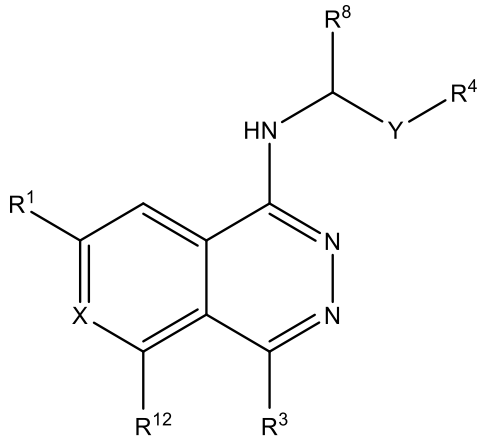
WE CLAIM:

1. A compound of Formula (I):




Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

$R^1$ is hydrogen, hydroxyl, C1 – C6 alkyl, alkoxy, $-N(R^6)_2$, $-NR^6C(O)R^6$, $-C(O)N(R^6)_2$, $-SO_2$alkyl, $-SO_2NR^6$alkyl, cycloalkyl, -Q-heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, the heterocyclyl, the aryl, and the heteroaryl are each optionally substituted with one or more $R^2$ or L-$R^2$;

each Q is independently a bond, O, or $NR^6$;

X is N or $CR^7$;

each $R^2$ is independently C1-C3 alkyl, oxo, hydroxy, halogen, cyano, hydroxyalkyl, haloalkyl, alkoxy, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-SO_2$alkyl, $-NR^6C(O)$C1 – C3 alkyl, -C(O)cycloalkyl, -C(O)C1-C3 alkyl,-C(O)heterocyclyl, aryl, heteroaryl or heterocyclyl,

wherein the cycloalkyl, the heterocyclyl, the aryl, the heteroaryl or the heterocyclyl are each optionally substituted with one or more $R^{11}$;

$R^3$ is hydrogen, C1 – C6 alkyl, alkoxy, $-N(R^{10})_2$, $-L-N(R^{10})_2$, cycloalkyl, haloalkyl or heterocyclyl, wherein the C1 – C6 alkyl, the cycloalkyl and the heterocyclyl, are each optionally substituted with one or more $R^9$;

Y is a bond or heteroarylene;

$R^4$ is aryl or heteroaryl, each optionally substituted with one or more $R^5$;

each $R^5$ is independently hydroxy, halogen, cyano, hydroxyalkyl, alkoxy, C1 – C3 alkyl, haloalkyl, haloalkyl-OH, $-N(R^6)_2$, $-L-N(R^6)_2$ or $-SO_2$alkyl;

L is C1 – C3 alkylene;

each $R^6$ is independently hydrogen, C1 – C3 alkyl, haloalkyl, or cycloalkyl;

$R^7$ is hydrogen, cyano, $CF_3$, F, or alkoxy;

$R^8$ is C1 –C2 alkyl or halo-C1 – C2 alkyl;

each $R^9$ is independently hydroxy, halogen, amino, cyano, alkoxy, or C1 – C3 alkyl;

each $R^{10}$ is independently hydrogen, C1 – C3 alkyl or cycloalkyl;

each $R^{11}$ is independently C1 – C3 alkyl, halogen or haloalkyl; and

$R^{12}$ is hydrogen, halogen or C1-C3 alkyl.

2. The compound according to claim 1, wherein X is N.

3. The compound according to claim 1, wherein X is $CR^7$.

4. The compound according to claim 1, wherein $R^1$ is alkoxy or -Q-heterocyclyl, wherein the heterocyclyl is optionally substituted with one or more $R^2$ or L-$R^2$.

5. The compound according to claim 4, wherein $R^1$ is -Q-heterocyclyl, and wherein Q is a bond or -O- and the heterocyclyl is morpholinyl, piperazinyl, or piperazinone.

6. The compound according to claim 5, wherein $R^1$ is -Q-heterocyclyl, and wherein the heterocyclyl is bridged morpholinyl, bridged piperazinyl, or bridged piperazinone.

7. The compound according to claim 4, wherein $R^1$ is -Q-heterocyclyl, and wherein the heterocyclyl is spirocyclic ring system containing two or more rings.

8. The compound according to claim 7, wherein the spirocyclic ring system comprises two rings each containing a heteroatom.

9. The compound according to claim 7, wherein the spirocyclic ring system contains a ring with no heteroatom.

10. The compound according to claim 1, wherein $R^1$ is heteroaryl, wherein the heteroaryl is optionally substituted with one or more $R^2$ or L-$R^2$.

11. The compound according to claim 10, wherein the heteroaryl is a bicyclic or tricyclic ring system comprising a non-aromatic ring.

12. The compound according to claim 11, wherein the bicyclic or tricyclic ring system is 5,6,7,8-tetrahydro-[1,2,4]triazolopyrazinyl, 5,6,7,8-tetrahydroimidazopyrazinyl, 2,4,5,6-tetrahydropyrrolopyrazolyl, 1,2,3,4-tetrahydrobenzo[4,5]imidazopyrazinyl or 4,5,6,7-tetrahydropyrazolopyrazinyl.

13. The compound according to claim 3, wherein $R^7$ is hydrogen.

14. The compound according to claim 1, wherein $R^1$ is hydrogen.

15. The compound according to claim 1, wherein $R^1$ is hydroxyl.

16. The compound according to claim 1, wherein $R^1$ is $-N(R^6)_2$.

17. The compound according to claim 1, wherein $R^1$ is $-NR^6C(O)R^6$.

18. The compound according to claim 1, wherein $R^1$ is $-C(O)N(R^6)_2$.

19. The compound according to claim 1, wherein $R^1$ is cycloalkyl optionally substituted with one or more $R^2$.

20. The compound according to claim 19, wherein the cycloalkyl is cyclobutyl, cyclopentyl or cyclohexyl, each optionally substituted with one or more $R^2$.

21. The compound according to claim 20, wherein the cyclobutyl, cyclopentyl or the cyclohexyl are substituted with one $R^2$, wherein $R^2$ is C1 – C3 alkyl, alkoxy, halogen, hydroxyl or $-N(R^6)_2$.

22. The compound according to claim 1, wherein $R^1$ is -Q-heterocyclyl optionally substituted with one or more $R^2$.

23. The compound according to claim 22, wherein Q is a bond and the heterocyclyl is morpholinyl, piperdinyl, piperazinyl, N-methylpiperazinyl, piperazin-2-one, 1-methyl-piperazin-2-one, diazepanyl, 6,6-difluoro-1,4-diazepan-1-yl, or 4-methylthiomorpholine 1,1-dioxide.

24. The compound according to claim 22, wherein Q is a bond and the heterocyclyl is pyrrolidinyl or tetrahydropyranyl, each optionally substituted with one or more $R^2$.

25. The compound according to claim 24, wherein the pyrrolidinyl or the tetrahydropyranyl are substituted with one $R^2$, wherein $R^2$ is C1 – C3 alkyl, alkoxy, hydroxyl or $-N(R^6)_2$.

26. The compound according to claim 23, wherein Q is a bond and the heterocyclyl is piperazinyl optionally substituted with one or more $R^2$.

27. The compound according to claim 26, wherein the piperazinyl is substituted with one $R^2$, wherein $R^2$ is heteroaryl, -C(O)cycloalkyl or -C(O)heterocyclyl, wherein the heteroaryl, or the cycloalkyl or heterocyclyl portion of the -C(O)cycloalkyl or -C(O)heterocyclyl are each optionally substituted with one or more $R^{11}$.

28. The compound according to claim 27, wherein $R^2$ is -C(O)cycloalkyl, wherein the cycloalkyl is cyclopropyl substituted with one $R^{11}$, wherein $R^{11}$ is C1 – C3 alkyl.

29. The compound according to claim 27, wherein $R^2$ is -C(O)cycloalkyl, wherein the cycloalkyl is cyclopropyl substituted with one $R^{11}$, wherein $R^{11}$ is haloalkyl.

30. The compound according to claim 27, wherein $R^2$ is -C(O)heterocyclyl, wherein the heterocyclyl is oxetanyl, tertrahydrofuranyl, or tetrahydropyranyl.

31. The compound according to claim 22, wherein Q is a bond and the heterocyclyl is a bicyclic heterocyclyl.

32. The compound according to claim 31, wherein the bicyclic heterocylyl is diazabicyclo[3.2.0]heptan-2-yl, (1R,5R)-2,6-diazabicyclo[3.2.0]heptan-2-yl, diazabicyclo[3.2.0]heptan-6-yl, (1R,5R)-2,6-diazabicyclo[3.2.0]heptan-6-yl, 6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl, 5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl, 1,3-dimethyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl or (R)-2-methylhexahydropyrrolo[1,2-a]pyrazin-6(2H)-one.

33. The compound accoding to claim 22, wherein Q is O and the heterocyclyl is azetidinyl, tetrahydrofuranyl, pyrrolidinyl, or piperdinyl.

34. The compound according to claim 1, wherein $R^1$ is aryl optionally substituted with one or more $R^2$.

35. The compound according to claim 34, wherein the aryl is phenyl optionally substituted with one or more $R^2$.

36. The compound according to claim 35, wherein the phenyl is substituted with one $R^2$, wherein $R^2$ is C1 – C3 alkyl, alkoxy, hydroxyl or $-N(R^6)_2$.

37. The compound according to claim 1, wherein $R^1$ is heteroaryl optionally substituted with one or more $R^2$.

38. The compound according to claim 37, wherein the heteroaryl is pyrazolyl optionally substituted with one or more $R^2$.

39. The compound according to claim 38, wherein the pyrazolyl is substituted with one $R^2$, wherein $R^2$ is C1 – C3 alkyl, alkoxy, hydroxyl or $-N(R^6)_2$.

40. The compound according to claim 1, wherein $R^7$ is cyano or alkoxy.

41. The compound according to claim 40, wherein $R^7$ is alkoxy, and the alkoxy is methoxy.

42. The compound according to claim 41, wherein $R^1$ is alkoxy.

43. The compound according to claim 42, wherein the alkoxy is methoxy.

44. The compound according to any of claims 1-44, wherein Y is heteroarylene.

45. The compound according to claim 44, wherein the heteroarylene is thiophenylene.

46. The compound according to any one of claims 1-45, wherein Y is a bond.

47. The compound according to any one of claims 44-46, wherein $R^4$ is is aryl or heteroaryl, each optionally substituted with one or more $R^5$.

48. The compound according to claim 47, wherein $R^4$ is aryl optionally substituted with one or more $R^5$.

49. The compound according to claim 48, wherein the aryl is phenyl optionally substituted with one or more $R^5$.

50. The compound according to claim 49, wherein the phenyl is substituted with one $R^5$, wherein $R^5$ is C1 – C4 alkyl, haloalkyl or -L-N$(R^6)_2$.

51. The compound according to claim 50, wherein $R^5$ is -L-N$(R^6)_2$, wherein L is methylene and one $R^6$ is hydrogen and the second $R^6$ is C1 – C3 alkyl.

52. The compound according to claim 51, wherein the second $R^6$ is methyl.

53. The compound according to claim 52, wherein $R^5$ is -L-N$(R^6)_2$, wherein L is methylene and each $R^6$ is C1 – C3 alkyl.

54. The compound according to claim 53, wherein each C1 – C3 alkyl is methyl.

55. The compound according to claim 49, wherein the phenyl is substituted with two $R^5$, wherein one $R^5$ is C1 – C3 alkyl and the second $R^5$ is haloalkyl.

56. The compound according to claim 55, wherein C1 – C3 alkyl is methyl and the haloalkyl is trifluoromethyl.

57. The compound according to claim 49, wherein the phenyl is substituted with two $R^5$, wherein one $R^5$ is C1 – C3 alkyl and the second $R^5$ is -L-N$(R^6)_2$,

58. The compound according to claim 51, wherein C1 – C3 alkyl is methyl, L is methylene and each $R^6$ is C1 – C3 alkyl.

59. The compound according to any one of claims 1-58, wherein $R^3$ is C1 – C6 alkyl.

60. The compound according to claim 59, wherein C1 – C6 alkyl is methyl, ethyl or isopropyl.

61. The compound according to any one of claims 1-58, wherein $R^3$ is haloalkyl.

62. The compound according to any one of claims 1-58, wherein $R^3$ is cycloalkyl optionally substituted with halogen amino, hydroxy or alkoxy.

63. The compound according to claim 62, wherein the cycloalkyl is cyclopropyl.

64. The compound according to any one of claims 1-58, wherein $R^3$ is alkoxy.

65. The compound according to any one of claims 1-58, wherein $R^3$ is $-N(R^{10})_2$.

66. The compound according to any one of claims 1-58, wherein $R^3$ is hydrogen.

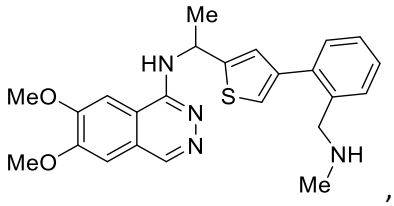
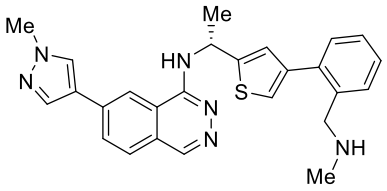
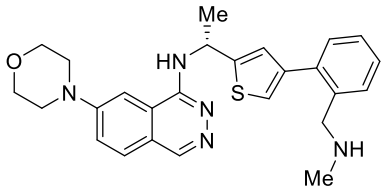
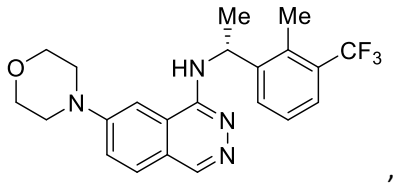
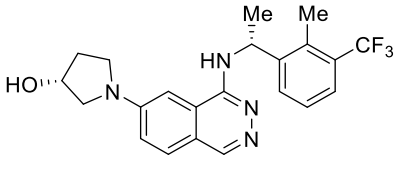
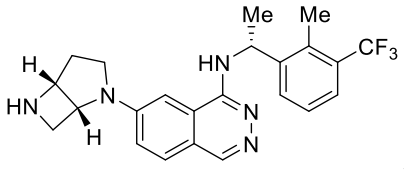
67. The compound according to any one of claims 1-66, wherein $R^8$ is C1 – C2 alkyl.

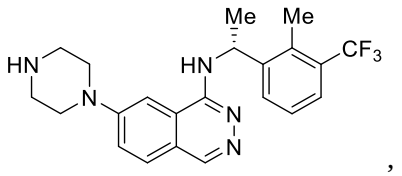
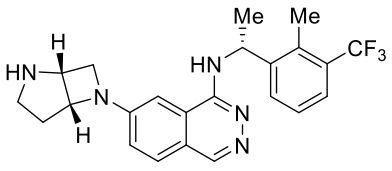
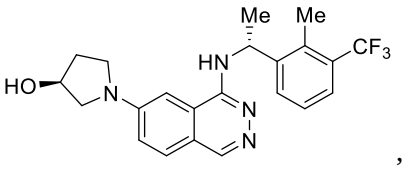
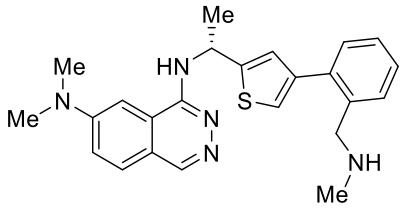
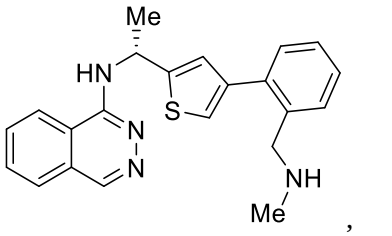
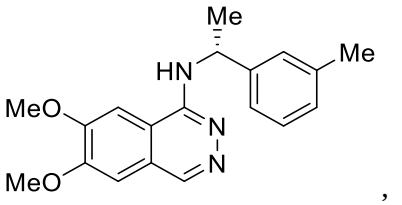
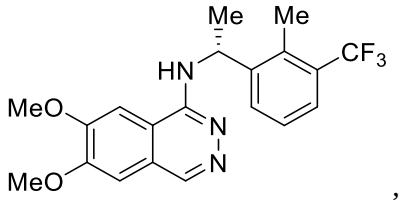
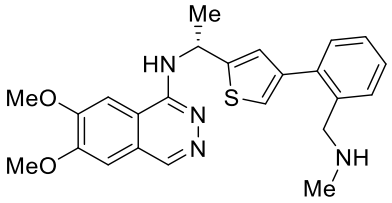
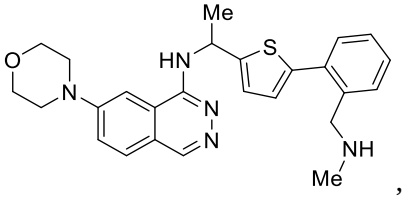
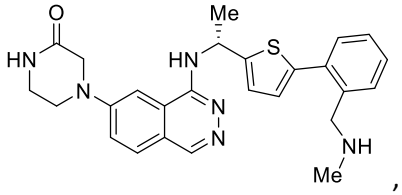
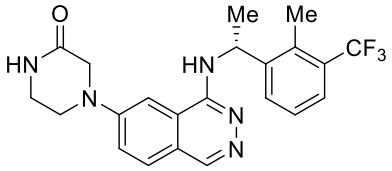
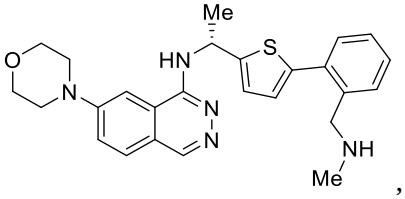
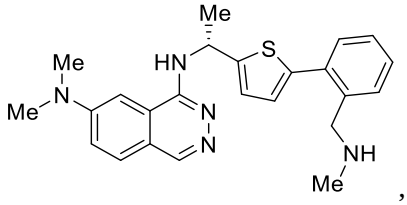
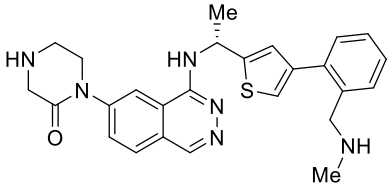
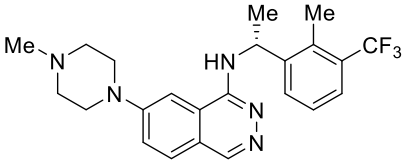
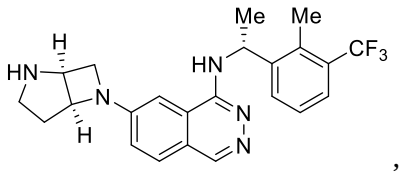
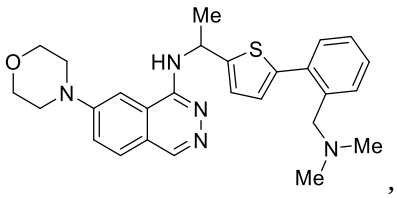
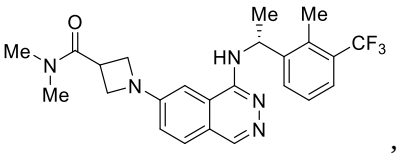
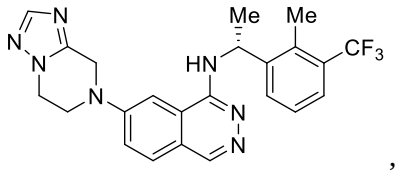
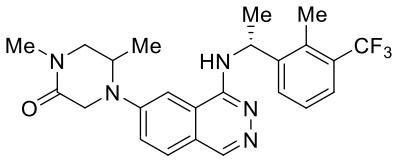
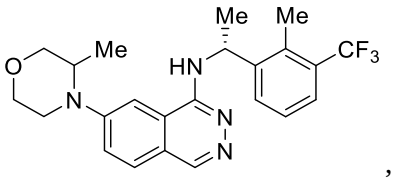
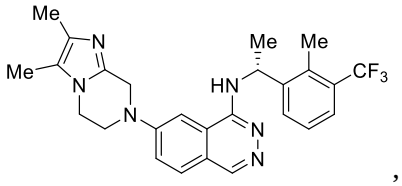
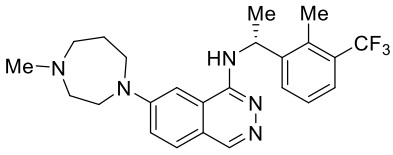
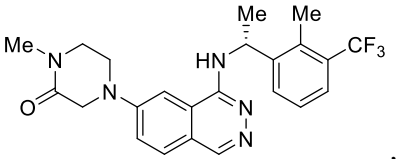
68. The compound according to claim 67, wherein the C1 – C2 alkyl is methyl.

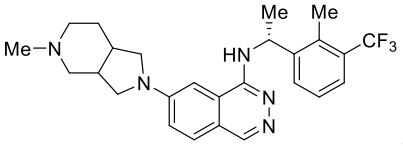
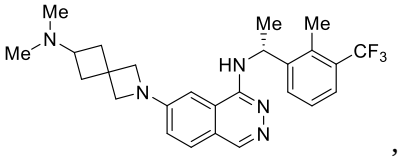
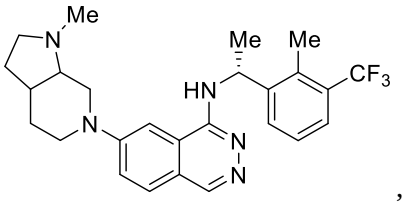
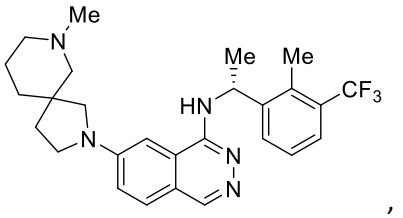
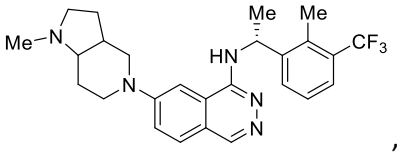
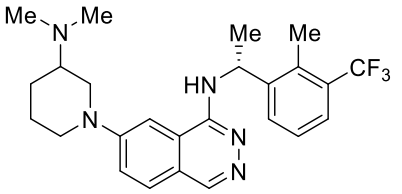
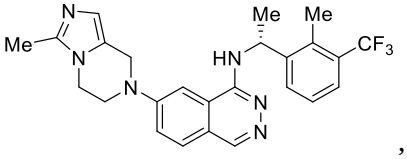
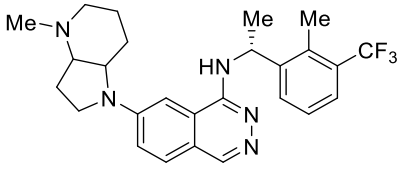
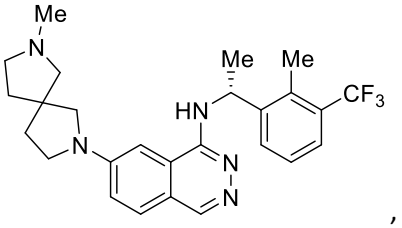
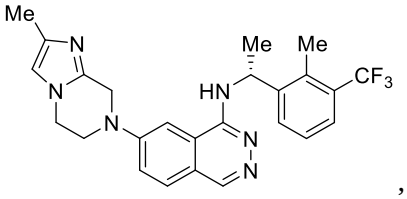
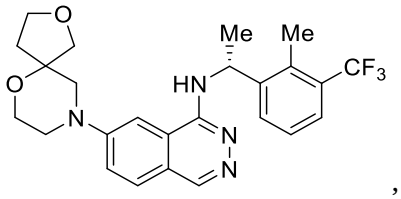
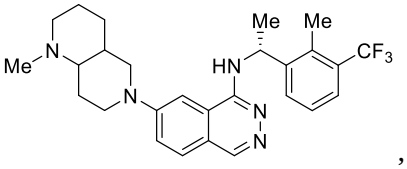
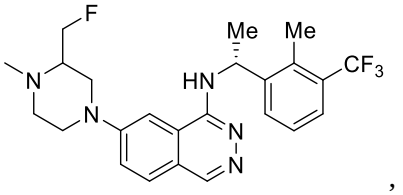
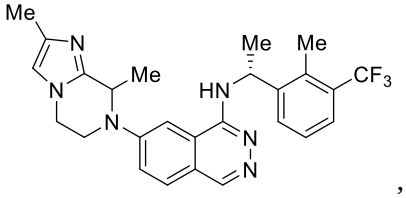
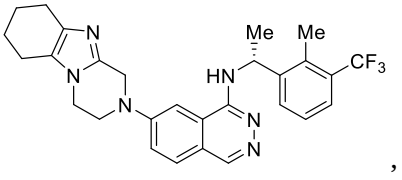
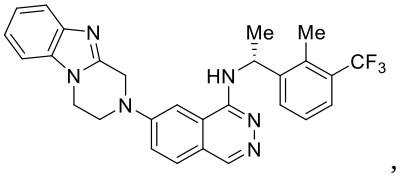
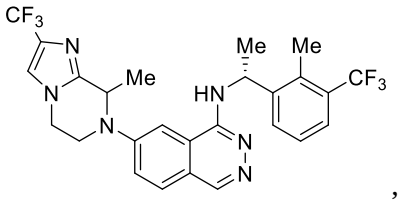
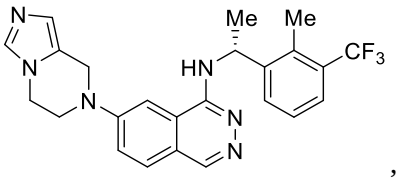
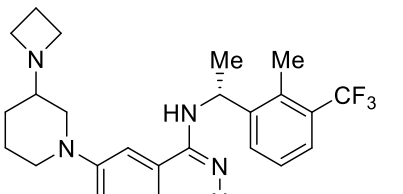
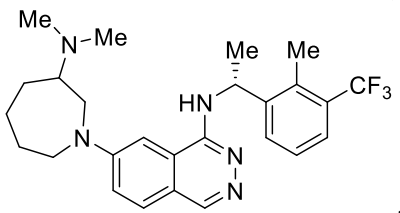
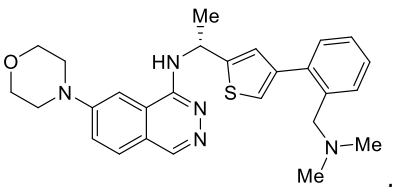
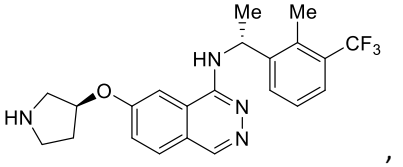
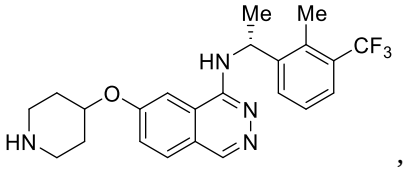
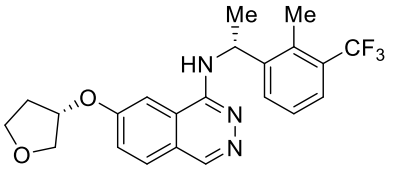
69. The compound according to any one of claims 1-68, wherein $R^8$ is haloC1 – C2 alkyl.

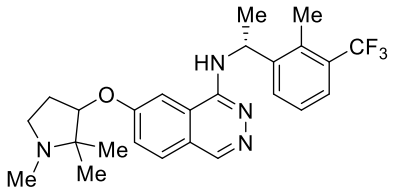
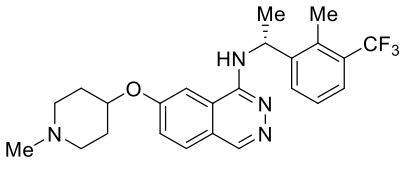
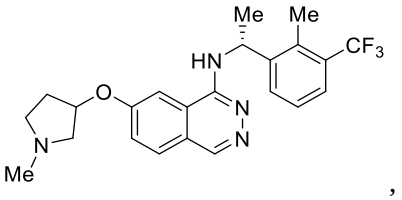
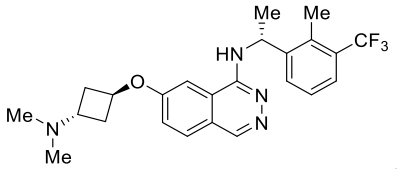
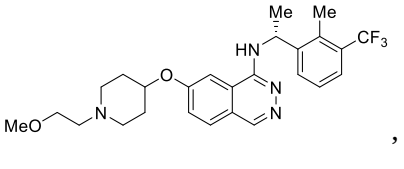
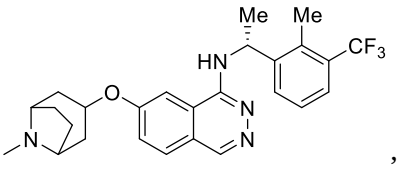
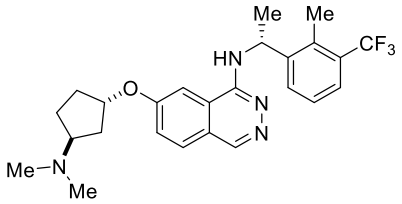
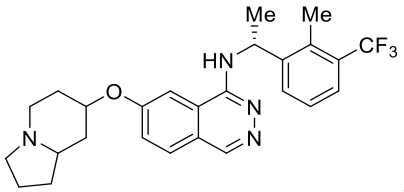
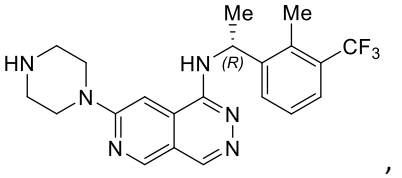
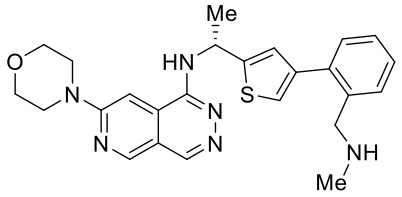
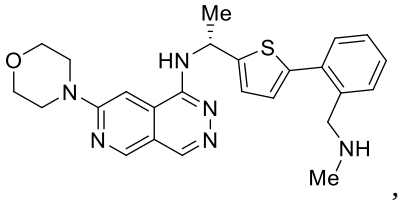
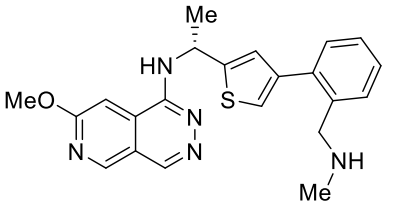
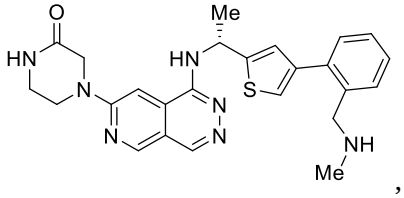
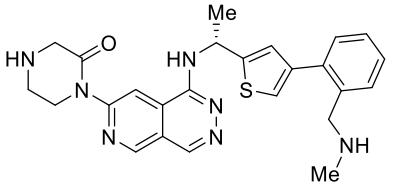
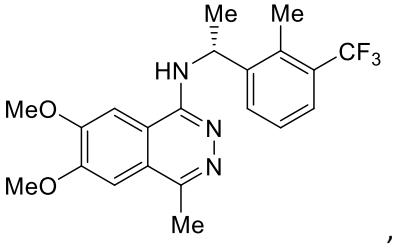
70. The compound according to claim 69, wherein the haloC1 – C2 alkyl is fluoromethyl, difluoromethyl or trifluoromethyl.

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


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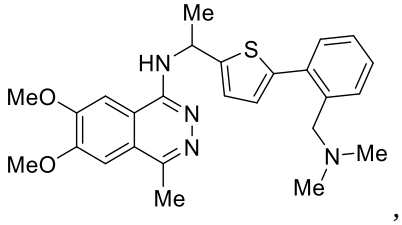
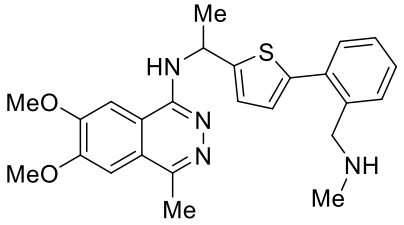
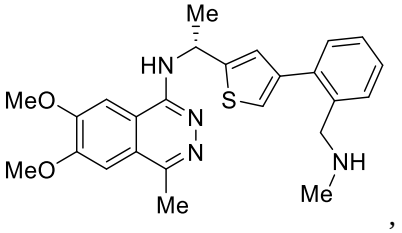
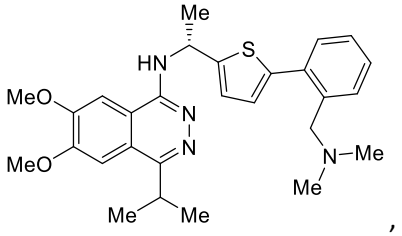
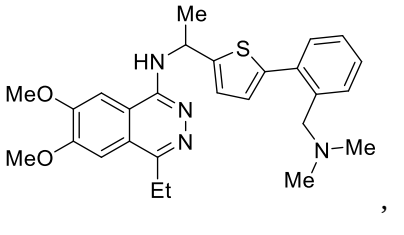
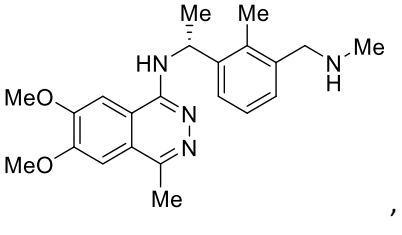

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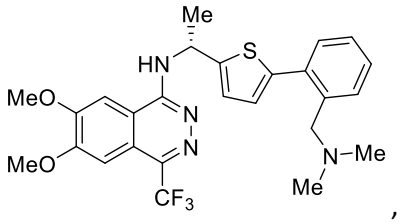
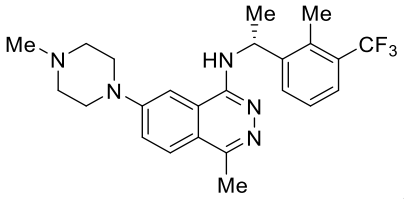
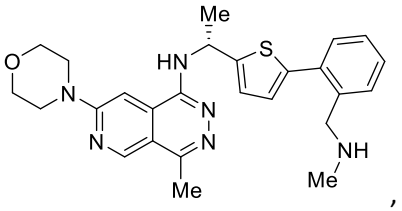
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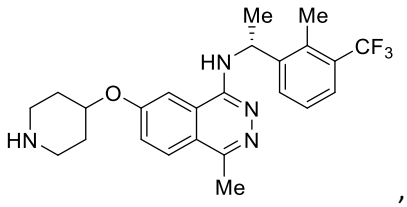
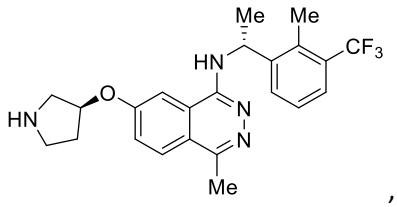
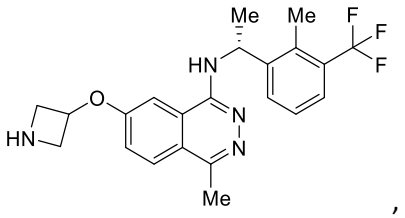
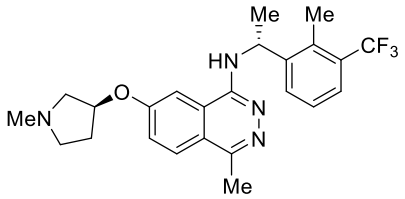
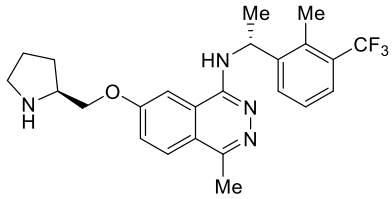
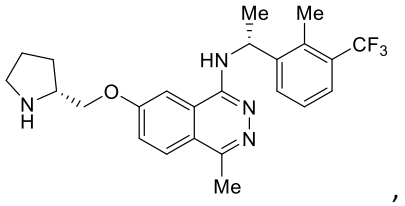
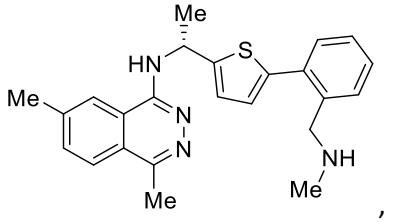
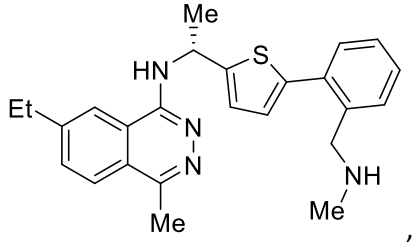
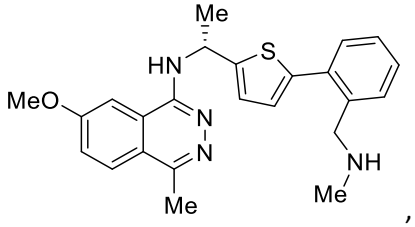
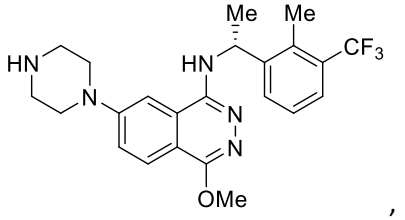
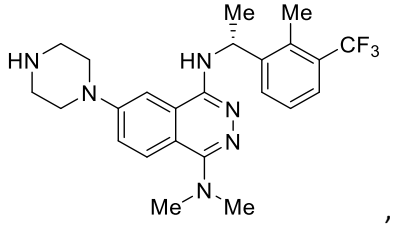
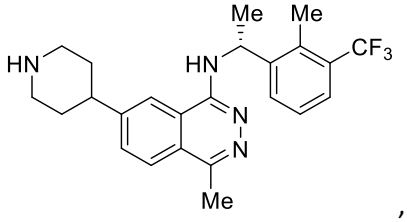
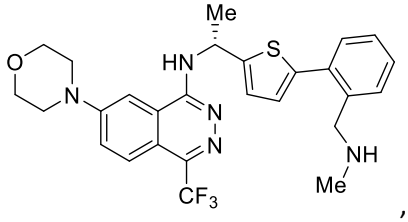
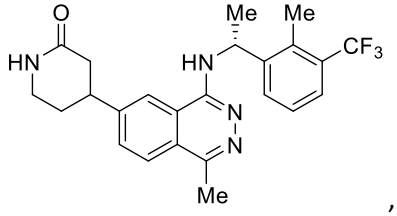
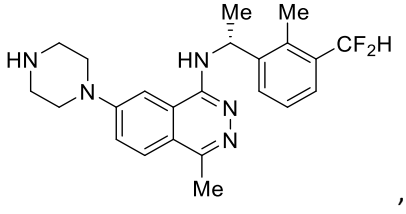
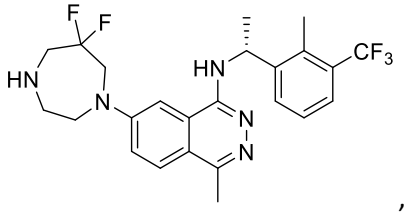
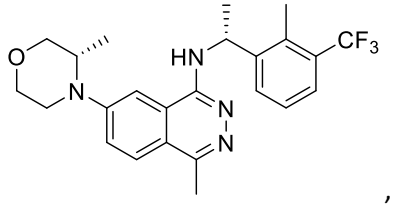
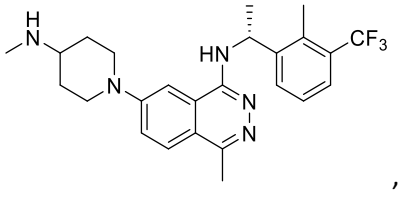
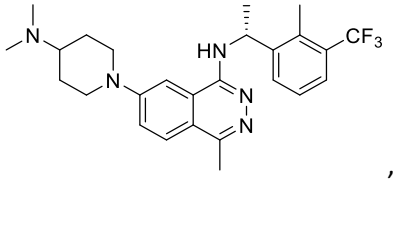
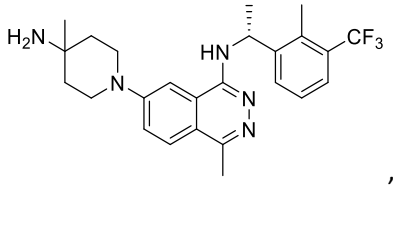
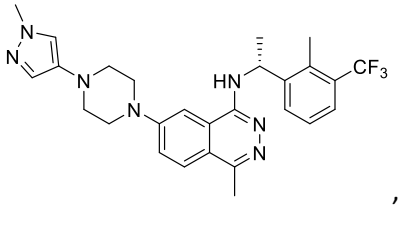
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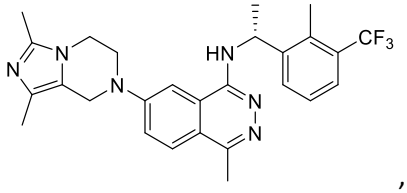
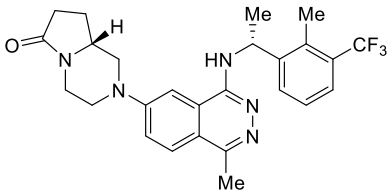
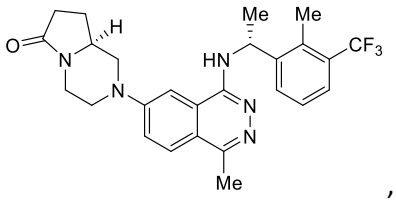
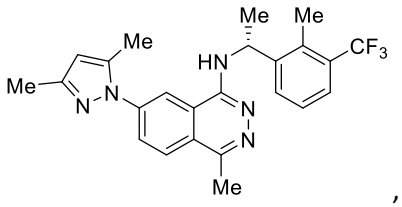
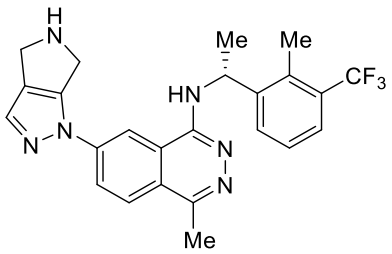
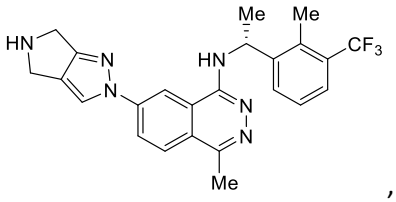
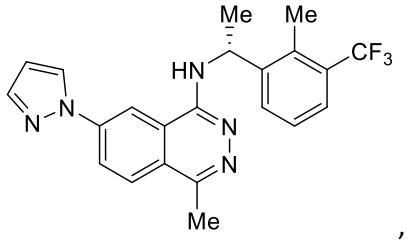
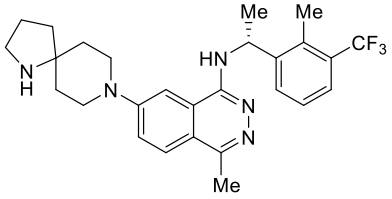
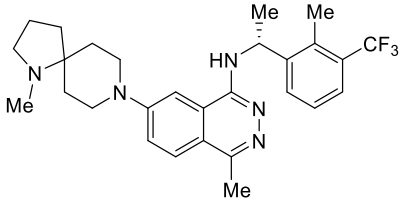
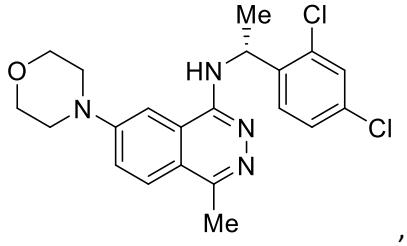
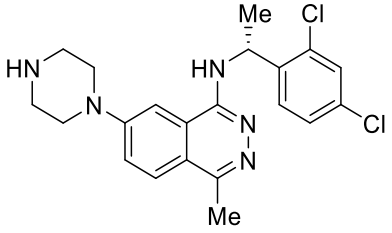
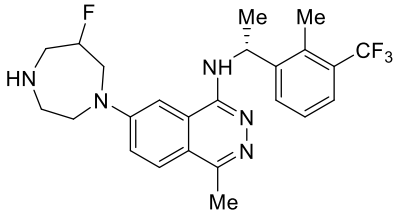
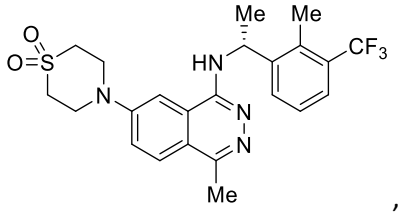
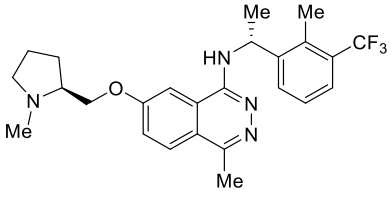
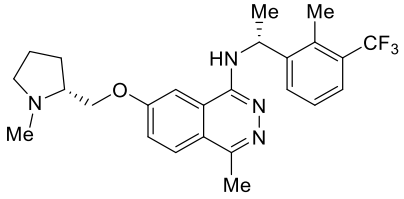
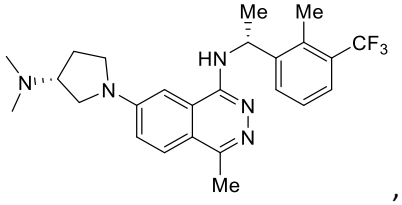
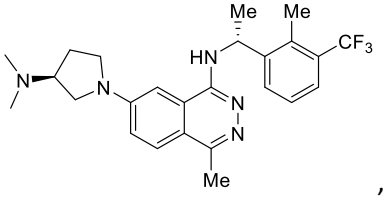
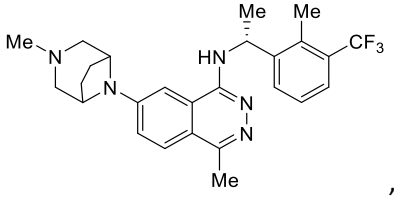
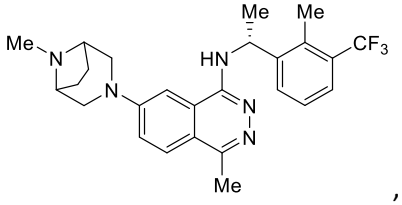
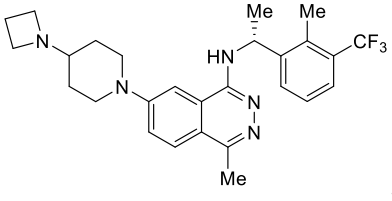
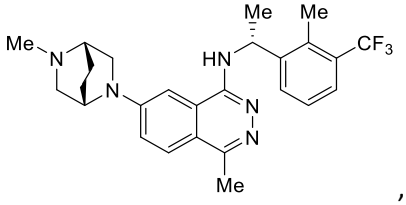

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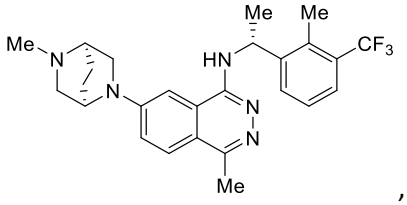
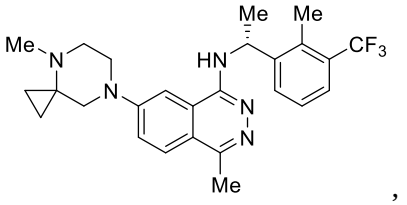
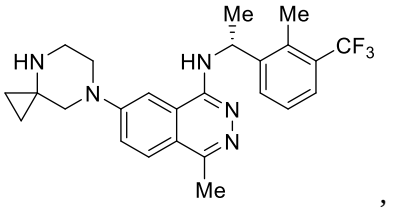
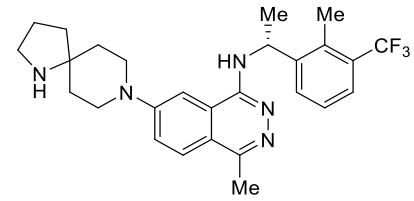
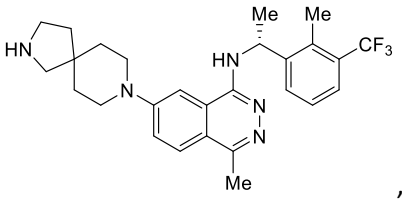
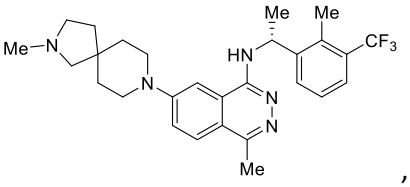
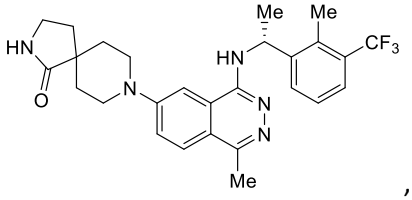
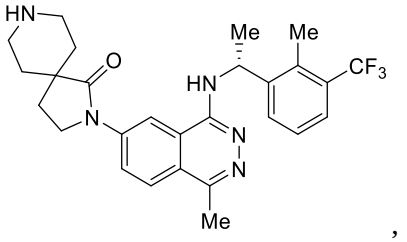
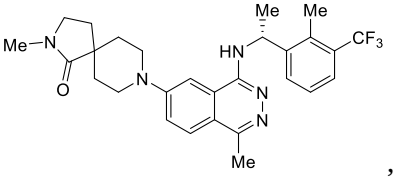
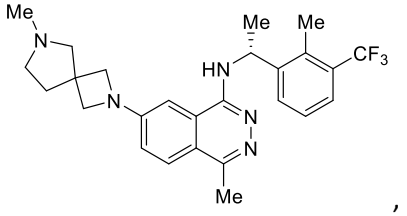
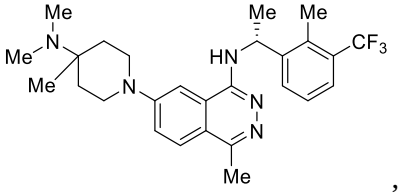
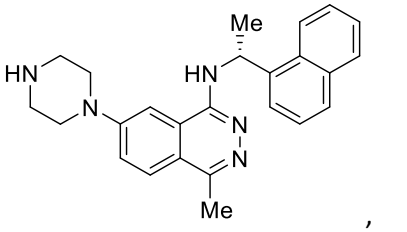
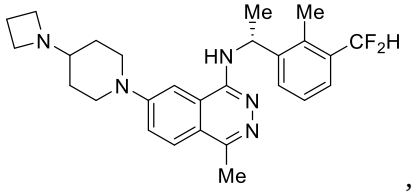
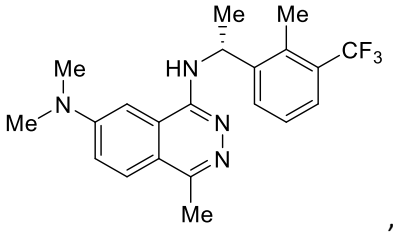
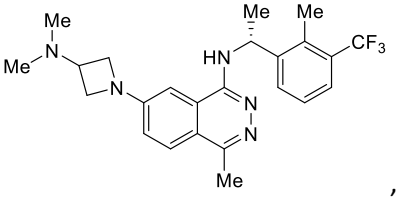
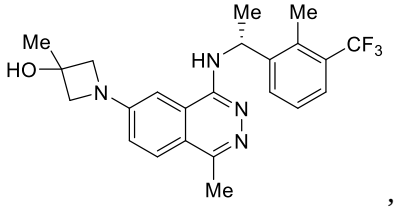
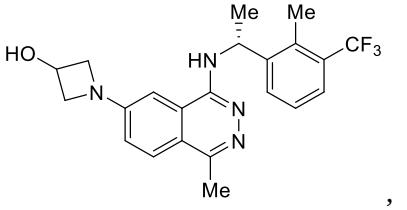
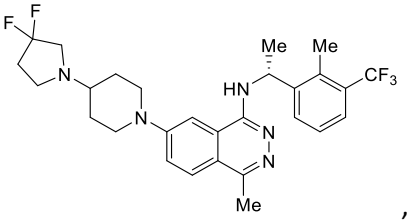
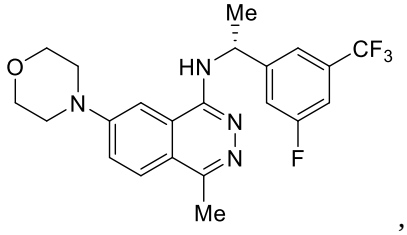
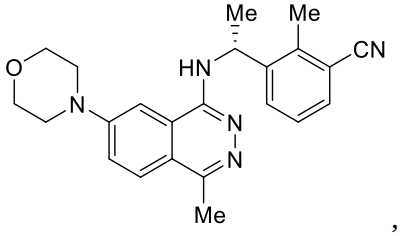
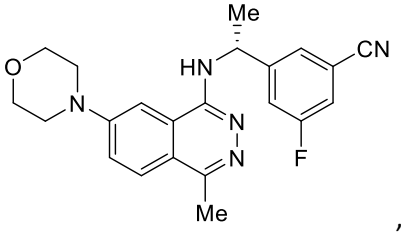
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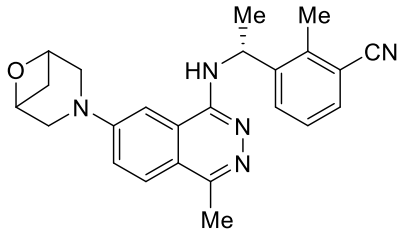
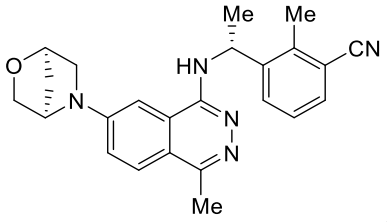
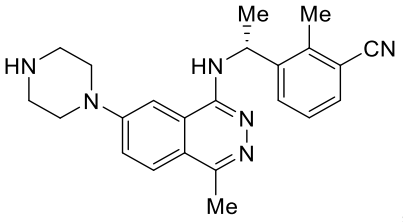
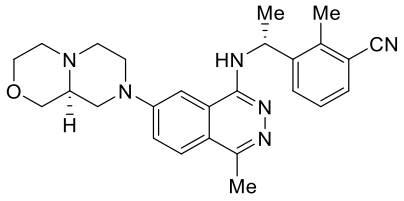
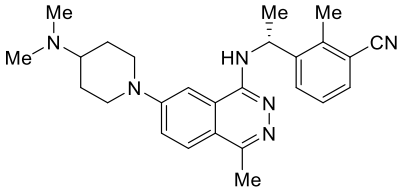
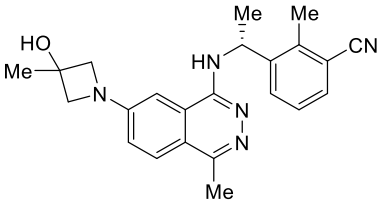
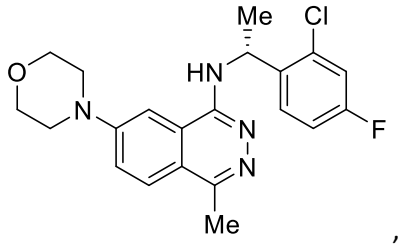
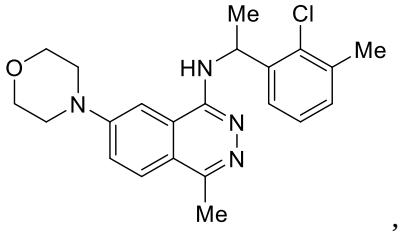
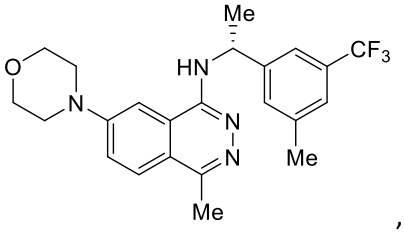
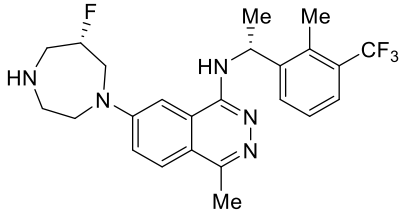
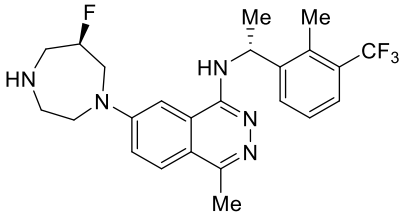
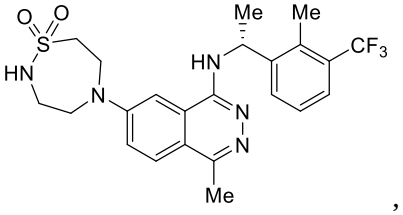
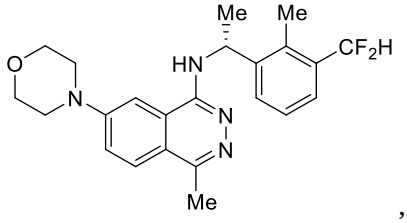
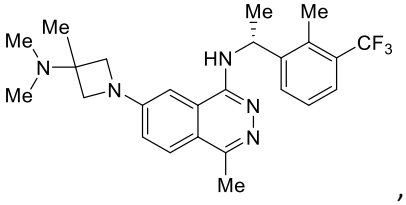
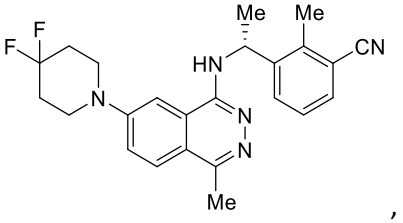
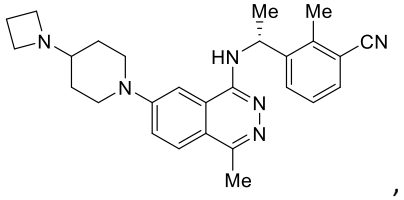
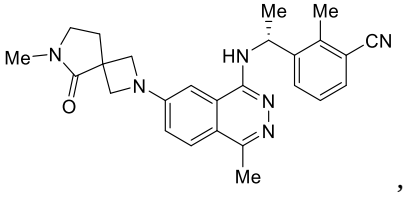
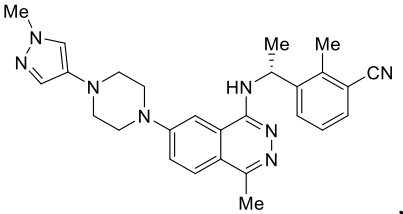
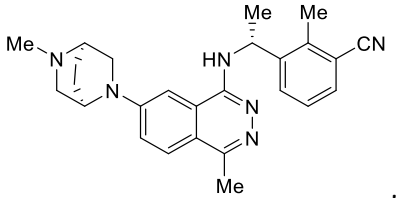
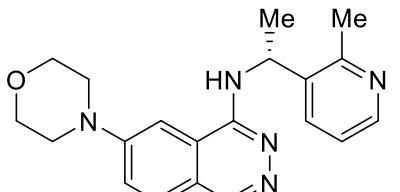
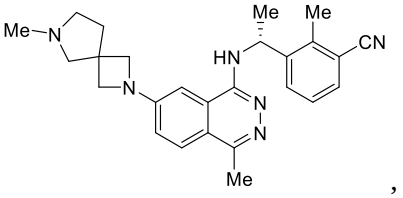
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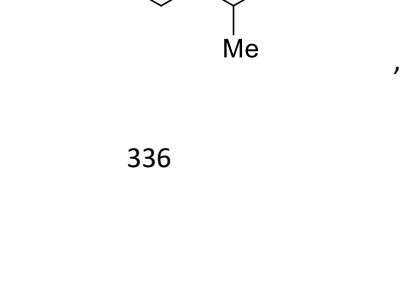

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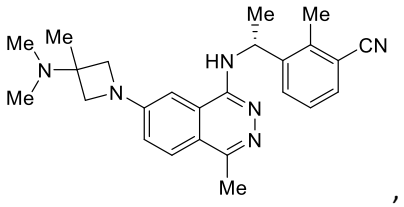
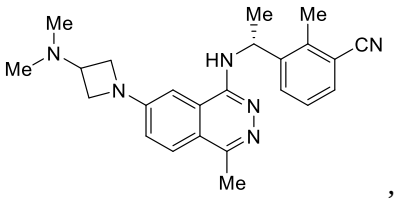
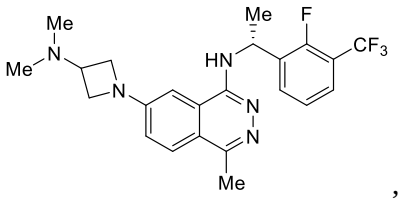
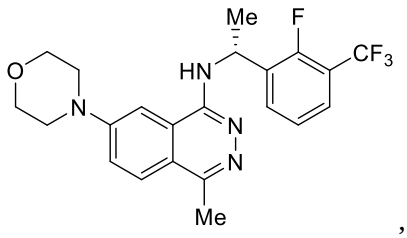
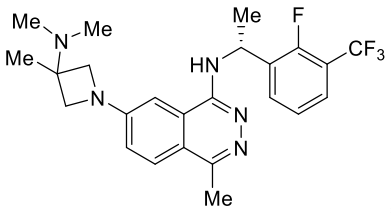
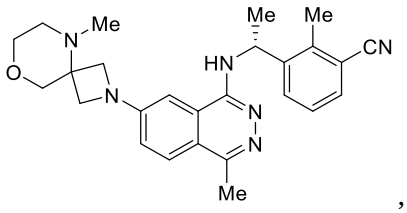
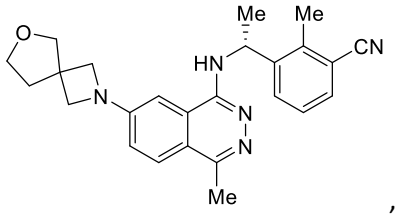
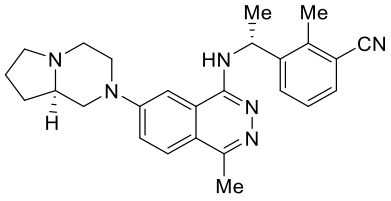
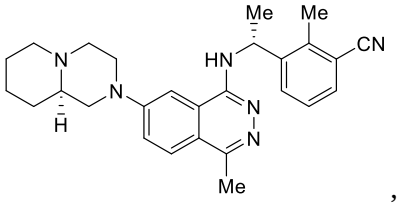
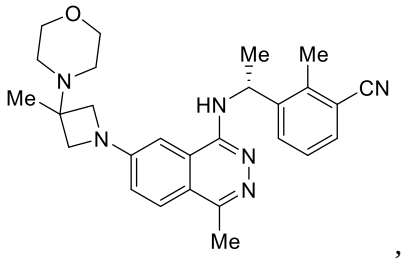
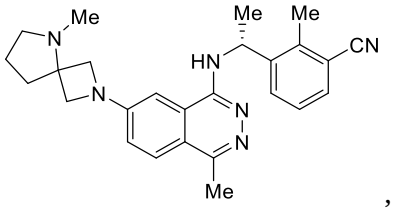
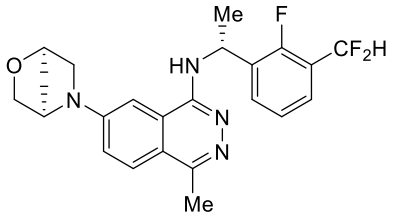
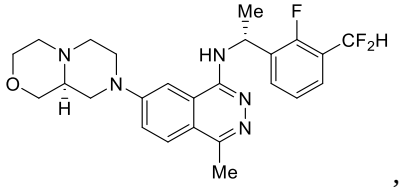
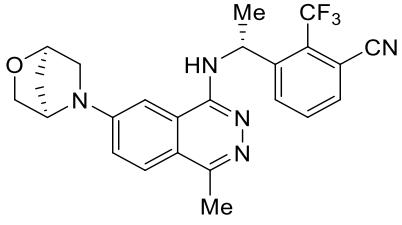
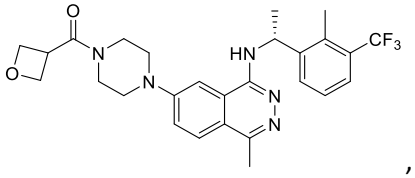
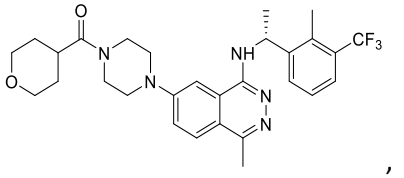
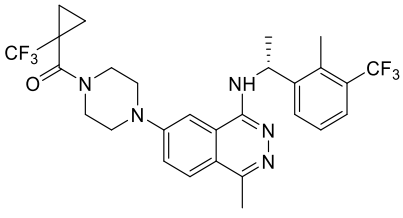
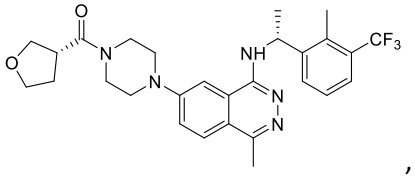
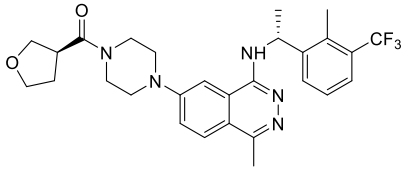
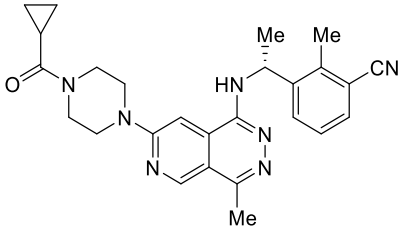
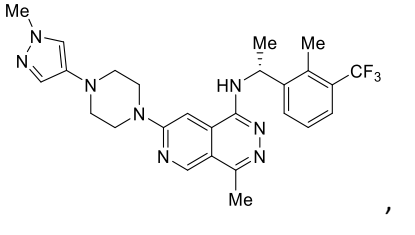
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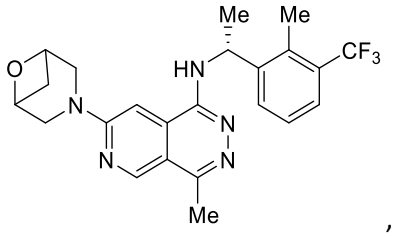
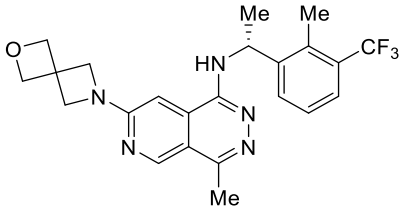
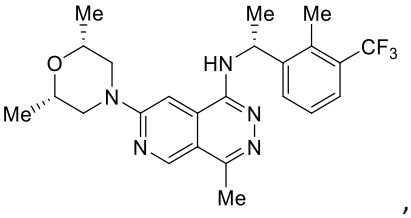
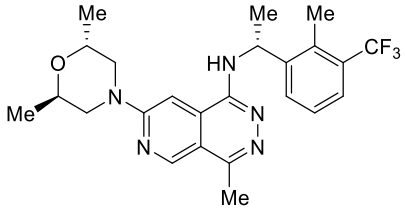
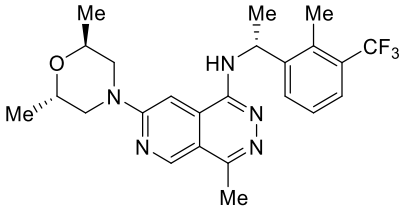
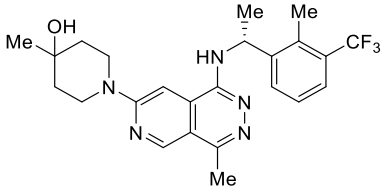
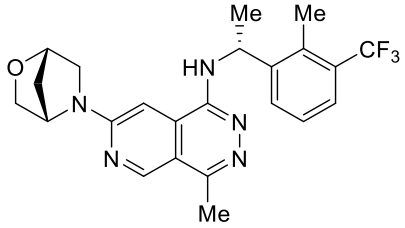
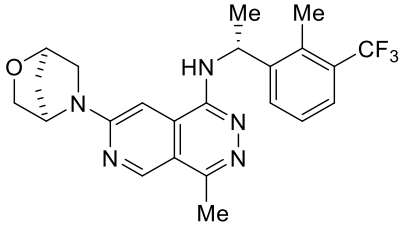
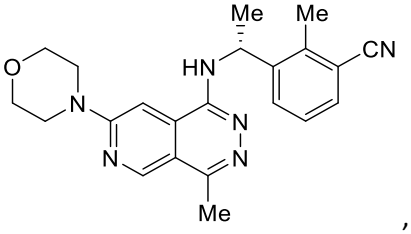
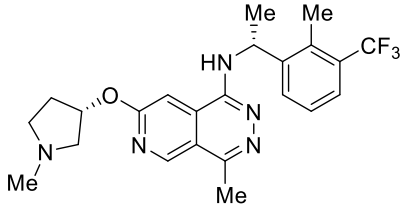
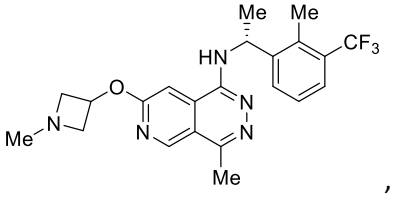
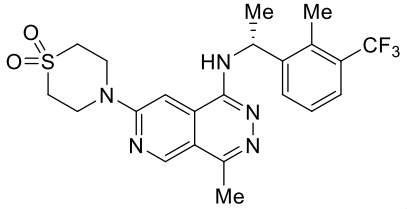
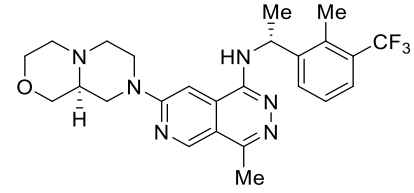
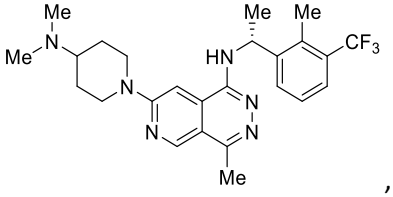
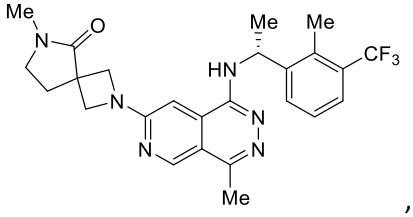
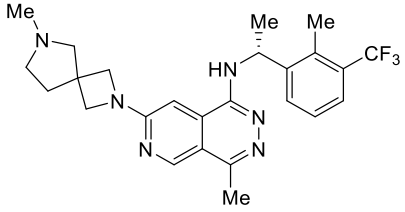
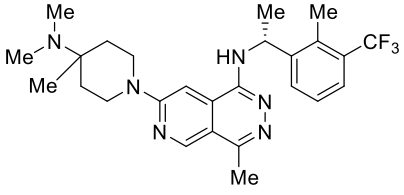
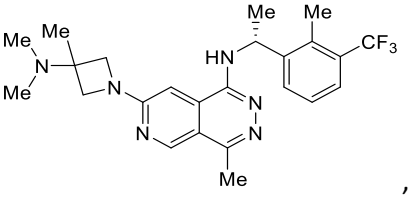
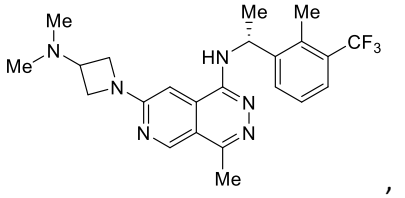
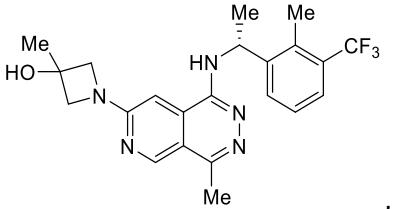
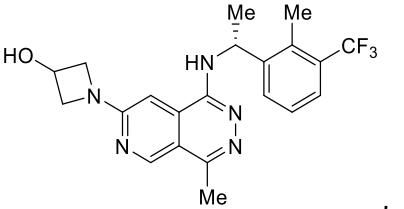
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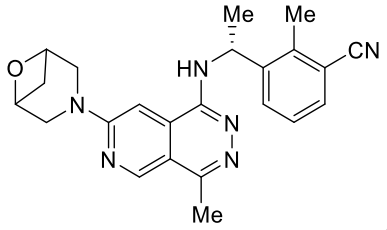
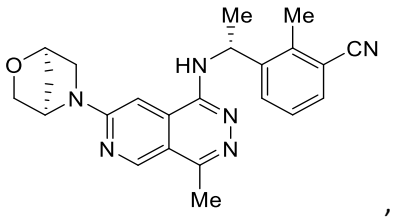
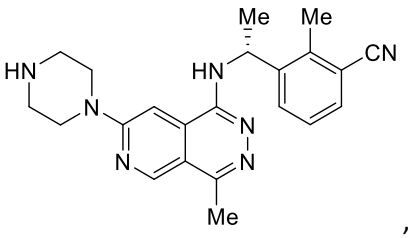
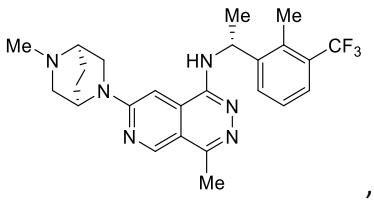
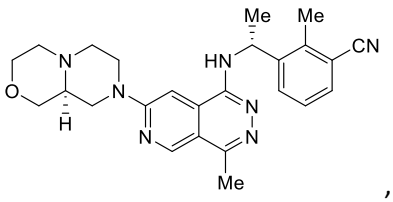
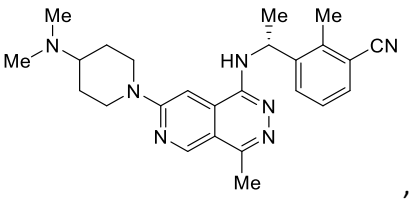
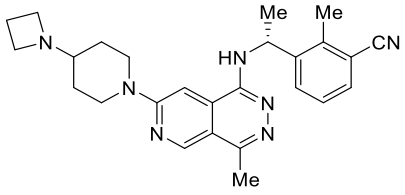
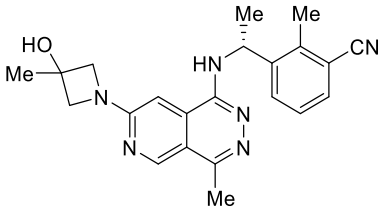
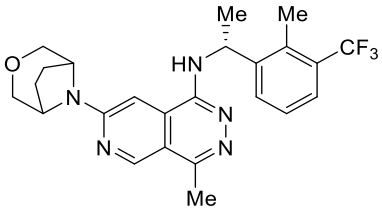
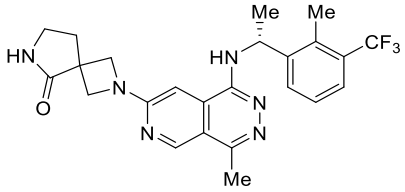
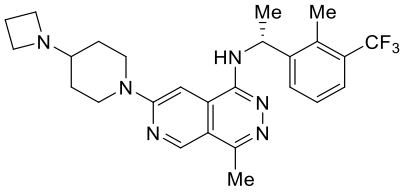
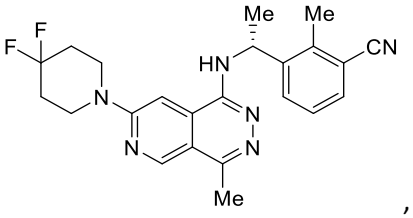
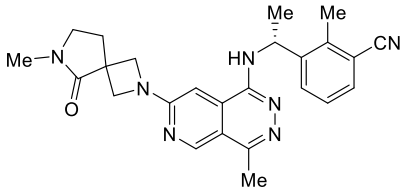
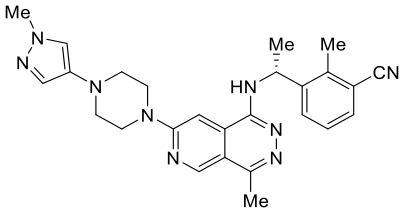
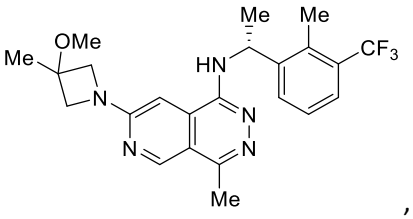
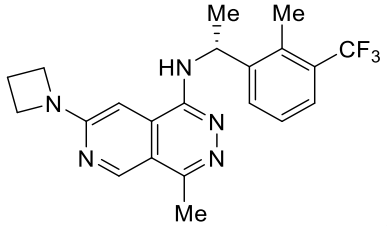
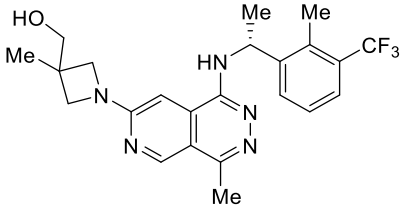
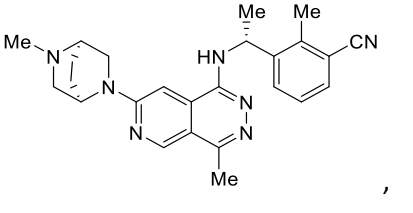
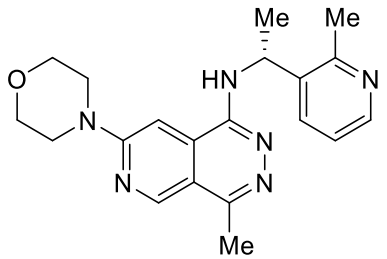
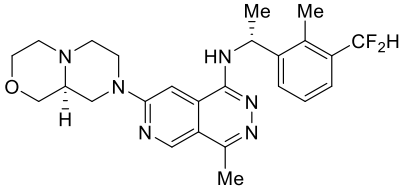
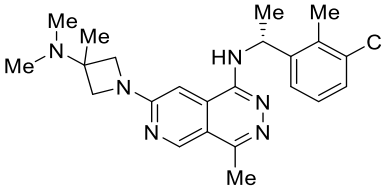
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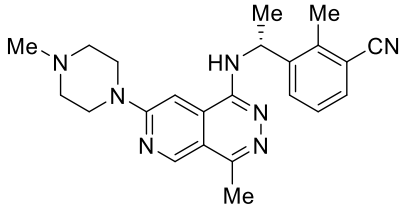
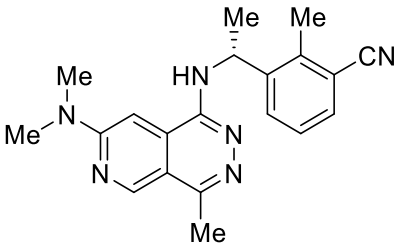
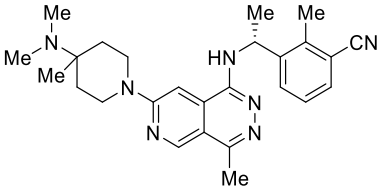
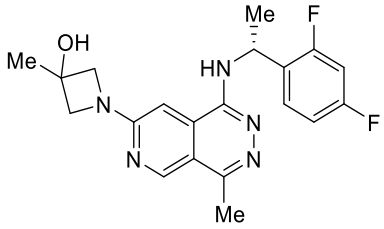
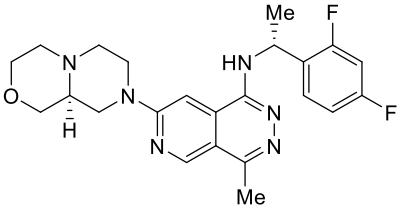
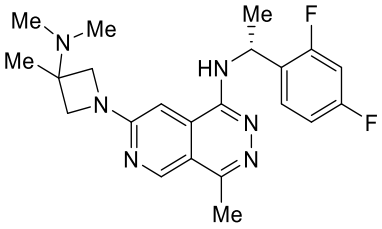
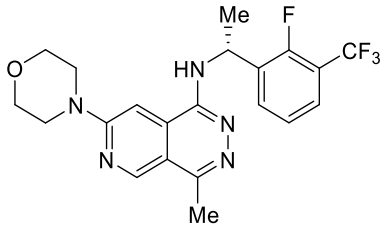
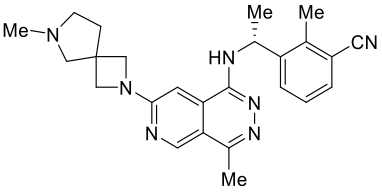
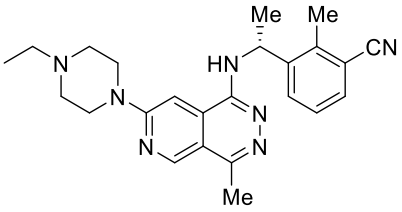
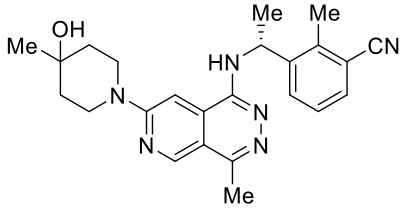
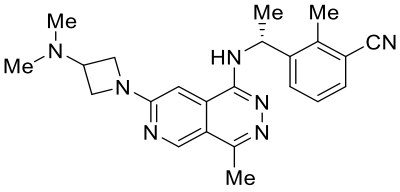
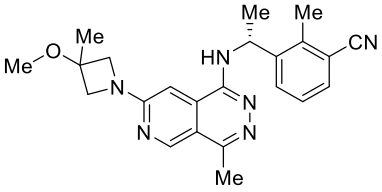
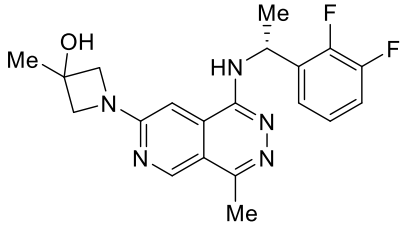
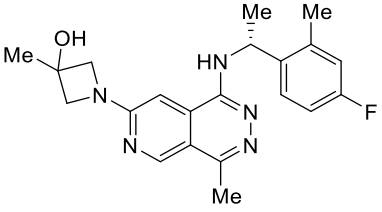
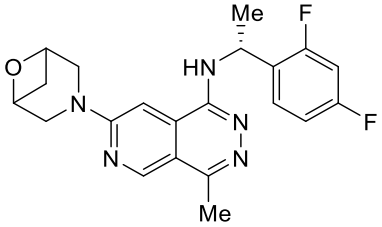
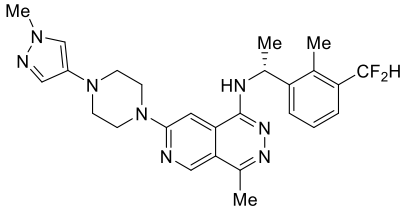
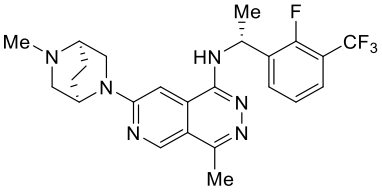
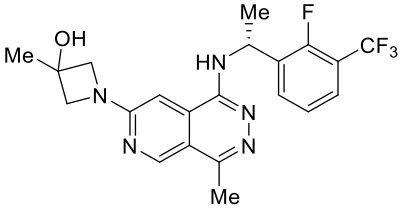
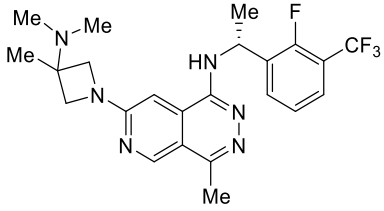
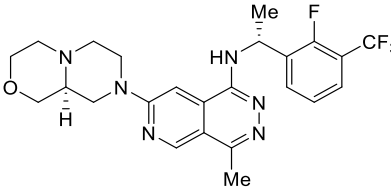
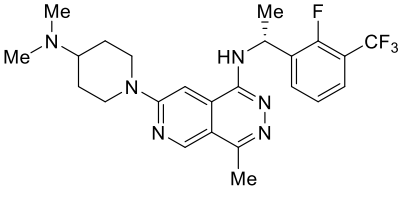
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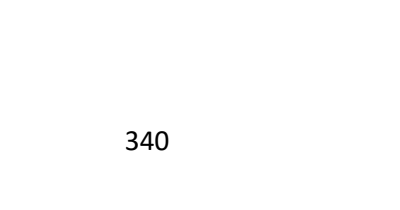

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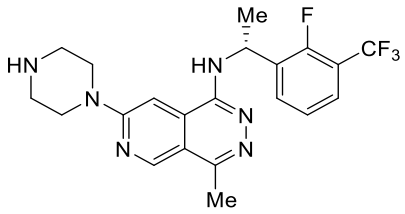
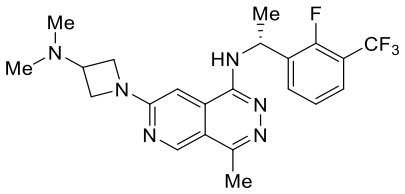
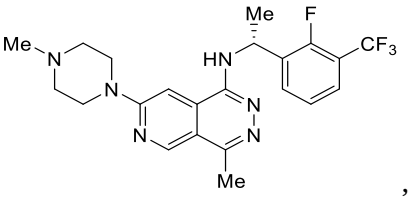
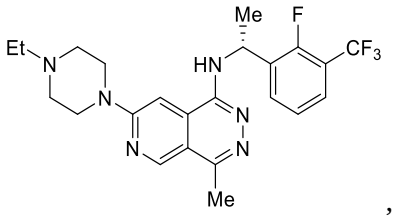
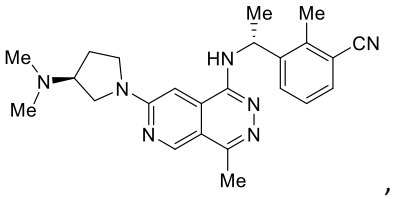
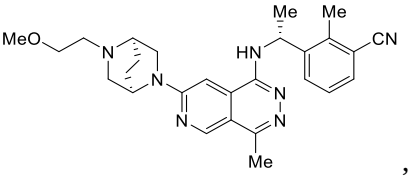
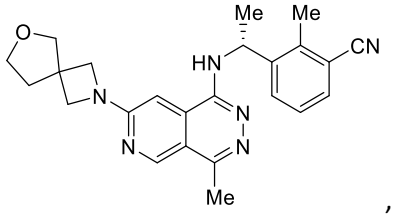
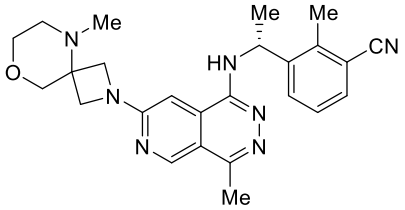
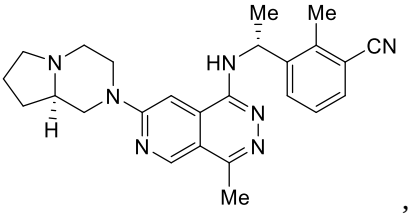
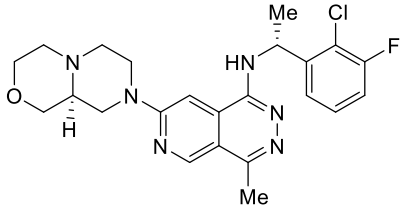
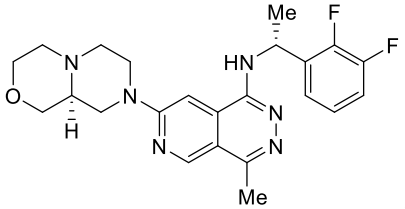
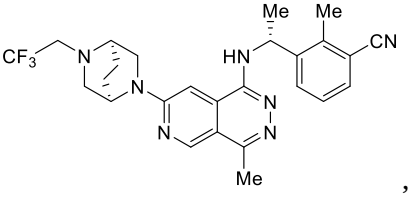
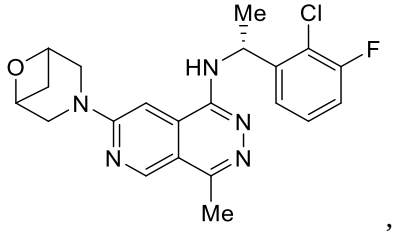
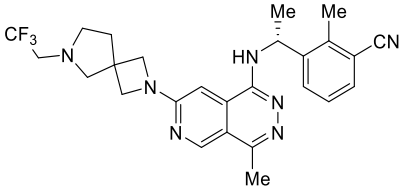
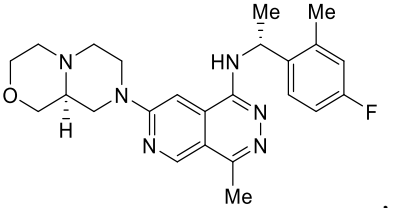
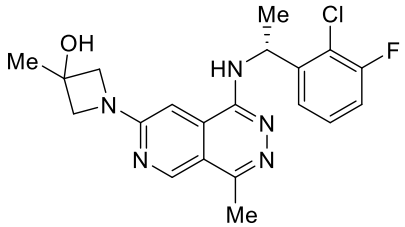
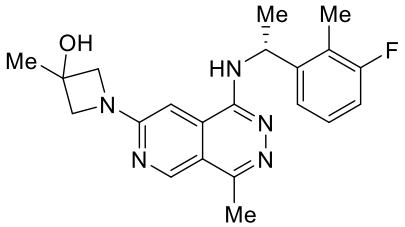
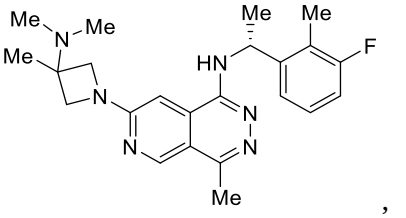
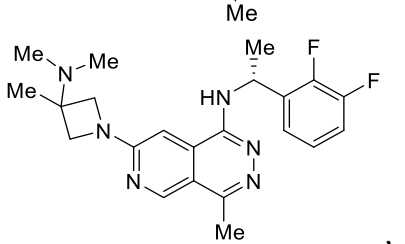
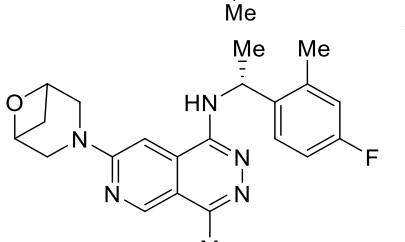
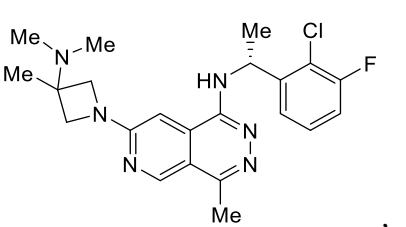
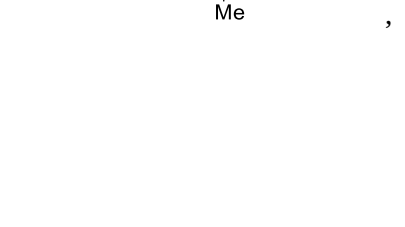
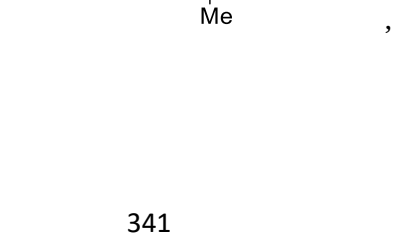
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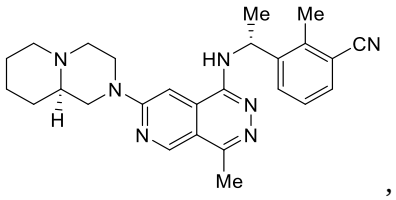
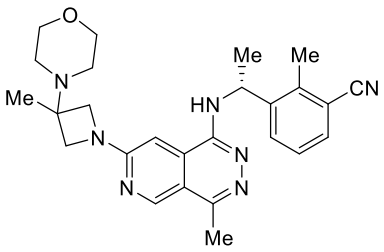
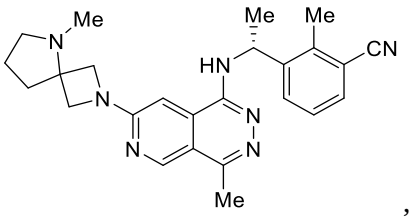
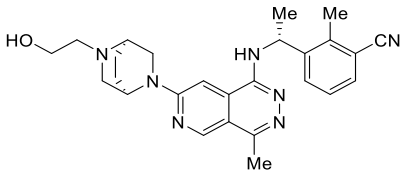
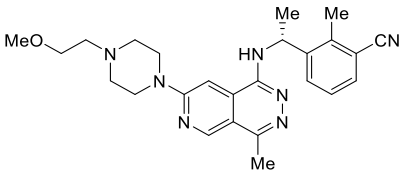
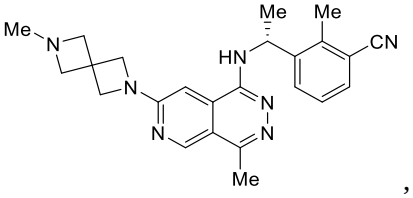
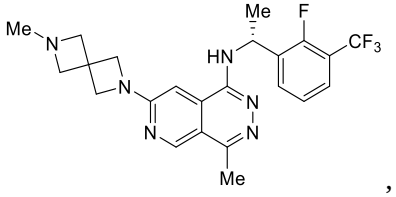
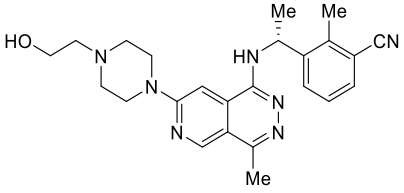
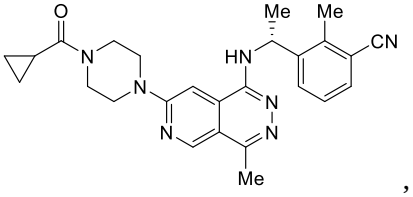
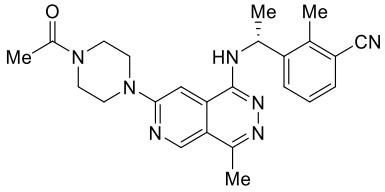
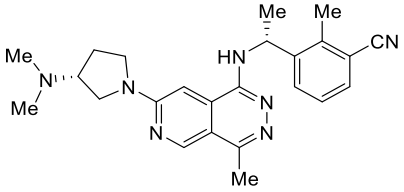
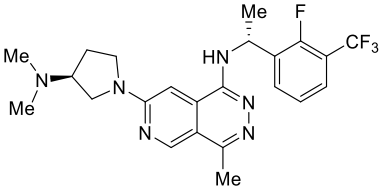
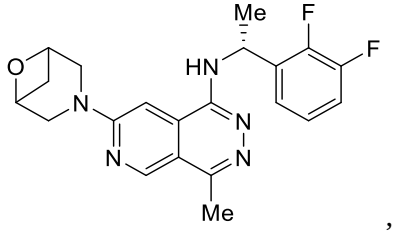
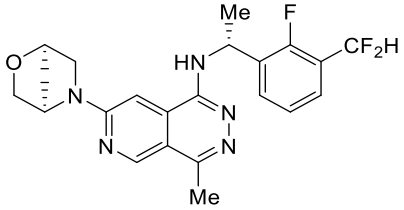
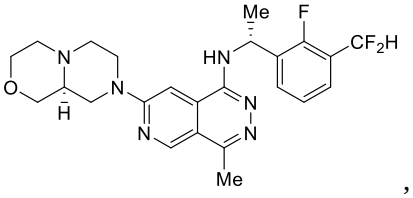
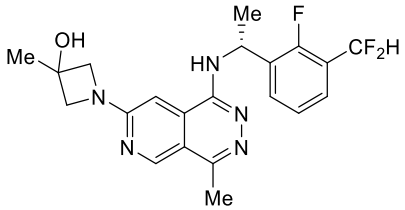
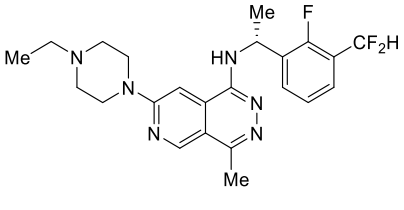
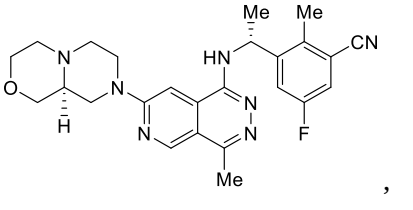
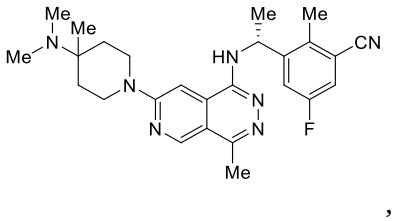
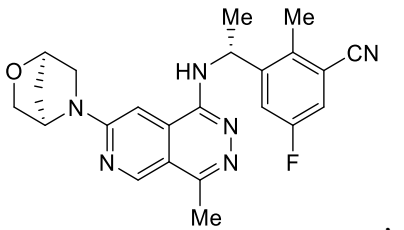
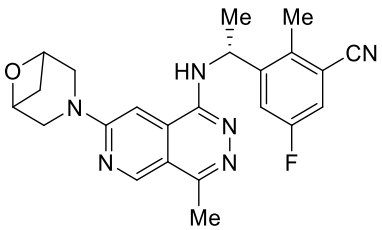

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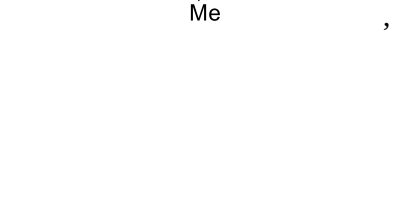
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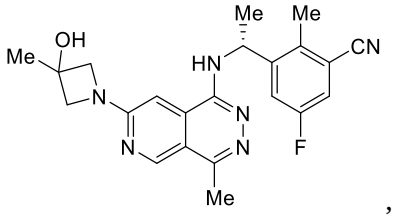
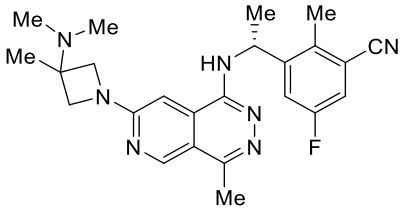
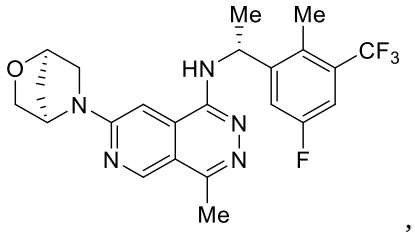
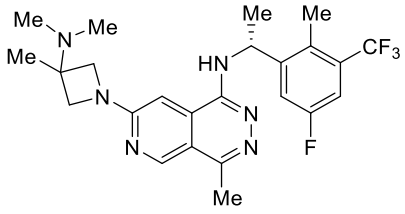
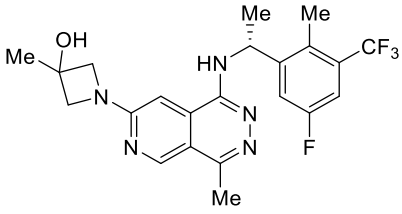
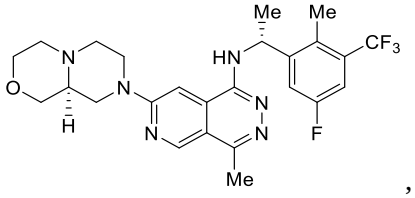
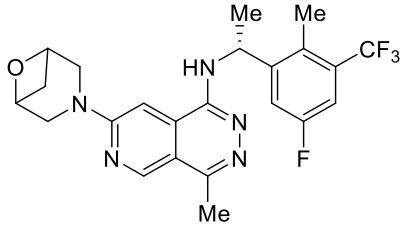
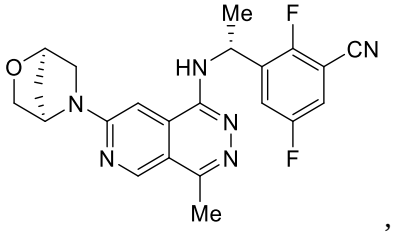
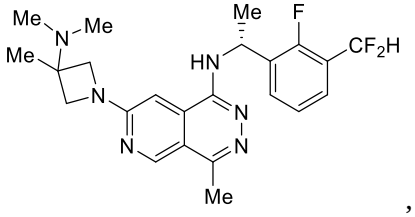
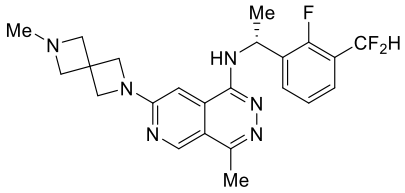
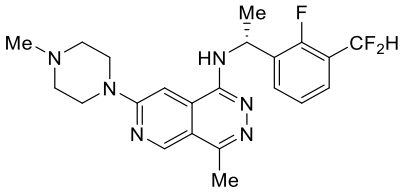
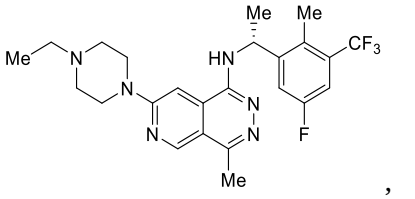
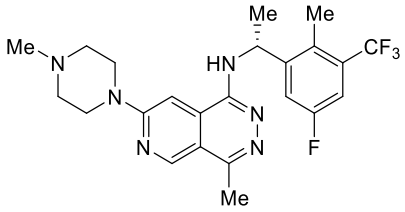
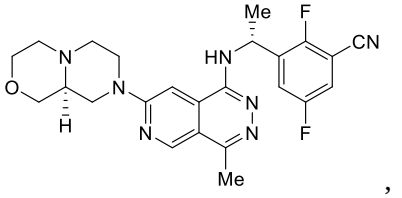
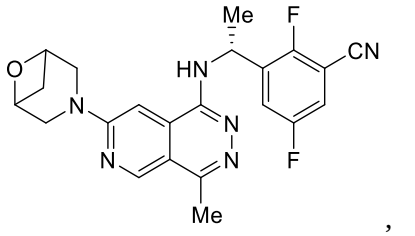
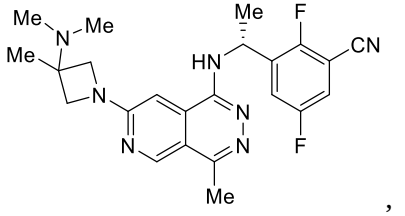
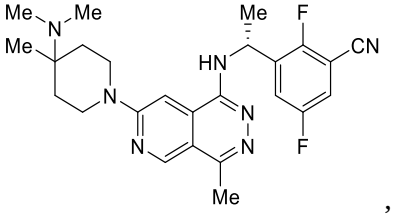
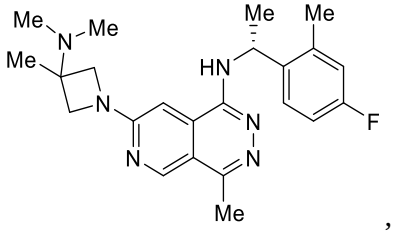
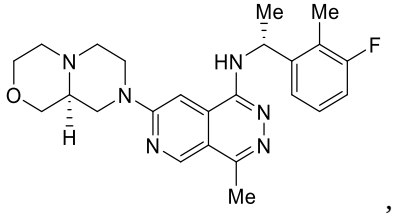
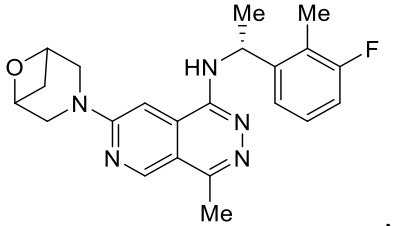
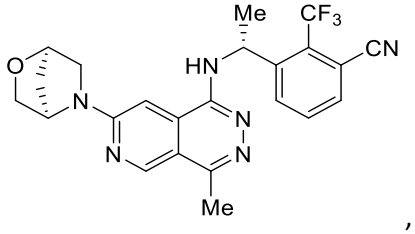

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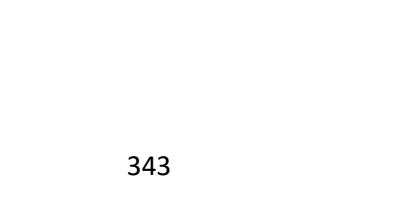
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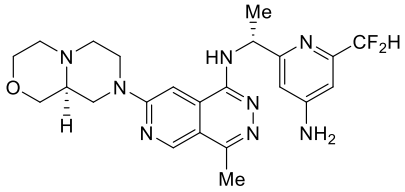
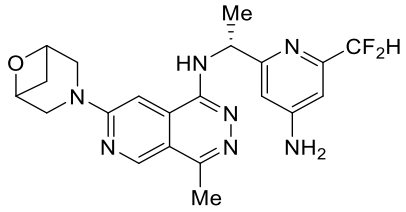
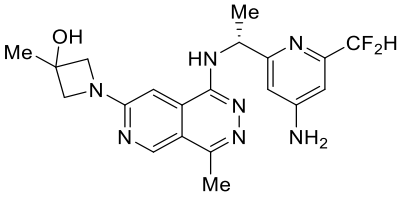
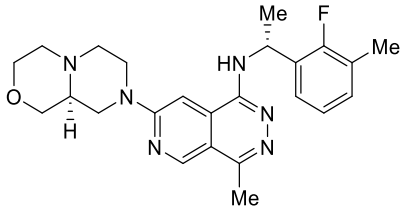
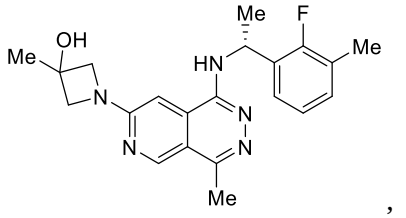
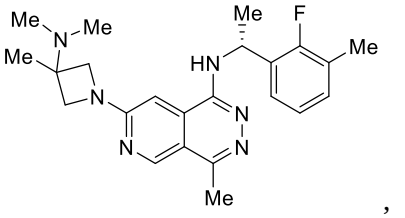
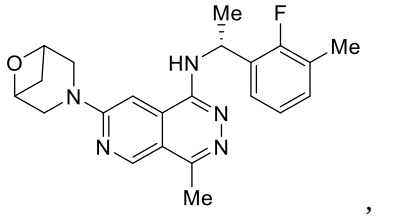
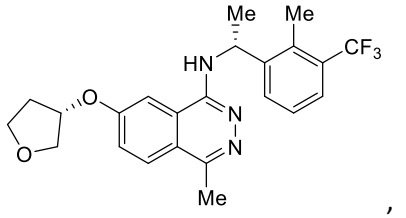
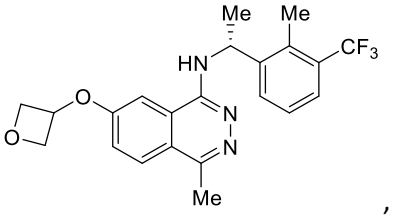
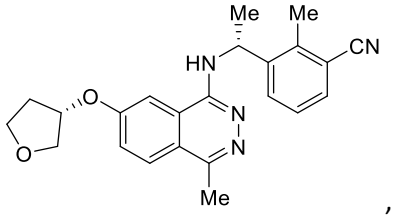
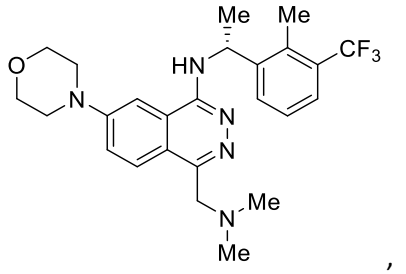
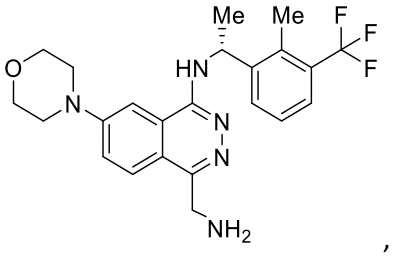
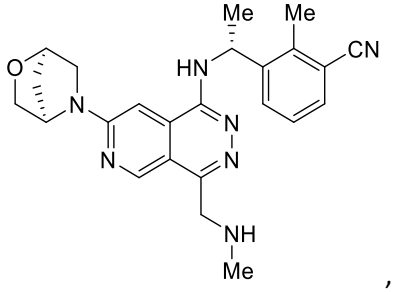
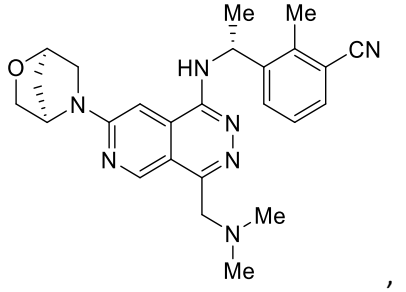
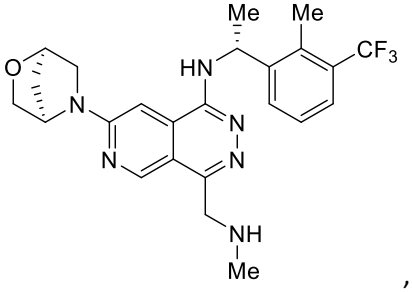
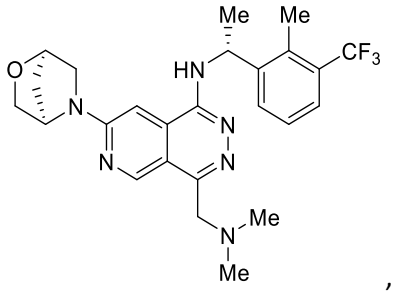
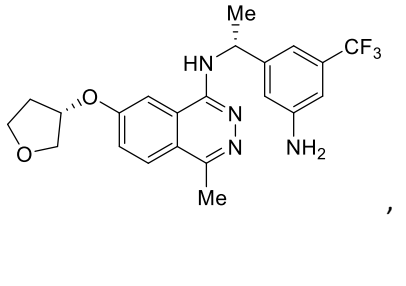
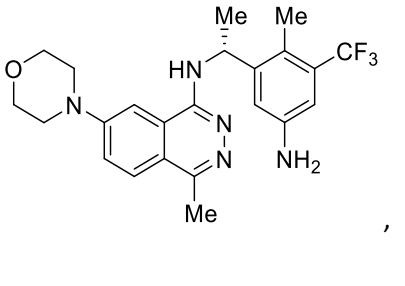
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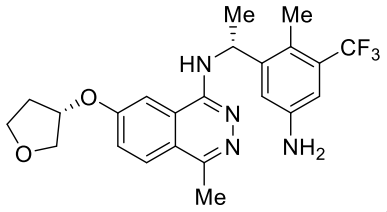
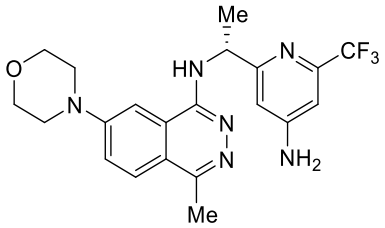
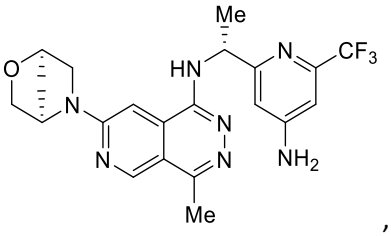
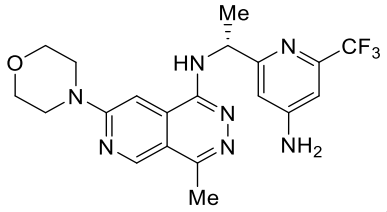
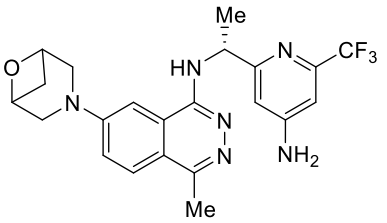
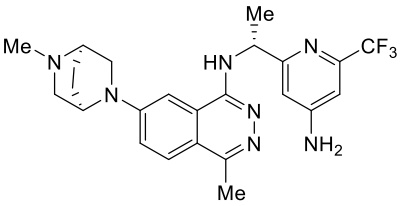
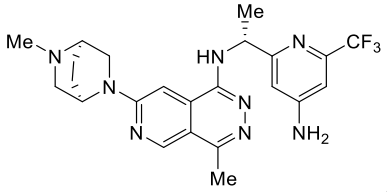
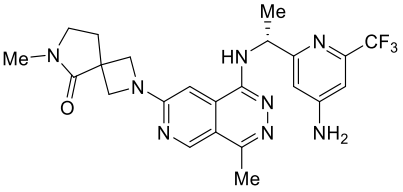
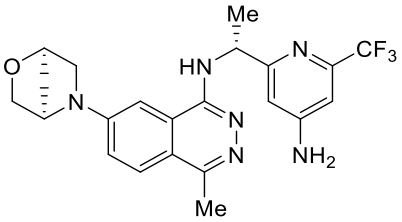
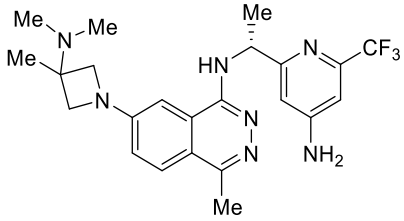
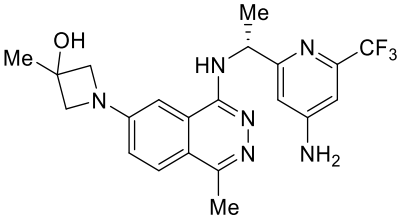
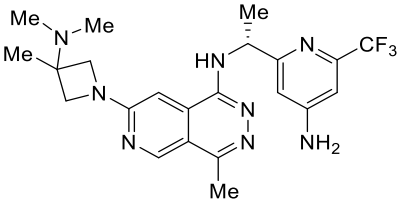
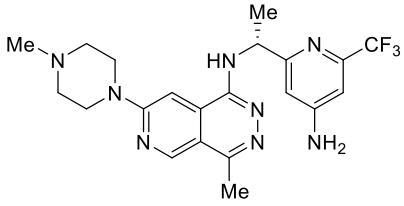
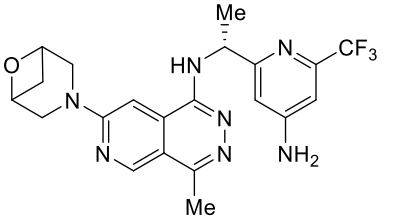
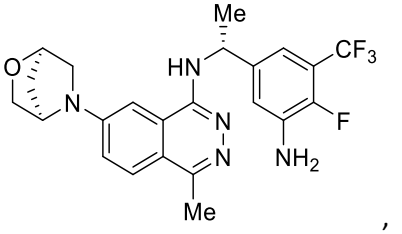
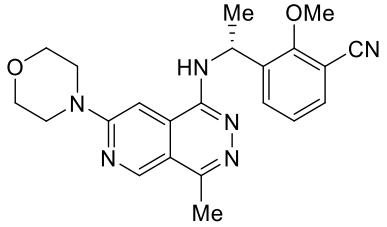
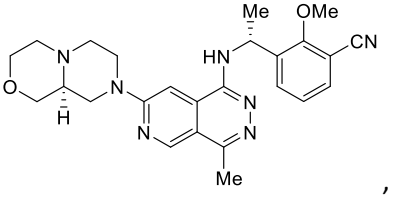
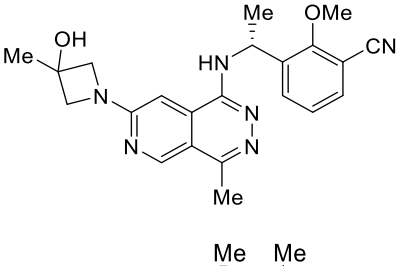
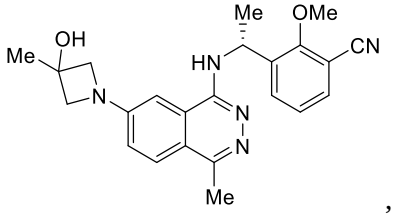
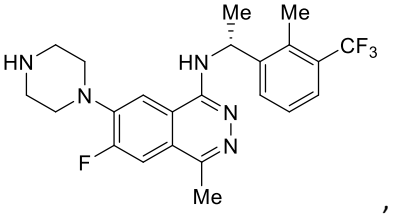
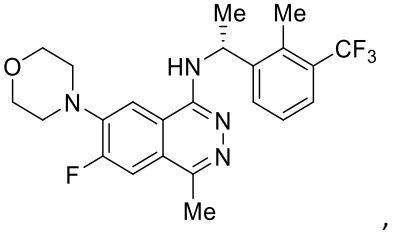
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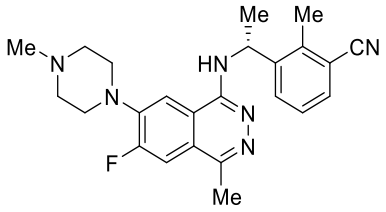
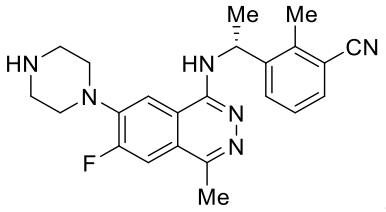
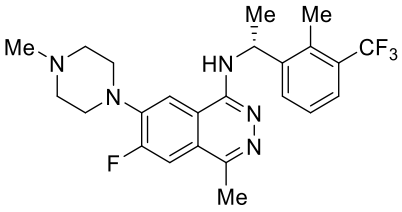
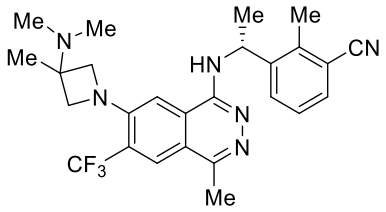
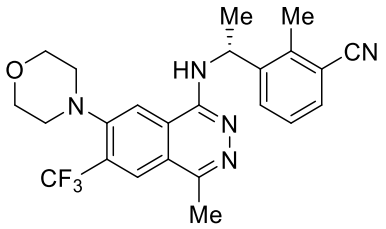
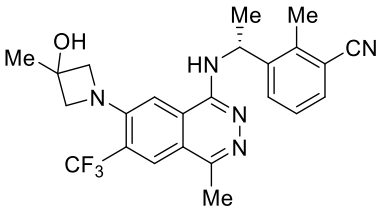
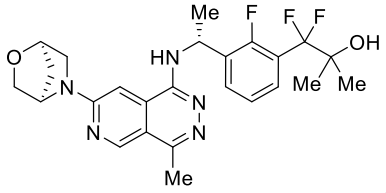
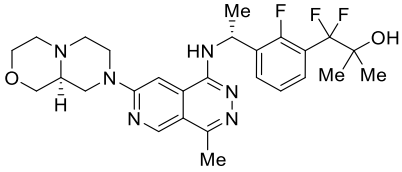
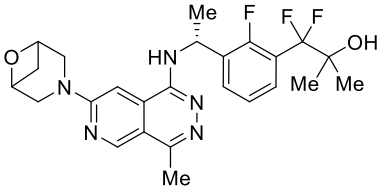
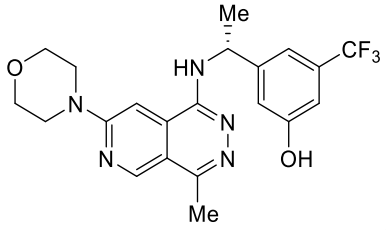
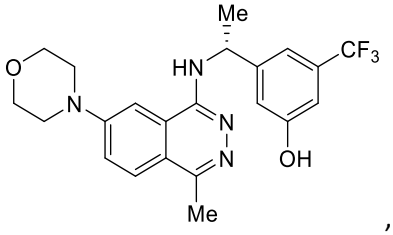
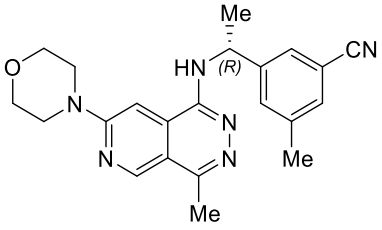
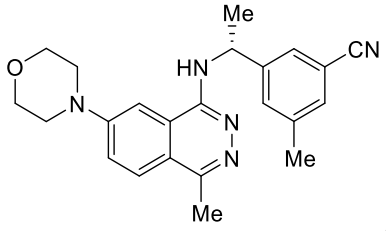
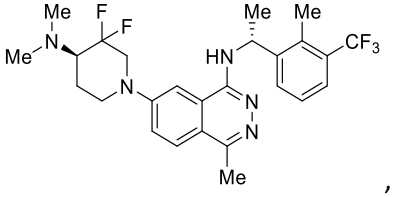
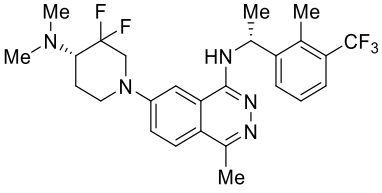
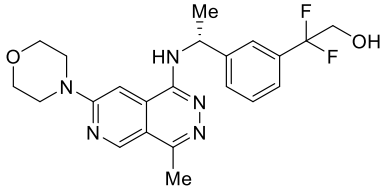
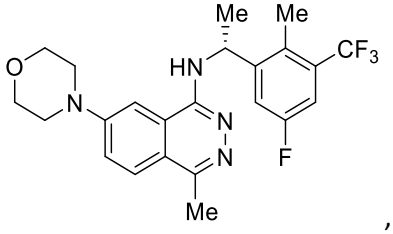
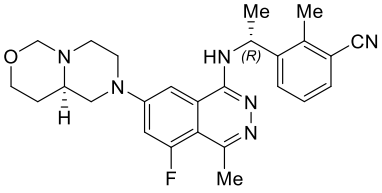
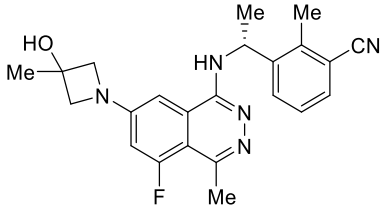
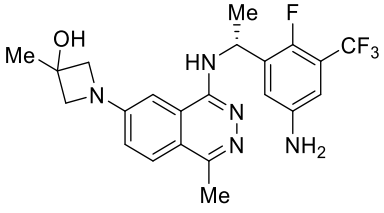
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and pharmaceutically acceptable salts thereof.

72. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of Formula (I) according to any one of claims 1-71 or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

73. A method for inhibiting SOS1 activity in a cell, comprising contacting the cell in which inhibition of SOS1 activity is desired with an effective amount of a compound of Formula (I) according to any one of claims 1-71 or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition according to claim 72.

74. The method according to claim 73, wherein the cell harbors an activating mutation in a RAS family-member gene.

75. The method according to claim 73, wherein the cell harbors an activating mutation in SOS1 gene.

76. The method according to claim 73, wherein the cell harbors an activating mutation in NF-1 or NF-2 gene.

77. Use of ~~A method for treating cancer comprising administering to a patient having cancer~~ a therapeutically effective amount of a compound of Formula (I) according to any one of claims 1-64 or a pharmaceutically acceptable salt or solvate thereof, ~~or a pharmaceutically acceptable salt or solvate thereof~~, alone or combined with a pharmaceutically acceptable carrier, excipient or diluents, in the manufacture of a medicament for treating cancer in a patient.

78. The ~~method~~ use according to claim 77, wherein the therapeutically effective amount of the compound is between about 0.01 to 300 mg/kg per day.

79. The ~~method~~ use according to claim 78, wherein the therapeutically effective amount of the compound is between about 0.1 to 100 mg/kg per day.

80. The ~~method~~ use according to any one of claims 77-79, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid

tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial wcarcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

81. The ~~method~~ use according to any one of claims 77-80, wherein the cancer is a Ras family-associated cancer.

82. The ~~method~~ use according to calim 81, wherein the Ras family-associated cancer is a KRas, HRas or NRas G12C-associated cancer, a KRas, HRas or NRas G12D-associated cancer, a KRas, HRas or NRas G12S-associated cancer, a KRas, HRas or NRas G12A-associated cancer, a KRas, HRas or NRas G13D-associated cancer, a KRas, HRas or NRas G13C-associated cancer, a KRas, HRas or NRas Q61X-associated cancer, a KRas,

HRas or NRas A146T-associated cancer, a KRas, HRas or NRas A146V-associated cancer or a KRas, HRas or NRas A146P-associated cancer.

83. The ~~method~~ use according to claim 82, wherein the Ras family-associated cancer is a KRas G12C-associated cancer.

84. The ~~method~~ use according to claim 83, wherein the Ras family-associated cancer is non-small cell lung cancer or pancreatic cancer.

85. The ~~method~~ use according to any one of claims 77-803, wherein the cancer is a SOS1-associated cancer.

86. The ~~method~~ use according to claim 85, wherein the SOS1-associated cancer is a SOS1 N233S-associated cancer or a SOS1 N233Y-associated cancer.

87. The ~~method~~ use according to any one of claims 85 or 86, wherein the SOS1-associated cancer is lung adenocarcinoma, embryonal rhabdomyosarcoma, Sertoli cell testis tumor or granular cell tumors of the skin.

88. The ~~method~~ use according to any one of claims 77-80, wherein the cancer is a NF-1/NF-2-associated cancer.