

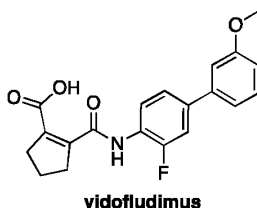
Heteroaromatic DHODH inhibitors

SUMMARY OF THE INVENTION

The present relates to novel dihydroorotate dehydrogenase (DHODH) inhibitors having a carboxylic acid, carboxamide or a bioisosteric moiety and being optionally deuterated, pharmaceutical formulations comprising them, a process for their preparation and their use as medicament, alone or in combination with one or more additional agents, for treating of various diseases, wherein the inhibition of DHODH is desirable (e.g. SARS-CoV-2 or IDH-mutated cancers).

BACKGROUND OF THE INVENTION

Vidofludimus calcium (IMU-838) is a selective and potent second-generation dihydroorotate dehydrogenase (DHODH) oral immunomodulator being developed for the treatment of several chronic inflammatory diseases, including relapsing-remitting Multiple Sclerosis (rrMS):



The mechanism of action of vidofludimus calcium, a small molecule selective immune modulator, is the inhibition of the intracellular metabolism of activated immune T- and B-cells by blocking the enzyme DHODH. The inhibition of the DHODH enzyme leads to metabolic stress in metabolically activated lymphocytes resulting in reduction in proinflammatory cytokines and subsequently to apoptosis of activated immune cells. Blocking of the DHODH enzyme activity has a selective effect to metabolically activated immune cells, to malignant cells and to virus-infected cells. Thus, DHODH inhibition should therefore not lead to general antiproliferative effects in other cells. IMU-838 as a second-generation DHODH inhibitor is being developed to separate the desired immunomodulatory effects from an undesirable side effect profile caused by off-target effects like neutropenia, alopecia and diarrhea. An additional benefit of DHODH inhibitors such as IMU-838 is their direct antiviral effect. During long-term treatment with immunosuppressive drugs, the reactivation of latent viruses has been observed. This can lead to serious infections, such as progressive multifocal leukoencephalopathy which can have a lethal outcome.

PP-001 is another DHODH inhibitor within the same structural class for the treatment of retinal diseases like uveitis, diabetic macular edema and retinal vein occlusion currently in clinical trials. In animal models the high effectiveness to treat dry eye disease and viral conjunctivitis has already been demonstrated.

So far, compounds from this structural class (e.g. IMU-838 or PP-001) contain a carboxylic acid functional group as an important constituent of the pharmacophore. However, the presence of this moiety can represent a liability. For instance, a diminished ability to passively diffuse across biological membranes can raise a significant challenge, particularly in the context of central nervous system drug discovery, where the blood-brain barrier can be relatively impermeable to negatively charged carboxylates. Furthermore, idiosyncratic drug toxicities arising from the metabolism of the carboxylic acid moiety (e.g. glucuronidation) have been linked to withdrawals of marketed drugs. The urate transporter 1 (URAT-1) is a urate transporter and urate-anion exchanger which regulates the level of urate in the blood. It is known that drugs containing a carboxylic acid (e.g. probenecid, salicylic acid or fenofibric acid) are recognized by and interact with URAT-1 affecting urinary uric acid excretion. Also, at high vidofludimus doses a decrease in blood uric acid levels and an increase in urine red blood cell count were observed, in very rare cases, presenting as symptomatic hematuria during the first 7 days of treatment (WO2019/101888). This effect is caused due to interaction of vidofludimus with URAT-1 (Drugs R&D 2019;19:351).

Therefore, there is still a need to develop novel DHODH inhibitors. In particular, there is a need to develop DHODH inhibitors with improved pharmacokinetic and pharmacodynamic properties. It is generally believed that a differentiated pharmacokinetic profile could enable potentially improved efficacy, less frequent dosing, improved tolerability, better brain penetration, reduced interpatient variability in drug metabolism and reduced drug-drug interactions.

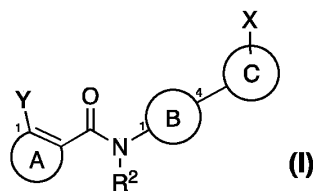
PRIOR ART

Compounds of Formula (I) mainly containing a carboxylic acid as residue Y are described in WO2004/056746, WO2004/056747, WO2004/056797, WO2010/052027, WO2010/128050, WO2012/001148, WO2012/001151, WO2015/169944, WO2015/154820, WO2018/177151, WO2019/170848, WO2019/101888, WO2019/175396, WO2022/214691 as well as in *Bioorg. Med. Chem. Lett.* 2004;14:55, *Bioorg. Med. Chem. Lett.* 2005;15:4854, *Bioorg. Med. Chem. Lett.* 2006;16:267, *J. Med. Chem.* 2006;49:1239 and *J. Med. Chem.* 2023;66:6391, however no examples were presented, wherein the A-ring is a 5-membered heteroaryl containing 2 to 3 heteroatoms selected from N, S and O.

In WO2023/118576, optionally deuterated derivatives having a carboxylic acid bioisoster as residue Y have been described. The only 5-membered heteroaryl containing 2 to 3 heteroatoms selected from N, S and O as A-ring are thiazole derivatives. As outlined in the experimental section, we surprisingly found that derivatives with 2 to 3 heteroatoms in the A-ring still exhibit high DHODH inhibitory activity with beneficial properties (e.g. reduced lipophilicity, improved microsomal stability/clearance, bioavailability and/or brain penetration).

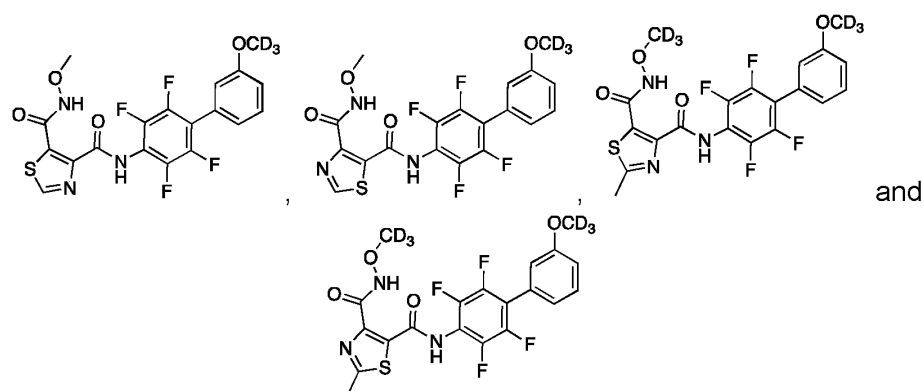
SUMMARY OF THE INVENTION

The present invention relates to compounds according to Formula (I)



5 or an enantiomer, diastereomer, tautomer, solvate, or pharmaceutically acceptable salt thereof, wherein

cycle A, B, C and residues X, Y and R^2 are defined as in claim 1, with the proviso, that the following structures are excluded:



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The compounds of the present invention have a similar or better DHODH inhibitory activity compared to known DHODH inhibitors. Furthermore, the compounds of the present invention exhibit additional beneficial properties like reduced lipophilicity or improved bioavailability. Additional improved microsomal stability and/or improved bioavailability can be obtained when used as medicament due to the replacement of hydrogen to deuterium at certain positions.

Thus, the present invention further relates to a pharmaceutical composition comprising a compound according to Formula (I) and at least one pharmaceutically acceptable carrier or excipient.

20

The present invention is further directed to compounds according to Formula (I) for use in the prophylaxis and/or treatment of diseases mediated by DHODH.

Accordingly, the present invention relates to the prophylaxis and/or treatment of the disease, disorder, therapeutic indication or medical condition which is selected from the group comprising rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by

5 malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and Pneumocystis carinii, fibrosis, uveitis, rhinitis, asthma, transplantation or arthropathy. Specifically, the disease, disorder or therapeutic indication is selected from the group comprising graft versus
10 host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, respiratory syncytial virus, influenza, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis. More specifically, the disease, disorder or therapeutic indication caused by malignant cell proliferation due to isocitrate dehydrogenase (NADP⁺) 1 (IDH1) mutation(s).

15 The present invention is further directed to a pharmaceutical composition comprising a compound according to Formula (I) and one or more additional therapeutic agents selected from anti-inflammatory agents, anti-viral agents, anti-cancer-agents, immunosuppressive and/or immunomodulatory agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics and suitable mixtures thereof.

DETAILED DESCRIPTION OF THE INVENTION

Compound 2-((3-fluoro-3'-methoxy-[1,1'-biphenyl]-4-yl)carbamoyl)cyclopent-1-ene-1-carboxylic acid, also known as vidofludimus is an orally administered DHODH inhibitor. The calcium salt of vidofludimus is known as IMU-838. IMU-838 is currently in a Phase 3 clinical trial for the treatment
20 of MS and also in clinical trials for ulcerative colitis and primary sclerosing cholangitis.

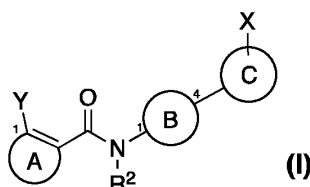
Compound 3-((2,3,5,6-tetrafluoro-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)carbamoyl)thiophene-2-carboxylic acid, also known as PP-001 is a topically administered DHODH inhibitor. PP-001 is currently in clinical trials for the treatment of keratoconjunctivitis and non-infectious uveitis.

Vidofludimus, IMU-838 and PP-001 has generally been well-tolerated in several clinical trials.
25 Despite the potential beneficial activities of vidofludimus, IMU-838 and PP-001, there is a continuing need for new compounds to treat the aforementioned diseases and conditions that have improved off-target and drug metabolism and pharmacokinetic (DMPK) properties. Improved off-target and DMPK properties have the potential to result in positive changes in safety profile, efficacy and tolerability of compounds.

30 Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulae. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. Rather, the invention is intended to cover all alternatives, modifications and equivalents that may be included within the scope of the present
35 invention as defined by the claims. The present invention is not limited to the methods and materials described herein but include any methods and materials similar or equivalent to those

described herein that could be used in the practice of the present invention. In the event that one or more of the incorporated literature references, patents or similar materials differ from or contradict this application, including but not limited to defined terms, term usage, described techniques or the like, this application controls.

5 In one aspect the invention relates to a compound of Formula (I):



or an enantiomer, diastereomer, tautomer, solvate, or pharmaceutically acceptable salt thereof, wherein

10 A is selected from a 5-membered heteroaryl containing 2 to 3 heteroatoms selected from N, S and O, having one or more hydrogen atoms optionally replaced by deuterium,

said A is unsubstituted or substituted with one substituent independently selected from the group consisting of H, halogen, -CN, -NO₂, SF₅, oxo, -OH, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, fluoro-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, -O-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, -O-(3- to 8-membered heterocycloalkyl), CO₂R¹¹, NR¹¹R¹²,
15 CONR¹¹R¹² phenyl, 5- or 6-membered heteroaryl

wherein alkyl, cycloalkyl, heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of D, halogen, -CN, OH, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl and -O-fluoro-C₁₋₄-alkyl,

20 ring A or its substituents having one or more hydrogen atoms optionally replaced by deuterium;
B is selected from the group consisting of phenyl and pyridyl,

wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl;

25 and wherein optionally two adjacent substituents in the phenyl and pyridyl moiety form a 5- to 8-membered partially unsaturated cycle optionally containing 1 to 3 heteroatoms independently selected from O, S or N,

wherein this additional cycle is optionally substituted with 1 to 4 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl;

30 and wherein the residue -NR² on ring B is in a 1,4-orientation with respect to ring C,

ring B or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

C is selected from the group consisting of phenyl and pyridyl,

wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl;

5 and wherein optionally two adjacent substituents in the phenyl and pyridyl moiety form a 5- to 8-membered partially unsaturated cycle optionally containing 1 to 3 heteroatoms independently selected from O, S or N,

wherein this additional cycle is optionally substituted with 1 to 4 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl;

10 ring C or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

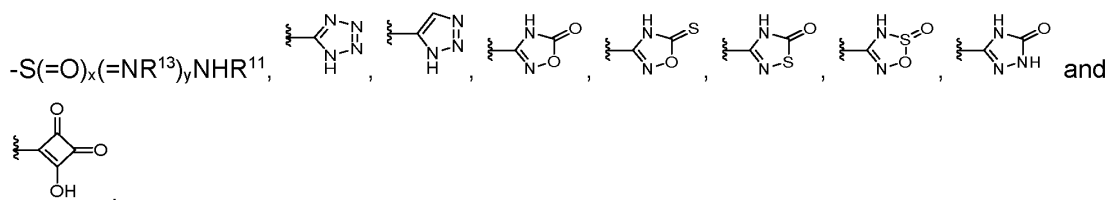
X is selected from H, D, halogen, -CN, -NO₂, C₁₋₆-alkyl, -O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₀₋₆-alkylene-OR²¹, C₀₋₆-alkylene-(3- to 6-membered cycloalkyl), C₀₋₆-alkylene-(3- to 8-membered heterocycloalkyl), C₀₋₆-alkylene-S(=O)_n(=NR²³)_mR²¹, C₀₋₆-alkylene-NR²¹S(=O)_x(=NR²³)_yR²¹, C₀₋₆-alkylene-S(=O)_x(=NR²³)_yNR²¹R²², C₀₋₆-alkylene-NR²¹S(=O)_x(=NR²³)_yNR²¹R²², C₀₋₆-alkylene-CO₂R²¹, C₀₋₆-alkylene-O-COR²¹, C₀₋₆-alkylene-CONR²¹R²², C₀₋₆-alkylene-NR²¹-COR²¹, C₀₋₆-alkylene-NR²¹-CONR²¹R²², C₀₋₆-alkylene-O-CONR²¹R²², C₀₋₆-alkylene-NR²¹-CO₂R²¹, C₀₋₆-alkylene-NR²¹R²², wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S.

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl.

X or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

Y is selected from $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^{10}$, $-\text{CONR}^{11}\text{R}^{12}$, $-\text{CONH-CN}$, $-\text{CONHOR}^{10}$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{H}$, $-\text{B(OH)}_2$,

25 $-\text{CONHS}(=\text{O})_x(=\text{NR}^{13})_y\text{R}^{10}$, $-\text{CONHS}(=\text{O})_x(=\text{NR}^{13})_y\text{NR}^{11}\text{R}^{12}$, $-\text{S}(=\text{O})_x(=\text{NR}^{13})_y\text{NHCOR}^{10}$,



Y having one or more hydrogen atoms optionally replaced by deuterium;

R² is selected from H and C₁₋₆-alkyl,

30 R² having one or more hydrogen atoms optionally replaced by deuterium;

R¹⁰ is selected from C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

R¹¹, R¹², R²¹, R²² are independently selected from H, C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

R¹¹ and/or R¹² and/or R²¹ and/or R²² having one or more hydrogen atoms optionally replaced by deuterium;

or R¹¹ and R¹², R²¹ and R²², respectively, when taken together with the nitrogen to which they are attached complete a 3- to 6-membered cycle containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N; and

wherein this cycle is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

R¹¹ and/or R¹² and/or R²¹ and/or R²² having one or more hydrogen atoms optionally replaced by deuterium;

R¹³, R²³ are independently selected from H, -CN, -NO₂, C₁₋₆-alkyl, -CO-O-C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

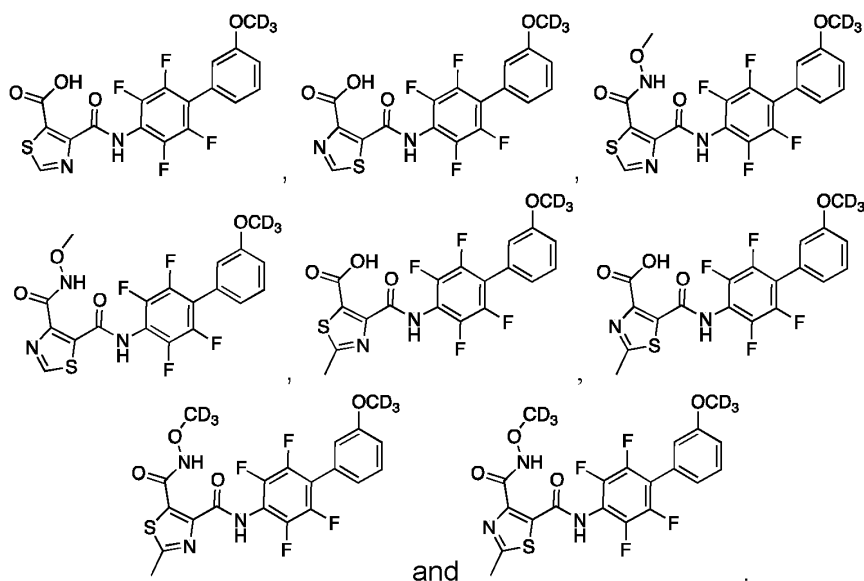
R¹³ and/or R²³ having one or more hydrogen atoms optionally replaced by deuterium;

x, y are independently selected from 0 to 2;

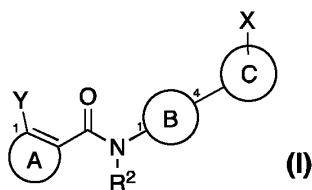
with the proviso that the sum of integer m and n for the residue linked to the same sulfur atom is independently selected from 0 to 2;

with the proviso that the sum of integer x and y for the residue linked to the same sulfur atom is independently selected from 1 or 2;

and with the proviso, that the following structures are excluded:



In one embodiment the invention relates to the compound of Formula (I):



or an enantiomer, diastereomer, tautomer, solvate, or pharmaceutically acceptable salt thereof, wherein

A is selected from a 5-membered heteroaryl containing 2 to 3 heteroatoms selected from N, S and O, having one or more hydrogen atoms optionally replaced by deuterium,

said A is unsubstituted or substituted with one substituent independently selected from the group consisting of H, halogen, -CN, -NO₂, SF₅, oxo, -OH, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, fluoro-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, -O-(3- to 6-membered cycloalkyl), 3- to 8-

membered heterocycloalkyl, -O-(3- to 8-membered heterocycloalkyl), CO₂R¹¹, NR¹¹R¹², CONR¹¹R¹² phenyl, 5- or 6-membered heteroaryl

5 wherein alkyl, cycloalkyl, heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of D, halogen, -CN, OH, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl and -O-fluoro-C₁₋₄-alkyl,

ring A or its substituents having one or more hydrogen atoms optionally replaced by deuterium; B is selected from the group consisting of phenyl and pyridyl,

10 wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl;

and wherein optionally two adjacent substituents in the phenyl and pyridyl moiety form a 5- to 8-membered partially unsaturated cycle optionally containing 1 to 3 heteroatoms independently selected from O, S or N,

15 wherein this additional cycle is optionally substituted with 1 to 4 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl;

and wherein the residue -NR² on ring B is in a 1,4-orientation with respect to ring C,

ring B or its substituents having one or more hydrogen atoms optionally replaced by deuterium; C is selected from the group consisting of phenyl and pyridyl,

20 wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl;

25 and wherein optionally two adjacent substituents in the phenyl and pyridyl moiety form a 5- to 8-membered partially unsaturated cycle optionally containing 1 to 3 heteroatoms independently selected from O, S or N,

wherein this additional cycle is optionally substituted with 1 to 4 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl;

ring C or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

30 X is selected from H, D, halogen, -CN, -NO₂, C₁₋₆-alkyl, -O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₀₋₆-alkylene-OR²¹, C₀₋₆-alkylene-(3- to 6-membered cycloalkyl), C₀₋₆-alkylene-(3- to 8-membered heterocycloalkyl), C₀₋₆-alkylene-S(=O)_n(=NR²³)_mR²¹, C₀₋₆-alkylene-NR²¹S(=O)_x(=NR²³)_yR²¹, C₀₋₆-alkylene-S(=O)_x(=NR²³)_yNR²¹R²², C₀₋₆-alkylene-NR²¹S(=O)_x(=NR²³)_yNR²¹R²², C₀₋₆-alkylene-CO₂R²¹, C₀₋₆-alkylene-O-COR²¹, C₀₋₆-alkylene-CONR²¹R²², C₀₋₆-alkylene-NR²¹-COR²¹, C₀₋₆-alkylene-NR²¹-CONR²¹R²², C₀₋₆-alkylene-O-CONR²¹R²², C₀₋₆-alkylene-NR²¹-CO₂R²¹, C₀₋₆-

alkylene-NR²¹R²², wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

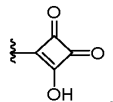
wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

X or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

Y is selected from -CONR¹¹R¹², -CONH-CN, -CONHOR¹⁰, -SO₃H, -SO₂H, -B(OH)₂,

-CONHS(=O)_x(=NR¹³)_yR¹⁰, -CONHS(=O)_x(=NR¹³)_yNR¹¹R¹², -S(=O)_x(=NR¹³)_yNHCOR¹⁰,

-S(=O)_x(=NR¹³)_yNHR¹¹, , , , , , , ,  and



Y having one or more hydrogen atoms optionally replaced by deuterium;

R² is selected from H and C₁₋₆-alkyl,

R² having one or more hydrogen atoms optionally replaced by deuterium;

R¹⁰ is selected from C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

R¹¹, R¹², R²¹, R²² are independently selected from H, C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

R¹¹ and/or R¹² and/or R²¹ and/or R²² having one or more hydrogen atoms optionally replaced by deuterium;

or R¹¹ and R¹², R²¹ and R²², respectively, when taken together with the nitrogen to which they are attached complete a 3- to 6-membered cycle containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N; and

5 wherein this cycle is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

R¹¹ and/or R¹² and/or R²¹ and/or R²² having one or more hydrogen atoms optionally replaced by deuterium;

10 R¹³, R²³ are independently selected from H, -CN, -NO₂, C₁₋₆-alkyl, -CO-O-C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

15 wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

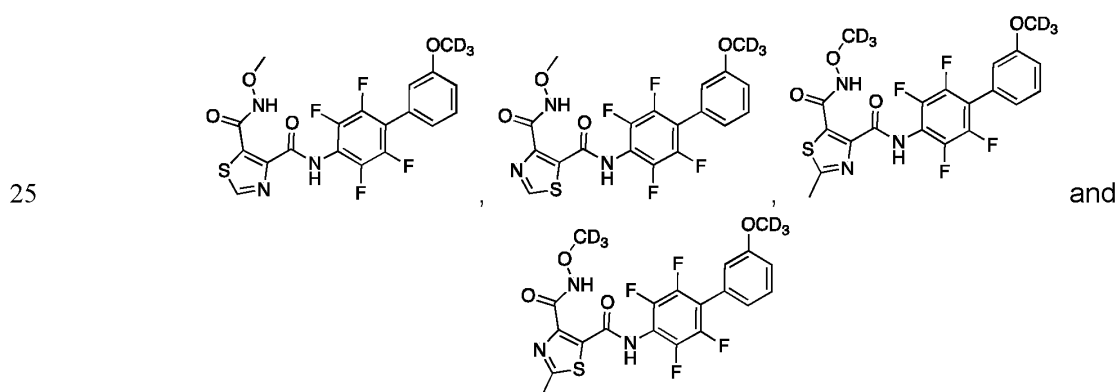
R¹³ and/or R²³ having one or more hydrogen atoms optionally replaced by deuterium;

x, y are independently selected from 0 to 2;

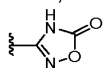
20 with the proviso that the sum of integer m and n for the residue linked to the same sulfur atom is independently selected from 0 to 2;

with the proviso that the sum of integer x and y for the residue linked to the same sulfur atom is independently selected from 1 or 2;

and with the proviso, that the following structures are excluded:



In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

Y is selected from $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^{10}$, $-\text{CONR}^{11}\text{R}^{12}$, $-\text{CONH-CN}$, $-\text{CONHOR}^{10}$,
 $-\text{CONHS(=O)}_x(\text{=NR}^{13})_y\text{R}^{10}$, $-\text{CONHS(=O)}_y(\text{=NR}^{13})_y\text{NR}^{11}\text{R}^{12}$,  or , preferably
 5 selected from $-\text{CONR}^{11}\text{R}^{12}$, $-\text{CONH-CN}$, $-\text{CONHOR}^{10}$, $-\text{CONHS(=O)}_x(\text{=NR}^{13})_y\text{R}^{10}$,

$-\text{CONHS(=O)}_y(\text{=NR}^{13})_y\text{NR}^{11}\text{R}^{12}$,  or  ;

R^{10} is selected from C_{1-4} -alkyl, cyclopropyl or oxetan-3-yl,

wherein alkyl, cyclopropyl or oxetan-3-yl is unsubstituted or substituted with 1 to 3
 substituents independently selected from F, -CN, Me, CHF_2 , CF_3 , -OH, oxo, -OMe, -OCHF₂
 10 and -OCF₃, R^{10} having one or more hydrogen atoms optionally replaced by deuterium;

R^{11} and R^{12} are independently selected from H or C_{1-3} -alkyl,

wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected
 from F, -CN, Me, CHF_2 , CF_3 , -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R^{11} and/or R^{12} having
 one or more hydrogen atoms optionally replaced by deuterium;

15 R^{13} is selected from H, -CN and C_{1-3} -alkyl,

wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected
 from F, -CN, Me, CHF_2 , CF_3 , -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R^{13} having one or more
 hydrogen atoms optionally replaced by deuterium;

x is 1 and y is 1 or x is 2 and y is 0.

20

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

Y is selected from $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}^{10}$ or $-\text{CONR}^{11}\text{R}^{12}$;

R^{10} is selected from C_{1-4} -alkyl, cyclopropyl or oxetan-3-yl,

25 wherein alkyl, cyclopropyl or oxetan-3-yl is unsubstituted or substituted with 1 to 3
 substituents independently selected from F, -CN, Me, CHF_2 , CF_3 , -OH, oxo, -OMe, -OCHF₂
 and -OCF₃, R^{10} having one or more hydrogen atoms optionally replaced by deuterium;

R^{11} and R^{12} are independently selected from H or C_{1-3} -alkyl,

wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected
 30 from F, -CN, Me, CHF_2 , CF_3 , -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R^{11} and/or R^{12} having
 one or more hydrogen atoms optionally replaced by deuterium;

In an even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein Y is selected from -CONHOR¹⁰, wherein R¹⁰ is selected from C₁₋₄-alkyl, cyclopropyl or oxetan-3-yl,

5 wherein alkyl, cyclopropyl or oxetan-3-yl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

In an even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein Y is selected from -CONHOCH₃, -CONHOCD₃, -CONHOCH₂CH₂OH and -CONHOCD₂CD₂OH.

10 In an even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein Y is selected from -CONHOCH₃ and -CONHOCD₃.

In an even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

15 Y is selected from -CO₂H, -CO₂Me, -CO₂Et, -CONH₂, -CONHMe, -CONHEt and -CONMe₂, preferably selected from -CONH₂, -CONHMe, -CONHEt and -CONMe₂.

In a most particular embodiment the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein Y is -CO₂H.

In a similar more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

20 Y is selected from -CONH-CN, -CONHOR¹⁰, -CONHS(=O)_x(=NR¹³)_yR¹⁰,



R¹⁰ is selected from C₁₋₄-alkyl, cyclopropyl or oxetan-3-yl,

25 wherein alkyl, cyclopropyl or oxetan-3-yl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

R¹¹ and R¹² are independently selected from H or C₁₋₃-alkyl,

30 wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium;

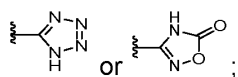
R¹³ is selected from H, -CN and C₁₋₃-alkyl,

wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹³ having one or more hydrogen atoms optionally replaced by deuterium;

x is 1 and y is 1 or x is 2 and y is 0.

- 5 In a similar even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

Y is selected from -CONH-CN, -CONHOR¹⁰, -CONHS(=O)₂R¹⁰, -CONHS(=O)₂NR¹¹R¹²,



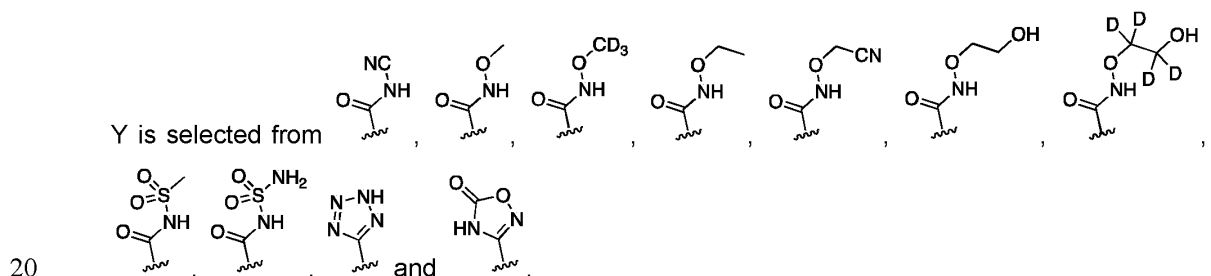
R¹⁰ is selected from C₁₋₄-alkyl,

- 10 wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

R¹¹ and R¹² are independently selected from H or C₁₋₃-alkyl,

- 15 wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium.

In a most particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



In one particular embodiment, Y is -CONHOR¹⁰, with R¹⁰ is selected from C₁₋₆-alkyl, which is optionally substituted with 1 to 3 substituents independently selected from fluoro, -CN, -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl; and R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium.

- 25 In a more particular embodiment, Y is -CONHOR¹⁰, with R¹⁰ is selected from C₁₋₃-alkyl, which is optionally substituted with 1 to 3 substituents independently selected from fluoro and -OH; and R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium.

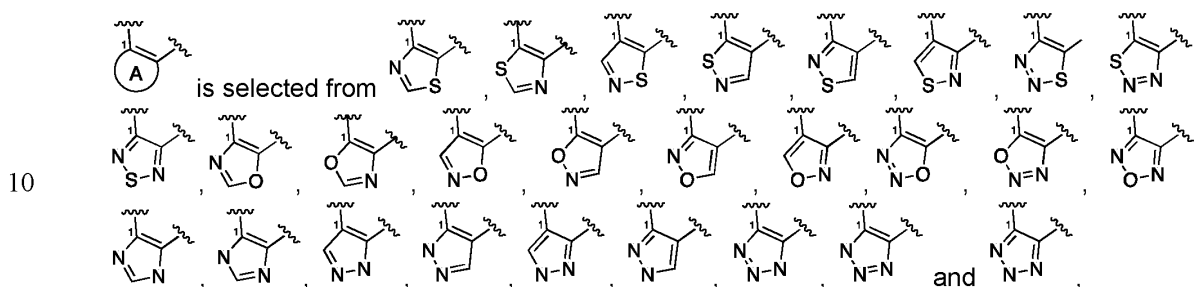
In one embodiment, Y is $-\text{CONHS}(=\text{O})_2\text{R}^{10}$, with R^{10} is selected from C_{1-3} -alkyl, which is optionally substituted with 1 to 3 fluoro substituents; and R^{10} having one or more hydrogen atoms optionally replaced by deuterium.

In a particular embodiment, Y is $-\text{CONHS}(=\text{O})_2\text{CH}_3$ or $\text{CONHS}(=\text{O})_2\text{CD}_3$.

5 In a more particular embodiment, Y is $-\text{CONHS}(=\text{O})_2\text{CH}_3$.

In another particular embodiment, Y is $-\text{CONHS}(=\text{O})_2\text{NH}_2$.

In a particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



said A is unsubstituted or substituted with one substituent independently selected from the group consisting of H, F, Cl, Br, $-\text{CN}$, $-\text{OH}$, C_{1-4} -alkyl, $-\text{O}-\text{C}_{1-4}$ -alkyl, fluoro- C_{1-4} -alkyl, $-\text{O}$ -fluoro- C_{1-4} -alkyl, CO_2R^{11} , $\text{NR}^{11}\text{R}^{12}$ and $\text{CONR}^{11}\text{R}^{12}$,

15 ring A or its substituent having one or more hydrogen atoms optionally replaced by deuterium;

R^2 is H;

R^{11} and R^{12} are independently selected from H, C_{1-6} -alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

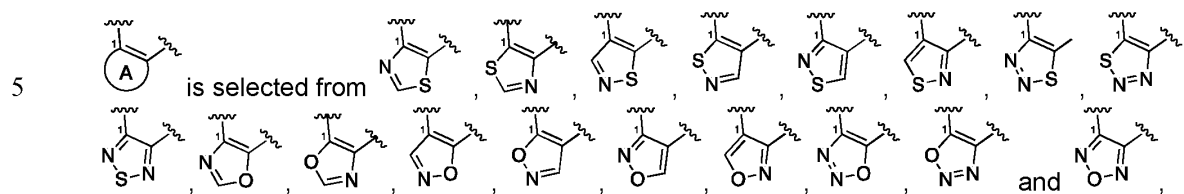
20 wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, $-\text{CN}$, C_{1-4} -alkyl, halo- C_{1-4} -alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), $-\text{OH}$, oxo, $-\text{O}-\text{C}_{1-4}$ -alkyl and $-\text{O}$ -halo- C_{1-4} -alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

25 or R^{11} and R^{12} , when taken together with the nitrogen to which they are attached complete a 3- to 6-membered cycle containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N; and

30 wherein this cycle is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, $-\text{CN}$, C_{1-4} -alkyl, halo- C_{1-4} -alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), $-\text{OH}$, oxo, $-\text{O}-\text{C}_{1-4}$ -alkyl and $-\text{O}$ -halo- C_{1-4} -alkyl,

R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium.

In a particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



said A is unsubstituted or substituted with one substituent independently selected from the group consisting of F, Cl, Br, -CN, -OH, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, fluoro-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, CO₂R¹¹, NR¹¹R¹² and CONR¹¹R¹²,

10 ring A or its substituent having one or more hydrogen atoms optionally replaced by deuterium;

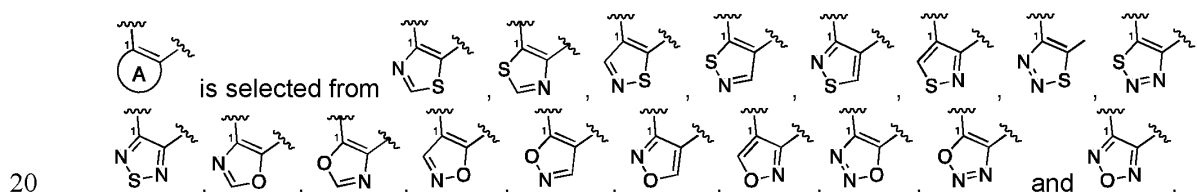
R² is H;

R¹¹ and R¹² are independently selected from H, C₁₋₆-alkyl,

wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

15 R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium.

In a particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

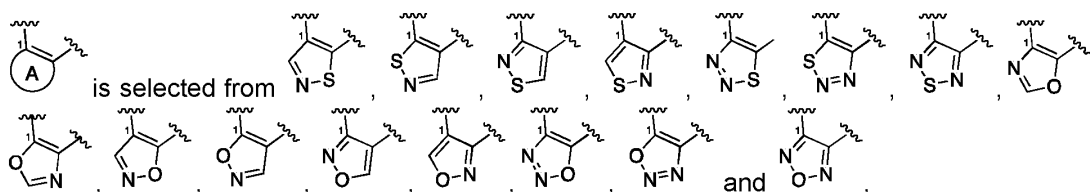


said A is unsubstituted or substituted with one substituent independently selected from the group consisting of D, F, Cl, -CN, -OH, Me, Et, -OMe, OEt, CHF₂, CF₃, -OCHF₂, -OCF₃, CO₂Me, NH₂, NHMe, NMe₂, NHCOMe, CONH₂, CONHMe and CONMe₂,

ring A or its substituent having one or more hydrogen atoms optionally replaced by deuterium;

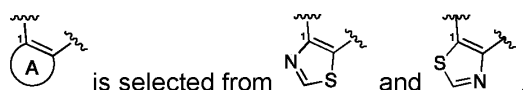
25 and R² is H.

In a particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



ring A having the hydrogen atom optionally replaced by deuterium; and R² is H.

5 In a particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



said A is unsubstituted or substituted with one substituent independently selected from the group consisting of F, Cl, Br, -CN, -OH, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, fluoro-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, CO₂R¹¹, NR¹¹R¹² and CONR¹¹R¹²,

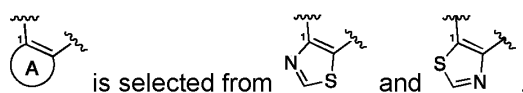
10 ring A or its substituent having one or more hydrogen atoms optionally replaced by deuterium; R² is H;

R¹¹ and R¹² are independently selected from H, C₁₋₆-alkyl,

wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

15 R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium.

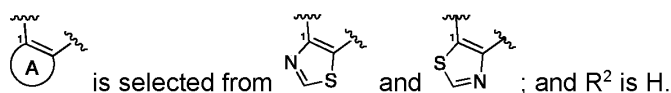
In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



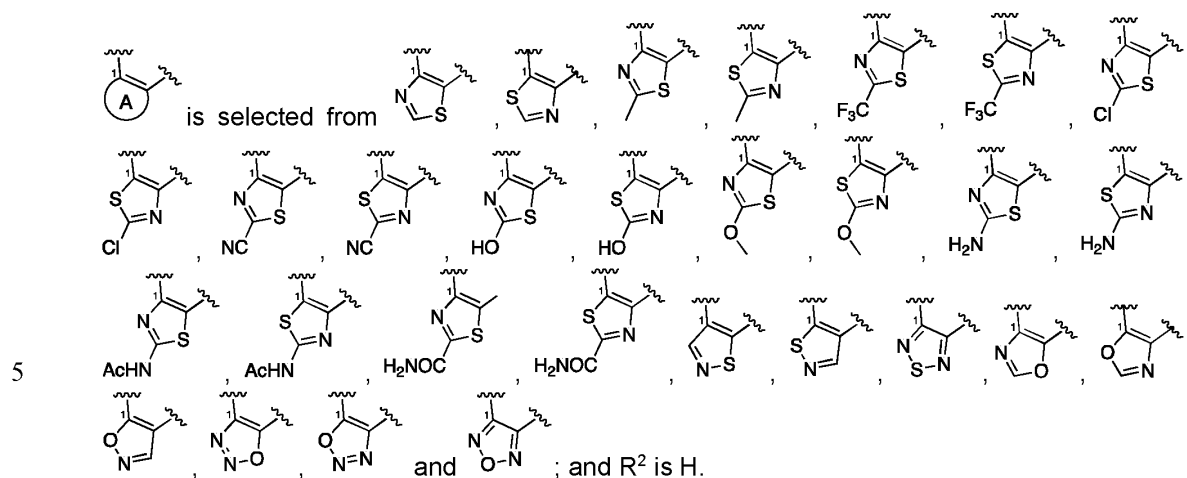
20 said ring A is unsubstituted or substituted with one substituent independently selected from the group consisting of D, F, Cl, -CN, -OH, Me, Et, -OMe, OEt, CHF₂, CF₃, -OCHF₂, -OCF₃, CO₂Me, NH₂, NHMe, NMe₂, NHCOMe, CONH₂, CONHMe and CONMe₂,

ring A or its substituent having one or more hydrogen atoms in alkyl optionally replaced by deuterium; and R² is H.

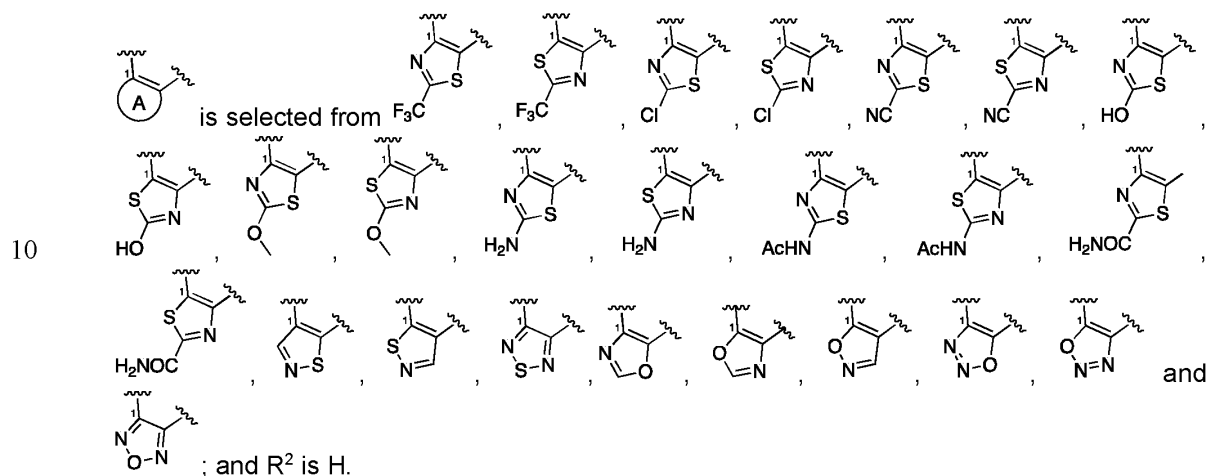
25 In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



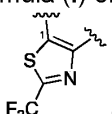
In a particular embodiment, the compound is represented by Formula (I) or a solvate or

pharmaceutically acceptable salt thereof, wherein  is selected from  ; and R² is H.

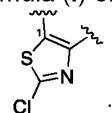
15 In a particular embodiment, the compound is represented by Formula (I) or a solvate or

pharmaceutically acceptable salt thereof, wherein  is selected from  ; and R² is H.

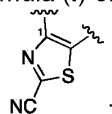
In an equally particular embodiment, the compound is represented by Formula (I) or a solvate or

pharmaceutically acceptable salt thereof, wherein  is selected from ; and R² is H.

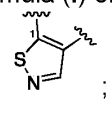
In an equally particular embodiment, the compound is represented by Formula (I) or a solvate or

pharmaceutically acceptable salt thereof, wherein  is selected from ; and R² is H.

5 In an equally particular embodiment, the compound is represented by Formula (I) or a solvate or

pharmaceutically acceptable salt thereof, wherein  is selected from ; and R² is H.

In an equally particular embodiment, the compound is represented by Formula (I) or a solvate or

pharmaceutically acceptable salt thereof, wherein  is selected from ; and R² is H.

10 In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein one or more hydrogen atom(s) in any substituent is replaced by deuterium.

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein one or more hydrogen atom(s) in any substituent is replaced by deuterium, provided, that the level of deuterium incorporation at each substituent designated as deuterium is at least 52.5%.

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein one or more hydrogen atom(s) in ring C or any substituent of ring C is replaced by deuterium.

20 In a most particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein one or more hydrogen atom(s) in residue X is replaced by deuterium.

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein residue X is OCH₃ or OCD₃.

25 In an upmost particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein residue X is OCD₃.

In one particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein one or more hydrogen atom(s) in residue Y is replaced by deuterium.

In one embodiment, R¹⁰ is selected from C₁₋₃-alkyl, cyclopropyl or oxetan-3-yl, wherein alkyl, cyclopropyl or oxetan-3-yl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃; R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium.

5 In one embodiment, R¹⁰ is selected from C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S; R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium.

10 In a particular embodiment, R¹⁰ is C₁₋₆-alkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl; R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium.

15 In a more particular embodiment, R¹⁰ is C₁₋₃-alkyl, which is unsubstituted or substituted with 1 to 3 substituents independently selected from fluoro, -CN and -OH; R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium.

In an even more particular embodiment, R¹⁰ is CH₃, CD₃, CH₂CH₂OH or CD₂CD₂OH.

20 In one embodiment, R¹¹ and R¹² are independently selected from H or C₁₋₃-alkyl, wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃; R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium.

In a particular embodiment, R¹¹ and R¹² are independently selected from H, CH₃, CD₃.

25 In a more particular embodiment, R¹¹ and R¹² are H.

In one embodiment, R¹³ is selected from H, -CN and C₁₋₃-alkyl, wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃; R¹³ having one or more hydrogen atoms optionally replaced by deuterium.

30 In a more particular embodiment, R¹³ is H.

In one embodiment, R²¹ and R²² are independently selected from H, CH₃, CD₃.

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein B is phenyl or pyridyl, wherein phenyl or pyridyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, ring B or

35

its substituents having one or more hydrogen atoms optionally replaced by deuterium; and wherein the residue $-NR^2$ on ring B is in a 1,4-orientation with respect to ring C.

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein B is phenyl or pyridyl, wherein phenyl or pyridyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of D, F, Cl, $-CN$, Me, CD_3 , $-OMe$, $-OCD_3$, CHF_2 and CF_3 ; and wherein the residue $-NR^2$ on ring B is in a 1,4-orientation with respect to ring C.

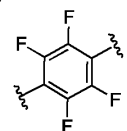
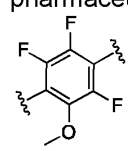
In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein B is phenyl, wherein phenyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, $-CN$, oxo, C_{1-4} -alkyl, C_{1-4} -alkyl, $-O-C_{1-4}$ -alkyl, $-O$ -fluoro- C_{1-4} -alkyl, ring B or its substituents having one or more hydrogen atoms optionally replaced by deuterium; and wherein the residue $-NR^2$ on ring B is in a 1,4-orientation with respect to ring C.

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein B is phenyl, wherein phenyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of D, F, Cl, $-CN$, Me, CD_3 , $-OMe$, $-OCD_3$, CHF_2 and CF_3 ; and wherein the residue $-NR^2$ on ring B is in a 1,4-orientation with respect to ring C.

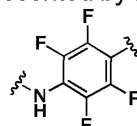
In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein B is phenyl, wherein phenyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of F, and $-OMe$; and wherein the residue $-NR^2$ on ring B is in a 1,4-orientation with respect to ring C.

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein B is phenyl, wherein phenyl is unsubstituted or substituted with 1 to 4 fluoro substituents; and wherein the residue $-NR^2$ on ring B is in a 1,4-orientation with respect to ring C.

In a most particular embodiment, the compound is represented by Formula (I) or a solvate or

pharmaceutically acceptable salt thereof, wherein $-NR^2B$ is selected from  and ; and wherein the residue $-NR^2$ on ring B is in a 1,4-orientation with respect to ring C.

In an upmost particular embodiment, the compound is represented by Formula (I) or a solvate or



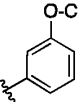
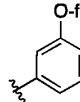
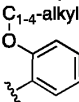
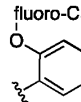
pharmaceutically acceptable salt thereof, wherein $-NR^2B$ is ; and wherein the residue $-NR^2$ on ring B is in a 1,4-orientation with respect to ring C.

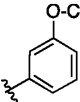
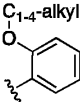
In a more particular embodiment, the compound is represented by Formula (I) or a solvate or
 5 pharmaceutically acceptable salt thereof, wherein C is selected from the group consisting of phenyl and pyridyl, wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, $-CN$, oxo, C_{1-4} -alkyl, C_{1-4} -alkyl, $-O-C_{1-4}$ -alkyl, $-O$ -fluoro- C_{1-4} -alkyl; ring C or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

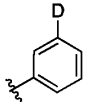
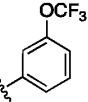
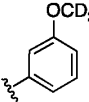
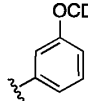
10 X is selected from H, D, F, Cl, $-CN$, C_{1-4} -alkyl, fluoro- C_{1-4} -alkyl, $O-C_{1-4}$ -alkyl and O -fluoro- C_{1-4} -alkyl, wherein alkyl having one or more hydrogen atoms optionally replaced by deuterium.

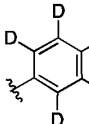
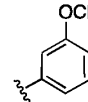
In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein C is phenyl, wherein phenyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of D, F, Cl,
 15 $-CN$, Me, CD_3 , CHF_2 , CF_3 , $-OMe$, $-OCD_3$, $-OCHF_2$ and $-OCF_3$;

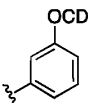
X is selected from H, D, F, Cl, $-CN$, Me, CD_3 , CHF_2 , CF_3 , Et, CD_2CD_3 , $-OMe$, $-OCD_3$, $-OCHF_2$, $-OCF_3$, $-OEt$, $-OCD_2CD_3$, $-OCH_2CH_2CH_3$, $-OCD_2CD_2CD_3$, $-OCH_2CH_2CH_2CH_3$ and $-OCD_2CD_2CD_2CD_3$.

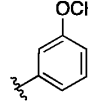
In one particular embodiment, $\text{---}\text{C}^{\oplus}\text{---X}$ is selected from , , ,
 20 ,  and ; ring C or its alkyl substituent having one or more hydrogen atoms optionally replaced by deuterium.

In one particular embodiment, $\text{---}\text{C}^{\oplus}\text{---X}$ is selected from , , and  ; ring C or its alkyl substituent having one or more hydrogen atoms optionally replaced by deuterium.

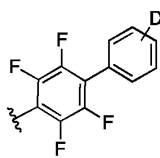
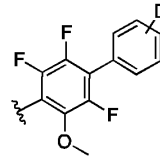
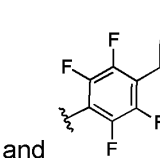
In one particular embodiment, $\text{---}\text{C}\text{---}\text{X}$ is selected from , , ,  and ; wherein the ring C is optionally substituted with 1 to 4 substituents selected from D and F.

In one particular embodiment, $\text{---}\text{C}\text{---}\text{X}$ is selected from ,  and .

5 In one particular embodiment, $\text{---}\text{C}\text{---}\text{X}$ is .

In one particular embodiment, $\text{---}\text{C}\text{---}\text{X}$ is .

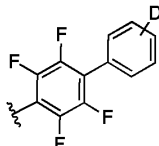
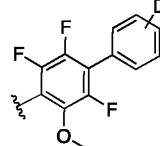
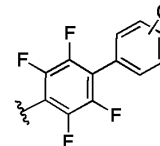
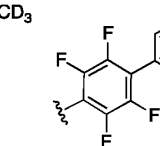
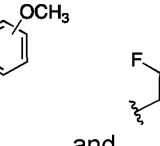
In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

$\text{---}\text{B}\text{---}\text{C}\text{---}\text{X}$ is selected from ,  and ;

10 wherein ring C is optionally substituted with 1 to 4 substituents independently selected from D or F.

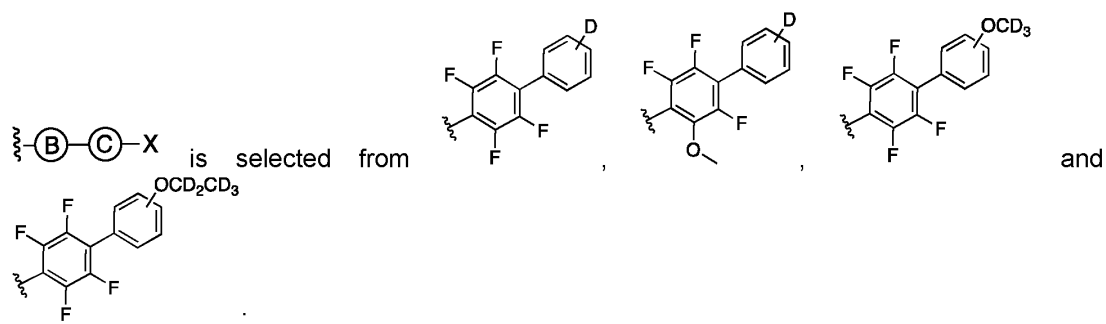
In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

$\text{---}\text{B}\text{---}\text{C}\text{---}\text{X}$ is selected from

15 , , ,  and ;

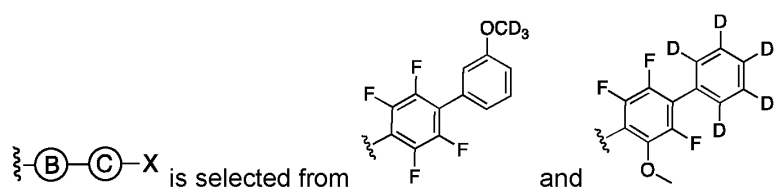
wherein ring C is optionally substituted with 1 to 4 substituents independently selected from D or F.

In a more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

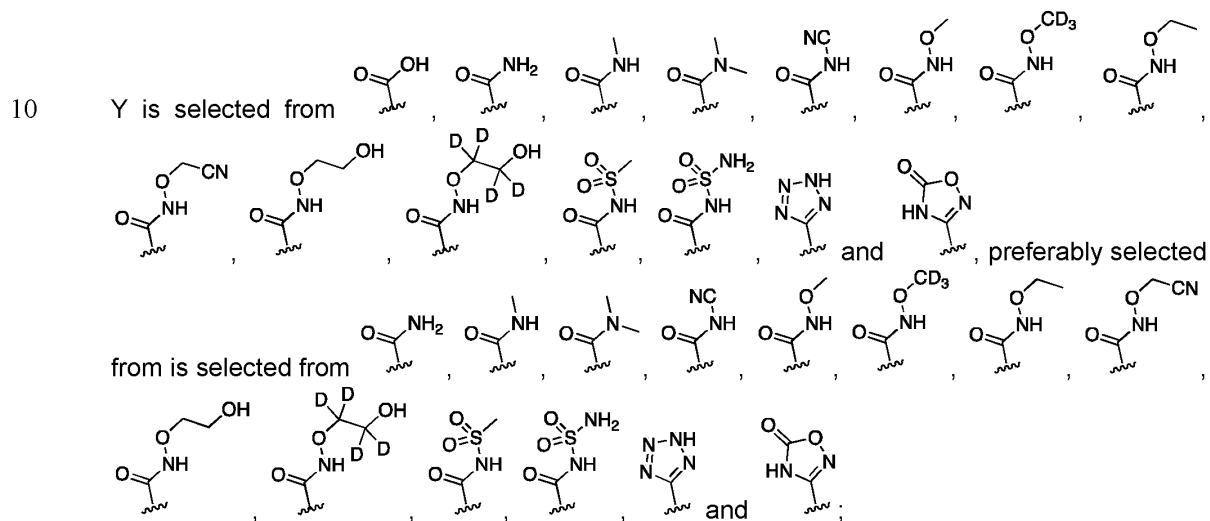


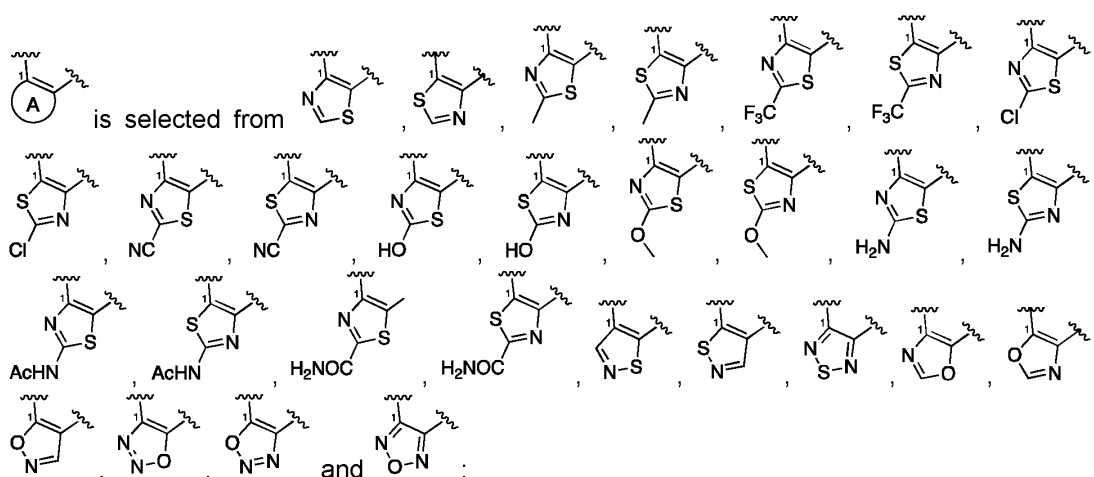
wherein ring C is optionally substituted with 1 to 4 substituents independently selected from D or F.

- 5 In a particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

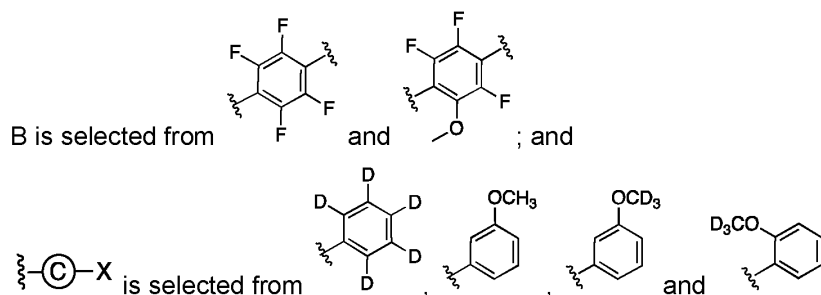


In one particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

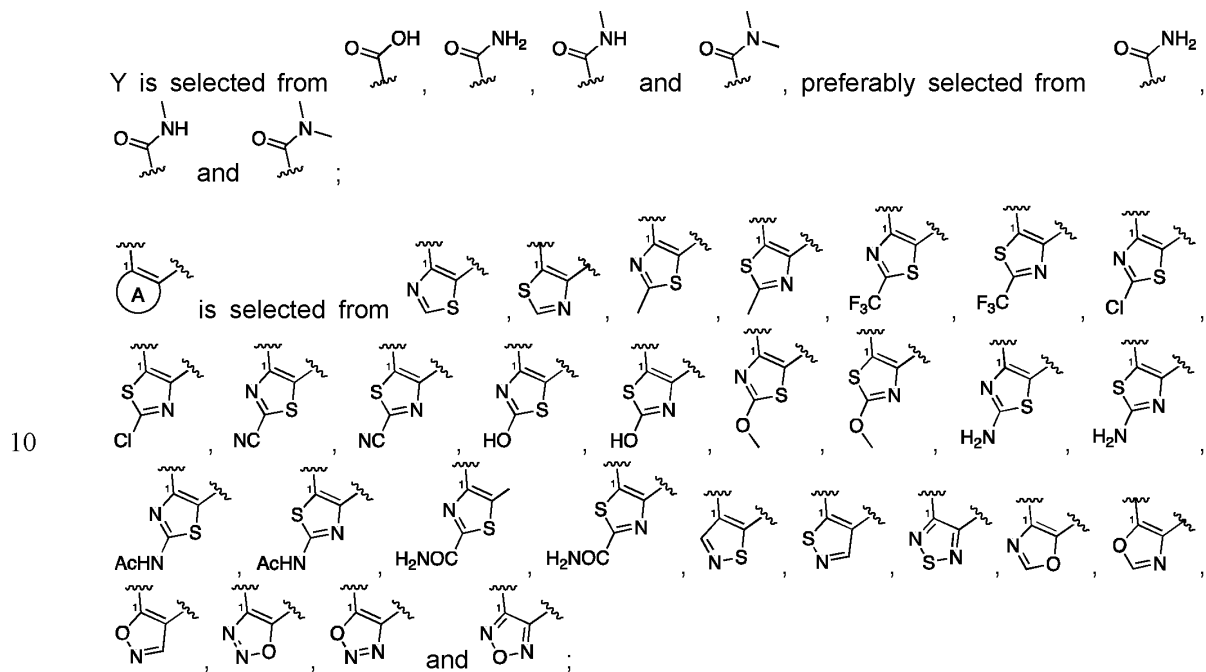




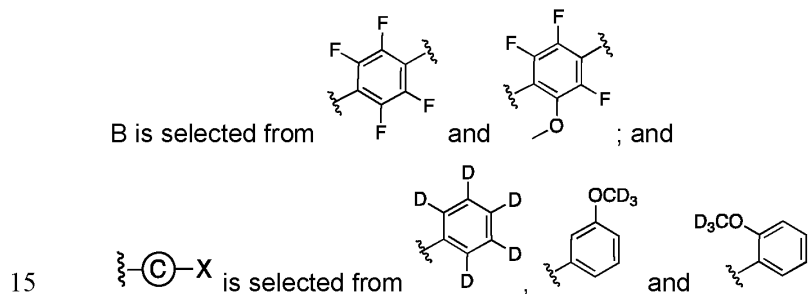
R² is H;



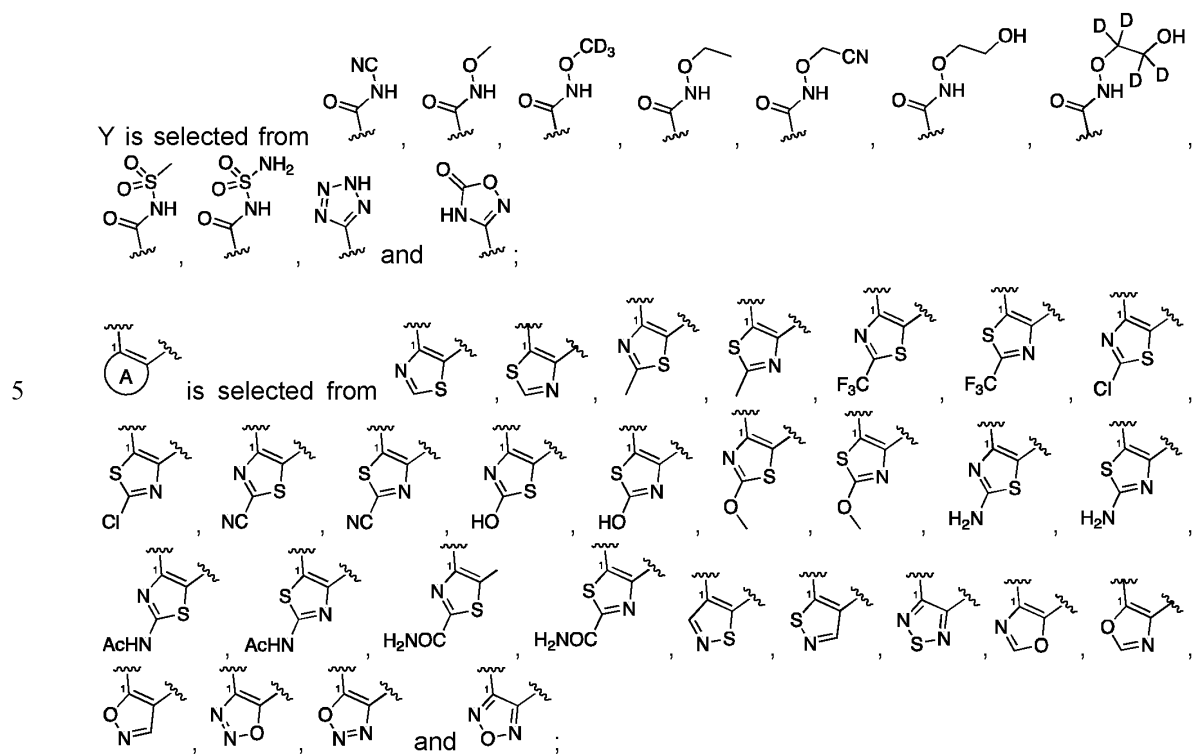
- 5 In an even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein



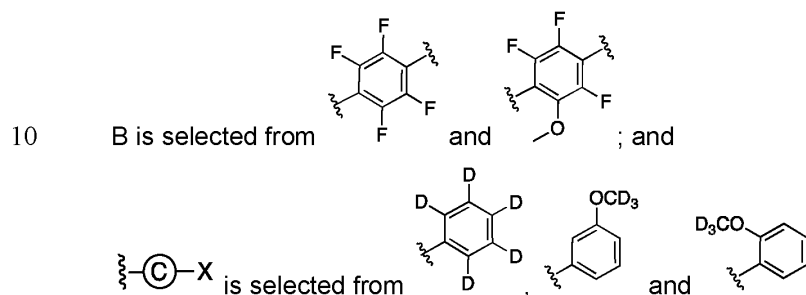
R² is H;



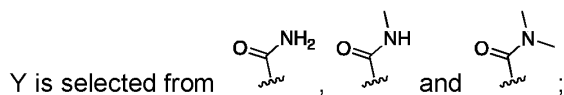
In an even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

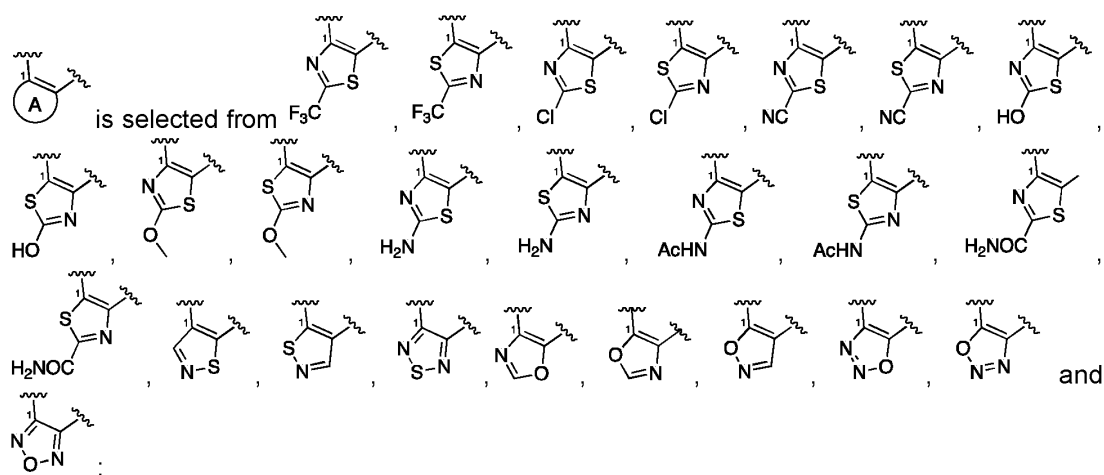


R^2 is H;

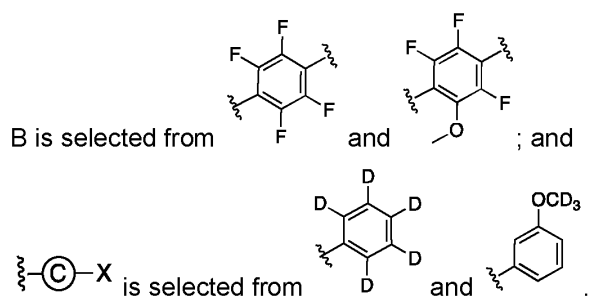


In an even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

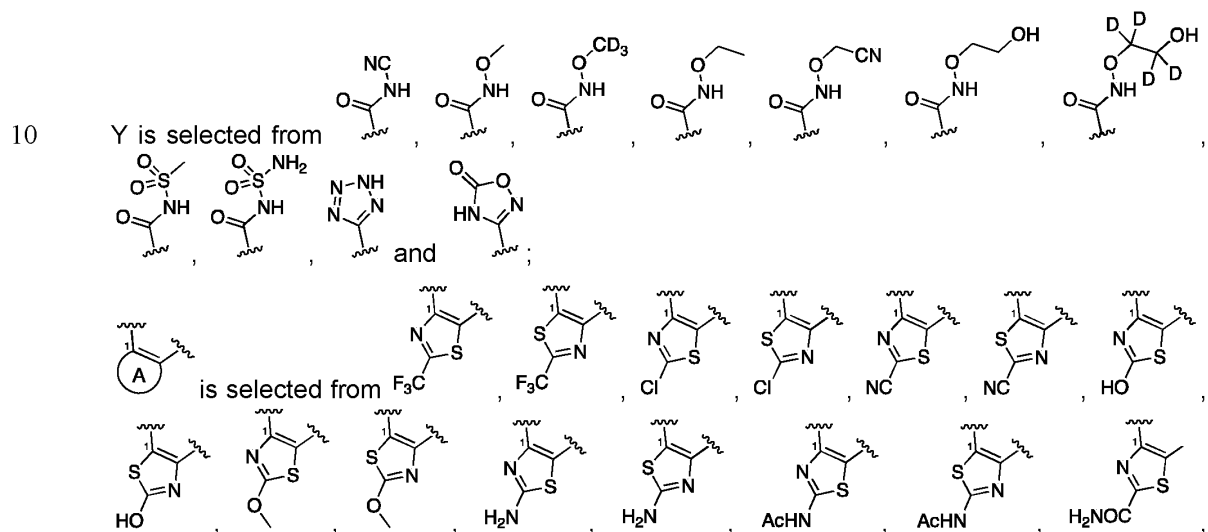


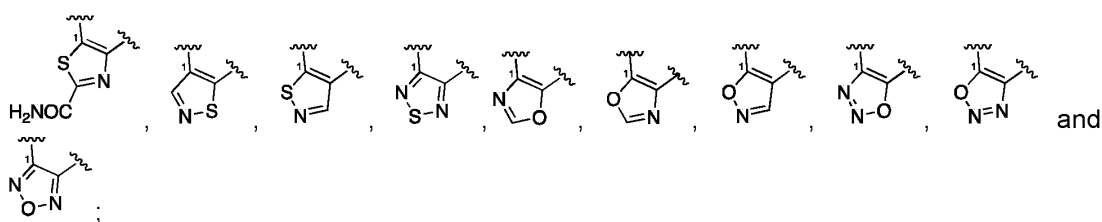
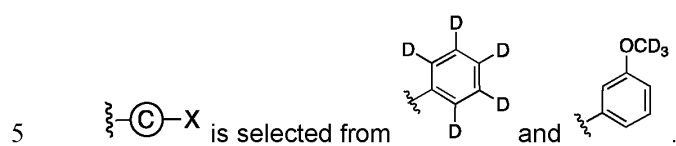
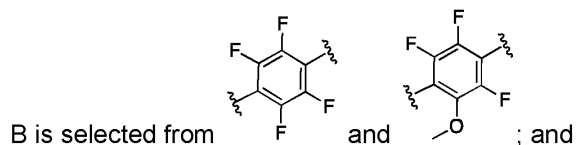


5 R^2 is H;



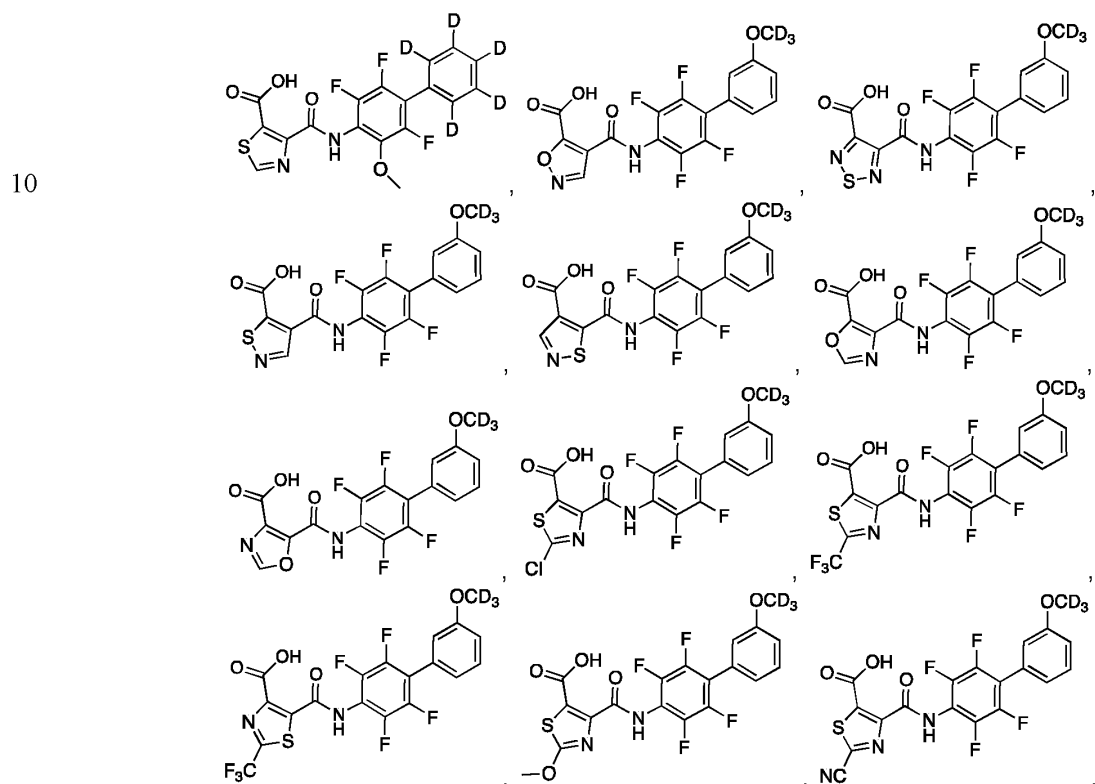
In an even more particular embodiment, the compound is represented by Formula (I) or a solvate or pharmaceutically acceptable salt thereof, wherein

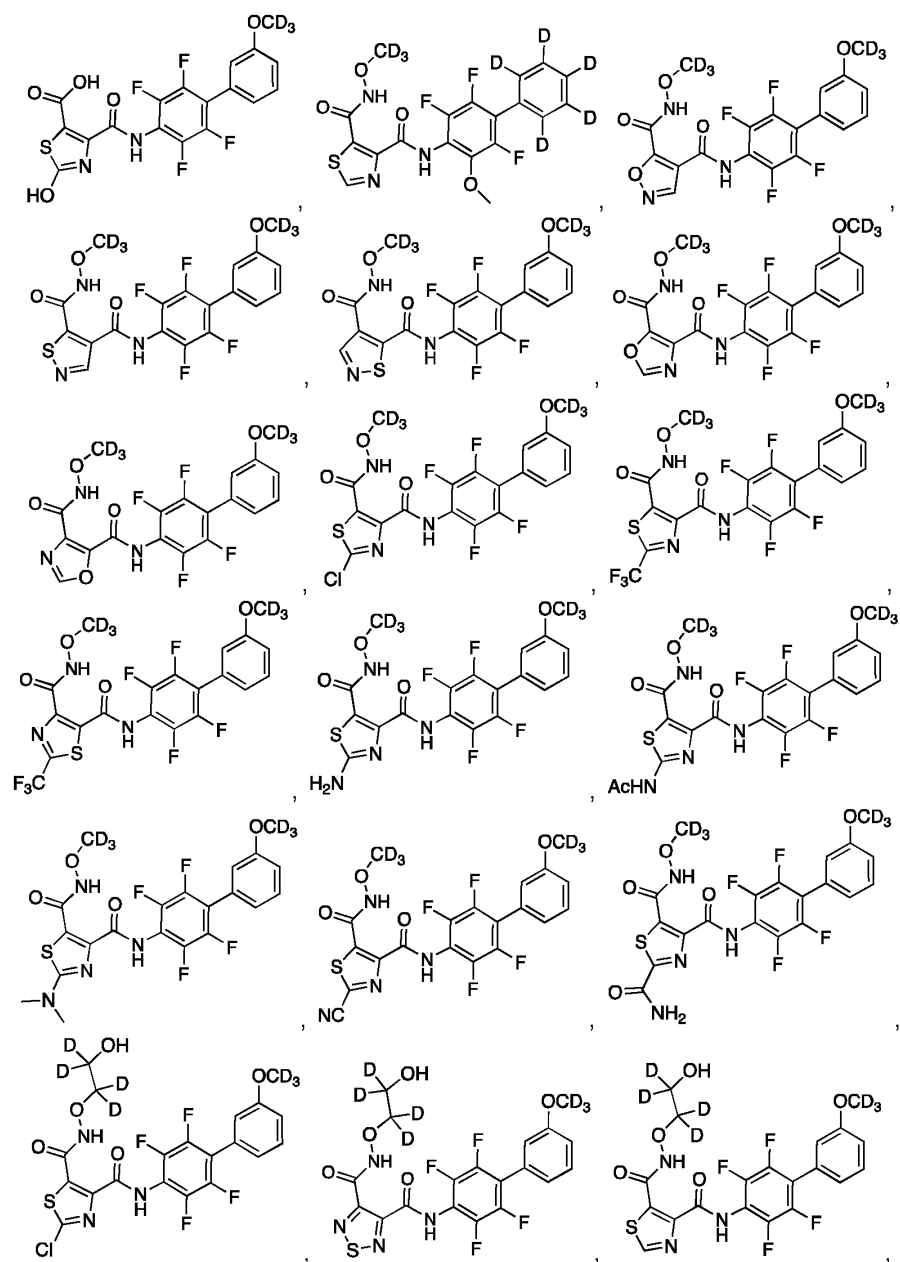


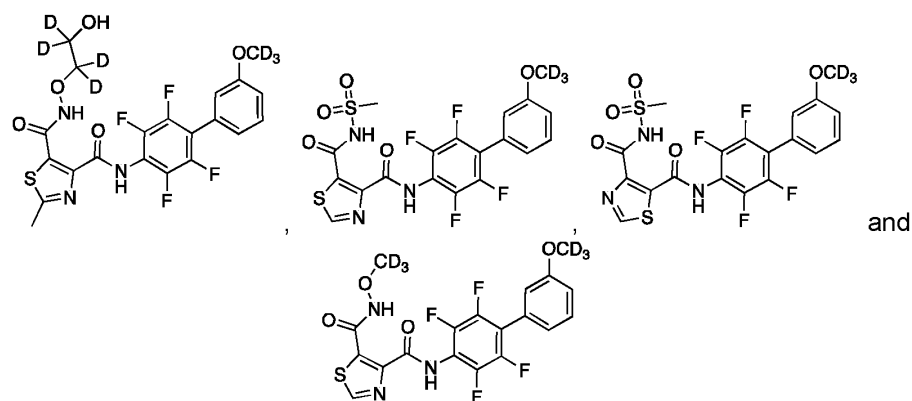
 R^2 is H ;

In a particular embodiment, the compound or a solvate or pharmaceutically acceptable salt thereof is selected from the Examples shown in the Experimental Part.

In a most particular embodiment, the compound or a solvate or pharmaceutically acceptable salt thereof is selected from

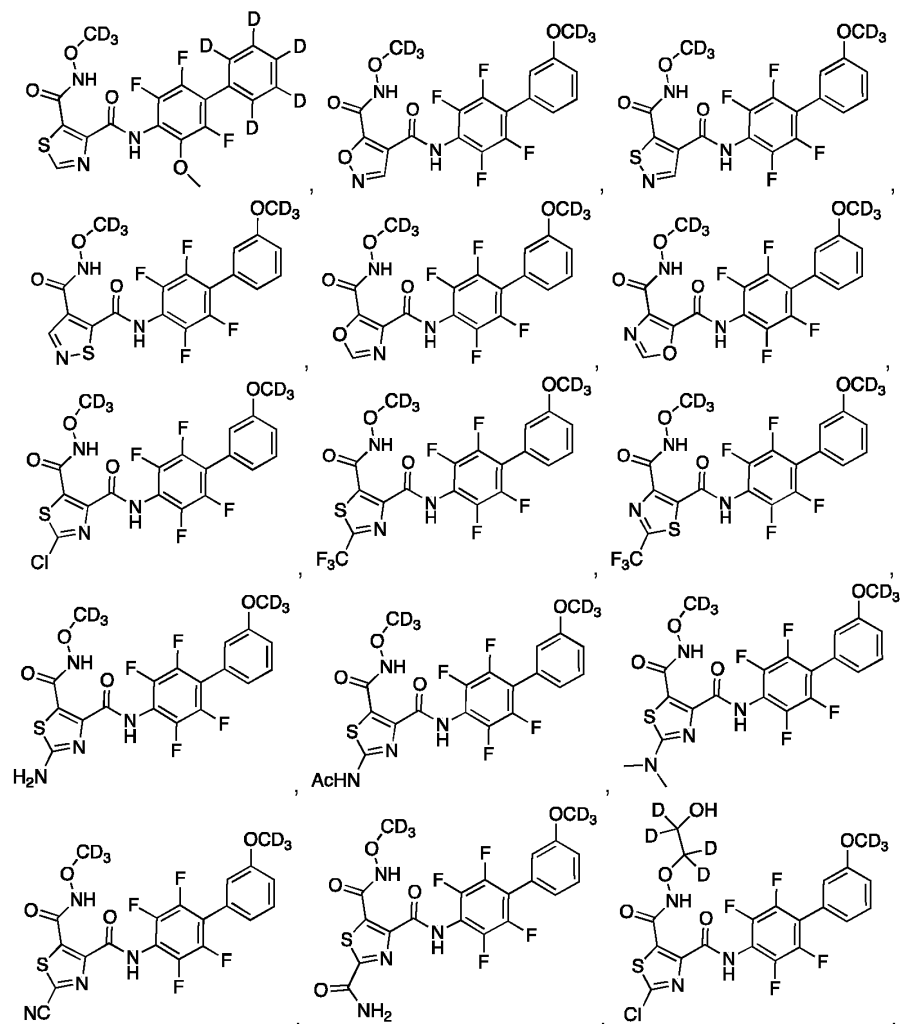


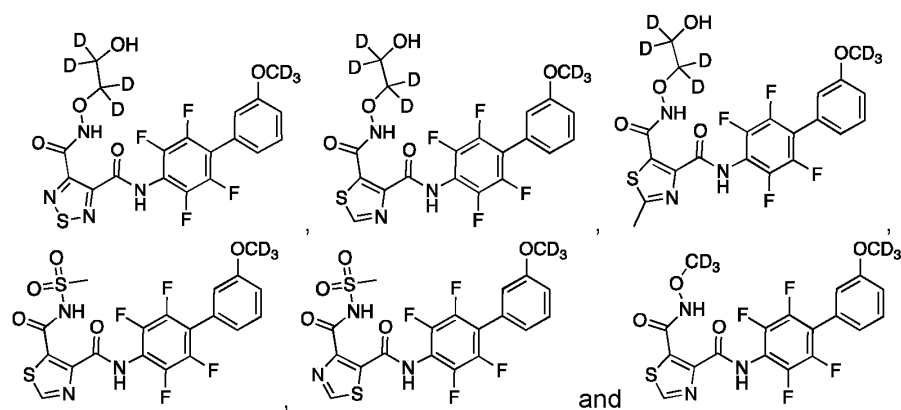




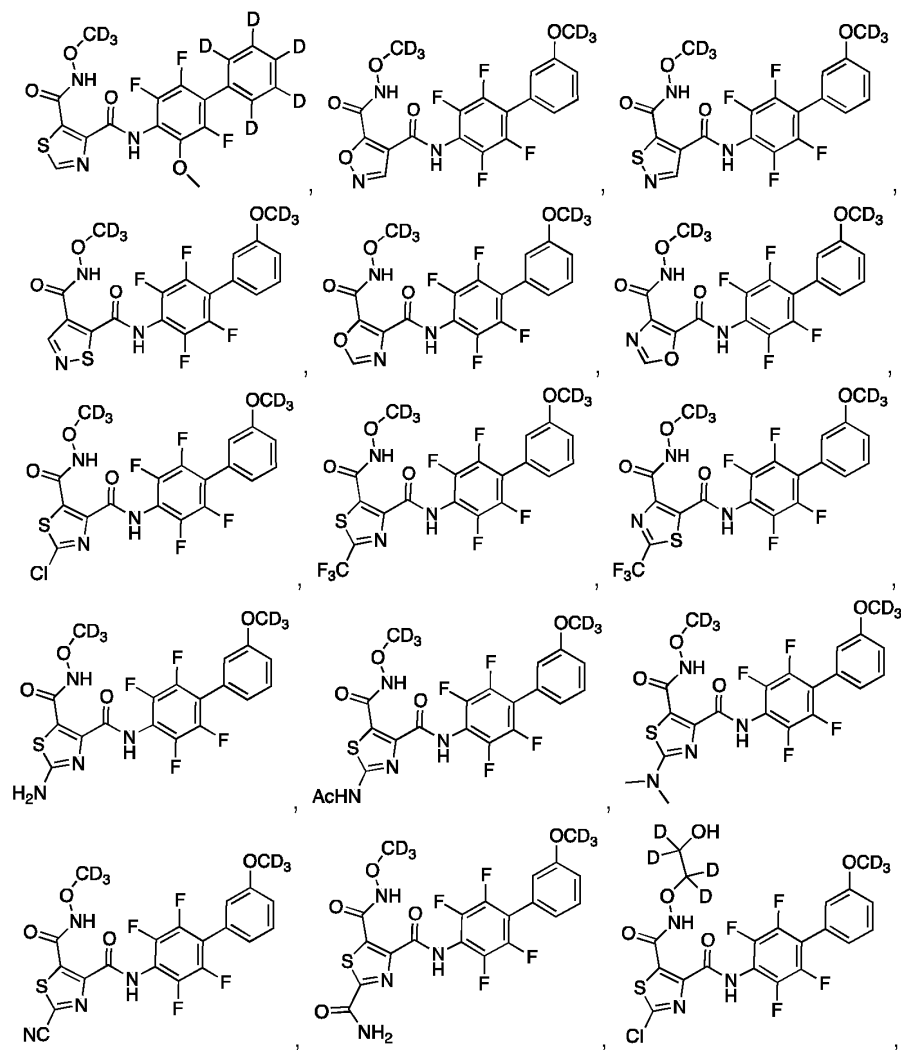
In another most particular embodiment, the compound or a solvate or pharmaceutically acceptable salt thereof is selected from

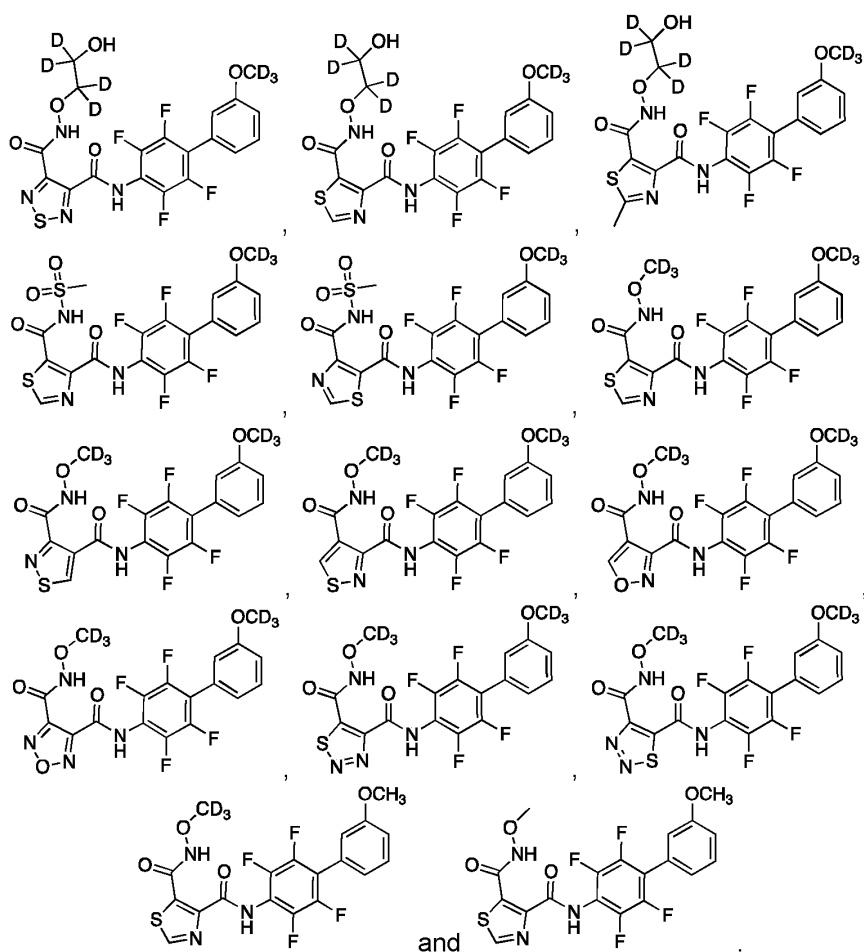
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In a similar most particular embodiment, the compound or a solvate or pharmaceutically acceptable salt thereof is selected from





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The invention also relates to the compound according to any of the preceding embodiments for the use as a medicament.

10

The invention also relates to the compound according to any of the preceding embodiments for use in the prophylaxis and/or treatment of diseases, disorders, therapeutic indications or medical conditions amenable for treatment with DHODH inhibitors.

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The invention also relates to the compound according to any of the preceding embodiments for use in the prophylaxis and/or treatment of a DHODH mediated disease selected from rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and pneumocystis carinii, fibrosis, uveitis, rhinitis, asthma, transplantation or arthropathy.

Specifically, the invention relates to a compound according to any of the preceding embodiments for use wherein the disease, disorder or therapeutic indication is selected from the group comprising graft versus host and host versus graft reactions, rheumatoid arthritis, multiple

sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, respiratory syncytial virus, influenza, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis.

5 More specifically, the invention relates to a compound according to any of the preceding embodiments for use wherein the disease, disorder or therapeutic indication is selected from the group comprising graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, influenza, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis.

10 More specifically, the disease, disorder or therapeutic indication caused by malignant cell proliferation due to isocitrate dehydrogenase (NADP⁺) 1 (IDH1) mutation(s).

Also provided is a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier or excipient.

15 Also provided is a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier or excipient and further comprising one or more additional therapeutic agents selected from anti-inflammatory agents, anti-viral agents, immunosuppressive and/or immunomodulatory agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics and suitable mixtures thereof. The term "pharmaceutically acceptable carrier" as used herein indicates that the carrier is approved or recognized for use in
20 animals, and more particularly in humans, i.e. it is not toxic to the host or patient. In addition, a carrier of choice will not interfere with the effectiveness of the biological activity of the active ingredient. The term "carrier" refers to any auxiliary material necessary for the particular mode of administration of choice and includes e.g. solvents, diluents, excipients or other additives with which the compound of the invention is administered. Typically used diluents pharmaceutical
25 carriers include sterile liquids, such as aqueous solutions and oils (e.g. of petroleum, animal, vegetable or synthetic origin), e.g. peanut oil, soybean oil, mineral oil, sesame oil and the like. Typically used aqueous liquids include water, saline solutions, aqueous dextrose and glycerol solutions and the like. Suitable pharmaceutical excipients include citric acid, ascorbic acid, starch, glucose, lactose, sucrose, gelatine, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol
30 monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Optionally the composition may comprise additives, such as wetting or emulsifying agents, pH buffering agents or binders. Examples of suitable pharmaceutical carriers are well known in the art and are described in e.g. "Remington's Pharmaceutical Sciences" by E.W. Martin (18th ed., Mack Publishing Co., Easton, PA (1990)).

35 According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the

scope of the invention are therefore all solvates and in particular all hydrates of the compounds of Formula (I) as well as all solvates and in particular all hydrates of the salts of the compounds of Formula (I).

5 The present invention further relates to methods of prophylaxis and/or treatment of diseases, disorders, therapeutic indications or medical conditions which are described herein, particularly a disease or medical condition in which the inhibition of DHODH is beneficial, more particularly a disease or medical condition selected from the group comprising rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and
10 animals, diseases that are caused by viral infections and pneumocystis carinii, fibrosis, uveitis, rhinitis, asthma, transplantation or arthropathy, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) as described herein. Analogously, the present invention further relates to methods as the one described above, which encompass the further embodiments described herein, in particular the medical uses and
15 compounds for use in medical treatments as described herein.

The present invention further relates to methods of prophylaxis and/or treatment of diseases, disorders, therapeutic indications or medical conditions which are described herein, particularly a disease or medical condition in which the inhibition of DHODH is beneficial, more particularly a disease or medical condition selected from graft versus host and host versus graft reactions,
20 rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, influenza, respiratory syncytial virus, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) as described herein.

25 The present invention further relates to methods of prophylaxis and/or treatment of diseases, disorders, therapeutic indications or medical conditions which are described herein, particularly a disease or medical condition in which the inhibition of DHODH is beneficial, more particularly a disease or medical condition selected from graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus,
30 inflammatory bowel disease, cancer, COVID-19, influenza, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis, said method comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) as described herein.

The present invention further relates to methods of prophylaxis and/or treatment of diseases, disorders, therapeutic indications or medical conditions caused by malignant cell proliferation due
35 to isocitrate dehydrogenase (NADP⁺) 1 (IDH1) mutation(s).

The present invention further relates to pharmaceutical compositions, kits and kits-of parts comprising the compounds according to the present invention.

5 The present invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the diseases, disorders, illnesses and/or conditions as mentioned herein.

The present invention further relates to the methods and medical uses described herein, encompassing the pharmaceutical compositions as described herein.

The pharmaceutical compositions as described herein comprise one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or excipient.

10 The pharmaceutical compositions as described herein comprise one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or excipient, further comprising one or more additional therapeutic agents selected from anti-inflammatory agents, anti-viral agents, anti-cancer agents, immunosuppressive and/or immunomodulatory agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics and suitable mixtures thereof.

15 The pharmaceutical compositions as described herein comprise one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or excipient, further comprising one or more additional therapeutic agents selected from anti-inflammatory agents, anti-viral agents, immunosuppressive and/or immunomodulatory agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics and suitable mixtures thereof.

20 Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective against the medical conditions as described herein, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating said medical conditions, and wherein said pharmaceutical agent comprises one or more compounds of Formula (I) according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

25 The pharmaceutical compositions according to this invention are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds of the invention (= active compounds) are either employed as such, or particularly in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a

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pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

5 The person skilled in the art is familiar with auxiliaries, vehicles, excipients, diluents, carriers or adjuvants which are suitable for the desired pharmaceutical formulations, preparations or compositions on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

10 Depending upon the particular disease, to be treated or prevented, additional therapeutic active agents, which are normally administered to treat or prevent that disease, may optionally be coadministered with the compounds according to the present invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease are known as appropriate for the disease being treated.

15 In a further aspect of the present invention, the compounds according to this invention or the salts or solvates of said compounds of Formula (I) may be combined with standard therapeutic agents which are commonly used for the treatment of the medical conditions as described herein.

20 The person skilled in the art is aware on the base of his/her expert knowledge of the total daily dosage(s) and administration form(s) of the additional therapeutic agent(s) coadministered. Said total daily dosage(s) can vary within a wide range. In practicing the present invention and depending on the details, characteristics or purposes of their uses mentioned above, the compounds according to the present invention may be administered in combination therapy separately, sequentially, simultaneously or chronologically staggered (e.g. as combined unit dosage forms, as separate unit dosage forms or a adjacent discrete unit dosage forms, as fixed or nonfixed combinations, as kit-of-parts or as admixtures) with one or more standard
25 therapeutics, in particular art-known chemotherapeutic or target specific anti-cancer agents, such as those mentioned above.

Thus, a further aspect of the present invention is a combination or pharmaceutical composition comprising a first active ingredient, which is a compound according to this invention or a pharmaceutically acceptable salt or solvate thereof, a second active ingredient, which is an art-
30 known standard therapeutic for the medical conditions as described herein, and optionally a pharmacologically acceptable carrier, diluent and/or excipient for sequential, separate, simultaneous or chronologically staggered use in therapy in any order, e.g. to treat, prevent or ameliorate in a patient the medical conditions as described herein. In this context, the present invention further relates to a combination comprising a first active ingredient, which is at least one
35 compound according to this invention, and a second active ingredient, which is at least one art-known standard therapeutic for the medical conditions as described herein, for separate,

sequential, simultaneous or chronologically staggered use in therapy, such as e.g. in therapy of those diseases mentioned herein.

The term "combination" according to this invention may be present as a fixed combination, a non-fixed combination or a kit-of-parts. A "fixed combination" is defined as a combination wherein the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a "fixed combination" is a pharmaceutical composition wherein the said first active ingredient and the said second active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a "fixed combination" is a pharmaceutical combination wherein the said first active ingredient and the said second active ingredient are present in one unit without being in admixture.

A "kit-of-parts" is defined as a combination wherein the said first active ingredient and the said second active ingredient are present in more than one unit. One example of a "kit-of-parts" is a combination wherein the said first active ingredient and the said second active ingredient are present separately. The components of the kit-of-parts may be administered separately, sequentially, simultaneously or chronologically staggered.

The first and second active ingredient of a combination or kit-of-parts according to this invention may be provided as separate formulations (i.e. independently of one another), which are subsequently brought together for simultaneous, sequential, separate or chronologically staggered use in combination therapy; or packaged and presented together as separate components of a combination pack for simultaneous, sequential, separate or chronologically staggered use in combination therapy. The type of pharmaceutical formulation of the first and second active ingredient of a combination or kit-of-parts according to this invention can be similar, i.e. both ingredients are formulated in separate tablets or capsules, or can be different, i.e. suited for different administration forms, such as e.g. one active ingredient is formulated as tablet or capsule and the other is formulated for e.g. intravenous administration. The amounts of the first and second active ingredients of the combinations, compositions or kits according to this invention may together comprise a therapeutically effective amount for the treatment, prophylaxis or amelioration of a medical condition as described herein.

A further aspect of the present invention is a method for treating co-therapeutically the medical conditions as described herein, in a patient in need of such treatment comprising administering separately, sequentially, simultaneously, fixed or non-fixed a therapeutically effective and tolerable amount of one or more of the compounds according to the present invention and a therapeutically effective and tolerable amount of one or more art-known therapeutic agents for the medical conditions as described herein, to said patient.

References and claims to the use of a compound of the Formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of a

disease or medical condition in their general and specific forms likewise refer to the corresponding methods of treating said disease or medical condition, said method comprising administering a therapeutically effective and tolerable amount of a compound of the Formula (I) or a pharmaceutically acceptable salt or solvate thereof to a subject in need thereof, compositions comprising a compound of the Formula (I) or a pharmaceutically acceptable salt or solvate thereof for the treatment of said disease or medical condition, a compound of the Formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of said disease or medical condition, and vice versa.

For the production of the pharmaceutical compositions, the compounds of the invention (= active compounds) are particularly mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions. The pharmaceutical compositions according to the invention are prepared by processes known per se.

The dosage of the active compounds is carried out in the customary order of magnitude. Topical application forms (such as ointments) thus contain the active compounds in a concentration of, for example, 0.1 to 99%. The customary dose in the case of systemic therapy (p.o.) is usually between 0.3 and 30 mg/kg per day, (i.v.) is usually between 0.3 and 30 mg/kg/h. The choice of the optimal dosage regime and duration of medication, particularly the optimal dose and manner of administration of the active compounds necessary in each case can be determined by a person skilled in the art on the basis of his/her expert knowledge.

The class of compounds of the present invention is useful for the development of medicaments suitable for the treatment of autoimmune or viral diseases and chronic inflammation or, more generally, for the treatment of diseases where the inhibition of DHODH is beneficial. The compounds of the present invention are also useful for the treatment of diseases such as rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and *Pneumocystis carinii*, fibrosis, uveitis, rhinitis, asthma, transplantation or arthropathy. Specifically, the disease is selected graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, respiratory syncytial virus, influenza, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis. More specifically, the disease is selected graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, influenza, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis.

The class of compounds of the present invention is useful for the treatment of viral diseases, especially acute viral infections selected from Coronavirus infections, COVID-19, SARS, flu/influenza (and avian influenza), HIV/Aids, chickenpox (Varicella), cytomegalovirus, Dengue Fever, German measles (Rubella), hand-foot-mouth disease, hantavirus infections, all forms of hepatitis, Lassa fever, Marburg virus infections, measles, meningitis, MERS-CoV, mumps, norovirus infections, herpes simplex virus infections, smallpox, rotavirus infections, Ebola virus, poliovirus infections, rhinovirus infections, parainfluenzavirus infections, RSV infections, HCMV infections and bannavirus infections. Most preferred as COVID-19, flu/influenza and rhinovirus infections, most preferred is COVID-19. It is understood, that also mutated forms of the virus (e.g. of SARS-CoV-2) are covered.

The class of compounds of the present invention is useful for the treatment of malignant cell proliferation or cancers.

The class of compounds of the present invention is useful for the treatment of malignant cell proliferation or cancers due to isocitrate dehydrogenase (NADP⁺) 1 (IDH1) mutation(s).

The class of compounds of the present invention is useful for the treatment of malignant cell proliferation or cancers selected from isocitrate dehydrogenase (NADP⁺) 1 (IDH1) mutated tumors, glioma e.g. oligodendroglioma or anaplastic oligodendroglioma, glioblastoma multiforme, diffuse or anaplastic astrocytoma, chondrosarcoma, acute myeloid leukemia, myelodysplastic syndrome, hormone receptor-positive (HR⁺) breast adenocarcinoma, prostate adenocarcinoma, thyroid cancer, thymoma, intrahepatic or extrahepatic cholangiocarcinoma, cutaneous squamous cell carcinoma, cutaneous melanoma, skin cancer, non-melanoma esophagogastric adenocarcinoma, colorectal adenocarcinoma, adenocarcinoma of the gastroesophageal junction, stomach adenocarcinoma, tubular stomach adenocarcinoma, head and neck squamous cell carcinoma, ampullary carcinoma, esophageal squamous cell carcinoma, renal clear cell carcinoma, uterine serous carcinoma, bladder urothelial carcinoma, uterine endometrioid carcinoma and esophagogastric cancer.

Combination or alternation therapy

The compounds or their pharmaceutically acceptable salts as described herein can be administered on top of the current standard of care for patients, or in combination or alternation with any other compound or therapy that the healthcare provider deems beneficial for the patient. The combination and/or alternation therapy can be therapeutic, adjunctive or palliative.

Especially preferred is a combination or alternation therapy for the treatment of anti-viral infections, especially Covid-19, influenza and RSV infections, preferably Covid-19:

It has been observed that high levels of the cytokine interleukin-6 (IL-6) are a precursor to

respiratory failure and death in COVID-19 patients. To treat this surge of an immune response, which may constitute a cytokine storm, patients can be administered an IL-6-targeting monoclonal antibody, pharmaceutical inhibitor or protein degrader such as a bispecific compound that binds to IL-6 and also to a protein that mediates degradation. Examples of antibodies include
5 tocilizumab, sarilumab, siltuximab, olokizumab and clazakizumab. In one embodiment, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered in combination or in alternation with tocilizumab or sarilumab. Additional nonlimiting examples of immunosuppressant drugs used to treat the overreacting immune system include Janus kinase inhibitors (tofacitinib, baricitinib, filgotinib); calcineurin inhibitors (cyclosporine), tacrolimus, mTOR
10 inhibitors (sirolimus, everolimus) and IMDH inhibitors (azathioprine). Additional antibodies and biologics include abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, ixekizumab, natalizumab, rituximab, secukinumab, tocilizumab, ustekinumab, vedolizumab, basiliximab and daclizumab.

IL-1 blocks the production of IL-6 and other proinflammatory cytokines. COVID patients are also
15 sometimes treated with anti-IL-1 therapy to reduce a hyperinflammatory response, for example, an intravenous administration of anakinra. Anti-IL-1 therapy generally may be for example, a targeting monoclonal antibody, pharmaceutical inhibitor or protein degrader such as a bispecific compound that binds to IL-1 and also to a protein that mediates degradation.

Patients with COVID often develop viral pneumonia, which can lead to bacterial pneumonia.
20 Patients with severe COVID-19 can also be affected by sepsis or "septic shock". Treatment for bacterial pneumonia secondary to COVID or for sepsis includes the administration of antibiotics, for example a macrolide antibiotic, including azithromycin, clarithromycin, erythromycin, or roxithromycin. Additional antibiotics include amoxicillin, doxycycline, cephalexin, ciprofloxacin, clindamycin, metronidazole, sulfamethoxazole, trimethoprim, amoxicillin, clavulanate or
25 levofloxacin. In one embodiment, thus a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered in combination or in alternation with an antibiotic, for example, azithromycin. Some of these antibiotics such as azithromycin have independent anti-inflammatory properties. Such drugs may be used both as anti-inflammatory agents for COVID patients and have a treatment effect on secondary bacterial infections.

30 A unique challenge in treating patients infected with COVID-19 is the relatively long-term need for sedation if patients require mechanical ventilation which might last up to or greater than 5, 10 or even 14 days. For ongoing pain during this treatment, analgesics can be added sequentially and for ongoing anxiety, sedatives can be added sequentially. Non-limiting examples of analgesics include acetaminophen, ketamine and PRN opioids (hydromorphone, fentanyl, and morphine).
35 Non-limiting examples of sedatives include melatonin, atypical antipsychotics with sedative-predominant properties (olanzapine, quetiapine), propofol or dexmedetomidine, haloperidol and

phenobarbital. In one embodiment, a compound of Formula (I) or a pharmaceutically acceptable salt, a solvate, a solvate of a salt, a hydrate or a polymorph thereof is administered in combination or in alternation with a pain reliever, such as acetaminophen, ketamine, hydromorphone, fentanyl, or morphine. In one embodiment, a compound of Formula (I) a pharmaceutically acceptable salt, a solvate, a solvate of a salt, a hydrate or a polymorph thereof is administered in combination or in alternation with a sedative, such as melatonin, olanzapine, quetiapine, propofol, dexmedetomidine, haloperidol or phenobarbital.

In one embodiment, a compound of the present invention is used in an effective amount in combination with a protease inhibitor such as PF-07304814, PF-00835231, PF-07321332 (nirmatrelvir), lopinavir or ritonavir. In one more special embodiment, protease inhibitor is PF-07321332 (nirmatrelvir).

In one embodiment, a compound of the present invention is used in an effective amount in combination with a RNA replication modulator such as *N*4-hydroxycytidine or a prodrug thereof may also be administered. In one special embodiment, the RNA replication modulator is a *N*4-hydroxycytidine prodrug as described in WO 2019/113462. In one more special embodiment, the RNA replication modulator is molnupiravir.

In one embodiment, a compound of the present invention is used in an effective amount in combination with halofuginol or an enantiomer, tautomer, solvate or pharmaceutically acceptable salt thereof.

In one embodiment, a compound of the present invention is used in an effective amount in combination with dipyridamole or a solvate or pharmaceutically acceptable salt thereof.

In one embodiment, a compound of the present invention is used in an effective amount in combination with gemcitabine or a solvate or pharmaceutically acceptable salt thereof.

In one embodiment, a compound of the present invention is used in an effective amount in combination with AT-527 (RO7496998) or a solvate or pharmaceutically acceptable salt thereof.

Additional drugs that may be used in the treatment of a COVID patient include, but are not limited to aspirin, colchicine, dimethyl fumarate, acalabrutinib, favipiravir, fingolimod, methylprednisolone, bevacizumab, tocilizumab, umifenovir, losartan and the monoclonal antibody combination of REGN3048 and REGN3051 or ribavirin. Any of these drugs or vaccines can be used in combination or alternation with an active compound provided herein to treat a viral infection susceptible to such.

In one embodiment, a compound of the present invention is used in an effective amount in combination with anti-coronavirus vaccine therapy, including but not limited to mRNA-1273 (Moderna), AZD-1222 (AstraZeneca and University of Oxford), BNT162b2 (BioNTech), CoronaVac (Sinovac), NVX-CoV 2372 (NovoVax), SCB-2019 (Sanofi and GSK), ZyCoV-D (Zyudus Cadila) and CoVaxin (Bharat Biotech). In another embodiment, a compound of the present

invention is used in an effective amount in combination with passive antibody therapy or convalescent plasma therapy.

SARS-CoV-2 is constantly mutating, which may increase virulence and transmission rates.

Drug-resistant variants of viruses may emerge after prolonged treatment with an antiviral agent.

5 Drug resistance may occur by mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against an RNA virus infection in certain cases can be prolonged, augmented or restored by administering the compound in combination or alternation with another and perhaps even two or three other, antiviral compounds that induce a different mutation or act through a different pathway, from that of the principle drug. A variant of a known
10 virus can refer to a virus carrying one or more nucleotide mutations in the viral genome as compared to the known virus, for instance at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 60, 100, 200, 300 or even more nucleotide mutations. Mutations can refer to nucleotide deletion, insertion, or substitution. In some cases, a variant can have at most 50%, 40%, 30%, 20%, 10%, 5%, 4%, 3%, 2% or 1% of the viral genome different than the genome of a known virus.

15

Alternatively, the pharmacokinetics, biodistribution, half-life or other parameter of the drug can be altered by such combination therapy (which may include alternation therapy if considered concerted).

20

Examples of other therapeutic agents that may be combined with a compound of Formula (I) or a pharmaceutically acceptable salt, a solvate, a solvate of a salt, a hydrate or a polymorph thereof, either administered separately, or in the same pharmaceutical composition include, but are not limited to a:

25

- (1) Protease inhibitor;
- (2) Polymerase inhibitor (e.g. gemcitabine);
- (3) Allosteric polymerase inhibitor;
- (4) Interferon alfa-2a, which may be pegylated or otherwise modified, and/or ribavirin;
- (5) Non-substrate-based inhibitor;
- (6) Helicase inhibitor;
- (7) Primase-helicase inhibitor;
- 30 (8) Antisense oligodeoxynucleotide (S-ODN);
- (9) Aptamer;
- (10) Nuclease-resistant ribozyme;
- (11) iRNA, including microRNA and siRNA;
- (12) Antibody, partial antibody or domain antibody to the virus;
- 35 (13) Viral antigen or partial antigen that induces a host antibody response;
- (14) NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3);

- (15) Glutamyl-prolyl-tRNA synthetase inhibitor (e.g. halofuginone);
 (16) Equilibrative nucleoside transporter (ENT) inhibitor (e.g. dipyridamole);
 (17) other DHODH inhibitors (e.g. brequinar, teriflunomide, leflunomide, PTC299, MEDS433, AG-636, ASLAN003, JNJ-74856665, RP7214, PP-001 and BAY2402234).

5

In one embodiment the compound of Formula (I) or a pharmaceutically acceptable salt, a solvate, a solvate of a salt, a hydrate or a polymorph thereof can be combined with known anti-cancer agents. Examples of anti-cancer agents include: ¹³¹I-chTNT, abarelix, abemaciclib, abiraterone, acalabrutinib, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, anacetim, anethole dithiolethione, anetumab ravtansine, angiotensin II, antithrombin III, apalutamide, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, avelumab, axicabtagene ciloleucel, axitinib, azacitidine, basiliximab, belotecan, bendamustine, besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, blinatumomab, bortezomib, bosutinib, buserelin, brentuximab vedotin, brigatinib, busulfan, cabazitaxel, cabozantinib, calcitonine, calcium folinate, calcium levofolinate, capecitabine, capromab, carbamazepine carboplatin, carboquone, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, cobimetinib, copanlisib, crisantaspase, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daratumumab, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftotox, denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin+estrone, dronabinol, durvalumab, eculizumab, edrecolomab, elliptinium acetate, elotuzumab, eltrombopag, enasidenib, endostatin, enocitabine, enzalutamide, epirubicin, epitioctanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, ethinylestradiol, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, inotuzumab ozogamicin, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (¹²³I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, ixazomib,

lanreotide, lansoprazole, lapatinib, lasocholine, lenalidomide, lenvatinib, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, lutetium Lu 177 dotatate, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, midostaurin, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, mvasi, nabilone, nabiximols, nafarelin, naloxone+pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine, neratinib, neridronic acid, netupitant/palonosetron, nivolumab, pentetretotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nintedanib, niraparib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaparib, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palbociclib, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, panobinostat, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pembrolizumab, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglucam, polyestradiol phosphate, polyvinylpyrrolidone+sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib, regorafenib, ribociclib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, romidepsin, romiplostim, romurtide, rucaparib, samarium (¹⁵³Sm) lexidronam, sargramostim, sarilumab, satumomab, secretin, siltuximab, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sonidegib, sorafenib, stanozolol, streptozocin, sunitinib, talaporf in, talimogene laherparepvec, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (^{99m}Tc) nofetumomab merpentan, ^{99m}Tc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur+gimeracil+oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tisagenlecleucel, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine+tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib, valrubicin, vandetanib, vaporeotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

Furthermore, a compound of Formula (I) or a pharmaceutically acceptable salt, a solvate, a solvate of a salt, a hydrate or a polymorph thereof may be administered in combination with a mutant IDH inhibitor.

5 Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyperproliferative and/or inflammatory disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of a compound of Formula (I) or a pharmaceutically acceptable salt, a solvate, a solvate of a salt, a hydrate or a polymorph thereof can readily be determined for treatment of each desired indication. 10 The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

15 It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of vidofludimus and compounds according to Formula (I) without any depicted deuterium will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, *Comp. Biochem. Physiol.* 1998;119A:725. 20

The term "isotopic enrichment factor" at a particular position normally occupied by hydrogen refers to the ratio between the abundance of deuterium at the position and the natural abundance of deuterium at that position. By way of example, an isotopic enrichment factor of 3500 means that 25 the amount of deuterium at the particular position is 3500-fold the natural abundance of deuterium, or that 52.5% of the compounds have deuterium at the particular position (i.e., 52.5% deuterium incorporation at the given position). The abundance of deuterium in the oceans of Earth is approximately one atom in 6500 hydrogen atoms (about 154 parts per million (ppm)). Deuterium thus accounts for approximately 0.015 percent (on a weight basis, 0.030 percent) of all naturally 30 occurring hydrogen atoms in the oceans on Earth; the abundance changes slightly from one kind of natural water to another.

When a particular position in a compound of the invention (e.g., a compound represented by Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof) is designated by name or structure as containing hydrogen or deuterium, it is to be understood that the position can 35 contain hydrogen at its natural abundance or can be enriched in deuterium with an isotopic enrichment factor of, for example, at least 835 (12.5% deuterium incorporation), of at least 1670 (25% deuterium incorporation, of at least 3500 (52.5% deuterium incorporation), at least 4500

(67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

5 When a particular position in a compound of the invention (e.g., a compound represented by Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof) is designated specifically by name or structure as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition.

10 When a particular position in a compound of the invention (e.g., a compound represented by Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof) is designated specifically by name or structure as “D” or “deuterium”, the position is understood to have deuterium at an abundance that is at least 3340 times of the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium), at least 3500 times of the natural abundance of deuterium (52.5% deuterium incorporation), at least 4500 times of the natural abundance of deuterium (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 times of the natural abundance of deuterium (82.5% deuterium incorporation), at least 6000 times of the natural abundance of deuterium (90% deuterium incorporation), at least 6333.3 times of the natural abundance of deuterium (95% deuterium incorporation), at least 6466.7 times of the natural abundance of deuterium (97% deuterium incorporation), at least 6600 times of the natural abundance of deuterium (99% deuterium incorporation), or at least 6633.3 times of the natural abundance of deuterium (99.5% deuterium incorporation).

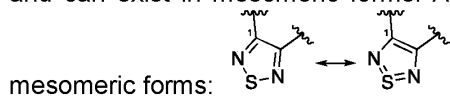
25 The percentage of deuterium incorporation can be obtained by quantitative analysis using a number of conventional methods, such as mass spectroscopy (peak area) or by quantifying the remaining residual ^1H -NMR signals of the specific deuteration site compared to signals from internal standards or other, non-deuterated ^1H signals in the compound.

When a chemical name or structure is silent as to whether a particular position in a compound normally occupied by hydrogen is isotopically enriched, it is intended that the particular position is occupied by hydrogen at its natural abundance. By way of example, the term “phenyl” or

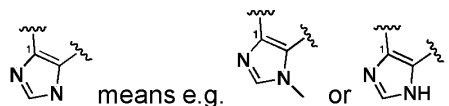


without any further designation as to isotopic enrichment indicates that all hydrogen atoms are present at natural abundance.

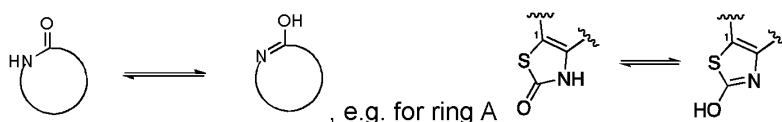
Since ring A is a 5-membered heteroaryl ring, the double bond is within a delocated π -system and can exist in mesomeric forms. An example is shown with the following 1,2,5-thiadiazole



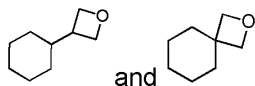
In case the valency of each atom is not fully shown for every atom in ring A, this atom is substituted as defined for ring A, e.g.



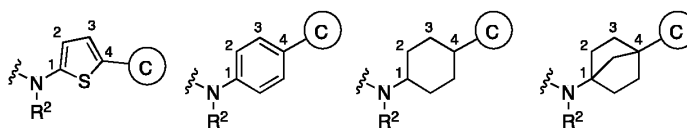
Furthermore, the compounds of the present invention are partly subject to tautomerism. For example, if a heteroaromatic group containing a nitrogen atom in the ring is substituted with a hydroxy group on the carbon atom adjacent to the nitrogen atom, the following tautomerism can appear:



A cycloalkyl or heterocycloalkyl group can be connected straight or spirocyclic, e.g. when cyclohexane is substituted with the heterocycloalkyl group oxetane, the following structures are possible:



The term "1,4-orientation" (as mentioned for ring B) denotes the specific relative position of the two substituents on the same ring and means that on a ring the substituents have at least one possibility, where 4 atoms are between the two substituents in the ring attached to the ring system:



The term "compound," when referring to any compound of this disclosure, including a compound represented by Formula (I) or a pharmaceutically acceptable salt and/or solvate thereof, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent hydrogen atoms of the molecules. The relative amount of isotopic variation in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound.

"D" and "d" both refer to deuterium. "H" refers to hydrogen.

"Substituted with deuterium" refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

Any formula or structure given herein, is also intended to represent deuterated compounds comprising in addition further isotopically labelled atoms. Examples of additional isotopes that can be incorporated into compounds of the disclosure include further isotopes of hydrogen (i.e. tritium or ^3H), as well as isotopes of carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl and ^{125}I . The disclosure further comprises various isotopically labelled compounds into which radioactive isotopes such as ^3H , ^{13}C and ^{14}C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or radioactive treatment of patients.

Halogen is selected from fluorine, chlorine, bromine and iodine, more preferably fluorine or chlorine and most preferably fluorine.

In the context of the present invention "C₁₋₄-alkyl" means a preferably saturated hydrocarbon chain having 1 to 4 carbon atoms which may be straight chained or branched. Examples thereof include methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl and *tert*-butyl. Preferred is C₁₋₃-alkyl, such as methyl, ethyl, propyl and isopropyl, most preferred is methyl. The term "alkyl" by itself or as a part of another substituent, e.g. halo-C₁₋₄-alkyl, unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as "unsaturated alkyl". An unsaturated alkyl group is one having one or more double bonds or triple bonds. Preferred unsaturated alkyl substituents are vinyl, 2-propenyl or prop-2-yn-1-yl.

In the context of the present invention the term "C₁₋₄-alkyl having one or more hydrogen atoms in alkyl optionally replaced by deuterium" encompasses, but is not limited to the following residues: -CD₃, -CH₂D, -CHD₂, CD₃CH₂(CH₂)_n-, CD₃CH₂(CHD)_n-, CD₃CH₂(CD₂)_n-, CH₂DCH₂(CH₂)_n-, CH₂DCH₂(CHD)_n-, CH₂DCH₂(CD₂)_n-, CHD₂CH₂(CH₂)_n-, CHD₂CH₂(CHD)_n-, CHD₂CH₂(CD₂)_n-, CD₃CHD(CH₂)_n-, CD₃CHD(CHD)_n-, CD₃CHD(CD₂)_n-, CH₂DCHD(CH₂)_n-, CH₂DCHD(CHD)_n-, CH₂DCHD(CD₂)_n-, CHD₂CHD(CH₂)_n-, CHD₂CHD(CHD)_n-, CHD₂CHD(CD₂)_n-, CH₃CHD(CH₂)_n-, CH₃CHD(CHD)_n-, CH₃CHD(CD₂)_n-, CD₃CD₂(CH₂)_n-, CD₃CD₂(CHD)_n-, CD₃CD₂(CD₂)_n-, CH₂DCD₂(CH₂)_n-, CH₂DCD₂(CHD)_n-, CH₂DCD₂(CD₂)_n-, CHD₂CD₂(CH₂)_n-, CHD₂CD₂(CHD)_n-, CHD₂CD₂(CD₂)_n-, CH₃CD₂(CH₂)_n-, CH₃CD₂(CHD)_n-, CH₃CD₂(CD₂)_n-, wherein n is an integer from 0 to 2, and CH₃CH₂(CHD)_m-, CH₃CH₂(CD₂)_m-, wherein m is an integer from 1 to 2, as well as -CD(CD₃)₂, -CH(CD₃)₂ and -C(CD₃)₃. Preferred C₁₋₂-alkyl containing deuterium are -CD₃ and -CD₃CD₂, most preferred is -CD₃.

A "C₀₋₆-alkylene" means that the respective group is divalent and connects the attached residue with the remaining part of the molecule. Moreover, in the context of the present invention, "C₀-alkylene" is meant to represent a bond, whereas C₁-alkylene means a methylene linker, C₂-alkylene means a ethylene linker or a methyl-substituted methylene linker and so on. In the context of the present invention, a C₀₋₆-alkylene preferably represents a bond, a methylene, a ethylene group or a propylene group. The term "alkylene", unless otherwise noted, is also meant to include a unsaturated divalent chain, if appropriate (i.e. possible for "C₂₋₆-alkylene"). A representative example for an unsaturated C₄-alkylene is -CH₂-CH=CH-CH₂-.

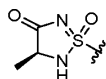
The term "fluoro-C₁₋₄-alkyl" or "O-fluoro-C₁₋₄-alkyl", respectively, means that one or more hydrogen atoms in the alkyl chain are replaced by one or more fluoro atoms. Preferred are CHF₂, CF₃, CH₂CF₃ and CF₂CF₃. A more preferred example thereof is the formation of a -CF₃ group.

Similar applies to "halo-C₁₋₄-alkyl" or "O-halo-C₁₋₄-alkyl", which means that one or more hydrogen atoms in the alkyl chain are replaced by one or more halogen atoms, independently selected from fluoro, chloro, bromo and iodo.

In the context of the present invention the term "fluoro-C₁₋₄-alkyl having one or more hydrogen atoms in alkyl optionally replaced by deuterium" means, that if the fluoro-C₁₋₄-alkyl contains one or more hydrogen atom(s), one or more hydrogen(s) can be replaced by fluorine(s), yielding the same as described above for the term "C₁₋₄-alkyl having one or more hydrogen atoms in alkyl optionally replaced by deuterium". It is understood that fluoro-C₁₋₄-alkyl can also be completely fluorinated. Preferred are fluoro-C₁₋₂-alkyl containing deuterium such as CDF₂, CD₂CF₃ and CD₂CF₂D. Most preferred is CDF₂.

A "3- to 6-membered cycloalkyl" group means a saturated or partially unsaturated mono-, bi-, spiro- or multicyclic ring system comprising 3 to 6 carbon atoms, wherein each of the atoms forming the ring system (i.e. skeletal atoms) is a carbon atom. Examples encompass, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentyl, bicyclo[2.1.0]pentyl and spiro[2.3]hexanyl. More preferred is cyclopropyl or cyclobutyl.

A "3- to 8-membered heterocycloalkyl containing 1 to 4 heteroatoms independently selected from N, O and S" group means a saturated or partially unsaturated 3 to 8 membered carbon mono-, bi-, spiro- or multicyclic ring wherein 1, 2, 3 or 4 carbon atoms are replaced by 1, 2, 3 or 4 heteroatoms, respectively, wherein the heteroatoms are independently selected from N, O or S. The sulfur heteroatom in the ring can also be oxidized to S=O or SO₂. The carbon atom in the ring can also be oxidized to C=O. Examples thereof include epoxidyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, 1,4-dioxanyl, morpholinyl, 1,4-dihydropyridinyl and 2-oxaspiro[3.3]heptyl. The heterocycloalkyl group can be connected with the remaining part of the molecule via a carbon, nitrogen (e.g. in morpholine or piperidine) or sulfur atom. An example for a S-linked heterocycloalkyl is the cyclic sulfonimidamide



"5- to 6-membered heteroaryl" means a monocyclic aromatic ring system containing up to 4 heteroatoms independently selected from N, O and S. Examples of monocyclic heteroaromatic rings include pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, furanyl, thiophenyl, tetrazolyl and oxazolyl.
5 The nitrogen or sulphur atom of the heteroaryl system may also be optionally oxidized to the corresponding *N*-oxide, *S*-oxide or *S,S*-dioxide.

The compounds of the invention may, depending on their structure, exist in tautomeric or stereoisomeric forms (enantiomers, diastereomers). The invention therefore also encompasses the tautomers, enantiomers or diastereomers and respective mixtures thereof. The
10 stereoisomerically uniform constituents can be isolated in a known manner from such mixtures of enantiomers and/or diastereomers.

The term "diastereomer" means stereoisomers that are not mirror images of one another and are non-superimposable on one another. The term "enantiomer" means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as
15 determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Thus, the compounds
20 of the present disclosure which contain acidic groups can be present on these groups and can be used according to the disclosure, for example, as alkali metal salts, alkaline earth metal salts or ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. The respective salts can be obtained
25 by customary methods which are known to the person skilled in the art like, for example, by contacting these with an organic or inorganic base in a solvent or dispersant, or by cation exchange with other salts. The present disclosure also includes all salts of the compounds of the present disclosure which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions
30 or for the preparation of pharmaceutically acceptable salts.

Further the compounds of the present disclosure may be present in the form of solvates, such as those which include as solvate water, or pharmaceutically acceptable solvates, such as alcohols, in particular ethanol. A stoichiometric or non-stoichiometric amount of solvent is bound by non-covalent intermolecular forces. When the solvent is water, the "solvate" is a "hydrate." It is
35 understood, that a "pharmaceutically acceptable salts" can in addition optionally contain a

"solvate".

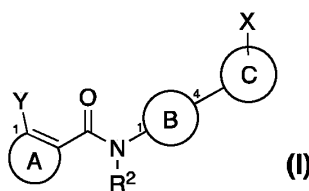
The term "polymorph" as used herein refers to a crystalline form of a compound or a salt, hydrate, or solvate thereof, in a particular crystal packing arrangement. All polymorphs have the same elemental composition. The term "crystalline" as used herein, refers to a solid state form which consists of orderly arrangement of structural units. Different crystalline forms of the same compound, or a salt, hydrate, or solvate thereof, arise from different packing of the molecules in the solid state, which results in different crystal symmetries and/or unit cell parameter. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility.

The term "effective amount" is meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of a disorder, disease, or condition being treated. The term "effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

As used herein, the term "subject" refers to any member of the animal kingdom including humans. In some embodiments, "subject" refers to humans, at any stage of development. In some embodiments, "subject" refers to a human patient. In some embodiments, "subject" refers to non-human animals. In some embodiments, the non-human animal is a mammal (e.g. a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate or a pig). In some embodiments, subjects include, but are not limited to, mammals, birds, reptiles, amphibians, fish or worms. In some embodiments, a subject may be a transgenic animal, genetically-engineered animal or a clone.

With the above context, the following consecutively numbered embodiments provide further specific aspects of the invention:

1. A compound of Formula (I):



or an enantiomer, diastereomer, tautomer, solvate, or pharmaceutically acceptable salt thereof, wherein

A is selected from a 5-membered heteroaryl containing 2 to 3 heteroatoms selected from N, S and O, having one or more hydrogen atoms optionally replaced by deuterium,

said A is unsubstituted or substituted with one substituent independently selected from the group consisting of H, halogen, -CN, -NO₂, SF₅, oxo, -OH, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, fluoro-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, -O-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, -O-(3- to 8-membered heterocycloalkyl), CO₂R¹¹, NR¹¹R¹²,
5 CONR¹¹R¹², phenyl, 5- or 6-membered heteroaryl

wherein alkyl, cycloalkyl, heterocycloalkyl, phenyl, heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of D, halogen, -CN, OH, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl and -O-fluoro-C₁₋₄-alkyl,

ring A or its substituents having one or more hydrogen atoms optionally replaced by deuterium;
10

B is selected from the group consisting of phenyl and pyridyl,

wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl;

15 and wherein optionally two adjacent substituents in the phenyl and pyridyl moiety form a 5- to 8-membered partially unsaturated cycle optionally containing 1 to 3 heteroatoms independently selected from O, S or N,

wherein this additional cycle is optionally substituted with 1 to 4 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl;

20 and wherein the residue -NR² on ring B is in a 1,4-orientation with respect to ring C,
ring B or its substituents having one or more hydrogen atoms optionally replaced by deuterium;
C is selected from the group consisting of phenyl and pyridyl,

wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl,
25 -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl;

and wherein optionally two adjacent substituents in the phenyl and pyridyl moiety form a 5- to 8-membered partially unsaturated cycle optionally containing 1 to 3 heteroatoms independently selected from O, S or N,

wherein this additional cycle is optionally substituted with 1 to 4 substituents
30 independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl;

ring C or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

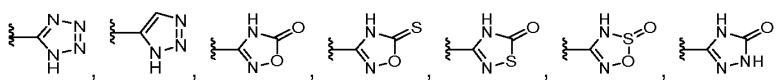
X is selected from H, D, halogen, -CN, -NO₂, C₁₋₆-alkyl, -O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₀₋₆-alkylene-OR²¹, C₀₋₆-alkylene-(3- to 6-membered cycloalkyl), C₀₋₆-alkylene-(3- to 8-membered heterocycloalkyl), C₀₋₆-alkylene-S(=O)_n(=NR²³)_mR²¹, C₀₋₆-alkylene-NR²¹S(=O)_x(=NR²³)_yR²¹, C₀₋₆-alkylene-S(=O)_x(=NR²³)_yNR²¹R²², C₀₋₆-alkylene-NR²¹S(=O)_x(=NR²³)_yNR²¹R²², C₀₋₆-alkylene-CO₂R²¹, C₀₋₆-alkylene-O-COR²¹, C₀₋₆-alkylene-CONR²¹R²², C₀₋₆-alkylene-NR²¹-COR²¹, C₀₋₆-alkylene-NR²¹-CONR²¹R²², C₀₋₆-alkylene-O-CONR²¹R²², C₀₋₆-alkylene-NR²¹-CO₂R²¹, C₀₋₆-alkylene-NR²¹R²², wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

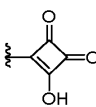
wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

X or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

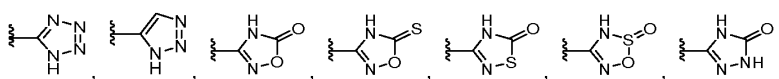
Y is selected from -CO₂H, -CO₂R¹⁰, -CONR¹¹R¹², -CONH-CN, -CONHOR¹⁰, -SO₃H, -SO₂H, -B(OH)₂,

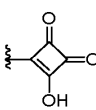
-CONHS(=O)_x(=NR¹³)_yR¹⁰, -CONHS(=O)_x(=NR¹³)_yNR¹¹R¹², -S(=O)_x(=NR¹³)_yNHCOR¹⁰,

-S(=O)_x(=NR¹³)_yNHR¹¹,  and

, preferably selected from -CONR¹¹R¹², -CONH-CN, -CONHOR¹⁰, -SO₃H, -SO₂H, -B(OH)₂,

-CONHS(=O)_x(=NR¹³)_yR¹⁰, -CONHS(=O)_x(=NR¹³)_yNR¹¹R¹², -S(=O)_x(=NR¹³)_yNHCOR¹⁰,

-S(=O)_x(=NR¹³)_yNHR¹¹,  and

,

Y having one or more hydrogen atoms optionally replaced by deuterium;

25

R² is selected from H and C₁₋₆-alkyl,

R² having one or more hydrogen atoms optionally replaced by deuterium;

5 R¹⁰ is selected from C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

10 R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

R¹¹, R¹², R²¹, R²² are independently selected from H, C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

15 wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

20 R¹¹ and/or R¹² and/or R²¹ and/or R²² having one or more hydrogen atoms optionally replaced by deuterium;

or R¹¹ and R¹², R²¹ and R²², respectively, when taken together with the nitrogen to which they are attached complete a 3- to 6-membered cycle containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N; and

25 wherein this cycle is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

30 R¹¹ and/or R¹² and/or R²¹ and/or R²² having one or more hydrogen atoms optionally replaced by deuterium;

R¹³, R²³ are independently selected from H, -CN, -NO₂, C₁₋₆-alkyl, -CO-O-C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

35 wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-

membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

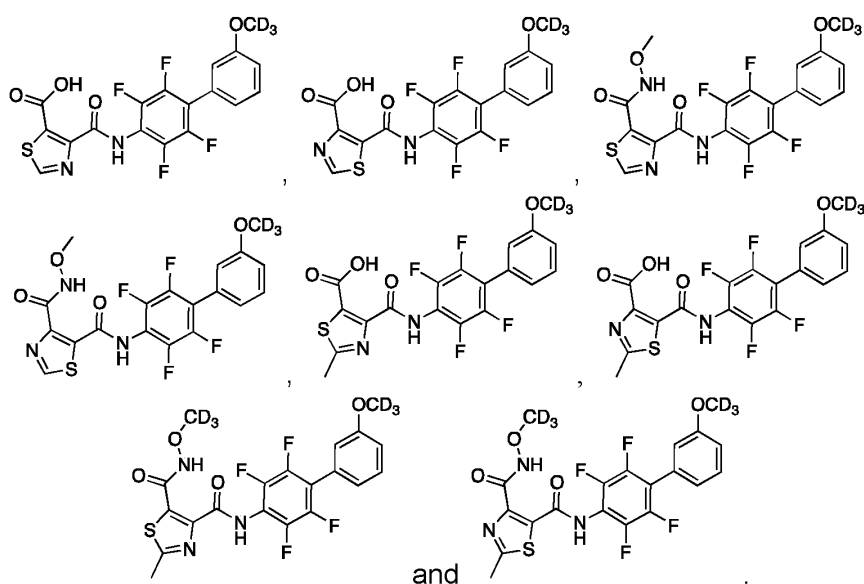
5 R¹³ and/or R²³ having one or more hydrogen atoms optionally replaced by deuterium;

x, y are independently selected from 0 to 2;

with the proviso that the sum of integer m and n for the residue linked to the same sulfur atom is independently selected from 0 to 2;

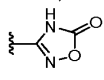
10 with the proviso that the sum of integer x and y for the residue linked to the same sulfur atom is independently selected from 1 or 2;

and with the proviso, that the following structures are excluded:



15

2. A compound of Formula (I) according to embodiment 1, or a solvate or pharmaceutically acceptable salt thereof, wherein

20 Y is selected from -CO₂H, -CO₂R¹⁰, -CONR¹¹R¹², -CONH-CN, -CONHOR¹⁰, -CONHS(=O)_x(=NR¹³)_yR¹⁰, -CONHS(=O)_y(=NR¹³)_yNR¹¹R¹²,  or , preferably selected from -CONR¹¹R¹², -CONH-CN, -CONHOR¹⁰, -CONHS(=O)_x(=NR¹³)_yR¹⁰, -CONHS(=O)_y(=NR¹³)_yNR¹¹R¹²,  or ; R¹⁰ is selected from C₁₋₄-alkyl, cyclopropyl or oxetan-3-yl,

wherein alkyl, cyclopropyl or oxetan-3-yl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

R¹¹ and R¹² are independently selected from H or C₁₋₃-alkyl,

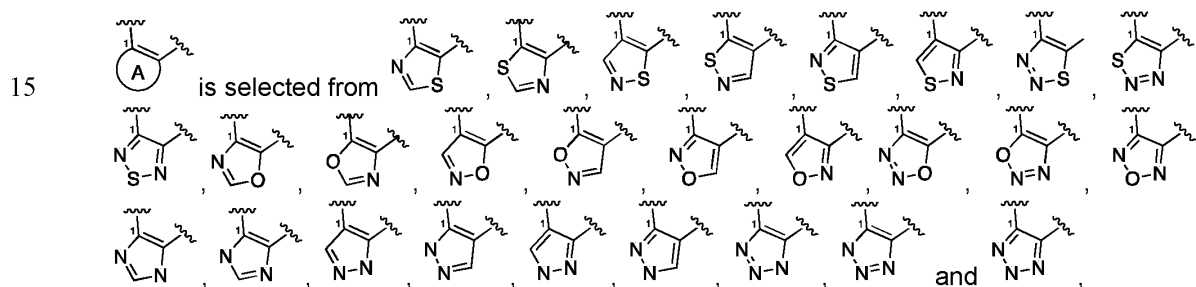
5 wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium;

R¹³ is selected from H, -CN and C₁₋₃-alkyl,

10 wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹³ having one or more hydrogen atoms optionally replaced by deuterium; and

x is 1 and y is 1 or x is 2 and y is 0.

3. A compound of Formula (I) according to embodiment 1 or 2, wherein



20 said A is unsubstituted or substituted with one substituent independently selected from the group consisting of H, F, Cl, Br, -CN, -OH, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, fluoro-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, CO₂R¹¹, NR¹¹R¹² and CONR¹¹R¹²,

ring A or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

R² is H;

R¹¹ and R¹² are independently selected from H, C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

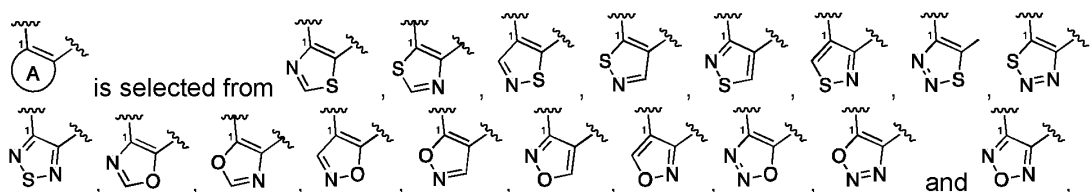
25 wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently
30 selected from N, O, or S,

or R¹¹ and R¹², when taken together with the nitrogen to which they are attached complete a 3- to 6-membered cycle containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N; and

- 5 wherein this cycle is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium.

- 10 4. A compound of Formula (I) according to any of embodiments 1 to 3, wherein



- 15 said A is unsubstituted or substituted with one substituent independently selected from the group consisting of D, F, Cl, -CN, -OH, Me, Et, -OMe, OEt, CHF₂, CF₃, -OCHF₂, -OCF₃, CO₂Me, NH₂, NHMe, NMe₂, NHCOMe, CONH₂, CONHMe and CONMe₂,

ring A or its substituents having one or more hydrogen atoms optionally replaced by deuterium; and R² is H.

- 20 5. A compound of Formula (I) according to any of embodiments 1 to 4, wherein

B is phenyl,

wherein phenyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of D, F, Cl, -CN, Me, CD₃, -OMe, -OCD₃, CHF₂ and CF₃; and wherein the residue -NR² on ring B is in a 1,4-orientation with respect to ring C.

- 25 6. A compound of Formula (I) according to any of embodiments 1 to 5, wherein

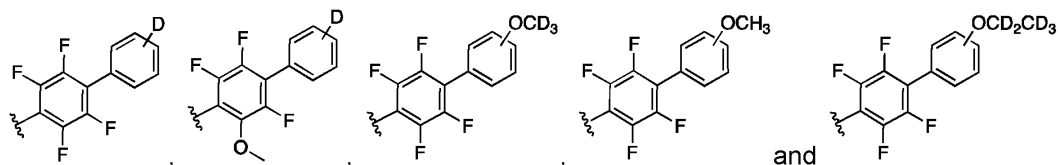
C is phenyl,

wherein phenyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of D, F, Cl, -CN, Me, CD₃, CHF₂, CF₃, -OMe, -OCD₃, -OCHF₂ and -OCF₃; and

- 30 X is selected from D, F, Cl, -CN, Me, CD₃, CHF₂, CF₃, Et, CD₂CD₃, -OMe, -OCD₃, -OCHF₂, -OCF₃, -OEt, -OCD₂CD₃, -OCH₂CH₂CH₃, -OCD₂CD₂CD₃, -OCH₂CH₂CH₂CH₃ and -OCD₂CD₂CD₂CD₃.

7. A compound of Formula (I) according to any of embodiments 1 to 6, wherein

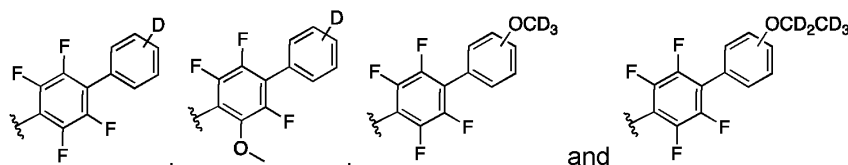
$\text{B}-\text{C}-\text{X}$ is selected from



5 wherein ring C is optionally substituted with 1 to 4 substituents independently selected from D or F.

8. A compound of Formula (I) according to any of embodiments 1 to 6, wherein

$\text{B}-\text{C}-\text{X}$ is selected from

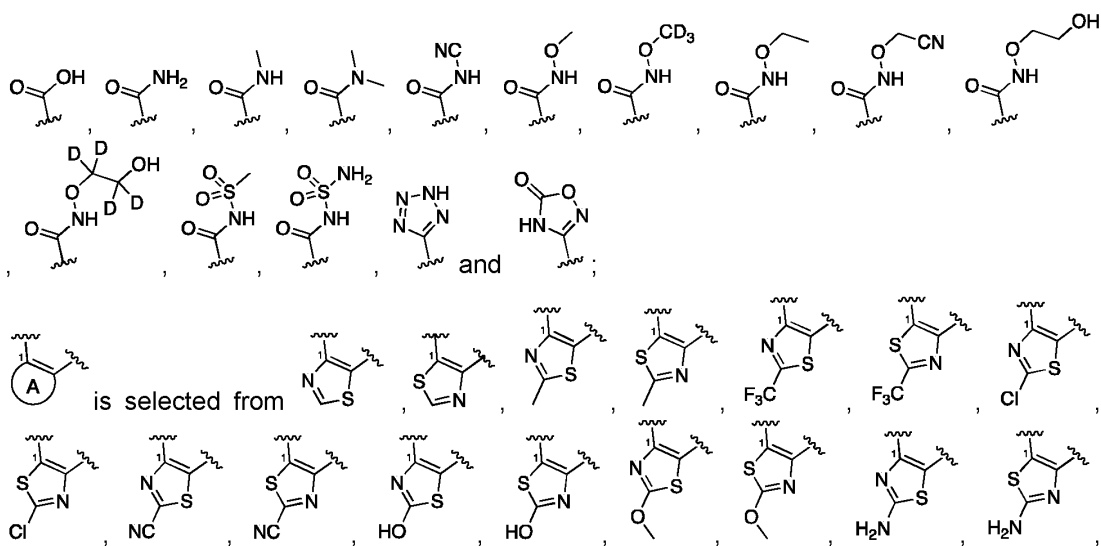


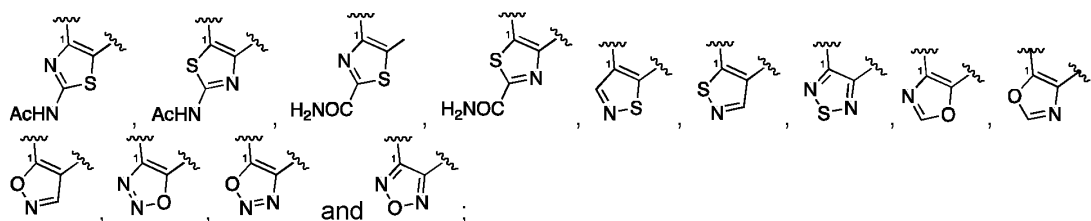
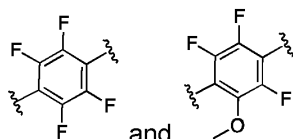
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wherein ring C is optionally substituted with 1 to 4 substituents independently selected from D or F.

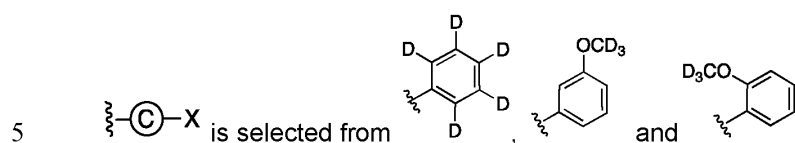
9. A compound of Formula (I) according to any of embodiments 1 to 8, wherein

15 Y is selected from



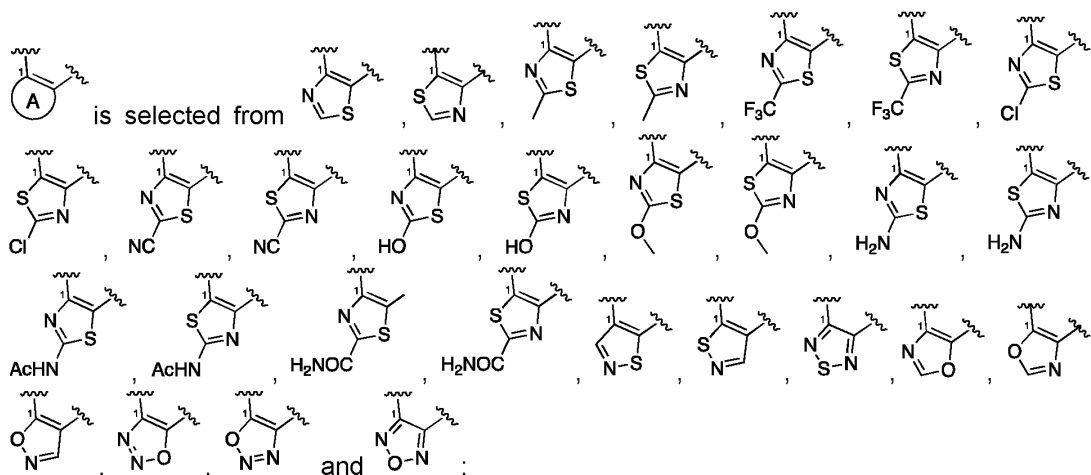
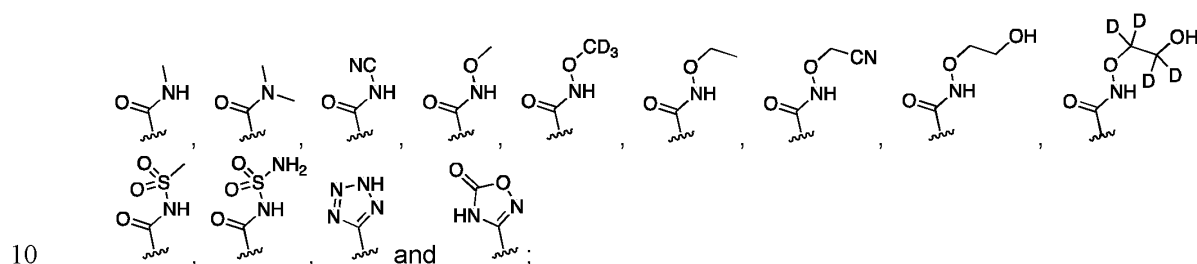
 R^2 is H ;

B is selected from F and O ; and

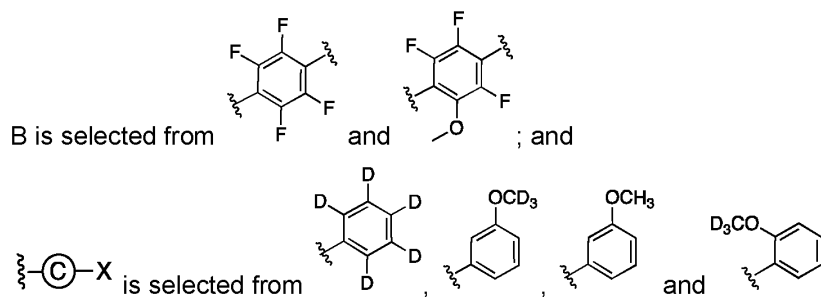


10. A compound of Formula (I) according to any of embodiments 1 to 8, wherein

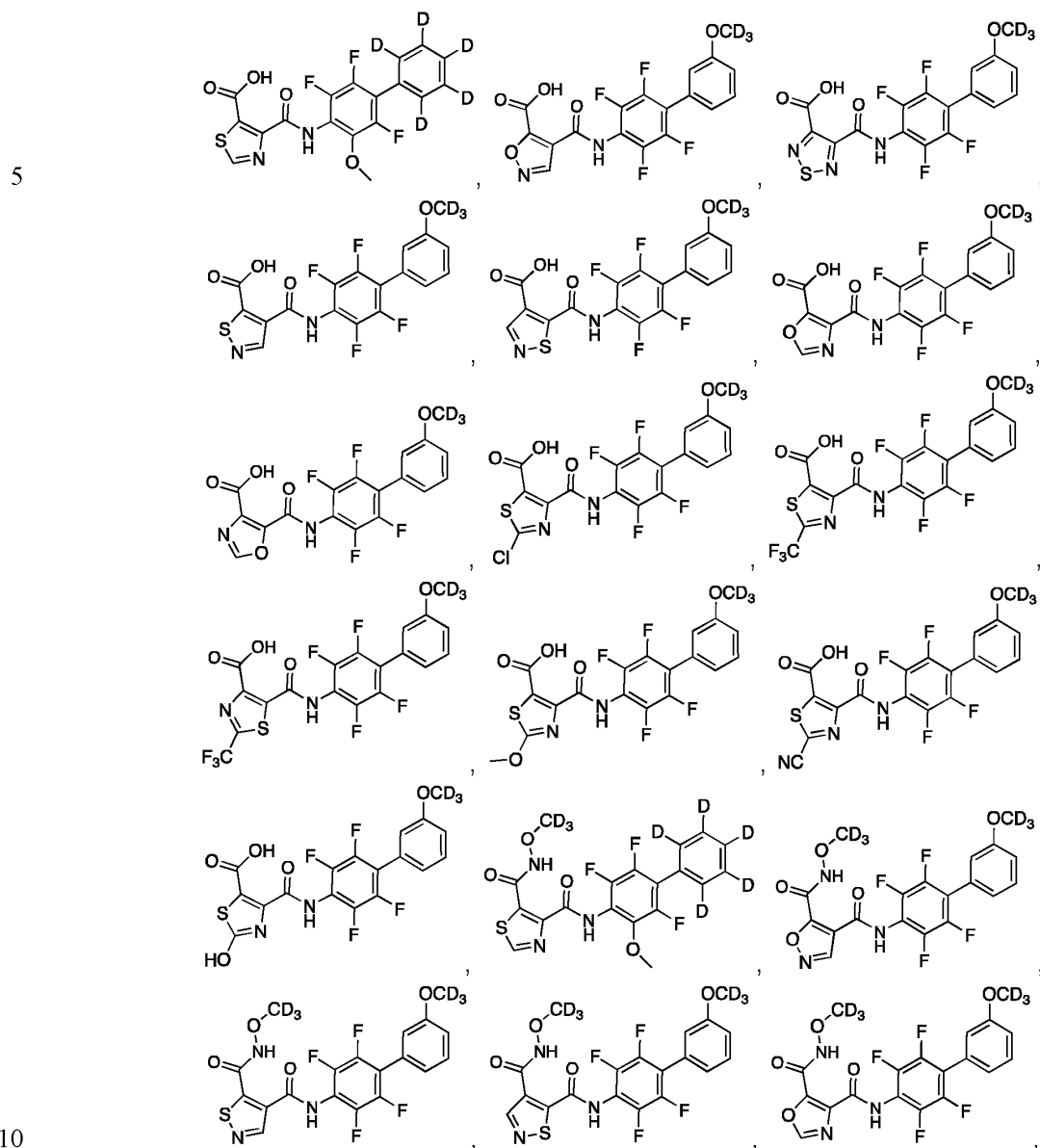
Y is selected from

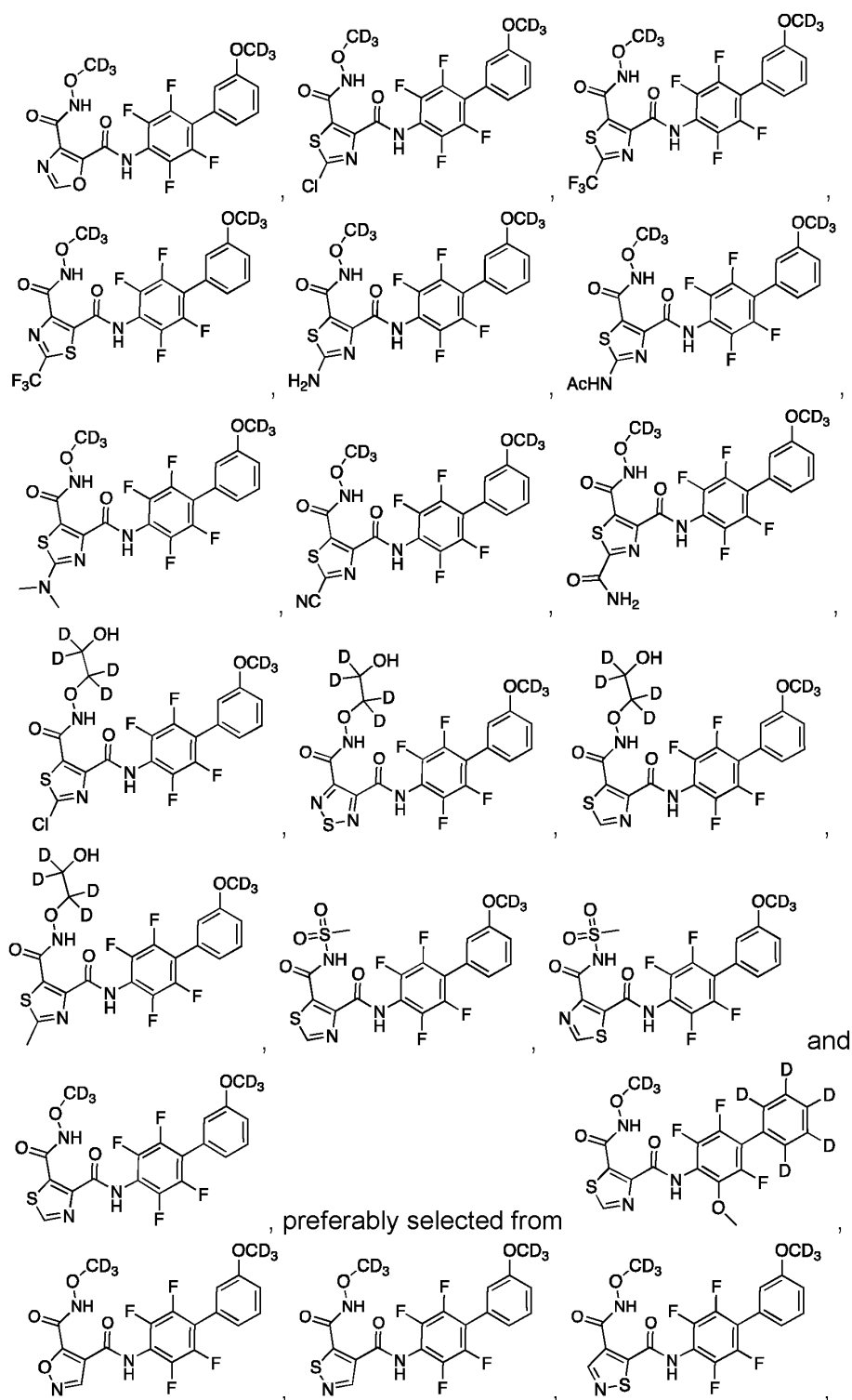


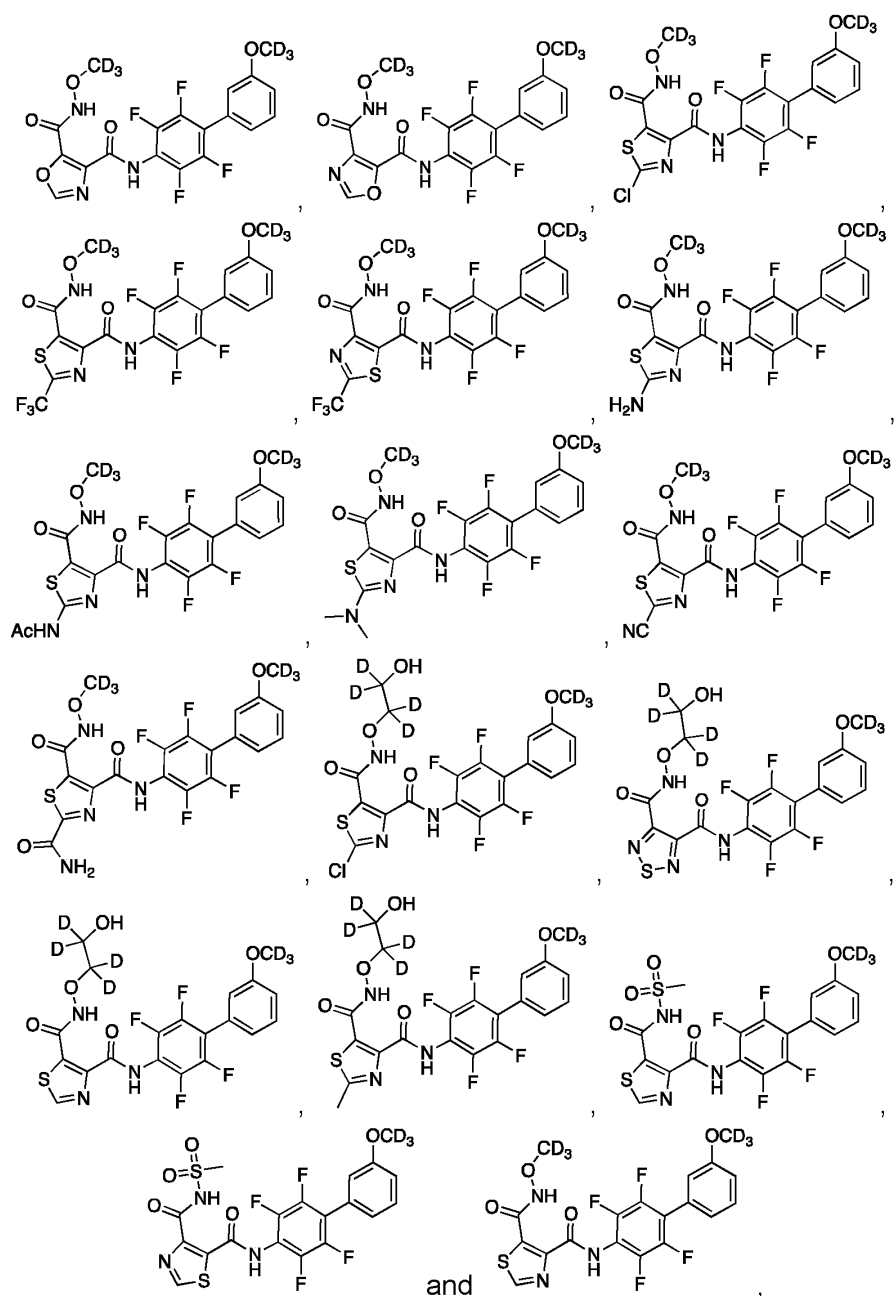
15 R^2 is H;

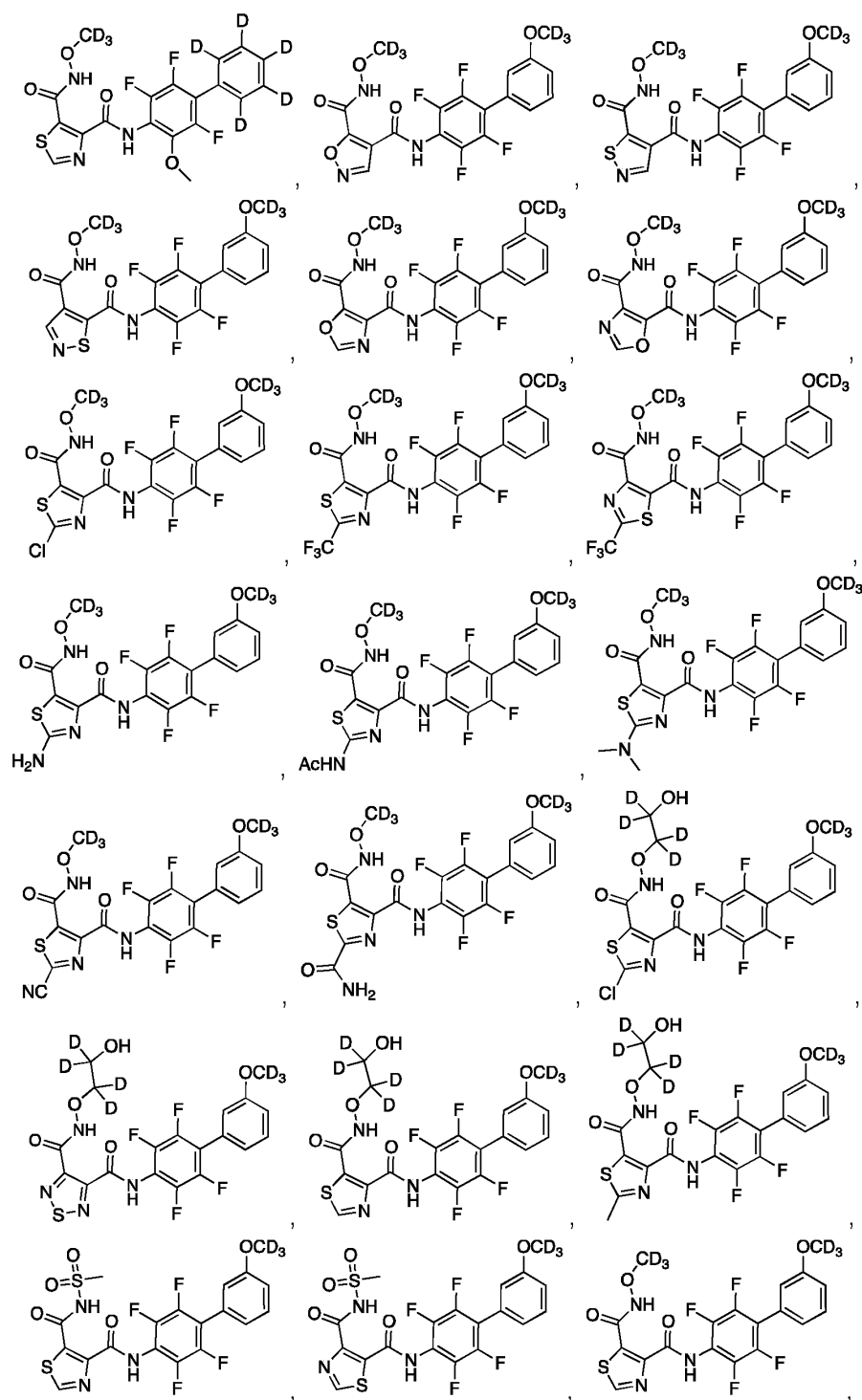


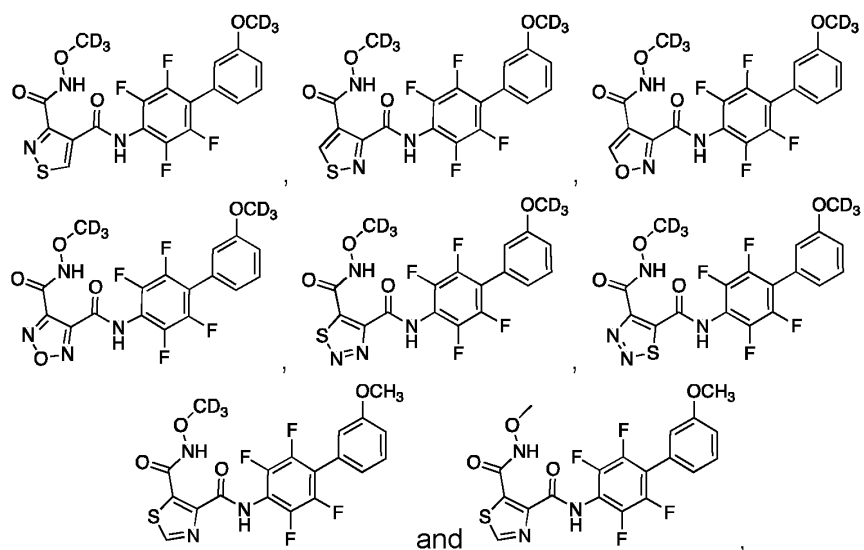
11. A compound of Formula (I) according to any of embodiments 1 to 10, which is selected from











or a solvate or pharmaceutically acceptable salt thereof.

5

13. A compound according to any one of the preceding embodiments for the use as a medicament.

14. A compound according to any one of embodiments 1 to 12 for use in the prophylaxis and/or treatment of diseases, disorders, therapeutic indications or medical conditions amenable for treatment with DHODH inhibitors.

15. A compound for use according to embodiment 14 wherein the disease, disorder, therapeutic indication or medical condition is selected from the group comprising rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and pneumocystis carinii, fibrosis, uveitis, rhinitis, asthma, transplantation or arthropathy.

16. A compound for use according to embodiment 15 wherein the disease, disorder or therapeutic indication is selected from the group comprising graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, respiratory syncytial virus, influenza, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis.

25

17. A compound for use according to embodiment 15 wherein the disease, disorder or therapeutic indication is selected from the group comprising graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, influenza, ulcerative colitis, Crohn's disease,
5 primary sclerosing cholangitis and psoriasis.

18. A compound for use according to embodiment 15 wherein the disease, disorder or therapeutic indication caused by malignant cell proliferation due to isocitrate dehydrogenase (NADP⁺) 1 (IDH1) mutation(s).

10

19. A pharmaceutical composition comprising a compound according to any one of embodiments 1 to 12 and a pharmaceutically acceptable carrier or excipient.

15

20. A pharmaceutical composition of embodiment 19, further comprising one or more additional therapeutic agents selected from anti-inflammatory agents, anti-viral agents, anti-cancer agents, immunosuppressive and/or immunomodulatory agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics and suitable mixtures thereof.

20

21. A pharmaceutical composition of embodiment 19, further comprising one or more additional therapeutic agents selected from anti-inflammatory agents, anti-viral agents, immunosuppressive and/or immunomodulatory agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics and suitable mixtures thereof.

EXPERIMENTAL PART

25

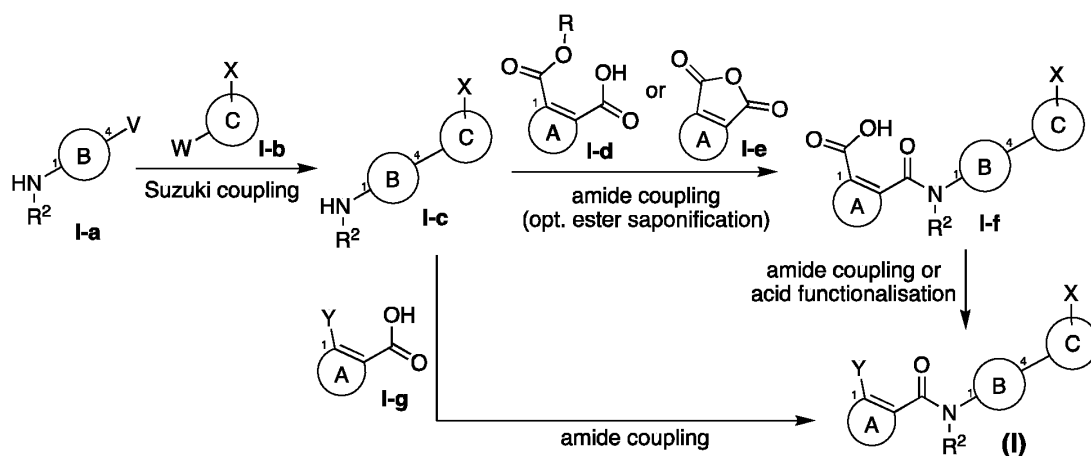
The carboxylic acid containing intermediates of the present invention can be prepared as outlined in WO2003/006425 and WO2004/056797 (and references cited therein). By using appropriate deuterated building blocks or via hydrogen-deuterium exchange (e.g. *Synthesis* 2019;51:1319 or *Angew. Chem. Int. Ed.* 2018;57:3022) the deuterated intermediates can be prepared.

30

The compounds of the present invention can be prepared by a combination of methods known in the art including the procedures described in Schemes I below. The synthetic route starts with the Suzuki coupling (V = boronic acid or boronic ester, W = Br, I or OM_s; or opposite functionalization) of B-ring I-a with C-ring I-b or by using another C-C-coupling procedure (see e.g. in WO2023/118576). The amino group of I-c is reacted with carboxylic acid I-d or anhydride I-e via an amide coupling (and optionally saponification of the ester in case of R = alkyl to furnish carboxylic acid I-f. It may be necessary to separate the two regioisomers have been formed (or after functionalization towards new residue Y). Finally, the carboxylic acid is transformed to residue Y in Formula (I), e.g. by coupling an alkoxyamine or alkylsulfonamide. Compounds of

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Formula (I) can also directly be prepared by amide coupling for suitable functionalized A-ring carboxylic acid I-g with amine I-c.



Scheme I: Synthesis of compounds of the present invention.

5

Abbreviations

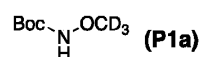
Ac	acetyl
aq.	aqueous
dba	dibenzylideneacetone
DCM	dichloromethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EA	ethyl acetate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
NMP	<i>N</i> -methyl-2-pyrrolidone
PE	petroleum ether
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl
prep.	preparative
rt	room temperature (20±4°C)
TBS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid

25

Experimental Section

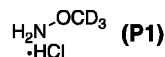
Preparative Example P1:

Step 1: *tert*-Butyl (methoxy-*d*3)carbamate (P1a)



To a solution of *tert*-butyl hydroxycarbamate (10 g) in MeCN (20 mL) was added K₂CO₃ (31 g) and CD₃I (4.7 mL). The mixture was stirred at 65°C for overnight, cooled, filtered, concentrated and purified by FCC (PE:EA = 20:1) to give compound **P1a** as a colorless oil. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 7.23 (s, 1H), 1.49 (s, 9H). LCMS (ESI): *m/z* 173.1 (M+Na)⁺.

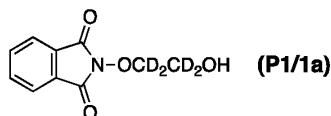
5 Step 2: O-(Methyl-*d*₃)hydroxylamine hydrochloride (**P1**)



10 To a solution of compound **P1a** (7.0 g) in 1,4 dioxane (15 mL) was added 4M HCl in dioxane (15 mL) and the mixture was stirred at rt for 16 h. The mixture was filtered and the filter cake was washed with 1,4 dioxane (15 mL) and then with PE twice again. The solid was dried in vacuum to afford **P1** as a white solid. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.03 (s, 3H). LCMS (ESI): *m/z* 51.1 (M-Cl)⁺.

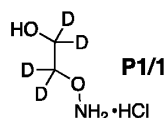
Preparative Example P1/1:

Step 1: 2-(2-Hydroxyethoxy-1,1,2,2-*d*₄)isoindoline-1,3-dione (**P1/1a**)



15 By reacting 2-hydroxyisoindoline-1,3-dione with 2-bromoethan-1,1,2,2-*d*₄-1-ol in MeCN and NEt₃ similar as described for the undeuterated bromide in WO2014/081025 the intermediate **P1/1a** can be prepared.

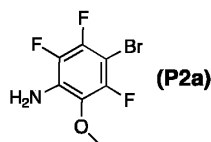
Step 2: 2-(Aminooxy)ethan-1,1,2,2-*d*₄-1-ol (**P1/1**)



20 By reacting intermediate **P1/1a** with hydrazine in ethanol similar as described for the undeuterated alcohol in *J. Chem. Soc. Perkin Trans. 1* 1987:2829, then slurrying the free amine in 4M HCl in 1,4-dioxane and finally evaporating the solvent the building block **P1/1** can be prepared.

25 **Preparative Example P2:**

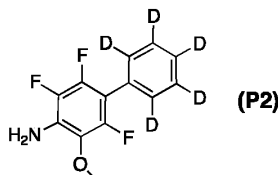
Step 1: 4-Bromo-2,3,5-trifluoro-6-methoxyaniline (**P2a**)



30 To a solution of 2,3,5-trifluoro-6-methoxyaniline (1.0 g) in MeOH (20 mL) was added bromine (988 mg) at 0°C. The mixture was stirred at 0°C for 30 min, quenched with saturated aq. NaHCO₃, extracted with EA (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by Botage Isolera One combiflash

chromatography (SEPAFLASH, 40-63 Å, 80 g silica gel column @60 mL/min, eluting with 0 to 33% EA in PE for 12 min to give intermediate **P2a** as a yellow solid. LCMS (ESI): m/z 256.1 (M+H)⁺.

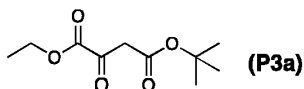
Step 2: 2,3,6-Trifluoro-5-methoxy-[1,1'-biphenyl]-2',3',4',5',6'-d5-4-amine (**P2**)



To a solution of intermediate **P2a** (700 mg) in 1,4-dioxane (10 mL) and H₂O (1 mL) was added (phenyl-*d*5)boronic acid (523 mg), Cs₂CO₃ (2.68 g) and Pd(dppf)Cl₂ (70 mg). The mixture was stirred at 90°C under N₂ for 16 h, cooled to rt, diluted with water and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated and purified by Botage Isolera One combiflash chromatography (SEPAFLASH, 40-63 Å, 40 g silica gel column @60 mL/min, eluting with 0 to 33% EA in PE for 25 min to give compound **P2** as a yellow solid. LCMS (ESI): m/z 259.3 (M+H)⁺.

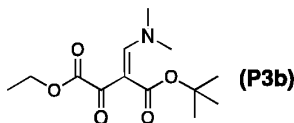
Preparative Example P3:

Step 1: 4-(*tert*-Butyl) 1-ethyl 2-oxosuccinate (**P3a**)



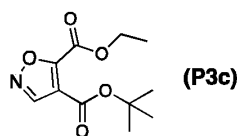
To a solution of NaH (6.58 g, 60wt%) in dry THF (300 mL) was added *tert*-butyl acetate (15.9 g) at 65°C under N₂ atmosphere. The mixture was stirred for 1 h at this temperature, then diethyl oxalate (20 g) was added and the mixture was heated to 65°C for 3 h, cooled to 0°C and adjusted carefully to pH to 3 with concentrated H₂SO₄ at 0°C, concentrated under reduced pressure to remove the THF and diluted with EA (300 mL), washed by brine (3 x 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford compound **P3a** as a colorless oil, which was used for the next step without further purification.

Step 2: 1-(*tert*-Butyl) 4-ethyl (Z)-2-((dimethylamino)methylene)-3-oxosuccinate (**P3b**)



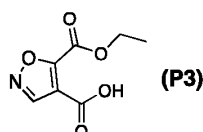
To the solution of compound **P3a** (25 g, crude) and 1,2-dichloroethane (300 mL) was added dimethylformamid-dimethylacetal (40 g) and the mixture was stirred for 4 h at rt and concentrated under reduced pressure to afford compound **P3b** as a yellow oil, which was used for the next step without purification.

Step 3: 4-(*tert*-Butyl) 5-ethyl isoxazole-4,5-dicarboxylate (**P3c**)



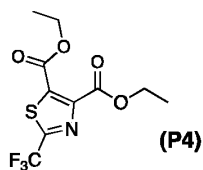
To a solution of compound **P3b** (30 g, crude) in MeOH (300 mL) was added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (14.3 g) at rt. The mixture was stirred for 2 h at 80°C , cooled to rt, concentrated and diluted with EA (300 mL) and filtered. The filter cake was washed by EA (3 x 50 mL) and the filtrate was concentrated and purified by Botage Isolera One combiflash chromatography (SEPAFLASH, 40-63 Å, 330 g silica gel column @100 mL/min, eluting with 0 to 10% EA in PE for 30 min to give compound **P3c** as a colorless oil. LCMS (ESI): m/z 186.0 ($\text{M}^{-1}\text{Bu}+\text{H}$)⁺.

Step 4: 5-(Ethoxycarbonyl)isoxazole-4-carboxylic acid (**P3**)



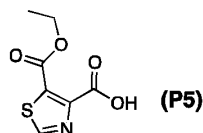
Compound **P3c** (500 mg) and TFA (5 mL) was stirred for 1 h at rt and concentrated under reduced pressure to afford compound **P3** as a yellow solid, which was used for the next step without purification. LCMS (ESI): m/z 186.3 ($\text{M}+\text{H}$)⁺.

Preparative Example P4: Diethyl 2-(trifluoromethyl)thiazole-4,5-dicarboxylate (**P4**)



A solution of 2,2,2-trifluoroacetamide (4 g) in ethanol (30 mL) was cool it to -10°C under nitrogen. A solution of diethyl 2-chloro-3-oxosuccinate (8.3 g) and TEA (3.5 mL) in ethanol (20 mL) was added and the mixture was allowed to reach rt for 30 min and then heated to 95°C overnight. The mixture was concentrated, diluted with water and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 , filtered, concentrated and purified by Botage Isolera One combiflash chromatography (SEPAFLASH, 40-63 Å, 40 g silica gel column @100 mL/min, eluting with 0 to 19% EA in PE for 25 min to give compound **P4** as a white solid. LCMS (ESI): m/z 298.1 ($\text{M}+\text{H}$)⁺.

Preparative Example P5: 5-(Ethoxycarbonyl)thiazole-4-carboxylic acid (**P5**)

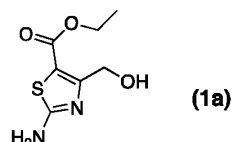


To a solution of intermediate **1e** (20 g) in MeOH (500 mL) was added Pd/C (10 g) and then the mixture was stirred at rt for 2 h in a hydrogen environment under a balloon, filtered, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 120 g Flash 50-

100 mL/min 200 psi (0.1% TFA in water, 10 to 100% ACN) to afford compound **P5** as a white solid. LCMS (ESI): m/z 202.1 (M+H)⁺.

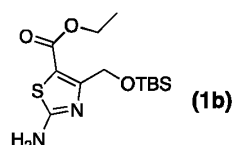
Example 1:

5 Step 1: Ethyl 2-amino-4-(hydroxymethyl)thiazole-5-carboxylate (**1a**)



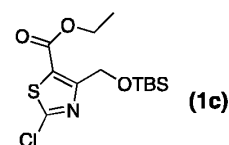
10 To a solution of 3-chlorofuran-2,4(3*H*,5*H*)-dione (25 g) in EtOH (100 mL) was added thiourea (17 g) and the mixture was stirred for 4 h at 80°C. Solvent was removed and the residue was dissolved in water with HCl (1M). The aqueous solution was basified with aq. Na₂CO₃ solution, the solid formed was filtered, washed with water and dried in vacuo to afford compound **1a** as a yellow solid. LCMS (ESI): m/z 203.1 (M+H)⁺.

Step 2: Ethyl 2-amino-4-(((*tert*-butyldimethylsilyl)oxy)methyl)thiazole-5-carboxylate (**1b**)



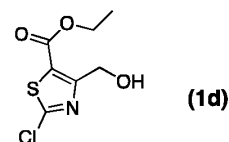
15 To a solution of compound **1a** (29 g) and imidazole (98 g) in CH₂Cl₂ (400 mL) was added TBSCl (43 g) and the mixture was stirred at rt for 2 h. The mixture was diluted with 0.1N aq. HCl and extracted with DCM (3 x 200 mL). The combined organic layer was washed with brine (200 mL), dried over Na₂SO₄, filtered, concentrated and purified by Botage Isolera One combiflash chromatography (SEPAFLASH, 40-63 Å, 120 g silica gel column @100 mL/min, eluting with 0 to 50% EE in PE for 25 min to give compound **1b** as a yellow solid. LCMS (ESI): m/z 317.3 (M+H)⁺.

20 Step 3: Ethyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-chlorothiazole-5-carboxylate (**1c**)



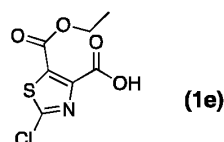
25 To a solution of compound **1b** (30.1 g, 95.3 mmol) and *tert*-butyl nitrite (14.7 g) in ACN (300 mL) was added CuCl₂ (19.1 g, 143 mmol). The mixture was heated to 80°C for 3 h, cooled to rt, concentrated under reduced pressure, diluted with water and extracted with EA (3 x 300 mL). The combined organic layer was washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated to afford compound **1c** as a white solid. LCMS (ESI): m/z 336.2 (M+H)⁺.

Step 4: Ethyl 2-chloro-4-(hydroxymethyl)thiazole-5-carboxylate (**1d**)



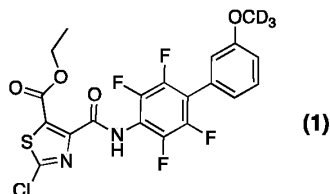
Compound **1c** (26.7 g) was dissolved in HCl in 1,4-dioxane (4M, 20 mL) and the solution was stirred at rt for 2 h, diluted with water and extracted with EA (3 x 200 mL). The combined organic layer was washed with brine (200 mL), dried over Na₂SO₄, filtered, concentrated and purified by Botage Isolera One combiflash chromatography (SEPAFLASH, 40-63 Å, 330 g silica gel column @100 mL/min, eluting with 0 to 33% EA in PE for 25 min to give compound **1d** as a yellow solid. LCMS (ESI): m/z 222.2 (M+H)⁺.

Step 5: 2-Chloro-5-(ethoxycarbonyl)thiazole-4-carboxylic acid (**1e**)



To a solution of compound **1d** (15.9 g) in acetone (200 mL) was added CrO₃ (14.4 g) and 20%w/w H₂SO₄ (30 mL). The mixture was stirred at 0°C for 2 h. Then isopropanol (10 mL) was added and the mixture was diluted with water and concentrated to remove the acetone. The mixture was extracted with EA (3 x 200 mL). The combined organic layer was washed with brine (200 mL), dried over Na₂SO₄, filtered, concentrated and purified by Botage Isolera One combiflash chromatography (SEPAFLASH, 40-63 Å, 330 g silica gel column @100 mL/min, eluting with 0 to 10% MeOH in CH₂Cl₂ for 25 min to afford compound **1e** as a dark green solid. LCMS (ESI): m/z 236.2 (M+H)⁺.

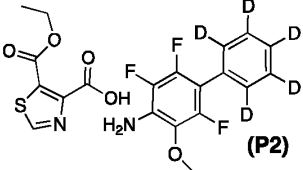
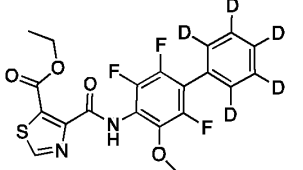
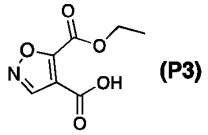
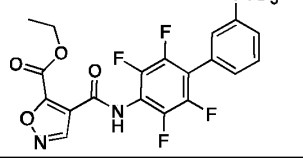
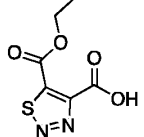
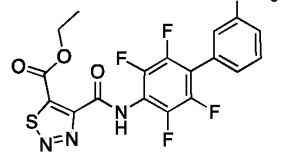
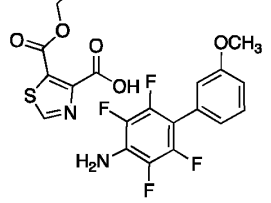
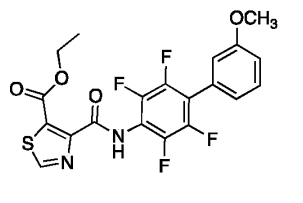
Step 5: Ethyl 2-chloro-4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylate (**1**)



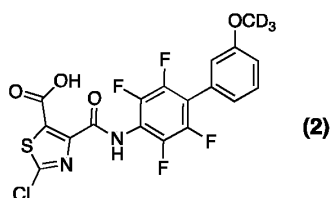
To a solution of compound **1e** (5 g) in dry CH₂Cl₂ (50 mL) were added SOCl₂ (5.1 g) at 0°C and then the mixture was stirred at 0°C for 2 h and concentrated under vacuum to afford the crude acid chloride intermediate. To a solution of 2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-amine (5.8 g) in dry THF (50 mL) was added NaH (4.1 g, 60%wt) at 0°C. The mixture was stirred at 0°C for 10 minutes, then the acid chloride intermediate was added at 0°C. The mixture was stirred at rt for 16 h, quenched with saturated aq. NH₄Cl and extracted with EA (3 x 50 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by reversed-phase flash chromatography (C18) (0.1% TFA in water, 10 to 100% MeCN) to give compound **1** as a white solid. LCMS (ESI): m/z 493.1 (M+H)⁺.

Example 1/1 to 1/4:

The following Examples were prepared similar as described for Example 1 above using the appropriate building block(s) as shown below.

#	building block(s)	structure	analytical data
1/1	 (P2)		LCMS (ESI): m/z 442.0 (M+H) ⁺
1/2	 (P3)		LCMS (ESI): m/z 442.2 (M+H) ⁺
1/3	 (P3)		LCMS (ESI): m/z 459.0 (M+H) ⁺
1/4	 (P3)		LCMS (ESI): m/z 455.0 (M+H) ⁺

Example 2: 2-Chloro-4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylic acid (**2**)

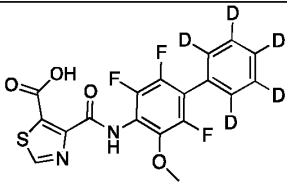
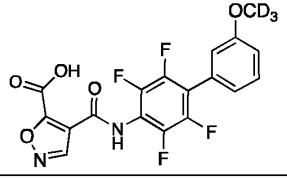
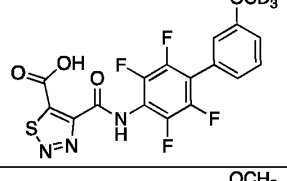
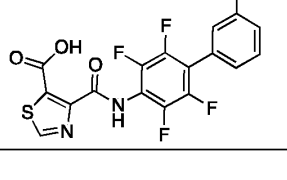


5 To a solution of compound **1** (5.6 g) in EtOH (50 mL) and THF (50 mL) was added 2N NaOH (50 mL) at 0°C. The mixture was stirred at rt for 8 h, adjusted to pH = 5-6 by 2N HCl and then purified by combiflash reversed-phase chromatography (C18) Boston ODS 330 g Flash 35-50 mL/min 200 psi (0.1% TFA in water, 10 to 100% ACN) to give compound **2** as a white solid. ¹H-NMR (400 MHz, MeOD-*d*4) δ 7.64 (dd, J = 7.6, 9.0 Hz, 1H), 7.06-7.04 (m, 3H). LCMS (ESI): m/z 464.0 (M+H)⁺.

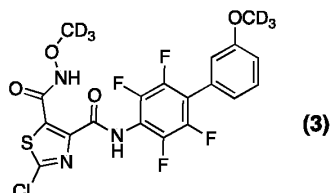
10

Example 2/1 to 2/4:

The following Examples were prepared similar as described for Example 2 above using the appropriate building block(s) as shown below.

#	building block(s)	structure	analytical data
2/1	Example 1/1		$^1\text{H-NMR}$ (400 MHz, $\text{MeOD-}d_4$) δ 8.92 (s, 1H), 3.94 (s, 3H). LCMS (ESI): m/z 414.0 ($\text{M}+\text{H}$) $^+$
2/2	Example 1/2		$^1\text{H-NMR}$ (400 MHz, $\text{MeOD-}d_4$) δ 8.98 (s, 1H), 7.43 (dd, $J = 7.2, 8.4$ Hz, 1H), 7.07-7.04 (m, 3H). LCMS (ESI): m/z 414.1 ($\text{M}+\text{H}$) $^+$
2/3	Example 1/3		
2/4	Example 1/4		$^1\text{H-NMR}$ (400 MHz, $\text{MeOD-}d_4$) δ 8.93 (s, 1H), 7.45-7.41 (m, 1H), 7.07-7.03 (m, 3H). LCMS (ESI): m/z 427.0 ($\text{M}+\text{H}$) $^+$

Example 3: 2-Chloro- N^5 -(methoxy- d_3)- N^4 -(2,3,5,6-tetrafluoro-3'-(methoxy- d_3)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**3**)



- 5 To a solution of compound **2** (4.5 g) and building block **P1** (1.7 g) in THF (10 mL) and NMP (10 mL) was added EDCI (3.7 g) in three portions. The mixture was stirred at rt for 4 h, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 330 g Flash 35-50 mL/min 200 psi (0.1% TFA in water, 10 to 100% ACN) to afford compound **3** as a white solid.
- 10 $^1\text{H-NMR}$ (400 MHz, $\text{MeOD-}d_4$) δ 7.42 (dd, $J = 7.6, 9.2$ Hz, 1H), 7.06-7.03 (m, 3H). LCMS (ESI): m/z 496.2 ($\text{M}+\text{H}$) $^+$.

Example 3/1 to 3/15:

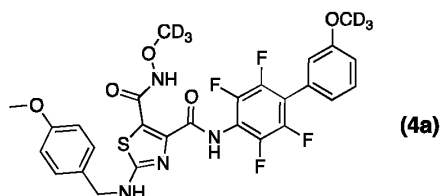
The following Examples were prepared similar as described for Example 3 above using the appropriate building block(s) as shown below.

#	building block(s)	structure	analytical data
3/1	Example 2/1		$^1\text{H-NMR}$ (500 MHz, $\text{MeOD-}d_4$) δ 9.19 (s, 1H), 3.96 (s, 3H). LCMS (ESI): m/z 446.2 ($\text{M}+\text{H}$) $^+$
3/2	Example 2/2		$^1\text{H-NMR}$ (400 MHz, $\text{MeOD-}d_4$) δ 9.02 (s, 1H), 7.43 (dd, J = 7.6, 8.8 Hz, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 446.3 ($\text{M}+\text{H}$) $^+$
3/3	Example 11/2		$^1\text{H-NMR}$ (400 MHz, $\text{MeOD-}d_4$) δ 8.90 (s, 1H), 7.42 (dd, J = 7.6, 8.8 Hz, 1H), 7.06-7.04 (m, 3H). LCMS (ESI): m/z 462.0 ($\text{M}+\text{H}$) $^+$
3/4	Example 11/3		$^1\text{H-NMR}$ (400 MHz, $\text{MeOD-}d_4$) δ 8.86 (s, 1H), 7.41 (dd, J = 7.2, 9.2 Hz, 1H), 7.05-7.03 (m, 3H). LCMS (ESI): m/z 462.0 ($\text{M}+\text{H}$) $^+$
3/5	Example 11/4		$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 12.70 (s, 1H), 11.56 (s, 1H), 8.90 (s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.16-7.10 (m, 3H). LCMS (ESI): m/z 446.1 ($\text{M}+\text{H}$) $^+$
3/6	Example 11/5		$^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 12.94 (s, 1H), 12.72 (s, 1H), 8.89 (s, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.14-7.09 (m, 3H). LCMS (ESI): m/z 446.1 ($\text{M}+\text{H}$) $^+$
3/7	Example 11/6		$^1\text{H-NMR}$ (500 MHz, $\text{MeOD-}d_4$) δ 7.43 (t, J = 8.3 Hz, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 530.1 ($\text{M}+\text{H}$) $^+$
3/8	Example 11/7		$^1\text{H-NMR}$ (500 MHz, $\text{MeOD-}d_4$) δ 7.42 (dd, J = 7.3, 9.3 Hz, 1H), 7.05-7.04 (m, 3H). LCMS (ESI): m/z 530.1 ($\text{M}+\text{H}$) $^+$

#	building block(s)	structure	analytical data
3/9	Example 21		¹ H-NMR (500 MHz, DMSO- <i>d</i> ₆) δ 12.05 (s, 1H), 11.28 (s, 1H), 9.69 (s, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.14-7.09 (m, 3H). LCMS (ESI): m/z 462.1 (M+H) ⁺
3/10	Example 21		¹ H-NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.61 (s, 1H), 11.01 (s, 1H), 9.39 (s, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.15-7.09 (m, s 3H). LCMS (ESI): m/z 462.1 (M+H) ⁺
3/11	Example 11/8		¹ H-NMR (400 MHz, MeOD- <i>d</i> ₄) δ 9.43 (s, 1H), 7.44 (dd, J = 7.6, 8.4 Hz, 1H), 7.08-7.05 (m, 3H). LCMS (ESI): m/z 446.1 (M+H) ⁺
3/12	Example 23		¹ H-NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.45-7.41 (m, 1H), 7.07-7.04 (m, 3H). LCMS (ESI): m/z 447.1 (M+H) ⁺
3/13	Example 2/3		¹ H-NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.44 (dd, J = 7.6, 8.4 Hz, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 463.0 (M+H) ⁺
3/14			¹ H-NMR (400 MHz, MeOD- <i>d</i> ₄) δ 9.01 (s, 1H), 7.46-7.41 (m, 1H), 7.07-7.05 (m, 3H), 3.85 (s, 1H). LCMS (ESI): m/z 459.1 (M+H) ⁺
3/15			¹ H-NMR (400 MHz, MeOD- <i>d</i> ₄) δ 8.98 (s, 1H), 7.46-7.41 (m, 1H), 7.07-7.05 (m, 3H), 3.85 (s, 3H), 3.79 (s, 3H). LCMS (ESI): m/z 456.1 (M+H) ⁺

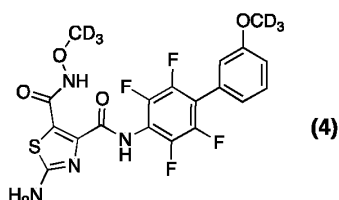
Example 4:

Step 1: *N*⁵-(Methoxy-*d*₃)-2-((4-methoxybenzyl)amino)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*₃)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**4a**)



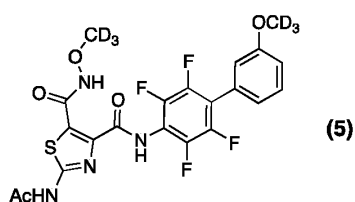
To a solution of compound **3** (500 mg) in THF (10 mL) was added (4-methoxyphenyl)methan-
amine (277 mg) and the mixture was heated to 60°C overnight, cooled to rt and purified by
combiflash reversed-phase chromatography (C18) Boston ODS 120 g Flash 35-50 mL/min 200
psi (0.1% TFA in water, 10 to 100% ACN) to give compound **4a** as a white solid. LCMS (ESI):
m/z 597.2 (M+H)⁺.

Step 2: 2-Amino-*N*⁵-(methoxy-*d*₃)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*₃)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**4**)



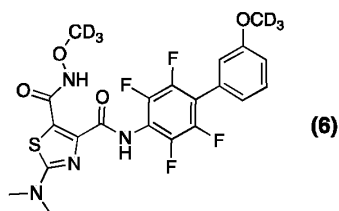
To a solution of compound **4a** (200 mg) in CH₂Cl₂ (5 mL) was added TFA (2 mL). The solution
was stirred at rt for 16 h, diluted with water and extracted with CH₂Cl₂ (3 x 10 mL). The combined
organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by
Botage Isolera One combiflash chromatography (SEPAFLASH, 40-63 Å, 40 g silica gel column
@60 mL/min, eluting with 0 to 33% EA in PE for 25 min to give compound **4** as a white solid. ¹H-
NMR (400 MHz, MeOD-*d*₄) δ 7.42 (dd, J = 7.6, 8.4 Hz, 1H), 7.07-7.04 (m, 3H). LCMS (ESI): m/z
477.1 (M+H)⁺.

Example 5: 2-Acetamido-*N*⁵-(methoxy-*d*₃)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*₃)-[1,1'-bi-phenyl]-4-yl)thiazole-4,5-dicarboxamide (**5**)



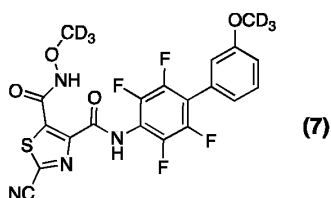
To a solution of compound **4** (50 mg) in CH₂Cl₂ (1 mL) was added Ac₂O (21 mg) and DIEA (68
mg). The mixture was stirred at rt for 16 h, diluted with water and extracted with CH₂Cl₂ (3 x 10
mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered,
concentrated and purified by Botage Isolera One combiflash chromatography (SEPAFLASH, 40-
63 Å, 12 g silica gel column @20 mL/min, eluting with 0 to 15% EA in PE for 20 min to give
compound **5** as a white solid. ¹H-NMR (500 MHz, MeOD-*d*₄) δ 7.45 (t, J = 8.0 Hz, 1H), 7.08-7.06
(m, 3H), 2.29 (s, 3H). LCMS (ESI): m/z 519.2 (M+H)⁺.

Example 6: 2-(Dimethylamino)-*N*⁶-(methoxy-*d*3)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**6**)



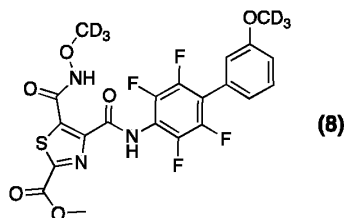
To a solution of compound **3** (200 mg) in THF (2 mL) was added dimethylamine hydrochloride (55 mg). The mixture was stirred at rt for 4 h, concentrated and purified by combiflash Reversed-phase chromatography (C18) Boston ODS 40 g Flash 35-50 mL/min 200 psi (0.1% NH₄HCO₃ in water, 10 to 100% ACN) to give compound **6** as a white solid. ¹H-NMR (400 MHz, MeOD-*d*4) δ 7.44 (t, J = 7.8 Hz, 1H), 7.07-7.05 (m, 3H), 3.20 (s, 6H). LCMS (ESI): m/z 505.2 (M+H)⁺.

Example 7: 2-Cyano-*N*⁶-(methoxy-*d*3)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**7**)



To a solution of compound **3** (500 mg) in DMF (3 mL) was added KCN (224 mg). The mixture was stirred at 120°C overnight, cooled to rt, diluted with water and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 40 g Flash 35-50 mL/min 200 psi (0.1% NH₄HCO₃ in water, 10 to 100% ACN) to give compound **7** as a white solid. ¹H-NMR (400 MHz, MeOD-*d*4) δ 7.46 (t, J = 6.2 Hz, 1H), 7.10-7.07 (m, 3H). LCMS (ESI): m/z 487.2 (M+H)⁺.

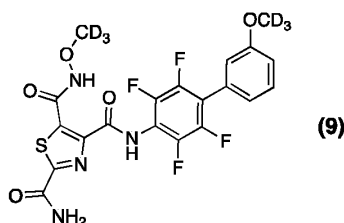
Example 8: Methyl 5-((methoxy-*d*3)carbamoyl)-4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-2-carboxylate (**8**)



To a solution of compound **3** (200 mg) in MeOH (1 mL) and DMF (3 mL) was added dppf (20 mg) and Pd₂(dba)₃ (23 mg). The mixture was stirred at 50°C under CO overnight, cooled to rt and filtered through a Celite pad. The filtrate was diluted with water and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated

and purified by combiflash reversed-phase chromatography (C18) Boston ODS 40 g Flash 35-50 mL/min 200 psi (0.1% NH_4HCO_3 in water, 10 to 100% ACN) to give compound **8** as a white solid. LCMS (ESI): m/z 520.2 ($\text{M}+\text{H}$)⁺.

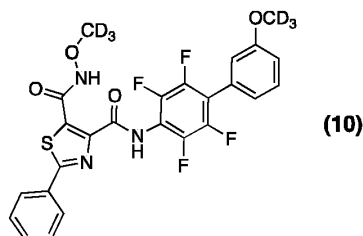
- 5 **Example 9:** *N*⁵-(Methoxy-*d*3)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)thiazole-2,4,5-tricarboxamide (**9**)



- 10 To a solution of compound **8** (100 mg) in THF (0.5 mL) was added $\text{NH}_3\cdot\text{H}_2\text{O}$ (2 mL). The solution was stirred at 100°C for 3 h, cooled to rt, diluted with water and extracted with EA (3 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 , filtered, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 40 g Flash 35-50 mL/min 200 psi (0.1% NH_4HCO_3 in water, 10 to 100% ACN) to give compound **9** as a white solid. ¹H-NMR (400 MHz, $\text{MeOD-}d_4$) δ 7.43 (dd, J = 7.2, 8.8 Hz, 1H), 7.07-7.04 (m, 3H). LCMS (ESI): m/z 505.3 ($\text{M}+\text{H}$)⁺.

15

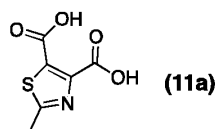
- Example 10:** *N*⁵-(Methoxy-*d*3)-2-phenyl-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**10**)



- 20 To a solution of compound **3** (200 mg) in 1,4-dioxane (10 mL) and H_2O (1 mL) was added phenylboronic acid (49 mg), Na_2CO_3 (129 mg) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (20 mg). The mixture was heated at 90°C for 4 h, cooled to rt, diluted with water and extracted with EA (3 x 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 , filtered, concentrated and purified by Botage Isolera One combiflash chromatography (SEPAFLASH, 40-63 Å, 40 g silica gel column @60 mL/min, eluting with 0 to 33% EA in PE for 25 min to give compound **10** as a white solid.
- 25 ¹H-NMR (400 MHz, $\text{MeOD-}d_4$) δ 8.14 (br s, 2H), 7.54 (s, 3H), 7.44 (t, J = 8.0 Hz, 1H), 7.07-7.06 (m, 3H). LCMS (ESI): m/z 538.1 ($\text{M}+\text{H}$)⁺.

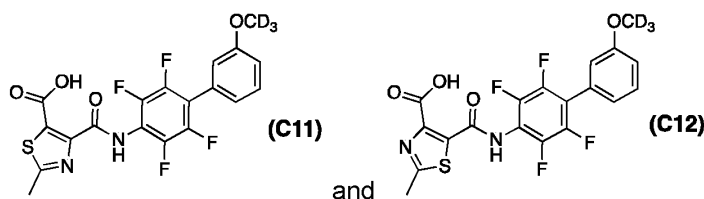
Comparative Example C11 and Example C12:

Step 1: 2-Methylthiazole-4,5-dicarboxylic acid (**C11a**)



To a solution of diethyl 2-methylthiazole-4,5-dicarboxylate (300 mg) in EtOH (1 mL) and THF (1 mL) was added 2N NaOH (1 mL) at 0°C. The mixture was stirred at rt for 8 h, adjusted to pH = 5-6 by 2N HCl and then purified by reversed-phase flash chromatography (C18) (0.1% TFA in water, 10 to 100% MeCN) to give compound **C11a** as a white solid. LCMS (ESI): m/z 188.1 (M+H)⁺.

Step 2: 2-Methyl-4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylic acid (**C11**) and 2-methyl-5-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-4-carboxylic acid (**C12**)

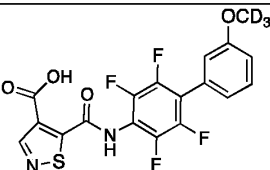
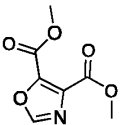
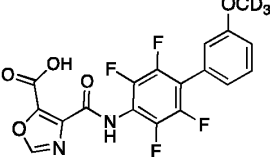
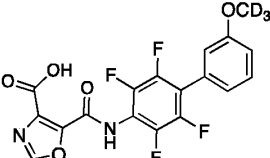
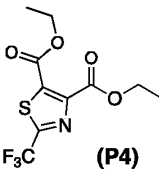
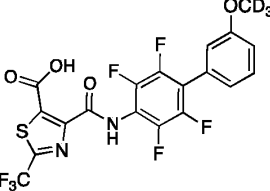
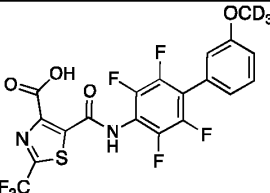
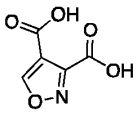
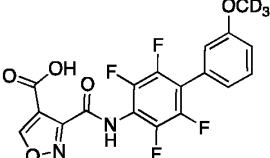


To a solution of compound **C11a** (200 mg) in dry DCM (2 mL) was added SOCl₂ (250 mg) at 0°C. The mixture was stirred at 0°C for 2 h and concentrated under vacuum to afford the crude acid chloride intermediate. To a solution of 2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-amine (293 mg) in dry THF (2 mL) was added NaH (213 mg, 60%wt) at 0°C and the mixture was stirred at 0°C for 10 minutes. Then the acid chloride intermediate was added at 0°C. The mixture was stirred at rt for 16 h, quenched with saturated aq. NH₄Cl and extracted with EA (3 x 5 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by reversed-phase flash chromatography (C18) (0.1% TFA in water, 10 to 100% MeCN) to give compound **C11** and compound **C12** as a white solids, respectively. **C11**: ¹H-NMR (400 MHz, MeOD-*d*4) δ 7.42 (dd, J = 7.4, 9.0 Hz, 1H), 7.06-7.03 (m, 3H), 2.67 (s, 3H). LCMS (ESI): m/z 444.2 (M+H)⁺; **C12**: ¹H-NMR (400 MHz, MeOD-*d*4) δ 7.42 (dd, J = 7.2, 9.2 Hz, 1H), 7.06-7.04 (m, 3H), 2.70 (s, 3H). LCMS (ESI): m/z 444.2 (M+H)⁺.

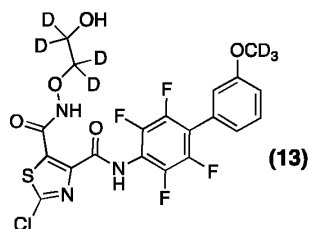
Example 11/1 to 11/8:

The following Examples were prepared similar as described for Example C11/12 above using the appropriate building block(s) as shown below.

#	building block(s)	structure	analytical data
11/1			¹ H-NMR (500 MHz, MeOD- <i>d</i> 4) δ 7.20 (dd, J = 7.5, 8.5 Hz, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 431.1 (M+H) ⁺
11/2			¹ H-NMR (400 MHz, MeOD- <i>d</i> 4) δ 9.00 (s, 1H), 7.43 (dd, J = 8.0, 8.8 Hz, 1H), 7.07-7.04 (m, 3H). LCMS (ESI): m/z 430.1 (M+H) ⁺

#	building block(s)	structure	analytical data
11/3			¹ H-NMR (400 MHz, MeOD- <i>d</i> 4) δ 9.01 (s, 1H), 7.43 (dd, J = 7.6, 8.8 Hz, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 430.2 (M+H) ⁺
11/4			¹ H-NMR (400 MHz, MeOD- <i>d</i> 4) δ 8.34 (s, 1H), 7.43 (dd, J = 7.8, 8.6 Hz, 1H), 7.06-7.04 (m, 3H). LCMS (ESI): m/z 414.1 (M+H) ⁺
11/5			¹ H-NMR (400 MHz, MeOD- <i>d</i> 4) δ 8.38 (s, 1H), 7.43 (dd, J = 7.6, 8.8 Hz, 1H), 7.07-7.04 (m, 3H). LCMS (ESI): m/z 414.1 (M+H) ⁺
11/6	 (P4)		¹ H-NMR (400 MHz, MeOD- <i>d</i> 4) δ 7.45-7.41 (m, 1H), 7.07-7.04 (m, 3H). LCMS (ESI): m/z 498.2 (M+H) ⁺
11/7			¹ H-NMR (500 MHz, MeOD- <i>d</i> 4) δ 7.43 (dd, J = 7.5, 9.0 Hz, 1H), 7.06-7.04 (m, 3H). LCMS (ESI): m/z 498.0 (M+H) ⁺
11/8			¹ H-NMR (400 MHz, MeOD- <i>d</i> 4) δ 9.49 (s, 1H), 7.44 (dd, J = 7.2, 9.2 Hz, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 414.1 (M+H) ⁺

Example 13: 2-Chloro-*N*⁶-(2-hydroxyethoxy-1,1,2,2-*d*4)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**13**)

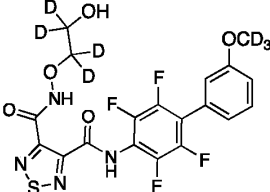


- 5 To a solution of compound **2** (500 mg) and building block **P1/1** (175 mg) in THF (2 mL) and NMP (2 mL) was added EDCI (413 mg) in three portions. The mixture was stirred at rt for 4 h,

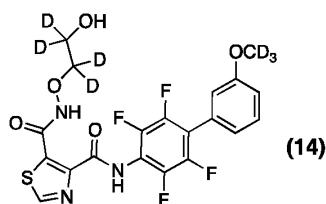
concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 120 g Flash 50-100 mL/min 200 psi (0.1% NH_4HCO_3 in water, 10 to 100% ACN) to give compound **13** as a white solid. LCMS (ESI): m/z 527.2 ($\text{M}+\text{H}$)⁺.

5 Example 13/1:

The following Example was prepared similar as described for Example 11 above using the appropriate building block(s) as shown below.

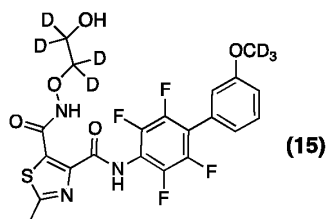
#	building block(s)	structure	analytical data
13/1	Example 11/1		¹ H-NMR (400 MHz, $\text{MeOD}-d_4$) δ 7.20 (t, J = 8.2 Hz, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 494.1 ($\text{M}+\text{H}$) ⁺

10 Example 14: *N*⁵-(2-Hydroxyethoxy-1,1,2,2-*d*₄)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*₃)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**14**)



To a solution of compound **13** (100 mg) in MeOH (2 mL) was added Pd/C (20 mg). The mixture was stirred for 1 h at rt in a hydrogen environment under a balloon, filtered, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 25 g Flash 35-50 mL/min 200 psi (0.1% NH_4HCO_3 in water, 10 to 100% ACN) to give compound **14** as a white solid. ¹H-NMR (400 MHz, $\text{MeOD}-d_4$) δ 9.20 (s, 1H), 7.45 (dd, J = 7.6, 8.4 Hz, 1H), 7.08-7.05 (m, 3H). LCMS (ESI): m/z 493.3 ($\text{M}+\text{H}$)⁺.

20 Example 15: *N*⁵-(2-Hydroxyethoxy-1,1,2,2-*d*₄)-2-methyl-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*₃)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**15**)

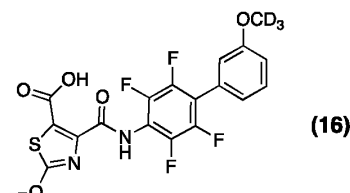


To a solution of compound **13** (250 mg) in 1,4-dioxane (2 mL) and H_2O (0.2 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (121 mg), Na_2CO_3 (153 mg) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (25 mg). The mixture was heated at 90°C for 4 h, cooled to rt, diluted with water and extracted with EA (3 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 , filtered,

concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 25 g Flash 35-50 mL/min 200 psi (0.1% NH_4HCO_3 in water, 10 to 100% ACN) to furnish compound **15** as a white solid. $^1\text{H-NMR}$ (400 MHz, $\text{MeOD-}d_4$) δ 7.45 (t, J = 7.8 Hz, 1H), 7.08-7.05 (m, 3H), 2.79 (s, 3H). LCMS (ESI): m/z 507.3 ($\text{M}+\text{H}$) $^+$.

5

Example 16: 2-Methoxy-4-((2,3,5,6-tetrafluoro-3'-(methoxy- d_3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylic acid (**16**)

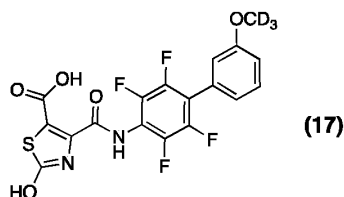


10

To a solution of compound **2** (500 mg) in MeOH (5 mL) was added a methanol solution of 30% sodium methoxide (5 mL). The mixture was stirred at 50°C for 2 h, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 120 g Flash 35-50 mL/min 200 psi (0.1% TFA in water, 10 to 100% ACN) to afford compound **16** as a white solid. $^1\text{H-NMR}$ (500 MHz, $\text{MeOD-}d_4$) δ 7.45 (dd, J = 7.5, 8.5 Hz, 1H), 7.08-7.06 (m, 3H), 4.26 (s, 3H). LCMS (ESI): m/z 459.9 ($\text{M}+\text{H}$) $^+$.

15

Example 17: 2-Hydroxy-4-((2,3,5,6-tetrafluoro-3'-(methoxy- d_3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylic acid (**17**)



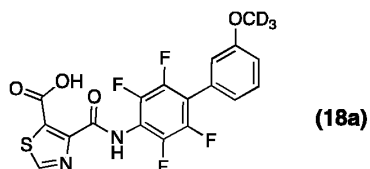
20

To a solution of compound **16** (100 mg) in NMP (2.5 mL) was added LiCl (91 mg). The mixture was stirred at 60°C for 2 h, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 120 g Flash 50-100 mL/min 200 psi (0.1% NH_4HCO_3 in water, 10 to 100% ACN) to afford compound **17** as a white solid. $^1\text{H-NMR}$ (500 MHz, $\text{MeOD-}d_4$) δ 7.45 (t, J = 8.3 Hz, 1H), 7.05-7.03 (m, 3H). LCMS (ESI): m/z 445.9 ($\text{M}+\text{H}$) $^+$.

25

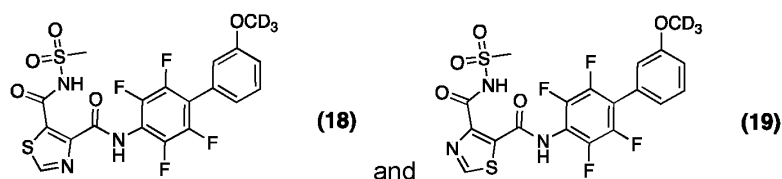
Example 18 and Example 19:

Step 1: 4-((2,3,5,6-Tetrafluoro-3'-(methoxy- d_3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylic acid (**18a**)



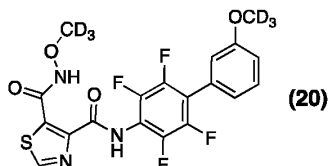
To a solution of compound **2** (4.5 g) in MeOH (500 mL) was added Pd/C (2.25 g). The mixture was stirred at rt for 2 h in a hydrogen environment under a balloon, filtered, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 120 g Flash 50-100 mL/min 200 psi (0.1% TFA in water, 10 to 100% ACN) to compound **18a** as a white solid. ¹H-NMR (500 MHz, DMSO-*d*₆) δ 11.30 (s, 1H), 9.38 (s, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.16-7.09 (m, 3H). LCMS (ESI): *m/z* 429.9 (M+H)⁺.

Step 2: *N*⁵-(Methylsulfonyl)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*₃)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**18**) and *N*⁴-(methylsulfonyl)-*N*⁵-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*₃)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**19**)



To a solution of compound **18a** (200 mg) and methanesulfonamide (132 mg) in CH₂Cl₂ (5 mL) were added dicyclohexylcarbodiimide (115 mg) and 4-dimethylaminopyridine (63 mg). The mixture was stirred at 60°C for 8 h, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 120 g Flash 35-50 mL/min 200 psi (0.1% NH₃·H₂O in water, 10 to 100% ACN) to compound **18** and compound **19** as white solids, respectively. **18**: ¹H-NMR (400 MHz, MeOD-*d*₄) δ 9.04 (s, 1H), 7.48 (dd, *J* = 7.2, 9.2 Hz, 1H), 7.07-7.05 (m, 3H), 3.18 (s, 3H). LCMS (ESI): *m/z* 507.0 (M+H)⁺; **19**: ¹H-NMR (400 MHz, MeOD-*d*₄) δ 9.11 (s, 1H), 9.38 (s, 1H), 7.48 (dd, *J* = 7.6, 8.8 Hz, 1H), 7.06-7.04 (m, 3H), 3.22 (s, 3H). LCMS (ESI): *m/z* 507.0 (M+H)⁺.

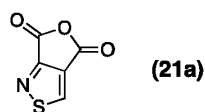
Example 20: *N*⁵-(methoxy-*d*₃)-*N*⁴-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*₃)-[1,1'-biphenyl]-4-yl)thiazole-4,5-dicarboxamide (**20**)



To a solution of compound **3** (700 mg) in MeOH (50 mL) was added Pd/C (350 mg) and then the mixture was stirred at rt for 2 h in a hydrogen environment under a balloon, filtered, concentrated and purified by combiflash reversed-phase chromatography (C18) Boston ODS 120 g Flash 35-50 mL/min 200 psi (0.1% NH₄HCO₃ in water, 10 to 100% ACN) to give compound **20** as a white solid. ¹H-NMR (500 MHz, MeOD-*d*₄) δ 9.19 (s, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.08-7.06 (m, 3H). LCMS (ESI): *m/z* 462.0 (M+H)⁺.

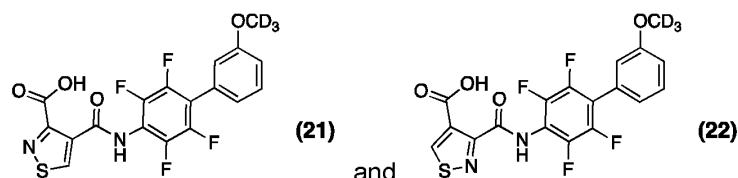
Example 21 and Example 22:

Step 1: 4*H*,6*H*-Furo[3,4-*c*]isothiazole-4,6-dione (**21a**)



To a solution of isothiazole-3,4-dicarboxylic acid (500 mg) in CH₂Cl₂ (5 mL) was added trifluoroacetic anhydride (3 mL). The mixture was stirred at rt for 3 h and concentrated under vacuum to afford compound **21a** as a yellow solid, which was used for the next step without purification.

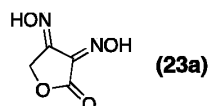
- 5 Step 2: 4-((2,3,5,6-Tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)isothiazole-3-carboxylic acid (**21**) and 3-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)isothiazole-4-carboxylic acid (**22**)



- 10 To a solution of compound **21a** (200 mg) in CH₃Cl (5 mL) were added 2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-amine (354 mg) and AlCl₃ (172 mg). The mixture was stirred at 70°C for 12 h, cooled to rt, quenched with saturated aq. NH₄Cl and extracted with EA (3 x 50 mL). The combined organic layer was dried over Na₂SO₄, concentrated and purified by reversed-phase flash chromatography (C18) (0.1% TFA in water, 10-100% MeCN) to give separated compound **21** and compound **22** as a white solid, respectively. **21**: ¹H-NMR (400 MHz, MeOD-*d*4) δ 9.52 (s, 1H), 7.43 (dd, J = 7.6, 8.4 Hz, 1H), 7.07-7.04 (m, 3H). LCMS (ESI): m/z 430.0 (M+H)⁺; **22**: ¹H-NMR (400 MHz, MeOD-*d*4) δ 9.65 (s, 1H), 7.45 (dd, J = 7.6, 8.4 Hz, 1H), 7.08-7.06 (m, 3H). LCMS (ESI): m/z 430.0 (M+H)⁺.
- 15

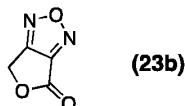
Example 23:

- 20 Step 1: (4*E*)-3,4-bis(Hydroxyimino)dihydrofuran-2(3*H*)-one (**23a**)



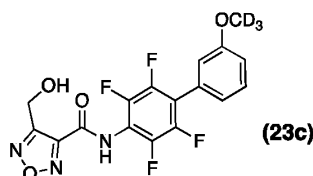
- To a solution of furan-2,4(3*H*,5*H*)-dione (500 mg) in 3N HCl (3 mL) were added NaNO₂ (345 mg) and hydroxylamine hydrochloride (700 mg) in water (8 mL). The mixture was stirred at rt for 3 h and concentrated under vacuum to afford compound **23a** as a yellow solid, which was used for the next step without purification.
- 25

- Step 2: 4*H*,6*H*-Furo[3,4-*c*][1,2,5]oxadiazol-4-one (**23b**)



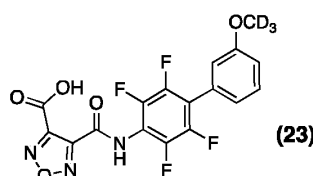
- To a solution of compound **23a** (300 mg) in CH₂Cl₂ (5 mL) was added SOCl₂ (248 mg). The mixture was stirred at rt for 3 h and concentrated under vacuum to afford compound **23b** as a yellow solid, which was used for the next step without purification.
- 30

- Step 3: 4-(Hydroxymethyl)-*N*-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)-1,2,5-oxadiazole-3-carboxamide (**23c**)



A solution of compound **23b** (200 mg) was treated as described in Example 21, step 2 to give compound **23c** as a white solid. LCMS (ESI): m/z 398.7 (M+H)⁺.

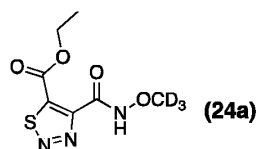
Step 4: 4-((2,3,5,6-Tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)-1,2,5-oxadiazole-3-carboxylic acid (**23**)



To a solution of compound **23c** (150 mg) in ACN (4 mL) and H₂O (2 mL) was added PhI(OAc)₂ (604 mg) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (71 mg). The mixture was stirred at 0°C for 10 min, filtered and purified by reversed-phase chromatography (C18) Boston ODS 330 g Flash 35-50 mL/min 200 psi (0.1% TFA in water, 10-100% ACN) to give compound **23** as a white solid. ¹H-NMR (500 MHz, MeOD-*d*4) δ 7.45-7.42 (m, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 415.0 (M+H)⁺.

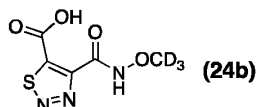
Example 24:

Step 1: Ethyl 4-((methoxy-*d*3)carbamoyl)-1,2,3-thiadiazole-5-carboxylate (**24a**)



To a solution of 5-(ethoxycarbonyl)-1,2,3-thiadiazole-4-carboxylic acid (200 mg) and O-(methyl-*d*3)hydroxylamine hydrochloride (258 mg) in THF (5 mL) and NMP (5 mL) was added EDCI (382 mg) in three portions. The mixture was stirred at rt for 4 h and concentrated. Purification by reversed-phase chromatography (C18) Boston ODS 120 g Flash 50-100 mL/min 200 psi (0.1% TFA in water, 10-100% ACN) afforded compound **24a** as a white solid. LCMS (ESI): m/z 235.1 (M+H)⁺.

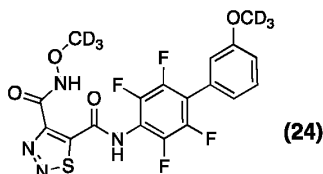
Step 2: 4-((Methoxy-*d*3)carbamoyl)-1,2,3-thiadiazole-5-carboxylic acid (**24b**)



To a solution of compound **24a** (100 mg) in EtOH (1 mL) and THF (1 mL) was added 2N NaOH (1 mL) at 0°C. The mixture was stirred at rt for 8 hours and adjusted to pH = 5-6 by 2N HCl. Purification by reversed-phase chromatography (C18) Boston ODS 120 g Flash 35-50 mL/min

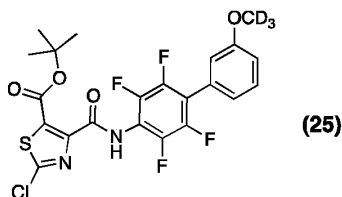
200 psi (0.1% TFA in water, 10-100% ACN) yielded compound **24b** as a white solid. LCMS (ESI): m/z 207.1 (M+H)⁺.

Step 3: *N*4-(Methoxy-*d*3)-*N*5-(2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)-1,2,3-thiadiazole-4,5-dicarboxamide (**24**)



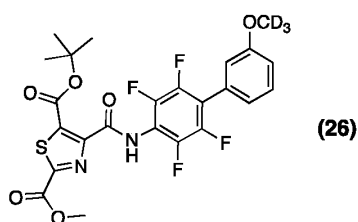
To a solution of compound **24b** (60 mg) in dry THF (2 mL) were added oxalyl chloride (69 mg) at 0°C and then the mixture was stirred at 0°C for 2 h. The mixture was concentrated under vacuum to afford the crude acid chloride intermediate. A solution of 2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-amine (79 mg) in dry THF (1 mL) were added NaH (58 mg, 60%wt) at 0°C and then the mixture was stirred at 0°C for 10 min. Then the acid chloride intermediate was added at 0°C. The mixture was stirred at rt for 16 h, quenched with a saturated aq. NH₄Cl solution and extracted with EA (3 x 5 mL). The combined organic layer was dried over Na₂SO₄, concentrated and purified by reversed-phase flash chromatography (C18) (0.1% NH₄HCO₃ in water, 10-100% MeCN) to give compound **24** as a white solid. ¹H-NMR (400 MHz, MeOD-*d*4) δ 7.44 (dd, *J* = 7.6, 8.4 Hz, 1H), 7.07-7.05 (m, 3H). LCMS (ESI): m/z 463.0 (M+H)⁺.

Example 25: *tert*-Butyl 2-chloro-4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylate (**25**)



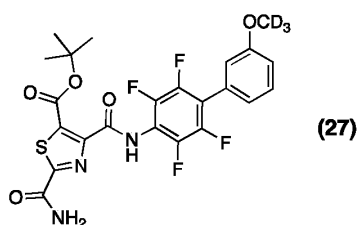
To a solution of Example 2 (2.0 g) and di-*tert*-butyl dicarbonate (2.8 g) in DMF (10 mL) and *t*-BuOH (5 mL) was added DMAP (52 mg, 0.43 mmol). The mixture was stirred at 60°C for 5 h, cooled to rt, concentrated and purified by reversed-phase flash chromatography (C18) (0.1% NH₄HCO₃ in water, 10-100% ACN) to give compound **25** as a white solid. ¹H-NMR (400 MHz, DMSO-*d*6) δ 11.07 (s, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.16-7.08 (m, 3H), 1.49 (s, 9H). LCMS (ESI): m/z 518.1 (M-H)⁻.

Example 26: 5-(*tert*-Butyl) 2-methyl 4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-2,5-dicarboxylate (**26**)



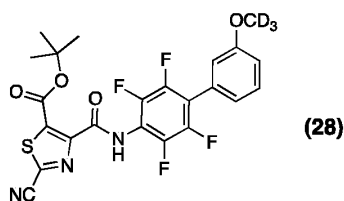
To a solution of compound **25** (500 mg) and Et₃N (0.27 mL) in toluene (10 mL) and MeOH (2 mL) were added Pd(OAc)₂ (22 mg) and (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (55 mg). The mixture was stirred at 60°C for 8 h, cooled to rt, filtered through a Celite pad and concentrated. Purification by reversed-phase flash chromatography (C18) (0.1% NH₄HCO₃ in water, 10-100% ACN) afforded compound **26** as a white solid. LCMS (ESI): m/z 542.2 (M-H)⁻.

Example 27: *tert*-Butyl 2-carbamoyl-4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylate (**27**)



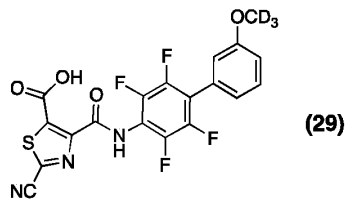
To a solution of compound **26** (120 mg) in THF (1.5 mL) was added NH₄OH (1 mL). The mixture was stirred at rt for 1 h, concentrated under vacuum and purified by reversed-phase flash chromatography (C18) (0.1% NH₄HCO₃ in water, 10-100% ACN) to give compound **27** as a white solid. LCMS (ESI): m/z 527.1 (M-H)⁻.

Example 28: *tert*-Butyl 2-cyano-4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylate (**28**)



To a solution of compound **27** (70 mg) in CH₂Cl₂ (2 mL) was added *N,N*-diethyl-*N*-[[[(methoxycarbonyl)amino]sulfonyl]ethanaminium inner salt (Burgess reagent) (317 mg). The mixture was stirred at rt for 16 h, concentrated under vacuum and purified by reversed-phase flash chromatography (C18) (0.1% NH₄HCO₃ in water, 10-100% ACN) to give compound **28** as a white solid. LCMS (ESI): m/z 509.1 (M-H)⁻.

Example 29: 2-Cyano-4-((2,3,5,6-tetrafluoro-3'-(methoxy-*d*3)-[1,1'-biphenyl]-4-yl)carbamoyl)thiazole-5-carboxylic acid (**29**)



To a solution of compound **28** (50 mg) in CH₂Cl₂ (1.5 mL) was added TFA (0.2 mL). The mixture was stirred at rt for 1 h, concentrated under vacuum and purified by reversed-phase flash chromatography (C18) (0.1% TFA in water, 10-100% ACN) to give compound **29** as a white solid.
¹H-NMR (400 MHz, MeOD-*d*₄) δ 7.46-7.42 (m, 1H), 7.08-7.05 (m, 3H). LCMS (ESI): m/z 455.0 (M+H)⁺.

Example 200: Human DHODH inhibition assay

The *in vitro* inhibition of hDHODH was measured using an *N*-terminally truncated recombinant hDHODH enzyme as described in *J. Med. Chem.* 2006;49:1239. Briefly, the hDHODH concentration was adjusted in a way that an average slope of approximately 0.2 AU/min served as the positive control (e.g. without inhibitor). The standard assay mixture contained 60 μM 2,6-dichloroindophenol, 50 μM decylubiquinone and 100 μM dihydroorotate. The hDHODH enzyme with or without at least six different concentrations of the compounds was added and measurements were performed in 50 mM TrisHCl, 150 mM KCl and 0.1% Triton X-100 at pH 8.0 and at 30°C. The reaction was started by adding dihydroorotate and measuring the absorption at 600 nm for 2 min. For the determination of the IC₅₀ values, each data point was recorded in triplicate. The following data was obtained:

Example #	IC ₅₀ range	Example #	IC ₅₀ range	Example #	IC ₅₀ range
2	++++	3/13	++++	11/8	+++
2/1	++++	3/14	++++	C12	++
2/2	+++	3/15	++++	13/1	+++
2/4	++++	4	+++	14	++++
3	++++	5	++	15	++++
3/1	++++	6	++	16	+++
3/2	++++	7	++++	17	+++
3/3	++++	9	++	18	+++
3/4	++++	10	0	19	++
3/5	++++	C11	++++	20	++++
3/6	++	11/1	+++	21	+++
3/7	++++	11/2	++++	22	+++
3/8	+++	11/3	+++	23	0
3/9	++++	11/4	+++	24	+++
3/10	++++	11/5	++	29	++
3/11	++++	11/6	+++		
3/12	++++	11/7	+++		

IC₅₀ ranges for the human DHODH assay as described herein: +++++: <10 nM; +++: 10 nM to <100 nM; ++: 100 nM to <1 μM; +: 1 μM to <10 μM; 0: ≥10 μM.

Example 201: Antiviral activity on SARS-CoV-2

The assay for viral replication (YFP) and the cell viability assay has been described in general in *Pathogens* 2021;10:1076 and applied to compounds of the present invention furnished the following results: EC₅₀ ranges for the SARS-CoV-2 assay as described herein:

Example #	EC ₅₀ range	CC ₅₀ range	Example #	EC ₅₀ range	CC ₅₀ range
3	++++	33	C12	0	>100
3/3	+++	4.9	14	+++	>100
3/4	+++	>100	20	++++	>100
C11	++	>100			

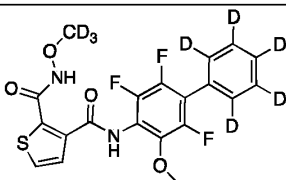
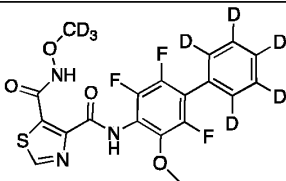
5 EC₅₀ ranges for the SARS-CoV-2 assay as described herein: +++++: <10 nM; +++: 10 nM to <100 nM; ++: 100 nM to <1 µM; +: 1 µM to <10 µM; 0: ≥10 µM.

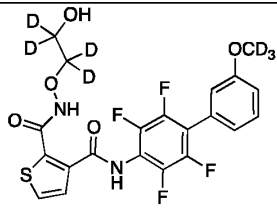
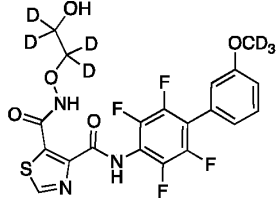
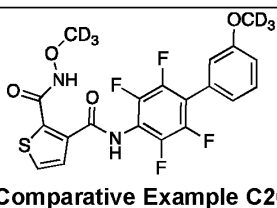
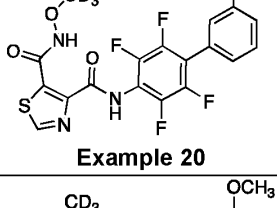
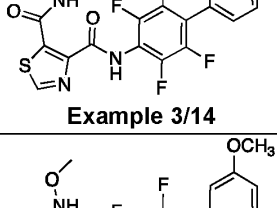
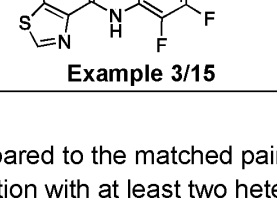
Example 203: Mouse blood and brain exposure

10 The brain exposure of representative compounds of the present invention was evaluated in 3 female mice (C57BL/6J, 8 week old) after oral cassette dosing. Dose was 20 mg/kg, application volume was 5 mL/kg and vehicle was 5% Solutol, 95% NaCl solution (at 0.9% saline concentration). At 2 h after dosing, 20 µL whole blood from the retrobulbar venous plexus under short isoflurane anesthesia were collected into Li-heparin tubes, frozen on dry ice within 1-2 minutes of sampling and stored at -20°C until processed for LC-MS analysis. Animals were sacrificed and perfused with PBS until PBS was transparent and brain was collected and stored at -20°C until processed for LC-MS analysis and ELISA assay for determination of albumin (the measured amounts of albumin in the brain fraction were negligible).

Comparative Example C3/1, C14 and C20 can be prepared as outlined in WO2023/118576.

The obtained data is as follows:

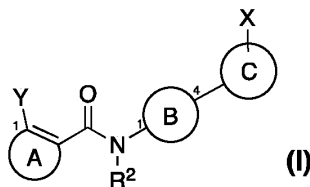
#	brain	blood	brain/blood ratio
 Comparative Example C3/1	2.73 µM	23.4 µM	0.12
 Example 3/1	5.16 µM	18.4 µM	0.28

#	brain	blood	brain/blood ratio
 Comparative Example C14	0.051 μM	9.68 μM	0.0053
 Example 14	2.82 μM	19.2 μM	0.15
 Comparative Example C20	0.550 μM	15.5 μM	0.035
 Example 20	2.05 μM	7.22 μM	0.28
 Example 3/14	3.71 μM	18.5 μM	0.20
 Example 3/15	4.09 μM	9.98 μM	0.41

Compared to the matched pair with only one heterocycle in ring A, the derivatives of the present invention with at least two heterocycles showed surprisingly a higher brain/blood ratio, given that a higher topological polar surface area (TPSA) or a lower clogD is normally not advantageous for this parameter. As can be seen with Comparative Example C20, the improved brain/blood-ratio is independent of the amount of deuteration.

CLAIMS:

1. A compound of Formula (I):



5 or an enantiomer, diastereomer, tautomer, solvate, or pharmaceutically acceptable salt thereof, wherein

A is selected from a 5-membered heteroaryl containing 2 to 3 heteroatoms selected from N, S and O, having one or more hydrogen atoms optionally replaced by deuterium,

10 said A is unsubstituted or substituted with one substituent independently selected from the group consisting of H, halogen, -CN, -NO₂, SF₅, oxo, -OH, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, fluoro-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, -O-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, -O-(3- to 8-membered heterocycloalkyl), CO₂R¹¹, NR¹¹R¹², CONR¹¹R¹², phenyl, 5- or 6-membered heteroaryl

15 wherein alkyl, cycloalkyl, heterocycloalkyl, phenyl, heteroaryl are unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of D, halogen, -CN, OH, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl and -O-fluoro-C₁₋₄-alkyl,

ring A or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

B is selected from the group consisting of phenyl and pyridyl,

20 wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl;

25 and wherein optionally two adjacent substituents in the phenyl and pyridyl moiety form a 5- to 8-membered partially unsaturated cycle optionally containing 1 to 3 heteroatoms independently selected from O, S or N,

wherein this additional cycle is optionally substituted with 1 to 4 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl;

and wherein the residue -NR² on ring B is in a 1,4-orientation with respect to ring C,

ring B or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

30 C is selected from the group consisting of phenyl and pyridyl,

wherein phenyl and pyridyl are unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of halogen, -CN, oxo, C₁₋₄-alkyl, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl;

and wherein optionally two adjacent substituents in the phenyl and pyridyl moiety form a 5- to 8-membered partially unsaturated cycle optionally containing 1 to 3 heteroatoms independently selected from O, S or N,

wherein this additional cycle is optionally substituted with 1 to 4 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl;

ring C or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

10

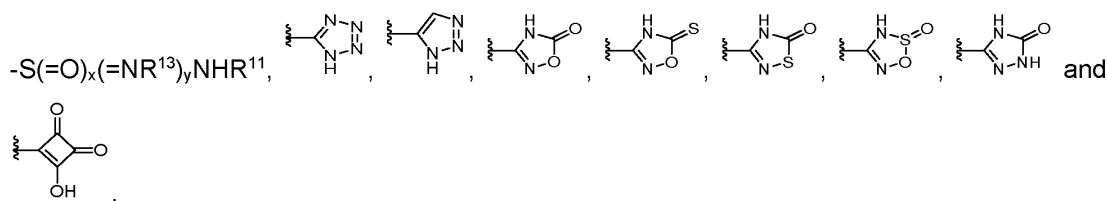
X is selected from H, D, halogen, -CN, -NO₂, C₁₋₆-alkyl, -O-C₁₋₆-alkyl, O-halo-C₁₋₆-alkyl, C₀₋₆-alkylene-OR²¹, C₀₋₆-alkylene-(3- to 6-membered cycloalkyl), C₀₋₆-alkylene-(3- to 8-membered heterocycloalkyl), C₀₋₆-alkylene-S(=O)_n(=NR²³)_mR²¹, C₀₋₆-alkylene-NR²¹S(=O)_x(=NR²³)_yR²¹, C₀₋₆-alkylene-S(=O)_x(=NR²³)_yNR²¹R²², C₀₋₆-alkylene-NR²¹S(=O)_x(=NR²³)_yNR²¹R²², C₀₋₆-alkylene-CO₂R²¹, C₀₋₆-alkylene-O-COR²¹, C₀₋₆-alkylene-CONR²¹R²², C₀₋₆-alkylene-NR²¹-COR²¹, C₀₋₆-alkylene-NR²¹-CONR²¹R²², C₀₋₆-alkylene-O-CONR²¹R²², C₀₋₆-alkylene-NR²¹-CO₂R²¹, C₀₋₆-alkylene-NR²¹R²², wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

wherein alkyl, alkylene, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 6 substituents independently selected from halogen, -CN, oxo, -OH, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

X or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

Y is selected from -CONR¹¹R¹², -CONH-CN, -CONHOR¹⁰, -SO₃H, -SO₂H, -B(OH)₂, -CONHS(=O)_x(=NR¹³)_yR¹⁰, -CONHS(=O)_x(=NR¹³)_yNR¹¹R¹², -S(=O)_x(=NR¹³)_yNHCOR¹⁰,

25



Y having one or more hydrogen atoms optionally replaced by deuterium;

30 R² is selected from H and C₁₋₆-alkyl,

R² having one or more hydrogen atoms optionally replaced by deuterium;

R¹⁰ is selected from C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl, wherein alkyl, cycloalkyl and heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

R¹¹, R¹², R²¹, R²² are independently selected from H, C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

R¹¹ and/or R¹² and/or R²¹ and/or R²² having one or more hydrogen atoms optionally replaced by deuterium;

or R¹¹ and R¹², R²¹ and R²², respectively, when taken together with the nitrogen to which they are attached complete a 3- to 6-membered cycle containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N; and

wherein this cycle is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

R¹¹ and/or R¹² and/or R²¹ and/or R²² having one or more hydrogen atoms optionally replaced by deuterium;

R¹³, R²³ are independently selected from H, -CN, -NO₂, C₁₋₆-alkyl, -CO-O-C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

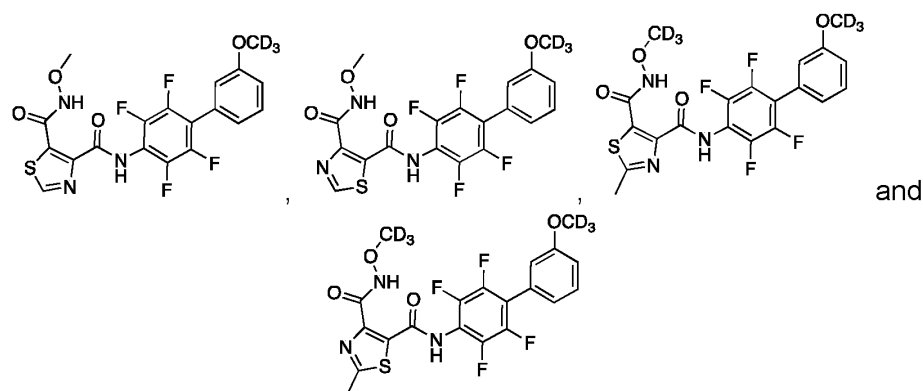
R¹³ and/or R²³ having one or more hydrogen atoms optionally replaced by deuterium;

x, y are independently selected from 0 to 2;

with the proviso that the sum of integer m and n for the residue linked to the same sulfur atom is independently selected from 0 to 2;

with the proviso that the sum of integer x and y for the residue linked to the same sulfur atom is independently selected from 1 or 2;

and with the proviso, that the following structures are excluded:



2. A compound of Formula (I) according to claim 1, or a solvate or pharmaceutically acceptable salt thereof, wherein

Y is selected from -CONR¹¹R¹², -CONH-CN, -CONHOR¹⁰, -CONHS(=O)_x(=NR¹³)_yR¹⁰,

-CONHS(=O)_y(=NR¹³)_yNR¹¹R¹²,  or  ;

R¹⁰ is selected from C₁₋₄-alkyl, cyclopropyl or oxetan-3-yl,

wherein alkyl, cyclopropyl or oxetan-3-yl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹⁰ having one or more hydrogen atoms optionally replaced by deuterium;

R¹¹ and R¹² are independently selected from H or C₁₋₃-alkyl,

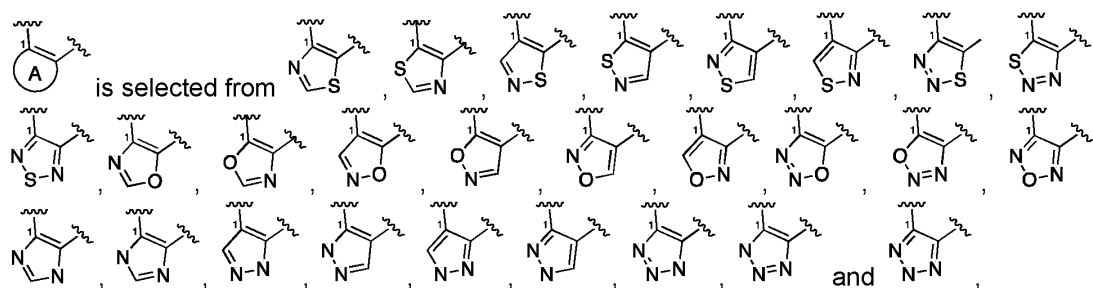
wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium;

R¹³ is selected from H, -CN and C₁₋₃-alkyl,

5 wherein alkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from F, -CN, Me, CHF₂, CF₃, -OH, oxo, -OMe, -OCHF₂ and -OCF₃, R¹³ having one or more hydrogen atoms optionally replaced by deuterium; and

x is 1 and y is 1 or x is 2 and y is 0.

10 3. A compound of Formula (I) according to claim 1 or 2, wherein



15 said A is unsubstituted or substituted with one substituent independently selected from the group consisting of H, F, Cl, Br, -CN, -OH, C₁₋₄-alkyl, -O-C₁₋₄-alkyl, fluoro-C₁₋₄-alkyl, -O-fluoro-C₁₋₄-alkyl, CO₂R¹¹, NR¹¹R¹² and CONR¹¹R¹²,

ring A or its substituents having one or more hydrogen atoms optionally replaced by deuterium;

R² is H;

20 R¹¹ and R¹² are independently selected from H, C₁₋₆-alkyl, 3- to 6-membered cycloalkyl or 3- to 8-membered heterocycloalkyl,

25 wherein alkyl, cycloalkyl or heterocycloalkyl is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl, wherein heterocycloalkyl comprises 1, 2, 3 or 4 heteroatoms independently selected from N, O, or S,

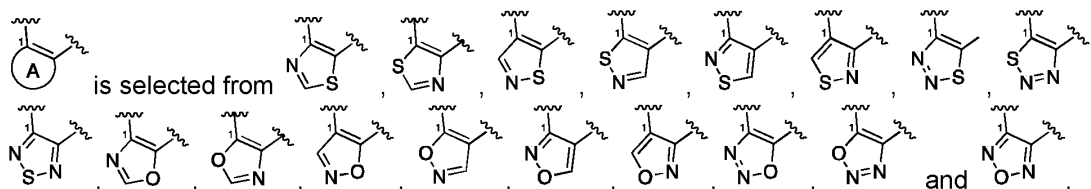
or R¹¹ and R¹², when taken together with the nitrogen to which they are attached complete a 3- to 6-membered cycle containing carbon atoms and optionally containing 1 or 2 heteroatoms selected from O, S or N; and

30 wherein this cycle is unsubstituted or substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₄-alkyl, halo-C₁₋₄-alkyl, 3- to 6-membered cycloalkyl, halo-

(3- to 6-membered cycloalkyl), 3- to 8-membered heterocycloalkyl, halo-(3- to 8-membered heterocycloalkyl), -OH, oxo, -O-C₁₋₄-alkyl and -O-halo-C₁₋₄-alkyl,

R¹¹ and/or R¹² having one or more hydrogen atoms optionally replaced by deuterium.

5 4. A compound of Formula (I) according to claim 1 or 3, wherein



10 said A is unsubstituted or substituted with one substituent independently selected from the group consisting of D, F, Cl, -CN, -OH, Me, Et, -OMe, OEt, CHF₂, CF₃, -OCHF₂, -OCF₃, CO₂Me, NH₂, NHMe, NMe₂, NHCOMe, CONH₂, CONHMe and CONMe₂,

ring A or its substituents having one or more hydrogen atoms optionally replaced by deuterium; and R² is H.

15 5. A compound of Formula (I) according to any of claims 1 to 4, wherein

B is phenyl,

wherein phenyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of D, F, Cl, -CN, Me, CD₃, -OMe, -OCD₃, CHF₂ and CF₃; and wherein the residue -NR² on ring B is in a 1,4-orientation with respect to ring C.

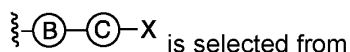
20 6. A compound of Formula (I) according to any of claims 1 to 5, wherein

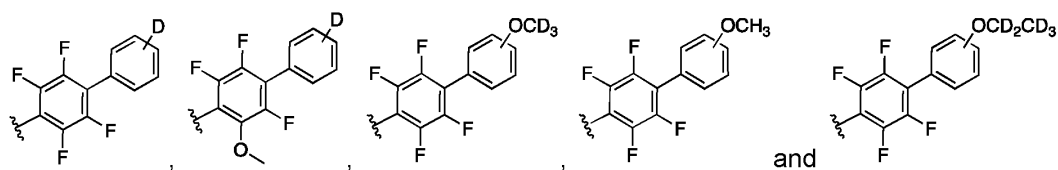
C is phenyl,

wherein phenyl is unsubstituted or substituted with 1 to 4 substituents independently selected from the group consisting of D, F, Cl, -CN, Me, CD₃, CHF₂, CF₃, -OMe, -OCD₃, -OCHF₂ and -OCF₃; and

25 X is selected from D, F, Cl, -CN, Me, CD₃, CHF₂, CF₃, Et, CD₂CD₃, -OMe, -OCD₃, -OCHF₂, -OCF₃, -OEt, -OCD₂CD₃, -OCH₂CH₂CH₃, -OCD₂CD₂CD₃, -OCH₂CH₂CH₂CH₃ and -OCD₂CD₂CD₂CD₃.

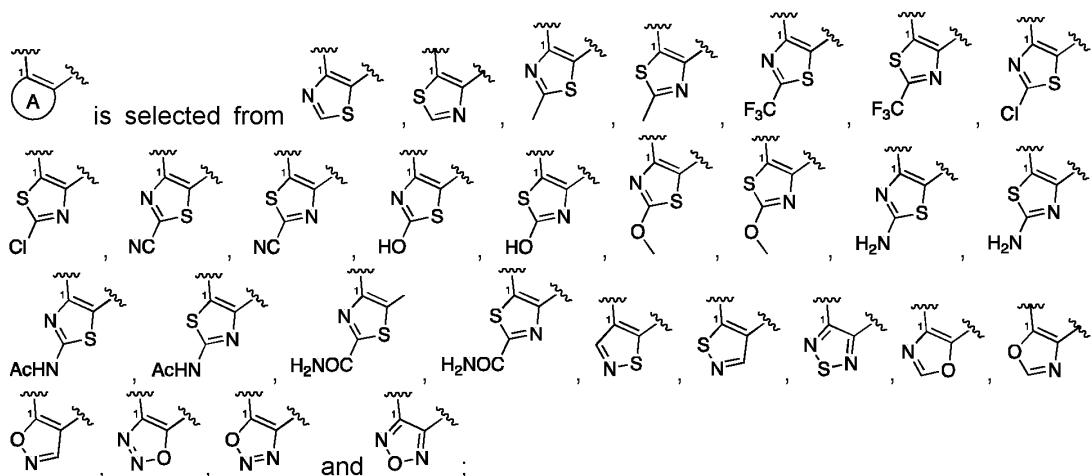
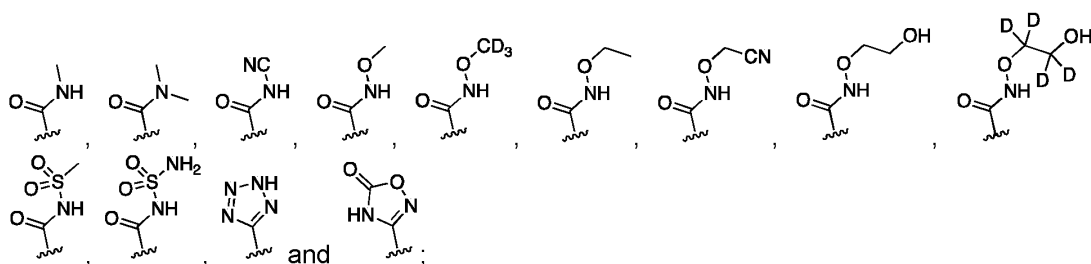
7. A compound of Formula (I) according to any of claims 1 to 6, wherein



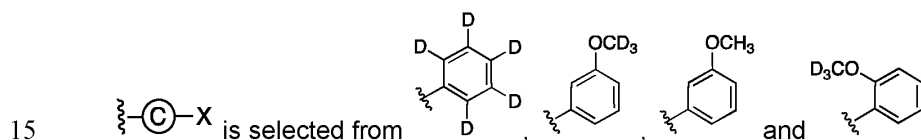
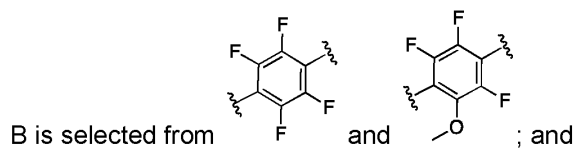


5 8. A compound of Formula (I) according to any of claims 1 to 7, wherein

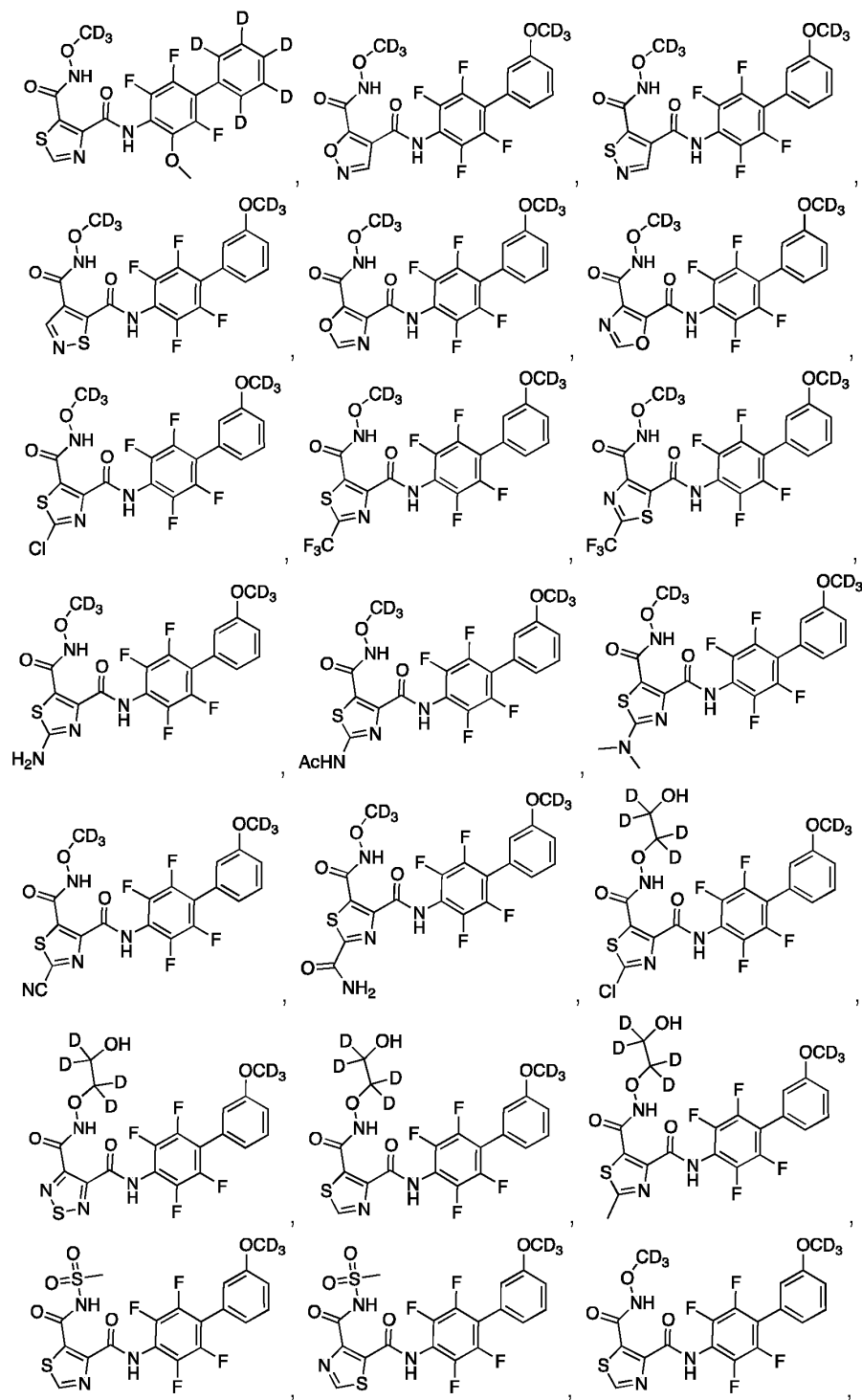
Y is selected from

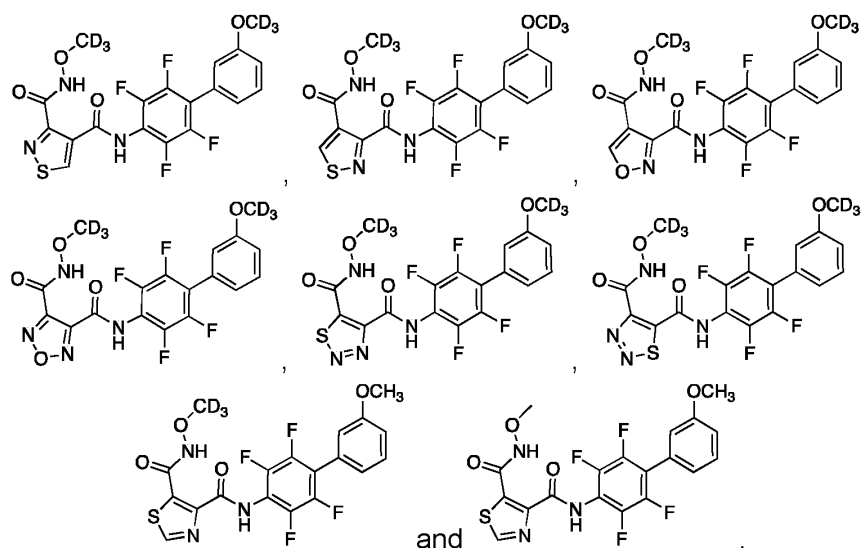


R^2 is H;



9. A compound of Formula (I) according to any of claims 1 to 8, which is selected from





or a solvate or pharmaceutically acceptable salt thereof.

5

10. A compound according to any one of the preceding claims for the use as a medicament.

11. A compound according to any one of claims 1 to 10 for use in the prophylaxis and/or treatment of diseases, disorders, therapeutic indications or medical conditions amenable for treatment with DHODH inhibitors.

10

12. A compound for use according to claim 11 wherein the disease, disorder, therapeutic indication or medical condition is selected from the group comprising rheumatism, acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, inflammatory diseases, diseases that are caused by protozoal infestations in humans and animals, diseases that are caused by viral infections and pneumocystis carinii, fibrosis, uveitis, rhinitis, asthma, transplantation or arthropathy.

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13. A compound for use according to claim 12 wherein the disease, disorder or therapeutic indication is selected from the group comprising graft versus host and host versus graft reactions, rheumatoid arthritis, multiple sclerosis, amyotrophic lateral sclerosis, lupus erythematosus, inflammatory bowel disease, cancer, COVID-19, respiratory syncytial virus, influenza, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis and psoriasis.

20

14. A compound for use according to claim 12 wherein the disease, disorder or therapeutic indication caused by malignant cell proliferation due to isocitrate dehydrogenase (NADP⁺) 1 (IDH1) mutation(s).

5 15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier or excipient.

10 16. A pharmaceutical composition of claim 15, further comprising one or more additional therapeutic agents selected from anti-inflammatory agents, anti-viral agents, anti-cancer agents, immunosuppressive and/or immunomodulatory agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics and suitable mixtures thereof.