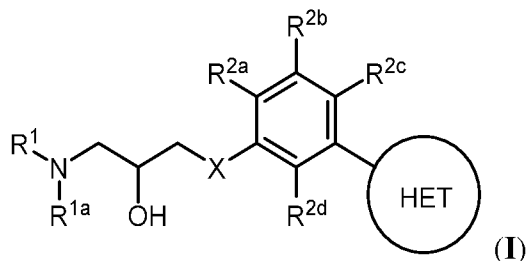


Claims

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

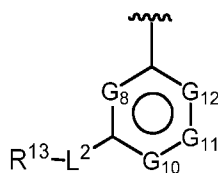
X is $-\text{O}-$, $-\text{S}-$, or $-\text{CH}_2-$;

R^1 is hydrogen or optionally substituted C_{1-4} aliphatic;

R^{1a} is hydrogen;

each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{R}^{\text{A}2}$, $-\text{C}(=\text{O})\text{OR}^{\text{A}2}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{A}2})_2$, $-\text{OR}^{\text{A}2}$, $-\text{SR}^{\text{A}2}$, $-\text{N}(\text{R}^{\text{A}2})_2$, $-\text{S}(=\text{O})\text{R}^{\text{A}2}$, $-\text{S}(=\text{O})_2\text{R}^{\text{A}2}$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, wherein each instance of $\text{R}^{\text{A}2}$ is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two $\text{R}^{\text{A}2}$ groups attached to the same nitrogen atom are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring;

Ring HET is a 6-membered monocyclic heteroaryl ring system of the Formula:



wherein:

G_8 is $\text{C}-\text{R}^8$ or N;

G_{10} is $\text{C}-\text{R}^{10}$ or N;

G_{11} is $\text{C}-\text{R}^{11}$ or N;

G_{12} is $\text{C}-\text{R}^{12}$ or N;

provided at least one instance of G_8 , G_{10} , G_{11} , or G_{12} is N;

each instance of R^8 , R^{10} , R^{11} , and R^{12} is independently selected from the group consisting of hydrogen, halo, $-CN$, $-NO_2$, $-C(=O)R'$, $-C(=O)OR'$, $-C(=O)N(R')_2$, optionally substituted alkyl, and $-L^1-R^3$;

each instance of R' is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R' groups attached to the same nitrogen are joined to form an optionally substituted heterocyclyl ring or optionally substituted heteroaryl ring;

each instance of L^1 and L^2 is independently a bond, $-O-$, $-N(R^L)-$, $-S-$, $-C(O)-$, $-C(O)O-$, $-C(O)S-$, $-C(O)N(R^L)-$, $-C(O)N(R^L)N(R^L)-$, $-OC(O)-$, $-OC(O)N(R^L)-$, $-NR^L C(O)-$, $-NR^L C(O)N(R^L)-$, $-NR^L C(O)N(R^L)N(R^L)-$, $-NR^L C(O)O-$, $-SC(O)-$, $-C(=NR^L)-$, $-C(=NNR^L)-$, $-C(=NOR^L)-$, $-C(=N R^L)N(R^L)-$, $-NR^L C(=NR^L)-$, $-C(S)-$, $-C(S)N(R^L)-$, $-NR^L C(S)-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-SO_2-$, $-N(R^L)SO_2-$, $-SO_2N(R^L)-$, $-N(R^L)SO_2N(R^L)-$, an optionally substituted C_{1-10} saturated or unsaturated hydrocarbon chain, wherein one or more moieties selected from the group consisting of $-O-$, $-N(R^L)-$, $-S-$, $-C(O)-$, $-C(O)O-$, $-C(O)S-$, $-C(O)N(R^L)-$, $-C(O)N(R^L)N(R^L)-$, $-OC(O)-$, $-OC(O)N(R^L)-$, $-NR^L C(O)-$, $-NR^L C(O)N(R^L)-$, $-NR^L C(O)N(R^L)N(R^L)-$, $-NR^L C(O)O-$, $-SC(O)-$, $-C(=NR^L)-$, $-C(=NNR^L)-$, $-C(=NOR^L)-$, $-C(=N R^L)N(R^L)-$, $-NR^L C(=NR^L)-$, $-C(S)-$, $-C(S)N(R^L)-$, $-NR^L C(S)-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-SO_2-$, $-N(R^L)SO_2-$, $-SO_2N(R^L)-$, and $-N(R^L)SO_2N(R^L)-$ is optionally and independently present between two carbon atoms of the hydrocarbon chain, and optionally and independently present at one or both ends of the hydrocarbon chain;

each R^L is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group, or R^L and R^3 taken together form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring, or R^L and R^{13} taken together form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, provided when R^3 is hydrogen, then L^1 is not a bond; and

R^{13} is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, wherein, and unless otherwise specified,

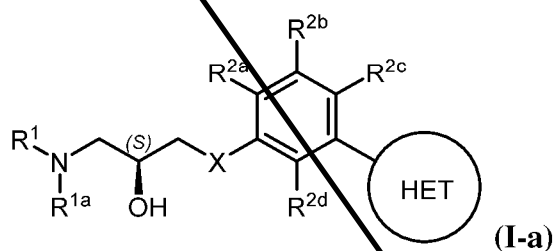
heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

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

aryl refers to a radical of a monocyclic or polycyclic $4n+2$ aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

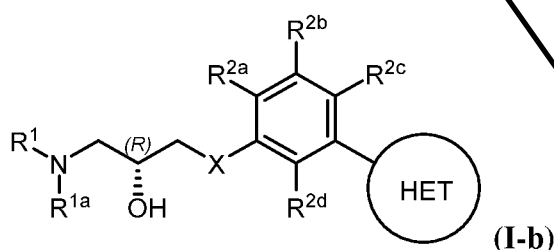
heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic $4n+2$ aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur.

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



or a pharmaceutically acceptable salt thereof.

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



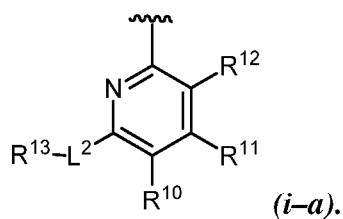
or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1-3, wherein X is –O–.

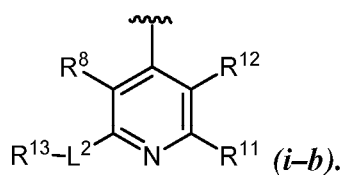
5. The compound of any one of claims 1-3, wherein X is –S–.

6. The compound of any one of claims 1-3, wherein X is $-\text{CH}_2-$.

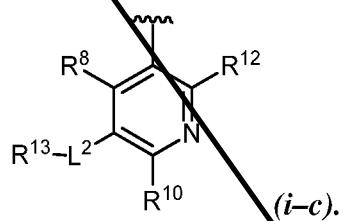
7. The compound of any one of claims 1-6, wherein Ring HET is:



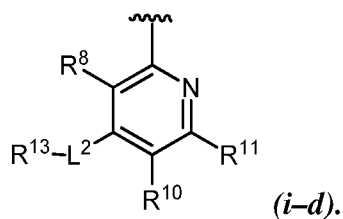
8. The compound of any one of claims 1-6, wherein Ring HET is:



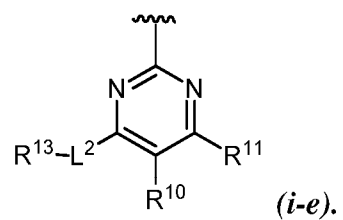
9. The compound of any one of claims 1-6, wherein Ring HET is:



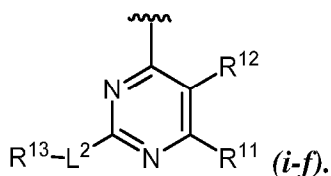
10. The compound of any one of claims 1-6, wherein Ring HET is:



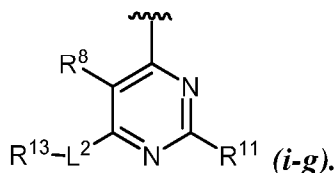
11. The compound of any one of claims 1-6, wherein Ring HET is:



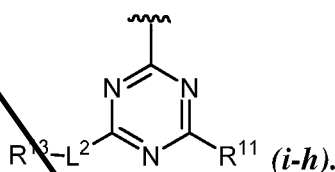
12. The compound of any one of claims 1-6, wherein Ring HET is:



13. The compound of any one of claims 1-6, wherein Ring HET is:



14. The compound of any one of claims 1-6, wherein Ring HET is:



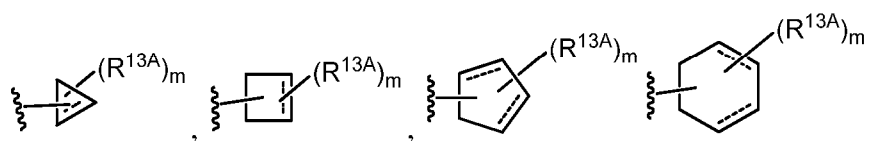
15. The compound of any one of claims 1-14, wherein R¹ is hydrogen, methyl, ethyl, n-propyl, isopropyl, or cyclopropyl.

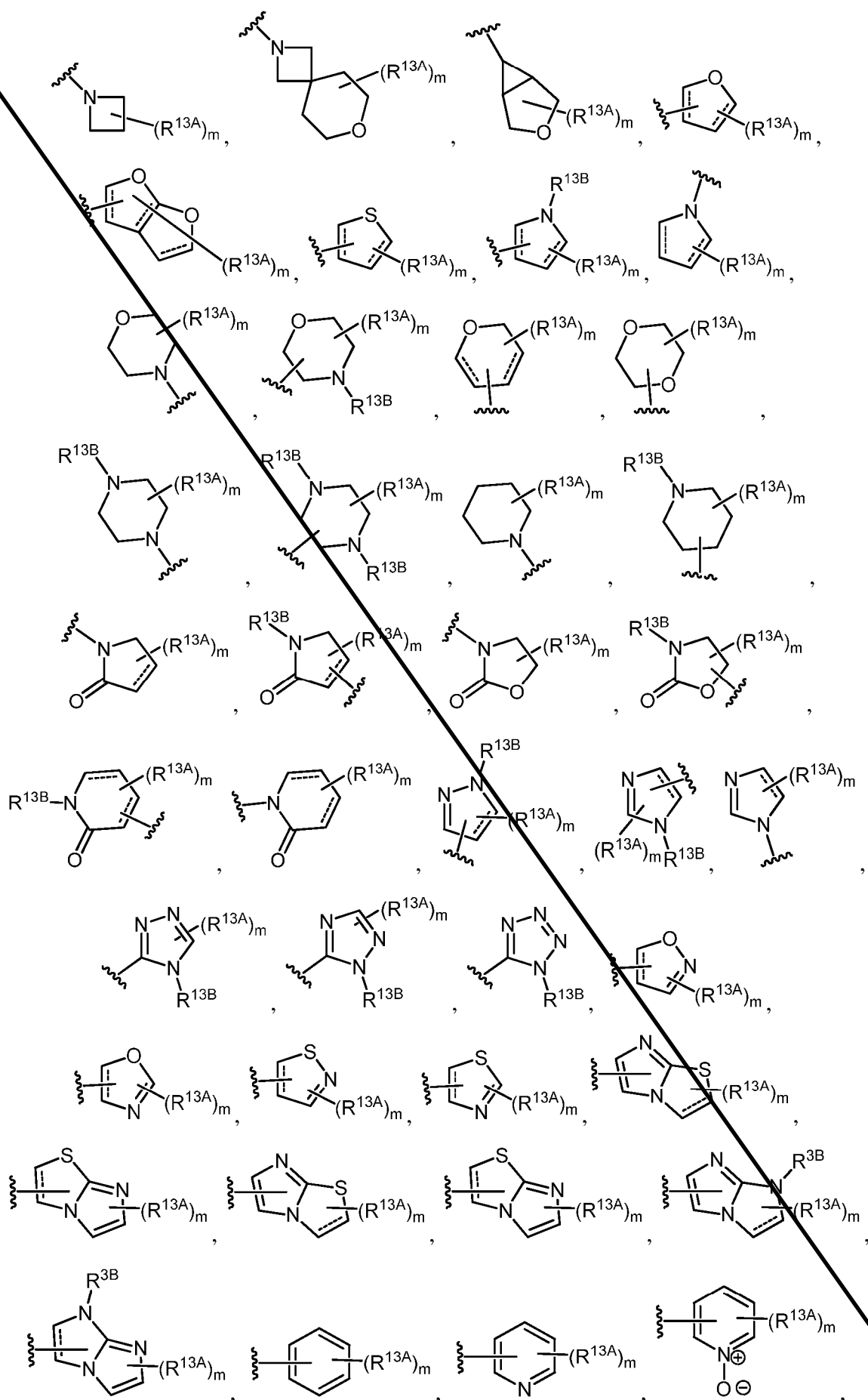
16. The compound of any one of claims 1-15, wherein R^{2a}, R^{2c}, and R^{2d} are hydrogen.

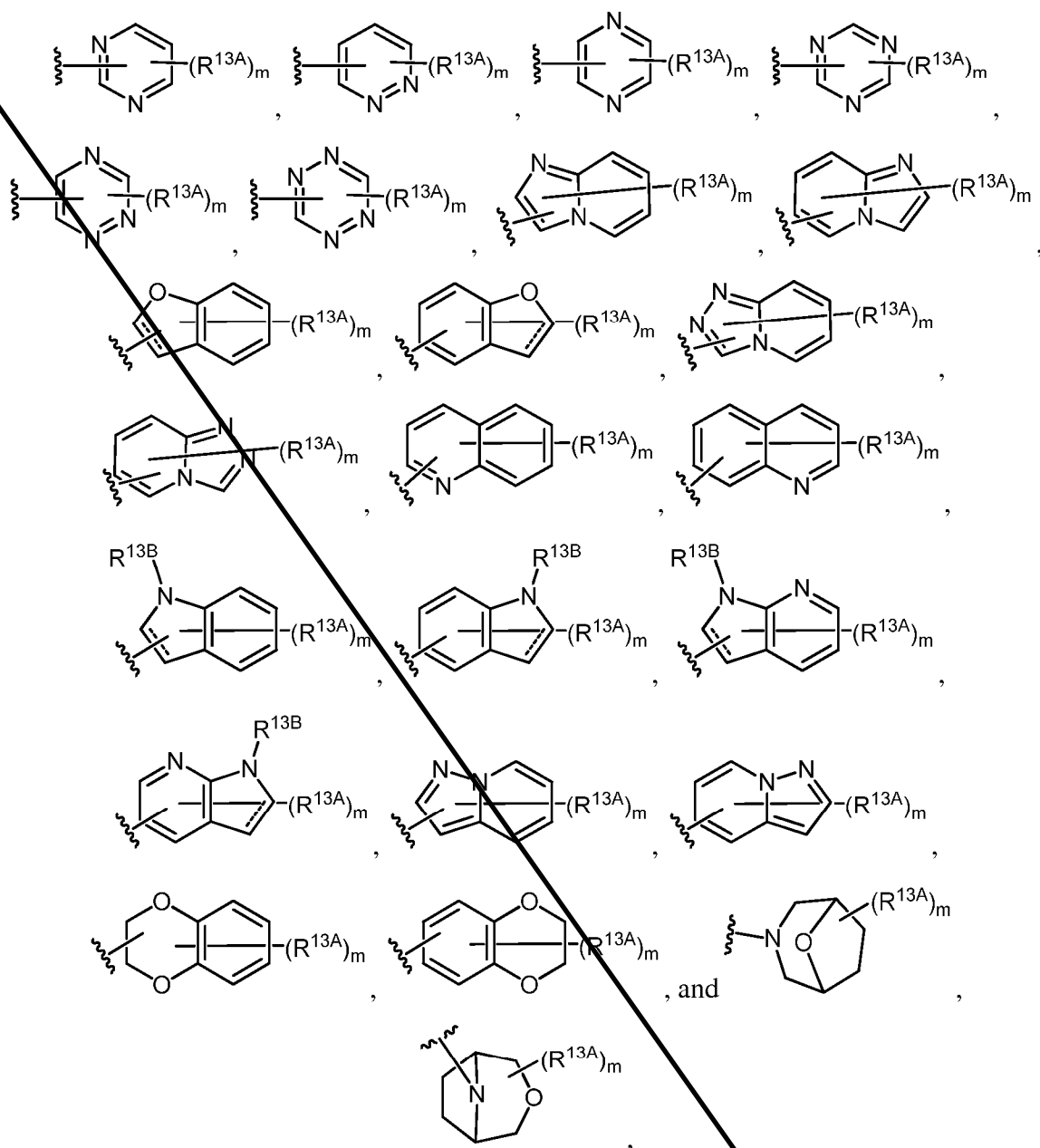
17. The compound of any one of claims 1-16, wherein R^{2b} is halogen or -OR^{A2}.

18. The compound of any one of claims 1-17, wherein L² is a bond, -N(R^L)-, -NR^LC(O)O-, -NR^LC(O)N(R^L)-, -N(R^L)-, -N(R^L)SO₂N(R^L)-, -NR^L-(CH₂)_x-C(O)O-, -NR^L-(CH₂)_x-O-, -NR^LC(O)N(R^L)-, -NR^L-(CH₂)_x-, -(CH₂)_x-NR^L-, -NR^LC(O)O(CH₂)_x-, -NR^LC(O)NR^L(CH₂)_x-, or -NR^L(CH₂)_xNR^LC(O)-.

19. The compound of any one of claims 1-18, wherein R¹³ is selected from the group consisting of:







wherein:

each instance of $\equiv$ independently represents a single or double bond;

m is 0, 1, 2, or 3;

each instance of R^{13A} is independently hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, sulfonyl, sulfinyl, -CN, -NO₂, halogen, optionally substituted alkyl, or two R^{13A} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring, or R^{13A} and R^{13B} group are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring; and

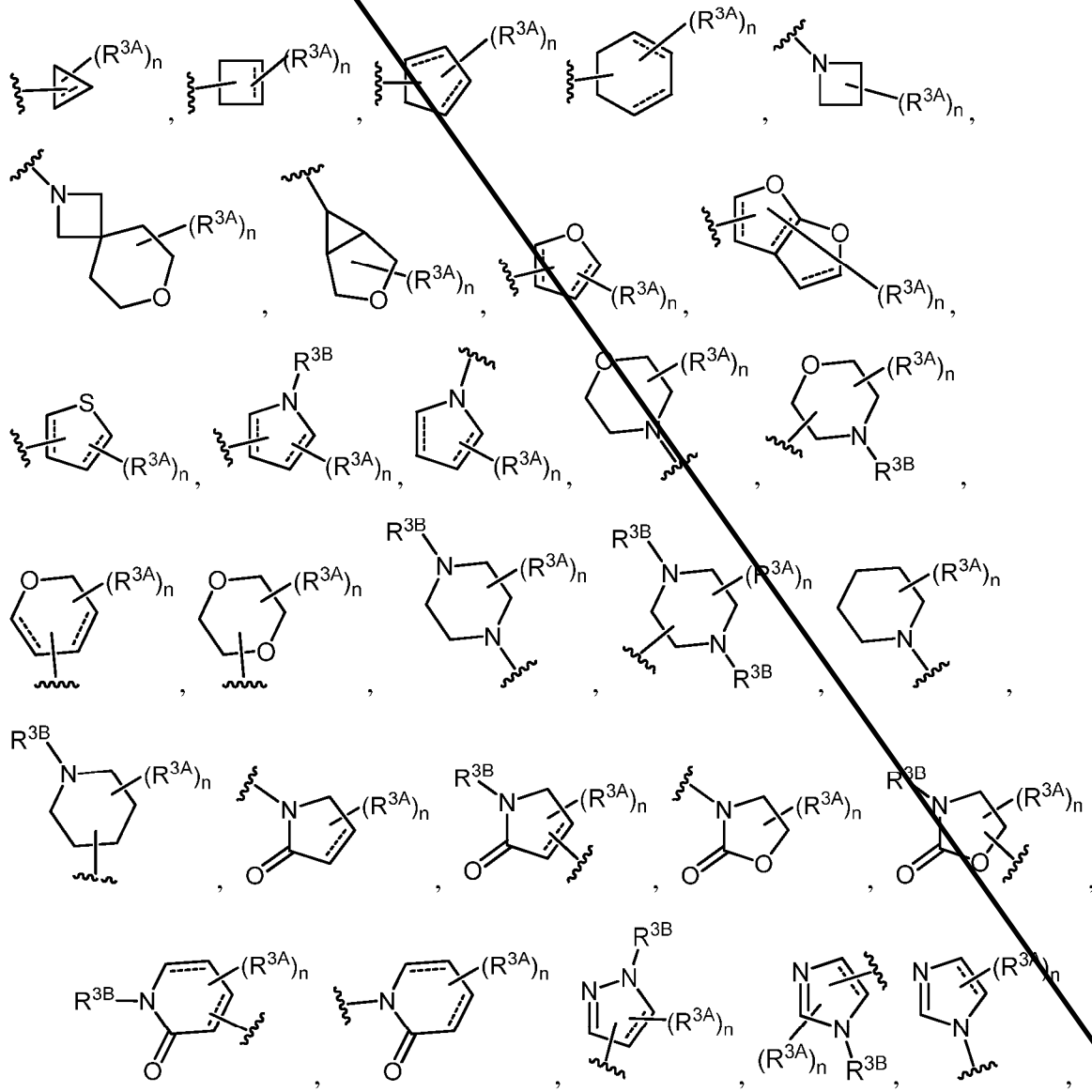
R^{13B} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group.

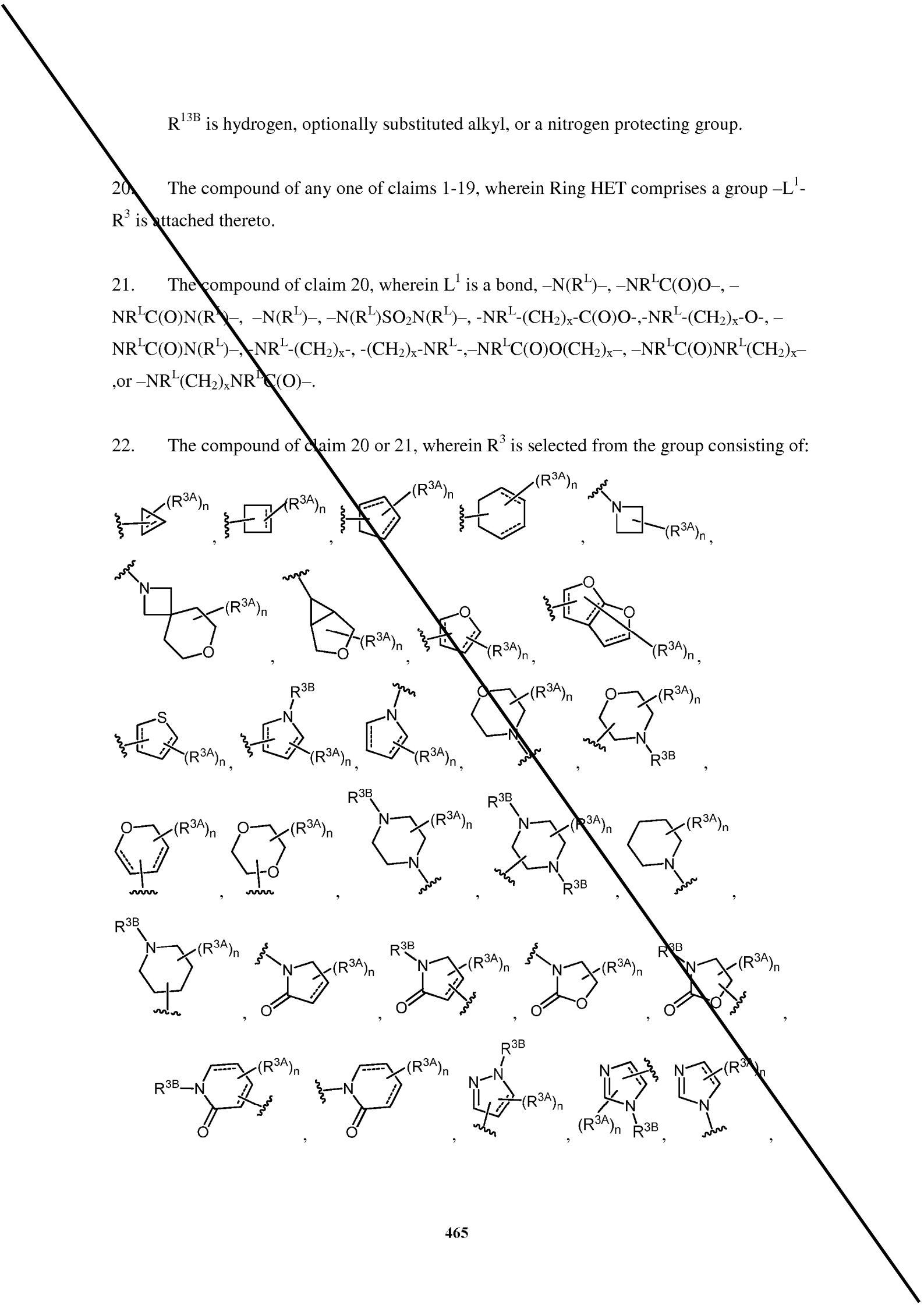
20. The compound of any one of claims 1-19, wherein Ring HET comprises a group $-L^1-$ R^3 is attached thereto.

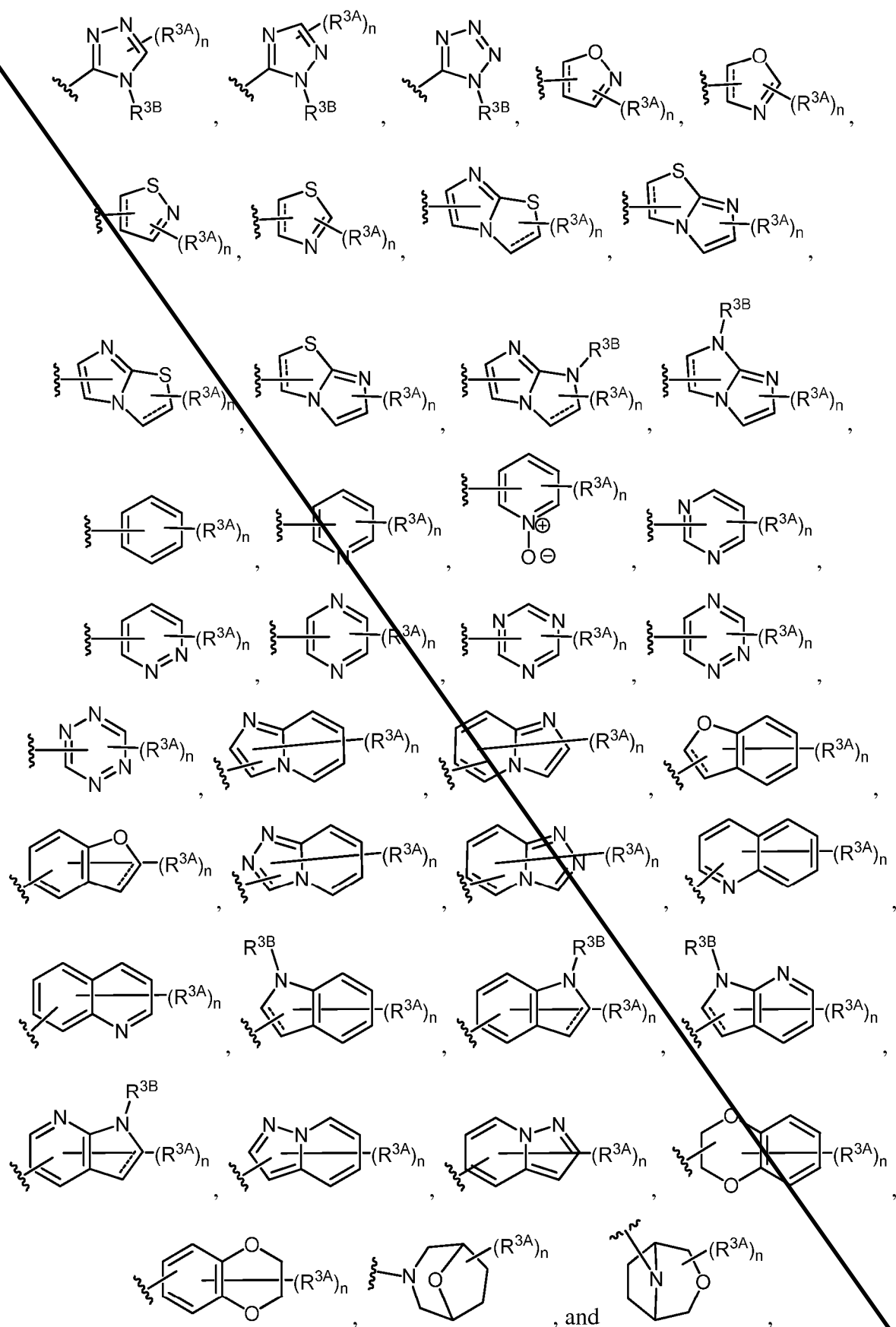
21. The compound of claim 20, wherein L^1 is a bond, $-N(R^L)-$, $-NR^L C(O)O-$, $-NR^L C(O)N(R^L)-$, $-N(R^L)-$, $-N(R^L)SO_2N(R^L)-$, $-NR^L-(CH_2)_x-C(O)O-$, $-NR^L-(CH_2)_x-O-$, $-NR^L C(O)N(R^L)-$, $-NR^L-(CH_2)_x-$, $-(CH_2)_x-NR^L-$, $-NR^L C(O)O(CH_2)_x-$, $-NR^L C(O)NR^L(CH_2)_x-$, or $-NR^L(CH_2)_xNR^L C(O)-$.

22. The compound of claim 20 or 21, wherein R^3 is selected from the group consisting of:

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- R^{13B} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group.
20. The compound of any one of claims 1-19, wherein Ring HET comprises a group $-L^1-$ R^3 is attached thereto.
21. The compound of claim 20, wherein L^1 is a bond, $-N(R^L)-$, $-NR^L C(O)O-$, $-NR^L C(O)N(R^L)-$, $-N(R^L)-$, $-N(R^L)SO_2N(R^L)-$, $-NR^L-(CH_2)_x-C(O)O-$, $-NR^L-(CH_2)_x-O-$, $-NR^L C(O)N(R^L)-$, $-NR^L-(CH_2)_x-$, $-(CH_2)_x-NR^L-$, $-NR^L C(O)O(CH_2)_x-$, $-NR^L C(O)NR^L(CH_2)_x-$, or $-NR^L(CH_2)_xNR^L C(O)-$.
22. The compound of claim 20 or 21, wherein R^3 is selected from the group consisting of:
- 
- 465





n is 0, 1, 2, or 3;

each instance of R^{3A} is independently hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, sulfonyl, sulfinyl, -CN, -NO₂, halogen, optionally substituted alkyl, or two R^{3A} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring, or R^{3A} and R^{3B} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring; and

R^{3B} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group.

23. The compound of claim 1, wherein the compound is selected from the group consisting of compounds depicted in Tables 1A and 2, or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a compound of any one of claims 1–23 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

25. A kit or packaged pharmaceutical comprising a compound of any one of claims 1–23 or a pharmaceutically acceptable salt thereof, and instructions for use thereof.

26. A method of treating a CARM1-mediated disorder, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1–23, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 24.

27. The method of claim 26, wherein the disorder is a proliferative disorder.

28. The method of claim 27, wherein the disorder is cancer.

29. The method of claim 28, wherein the cancer is associated with E2F1 upregulation.

30. The method of claim 27 or 28, wherein the cancer is associated with aberrant CARM1 activity.

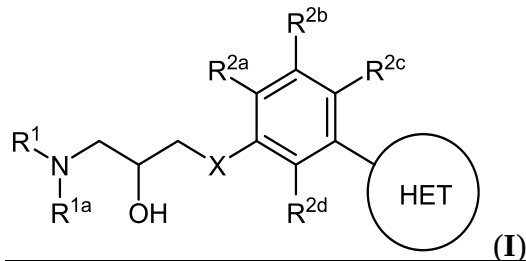
31. The method of any one of claims 28–30, wherein the cancer is breast cancer, prostate cancer, or colorectal cancer.

32. The method of any one of claims 28-30, wherein the cancer is ER α -dependent breast cancer.
33. The method of any one of claims 28-30, wherein the cancer is castration-resistant prostate cancer.
34. The method of any one of claims 28-30, wherein the cancer is colorectal cancer associated with dysregulated WNT/ β -catenin signaling.
35. The method of claim 26, wherein the disorder is a metabolic disorder.

Claims

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

X is -O-, -S-, or -CH₂-;

R¹ and R^{1a} are each independently hydrogen or optionally substituted C₁₋₄ aliphatic, or R¹ and R^{1a} may be joined to form a substituted or unsubstituted heterocyclic, or substituted or unsubstituted heteroaryl ring;

each of R^{2a}, R^{2b}, R^{2c}, and R^{2d} is independently hydrogen, halogen, -CN, -NO₂, -C(=O)R^{A2}, -C(=O)OR^{A2}, -C(=O)N(R^{A2})₂, -OR^{A2}, -SR^{A2}, -N(R^{A2})₂, -S(=O)R^{A2}, -S(=O)₂R^{A2}, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, wherein each instance of R^{A2} is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R^{A2} groups attached to the same nitrogen atom are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring;

Ring HET is a 6-membered monocyclic heteroaryl ring system of the Formula:

S(O)₂O-, -SO₂-, -N(R^L)SO₂-, -SO₂N(R^L)-, and -N(R^L)SO₂N(R^L)- is optionally and independently present between two carbon atoms of the hydrocarbon chain, and optionally and independently present at one or both ends of the hydrocarbon chain;

each R^L is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group, or R^L and R³ taken together form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring, or R^L and R¹³ taken together form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring;

R³ is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, provided when R³ is hydrogen, then L¹ is not a bond; and

R¹³ is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl,
wherein, and unless otherwise specified,

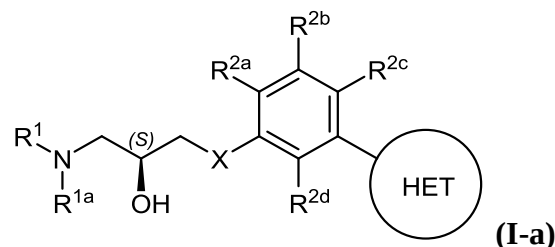
heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

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

aryl refers to a radical of a monocyclic or polycyclic 4n+2 aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

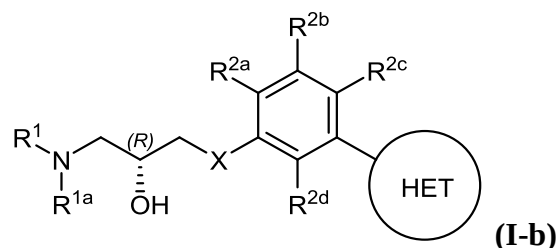
heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur.

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



or a pharmaceutically acceptable salt thereof.

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



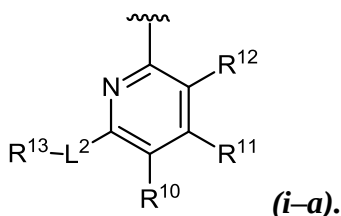
or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1-3, wherein X is $-O-$.

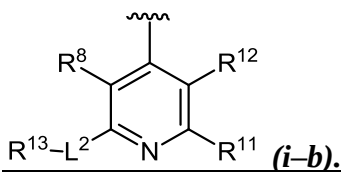
5. The compound of any one of claims 1-3, wherein X is $-S-$.

6. The compound of any one of claims 1-3, wherein X is $-CH_2-$.

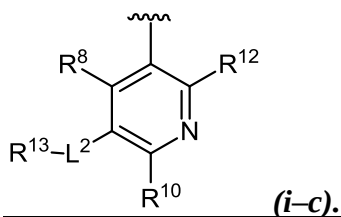
7. The compound of any one of claims 1-6, wherein Ring HET is:



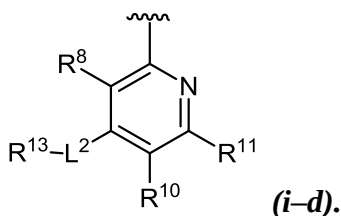
8. The compound of any one of claims 1-6, wherein Ring HET is:



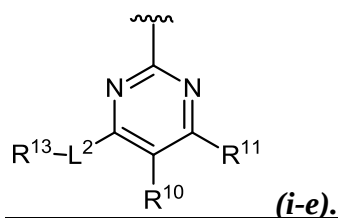
9. The compound of any one of claims 1-6, wherein Ring HET is:



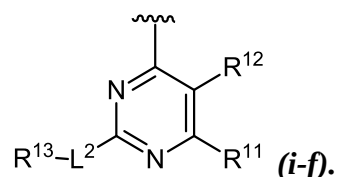
10. The compound of any one of claims 1-6, wherein Ring HET is:



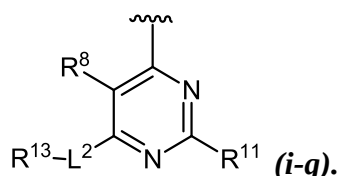
11. The compound of any one of claims 1-6, wherein Ring HET is:



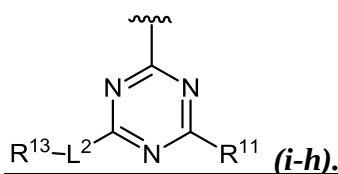
12. The compound of any one of claims 1-6, wherein Ring HET is:



13. The compound of any one of claims 1-6, wherein Ring HET is:



14. The compound of any one of claims 1-6, wherein Ring HET is:



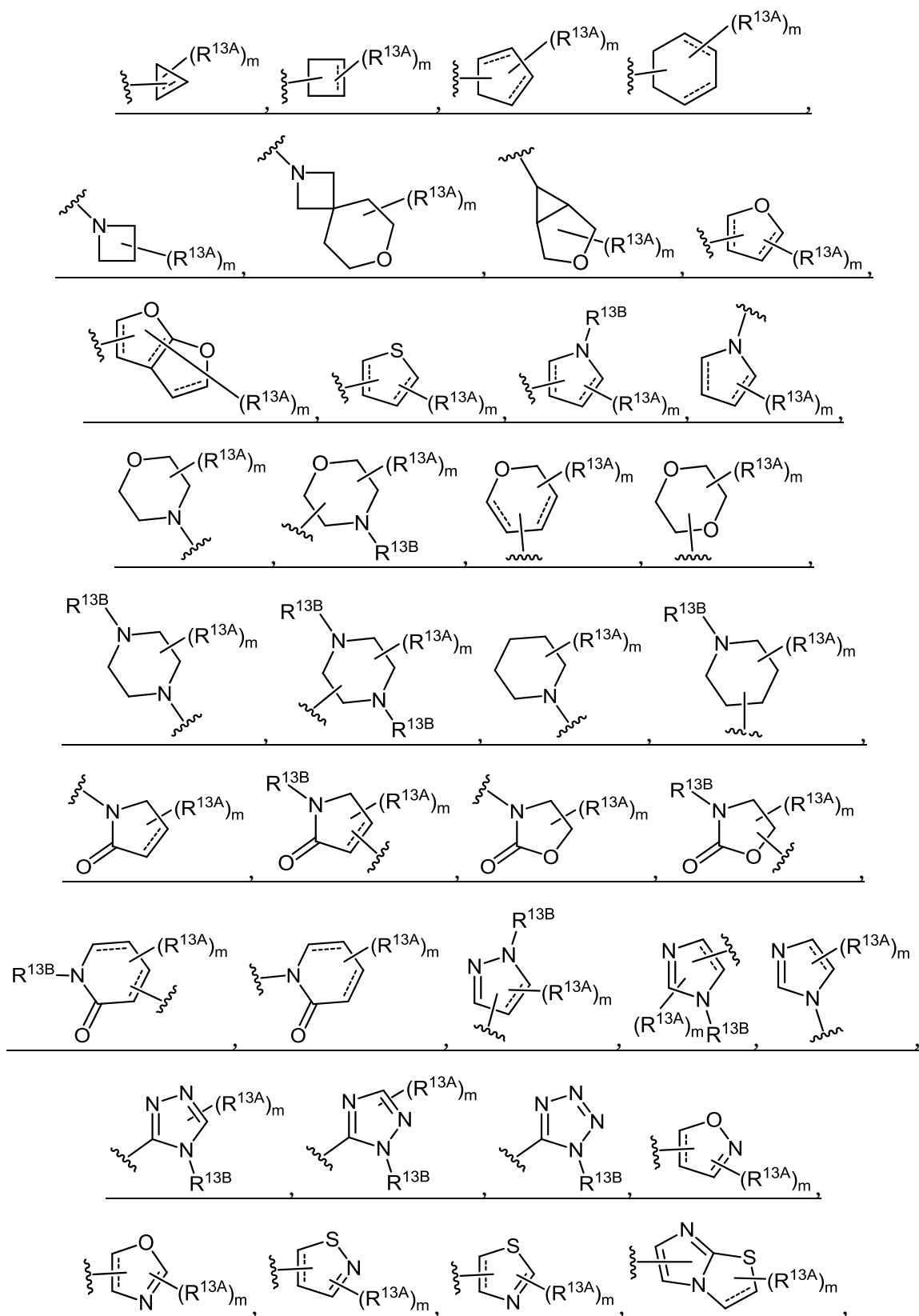
15. The compound of any one of claims 1-14, wherein R¹ is hydrogen, methyl, ethyl, n-propyl, isopropyl, or cyclopropyl.

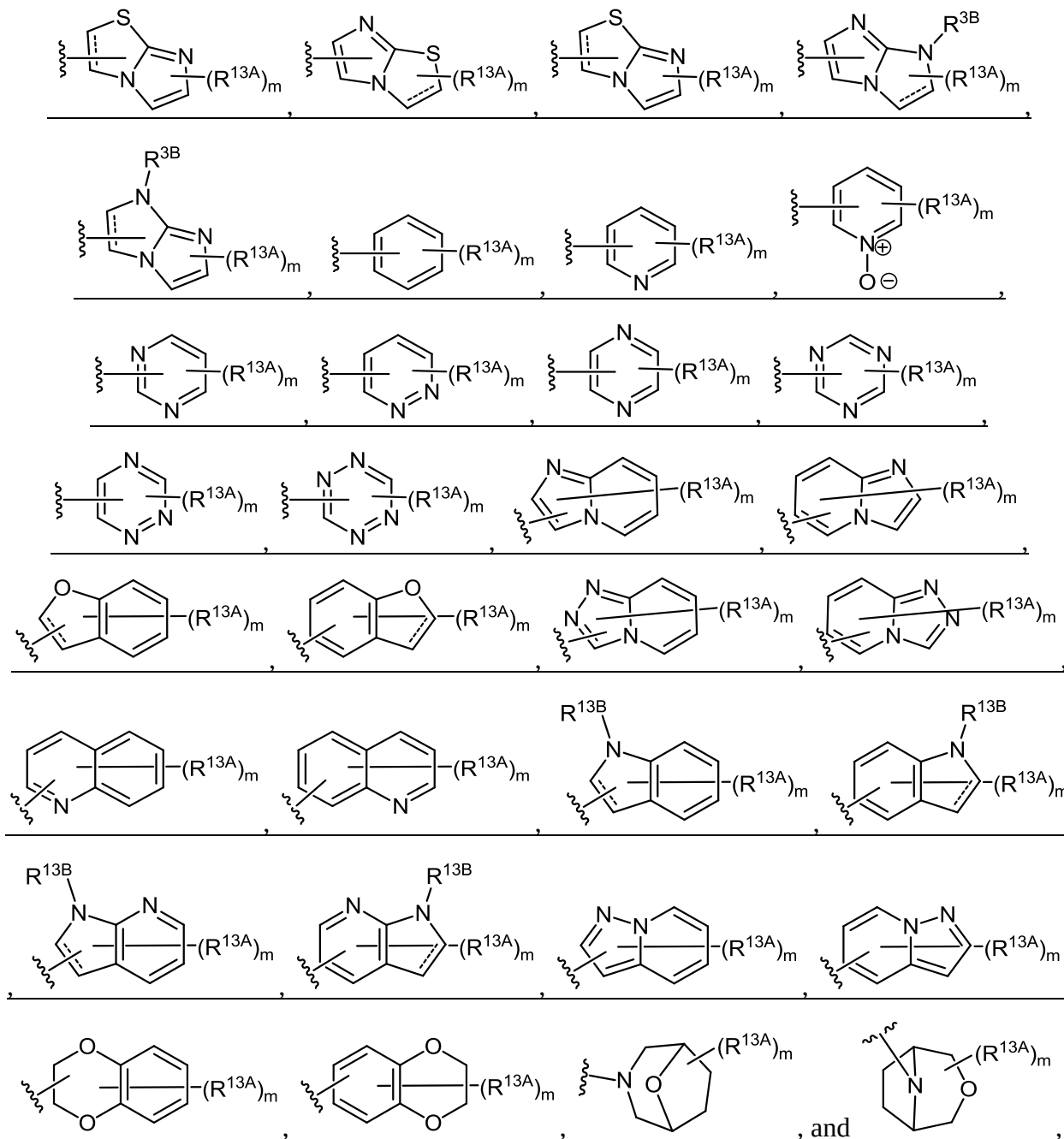
16. The compound of any one of claims 1-15, wherein R^{2a}, R^{2b}, and R^{2d} are hydrogen.

17. The compound of any one of claims 1-15, wherein at least one of R^{2a}, R^{2b}, R^{2c}, and R^{2d} is halo.

18. The compound of any one of claims 1-17, wherein L² is a bond, -N(R^L)-, -NR^LC(O)O-, -NR^LC(O)N(R^L)-, -N(R^L)-, -N(R^L)SO₂N(R^L)-, -NR^L-(CH₂)_x-C(O)O-, -NR^L-(CH₂)_x-O-, -NR^LC(O)N(R^L)-, -NR^L-(CH₂)_x-, -(CH₂)_x-NR^L-, -NR^LC(O)O(CH₂)_x-, -NR^LC(O)NR^L(CH₂)_x-, or -NR^L(CH₂)_xNR^LC(O)-, wherein x is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

19. The compound of any one of claims 1-18, wherein R¹³ is selected from the group consisting of:





wherein:

each instance of ----- independently represents a single or double bond;

m is 0, 1, 2, or 3;

each instance of R^{13A} is independently hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, sulfonyl, sulfinyl, -CN, -NO₂, halogen, optionally substituted alkyl, or two R^{13A} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted

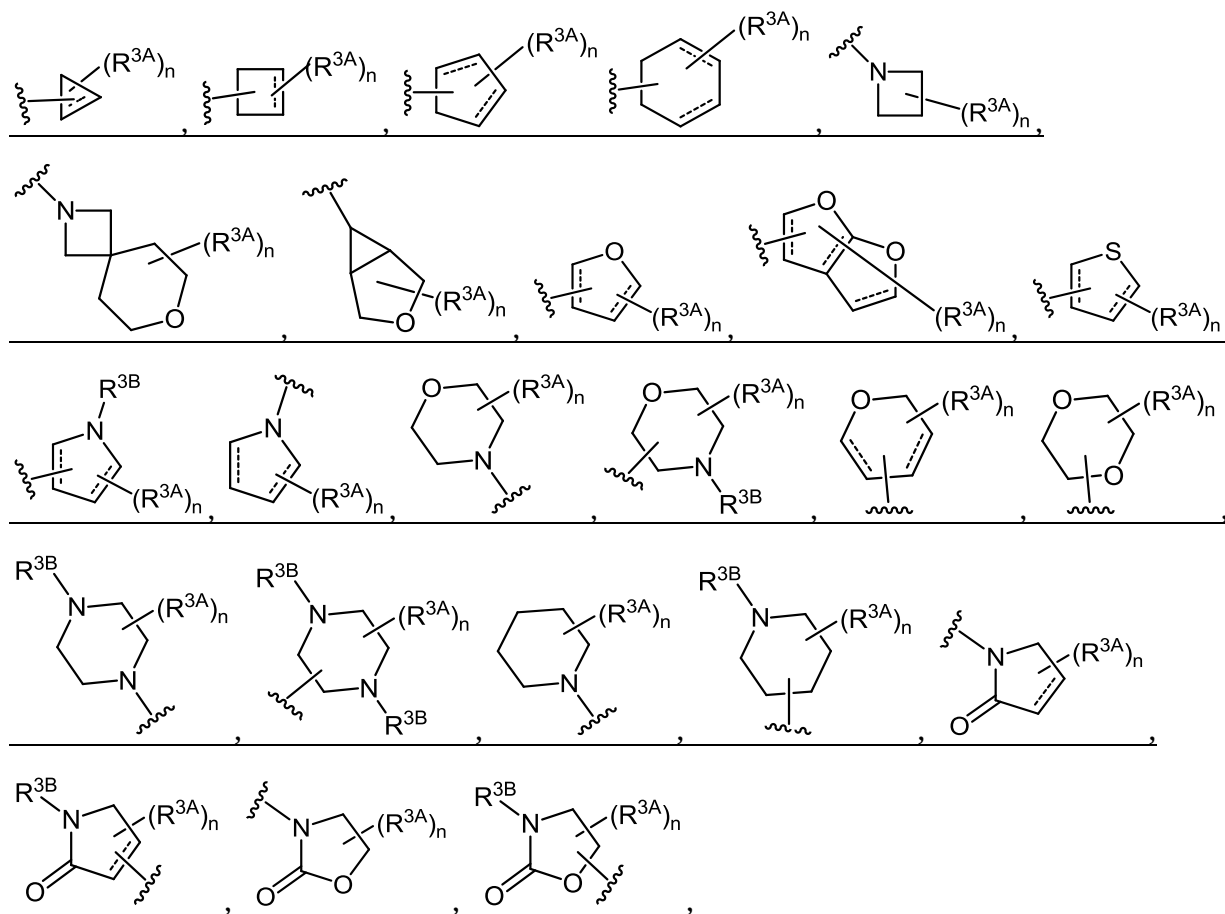
heteroaryl ring, or R^{13A} and R^{13B} group are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring; and

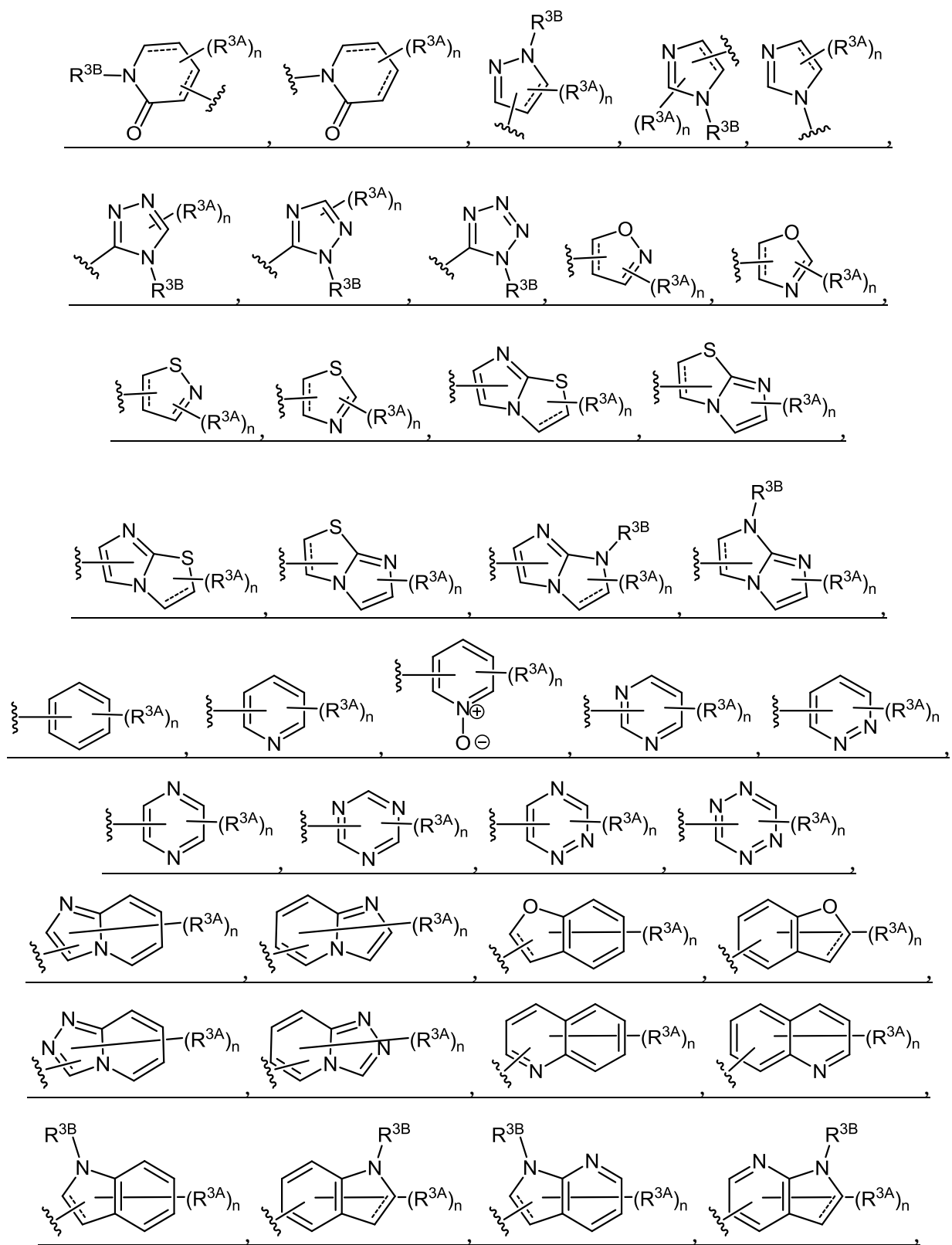
R^{3B} and R^{13B} are independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group.

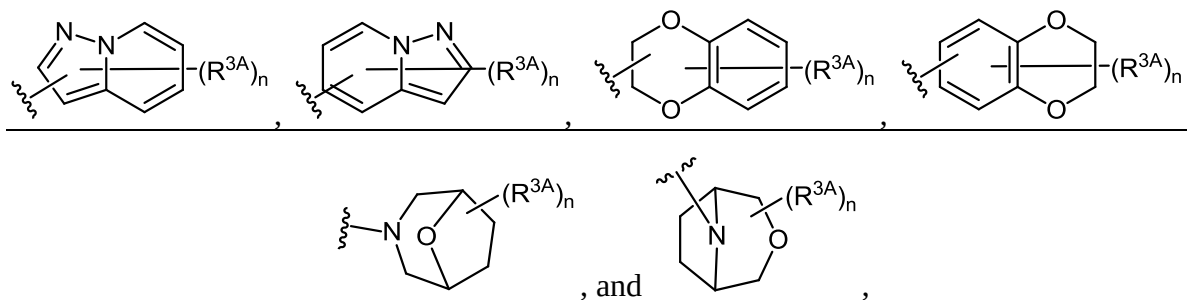
20. The compound of any one of claims 1-19, wherein Ring HET comprises a group $-L^1-R^3$ attached thereto.

21. The compound of claim 20, wherein L^1 is a bond, $-N(R^L)-$, $-NR^LC(O)O-$, $-NR^LC(O)N(R^L)-$, $-N(R^L)-$, $-N(R^L)SO_2N(R^L)-$, $-NR^L-(CH_2)_x-C(O)O-$, $-NR^L-(CH_2)_x-O-$, $-NR^LC(O)N(R^L)-$, $-NR^L-(CH_2)_x-$, $-(CH_2)_x-NR^L-$, $-NR^LC(O)O(CH_2)_x-$, $-NR^LC(O)NR^L(CH_2)_x-$, or $-NR^L(CH_2)_xNR^LC(O)-$, wherein x is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

22. The compound of claim 20 or 21, wherein R^3 is selected from the group consisting of:







wherein:

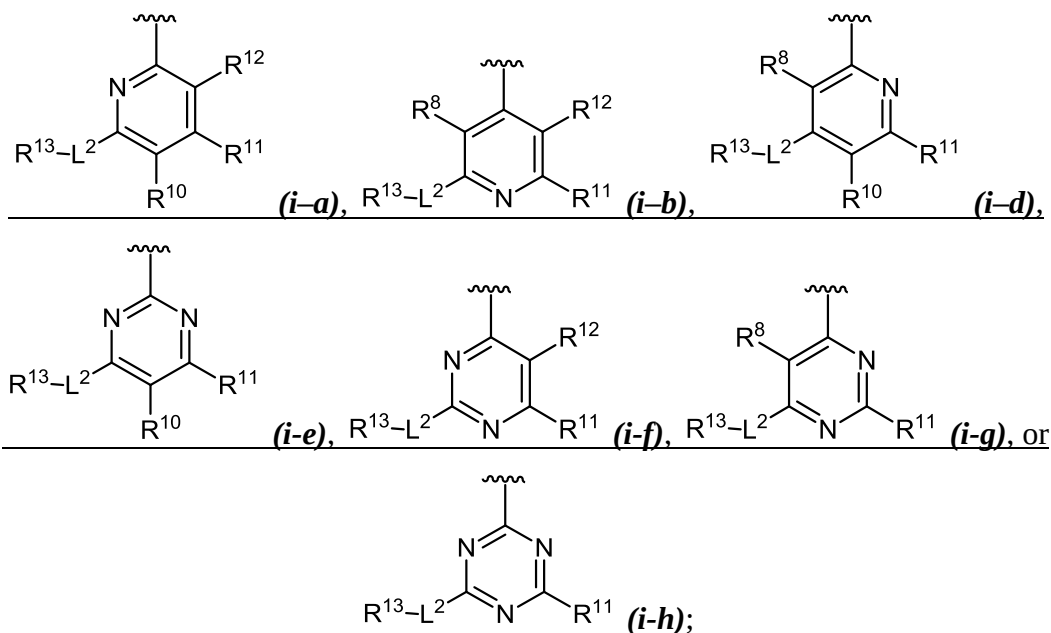
each instance of --- independently represents a single or double bond;

n is 0, 1, 2, or 3;

each instance of R^{3A} is independently hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, sulfonyl, sulfinyl, -CN, -NO₂, halogen, optionally substituted alkyl, or two R^{3A} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring, or R^{3A} and R^{3B} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring; and

R^{3B} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group.

23. The compound of any one of claims 1-6 or 15-22, wherein Ring HET is a 6-membered monocyclic heteroaryl ring system of the Formula:

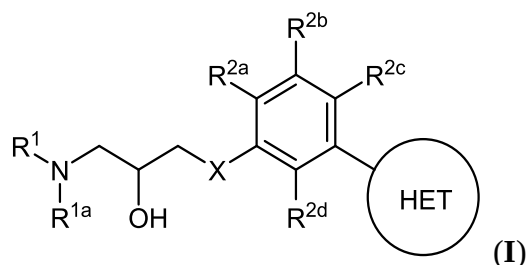


each instance of R^8 , R^{10} , and R^{12} is independently selected from the group consisting of hydrogen, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{R}'$, $-\text{C}(=\text{O})\text{OR}'$, $-\text{C}(=\text{O})\text{N}(\text{R}')_2$, and optionally substituted alkyl;

R^{11} is $-\text{L}^1\text{-R}^3$; and

R^3 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl.

24. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof;

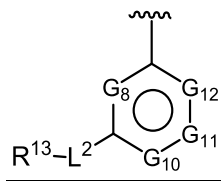
wherein:

X is $-\text{O}-$, $-\text{S}-$, or $-\text{CH}_2-$;

R^1 and R^{1a} are each independently hydrogen or optionally substituted C_{1-4} aliphatic, or R^1 and R^{1a} may be joined to form a substituted or unsubstituted heterocyclic, or substituted or unsubstituted heteroaryl ring;

each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(=\text{O})\text{R}^{\text{A}2}$, $-\text{C}(=\text{O})\text{OR}^{\text{A}2}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{A}2})_2$, $-\text{OR}^{\text{A}2}$, $-\text{SR}^{\text{A}2}$, $-\text{N}(\text{R}^{\text{A}2})_2$, $-\text{S}(=\text{O})\text{R}^{\text{A}2}$, $-\text{S}(=\text{O})_2\text{R}^{\text{A}2}$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, wherein each instance of $R^{\text{A}2}$ is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two $R^{\text{A}2}$ groups attached to the same nitrogen atom are joined to form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring;

Ring HET is a 6-membered monocyclic heteroaryl ring system of the Formula:



wherein:

G₈ is C–R⁸ or N;

G₁₀ is C–R¹⁰ or N;

G₁₁ is C–R¹¹ or N;

G₁₂ is C–R¹² or N;

provided at least one instance of G₈, G₁₀, G₁₁, or G₁₂ is N;

each instance of R⁸, R¹⁰, R¹¹, and R¹² is independently selected from the group consisting of hydrogen, halo, –CN, –NO₂, –C(=O)R', –C(=O)OR', –C(=O)N(R')₂, optionally substituted alkyl, optionally substituted C₃₋₄cycloalkyl, and –L¹-R³;

each instance of R' is independently hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R' groups attached to the same nitrogen are joined to form an optionally substituted heterocyclyl ring or optionally substituted heteroaryl ring;

each instance of L¹ and L² is independently a bond, –O–, –N(R^L)–, –S–, –C(O)–, –C(O)O–, –C(O)S–, –C(O)N(R^L)–, –C(O)N(R^L)N(R^L)–, –OC(O)–, –OC(O)N(R^L)–, –NR^LC(O)–, –NR^LC(O)N(R^L)–, –NR^LC(O)N(R^L)N(R^L)–, –NR^LC(O)O–, –SC(O)–, –C(=NR^L)–, –C(=NNR^L)–, –C(=NOR^L)–, –C(=N R^L)N(R^L)–, –NR^LC(=NR^L)–, –C(S)–, –C(S)N(R^L)–, –NR^LC(S)–, –S(O)–, –OS(O)₂–, –S(O)₂O–, –SO₂–, –N(R^L)SO₂–, –SO₂N(R^L)–, –N(R^L)SO₂N(R^L)–, or an optionally substituted C₁₋₁₀ saturated or unsaturated hydrocarbon chain, wherein one or more moieties selected from the group consisting of –O–, –N(R^L)–, –S–, –C(O)–, –C(O)O–, –C(O)S–, –C(O)N(R^L)–, –C(O)N(R^L)N(R^L)–, –OC(O)–, –OC(O)N(R^L)–, –NR^LC(O)–, –NR^LC(O)N(R^L)–, –NR^LC(O)N(R^L)N(R^L)–, –NR^LC(O)O–, –SC(O)–, –C(=NR^L)–, –C(=NNR^L)–, –C(=NOR^L)–, –C(=N R^L)N(R^L)–, –NR^LC(=NR^L)–, –C(S)–, –C(S)N(R^L)–, –NR^LC(S)–, –S(O)–, –OS(O)₂–, –S(O)₂O–, –SO₂–, –N(R^L)SO₂–, –SO₂N(R^L)–, and –N(R^L)SO₂N(R^L)– is optionally and independently present between two carbon atoms of the hydrocarbon chain, and optionally and independently present at one or both ends of the hydrocarbon chain;

each R^L is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group, or R^L and R^3 taken together form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring, or R^L and R^{13} taken together form an optionally substituted heterocyclyl or optionally substituted heteroaryl ring;

R^3 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{aa}, -N(R^{bb})₂, -SH, -SR^{aa}, -C(=O)R^{aa}, -CO₂H, -CHO, -CO₂R^{aa}, -OC(=O)R^{aa}, -OCO₂R^{aa}, -C(=O)N(R^{bb})₂, -OC(=O)N(R^{bb})₂, C₁₋₄ alkyl, C₁₋₄ perhaloalkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl, provided when R^3 is hydrogen, then L^1 is not a bond; and

R^{13} is optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{aa}, -N(R^{bb})₂, -SH, -SR^{aa}, -C(=O)R^{aa}, -CO₂H, -CHO, -CO₂R^{aa}, -OC(=O)R^{aa}, -OCO₂R^{aa}, -C(=O)N(R^{bb})₂, -OC(=O)N(R^{bb})₂, C₁₋₄ alkyl, C₁₋₄ perhaloalkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

wherein:

each instance of R^{aa} is, independently, C₁₋₄ alkyl; and

each instance of R^{bb} is, independently, hydrogen or C₁₋₄ alkyl, or two R^{bb} groups are joined to form a 3-6 membered heterocyclyl or 5-6 membered heteroaryl ring; wherein, and unless otherwise specified,

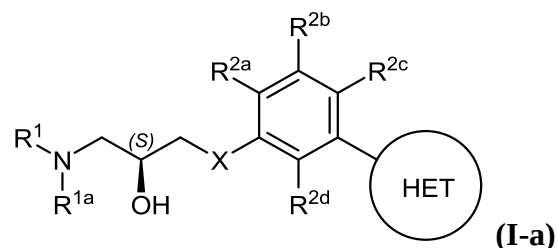
heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

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

aryl refers to a radical of a monocyclic or polycyclic 4n+2 aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

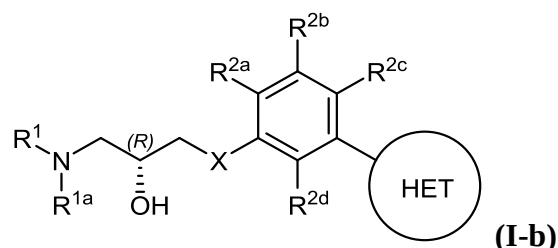
heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur.

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



or a pharmaceutically acceptable salt thereof.

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



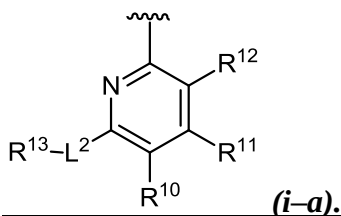
or a pharmaceutically acceptable salt thereof.

27. The compound of any one of claims 24-26, wherein X is -O-.

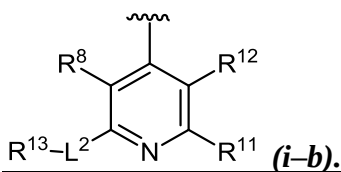
28. The compound of any one of claims 24-26, wherein X is -S-.

29. The compound of any one of claims 24-26, wherein X is -CH₂-.

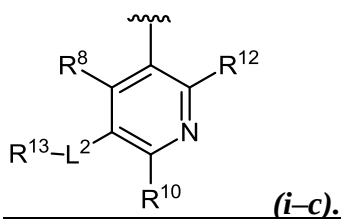
30. The compound of any one of claims 24-30, wherein Ring HET is:



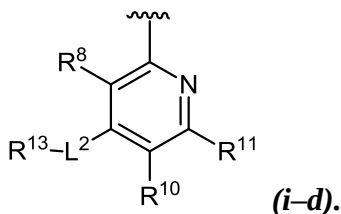
31. The compound of any one of claims 24-30, wherein Ring HET is:



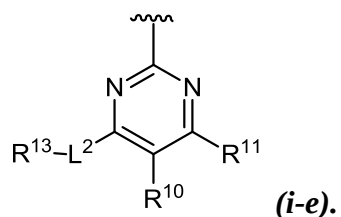
32. The compound of any one of claims 24-30, wherein Ring HET is:



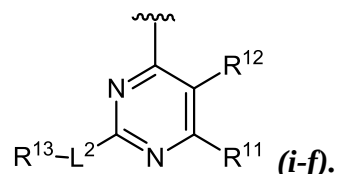
33. The compound of any one of claims 24-30, wherein Ring HET is:



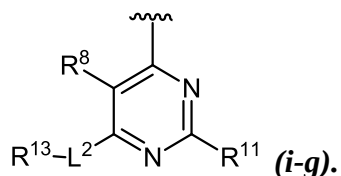
34. The compound of any one of claims 24-30, wherein Ring HET is:



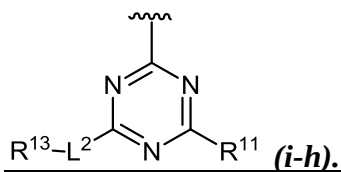
35. The compound of any one of claims 24-30, wherein Ring HET is:



36. The compound of any one of claims 24-30, wherein Ring HET is:



37. The compound of any one of claims 24-30, wherein Ring HET is:



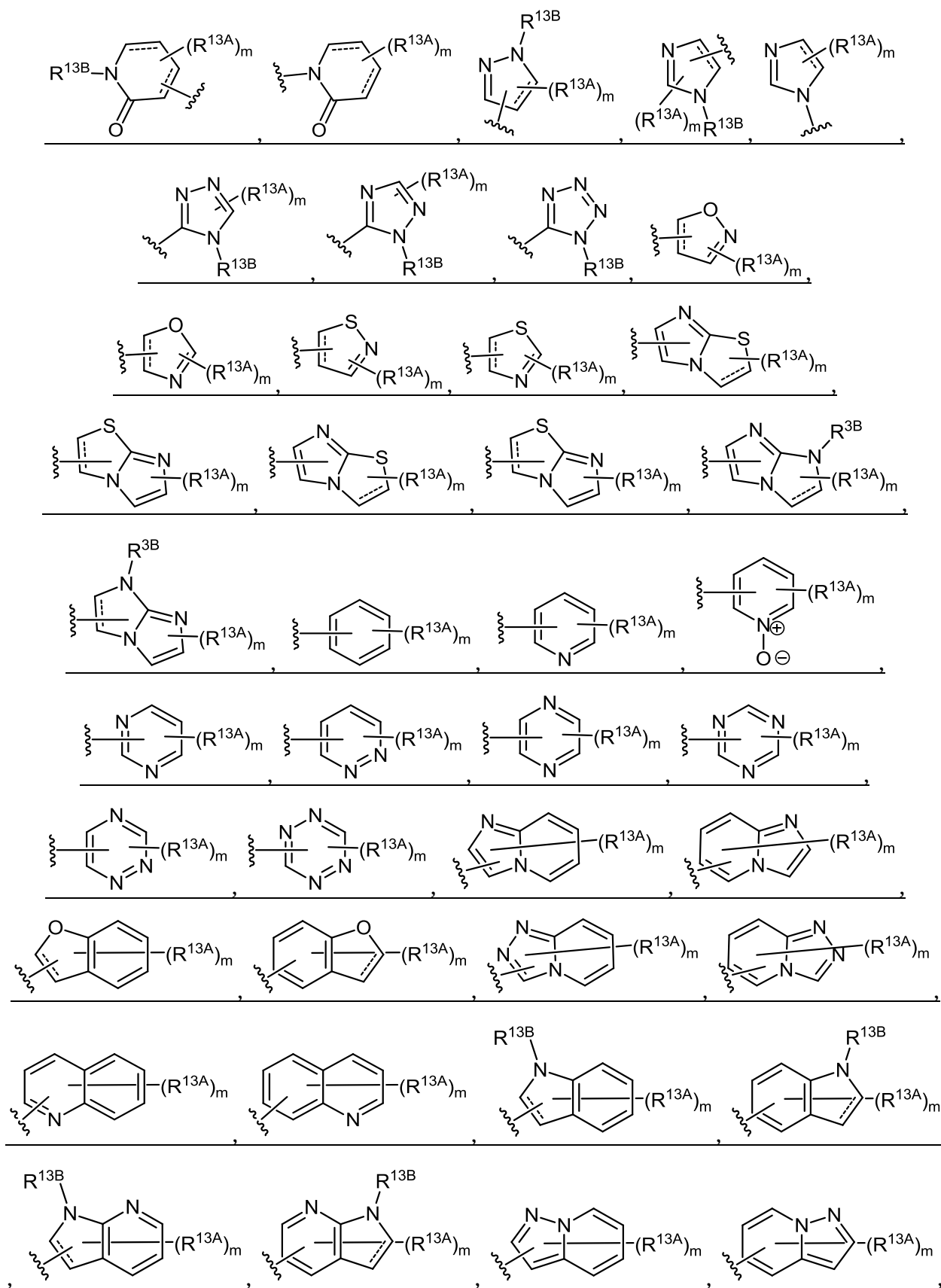
38. The compound of any one of claims 24-37, wherein R¹ is hydrogen, methyl, ethyl, n-propyl, isopropyl, or cyclopropyl.

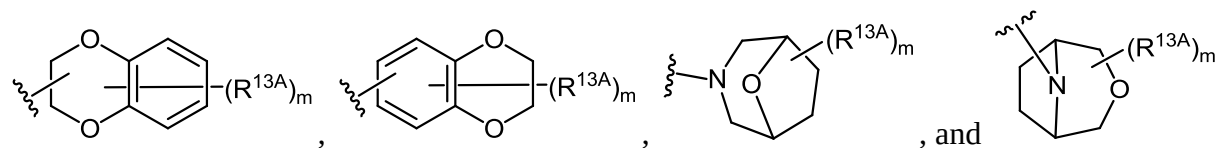
39. The compound of any one of claims 24-38, wherein R^{2a}, R^{2b}, and R^{2d} are hydrogen.

41. The compound of any one of claims 24-40, wherein L² is a bond, -N(R^L)-, -NR^LC(O)O-
, -NR^LC(O)N(R^L)-, -N(R^L)-, -N(R^L)SO₂N(R^L)-, -NR^L-(CH₂)_x-C(O)O-, -NR^L-(CH₂)_x-O-, -
NR^LC(O)N(R^L)-, -NR^L-(CH₂)_x-, -(CH₂)_x-NR^L-, -NR^LC(O)O(CH₂)_x-, -NR^LC(O)NR^L(CH₂)_x-, or
-NR^L(CH₂)_xNR^LC(O)-, wherein x is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

Chemical structures illustrating various substituted heterocyclic systems, including:

- Substituted cyclopropanes, cyclobutanes, cyclopentenes, and cyclohexenes.
- Substituted azetidines, morpholines, and oxazolidinones.
- Substituted pyrrolidines, imidazolidines, and thiazolidines.
- Substituted tetrahydropyranes, tetrahydropyridines, and tetrahydrofurans.
- Substituted piperidines, morpholines, and oxazepanes.
- Substituted pyrrolidines, imidazolidines, and thiazolidines.
- Substituted pyrrolidines, imidazolidines, and thiazolidines.





wherein:

each instance of ----- independently represents a single or double bond;

m is 0, 1, 2, or 3;

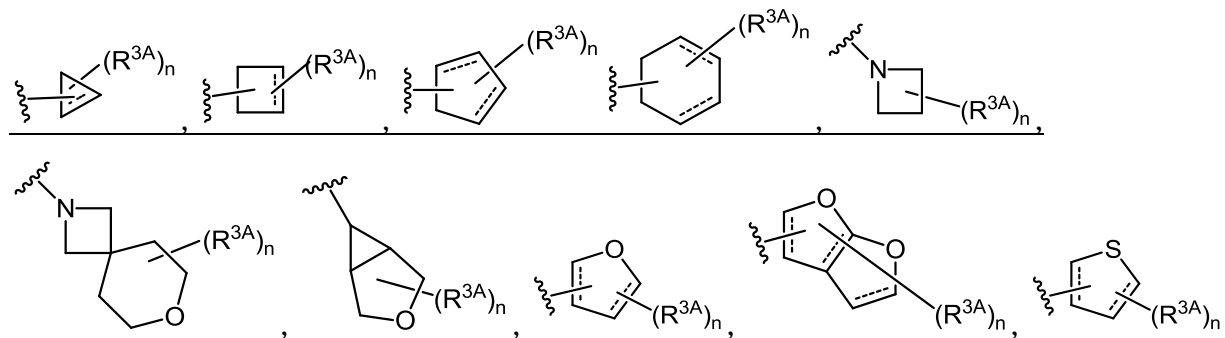
each instance of R^{13A} is independently hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, sulfonyl, sulfinyl, -CN, -NO₂, halogen, or optionally substituted alkyl, or two R^{13A} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring, or R^{13A} and R^{13B} group are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring; and

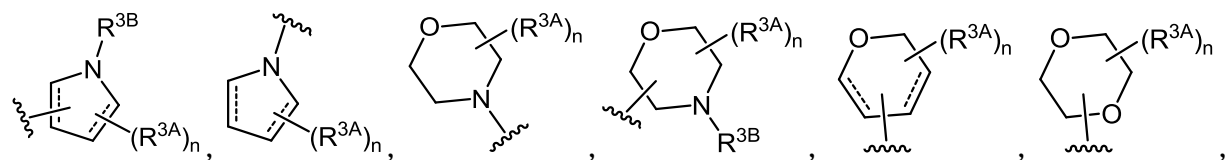
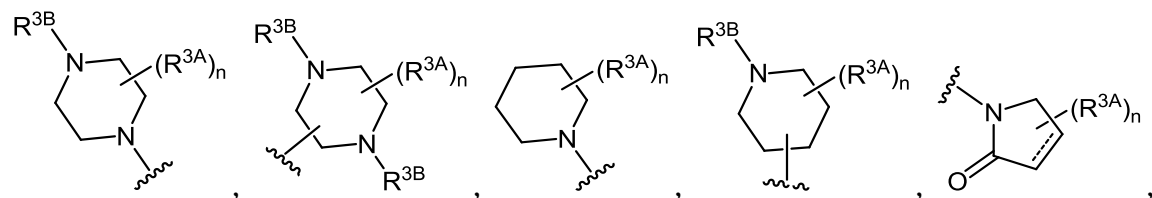
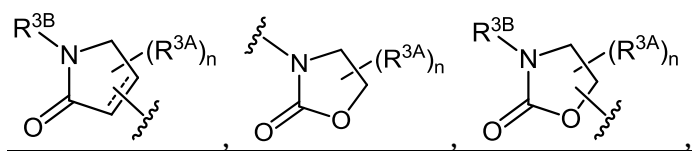
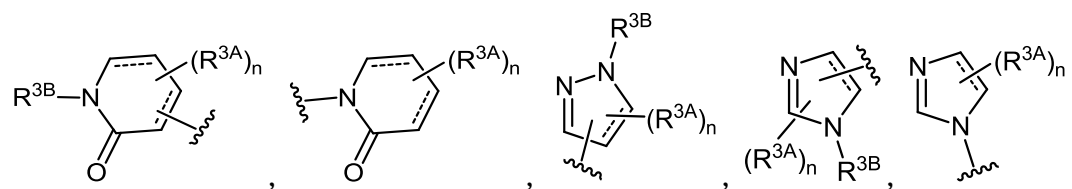
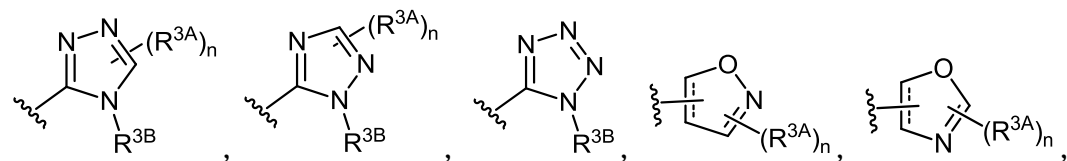
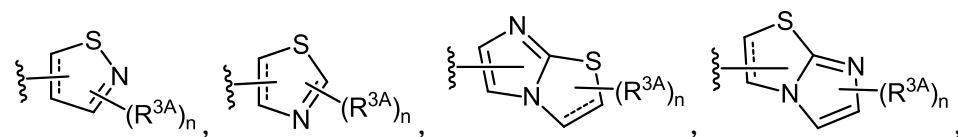
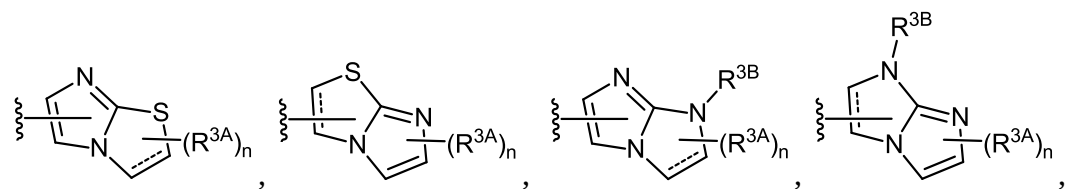
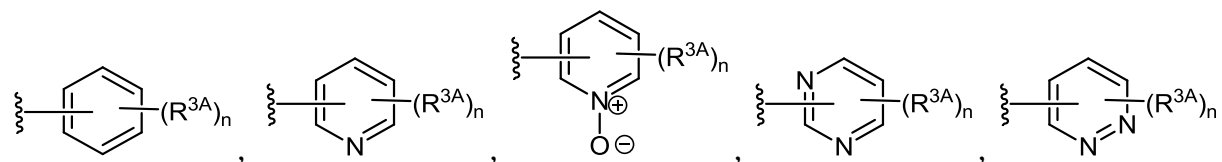
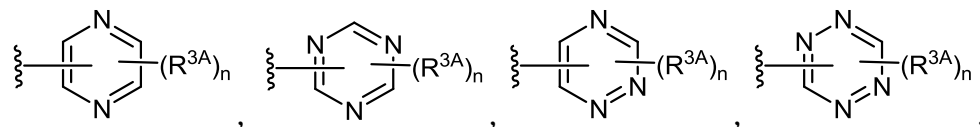
R^{3B} and R^{13B} are independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group.

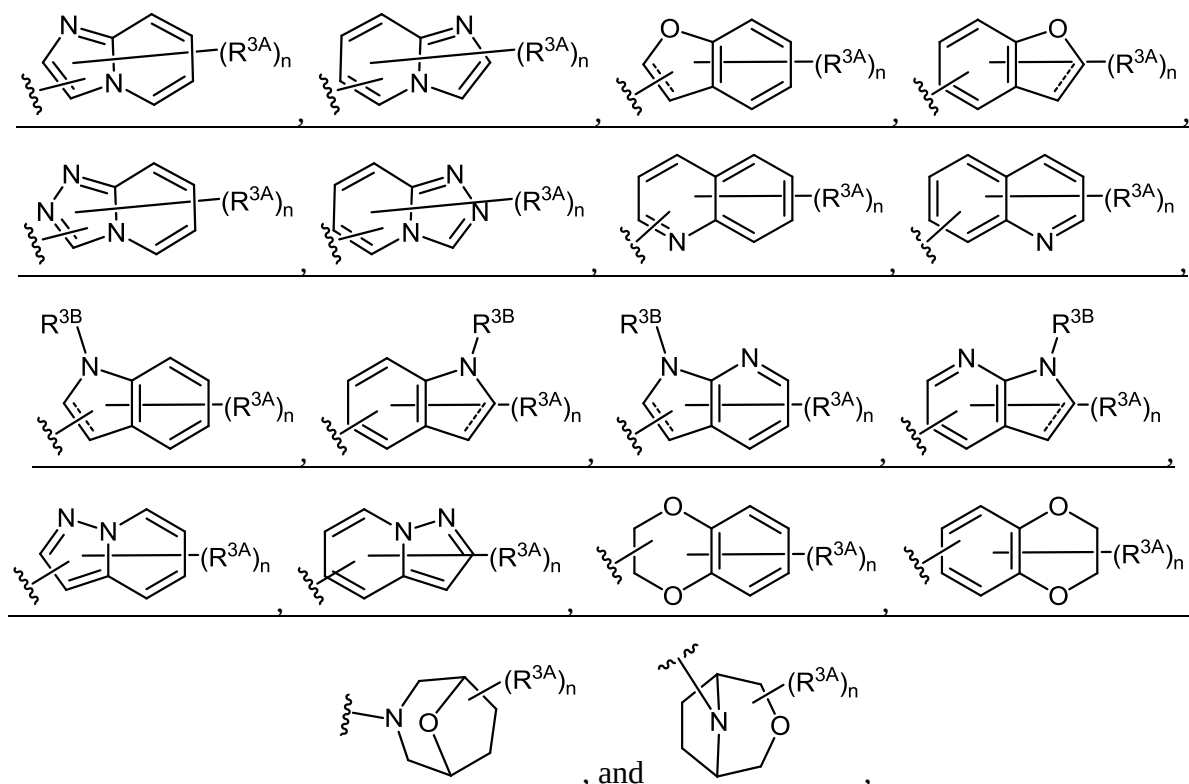
43. The compound of any one of claims 24-42, wherein Ring HET comprises a group $-L^1-R^3$ attached thereto.

44. The compound of claim 43, wherein L^1 is a bond, $-N(R^L)-$, $-NR^LC(O)O-$, $-NR^LC(O)N(R^L)-$, $-N(R^L)-$, $-N(R^L)SO_2N(R^L)-$, $-NR^L-(CH_2)_x-C(O)O-$, $-NR^L-(CH_2)_x-O-$, $-NR^LC(O)N(R^L)-$, $-NR^L-(CH_2)_x-$, $-(CH_2)_x-NR^L-$, $-NR^LC(O)O(CH_2)_x-$, $-NR^LC(O)NR^L(CH_2)_x-$, or $-NR^L(CH_2)_xNR^LC(O)-$, wherein x is 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

45. The compound of claim 43 or 44, wherein R^3 is selected from the group consisting of:







wherein:

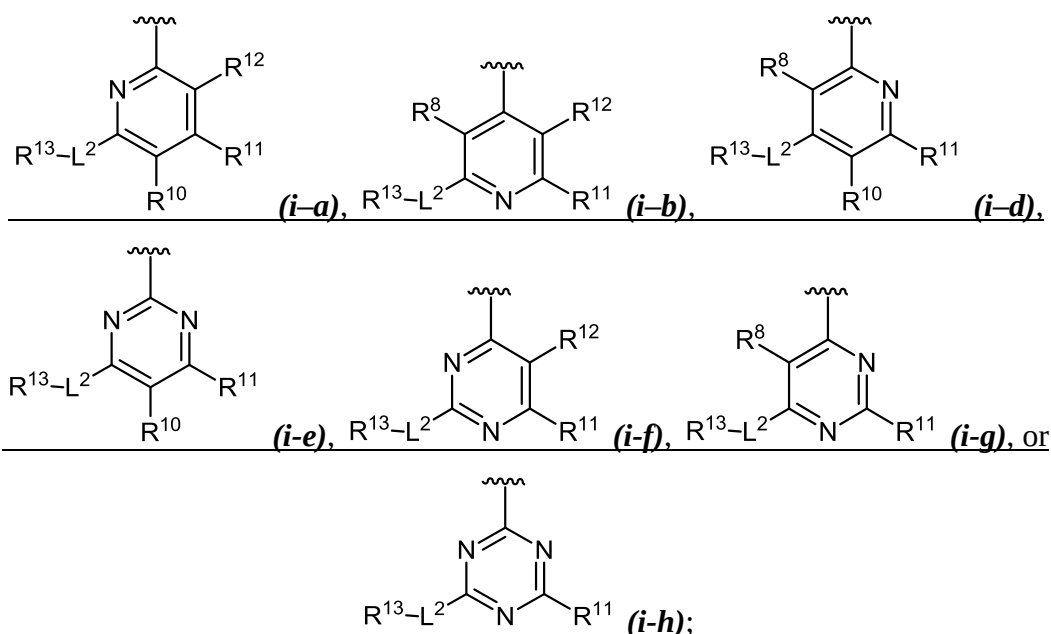
each instance of ----- independently represents a single or double bond;

n is 0, 1, 2, or 3;

each instance of R^{3A} is independently hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, substituted amino, carbonyl, sulfonyl, sulfinyl, -CN, -NO₂, halogen, optionally substituted alkyl, or two R^{3A} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring, or R^{3A} and R^{3B} groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring; and

R^{3B} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group.

46. The compound of any one of claims 24-29 or 38-45, wherein Ring HET is a 6-membered monocyclic heteroaryl ring system of the Formula:



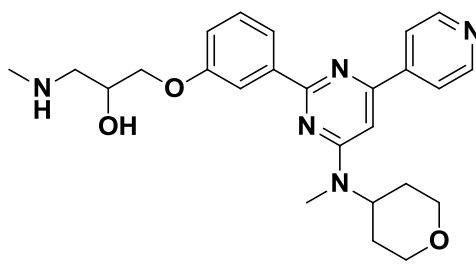
each instance of R^8 , R^{10} , and R^{12} is independently selected from the group consisting of hydrogen, halo, $-CN$, $-NO_2$, $-C(=O)R'$, $-C(=O)OR'$, $-C(=O)N(R')_2$, and optionally substituted alkyl;

R^{11} is $-L^1-R^3$; and

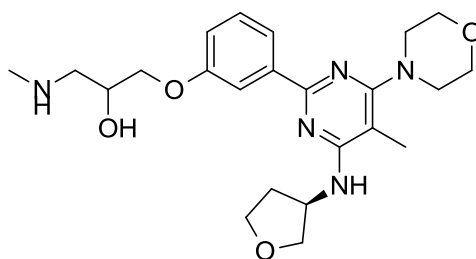
R^3 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-N(R^{bb})_2$, $-SH$, $-SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, C_{1-4} alkyl, C_{1-4} perhaloalkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl.

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

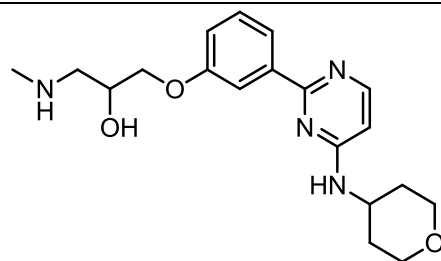
1-1



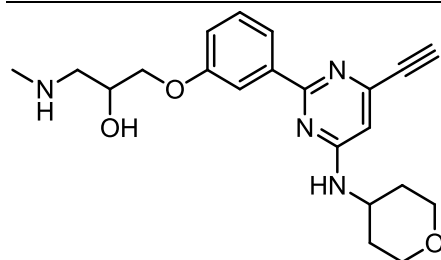
3-1



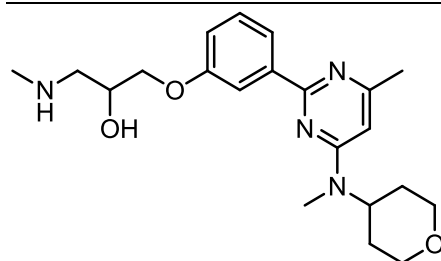
4-1



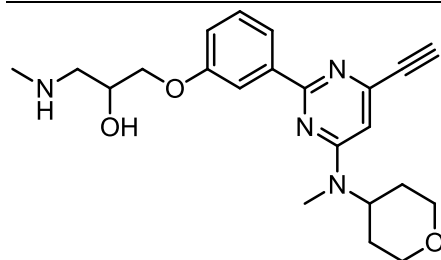
5-1



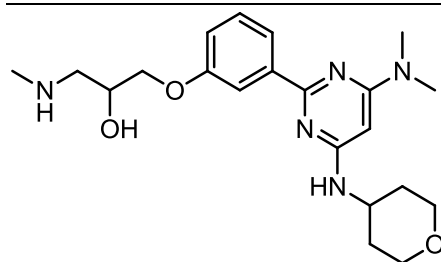
6-1



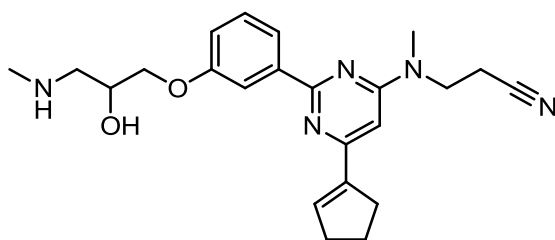
7-1



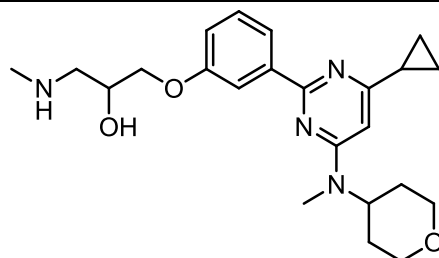
8-1



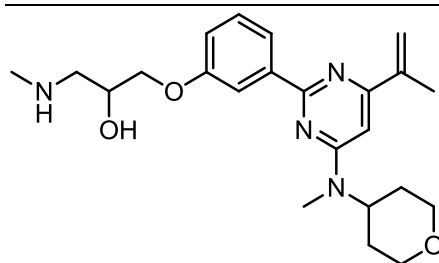
9-1



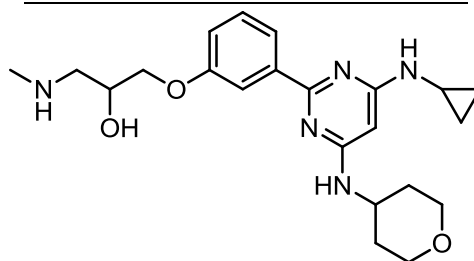
10-1



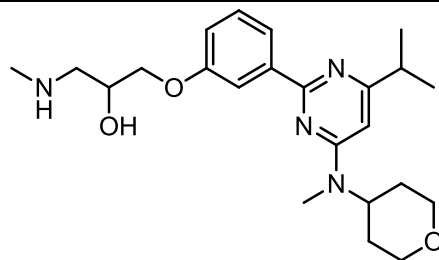
11-1



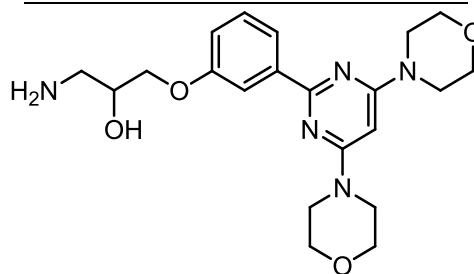
12-1



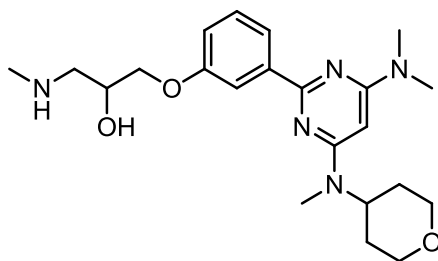
13-1



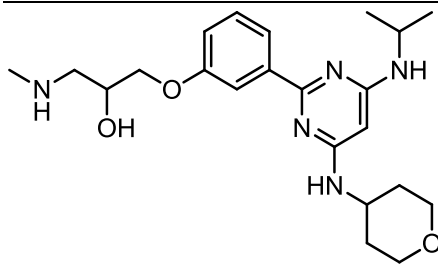
14-1



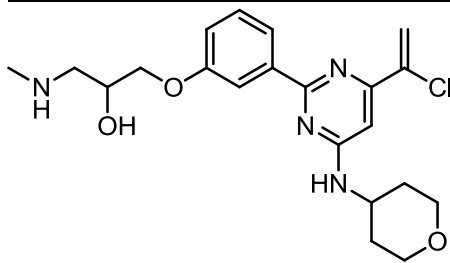
15-1



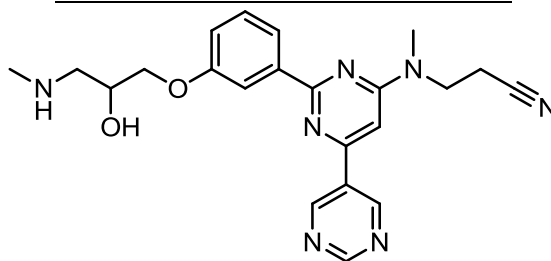
16-1



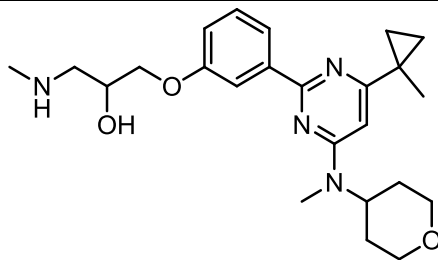
17-1



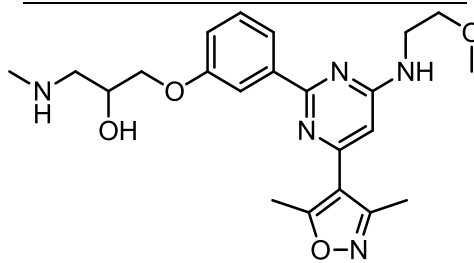
18-1



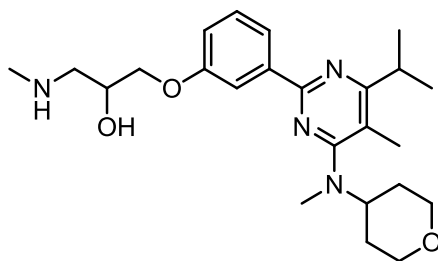
19-1



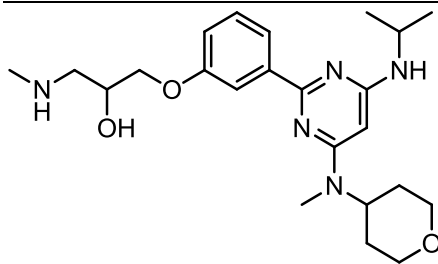
20-1



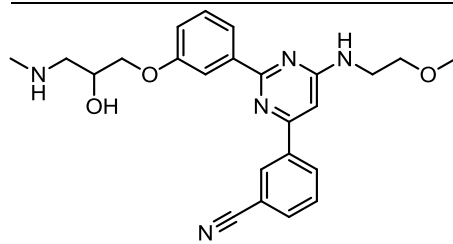
21-1



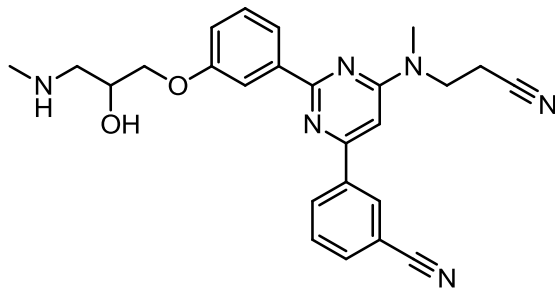
22-1



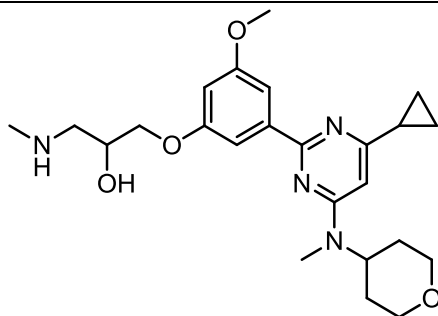
23-1



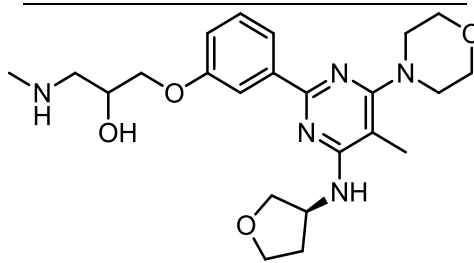
24-1



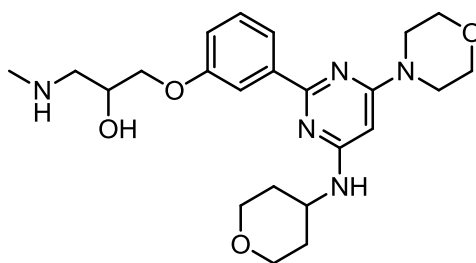
25-1



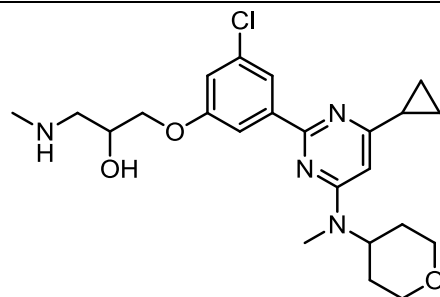
26-1



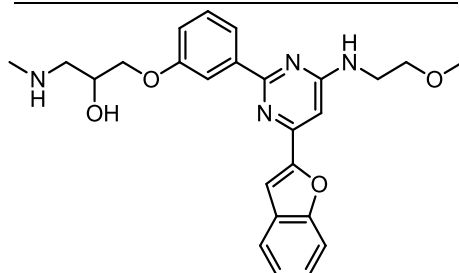
27-1



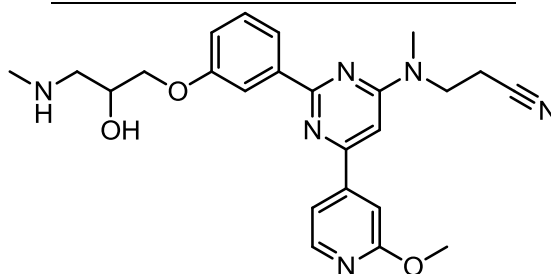
28-1



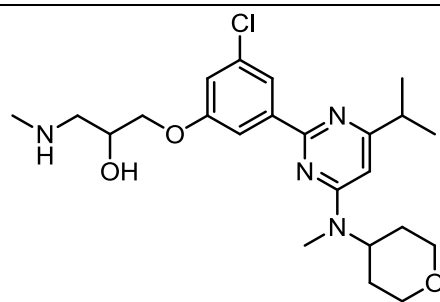
29-1



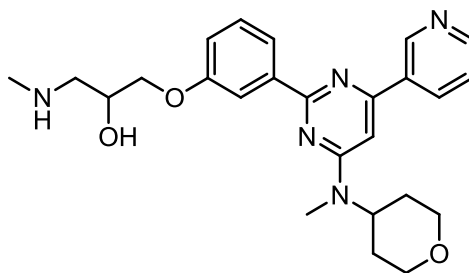
30-1



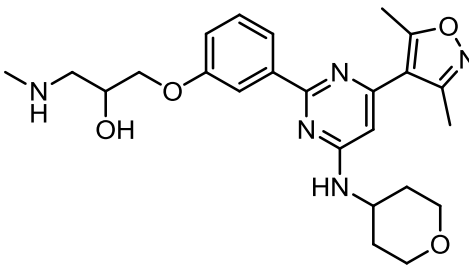
31-1



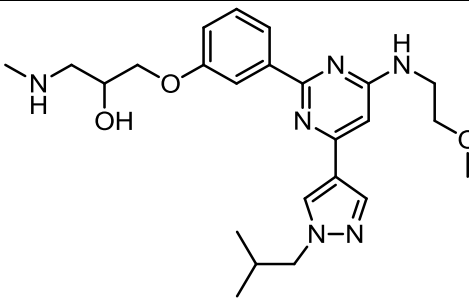
32-1



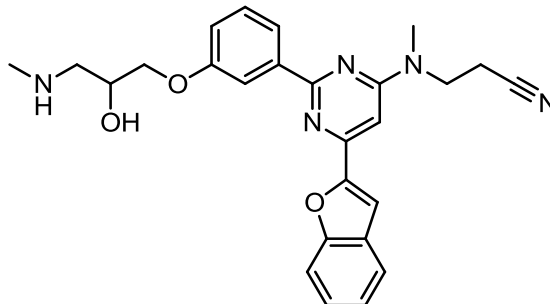
33-1



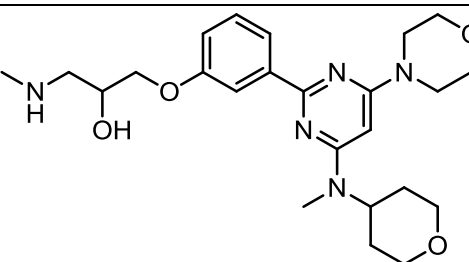
34-1



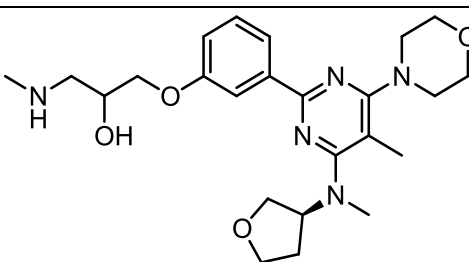
35-1



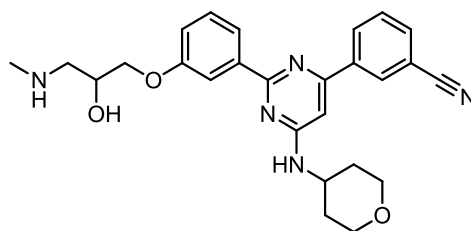
36-1



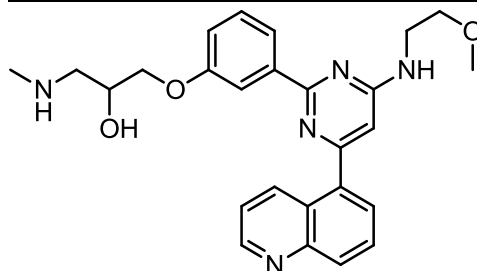
37-1



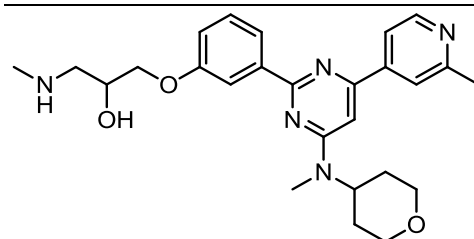
38-1



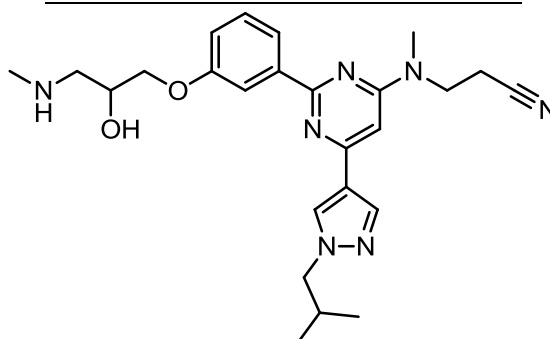
39-1



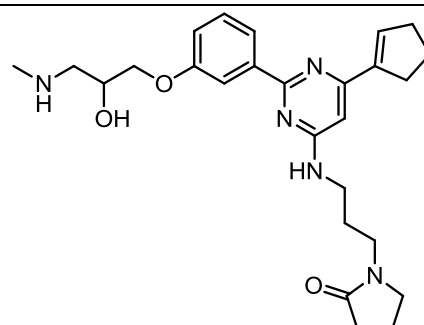
40-1



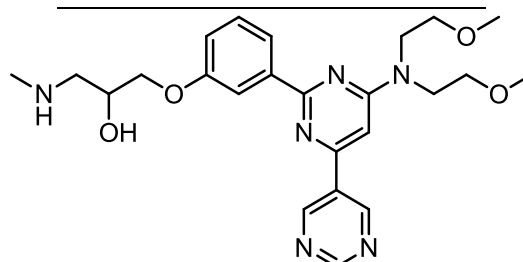
41-1



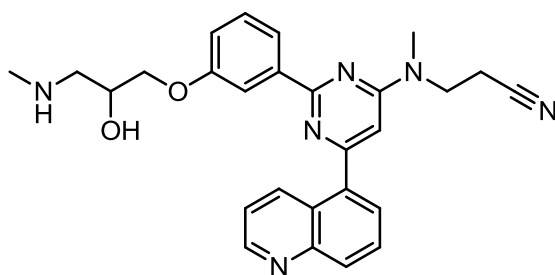
42-1



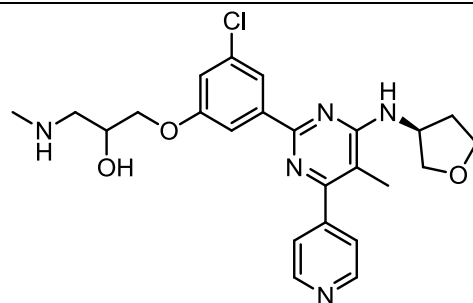
43-1



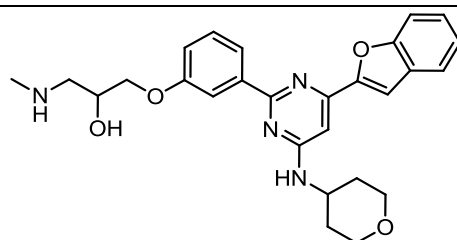
44-1



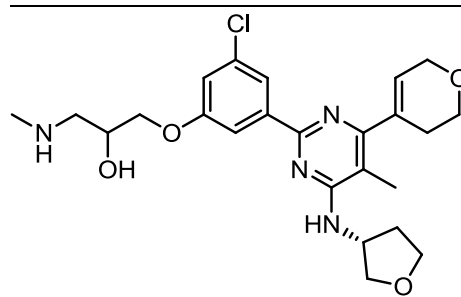
45-1



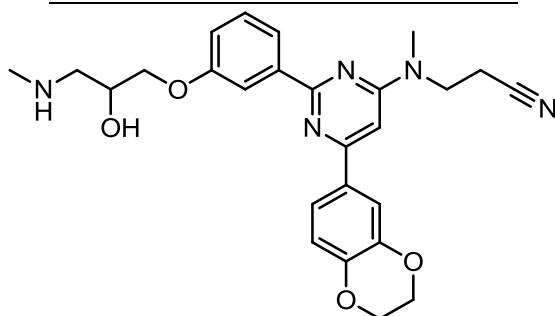
46-1



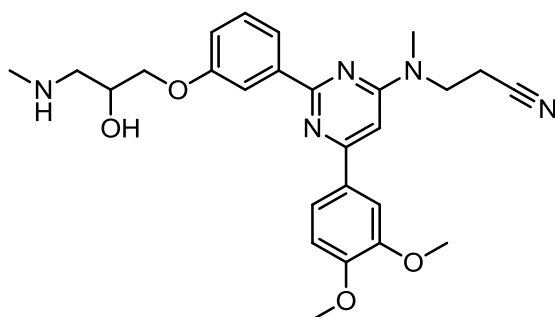
47-1



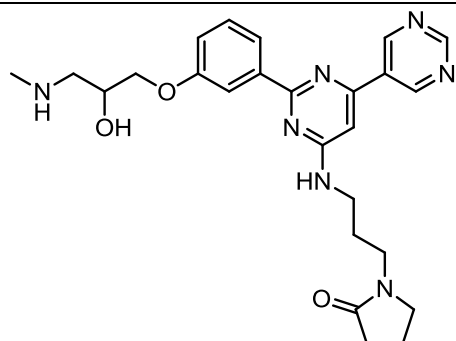
48-1



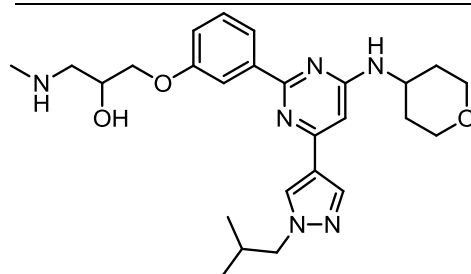
49-1



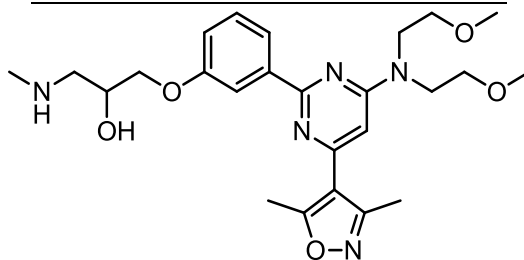
50-1



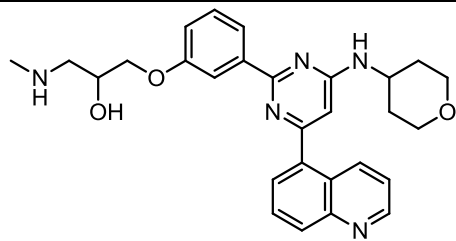
51-1



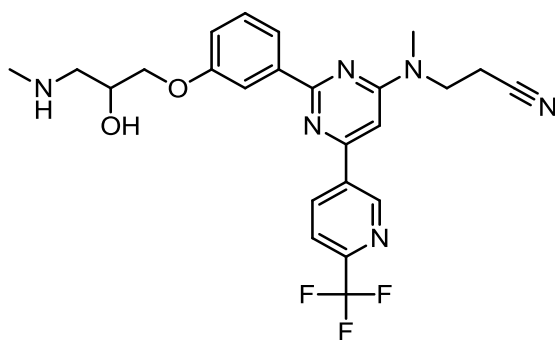
52-1



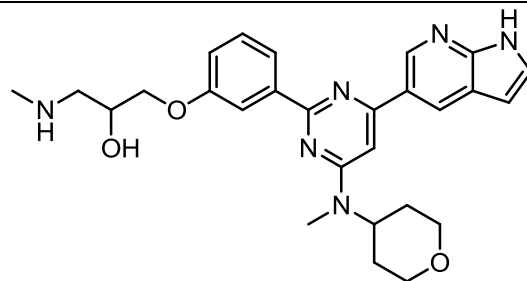
53-1



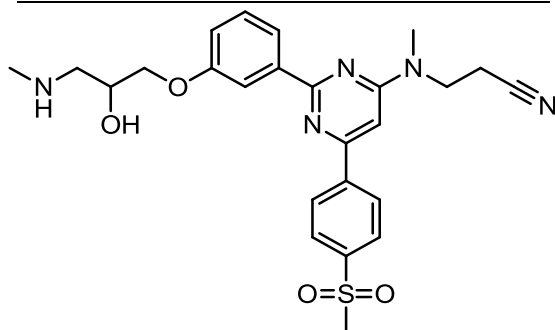
54-1



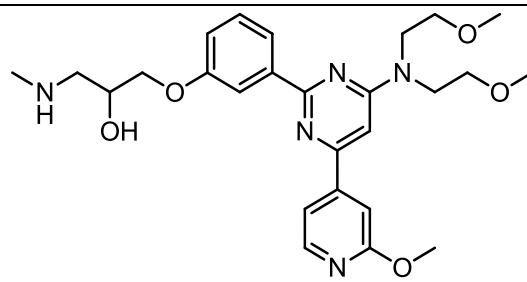
55-1



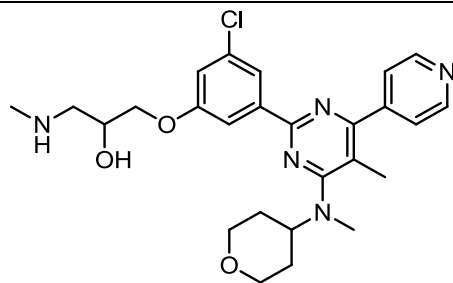
56-1



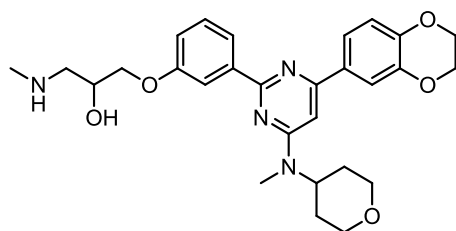
57-1



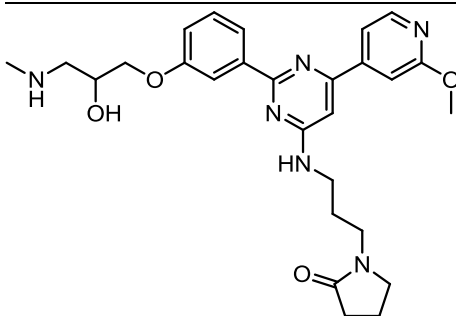
58-1



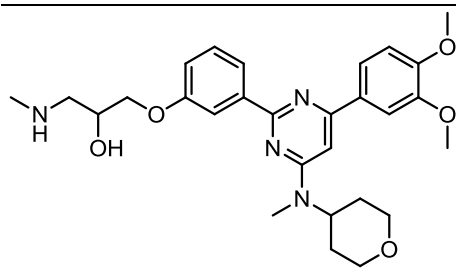
59-1



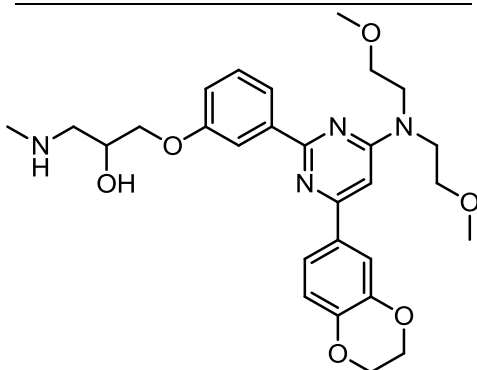
60-1



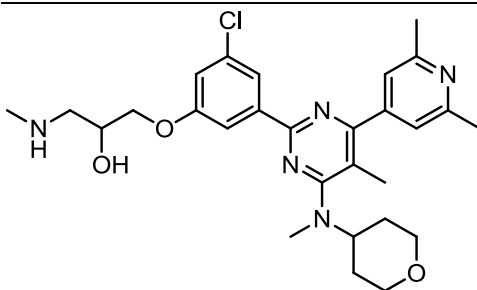
61-1



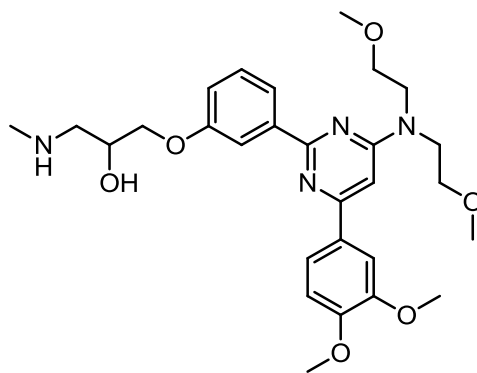
62-1



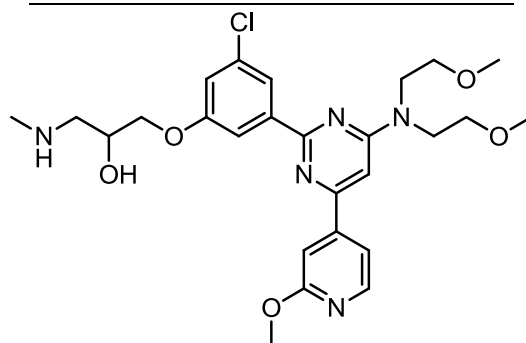
63-1



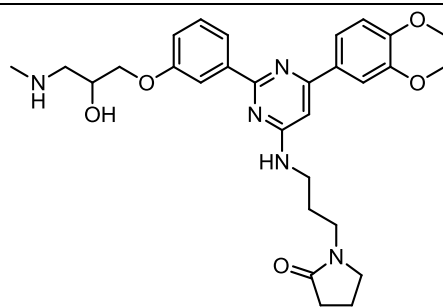
64-1



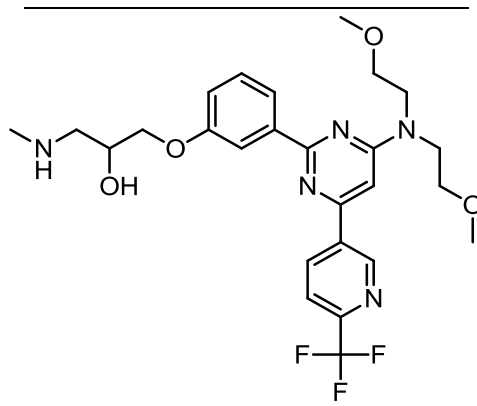
65-1



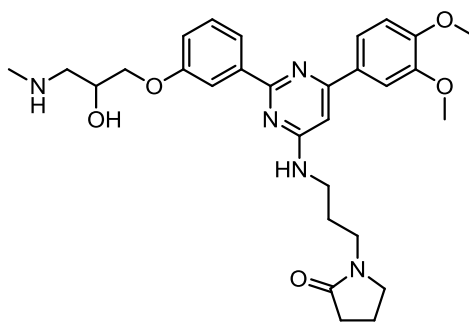
66-1



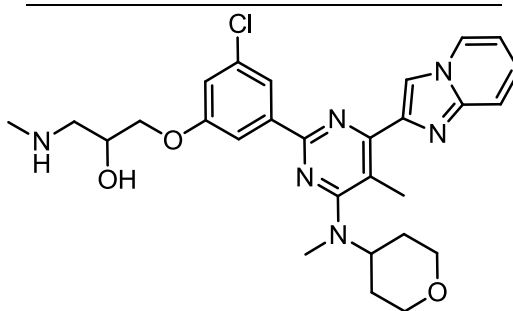
67-1



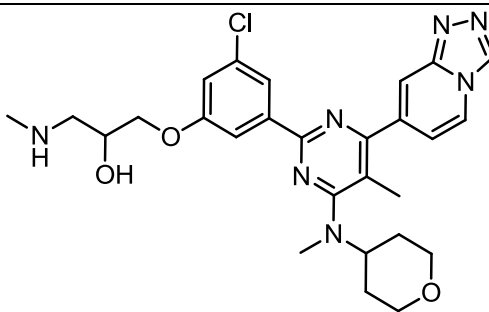
68-1



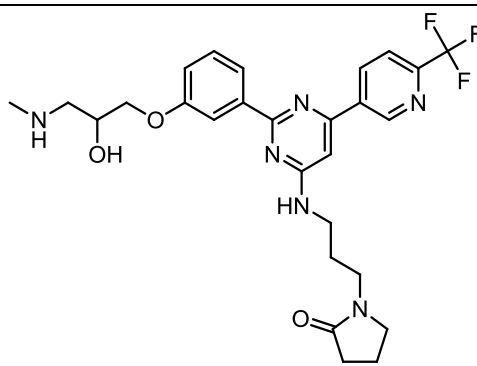
69-1



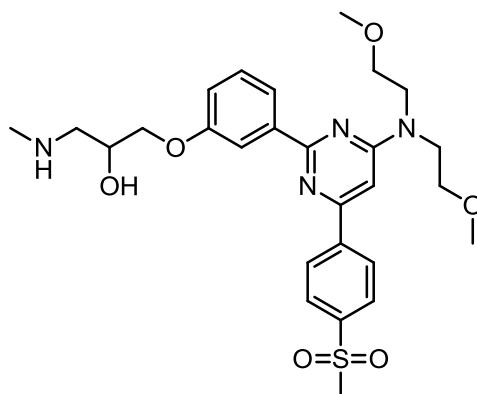
70-1



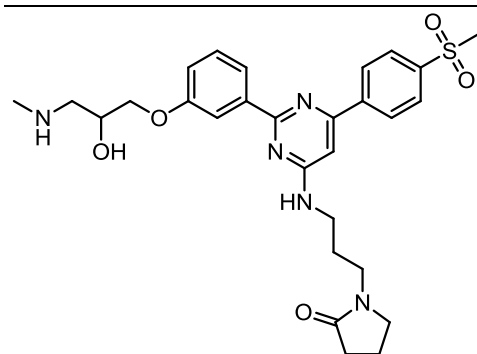
71-1



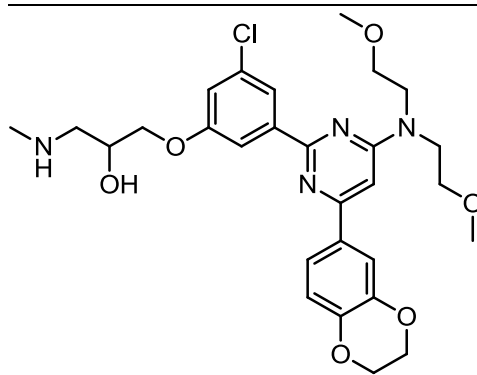
72-1



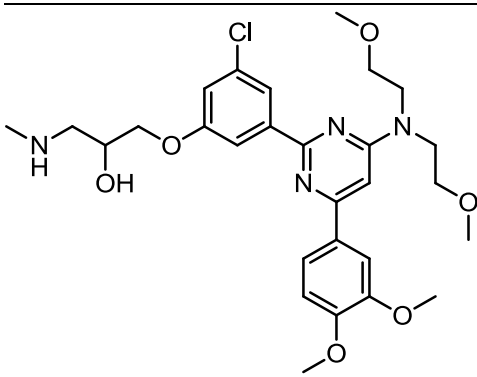
73-1



74-1



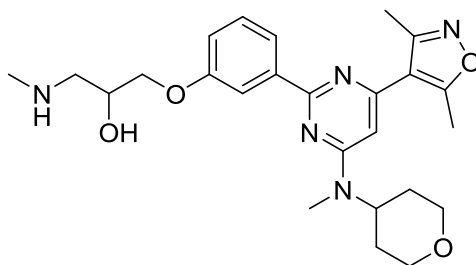
75-1



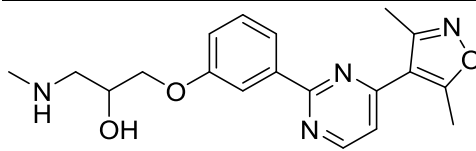
and pharmaceutically acceptable salts thereof.

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

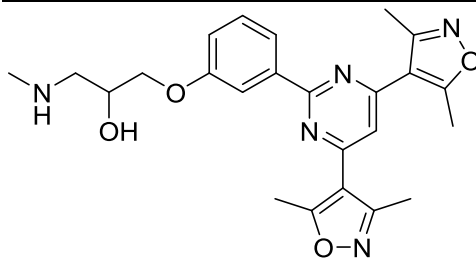
1-1a



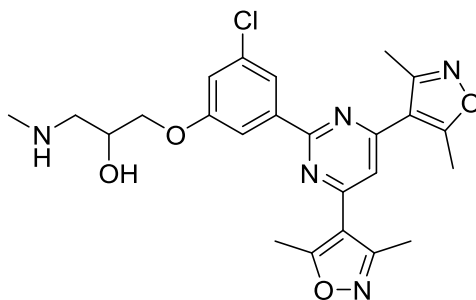
2-1a



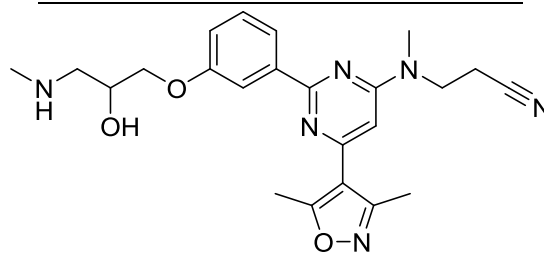
3-1a



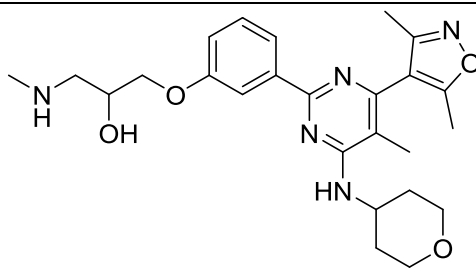
4-1a



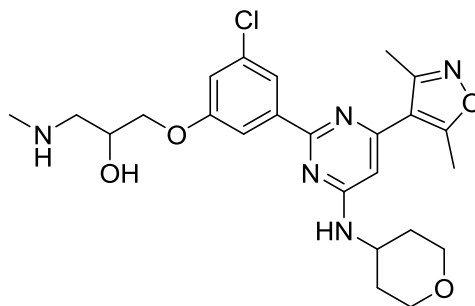
5-1a



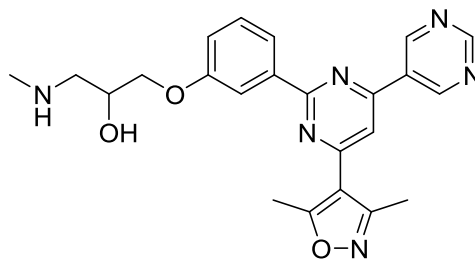
6-1a



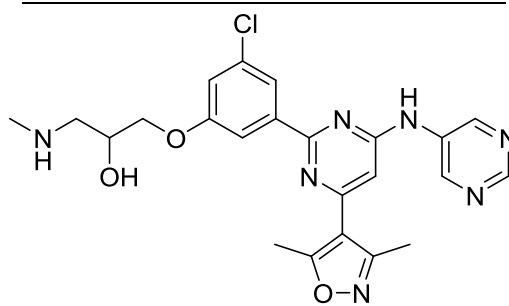
7-1a



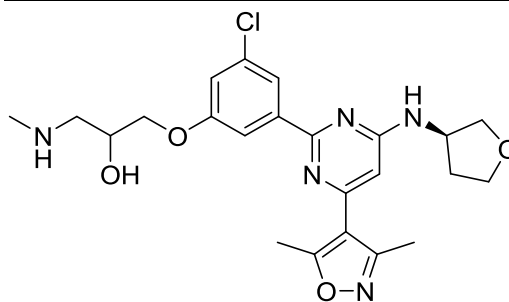
8-1a



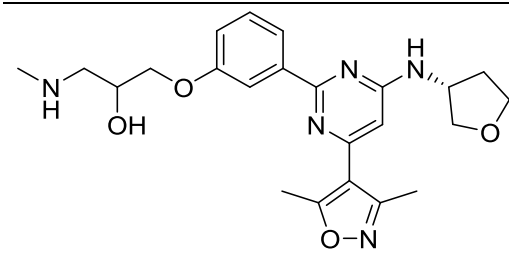
9-1a



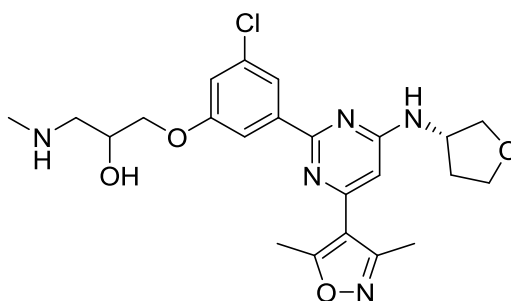
10-1a



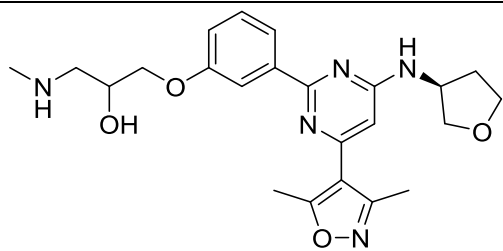
11-1a



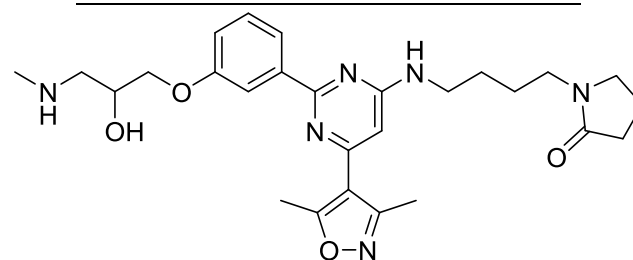
12-1a



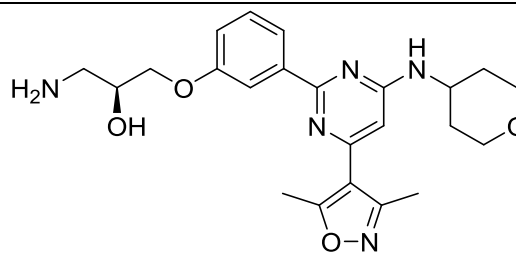
13-1a



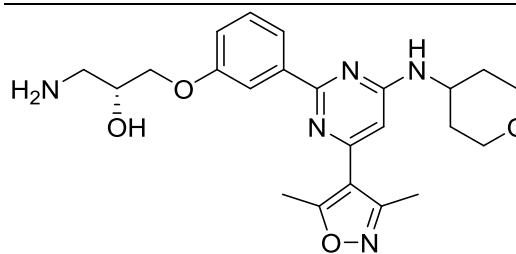
14-1a



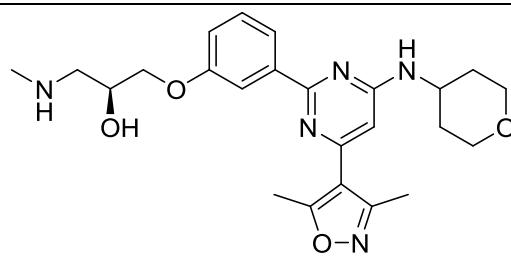
15-1a



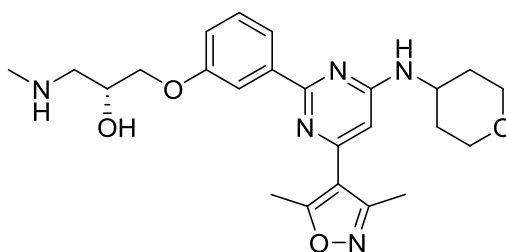
16-1a



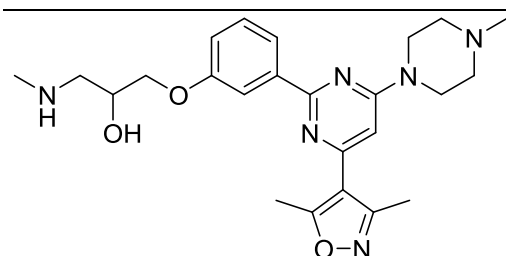
17-1a



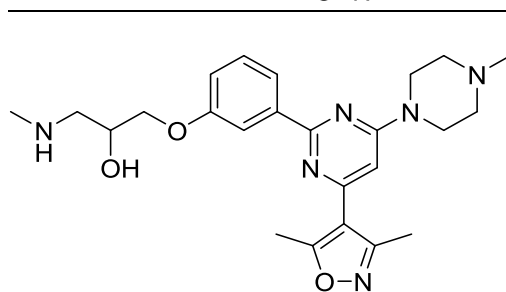
18-1a



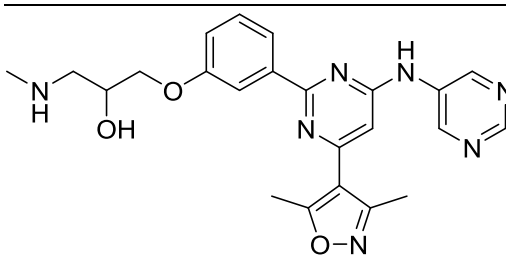
19-1a



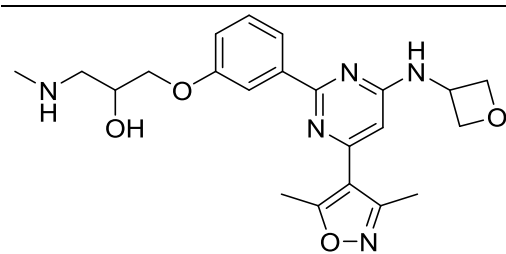
20-1a



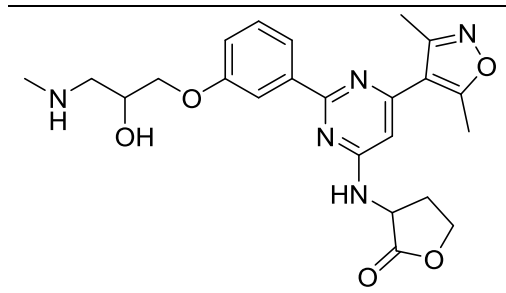
21-1a



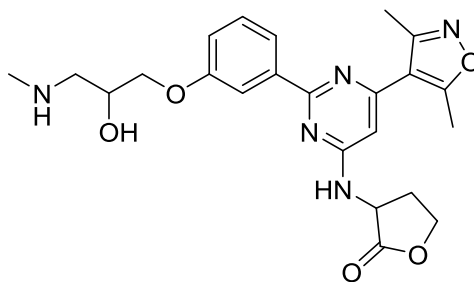
22-1a



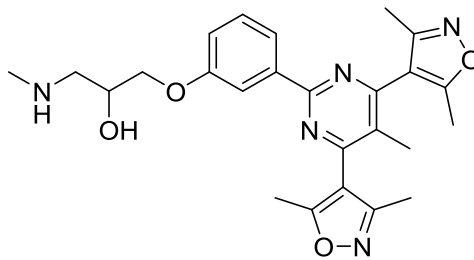
23-1a



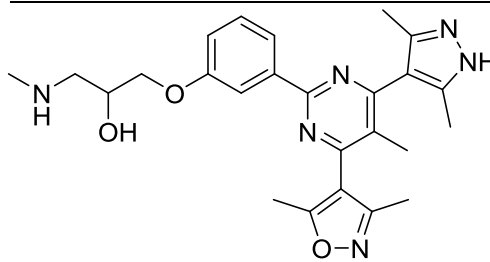
24-1a



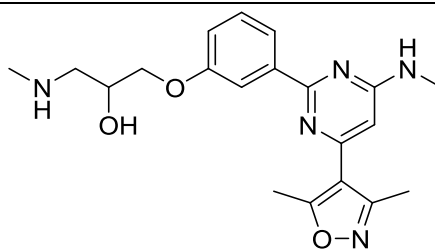
25-1a



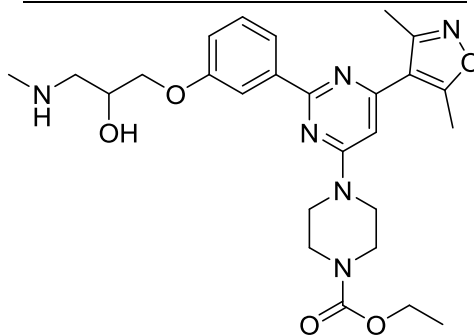
26-1a



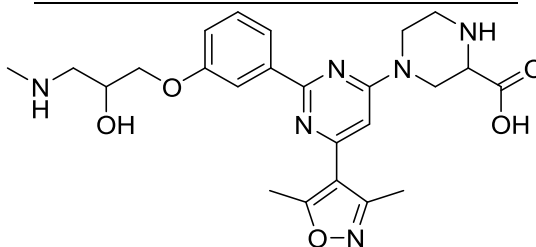
27-1a



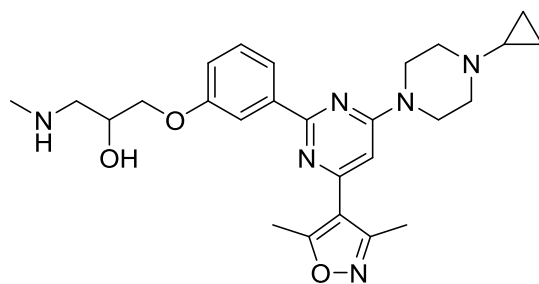
28-1a



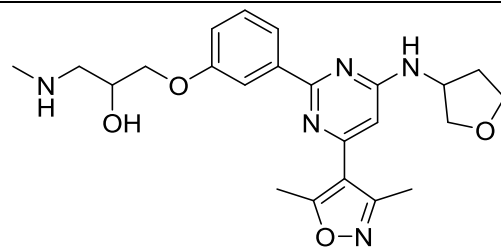
29-1a



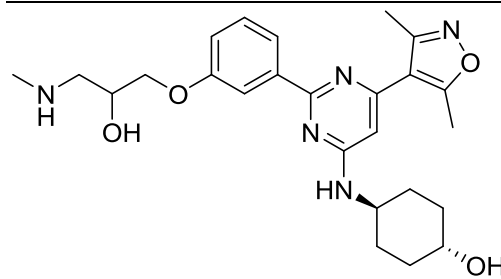
30-1a



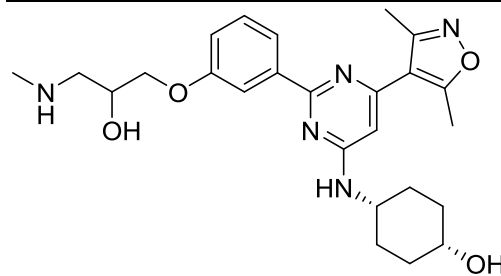
31-1a



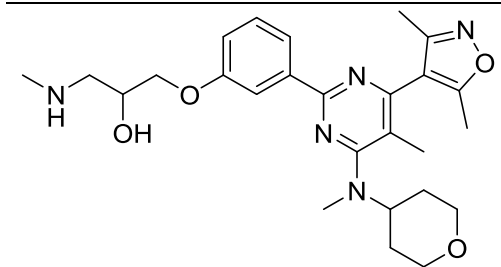
32-1a



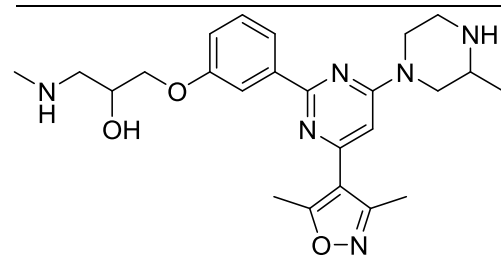
33-1a



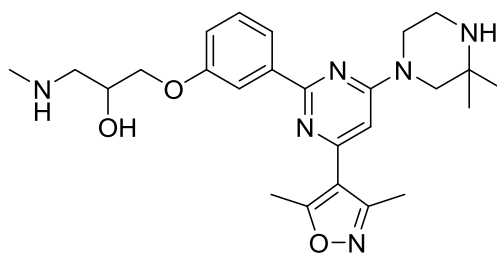
34-1a



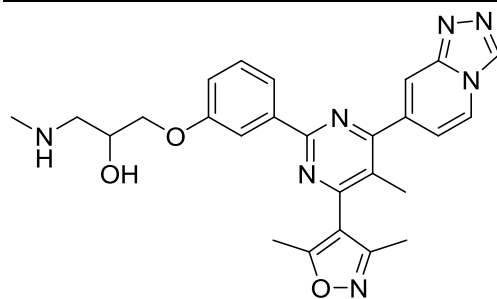
35-1a



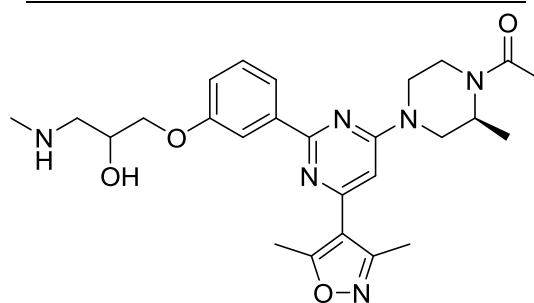
36-1a



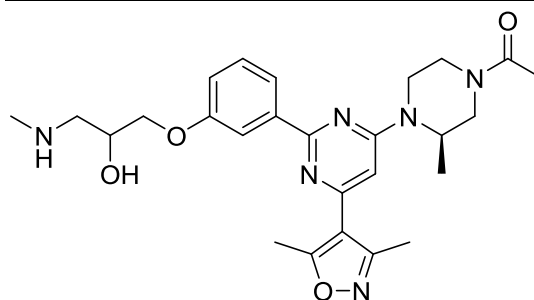
37-1a



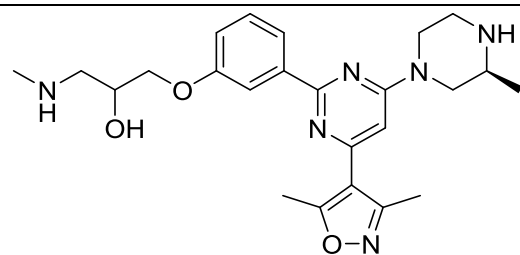
38-1a



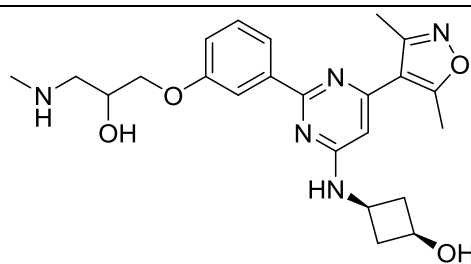
39-1a



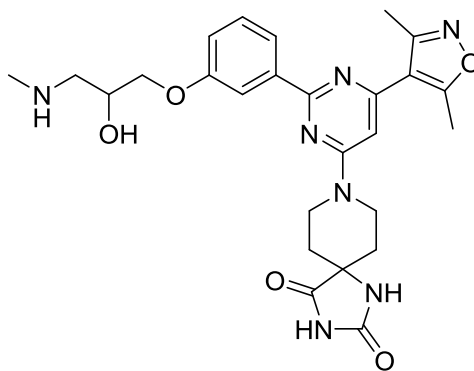
40-1a



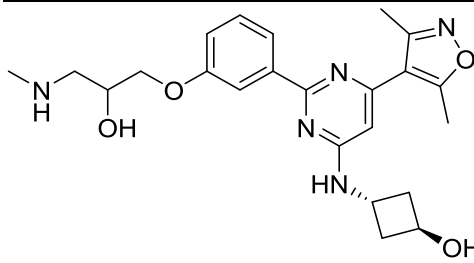
41-1a



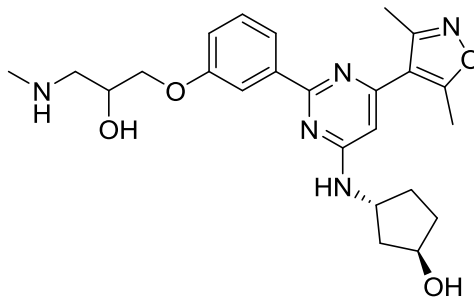
42-1a



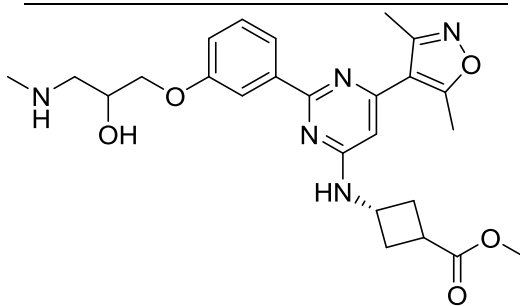
43-1a



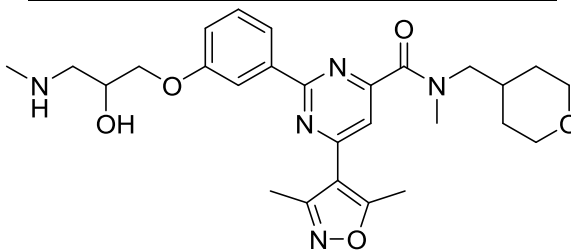
44-1a



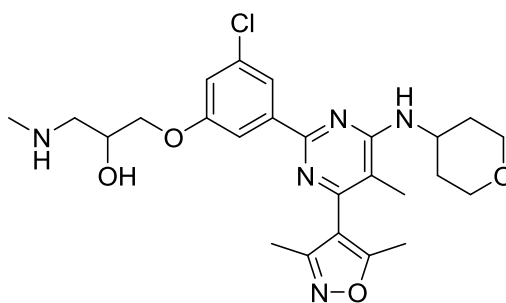
45-1a



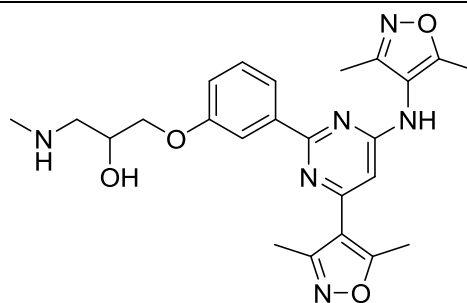
46-1a



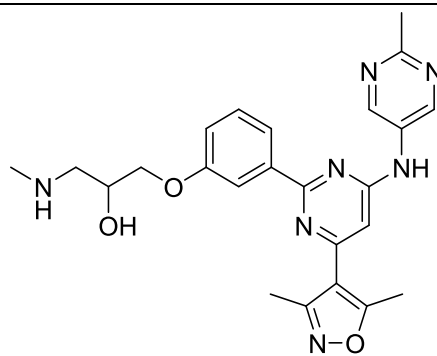
47-1a



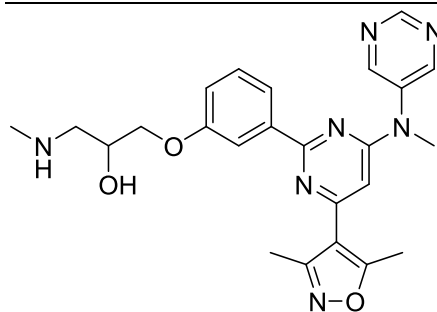
48-1a



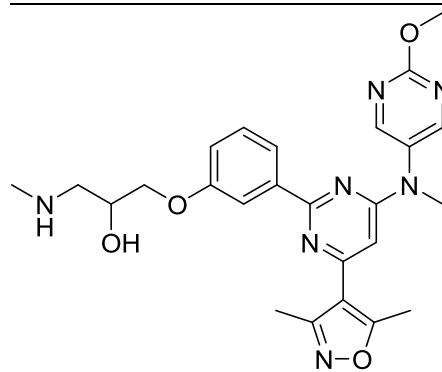
49-1a



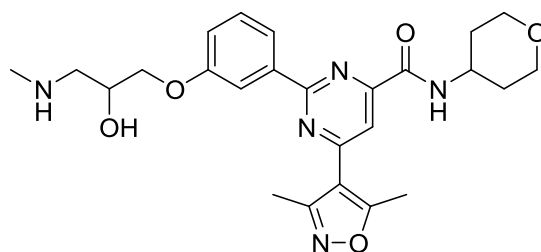
50-1a



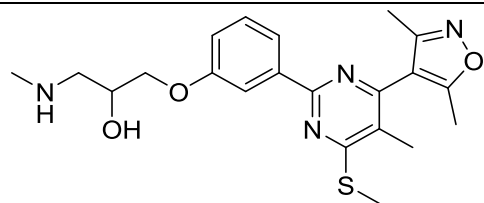
51-1a



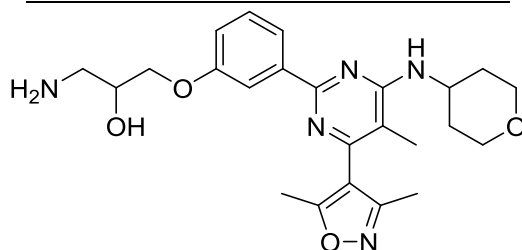
52-1a



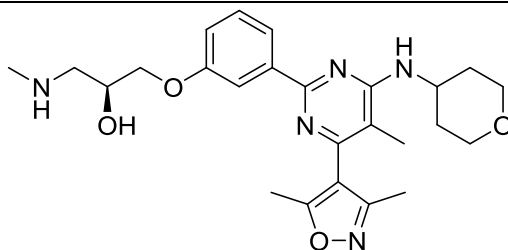
53-1a



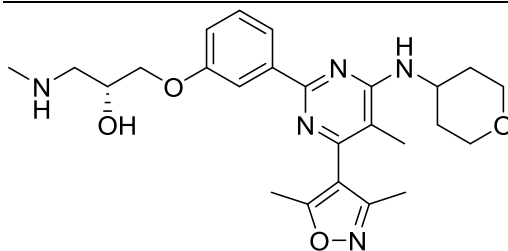
54-1a



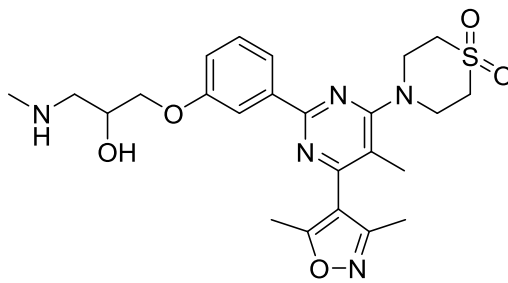
55-1a



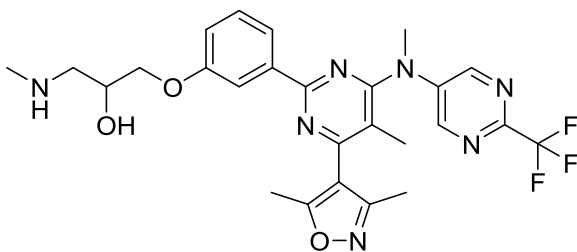
56-1a



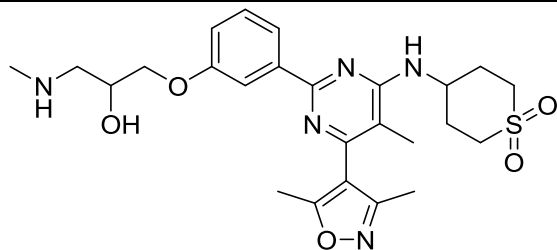
57-1a



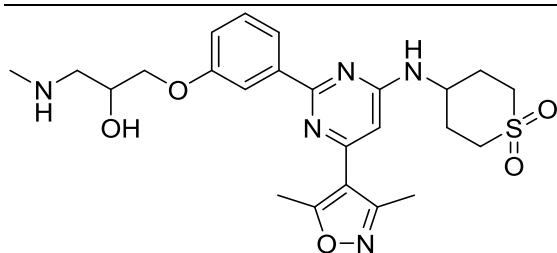
58-1a



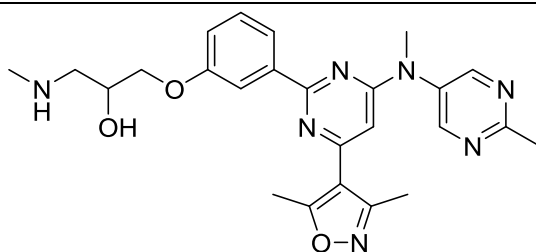
59-1a



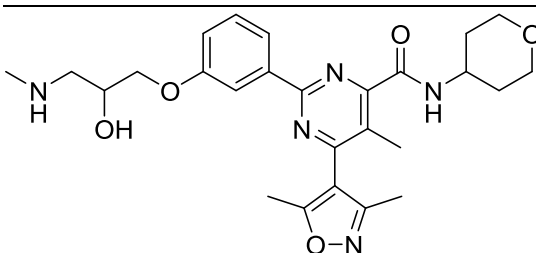
60-1a



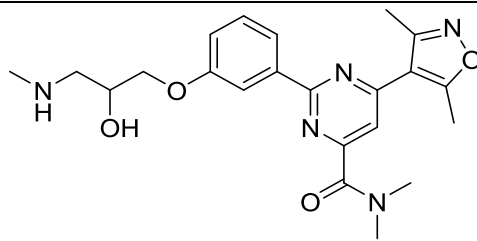
61-1a



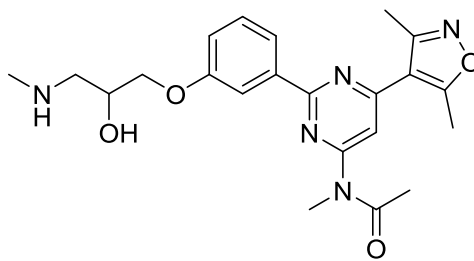
62-1a



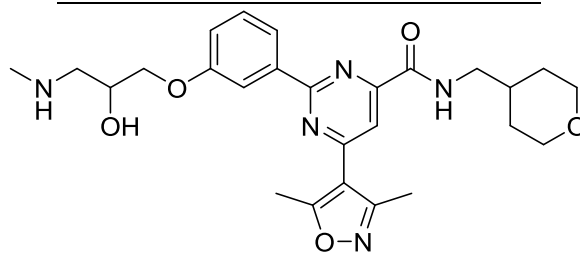
63-1a



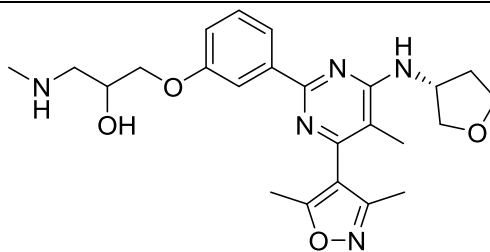
64-1a



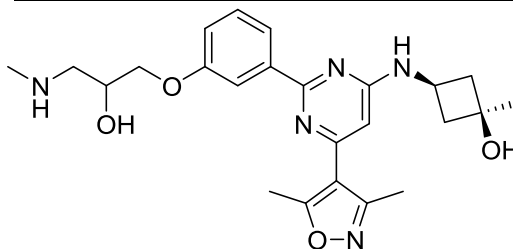
65-1a



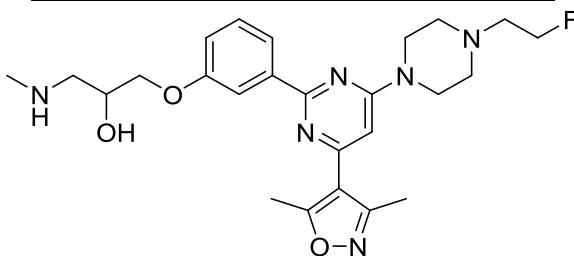
66-1a



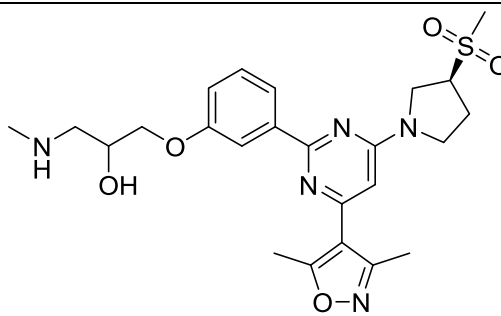
67-1a



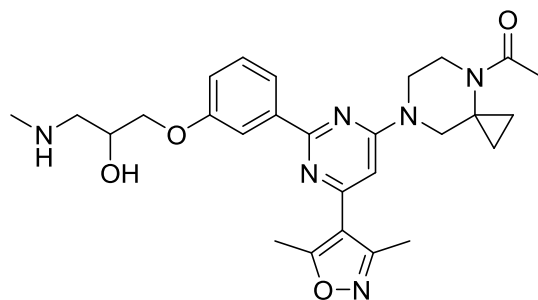
68-1a



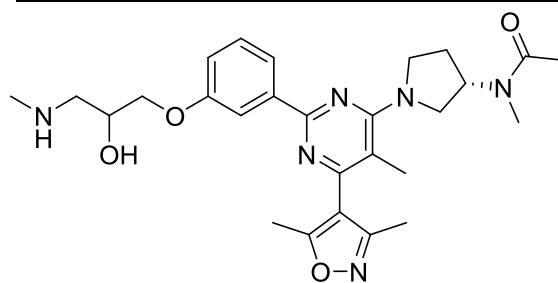
69-1a



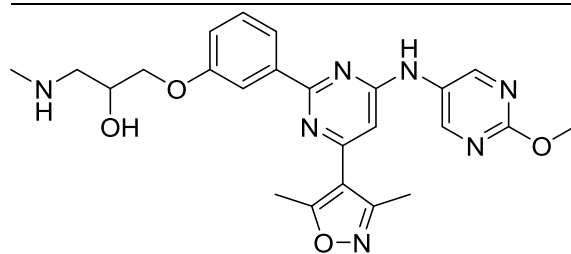
70-1a



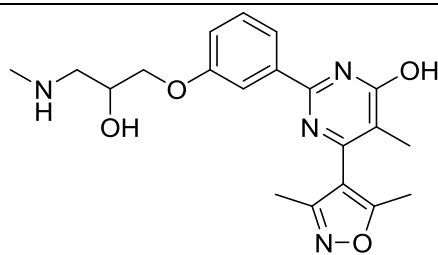
71-1a



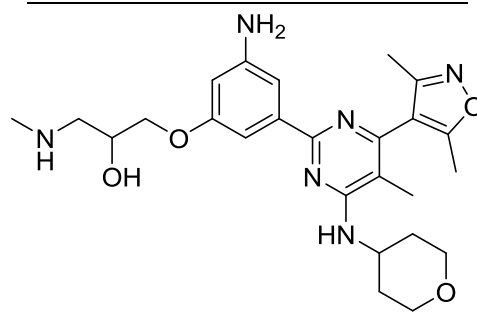
72-1a



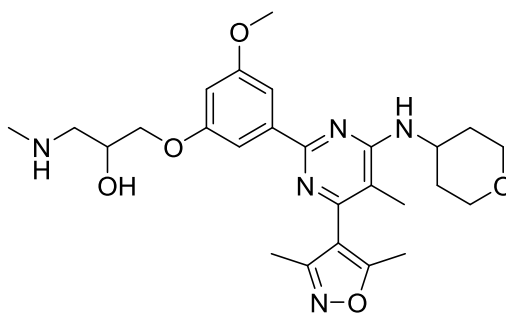
73-1a



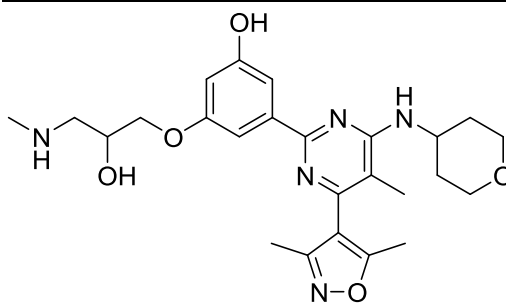
74-1a



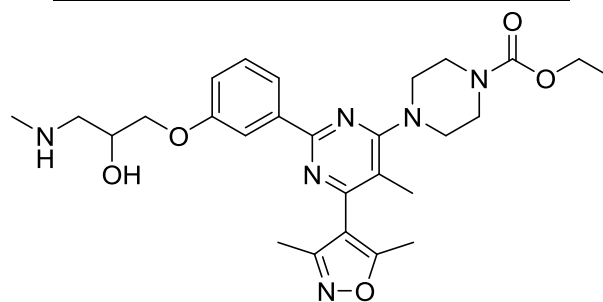
75-1a



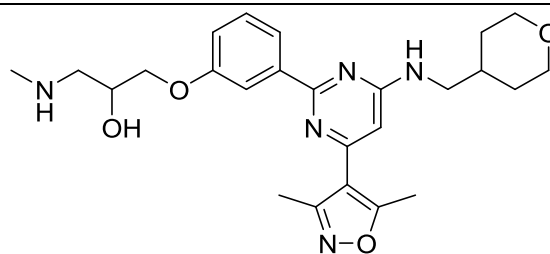
76-1a



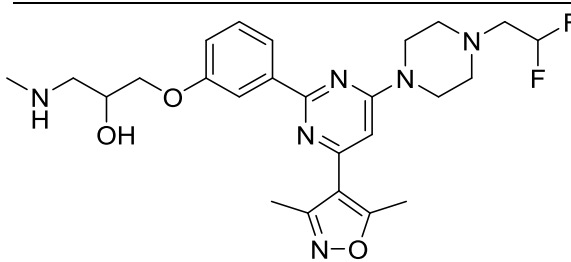
77-1a



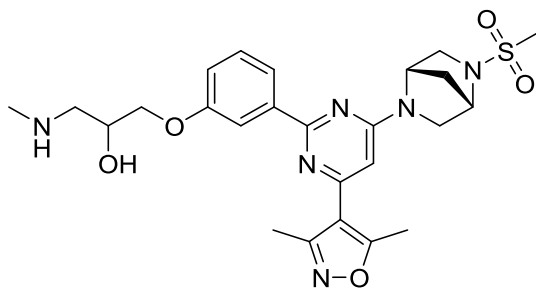
78-1a



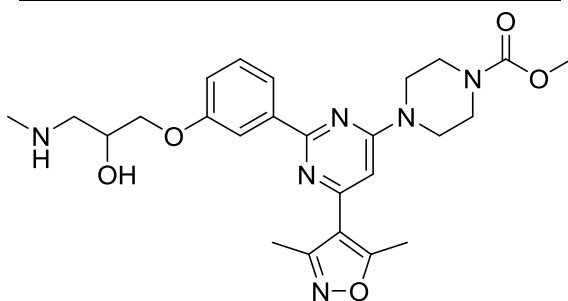
79-1a



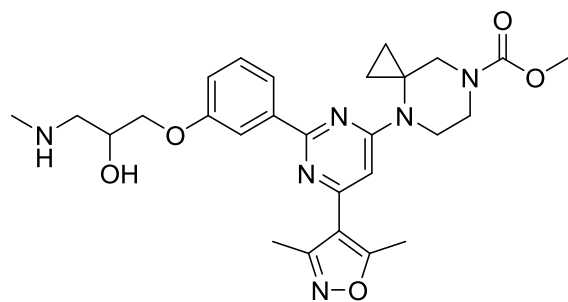
80-1a



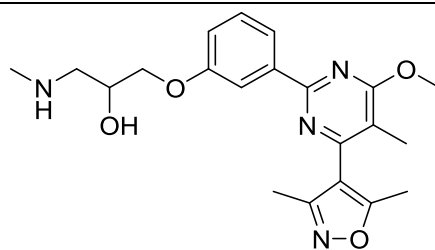
81-1a



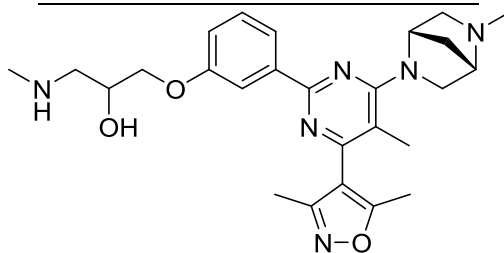
82-1a



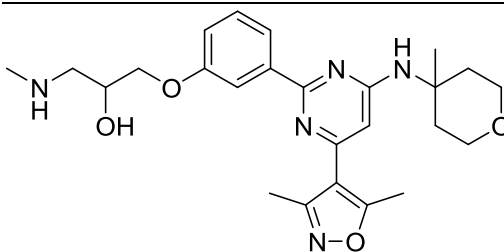
83-1a



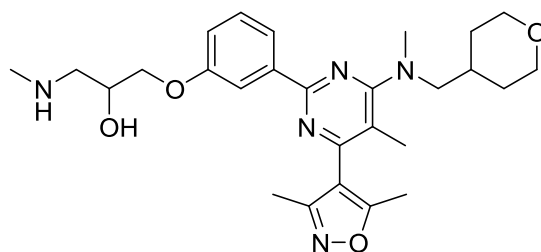
84-1a



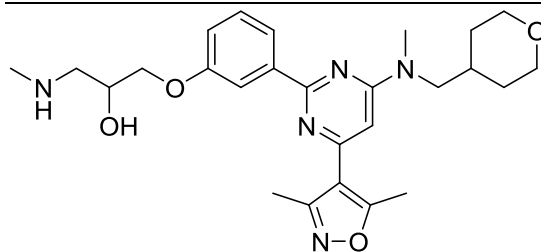
85-1a



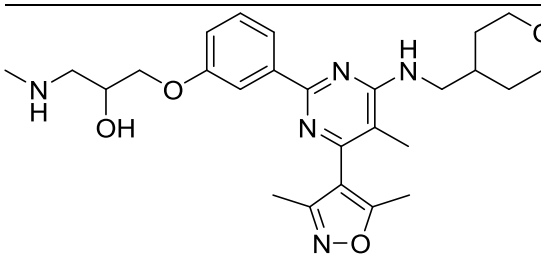
86-1a



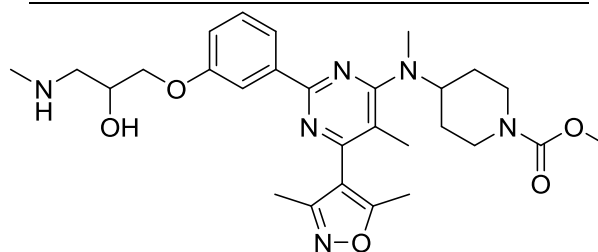
87-1a



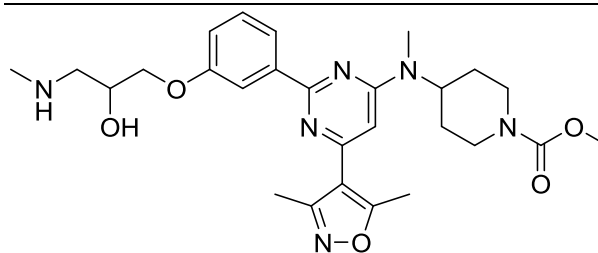
88-1a



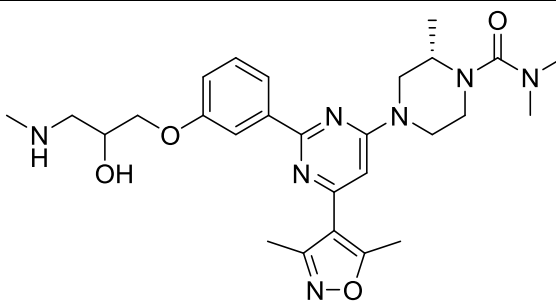
89-1a



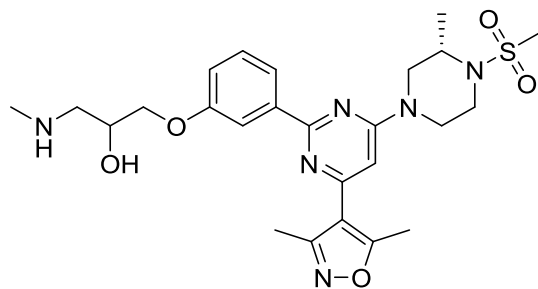
90-1a



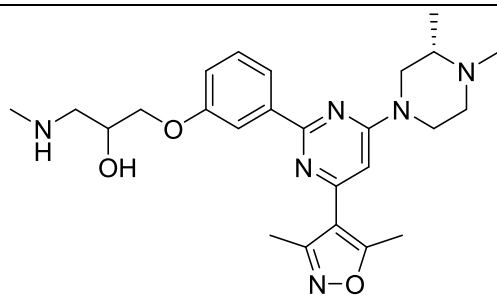
91-1a



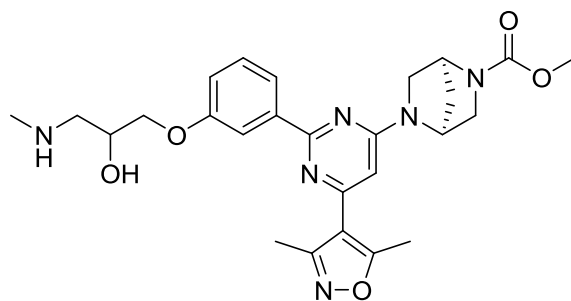
92-1a



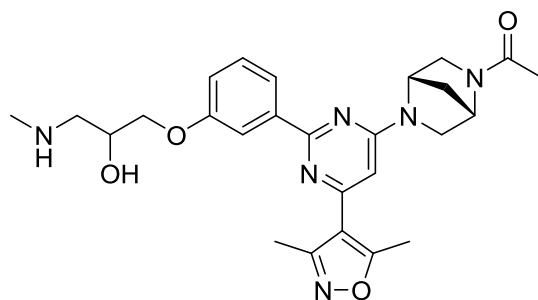
93-1a



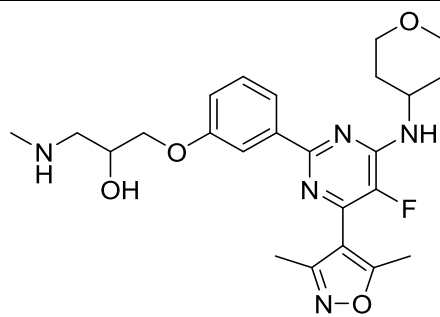
94-1a



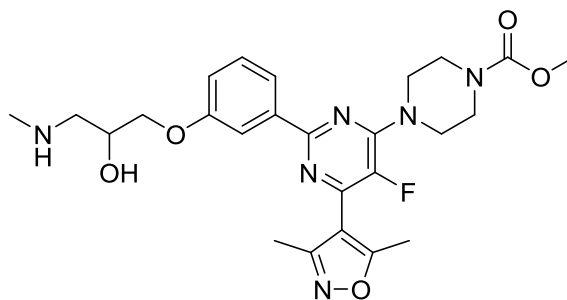
95-1a



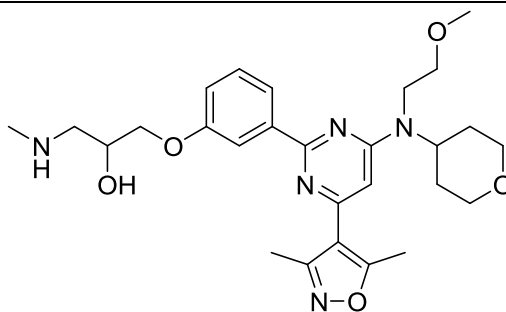
96-1a



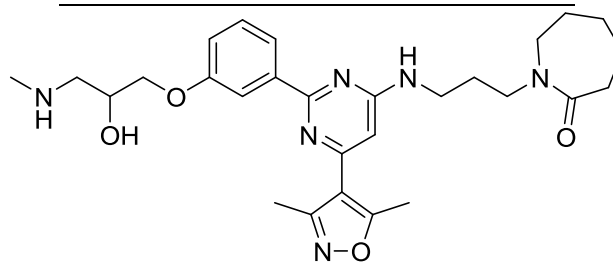
97-1a



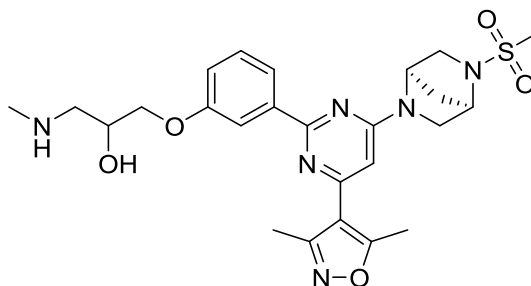
98-1a



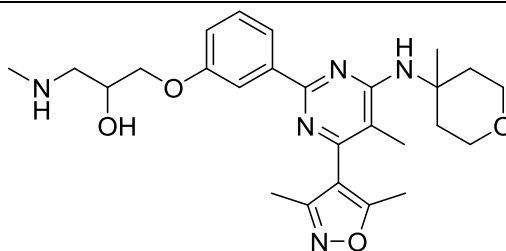
99-1a



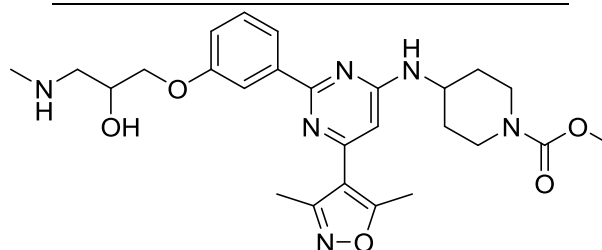
100-1a



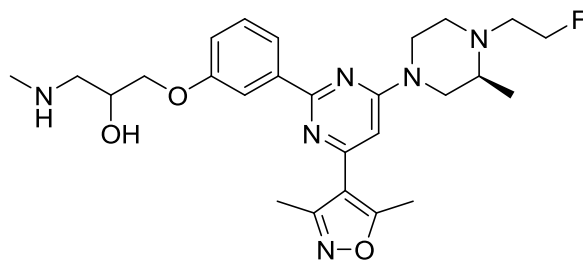
101-1a



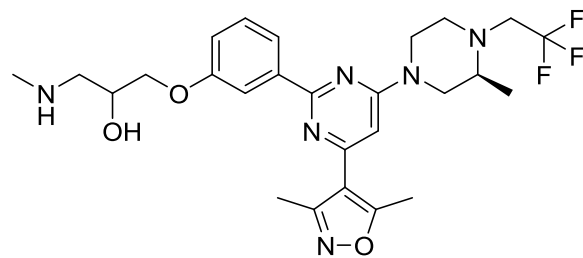
102-1a



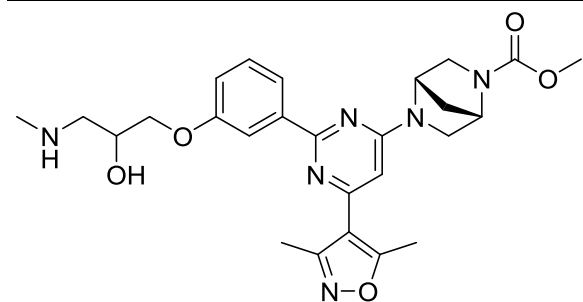
103-1a



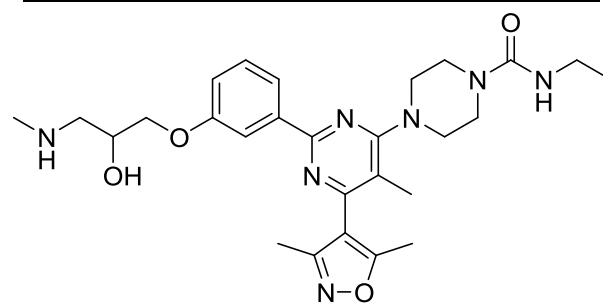
104-1a



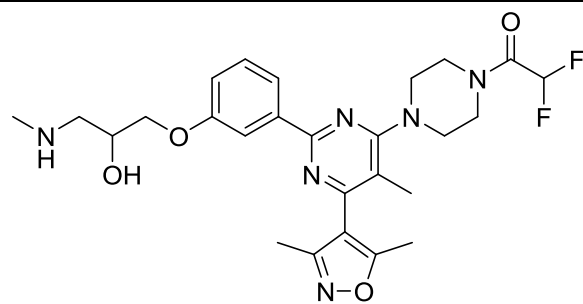
105-1a



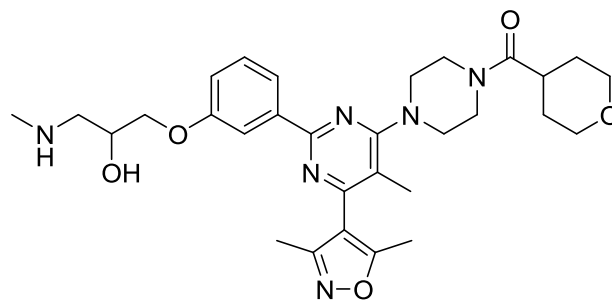
106-1a



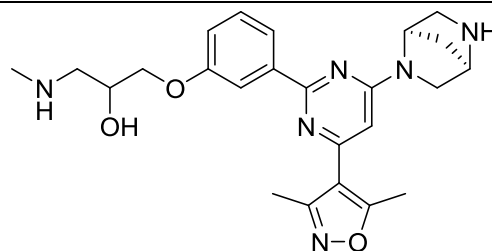
107-1a



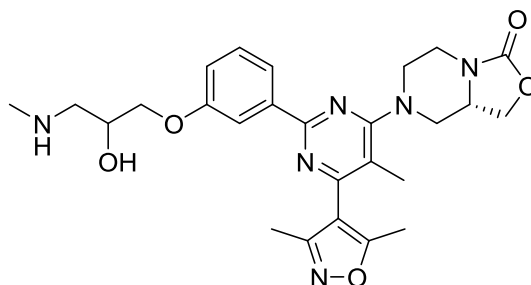
108-1a



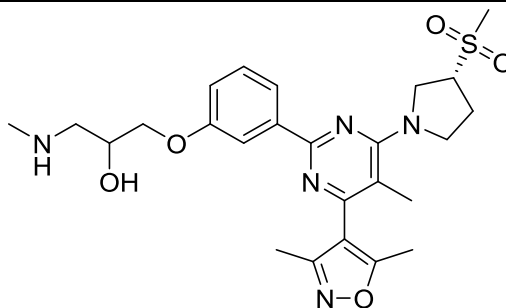
109-1a



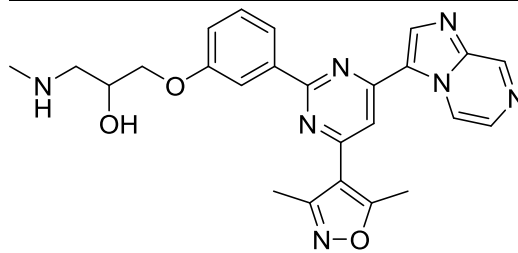
110-1a



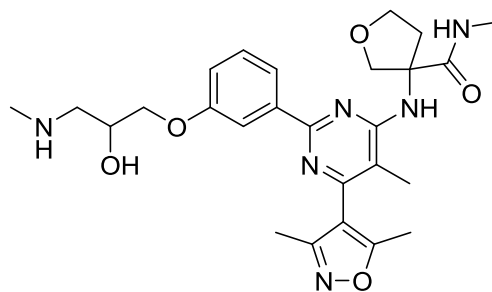
111-1a



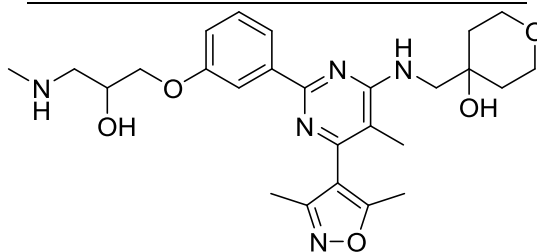
112-1a



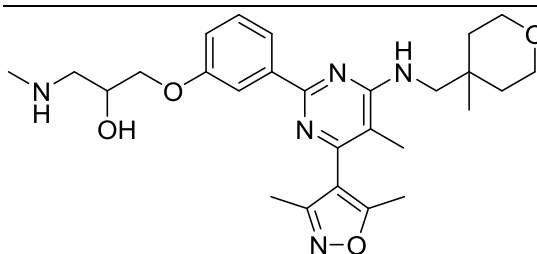
113-1a



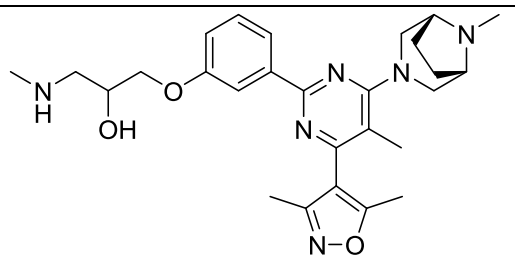
114-1a



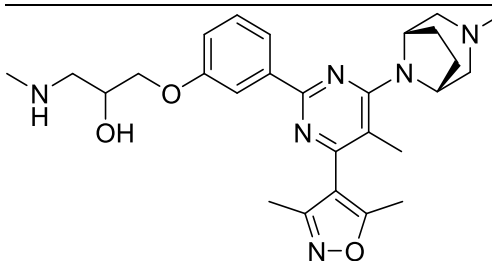
115-1a



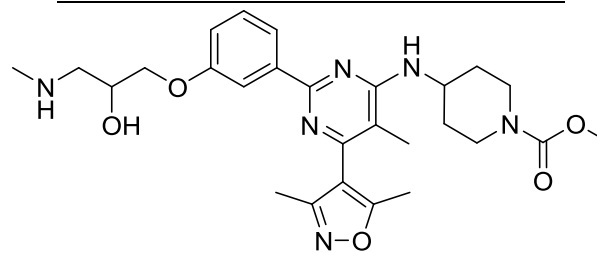
116-1a



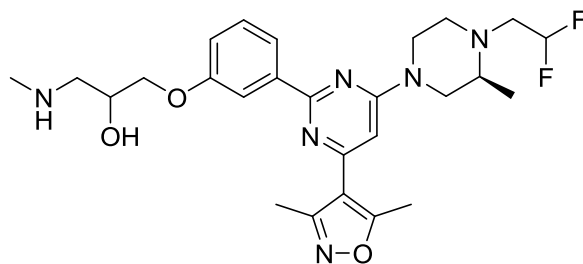
117-1a



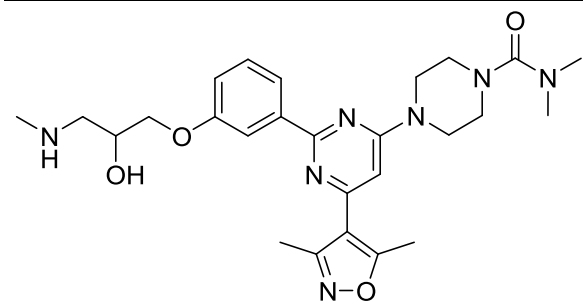
118-1a



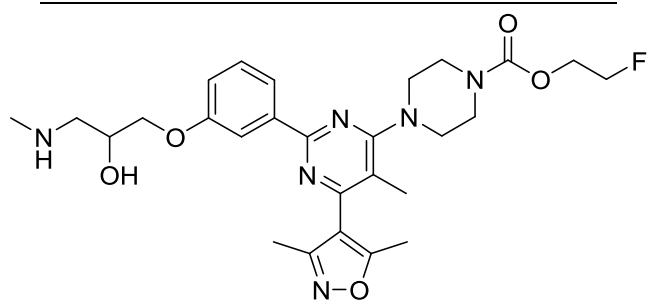
119-1a



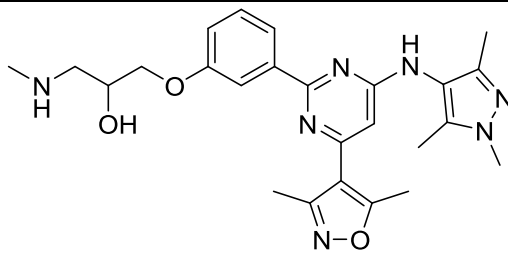
120-1a



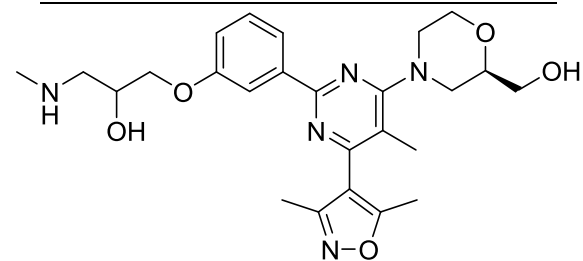
121-1a



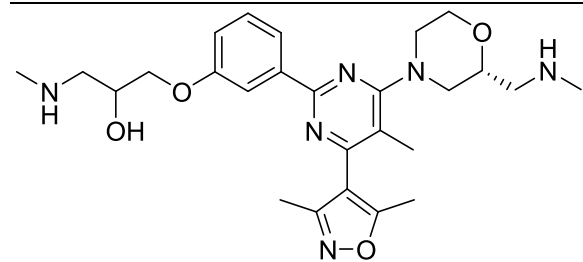
122-1a



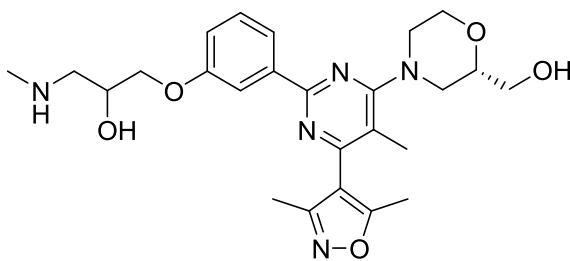
123-1a



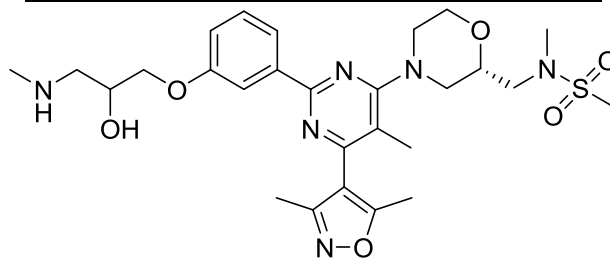
124-1a



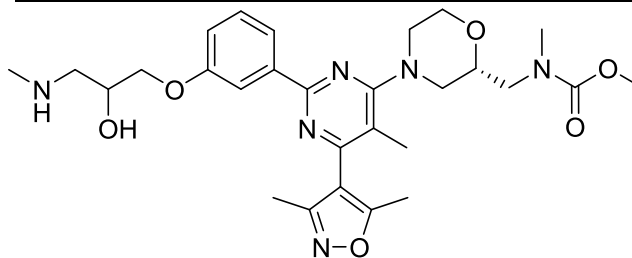
125-1a



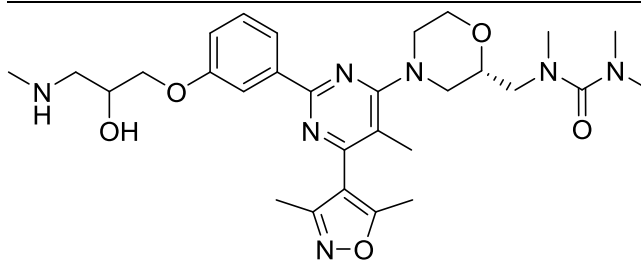
126-1a



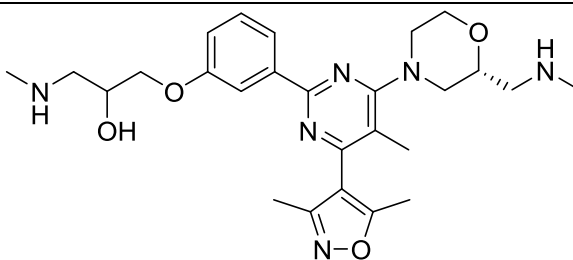
127-1a



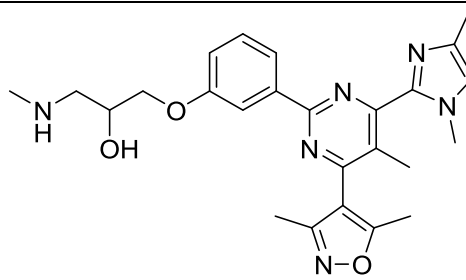
128-1a



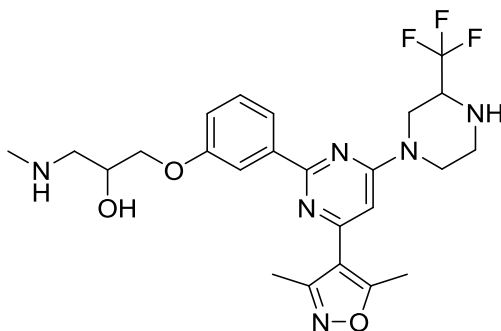
129-1a



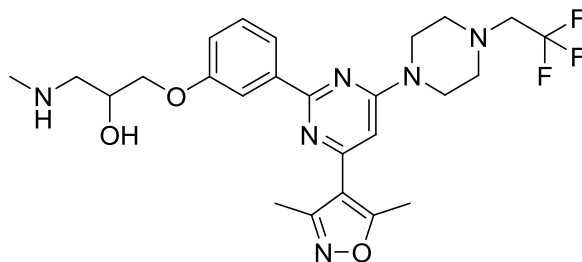
130-1a



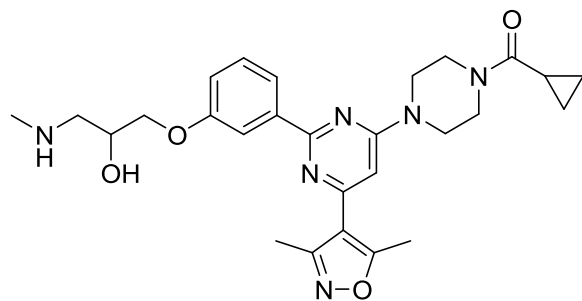
131-1a



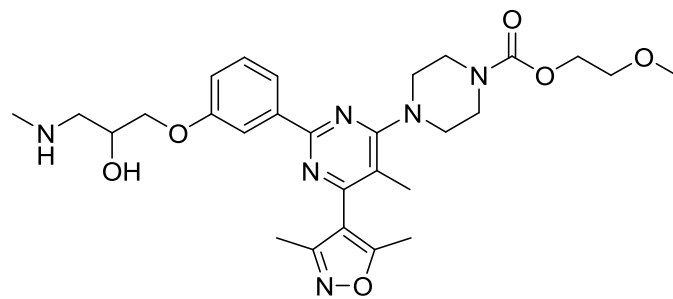
132-1a



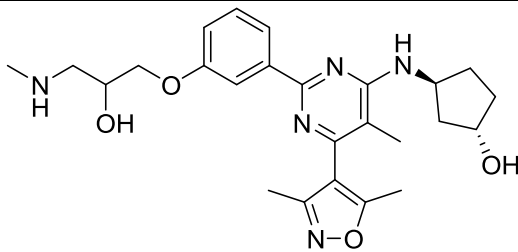
133-1a



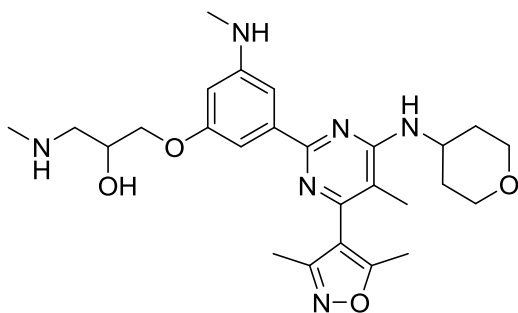
134-1a



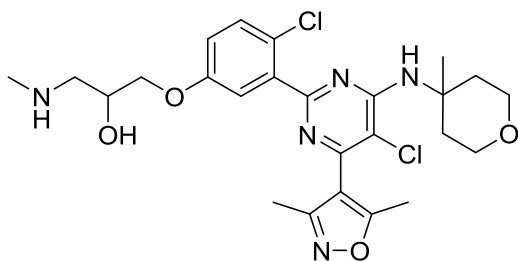
135-1a



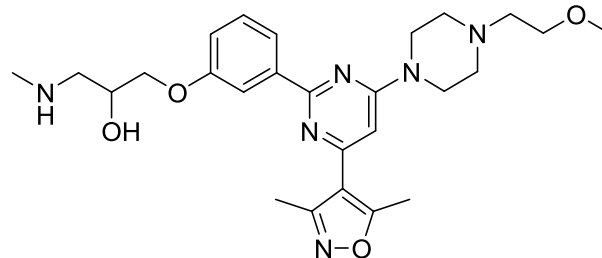
136-1a



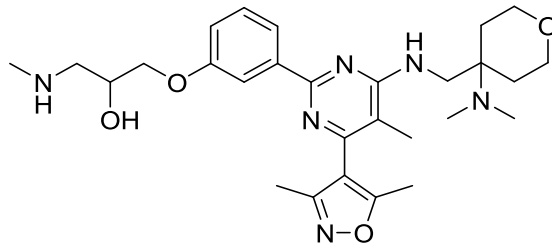
137-1a



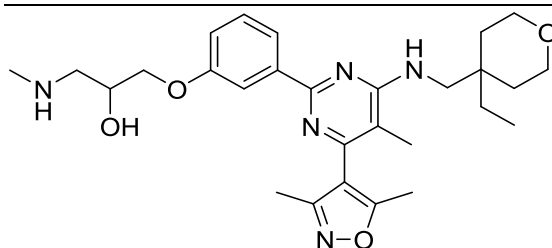
139-1a



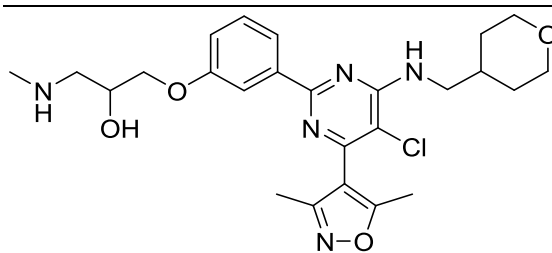
140-1a



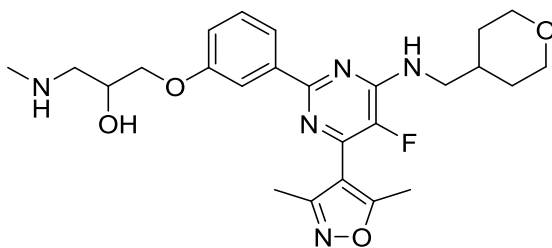
141-1a



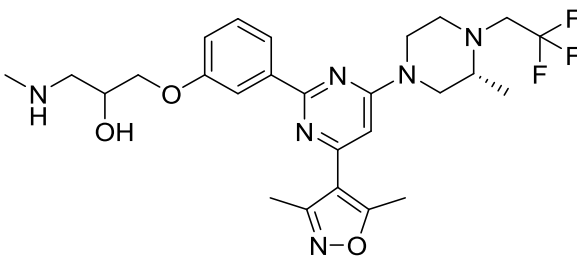
142-1a



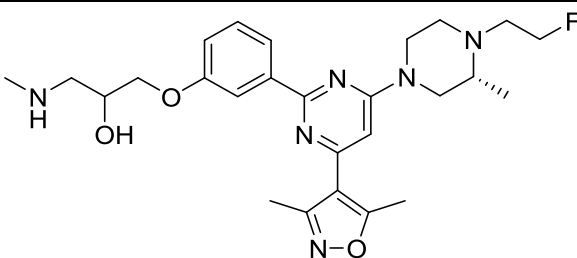
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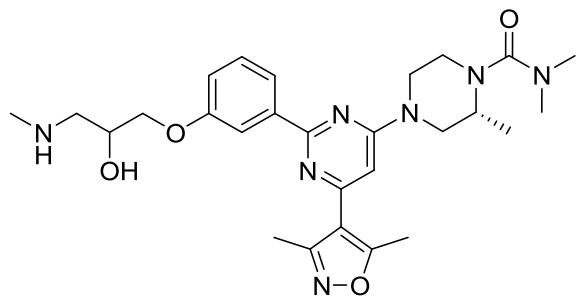
144-1a



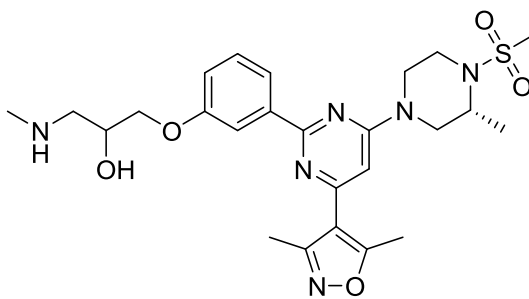
145-1a



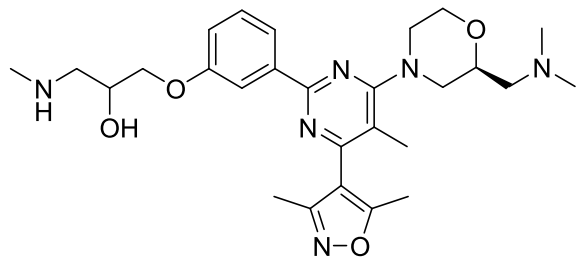
146-1a



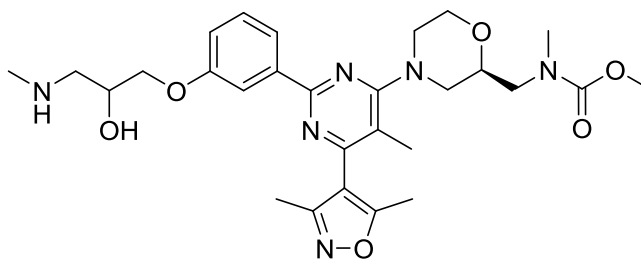
147-1a



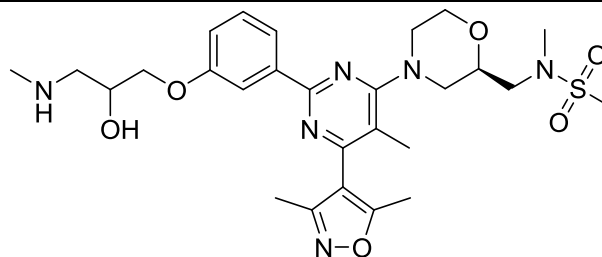
148-1a



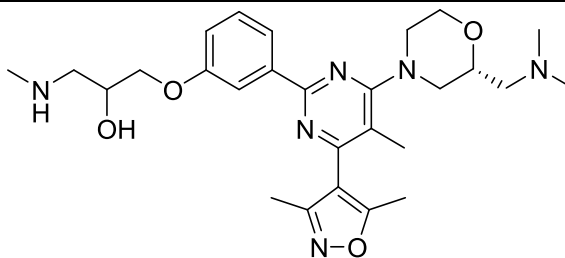
149-1a



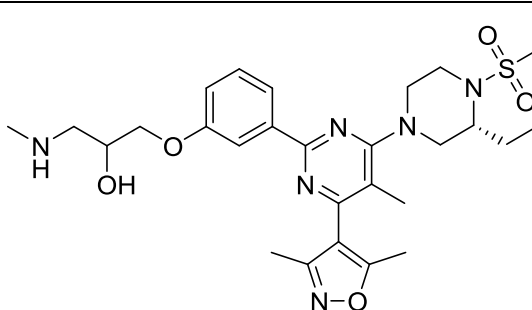
150-1a



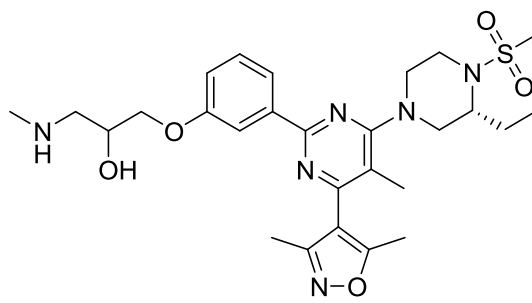
151-1a



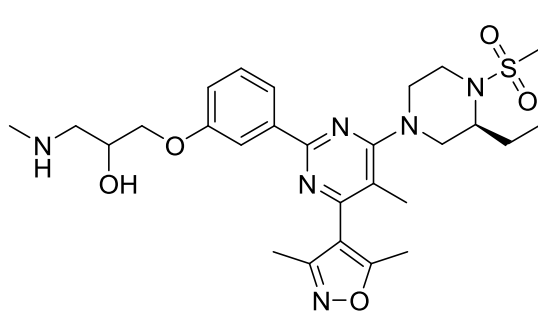
152-1a



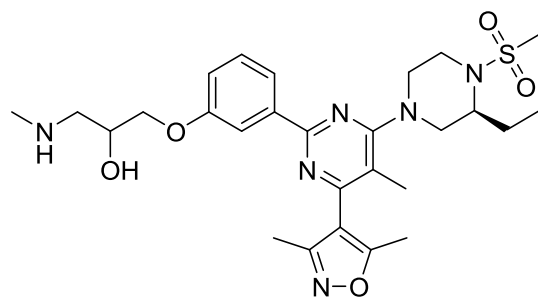
153-1a



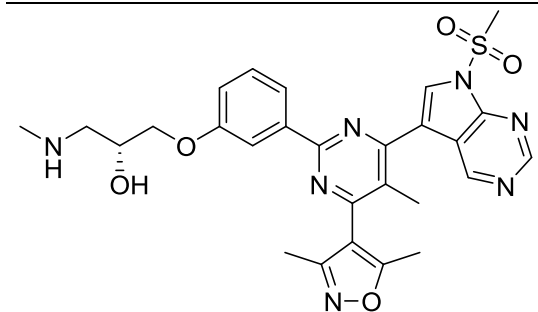
154-1a



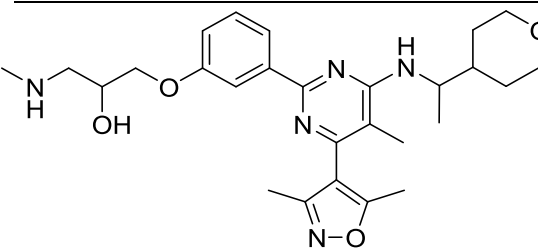
155-1a



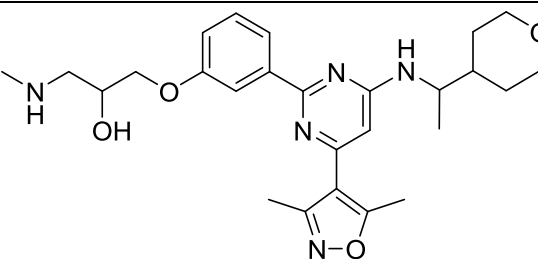
156-1a



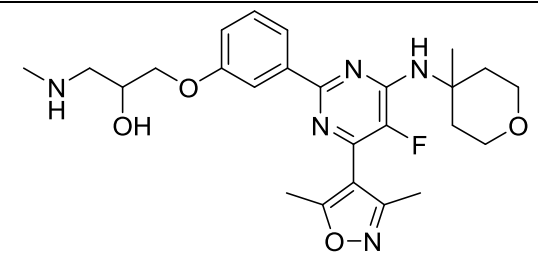
157-1a



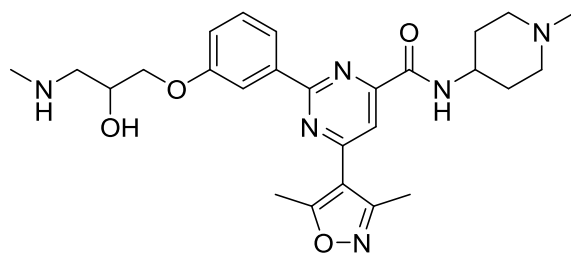
158-1a



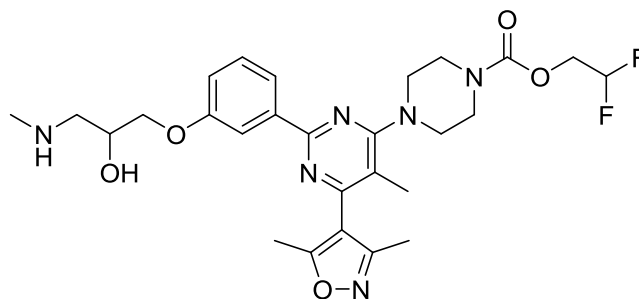
159-1a



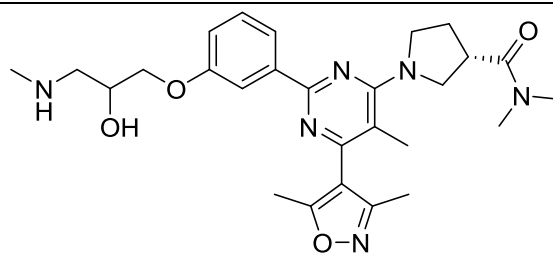
160-1a



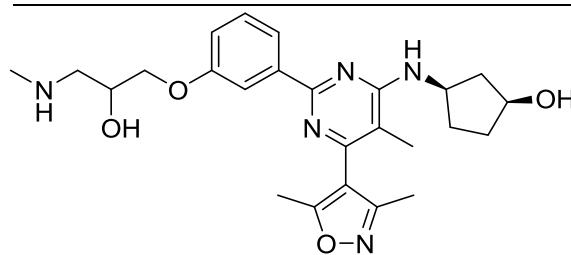
161-1a



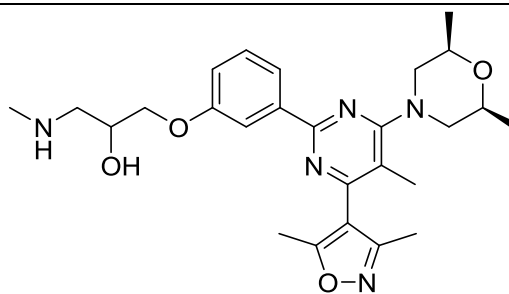
162-1a



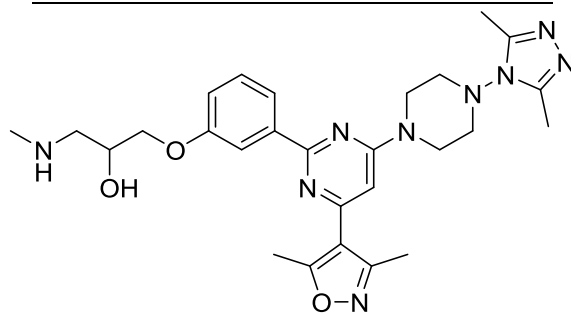
163-1a



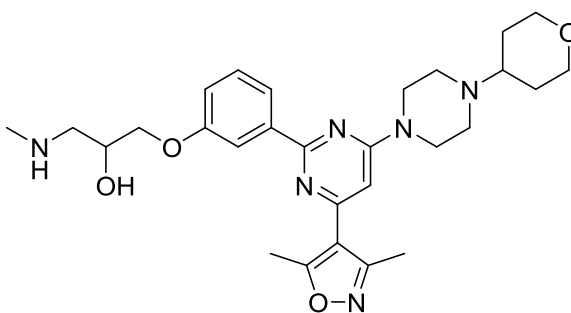
164-1a



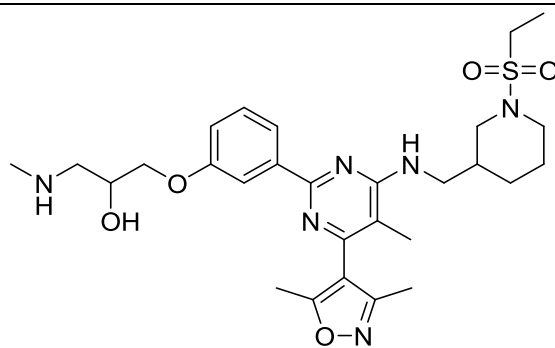
165-1a



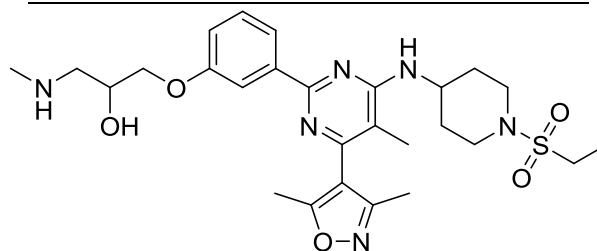
166-1a



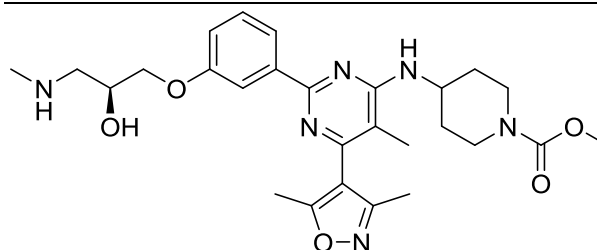
167-1a



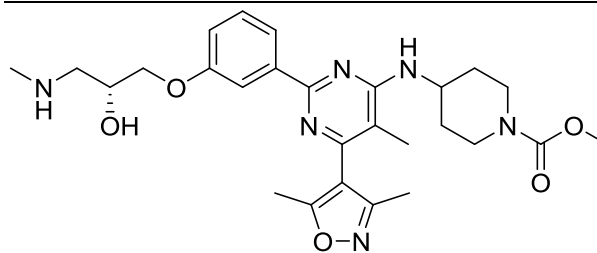
168-1a



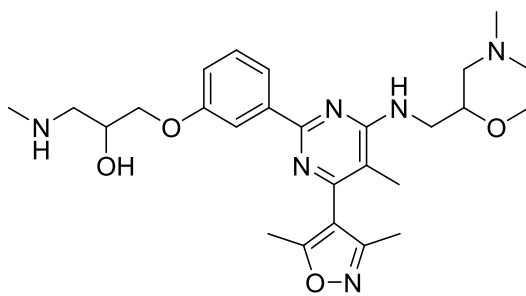
169-1a



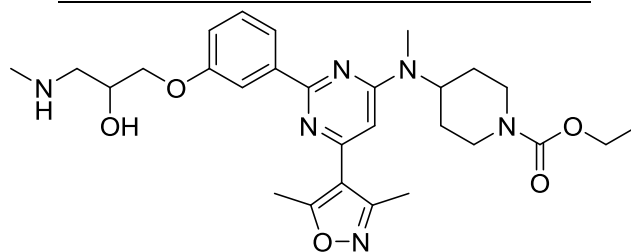
170-1a



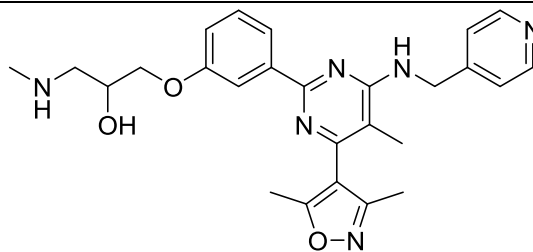
171-1a



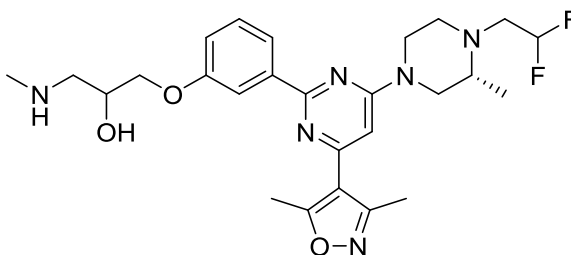
172-1a



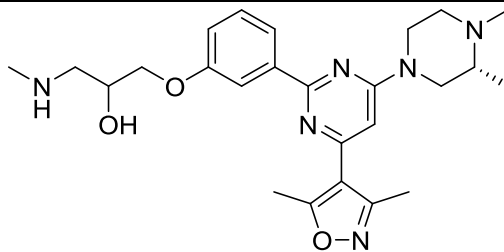
173-1a



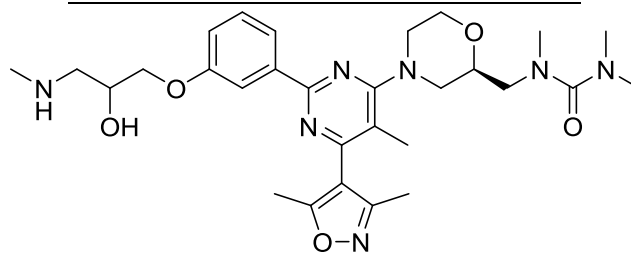
174-1a



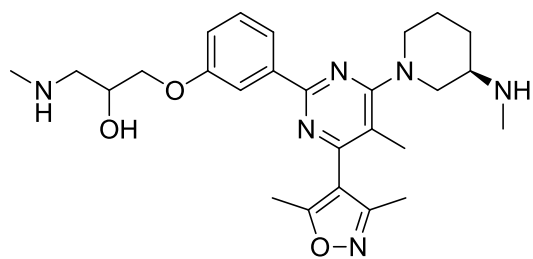
175-1a



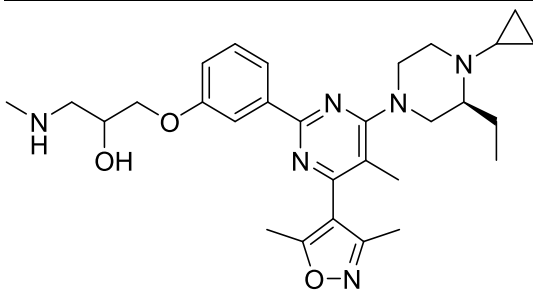
176-1a



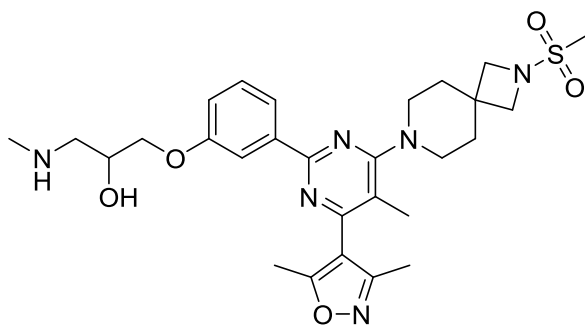
177-1a



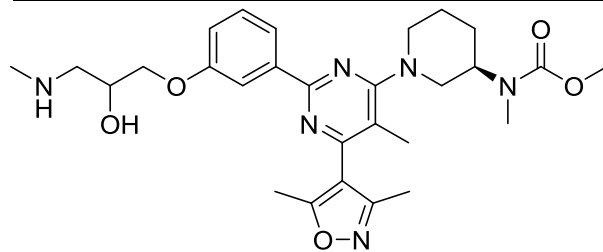
178-1a



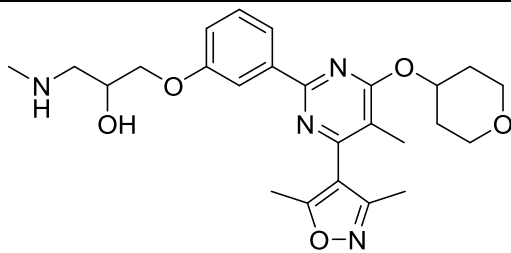
179-1a



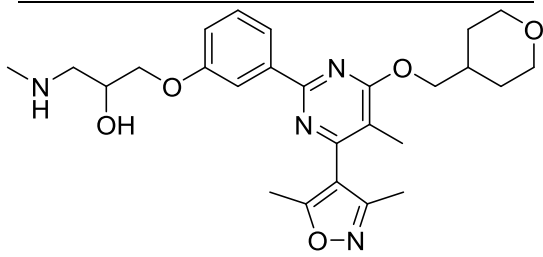
180-1a



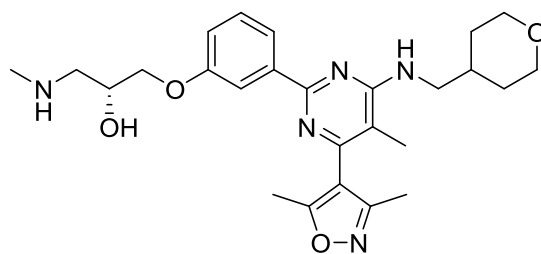
181-1a



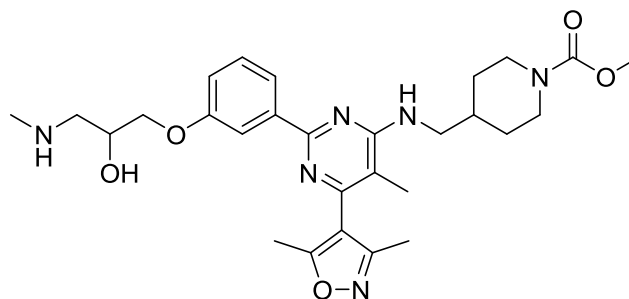
182-1a



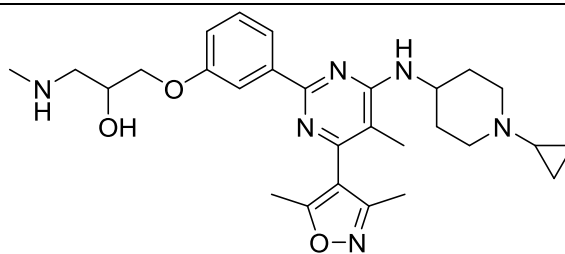
183-1a



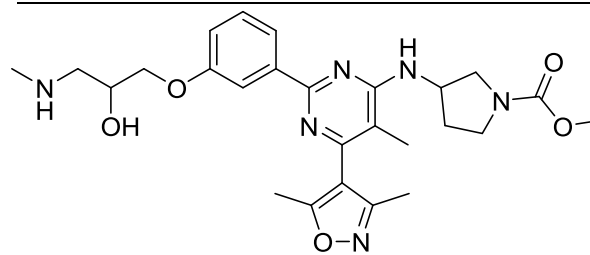
184-1a



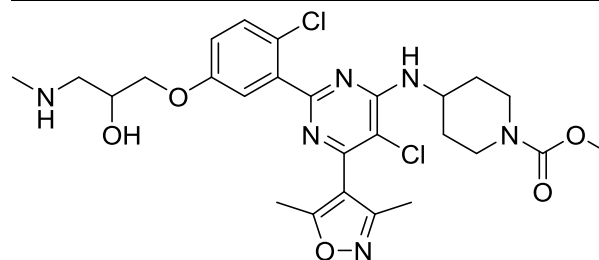
185-1a



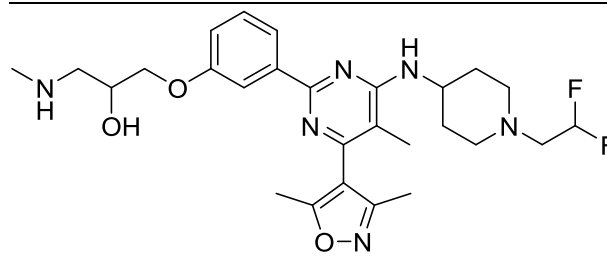
186-1a



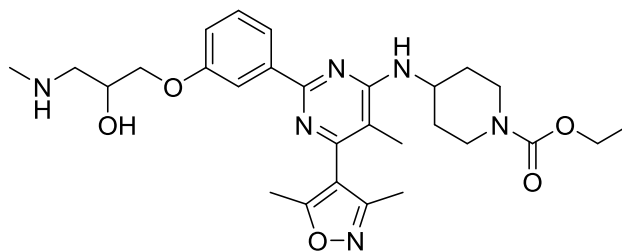
187-1a



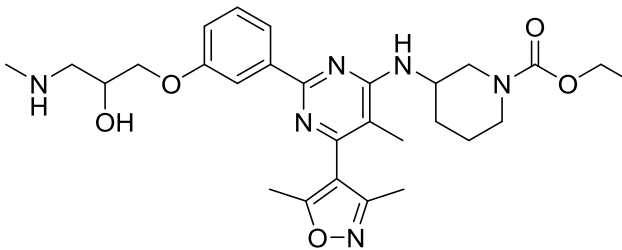
188-1a



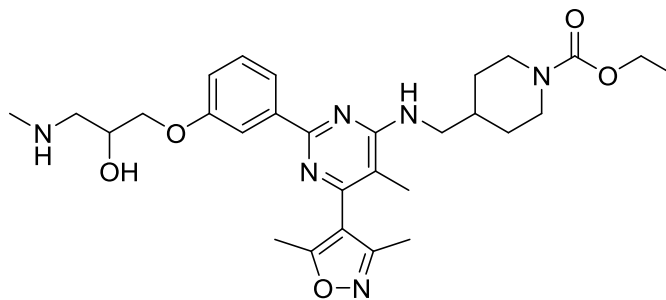
189-1a



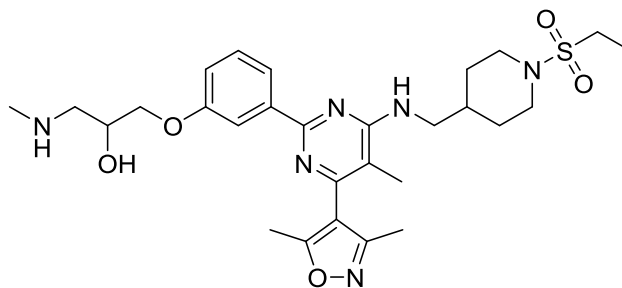
190-1a



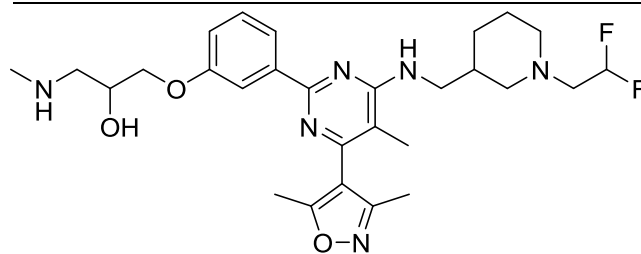
191-1a



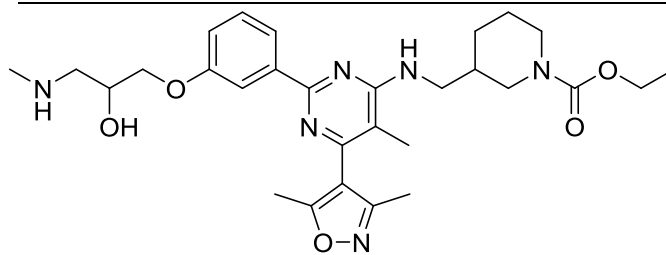
192-1a



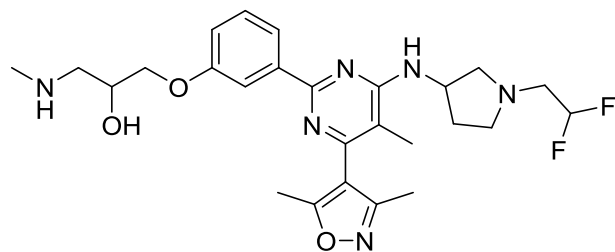
193-1a



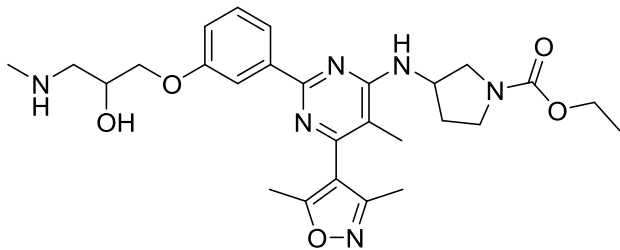
194-1a



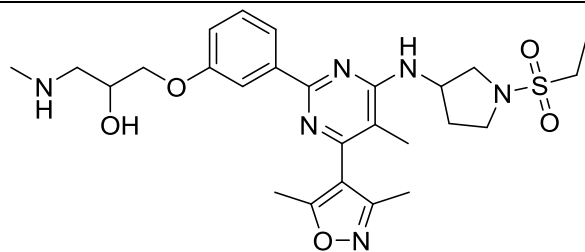
195-1a



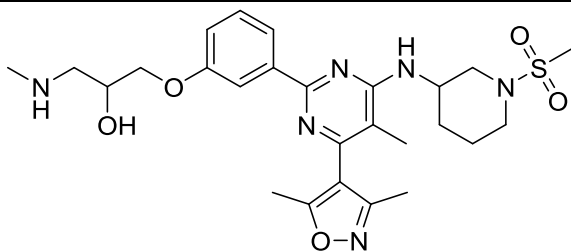
196-1a



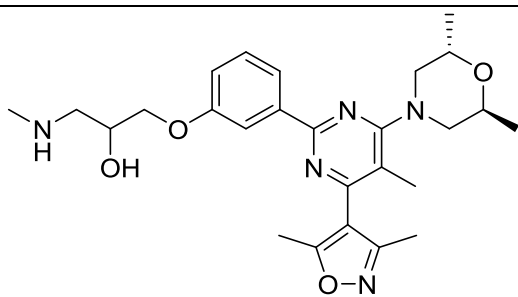
197-1a



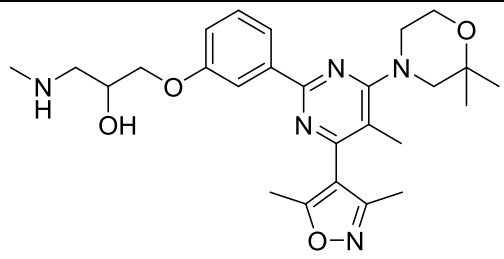
198-1a



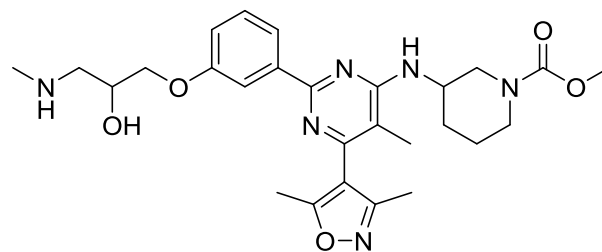
199-1a



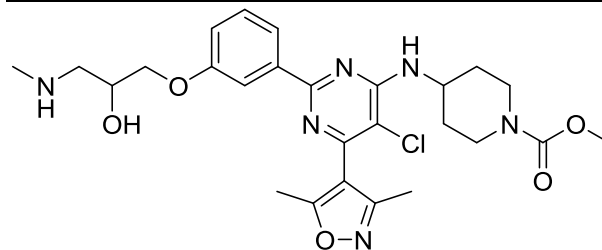
200-1a



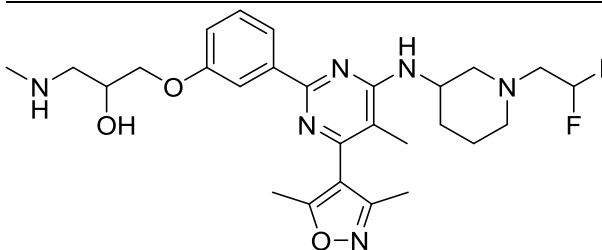
201-1a



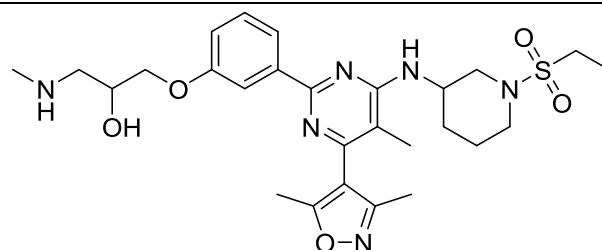
202-1a



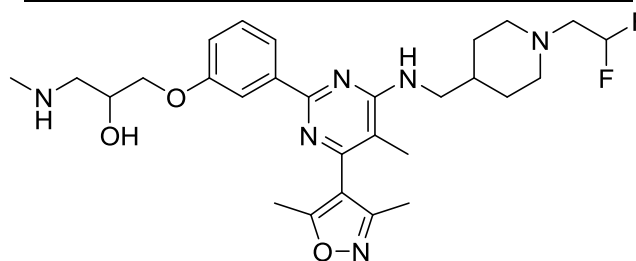
203-1a



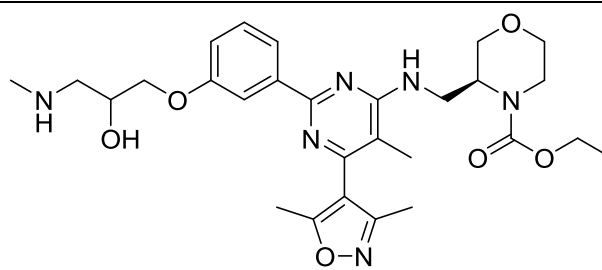
204-1a



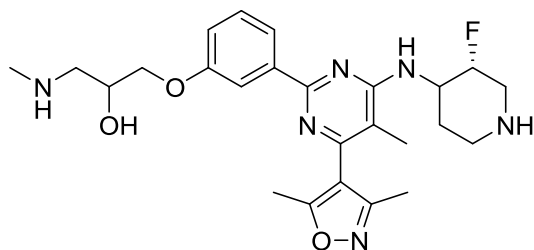
205-1a



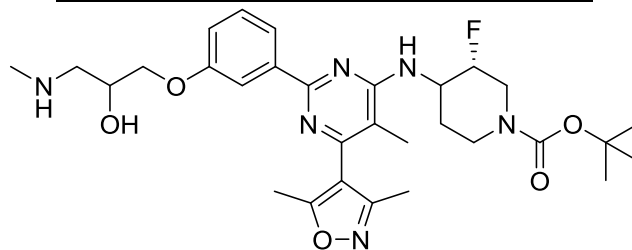
206-1a



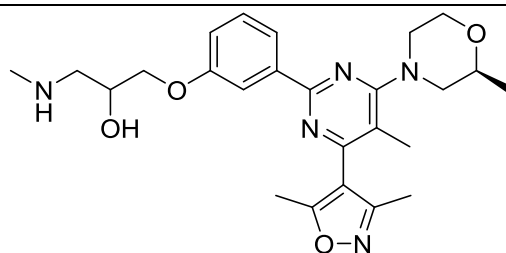
207-1a



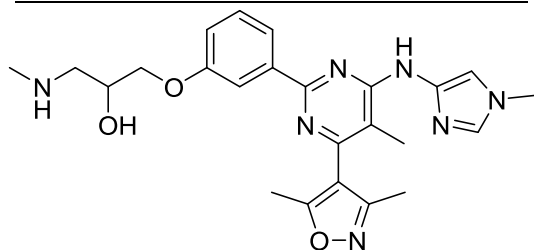
208-1a



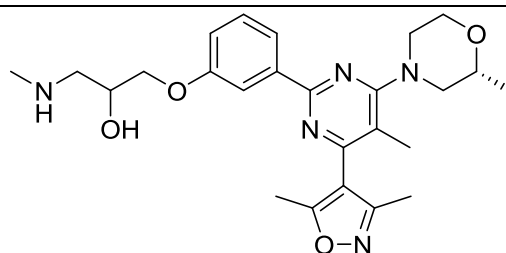
209-1a



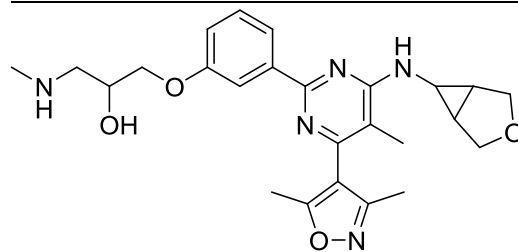
210-1a



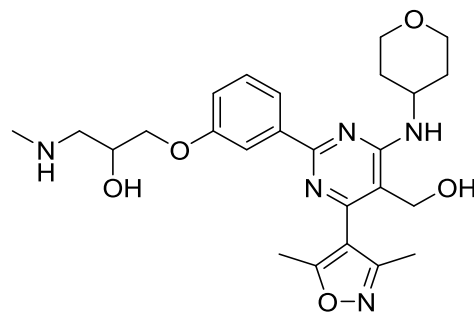
211-1a



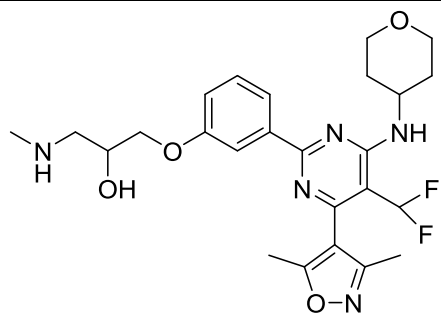
212-1a



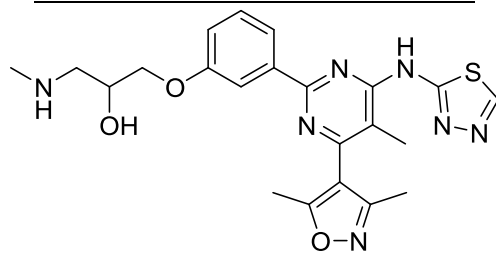
213-1a



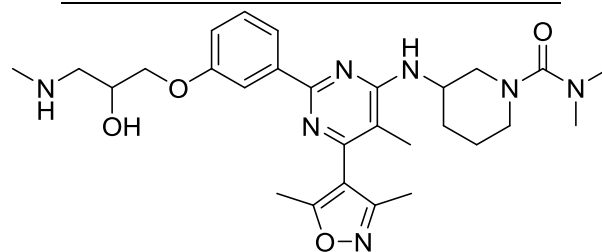
214-1a



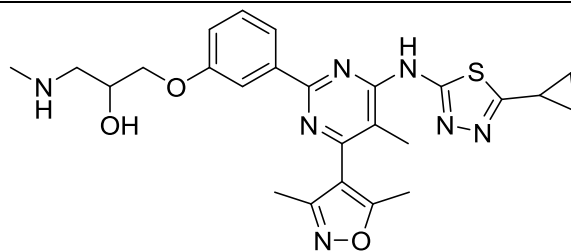
215-1a



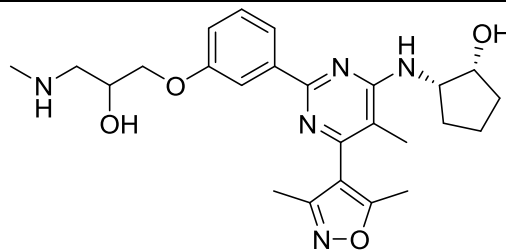
216-1a



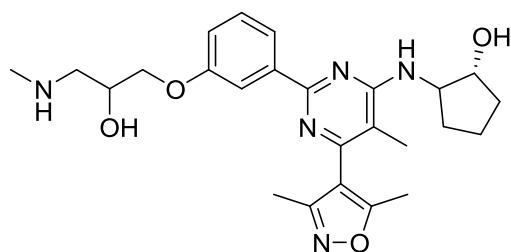
217-1a



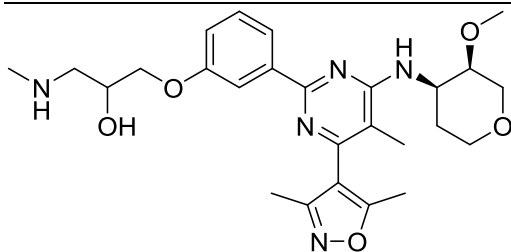
218-1a



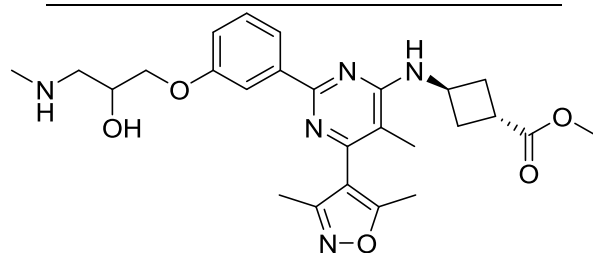
219-1a



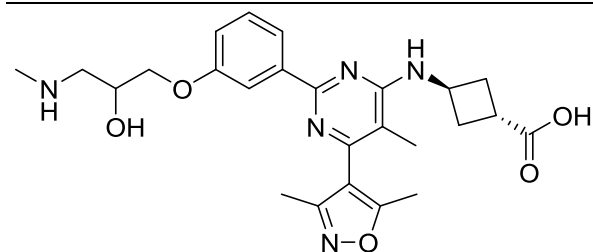
220-1a



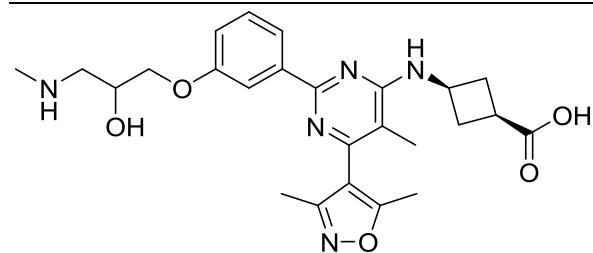
221-1a



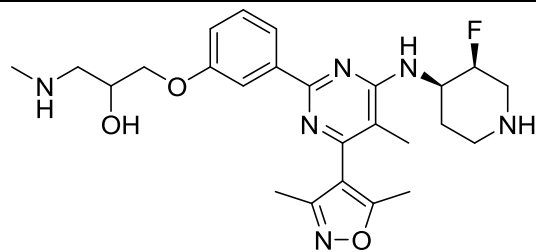
222-1a



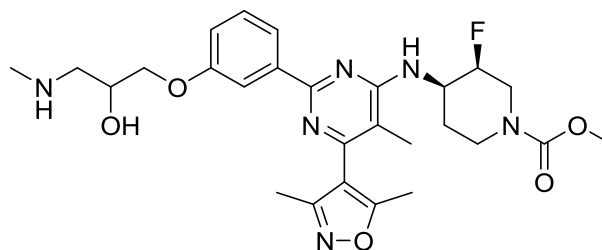
223-1a



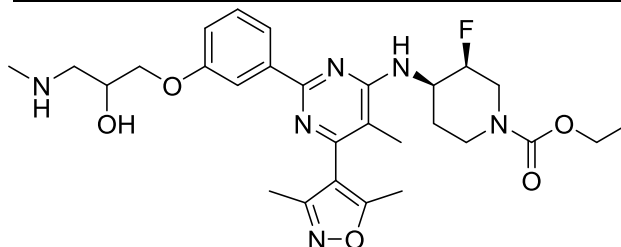
224-1a



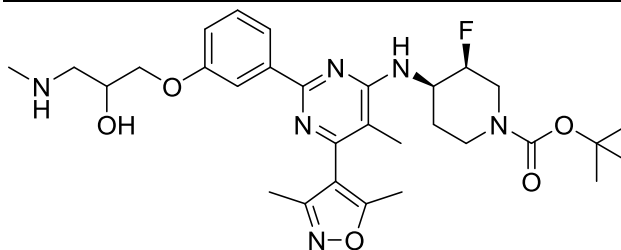
225-1a



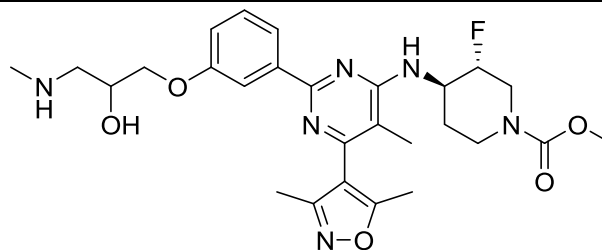
226-1a



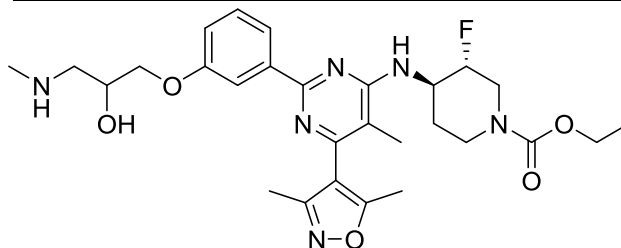
227-1a



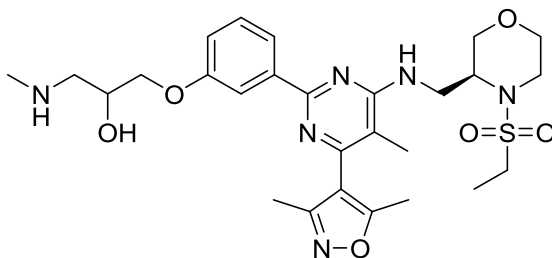
228-1a



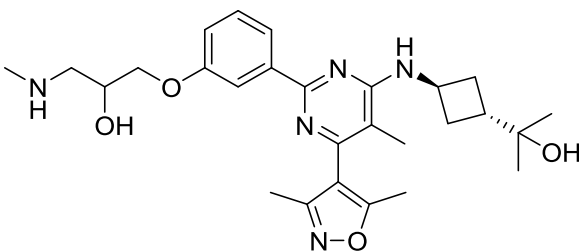
229-1a



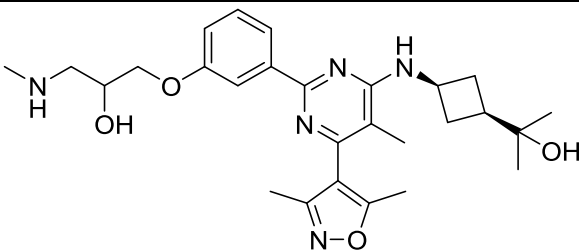
230-1a



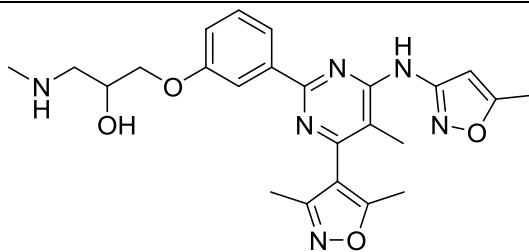
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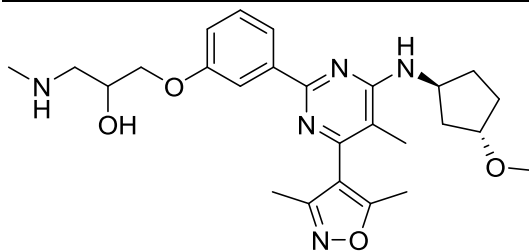
232-1a



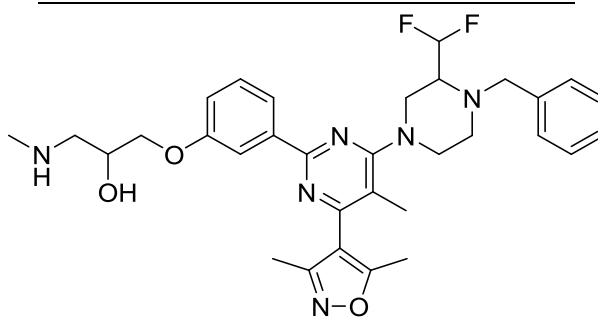
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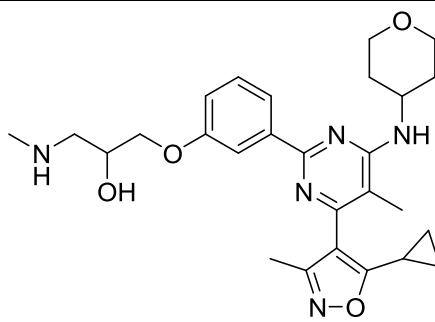
234-1a



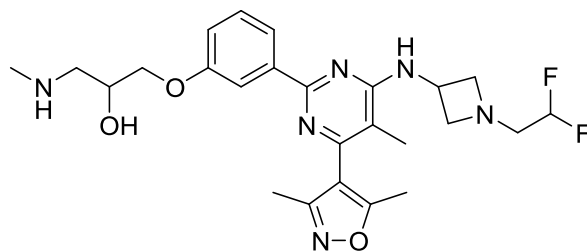
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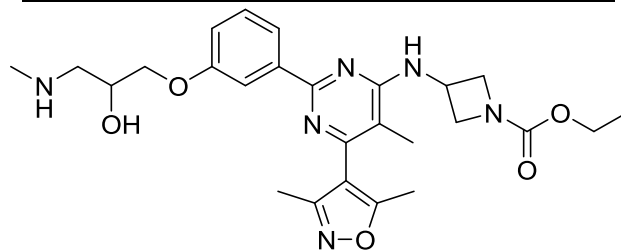
236-1a



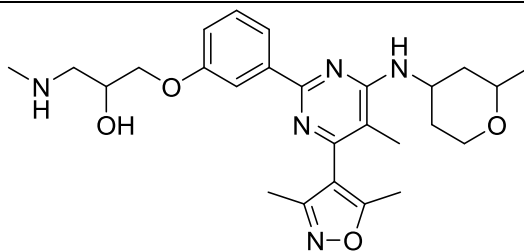
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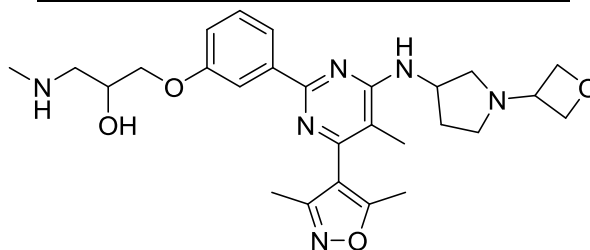
238-1a



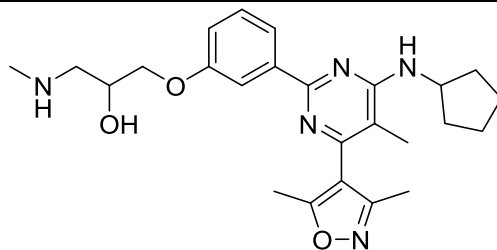
239-1a



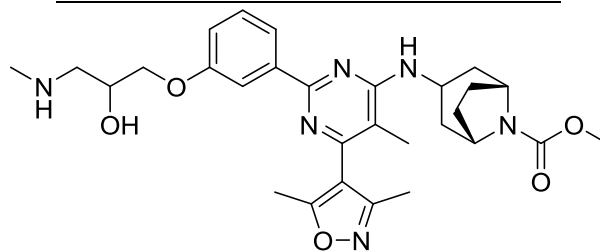
240-1a



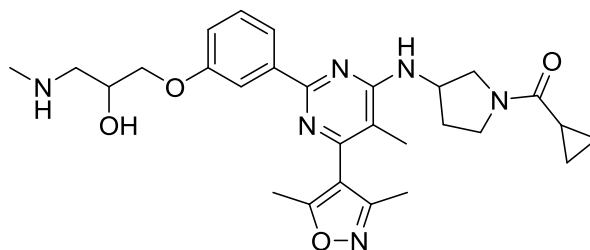
241-1a



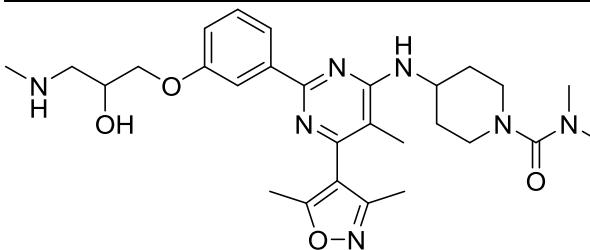
242-1a



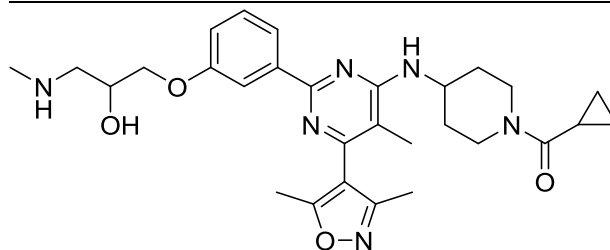
243-1a



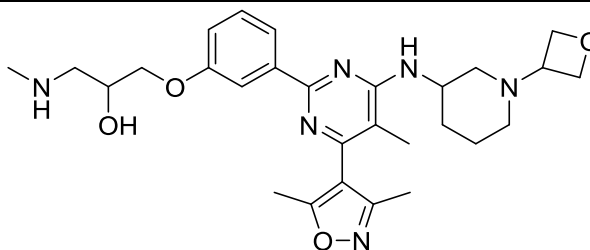
244-1a



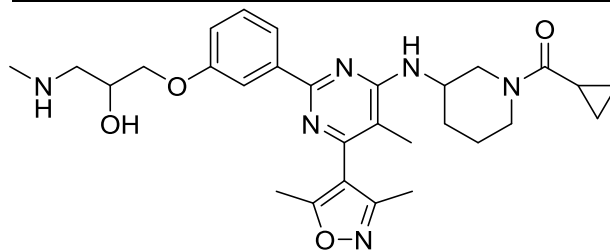
245-1a



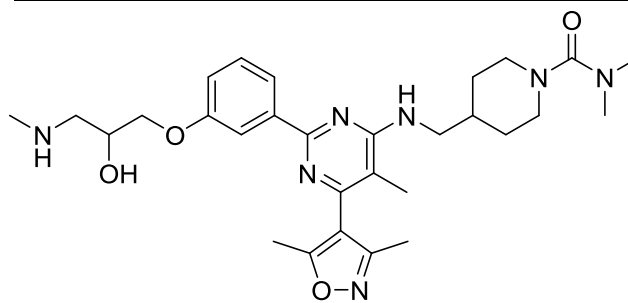
246-1a



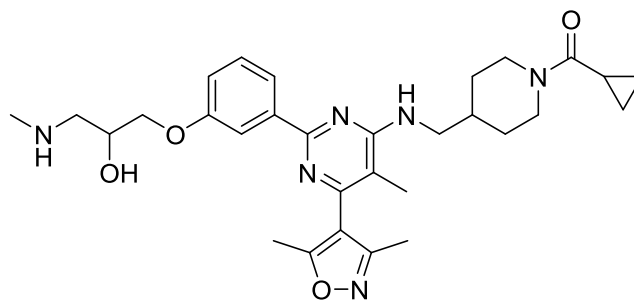
247-1a



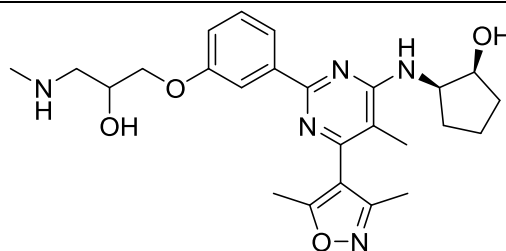
248-1a



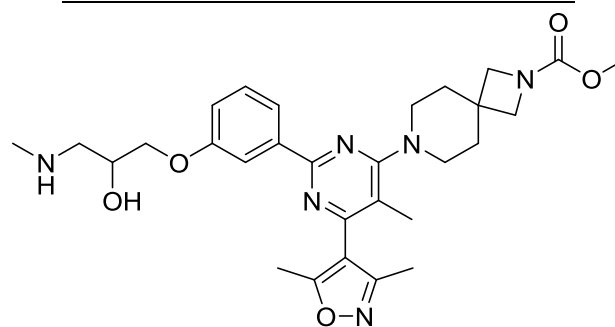
249-1a



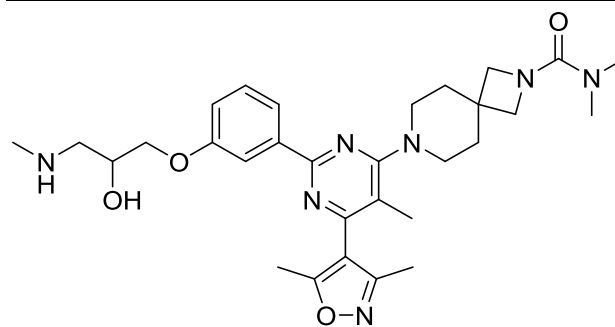
250-1a



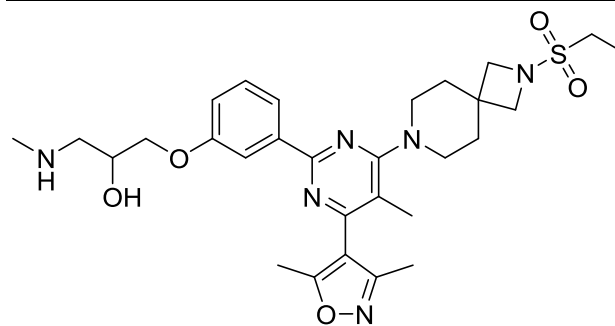
251-1a



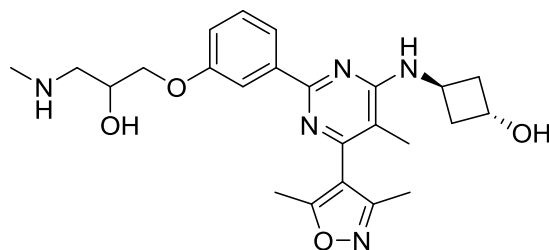
252-1a



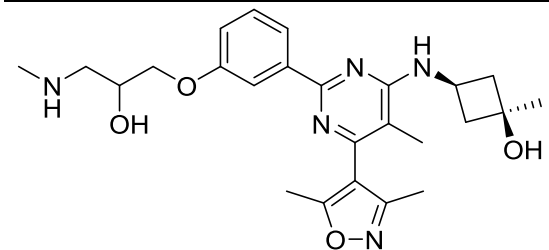
253-1a



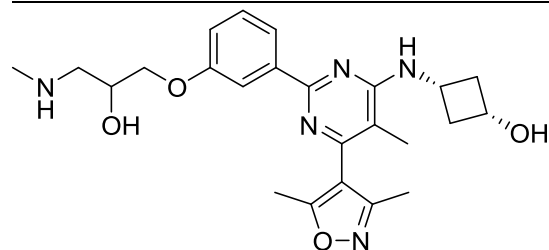
254-1a



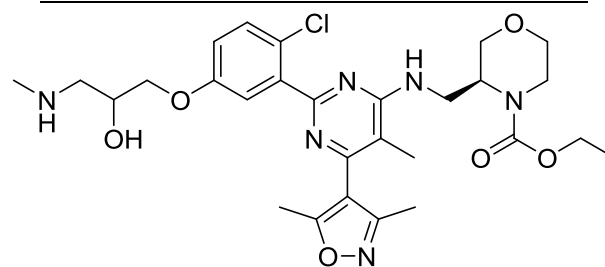
255-1a



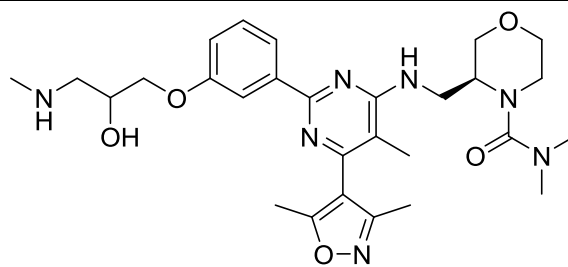
256-1a



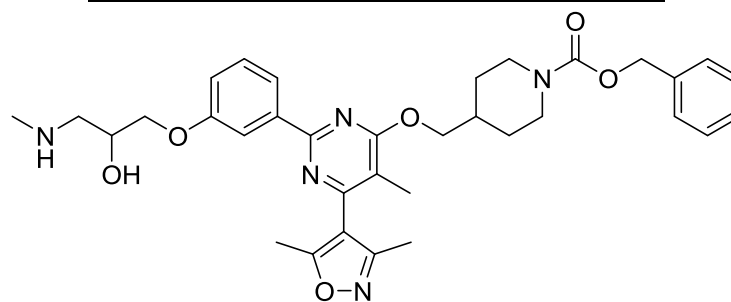
257-1a



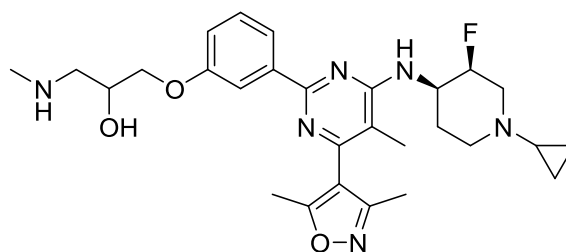
258-1a



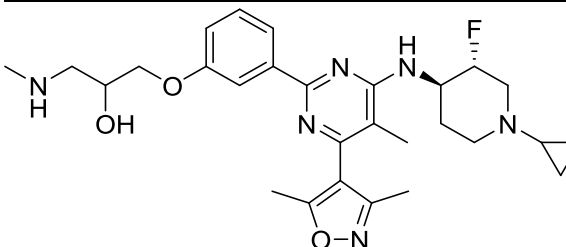
259-1a



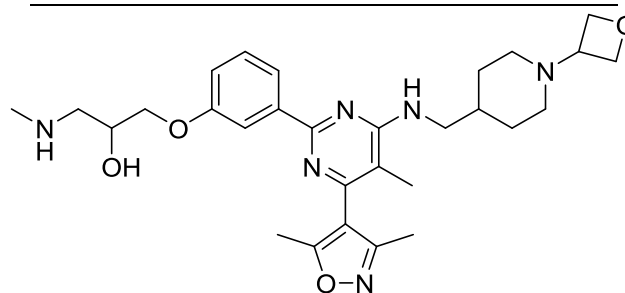
260-1a



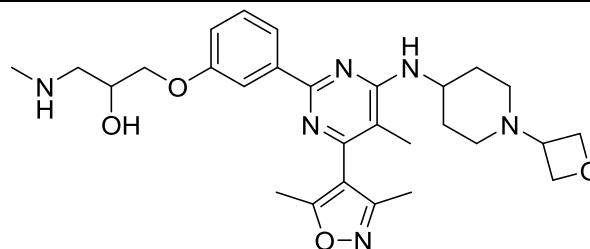
261-1a



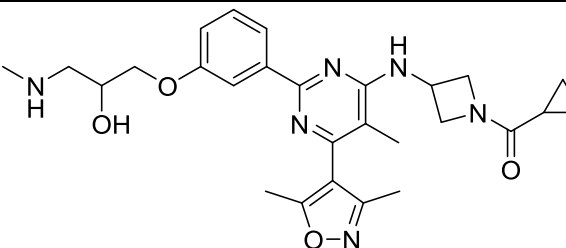
262-1a



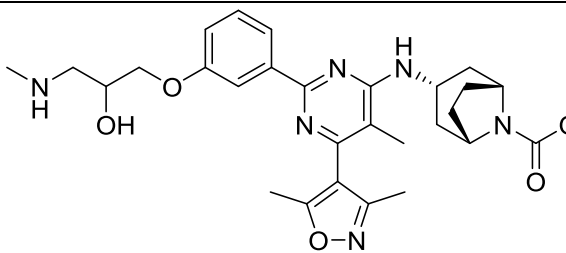
263-1a



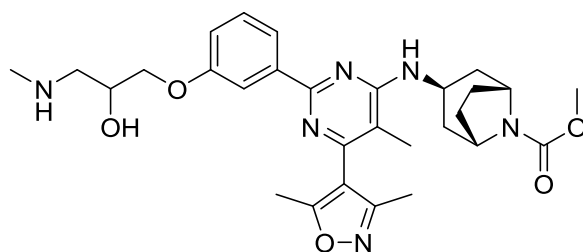
264-1a



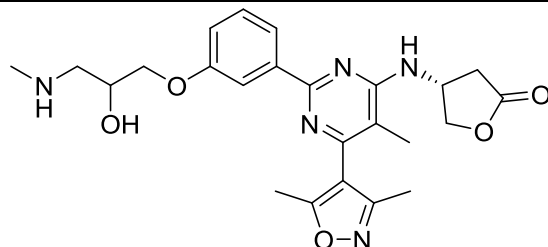
265-1a



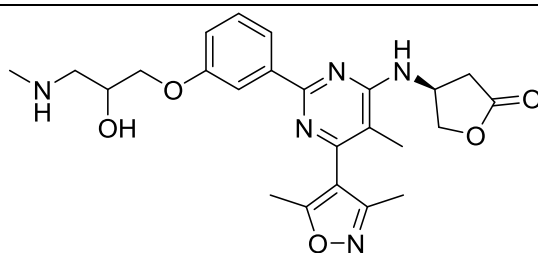
266-1a



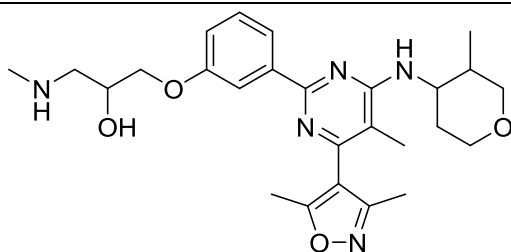
267-1a



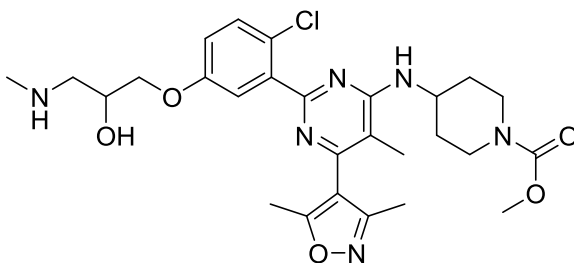
268-1a



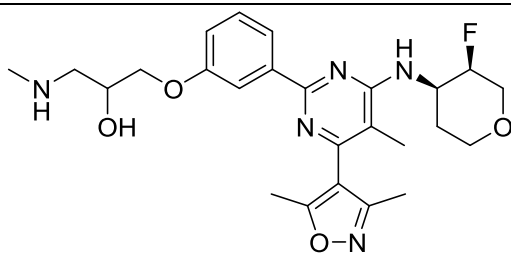
269-1a



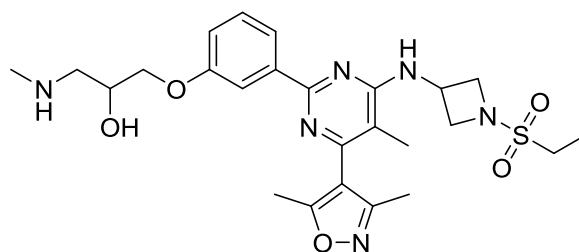
270-1a



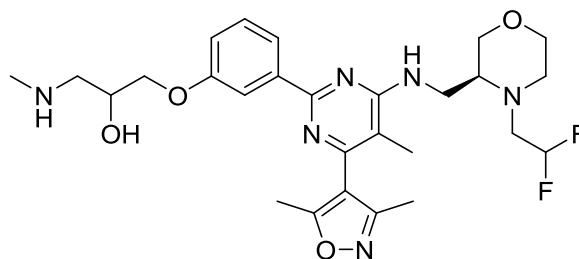
271-1a



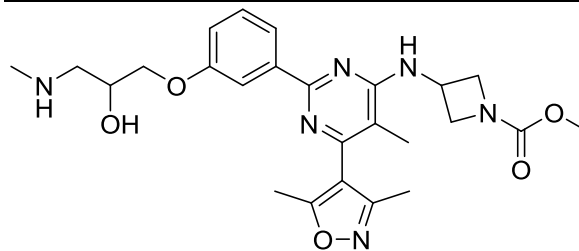
273-1a



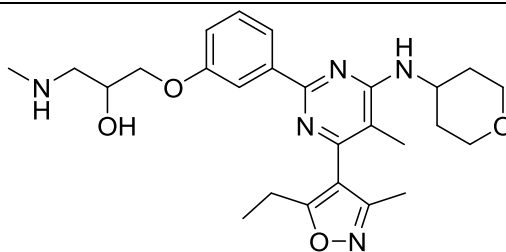
274-1a



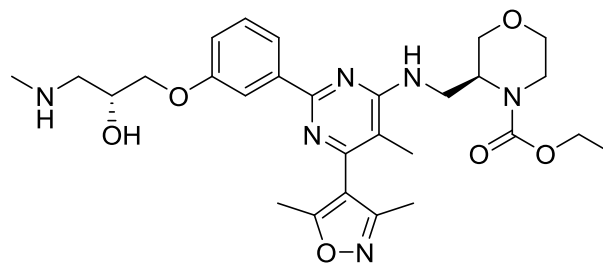
275-1a



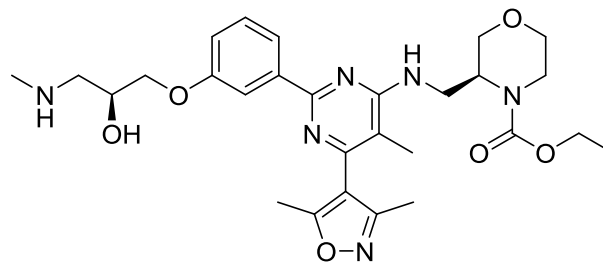
276-1a



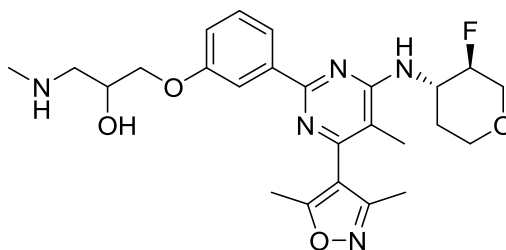
277-1a



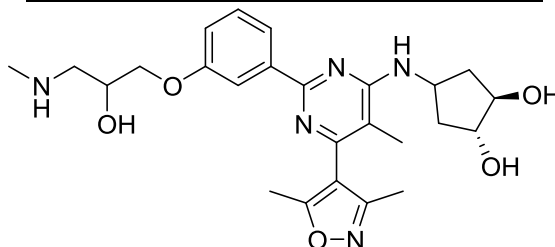
278-1a



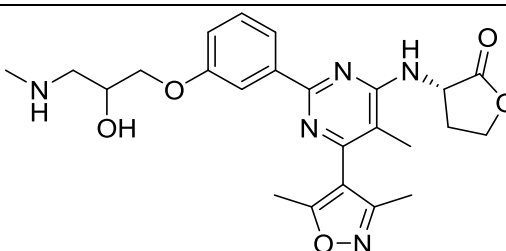
279-1a



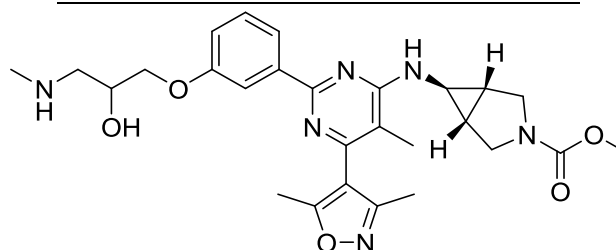
280-1a



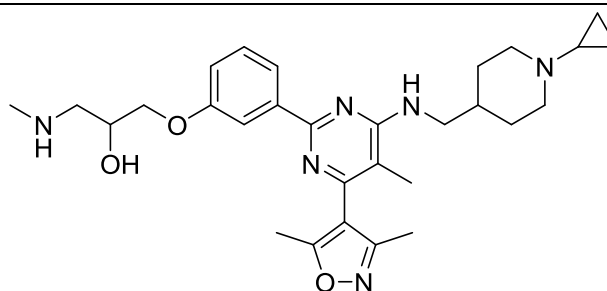
281-1a



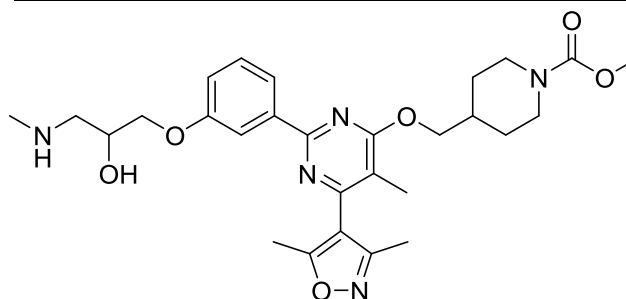
282-1a



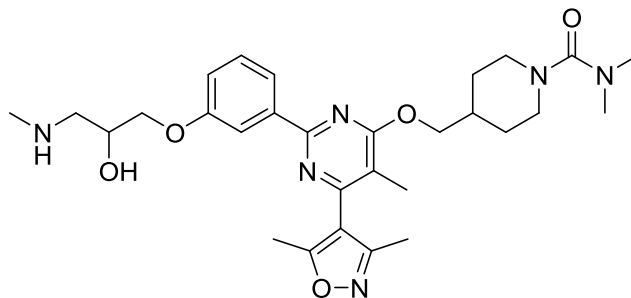
283-1a



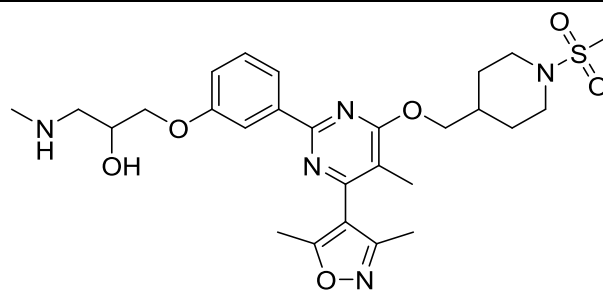
284-1a



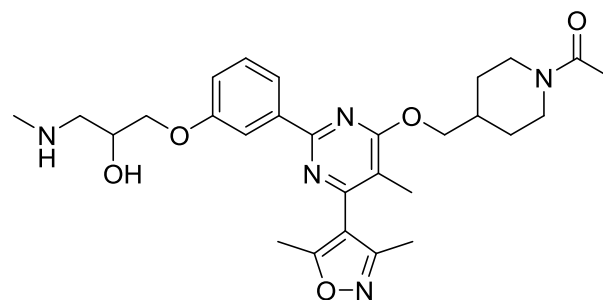
285-1a



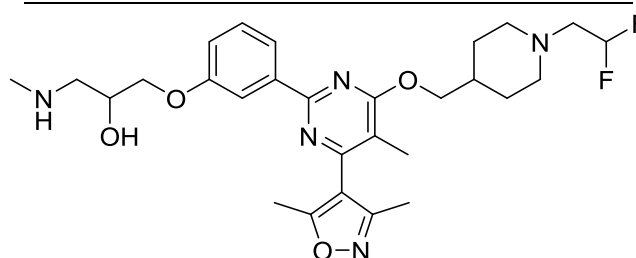
286-1a



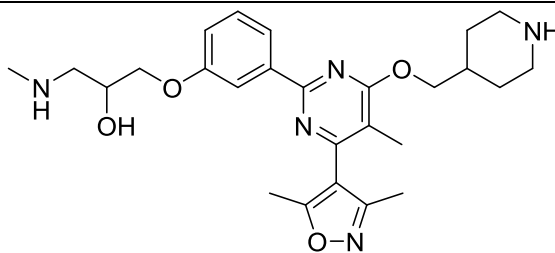
287-1a



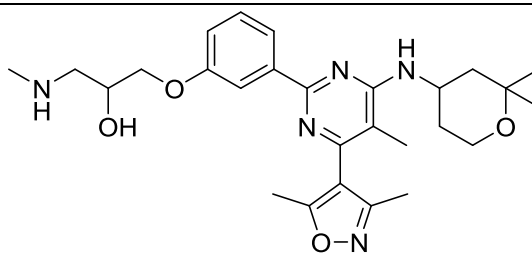
288-1a



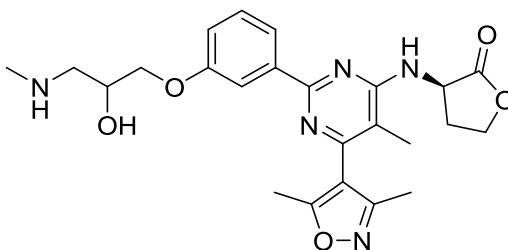
289-1a



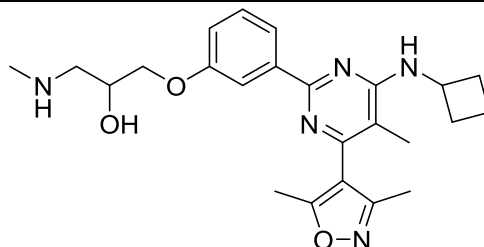
290-1a



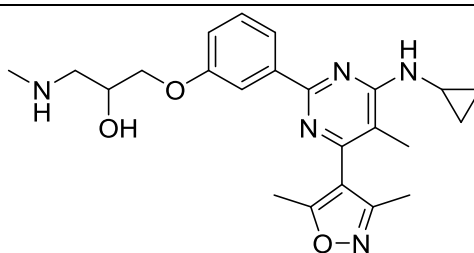
291-1a



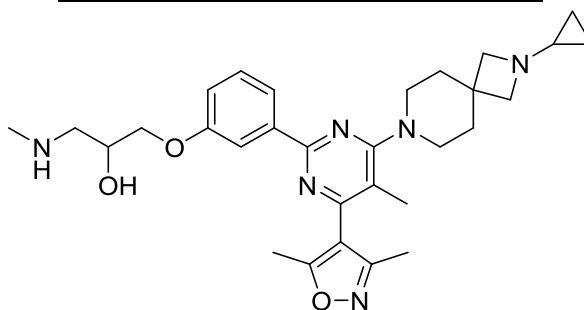
292-1a



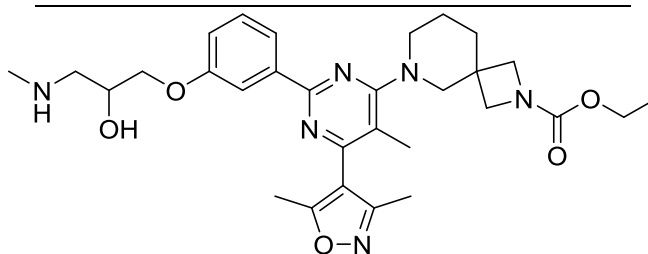
293-1a



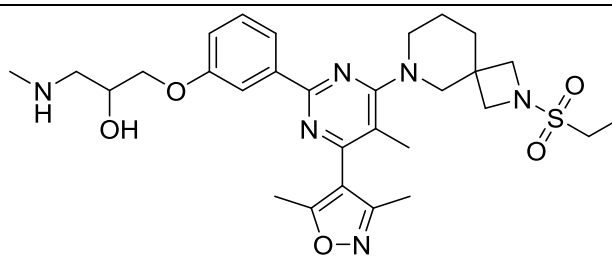
294-1a



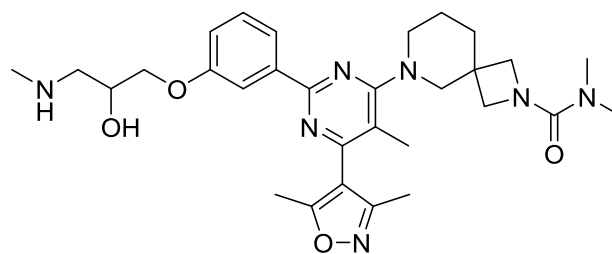
295-1a



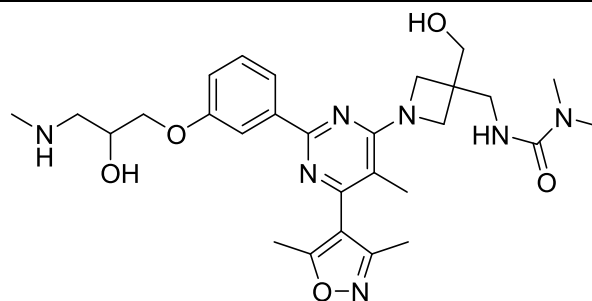
296-1a



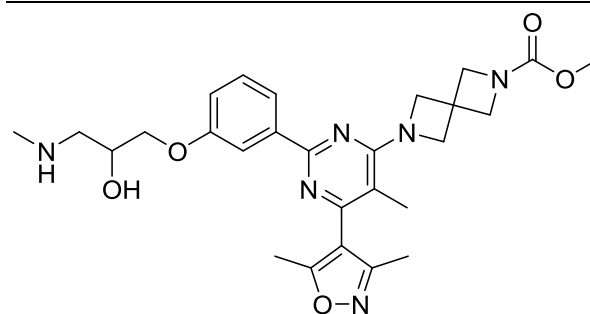
297-1a



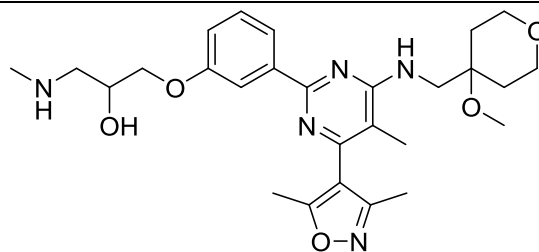
298-1a



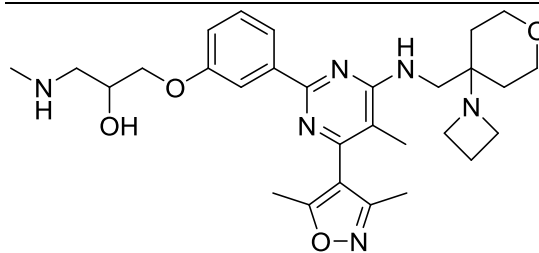
299-1a



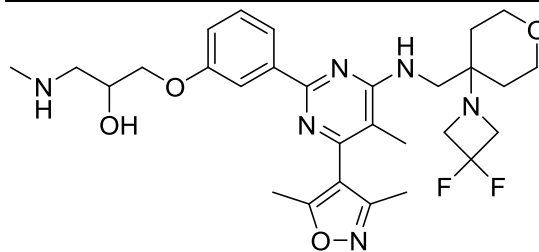
300-1a



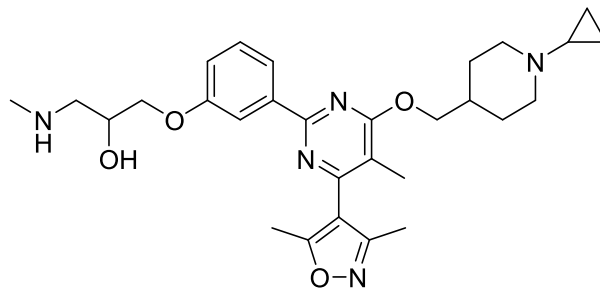
301-1a



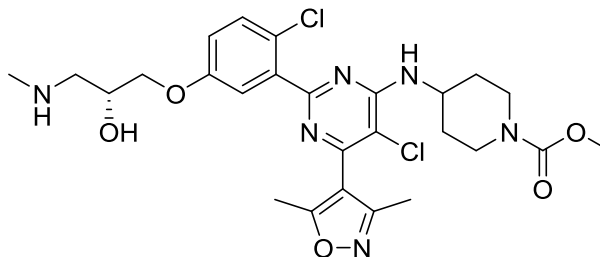
302-1a



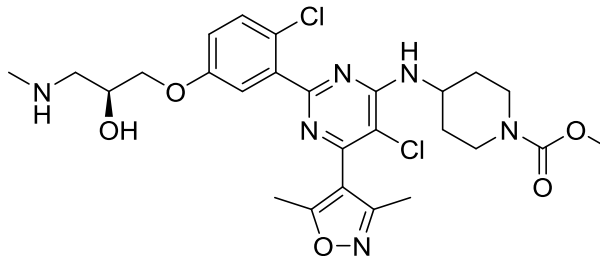
303-1a



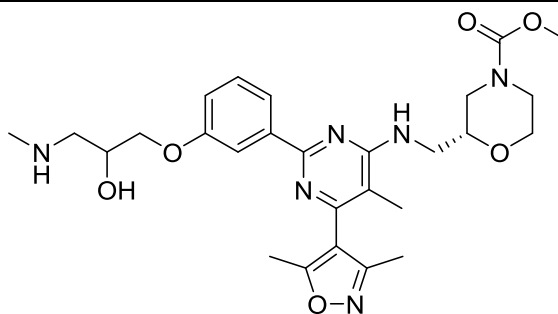
304-1a



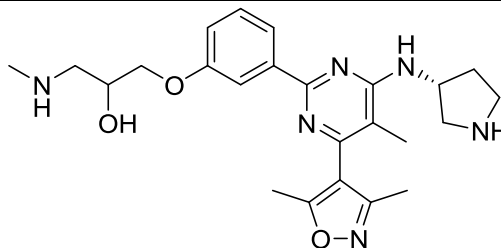
305-1a



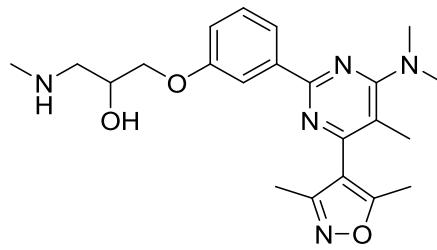
306-1a



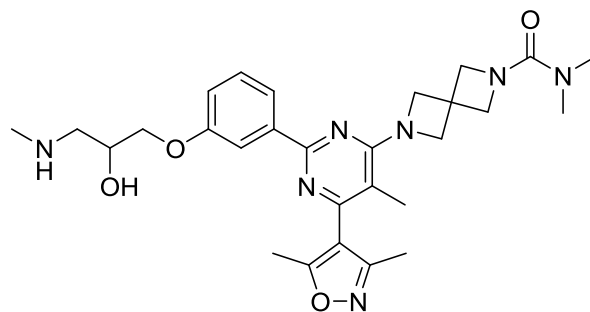
307-1a



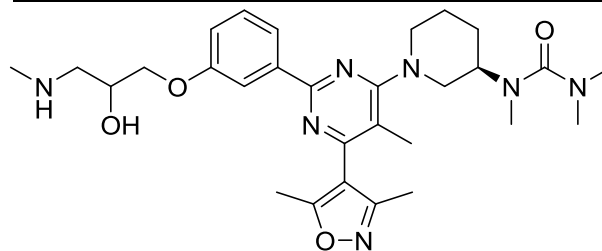
308-1a



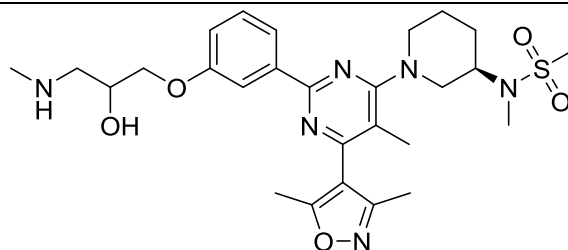
309-1a



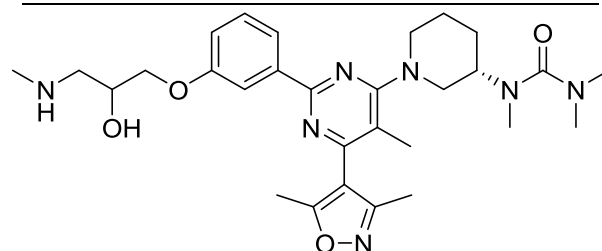
310-1a



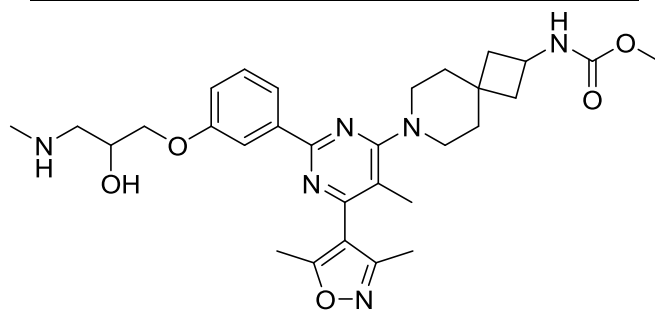
311-1a



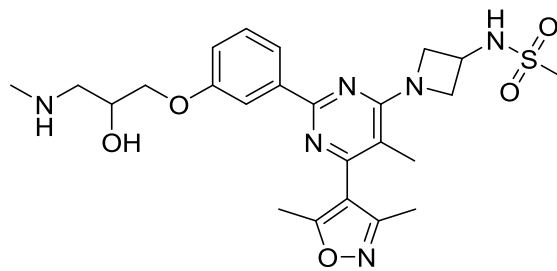
312-1a



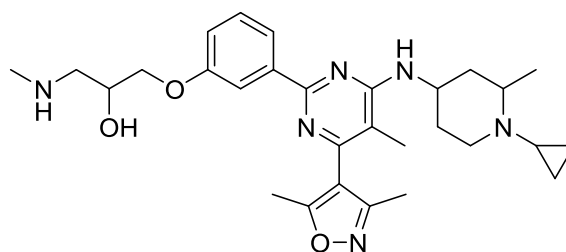
313-1a



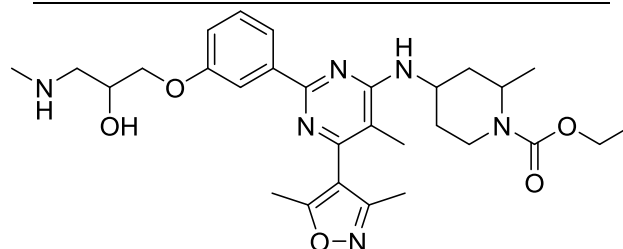
314-1a



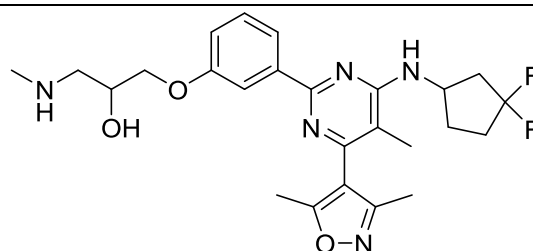
315-1a



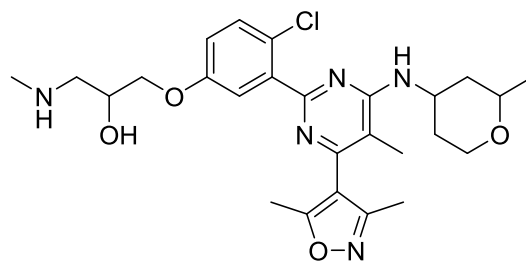
316-1a



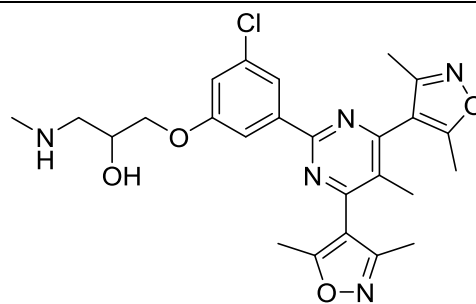
317-1a



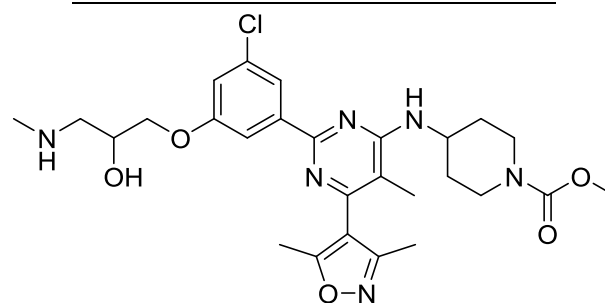
318-1a



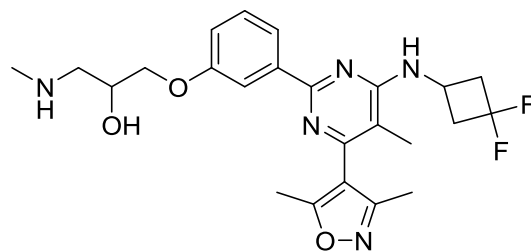
319-1a



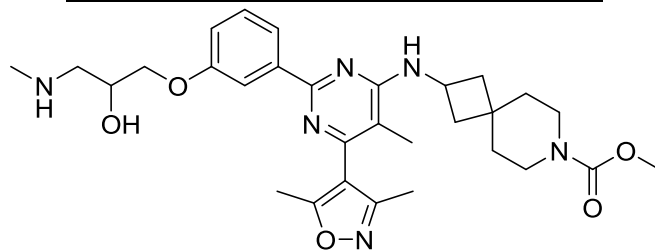
320-1a



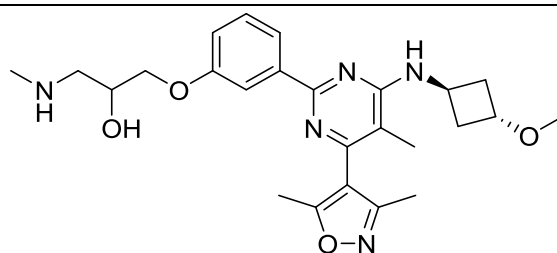
321-1a



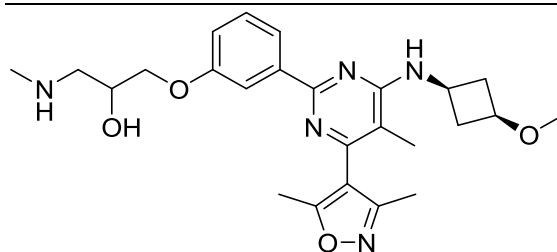
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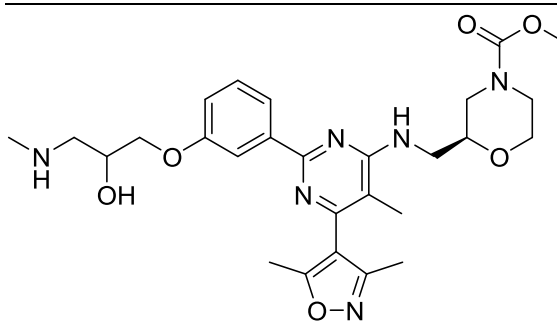
323-1a



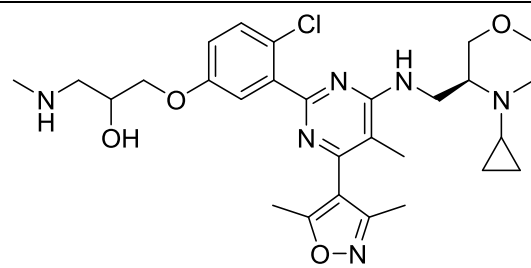
324-1a



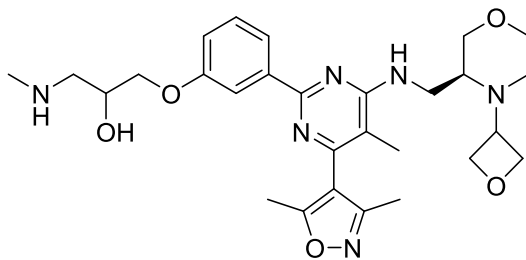
325-1a



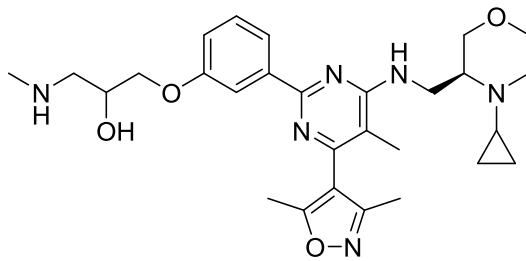
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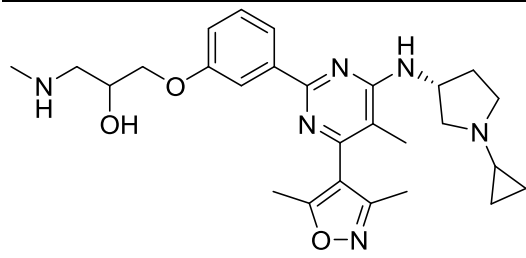
327-1a



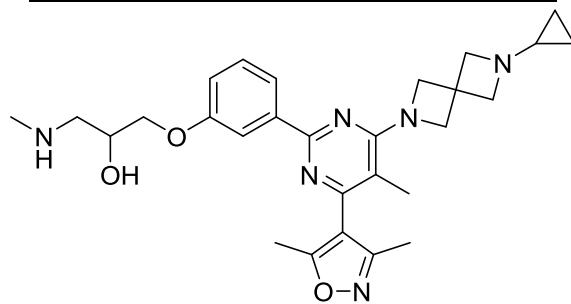
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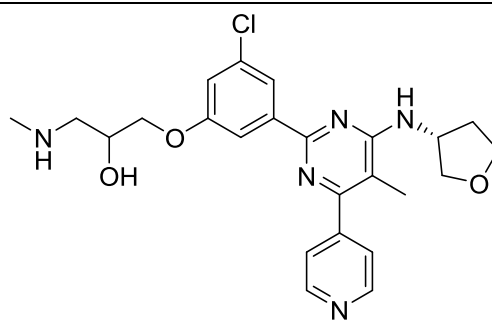
329-1a



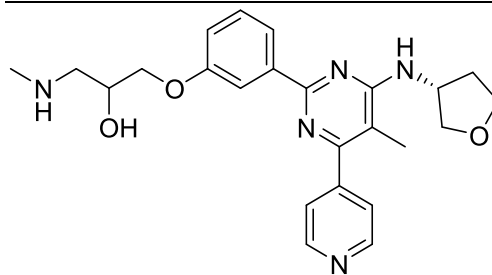
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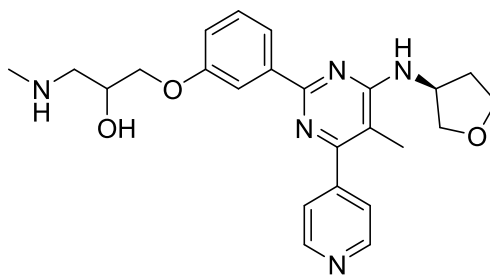
331-1a



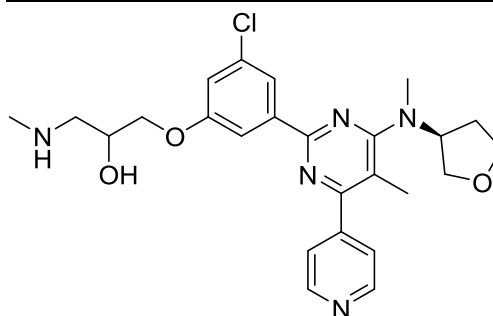
332-1a



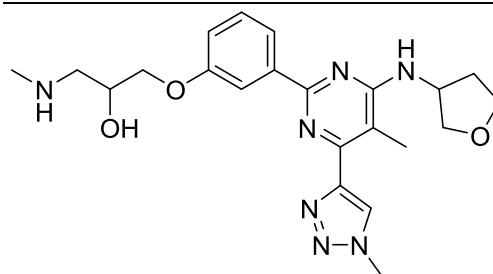
333-1a



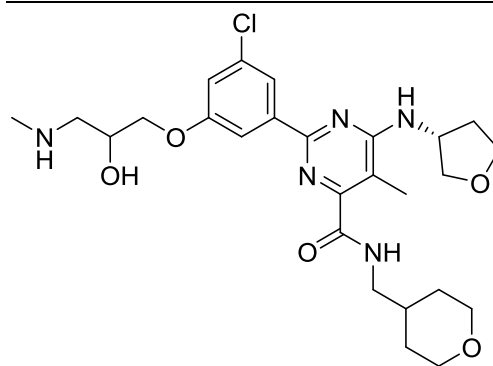
334-1a



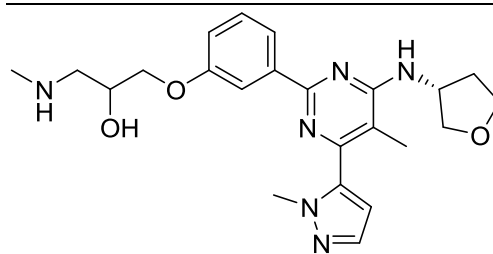
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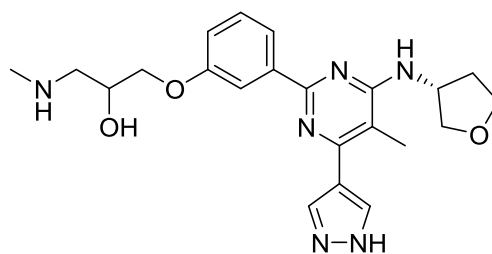
336-1a



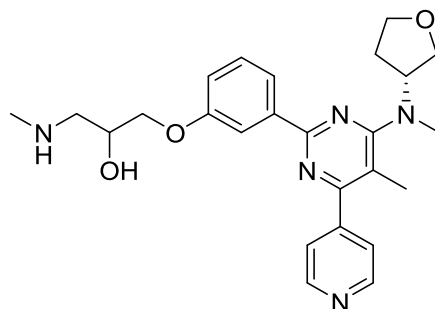
337-1a



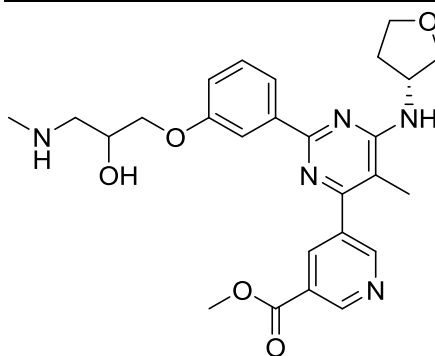
338-1a



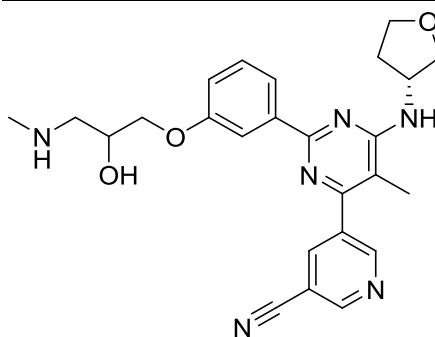
339-1a



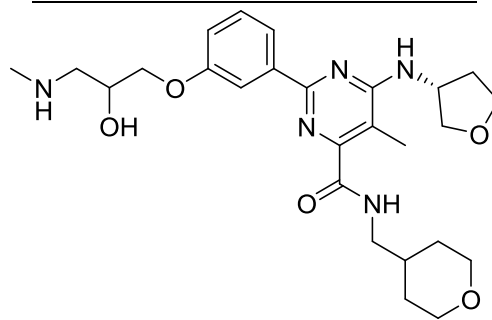
340-1a



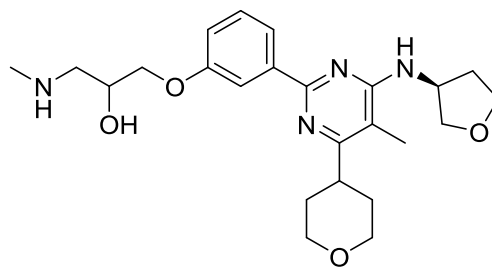
341-1a



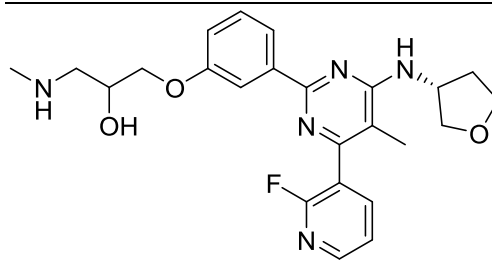
346-1a



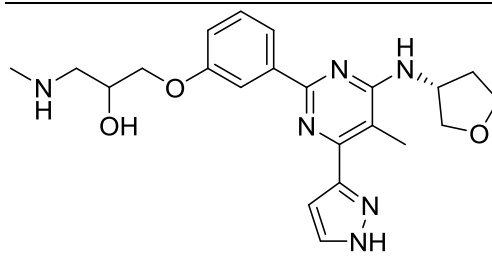
347-1a



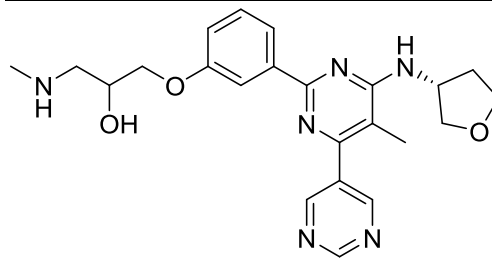
348-1a



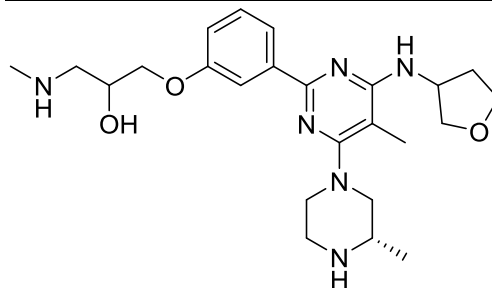
349-1a



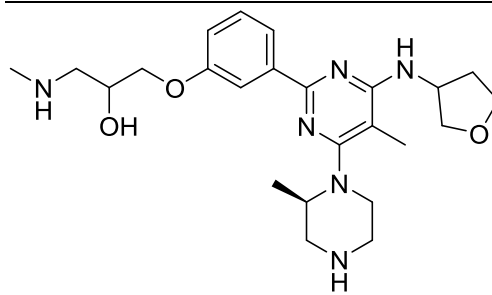
350-1a



351-1a

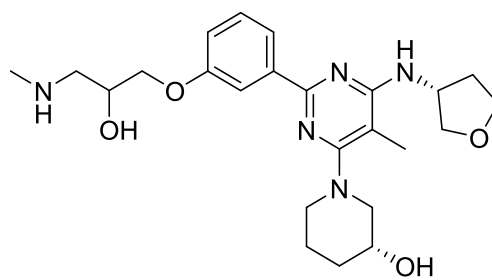


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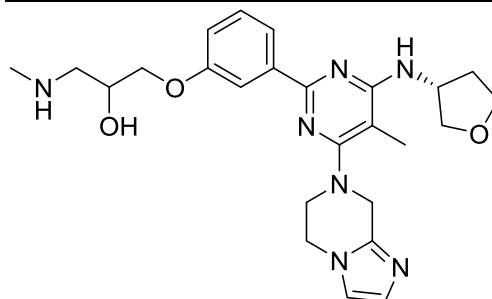


CNCC(O)COc1ccc(Cl)c(N2C=NC(=C(C2)C(=O)N(C)CC3OCCCO3)N[C@H]4OCCO4)c1CN(C)CC(O)COc1ccc(cc1)-c2nc(C)c(c3c2c(C)n(C)n3)C4=CC=CC=C4CN(C)CC(O)COc1ccc(cc1)-c2nc3c(ncn3C)C4=C(C2)C5=CC=CC=C5N4CC1(C)NCC(O)COc2ccc(cc2)-c3nc(C)c(NC4COC4)c5nnc3c5-c6nc7c(ncn6C)OCCN(C)CC(O)COc1ccc(cc1)-c2nc(C)c(c3nc(C4=CN(C(=O)NC4)C=C3)N)N2C5COCCO5

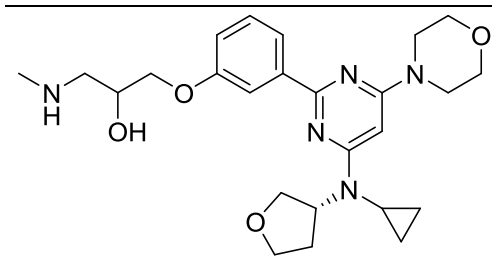
358-1a



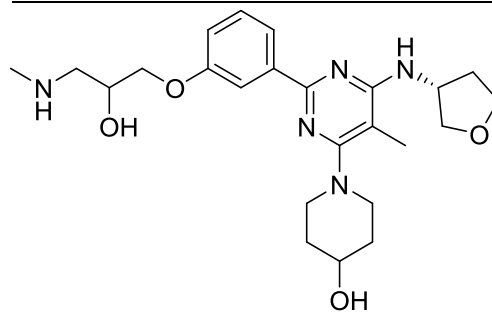
359-1a



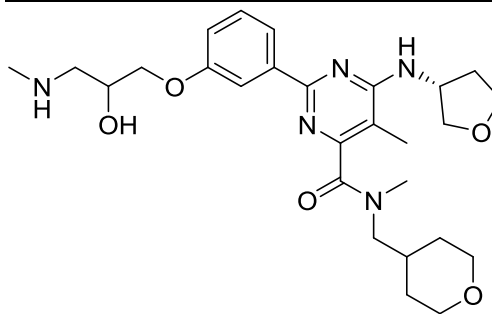
360-1a



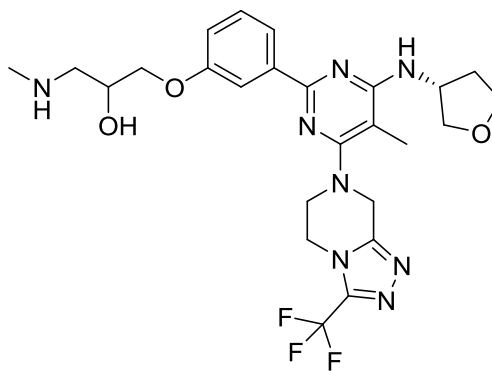
361-1a



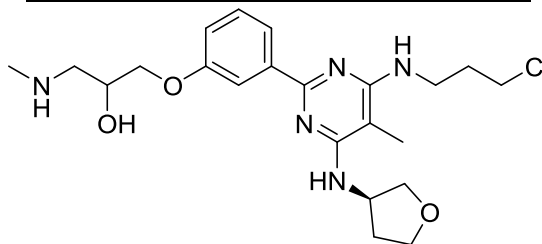
364-1a



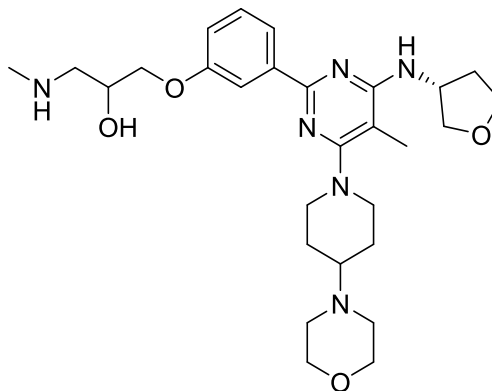
365-1a



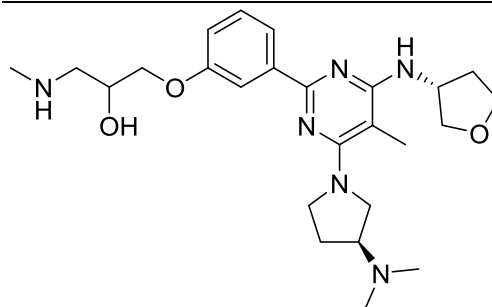
366-1a



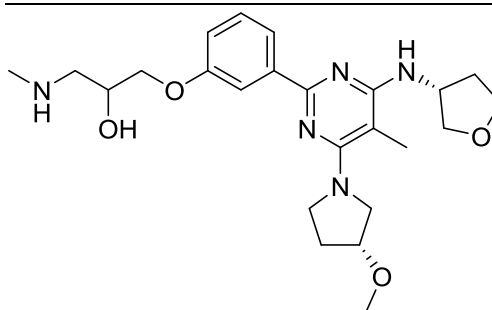
367-1a



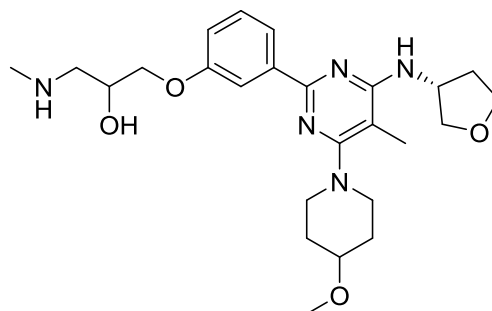
368-1a



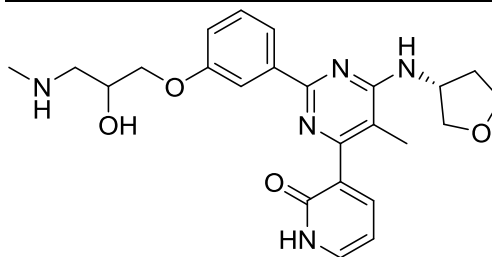
369-1a



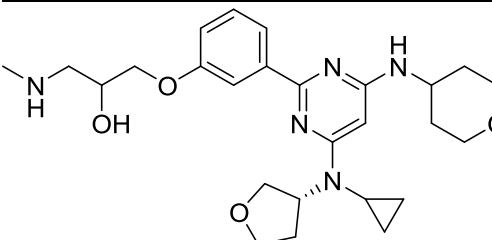
370-1a



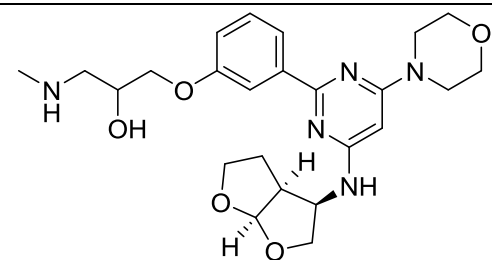
371-1a



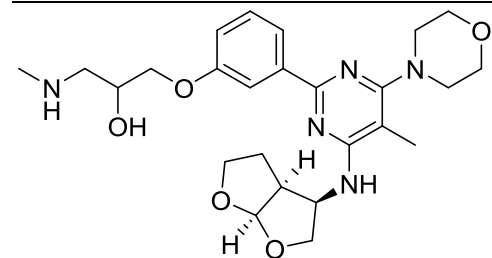
372-1a



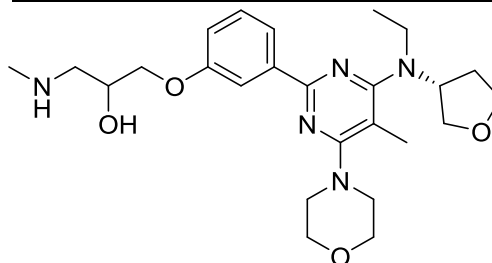
373-1a



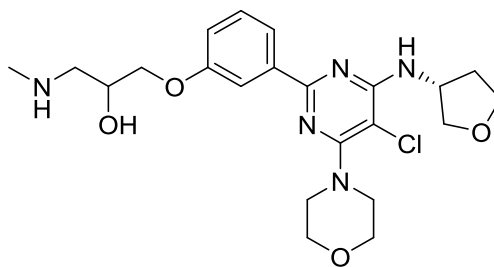
374-1a



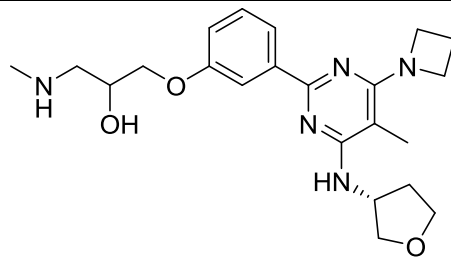
375-1a



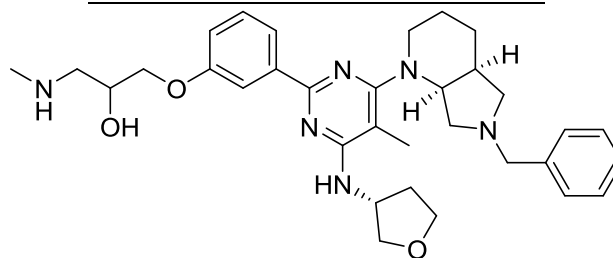
376-1a



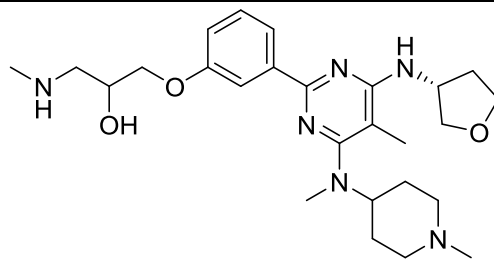
377-1a



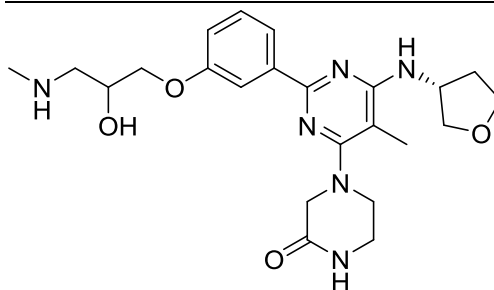
378-1a



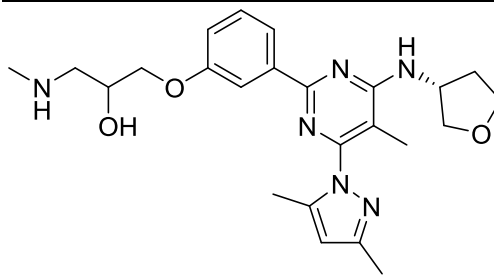
379-1a



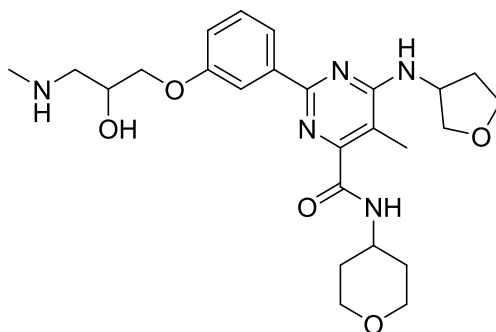
380-1a



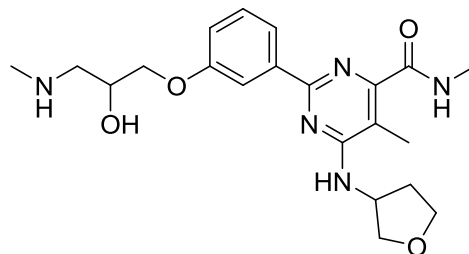
382-1a



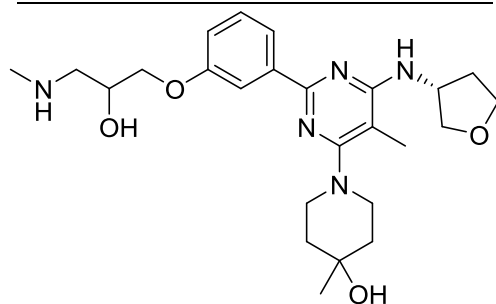
383-1a



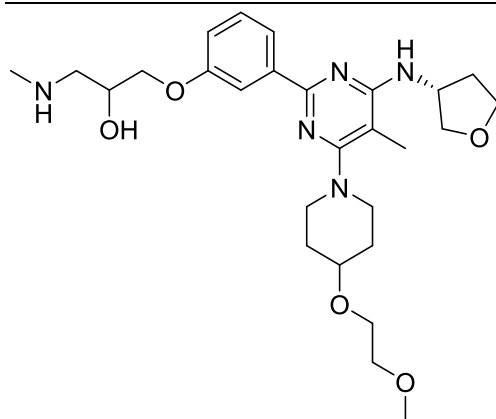
384-1a



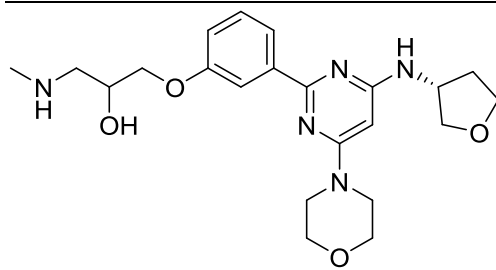
385-1a



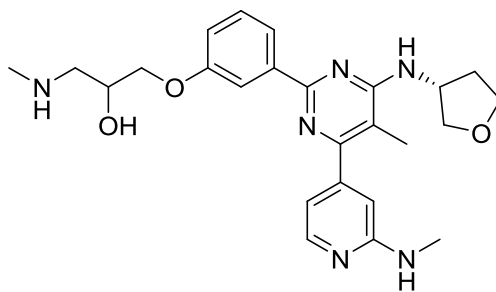
386-1a



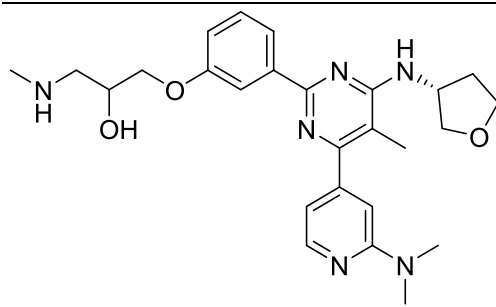
387-1a



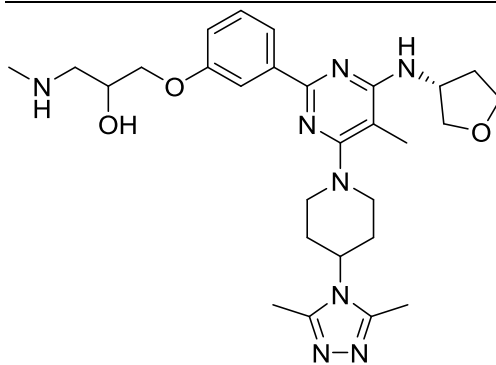
388-1a



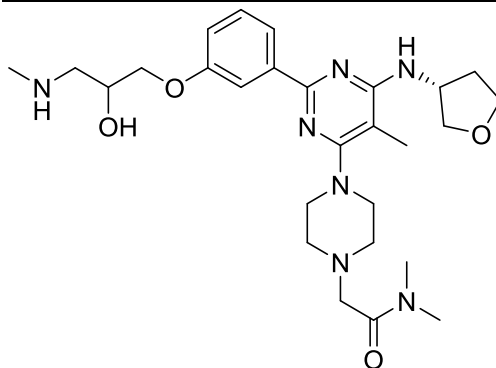
389-1a



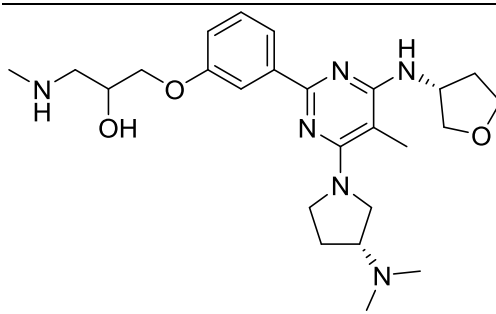
390-1a



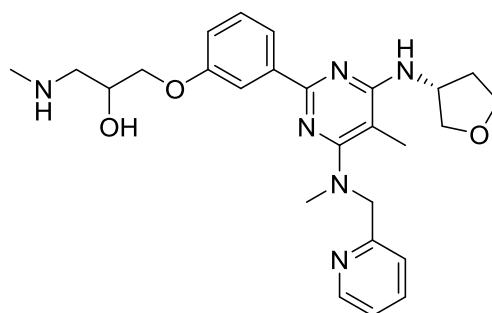
391-1a



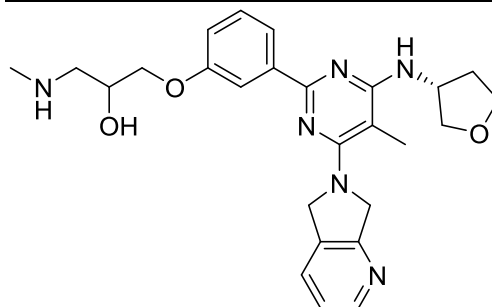
392-1a



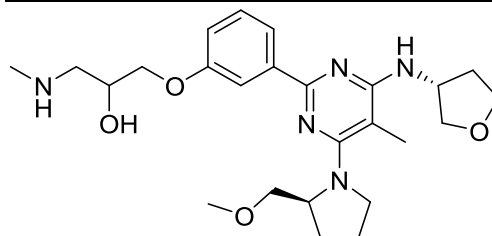
393-1a



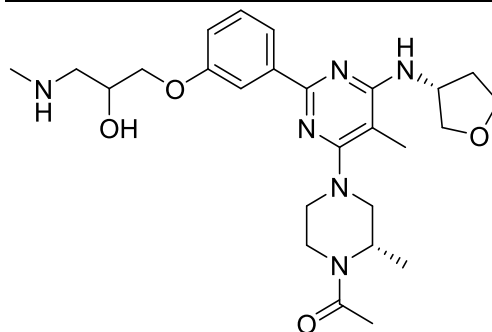
394-1a



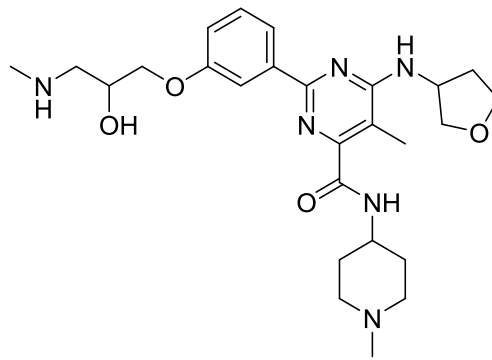
395-1a



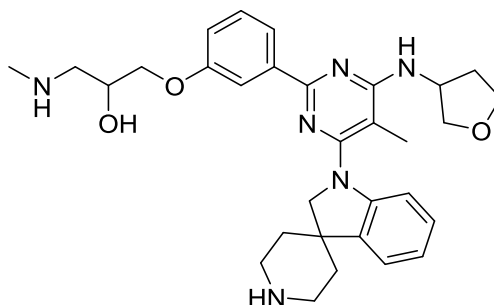
396-1a



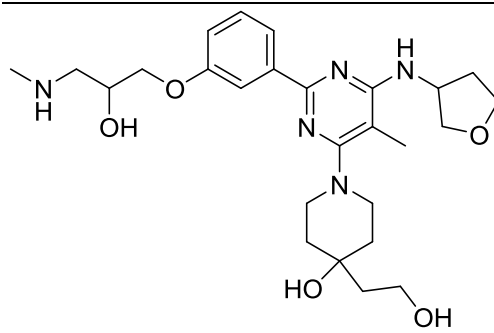
397-1a



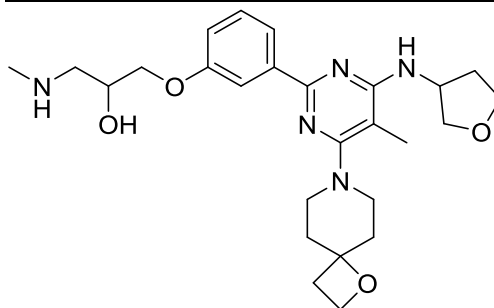
398-1a



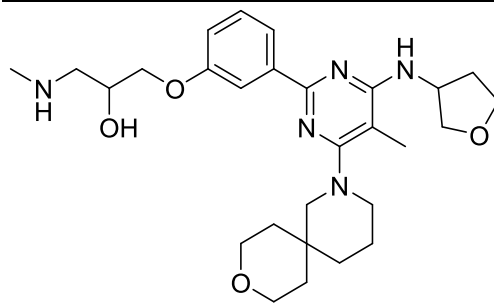
399-1a



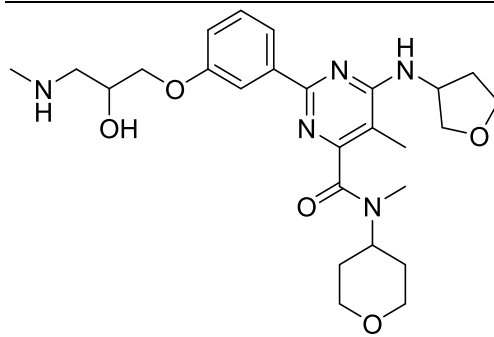
400-1a



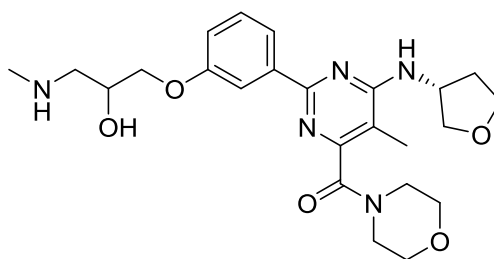
401-1a



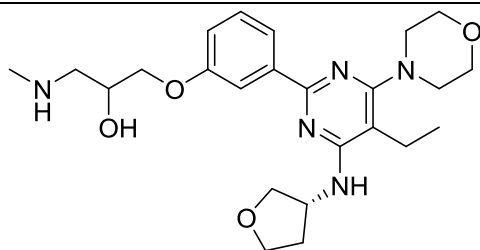
402-1a



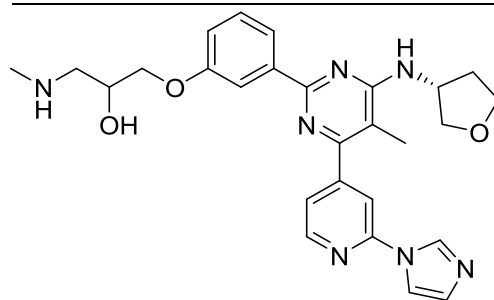
403-1a



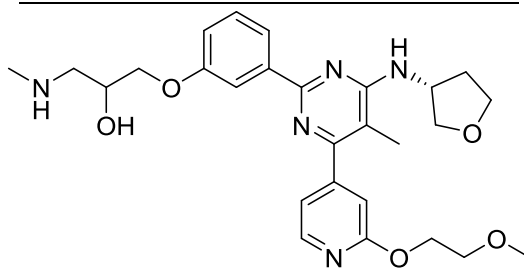
404-1a



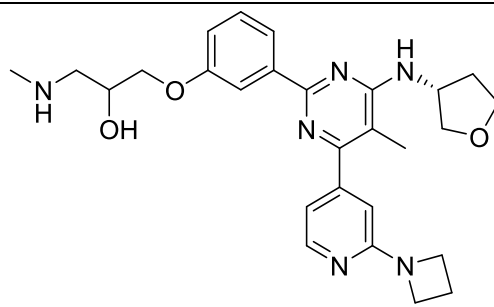
405-1a



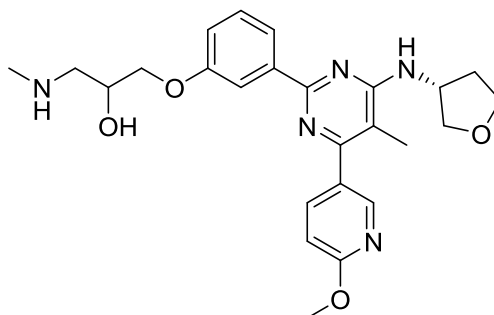
406-1a



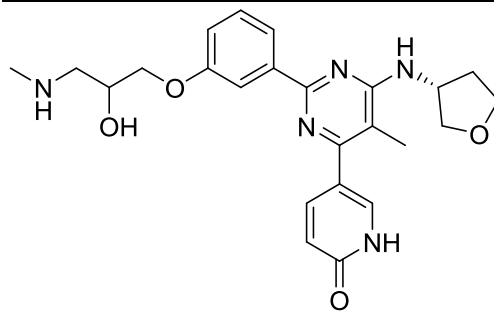
407-1a



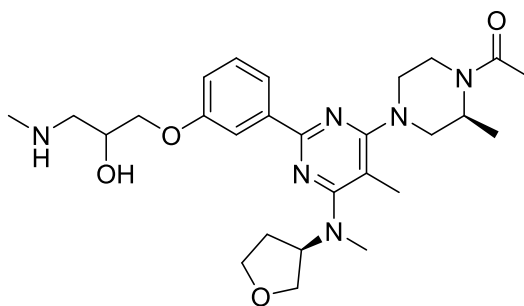
408-1a



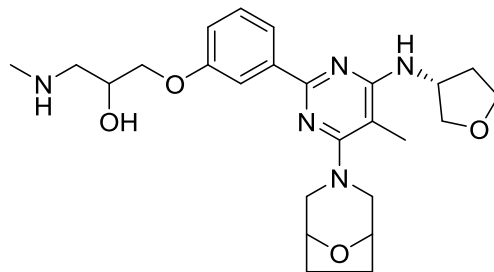
409-1a



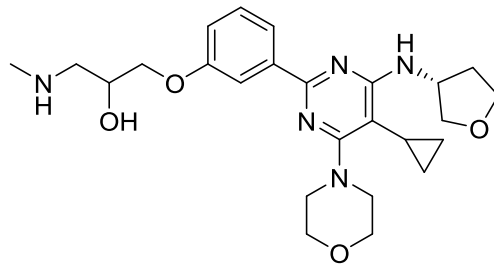
410-1a



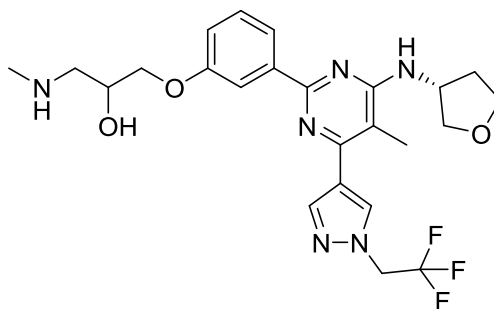
412-1a



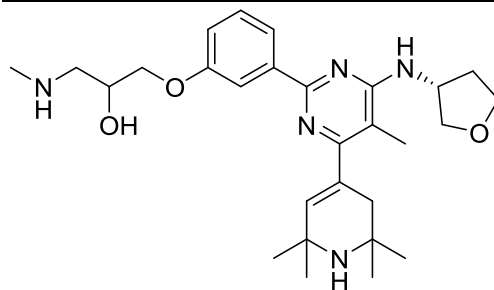
413-1a



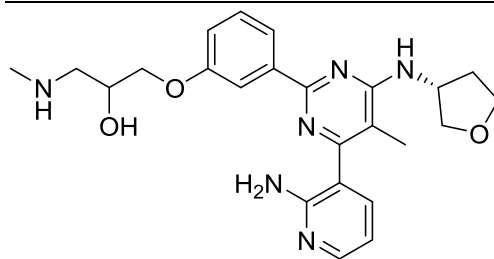
414-1a



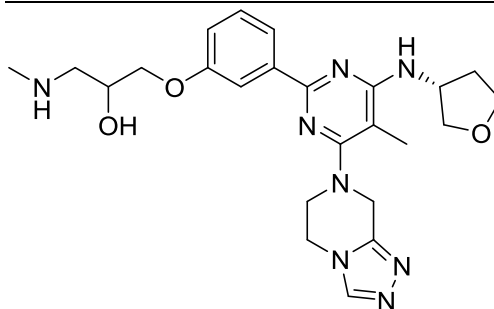
415-1a



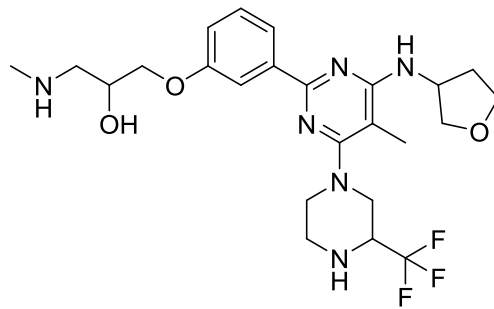
416-1a



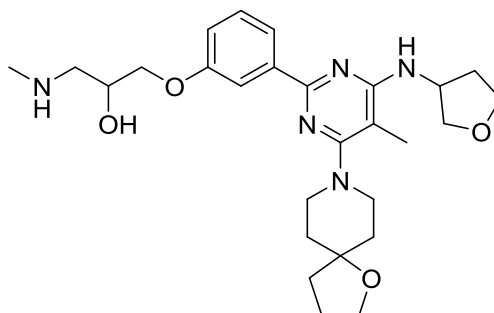
418-1a



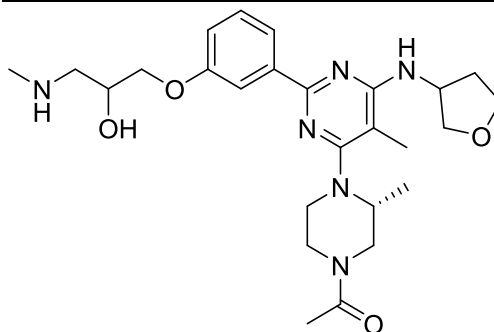
419-1a



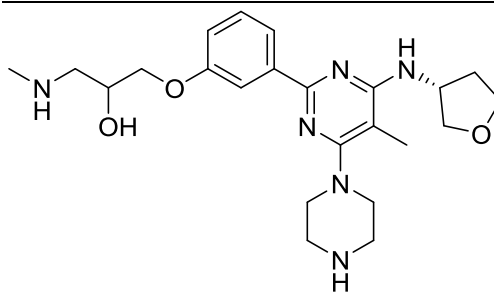
420-1a



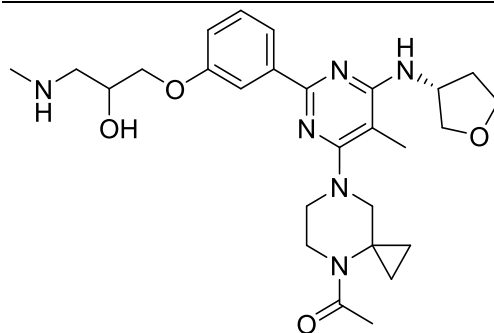
421-1a



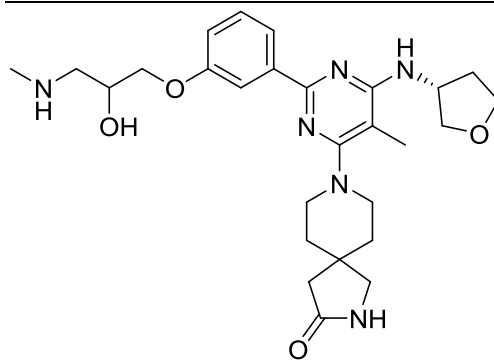
422-1a



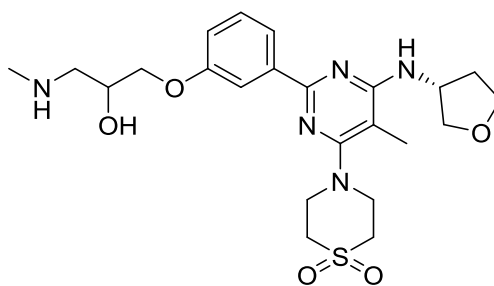
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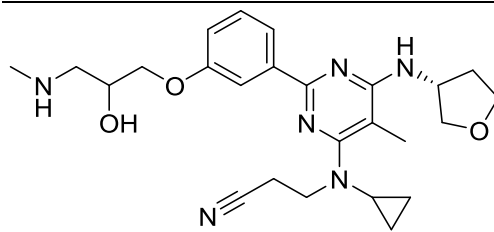
424-1a



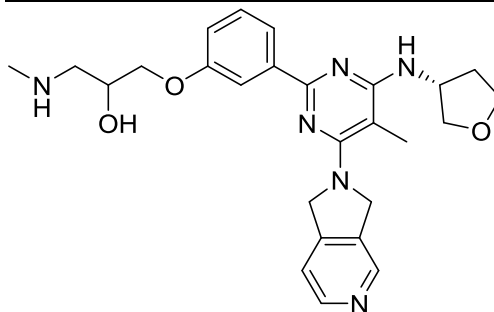
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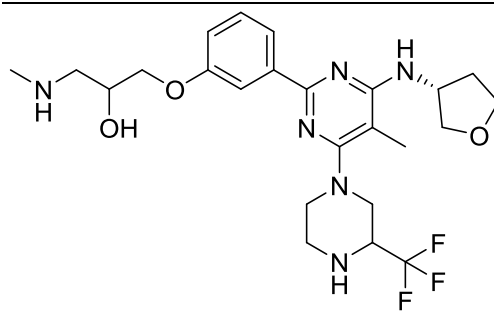
426-1a



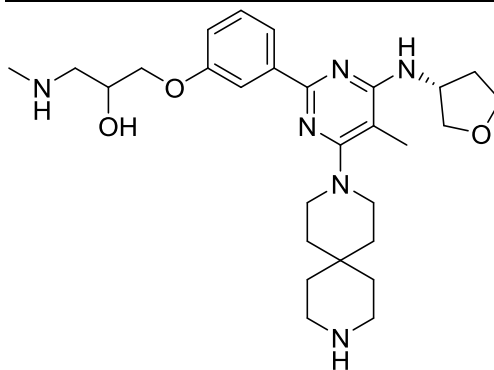
427-1a



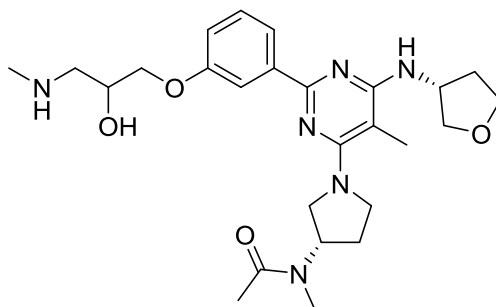
428-1a



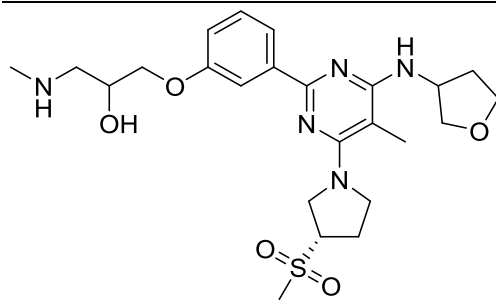
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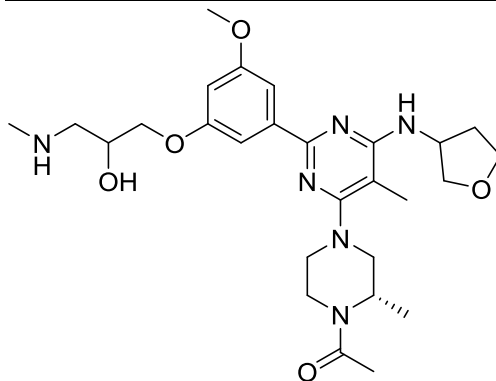
430-1a



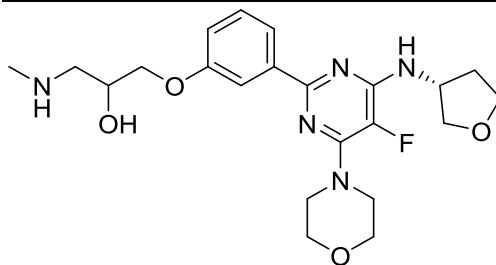
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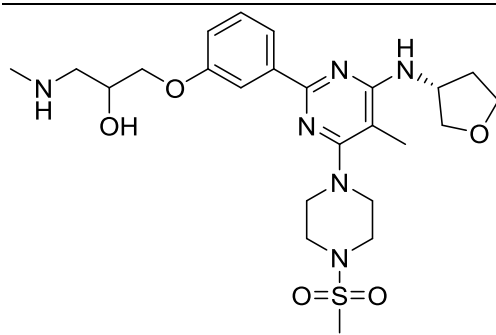
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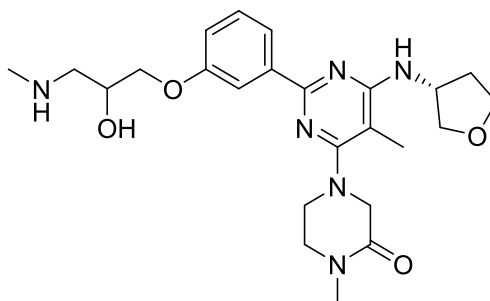
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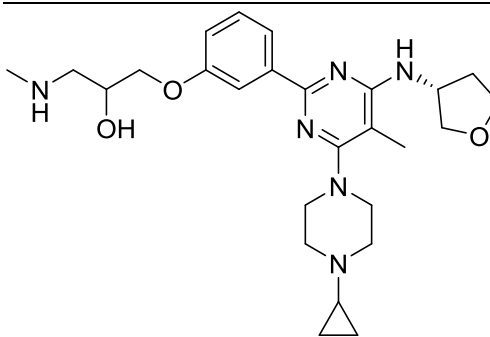
434-1a



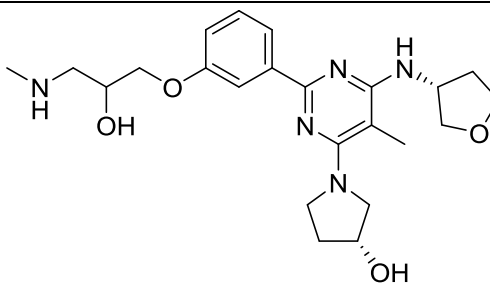
435-1a



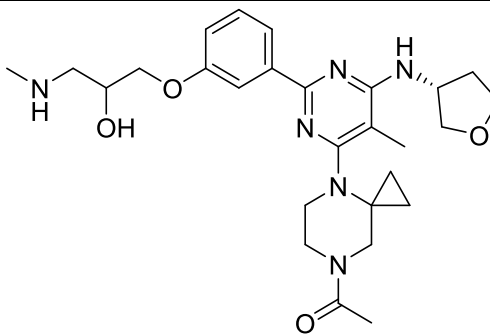
436-1a



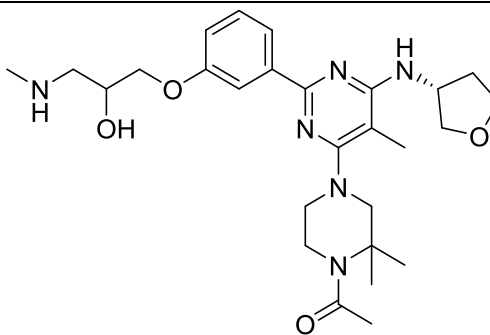
437-1a



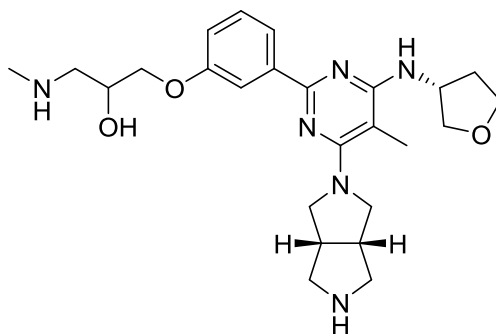
438-1a



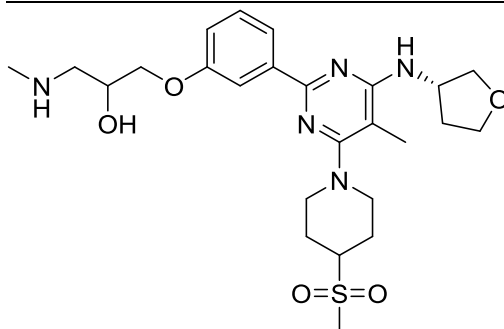
439-1a



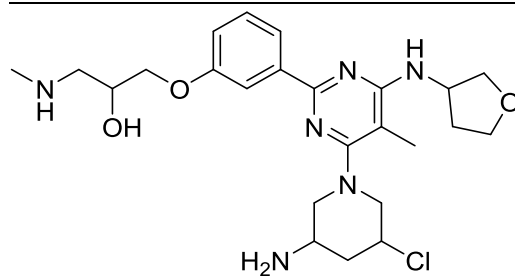
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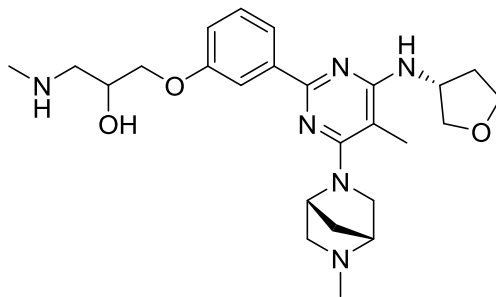
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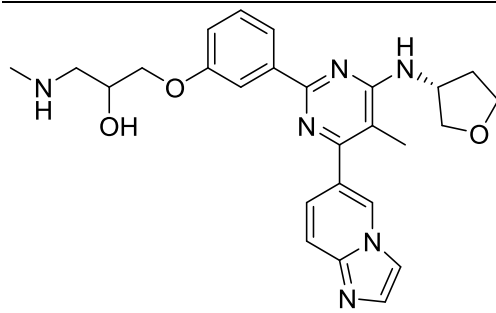
442-1a



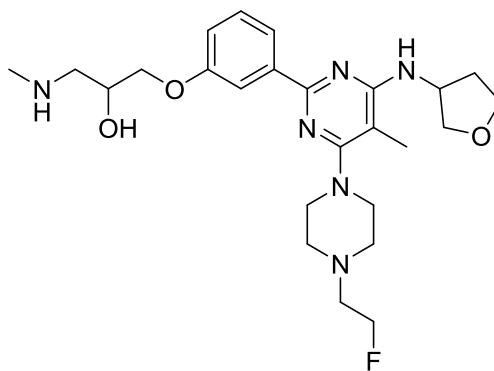
443-1a



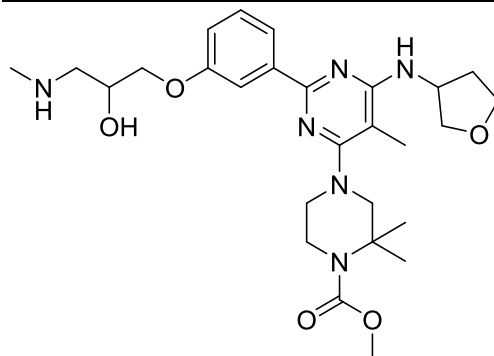
445-1a



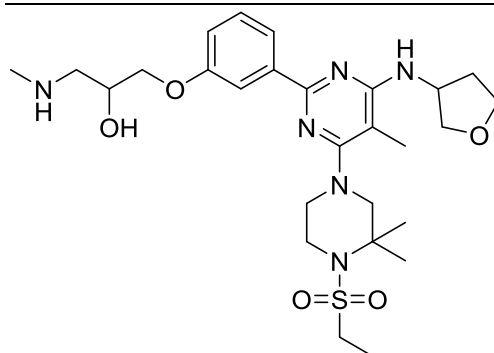
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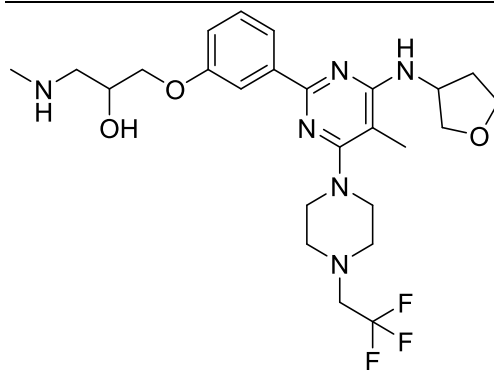
447-1a



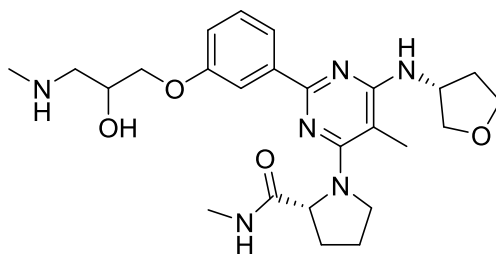
448-1a



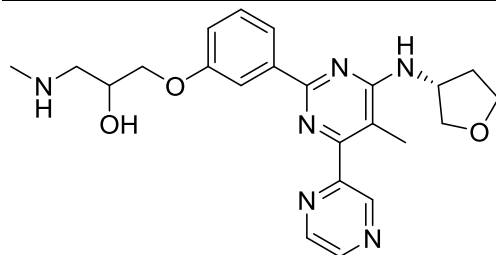
449-1a



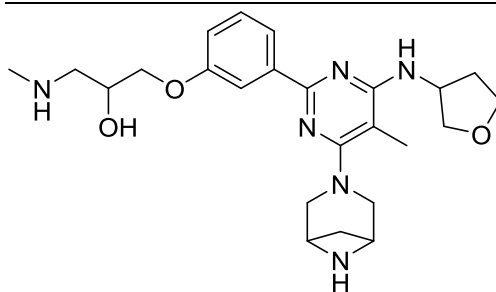
450-1a



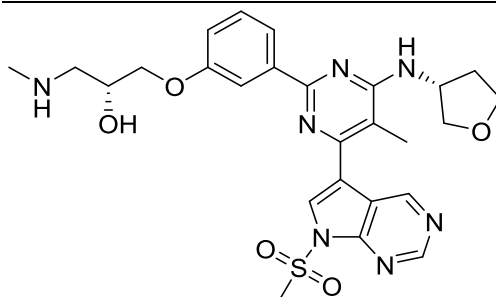
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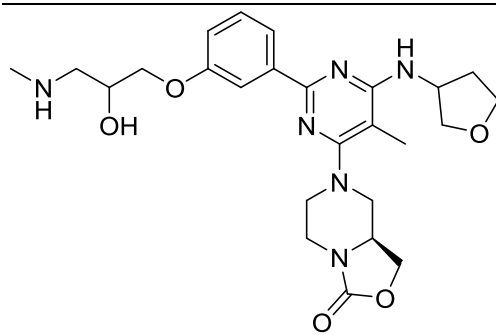
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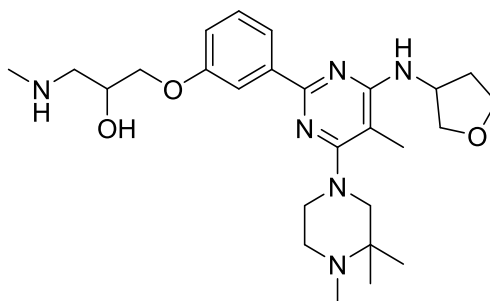
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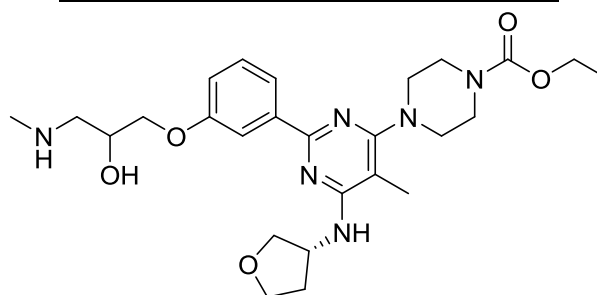
454-1a



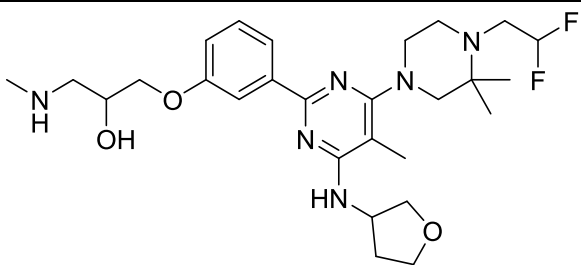
455-1a



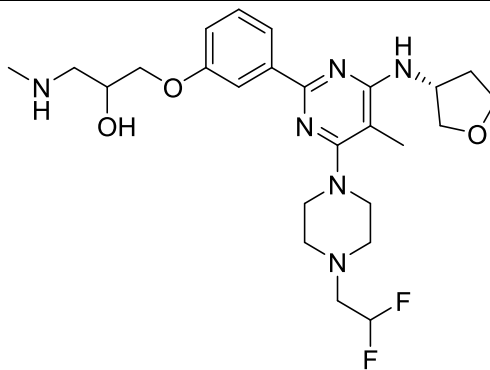
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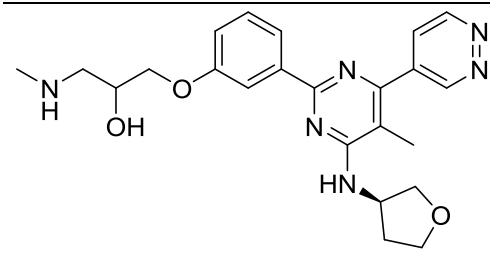
457-1a



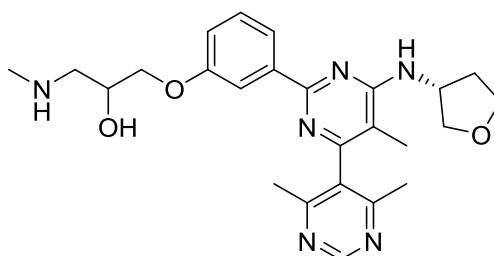
458-1a



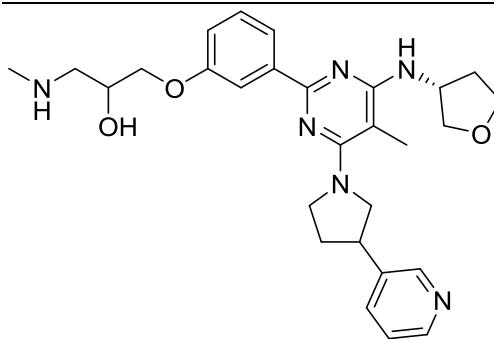
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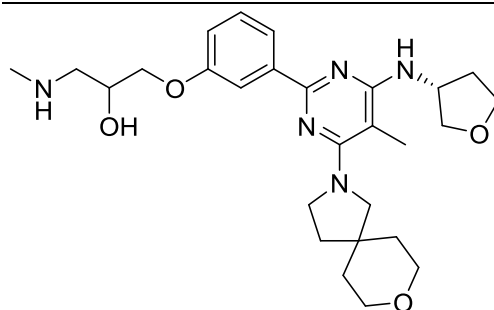
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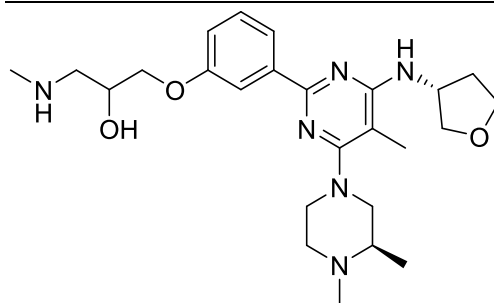
461-1a



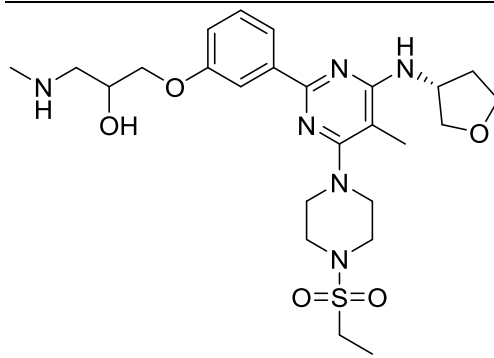
462-1a



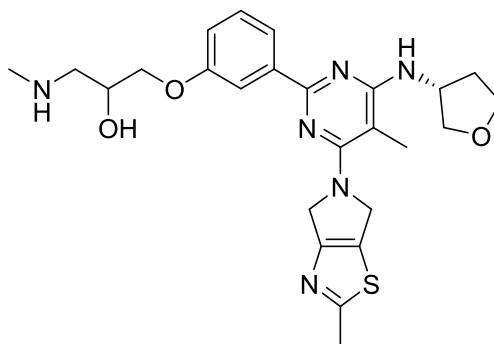
463-1a



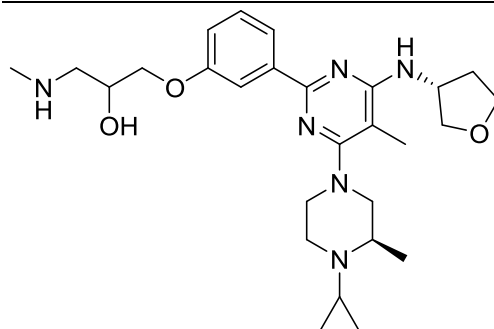
464-1a



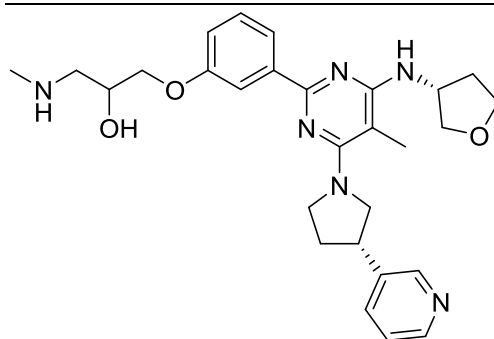
465-1a



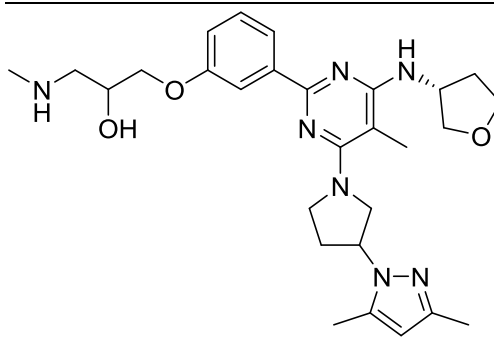
466-1a



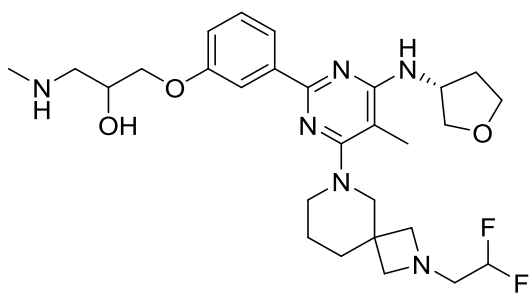
467-1a



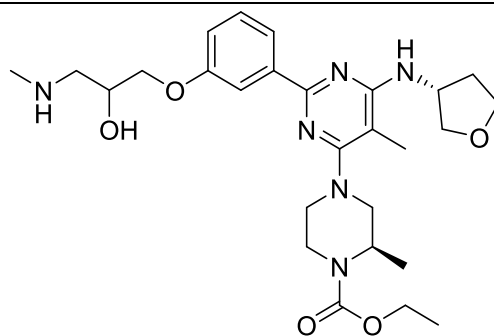
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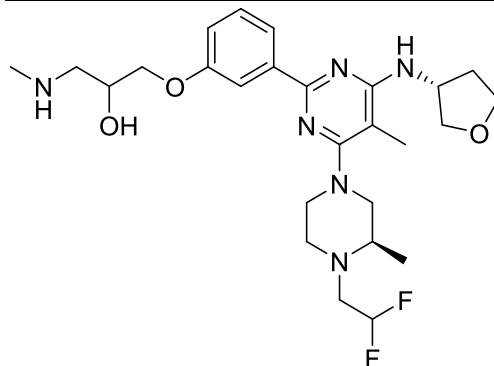
469-1a



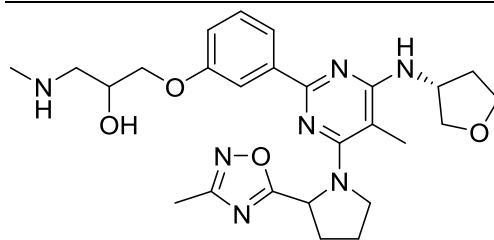
470-1a



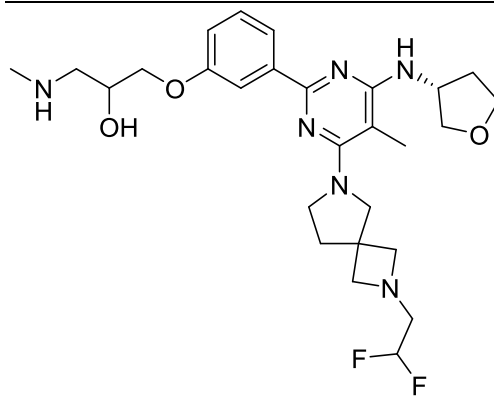
471-1a



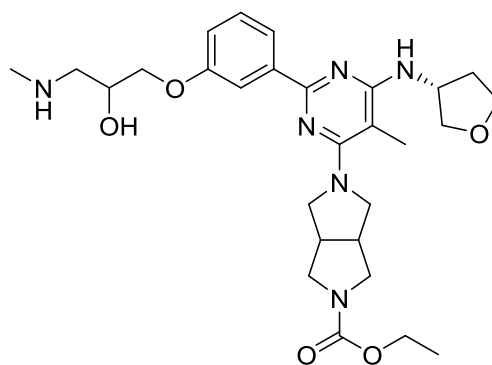
472-1a



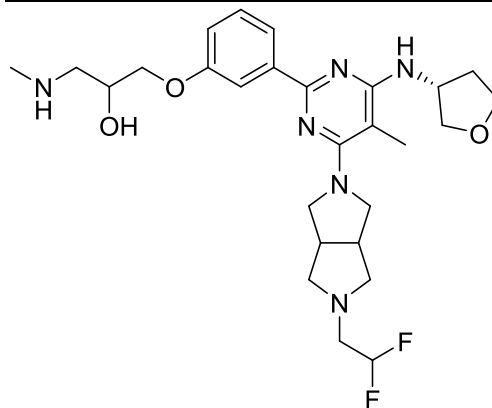
475-1a



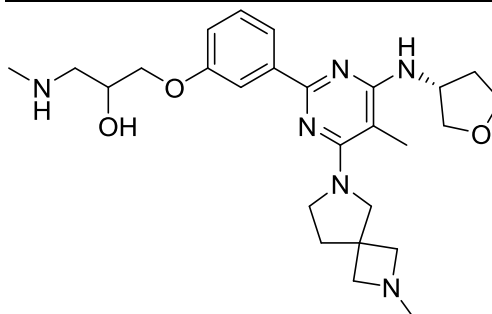
478-1a



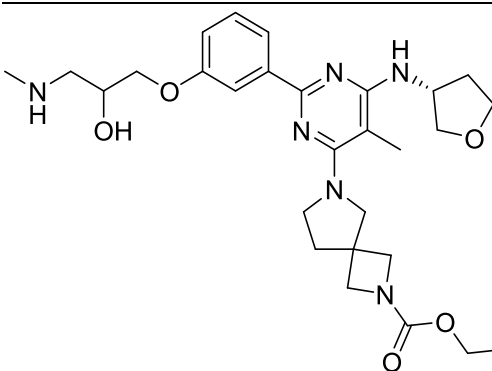
479-1a



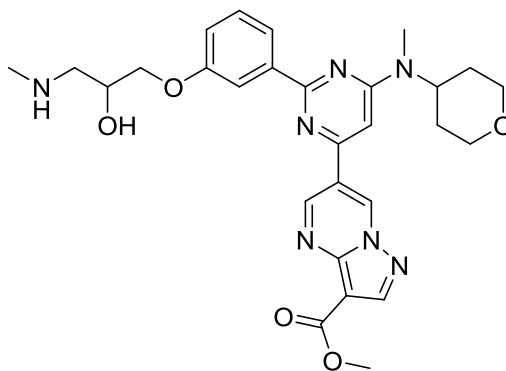
480-1a



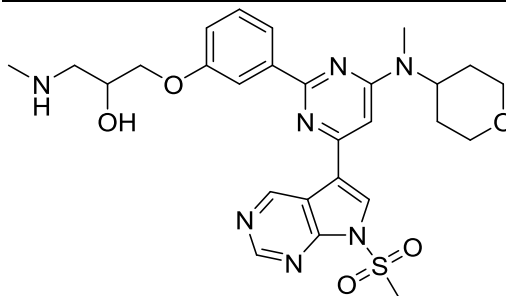
481-1a



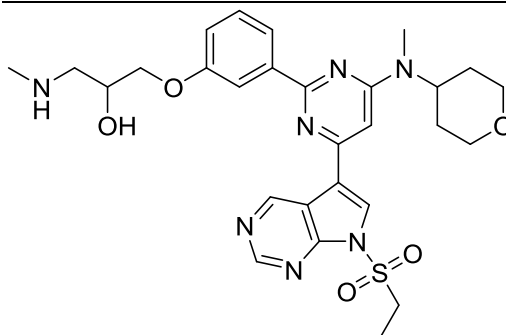
482-1a



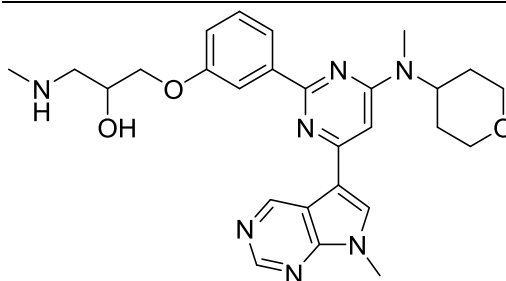
483-1a



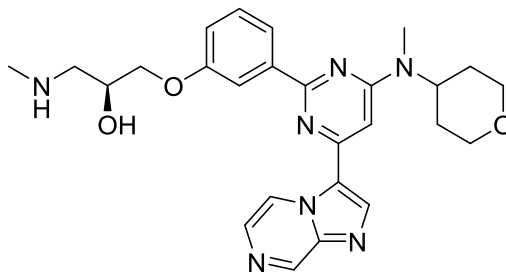
484-1a



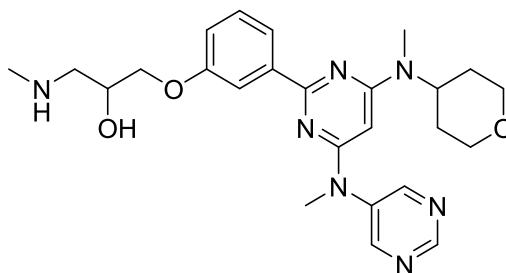
485-1a



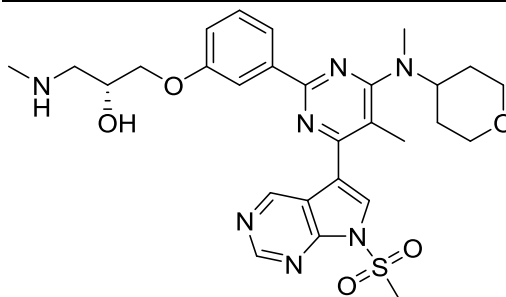
486-1a



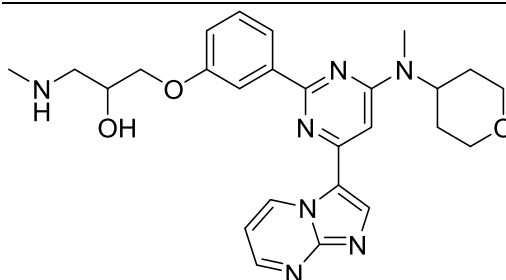
487-1a



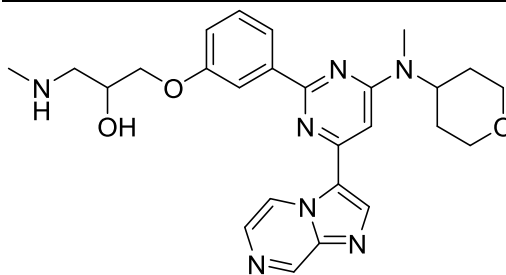
488-1a



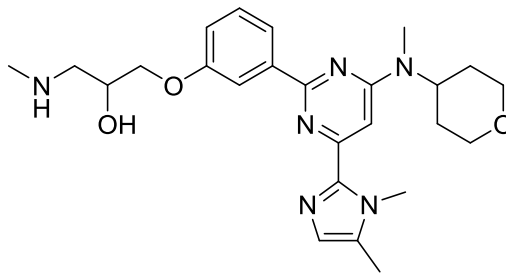
489-1a



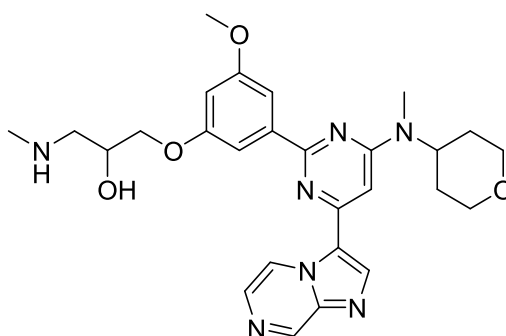
490-1a



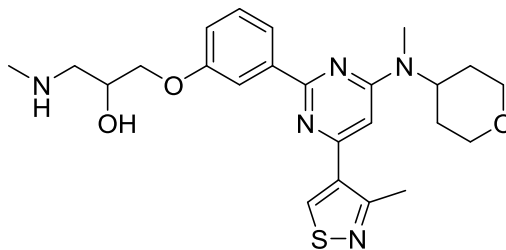
491-1a



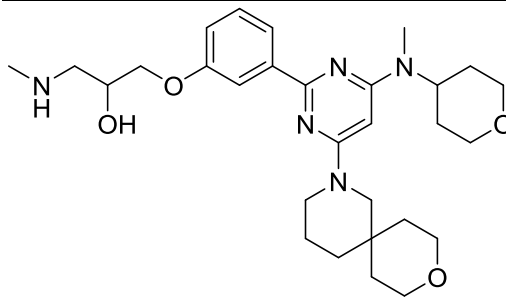
492-1a



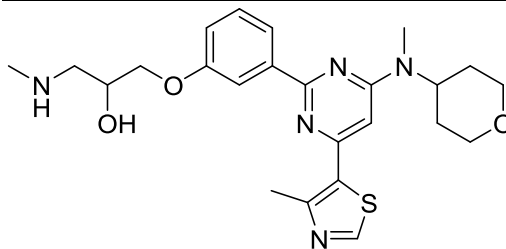
493-1a



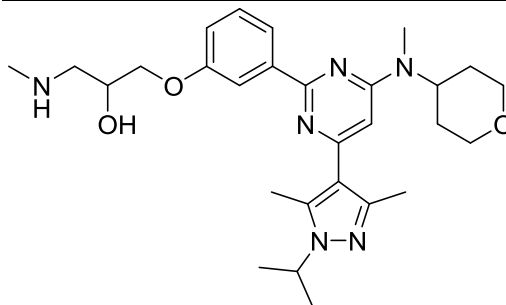
494-1a



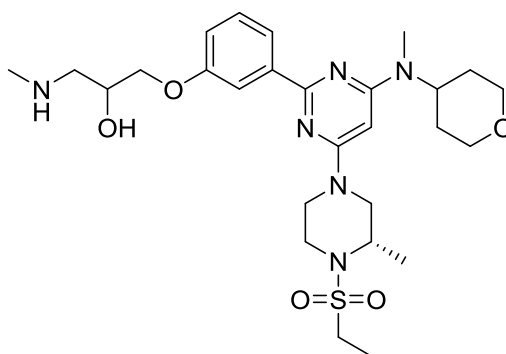
495-1a



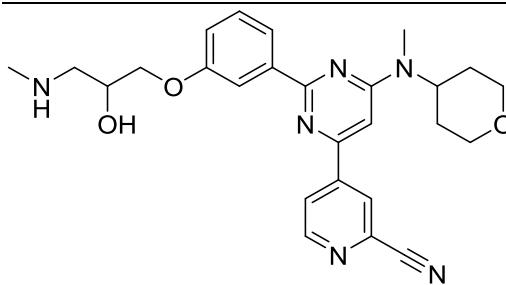
496-1a



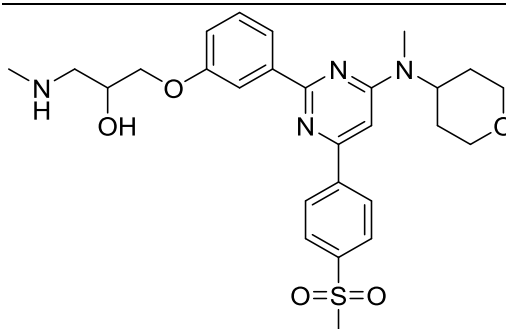
497-1a



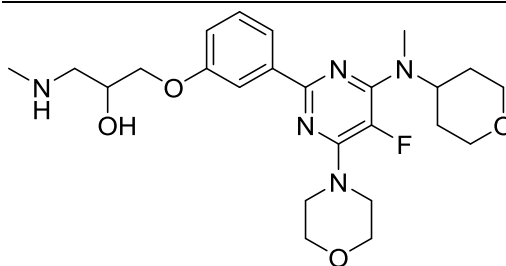
498-1a



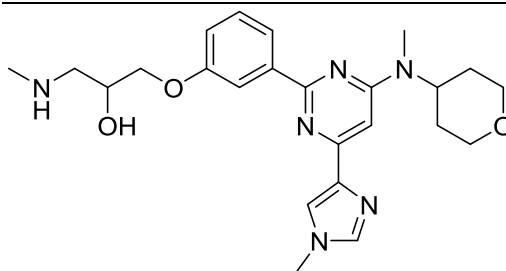
499-1a



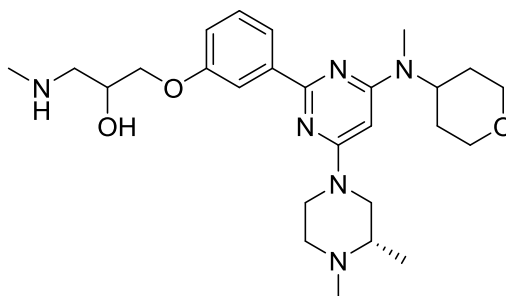
500-1a



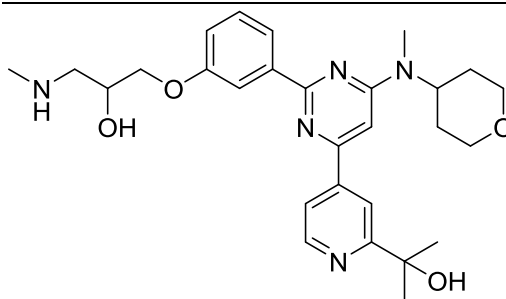
501-1a



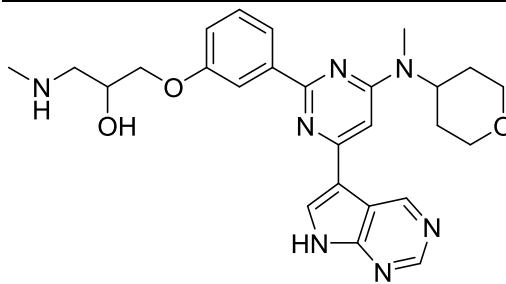
502-1a



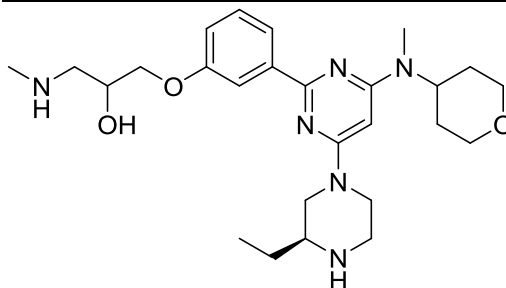
503-1a



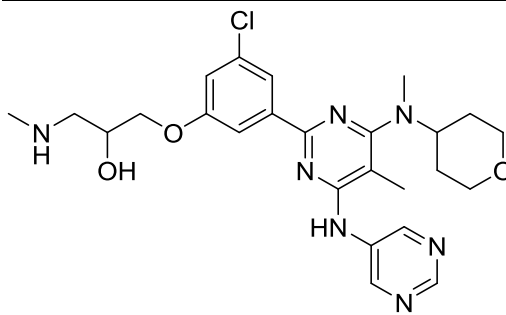
504-1a



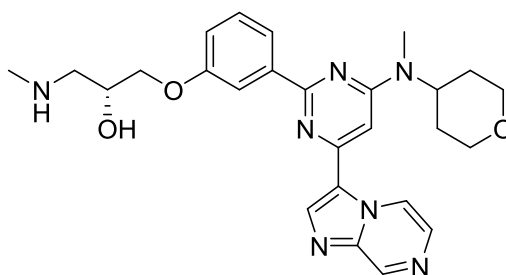
505-1a



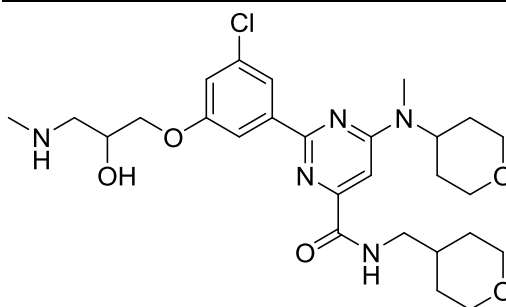
506-1a



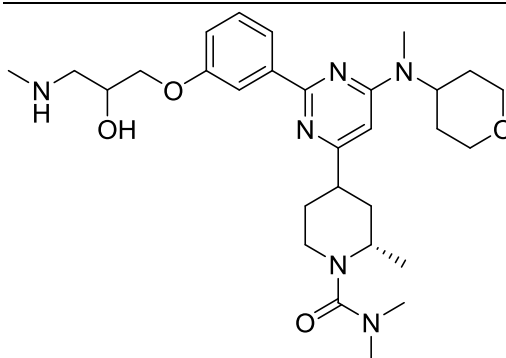
507-1a



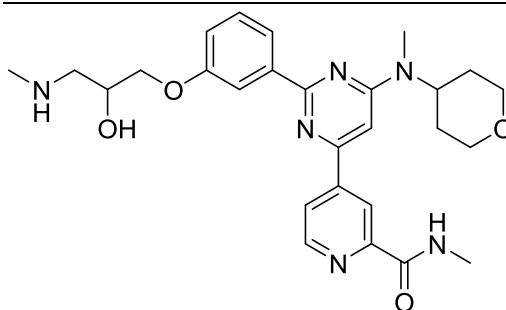
508-1a



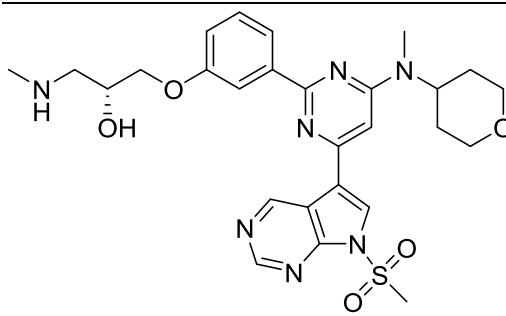
509-1a



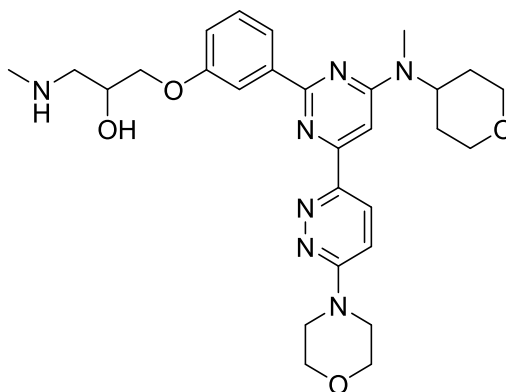
510-1a



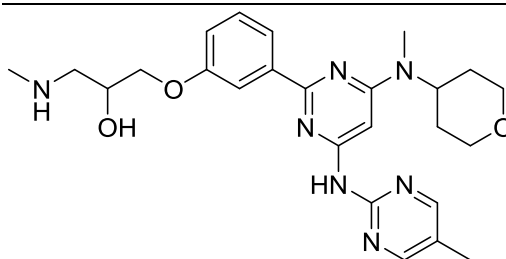
511-1a



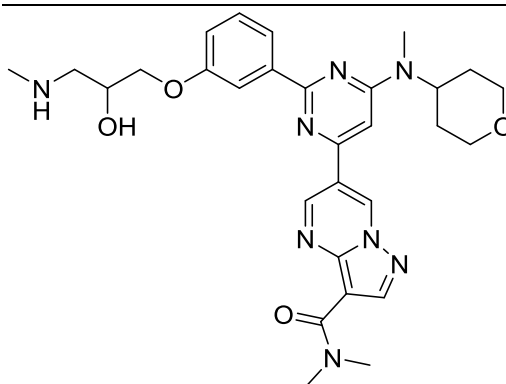
512-1a



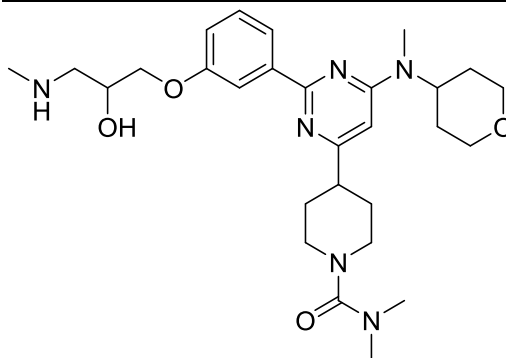
513-1a



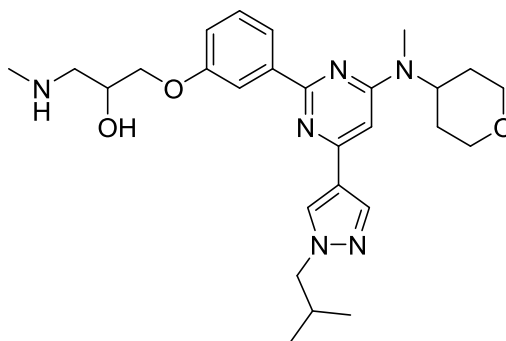
514-1a



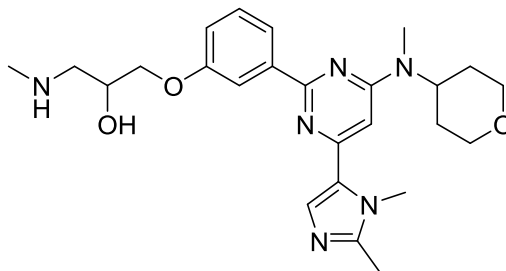
515-1a



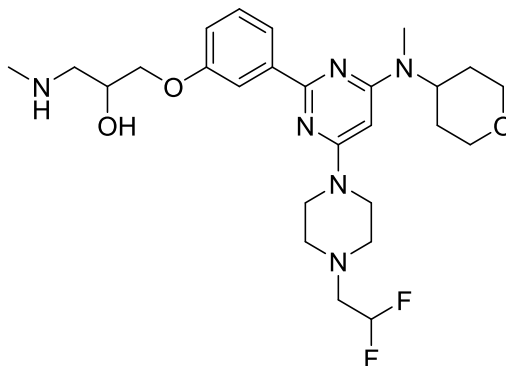
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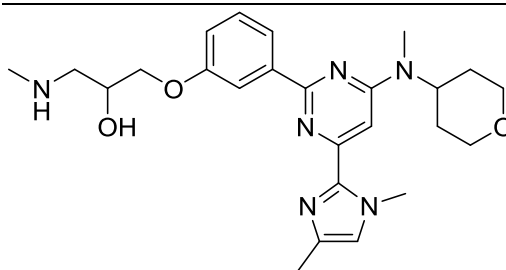
517-1a



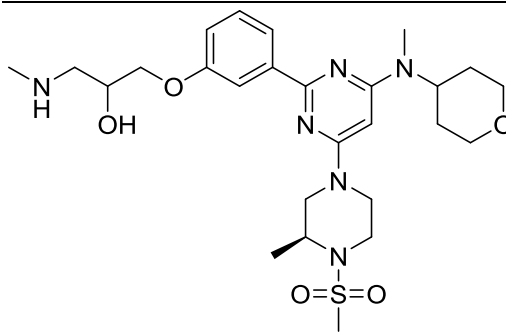
518-1a



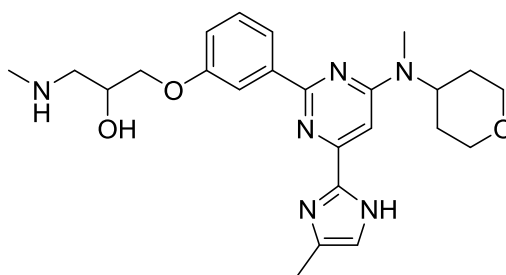
519-1a



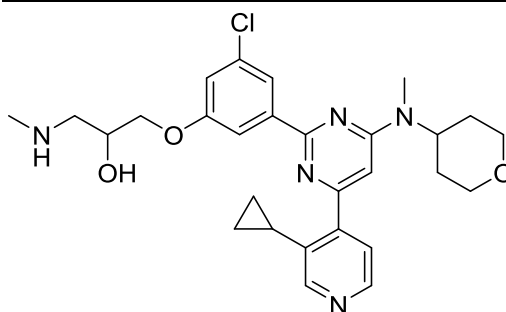
520-1a



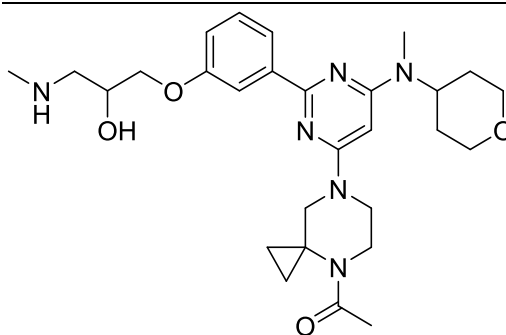
521-1a



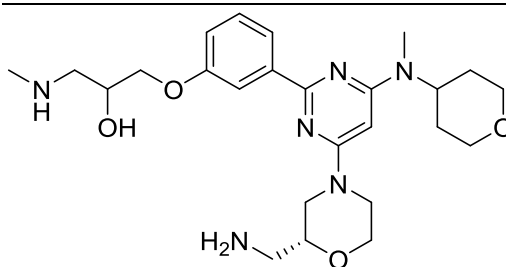
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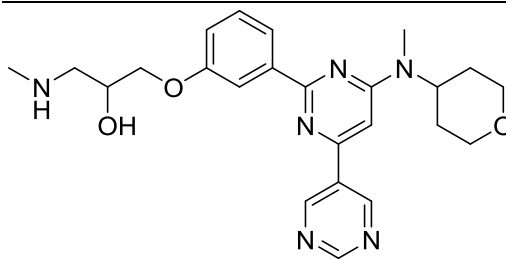
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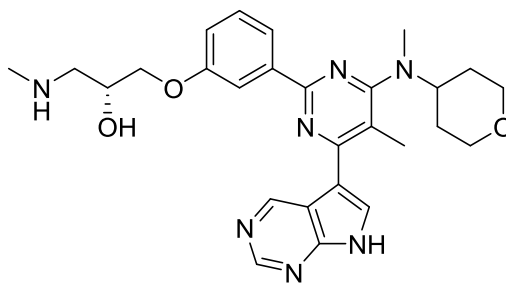
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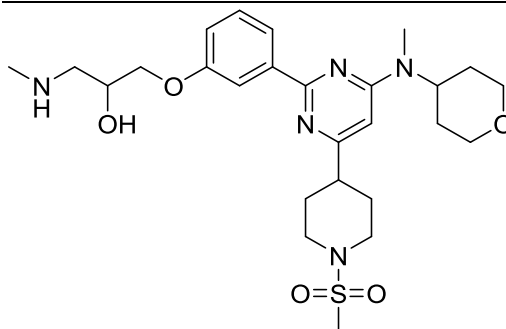
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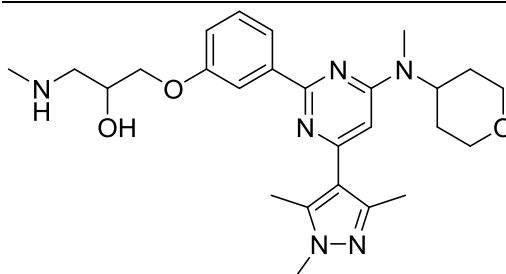
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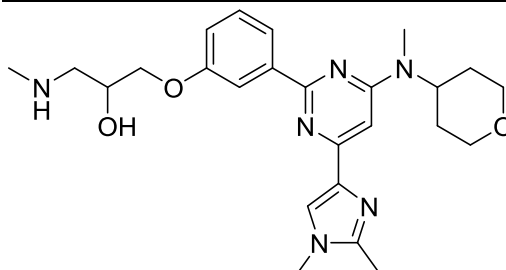
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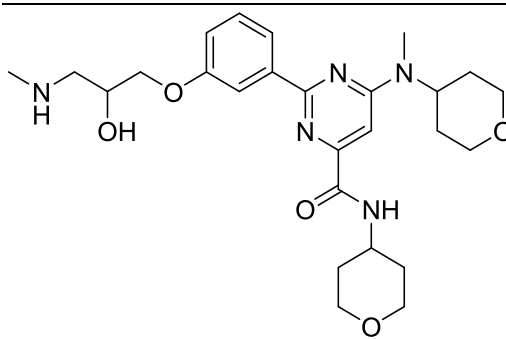
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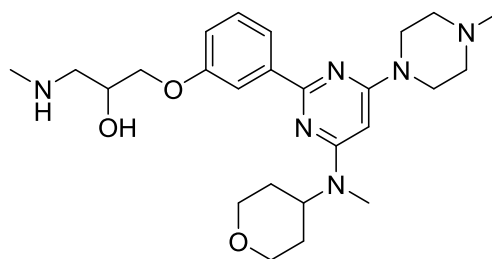
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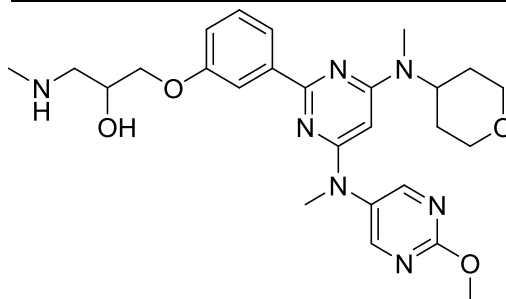
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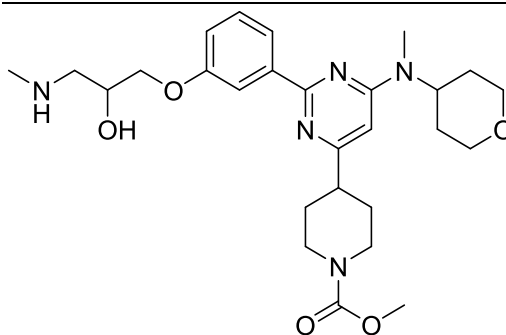
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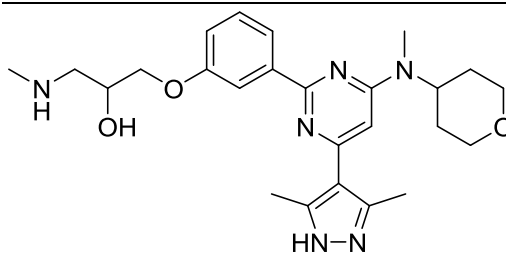
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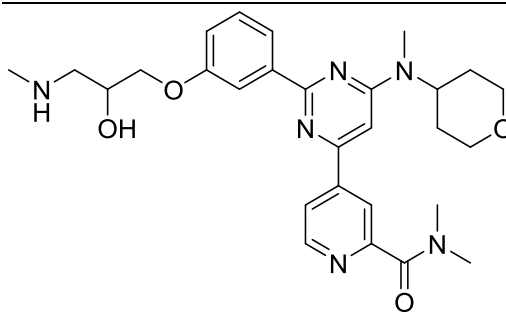
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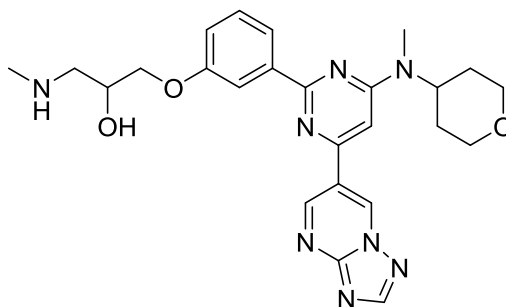
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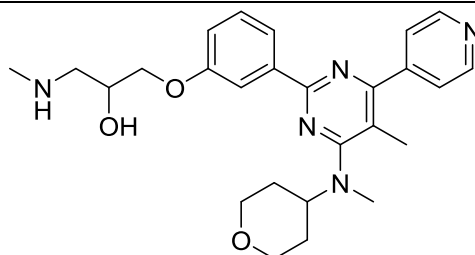
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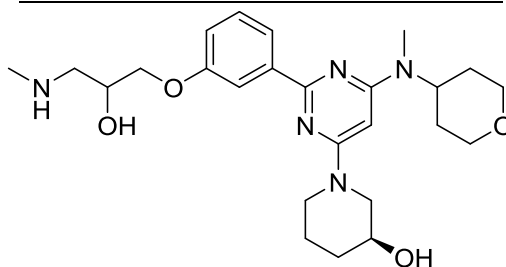
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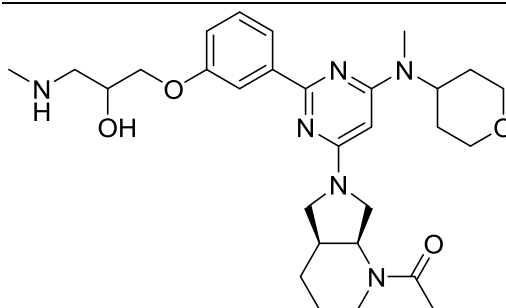
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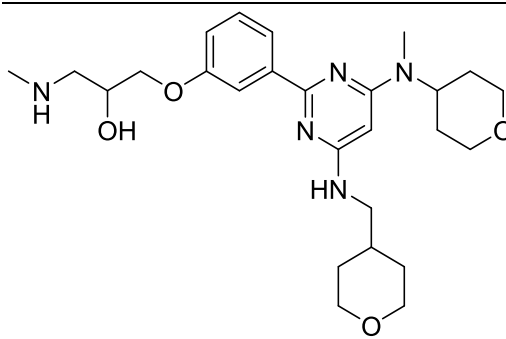
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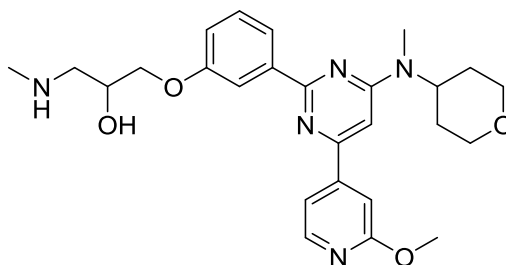
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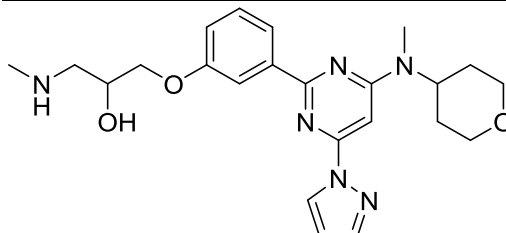
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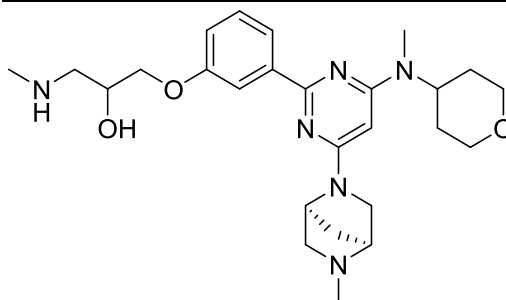
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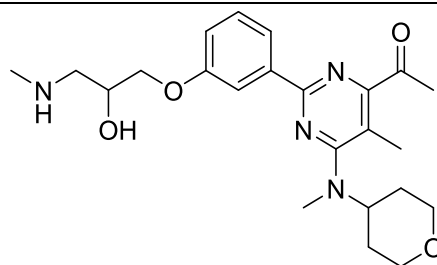
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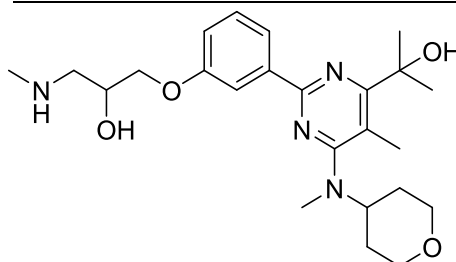
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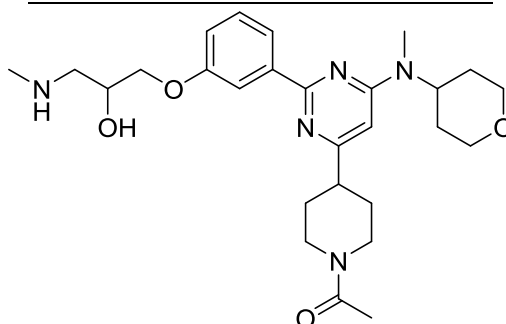
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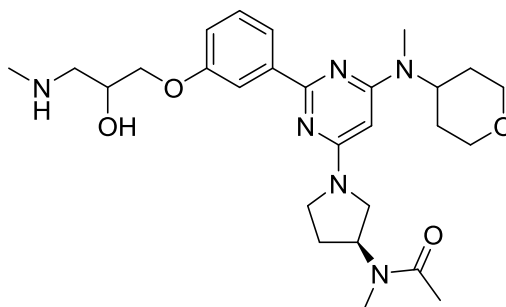
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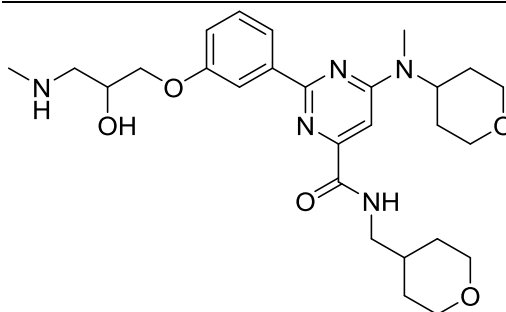
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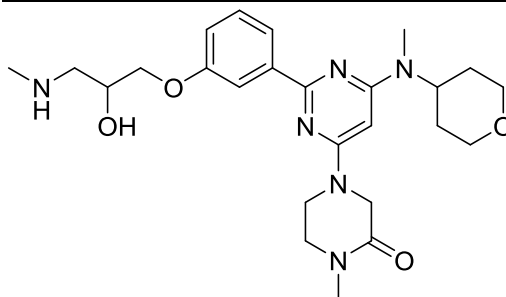
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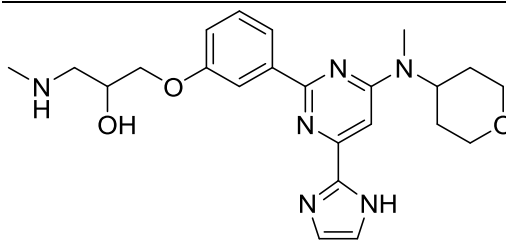
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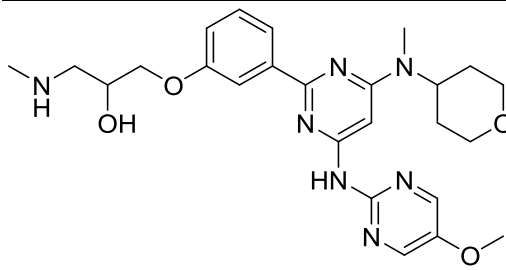
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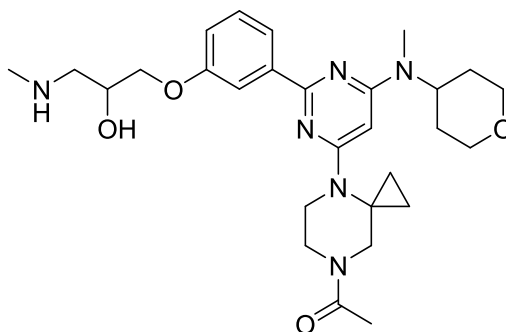
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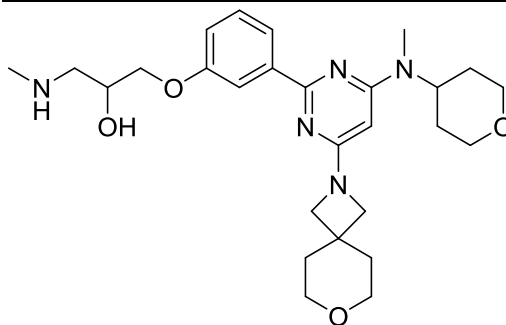
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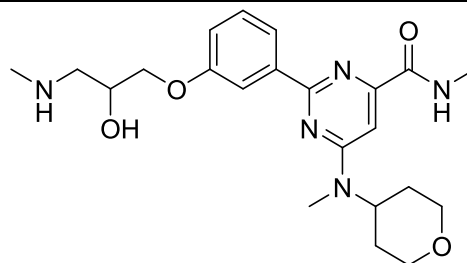
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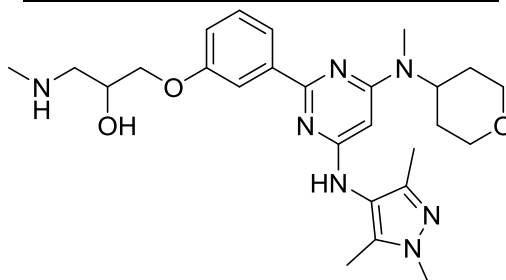
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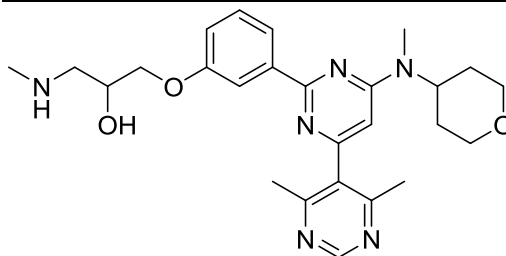
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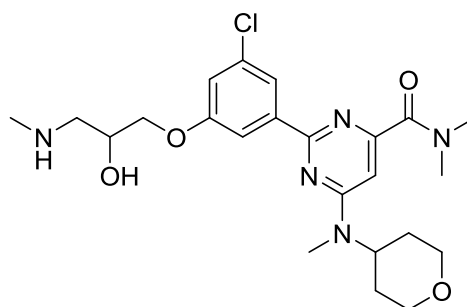
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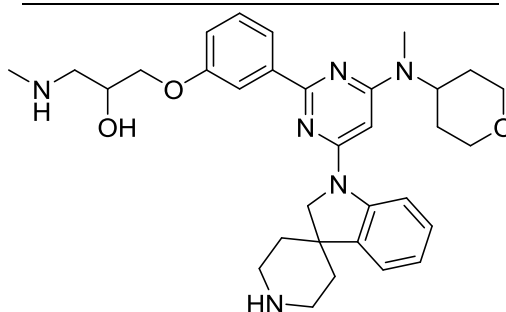
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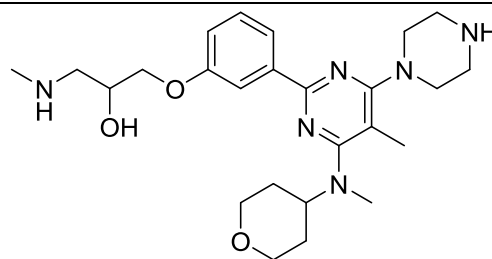
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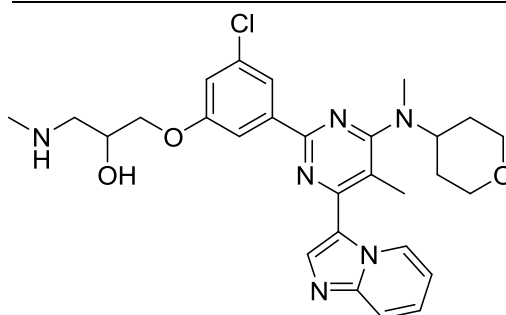
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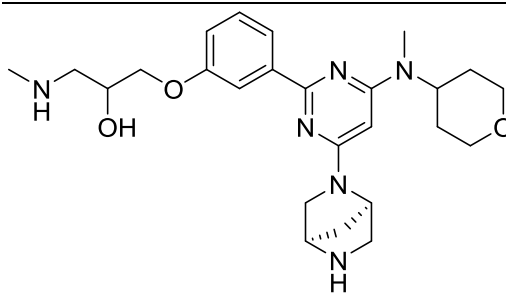
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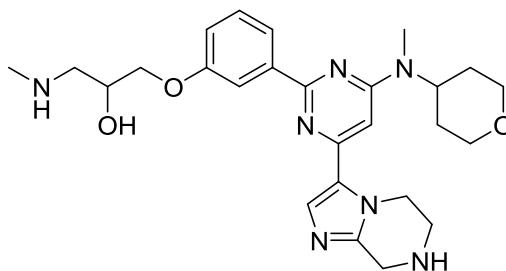
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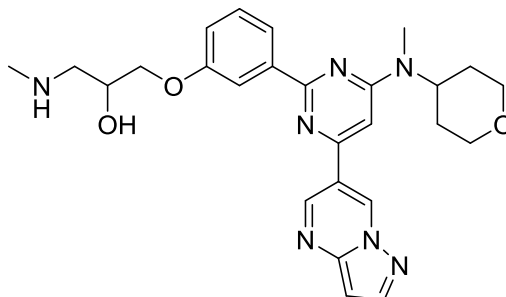
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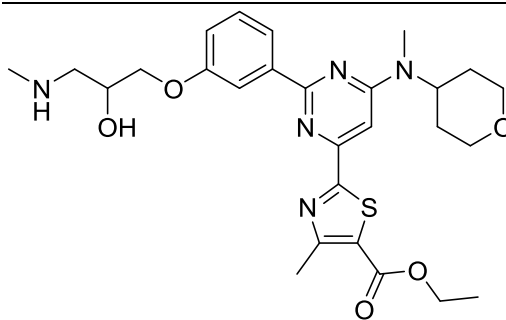
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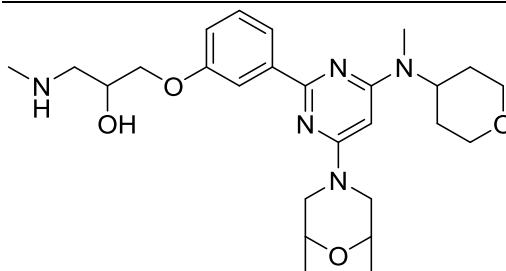
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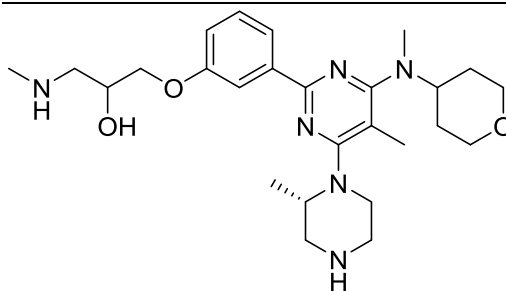
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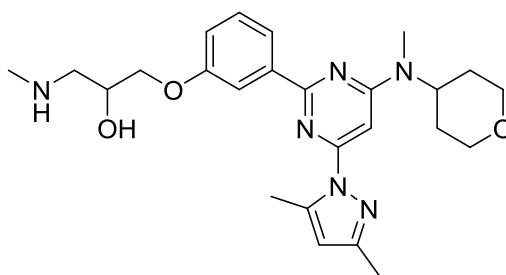
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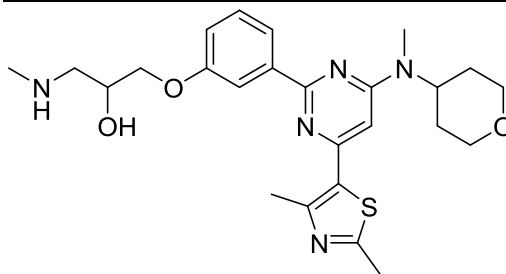
567-1a



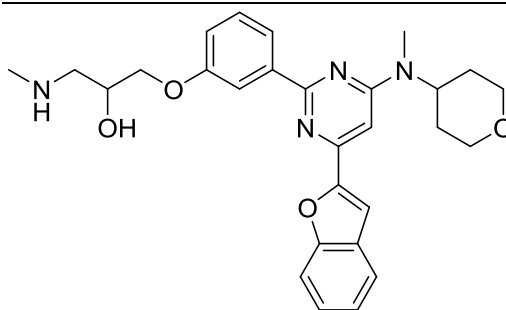
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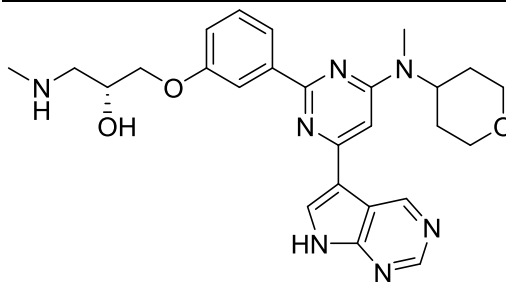
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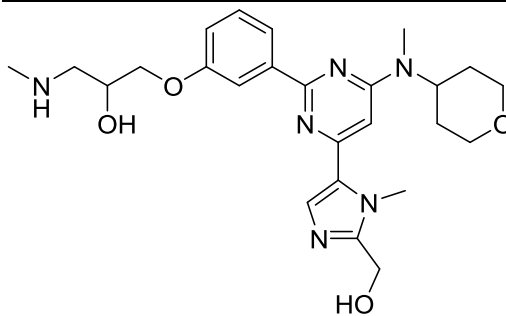
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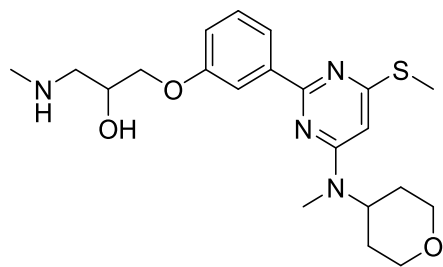
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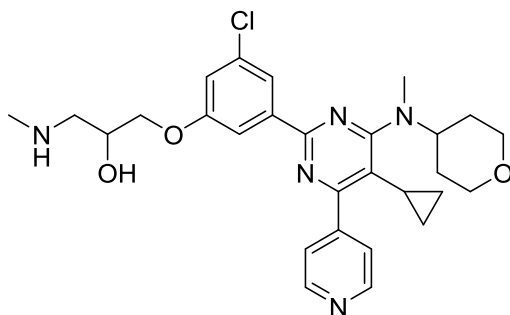
572-1a



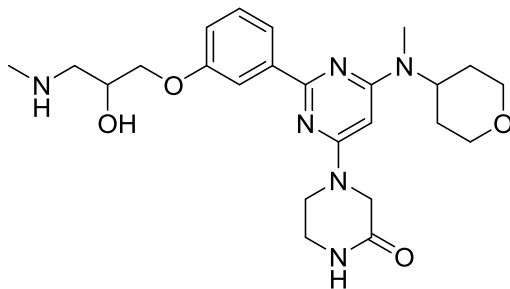
573-1a



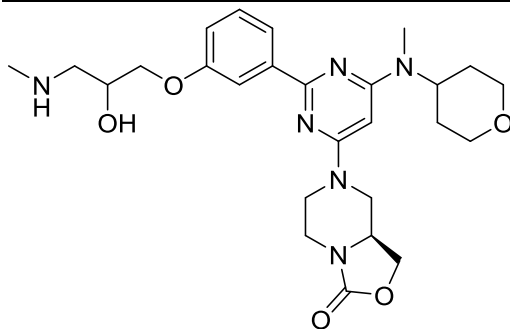
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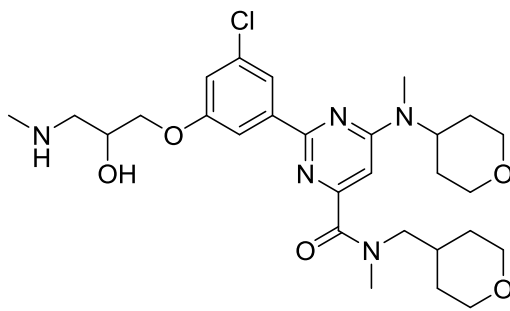
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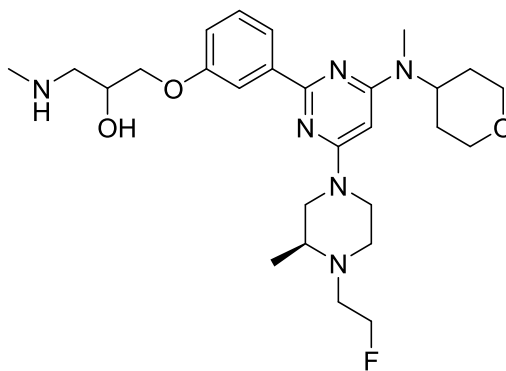
576-1a



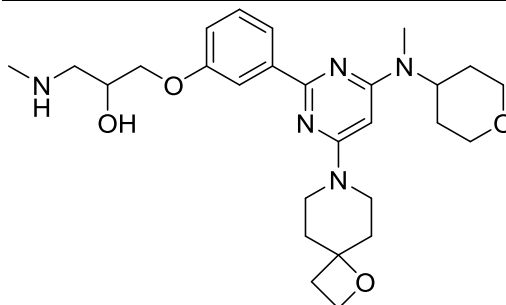
577-1a



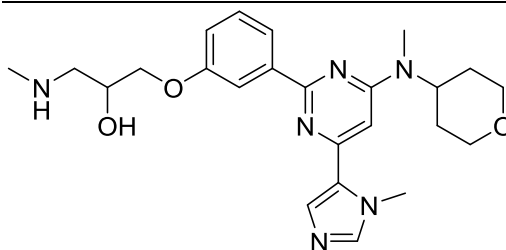
578-1a



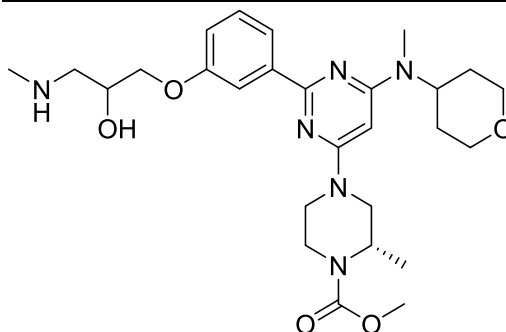
579-1a



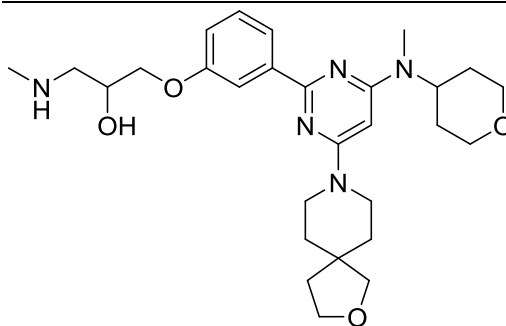
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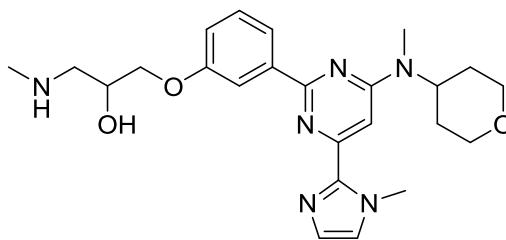
581-1a



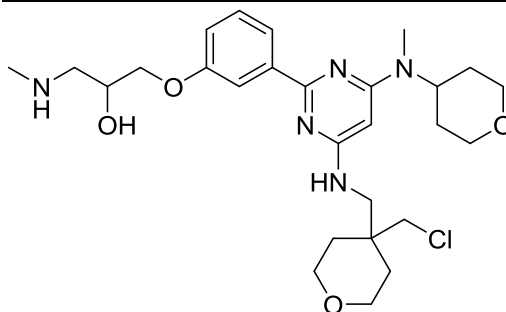
582-1a



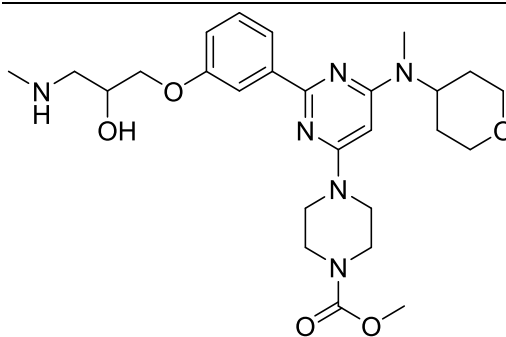
583-1a



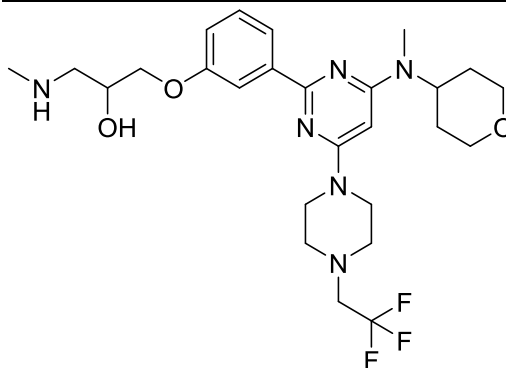
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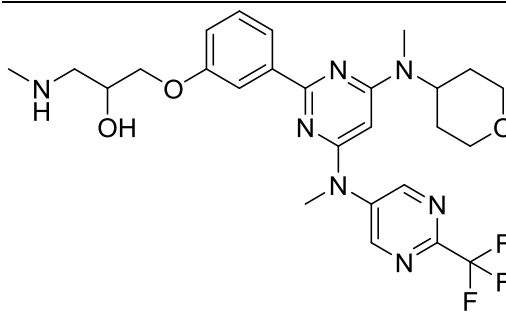
585-1a



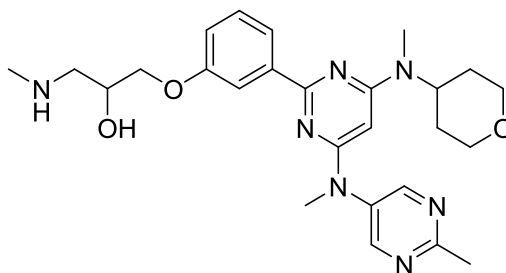
586-1a



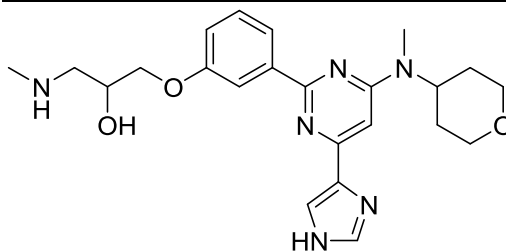
587-1a



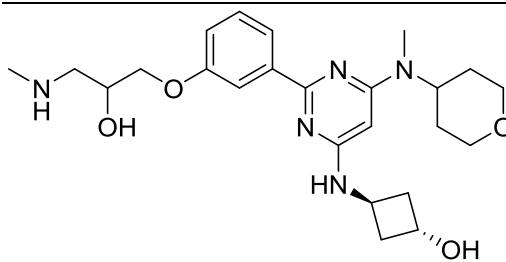
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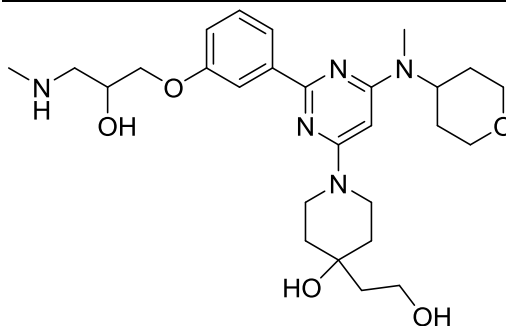
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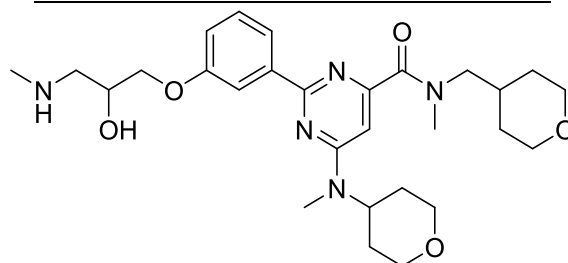
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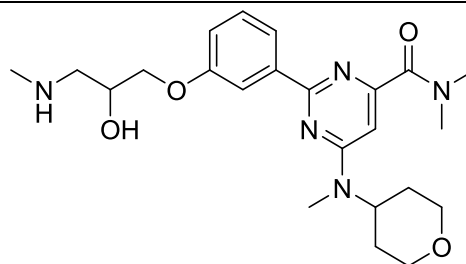
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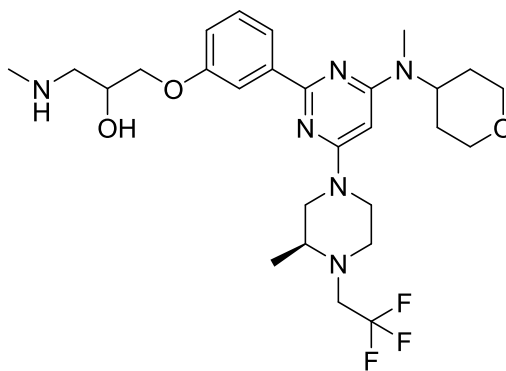
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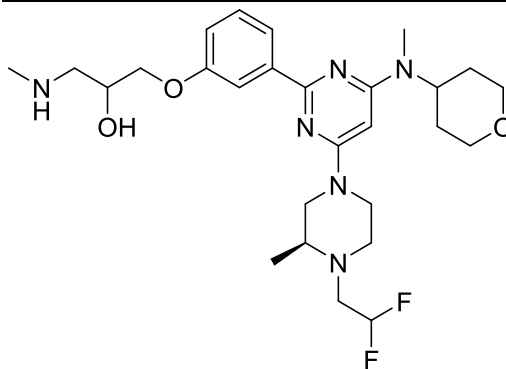
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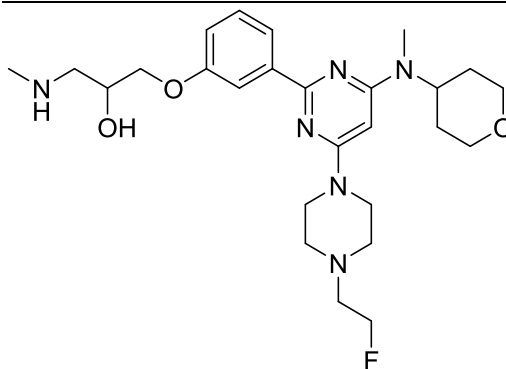
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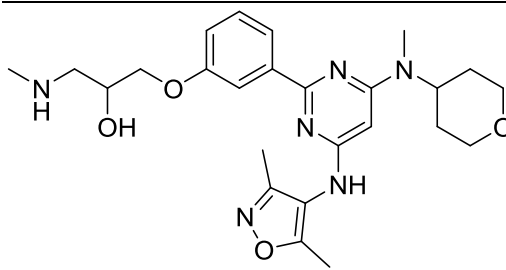
595-1a



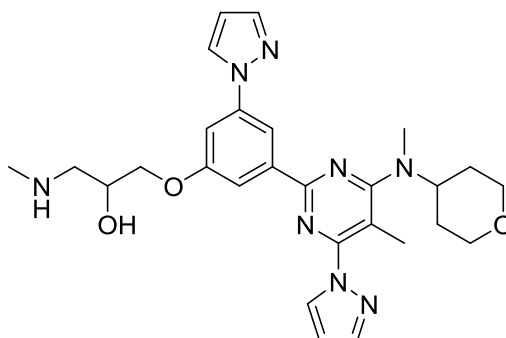
596-1a



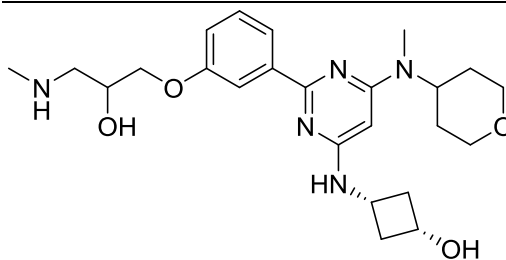
597-1a



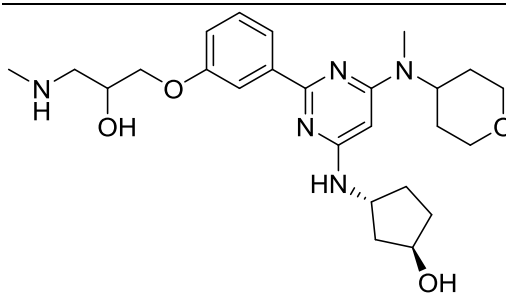
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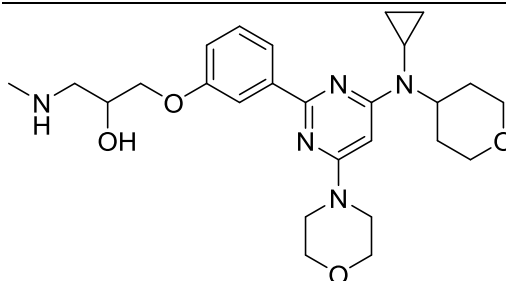
599-1a



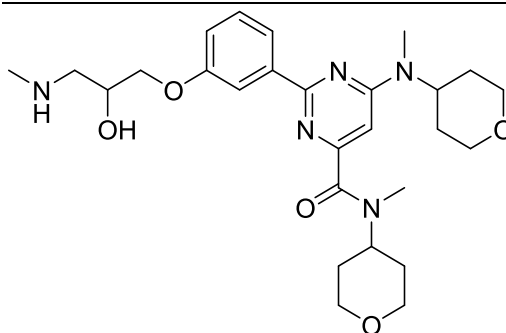
600-1a



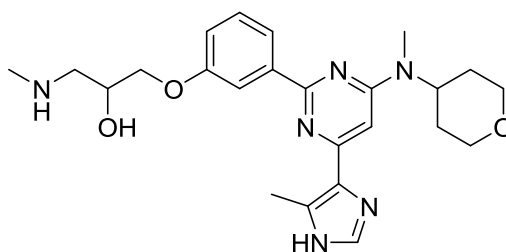
601-1a



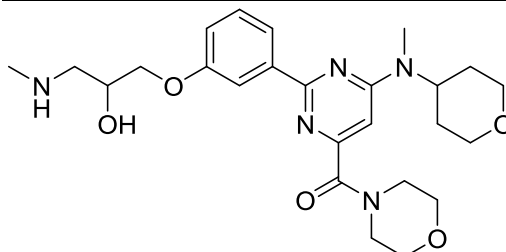
602-1a



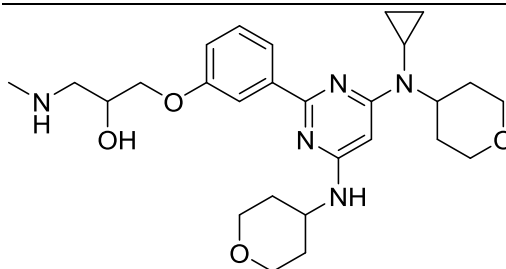
603-1a



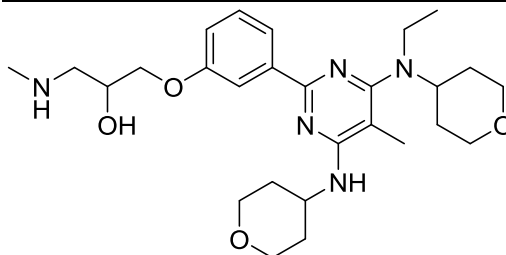
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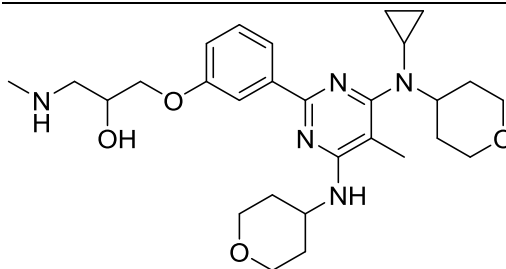
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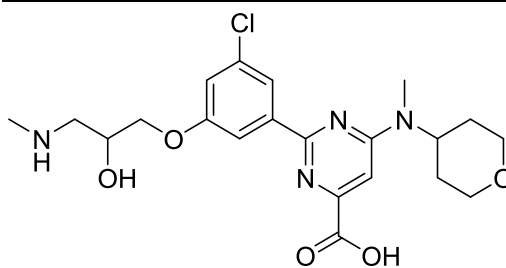
606-1a



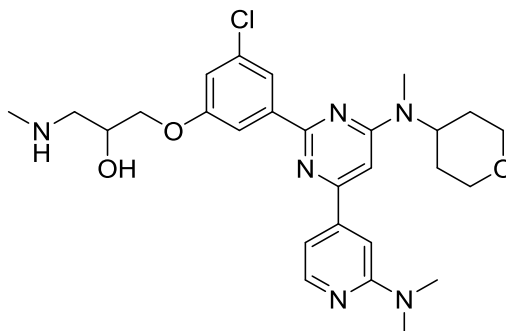
607-1a



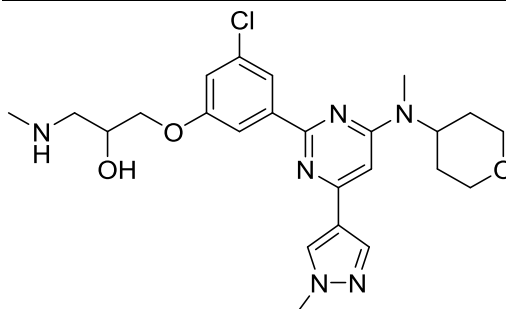
608-1a



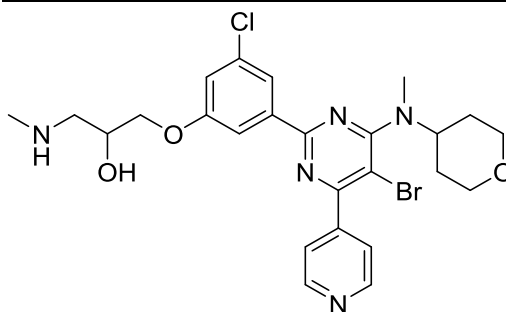
609-1a



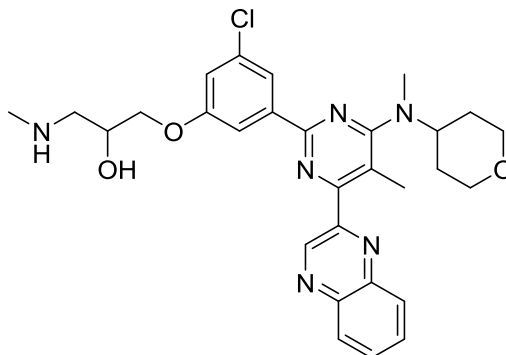
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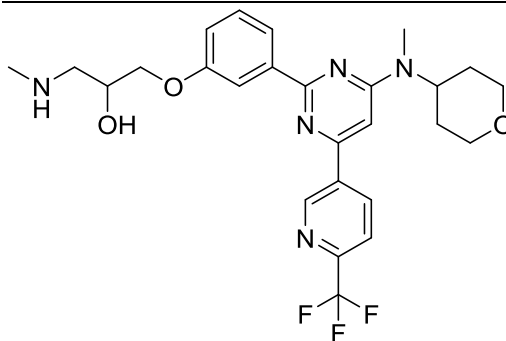
611-1a



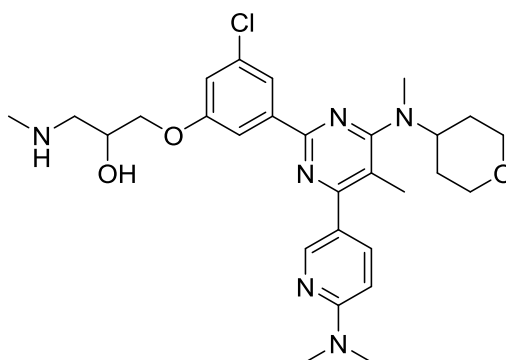
612-1a



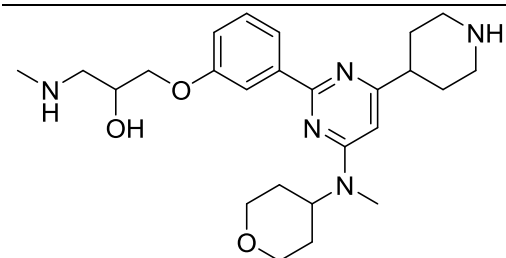
613-1a



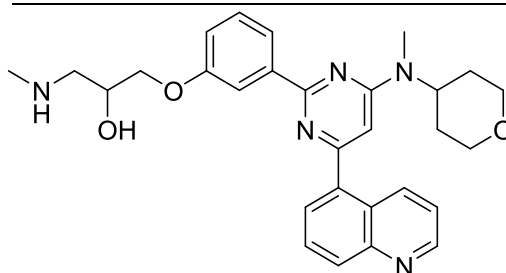
614-1a



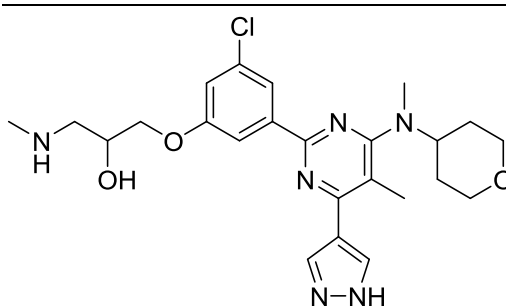
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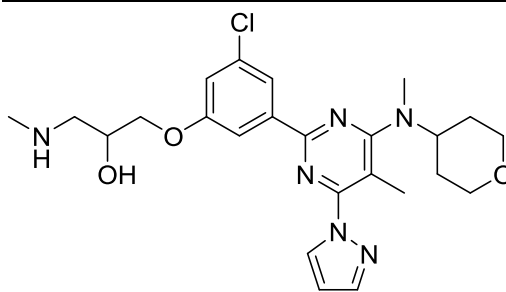
616-1a



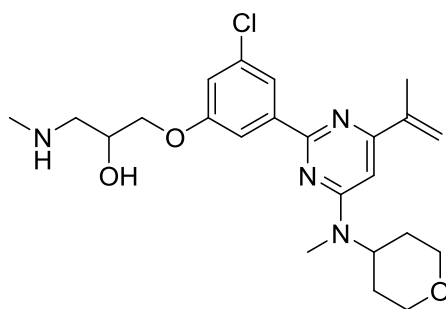
617-1a



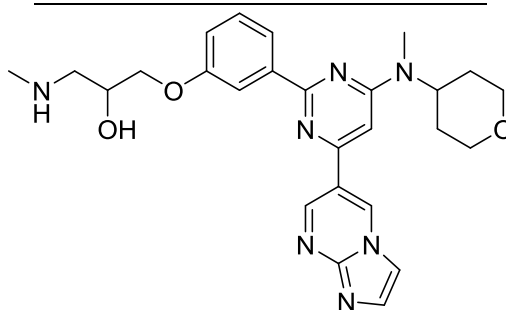
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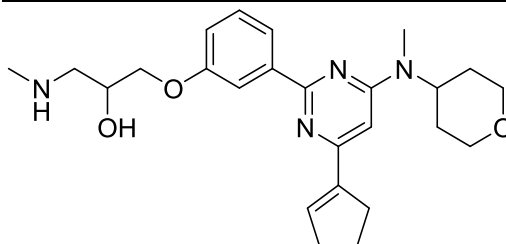
619-1a



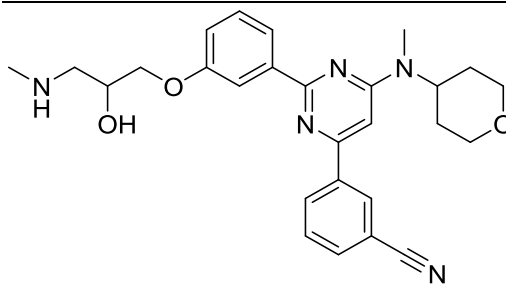
620-1a



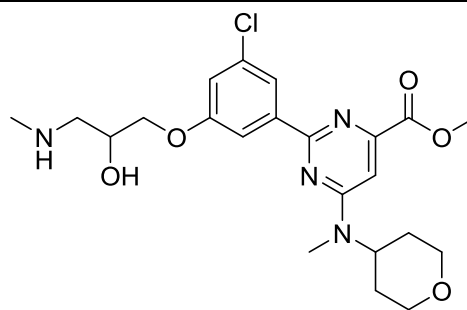
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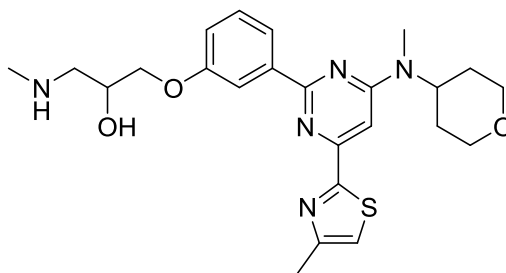
622-1a



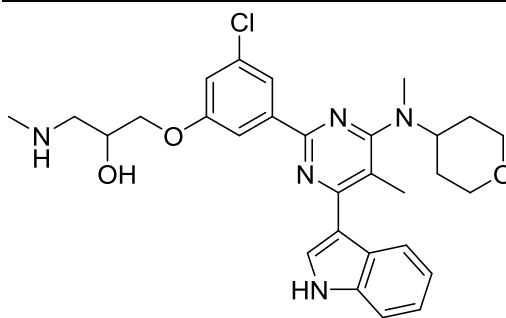
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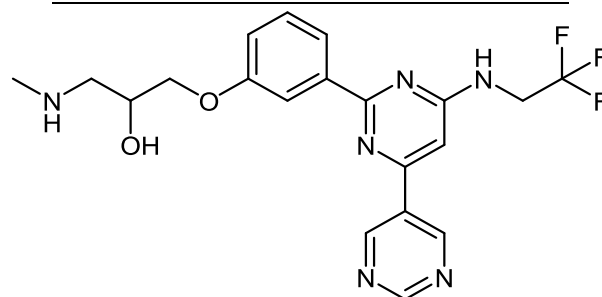
624-1a



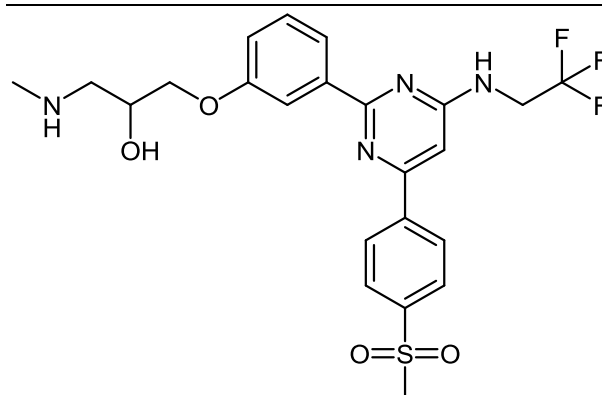
625-1a



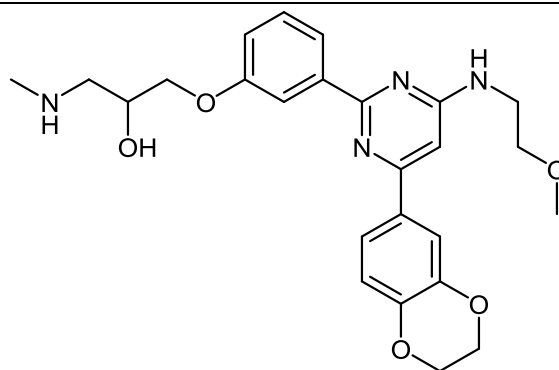
626-1a



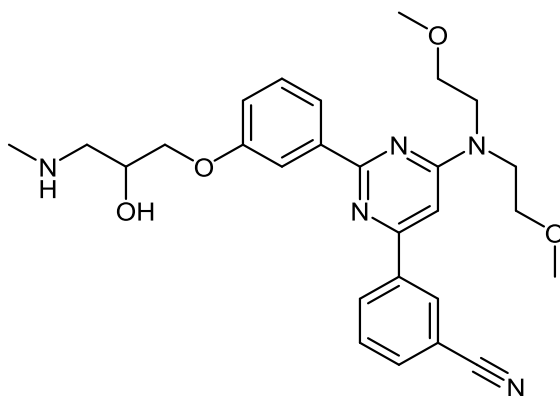
627-1a



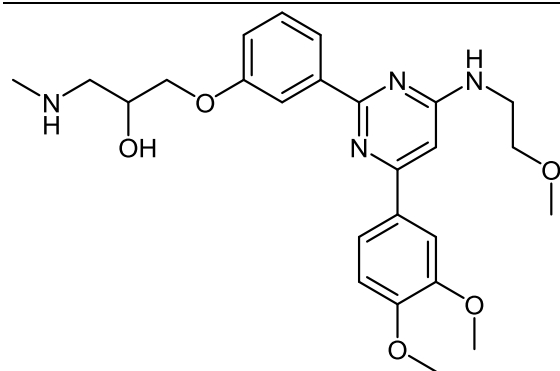
628-1a



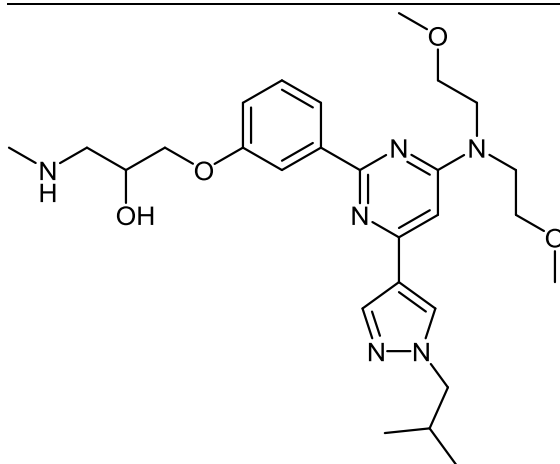
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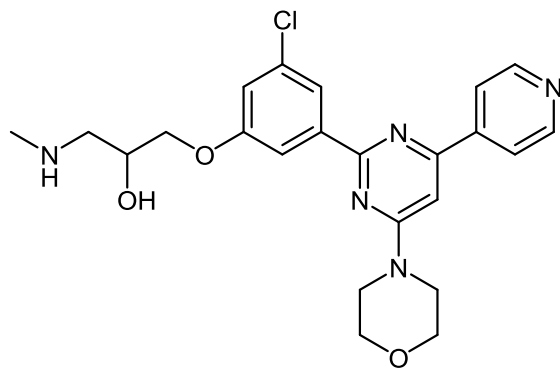
630-1a



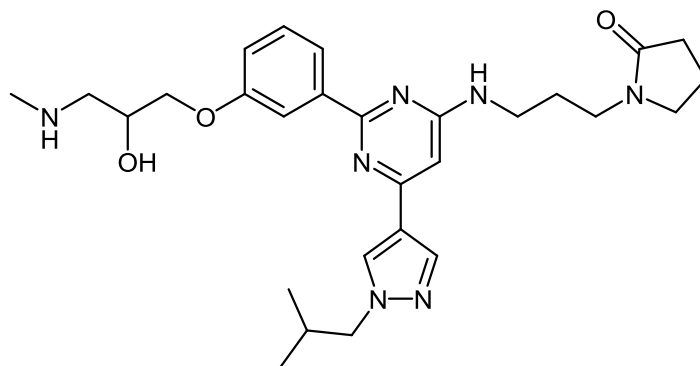
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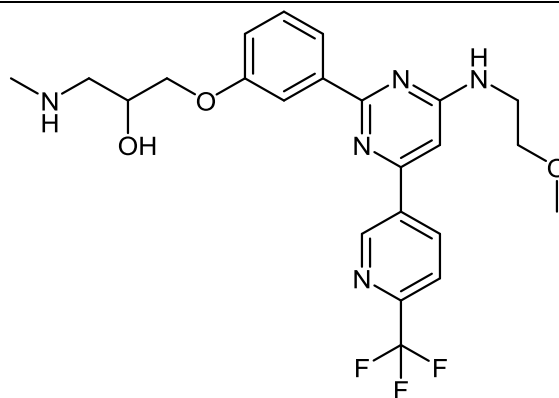
632-1a



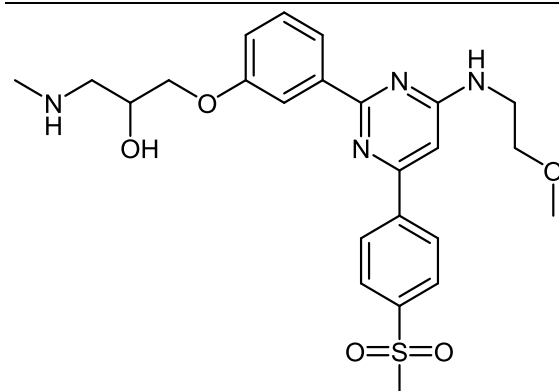
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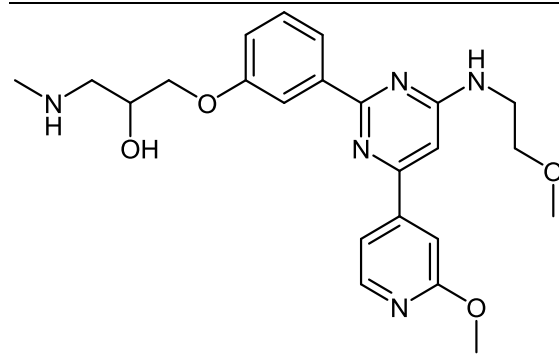
636-1a



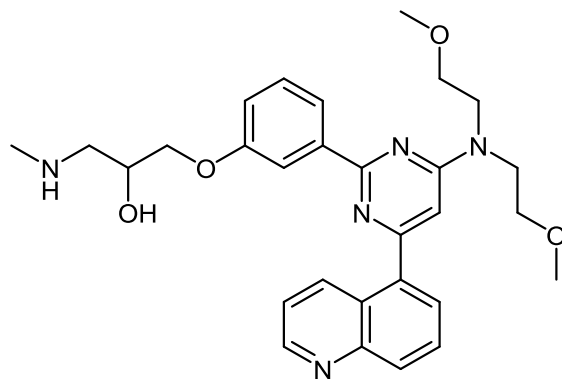
637-1a



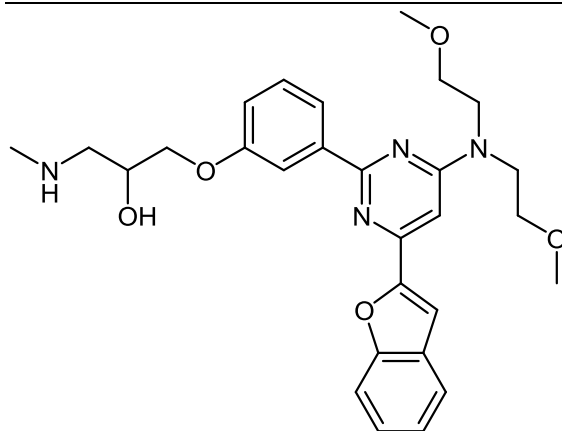
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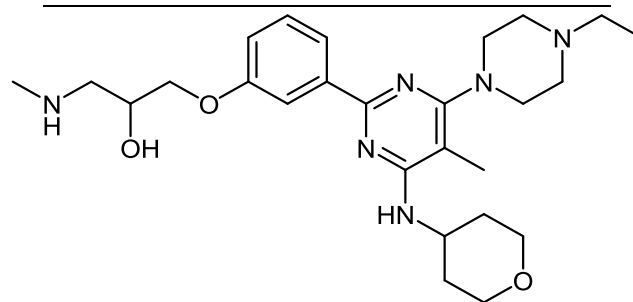
639-1a



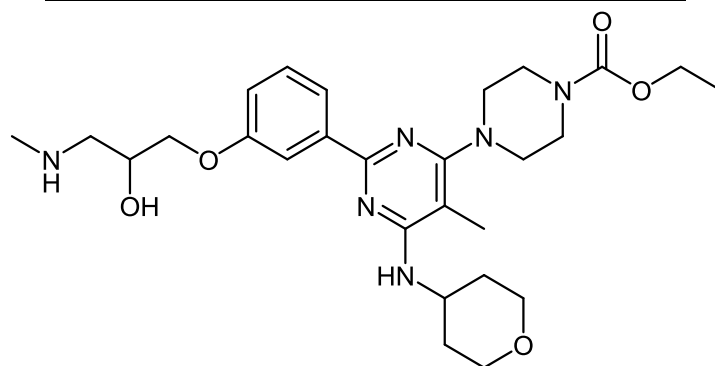
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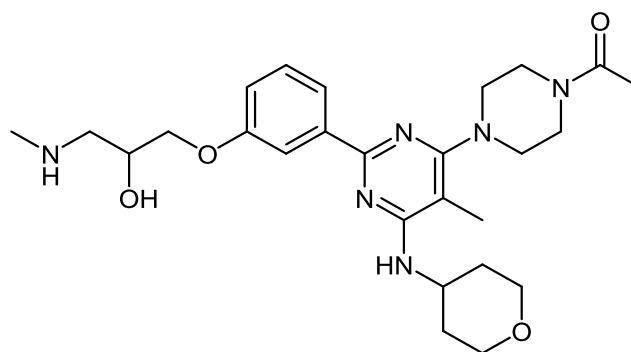
641-1a



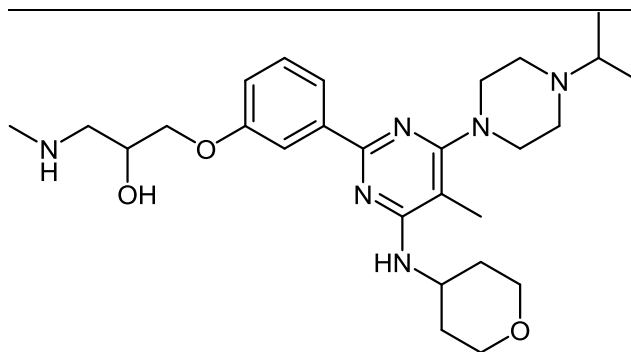
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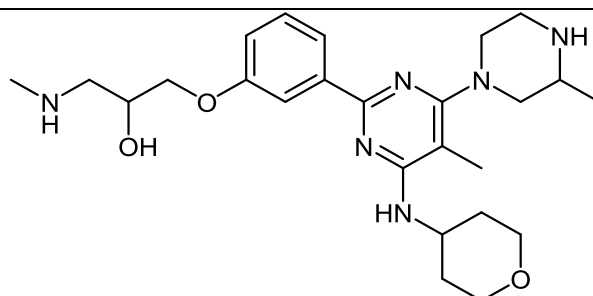
643-1a



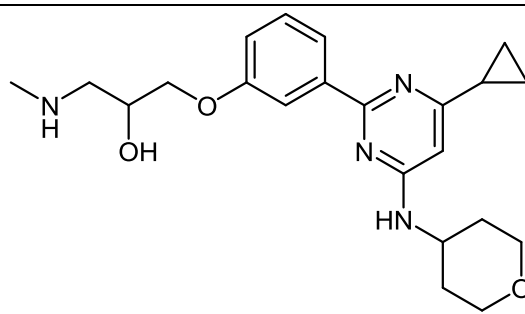
644-1a



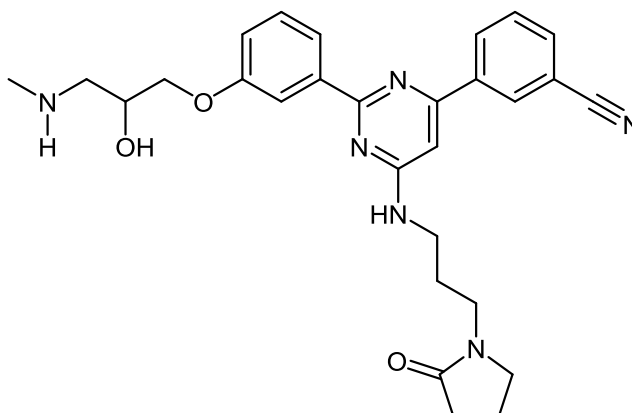
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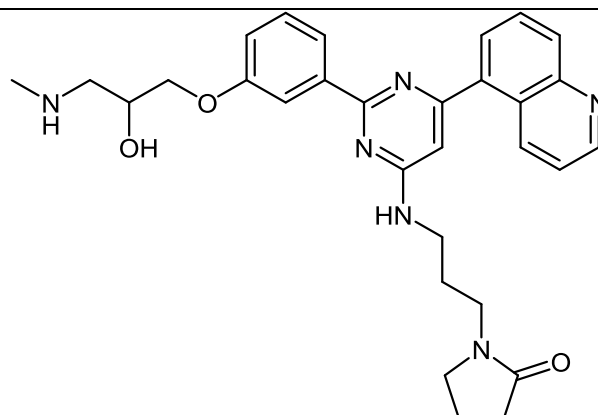
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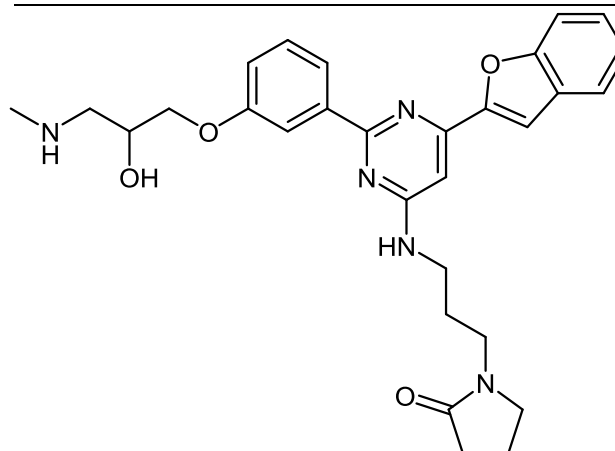
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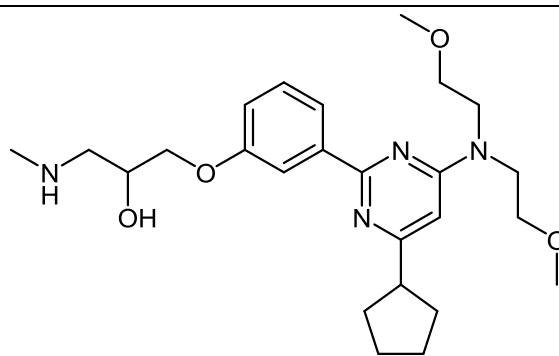
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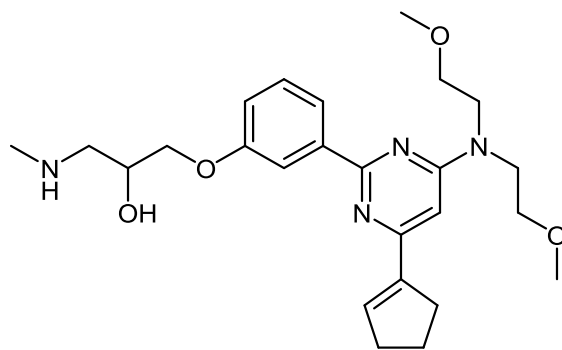
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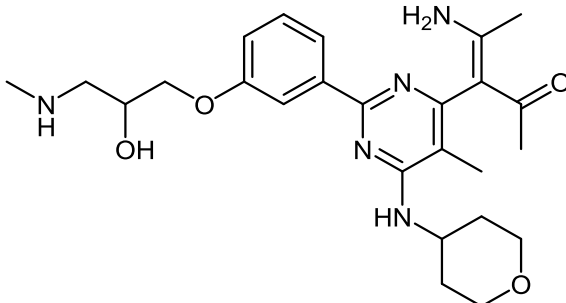
650-1a



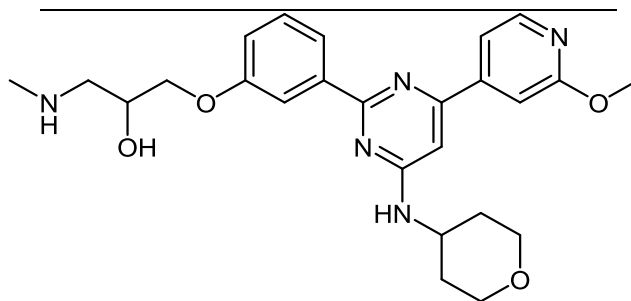
651-1a



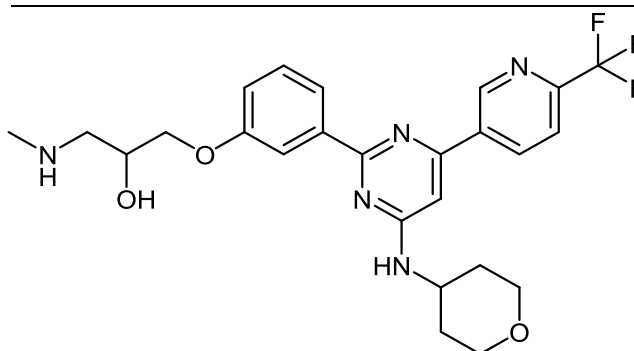
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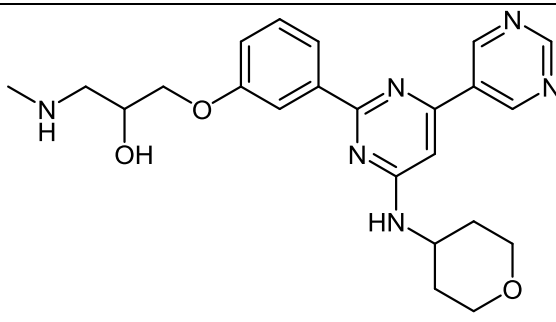
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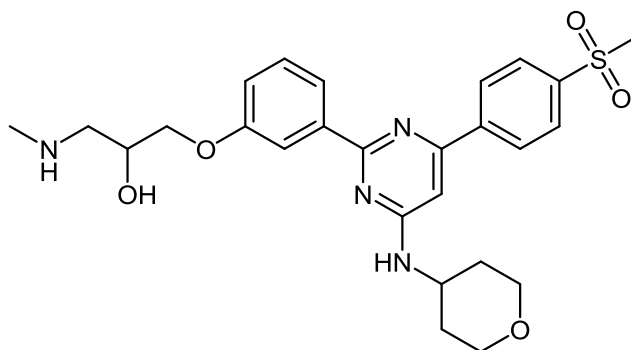
654-1a



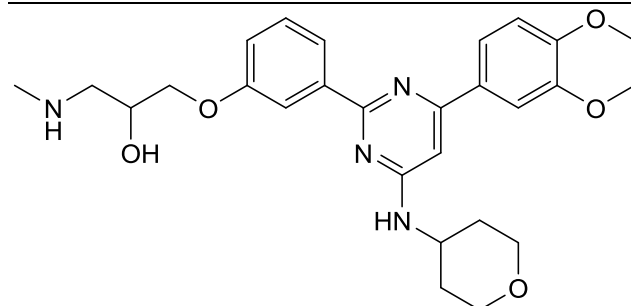
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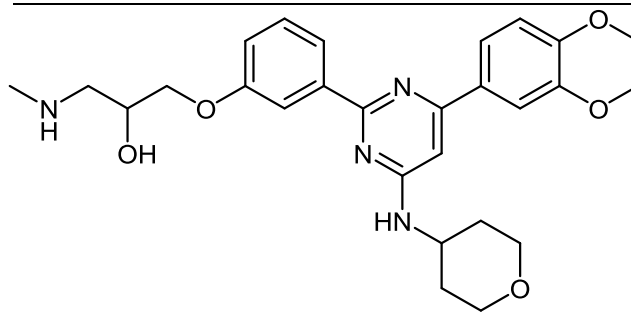
656-1a



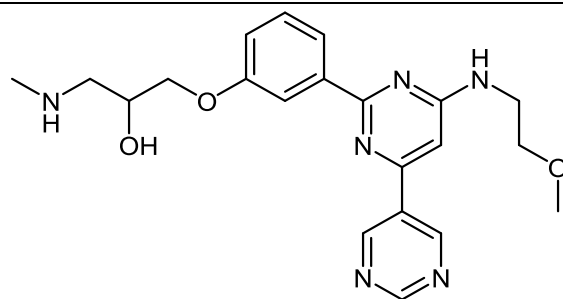
657-1a



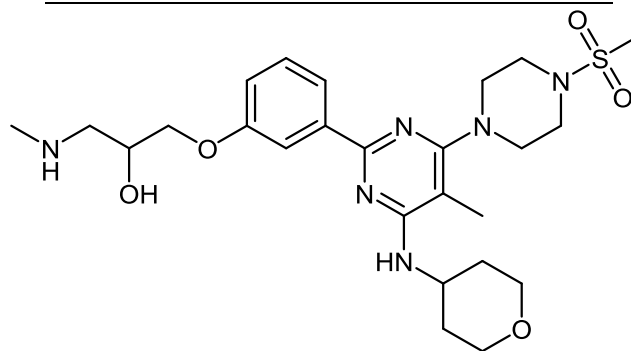
658-1a



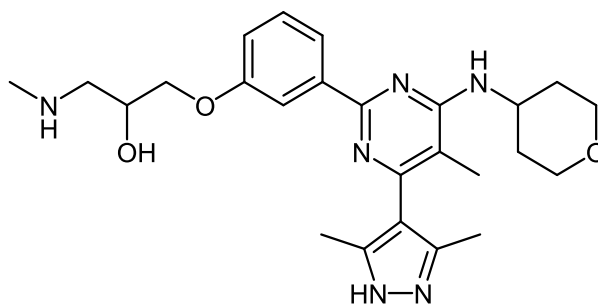
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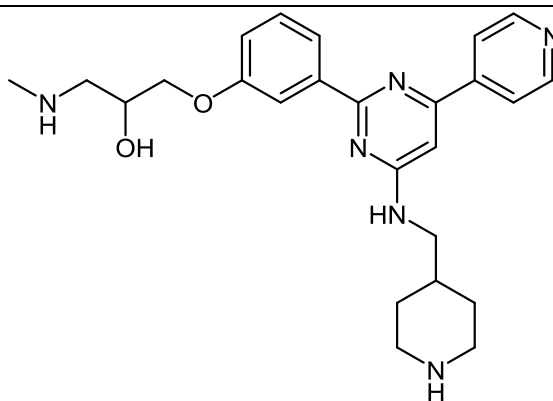
660-1a



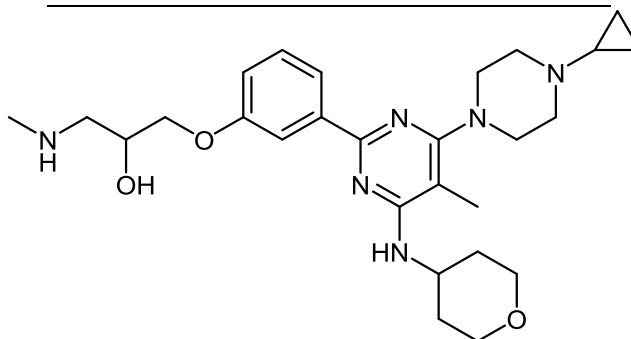
661-1a



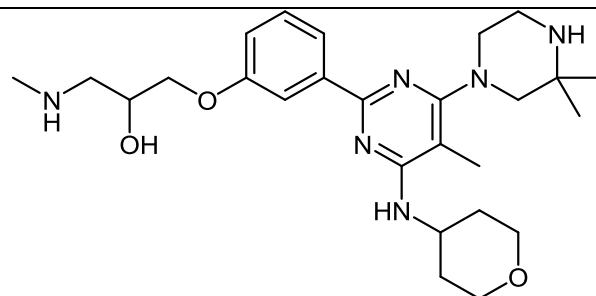
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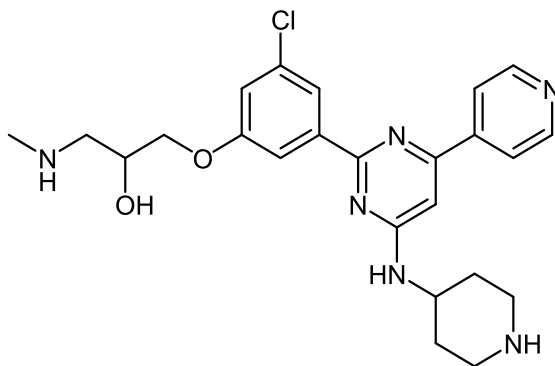
663-1a



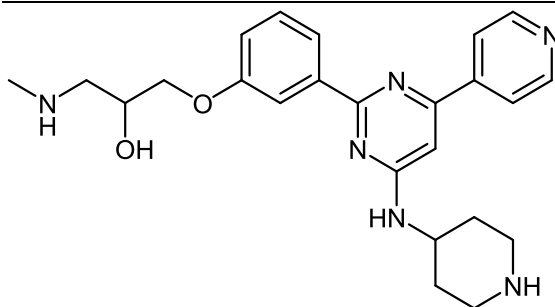
664-1a



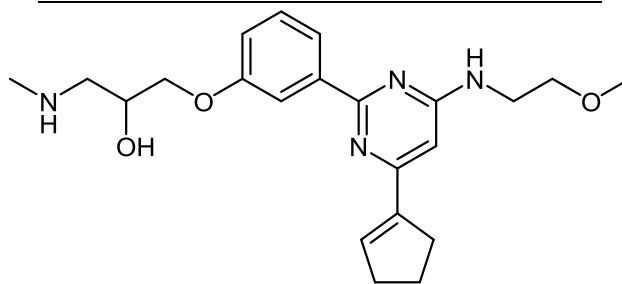
665-1a



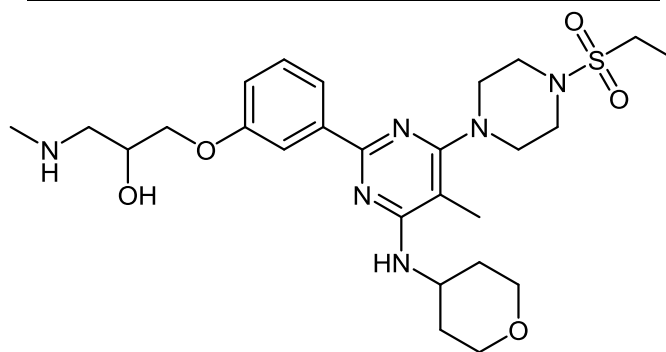
666-1a



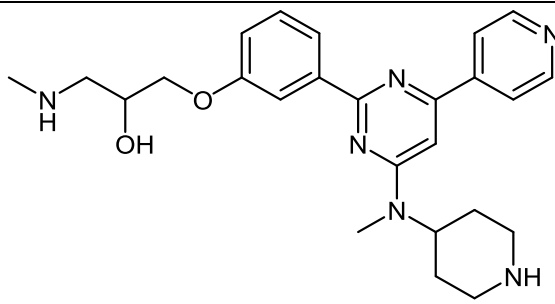
667-1a



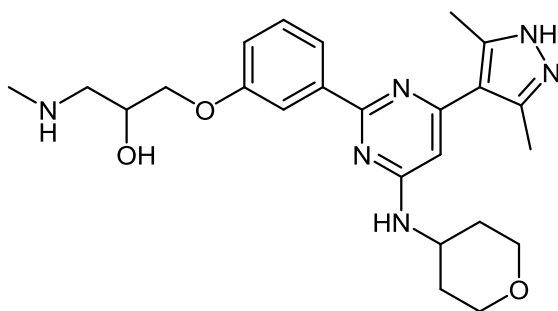
668-1a



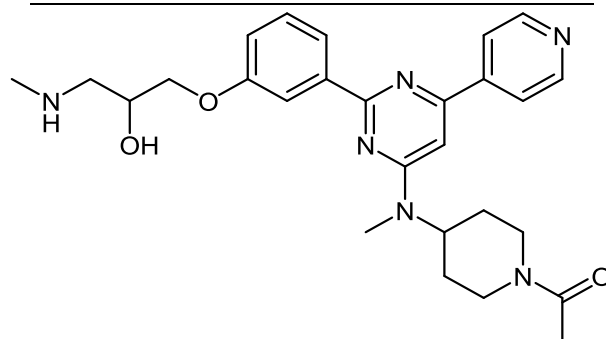
669-1a



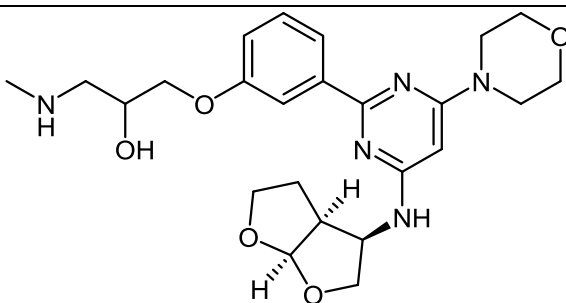
670-1a



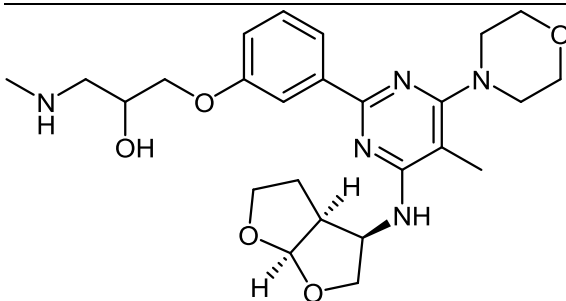
671-1a



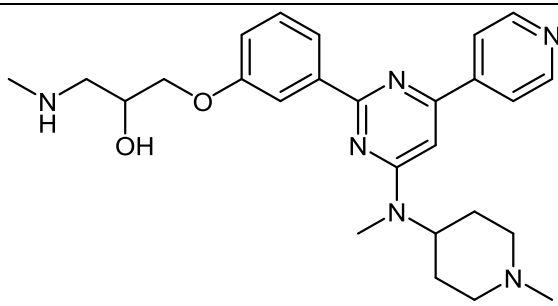
672-1a



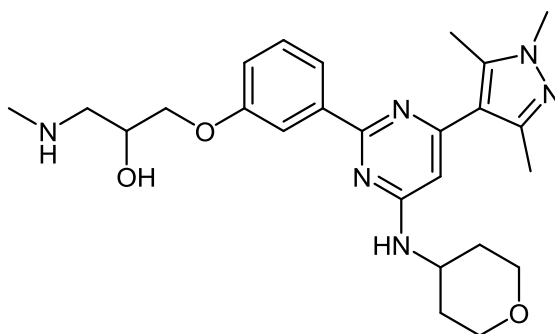
673-1a



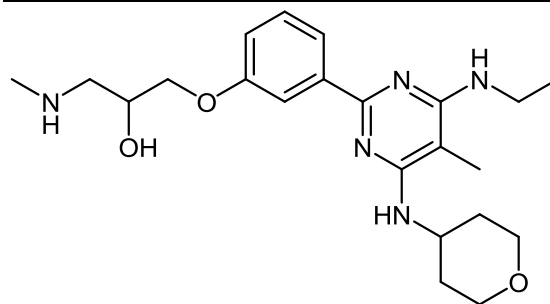
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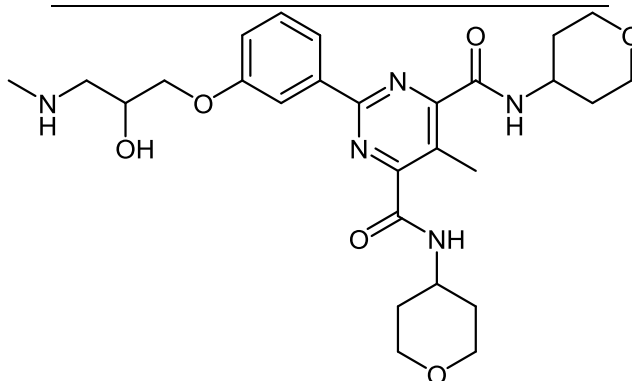
675-1a



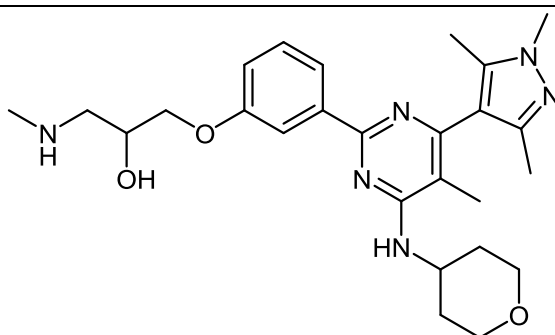
676-1a



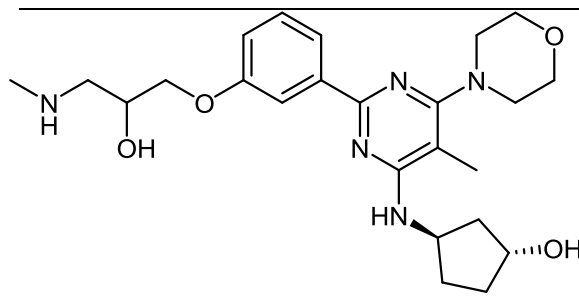
677-1a



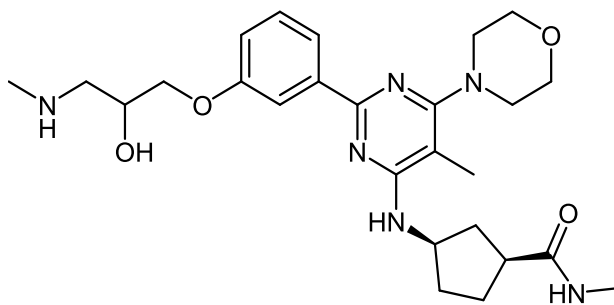
678-1a



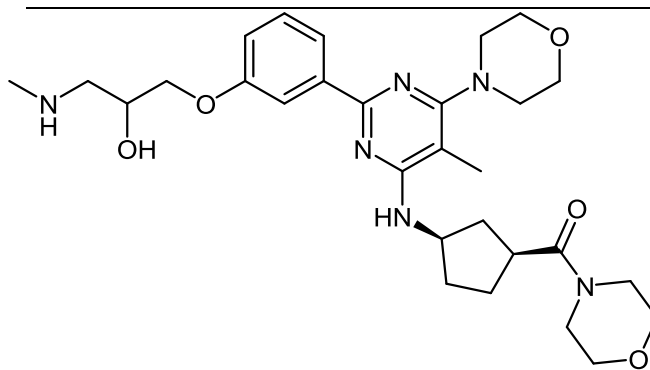
679-1a



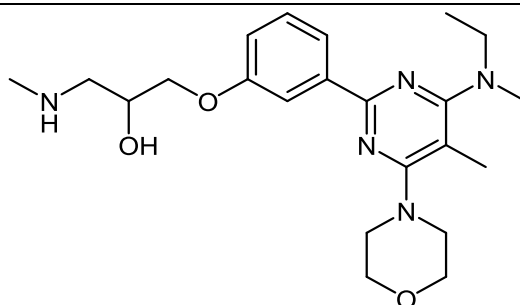
680-1a



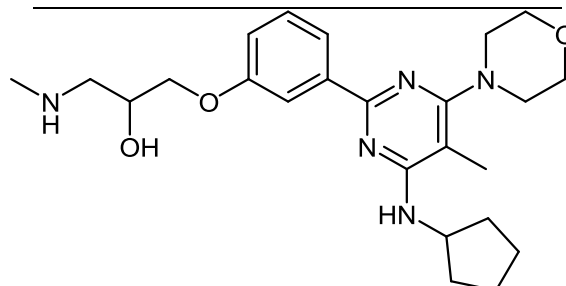
681-1a



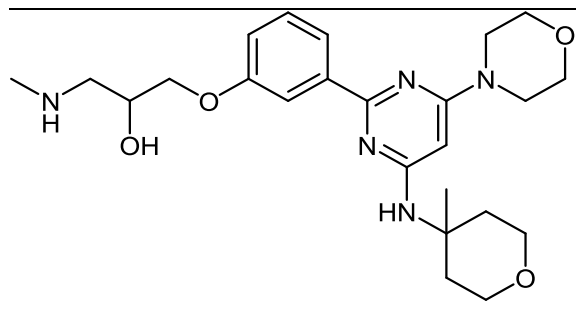
682-1a



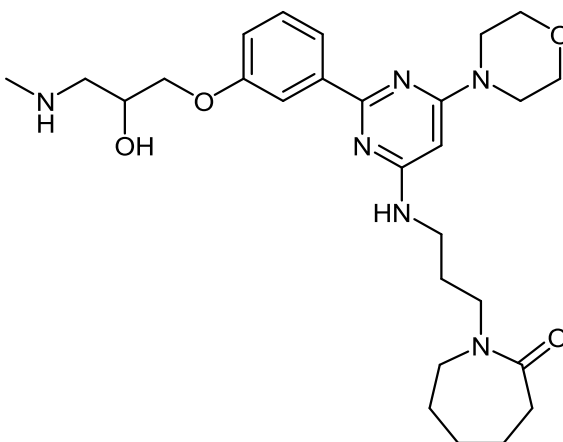
683-1a



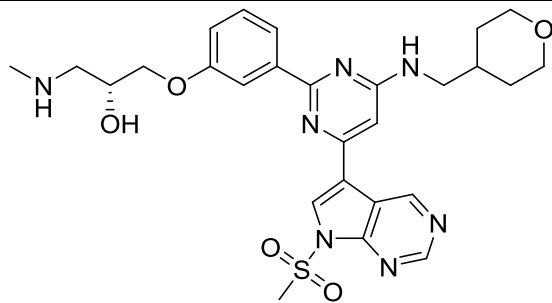
684-1a



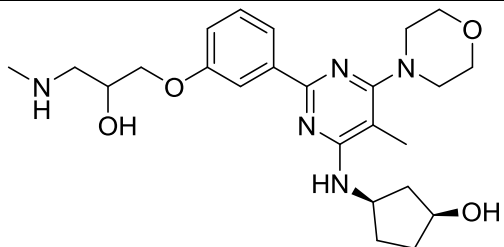
685-1a



686-1a



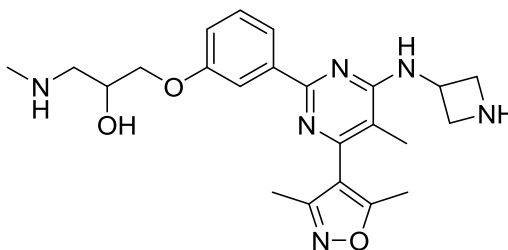
687-1a



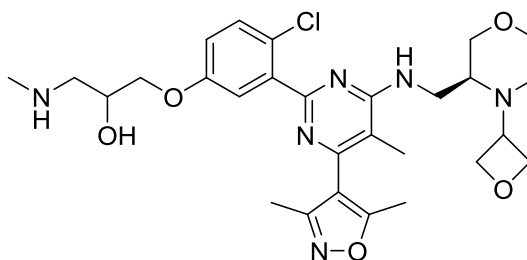
and pharmaceutically acceptable salts thereof.

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

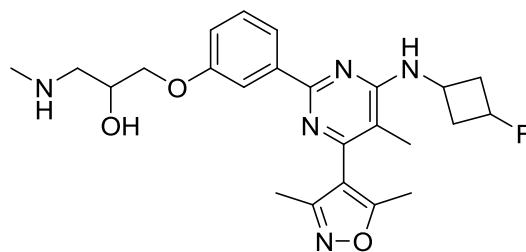
1-3



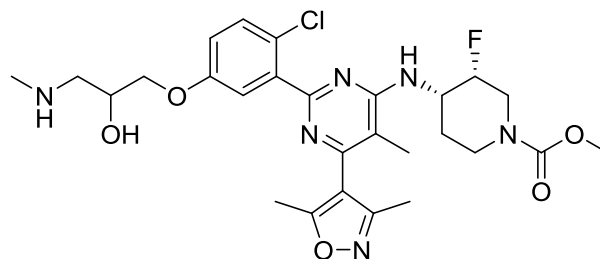
2-3



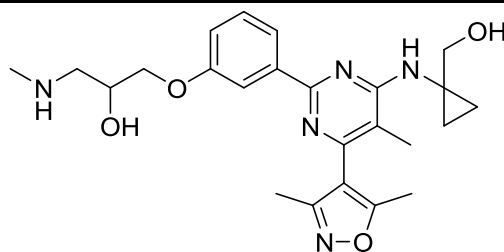
3-3



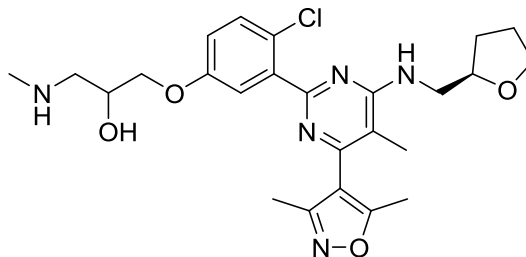
4-3



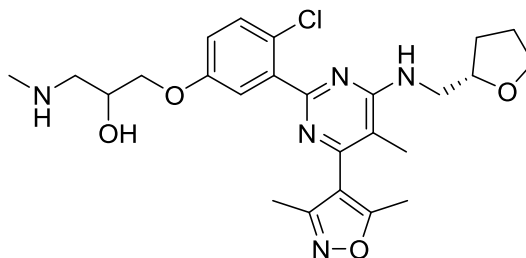
5-3



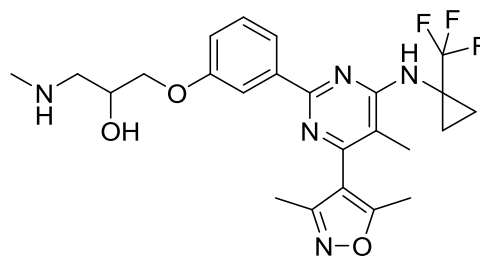
6-3



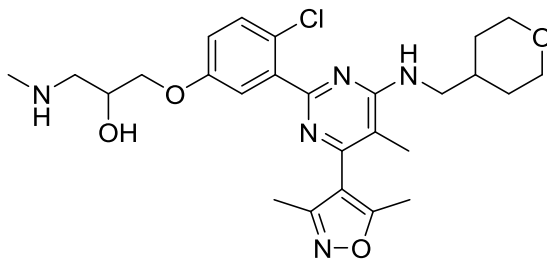
7-3



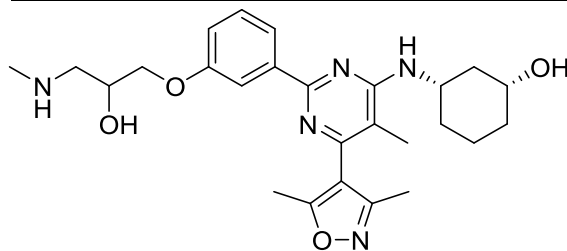
8-3



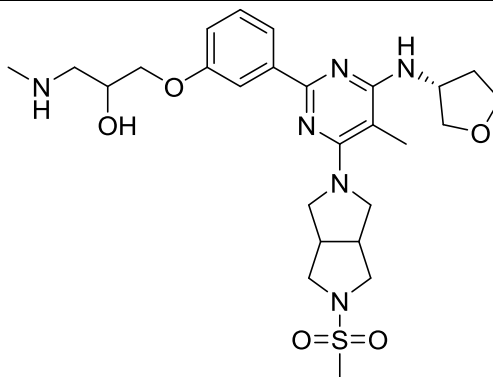
9-3



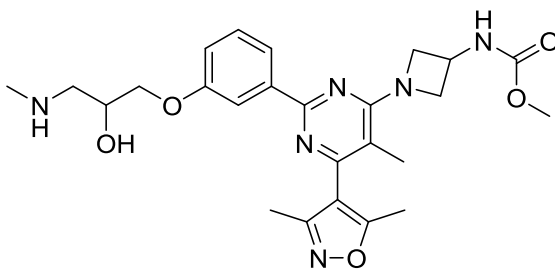
10-3



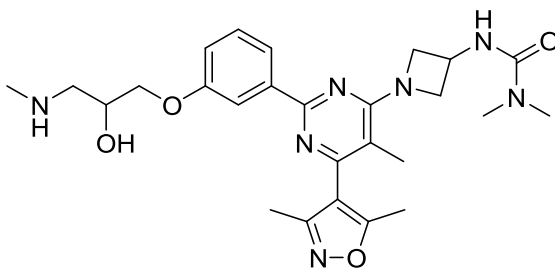
11-3



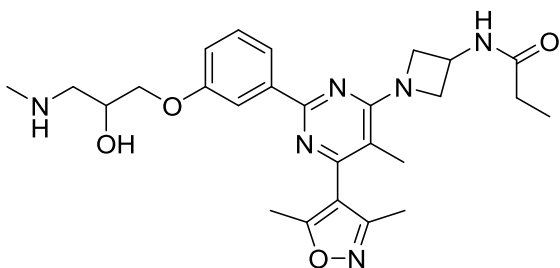
12-3



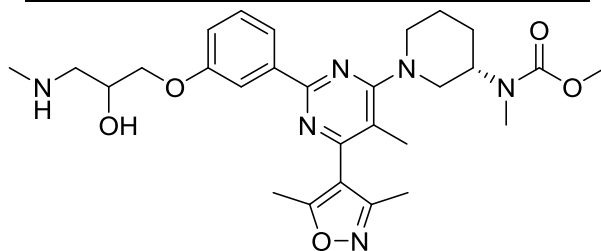
13-3



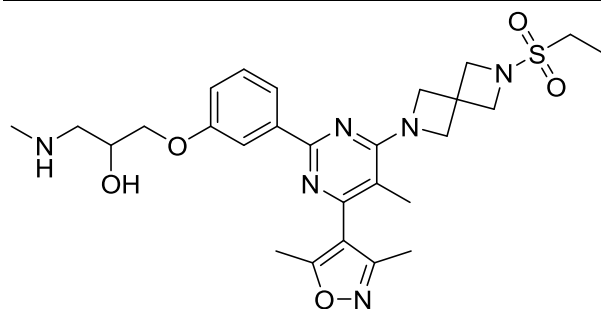
14-3



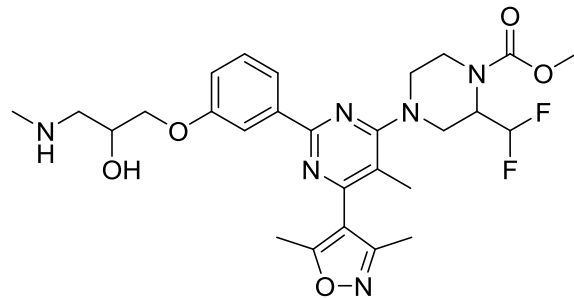
15-3



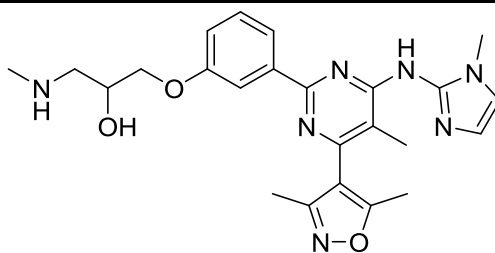
16-3



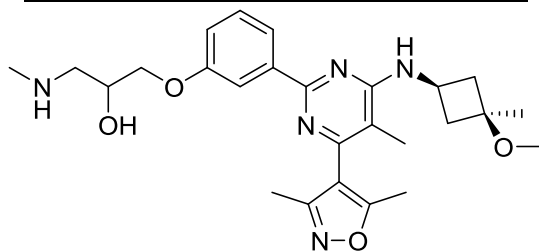
17-3



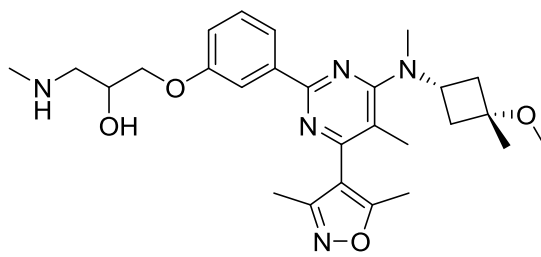
18-3



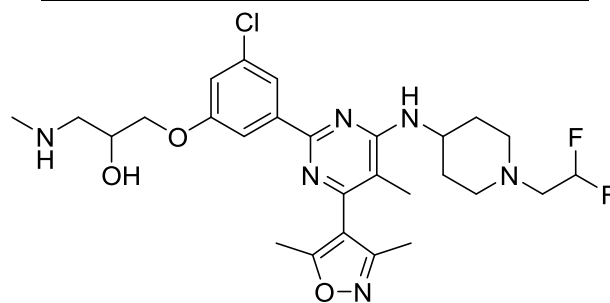
19-3



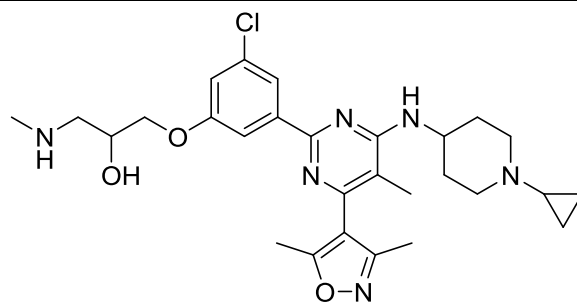
20-3



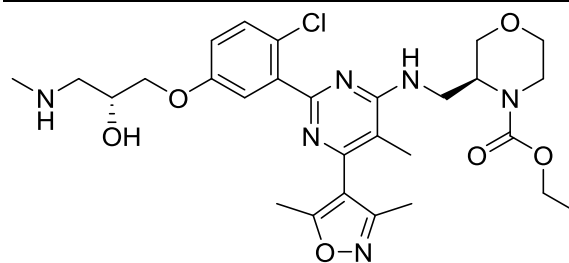
21-3



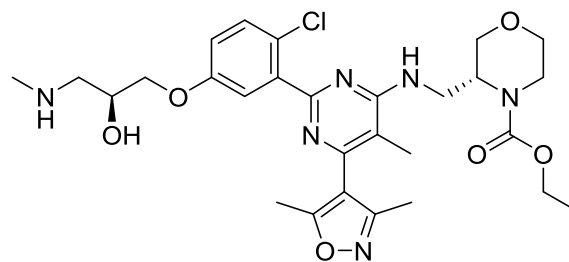
22-3



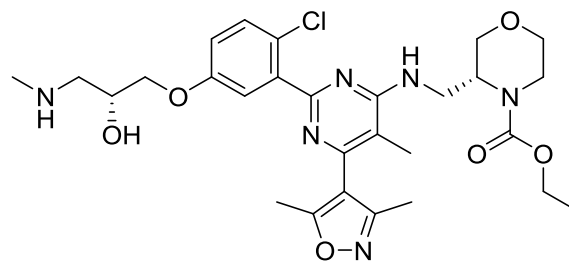
23-3



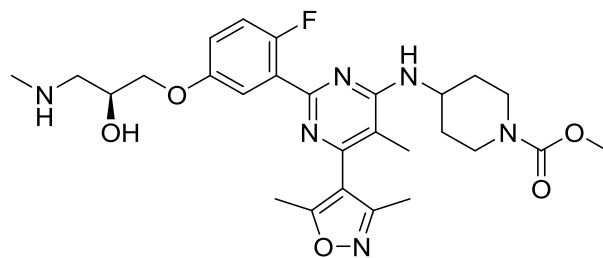
24-3



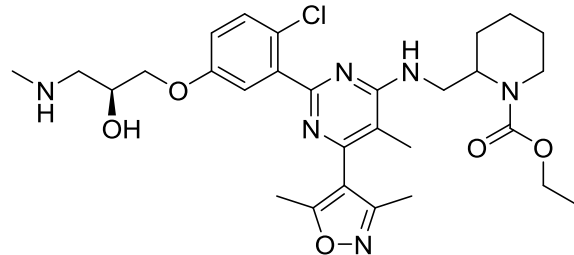
25-3



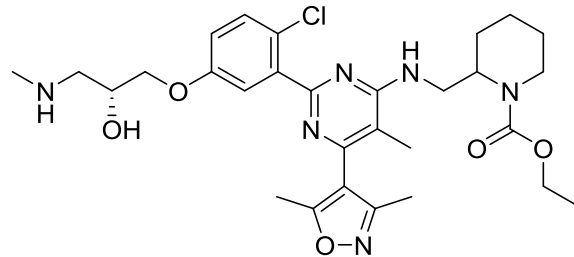
26-3



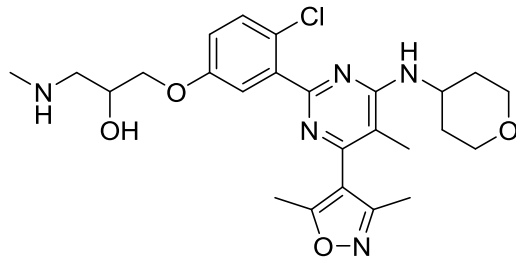
27-3



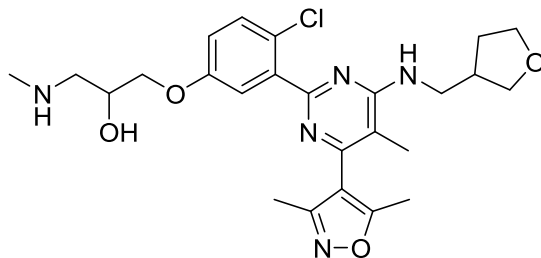
28-3



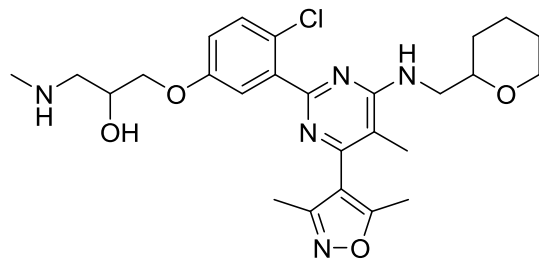
29-3



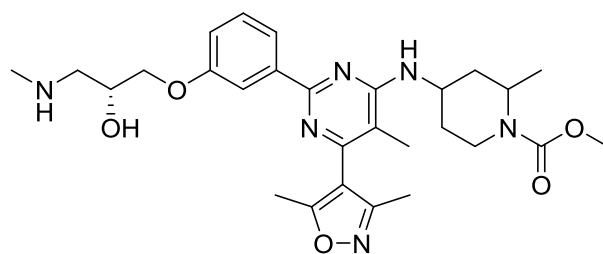
30-3



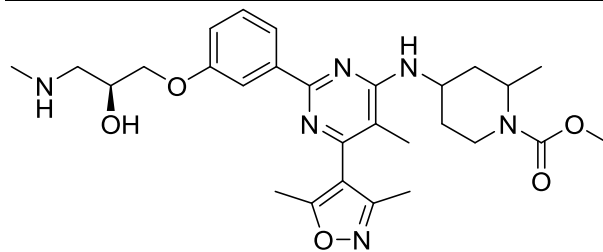
31-3



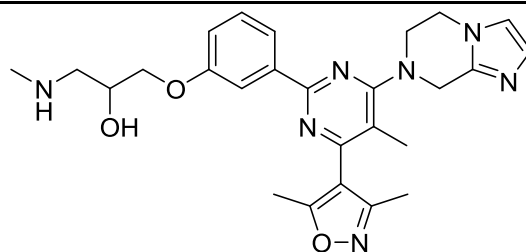
32-3



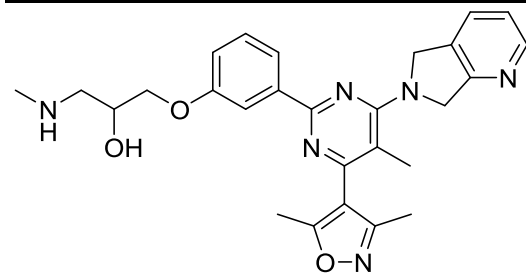
33-3



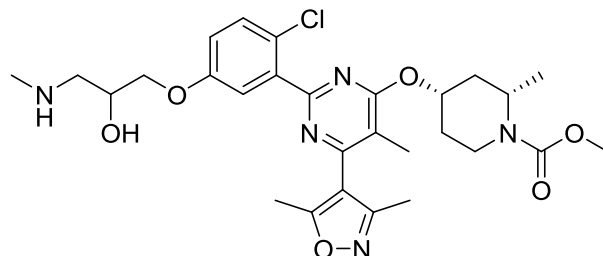
34-3



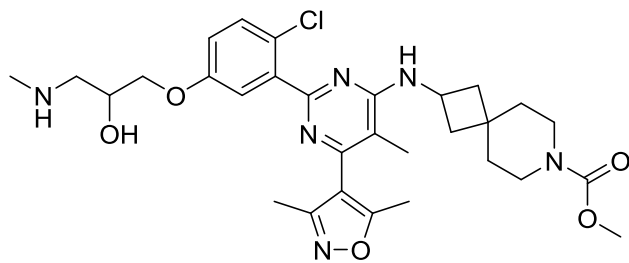
35-3



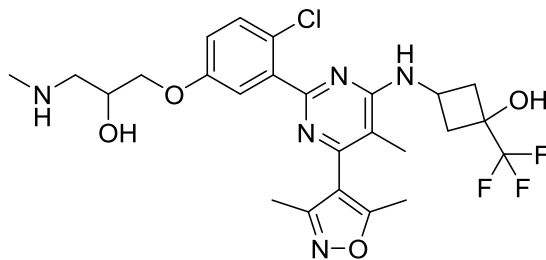
36-3



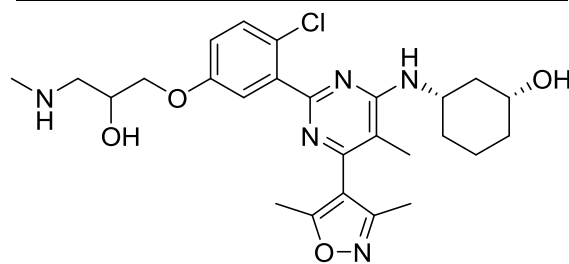
37-3



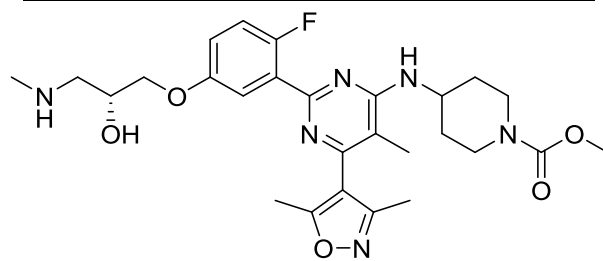
38-3



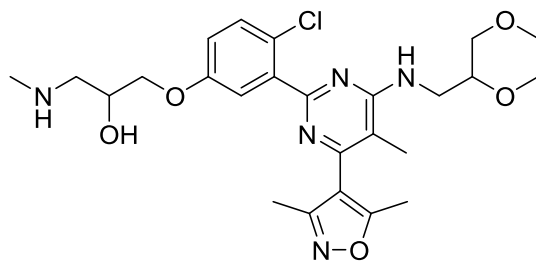
39-3



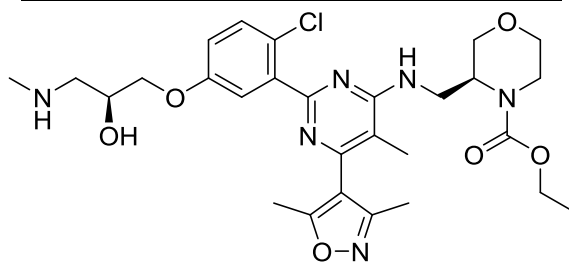
40-3



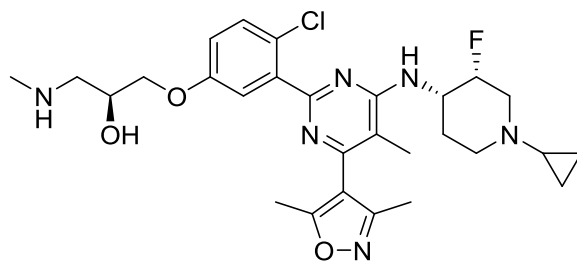
41-3



42-3



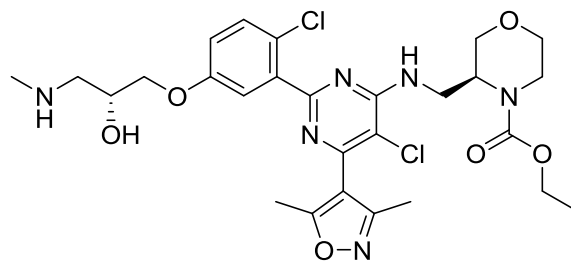
43-3



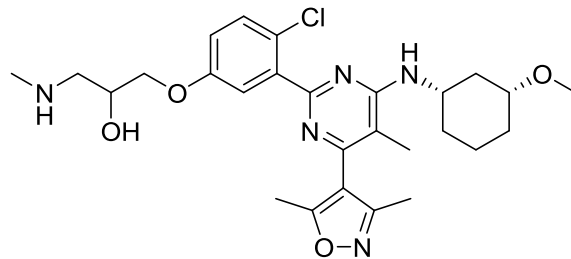
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CCCCOc1nc2c(nc3c2c(c1)C3=NO)c4cc(F)ccc4OCC(O)CNCC1(C)C(=O)OCC1Nc2nc(C)c(C3=C(C)C=C(C3)[N+]([O-])=O)c2N=C(c4ccc(OC(CO)CN)cc4F)c5ccccc5CNCC(O)COc1ccc(cc1F)c2nc3c(ncn3C4CCOCC4)c5c(C)c(C)oc5n2CNCC(O)COc1ccc(Cl)c(c1)-c2nc3c(ncn3C)C4=C(C)C(=C5C4=CC=C(C)N5O)C6=C(C)C=C(C)C6CNCC(O)[C@H](O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)c4c(C)c(C)c(C)c4n2CNCC(O)COc1ccc(Cl)c(N2C=NC3=C(C)C(=C2C4=C(C)C(=C(C5=CC=C(C=C5)N4O)N3)N2C6CC7CCN(CC7)CC6)C1

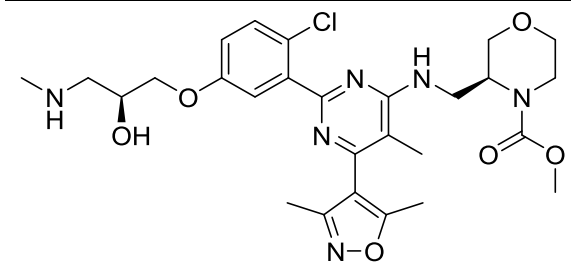
56-3



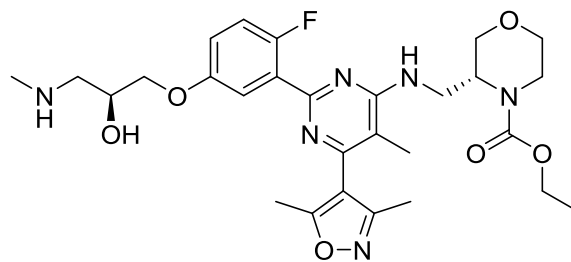
57-3



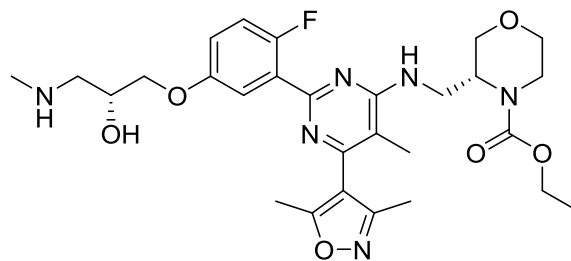
58-3



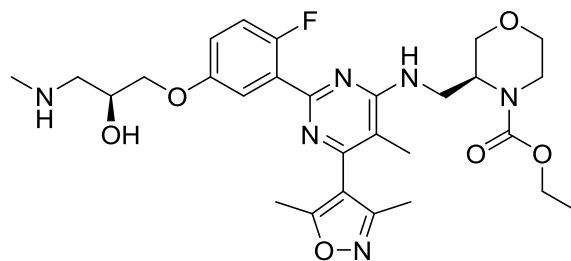
59-3



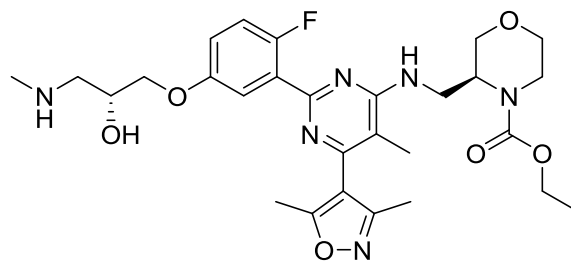
60-3



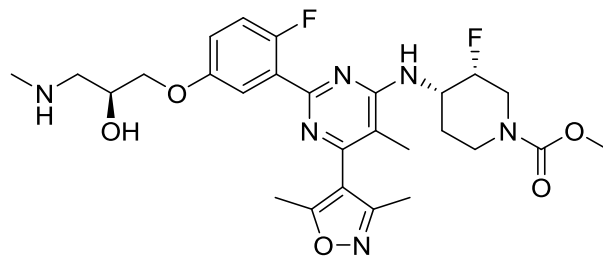
61-3



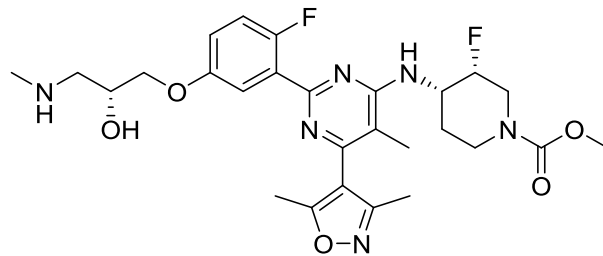
62-3



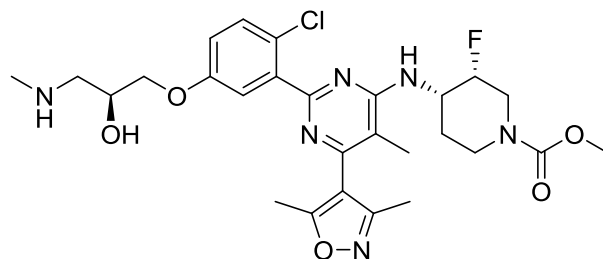
63-3



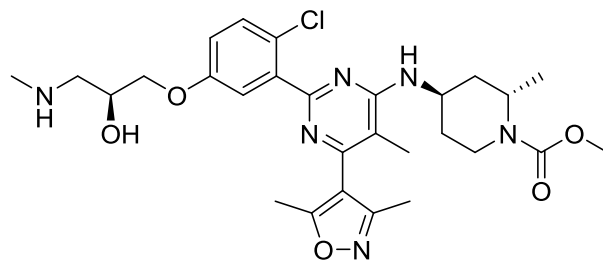
64-3



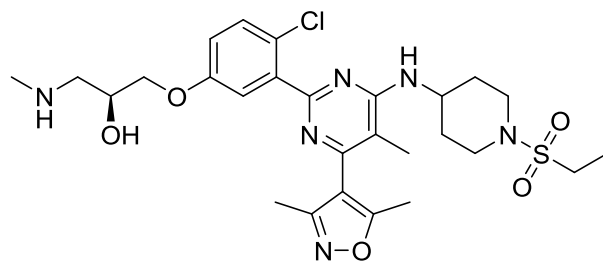
65-3



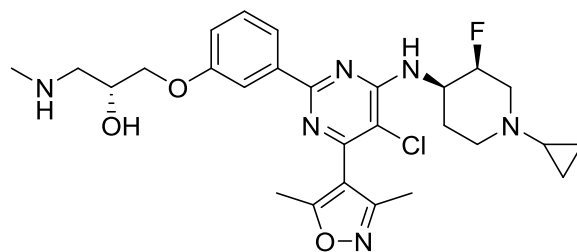
66-3



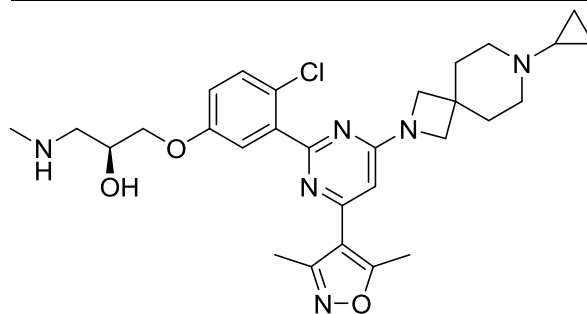
67-3



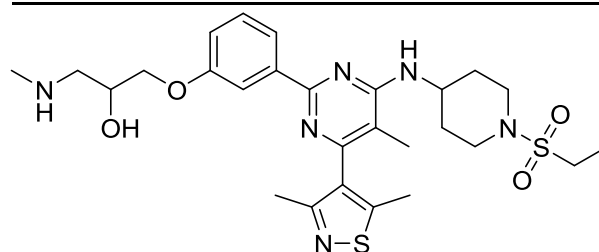
68-3



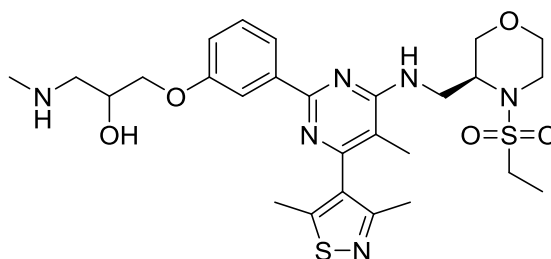
69-3



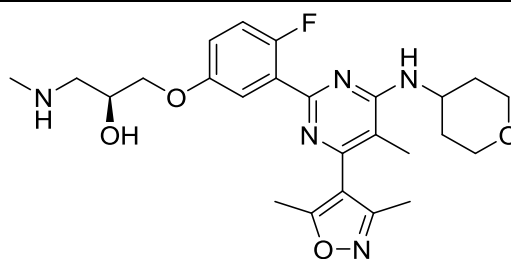
70-3



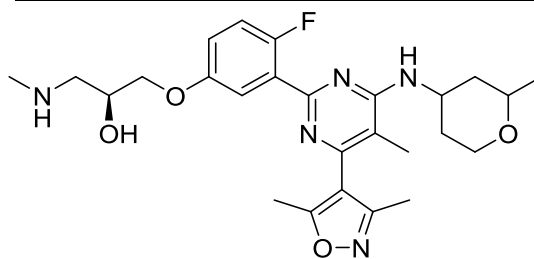
71-3



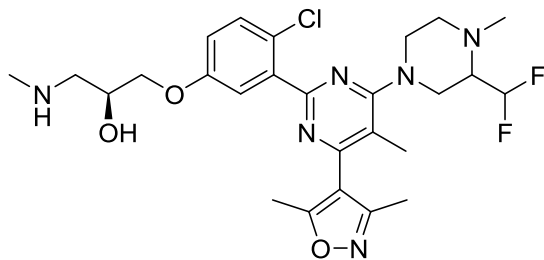
72-3



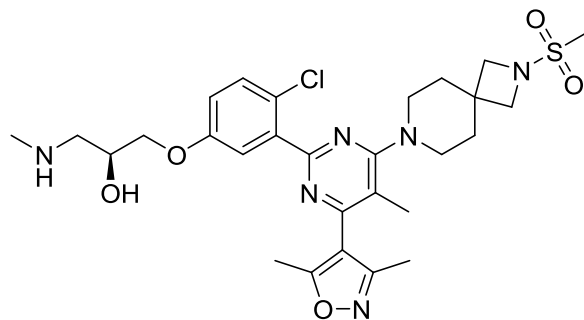
73-3



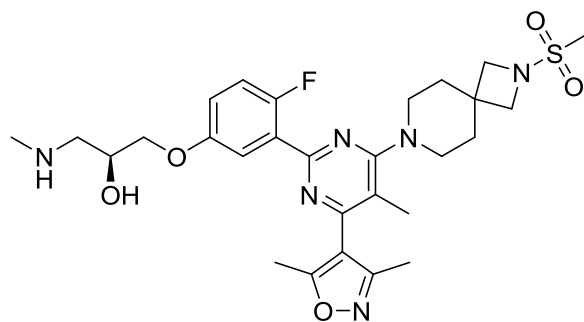
74-3



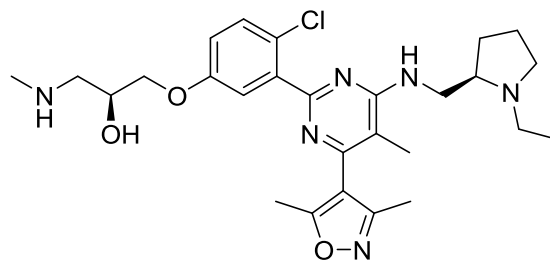
75-3



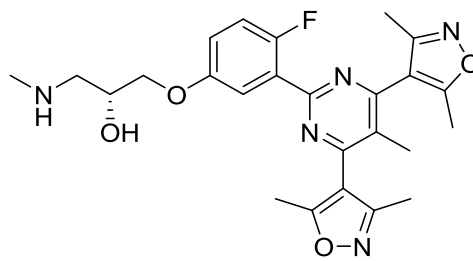
76-3



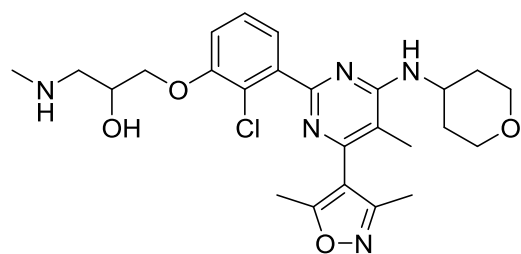
77-3



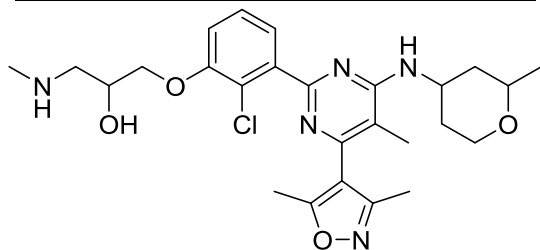
78-3



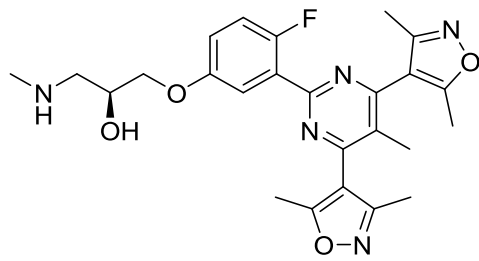
79-3



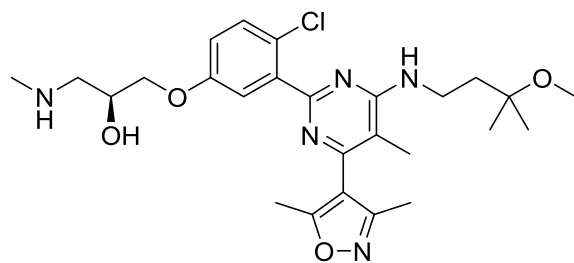
80-3



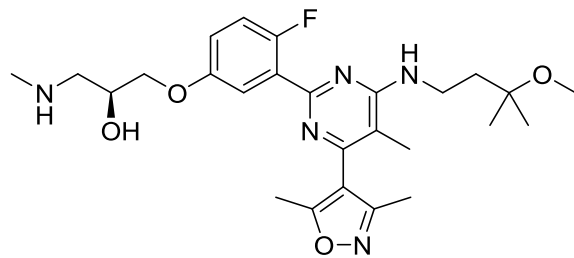
81-3



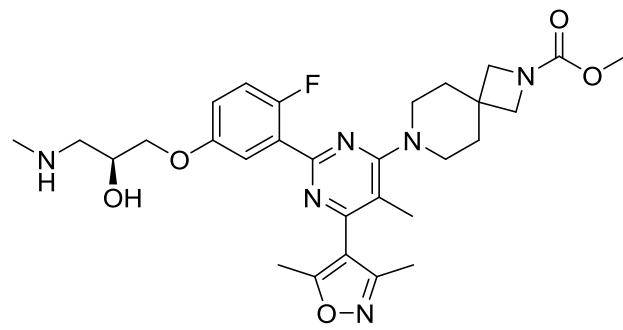
82-3



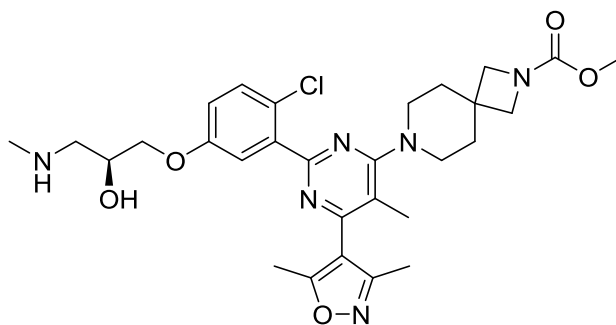
83-3



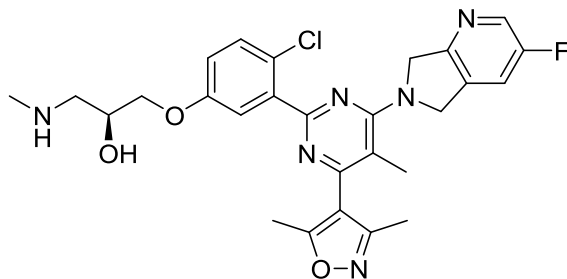
84-3



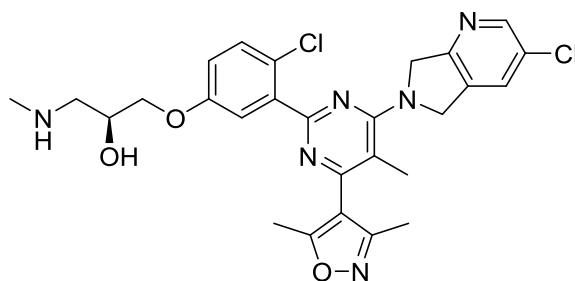
85-3



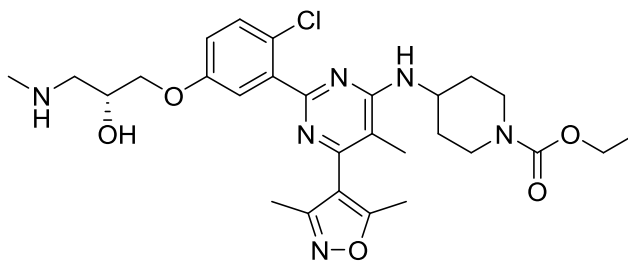
86-3



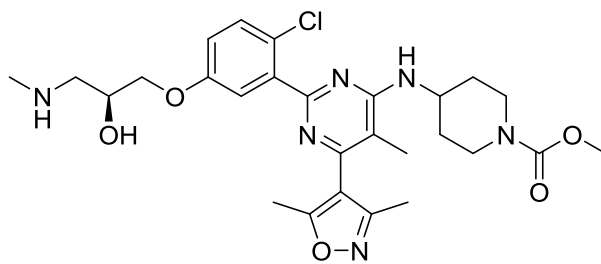
87-3



88-3

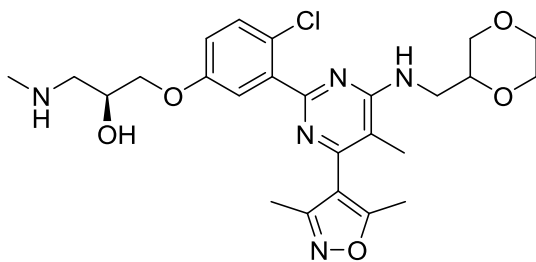


89-3

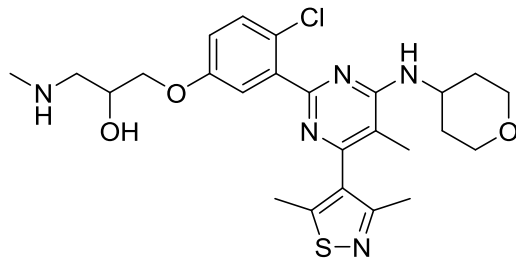


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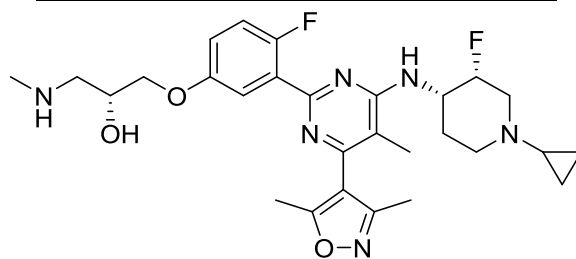
96-3



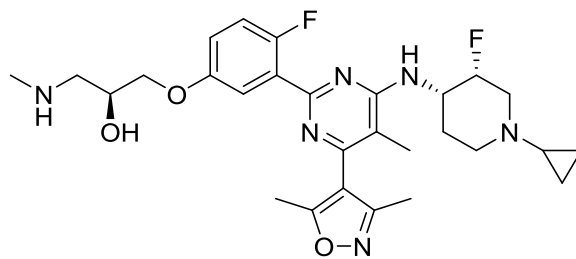
97-3



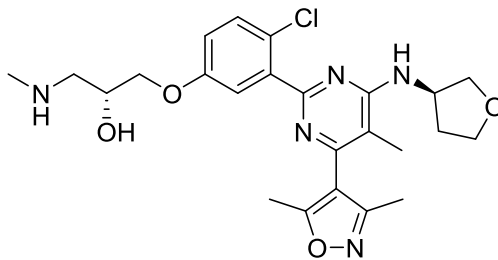
98-3



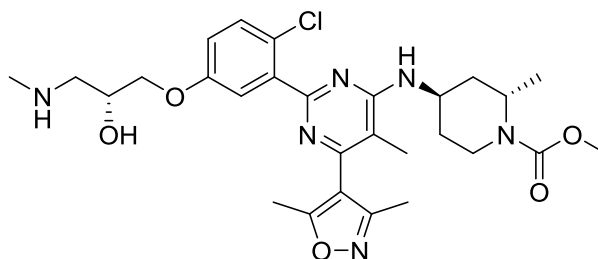
99-3



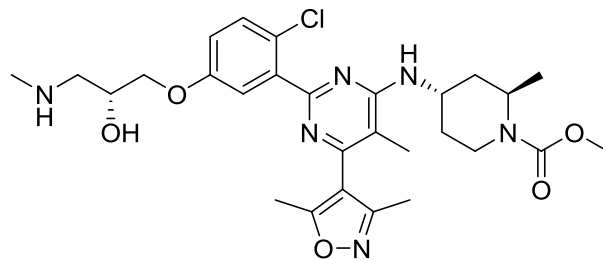
100-3



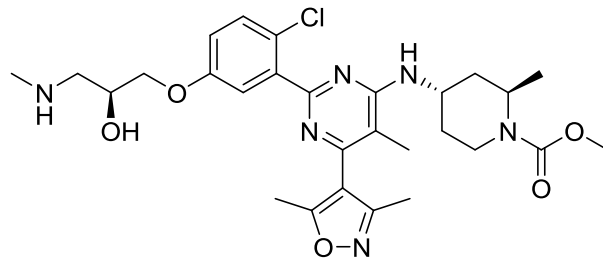
101-3



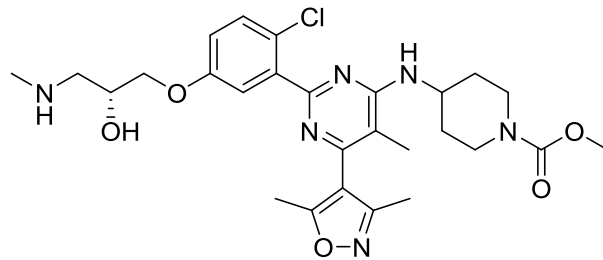
102-3



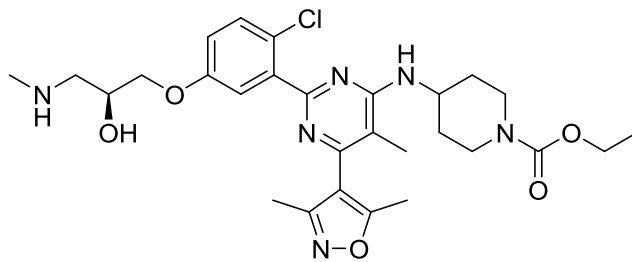
103-3



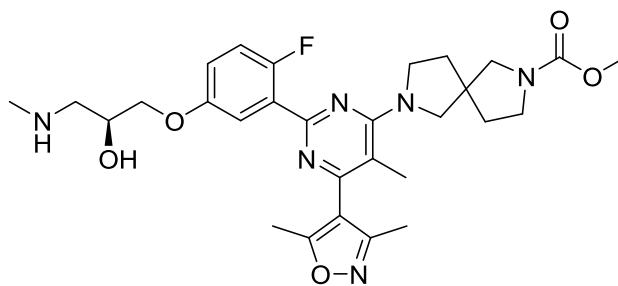
104-3



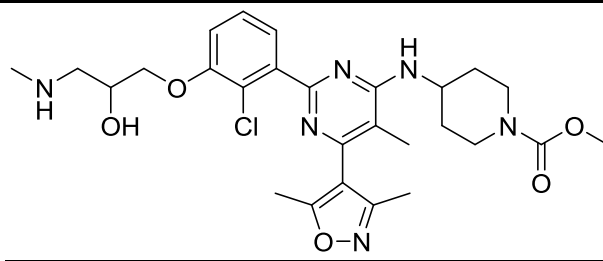
105-3



106-3



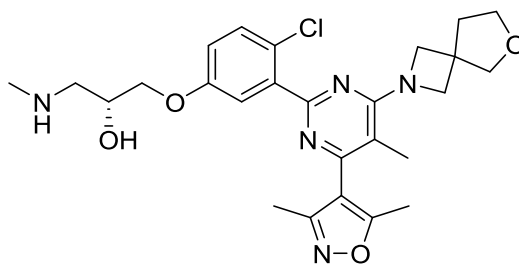
107-3



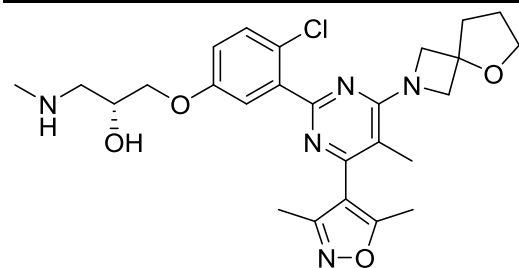
CCNCC(O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)C(C)=C2C4=CC(=C(C=C4)N5C6CC7C(C6)CCN(C7)CC5)CCNCC(O)COc1ccc(Cl)cc1-c2nc3c(ncn3C)C4=CC(=C(C)C)N=O4C5CC[C@H](C5)OCCNCC(O)COc1ccc(Cl)c(c1)c2nc3c(nc(=N3)C)C4=C(C)C(=C(C)C4)O=N5C=C(C)C=C5N[C@H]6CCCC6CCNCC[C@H](O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)C4=C(C)C(=C5C4=CC(=C5)ON5C)C5CN(C)CC(O)COc1ccc(cc1F)c2nc3c(ncn3C4=CN=CN=C5C4=CN=CN=C5)c6c(C)c(C)nc7c6[nH]7

CNCC(O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)c4c(O[N+]([O-])=O)c(C)c(C)c4CNCC(O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)c4c(C)c(C)c(C)n4O[C@H]5CCOCC5CNCC(O)COc1ccc(Cl)c(c1)/N=C2/C=C(C)/C(=N2)c3c(C)c(C)nn3O[C@H]4CCCC4CN(C)CC[C@H](O)COc1ccc(Cl)c2nc3c(nc4c3c(C)c5c4n(O)c(C)c5)c6c2N7CCCCC7C6CC(C)NCC[C@H](O)COc1ccc(Cl)c2c1nc3c2c(C)c4c(C)c(C)n(C4)c5c3CC6CCCCC6N5

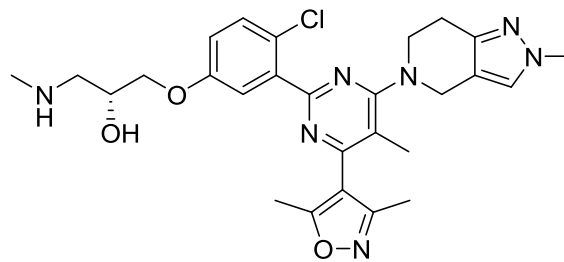
120-3



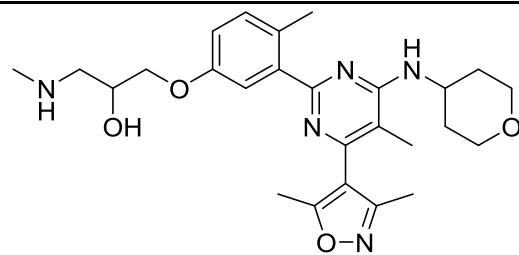
121-3



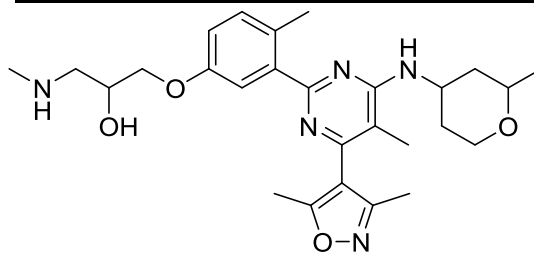
122-3



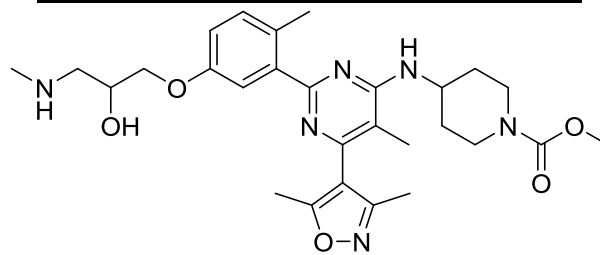
123-3



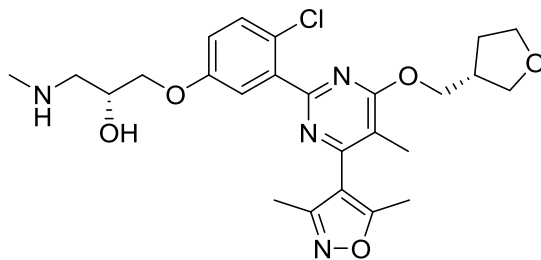
124-3



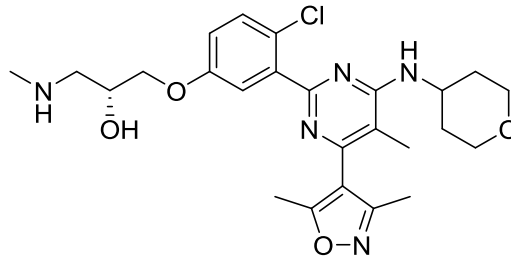
125-3



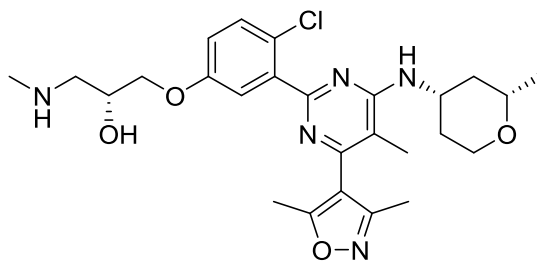
126-3



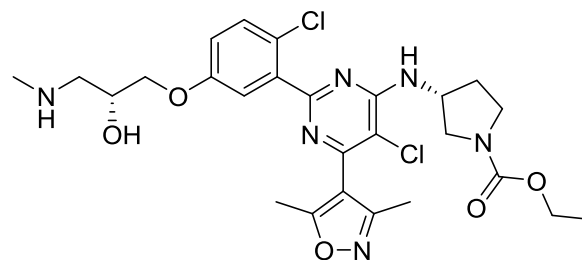
127-3



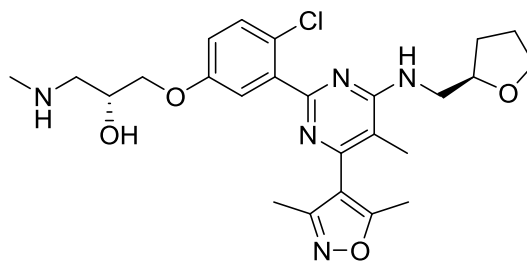
128-3



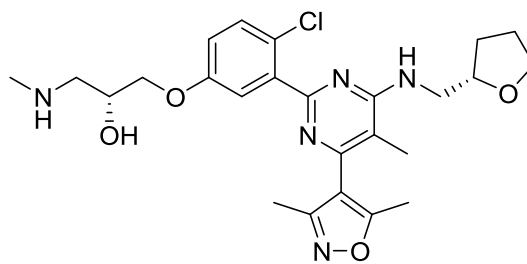
129-3



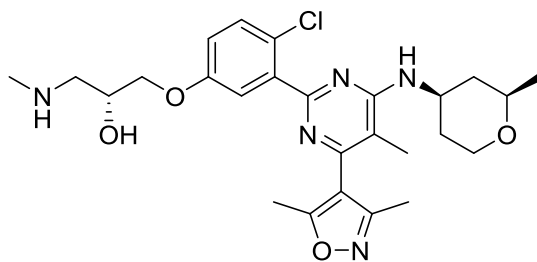
130-3



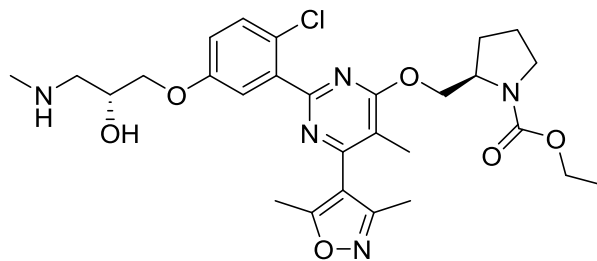
131-3



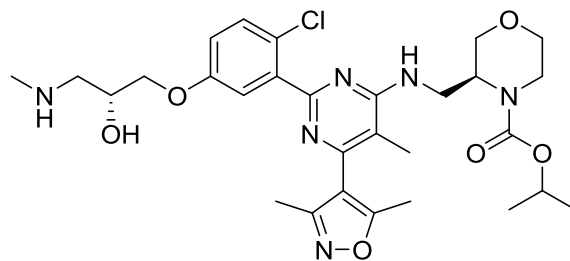
132-3



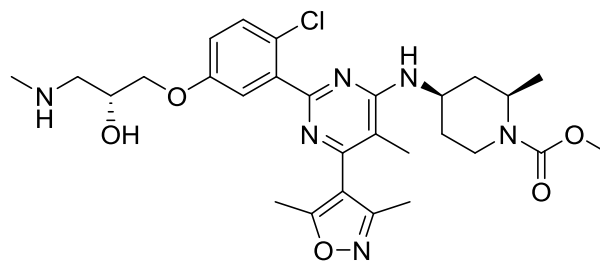
133-3



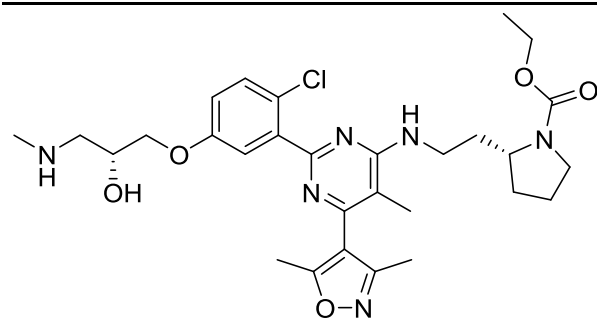
134-3



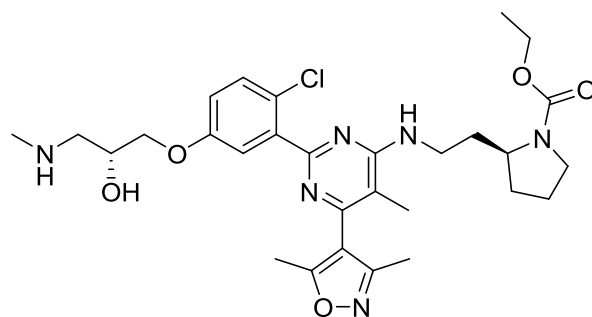
135-3



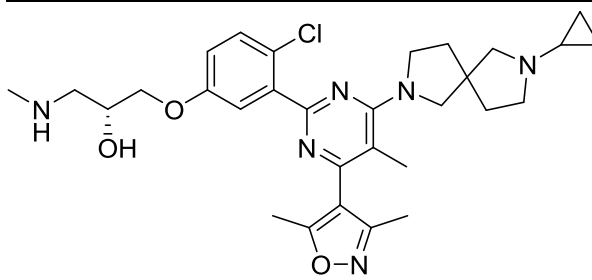
136-3



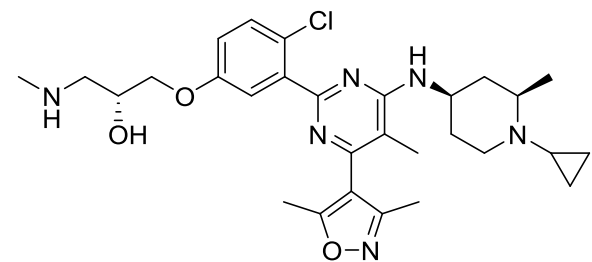
137-3



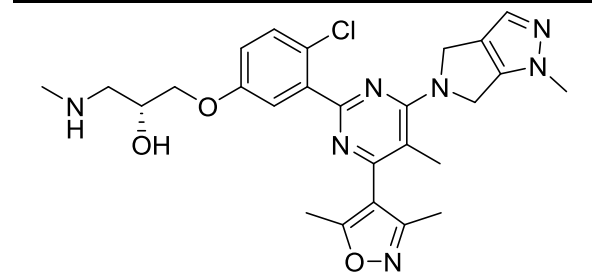
138-3



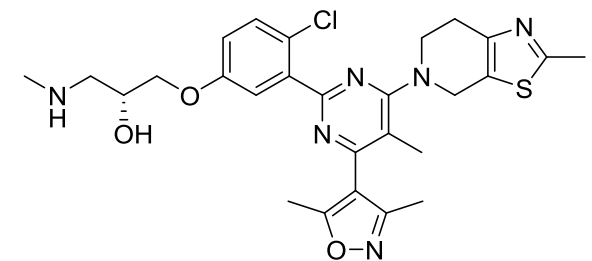
139-3



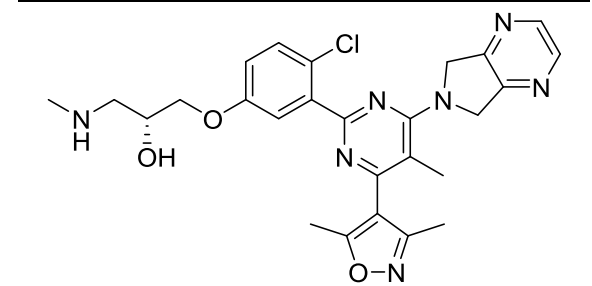
140-3



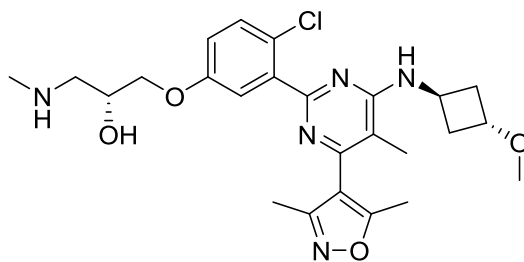
141-3



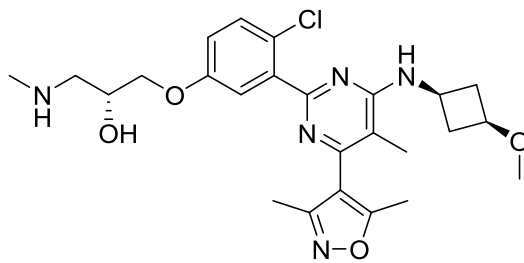
142-3



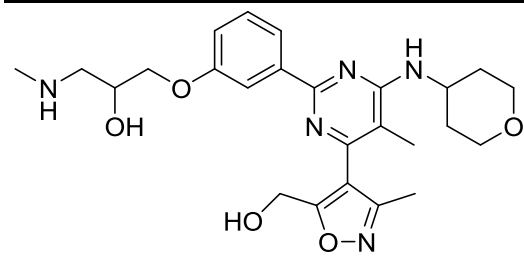
143-3



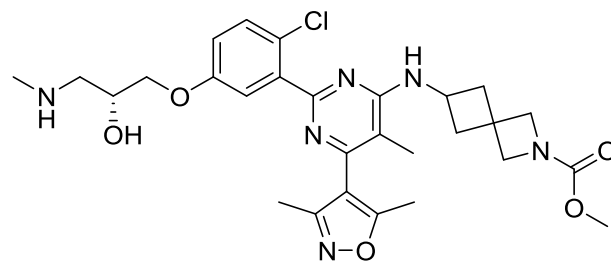
144-3



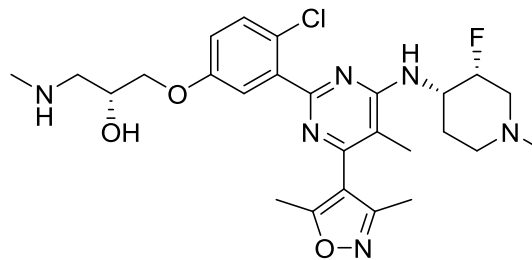
145-3



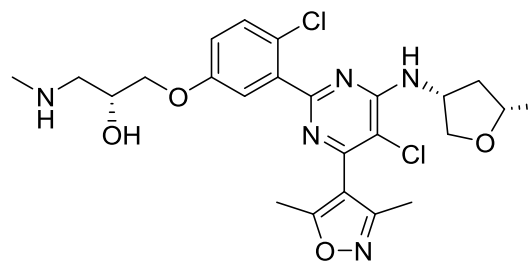
146-3



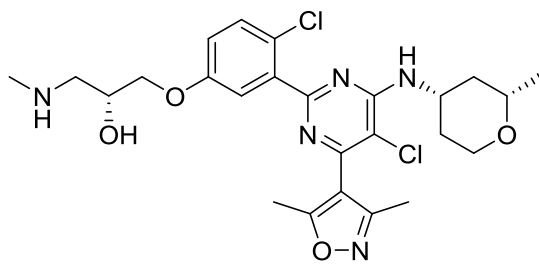
147-3



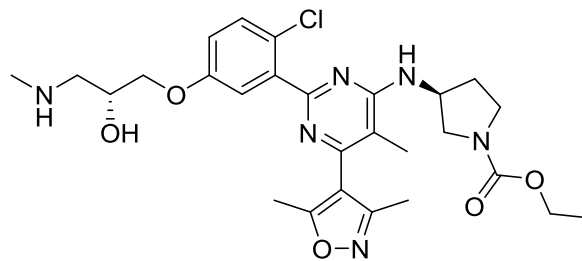
148-3



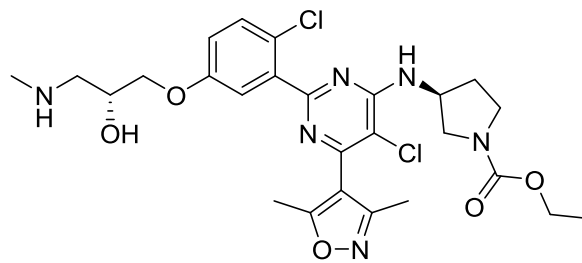
149-3



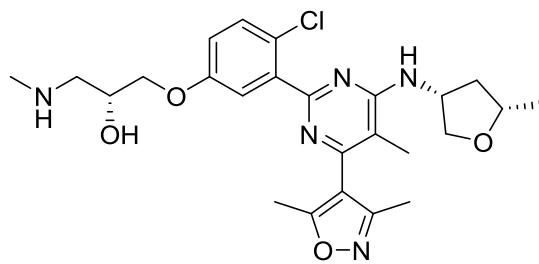
150-3



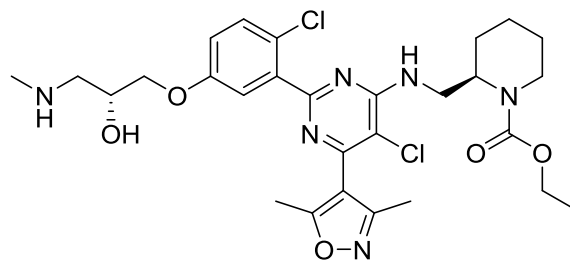
151-3



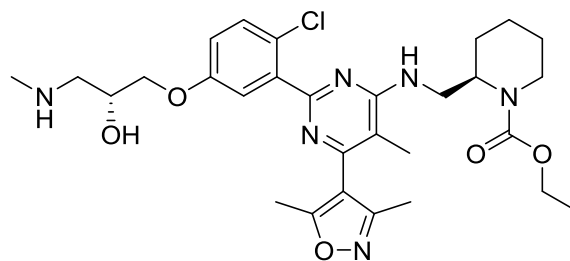
152-3



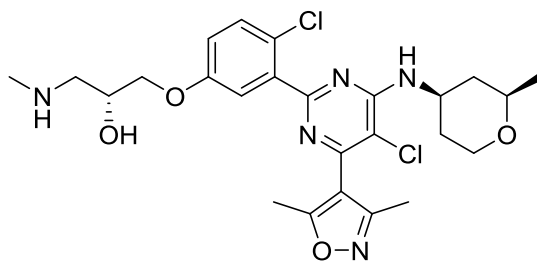
153-3



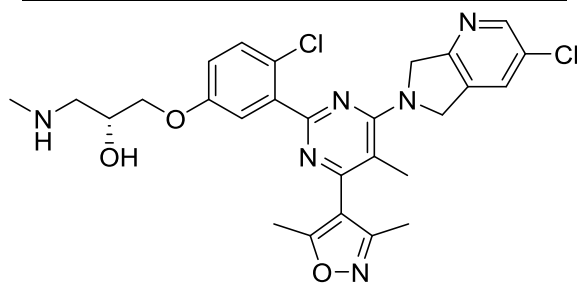
154-3



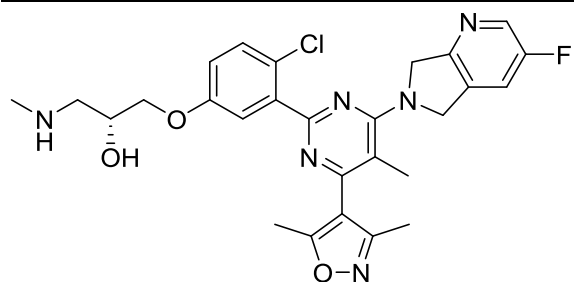
155-3



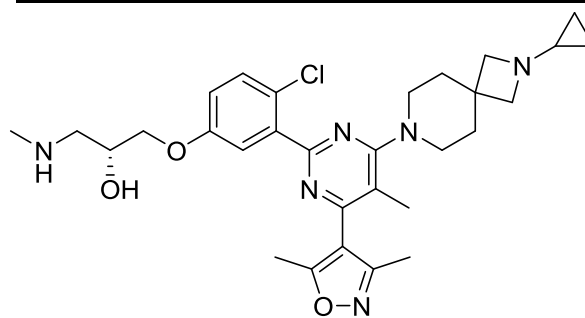
156-3



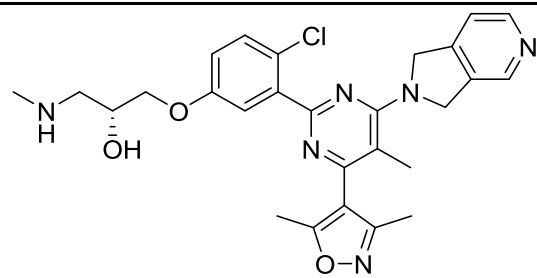
157-3



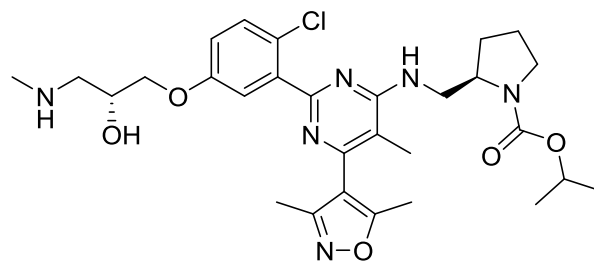
158-3



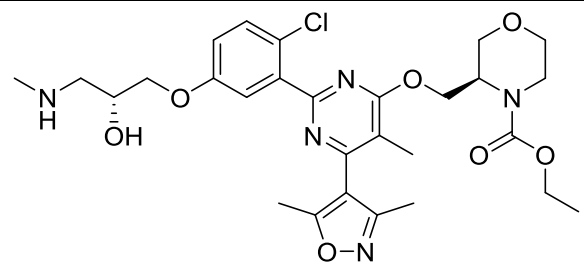
159-3



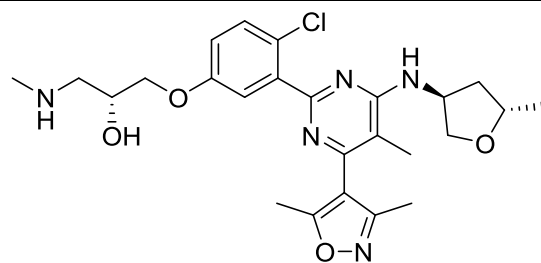
160-3



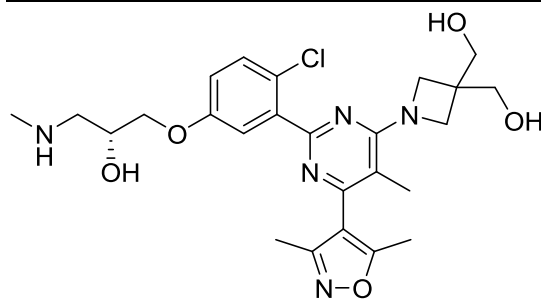
161-3



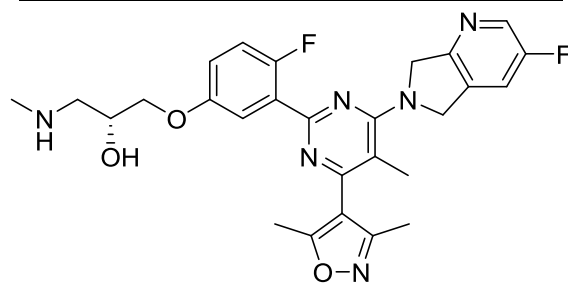
162-3



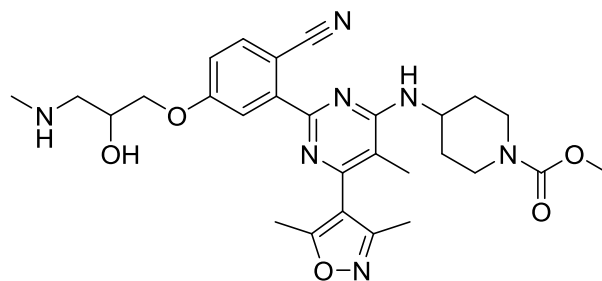
163-3



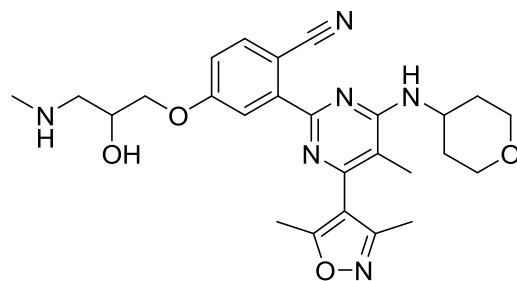
164-3



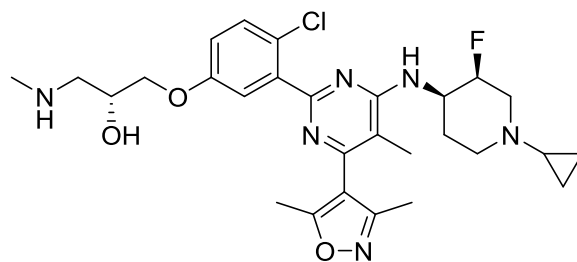
165-3



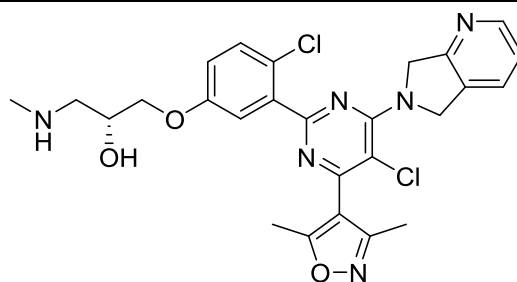
166-3



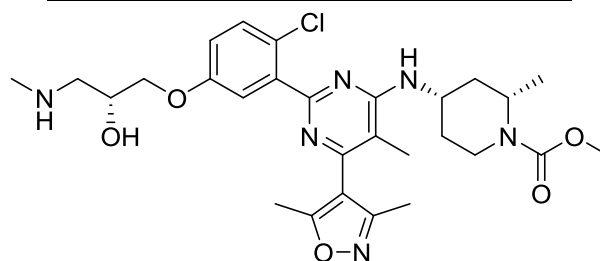
167-3



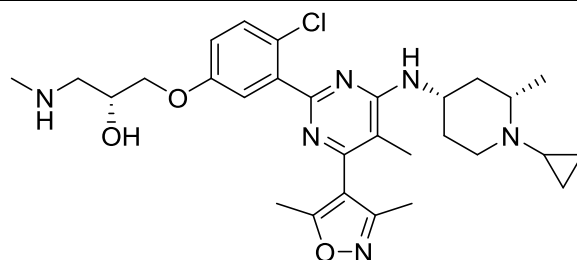
168-3



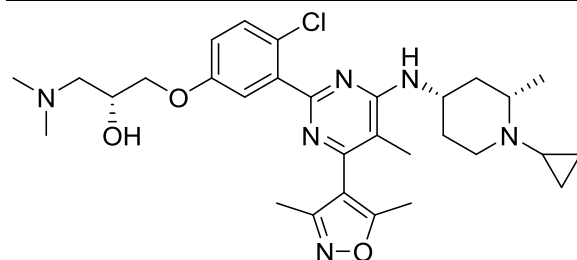
169-3



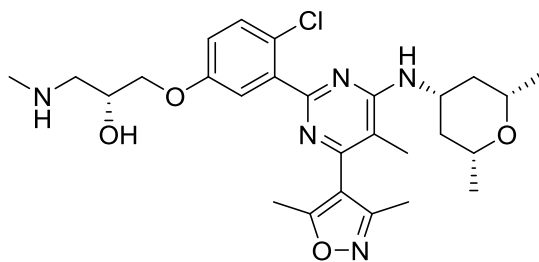
170-3



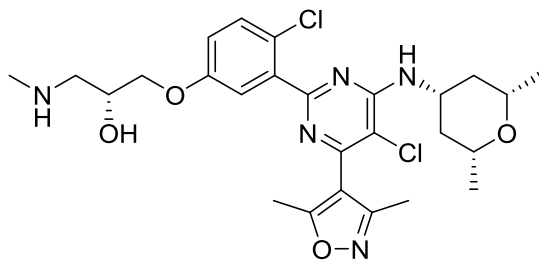
171-3



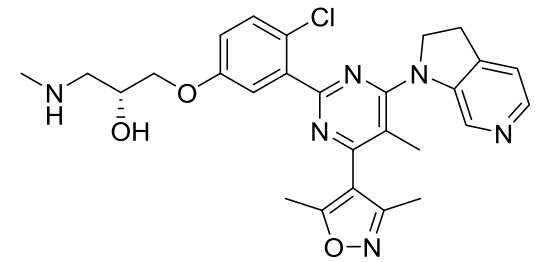
172-3



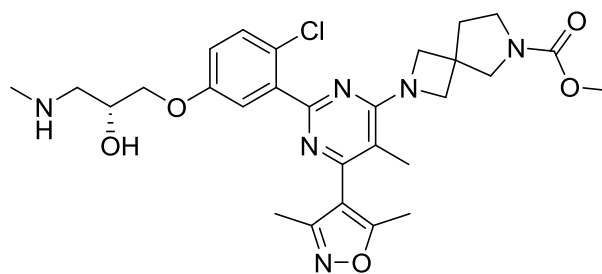
173-3



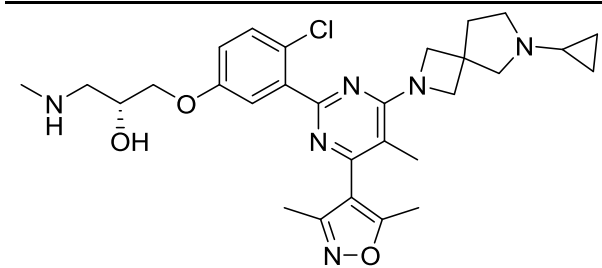
174-3



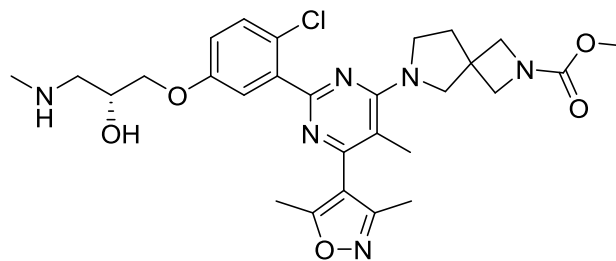
175-3



176-3

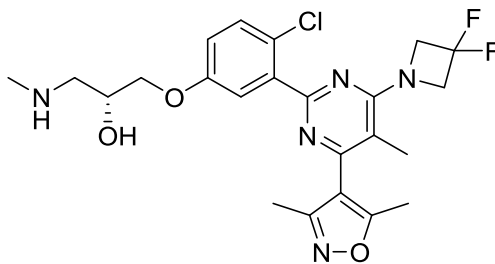


177-3

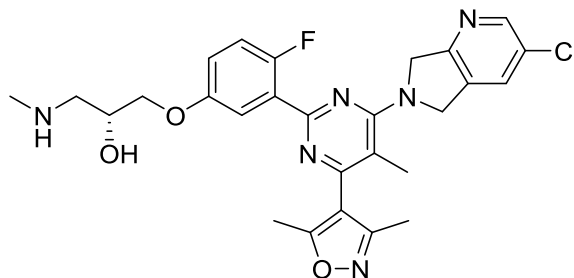


CC(C)N1CC2CC(C1)CC2c3c(C)c(C)c(C4=CN(C)C=C5C(=C(C)C)O=N5)nn3c3ccc(OC[C@H](O)CN(C)C)cc3ClCNCC(O)COc1ccc(Cl)c(c1)c2nc3c(nc(=N)c3C)c4c(C)c(C)c(C)c4[nH]5C[C@H](C)[C@@H](O5)NCNCC[C@H](O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C[C@H]4O[C@@H](C)[C@H](O)[C@H]4)c5c(C)c(C)on5CNCC[C@H](O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C[C@H]4OCC[C@H]4)c5c(C)c(C)on5CNCC(O)COc1ccc(Cl)c(c1)c2nc3c(nc(=N)c3C)c4c(C)c(C)c(C)c4OCNCC(O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C4COC(=O)C4)c5c(C)c(C)on5

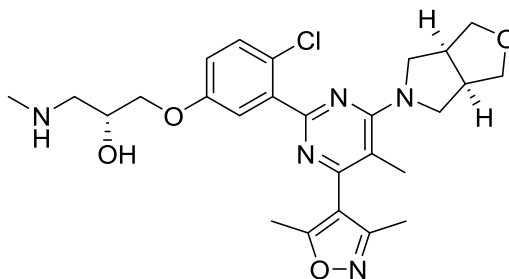
184-3



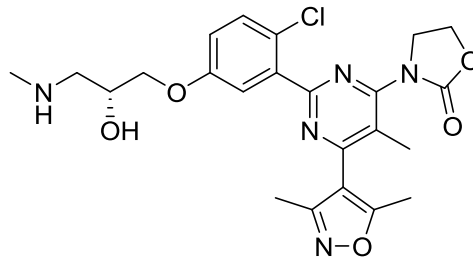
185-3



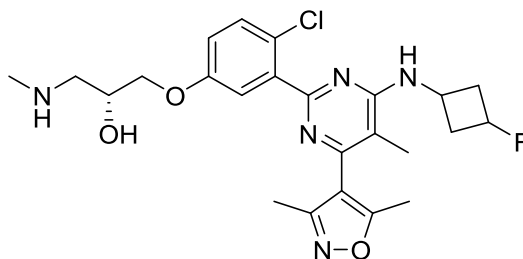
186-3



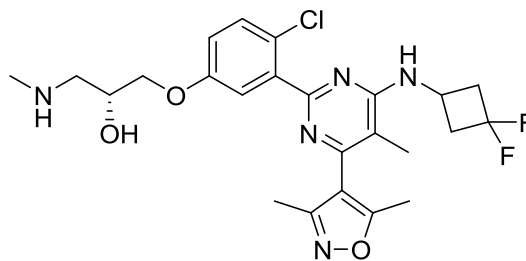
187-3



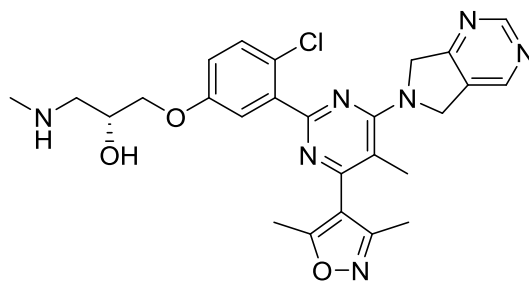
188-3



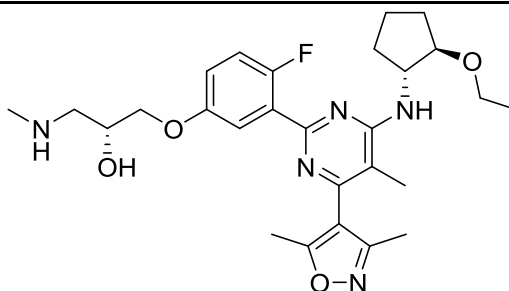
189-3



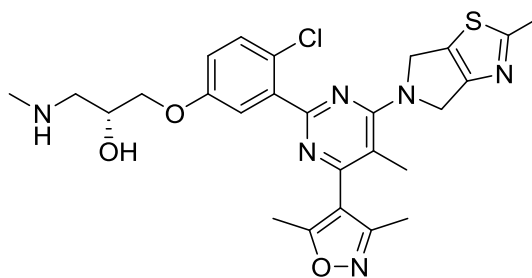
190-3



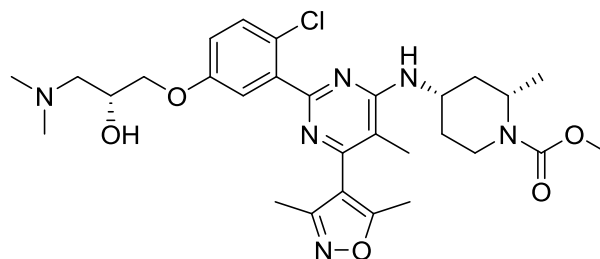
191-3



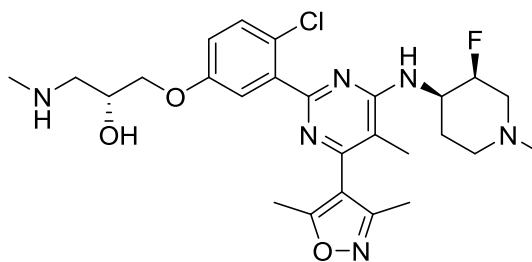
192-3



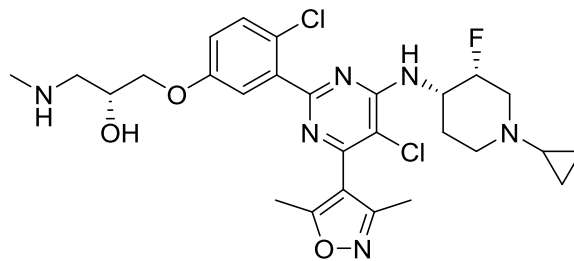
193-3



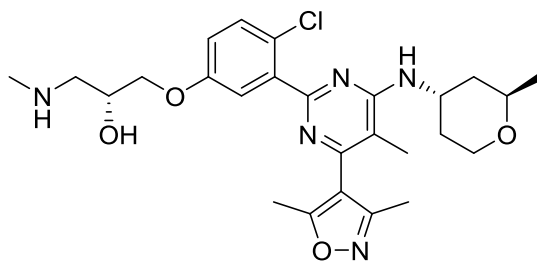
194-3



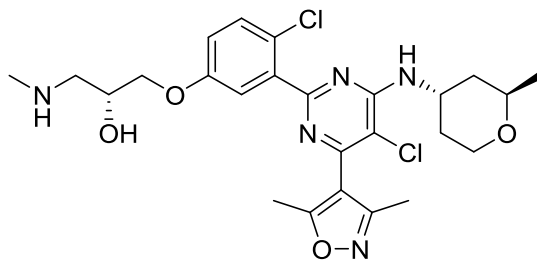
195-3



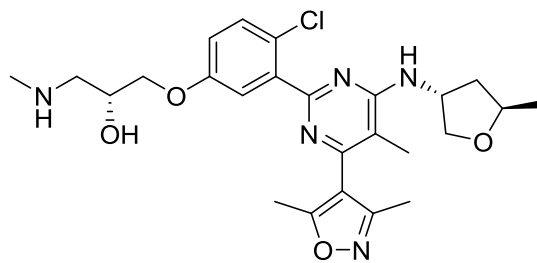
196-3



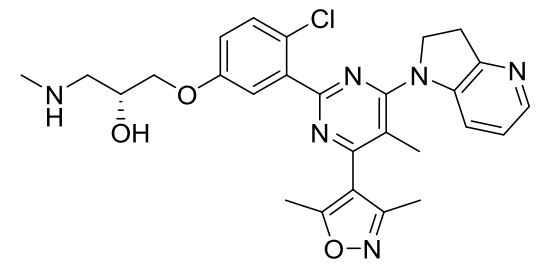
197-3



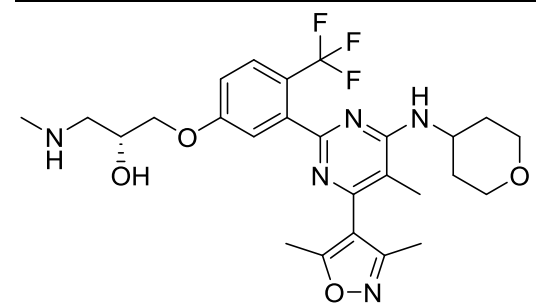
198-3



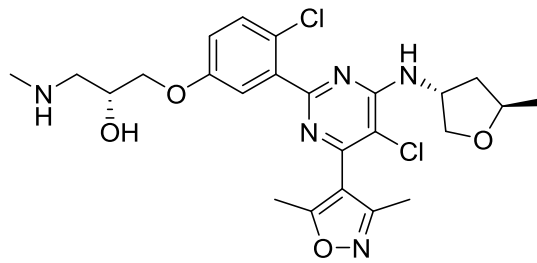
199-3



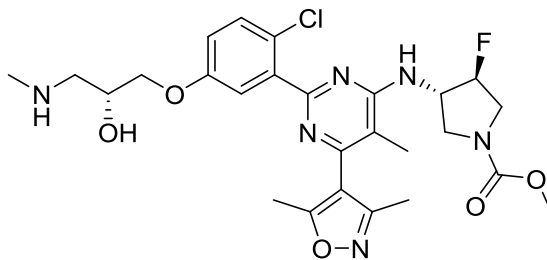
200-3



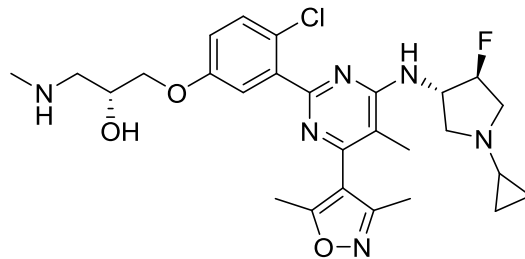
201-3



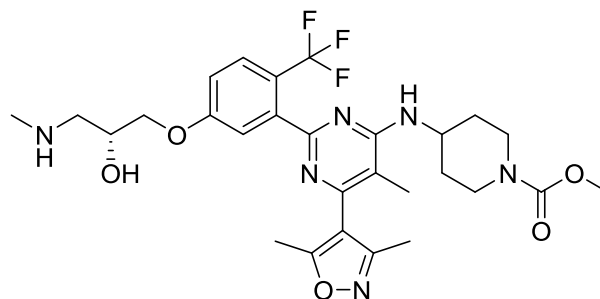
202-3



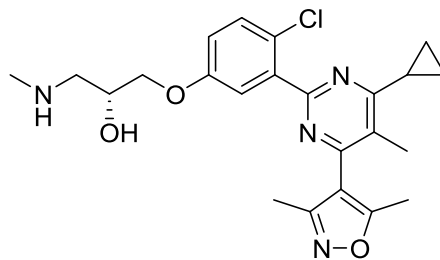
203-3



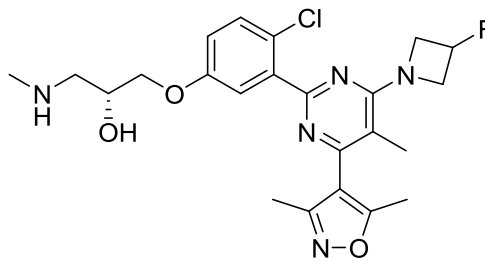
204-3



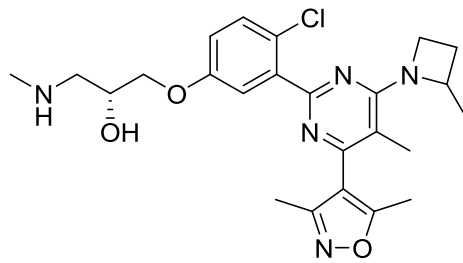
205-3



206-3

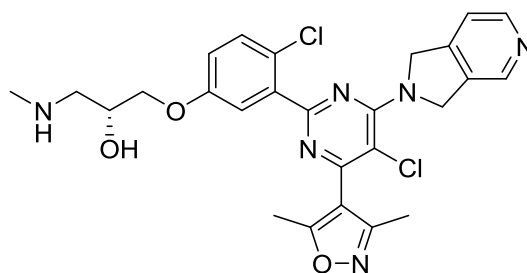


207-3

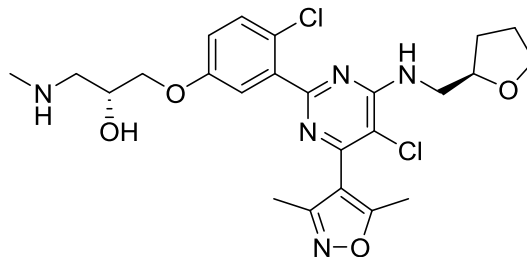


CNCC(O)COc1ccc(Cl)c(N2C=NC3=C(C(=N2)C4=C(C)C(=C(C4)O5N=CC=C5C)C)C(=C3)N[C@@H]6CC(F)CCN6C)c1CN(C)CC(O)COc1ccc(Cl)c(c1)-c2nc3c(ncn3C)c4c(C)c(C)c5c4O[N+]([O-])=O5CN(C)CC[C@H](O)COc1ccc(Cl)c(c1)-c2nc3c(ncn3C[C@@H]4CCN(C)CC4F)c5c(C)c(C)[n+]([O-])c5CNCC(O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C[C@H]4CCN(C4)C5CC5)c6c(c2)oc(C)c6ClCNCC(O)COc1ccc(Cl)c(c1)c2nc3c(nc4c3c(C)c(C)c5c4c(C)c(C)c(C)c5n2)N[C@H]6CC[C@@H](OC)C6CNCC(O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)C(C)=C2C4=CC(OC)CC[C@H]4N(C)C

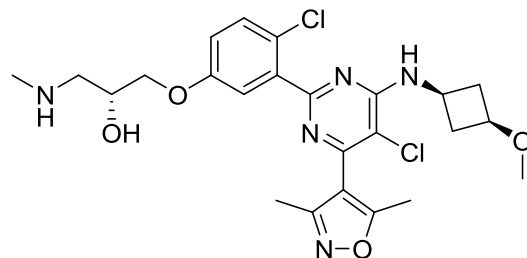
214-3



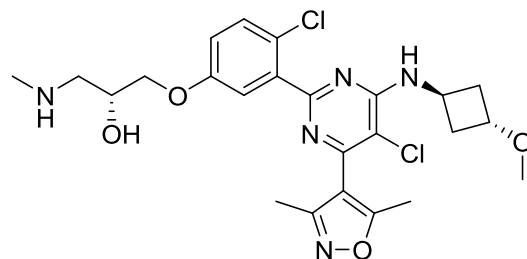
215-3



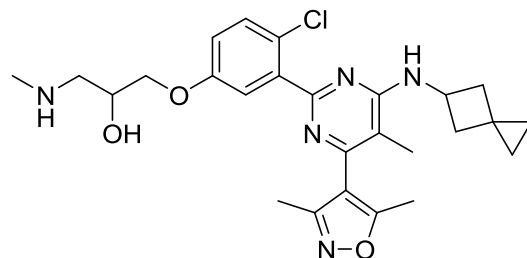
216-3



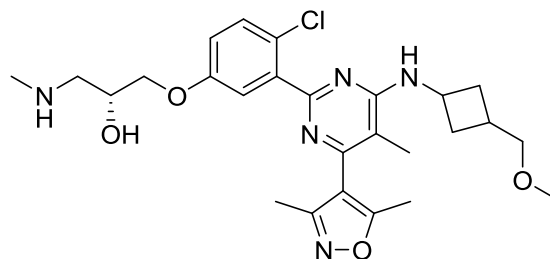
217-3



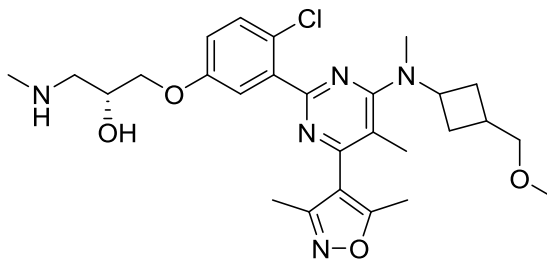
218-3



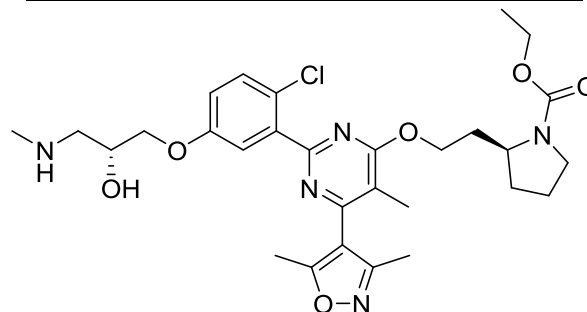
219-3



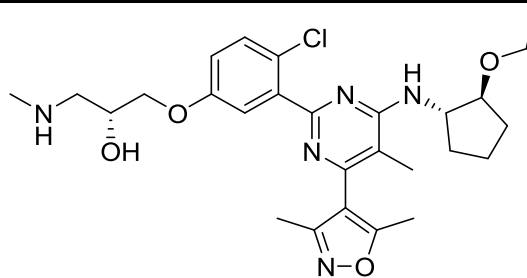
220-3



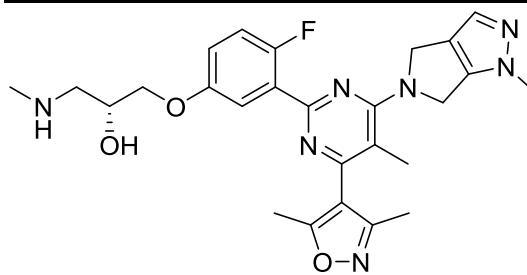
221-3



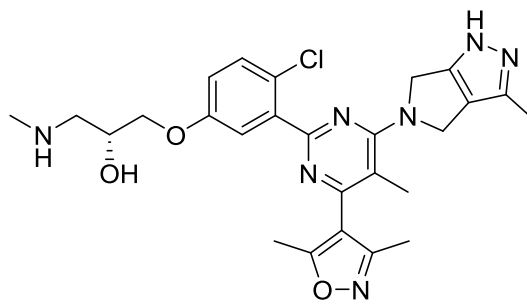
222-3



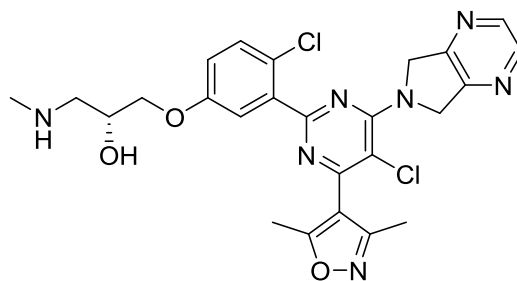
223-3



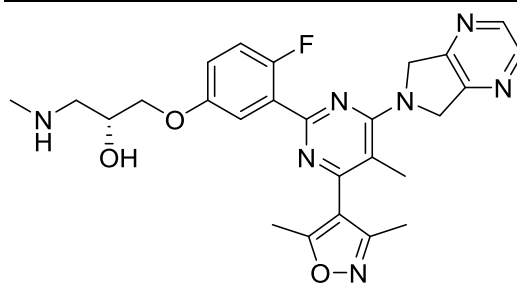
224-3



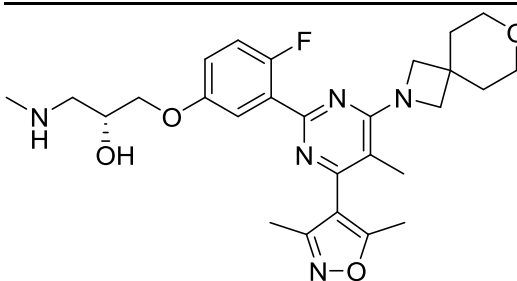
225-3



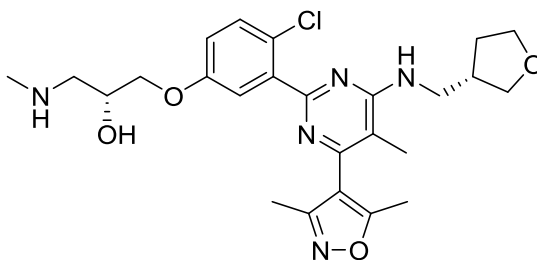
226-3



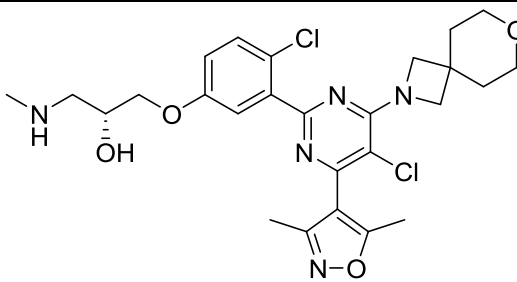
227-3



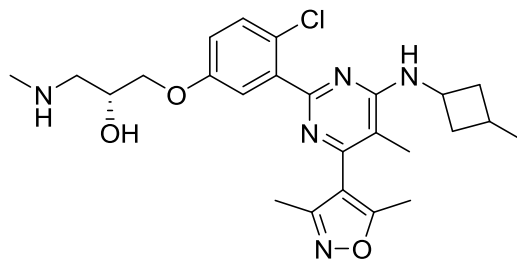
228-3



229-3

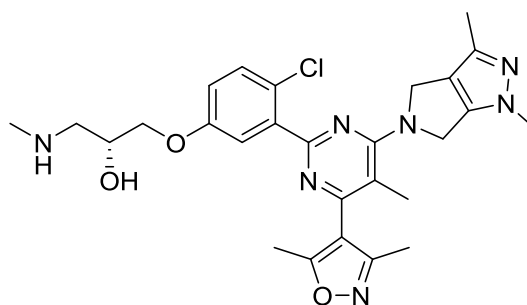


230-3

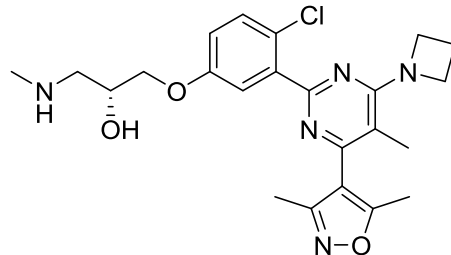


CNCC(O)COc1ccc(Cl)c2c1nc3c2c(C)c4c(C)c(C5=CN=CN5)nn34CCNCC(O)COc1ccc(Cl)c(c1)c2nc3c(nc(=N)c3C)c4c5c(nc(=O)c5C)c6cc(OC)nc6N7CCN7C2CNCC(O)COc1ccc(Cl)c(c1)/N=C2/C(=N/C(=C2C)C3=C(C)C=C(C3)N4OCC4)NC[C@H]5CCOCC5CNCC(O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C45CC6CC(C4)CC65)c7c(C)c(C)oc7[N+](=O)[O-]CN(C)CC(O)COc1ccc(Cl)c(c1)-c2nc3c(ncn3C45CC6CC7CC8CC4CC8CC5C6)c5c(C)c(C)oc5NCN(C)CC[C@H](O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)c4c5c(c2)nnn5C6=C(C)C(=C(C)C)O=N6

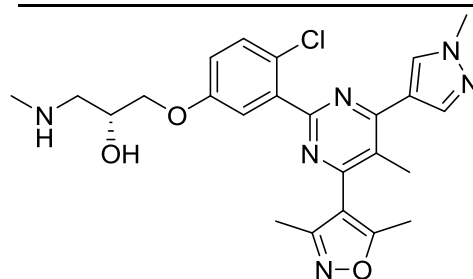
237-3



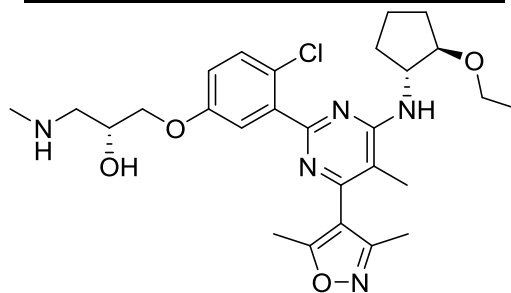
238-3



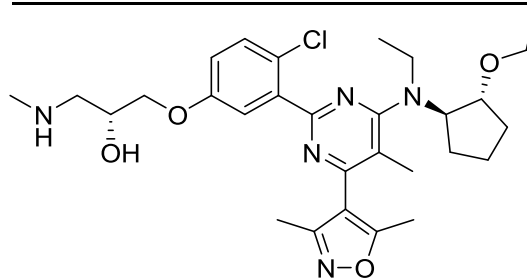
239-3



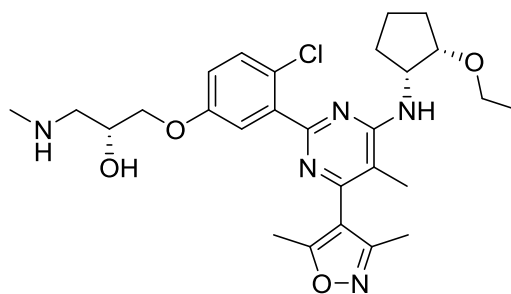
240-3



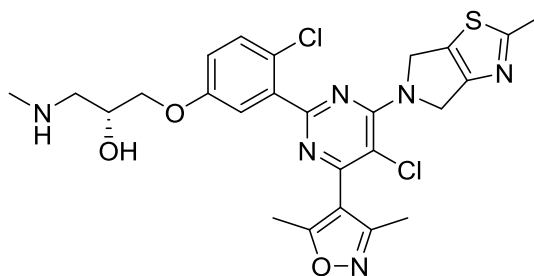
241-3



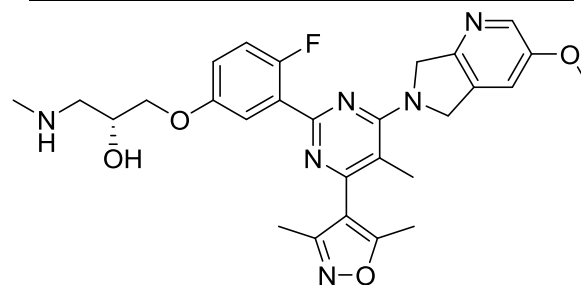
242-3



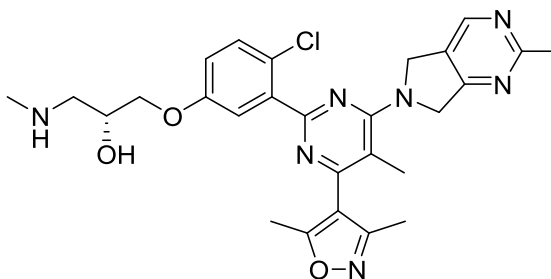
243-3



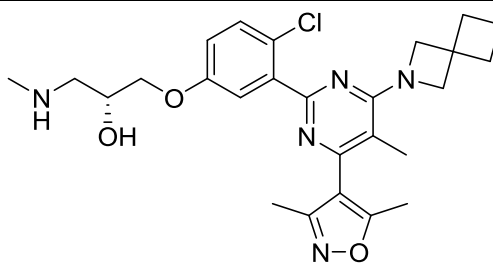
244-3



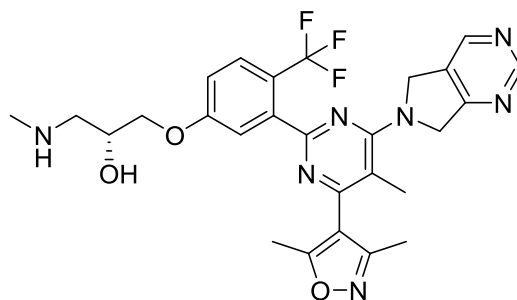
245-3



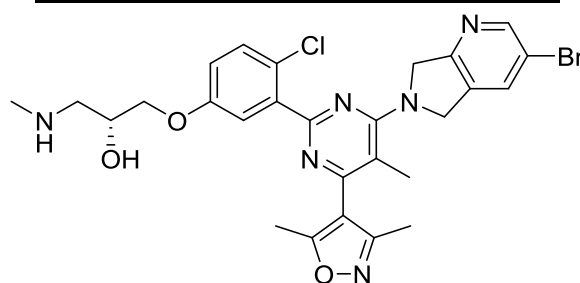
246-3



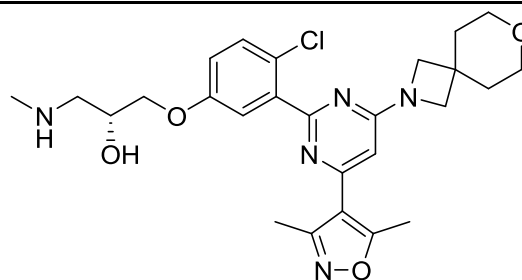
247-3



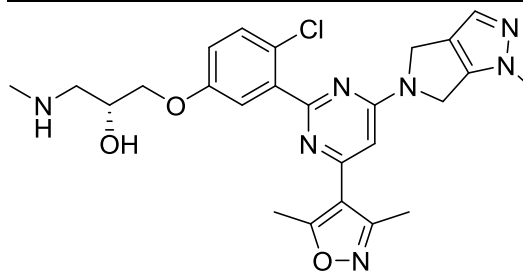
248-3



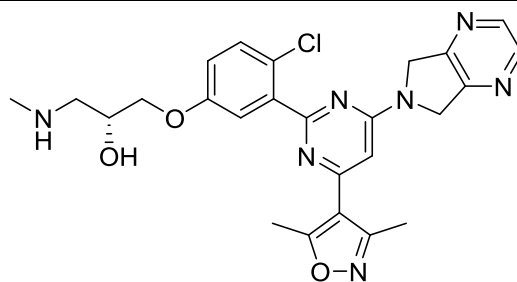
249-3



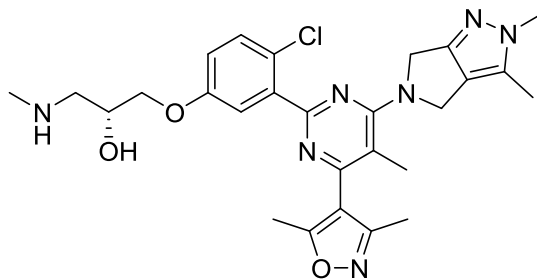
250-3



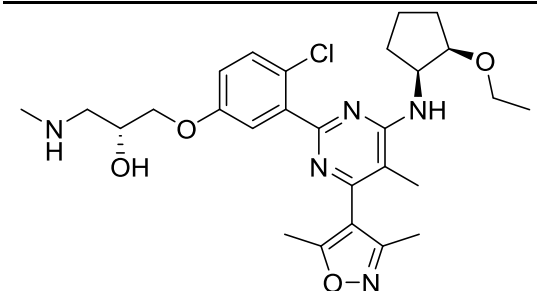
251-3



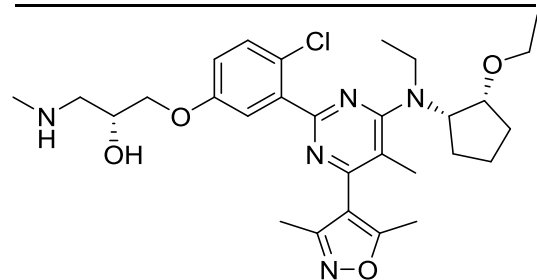
252-3



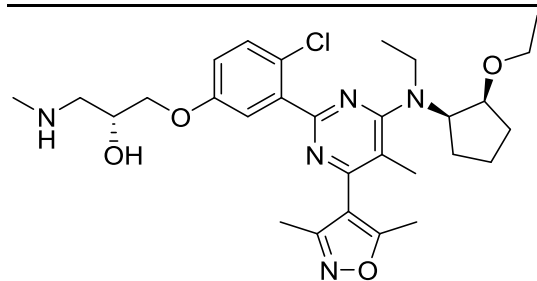
253-3



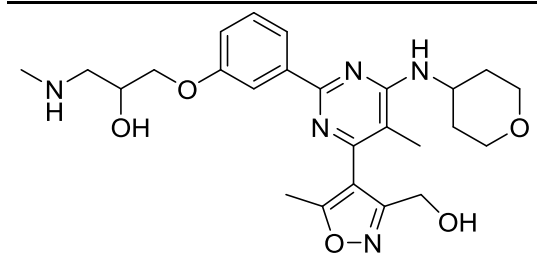
254-3



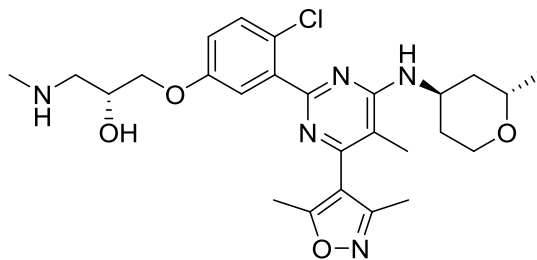
255-3



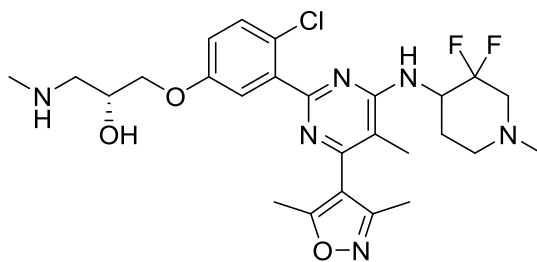
256-3



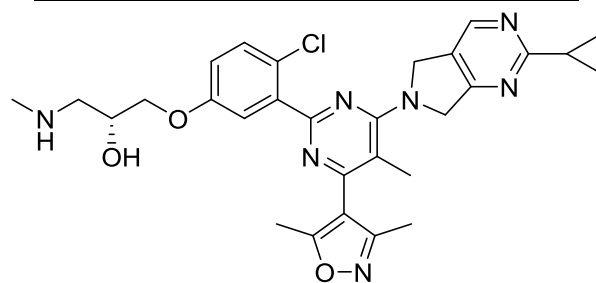
257-3



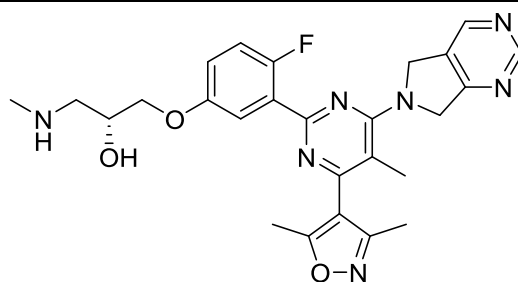
258-3



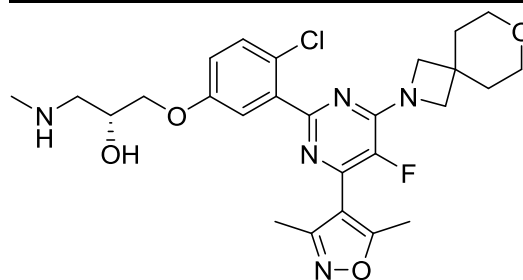
259-3



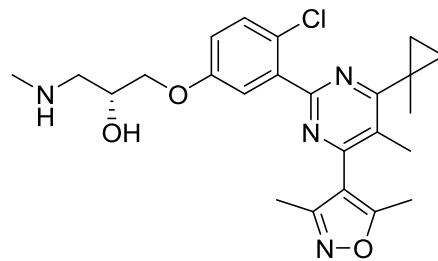
260-3



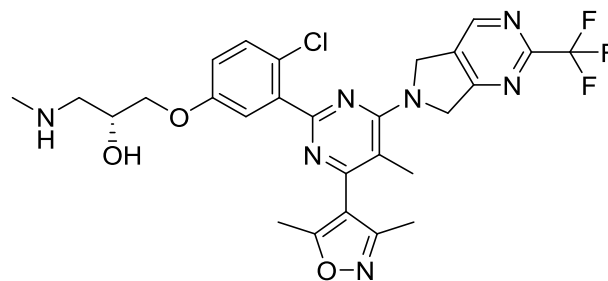
261-3



262-3

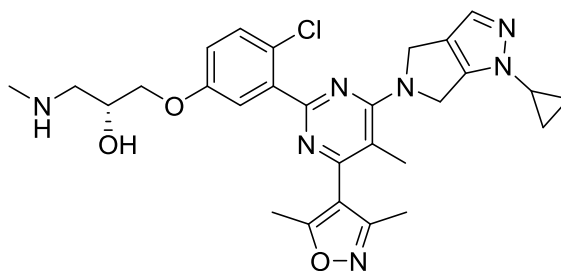


263-3

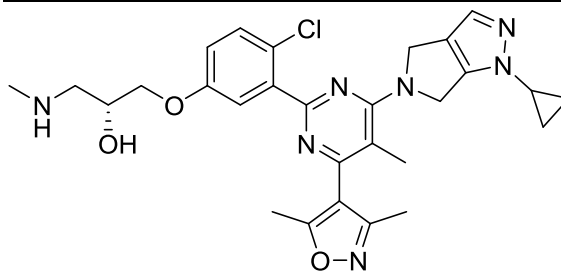


CC(C)C1=NC2=C(N1)C=NC=C2C3=NC(=C(C=C3)C)N(C4=CC(=CC=C4)C(=C5C=CC(=C5)C=C(C=C5)COC(CN(C)C)O)C5)C6=CC(=CC=C6)C7=CC(=CC=C7)N(C)C8=CC(=CC=C8)C(=C9C=CC(=C9)C=C(C=C9)C)N(C)C8CNCC(O)COc1ccc(Cl)c(c1)/N=C2\N=C(C)/C(=N2)c3c(C)oc([N+](=O)[O-])c3N4C=CN5C(=N4)C=C(C5)CN(C)C(F)(F)FCNCC(O)COc1ccc(cc1C2=NC3=C(C)C(=C2C4=CC(=C(C)C4)[N+]([O-])=O)N3)C5=C(F)C=CC=C5N6Cc7ccccc7F6CNCC(O)COc1ccc(Cl)c(c1)c2nc3c(nc(=O)c3C)c4c5ccccc4N5Cc6ccccc6FCNCC(O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)C4=CC(=C(C)C)O=N4C5CCCCC5CN(C)CC(O)COc1ccc(cc1C2=NC3=C(C)C(=C2)C4=CC(=C(C)C4)N=O)C(F)=C5C(=N3)N(C67CC8CCOC8CC6)CC7

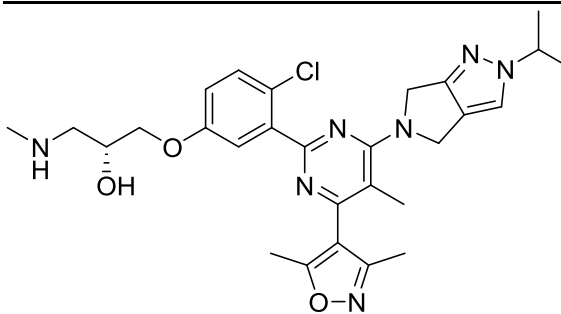
270-3



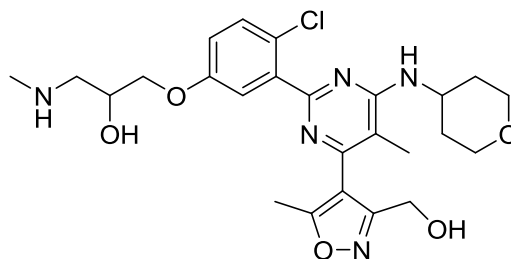
271-3



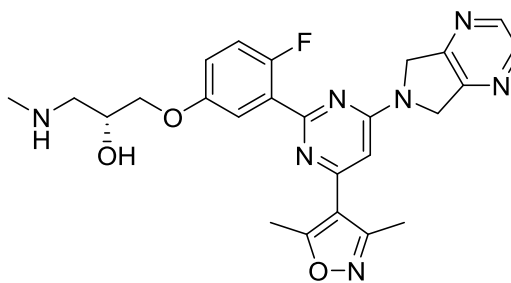
272-3



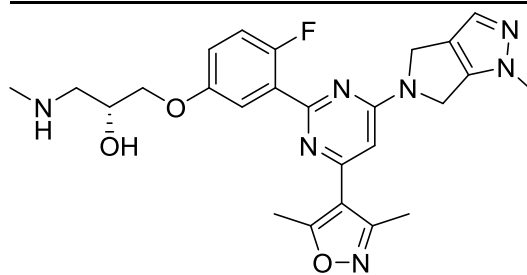
273-3



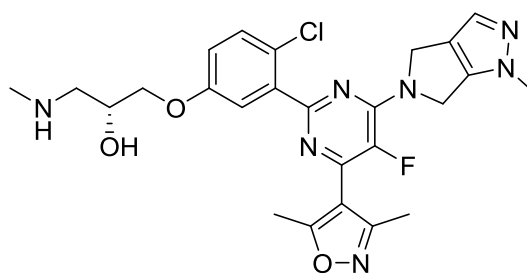
274-3



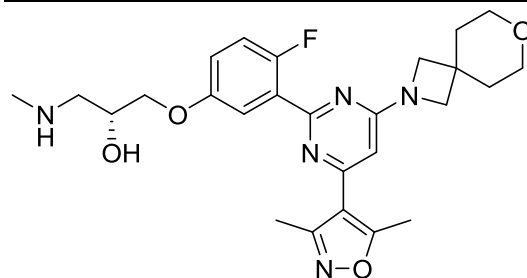
275-3



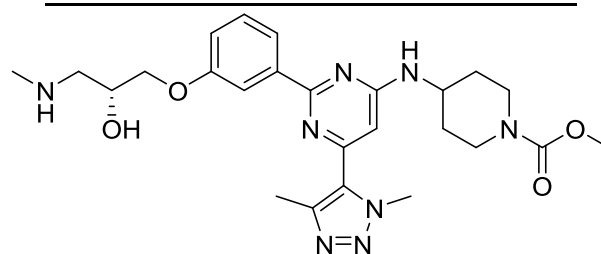
276-3



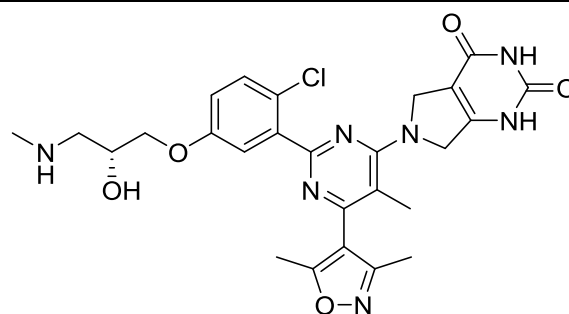
277-3



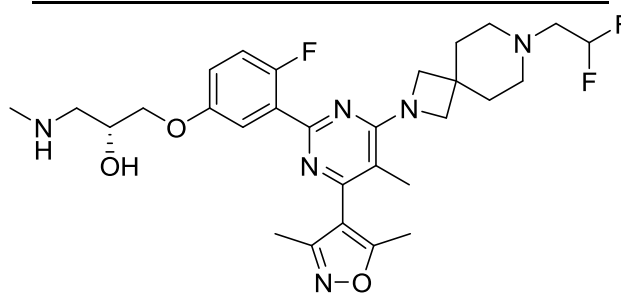
278-3



279-3

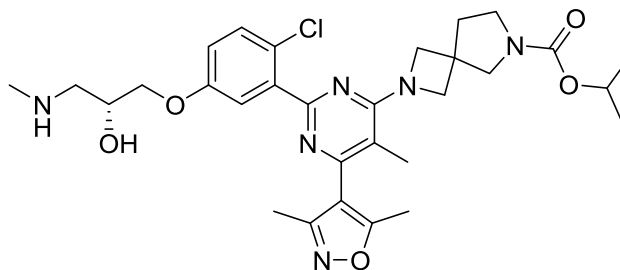


280-3

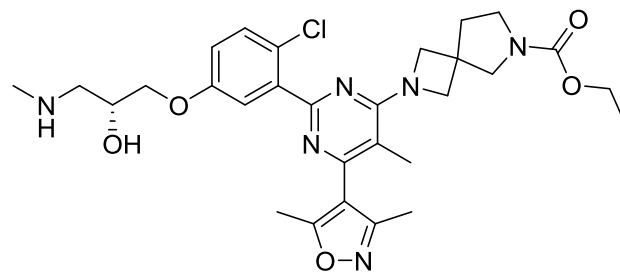


CC(C)OC(=O)N1CC2CC3CC1CC2N3C4=NC5=C(C)N(C)C(C5=N4)C6=CC(=CC=C6)C(=C7C=CC(=C7)OC[C@H](C)NC)C(F)=C4CCNCC[C@H](O)COc1ccc(F)c(c1)c2nc3c(ncn3C45CC6CCN(CC6)CC45)c7c(nc8c7C)on8CCN(C)CC(O)COc1ccc(Cl)c2nc3c(nc4c3c(C)c(C5=C4N=O)C5)c6n7c2CC8CCN(C8)CC(F)F7CC(C)OC(=O)N1CC2CC3CC1CC2N3C4=NC5=C(C)N(C6=CC(=CC=C6CO[C@@H](C)CN)C=C5C7=C(C)C(=N1O)C=C7CCCNCC[C@H](O)COc1ccc(Cl)c(c1)c2nc3c(ncn3C)c4c(C)c(C)c5c4O[N+]([O-])=C5C67CC8CCN(CC8)CC6C7C(=O)OCC

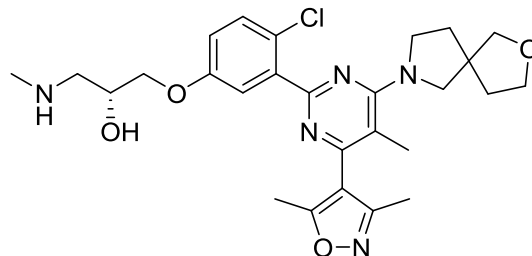
286-3



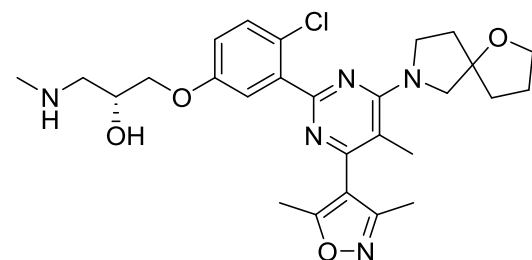
287-3



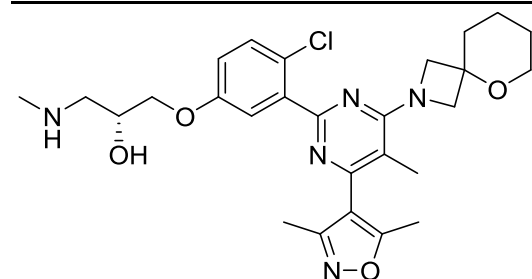
288-3



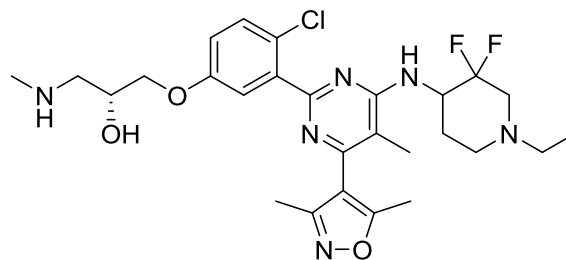
289-3



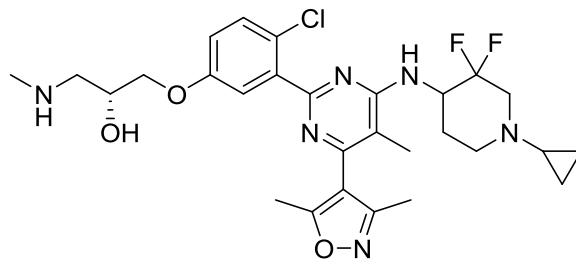
290-3



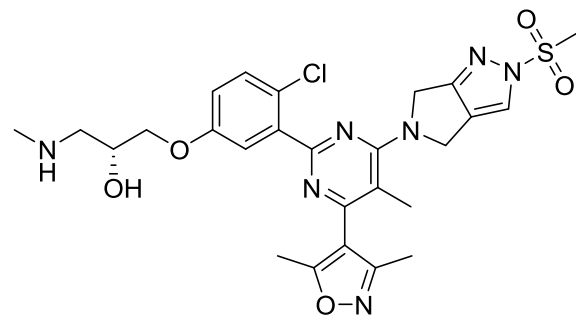
291-3



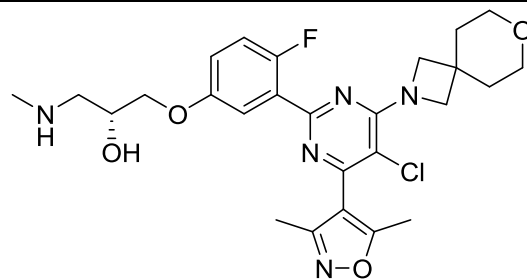
292-3



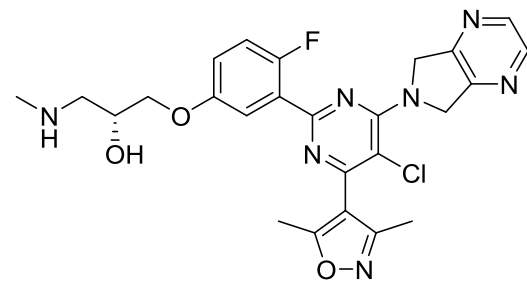
293-3



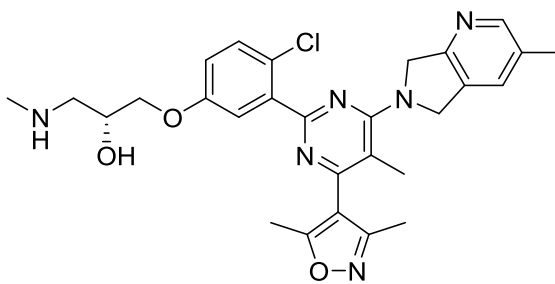
294-3



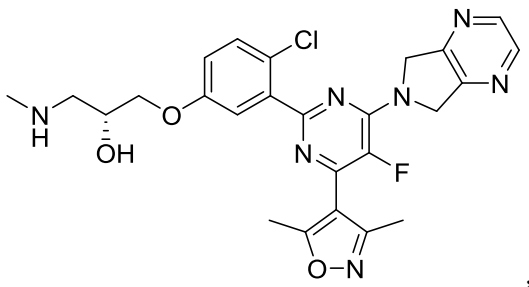
295-3



296-3



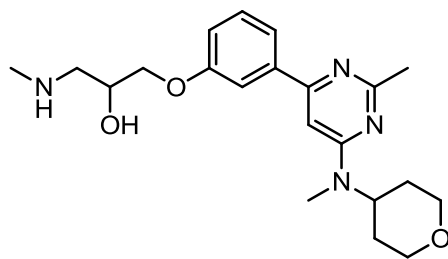
297-3



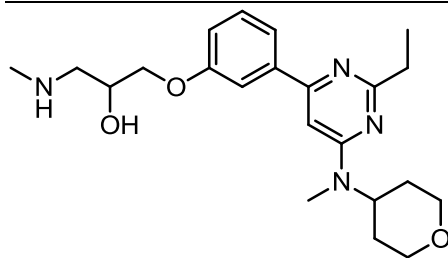
and pharmaceutically acceptable salts thereof.

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

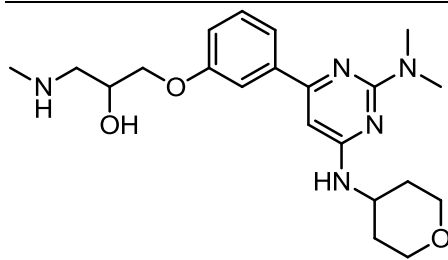
1-2



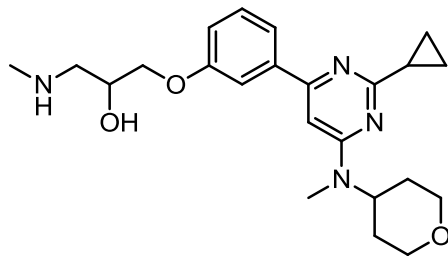
2-2



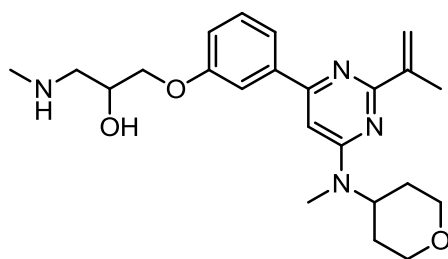
3-2



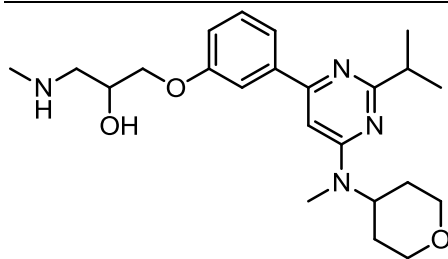
4-2



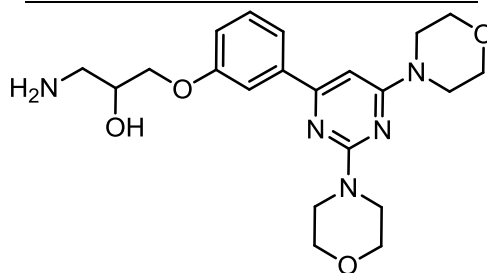
5-2



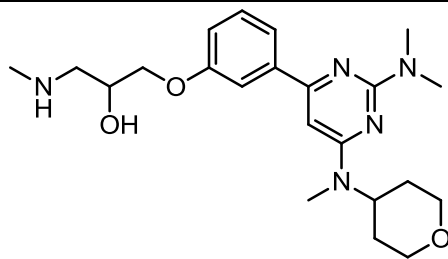
6-2



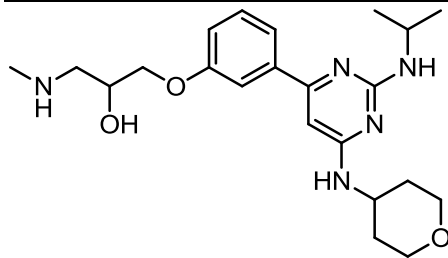
7-2



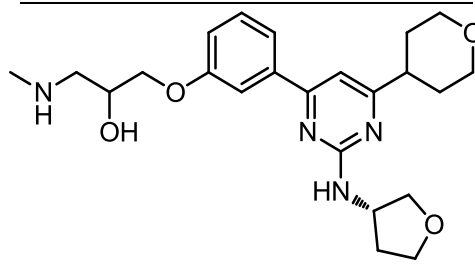
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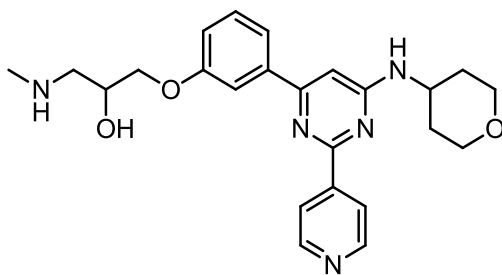
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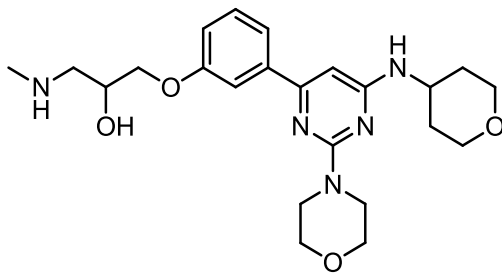
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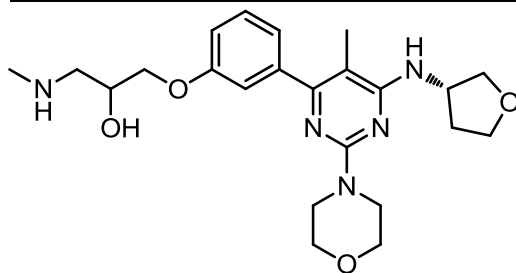
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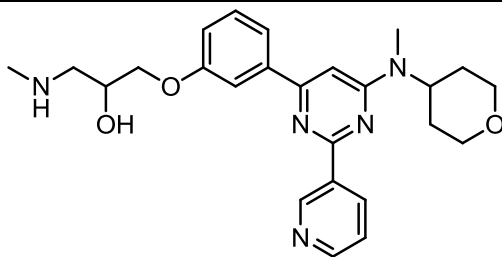
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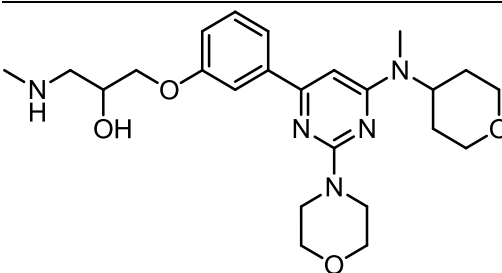
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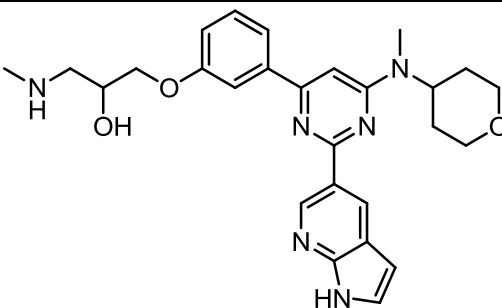
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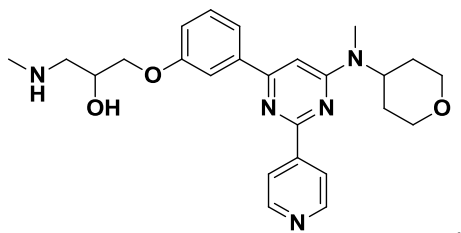
15-2



16-2

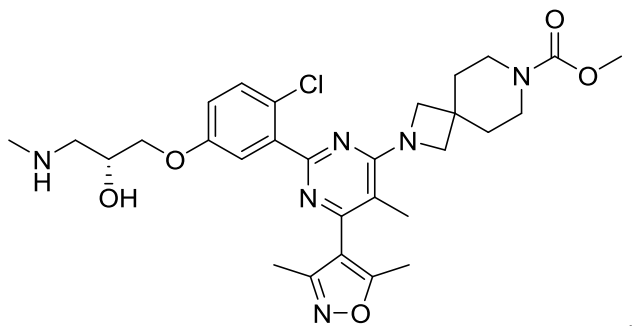


2-1



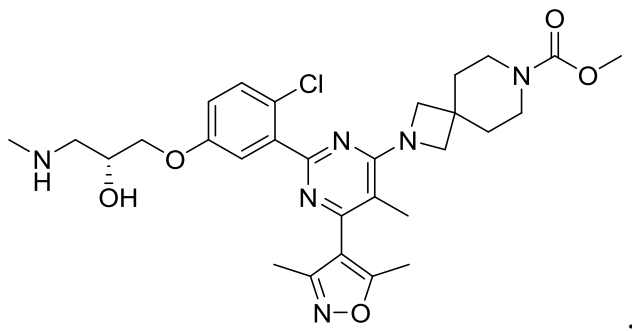
_____ ,
and pharmaceutically acceptable salts thereof.

51. A compound of formula:

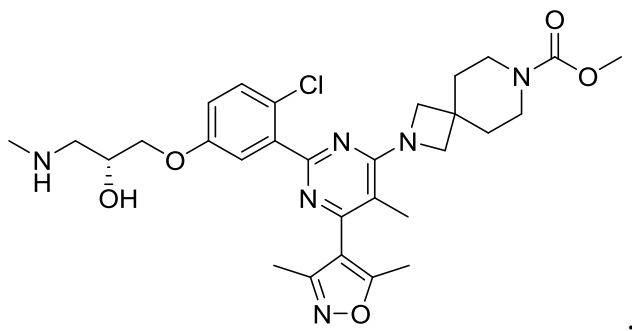


_____ ,
or a pharmaceutically acceptable salt thereof.

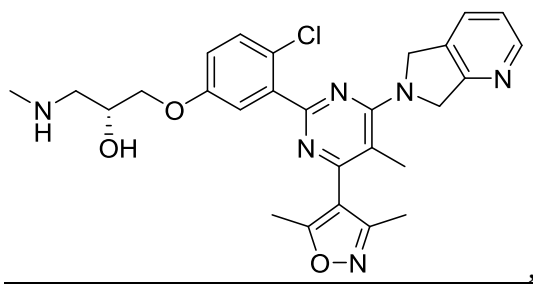
52. The compound of claim 51, wherein the compound is:



53. The compound of claim 51, wherein the compound is a pharmaceutically acceptable salt
of:

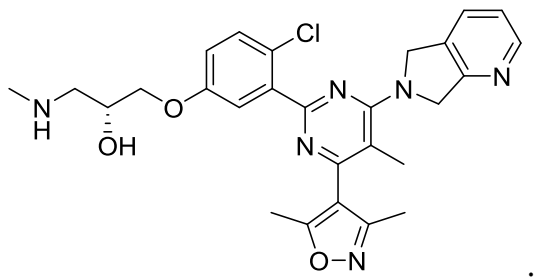


54. A compound of formula:

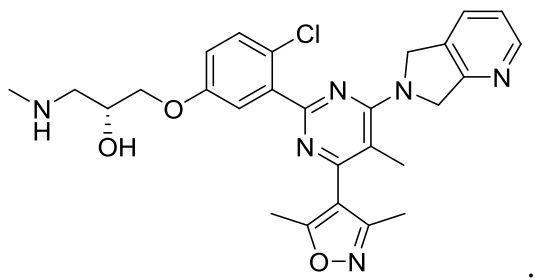


or a pharmaceutically acceptable salt thereof.

55. The compound of claim 54, wherein the compound is:



56. The compound of claim 54, wherein the compound is a pharmaceutically acceptable salt of:



57. A pharmaceutical composition comprising a compound of any one of claims 1–47, and a pharmaceutically acceptable excipient.

58. A pharmaceutical composition comprising a compound of claim 48, and a pharmaceutically acceptable excipient.

59. A pharmaceutical composition comprising a compound of claim 49, and a pharmaceutically acceptable excipient.

60. A pharmaceutical composition comprising a compound of claim 50, and a pharmaceutically acceptable excipient.

61. A pharmaceutical composition comprising a compound of claim 51, and a pharmaceutically acceptable excipient.

62. A pharmaceutical composition comprising a compound of claim 52, and a pharmaceutically acceptable excipient.

63. A pharmaceutical composition comprising a compound of claim 53, and a pharmaceutically acceptable excipient.

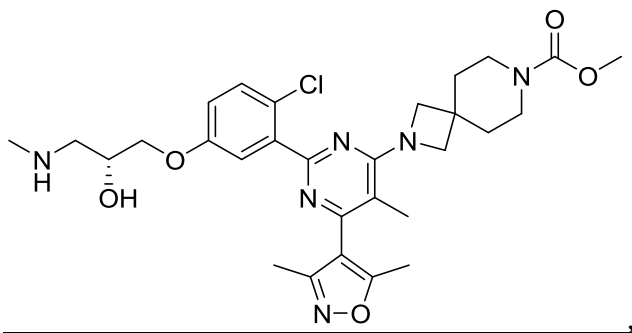
64. A pharmaceutical composition comprising a compound of claim 54, and a pharmaceutically acceptable excipient.

65. A pharmaceutical composition comprising a compound of claim 55, and a pharmaceutically acceptable excipient.

66. A pharmaceutical composition comprising a compound of claim 56, and a pharmaceutically acceptable excipient.

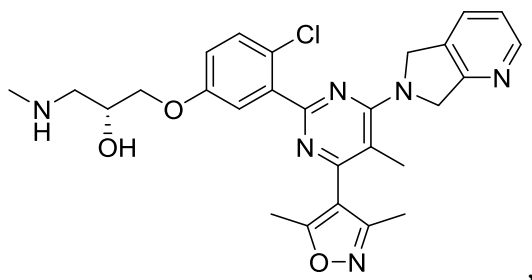
67. A kit or packaged pharmaceutical comprising a compound of any one of claims 1–56 or a pharmaceutically acceptable salt thereof, and instructions for use thereof.

68. The kit or packaged pharmaceutical of claim 67, wherein the compound is



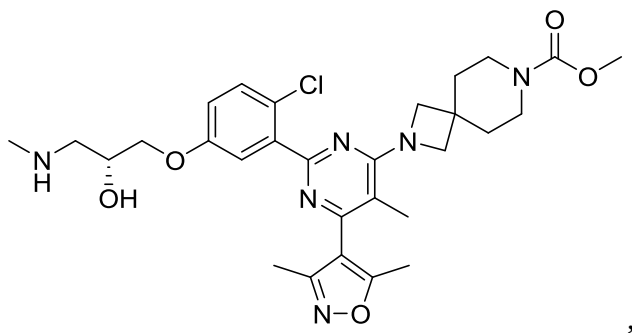
or a pharmaceutically acceptable salt thereof.

69. The kit or packaged pharmaceutical of claim 67, wherein the compound is



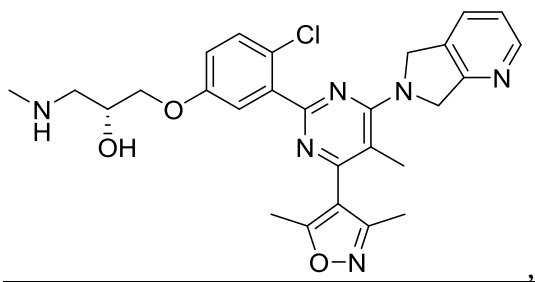
or a pharmaceutically acceptable salt thereof.

70. Use of a compound of any one of claims 1–56 in the preparation of a medicament for use in treating a CARM1-mediated disorder.
71. The use of claim 70, wherein the disorder is a proliferative disorder.
72. The use of claim 71, wherein the disorder is cancer.
73. The use of claim 72, wherein the cancer is associated with E2F1 upregulation.
74. The use of claim 71 or 72, wherein the cancer is associated with aberrant CARM1 activity.
75. The use of any one of claims 72-74, wherein the cancer is breast cancer, prostate cancer, or colorectal cancer.
76. The use of any one of claims 72-74, wherein the cancer is ER α -dependent breast cancer.
77. The use of any one of claims 72-74, wherein the cancer is castration-resistant prostate cancer.
78. The use of any one of claims 72-74, wherein the cancer is colorectal cancer associated with dysregulated WNT/ β -catenin signaling.
79. The use of claim 70, wherein the disorder is a metabolic disorder.
80. The use of any one of claims 70-79, wherein the compound is



or a pharmaceutically acceptable salt thereof.

81. The use of any one of claims 70-79, wherein the compound is



or a pharmaceutically acceptable salt thereof.