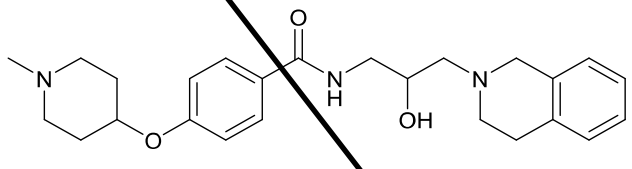
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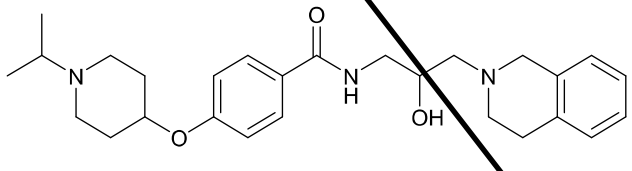
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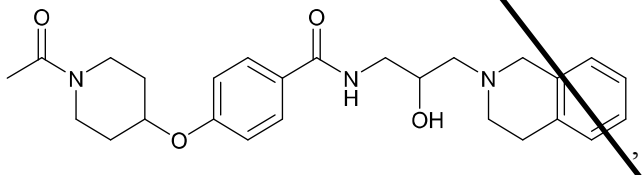
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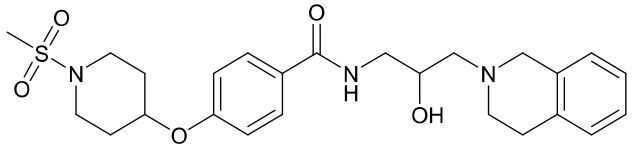
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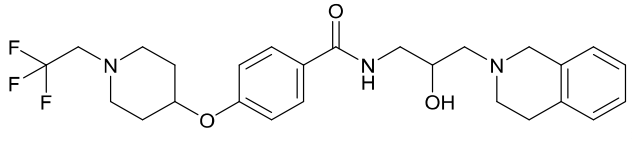
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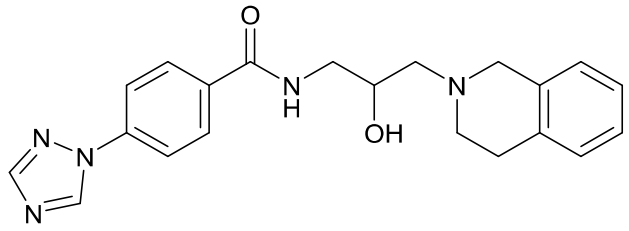
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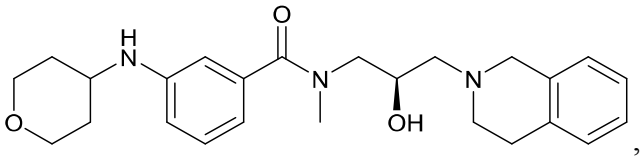
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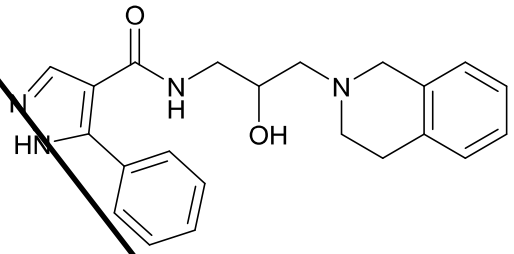
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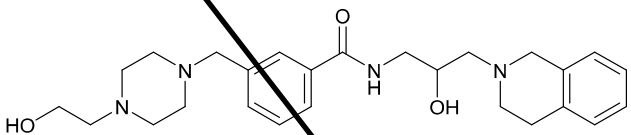
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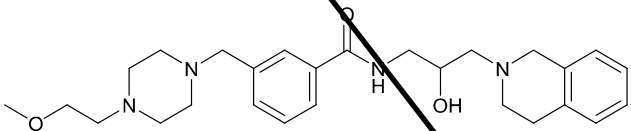
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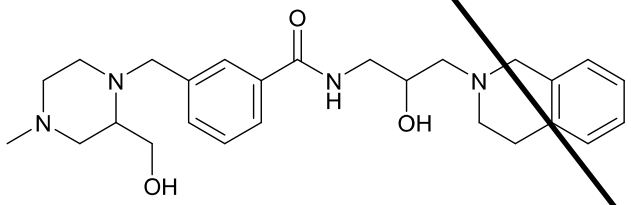
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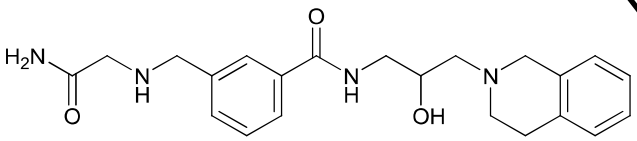
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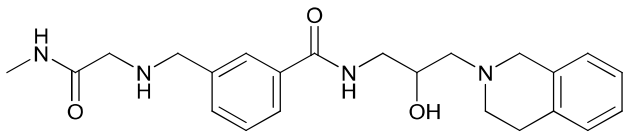
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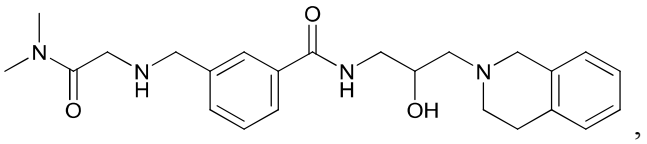
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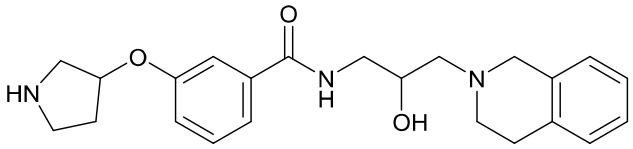
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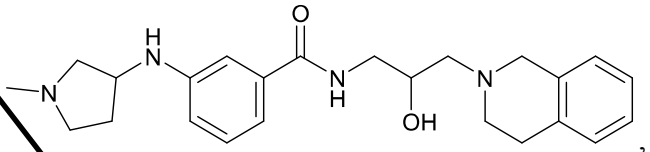
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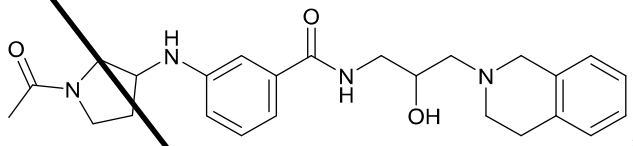
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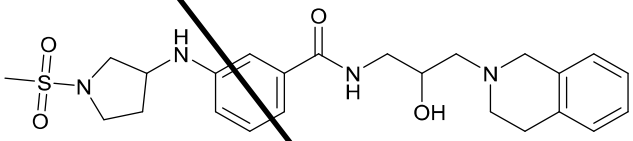
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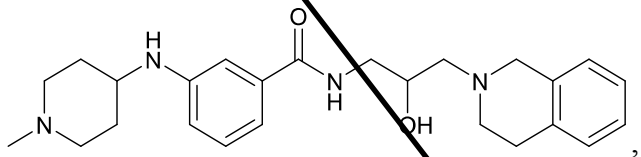
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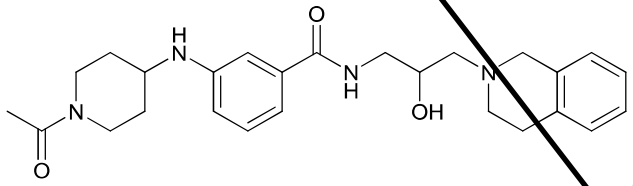
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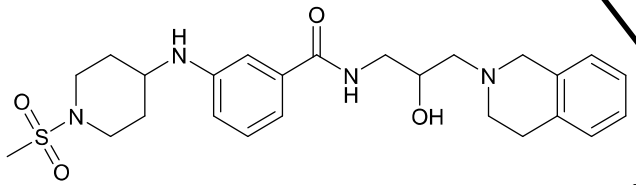
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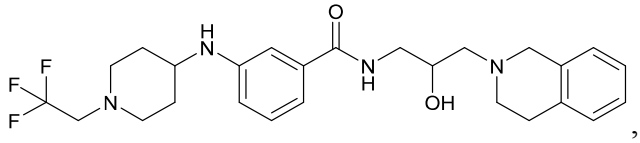
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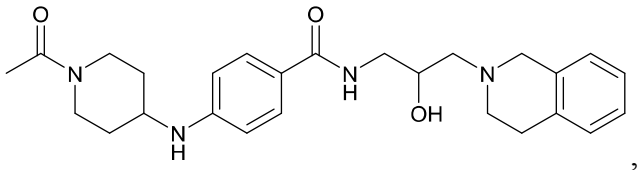
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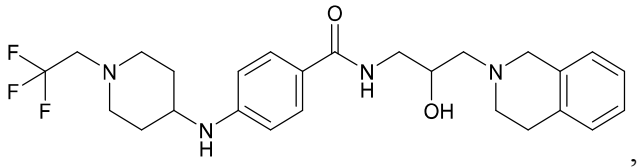
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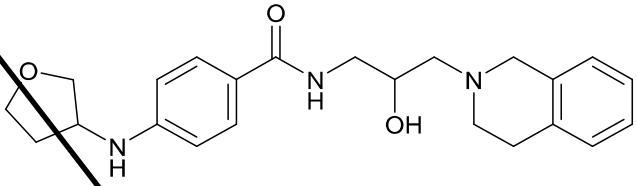
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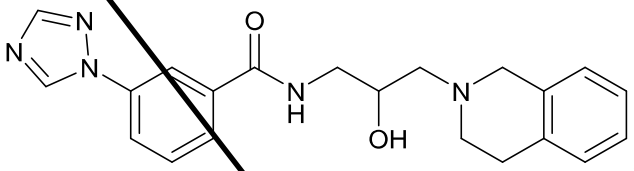
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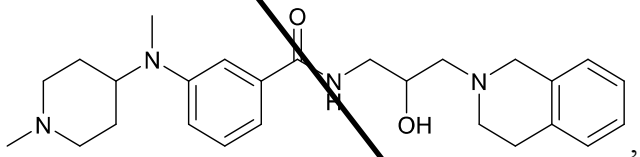
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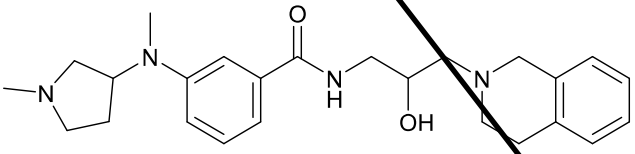
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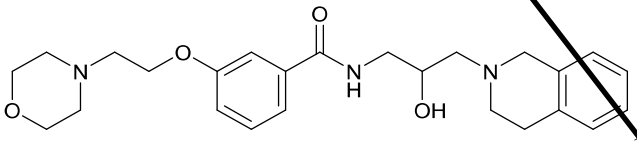
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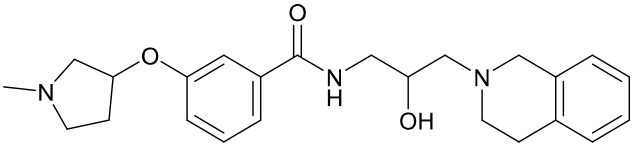
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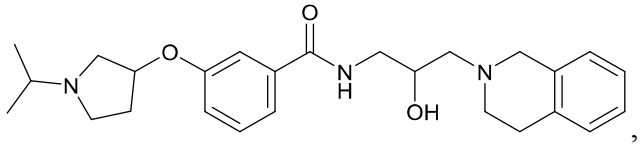
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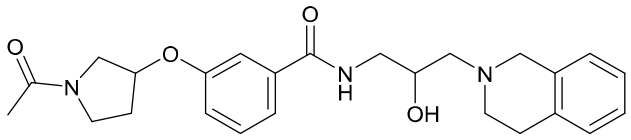
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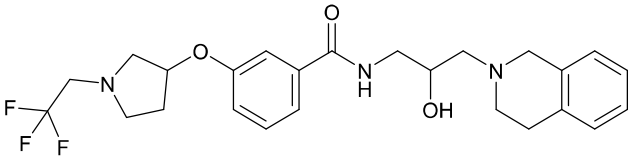
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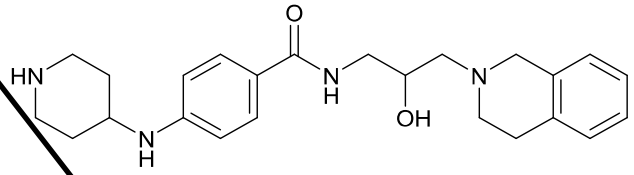
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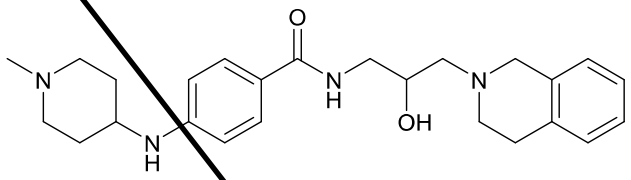
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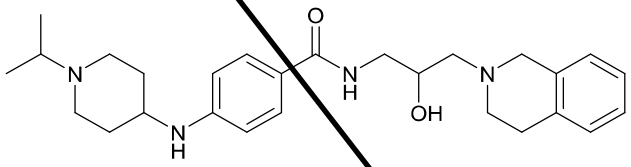
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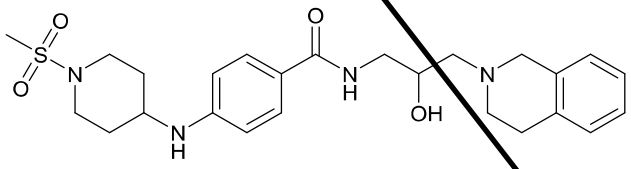
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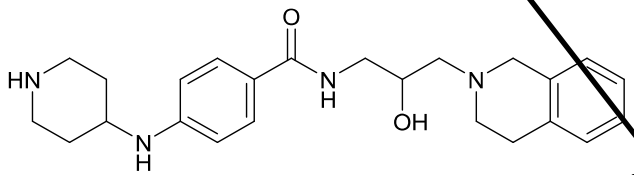
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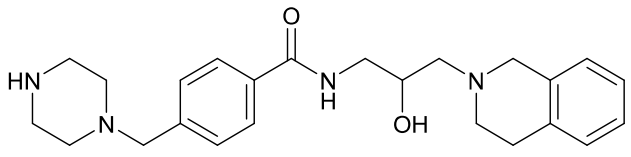
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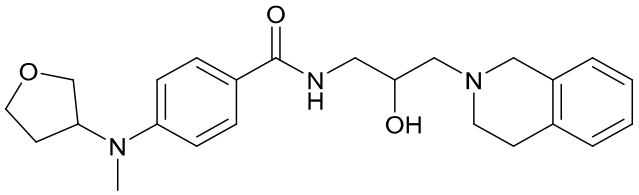
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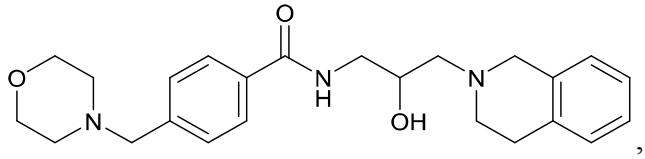
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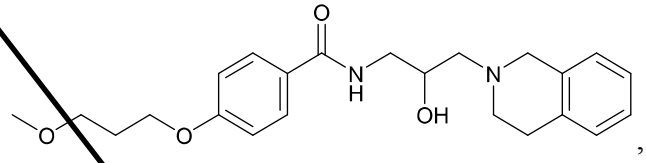
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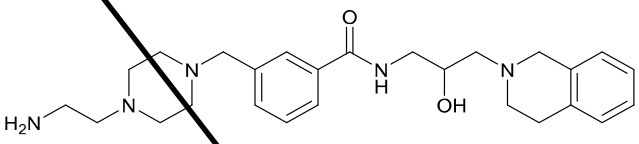
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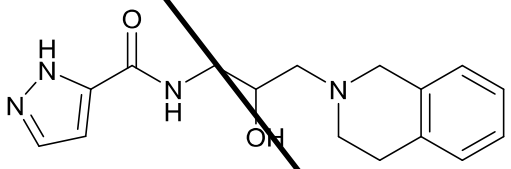
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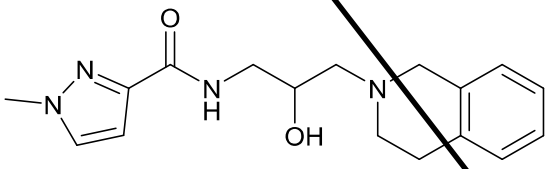
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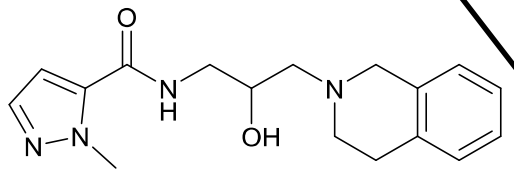
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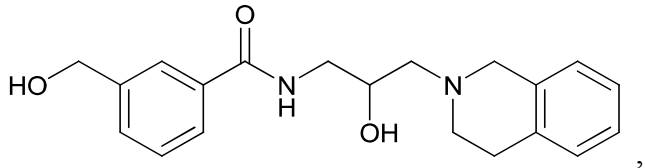
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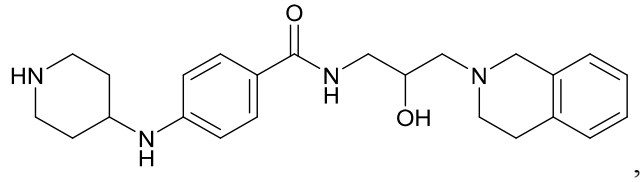
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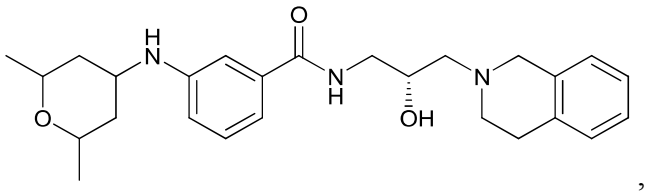
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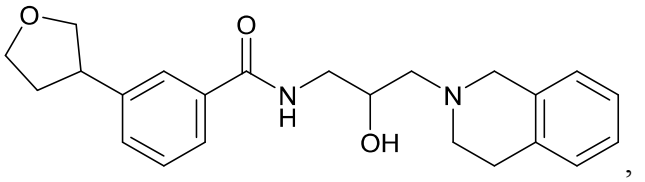
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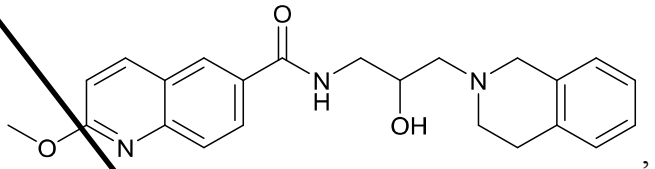
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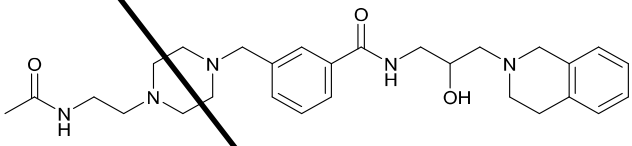
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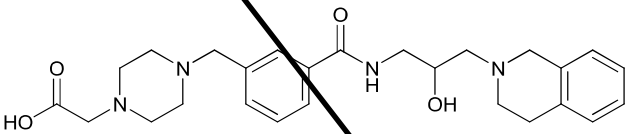
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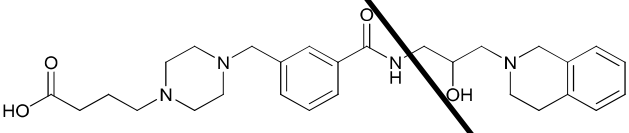
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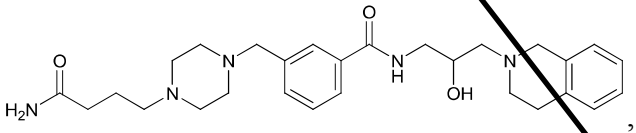
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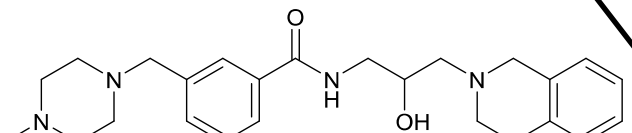
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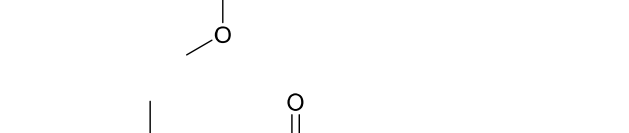
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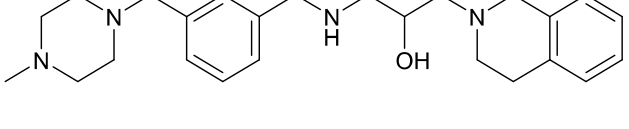
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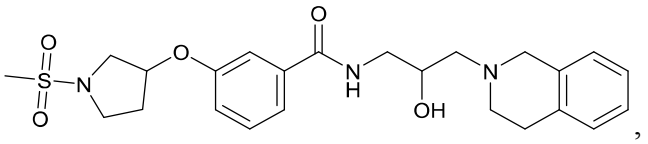
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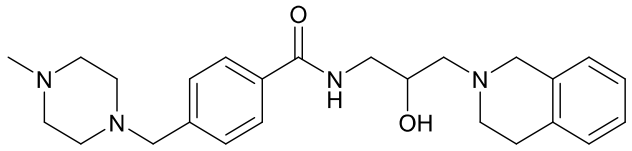
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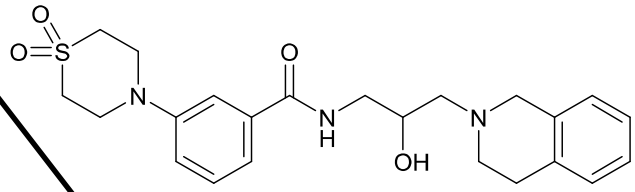
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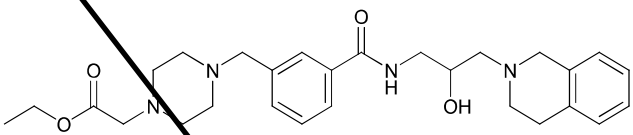
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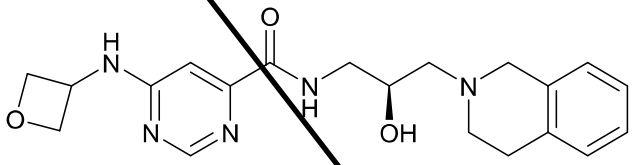
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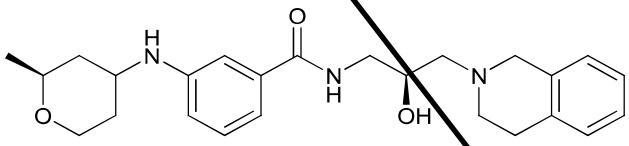
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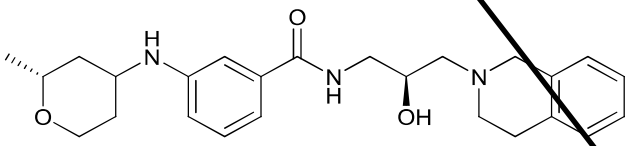
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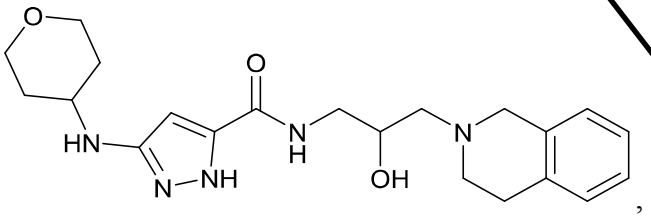
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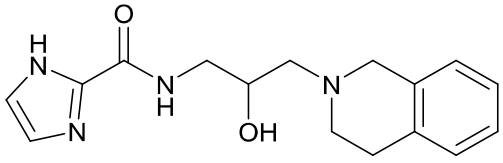
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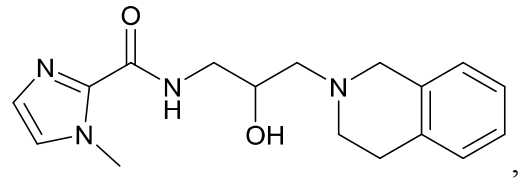
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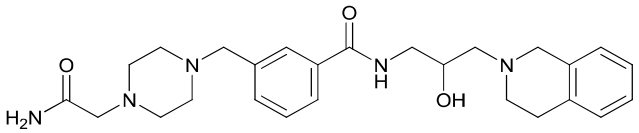
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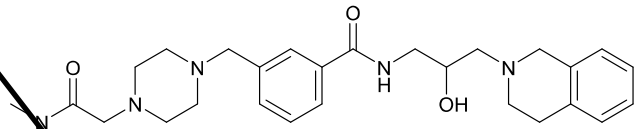
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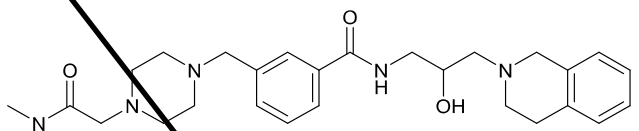
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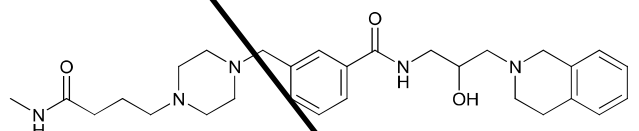
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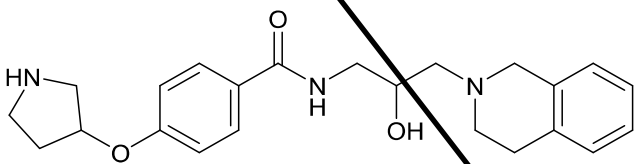
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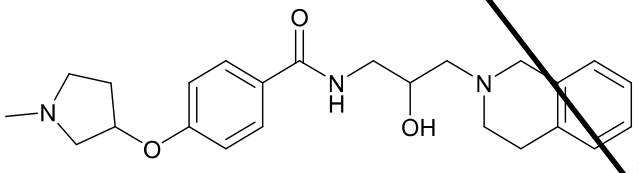
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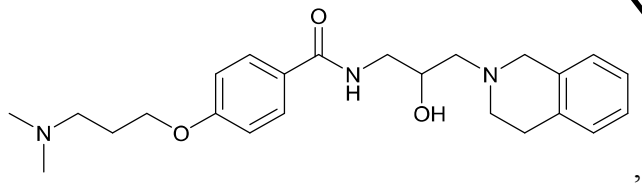
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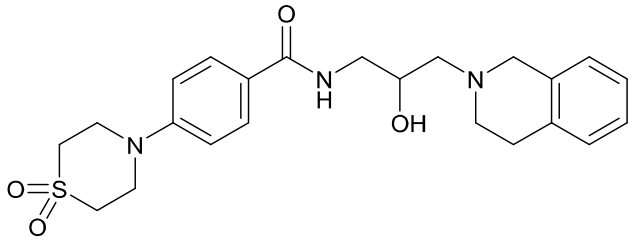
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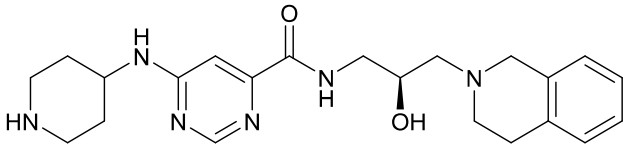
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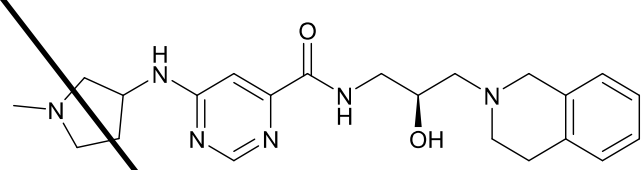
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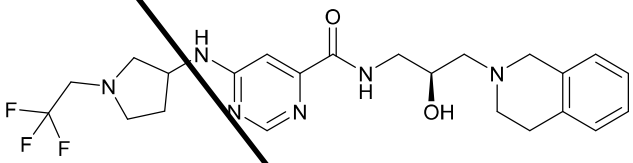
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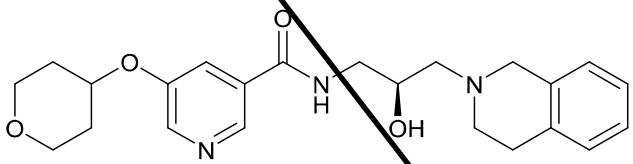
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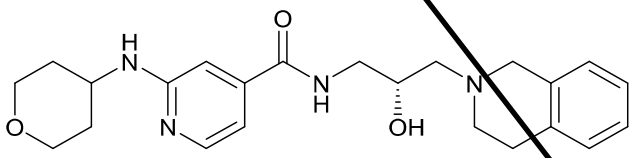
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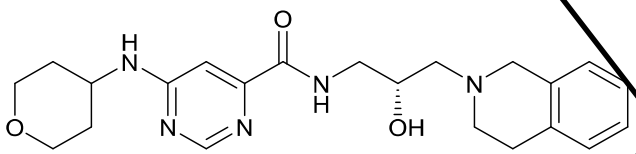
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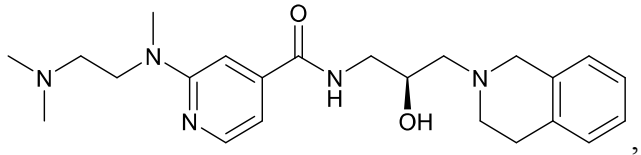
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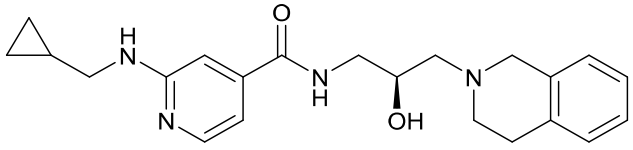
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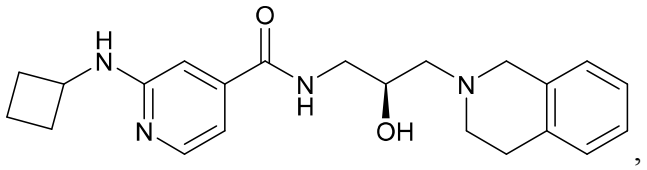
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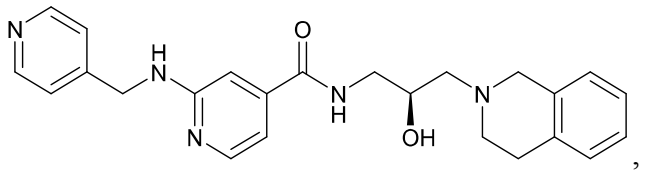
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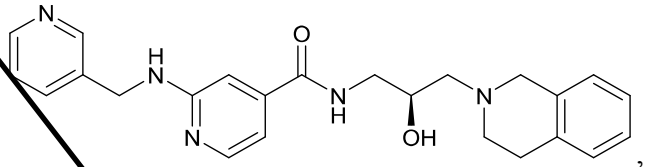
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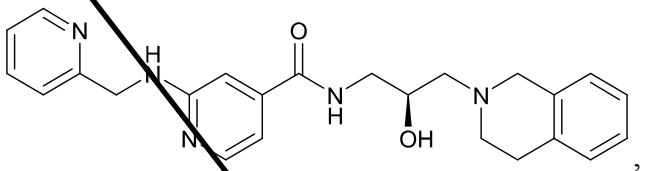
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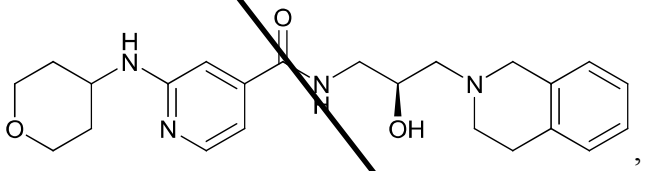
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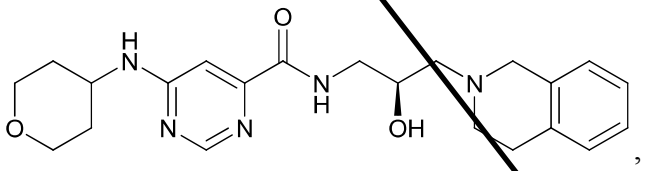
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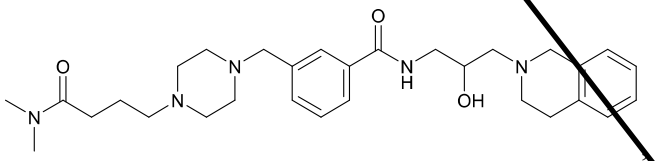
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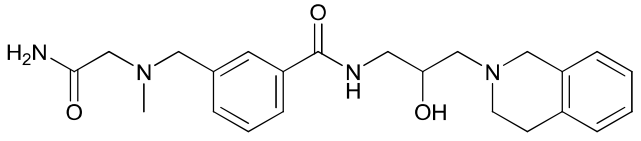
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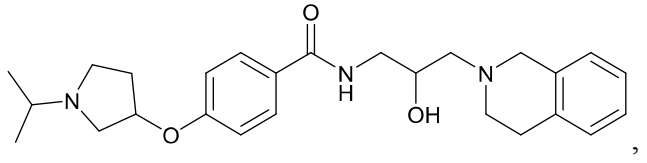
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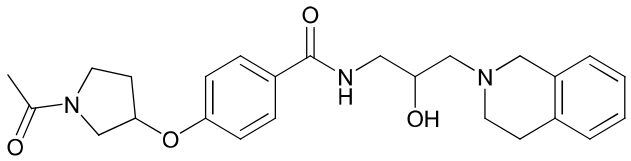
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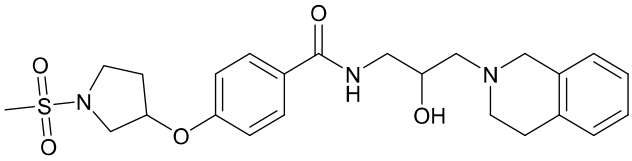
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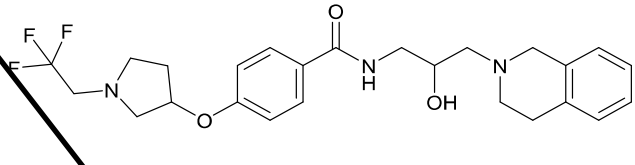
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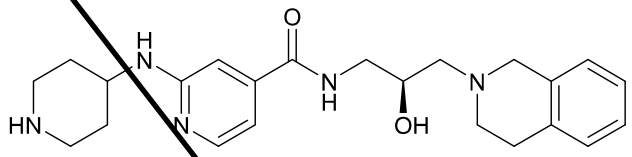
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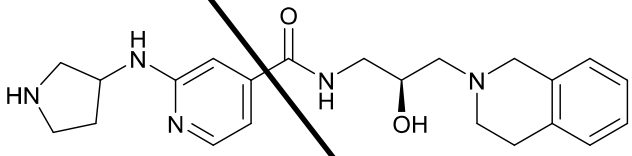
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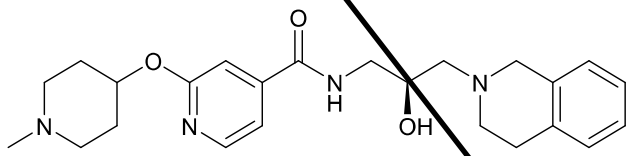
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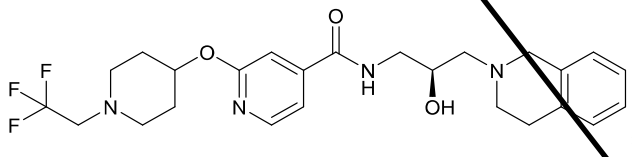
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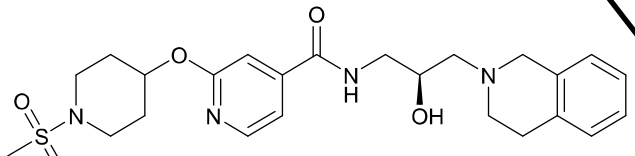
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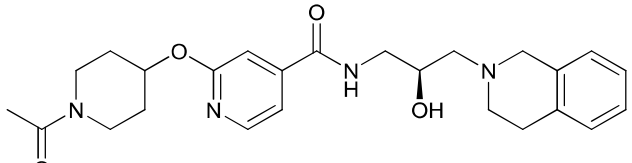
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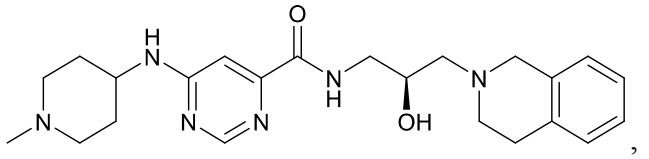
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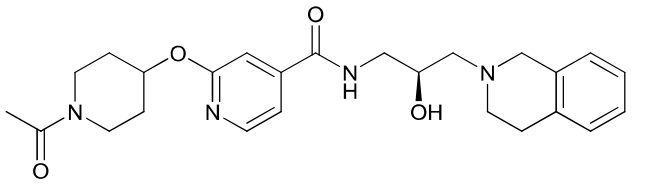
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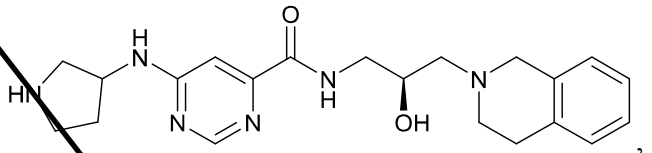
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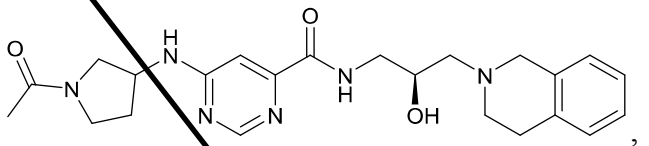
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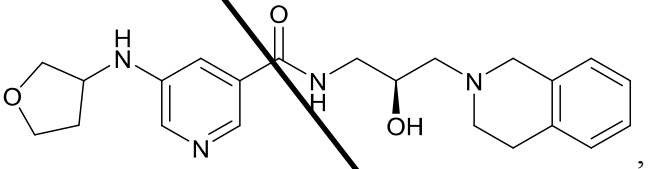
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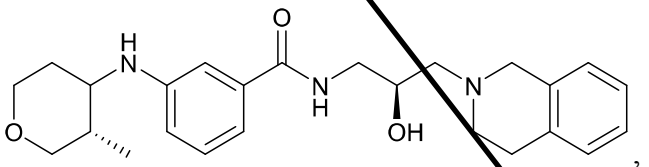
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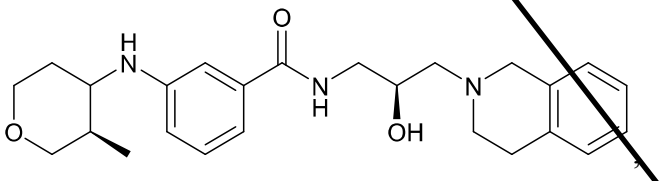
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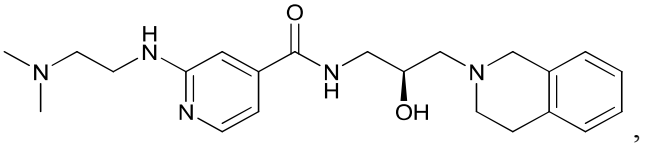
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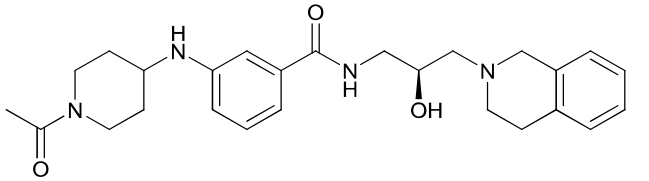
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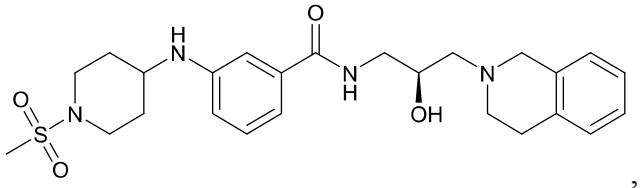
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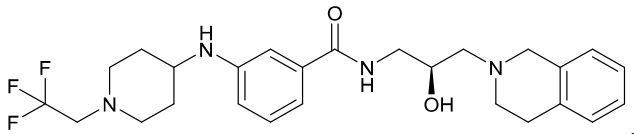
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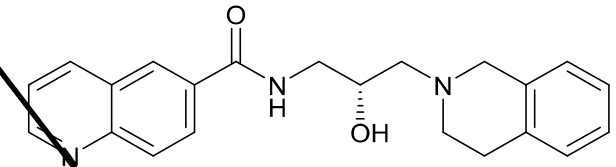
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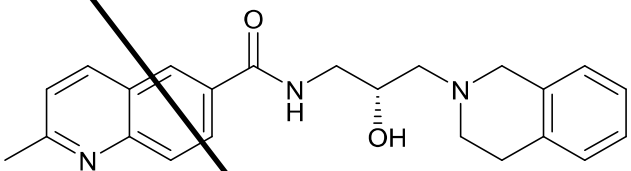
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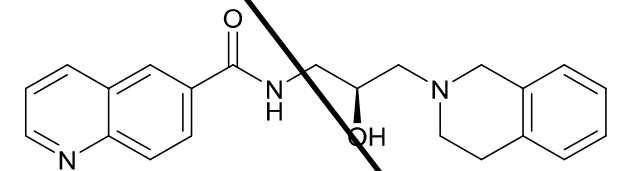
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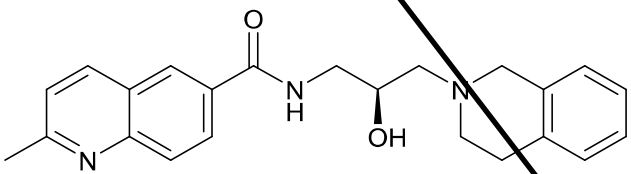
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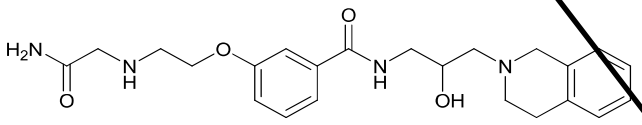
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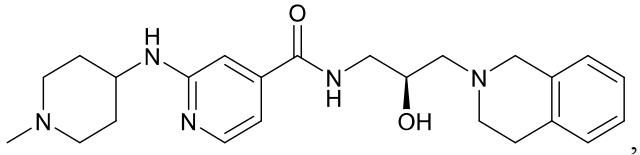
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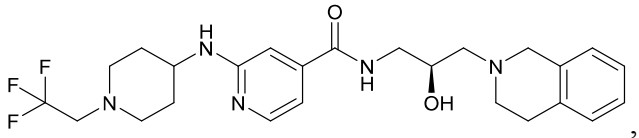
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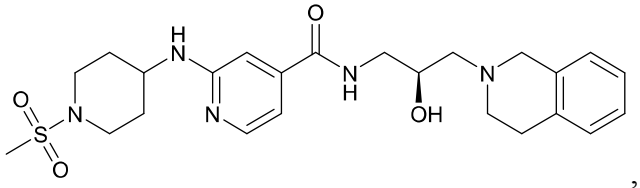
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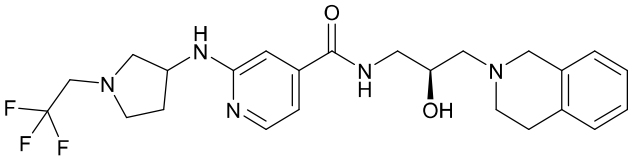
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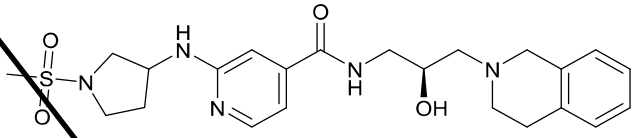
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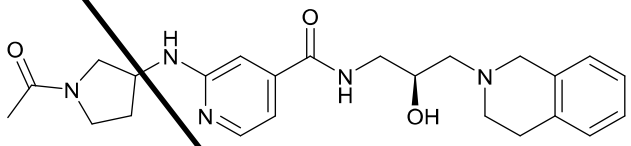
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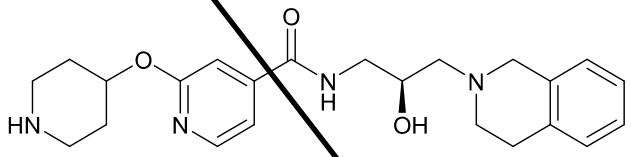
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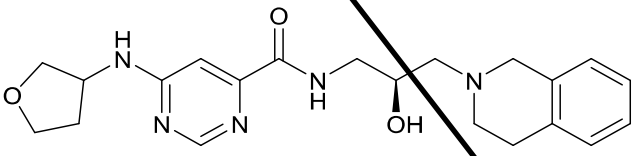
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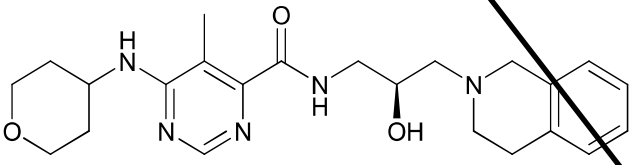
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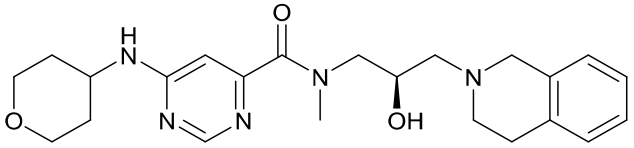
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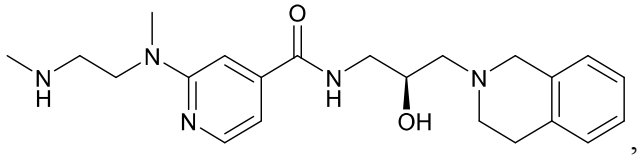
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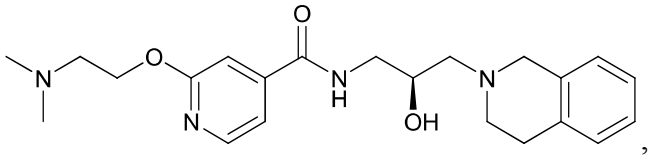
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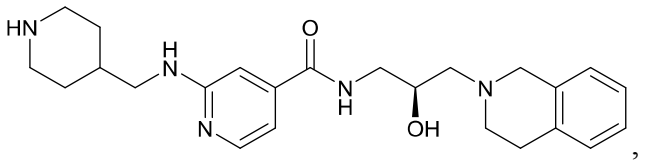
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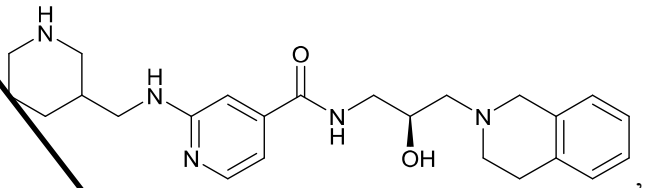
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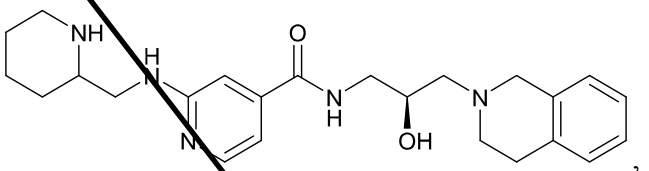
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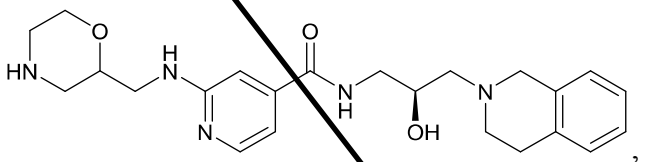
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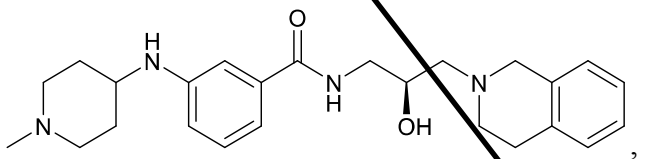
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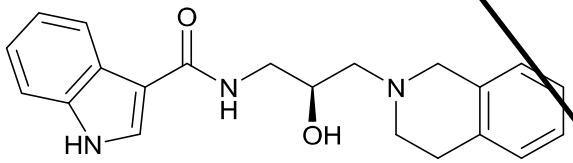
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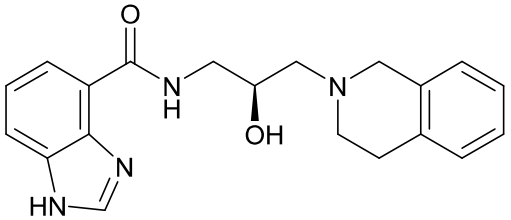
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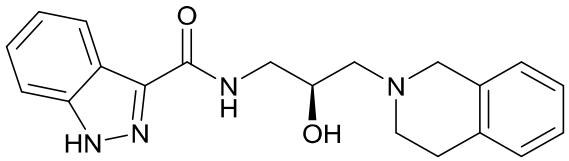
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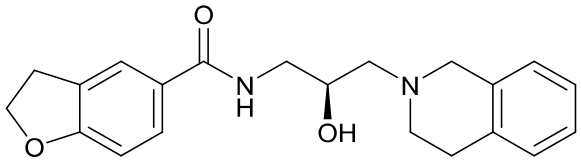
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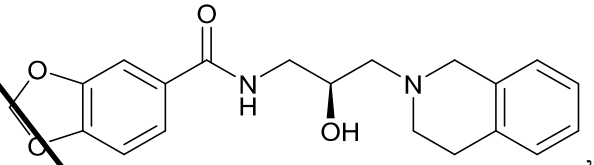
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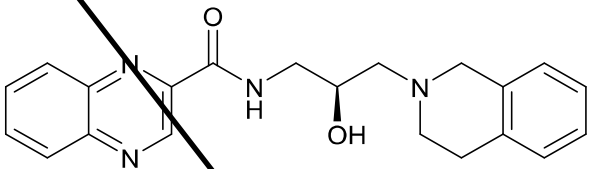
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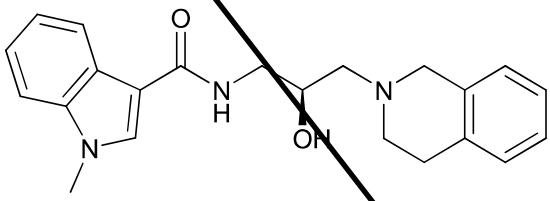
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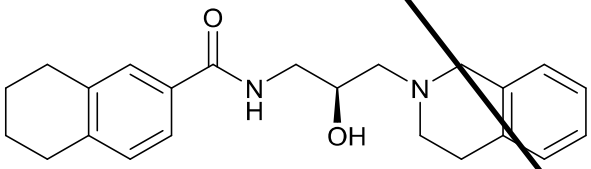
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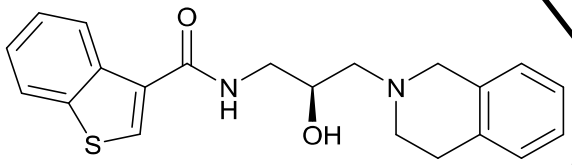
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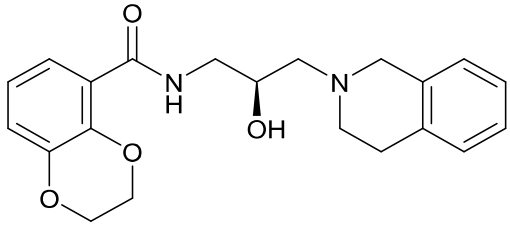
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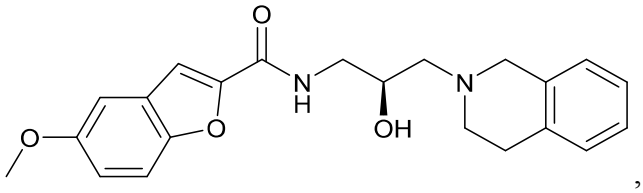
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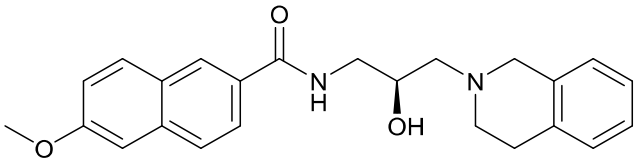
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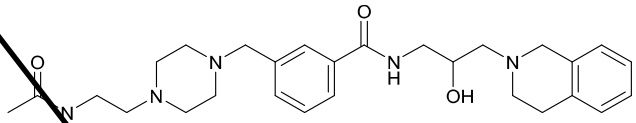
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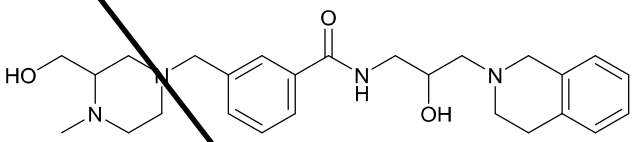
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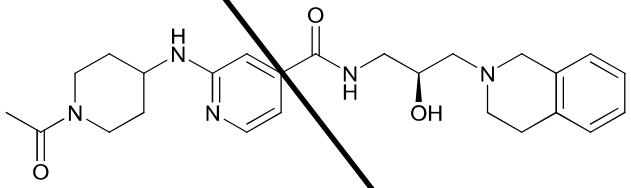
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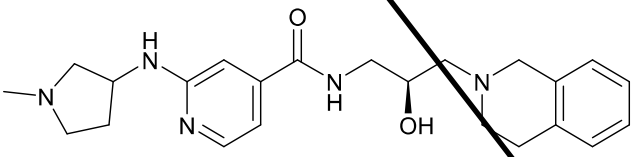
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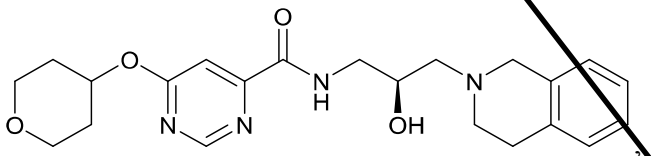
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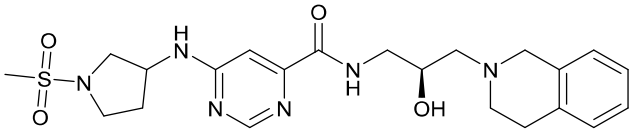
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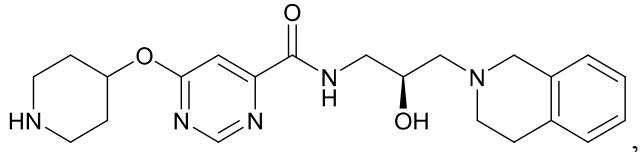
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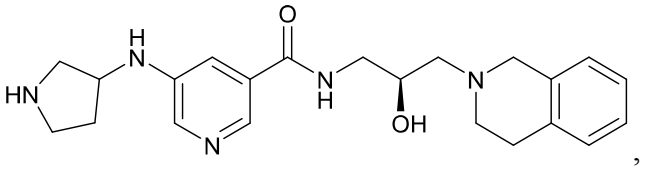
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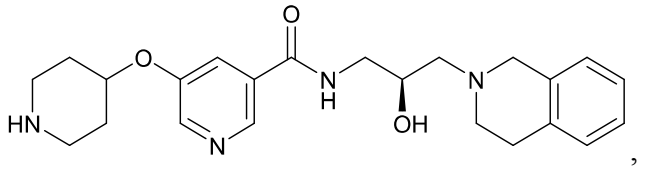
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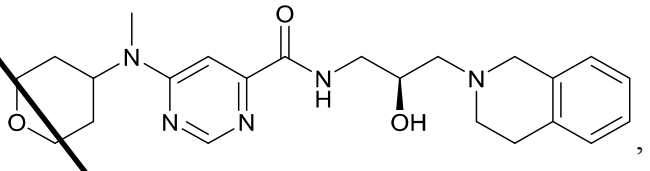
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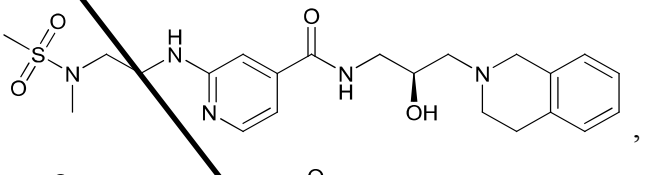
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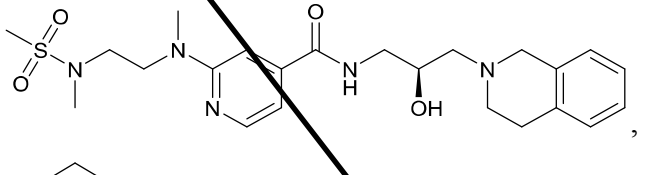
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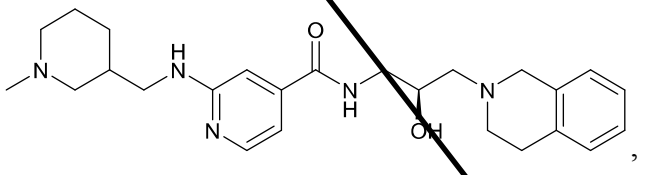
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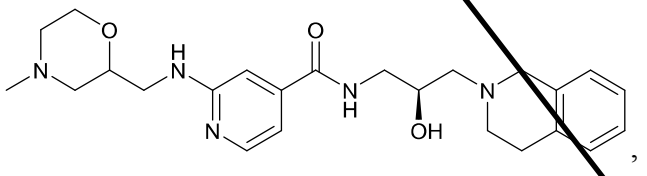
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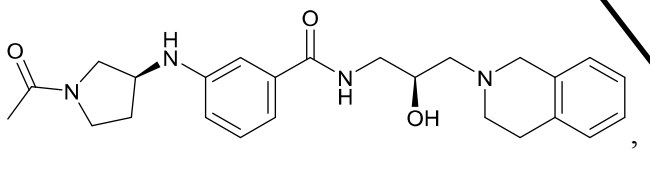
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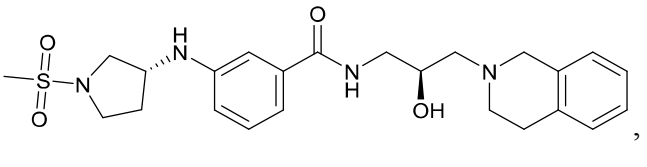
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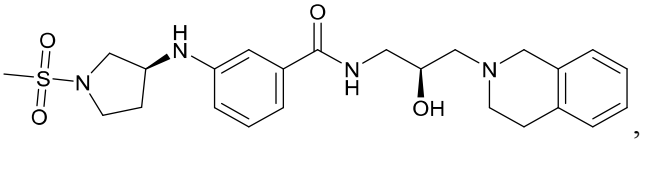
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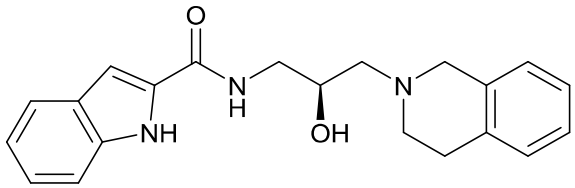
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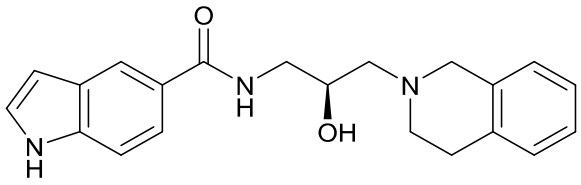
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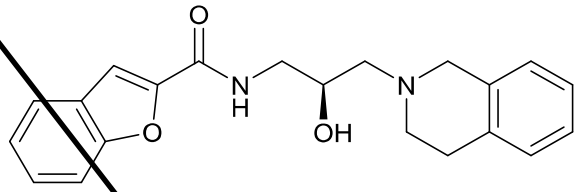
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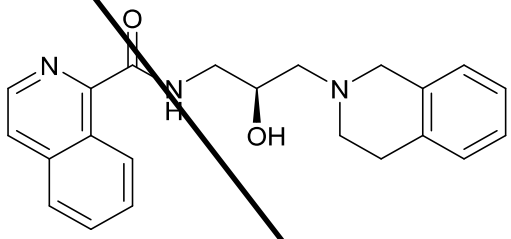
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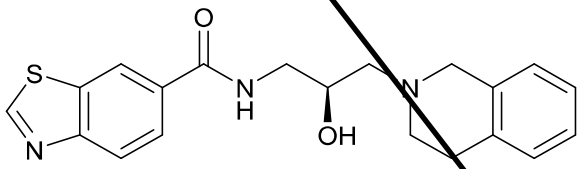
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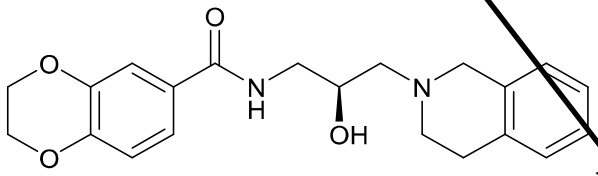
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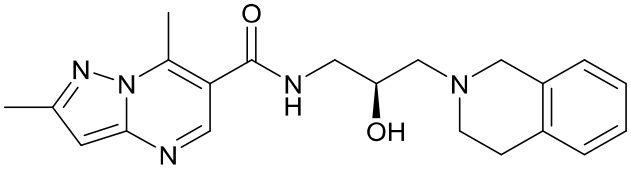
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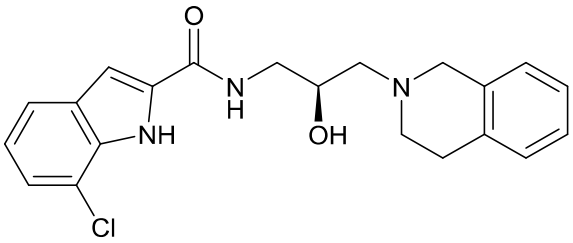
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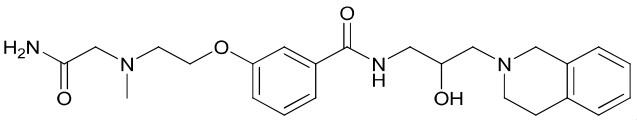
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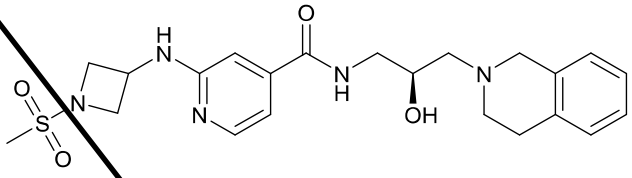
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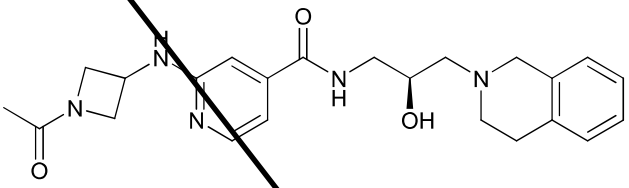
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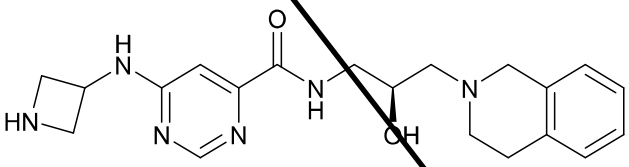
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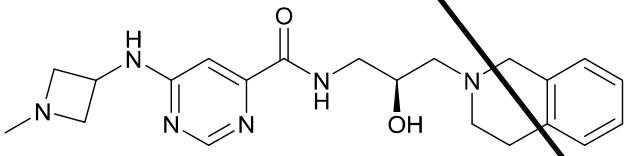
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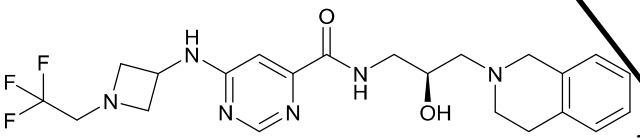
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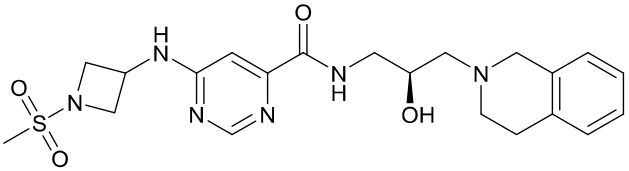
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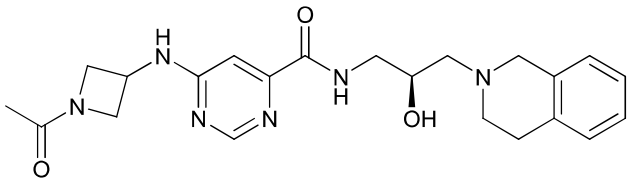
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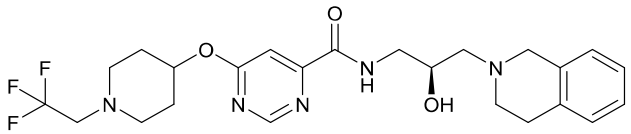
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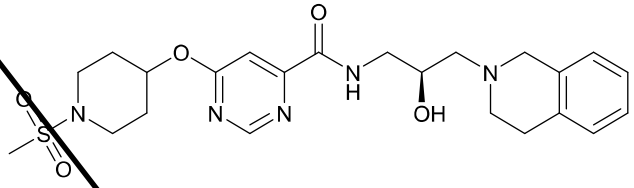
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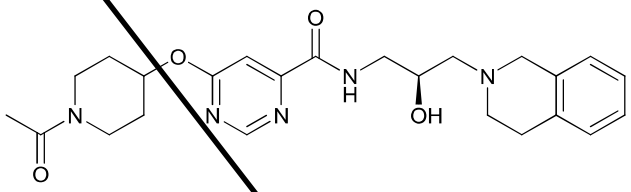
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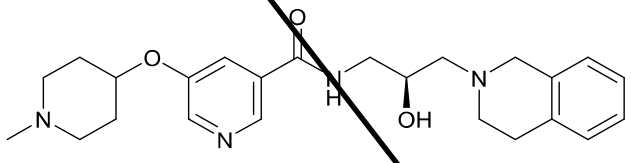
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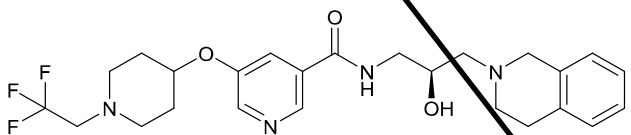
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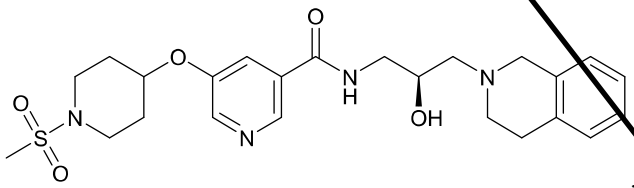
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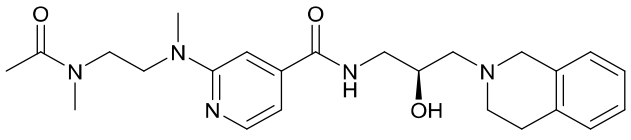
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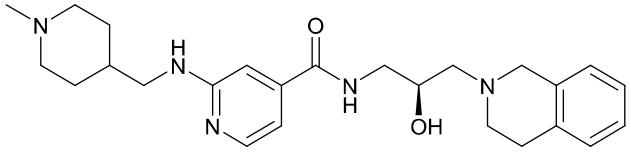
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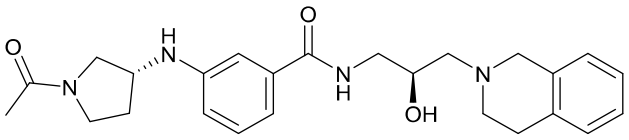
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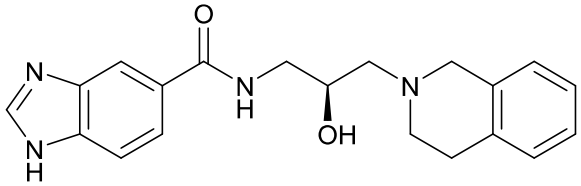
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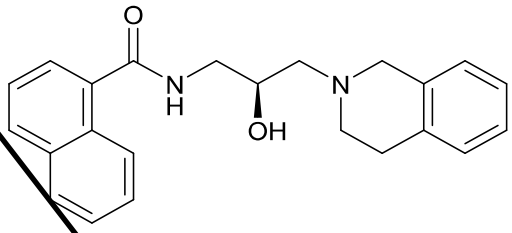
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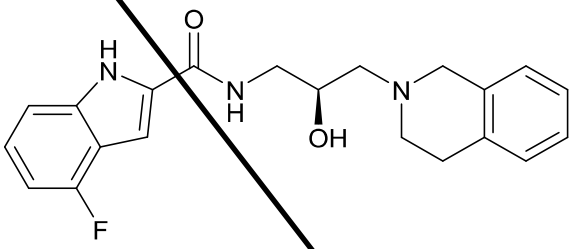
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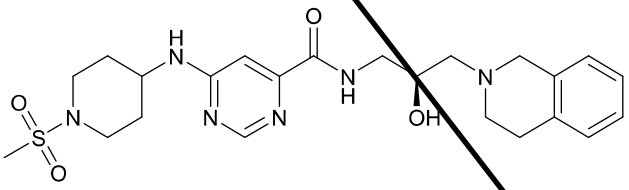
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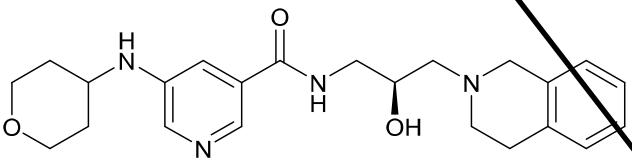
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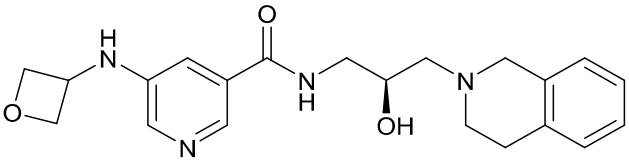
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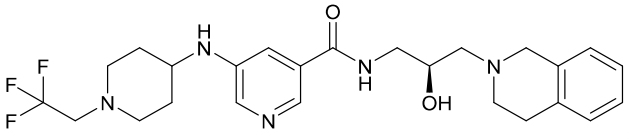
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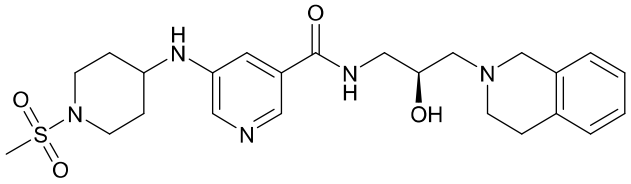
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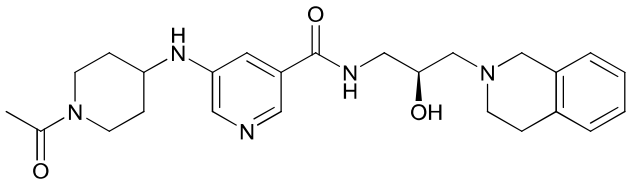
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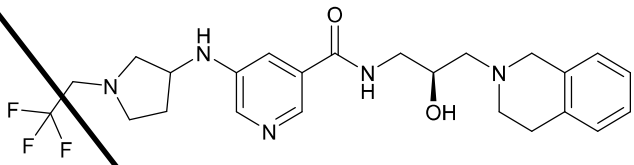
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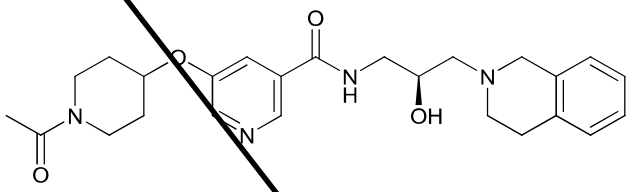
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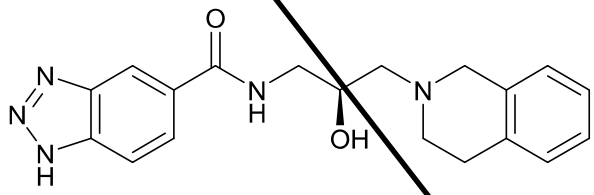
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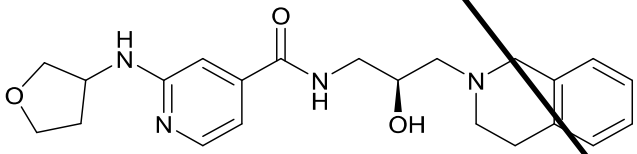
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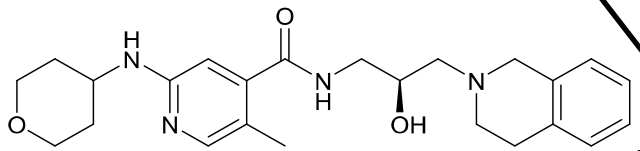
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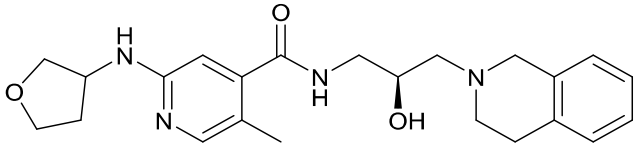
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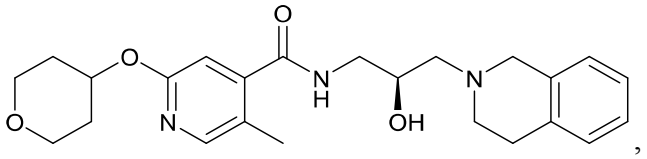
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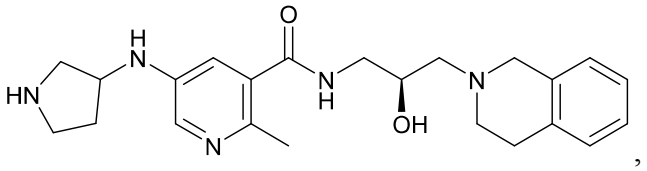
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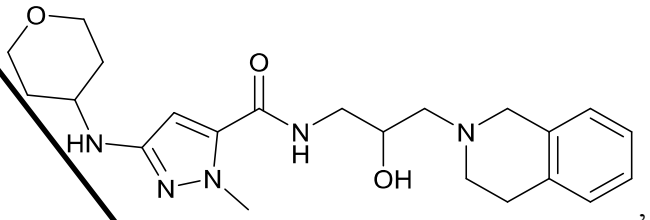
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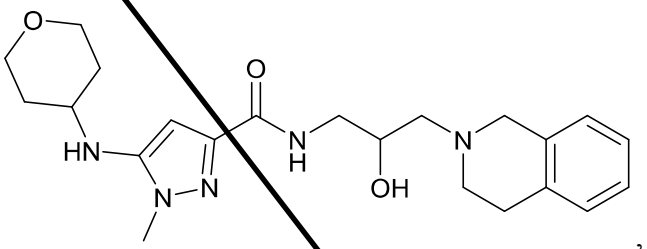
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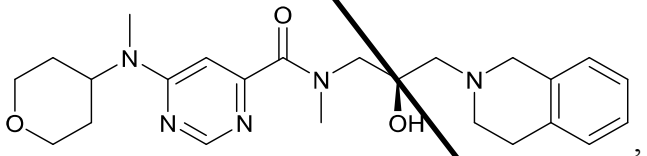
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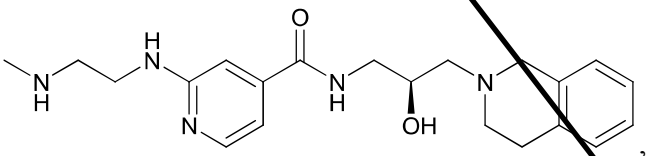
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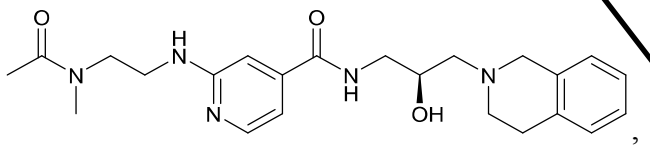
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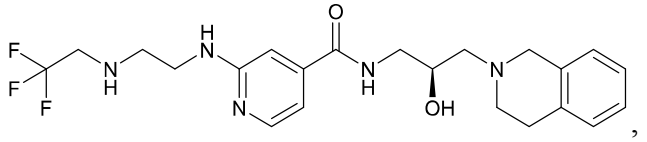
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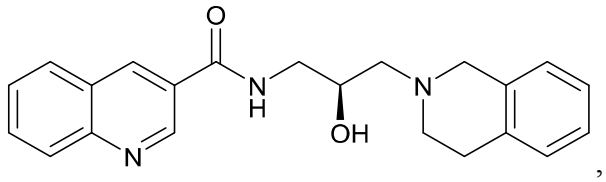
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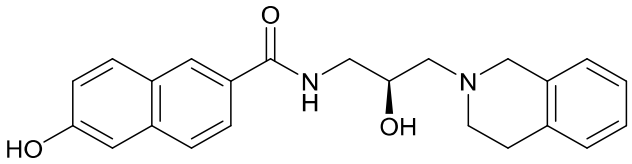
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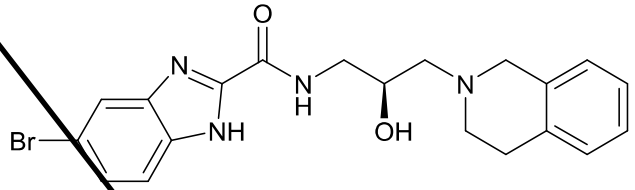
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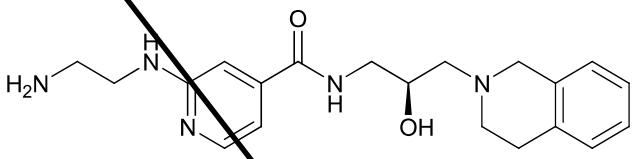
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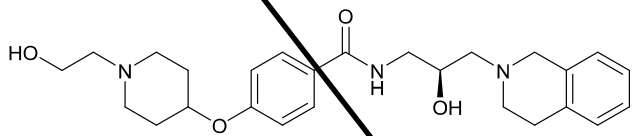
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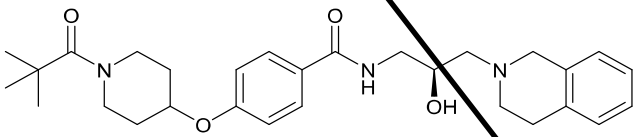
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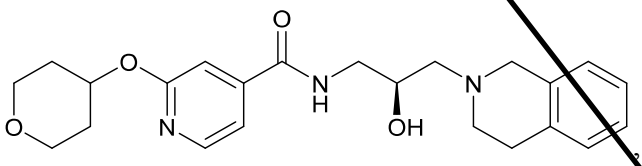
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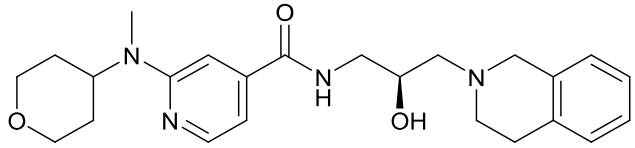
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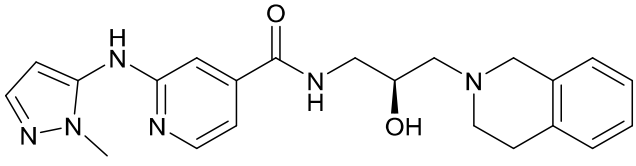
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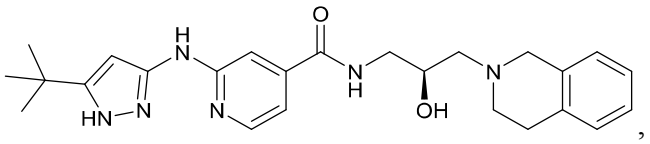
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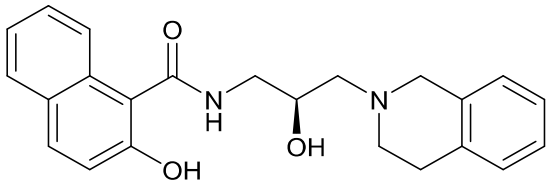
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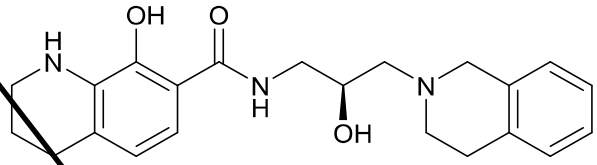
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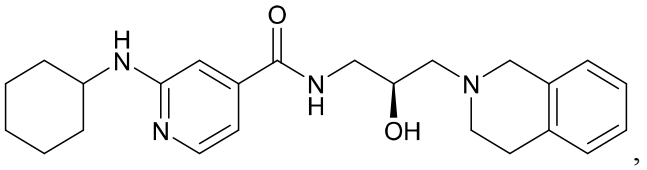
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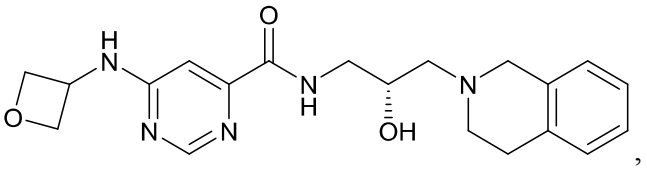
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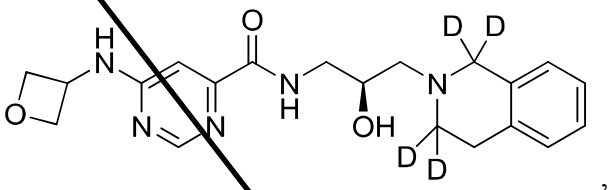
and pharmaceutically acceptable salts thereof.

109. The compound of claim 1, wherein the compound is selected from the group consisting of: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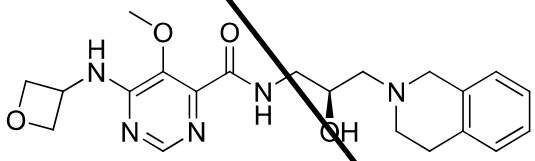
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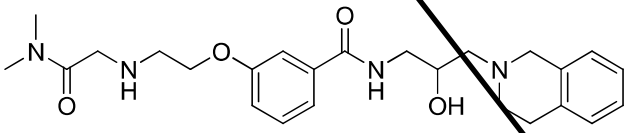
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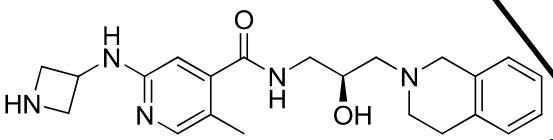
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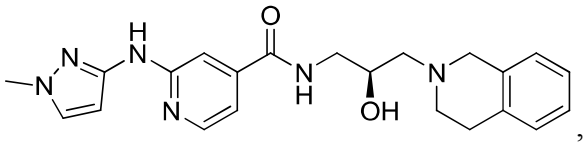
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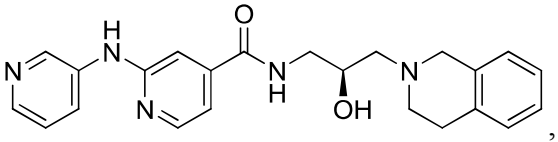
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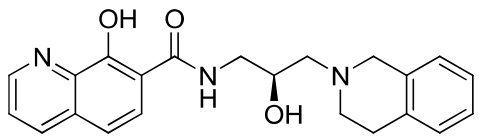
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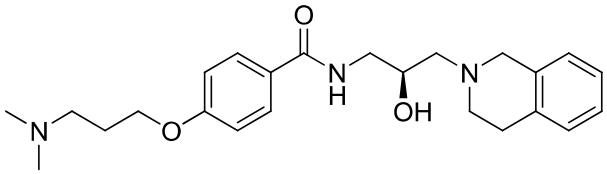
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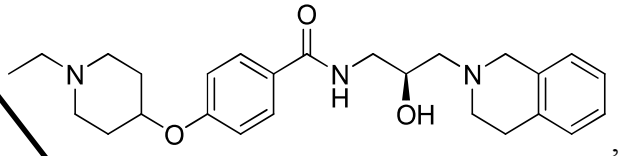
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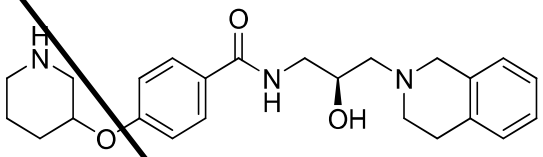
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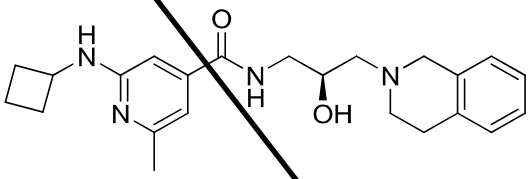
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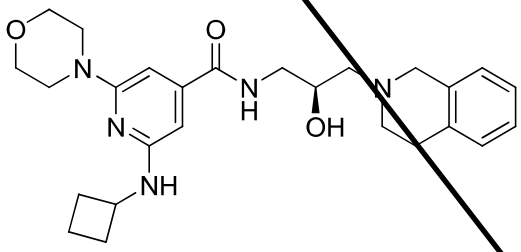
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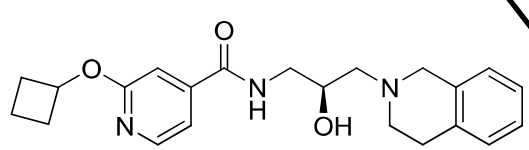
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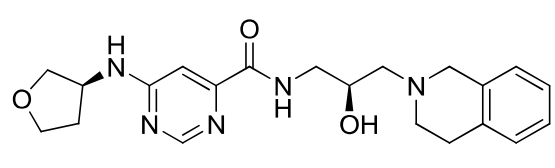
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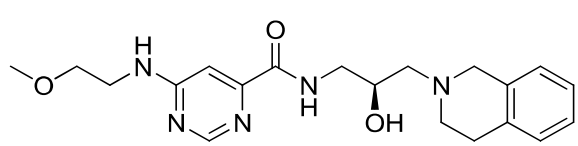
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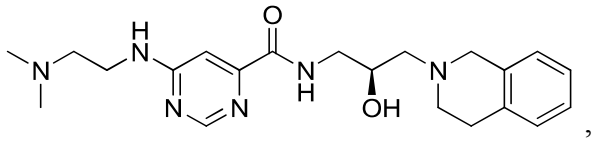
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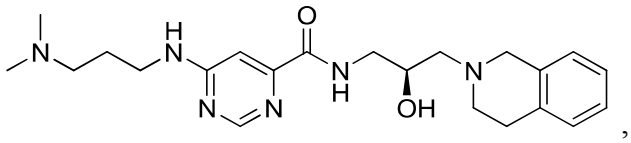
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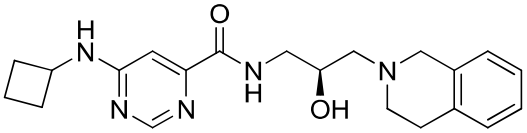
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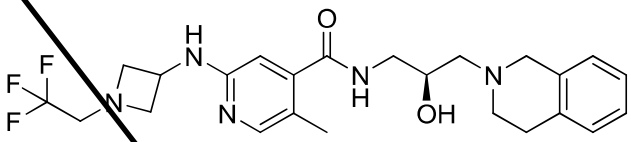
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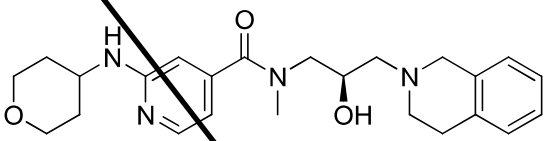
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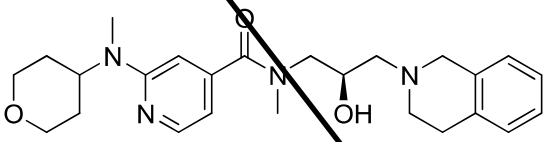
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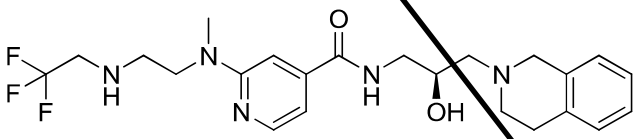
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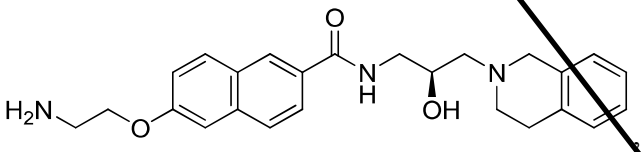
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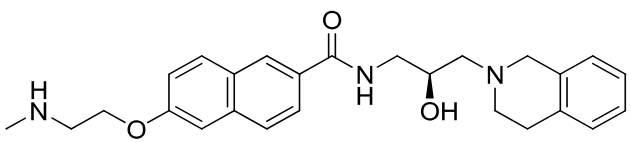
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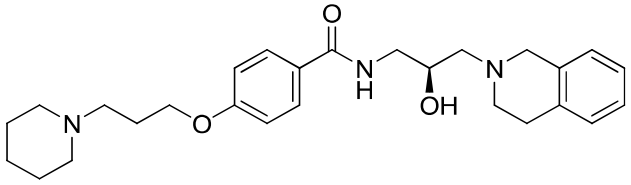
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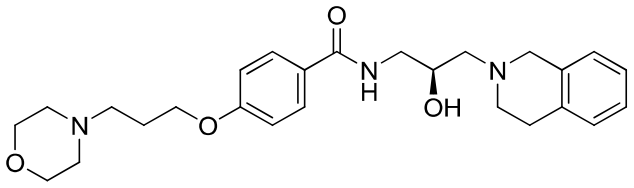

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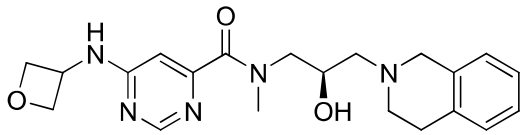

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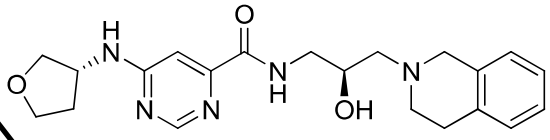

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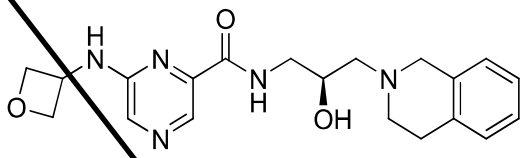

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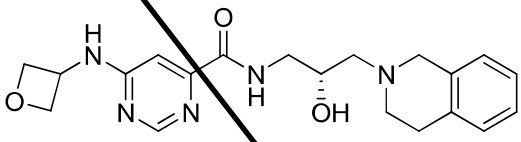

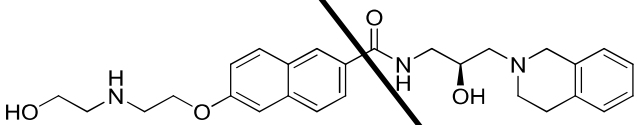

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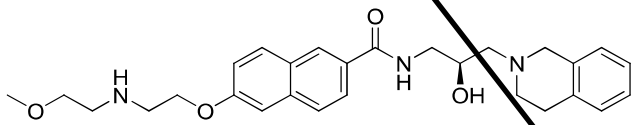

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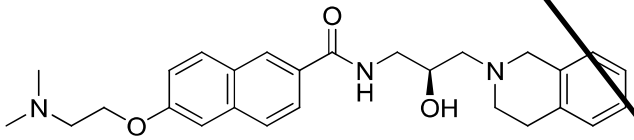

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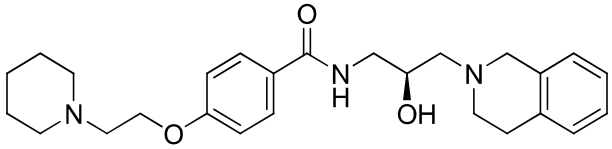

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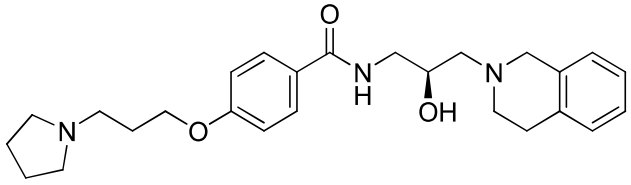

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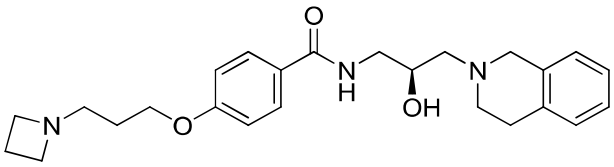
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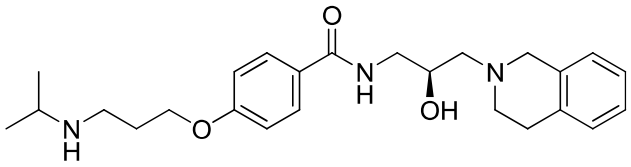
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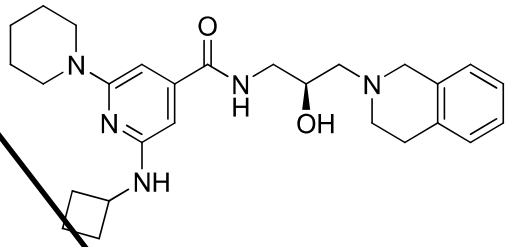
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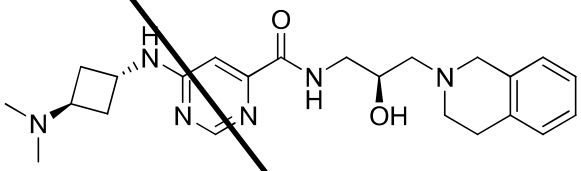
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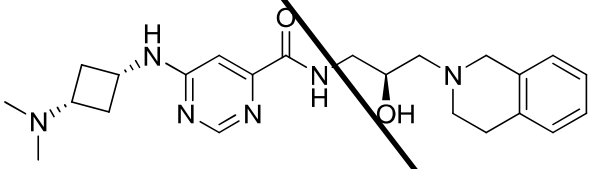
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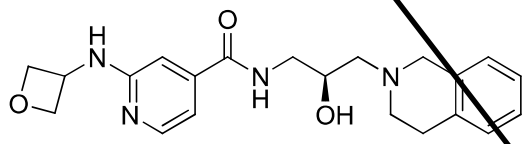
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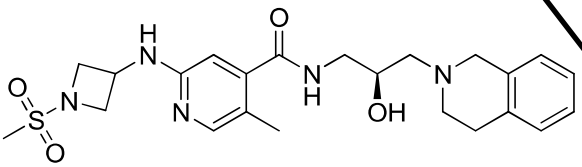
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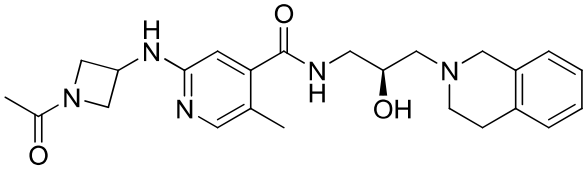
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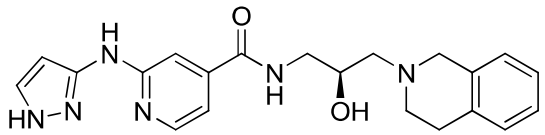
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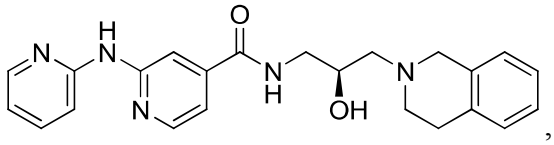
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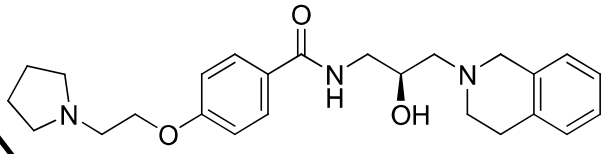
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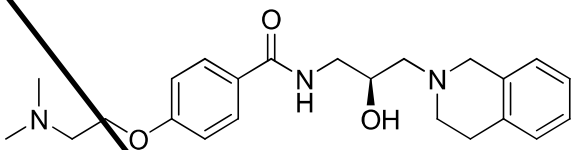
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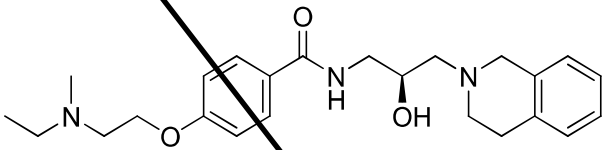
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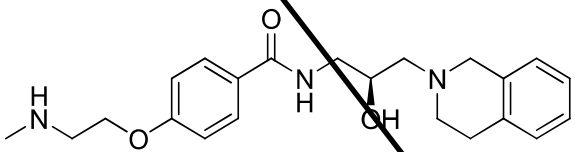
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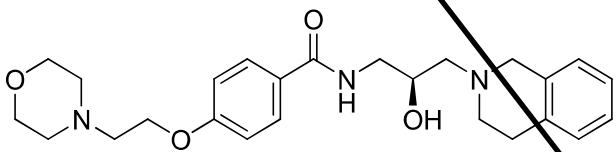
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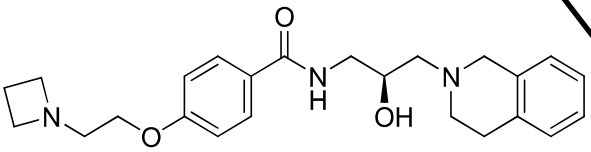
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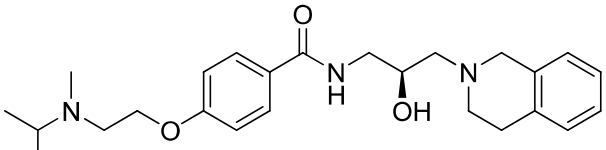

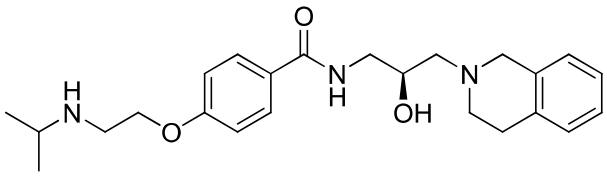
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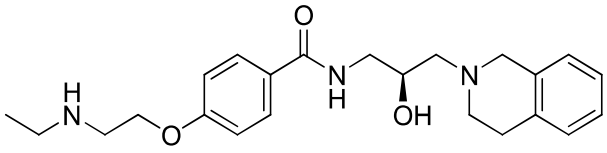
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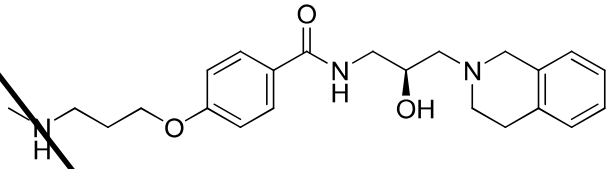
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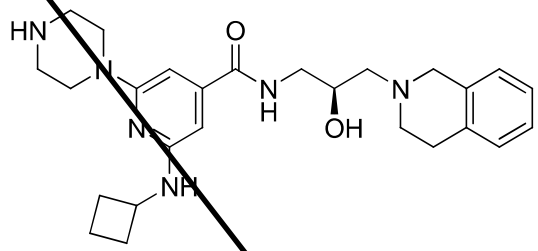
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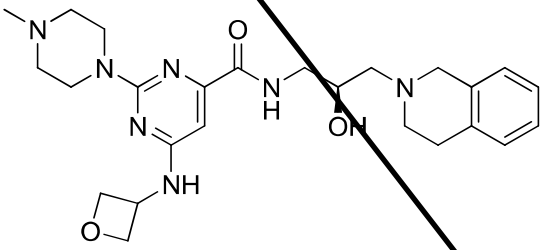
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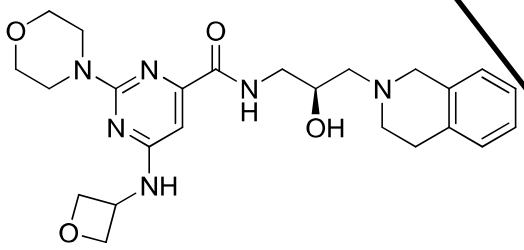
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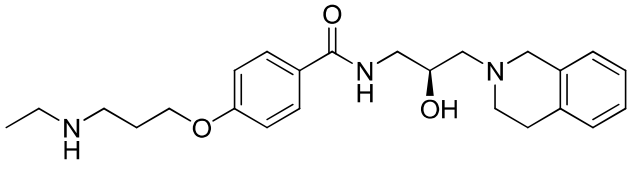
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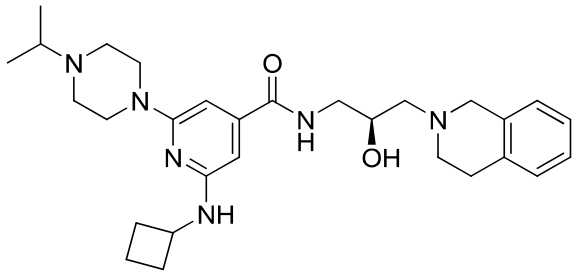
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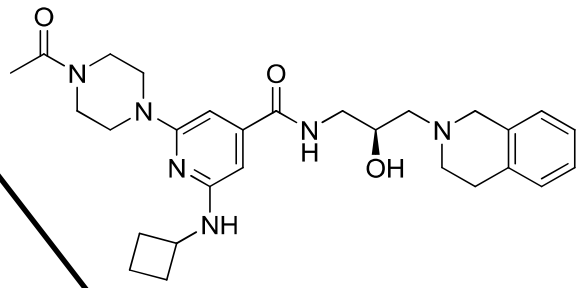
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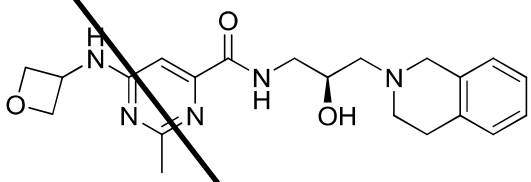
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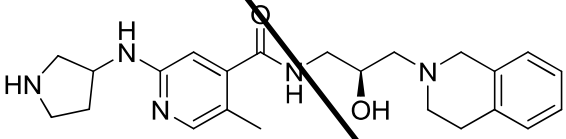
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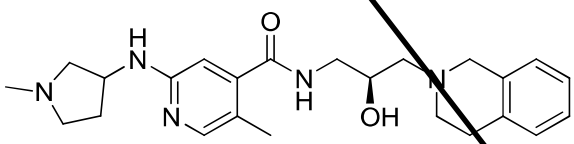
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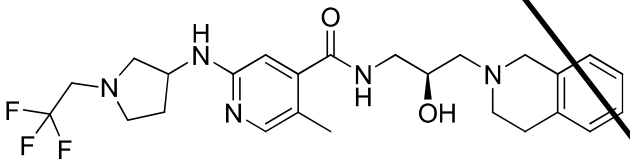
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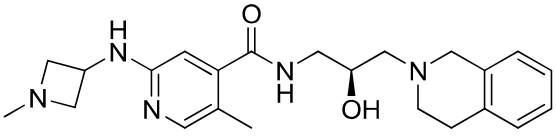
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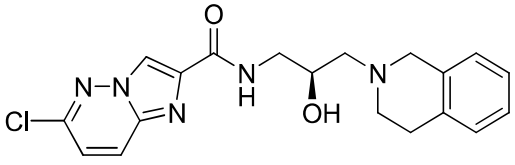
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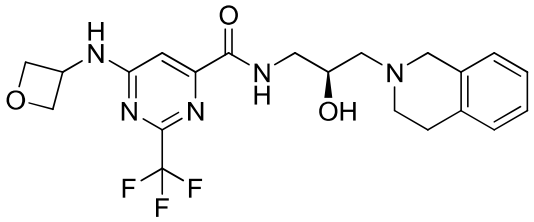
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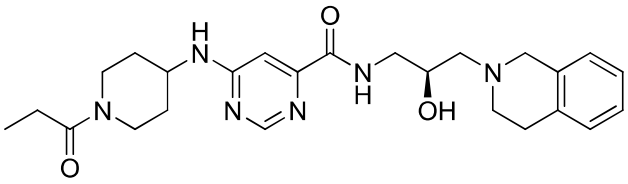
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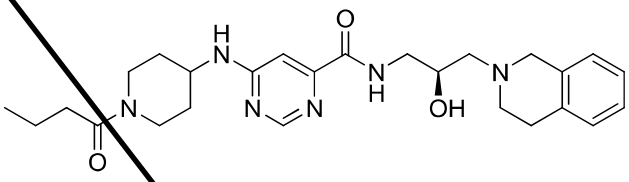
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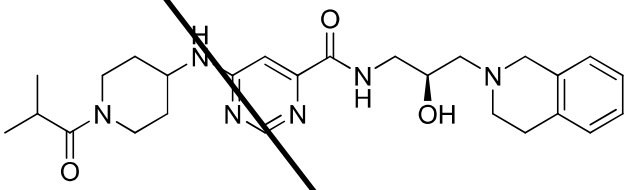
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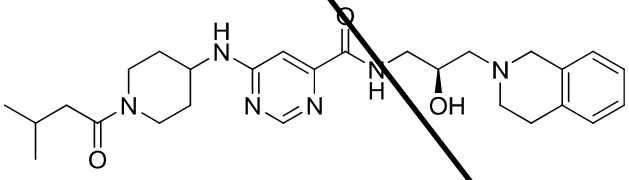
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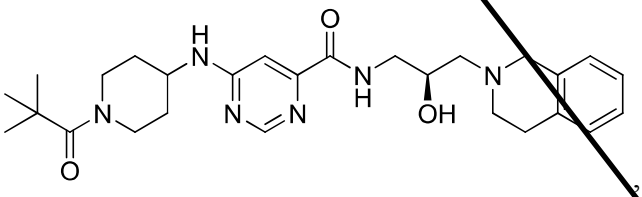
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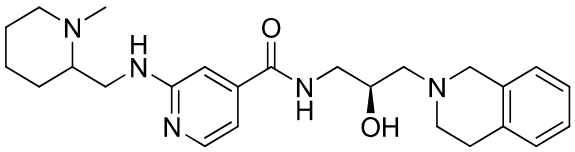
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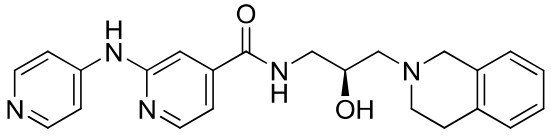
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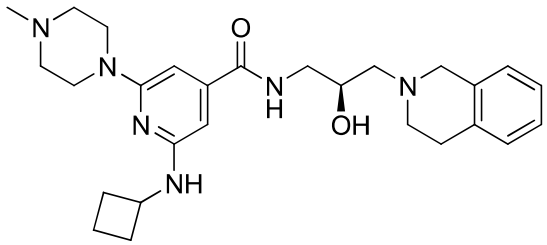
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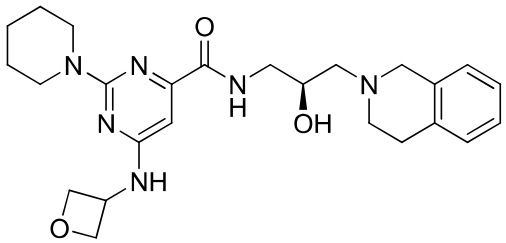
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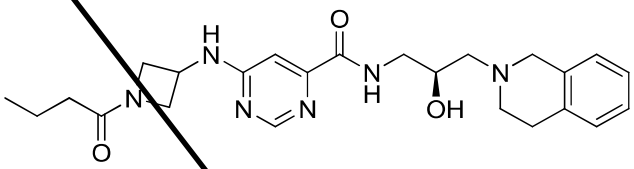
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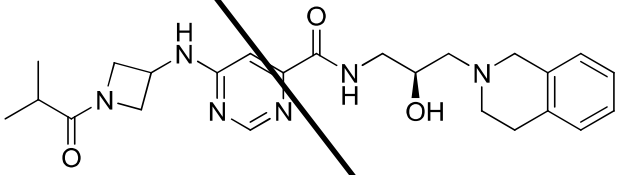
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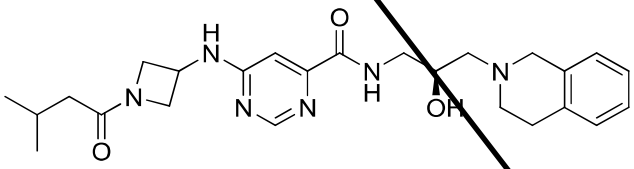
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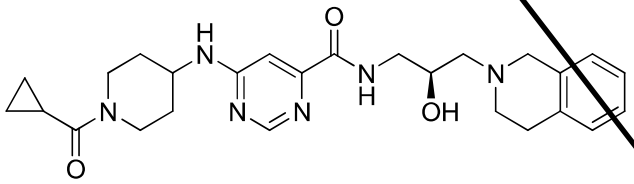
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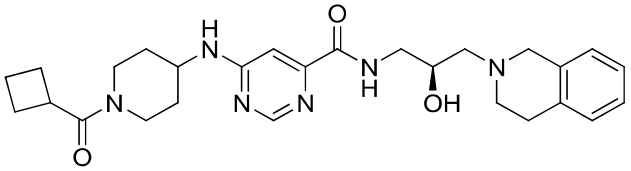
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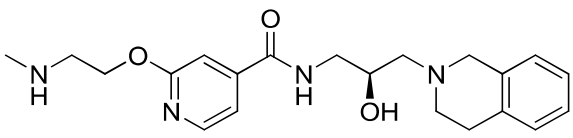
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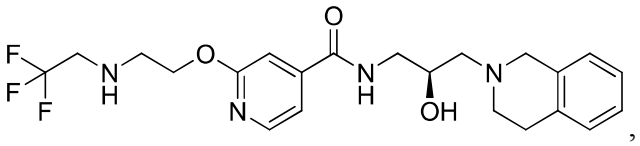
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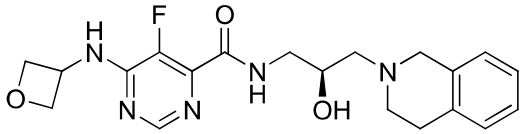
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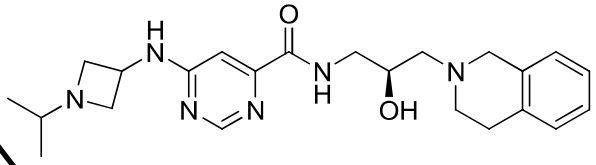
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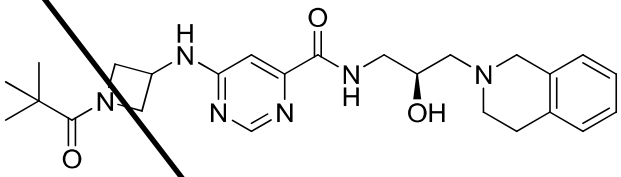
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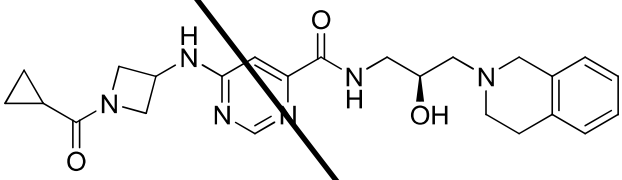
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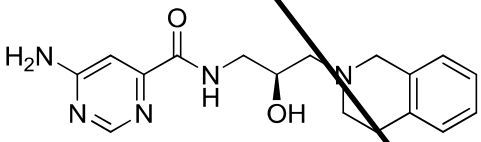
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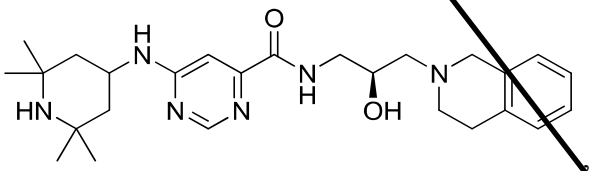
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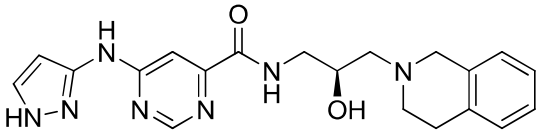
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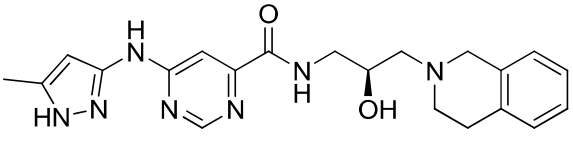
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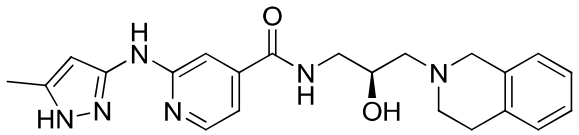
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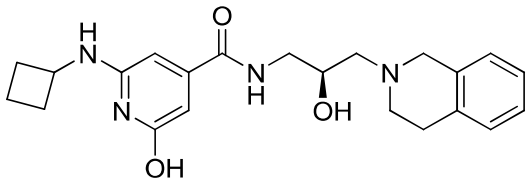
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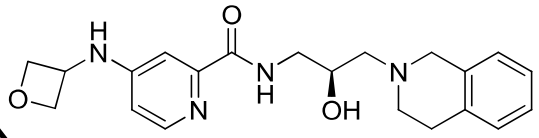
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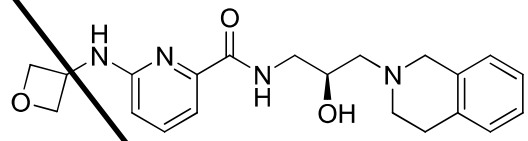
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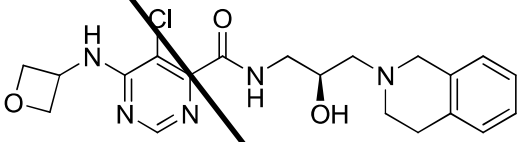
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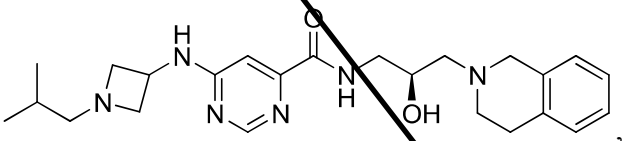
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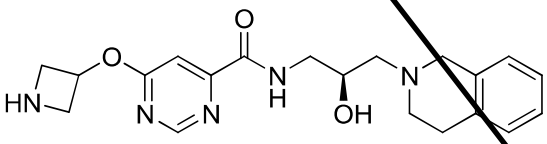
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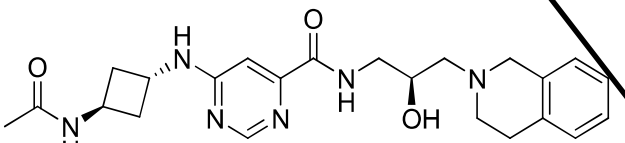
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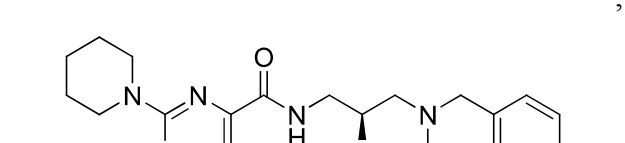
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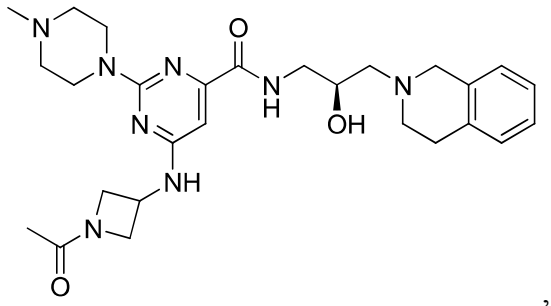

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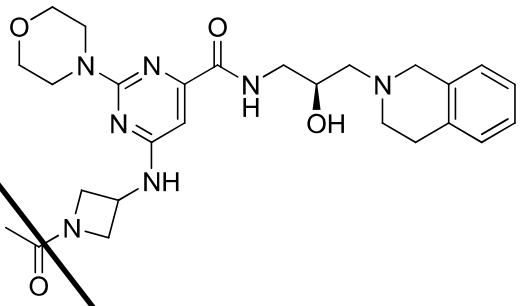

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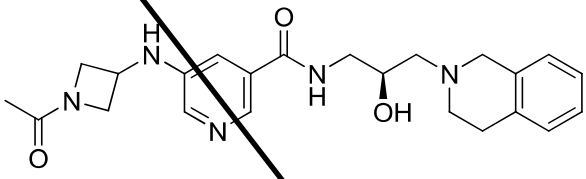

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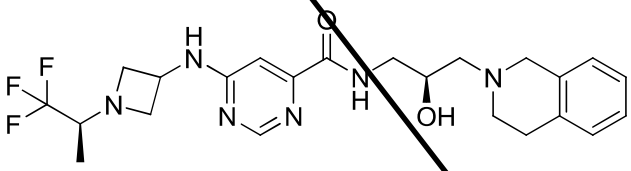

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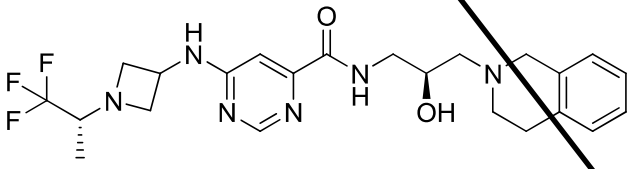

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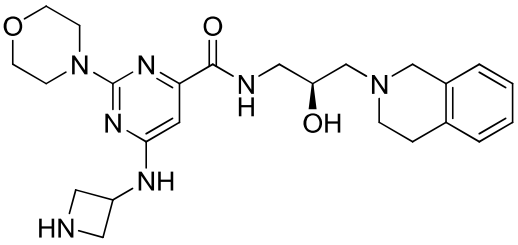

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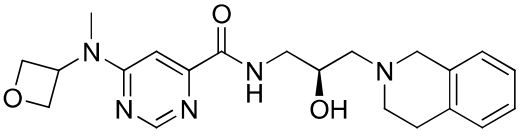

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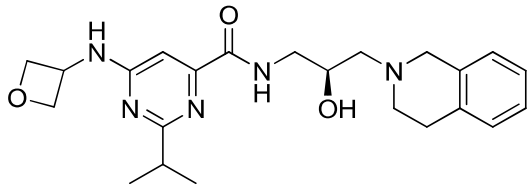

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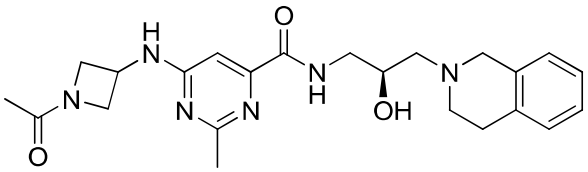

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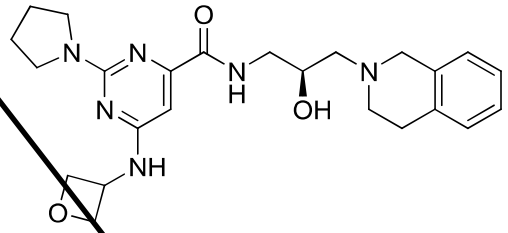

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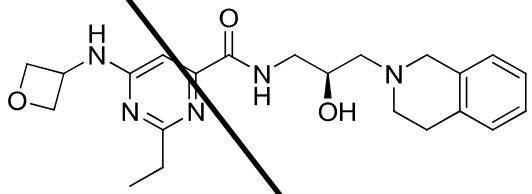

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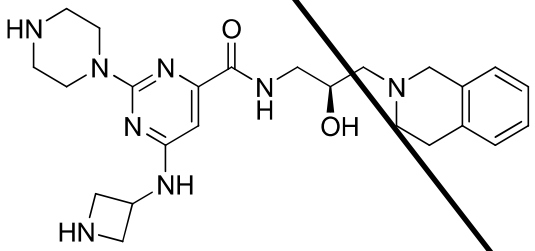

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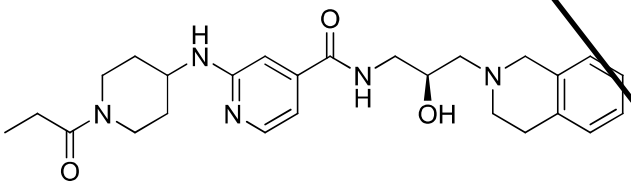

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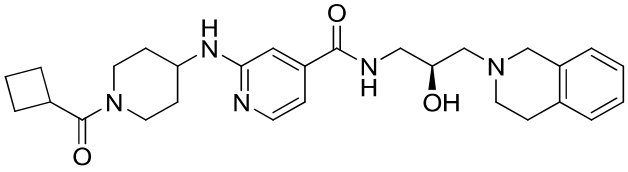

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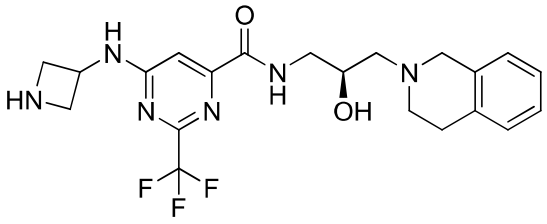

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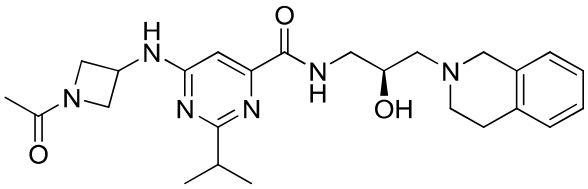

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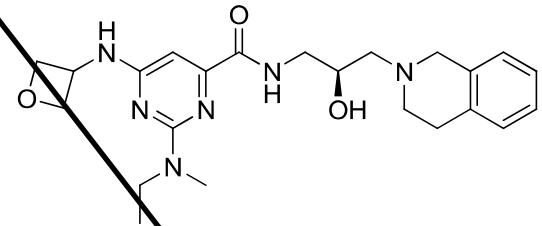

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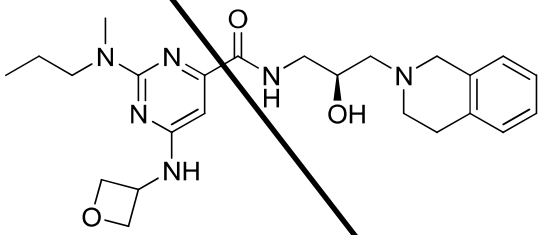

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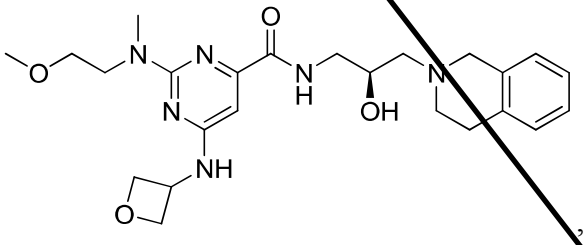

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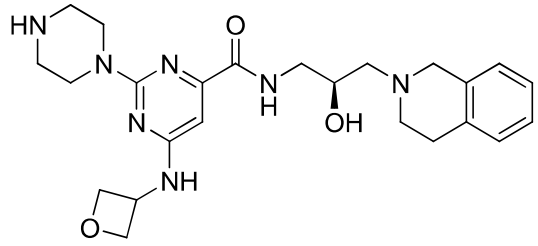

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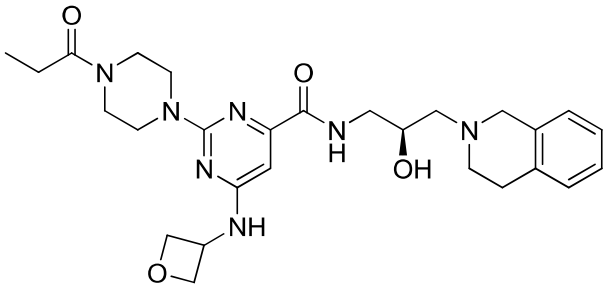

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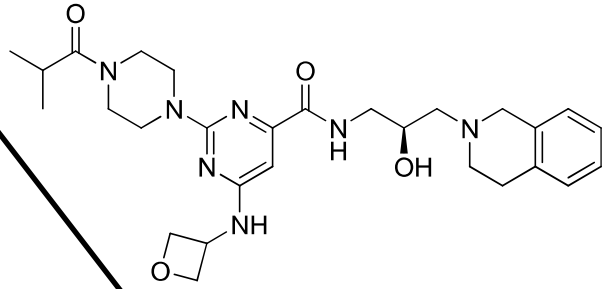

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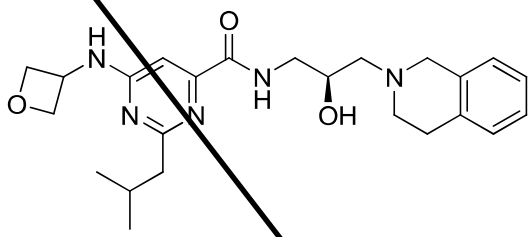

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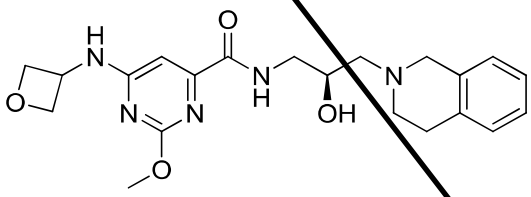

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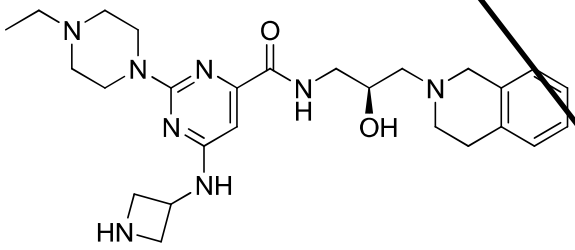

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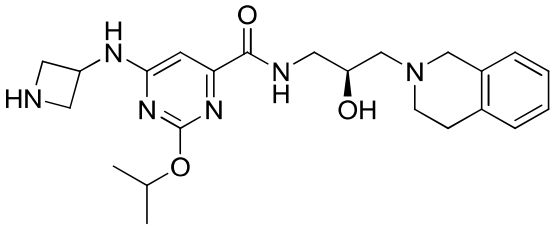

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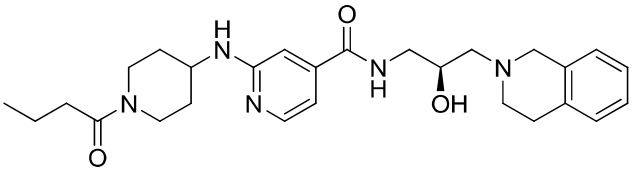
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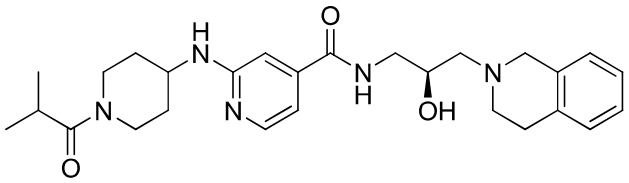
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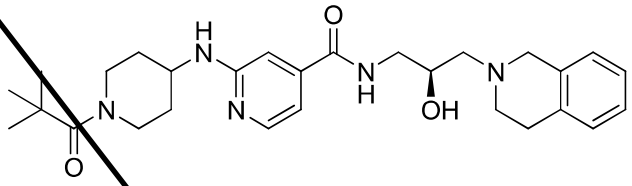
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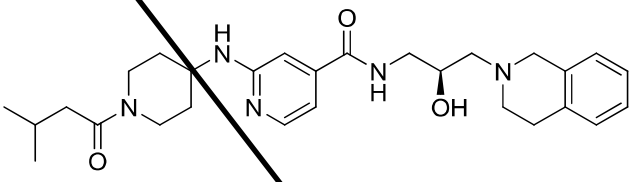
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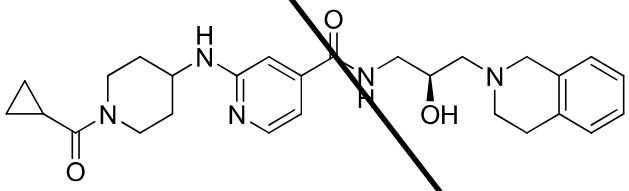
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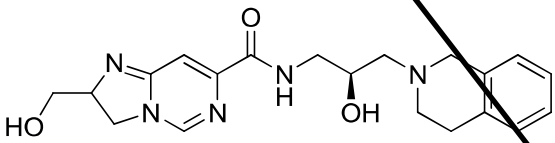
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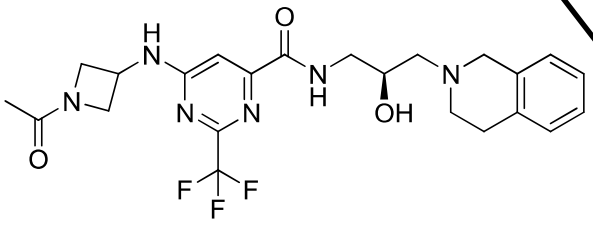
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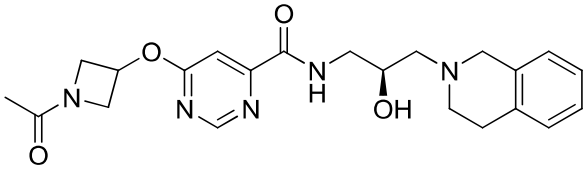
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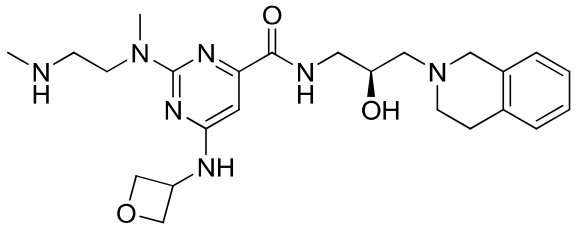

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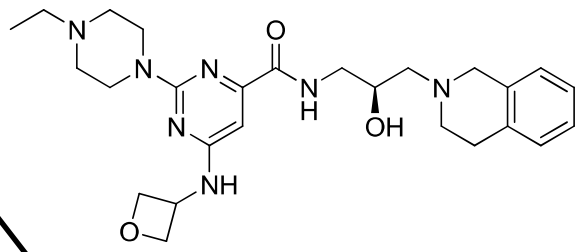

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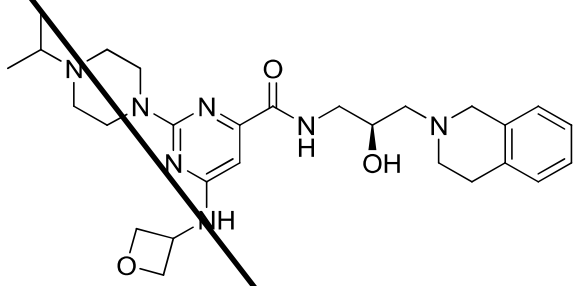

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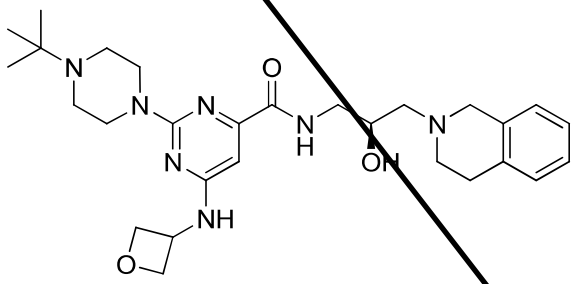

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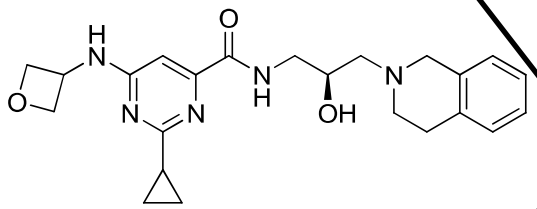

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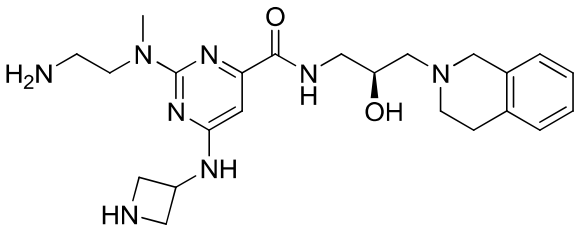

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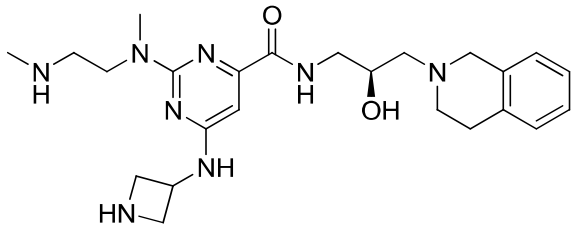

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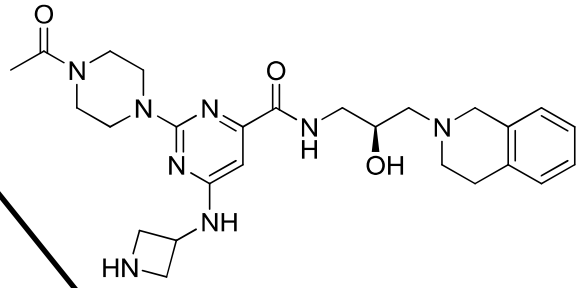

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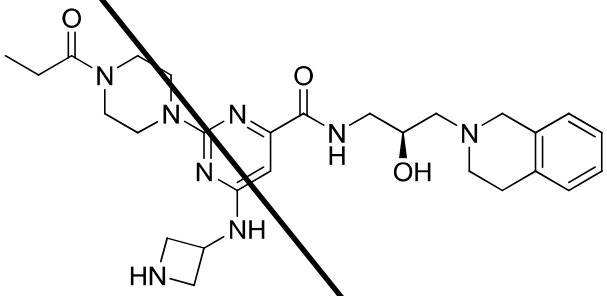

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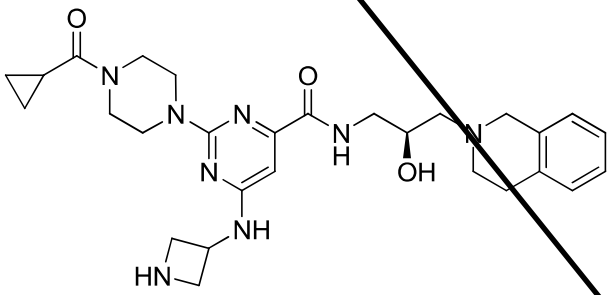

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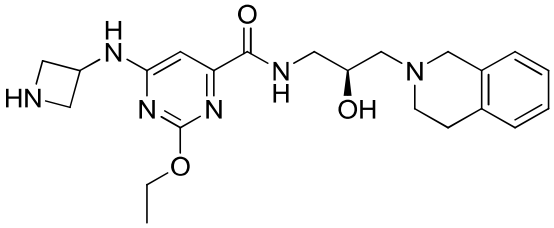

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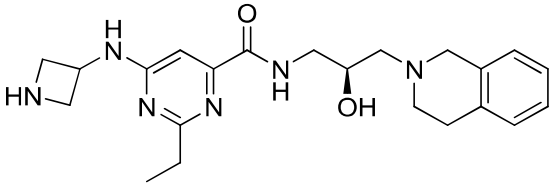

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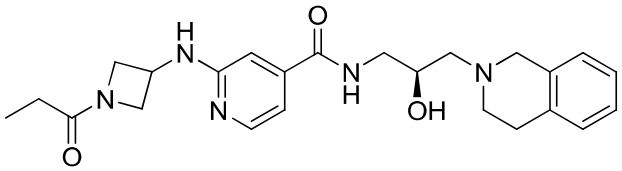
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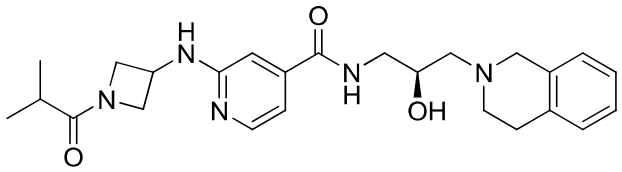
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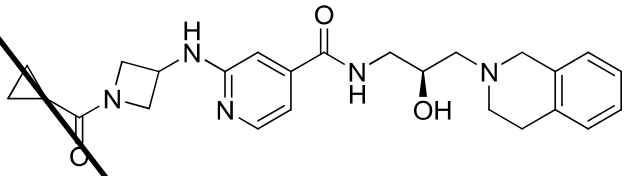
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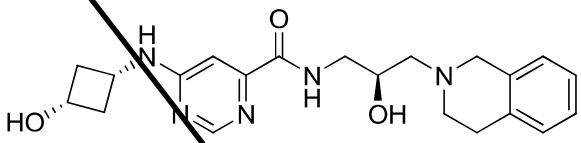
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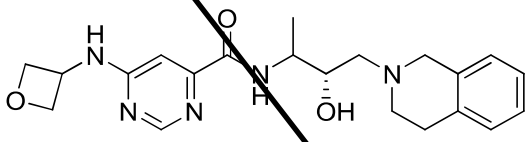
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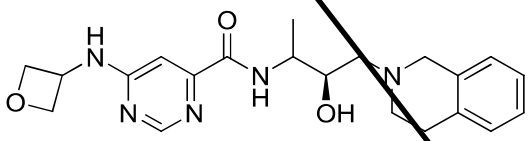
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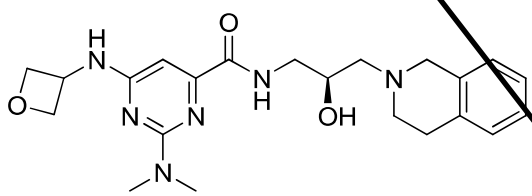
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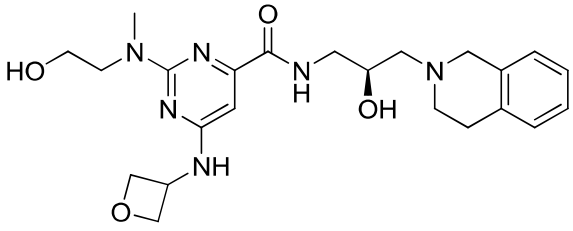
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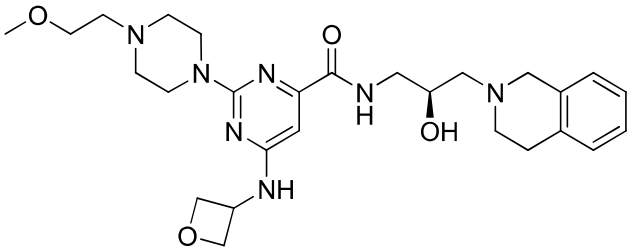

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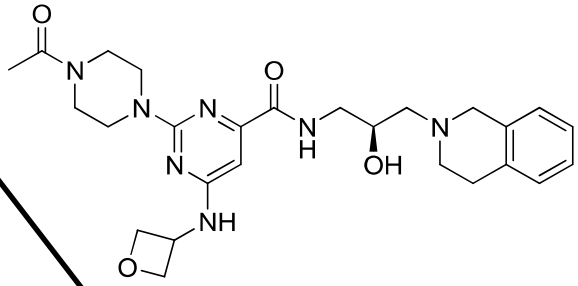

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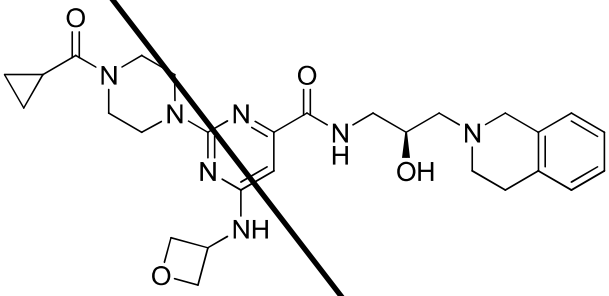

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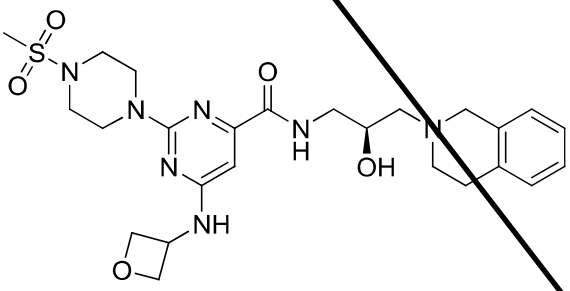

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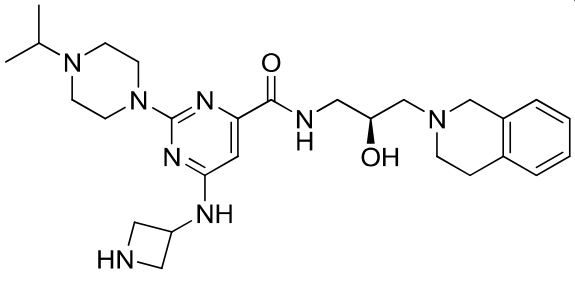

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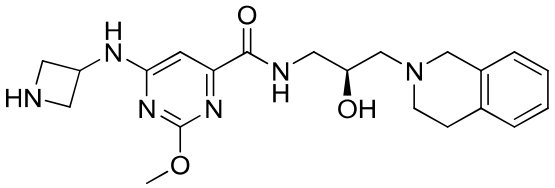

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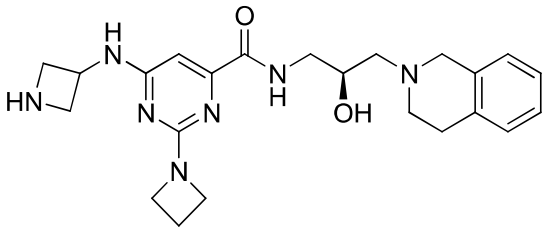

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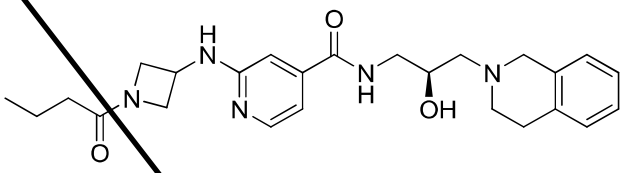

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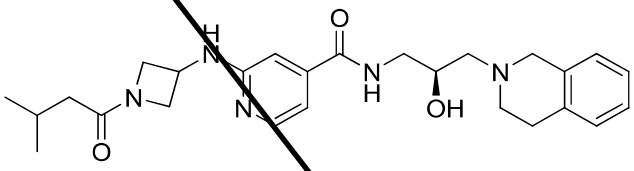

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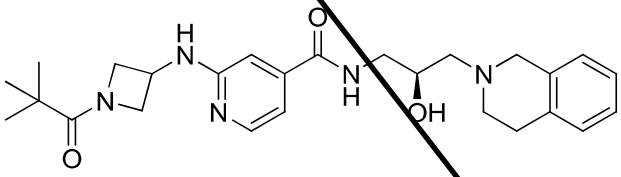

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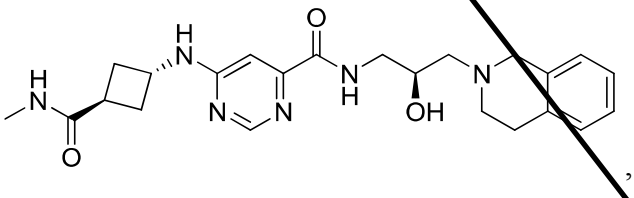

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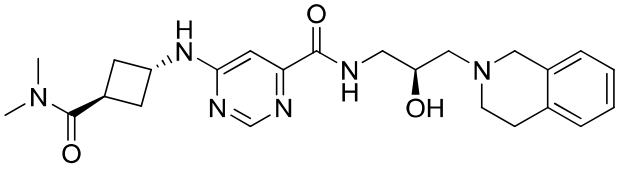

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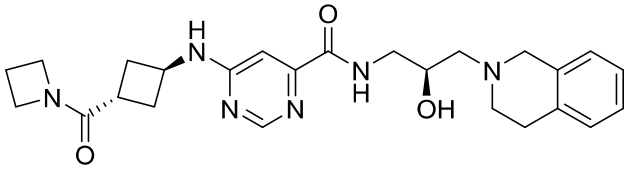

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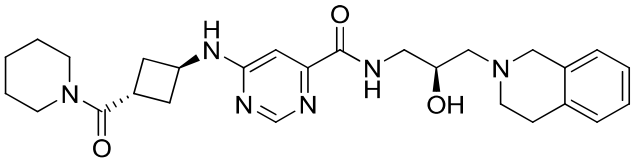
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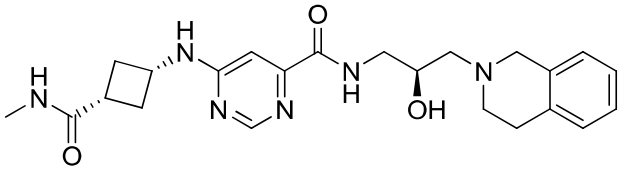
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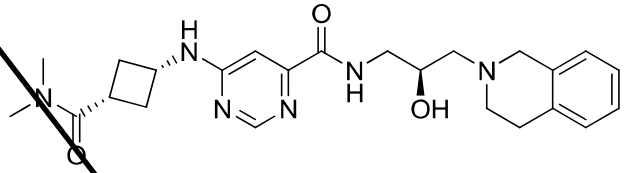
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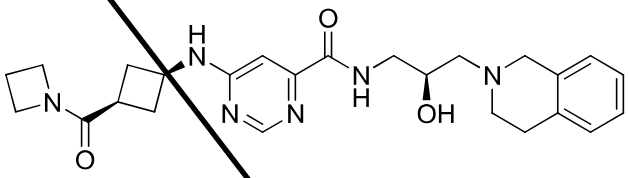
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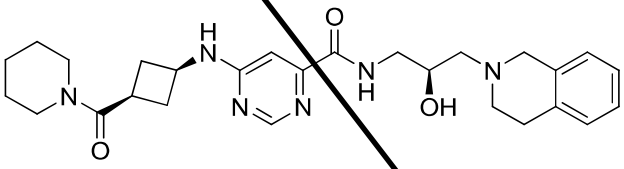
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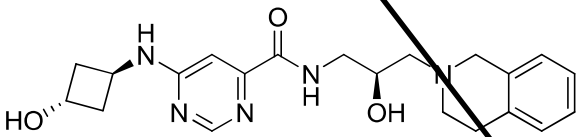
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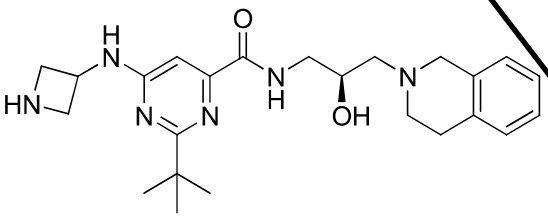
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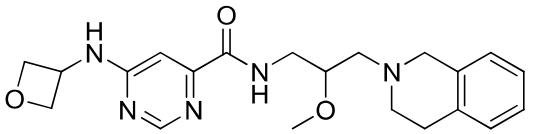
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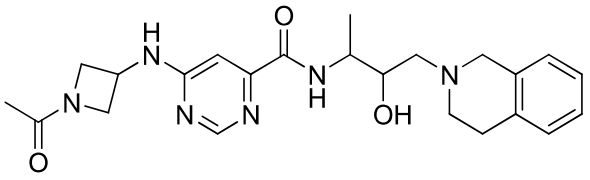

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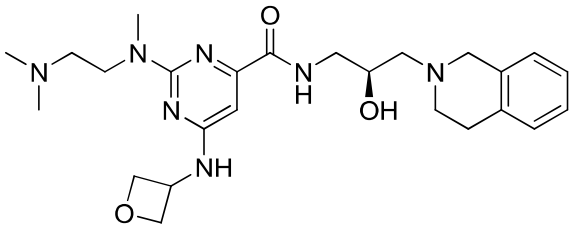

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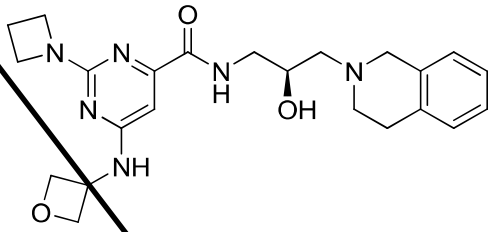

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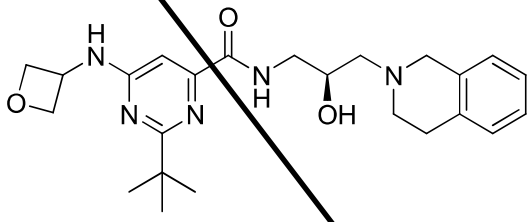

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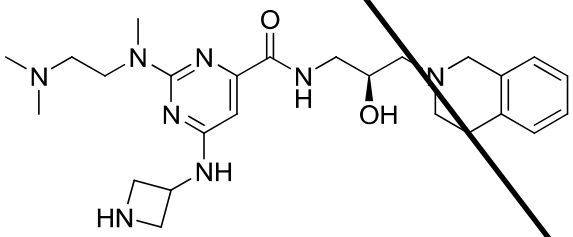

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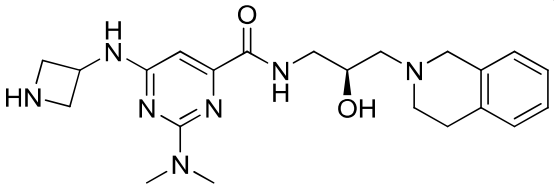

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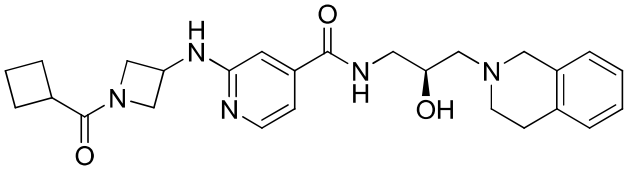

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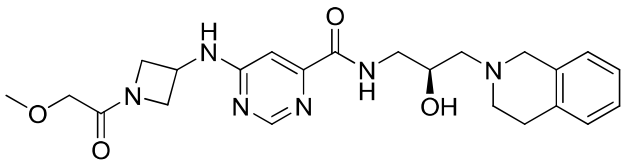
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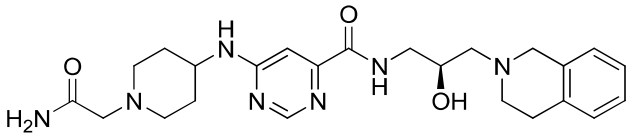
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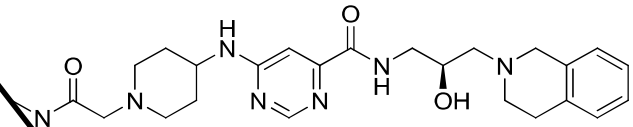
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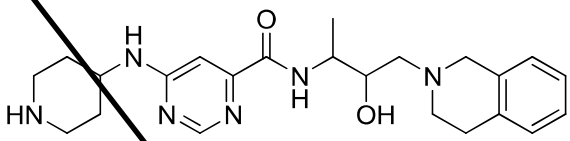
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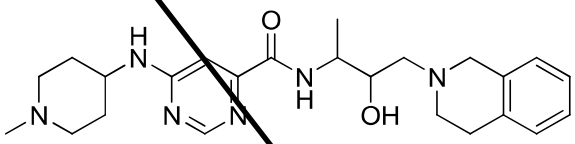
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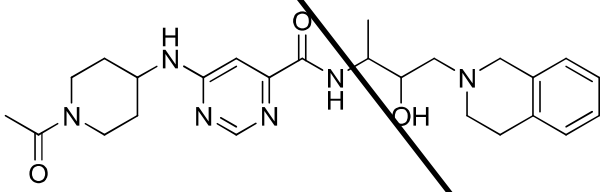
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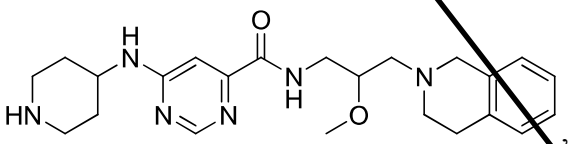
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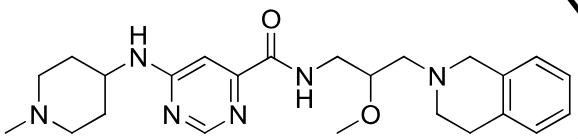
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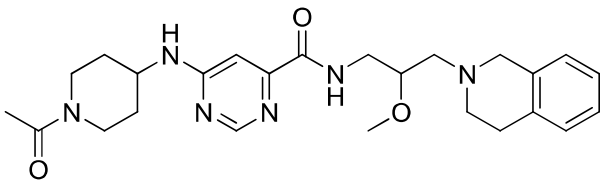
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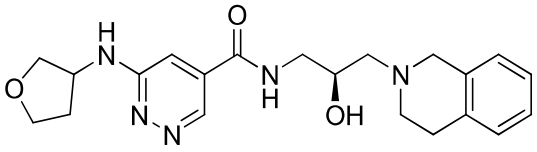
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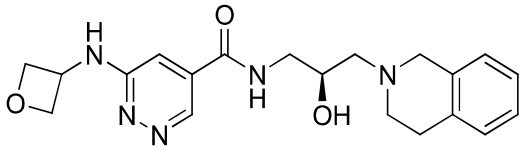
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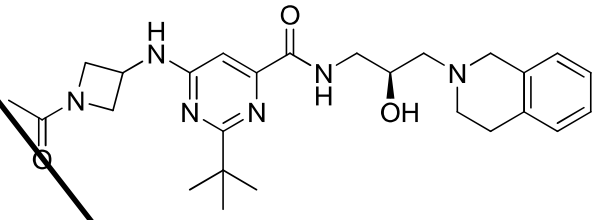
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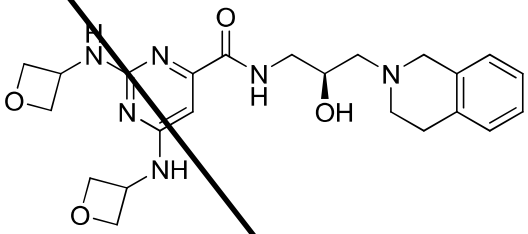
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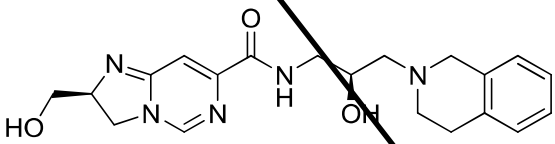
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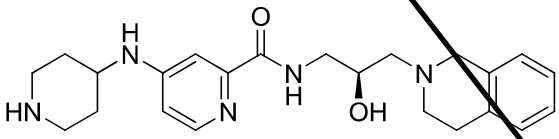
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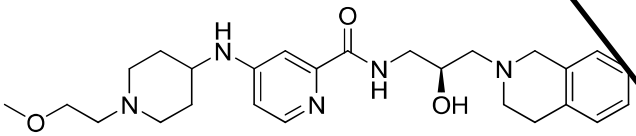
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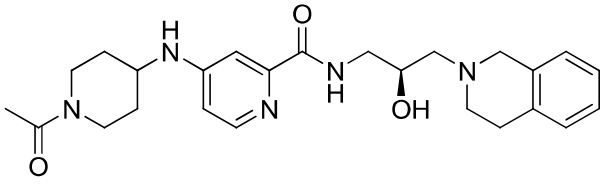
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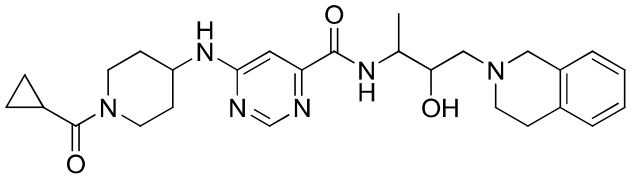
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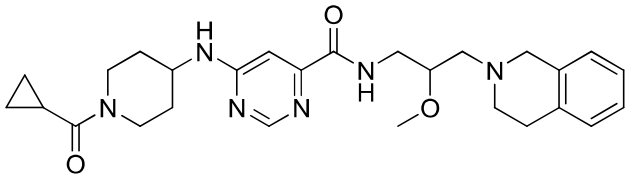
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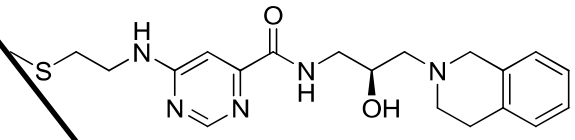
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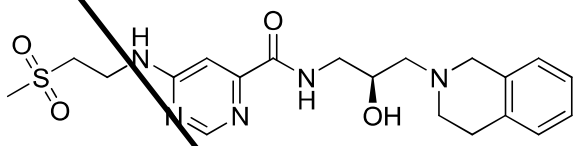
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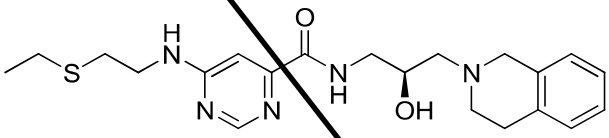
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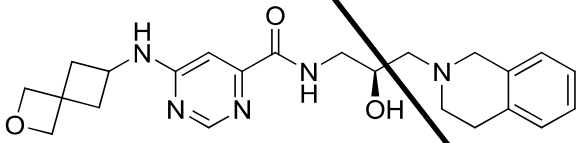
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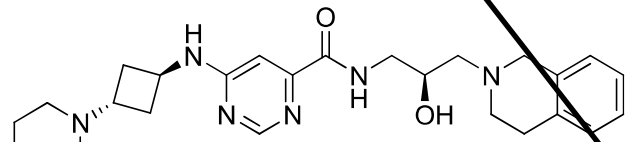
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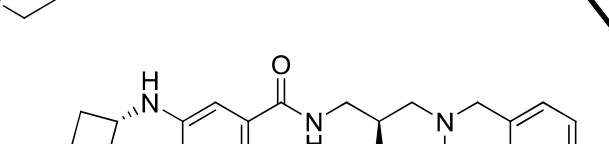
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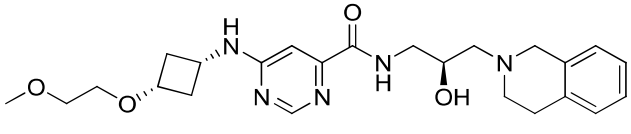
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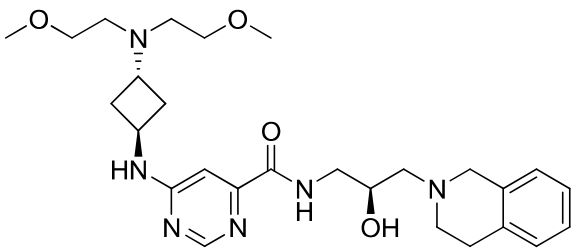

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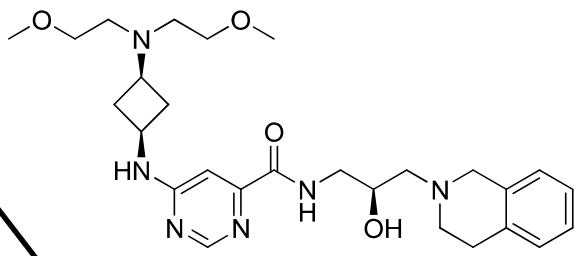

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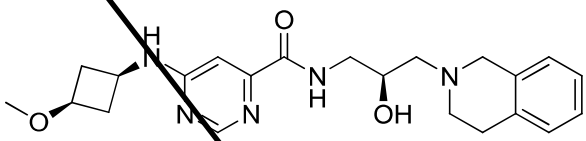

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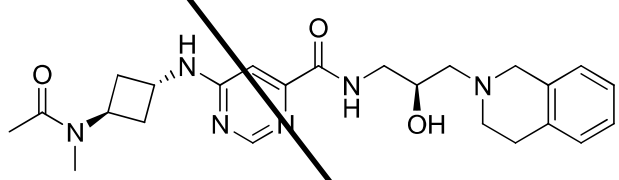

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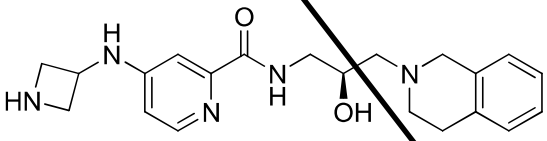

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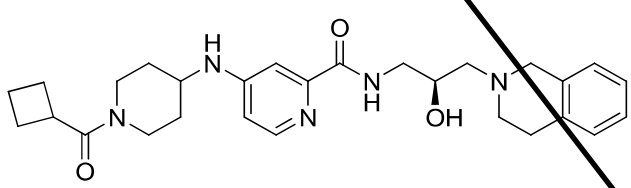

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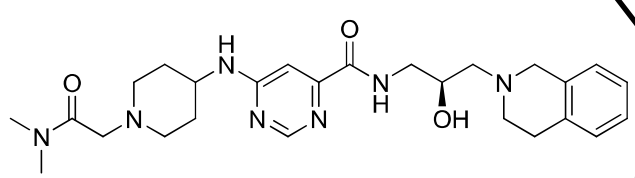

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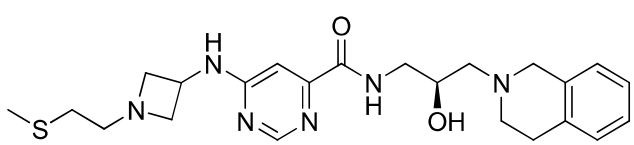

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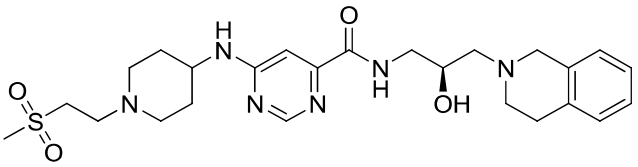
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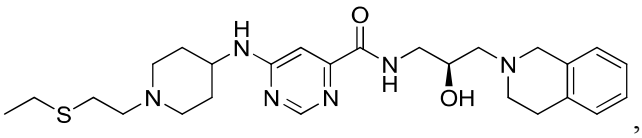
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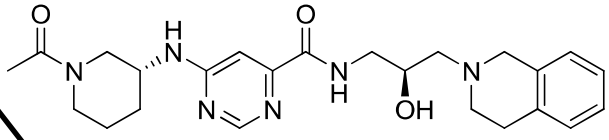
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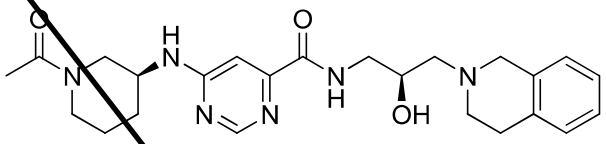
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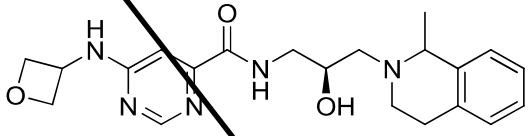
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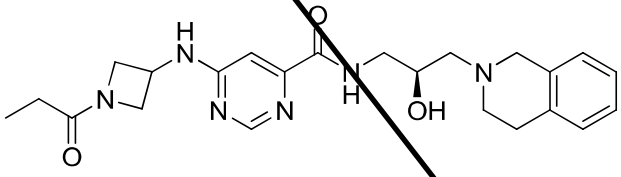
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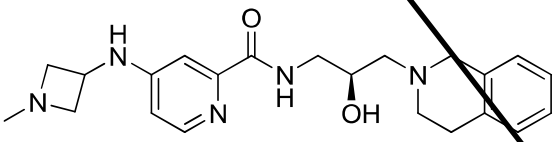
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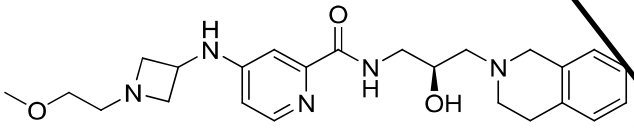
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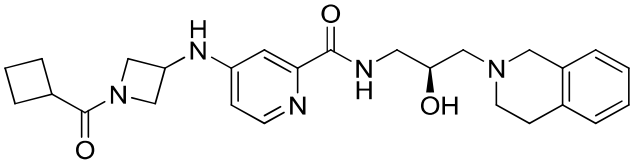
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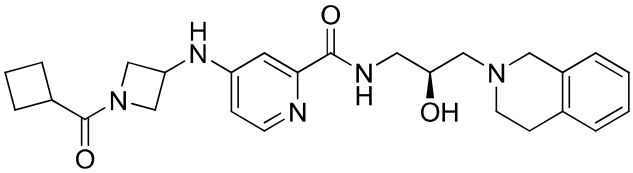
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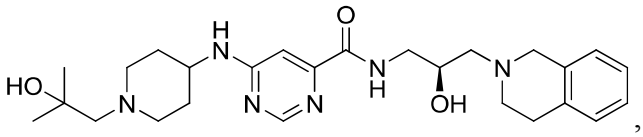
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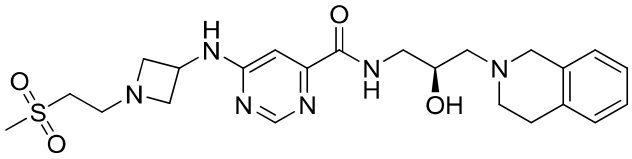
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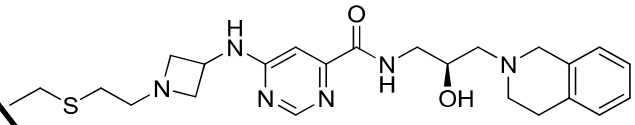
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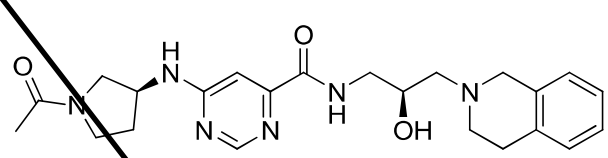
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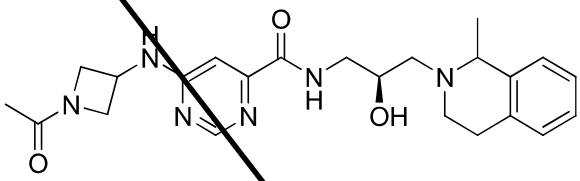
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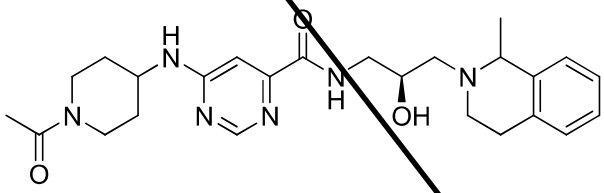
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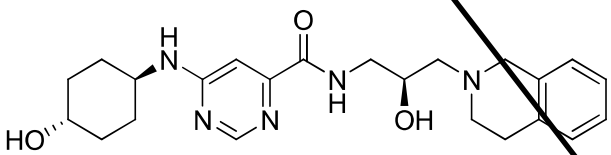
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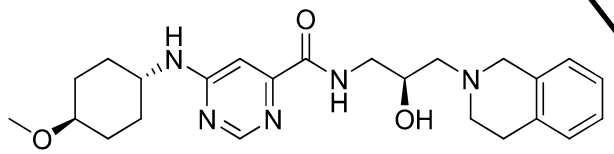
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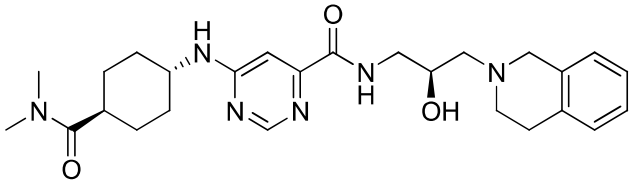
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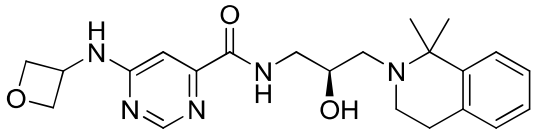
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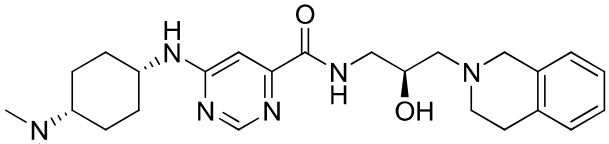
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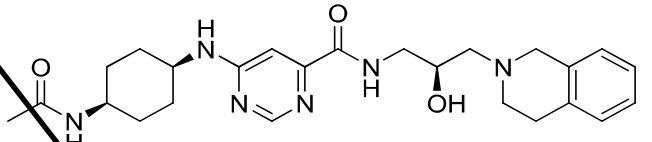
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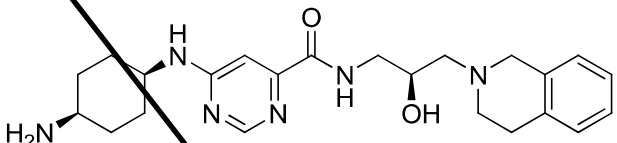
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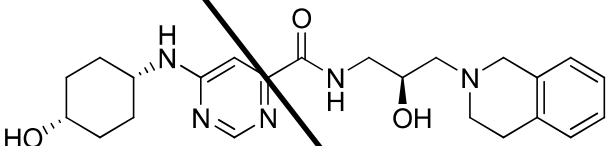
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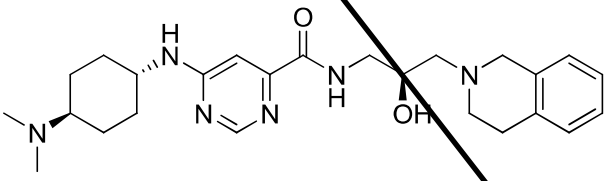
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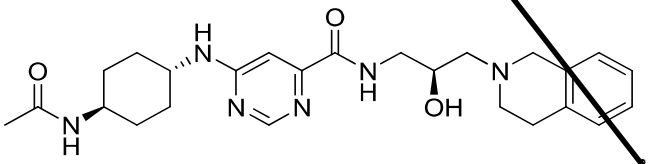
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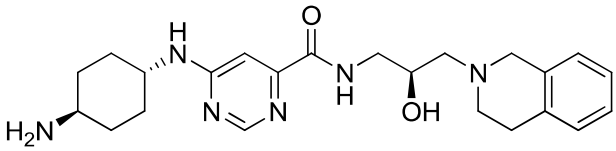
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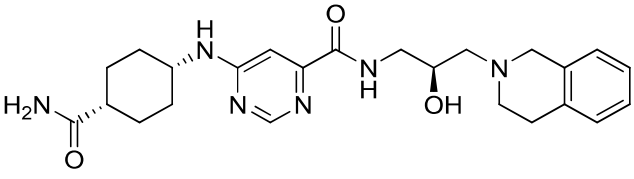
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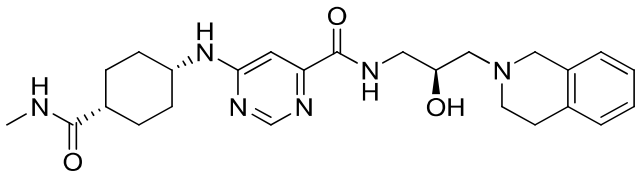
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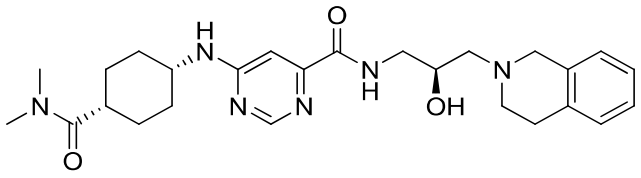
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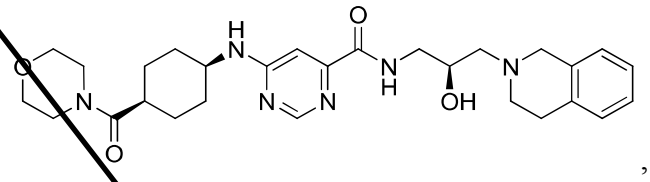
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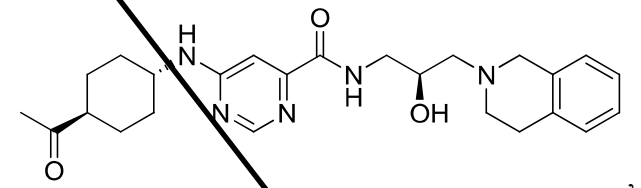
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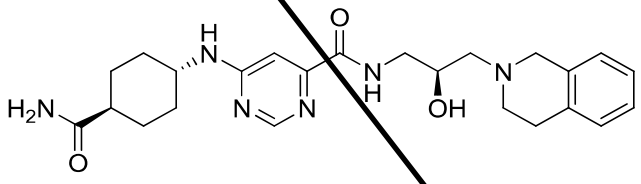
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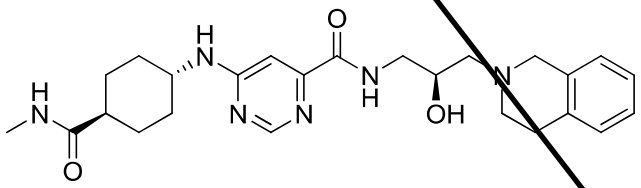
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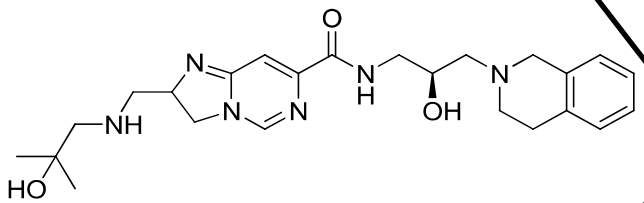
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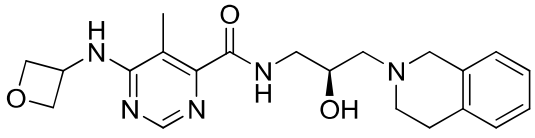
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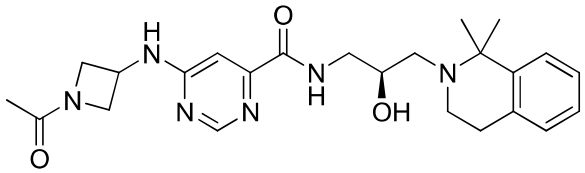
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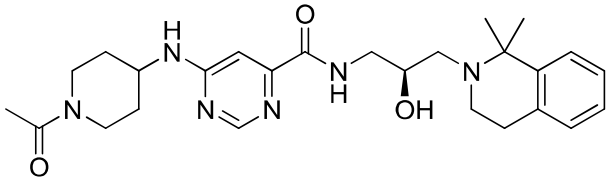
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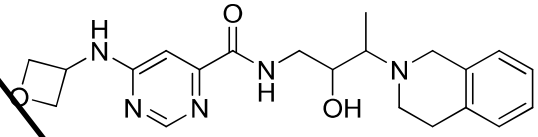
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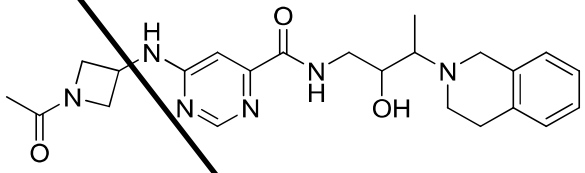
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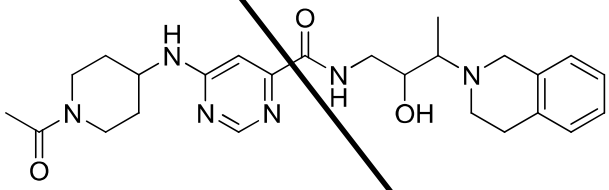
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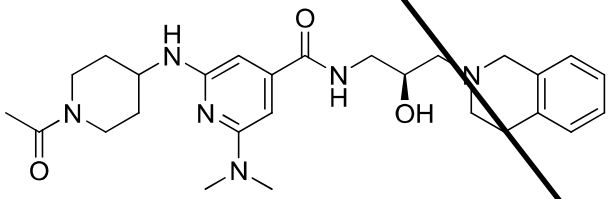
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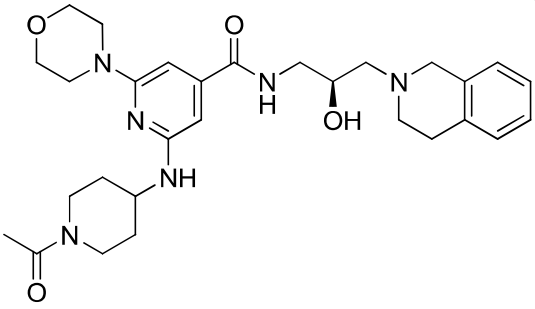
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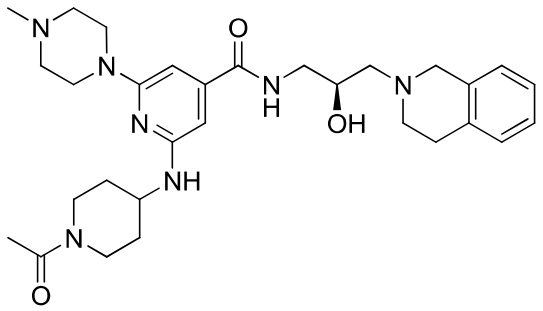
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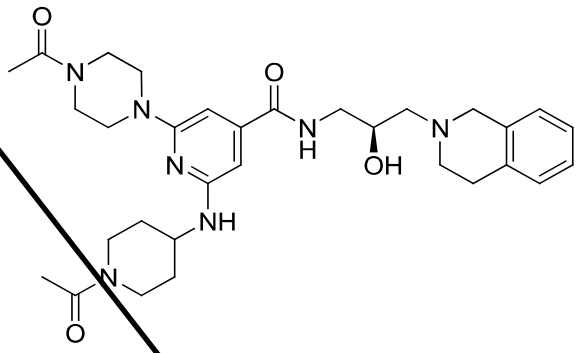
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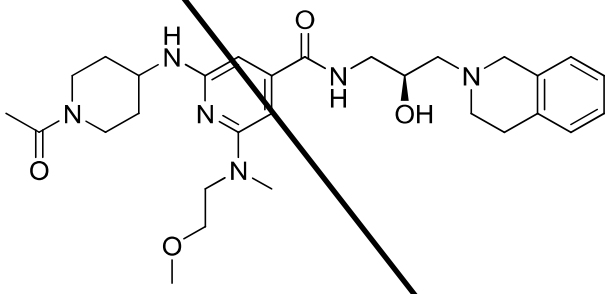
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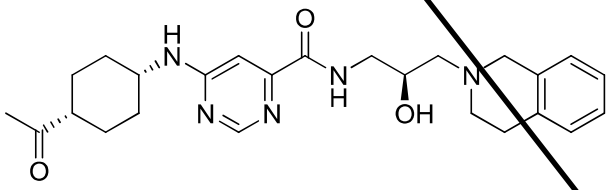
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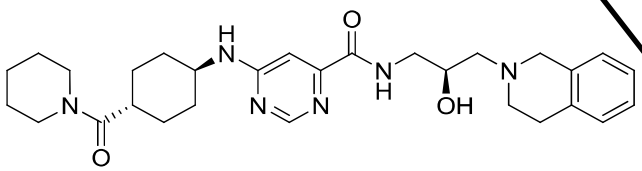
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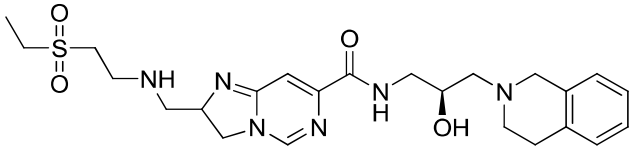
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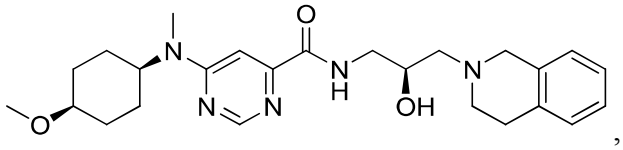
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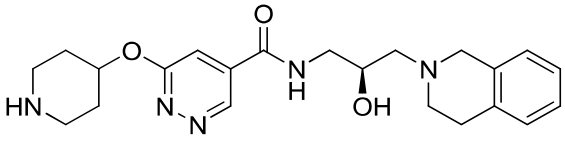
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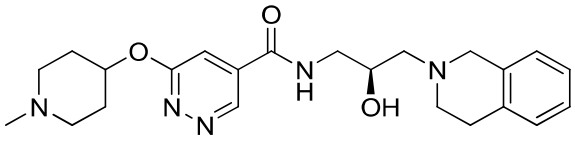
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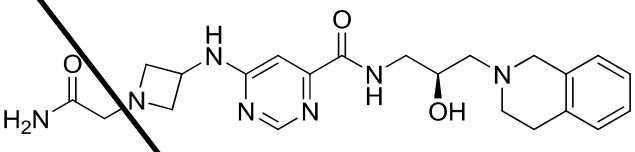
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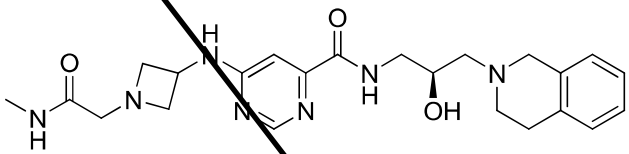
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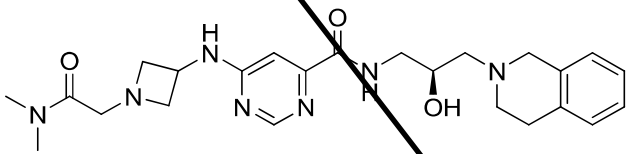
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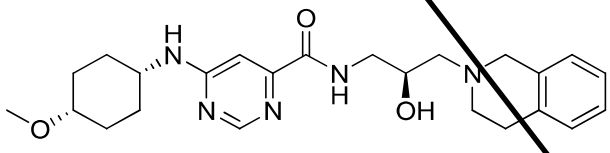
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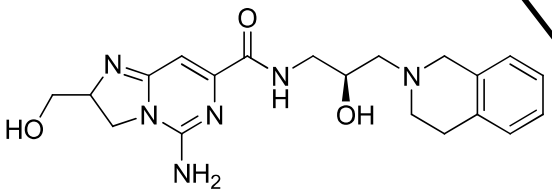
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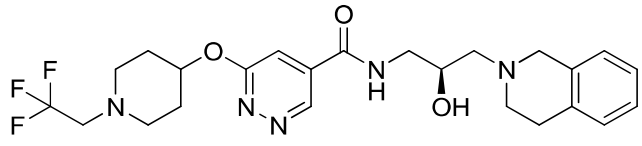
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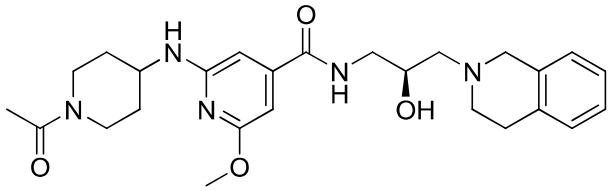
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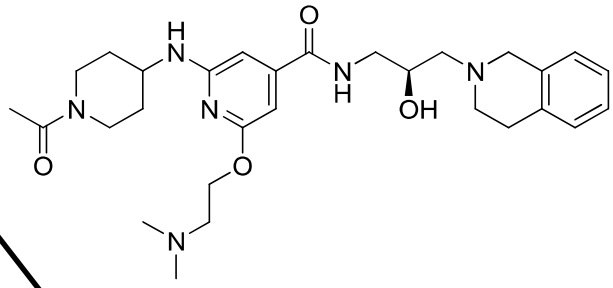
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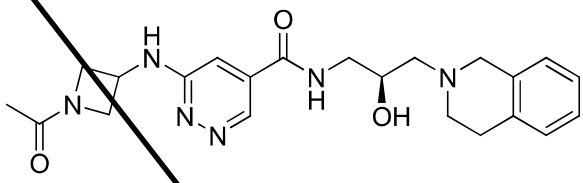
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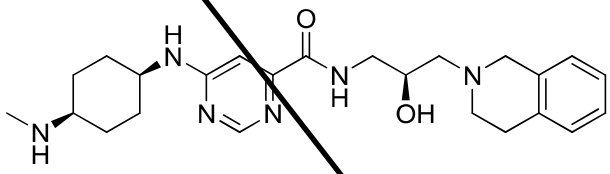
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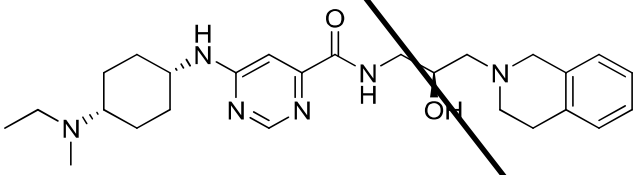
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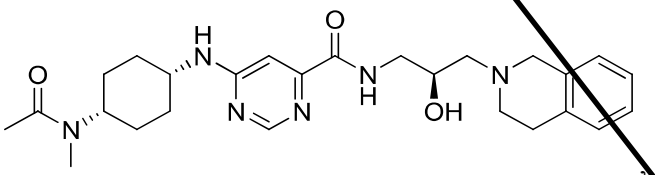
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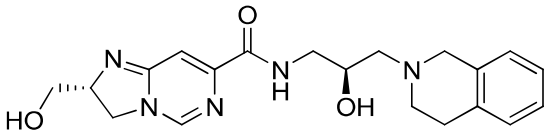
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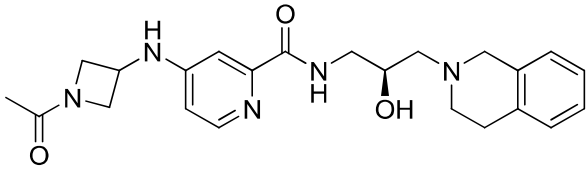
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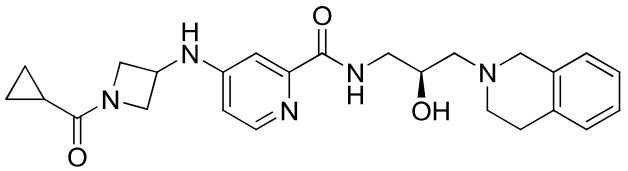
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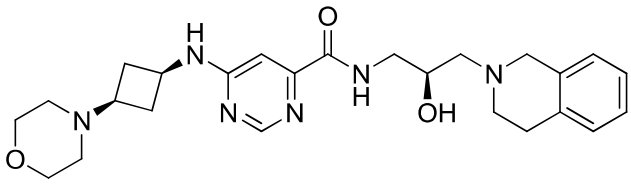
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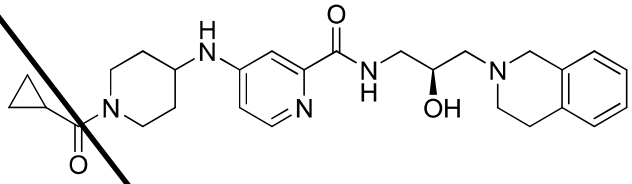
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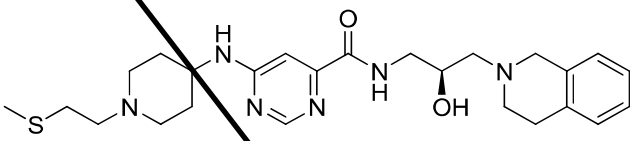
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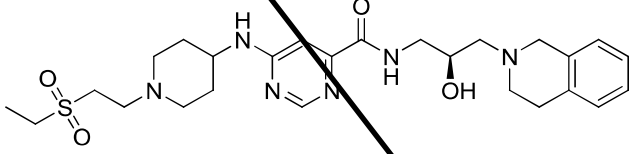
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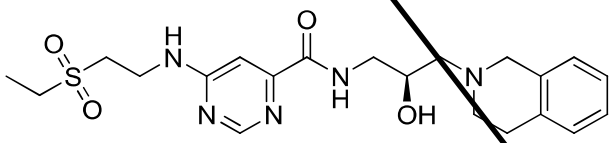
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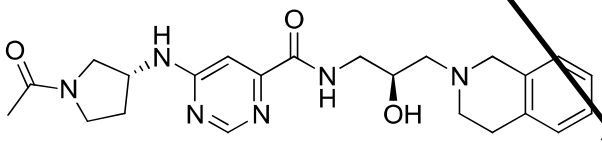
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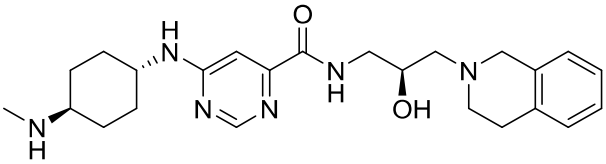
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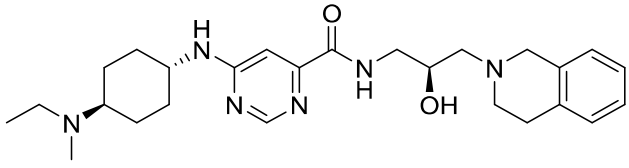
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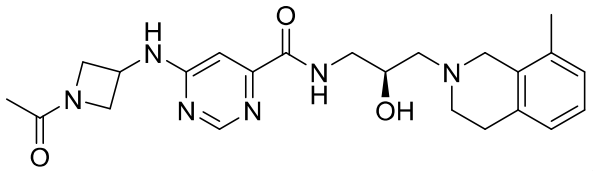
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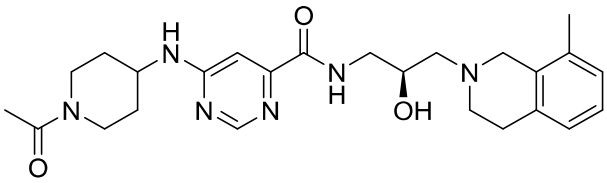
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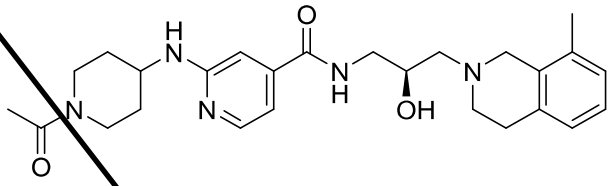
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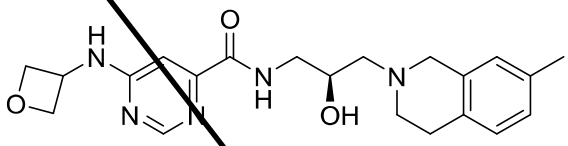
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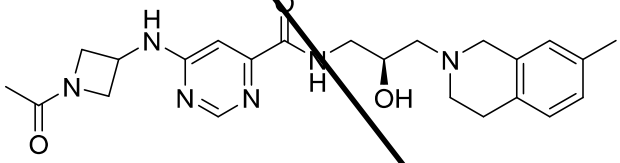
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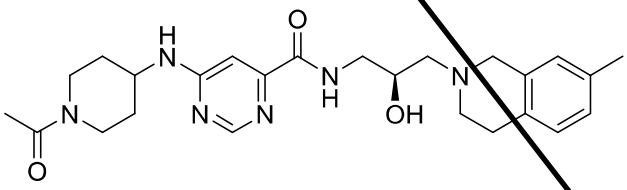
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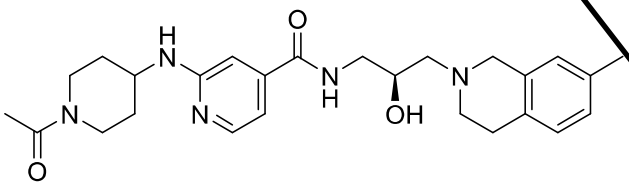
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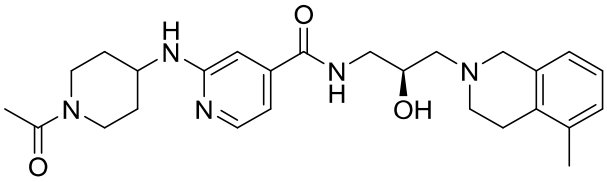
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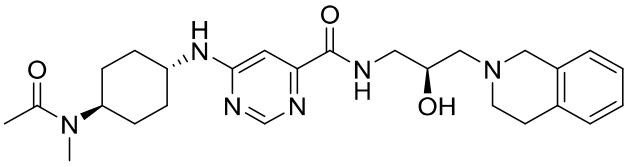
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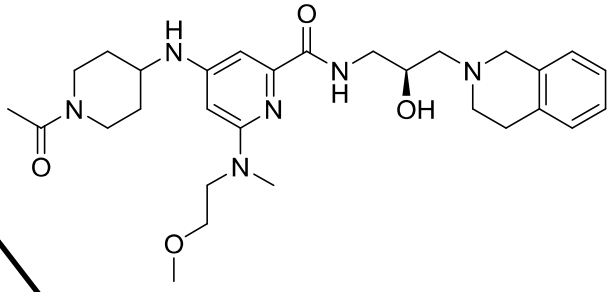
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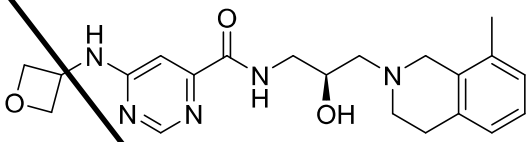
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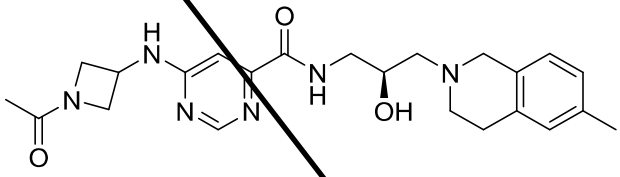
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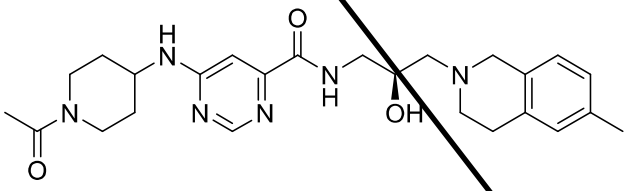
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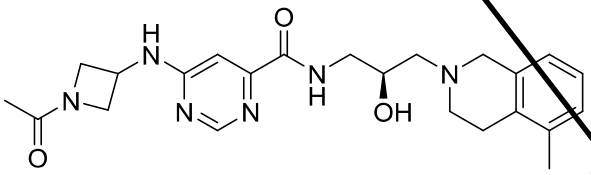
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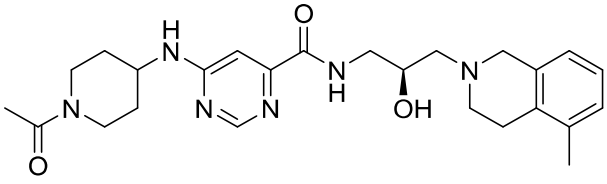
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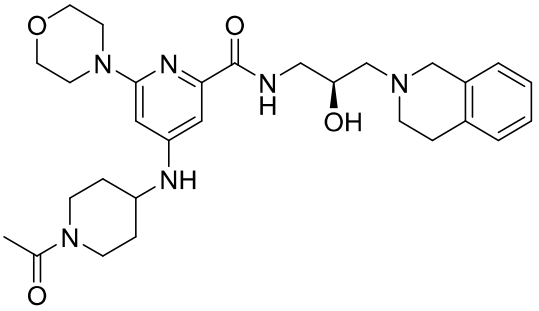

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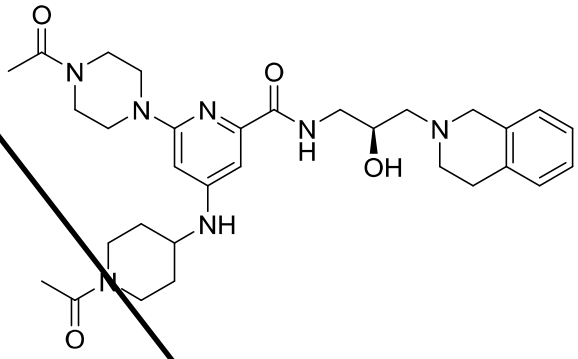

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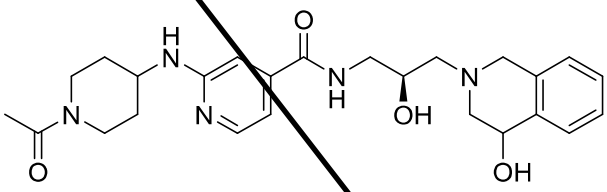

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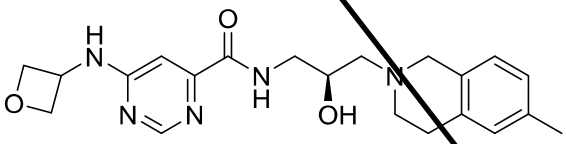

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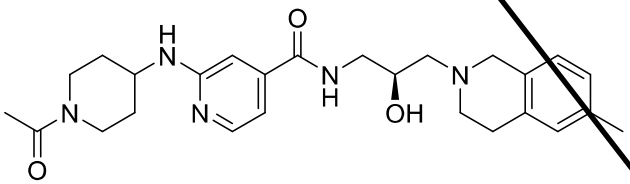

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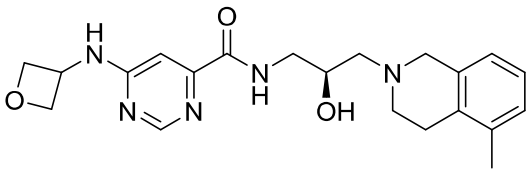

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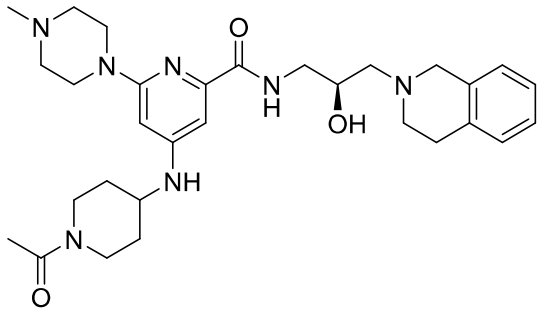

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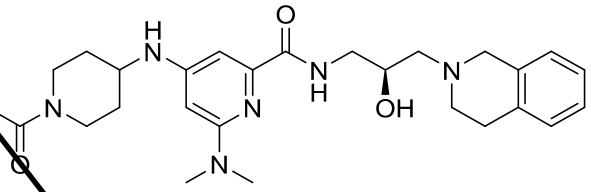

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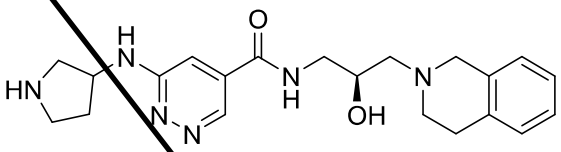

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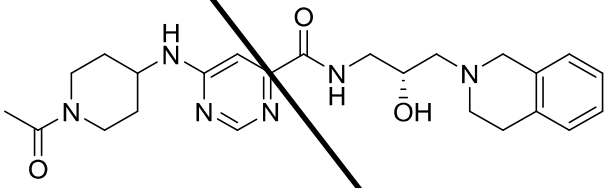

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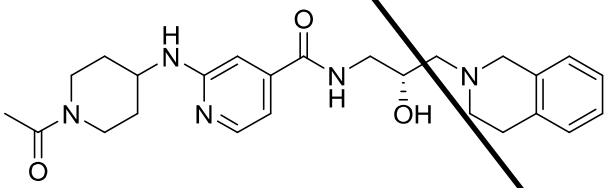

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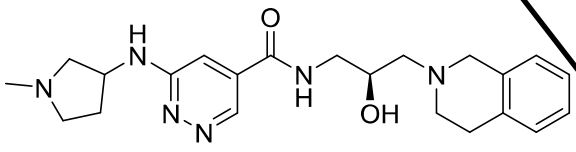

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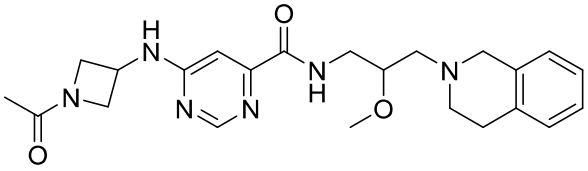

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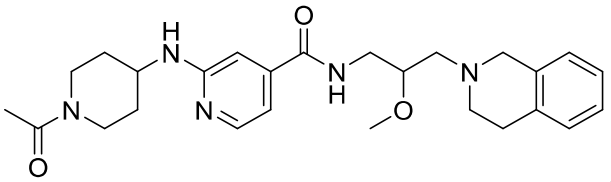
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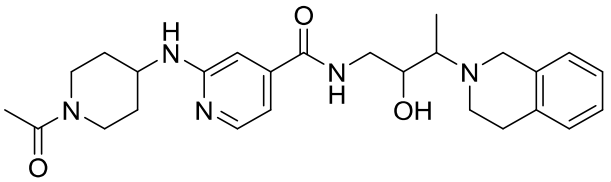
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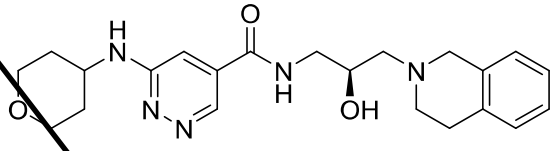
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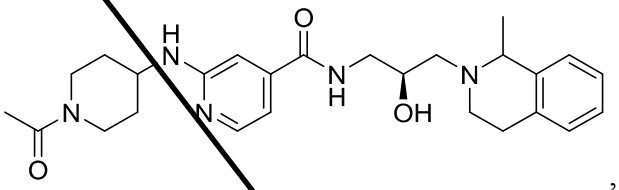
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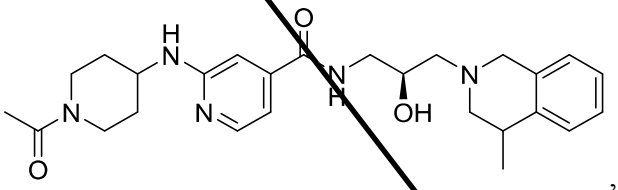
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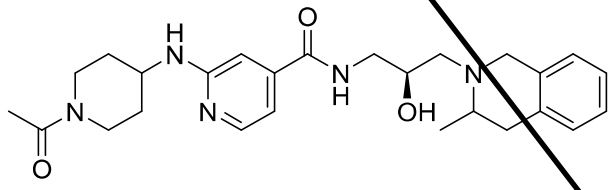
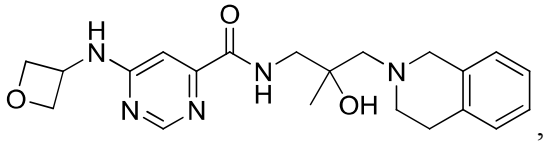

,
and pharmaceutically acceptable salts thereof.

110. The compound of claim 1, wherein the compound is selected from the group consisting of: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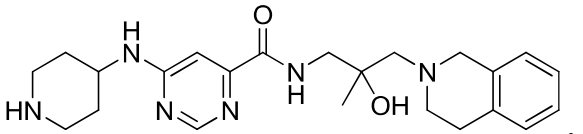
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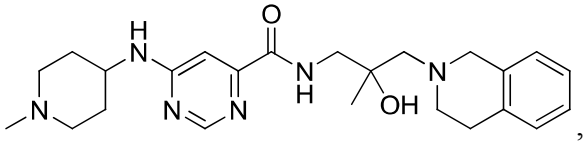
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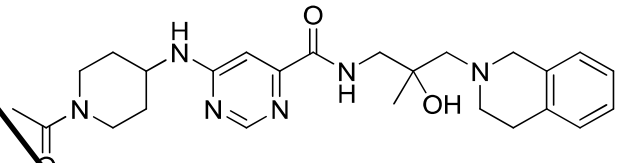
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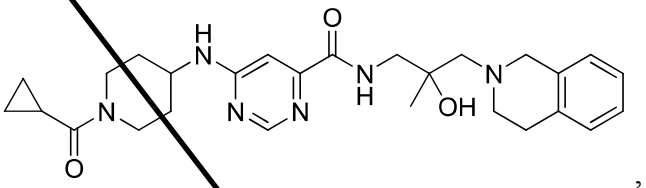
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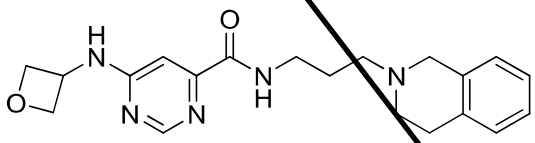
and pharmaceutically acceptable salts thereof.

111. A compound selected from the group consisting of: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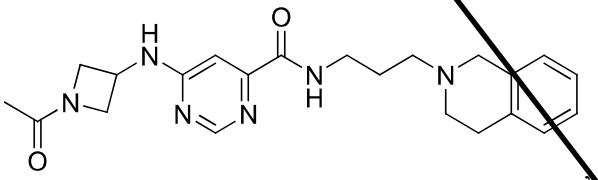
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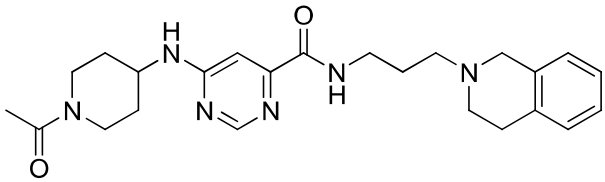
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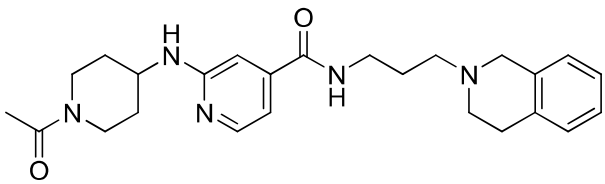
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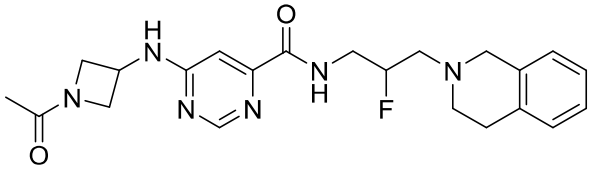
and pharmaceutically acceptable salts thereof.

112. A compound selected from the group consisting of: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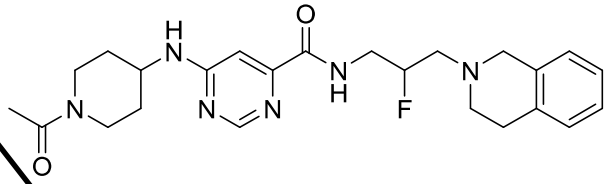
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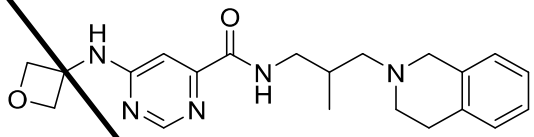
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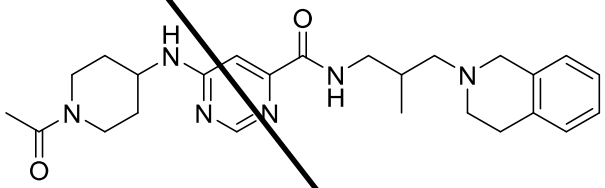
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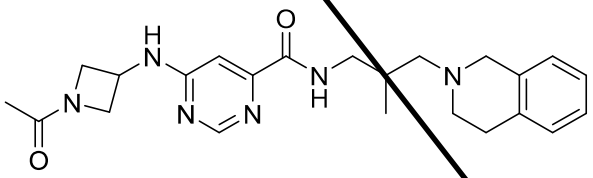
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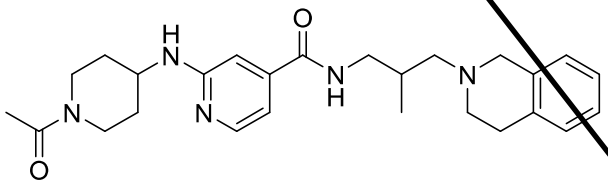
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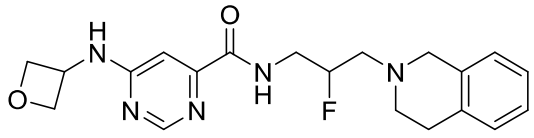
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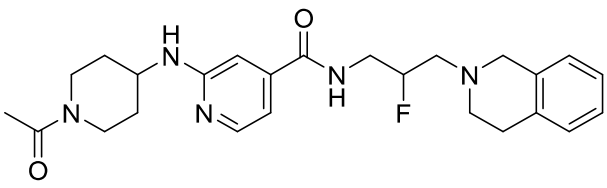
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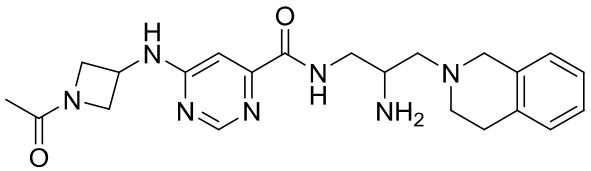
and pharmaceutically acceptable salts thereof.

113. A compound selected from the group consisting of:



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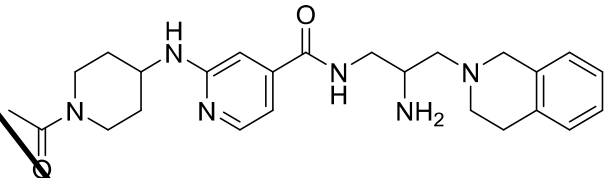

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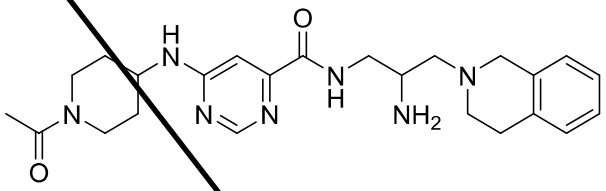

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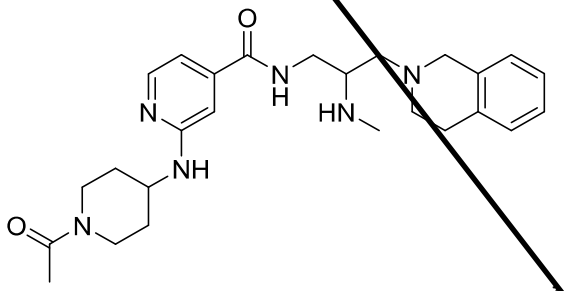
and pharmaceutically acceptable salts thereof.

114. A compound selected from the group consisting of:



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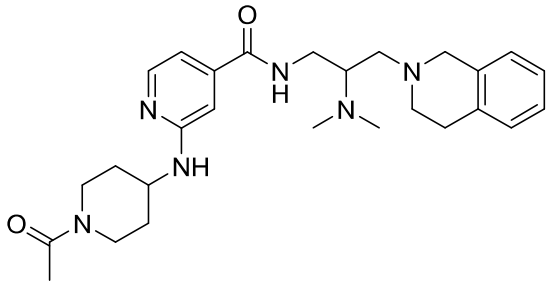

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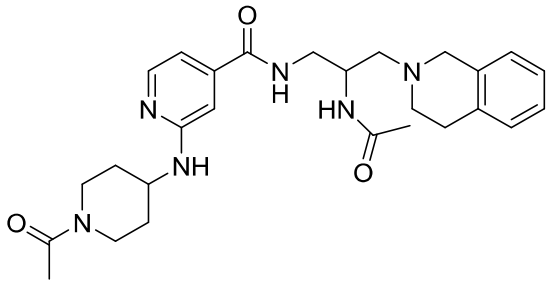
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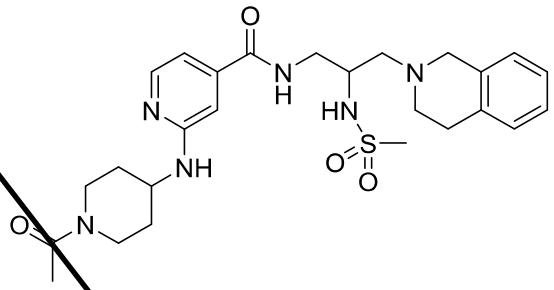
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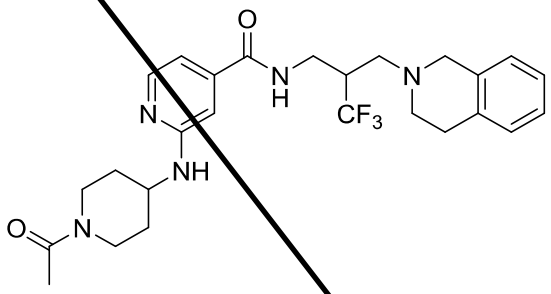
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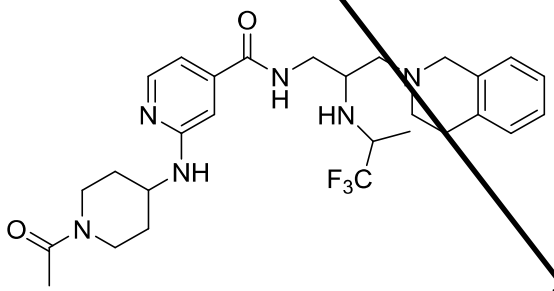
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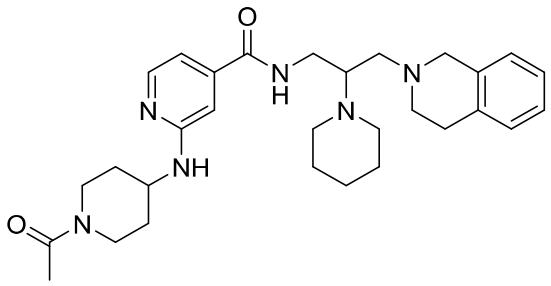
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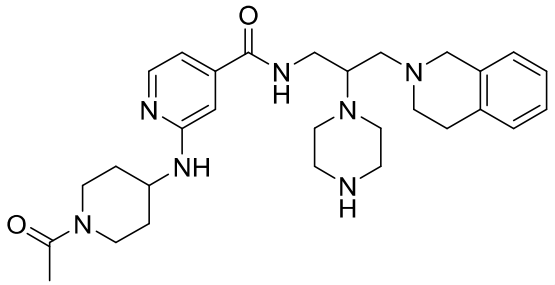
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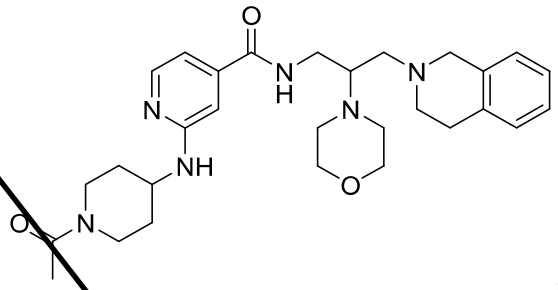
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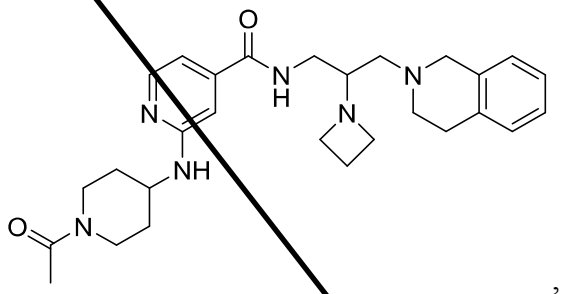
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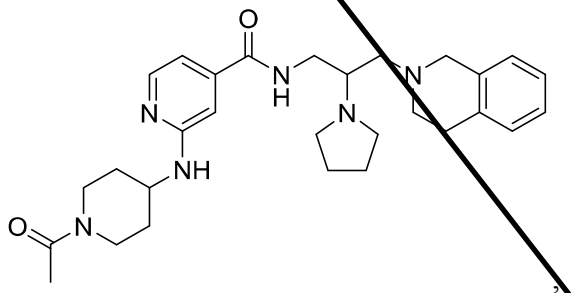
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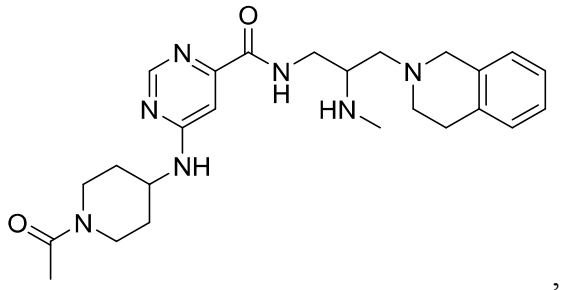
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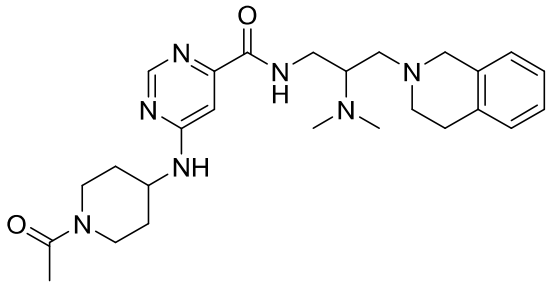

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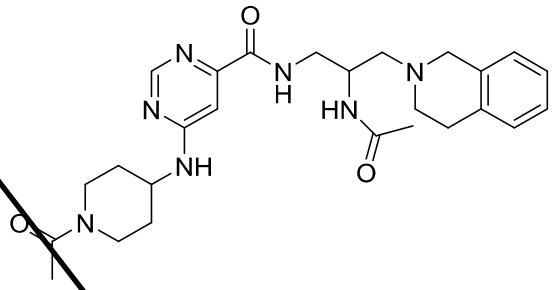

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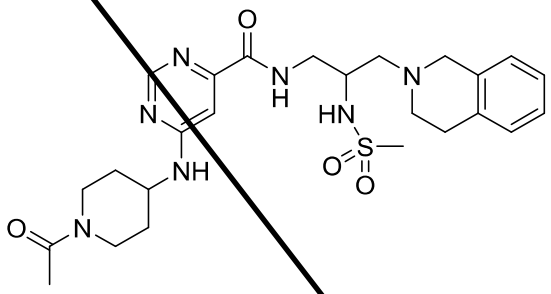

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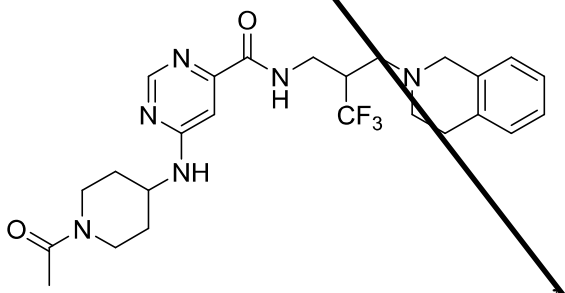

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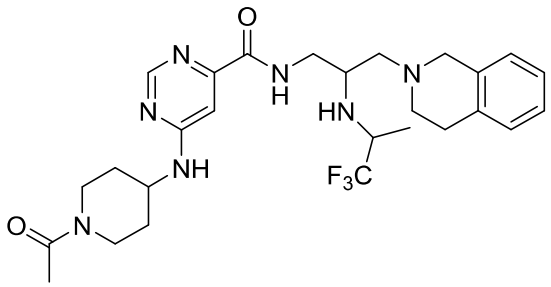

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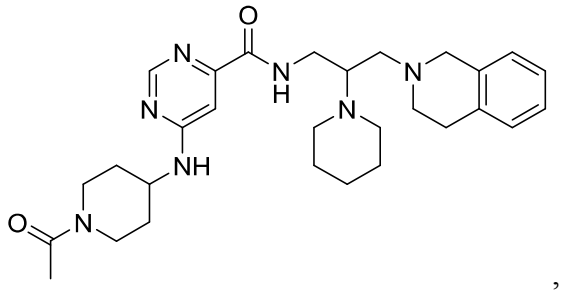
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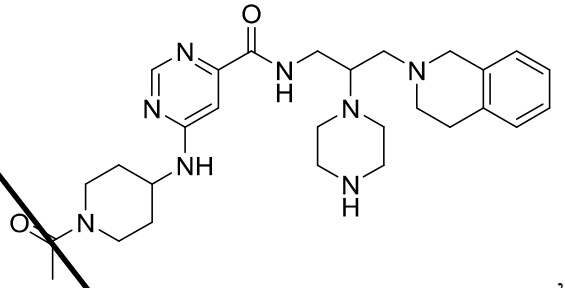
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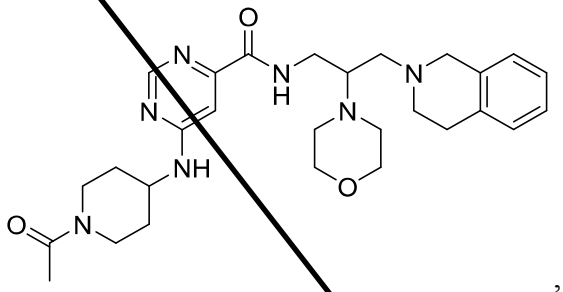
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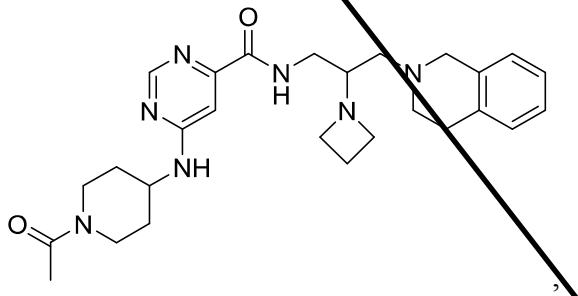
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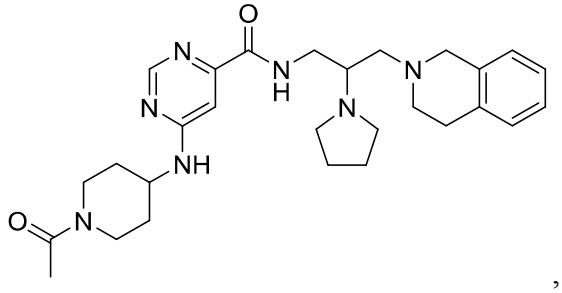
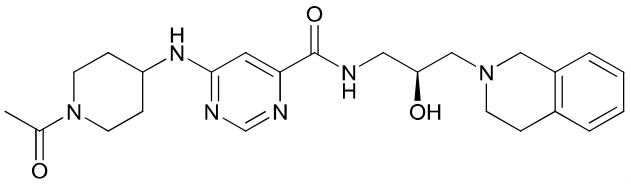

,

and pharmaceutically acceptable salts thereof.

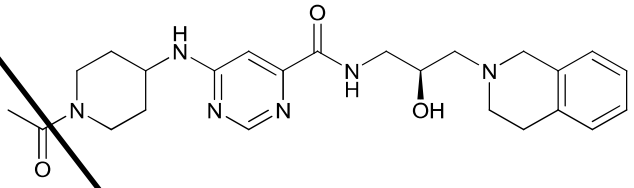
115. A compound of formula:



,

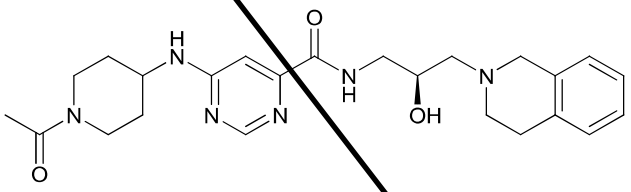
or a pharmaceutically acceptable salt thereof.

116. The compound of claim 115, wherein the compound is:



.

117. The compound of claim 115, wherein the compound is a pharmaceutically acceptable salt of:



.

118. A compound which is (*S*)-6-((1-acetylpiperidin-4-yl)amino)-*N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)pyrimidine-4-carboxamide.

119. A pharmaceutical composition comprising a compound of any one of claims 1-118, and a pharmaceutically acceptable excipient.

120. A pharmaceutical composition comprising a compound of claim 115, and a pharmaceutically acceptable excipient.

121. A pharmaceutical composition comprising a compound of claim 116, and a pharmaceutically acceptable excipient.

122. A pharmaceutical composition comprising a compound of claim 117, and a pharmaceutically acceptable excipient.

123. A pharmaceutical composition comprising a compound of claim 118, and a pharmaceutically acceptable excipient.

124. A kit or packaged pharmaceutical comprising a compound of any one of claims 1-118 and instructions for use thereof.

125. Use of a compound of any one of claims 1-118 in the preparation of a medicament for inhibiting PRMT5, wherein inhibiting PRMT5 comprises contacting a cell with an effective amount of the compound.

126. Use of a compound of any one of claims 1-118 in the preparation of a medicament for altering gene expression, wherein altering gene expression comprises contacting a cell with an effective amount of the compound.

127. Use of a compound of any one of claims 1-118 in the preparation of a medicament for altering transcription, wherein altering transcription comprises contacting a cell with an effective amount of the compound.

128. The use of any one of claims 125-127, wherein the cell is *in vitro*.

129. The use of any one of claims 125-127, wherein the cell is in a subject.

130. Use of a compound of any one of claims 1-118 in the manufacture of a medicament for treating or preventing a PRMT5-mediated disorder in a subject in need thereof.

131. The use of claim 130, wherein the disorder is a proliferative disorder.

132. The use of claim 131, wherein the disorder is cancer.

133. The use of claim 132, wherein the cancer is hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer.

134. The use of claim 130, wherein the disorder is a metabolic disorder.

135. The use of claim 134, wherein the metabolic disorder is diabetes.

136. The use of claim 134, wherein the metabolic disorder is obesity.

137. The use of claim 130, wherein the disorder is a blood disorder.

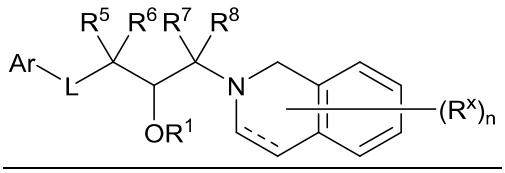
138. The use of claim 137, wherein the blood disorder is a hemoglobinopathy.

139. The use of claim 138, wherein the blood disorder is sickle cell anemia.

140. The use of claim 138], wherein the blood disorder is β-thalessemia.

Claims

1. A compound of Formula (**I**):



I

or a pharmaceutically acceptable salt thereof,

wherein

------ represents a single or double bond;

R^1 is hydrogen, R^z, or –C(O)R^z, wherein R^z is optionally substituted C_{1-6} alkyl;

L is –N(R)C(O)–, –C(O)N(R)–,–N(R)C(O)O–, or –OC(O)N(R)–;

each R is independently hydrogen or optionally substituted C_{1-6} aliphatic;

Ar is a monocyclic or bicyclic aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein Ar is substituted with 0, 1, 2, 3, 4, or 5 R^y groups, as valency permits;

each R^y is independently selected from the group consisting of halo, -CN, -NO_2, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -$N(R^B)_2$, -SR^A, -$C(=O)R^A$, -$C(O)OR^A$, -$C(O)SR^A$, -$C(O)N(R^B)_2$, -$C(O)N(R^B)N(R^B)_2$, -$OC(O)R^A$, -$OC(O)N(R^B)_2$, -$NR^BC(O)R^A$, -$NR^BC(O)N(R^B)_2$, -$NR^BC(O)N(R^B)N(R^B)_2$, -$NR^BC(O)OR^A$, -$SC(O)R^A$, -$C(=NR^B)R^A$, -$C(=NNR^B)R^A$, -$C(=NOR^A)R^A$, -$C(=NR^B)N(R^B)_2$, -$NR^BC(=NR^B)R^B$, -$C(=S)R^A$, -$C(=S)N(R^B)_2$, -$NR^BC(=S)R^A$, -$S(O)R^A$, -$OS(O)_2R^A$, -SO_2R^A, -$NR^BSO_2R^A$, and -$SO_2N(R^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^5, R^6, R^7, and R^8 are independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, -OR', and $-N(R'')_2$;

R' is hydrogen or optionally substituted aliphatic;

each R" is independently hydrogen or optionally substituted aliphatic, or two R" are taken together with their intervening atoms to form a heterocyclic ring; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

wherein, and unless otherwise specified,

heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

carbocyclyl or carbocyclic refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms and zero heteroatoms in the non–aromatic ring system;

aryl refers to a radical of a monocyclic or polycyclic aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur,

wherein

each instance of substituted, when on a carbon atom, is independently selected from the group consisting of halogen, –CN, –OH, $–OR^{aa}$, $–N(R^{bb})_2$, –SH, $–SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2H$, –CHO, $–C(OR^{cc})_2$, $–CO_2R^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–OC(=O)N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–NR^{bb}CO_2R^{aa}$, $–NR^{bb}C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–OC(=NR^{bb})N(R^{bb})_2$, –

$NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $–C(=O)NR^{bb}SO_2R^{aa}$, $–NR^{bb}SO_2R^{aa}$, $–SO_2N(R^{bb})_2$, $–SO_2R^{aa}$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; or two geminal hydrogens on a carbon atom are replaced with the group =O;

each instance of substituted, when on a nitrogen atom, is independently selected from the group consisting of hydrogen, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{aa} is, independently, selected from $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

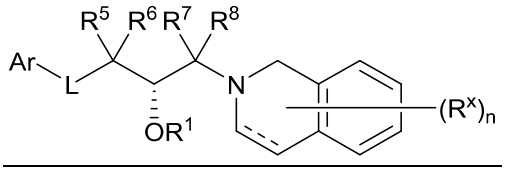
each instance of R^{dd} is, independently, selected from halogen, –CN, –SO_2H, –SO_3H, –OH, –OR^{ee}, –$ON(R^{ff})_2$, –$N(R^{ff})_2$, –SH, –SR^{ee}, –$C(=O)R^{ee}$, –CO_2H, –CO_2R^{ee}, –$OC(=O)R^{ee}$, –OCO_2R^{ee}, –$C(=O)N(R^{ff})_2$, –$OC(=O)N(R^{ff})_2$, –$NR^{ff}C(=O)R^{ee}$, –$NR^{ff}CO_2R^{ee}$, –$NR^{ff}C(=O)N(R^{ff})_2$, –$C(=NR^{ff})OR^{ee}$, –$OC(=NR^{ff})R^{ee}$, –$OC(=NR^{ff})OR^{ee}$, –$C(=NR^{ff})N(R^{ff})_2$, –$OC(=NR^{ff})N(R^{ff})_2$, –$NR^{ff}C(=NR^{ff})N(R^{ff})_2$, –$NR^{ff}SO_2R^{ee}$, –$SO_2N(R^{ff})_2$, –$SO_2R^{ee}$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, –SO_2H, –SO_3H, –OH, –$OC_{1–6}$ alkyl, –$ON(C_{1–6}$ alkyl$)_2$, –$N(C_{1–6}$ alkyl$)_2$, –$N(C_{1–6}$ alkyl$)_3^+X^–$, –SH, –$SC_{1–6}$ alkyl, –$C(=O)(C_{1–6}$ alkyl), –CO_2H, –$CO_2(C_{1–6}$ alkyl), –$OC(=O)(C_{1–6}$ alkyl), –$OCO_2(C_{1–6}$ alkyl), –$C(=O)NH_2$, –$C(=O)N(C_{1–6}$ alkyl$)_2$, –$OC(=O)NH(C_{1–6}$ alkyl), –$NHC(=O)(C_{1–6}$ alkyl), –$N(C_{1–6}$ alkyl$)C(=O)(C_{1–6}$ alkyl), –$NHCO_2(C_{1–6}$ alkyl), –$NHC(=O)N(C_{1–6}$ alkyl$)_2$, –$NHC(=O)NH(C_{1–6}$ alkyl), –$NHC(=O)NH_2$, –$C(=NH)O(C_{1–6}$ alkyl), –$OC(=NH)(C_{1–6}$ alkyl), –$OC(=NH)OC_{1–6}$ alkyl, –$C(=NH)N(C_{1–6}$ alkyl$)_2$, –$C(=NH)NH(C_{1–6}$ alkyl), –$C(=NH)NH_2$, –$OC(=NH)N(C_{1–6}$ alkyl$)_2$, –$OC(NH)NH(C_{1–6}$ alkyl), –$OC(NH)NH_2$, –$NHC(NH)N(C_{1–6}$ alkyl$)_2$, –$NHC(=NH)NH_2$, –$NHSO_2(C_{1–6}$ alkyl), –$SO_2N(C_{1–6}$ alkyl$)_2$, –$SO_2NH(C_{1–6}$ alkyl), –SO_2NH_2,–$SO_2C_{1–6}$ alkyl, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein $X^–$ is a counterion.

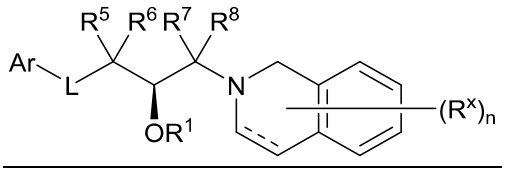
2. The compound of claim 1, wherein the compound is of Formula (**I-a**):



I-a

or a pharmaceutically acceptable salt thereof.

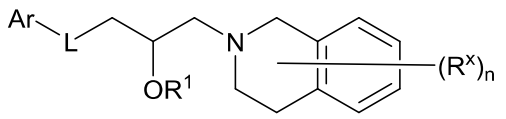
3. The compound of claim 1, wherein the compound is of Formula (**I-b**):



I-b

or a pharmaceutically acceptable salt thereof.

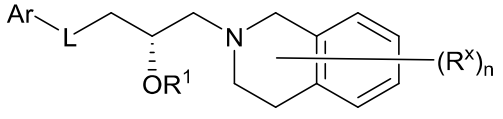
4. The compound of claim 1, wherein the compound is of Formula (**I'**):



I'

or a pharmaceutically acceptable salt thereof.

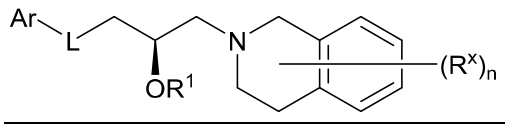
5. The compound of claim 4, wherein the compound is of Formula (**I'-a**):



I'-a

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 4, wherein the compound is of Formula (**I'-b**):



I'-b

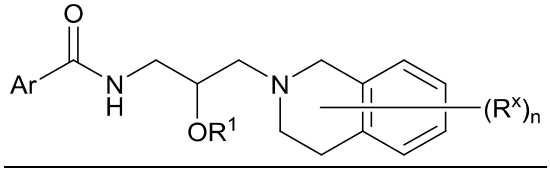
or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, wherein L is –C(O)N(R)–.

8. The compound of any one of claims 1-6, wherein L is –N(R)C(O)–.

9. The compound of any one of claims 1-6, wherein L is –OC(O)NH-.

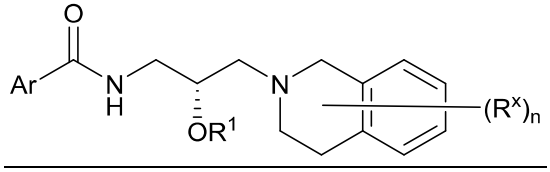
10. The compound of claim 1, wherein the compound is of Formula (**II**):



II

or a pharmaceutically acceptable salt thereof.

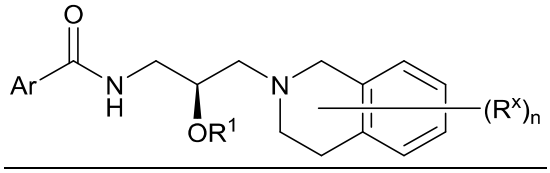
11. The compound of claim 10, wherein the compound is of Formula (**II-a**):



II-a

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 10, wherein the compound is of Formula (**II-b**):



II-b

or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1-12, wherein R^1 is hydrogen.

14. The compound of any one of claims 1-13, wherein n is 0.

15. The compound of any one of claims 1-13, wherein n is 1.

16. The compound of any one of claims 1-13, wherein n is 2.

17. The compound of any one of claims 1-16, wherein Ar is phenyl.

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

19. The compound of claim 18, wherein Ar is a 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

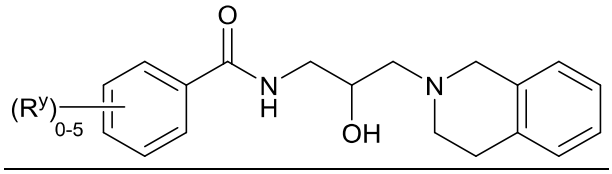
20. The compound of claim 19, wherein Ar is pyridyl.

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

22. The compound of any one of claims 1-20, wherein Ar is substituted with 1 or 2 R^y groups.

23. The compound of claim 22, wherein Ar is substituted with one R^y group.

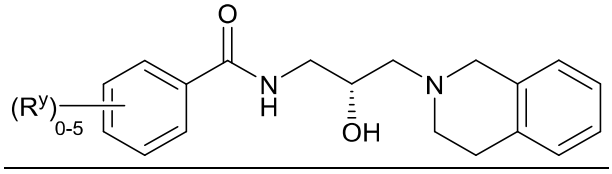
24. The compound of claim 1, wherein the compound is of Formula (**III**):



III

or a pharmaceutically acceptable salt thereof.

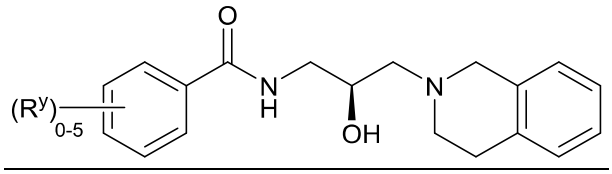
25. The compound of claim 24, wherein the compound is of Formula (**III-a**):



III-a

or a pharmaceutically acceptable salt thereof.

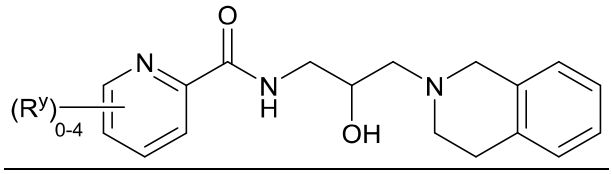
26. The compound of claim 24, wherein the compound is of Formula (**III-b**):



III-b

or a pharmaceutically acceptable salt thereof.

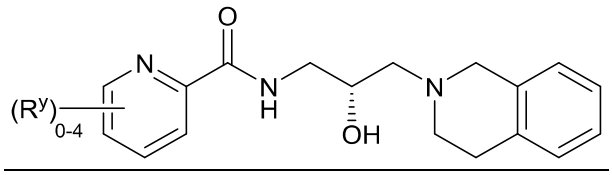
27. The compound of claim 1, wherein the compound is of Formula (**IV**):



IV

or a pharmaceutically acceptable salt thereof.

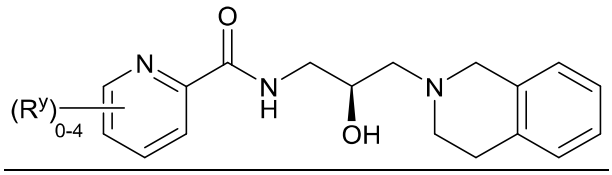
28. The compound of claim 1, wherein the compound is of Formula (**IV-a**):



IV-a

or a pharmaceutically acceptable salt thereof.

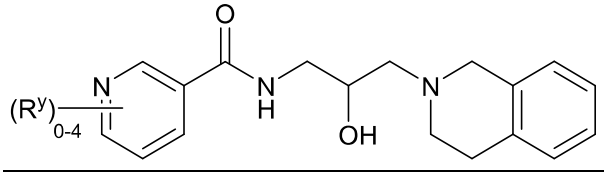
29. The compound of claim 1, wherein the compound is of Formula (**IV-b**):



IV-b

or a pharmaceutically acceptable salt thereof.

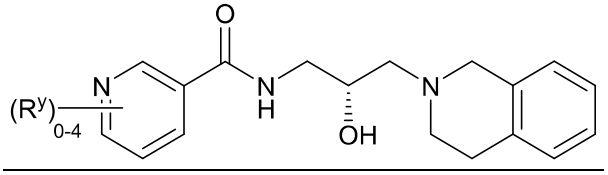
30. The compound of claim 1, wherein the compound is of Formula (**V**):



V

or a pharmaceutically acceptable salt thereof.

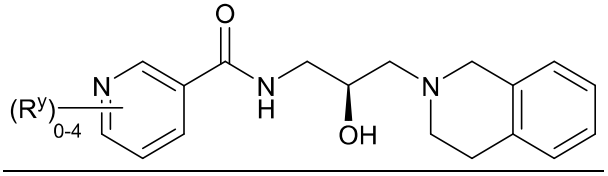
31. The compound of claim 1, wherein the compound is of Formula (**V-a**):



V-a

or a pharmaceutically acceptable salt thereof.

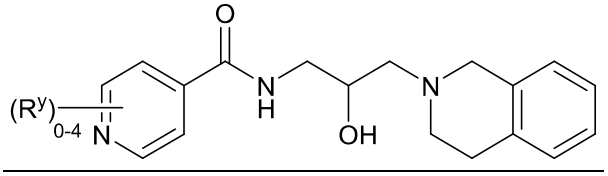
32. The compound of claim 1, wherein the compound is of Formula (**V-b**):



V-b

or a pharmaceutically acceptable salt thereof.

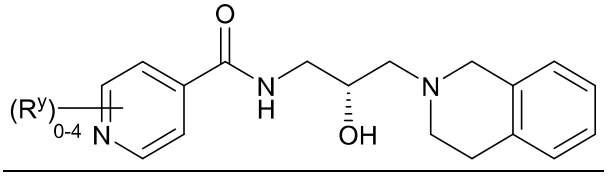
33. The compound of claim 1, wherein the compound is of Formula (**VI**):



VI

or a pharmaceutically acceptable salt thereof.

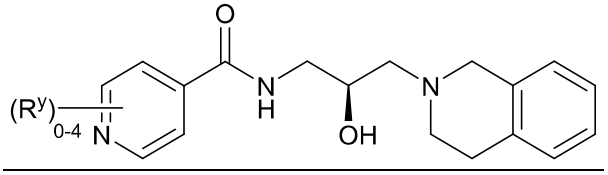
34. The compound of claim 1, wherein the compound is of Formula (**VI-a**):



VI-a

or a pharmaceutically acceptable salt thereof.

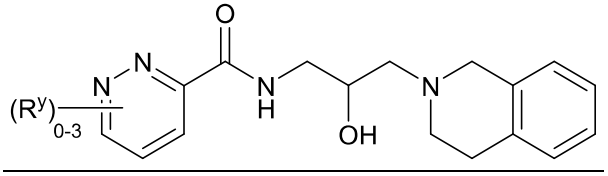
35. The compound of claim 1, wherein the compound is of Formula (**VI-b**):



VI-b

or a pharmaceutically acceptable salt thereof.

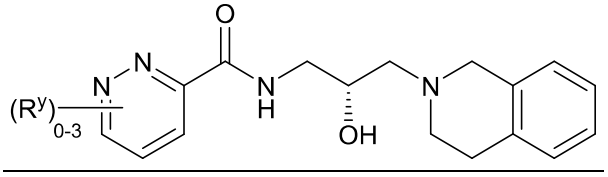
36. The compound of claim 1, wherein the compound is of Formula (**VII**):



VII

or a pharmaceutically acceptable salt thereof.

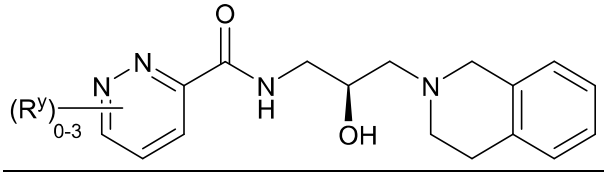
37. The compound of claim 1, wherein the compound is of Formula (**VII-a**):



VII-a

or a pharmaceutically acceptable salt thereof.

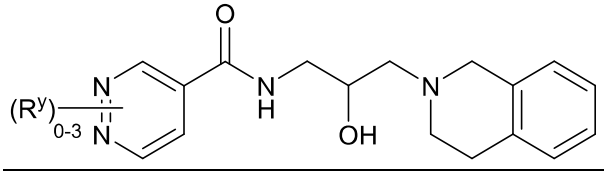
38. The compound of claim 1, wherein the compound is of Formula (**VII-b**):



VII-b

or a pharmaceutically acceptable salt thereof.

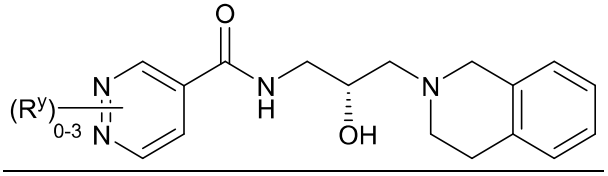
39. The compound of claim 1, wherein the compound is of Formula (**VIII**):



VIII

or a pharmaceutically acceptable salt thereof.

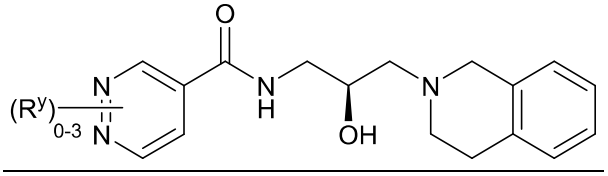
40. The compound of claim 1, wherein the compound is of Formula (**VIII-a**):



VIII-a

or a pharmaceutically acceptable salt thereof.

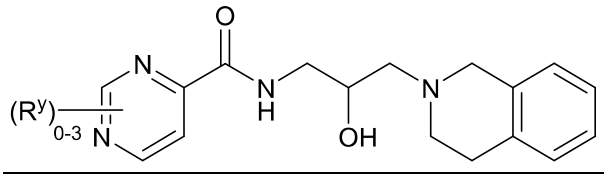
41. The compound of claim 1, wherein the compound is of Formula (**VIII-b**):



VIII-b

or a pharmaceutically acceptable salt thereof.

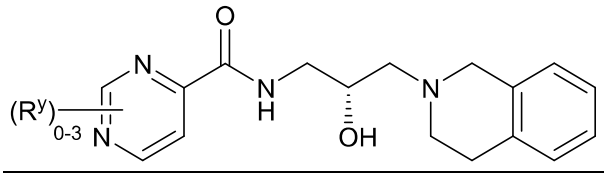
42. The compound of claim 1, wherein the compound is of Formula (**IX**):



IX

or a pharmaceutically acceptable salt thereof.

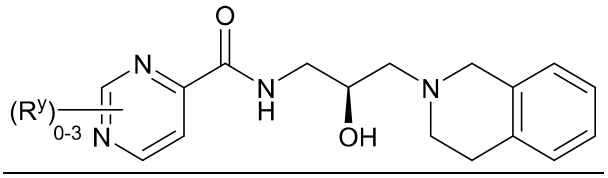
43. The compound of claim 1, wherein the compound is of Formula (**IX-a**):



IX-a

or a pharmaceutically acceptable salt thereof.

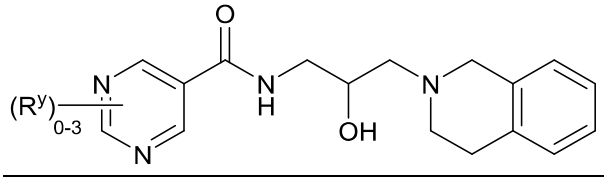
44. The compound of claim 1, wherein the compound is of Formula (**IX-b**):



IX-b

or a pharmaceutically acceptable salt thereof.

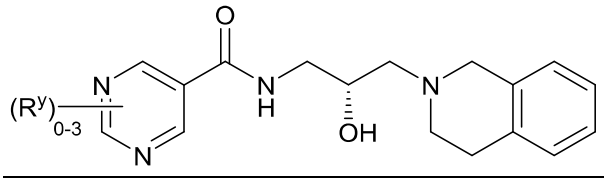
45. The compound of claim 1, wherein the compound is of Formula (**X**):



X

or a pharmaceutically acceptable salt thereof.

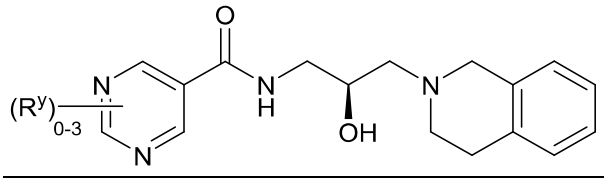
46. The compound of claim 1, wherein the compound is of Formula (**X-a**):



X-a

or a pharmaceutically acceptable salt thereof.

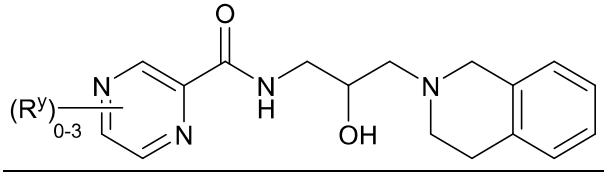
47. The compound of claim 1, wherein the compound is of Formula (**X-b**):



X-b

or a pharmaceutically acceptable salt thereof.

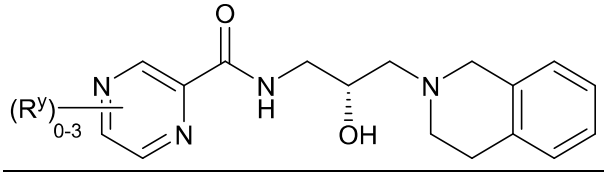
48. The compound of claim 1, wherein the compound is of Formula (**XI**):



XI

or a pharmaceutically acceptable salt thereof.

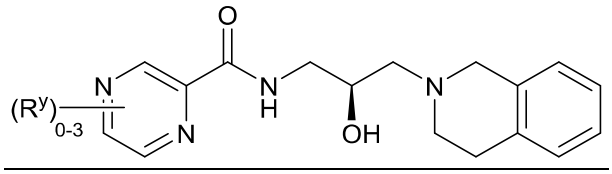
49. The compound of claim 1, wherein the compound is of Formula (**XI-a**):



XI-a

or a pharmaceutically acceptable salt thereof.

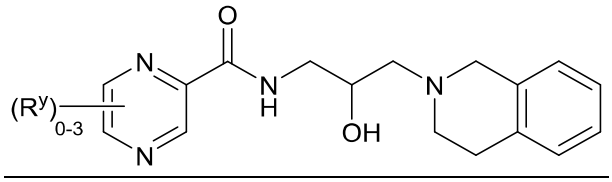
50. The compound of claim 1, wherein the compound is of Formula (**XI-b**):



XI-b

or a pharmaceutically acceptable salt thereof.

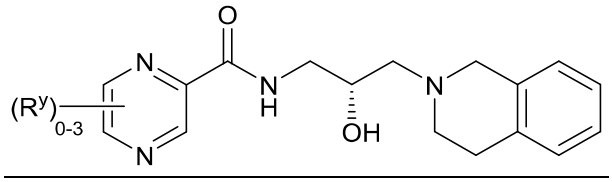
51. The compound of claim 1, wherein the compound is of Formula (**XII**):



XII

or a pharmaceutically acceptable salt thereof.

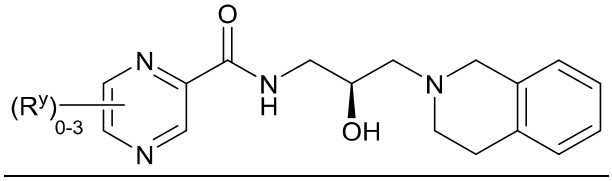
52. The compound of claim 1, wherein the compound is of Formula (**XII-a**):



XII-a

or a pharmaceutically acceptable salt thereof.

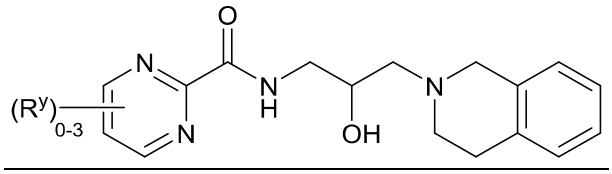
53. The compound of claim 1, wherein the compound is of Formula (**XII-b**):



XII-b

or a pharmaceutically acceptable salt thereof.

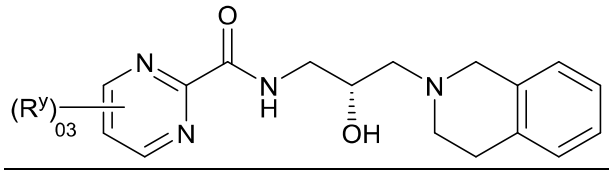
54. The compound of claim 1, wherein the compound is of Formula (**XIII**):



XIII

or a pharmaceutically acceptable salt thereof.

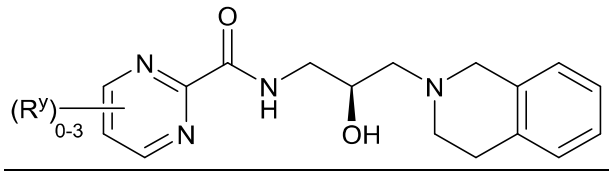
55. The compound of claim 1, wherein the compound is of Formula (**XIII-a**):



XIII-a

or a pharmaceutically acceptable salt thereof.

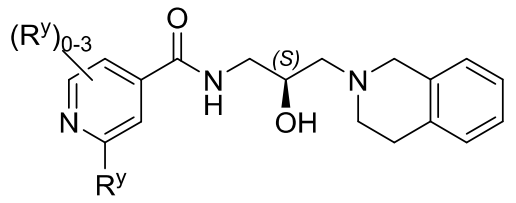
56. The compound of claim 1, wherein the compound is of Formula (**XIII-b**):



XIII-b

or a pharmaceutically acceptable salt thereof.

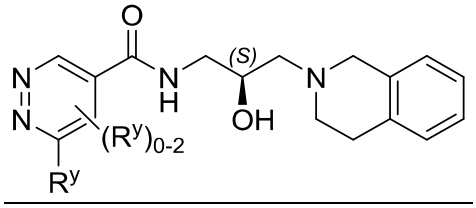
57. The compound of claim 1, wherein the compound is of Formula (**XV**):



XV

or a pharmaceutically acceptable salt thereof.

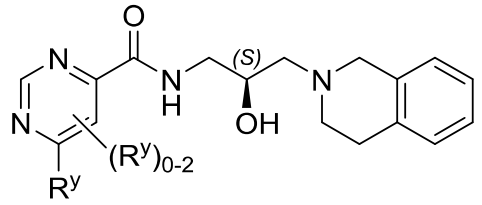
58. The compound of claim 1, wherein the compound is of Formula (**XVI**):



XVI

or a pharmaceutically acceptable salt thereof.

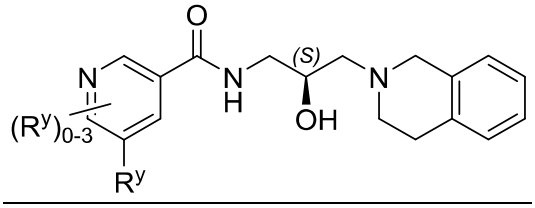
59. The compound of claim 1, wherein the compound is of Formula (**XVII**):



XVII

or a pharmaceutically acceptable salt thereof.

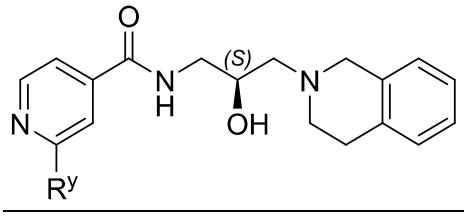
60. The compound of claim 1, wherein the compound is of Formula (**XVIII**):



XVIII

or a pharmaceutically acceptable salt thereof.

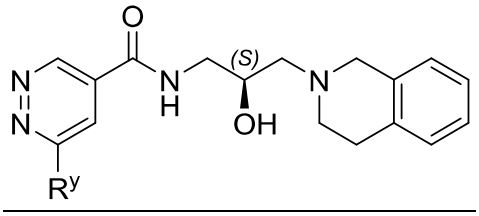
61. The compound of claim 1, wherein the compound is of Formula (**XV-a**):



XV-a

or a pharmaceutically acceptable salt thereof.

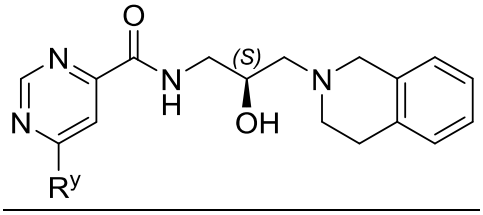
62. The compound of claim 1, wherein the compound is of Formula (**XVI-a**):



XVI-a

or a pharmaceutically acceptable salt thereof.

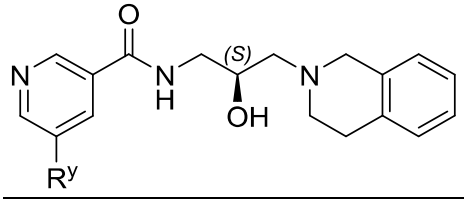
63. The compound of claim 1, wherein the compound is of Formula (**XVII-a**):



XVII-a

or a pharmaceutically acceptable salt thereof.

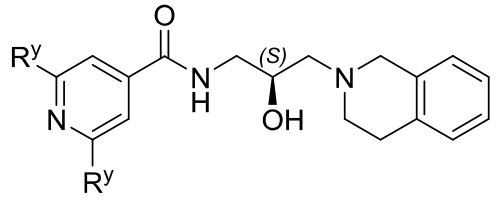
64. The compound of claim 1, wherein the compound is of Formula (**XVIII-a**):



XVIII-a

or a pharmaceutically acceptable salt thereof.

65. The compound of claim 1, wherein the compound is of Formula (**XV-b**):



XV-b

or a pharmaceutically acceptable salt thereof.

66. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is heteroaryl or heterocyclyl.

67. The compound of claim 66, wherein at least one R^y is 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

68. The compound of claim 67, wherein at least one R^y is a 6-membered heteroaryl having 1-3 nitrogens.

69. The compound of claim 68, wherein at least one R^y is pyridyl.

70. The compound of claim 67, wherein at least one R^y is a 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

71. The compound of claim 70, wherein at least one R^y is optionally substituted pyrazole.

72. The compound of claim 70, wherein at least one R^y is pyrrole.

73. The compound of claim 66, wherein at least one R^y is a 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

74. The compound of claim 73, wherein at least one R^y is a 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur.

75. The compound of claim 74, wherein at least one R^y is optionally substituted pyrrolidine.

76. The compound of claim 73, wherein at least one R^y is a 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

77. The compound of claim 76, wherein at least one R^y is optionally substituted piperazine.

78. The compound of claim 76, wherein at least one R^y is morpholine.

79. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is optionally substituted aliphatic.

80. The compound of claim 79, wherein at least one R^y is optionally substituted C_{1-6} alkyl.

81. The compound of claim 80, wherein at least one R^y is C_{1-6} alkyl substituted with an aryl, heteroaryl, or heterocyclyl.

82. The compound of claim 81, wherein at least one R^y is $–CH_2$-aryl, $-CH_2$-heteroaryl, or $–CH_2$-heterocyclyl.

83. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is $-N(R^B)_2$.

84. The compound of claim 83, wherein one R^B is optionally substituted heterocyclyl, and the other R^B is C_{1-4} alkyl.

85. The compound of claim 83, wherein one R^B is optionally substituted heteroaryl, and the other R^B is C_{1-4} alkyl.

86. The compound of claim 83, wherein one R^B is optionally substituted cycloalkyl, and the other R^B is C_{1-4} alkyl.

87. The compound of claim 83, wherein at least one R^y is $–NHR^B$.

88. The compound of claim 87, wherein R^B is optionally substituted heterocyclyl.

89. The compound of claim 87, wherein R^B is optionally substituted heteroaryl.

90. The compound of claim 87, wherein R^B is optionally substituted cycloalkyl.

91. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is $-SO_2N(R^B)_2$.

92. The compound of claim 91, wherein at least one R^y is $–SO_2NHR^B$.

93. The compound of claim 92, wherein at least one R^y is $–SO_2NH_2$.

94. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is $-C(O)N(R^B)_2$.

95. The compound of claim 94, wherein at least one R^y is $-C(O)NHR^B$.

96. The compound of claim 95, wherein at least one R^y is $-C(O)NH_2$.

97. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is $-NR^BC(O)R^A$.

98. The compound of claim 97, wherein at least one R^y is $-NHC(O)R^A$.

99. The compound of claim 98, wherein at least one R^y is $-NHC(O)CH_3$.

100. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is $-NR^BSO_2R^A$.

101. The compound of claim 100, wherein at least one R^y is $-NHSO_2R^A$.

102. The compound of claim 101, wherein at least one R^y is $-NHSO_2CH_3$.

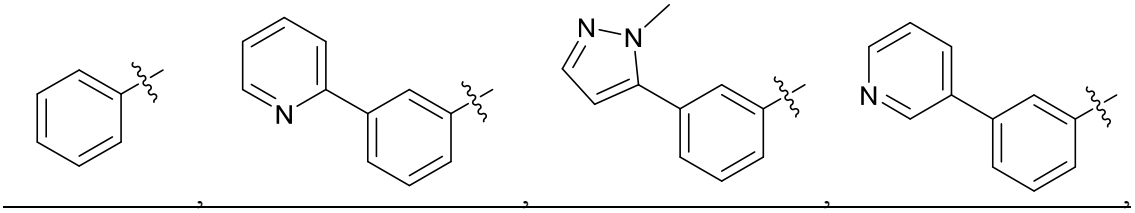
103. The compound of any one of claims 1-20 and 22-65, wherein at least one R^y is $-OR^A$.

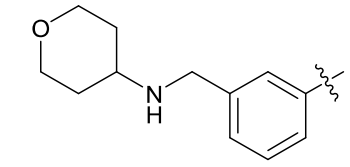
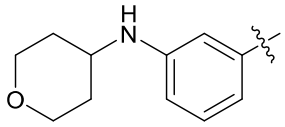
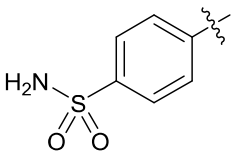
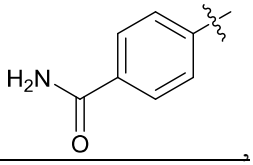
104. The compound of claim 103, wherein R^A is optionally substituted heterocyclyl.

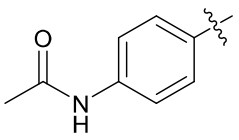
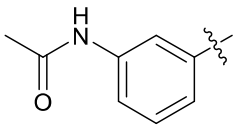
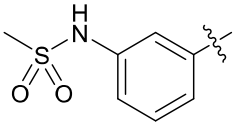
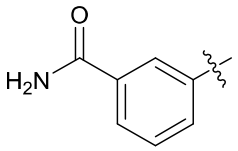
105. The compound of claim 103, wherein R^A is optionally substituted heteroaryl.

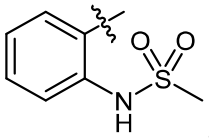
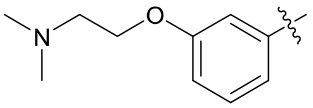
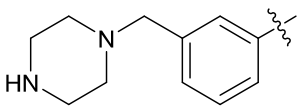
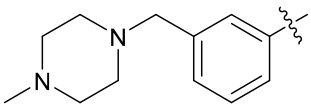
106. The compound of claim 103, wherein R^A is optionally substituted cycloalkyl.

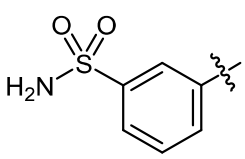
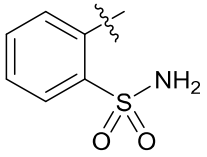
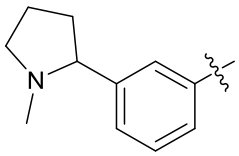
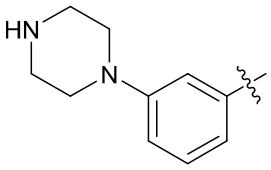
107. The compound of any one of claims 1-16, wherein Ar is selected from the group consisting of:

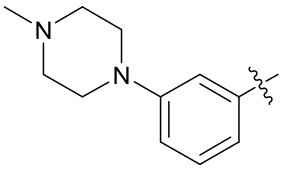
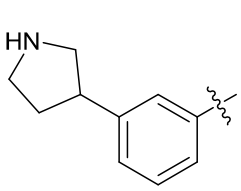
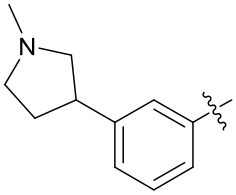
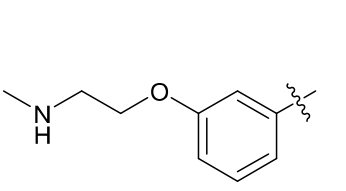


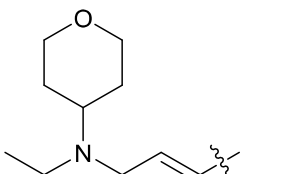
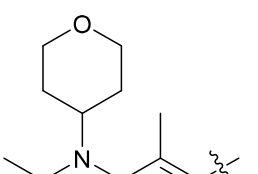
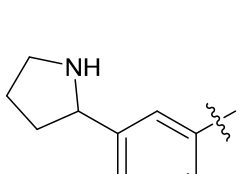
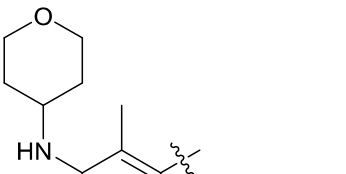





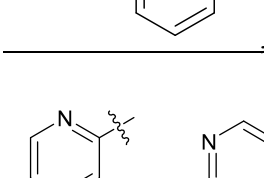
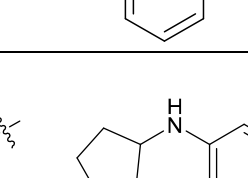
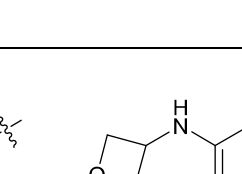
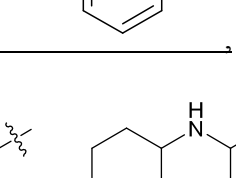





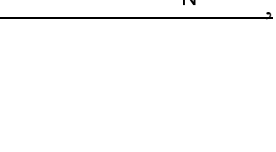





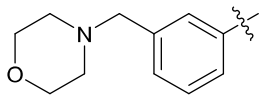
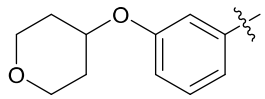
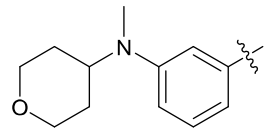
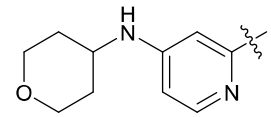





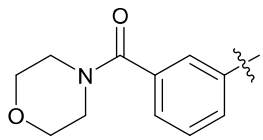
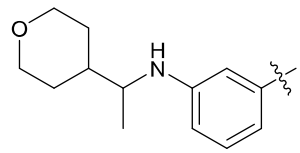
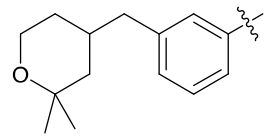
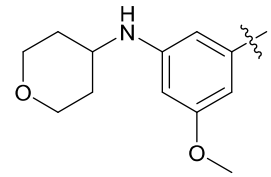





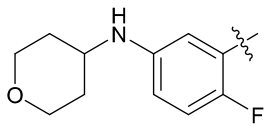
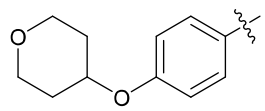





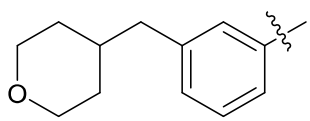
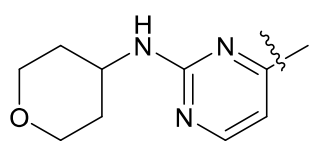
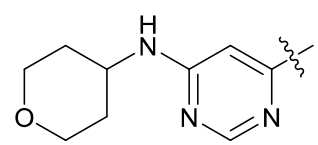


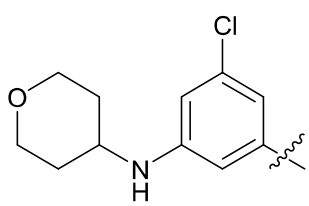
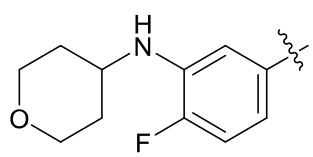
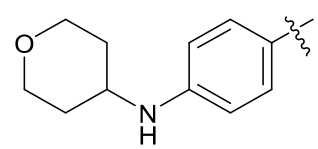
 ,  ,  ,  ,

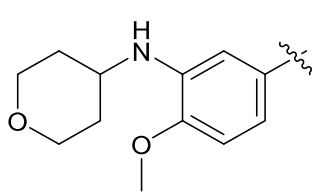
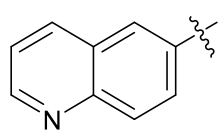
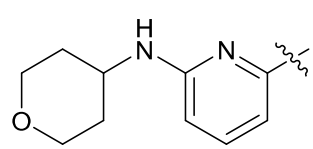
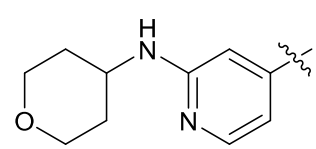
 ,  ,  ,  ,

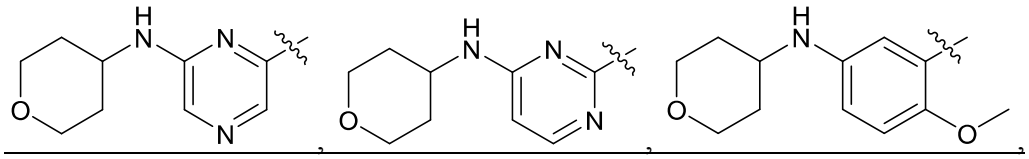
 , and  .

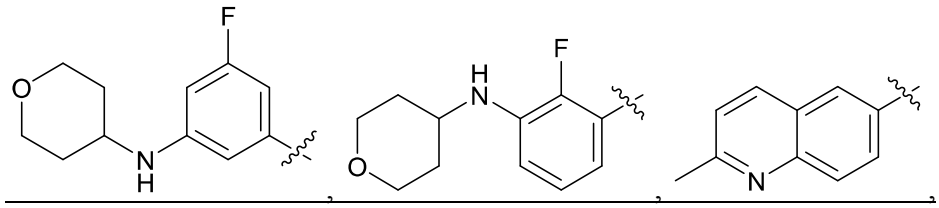
108. The compound of any one of claims 1-16, wherein Ar is selected from the group consisting of:

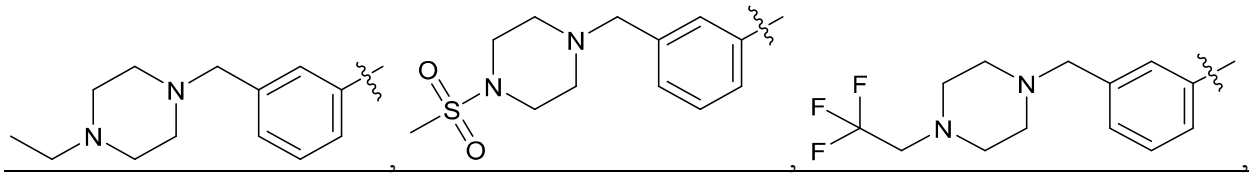
 ,  ,  ,

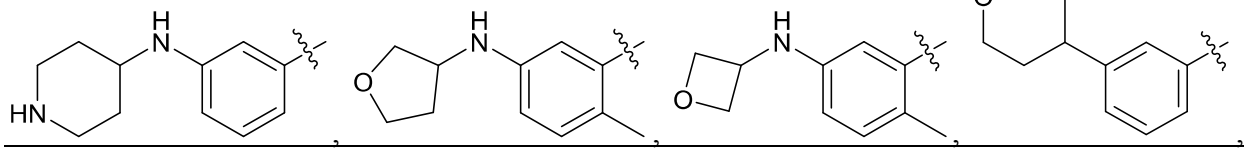
 ,  ,  ,

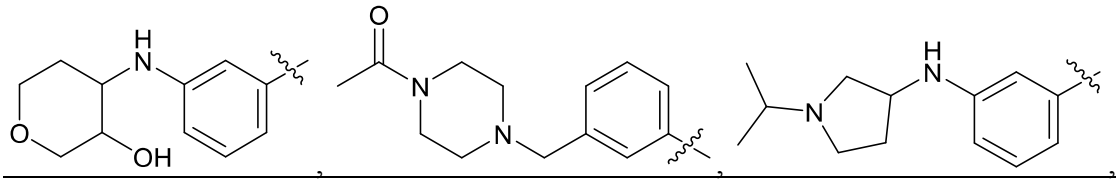
 ,  ,  ,  ,

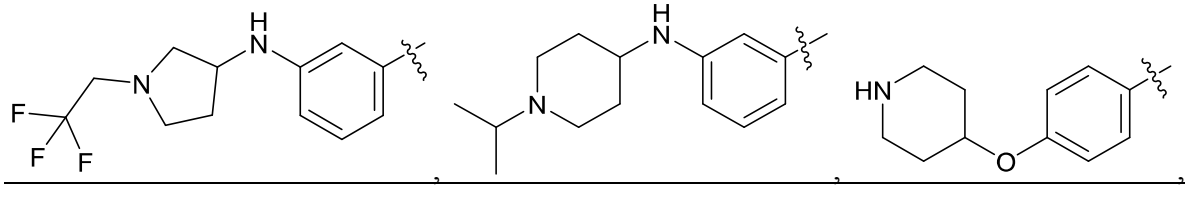


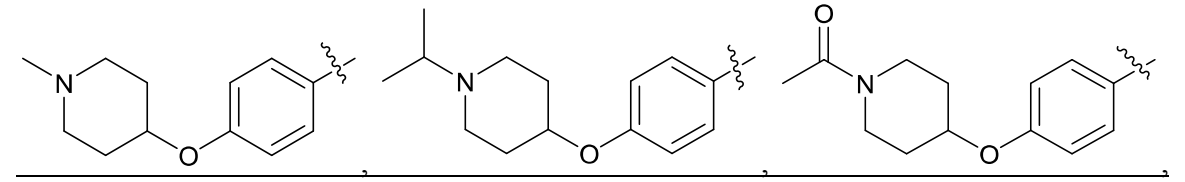


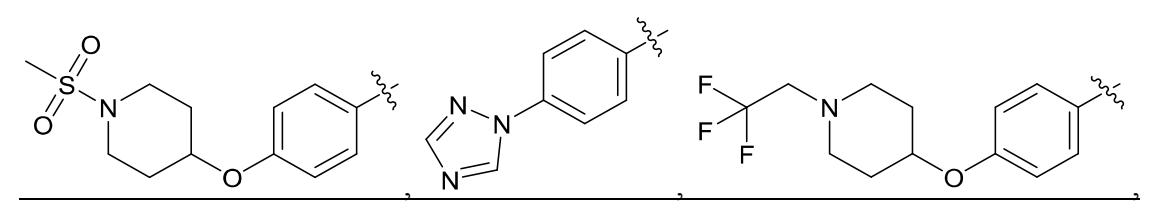


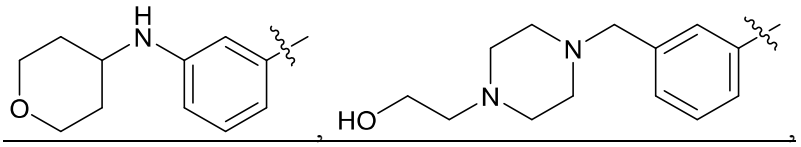


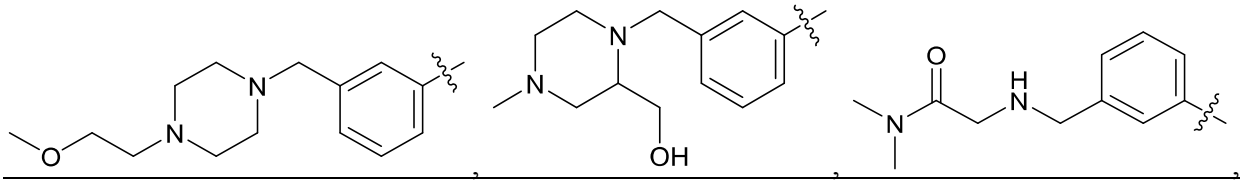


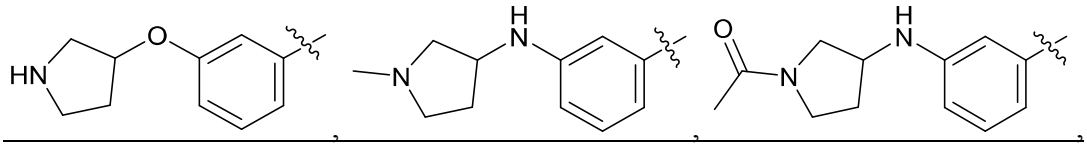


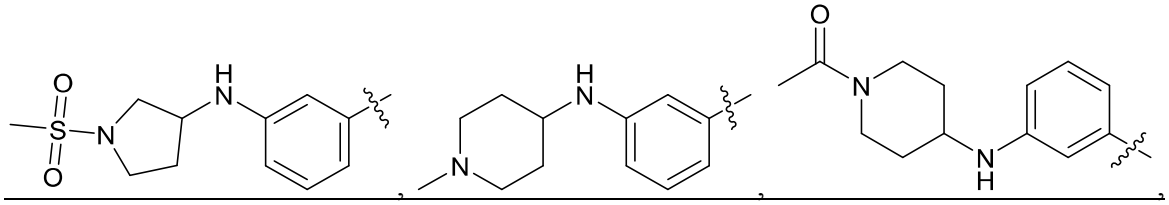


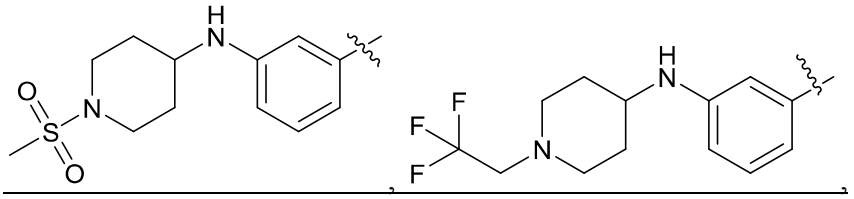


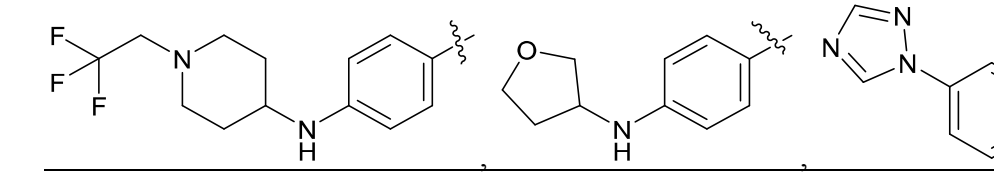


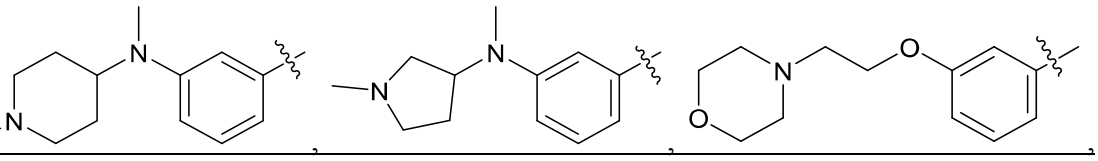


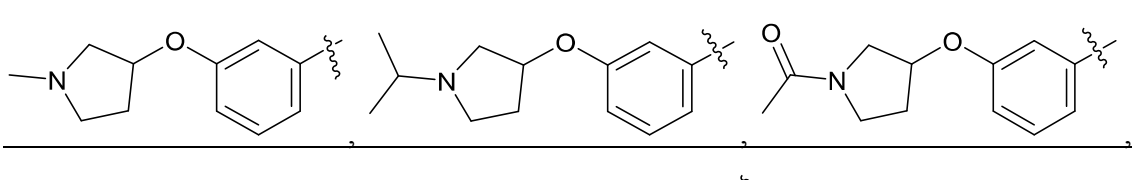


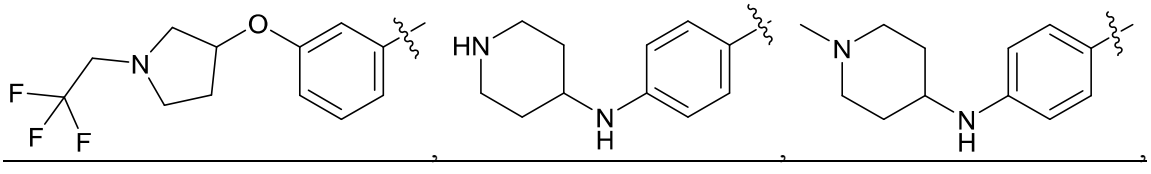


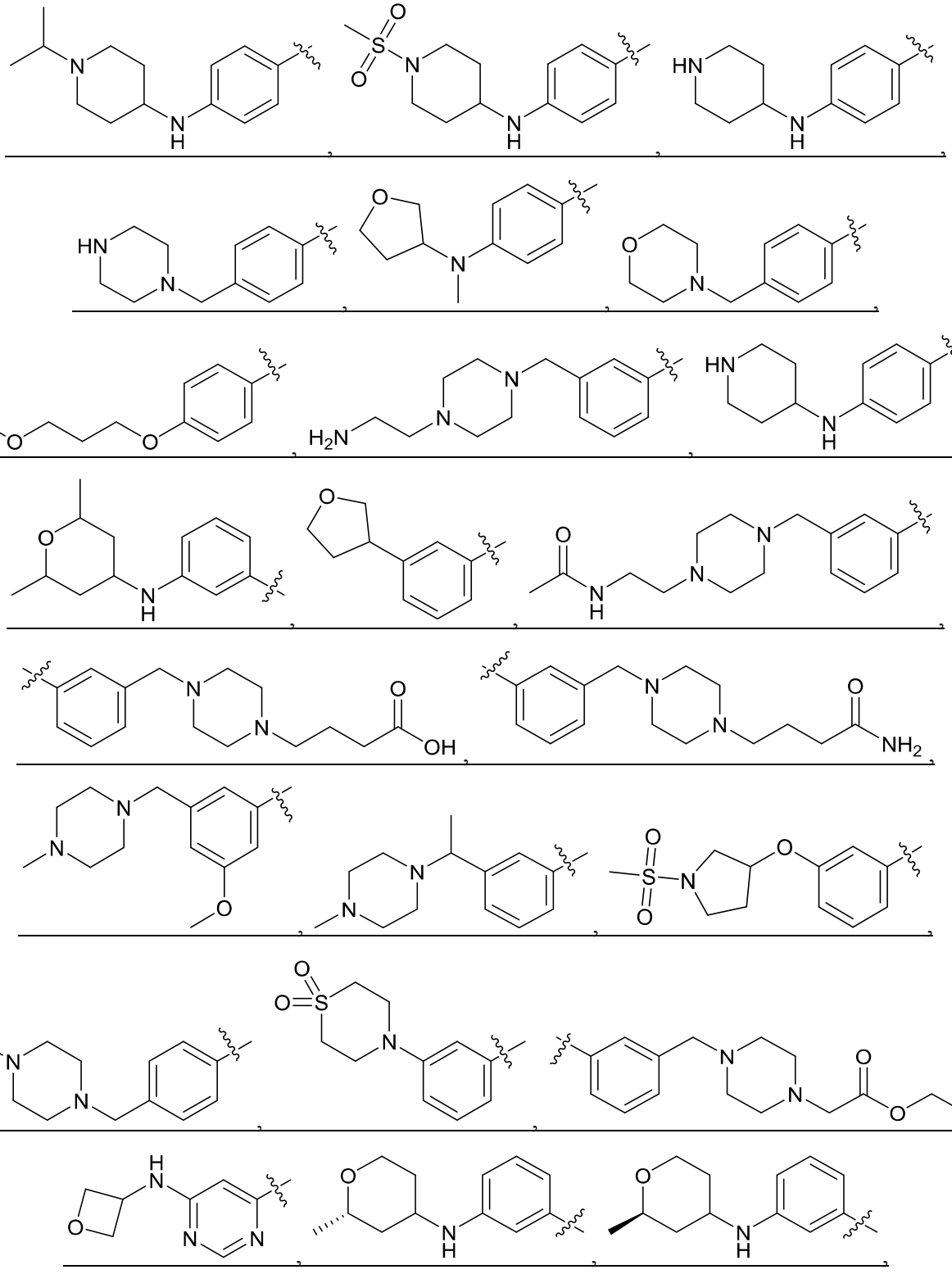


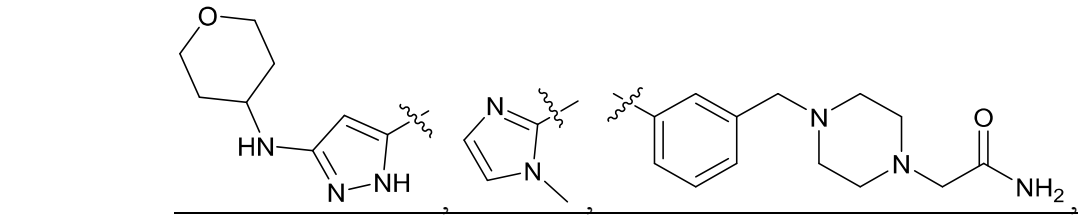


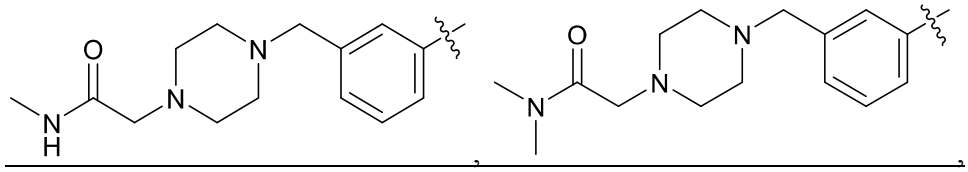


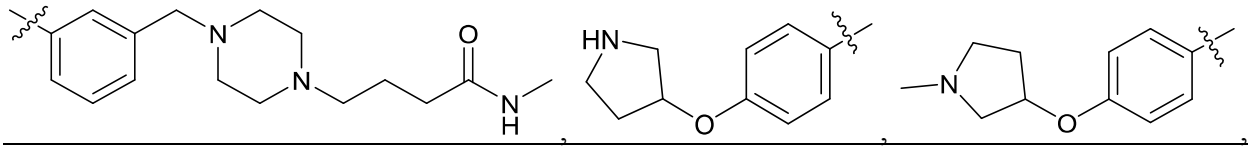


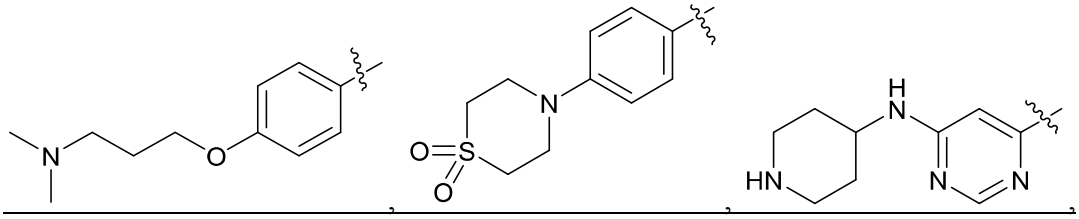


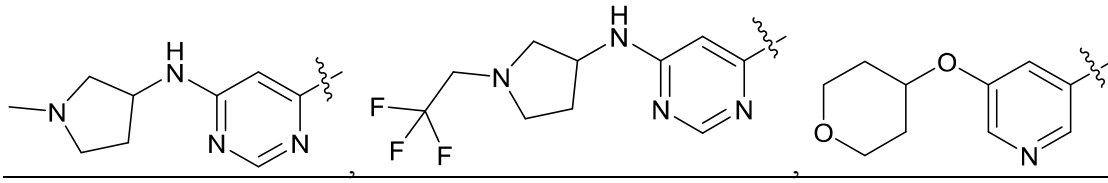


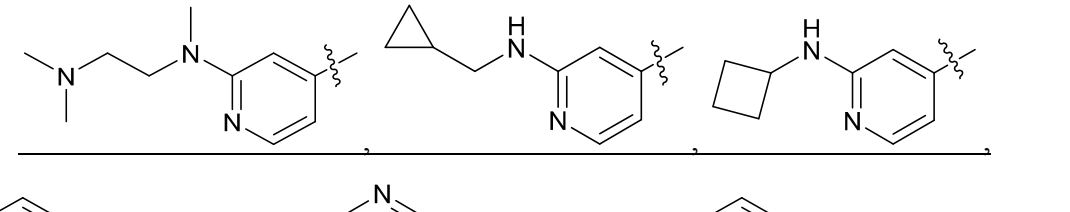


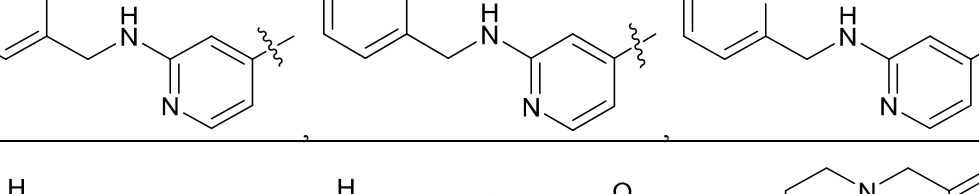


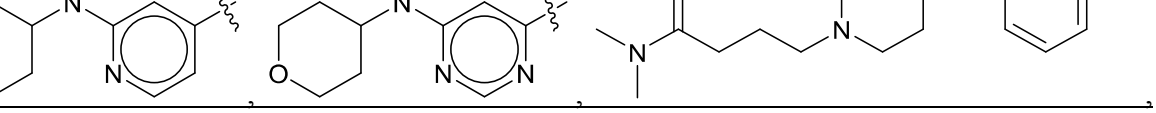


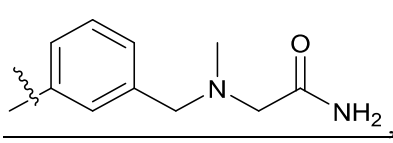
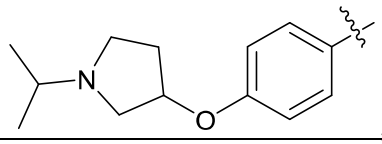
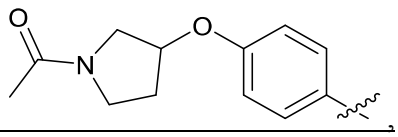
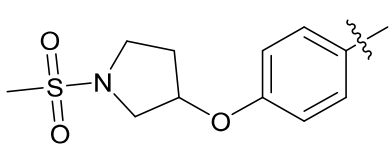
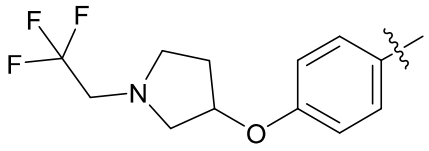
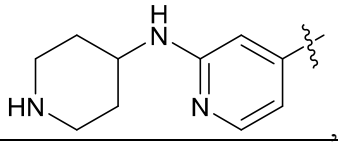
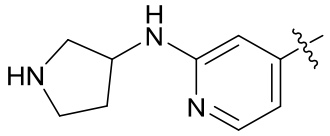
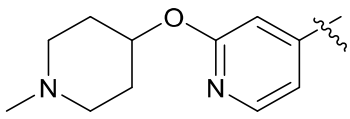
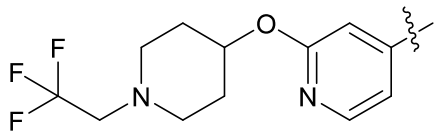
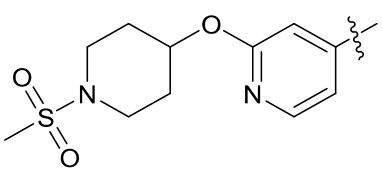
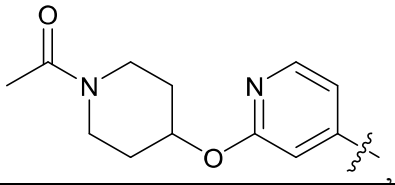
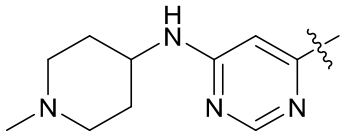
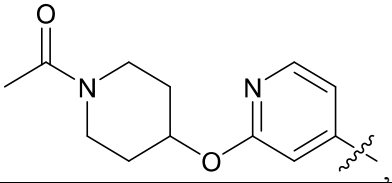
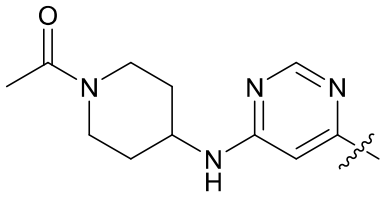
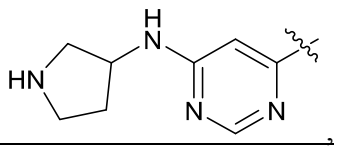
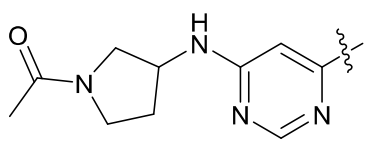


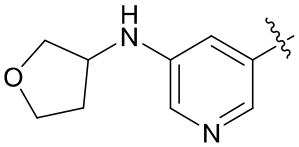
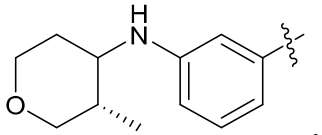
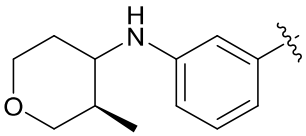
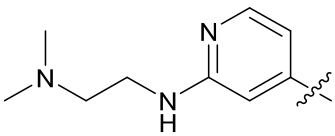
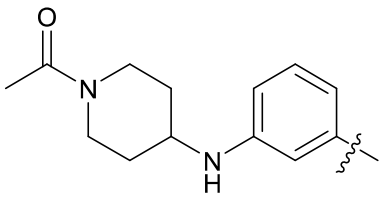
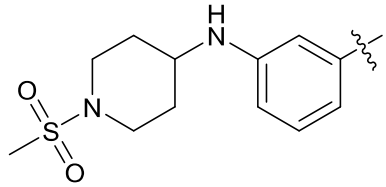
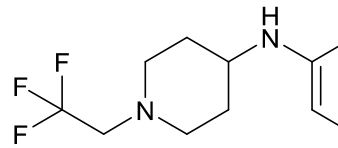


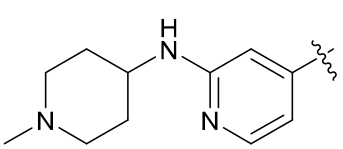


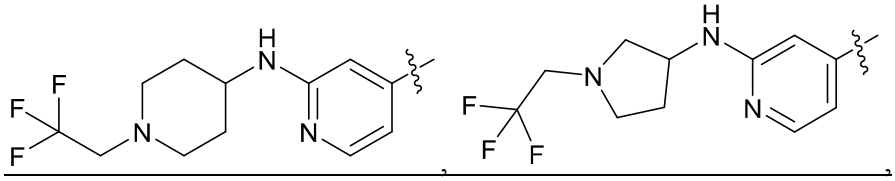


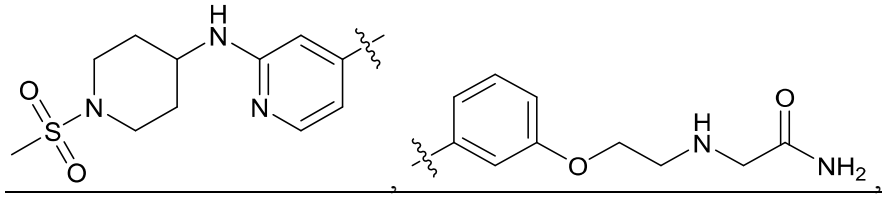


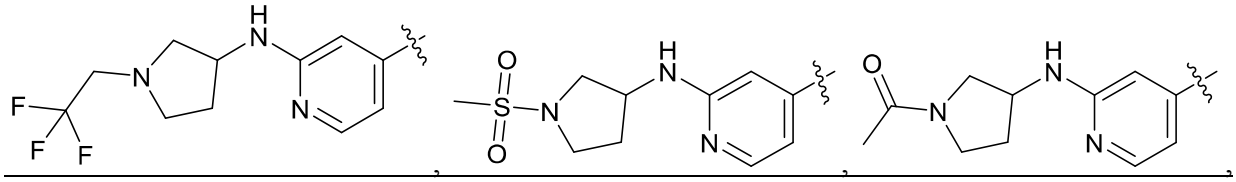

















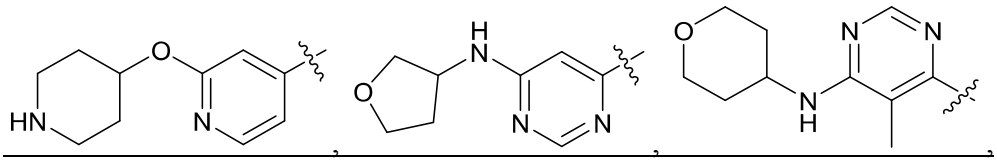








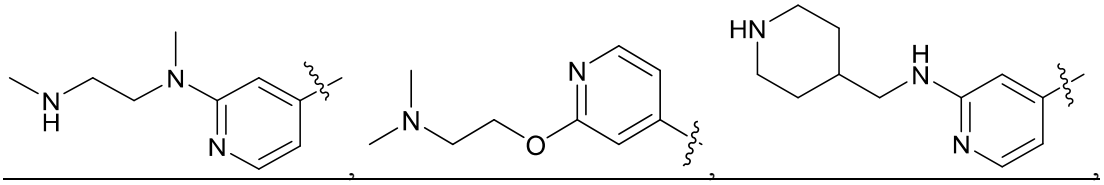


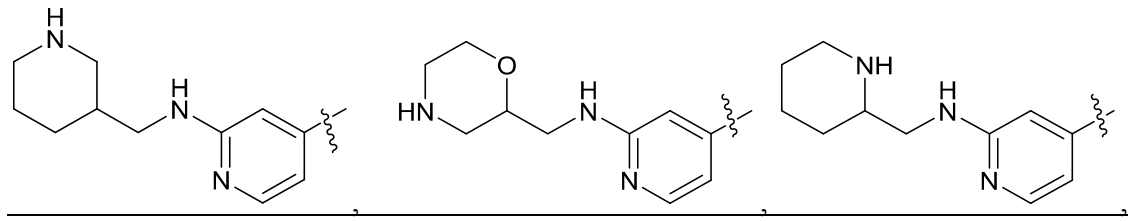


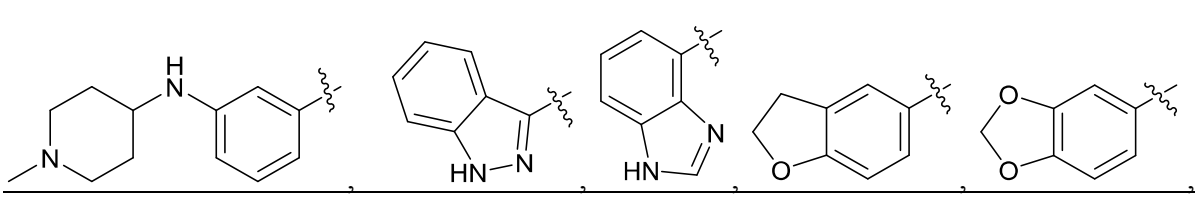


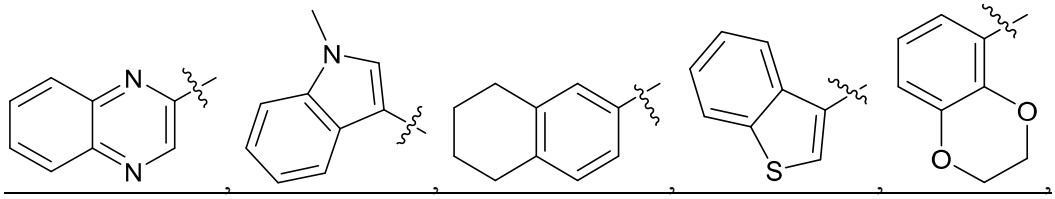


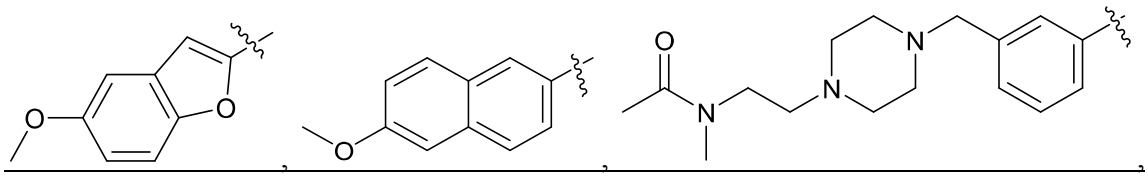


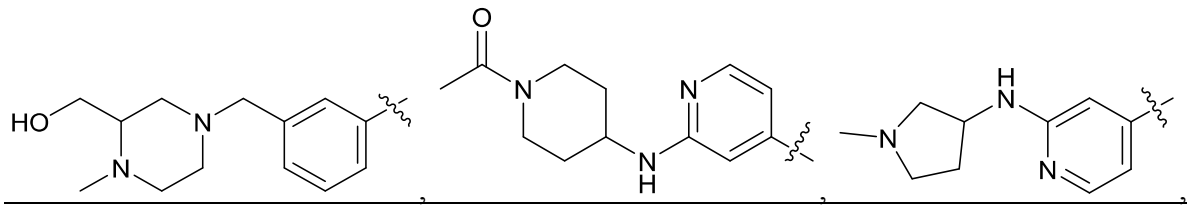


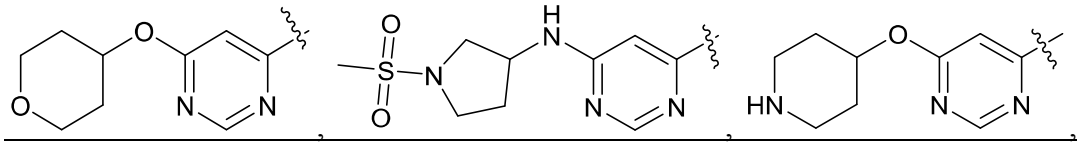


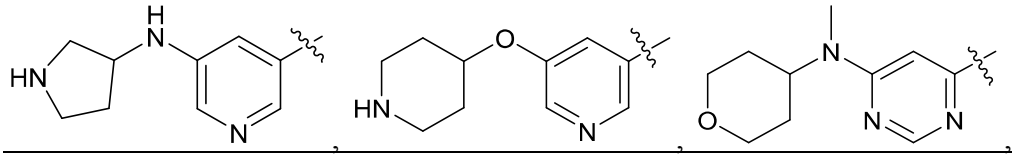


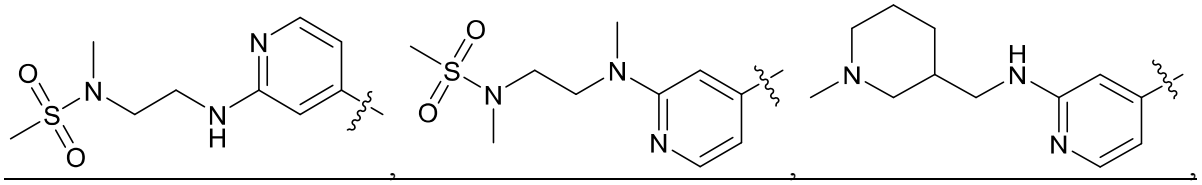


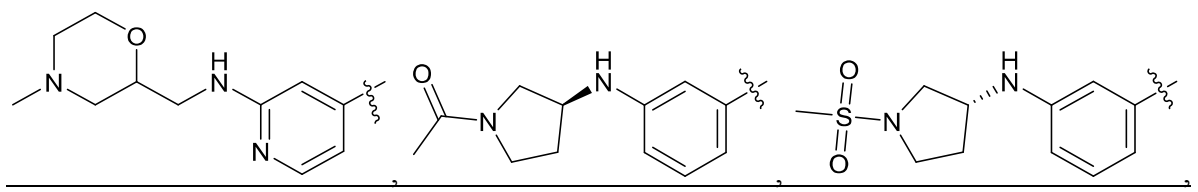


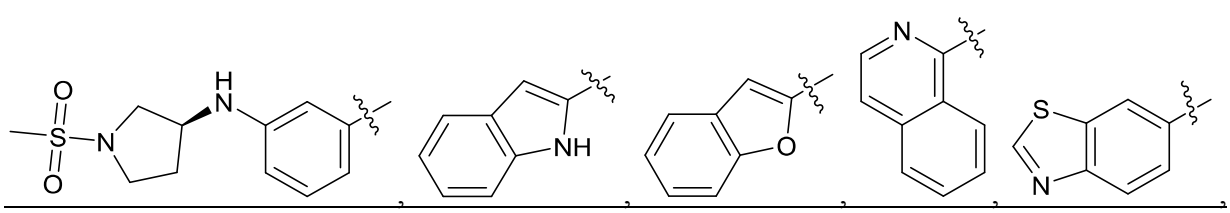


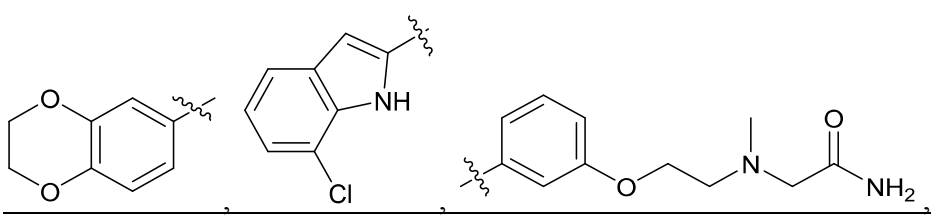


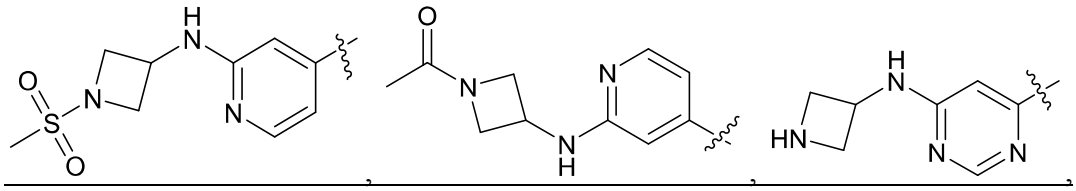


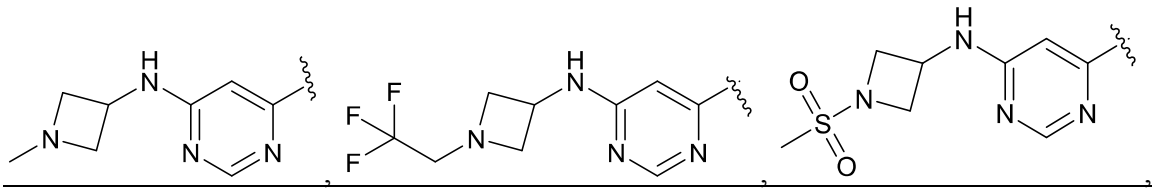


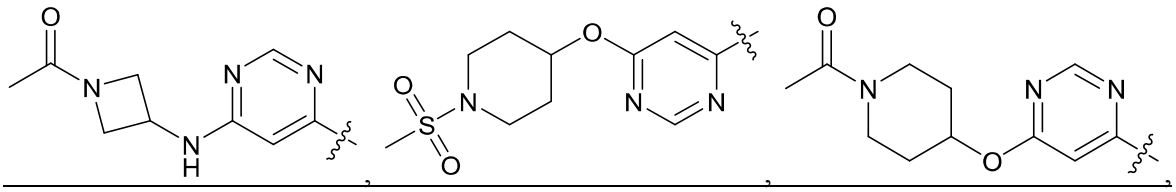


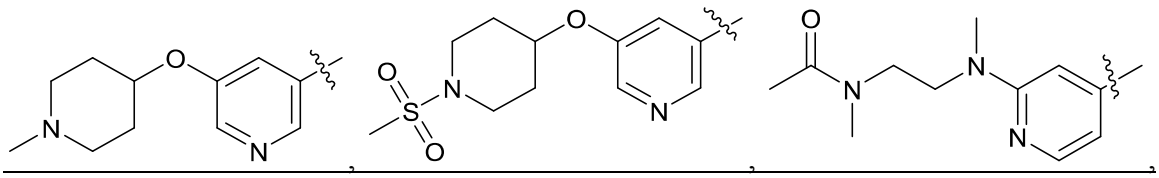


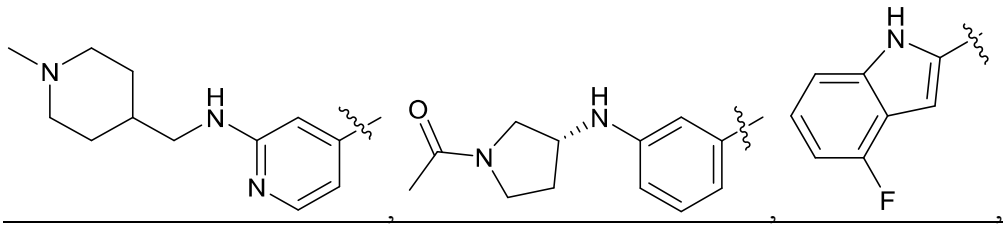


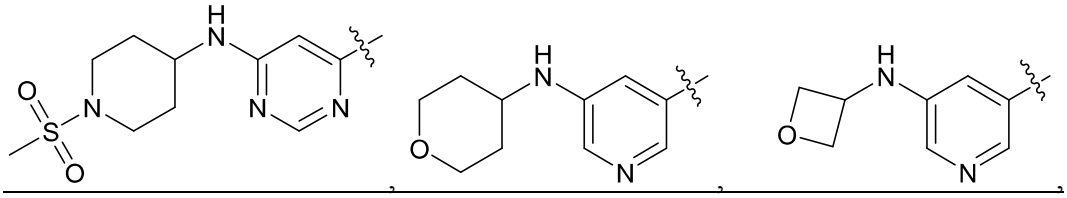


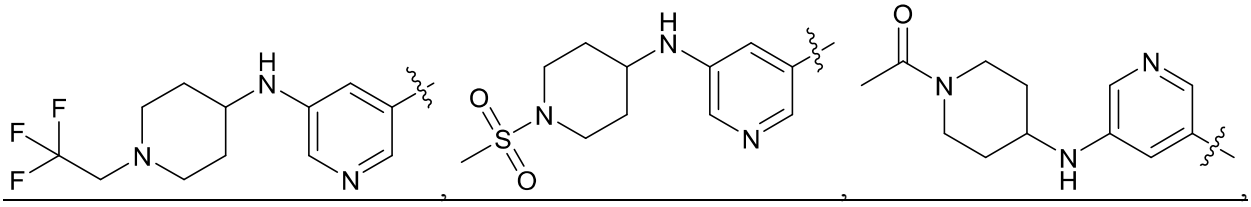


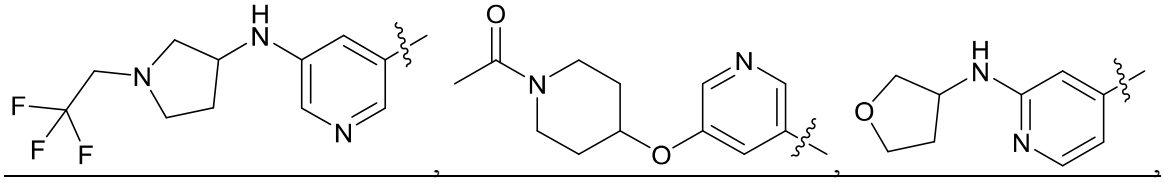


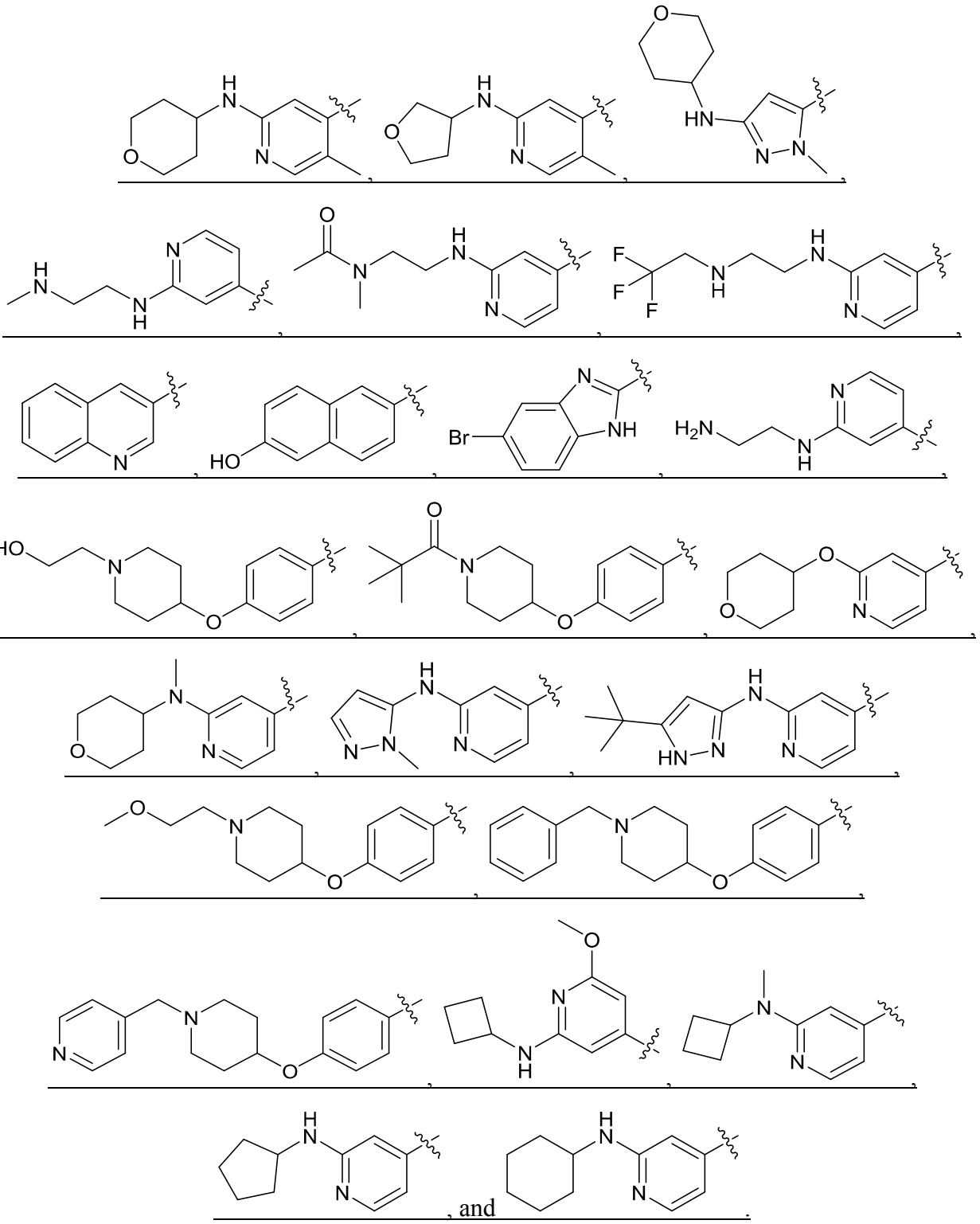












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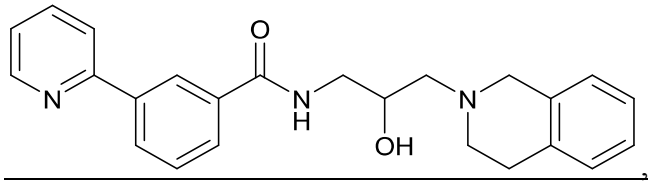
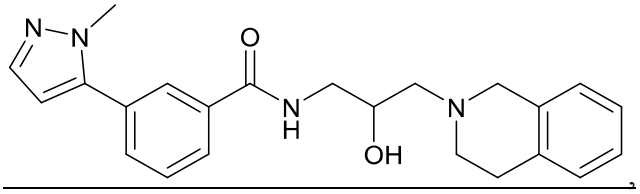
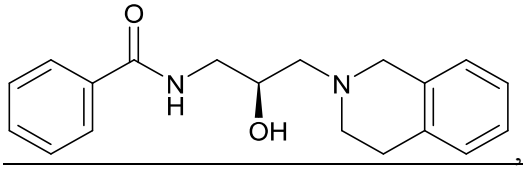
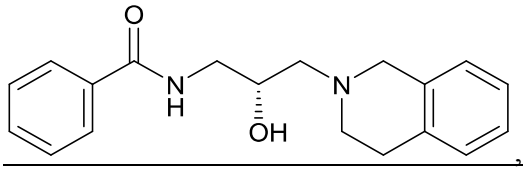
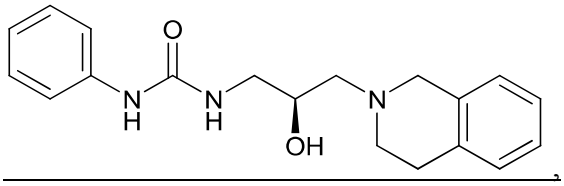
109. The compound of claim 1, wherein the compound is selected from the group consisting of:

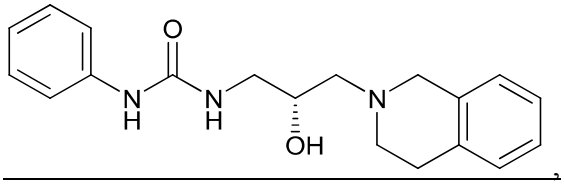


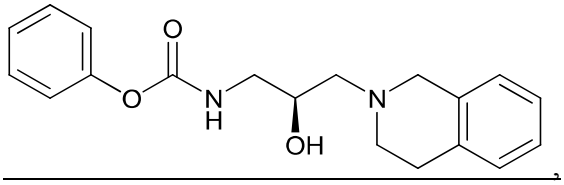


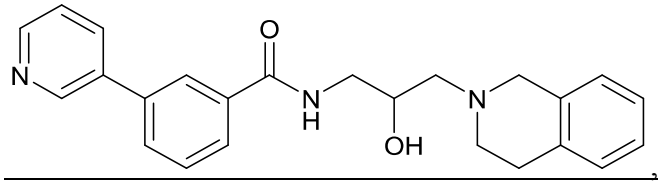


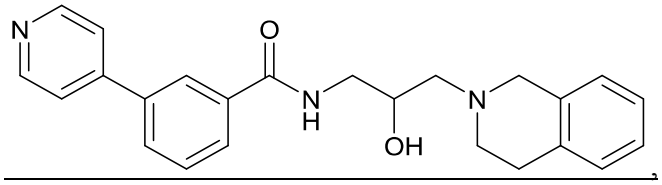


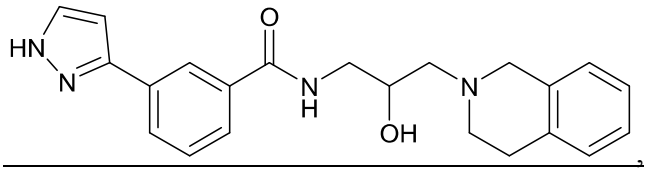


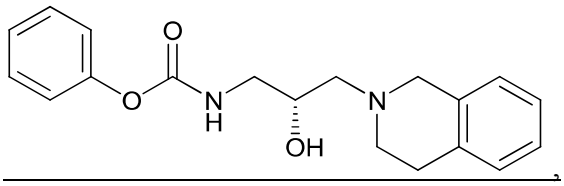


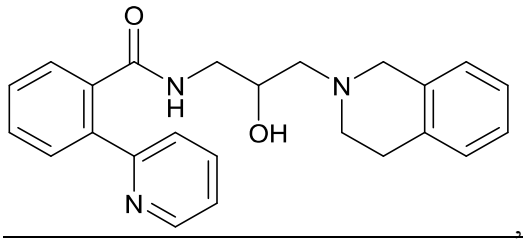


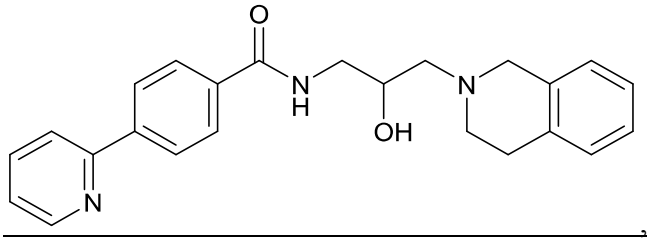


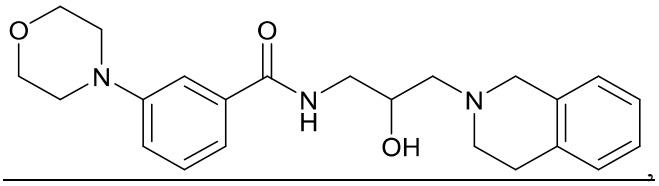


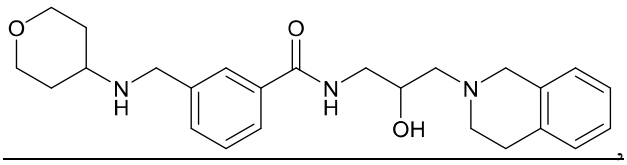


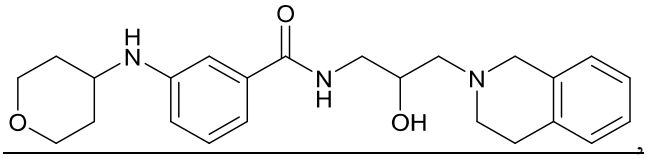


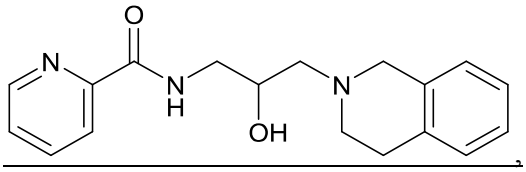


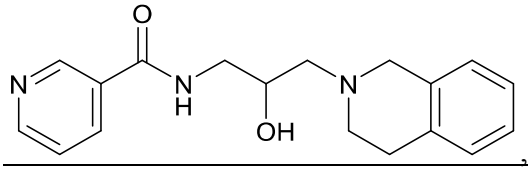


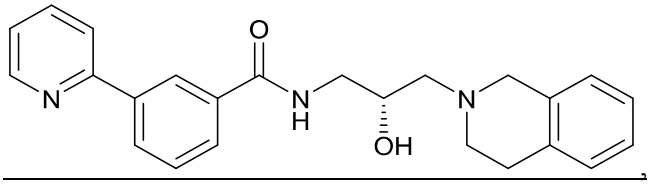


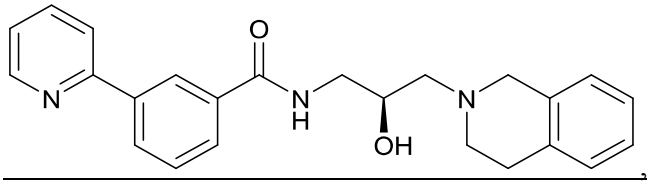


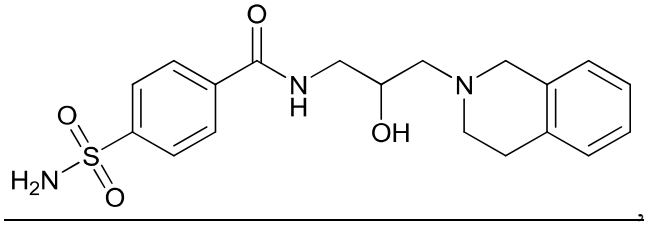


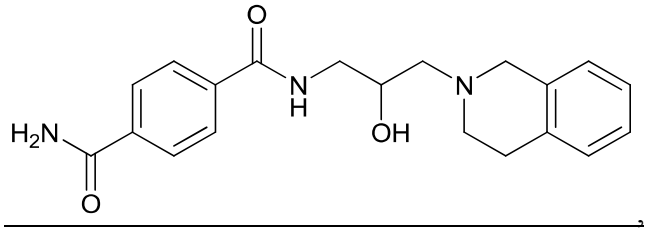


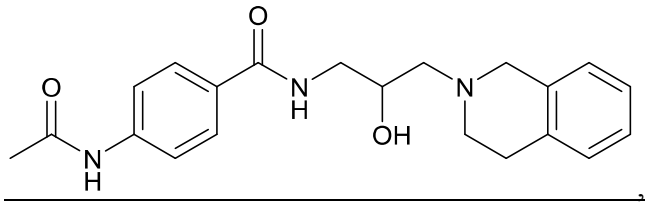


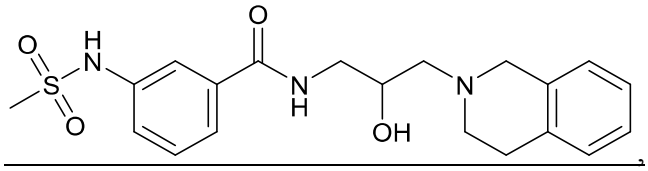


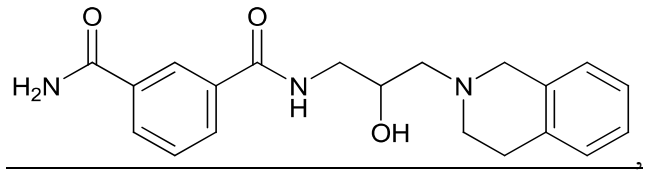


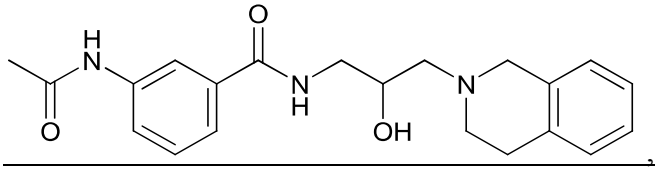


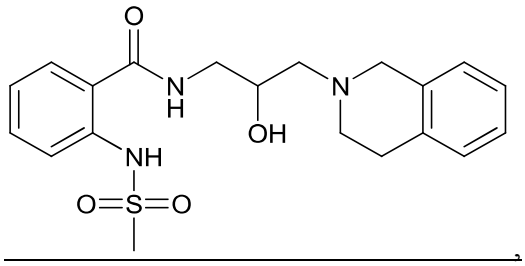


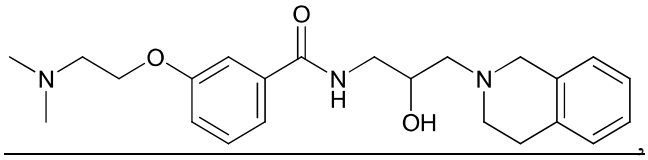


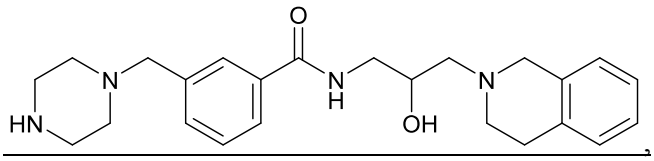


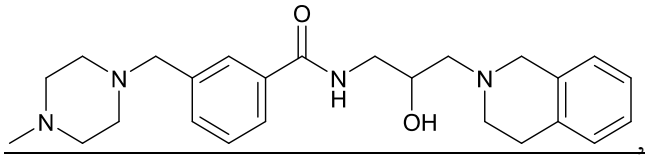


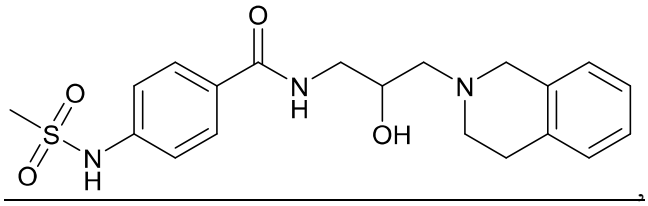


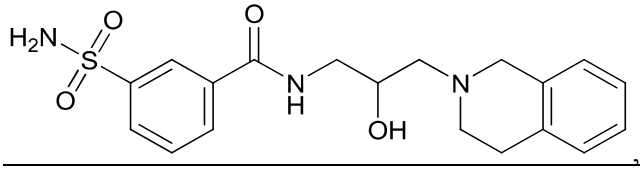


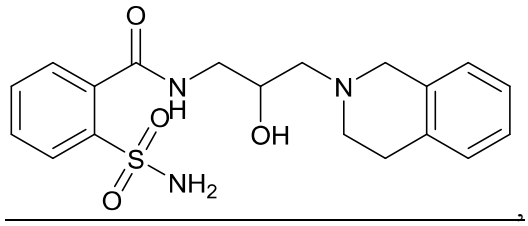


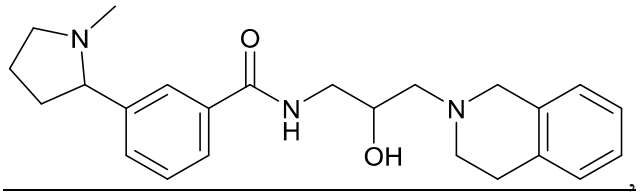


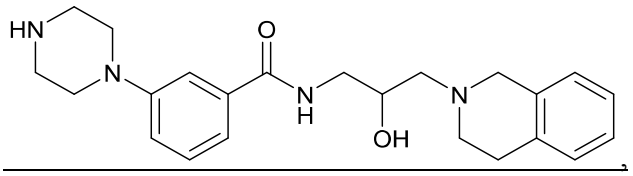


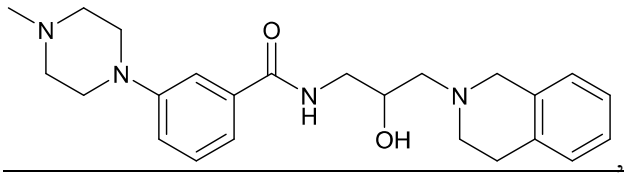


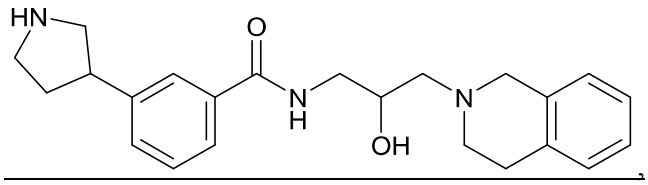


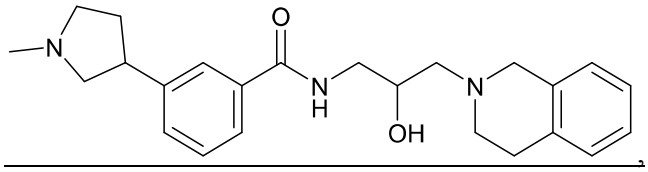


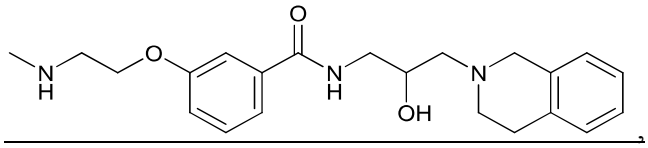


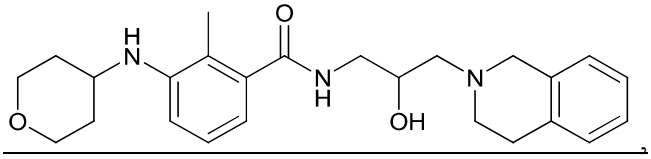


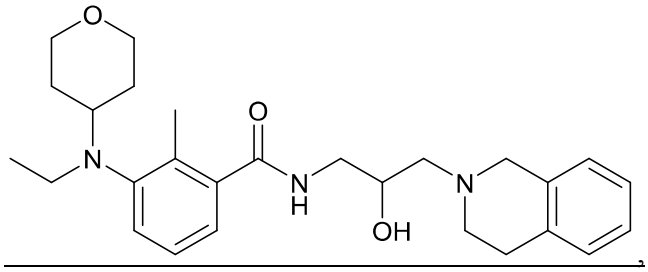


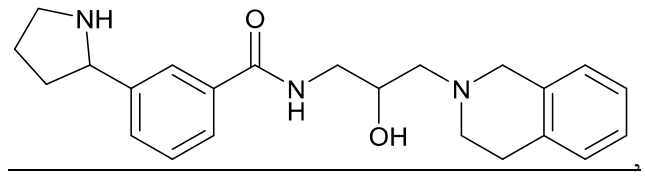


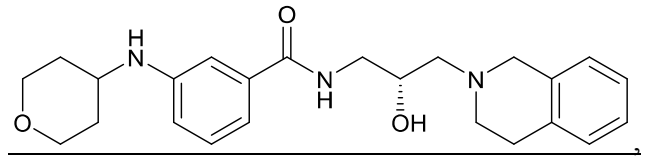


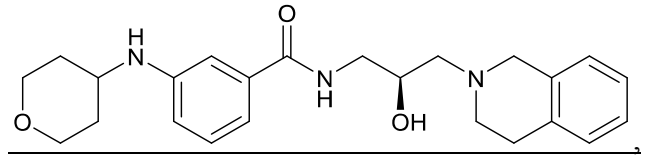


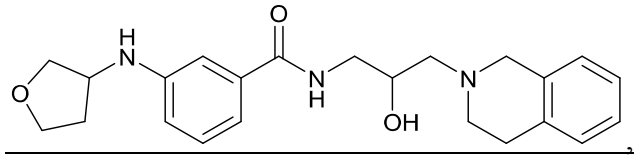


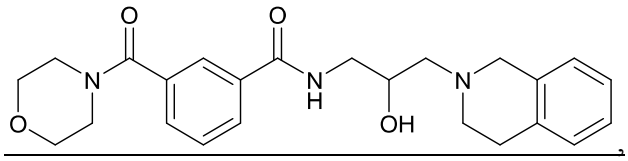


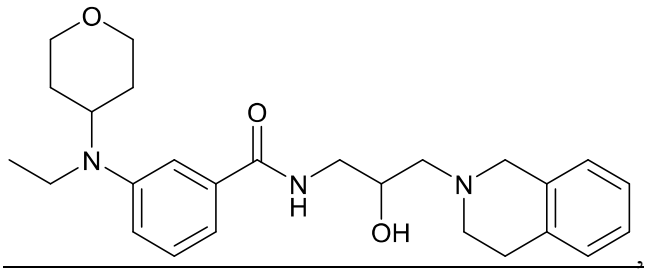


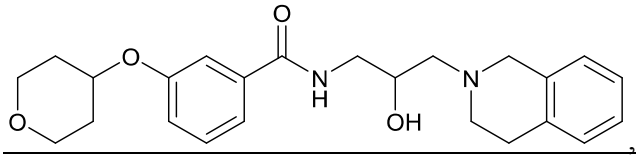


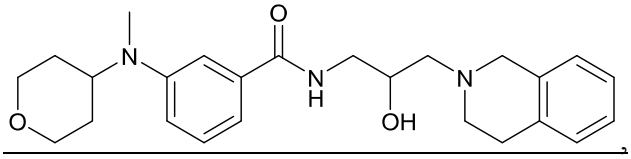


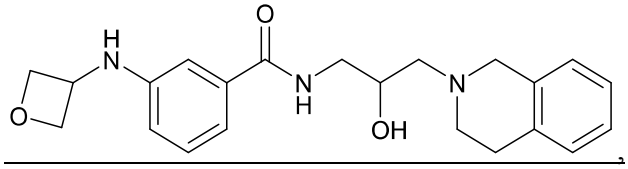


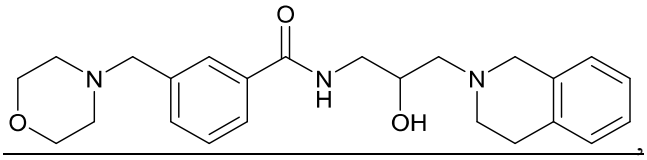


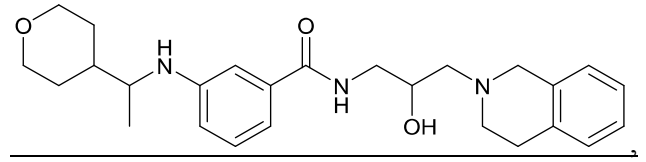


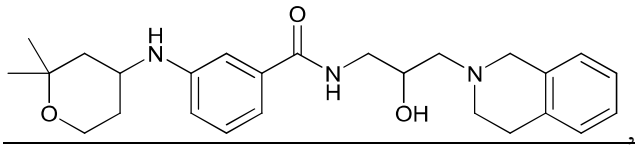


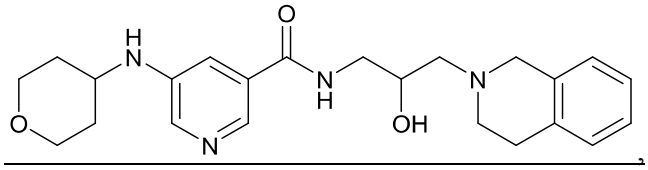


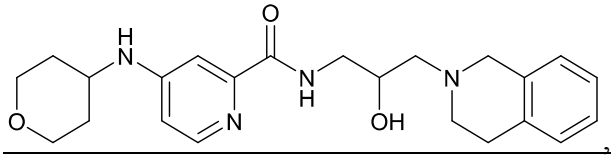


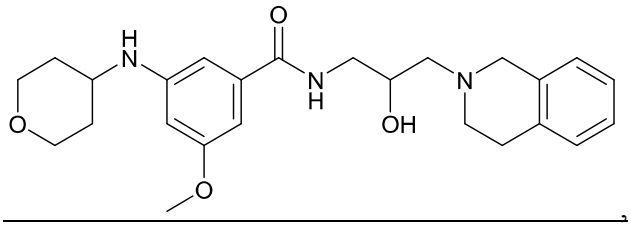


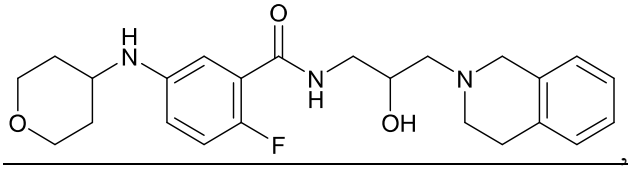


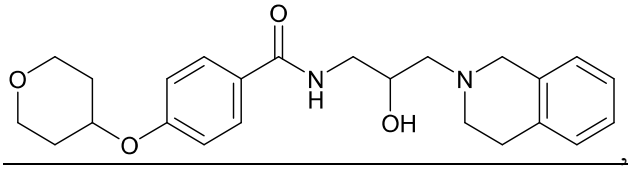


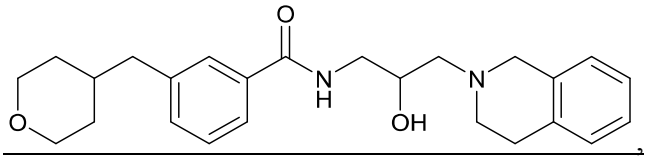


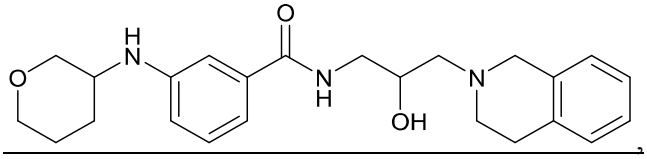


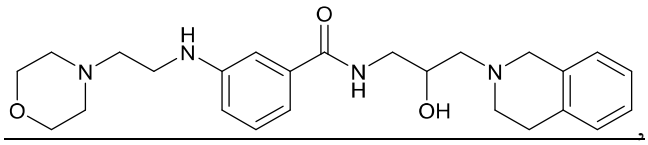


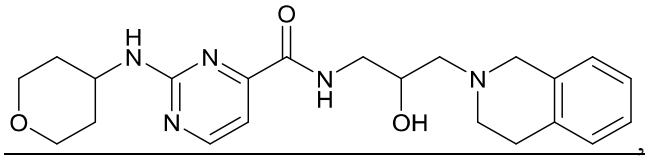


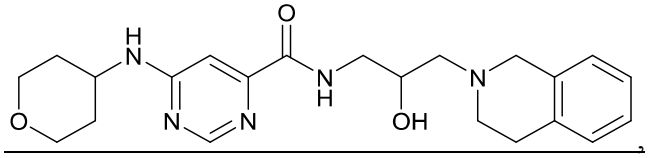


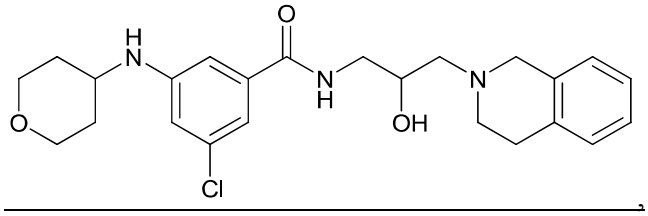


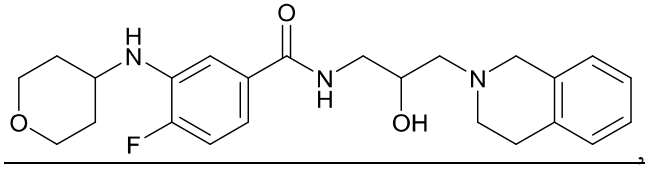


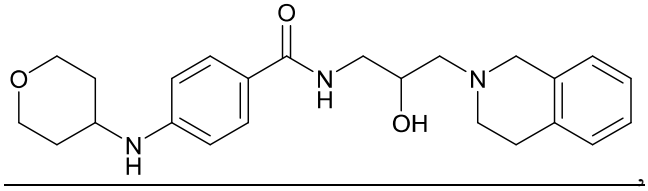


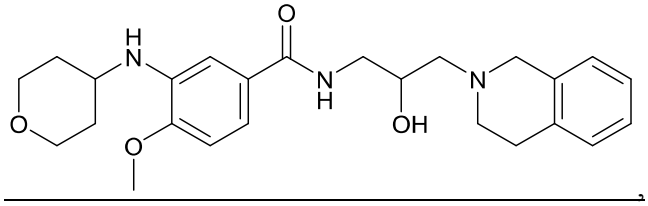


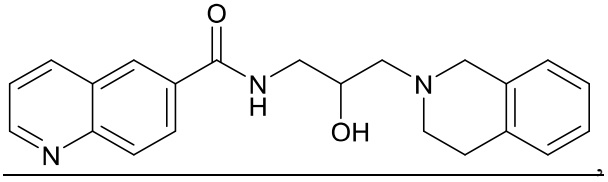


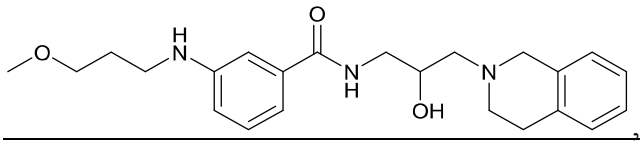


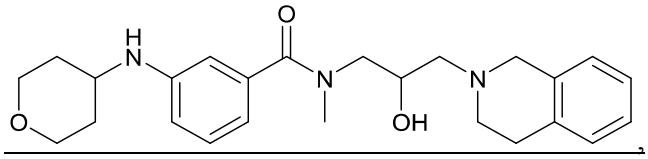


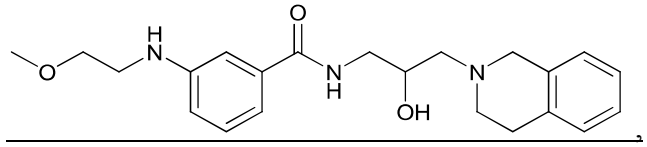


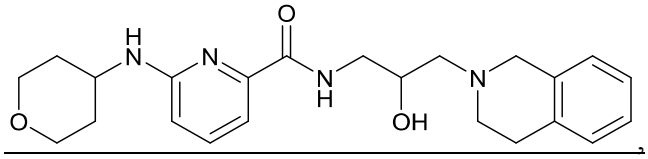


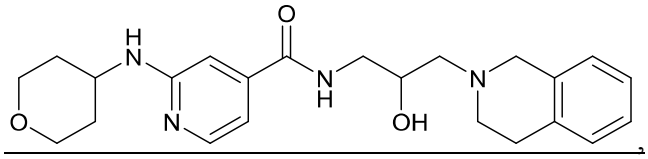


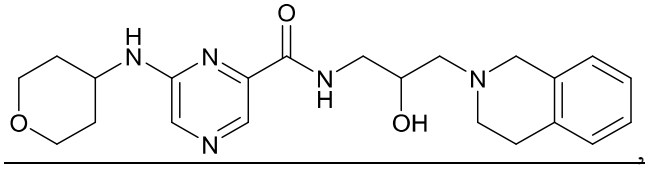


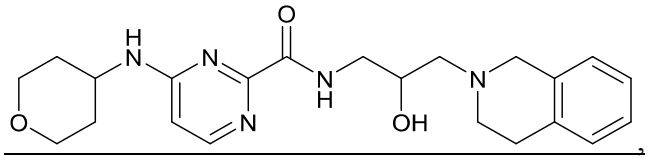


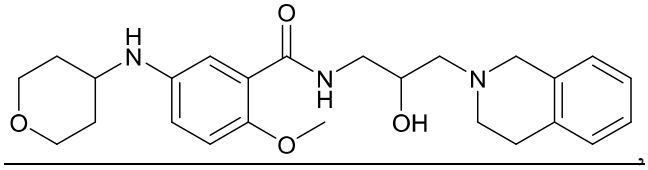


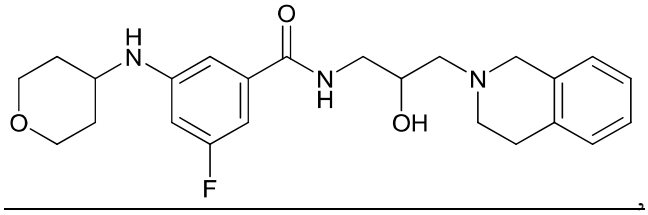


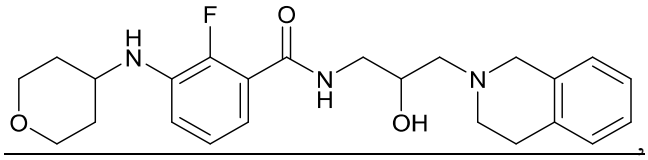


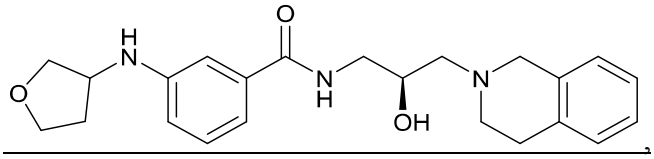


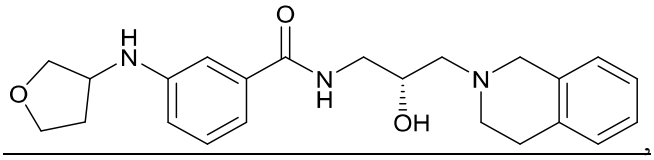


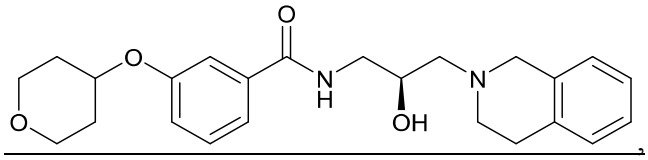


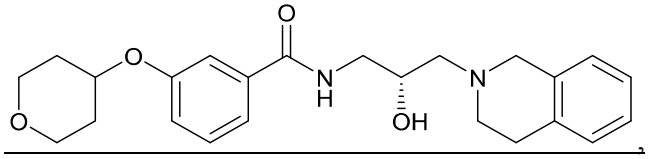


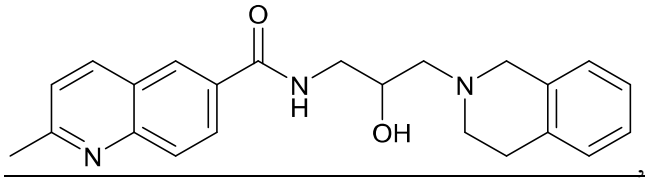


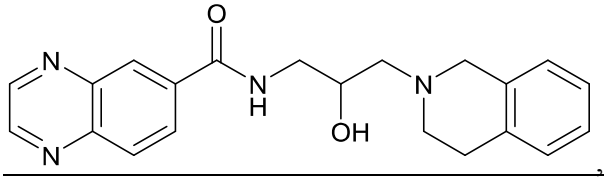


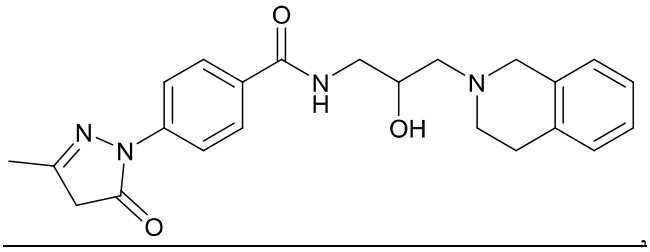


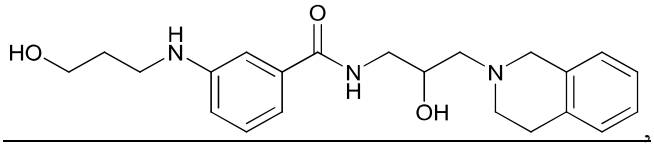


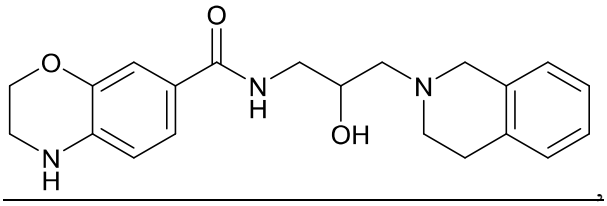


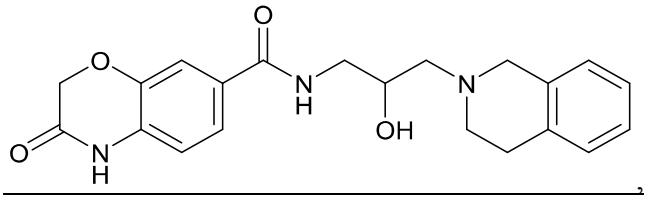


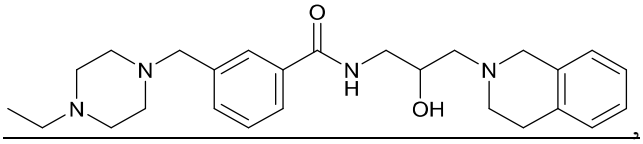


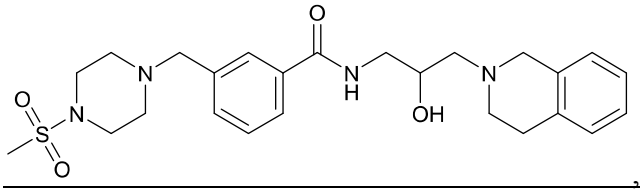


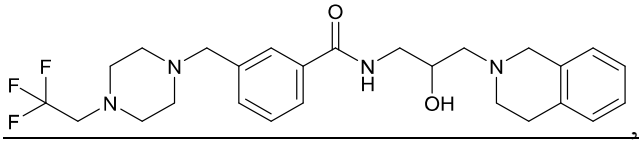


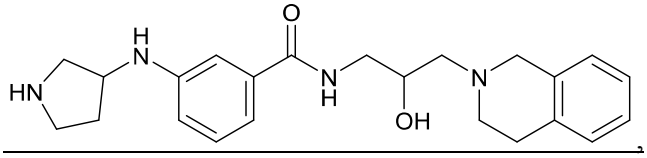


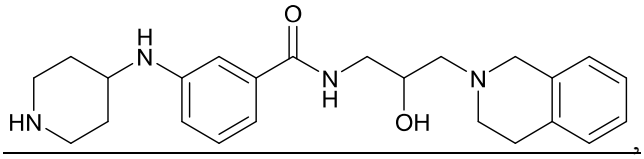


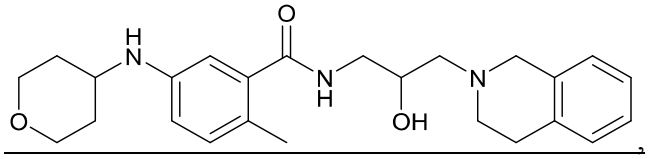


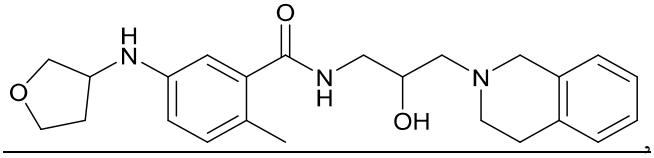


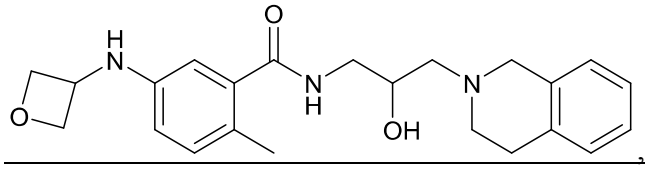


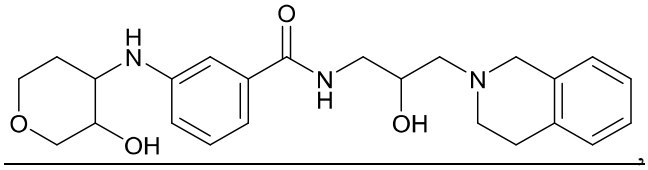


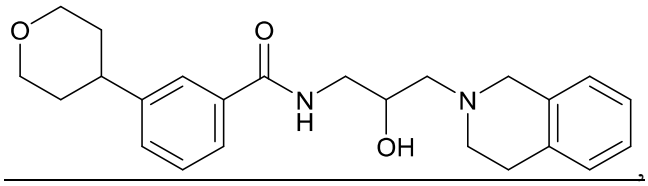


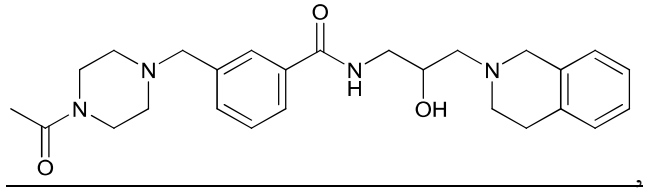


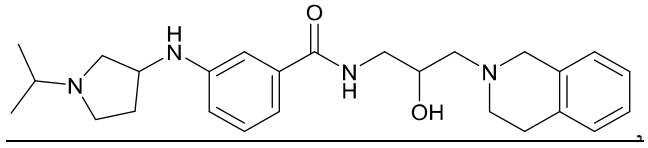


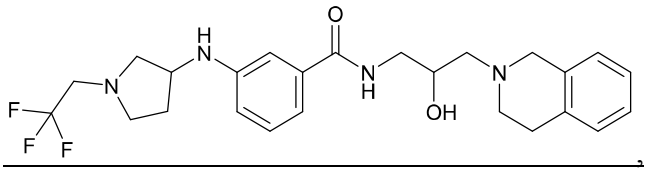


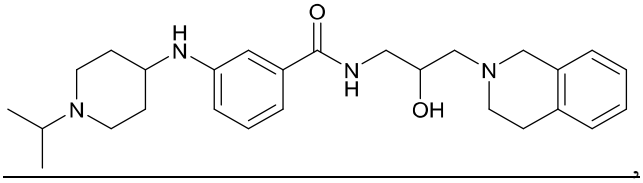


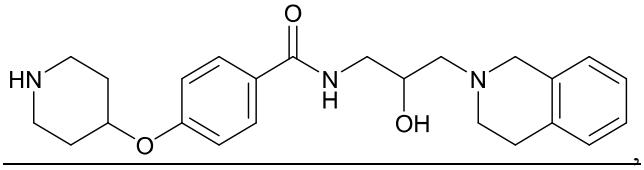


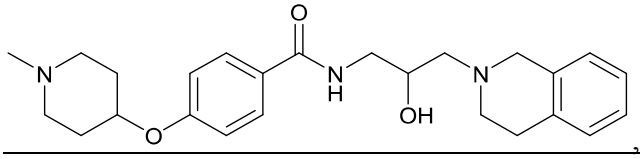


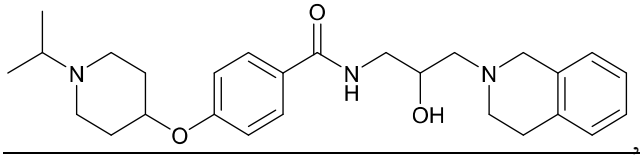


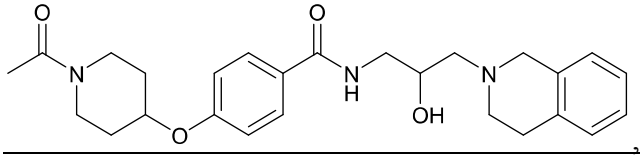


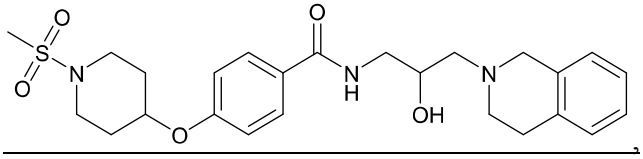


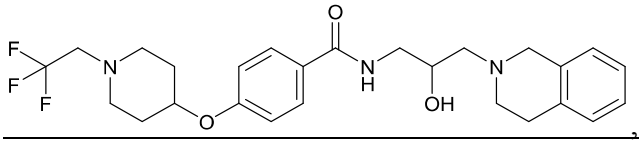


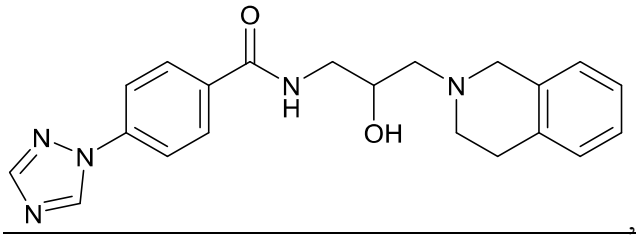


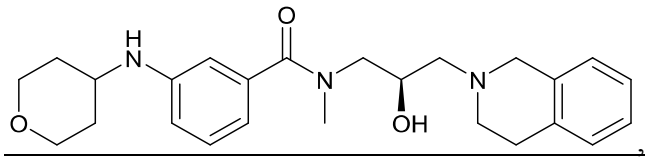


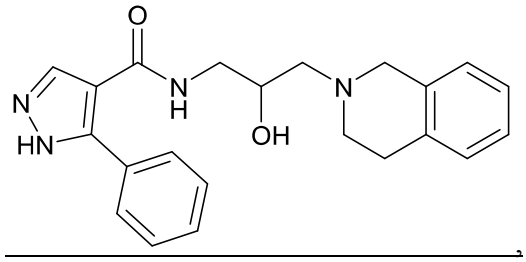


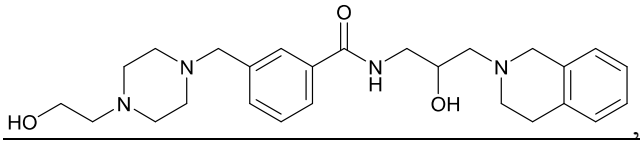


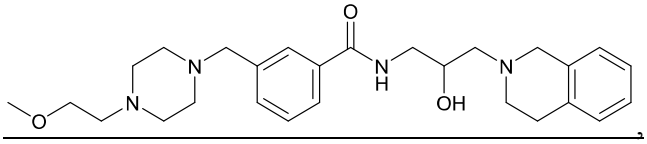


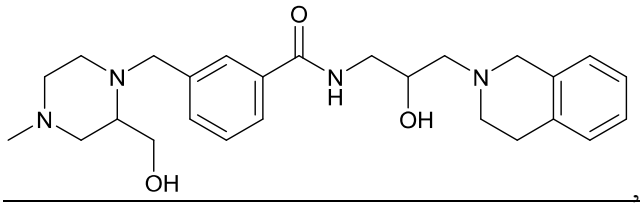


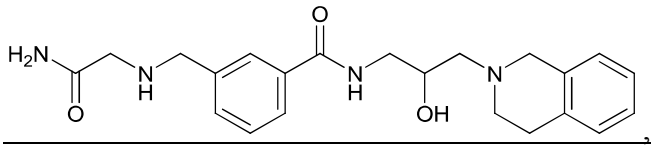


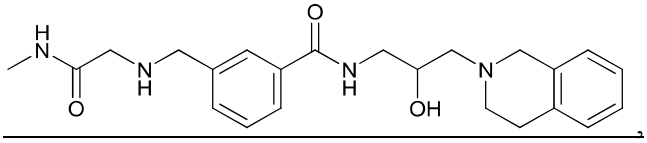


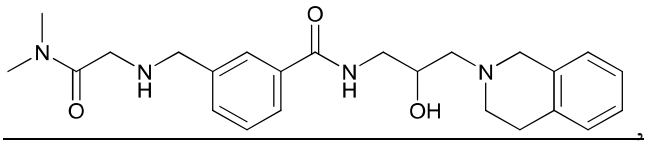


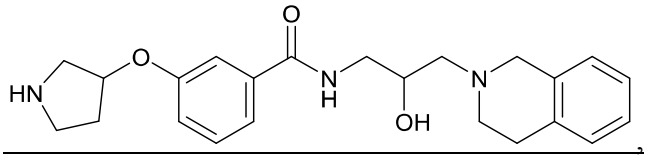


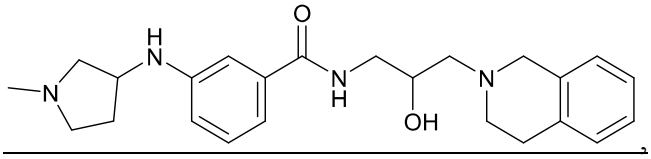


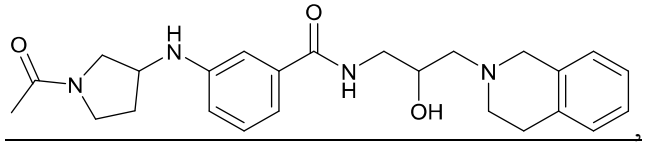


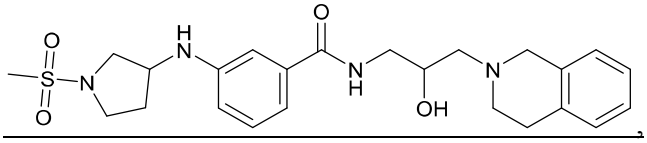


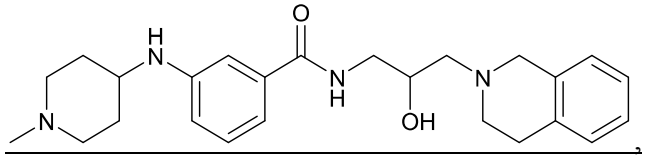


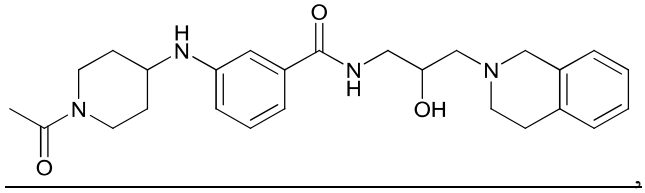


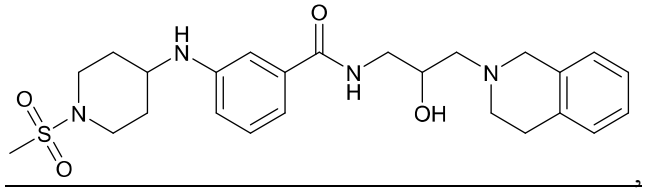


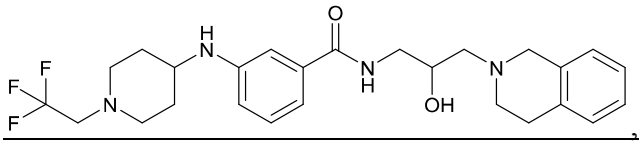


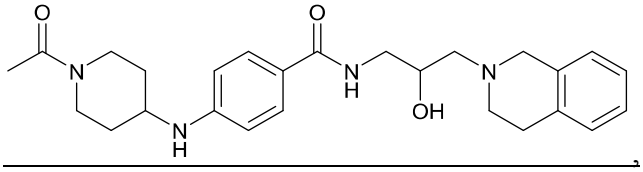


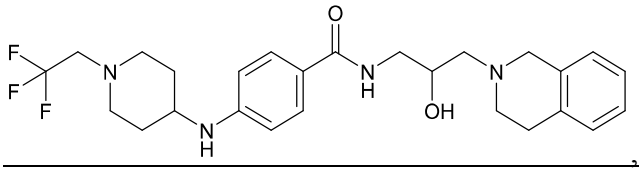


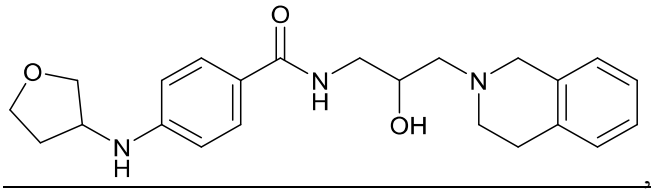


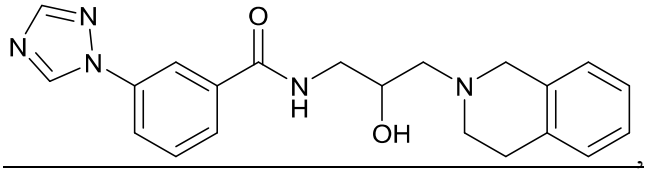


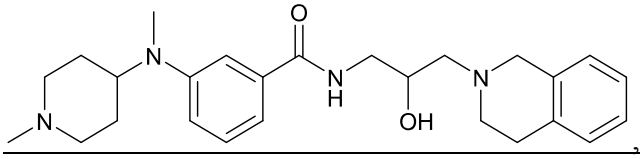


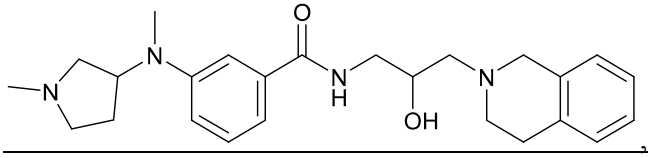


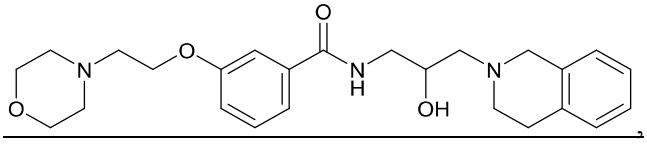


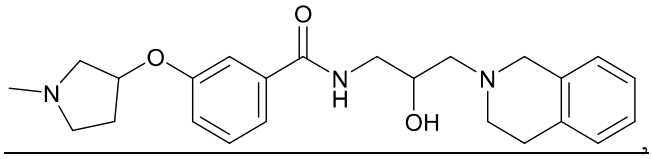


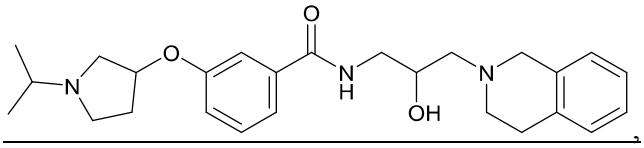


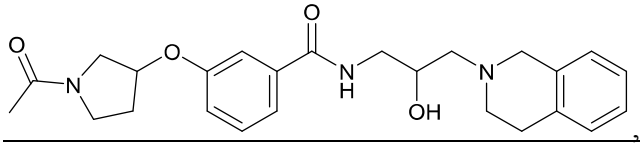


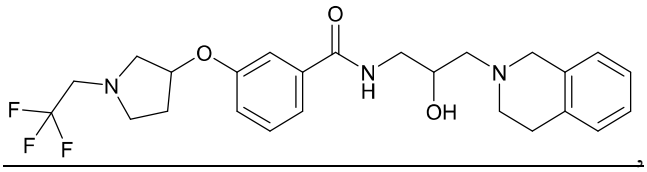


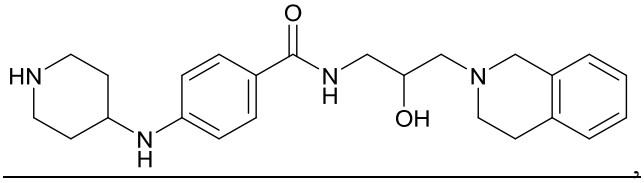


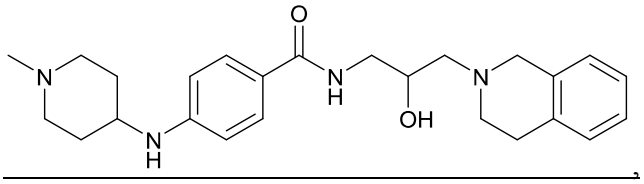


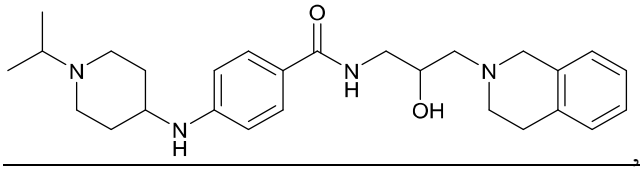


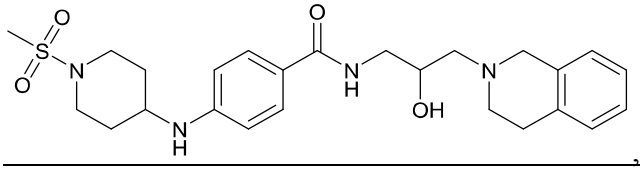


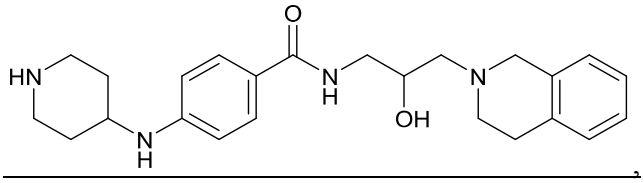


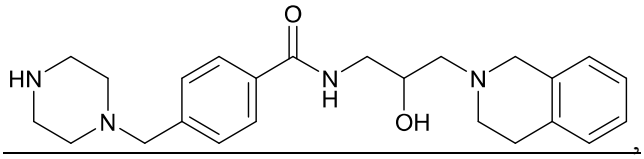


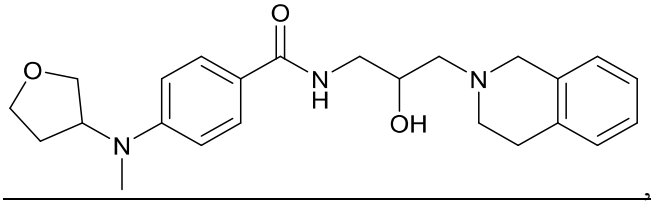


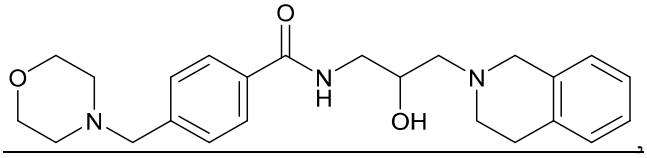


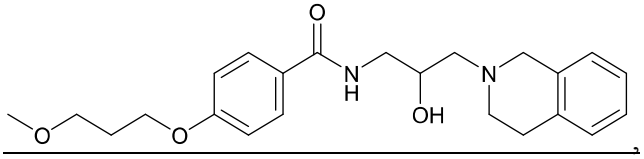


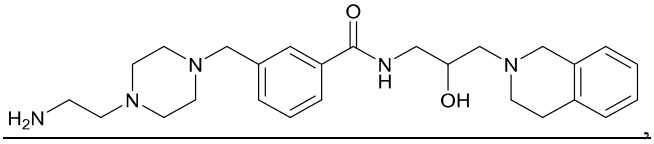


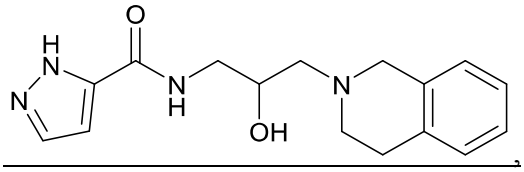


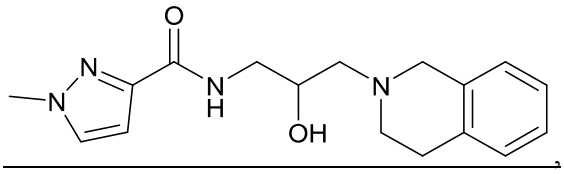


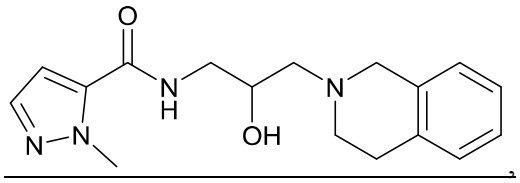


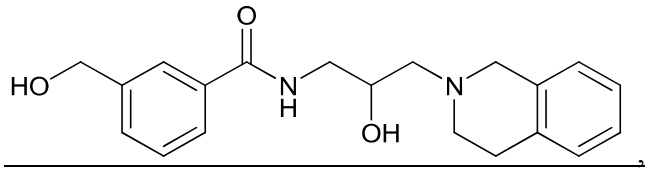


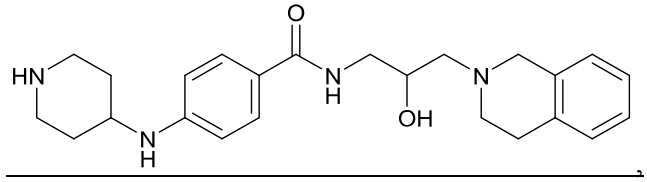


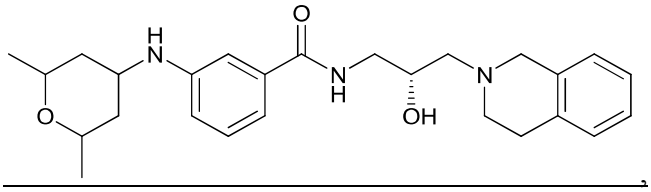


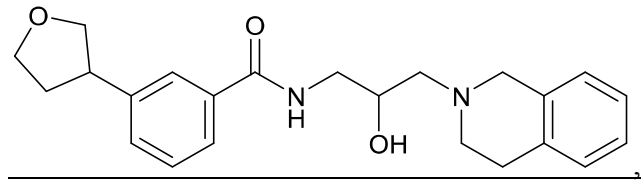


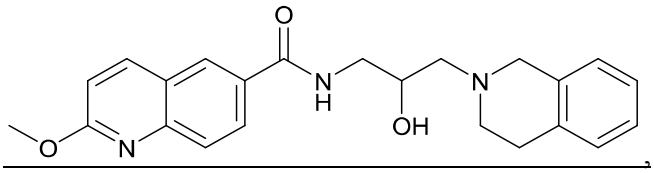


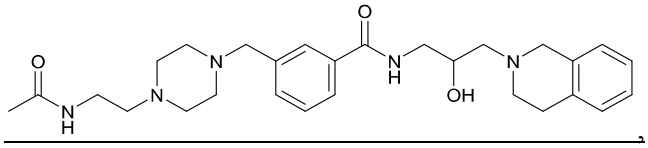


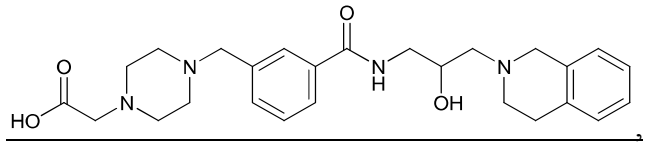


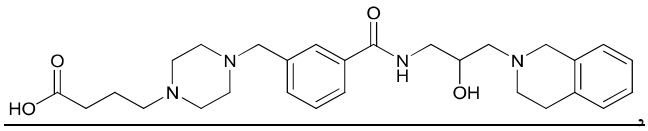


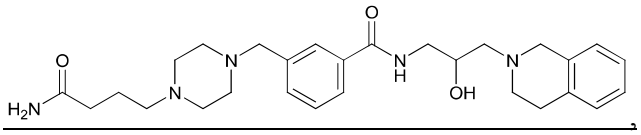


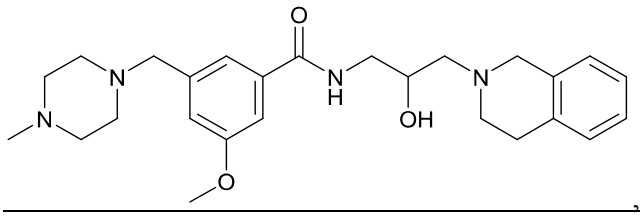


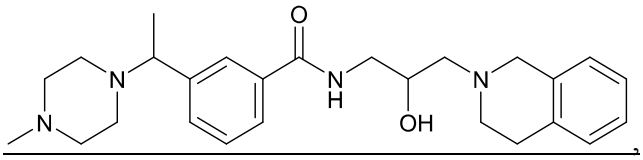


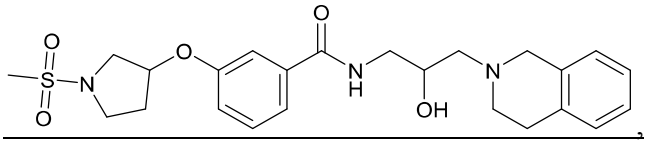


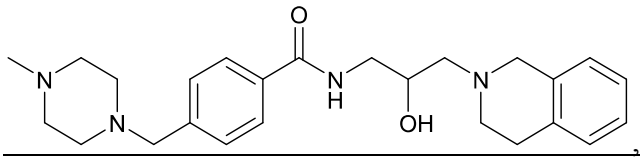


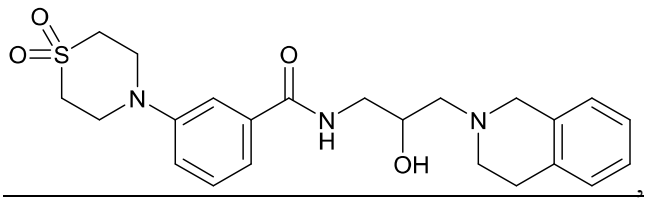


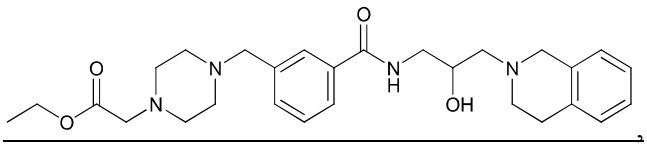


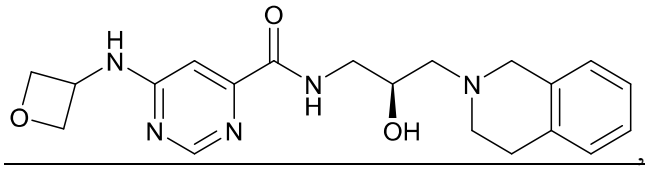


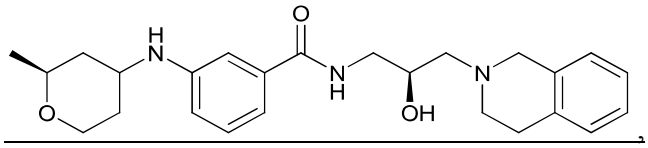


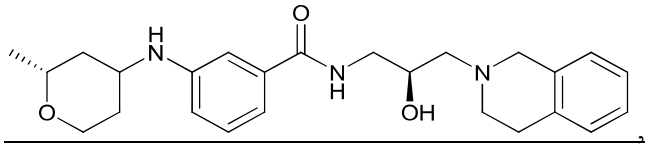


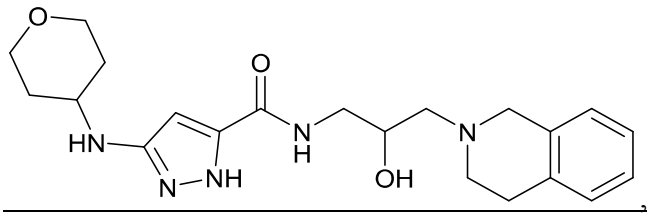


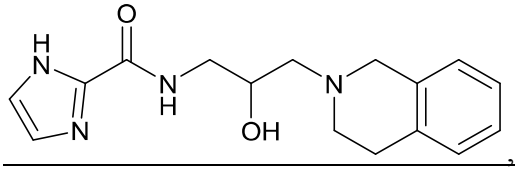


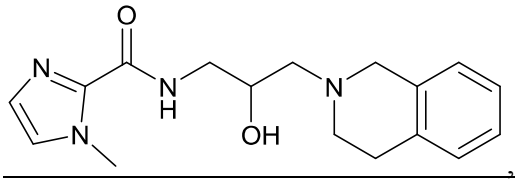


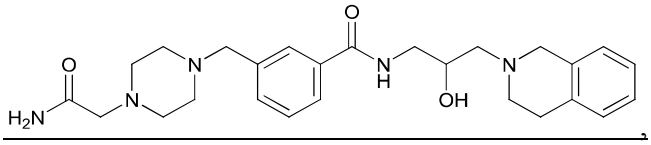


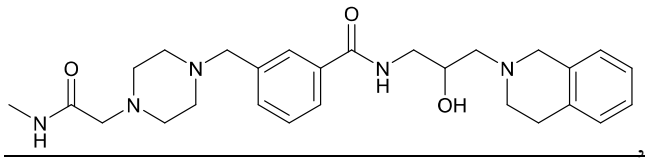


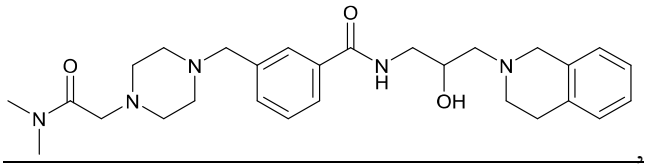


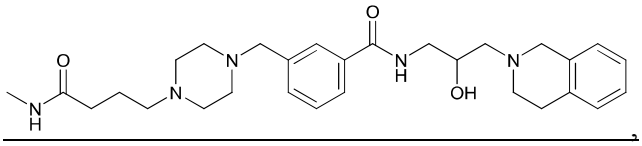


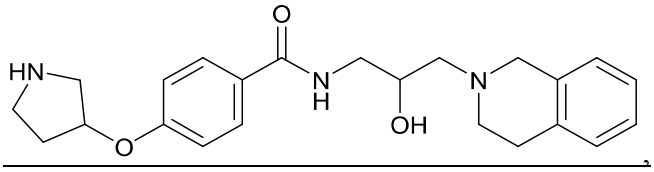


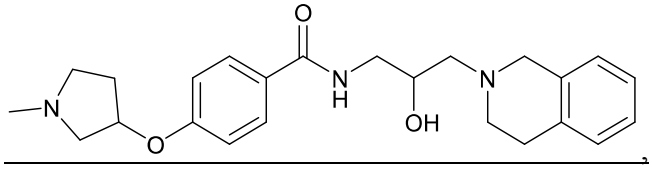


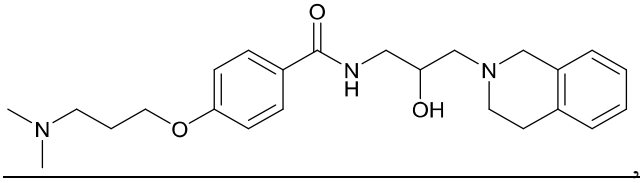


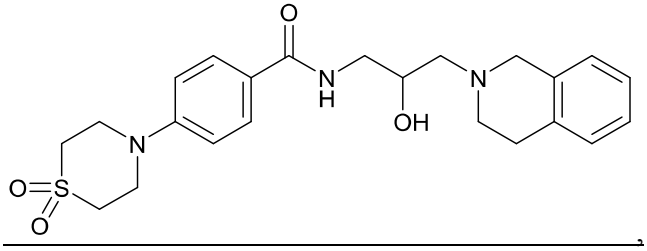


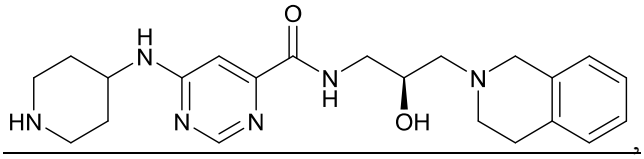


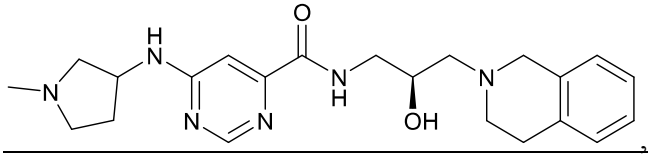


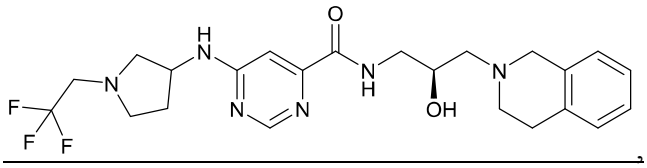


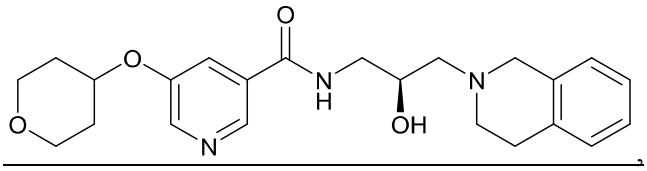


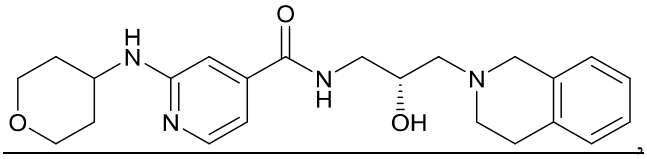


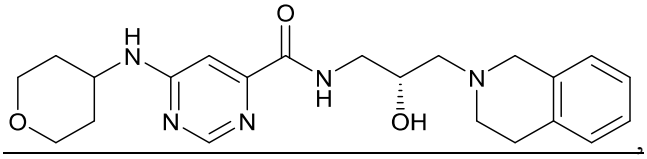


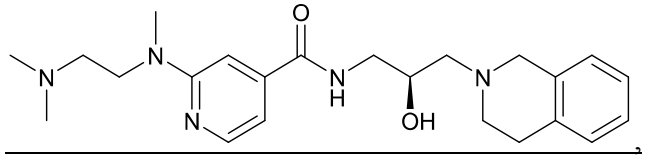


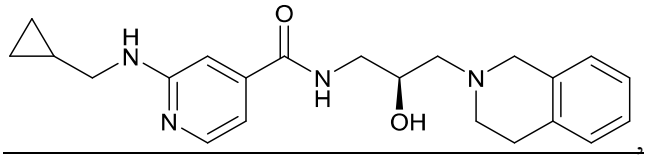


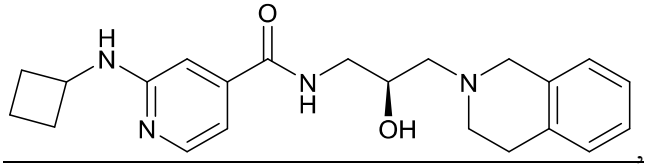


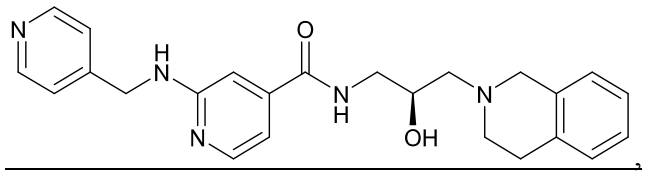


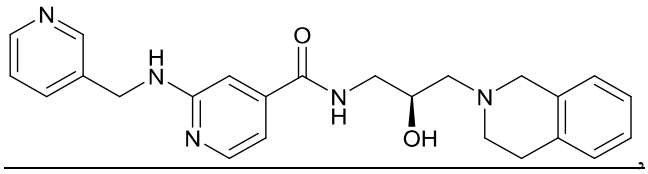


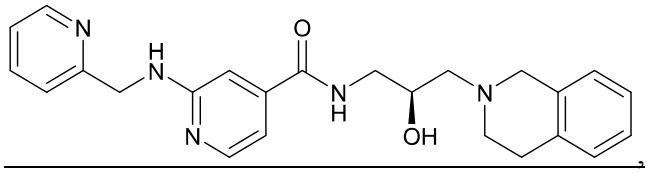


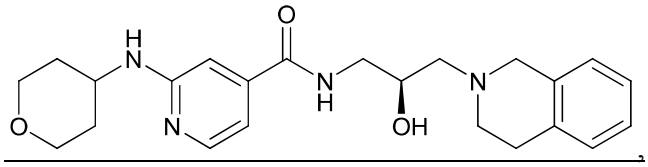


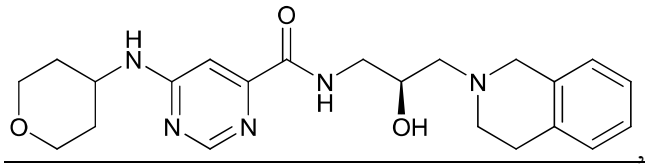


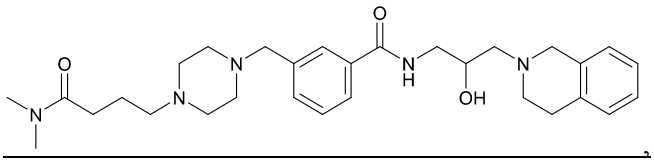


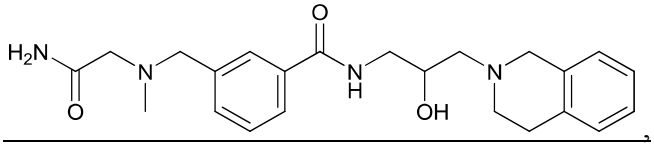


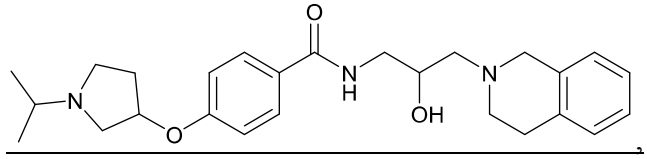


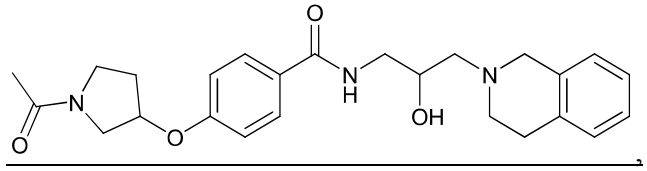


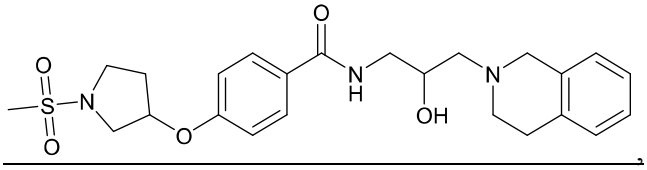


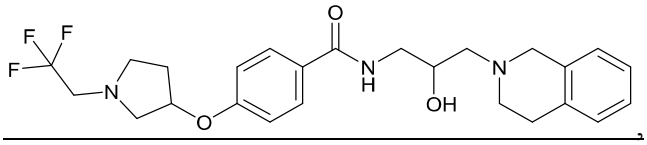


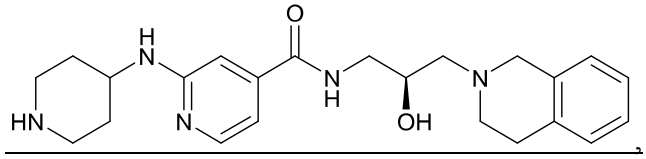


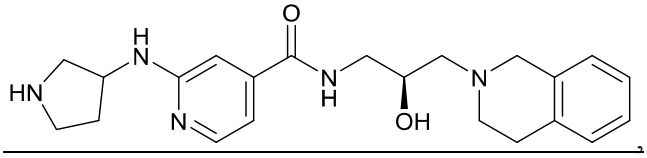


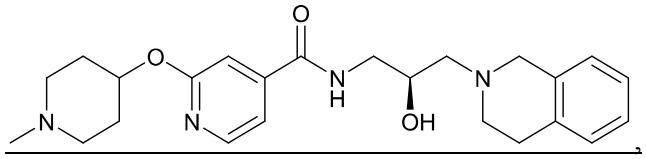


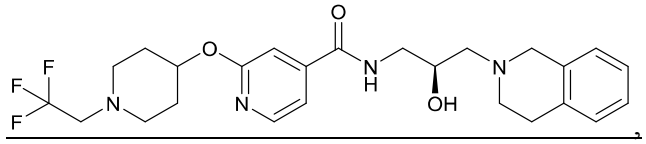


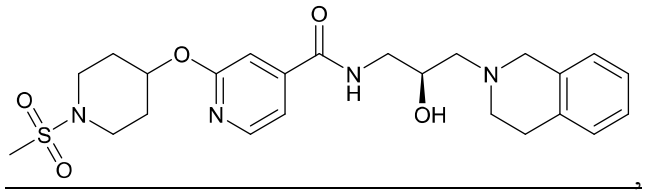


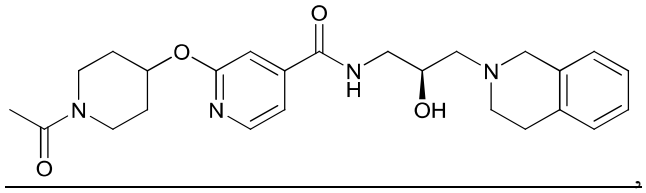


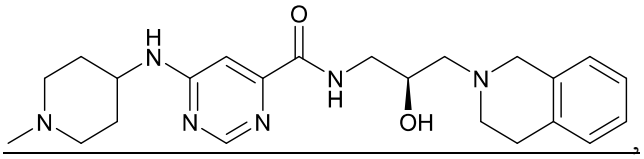


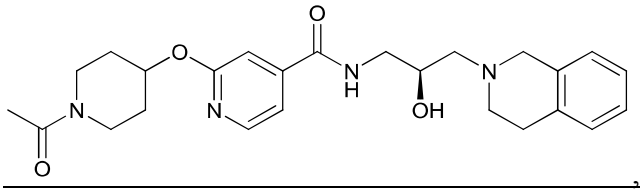


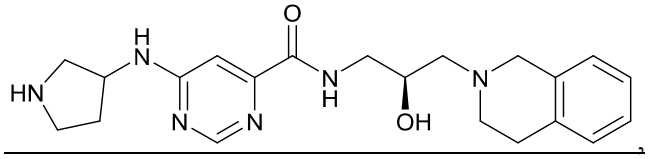


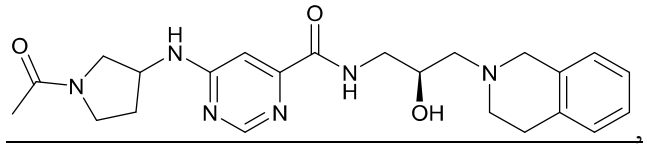


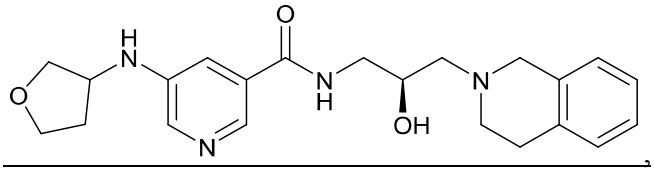


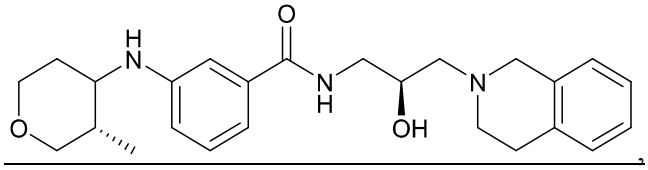


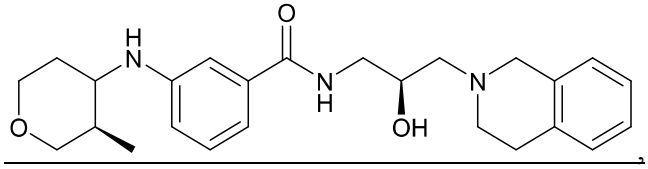


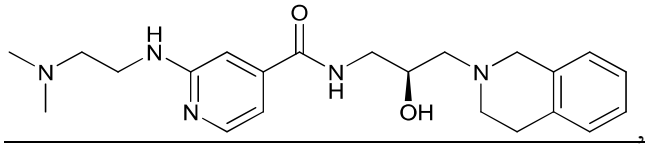


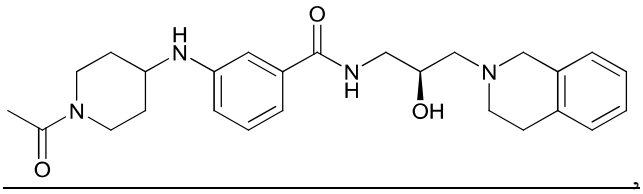


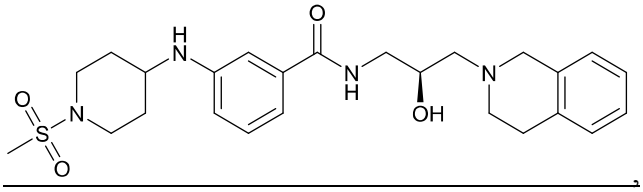


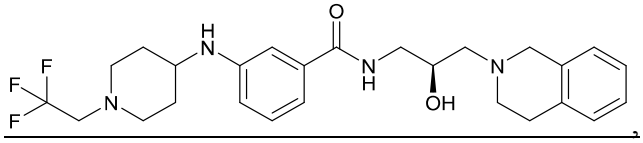


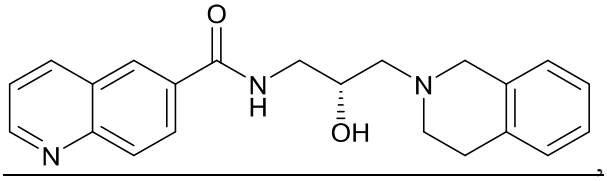


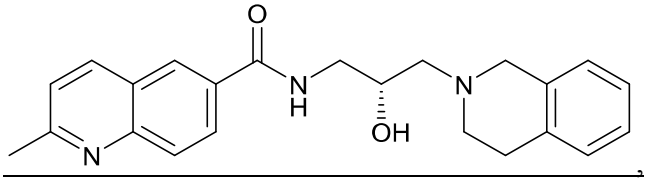


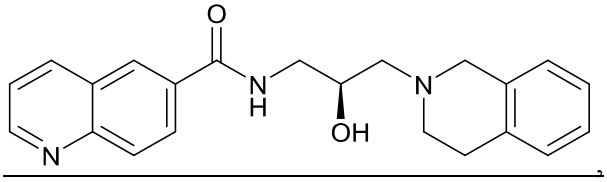


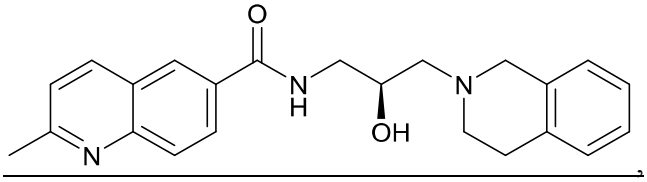


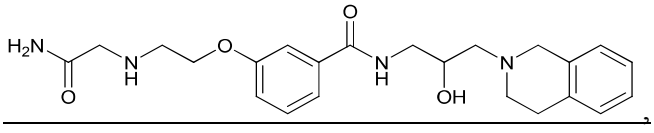


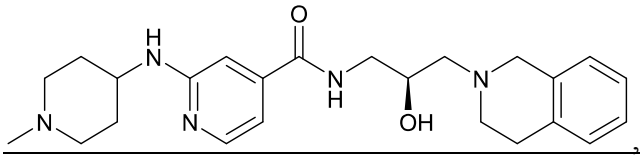


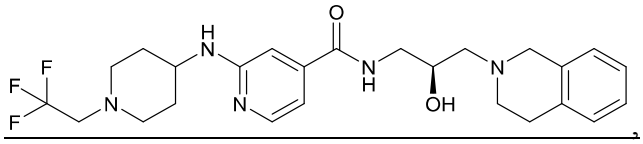


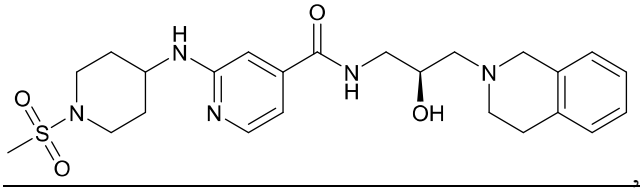


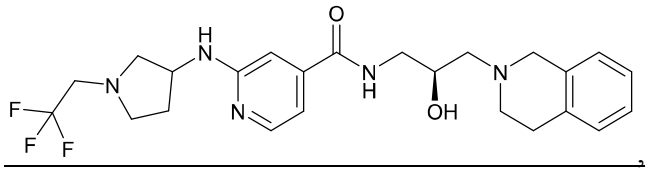


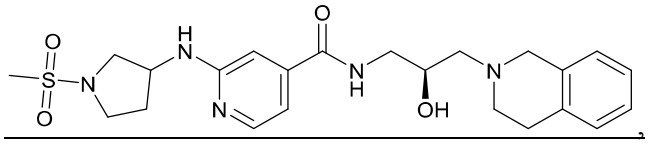


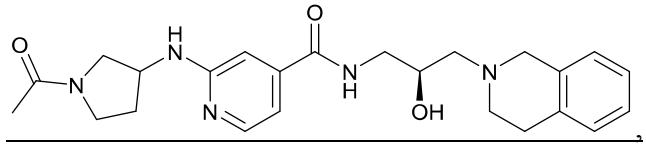


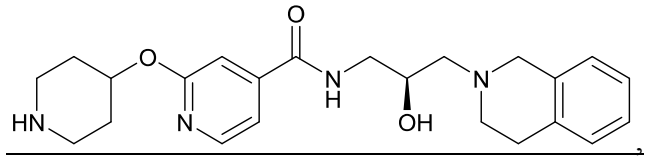


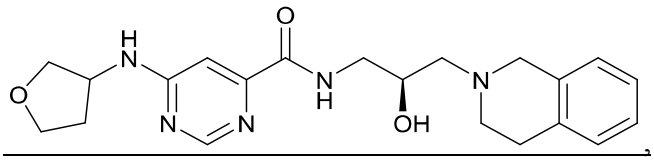


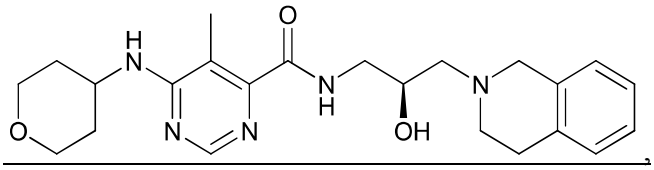


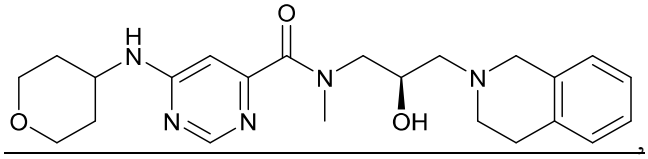


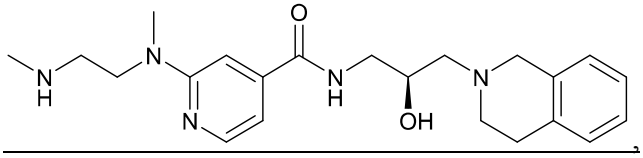


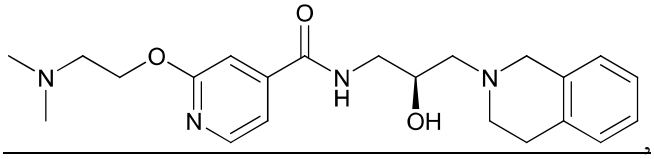


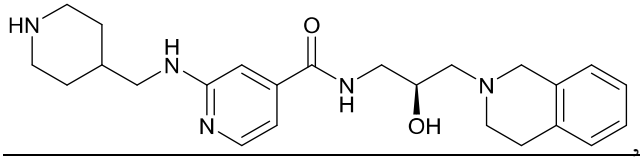


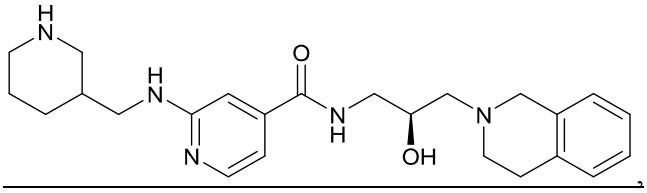


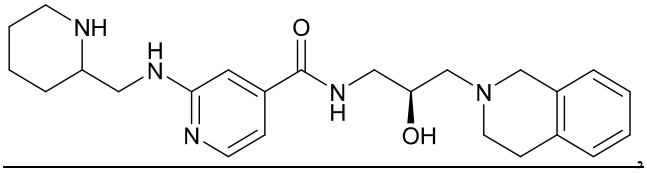


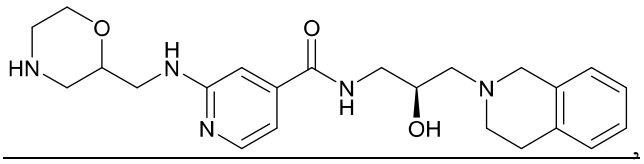


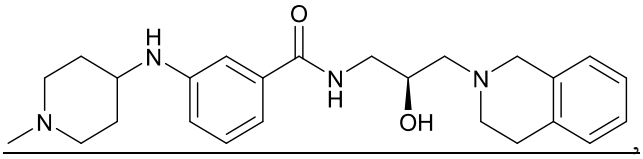


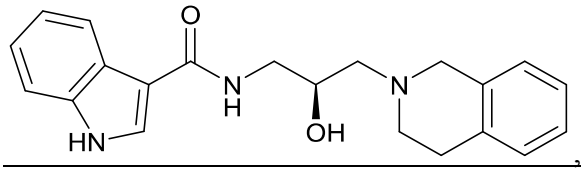


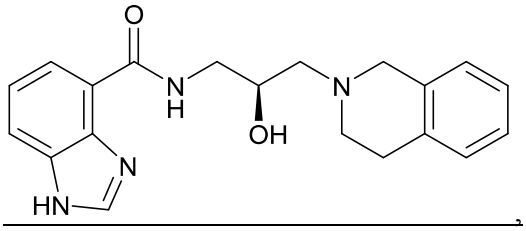


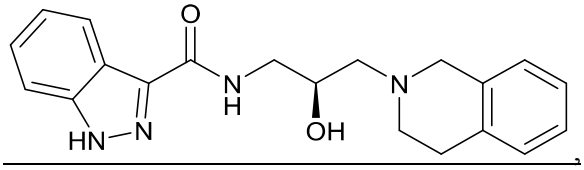


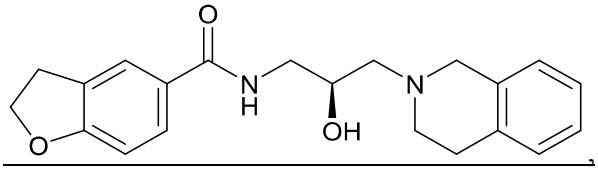


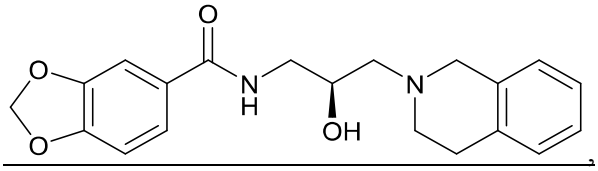


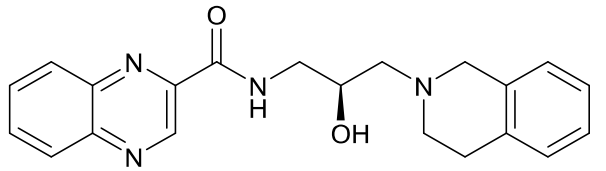


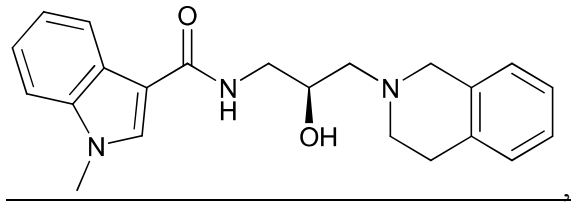


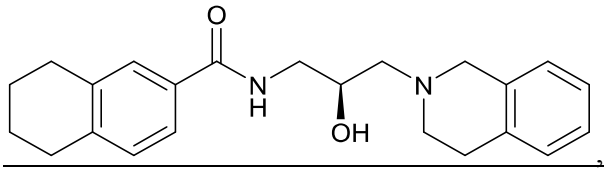


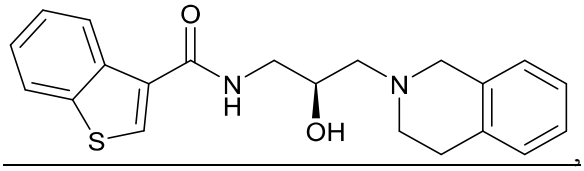


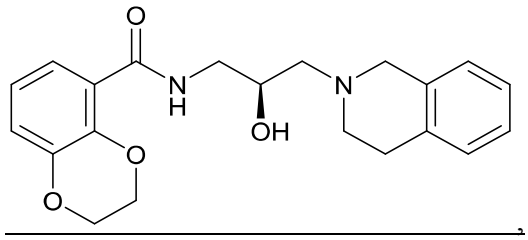


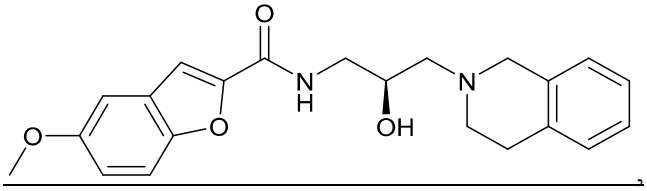


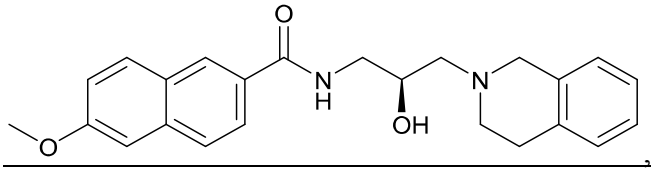


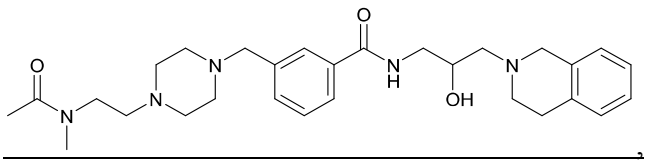


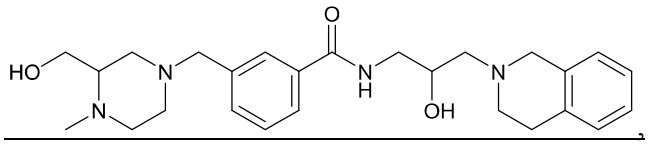


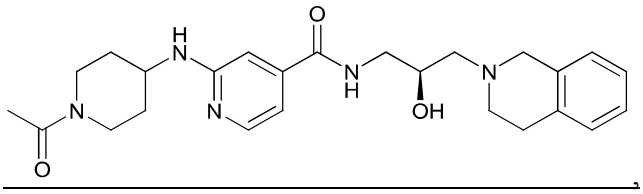


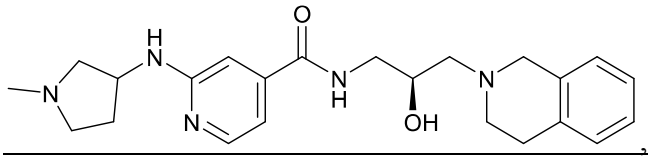


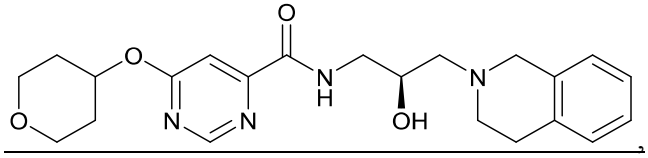


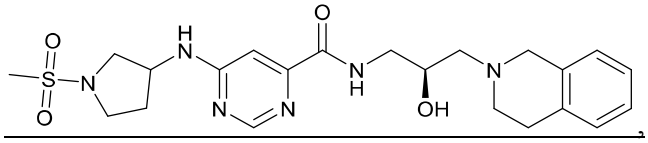


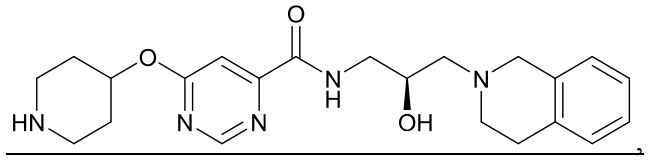


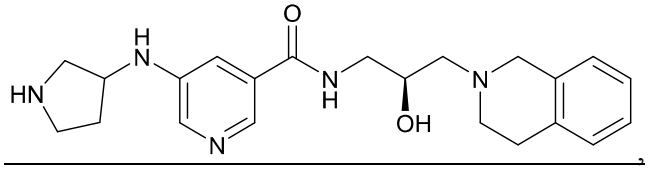


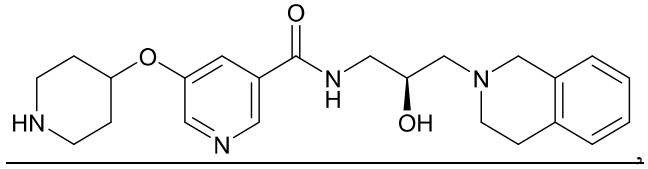


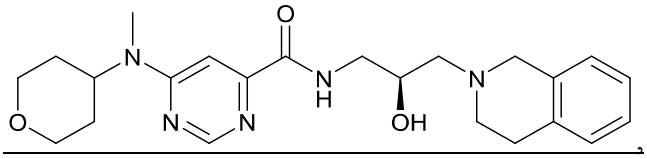


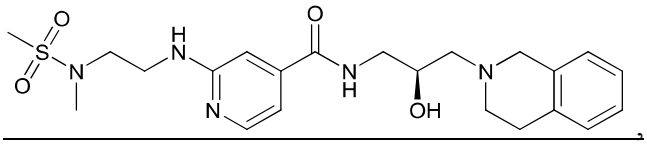


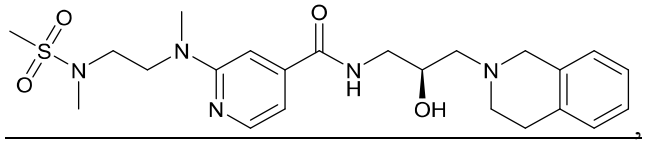


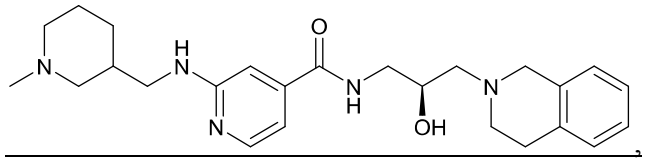


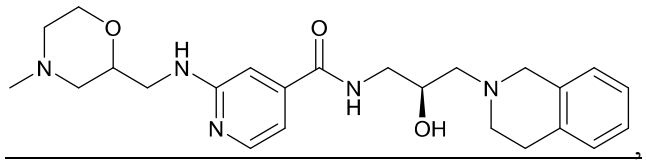


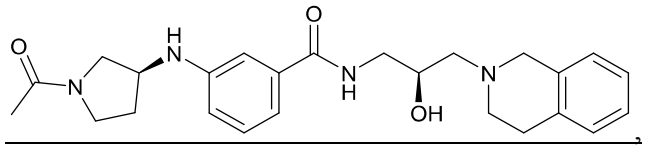


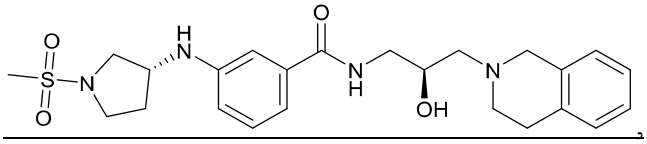


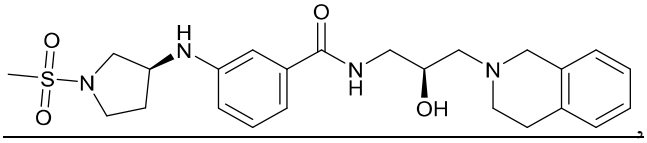


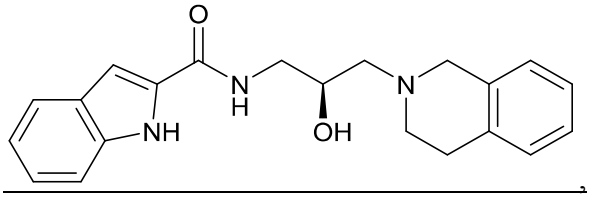


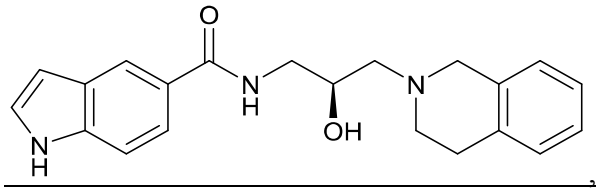


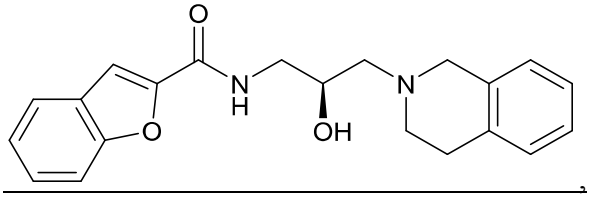


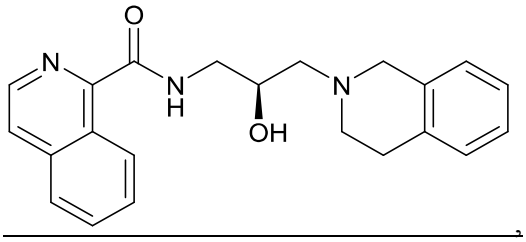


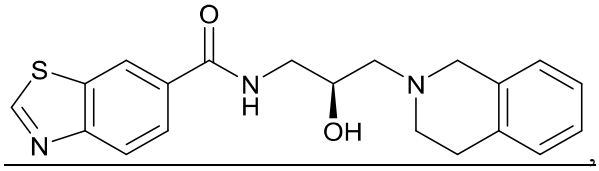


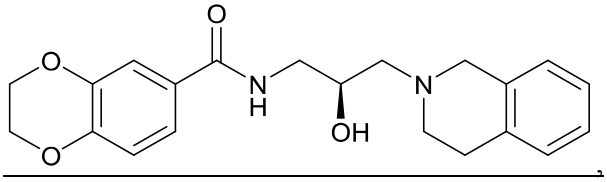


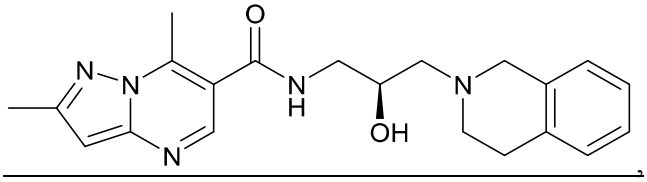


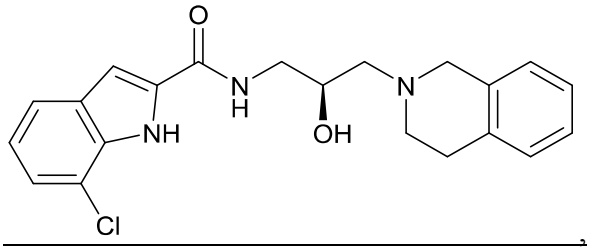


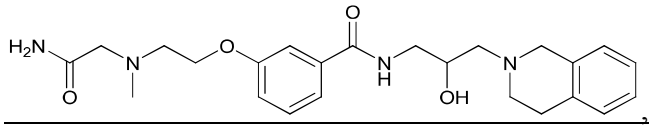


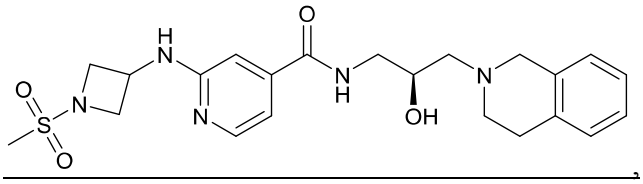


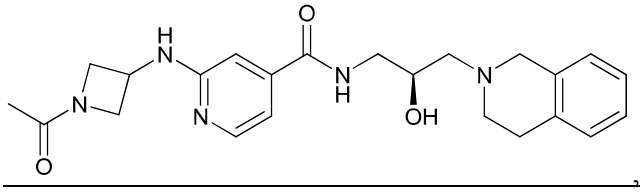


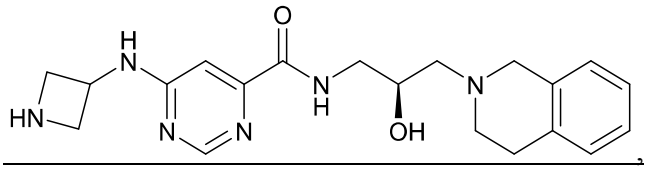


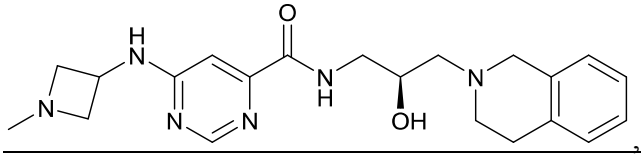


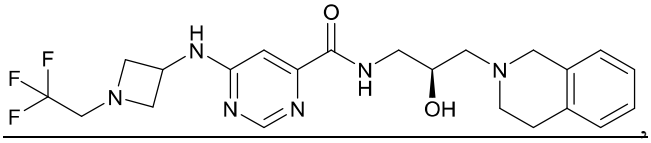


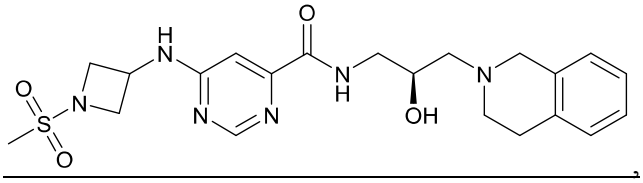


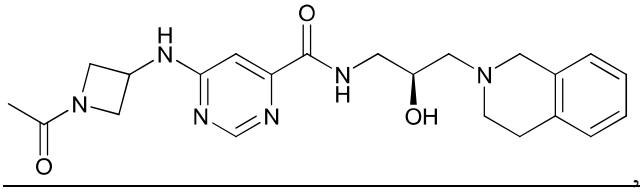


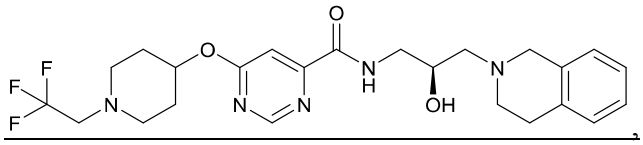


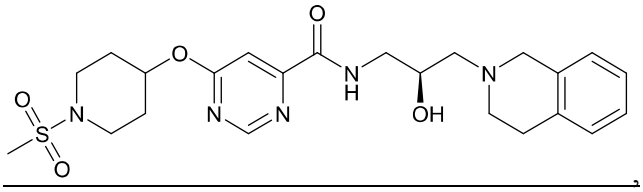


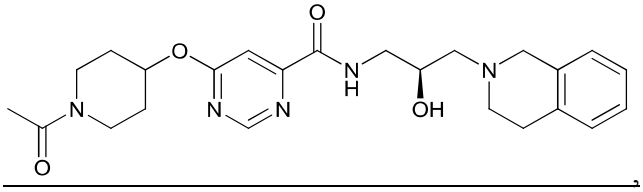


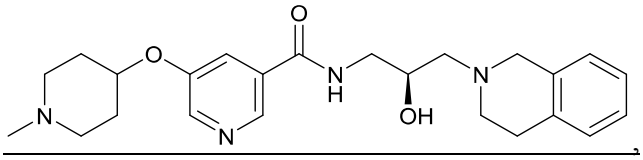


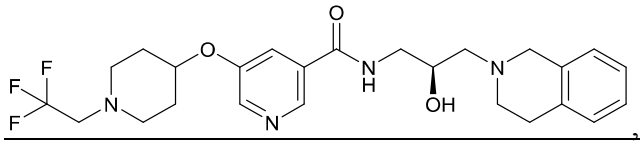


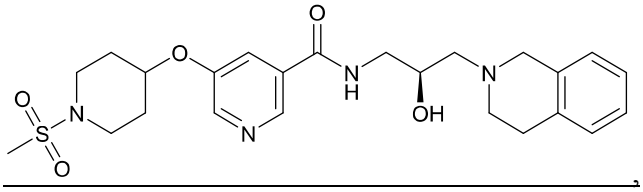


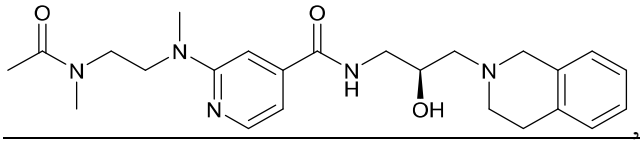


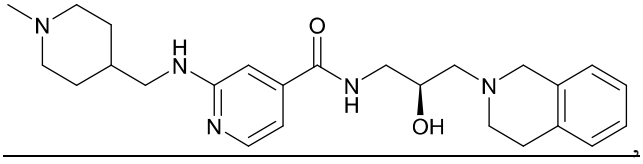


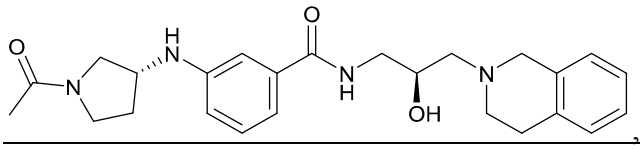


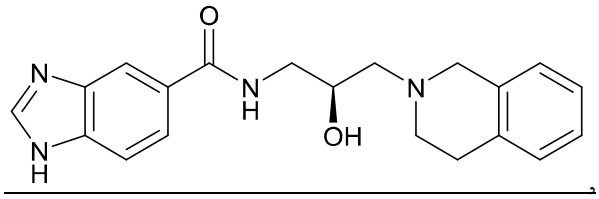


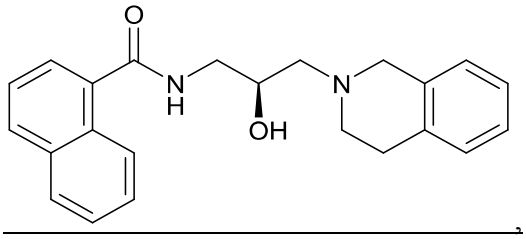


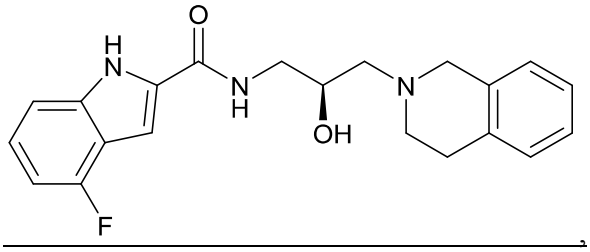


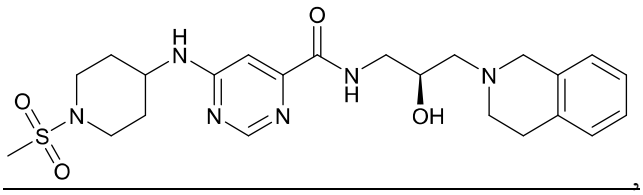


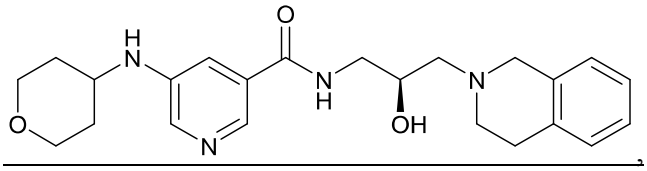


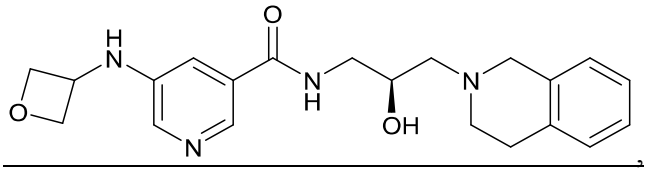


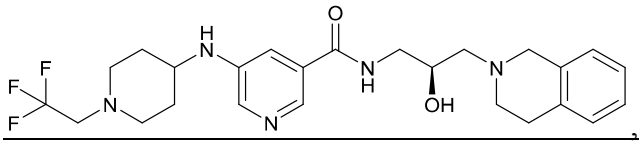


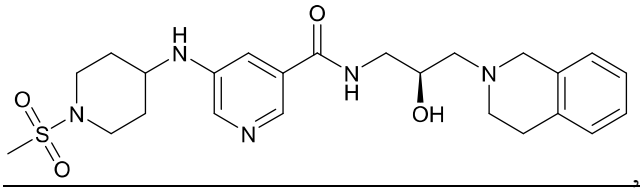


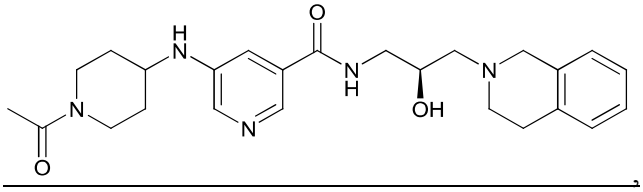


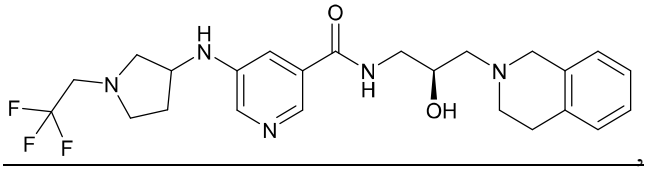


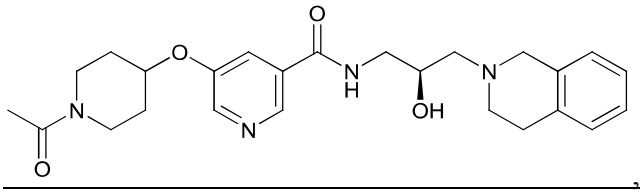


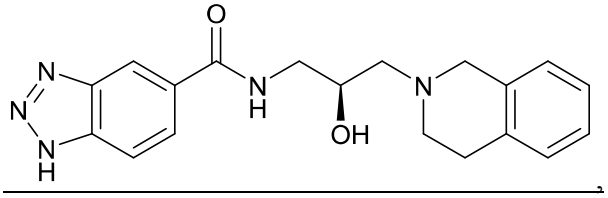


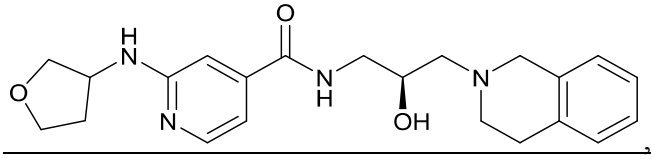


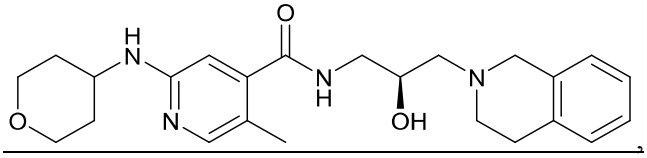


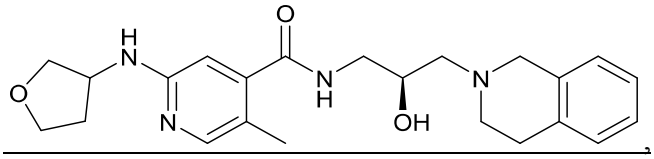


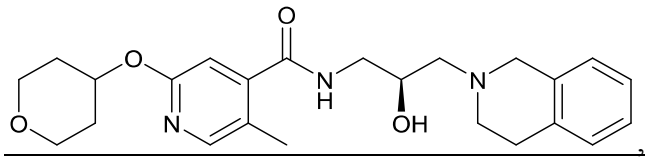


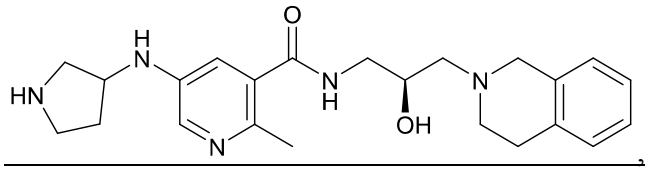


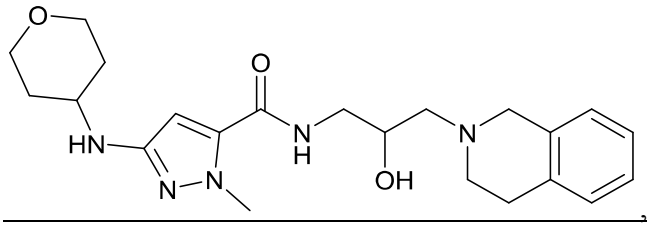


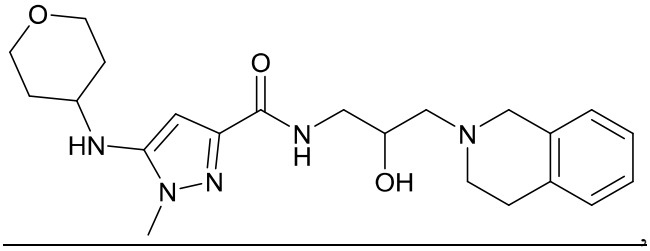


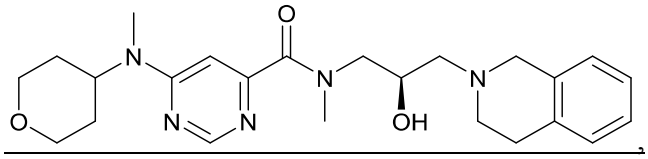


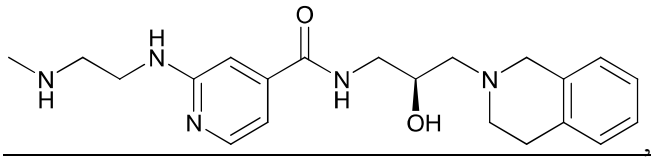


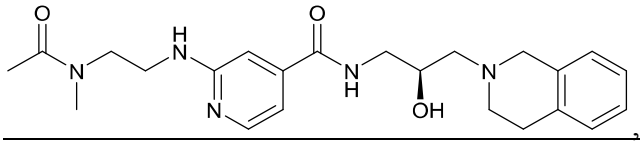


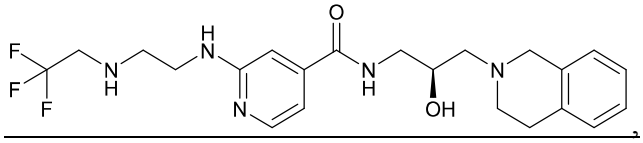


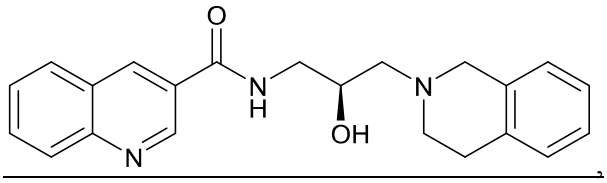


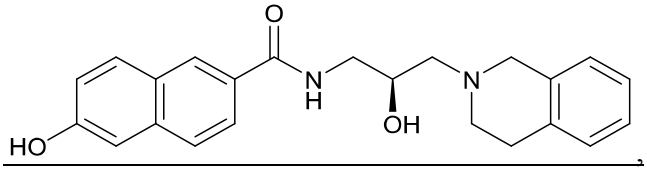


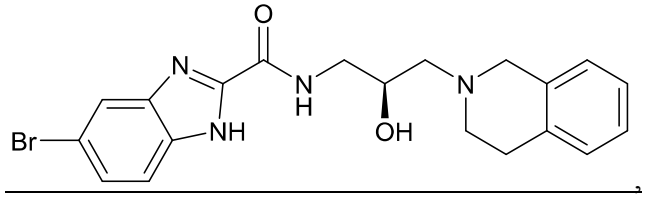


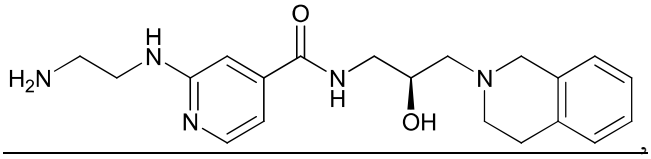


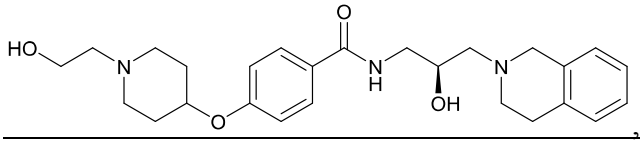


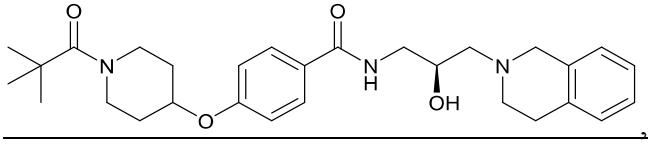


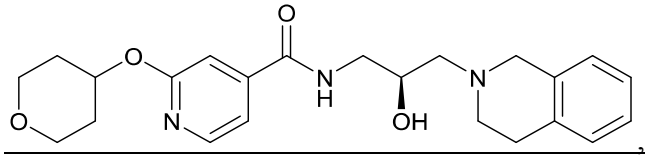


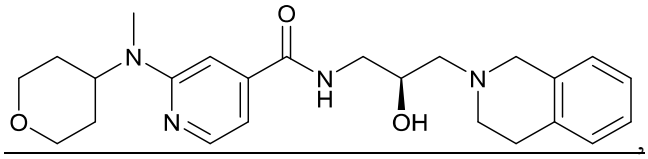


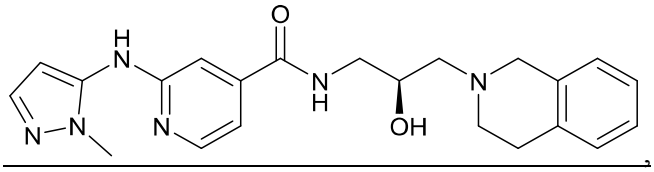


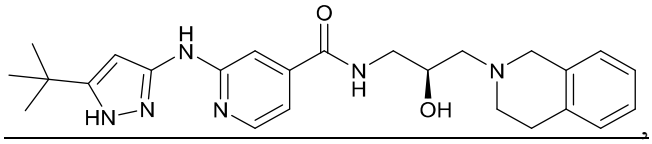


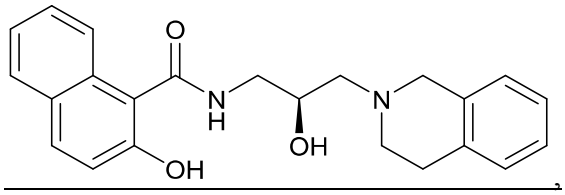


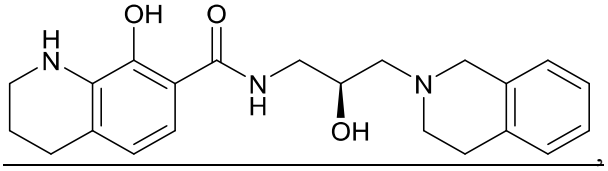


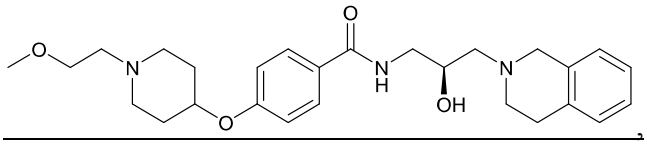


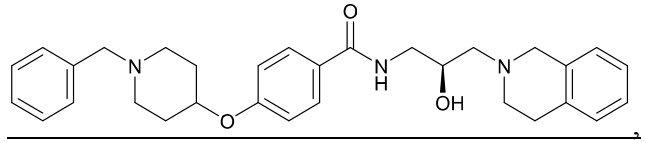


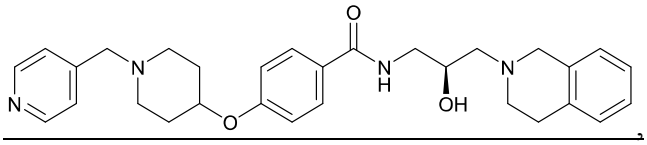


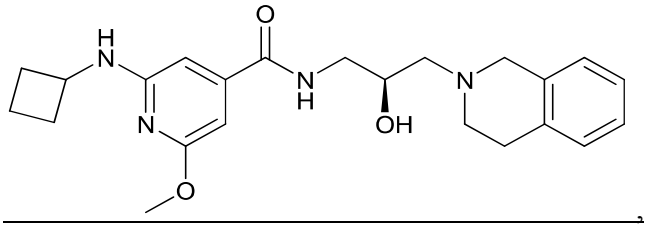


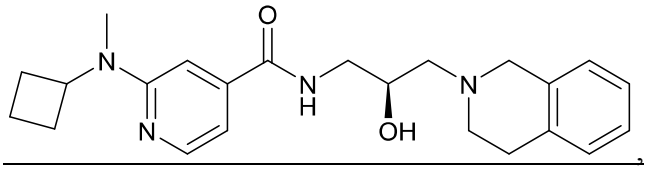


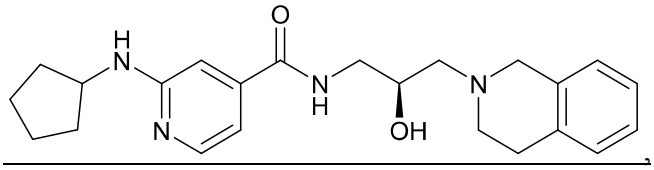


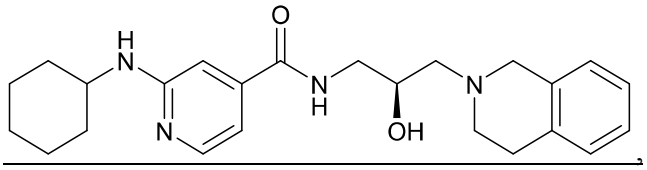


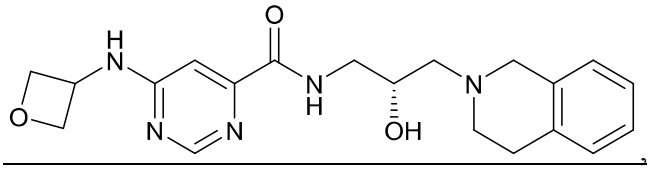






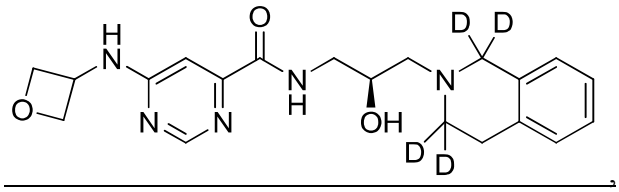


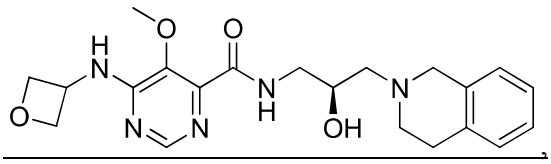


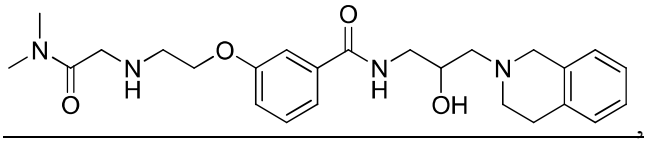


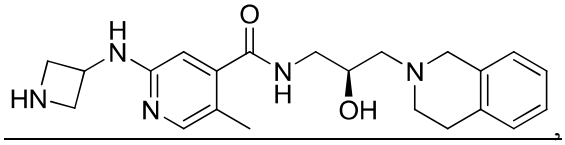
and pharmaceutically acceptable salts thereof.

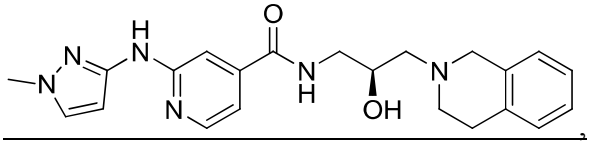
110. The compound of claim 1, wherein the compound is selected from the group consisting of:

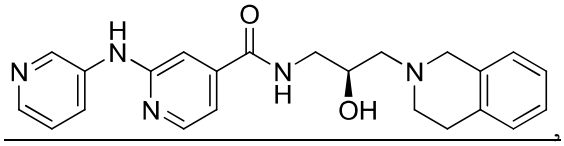


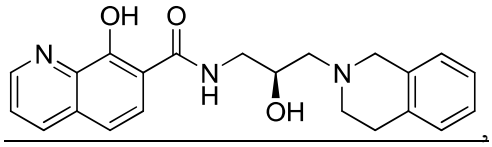


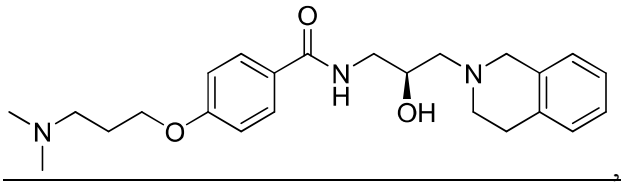


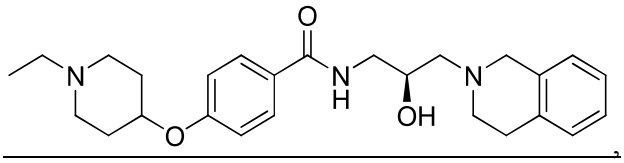


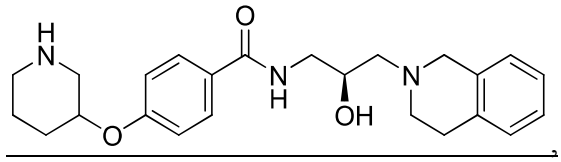


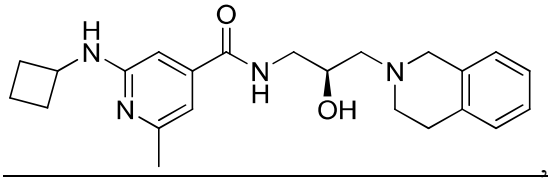


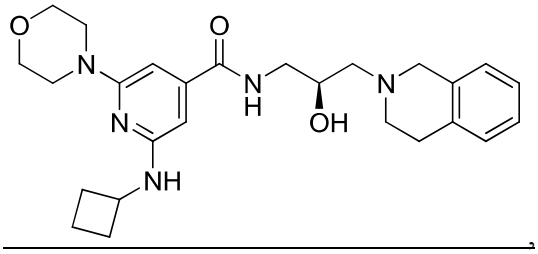


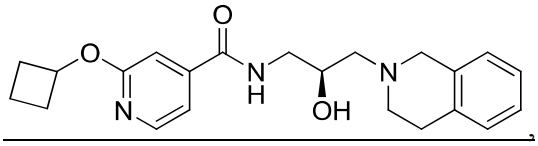


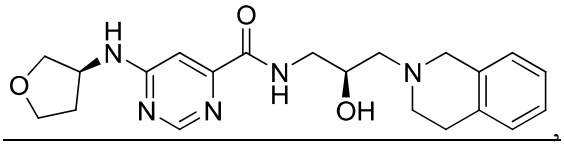


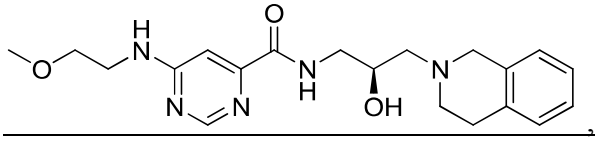


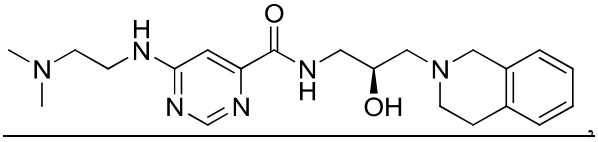


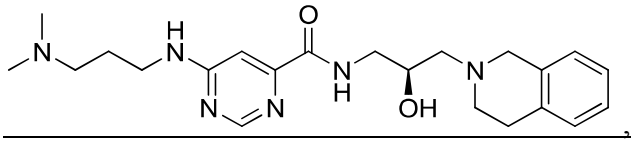


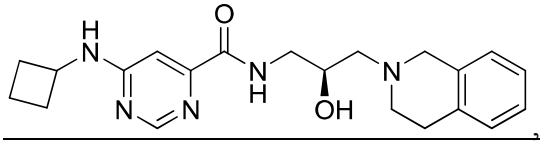


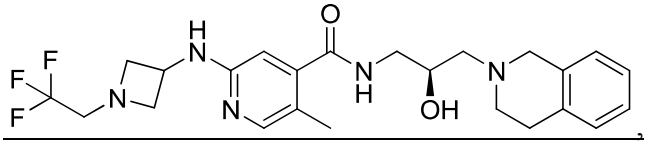


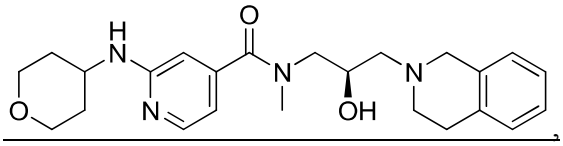


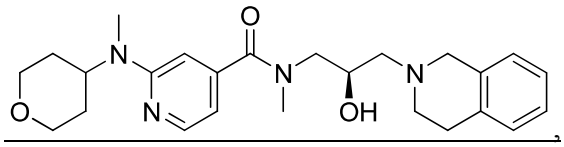


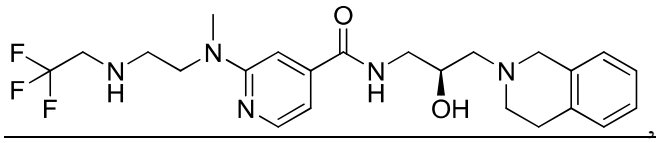


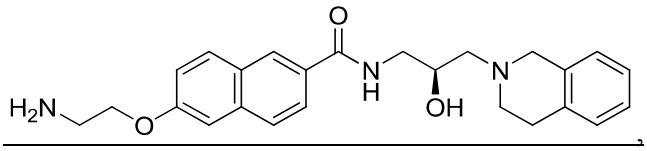


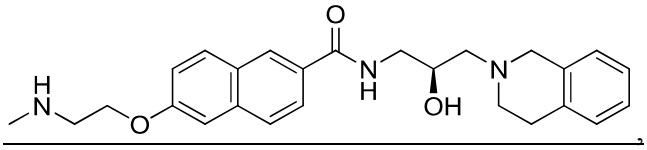


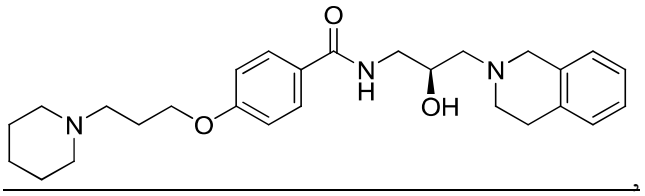


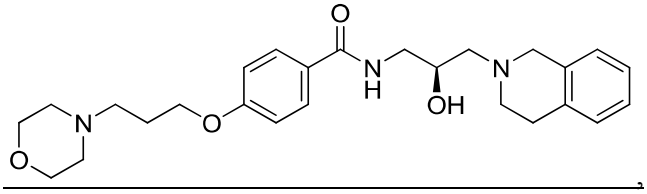


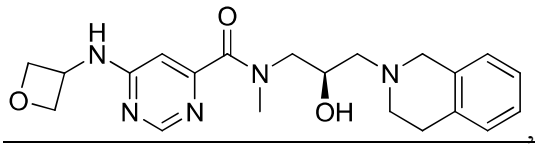


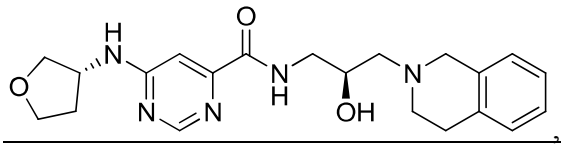


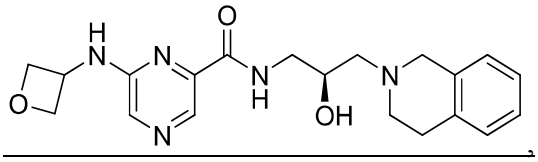


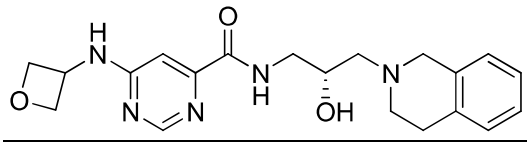


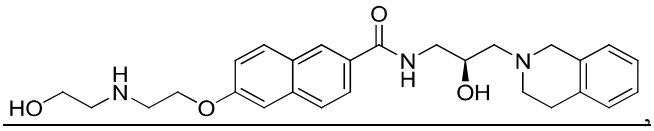


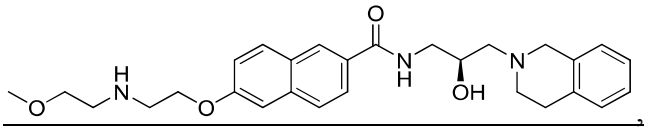


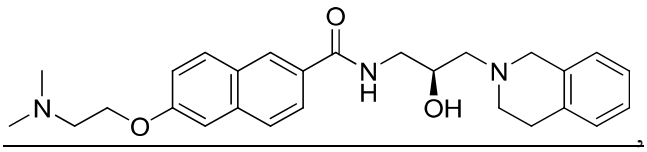


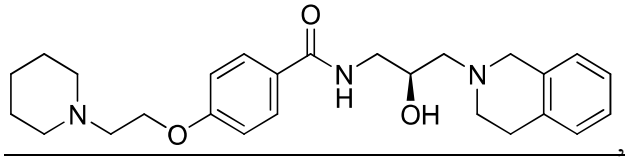


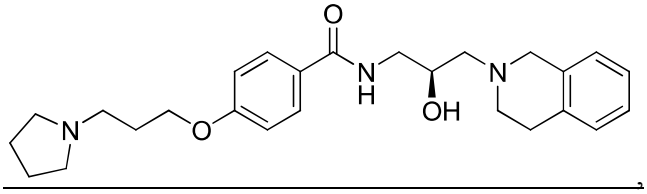


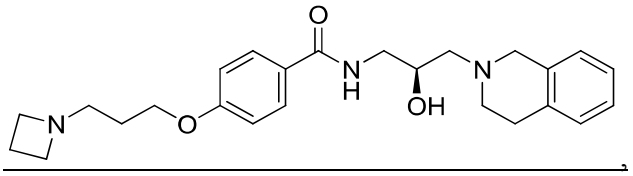


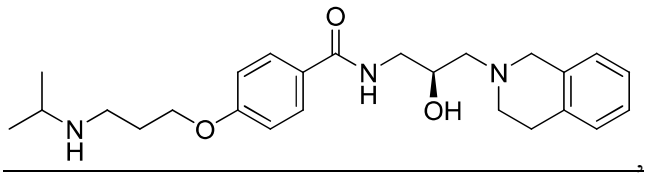


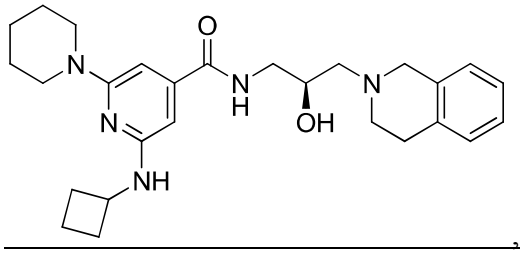


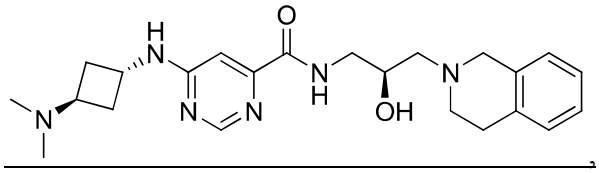


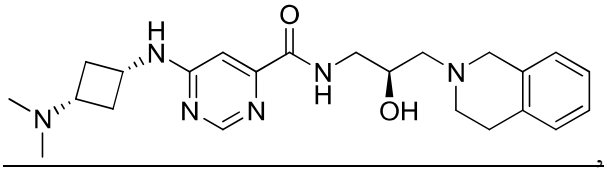


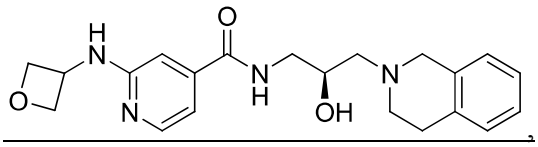


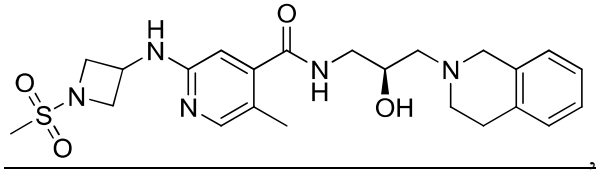


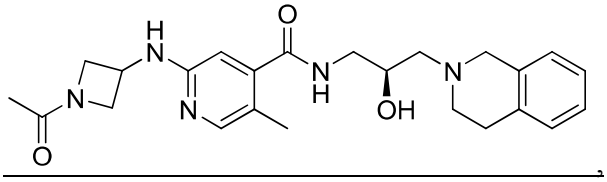


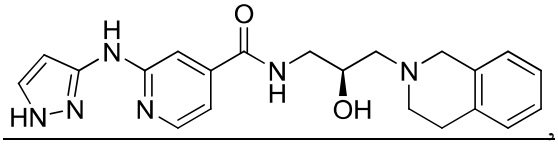


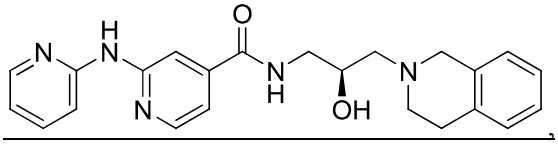


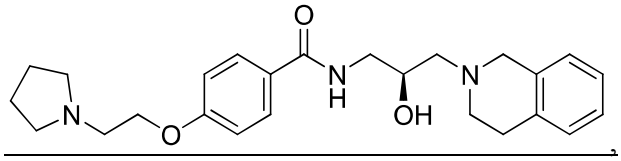


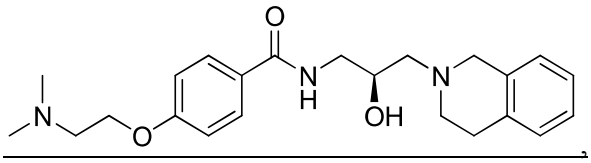


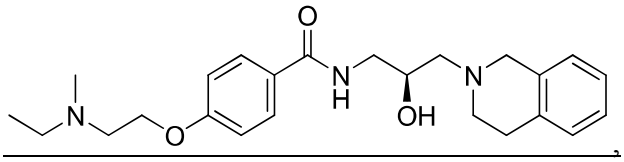


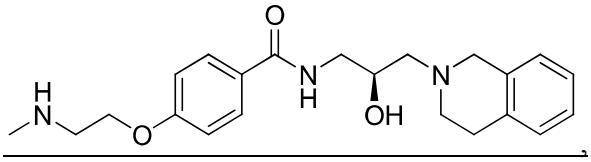


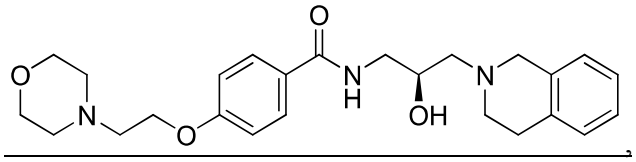


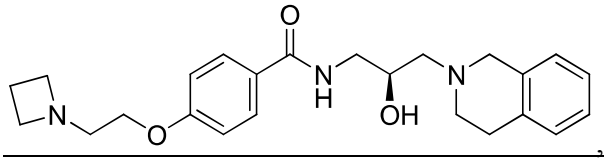


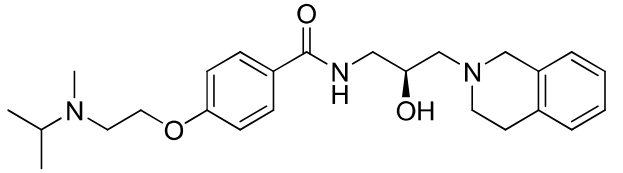


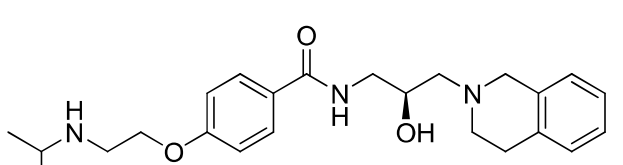


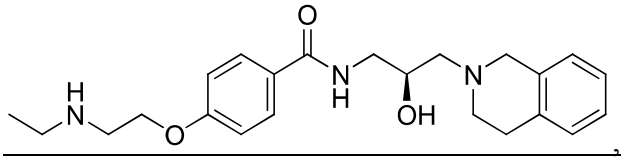


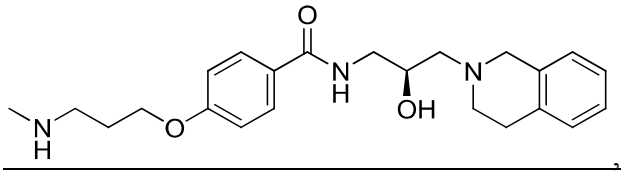


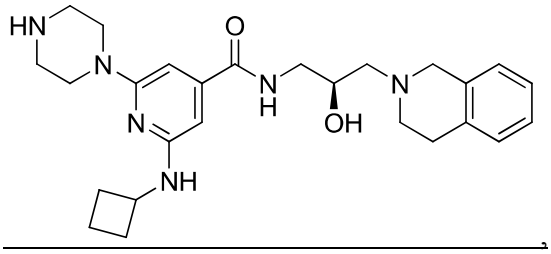


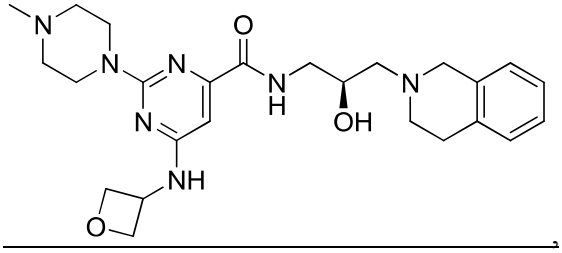


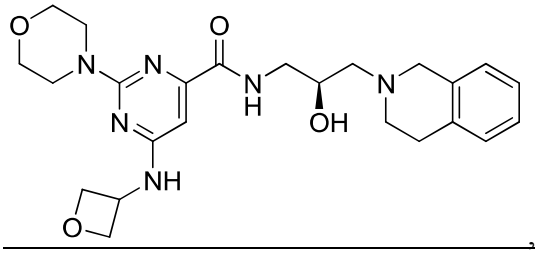


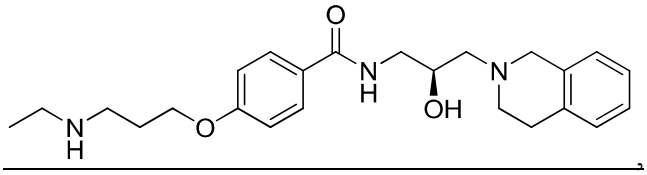


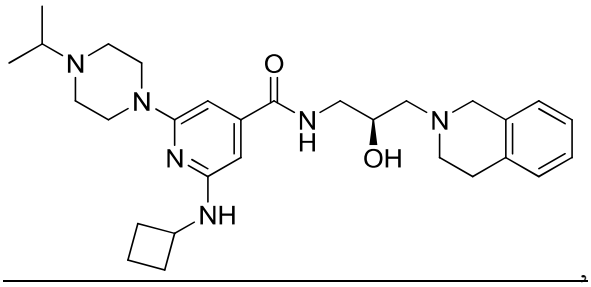


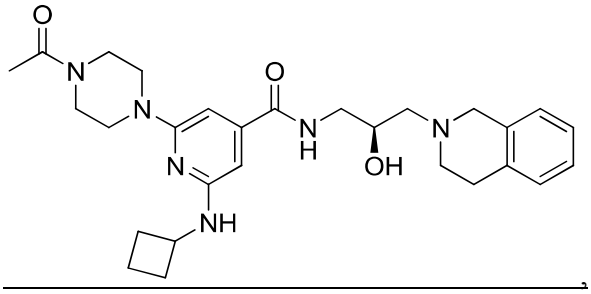


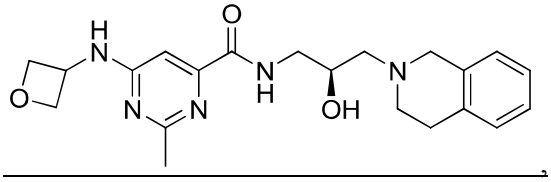


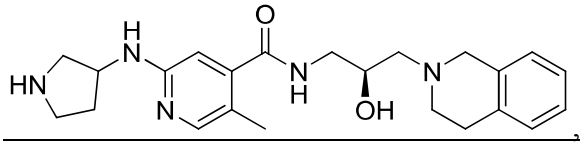


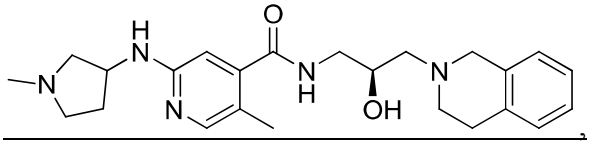


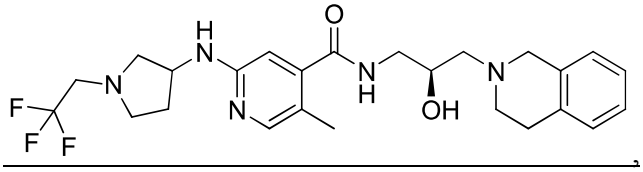


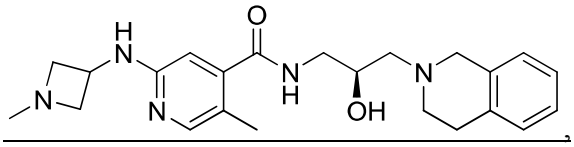


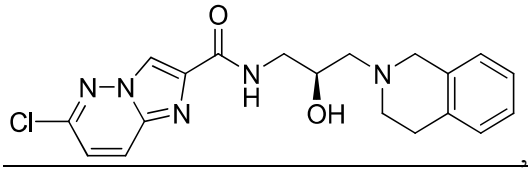


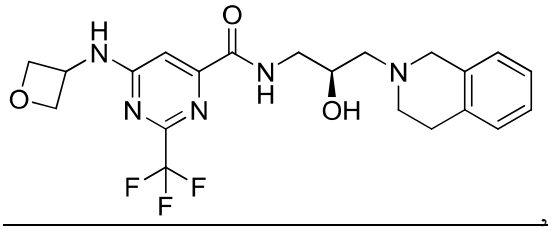


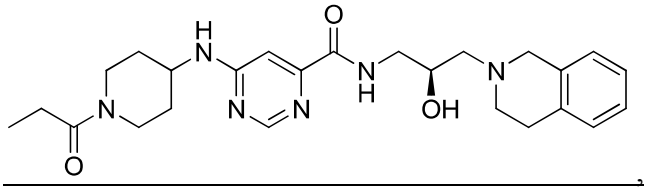


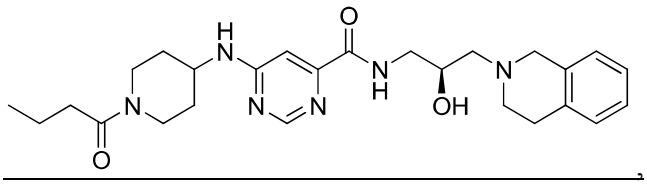


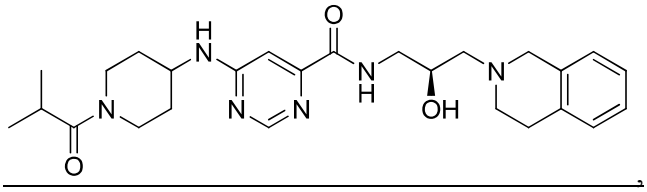


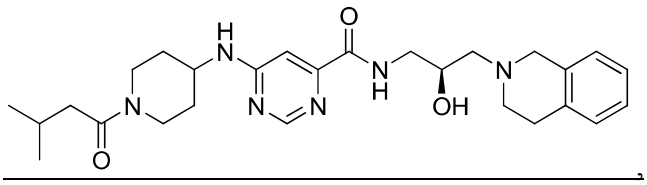


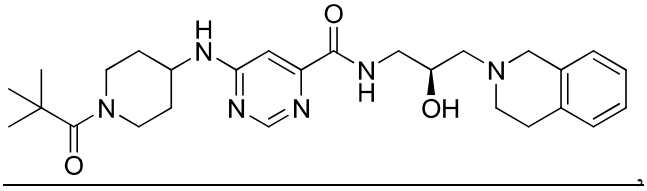


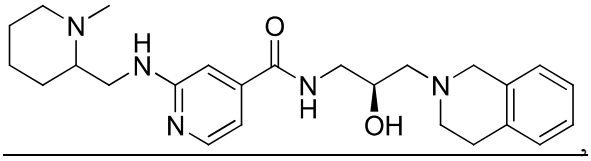


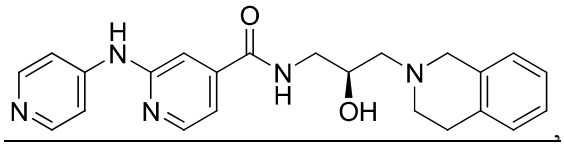


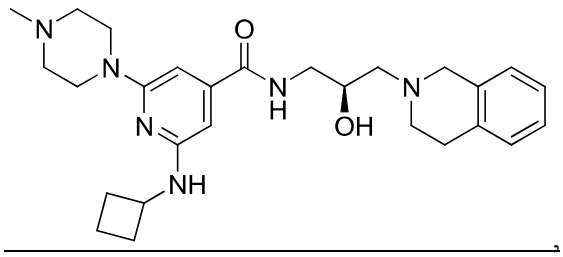


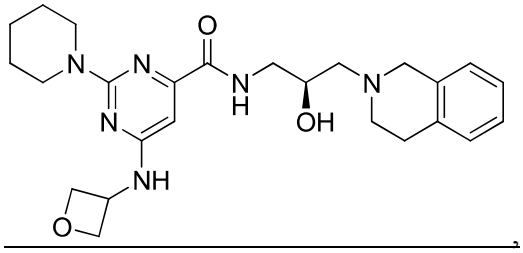


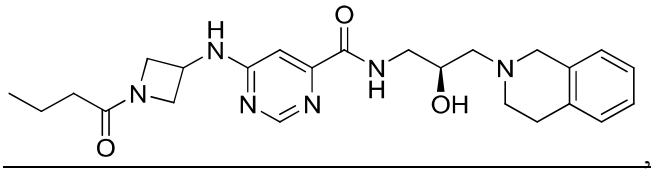


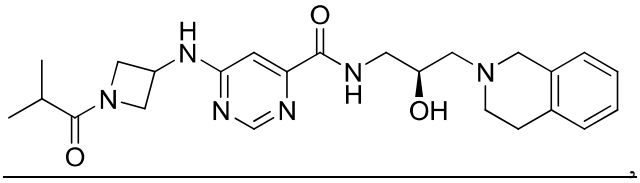


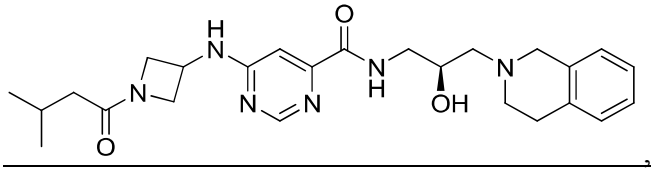


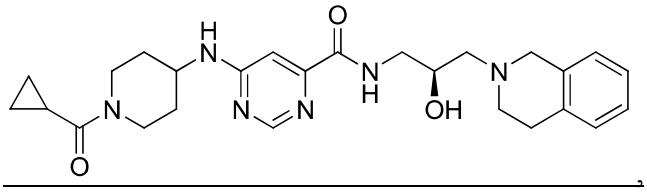


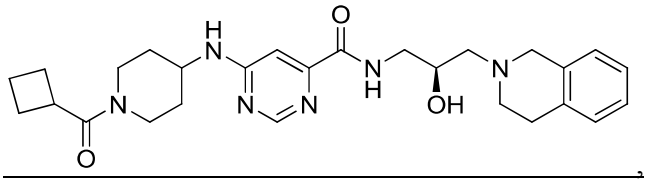


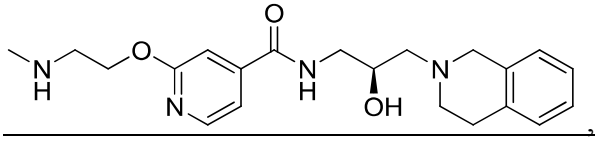


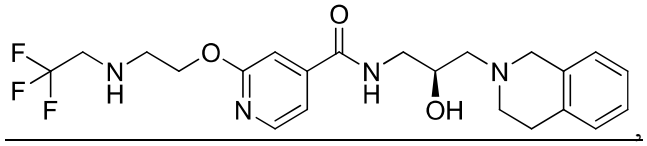


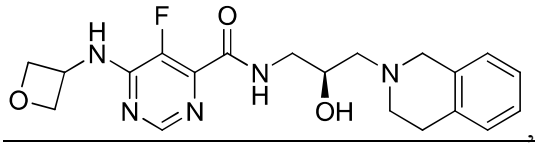


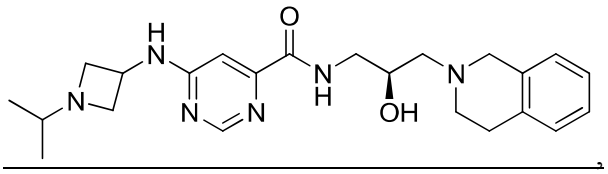


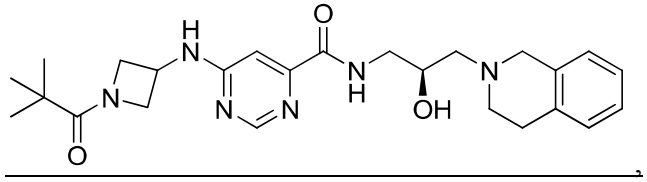


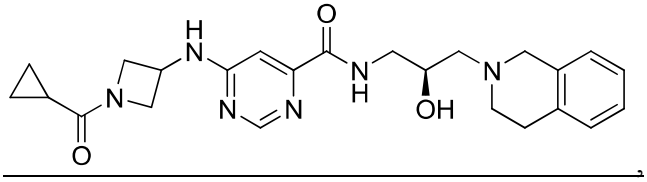


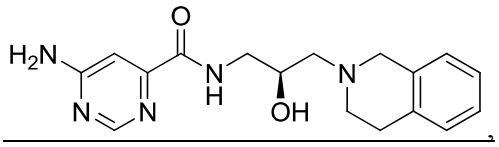


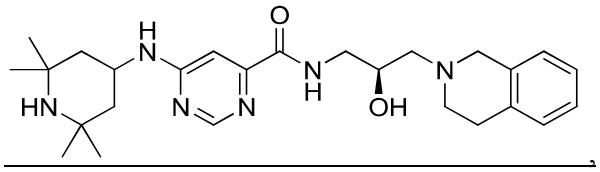


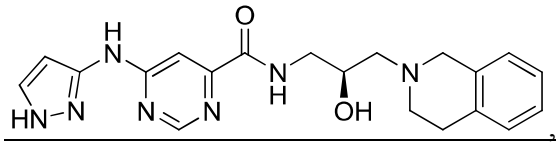


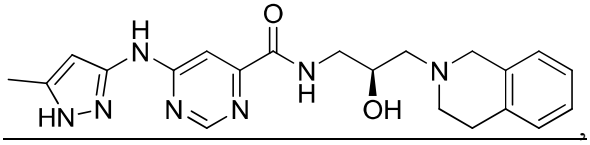


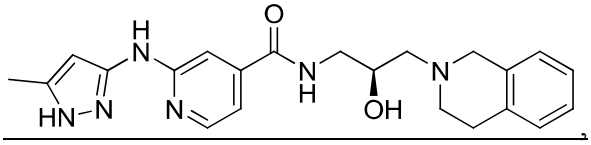


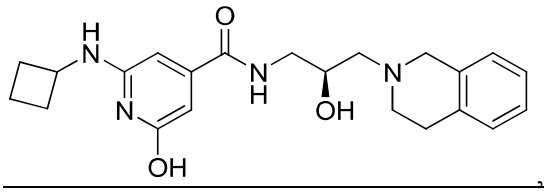


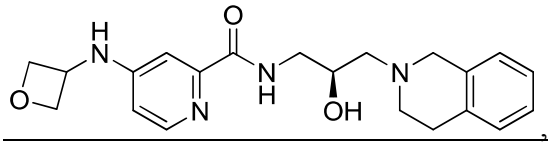


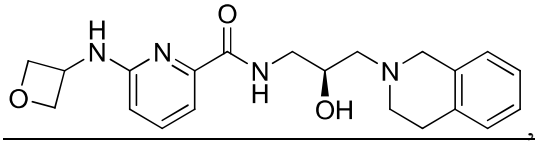


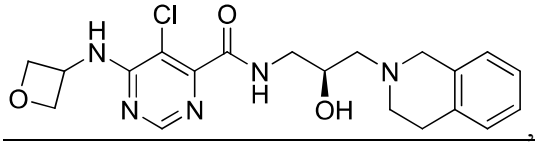


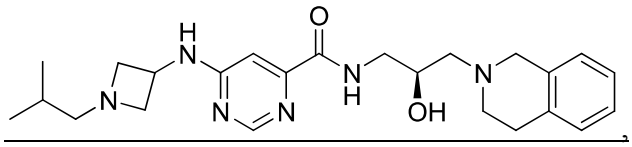


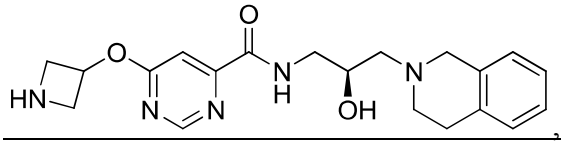


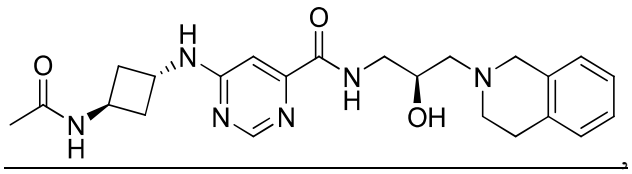


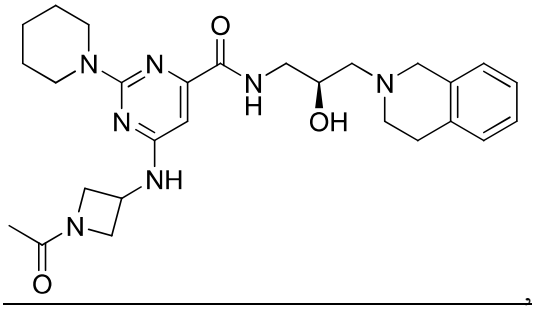


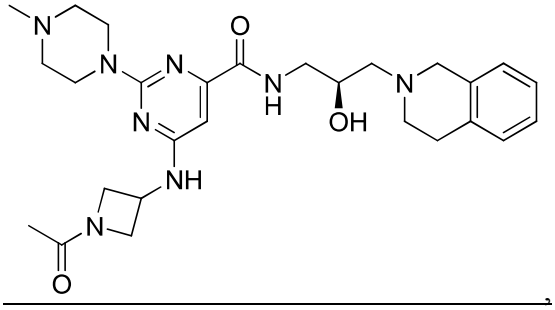


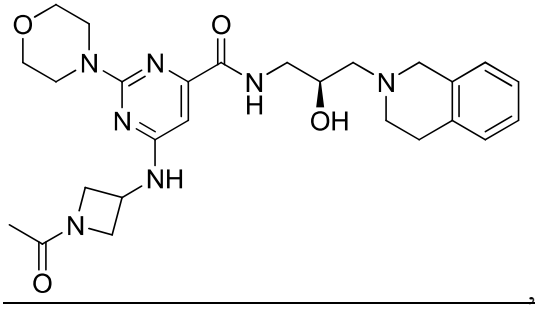


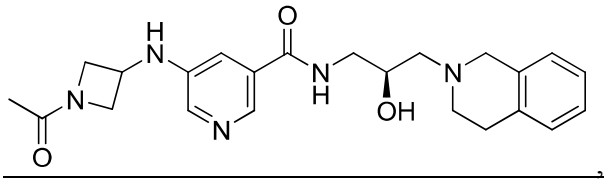


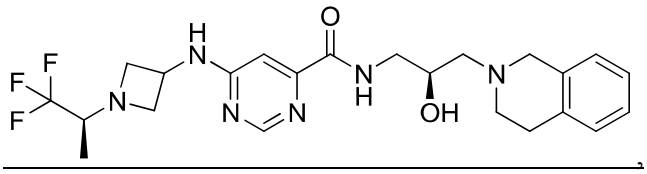


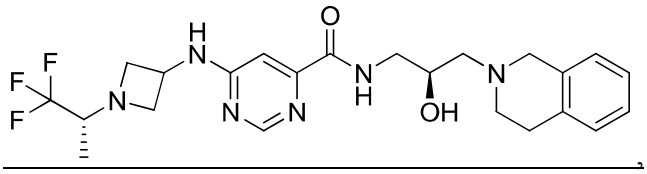


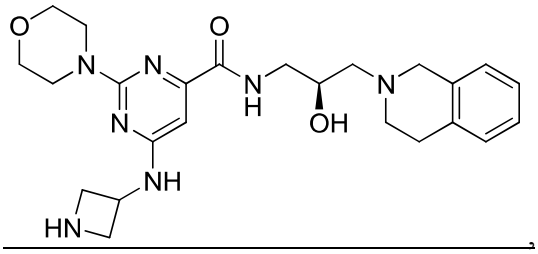


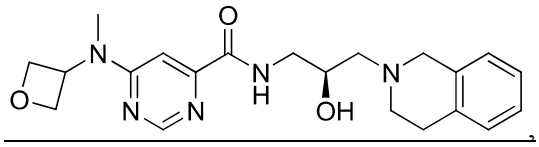


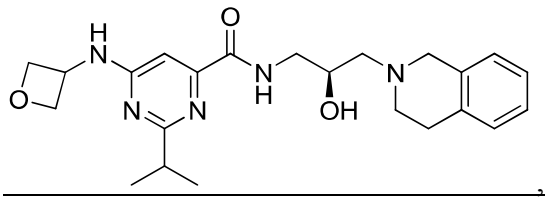


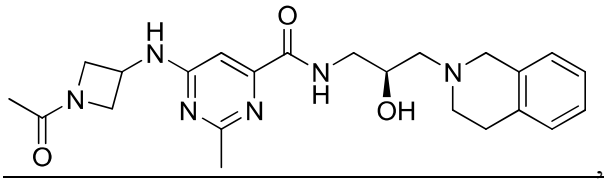


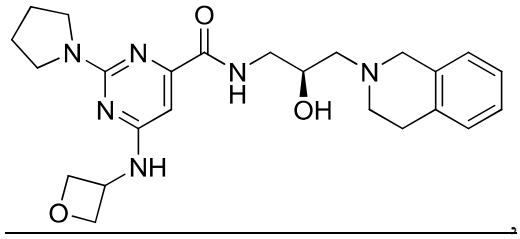


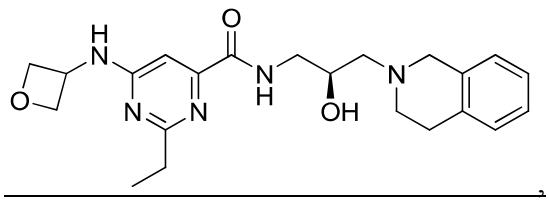


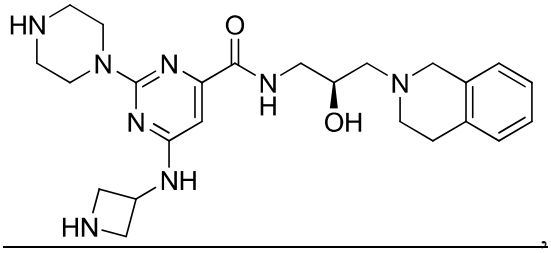


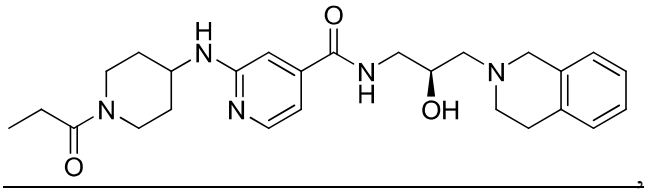


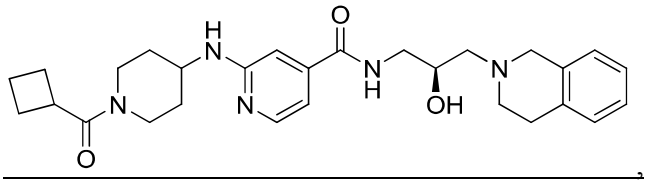


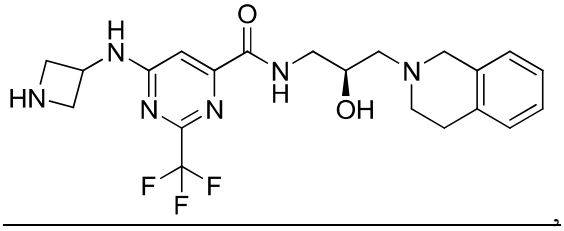


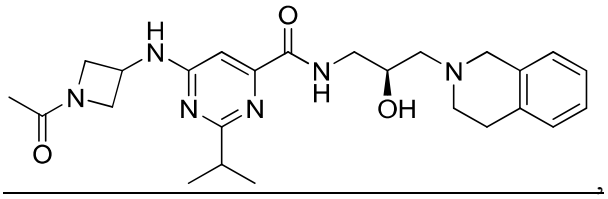


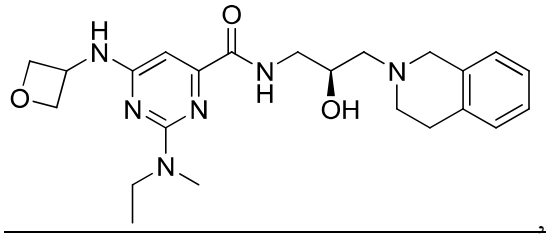


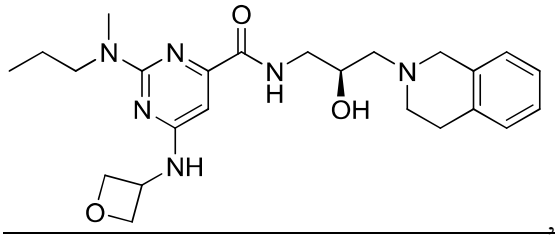


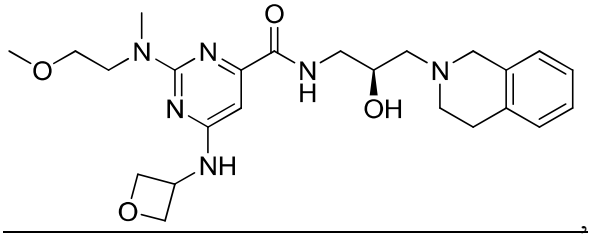


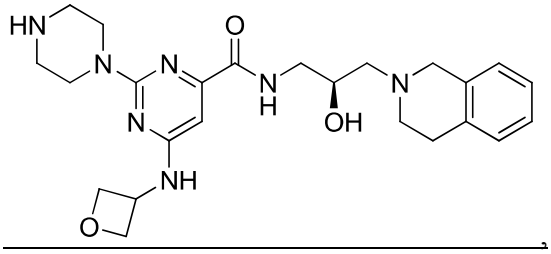


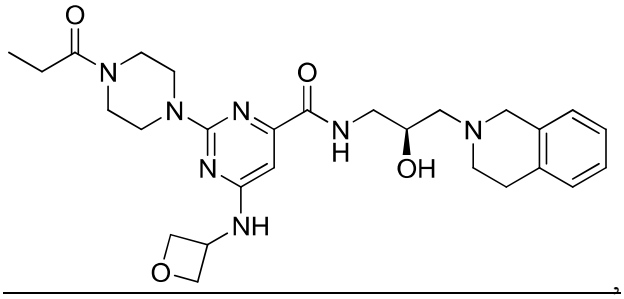


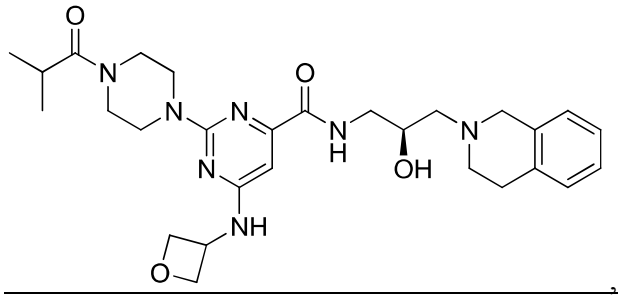


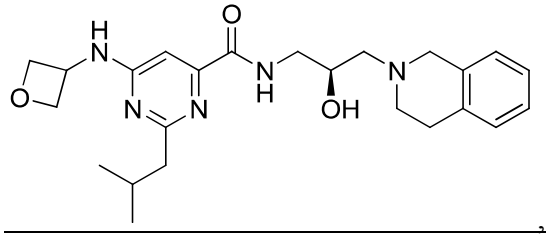


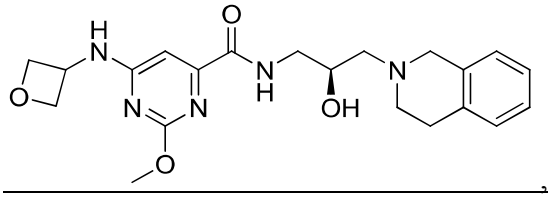


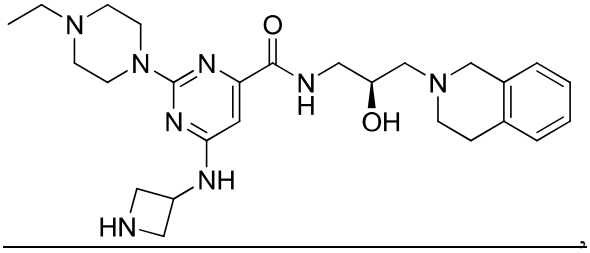


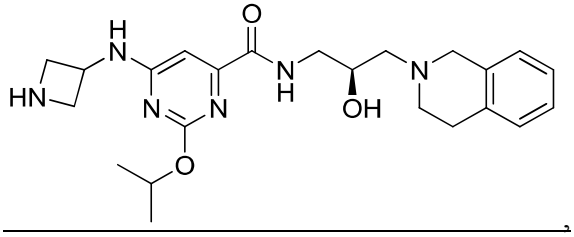


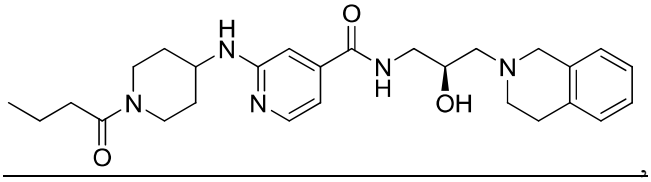


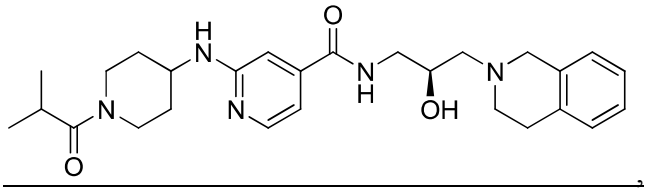


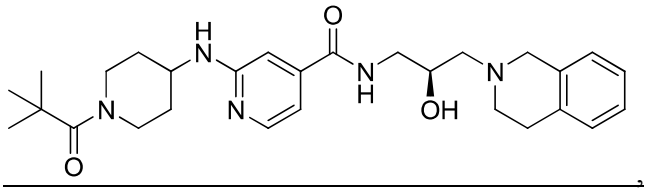


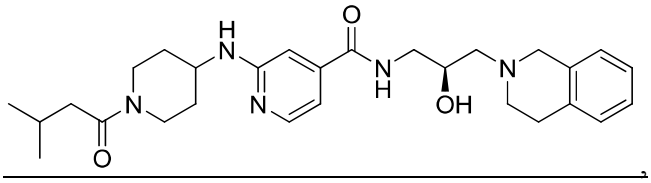


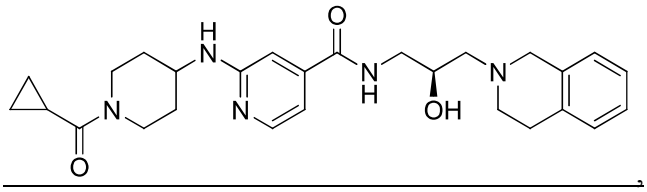


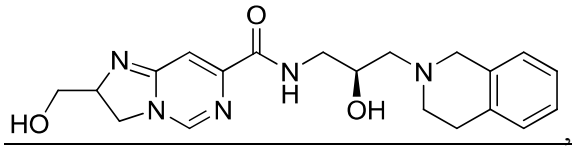


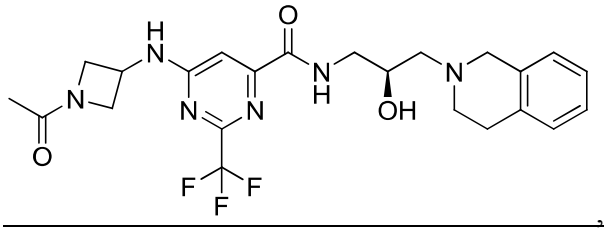


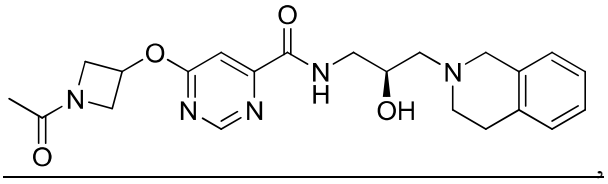


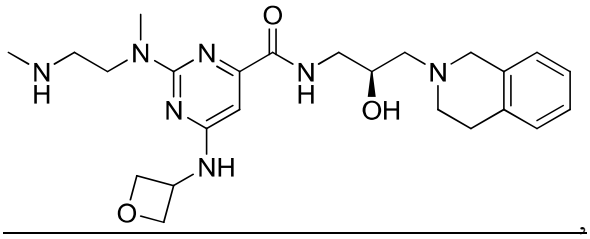


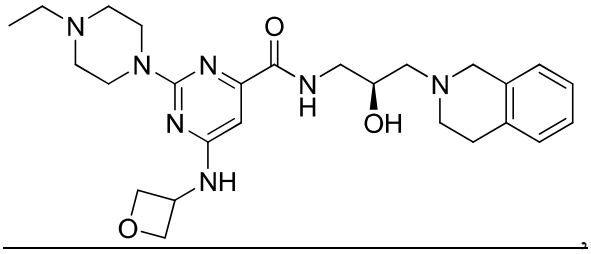


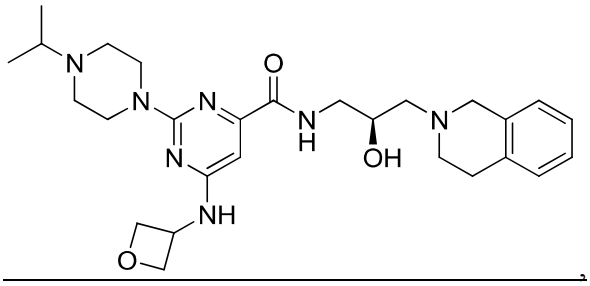


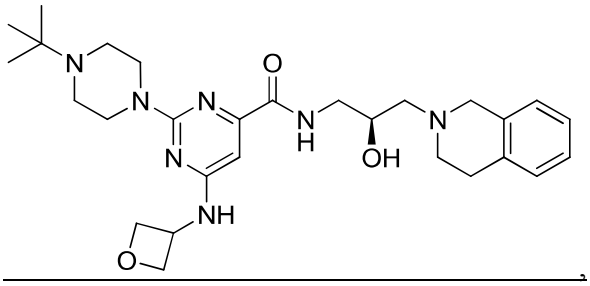


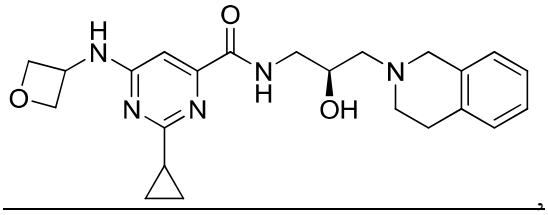


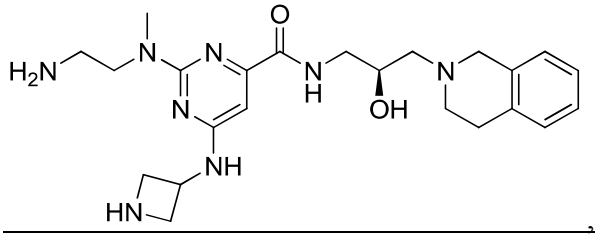


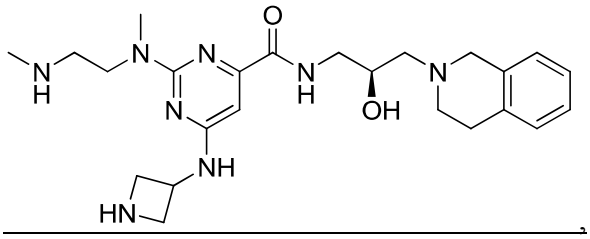


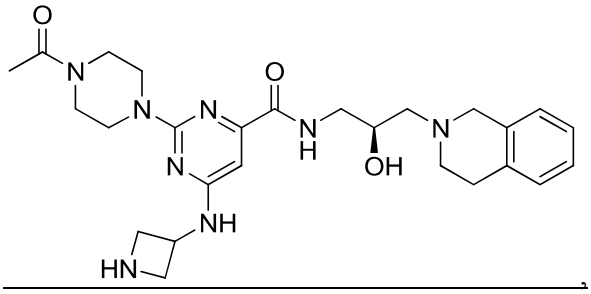


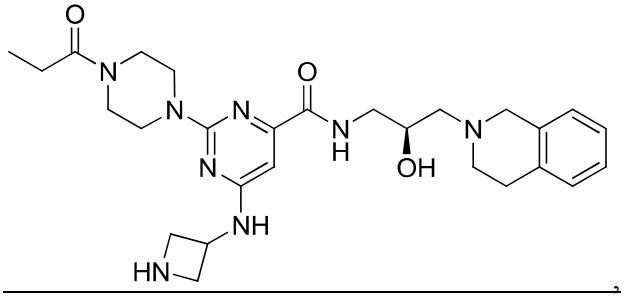


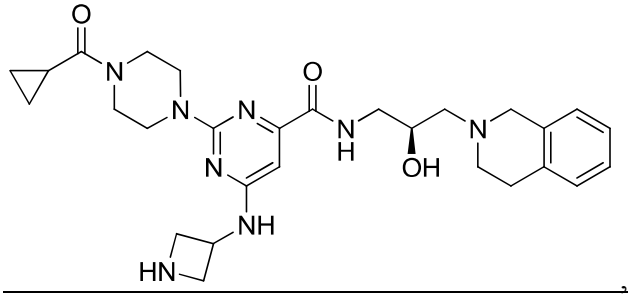


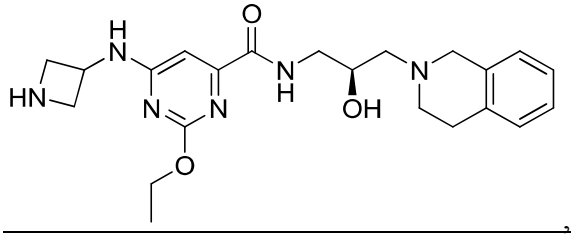


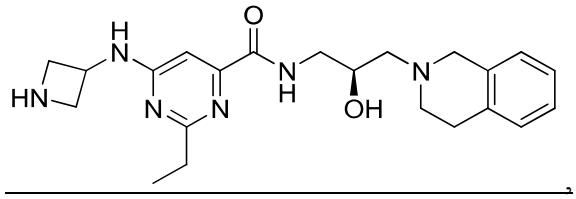


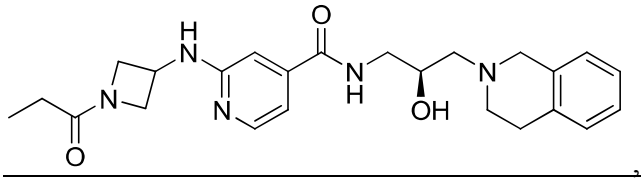


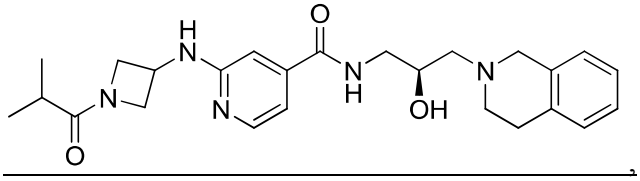


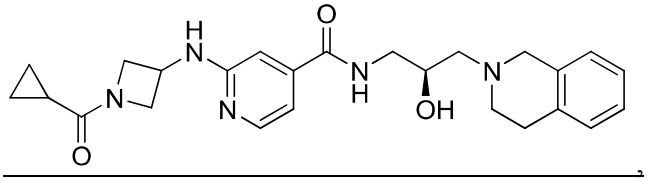


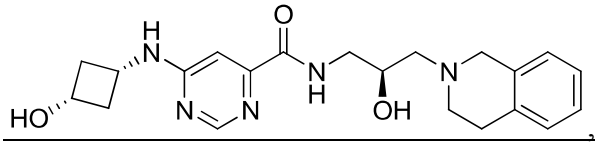


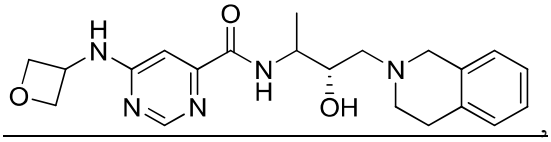


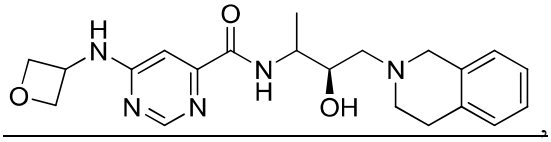


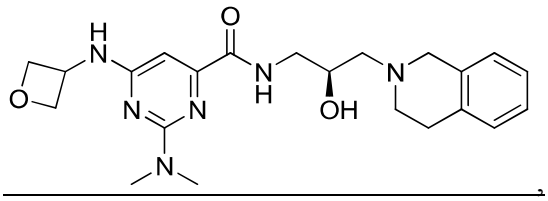


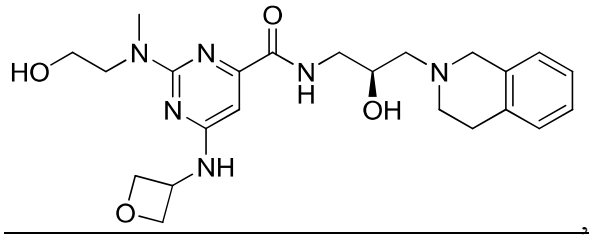


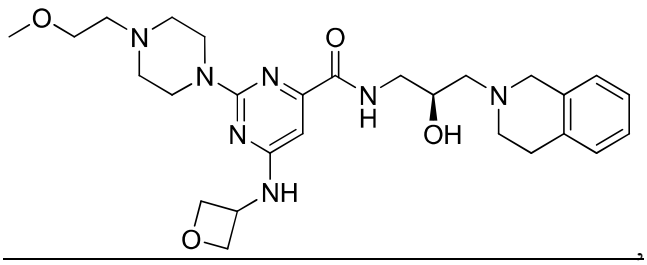


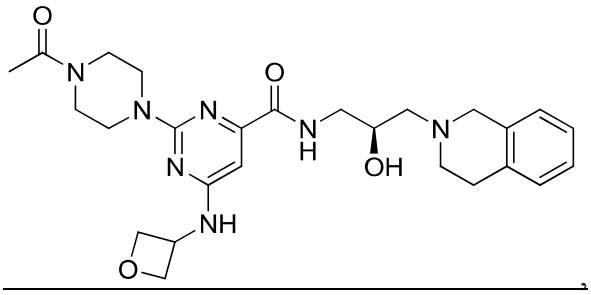


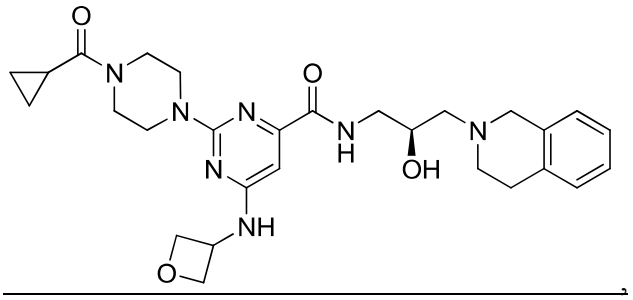


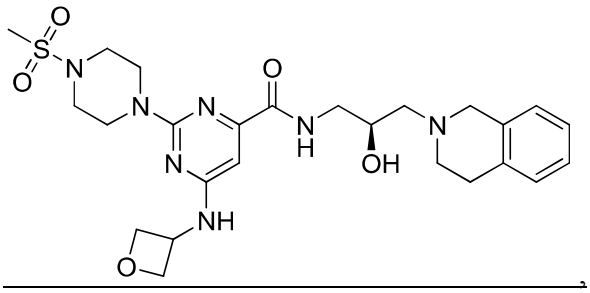


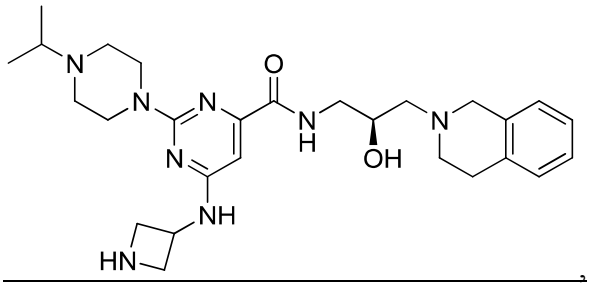


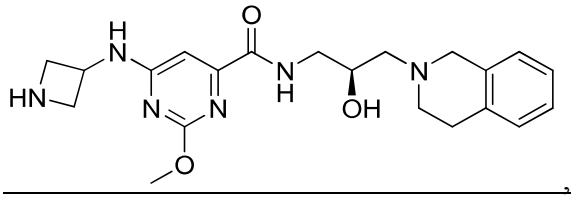


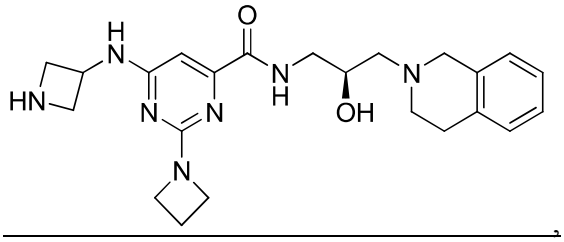


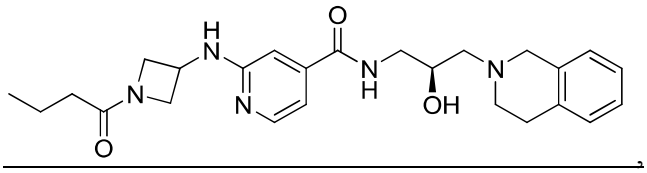


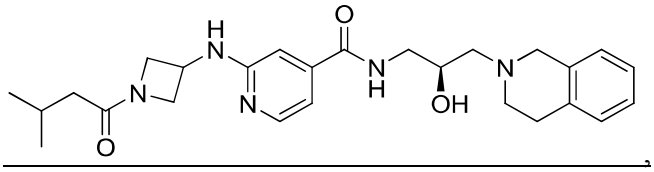


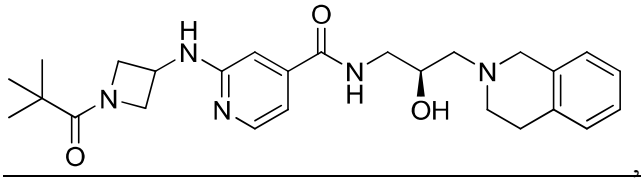


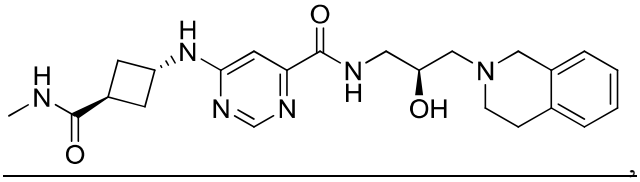


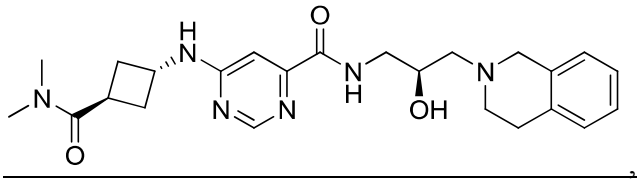


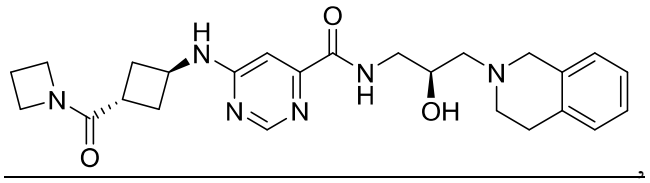


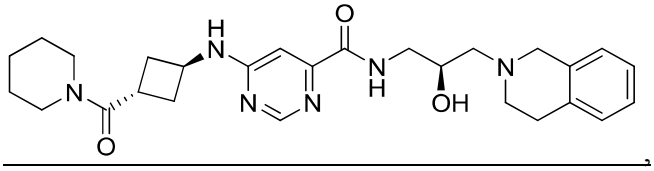


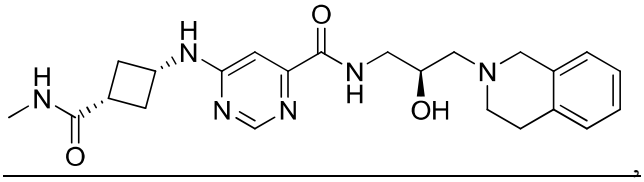


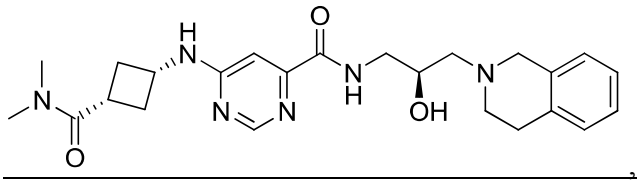


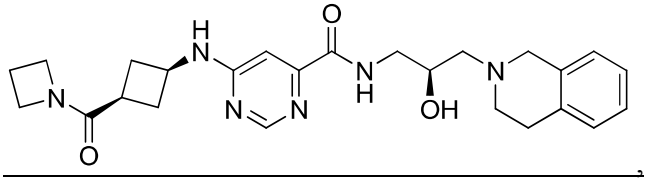


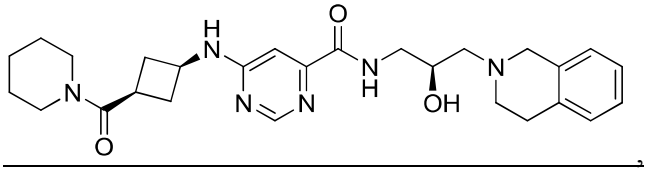


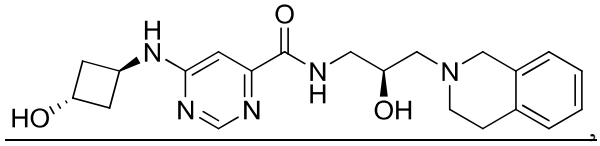


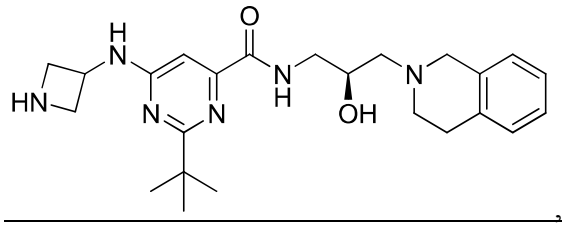


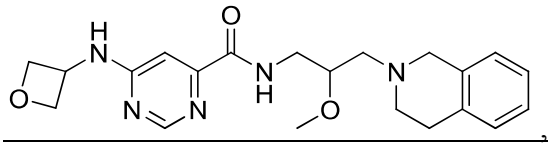


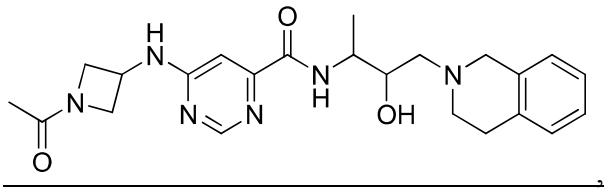


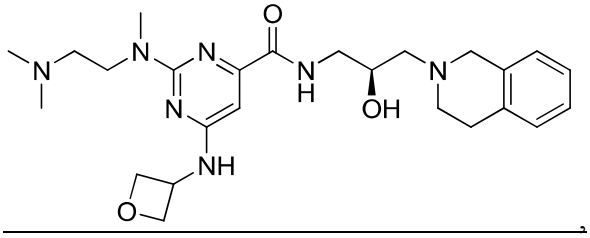


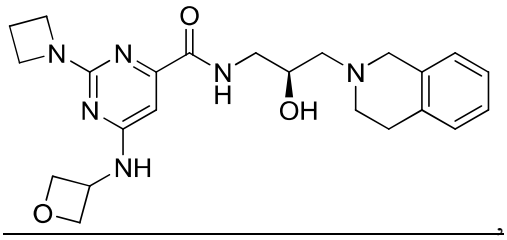


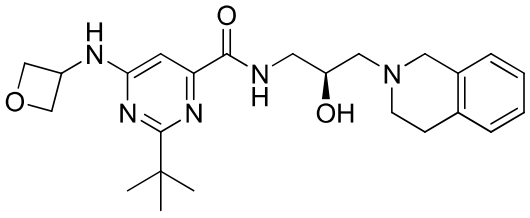


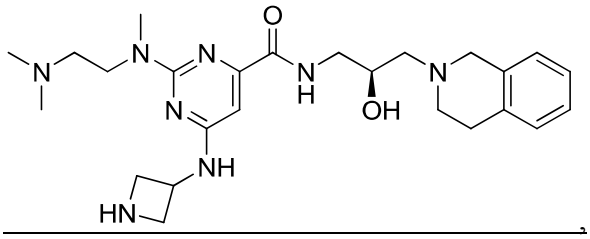


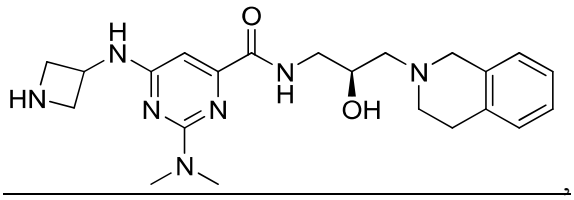


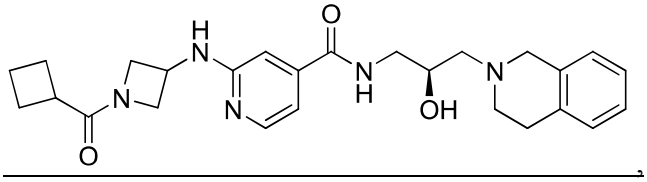


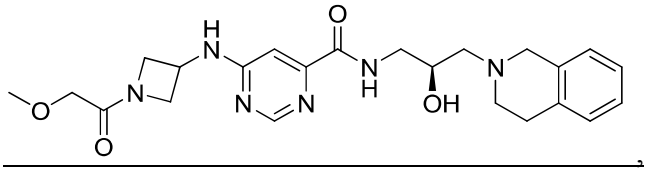


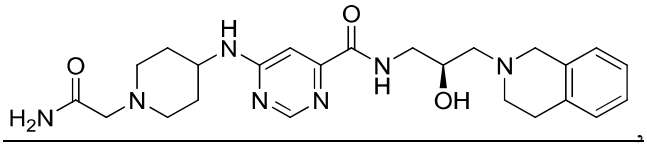


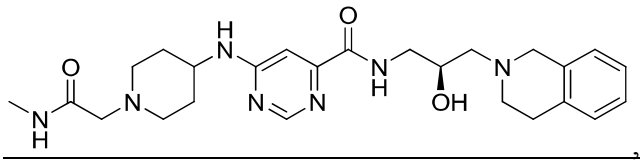


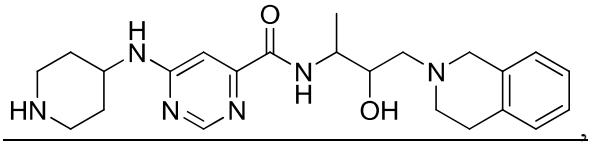


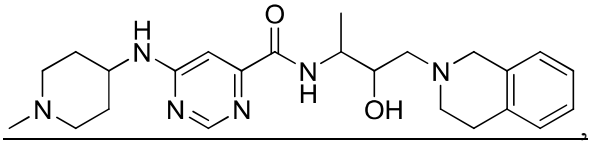


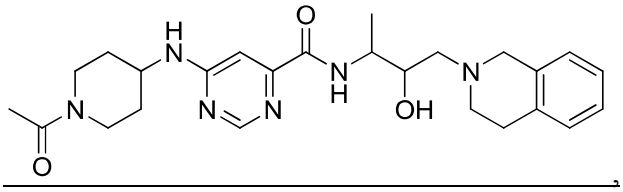


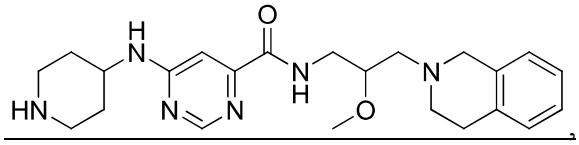


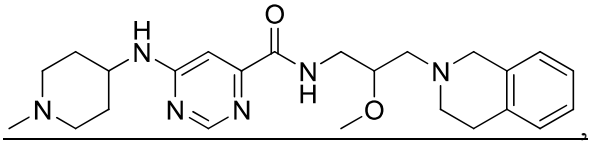


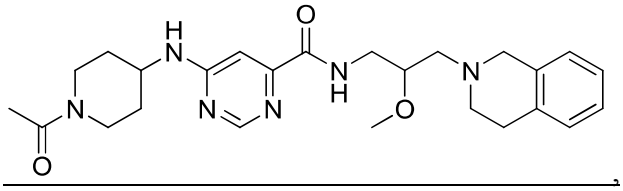


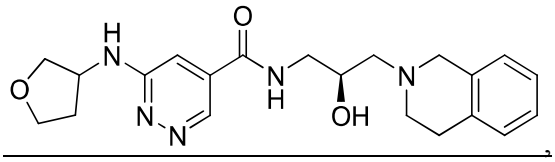


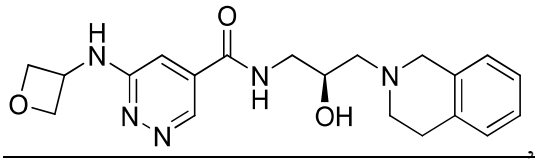


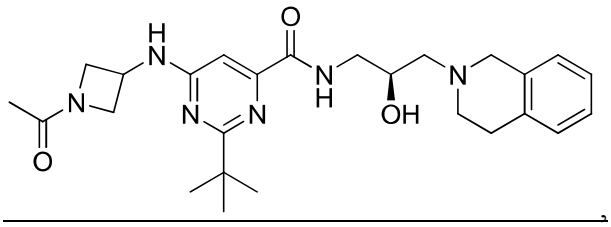


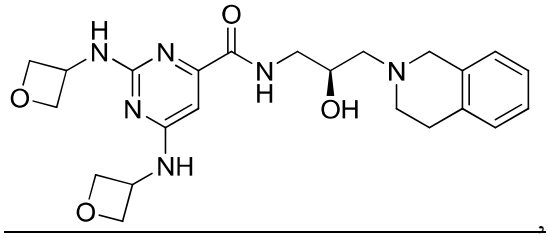


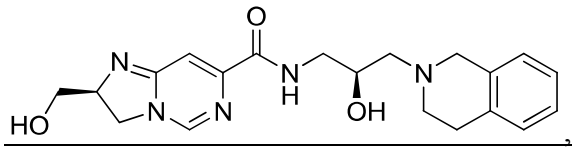


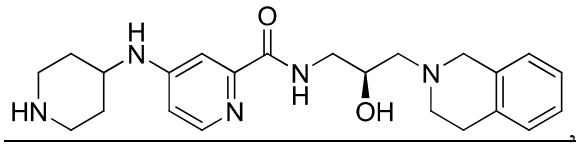


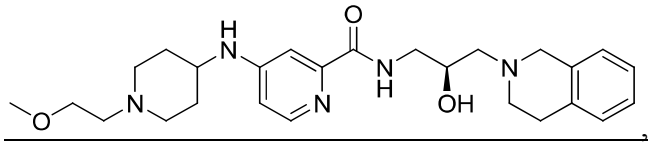


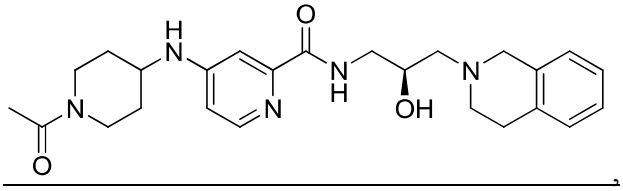


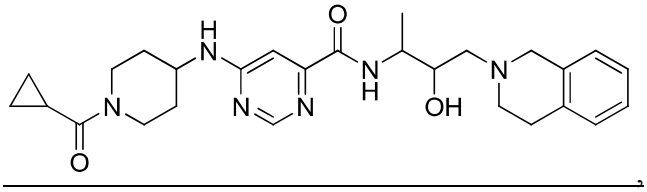


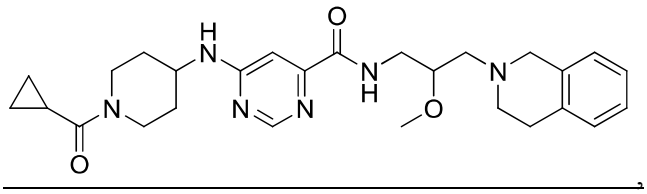


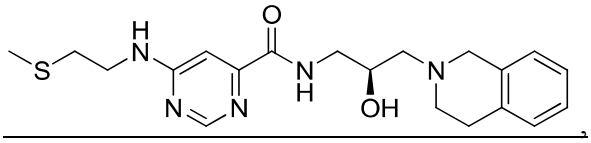


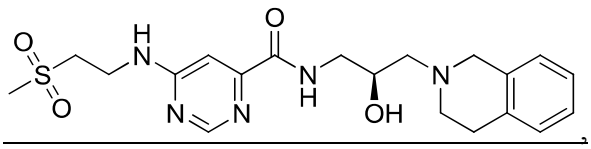


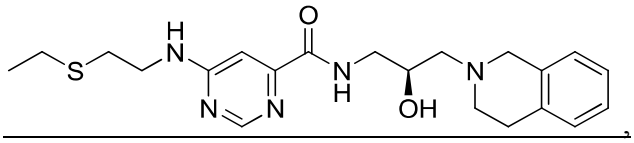


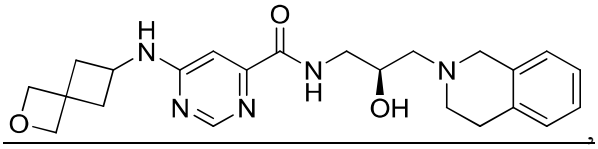


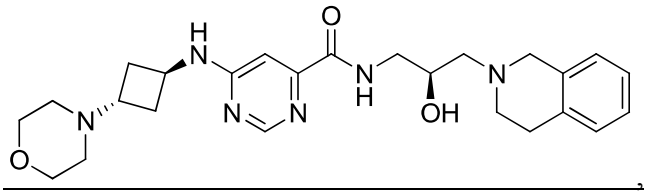


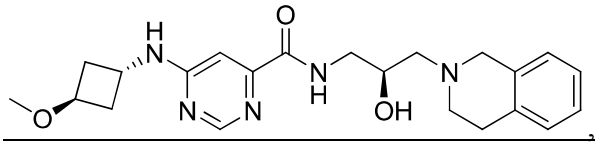


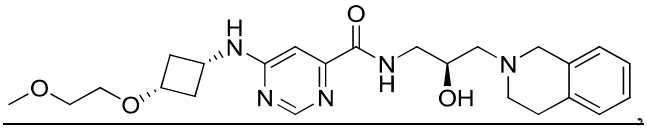


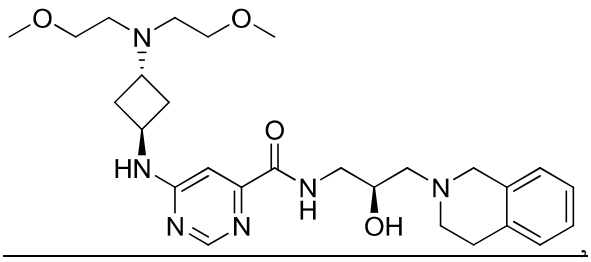


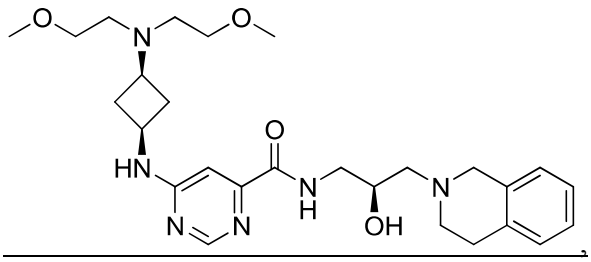


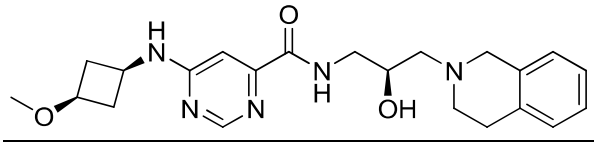


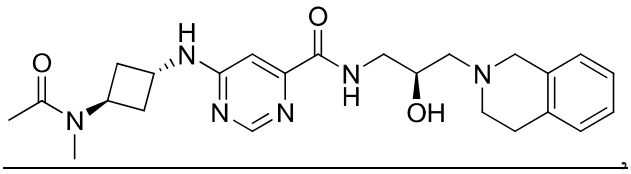


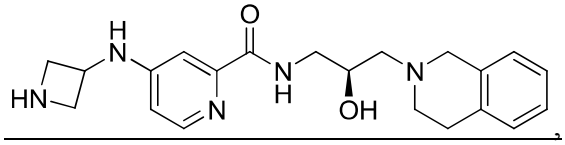


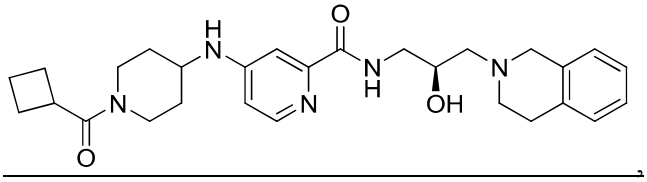


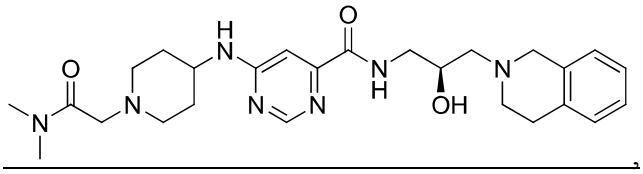


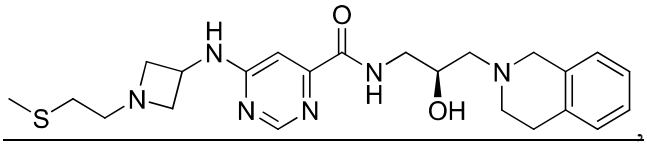


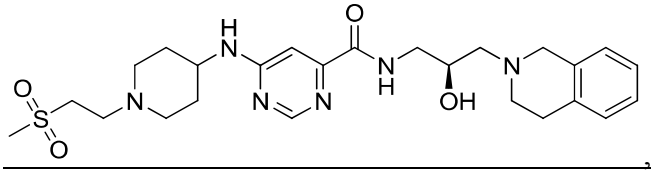


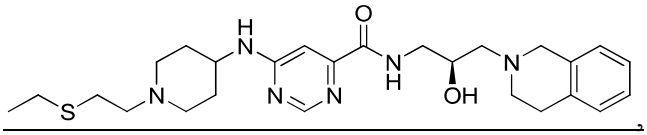


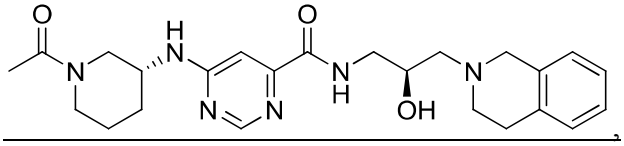


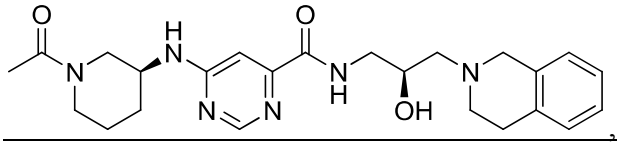


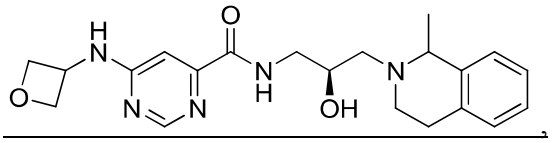


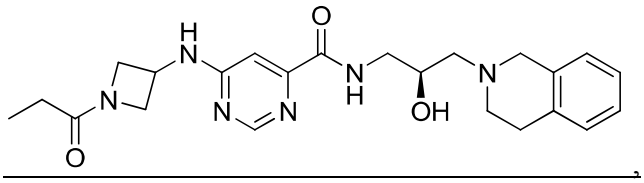


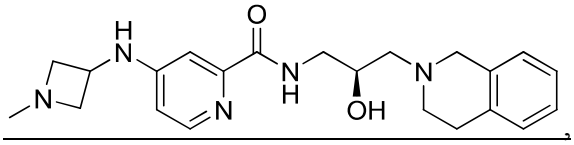


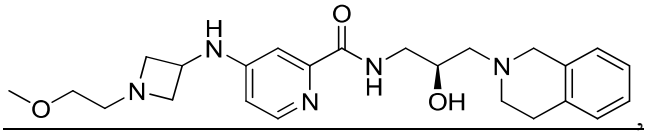


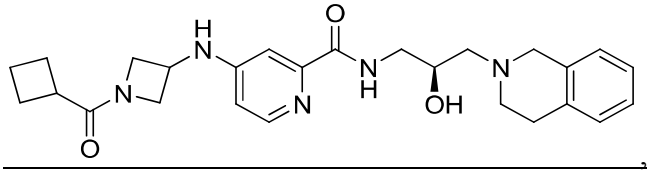


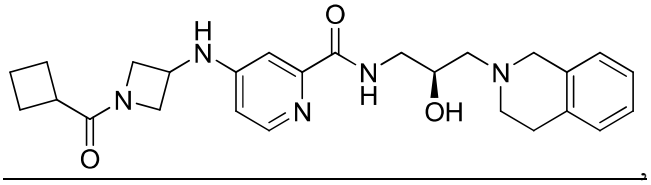


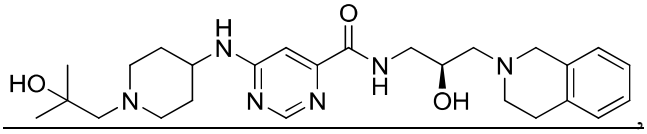


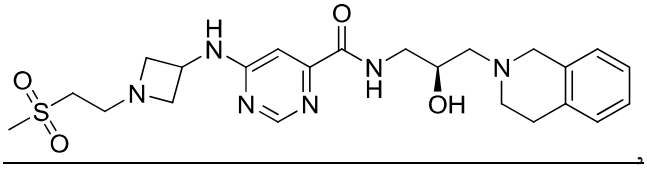


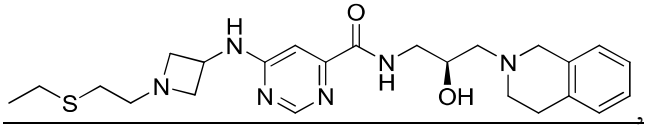


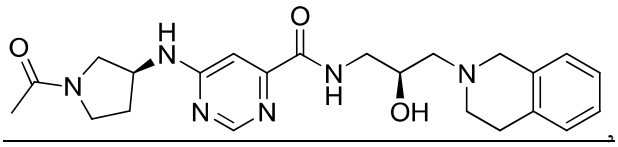


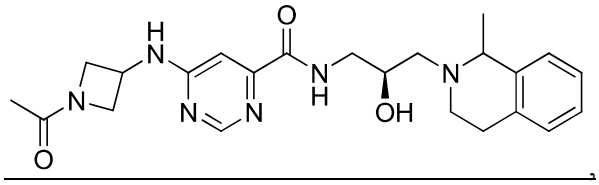


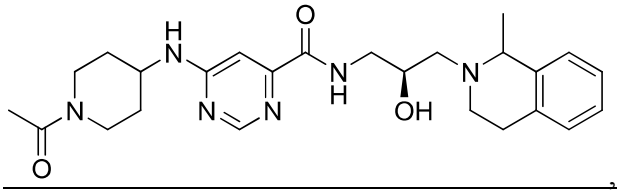


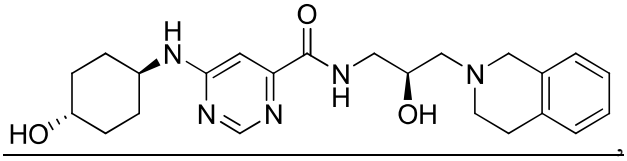


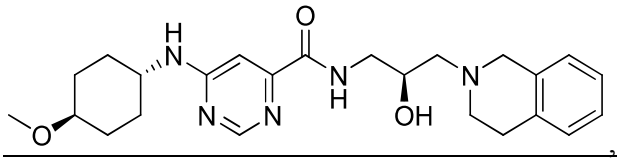


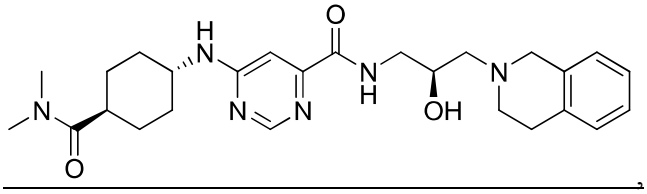


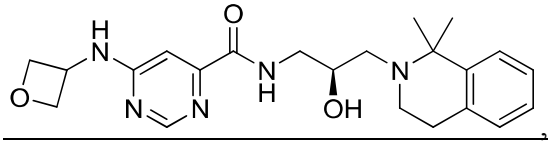


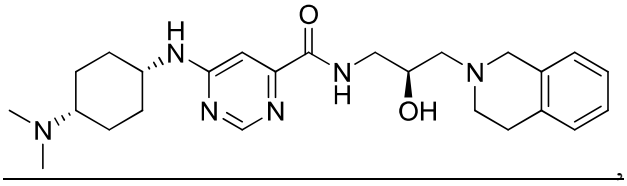


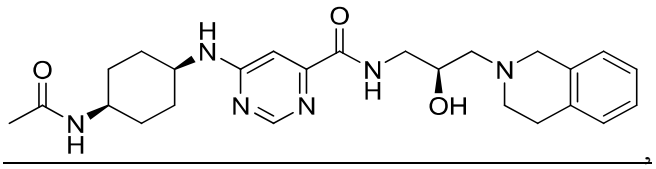


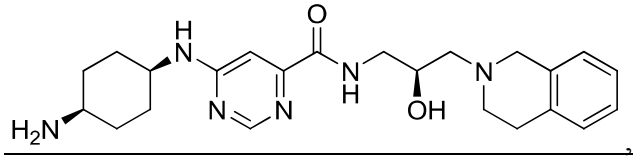


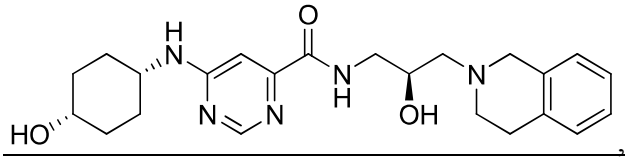


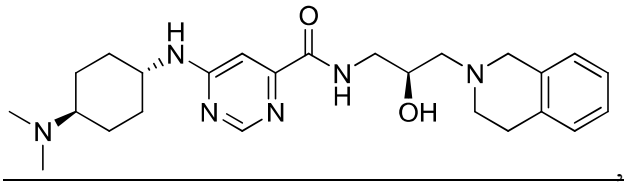


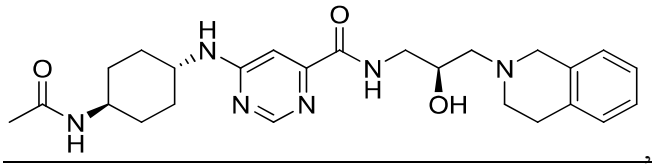


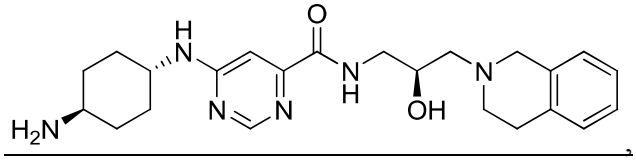


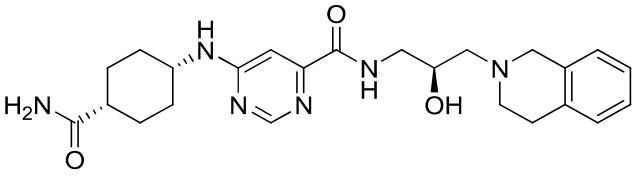


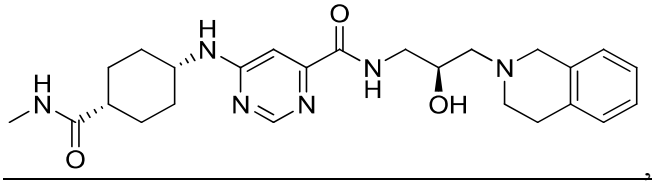


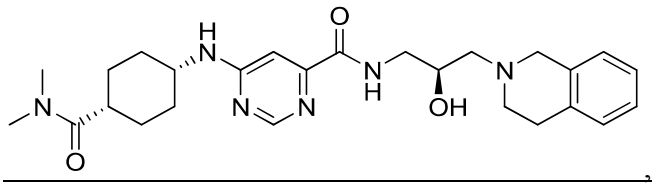


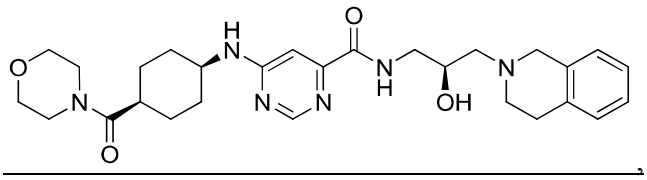


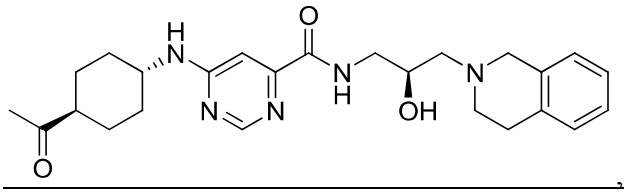


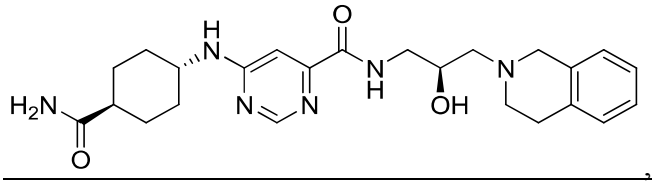


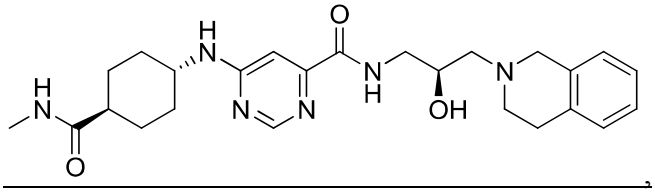


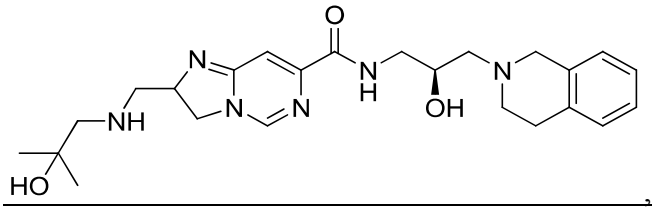


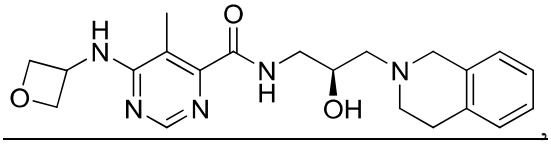


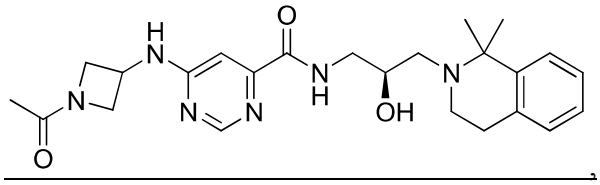


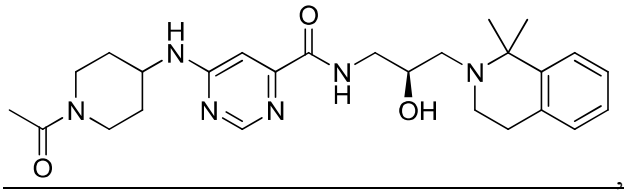


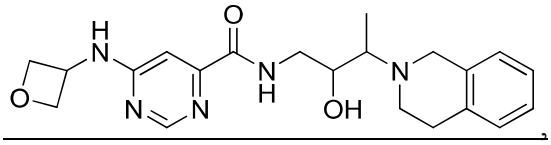


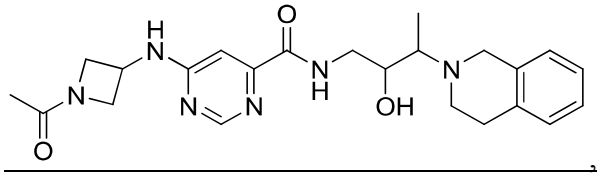


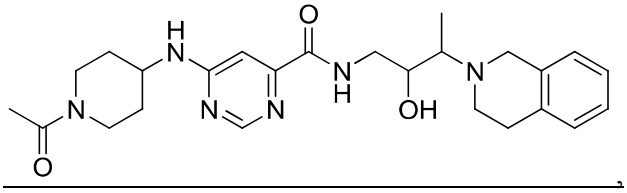


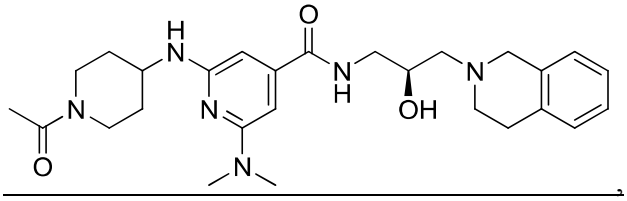


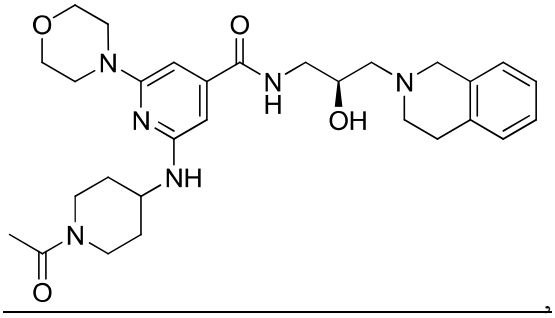


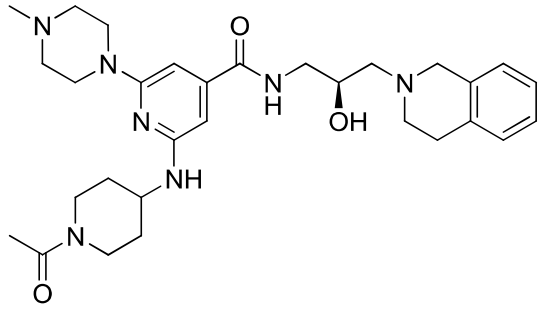


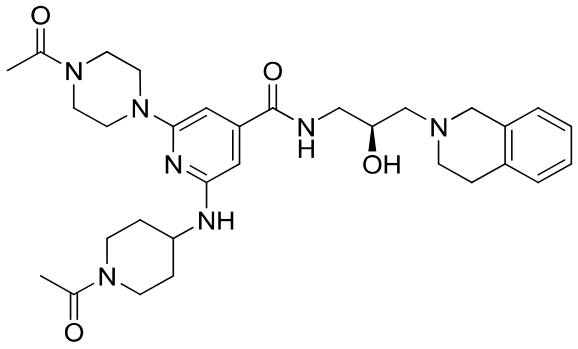


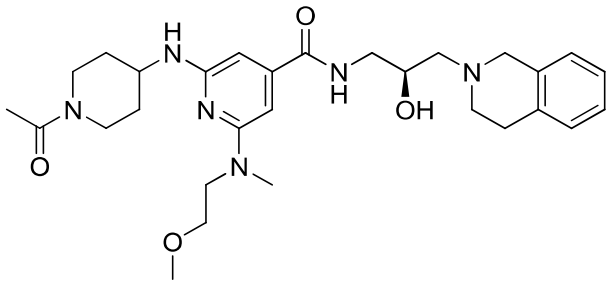


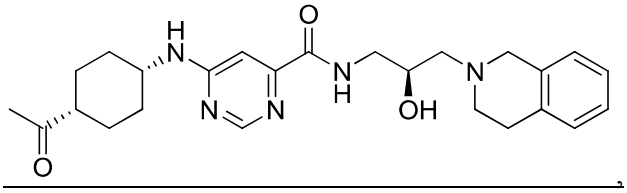


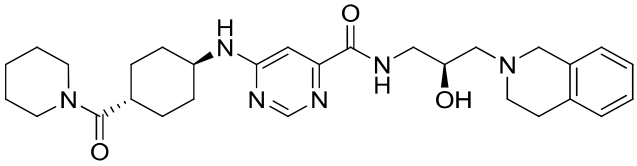


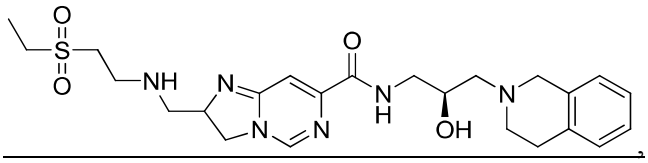


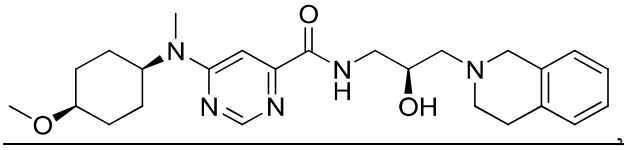


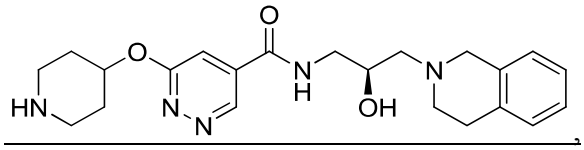


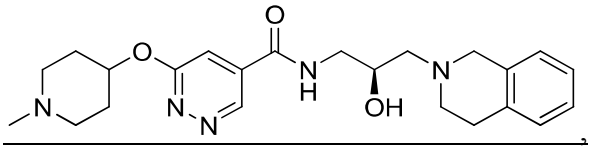


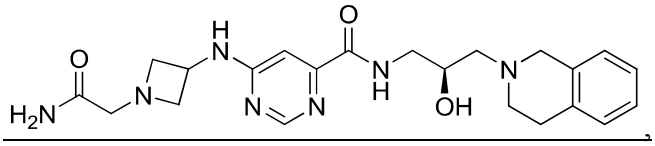


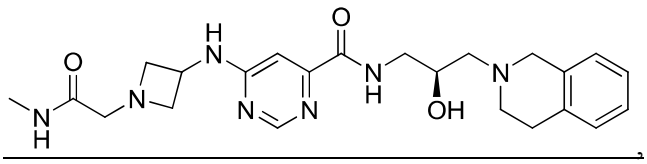


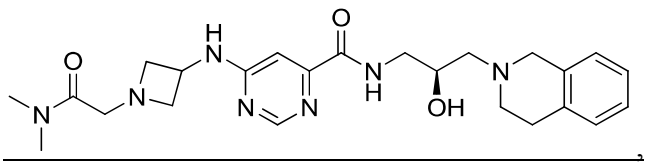


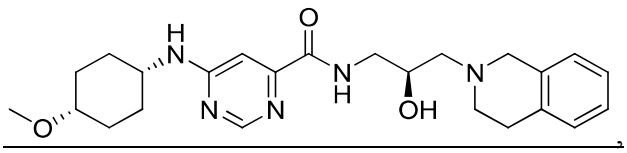


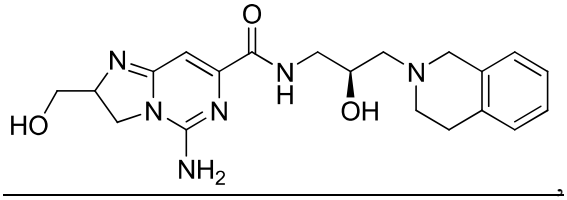


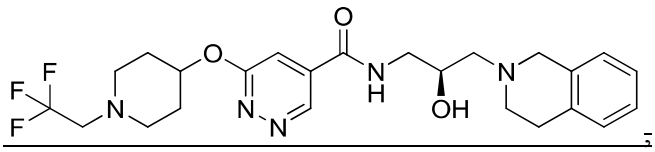


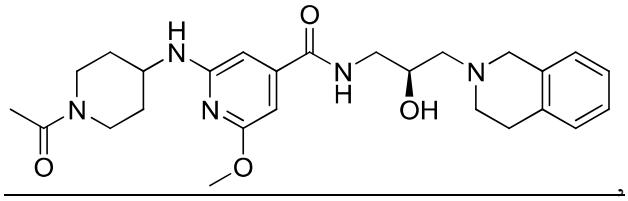


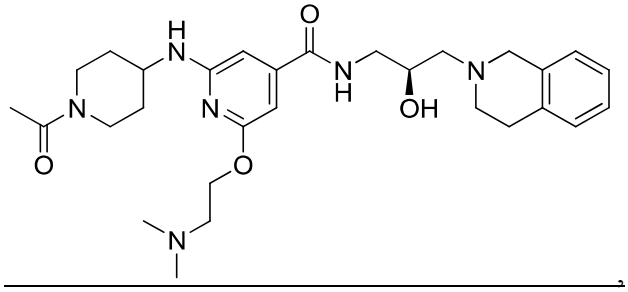


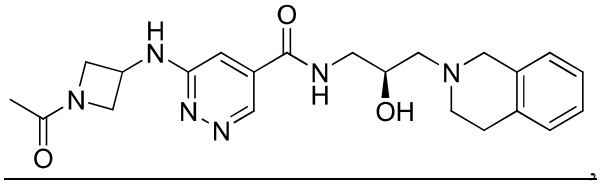


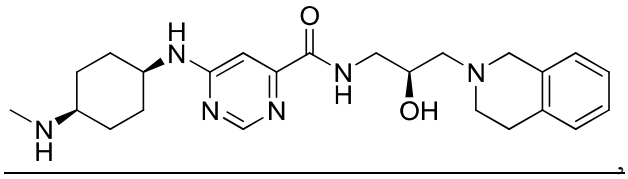


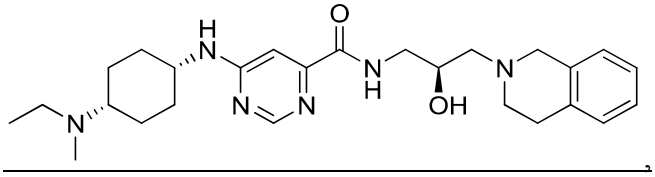


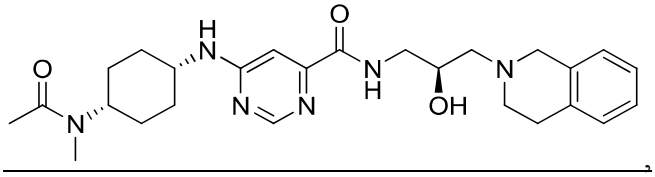


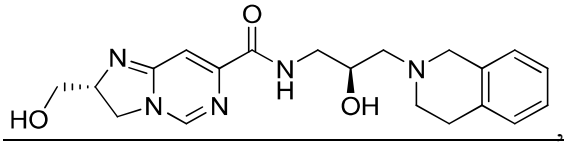


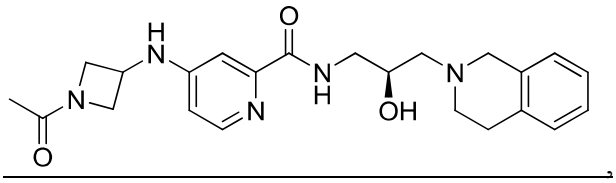


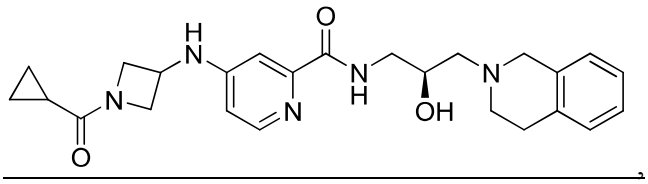


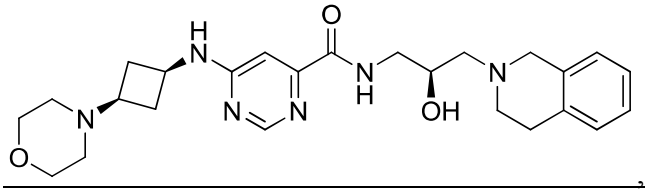


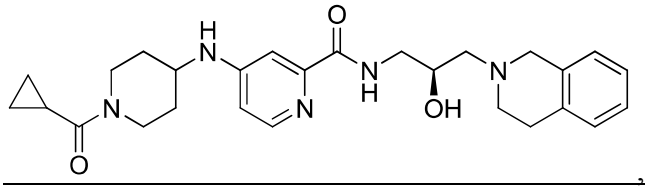


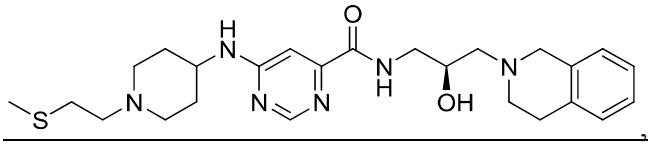


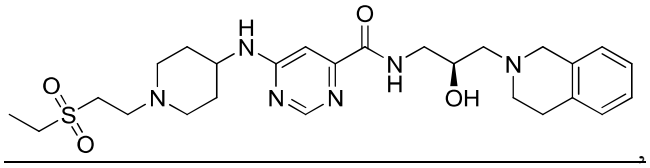


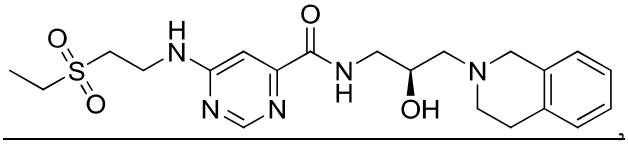


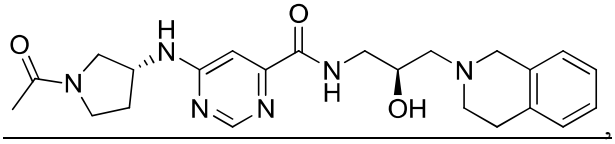


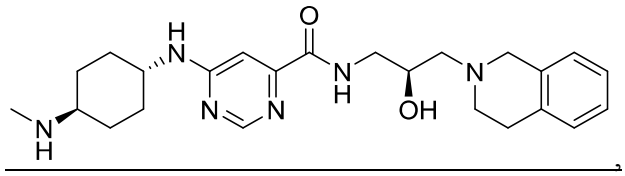


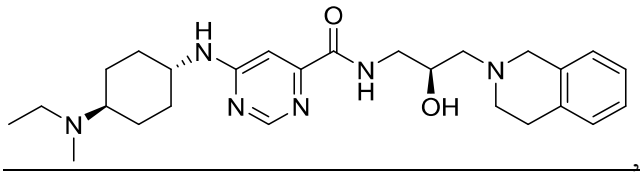


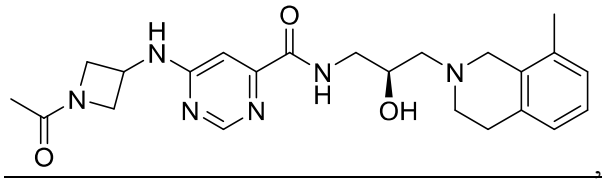


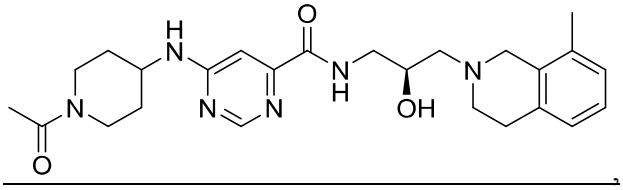


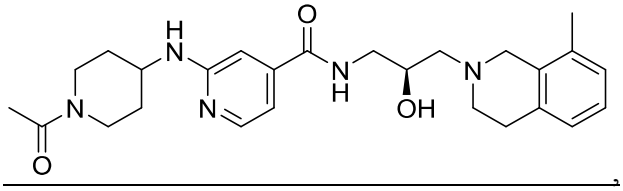


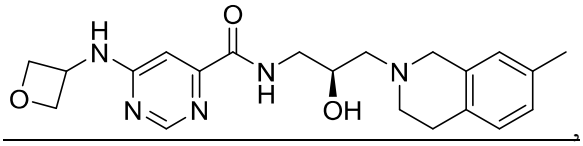


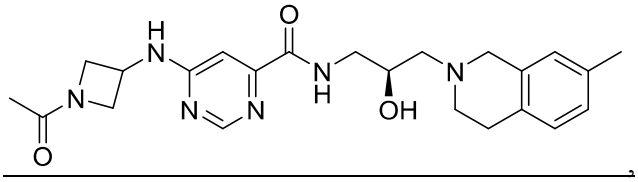


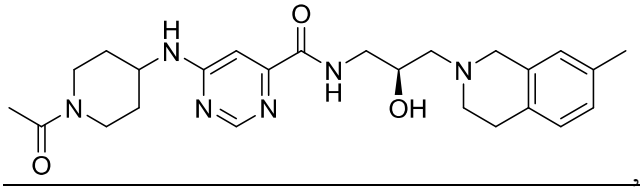


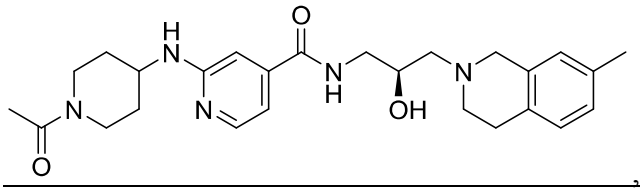


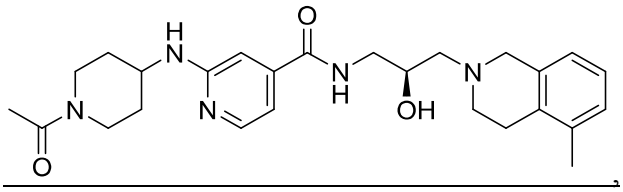


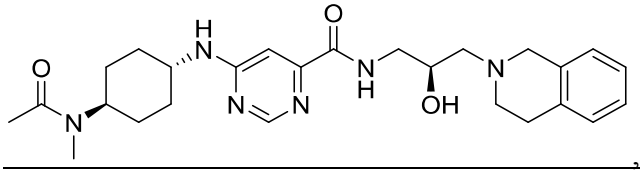


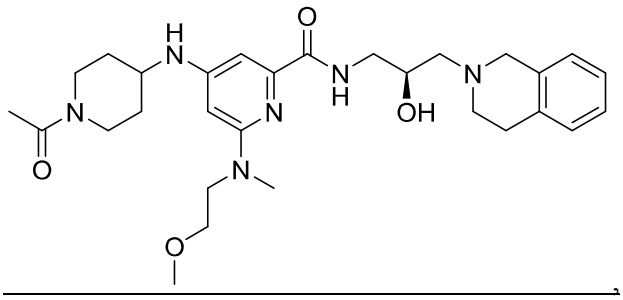


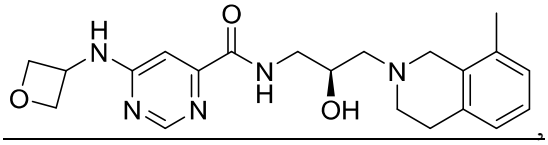


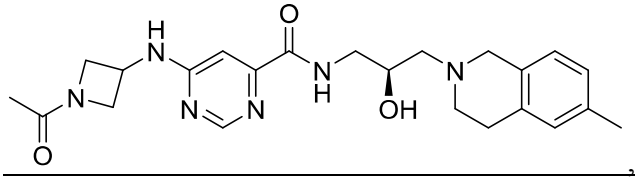


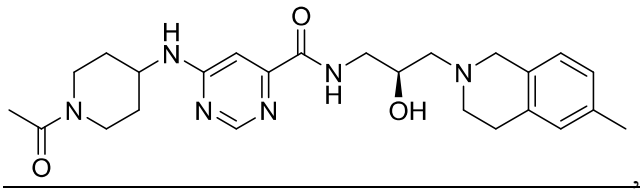


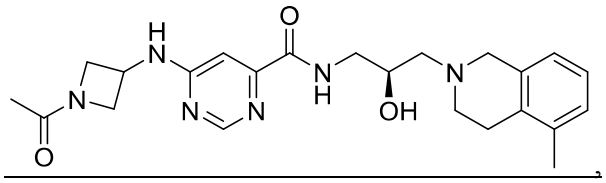


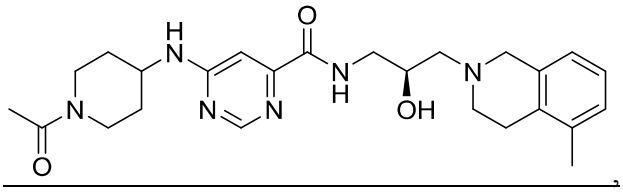


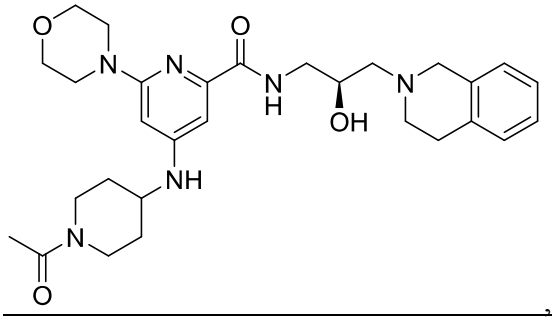


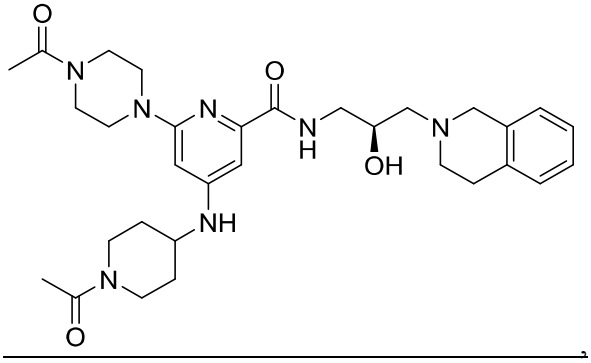


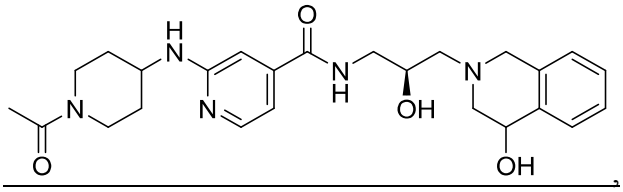


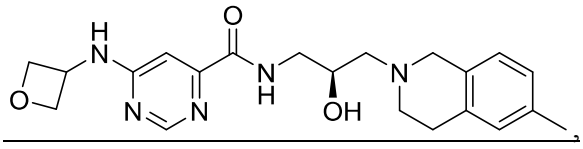


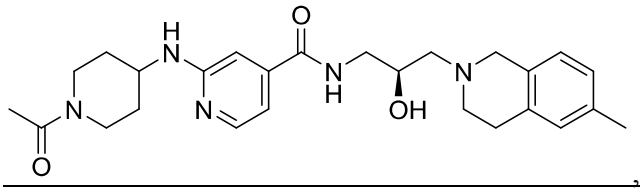


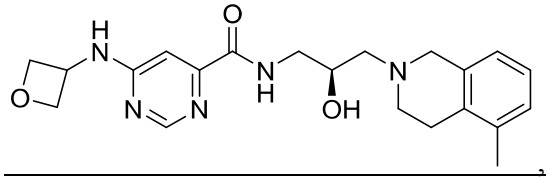


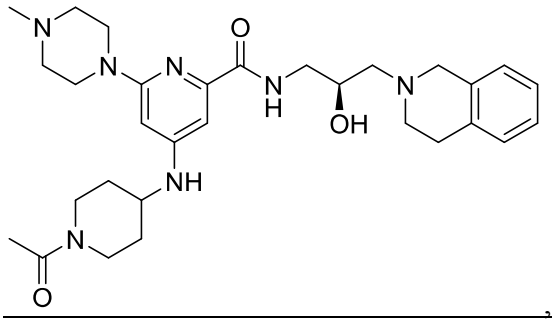


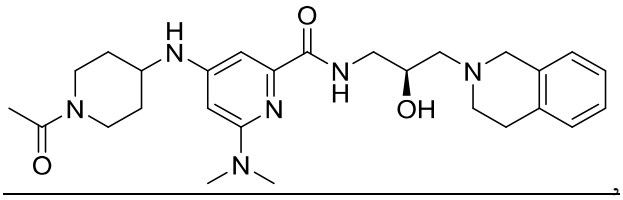


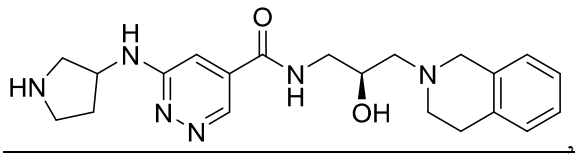


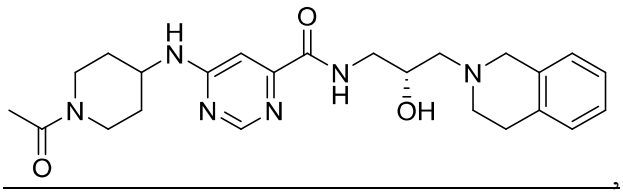


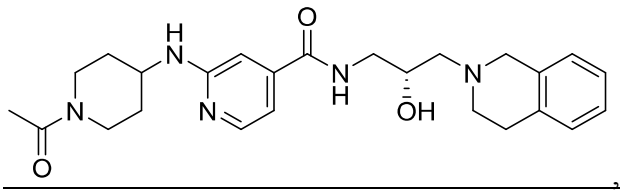


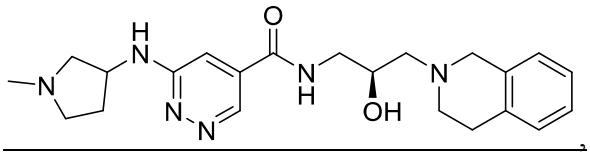


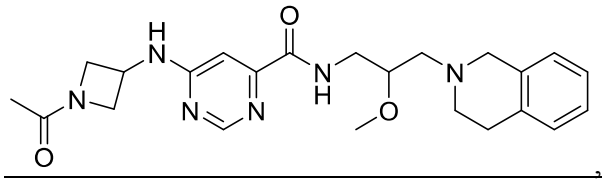


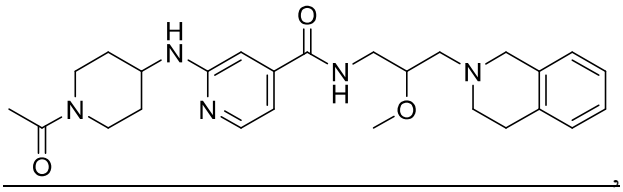


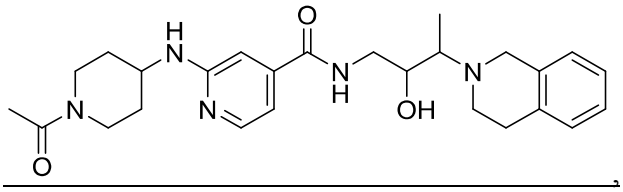


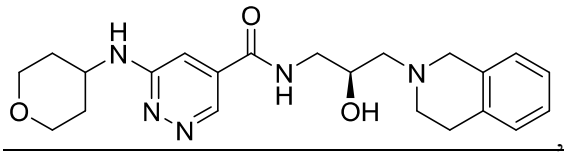


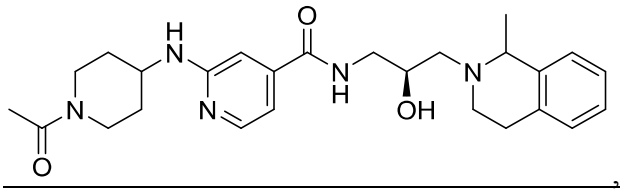


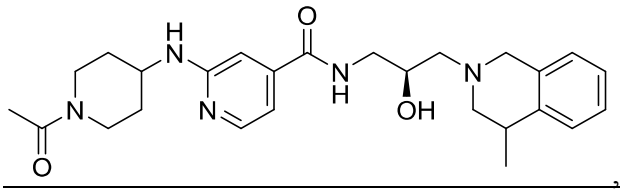


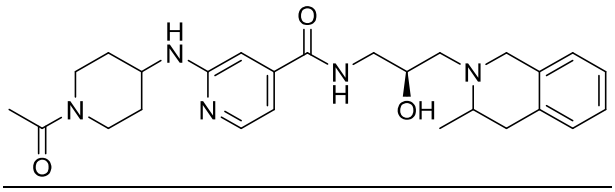






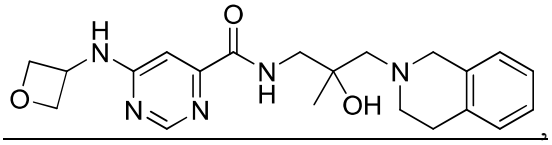


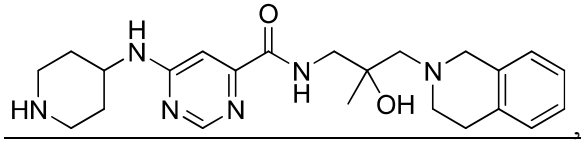


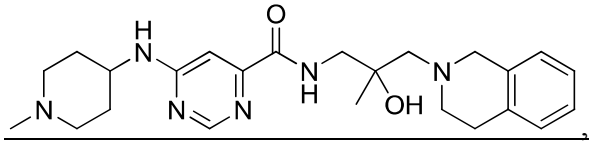


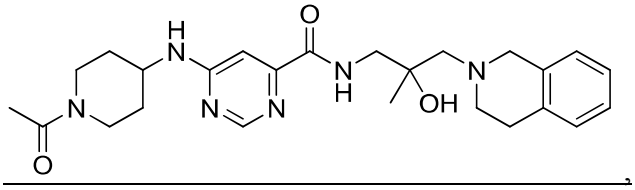
and pharmaceutically acceptable salts thereof.

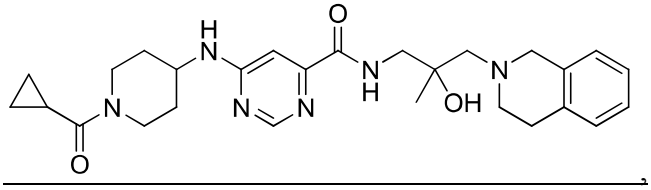
111. The compound of claim 1, wherein the compound is selected from the group consisting of:





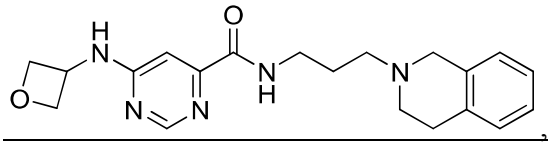


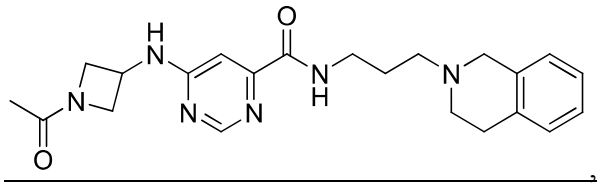


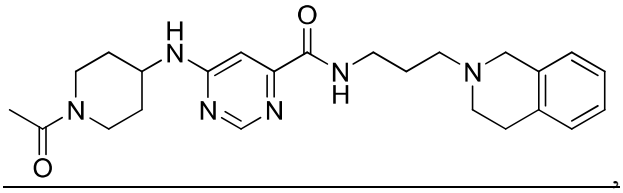


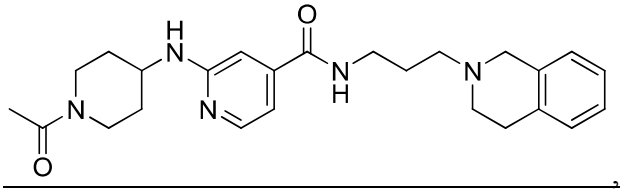
and pharmaceutically acceptable salts thereof.

112. A compound selected from the group consisting of:



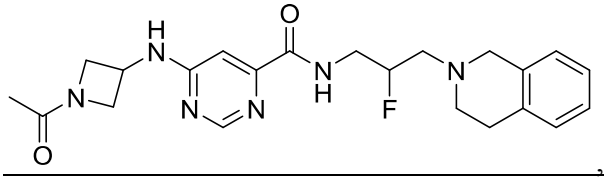


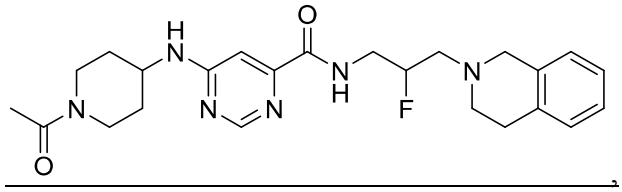


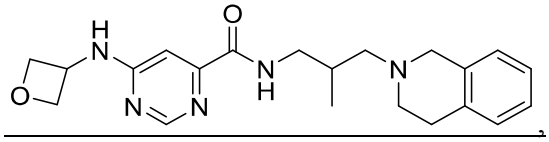


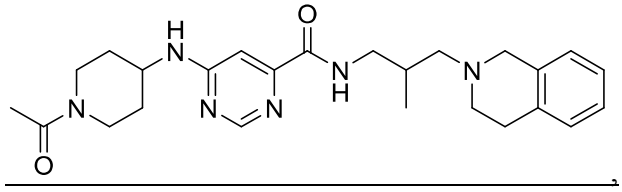
and pharmaceutically acceptable salts thereof.

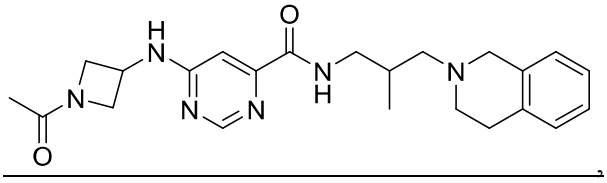
113. A compound selected from the group consisting of:

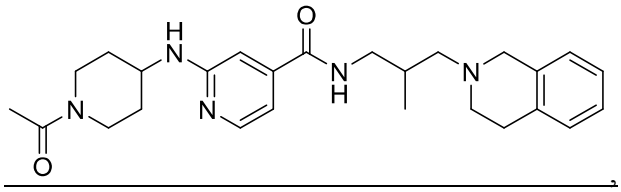


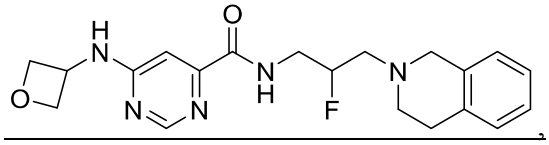


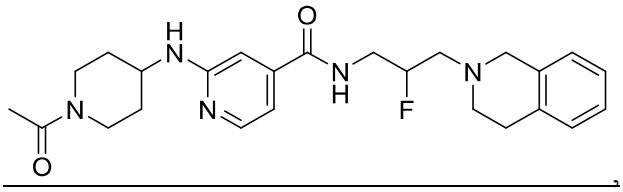






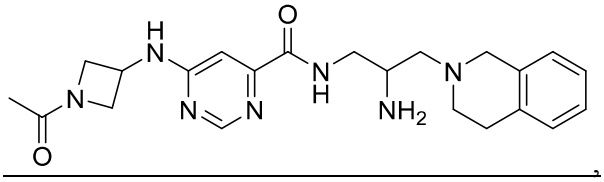


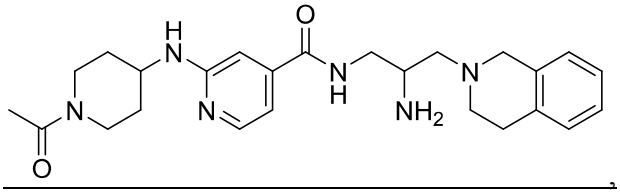


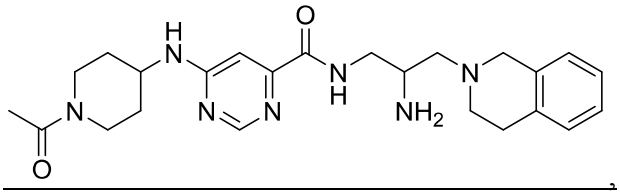


and pharmaceutically acceptable salts thereof.

114. A compound selected from the group consisting of:

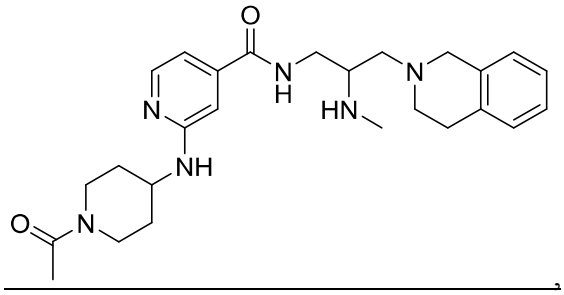


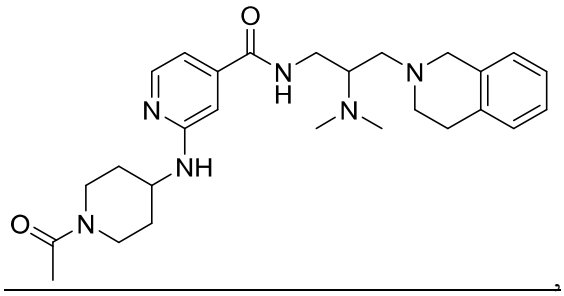


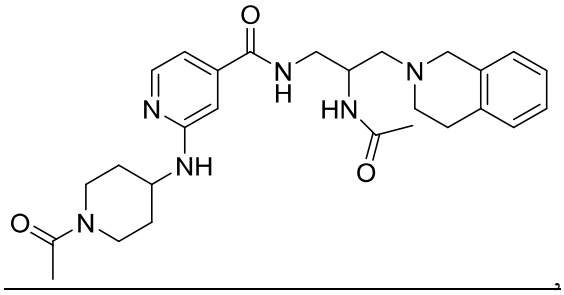


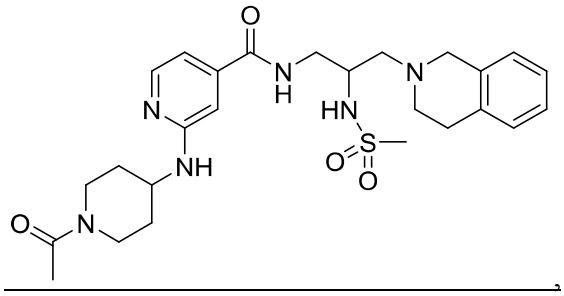
and pharmaceutically acceptable salts thereof.

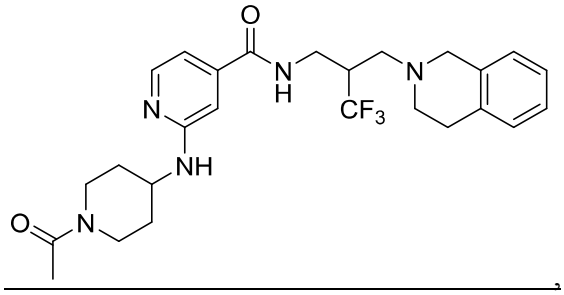
115. A compound selected from the group consisting of:

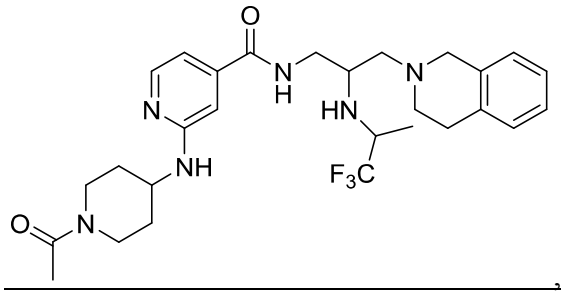


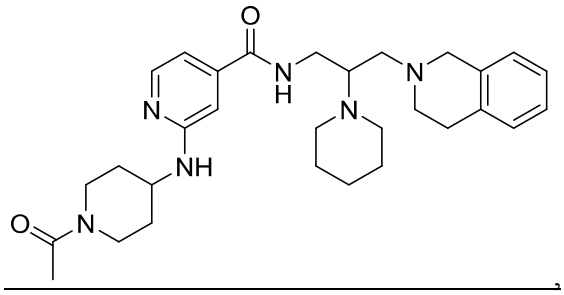


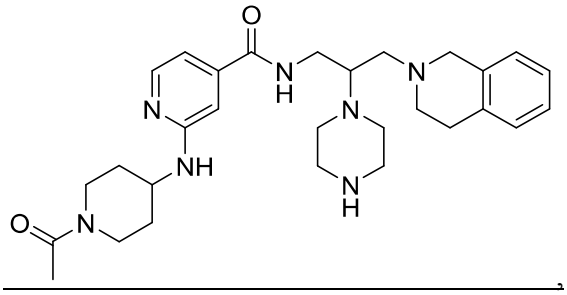


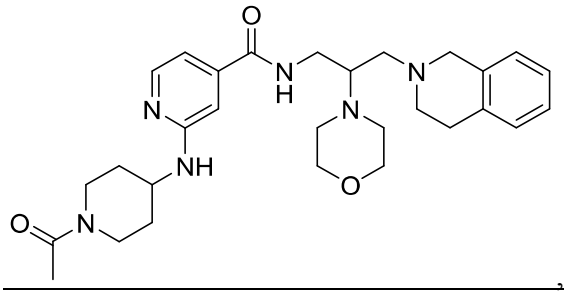


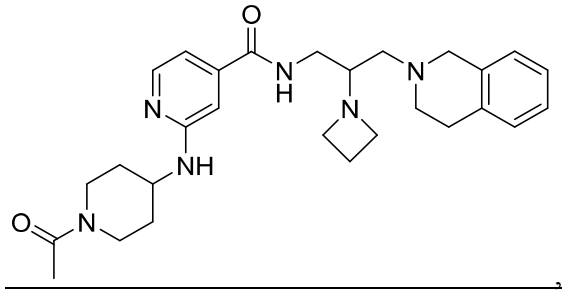


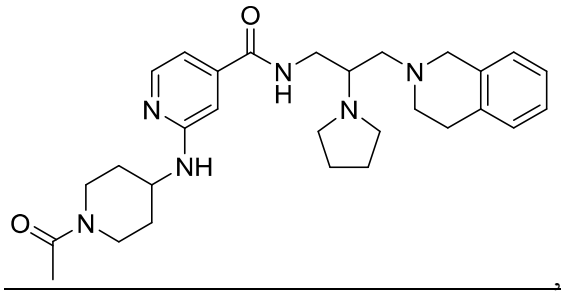


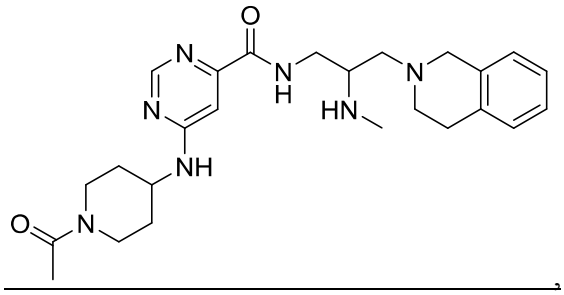


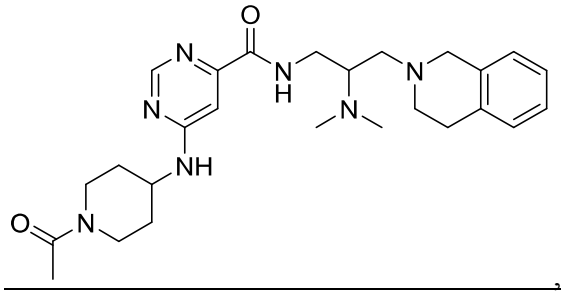


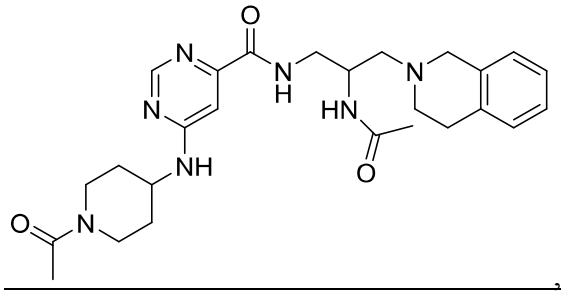


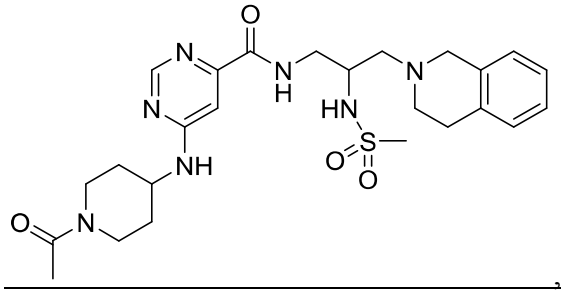


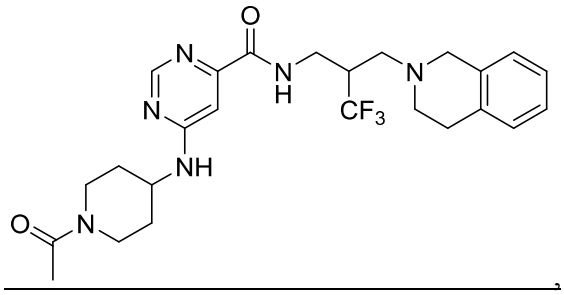


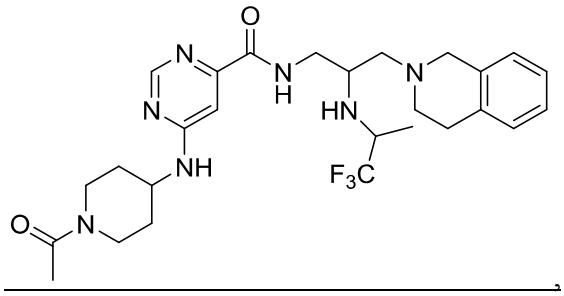


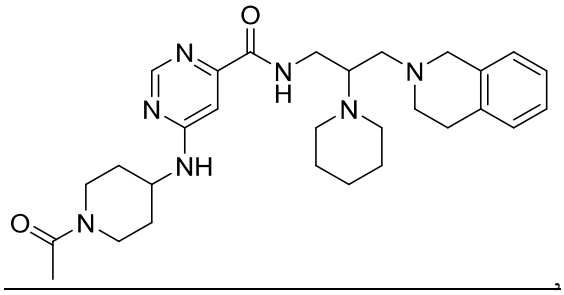


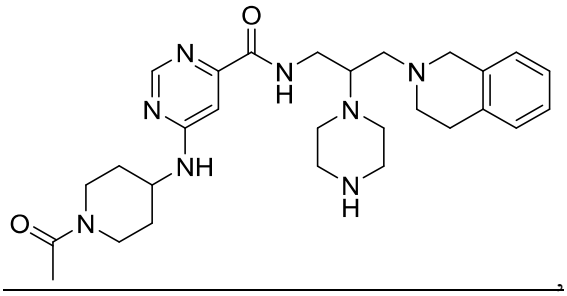


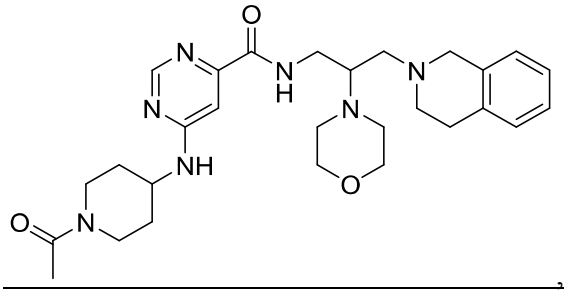


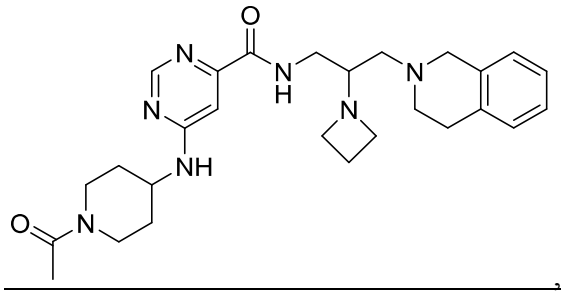


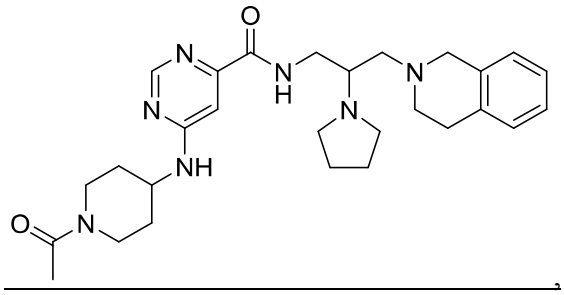






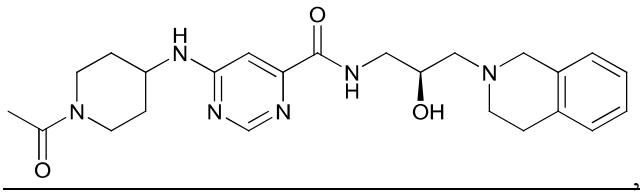






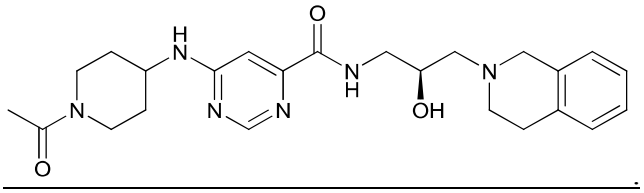
and pharmaceutically acceptable salts thereof.

116. A compound of formula:

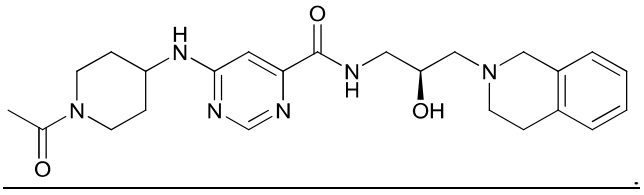


or a pharmaceutically acceptable salt thereof.

117. The compound of claim 115, wherein the compound is:



118. The compound of claim 115, wherein the compound is a pharmaceutically acceptable salt of:



119. A pharmaceutical composition comprising a compound of any one of claims 1-115, and a pharmaceutically acceptable excipient.

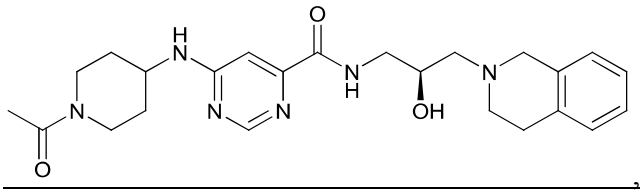
120. A pharmaceutical composition comprising a compound of claim 116, and a pharmaceutically acceptable excipient.

121. A pharmaceutical composition comprising a compound of claim 117, and a pharmaceutically acceptable excipient.

122. A pharmaceutical composition comprising a compound of claim 118, and a pharmaceutically acceptable excipient.

124. A kit or packaged pharmaceutical comprising a compound of any one of claims 1-116 and instructions for use thereof.

125. The kit or packaged pharmaceutical of claim 124, wherein the compound is



,

or a pharmaceutically acceptable salt thereof.

126. Use of a compound of any one of claims 1-116 in the manufacture of a medicament for treating or preventing a breast cancer, esophageal cancer, bladder cancer, lymphoma, medulloblastoma, rectum adenocarcinoma, colon adenocarcinoma, gastric cancer, liver cancer, adenoid cystic carcinoma, lung adenocarcinoma, head and neck squamous cell carcinoma, brain cancer, hepatocellular carcinoma, renal cell carcinoma, oligodendroglioma, ovarian clear cell carcinoma, ovarian serous cystadenocarcinoma, hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer in a subject in need thereof.

127. The method of claim 126, wherein the cancer is lymphoma.

128. The method of claim 127, wherein the lymphoma is non-Hodgkin lymphoma.

129. The method of claim 126, wherein the cancer is breast cancer.

130. The method of claim 126, wherein the cancer is bladder cancer.

131. The method of claim 126, wherein the cancer is brain cancer.

132. Use of a compound of any one of claims 1-116 in the manufacture of a medicament for treating or preventing a metabolic disorder selected from diabetes and obesity in a subject in need thereof.

133. The use of claim 132, wherein the metabolic disorder is diabetes.

134. The use of claim 132, wherein the metabolic disorder is obesity.

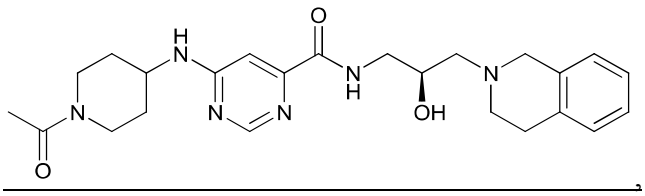
135. Use of a compound of any one of claims 1-116 in the manufacture of a medicament for treating or preventing a blood disorder selected from hemoglobinopathy, sickle cell anemia, and β-thalassemia in a subject in need thereof.

136. The use of claim 135, wherein the blood disorder is a hemoglobinopathy.

137. The use of claim 135, wherein the blood disorder is sickle cell anemia.

138. The use of claim 135, wherein the blood disorder is β-thalessemia.

139. The use of any one of claims 126-138, wherein the compound is



or a pharmaceutically acceptable salt thereof.