COMPOUNDS AND USES THEREOF

Background

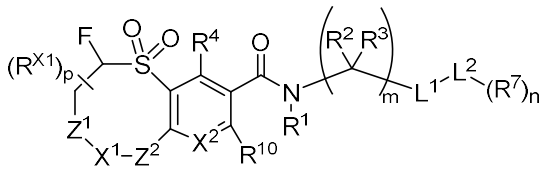
The invention relates to compounds useful for modulating BRG1- or BRM-associated factors (BAF) complexes. In particular, the invention relates to compounds useful for treatment of disorders associated with BAF complex function.

Chromatin regulation is essential for gene expression, and ATP-dependent chromatin remodeling is a mechanism by which such gene expression occurs. The human Switch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex, also known as BAF complex, has two SWI2-like ATPases known as BRG1 (Brahma-related gene-1) and BRM (Brahma). The transcription activator BRG1, also known as ATP-dependent chromatin remodeler SMARCA4, is encoded by the SMARCA4 gene on chromosome 19. BRG1 is overexpressed in some cancer tumors and is needed for cancer cell proliferation. BRM, also known as probable global transcription activator SNF2L2 and/or ATP-dependent chromatin remodeler SMARCA2, is encoded by the SMARCA2 gene on chromosome 9 and has been shown to be essential for tumor cell growth in cells characterized by loss of BRG1 function mutations. Deactivation of BRG and/or BRM results in downstream effects in cells, including cell cycle arrest and tumor suppression.

Summary

The present disclosure features compounds useful for modulating a BAF complex. In some examples, the compounds are useful for the treatment of disorders associated with an alteration in a BAF complex, e.g., a disorder associated with an alteration in one or both of the BRG1 and BRM proteins. The compounds of the disclosure, alone or in combination with other pharmaceutically active agents, can be used for treating such disorders.

In one aspect, the disclosure provides a compound having the structure:



Formula I

where

m is 0, 1, 2, or 3;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, or 3;

X^1 is O, NR^5, or $(C(R^5)(R^6))$, and each of Z^1 and Z^2 is independently absent or $(C(R^9)_2)$ or O, provided that, if X^1 is O, then each of Z^1 and Z^2 is independently absent or $(C(R^9)_2)$;

X^2 is N or CR^8;

each R^{X1} is independently deuterium, optionally substituted C_1-C_6 alkyl, or halo, or two *geminal* R^{X1} groups, together with the atom to which they are attached, combine to form a carbonyl;

L^1 is optionally substituted 9- or 10-membered bicyclic heterocyclyl, optionally substituted 9- or 10-membered bicyclic heteroaryl, optionally substituted monocyclic 6-membered heteroarylvinyl, optionally substituted monocyclic 6-membered heteroaryl-C_3-C_8-cycloalkyl, or optionally substituted monocyclic 6-membered heteroarylethynyl;

L^2 is absent, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5- to 10-membered heteroaryl, or optionally substituted 4- to 10-membered heterocyclyl;

R^1 is hydrogen or optionally substituted C_1-C_6 alkyl;

each R^2 and each R^3 are independently hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^4 is hydrogen, halo, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} cycloalkyl;

R^5 is hydrogen, deuterium, or optionally substituted C_1-C_6 alkyl;

R^6 is hydrogen, deuterium, optionally substituted C_1-C_6 alkyl, or halo, and each R^9 is independently hydrogen, deuterium, optionally substituted C_1-C_6 alkyl, or halo; or R^6 and one *vicinal* R^9, together with the atoms to which they are attached combine to form optionally substituted C_3-C_8 cycloalkyl, and the remaining R^9 groups, if present, are independently deuterium, optionally substituted C_1-C_6 alkyl, or halo;

each R^7 is independently optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, halo, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 10-membered heteroaryl, optionally substituted 4- to 10-membered heterocyclyl, $-N(R^{7A})_2$, or $-OR^{7A}$, wherein each R^{7A} is independently H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5- to 10-membered heteroaryl, or optionally substituted 4- to 10-membered heterocyclyl, or two *geminal* R^{7A} groups, together with the atom to which they are attached, combine to form optionally substituted 5- to 10-membered heteroaryl or optionally substituted 4- to 10-membered heterocyclyl;

R^8 is hydrogen, halo, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} cycloalkyl; and

R^{10} is hydrogen or halo;

or a pharmaceutically acceptable salt thereof.

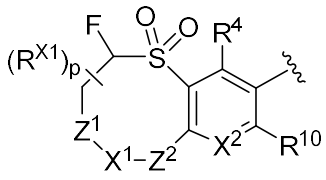
In some examples, Z^1 is $(C(R^9)_2)$. In some examples, Z^1 is absent. In some examples, Z^1 is O.

In some examples, Z^2 is $(C(R^9)_2)$. In some examples, Z^2 is absent. In some examples, Z^2 is O.

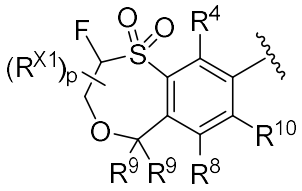
In some examples, X^1 is O. In some examples, X^1 is NR^5. In some examples, X^1 is $(C(R^5)(R^6)$.

In some examples, X^2 is CR^8.

In some examples, the group

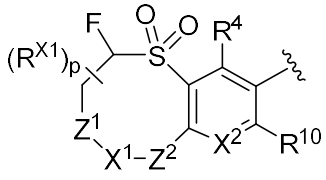


is a group of the following structure

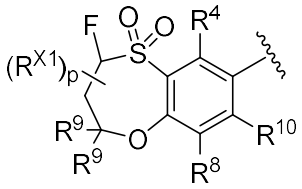


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In some examples, the group

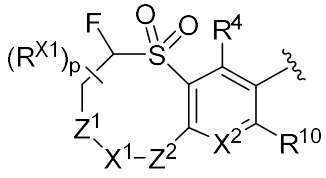


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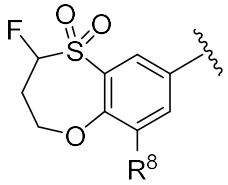


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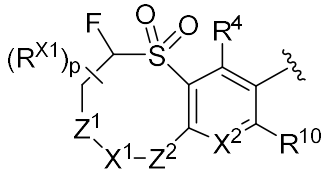


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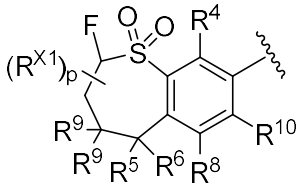


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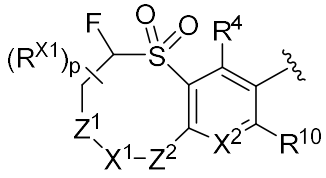


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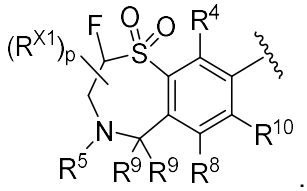


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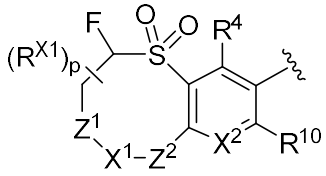


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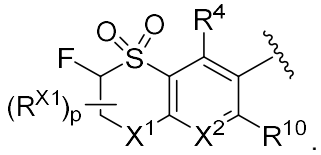


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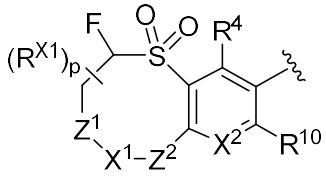


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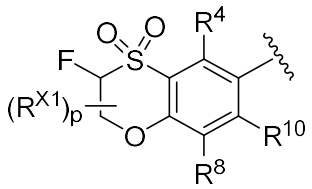


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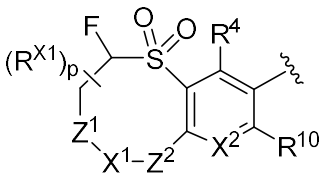


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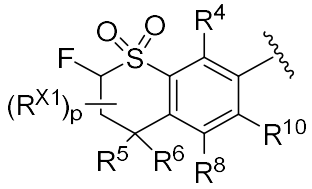


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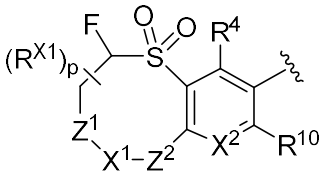


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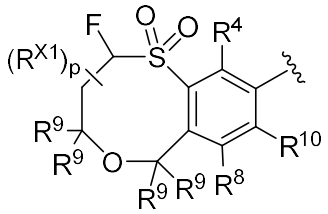


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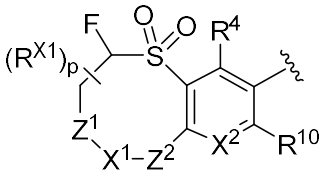


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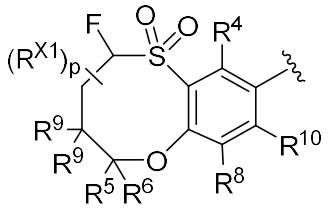


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In some examples, the group



is a group of the following structure

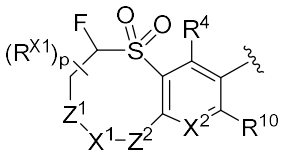


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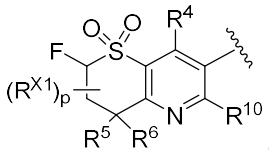
In some examples, R^8 is hydrogen. In some examples, R^8 is halo (e.g., fluoro). In some examples, R^8 is optionally substituted C_2-C_6 alkynyl. In some examples, R^8 is optionally substituted C_1-C_6 heteroalkyl. In some examples, R^8 is optionally substituted C_3-C_{10} cycloalkyl.

In some examples, X^2 is N.

In some examples, the group



is a group of the following structure



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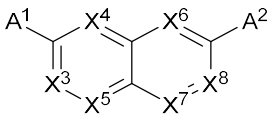
In some examples, R^4 is hydrogen. In some examples, R^4 is halogen.

In some examples, R^{10} is hydrogen. In some examples, R^{10} is halogen.

In some examples, at least one R^{X1} is optionally substituted C_1-C_6 alkyl. In some examples, at least one R^{X1} is halo. In some examples, at least one R^{X1} is deuterium.

In some examples, p is 3. In some examples, p is 2. In some examples, p is 1. In some examples, p is 0.

In some examples, L^1 is optionally substituted 9- or 10-membered bicyclic heteroaryl. In some examples, L^1 is



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Formula A

wherein

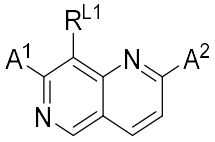
each of X^3, X^4, X^5, X^6, X^7, and X^8 is independently N or CR^{L1};

each R^{L1} is independently H, halo, optionally substituted C_1-C_6 alkyl;

A^1 is a bond to $-(C(R^2)(R^3))_m-$; and

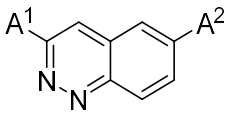
A^2 is a bond to L^2.

In some examples, L^1 is



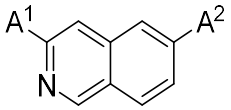
. In some examples, R^{L1} is hydrogen.

In some examples, L^1 is



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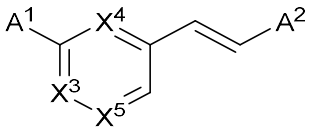
In some examples, L^1 is



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In some examples, L^1 is optionally substituted monocyclic 6-membered heteroarylvinyl.

In some examples, L^1 is



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Formula B

wherein

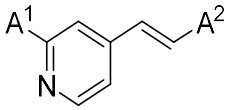
each of X^3, X^4, and X^5 is independently N or CR^{L1};

each R^{L1} is independently H, halo, optionally substituted C_1-C_6 alkyl;

A^1 is a bond to $-(C(R^2)(R^3))_m$-; and

A^2 is a bond to L^2.

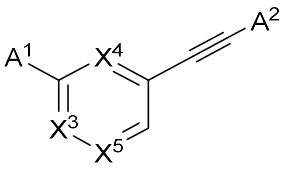
In some examples, L^1 is



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In some examples, L^1 is optionally substituted monocyclic 6-membered heteroarylethynyl.

In some examples, L^1 is



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Formula C

wherein

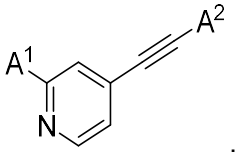
each of X^3, X^4, and X^5 is independently N or CR^{L1};

each R^{L1} is independently H, halo, optionally substituted C_1-C_6 alkyl;

A^1 is a bond to $-(C(R^2)(R^3))_m$-; and

A^2 is a bond to L^2.

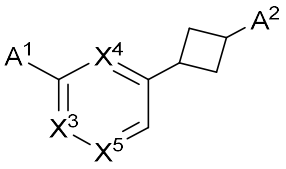
In some examples, L^1 is



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In some examples, L^1 is optionally substituted monocyclic 6-membered heteroaryl-C_3-C_8-cycloalkyl.

In some examples, L^1 is



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Formula D

wherein

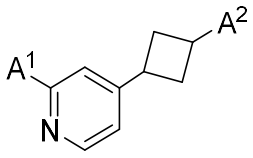
each of X^3, X^4, and X^5 is independently N or CR^{L1};

each R^{L1} is independently H, halo, optionally substituted C_1-C_6 alkyl;

A^1 is a bond to $–(C(R^2)(R^3))_m$-; and

A^2 is a bond to L^2.

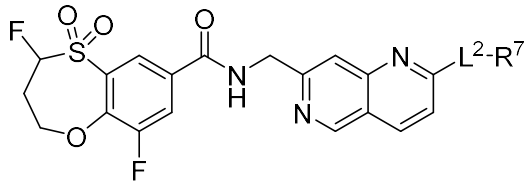
In some examples, L^1 is



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In some examples, L^1 is optionally substituted 9- or 10-membered bicyclic heterocyclyl.

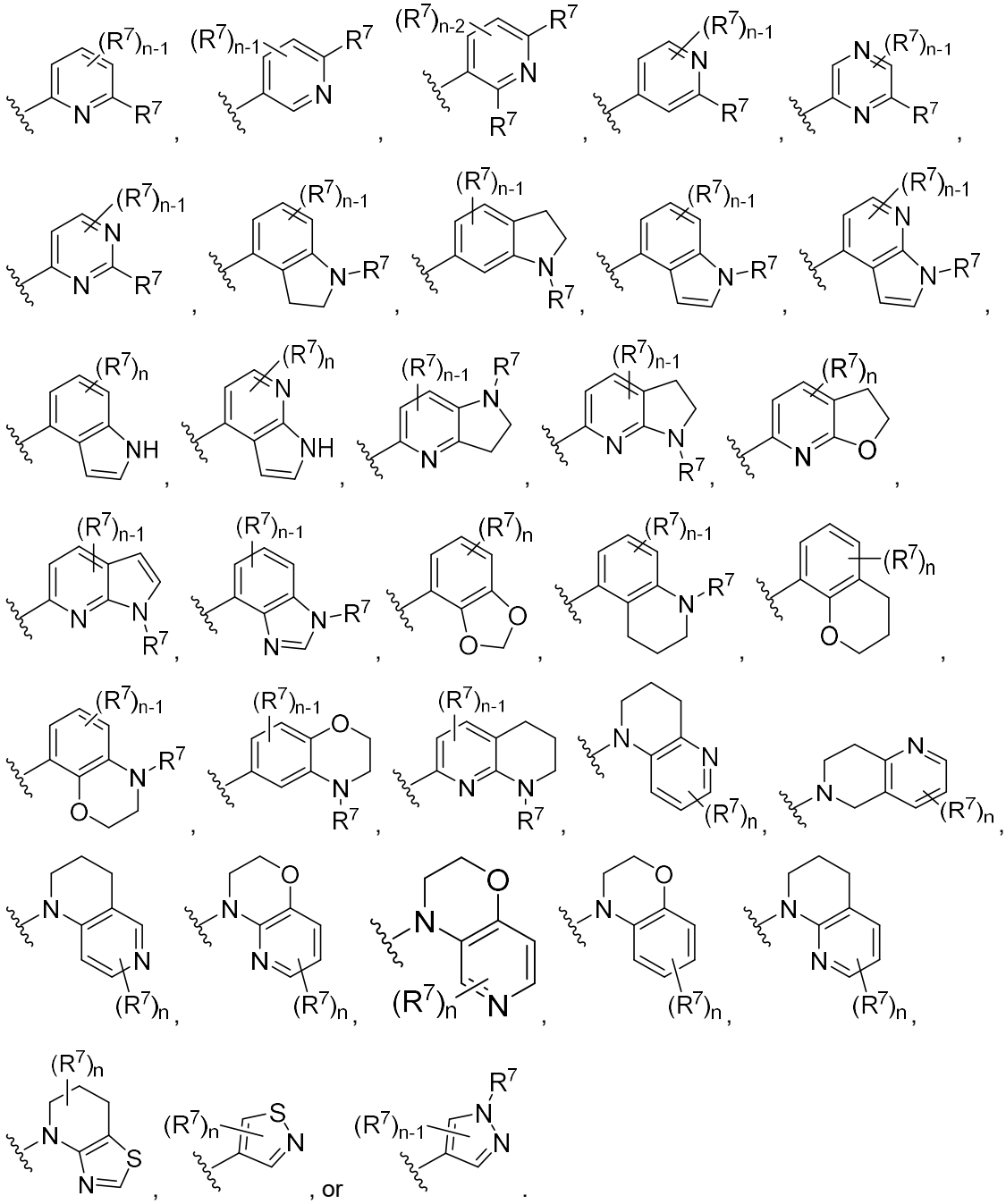
In some examples, the compound has the structure:



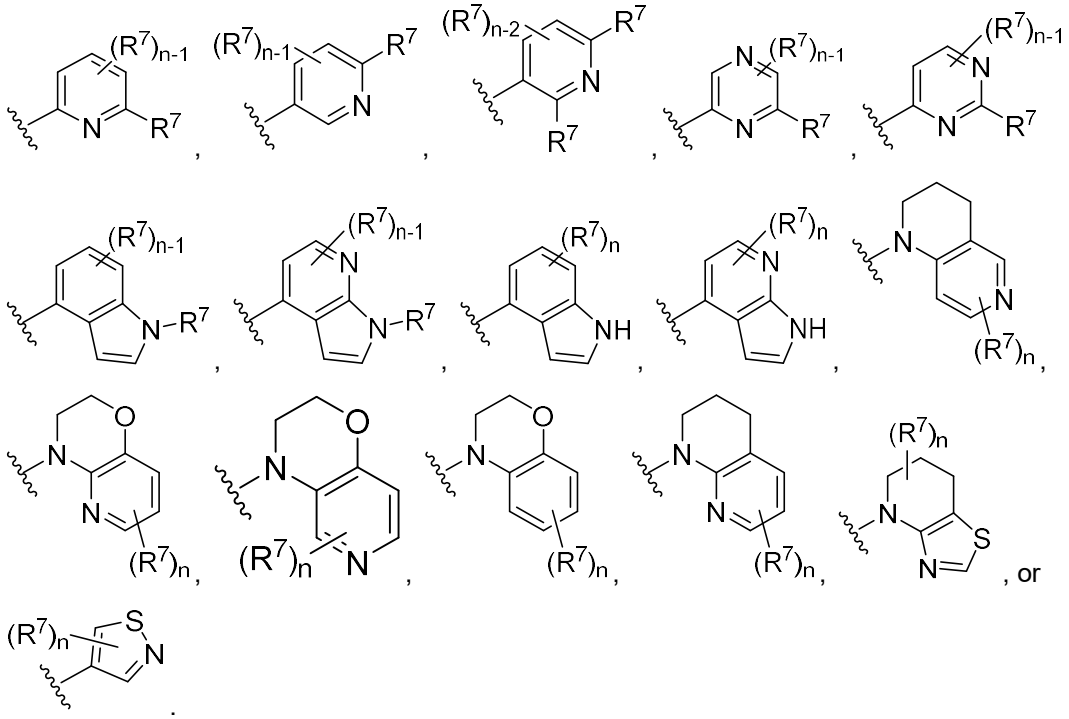
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In some examples, L^2 is optionally substituted 5- to 10-membered heteroaryl.

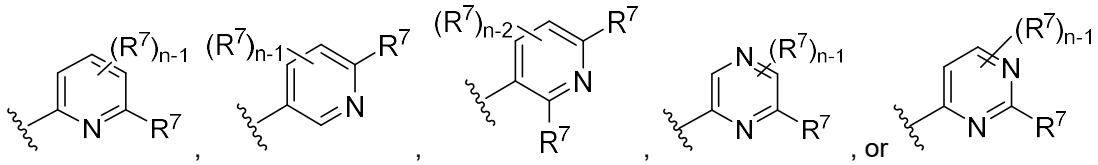
In some examples, $-L^2-(R^7)_n$ is a group of the following structure:



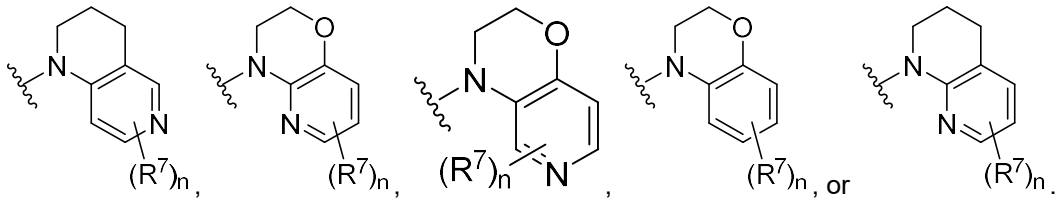
In some examples, -L^2-$(R^7)_n$ is a group of the following structure:



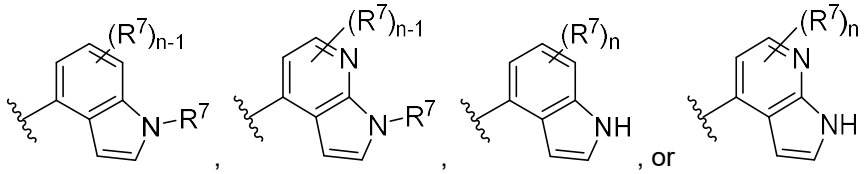
In some examples, -L^2-$(R^7)_n$ is a group of the following structure:



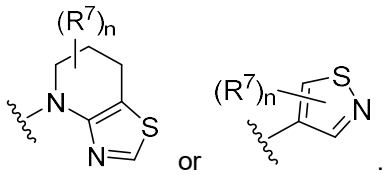
In some examples, -L^2-$(R^7)_n$ is a group of the following structure:



In some examples, -L^2-$(R^7)_n$ is a group of the following structure:



In some examples, -L^2-$(R^7)_n$ is a group of the following structure:



In some examples, L^2 is optionally substituted C_6-C_{10} aryl. In some examples, L^2 is optionally substituted phenyl.

In some examples, n is 1. In some examples, n is 2. In some examples, n is 3.

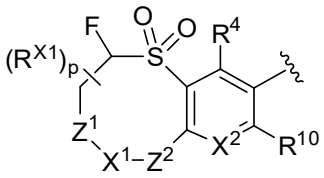
In some examples, R^7 is optionally substituted C_1-C_6 alkyl. In some examples, R^7 is optionally substituted C_1-C_6 heteroalkyl. In some examples, R^7 is optionally substituted 4- to 10-membered heterocyclyl. In some examples, R^7 is optionally substituted azetidinyl or optionally substituted morpholinyl. In some examples, R^7 is optionally substituted C_3-C_{10} cycloalkyl. In some examples, R^7 is optionally substituted cyclopropyl or optionally substituted cyclobutyl. In some examples, R^7 is $-N(R^{7A})_2$. In some examples, R^7 is optionally substituted N-azetidinyl or optionally substituted N-morpholinyl. In some examples, two *geminal* R^7 groups, together with the atom to which they are attached, combine to form optionally substituted 4- to 10-membered heterocyclyl. In some examples, at least one R^7 is $-OR^{7A}$. In some examples, R^{7A} is optionally substituted $C_{1\text{-}6}$ alkyl.

In some examples, n is 0.

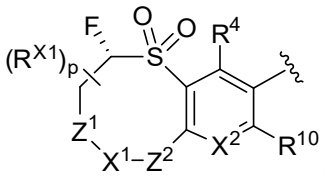
In some examples, at least one R^7 is difluoromethyl, cyclopropyl, 2,2-difluorocyclopropyl, difluoromethoxy, 2,6-dimethylmorpholin-4-yl, N-azetidinyl, 3-fluorocyclobutyl, 2-methoxyethyl, ethoxy, methoxy, 2,2-difluoroethoxy, 2,2-difluoroethyl, trifluoromethyl, isopropyl, methyl, acetyl, fluoro, chloro, 1-methylpyrazol-3-yl, dimethylamino, N-methyl-N-(2-methoxyethyl)-amino, N-ethyl-N-(2-methoxyethyl)-amino, N-(2-propyl)-N-(2-methoxyethyl)-amino, 2-methoxyethylamino, 3-aza-8-oxa-bicyclo[4.3.0]non-3-yl, 3-aza-7-oxa-bicyclo[4.3.0]non-3-yl, 1-fluorocyclobut-1-yl, 3-fluoropyrrolidin-1-yl, 3-methoxypyrrolidin-1-yl, oxetan-3-yl, N-methylindolin-4-yl, 2,2-difluoro-3-methylcycloprop-1-yl, 3-methoxyazetidin-1-yl, 3-methoxypiperidin-1-yl, 1,2-dimethyl-7-azaindol-4-yl, 1-methyl-7-azaindol-4-yl, 2,3-methylenedioxyphenyl, N-methyl-N-(3-oxetanyl)amino, 3-oxetanyloxy, 1,1-difluoro-5-azaspiro[2.3]hex-5-yl, 1-fluoromethyl-cyclopropyl, N-(3-tetrahydrofuranyl)methylamino, N-indolinyl, N-1,4-oxazepanyl, 2-fluoro-2-propyl, 1,1-difluoro-2-propyl, 2,2-difluoro-1-methylcycloprop-1-yl, 1-methylcyclopropyl, 4,4-difluoropiperidin-1-yl, 2-methoxyethoxy, 3,3-difluorocyclobut-1-yl, N-methyl-N-1-methoxyprop-2-ylamino, 1-methoxyprop-2-ylamino, 1-methoxyethyl, 4-methylpiperazinyl, 3-methylmorpholinyl, 2,2-difluoropropoxy, 3-methoxycyclobutyl, methylamino, 4-dimethylamino-3,3-difluoropiperidinyl, 4-methylamino-3,3-difluoropiperidinyl, 3,3-difluoropyrrolidinyl, N-methyl-N-3-methoxycyclobutylamino, 1-methylpyrazol-5-yl, 6-oxa-3-azabicyclo[3.1.1]hept-3-yl, cyclopropyloxy, 2,6-dimethylpyrid-4-yl, 2-methylpyrrolidinyl, 4-oxabicyclo[4.1.0]hept-1-yl, N-methyl-N-(2,6-dimethyltetrahydropyran-4-yl)amino, or N-methyl-N-3-methyloxetan-3-ylmethylamino.

In some examples, R^1 is hydrogen.

In some examples, the group

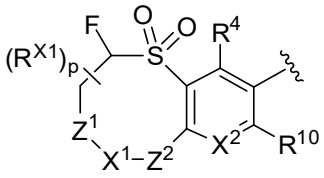


is a group of the following structure

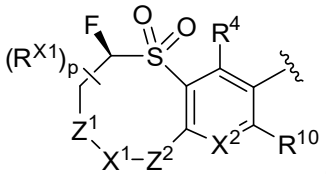


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In some examples, the group



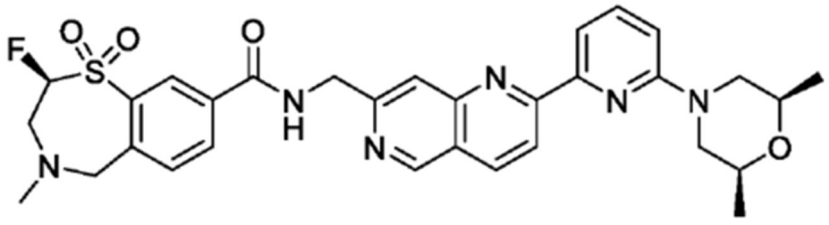
is a group of the following structure

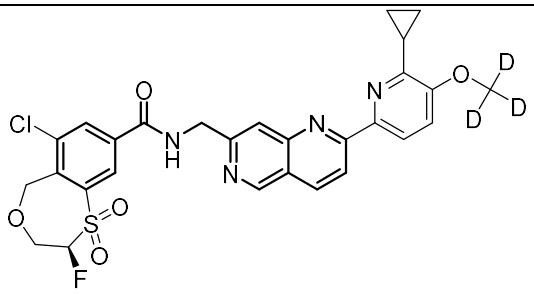


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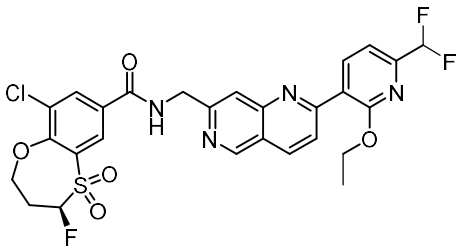
In some examples, the compound is selected from the group consisting of compounds 1-523 and pharmaceutically acceptable salts thereof.

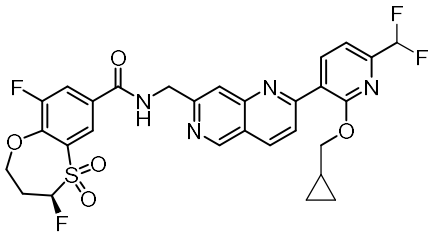
Table 1. Compounds of the disclosure

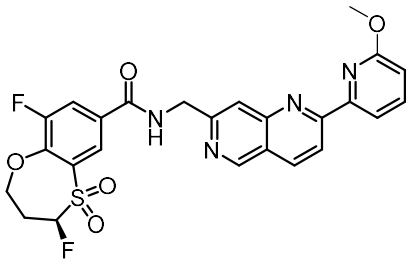
#	Structure
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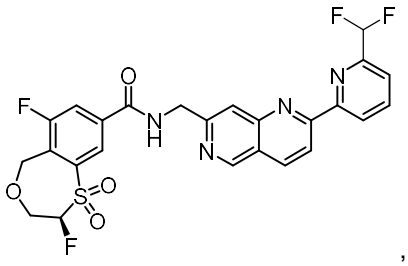
523	

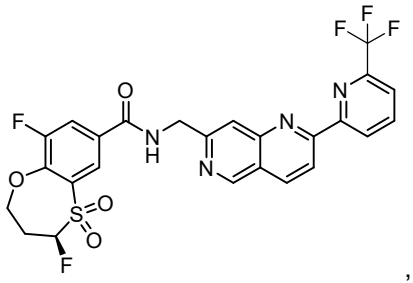
In another aspect, the disclosure features a compound selected from the group consisting of


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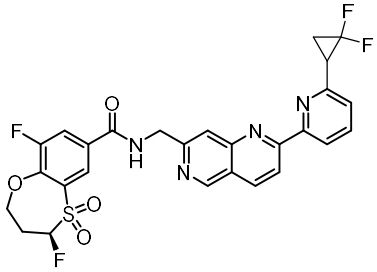

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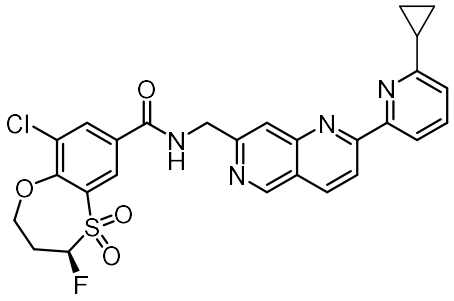

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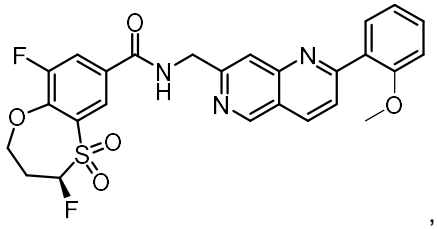
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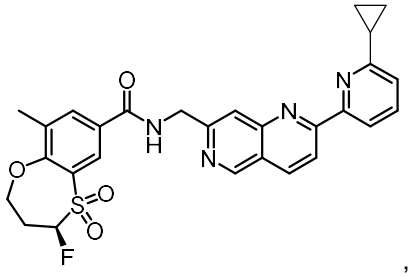
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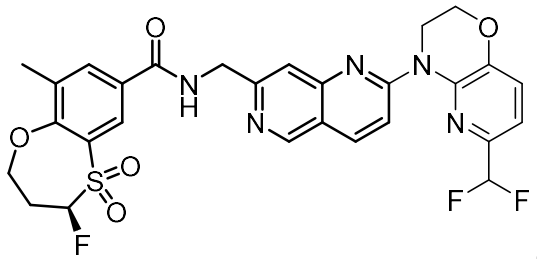
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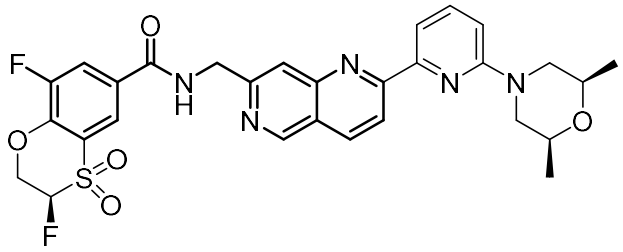
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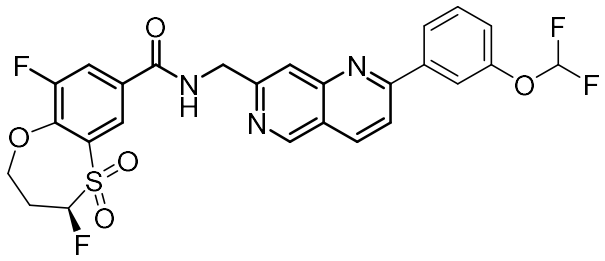
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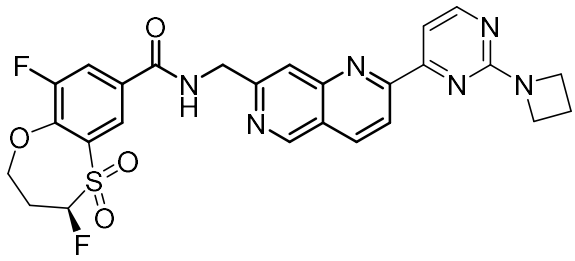
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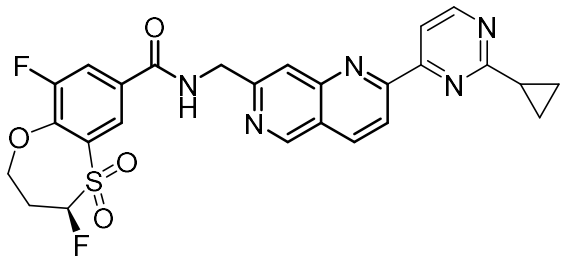
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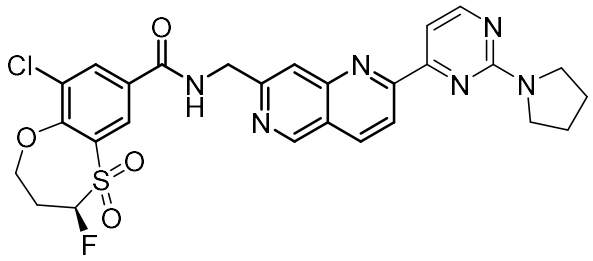
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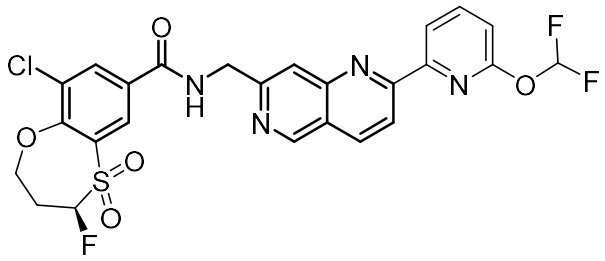
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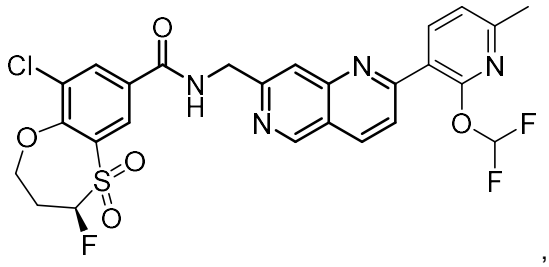
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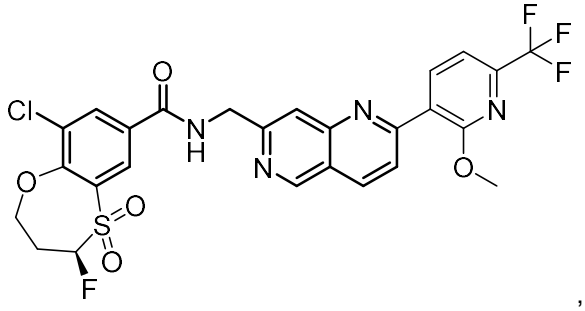
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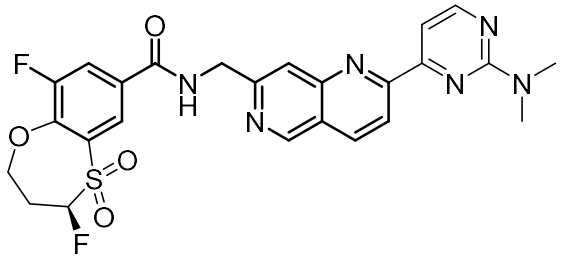
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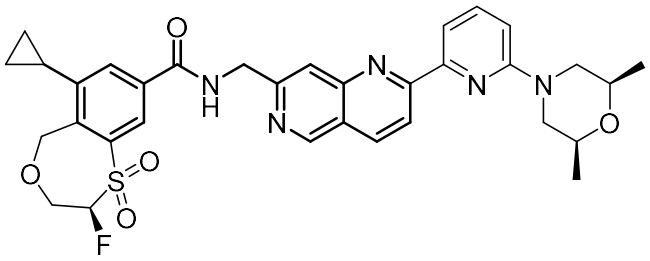
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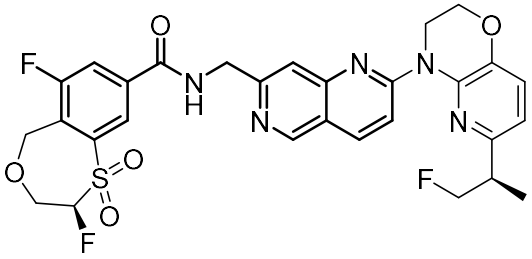
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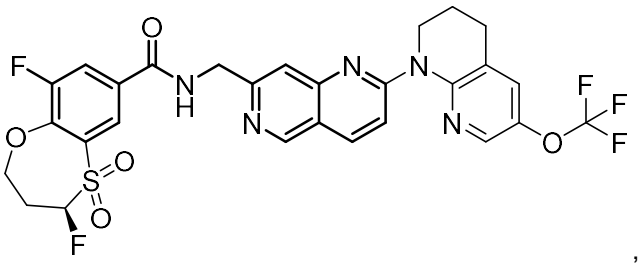
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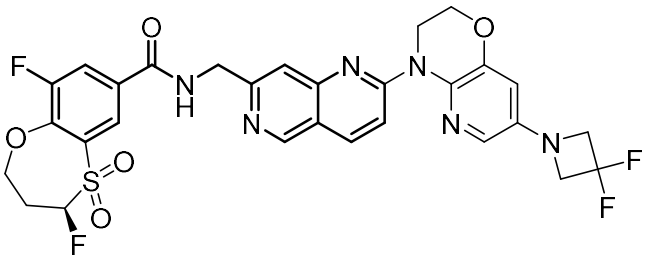
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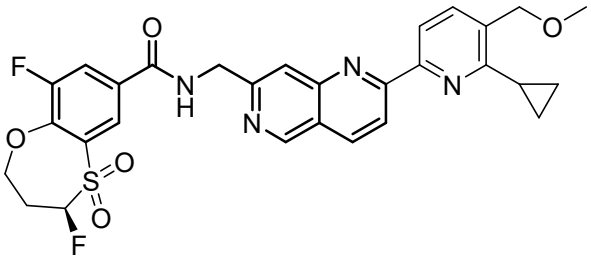
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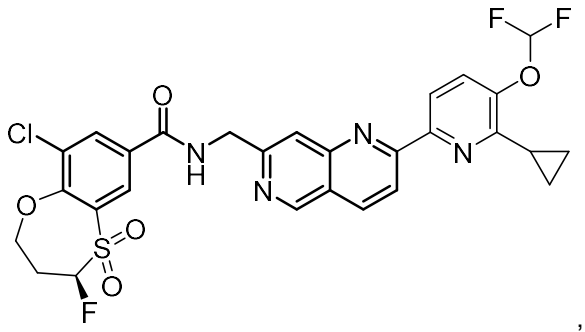
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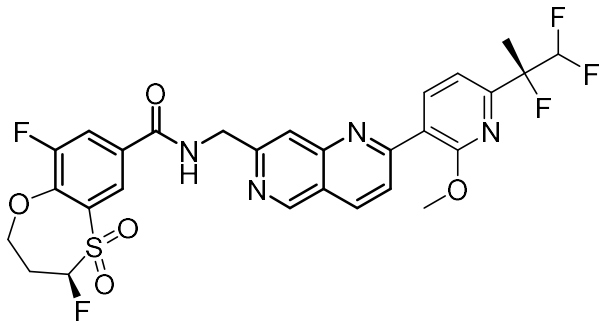
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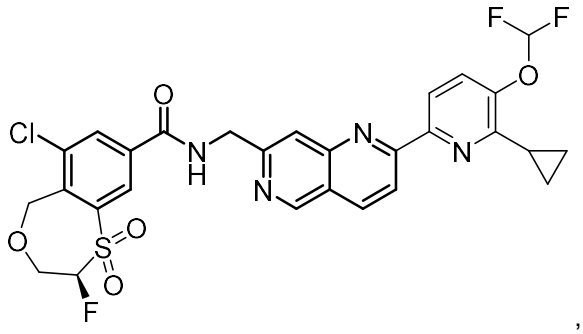
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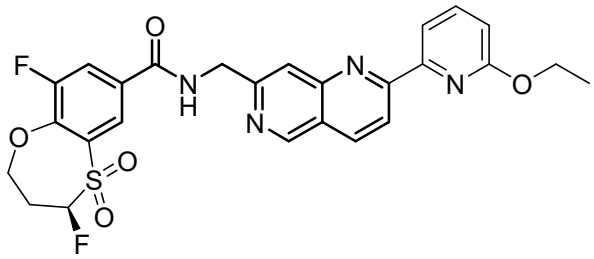
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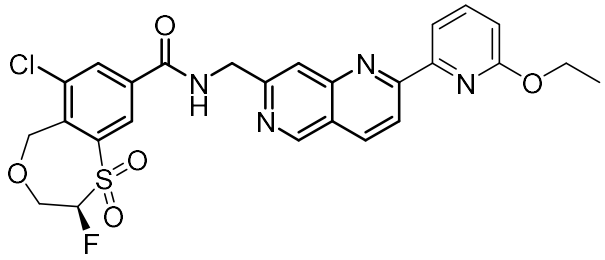
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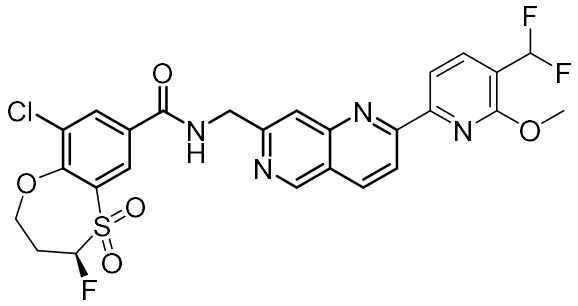
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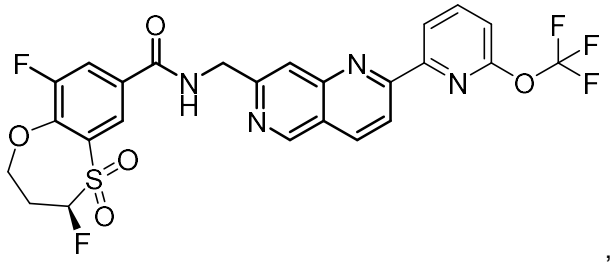
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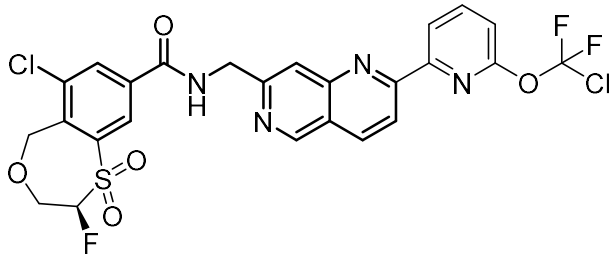
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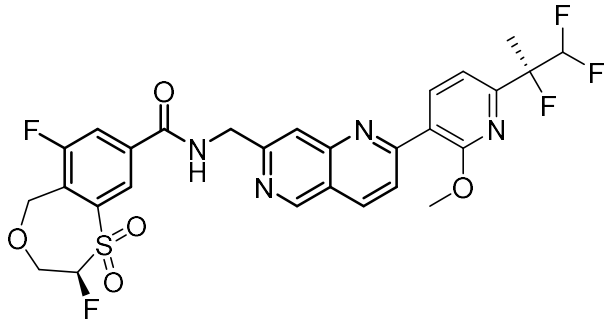
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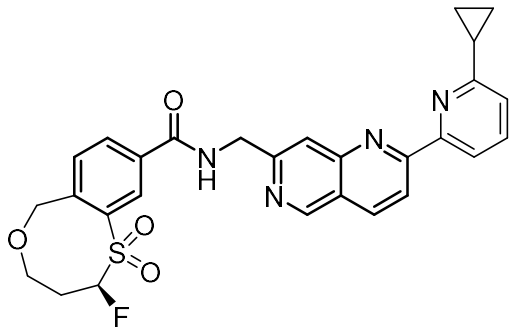
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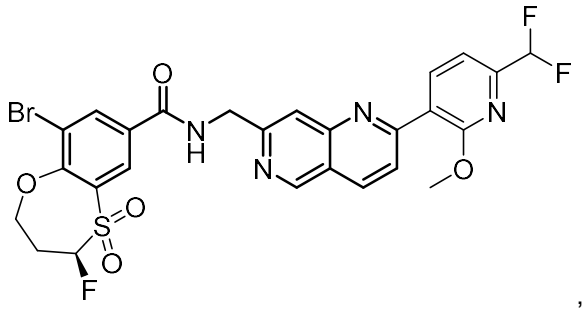
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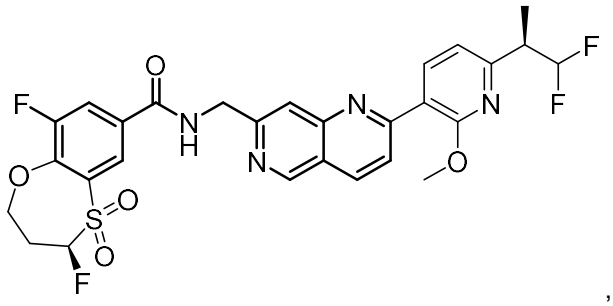
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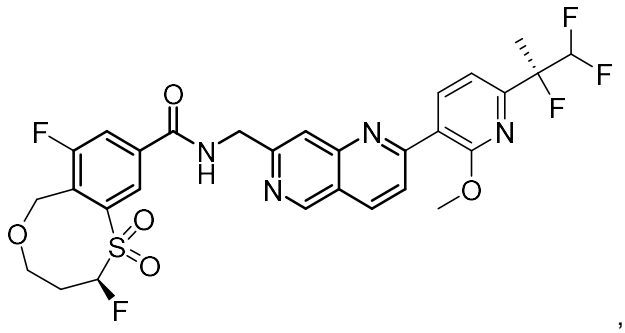
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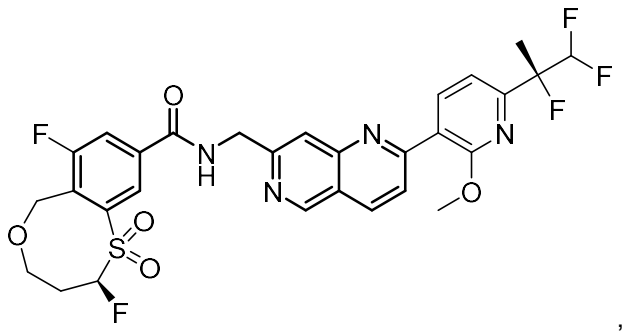
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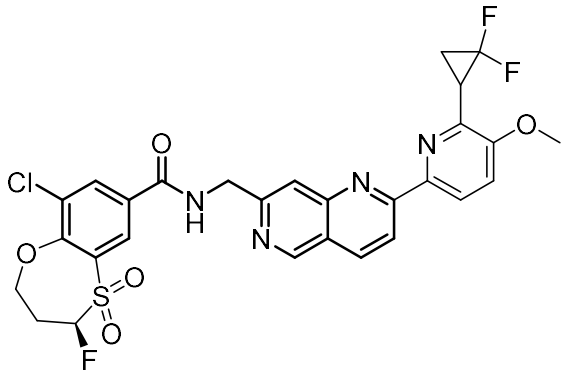
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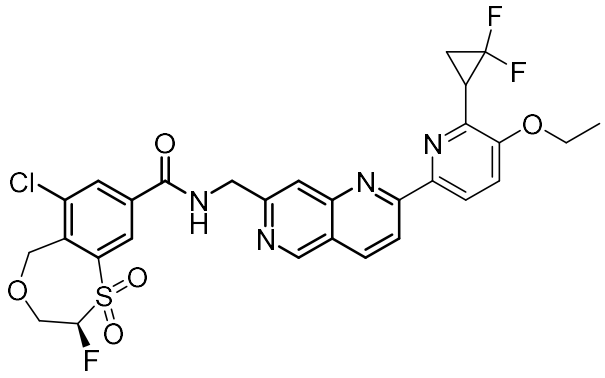
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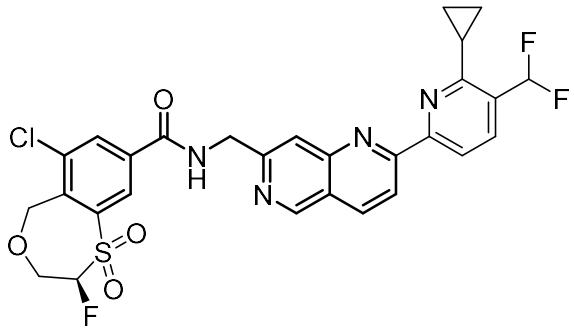
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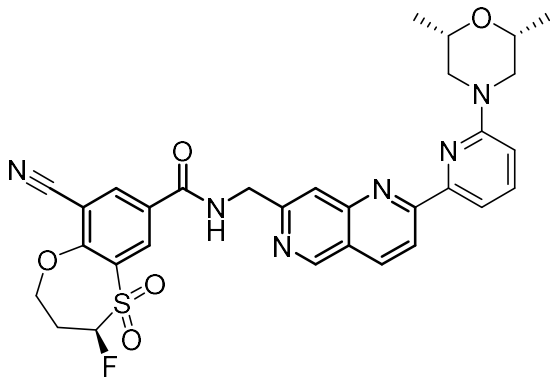
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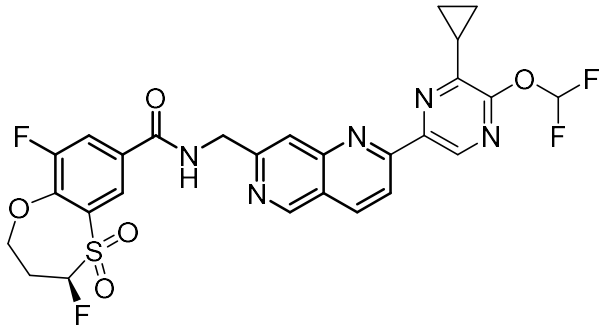
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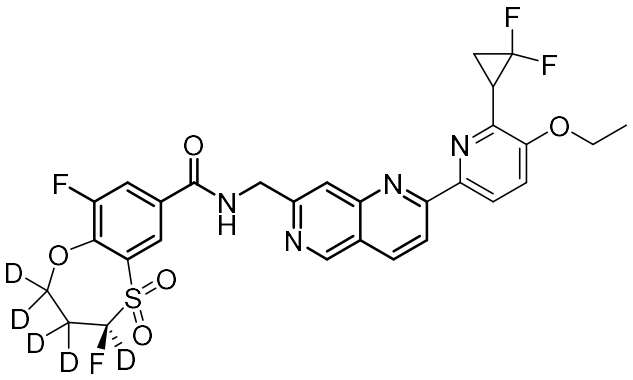
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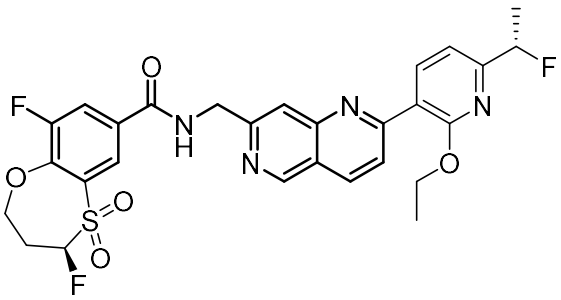
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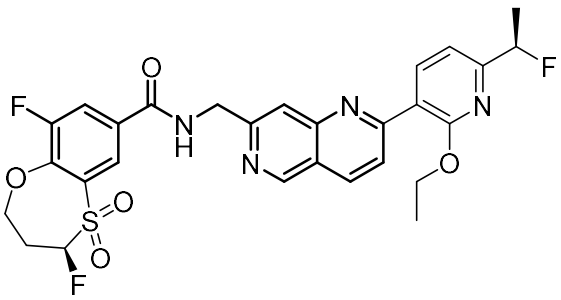
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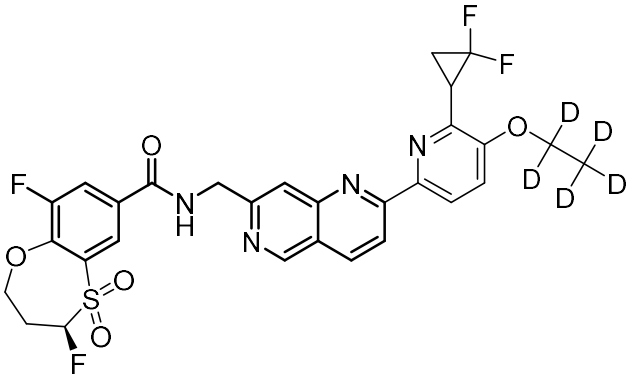
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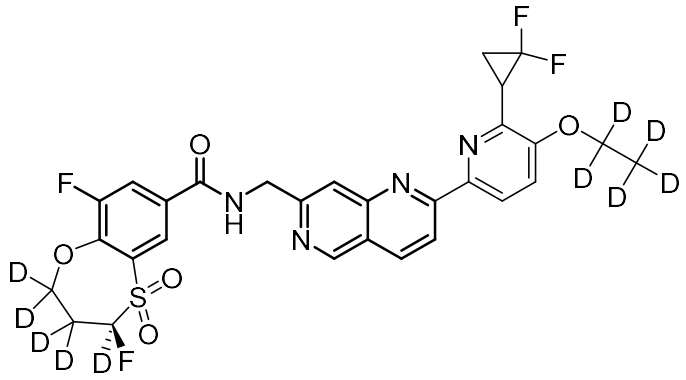
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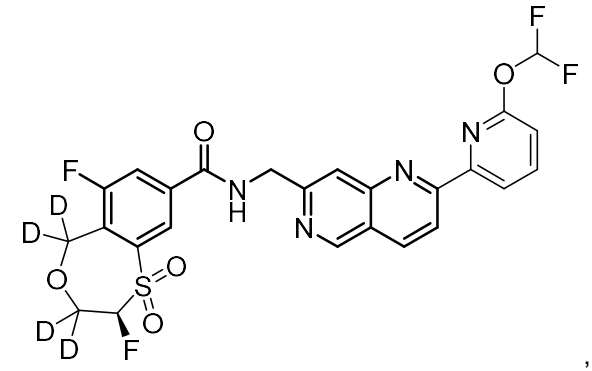
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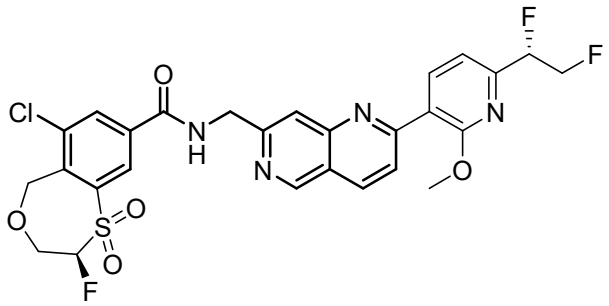
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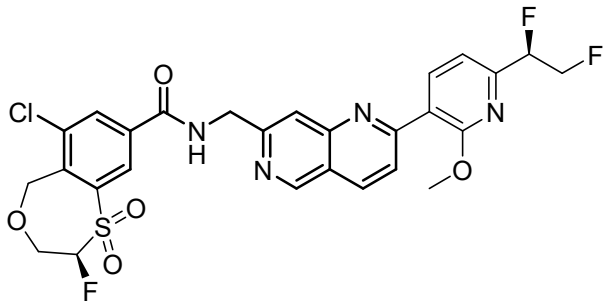
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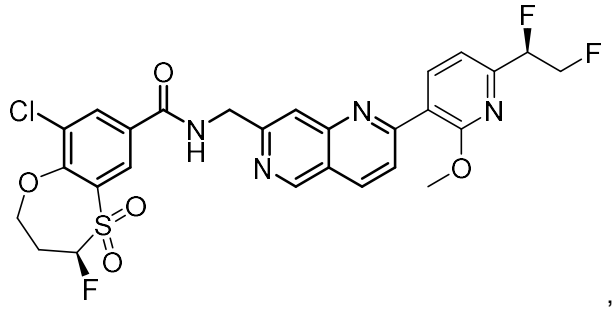
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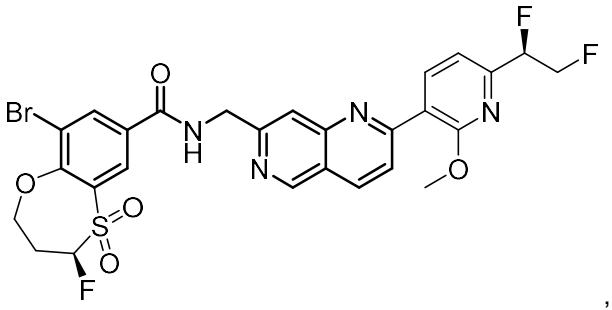
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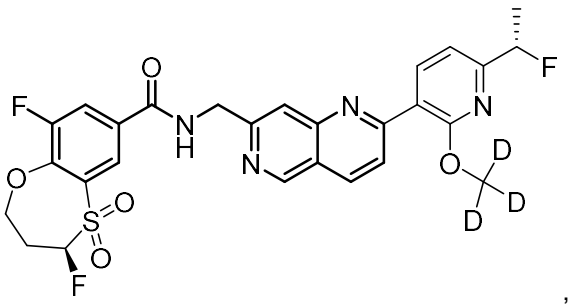
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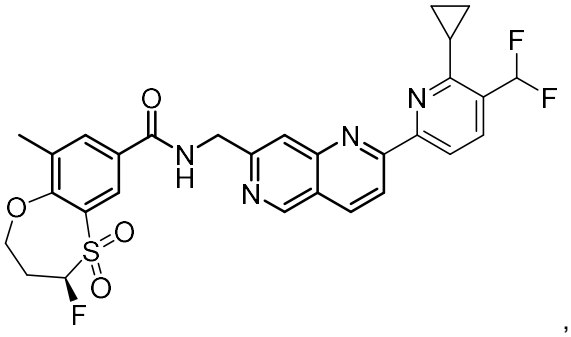
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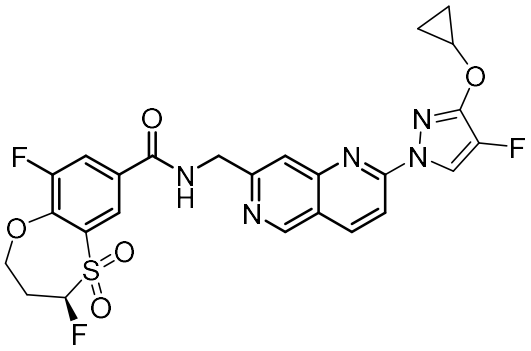
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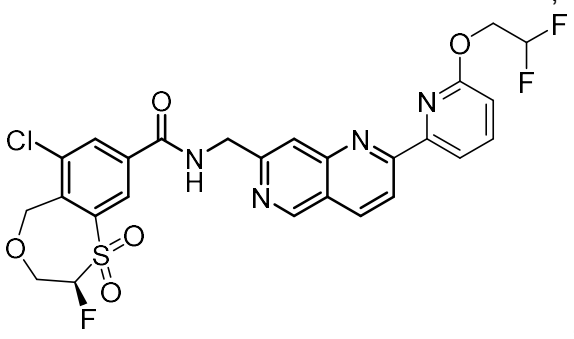
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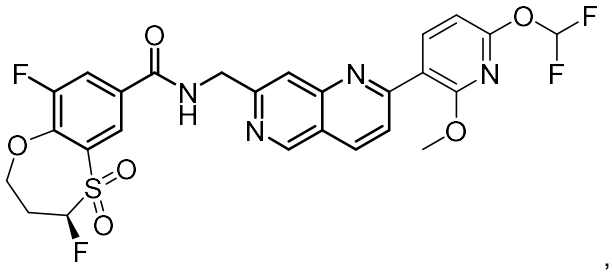
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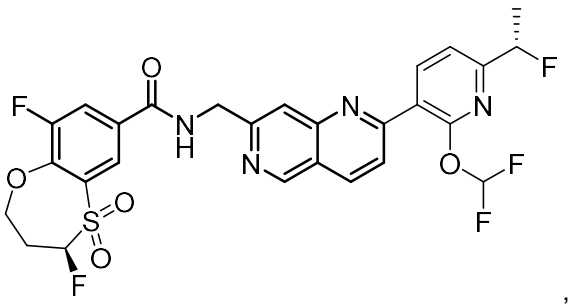
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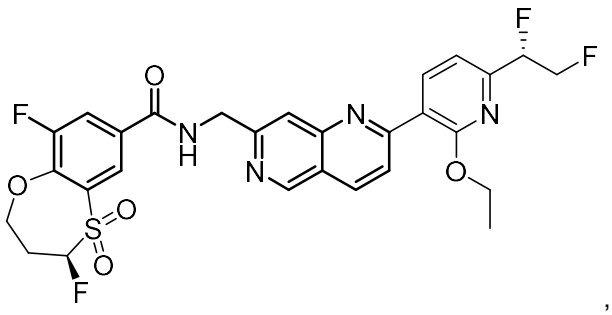
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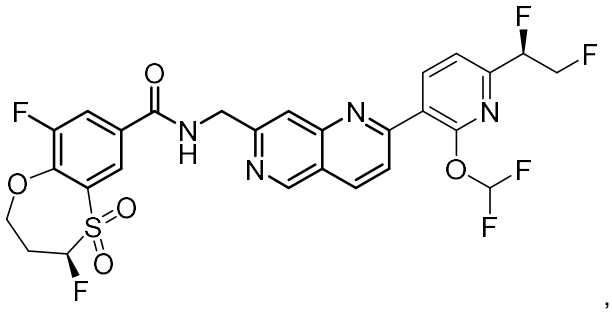
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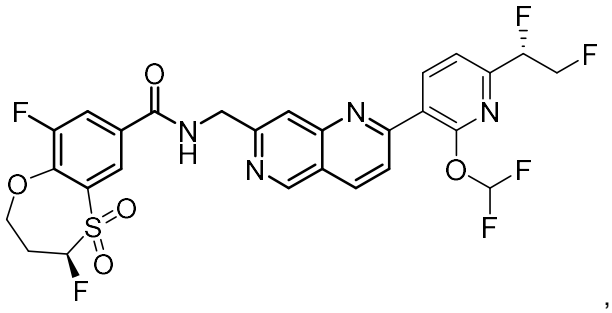
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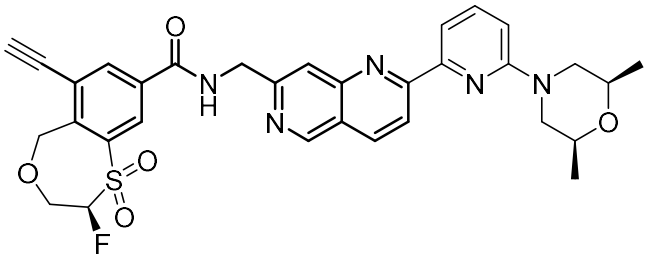
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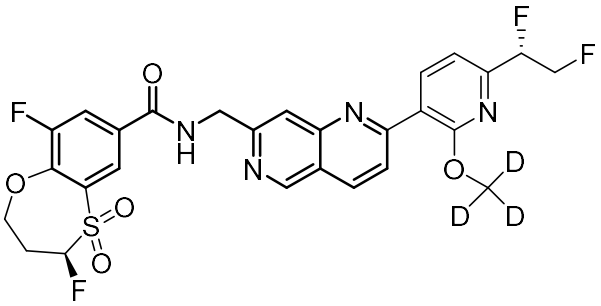
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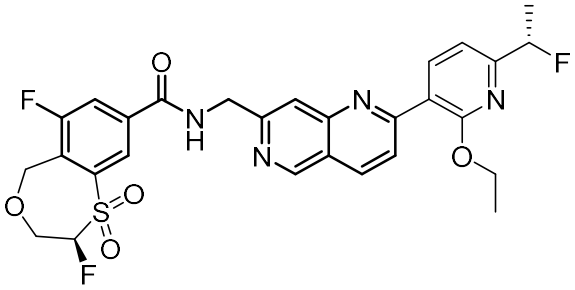
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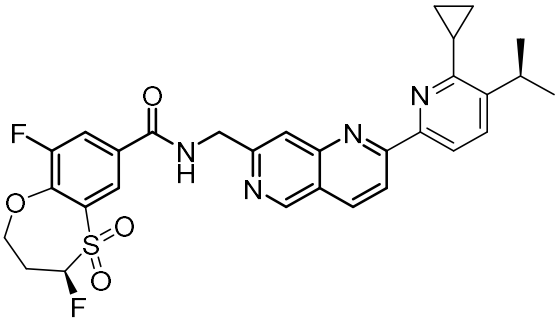
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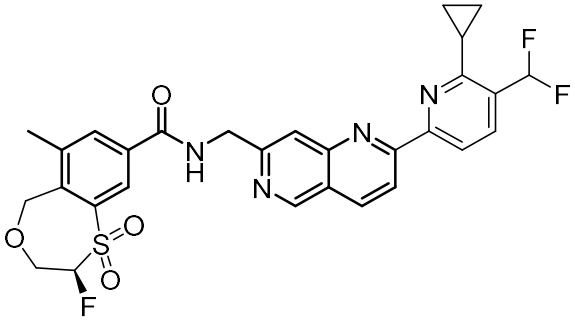
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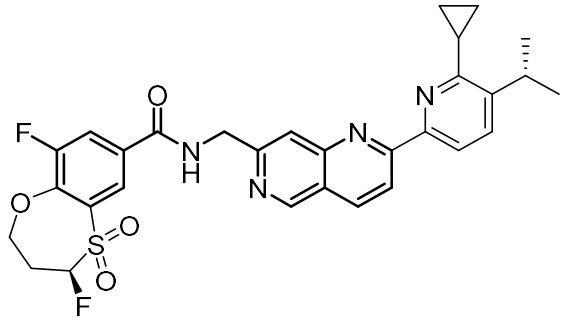
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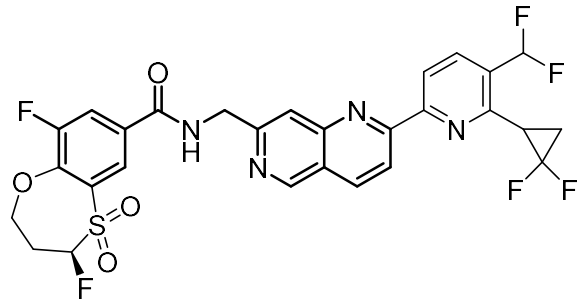
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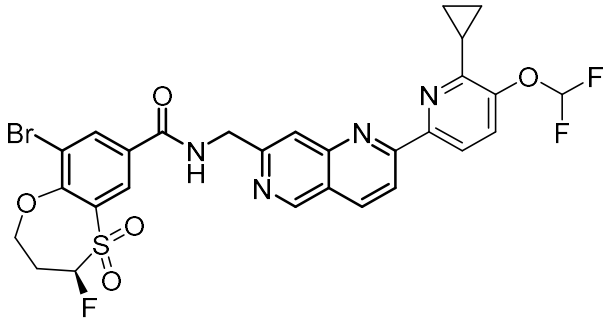
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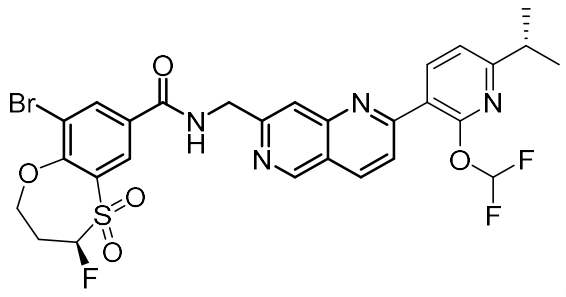
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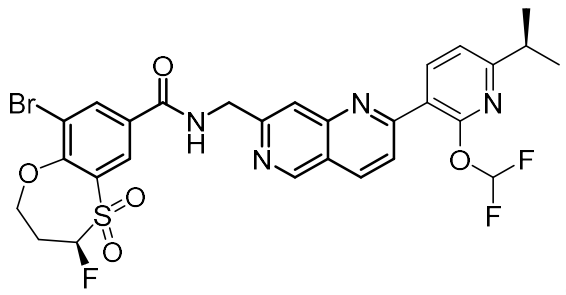
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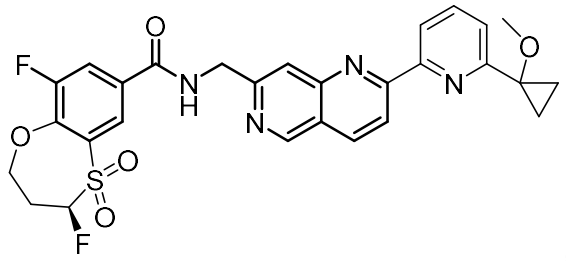
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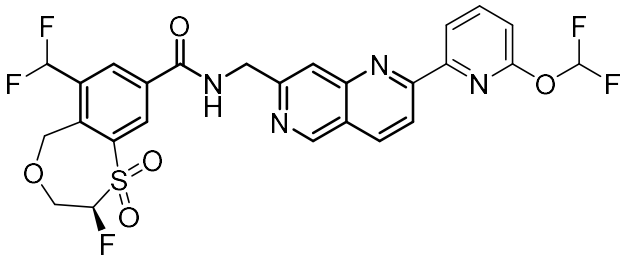
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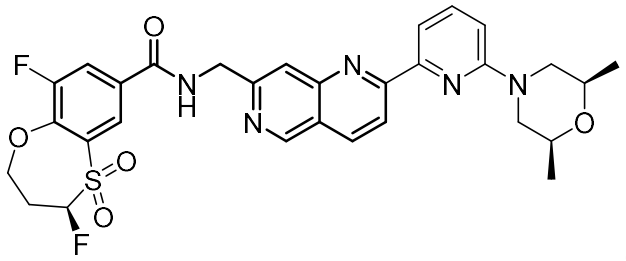
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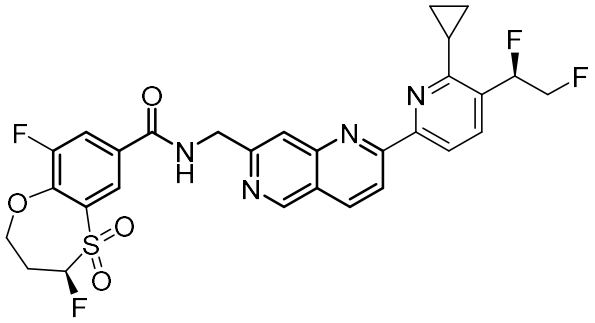
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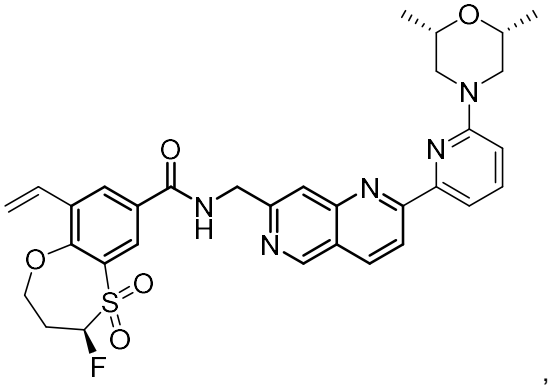
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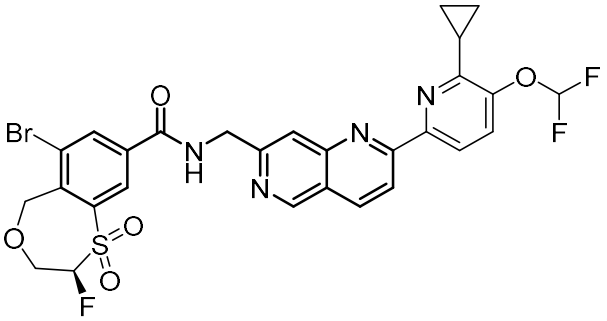
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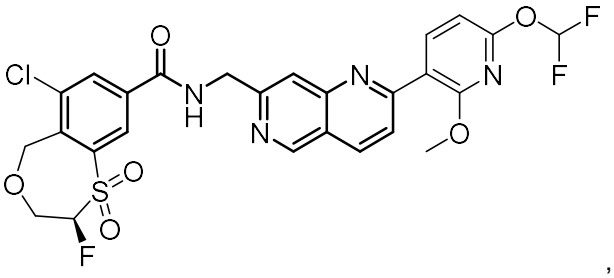
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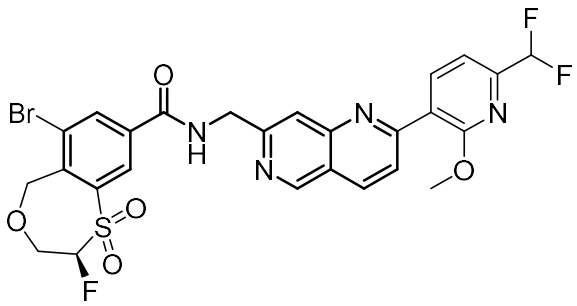
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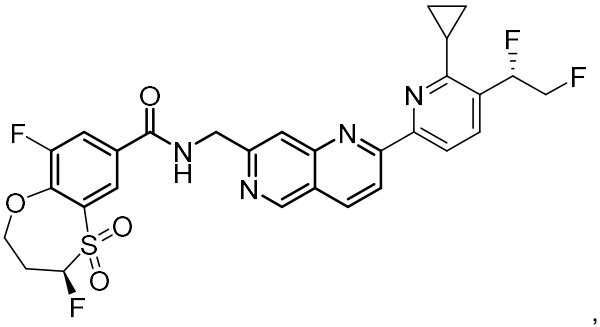
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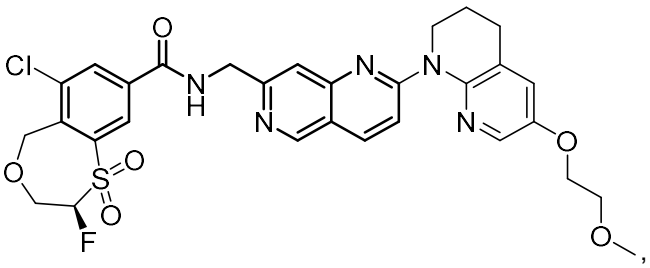
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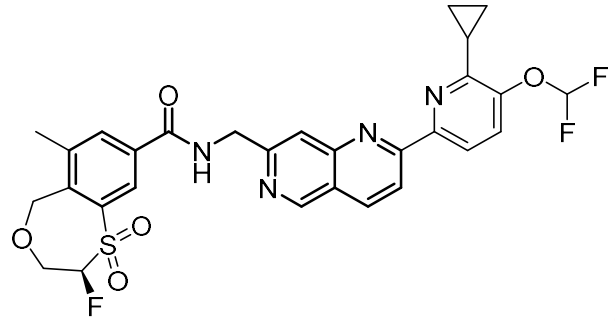
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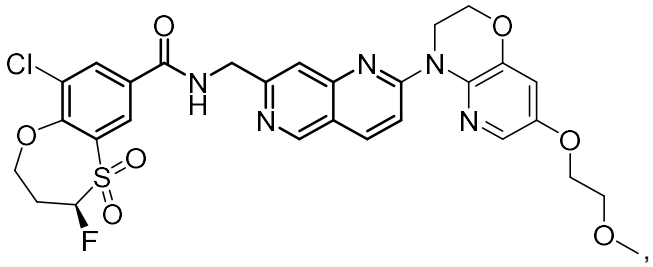
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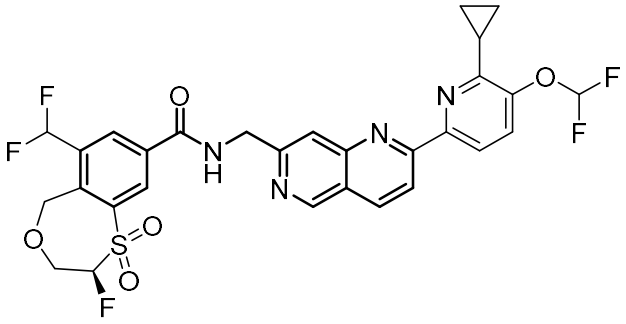
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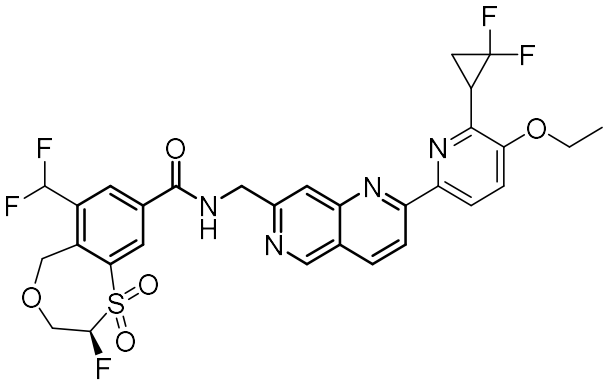
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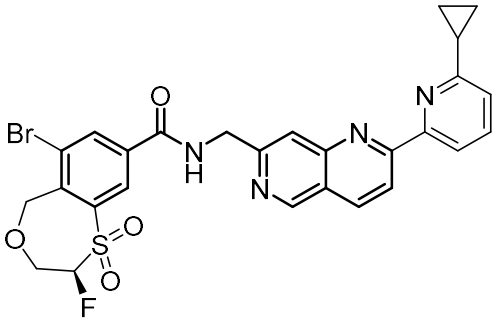
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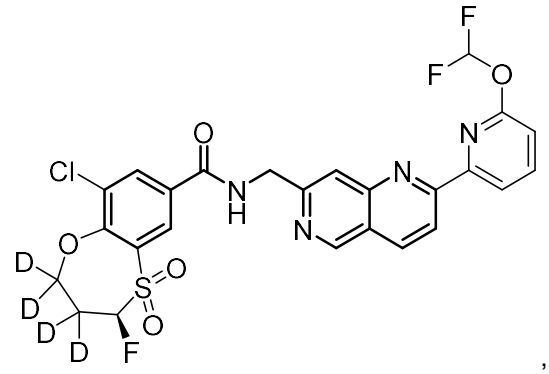
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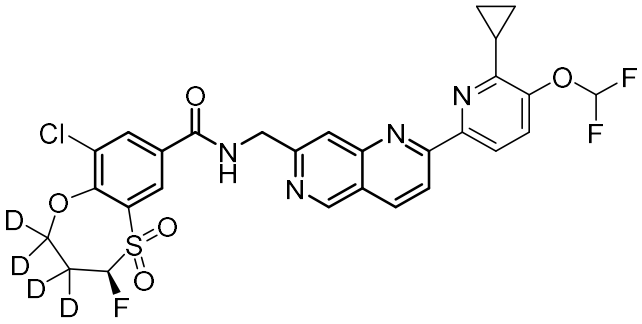
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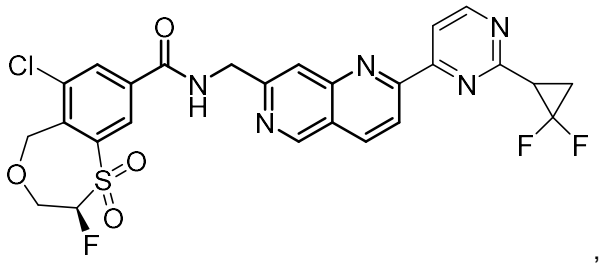
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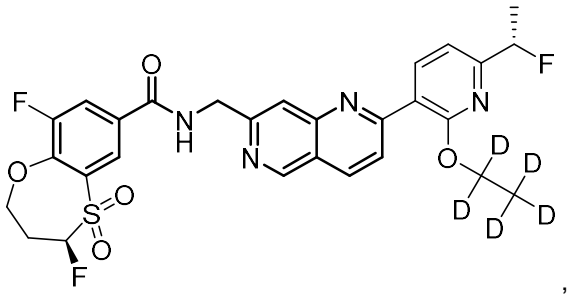
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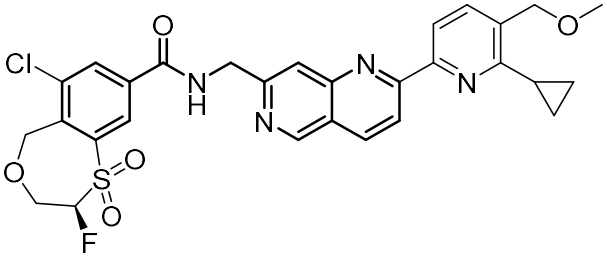
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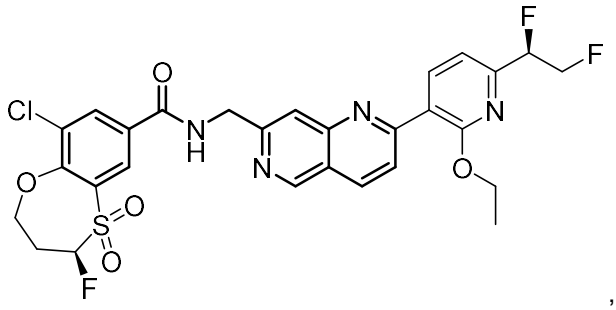
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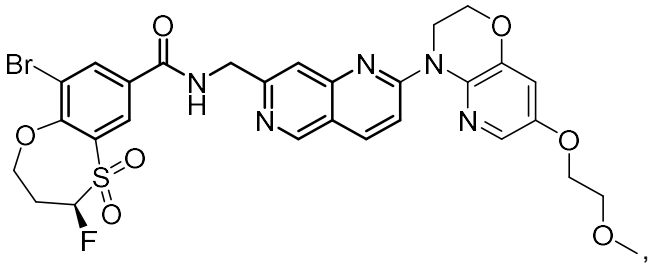
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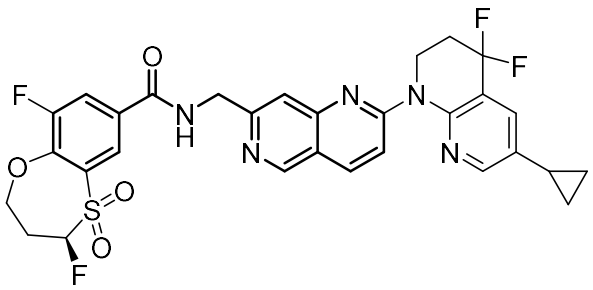
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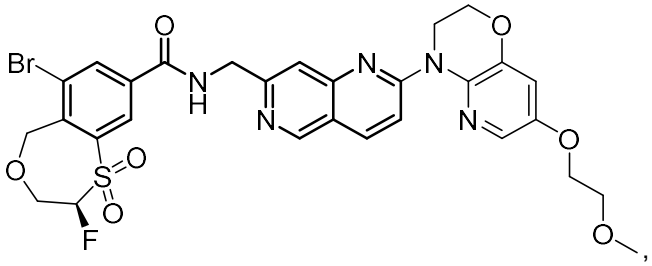
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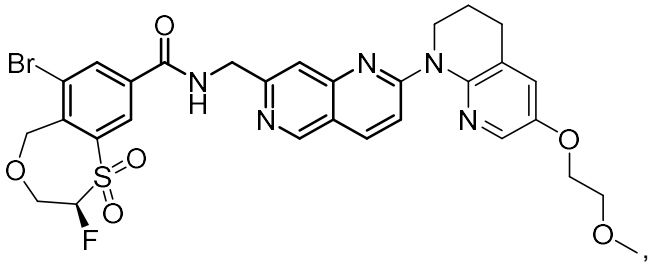
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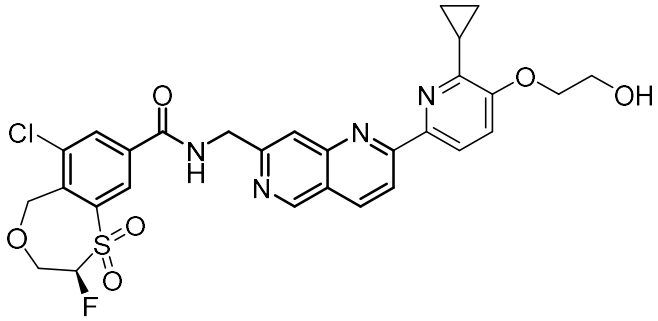
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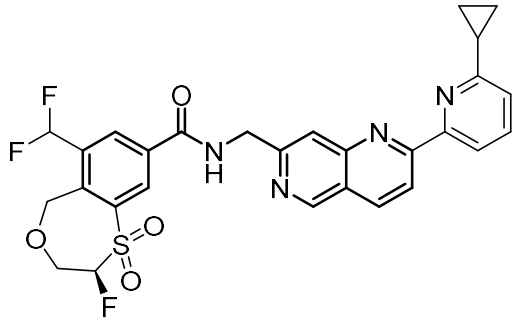
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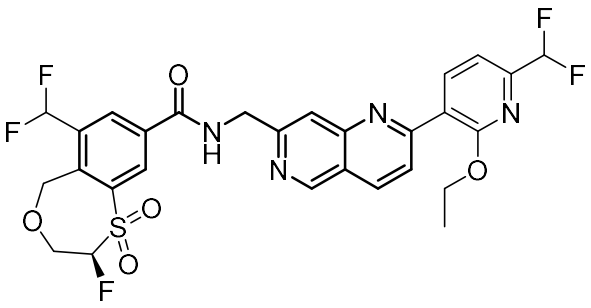
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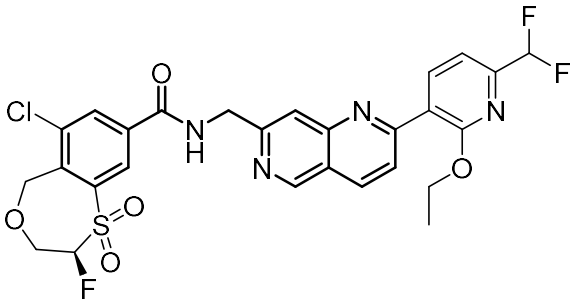
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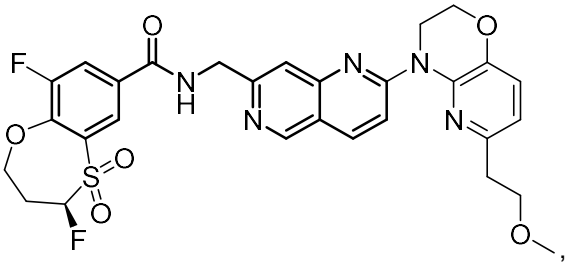
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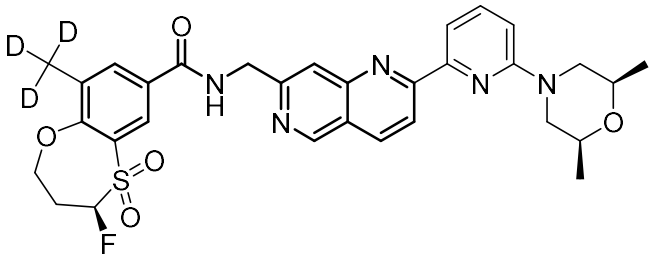
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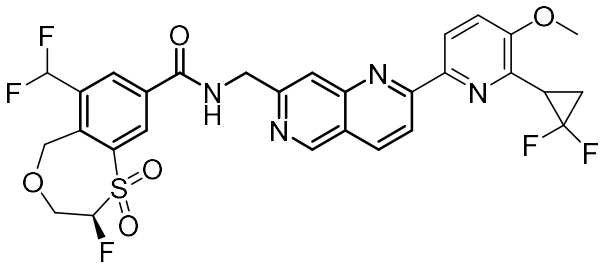
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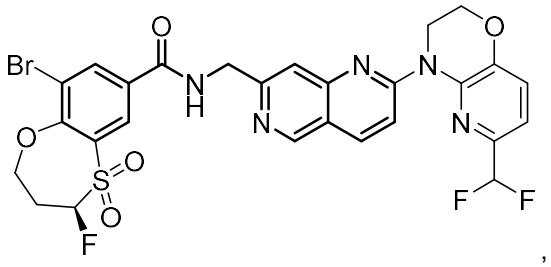
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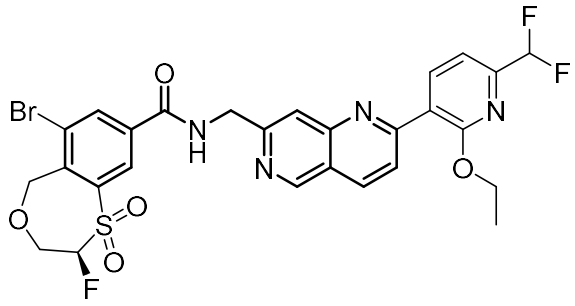
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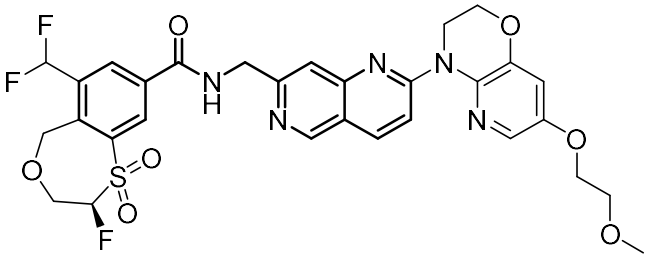
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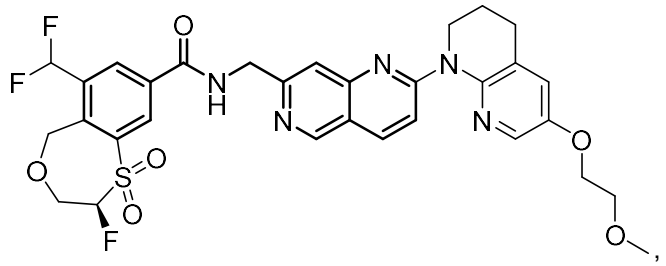
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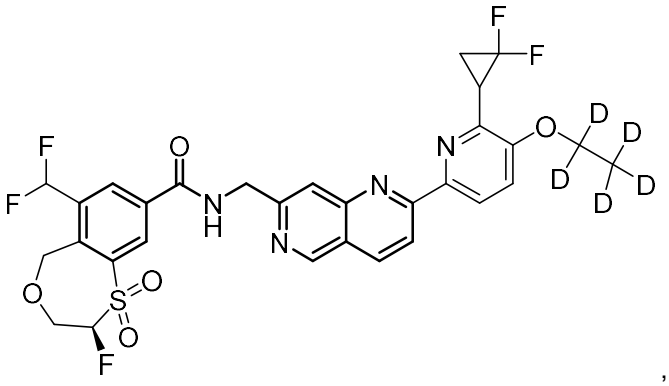


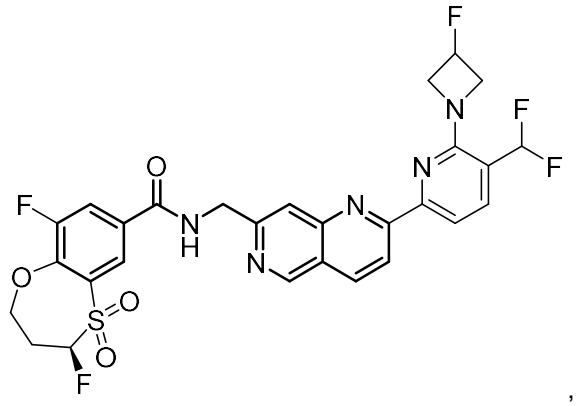
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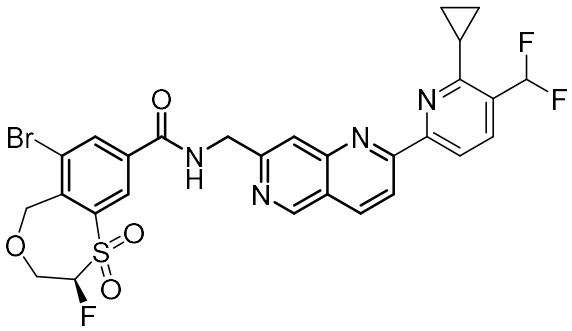


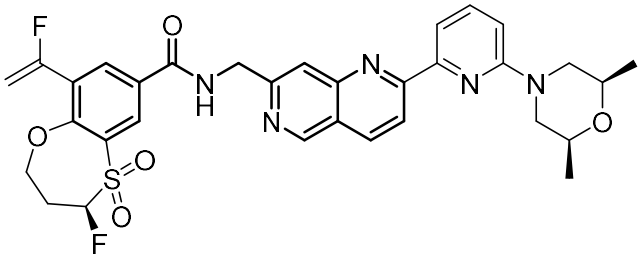
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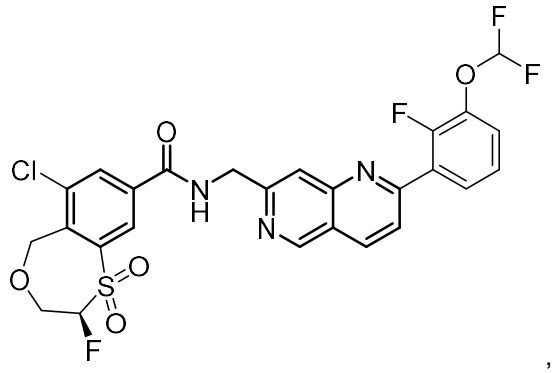




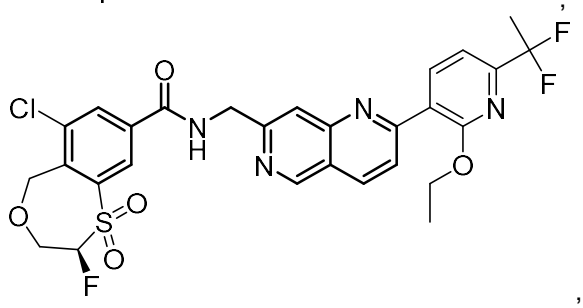




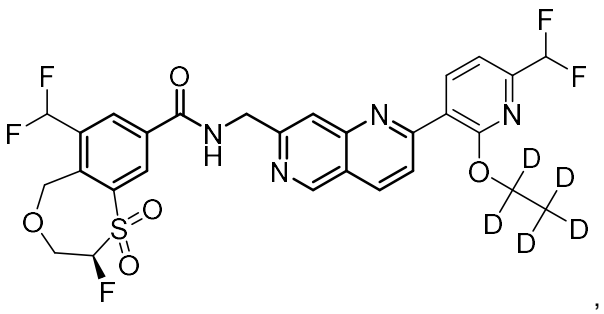




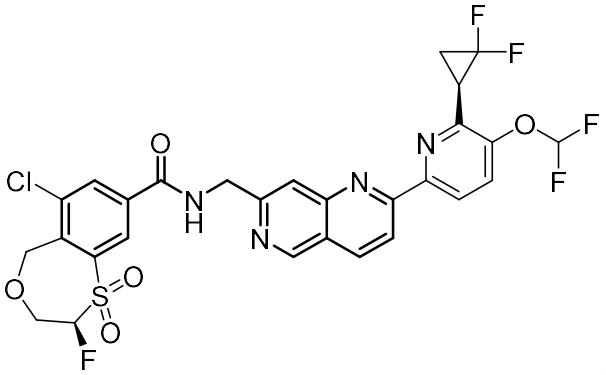
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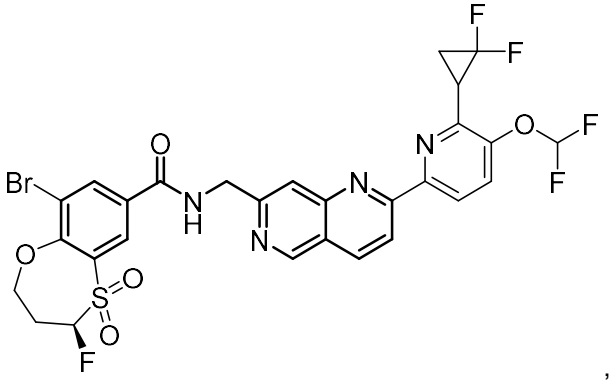
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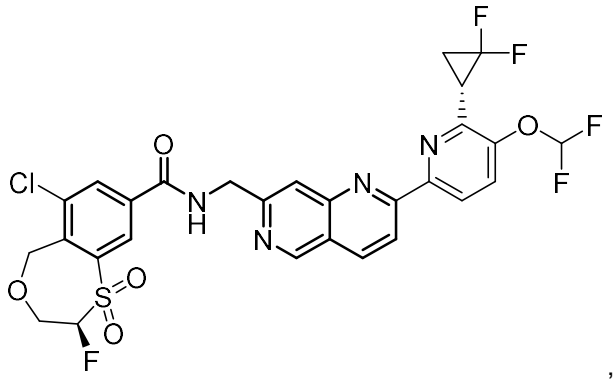
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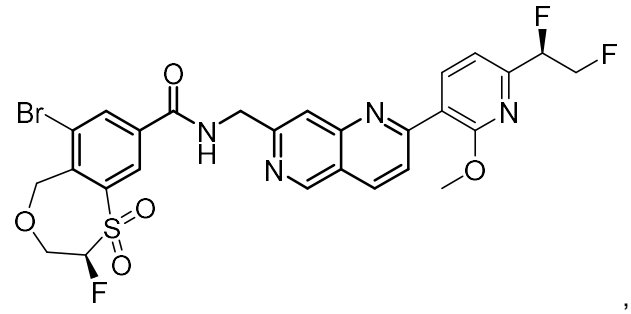
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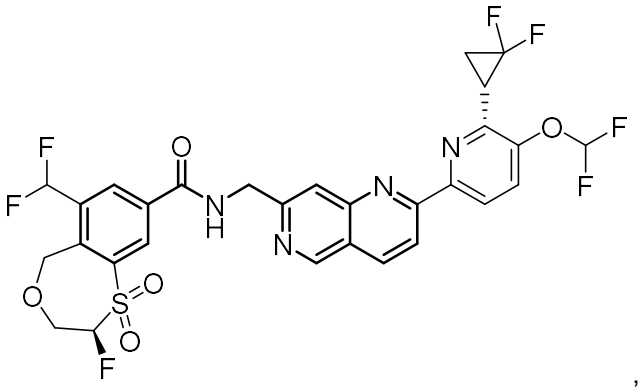
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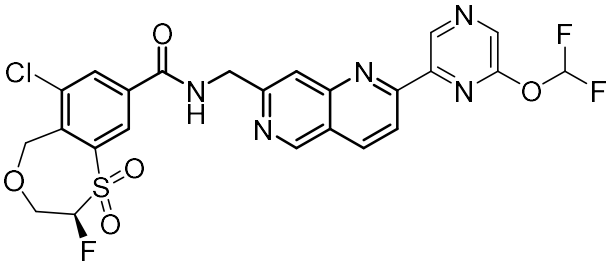
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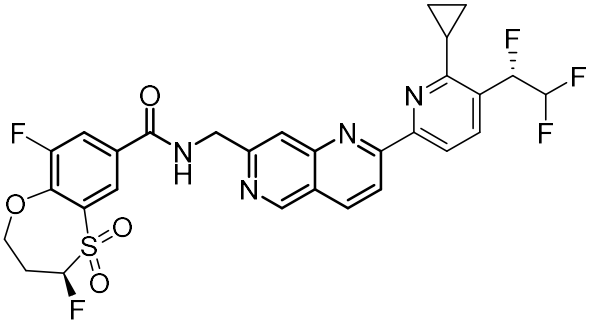
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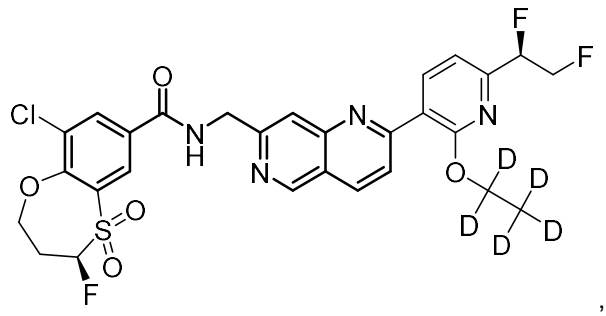
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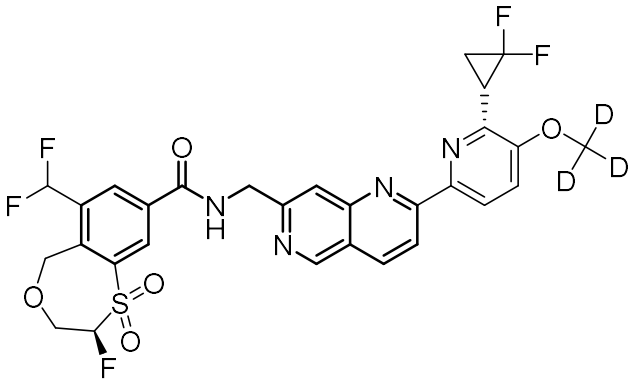
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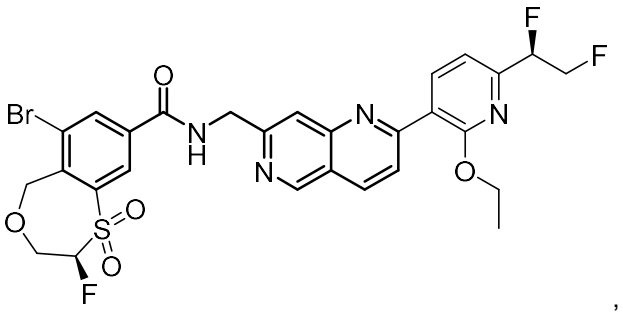
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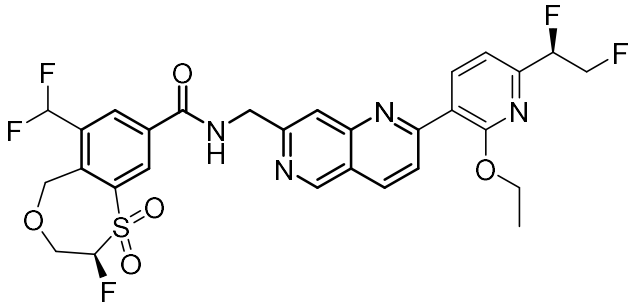
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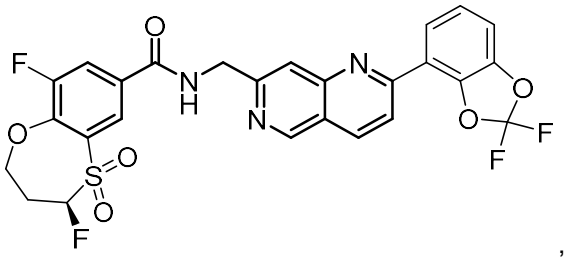
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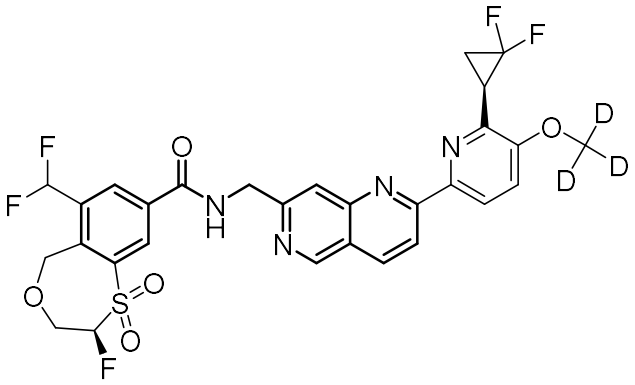
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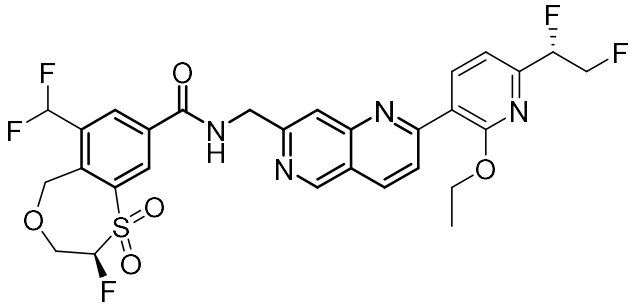
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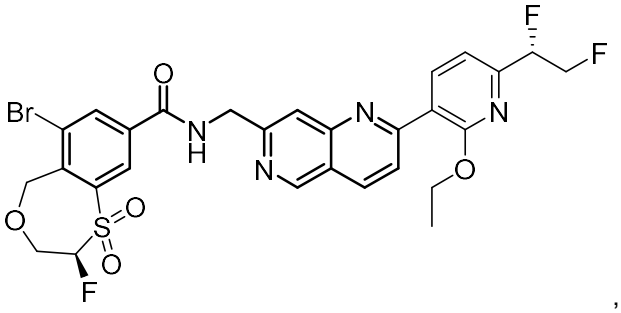
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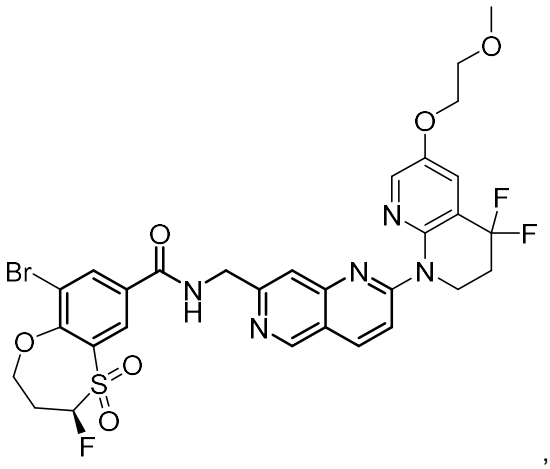
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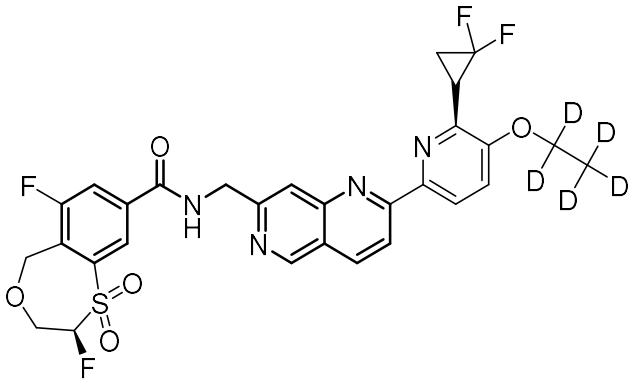
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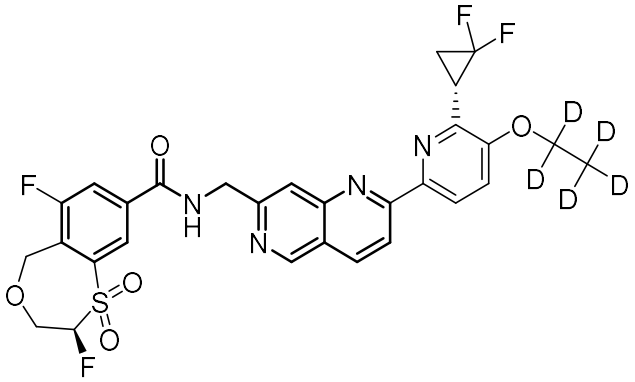
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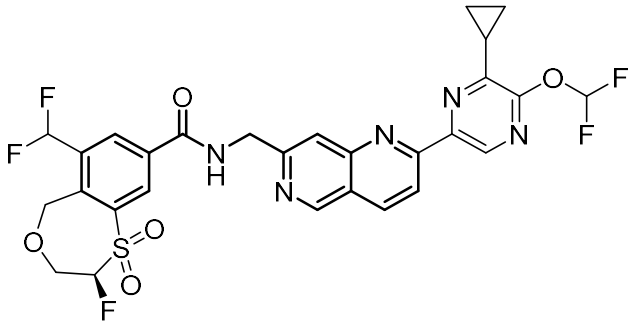
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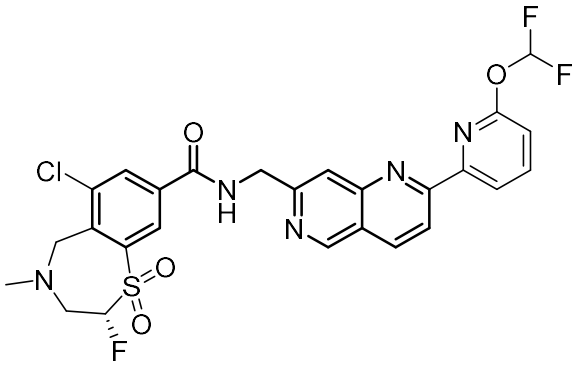
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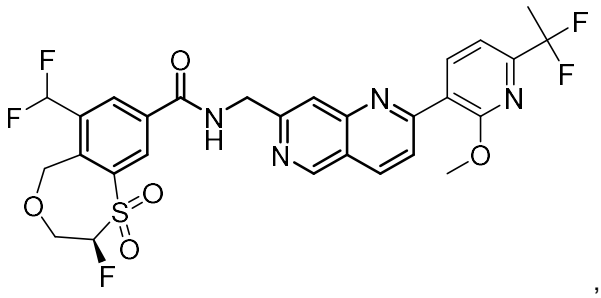
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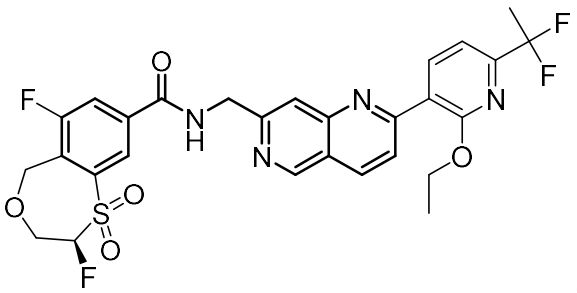
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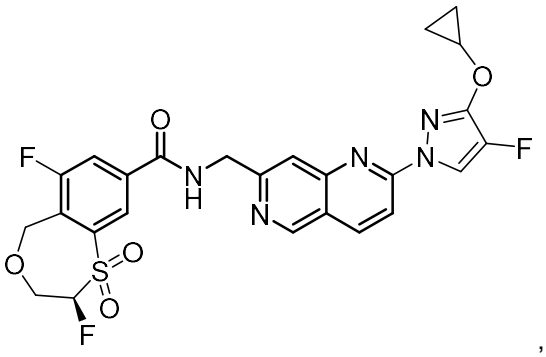
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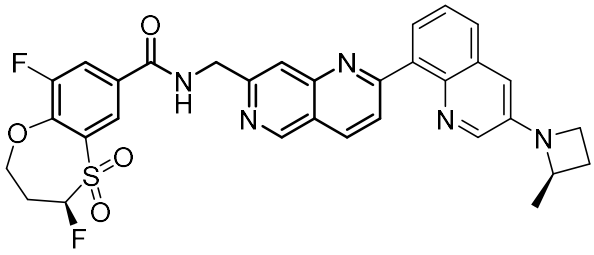
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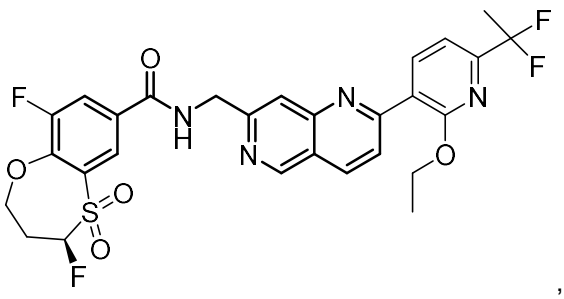
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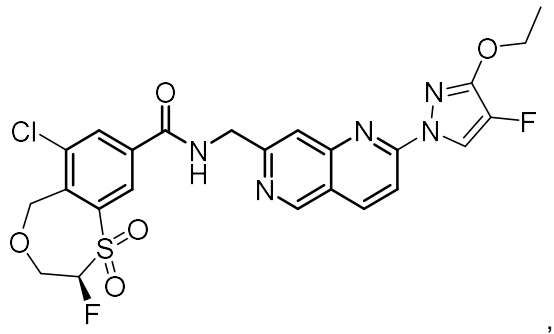
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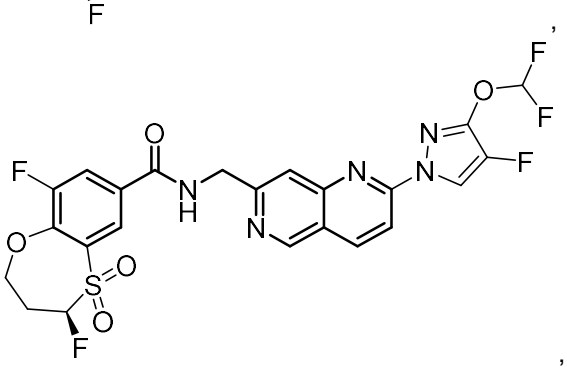


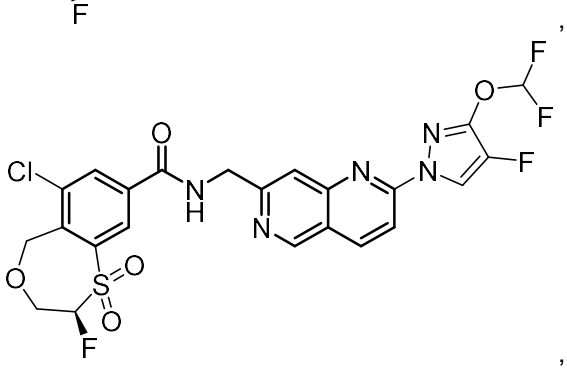
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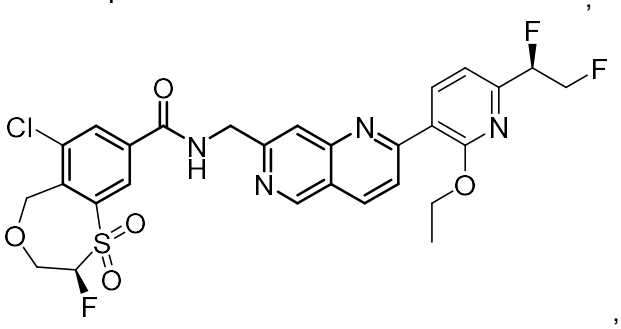


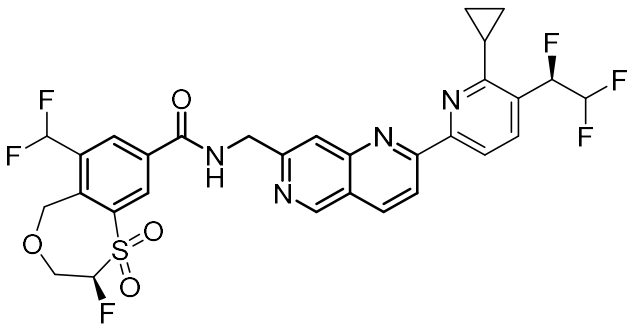
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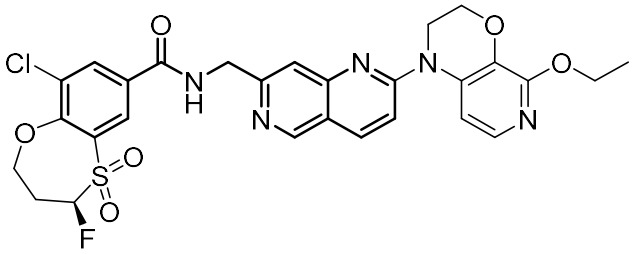




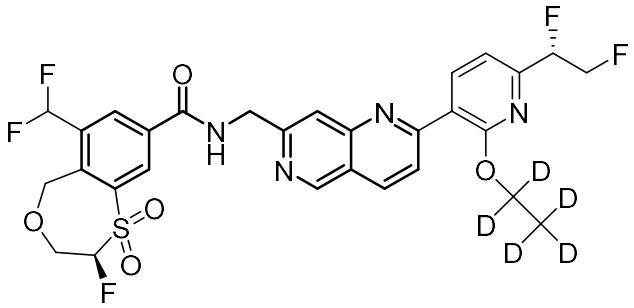




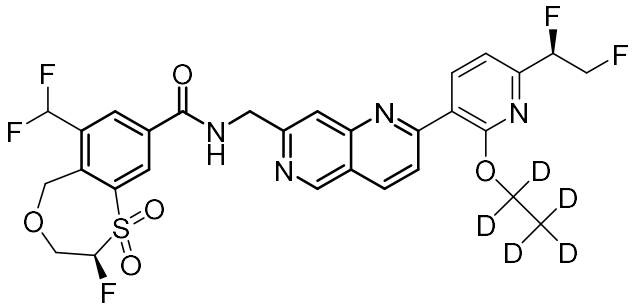




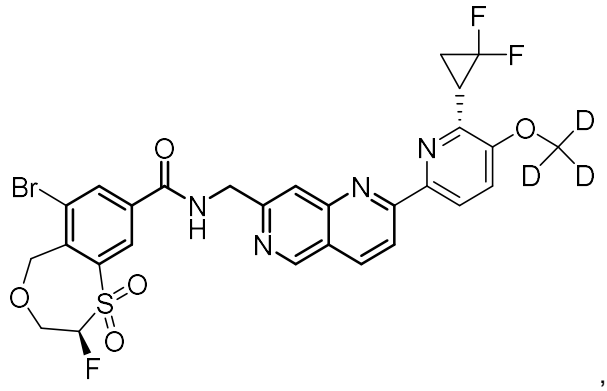
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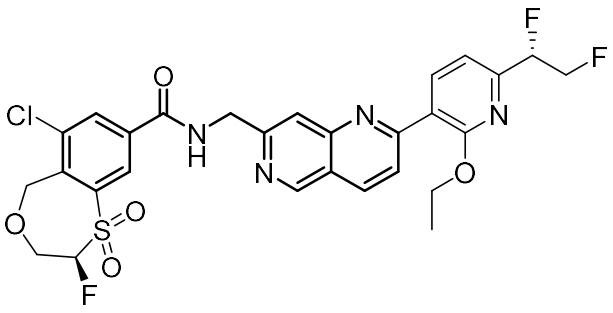
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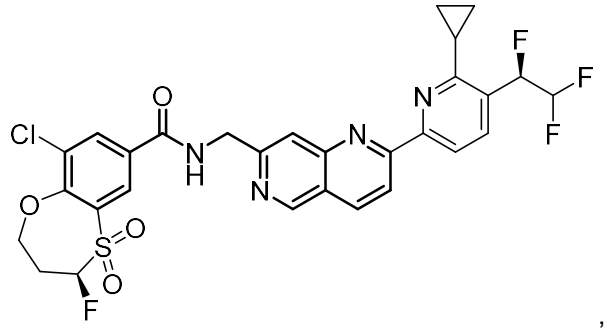


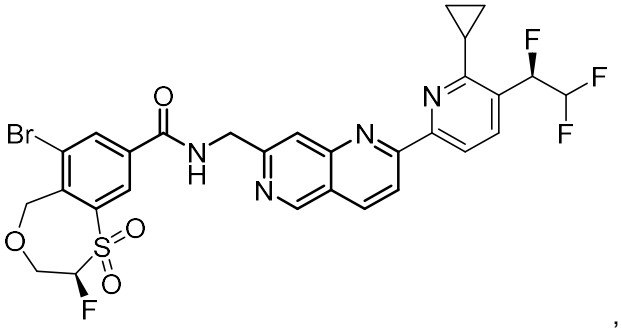
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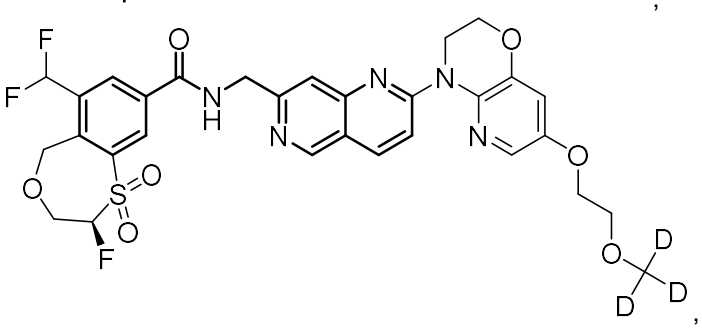


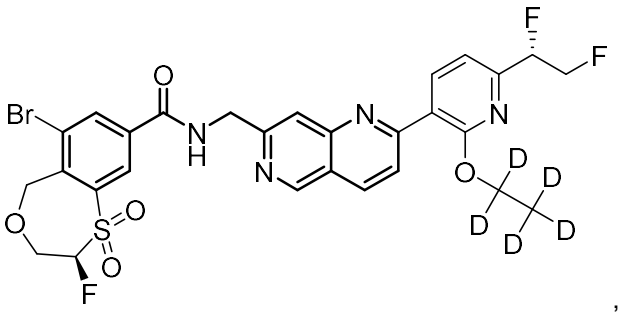
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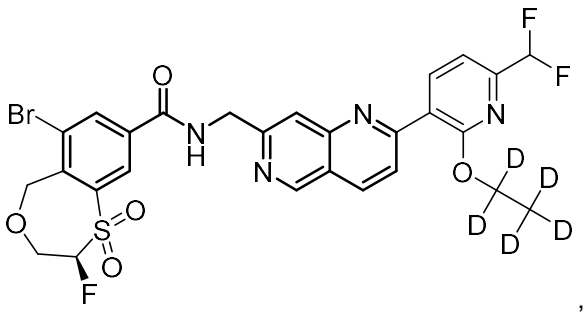
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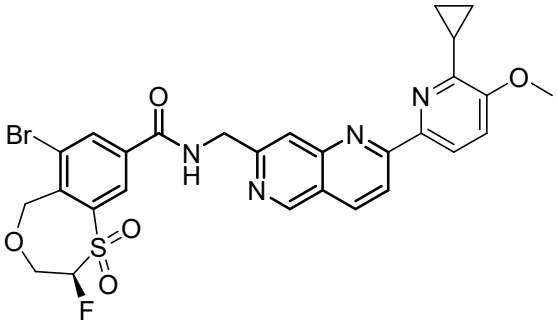

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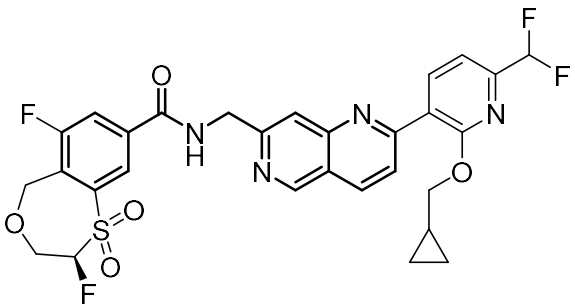

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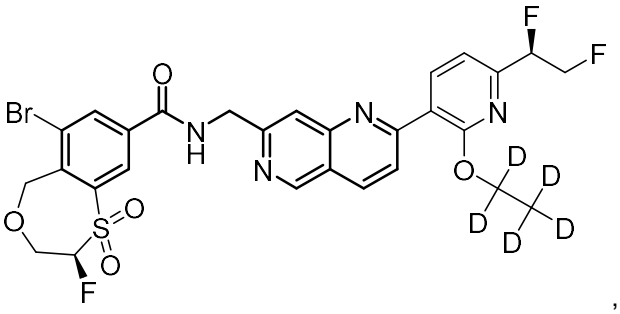

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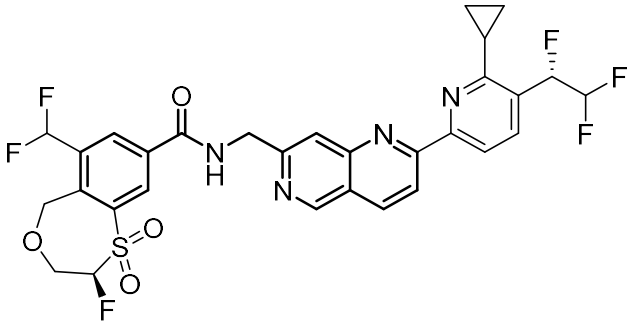
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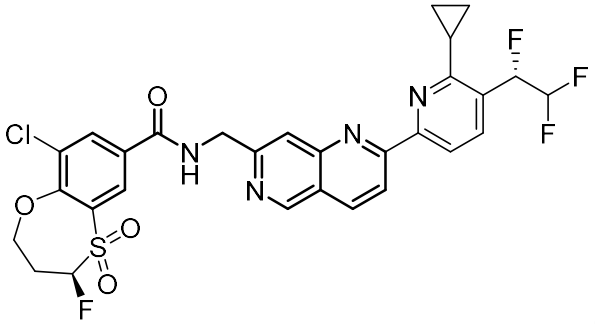
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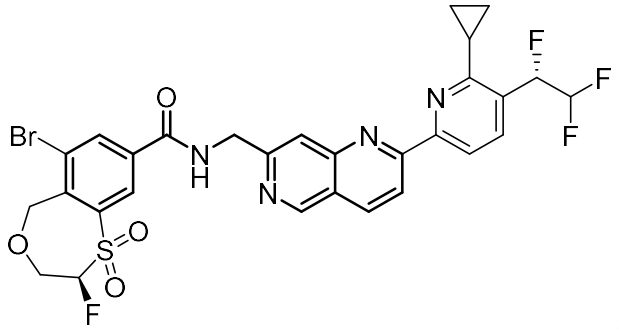
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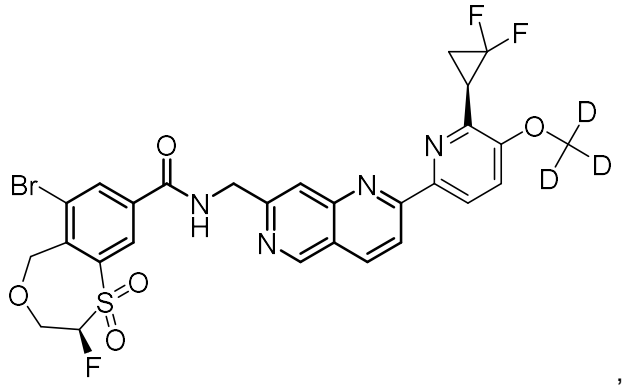
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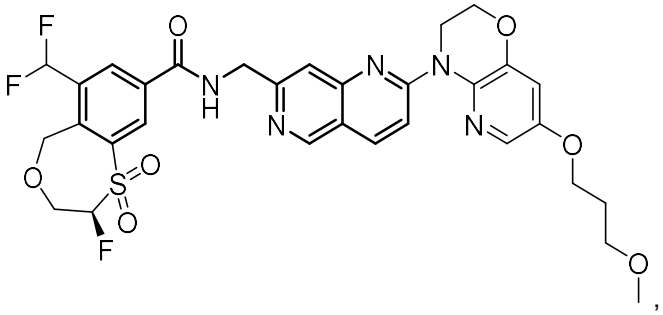
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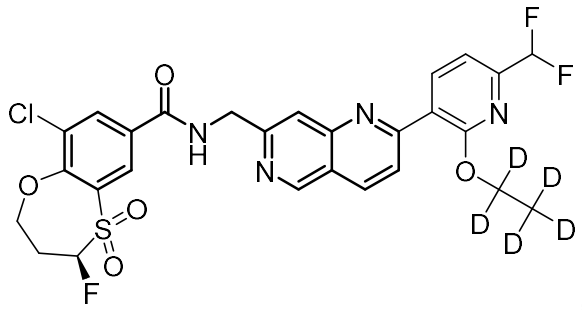
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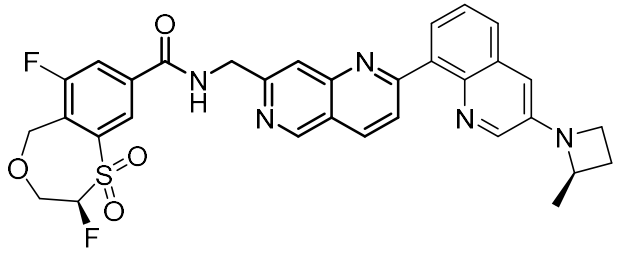
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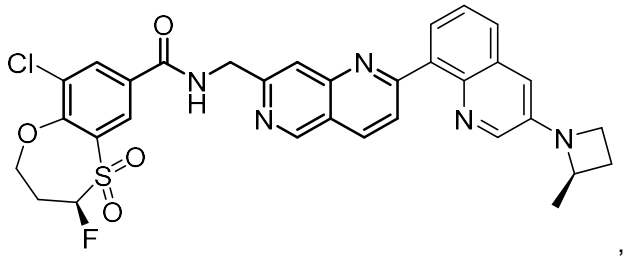


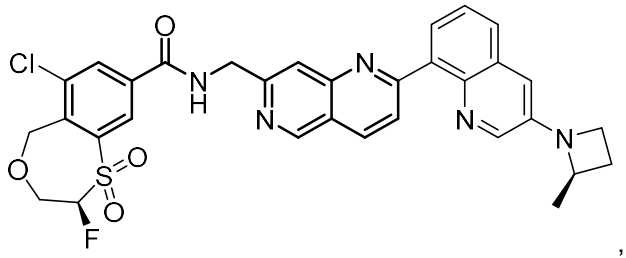
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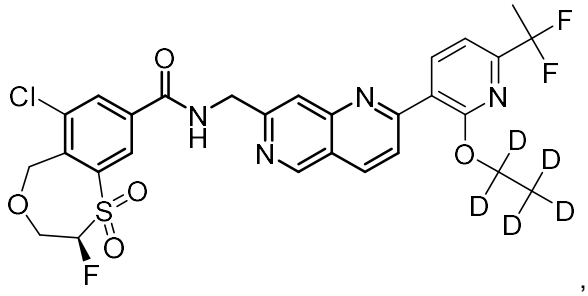


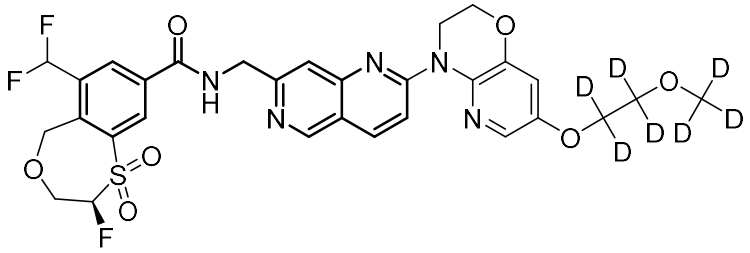
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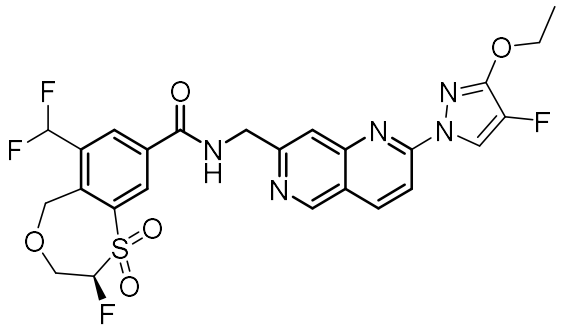
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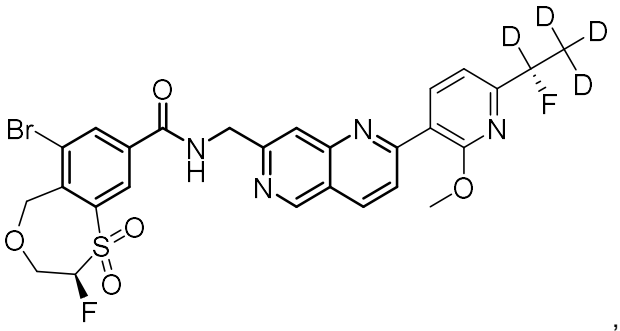

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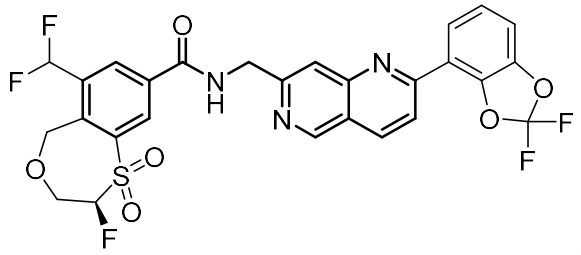

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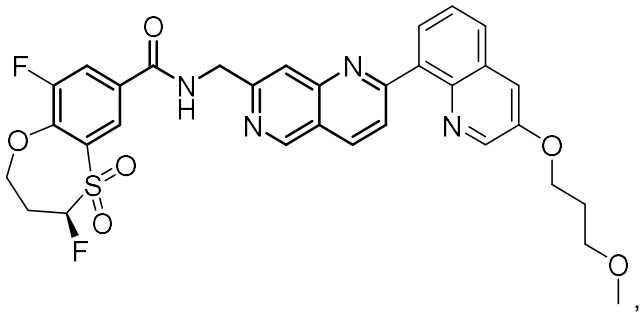

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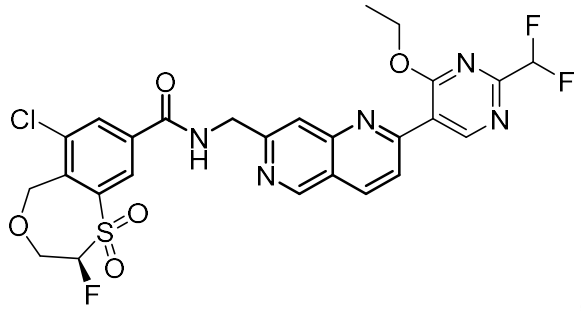

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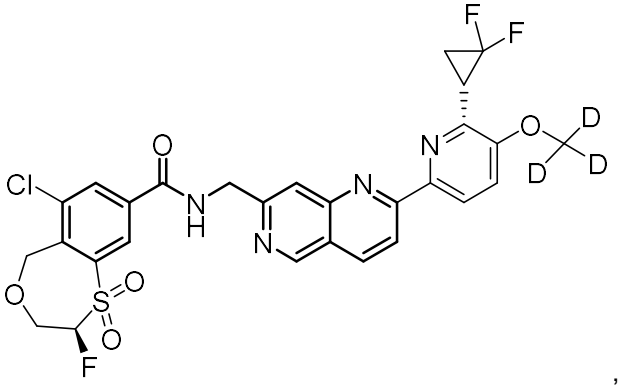
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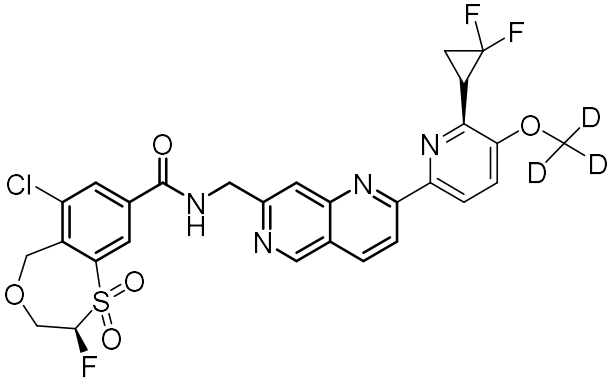

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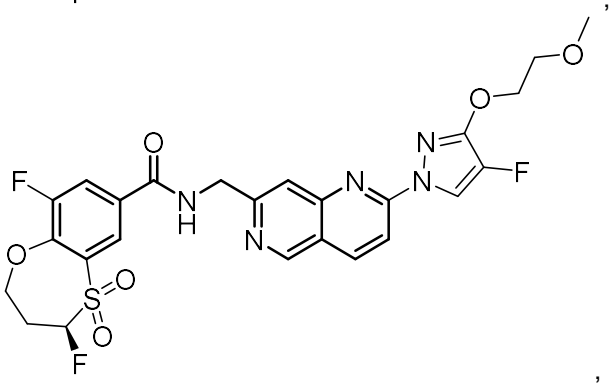

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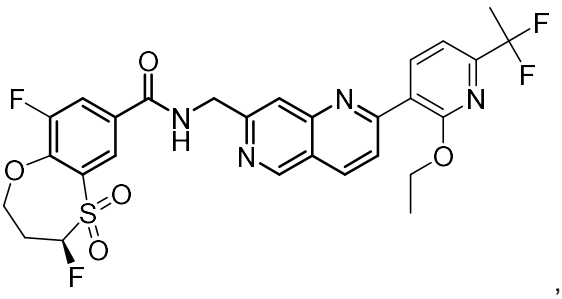

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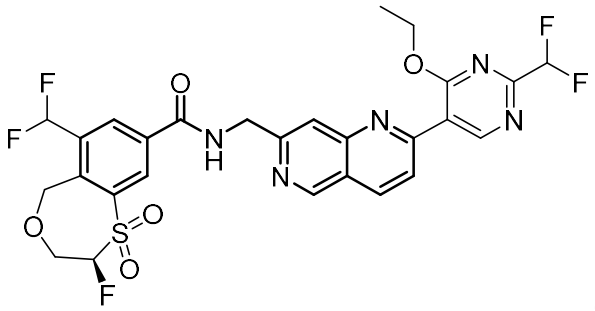
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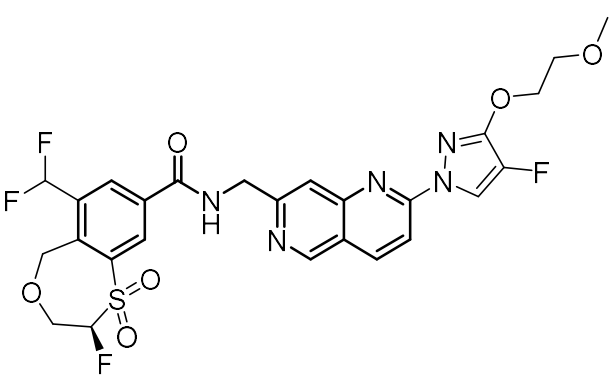
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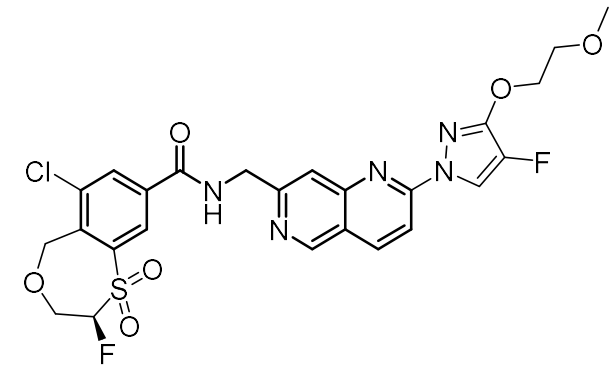
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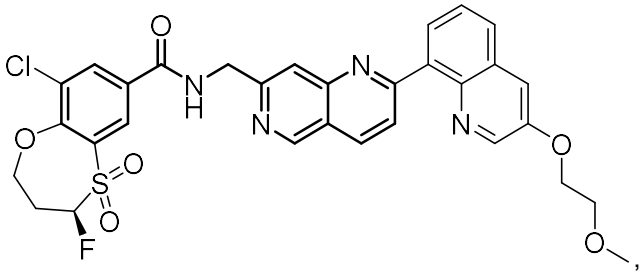
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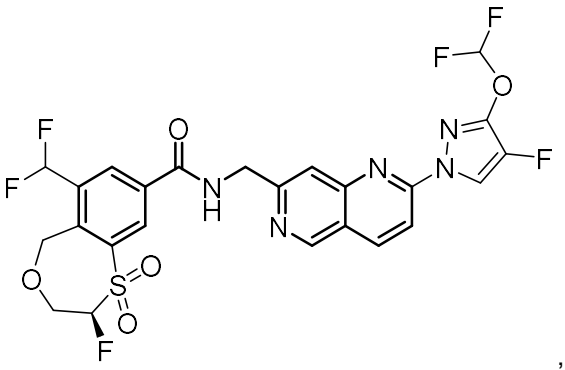
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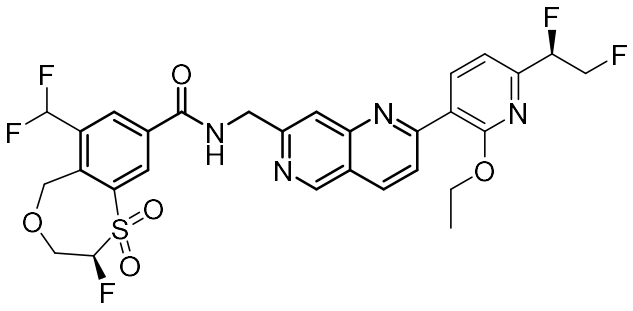
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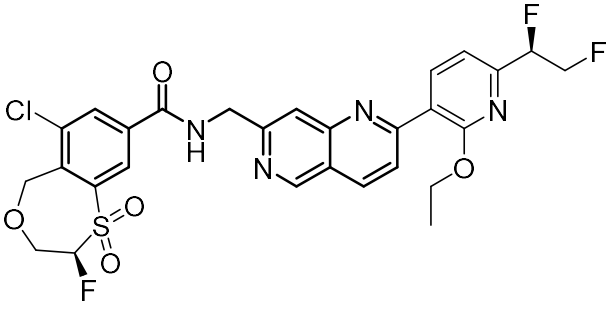
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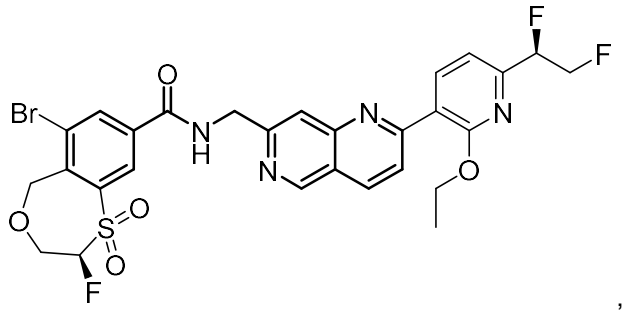
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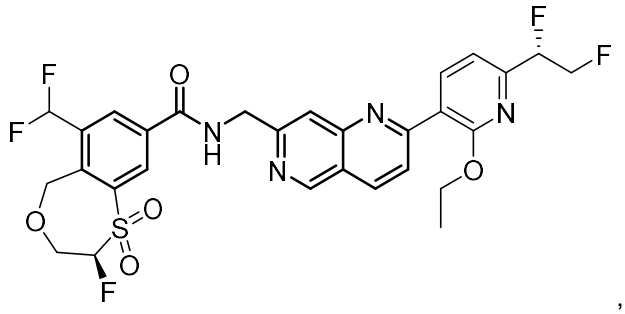
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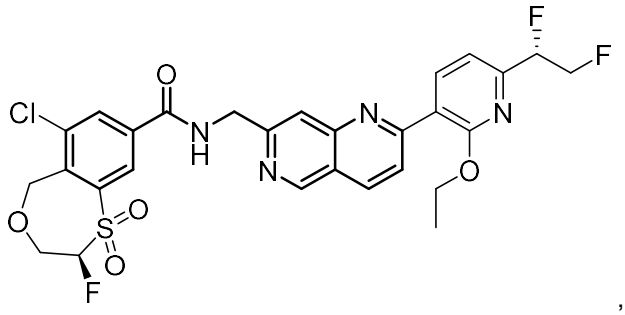
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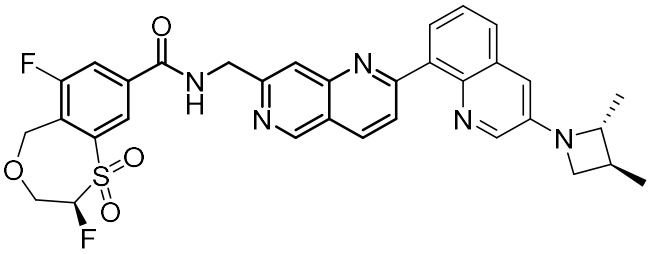
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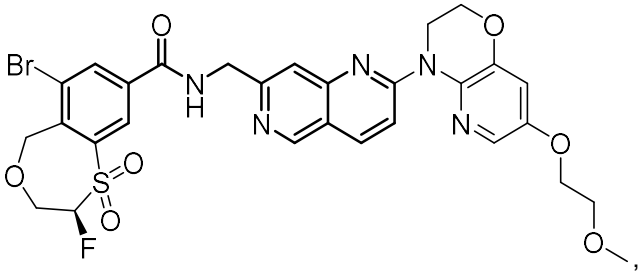
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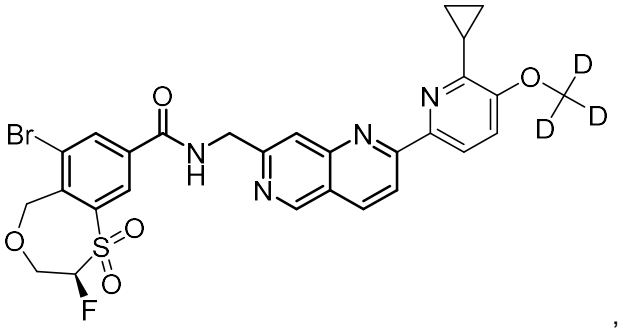
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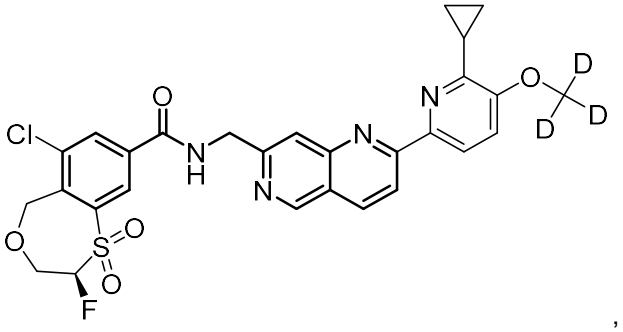
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and pharmaceutically acceptable salts thereof.

In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 5. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 7. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 10. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 15. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 20. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 25. In some examples, the compound has a ratio of BRG1 IC_{50} to BRM IC_{50} of at least 30.

In another aspect, the disclosure features a pharmaceutical composition comprising any one of the above compounds and a pharmaceutically acceptable excipient.

In another example, the disclosure features a method of decreasing the activity of a BAF complex in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some examples, the cell is a cancer cell.

In another example, the disclosure features a method of treating a BAF complex-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some examples, the BAF complex-related disorder is cancer.

In a further example, the disclosure features a method of inhibiting BRM, the method involving contacting a cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In some examples, the cell is a cancer cell.

In another example, the disclosure features a method of inhibiting BRG1, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In some examples, the cell is a cancer cell.

In a further example, the disclosure features a method of inhibiting BRM and BRG1, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In some examples, the cell is a cancer cell.

In another example, the disclosure features a method of treating a disorder related to a BRG1 loss of function mutation in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some examples, the disorder related to a BRG1 loss of function mutation is cancer. In other examples, the subject is determined to have a BRG1 loss of function disorder, for example, is determined to have a BRG1 loss of function cancer (for example, the cancer has been determined to include cancer cells with loss of BRG1 function).

In another example, the disclosure features a method of inducing apoptosis in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof. In some examples, the cell is a cancer cell.

In a further example, the disclosure features a method of treating cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds or a pharmaceutical composition thereof.

In some examples of any of the foregoing methods, the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, small-cell lung cancer, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, or penile cancer.

In some examples of any of the foregoing methods, the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, or penile cancer.

In some examples of any of the foregoing methods, the cancer is a drug resistant cancer or has failed to respond to a prior therapy (e.g., vemurafenib, dacarbazine, a CTLA4 inhibitor, a PD1 inhibitor, interferon therapy, a BRAF inhibitor, a MEK inhibitor, radiotherapy, temozolimide, irinotecan, a CAR-T therapy, herceptin, perjeta, tamoxifen, xeloda, docetaxol, platinum agents such as carboplatin, taxanes such as paclitaxel and docetaxel, ALK inhibitors, MET inihibitors, alimta, abraxane, Adriamycin®, gemcitabine, avastin, halaven, neratinib, a PARP inhibitor, ARN810, an mTOR inhibitor, topotecan, gemzar, a VEGFR2 inhibitor, a folate receptor antagonist, demcizumab, fosbretabulin, or a PDL1 inhibitor).

In some examples of any of the foregoing methods, the cancer has or has been determined to have BRG1 mutations. In some examples of any of the foregoing methods, the BRG1 mutations are homozygous. In some examples of any of the foregoing methods, the cancer does not have, or has been determined not to have, an epidermal growth factor receptor

(EGFR) mutation. In some examples of any of the foregoing methods, the cancer does not have, or has been determined not to have, an anaplastic lymphoma kinase (ALK) driver mutation. In some examples of any of the foregoing methods, the cancer has, or has been determined to have, a KRAS mutation. In some examples of any of the foregoing methods, the BRG1 mutation is in the ATPase catalytic domain of the protein. In some examples of any of the foregoing methods, the BRG1 mutation is a deletion at the C-terminus of BRG1.

In another example, the disclosure provides a method treating a disorder related to BAF (e.g., cancer or viral infections) in a subject in need thereof. This method includes contacting a cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions. In some examples, the disorder is a viral infection is an infection with a virus of the Retroviridae family such as the lentiviruses (e.g., Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)), Hepadnaviridae family (e.g., hepatitis B virus (HBV)), Flaviviridae family (e.g., hepatitis C virus (HCV)), Adenoviridae family (e.g., Human Adenovirus), Herpesviridae family (e.g., Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus), Papillomaviridae family (e.g., Human Papillomavirus (HPV, HPV E1)), Parvoviridae family (e.g., Parvovirus B19), Polyomaviridae family (e.g., JC virus and BK virus), Paramyxoviridae family (e.g., Measles virus), Togaviridae family (e.g., Rubella virus). In some examples, the disorder is Coffin Siris, Neurofibromatosis (e.g., NF-1, NF-2, or Schwannomatosis), or Multiple Meningioma.

In another example, the disclosure provides a method for treating a viral infection in a subject in need thereof. This method includes administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions. In some examples, the viral infection is an infection with a virus of the Retroviridae family such as the lentiviruses (e.g., Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)), Hepadnaviridae family (e.g., hepatitis B virus (HBV)), Flaviviridae family (e.g., hepatitis C virus (HCV)), Adenoviridae family (e.g., Human Adenovirus), Herpesviridae family (e.g., Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus), Papillomaviridae family (e.g., Human Papillomavirus (HPV, HPV E1)), Parvoviridae family (e.g., Parvovirus B19), Polyomaviridae family (e.g., JC virus and BK virus), Paramyxoviridae family (e.g., Measles virus), or Togaviridae family (e.g., Rubella virus).

In another example, the disclosure features a method of treating melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another example, the disclosure features a method of reducing tumor growth of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another example, the disclosure features a method of suppressing metastatic progression of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject, the method including administering an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another example, the disclosure features a method of suppressing metastatic colonization of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or a hematologic cancer in a subject, the method including administering an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In another example, the disclosure features a method of reducing the level and/or activity of BRG1 and/or BRM in a melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cancer cell, the method including contacting the cell with an effective amount of any of the foregoing compounds or pharmaceutical compositions thereof.

In some examples, the melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, or hematologic cell is in a subject.

In some examples, the effective amount of the compound reduces the level and/or activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some examples, the effective amount of the compound that reduces the level and/or activity of BRG1 by at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some examples, the effective amount of the compound that reduces the level and/or activity of BRG1 by at least 90% (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%).

In some examples, the effective amount of the compound reduces the level and/or activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 12 hours (e.g., 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 30 hours, 36 hours, 48 hours, 72 hours, or more). In some examples, the effective amount of the compound that reduces the level and/or activity of BRG1 by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 4 days (e.g., 5 days, 6 days, 7 days, 14 days, 28 days, or more).

In some examples, the effective amount of the compound reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as

compared to a reference. In some examples, the effective amount of the compound that reduces the level and/or activity of BRM by at least 50% (e.g., 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference. In some examples, the effective amount of the compound that reduces the level and/or activity of BRM by at least 90% (e.g., 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%).

In some examples, the effective amount of the compound reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 12 hours (e.g., 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 30 hours, 36 hours, 48 hours, 72 hours, or more). In some examples, the effective amount of the compound that reduces the level and/or activity of BRM by at least 5% (e.g., 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) as compared to a reference for at least 4 days (e.g., 5 days, 6 days, 7 days, 14 days, 28 days, or more).

In some examples, the subject has cancer. In some examples, the cancer expresses BRG1 and/or BRM protein and/or the cell or subject has been identified as expressing BRG1 and/or BRM. In some examples, the cancer expresses BRG1 protein and/or the cell or subject has been identified as expressing BRG1. In some examples, the cancer expresses BRM protein and/or the cell or subject has been identified as expressing BRM. In some examples, the cancer is melanoma (e.g., uveal melanoma, mucosal melanoma, or cutaneous melanoma). In some examples, the cancer is prostate cancer. In some examples, the cancer is a hematologic cancer, e.g., multiple myeloma, large cell lymphoma, acute T-cell leukemia, acute myeloid leukemia, myelodysplastic syndrome, immunoglobulin A lambda myeloma, diffuse mixed histiocytic and lymphocytic lymphoma, B-cell lymphoma, acute lymphoblastic leukemia (e.g., T-cell acute lymphoblastic leukemia or B-cell acute lymphoblastic leukemia), diffuse large cell lymphoma, or non-Hodgkin’s lymphoma. In some examples, the cancer is breast cancer (e.g., an ER positive breast cancer, an ER negative breast cancer, triple positive breast cancer, or triple negative breast cancer). In some examples, the cancer is a bone cancer (e.g., Ewing’s sarcoma). In some examples, the cancer is a renal cell carcinoma (e.g., a Microphthalmia Transcription Factor (MITF) family translocation renal cell carcinoma (tRCC)). In some examples, the cancer is metastatic (e.g., the cancer has spread to the liver). The metastatic cancer can include cells exhibiting migration and/or invasion of migrating cells and/or include cells exhibiting endothelial recruitment and/or angiogenesis. In other examples, the migrating cancer is a cell migration cancer. In still other examples, the cell migration cancer is a non-metastatic cell migration cancer. The metastatic cancer can be a cancer spread via seeding the surface of the peritoneal, pleural, pericardial, or subarachnoid spaces. Alternatively, the metastatic cancer can be a cancer spread via the lymphatic system, or

a cancer spread hematogenously. In some examples, the effective amount of a compound of the disclosure is an amount effective to inhibit metastatic colonization of the cancer to the liver.

In some examples the cancer harbors a mutation in GNAQ. In some examples the cancer harbors a mutation in GNA11. In some examples the cancer harbors a mutation in PLCB4. In some examples the cancer harbors a mutation in CYSLTR2. In some examples the cancer harbors a mutation in BAP1. In some examples the cancer harbors a mutation in SF3B1. In some examples the cancer harbors a mutation in EIF1AX. In some examples the cancer harbors a TFE3 translocation. In some examples the cancer harbors a TFEB translocation. In some examples the cancer harbors a MITF translocation. In some examples the cancer harbors an EZH2 mutation. In some examples the cancer harbors a SUZ12 mutation. In some examples the cancer harbors an EED mutation.

In some examples of any of the foregoing methods, the method further includes administering to the subject or contacting the cell with an anticancer therapy, e.g., a chemotherapeutic or cytotoxic agent, immunotherapy, surgery, radiotherapy, thermotherapy, or photocoagulation, or a combination thereof. In some examples, the anticancer therapy is a chemotherapeutic or cytotoxic agent, e.g., an antimetabolite, antimitotic, antitumor antibiotic, asparagine-specific enzyme, bisphosphonates, antineoplastic, alkylating agent, DNA-Repair enzyme inhibitor, histone deacetylase inhibitor, corticosteroid, demethylating agent, immunomodulatory, janus-associated kinase inhibitor, phosphinositide 3-kinase inhibitor, proteasome inhibitor, or tyrosine kinase inhibitor, or a combination thereof.

In some examples of any of the foregoing methods, the compound of the disclosure is used in combination with another anti-cancer therapy used for the treatment of uveal melanoma such as surgery, a MEK inhibitor, and/or a PKC inhibitor. For example, the method further includes performing surgery prior to, subsequent to, or at the same time as administration of the compound of the disclosure. In some examples, the method further includes administration of a MEK inhibitor and/or a PKC inhibitor prior to, subsequent to, or at the same time as administration of the compound of the disclosure.

In some examples, the anticancer therapy and the compound of the disclosure are administered within 28 days of each other and each in an amount that together are effective to treat the subject.

In some examples, the subject or cancer has and/or has been identified as having a BRG1 loss of function mutation.

In some examples, the cancer is resistant to one or more chemotherapeutic or cytotoxic agents (e.g., the cancer has been determined to be resistant to chemotherapeutic or cytotoxic agents such as by genetic markers, or is likely to be resistant, to chemotherapeutic or cytotoxic agents such as a cancer that has failed to respond to a chemotherapeutic or cytotoxic agent). In some examples, the cancer has failed to respond to one or more chemotherapeutic or cytotoxic agents. In some examples, the cancer is resistant or has failed to respond to

dacarbazine, temozolomide, cisplatin, treosulfan, fotemustine, IMCgp100, a CTLA-4 inhibitor (e.g., ipilimumab), a PD-1 inhibitor (e.g., Nivolumab or pembrolizumab), a PD-L1 inhibitor (e.g., atezolizumab, avelumab, or durvalumab), a mitogen-activated protein kinase (MEK) inhibitor (e.g., selumetinib, binimetinib, or tametinib), and/or a protein kinase C (PKC) inhibitor (e.g., sotrastaurin or IDE196).

In some examples, the cancer is resistant to or failed to respond to a previously administered therapeutic used for the treatment of uveal melanoma such as a MEK inhibitor or PKC inhibitor. For example , the cancer is resistant to or failed to respond to a mitogen-activated protein kinase (MEK) inhibitor (e.g., selumetinib, binimetinib, or tametinib), and/or a protein kinase C (PKC) inhibitor (e.g., sotrastaurin or IDE196).

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in therapy.

In another aspect, the disclosure provides the compound disclosed herein or the pharmaceutical composition disclosed herein for use in therapy.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in decreasing the activity of a BAF complex in a cell.

In some examples, the BAF complex is in a cancer cell.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in treating a BAF complex-related disorder.

In some examples, the BAF complex-related disorder is cancer or a viral infection.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in inhibiting BRM in a cell.

In some examples, the cell is a cancer cell.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in treating a disorder related to a BRG1 loss of function mutation.

In some examples, the disorder related to a BRG1 loss of function mutation is cancer.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in inducing apoptosis in a cell.

In some examples, the cell is a cancer cell.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in treating cancer.

In some examples, the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary

cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, small-cell lung cancer, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, or penile cancer.

In some examples, the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, or penile cancer.

In some examples, the cancer is non-small cell lung cancer. In some examples, the cancer is soft tissue sarcoma.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in treating a cancer selected from the group consisting of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, and a hematologic cancer.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in reducing tumor growth of a cancer selected from the group consisting of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, and a hematologic cancer.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in suppressing metastatic progression of a cancer selected from the group consisting of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, and a hematologic cancer.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in suppressing metastatic colonization of a cancer selected from the group consisting of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, and a hematologic cancer.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in reducing the level and/or activity of BRM in a cancer cell selected from the group consisting of melanoma, prostate cancer, breast cancer, bone cancer, renal cell carcinoma, and hematologic cancer.

In some examples, the cell is in a subject.

In some examples, the cancer is metastatic.

In some examples, the use further includes an anticancer therapy.

In some examples, the anticancer therapy is a chemotherapeutic or cytotoxic agent, immunotherapy, surgery, radiotherapy, thermotherapy, or photocoagulation.

In some examples, the anticancer therapy is surgery.

In some examples, the anticancer therapy is a chemotherapeutic or cytotoxic agent.

In some examples, the chemotherapeutic or cytotoxic agent is an antimetabolite, antimitotic, antitumor antibiotic, asparagine-specific enzyme, bisphosphonates, antineoplastic, alkylating agent, DNA-Repair enzyme inhibitor, histone deacetylase inhibitor, corticosteroid, demethylating agent, immunomodulatory, janus-associated kinase inhibitor, phosphinositide 3-kinase inhibitor, proteasome inhibitor, or tyrosine kinase inhibitor.

In some examples, the one or more chemotherapeutic or cytotoxic agent is dacarbazine, temozolomide, cisplatin, treosulfan, fotemustine, IMCgp100, a CTLA-4 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a mitogen-activated protein kinase inhibitor, and/or a protein kinase C inhibitor.

In some examples, the anticancer therapy and the compound disclosed herein or a pharmaceutical composition disclosed herein are administered within 28 days of each other and each in an amount that together are effective to treat the subject.

In some examples, the subject or cancer has and/or has been identified as having a BRG1 loss of function mutation.

In some examples, the cancer has failed to respond to or progressed after administration of one or more chemotherapeutic or cytotoxic agents.

In some examples, the cancer is resistant to, or predicted to be resistant to one or more chemotherapeutic agents.

In some examples, the one or more chemotherapeutic or cytotoxic agents is dacarbazine, temozolomide, cisplatin, treosulfan, fotemustine, IMCgp100, a CTLA-4 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a mitogen-activated protein kinase inhibitor, and/or a protein kinase C inhibitor.

In some examples, the cancer is melanoma. In some examples, the melanoma is uveal melanoma. In some examples, the melanoma is mucosal melanoma. In some examples, the melanoma is cutaneous melanoma. In some examples, the cancer is a hematologic cancer. In some examples, the hematologic cancer is multiple myeloma, large cell lymphoma, acute T-cell leukemia, acute myeloid leukemia, myelodysplastic syndrome, immunoglobulin A lambda myeloma, diffuse mixed histiocytic and lymphocytic lymphoma, B-cell lymphoma, acute lymphoblastic leukemia, diffuse large cell lymphoma, or non-Hodgkin’s lymphoma. In some examples, the cancer is prostate cancer. In some examples, the cancer is breast cancer. In some examples, the breast cancer is an ER positive breast cancer, an ER negative breast cancer, triple positive breast cancer, or triple negative breast cancer. In some examples, the cancer is bone cancer. In some examples, the bone cancer is Ewing’s sarcoma. In some examples, the cancer is renal cell carcinoma. In some examples, the renal cell carcinoma is Microphthalmia Transcription Factor (MITF) family translocation renal cell carcinoma.

In an example, the disclosure provides a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in treating a viral infection.

In some example, the viral infection is an infection with a virus of the Retroviridae family, Hepadnaviridae family, Flaviviridae family, Adenoviridae family, Herpesviridae family, Papillomaviridae family, Parvoviridae family, Polyomaviridae family, Paramyxoviridae family, or Togaviridae family.

In an example, the disclosure provides the use of any of the foregoing compounds (e.g., a BRM/BRG1 dual inhibitor compound or a BRM-selective compound), or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions in the manufacture of a medicament. In some examples, the use is as described for the methods described herein.

In another aspect, the disclosure provides use of a compound disclosed herein, in the manufacture of a medicament for treating cancer, wherein the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, small-cell lung cancer, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, or penile cancer.

Chemical Terms

The terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.

For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as H atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C_2 alkyl group has the formula $–CH_2CH_3$. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.

The term “acyl,” as used herein, represents a H or an alkyl group that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

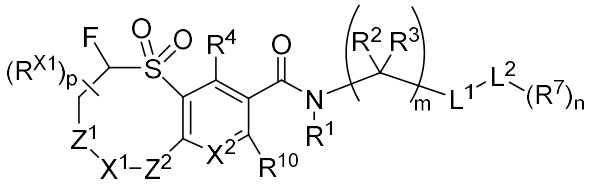
The term “alkyl,” as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 3 carbon atoms).

An alkylene is a divalent alkyl group. The term “alkenyl,” as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6 carbon atoms, or 2 carbon atoms).

The term “alkynyl,” as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2

Claims

1. A compound having the structure:



Formula I

wherein

m is 0, 1, 2, or 3;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, or 3;

X^1 is O, NR^5, or $(C(R^5)(R^6))$, and each of Z^1 and Z^2 is independently absent or $(C(R^9)_2)$ or O, provided that, if X^1 is O, then each of Z^1 and Z^2 is independently absent or $(C(R^9)_2)$;

X^2 is N or CR^8;

each R^{X1} is independently deuterium, optionally substituted C_1-C_6 alkyl, or halo, or two *geminal* R^{X1} groups, together with the atom to which they are attached, combine to form a carbonyl;

L^1 is optionally substituted 9- or 10-membered bicyclic heterocyclyl, optionally substituted 9- or 10-membered bicyclic heteroaryl, optionally substituted monocyclic 6-membered heteroarylvinyl, optionally substituted monocyclic 6-membered heteroaryl-C_3-C_8-cycloalkyl, or optionally substituted monocyclic 6-membered heteroarylethynyl;

L^2 is absent, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5- to 10-membered heteroaryl, or optionally substituted 4- to 10-membered heterocyclyl;

R^1 is hydrogen or optionally substituted C_1-C_6 alkyl;

each R^2 and each R^3 are independently hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^4 is hydrogen, halo, optionally substituted C_1-C_6 alkyl, or optionally substituted C_3-C_{10} cycloalkyl;

R^5 is hydrogen, deuterium, or optionally substituted C_1-C_6 alkyl;

R^6 is hydrogen, deuterium, optionally substituted C_1-C_6 alkyl, or halo, and each R^9 is independently hydrogen, deuterium, optionally substituted C_1-C_6 alkyl, or halo; or R^6 and one *vicinal* R^9, together with the atoms to which they are attached combine to form optionally substituted C_3-C_8 cycloalkyl, and the remaining R^9 groups, if present, are independently deuterium, optionally substituted C_1-C_6 alkyl, or halo;

each R^7 is independently optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, halo, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted 5- to 10-membered heteroaryl, optionally substituted 4- to 10-membered heterocyclyl, $-N(R^{7A})_2$, or $-OR^{7A}$, wherein each R^{7A} is independently H, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally

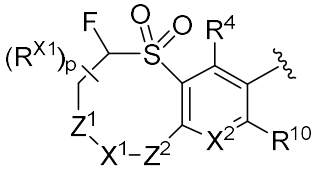
substituted C_3-C_{10} cycloalkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5- to 10-membered heteroaryl, or optionally substituted 4- to 10-membered heterocyclyl, or two *geminal* R^{7A} groups, together with the atom to which they are attached, combine to form optionally substituted 5- to 10-membered heteroaryl or optionally substituted 4- to 10-membered heterocyclyl;

R^8 is hydrogen, halo, cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} cycloalkyl; and

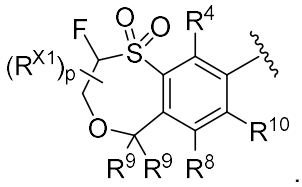
R^{10} is hydrogen or halo;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

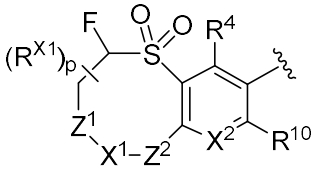


is a group of the following structure

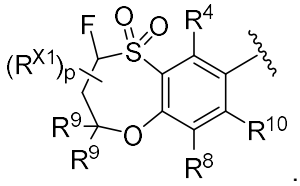


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3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

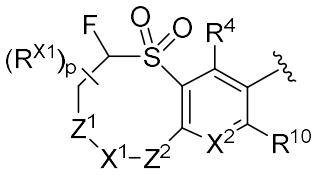


is a group of the following structure

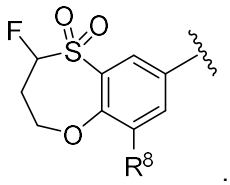


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4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein

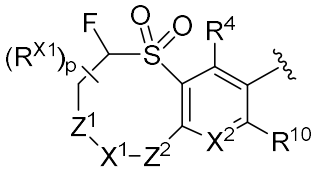


is a group of the following structure

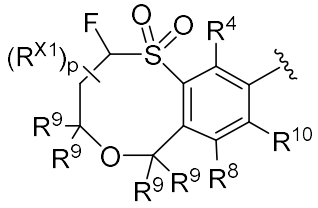


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5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

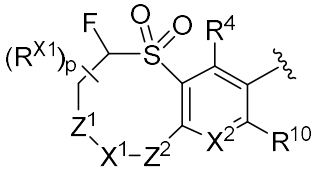


is a group of the following structure

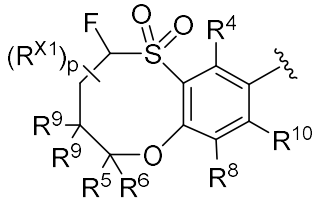


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6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein



is a group of the following structure



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7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^8 is hydrogen.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^8 is halo.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^8 is fluoro.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^8 is optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 heteroalkyl, or optionally substituted C_3-C_{10} cycloalkyl.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen or halogen.

12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{10} is hydrogen.

13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{10} is halogen.

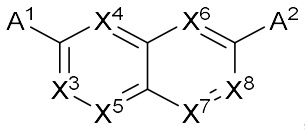
14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one R^{X1} is optionally substituted C_1-C_6 alkyl.

15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one R^{X1} is halo.

16. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one R^{X1} is deuterium.

17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^1 is optionally substituted 9- or 10-membered bicyclic heteroaryl.

18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^1 is



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Formula A

wherein

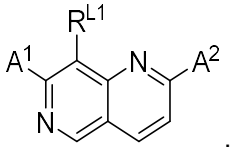
each of X^3, X^4, X^5, X^6, X^7, and X^8 is independently N or CR^{L1};

each R^{L1} is independently H, halo, optionally substituted C_1-C_6 alkyl;

A^1 is a bond to $–(C(R^2)(R^3))_m-$; and

A^2 is a bond to L^2.

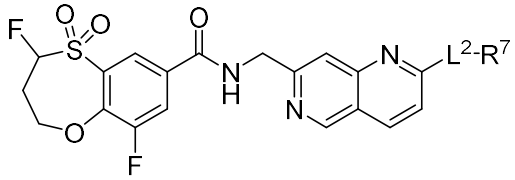
19. The compound of claim 18, or a pharmaceutically acceptable salt thereof, wherein L^1 is



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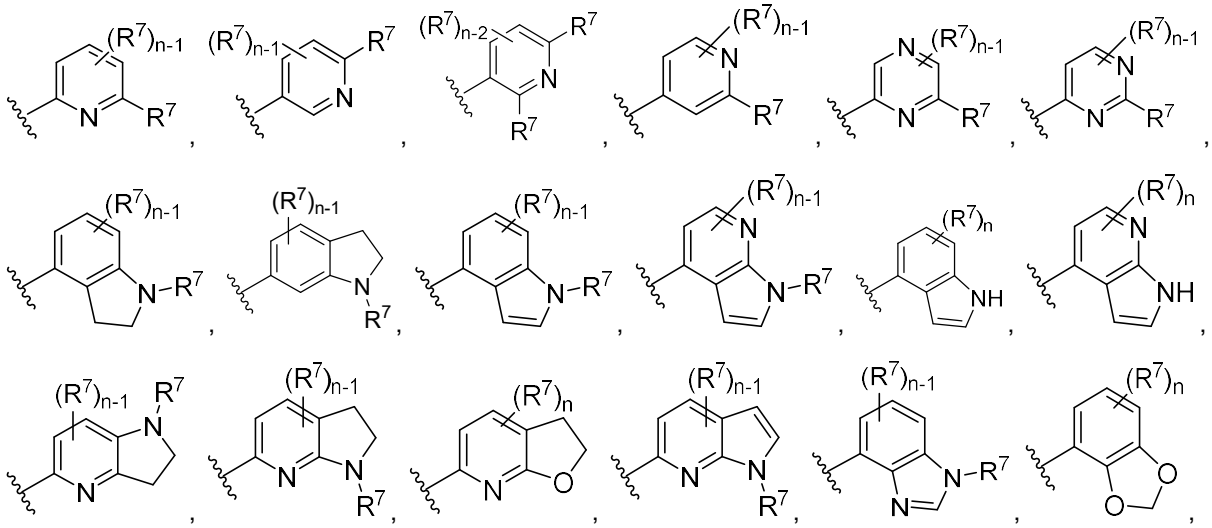
20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein R^{L1} is hydrogen.

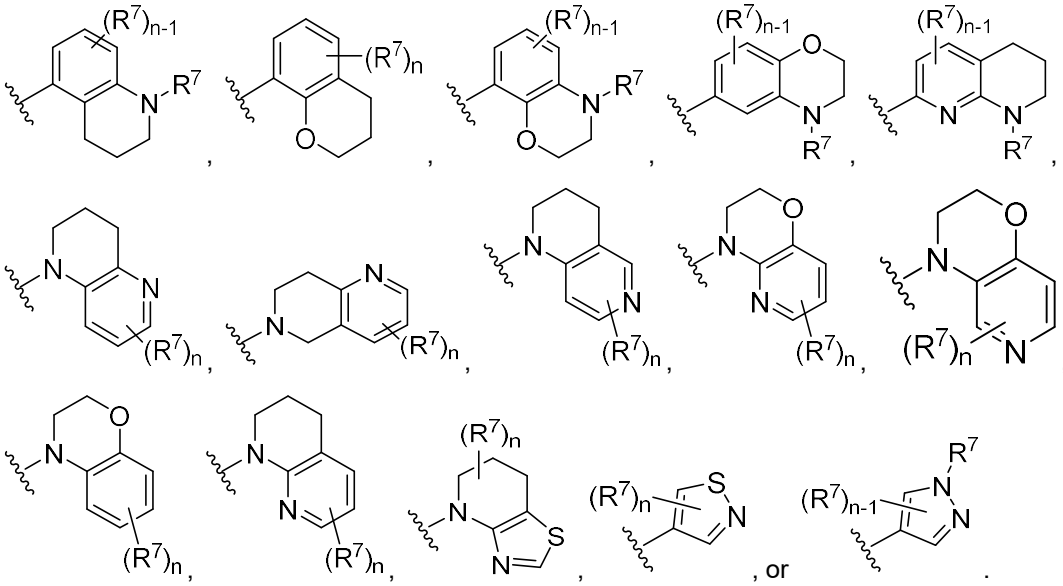
21. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:



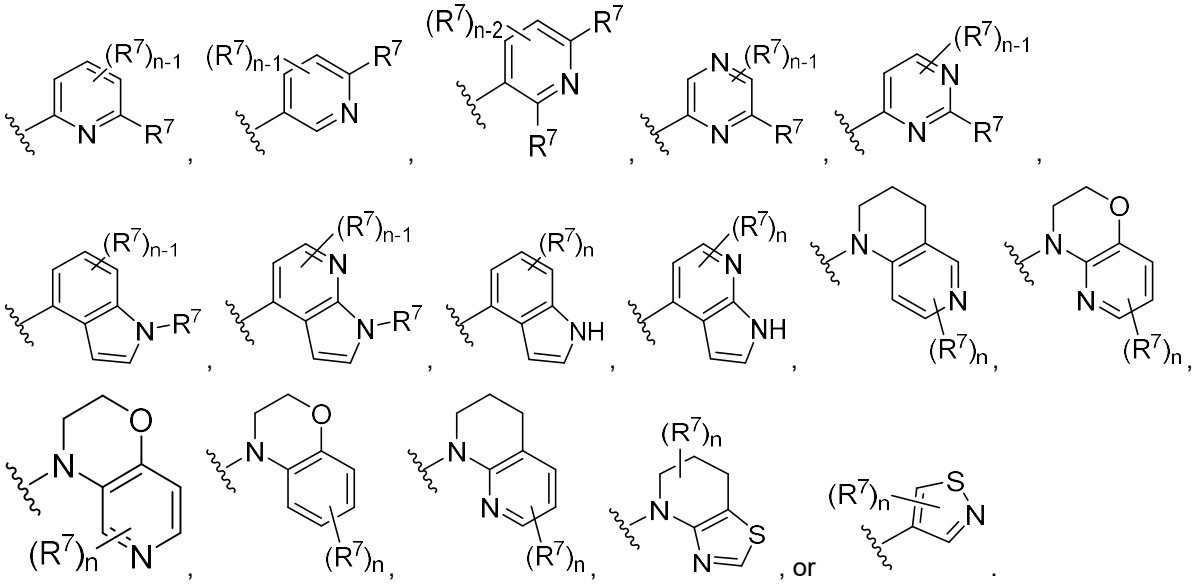
22. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^2 is optionally substituted 5- to 10-membered heteroaryl.

23. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein $-L^2-(R^7)_n$ is a group of the following structure:

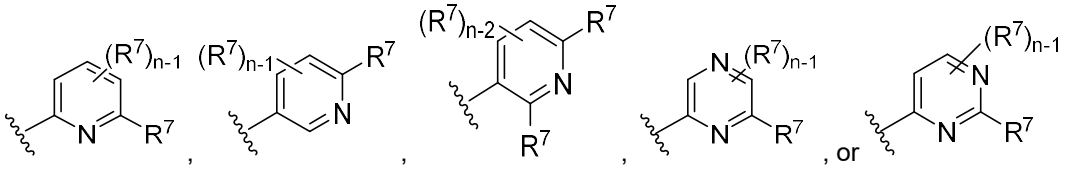


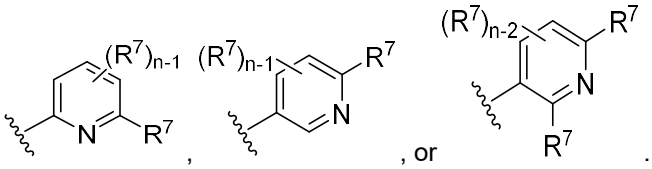


24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein $-L^2-(R^7)_n$ is a group of the following structure:

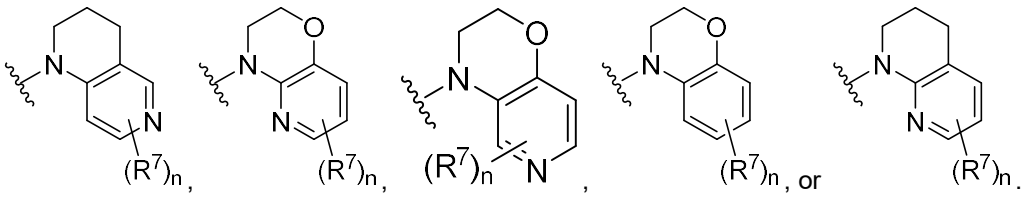


25. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein $-L^2-(R^7)_n$ is a group of the following structure:

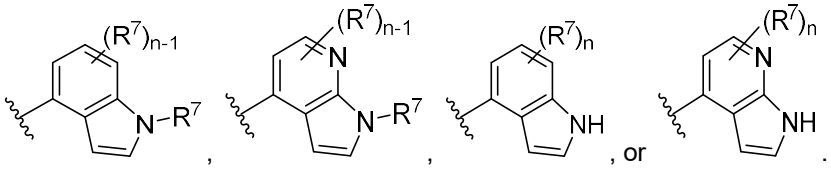


26. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein -L^2-$(R^7)_n$ is a group of the following structure: .

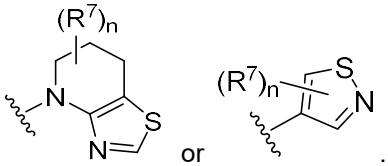
27. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein -L^2-$(R^7)_n$ is a group of the following structure:



28. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein -L^2-$(R^7)_n$ is a group of the following structure:



29. The compound of claim 24, or a pharmaceutically acceptable salt thereof, wherein -L^2-$(R^7)_n$ is a group of the following structure:

.

30. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L^2 is optionally substituted C_6-C_{10} aryl.

31. The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein L^2 is optionally substituted phenyl.

32. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 1.

33. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 2.

34. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 3.

35. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^7 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl.

36. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^7 is optionally substituted 4- to 10-membered heterocyclyl, wherein the heterocyclyl is optionally substituted azetidinyl or optionally substituted morpholinyl.

37. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^7 is optionally substituted C_3-C_{10} cycloalkyl wherein the cycloalkyl group is optionally substituted cyclopropyl or optionally substituted cyclobutyl.

38. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein two *geminal* R^7 groups, together with the atom to which they are attached, combine to form optionally substituted 4- to 10-membered heterocyclyl.

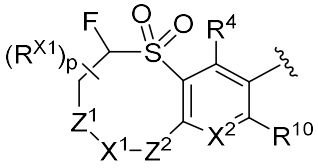
39. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one R^7 is $-OR^{7A}$, wherein R^{7A} is optionally substituted C_{1-6} alkyl.

40. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein at least one R^7 is difluoromethyl, cyclopropyl, 2,2-difluorocyclopropyl, difluoromethoxy, 2,6-dimethylmorpholin-4-yl, N-azetidinyl, 3-fluorocyclobutyl, 2-methoxyethyl, ethoxy, methoxy, 2,2-difluoroethoxy, 2,2-difluoroethyl, trifluoromethyl, isopropyl, methyl, acetyl, fluoro, chloro, 1-methylpyrazol-3-yl, dimethylamino, N-methyl-N-(2-methoxyethyl)-amino, N-ethyl-N-(2-methoxyethyl)-amino, N-(2-propyl)-N-(2-methoxyethyl)-amino, 2-methoxyethylamino, 3-aza-8-oxa-bicyclo[4.3.0]non-3-yl, 3-aza-7-oxa-bicyclo[4.3.0]non-3-yl, 1-fluorocyclobut-1-yl, 3-fluoropyrrolidin-1-yl, 3-methoxypyrrolidin-1-yl, oxetan-3-yl, N-methylindolin-4-yl, 2,2-difluoro-3-methylcycloprop-1-yl, 3-methoxyazetidin-1-yl, 3-methoxypiperidin-1-yl, 1,2-dimethyl-7-azaindol-4-yl, 1-methyl-7-azaindol-4-yl, 2,3-methylenedioxyphenyl, N-methyl-N-(3-oxetanyl)amino, 3-oxetanyloxy, 1,1-difluoro-5-azaspiro[2.3]hex-5-yl, 1-fluoromethyl-cyclopropyl, N-(3-tetrahydrofuranyl)methylamino, N-indolinyl, N-1,4-oxazepanyl, 2-fluoro-2-propyl, 1,1-difluoro-2-propyl, 2,2-difluoro-1-methylcycloprop-1-yl, 1-methylcyclopropyl, 4,4-difluoropiperidin-1-yl, 2-methoxyethoxy, 3,3-difluorocyclobut-1-yl, N-methyl-N-1-methoxyprop-2-ylamino, 1-methoxyprop-2-ylamino, 1-methoxyethyl, 4-methylpiperazinyl, 3-methylmorpholinyl, 2,2-difluoropropoxy, 3-methoxycyclobutyl, methylamino, 4-dimethylamino-3,3-difluoropiperidinyl, 4-methylamino-3,3-difluoropiperidinyl, 3,3-difluoropyrrolidinyl, N-methyl-N-3-

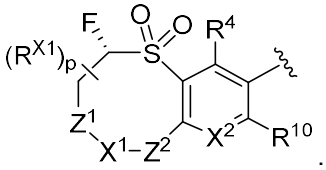
methoxycyclobutylamino, 1-methylpyrazol-5-yl, 6-oxa-3-azabicyclo[3.1.1]hept-3-yl, cyclopropyloxy, 2,6-dimethylpyrid-4-yl, 2-methylpyrrolidinyl, 4-oxabicyclo[4.1.0]hept-1-yl, N-methyl-N-(2,6-dimethyltetrahydropyran-4-yl)amino, or N-methyl-N-3-methyloxetan-3-ylmethylamino.

41. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

42. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

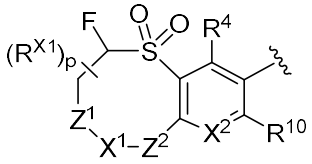


is a group of the following structure

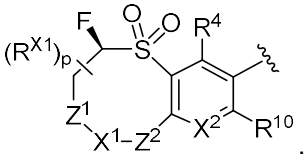


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43. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

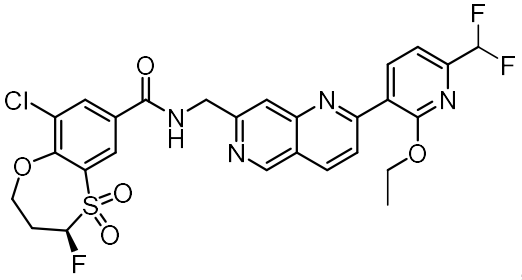


is a group of the following structure

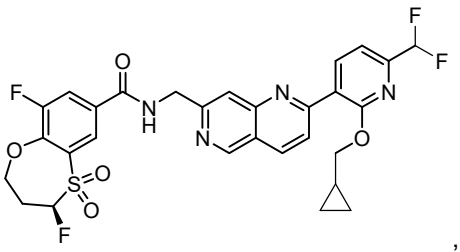


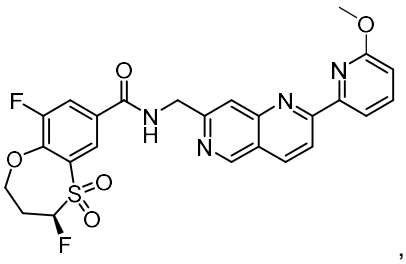
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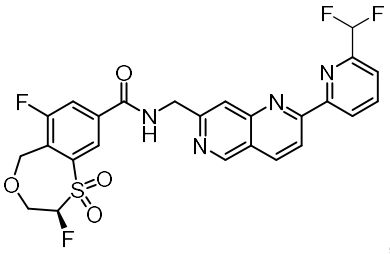
44. A compound selected from the group consisting of

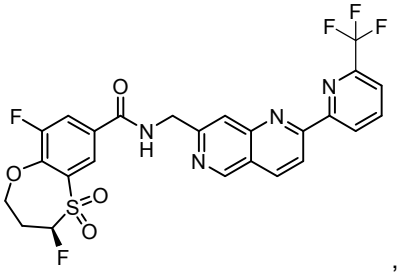


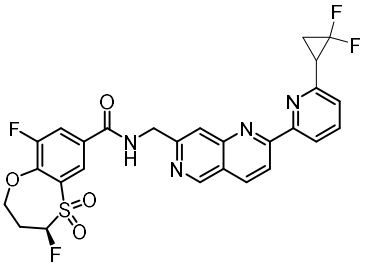
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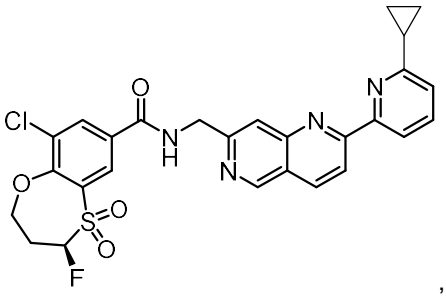

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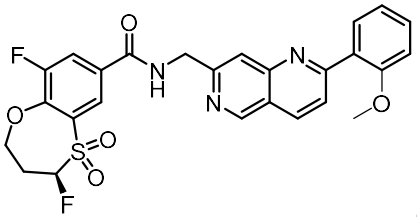

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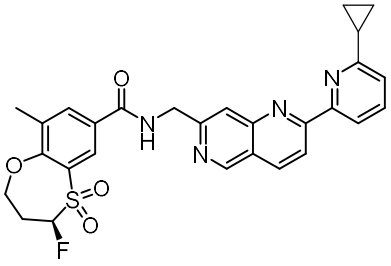

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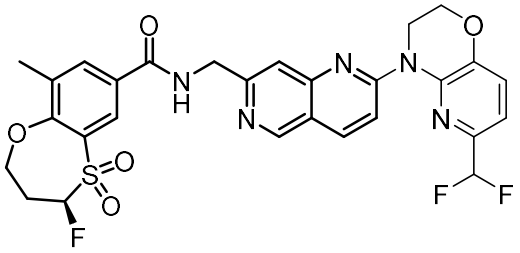
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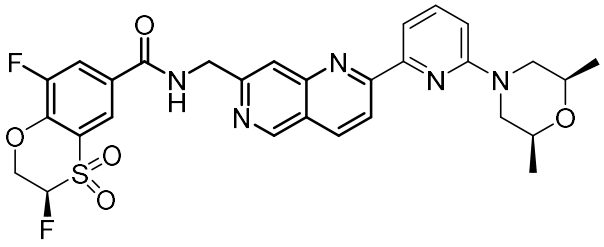
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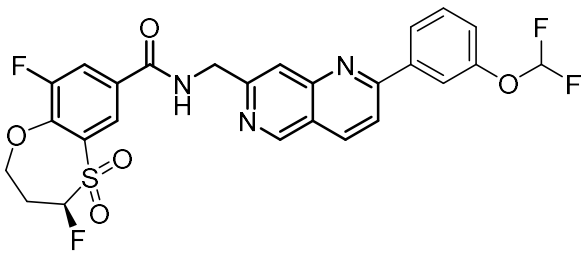
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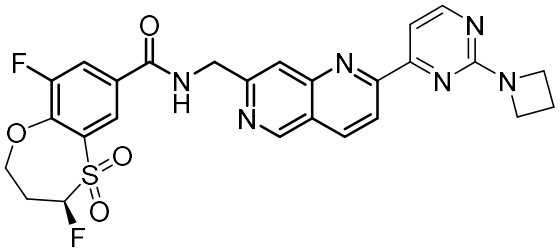
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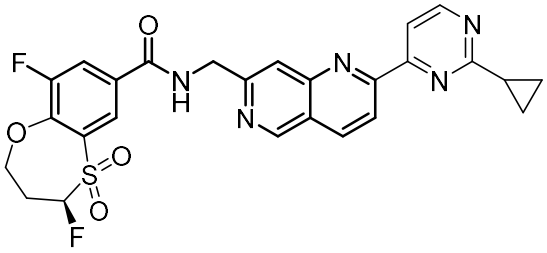
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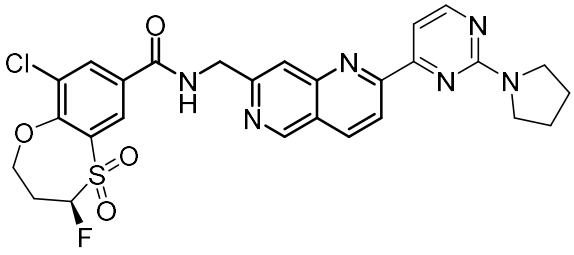
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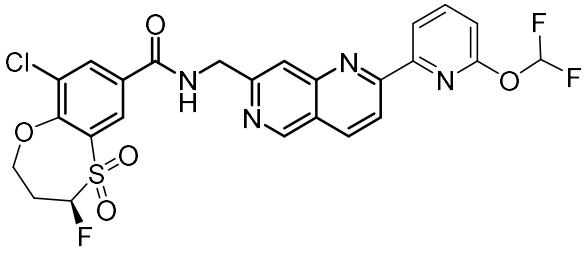
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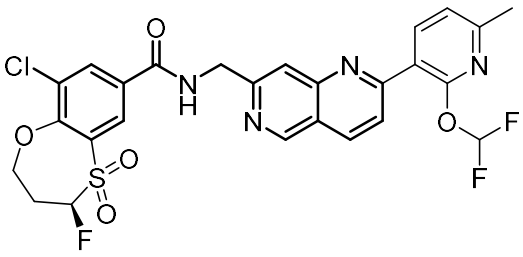
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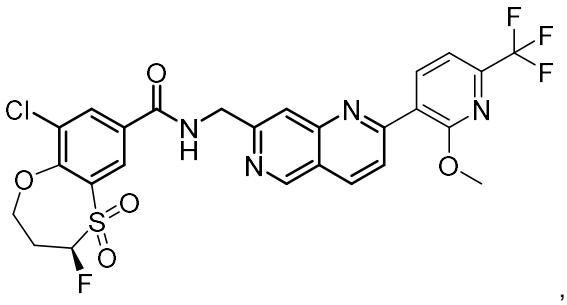
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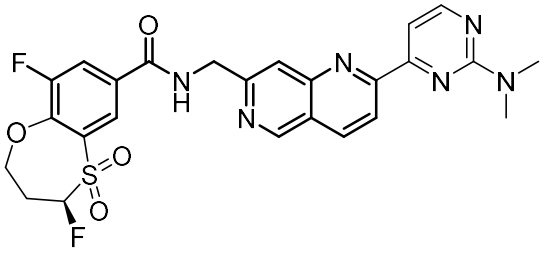
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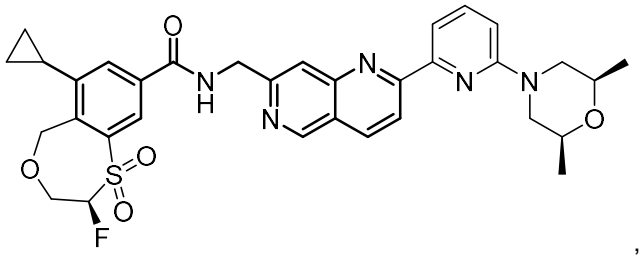
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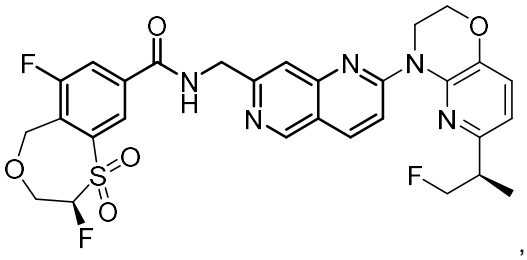
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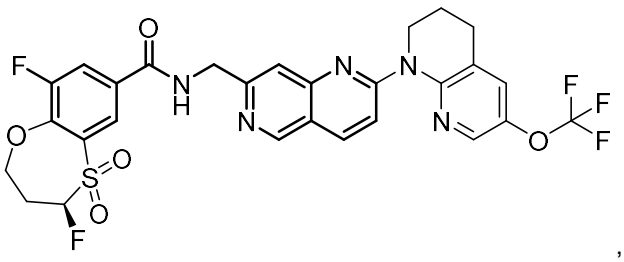
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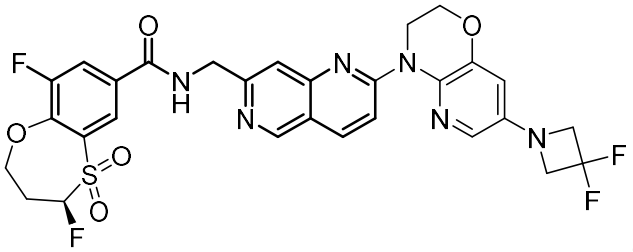
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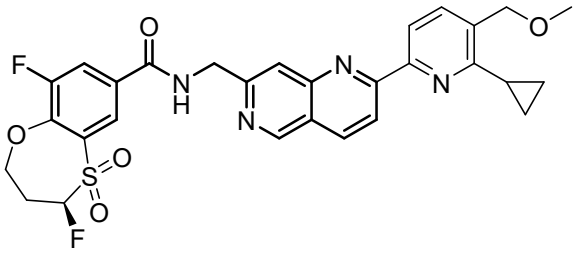
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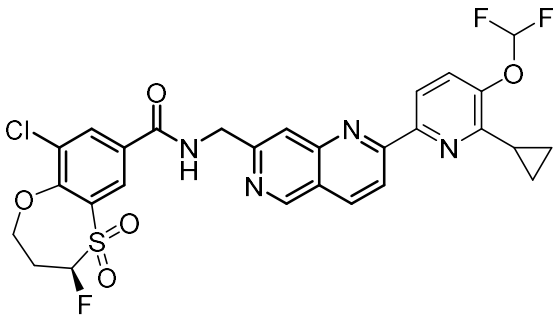
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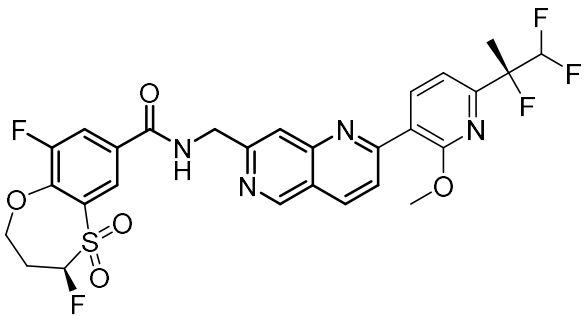
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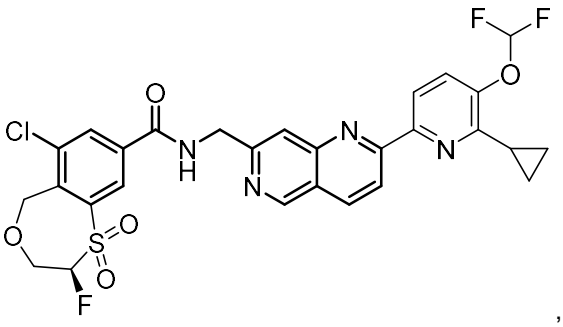
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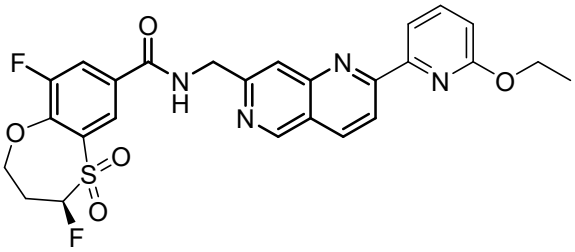
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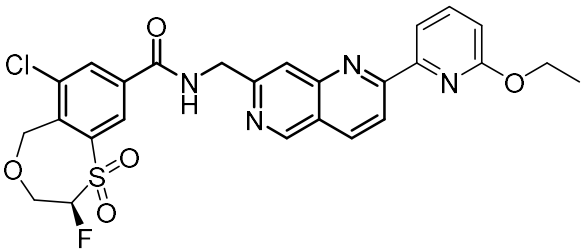
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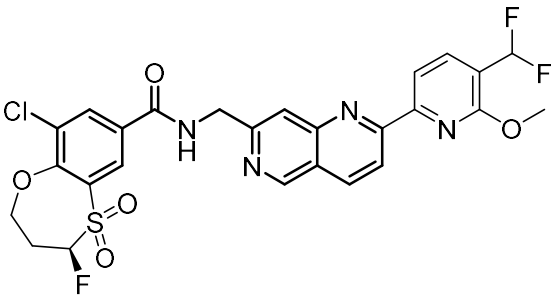
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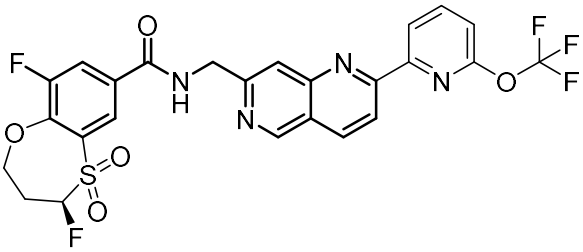
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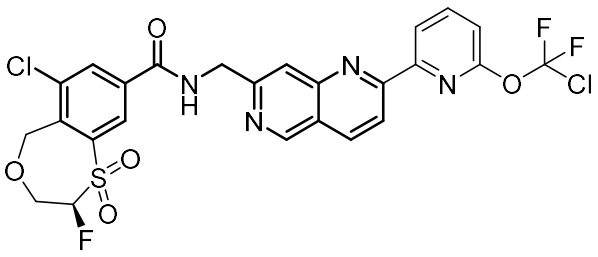
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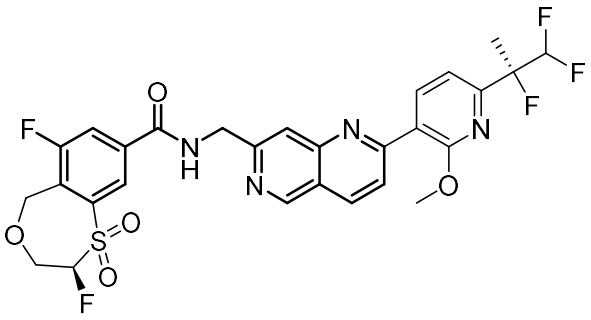
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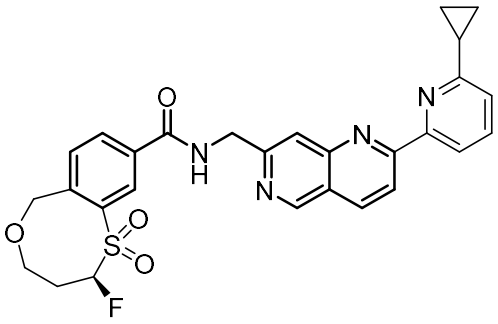
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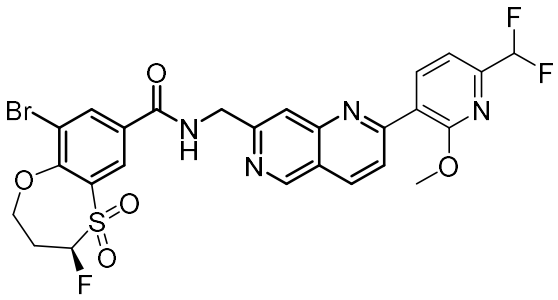
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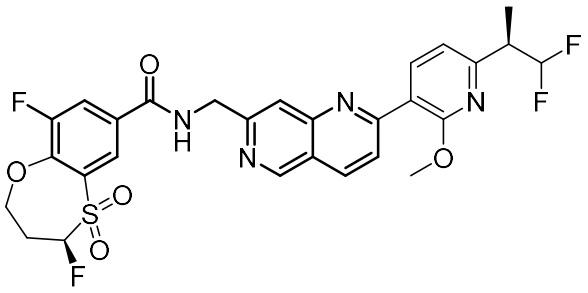
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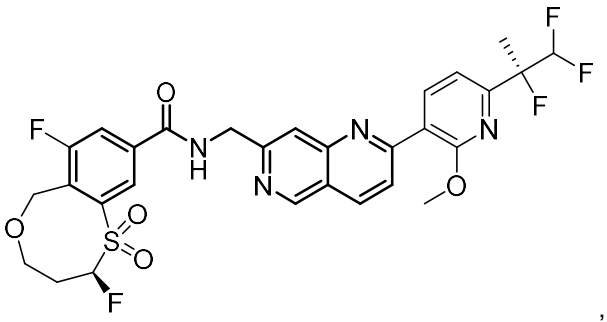
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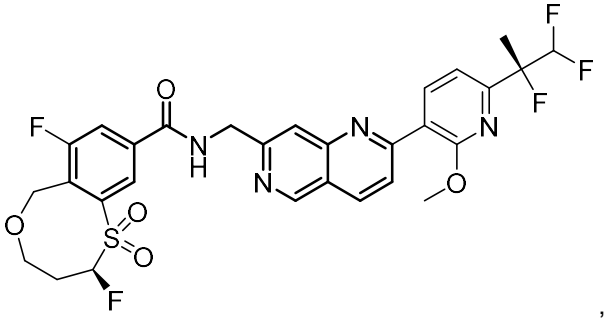
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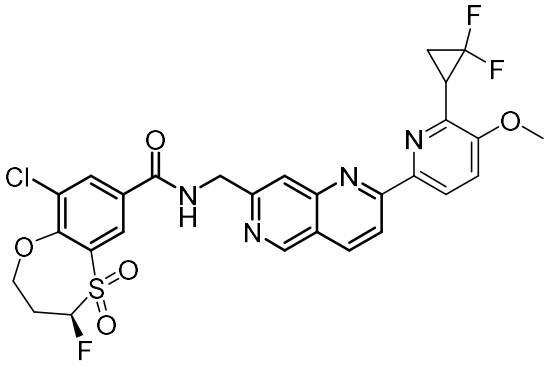
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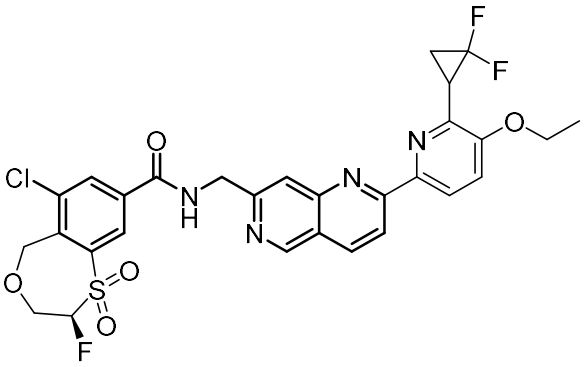
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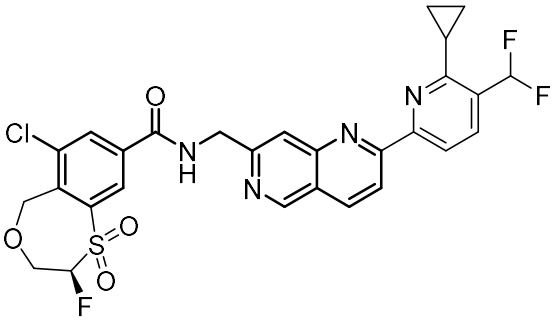
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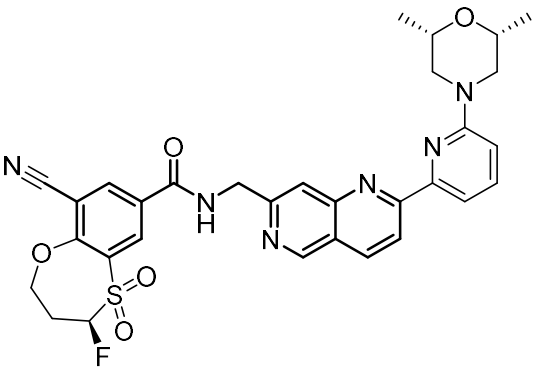
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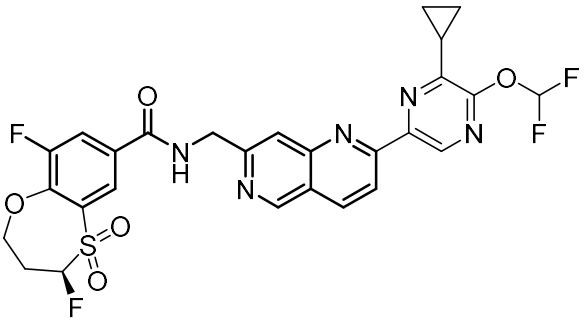
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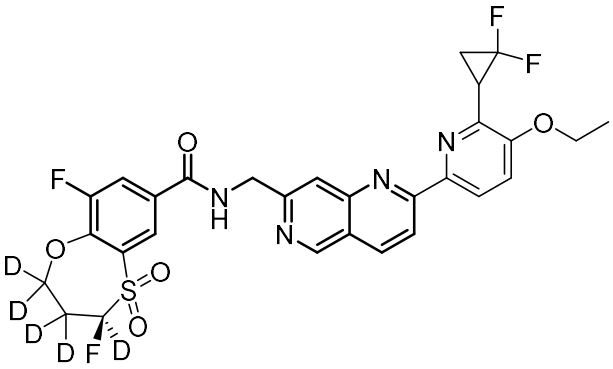
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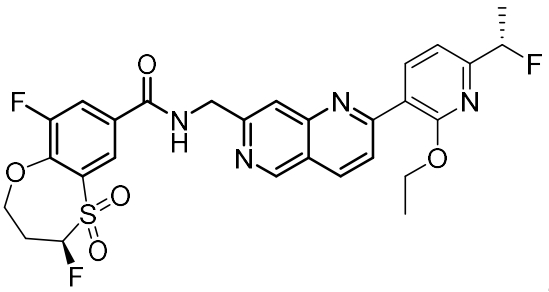
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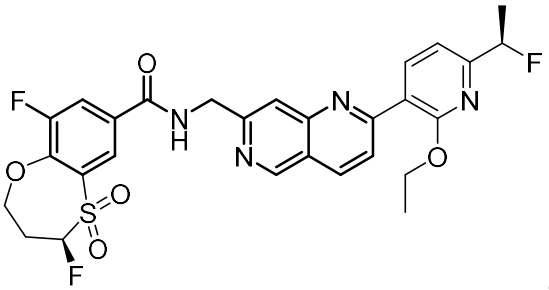
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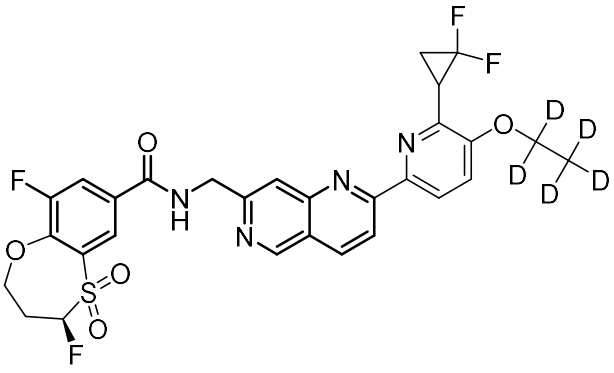
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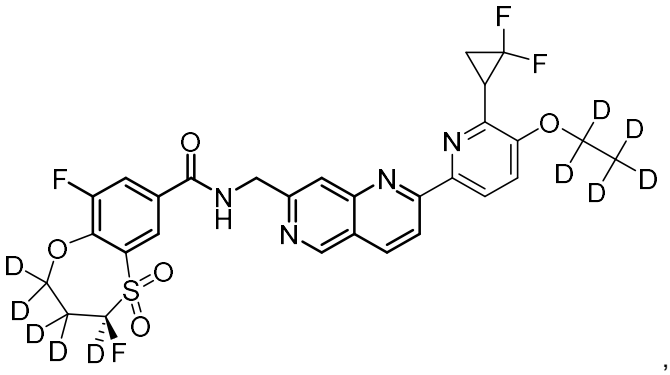
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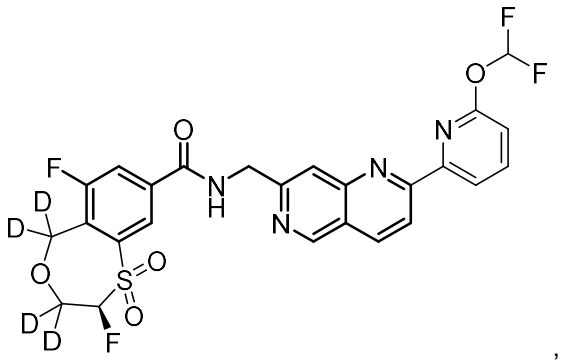
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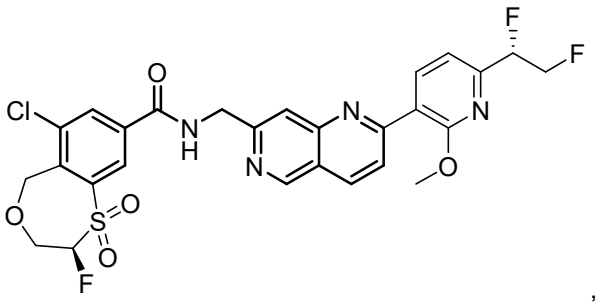
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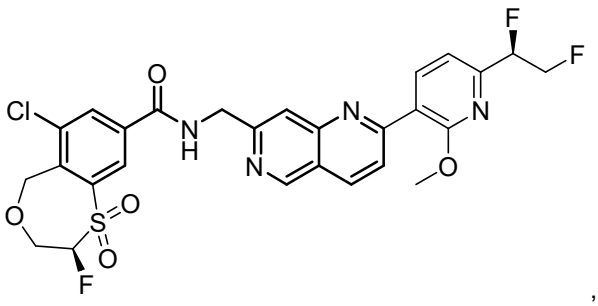
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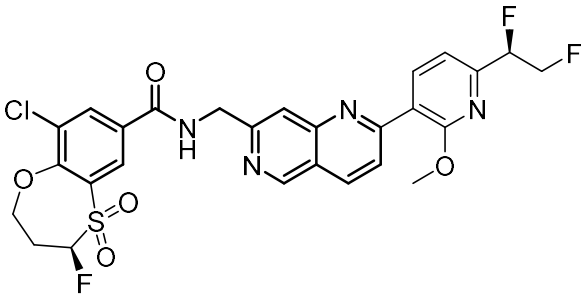
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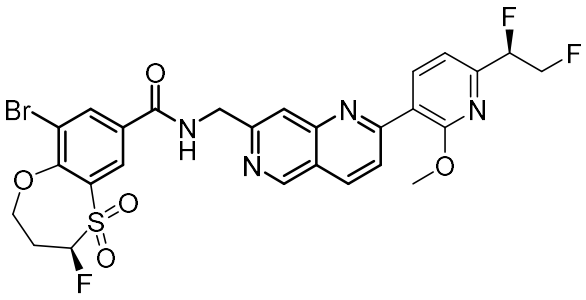
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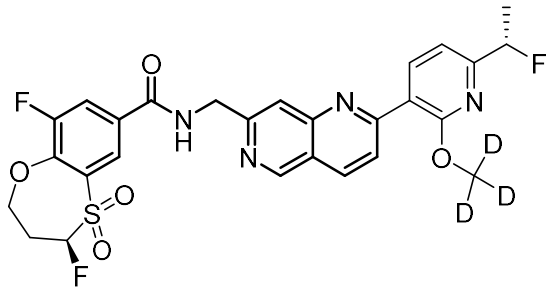
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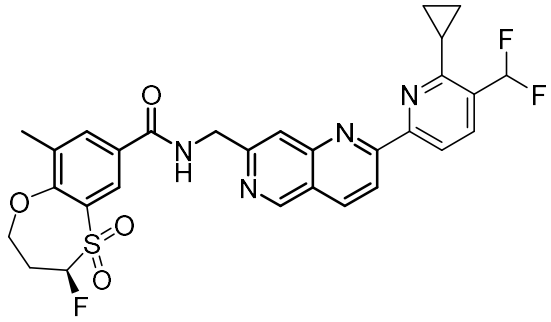
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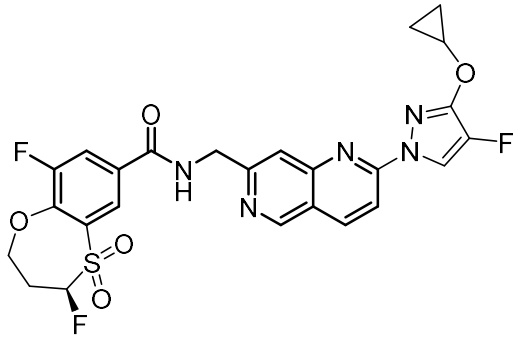
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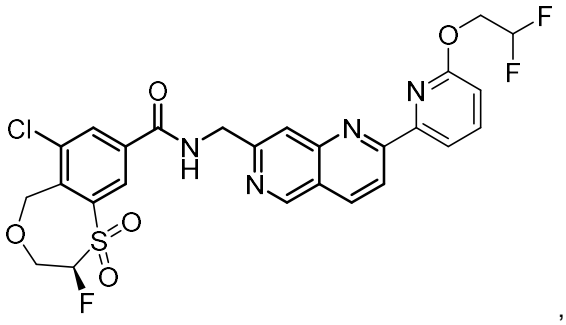
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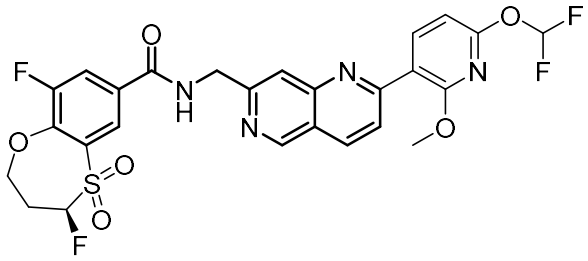
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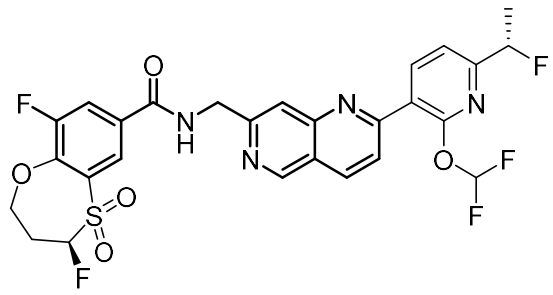
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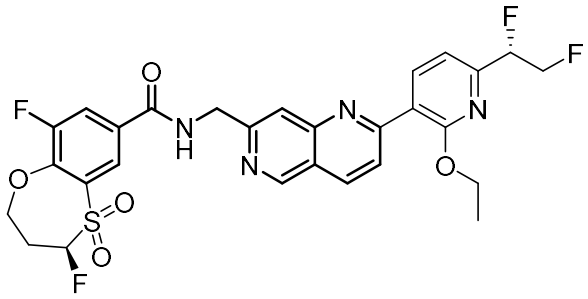
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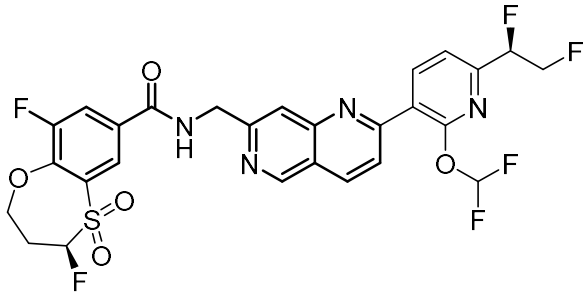
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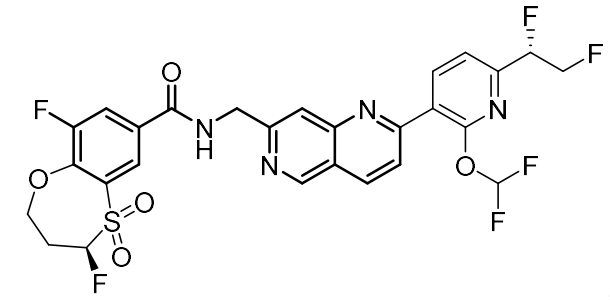
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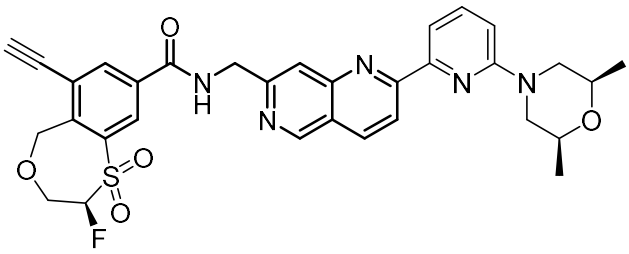
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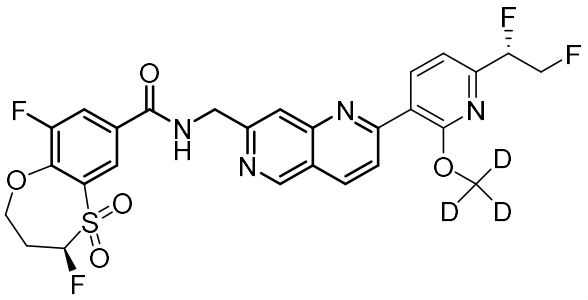
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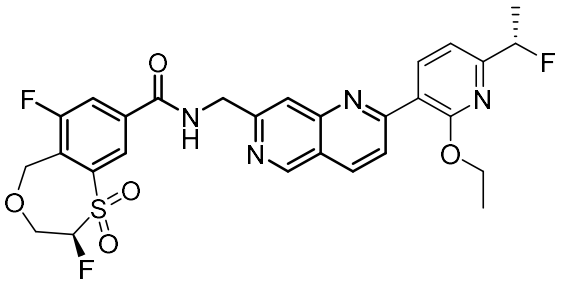
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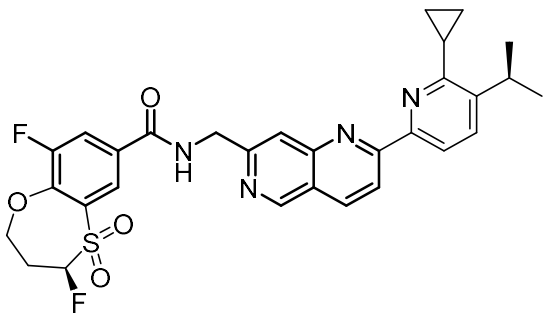
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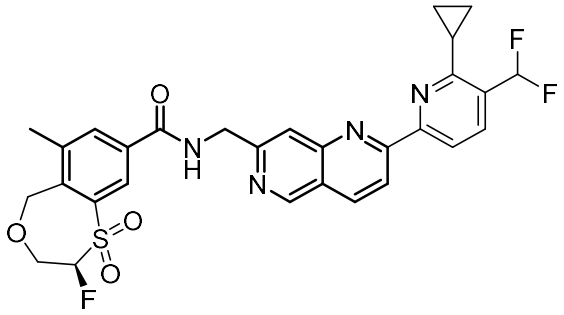
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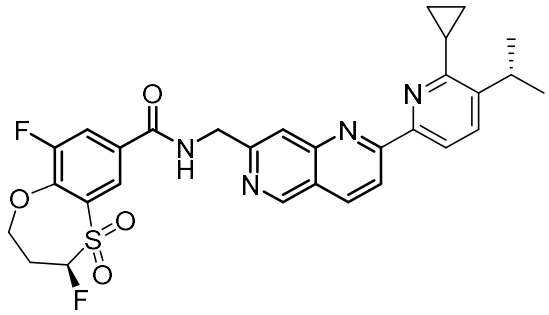
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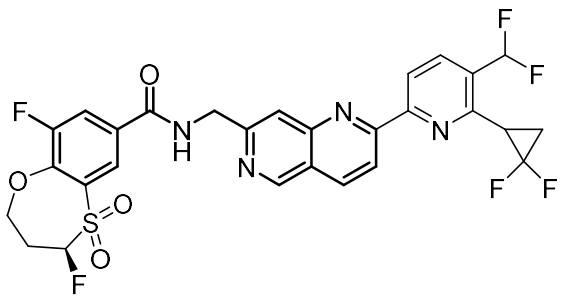
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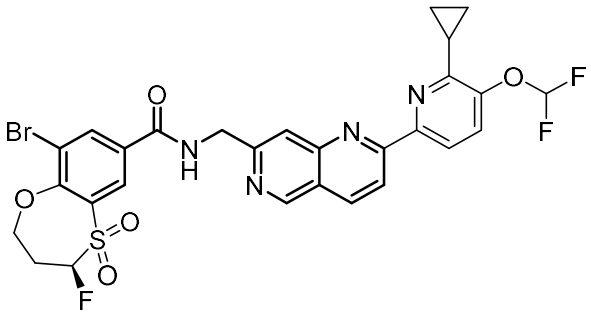
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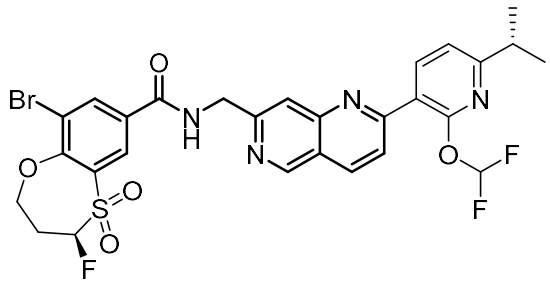
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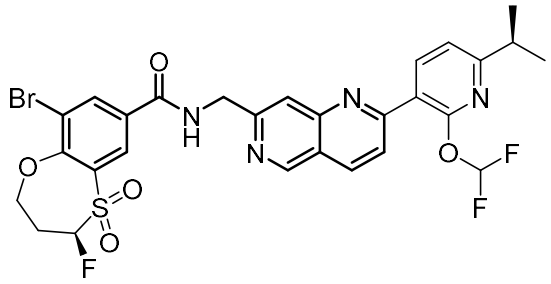
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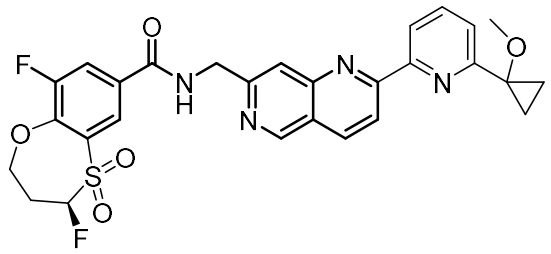
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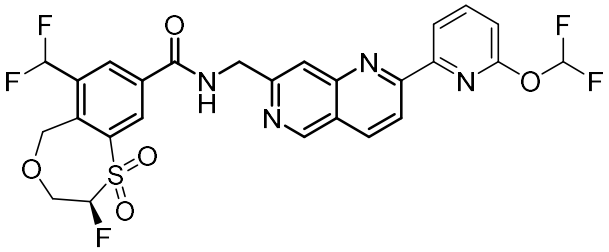
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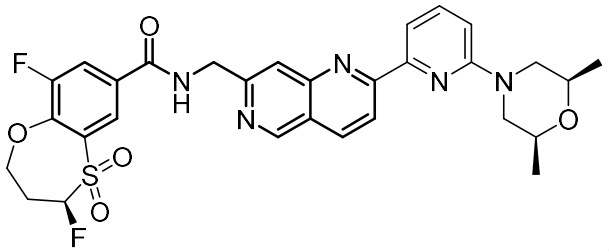
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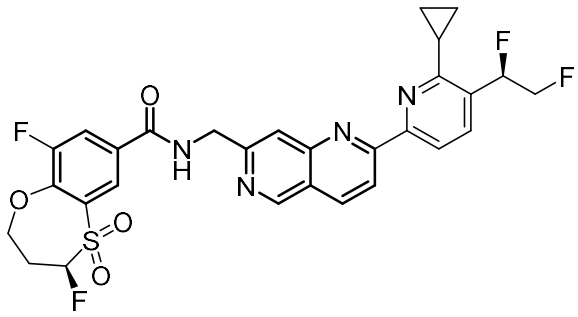
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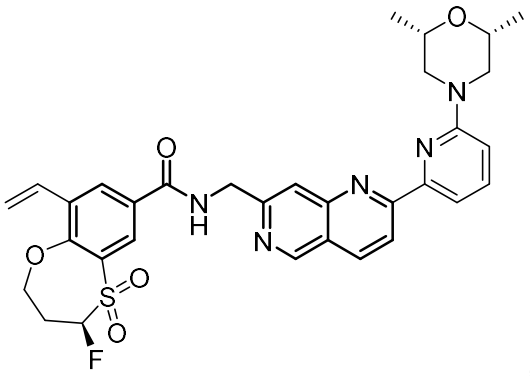
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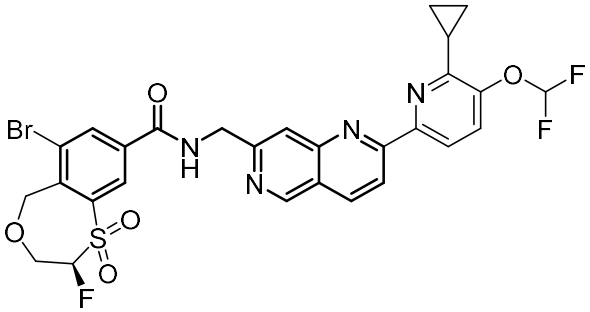
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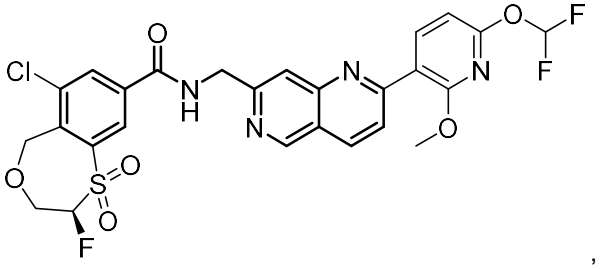
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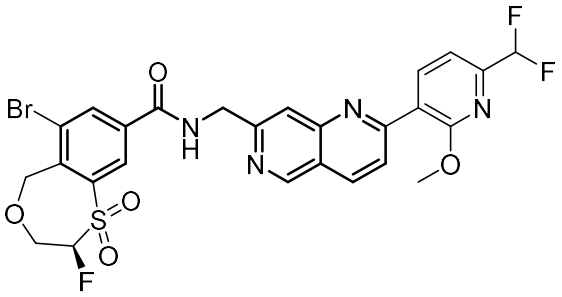
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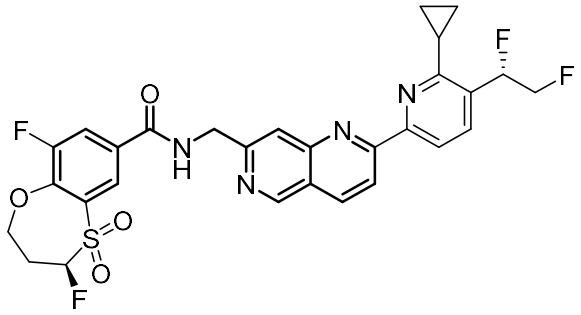
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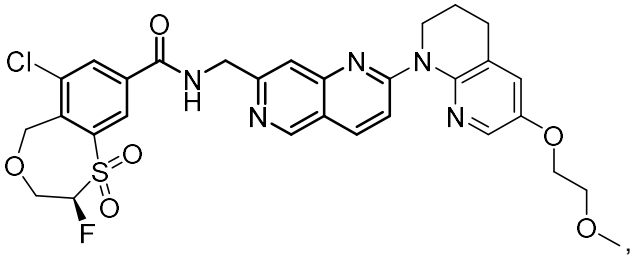
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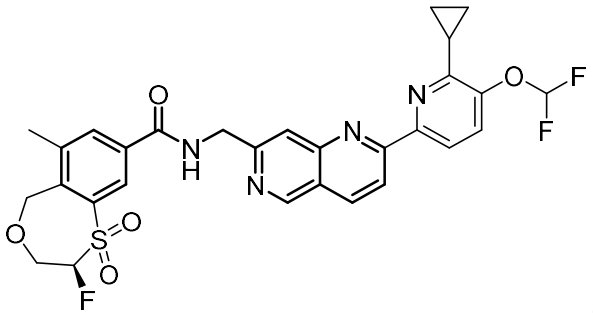
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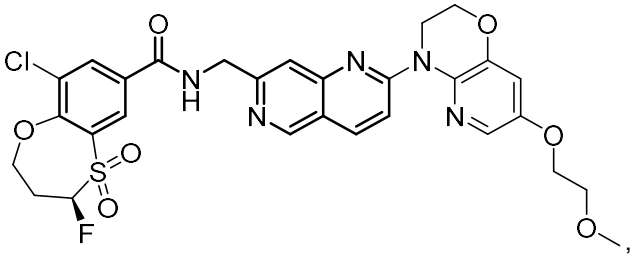
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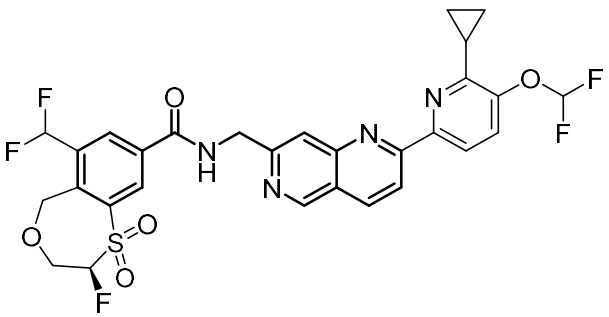
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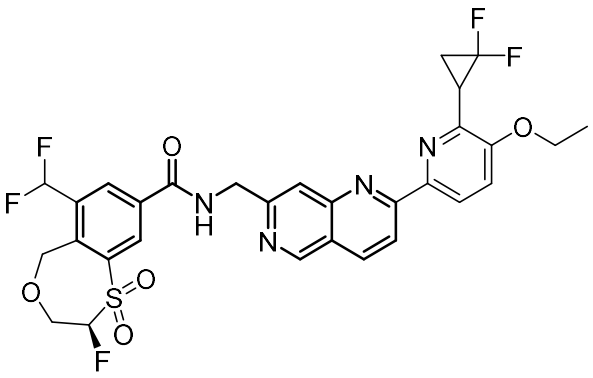
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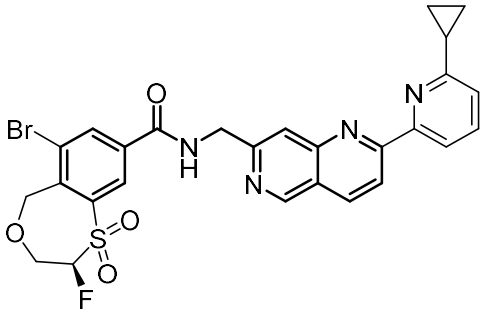
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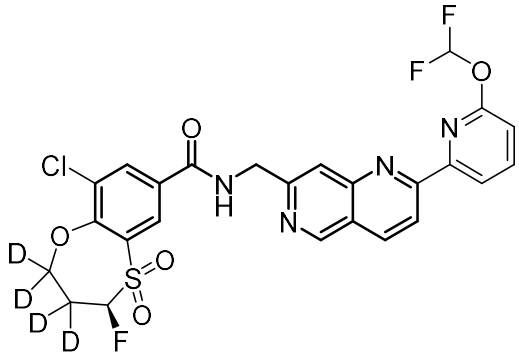
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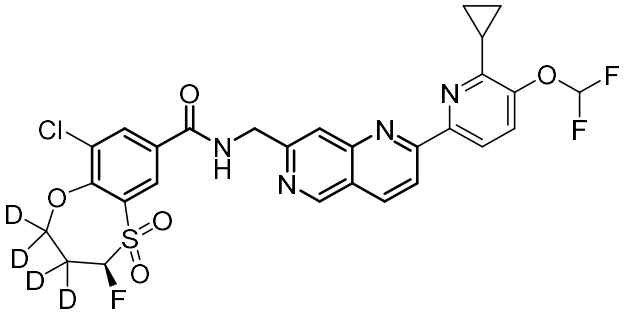
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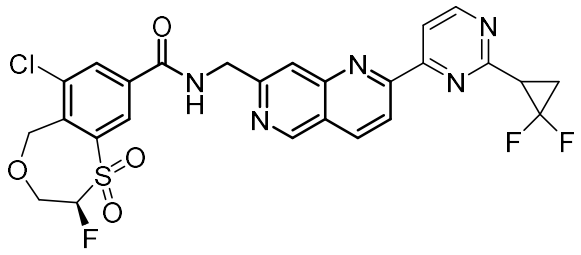
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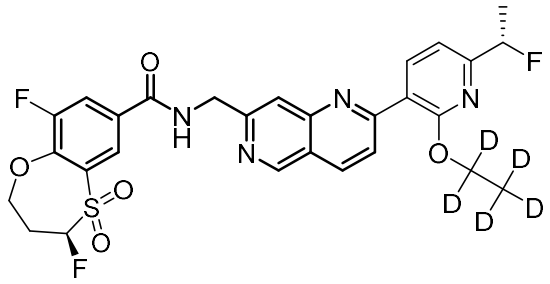
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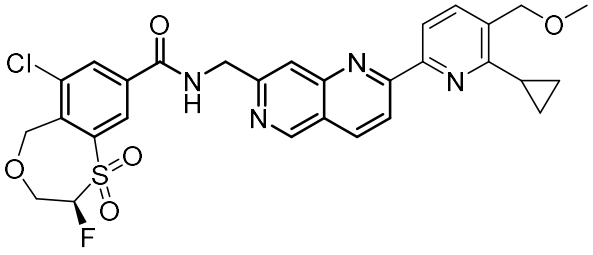
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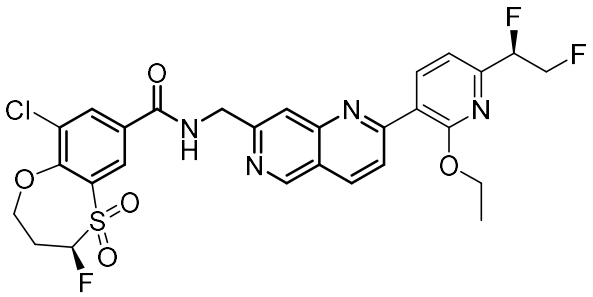
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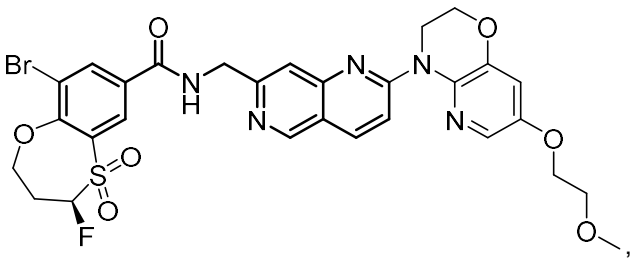
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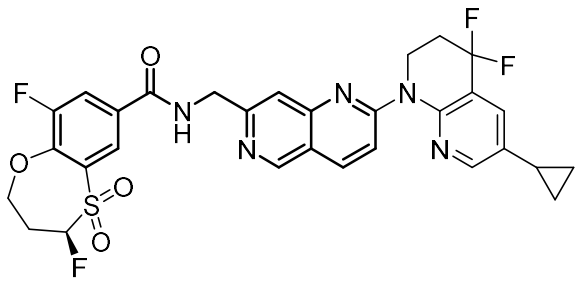
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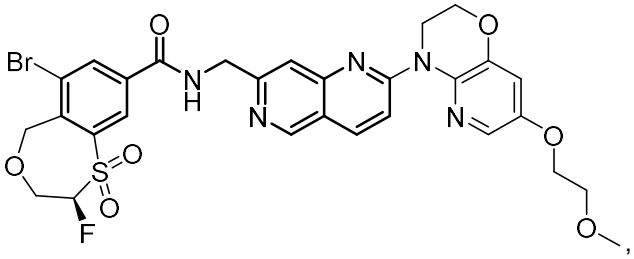
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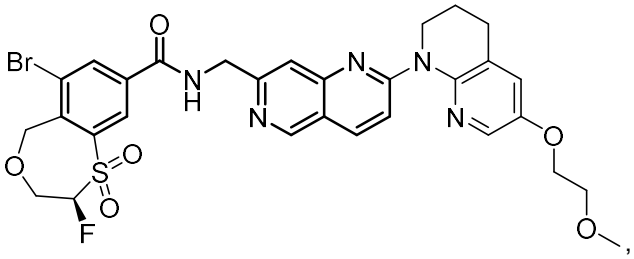
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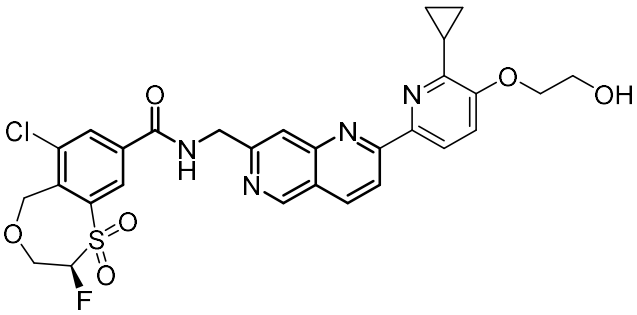
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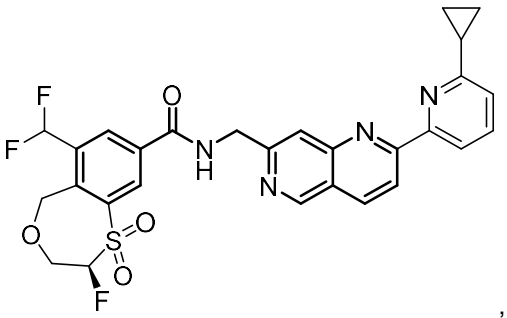
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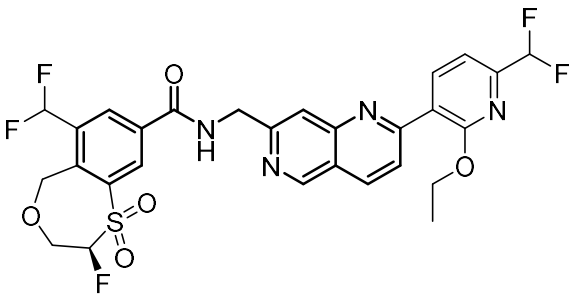
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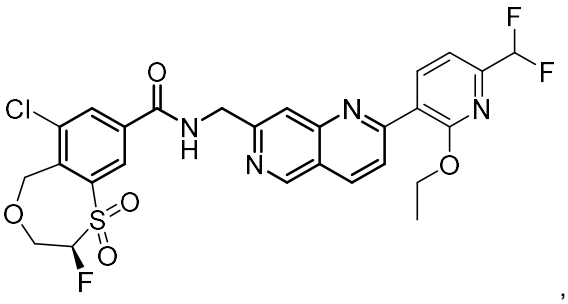
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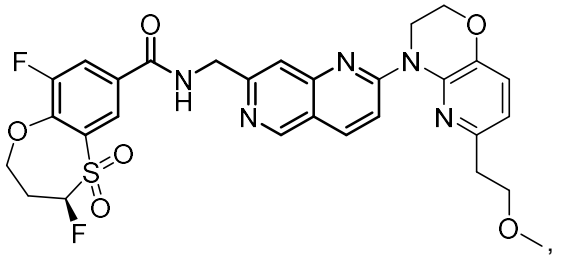
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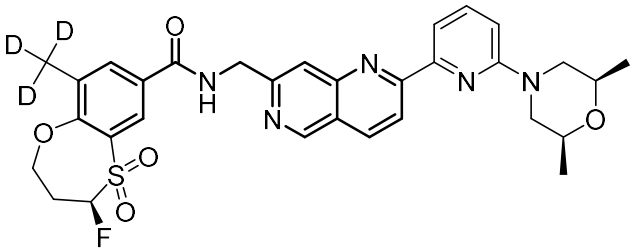
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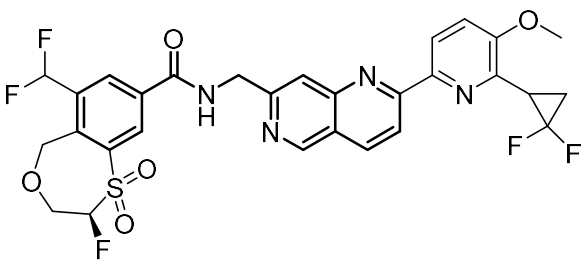
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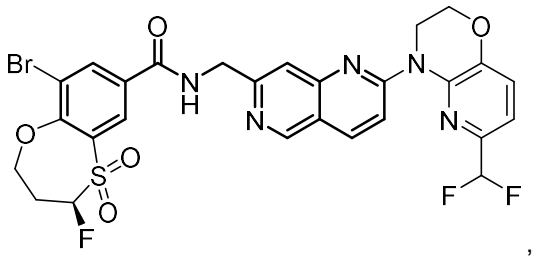
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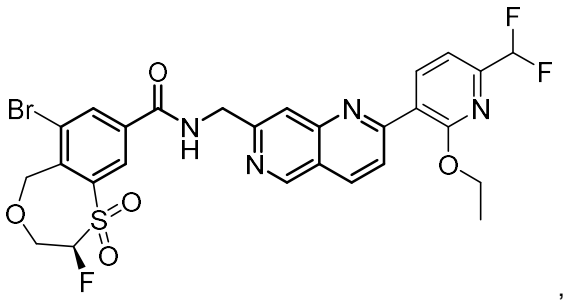
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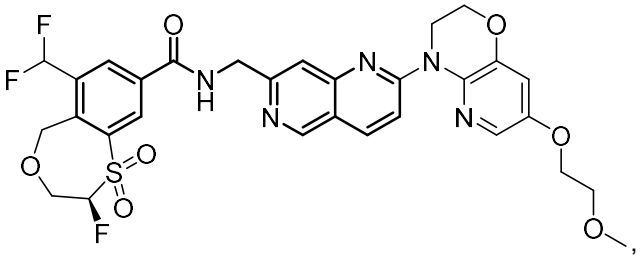
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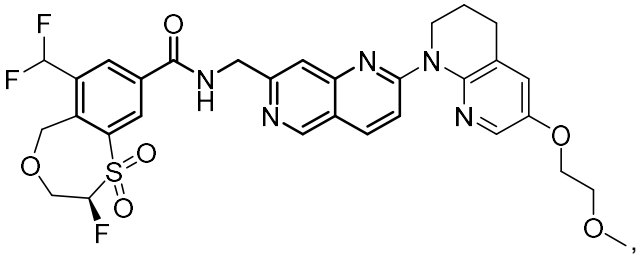
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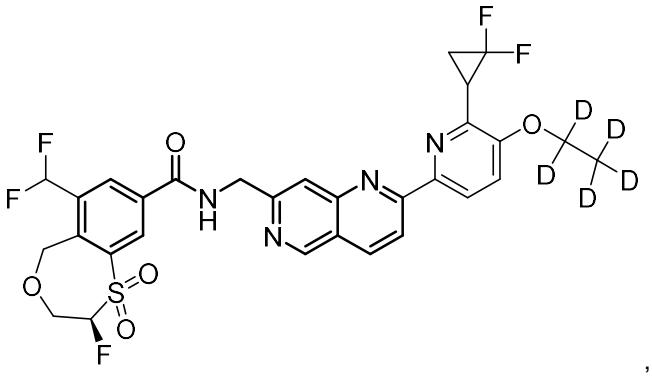
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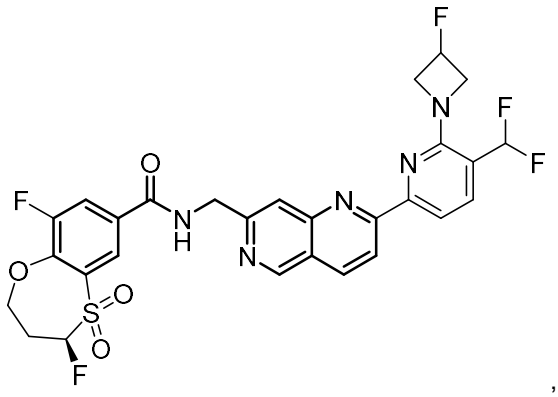
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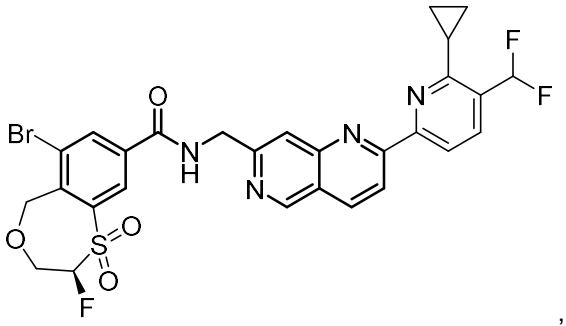
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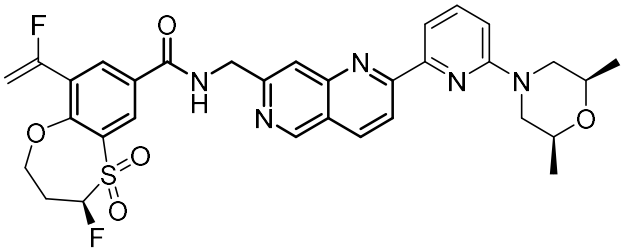
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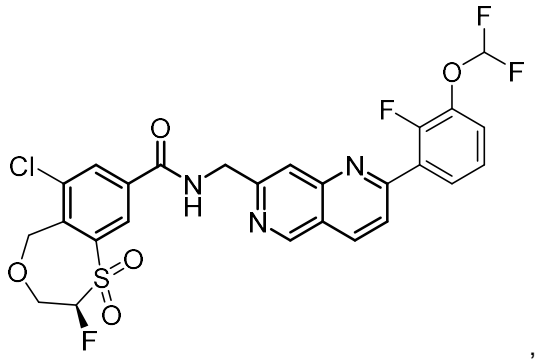
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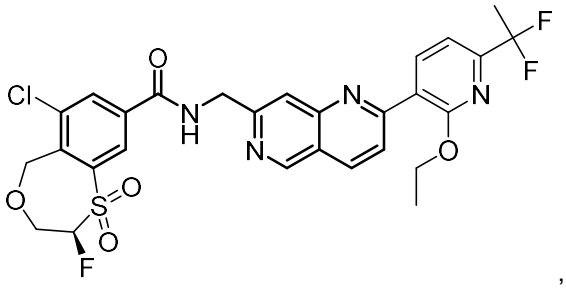
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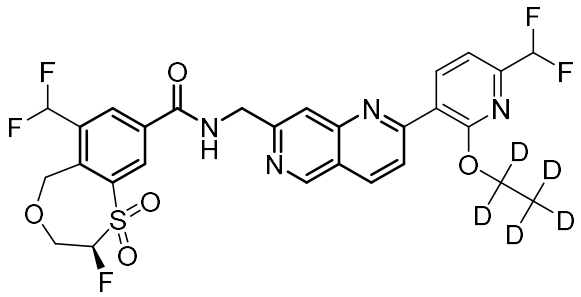
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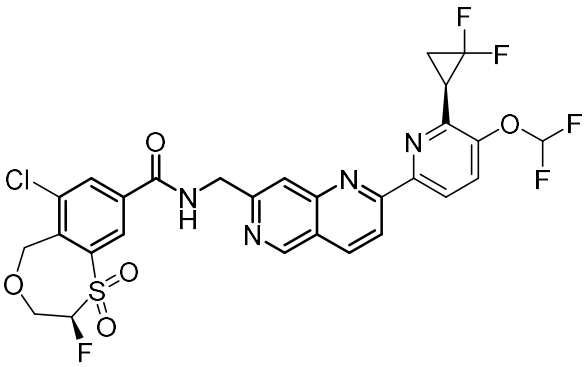
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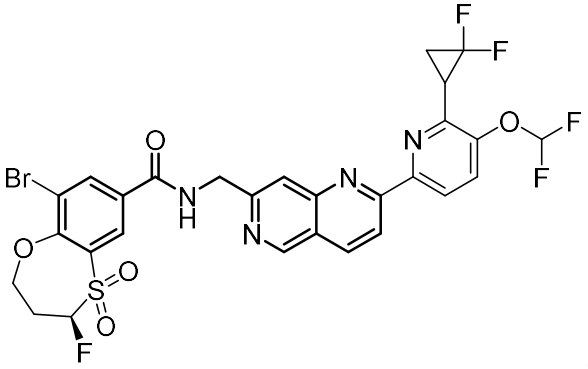
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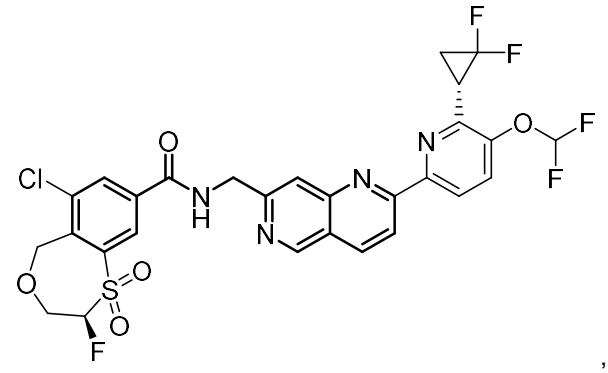
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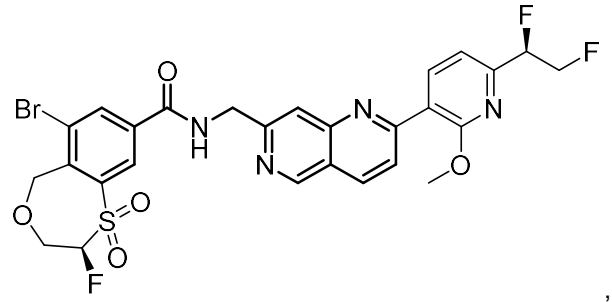
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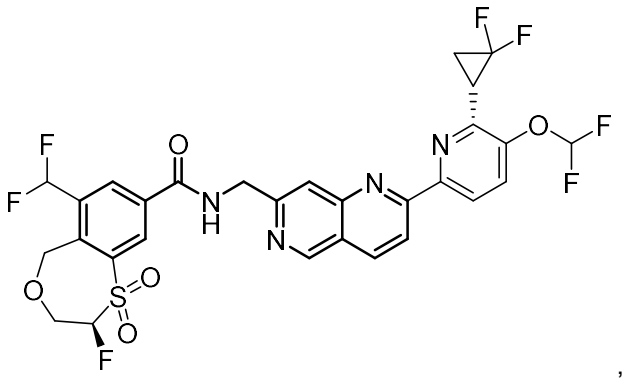
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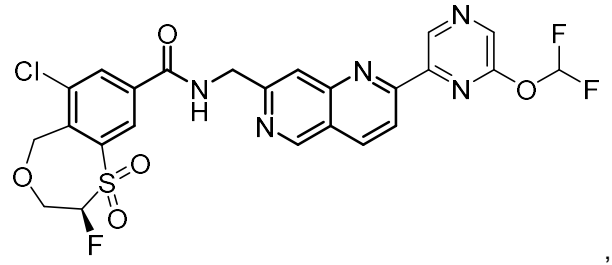
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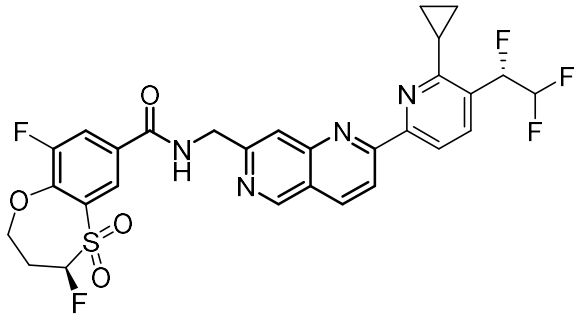
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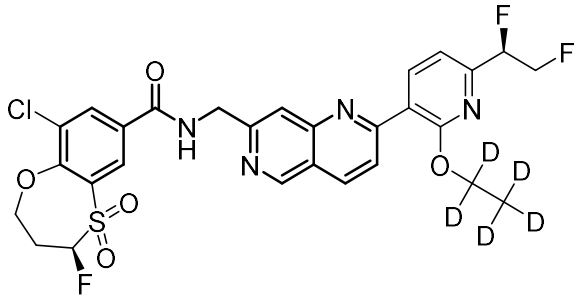
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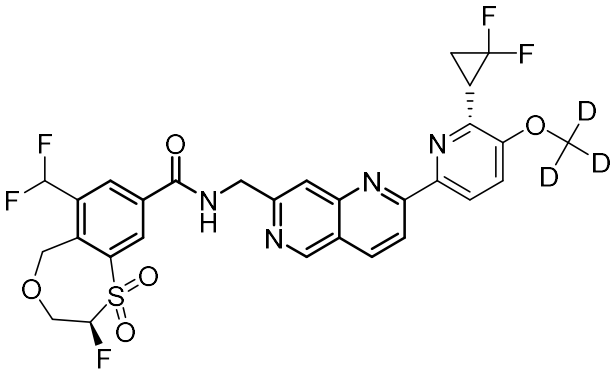
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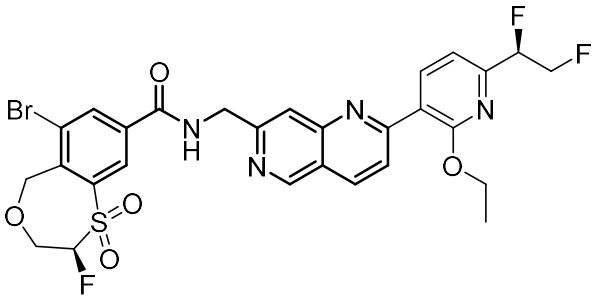
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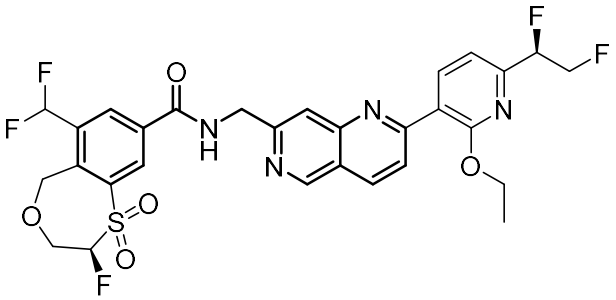
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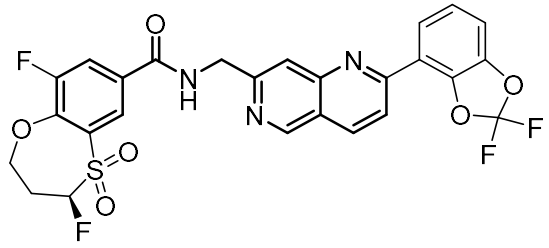
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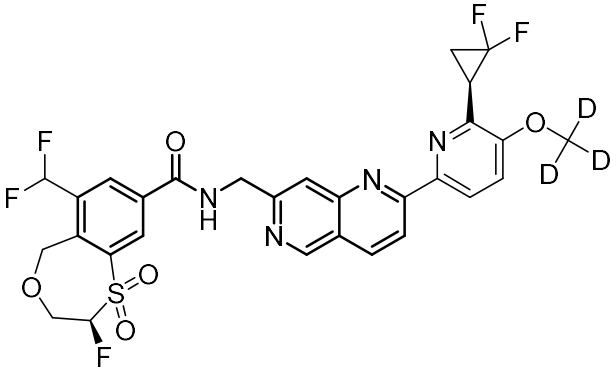
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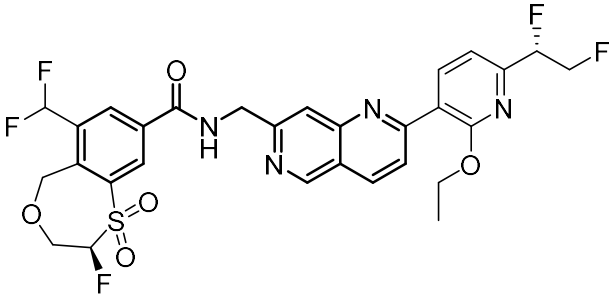
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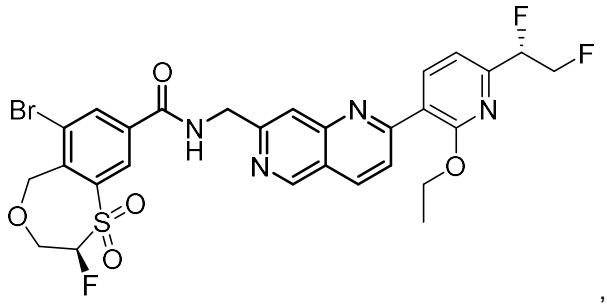
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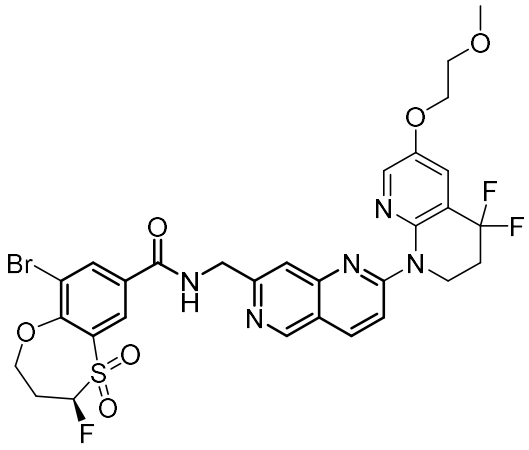
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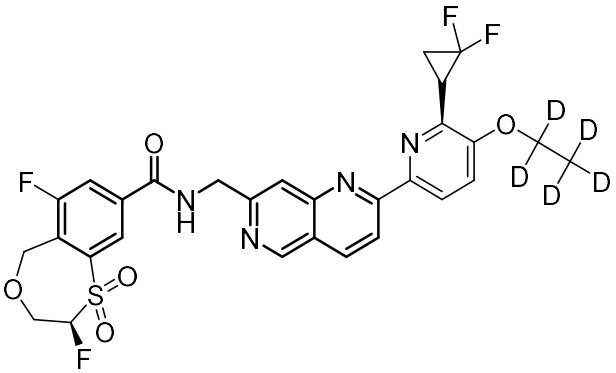
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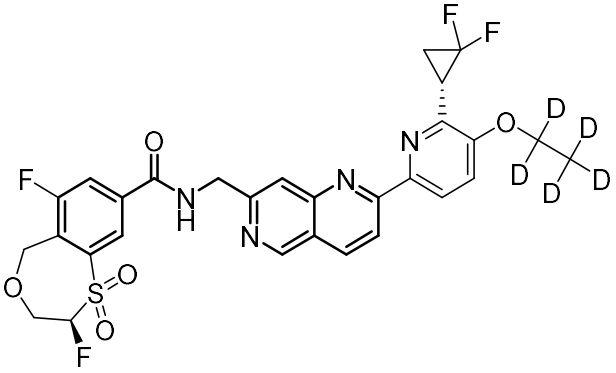
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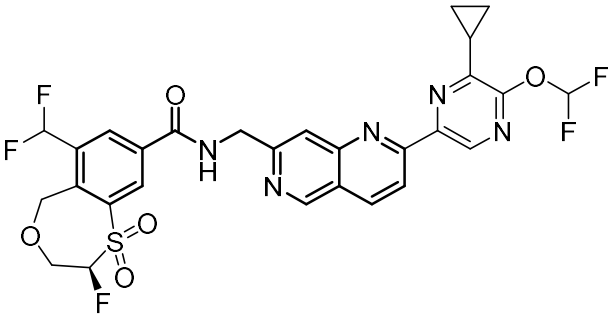
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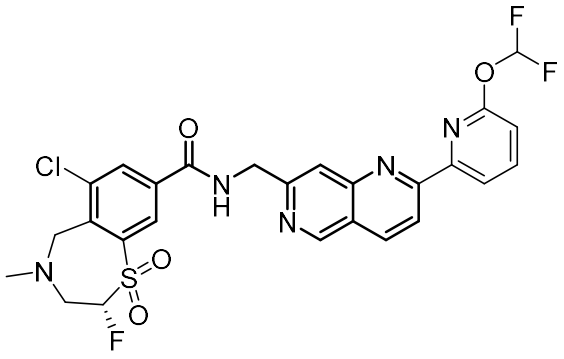
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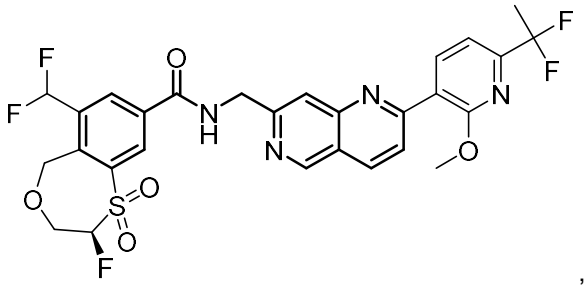
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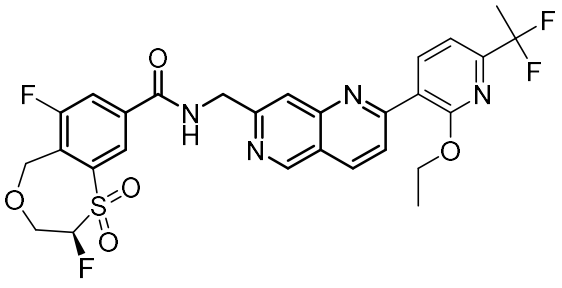
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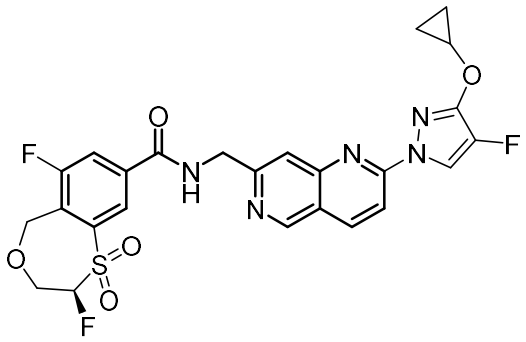
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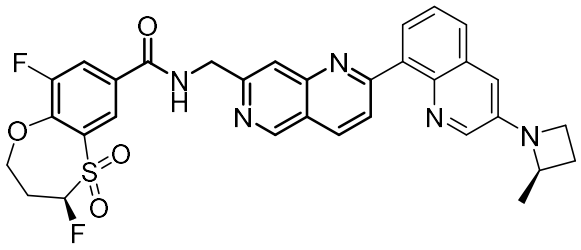
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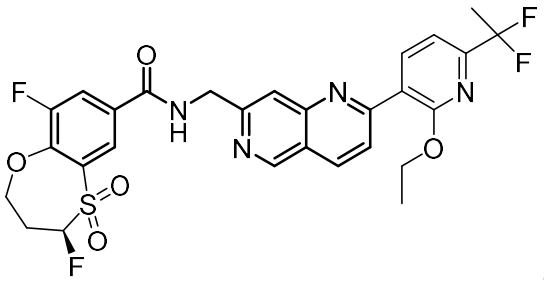
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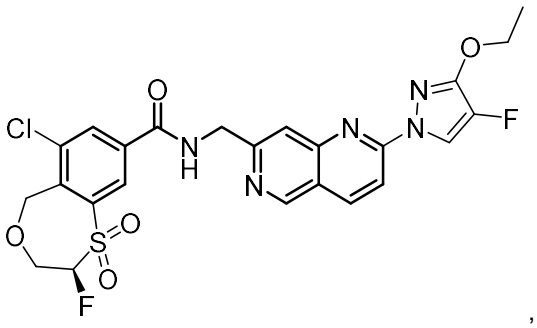
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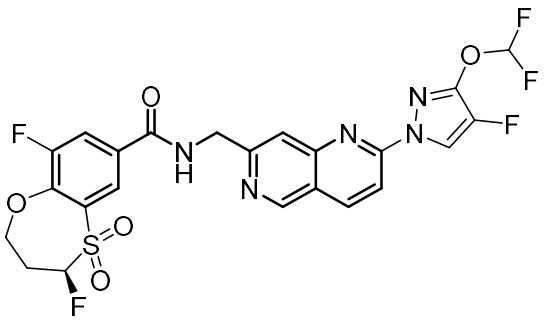
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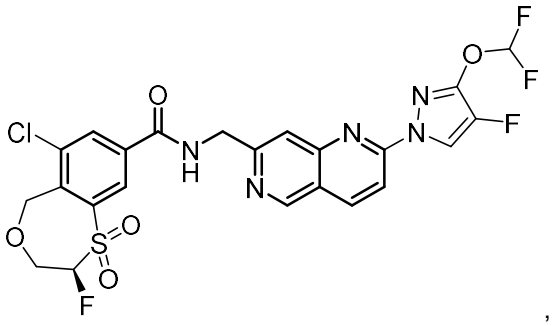
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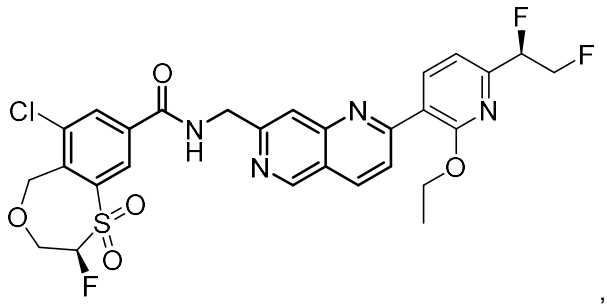
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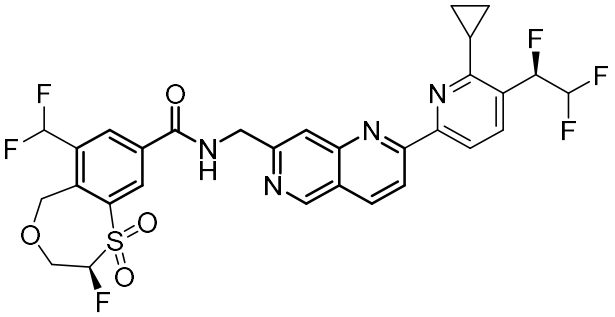
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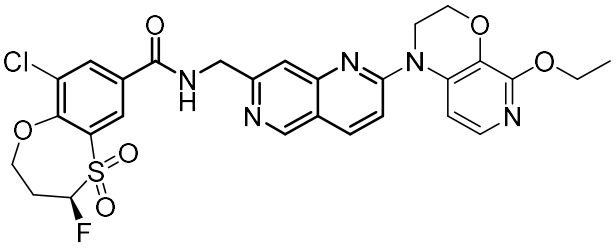
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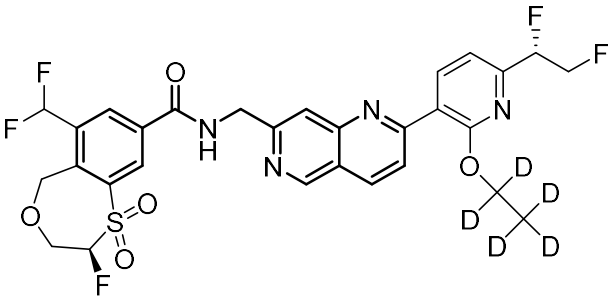
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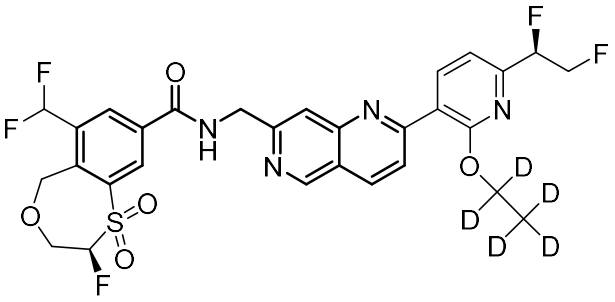
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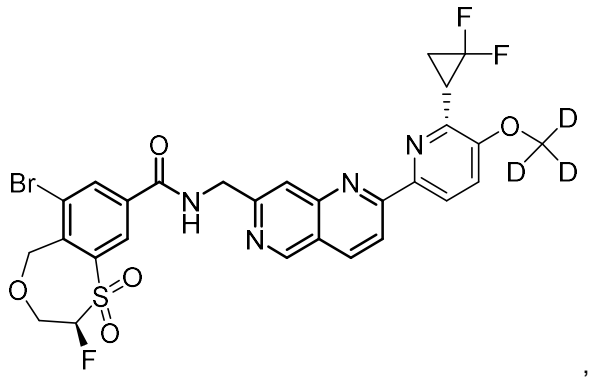
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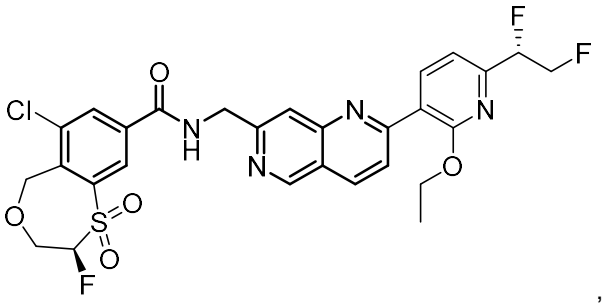
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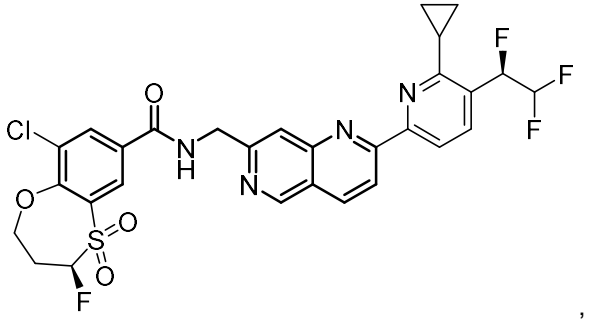
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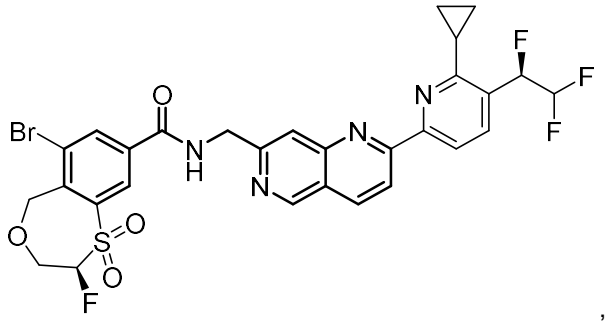
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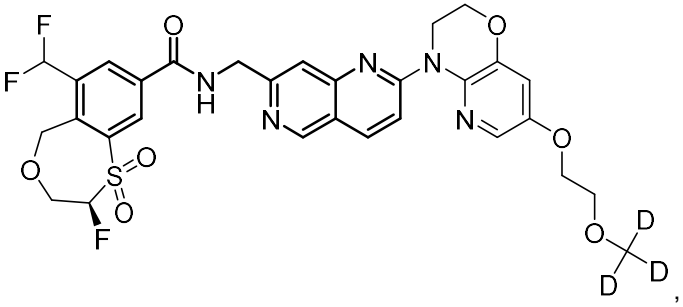
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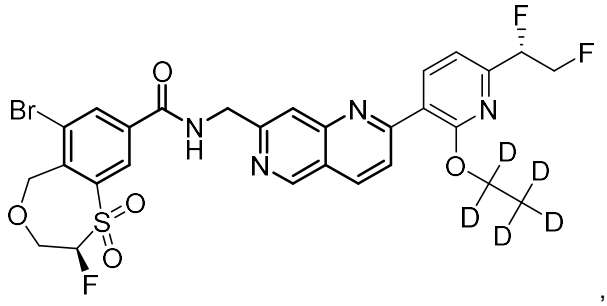
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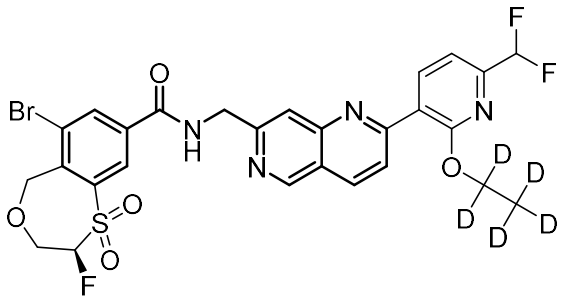
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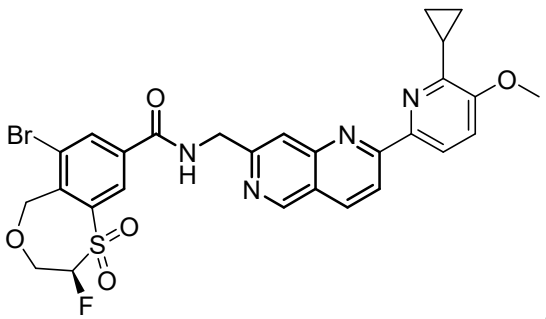
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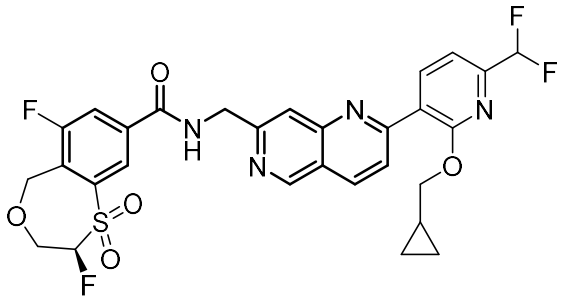
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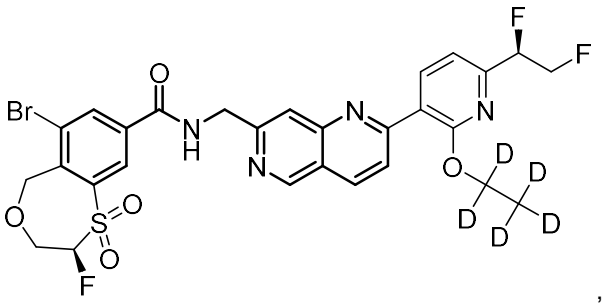
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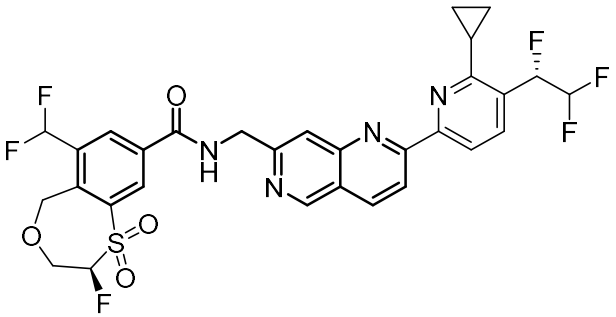
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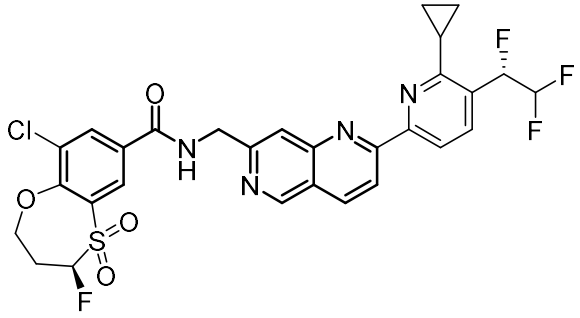
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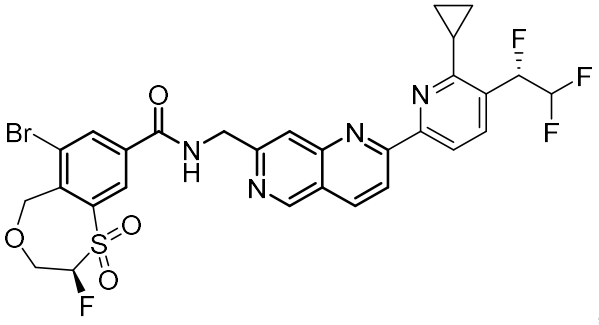
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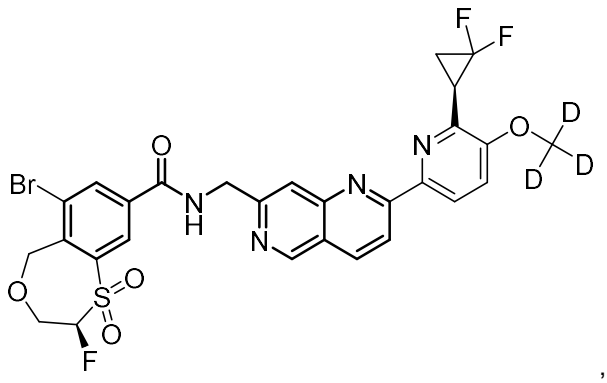
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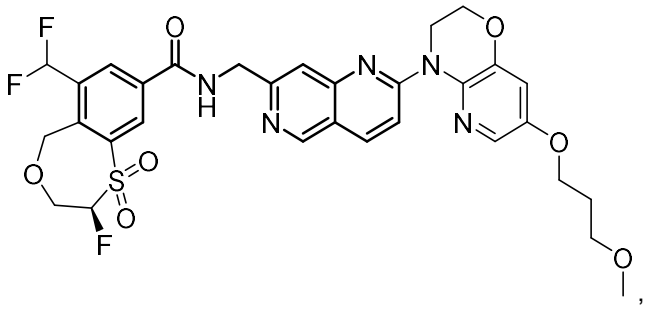
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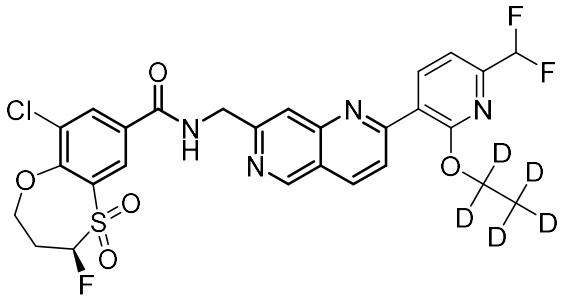
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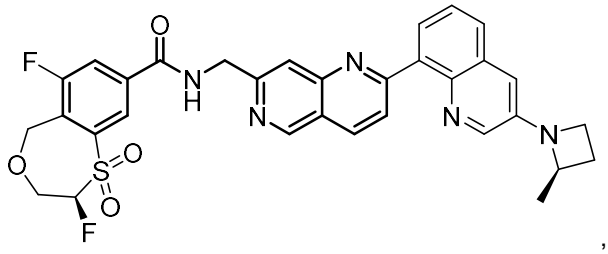
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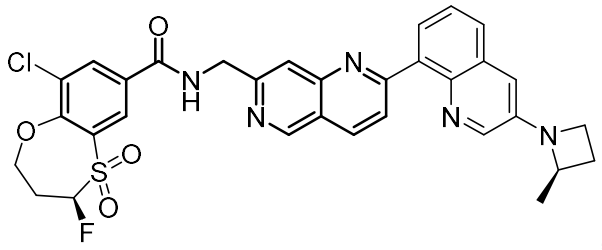
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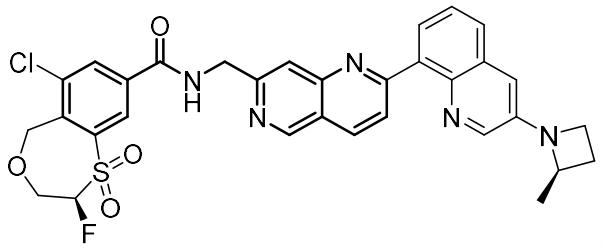
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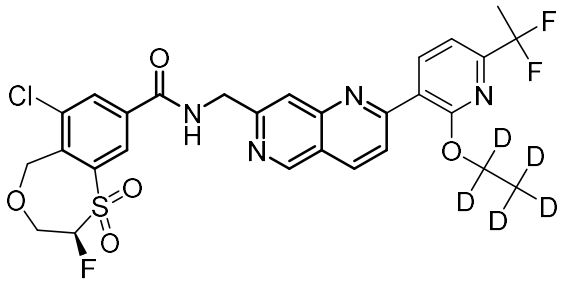
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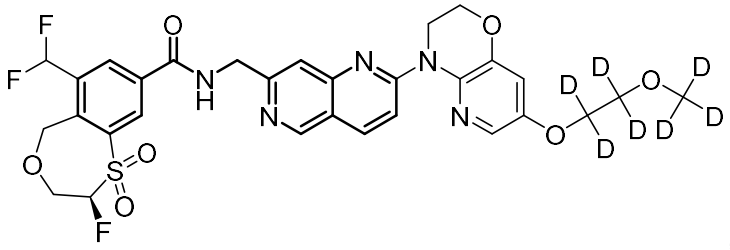
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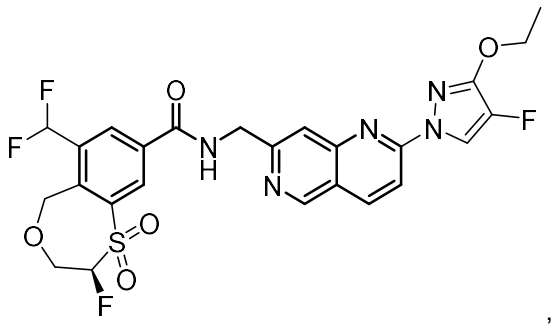
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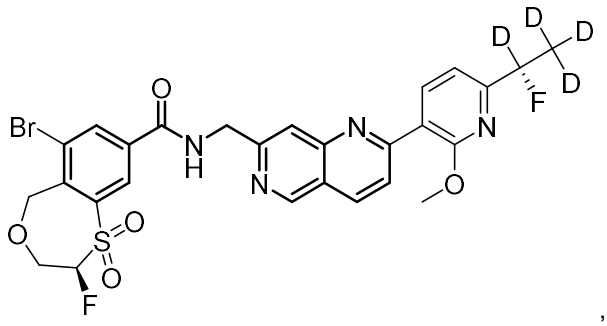
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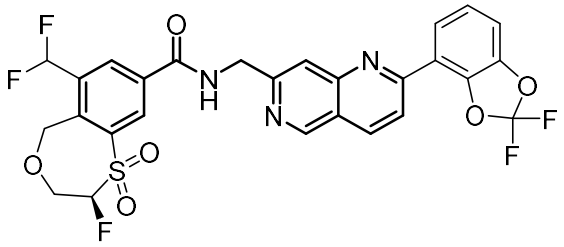
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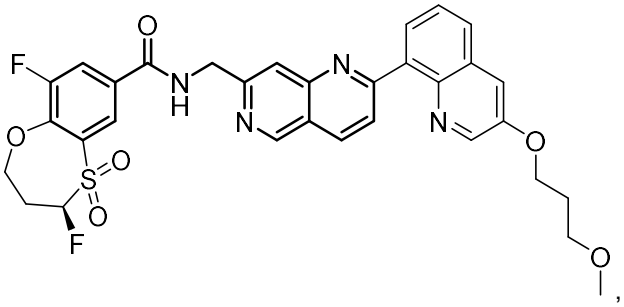
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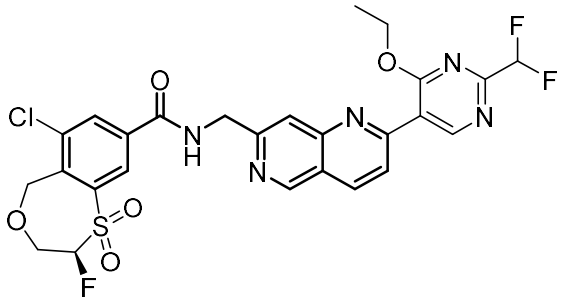
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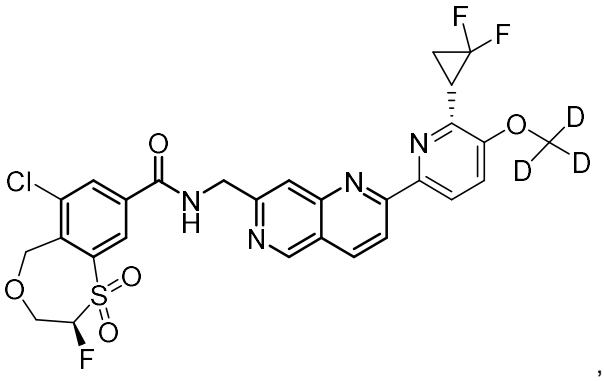
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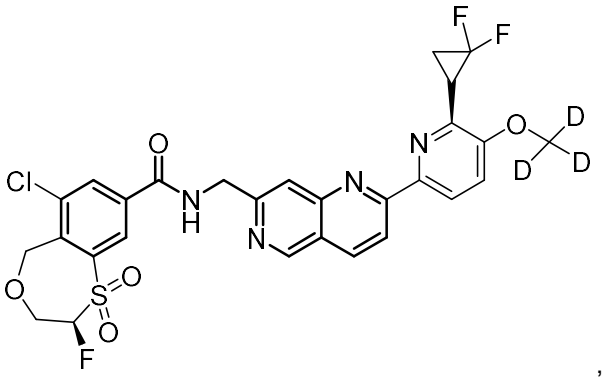
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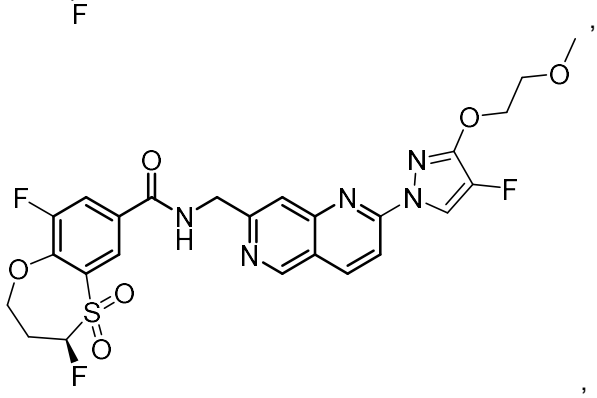
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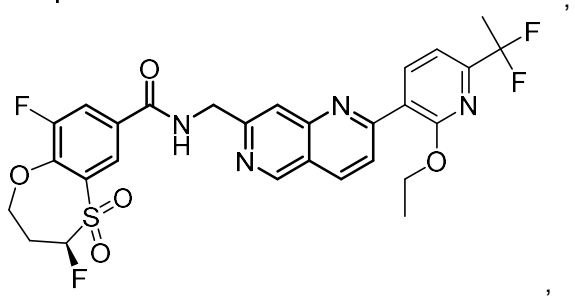
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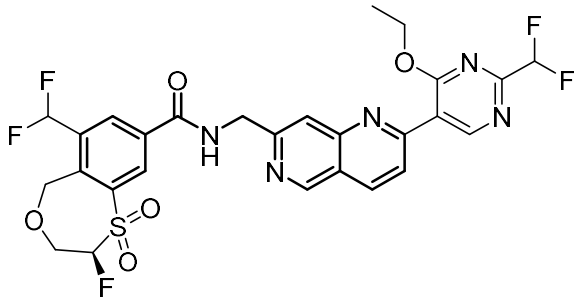
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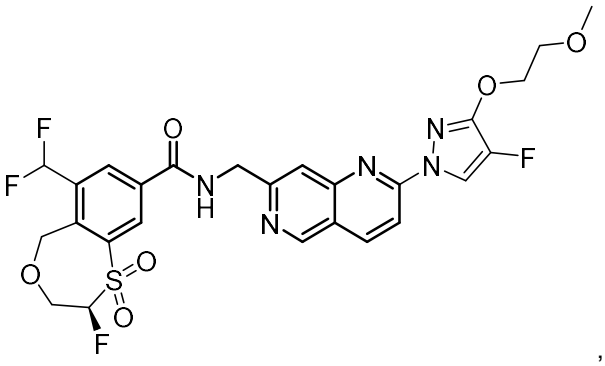
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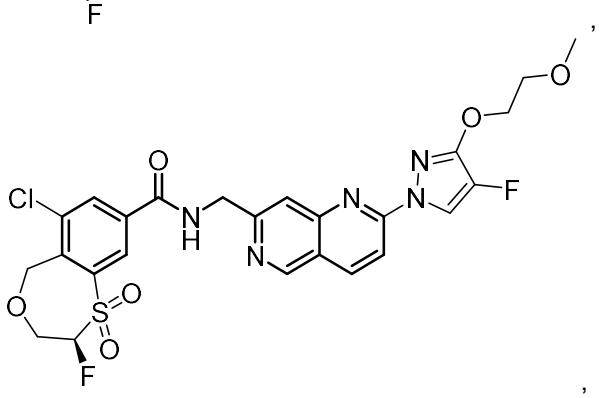
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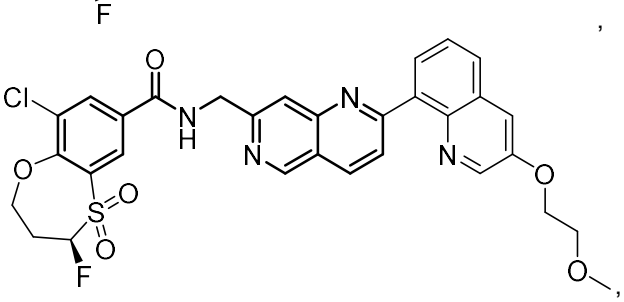
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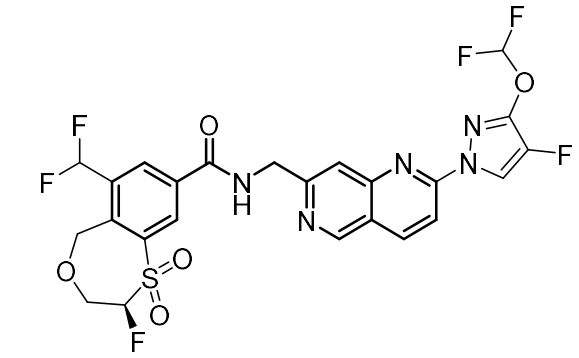
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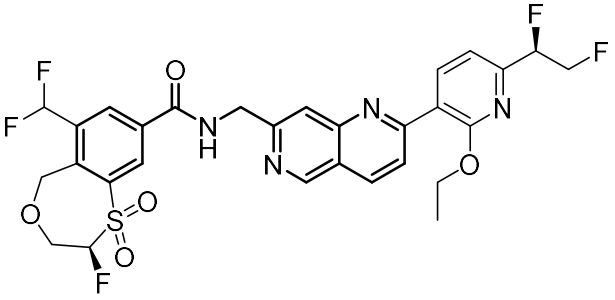
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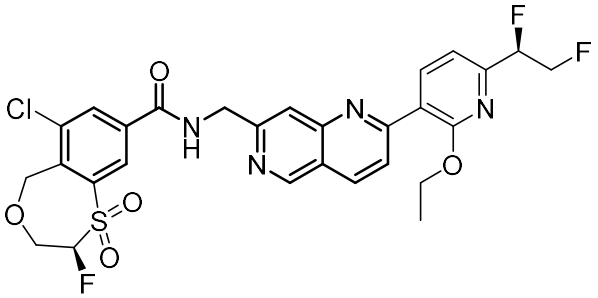
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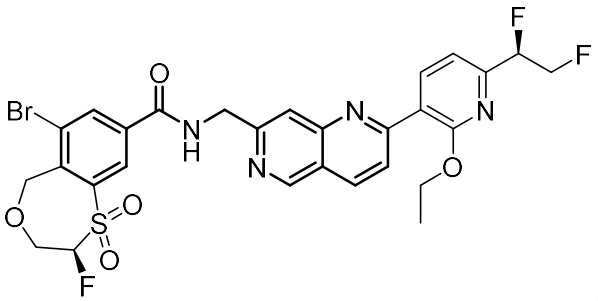
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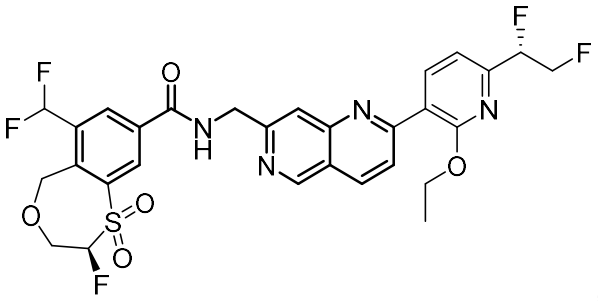
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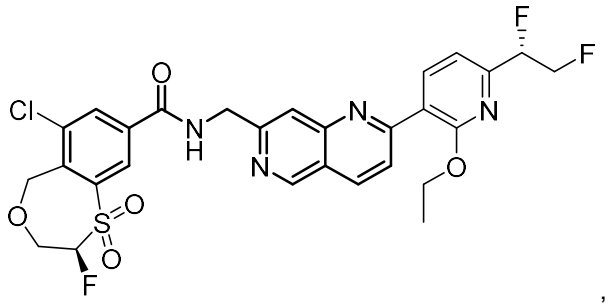
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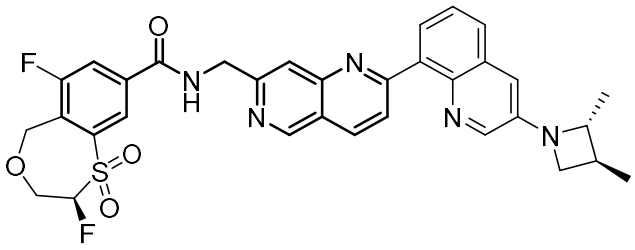
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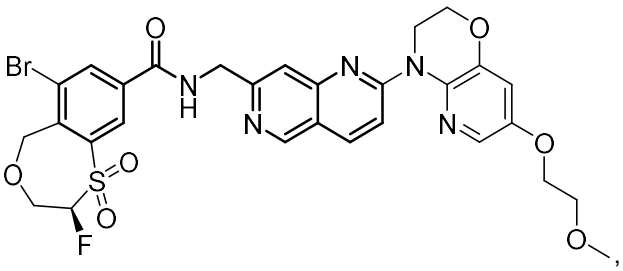
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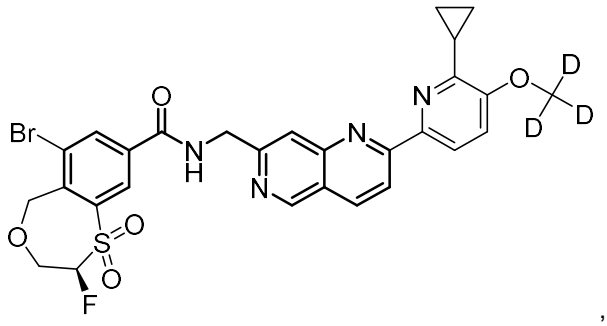
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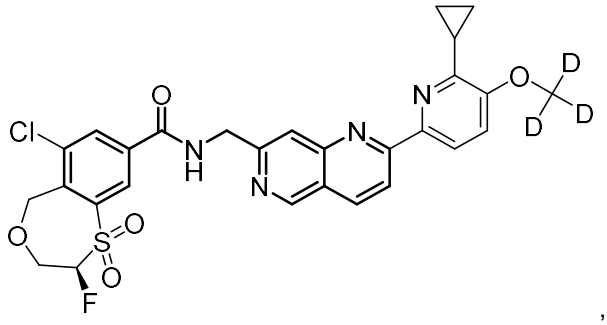
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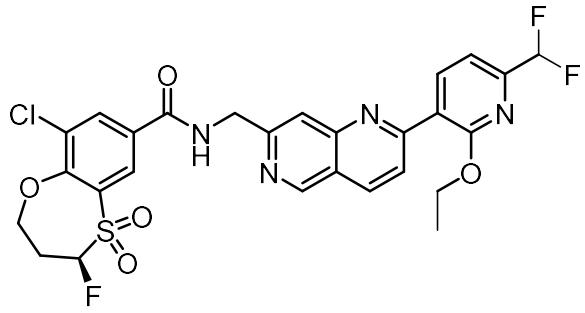
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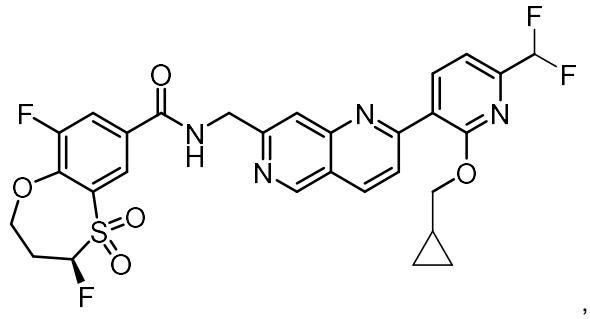
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and pharmaceutically acceptable salts thereof.

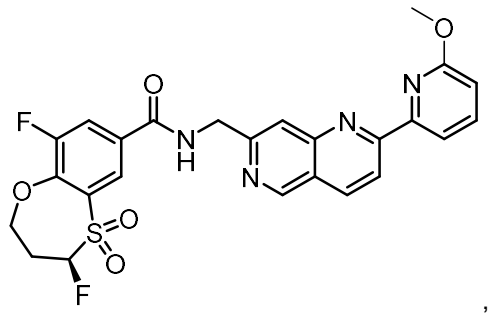
45. The compound of claim 1 that is selected from the group consisting of



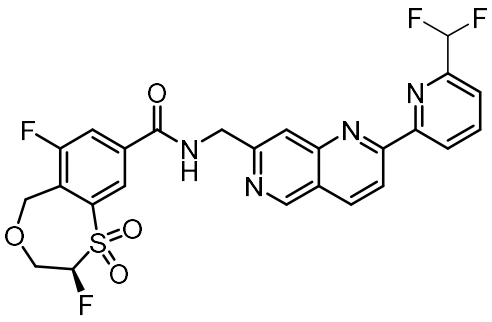
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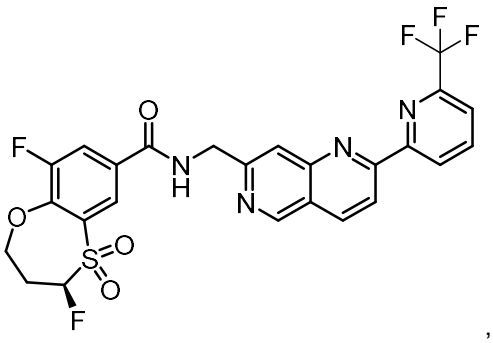
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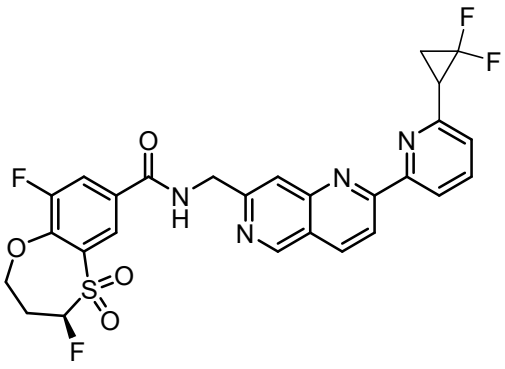
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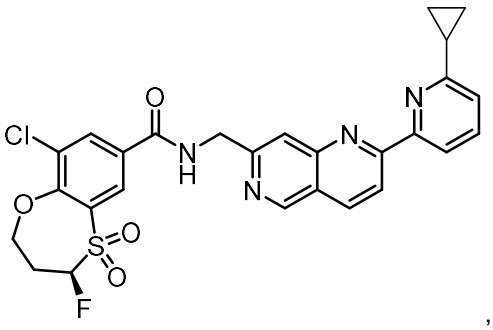
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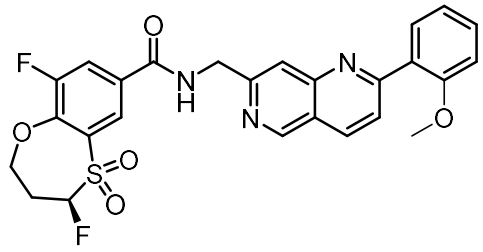
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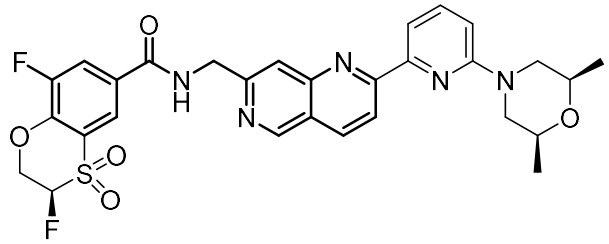
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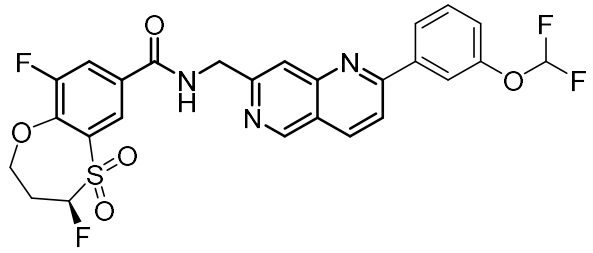
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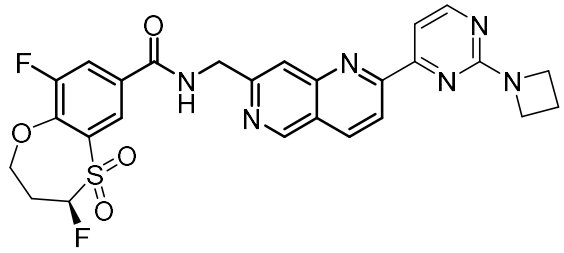
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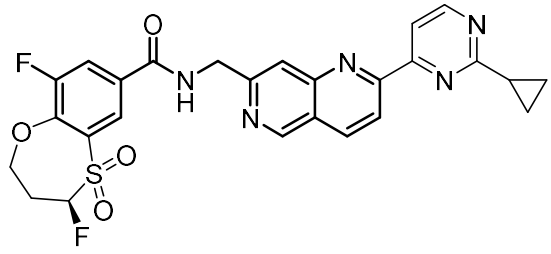
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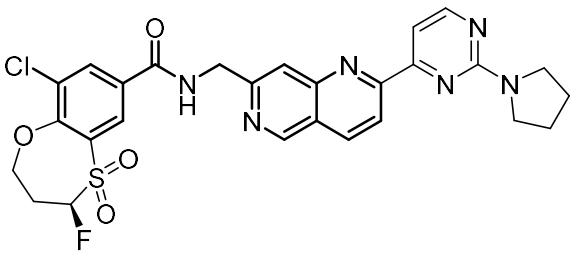
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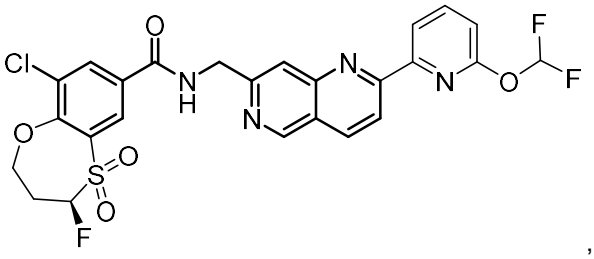
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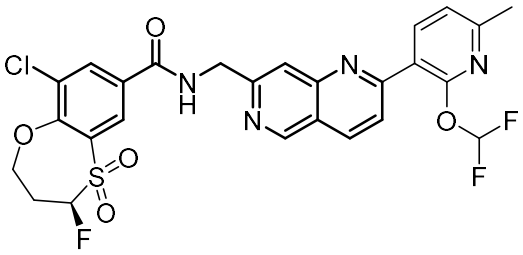
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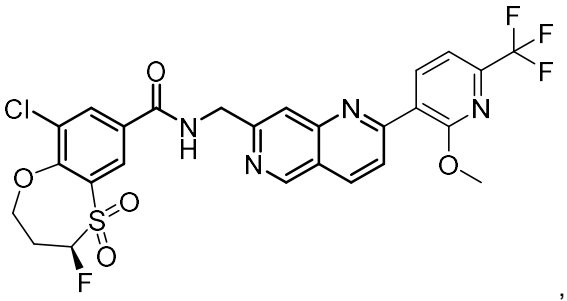
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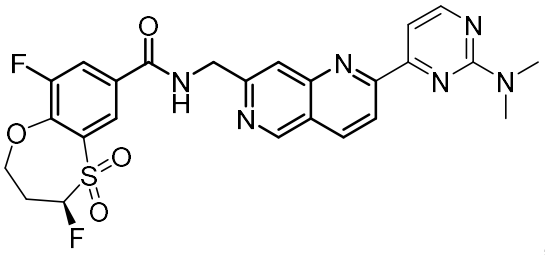
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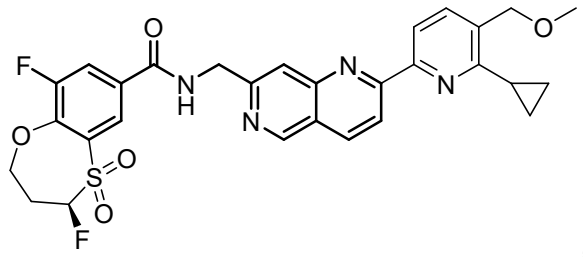
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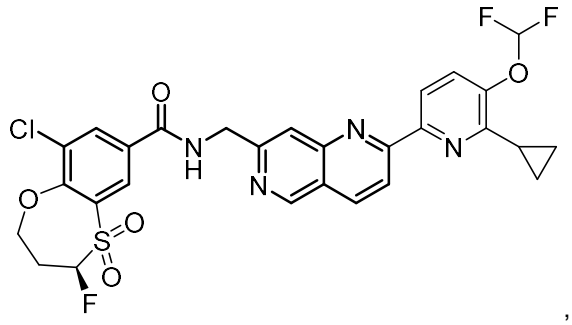
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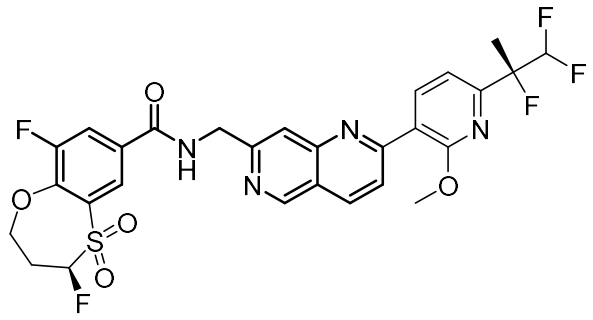
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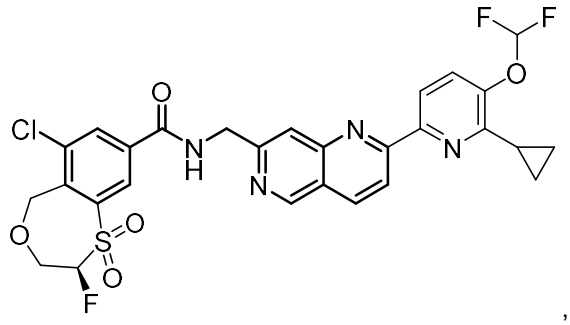
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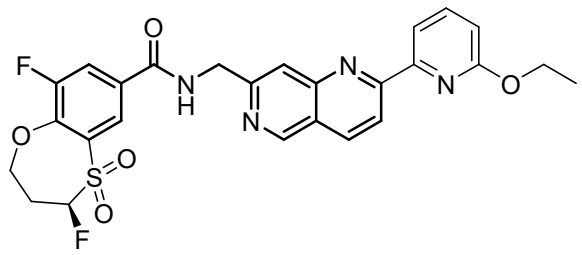
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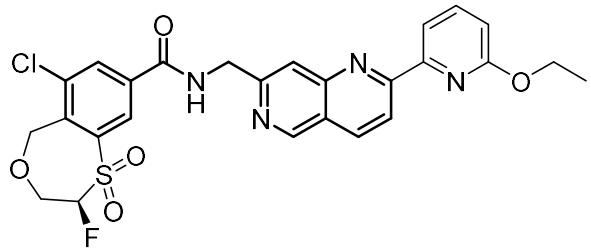
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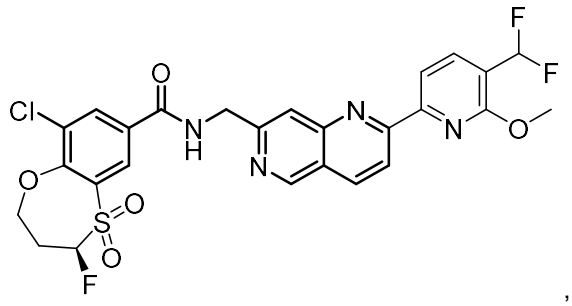
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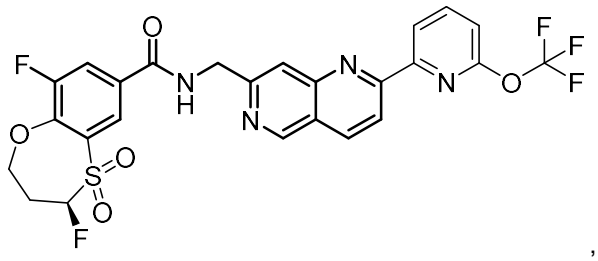
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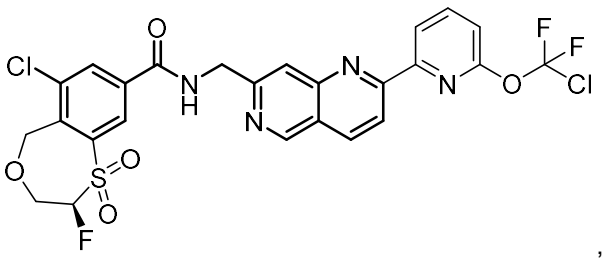
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or pharmaceutically acceptable salts thereof.

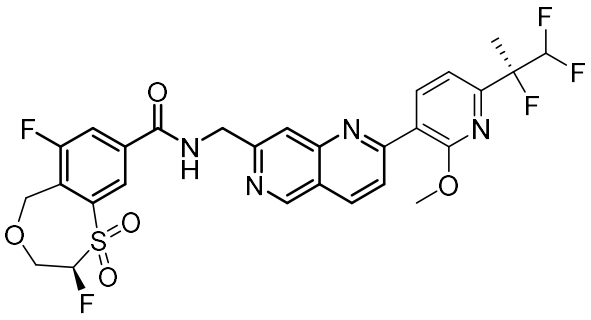
46. The compound of claim 1 that is selected from the group consisting of



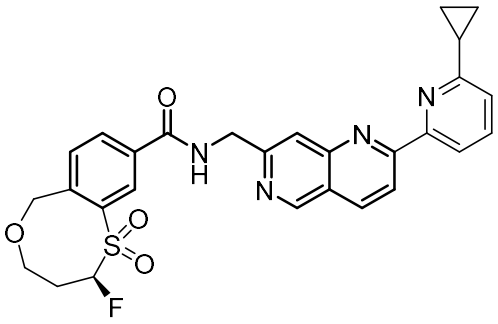
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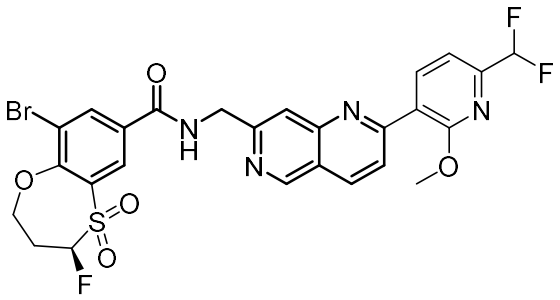
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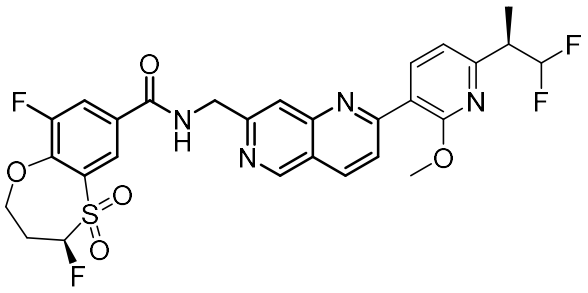
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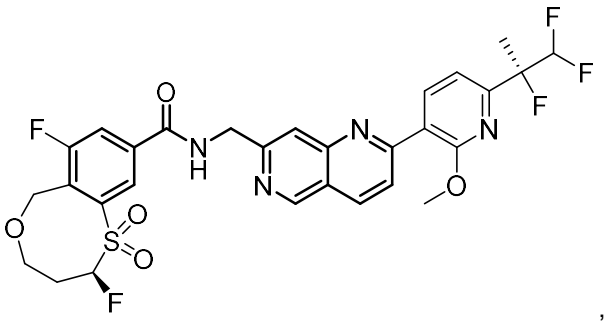
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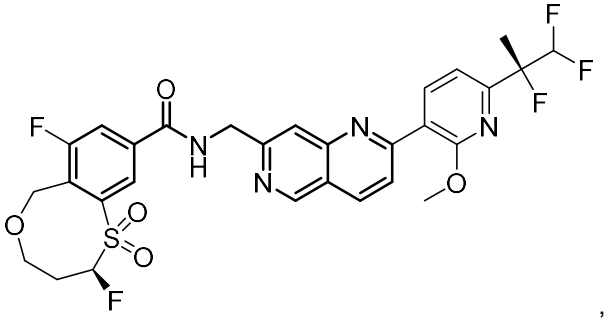
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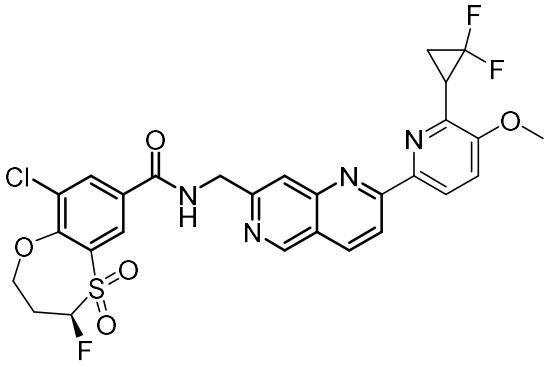
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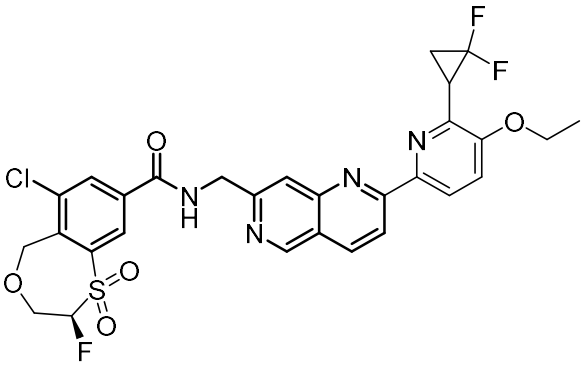
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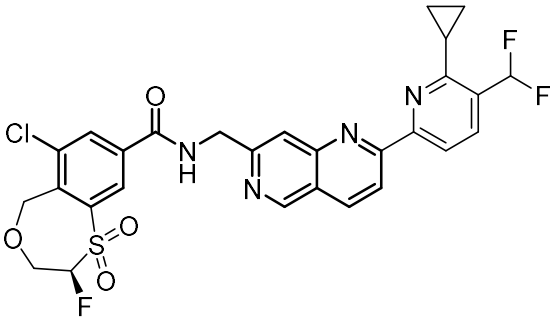
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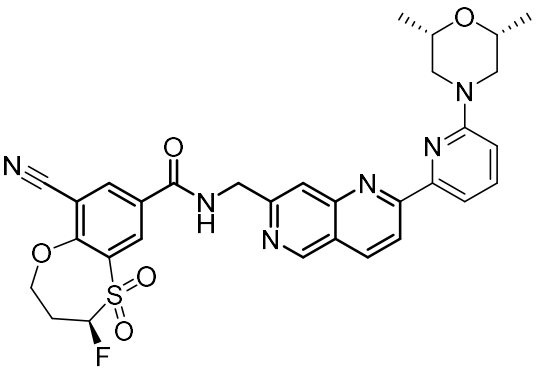
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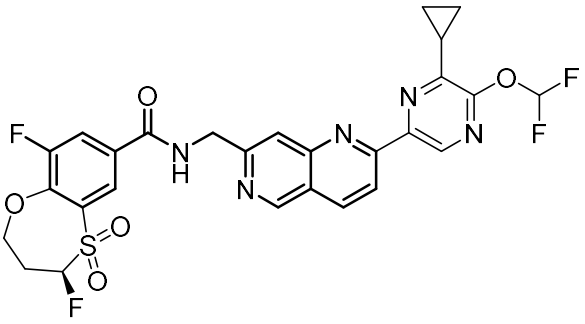
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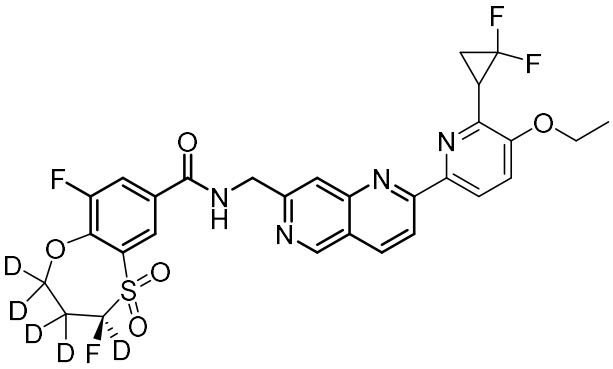
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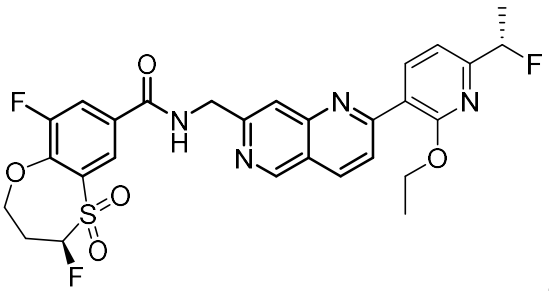
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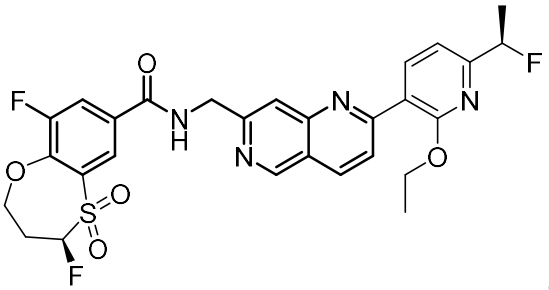
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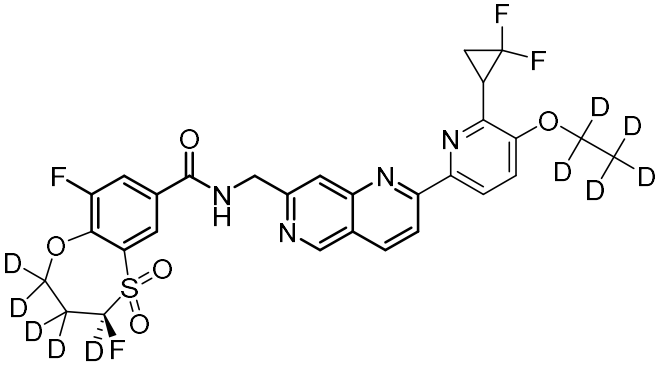
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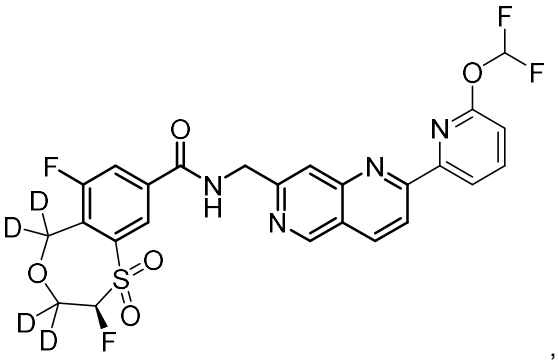
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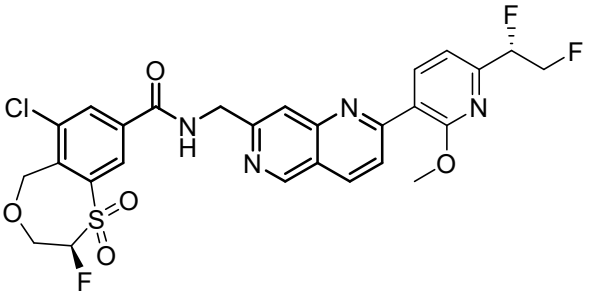
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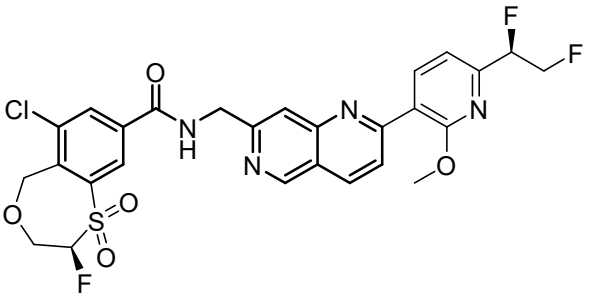
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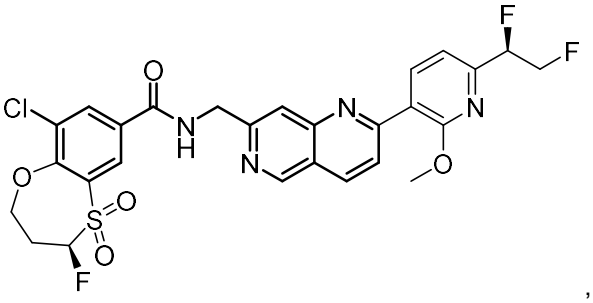
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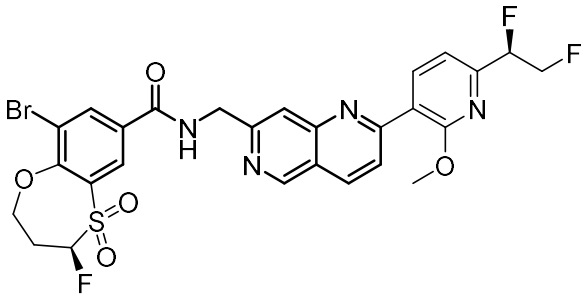
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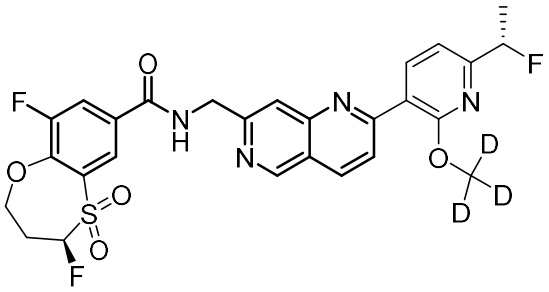
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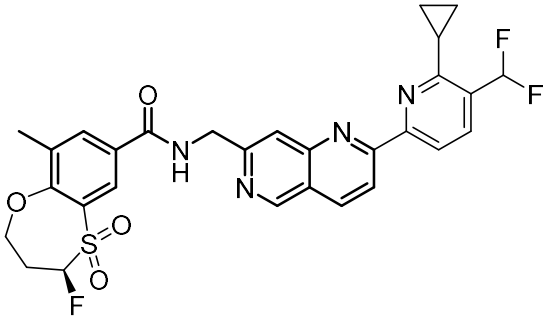
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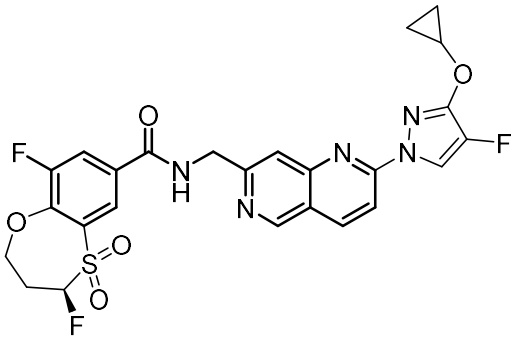
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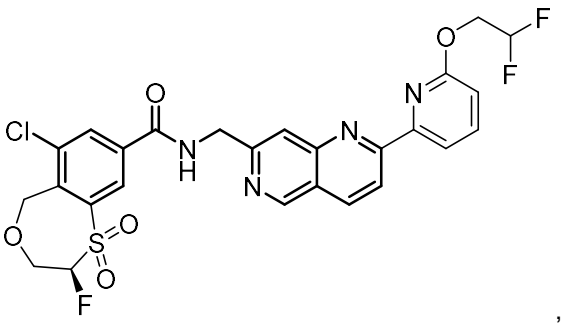
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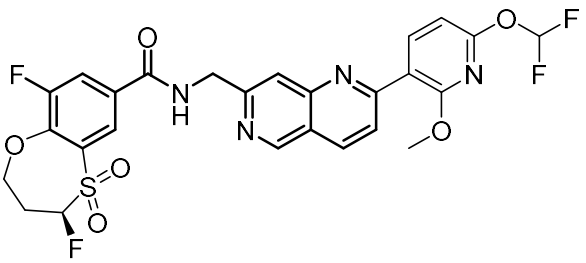
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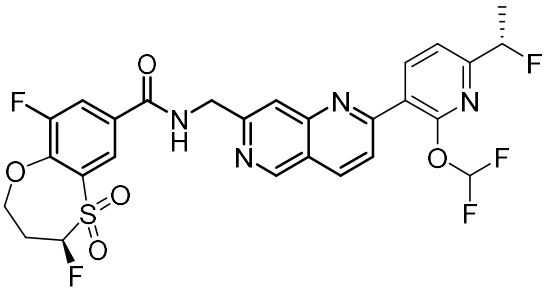
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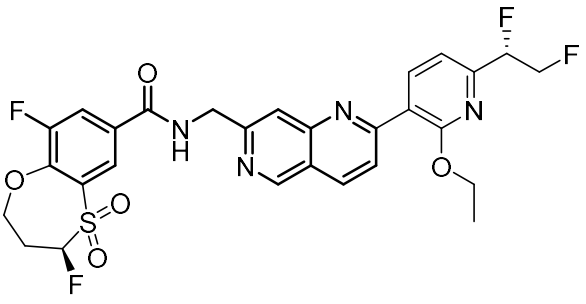
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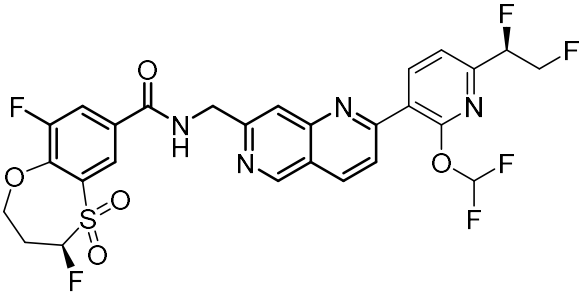
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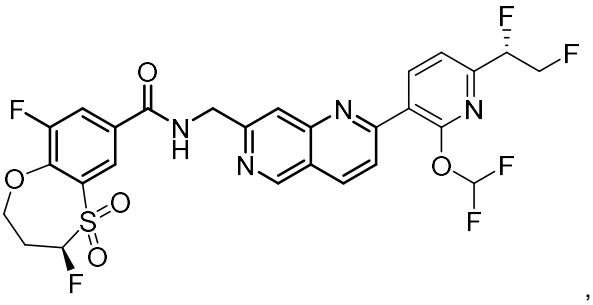
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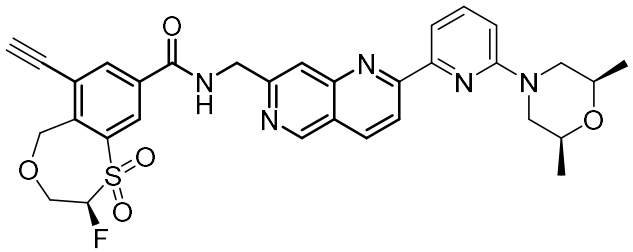
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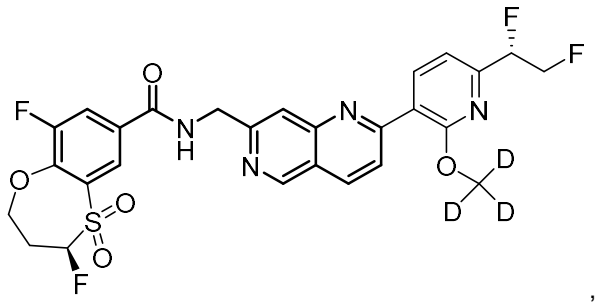
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or pharmaceutically acceptable salts thereof.

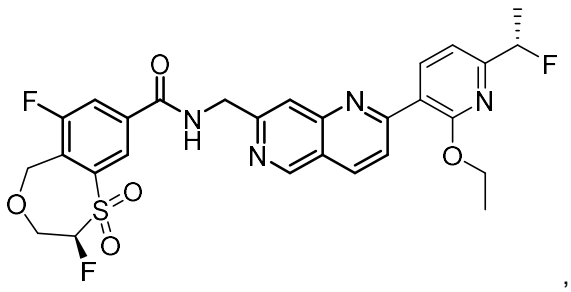
47. The compound according to claim 1 that is selected from the group consisting of



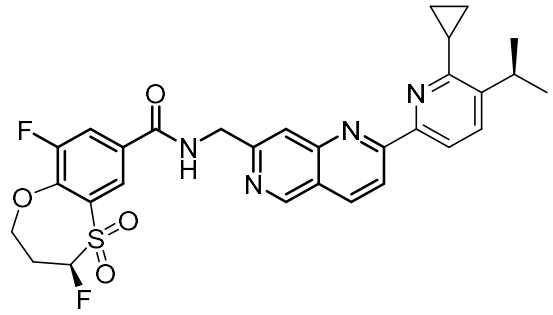
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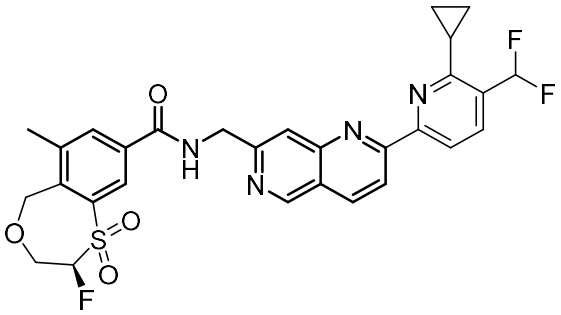
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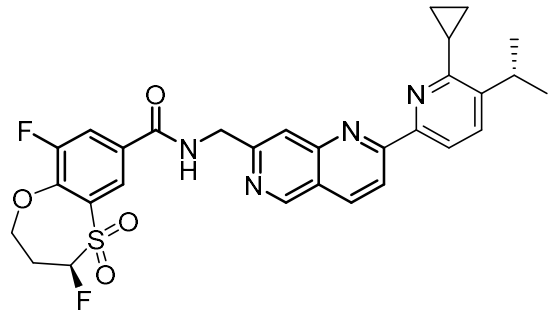
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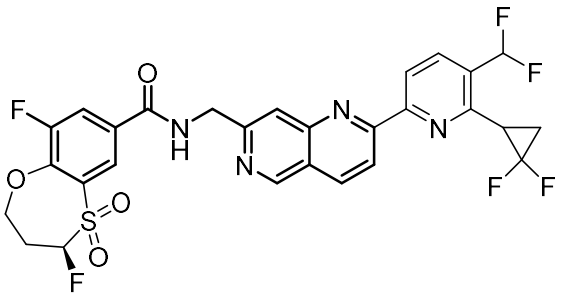
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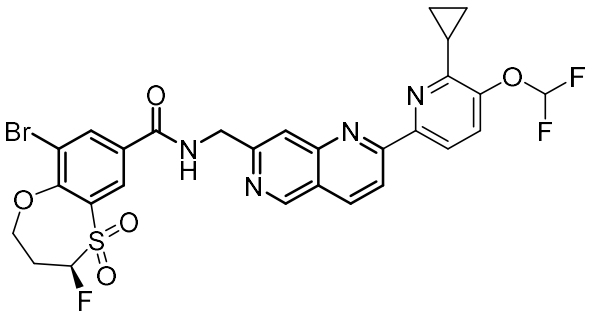
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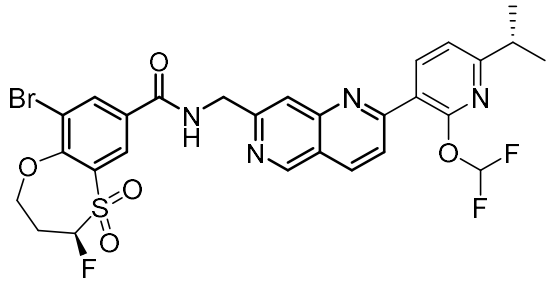
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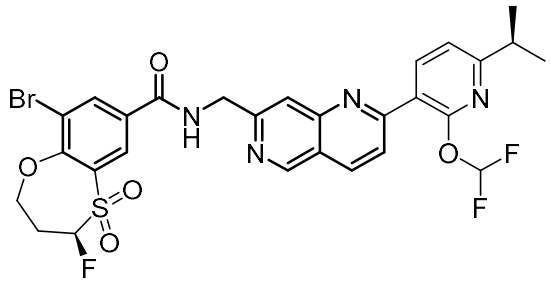
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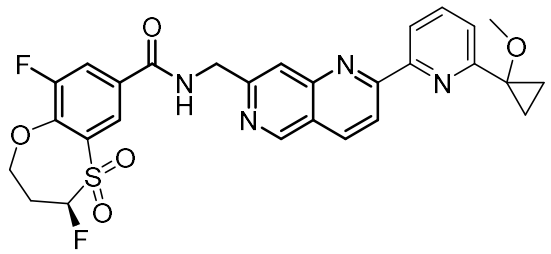
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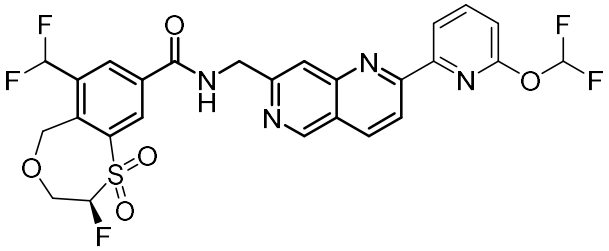
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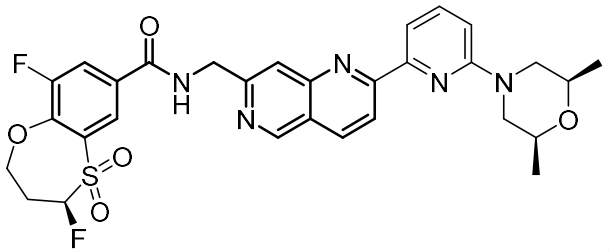
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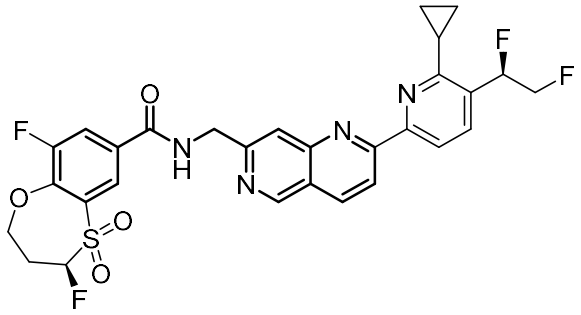
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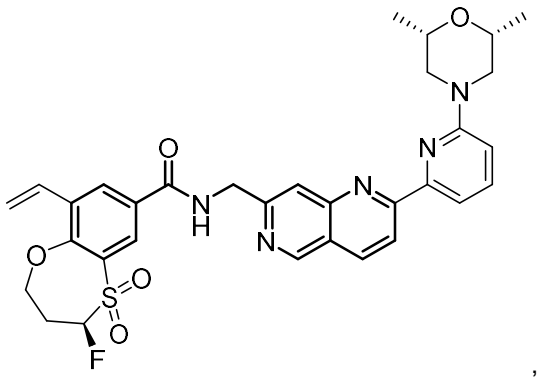
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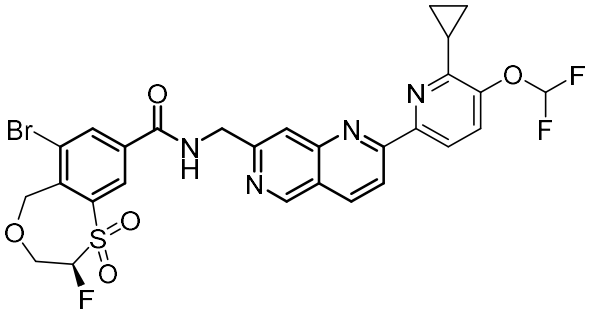
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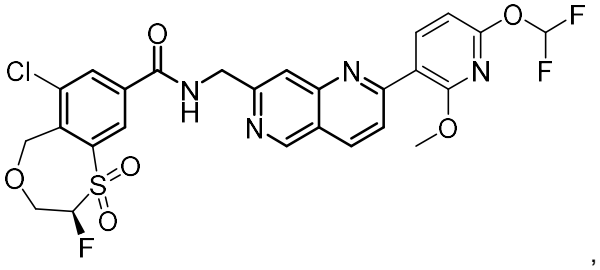
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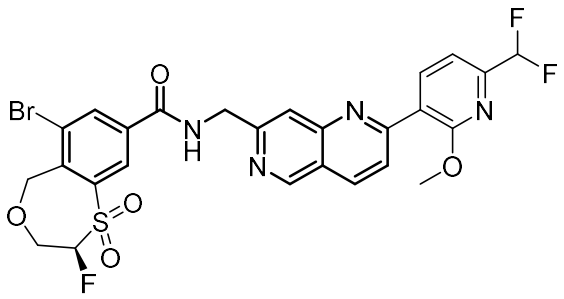
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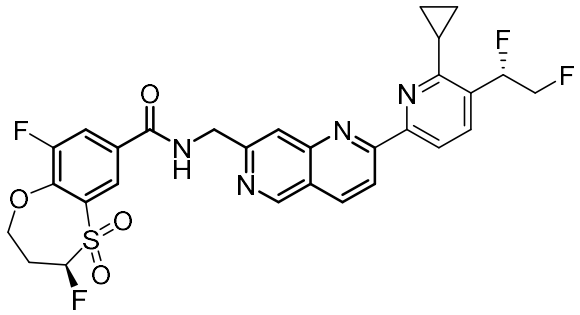
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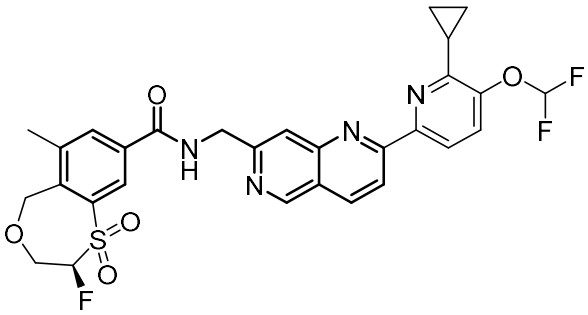
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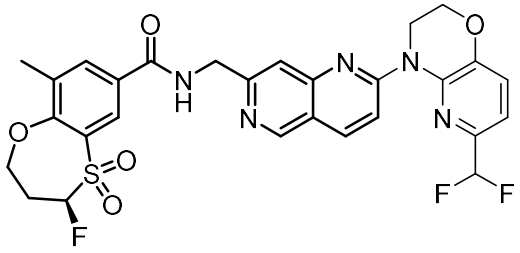
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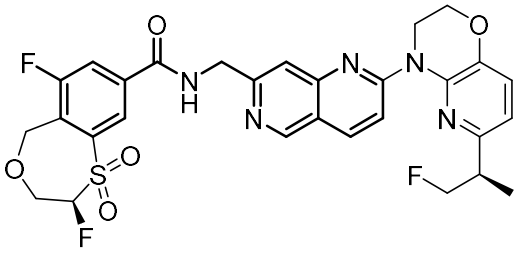
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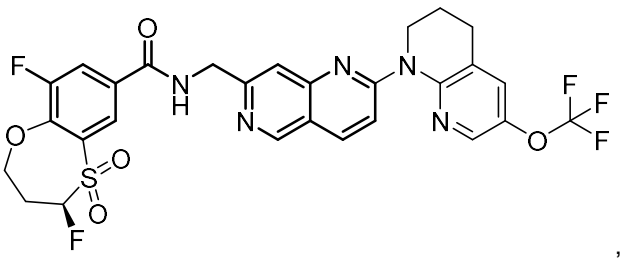
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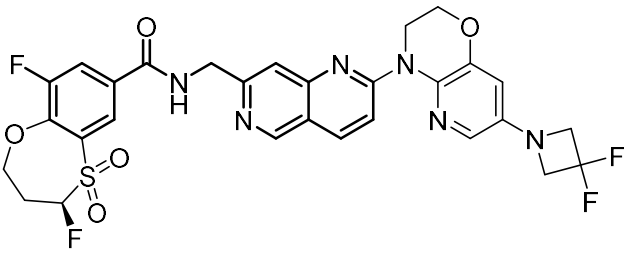
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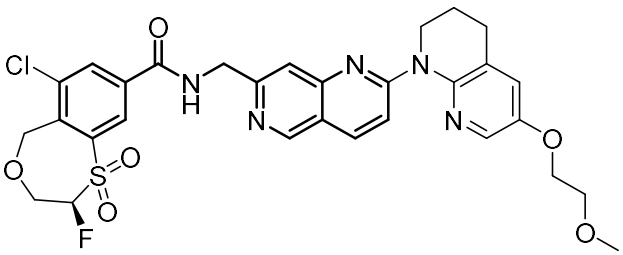
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or a pharmaceutically acceptable salt thereof.

48. A pharmaceutical composition comprising a compound of any one of claims 1 to 47 and a pharmaceutically acceptable excipient.

49. Use a compound of any one of claims 1 to 47, in the manufacture of a medicament for treating cancer, wherein the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, esophagogastric cancer, pancreatic cancer, hepatobiliary cancer, soft tissue sarcoma, ovarian cancer, head and neck cancer, renal cell carcinoma, bone cancer, non-Hodgkin lymphoma, small-cell lung cancer, prostate cancer, embryonal tumor, germ cell tumor, cervical cancer, thyroid cancer, salivary gland cancer, gastrointestinal neuroendocrine tumor, uterine sarcoma, gastrointestinal stromal tumor, CNS cancer, thymic tumor, Adrenocortical carcinoma, appendiceal cancer, small bowel cancer, or penile cancer.

50. The use of claim 49, wherein the cancer is non-small cell lung cancer, colorectal cancer, bladder cancer, cancer of unknown primary, glioma, breast cancer, melanoma, non-melanoma skin cancer, endometrial cancer, soft tissue sarcoma, or penile cancer.

51. The compound of any one of claims 1 to 47 or the pharmaceutical composition of claim 48 for use in therapy.