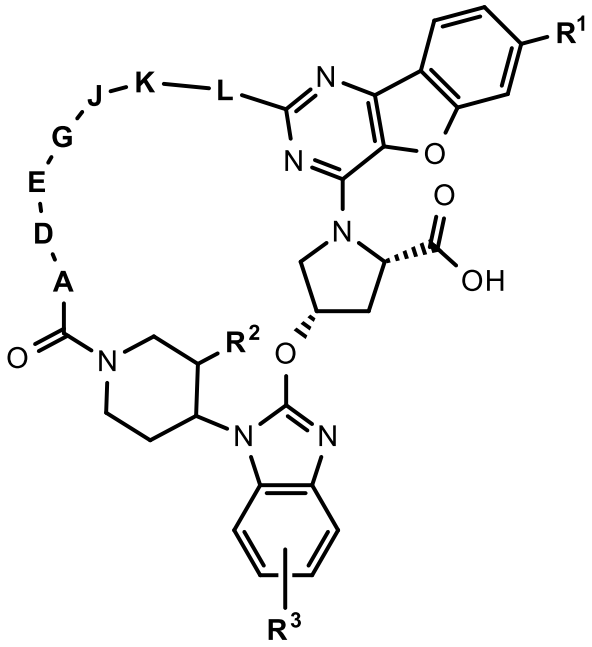
selectivity for cGAS inhibition have a high probability to also exhibit a good therapeutic effect in the patient. Due to their high cellular inhibitory potency compounds with this particular pharmacological profile should be able to pass the cell membrane barrier and therefore reach their intracellular 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.

1.3 Summary

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



I,

wherein

R^1 is selected from the group consisting of hydrogen, halogen, methyl, ethyl, -CF_3, -CHF_2, -CFH_2 and methoxy,

R^2 is selected from the group consisting of hydrogen and methyl,

R^3 is selected from the group consisting of hydrogen, methyl and halogen,

and wherein

A is selected from the group consisting of -CH_2-, -O-, -CF_2-, -CHF-, -N(CH_3)-,-NH- and -$CHCH_3$-;

D is selected from the group consisting of -CH_2-, -O-, -CF_2-, -CHF- and -$CHCH_3$-;

E is selected from the group consisting of -CH_2-, -O-, -$C(CH_3)_2$-, -CHF-, CF_2- and -$CHCH_3$-;

G is selected from the group consisting of -NH-, -NCH_3-, -CH_2-, -O-, -CF_2-, -CHF-, -$CHCH_3$- and -$C(CH_3)_2$;

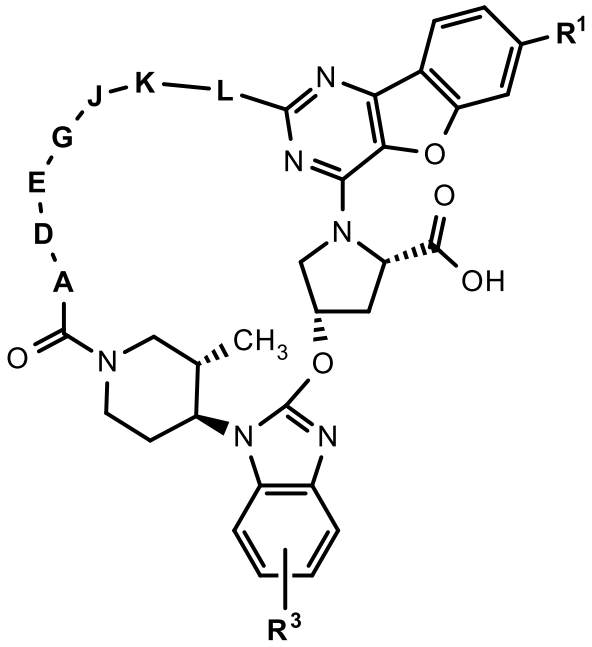
J is selected from the group consisting of -CO-, -CH_2-, -O-, -CHF-, -CF_2- and -$CHCH_3$-;

K is selected from the group consisting of -CH_2-, -CF_2-, -O- or is absent;

L is selected from the group consisting of -CH_2-, -O-, -$CHCH_3$-, -CHF-, -CF_2- or is absent;

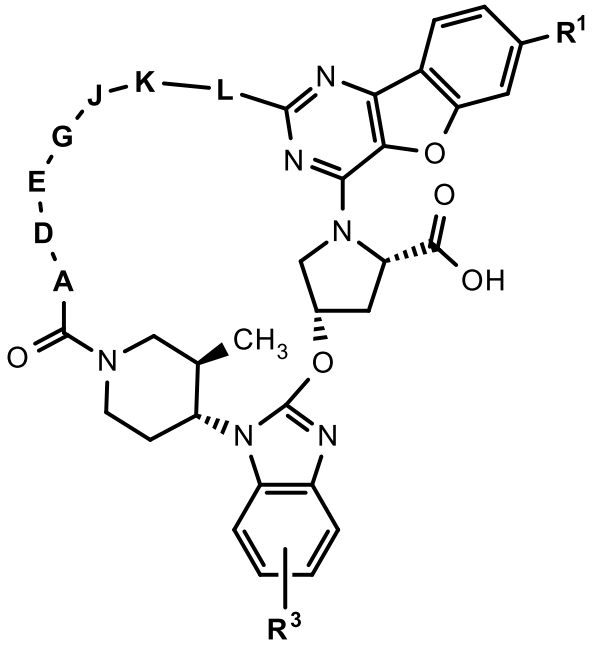
and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof .

In another aspect, the present disclosure provides the compound of formula **II**



II

or the compound of formula **III**

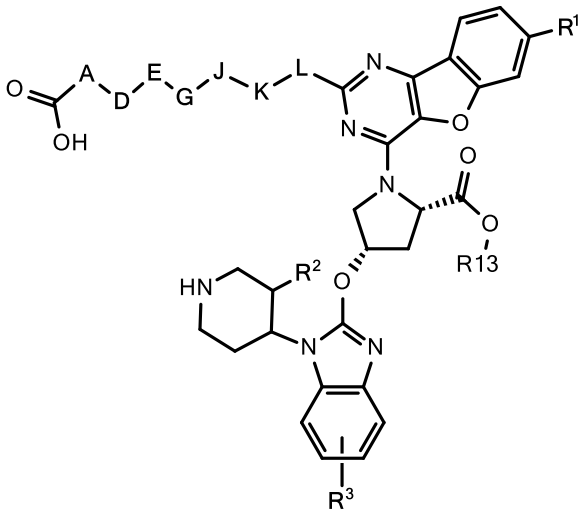


III

as described herein, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

In another aspect, the present disclosure provides an intermediate compound of

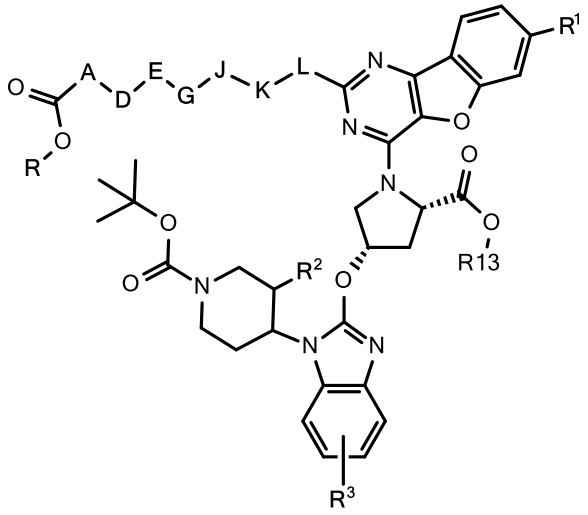
- formula (A-I)



(A-I),

wherein **R[1]**, **R[2]**, **R[3]**, **A**, **D**, **E**, **G**, **J**, **K** and **L** are defined as above-mentioned and wherein R13 is selected from the group consisting of hydrogen, methyl, ethyl and tert-butyl,

- of formula (A-II),

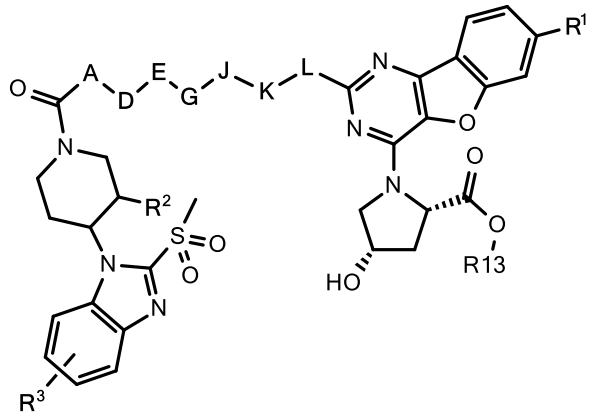


(A-II),

wherein **R[1]**, **R[2]**, **R[3]**, **A**, **D**, **E**, **G**, **J**, **K** and **L** are defined as above-mentioned and wherein R13 is selected from the group consisting of hydrogen, methyl, ethyl and tert-butyl,

and wherein **R** is either hydrogen or a protecting group selected from the group consisting of tert-butyl, methyl, ethyl and benzyl,

- of formula (B-I)

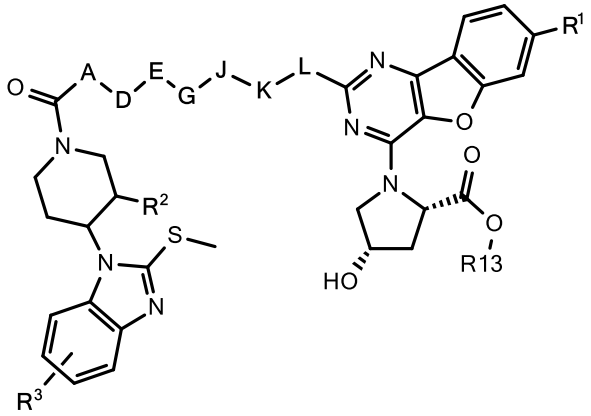


(B-I),

wherein **R[1]**, **R[2]**, **R[3]**, **A**, **D**, **E**, **G**, **J**, **K** and **L** are defined as above-mentioned and wherein R13 is selected from the group consisting of hydrogen, methyl, ethyl and tert-butyl,

or

- of formula (B-II)



(B-II),

wherein **R[1]**, **R[2]**, **R[3]**, **A**, **D**, **E**, **G**, **J**, **K** and **L** are defined as above-mentioned and wherein R13 is selected from the group consisting of hydrogen, methyl, ethyl and tert-butyl.

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

In another aspect, the present disclosure provides use of the compound of formula **I** as described herein or of the compound of formula **II** or **III** 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 (AGS), COPA syndrome, familial chilblain lupus, age-related macular degeneration (AMD), amyotrophic lateral sclerosis (ALS), retinopathy, glaucoma, diabetes, obesity, inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, dermatomyositis, Sjogren's syndrome, Parkinsons disease, heart failure, cancer, aging, muscle disorders, sepsis, rheumatoid arthritis, osteoarthritis, COVID-19, 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 the compound of formula **I** as described herein or of the compound of formula **II** or **III** 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 (AGS), COPA syndrome, familial chilblain lupus, dermatomyositis, age-related macular degeneration (AMD), amyotrophic lateral sclerosis (ALS), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, Sjogren's syndrome, rheumatoid arthritis and Parkinsons disease.

In another aspect, the present disclosure provides use of the compound of formula **I** as described herein or of the compound of formula **II** or **III** as described herein in the manufacture of a medicament for the treatment of a 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 the compound of formula **I** as described herein or of the compound of formula **II** or **III** 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), retinopathy, glaucoma, diabetis, obesity, aging, muscle disorders, sepsis, osteoarthritis, 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 the compound of formula **I** as described herein or the compound of formula **II** or **III** as described herein and optionally one or more pharmaceutically acceptable carriers and/or excipients.

In another aspect, the present disclosure provides pharmaceutical composition comprising the compound of formula **I** as described herein or the compound of formula **II** or **III** 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,

and optionally one or more pharmaceutically acceptable carriers and/or excipients.

In another aspect, the present disclosure provides pharmaceutical composition comprising the compound of formula **I** as described herein or the compound of formula **II** or **III** as described herein in combination with one or more anti-fibrotic agents selected from the group consisting of Pirfenidon and Nintedanib, and optionally one or more pharmaceutically acceptable carriers and/or excipients.

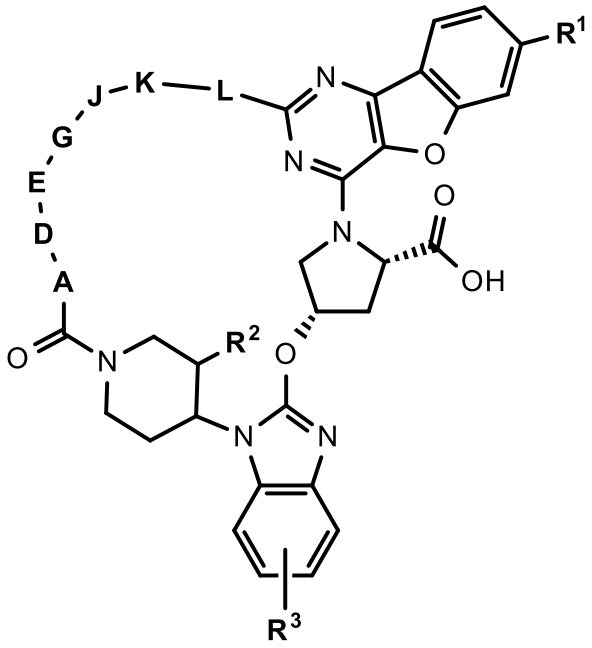
In another aspect, the present disclosure provides pharmaceutical composition comprising the compound of formula **I** as described herein or the compound of formula **II** or **III** as described herein in combination with one or more anti-inflammatory agents selected from the group consisting of NSAIDs and corticosteroids, and optionally one or more pharmaceutically acceptable carriers and/or excipients.

In another aspect, the present disclosure provides pharmaceutical composition comprising the compound of formula **I** as described herein or the compound of formula **II** or **III** as described herein in combination with one or more active agents selected from the group of bronchodilators, beta 2 agonists /betamimetics, adrenergic agonists and anticholinergic agents, and optionally one or more pharmaceutically acceptable carriers and/or excipients.

In another aspect, the present disclosure provides pharmaceutical composition comprising the compound of formula **I** as described herein or the compound of formula **II** or **III** as described herein and 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.

PATENT CLAIMS

1. A compound of formula **I**



I,

wherein

R^1 is selected from the group consisting of hydrogen, halogen, methyl, ethyl, $-CF_3$, $-CHF_2$, $-CFH_2$ and methoxy,

R^2 is selected from the group consisting of hydrogen and methyl,

R^3 is selected from the group consisting of hydrogen, methyl and halogen,

and wherein

A is selected from the group consisting of $-CH_2-$, -O-, $-CF_2-$, -CHF-, $-N(CH_3)-$,-NH- and $-CHCH_3-$;

D is selected from the group consisting of $-CH_2-$, -O-, $-CF_2-$, -CHF- and $-CHCH_3-$;

E is selected from the group consisting of $-CH_2-$, -O-, $-C(CH_3)_2-$, -CHF-, CF_2- and $-CHCH_3-$;

G is selected from the group consisting of -NH-, $-NCH_3-$, $-CH_2-$, -O-, $-CF_2-$, -CHF-, $-CHCH_3-$ and $-C(CH_3)_2$;

J is selected from the group consisting of -CO-, $-CH_2-$, -O-, -CHF-, $-CF_2-$ and $-CHCH_3-$;

K is selected from the group consisting of $-CH_2-$, $-CF_2-$, -O- or is absent;

L is selected from the group consisting of -CH_2-, -O-, -$CHCH_3$-, -CHF-, -CF_2- or is absent;

and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

2. The compound of formula **I** according to claim 1, wherein
   wherein
   $\mathbf{R^1}$ is selected from the group consisting of hydrogen, Cl and F,
   $\mathbf{R^2}$ is selected from the group consisting of hydrogen and methyl,
   $\mathbf{R^3}$ is selected from the group consisting of hydrogen, methyl, Cl and F,

   and wherein
   A is selected from the group consisting of -CH_2-, -O-, -CF_2- and -$N(CH_3)$-,
   D is selected from the group consisting of -CH_2-, -O- and -$CHCH_3$-,
   E is selected from the group consisting of -CH_2-, -O- and -$C(CH_3)_2$-,
   G is selected from the group consisting of -NH-, -CH_2-, -O-, -$CHCH_3$-,
   J is selected from the group consisting of -CO-, -CH_2-, -O-, and -$CHCH_3$-;
   K is selected from the group consisting of -CH_2-, -CF_2-, -O- or is absent;
   L is selected from the group consisting of -CH_2-, -CF_2- or is absent;
   and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

3. The compound of formula **I** according to at least one of claims 1 or 2, wherein **L** is absent, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

4. The compound of formula **I** according to at least one of claims 1 or 2, wherein **L** is absent and wherein **A** is selected from the group consisting of -CH_2- and -CF_2-,
   and prodrugs, pharmaceutical acceptable salts thereof or deuterated analogues thereof.

5. The compound of formula **I** according to claim 1 or 2, wherein **L** is absent and wherein **K** is CF_2, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

6. The compound of formula **I** according to at least one of claims 1 to 5, wherein $\mathbf{R^3}$ is halogen, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

7. The compound of formula **I** according to claim 6, wherein $\mathbf{R^3}$ is Cl or F, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

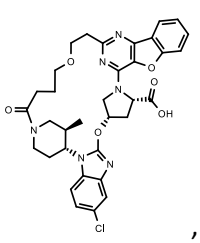
8. The compound of formula **I** according to claim 7, wherein $\mathbf{R^3}$ is Cl or F and is located in the 5-position of the benzimidazole moiety, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

9. The compound of formula **I** according to at least one of claims 1 to 8, wherein $\mathbf{R^1}$ is halogen and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

10. The compound of formula **I** according to claim 9, wherein $\mathbf{R^1}$ is Cl or F and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

11. The compound of formula **I** according to at least one of claims 1 to 8, wherein $\mathbf{R^1}$ is hydrogen, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

12. The compound of formula **I** according to at least one of claims 1 or 2 which is selected from the group consisting of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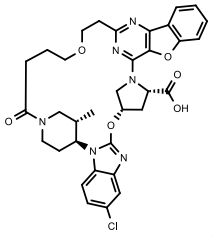
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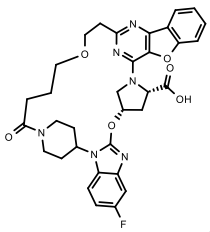
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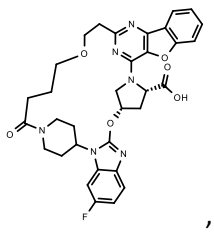
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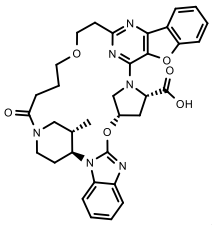
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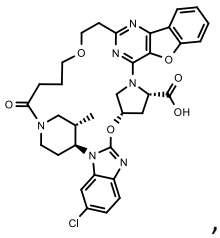
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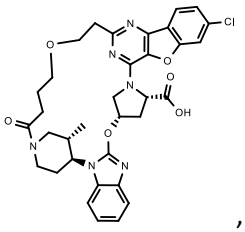
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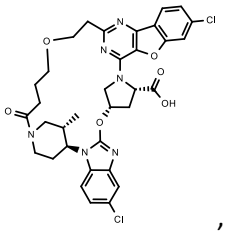
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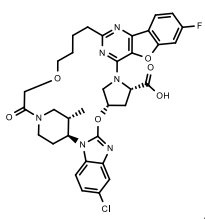
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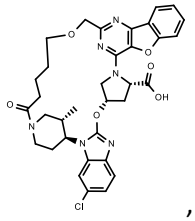
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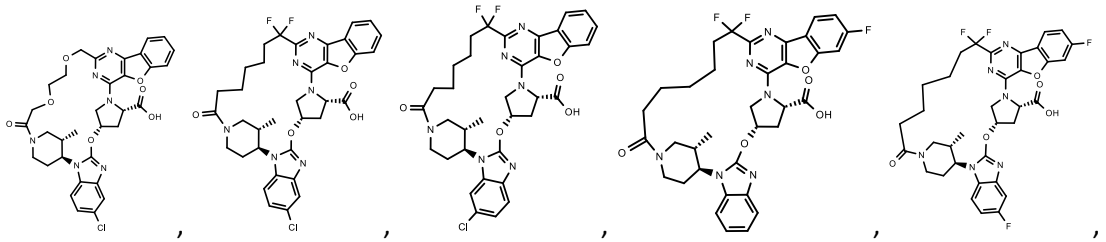
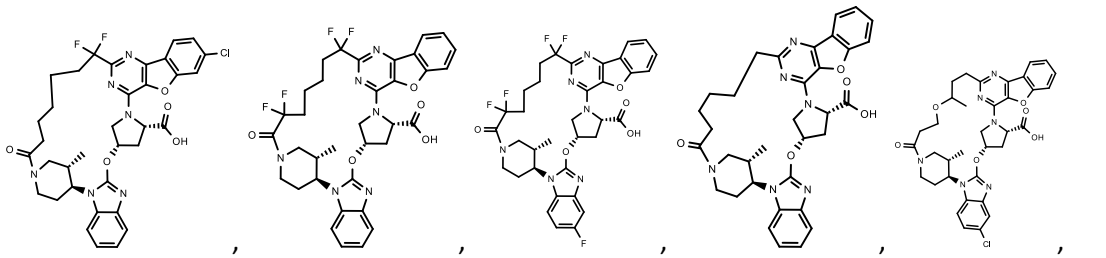
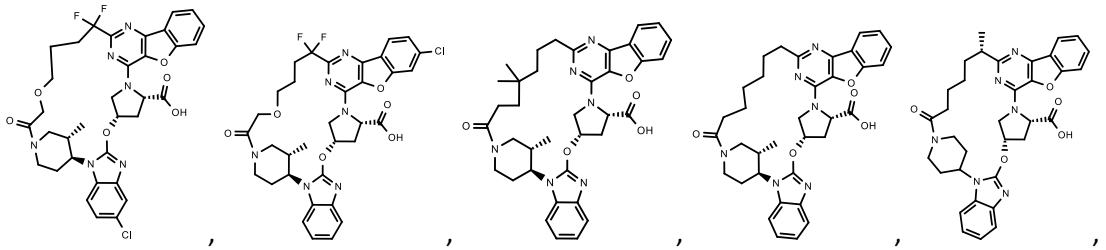
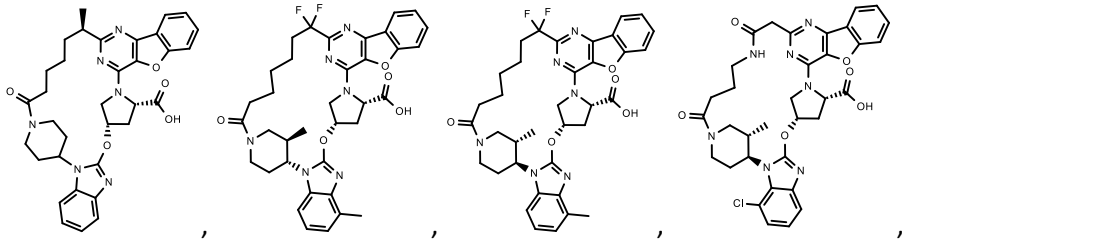
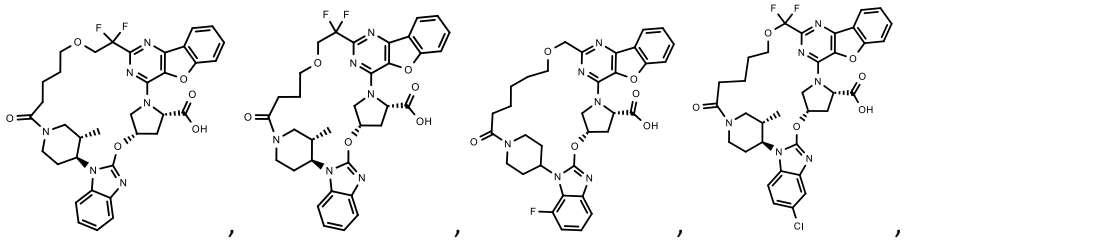
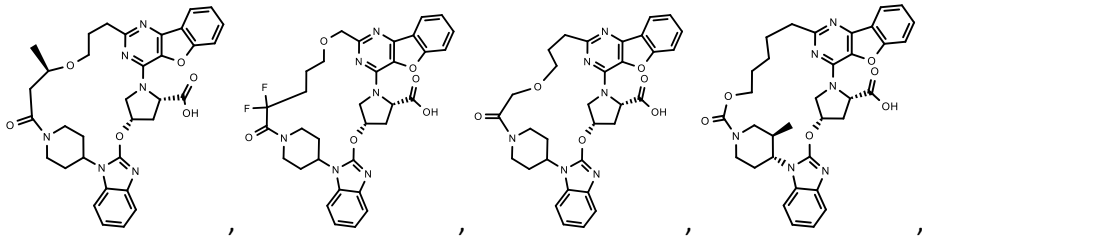


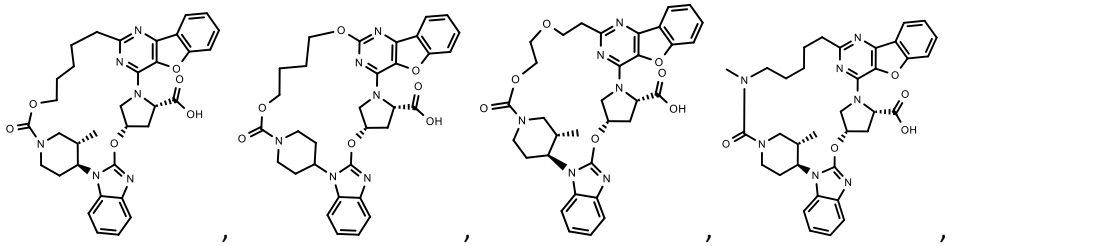












and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

13. The compound of formula **I** according to at least one of claims 1 or 2, wherein

    A is selected from the group consisting of -CH_2- and -CF_2-,

    D and **E** are each -CH_2-,

    G is selected from the group consisting of -CH_2- and -O-,

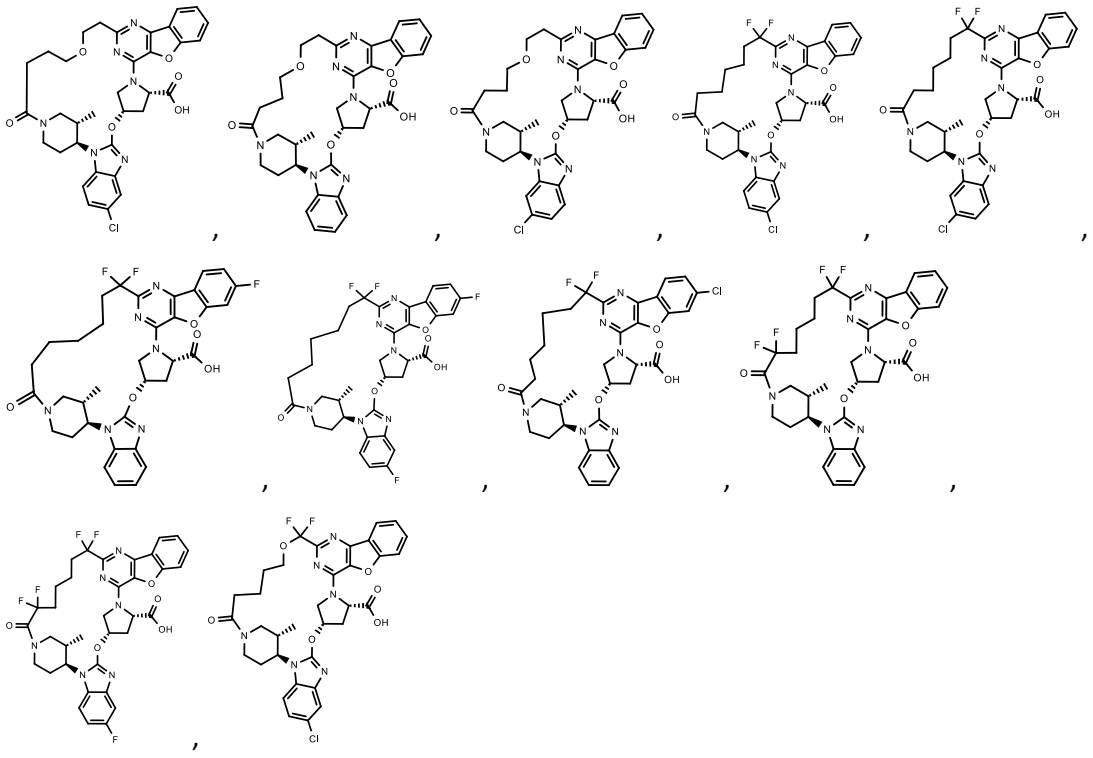
    J is selected from the group consisting of -CH_2-and -O-,

    K is selected from the group consisting of -CF_2- and -CH_2-,

    and **L** is absent,

    and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

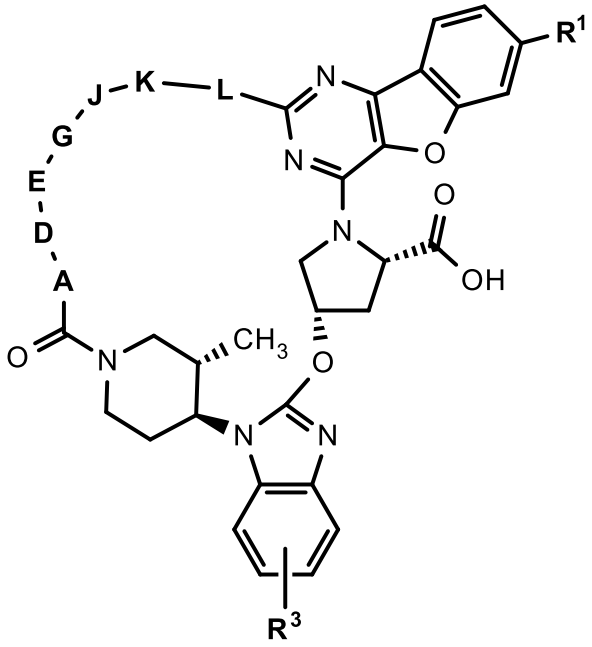
14. The compound of formula **I** according to claim 13, which is selected from the group consisting of



    and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

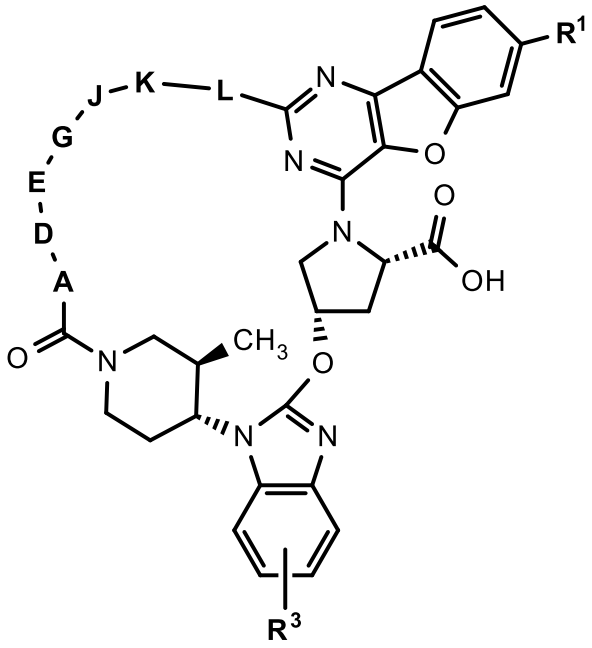
15. The compound of formula **I** according to claim 1, wherein $\mathbf{R_2}$ is methyl, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

16. The compound of formula **II**



II

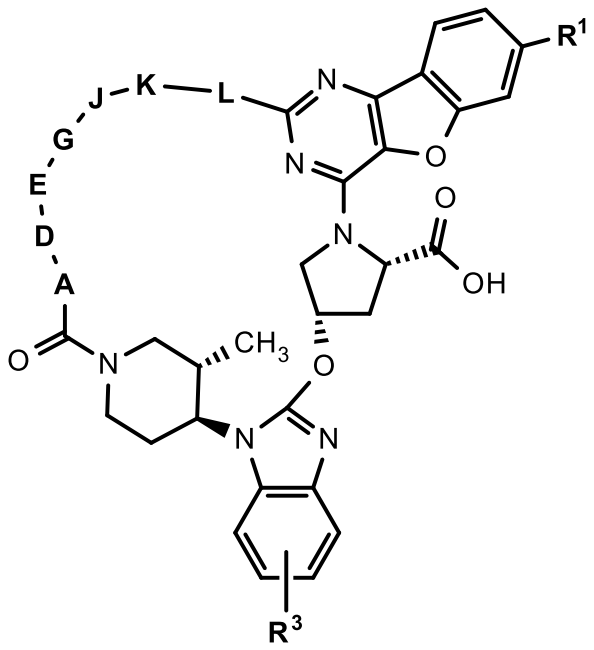
or the compound of formula **III**



III

according to claim 15, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

17. The compound of formula **II**



II

according to claim 16, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

18. The compound of formula **II** according to at least one of claims 16 or 17 or the compound of formula **III** according to claim 16, wherein **L** is absent, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

19. The compound of formula **II** according to at least one of claims 16 or 17 or the compound of formula **III** according to claim 16, wherein **L** is absent and wherein **K** is CF_2, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

20. The compound of formula **II** according to at least one of claims 16 or 17 or the compound of formula **III** according to claim 16, wherein $\mathbf{R^3}$ is halogen, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

21. The compound of formula **II** or of formula **III** according to claim 20, wherein $\mathbf{R^3}$ is Cl or F, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

22. The compound of formula **II** or of formula **III** according to claim 21, wherein $\mathbf{R^3}$ is Cl or F, and is located in the 5-position of the benzimidazole moiety, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

23. The compound of formula **II** according to at least one of claims 16 or 17 or the compound of formula **III** according to claim 16, wherein $\mathbf{R^3}$ is hydrogen, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

24. The compound of formula **II** according to at least one of claims 16 or 17 or the compound of formula **III** according to claim 16, wherein $\mathbf{R^1}$ is halogen, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

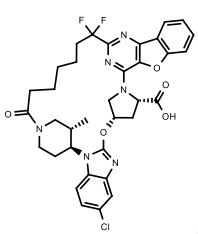
25. The compound of formula **II** or of formula **III** according to claim 24, wherein $\mathbf{R^1}$ is selected from the group consisting of Cl or F, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

26. The compound of formula **II** according to at least one of claims 16 or 17 or the compound of formula **III** according to claim 16, wherein $\mathbf{R^1}$ is hydrogen, and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

27. The compound of formula **II** according to at least one of claims 16 or 17 or the compound of formula **III** according to claim 16, wherein
A is selected from the group consisting of $-CH_2-$ and $-CF_2-$,
D and **E** are each $-CH_2-$,
G is selected from the group consisting of $-CH_2-$ and -O-,
J is selected from the group consisting of $-CH_2-$and -O-,
K is selected from the group consisting of $-CF_2-$ and $-CH_2-$,
and **L** is absent,

and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

28. The compound of formula **II** according to claim 27, which is selected from the group consisting of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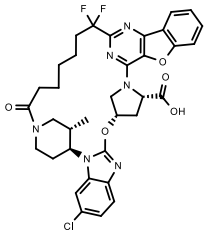
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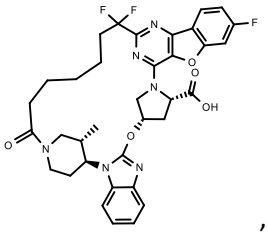
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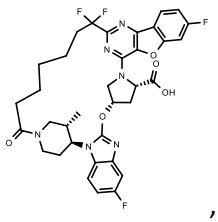
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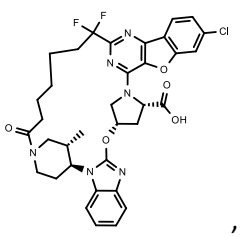
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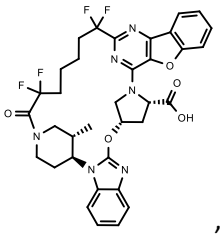
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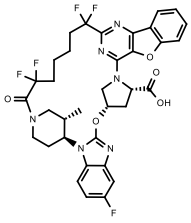
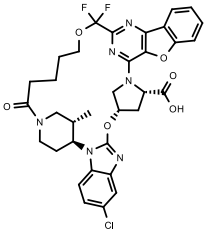
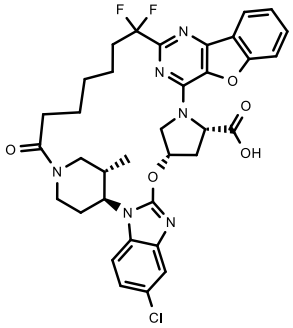



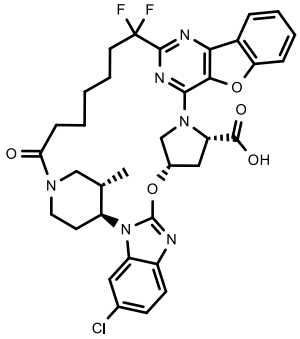
and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

29. The compound of formula **II** according to claim 28, which is



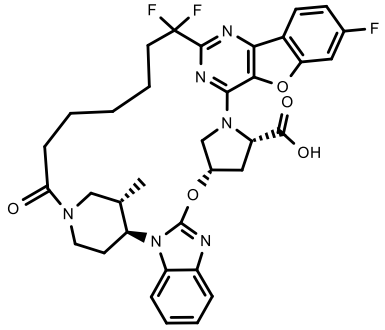
and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

30. The compound of formula **II** according to claim 28, which is



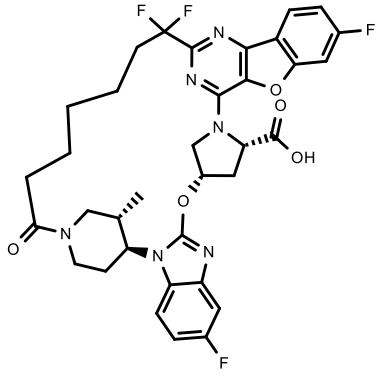
and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

31. The compound of formula **II** according to claim 28, which is



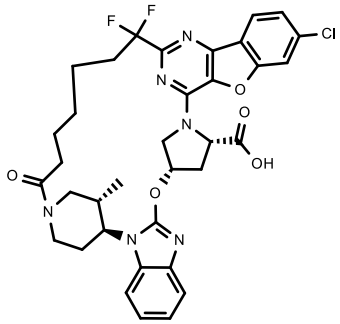
and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

32. The compound of formula **II** according to claim 28, which is



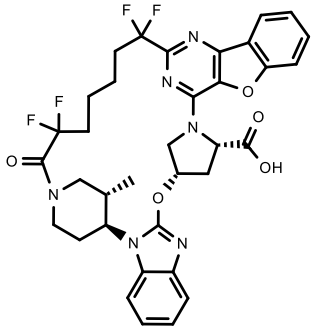
and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

33. The compound of formula **II** according to claim 28, which is



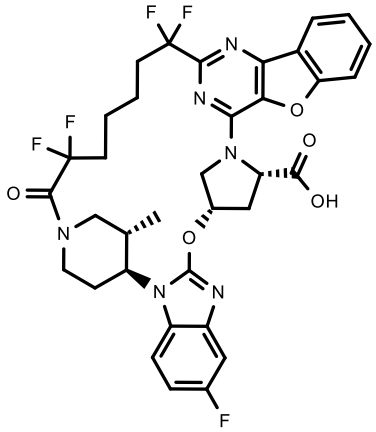
and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

34. The compound of formula **II** according to claim 28, which is



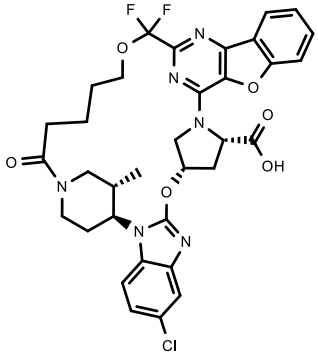
and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

35. The compound of formula **II** according to claim 28, which is



and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

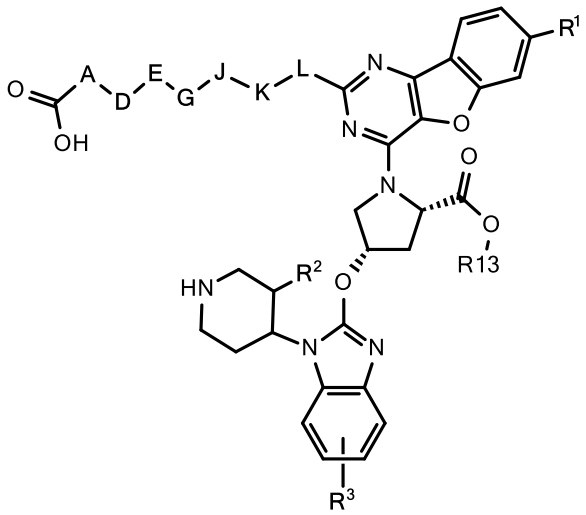
36. The compound of formula **II** according to claim 28, which is



and prodrugs, deuterated analogues and pharmaceutical acceptable salts thereof.

37. An intermediate compound of

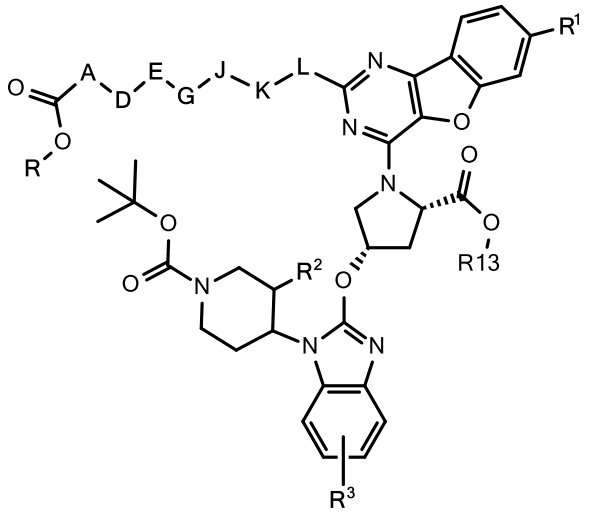
- formula (A-I)



(A-I),

wherein **R[1]**, **R[2]**, **R[3]**, **A**, **D**, **E**, **G**, **J**, **K** and **L** are defined as above-mentioned and wherein R13 is selected from the group consisting of hydrogen, methyl, ethyl and tert-butyl,

- of formula (A-II),

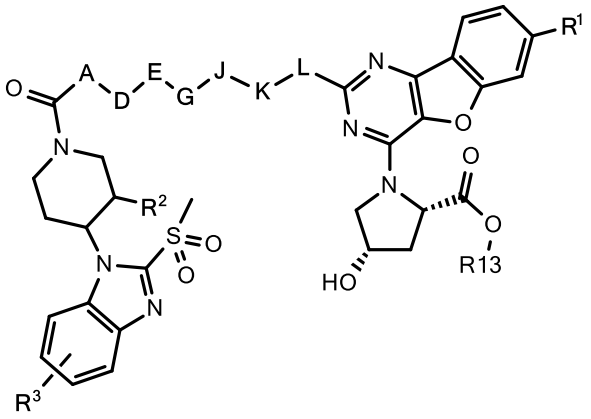


(A-II),

wherein **R[1]**, **R[2]**, **R[3]**, **A**, **D**, **E**, **G**, **J**, **K** and **L** are defined as above-mentioned and wherein R13 is selected from the group consisting of hydrogen, methyl, ethyl and tert-butyl,

and wherein **R** is either hydrogen or a protecting group selected from the group consisting of tert-butyl, methyl, ethyl and benzyl,

- of formula (B-I)

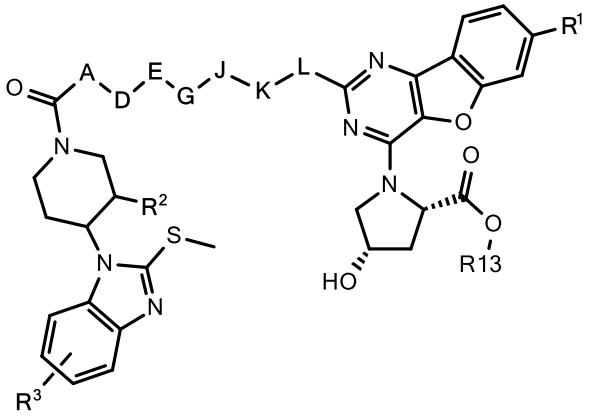


(B-I),

wherein **R[1]**, **R[2]**, **R[3]**, **A**, **D**, **E**, **G**, **J**, **K** and **L** are defined as above-mentioned and wherein R13 is selected from the group consisting of hydrogen, methyl, ethyl and tert-butyl,

or

- of formula (B-II)



(B-II),

wherein **R[1]**, **R[2]**, **R[3]**, **A**, **D**, **E**, **G**, **J**, **K** and **L** are defined as above-mentioned and wherein R13 is selected from the group consisting of hydrogen, methyl, ethyl and tert-butyl.

38. The compound of formula **I** according to one or more of claims 1 to 15 or the compound of formula **II** or **III** according to one or more of claims 16 to 36 for use in the treatment of a disease that can be treated by the inhibition of cGAS.

39. Use of the compound of formula **I** according to one or more of claims 1 to 15 or of the compound of formula **II** or **III** according to one or more of claims 16 to 36 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 (AGS),

COPA syndrome, familial chilblain lupus, age-related macular degeneration (AMD), amyotrophic lateral sclerosis (ALS), retinopathy, glaucoma, diabetes, obesity, inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, dermatomyositis, Sjogren's syndrome, Parkinsons disease, heart failure, cancer, aging, muscle disorders, sepsis, rheumatoid arthritis, osteoarthritis, COVID-19, 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).

40. Use of the compound of formula **I** according to one or more of claims 1 to 15 or of the compound of formula **II** or **III** according to one or more of claims 16 to 36 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 (AGS), COPA syndrome, familial chilblain lupus, dermatomyositis, age-related macular degeneration (AMD), amyotrophic lateral sclerosis (ALS), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, Sjogren's syndrome, rheumatoid arthritis and Parkinsons disease.
41. Use of the compound of formula **I** according to one or more of claims 1 to 15 or of the compound of formula **II** or **III** according to one or more of claims 16 to 36 in the manufacture of a medicament for the treatment of a 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).

42. Use of the compound of formula **I** according to one or more of claims 1 to 15 or of the compound of formula **II** or **III** according to one or more of claims 16 to 36 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of age-related macular degeneration (AMD), retinopathy, glaucoma, diabetis, obesity, aging, muscle disorders, sepsis, osteoarthritis, heart failure, COVID-19/SARS-CoV-2 infection, renal inflammation, renal fibrosis, dysmetabolism, vascular diseases, cardiovascular diseases and cancer.

43. Pharmaceutical composition comprising the compound of formula **I** according to one or more of claims 1 to 15 or the compound of formula **II** or **III** according to one or more of claims 16 to 36 and optionally one or more pharmaceutically acceptable carriers and/or excipients.

44. Pharmaceutical composition comprising the compound of formula **I** according to one or more of claims 1 to 15 or the compound of formula **II** or **III** according to one or more of claims 16 to 36 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,
and optionally one or more pharmaceutically acceptable carriers and/or excipients.

45. Pharmaceutical composition comprising the compound of formula **I** according to one or more of claims 1 to 15 or the compound of formula **II** or **III** according to one or more of claims 16 to 36 in combination with one or more anti-fibrotic agents selected from the group consisting of Pirfenidon and Nintedanib, and optionally one or more pharmaceutically acceptable carriers and/or excipients.
46. Pharmaceutical composition comprising the compound of formula **I** according to one or more of claims 1 to 15 or the compound of formula **II** or **III** according to one or more of claims 16 to 36 in combination with one or more anti-inflammatory agents selected from the group consisting of NSAIDs and corticosteroids, and optionally one or more pharmaceutically acceptable carriers and/or excipients.

47. Pharmaceutical composition comprising the compound of formula **I** according to one or more of claims 1 to 15 or the compound of formula **II** or **III** according to one or more of claims 16 to 36 in combination with one or more active agents selected from the group of bronchodilators, beta 2 agonists /betamimetics, adrenergic agonists and anticholinergic agents, and optionally one or more pharmaceutically acceptable carriers and/or excipients.

48. Pharmaceutical combination comprising the compound of formula **I** according to one or more of claims 1 to 15 or the compound of formula **II** or **III** according to one or more of claims 16 to 36 and 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.