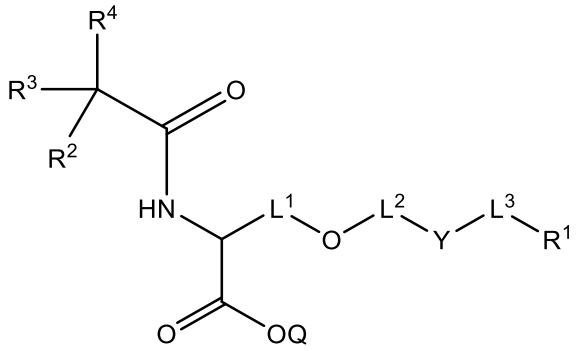
CLAIMS

What is claimed is:

1. A compound of formula (A):



(A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is 5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl optionally substituted by one or more R^{1a}, 1,2,3,4-tetrahydro-1,8-naphthyridin-2-yl optionally substituted by one or more R^{1b}, 6-aminopyridin-2-yl optionally substituted by one or more R^{1c}, or (pyridin-2-yl)amino optionally substituted by one or more R^{1d};

R^2 is H or C_1-C_6 alkyl;

R^3 is H or C_1-C_6 alkyl;

or R^2 and R^3 are taken together with the carbon atom to which they are attached to form a C_3-C_6 cycloalkyl or a 3-to-6-membered heterocyclyl, each of which is optionally substituted by R^{2a};

R^4 is phenyl, 5-to-6-membered heteroaryl, 6-membered heterocyclyl, or C_1-C_6 haloalkyl;

wherein the 5-to-6-membered heteroaryl contains at least one nitrogen atom and is optionally fused to a phenyl group;

wherein the 6-membered heterocyclyl contains at least one nitrogen atom and is optionally fused to a phenyl group;

wherein the phenyl and 5-to-6-membered heteroaryl are optionally substituted by one or more R^{4a}; and

wherein the 6-membered heterocyclyl is optionally substituted by one or more groups selected from the group consisting of R^{4a} and oxo;

or R^2, R^3, and R^4 are taken together to form a 5-membered heteroaryl containing two nitrogen atoms and substituted with phenyl, wherein the phenyl group is optionally substituted by one or more R^{4a};

each R^{4a} is independently halo, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), C_3-C_6 cycloalkyl, -OH, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -S(O)$_2$(C_1-C_6 alkyl), or -C(=O)-NH_2;

or R^{4a} and R^2 are taken together with the atoms to which they are attached to form a 6-membered heterocyclyl, wherein the heterocyclyl contains one oxygen atom;

Q is H or C_1-C_8 alkyl;

L^1 is C_2-C_4 alkylene optionally substituted by one or more L^{1a};

L^2 is a bond or C_1-C_3 alkylene optionally substituted by one or more L^{2a};

L^3 is C_2-C_4 alkylene optionally substituted by one or more L^{3a};

Y is a bond;

R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{2a}, L^{1a}, L^{2a}, and L^{3a} are each independently selected from R^A;

two R^{1a} groups on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C_3-C_6 cycloalkyl;

two R^{1b} groups on the same carbon atom are optionally taken together with the carbon atom to which they are attached to form a C_3-C_6 cycloalkyl;

each R^A is independently deuterium, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, -CN, -OR^5, -SR^5, -NR^6R^7, -NO_2, -C=NH(OR^5), -C(O)R^5, -OC(O)R^5, -C(O)OR^5, -C(O)NR^6R^7, -NR^5C(O)R^6, -NR^5C(O)OR^6, -NR^5C(O)NR^6R^7, -S(O)R^5, -S(O)$_2R^5$, -NR^5S(O)R^6, -NR^5S(O)$_2R^6$, -S(O)NR^6R^7, -S(O)$_2NR^6R^7$, or -P(O)(OR^5)(OR^6), wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, C_6-C_{14} aryl, and 5- to 10-membered heteroaryl of R^A are independently optionally substituted by one or more R^{Aa};

each R^{Aa} is independently deuterium, halogen, oxo, -OR^8, -NR^8R^9, -C(O)R^8, -C(O)OR^8, -NR^8C(O)OR^{10}, -CN, -S(O)R^8, -S(O)$_2R^8$, -P(O)(OR^8)(OR^9), C_3-C_8 cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, or C_1-C_6 alkyl, wherein the 3- to 12-membered heterocyclyl, 5- to 10-membered heteroaryl, C_6-C_{14} aryl, and C_1-C_6 alkyl of R^{Aa} are independently optionally substituted by one or more R^{Ab};

each R^{Ab} is independently deuterium, oxo, -OH, -O(^{2}H), halogen, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, -OH, -O(^{2}H), or oxo;

each R^5 is independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl of R^5 are each independently optionally substituted by one or more R^{5a};

each R^{5a} is independently halogen, deuterium, oxo, -CN, -OR^{10}, -$NR^{11}R^{12}$, -$P(O)(OR^{11})(OR^{12})$, 3- to 12-membered heterocyclyl, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, -OH, -$O(^2H)$, or oxo;

each R^6 is independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, or 3- to 6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, and 3- to 6-membered heterocyclyl of R^6 are independently optionally substituted by one or more of deuterium, halogen, oxo, -CN, -OR^{10}, -$NR^{11}R^{12}$, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, -OH, -$O(^2H)$, or oxo;

each R^7 is independently hydrogen, deuterium, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, or 3- to 6-membered heterocyclyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5- to 10-membered heteroaryl, and 3- to 6-membered heterocyclyl of R^7 are independently optionally substituted by one or more of deuterium, halogen, oxo, -CN, -OR^{10}, -$NR^{11}R^{12}$, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, -OH, -$O(^2H)$, or oxo;

or R^6 and R^7 are taken together with the atom to which they are attached to form a 3- to 10-membered heterocyclyl optionally substituted by one or more of deuterium, halogen, oxo, -OR^{10}, -$NR^{11}R^{12}$, or C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, oxo, -OH, or -$O(^2H)$;

each R^8 is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo;

each R^9 is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or

more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo;

each R^{10} is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo;

each R^{11} is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo; and

each R^{12} is independently hydrogen, deuterium, C_1-C_6 alkyl optionally substituted by one or more of deuterium, halogen, or oxo, C_2-C_6 alkenyl optionally substituted by one or more of deuterium, halogen, or oxo, or C_2-C_6 alkynyl optionally substituted by one or more of deuterium, halogen, or oxo;

or R^{11} and R^{12} are taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by one or more of deuterium, halogen, oxo or C_1-C_6 alkyl optionally substituted by one or more of deuterium, oxo, or halogen.

2. The compound of claim 1, wherein

R^2 is H or C_1-C_6 alkyl;

R^3 is H or C_1-C_6 alkyl;

or R^2 and R^3 are taken together with the carbon atom to which they are attached to form a C_3-C_6 cycloalkyl or a 3-to-6-membered heterocyclyl;

R^4 is phenyl, 5-to-6-membered heteroaryl, or 6-membered heterocyclyl,

wherein the 5-to-6-membered heteroaryl contains at least one nitrogen atom and is optionally fused to a phenyl group;

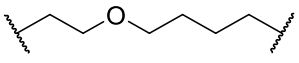
wherein the 6-membered heterocyclyl contains at least one nitrogen atom and is optionally fused to a phenyl group;

wherein the phenyl and 5-to-6-membered heteroaryl are optionally substituted by one or more R^{4a}; and

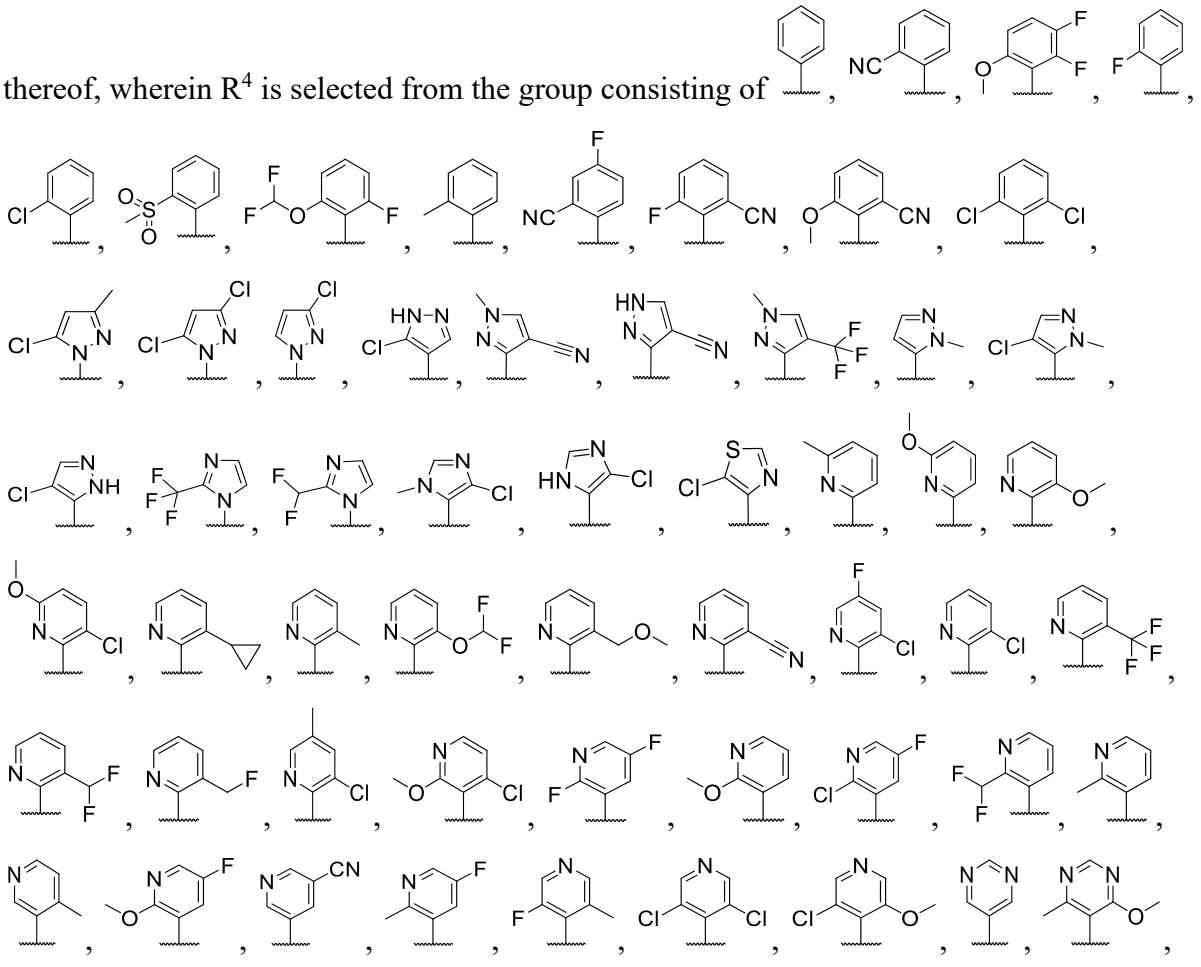
wherein the 6-membered heterocyclyl is optionally substituted by one or more groups selected from the group consisting of R^{4a} and oxo; and

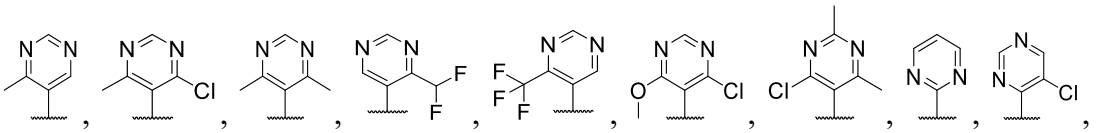
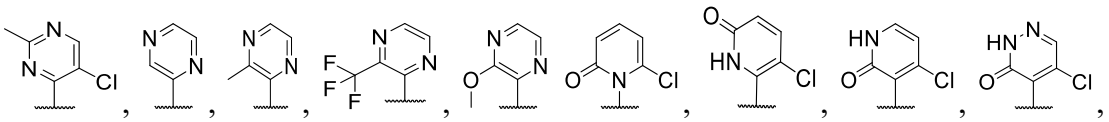
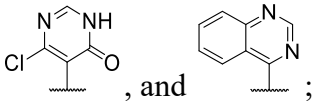
each R^{4a} is independently halo, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), C_3-C_6 cycloalkyl, -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), or -$S(O)_2$(C_1-C_6 alkyl);

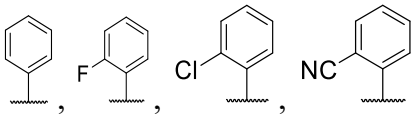
or R^{4a} and R^2 are taken together with the atoms to which they are attached to form a 6-membered heterocyclyl, wherein the heterocyclyl contains one oxygen atom.

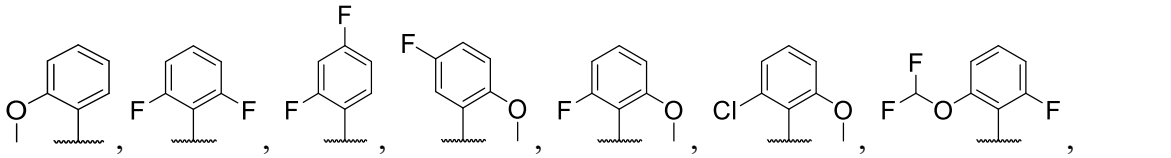
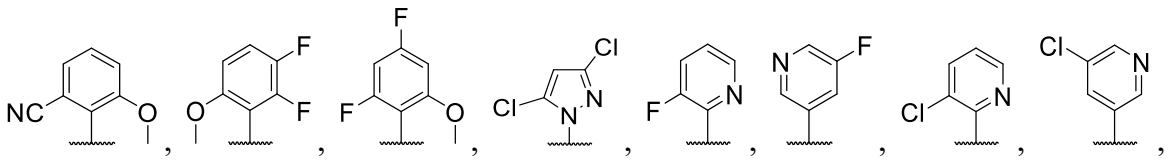
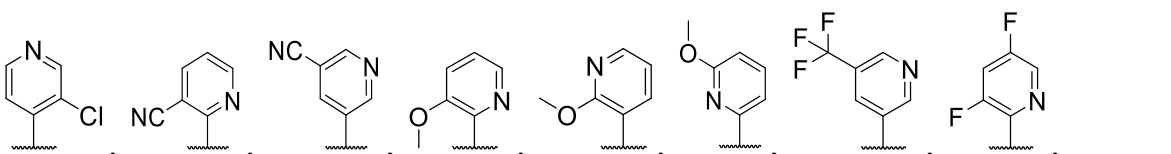
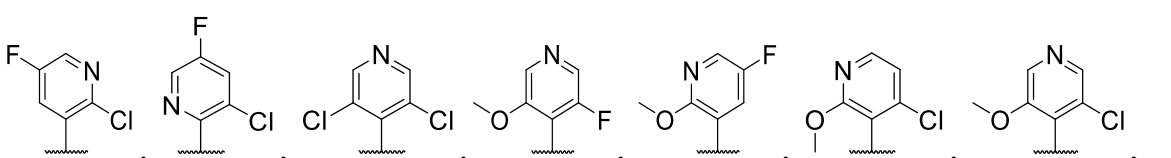
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein -L^1-O-L^2-Y-L^3- are taken together to form .

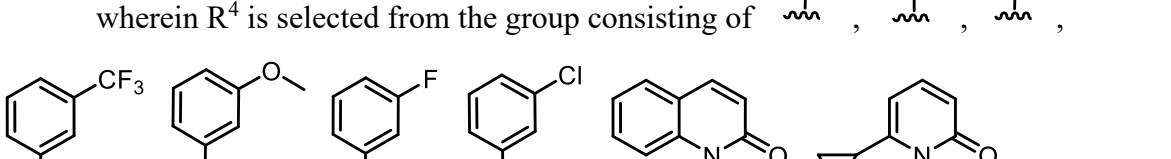
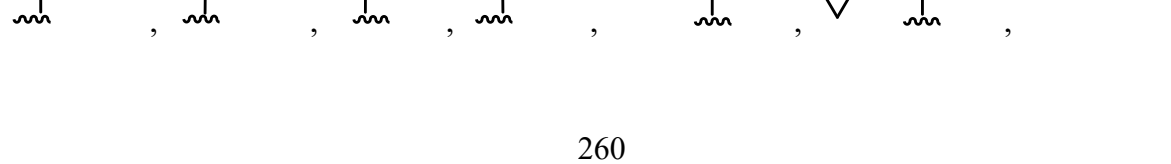
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are taken together with the carbon atom to which they are attached to form cyclopropyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of .




, and ; or

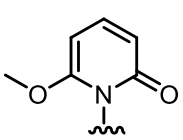
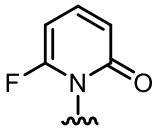
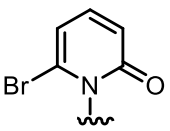
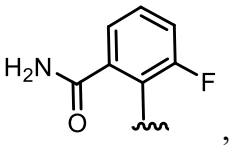
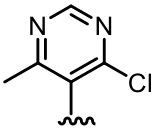
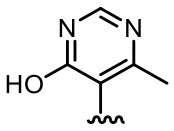
wherein R^4 is selected from the group consisting of 

, and ; or

wherein R^4 is selected from the group consisting of


, 
, 
, 
, 
, and 
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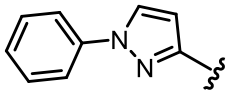
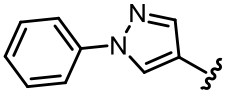
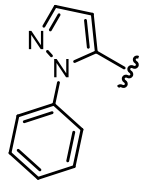
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, and R^4 are taken together to form:


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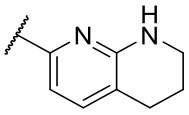
7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^1 is ;

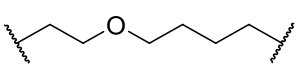
R^2 and R^3 are independently H or methyl, or R^2 and R^3 are taken together with the carbon atom to which they are attached to form cyclopropyl;

R^4 is phenyl, pyrazolyl, imidazolyl, thiazolyl, pyridinyl, 2-oxopyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyridazinyl, or quinazolinyl, wherein:

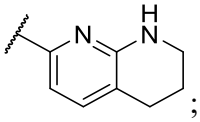
the phenyl, pyrazolyl, imidazolyl, thiazolyl, pyridinyl, 2-oxopyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or quinazolinyl are optionally substituted by one or more R^{4a} groups,

the dihydropyridinyl, dihydropyrimidinyl, or dihydropyridazinyl are optionally substituted by one or more groups selected from the group consisting of R^{4a} and oxo, and

each R^{4a} is independently halo, CN, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -(C_1-C_3 alkylene)-O-(C_1-C_3 alkyl), C_3-C_6 cycloalkyl, -O-(C_1-C_3 alkyl), -O-(C_1-C_3 haloalkyl), or -$S(O)_2$(C_1-C_3 alkyl); Q is H; and

-L^1-O-L^2-Y-L^3- are taken together to form .

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

R^1 is ;

R^2 and R^3 are taken together with the carbon atom to which they are attached to form cyclopropyl;

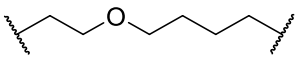
R^4 is phenyl, pyrazolyl, imidazolyl, thiazolyl, pyridinyl, 2-oxopyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyridazinyl, or quinazolinyl; wherein:

the phenyl, pyrazolyl, imidazolyl, thiazolyl, pyridinyl, 2-oxopyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or quinazolinyl are optionally substituted by one or more R^{4a} groups,

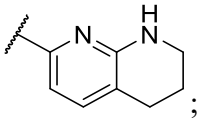
the dihydropyridinyl, dihydropyrimidinyl, or dihydropyridazinyl are optionally substituted by one or more groups selected from the group consisting of R^{4a} and oxo, and

each R^{4a} is independently halo, CN, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -(C_1-C_3 alkylene)-O-(C_1-C_3 alkyl), C_3-C_6 cycloalkyl, -O-(C_1-C_3 alkyl), -O-(C_1-C_3 haloalkyl), or -$S(O)_2$(C_1-C_3 alkyl);

Q is H; and

-L^1-O-L^2-Y-L^3- are taken together to form .

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

R^1 is ;

R^2 and R^3 are taken together with the carbon atom to which they are attached to form cyclopropyl;

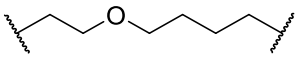
R^4 is pyrazolyl, imidazolyl, thiazolyl, pyridinyl, 2-oxopyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyridazinyl, or quinazolinyl; wherein:

the pyrazolyl, imidazolyl, thiazolyl, pyridinyl, 2-oxopyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, or quinazolinyl are optionally substituted by one or more R^{4a} groups,

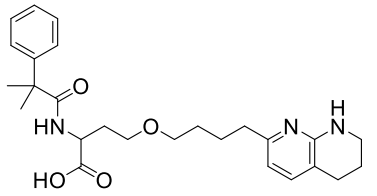
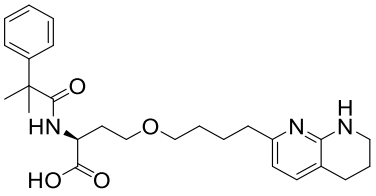
wherein the dihydropyridinyl, dihydropyrimidinyl, or dihydropyridazinyl are optionally substituted by one or more groups selected from the group consisting of R^{4a} and oxo, and

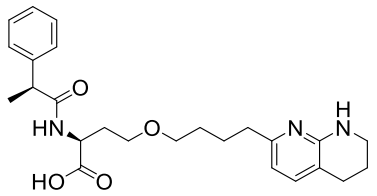
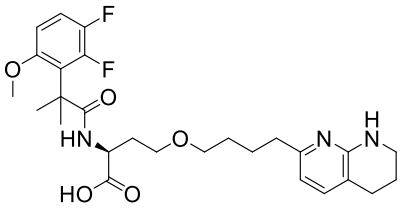
each R^{4a} is independently halo, CN, C_1-C_3 alkyl, C_1-C_3 haloalkyl, -(C_1-C_3 alkylene)-O-(C_1-C_3 alkyl), C_3-C_6 cycloalkyl, -O-(C_1-C_3 alkyl), -O-(C_1-C_3 haloalkyl), or -$S(O)_2$(C_1-C_3 alkyl);

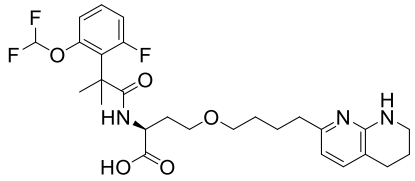
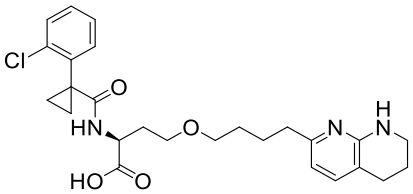
Q is H; and

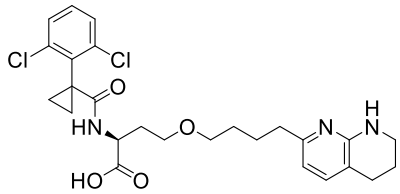
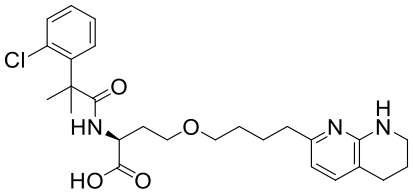
-L^1-O-L^2-Y-L^3- are taken together to form .

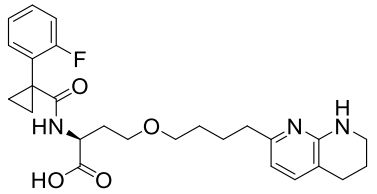
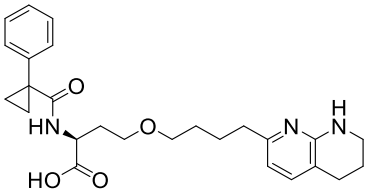
10. The compound of claim 1, wherein the compound is selected from the group consisting of

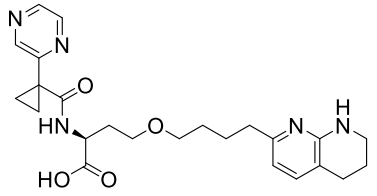
 ;  ;

 ;  ;

 ;  ;

 ;  ;

 ;  ;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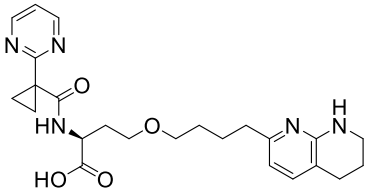
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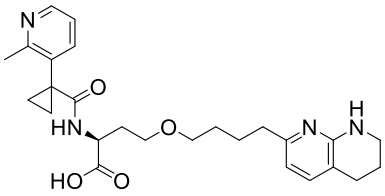
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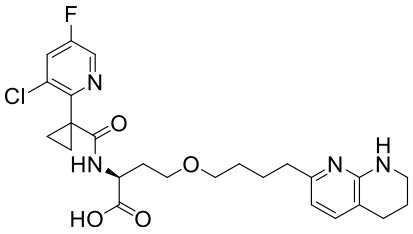
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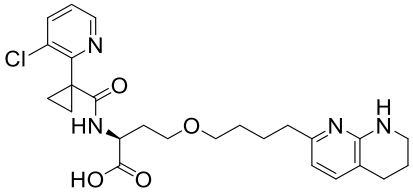
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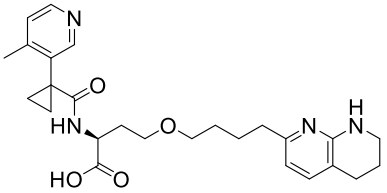
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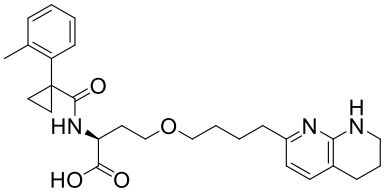
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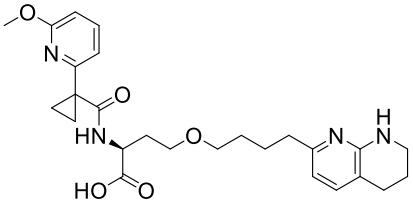
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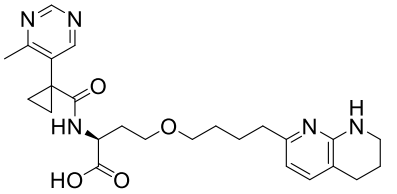
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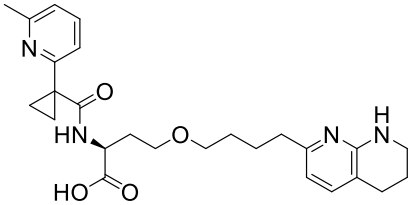
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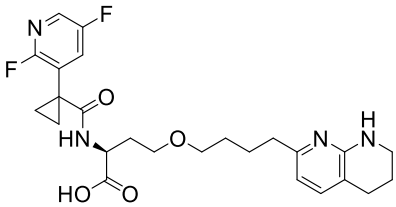
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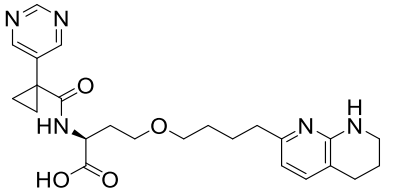
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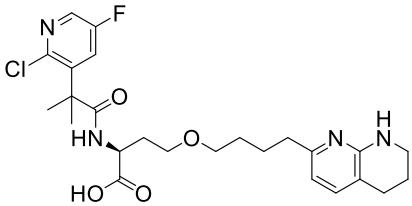
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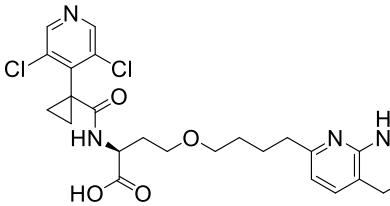
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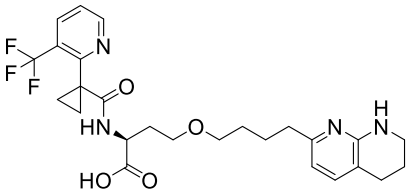
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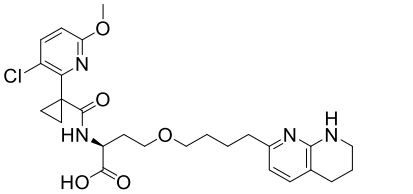
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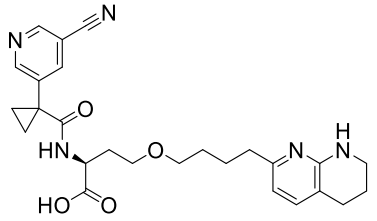
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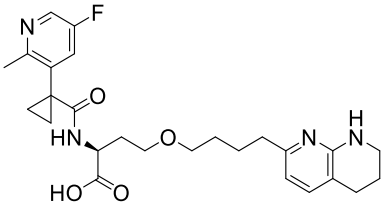
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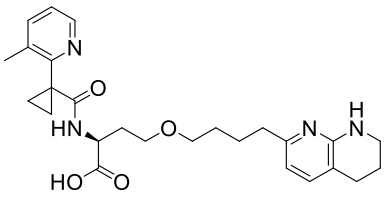
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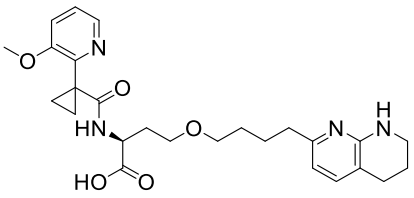
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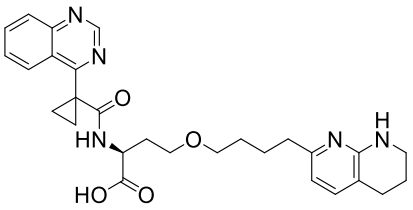
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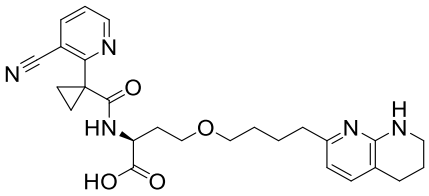
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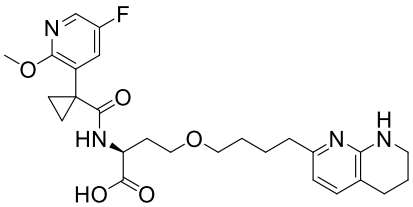
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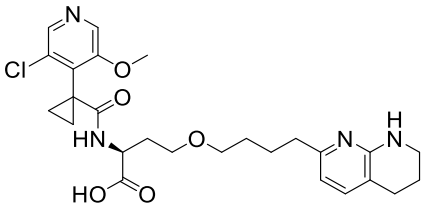
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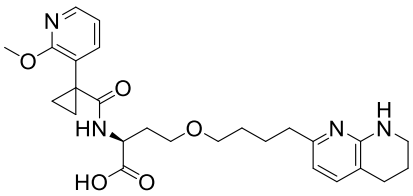
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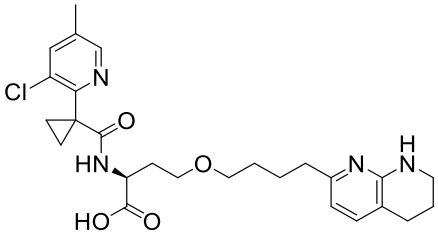
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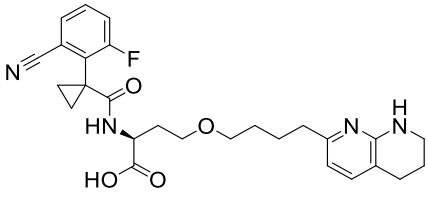
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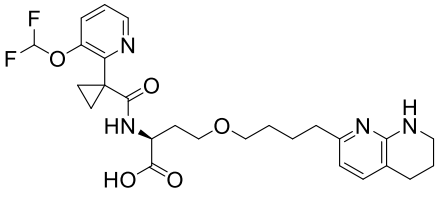
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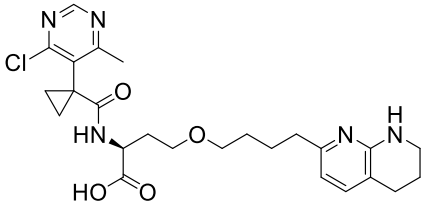
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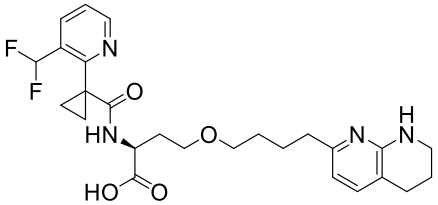
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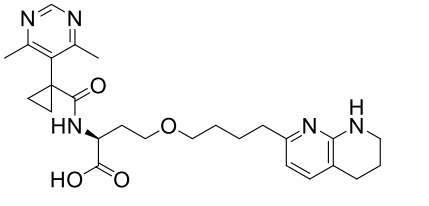
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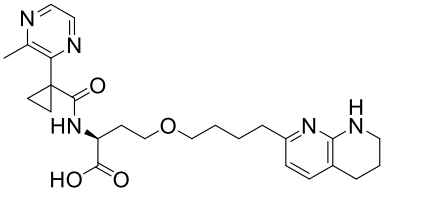
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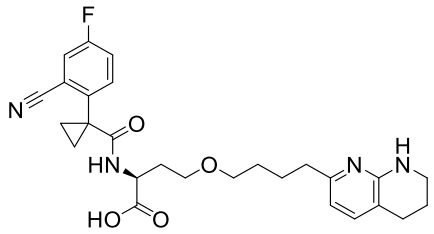
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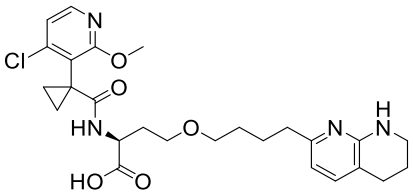
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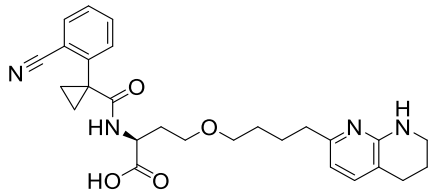
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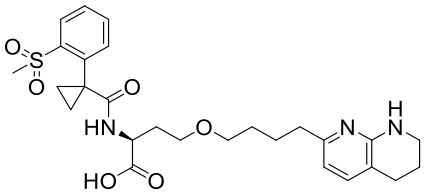
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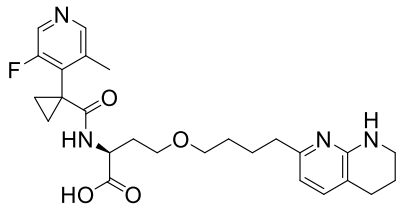
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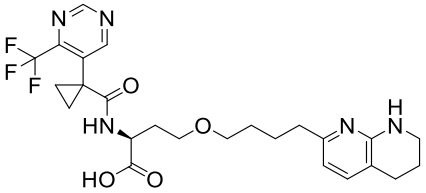
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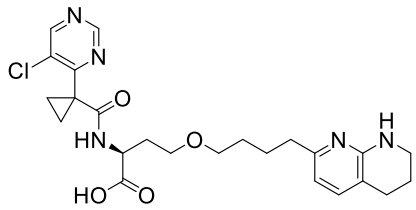
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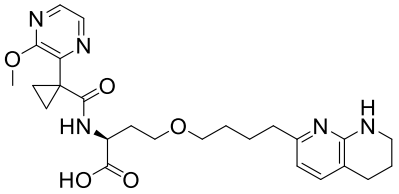
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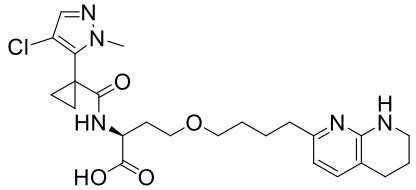
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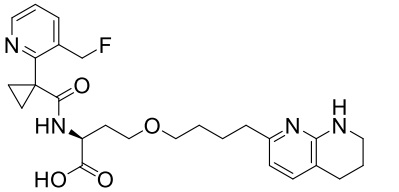
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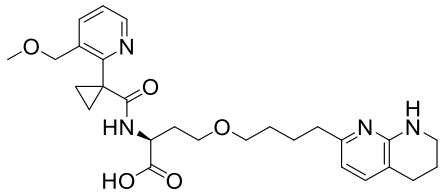
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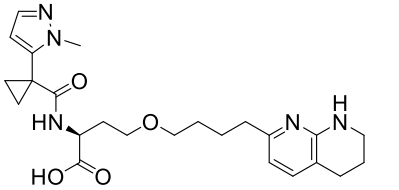
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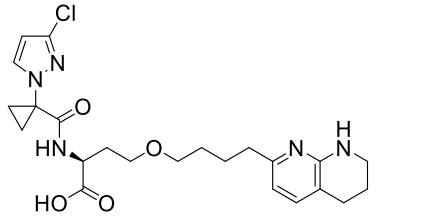
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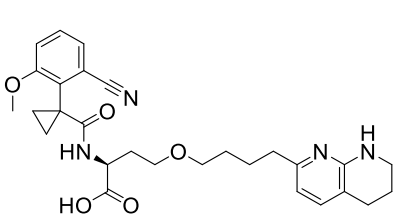
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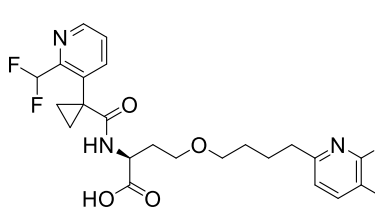
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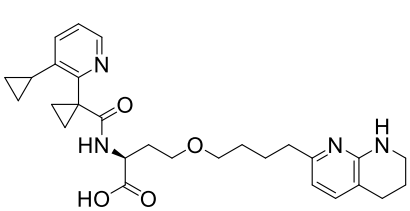
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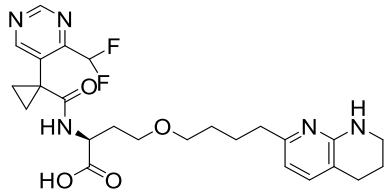
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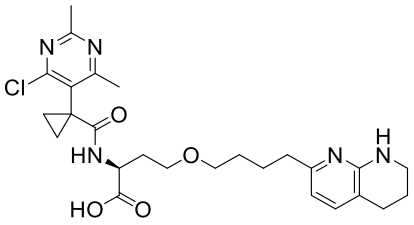
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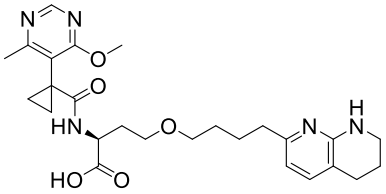
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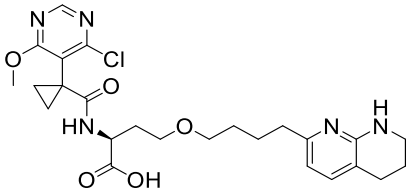
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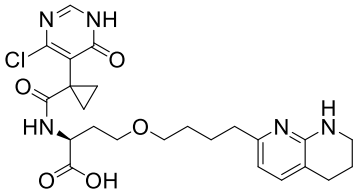
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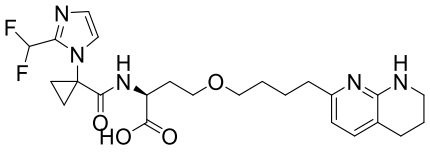
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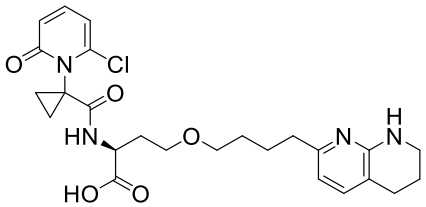
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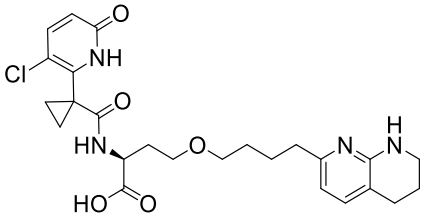
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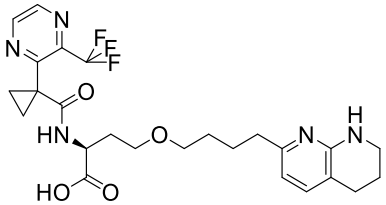
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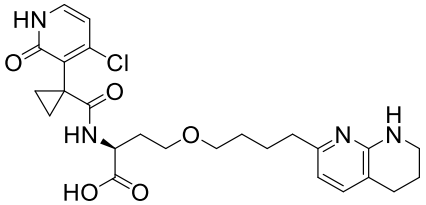
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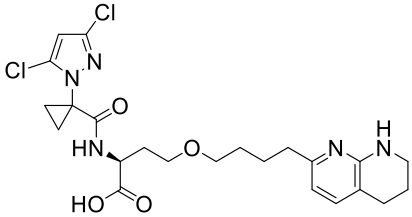
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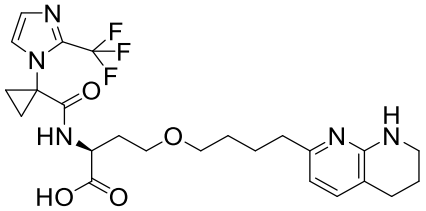
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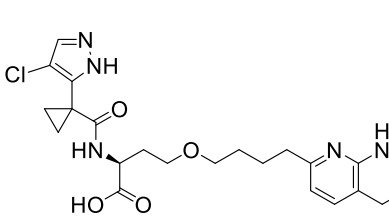
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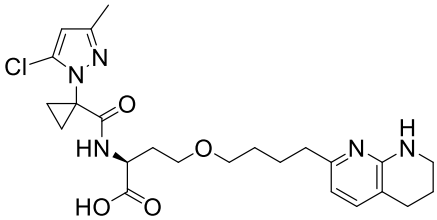
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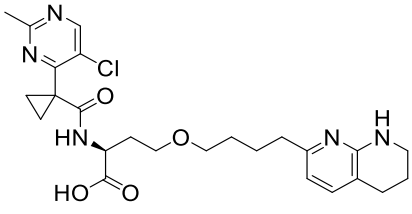
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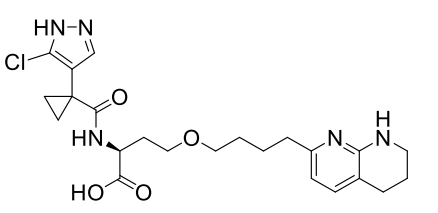
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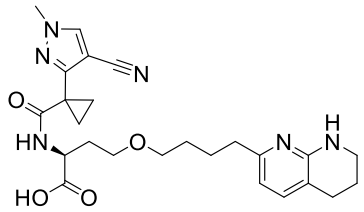
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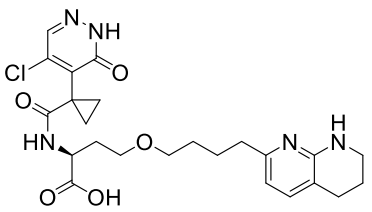
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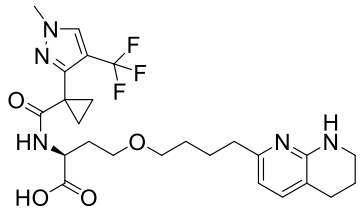
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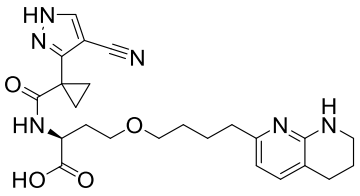
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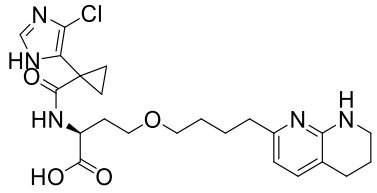
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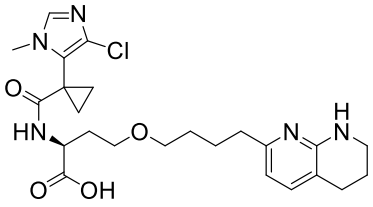
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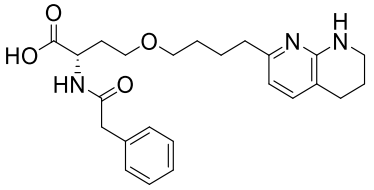
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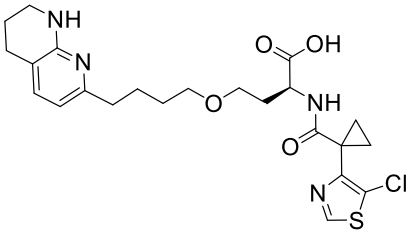
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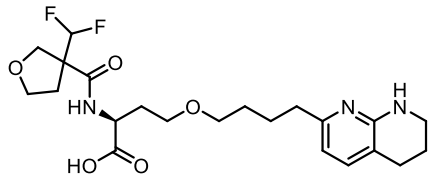
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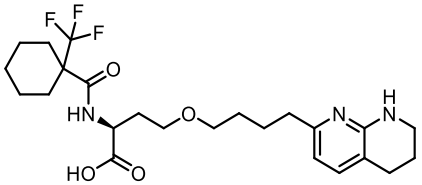
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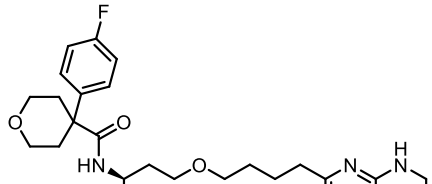
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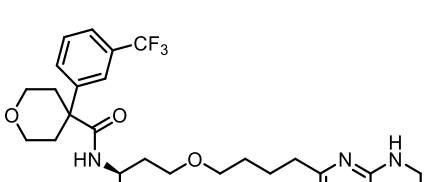
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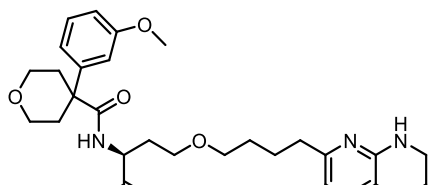
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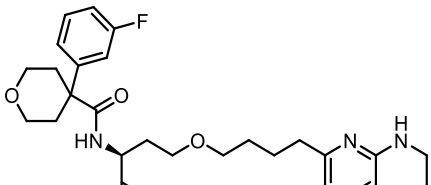
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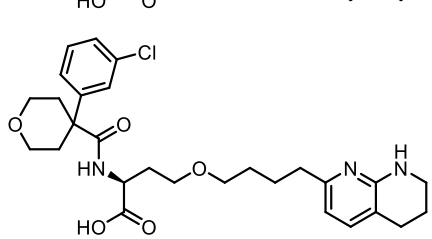
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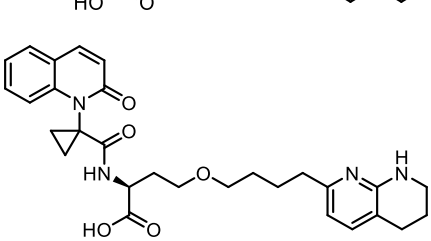
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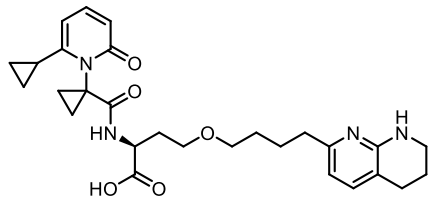
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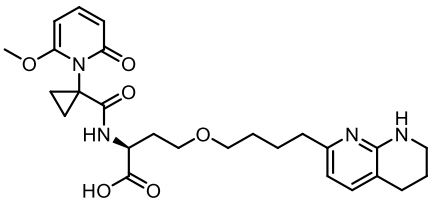
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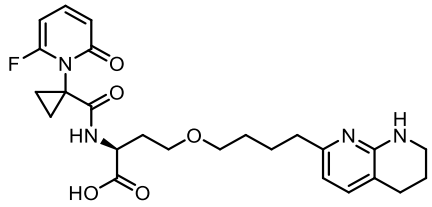
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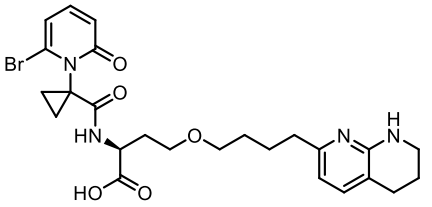
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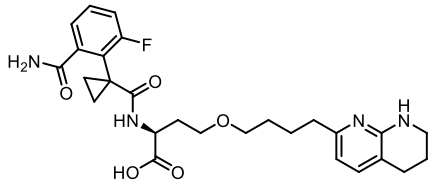
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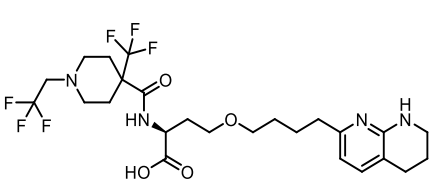
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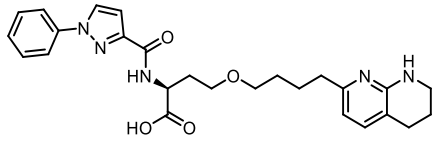
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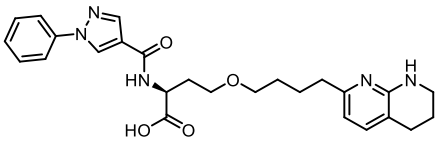
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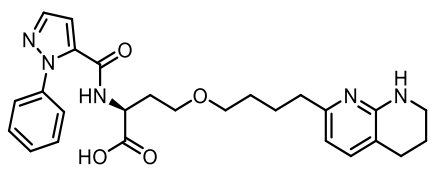
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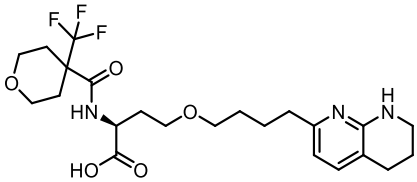
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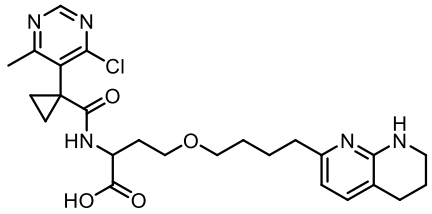
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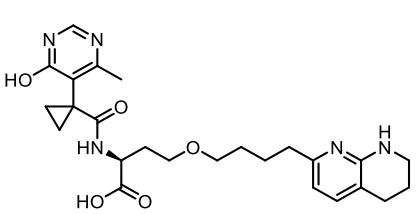
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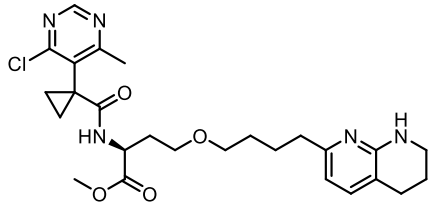
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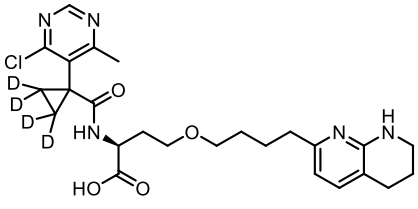
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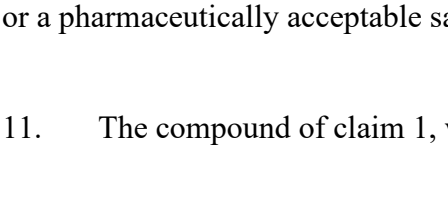
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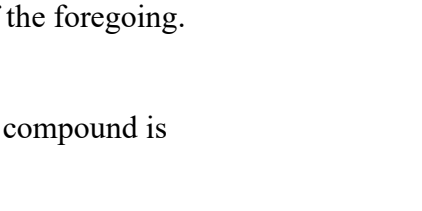
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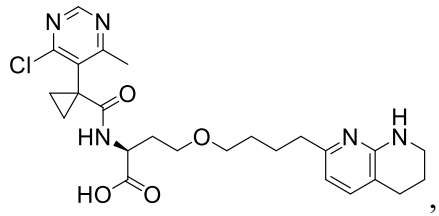
or a pharmaceutically acceptable salt of any of the foregoing.

11. The compound of claim 1, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

13. Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 12, in the manufacture of a medicament for the treatment of a fibrotic disease in an individual in need thereof, optionally wherein the fibrotic disease is pulmonary fibrosis, liver fibrosis, skin fibrosis, cardiac fibrosis, kidney fibrosis, gastrointestinal fibrosis, primary sclerosing cholangitis, or biliary fibrosis.

14. A kit comprising a compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 12, optionally further comprising instructions for the treatment of a fibrotic disease, or further comprising instructions directing a user to treat cancer in a subject in need thereof, the instructions comprising directing the user to administer to the subject the compound or the pharmaceutically acceptable salt thereof.

15. Use of a composition comprising a compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 12, in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, optionally wherein

the cancer comprises a solid tumor;

the cancer is selected from the group consisting of melanoma, colon cancer, non-small cell lung cancer, head and neck squamous cell carcinoma, squamous cell lung cancer, renal cell carcinoma, cutaneous squamous cell carcinoma (CSCC), urothelial carcinoma, metastatic Merkel cell carcinoma, gastric cancer, lung cancer, pancreatic cancer, and mesothelioma;

the cancer is breast cancer; or

the cancer is pancreatic ductal adenocarcinoma (PDAC).

16. The use of claim 15, wherein a chemotherapy agent is to be administered prior to, concurrently with, or subsequent the compound or the pharmaceutical composition;

optionally wherein the chemotherapy agent is selected from the group consisting of gemcitabine and Abraxane;

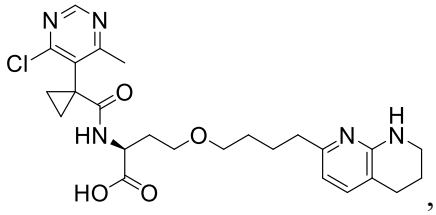
optionally wherein administration of the chemotherapy agent prior to, concurrently with, or subsequent the compound or the pharmaceutical composition reduces at least one of a weight of a tumor in the subject and lung metastases in the subject.

17. The use of claim 15, wherein a chemotherapy regimen is to be administered prior to, concurrently with, or subsequent the compound or the pharmaceutical composition;

optionally wherein the chemotherapy regimen comprises folfirinox;

optionally wherein administration of the chemotherapy regimen prior to, concurrently with, or subsequent the compound or the pharmaceutical composition reduces a weight of a tumor in the subject, optionally wherein the tumor is resistant to a chemotherapy regimen, optionally wherein the tumor is resistant to folfirinox.

18. The use of claim 15, wherein the cancer is selected from the group consisting of colon cancer, melanoma, breast cancer, pancreatic cancer, and pancreatic ductal adenocarcinoma (PDAC).

19. The use of claim 18, wherein the compound is 

, or a pharmaceutically acceptable salt thereof.

20. The use of claim 18 or 19, wherein the cancer is pancreatic cancer.

21. The use of claim 18 or 19, wherein the cancer is pancreatic ductal adenocarcinoma (PDAC).

22. The use of claim 15, wherein a checkpoint inhibitor that inhibits PD-1 is to be administered to the individual.

23. The composition for use of claim 22, wherein the checkpoint inhibitor that inhibits PD-1 is pembrolizumab.