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(54) Title: NOVEL USES OF PYRAZOLO PIPERIDINE DERIVATIVES

(57) Abstract: The present invention relates to the use of certain pyrazolo piperidine derivatives in the treatment of diseases and conditions associated with the interaction of the toll like receptor. More particularly, the said treatment pertains to the treatment of NPSLE.



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Novel Uses of Pyrazolo Piperidine Derivatives

FIELD OF THE INVENTION

The invention relates to the use of certain pyrazole derivatives in the treatment of diseases and conditions potentially associated with the interaction of Toll like receptors. More specifically, the said treatment pertains to the treatment of neuropsychiatric lupus erythematosus (NPSLE), including central nervous system (CNS)-lupus.

BACKGROUND OF THE INVENTION

US 9,126,999 B2 and WO 2018/047081 describes the synthesis and some utilities of certain pyrazolo-piperidine derivatives. Said compounds are known to antagonize the Toll like receptors 7 and 8 (TLR7, TLR8) and shall be useful in the treatment of SLE and lupus nephritis. However, US 9,126,999 B2 and WO 2018/047081 are silent with respect to treatment of NPSLE.

The underlying pathophysiologic mechanisms of NPSLE, including CNS-lupus, are still largely unknown.

However, several pathogenic pathways have been identified, including the type I interferon dependent pathways (see Bialas *et al.* Nature. 2017, Jun 22:546(7659):539-543). Currently, it is believed that there is no treatment available for treatment of NPSLE, including CNS lupus, hence there is a high medical need for a respective treatment.

SUMMARY OF THE INVENTION

The present invention provides a novel method for treating and/or preventing NPSLE in a subject in need of such treatment, comprising administering an effective amount of a TLR7/TLR8 antagonist such as a compound of formula (I) or a compound of Formula (II); or a pharmaceutically acceptable salt thereof to a patient suffering from NPSLE .

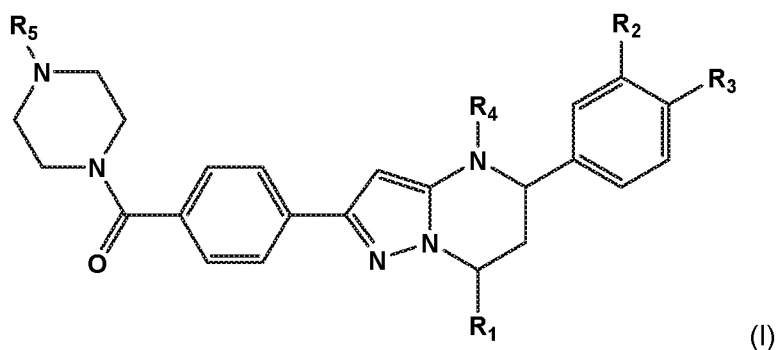
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Efficacy of compound of Formula (Ib) on systemic disease parameters in the NZBW/F1 model.

Figure 2: Efficacy of compound of Formula (IIc) on systemic and neuropathological disease parameters in NZBW/F1 model.

DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of NPSLE. Compounds of formula (I) or pharmaceutically acceptable salts thereof, are represented by the following structure:



wherein

R_1 is hydrogen, or C_1 - C_4 alkyl optionally substituted one or more times by halogen;

R_2 and R_3 are independently from each other hydrogen or C_1 - C_6 alkoxy;

R_4 is hydrogen or C_1 - C_6 alkyl; and

R_5 is hydrogen or C_1 - C_6 alkyl.

In a second embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in accordance to the first embodiment, wherein

R_1 is C_1 - C_4 alkyl optionally substituted one or more times by halogen;

R_2 and R_3 are independently from each other C_1 - C_6 alkoxy;

R_4 is hydrogen or C_1 - C_6 alkyl; and

R_5 is hydrogen or methyl.

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In a third embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in accordance to the first embodiment wherein

R₁ is C₁-C₄alkyl substituted one or more times by halogen;

R₂ and R₃ are independently from each other C₁-C₆alkoxy;

5 R₄ is hydrogen or C₁-C₆alkyl; and

R₅ is hydrogen.

In a forth embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in accordance to the first embodiment wherein

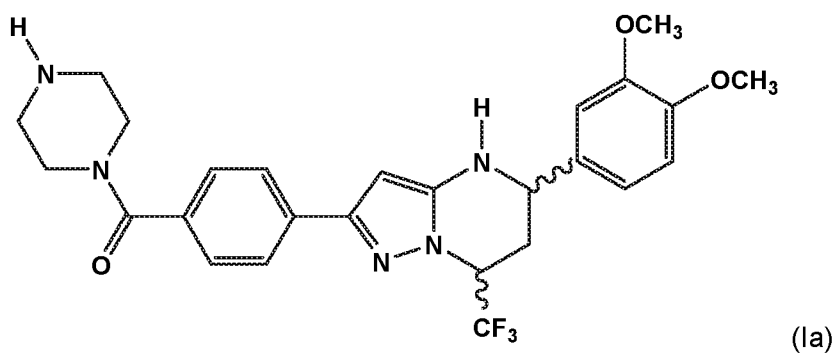
10 R₁ is trifluoromethyl or difluoromethyl;

R₂ and R₃ are both methoxy;

R₄ is hydrogen; and

R₅ is hydrogen or methyl.

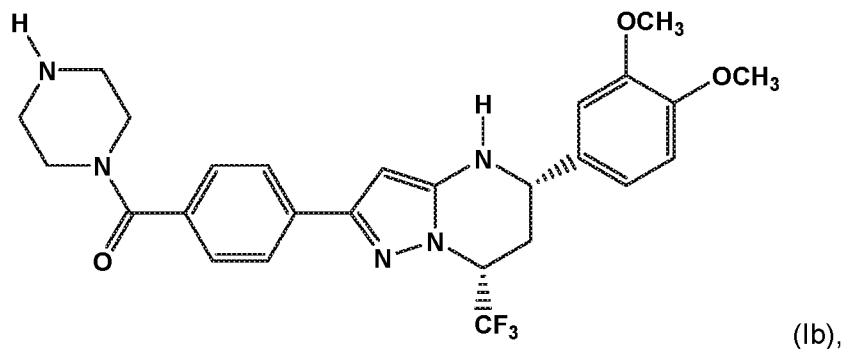
15 In a fifth embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in accordance to the first embodiment wherein said compound is a compound of formula (Ia),



20 or a pharmaceutically acceptable salt thereof.

In a sixth embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in accordance to the first embodiment wherein said compound is a compound of formula (Ib),

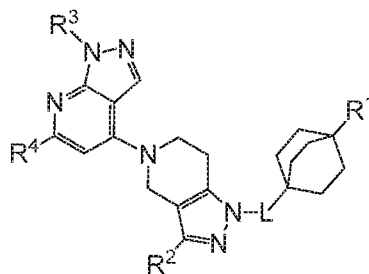
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or a pharmaceutically acceptable salt thereof.

In a seventh embodiment, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in accordance to the first embodiment wherein said compound is (4-((5S,7R)-5-(3,4-dimethoxyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)phenyl) (piperazin-1-yl)methanone.

In embodiment 8, the invention provides a compound of Formula (II) or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of NPSLE. Compounds of Formula (II) or pharmaceutically acceptable salts thereof, are represented by the following structure:



Formula (II)

wherein

L is $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$;

R^1 is $-\text{NHC}(=\text{O})\text{R}^6$, $-\text{NHC}(=\text{O})(\text{CH}_2)_n\text{R}^6$, $-\text{NHC}(=\text{O})(\text{CH}_2)_m\text{NHR}^5$, $-\text{NHC}(=\text{O})(\text{CH}_2)_m\text{N}(\text{R}^5)_2$, $-\text{NHC}(=\text{O})(\text{CHR}^7)_m\text{NHR}^5$, $-\text{NHC}(=\text{O})(\text{CH}_2)_m\text{NH}_2$, $-\text{NHC}(=\text{O})(\text{CH}_2)_n\text{OR}^7$, $-\text{NHC}(=\text{O})\text{OR}^7$, $-\text{NHC}(=\text{O})(\text{CHR}^7)_n\text{R}^6$, $-\text{NHC}(=\text{O})(\text{CHR}^7)_n\text{N}(\text{R}^8)_2$, $-\text{NHC}(=\text{O})(\text{CHR}^7)_n\text{NHR}^8$, $-\text{NHC}(=\text{O})(\text{CH}_2)_n\text{N}(\text{CD}_3)_2$, $-\text{NR}^7\text{C}(=\text{O})\text{R}^5$, $-\text{NR}^7\text{C}(=\text{O})(\text{CH}_2)_n\text{R}^5$, $-\text{NR}^7\text{C}(=\text{O})\text{OR}^5$, $-\text{NHS}(=\text{O})_2\text{R}^5$, $-\text{NHC}(=\text{O})(\text{CH}_2)_n\text{NR}^7\text{C}(=\text{O})\text{R}^5$ or $-\text{NHC}(=\text{O})(\text{CH}_2)_n\text{NR}^7\text{S}(=\text{O})_2\text{R}^5$;

R^2 is H, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ haloalkyl;

R^3 is H, $\text{C}_1\text{-C}_6$ alkyl or $-\text{CD}_3$;

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R^4 is H, NH_2 , C_1 - C_6 alkyl or halo;

each R^5 is independently selected from C_1 - C_6 alkyl, $-CD_3$ and $-(CH_2)_nOR^7$;

R^6 is a C_3 - C_6 cycloalkyl or a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, $N(C_1$ - C_6 alkyl) and O which is unsubstituted or is substituted with 1-2 R^9 groups;

each R^7 is independently selected from H and C_1 - C_6 alkyl;

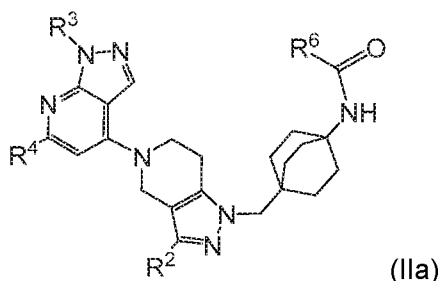
each R^8 is independently selected from C_1 - C_6 haloalkyl, $-(C(R^7)_2)_nOR^7$ and a C_1 - C_6 alkyl substituted with 1 to 3 $-OH$;

each R^9 is independently selected from C_1 - C_6 alkyl, hydroxyl, halo and a C_1 - C_6 alkyl substituted with 1 to 3 $-OH$;

n is 1, 2, 3, 4, 5 or 6; and

m is 1, 2, 3, 4, 5 or 6.

In embodiment 9, the invention provides a compound of Formula (II), or a pharmaceutically acceptable salt thereof, for use according to embodiment 8, wherein said compound is a compound of Formula (IIa):



R^2 is H, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^3 is H, C_1 - C_6 alkyl or $-CD_3$;

R^4 is H, NH_2 , C_1 - C_6 alkyl or halo;

R^6 is a C_3 - C_6 cycloalkyl or a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, $N(C_1$ - C_6 alkyl) and O which is unsubstituted or is substituted with 1-2 R^9 groups;

each R^9 is independently selected from C_1 - C_6 alkyl, hydroxyl, halo and a C_1 - C_6 alkyl substituted with 1 to 3 $-OH$;

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In embodiment 10, the invention provides a compound of Formula (IIa), or a pharmaceutically acceptable salt thereof, for use according to embodiment 9, wherein

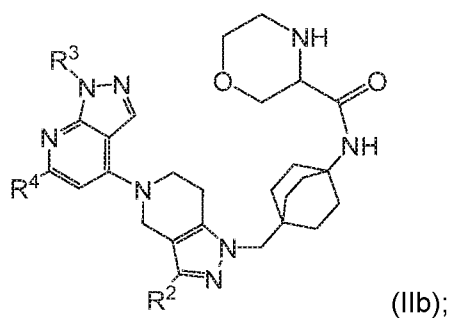
R² is C₁-C₄alkyl;

R³ is C₁-C₄alkyl;

5 R⁴ is C₁-C₄alkyl or halo;

R⁶ is a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, N(C₁-C₆alkyl) and O.

10 In embodiment 11, the invention provides a compound of Formula (IIa), or a pharmaceutically acceptable salt thereof, for use according to embodiment 9 or 10, wherein said compound is a compound of Formula (IIb):

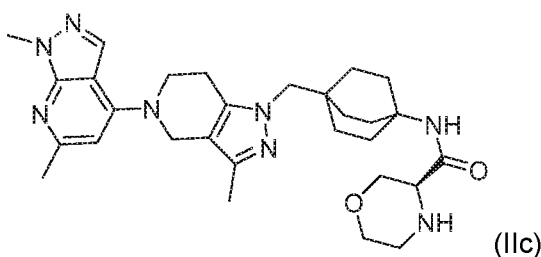


R² is C₁-C₄alkyl;

R³ is C₁-C₄alkyl;

15 R⁴ is C₁-C₄alkyl.

In embodiment 12, the invention provides a compound of Formula (II), (IIa) or (IIb), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiment 8 to 11, wherein the compound is (S)-N-(4-((5-(1,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-3-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)bicyclo[2.2.2]octan-1-yl)morpholine-3-carboxamide; or a pharmaceutically acceptable salt thereof. This compound is also represented by Formula (IIc):



In embodiment 12a, the invention provides a compound of Formula (IIc) in its free form for use according to any one of embodiment 8 to 11.

In embodiment 12b, the invention provides a compound of Formula (IIc) in a hydrate form for use according to any one of embodiment 8 to 11.

5 In embodiment 12c, the invention provides a crystalline form of a hydrate of (S)-N-(4-((5-(1,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-3-methyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)bicyclo[2.2.2]octan-1-yl)morpholine-3-carboxamide in for use according to any one of embodiment 8 to 11. In a further aspect of this embodiment, the invention provides a crystalline form of a heptahydrate of (S)-N-(4-((5-(1,6-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-3-methyl-
10 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)methyl)bicyclo[2.2.2]octan-1-yl)morpholine-3-carboxamide in for use according to any one of embodiment 8 to 11. Such crystalline form is described in patent application PCT/CN2018/087448 filed on May 18, 2018 (attorney docket number: PAT058103-WO-PCT) which is hereby incorporated by reference.

15 As used herein neuropsychiatric systemic lupus erythematosus (NPSLE) refers to different neurological and/or behavioral clinical syndromes in patients suffering from systemic lupus erythematosus (SLE), which includes central nervous system (CNS) manifestations (CNS-lupus) and neuropathies in the peripheral nervous system (PNS). The neuropsychiatric manifestations of lupus vary from mild to severe (see Kivity *et al.* BMC Med. 2015 Mar 4;13:43) and affect up to 75%
20 of patients with SLE. The effect of neuropsychiatric manifestations on disease severity, quality of life, and prognosis is considered one of the major causes of morbidity and mortality in patients with SLE.

The present invention relates to the treatment of NPSLE patients typically via inhibition of
25 the Toll-like receptors (TLR), and may especially include the inhibition of TLR7. Importantly, since applicant does not wish to be bound to mechanistic considerations, the present invention relates to a compound of formula (I) or a compound of Formula (II) in accordance to any one of embodiments 1 to 12, or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of NPSLE.

30 In a further embodiment the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a compound of Formula (II) or a compound according to any one of the embodiments 1 to 12; or a pharmaceutically acceptable salt thereof together with

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one or more pharmaceutically acceptable carrier for use in the treatment and/or prevention of NPSLE.

5 In a still further embodiment the present invention provides a method for treating and/or preventing NPSLE in a patient in need thereof comprising administering an effective amount of a compound of Formula (I) wherein the compound is as described in any one of embodiments 1 to 7; or a pharmaceutically acceptable salt thereof.

10 In a still further embodiment the present invention provides a method for treating and/or preventing NPSLE in a patient in need thereof comprising administering an effective amount of a compound of Formula (II), wherein the compound is as described in any one of embodiments 8 to 12; or a pharmaceutically acceptable salt thereof.

15 In a still further embodiment the present invention provides a method for treating and/or preventing NPSLE in a patient in need thereof comprising administering a pharmaceutical composition comprising an effective amount of a compound of formula (I) in accordance to any one of embodiments 1 to 7; or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carrier.

20 In a still further embodiment the present invention provides a method for treating and/or preventing NPSLE in a patient in need thereof comprising administering a pharmaceutical composition comprising an effective amount of a compound of formula (II) in accordance to any one of embodiments 8 to 12; or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carrier.

25

In a still further embodiment the present invention provides the use of a compound in accordance to formula (I) in accordance to any one of embodiments 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating and/or preventing NPSLE.

30 In a still further embodiment the present invention provides the use of a compound in accordance to formula (II) in accordance to embodiment 7 to 12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating and/or preventing NPSLE.

For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa.

As used herein, the term "alkyl" refers to a fully saturated branched or unbranched hydrocarbon moiety having up to 20 carbon atoms. Unless otherwise provided, alkyl refers to hydrocarbon moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2- dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

As used herein, the term "alkoxy" refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, hexyloxy, and the like. Typically, alkoxy groups have about 1-6, more preferably about 1-4 carbons.

As used herein the term halogen refers to a fluoro, chloro, bromo or iodo radical or residue. Halogen may preferably be fluoro.

As used herein, the term alkyl optionally substituted one or more times by halogen may for example refer to methyl, ethyl, propyl, *tert*-butyl, monofluoromethyl, difluoromethyl, trifluoromethyl, trifluoroethyl, tetrafluoroethyl or pentafluoroethyl.

Pharmaceutically acceptable acid addition salts may be formed with inorganic acids and organic acids.

Pharmaceutically acceptable base addition salts may be formed with inorganic and organic bases.

The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide,

bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlorthephylionate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, 5 octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, 10 hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic 15 acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived 20 from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic 25 amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a 30 basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two.

Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

As used herein, the term "free form" refers to the compound per se without salt formation.

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response in a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease (e.g. ameliorating the symptoms associated with NPSLE; alleviating the NPSLE condition, slow or delay the progression of NPSLE)

As used herein, the term "subject" refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human. In some embodiment, human subject is also referred to as patient.

As used herein, the term "inhibit", "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat", "treating" or "treatment" refers to alleviating or ameliorating at least one

physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat", "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In one embodiment, treating NPSLE refers to treating different
5 neurological and/or behavioral clinical syndromes in patients suffering from systemic lupus erythematosus (SLE). Those neurological and/or behavioral clinical syndromes include 19 syndromes, according to the American College of Rheumatology definition (Arthritis Rheum 1999, 42(4):599-608): aseptic meningitis, cerebrovascular diseases, demyelinating syndrome, headache, movement disorder, myelopathy, seizure disorders, acute confusional state, anxiety disorder,
10 cognitive dysfunction, neuropathy, mood disorder and psychosis as well as the peripheral syndromes Guillain Barré syndrome, autonomic neuropathy, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy and polyneuropathy.

As used herein, the term "preventing" refers to delaying the onset or development or progression of the disease or disorder (i.e. delaying the onset or development or progression of the
15 neurological and/or behavioral clinical syndromes as defined above)

As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and
20 plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

25 Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at
30 least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein the use of a compound of the present invention may be in the form of one of the possible isomers such as rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers

(antipodes), racemates or mixtures thereof. For clarity, positional isomer are not encompassed by the above.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high performance liquid chromatography (HPLC) or supercritical fluid chromatography (SFC) using a chiral adsorbent.

Administration and Pharmaceutical Compositions

For the therapeutic uses of compounds of the invention, such compounds are administered in therapeutically effective amounts either alone or as part of a pharmaceutical composition. Accordingly, the present invention provides a pharmaceutical composition, which comprises a compound of the invention, or pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. For purposes of the present invention, unless designated otherwise, solvates and hydrates are generally considered compositions. Preferably, pharmaceutically acceptable carriers are sterile.

The pharmaceutical composition of the present invention may be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, e.g., aqueous solutions, and *in vivo* either enterally, parenterally, advantageously

intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg.

5 The pharmaceutical compositions of the invention can be prepared using processes which include admixing a compound of the invention, or pharmaceutically acceptable salts thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. By way of example, the pharmaceutical compositions of the inventions are manufactured by mixing, granulating and/or coating methods using a compound of the invention in free form, or in a pharmaceutically
10 acceptable salt form, in association with at least one pharmaceutically acceptable carrier, diluent or excipient.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water may facilitate the degradation of certain compounds.

15 Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary
20 kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e. g., vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient may decompose. Such agents, which are referred to herein as "stabilizers,"
25 include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, rectal administration, transdermal administration, parenteral, intravenous administration, intramuscular administration, pulmonary administration, inhalation administration, intranasal administration, ophthalmic administration and topical administration.

30 Oral Administration Dosage Forms

The pharmaceutical compositions of the invention may be administered orally as discrete dosage forms, wherein such dosage forms include, but are not limited to, capsules, gelatin capsules, caplets, tablets, chewable tablets, lozenges, dispersible powders, granules, syrups,
35 flavored syrups, solutions or suspensions in aqueous or non-aqueous liquids, edible foams or

whips, and oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Accordingly, for oral administration the pharmaceutical compositions of the invention comprising an effective amount of a compound of the invention can be made up in a solid form including without limitation capsules, gelatin capsules, hard or soft capsules, tablets, chewable tablets, lozenges, caplets, pills, granules or dispersible powders, or in a liquid form including without limitation solutions, aqueous or oily suspensions, syrups, elixirs, foams, whips or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc.

Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

- a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also
- c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired
- d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and
- e) absorbents, colorants, flavors and sweeteners.

Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. Tablets may be either film coated or enteric coated according to methods known in the art. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium

carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Parenteral Dosage Forms

5 In certain embodiments pharmaceutical compositions of the invention may be administered parenterally by various routes including, but not limited to, subcutaneous, intravenous including bolus injection, intramuscular, and intraarterial.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said
10 compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and typically contain about 0.1-75%, or about 1-50%, of the active ingredient.

15 Topical Dosage Forms

In certain embodiments pharmaceutical compositions of the invention may be administered by topical application of a pharmaceutical composition containing a compound of the invention in the form of a lotion, gel, ointment, solution, emulsion, suspension or cream.

20 Suitable compositions for topical application, e.g., to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, e.g., for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, e.g., for the treatment of skin cancer, e.g., for prophylactic use in sun creams, lotions, sprays and the like. They are thus particularly suited for use in topical, including cosmetic,
25 formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with
30 phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurized container, pump, spray, atomizer or nebulizer, with or without the use of a suitable propellant.

Rectal Administration

In certain embodiments pharmaceutical compositions of the invention of the invention may be
35 administered rectally in the form of suppositories, enemas, ointment, creams rectal foams or rectal

gels. In certain embodiments such suppositories are prepared from fatty emulsions or suspensions, cocoa butter or other glycerides.

Depot Administration

5 In certain embodiments pharmaceutical compositions of the invention of the invention may be formulated as a depot preparation. Such formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, such formulations include polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a
10 sparingly soluble salt.

In one embodiment, the compound of Formula (I) or (II) according to any one of embodiments 1 to 12, is preferably administered by oral route.

15 Combination Treatment

Compounds of the invention and pharmaceutical compositions provided herein may be administered singly or in combination with one or more additional therapeutic agents, e.g. low molecular weight antimalarials or biologics selected e.g. from anti-CD40 antibodies.

20 The combination of the present invention may be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg. The therapeutically effective dosage of the combinations is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill may readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

25 The above-cited dosage properties are typically demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention may be applied *in vitro* in the form of solutions, e.g., aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The dosage *in vitro* may range
30 between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg.

The compound of the present invention may be administered either simultaneously, or before or after, with one or more other therapeutic agent. The compound of the present invention may be

administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents. A therapeutic agent is, for example, a chemical compound, peptide, antibody, antibody fragment or nucleic acid, which is therapeutically active or enhances the therapeutic activity when administered to a patient in combination with a compound of the invention.

The additional therapeutic agents used in combination with a compound of the invention, include, but are not limited to anti-inflammatory agents, immunomodulatory agents, immunosuppressive agents, cytokines, nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarial compounds, anti-rheumatic compounds, inhibitors of B-cell activating factor (BAFF), inhibitors of B-lymphocyte stimulator (BLyS), and steroid hormones, neurological drugs and anticoagulants.

Nonsteroidal anti-inflammatory drugs (NSAIDs) used in combination with compounds of the invention, include, but are not limited to, salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, ibuprofen, naproxen, naproxen sodium, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetone, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide.

Anti-rheumatic compound used in combination with compounds of the invention, include, but are not limited to, methotrexate.

Antimalarial compound used in combination with compounds of the invention, include, but are not limited to, chloroquine and hydroxychloroquine.

Inhibitors of B-cell activating factor (BAFF), also known as inhibitors of B-lymphocyte stimulator (BLyS), used in combination with compounds of the invention, include, but are not limited to, belimumab (Benlysta®), Blisibimod and BR3-Fc.

Immunosuppressive agents used in combination with compounds of the invention, include, but are not limited to, mycophenolate mofetil (MMF), mycophenolic acid, cyclophosphamide, azathioprine and Laquinimod (5-chloro-N-ethyl-4-hydroxy-1-methyl-2-oxo- N-phenyl-1,2-dihydroquinoline-3-carboxamide).

Steroid hormones used in combination with compounds of the invention, include, but are not limited to, dehydroepiandrosterone (DHEA)

Depending on the specific neuropsychiatric manifestation of NPSLE, a combination with neuroleptic drugs, including but not limited to antidepressants, antiepileptic drugs, antipsychotic

drugs could be envisaged. Since thrombi are suspected as one of the causes of NPSLE, a combination with antiplatelet treatments or anticoagulants could be envisaged.

5 Experimental Part

Preparation of the compounds for use in the invention:

The synthesis of the compounds of Formula (I) and Formula (II) has been described in US Patent No. 9,126,999 and PCT application WO2018/047081 respectively. Both US9,126,999 and
10 WO2018/047081 are therefore incorporated by reference.

State of the Art and Significance:

An anti-type 1 interferon receptor (IFNAR) antibody has recently shown efficacy in a Ph2b study in lupus patients (published by R. Furie et al., Arthritis and Rheumatology, 69, 376-386, 2017).
15 Blockade of IFNAR also reduced the autoimmune phenotype in the 564Igi murine model of lupus. In this model, follicular dendritic cells (FDC) have been identified as a major source IFN α : Immune complexes of autoantibodies and nucleoli elicit IFN α from FDCs via the endosomal receptor TLR7 (published by A. Das et al., Immunity 46, 106-119, 2017).
In a related study in the 564Igi model, anti-IFNAR treatment was protective against CNS pathology
20 (reactive microglia, synapse loss, and microglia engulfment of neuronal material), and behavioral phenotypes (published by Bialas et al., Nature 546, pp 539, 2017).

Concept:

Based on the above, the inventors developed the scientific concept that a TLR7 antagonist, e.g. a
25 compound of the invention, e.g. a compound of formula (I) or in particular a compound of formula (Ia) or formula (Ib), or a compound of Formula (II) and in particular a compound of Formula (IIa) or (IIb) or (IIc) blocks IFN α production, restores B cell tolerance, halts the progression of peripheral autoimmunity and hence reduces CNS pathology in the 564Igi mice lupus model.

30 Experiments and Considerations:

A staggered two-step approach is used to study the efficacy of the compound of formula (Ib) and a compound of Formula (IIc) in 564Igi mice.

It is known from the literature (see Forsbach et al, J.Immunol., 2008, 180: 3729-3738) that TLR8 is non-functional in rodents. However from US 9,126,999 B2 it is known that their underlying
35 compounds, including compound of formula (Ib), are dual TLR7/8 antagonists. It is also known from

- 20 -

WO2018/047081 that compounds of Formula (II), (IIa), (IIb) or (IIc) are dual TLR7/8 antagonists. For this reason, the results of the compounds of the present invention may or may not depend on the efficacy of the compound on the TLR7 and the TLR8 receptor, since as eluded above TLR8 is non-functional in rodents. Consequently, the effect of the compounds of the invention obtained in the below animal experiments may not necessarily be linkeable to TLR8.

(1) Testing the ability of compound of Formula (Ib) or a compound of Formula (Iic) to reduce IFN α -dependent autoimmunity:

564Igi mice (n=5 per group) are treated with a compound of formula (Ib) or with vehicle via the food for a period of two weeks. The compound of formula (Ib) is a potent TLR7 antagonist, i.e. has an IC₅₀ of 35 nM as determined by suppression of IFN α secretion from human peripheral blood mononuclear cells (PBMCs) following stimulation with single stranded RNA (ssRNA) complexed with a liposomal transfection reagent. The compound has also a TLR8 antagonist component as it suppresses TNF α in a similar assay with an IC₅₀ of 36 nM.

The compound of formula (Iic) is a potent TLR7 antagonist, i.e. has an IC₅₀ of 4 nM as determined by huPBMC TLR7 Antagonist IFN α Assay disclosed in WO2018/04081, filed Septmber 6, 2017. The compound has also a TLR8 antagonist component as it suppresses TNF α in a similar assay with an IC₅₀ of 166 nM.

Mice are bled periodically, and blood cells are assayed for expression of interferon stimulated genes (ISGs) by qPCR. CD69 expression is measured from blood following *ex vivo* R848 stimulation as a pharmacodynamic marker, and compound exposure is determined in blood. On day 15, mice are sacrificed and spleen and lymph nodes is taken for flow cytometry analysis and immunohistochemistry. This analysis focuses on the frequency of auto-antibody specific (Id pos) B cells, germinal center B cells (GC) and plasmablasts and expression of IFN α . Spleen tissue is harvested for ISG analysis. Anti-nucleolar antibody titers are determined from serum by ELISA.

Experimental Results: ISGs and *ex vivo* stimulated CD69 is inhibited in 564 Igi mice which are treated with a compound of formula (Ib) or a compound of Formula (Iic) as opposed to the vehicle group, confirming that the 564 Igi model is TLR7 dependent.

(2) Testing the ability of a compound of Formula (Ib) or a compound of Formula (Iic) to reduce NPSLE symptoms:

564lgi and NZB/W F1 mice (n=10 per group) are treated with a compound of Formula (Ib) or a compound of Formula (IIc) or with vehicle via the food for a period of 6 weeks, beginning at 8 weeks of age until 14 weeks of age. In analogy to the above experiment 1, mice are bled periodically, and blood cells are being assayed for expression of interferon stimulated genes (ISGs) by qPCR. CD69 expression is measured from blood following *ex vivo* R848 stimulation as a pharmacodynamic marker, and compound exposure is determined in blood.

Starting at 12 weeks of age, mice will undergo behavioral testing, such as the elevated plus maze, the novelty Y maze, the three-chamber social interaction assay, and pre-pulse inhibition testing. At the end of the experiment, mice are sacrificed for harvesting serum, cerebrospinal fluid (CSF), spleen, and brain tissue for carrying out the following analyses:

Spleens are analyzed for ISG expression by qPCR, and for auto-antibody specific (Id pos) B cells, germinal center B cells (GC) and plasmablasts by immunohistochemistry and flow cytometry. Anti-nucleolar antibody titers are determined from serum by ELISA. Brain is analyzed by qPCR for ISGs and microglia is studied by immunohistochemistry and by flow cytometry. In addition, CD69 expression is measured from blood following *ex vivo* R848 stimulation as a pharmacodynamic marker, compound exposure is determined in blood and metabolite levels are determined in serum, brain and CSF.

Experimental Results: 564lgi or NZB/W F1 mice which are treated with a compound of Formula (Ib) or a compound of Formula (IIc) - as opposed to mice of the vehicle group - show reduced progression of NPSLE symptoms, i.e. reduced aberrant behavior in the different behavioral tests, fewer histological and molecular changes to the CNS which are indicative of interferon signaling and neuropathological symptoms, and lower amounts of potentially neurotoxic metabolites. In parallel to these neuropathological findings, lower titers of anti-nucleolar antibodies and antibodies directed against neuronal components in peripheral blood and lower expression of ISGs in spleens. Together, weaker neuropathological findings in 564lgi or NZB/W F1 animal models of NPSLE after treatment with the compound of formula (Ib) or with a compound of Formula (IIc) may *inter alia* indicate a pathogenic role of TLR7 in NPSLE.

3) Neuroprotection conferred by TLR7/8 antagonists in a mouse model of NPSLE

The diagnosis of NPSLE defines a subgroup of SLE patients with CNS involvement. The NZBW/F1 mouse model of lupus shows neuropathological symptoms (Bialas et al., Nature 2017 546 (7659):

539-543; Kier et al. J Comp Pathol 1990, 102(2):165-177), and compound of Formula confers protection on systemic readouts in this model, e.g. kidney pathology (**Figure 1**).

Figure 1: Efficacy of compound of Formula (Ib) on systemic disease parameters in the

NZBW/F1 model. NZBW/F1 mice were treated q.d. with 100 mg/kg compound of Formula (Ib) p.o. (filled circles) or vehicle (open circles), starting at 28 weeks of age. Proteinuria (Uristix, Bayer, Leverkusen, Germany) and body weight of NZB/W F1 mice were recorded weekly throughout the experiment, starting at 20 weeks of age. At a proteinuria score of 2 (Score 0: no protein detected, 1: trace, 2: >30 mg/dl, 3: >100 mg/dl, 4: >300mg/dl, 5: >2000mg/dl), animals were randomized to experimental groups of n=15. Individual animals were taken out of the experiment once body weight loss had reached 20% or once an animal had two consecutive proteinuria scores of 5, and its last proteinuria score was recorded for the remainder of the experiment. The study was terminated as soon as 50% of animals of any group had been taken out of the experiment. **A**, survival, p=0.02, log rank test, **B**, proteinuria, *, p<0.05, **, p<0.01, *** p<0,001, ****, p<0.0001, unpaired t-test. Dots represent means $\pm$ SEM

Compound of Formula (IIc) was found to reduce specific markers of brain pathology in this model. Compound of Formula (IIc) blocked systemic readouts (**Figure 2a,b**), and dose-dependently inhibited the expression of NMDAR autoantibodies (**Figure 2c**), which are associated with NPSLE in humans (Omdal et al., Eur J Neurol 2005 12(5):392-398; Robbins et al., Arthritis Rheum 1998 31(5):623-31) and directly disturb neuronal function (Faust et al., PNAS 2010, 107(43):18569-74). In addition, compound of Formula (IIc) blocked NF-L levels in the circulation (**Figure 2d**) and NF-L is a widely used clinical biomarker of inflammatory damage to the CNS (e.g. Cai et al., Neuropsychiatr Dis.Treat, 2018 14:2241-2254). Since compound of Formula (IIc) inhibited serum levels of anti-NMDAR autoantibodies and NF-L, it was demonstrated that compound of Formula (IIc) has a neuroprotective role in NPSLE.

Materials and Methods

Female 12-week-old NZB/W F1 mice (NZBNZWF1/OlaHsd) were obtained from

Envigo

RMS Limited (Blackthorn, Bicester, UK). Mice were housed (3-5 mice/Individually Ventilated Cage, IVC) at 21 $\pm$ 2°C and 55 $\pm$ 10% relative humidity with a time-regulated light period from 6:00 a.m. to 6:00 p.m., and fed *ad libitum*. In the Health Monitoring Report from Envigo (Report Reference: 17-9212; from 4 Jan 2017) the following

opportunistic bacterial infections were reported: *Escherichia coli*, *Lactobacillus spp*, *Staphylococcus spp* (incl. *S. aureus*), *Streptococcus spp* (incl. alpha-haemolytic). At 15 weeks of age, radiofrequency identification transponders (T-SL Slim Polymer Microchip, DataMars) were injected subcutaneously with a lancet into the nape of the neck under isoflurane anesthesia to uniquely identify the mice. All studies were performed under strict adherence to the Swiss law for animal protection and were approved by the Veterinary Office Basel Stadt (Animal License No. BS-2868).

Monitoring of body weight and proteinuria

From arrival until 20 weeks of age, body weight was recorded weekly. Starting at 20 weeks of age, body weight was recorded twice weekly and proteinuria was measured weekly until the end of the experiment. Drug treatment started when mice were 23 weeks old.

For weekly proteinuria measurements, urine was sampled into glass capillaries by massaging the abdomen and immediately transferred into ice-cold 96 well plates.

Protein levels in fresh urine were measured using a quantitative Protein Assay (Bio-Rad, Hercules, CA #5000006) with Bovine Serum Albumin (BSA) as a standard (SigmaAldrich, St. Louis, MO, A-8806). Mice were assigned to the different treatment groups when a majority had reached proteinuria levels of approximately 0.5 mg/ml. Individual mice were taken out of the experiment once body weight loss had reached 20% compared to 10 days before or an animal had two consecutive proteinuria levels ≥ 10 mg/ml (24-48 h apart). The study was terminated as soon as 50% of animals of the control group (also called "vehicle" group, receiving drug-free food) had developed clinically relevant proteinuria (≥ 5 mg/ml).

Preparation of compound-loaded food (Compound of Formula (Ic))

Compound of Formula (Ic) was mixed into mouse chow as follows: compound of Formula (Ic) was added to dry powdered food (Maus/Ratte Haltung "GLP" NAFAG3890 and NAFAG3302 for the last 2.5 weeks of the experiment, Provimi Kliba, Kaiseraugst, Switzerland). Water (50% w/w) was added to result in a homogenous dough, which was extruded and cut into 1.5-2.0 cm-long pellets. Pellets were dehydrated for 24 h at 37°C in a dehydrator (Excalibur EXC10EL, Sacramento, CA). Drug-free control pellets were prepared in parallel.

A pilot PK/PD study in female NZB/W F1 mice using compound mixed to chow suggested 0.03% in food as the lowest fully efficacious dose based on ex vivo blood

PD readouts. Based on this, 0.01% and 0.1% of compound of Formula (IIc), i.e. 0.1 or 1 g/kg food were selected for the present study.

Mice received fresh food every two weeks and daily food consumption per mouse was calculated by dividing food intake by the number of days and number of mice per cage. Food consumption was defined as food given minus food left in the cage.

Treatment groups

At 23 weeks of age, mice were assigned to one of four treatment groups:

- (1) 0.01% compound of Formula (IIc) in food (n=14), proteinuria 0.5 mg/ml at start,
- (2) 0.1% compound of Formula (IIc) in food (n=14), proteinuria 0.5 mg/ml at start,
- (3) Control food (n=14), no compound added, proteinuria 0.5 mg/ml at start (i.e. "vehicle" group)

Treatments for all mice started on the same day and were maintained until the end of the experiment, i.e. 41 weeks of age. Blood was sampled for drug exposure (PK), PD and ANA measurements at the indicated time points during the experiment.

1. Measurement of autoantibodies in serum

NZB/W F1 mice were bled from the tail vein (in-life) or by heart puncture (terminal) into micro tubes Z-gel (Sarstedt, Nümbrecht, Germany). Serum was isolated by centrifugation (10000 g, 10 min, RT) and kept at -80°C.

Nunc Maxisorp plates (Huberlab, Aesch, Switzerland) were coated in PBS at 4°C overnight with either diluted 100 µg/ml salmon sperm DNA (Thermo Fisher Scientific, Waltham, MA), 10 µg/ml calf thymus histone (Sigma-Aldrich, St. Louis, MI), 1 unit/well ribosomal P (Immunovision, Springdale, AK), 1 unit/well Smith antigen (Immunovision), or 20 µg/ml DWEYS peptide (Ac-Asp-Trp-Glu-Tyr-Ser-Val-Trp-Leu-Ser-Asn-AEEAc-NH₂ trifluoroacetate, Bachem, Bubendorf, Switzerland) for detection of anti-N-methyl-D-aspartate receptor (NMDAR) subunit 2A (NR2A) antibodies. Plates were washed in PBS/0.05% Tween-20 (Bio-Rad), incubated with PBS/1% v/v BSA (Merck, Darmstadt, Germany) at room temperature for 1 h and washed in PBS/0.05% Tween-20. Serum dilutions of 1:100 or 1:300 in PBS/1% BSA (100 µl) were added for 2 h at RT, plates were washed in PBS/0.05% Tween-20 and HRP-conjugated isotype-specific detection antibodies were added for 2 h at RT (1/5000 for polyclonal goat anti-mouse IgG1, polyclonal goat anti-mouse IgG2a,

polyclonal goat antimouse IgG3 and polyclonal goat anti-mouse IgM, all from Southern Biotechnology, Birmingham, AL; 1/10000 for polyclonal goat anti-mouse IgG, Sigma Aldrich). Plates were washed and 100 μ l/well TMB substrate (BD Biosciences) was added. The reaction was stopped by adding 100 μ l/well 1 N HCl and the OD measured at λ =450 nm (Spectramax M5, Molecular Devices, Sunnyvale, CA). Data were expressed as OD (450 nm) / (x-background).

SS-A pre-coated plates (Elisa kit from Alpha diagnostic, San Antonio, TX) were incubated with 100 μ l of calibrators or 1/100 diluted serum. After 1 h at room temperature plates were washed with wash buffer and 1/100 goat anti-mouse Ig HRP provided in the kit was added for 30 min at room temperature. Plates were washed and 100 μ l/well TMB substrate was added. The reaction was stopped by adding 100 μ l/well stop solution and the OD measured at λ =450 nm (Spectramax M5). Percent autoantibody levels were calculated by expressing each autoantibody level for each compound-treated animals as percent, with 100% defined as the mean level of the corresponding autoantibody in the vehicle-treated group. Percentages for anti-Smith, antiribosomal P, and anti-NMDAR (IgG2a, IgG2, IgG) were averaged for a composite score.

2. Measurement of Neurofilament light chains in serum

Neurofilament light chains (NF-L) in serum were measured using a sandwich ELISA. MultiArray 96 plates (Meso Scale Diagnostics, Rockville, MD) were coated with 50 μ l/well of 1.25 μ g/ml anti-NF-L mouse monoclonal antibody (47:3 (UD1), UmanDiagnostics, Umea, Sweden) in 0.05 M Carbonate-Bicarbonate buffer (pH 9.6, Sigma Aldrich) overnight at 4°C with agitation at 550 rpm. The next day, plates were blocked using 100 μ l/well TBS/3% BSA (both from Sigma Aldrich) at RT for 1 h with agitation (800 rpm). In the meantime the NF-L Standard purified from bovine spinal cord (Uman Diagnostics) was prepared in Assay Diluent (Tris-buffered saline TBS/0.1%Tween-20/1% BSA) containing 300 μ g/ml HeteroBlock (Omega Biologicals, Bozeman, MT) to obtain a serial two-fold 10-point standard curve ranging from 4000 pg/ml to 7.8125 pg/ml. Plates were washed with TBS/0.1% Tween-20, and 25 μ l/well of Assay Diluent containing 300 μ g/ml of HeteroBlock for standard wells or 600 μ g/ml of HeteroBlock for sample wells were added. Standards or undiluted samples (25 μ l/well) were added to the plate and incubated at RT for 2 h with agitation (800 rpm). Plates were washed with TBS/0.1% Tween-20 and 25 μ l/well of 0.1875 μ g/ml

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biotinylated anti-NFL mouse monoclonal antibody (2:1 (UD3), Uman Diagnostics) in Assay Diluent was added. Plates were incubated at RT for 1 h with agitation (800 rpm), washed with TBS/0.1% Tween20 and 25 μ l/well SULFO-TAG labelled Streptavidin (0.25 μ g/ml, Meso Scale Diagnostics) in Assay Diluent was added.

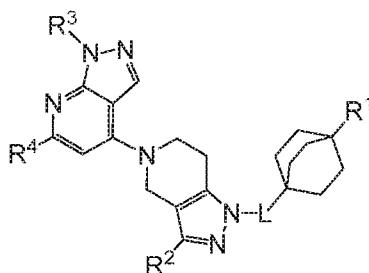
5 Plates were incubated at RT for 1 h with agitation (800 rpm), washed with TBS/0.1% Tween-20 and 150 μ l/well of Read Buffer T (Meso Scale Diagnostics) was added. Electrochemiluminescence was quantified using Meso Sector S600 Reader (Meso Scale Diagnostics).

10

Other enumerated embodiments

Embodiment 1a. A method of treating and/or preventing NPSLE, comprising administering to a patient in need thereof, an effective amount of a compound of formula (II):

15



Formula (II)

wherein

L is -CH₂- or -CH₂CH₂-;

20 R¹ is -NHC(=O)R⁶, -NHC(=O)(CH₂)_nR⁶, -NHC(=O)(CH₂)_mNHR⁵, -NHC(=O)(CH₂)_mN(R⁵)₂, -NHC(=O)(CHR⁷)_mNHR⁵, -NHC(=O)(CH₂)_mNH₂, -NHC(=O)(CH₂)_nOR⁷, -NHC(=O)OR⁷, -NHC(=O)(CHR⁷)_nR⁶, -NHC(=O)(CHR⁷)_nN(R⁸)₂, -NHC(=O)(CHR⁷)_nNHR⁸, -NR⁷C(=O)OR¹¹, -NHC(=O)(CH₂)_nN(CD₃)₂, -NR⁷C(=O)R⁵, -NR⁷C(=O)(CH₂)_nR⁵, -NR⁷C(=O)OR⁵, -NHS(=O)₂R⁵, -NHC(=O)(CH₂)_nNR⁷C(=O)R⁵ or -NHC(=O)(CH₂)_nNR⁷S(=O)₂R⁵;

25 R² is H, C₁-C₆alkyl or C₁-C₆haloalkyl;

R³ is H, C₁-C₆alkyl or -CD₃;

R⁴ is H, NH₂, C₁-C₆alkyl or halo;

each R⁵ is independently selected from C₁-C₆alkyl, -CD₃ and -(CH₂)_nOR⁷;

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R^6 is a C_3 - C_6 cycloalkyl or a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, $N(C_1-C_6\text{alkyl})$ and O which is unsubstituted or is substituted with 1-2 R^9 groups;

each R^7 is independently selected from H and $C_1-C_6\text{alkyl}$;

5 each R^8 is independently selected from $C_1-C_6\text{haloalkyl}$, $-(C(R^7)_2)_nOR^7$ and a $C_1-C_6\text{alkyl}$ substituted with 1 to 3 $-OH$;

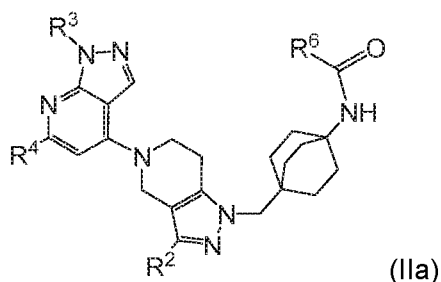
each R^9 is independently selected from $C_1-C_6\text{alkyl}$, hydroxyl, halo and a $C_1-C_6\text{alkyl}$ substituted with 1 to 3 $-OH$;

n is 1, 2, 3, 4, 5 or 6; and

10 m is 1, 2, 3, 4, 5 or 6; or a pharmaceutically acceptable salt thereof

Embodiment 2a. The method according to embodiment 1a wherein said compound is a compound of Formula (IIa):

15



wherein

R^2 is H, $C_1-C_6\text{alkyl}$ or $C_1-C_6\text{haloalkyl}$;

R^3 is H, $C_1-C_6\text{alkyl}$ or $-CD_3$;

20 R^4 is H, NH_2 , $C_1-C_6\text{alkyl}$ or halo;

R^6 is a C_3 - C_6 cycloalkyl or a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, $N(C_1-C_6\text{alkyl})$ and O which is unsubstituted or is substituted with 1-2 R^9 groups;

25 each R^9 is independently selected from $C_1-C_6\text{alkyl}$, hydroxyl, halo and a $C_1-C_6\text{alkyl}$ substituted with 1 to 3 $-OH$; or a pharmaceutically acceptable salt thereof.

Embodiment 3a. The method according to embodiment 2a wherein the compound is a compound of Formula (IIa) and:

R^2 is $C_1-C_4\text{alkyl}$;

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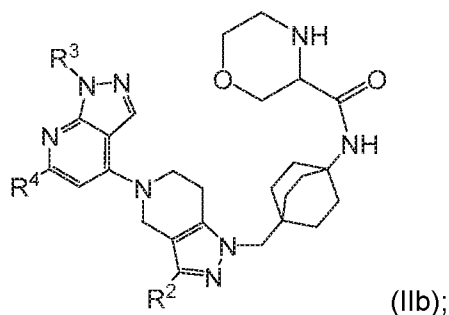
R^3 is C_1 - C_4 alkyl;

R^4 is C_1 - C_4 alkyl or halo;

R^6 is a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, $N(C_1$ - C_6 alkyl) and O; or a pharmaceutically acceptable salt thereof.

5

Embodiment 4a. The method according to any one of embodiments 1a to 3a wherein said compound is a compound of Formula (IIb):



wherein

10

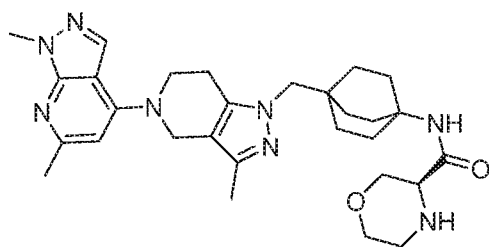
R^2 is C_1 - C_4 alkyl;

R^3 is C_1 - C_4 alkyl;

R^4 is C_1 - C_4 alkyl; or a pharmaceutically acceptable salt thereof.

15

Embodiment 5a. The method according to any one of embodiments 1a to 4a wherein said compound is of Formula (IIc):

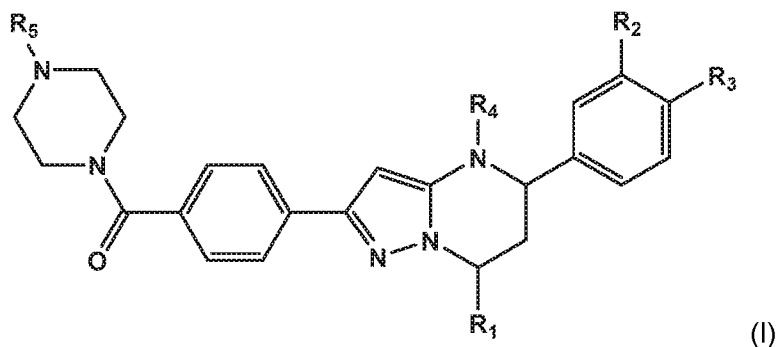


(IIc); or a pharmaceutically acceptable salt thereof.

20

Embodiment 6a. A method of treating and/or preventing NPSLE, comprising administering to a patient in need thereof, an effective amount of a compound of formula (I):

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wherein

R₁ is hydrogen, or C₁-C₄alkyl optionally substituted one or more times by halogen;

R₂ and R₃ are independently from each other hydrogen or C₁-C₆alkoxy;

5 R₄ is hydrogen or C₁-C₆alkyl; and

R₅ is hydrogen or C₁-C₆alkyl; or a pharmaceutically acceptable salt thereof.

Embodiment 7a. The method in accordance to embodiment 6a, wherein the compound is a compound of Formula (I) and

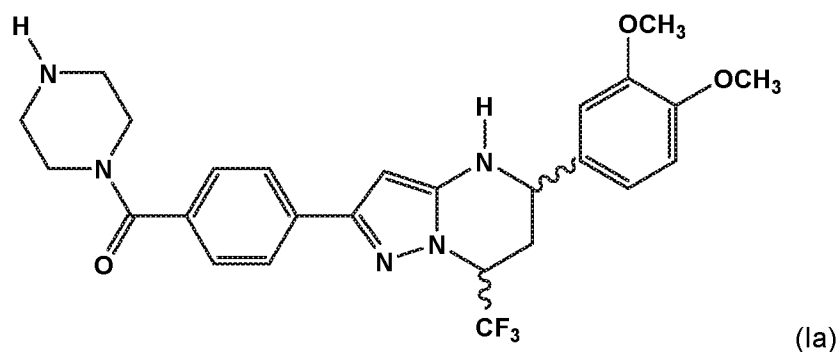
10 R₁ is trifluoromethyl or difluoromethyl;

R₂ and R₃ are both methoxy;

R₄ is hydrogen; and

R₅ is hydrogen or methyl; or a pharmaceutically acceptable salt thereof.

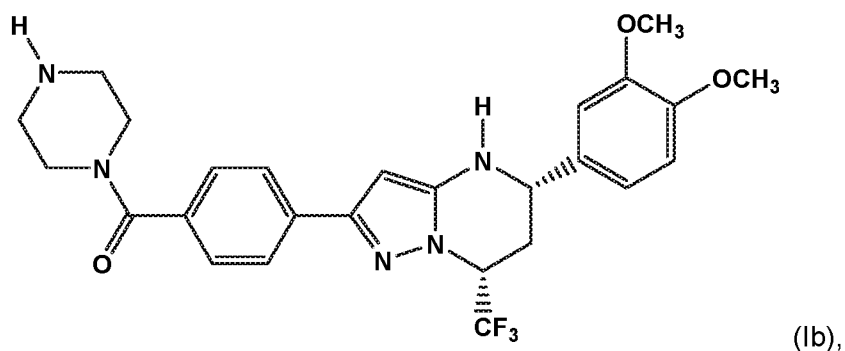
15 Embodiment 8a. The method according to embodiment 6a or 7a wherein said compound is a compound of formula (Ia),



or a pharmaceutically acceptable salt thereof.

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Embodiment 9a. The method according to embodiment 6a, 7a or 8a, wherein said compound is a compound of formula (Ib),



or a pharmaceutically acceptable salt thereof.

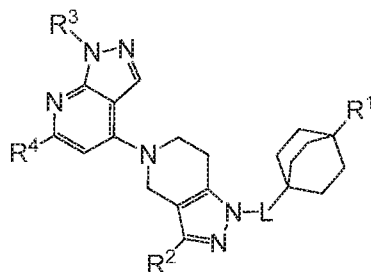
5

Embodiment 10a. The method according to any one of embodiments 1a to 9a, wherein NPSLE refers to different neurological and/or behavioral clinical syndromes in patients suffering from systemic lupus erythematosus (SLE).

10

Claims

1. A compound of Formula (II) or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prevention of NPSLE,



Formula (II)

wherein

L is -CH₂- or -CH₂CH₂-;

- 10 R¹ is -NHC(=O)R⁶, -NHC(=O)(CH₂)ₙR⁶, -NHC(=O)(CH₂)ₘNHR⁵, -NHC(=O)(CH₂)ₘN(R⁵)₂, -NHC(=O)(CHR⁷)ₘNHR⁵, -NHC(=O)(CH₂)ₘNH₂, -NHC(=O)(CH₂)ₙOR⁷, -NHC(=O)OR⁷, -NHC(=O)(CHR⁷)ₙR⁶, -NHC(=O)(CHR⁷)ₙN(R⁸)₂, -NHC(=O)(CHR⁷)ₙNHR⁸, -NR⁷C(=O)OR¹¹, -NHC(=O)(CH₂)ₙN(CD₃)₂, -NR⁷C(=O)R⁵, -NR⁷C(=O)(CH₂)ₙR⁵, -NR⁷C(=O)OR⁵, -NHS(=O)₂R⁵, -NHC(=O)(CH₂)ₙNR⁷C(=O)R⁵ or -NHC(=O)(CH₂)ₙNR⁷S(=O)₂R⁵;

- 15 R² is H, C₁-C₆alkyl or C₁-C₆haloalkyl;

R³ is H, C₁-C₆alkyl or -CD₃;

R⁴ is H, NH₂, C₁-C₆alkyl or halo;

each R⁵ is independently selected from C₁-C₆alkyl, -CD₃ and -(CH₂)ₙOR⁷;

- 20 R⁶ is a C₃-C₆cycloalkyl or a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, N(C₁-C₆alkyl) and O which is unsubstituted or is substituted with 1-2 R⁹ groups;

each R⁷ is independently selected from H and C₁-C₆alkyl;

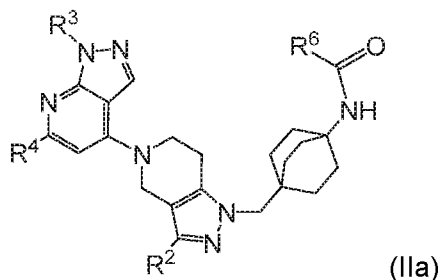
each R⁸ is independently selected from C₁-C₆haloalkyl, -(C(R⁷)₂)ₙOR⁷ and a C₁-C₆alkyl substituted with 1 to 3 -OH;

- 25 each R⁹ is independently selected from C₁-C₆alkyl, hydroxyl, halo and a C₁-C₆alkyl substituted with 1 to 3 -OH;

n is 1, 2, 3, 4, 5 or 6; and

m is 1, 2, 3, 4, 5 or 6.

2. A compound of Formula (II) for use according to claim 1, wherein said compound is a compound of Formula (IIa):



wherein

R^2 is H, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

R^3 is H, C_1 - C_6 alkyl or $-CD_3$;

R^4 is H, NH_2 , C_1 - C_6 alkyl or halo;

R^6 is a C_3 - C_6 cycloalkyl or a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, $N(C_1$ - C_6 alkyl) and O which is unsubstituted or is substituted with 1-2 R^9 groups;

each R^9 is independently selected from C_1 - C_6 alkyl, hydroxyl, halo and a C_1 - C_6 alkyl substituted with 1 to 3 $-OH$; or a pharmaceutically acceptable salt thereof.

3. A compound of Formula (IIa), or a pharmaceutically acceptable salt thereof, for use according to claim 1 or 2, wherein

R^2 is C_1 - C_4 alkyl;

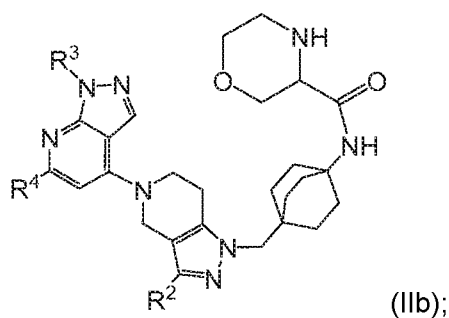
R^3 is C_1 - C_4 alkyl;

R^4 is C_1 - C_4 alkyl or halo;

R^6 is a 4-6 membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NH, $N(C_1$ - C_6 alkyl) and O.

4. A compound of Formula (IIa), for use according to any one of claims 1 to 3, wherein said compound is a compound of Formula (IIb):

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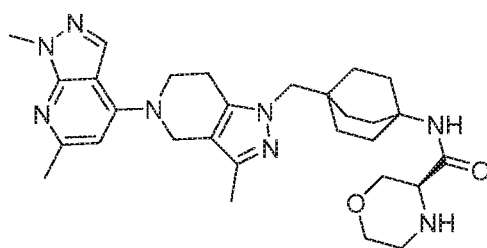
wherein

R² is C₁-C₄alkyl;

R³ is C₁-C₄alkyl;

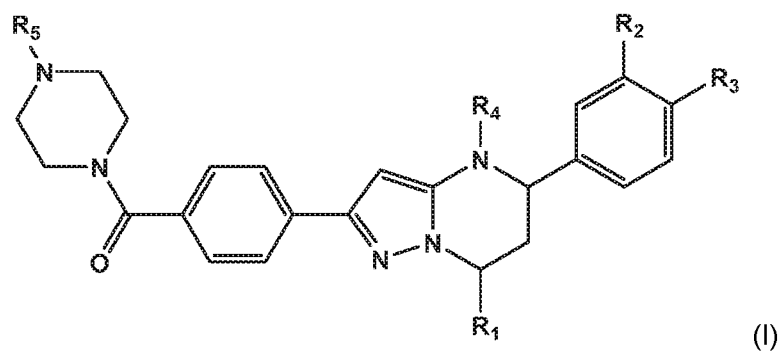
5 R⁴ is C₁-C₄alkyl; or a pharmaceutically acceptable salt thereof.

5. A compound of Formula (II), for use according to any one of claims 1 to 4, wherein said compound is of Formula (IIc):



10

6. A compound of formula (I) for use in the treatment and/or prevention of NPSLE,



wherein

15 R₁ is hydrogen, or C₁-C₄alkyl optionally substituted one or more times by halogen;

R₂ and R₃ are independently from each other hydrogen or C₁-C₆alkoxy;

R₄ is hydrogen or C₁-C₆alkyl; and

R₅ is hydrogen or C₁-C₆alkyl; or a pharmaceutically acceptable salt thereof.

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7. A compound of formula (I) or a pharmaceutically acceptable salt thereof for use in accordance to claim 6, wherein

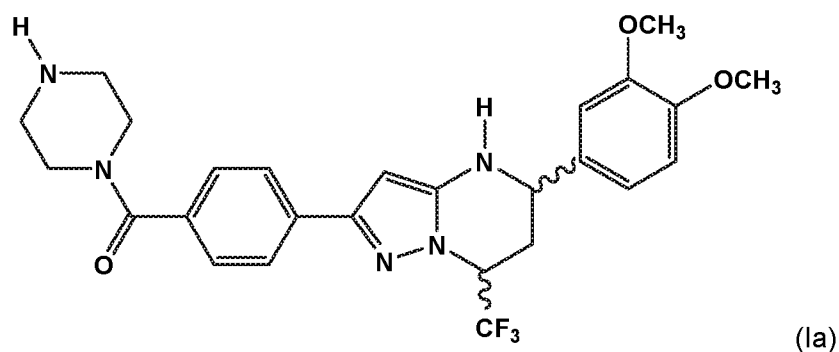
R₁ is trifluoromethyl or difluoromethyl;

5 R₂ and R₃ are both methoxy;

R₄ is hydrogen; and

R₅ is hydrogen or methyl.

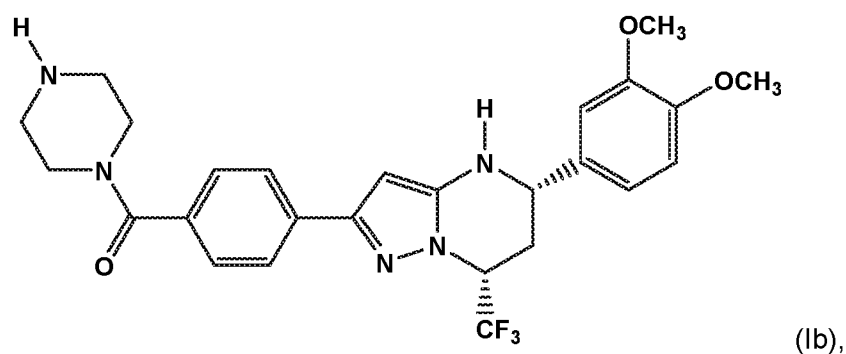
10 8. A compound of formula (I) for use in accordance to claim 6, wherein said compound is a compound of formula (Ia),



or a pharmaceutically acceptable salt thereof.

15

9. A compound of formula (I) for use in accordance to claim 6, wherein said compound is a compound of formula (Ib),



or a pharmaceutically acceptable salt thereof.

20

10. A compound of formula (II) or a pharmaceutically acceptable salt thereof for use according to any one of claims 1 to 5, wherein NPSLE refers to different neurological and/or behavioral clinical syndromes in patients suffering from systemic lupus erythematosus (SLE).

5 11. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use according to any one of claims 6 to 9, wherein NPSLE refers to different neurological and/or behavioral clinical syndromes in patients suffering from systemic lupus erythematosus (SLE).

10 12. A pharmaceutical composition comprising a compound of formula (II) or a pharmaceutically acceptable salt thereof in accordance to any one of claims 1 to 5 together with one or more pharmaceutically acceptable carrier for use in the treatment and/or prevention of NPSLE.

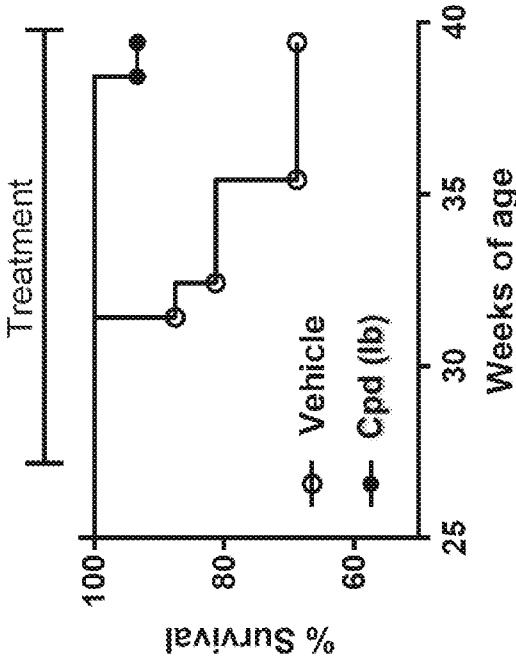
15 13. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in accordance to any one of claims 6 to 9 together with one or more pharmaceutically acceptable carrier for use in the treatment and/or prevention of NPSLE.

20 14. Use of a compound in accordance to formula (II) in accordance to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating NPSLE.

25 15. Use of a compound in accordance to formula (I) in accordance to any one claims 6 to 9, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating NPSLE.

FIGURE 1

A)



B)

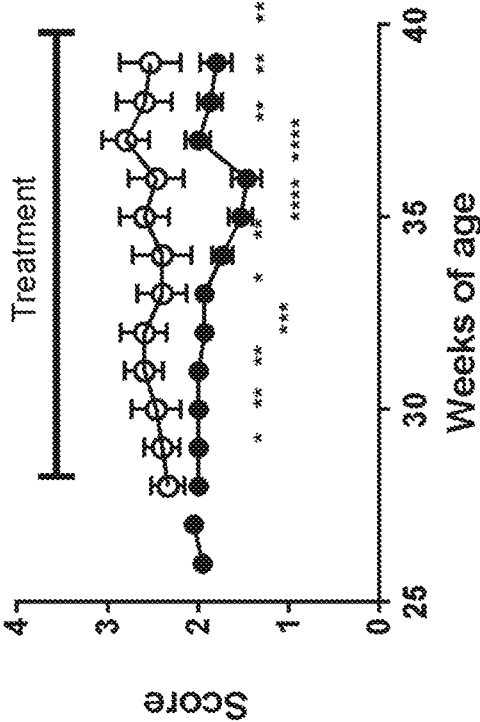


FIGURE 2

