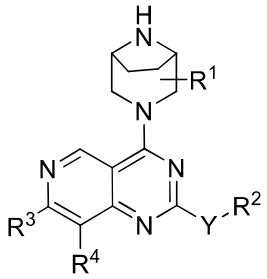
develop inhibitors of KRas for treating cancer, no KRas inhibitor has yet demonstrated sufficient safety and/or efficacy to obtain regulatory approval (e.g., see McCormick (2015) Clin Cancer Res. 21 (8):1797-1801).

[0005] Compounds that inhibit KRas activity are still highly desirable and under investigation, including those that disrupt effectors such as guanine nucleotide exchange factors (e.g., see Sun et al., (2012) Agnew Chem Int Ed Engl. 51(25):6140-6143 doi: 10.1002/anie201201358) as well recent advances in the covalent targeting of an allosteric pocket of KRas G12C (e.g., see Ostrem et al., (2013) Nature 503:548-551 and Fell et al., (2018) ACS Med. Chem. Lett. 9:1230-1234). Clearly there remains a continued interest and effort to develop inhibitors of KRas, particularly inhibitors of activating KRas mutants, especially KRas G12D.

[0006] Thus, there is a need to develop new KRas G12D inhibitors that demonstrate sufficient efficacy for treating KRas G12D-mediated cancer.

SUMMARY

[0006a] In an aspect, there is provided a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen, hydroxy, halogen, $C_1 – C_3$ alkyl, C_1 - C_3 cyanoalkyl, C_1 - C_3 hydroxyalkyl, HC(=O)-, $-CO_2R^5$, $-C(O)N(R^5)_2$ or a 5-6 membered heteroaryl;

Y is a bond, O or NR^5;

R^2 is hydrogen, -$N(R^5)_2$, heterocyclyl, $C_1 – C_6$ 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-C_1-C_6 haloalkyl, -L-OR^5, -L-NR^5C(O)-aryl, -L-COOH, or -LC(=O)OC_1-C_6 alkyl, wherein the heterocyclyl, the aryl portion of -L-NR^5C(O)-aryl, 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 $C_1 – C_4$ alkylene optionally substituted with hydroxy, $C_1 – C_4$ 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 $C_1 – C_3$ alkyl;

each R^5 is independently hydrogen or $C_1 – C_3$ alkyl;

each R^6 is independently halogen, hydroxy, C_1 - C_3 hydroxyalkyl, $C_2 – C_3$ alkyl, C_1 - C_3 haloalkyl, C_1-C_3 alkoxy, cyano, -Q-phenyl, -Q-phenylSO_2F, -NHC(O)phenyl, -NHC(O)phenylSO_2F, C_1-C_3 alkyl substituted pyrazolyl, araC_1-C_3 alkyl-, tert-butyldimethylsilyloxyCH_2- , -$N(R^5)_2$, (C_1-C_3 alkoxy)C_1-C_3 alkyl-, (C_1-C_3 alkyl)C(=O), oxo, (C_1-C_3 haloalkyl)C(=O)-, -SO_2F, (C_1-C_3 alkoxy)C_1-C_3 alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC_1$-C_6 alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C_1$-C_6 alkyl, -CH_2(pyrazolyl), -$CH_2NHSO_2C_1$-C_6 alkyl, -$CH_2OC(O)$heterocyclyl, -OC(O)$N(R^5)_2$, -OC(O)NH(C_1-C_3 alkyl)O(C_1-C_3 alkyl), -OC(O)NH(C_1-C_3 alkyl)O(C_1-C_3 alkyl)phenyl(C_1-C_3 alkyl)$N(CH_3)_2$, -OC(O)NH(C_1-C_3 alkyl)O(C_1-C_3 alkyl)phenyl or -OC(O)heterocyclyl, -CH_2heterocyclyl, wherein the phenyl of -NHC(O)phenyl or -OC(O)NH(C_1-C_3 alkyl)O(C_1-C_3 alkyl)phenyl is optionally substituted with -C(O)H or OH and wherein the heterocyclyl of -CH_2heterocyclyl is optionally substituted with oxo;

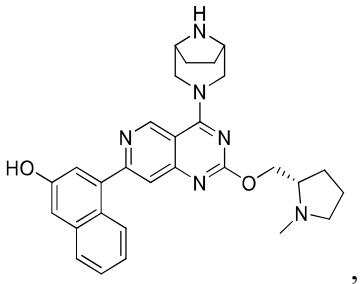
Q is a bond or O;

each R^7 is independently halogen, hydroxy, HC(=O)-, $C_1 – C_4$ alkyl, $C_1 – C_4$ alkoxy, $C_1 – C_4$ haloalkyl, $C_1 – C_4$ hydroxyalkyl, or -$N(R^5)_2$; and

each R^8 is independently halogen, cyano, hydroxy, C_1 - C_4 alkyl, -S-C_1 - C_3 alkyl, $C_2 – C_4$ alkenyl, $C_2 – C_4$ alkynyl, $C_2 – C_4$ hydroxyalkynyl, C_1-C_3 cyanoalkyl , triazolyl, C_1 - C_3 haloalkyl, -O- C_1 - C_3 haloalkyl, -S- C_1 - C_3 haloalkyl, C_1-C_3 alkoxy, hydroxyC_1-C_3 alkyl,

-$CH_2C(=O)N(R^5)_2$, -C_3-C_4 alkynyl$(NR^5)_2$, -$N(R^5)_2$, deuteroC_2-C_4 alkynyl, (C_1-C_3 alkoxy)haloC_1-C_3 alkyl-, or C_3-C_6 cycloalkyl wherein said C_3-C_6 cycloalkyl is optionally substituted with halogen or C_1-C_3 alkyl.

[0006b] In another aspect, there is provided a compound selected from: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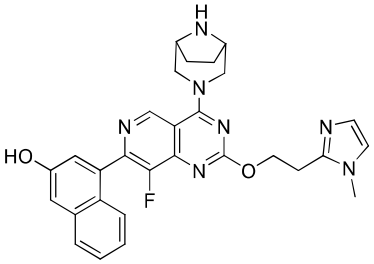
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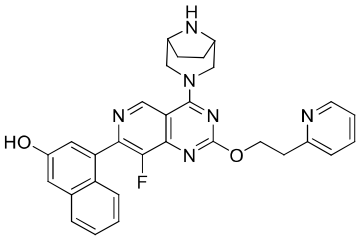
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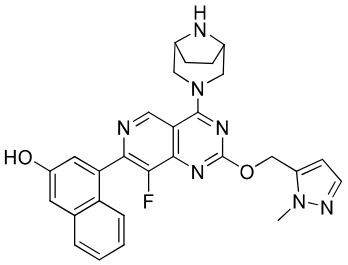
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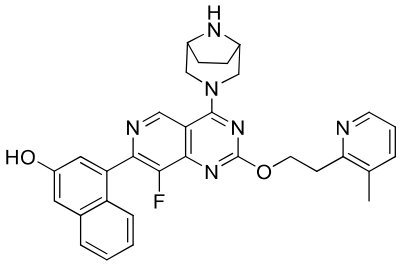
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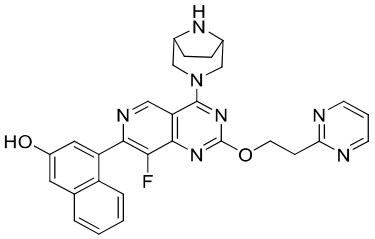
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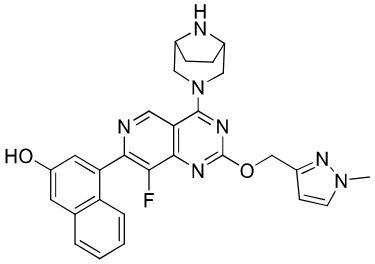
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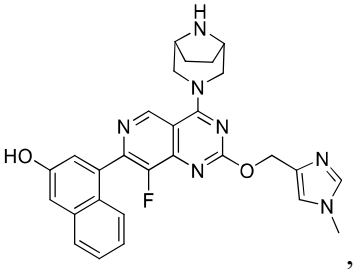
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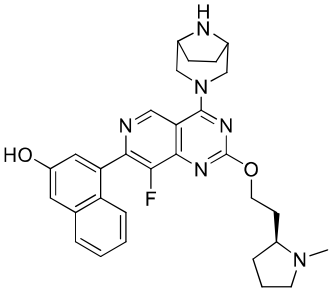
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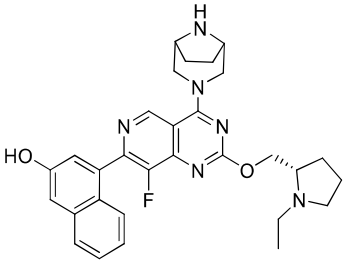
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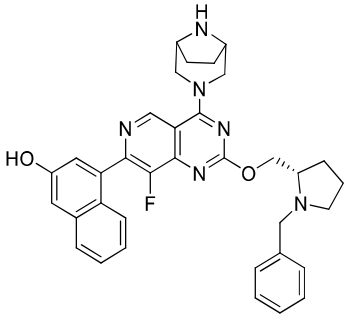
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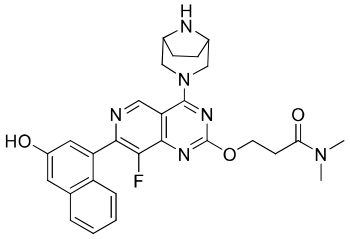
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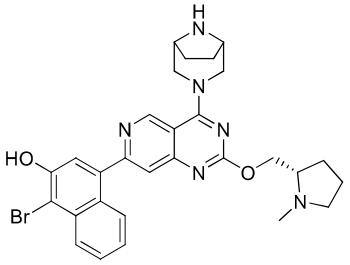
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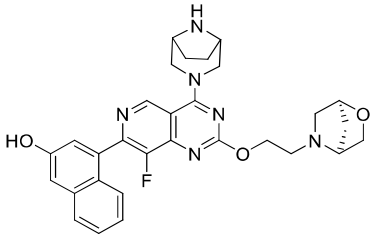
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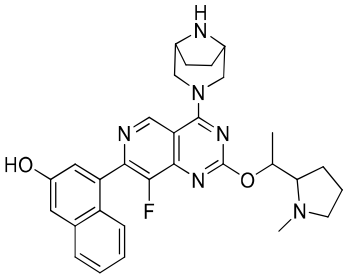
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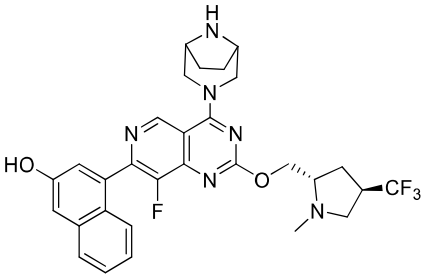
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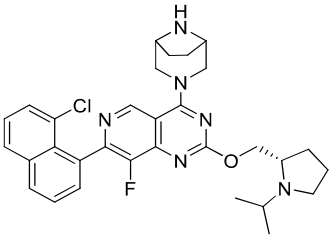
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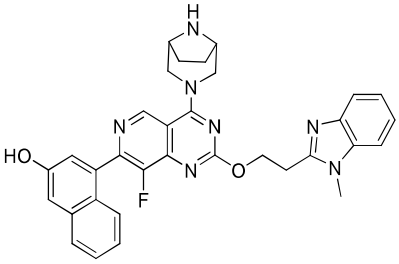
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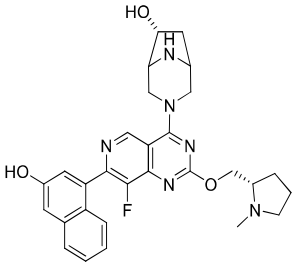
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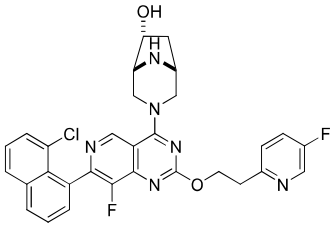
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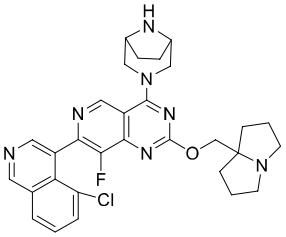
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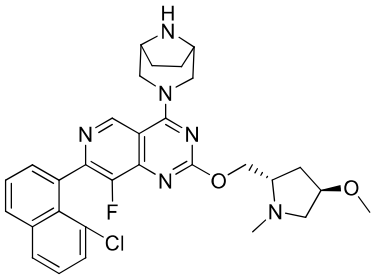
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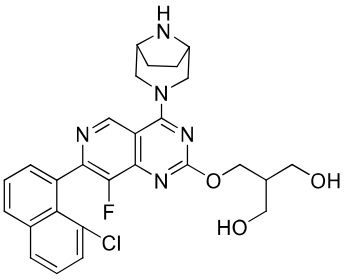
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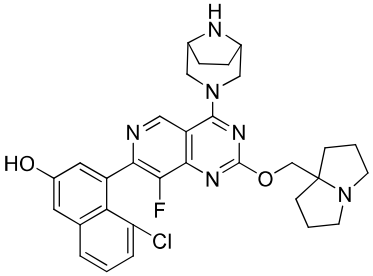
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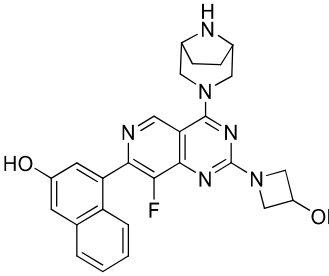
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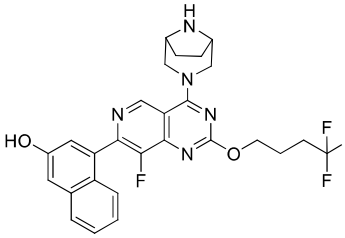
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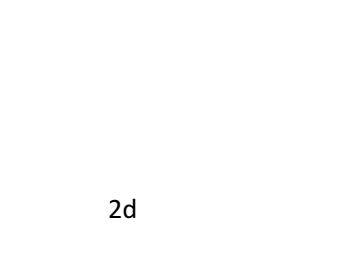
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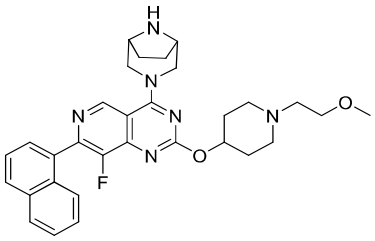
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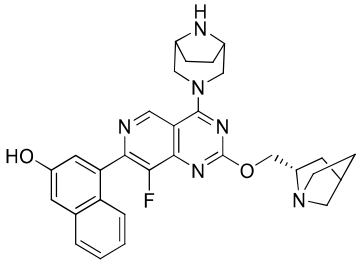
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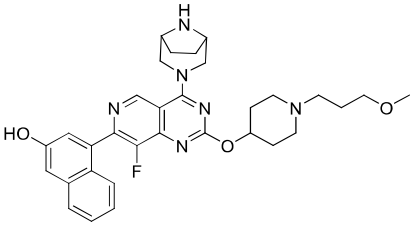
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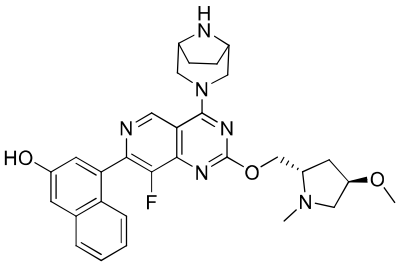
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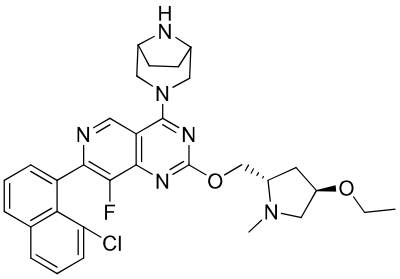
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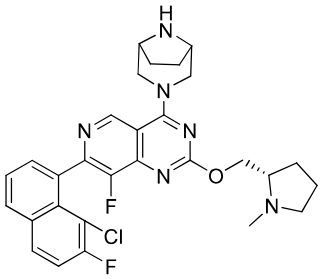
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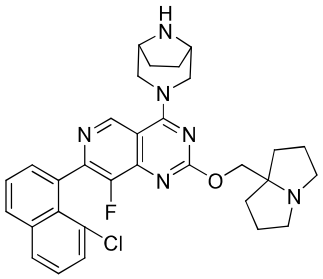
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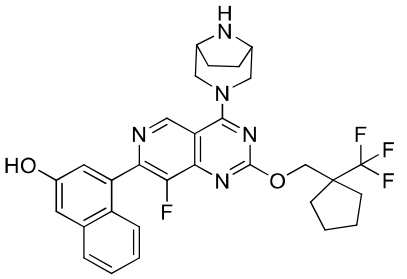
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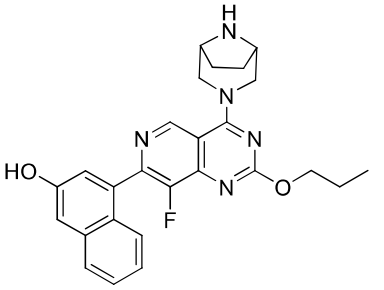
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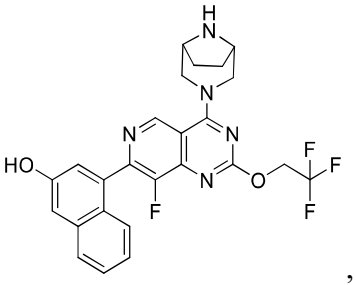
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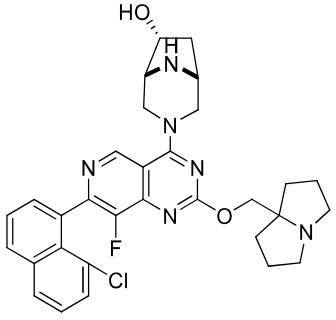
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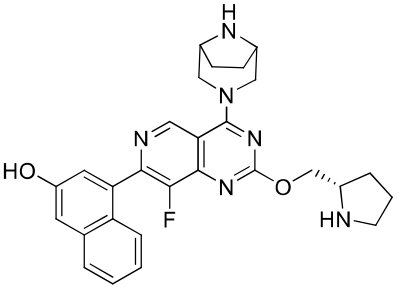
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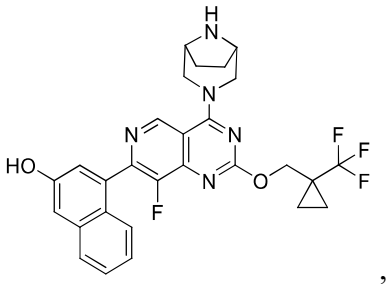
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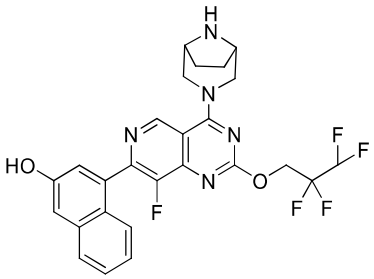
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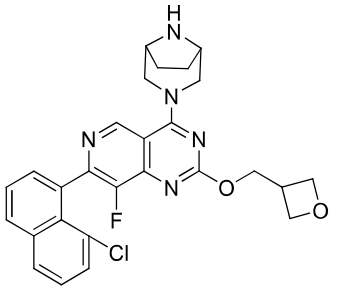
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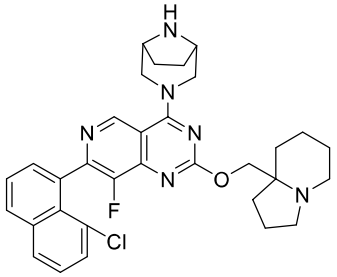
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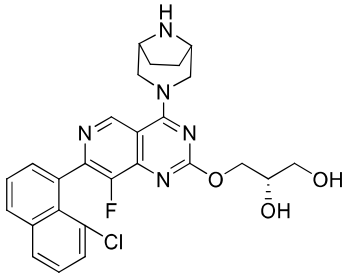
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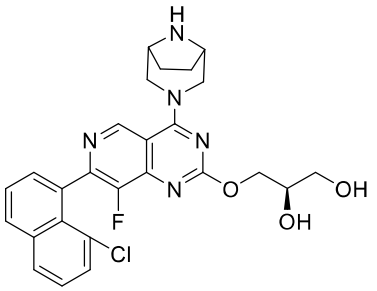
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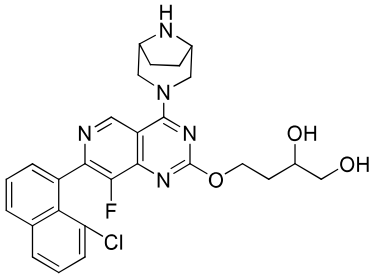
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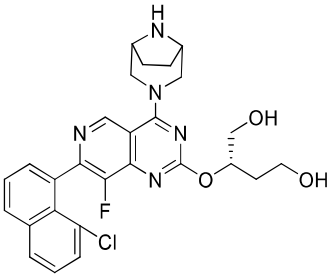
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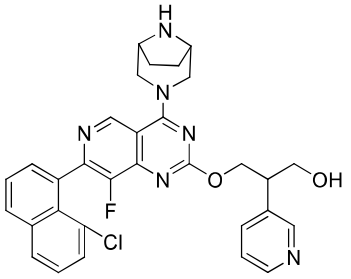
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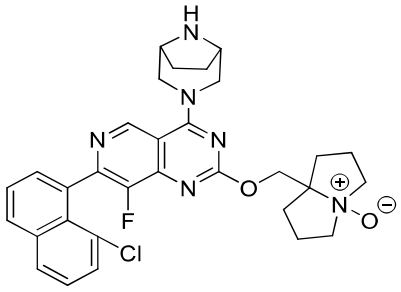
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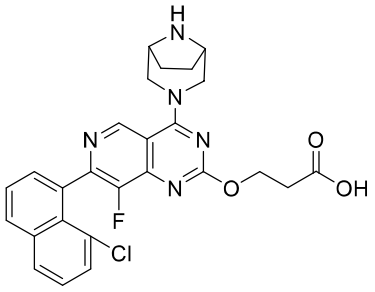
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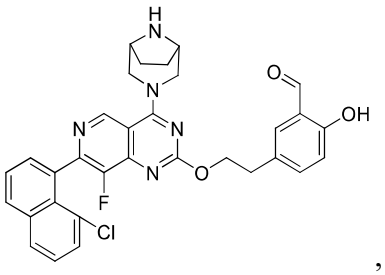
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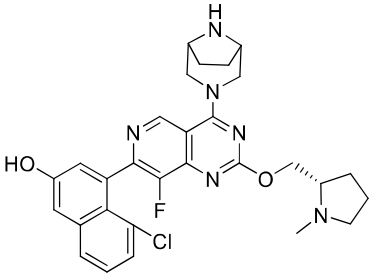
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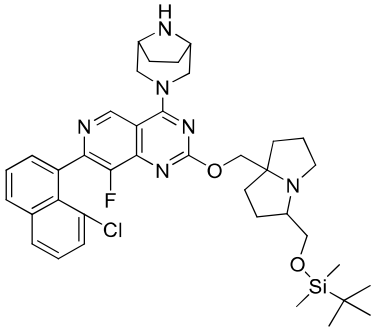
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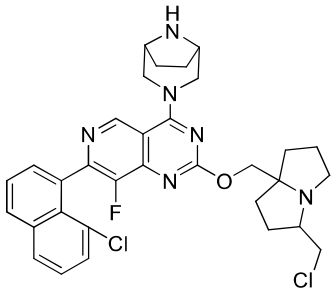
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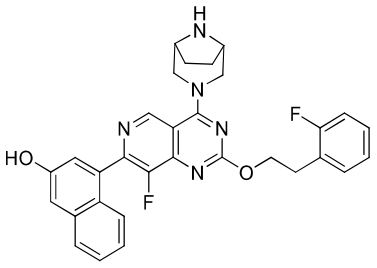
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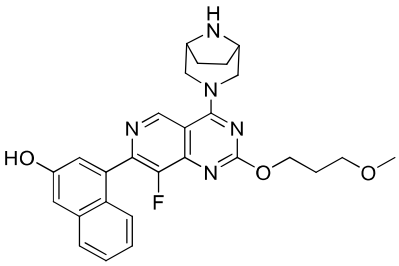
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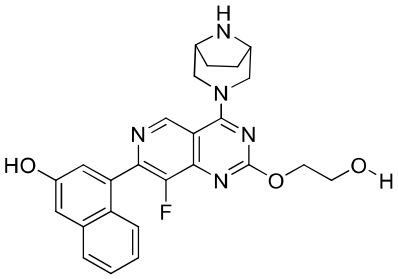
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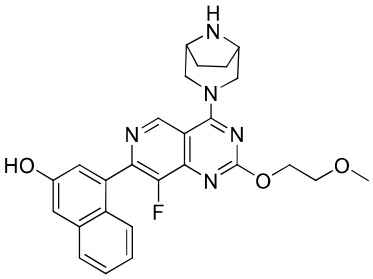
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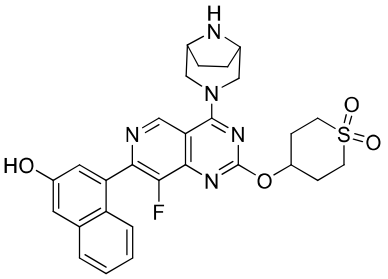
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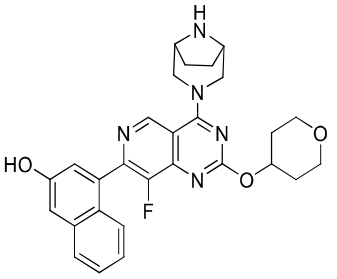
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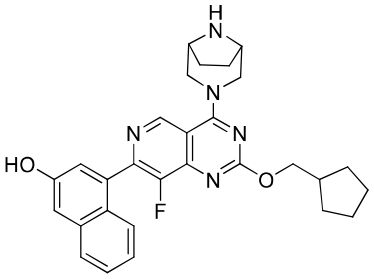
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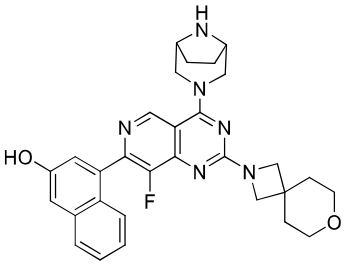
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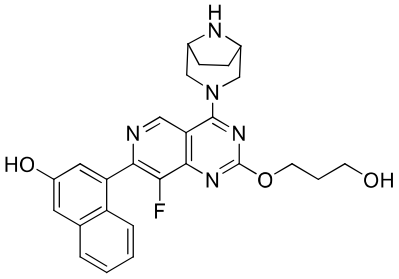
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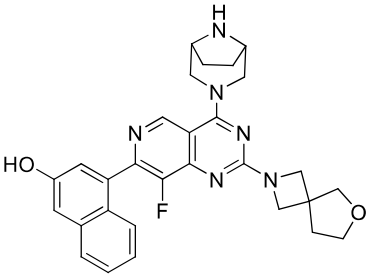
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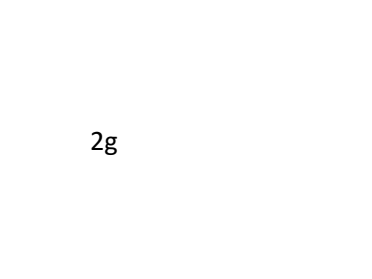
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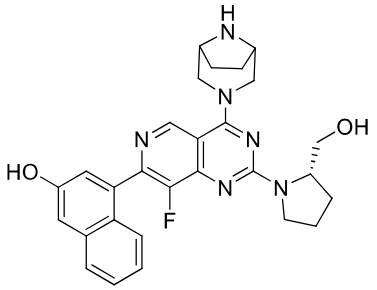
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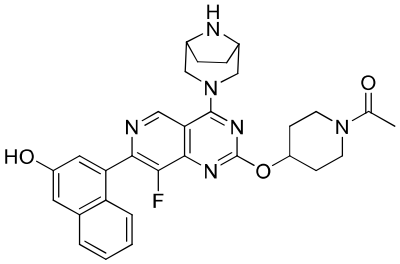
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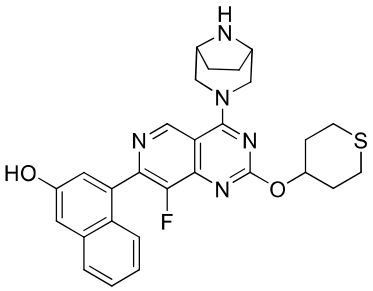
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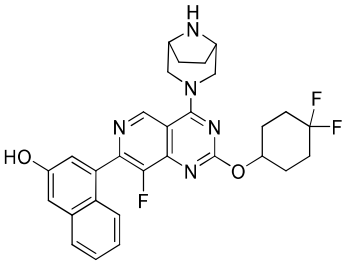
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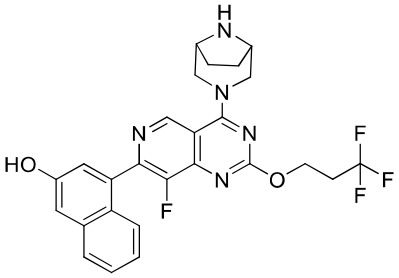
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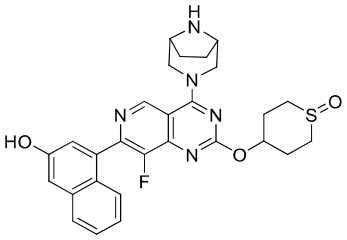
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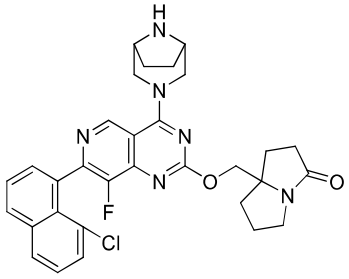
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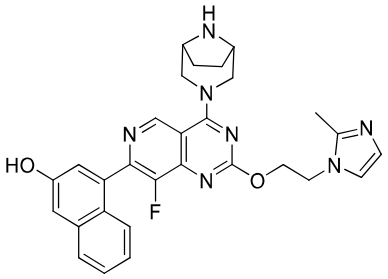
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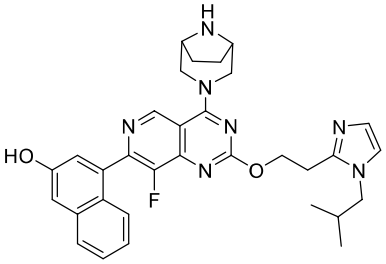
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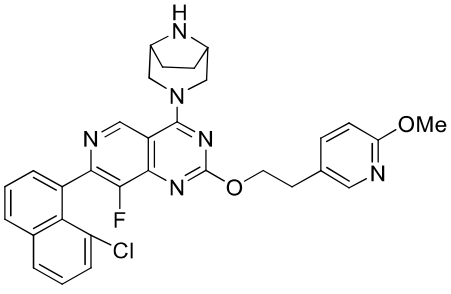
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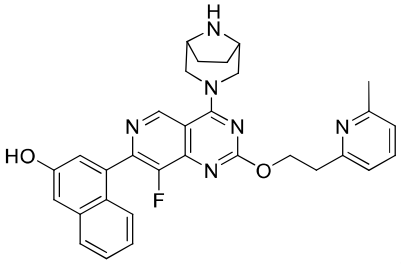
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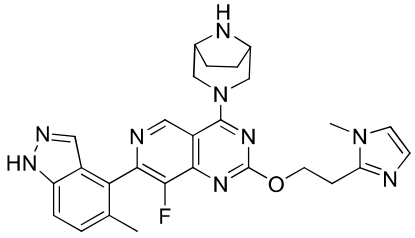
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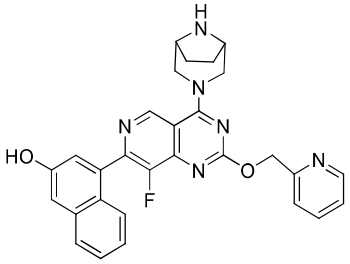
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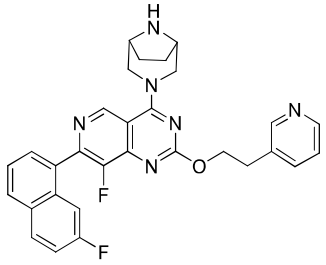
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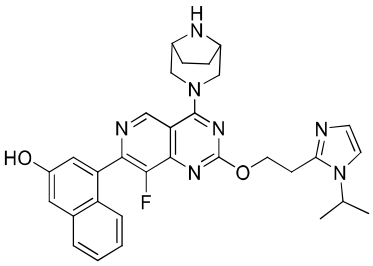
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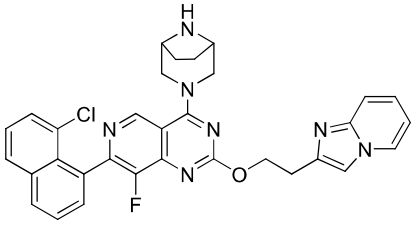
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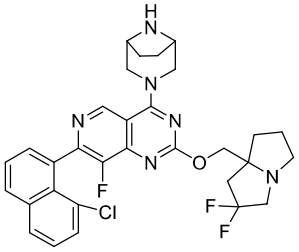
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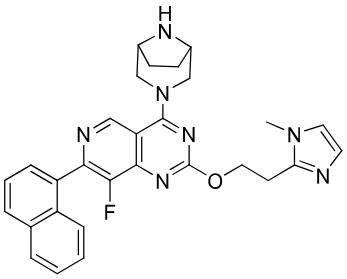
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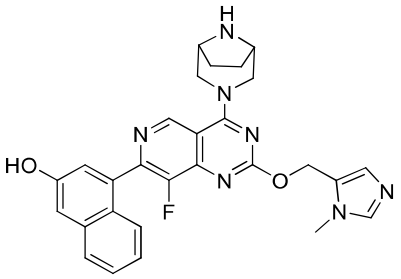
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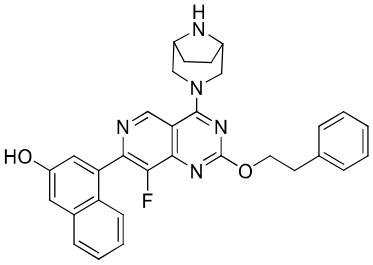
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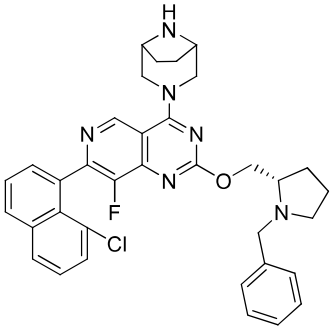
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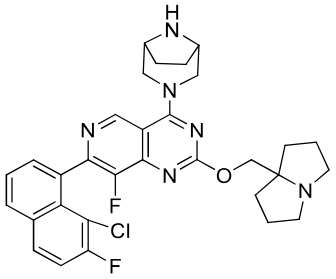
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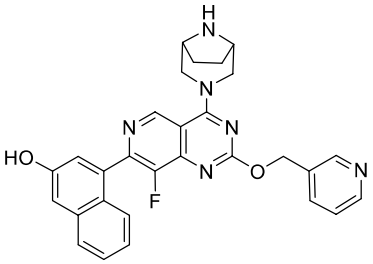
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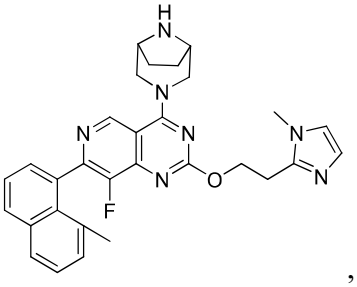
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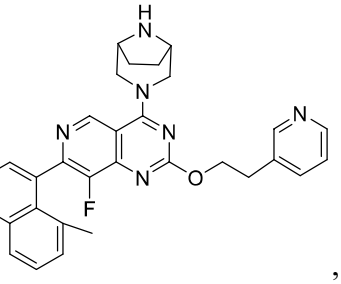
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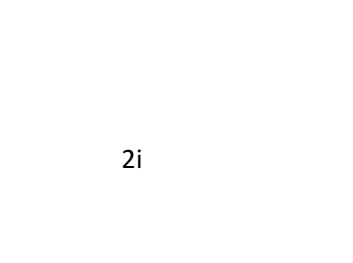
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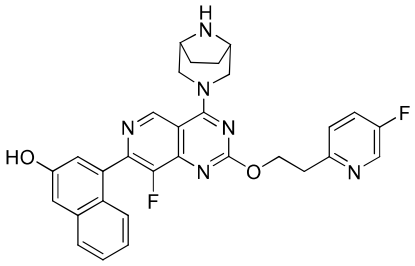
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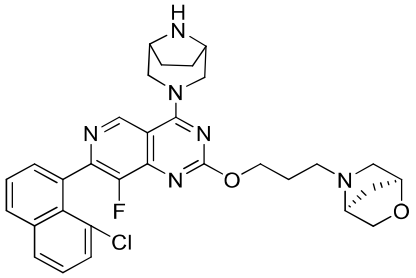
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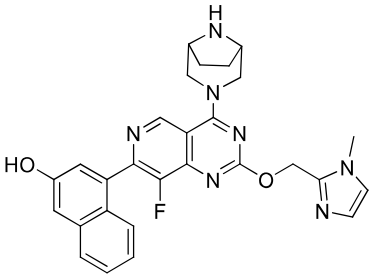
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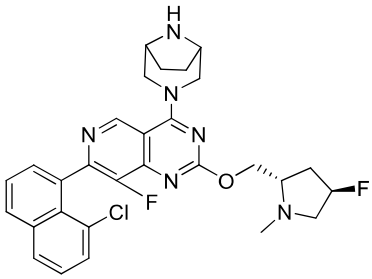
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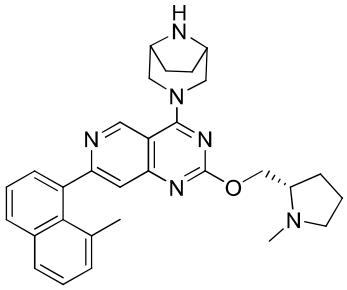
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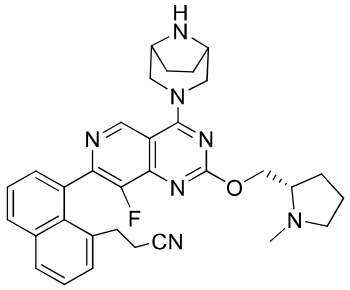
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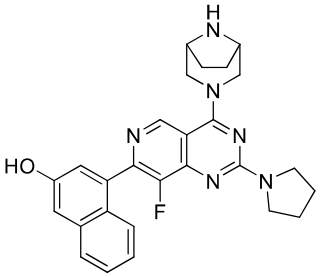
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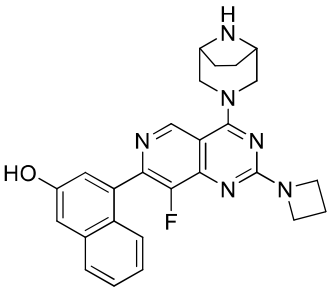
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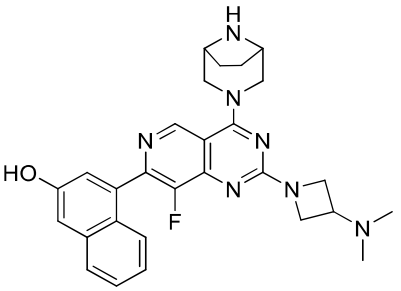
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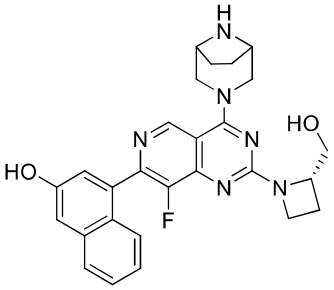
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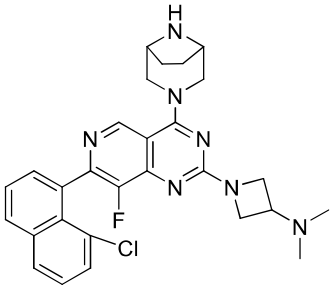
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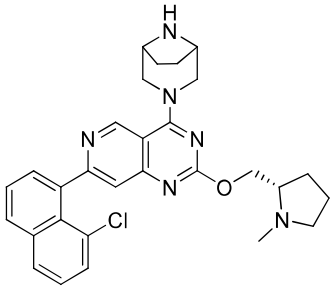
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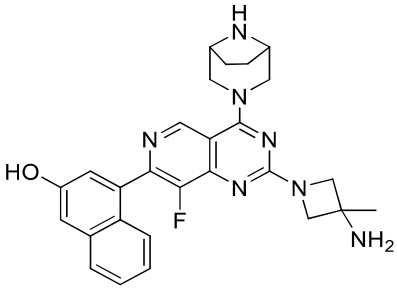
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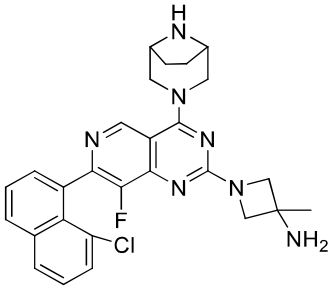
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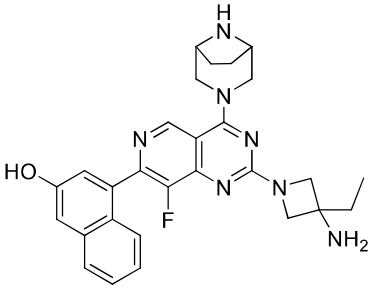
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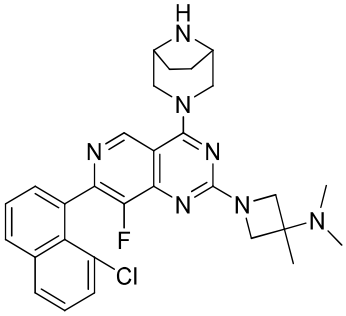
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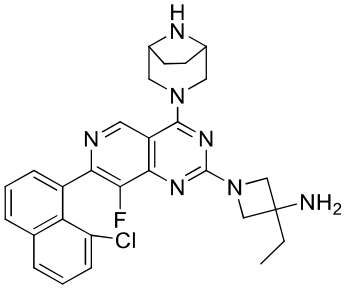
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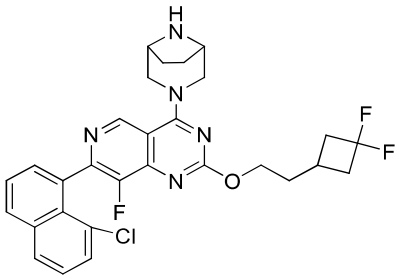
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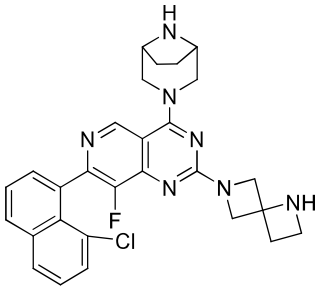
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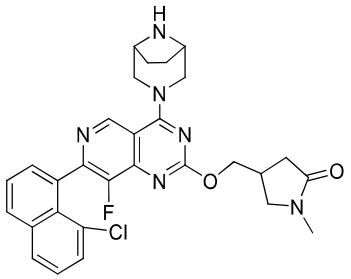
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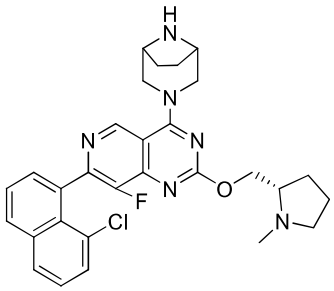
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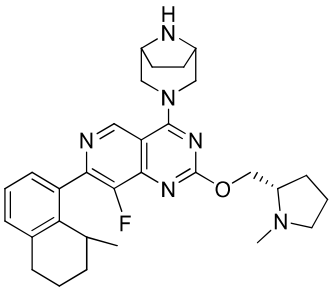
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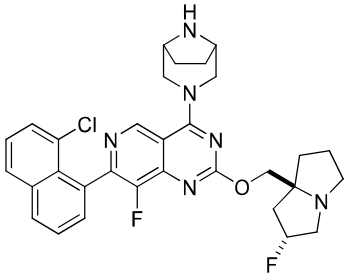
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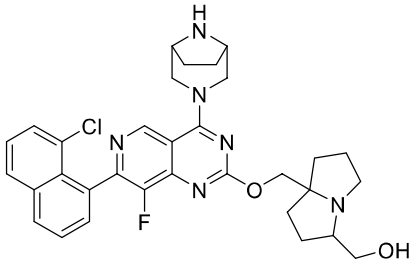
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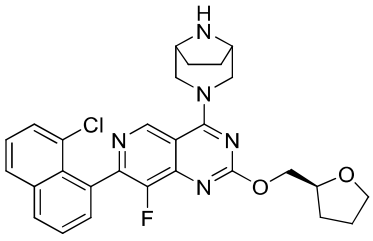
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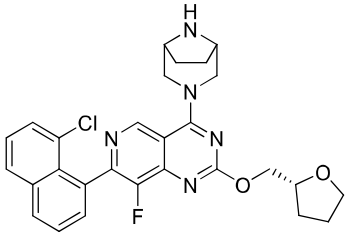
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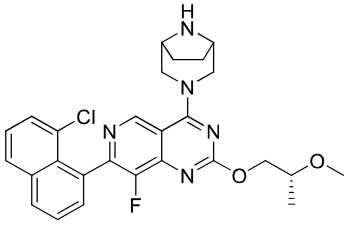
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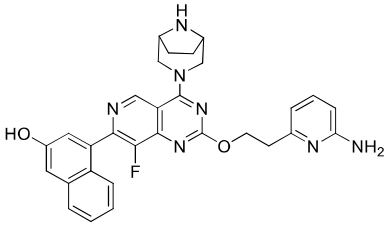
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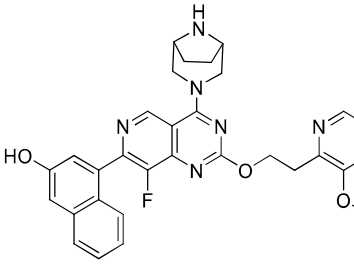
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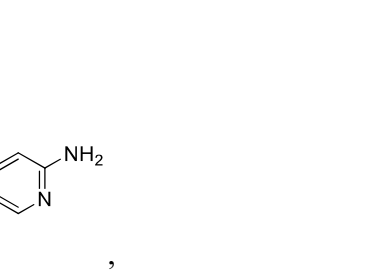
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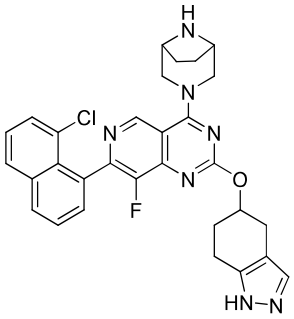
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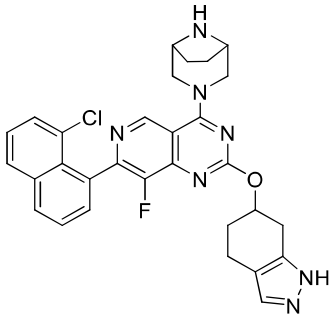
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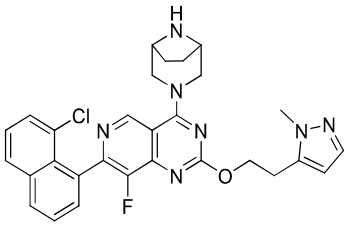
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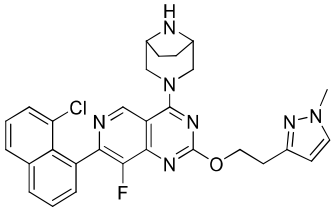
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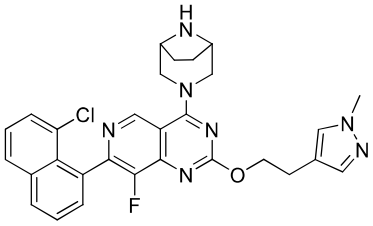
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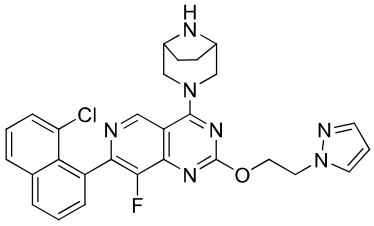
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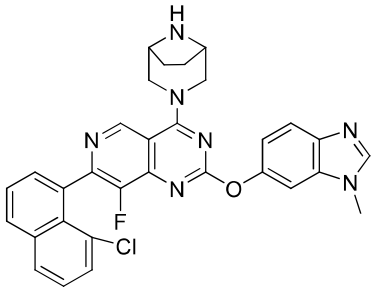
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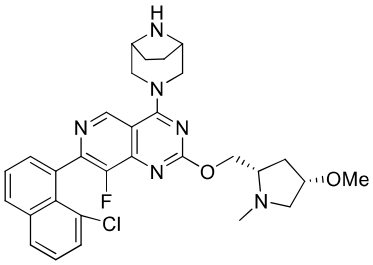
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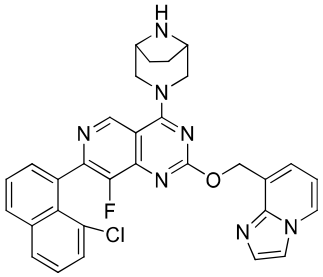
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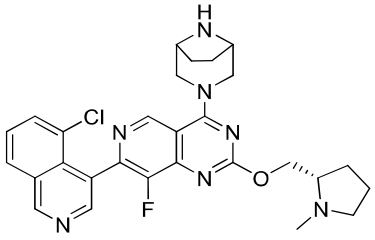
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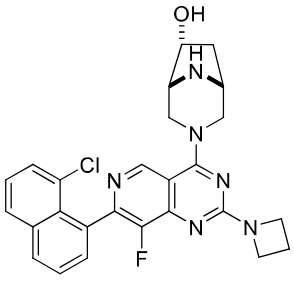
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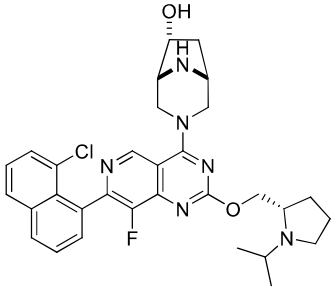
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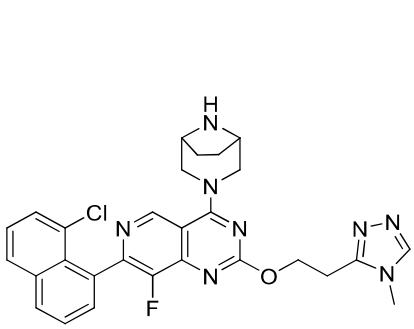
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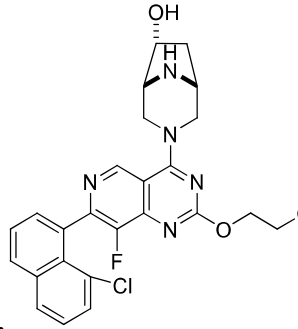
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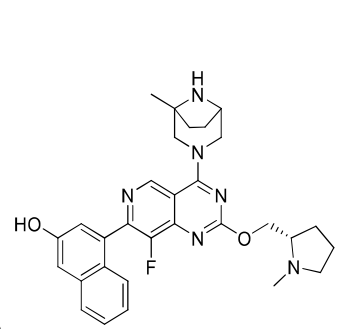
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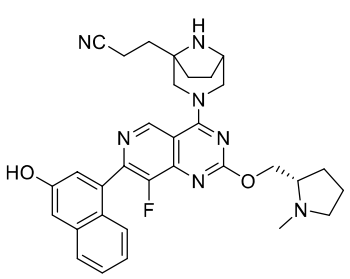
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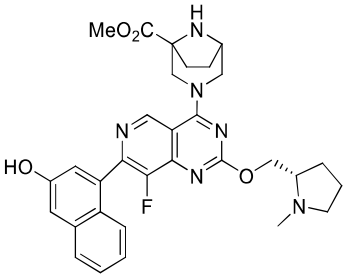
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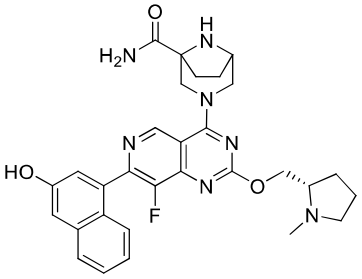
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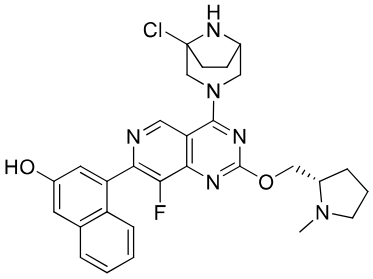
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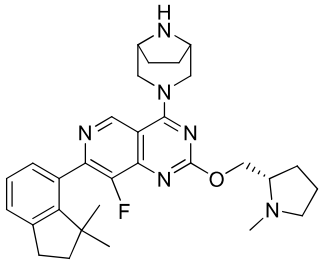
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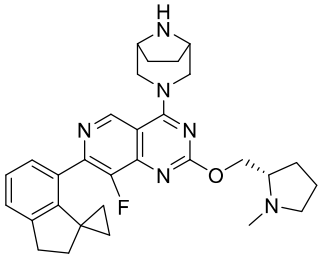
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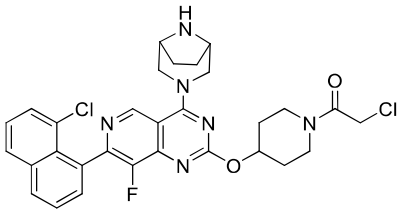
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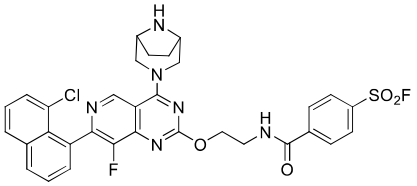
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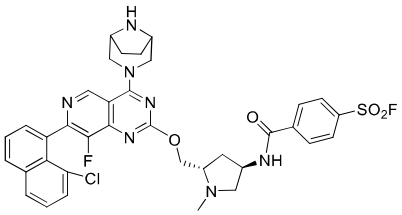
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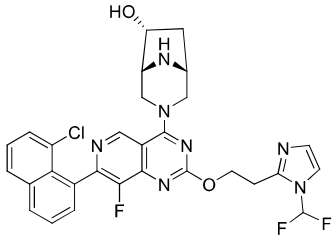
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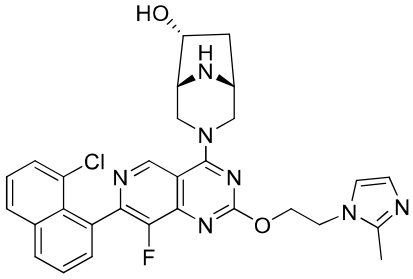
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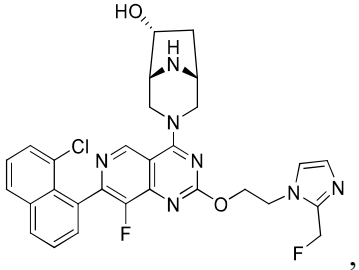
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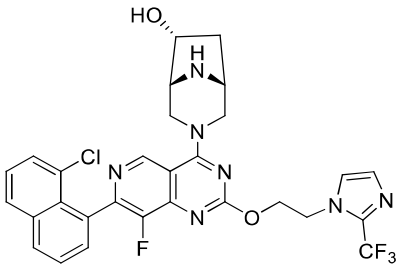
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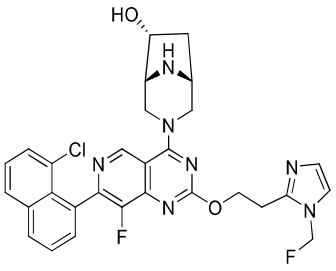
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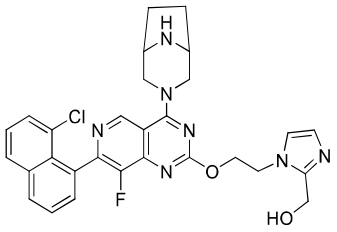
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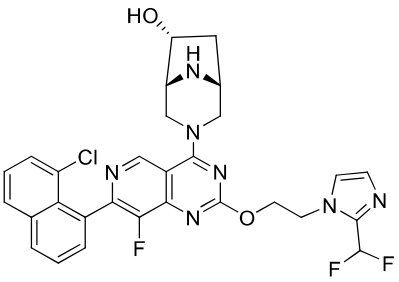
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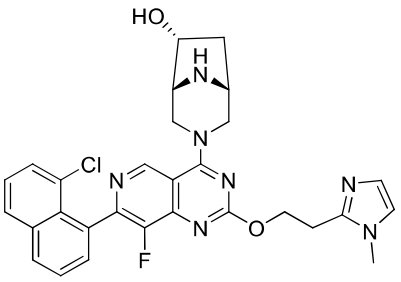
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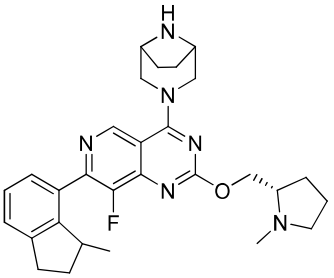
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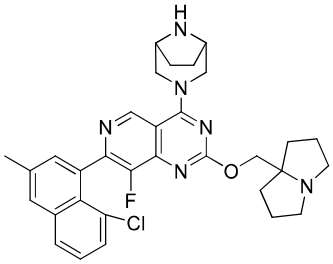
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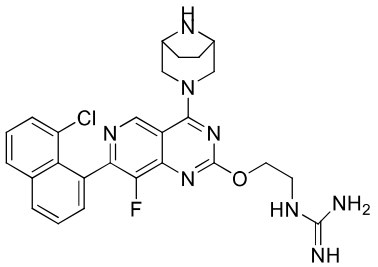
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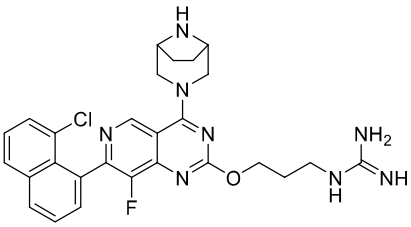
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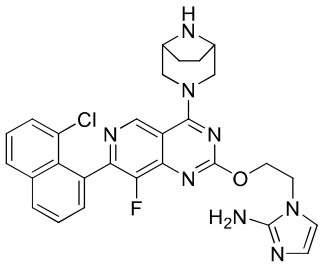
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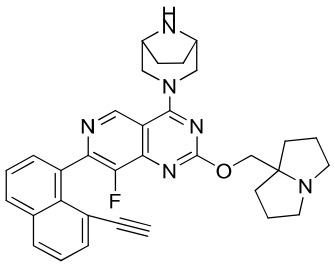
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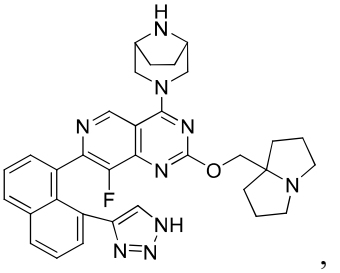
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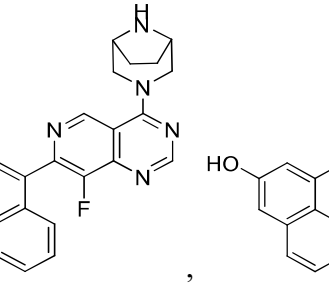
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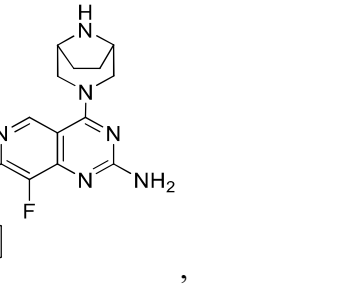
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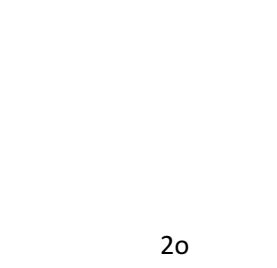
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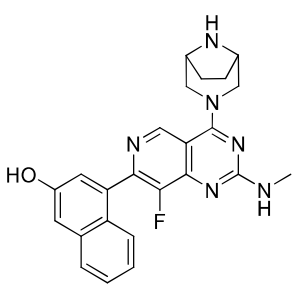
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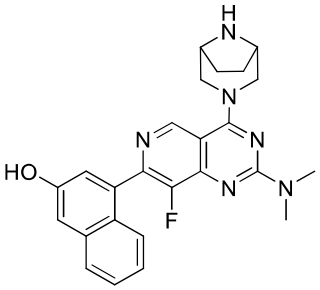
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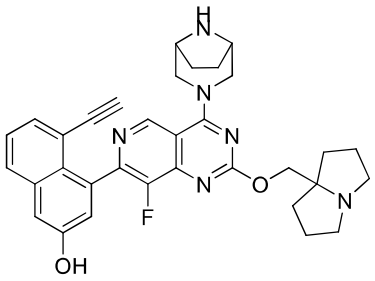
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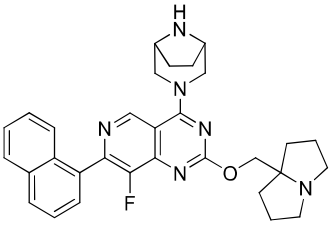
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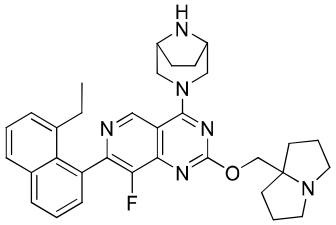
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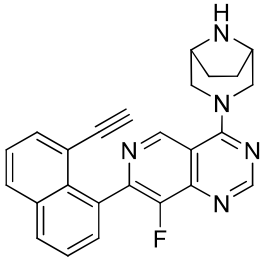
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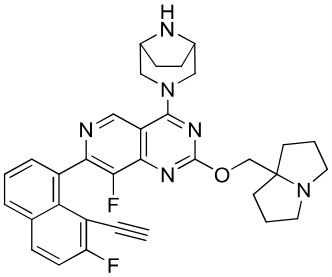
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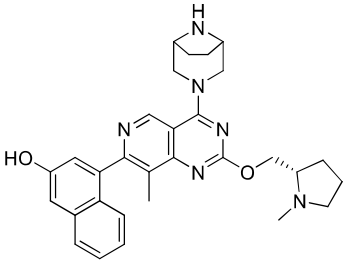
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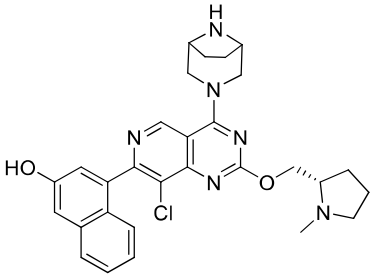
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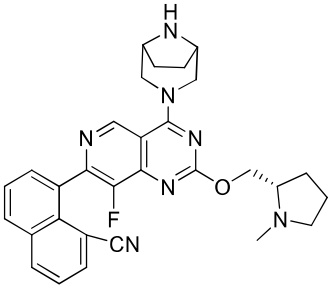
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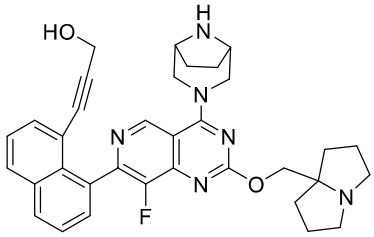
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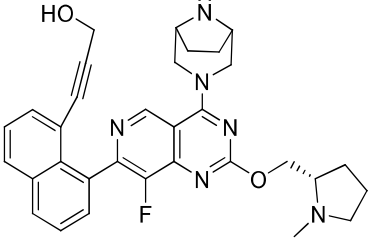
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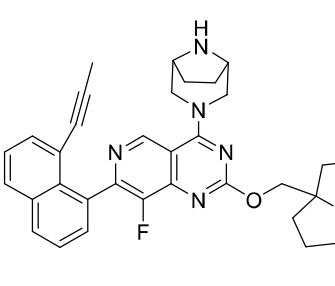
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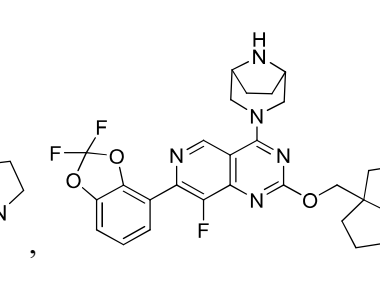
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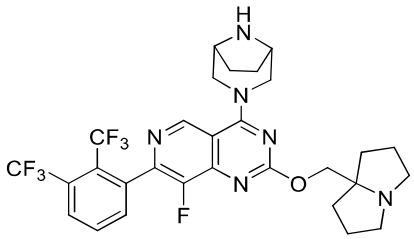
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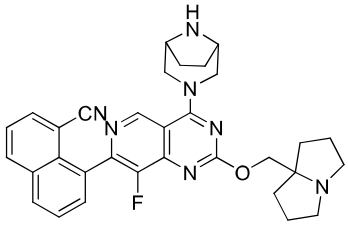
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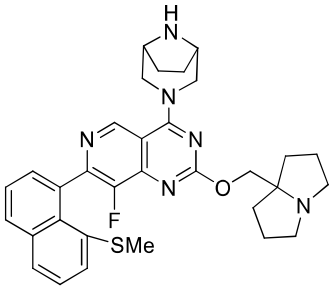
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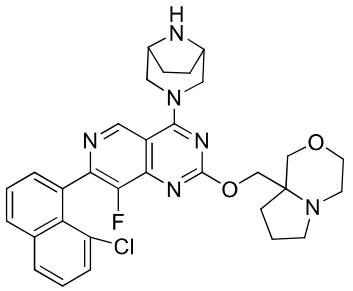
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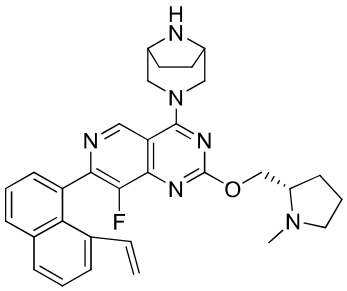
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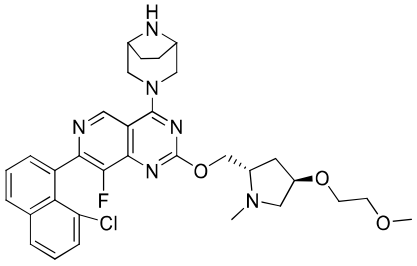
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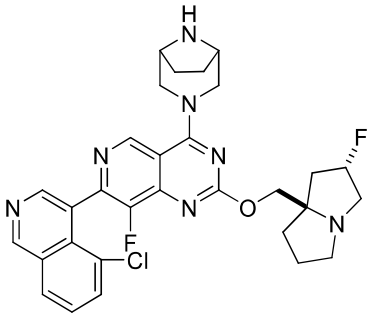
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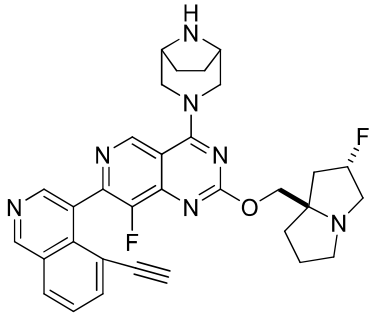
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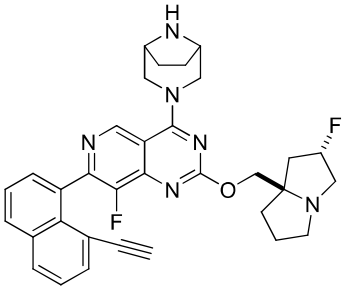
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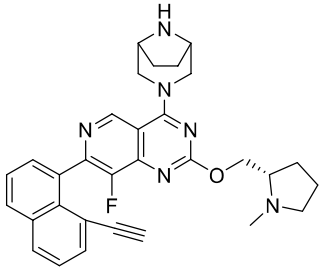
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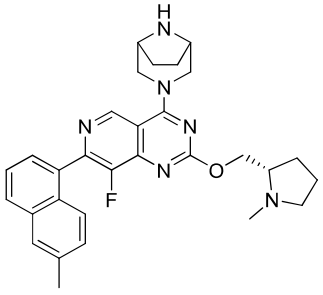
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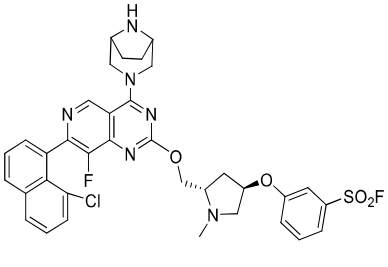
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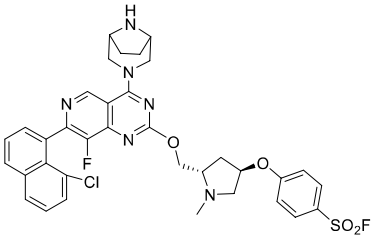
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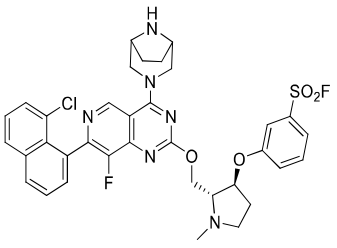
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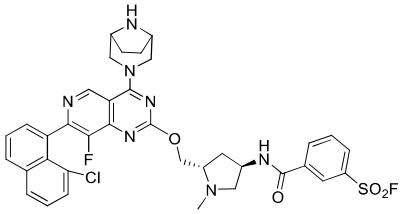
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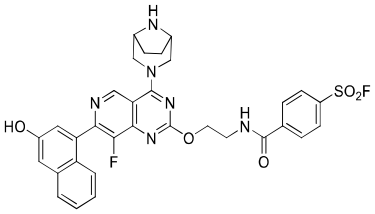
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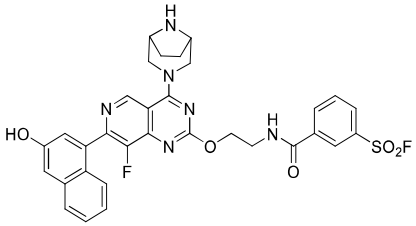
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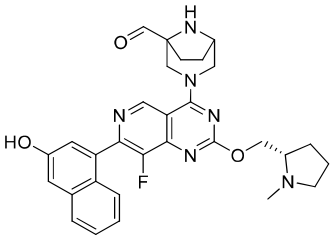
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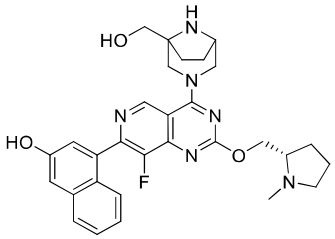
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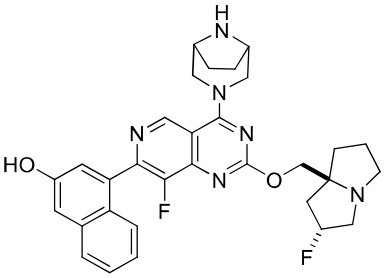
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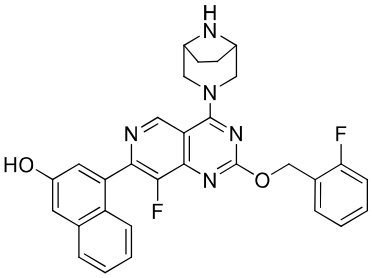
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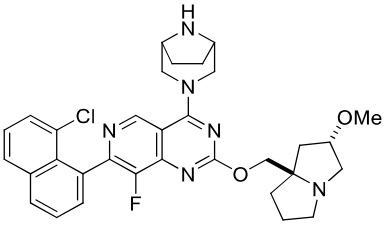
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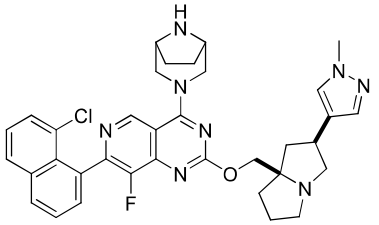
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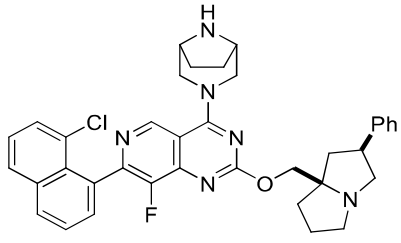
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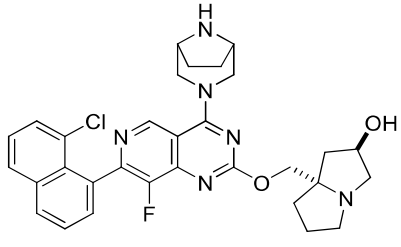
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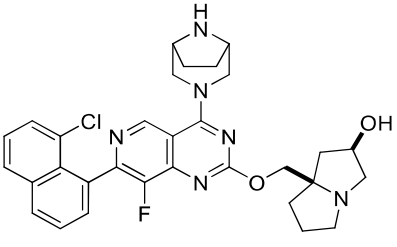
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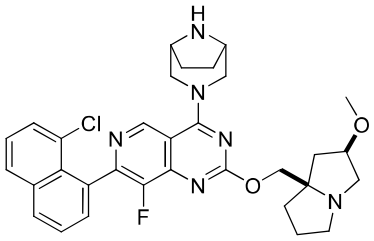
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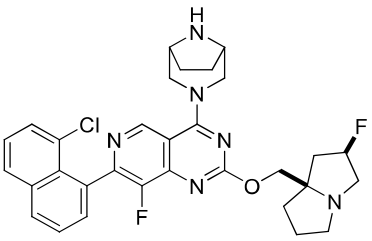
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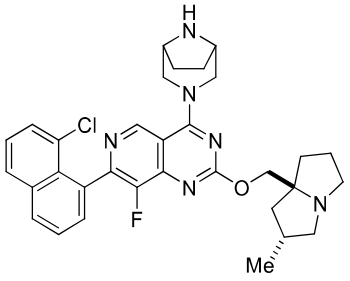
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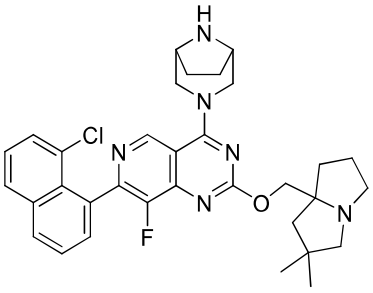
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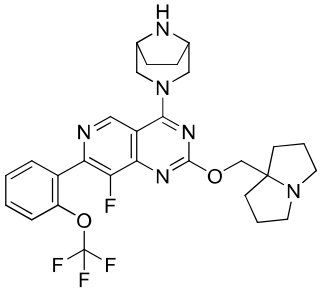
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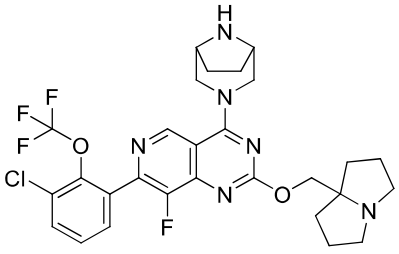
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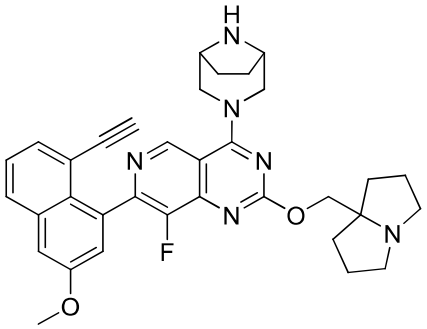
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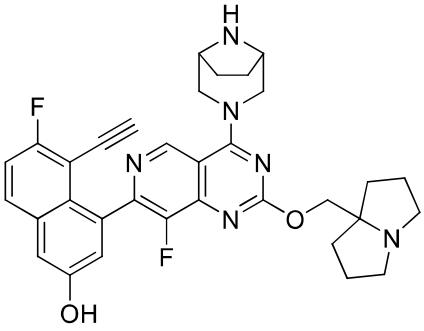
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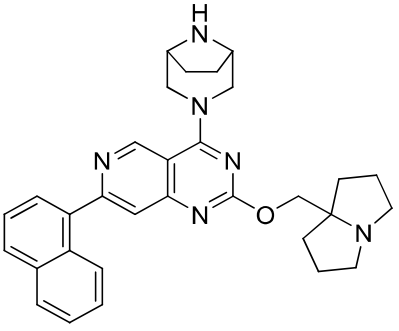
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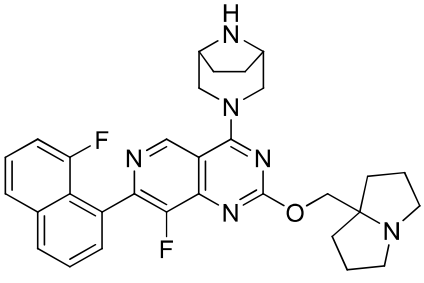
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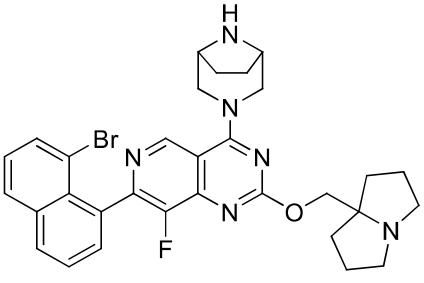

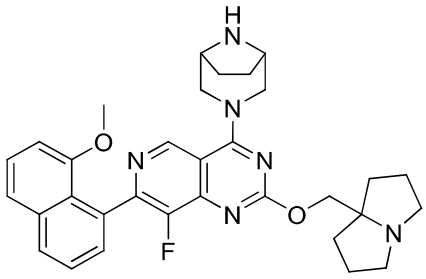
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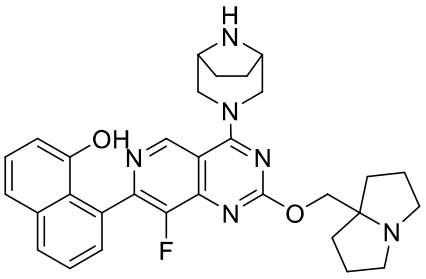
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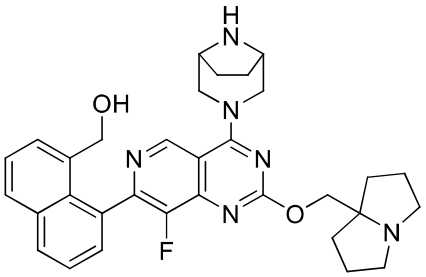
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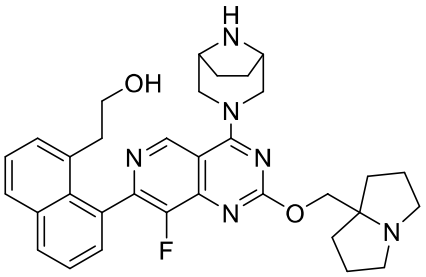
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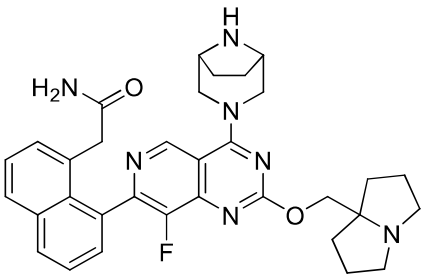
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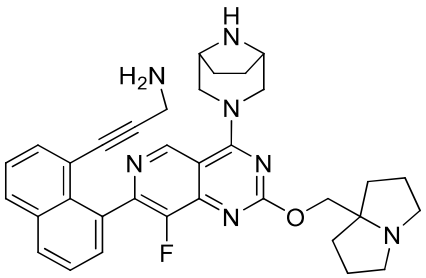
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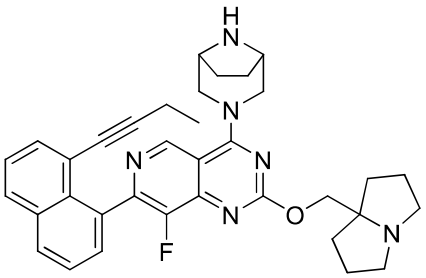
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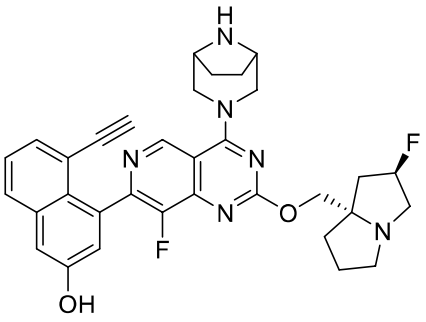
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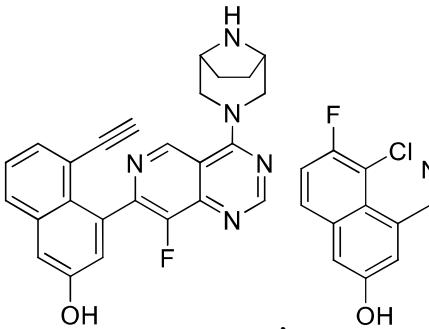
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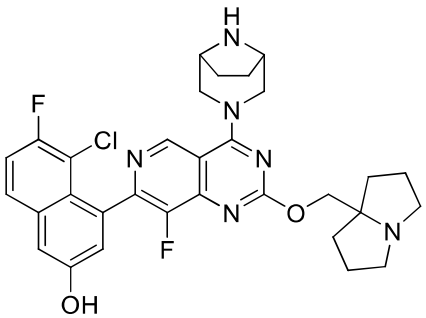
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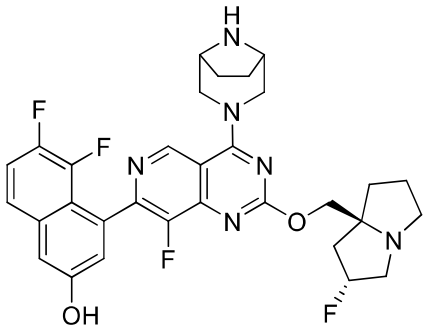
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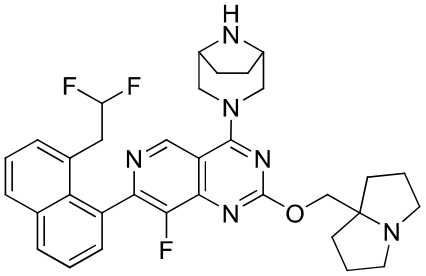
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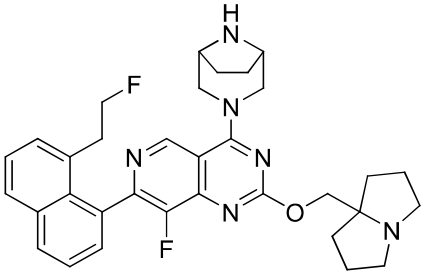
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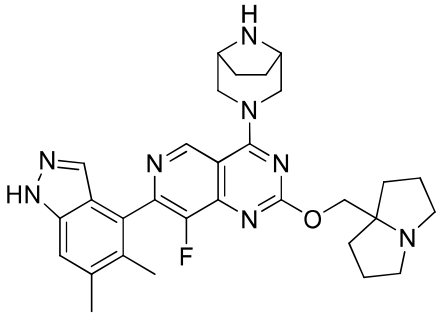
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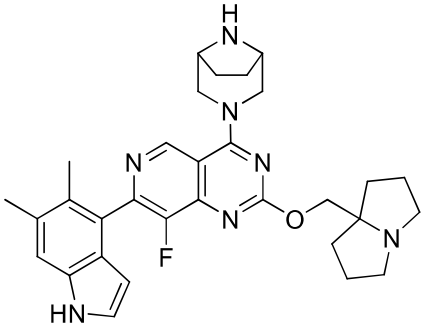
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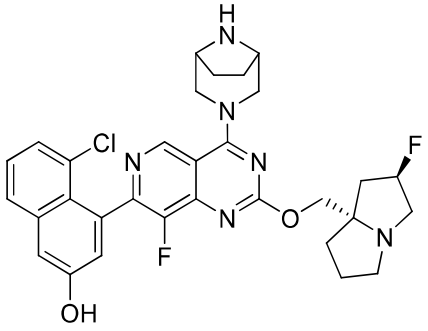
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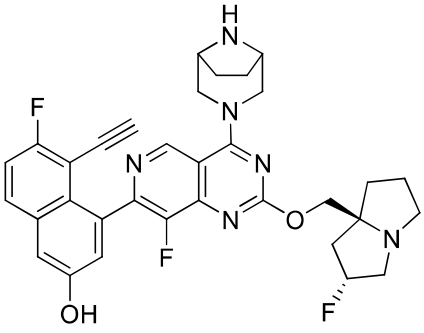
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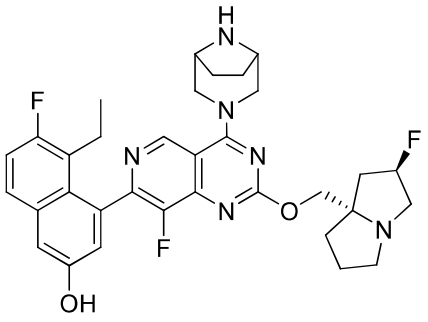
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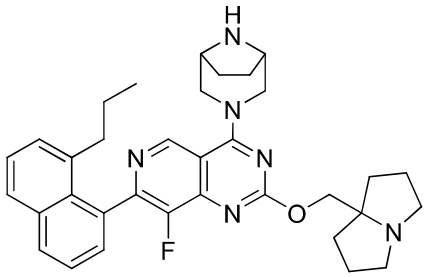
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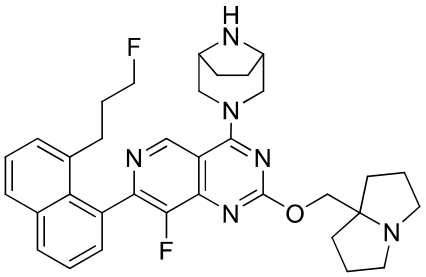
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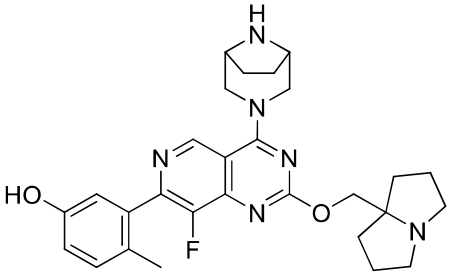
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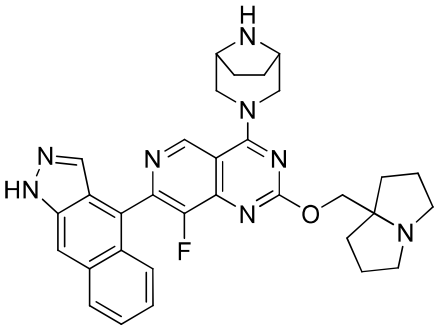
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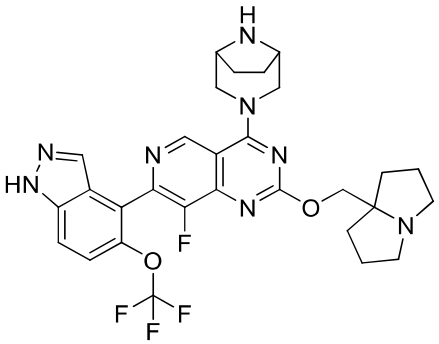
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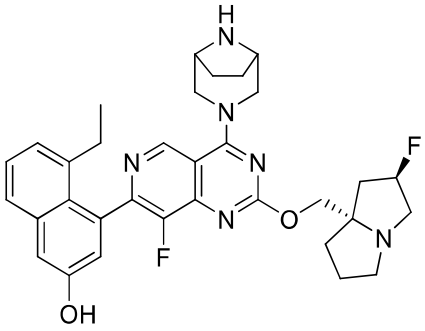
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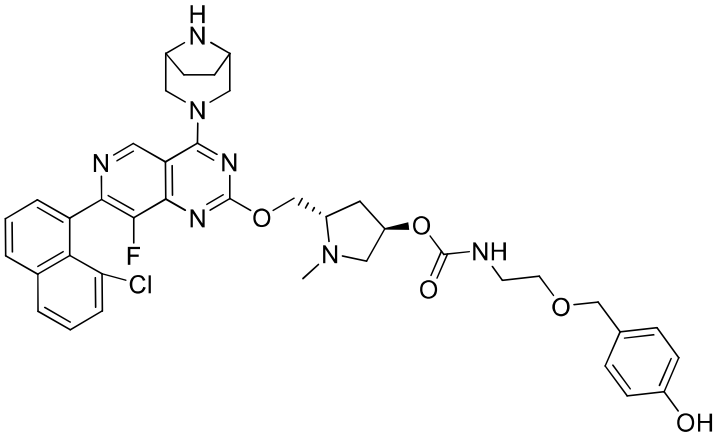
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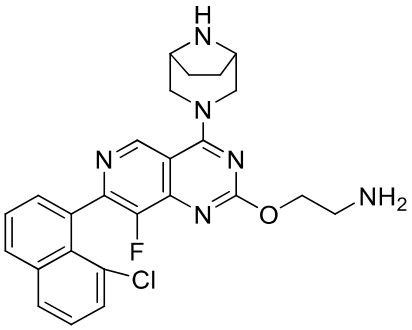
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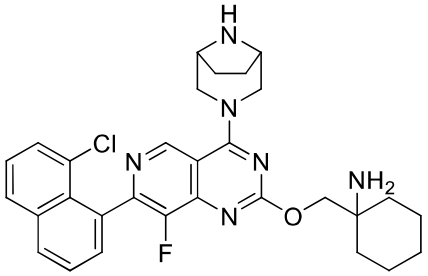
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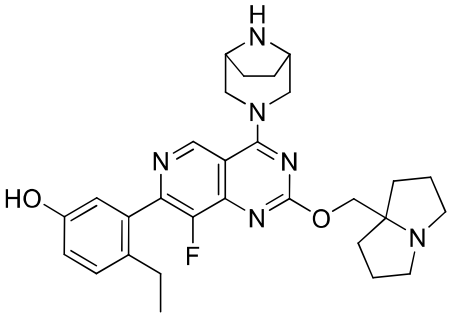
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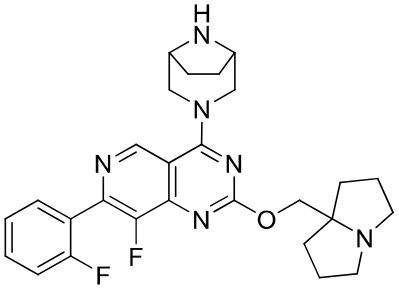
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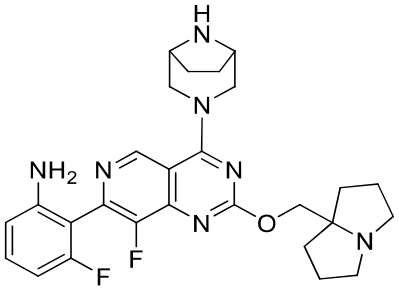
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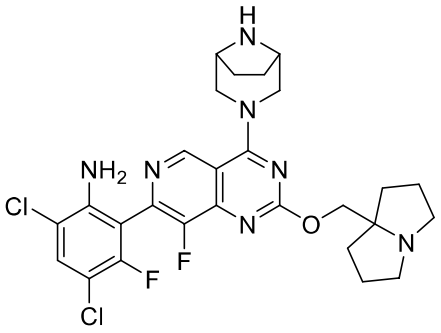
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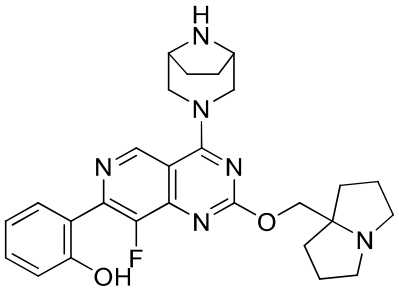
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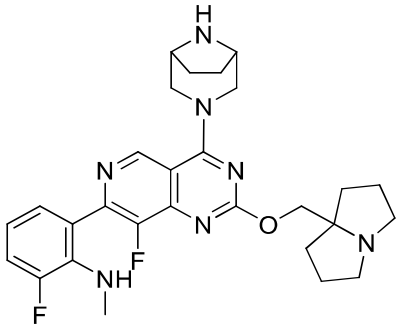
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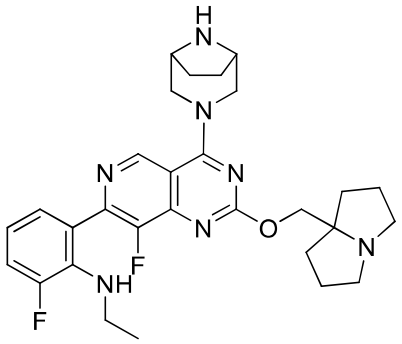
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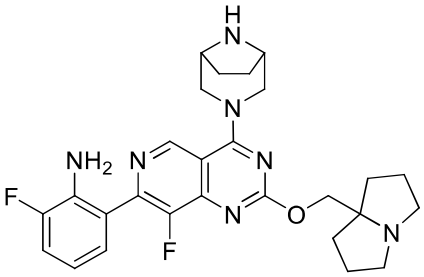
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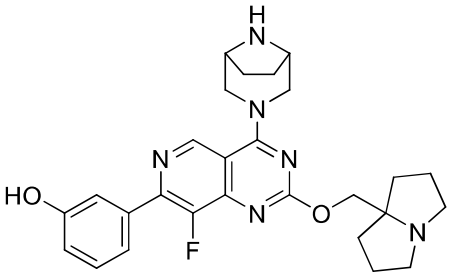
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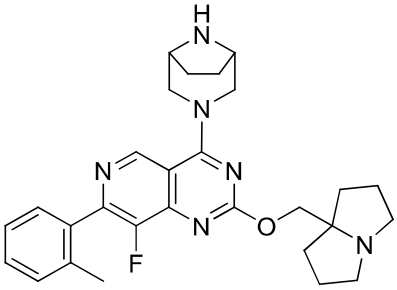
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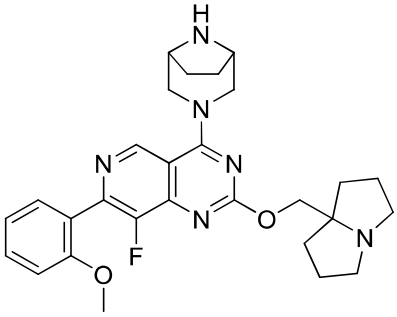
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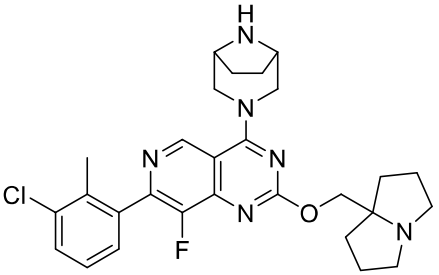
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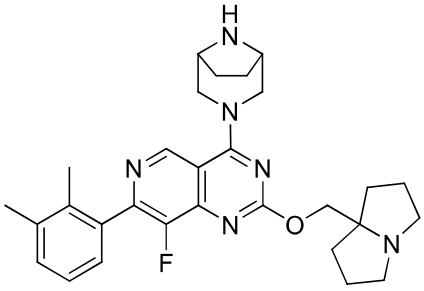
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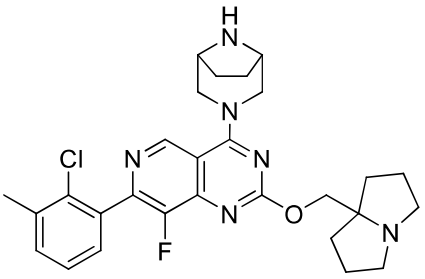
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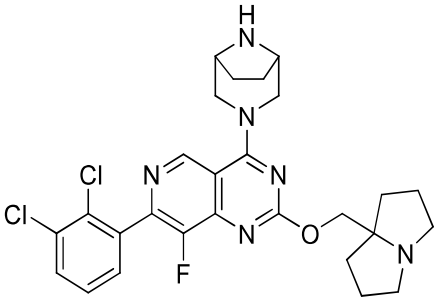
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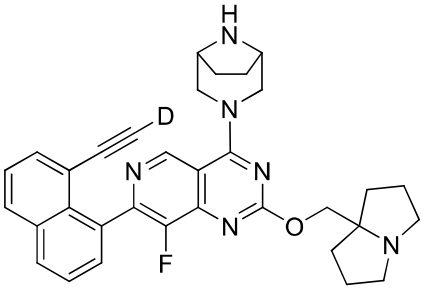
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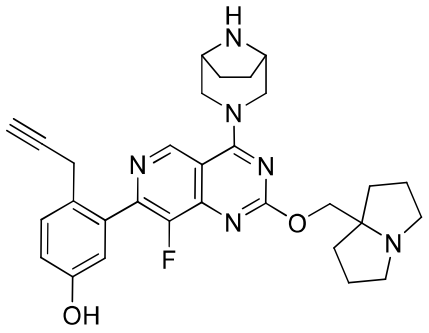
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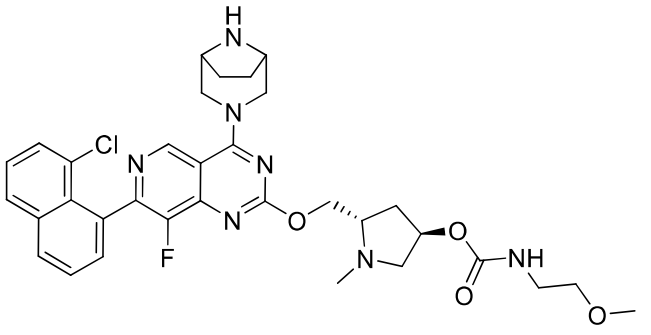
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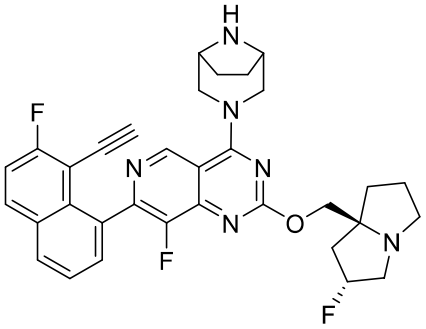
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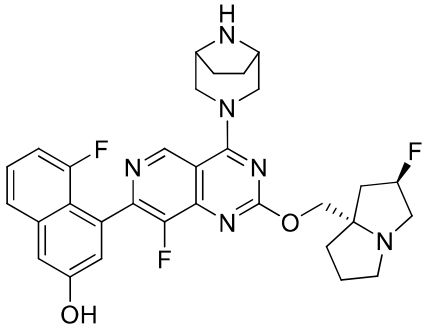
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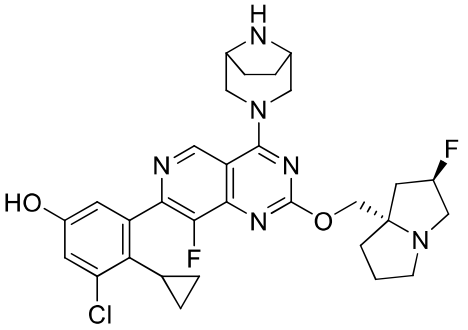
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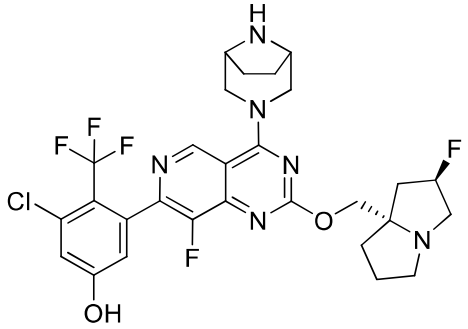
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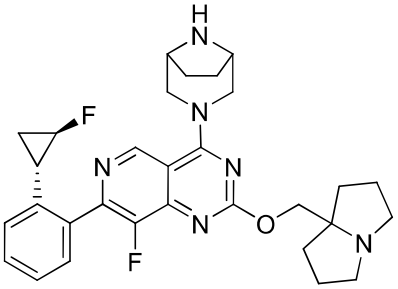
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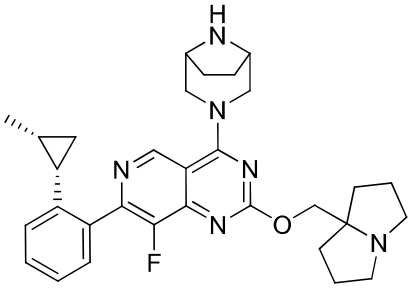
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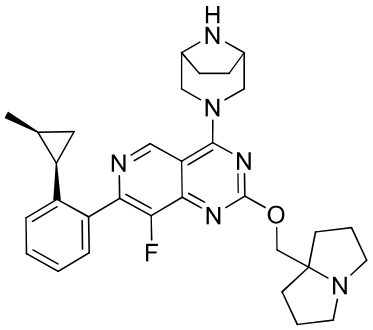
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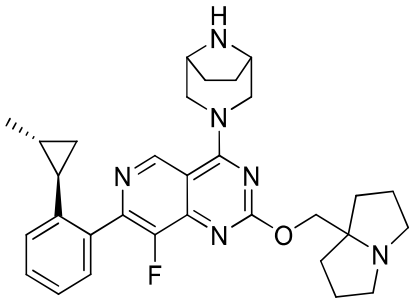
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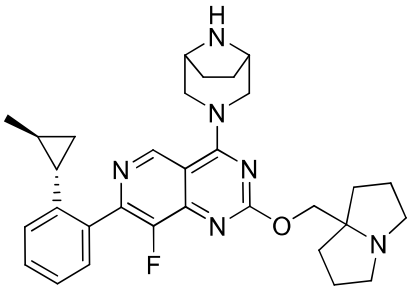
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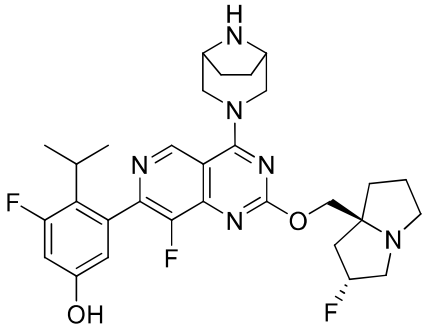
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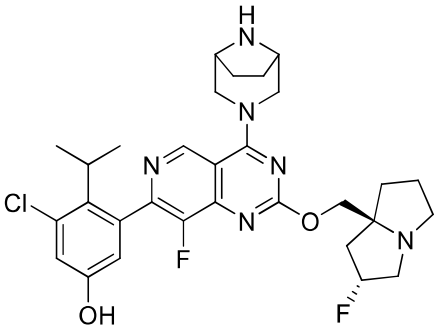
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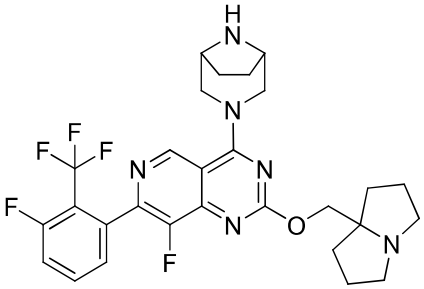
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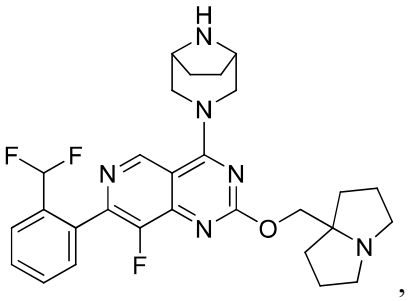
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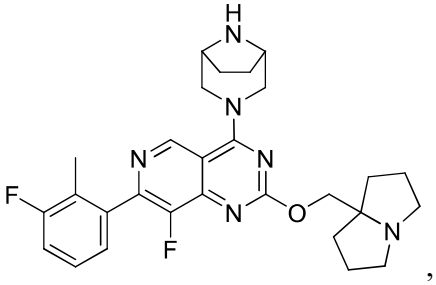
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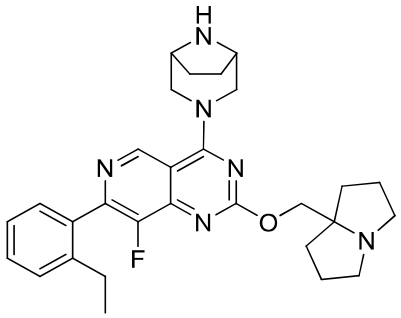
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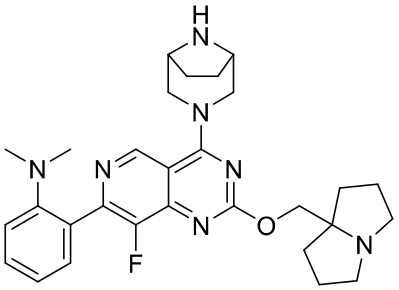
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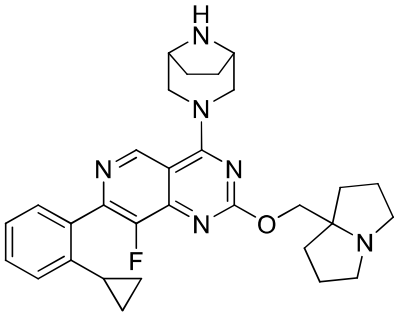
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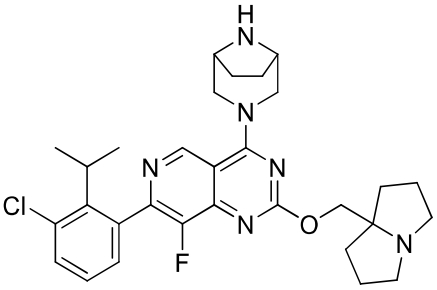
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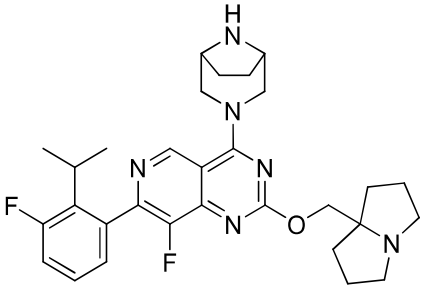
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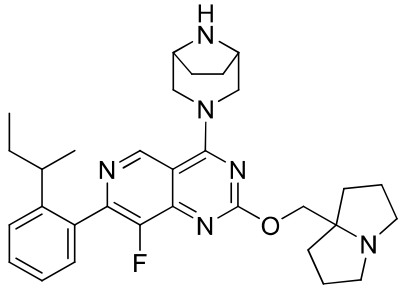
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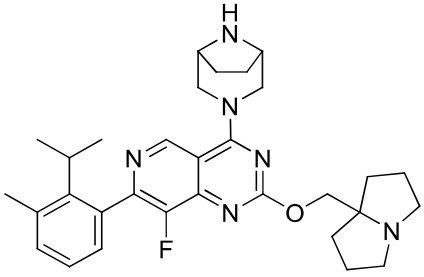
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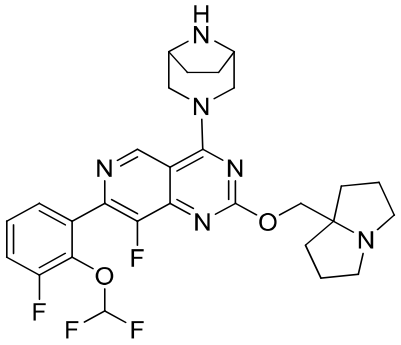
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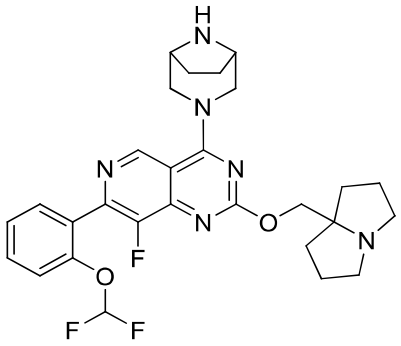
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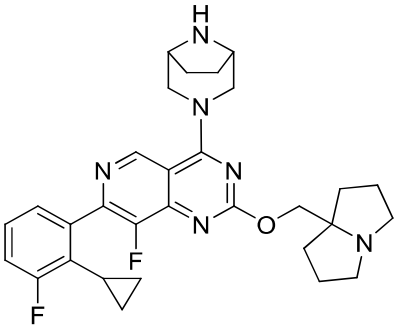
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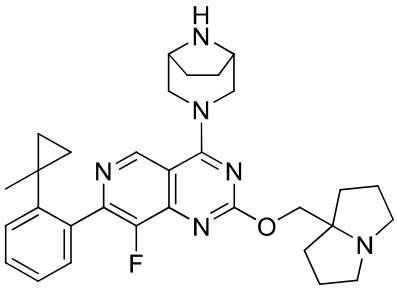
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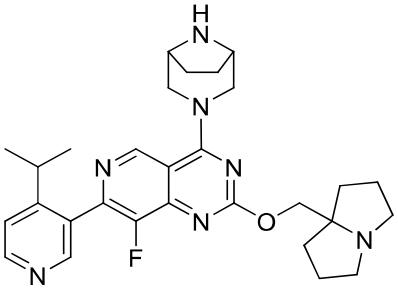
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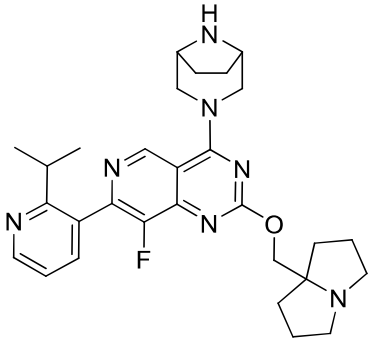
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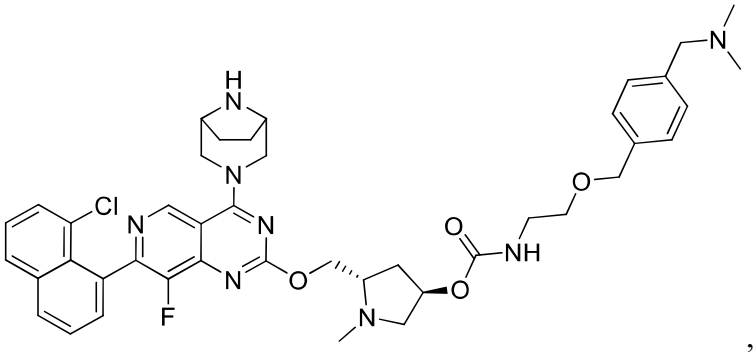
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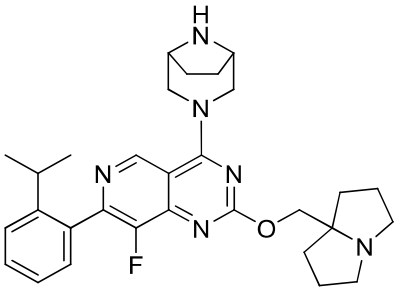
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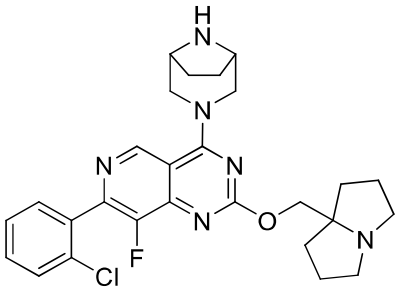
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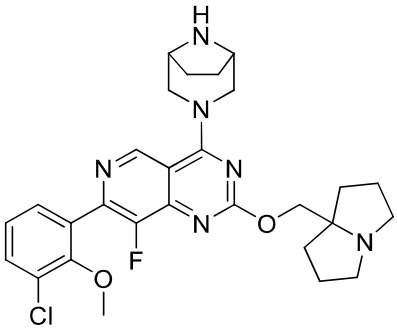
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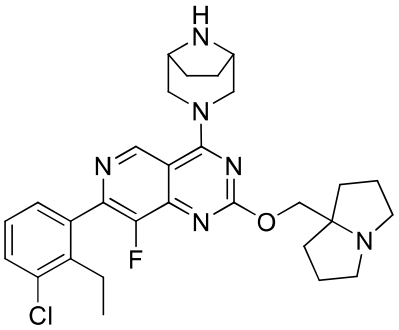
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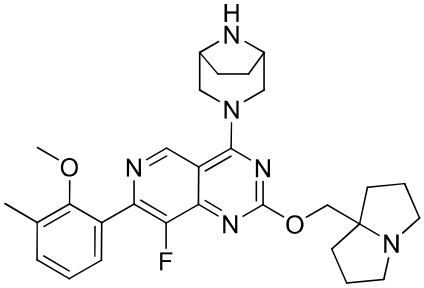
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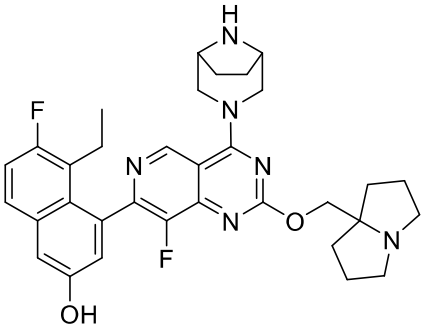
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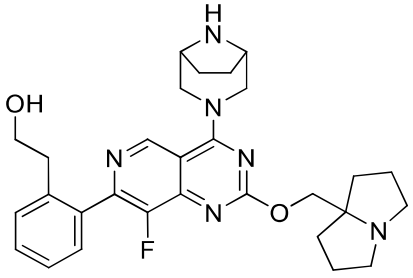
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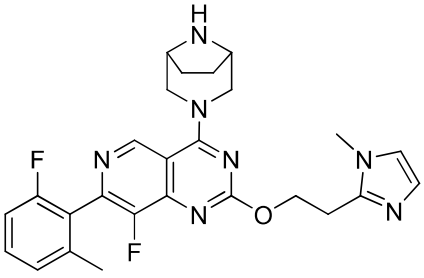
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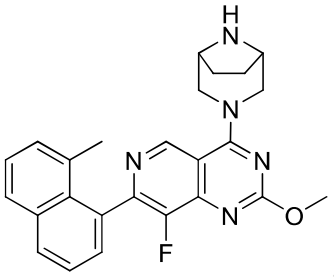
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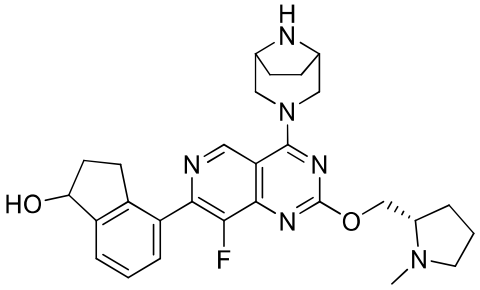
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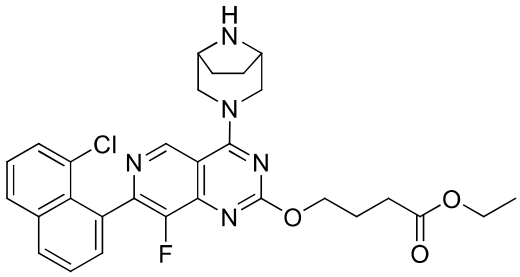
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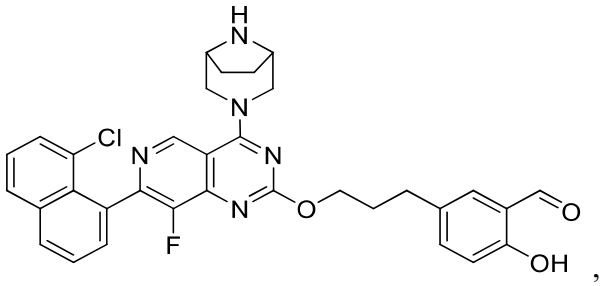
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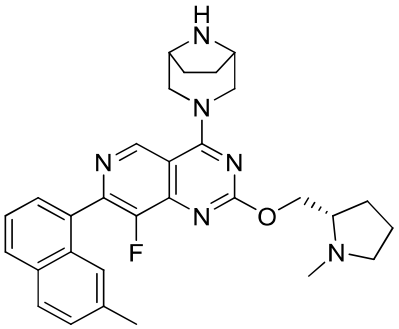
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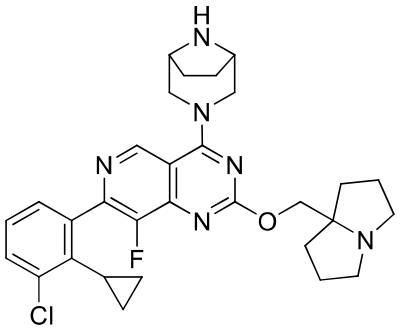
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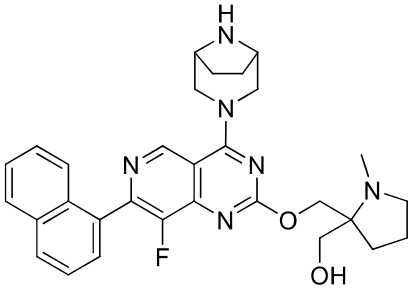
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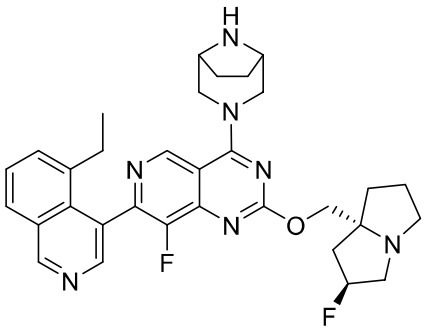
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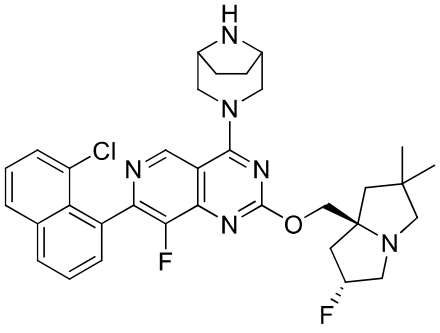
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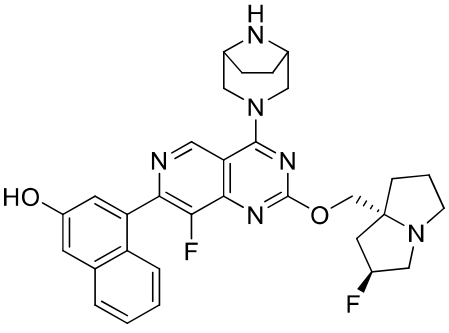
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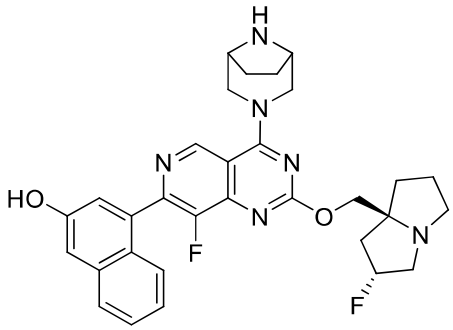
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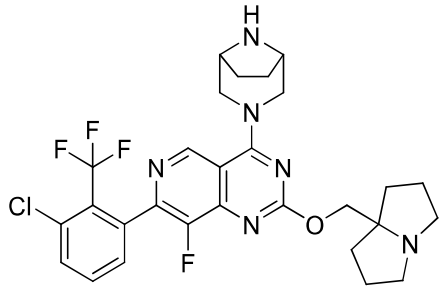
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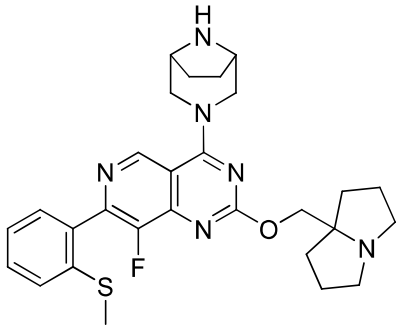
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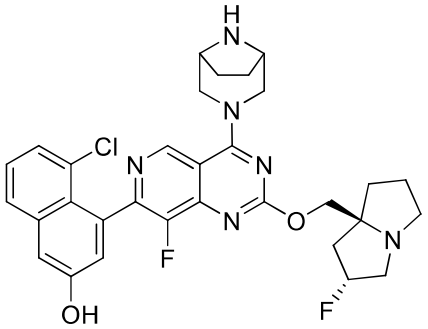
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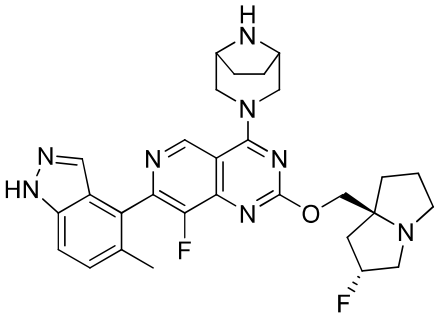
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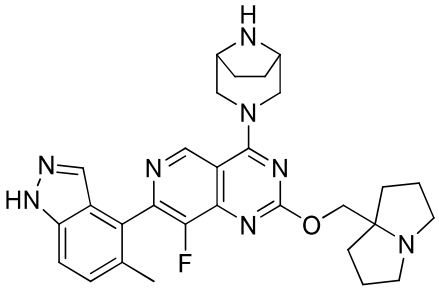
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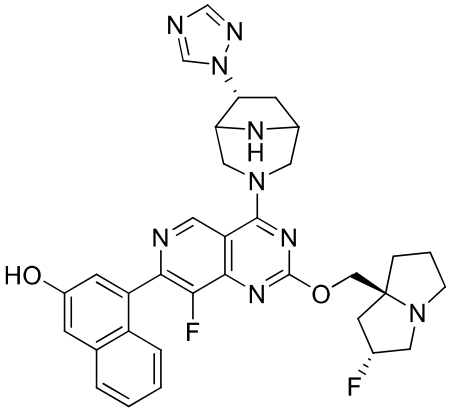
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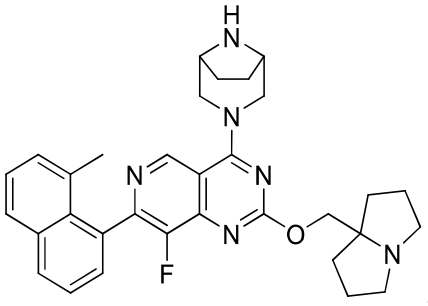
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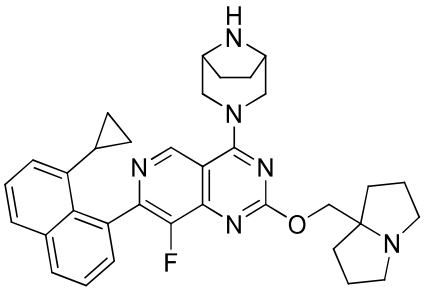
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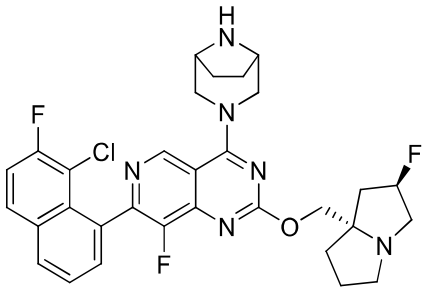
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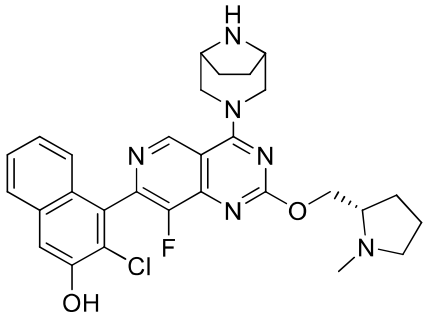
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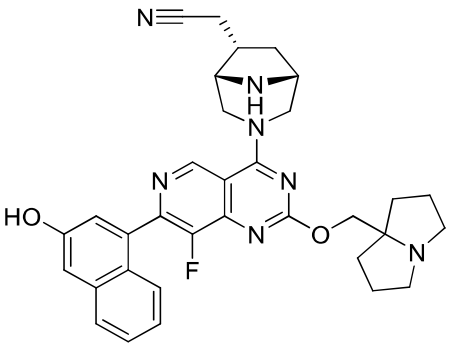
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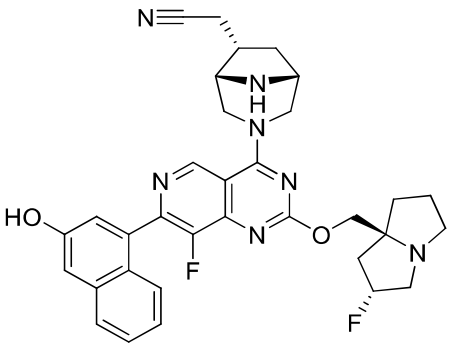
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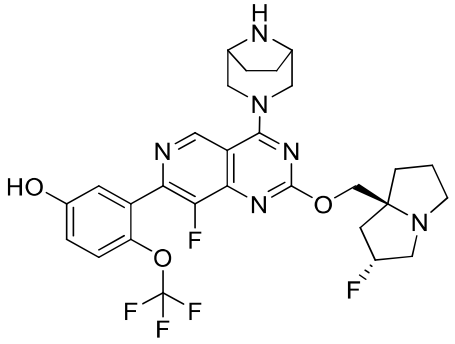
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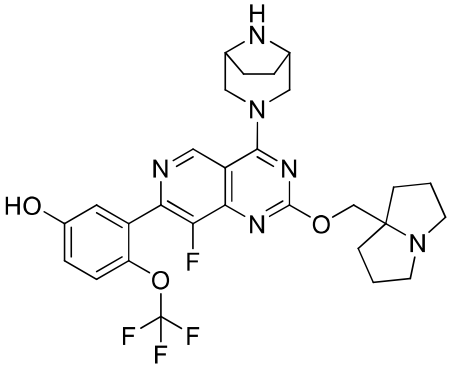
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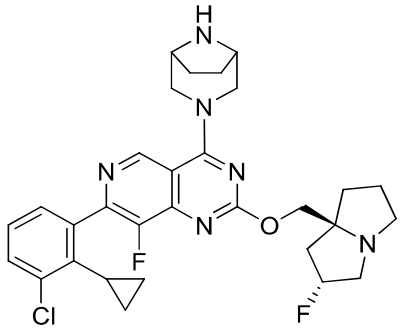

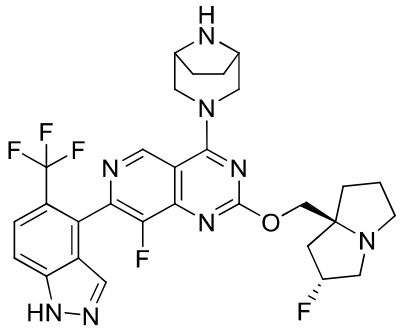
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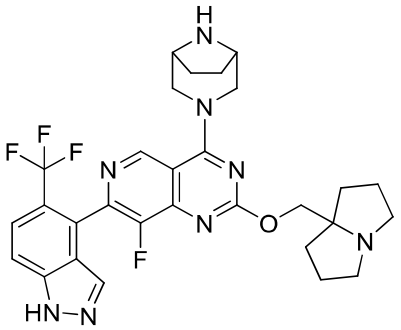
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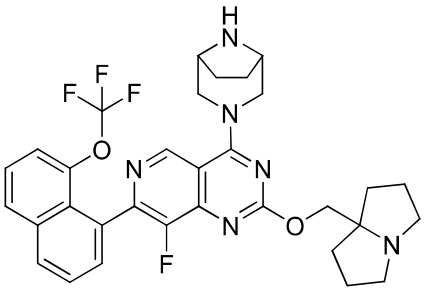
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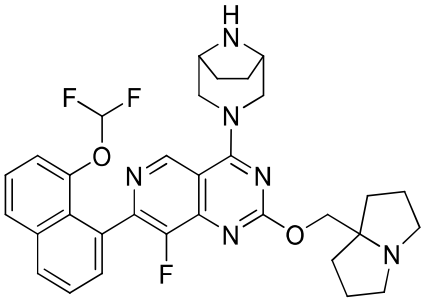
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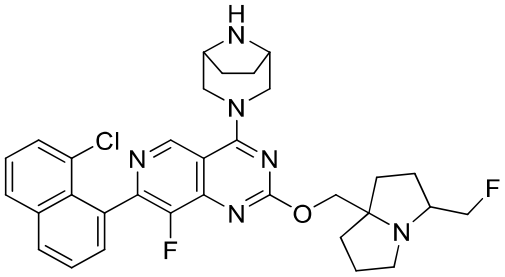
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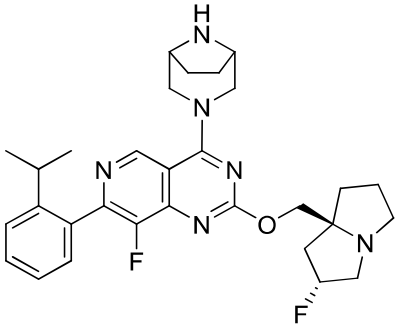
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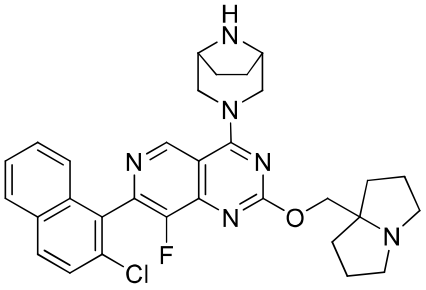
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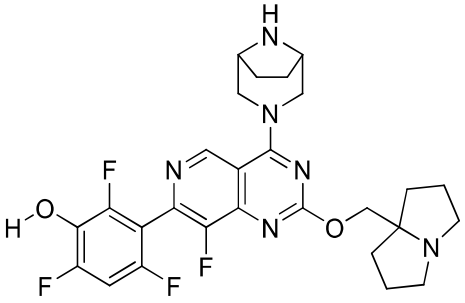
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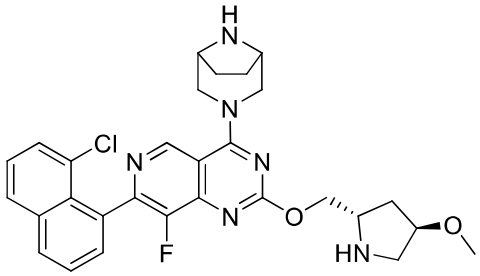
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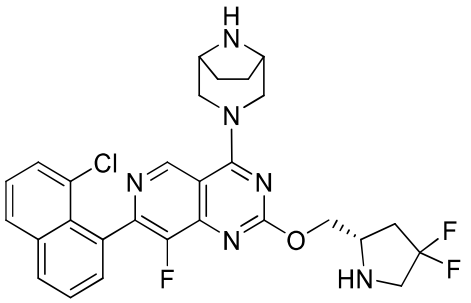
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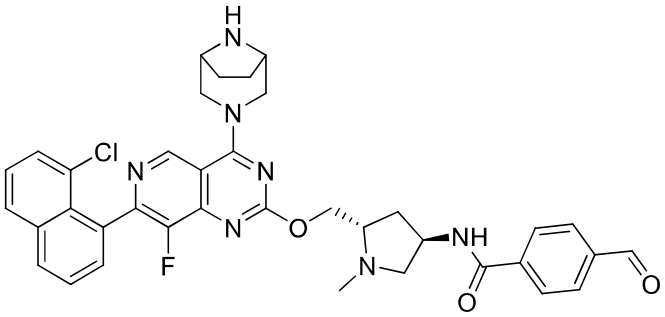
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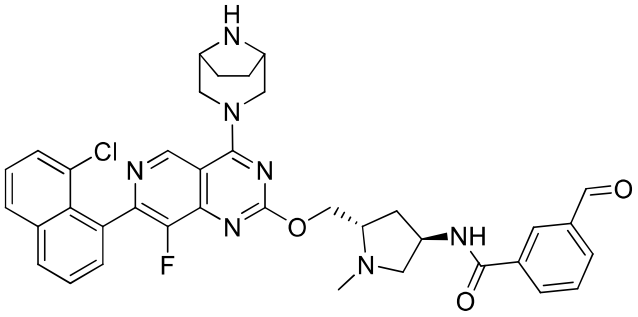
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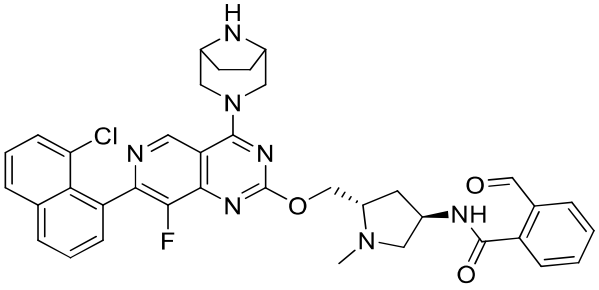
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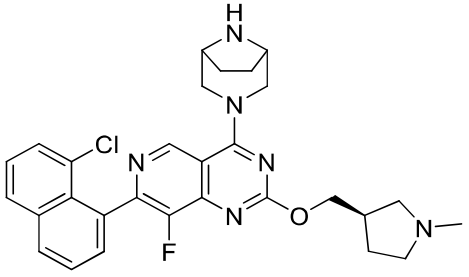
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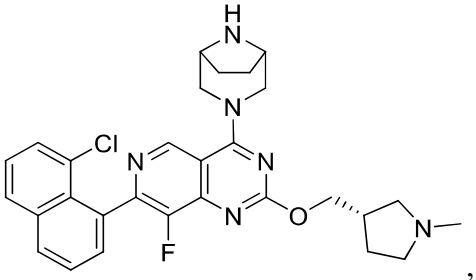
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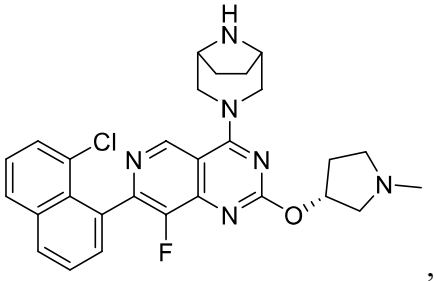
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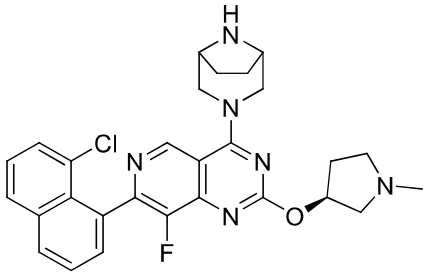
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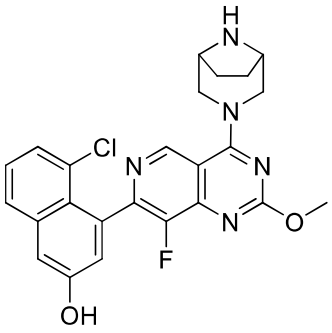
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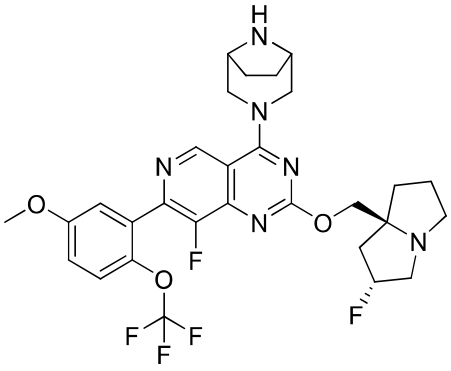
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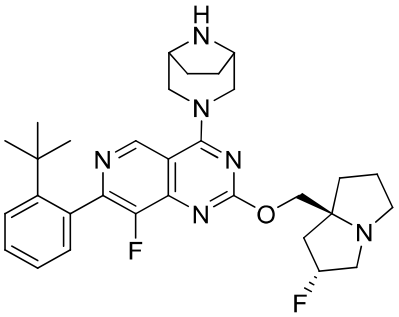
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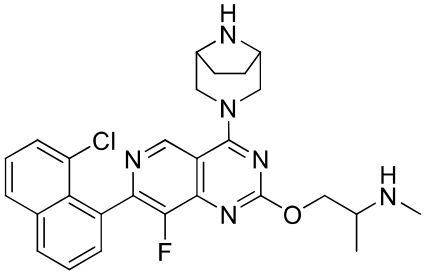
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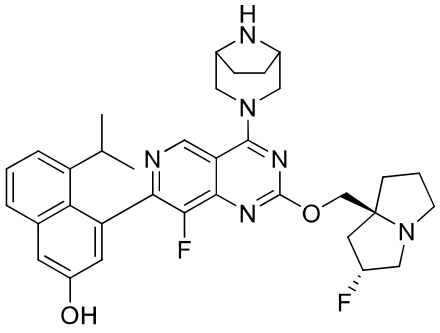
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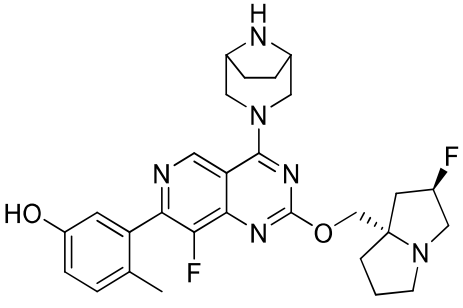
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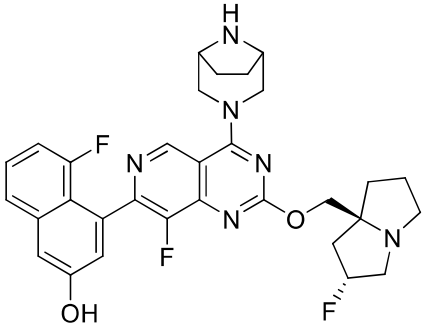
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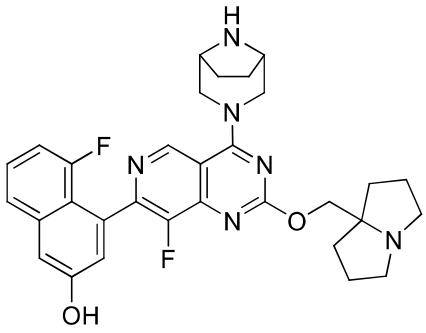
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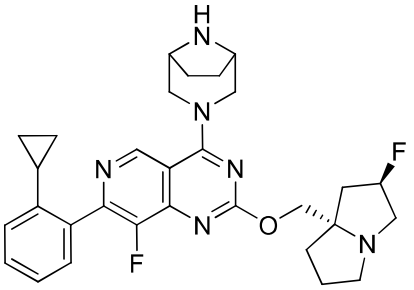
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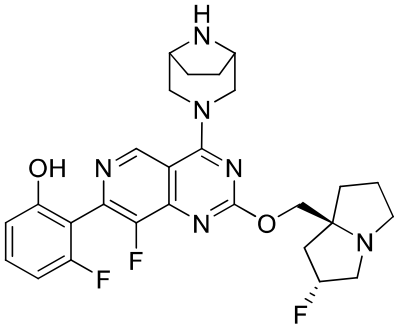
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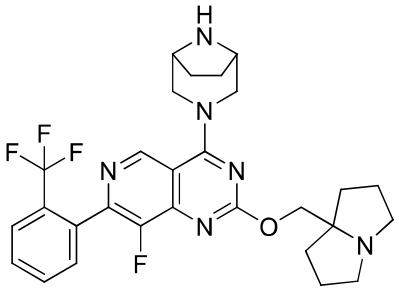
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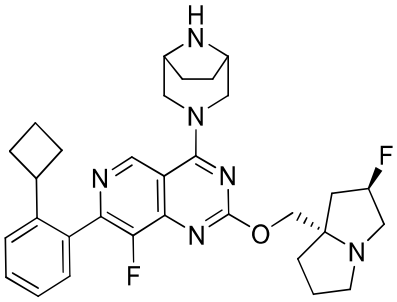
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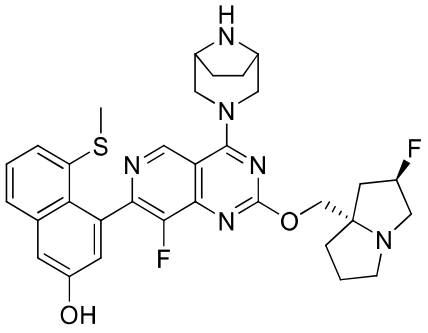
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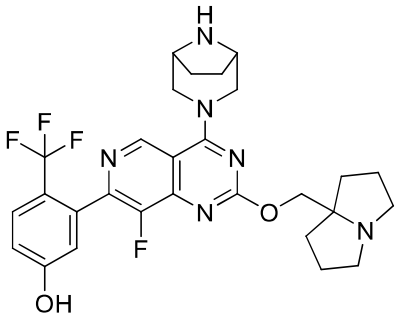
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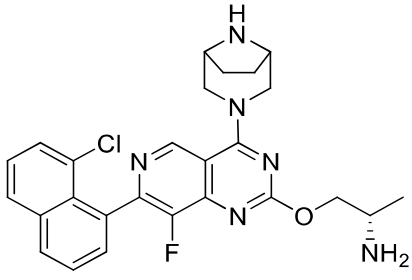
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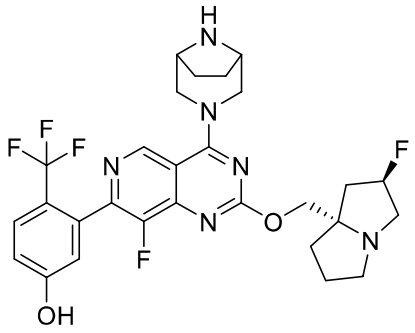
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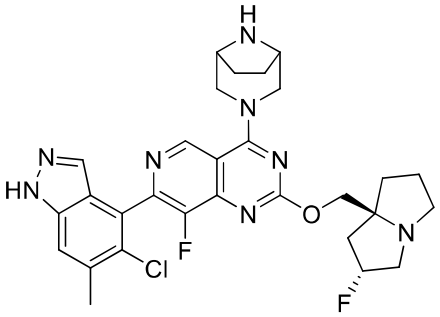
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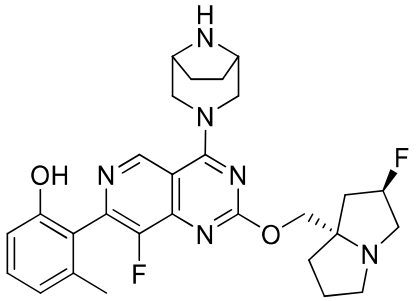
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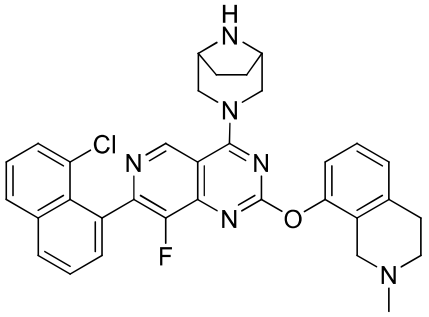
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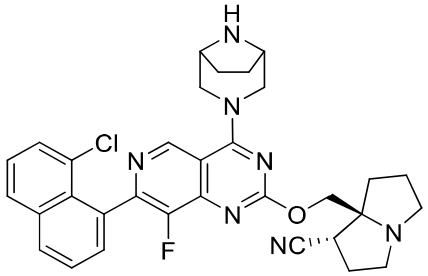
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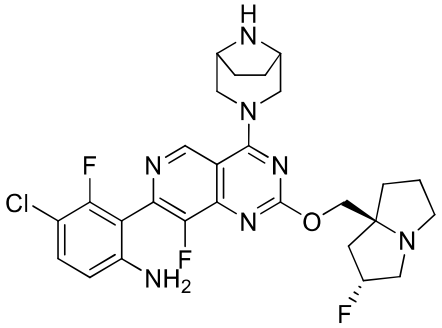
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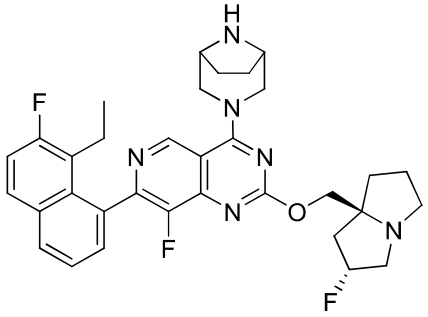
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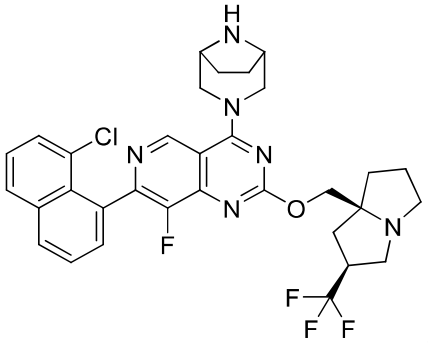

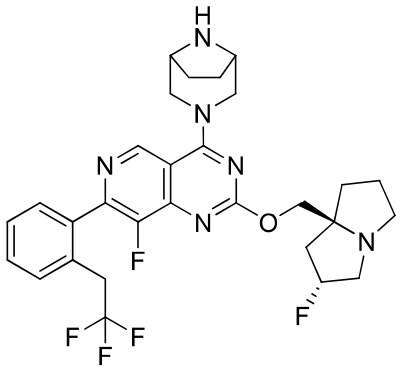
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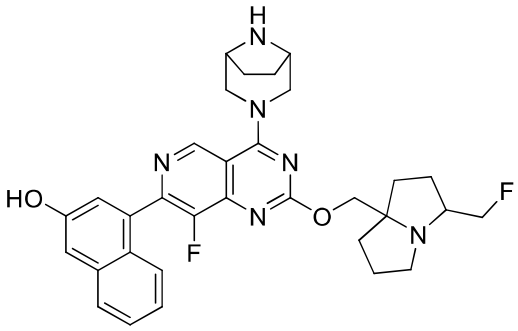
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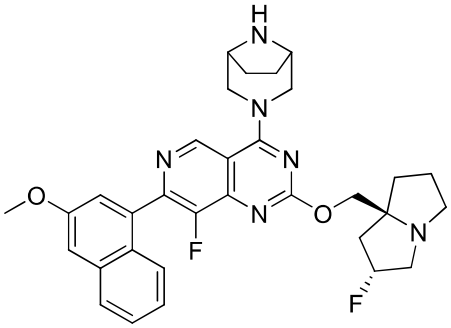
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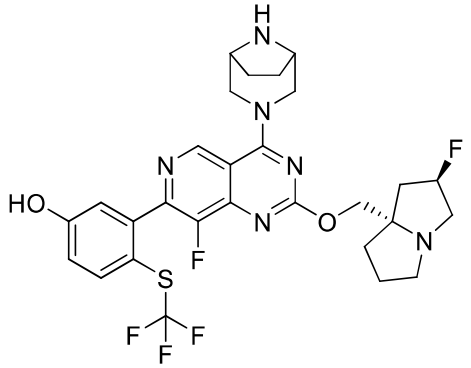
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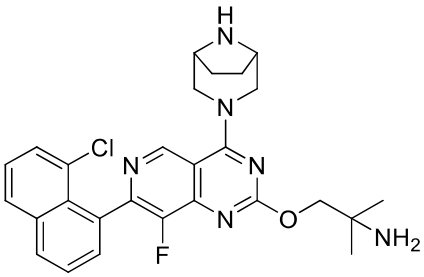
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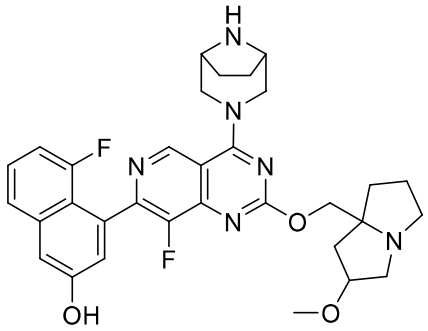
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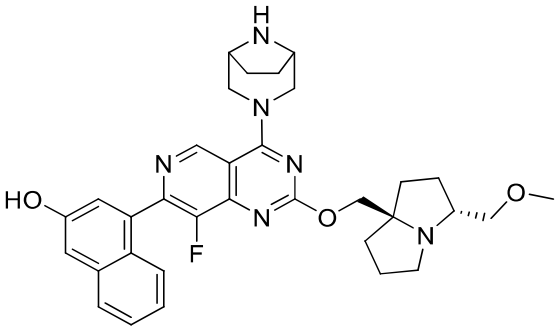
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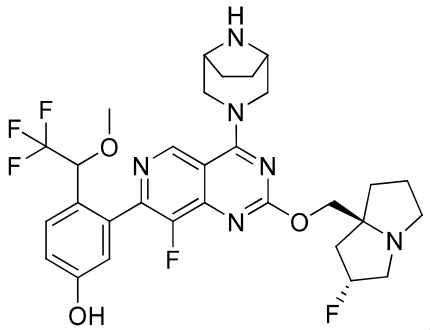
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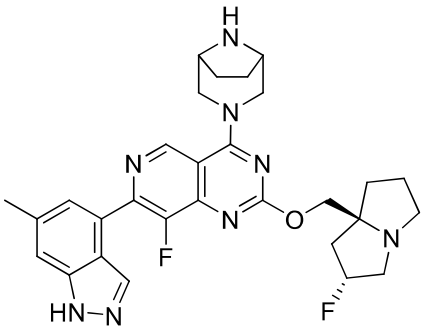
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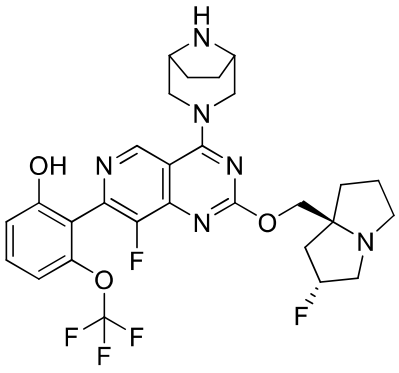
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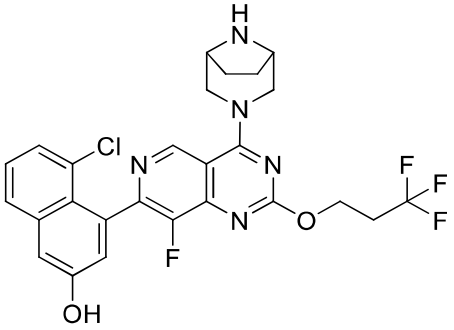
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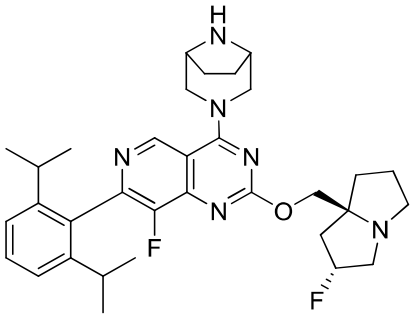
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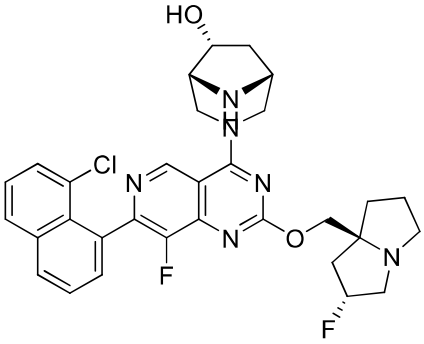
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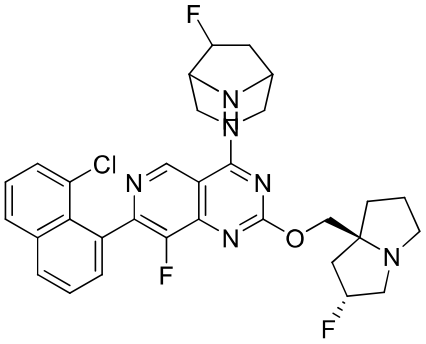
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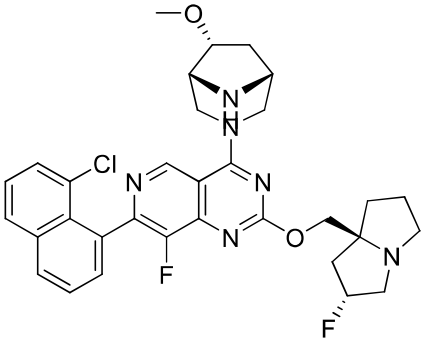
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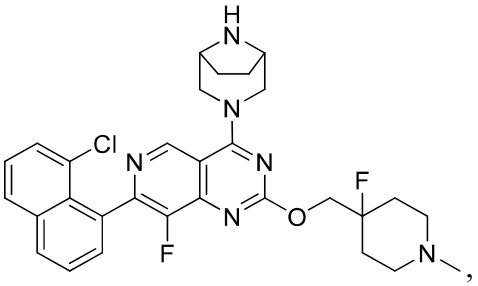
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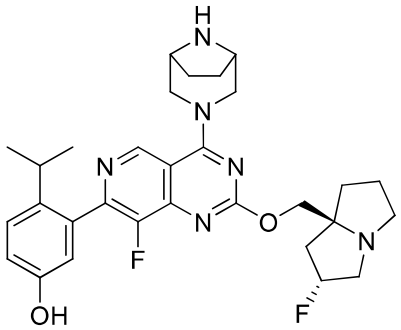
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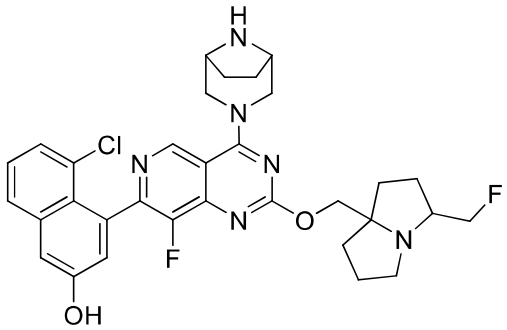
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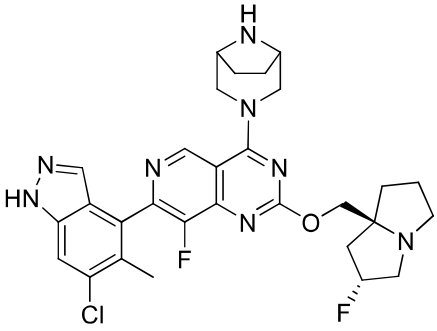
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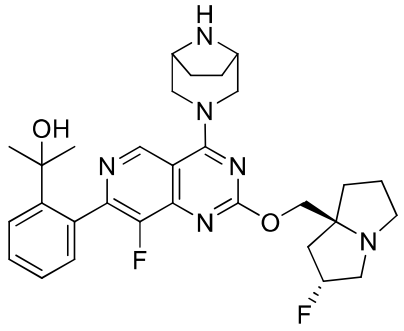
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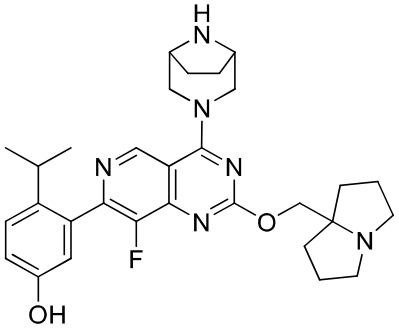
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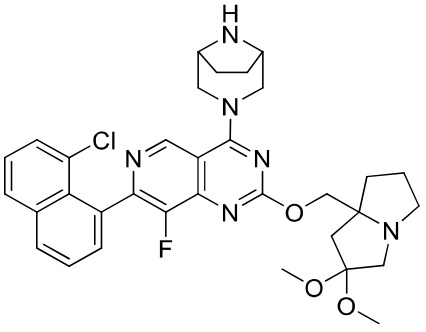
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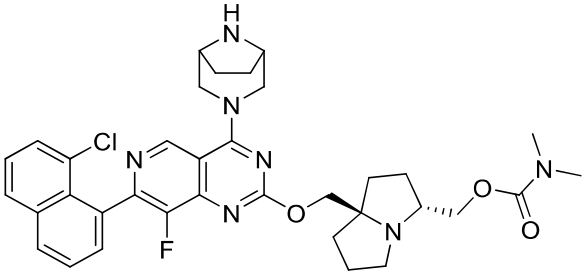
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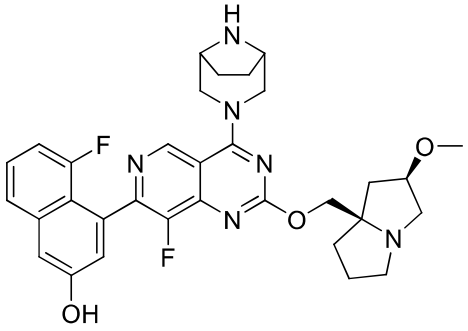
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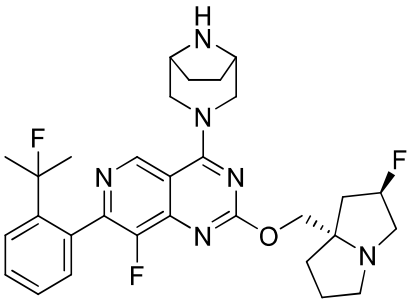
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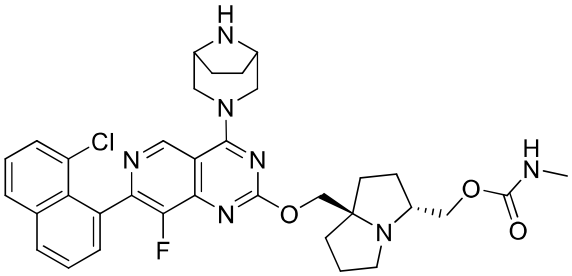
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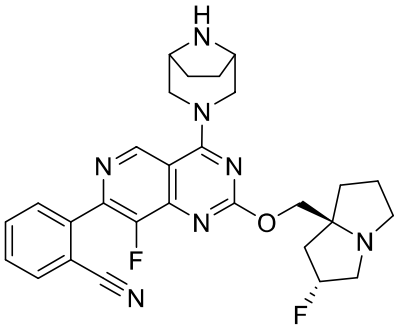
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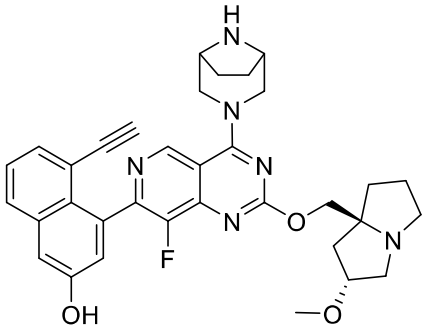
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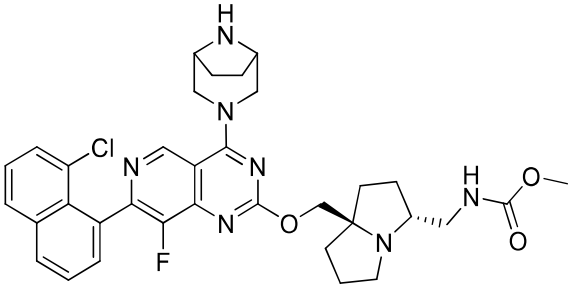
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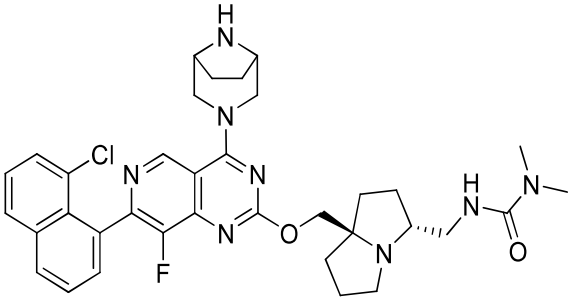
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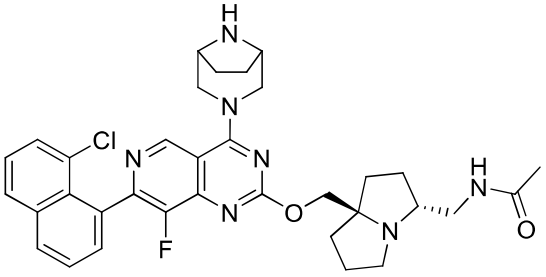
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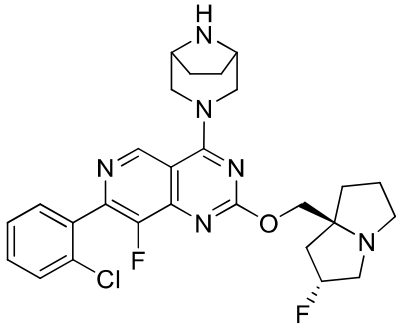
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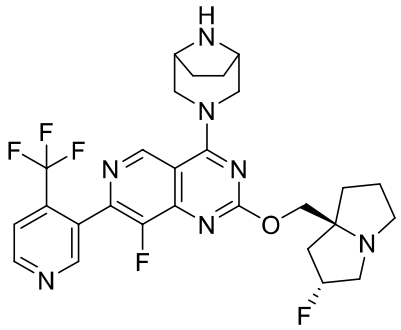
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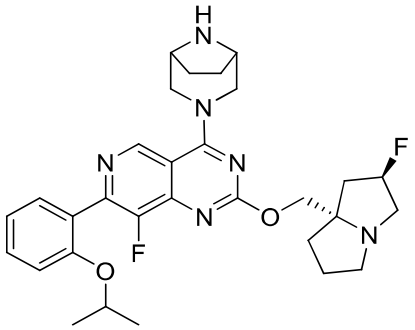
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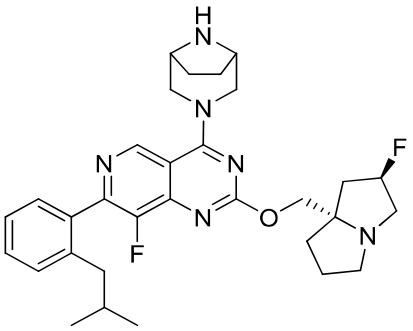
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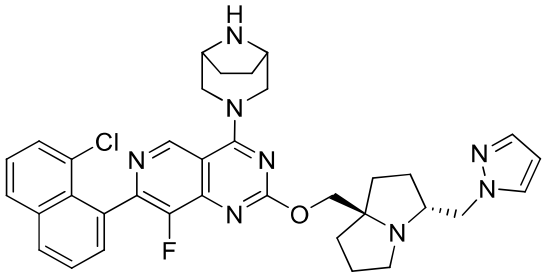
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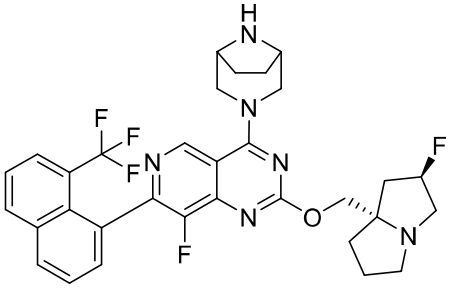
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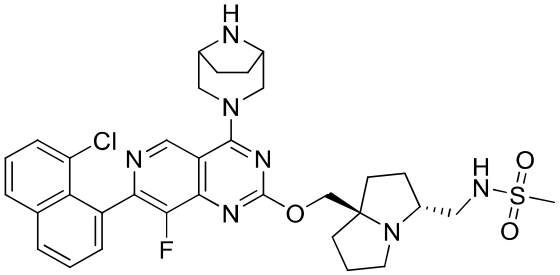
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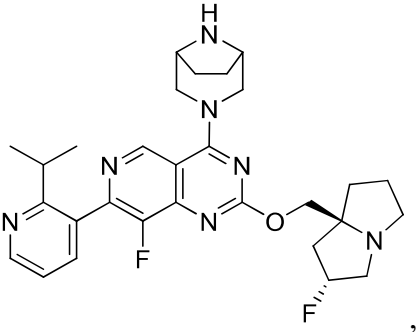
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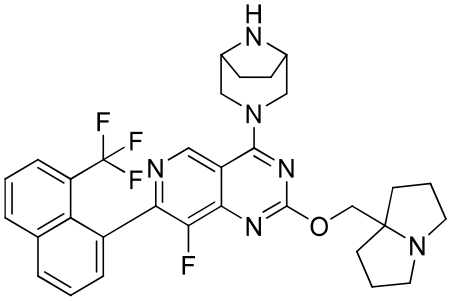
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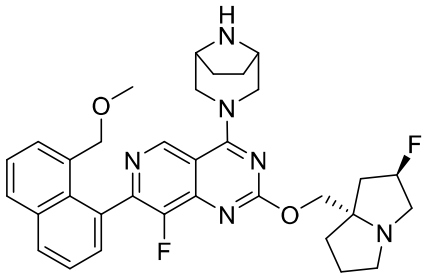
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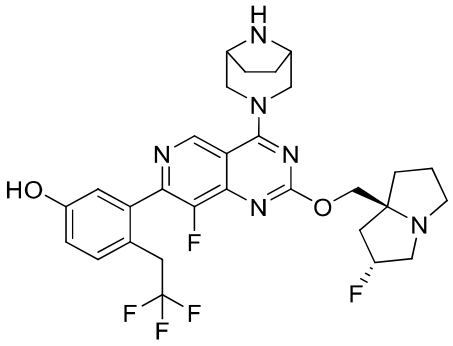
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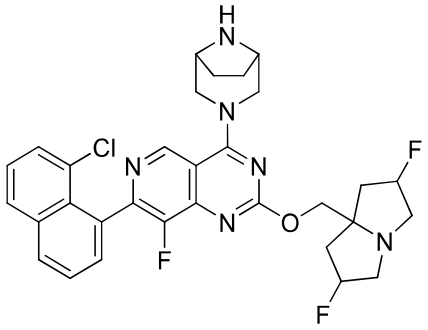
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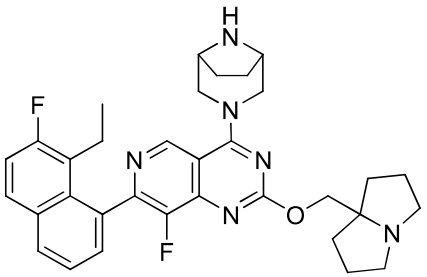
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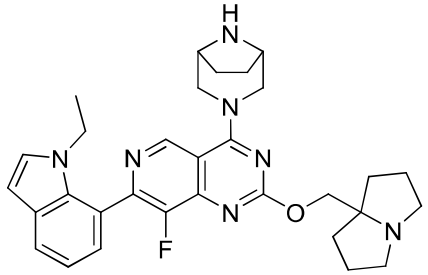
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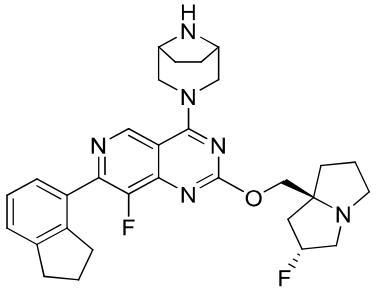
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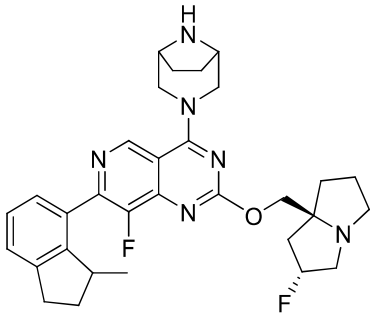
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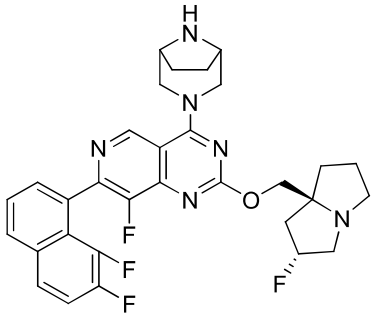
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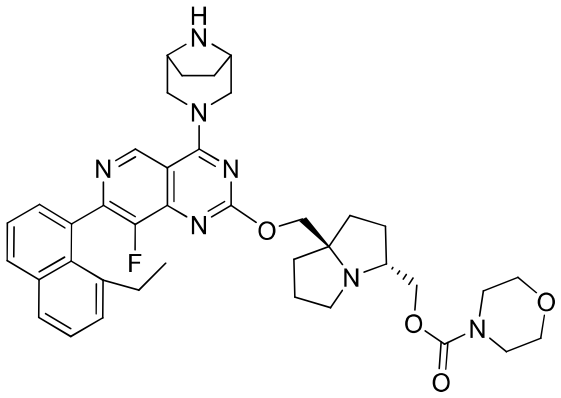
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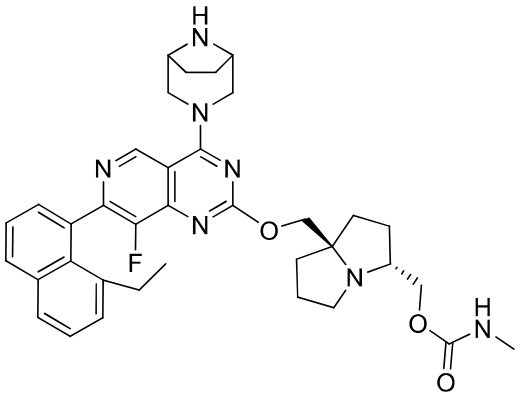
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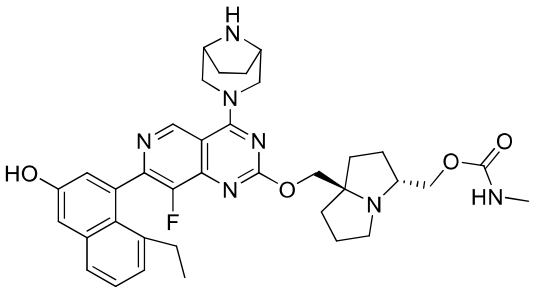
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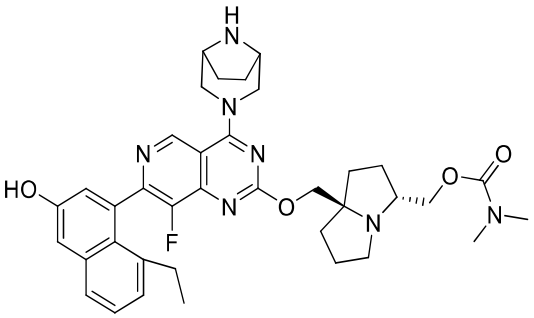
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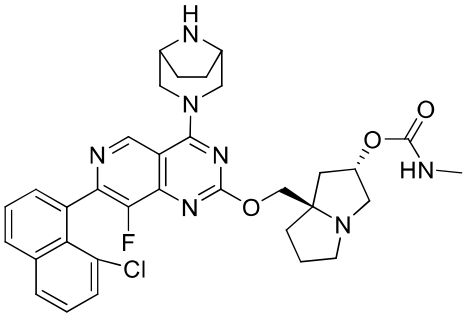
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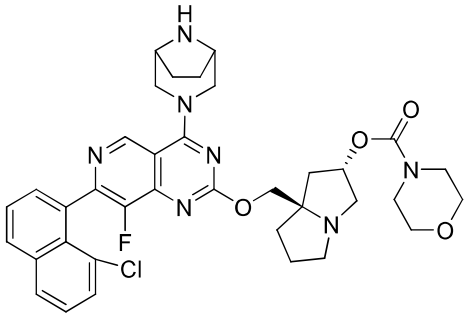
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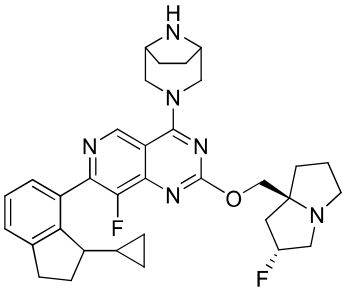
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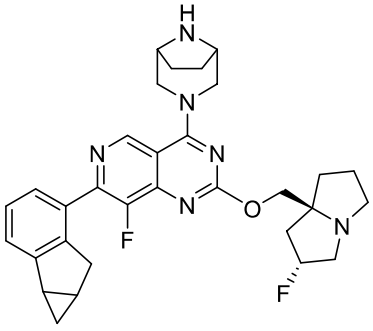
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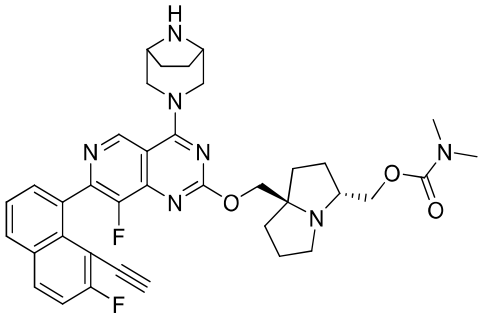
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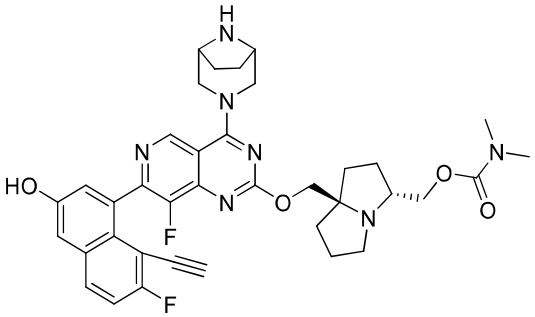
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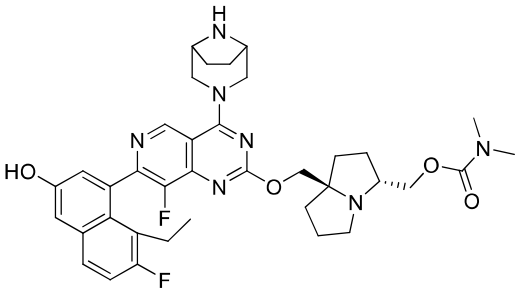
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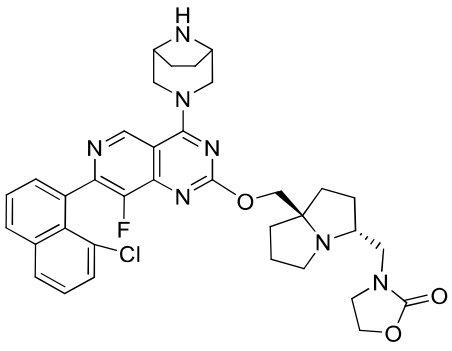
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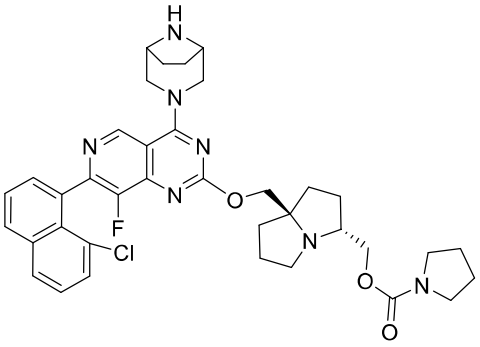
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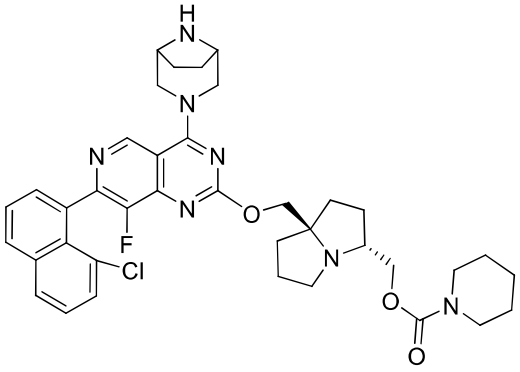
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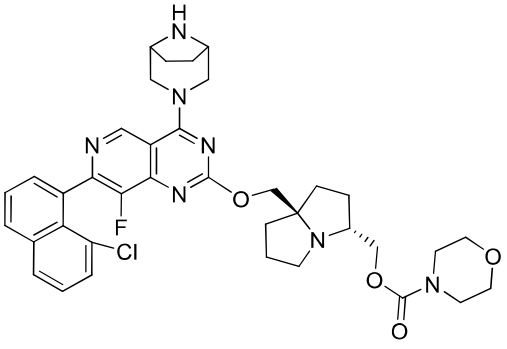
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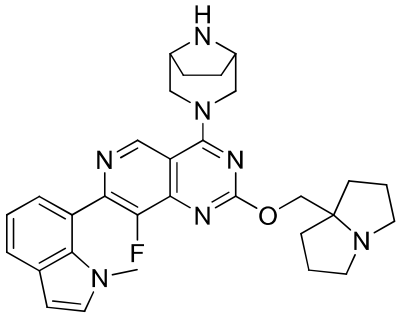
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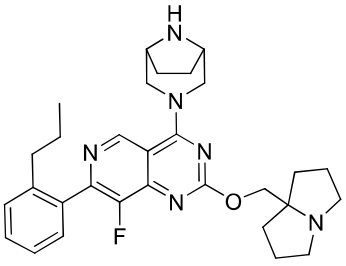
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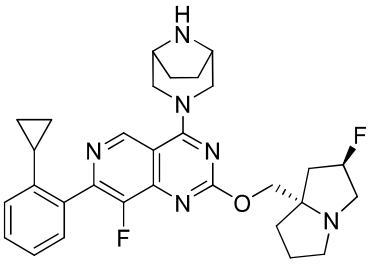
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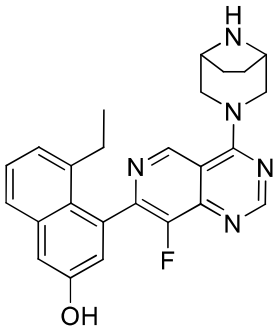
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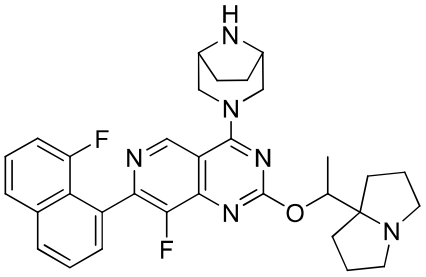
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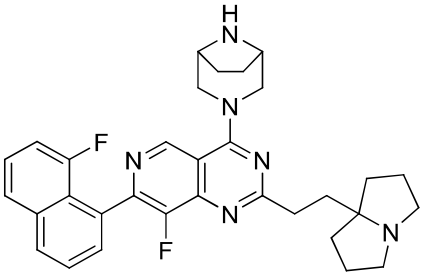
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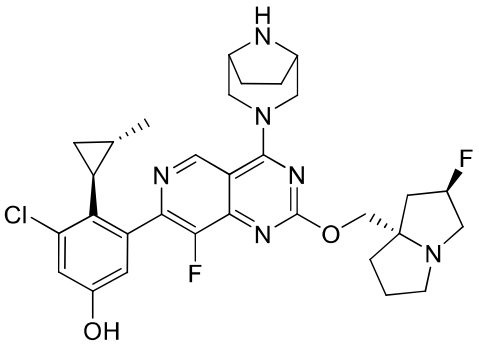
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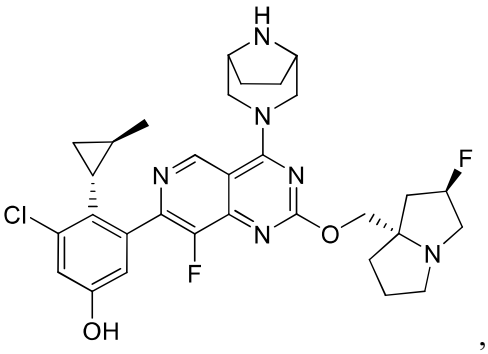
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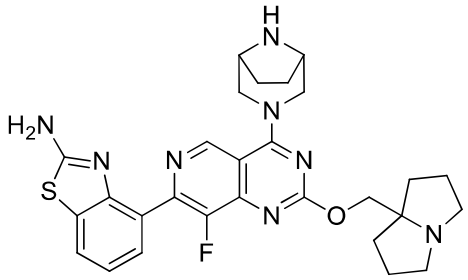
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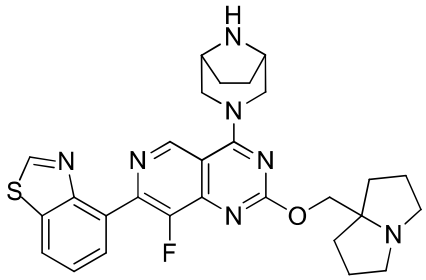
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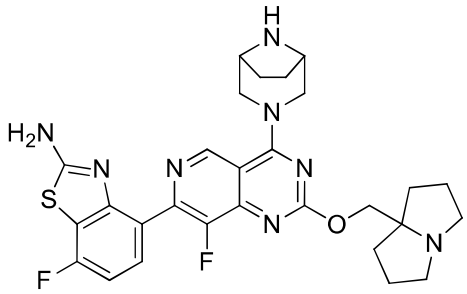
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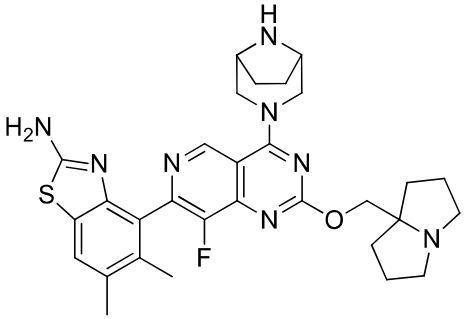
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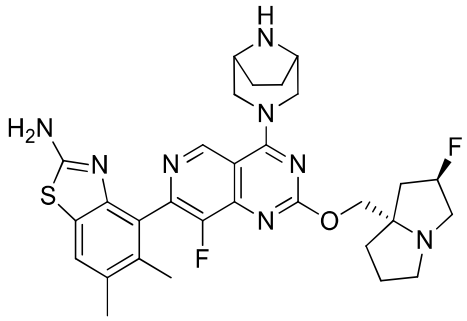
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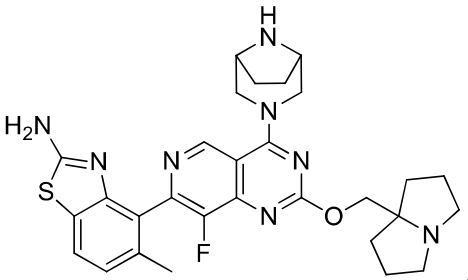
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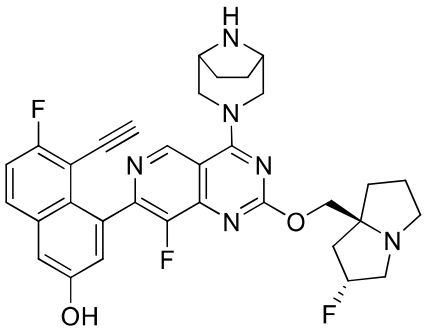
or a pharmaceutically acceptable salt thereof.

[0006c] In another aspect, there is provided a compound having the following structure: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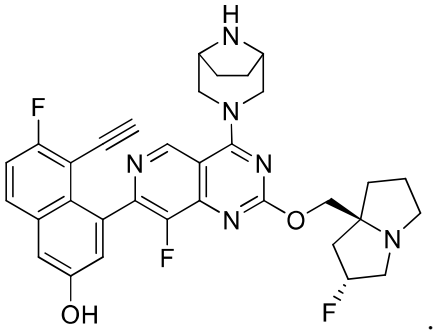
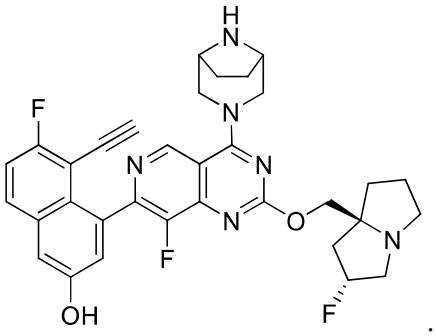
or a pharmaceutically acceptable salt thereof.

[0006d] In another aspect, there is provided a compound having the following structure:



[0006e] In another aspect, there is provided a pharmaceutically acceptable salt of a compound having the following structure:



[0006f] In another aspect, there is provided a pharmaceutical composition, comprising a therapeutically effective amount of a compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0006g] In another aspect, there is provided 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 as defined above, a pharmaceutically acceptable salt thereof or a pharmaceutical composition as defined above.

[0006h] In another aspect, there is provided the use of a compound as defined above, a pharmaceutically acceptable salt thereof or a pharmaceutical composition as defined above in the manufacture of a medicament for the treatment of cancer, wherein KRas G12D activity is to be inhibited in a cell, wherein an effective amount of the compound, the pharmaceutically

acceptable salt thereof or the pharmaceutical composition is to be contacted with the cell in which inhibition of KRas G12D activity is desired.

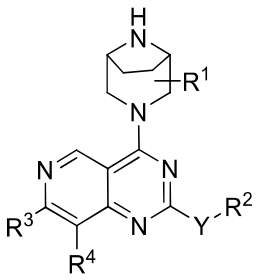
[0006i] In another aspect, there is provide the use of a compound as defined above, a pharmaceutically acceptable salt thereof or a pharmaceutical composition as defined above in the manufacture of a medicament for treating a KRas G12D-associated cancer, wherein a therapeutically effective amount of the compound, the pharmaceutically acceptable salt thereof or the pharmaceutical composition is to be administered to a patient in need thereof, 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 wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.

[0006j] In another aspect, there is provided the use of a compound of as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for treating cancer in a patient in need thereof, wherein (a) it is to be determined that the cancer has a KRas G12D mutation; and (b) a therapeutically effective amount of the compound or the pharmaceutical composition is to be administered to the patient, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal

carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial `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 wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.

[0007] In one example of the disclosure, compounds are provided that inhibit KRas G12D activity. In certain examples, the compounds are represented by Formula (I):



Formula (I)

[0008] or a pharmaceutically acceptable salt thereof:

[0009] wherein:

[00010] R^1 is hydrogen, hydroxy, halogen, C1 – C3 alkyl, C1 - C3 cyanoalkyl, C1 - C3 hydroxyalkyl, HC(=O)-, $-CO_2R^5$, $-C(O)N(R^5)_2$ or a 5-6 membered heteroaryl;

[00019] 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

[00020] 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.

[0010] In another example of the disclosure, pharmaceutical compositions are provided comprising a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0011] In yet another example of the disclosure, methods for inhibiting KRas G12D activity in a in a cell, comprising contacting the cell with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein. In one example, the contacting is in vitro. In one example, the contacting is in vivo.

[0012] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

[0013] Also provided are methods for treating cancer in a patient comprising administering a therapeutically effective amount of a compound or pharmaceutical composition of the present disclosure or a pharmaceutically acceptable salt thereof to a patient in need thereof.

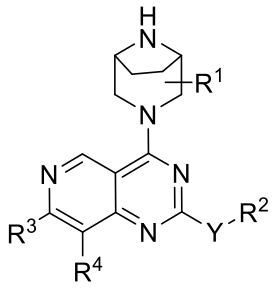
[0014] Also provided herein is a method of treating a KRas G12D-associated disease or disorder in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

[0015] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

CLAIMS

WE CLAIM:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is hydrogen, hydroxy, halogen, $C_1 – C_3$ alkyl, C_1 - C_3 cyanoalkyl, C_1 - C_3 hydroxyalkyl, HC(=O)-, $-CO_2R^5$, $-C(O)N(R^5)_2$ or a 5-6 membered heteroaryl;

Y is a bond, O or NR^5;

R^2 is hydrogen, $-N(R^5)_2$, heterocyclyl, $C_1 – C_6$ alkyl, -L-heterocyclyl, -L-aryl, -L-heteroaryl, -L-cycloalkyl, $-L-N(R^5)_2$, $-L-NHC(=NH)NH_2$, $-L-C(O)N(R^5)_2$, $-L-C_1-C_6$ haloalkyl, $-L-OR^5$, $-L-NR^5C(O)$-aryl, -L-COOH, or $-LC(=O)OC_1-C_6$ alkyl, wherein the heterocyclyl, the aryl portion of $-L-NR^5C(O)$-aryl, 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 $C_1 – C_4$ alkylene optionally substituted with hydroxy, $C_1 – C_4$ 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 $C_1 – C_3$ alkyl;

each R^5 is independently hydrogen or $C_1 – C_3$ alkyl;

each R^6 is independently halogen, hydroxy, C_1 - C_3 hydroxyalkyl, $C_2 – C_3$ alkyl, C_1 - C_3 haloalkyl, C_1-C_3 alkoxy, cyano, -Q-phenyl, -Q-phenylSO_2F, -NHC(O)phenyl, -NHC(O)phenylSO_2F, C_1-C_3 alkyl substituted pyrazolyl, araC_1-C_3 alkyl-, tert-butyldimethylsilyloxyCH_2- , -$N(R^5)_2$, (C_1-C_3 alkoxy)C_1-C_3 alkyl-, (C_1-C_3 alkyl)C(=O), oxo, (C_1-C_3 haloalkyl)C(=O)-, -SO_2F, (C_1-C_3 alkoxy)C_1-C_3 alkoxy, -$CH_2OC(O)N(R^5)_2$, -$CH_2NHC(O)OC_1$-C_6 alkyl, -$CH_2NHC(O)N(R^5)_2$, -$CH_2NHC(O)C_1$-C_6 alkyl, -CH_2(pyrazolyl), -$CH_2NHSO_2C_1$-C_6 alkyl, -$CH_2OC(O)$heterocyclyl, -$OC(O)N(R^5)_2$, -OC(O)NH(C_1-C_3 alkyl)O(C_1-C_3 alkyl), -OC(O)NH(C_1-C_3 alkyl)O(C_1-C_3 alkyl)phenyl(C_1-C_3 alkyl)$N(CH_3)_2$, -OC(O)NH(C_1-C_3 alkyl)O(C_1-C_3 alkyl)phenyl or -OC(O)heterocyclyl, -CH_2heterocyclyl, wherein the phenyl of -NHC(O)phenyl or -OC(O)NH(C_1-C_3 alkyl)O(C_1-C_3 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)-, $C_1 – C_4$ alkyl, $C_1 – C_4$ alkoxy, $C_1 – C_4$ haloalkyl, $C_1 – C_4$ hydroxyalkyl, or -$N(R^5)_2$; and

each R^8 is independently halogen, cyano, hydroxy, C_1 - C_4 alkyl, -S-C_1 - C_3 alkyl, $C_2 – C_4$ alkenyl, $C_2 – C_4$ alkynyl, $C_2 – C_4$ hydroxyalkynyl, C_1-C_3 cyanoalkyl , triazolyl, C_1 - C_3 haloalkyl, -O- C_1 - C_3 haloalkyl, -S- C_1 - C_3 haloalkyl, C_1-C_3 alkoxy, hydroxyC_1-C_3 alkyl, -$CH_2C(=O)N(R^5)_2$, -C_3-C_4 alkynyl$(NR^5)_2$, -$N(R^5)_2$, deuteroC_2-C_4 alkynyl, (C_1-C_3 alkoxy)haloC_1-C_3 alkyl-, or C_3-C_6 cycloalkyl wherein said C_3-C_6 cycloalkyl is optionally substituted with halogen or C_1-C_3 alkyl.

2. The compound or pharmaceutically acceptable salt thereof of claim 1, wherein R^1 is hydrogen, halogen, hydroxy, $C_1 – C_3$ alkyl, C_1- C_3 cyanoalkyl, C_1- C_3 hydroxyalkyl, HC(=O)-, -CO_2R^5, or -$C(O)N(R^5)_2$.

3. The compound or pharmaceutically acceptable salt thereof of claim 1 or 2, wherein Y is O and R^2 is $C_1 – C_6$ alkyl or -L-heterocyclyl optionally substituted with one or more R^6.

4. The compound or pharmaceutically acceptable salt thereof of claim 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-2-azaspiro[3.4]octanyl, 7-oxa-2-azaspiro[3.5]nonanyl, 2',3'-dihydrospiro[cyclopropane-1,1'-inden]-yl, (2S)-1-azabicyclo[2.2.1]heptan-2-yl, or tetrahydrofuranyl, each optionally substituted with one or more R^6.

5. The compound or pharmaceutically acceptable salt thereof of claim 3, wherein L is methylene and the heterocyclyl is hexahydro-1*H*-pyrrolizinyl, preferably wherein heterocyclyl is hexahydro-1*H*-pyrrolizinyl substituted with one R^6, wherein R^6 is halogen, hydroxy, C_1 - C_3 hydroxyalkyl, C_1 - C_3 haloalkyl, C_2 – C_3 alkyl, C_1 - C_3 alkoxy, phenyl or C_1-C_3 alkyl substituted pyrazolyl, preferably wherein the halogen is fluorine.

6. The compound or pharmaceutically acceptable salt thereof of claim 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 C_2 – C_3 alkyl;

   wherein the heterocyclyl is azetidinyl substituted with one R^6, wherein R^6 is C_2 – C_3 alkyl;

   wherein the heterocyclyl is pyrrolidinyl substituted with one R^6, wherein R^6 is C_1 – C_3 hydroxyalkyl, C_1 – C_3 haloalkyl, C_2 – C_3 alkyl, C_1 - C_3 alkoxy, araC_1-C_3 alkyl, -Q-phenyl, -Q-phenylSO_2F, -NHC(O)phenylSO_2F, or -NHC(O)phenyl;

   wherein the heterocyclyl is pyrrolidinyl substituted with two R^6 groups wherein one R^6 is C_2 – C_3 alkyl and the other R^6 is C_1-C_3 alkoxy or halogen;

   wherein the heterocyclyl is pyrrolidin-2-one substituted with one R^6, wherein R^6 is C_2 – C_3 alkyl;

wherein the heterocyclyl is piperidinyl substituted with one R^6, wherein R^6 is acetyl, (C_1-C_3 alkoxy)C_1-C_3 alkoxy, or -C(O)CH_2Cl; or

wherein Y is O, L is ethylene or propylene and the heterocyclyl is morpholinyl or oxa-5-azabicyclo[2.2.1]heptan-5-yl.

7. The compound or pharmaceutically acceptable salt thereof of claim 1 or 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 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:

   wherein the heteroaryl is pyridyl substituted with one R^7, wherein R^7 is halogen, C_1 – C_4 alkyl, -N(R^5)$_2$, or C_1-C_4 alkoxy;

   wherein the heteroaryl is pyrazolyl substituted with one R^7, wherein R^7 is C_1 – C_4 alkyl or -N(R^5)$_2$;

   wherein the heteroaryl is imidazolyl substituted with one R^7, wherein R^7 is C_1 – C_4 alkyl, C_1 – C_4 haloalkyl, or C_1 – C_4 hydroxyalkyl; or

   wherein the heteroaryl is triazolyl substituted with one R^7, wherein R^7 is C_1 – C_4 alkyl.

8. The compound or pharmaceutically acceptable salt thereof of claim 1 or 2, wherein Y is O and R^2 is -L-aryl, wherein the aryl portion is optionally substituted with one or more R^7;

   wherein Y is O and R^2 is -L-cycloalkyl, wherein the cycloalkyl portion is optionally substituted with one or more R^6;

   wherein Y is O, and R^2 is -L-N(R^5)$_2$, preferably wherein L is ethylene and each R^5 is an independently selected C_1 – C_3 alkyl;

wherein Y is O, and R^2 is -L-NHC(=NH)-NH_2, preferably wherein L is ethylene or propylene;

wherein Y is O, and R^2 is -L-C_1-C_6 haloalkyl;

wherein Y is O, and R^2 is -L-OR^5;

or

wherein Y is O, and R^2 is -L-$NR^5C(O)$-aryl.

9. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-8, wherein R^3 is aryl optionally substituted with one or more R^8, preferably wherein the aryl is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalenyl or 2,3-dihydro-1H-indenyl, each optionally substituted with one or more R^8; or

   wherein R^3 is heteroaryl optionally substituted with one or more R^8, preferably wherein the heteroaryl is isoquinolinyl, indazolyl, or benzo[d][1,3]dioxolyl optionally substituted with one or more R^8, more preferably wherein the heteroaryl is isoquinolinyl substituted with one R^8, wherein R^8 is halogen or C_2 - C_4 alkynyl, wherein the heteroaryl is indazolyl substituted with one R^8, wherein R^8 is C_1 - C_3 alkyl, or wherein the heteroaryl is benzo[d][1,3]dioxolyl substituted with two R^8 groups, wherein the R^8 groups are independently selected halogens.

10. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-9, wherein R^4 is halogen, or C_1 – C_3 alkyl, preferably wherein the halogen is fluorine, or wherein the C_1 – C_3 alkyl is methyl.

11. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-10, wherein R^1 is hydrogen.

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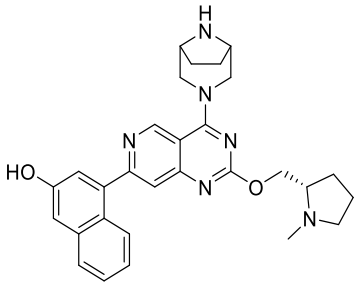
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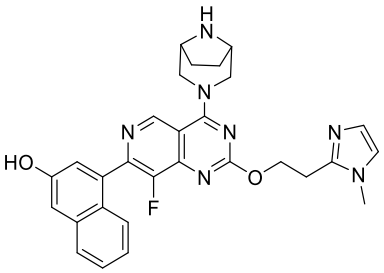
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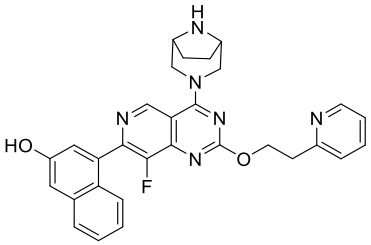
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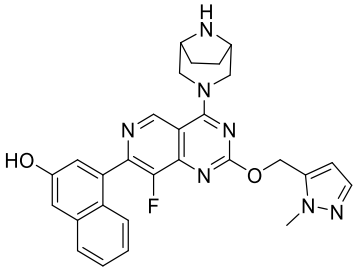
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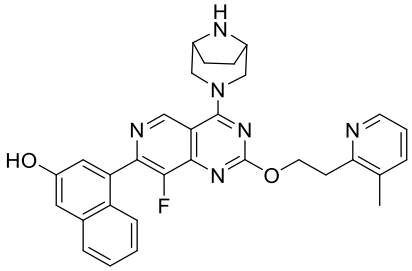
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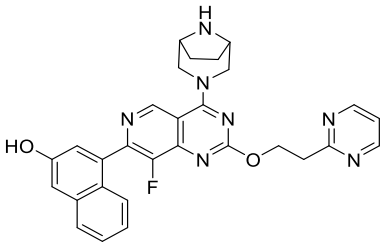
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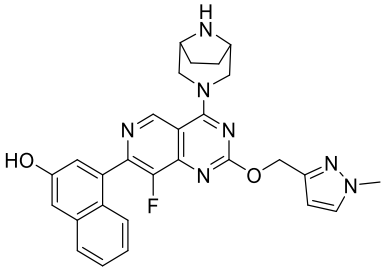
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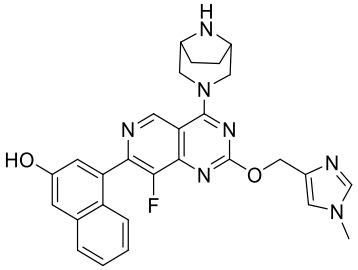
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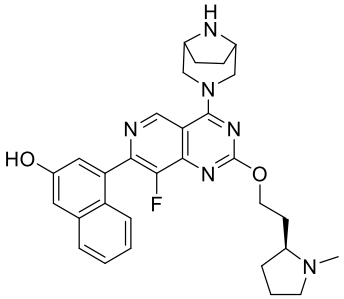
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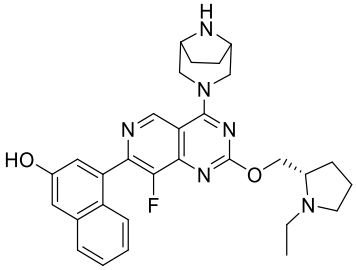
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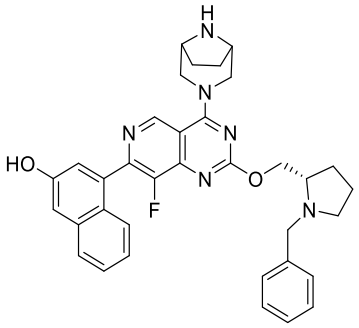
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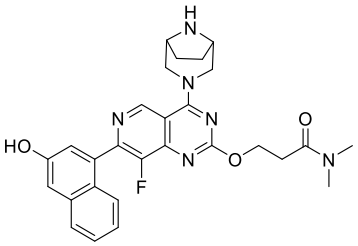
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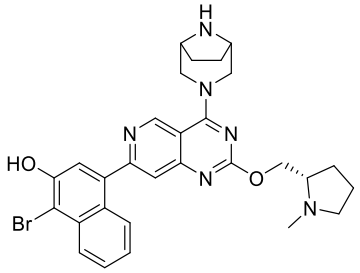
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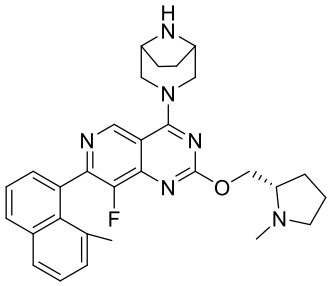
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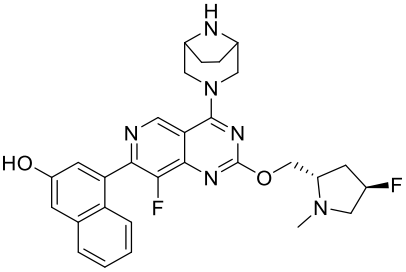
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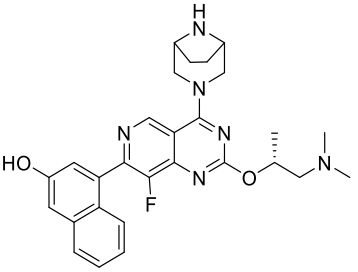
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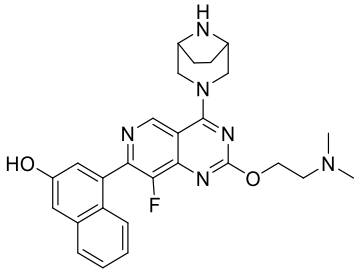
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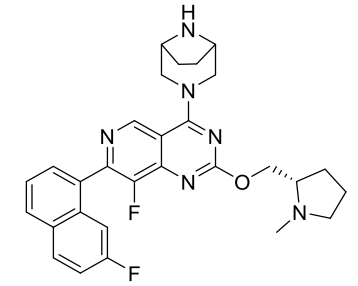
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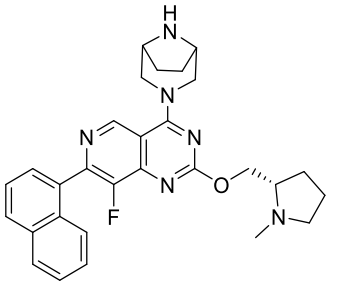
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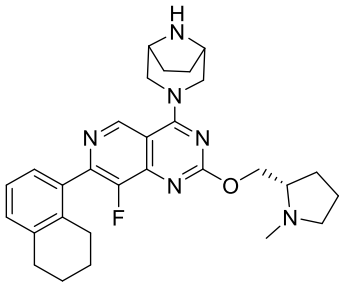
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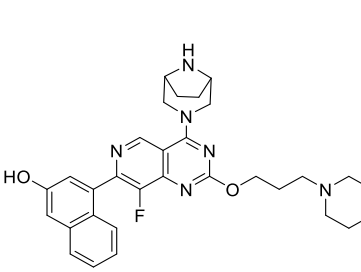
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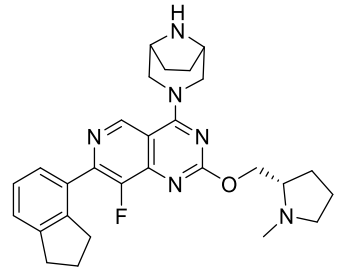
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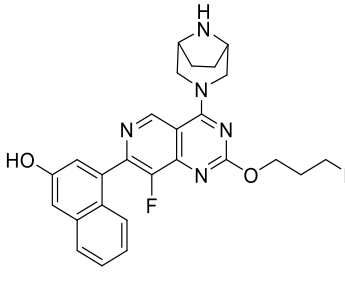
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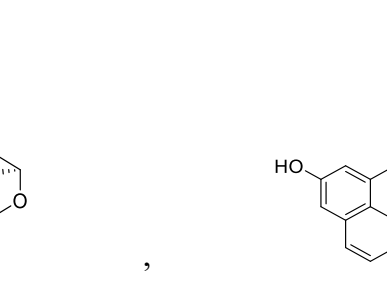
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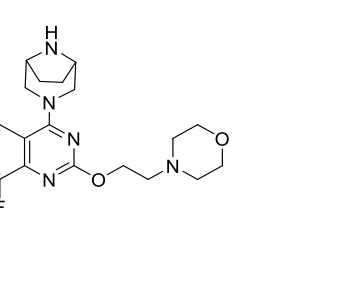
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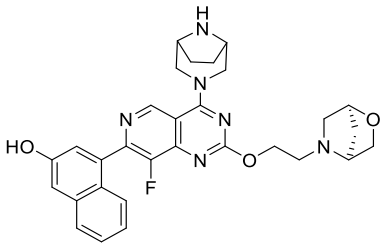
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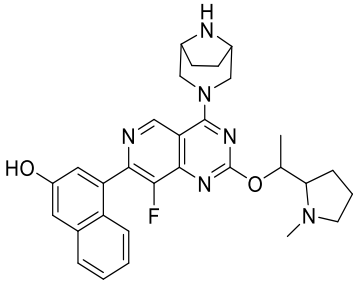
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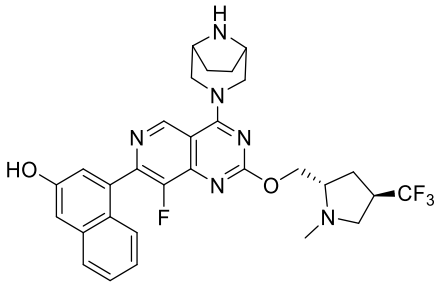
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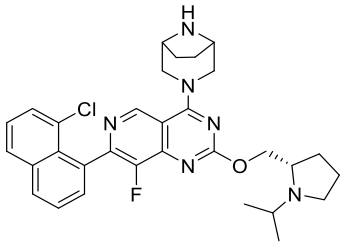
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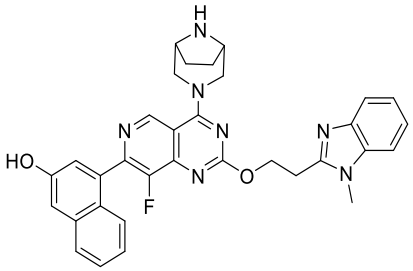
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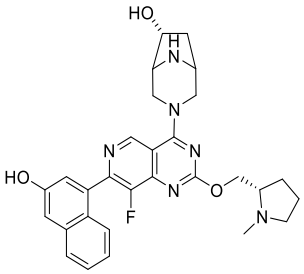
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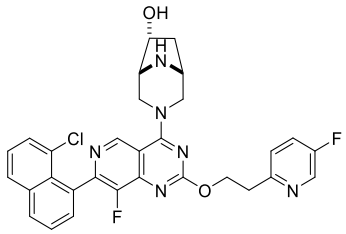
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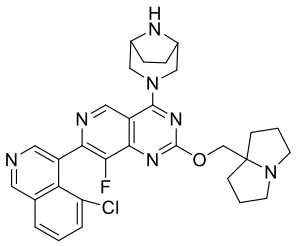
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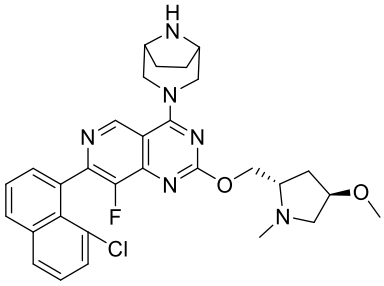
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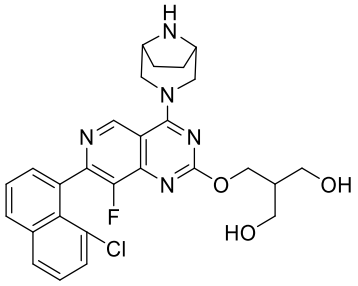
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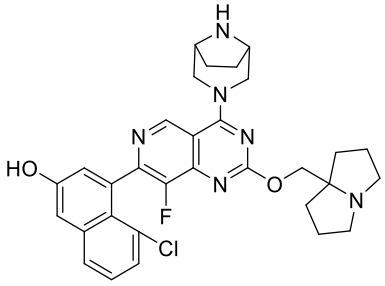
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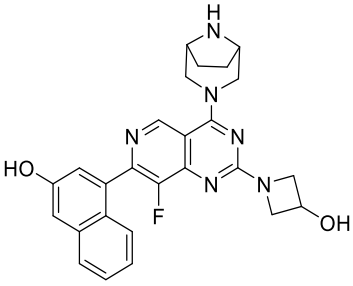
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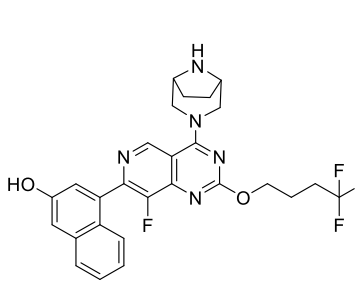
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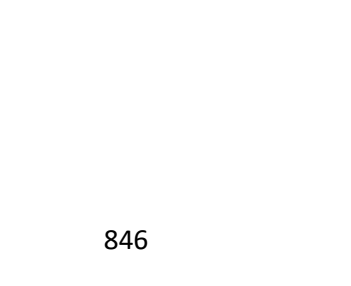
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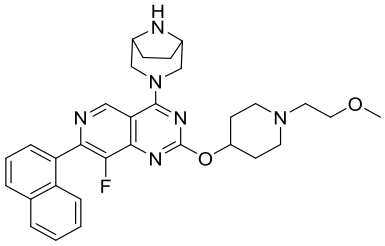
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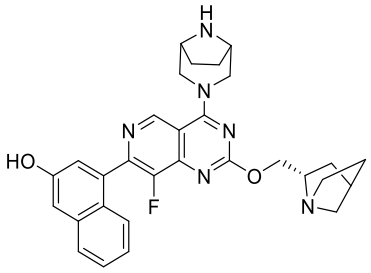
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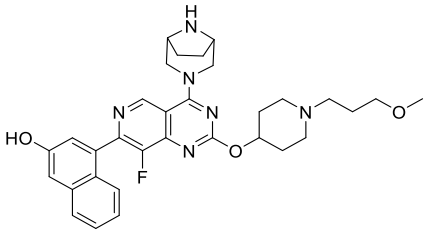
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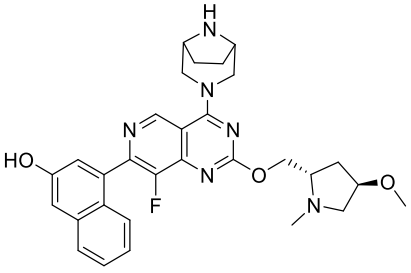
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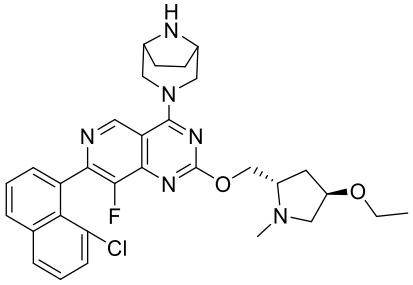
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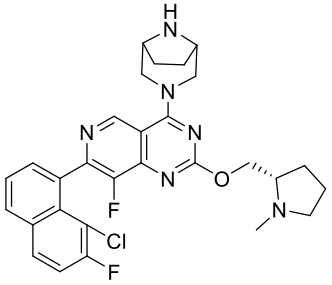
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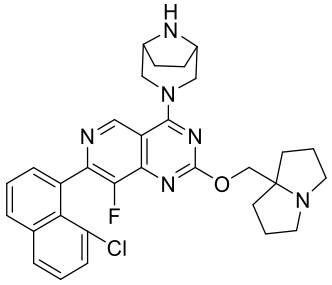
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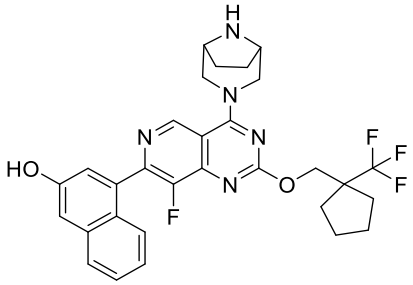
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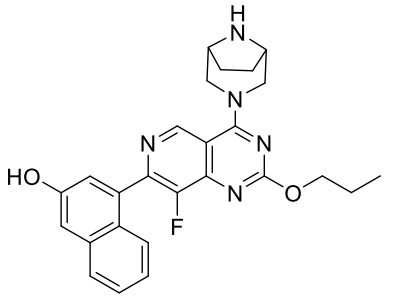
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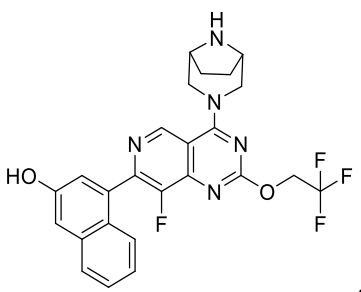
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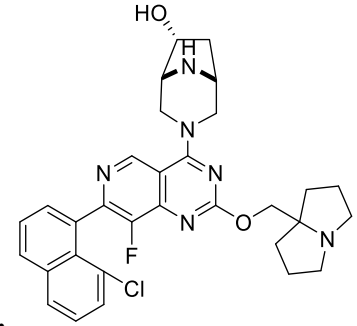
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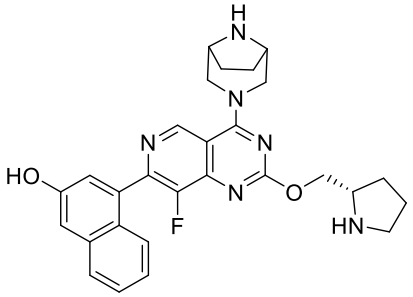
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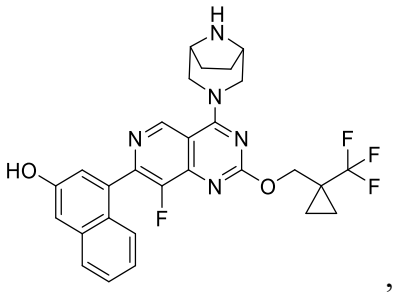
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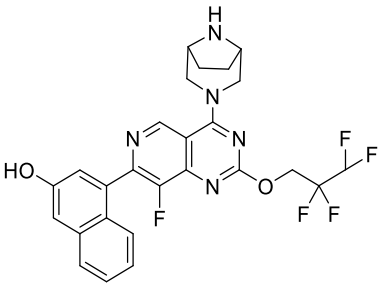
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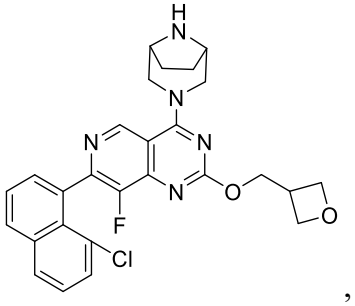
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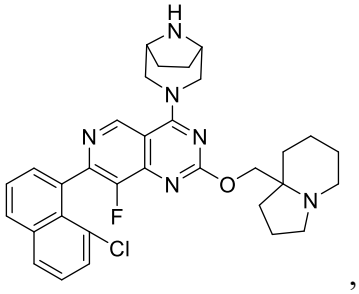
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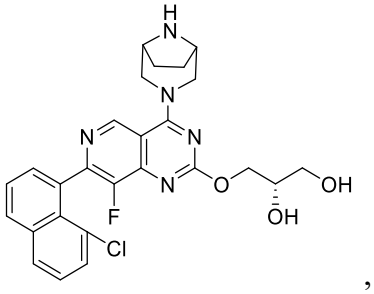
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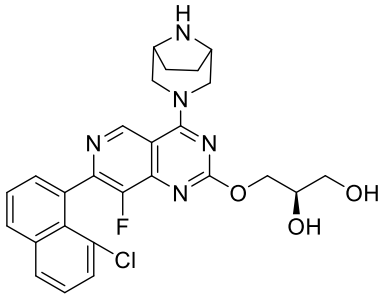
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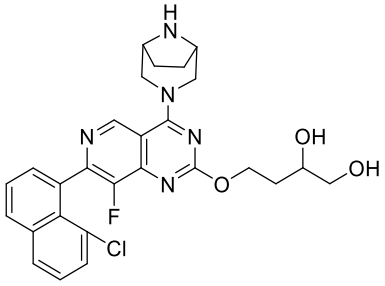
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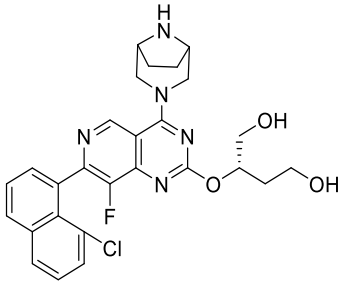
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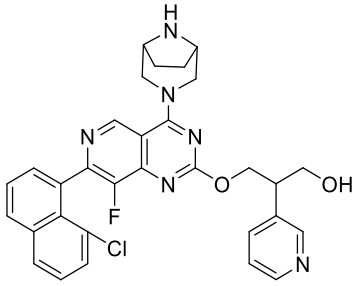
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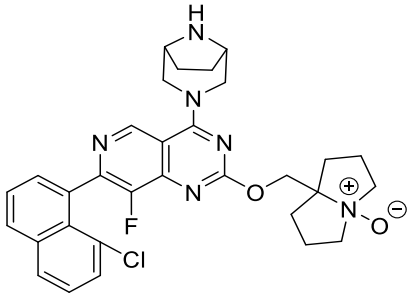
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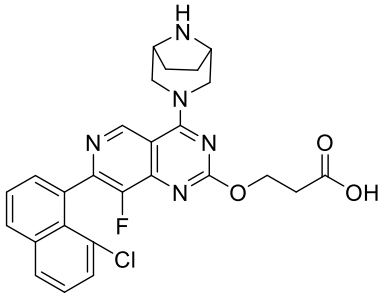
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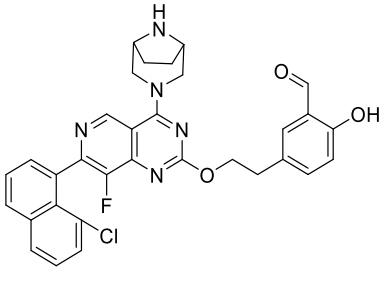
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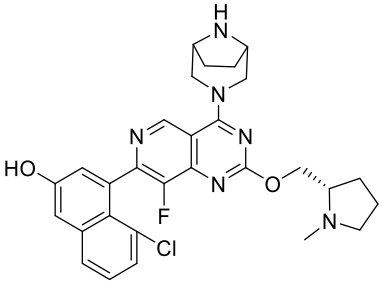
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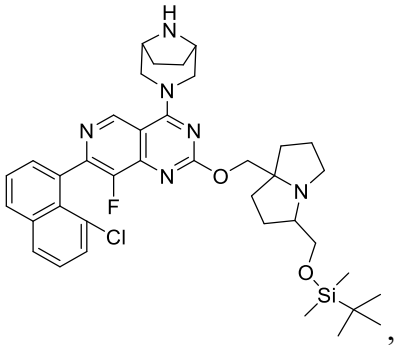
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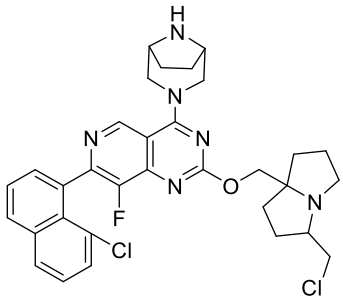
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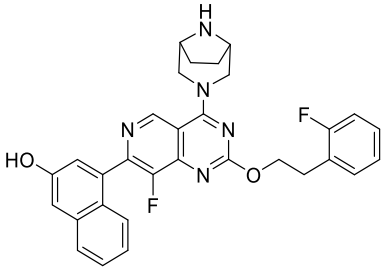
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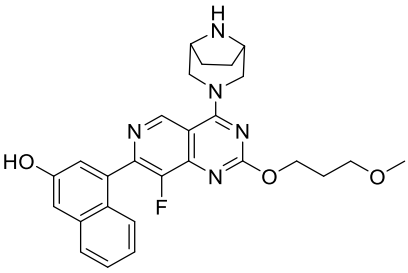
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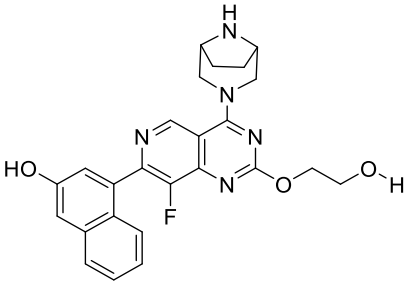
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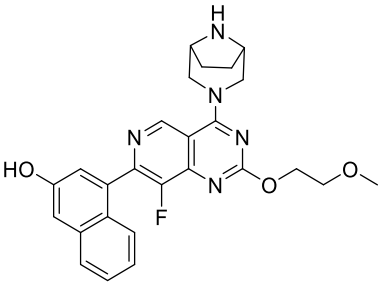
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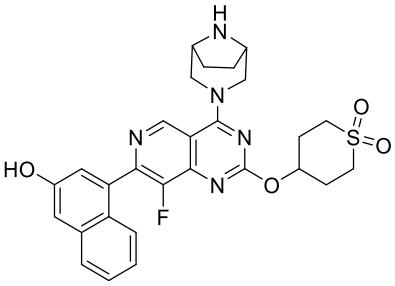
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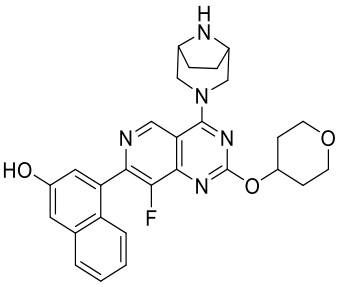
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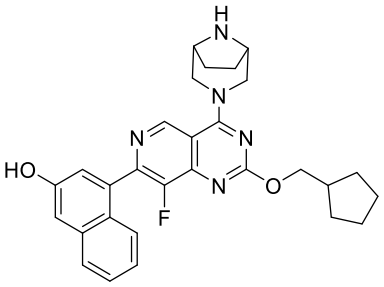
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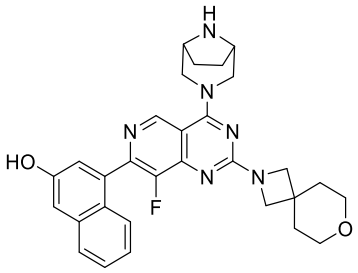
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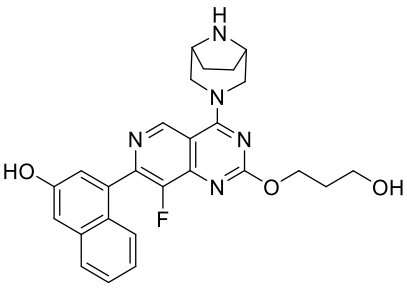
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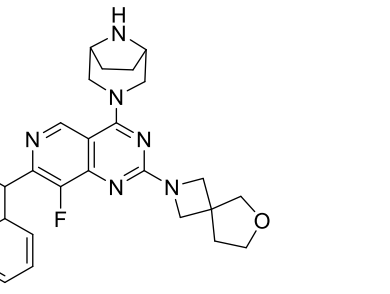
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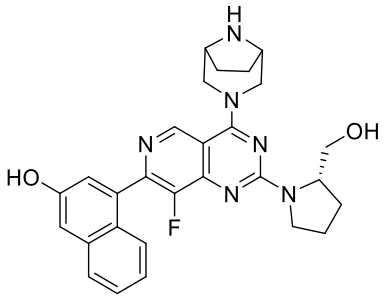
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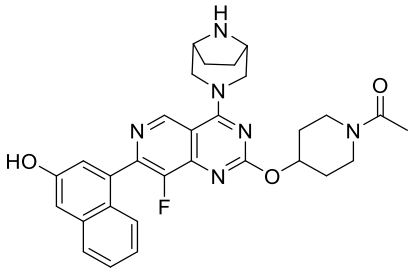
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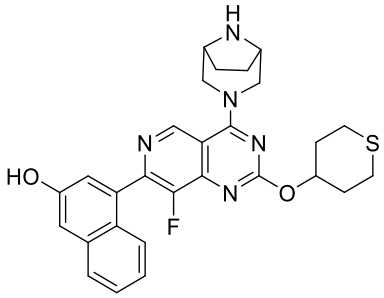
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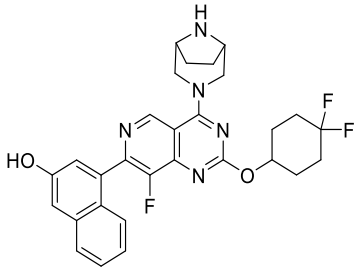
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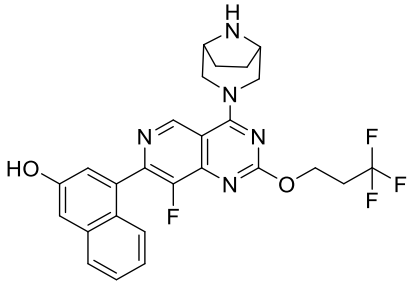
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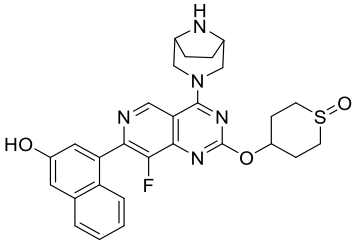
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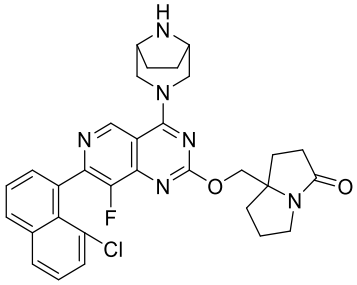
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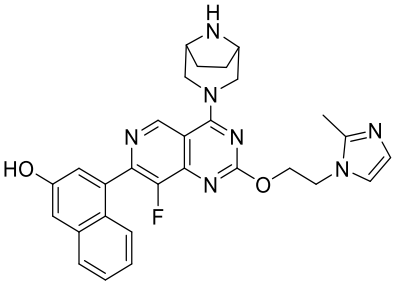
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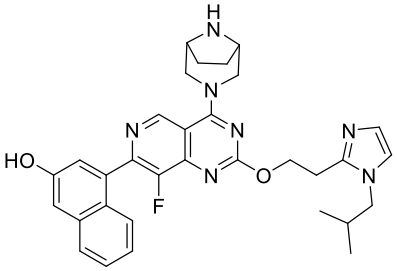
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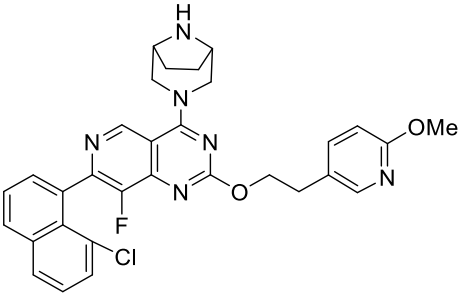
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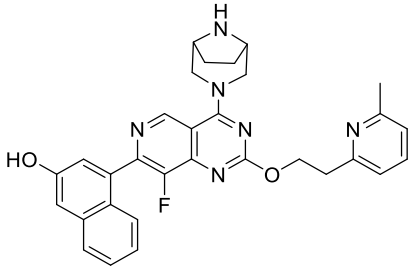
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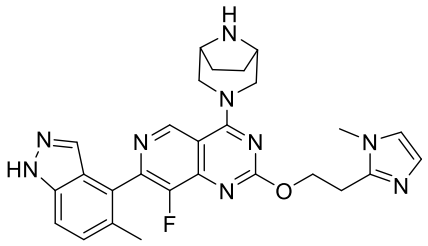
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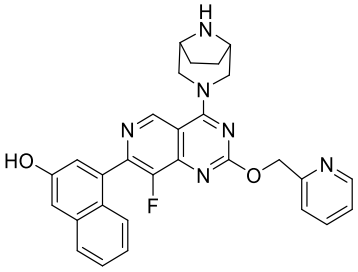
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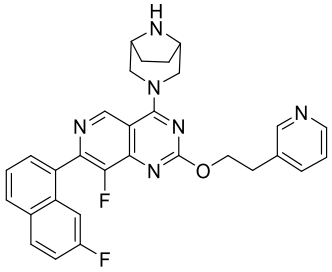
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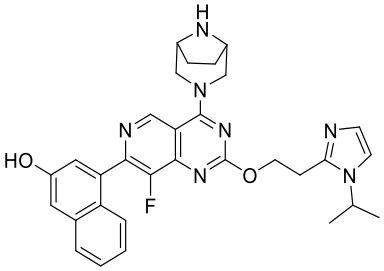
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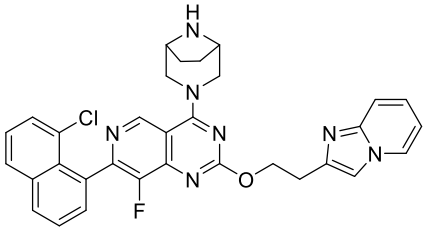
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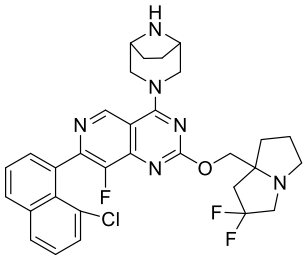
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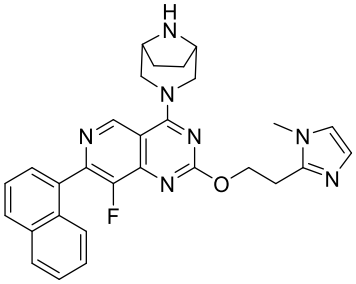
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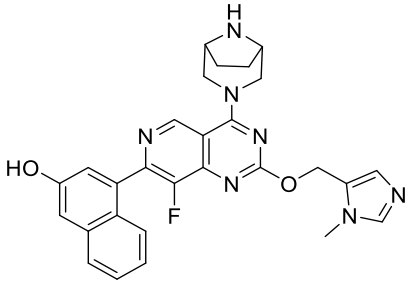
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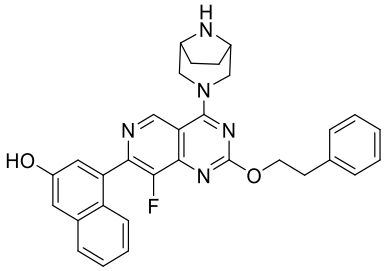
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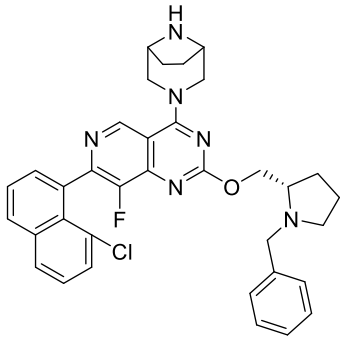
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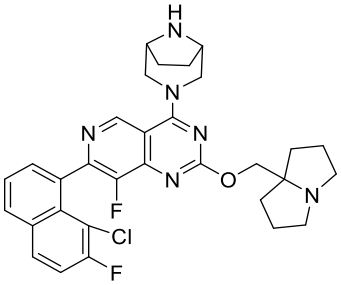
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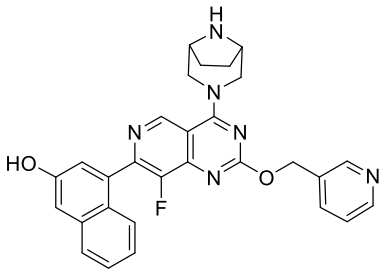

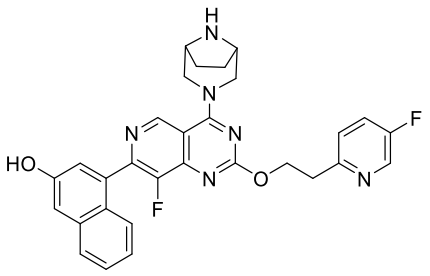
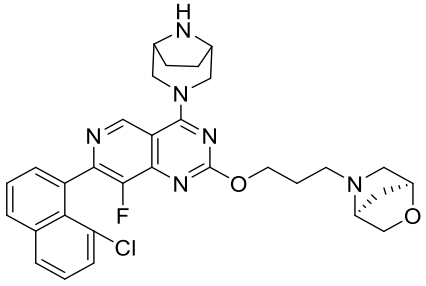
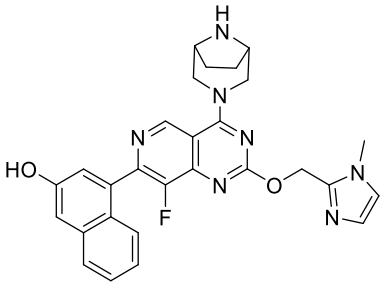
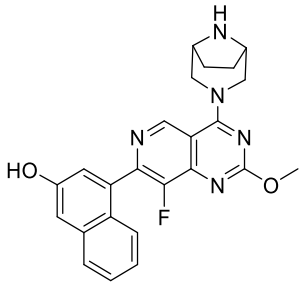
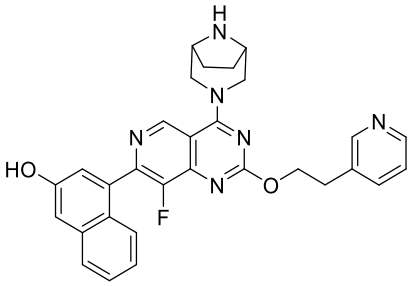
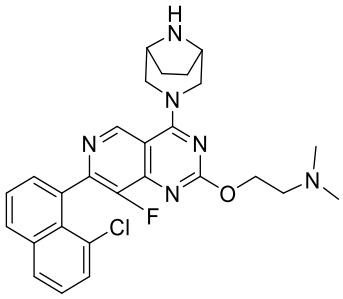
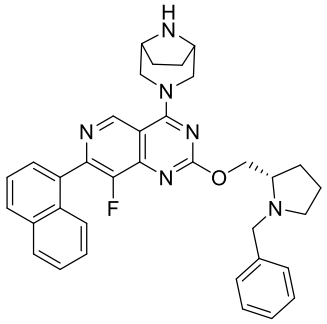
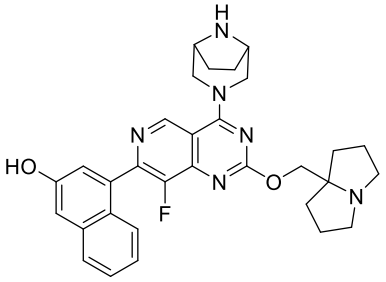
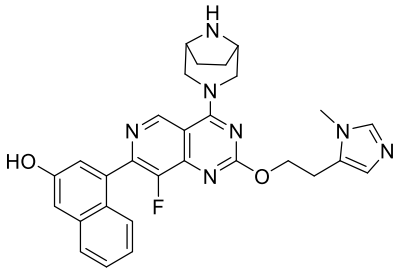
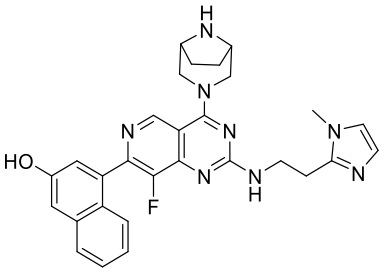
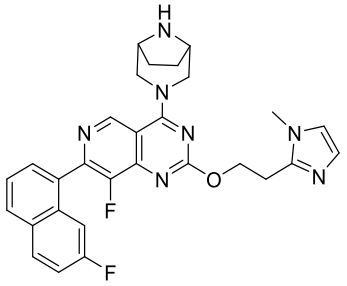
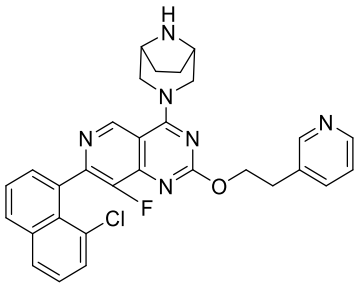
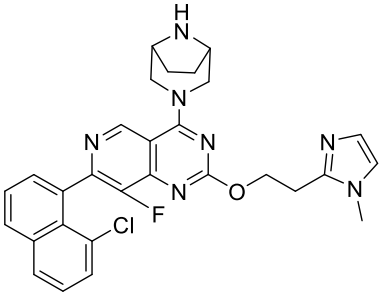

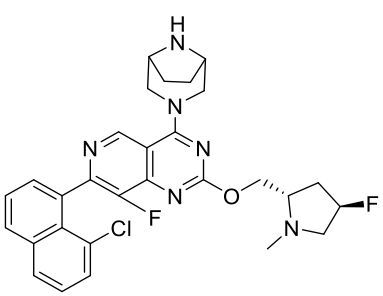
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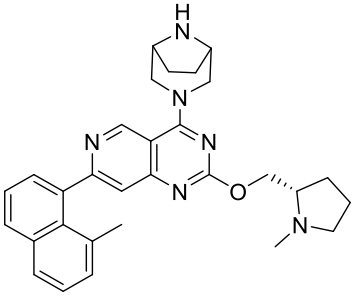
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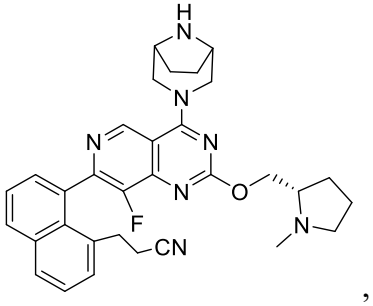
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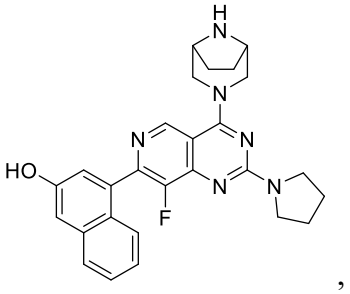
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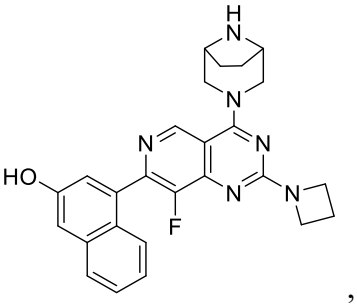
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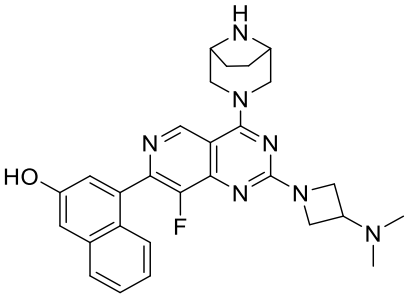
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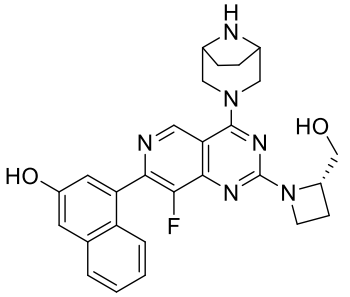
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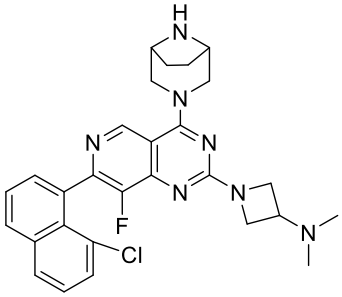
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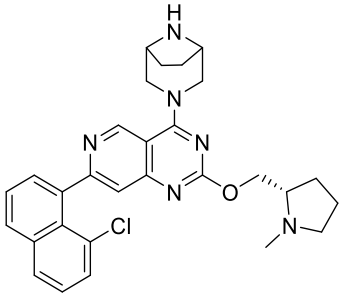
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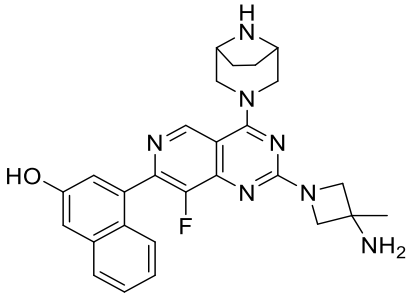
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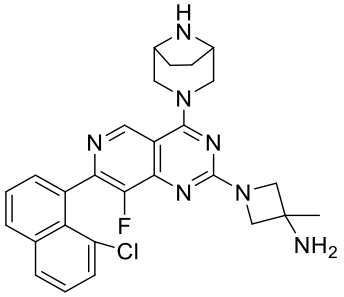
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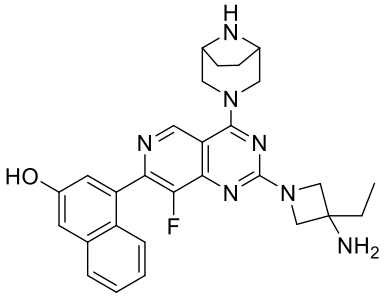
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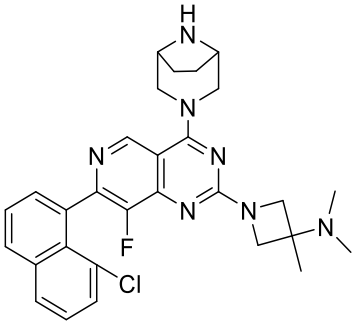
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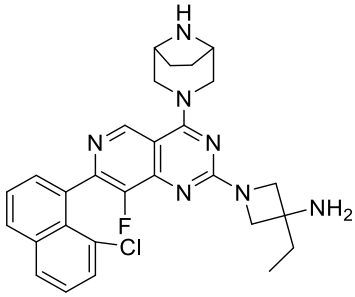
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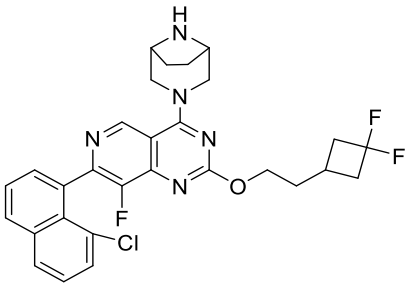
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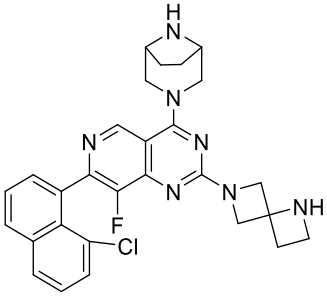
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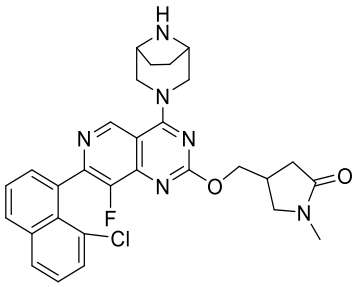
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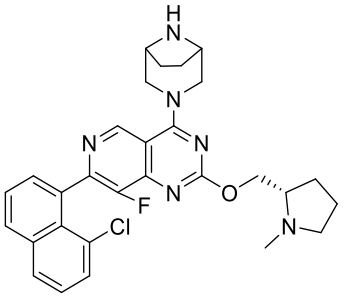
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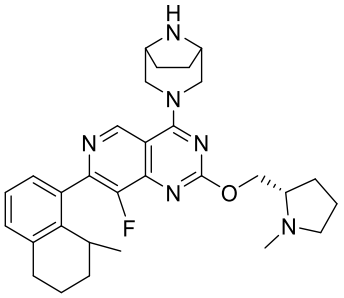
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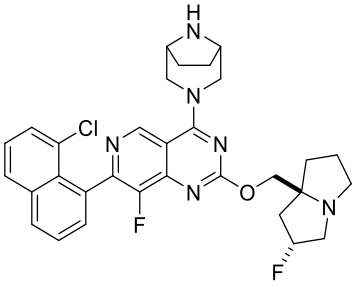
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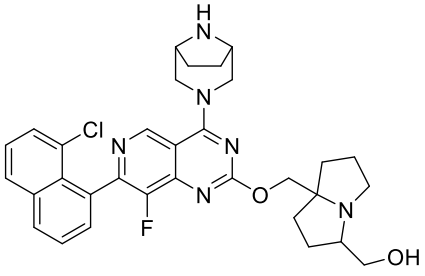
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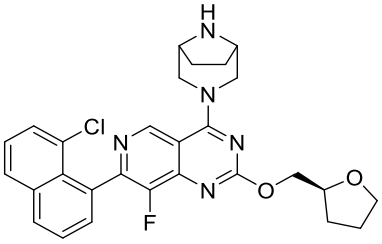
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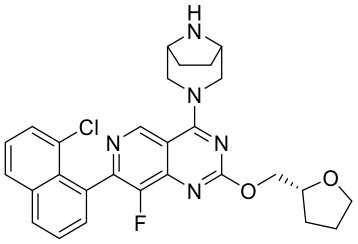
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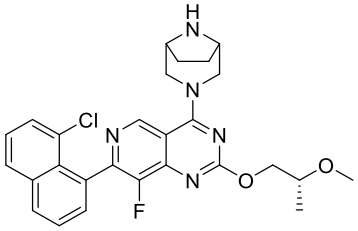
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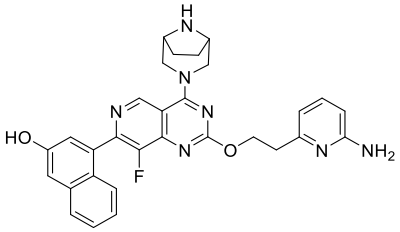
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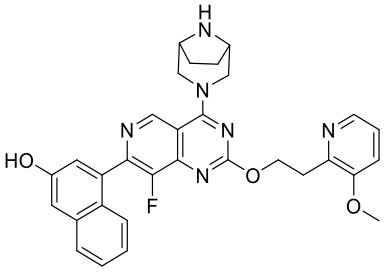
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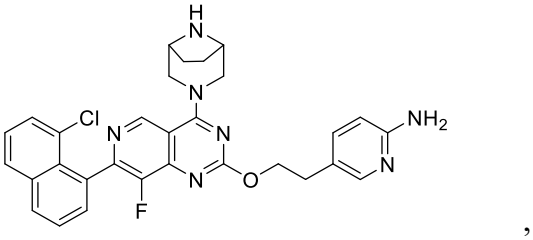
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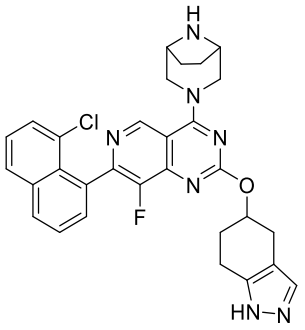
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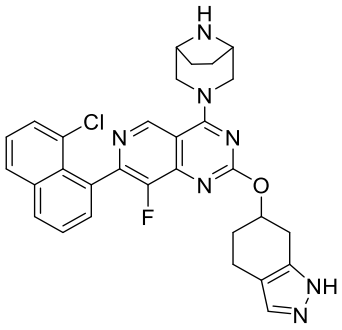
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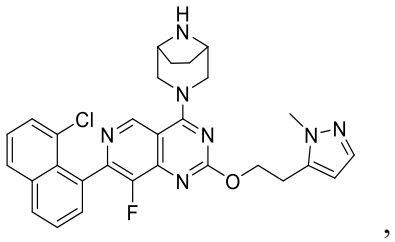
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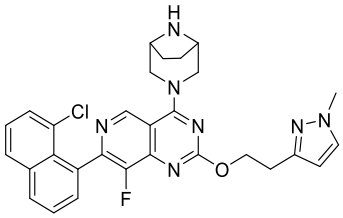
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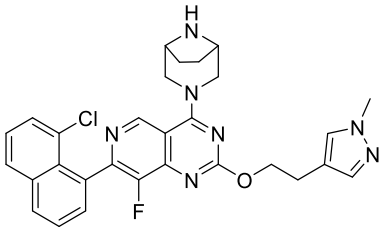
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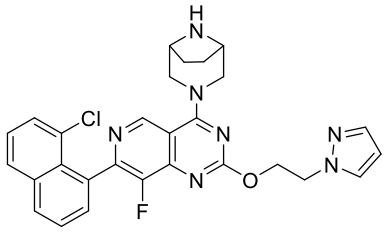
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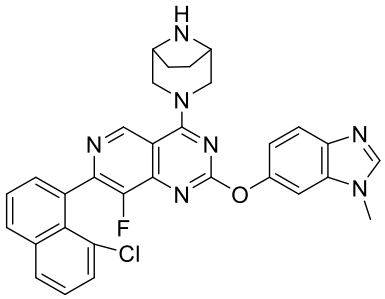
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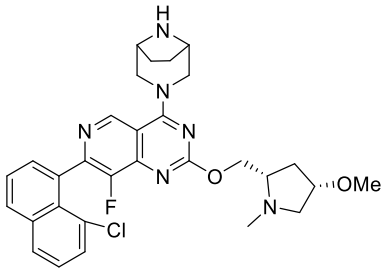
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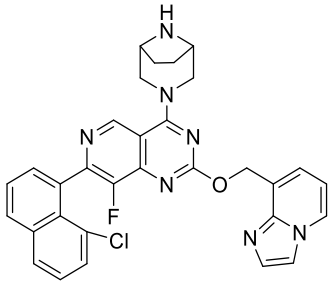
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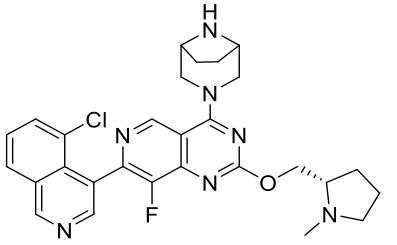
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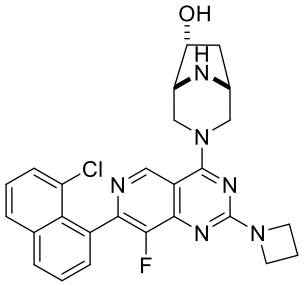
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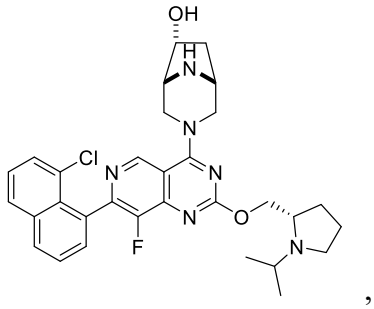
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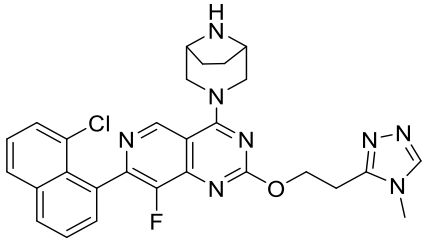
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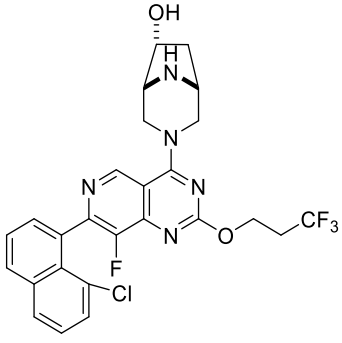
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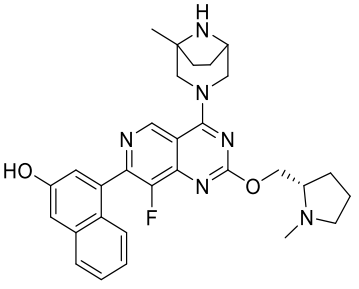

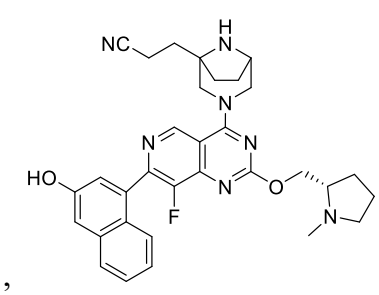
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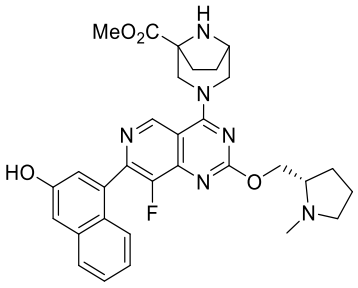
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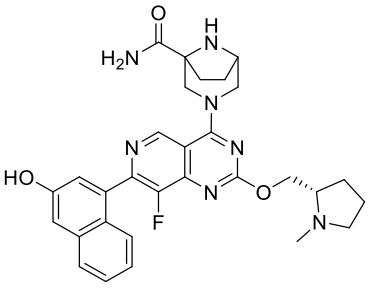
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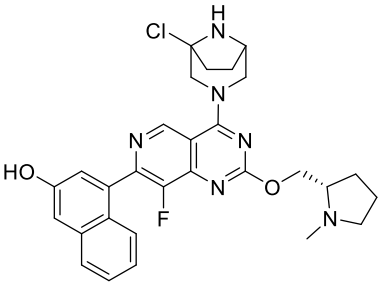
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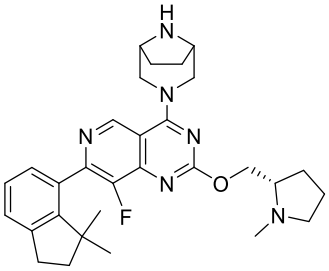
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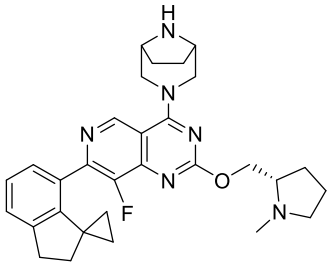
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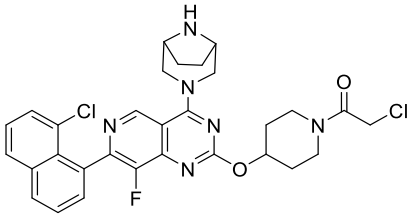
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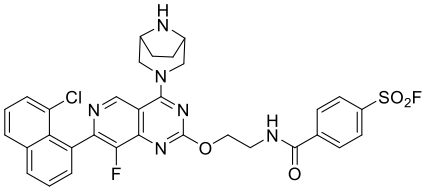
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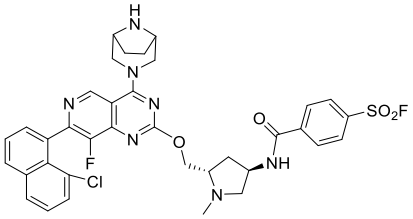
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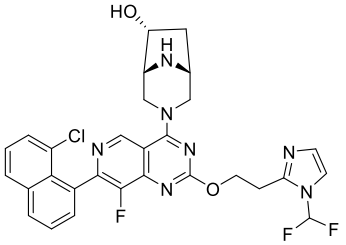
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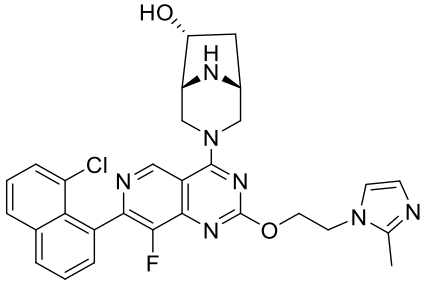
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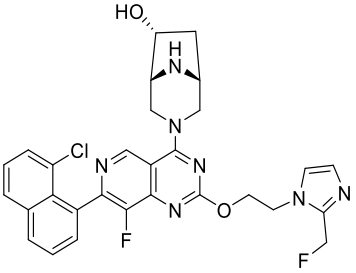
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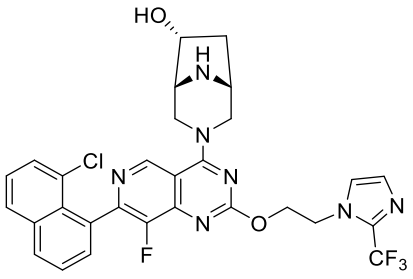
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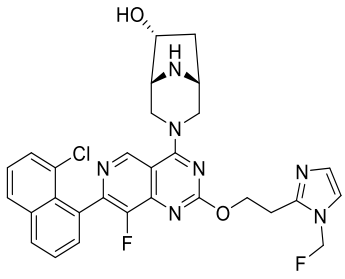
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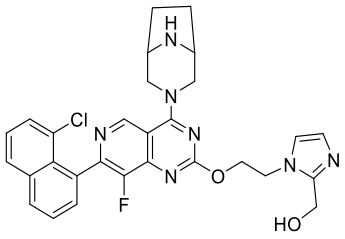
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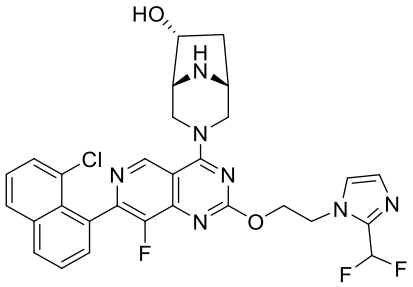
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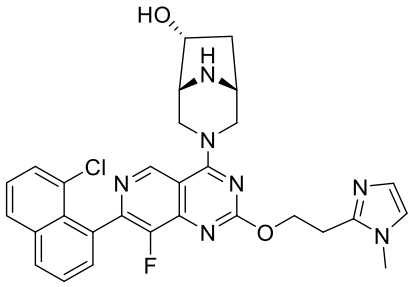
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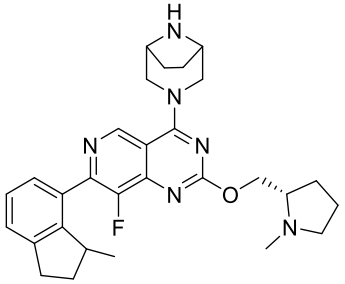
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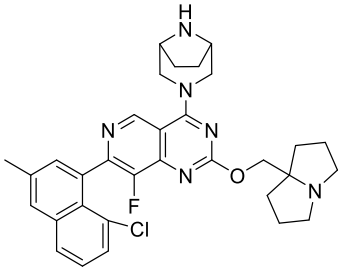
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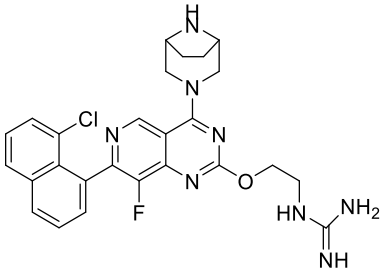
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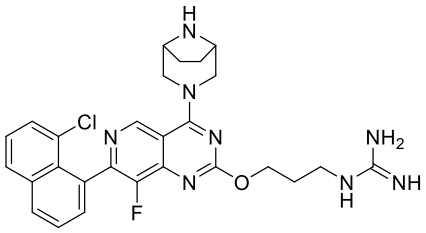
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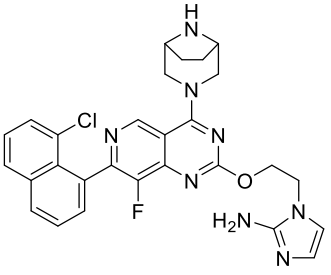
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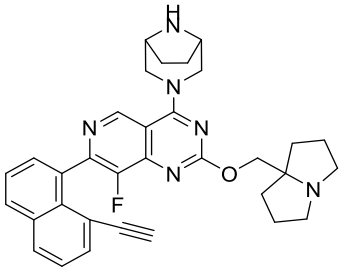
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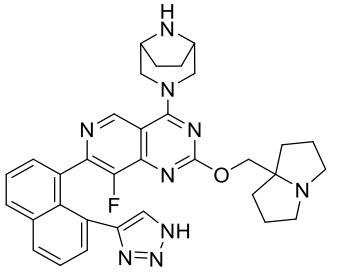
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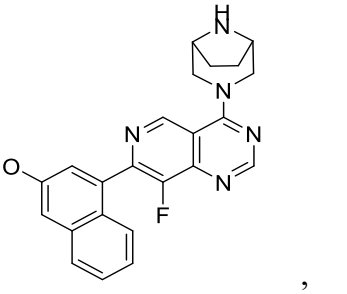
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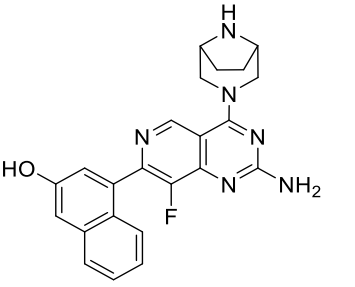
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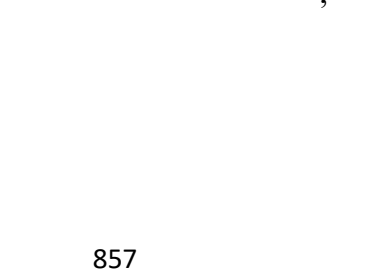
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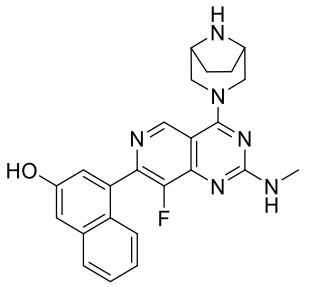
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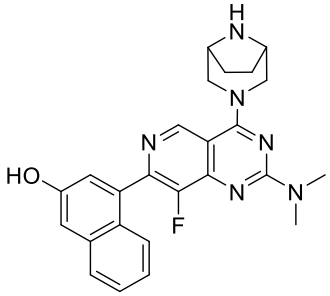
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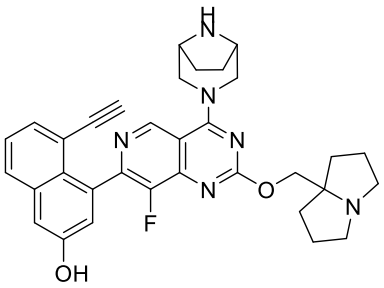
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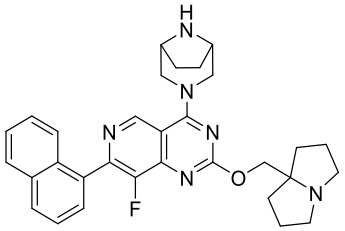
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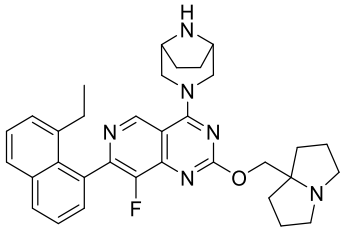
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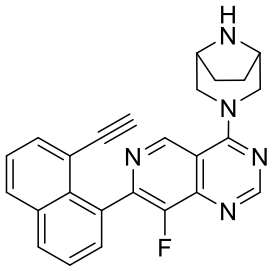
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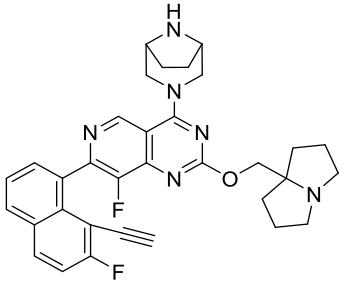
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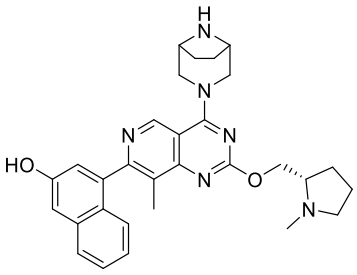
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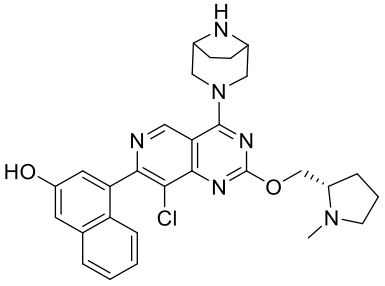
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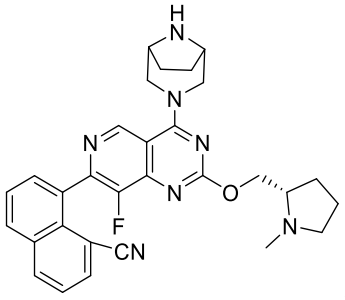
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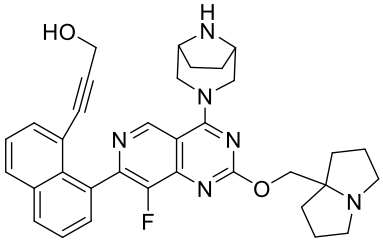
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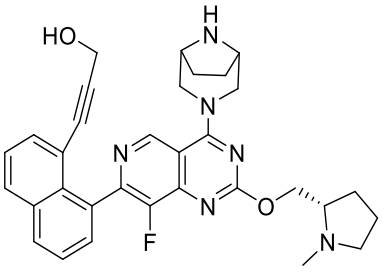
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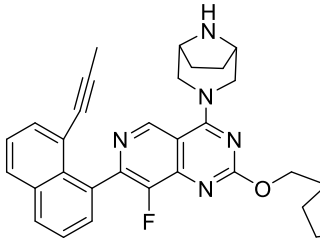
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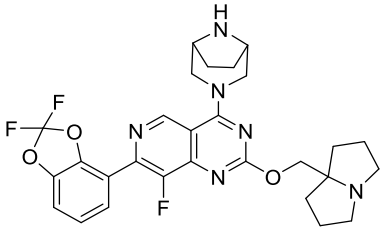
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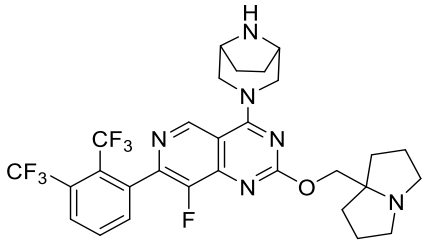
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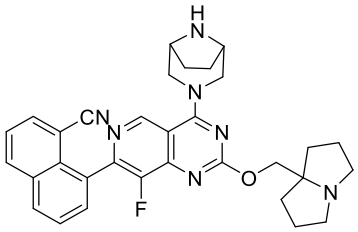
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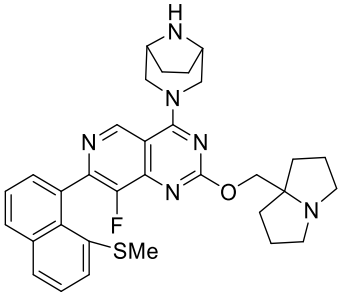
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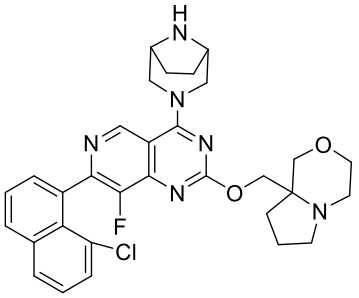
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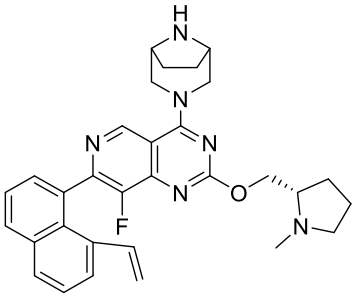
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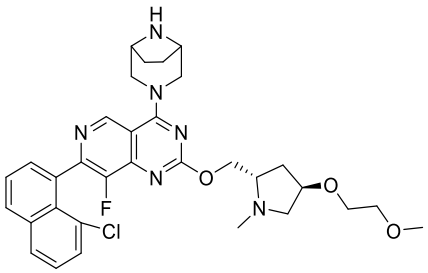
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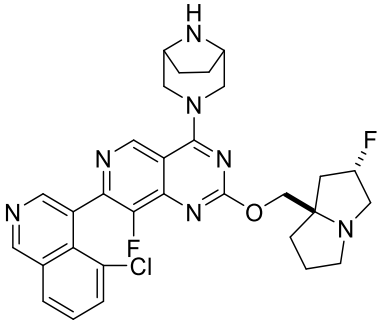
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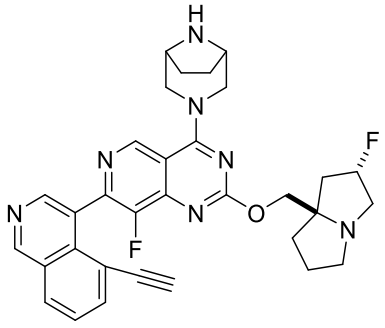
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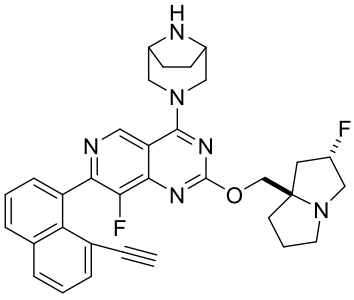
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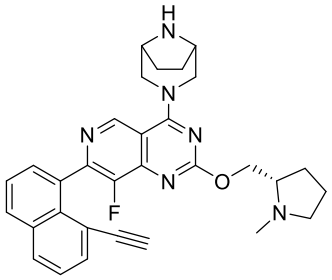
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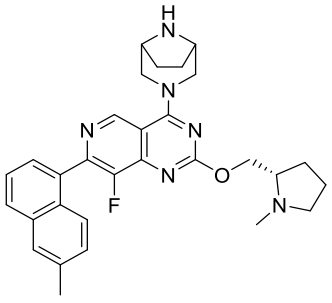
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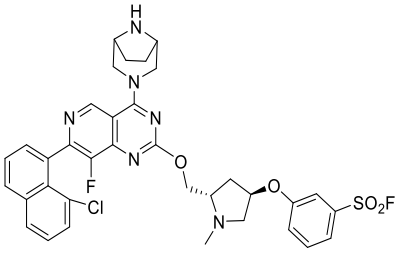
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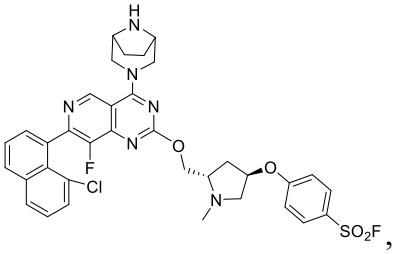
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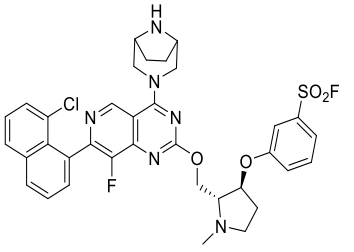
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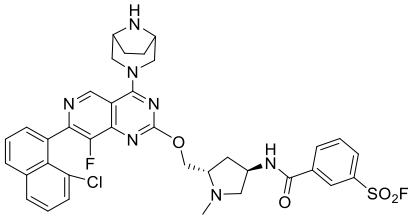
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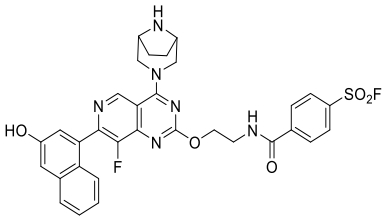
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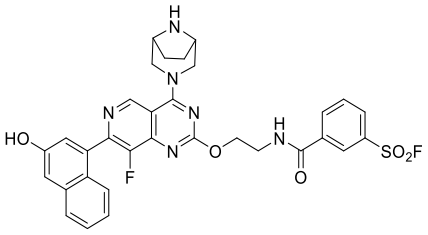
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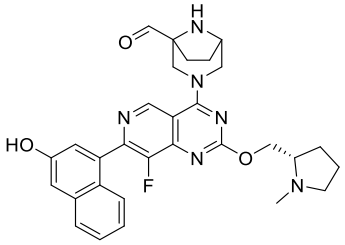
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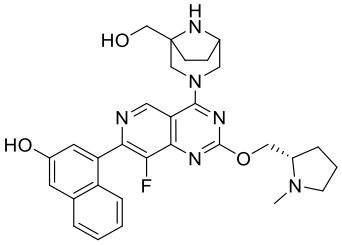
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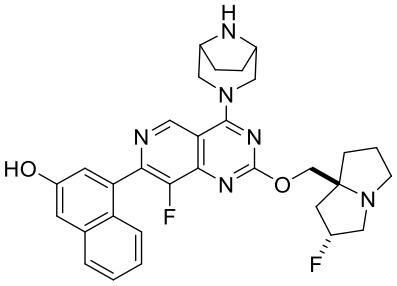
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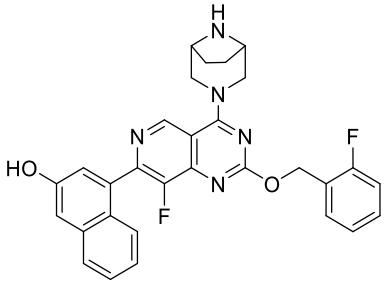
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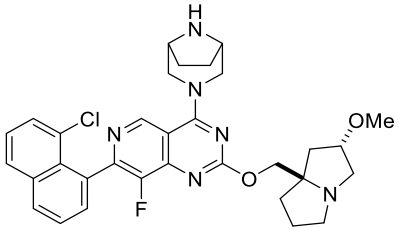
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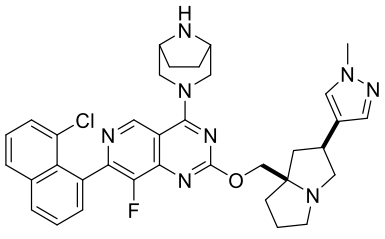
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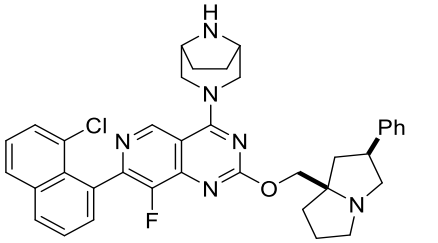
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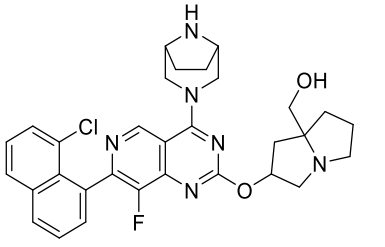
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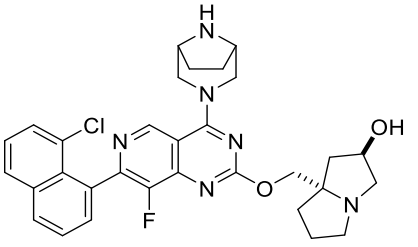
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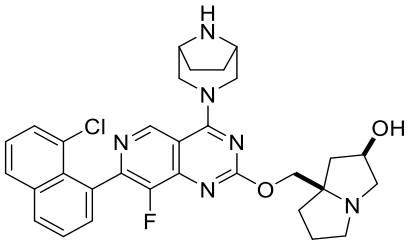
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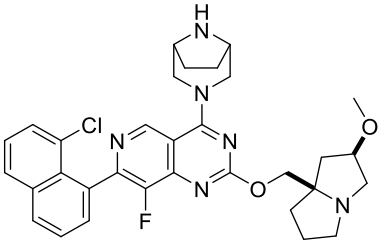
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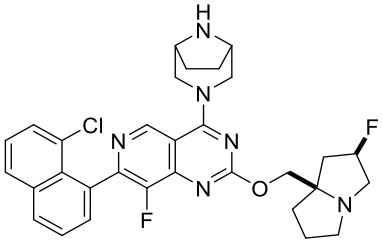
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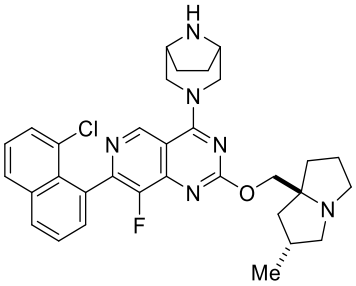
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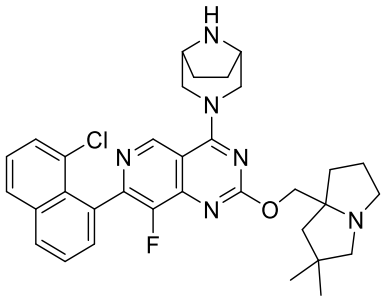
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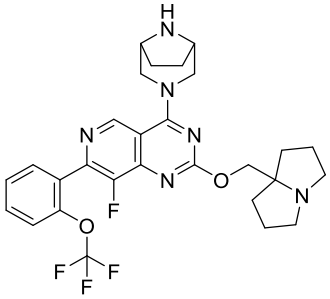
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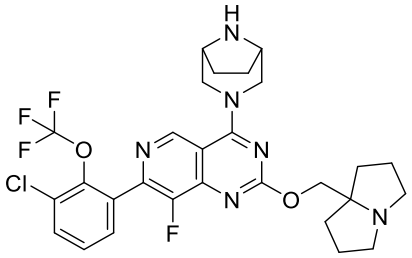
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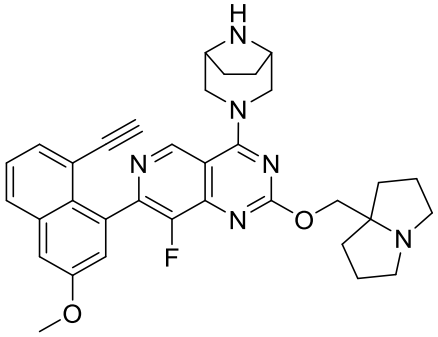
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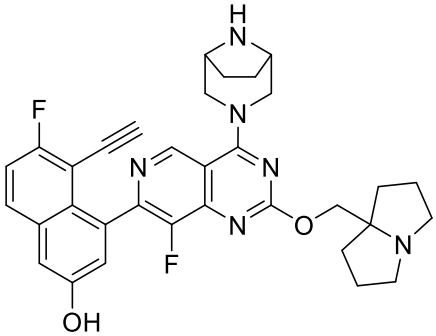
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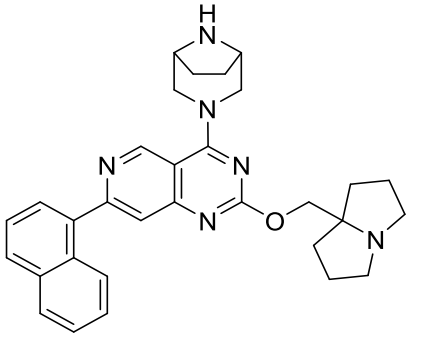
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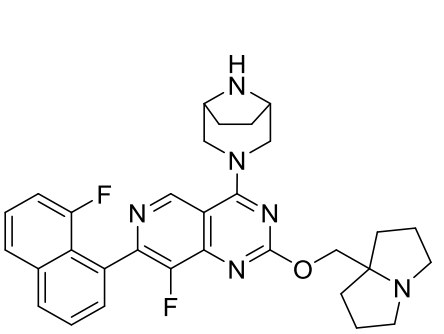
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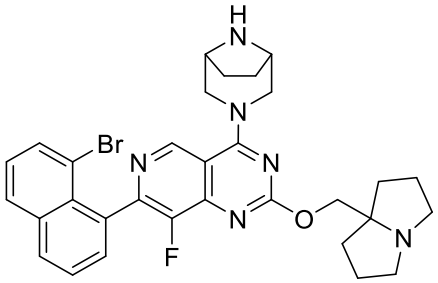
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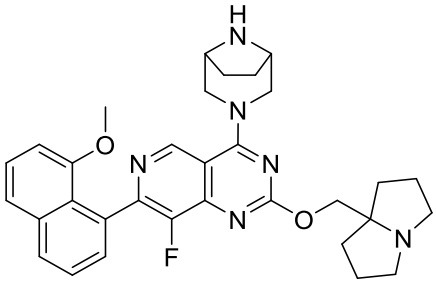
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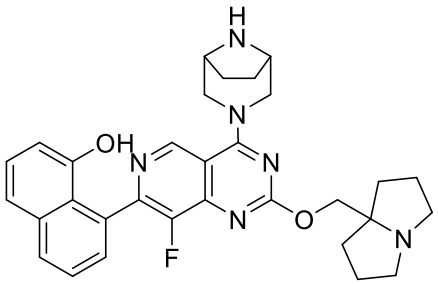
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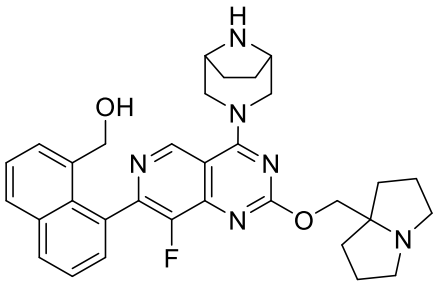
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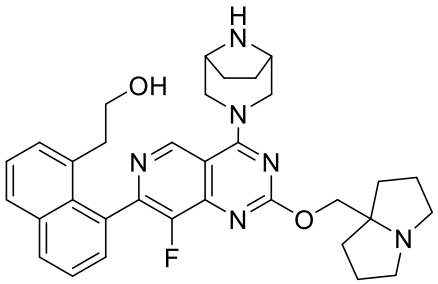
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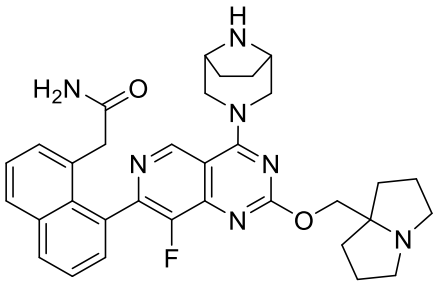
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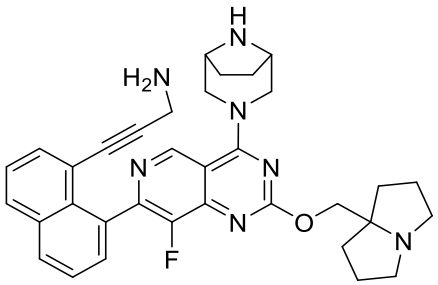
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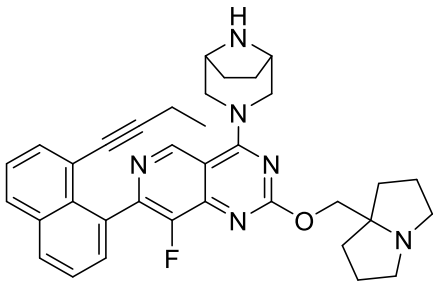
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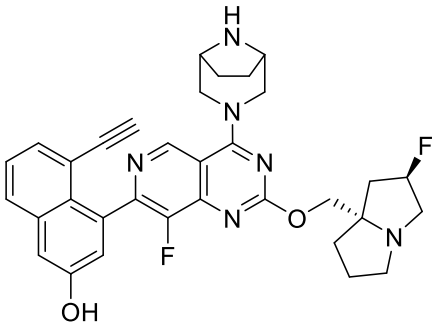
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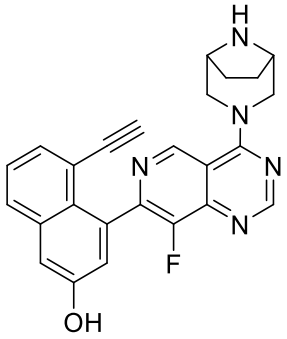
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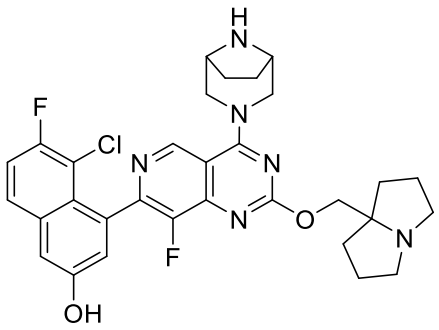
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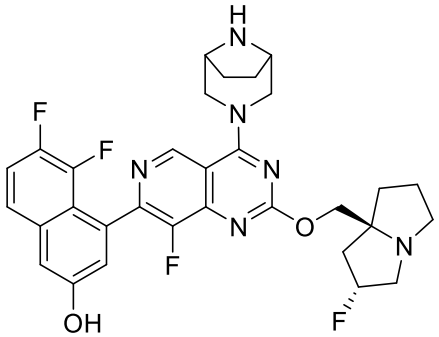
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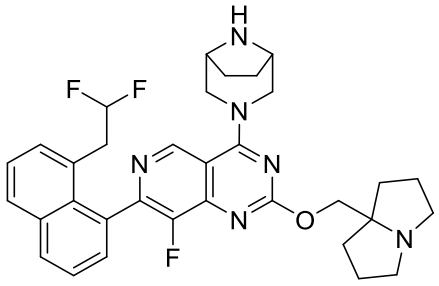
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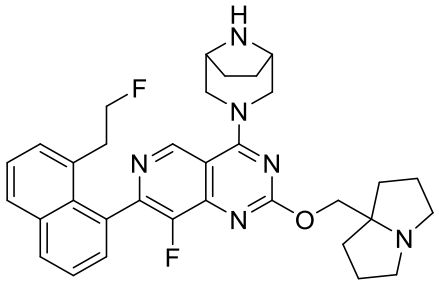
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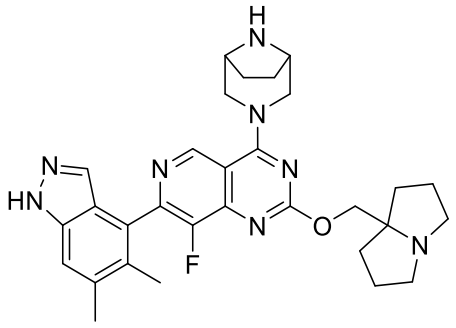
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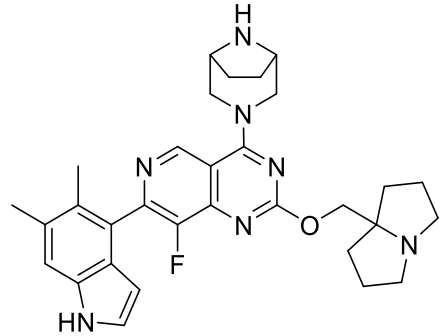
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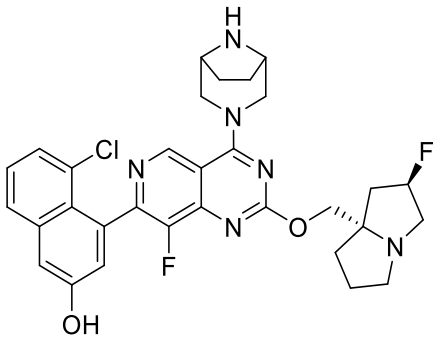
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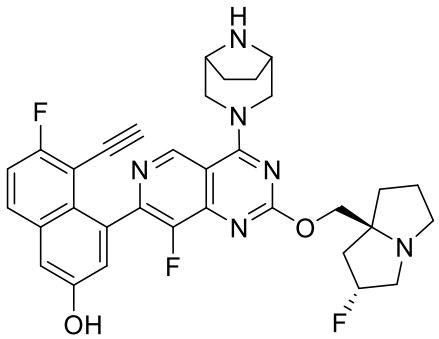
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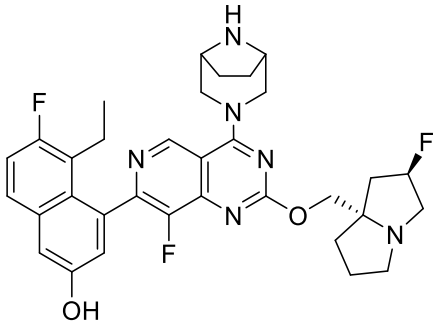
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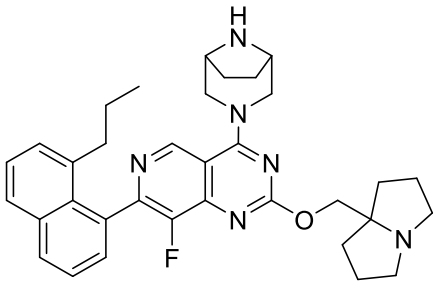
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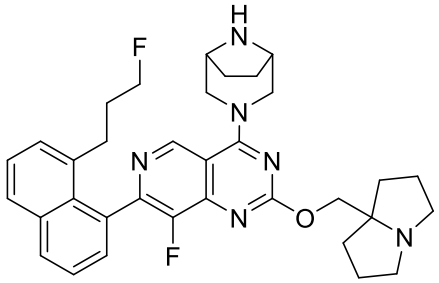
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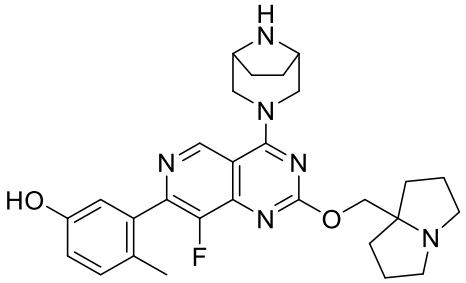
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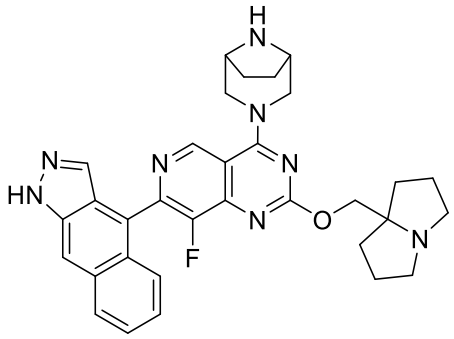
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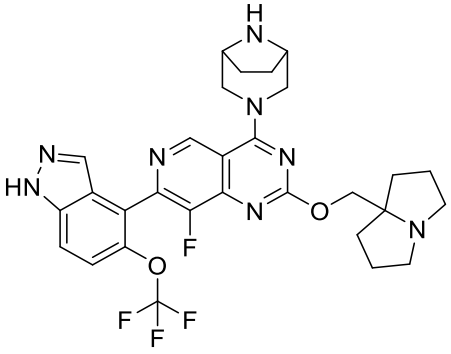
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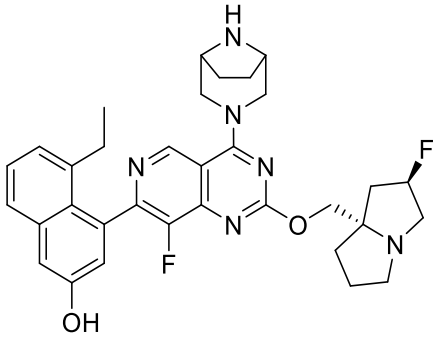
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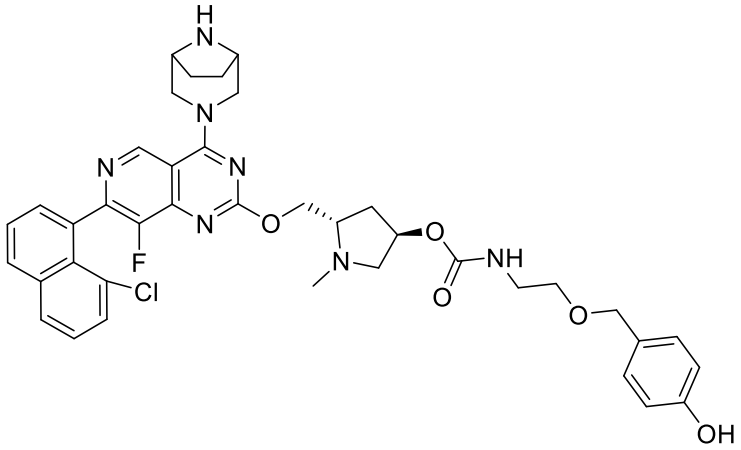
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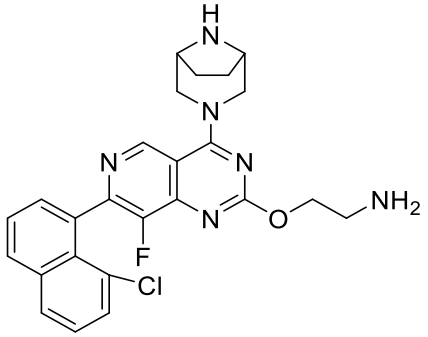
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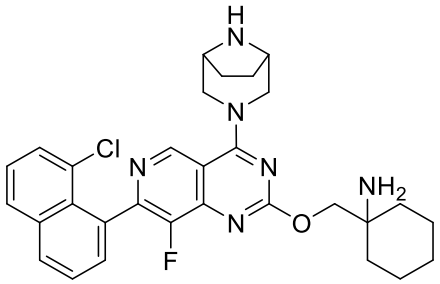
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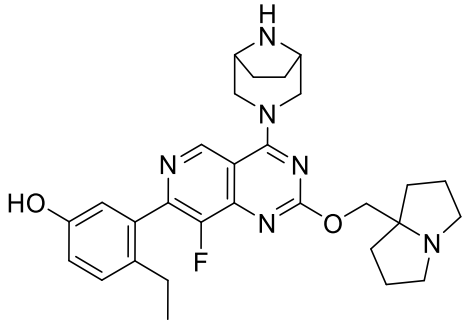
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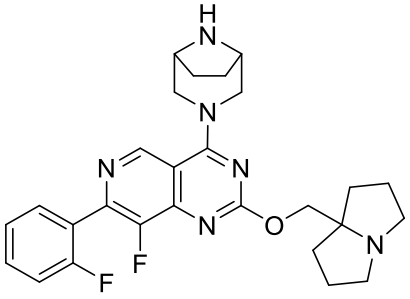
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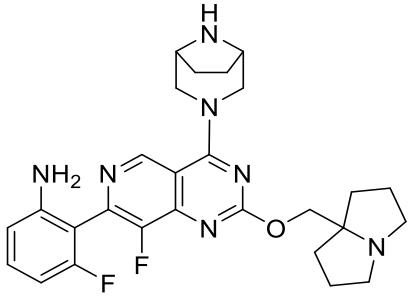
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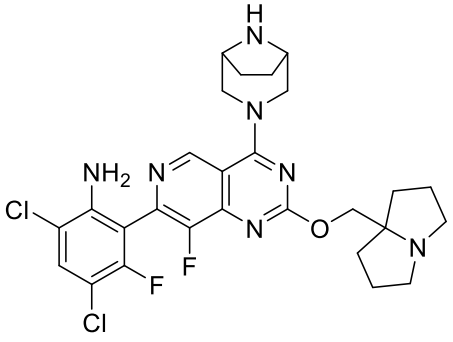
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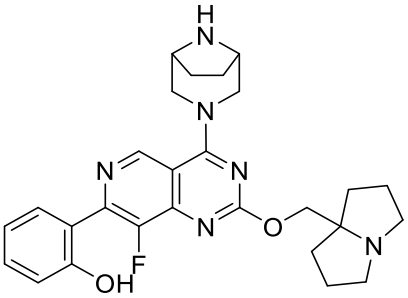
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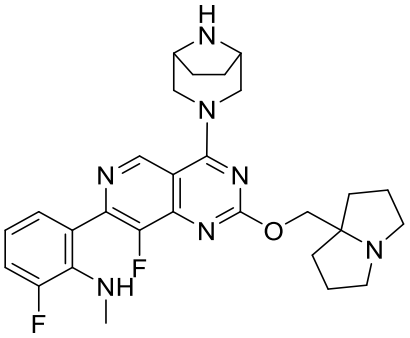
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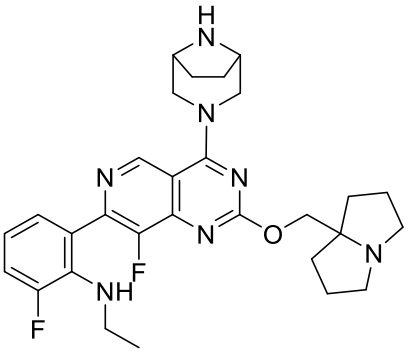
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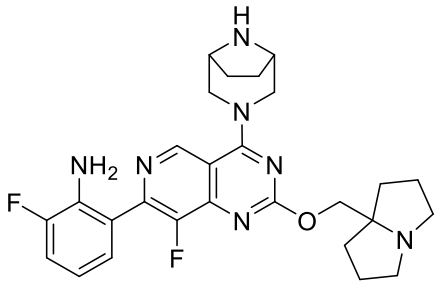
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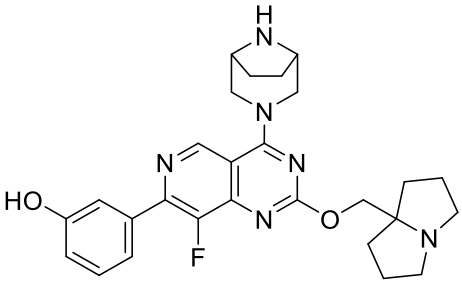
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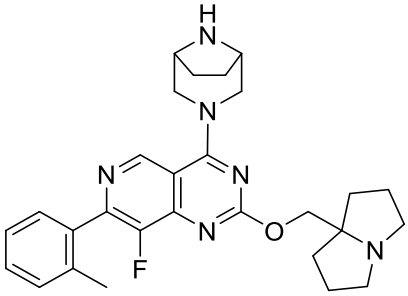
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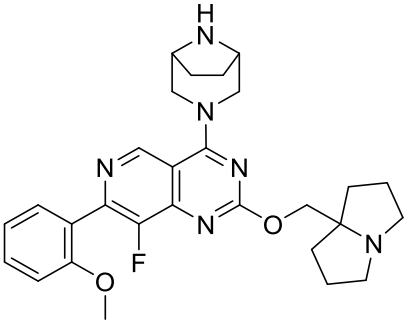
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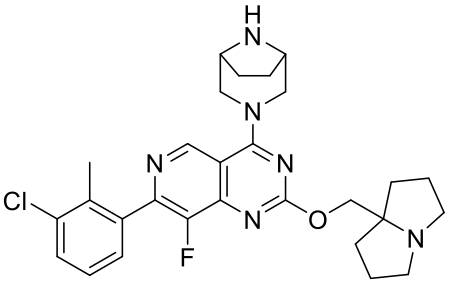
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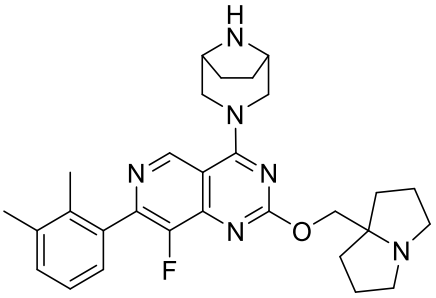
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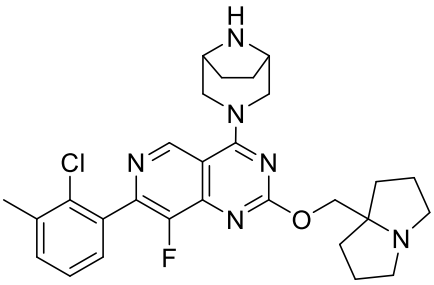
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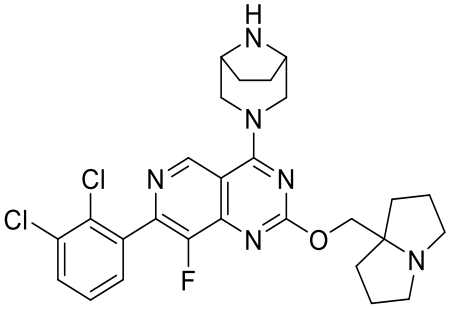
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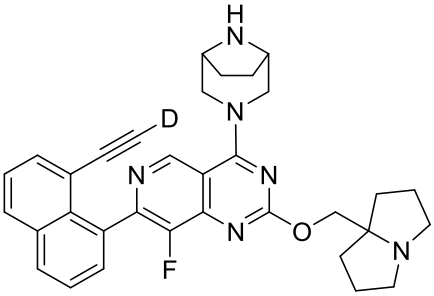
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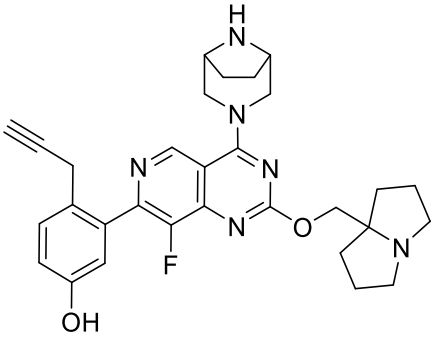
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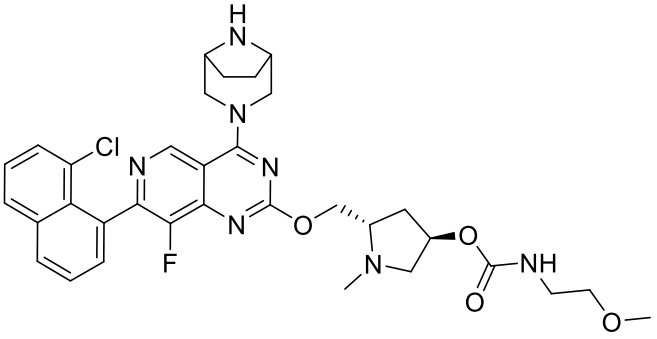
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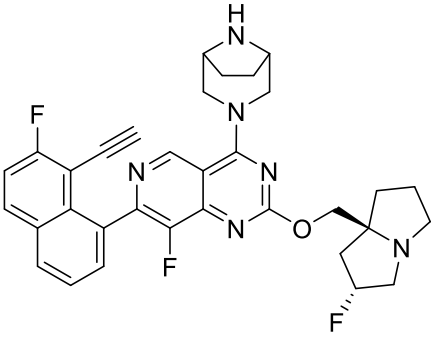
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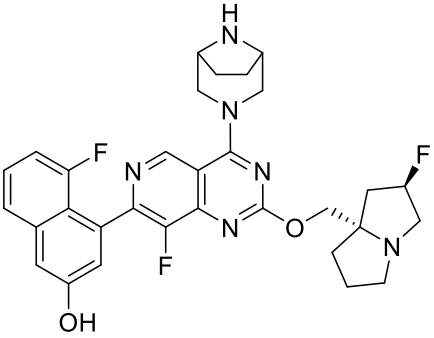
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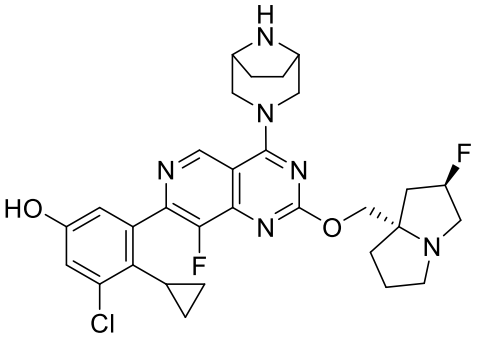
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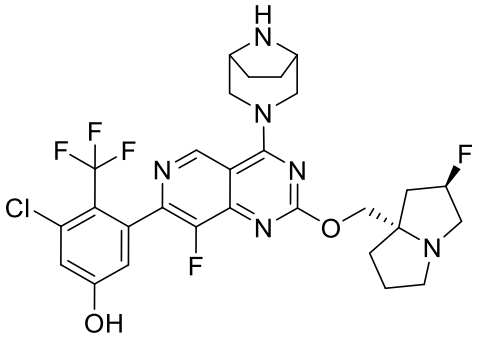
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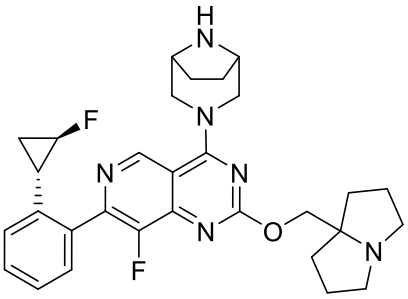
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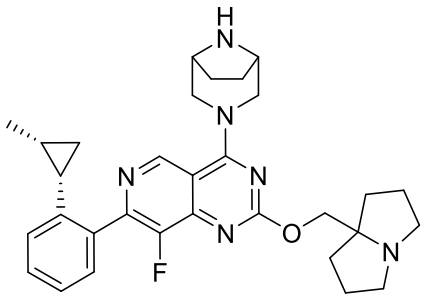
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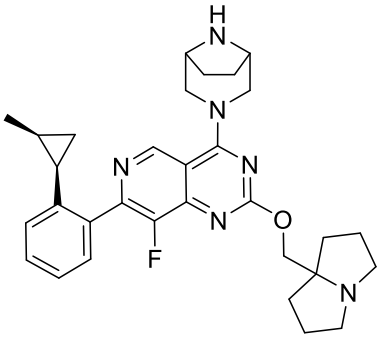
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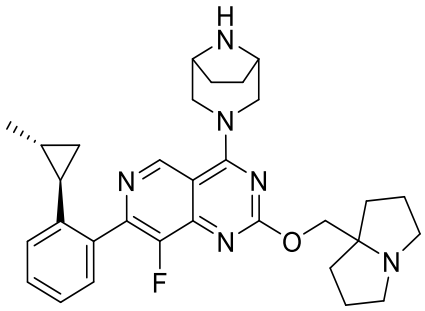
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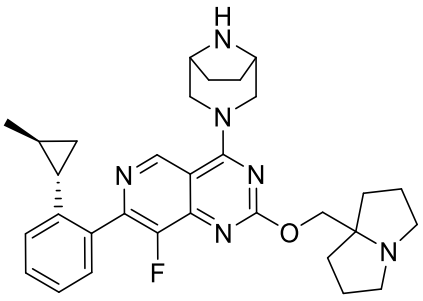
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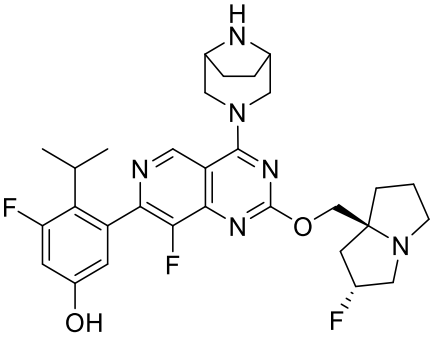
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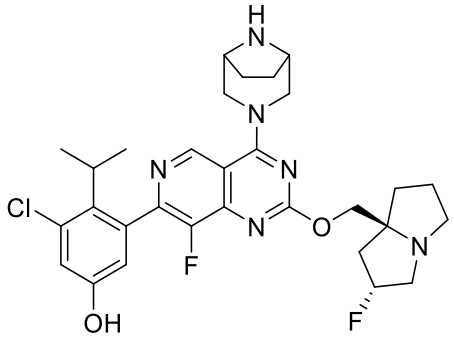
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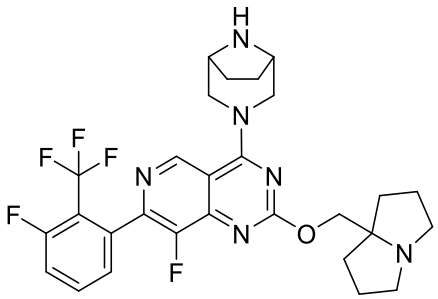
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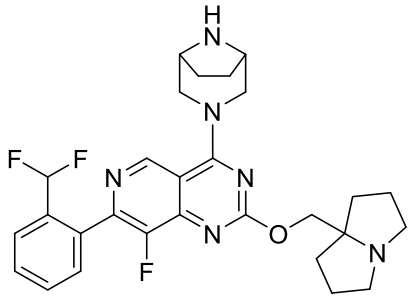
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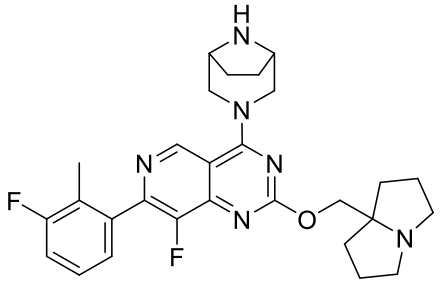
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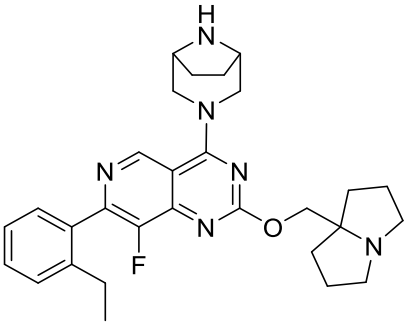
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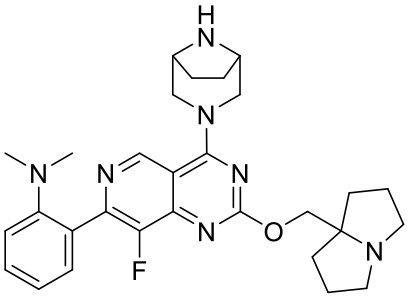
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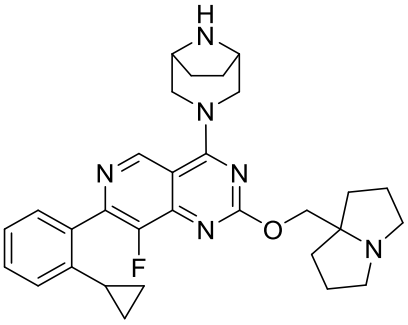
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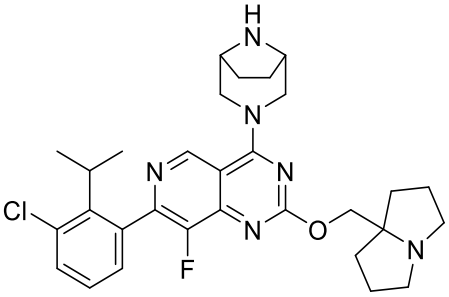
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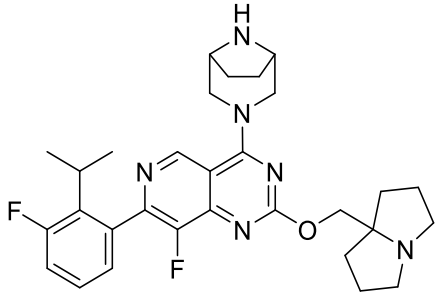
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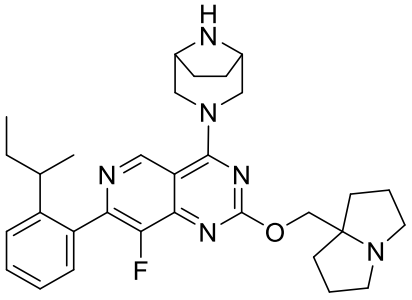
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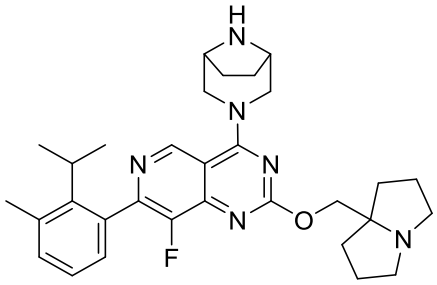
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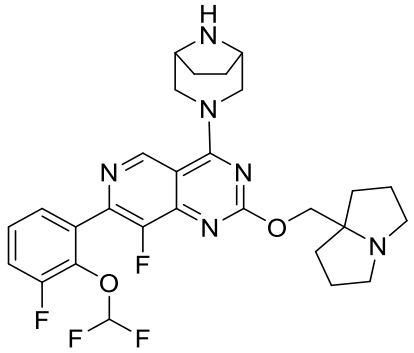
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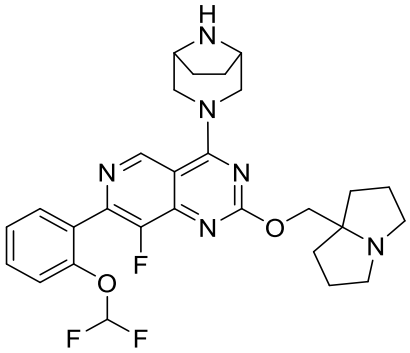
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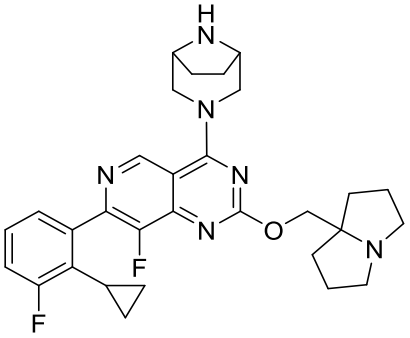
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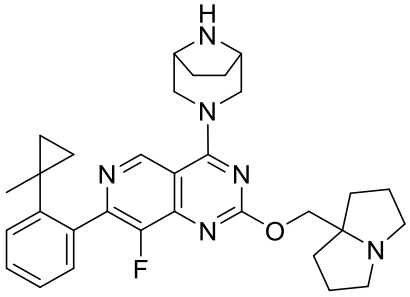
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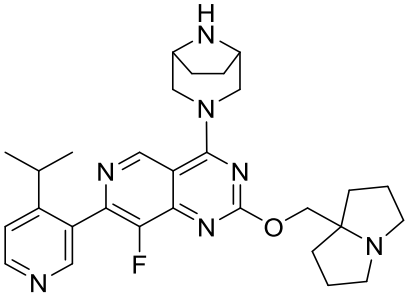
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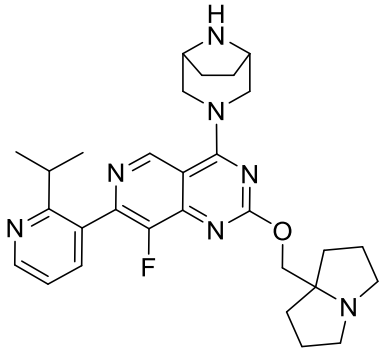
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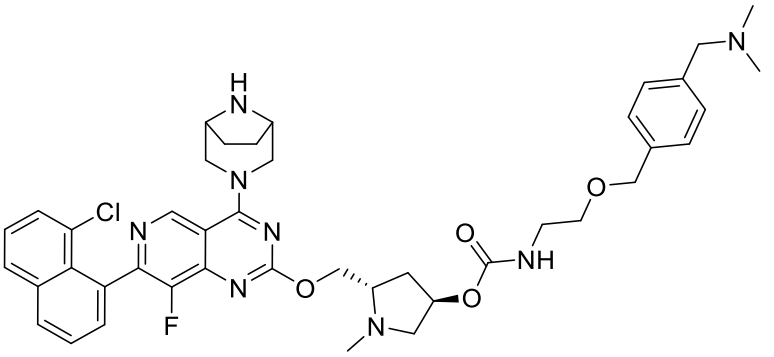
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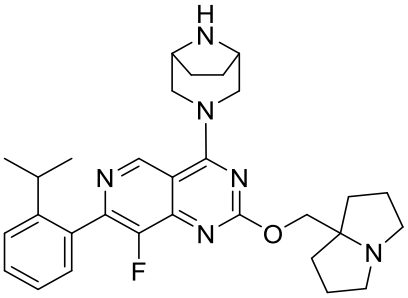
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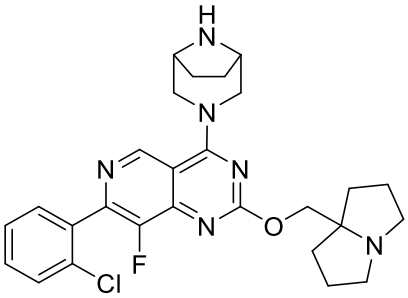
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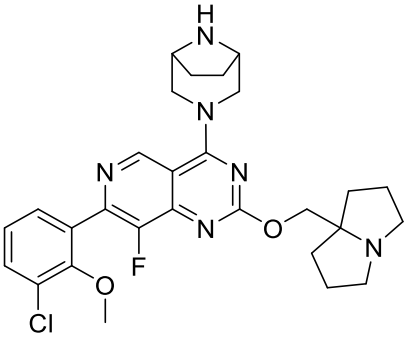
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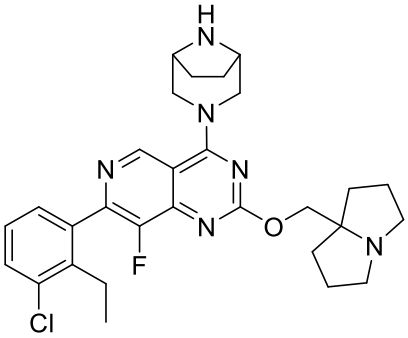
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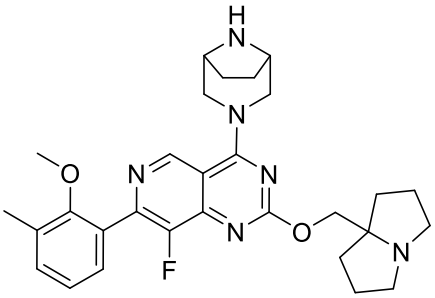
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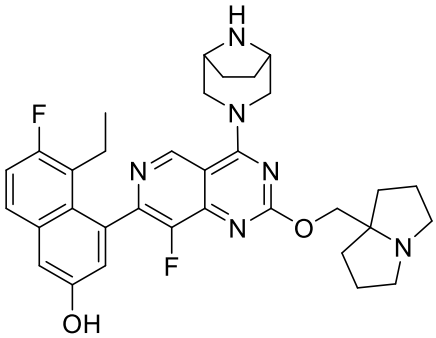
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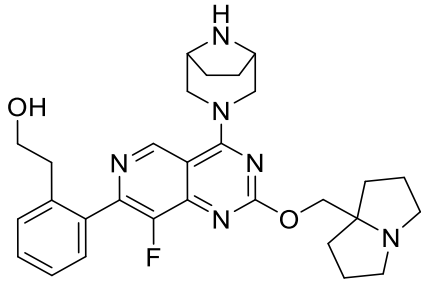
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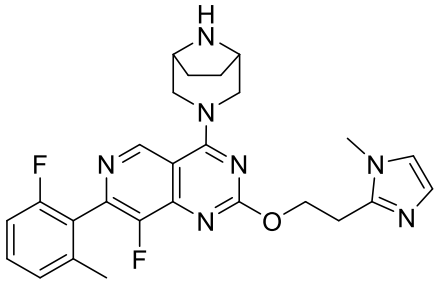
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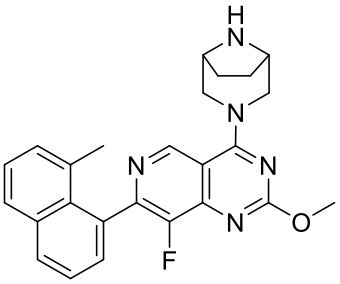
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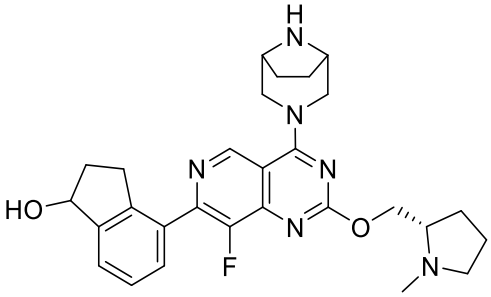
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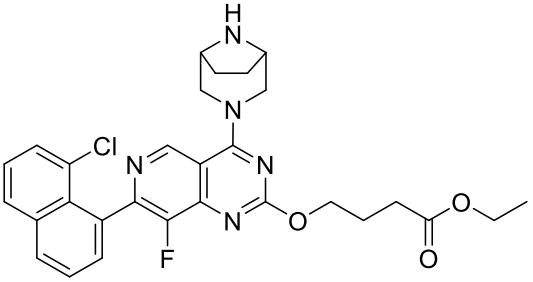
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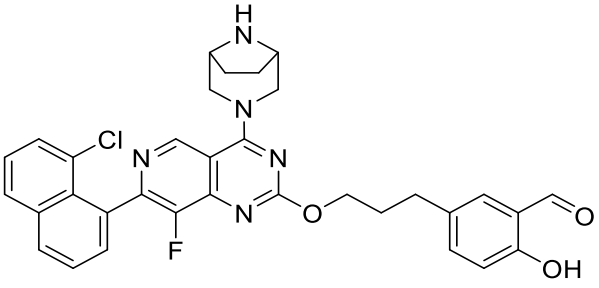
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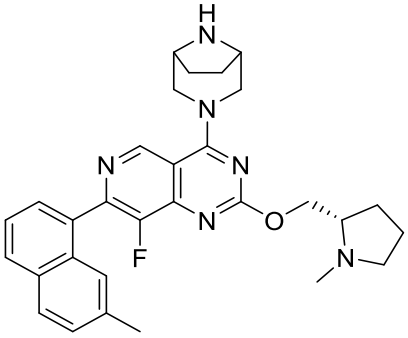
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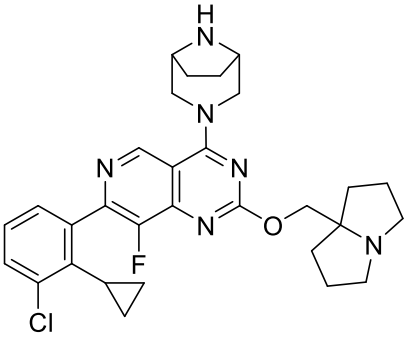
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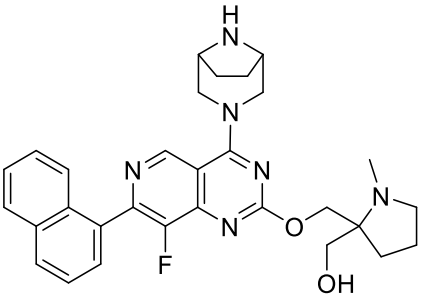
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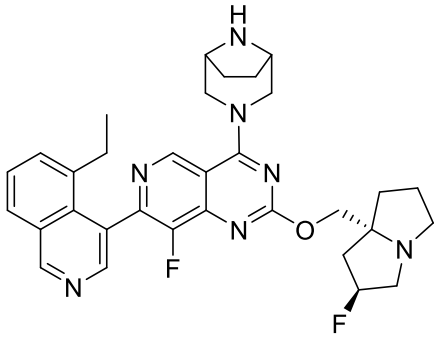
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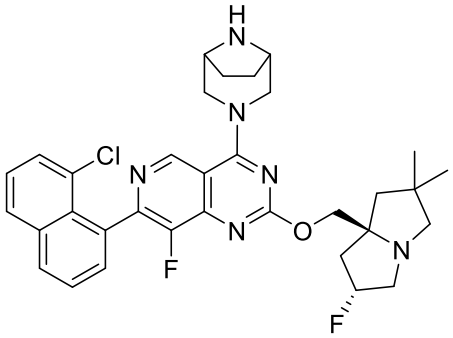
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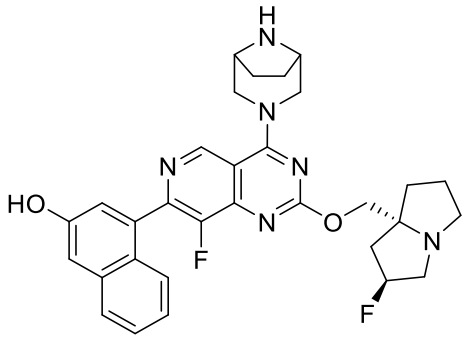
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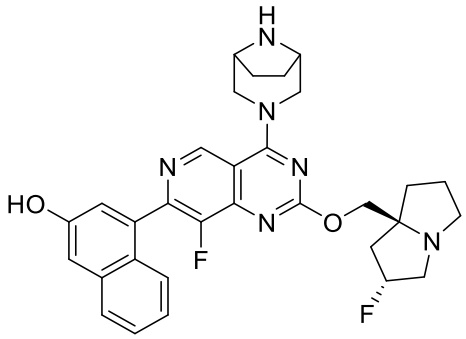
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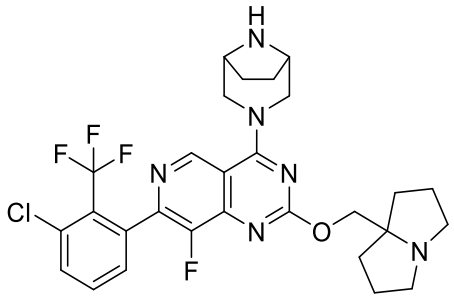
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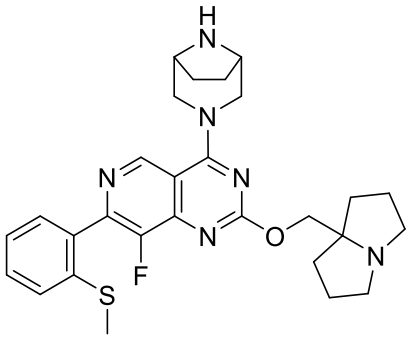
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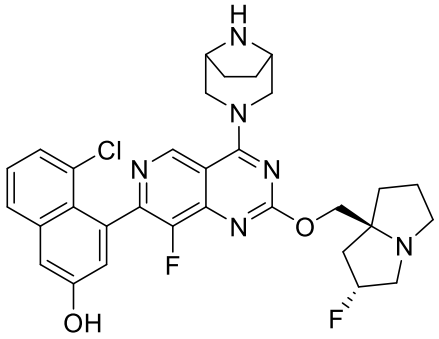
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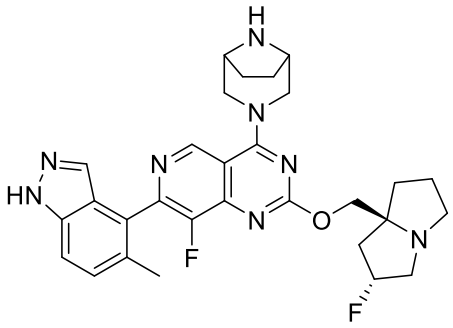
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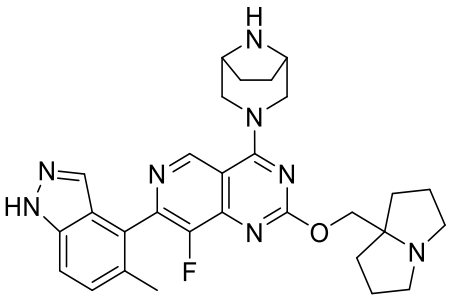
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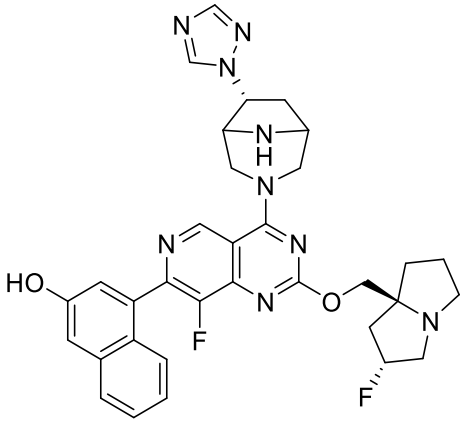
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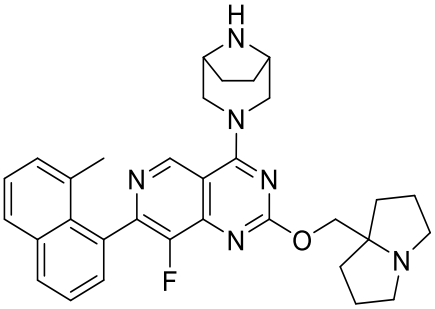
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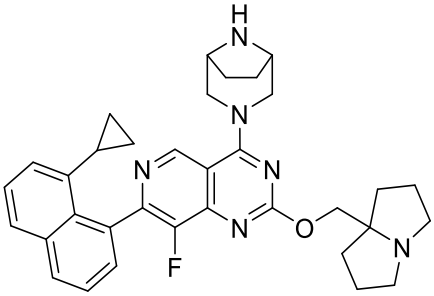
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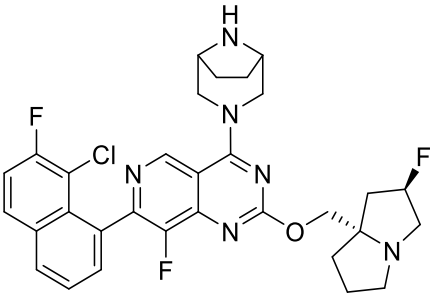
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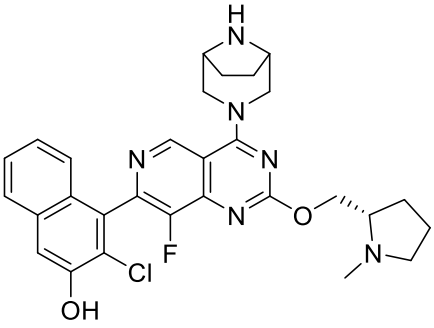
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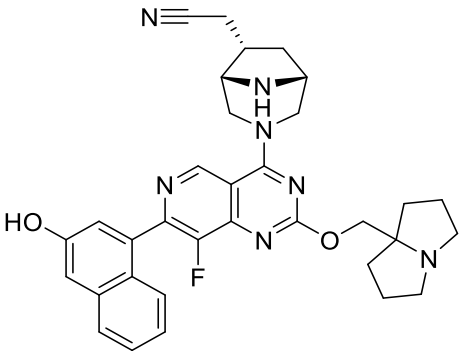
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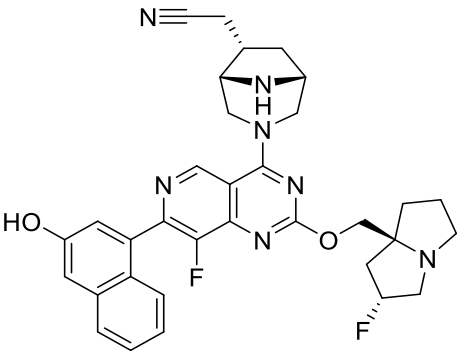
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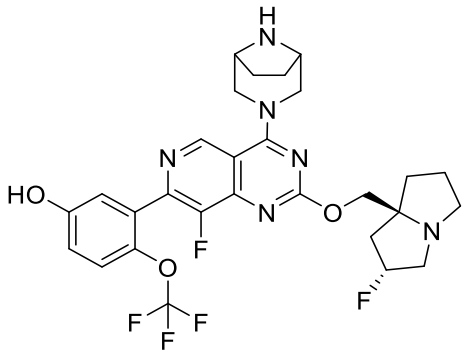
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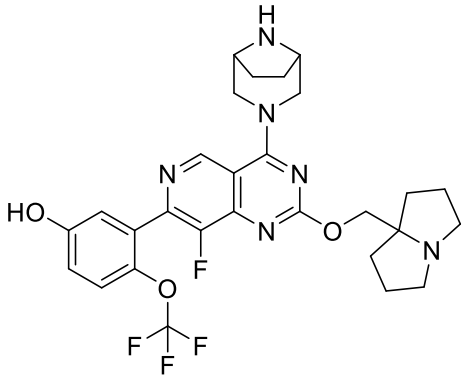
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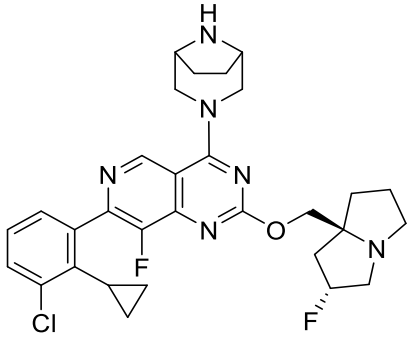
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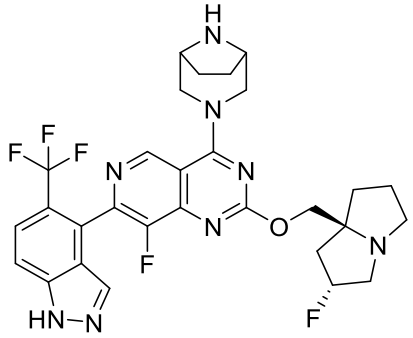
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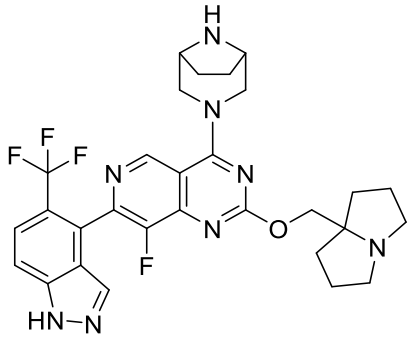
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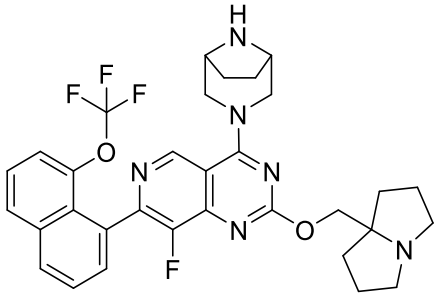
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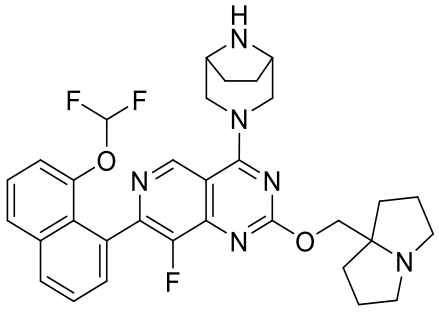
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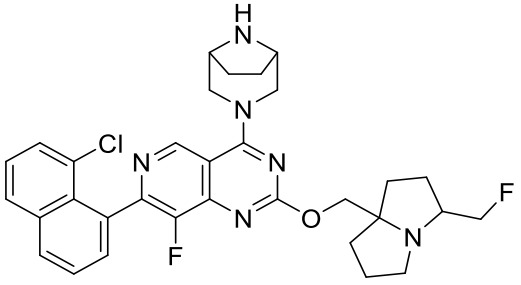
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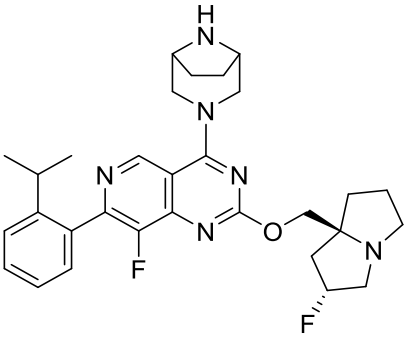
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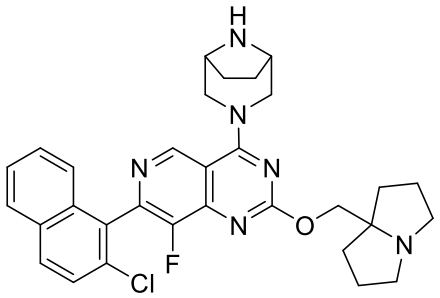
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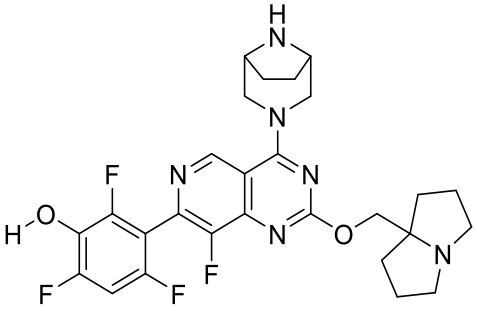
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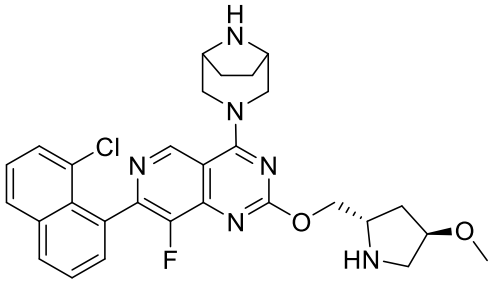
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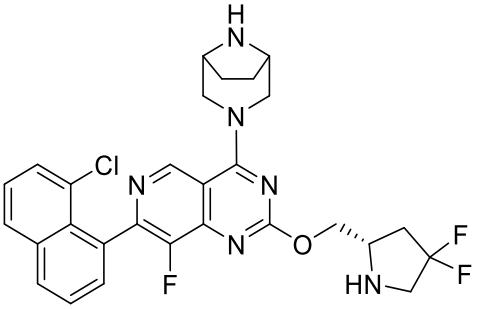
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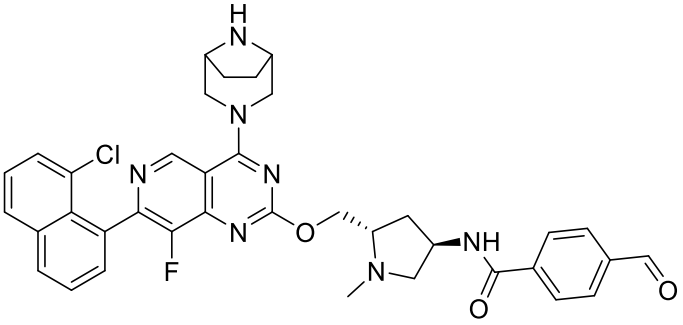
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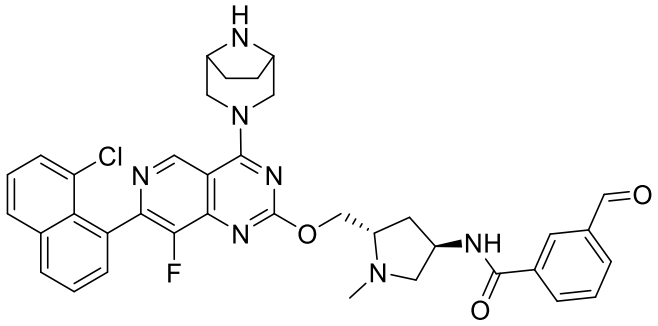
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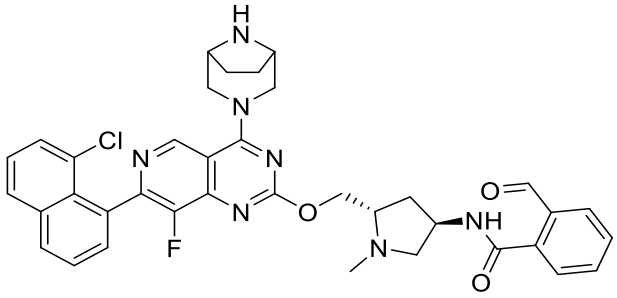
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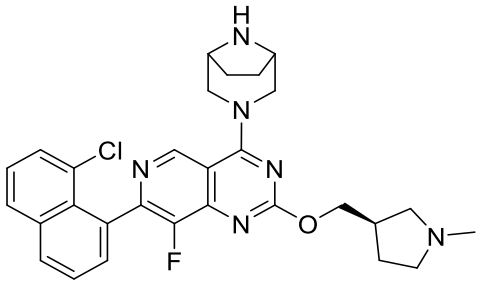
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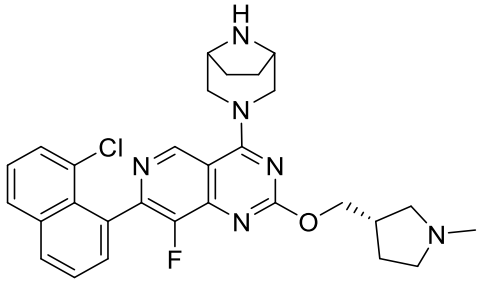
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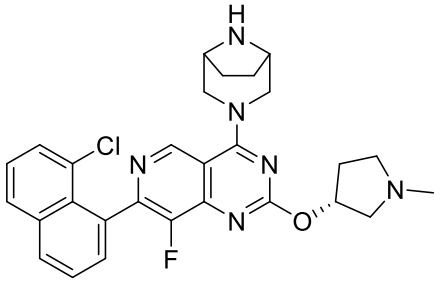
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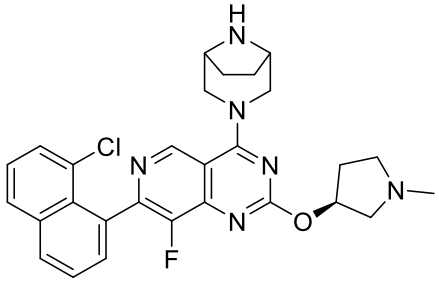
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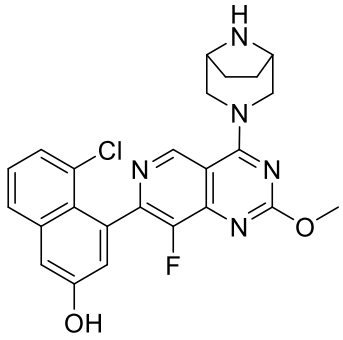
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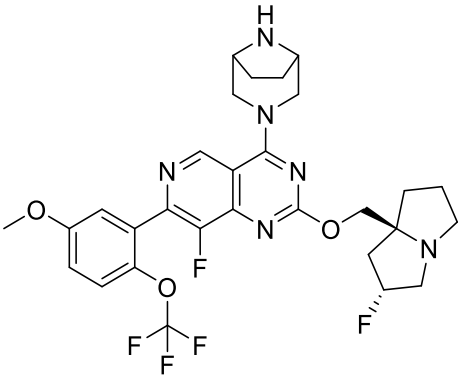
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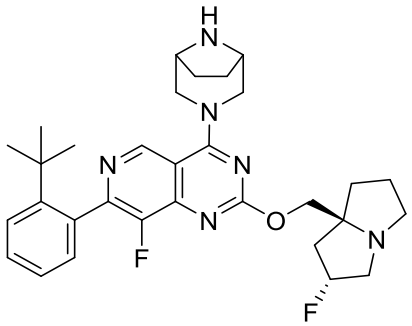
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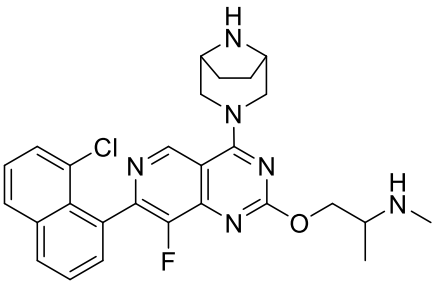
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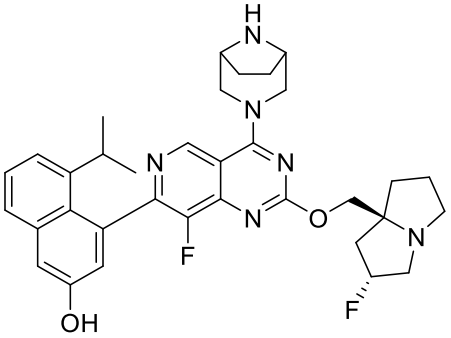
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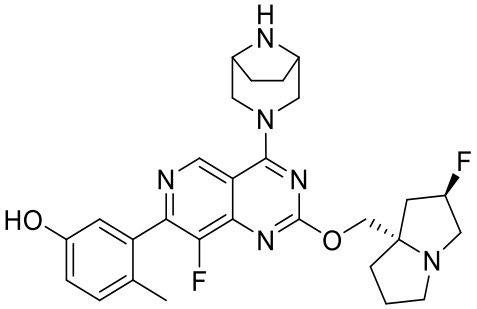
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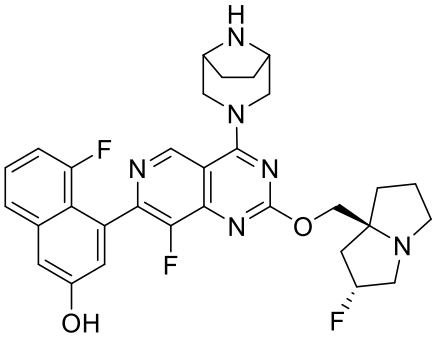
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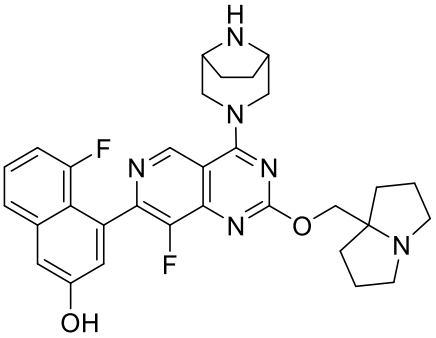
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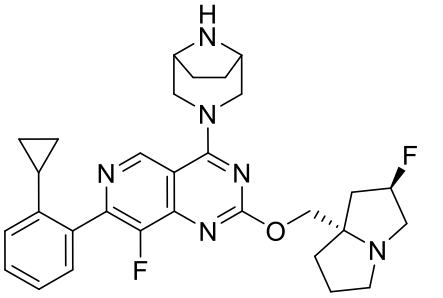
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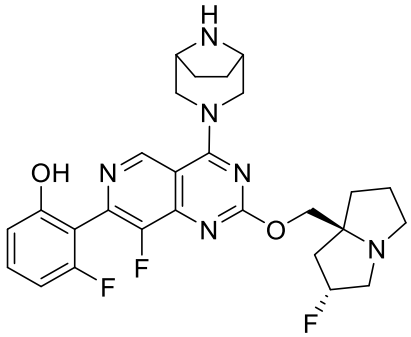
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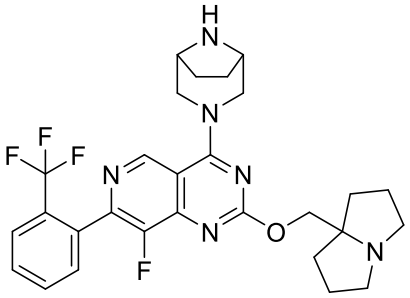
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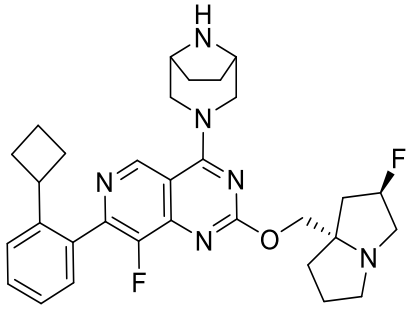
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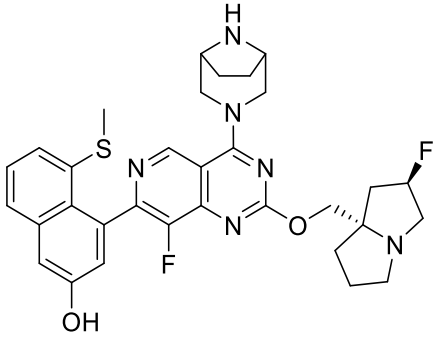
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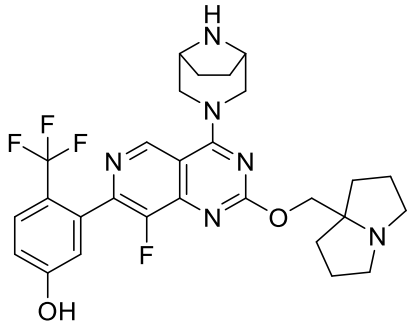
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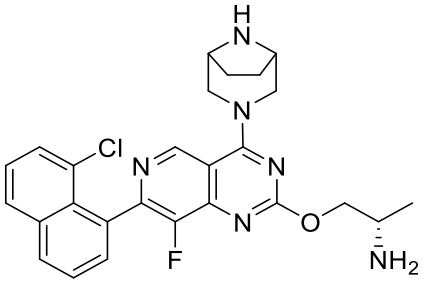
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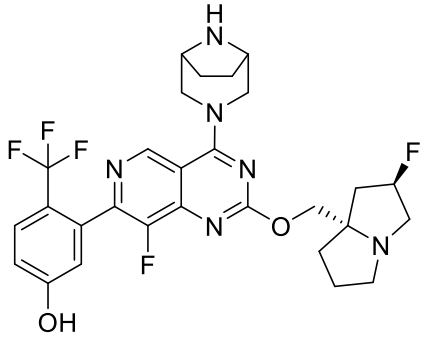
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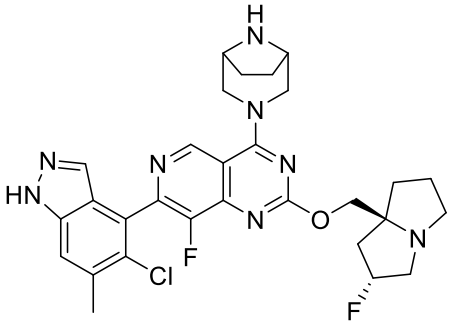
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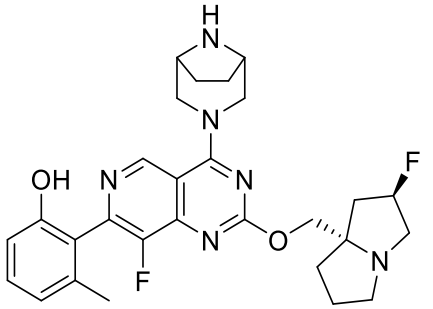
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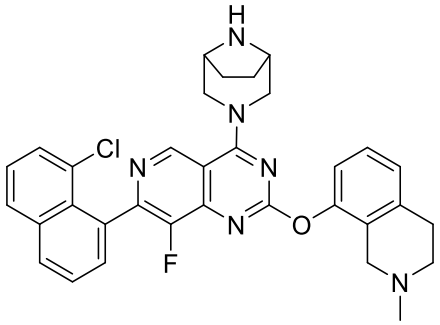
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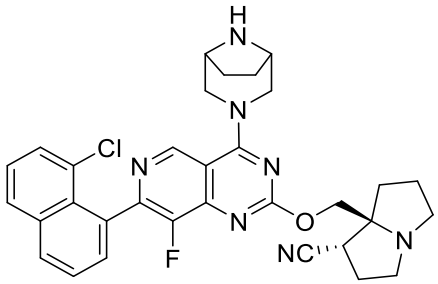
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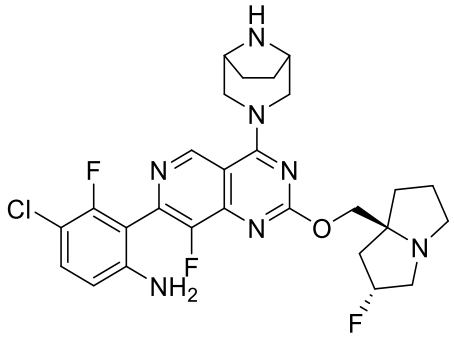
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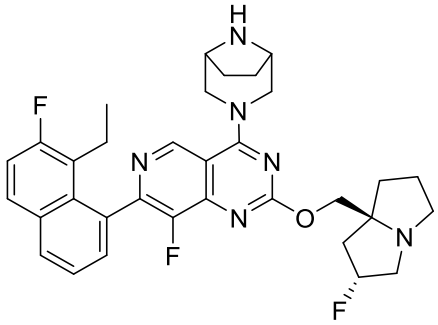
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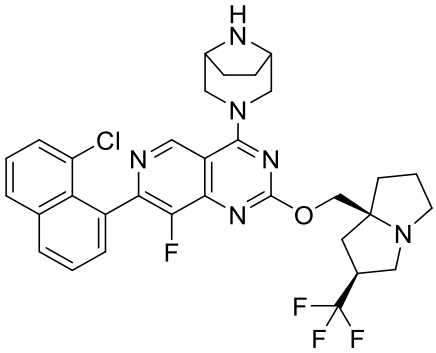
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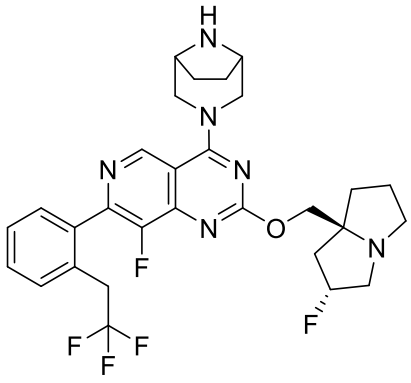
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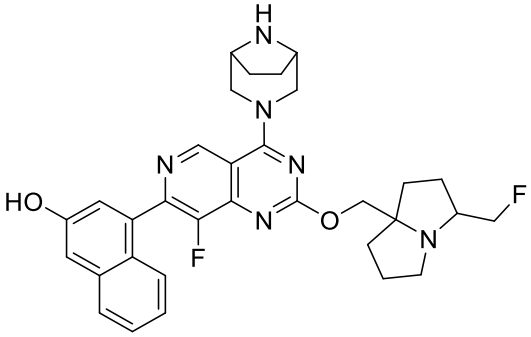
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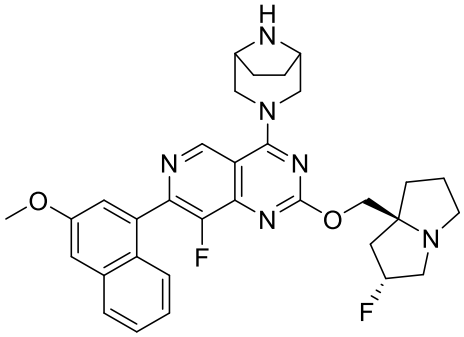
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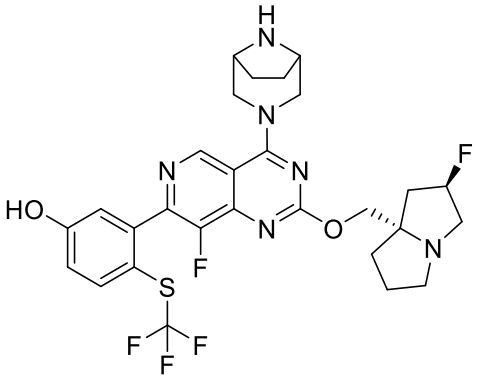
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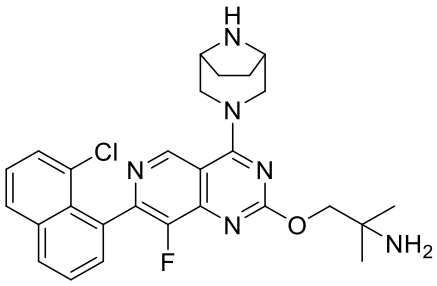
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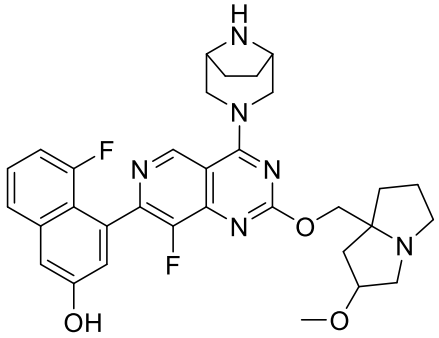
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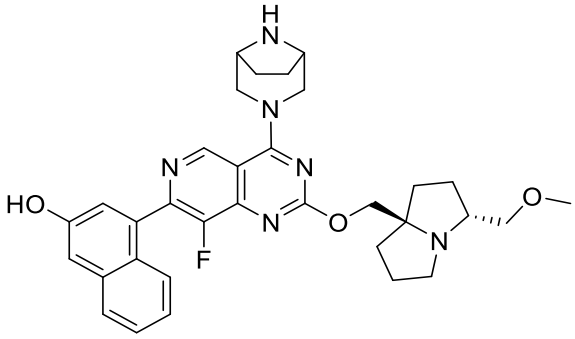
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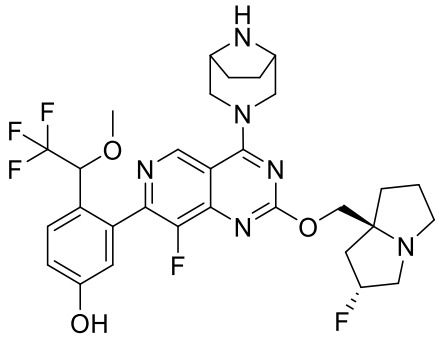
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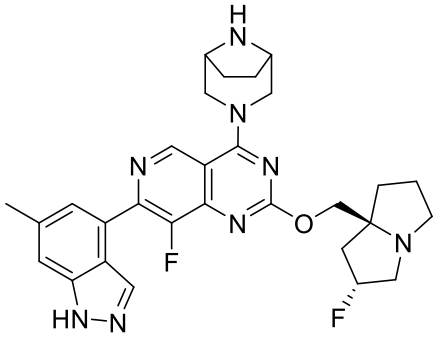
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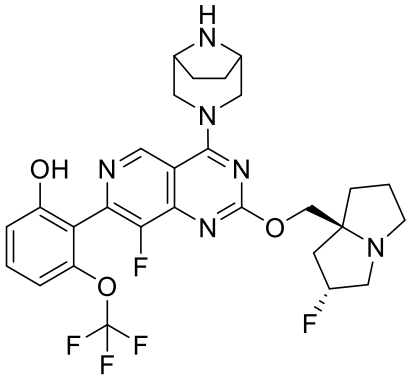
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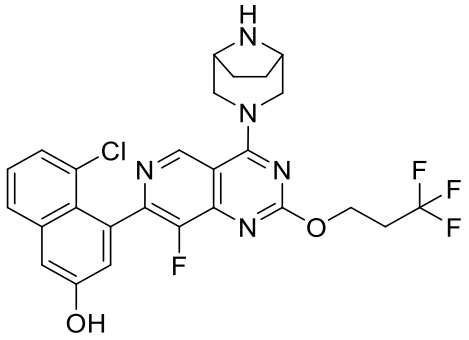
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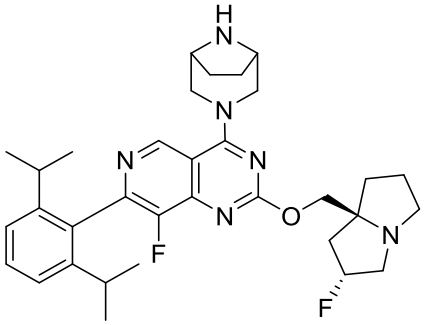
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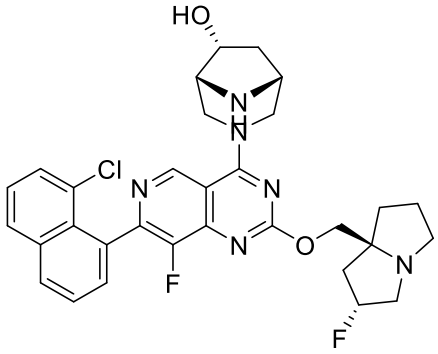
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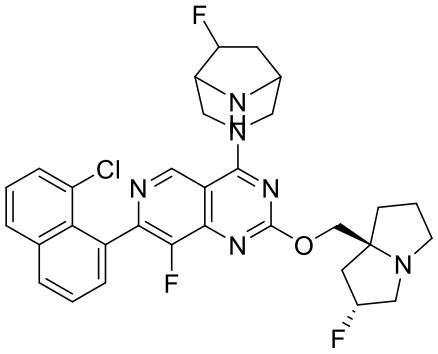
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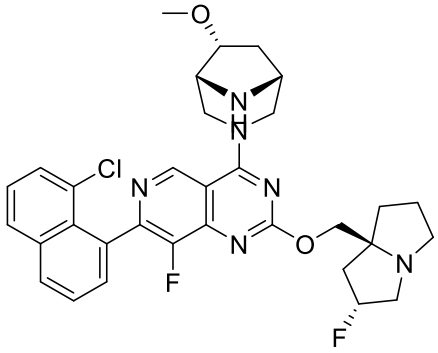
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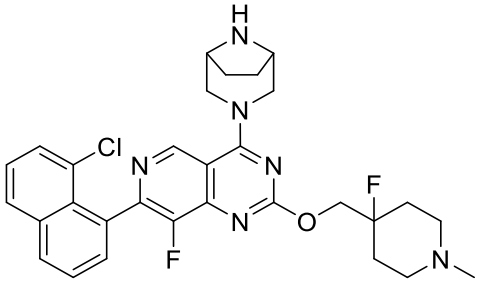
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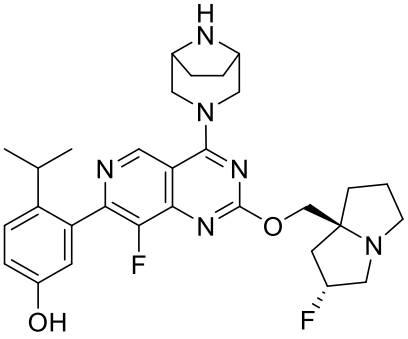
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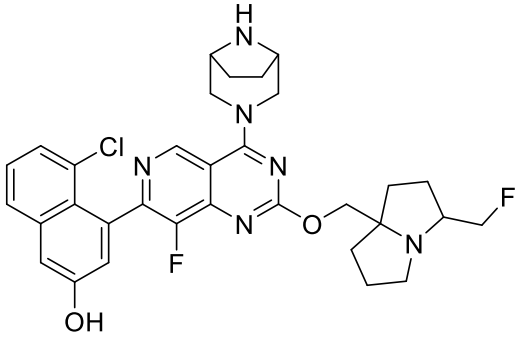
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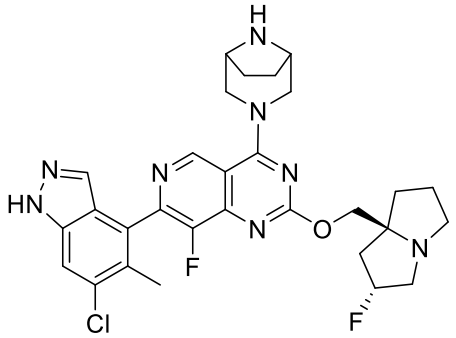
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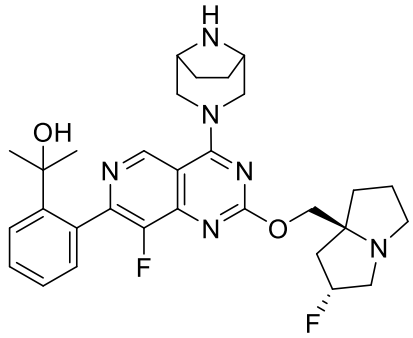
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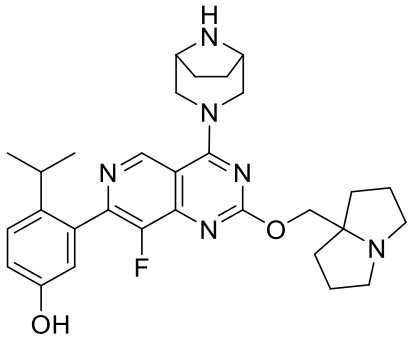
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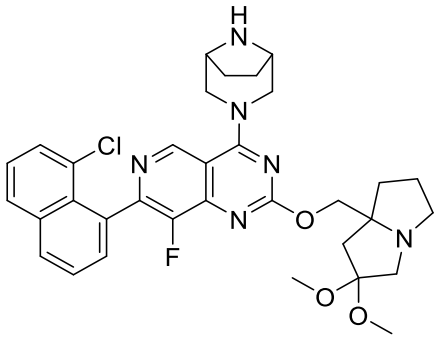
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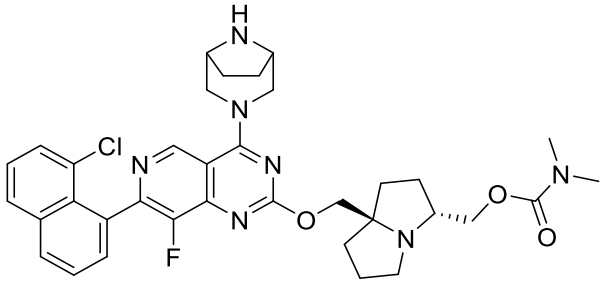
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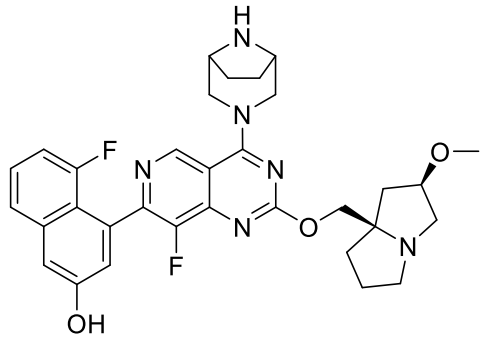
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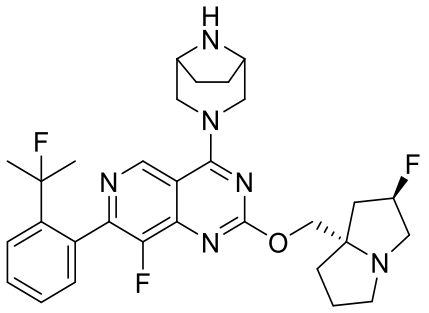
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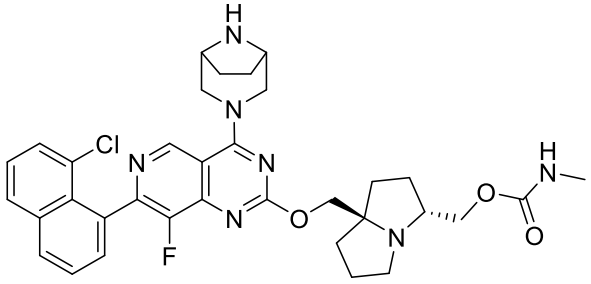
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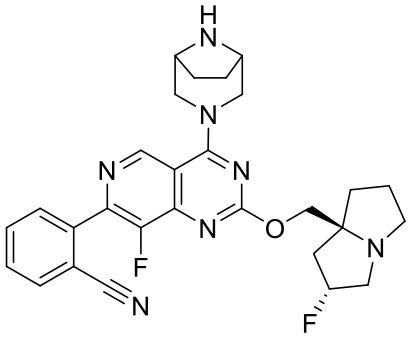
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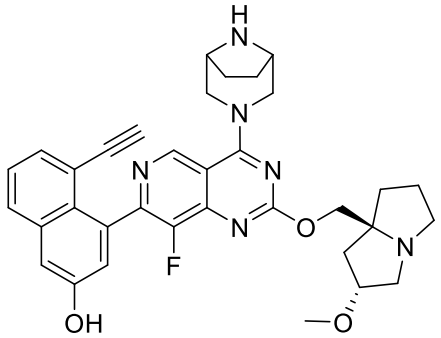
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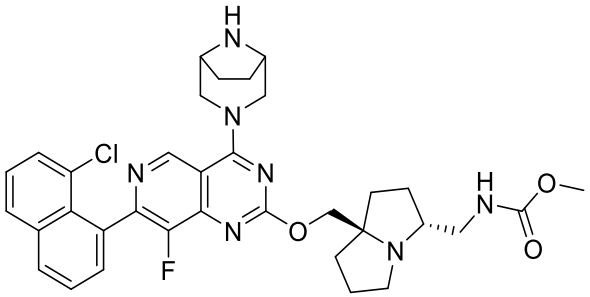
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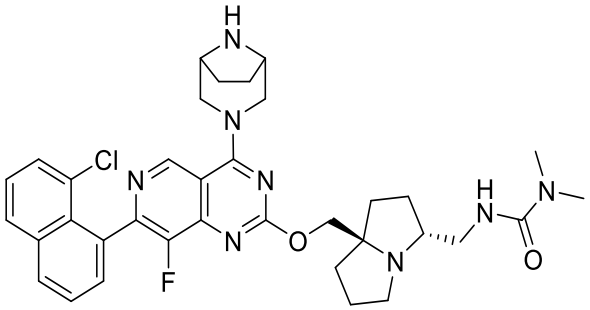
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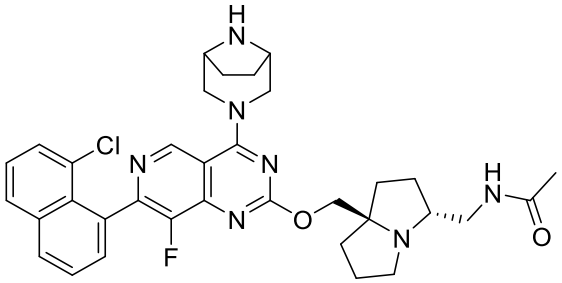
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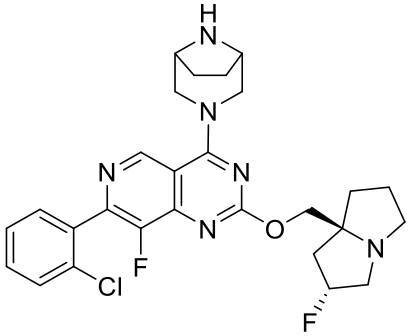
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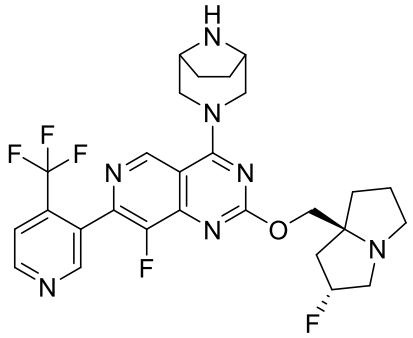
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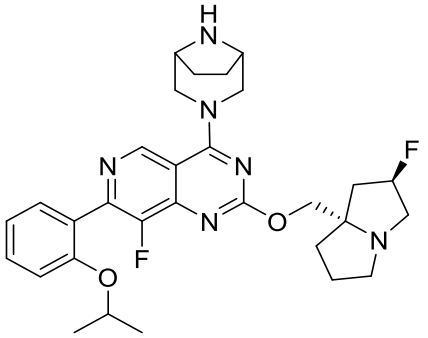
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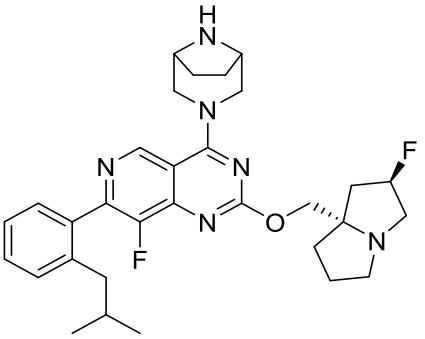
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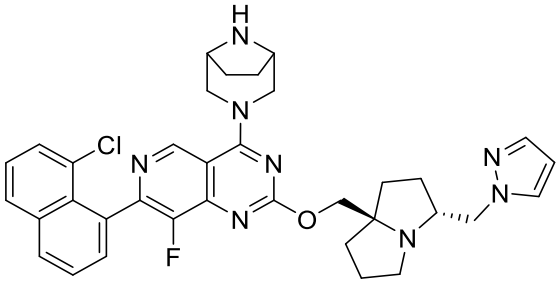
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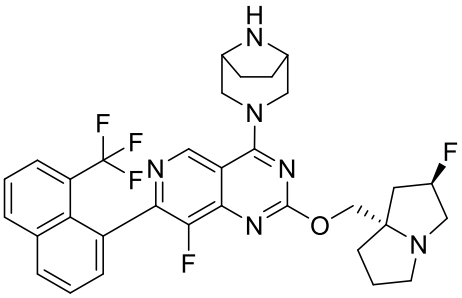
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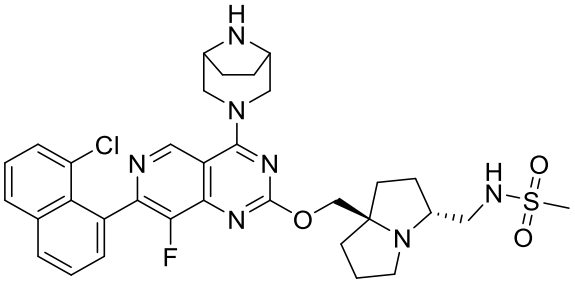
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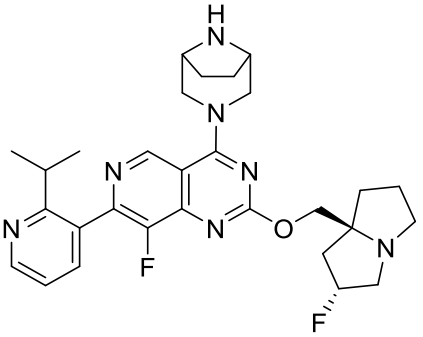
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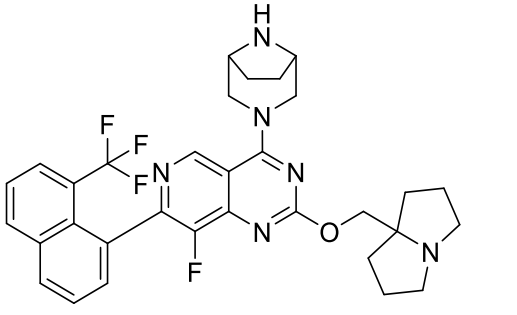
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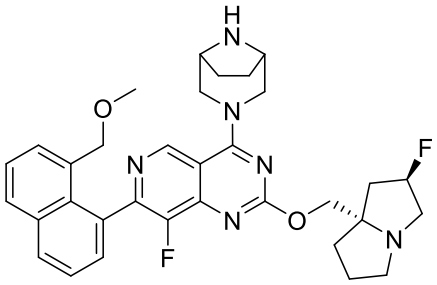
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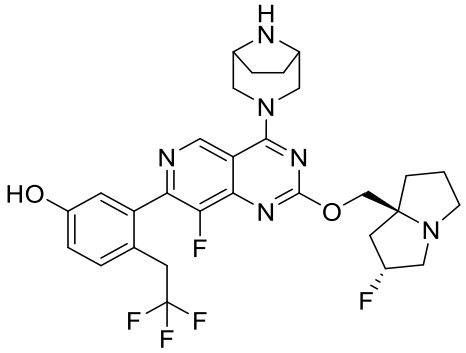
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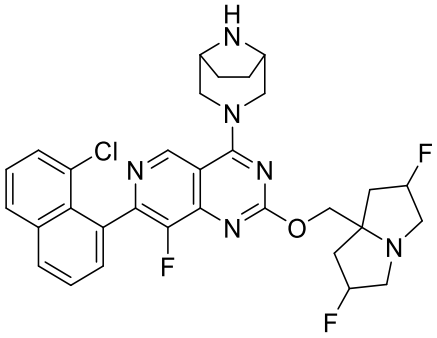
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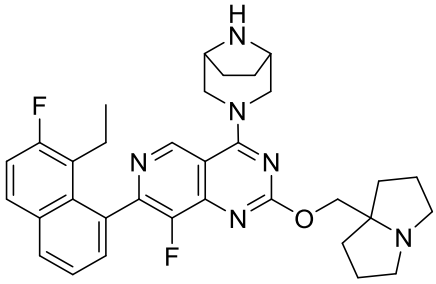
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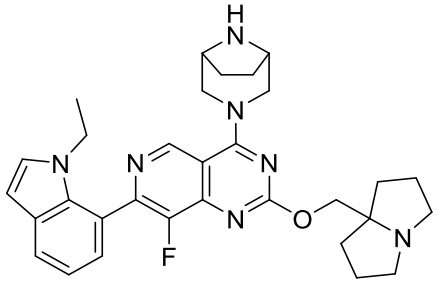
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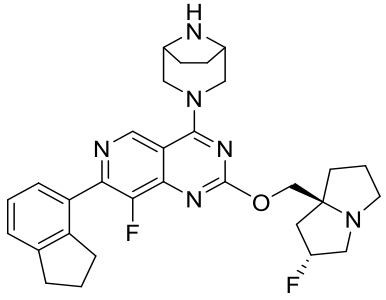
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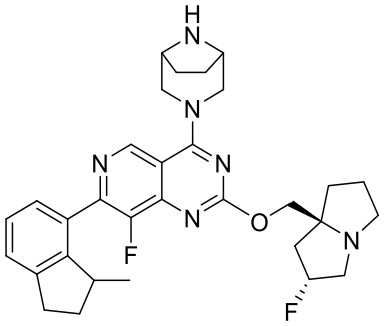
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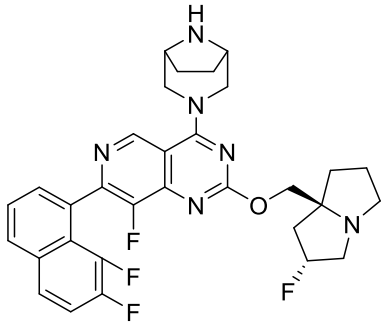
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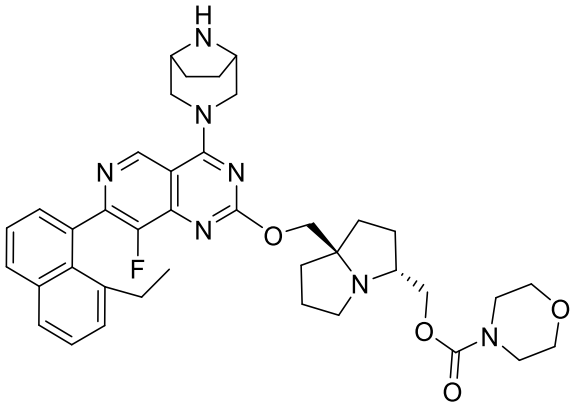
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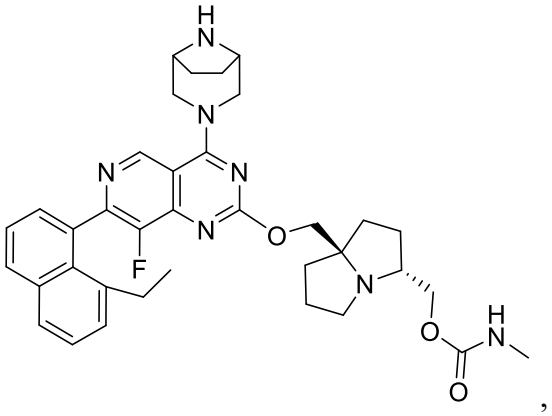
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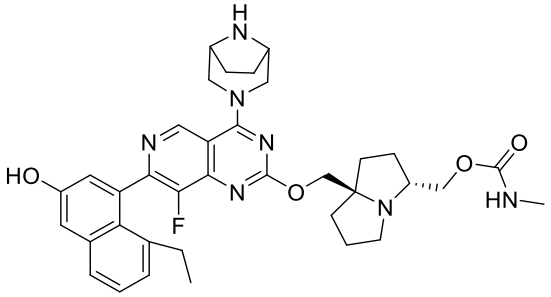
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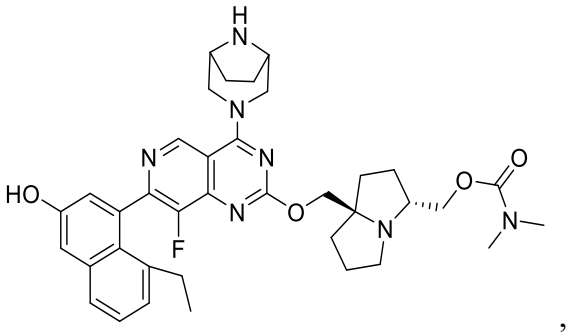
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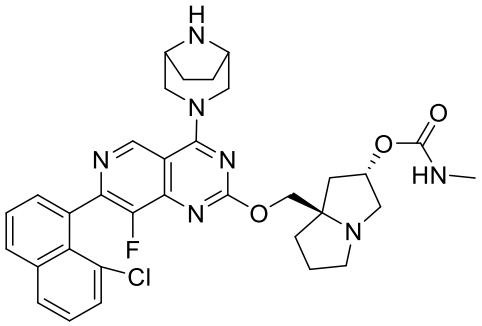
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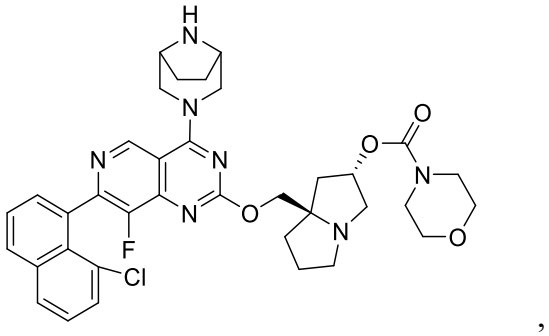
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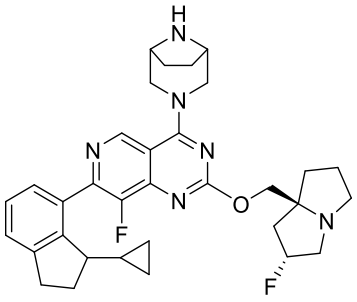
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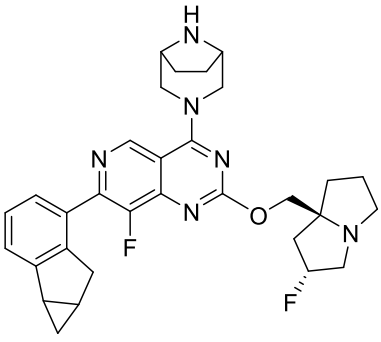
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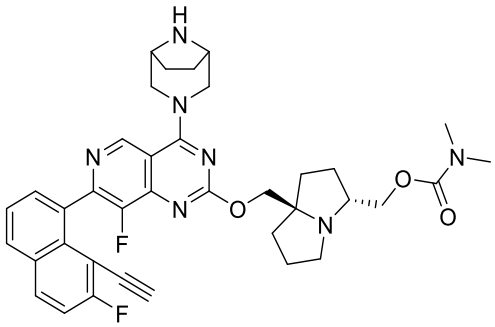
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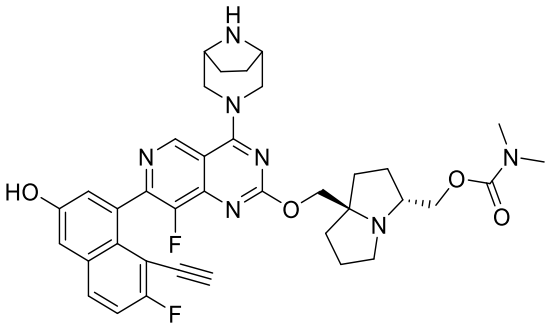
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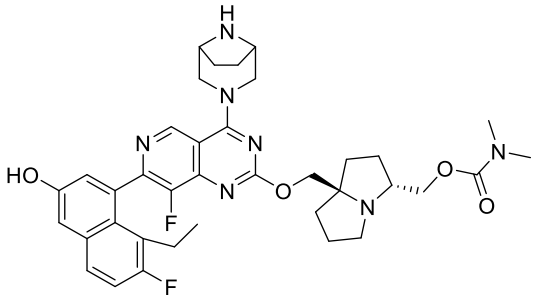
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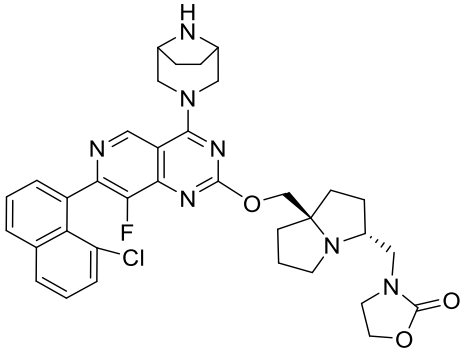
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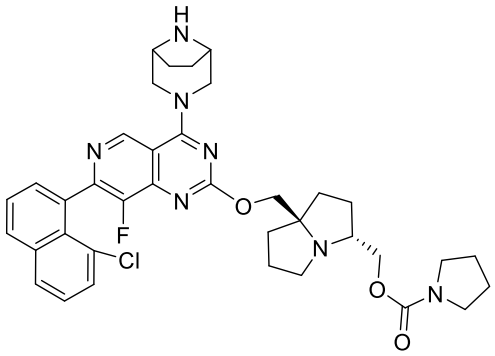
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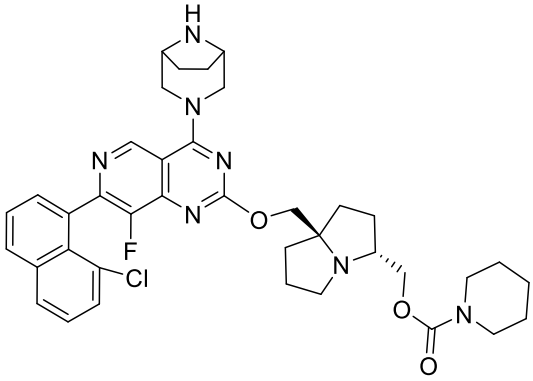
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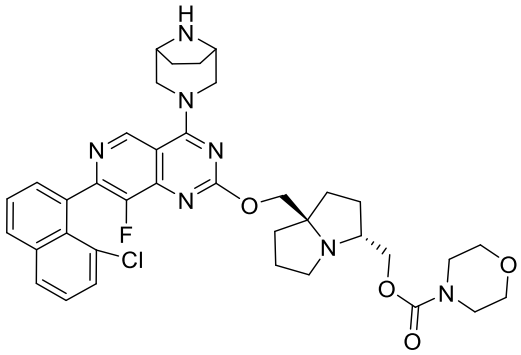
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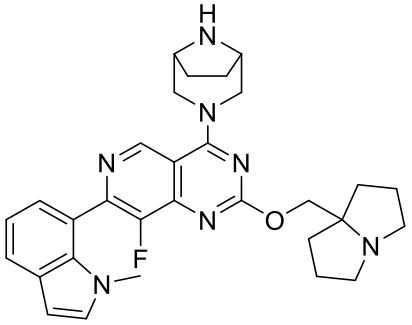
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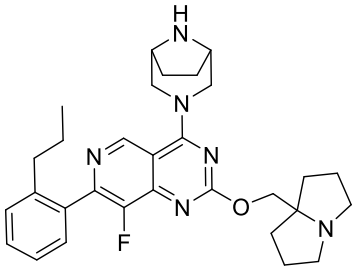
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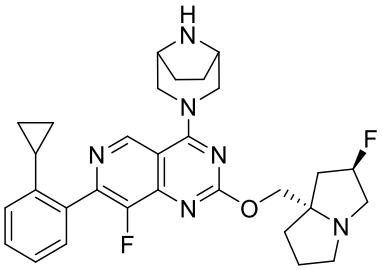
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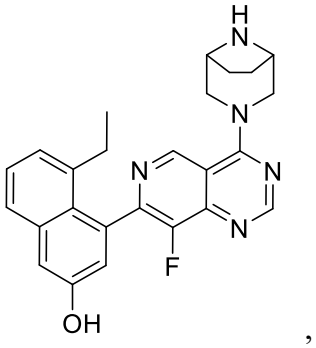
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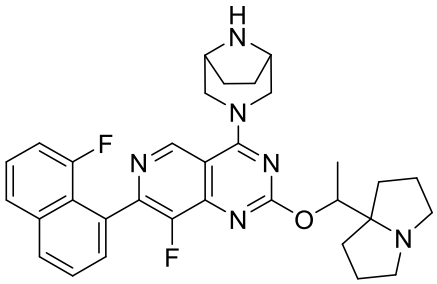
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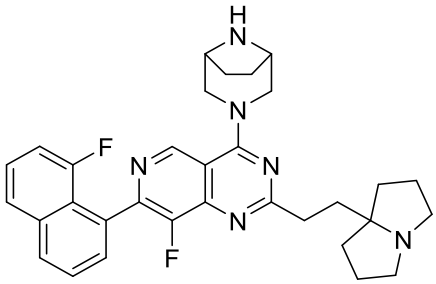
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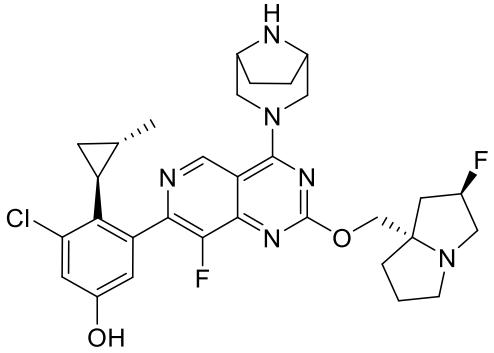
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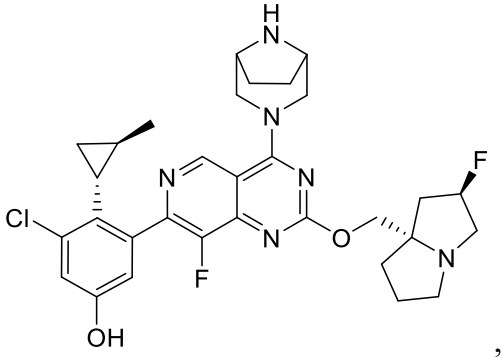
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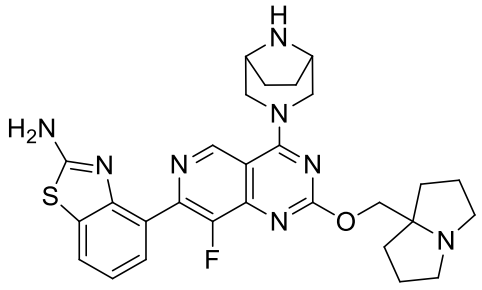
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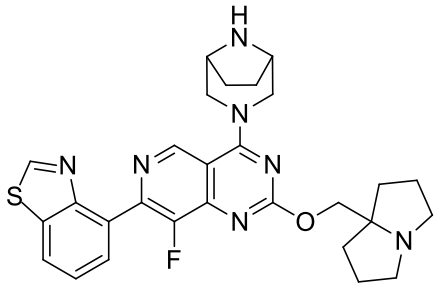
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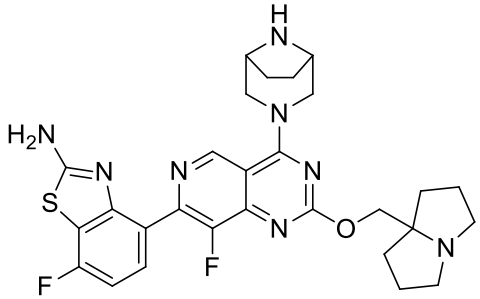
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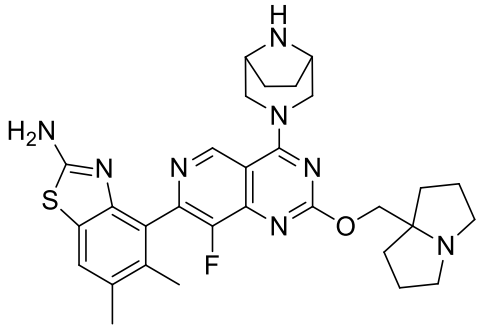
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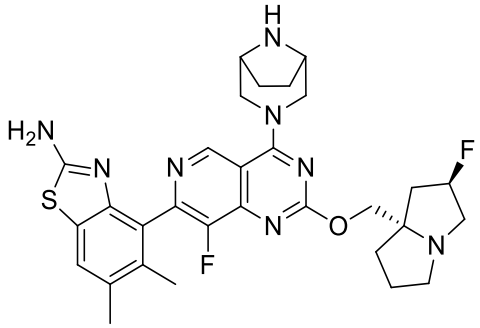
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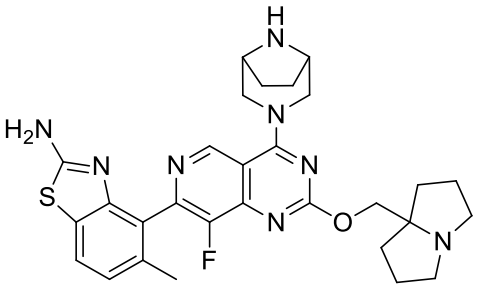
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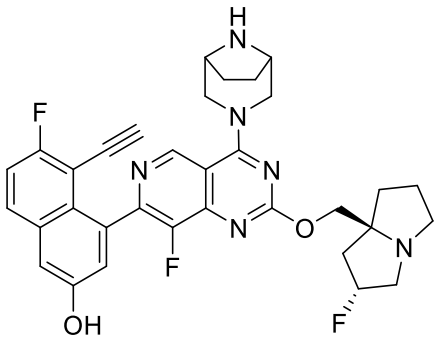
or a pharmaceutically acceptable salt thereof.

13. A compound having the following structure: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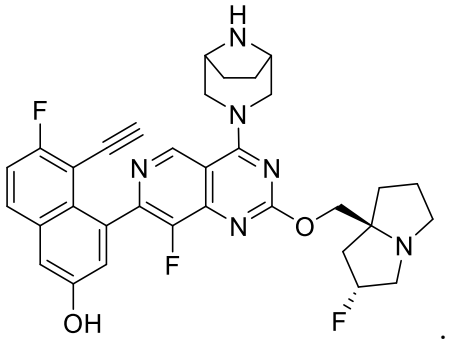
or a pharmaceutically acceptable salt thereof.

14. A compound having the following structure:



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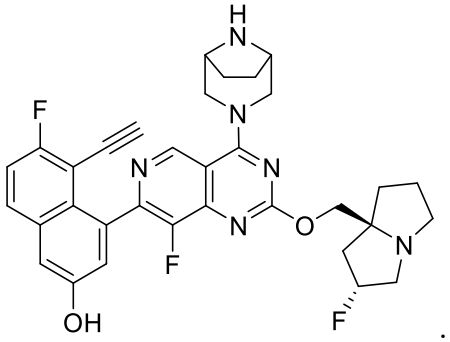
15. A pharmaceutically acceptable salt of a compound having the following structure:



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16. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-15 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

17. 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 any one of claims 1-15, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 16.

18. Use of a compound of any one of claims 1-15, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 16 in the manufacture of a medicament for the treatment of cancer, wherein KRas G12D activity is to be inhibited in a cell, wherein an effective amount of the compound, the pharmaceutically acceptable salt thereof or the

pharmaceutical composition is to be contacted with the cell in which inhibition of KRas G12D activity is desired.

19. Use of a compound of any one of claims 1-15, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of claim 16 in the manufacture of a medicament for treating a KRas G12D-associated cancer, wherein a therapeutically effective amount of the compound, the pharmaceutically acceptable salt thereof or the pharmaceutical composition is to be administered to a patient in need thereof, 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 wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.

20. The use of claim 19, wherein the therapeutically effective amount of the compound is between about 0.01 to 100 mg/kg per day.

21. The use of a compound of any one of claims 1-15 or a pharmaceutical composition of claim 16 in the manufacture of a medicament for treating cancer in a patient in need thereof, wherein (a) it is to be determined that the cancer has a KRas G12D mutation; and (b) a therapeutically effective amount of the compound or the pharmaceutical composition is to be administered to the patient, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma

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

22. The use of claim 21 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, intratracheal, intrarectal, subcutaneous, and topical administration, preferably wherein the administering is done via an intravenous injection, the administering is done via an intramuscular injection, the administering comprises utilizing a delivery device or the administering is done in a hospital setting.