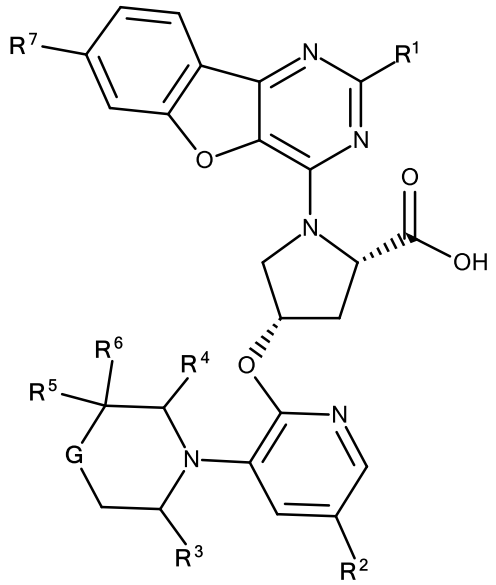
The cGAS inhibitors of the invention with this particular pharmacological profile which combines an excellent in vitro inhibitory potency and an excellent cellular inhibitory potency with a high selectivity for cGAS inhibition have a high probability to also exhibit a good therapeutic effect in the patient. Due to their high cellular inhibitory potency compounds with this particular pharmacological profile should be able to pass the cell membrane barrier and therefore reach their intracellular target location and due to their selectivity to exclusively inhibit cGAS activity, these compounds should not show unwanted off target effects, for example side effects somewhere within the signaling pathway downstream of cGAS or cytotoxic effects.

1a Summary

In one aspect, the present disclosure provides a compound of formula **(I)**,



(I),

wherein

R[1] is selected from methyl, ethyl, halomethyl, haloethyl and halogen,

wherein

G is selected from O, N**R[8]**, CH_2, C and C**R[8]R[9]**,

wherein

R[2] is selected from H, halogen, cyclopropyl, C_{1-3}-alkyl, -C_{2-5}-alkynyl, -S-methyl and CN,

or wherein **R[2]** is a cyclic group, wherein this cyclic group is selected from the group consisting of a phenyl or a five- to six-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms each independently selected from N, S and O, wherein this cyclic group is substituted by one or two, identical or different substituents **R[10]**,

wherein

R[3] is H or methyl,

R[4] is H or methyl,

R[5] is selected from H, methyl, -CN, -methylene-OH and -CF_3,

or **R[5]** may be absent,

R[6] is selected from H, methyl, -CN, -methylene-OH and -CF_3,

or **R[5]** and **R[6]** together with the C-atoms in between form a ring selected from oxetane, tetrahydrofurane and cyclopropane,

R[7] is selected from H, halogen, (C_{1-3})-alkyl and halo-(C_{1-3})-alkyl,

R[8] is selected from CN, H and methyl,

R[9] is selected from H, methyl and halogen

or **R[9]** may be absent,

wherein each **R[10]** is independently selected from the group consisting of hydrogen, halogen, haloalkyl, -methyl, -ethyl, -NH-CO-methyl, -$N(CH_3)_2$, -CH_2-OH, -$NH(CH_3)$, -O-(C_{1-3}-alkyl), -CN, -S-CH_3, -CO-NH_2, -CH_2-$NH(CH_3)$, -CH_2-NH_2, -SO-(CH_3), cyclopropyl and -O-**R[11]**,

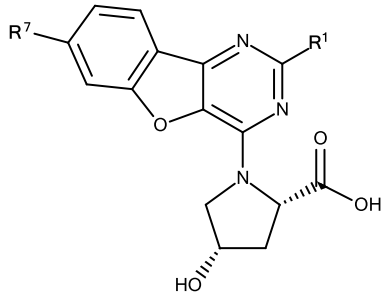
wherein **R[11]** is a five- or six-membered heterocycle with one or two heteroatoms each independently selected from N, O and S,

or **G** is C**R**^{8}**R**^{9}, **R**^{5} and **R**^{9} are absent, and **R**^{8} and **R**^{6} and the two C-atoms in between **R**^{8} and **R**^{6} form an annulated five-membered aromatic or non-aromatic heterocycle comprising one, two or three heteroatoms each independently selected from N, S and O,

or **G** is C**R**^{8}**R**^{9}, **R**^{5} and **R**^{9} are absent, and **R**^{8} and **R**^{9} form together with the C-atom in between **R**^{8} and **R**^{9} a diazirine ring,

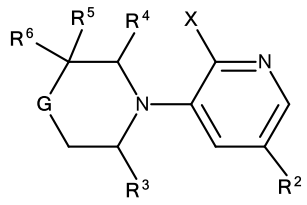
and prodrugs or pharmaceutically acceptable salts thereof.

In another aspect, the present disclosure provides an intermediate of formula **(IV)**



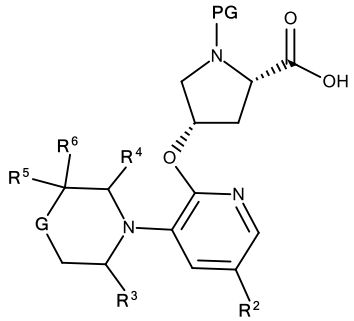
(IV),

or formula **(V)**



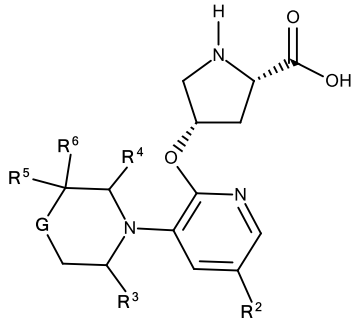
(V),

or formula **(X)**



(X)

or formula **(XI)**



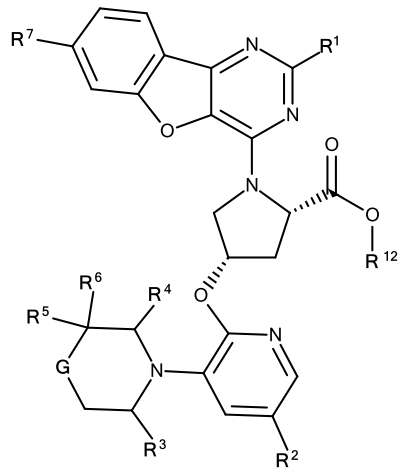
(XI),

wherein **G**, **R^1**, **R^2**, **R^3**, **R^4**, **R^5**, **R^6** and **R^7** are described herein
and wherein **X** is F or NO_2,

and wherein **PG** is a protecting group selected from the group consisting of *tert*-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), fluorenylmethylenoxycarbonyl (Fmoc) and allyloxycarbonyl (Alloc).

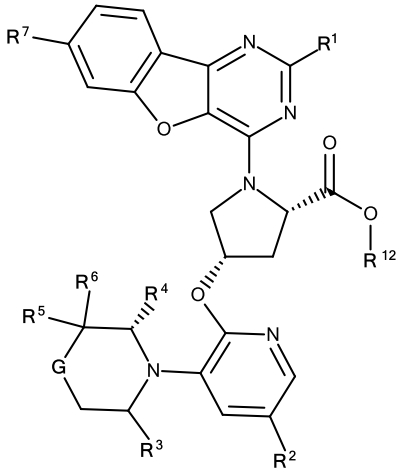
In another aspect, the present disclosure provides a prodrug of any of the compounds as described herein,

of formula **(A)**



(A),

or of formula **(A')**



(A'),

wherein $\mathbf{R^{12}}$ is C_{1-4}-alkyl, aryl, -CH_2-aryl, NH-SO_2-C_{1-3}-alkyl.

In another aspect, the present disclosure provides use of a compound of formula **(I)** or of formula **(I')** as described herein in the manufacture of a medicament for the treatment of a disease that can be treated by the inhibition of cGAS.

In another aspect, the present disclosure provides use of a compound of formula **(I)** or of formula **(I')** as described herein in the manufacture of a medicament for the treatment of a disease selected from the group consisting of systemic lupus erythematosus (SLE), interferonopathies, Aicardi-Goutières syndrome, age-related macular degeneration (AMD), amyotrophic lateral sclerosis (ALS), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, Sjogren's syndrome, Parkinsons disease, heart failure and cancer, systemic sclerosis (SSc), non-alcoholic steatotic hepatitis (NASH), interstitial lung disease (ILD), preferably progressive fibrosing interstitial lung disease (PF-ILD), in particular idiopathic pulmonary fibrosis (IPF).

In another aspect, the present disclosure provides use of a compound of formula **(I)** or of formula **(I')** as described herein in the manufacture of a medicament for the treatment of a disease selected from the group consisting of systemic lupus erythematosus (SLE), interferonopathies, Aicardi-Goutières syndrome, age-related macular degeneration (AMD), amyotrophic lateral sclerosis (ALS), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, Sjogren's syndrome and Parkinsons disease.

In another aspect, the present disclosure provides use of a compound of formula **(I)** or of formula **(I')** as described herein in the manufacture of a medicament for the treatment of a fibrosing disease selected from the group consisting of systemic sclerosis (SSc), non-alcoholic steatohepatitis (NASH), interferonopathies, interstitial lung disease (ILD), preferably progressive fibrosing interstitial lung disease (PF-ILD), in particular idiopathic pulmonary fibrosis (IPF).

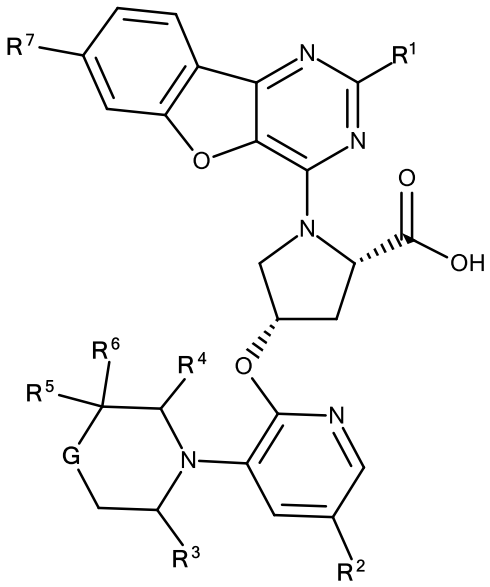
In another aspect, the present disclosure provides use of a compound of formula **(I)** or of formula **(I')** as described herein in the manufacture of a medicament for the treatment of a disease selected from the group consisting of, age-related macular degeneration (AMD), heart failure, COVID-19/SARS-CoV-2 infection, renal inflammation, renal fibrosis, dysmetabolism, vascular diseases, cardiovascular diseases and cancer.

In another aspect, the present disclosure provides pharmaceutical composition comprising a compound of formula **(I)** or of formula **(I')** described herein and optionally one or more pharmaceutically acceptable carriers and/or excipients.

In another aspect, the present disclosure provides pharmaceutical composition comprising a compound of formula **(I)** or of formula **(I')** as described herein in combination with one or more active agents selected from the group consisting of anti-inflammatory agents, anti-fibrotic agents, anti-allergic agents/ anti-histamines, bronchodilators, beta 2 agonists /betamimetics, adrenergic agonists, anticholinergic agents, methotrexate, mycophenolate mofetil, leukotriene modulators, JAK inhibitors, anti-interleukin antibodies, non-specific immunotherapeutics such as interferons or other cytokines/chemokines, cytokine/chemokine receptor modulators, toll-like receptor agonists, immune checkpoint regulators, an anti-TNF antibody such as Humira™, an anti-BAFF antibody such as Belimumab and Etanercept.

2 DESCRIPTION OF THE INVENTION

The invention concerns compounds of formula **(I)**,



(I),

wherein

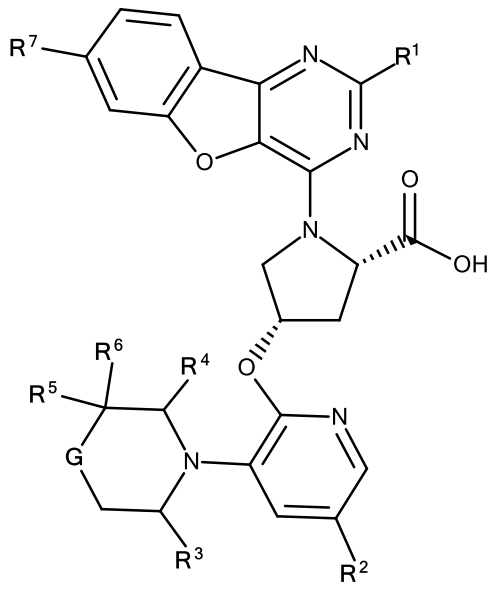
R^1 is selected from methyl, ethyl, halomethyl, haloethyl, and halogen,

wherein

G is selected from O, N**R^8**, CH_2, C and C**R^8R^9**,

PATENT CLAIMS

1. A compound of formula **(I)**,



(I),

wherein

R[1] is selected from methyl, ethyl, halomethyl, haloethyl and halogen,

wherein

G is selected from O, N**R[8]**, CH_2, C and C**R[8]R[9]**,

wherein

R[2] is selected from H, halogen, cyclopropyl, C_{1-3}-alkyl, -C_{2-5}-alkynyl, -S-methyl and CN,

or wherein **R[2]** is a cyclic group, wherein this cyclic group is selected from the group consisting of a phenyl or a five- to six-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms each independently selected from N, S and O, wherein this cyclic group is substituted by one or two, identical or different substituents **R[10]**,

wherein

R[3] is H or methyl,

R[4] is H or methyl,

R[5] is selected from H, methyl, -CN, -methylene-OH and -CF_3,

or **R**^{5} may be absent,

R^{6} is selected from H, methyl, -CN, -methylene-OH and -CF_3,

or **R**^{5} and **R**^{6} together with the C-atoms in between form a ring selected from oxetane, tetrahydrofurane and cyclopropane,

R^{7} is selected from H, halogen, (C_{1-3})-alkyl and halo-(C_{1-3})-alkyl,

R^{8} is selected from CN, H and methyl,

R^{9} is selected from H, methyl and halogen

or **R**^{9} may be absent,

wherein each **R**^{10} is independently selected from the group consisting of hydrogen, halogen, haloalkyl, -methyl, -ethyl, -NH-CO-methyl, -$N(CH_3)_2$, -CH_2-OH, -$NH(CH_3)$, -O-(C_{1-3}-alkyl), -CN, -S-CH_3, -CO-NH_2, -CH_2-$NH(CH_3)$, -CH_2-NH_2, -SO-(CH_3), cyclopropyl and -O-**R**^{11},

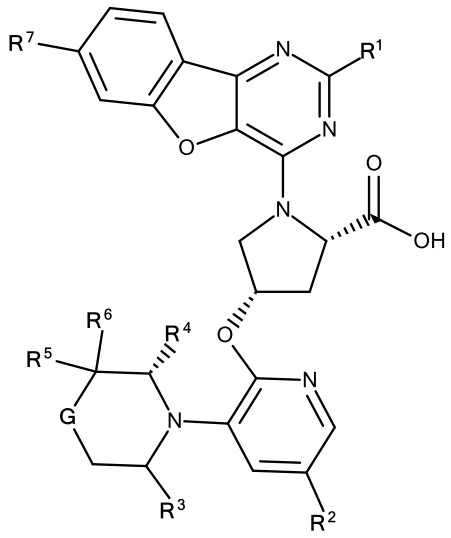
wherein **R**^{11} is a five- or six-membered heterocycle with one or two heteroatoms each independently selected from N, O and S,

or **G** is C**R**^{8}**R**^{9}, **R**^{5} and **R**^{9} are absent, and **R**^{8} and **R**^{6} and the two C-atoms in between **R**^{8} and **R**^{6} form an annulated five-membered aromatic or non-aromatic heterocycle comprising one, two or three heteroatoms each independently selected from N, S and O,

or **G** is C**R**^{8}**R**^{9}, **R**^{5} and **R**^{9} are absent, and **R**^{8} and **R**^{9} form together with the C-atom in between **R**^{8} and **R**^{9} a diazirine ring,

and prodrugs or pharmaceutically acceptable salts thereof.

2. The compound according to claim 1 of formula **(I')**,



(I'),

wherein **R**^{1}, **R**^{2}, **R**^{3}, **R**^{4}, **R**^{5}, **R**^{6}, **R**^{7}, **R**^{8}, **R**^{9}, **R**^{10}, **R**^{11} and **G** are defined as in claim 1

and prodrugs or pharmaceutically acceptable salts thereof.

3. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, wherein $\mathbf{R^7}$ is selected from H, F, Cl, methyl, ethyl, halomethyl and haloethyl,

and prodrugs or pharmaceutically acceptable salts thereof.

4. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, wherein $\mathbf{R^1}$ is selected from halomethyl, haloethyl and methyl,

and prodrugs or pharmaceutically acceptable salts thereof.

5. The compound according to claim 3, wherein $\mathbf{R^1}$ is a fluoromethyl selected from the group consisting of $–CF_3$, $–CHF_2$ and $-CH_2F$,

and prodrugs or pharmaceutically acceptable salts thereof.

6. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, wherein at least one of $\mathbf{R^3}$ and $\mathbf{R^4}$ is methyl,

and prodrugs or pharmaceutically acceptable salts thereof.

7. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, wherein one of $\mathbf{R^3}$ and $\mathbf{R^4}$ is methyl and the other one is H,

and prodrugs or pharmaceutically acceptable salts thereof.

8. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, wherein **G** is O

and prodrugs or pharmaceutically acceptable salts thereof.

9. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2,

wherein **G** is O,

and wherein one of $\mathbf{R^3}$ or $\mathbf{R^4}$ is methyl and the other one is H

and prodrugs or pharmaceutically acceptable salts thereof.

10. The compound according to claim 8,

wherein $\mathbf{R^4}$ is methyl and $\mathbf{R^3}$ is H,

wherein $\mathbf{R^5}$ and $\mathbf{R^6}$ together with the C-atoms in between form an oxetane ring,

and prodrugs or pharmaceutically acceptable salts thereof.

11. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2,

wherein $\mathbf{R^2}$ is selected from the group consisting of H, ethynyl, 1-propynyl, -S-methyl, halogen,

and prodrugs or pharmaceutically acceptable salts thereof.

12. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, wherein $\mathbf{R^2}$ is ethynyl

and prodrugs or pharmaceutically acceptable salts thereof.

13. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, wherein $\mathbf{R^4}$ is methyl and $\mathbf{R^3}$ is H,

wherein **G** is O,

wherein $\mathbf{R^5}$ and $\mathbf{R^6}$ together form an oxetane ring

wherein $\mathbf{R^2}$ is selected from the group consisting of H, ethynyl, 1-propynyl, -S-methyl, halogen,

and prodrugs or pharmaceutically acceptable salts thereof.

14. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2,

wherein $\mathbf{R^2}$ is a cyclic group wherein the cyclic group is selected from the group consisting of a phenyl or a five- to six-membered heteroaryl comprising 1, 2 or 3 heteroatoms selected from N, S and O, wherein this cyclic group is substituted by one or two, identical or different substituents $\mathbf{R^{10}}$,

wherein each $\mathbf{R^{10}}$ is independently selected from the group consisting of hydrogen, halogen, haloalkyl, -methyl, -ethyl, -NH-CO-methyl, $-N(CH_3)_2$, -CH2-OH, $-NH(CH_3)$, $-O-CH_3$, -CN, $-S-CH_3$, $-CO-NH_2$, $-CH_2-NH(CH_3)$, $-CH_2-NH_2$, $-SO-(CH_3)$, cyclopropyl and -O-$\mathbf{R^{11}}$,

wherein each $\mathbf{R^{11}}$ is selected from a five- or six-membered heterocycle with one or two heteroatoms each independently selected from N and O,

and prodrugs or pharmaceutically acceptable salts thereof.

15. The compound according to claim 14, wherein $\mathbf{R^2}$ is a cyclic group selected from the group consisting of pyrazolyl, pyridinyl, imidazolyl, phenyl and isoxazolyl,

wherein this cyclic group is substituted by one or two, identical or different substituents $\mathbf{R^{10}}$,

wherein each **R^{10}** is independently selected from the group consisting of hydrogen, halogen, haloalkyl, -methyl, -ethyl, -NH-CO-methyl, -$N(CH_3)_2$, -CH2-OH, -$NH(CH_3)$, -$O-CH_3$, -CN, -$S-CH_3$, -$CO-NH_2$, -CH_2-$NH(CH_3)$, -CH_2-NH_2, -$SO-(CH_3)$, cyclopropyl and -O-**R^{11}**,

wherein each **R^{11}** is tetrahydropyrane,

and prodrugs or pharmaceutically acceptable salts thereof.

16. The compound according to claim 15,

wherein **G** is O,
wherein one of **R^3** or **R^4** is methyl and the other one is H,
and prodrugs or pharmaceutically acceptable salts thereof.

17. The compound according to claim 16,

wherein **R^4** is methyl and **R^3** is H,
wherein **R^5** and **R^6** together with the C-atom in between form an oxetane ring
and prodrugs or pharmaceutically acceptable salts thereof.

18. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, wherein

G is C**R^8R^9**

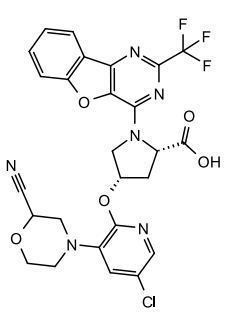
and wherein

R^8 and **R^6** and the two C-atoms in between **R^8** and **R^6** form an annulated five-membered aromatic heterocycle comprising one or two heteroatoms each independently selected from N and O which is selected from an annulated isoxazolyl ring, an annulated pyrazolyl ring, an annulated pyrrolyl ring and an annulated furanyl ring

wherein **R^9** and **R^5** are absent,

and prodrugs or pharmaceutically acceptable salts thereof.

19. The compound of formula **(I)** according to claim 1 or of formula **(I')** according to claim 2, which is selected from the group consisting of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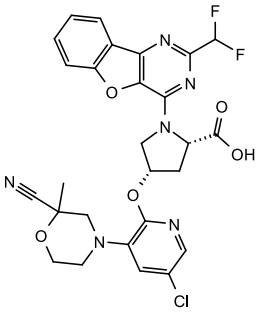
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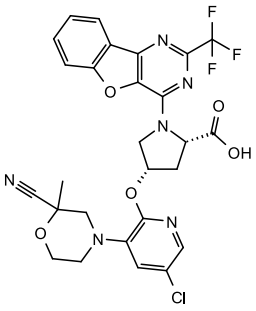
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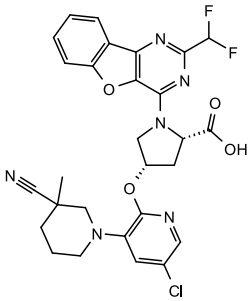
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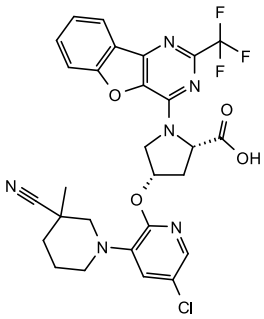
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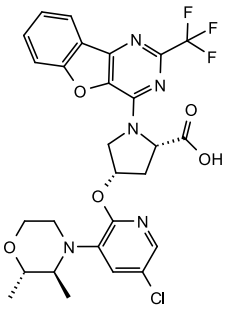
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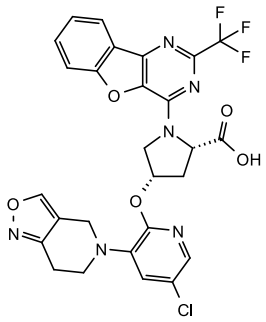
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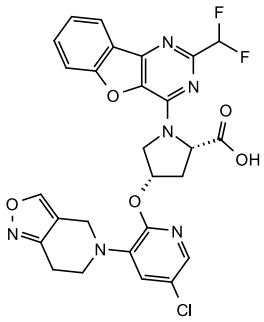
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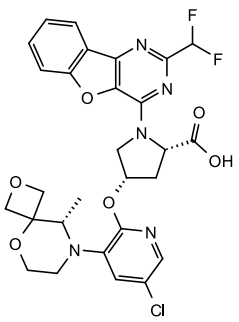
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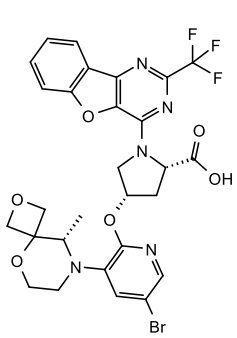
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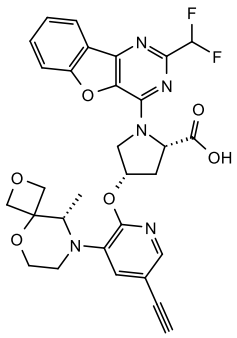
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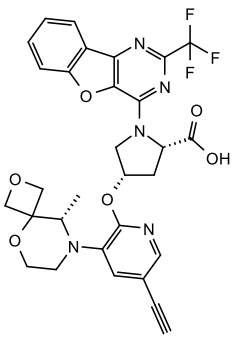
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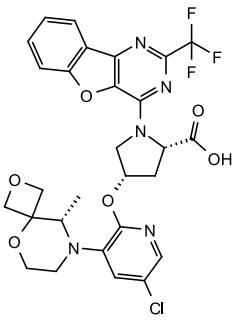
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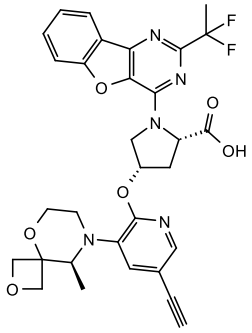
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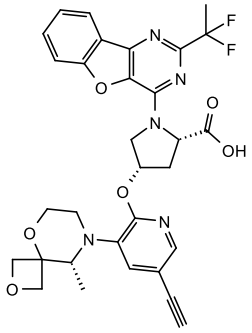
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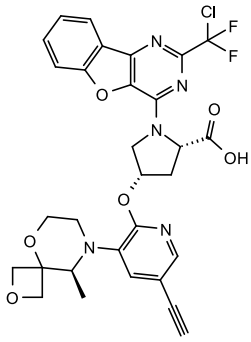
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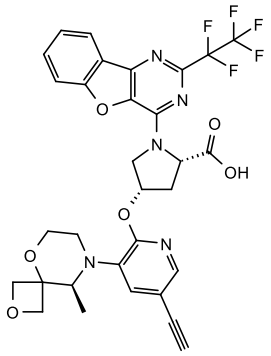
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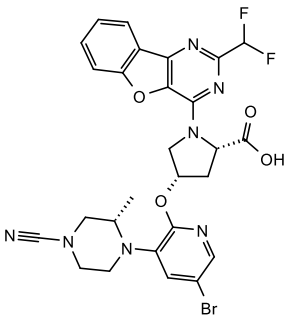
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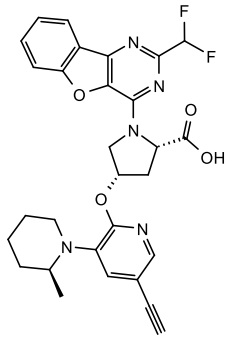
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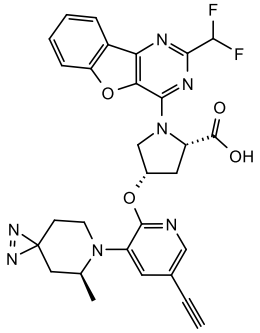
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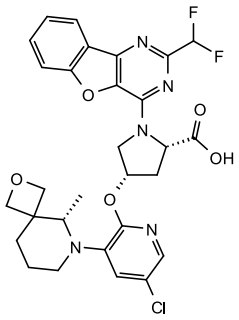
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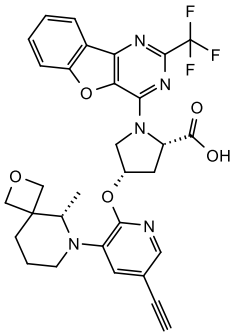
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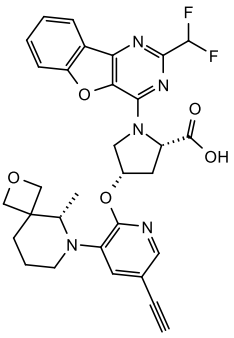
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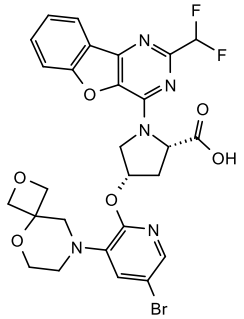
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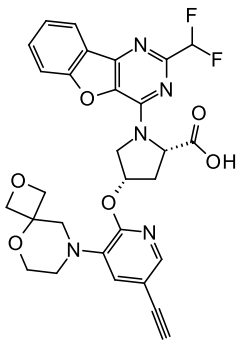
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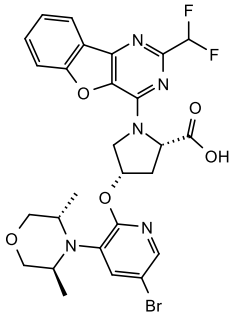
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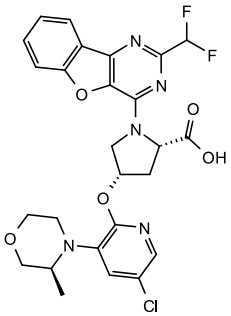
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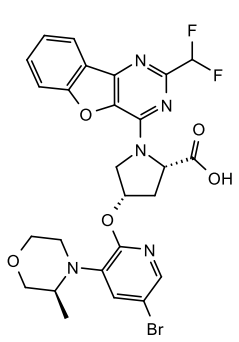
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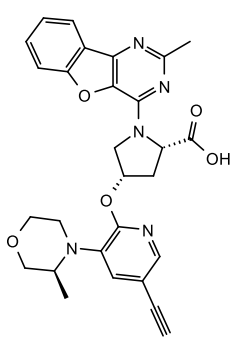
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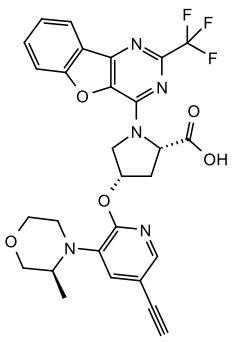
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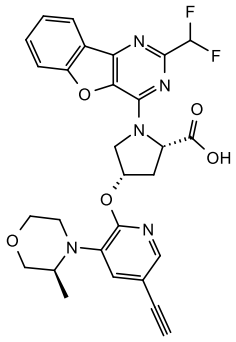
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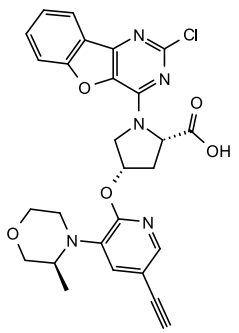
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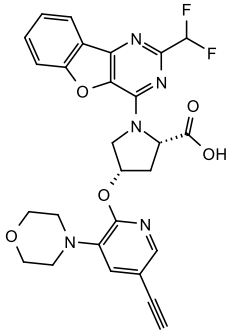
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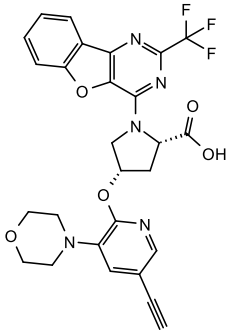
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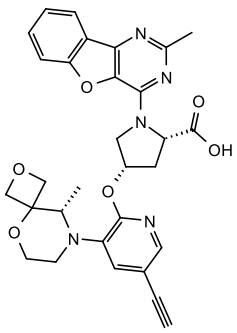
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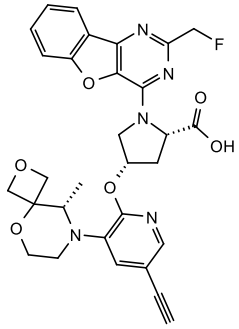
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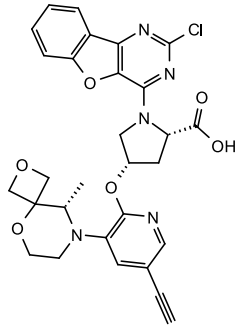
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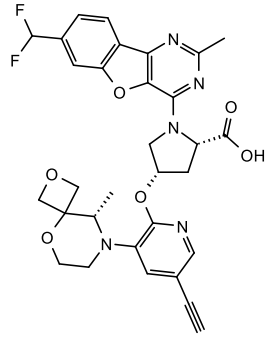
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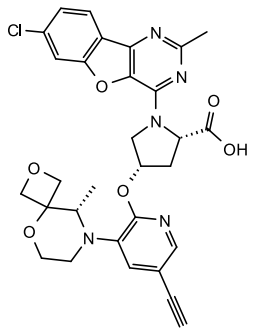
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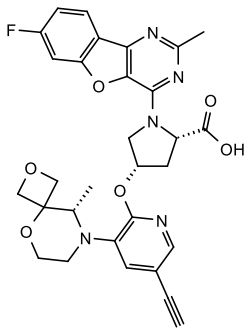
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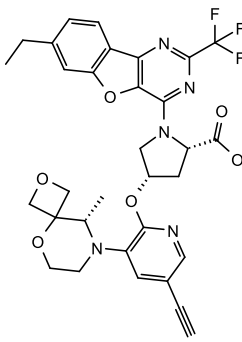
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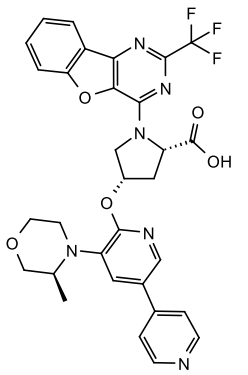
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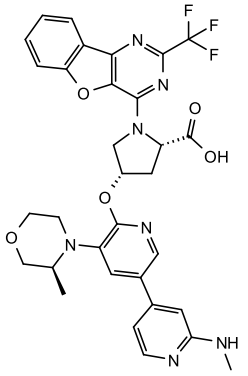
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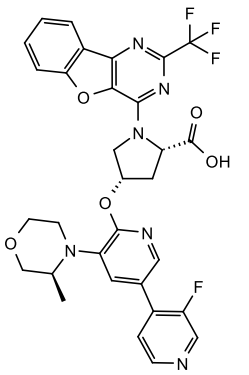
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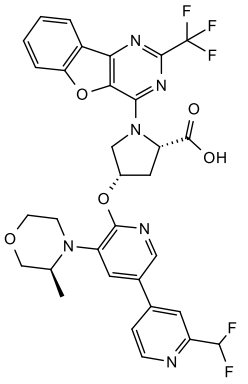
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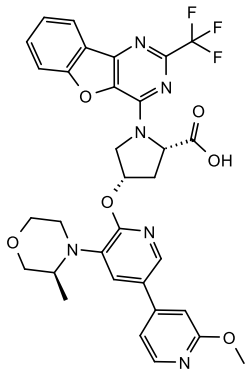
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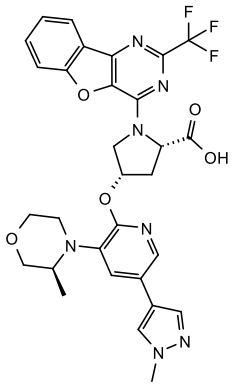
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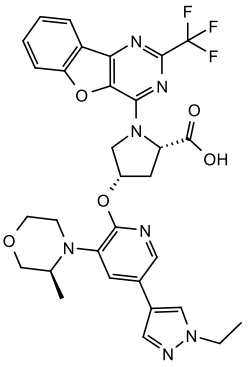
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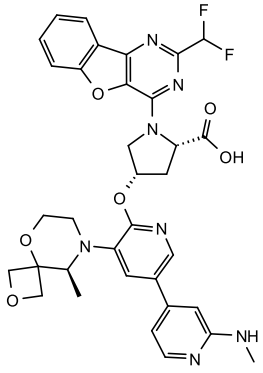
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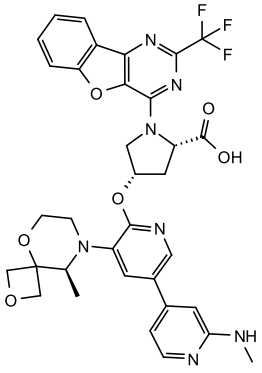
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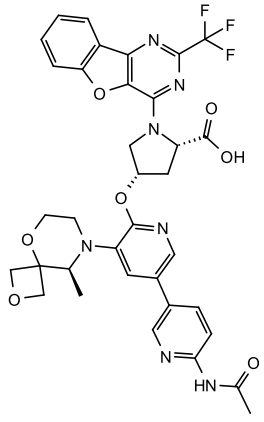
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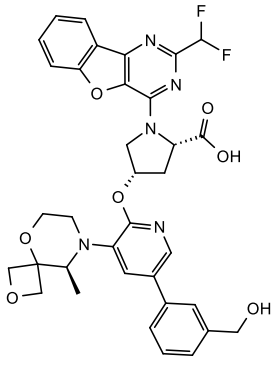
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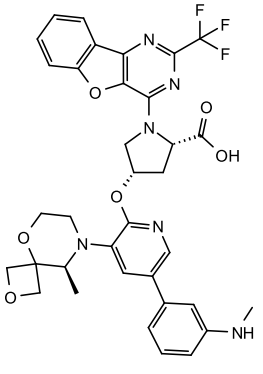
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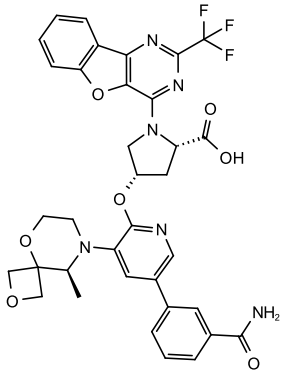
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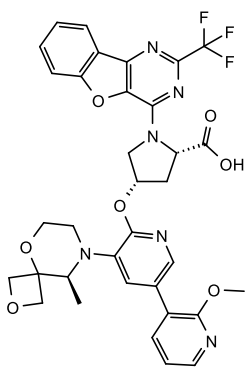
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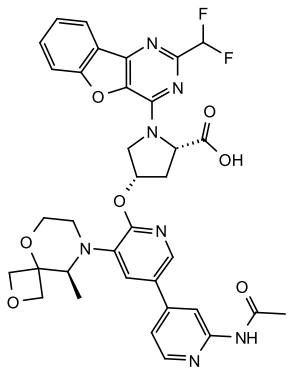
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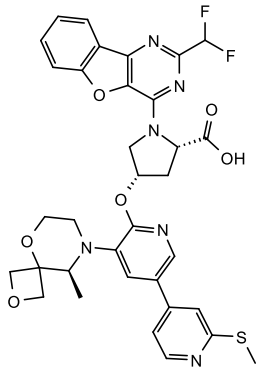
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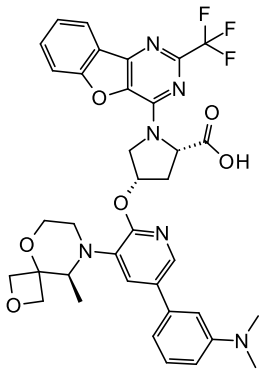
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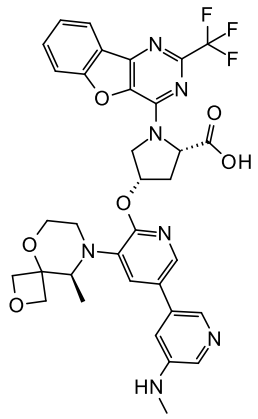
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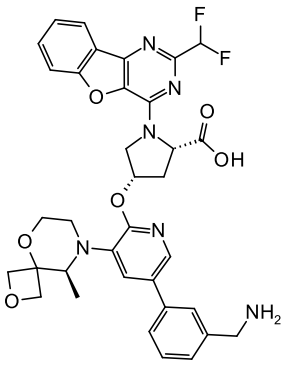
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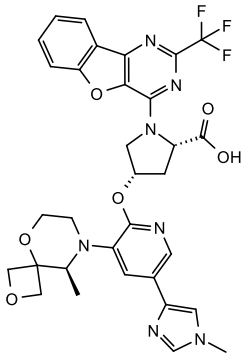
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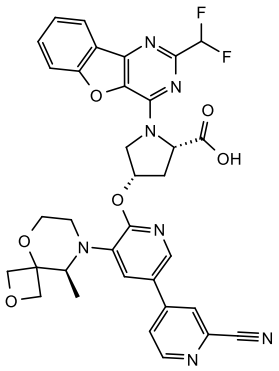
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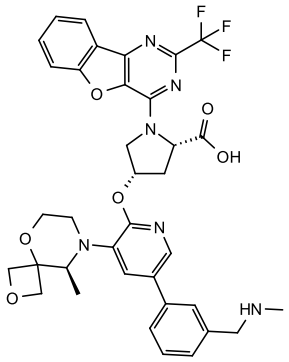
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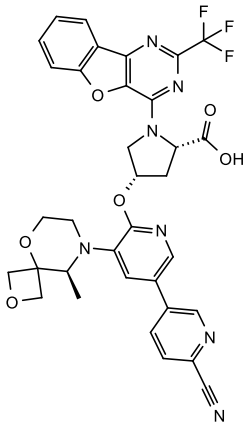
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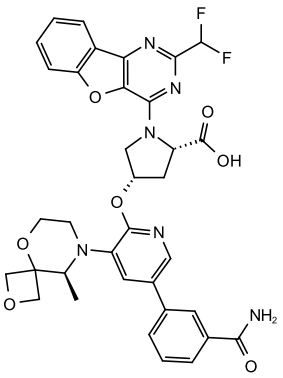
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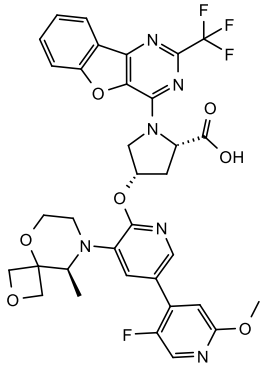
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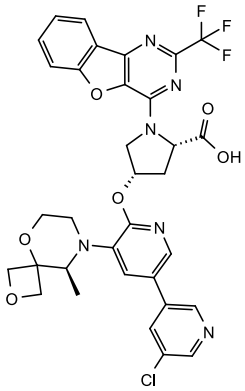
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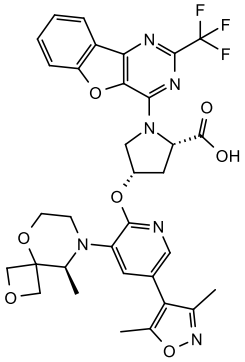
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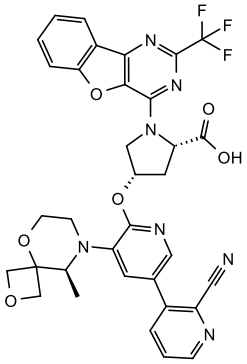
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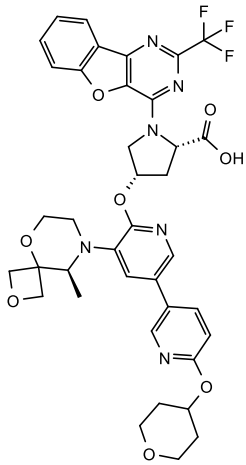
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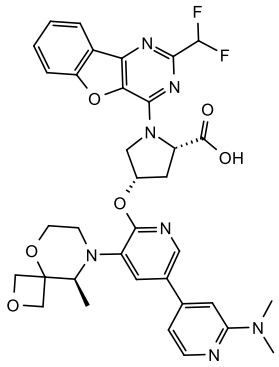
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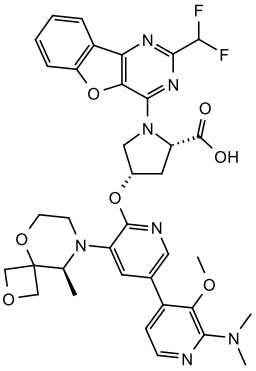
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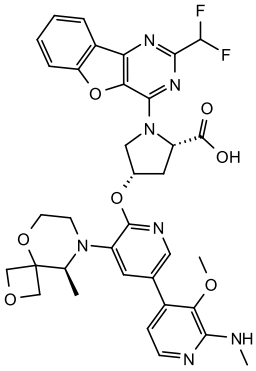
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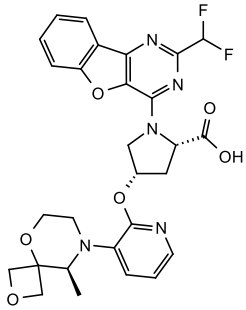
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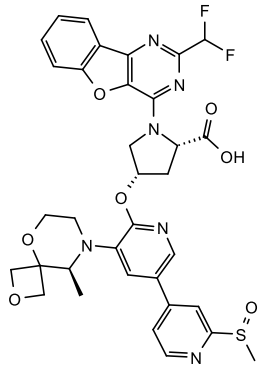
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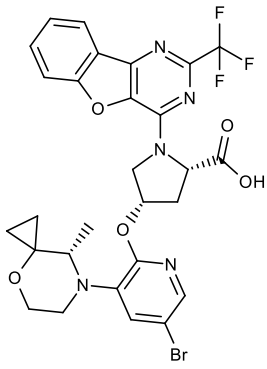
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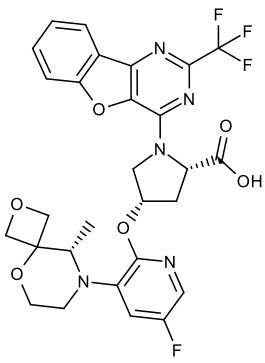
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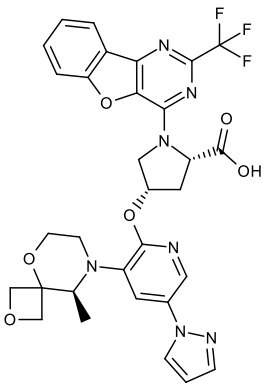
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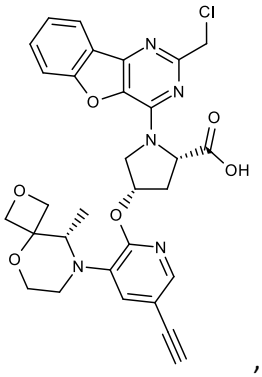
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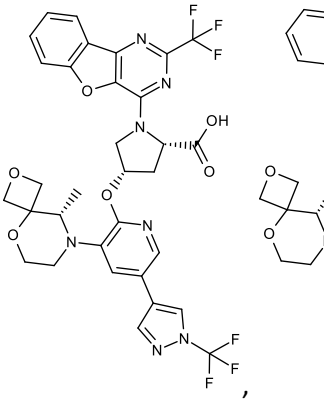
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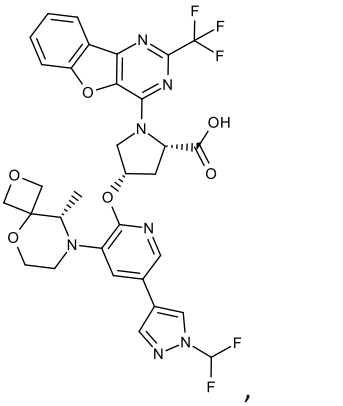
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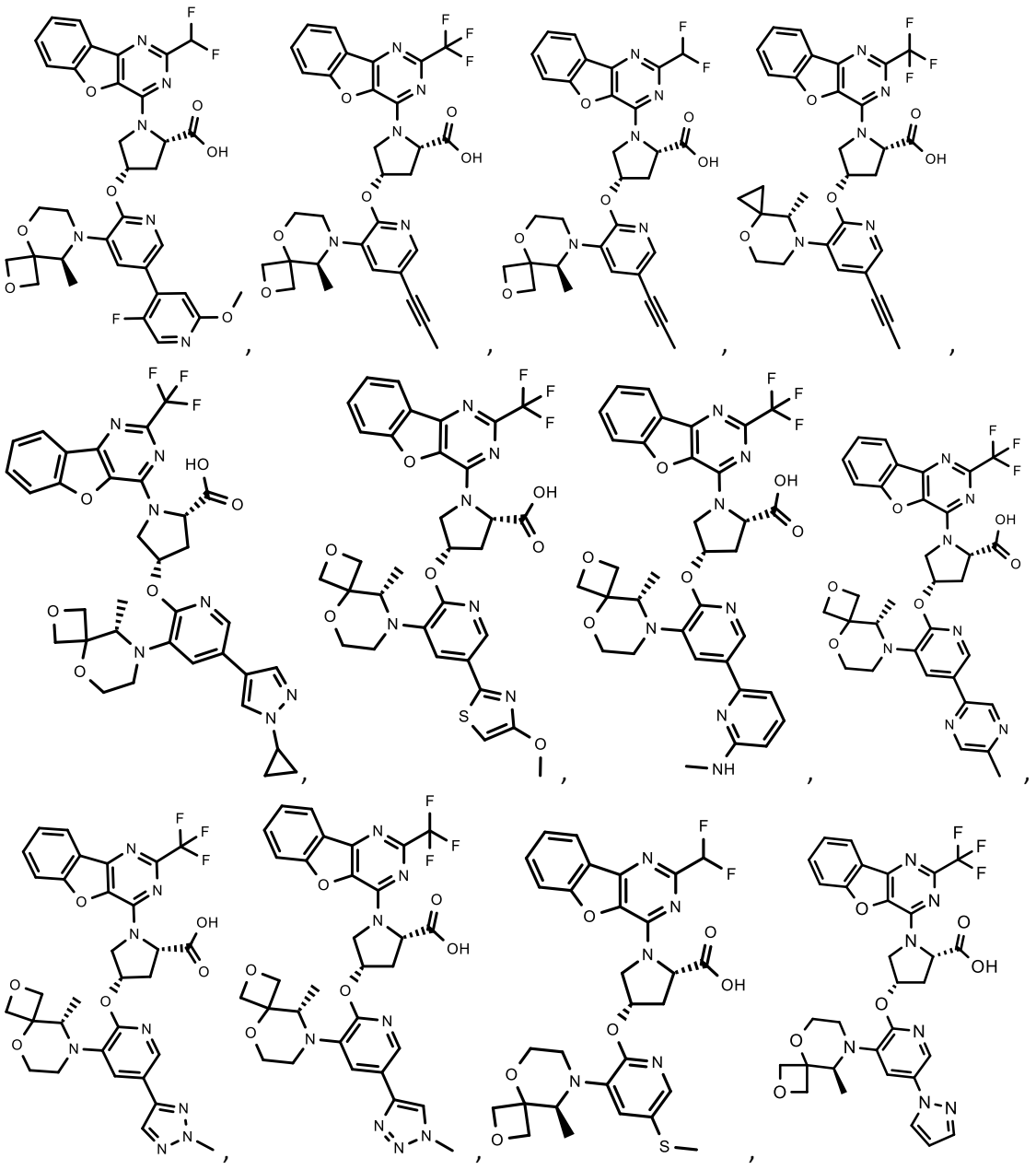
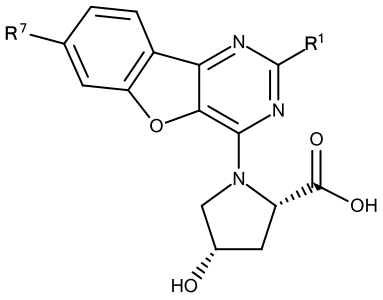


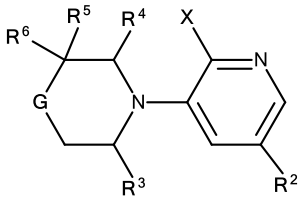
and prodrugs or pharmaceutically acceptable salts thereof.

20. An intermediate of formula **(IV)**



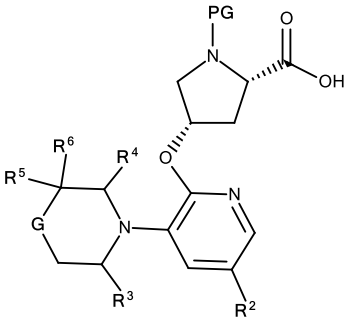
(IV),

or formula **(V)**



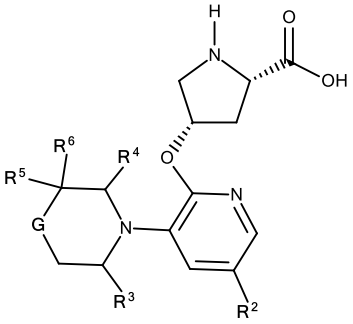
(V),

or formula **(X)**



(X)

or formula **(XI)**

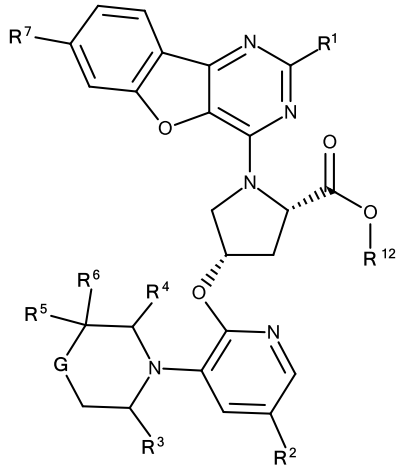


(XI),

wherein **G**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$ and $\mathbf{R^7}$ are defined as in claim 1
and wherein **X** is F or NO_2,
and wherein **PG** is a protecting group selected from the group consisting of *tert*-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz), fluorenylmethylenoxycarbonyl (Fmoc) and allyloxycarbonyl (Alloc).

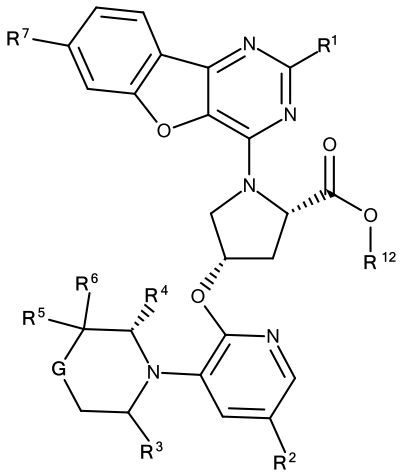
21. A prodrug of any of the compounds as defined in any of claims 1 to 19,

of formula **(A)**



(A),

or of formula **(A')**



(A'),

wherein $\mathbf{R^{12}}$ is is $C_{1\text{-}4}$-alkyl, aryl, -CH_2-aryl, NH-SO_2-$C_{1\text{-}3}$-alkyl.

22. The prodrug of formula **(A)** or of formula **(A')** according to claim 21, wherein $\mathbf{R^{12}}$ is methyl.

23. Use of a compound of formula **(I)** or of formula **(I')** according to any of claims 1 to 19 in the manufacture of a medicament for the treatment of a disease that can be treated by the inhibition of cGAS.

24. Use of a compound of formula **(I)** or of formula **(I')** according to any of claims 1 to 19 in the manufacture of a medicament for the treatment of a disease selected from the group

consisting of systemic lupus erythematosus (SLE), interferonopathies, Aicardi- Goutières syndrome, age-related macular degeneration (AMD), amyotrophic lateral sclerosis (ALS), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, Sjogren's syndrome, Parkinsons disease, heart failure and cancer, systemic sclerosis (SSc), non-alcoholic steatotic hepatitis (NASH), interstitial lung disease (ILD), preferably progressive fibrosing interstitial lung disease (PF-ILD), in particular idiopathic pulmonary fibrosis (IPF).

25. Use of a compound of formula **(I)** or of formula **(I')** according to any of claims 1 to 19 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of systemic lupus erythematosus (SLE), interferonopathies, Aicardi- Goutières syndrome, age-related macular degeneration (AMD), amyotrophic lateral sclerosis (ALS), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, Sjogren's syndrome and Parkinsons disease.

26. Use of a compound of formula **(I)** or of formula **(I')** according to any of claims 1 to 19 in the manufacture of a medicament for the treatment of a fibrosing disease selected from the group consisting of systemic sclerosis (SSc), non-alcoholic steatohepatitis (NASH), interferonopathies, interstitial lung disease (ILD), preferably progressive fibrosing interstitial lung disease (PF-ILD), in particular idiopathic pulmonary fibrosis (IPF).

27. Use of a compound of formula **(I)** or of formula **(I')** according to any of claims 1 to 19 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of, age-related macular degeneration (AMD), heart failure, COVID-19/SARS-CoV-2 infection, renal inflammation, renal fibrosis, dysmetabolism, vascular diseases, cardiovascular diseases and cancer.

28. Pharmaceutical composition comprising a compound of formula **(I)** or of formula **(I')** according to any of claims 1 to 19 and optionally one or more pharmaceutically acceptable carriers and/or excipients.

29. Pharmaceutical composition comprising a compound of formula **(I)** or of formula **(I')** according to any of claims 1 to 19 in combination with one or more active agents selected from the group consisting of anti-inflammatory agents, anti-fibrotic agents, anti-allergic agents/ anti-histamines, bronchodilators, beta 2 agonists /betamimetics, adrenergic agonists, anticholinergic agents, methotrexate, mycophenolate mofetil, leukotriene modulators, JAK inhibitors, anti-interleukin antibodies, non-specific immunotherapeutics

such as interferons or other cytokines/chemokines, cytokine/chemokine receptor modulators, toll-like receptor agonists, immune checkpoint regulators, an anti-TNF antibody such as Humira™, an anti-BAFF antibody such as Belimumab and Etanercept.

30. Pharmaceutical composition according to claim 29, wherein the compound of formula **(I)** or of formula **(I')** is combined with one or more anti-fibrotic agents selected from the group consisting of Pirfenidon and Nintedanib.

31. Pharmaceutical composition according to claim 29, wherein the compound of formula **(I)** or of formula **(I')** is combined with one or more anti-inflammatory agents selected from the group consisting of NSAIDs and corticosteroids.

32. Pharmaceutical composition according to claim 29, wherein the compound of formula **(I)** or of formula **(I')** is combined with one or more active agents selected from the group of bronchodilators, beta 2 agonists /betamimetics, adrenergic agonists and anticholinergic agents.

33. Pharmaceutical composition according to claim 29, wherein the compound of formula **(I)** or of formula **(I')** is combined with one or more anti-interleukin antibodies selected from the group consisting of anti-IL-23 such as Risankizumab, anti-IL-17 antibodies, anti-IL-1 antibodies, anti-IL-4 antibodies, anti-IL-13 antibodies, anti-lL-5 antibodies, anti-IL-6 antibodies such as Actemra™, anti-IL-12 antibodies and anti-IL-15 antibodies.