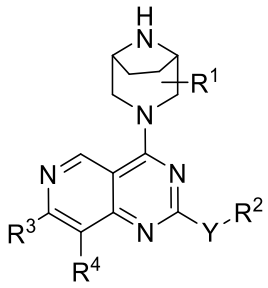
CLAIMS

WE CLAIM:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen, hydroxy, halogen, C1 – C3 alkyl, C1 - C3 cyanoalkyl, C1 - C3 hydroxyalkyl, HC(=O)-, $-CO_2R^5$, $-CO_2N(R^5)_2$ or a 5-6 membered heteroaryl;

Y is a bond, O or NR^5;

R^2 is hydrogen, $-N(R^5)_2$, heterocyclyl, C1 – C6 alkyl, -L-heterocyclyl, -L-aryl, -L-heteroaryl, -L-cycloalkyl, $-L-N(R^5)_2$, $-L-NHC(=NH)NH_2$, $-L-C(O)N(R^5)_2$, -L-C1-C6 haloalkyl, $-L-OR^5$, $-L-(CH_2OR^5)(CH_2)_nOR^5$, $-L-NR^5C(O)$-aryl, -L-COOH, or -LC(=O)OC1-C6 alkyl, wherein the heterocyclyl and the aryl portion of $-L-NR^5C(O)$-aryl and the heterocyclyl portion of -L-heterocyclyl and the cycloalkyl portion of the -L-cycloalkyl may be optionally substituted with one or more R^6, and wherein the aryl or heteroaryl of the -L-aryl and the -L-heteroaryl may be optionally substituted with one or more R^7;

each L is independently a C1 – C4 alkylene optionally substituted with hydroxy, C1 – C4 hydroxyalkyl or heteroaryl;

R^3 is aryl or heteroaryl, wherein the aryl or the heteroaryl is optionally substituted with one or more R^8;

R^4 is hydrogen, halogen or C1 – C3 alkyl;

each R^5 is independently hydrogen or C1 – C3 alkyl;

each R^6 is independently halogen, hydroxy, C1 - C3 hydroxyalkyl, C1 – C3 alkyl, C1 - C3 haloalkyl, C1-C3 alkoxy, cyano, -Q-phenyl, -Q-phenylSO_2F, -NHC(O)phenyl, -NHC(O)phenylSO_2F, C1-C3 alkyl substituted pyrazolyl, araC1-C3 alkyl-, tert-butyldimethylsilyloxyCH_2- , -$N(R^5)_2$, (C1-C3 alkoxy)C1-C3 alkyl-, (C1-C3 alkyl)C(=O), oxo, (C1-C3 haloalkyl)C(=O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC$1-C6 alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)$C1-C6 alkyl, -CH_2(pyrazolyl), -CH_2NHSO_2C1-C6 alkyl, -$CH_2OC(O)$heterocyclyl, -$OC(O)N(R^5)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)$N(CH_3)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl or -OC(O)heterocyclyl, -CH_2heterocyclyl, wherein the phenyl of -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with -C(O)H or OH and wherein the heterocyclyl of -CH_2heterocyclyl is optionally substituted with oxo;

Q is a bond or O;

each R^7 is independently halogen, hydroxy, HC(=O)-, C1 – C4 alkyl, C1 – C4 alkoxy, C1 – C4 haloalkyl, C1 – C4 hydroxyalkyl, or -$N(R^5)_2$; and

each R^8 is independently halogen, cyano, hydroxy, C1 - C4 alkyl, -S-C1 - C3 alkyl, C2 – C4 alkenyl, C2 – C4 alkynyl, C2 – C4 hydroxyalkynyl, C1-C3 cyanoalkyl , triazolyl, C1 - C3 haloalkyl, -O- C1 - C3 haloalkyl, -S- C1 - C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, -$CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl$(NR^5)_2$, -$N(R^5)_2$, deuteroC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl.

2. The compound or salt of claim 1, wherein R^1 is hydrogen, halogen, hydroxy, C1 – C3 alkyl, C1- C3 cyanoalkyl, hydroxyalkyl, HC(=O)-, -CO_2R^5, or -$CO_2N(R^5)_2$.

~~3. The compound or salt of claim 2, wherein R^5 is hydrogen, C1 – C3 alkyl or C1 - C3 cyanoalkyl.~~

~~4~~3. The compound or salt of claim 2, wherein Y is O and R^2 is C1 – C6 alkyl or -L-heterocyclyl optionally substituted with one or more R^6.

~~5.The compound or salt of claim 4, wherein the C1 – C6 alkyl is methyl, ethyl, isopropyl or isobutyl.~~

~~6~~4. The compound or salt of claim ~~4~~3, wherein L is methylene and the heterocyclyl is hexahydro-1*H*-pyrrolizinyl, hexahydro-3H-pyrrolizin-3-one, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, octahydroindolizinyl, hexahydropyrrolizine 4(1H)-oxide, azetidinyl, pyrrolidinyl, pyrrolidin-2-one, oxetanyl, piperidinyl, 1-azabicyclo[2.2.1]heptanyl, morpholinyl, oxa-5-azabicyclo[2.2.1]heptan-5-yl, thiopyranyl, 6-oxa-2λ^2-azaspiro[3.4]octanyl, 7-oxa-2λ^2-azaspiro[3.5]nonanyl, 2',3'-dihydrospiro[cyclopropane-1,1'-indenyl], (2S)-1-azabicyclo[2.2.1]heptan-2-yl, or tetrahydrofuranyl, each optionally substituted with one or more R^6.

~~7~~5. The compound or salt of claim ~~4~~3, wherein L is methylene and the heterocyclyl is hexahydro-1*H*-pyrrolizinyl~~,~~ preferably

~~8. The compound or salt of claim 7,~~ wherein heterocyclyl is hexahydro-1*H*-pyrrolizinyl substituted with one R^6, wherein R^6 is halogen, hydroxy, C1 - C3 hydroxyalkyl, C1 - C3 haloalkyl, C1 – C3 alkyl, C1 - C3 alkoxy, phenyl or pyrazolyl, preferably~~.~~

~~9. The compound or salt of claim 8,~~ wherein the halogen is fluorine.

~~10~~6. The compound or salt of claim ~~6~~4, wherein the heterocyclyl is hexahydro-1*H*-pyrrolizinyl further substituted with two additional R^6 groups, wherein the two additional R^6 groups are independently C1 – C3 alkyl; ~~.~~

~~11. The compound or salt of claim 6,~~ wherein the heterocyclyl is azetidinyl substituted with one R^6, wherein R^6 is C1 – C3 alkyl;~~.~~

~~12. The compound or salt of claim 6,~~ wherein the heterocyclyl is pyrrolidinyl substituted with one R^6, wherein R^6 is hydroxalkyl, haloalkyl, C1 – C3 alkyl, alkoxy, araC1-C3 alkyl, -Q-phenyl and -NHC(O)phenyl, and wherein the aryl portion of the araC1-C3 alkyl or the phenyl portion of the -Q-phenyl and -NHC(O)phenyl are each optionally substituted with one or more R^6, preferably~~.~~

~~13. The compound or salt of claim 12,~~ wherein the phenyl group of the -Q-phenyl or the -NHC(O)phenyl is substituted with SO_2F;~~.~~

~~14. The compound or salt of claim 6,~~ wherein the heterocyclyl is pyrrolidinyl substituted with two R^6 groups wherein one R^6 is C1 – C3 alkyl and the other R^6 is C1-C3 alkoxy or halogen;~~.~~

~~15. The compound or salt of claim 6,~~ wherein the heterocyclyl is pyrrolidin-2-one substituted with one R^6, wherein R^6 is C1 – C3 alkyl;~~.~~

~~16. The compound or salt of claim 6,~~

wherein the heterocyclyl is piperidinyl substituted with one R^6, wherein R^6 is acetyl, (C1-C3 alkoxy)C1-C3 alkoxy, or -C(O)CH_2Cl; or~~.~~

~~17. The compound or salt of claim 6,~~ wherein Y is O, L is ethylene or propylene and the heterocyclyl is morpholinyl or oxa-5-azabicyclo[2.2.1]heptan-5-yl.

~~18~~7. The compound or salt of claim 2, wherein Y is O and R^2 is -L-heteroaryl, wherein the heteroaryl portion is optionally substituted with one or more R^7, preferably~~.~~

~~19. The compound or salt of claim 18,~~ wherein L is methylene or ethylene and the heteroaryl is pyridyl, pyrazolyl, imidazolyl, triazolyl, 4,5,6,7-tetrahydro-1*H*-indazolyl, benzimidazolyl, imidazo[1,2-a]pyridinyl, or pyrimidinyl, each optionally substituted with one or more R^7, preferably:~~.~~

~~20. The compound or salt of claim 19,~~ wherein the heteroaryl is pyridyl substituted with one R^7, wherein R^7 is halogen, C1 – C4 alkyl, -N(R^5)$_2$, or C1-C4 alkoxy;~~.~~

~~21. The compound or salt of claim 19,~~ wherein the heteroaryl is pyrazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl or -N(R^5)$_2$;~~.~~

~~22. The compound or salt of claim 19,~~ wherein the heteroaryl is imidazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl, C1 – C4 haloalkyl, or C1 – C4 hydroxyalkyl; or~~.~~

~~23. The compound or salt of claim 19,~~ wherein the heteroaryl is triazolyl substituted with one R^7, wherein R^7 is C1 – C4 alkyl.

~~24~~8. The compound or salt of claim 2, wherein Y is O and R^2 is -L-aryl, wherein the aryl portion is optionally substituted with one or more R^7;~~.~~

~~25. The compound or salt of claim 2,~~ wherein Y is O and R^2 is -L-cycloalkyl, wherein the cycloalkyl portion is optionally substituted with one or more R^7;~~.~~

~~26. The compound or salt of claim 2,~~ wherein Y is O, and R^2 is -L-$N(R^5)_2$, preferably~~.~~

~~27. The compound or salt of claim 26,~~ wherein L is ethylene and each R^5 is an independently selected C1 – C3 alkyl;~~.~~

~~28. The compound or salt of claim 2,~~ wherein Y is O, and R^2 is -L-NC(=NH)-NH_2, preferably~~.~~

~~29. The compound or salt of claim 28,~~ wherein L is ethylene or propylene;~~.~~

~~30. The compound or salt of claim 2,~~ wherein Y is O, and R^2 is -L-C1-C6 haloalkyl~~;~~.

~~31. The compound or salt of claim 2,~~ wherein Y is O, and R^2 is -L-OR^5~~;~~.

~~32. The compound or salt of claim 2,~~ wherein Y is O, and R^2 is -L-$(CH_2OR^5)(CH_2)_nOR^5$; or~~.~~

~~33. The compound or salt of claim 2,~~ wherein Y is O, and R^2 is -L-$NR^5C(O)$-aryl.

~~34~~9. The compound or salt of claim 2, wherein R^3 is aryl optionally substituted with one or more R^8, preferably~~.~~

~~35. The compound or salt of claim 34,~~ wherein the aryl is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl and 2,3-dihydro-1H-indenyl, each optionally substituted with one or more R^8; or~~.~~

~~36. The compound or salt of claim 2,~~ wherein R^3 is heteroaryl optionally substituted with one or more R^8, preferably~~.~~

~~37. The compound or salt of claim 42,~~ wherein the heteroaryl is isoquinolinyl, indazolyl, or benzo[d][1,3]dioxolyl optionally substituted with one or more R^8, more preferably~~.~~

~~38. The compound or salt of claim 37,~~ wherein the heteroaryl is isoquinolinyl substituted with one R^8, wherein R^8 is halogen or C2 - C4 alkynyl~~.~~.

~~39. The compound or salt of claim 37,~~ wherein the heteroaryl is indazolyl substituted with one R^8, wherein R^8 is C1 - C3 alkyl, or~~.~~

~~40. The compound or salt of claim 37,~~ wherein the heteroaryl is benzo[d][1,3]dioxolyl substituted with two R^8 groups, wherein the R^8 groups are independently selected halogens.

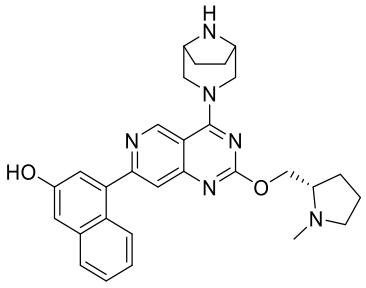
~~41~~10. The compound or salt of claim 2, wherein R^4 is halogen, or C1 – C3 alkyl, preferably ~~.~~

~~42. The compound or salt of claim 41,~~ wherein the halogen is fluorine, or~~.~~

~~43. The compound or salt of claim 41,~~ wherein the C1 – C3 alkyl is methyl.

~~44~~11. The compound or salt according to claim 1, wherein R^1 is hydrogen.

~~45~~12. The compound of claim 1, wherein the compound is selected from: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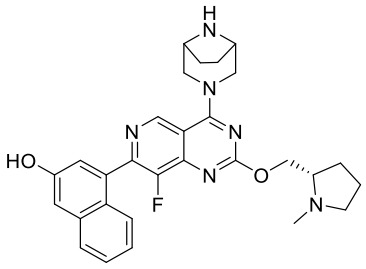
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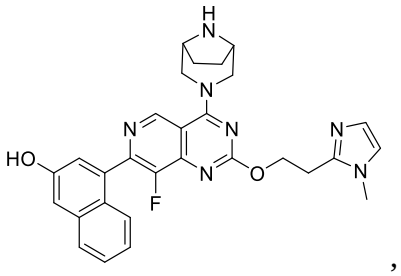
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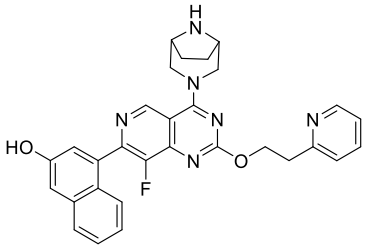
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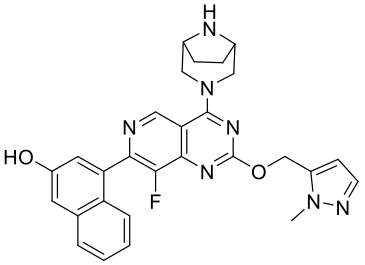
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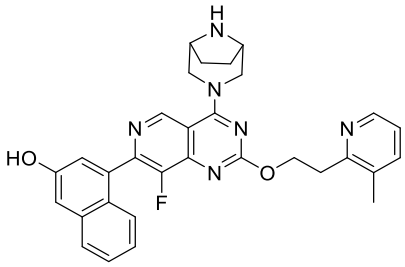
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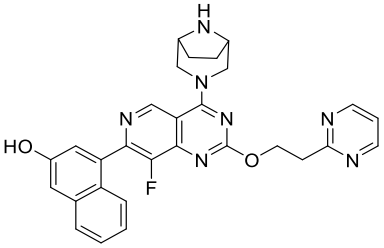
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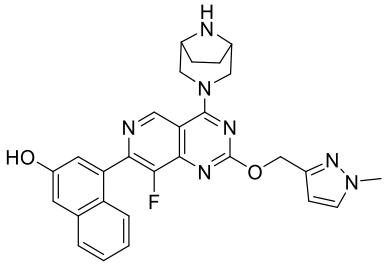
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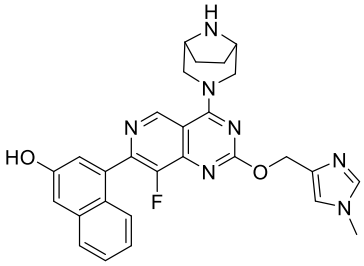
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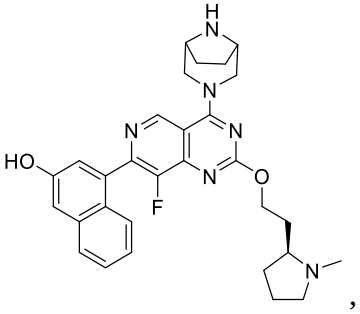
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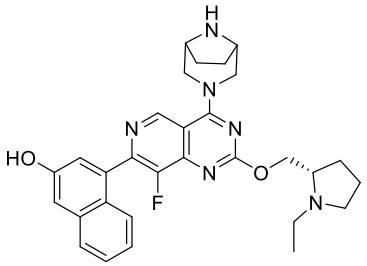
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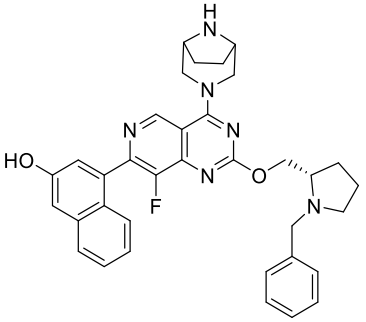
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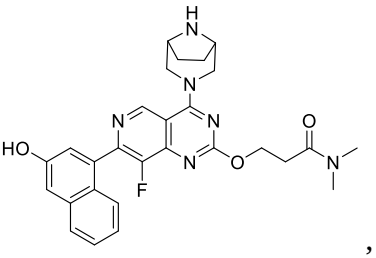
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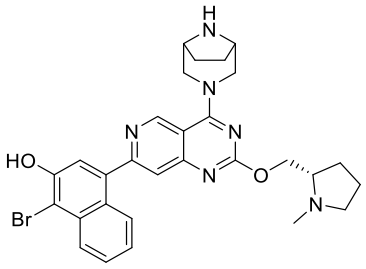
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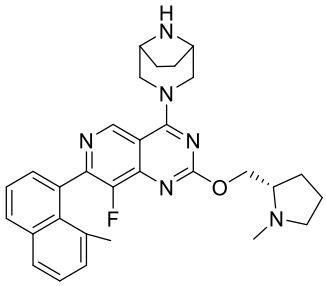
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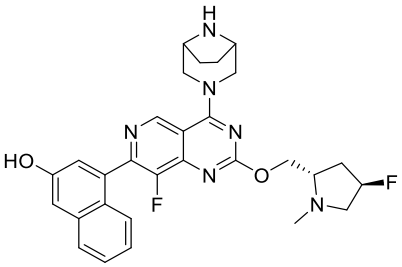
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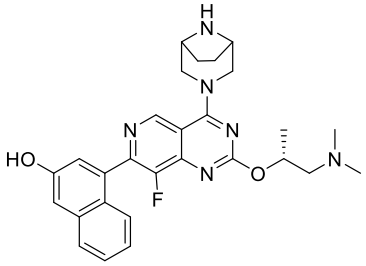
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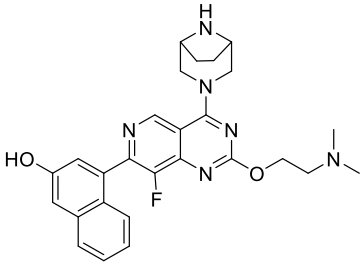
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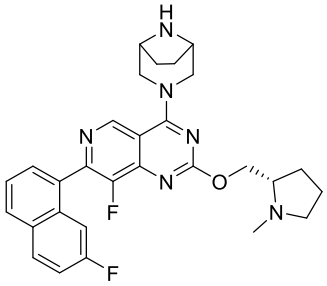
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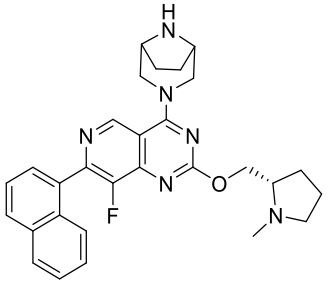
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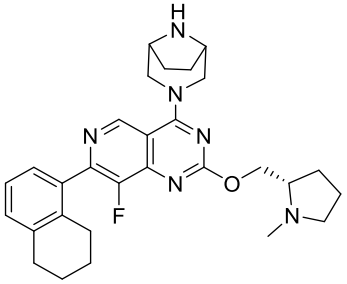
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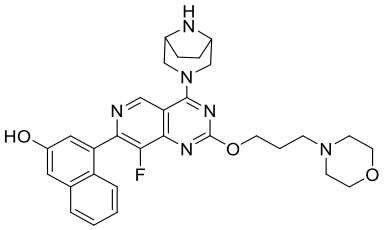
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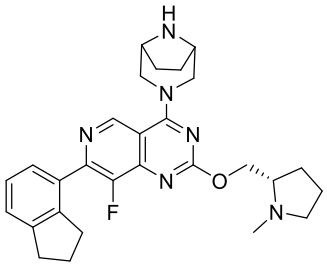
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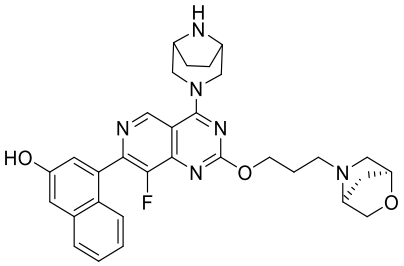
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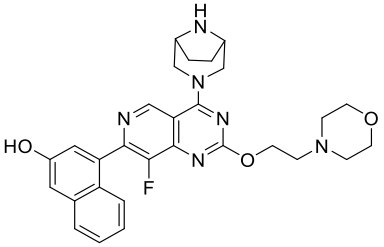
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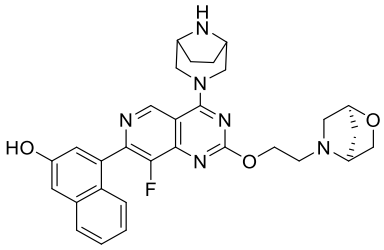
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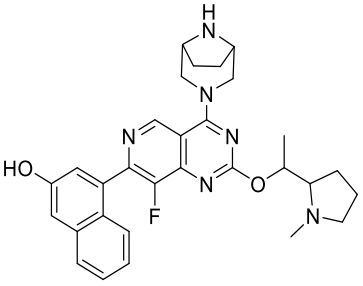
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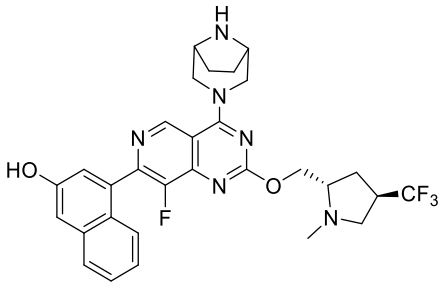
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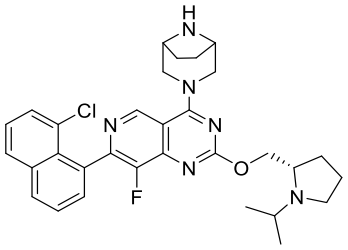
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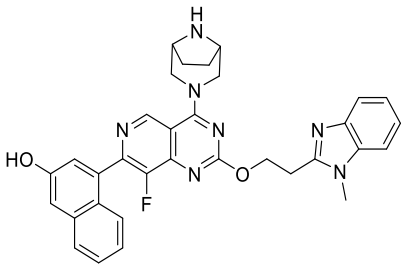
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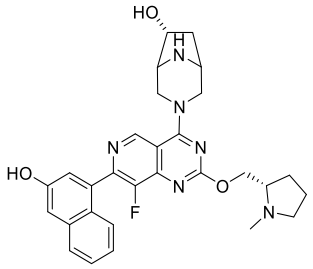
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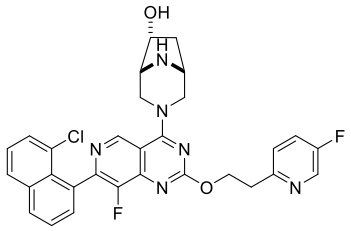
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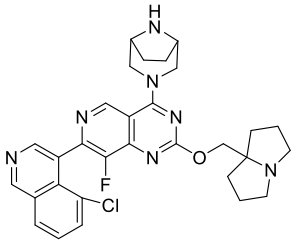
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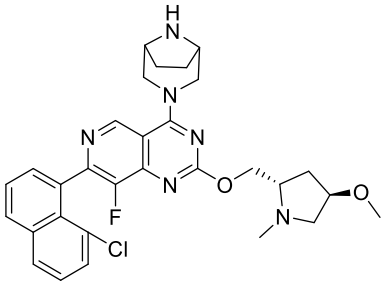
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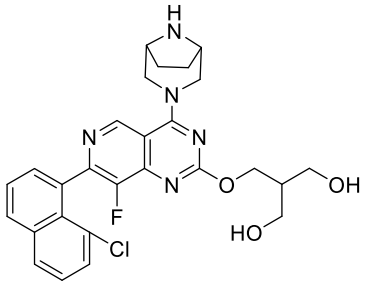
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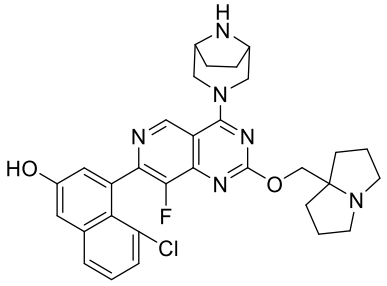
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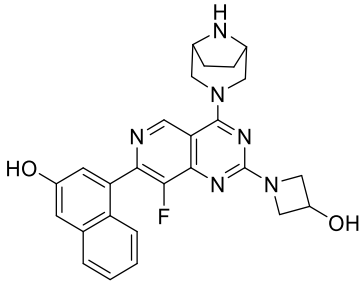
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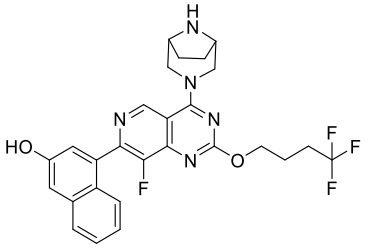
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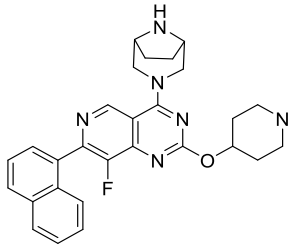
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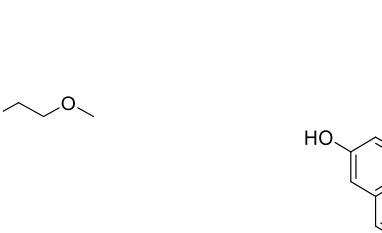
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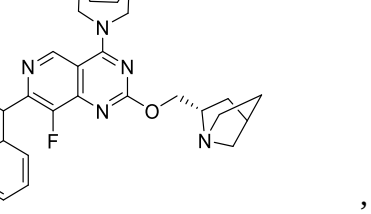
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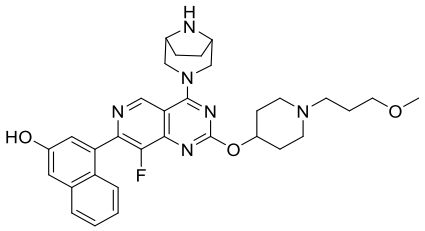
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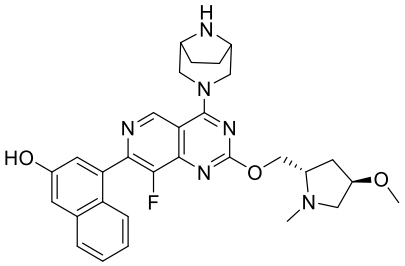
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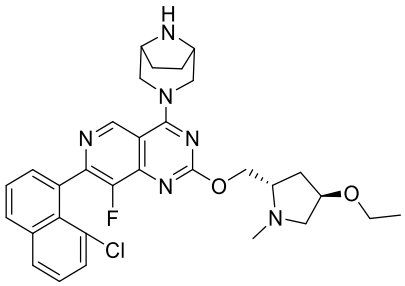
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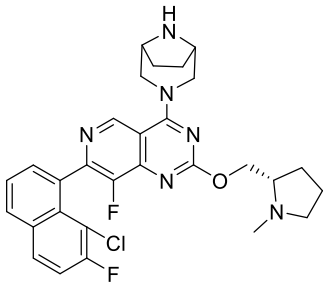
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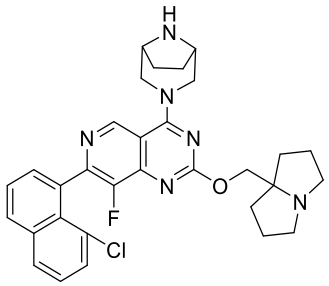
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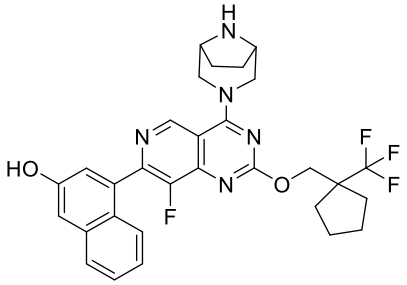
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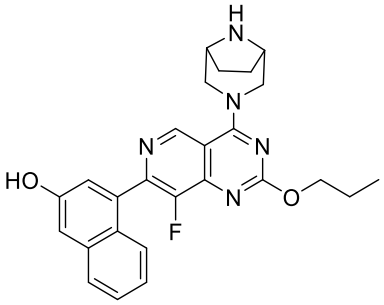
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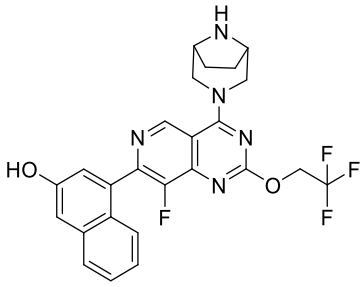
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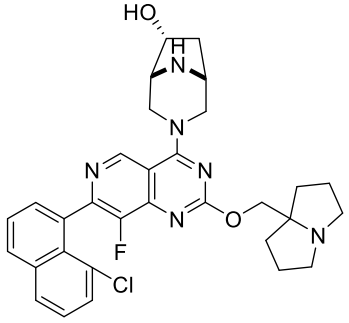
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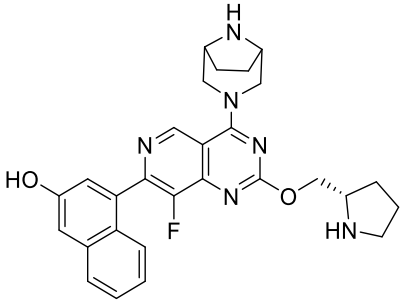
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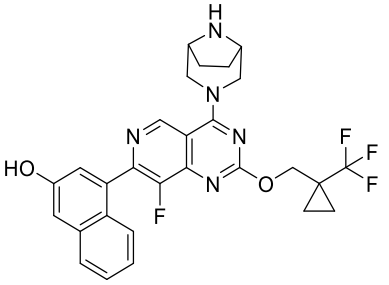
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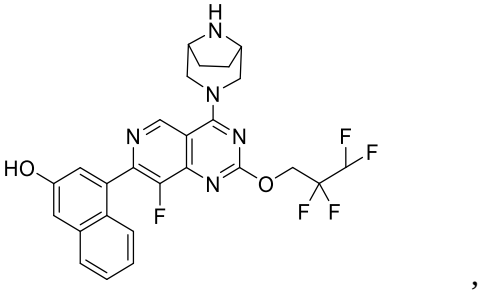
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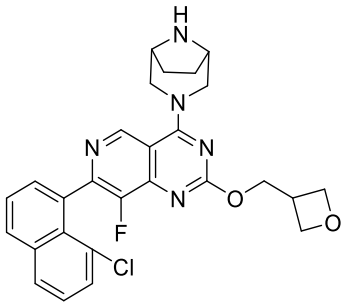
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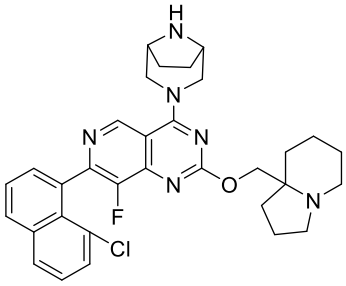
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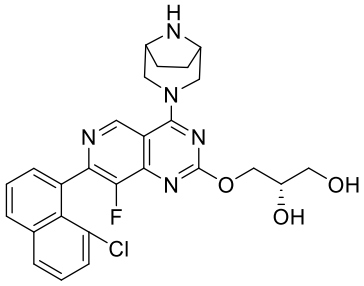
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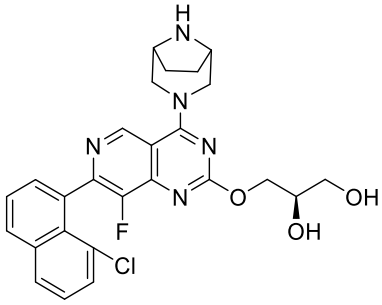
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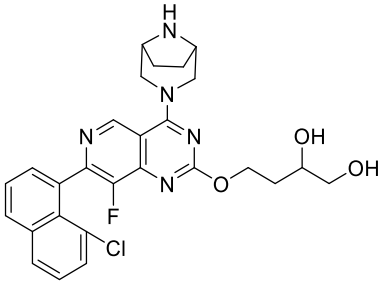
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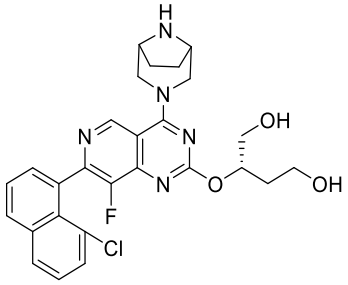
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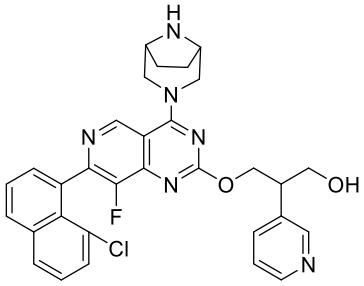
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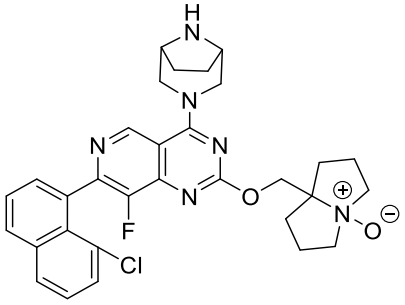
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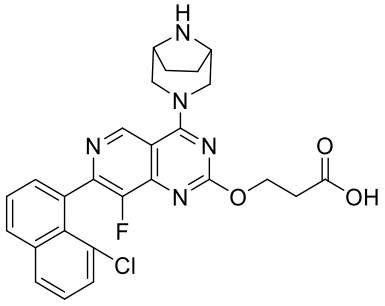
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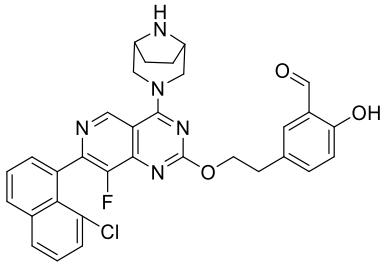
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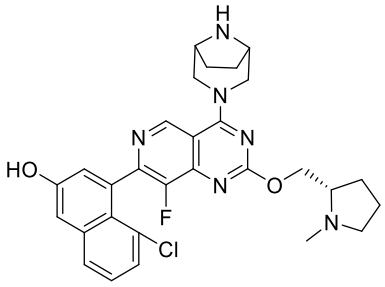
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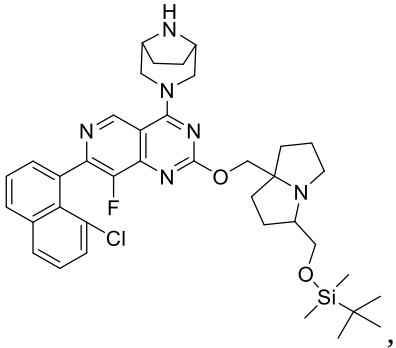
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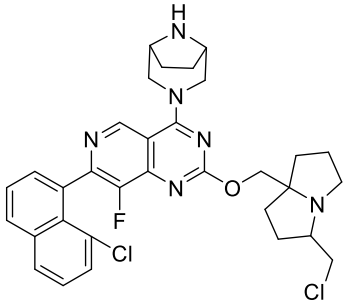

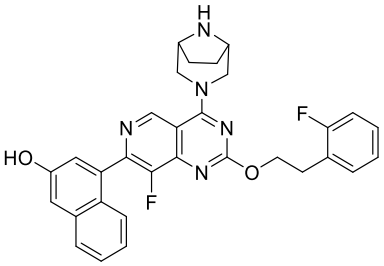
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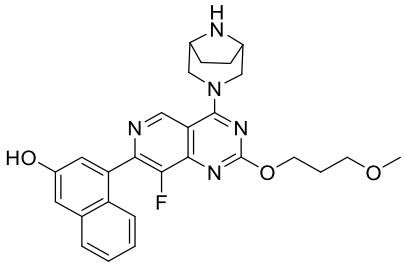
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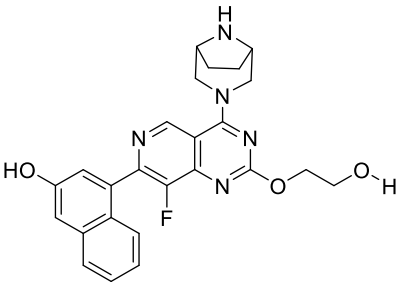
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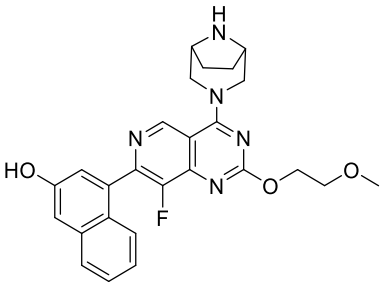
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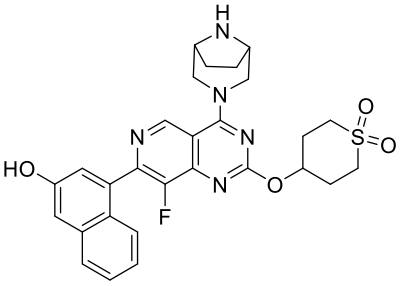
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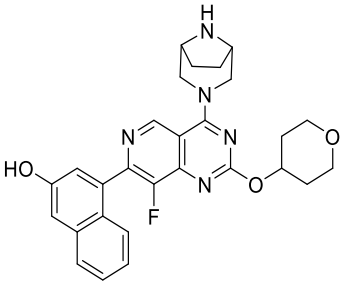
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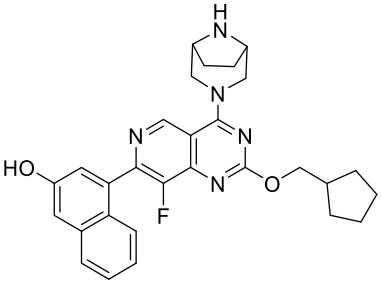
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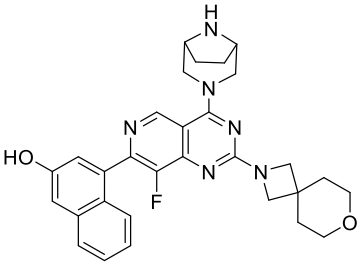
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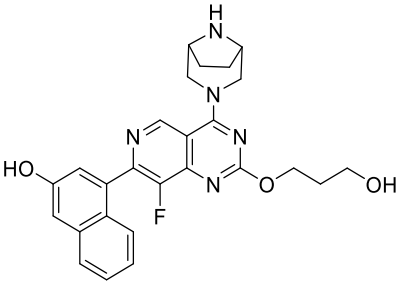
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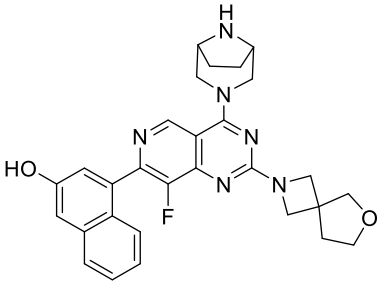
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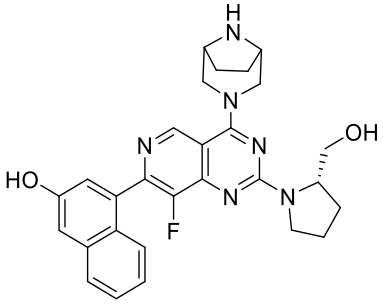
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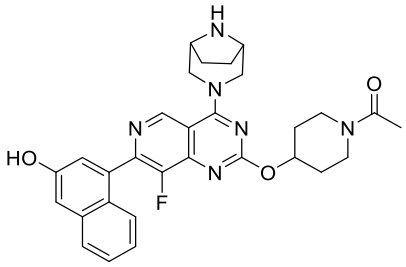
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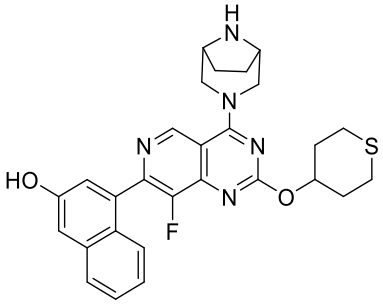
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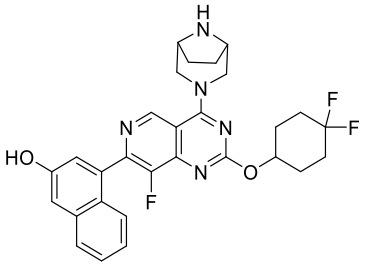
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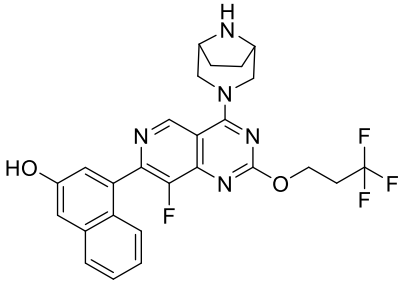
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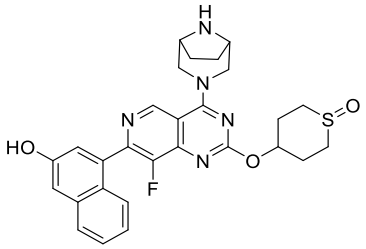
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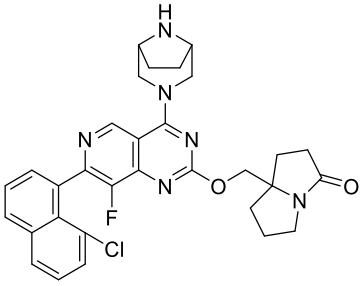
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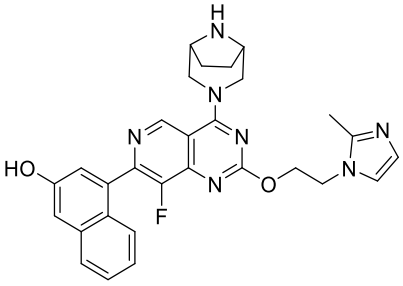
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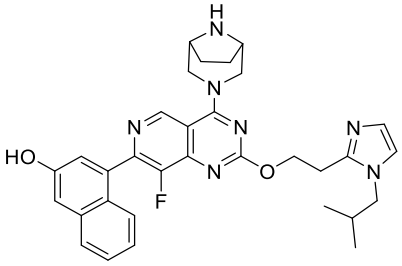
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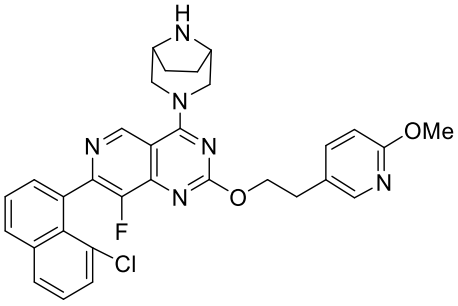
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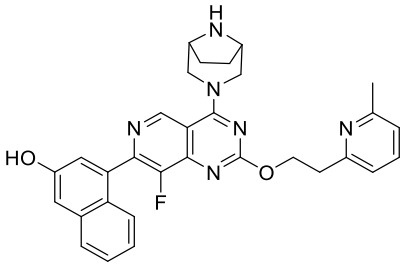
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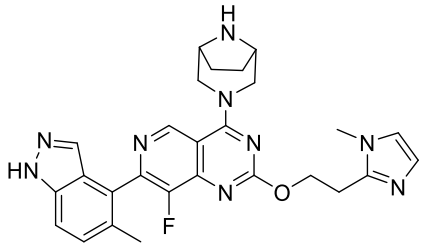
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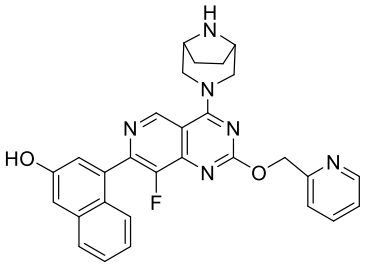
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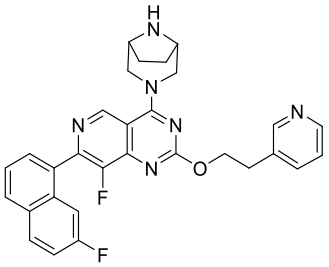
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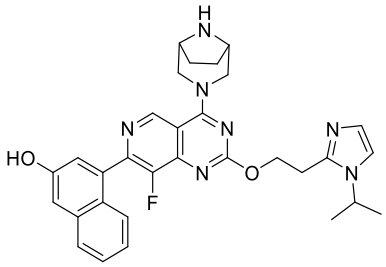
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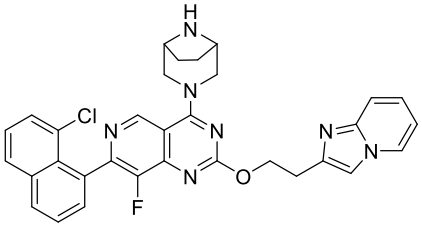
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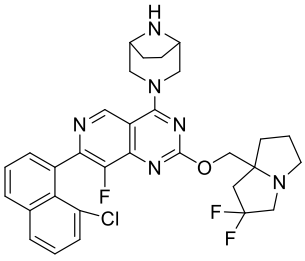
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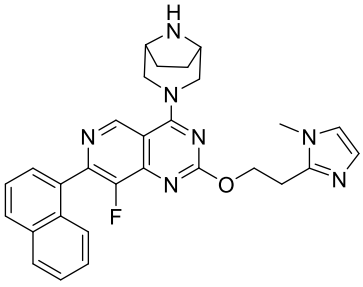
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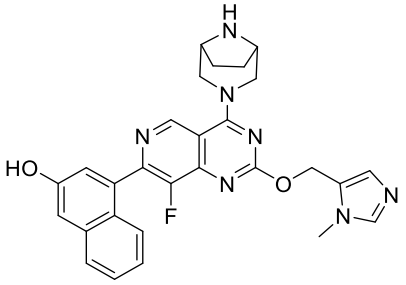
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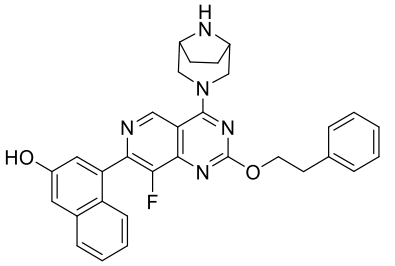
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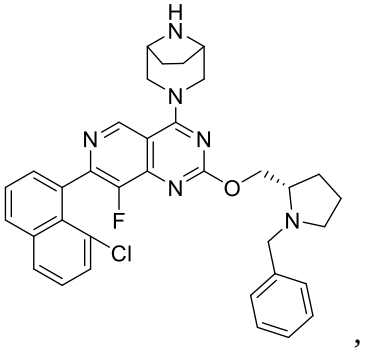
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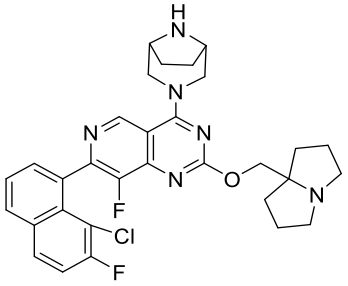
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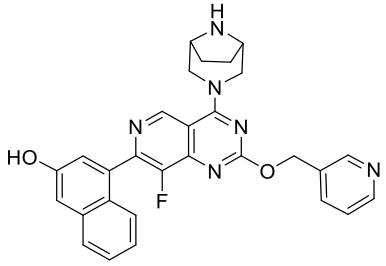
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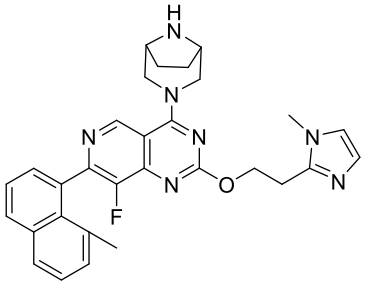
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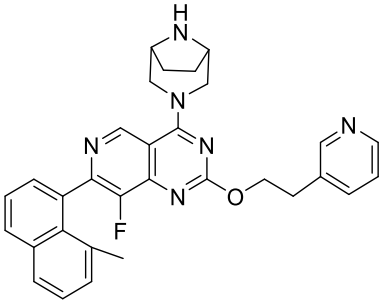
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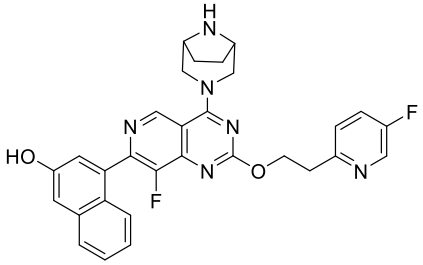
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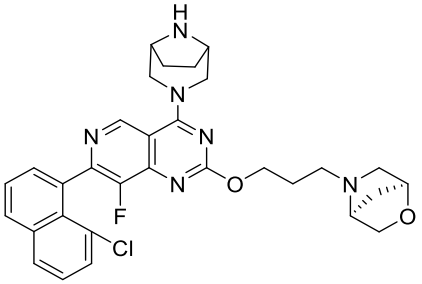
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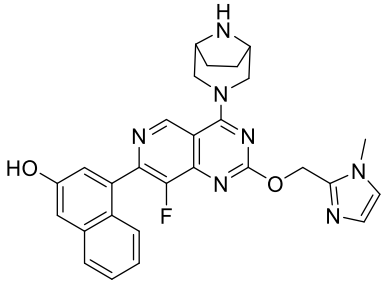
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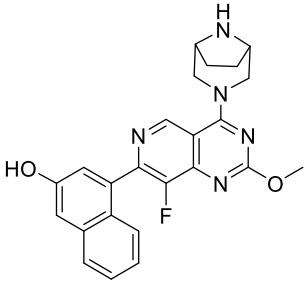
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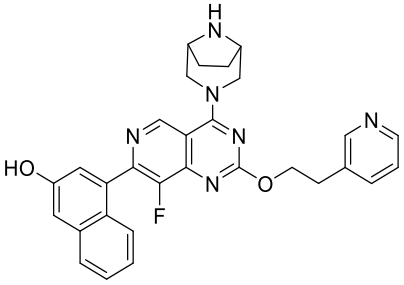
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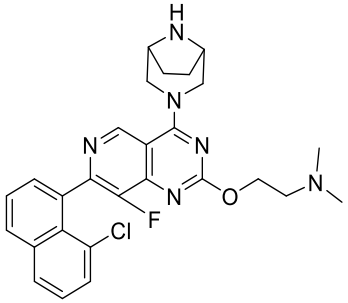
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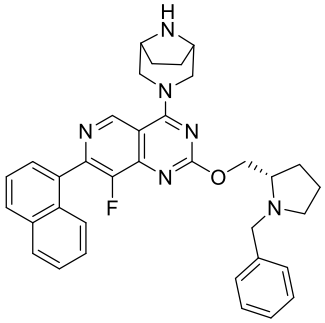
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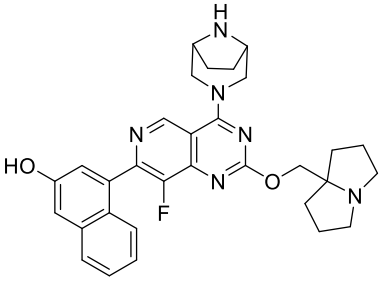
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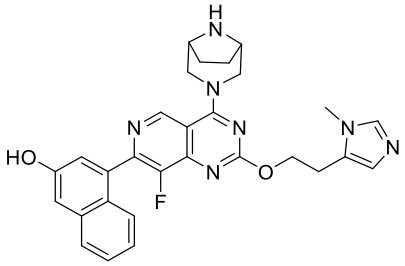
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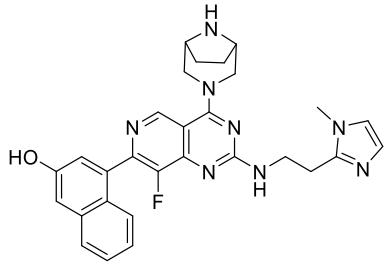
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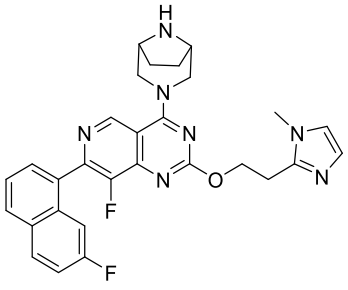
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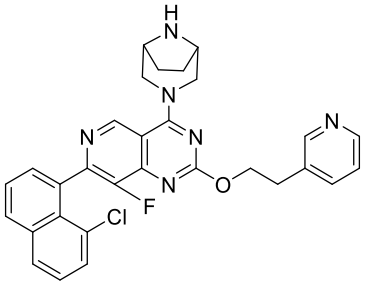
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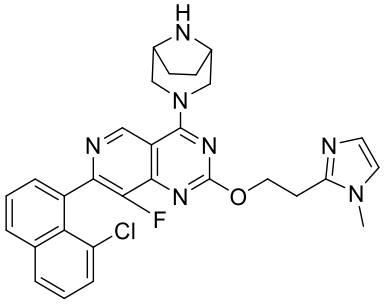
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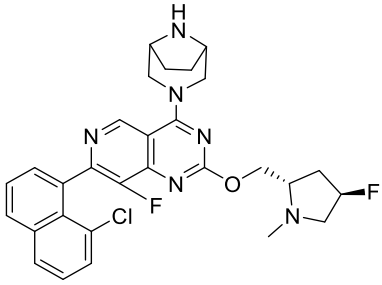
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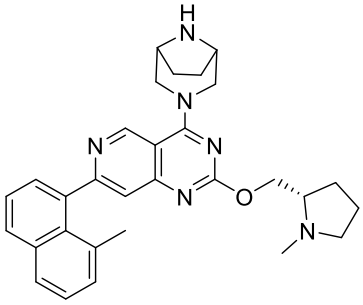
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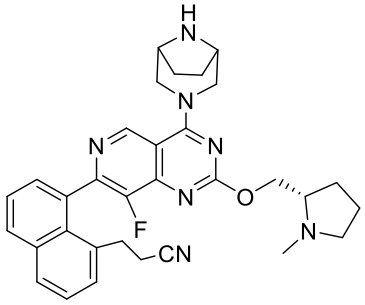
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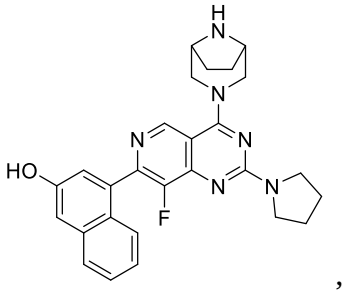
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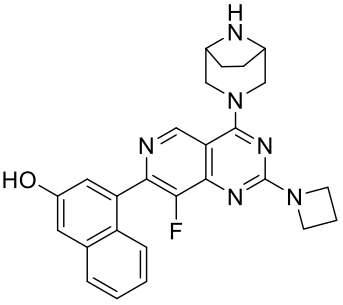
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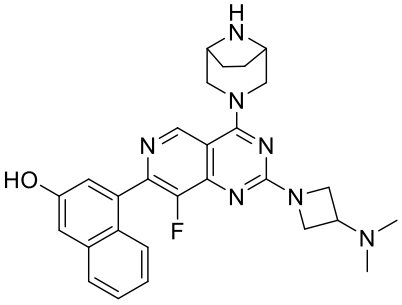
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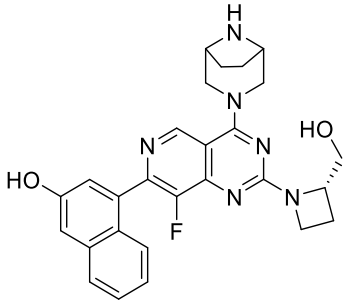
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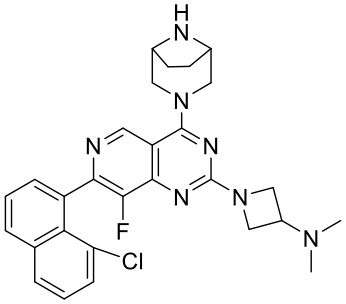
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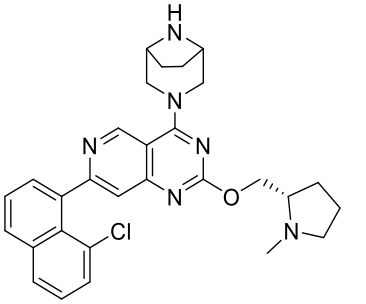
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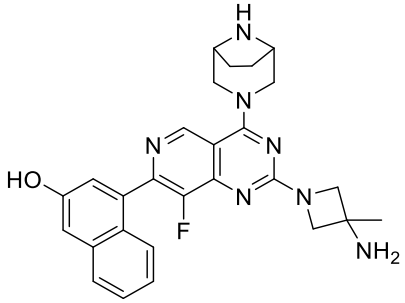
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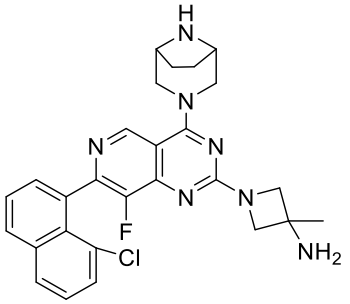
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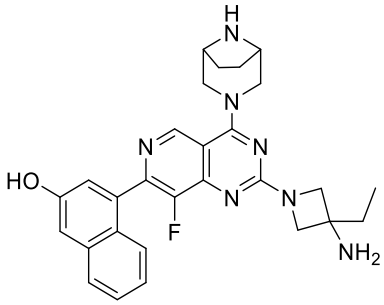
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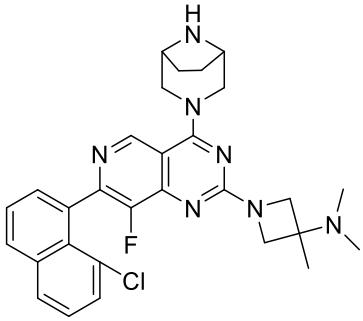
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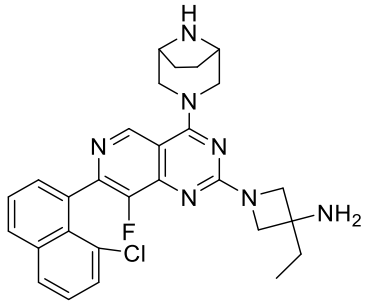
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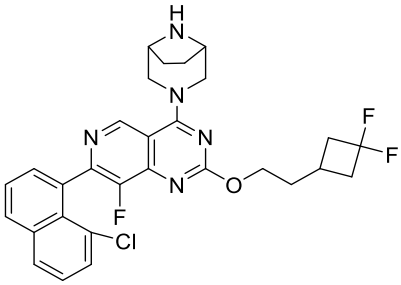
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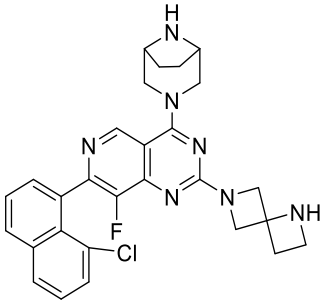
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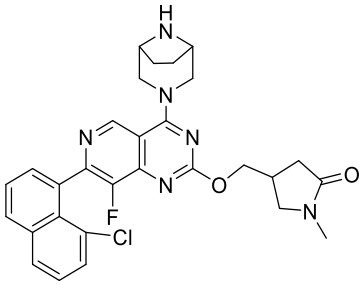
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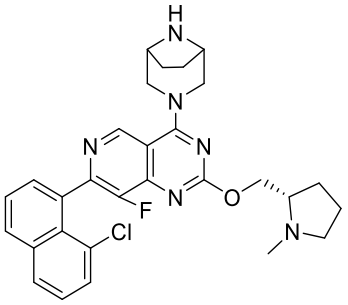
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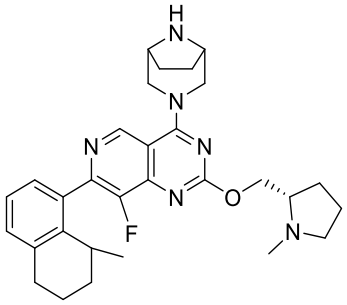
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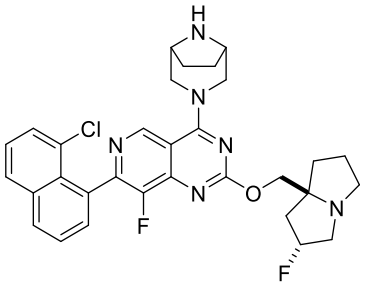
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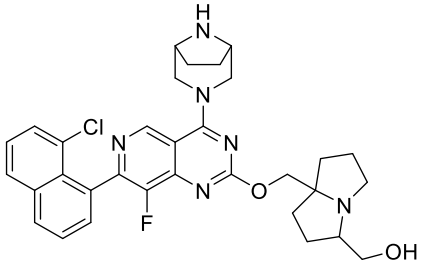
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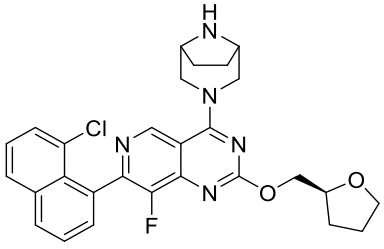
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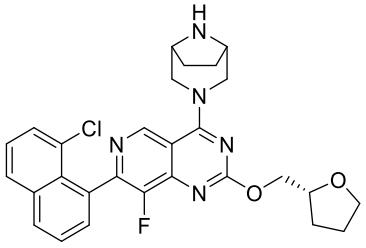
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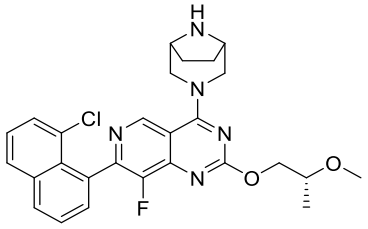
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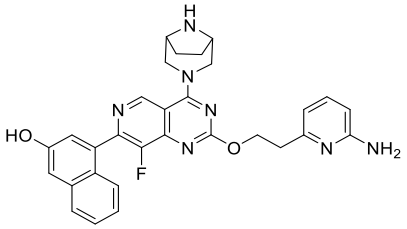
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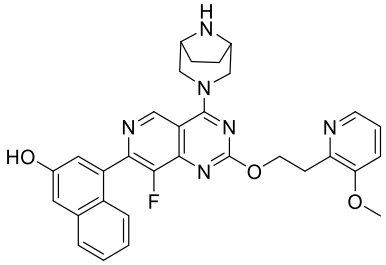
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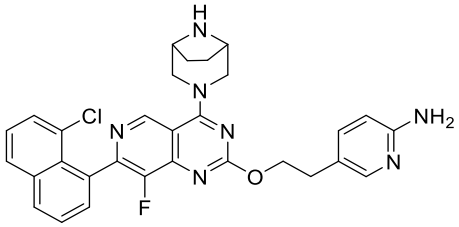
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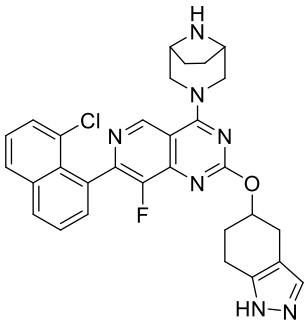
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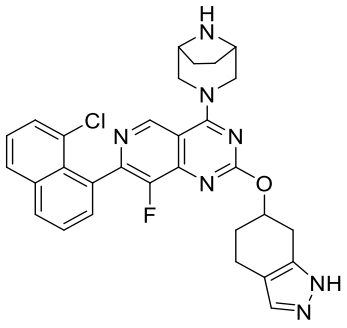
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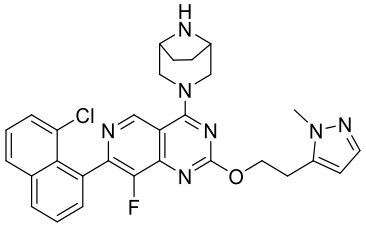
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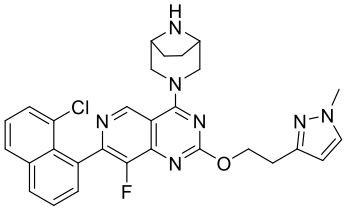
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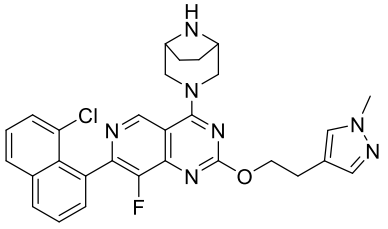
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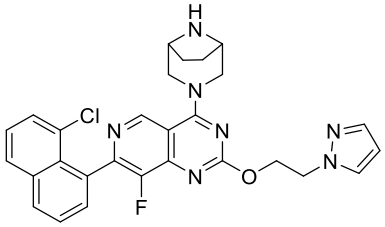
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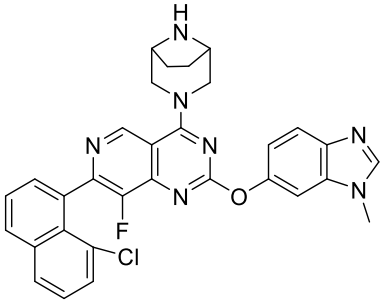
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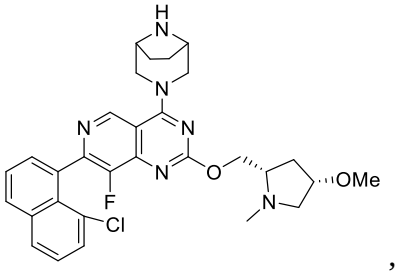
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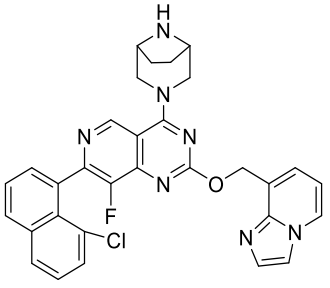
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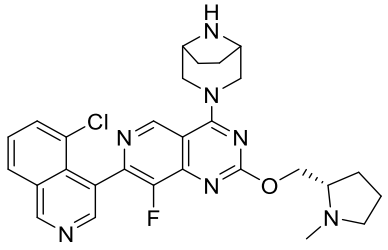
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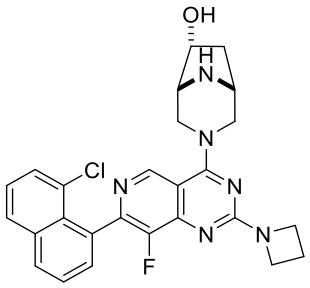
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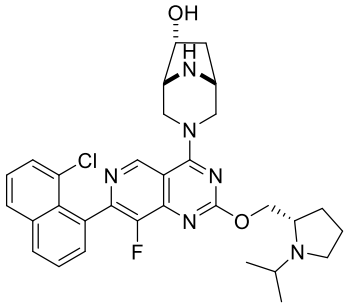
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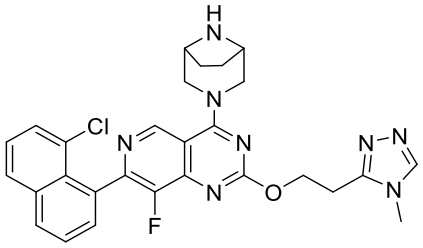
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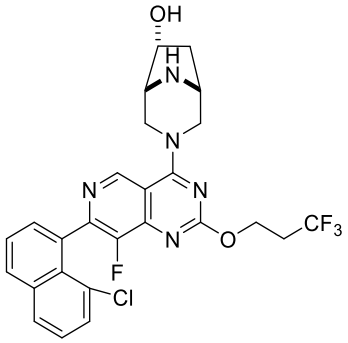
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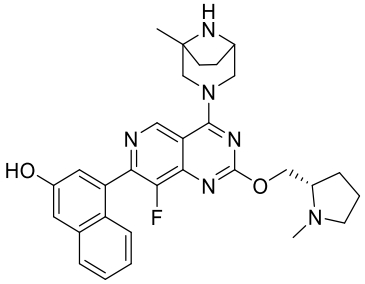
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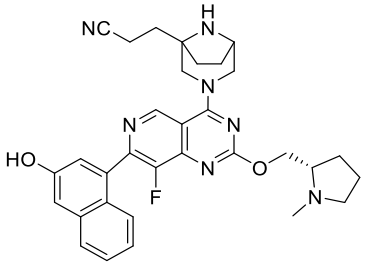
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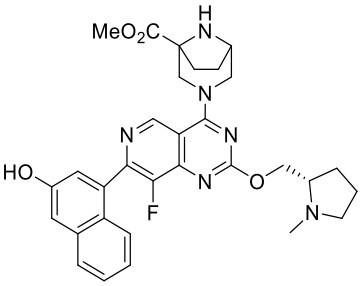
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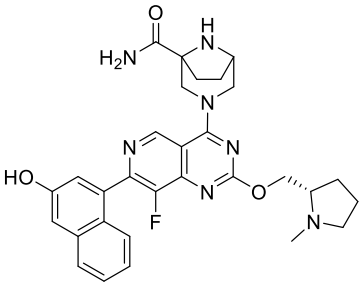
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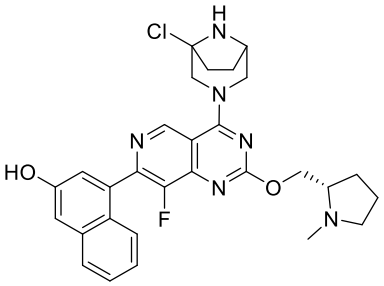
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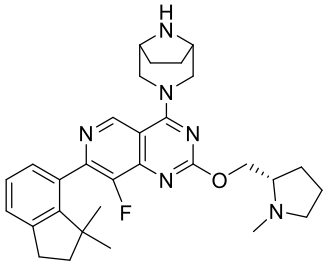
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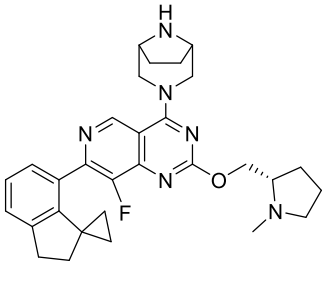
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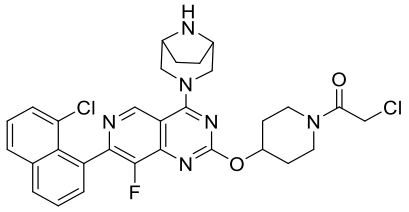
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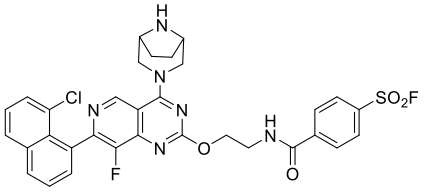
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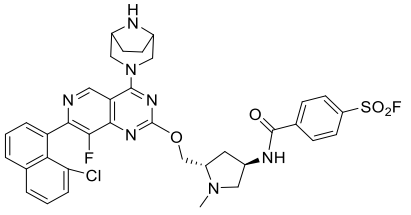
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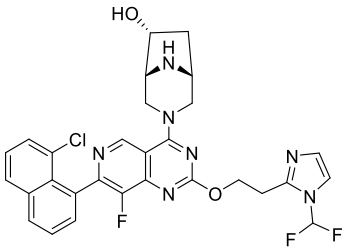
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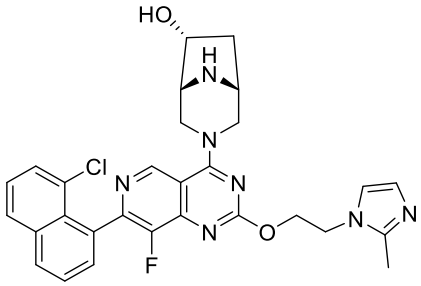
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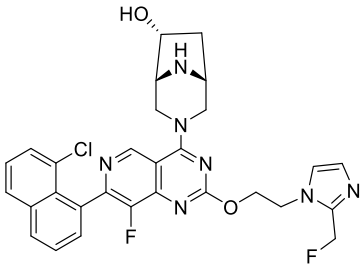
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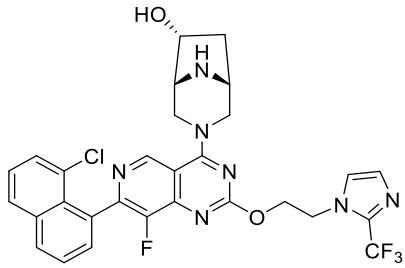
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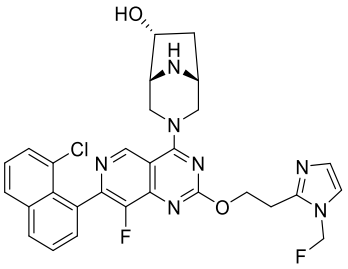
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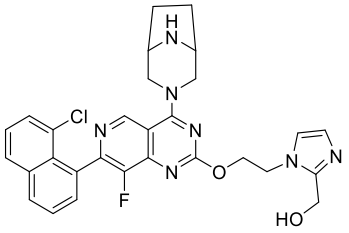
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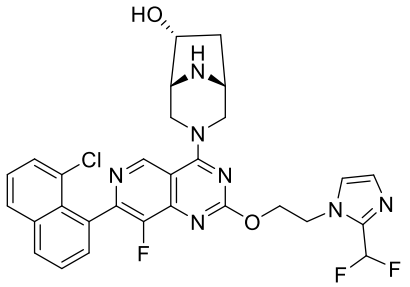
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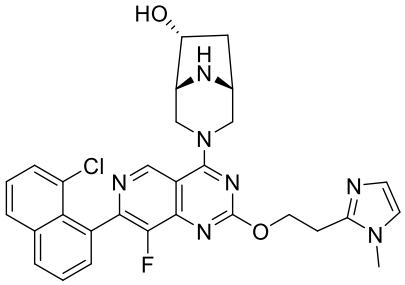
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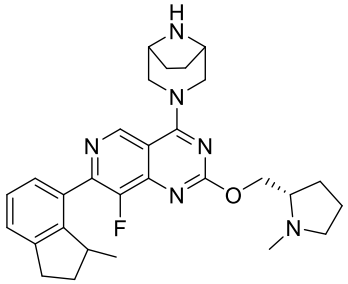
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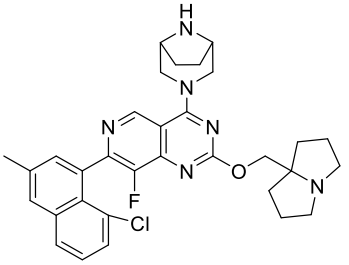
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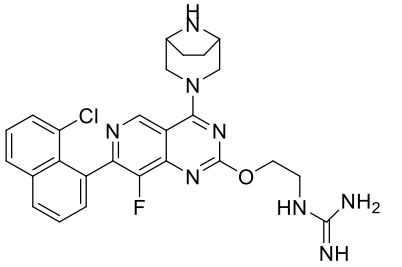
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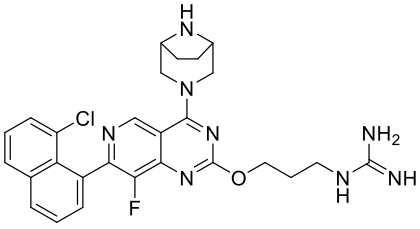
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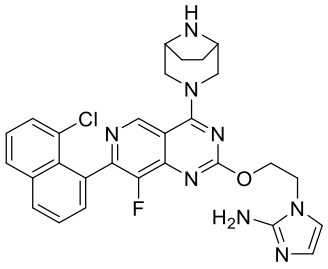
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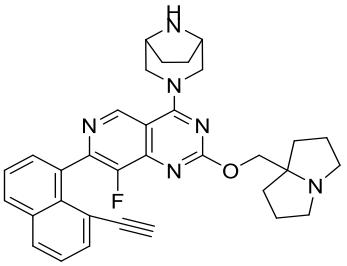
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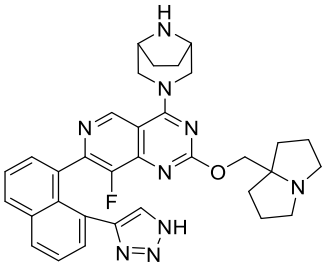
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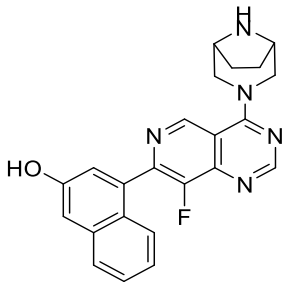
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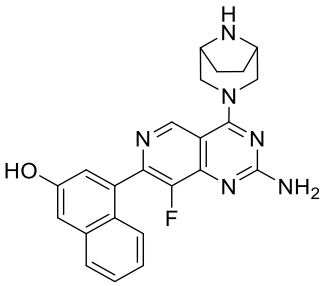
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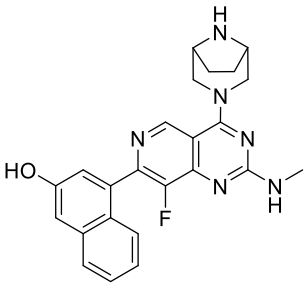
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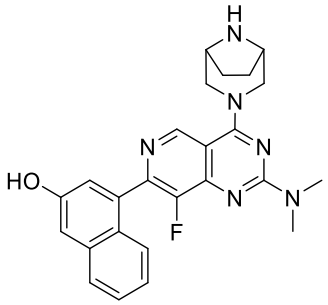
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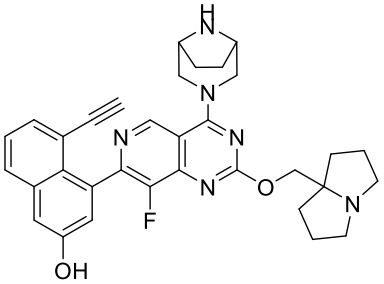
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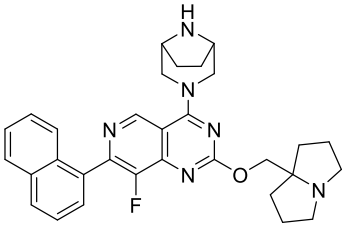
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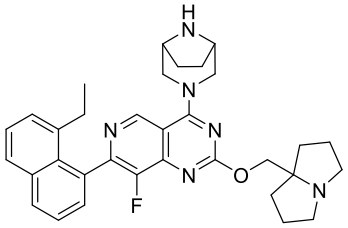
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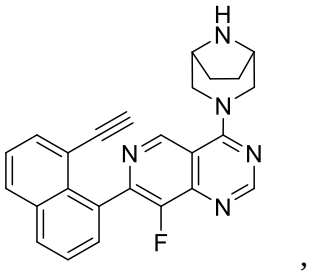
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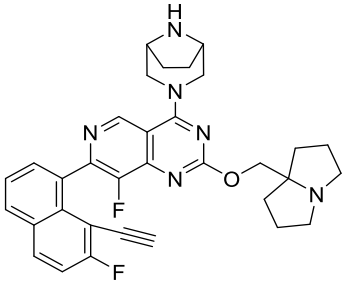
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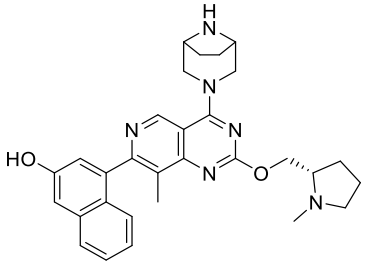
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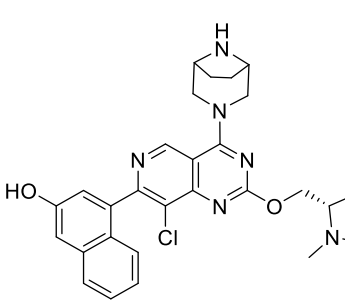
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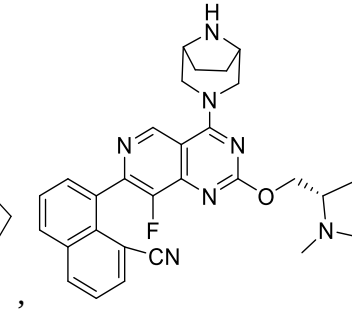
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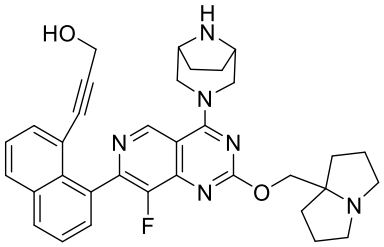
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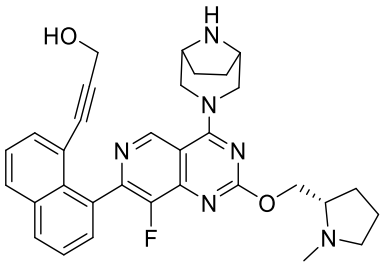
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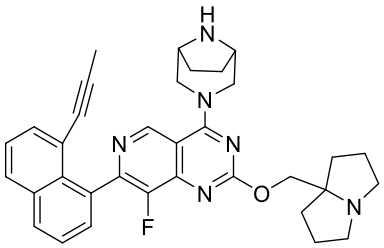
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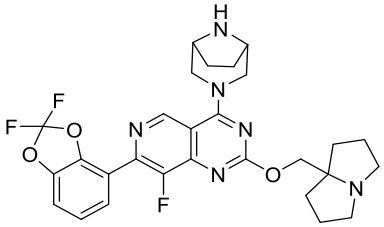
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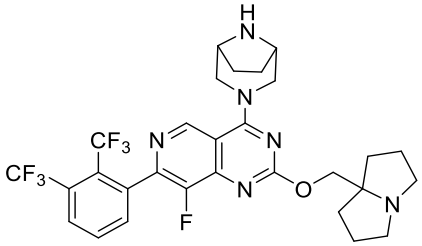
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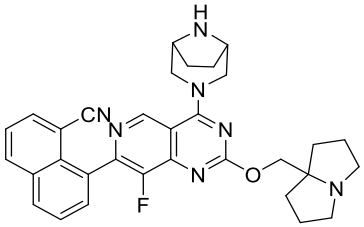
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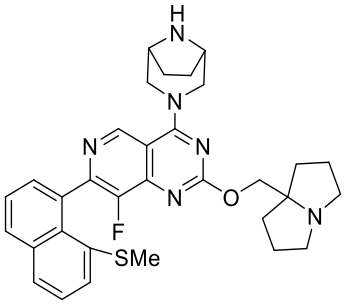
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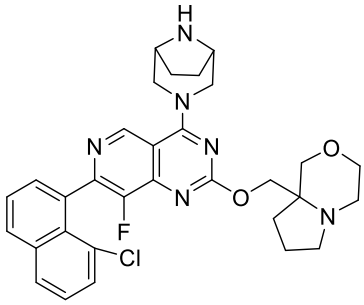
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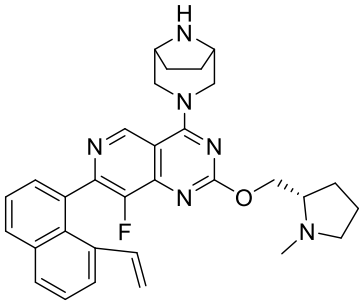
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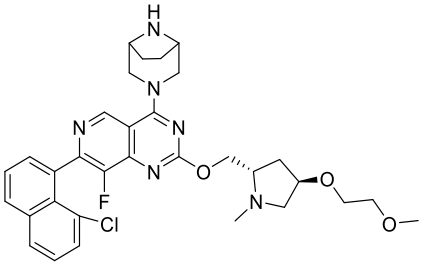
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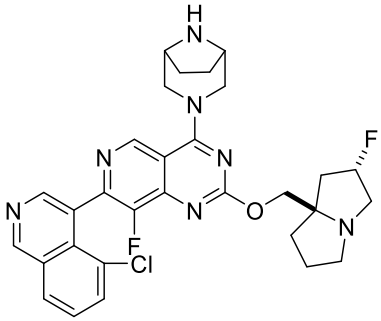
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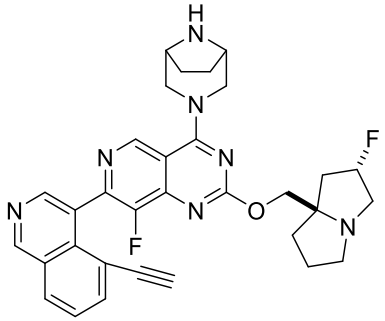
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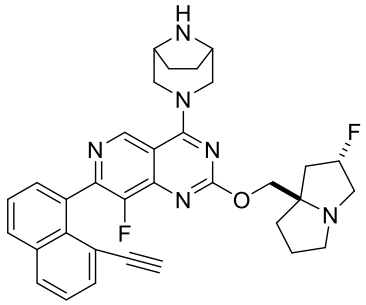
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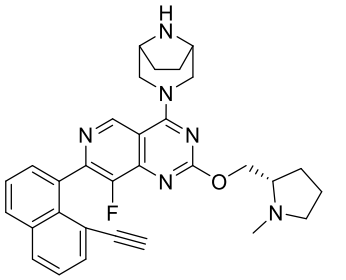
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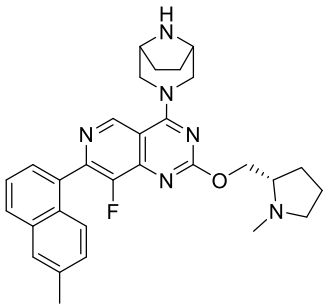
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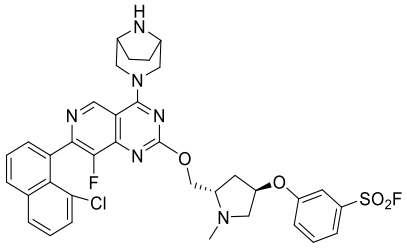
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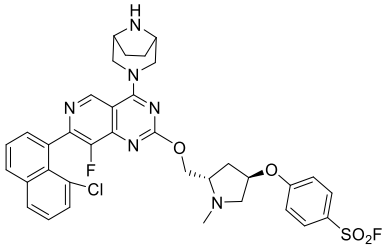
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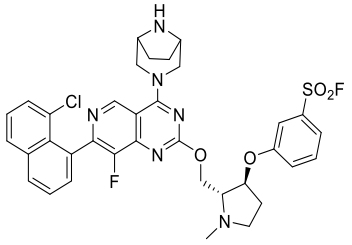
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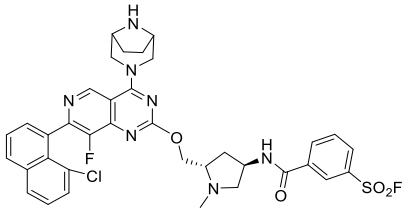
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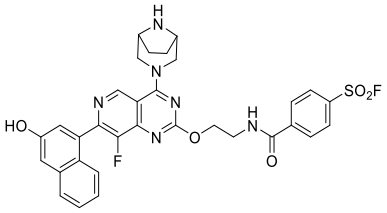
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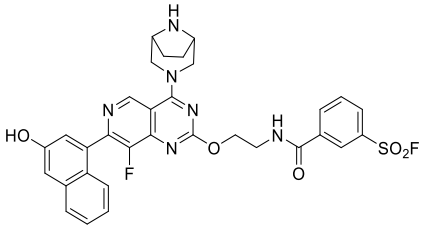
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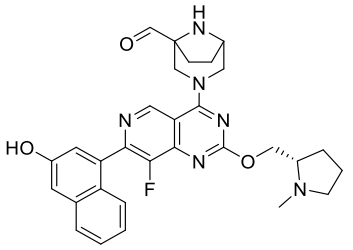
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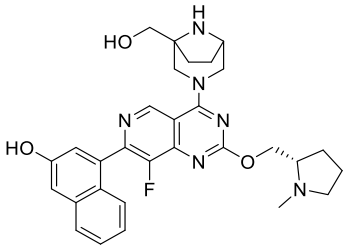
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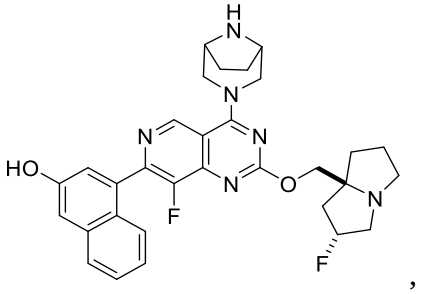
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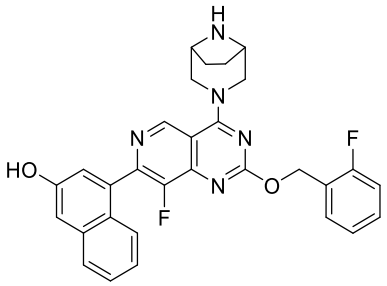
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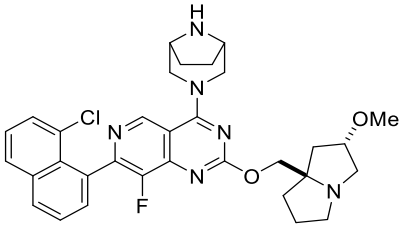
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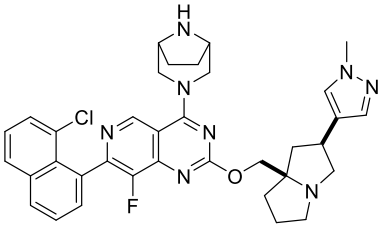
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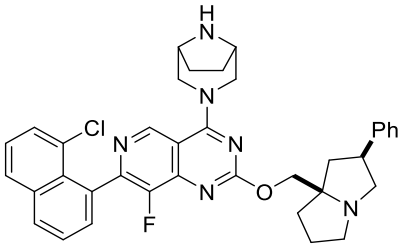
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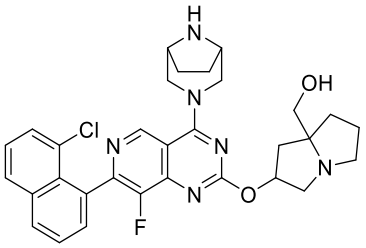
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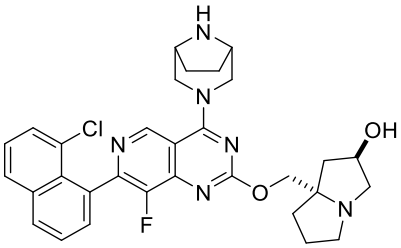
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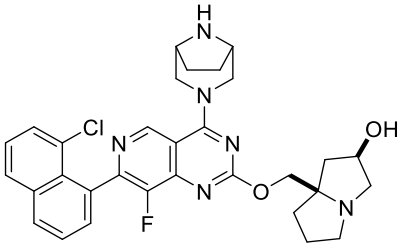
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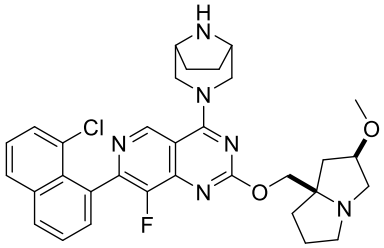
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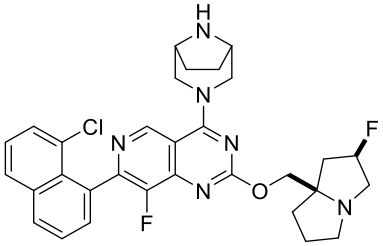
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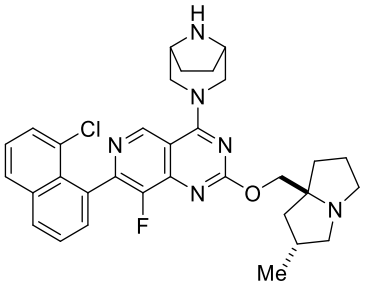
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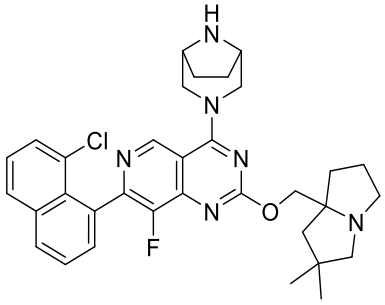
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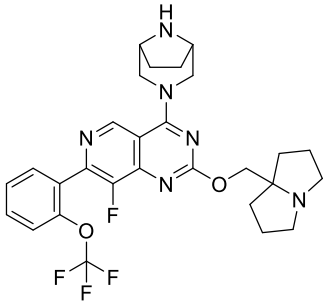
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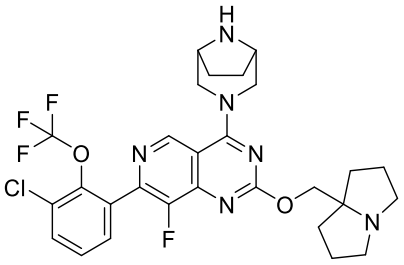
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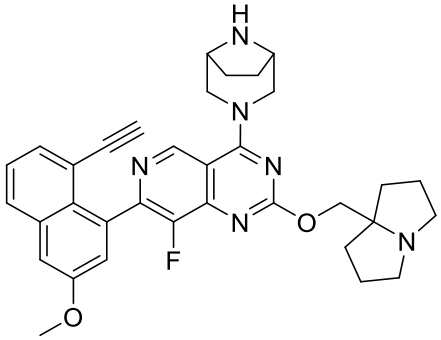
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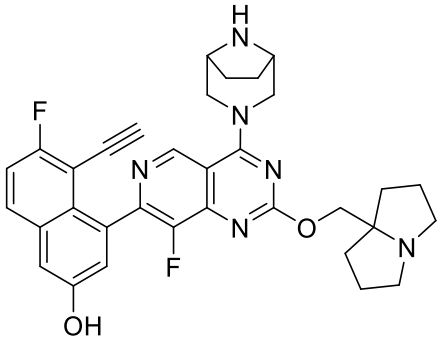
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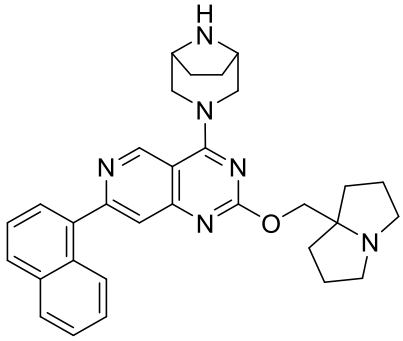
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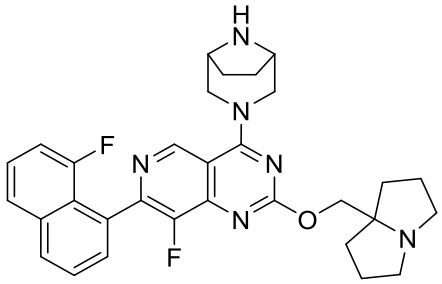
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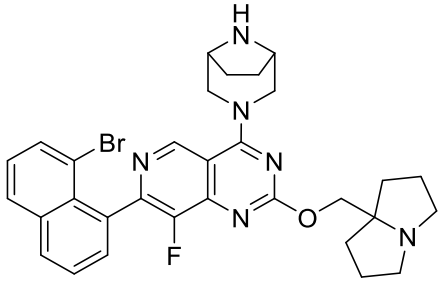
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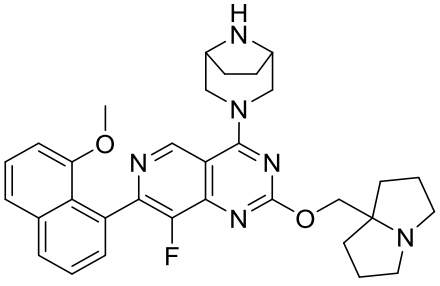
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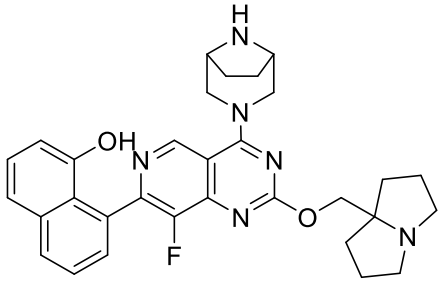
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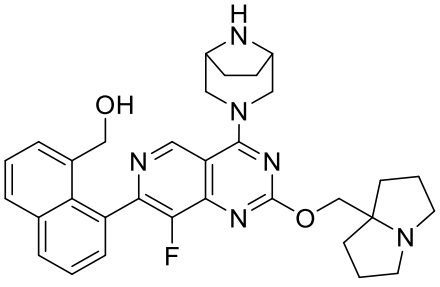
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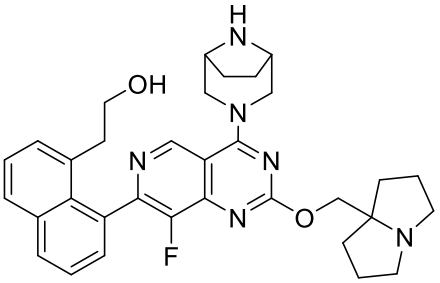
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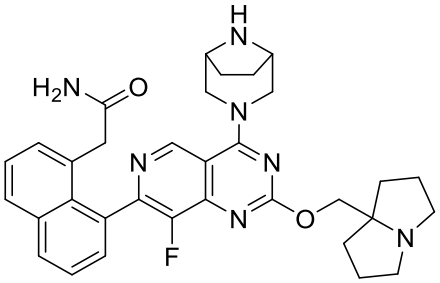
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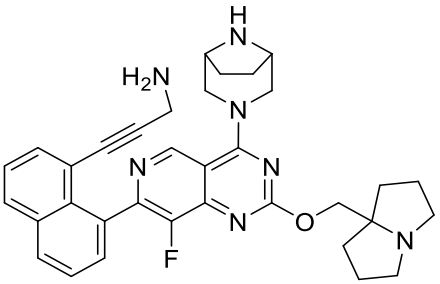
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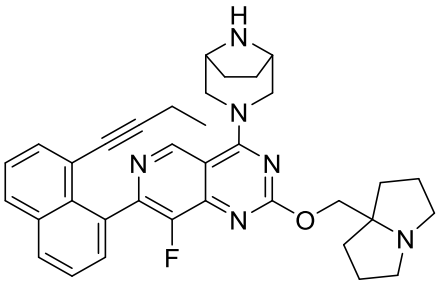
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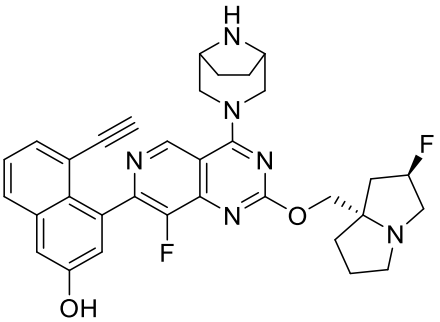
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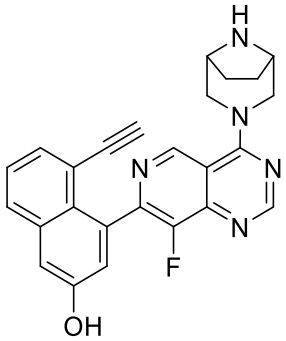
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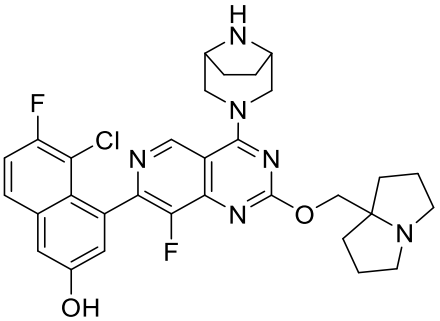
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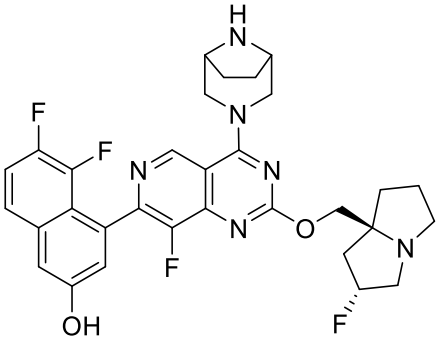
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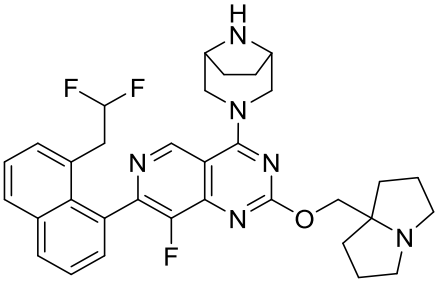
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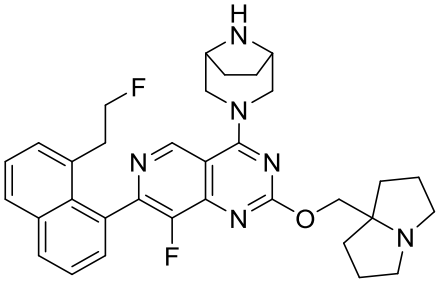
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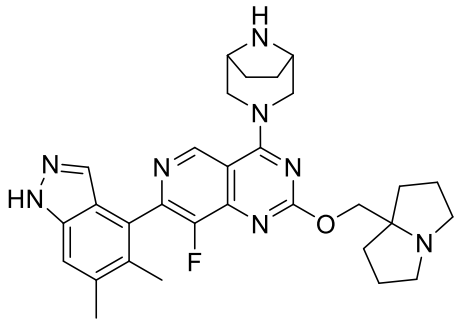
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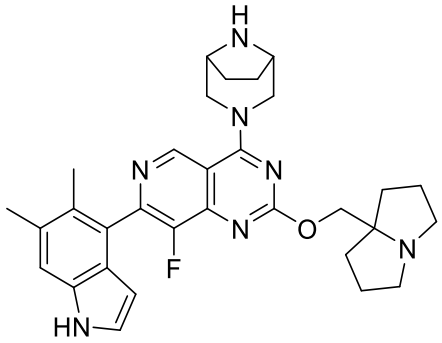
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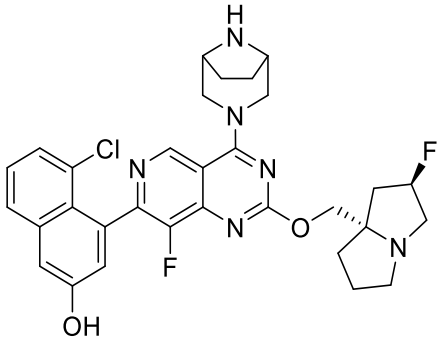
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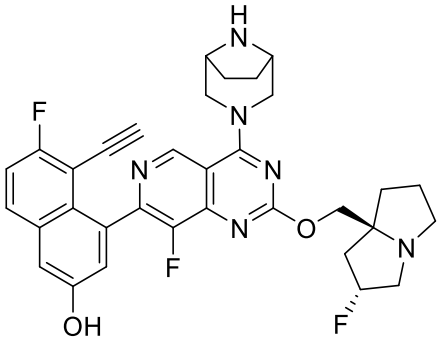
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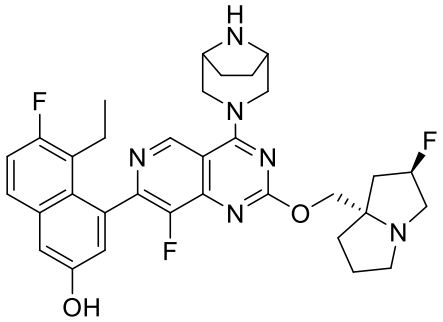
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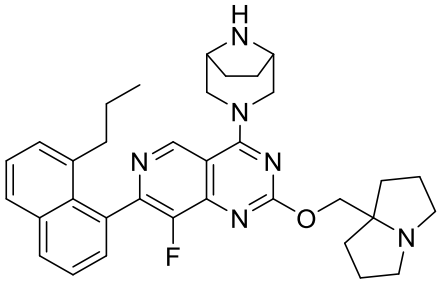
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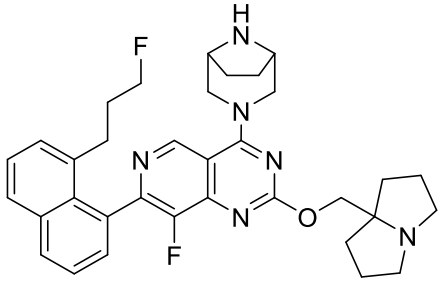
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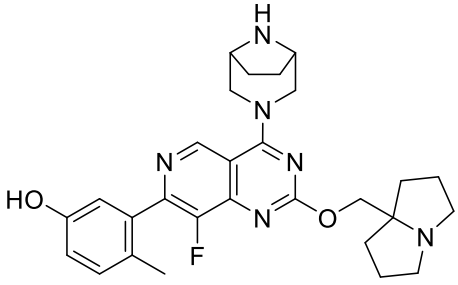
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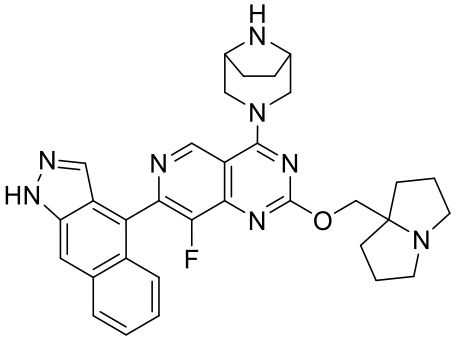
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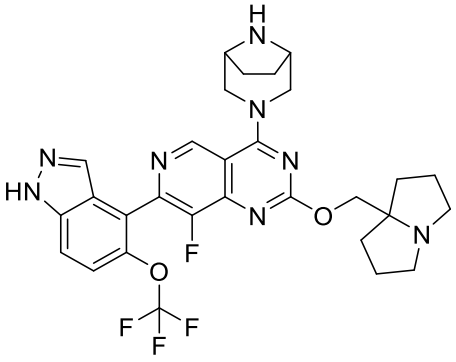
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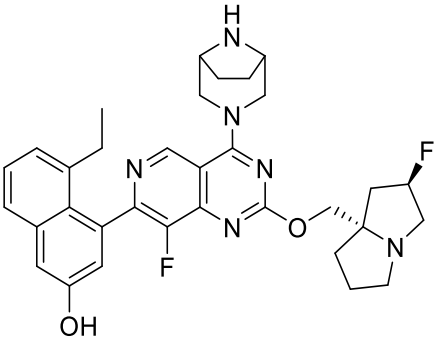
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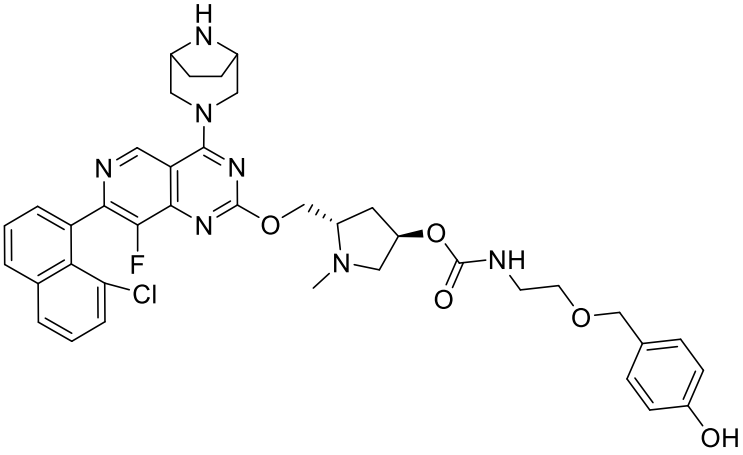
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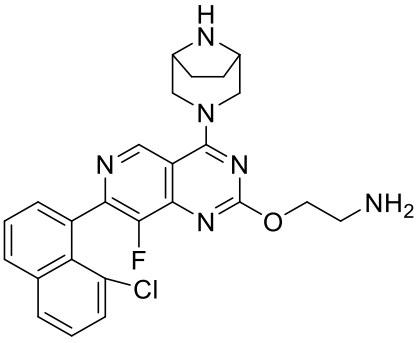
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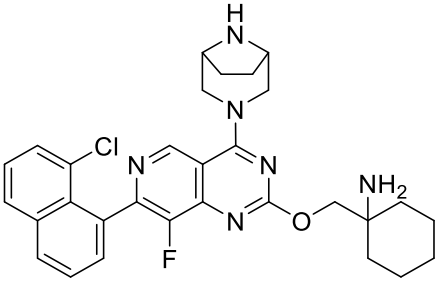
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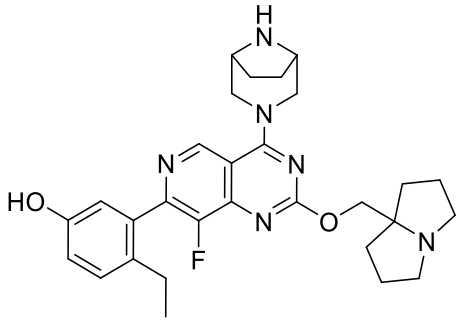
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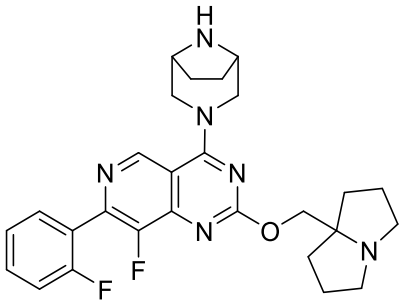
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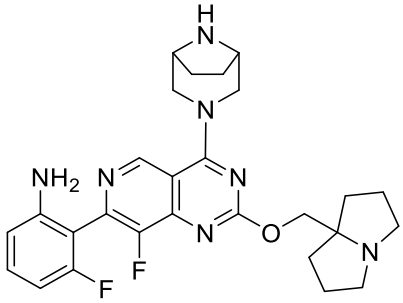
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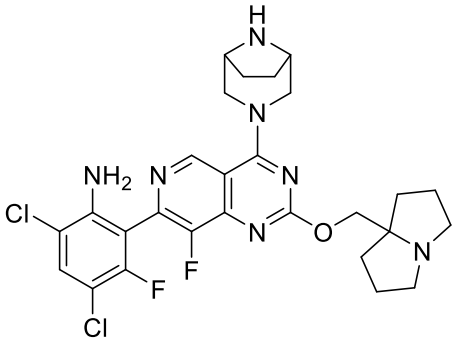
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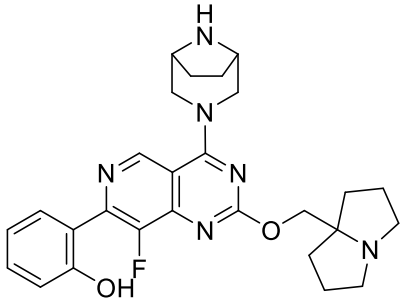
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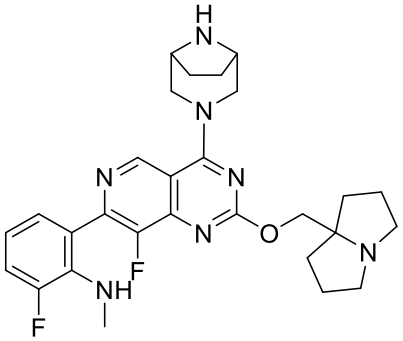
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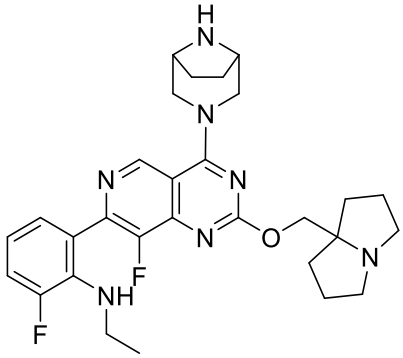
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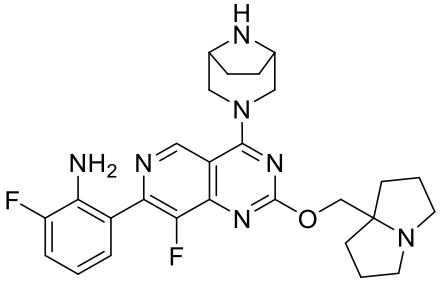
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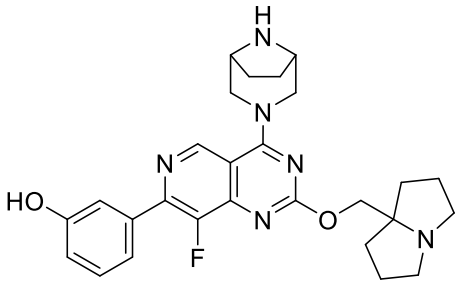
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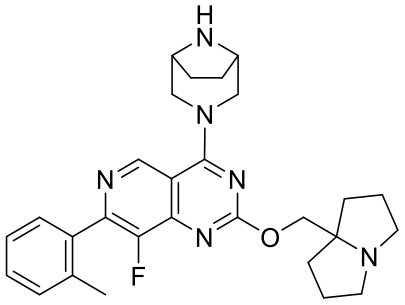
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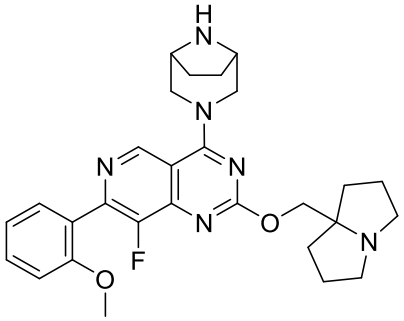
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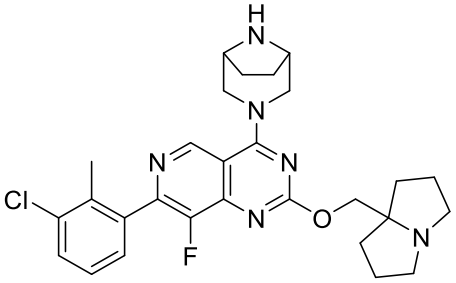
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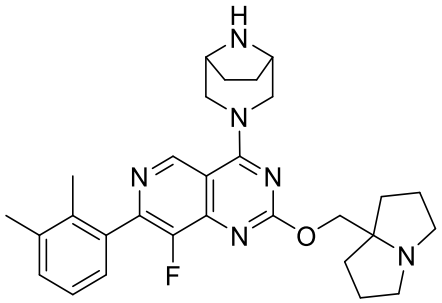
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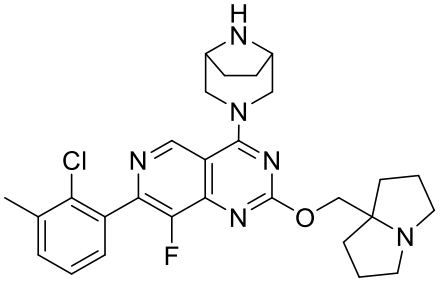
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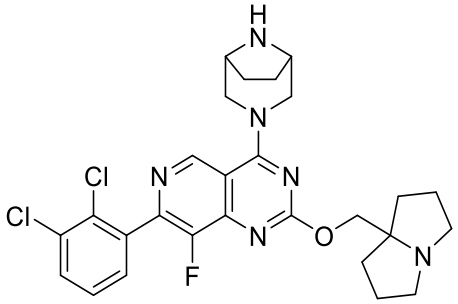
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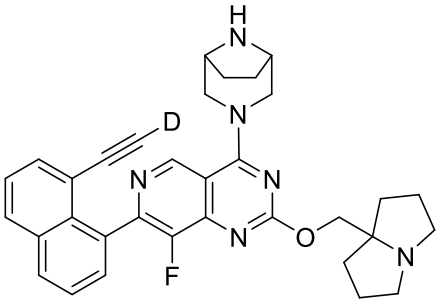
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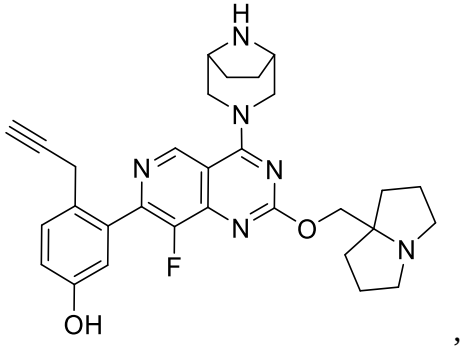
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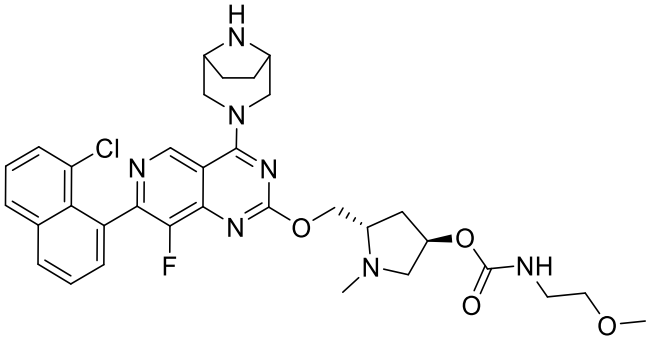
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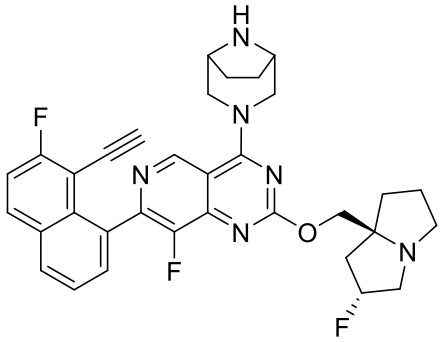
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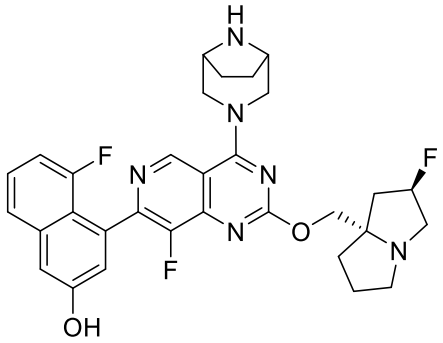
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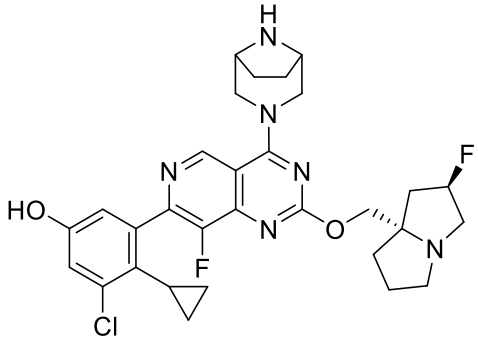
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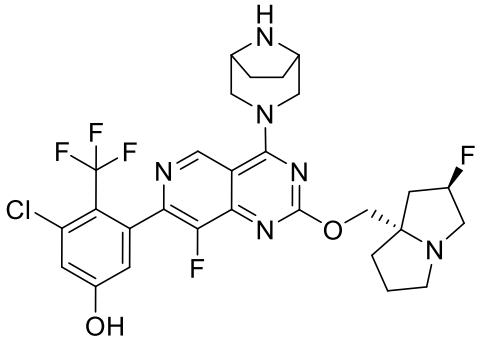
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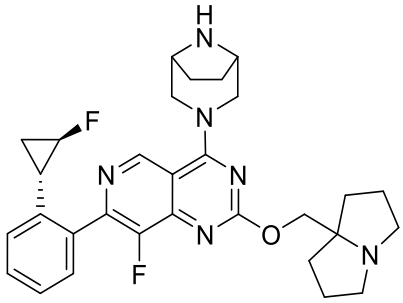
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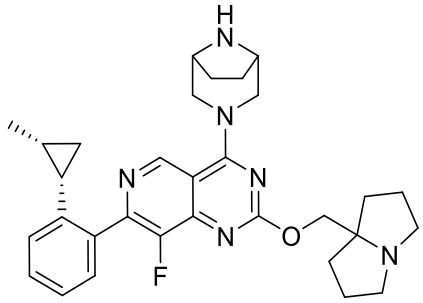
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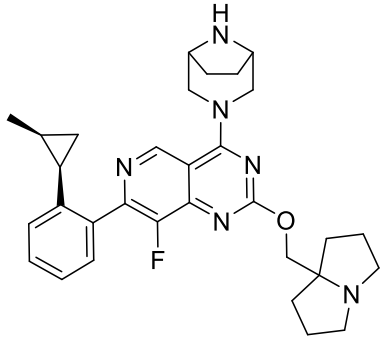
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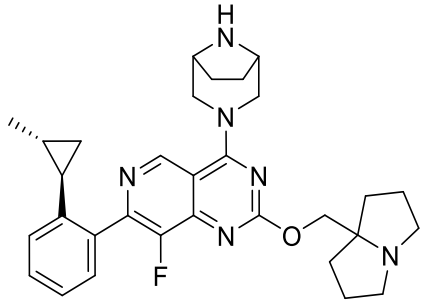
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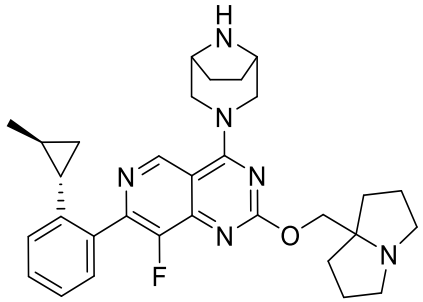
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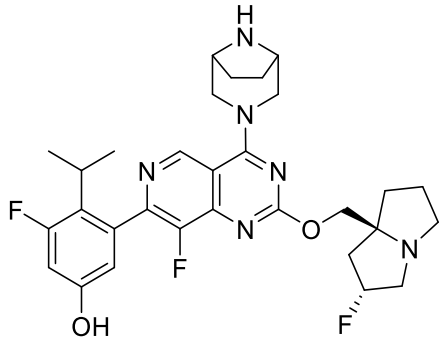
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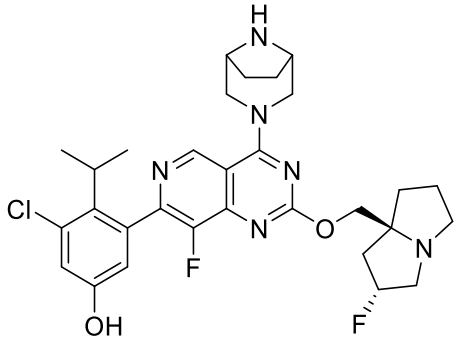
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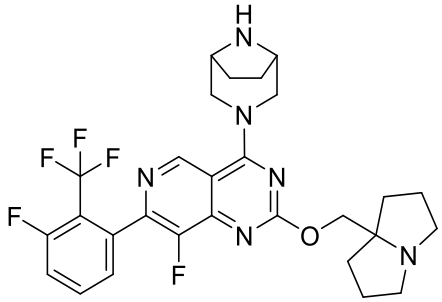
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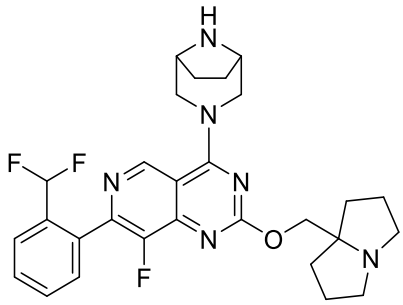
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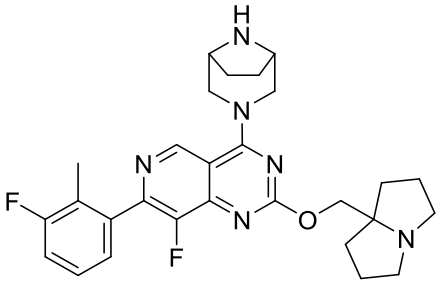
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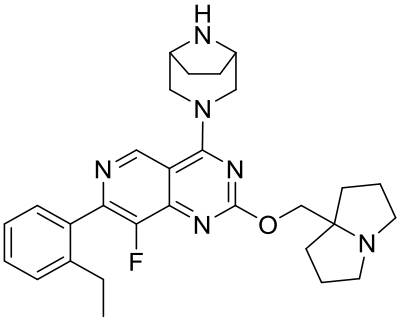
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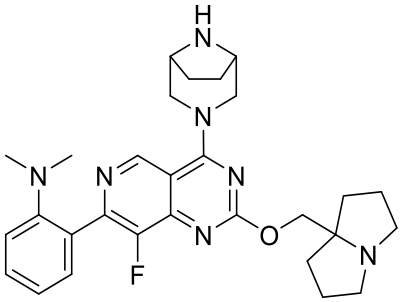
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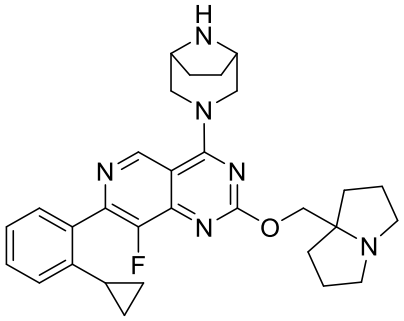
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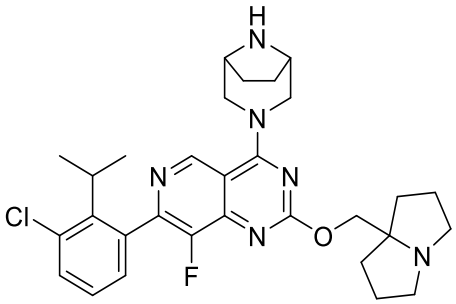
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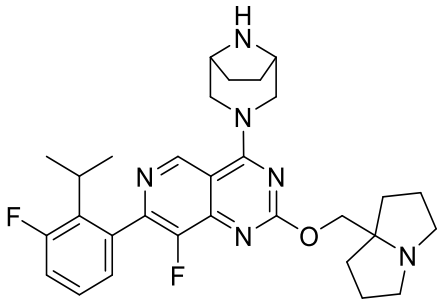
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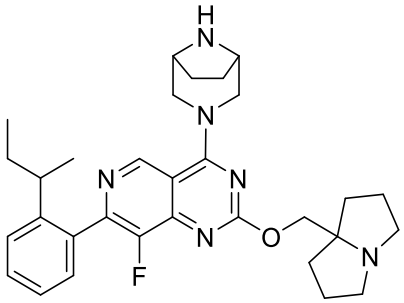
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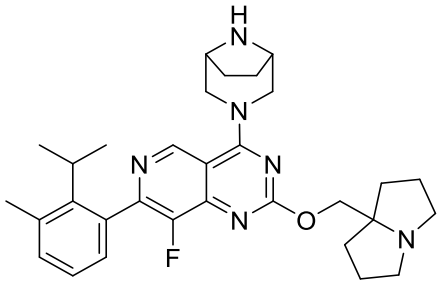
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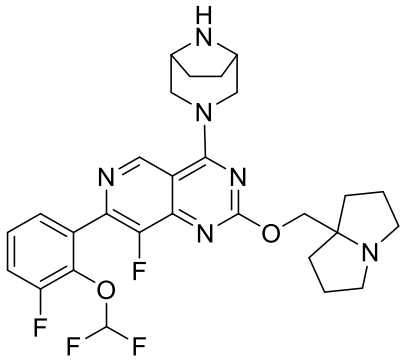
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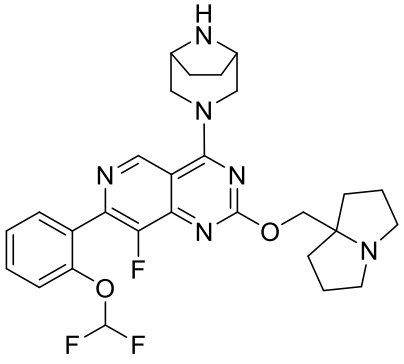
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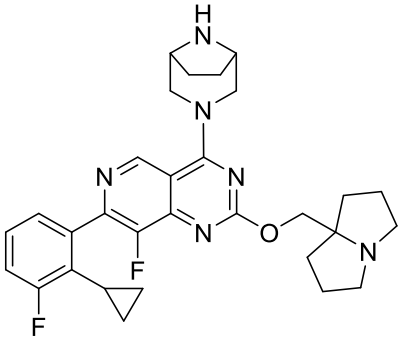
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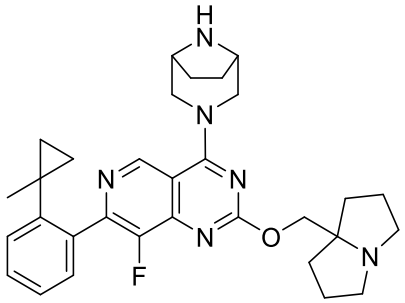
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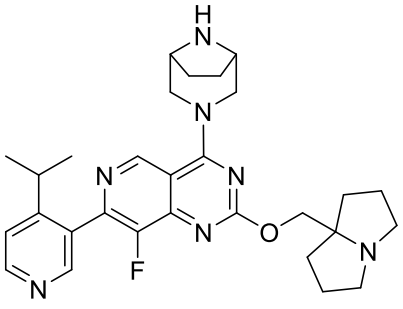
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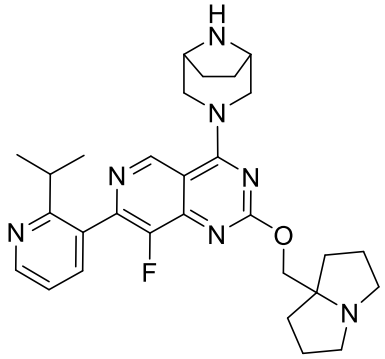
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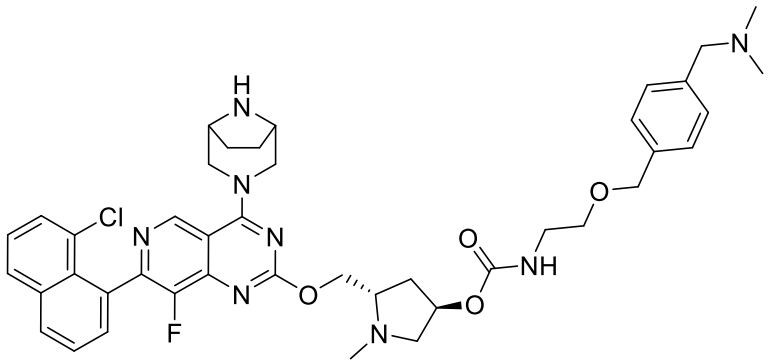
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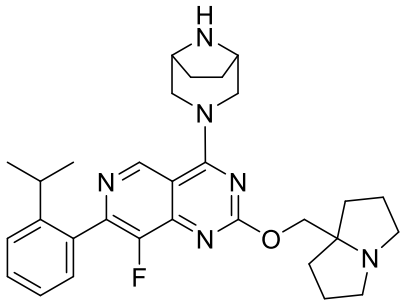
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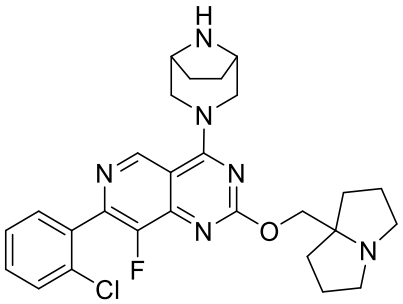
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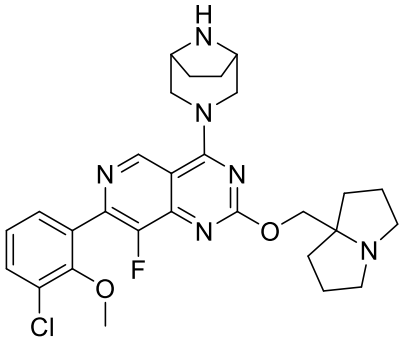
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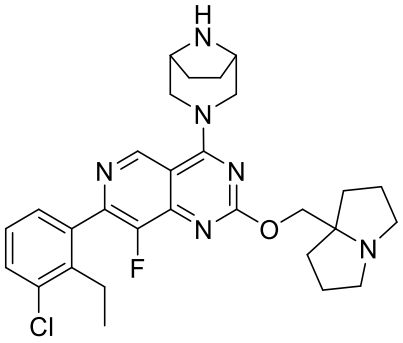
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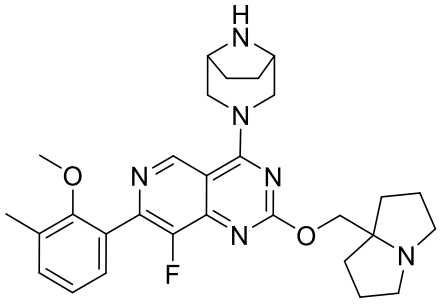
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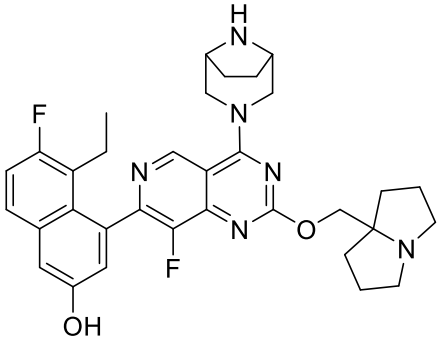
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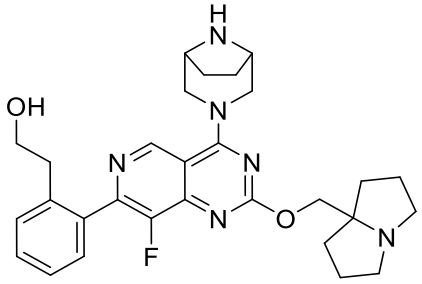
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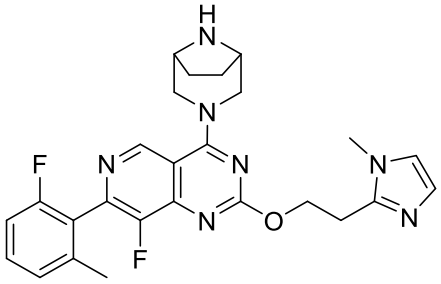
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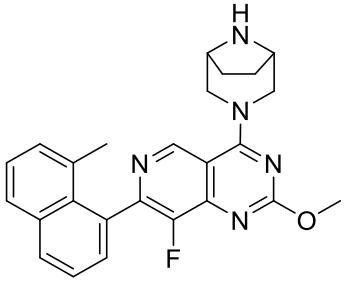
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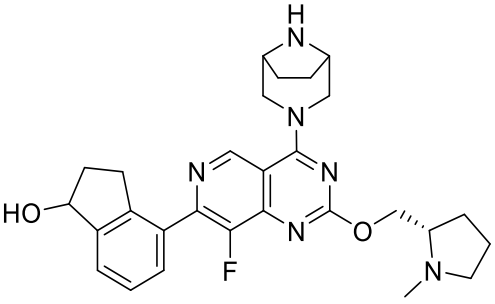
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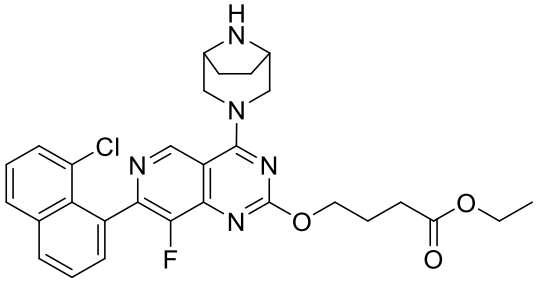
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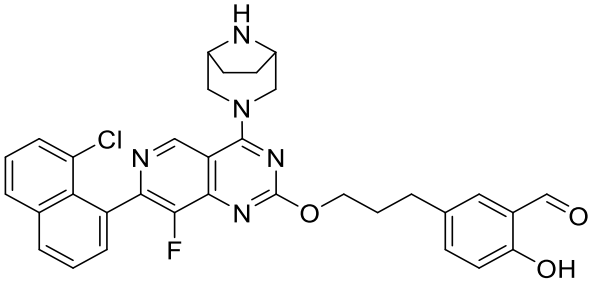

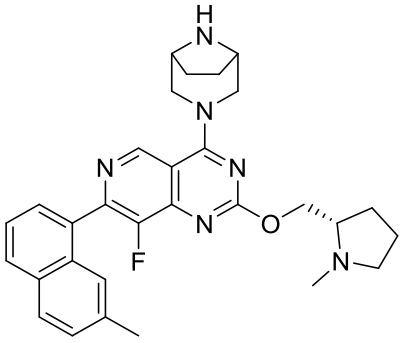
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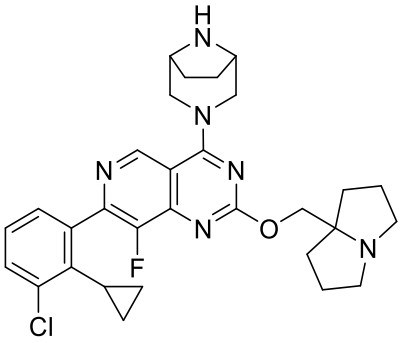
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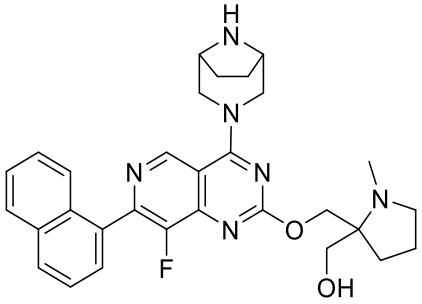
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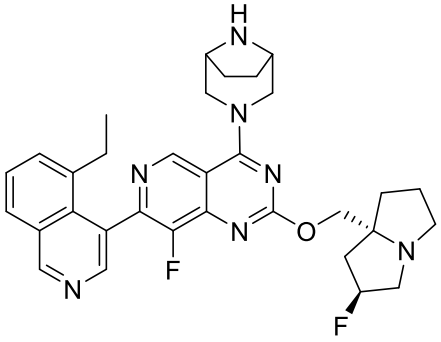
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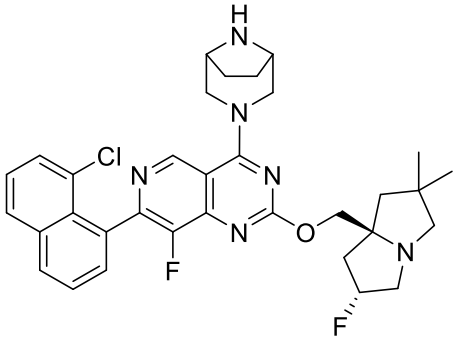
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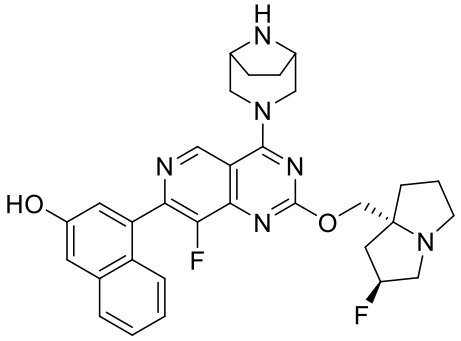
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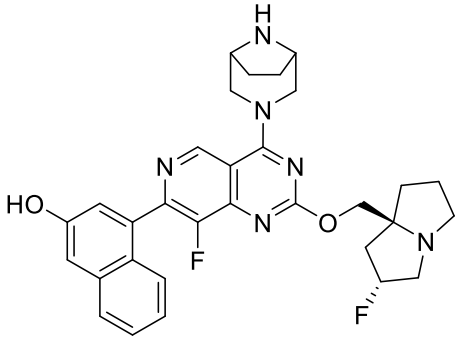
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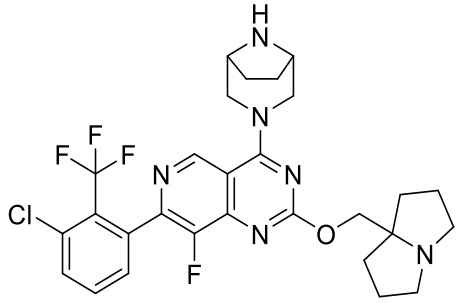
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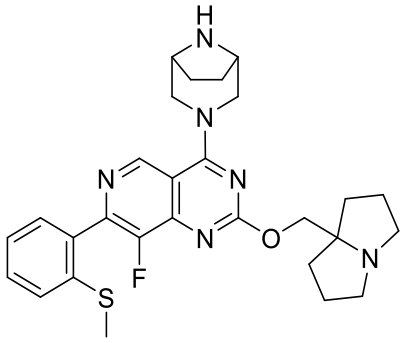
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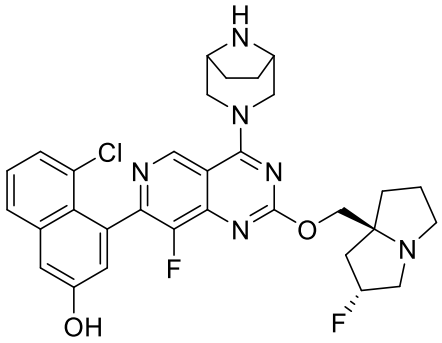
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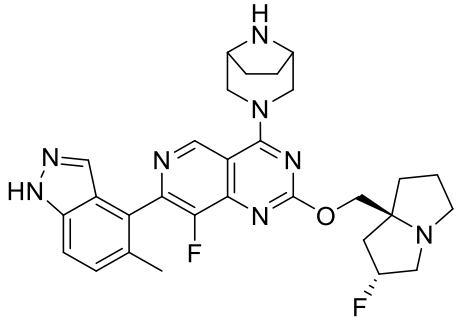
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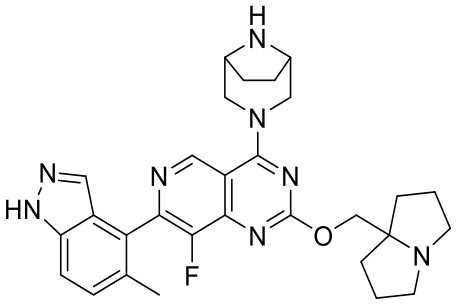
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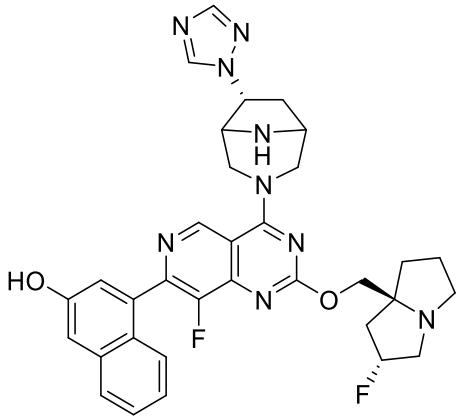
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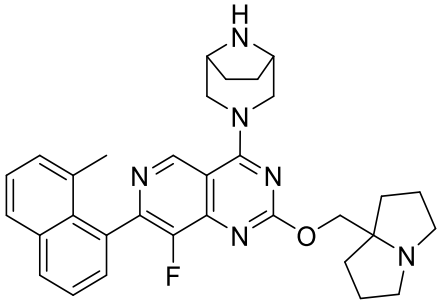
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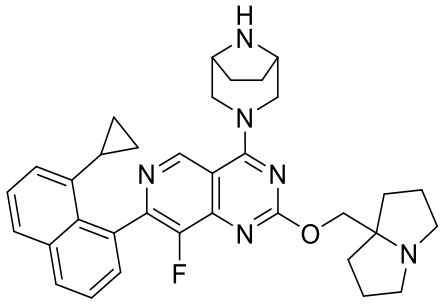
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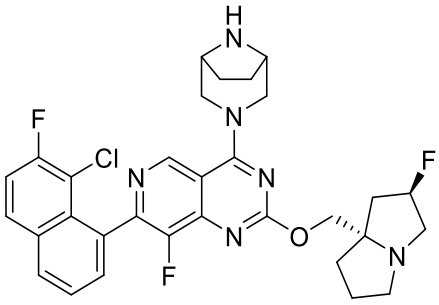
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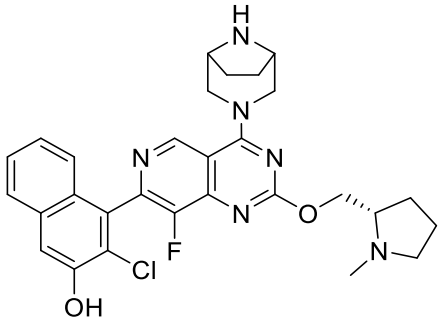
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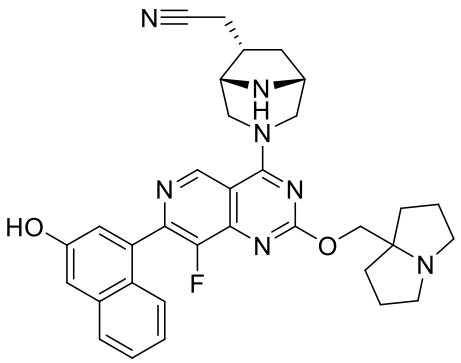
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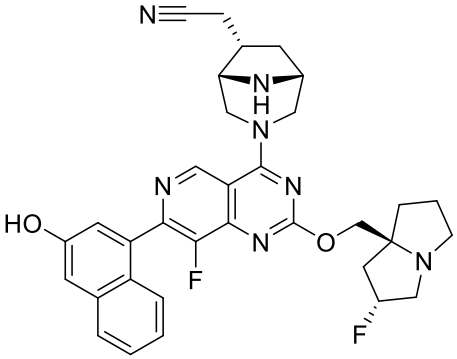
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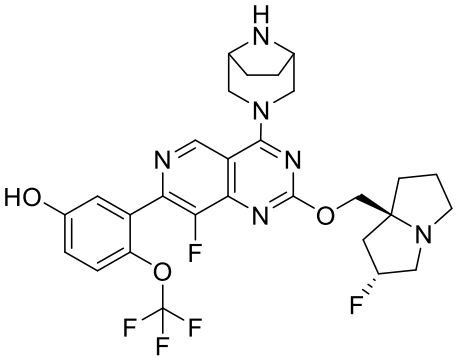
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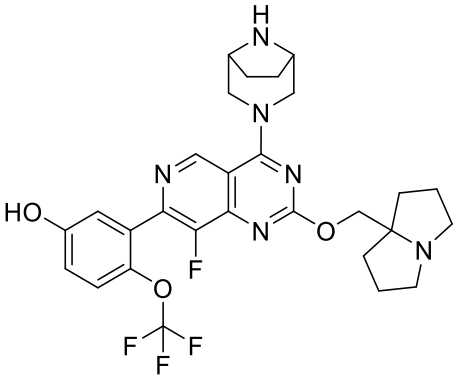
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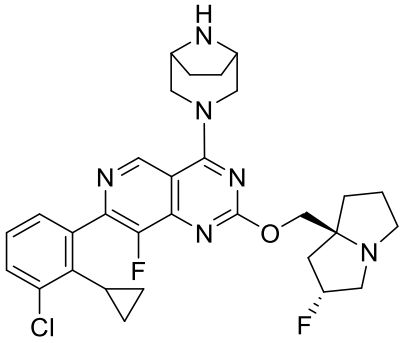
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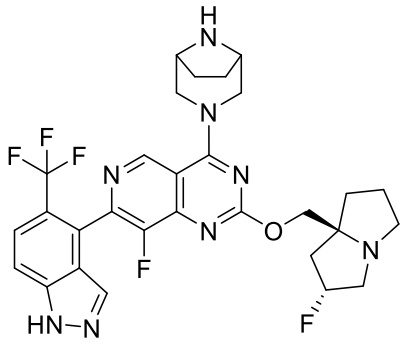
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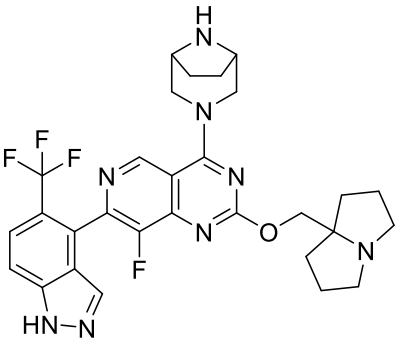
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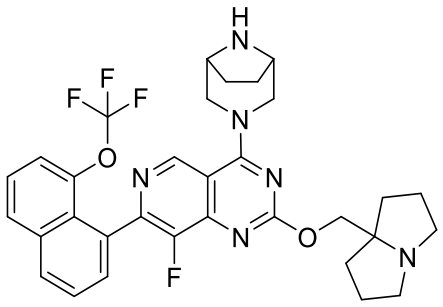
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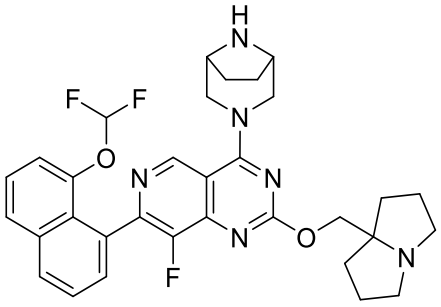
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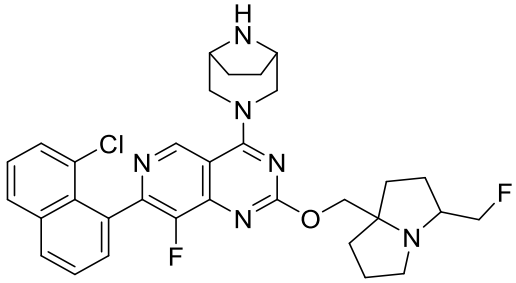
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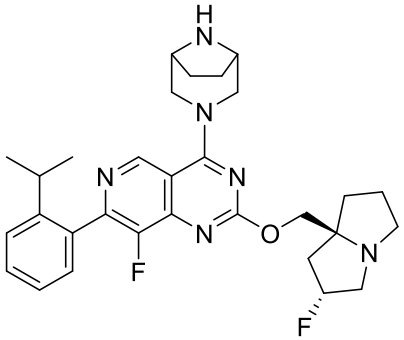
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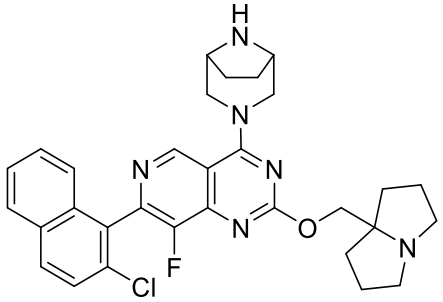
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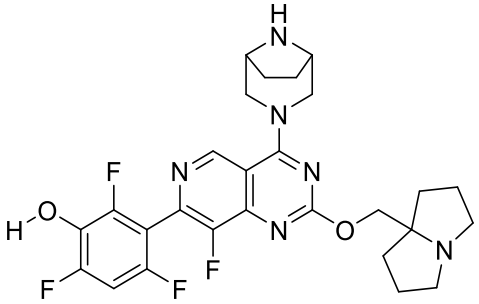
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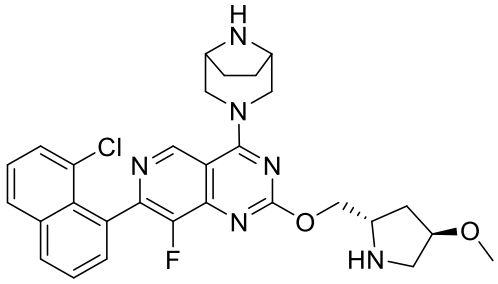
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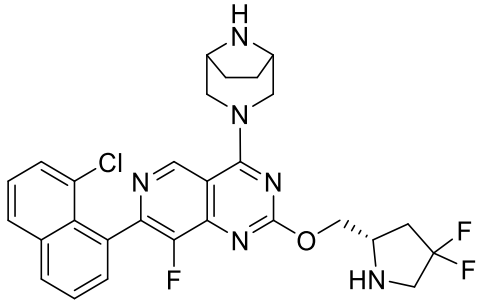
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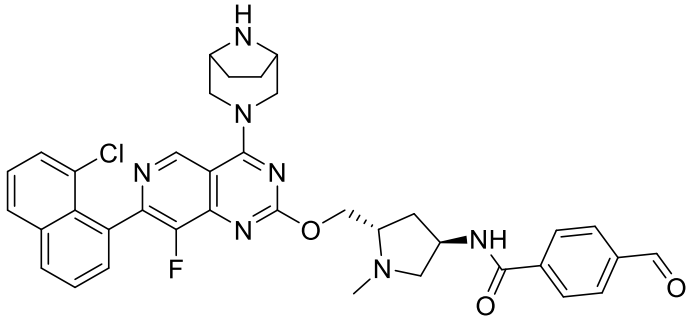
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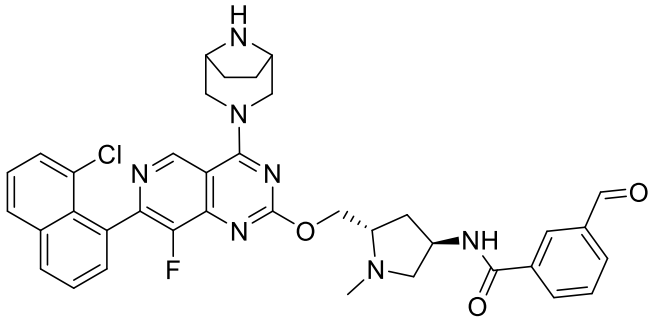
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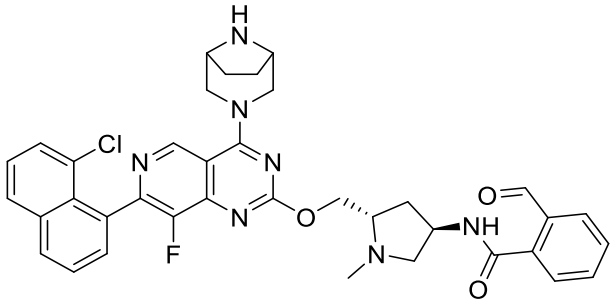
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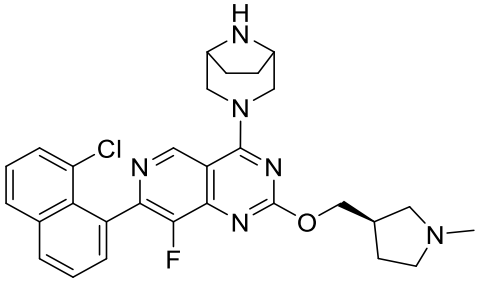
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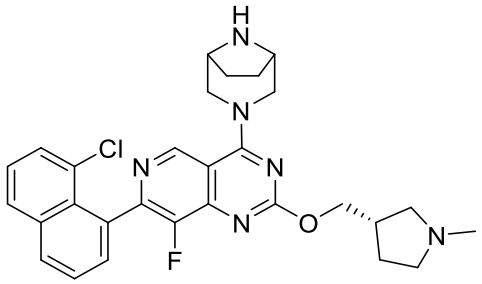
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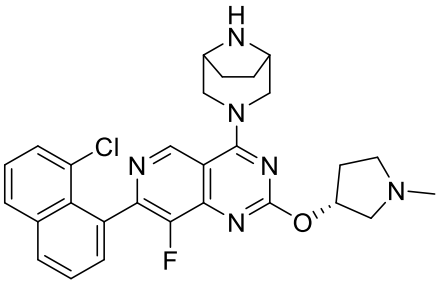
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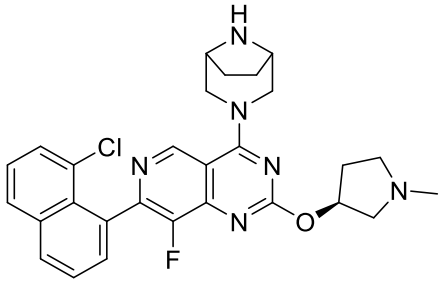
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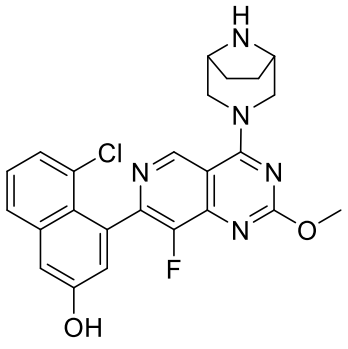
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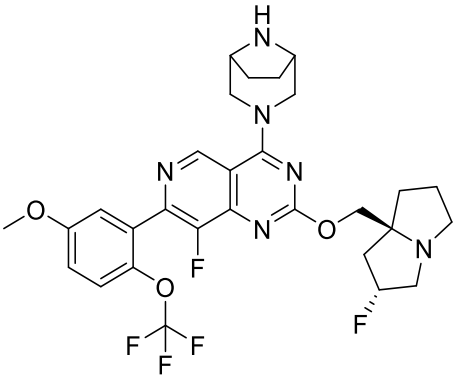
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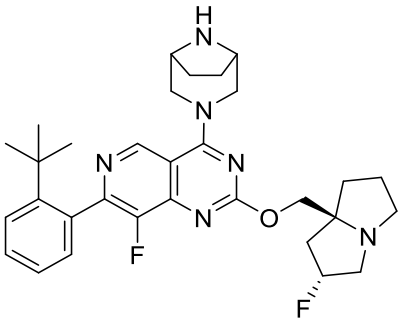
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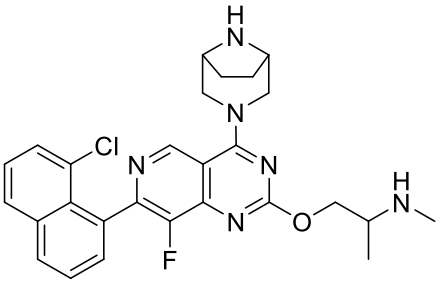
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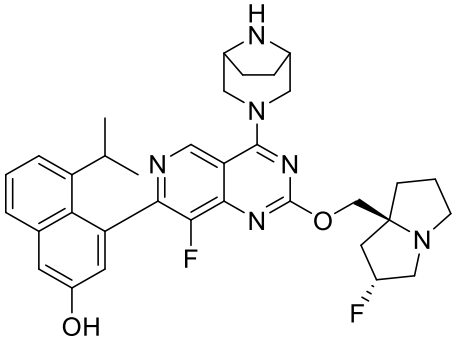
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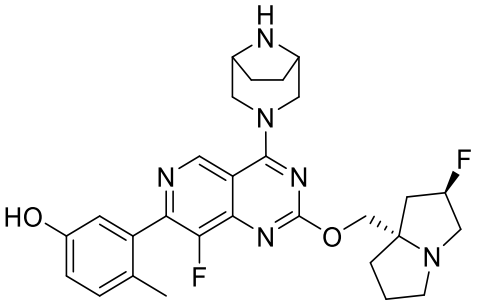
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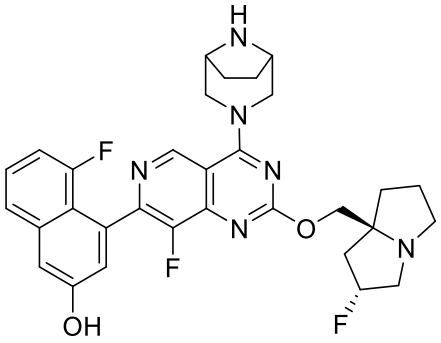
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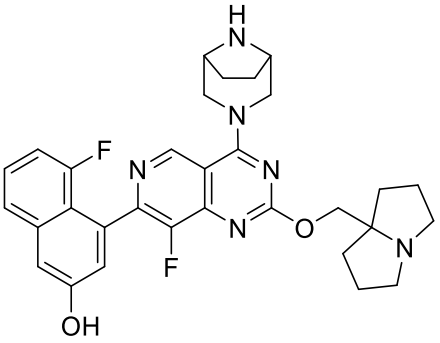
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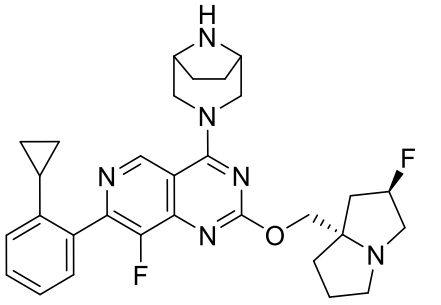
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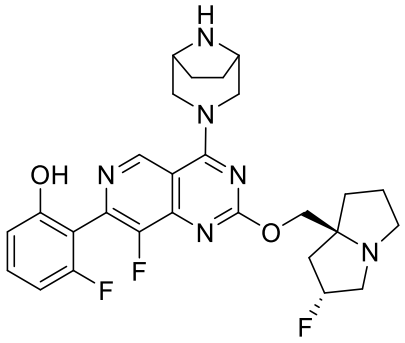
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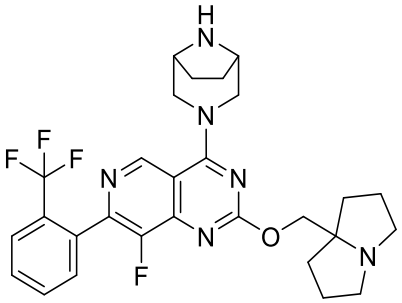
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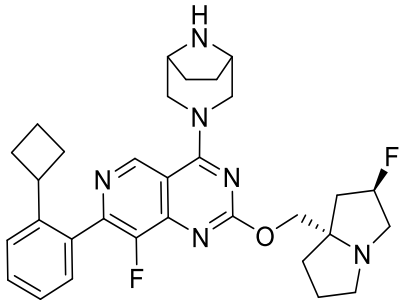
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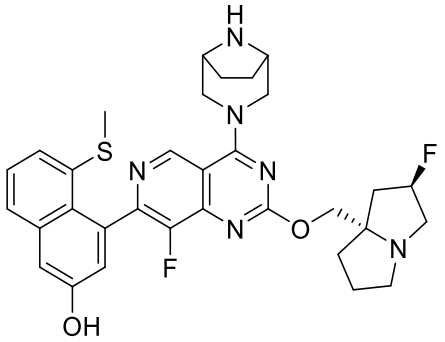
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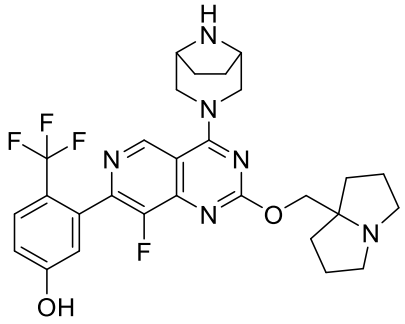
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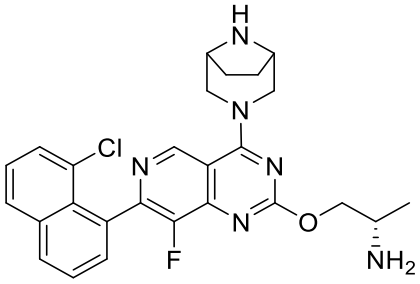
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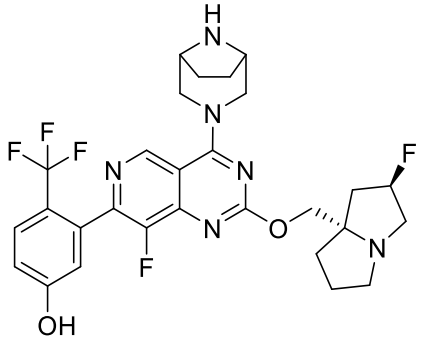
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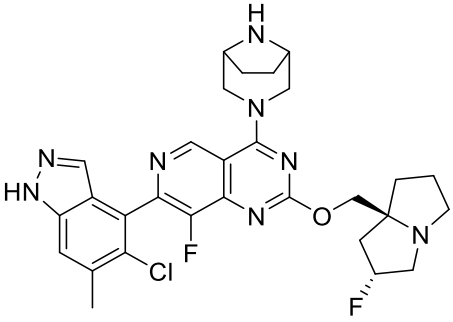
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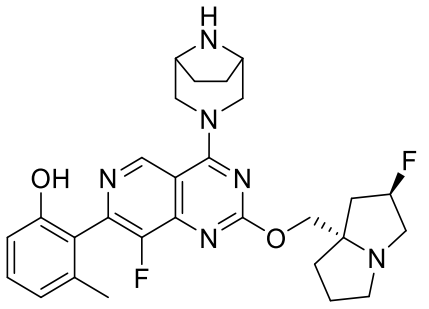
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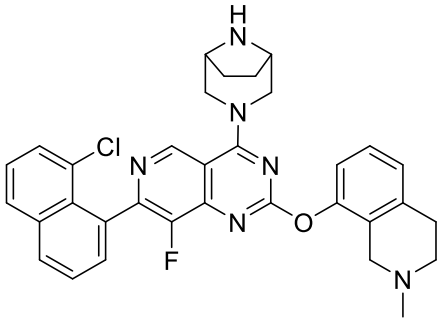
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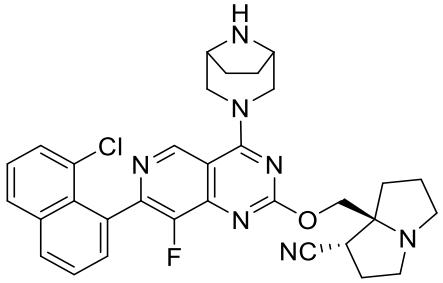
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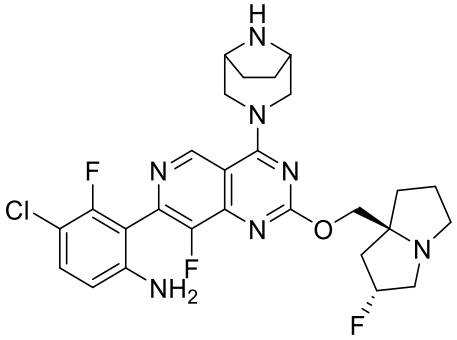
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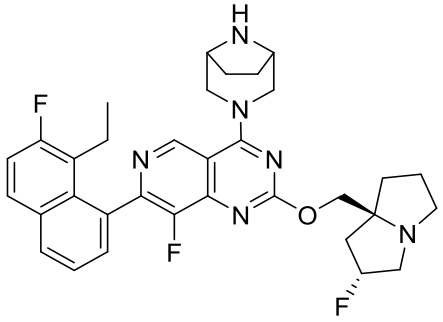
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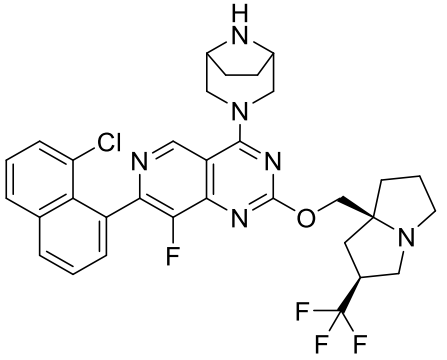
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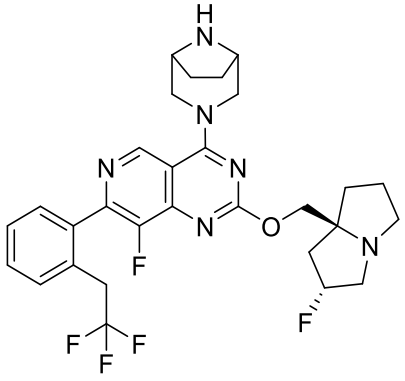
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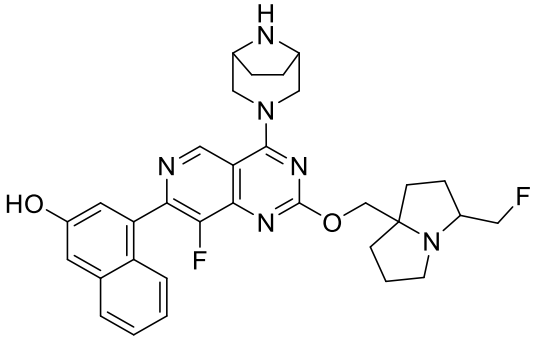
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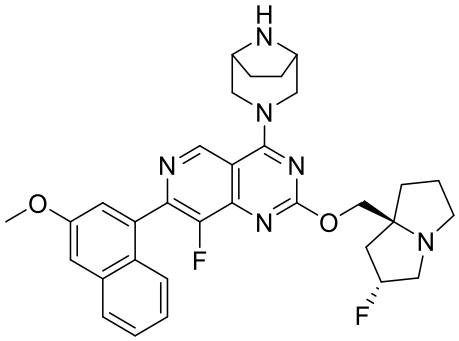
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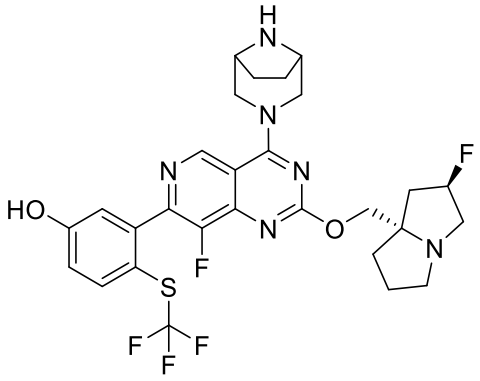
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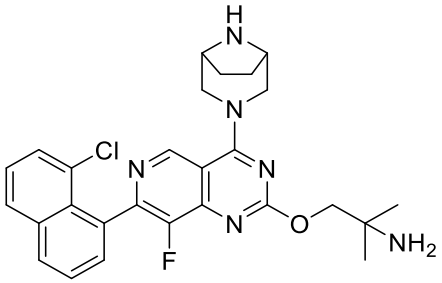
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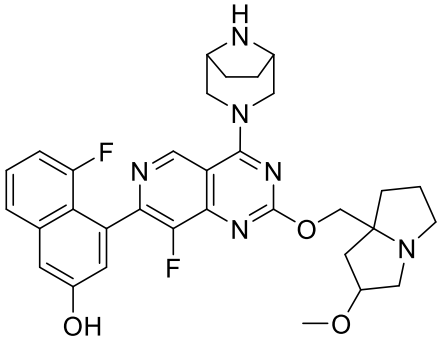
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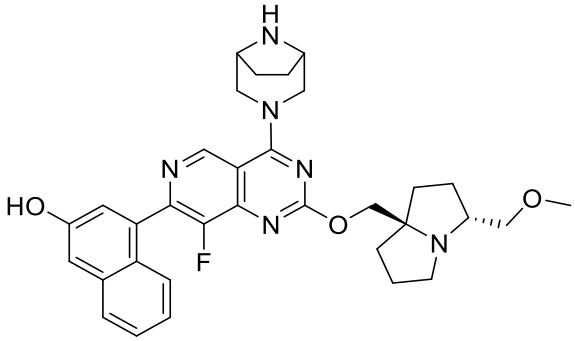
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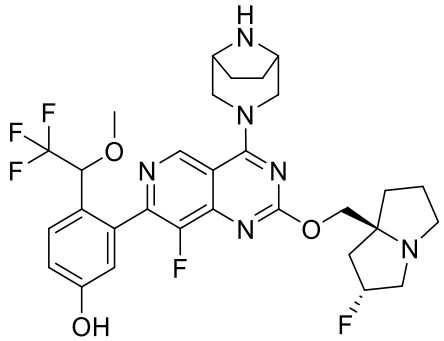
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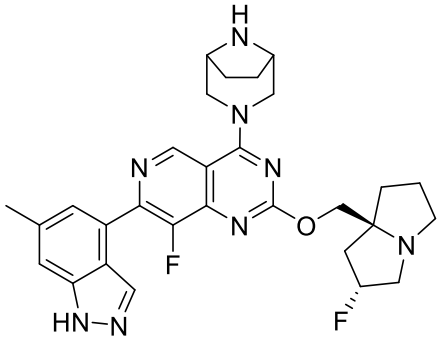
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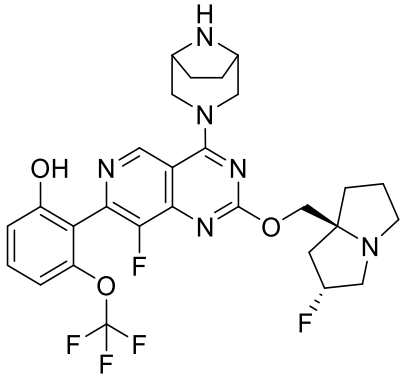
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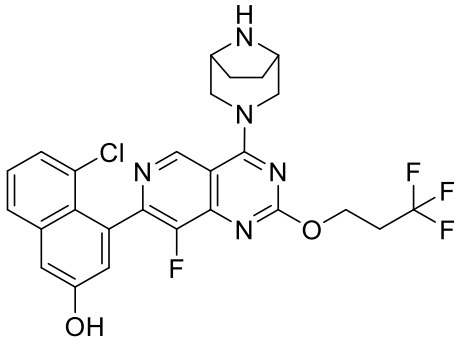
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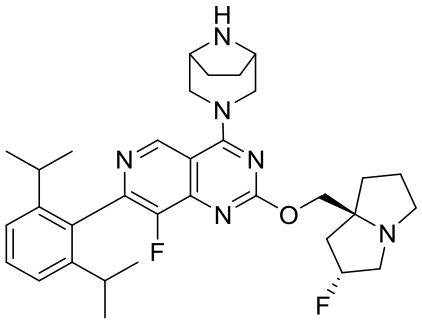
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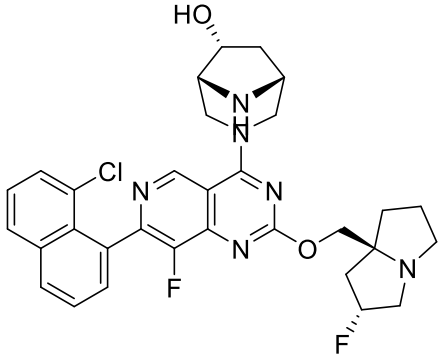
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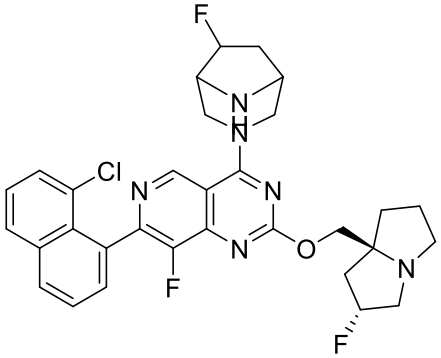
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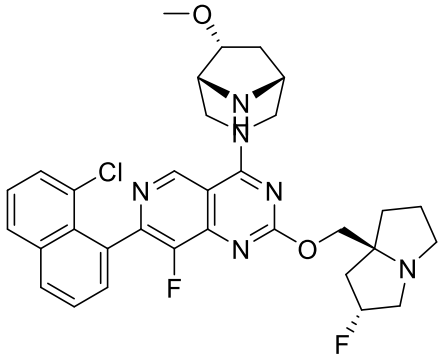
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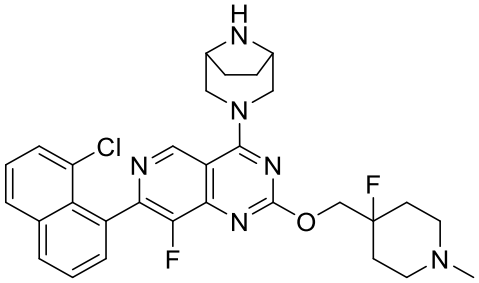
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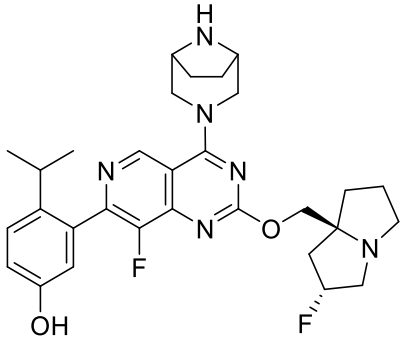
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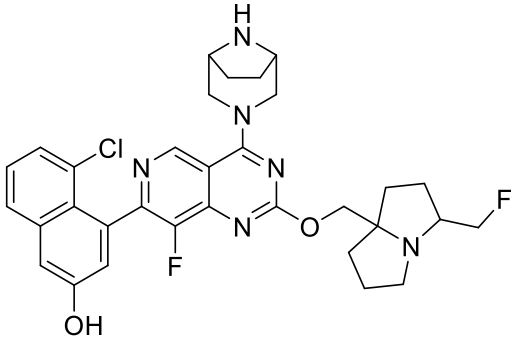
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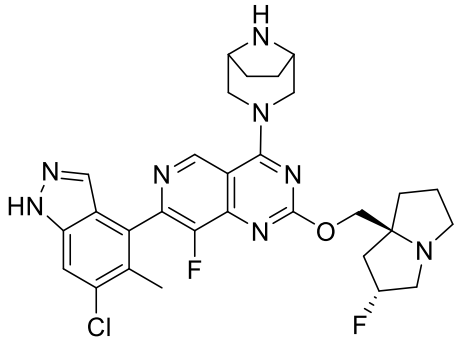
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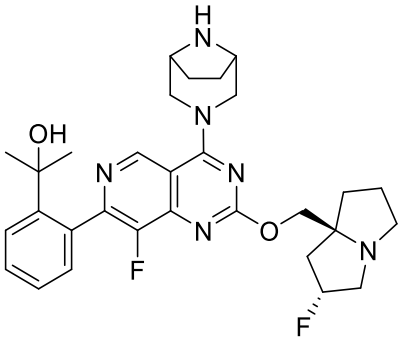
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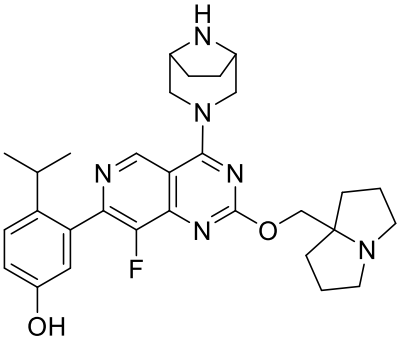
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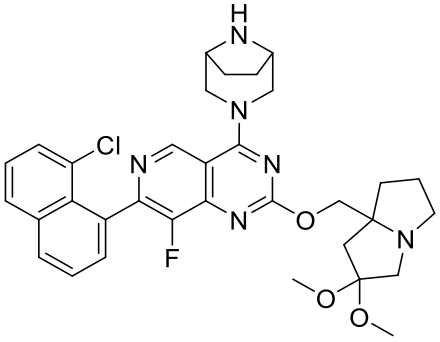
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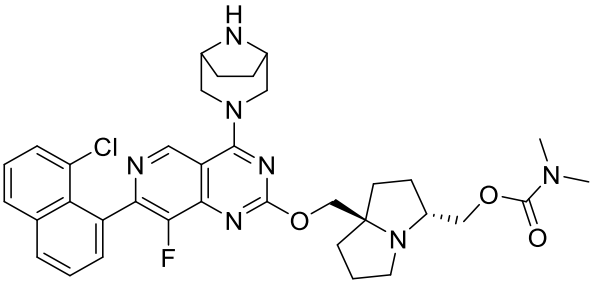
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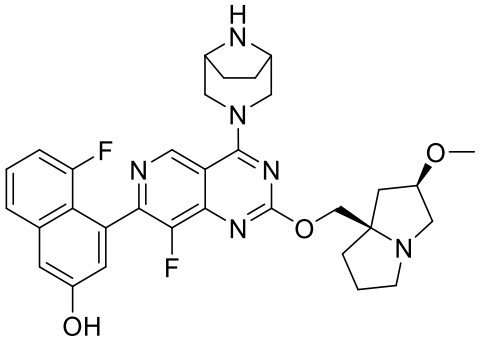
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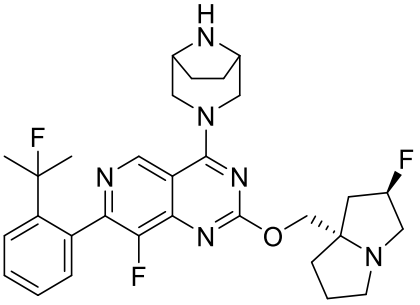
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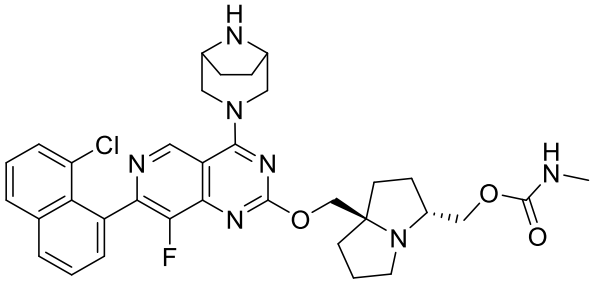
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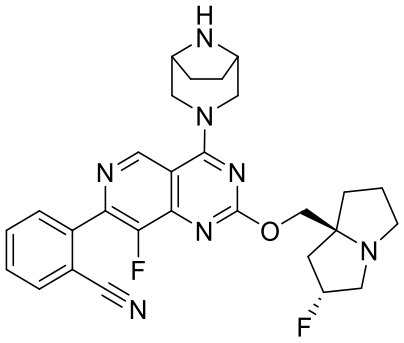
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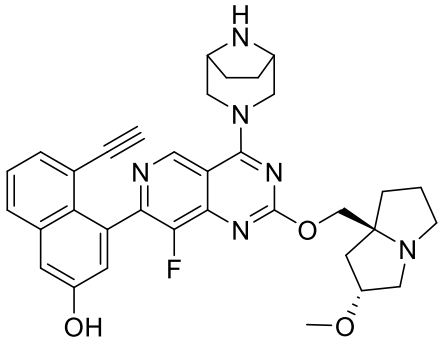
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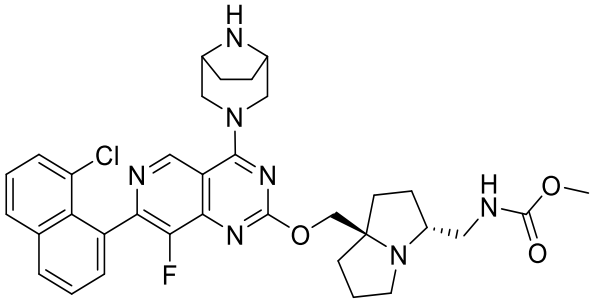
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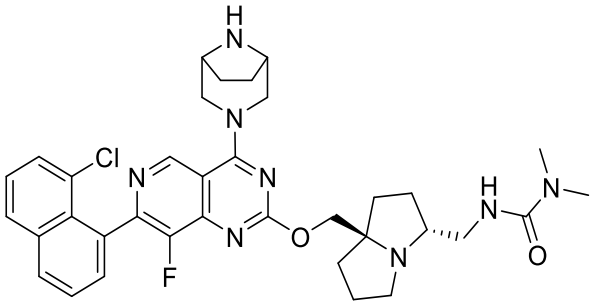
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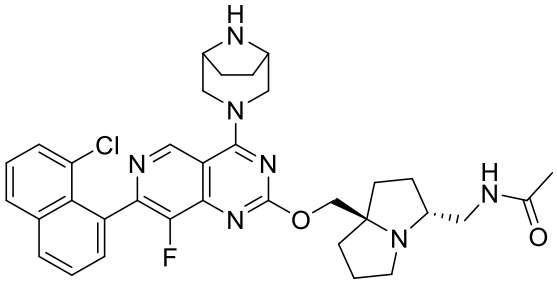
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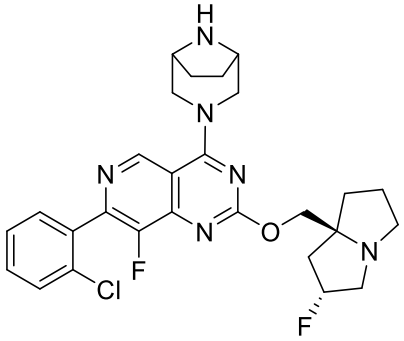
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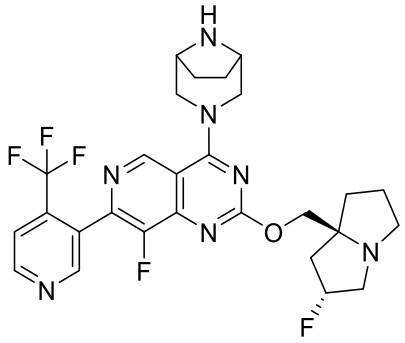
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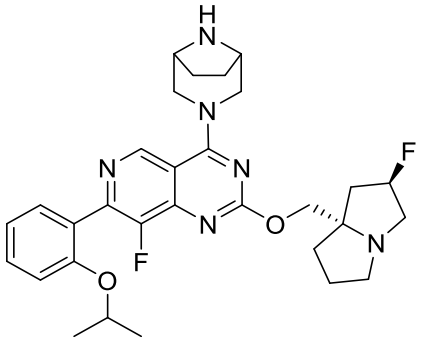
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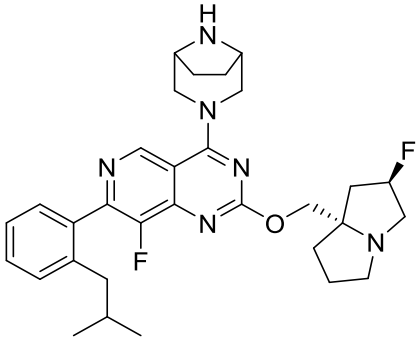
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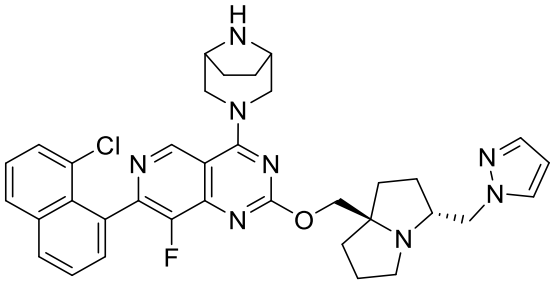
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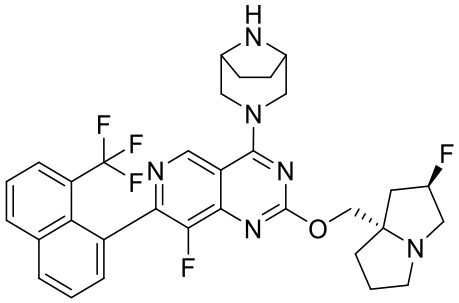
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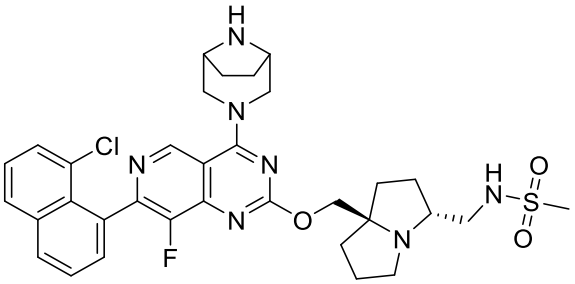
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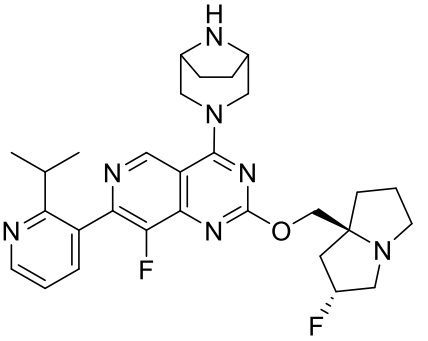
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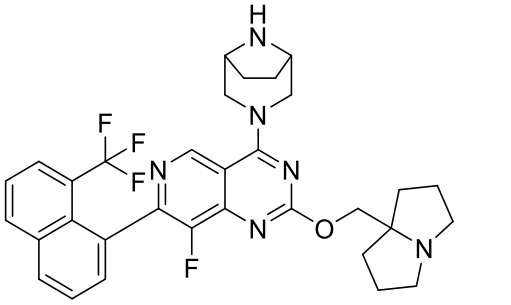
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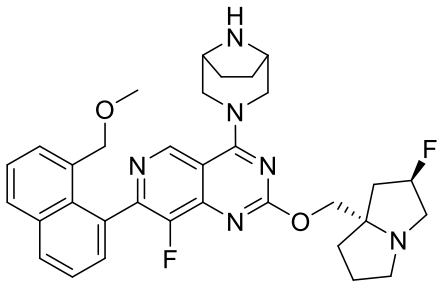
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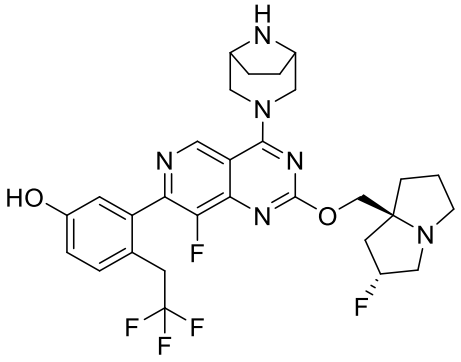
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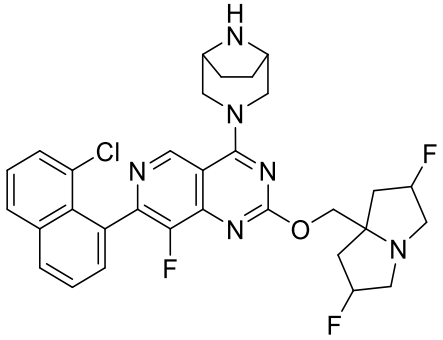
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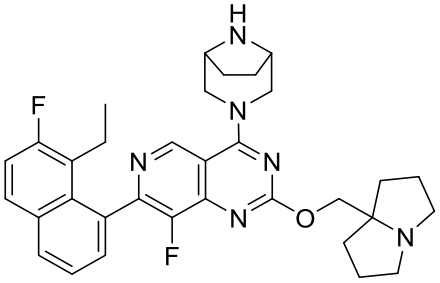
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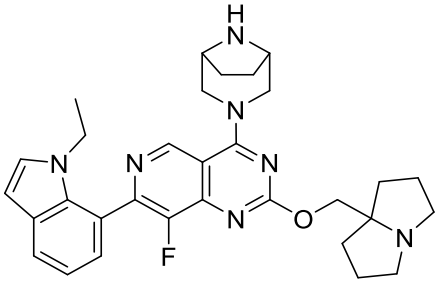
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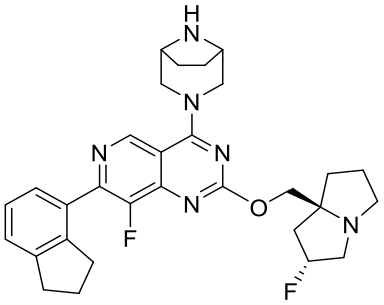
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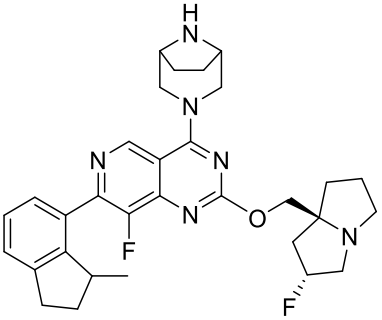
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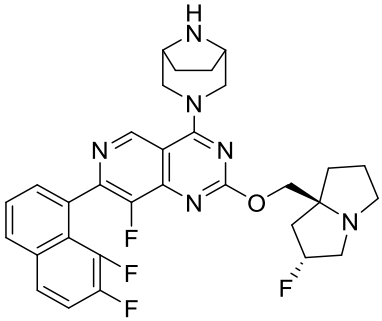
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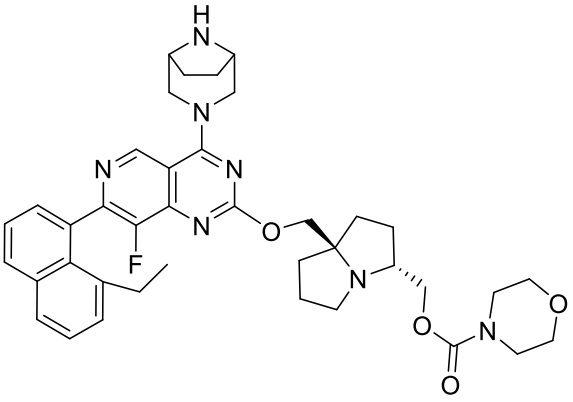
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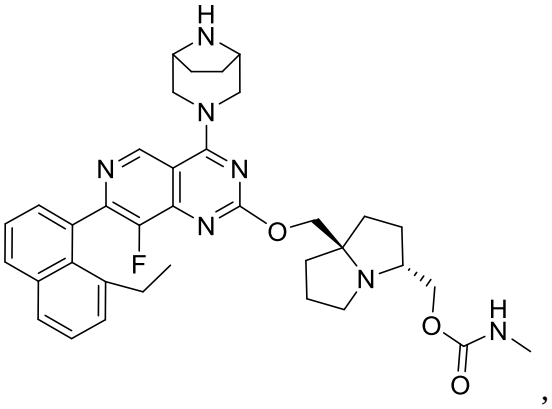
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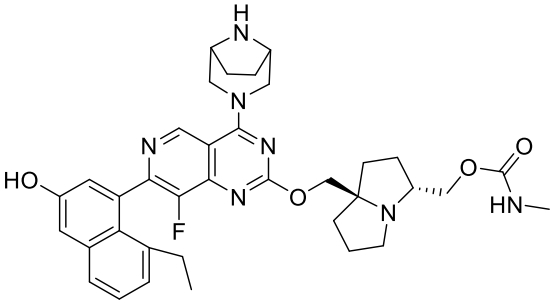
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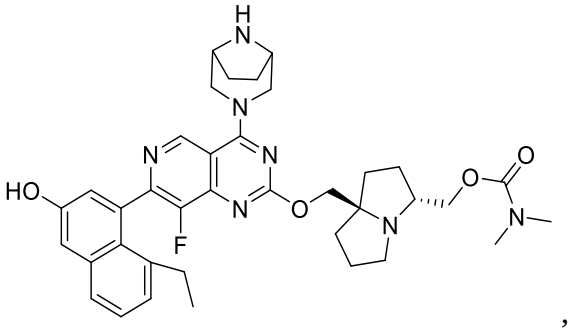
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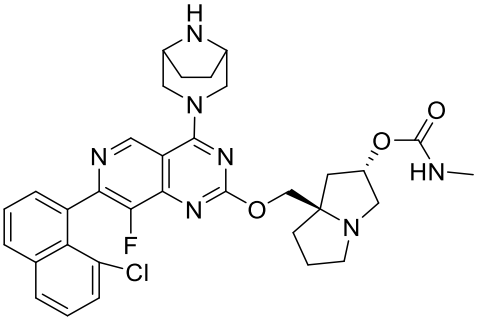
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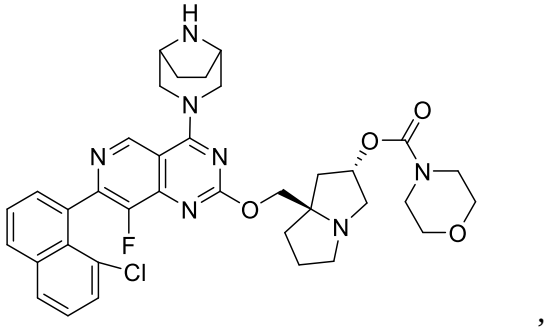
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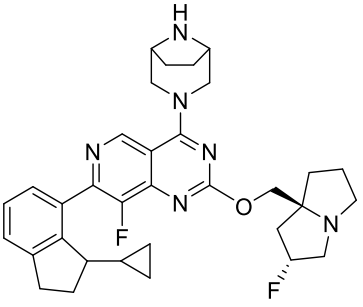
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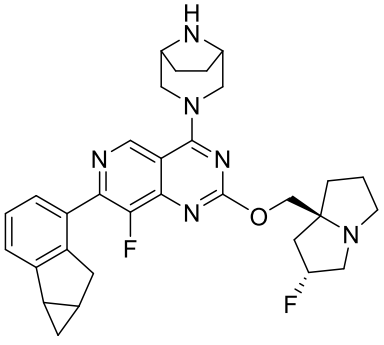
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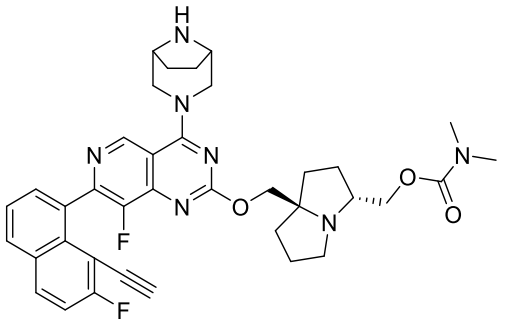
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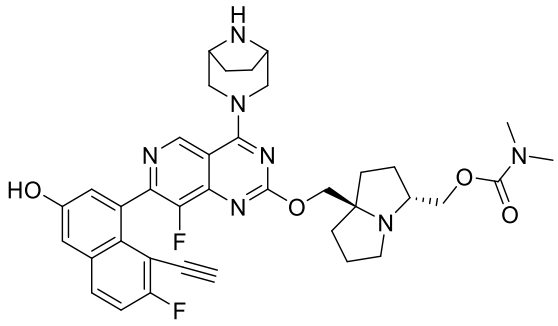
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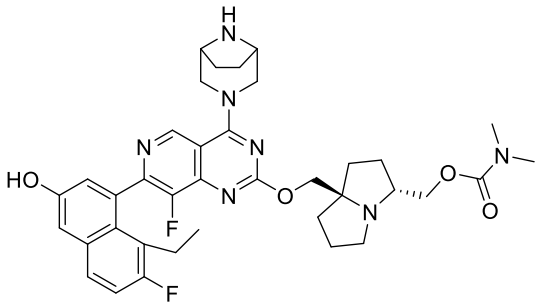
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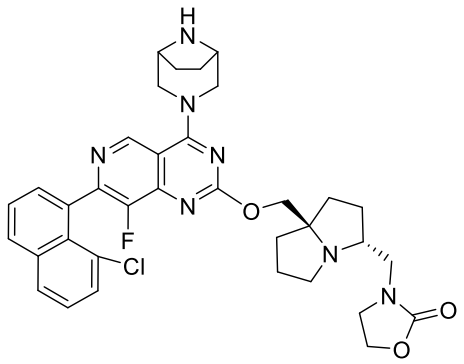
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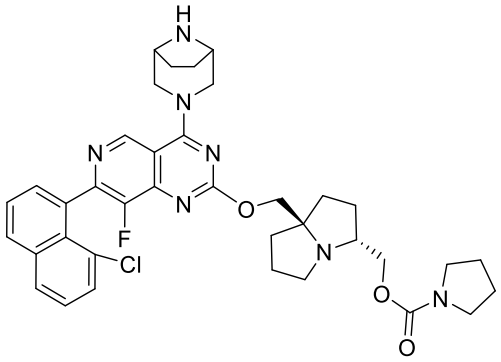
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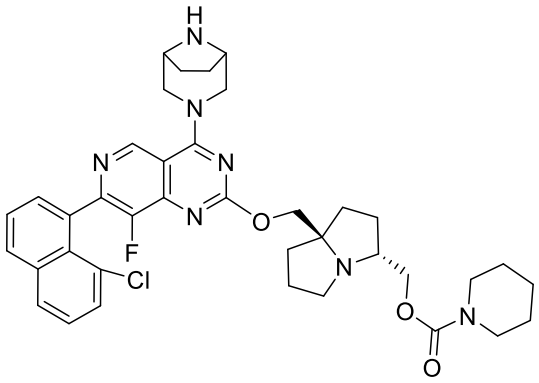
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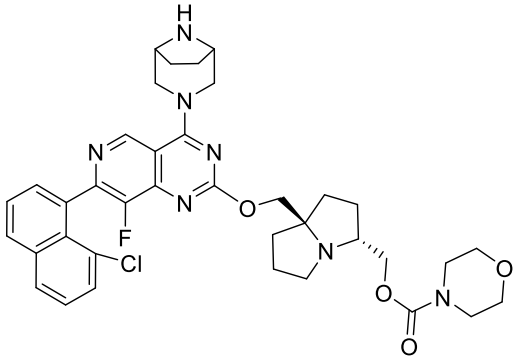
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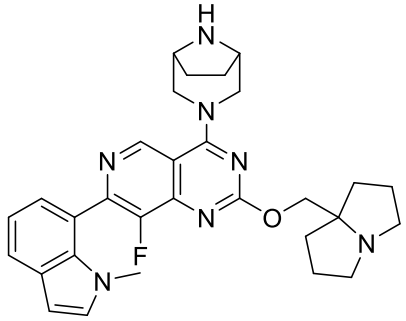
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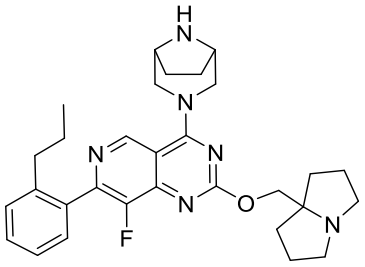
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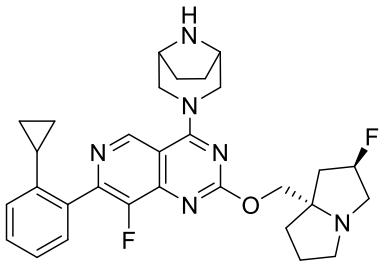
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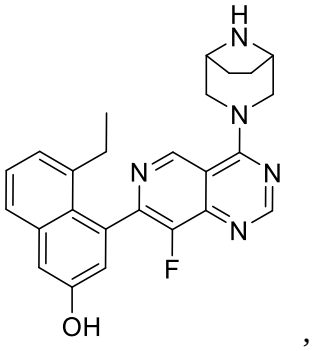
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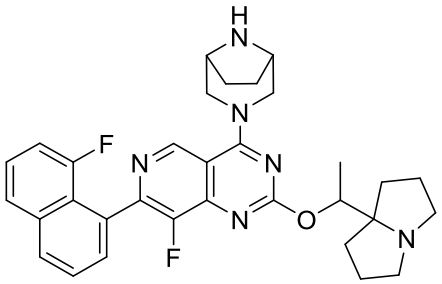
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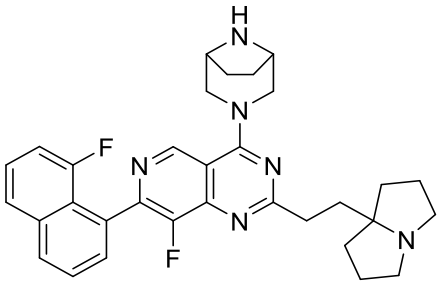
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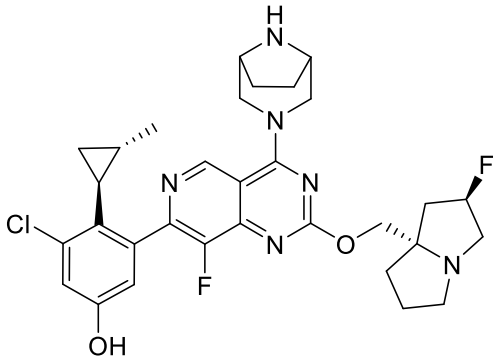
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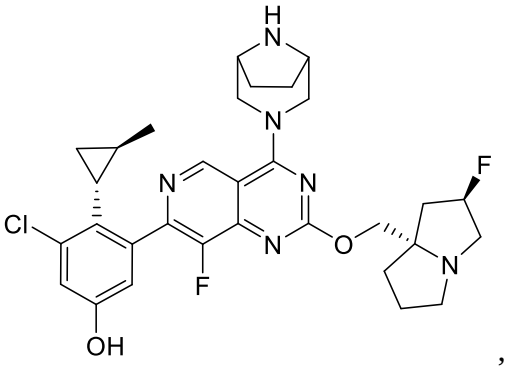
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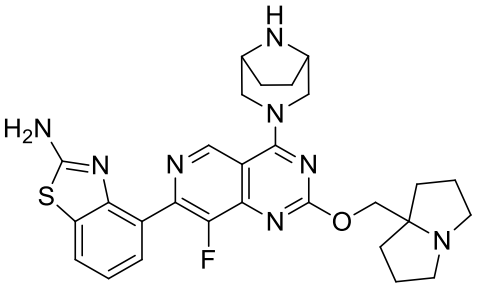
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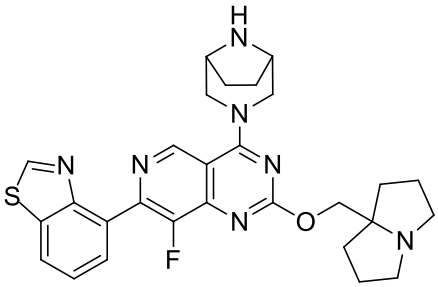
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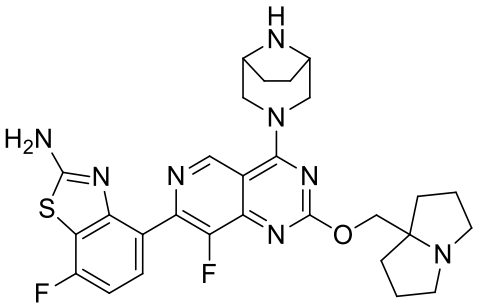
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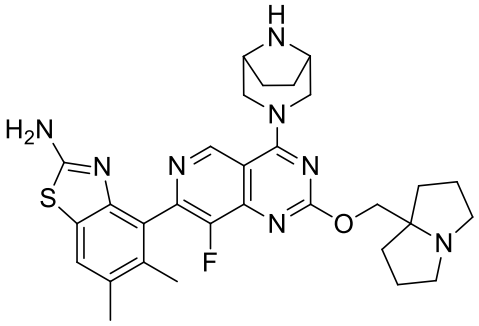
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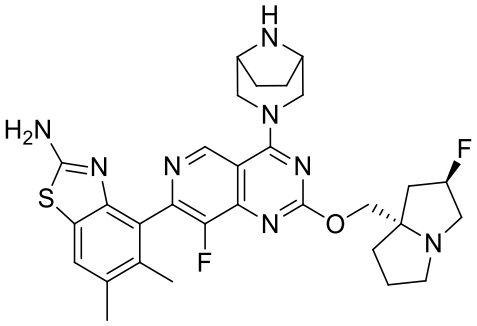
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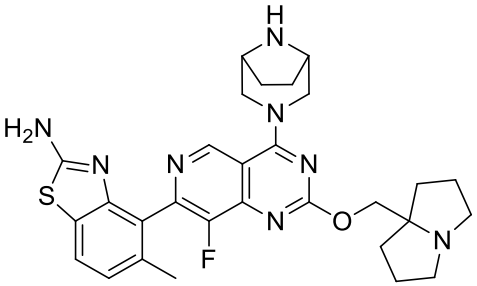

and pharmaceutically acceptable salts thereof.

~~46~~13. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of claim 1or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

~~47~~14. An in vitro method for inhibiting KRas G12D activity in a cell, comprising contacting the cell in which inhibition of KRas G12D activity is desired with an effective amount of a compound ~~of~~ according to claim 1, ~~or~~ a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 13.

~~48. A method for inhibiting KRas G12D activity in a cell, comprising contacting the cell in which inhibition of KRas G12D activity is desired with the pharmaceutical composition of claim 46.~~

15. Use of a compound according to claim 1, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 13 in the manufacture of a medicament for inhibiting KRas G12D activity in a cell, wherein an effective amount of the compound according to claim 1, the pharmaceutically acceptable salt thereof or the pharmaceutical composition of claim 13 is to be contacted with the cell in which inhibition of KRas G12D activity is desired.

~~49~~16. Use of a compound according to claim 1, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 13 in the manufacture of a medicament ~~A method~~ for treating a KRas G12D-associated cancer, wherein a therapeutically effective amount of the compound according to claim 1, the pharmaceutically acceptable salt thereof or the pharmaceutical composition of claim 13 is to be administered ~~comprising administering~~ to a patient in need thereof ~~a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof~~.

~~50. A method for treating a KRas G12D-associated cancer comprising administering to a patient in need thereof the pharmaceutical composition of claim 46.~~

~~51~~17. The use according to ~~method of~~ claim ~~50~~16, wherein the therapeutically effective amount of the compound is between about 0.01 to 100 mg/kg per day.

~~52~~18. The use according to ~~method of~~ claim ~~50~~16, wherein the KRas G12D-associated cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma,

fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial `carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell

carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma, preferably.

~~53. The method of claim 52,~~ wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.

~~54~~19. The use of a compound according to claim 1 or a pharmaceutical composition of claim 13 in the manufacture of a medicament ~~A method~~ for treating cancer in a patient in need thereof, ~~the method comprising~~wherein (a) ~~determining~~ it is to be determined that the cancer is associated with a KRas G12D mutation (e.g., a KRas G12D-associated cancer); and (b) a therapeutically effective amount of the compound according to claim 1 or the pharmaceutical composition of claim 13 is to be administered~~administering~~ to the patient ~~a therapeutically effective amount of a compound according to claim 1~~.

~~55. A method for treating cancer in a patient in need thereof, the method comprising (a) determining that the cancer is associated with a KRas G12D mutation (e.g., a KRas G12D-associated cancer); and (b) administering to the patient the pharmaceutical composition of claim 52.~~

~~56~~20. The use according to ~~method of~~ claim ~~55~~19 wherein the administering is done via a route selected from the group consisting of parenteral, intraperitoneal, intradermal, intracardiac, intraventricular, intracranial, intracerebrospinal, intrasynovial, intrathecal

administration, intramuscular injection, intravitreous injection, intravenous injection, intra-arterial injection, oral, buccal, sublingual, transdermal, topical, intratracheal, intrarectal, subcutaneous, and topical administration, preferably.

57. The method of claim 56, wherein the administering is done via an intravenous injection, .

58. The method of claim 56, wherein the administering is done via an intramuscular injection, .

59. The method of claim 56, wherein the administering is done via an intramuscular injection.

60. The method of claim 56, wherein the administering comprises utilizing a delivery device or.

61. The method of claim 56, wherein the administering is done in a hospital setting.