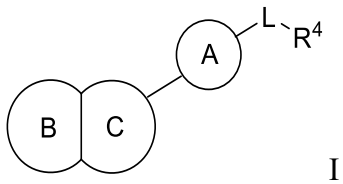
chromosome breakage. Thus, inhibiting the WRN helicase is an attractive strategy for the treatment of MSI-H cancers.

SUMMARY

[0005] There remains a need for new treatments and therapies for the treatment of cancer, and in particular cancers characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), including colorectal, gastric or endometrial cancer. The disclosure provides compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, said compounds being inhibitors of Werner Syndrome RecQ DNA Helicase (WRN). The disclosure further provides methods of treating, preventing, or ameliorating a disease or condition, comprising administering to a subject in need thereof an effective amount of a WRN inhibitor. The disclosure also provides compounds, pharmaceutically acceptable salts thereof, pharmaceutical compositions thereof and combinations thereof, said compounds being useful for the treatment of cancer, in particular cancers characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Also provided are compounds that bind to, and/or inhibit WRN, and are therefore useful as research chemicals, e.g., as a chemical probe, and as tool compounds. Various examples of the disclosure are described herein.

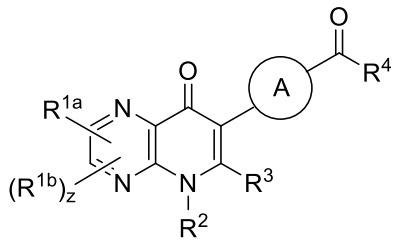
[0006] The disclosure provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:



I

wherein bicyclic Ring BC, linker L, R^4, and Ring A are as described and defined herein.

[0006a] In one aspect, the disclosure provides a compound of formula **II-e**:



II-e

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} is selected from groups a)-d)

a) a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from C_3-C_6cycloalkyl and C_3-C_6cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B;

b) a 4-6 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, NR_2, optionally substituted C_1-C_4aliphatic, -OR, azetidinyl optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen;

c) a 6-8 membered saturated or partially unsaturated bridged bicyclic heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, NR_2, optionally substituted C_1-C_4aliphatic, -OR, azetidinyl optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen; and

d) H, halogen, C_1-C_6alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, CN, -OR^{10}, -$NR^{10}R^{11}$, –$C(O)NR^{10}R^{11}$, –$CH_2NR^{10}R^{11}$, –SO_2R^{12}, or a 3-7 membered carbocyclyl, wherein said C_1-C_6alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, or 3-7 membered carbocyclyl is substituted with 0-3 independently selected R^B;

and wherein each R^{1b} group is independently selected from H, halogen, CN, OH, C_1-C_6alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylene-O-C_1-C_6alkyl, and C_3-C_6cycloalkoxy, wherein said C_1-C_6alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylene-O-C_1-C_6alkyl, and C_3-C_6cycloalkoxy are each independently optionally substituted with 1-5 halogen, OH, CN, C_1-C_6alkyl, and C_3-C_6cycloalkyl; wherein z is 0, 1, or 2;

Ring A is:

a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms); or

a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

wherein Ring A is substituted with 0-4 independently selected R^B substituents;

R^2 is $C(R^C)_2C(O)N(R)R^{2A}$;

R^{2A} is phenyl or pyridyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1-C_4aliphatic, haloC_1-C_4alkyl, C_3-C_6cycloalkyl, haloC_3-C_6cycloalkyl, -OH, -CN, C_1-C_4alkoxy, haloC_1-C_4alkoxy, and $–SF_5$, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, form a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) fused to the phenyl or pyridyl, wherein said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen; or

R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinolinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1-$_4$alkyl, and -OH;

R^3 is hydrogen, C_1-C_4aliphatic, C_3-C_5cycloalkyl, C_1-C_4alkoxy, -NHR^{3A}, -$N(R^{3A})_2$, or C_1-C_4alkylthio, each of which, besides hydrogen, is optionally substituted with -OH, 1-5 independently selected halogen, OR, -$C(O)NR^{10}R^{11}$, or N(R)C(O)R;

each R^{3A} is independently selected from C_1-C_4alkyl;

R^4 is phenyl or a first 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) wherein said phenyl or first 5-6 membered heteroaryl is substituted with 0-5 R^B; and optionally two adjacent atoms of said phenyl or first 5-6 membered heteroaryl have two substituents that together with said adjacent atoms form a cyclic group fused to the phenyl or first 5-6 membered heteroaryl selected from a 4-7 membered carbocyclyl, a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or a second 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said fused cyclic group is substituted with 0-3 independently selected R^B; or

R^4 is a C_1-C_4aliphatic, C_1-C_4alkoxy, or C_3-C_6cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocyclyloxy;

R^{10} is H, C_1-C_6aliphatic, haloC_1-C_6alkyl, C_3-C_6cycloalkyl, haloC_3-C_6cycloalkyl, –$C(O)C_1$-C_6alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R^{10} except H being optionally substituted with 1 or 2 independently selected R^B;

R^{11} is H, C_1-C_6aliphatic, or C_3-C_6cycloalkyl, or R^{10} and R^{11} are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C_1-C_4alkoxy, and haloC_1-C_4alkoxy;

R^{12} is C_1-C_6aliphatic, C_3-C_6cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R^{12} optionally substituted with 1

or 2 groups independently selected from halogen, C_1-C_6aliphatic, haloC_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, and C_3-C_6cycloalkoxy;

R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C_1-C_6aliphatic, haloC_1-C_6alkyl, C_3-C_6cycloalkyl, haloC_3-C_6cycloalkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_3-C_6cycloalkoxy, haloC_3-C_6cycloalkoxy, C_1-C_6alkylene-O-C_1-C_6alkyl, –CN, –NO_2, oxo, –OR, –SR, NR_2, $S(O)_2R$, $S(O)_2NR_2$, S(O)R, $S(O)NR_2$, C(O)R, C(O)OR, –$C(O)NR_2$, C(O)N(R)OR, OC(O)R, $OC(O)NR_2$, -N(R)C(O)OR, N(R)C(O)R, $N(R)C(O)NR_2$, $N(R)C(NR)NR_2$, $N(R)S(O)_2NR_2$, and –$N(R)S(O)_2R$;

R^C is independently selected at each occurrence from hydrogen, -CH_3, or -CH_2CH_3, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring;

each R is independently hydrogen, or an optionally substituted C_{1-6}aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said 4-7 membered saturated ring or 4-7 membered partially unsaturated ring has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0006b] In another aspect, the disclosure provides a compound selected from one of those shown in Table 1, Table 1a, Table 2, or Table 2a; or a pharmaceutically acceptable salt thereof.

[0007] In another aspect, the disclosure provides a pharmaceutical composition comprising a compound of Formula I of the present disclosure and one or more pharmaceutically acceptable carriers.

[0008] In another example, the disclosure provides a combination, in particular a pharmaceutical combination, comprising a compound of Formula I of the present disclosure and one or more therapeutically active agents.

[0008a] In another aspect, the disclosure provides a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0009] In another example, the disclosure provides a compound of Formula I of the present disclosure for use as a medicament, in particular for the treatment of a disorder or disease which can be treated by WRN inhibition.

[0009a] In another aspect, the disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder or disease which can be treated by WRN inhibition in a subject.

[0009b] In another aspect, the disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating WRN activity in a subject.

[0010] In another example, the disclosure provides a compound of Formula I of the present disclosure for use in the treatment of cancer, particularly wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

[0010a] In another aspect, the disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject, wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

[0011] In another example, the disclosure provides a method of treating a disorder or disease which can be treated by WRN inhibition in a subject, comprising administering to the subject a therapeutically effective amount of a compound of Formula I of the present disclosure.

[0012] In another example, the disclosure provides a method of treating cancer in a subject, more particularly wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), comprising administering to the subject a therapeutically effective amount of a compound of Formula I of the present disclosure.

[0013] In another example, the disclosure provides the use of a compound of Formula I of the present disclosure in the manufacture of a medicament for the treatment of a disorder or disease which can be treated by WRN inhibition.

[0013a] In another aspect, the disclosure provides use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting WRN in a subject.

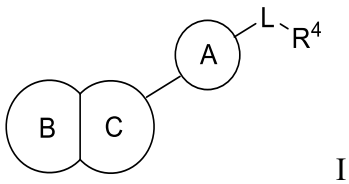
[0014] In another example, the disclosure provides a compound of Formula I of the present disclosure for use as a research chemical, for example as a chemical probe or as a tool compound.

[0015] In another example, the disclosure provides a solid form, process or intermediate as described herein.

DETAILED DESCRIPTION

1. General Description of Certain Embodiments of the Invention:

[0016] In one aspect, the disclosure provides a compound of Formula I, or a pharmaceutically acceptable salt thereof:

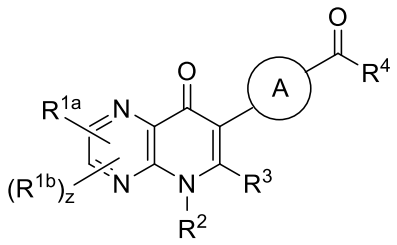


I

CLAIMS

We claim:

1. A compound of formula **II-e**:



II-e

or a pharmaceutically acceptable salt thereof;

wherein R^{1a} is selected from groups a)-d)

a) a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) optionally substituted with 1 or 2 groups independently selected from C_3-C_6cycloalkyl and C_3-C_6cycloalkoxy, wherein said 5-6 membered heteroaryl is further substituted with 0-3 independently selected R^B;

b) a 4-6 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, NR_2, optionally substituted C_1-C_4aliphatic, -OR, azetidinyl optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen;

c) a 6-8 membered saturated or partially unsaturated bridged bicyclic heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, NR_2, optionally

substituted C_1-C_4aliphatic, -OR, azetidinyl optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen; and

d) H, halogen, C_1-C_6alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, CN, -OR^{10}, -$NR^{10}R^{11}$, –$C(O)NR^{10}R^{11}$, –$CH_2NR^{10}R^{11}$, –SO_2R^{12}, or a 3-7 membered carbocyclyl, wherein said C_1-C_6alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, or 3-7 membered carbocyclyl is substituted with 0-3 independently selected R^B;

and wherein each R^{1b} group is independently selected from H, halogen, CN, OH, C_1-C_6alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylene-O-C_1-C_6alkyl, and C_3-C_6cycloalkoxy, wherein said C_1-C_6alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, C_1-C_6alkylene-O-C_1-C_6alkyl, and C_3-C_6cycloalkoxy are each independently optionally substituted with 1-5 halogen, OH, CN, C_1-C_6alkyl, and C_3-C_6cycloalkyl; wherein z is 0, 1, or 2;

Ring A is:

a 4-7 membered saturated or partially unsaturated bivalent monocyclic carbocyclylene or 4-7 membered saturated or partially unsaturated bivalent heterocyclylene ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and 0 or 1 nitrogen atoms in addition to the 1-4 heteroatoms); or

a 4-12 membered saturated or partially unsaturated bivalent bicyclic ring system that is fused, bridged, or spirocyclic selected from carbocyclylene or heterocyclylene (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur);

wherein Ring A is substituted with 0-4 independently selected R^B substituents;

R^2 is $C(R^C)_2C(O)N(R)R^{2A}$;

R^{2A} is phenyl or pyridyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1-C_4aliphatic, haloC_1-C_4alkyl, C_3-C_6cycloalkyl, haloC_3-C_6cycloalkyl, -OH, -CN, C_1-C_4alkoxy, haloC_1-C_4alkoxy, and –SF_5, and wherein two substituents on adjacent atoms of the phenyl or pyridyl, together with said adjacent atoms, form a 4-7 membered carbocyclyl fused to the phenyl or pyridyl, and wherein two substituents on adjacent atoms of the phenyl or pyridyl together with said adjacent atoms form a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and

sulfur) fused to the phenyl or pyridyl, wherein said fused 4-7 membered carbocyclyl or fused 4-7 membered heterocyclyl is substituted with 0-5 independently selected halogen; or

R^{2A} is 2-benzimidazolyl, 2-naphthyl, or 3-quinolinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halogen, C_1-$_4$alkyl, and -OH;

R^3 is hydrogen, C_1-C_4aliphatic, C_3-C_5cycloalkyl, C_1-C_4alkoxy, -NHR^{3A}, -$N(R^{3A})_2$, or C_1-C_4alkylthio, each of which, besides hydrogen, is optionally substituted with -OH, 1-5 independently selected halogen, OR, -$C(O)NR^{10}R^{11}$, or N(R)C(O)R;

each R^{3A} is independently selected from C_1-C_4alkyl;

R^4 is phenyl or a first 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur) wherein said phenyl or first 5-6 membered heteroaryl is substituted with 0-5 R^B; and optionally two adjacent atoms of said phenyl or first 5-6 membered heteroaryl have two substituents that together with said adjacent atoms form a cyclic group fused to the phenyl or first 5-6 membered heteroaryl selected from a 4-7 membered carbocyclyl, a 4-7 membered heterocyclyl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or a second 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said fused cyclic group is substituted with 0-3 independently selected R^B; or

R^4 is a C_1-C_4aliphatic, C_1-C_4alkoxy, or C_3-C_6cycloalkyl, each of which is substituted with 0-3 groups independently selected from halogen, -CN, -OH, C_1-C_4alkyl, C_1-C_4alkoxy, optionally substituted 5-6 membered heterocyclyl, and optionally substituted 5-6 membered heterocyclyloxy;

R^{10} is H, C_1-C_6aliphatic, haloC_1-C_6alkyl, C_3-C_6cycloalkyl, haloC_3-C_6cycloalkyl, –$C(O)C_1$-C_6alkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R^{10} except H being optionally substituted with 1 or 2 independently selected R^B;

R^{11} is H, C_1-C_6aliphatic, or C_3-C_6cycloalkyl, or R^{10} and R^{11} are taken together with the nitrogen atom to which they are attached to form a 5-6 membered ring optionally substituted with 1, 2, or 3 substituents independently selected from halogen, -OH, -CN, C_1-C_4alkoxy, and haloC_1-C_4alkoxy;

R^{12} is C_1-C_6aliphatic, C_3-C_6cycloalkyl, or a 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); each R^{12} optionally substituted with 1 or 2 groups independently selected from halogen, C_1-C_6aliphatic, haloC_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_6cycloalkyl, and C_3-C_6cycloalkoxy;

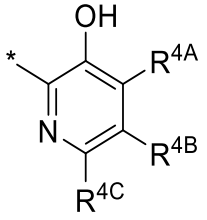
R^B is independently selected at each occurrence from the group consisting of optionally substituted phenyl, optionally substituted 5-6 membered heteroaryl (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur), optionally substituted 4-7 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), halogen, optionally substituted C_1-C_6aliphatic, haloC_1-C_6alkyl, C_3-C_6cycloalkyl, haloC_3-C_6cycloalkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy, C_3-C_6cycloalkoxy, haloC_3-C_6cycloalkoxy, C_1-C_6alkylene-O-C_1-C_6alkyl, –CN, $–NO_2$, oxo, –OR, –SR, NR_2, $S(O)_2R$, $S(O)_2NR_2$, S(O)R, $S(O)NR_2$, C(O)R, C(O)OR, $–C(O)NR_2$, C(O)N(R)OR, OC(O)R, $OC(O)NR_2$, -N(R)C(O)OR, N(R)C(O)R, $N(R)C(O)NR_2$, $N(R)C(NR)NR_2$, $N(R)S(O)_2NR_2$, and $–N(R)S(O)_2R$;

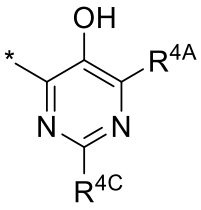
R^C is independently selected at each occurrence from hydrogen, $-CH_3$, or $-CH_2CH_3$, or two R^C taken together with the carbon to which they are attached form a cyclopropyl ring;

each R is independently hydrogen, or an optionally substituted C_{1-6}aliphatic group, an optionally substituted phenyl, an optionally substituted 3-7 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 3-7 membered saturated or partially unsaturated heterocyclic ring (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), or an optionally substituted 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); or

two R groups on the same atom are taken together with the same atom to form a cyclic group selected from an optionally substituted 4-7 membered saturated ring, a 4-7 membered partially unsaturated ring, or a 5-6 membered heteroaryl ring (having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur); wherein said 4-7 membered saturated ring or 4-7 membered partially unsaturated ring has 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is a Ring E that is selected from the group consisting of:



and


;

wherein * is a point of attachment to -C(O)-;

R^{4A} is hydrogen, halogen, $-CH_3$, $-CH_2CH_3$, -F, $-CF_2H$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-OCH_2CH_3$, or $-OCHF_2$;

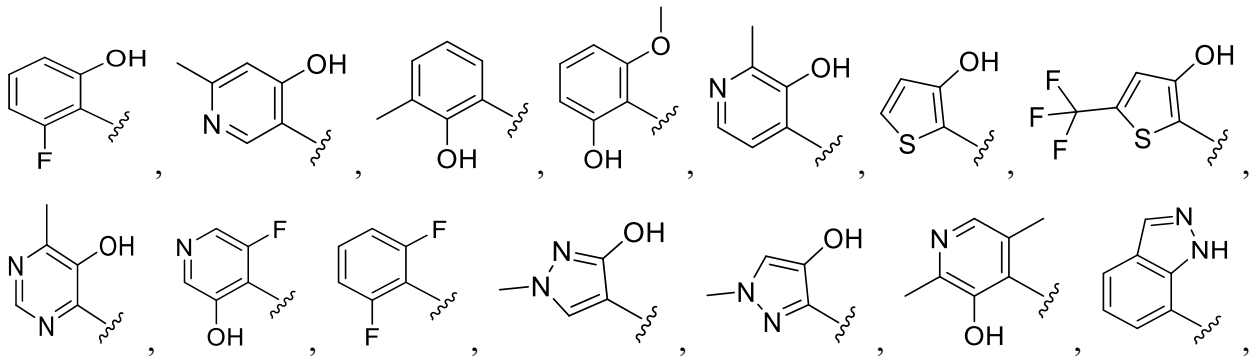
R^{4B} and R^{4C} are each independently selected from hydrogen, -CN, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, haloC_1-C_4alkyl, C_1-C_3alkyl substituted with -OH, $-OCH_3$, or $-OCH_2CH_3$, haloC_1-C_4alkoxy, C_3-C_6cycloalkyl, C_3-C_6cycloalkoxy, and $NR^{13}R^{14}$; and

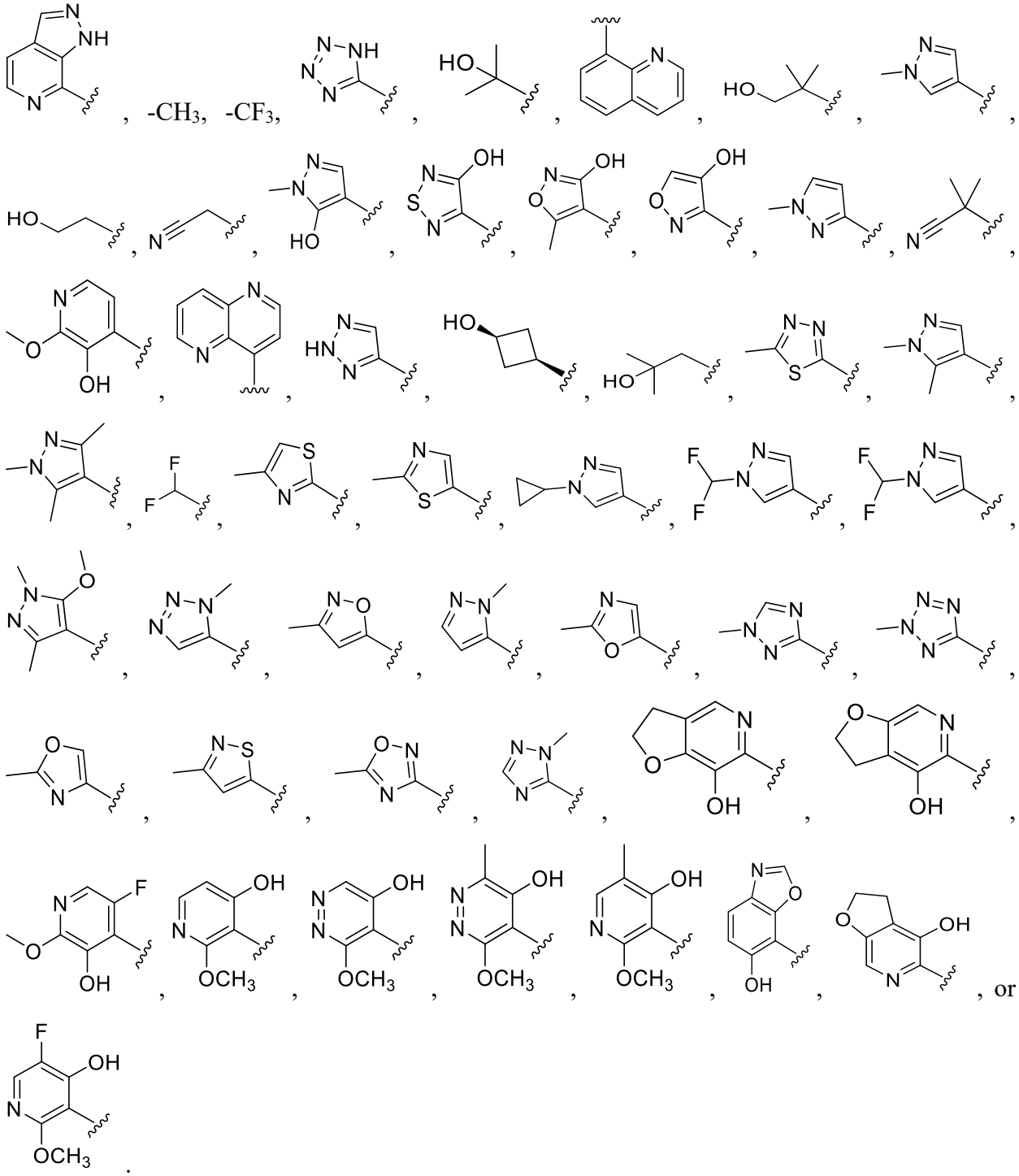
R^{13} is independently selected at each occurrence from hydrogen or C_1-C_4alkyl optionally substituted with -OH, $-OCH_3$, or $-OCH_2CH_3$; and

R^{14} is H; or

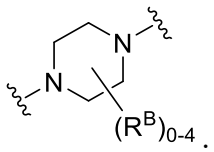
$NR^{13}R^{14}$, taken in combination, form a heterocyclic ring selected from azetidinyl, pyrrolidinyl, and piperidinyl; wherein said heterocyclic ring is optionally substituted with one or more $-CH_3$ groups.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^4 is

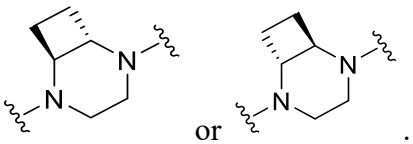




4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein Ring A and the 0-4 independently selected R^B substituents with which Ring A is substituted, is:



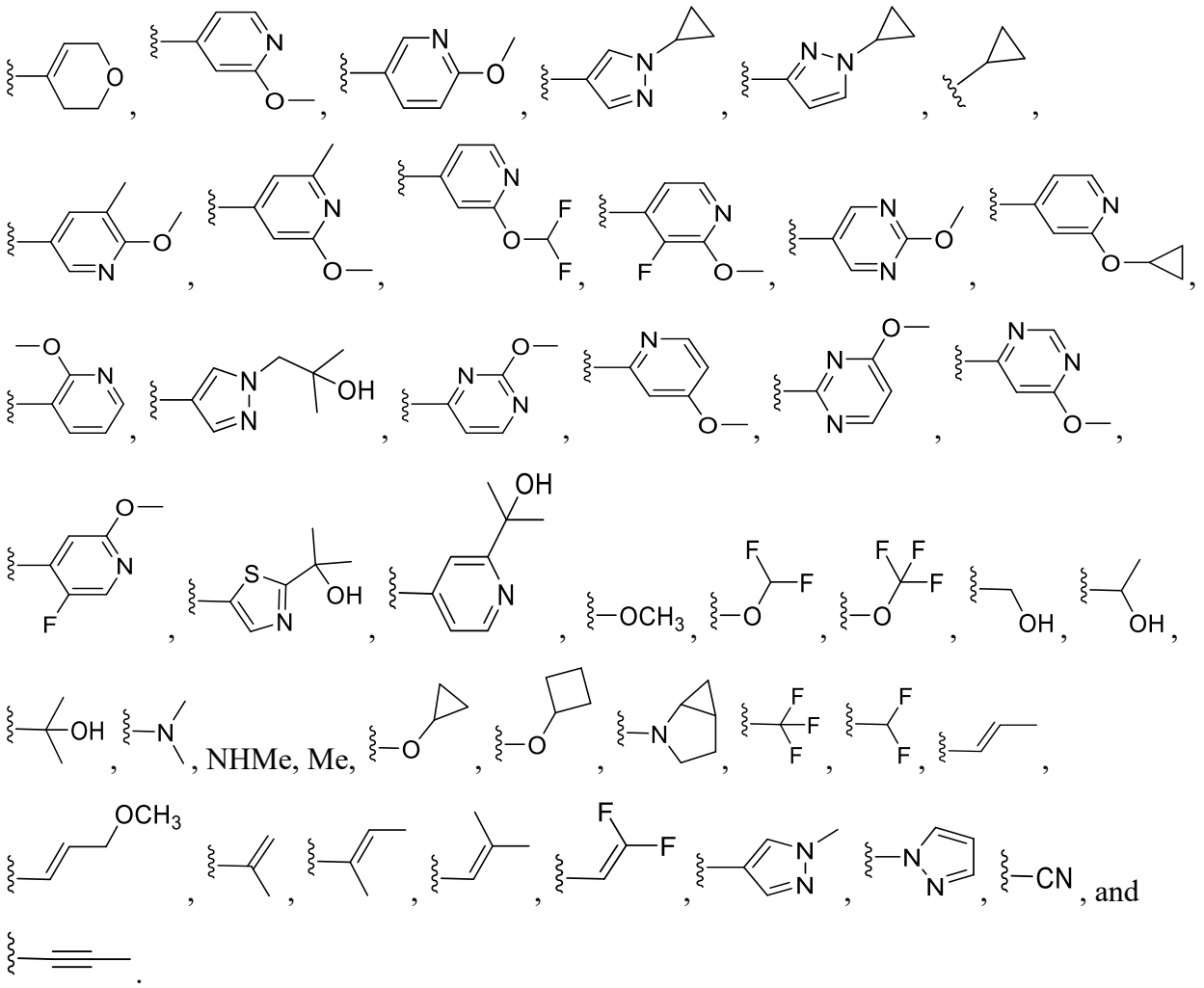
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein Ring A is:



6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is a 4-6 membered saturated or partially unsaturated heterocyclyl (having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur), said heterocyclyl substituted with 0-2 R^B groups independently selected from halogen, oxo, NR_2, optionally substituted C_{1-4}aliphatic, -OR, azetidinyl optionally substituted with 1 or 2 independently selected halogen, and pyrrolidinyl optionally substituted with 1 or 2 independently selected halogen; and R^{1b} is selected from H, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, and haloC_1-C_6alkoxy.

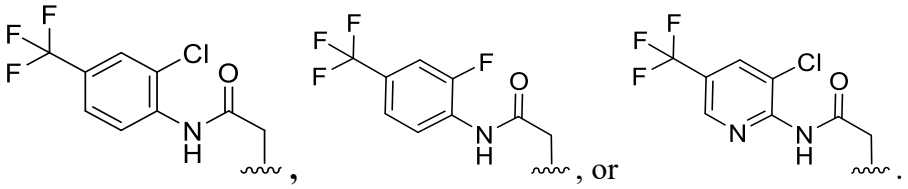
7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R^{1a} is halogen, C_1-C_6alkyl, C_2-C_4alkene, C_2-C_4alkyne, CN, -OR^{10}, -$NR^{10}R^{11}$, –$C(O)NR^{10}R^{11}$, –$CH_2NR^{10}R^{11}$, –SO_2R^{12}, or a C_3-C_7cycloalkyl, wherein said C_1-C_6alkyl, C_2-C_4alkene, C_2-C_4alkyne, and C_3-C_7cycloalkyl is substituted with 0-3 R^B groups independently selected from halogen, C_3-C_6cycloalkyl, haloC_3-C_6cycloalkyl, -OH, -CN, C_1-C_4alkoxy, and haloC_1-C_4alkoxy; and R^{1b} is selected from H, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, and haloC_1-C_6alkoxy.

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



9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^{2A} is phenyl comprising a -CF_3 substituent or pyridyl comprising a -CF_3 substituent.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein R^2 is:



11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_1-C_4alkyl or C_3-C_5cycloalkyl.

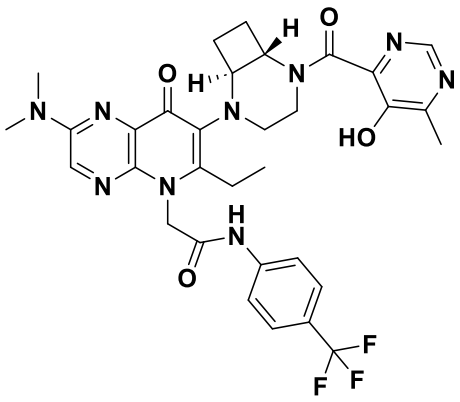
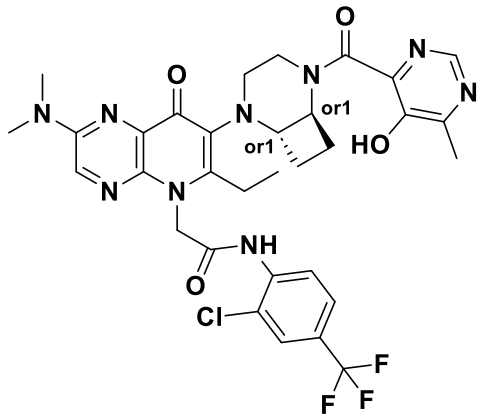
12. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_1-C_4alkyl optionally substituted with -OH, 1-5 independently selected halogen, or C_1-C_4alkoxy.

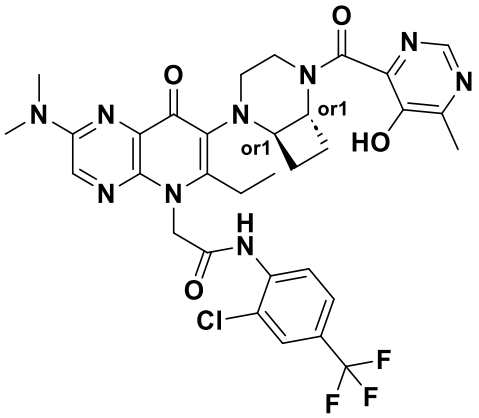
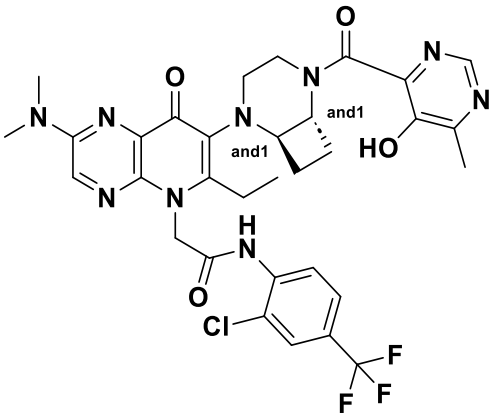
13. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein R^3 is C_1-C_4alkyl.

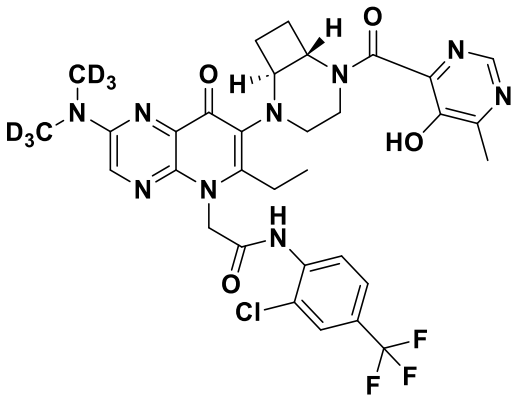
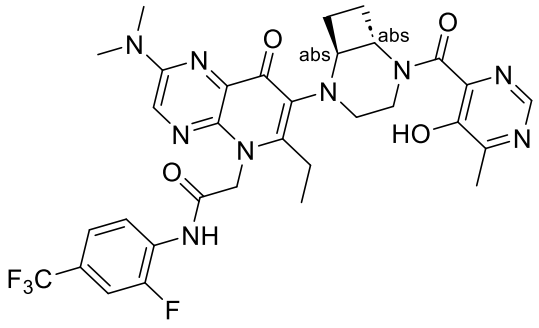
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^3 is $-CH_2CH_3$.

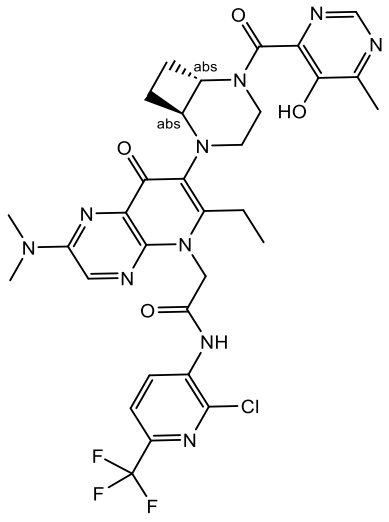
15. A compound selected from one of those shown in Table 1, Table 1a, Table 2, or Table 2a; or a pharmaceutically acceptable salt thereof.

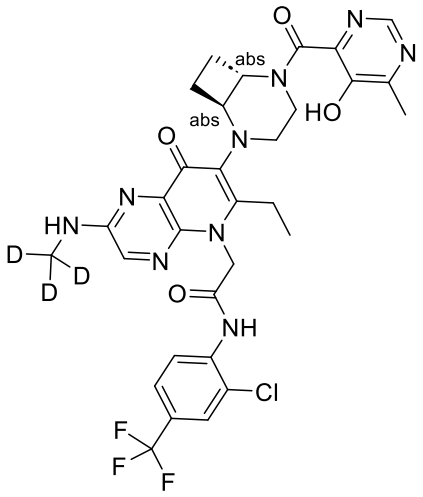
16. A compound of claim 1, selected from

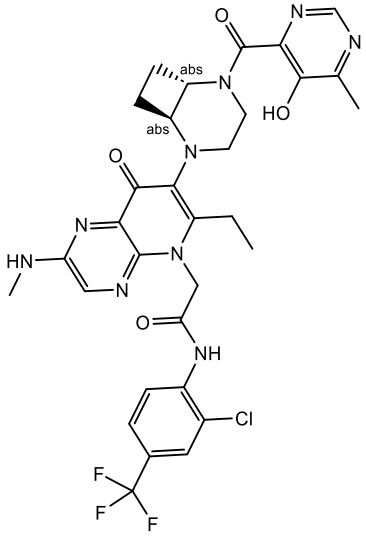
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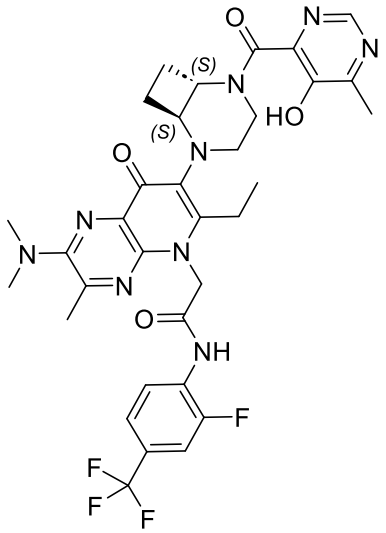
1-39  , I-34  ,

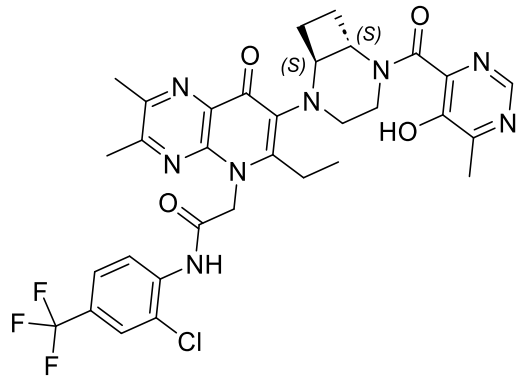
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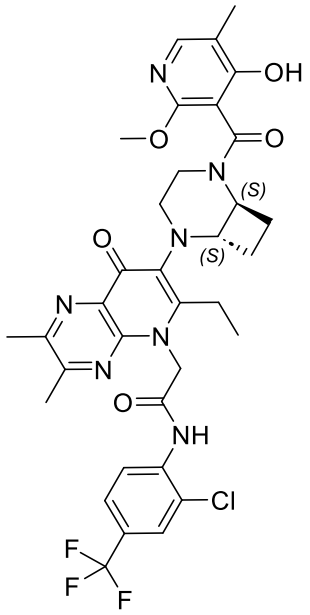
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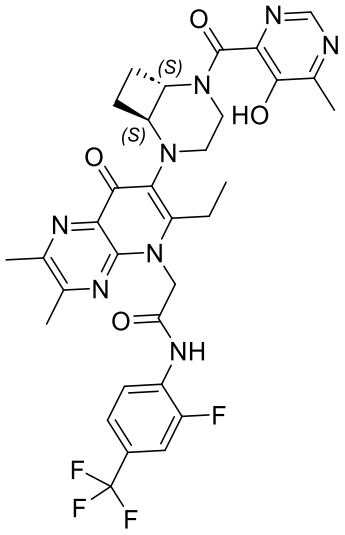
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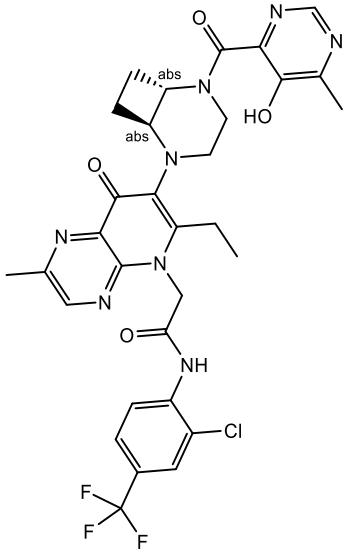
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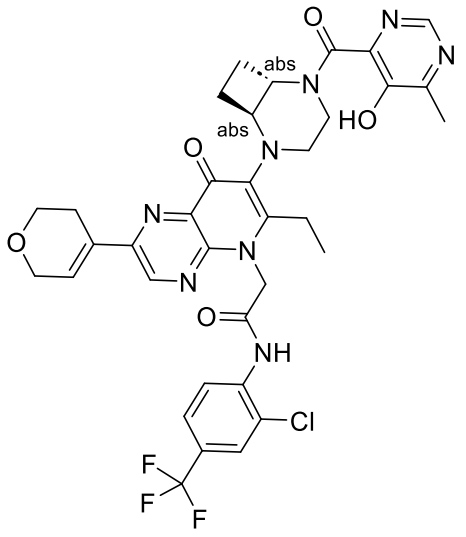
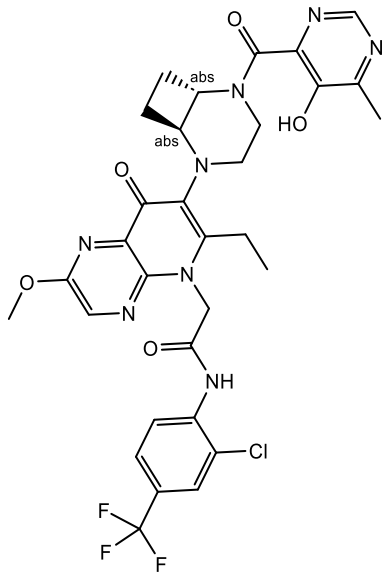
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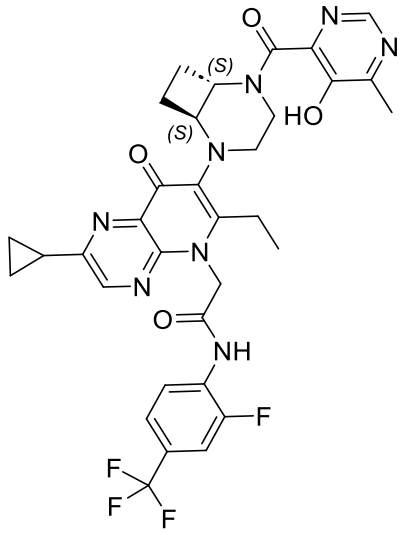
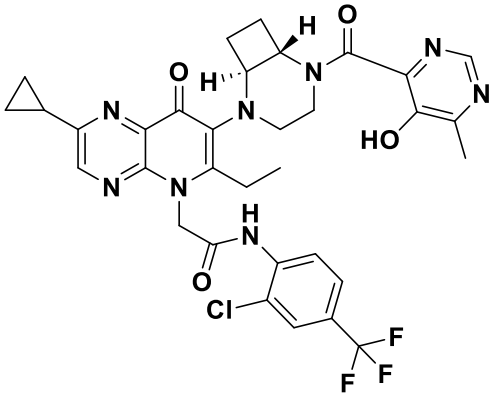
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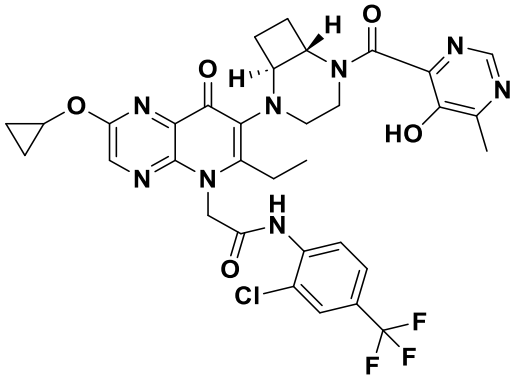
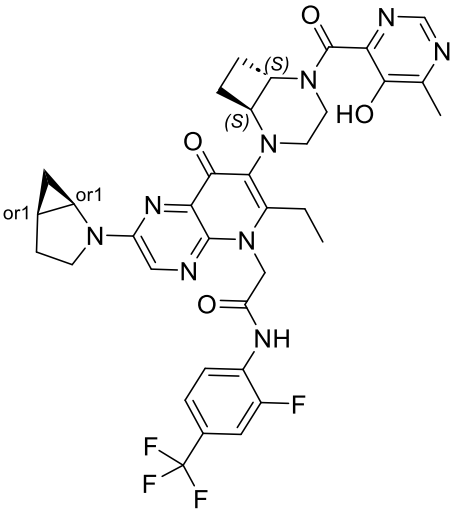
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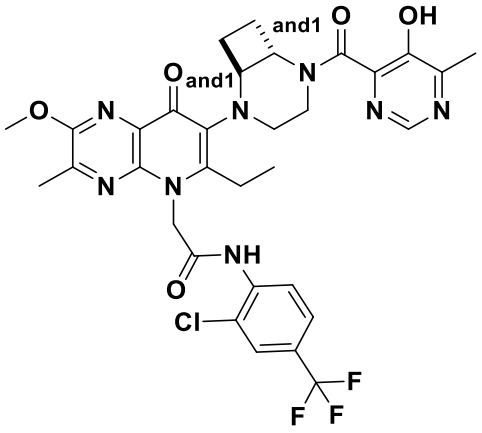
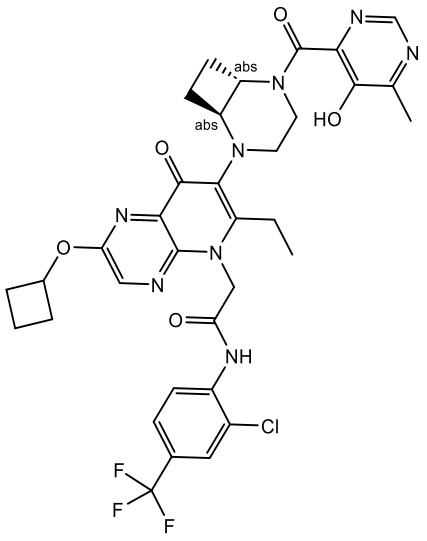
I-128  ,

I-262  ,

I-284 , I-182 ,

I-125 , I-100 ,

I-102 , I-122 ,

I-16  , or I-181  , or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of any one of claims 1-16, and one or more pharmaceutically acceptable carriers.

18. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject, wherein the cancer is characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

19. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating WRN activity in a subject.

20. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disorder or disease which can be treated by WRN inhibition in a subject.

21. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting WRN in a subject.

22. The use of claim 21, wherein the disorder or disease is a cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

23. The use of claim 22, wherein the cancer characterized as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) is selected from colorectal, gastric, prostate, endometrial, adrenocortical, uterine, cervical, esophageal, breast, kidney and ovarian cancer.

24. A compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, for use in therapy.