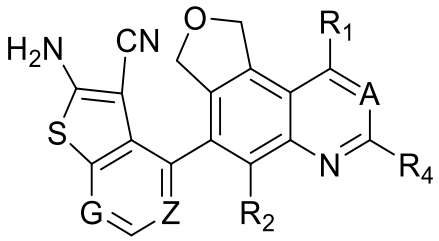
[0005a] In an aspect of the present disclosure, there is provided a compound of the formula:



wherein:

A is -C(H)- or -N-;

Z is -C(R_{3c})- or -N-;

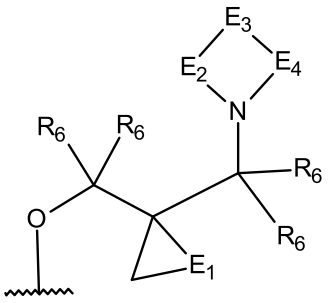
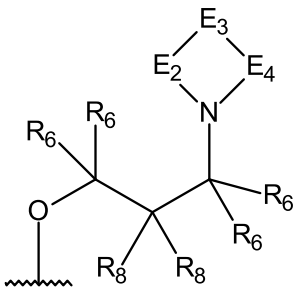
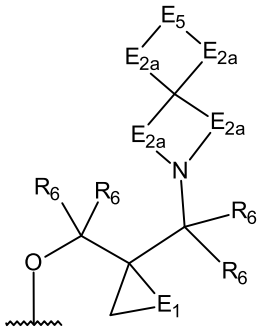
G is -C(R_{3b})- or -N-;

R_1 is H;

R_2 is H, halogen, or methyl;

R_{3b}, and R_{3c} are each independently H, halogen, or methyl;

R_4 is a N-linked cyclic amine or a group of the formula


, 
, or 
;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, morpholine, diazepane, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen; hydroxyl; -$NR_{6a}R_{6a}$; (1-methylpiperidin-4-yl)oxy; C_{1-3}

alkoxy optionally substituted with -$NR_{6a}R_{6a}$; C_{1-3} alkyl optionally substituted with one or more halogen, -$NR_{6a}R_{6a}$ or hydroxyl; an imidazole optionally substituted with a methyl; a monocyclic ring selected from azetidine, piperidine, piperazine, morpholine, oxazepane, or diazepane; a bicycle selected from hexahydro-1H-furo[3,4-c]pyrrole, octahydropyrrolo[3,4-c]pyrrole, or octahydropyrrolo[1,2-a]pyrazine; or a spirocycle selected from 4,7-diazaspiro[2.5]octane, 2-oxa-7-azaspiro[3.5]nonane, 2,6-diazaspiro[3.4]octane, or 2-azaspiro[3.3]heptane; wherein the monocyclic ring is optionally bridged by a C_{1-3} alkylene, and can optionally be substituted with one or more halogen, hydroxyl, -CN, C_{1-3} alkoxy, -$NR_{10}R_{10}$, cyclopropyl, oxetane, -CO-C_{1-3} alkyl, or a C_{1-3} alkyl optionally substituted with hydroxyl, C_{1-3} alkoxy, -$NR_{10}R_{10}$, halogen, or -CF_3; and wherein the bicyclo or spirocyclo is each optionally substituted with a methyl or a halogen; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.1]octane, 2,6-diazabicyclo[3.2.1]octane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-1H-pyrrolo[3,2-b]pyridine, octahydro-6H-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, hexahydro-1H-furo[3,4-b]pyrrole, octahydro-1H-pyrrolo[3,2-b]pyridine, (3as,6as)-tetrahydro-1H,4H-3a,6a-(methanooxymethano)pyrrolo[3,4-c]pyrrole, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, 5-azaspiro[2.4]heptane, 2-oxa-6-azaspiro[3.4]octane, 2,7-diazaspiro[4.4]nonane, 2-oxa-6-azaspiro[3.4]octane or1-oxa-7-azaspiro[4.4]nonane; each of which is optionally substituted with one or more halogen, -$NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with -$NR_{6a}R_{6a}$ or hydroxyl;

R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or -$NR_{6a}R_{6a}$;

R_{4b} is H, hydroxyl, or C_{1-3} alkyl;

R_{4c} is independently cyclopropyl, or oxetane;

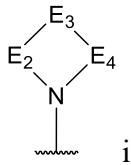
R_{4d} is independently C_{1-3} alkyl;

each R_6 is independently H or deuterium;

each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl, a N-methyl pyrrolidine, tetrahydrofuran, tetrahydropyran, bicyclo[1.1.1]pentan-1-yl, bicyclo[1.1.1]pentan-1-ol, or a C_{1-3} alkyl optionally substituted with one or more deuterium, hydroxyl, methyl, methoxy, halogen, cyclopropyl, oxetane, tetrahydrofuran, tetrahydropyran, -CO-NHMe, or -CO-NH_2, wherein the C_{3-5} cycloalkyl is optionally substituted with one or more hydroxyl or methyl;

E_1 is -O-C_{1-3} alkylene, or C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyl, C_{1-3} alkoxy or halogen, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene; and E_3 is -O-, -CR_7R_7-, -NR_9-, or -CO-NR_{6a}-; or

the ring 

is hexahydro-1H-furo[3,4-c]pyrrole;

each E_{2a} is independently a C_{1-3} alkylene optionally substituted with one or more hydroxyls;

E_5 is -O-, -CR_7R_7-, or -NR_9-;

each R_7 is independently H, halogen, CN, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls;

each R_8 is independently a C_{1-3} alkyl;

R_9 is each independently H, optionally substituted C_{1-3} alkyl or -CO-C_{1-3} alkyl; wherein the optionally substituted C_{1-3} alkyl is optionally substituted with one or more halogens; and

R_{10} is H or C_{1-3} alkyl optionally substituted with one or more deuterium; or a pharmaceutically acceptable salt thereof.

[0005b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

[0006] Also provided herein are methods of using the compounds of Formula I, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, to treat cancer, in particular for the treatment of lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer. The methods include administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

[0007] Further provided herein, are compounds of Formula I, and pharmaceutically acceptable salts thereof, for use in therapy. Additionally provided herein, are the compounds of Formula I, and pharmaceutically acceptable salts thereof, for use in the treatment of cancer, in particular for the treatment of lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer. Also additionally provided herein is the use of compounds of Formula I, or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating cancer, in particular for the treatment of lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

[0007a] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a patient for cancer, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

[0007b] In another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient for cancer, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

[0007c] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient with a cancer that has a KRas G12C, G12D, and/or G12V mutation.

[0007d] In another aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, as disclosed herein, for use in therapy.

[0007e] In a further aspect of the present disclosure, there is provided a use of the compound, or a pharmaceutically acceptable salt thereof, as disclosed herein, in the manufacture of a medicament for the treatment of cancer

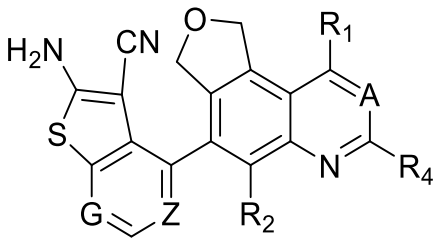
Detailed Description

[0008] Novel inhibitors of the KRas gain of function mutation G12C, G12D, and/or G12V are described herein. These new compounds could address the needs noted above for inhibitors of KRas GTP activity in gain of function mutants in the treatment of cancers such as lung cancer, colorectal cancer, pancreatic cancer, bladder cancer, cervical cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma or esophageal cancer. Some of these new KRas inhibitor compounds are selective to KRas G12D mutants over wild-type KRas (and likely other mutant types such as G12C or G12V). Additionally, some of these new KRas inhibitor compounds are non-selective and inhibit both wild-type KRas and KRas G12D mutants (and/or possibly other mutant types such as G12C or G12V). Also, some of these new KRas inhibitor compounds are non-selective and inhibit both wild-type KRas and Kras G12C, G12D, and/or G12V mutants.

[0009] The present invention provides a compound of Formula I:

What is Claimed is

1. A compound of the formula:



wherein:

A is -C(H)- or -N-;

Z is -C(R_{3c})- or -N-;

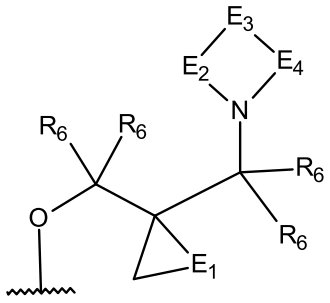
G is -C(R_{3b})- or -N-;

R_1 is H;

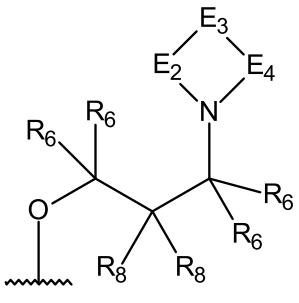
R_2 is H, halogen, or methyl;

R_{3b}, and R_{3c} are each independently H, halogen, or methyl;

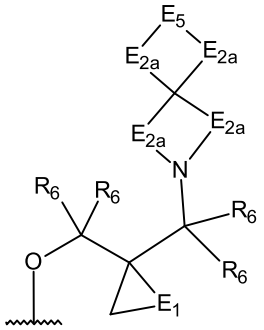
R_4 is a N-linked cyclic amine or a group of the formula



,



, or



;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, morpholine, diazepane, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen; hydroxyl; $-NR_{6a}R_{6a}$; (1-methylpiperidin-4-yl)oxy; C_{1-3} alkoxy optionally substituted with $-NR_{6a}R_{6a}$; C_{1-3} alkyl optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or hydroxyl; an imidazole optionally substituted with a methyl; a monocyclic ring selected from azetidine, piperidine, piperazine, morpholine, oxazepane, or diazepane; a bicycle selected from hexahydro-1H-furo[3,4-c]pyrrole, octahydropyrrolo[3,4-c]pyrrole, or octahydropyrrolo[1,2-a]pyrazine; or a spirocycle selected from 4,7-diazaspiro[2.5]octane, 2-oxa-7-azaspiro[3.5]nonane, 2,6-diazaspiro[3.4]octane, or 2-azaspiro[3.3]heptane; wherein the monocyclic ring is optionally bridged by a C_{1-3} alkylene, and can optionally be substituted with one or more halogen, hydroxyl, -CN, C_{1-3} alkoxy, $-NR_{10}R_{10}$, cyclopropyl, oxetane, $-CO-C_{1-3}$ alkyl, or a C_{1-3} alkyl optionally substituted with hydroxyl, C_{1-3} alkoxy, $-NR_{10}R_{10}$, halogen, or $-CF_3$; and wherein the bicyclo or spirocyclo is each optionally substituted with a methyl or a halogen; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.1]octane, 2,6-diazabicyclo[3.2.1]octane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-1H-pyrrolo[3,2-b]pyridine, octahydro-6H-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, hexahydro-1H-furo[3,4-b]pyrrole, octahydro-1H-pyrrolo[3,2-b]pyridine, (3as,6as)-tetrahydro-1H,4H-3a,6a-(methanooxymethano)pyrrolo[3,4-c]pyrrole, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, 5-azaspiro[2.4]heptane, 2-oxa-6-azaspiro[3.4]octane, 2,7-diazaspiro[4.4]nonane, 2-oxa-6-azaspiro[3.4]octane or1-oxa-7-azaspiro[4.4]nonane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$ or hydroxyl;

R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, piperazine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$;

R_{4b} is H, hydroxyl, or C_{1-3} alkyl;

R_{4c} is independently cyclopropyl, or oxetane;

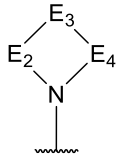
R_{4d} is independently C_{1-3} alkyl;

each R_6 is independently H or deuterium;

each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl, a N-methyl pyrrolidine, tetrahydrofuran, tetrahydropyran, bicyclo[1.1.1]pentan-1-yl, bicyclo[1.1.1]pentan-1-ol, or a C_{1-3} alkyl optionally substituted with one or more deuterium, hydroxyl, methyl, methoxy, halogen, cyclopropyl, oxetane, tetrahydrofuran, tetrahydropyran, -CO-NHMe, or $-CO-NH_2$, wherein the C_{3-5} cycloalkyl is optionally substituted with one or more hydroxyl or methyl;

E_1 is $-O-C_{1-3}$ alkylene, or C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyl, C_{1-3} alkoxy or halogen, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene; and E_3 is -O-, $-CR_7R_7-$, $-NR_9-$, or $-CO-NR_{6a}-$; or



the ring is hexahydro-1H-furo[3,4-c]pyrrole;

each E_{2a} is independently a C_{1-3} alkylene optionally substituted with one or more hydroxyls;

E_5 is -O-, $-CR_7R_7-$, or $-NR_9-$;

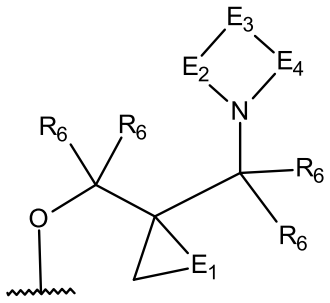
each R_7 is independently H, halogen, CN, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls;

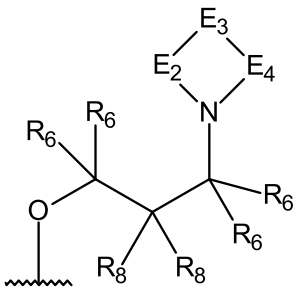
each R_8 is independently a C_{1-3} alkyl;

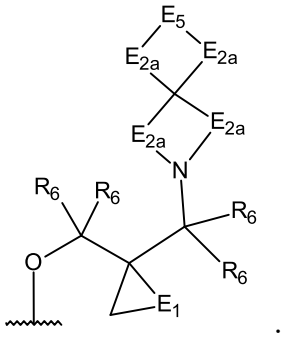
R_9 is each independently H, optionally substituted C_{1-3} alkyl or -CO-C_{1-3} alkyl; wherein the optionally substituted C_{1-3} alkyl is optionally substituted with one or more halogens; and

R_{10} is H or C_{1-3} alkyl optionally substituted with one or more deuterium; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R_4 is a N-linked cyclic amine or a group of the formula



,


, or


;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, morpholine, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, C_{1-3} alkoxy, -$NR_{6a}R_{6a}$, azetidine, piperazine, morpholine, a C_{1-3} alkyl, or an imidazole optionally substituted with a methyl; wherein the azetidine is optionally substituted with hydroxyl or C_{1-3} alkoxy; the piperazine is optionally substituted with a methyl, and the C_{1-3} alkyl is optionally substituted with one or more halogen, -$NR_{6a}R_{6a}$ or hydroxyl; or

iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.1]octane, 2,6-diazabicyclo[3.2.1]octane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-1H-pyrrolo[3,2-b]pyridine, octahydro-6H-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-

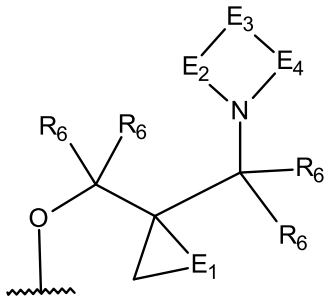
b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, 5-azaspiro[2.4]heptane, or 2-oxa-6-azaspiro[3.4]octane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$;

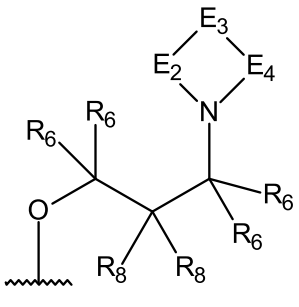
R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$;

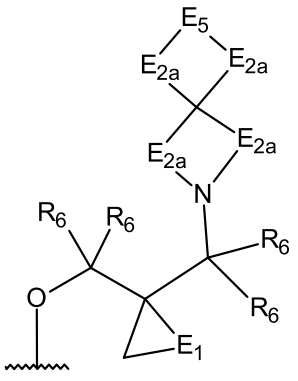
each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl, tetrahydrofuran, tetrahydropyran, bicyclo[1.1.1]pentan-1-yl, or a C_{1-3} alkyl optionally substituted with one or more hydroxyl, methyl, methoxy, halogen, cyclopropyl, oxetane, tetrahydrofuran, tetrahydropyran,

-CO-NHMe, or $-CO-NH_2$, wherein the C_{3-5} cycloalkyl is optionally substituted with one or more hydroxyl or methyl; or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein R_4 is a N-linked cyclic amine or a group of the formula



,


, or


;

wherein the N-linked cyclic amine is a N-linked:

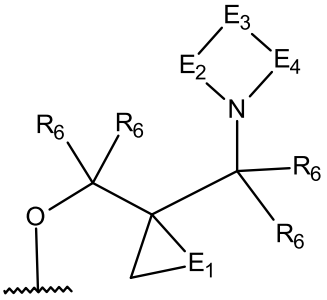
i. azetidine substituted with R_{4a} and R_{4b};

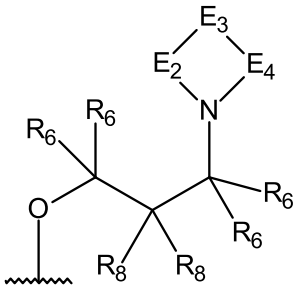
ii pyrrolidine, piperidine, piperazine, morpholine, imidazole or pyrazole; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, C_{1-3} alkoxy, $-NR_{6a}R_{6a}$, azetidine, a C_{1-3} alkyl, or an imidazole optionally substituted with a methyl; wherein the azetidine is optionally substituted with hydroxyl or C_{1-3} alkoxy; and the C_{1-3} alkyl is optionally substituted with halogen-$NR_{6a}R_{6a}$ or hydroxyl; or

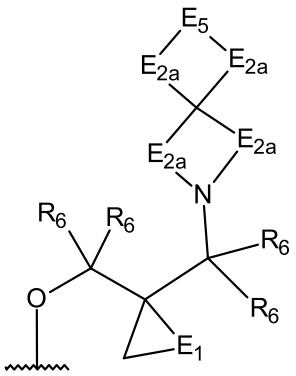
iii. 2,6-diazabicyclo[3.2.0]heptane, 3,6-diazabicyclo[3.2.0]heptane, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, octahydro-1H-pyrrolo[3,4-b]pyridine, octahydro-6-pyrrolo[3,4-b]pyrazine, octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,2-b]pyrrole, octahydropyrrolo[3,4-b][1,4]oxazine, octahydropyrrolo[3,4-b]pyrrole, octahydropyrrolo[3,4-c]pyrrole, tetrahydrofuro[3,4-d]oxazol-2(3H)-one, (R)-1,7-diazaspiro[4.4]nonane, (S)-1,7-diazaspiro[4.4]nonane, 1,6-diazaspiro[3.3]heptane, 1,6-diazaspiro[3.4]octane, 2,5-diazaspiro[3.4]octane, 2,5-diazaspiro[3.5]nonane, 2,6-diazaspiro[3.3]heptane, 2,6-diazaspiro[3.4]octane, 2-azaspiro[3.3]heptane, 4-azaspiro[2.4]heptane, or 5-azaspiro[2.4]heptane; each of which is optionally substituted with one or more halogen, $-NR_{6a}R_{6a}$ or a C_{1-3} alkyl optionally substituted with $-NR_{6a}R_{6a}$;

R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, piperidine, morpholine or imidazole, wherein the cyclopropyl, azetidine, pyrrolidine, piperidine, or morpholine is optionally substituted with halogen, hydroxyl, C_{1-3} alkoxy or $-NR_{6a}R_{6a}$; and each R_{6a} is independently H, trideuteromethyl, a C_{3-5} cycloalkyl or a C_{1-3} alkyl optionally substituted with hydroxyl; or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1-3, wherein R_{3b}, and R_{3c} are each independently H or halogen, and R_4 is a N-linked cyclic amine or a group of the formula



, 

, or 

;

wherein the N-linked cyclic amine is a N-linked:

i. azetidine substituted with R_{4a} and R_{4b};

ii. pyrrolidine, piperidine, piperazine, or morpholine; each of which is optionally bridged by a C_{1-3} alkylene, and each of which is optionally substituted with one or more halogen, hydroxyl, $-NR_{6a}R_{6a}$, imidazole or a C_{1-3} alkyl; wherein the imidazole is optionally substituted with a methyl; and the C_{1-3} alkyl is optionally substituted with $-NR_{6a}R_{6a}$ or hydroxyl; or

iii. octahydropyrrolo[1,2-a]pyrazine, octahydropyrrolo[3,4-c]pyrrole, 1,6-diazaspiro[3.3]heptane, or 1,6-diazaspiro[3.4]octane; each of which is optionally substituted with one or more halogen, or a C_{1-3} alkyl;

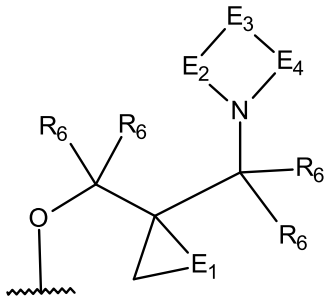
R_{4a} is $NR_{4c}R_{4d}$, cyclopropyl, azetidine, pyrrolidine, morpholine, wherein the cyclopropyl, azetidine, pyrrolidine or morpholine is optionally substituted with halogen, or $-NR_{6a}R_{6a}$;

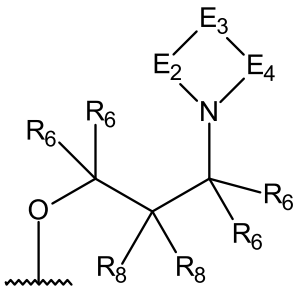
R_{4b} is H, or C_{1-3} alkyl;

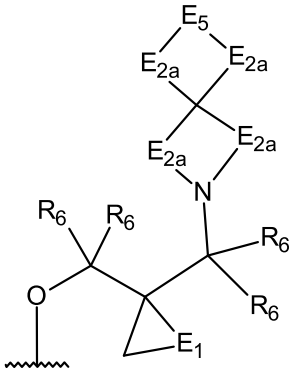
each R_{6a} is independently H or C_{1-3} alkyl;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyl or halogen, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene; and E_3 is -O-, $-CR_7R_7-$, $-NR_9-$, or $-CO-NR_{6a}-$; or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1-4, wherein R_{3b}, and R_{3c} are each independently H or halogen, and R_4 is a group of the formula



, 

, or 

;

E_1 is C_{1-3} alkylene optionally substituted with one or more halogens;

E_2, and E_4 are each independently C_{1-3} alkylene optionally substituted with one or more hydroxyls, and wherein E_2 and E_4 can optionally be bridged by a bond or a C_{1-3} alkylene;

E_3 is -O-, $-CR_7R_7$-, $-NR_9$-, or $-CO-NR_{6a}$-;

each R_{6a} is independently H or C_{1-3} alkyl;

each R_7 is independently H, halogen, hydroxyl, C_{1-3} alkoxy, or C_{1-3} alkyl optionally substituted with one or more halogens or hydroxyls; and

R_9 is each independently H, C_{1-3} alkyl or $-CO-C_{1-3}$ alkyl; or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1-5, wherein G is -N-, or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of claims 1-5, wherein G is $-C(R_{3b})$-, or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 7, wherein R_{3b} is F, or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of claims 1-8, wherein Z is -N-, or a pharmaceutically acceptable salt thereof.

10. The compound according to any one of claims 1-8, wherein Z is -C(R_{3c})-, or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10, wherein R_{3c} is H or F, or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of claims 1-5, 7 or 10, wherein R_{3b}, and R_{3c} are each independently H or halogen, or a pharmaceutically acceptable salt thereof.

13. The compound according to any one of claims 1-12, wherein A is -N-, or a pharmaceutically acceptable salt thereof.

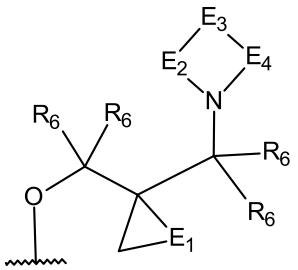
14. The compound according to any one of claims 1-12, wherein A is -C(H)-, or a pharmaceutically acceptable salt thereof.

15. The compound according to any one of claims 1-14, wherein R_2 is F or Cl, or a pharmaceutically acceptable salt thereof.

16. The compound according to any one of claims 1-14, wherein R_2 is F, or a pharmaceutically acceptable salt thereof.

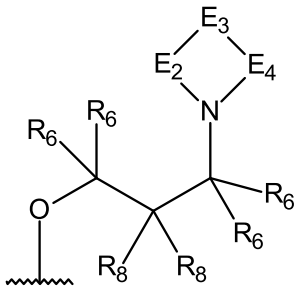
17. The compound according to any one of claims 1-14, wherein R_2 is Cl, or a pharmaceutically acceptable salt thereof.

18. The compound according to any one of claims 1-17, wherein R_4 is



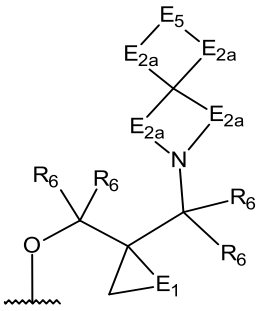
, or a pharmaceutically acceptable salt thereof.

19. The compound according to any one of claims 1-17, wherein R_4 is



, or a pharmaceutically acceptable salt thereof.

20. The compound according to any one of claims 1-17, wherein R_4 is

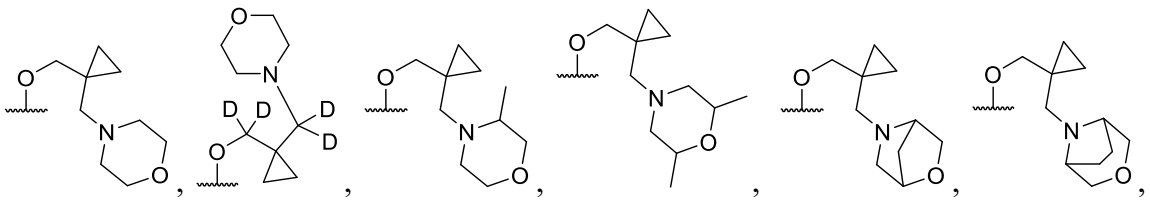


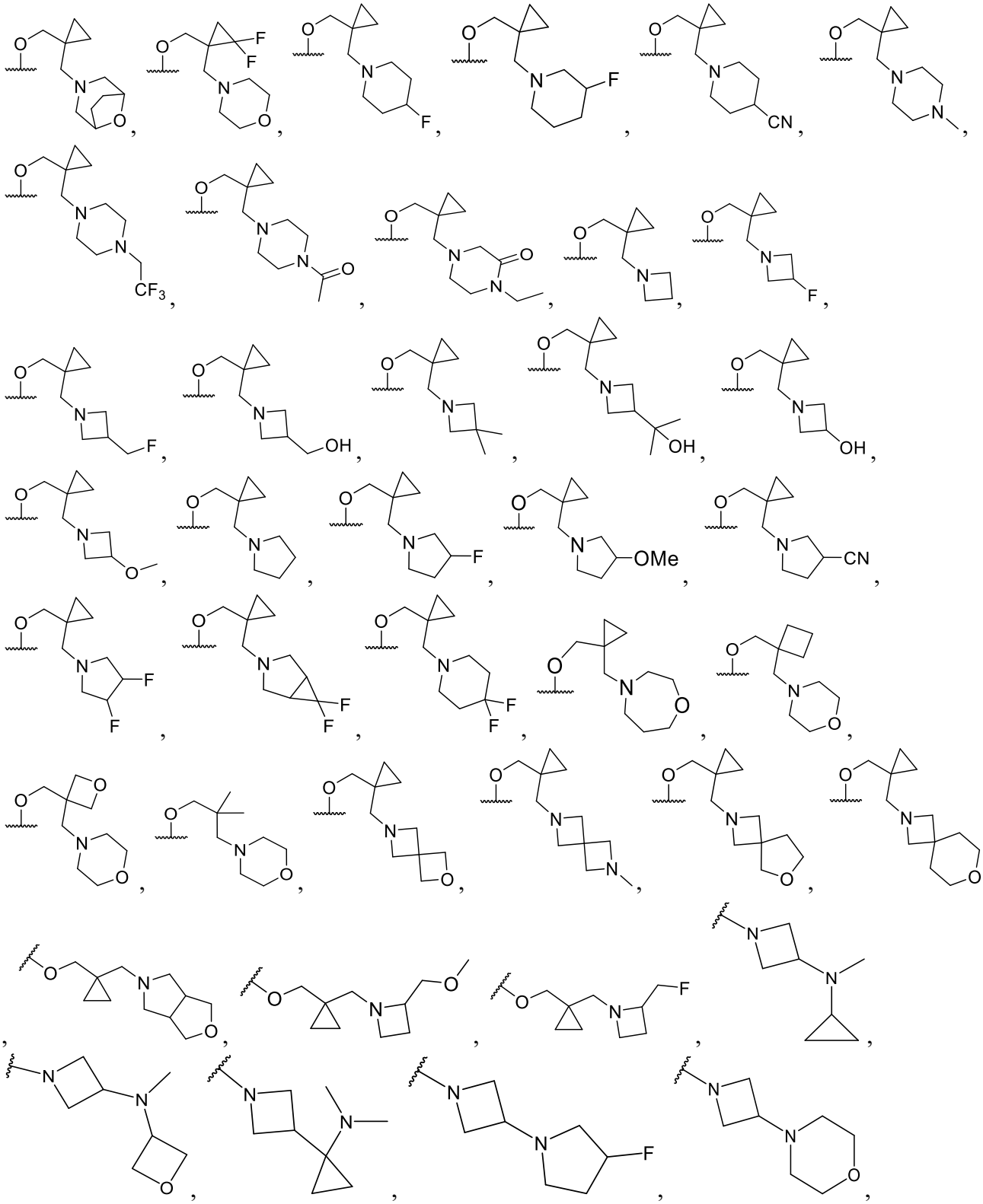
, or a pharmaceutically acceptable salt thereof.

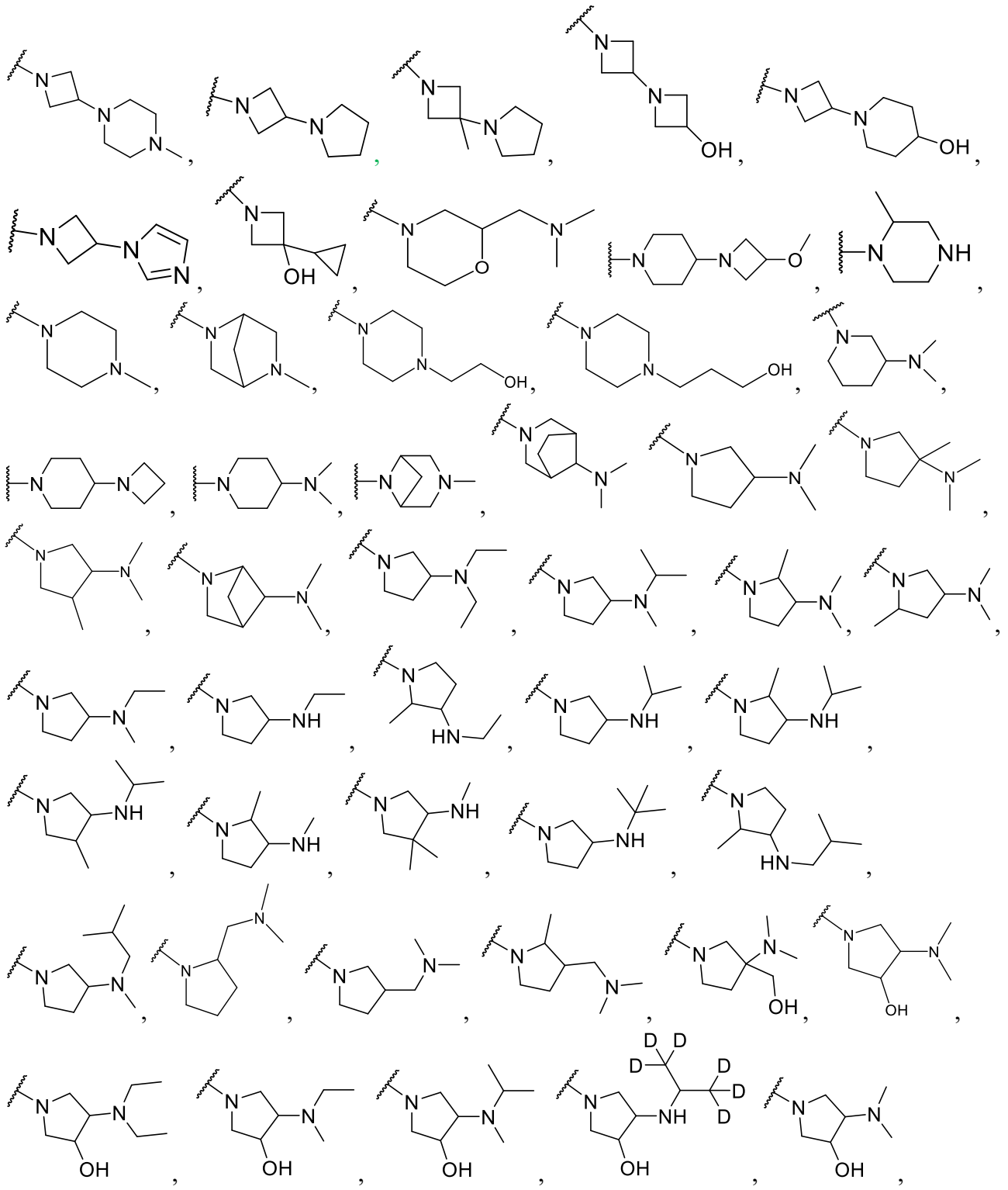
21. The compound according to any one of claims 1-20, wherein each R_6 is H, or a pharmaceutically acceptable salt thereof.

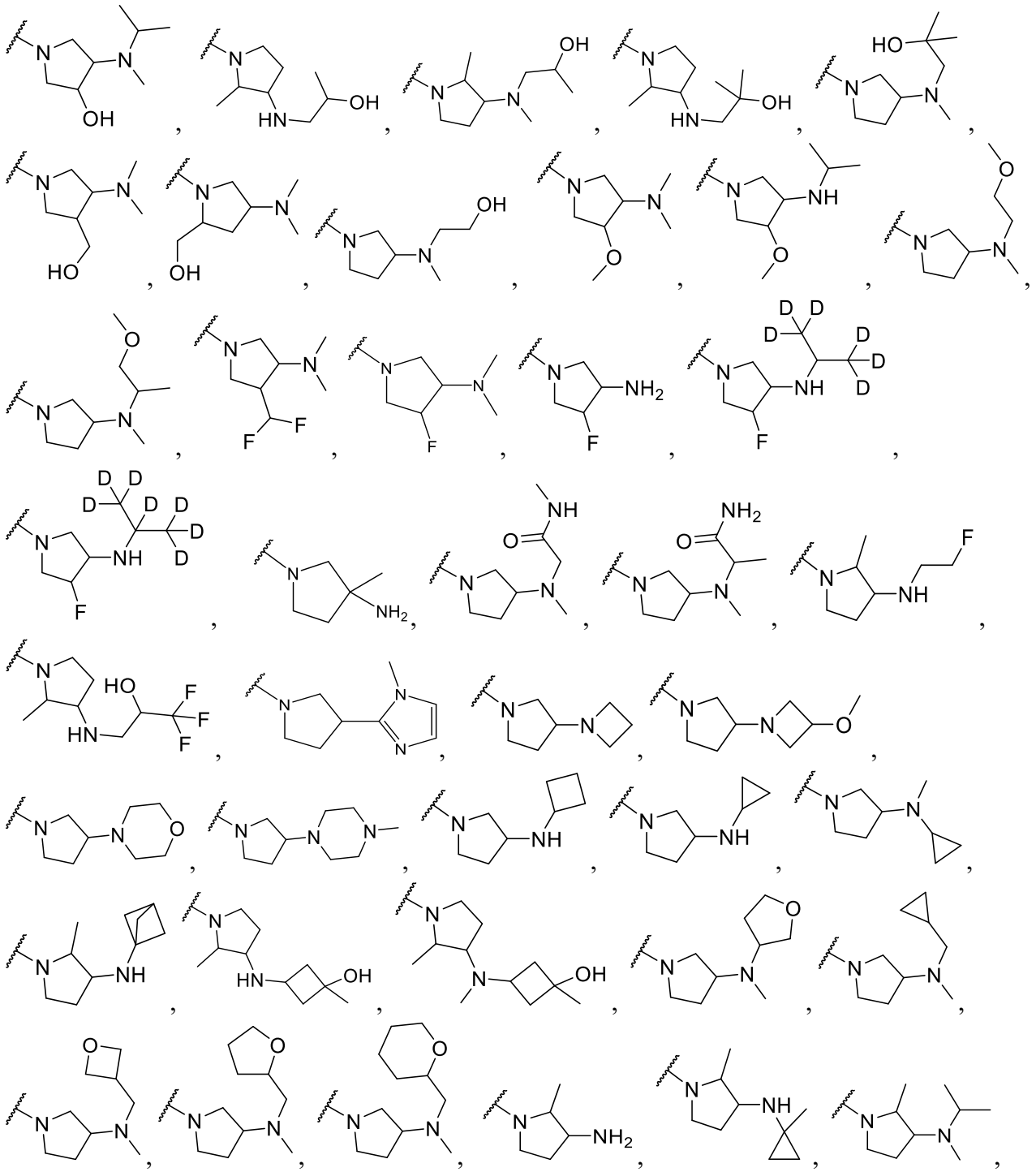
22. The compound according to any one of claims 1-4 and 6-17, wherein R_4 is a N-linked cyclic amine, or a pharmaceutically acceptable salt thereof.

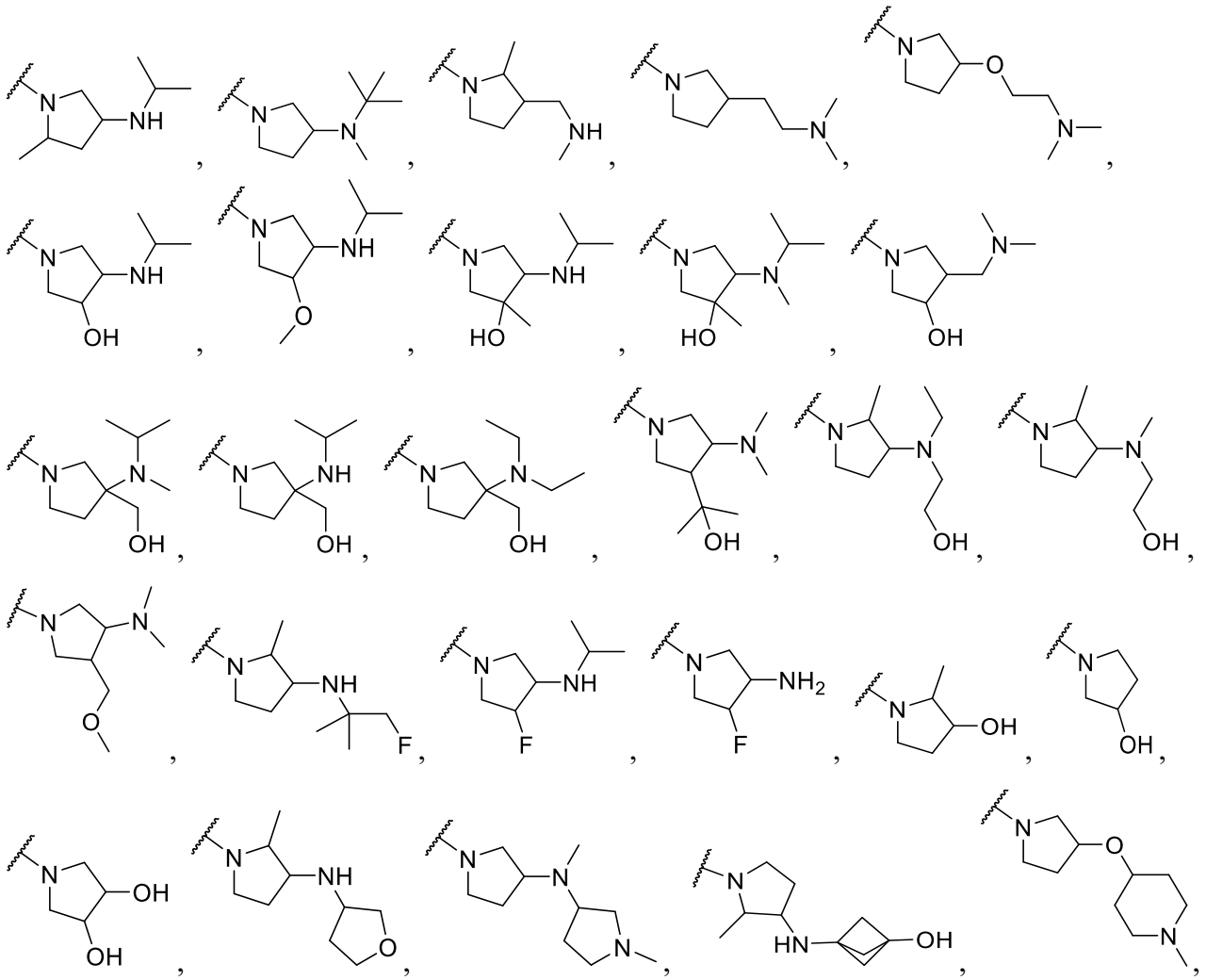
23. The compound according to any one of claims 1 and 6-17, wherein R_4 is selected from

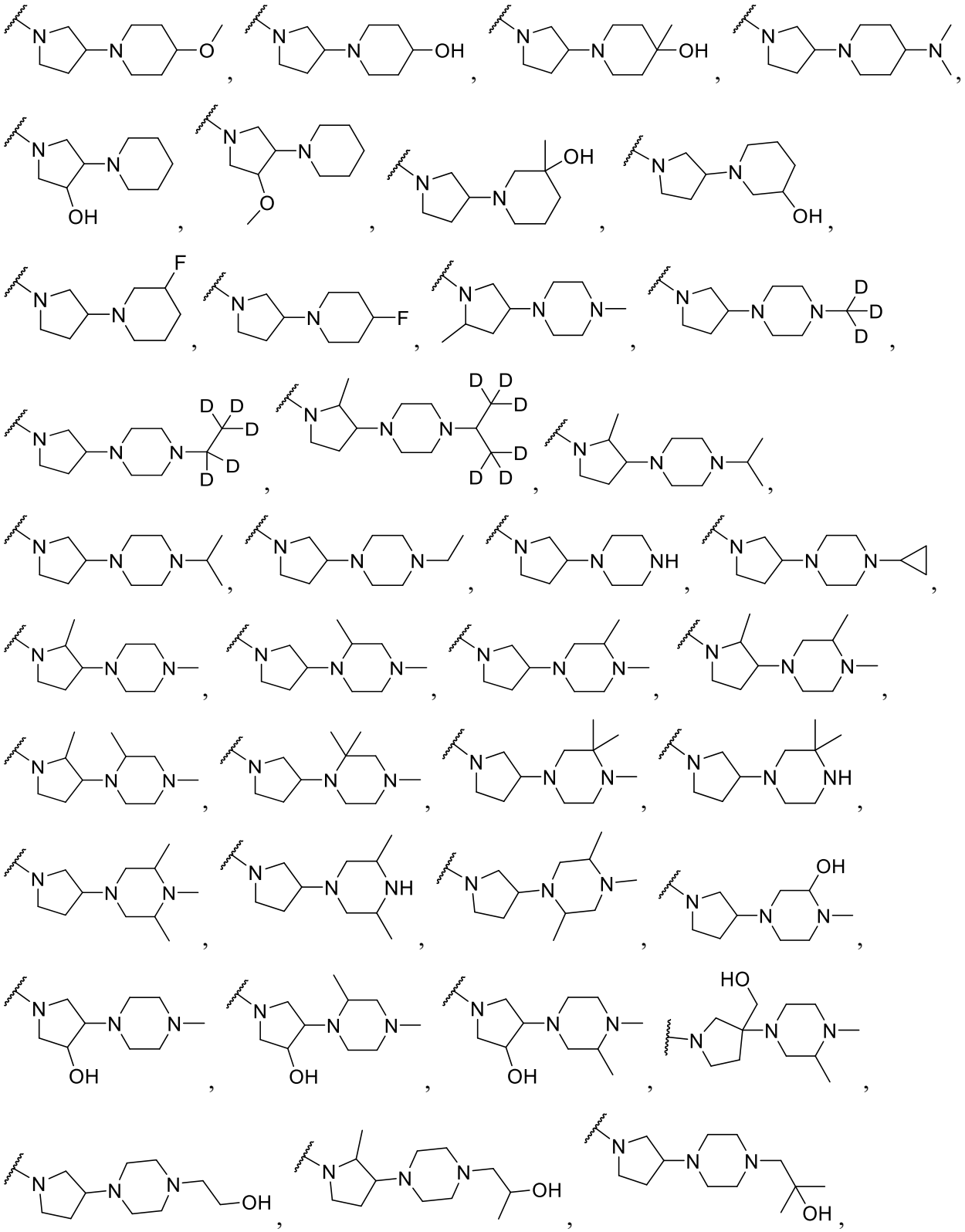


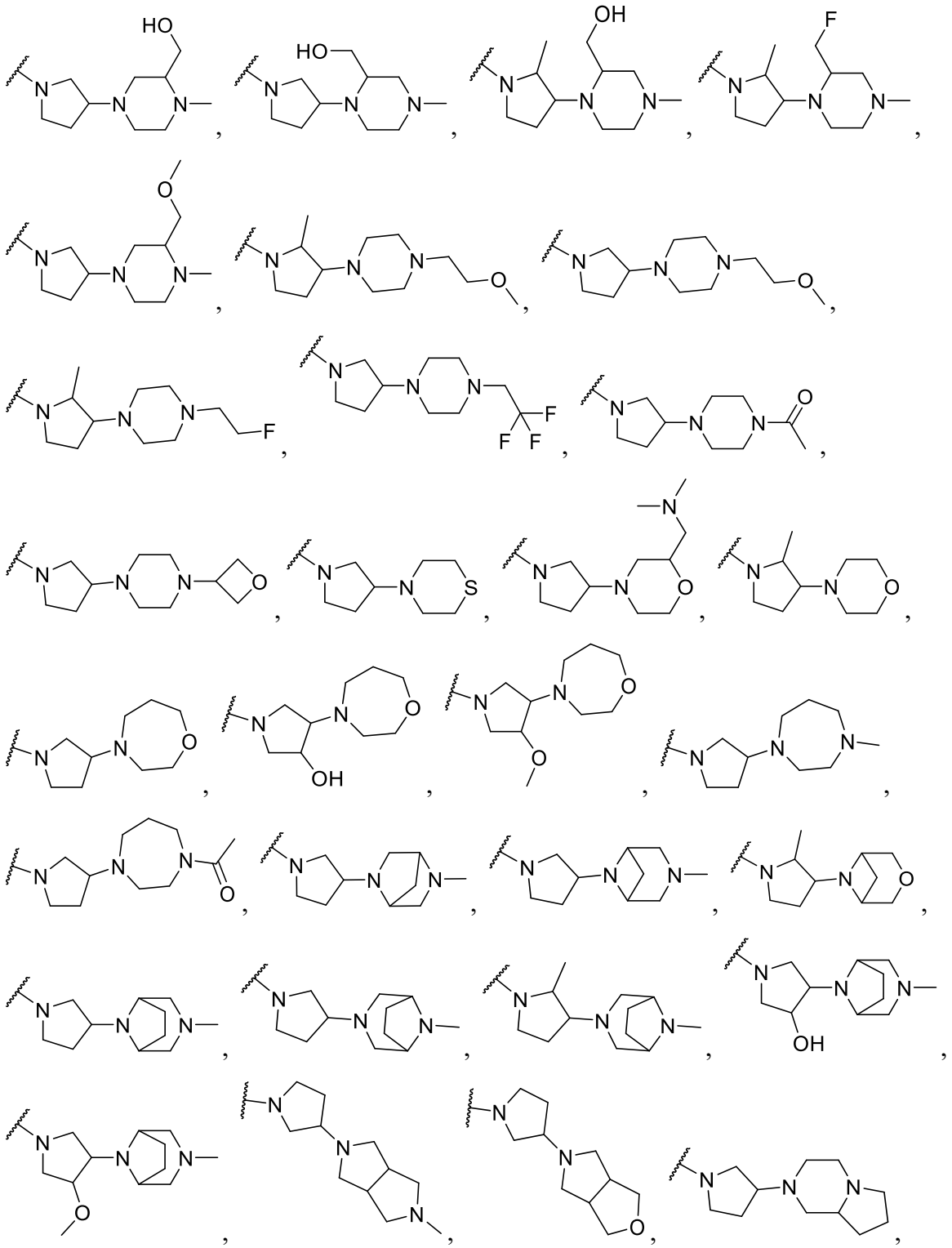


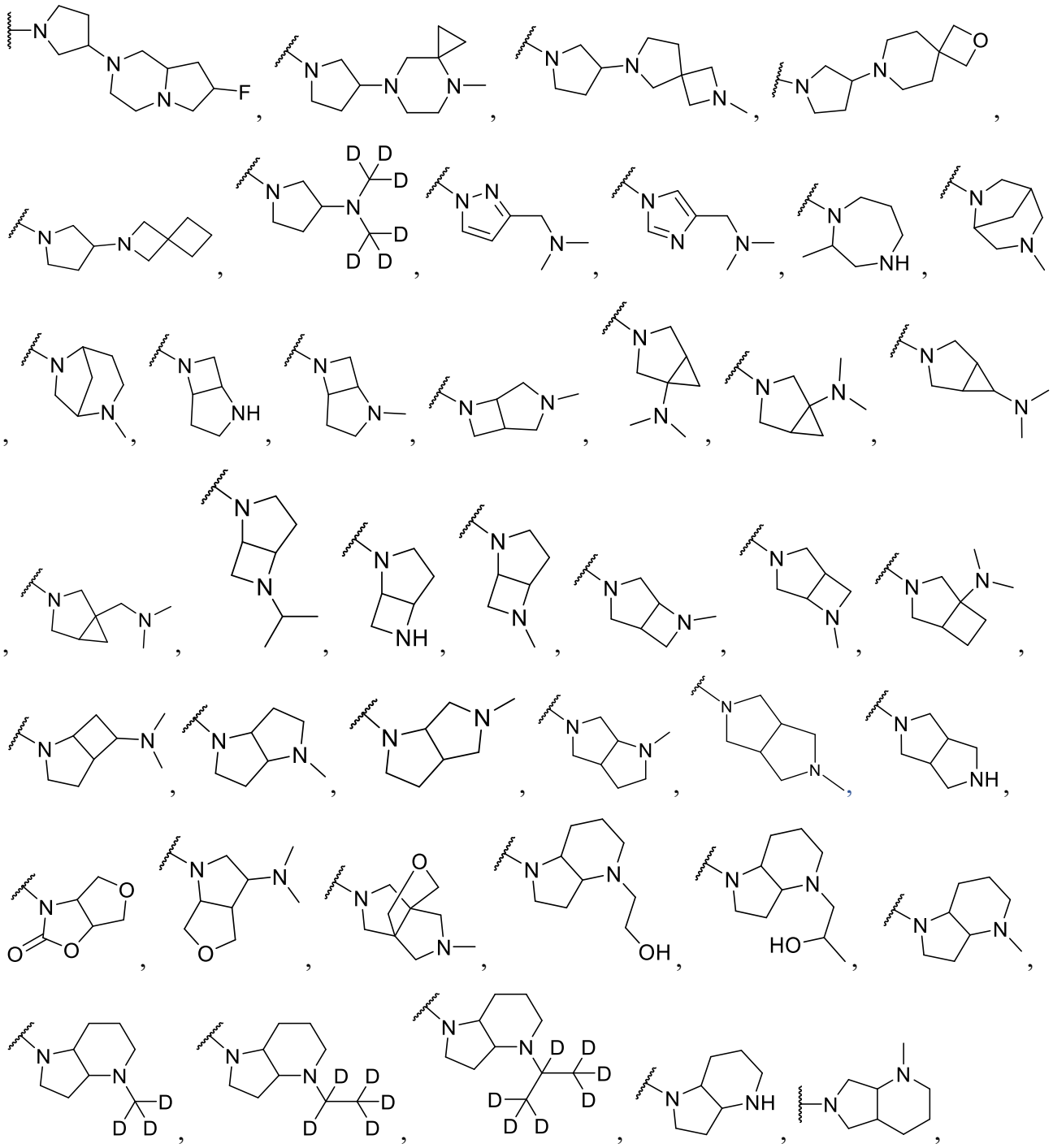


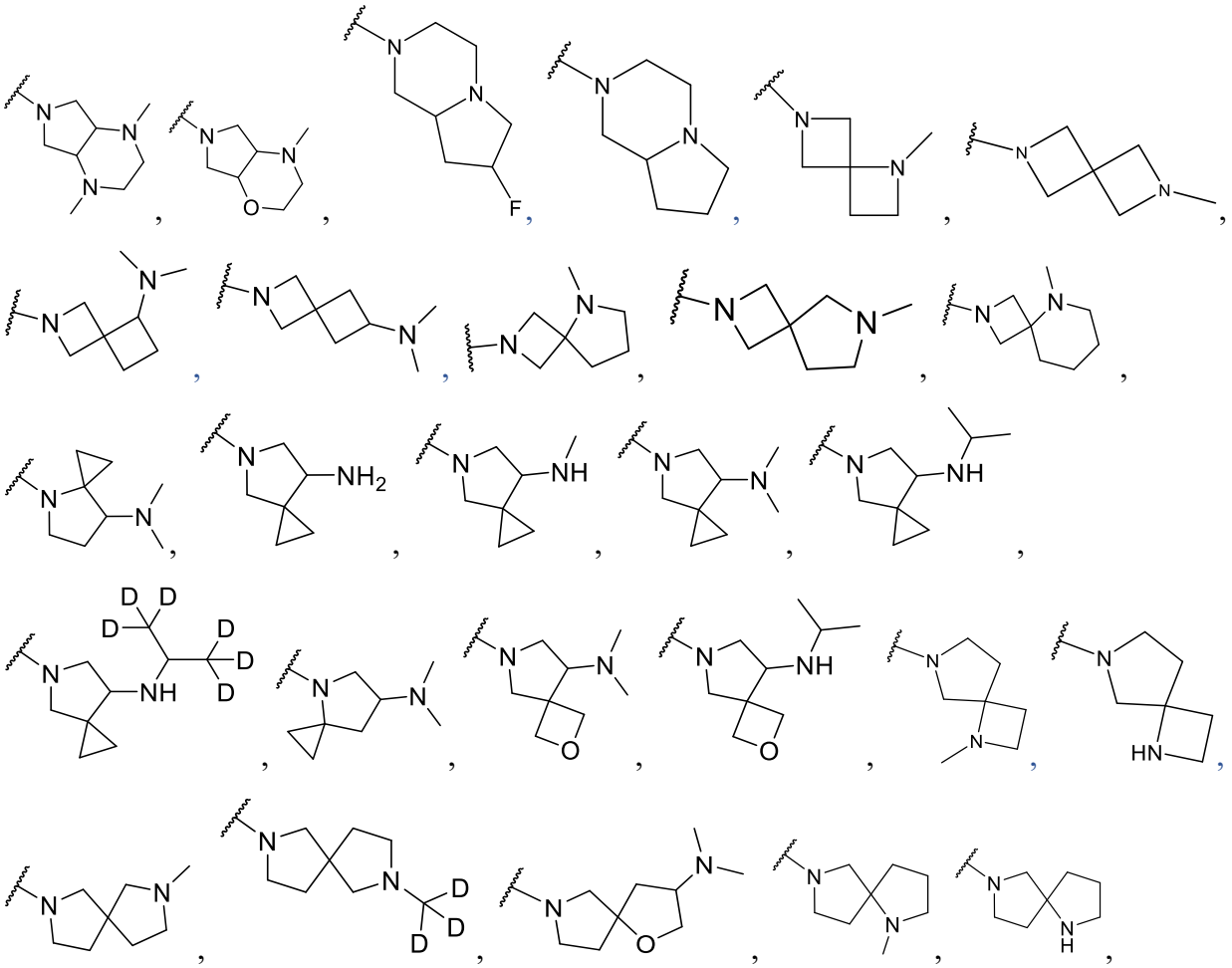






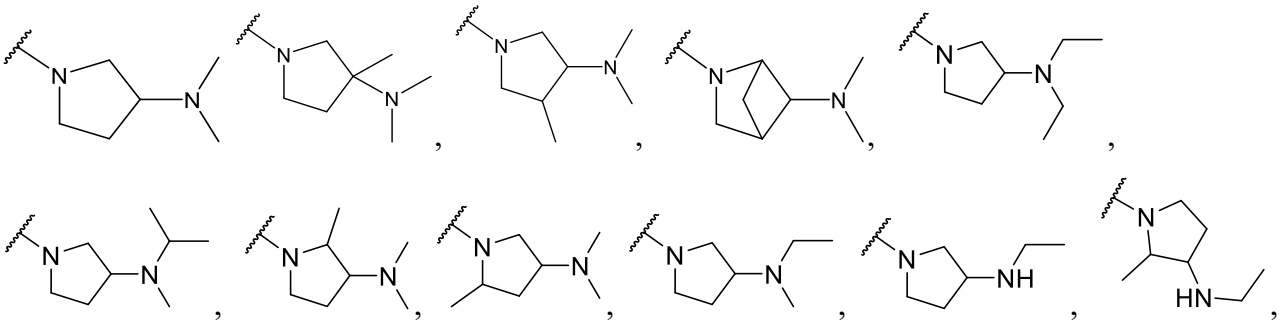


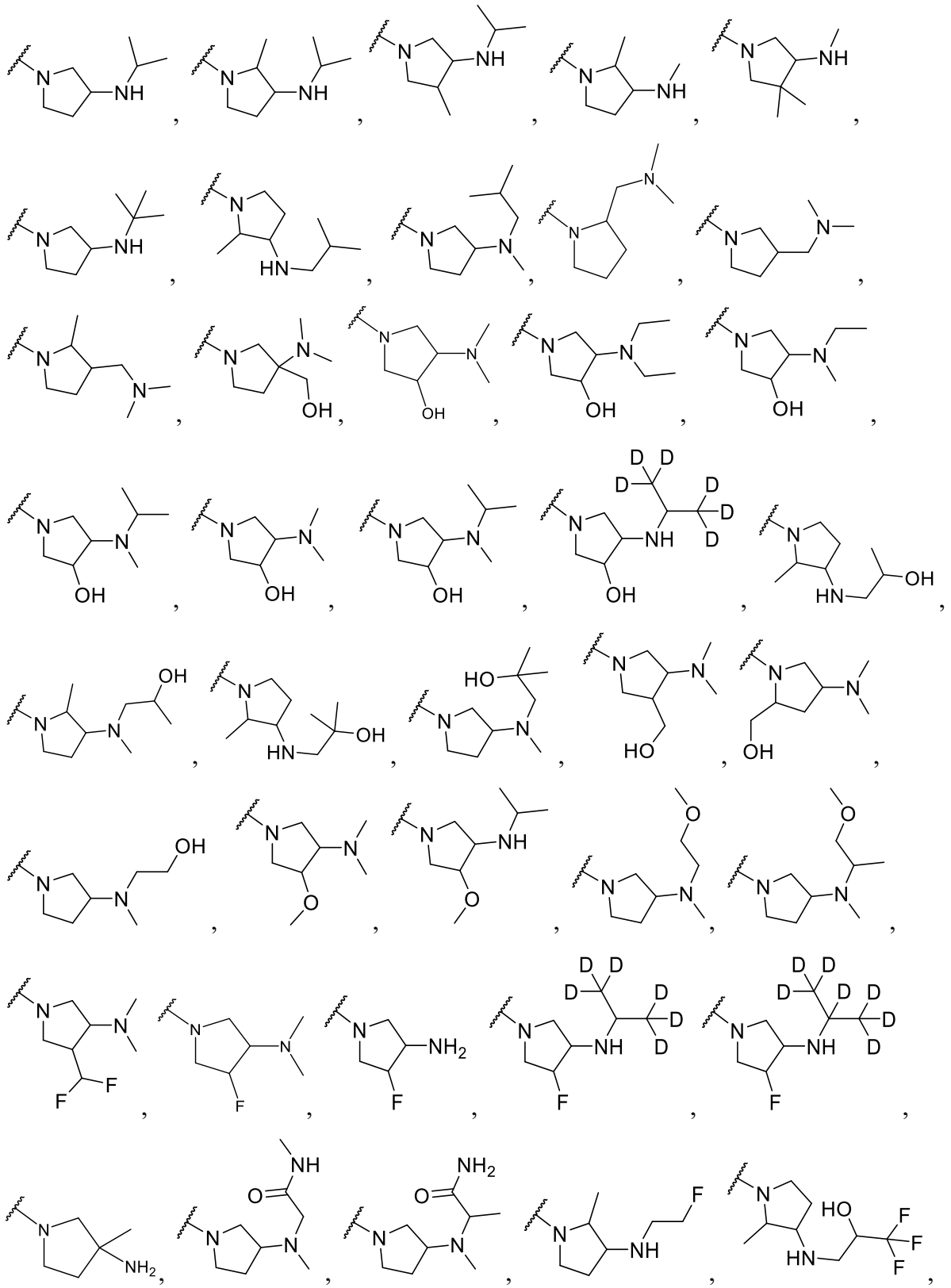


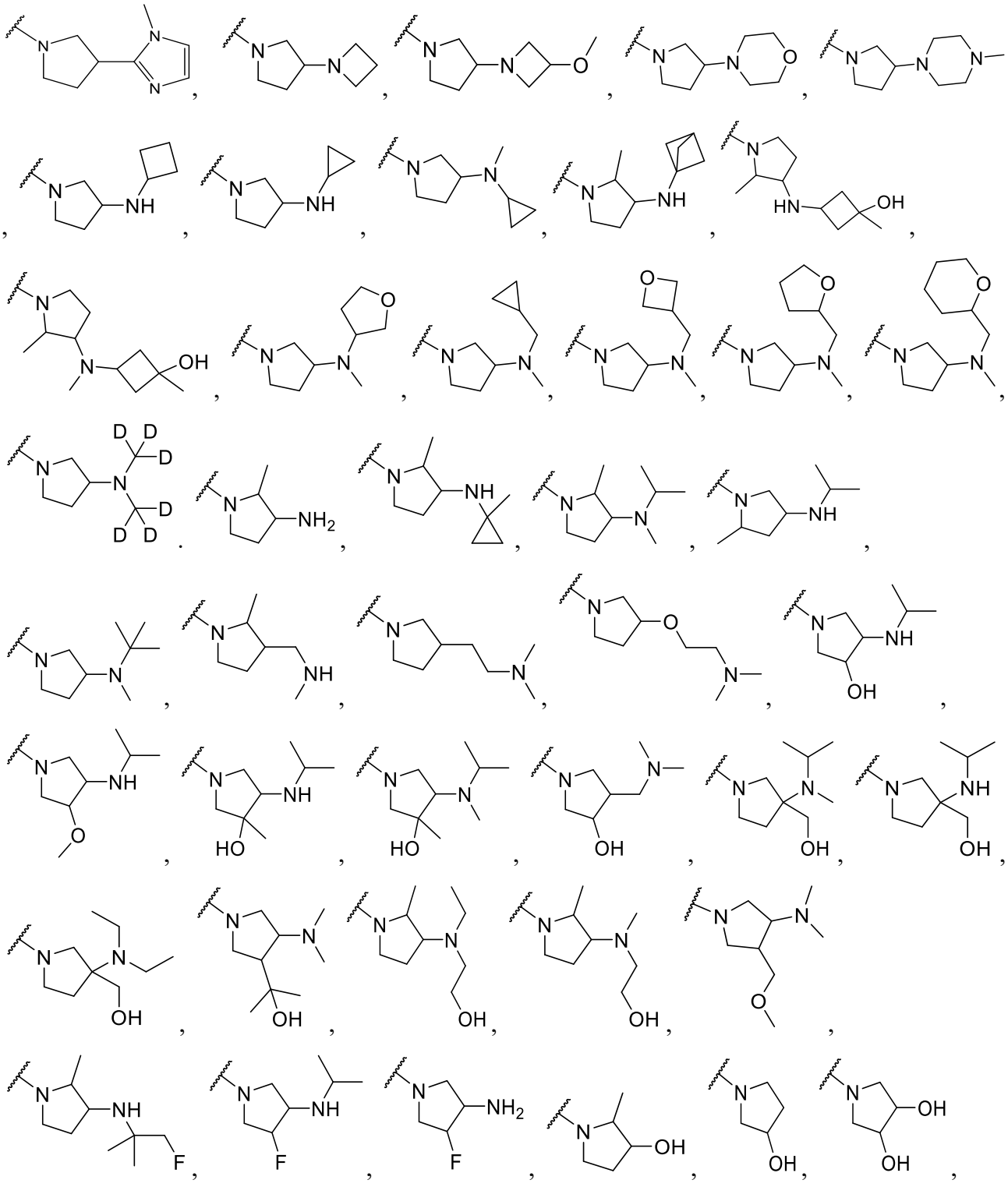


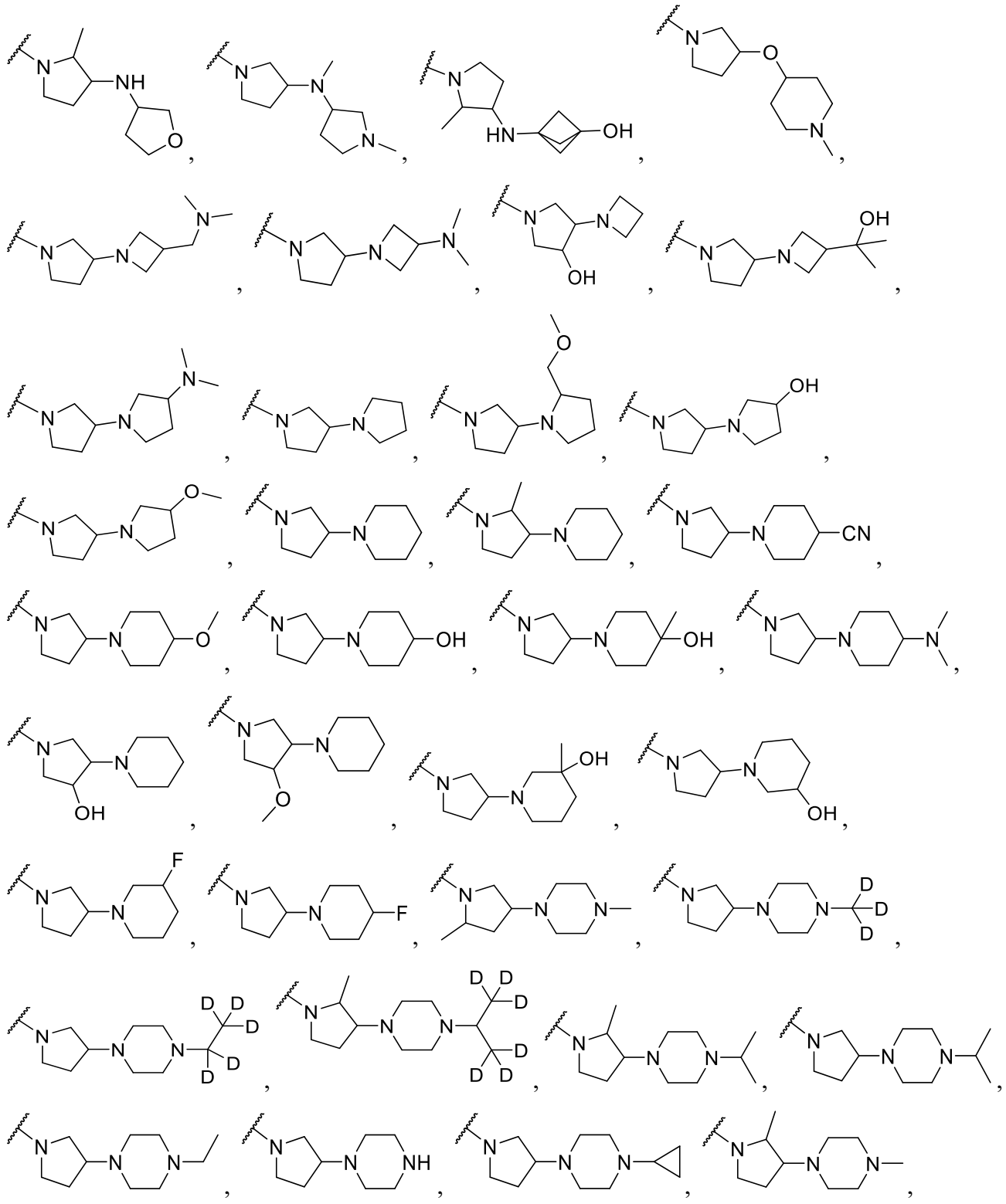
, or , or a pharmaceutically acceptable salt thereof.

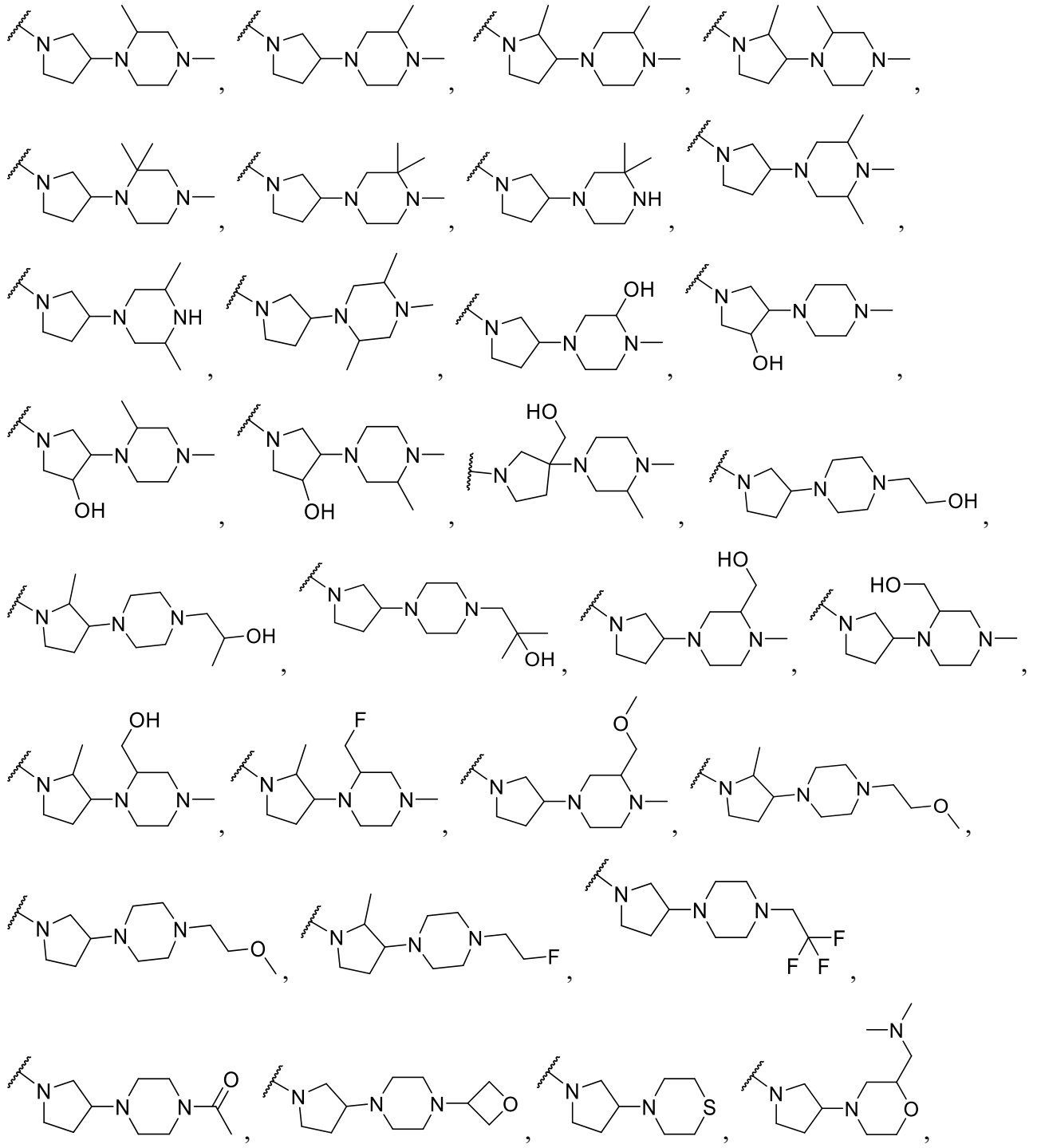
24. The compound according to any one of claims 1 and 6-17, wherein R_4 is selected from

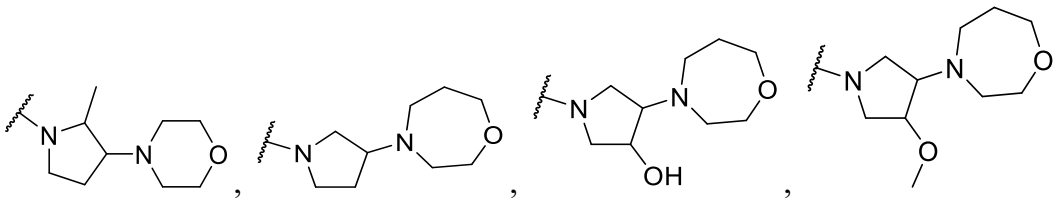
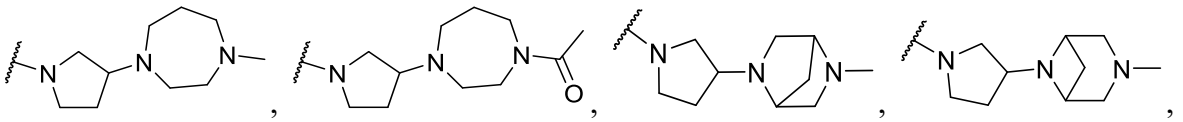
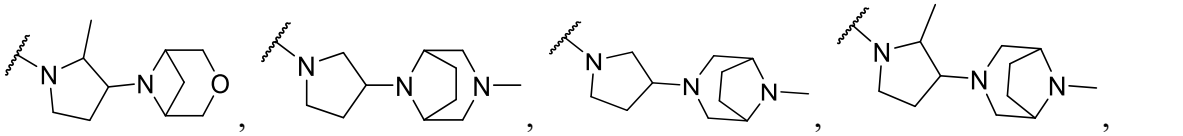
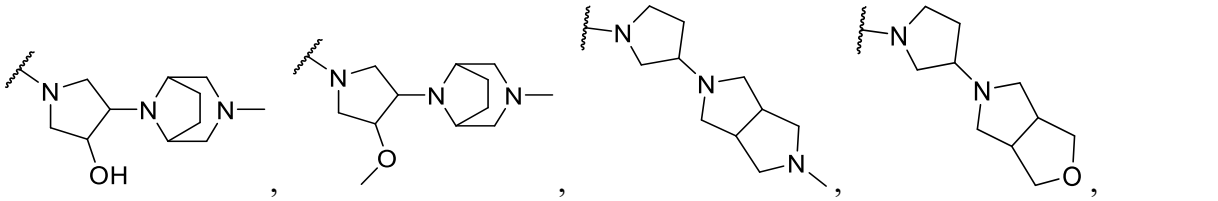
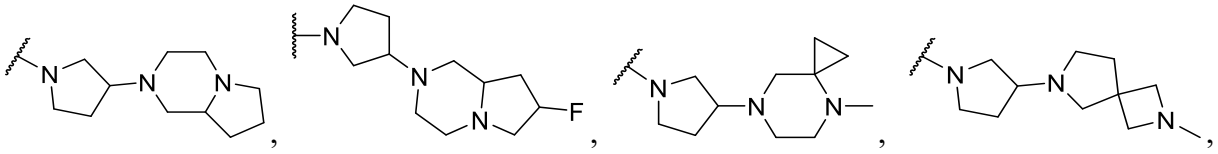
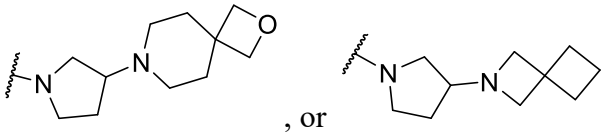




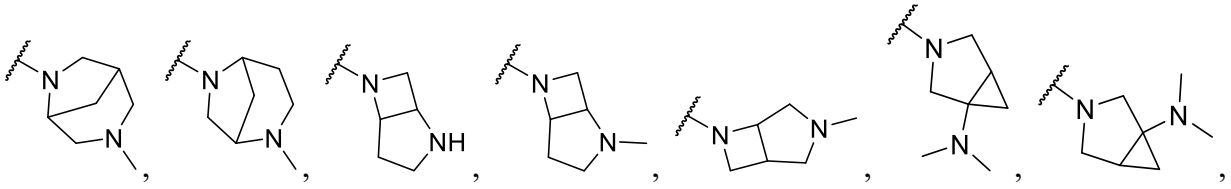
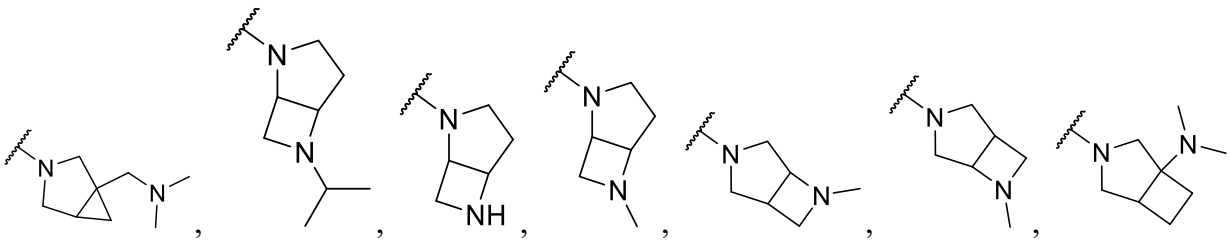


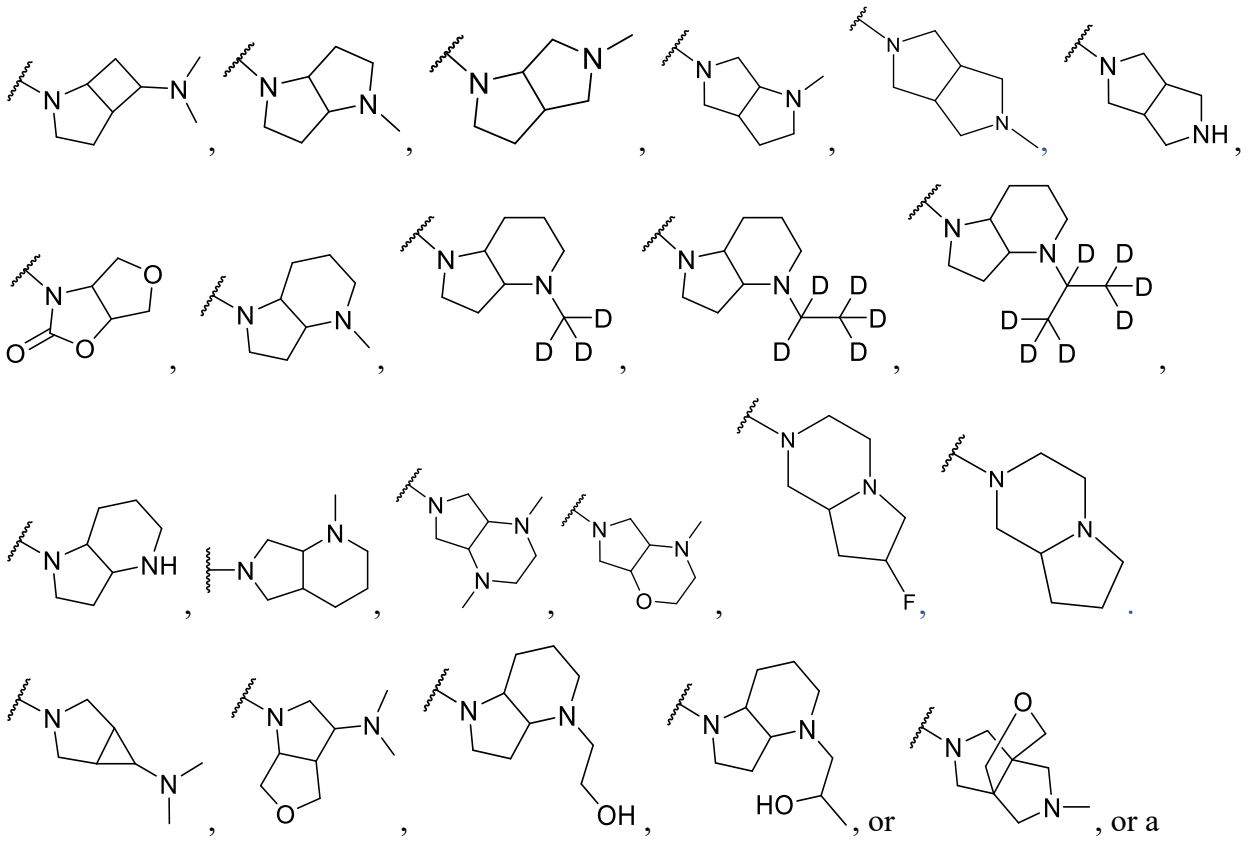










, or a pharmaceutically acceptable salt thereof.

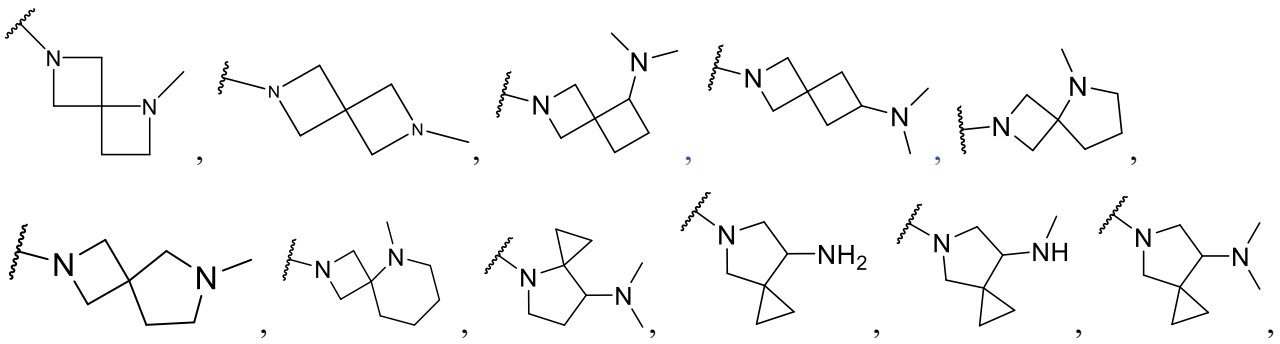
25. The compound according to any one of claims 1 and 6-17, wherein R_4 is selected from

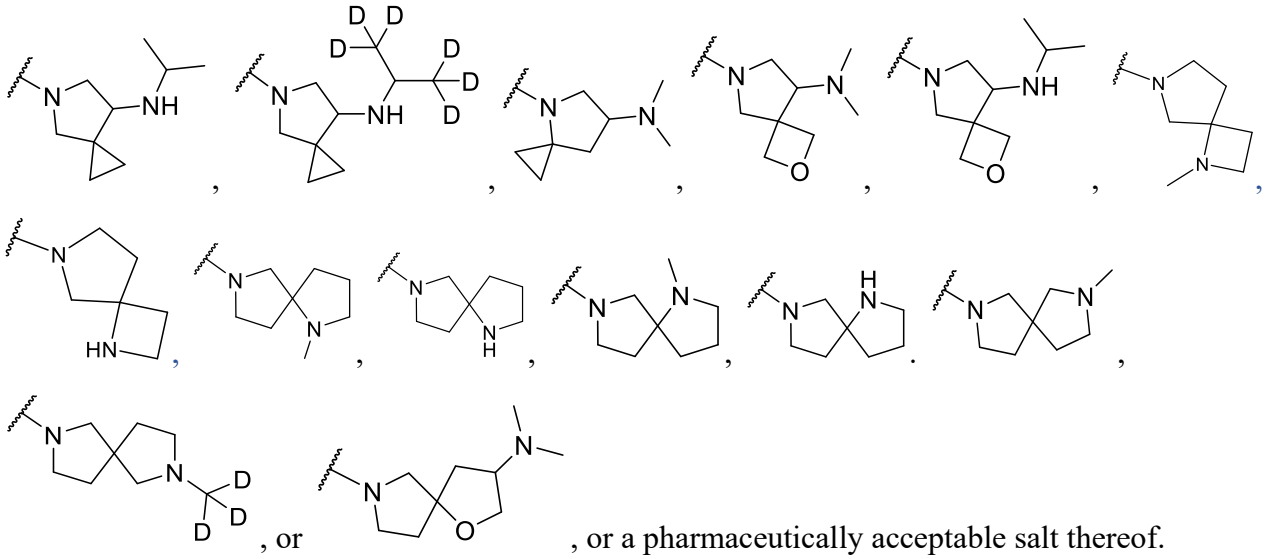





pharmaceutically acceptable salt thereof.

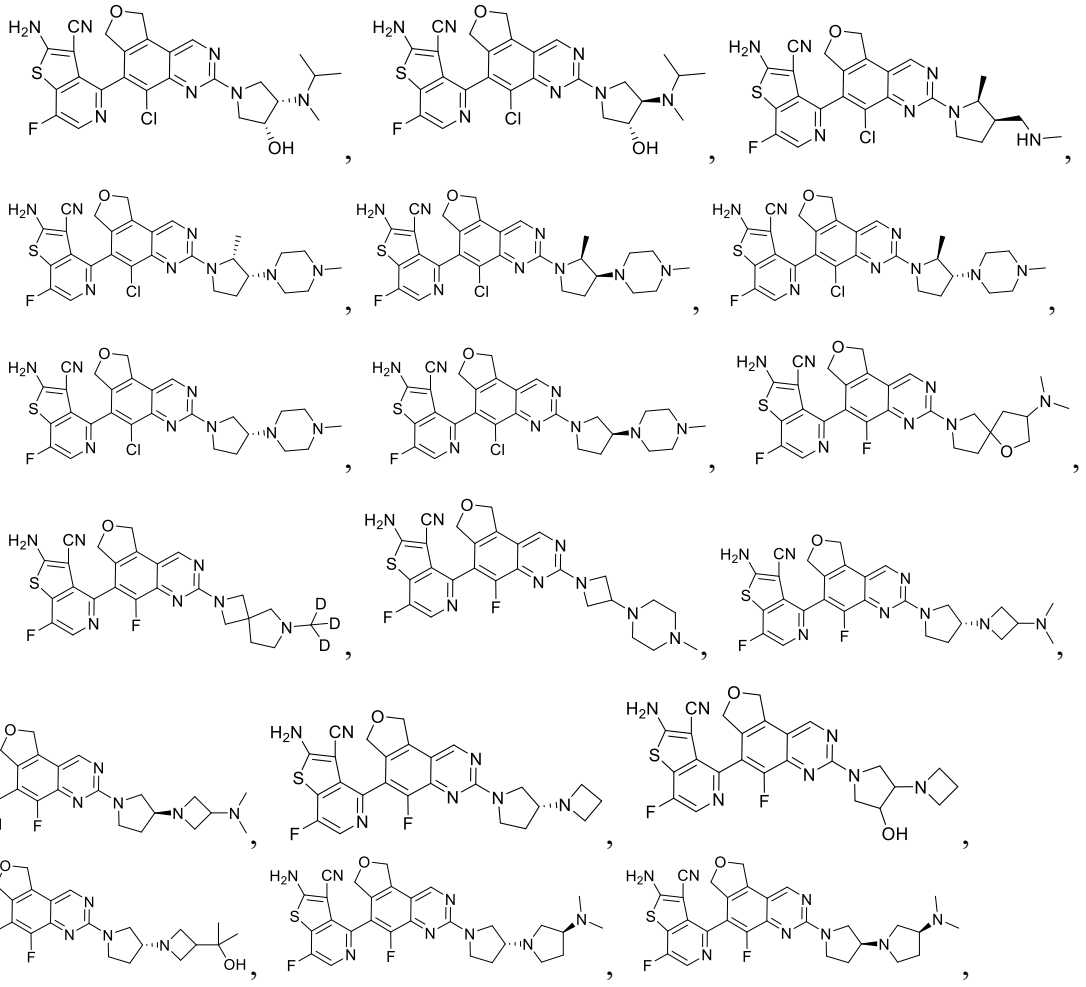
26. The compound according to any one of claims 1 and 6-17, wherein R_4 is selected from

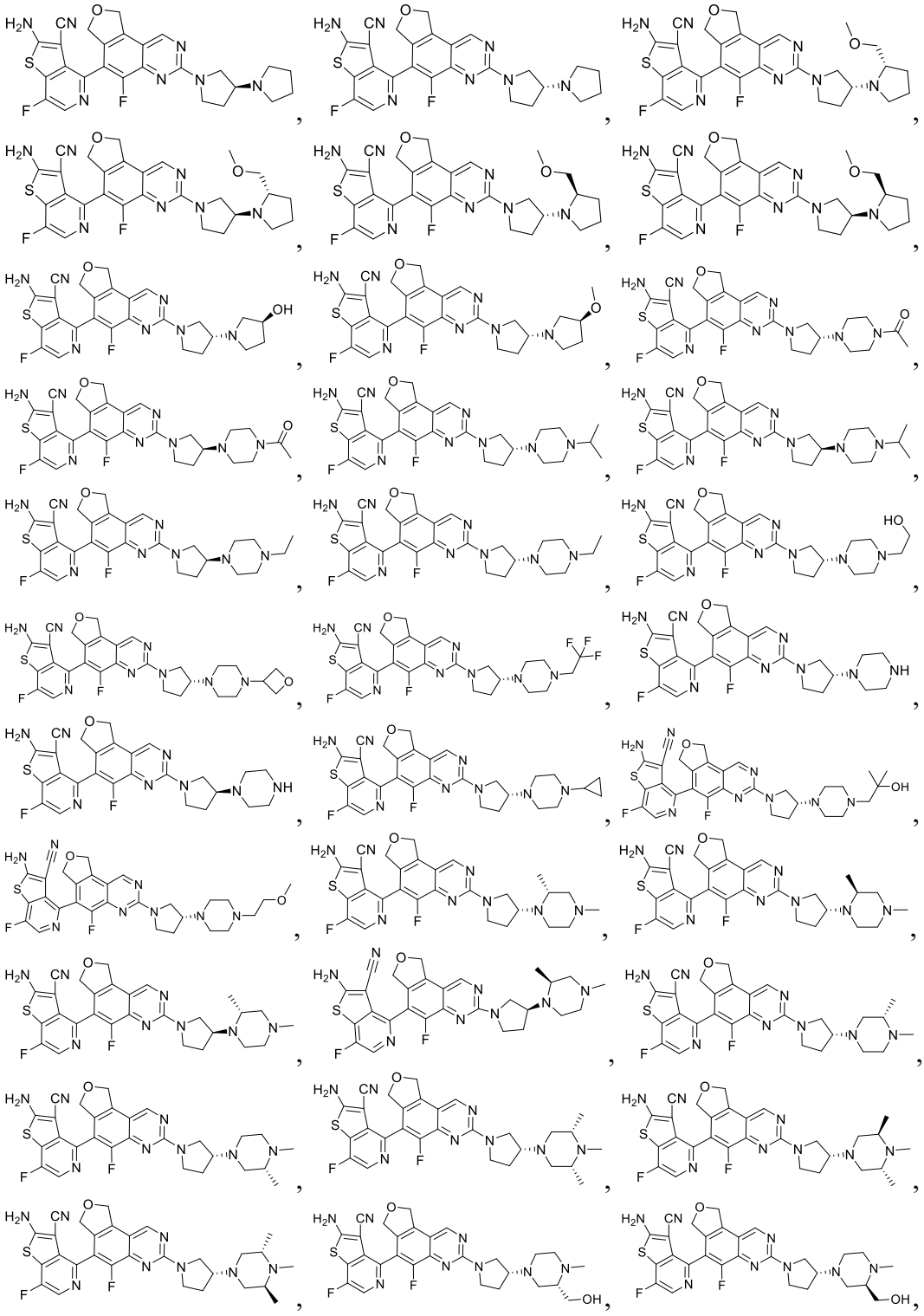


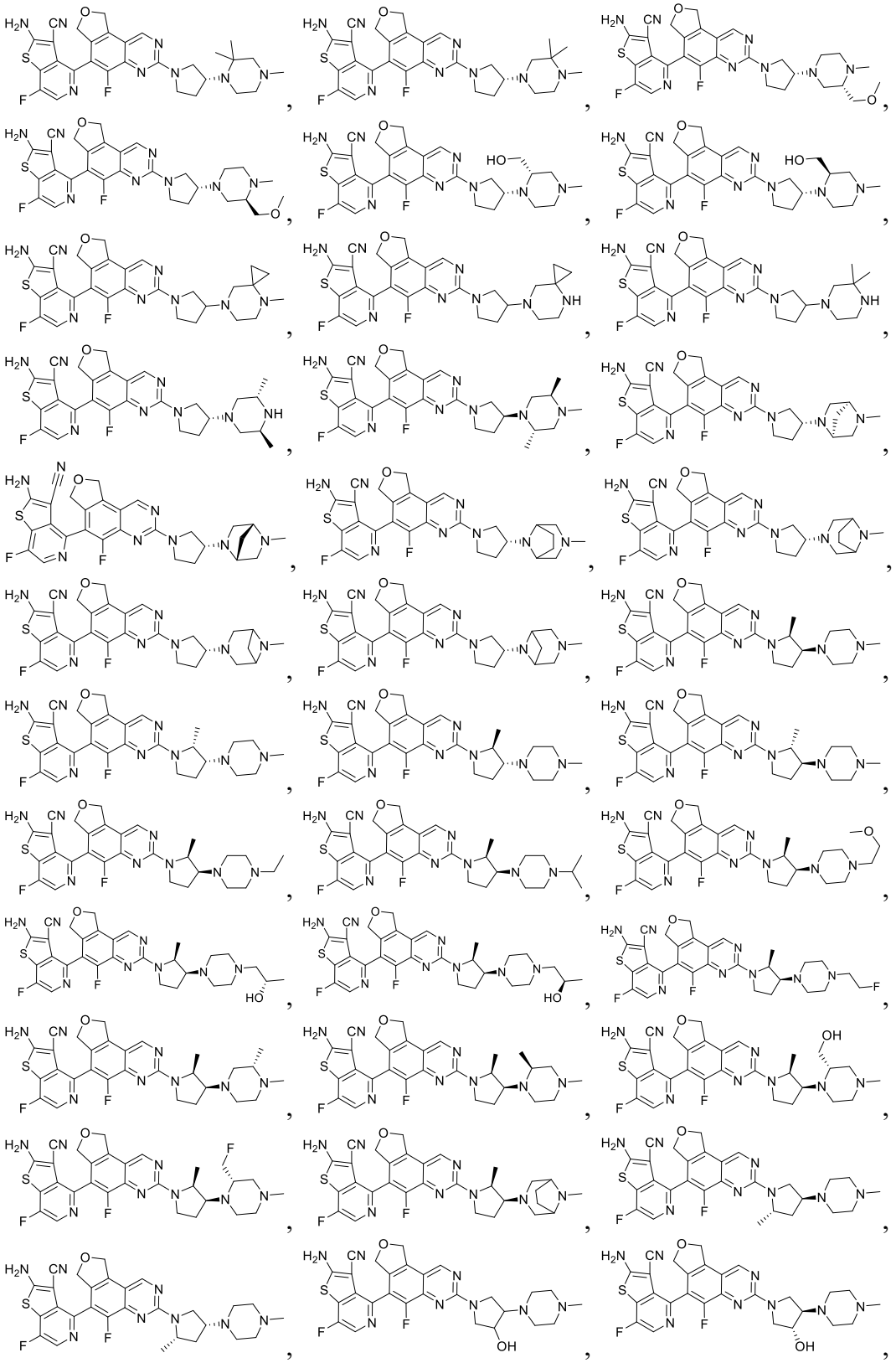


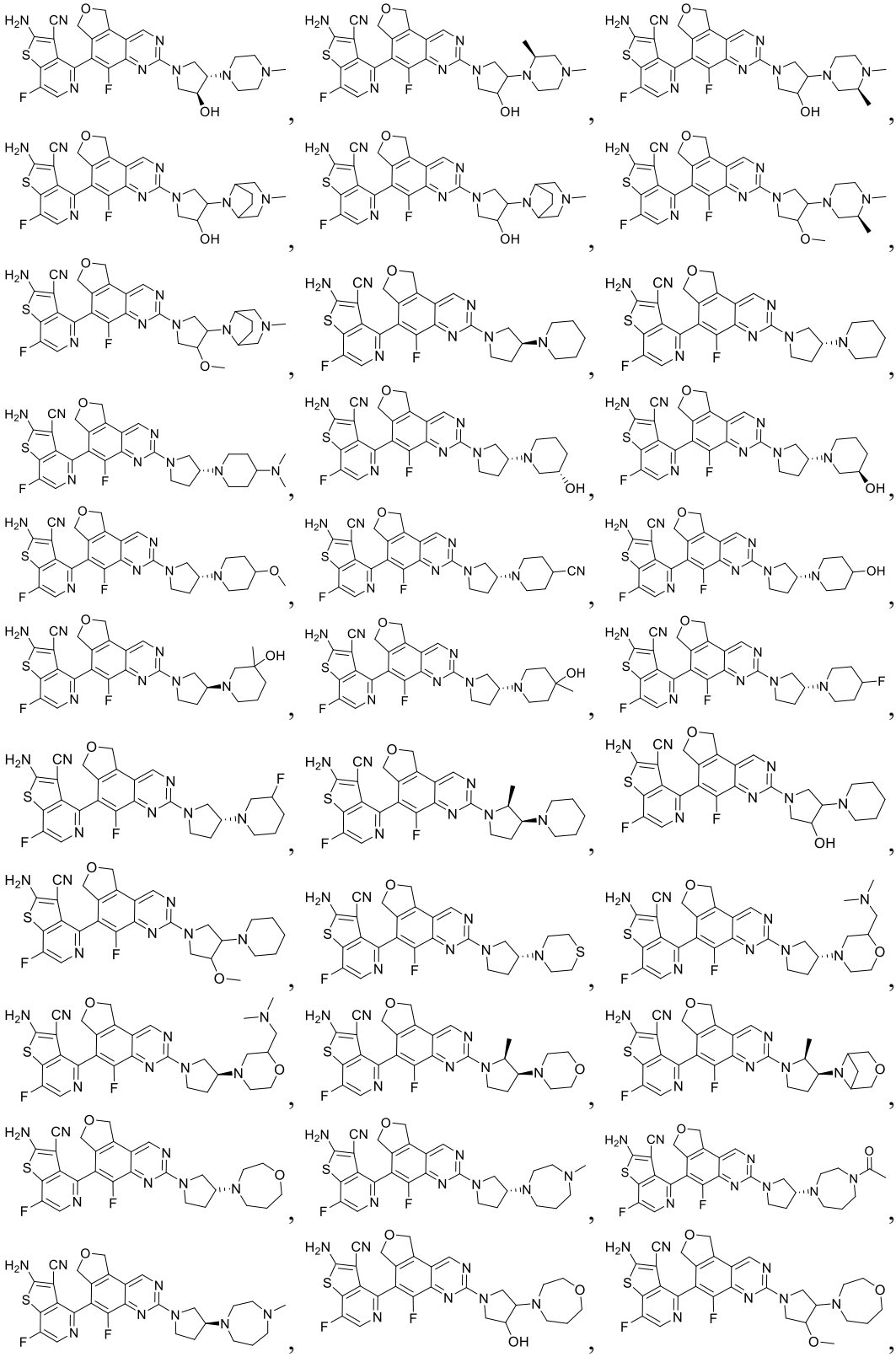
, or a pharmaceutically acceptable salt thereof.

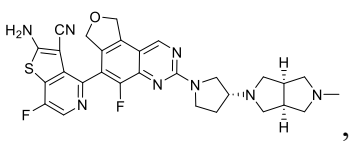
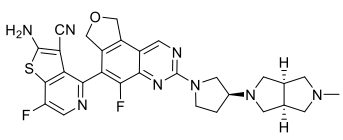
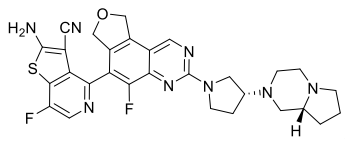
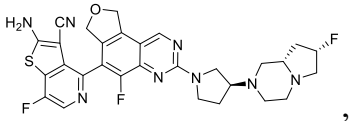
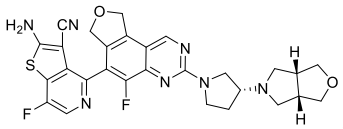
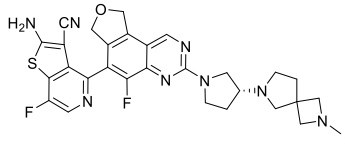
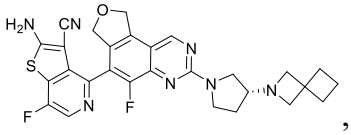
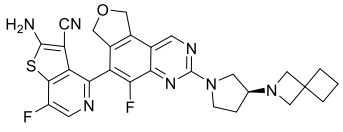
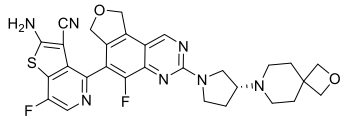
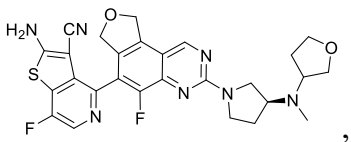
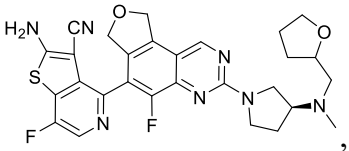
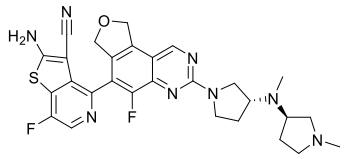
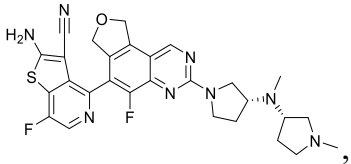
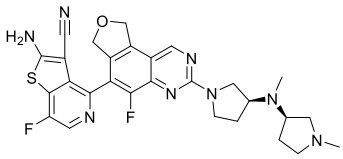
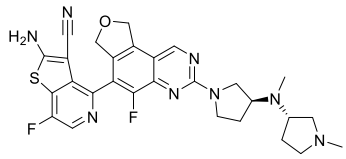
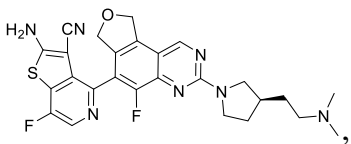
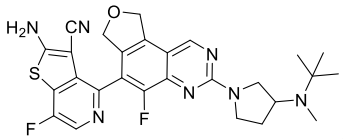
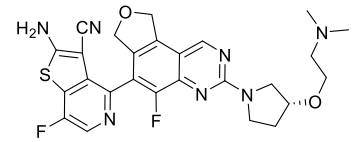
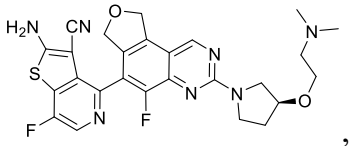
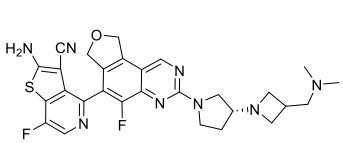
27. The compound according to claim 1, wherein the compound is selected from

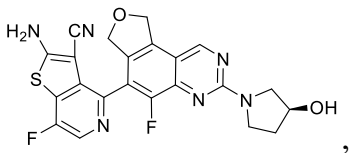
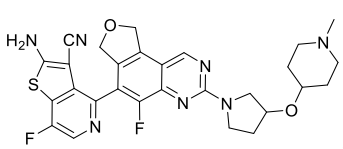
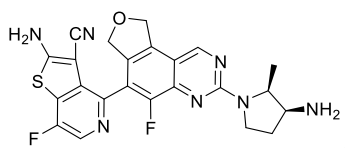
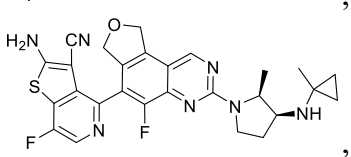
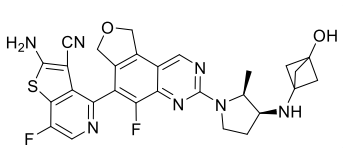
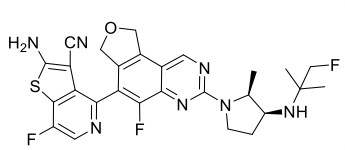
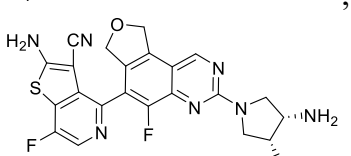
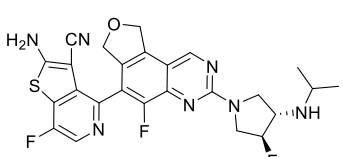
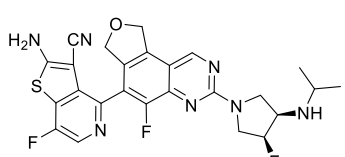








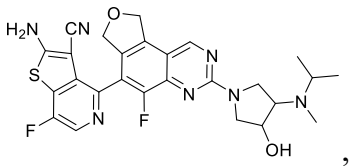
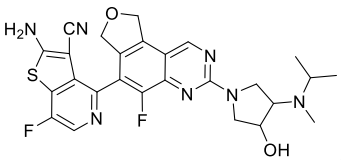
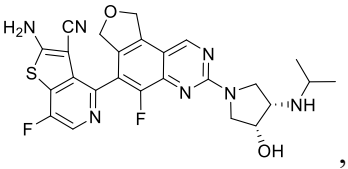
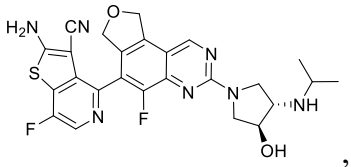
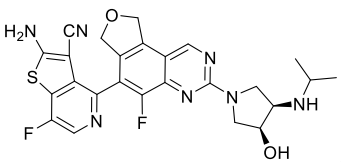
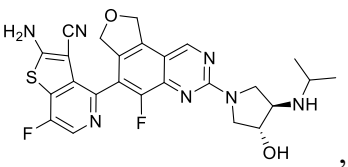
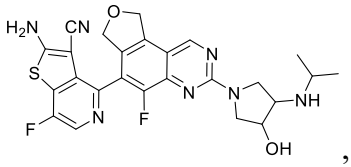
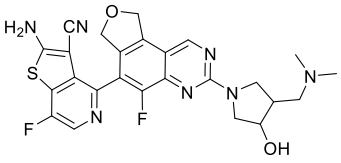
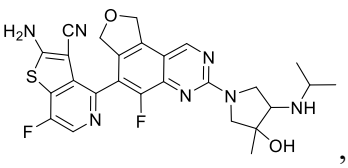
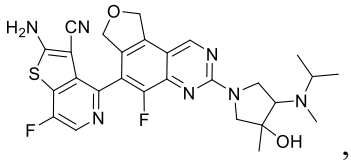
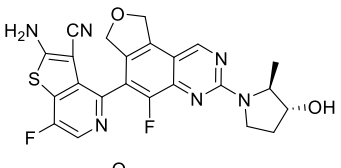
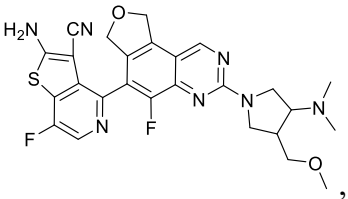
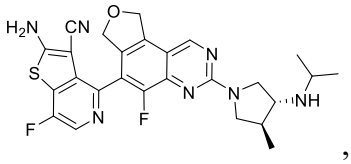
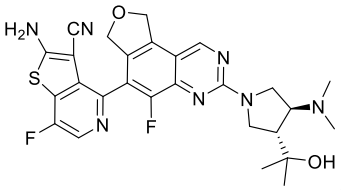
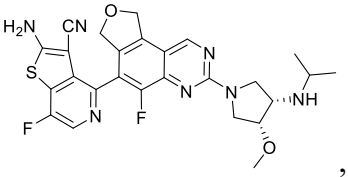
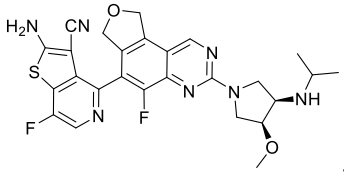
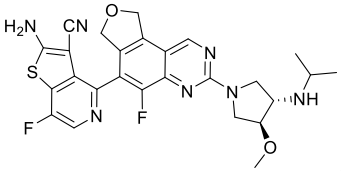
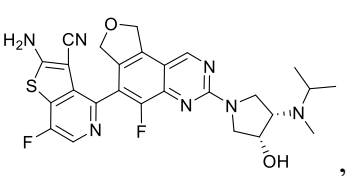
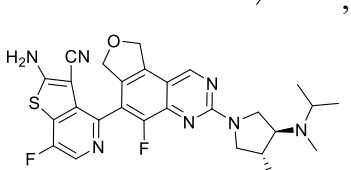
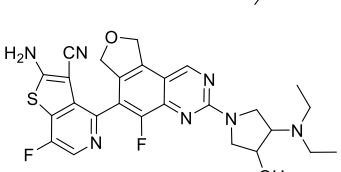
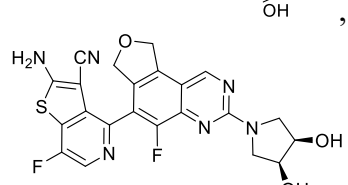
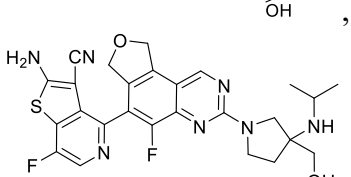
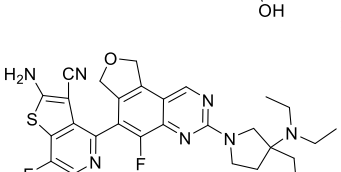
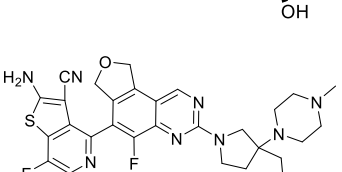
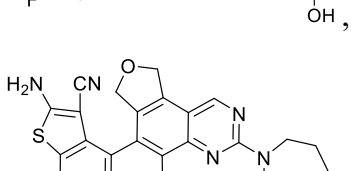
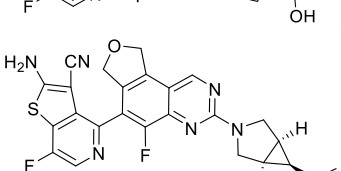
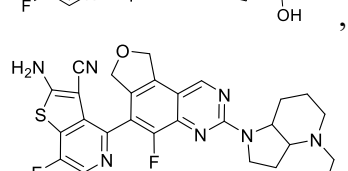
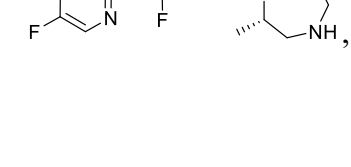
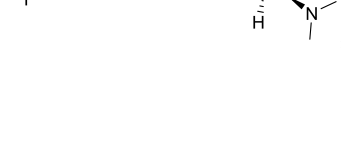
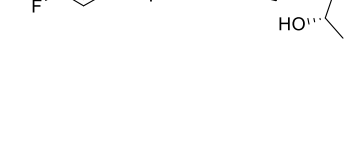

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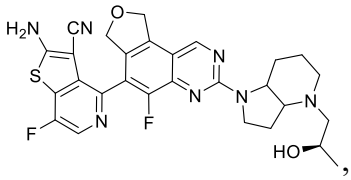
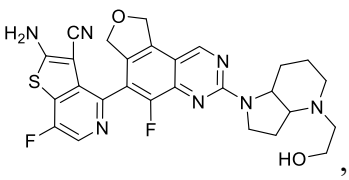
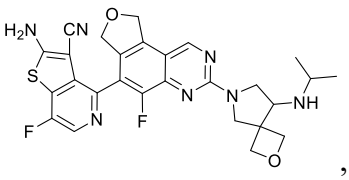
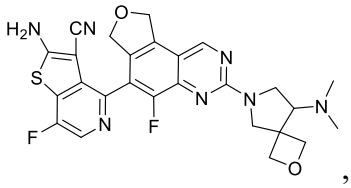
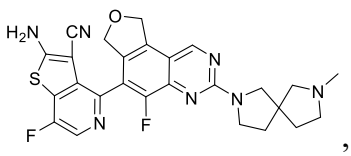
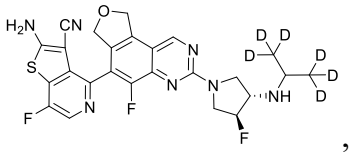
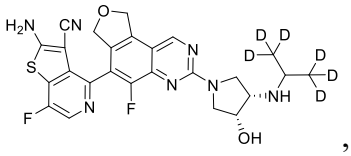
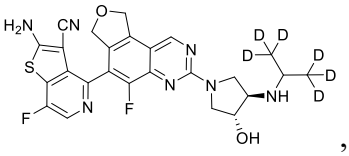
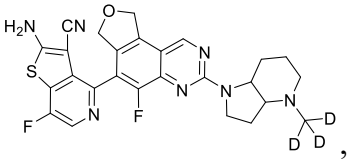
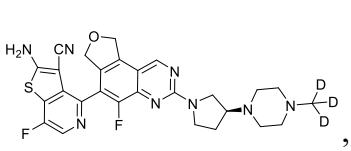
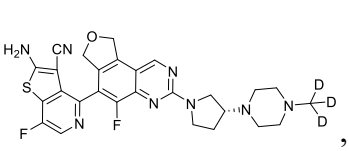
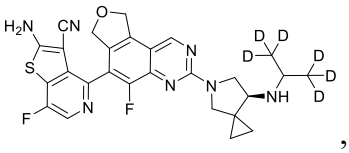
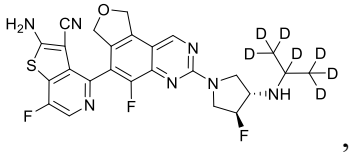
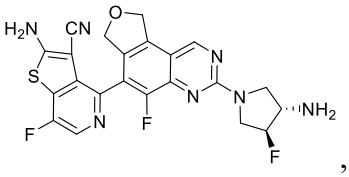
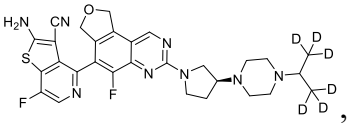
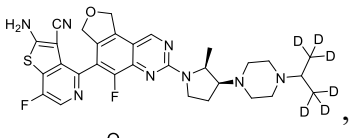
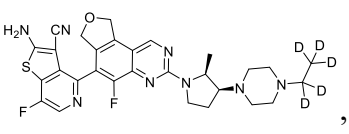
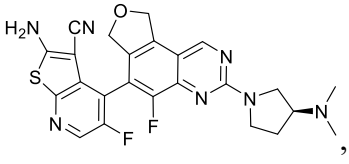
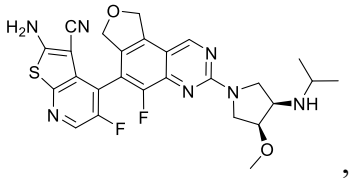
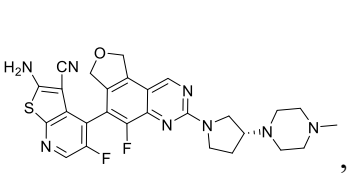
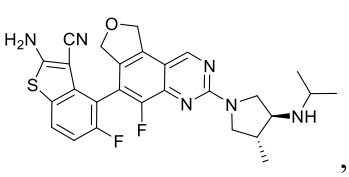
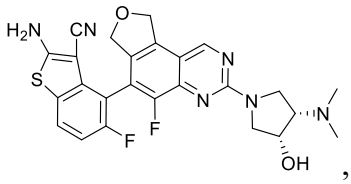
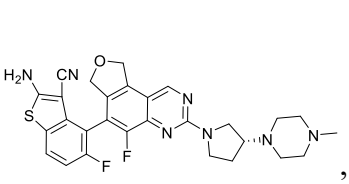
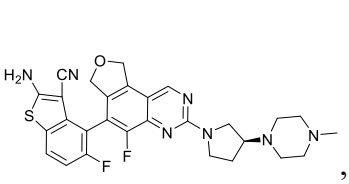
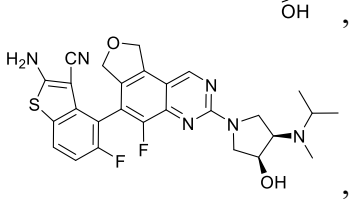
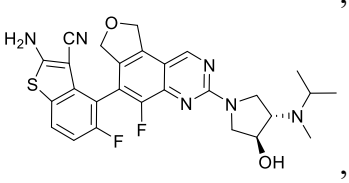
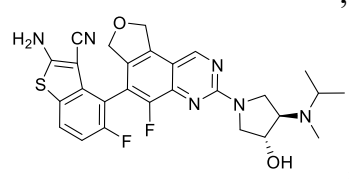
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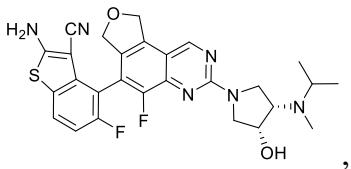
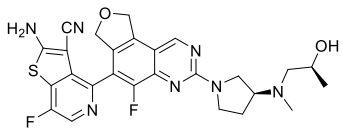
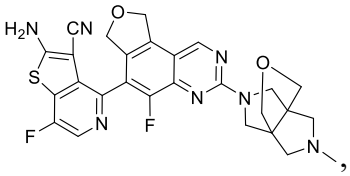
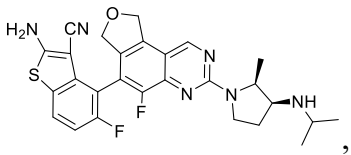
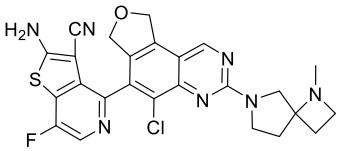
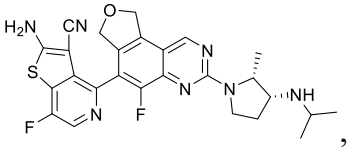
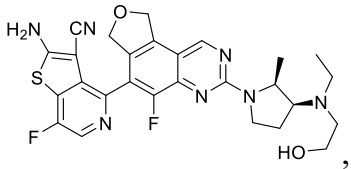
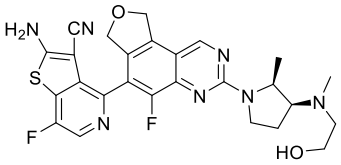
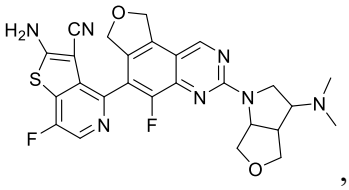
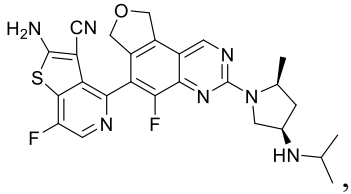
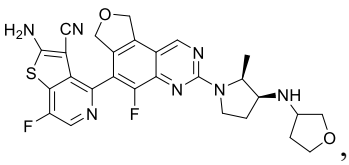
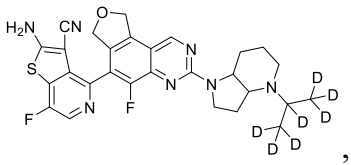
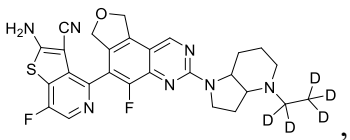
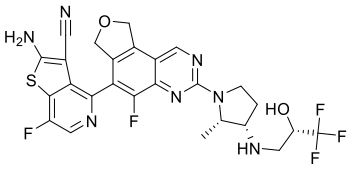
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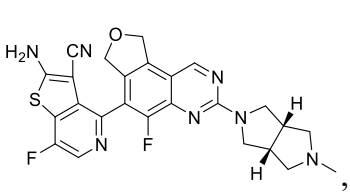
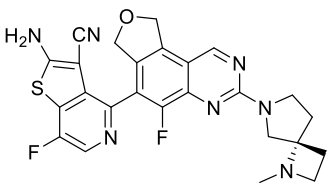
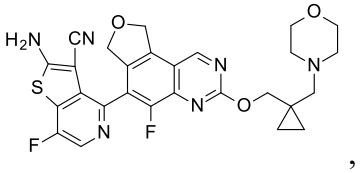
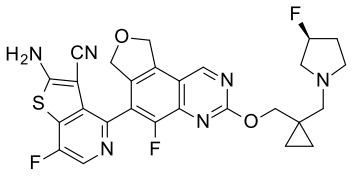
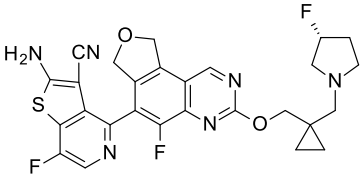
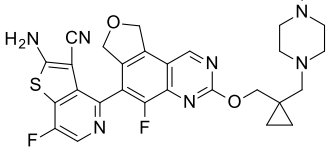
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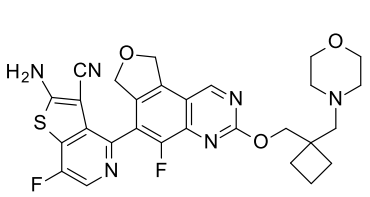
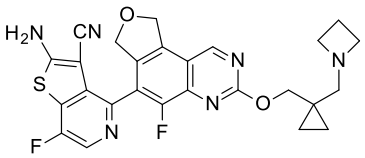
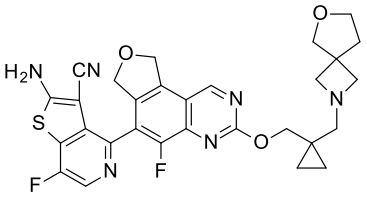
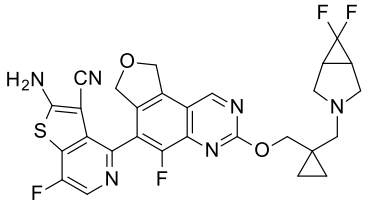
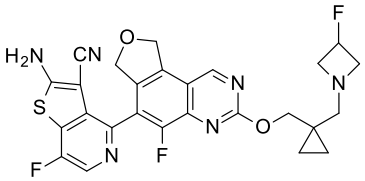
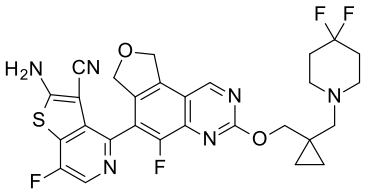
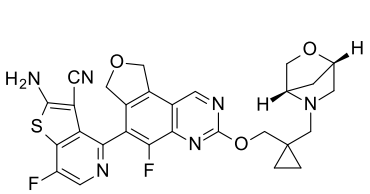
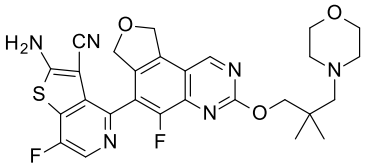
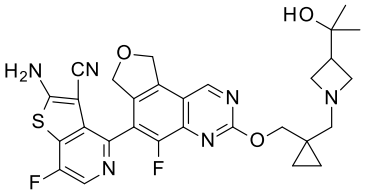
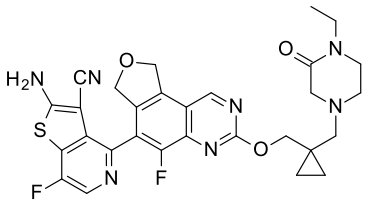
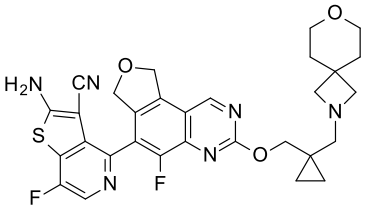
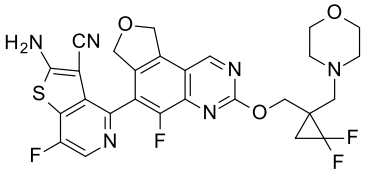
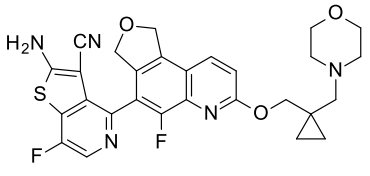
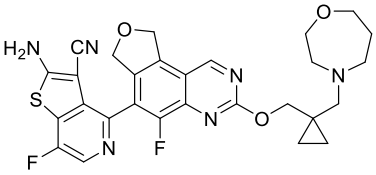
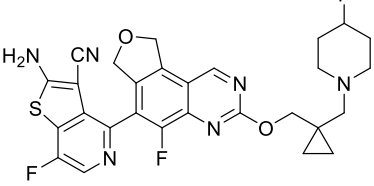
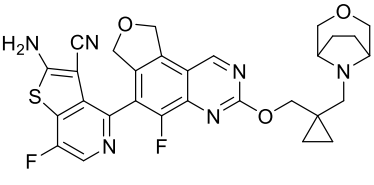
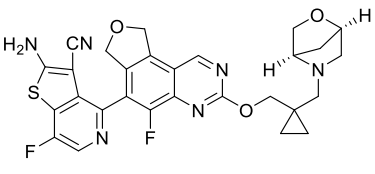
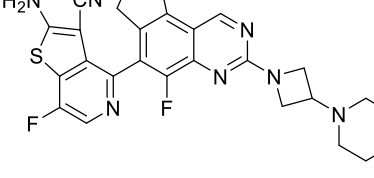

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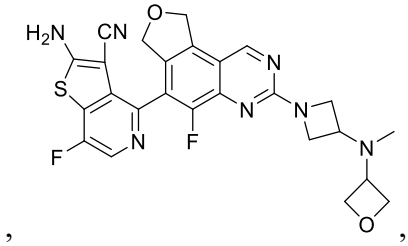
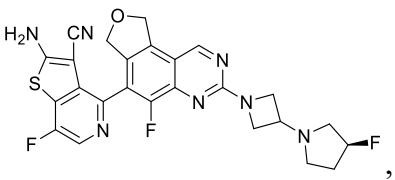
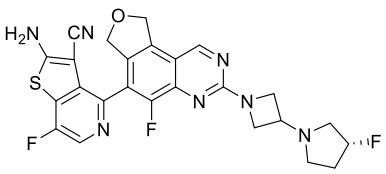
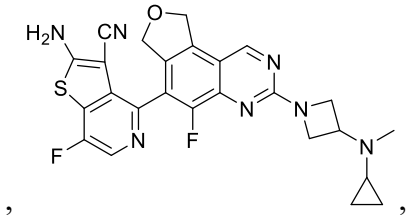
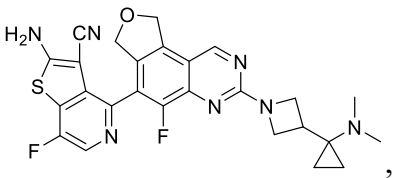
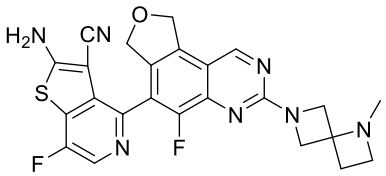
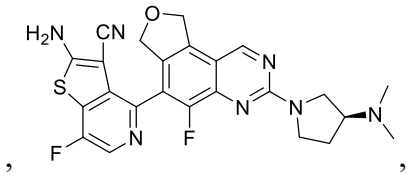
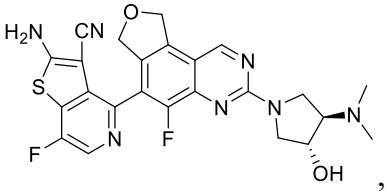
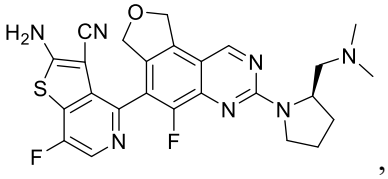
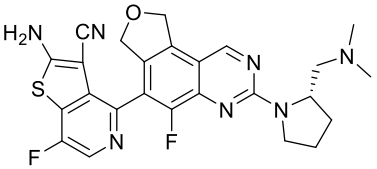
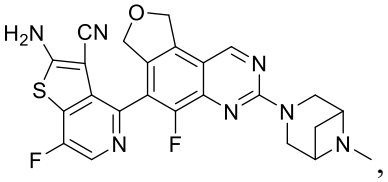
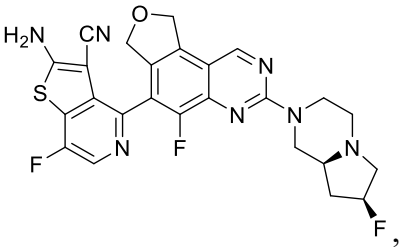
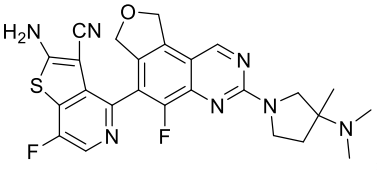
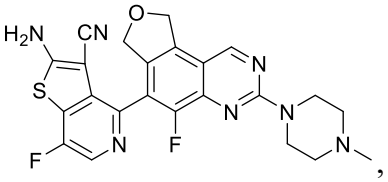
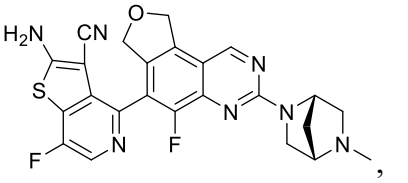
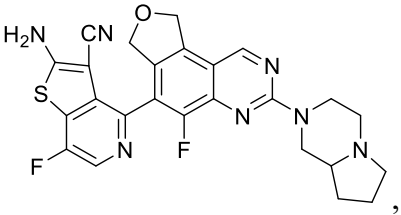
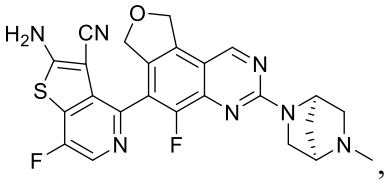
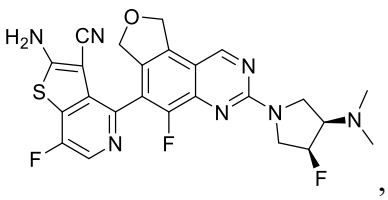
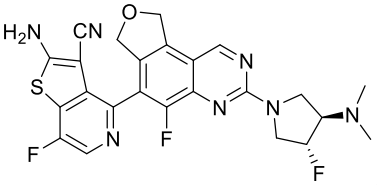
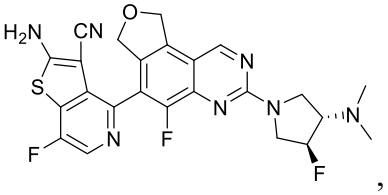
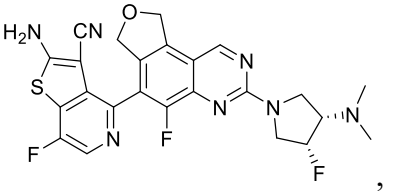
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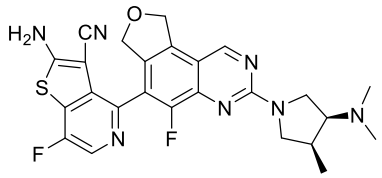
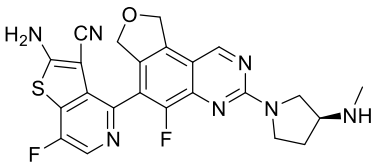
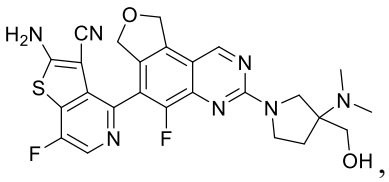
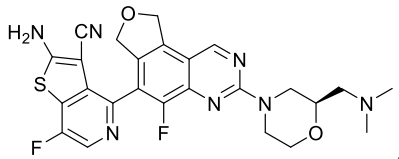
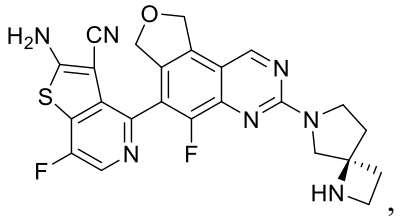
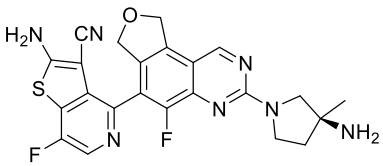
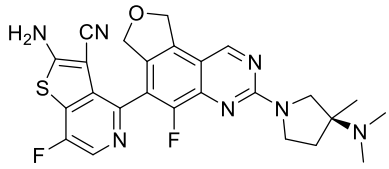
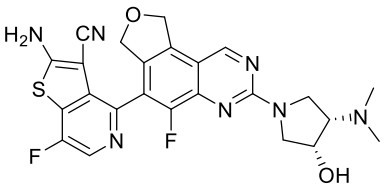
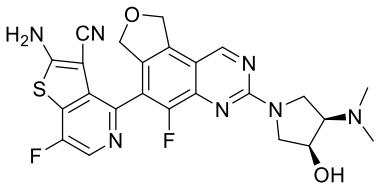
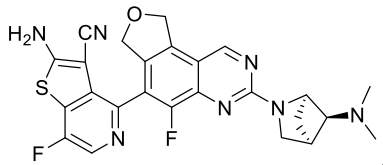
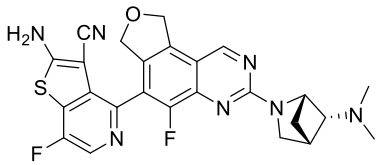
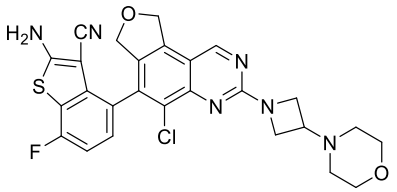
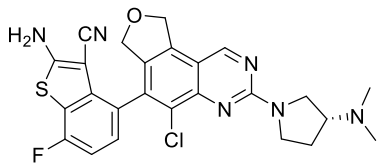
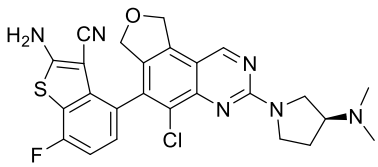
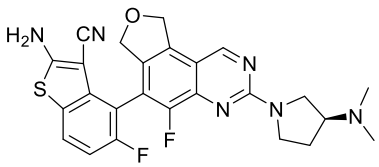
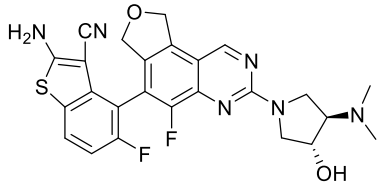
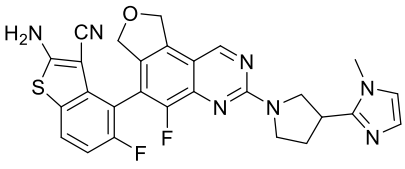
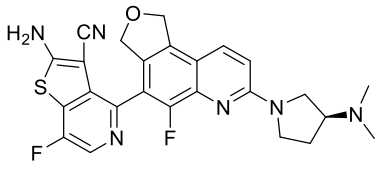
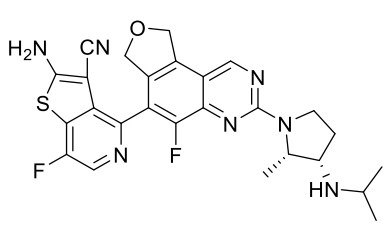
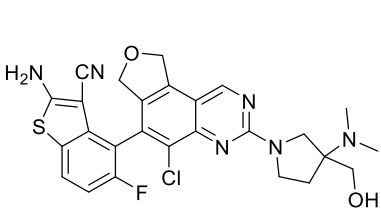
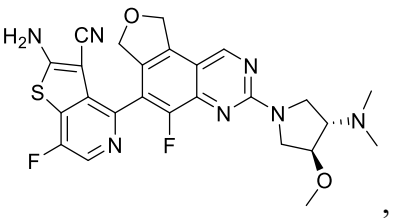
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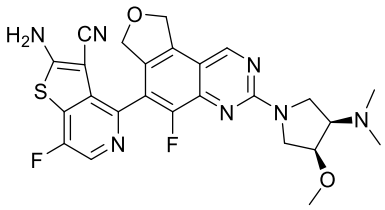
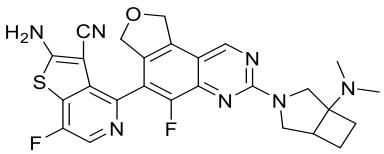
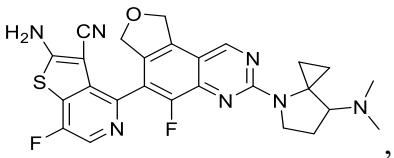
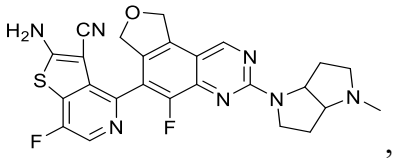
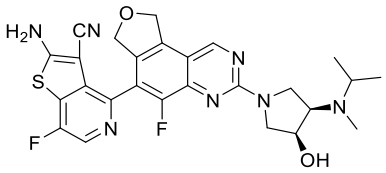
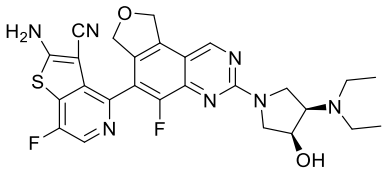
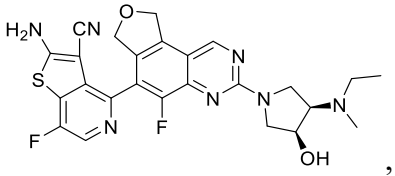
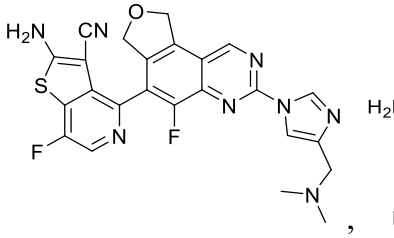
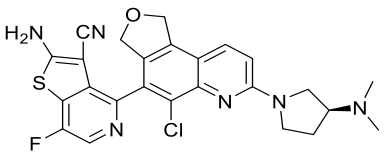
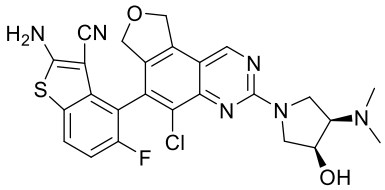
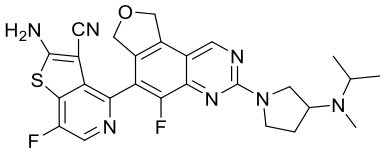
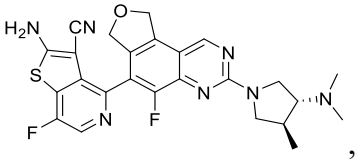
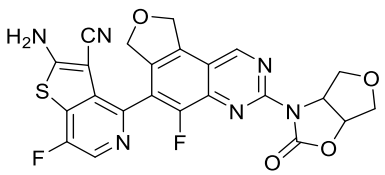
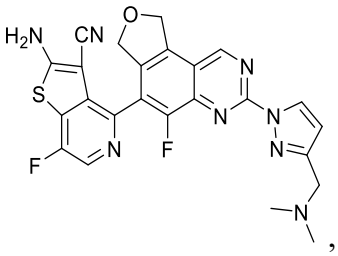
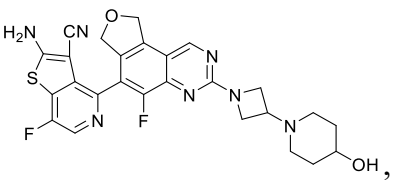
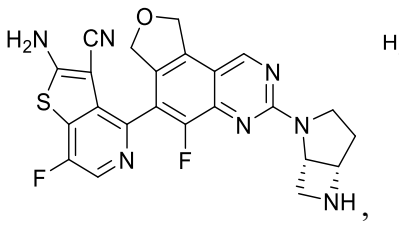
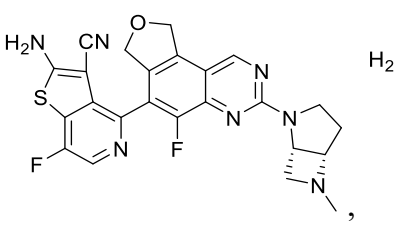
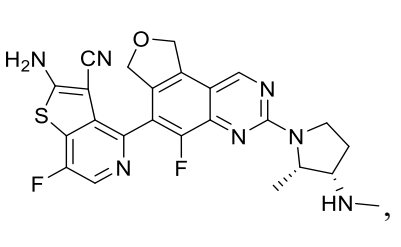
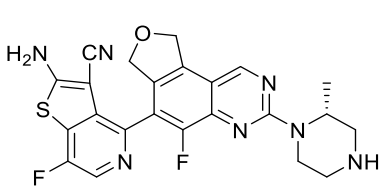
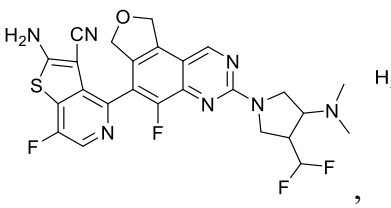
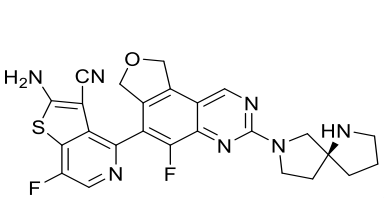

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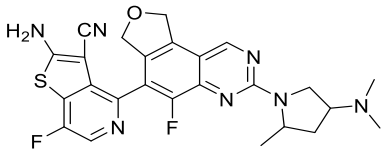
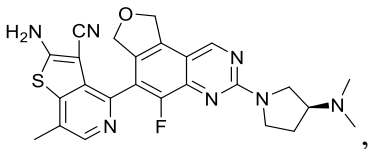
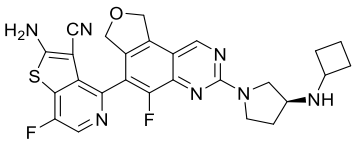
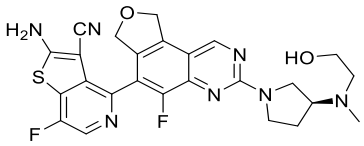
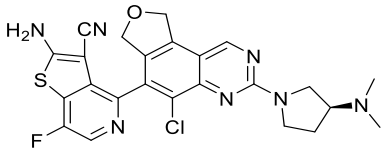
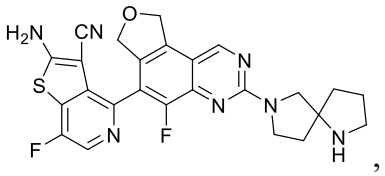
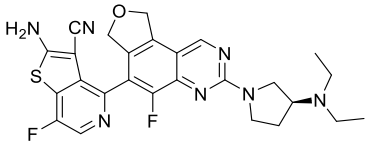
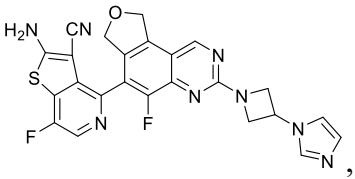
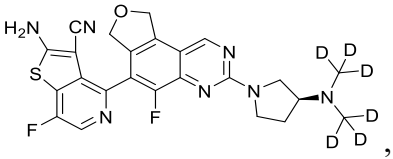
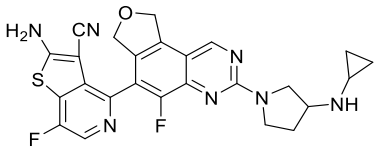
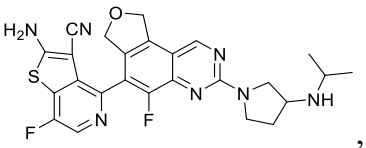
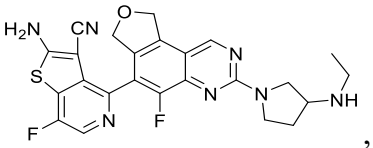
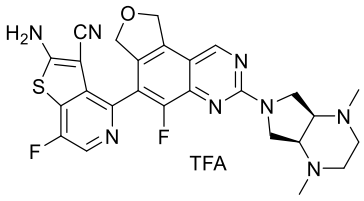
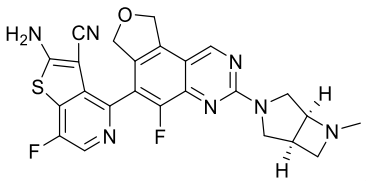
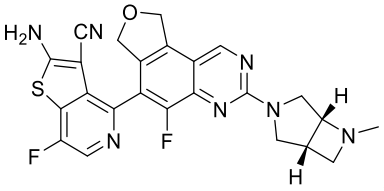
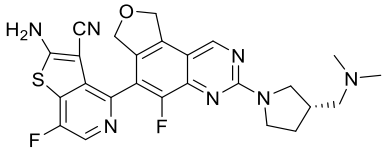
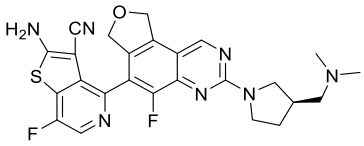
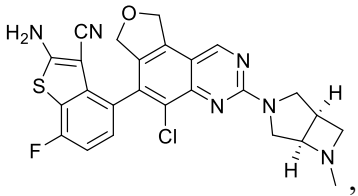
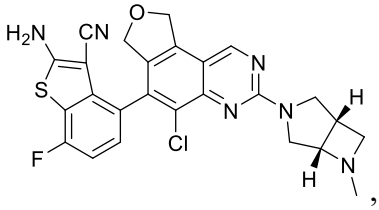
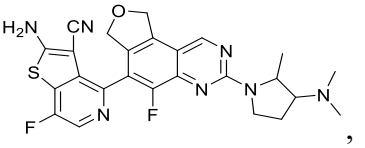
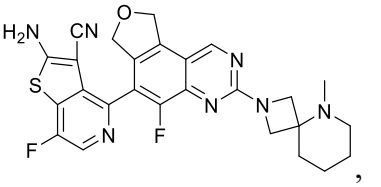
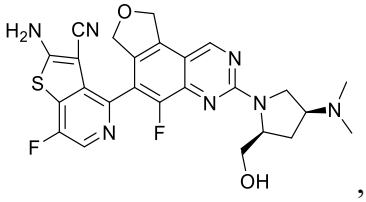
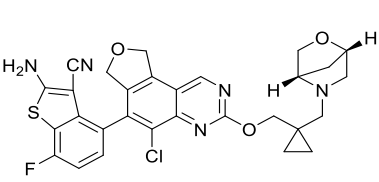
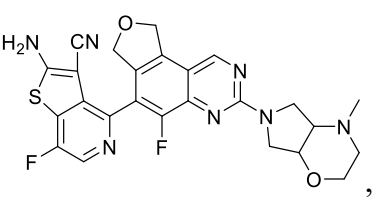

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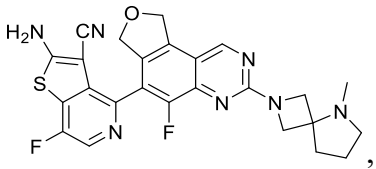
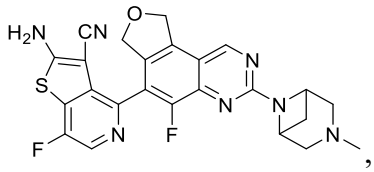
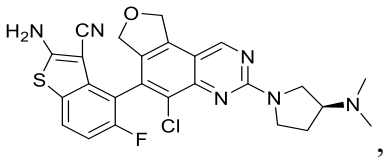
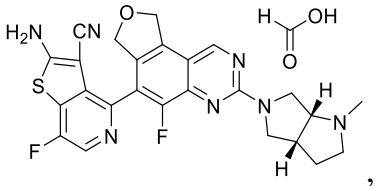
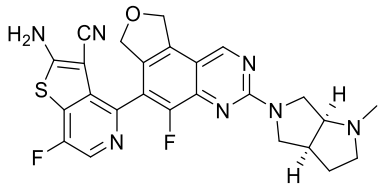
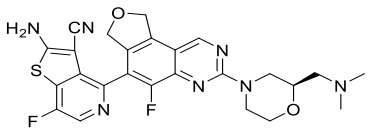
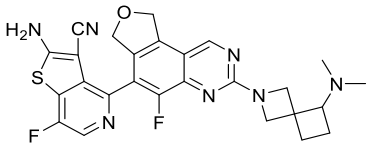
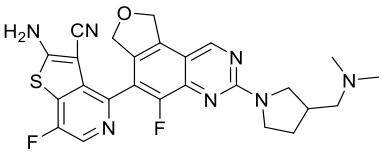
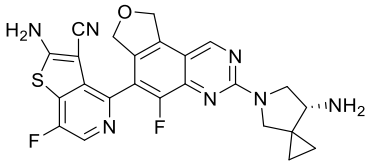
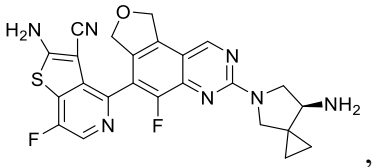
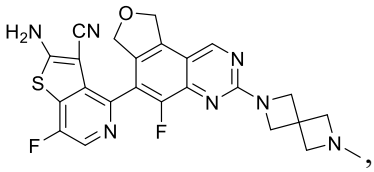
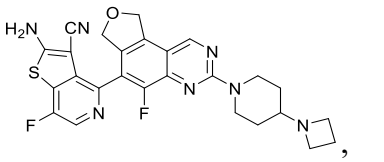
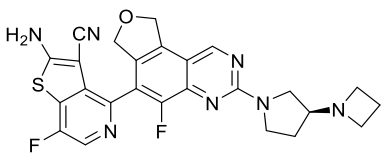
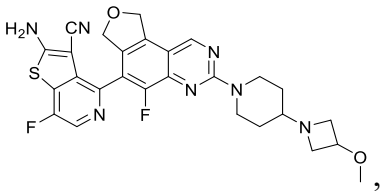
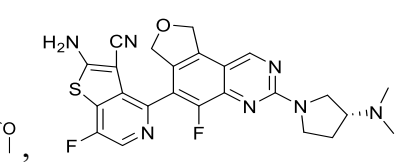
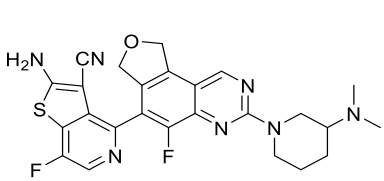
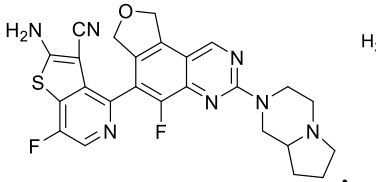
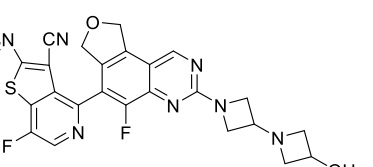
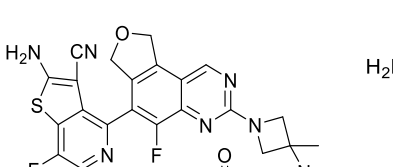
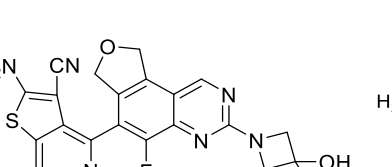
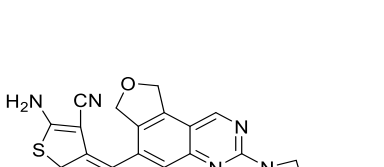
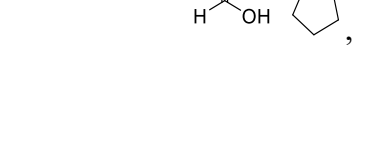
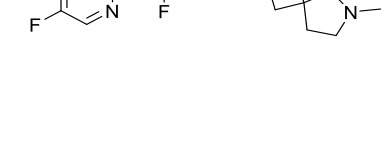
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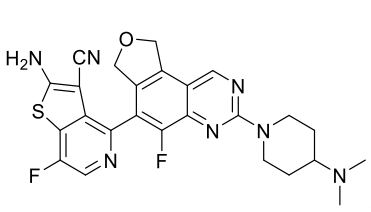
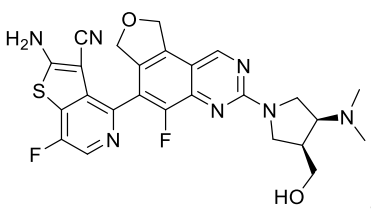
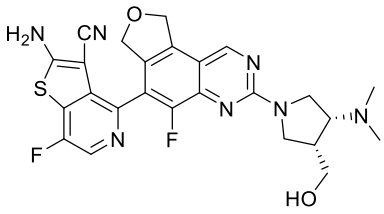
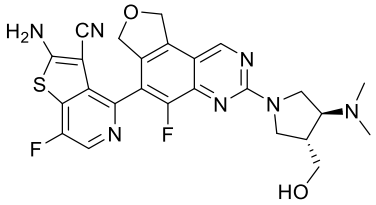
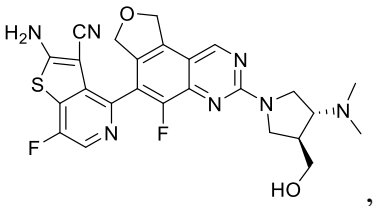
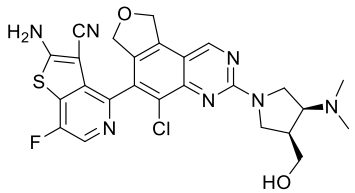
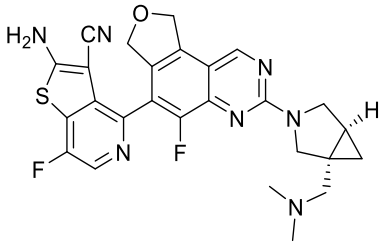
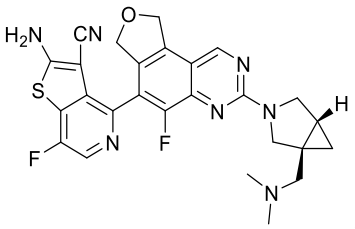
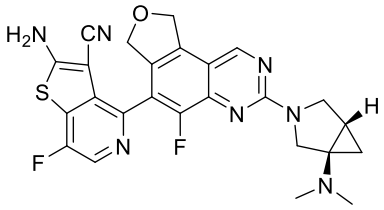
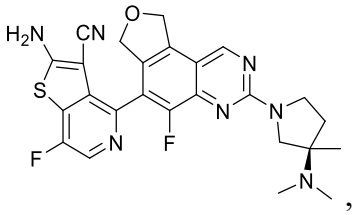
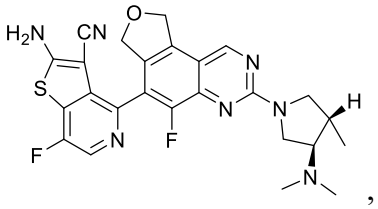
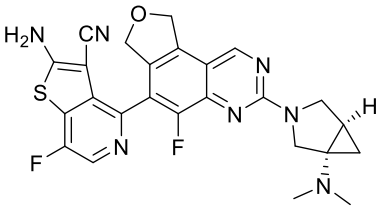
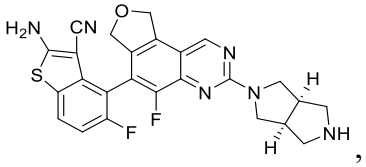
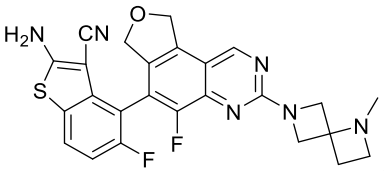
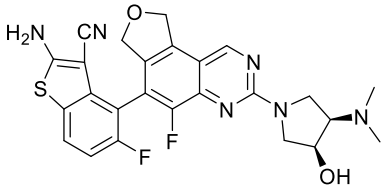
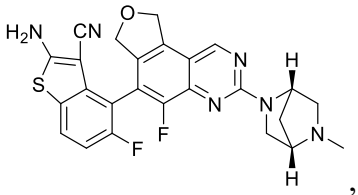
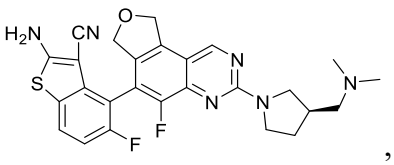
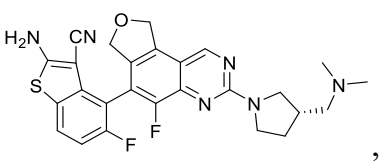
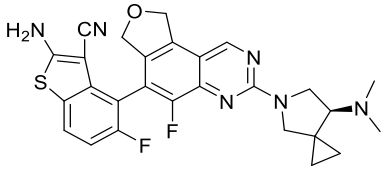
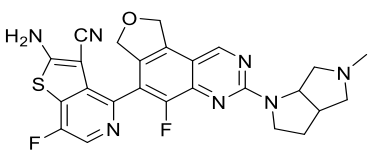
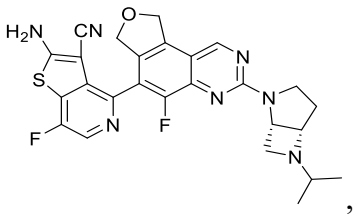
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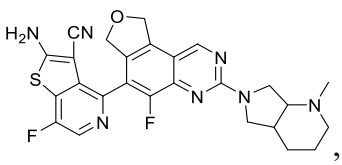
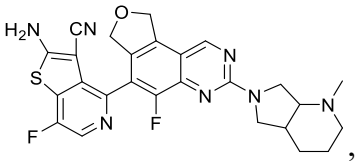
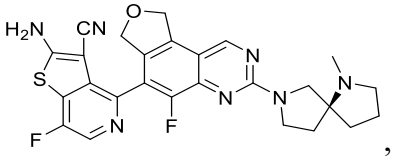
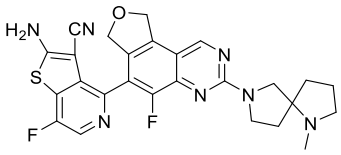
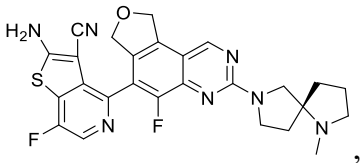
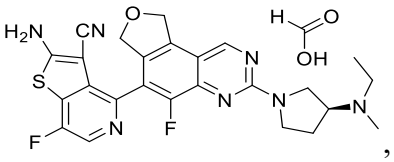
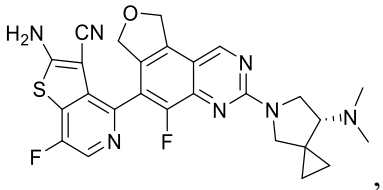
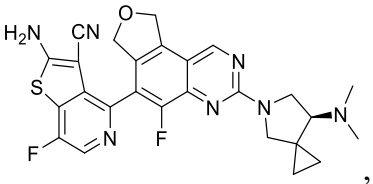
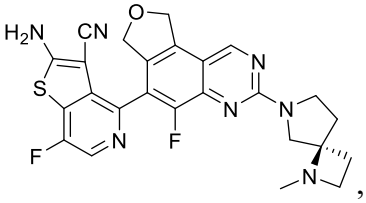
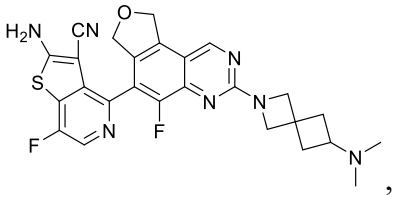
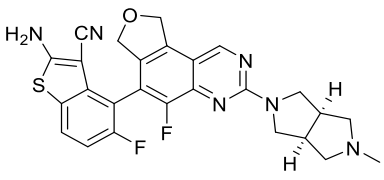
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, and
, or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising a compound according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

30. Use of a pharmaceutical composition according to claim 29 in the manufacture of a medicament for treating a patient for cancer, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

31. Use of a compound according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient for cancer, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

32. The use according to claim 30 or 31 wherein the compound or a pharmaceutically acceptable salt thereof is to be administered to the patient and wherein the patient has a cancer that

was determined to have one or more cells expressing the KRas G12C, G12D, and/or G12V mutant proteins prior to administration of the compound or a pharmaceutically acceptable salt thereof.

33. The use according to claim 30 or 31, wherein the cancer has one or more cells that express a KRas G12C, G12D, and/or G12V mutant protein.

34. Use of a compound according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a patient with a cancer that has a KRas G12C, G12D, and/or G12V mutation.

35. The use according to claim 34, wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, mutant ovarian cancer, cholangiocarcinoma, and colorectal cancer.

36. The use according to any one of claims 30-35, wherein the compound or a pharmaceutically acceptable salt thereof and one or more of a PD-1 inhibitor, a PD-L1 inhibitor, a CDK4/CDK6 inhibitor, an EGFR inhibitor, an ERK inhibitor, an Aurora A inhibitor, a SHP2 inhibitor, a platinum agent, and pemetrexed, or pharmaceutically acceptable salts thereof are to be administered to the patient.

37. The compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-28, for use in therapy.

38. Use of the compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-28, in the manufacture of a medicament for the treatment of cancer.

39. The use according to claim 38 wherein the cancer has a KRas G12C, G12D, and/or G12V mutation.

40. The use according to claim 38 or 39 wherein the cancer is selected from lung cancer, pancreatic cancer, cervical cancer, esophageal cancer, endometrial cancer, ovarian cancer, cholangiocarcinoma, and colorectal cancer.

41. The use according to claim 38 wherein the compound, or a pharmaceutically acceptable salt thereof, is to be used in simultaneous, separate, or sequential combination with one or more of a PD-1 or PD-L1 inhibitor, a CDK4/CDK6 inhibitor, an EGFR inhibitor, an ERK inhibitor,

an Aurora A inhibitor, a SHP2 inhibitor, a platinum agent, and pemetrexed, or pharmaceutically acceptable salts thereof, in the treatment of cancer.