

Tetrahydropyrazolopyrimidine Compounds

CROSS-REFERENCE TO RELATED APPLICATIONS

[1] This application claims the benefit of United States Provisional Patent Application No. 61/654,023, filed on May 31, 2012. That application is incorporated by reference herein.

BACKGROUND

[2] Field of the Disclosure

[3] Embodiments of the disclosure relate to tetrahydropyrazolopyrimidine ("THPP") compounds and pharmaceutical agents comprising one or more of those compounds as active ingredient(s). More particularly, embodiments of the disclosure relate to a THPP compound that acts as an antagonist or inhibitor for Toll-like receptors (TLR) 7 and 8, and its use in a pharmaceutical composition effective for treatment of systemic lupus erythematosus (SLE) and lupus nephritis.

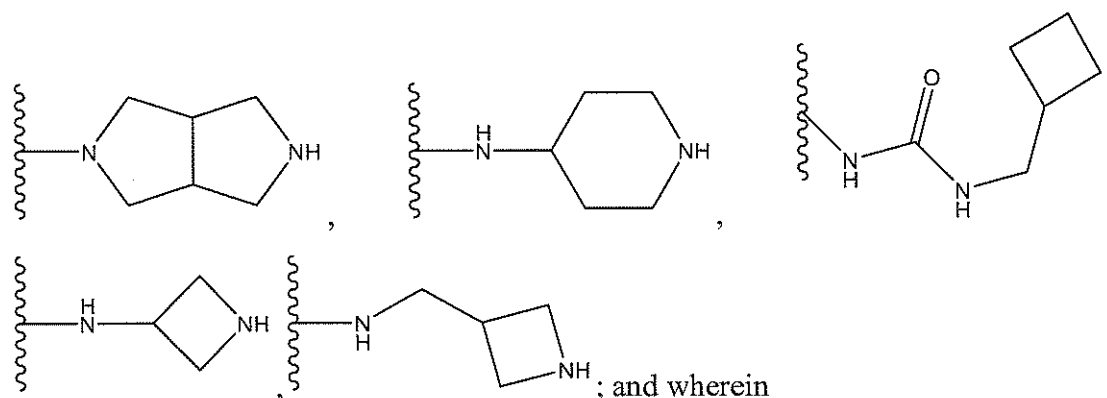
[4] Description of Related Art

[5] Systemic lupus erythematosus (SLE) and lupus nephritis are autoimmune diseases characterized by inflammation and tissue damage. For example, SLE may cause damage to the skin, liver, kidneys, joints, lungs, and central nervous system. SLE sufferers may experience general symptoms such as extreme fatigue, painful and swollen joints, unexplained fever, skin rash, and kidney dysfunction. Because organ involvement differs amongst patients, symptoms may vary. SLE is predominantly a disease of younger women, with peak onset between 15-40 years of age and an approximate 10-fold higher prevalence in women vs. men.

[6] Current treatments for SLE typically involve immunomodulatory drugs such as hydroxychloroquine, prednisone, and cyclophosphamide. All of these drugs may have dose-limiting side effects.

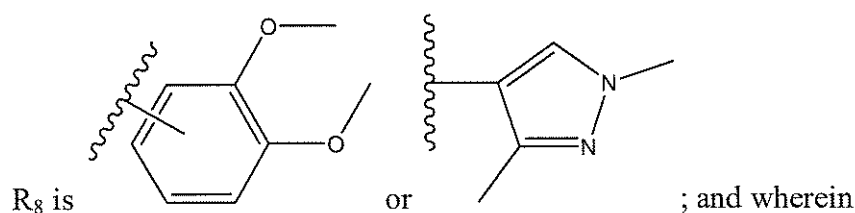
BRIEF SUMMARY OF THE DISCLOSURE

[7] ~~Embodiments~~Examples of the disclosure provide compounds and methods of use for preventing or treating diseases or conditions characterized by Toll-like receptor 7 or 8 activation in patients. In a first aspect, the present invention refers to a compound as defined in claim 1. One ~~embodiment~~example features a compound of formula (I):



R_6 is H, F, $-\text{CH}_3$, $-\text{CF}_3$, or, with R_5 and the atoms at c and d, forms an optionally substituted benzene or an optionally substituted pyrazole; and wherein

R_7 is H, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CF}_2\text{CH}_3$, $-\text{CH}_3$, or $-\text{C}(\text{CH}_3)_3$; and wherein



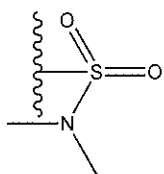
R_9 is Br, Cl, F, I, or H.

[8] In some ~~embodiments~~examples of the disclosure one or more provisos are applied. These provisos typically exclude one or more compounds that might otherwise be included within a stated genus. When reviewing the provisos below, it will be understood that the converse is also true. For example, if a proviso states that when R_4 is F: then R_2 is not CH_3 or F, then it is also true that when R_2 is selected to be $-\text{CH}_3$ or F, then R_4 is not F. It will also be noted that when a proviso is presented as a series of statements, the later statements are not related unless directly presented as provisos elsewhere in the document. For example, if a proviso states that when R_4 is F: R_2 is not $-\text{CH}_3$ or F; and R_3 is not $-\text{CH}_3$, then the implication should not be made from that statement alone that when R_3 is $-\text{CH}_3$, then R_2 is not $-\text{CH}_3$ or F.

[9] One or more of the following provisos may be applied in various ~~embodiments~~examples presented herein:

when R_4 is F: R_2 is not $-\text{CH}_3$ or F; R_3 is not $-\text{CH}_3$, $-\text{CN}$, F, Cl, or $-\text{OCH}_3$; R_5 is not $-\text{CH}_3$, F, Cl, or $-\text{OCH}_3$; and R_6 is not $-\text{CH}_3$ or F;

when R_4 is Cl: R_2 is not F; R_3 is not F or $-\text{CN}$; R_5 is not F, $-\text{CN}$, or $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$; R_6 is not $-\text{CF}_3$ or F; D is not nitrogen; and either R_5 is $-\text{C}(\text{O})\text{NH}_2$ or one of R_2 , R_3 , R_5 , and R_6 is $-\text{CH}_3$;

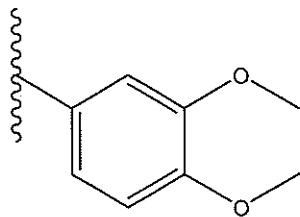


R_3 is not ;

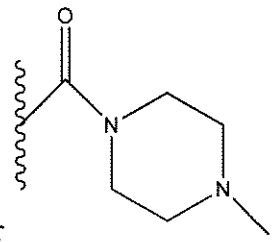
when R_2 is F: R_5 is not $-C(O)NH_2$;

when R_2 is $-CH_3$, R_4 and R_5 do not form a pyrazole with atoms at c and d; and

when B is nitrogen, R_3 and R_4 do not form an optionally substituted imidazole with the atoms at b and c; and



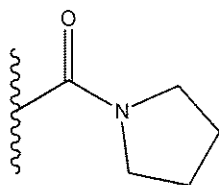
wherein, when R_8 is , then following provisos are in effect:



R_4 is not $-CH_3$, $-C(O)NHCH_2CH_2OH$, $-NHC(O)CH(CH_3)_2$, or

when R_4 is $C(O)NHCH_3$, at least one of R_2 , R_3 , R_5 , and R_6 is not H;

when R_4 is $-OCH_3$; R_3 is not F or $-CH_3$; and R_5 is not F or $-CH_3$;



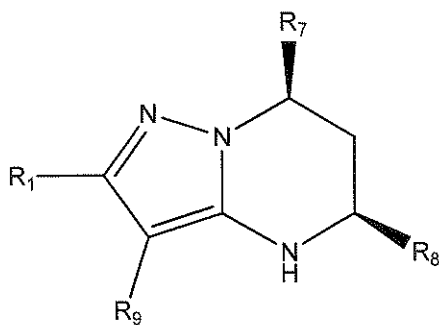
when R_4 is : R_3 is not Cl; and R_5 is not Cl;

when R_4 is $-C(O)NHCH(CH_3)_2$ or $-C(O)N(CH_2CH_3)_2$: at least one of R_3 and R_5 is not H;

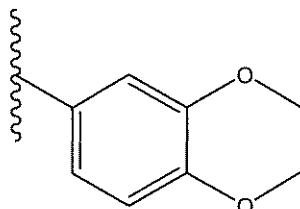
R_5 is not $-C(O)NH_2$; and

R_6 is not $-CF_3$.

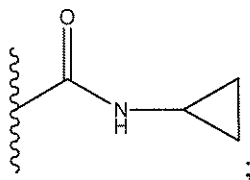
[10] In a further ~~embodiment~~example the compound of formula (I) has the absolute stereochemistry set forth in formula (II):



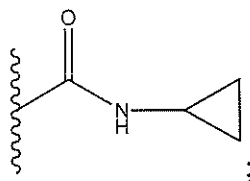
Formula (II)



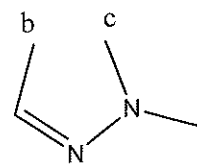
with the proviso that, when R_8 is



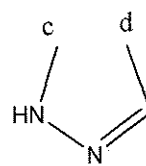
when R_3 is F, R_4 is not



when R_5 is F, R_4 is not

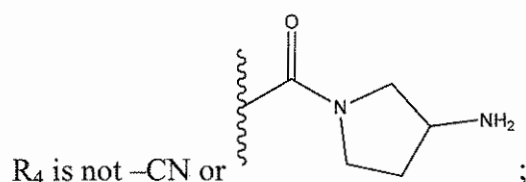


when R_5 is $-\text{CH}_3$, R_3 and R_4 , with atoms at b and c, do not form



when R_3 is $-\text{CH}_3$, R_4 and R_5 , with the atoms at c and d, do not form

[11] In a further ~~embodiment~~example the compound of formula (I) has the absolute stereochemistry set forth in formula (III):



when R_5 is $-\text{CH}_3$, R_3 and R_4 do not form an optionally substituted pyrazolyl with the atoms at b and c;

when R_5 is Cl : R_4 is not $-\text{C}(\text{O})\text{NH}_2$;

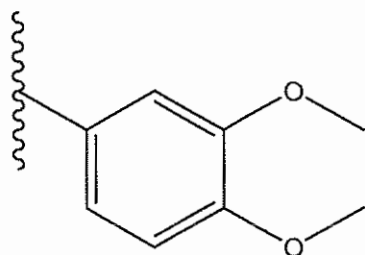
when R_5 is F : R_4 is not $\text{C}(\text{O})\text{NH}_2$;

R_5 is not pyrazolyl;

when R_6 is $-\text{CH}_3$: R_4 and R_5 do not form an optionally substituted pyrazolyl with the atoms at c and d; and

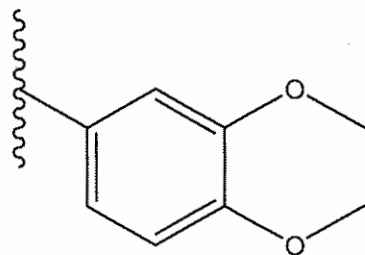
when B is nitrogen, R_4 is not $-\text{C}(\text{O})\text{NHCH}_3$.

[12] In one ~~embodiment~~example, R_1 is piperidinyl or pyridyl; R_7 is $-\text{CF}_3$; R_8 is



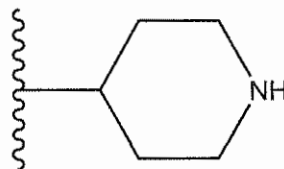
; and R_9 is F, Cl, Br, or I.

[13] In another ~~embodiment~~example, R_1 is $-\text{C}(\text{O})\text{Z}$, where Z is piperazinyl, piperidinyl, pyrrolopyrrolyl, or piperidinyl propyl; R_7 is $-\text{CF}_3$; R_8 is

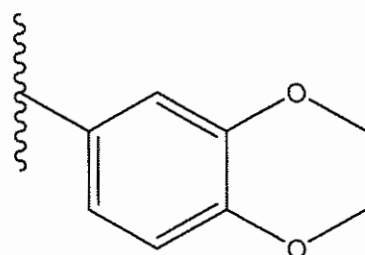


; and R_9 is H.

[14] In another ~~embodiment~~example, R_1 is



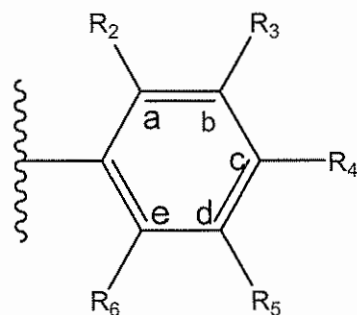
; R_7 is $-\text{CF}_3$, R_8 is



, and R_9 is H.

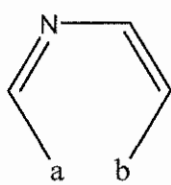
[15]

In another ~~embodiment~~ example, R_1 is

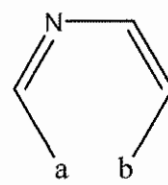


, R_2 is H, -

CH_3 , or, with R_3 , forms

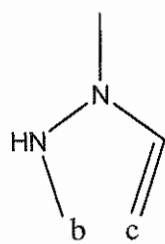


; R_3 is H or, with R_2 , forms

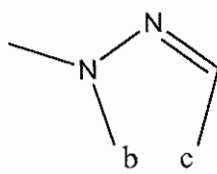


, or, with R_4 ,

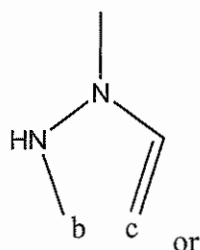
forms



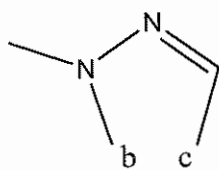
or



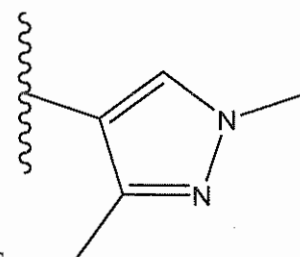
; R_4 is H, $-\text{CH}_3$, $-\text{NHC(O)NH}_2$, or, with R_3 , forms



or



; R_5 is H; R_6 is H; R_7 is $-\text{CF}_3$; R_8 is

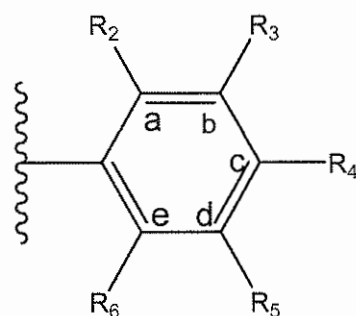


;

and R_9 is H.

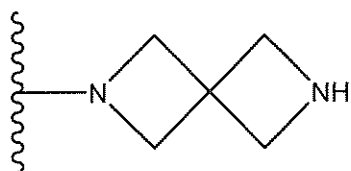
[16]

In another ~~embodiment~~ example R_1 is

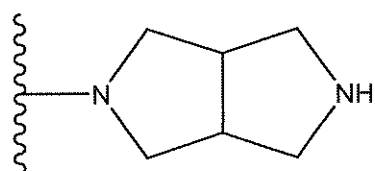
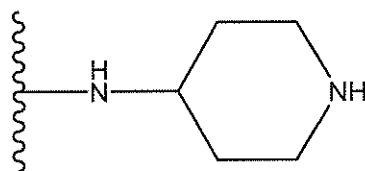
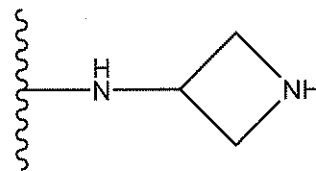


; R_2 is H, F,

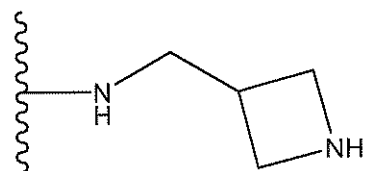
or $-\text{CH}_3$, R_3 is H or F; R_4 is $-(q)-\text{C(O)X}$, where q is a bond or $-\text{CH}_2-$, and X is piperazinyl attached through a nitrogen to the carbonyl group of R_4 , pyrrolidinyl attached through a nitrogen to the carbonyl group of R_4 , pyrrolopyrrolyl attached through a nitrogen to the carbonyl group of R_4 , azetidiny attached through a nitrogen to the carbonyl group of R_4 , or



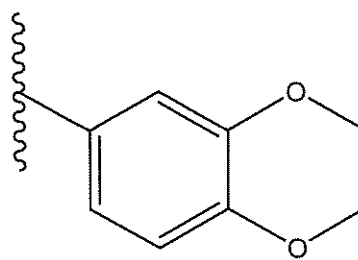
, or X is $-NR_{11}R_{12}$, where one of R_{11} and R_{12} is H and the other is optionally substituted pyrrolidinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, or optionally substituted azetidinyl; R_5 is H or $C(O)Y$, where Y is, $-NH(CH_3)_2$, optionally substituted piperazinyl, optionally substituted piperidinyl,



, or

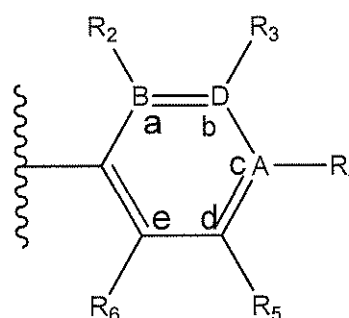


; R_6 is H, R_7 is $-CHF_2$, R_8 is

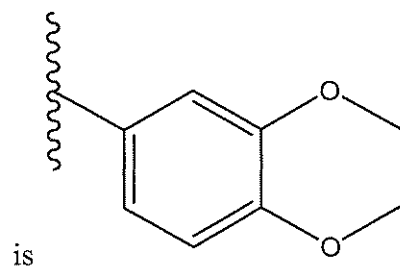


, and R_9

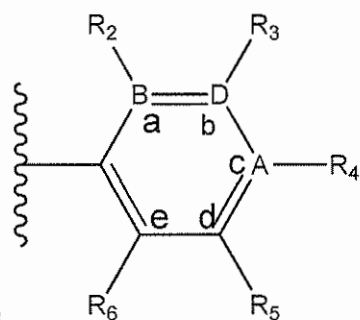
is H.



[17] In a further embodiment example, R_1 is , where A, B, and D may all be carbon, or where two of A, B, and D are carbon and the other is nitrogen, and when A is nitrogen R_4 is absent, when B is nitrogen R_2 is absent, and when D is nitrogen R_3 is absent; R_2 is H; R_3 is H or $-CH_3$; R_4 is $-C(O)X$, where X is optionally substituted piperazinyl, or X is $-NR_{11}R_{12}$, where R_{11} and R_{12} are H, or where one of R_{11} or R_{12} is H, and the other is piperidinyl, pyrrolidinyl, or $-CH_3$; R_5 is $-OCH_3$, H, or Cl; R_6 is H, R_7 is $-CF_3$, R_8

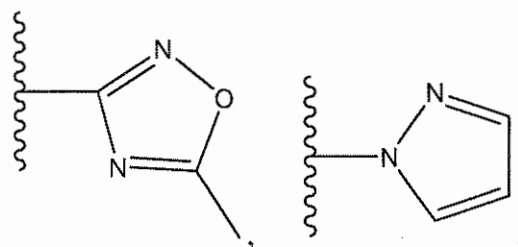


is , and R_9 is H.

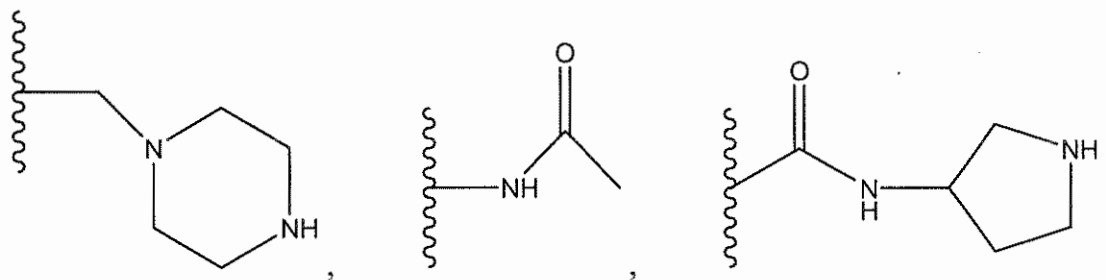
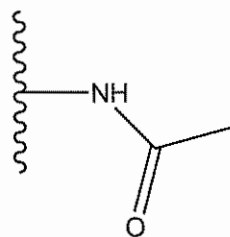


[18] In a further embodiment example, R_1 is , where A, B, and D are carbon;

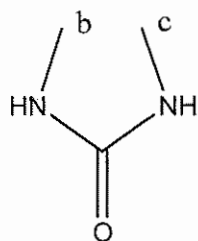
R_2 is H, $-CH_3$, or F, or, with R_3 and the atoms at positions a and b, forms an optionally substituted pyrazole;



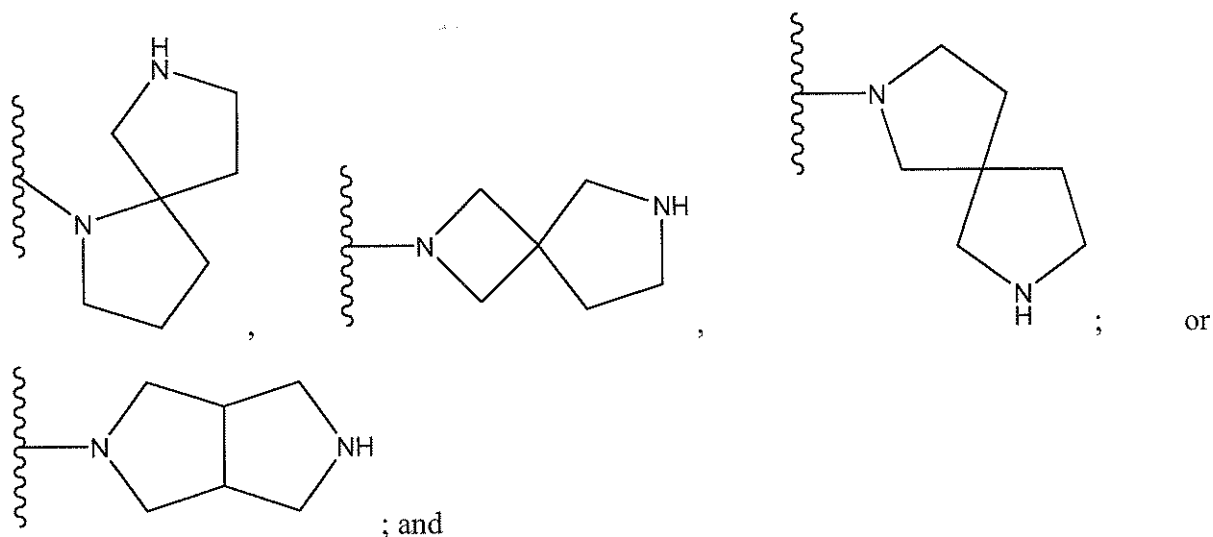
R_3 is H, F, Cl, $-CN$, $-CH_3$,



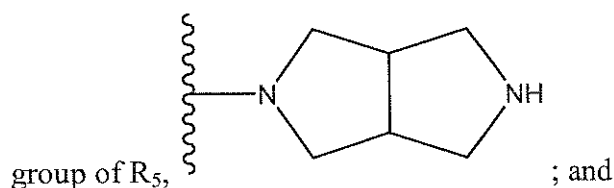
, or, with R_4 and the atoms at b and c, forms optionally substituted



pyrazole or or, with R_2 and the atoms at a and b, forms an optionally substituted pyrazole;

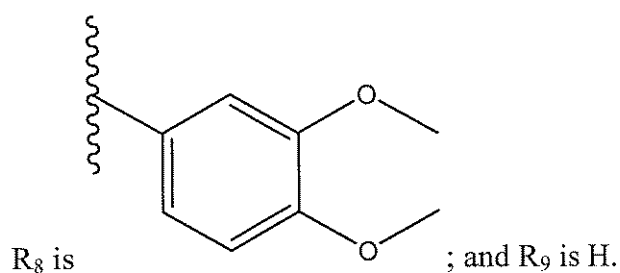


R_5 is H, or, with R_4 and the atoms at c and d, forms an optionally substituted benzene, an optionally substituted pyrazole, or, with R_6 and the atoms at d and e, forms an optionally substituted pyridine, or R_5 is $C(O)Y$, where Y is $-NH_2$, $-NH(CH_3)_2$, optionally substituted piperazinyl attached through a nitrogen to the carbonyl group of R_5 , optionally substituted piperidinyl attached through a nitrogen to the carbonyl

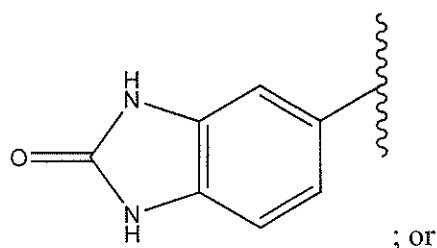


R_6 is H, F, $-CH_3$, or, with R_5 and the atoms at c and d, forms an optionally substituted pyrazole;

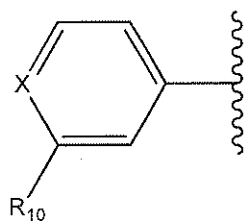
R_7 is $-CF_3$;



[19] Another embodiment aspect includes a compound of formula (IV)



; or



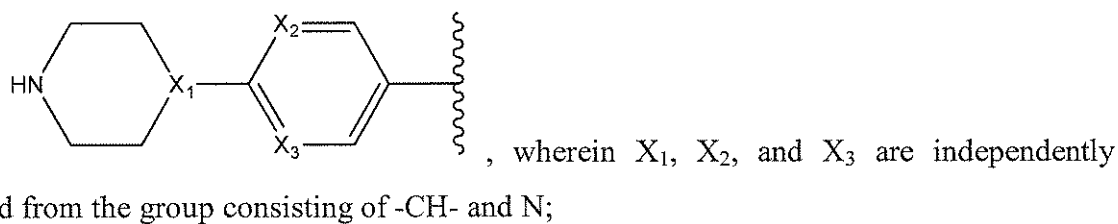
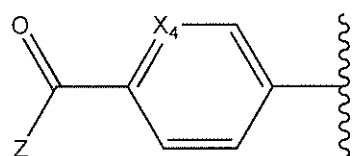
, wherein X is N or -CH- wherein the C is optionally substituted by -CH₃, F, or Cl, and wherein

R₁₀ is -C(O)NH- wherein the nitrogen is substituted by a four to seven member cyclic amine; -C(O)- substituted by a seven to ten member bicyclodiamine; -C(O)- substituted by a seven to eleven member spirodiamine; pyrazole; [1,2,4]oxadiazole optionally substituted by -CH₃ on a carbon atom of the oxadiazole; -NHC(O)CH₃; -CH₂- substituted by a piperazine; -CH₂- substituted by a piperazine including a methyl substituent; -C(O)- substituted by a five to seven member cyclic diamine; -C(O)NHCH₂- wherein the -CH₂- is substituted by azetidine; or -C(O)- substituted with a five to seven member cyclic amine wherein the amine includes an -NH₂ substituent; or

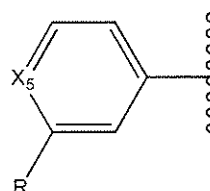
cyanophenyl; isoquinoline; cyclohexene substituted with -NH₂ at the 4' position; 1,4-dimethylindazole-5-yl; 1,6-dimethylindazole-5-yl; cyclohexene substituted with spiropiperidine at the 4' position; 1-piperidinopyrazole; or o-methoxypyridine.

[20] In a further ~~embodiment~~example, a compound or pharmaceutically effective salt of the preceding paragraph of this disclosure has an IC₅₀ less than or equal to 100 nM against human TLR7 receptors expressed in a HEK-293 cell line. In a further ~~embodiment~~example C₅₀ against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line stably expressing TLR7 in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum at a density of 2.22X10⁵ cells/ml into a 384-well plate and incubating for 2 days at 37°C, 5% CO₂; (2) adding the compound or pharmaceutically acceptable salt thereof and incubating the cells for 30 minutes; (3) adding CL097 (InvivoGen) at 3ug/ml and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence..

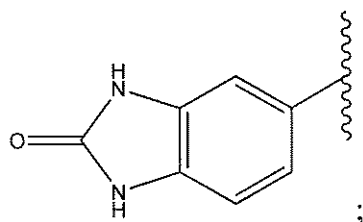
[21] A further ~~embodiment~~example includes a compound of formula IV, or pharmaceutically effective salt thereof, wherein Ring A is:

, wherein X₄ is -CH- or N; and wherein Z is piperazine, optionally bridged or substituted on a carbon by -CH₃; hexahydropyrrolo[3,4]pyrrole; a four to seven member cyclic amine substituted with -OH or -NH₂; or -NH- substituted with a four to seven member cyclic amine;



, wherein X₅ is -CH- or N; and wherein R is pyrazole; [1,2,4]oxadiazole optionally substituted by a -CH₃ on a carbon of the oxadiazole; or -C(O)NH- substituted on its nitrogen by a four to seven member cyclic amine;

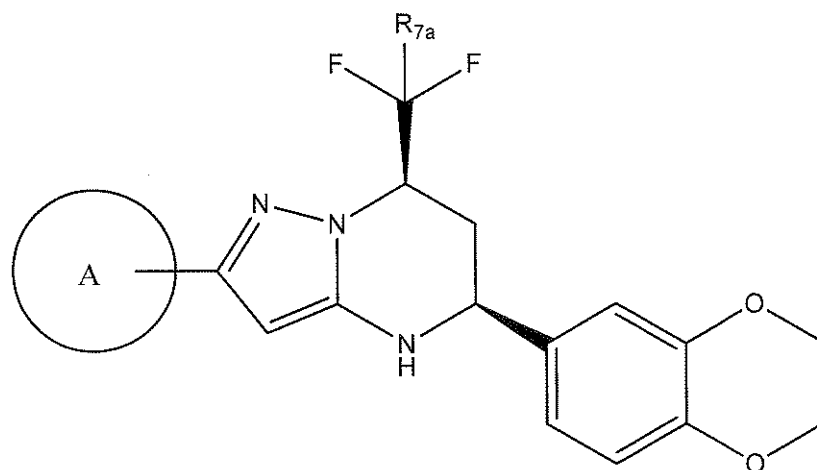


1,4-dimethylindazole-5-yl; 1,6-dimethylindazole-5-yl; 1-piperidinopyrazole; cyclohexene substituted with -NH₂ at the 4' position; cyclohexene substituted with spiropiperidine at the 4' position; or 2-methoxypyridine-4-yl.

[22] In a further ~~embodiment~~example the compound or pharmaceutically effective salt thereof of the preceding paragraph of this disclosure has an IC₅₀ less than or equal to 20 nM against human TLR7 receptors expressed in a HEK-293 cell line. In a further ~~embodiment~~example the compound or pharmaceutically effective salt thereof of the preceding paragraph of this disclosure has an IC₅₀ less than or equal to 100 nM against human TLR7 receptors expressed in a HEK-293 cell line. In a further ~~embodiment~~example the IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line

stably expressing TLR7 in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum at a density of 2.22×10^5 cells/ml into a 384-well plate and incubating for 2 days at 37°C, 5% CO₂; (2) adding the compound or pharmaceutically acceptable salt thereof and incubating the cells for 30 minutes; (3) adding CL097 (InvivoGen) at 3 µg/ml and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence..

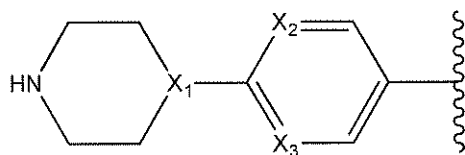
[23] A further ~~embodiment~~example includes a compound having the absolute stereochemistry set forth in formula (V):



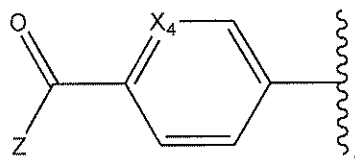
Formula

(V)

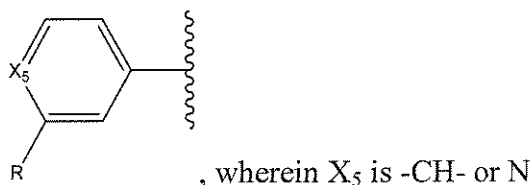
or pharmaceutically acceptable salt thereof, wherein: R_{7a} is H or F; wherein Ring A is:



, wherein X₁, X₂, and X₃ are independently selected from the group consisting of -CH- and N;

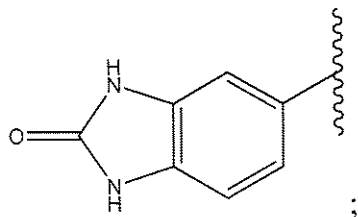


, wherein X₄ is -CH- or N; and wherein Z is piperazine, optionally bridged or substituted on a carbon by -CH₃; hexahydropyrrolo[3,4]pyrrole; a four to seven member cyclic amine substituted with -OH or -NH₂; or -NH- substituted with a four to seven member cyclic amine;



; and wherein R is pyrazole; [1,2,4]oxadiazole optionally substituted by a -CH₃ on a carbon of the oxadiazole; or -C(O)NH- substituted on its nitrogen by a four to seven member cyclic amine;

1,4-dimethylindazole-5-yl; 1,6-dimethylindazole-5-yl;



1-piperidinopyrazole; cyclohexene substituted with -NH₂ at the 4' position; cyclohexene substituted with spiro piperidine at the 4' position; or 2-methoxypyridine-4-yl.

[24] In a further ~~embodiment~~example the compound or pharmaceutically effective salt thereof of the preceding paragraph has an IC₅₀ less than or equal to 20 nM against human TLR7 receptors expressed in a HEK-293 cell line. In a further ~~embodiment~~example the compound or pharmaceutically effective salt thereof of the preceding paragraph of this disclosure has an IC₅₀ less than or equal to 100 nM against human TLR7 receptors expressed in a HEK-293 cell line. In a further ~~embodiment~~example the IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line stably expressing TLR7 in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum at a density of 2.22X10⁵ cells/ml into a 384-well plate and incubating for 2 days at 37°C, 5% CO₂; (2) adding the compound or pharmaceutically acceptable salt thereof and incubating the cells for 30 minutes; (3) adding CL097 (InvivoGen) at 3ug/ml and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence.

[25] In further ~~embodiments~~examples of the disclosure, compounds have an IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line less than or equal to 200 nM, less than or equal to 180 nM, less than or equal to 160 nM, less than or equal to 140 nM, less than or equal to 120 nM, less than or equal to 100 nM, less than or equal to 80 nM, less than or equal to 60 nM, less than or equal to 40 nM, or less than or equal to 20 nM. In further ~~embodiments~~examples of the disclosure, compounds have an IC₅₀ against human TLR7 receptors

expressed in a HEK-293 cell line from 10 nM to 30 nM, from 10 nM to 50 nM, from 10 nM to 100 nM, from 30 nM to 50 nM, from 30 nM to 100 nM, or from 50 nM to 100 nM. In further ~~embodiments~~examples the IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line stably expressing TLR7 in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum at a density of 2.22X10⁵ cells/ml into a 384-well plate and incubating for 2 days at 37°C, 5% CO₂; (2) adding the compound or pharmaceutically acceptable salt thereof and incubating the cells for 30 minutes; (3) adding CL097 (InvivoGen) at 3ug/ml and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence.

In another aspect, the present invention refers to use of a compound or pharmaceutically acceptable salt of the present invention in the manufacture of a medicament.

In another aspect, the present invention refers to use of a compound or pharmaceutically acceptable salt of the present invention in the manufacture of a medicament for antagonizing TLR7.

In another aspect, the present invention refers to use of a compound or pharmaceutically acceptable salt of the present invention in the manufacture of a medicament for antagonizing TLR8.

[26] Further ~~embodiments~~examples provide methods for treatment of a systematic lupus erythematosus or lupus including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[27] Further ~~embodiments~~examples provide methods for antagonizing TLR7, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[28] Further ~~embodiments~~examples provide methods for antagonizing TLR8, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[29] Further ~~embodiments~~examples provide pharmaceutical compositions comprising at least one compound or pharmaceutically acceptable salt of the disclosure and at least one pharmaceutically acceptable carrier.

[30] Further ~~embodiments~~examples provide methods for treatment of a systematic lupus erythematosus or lupus, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[31] Further ~~embodiments~~examples provide methods for antagonizing TLR7, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[32] Further ~~embodiments~~examples provide methods for antagonizing TLR8, including administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of the disclosure.

[33] Further ~~embodiments~~examples provide pharmaceutical compositions comprising at least one compound or pharmaceutically acceptable salt of the disclosure and at least one pharmaceutically acceptable carrier.

[34] The term “optionally substituted,” as used herein, means that the subject structure may include, but is not required to include, one or more substituents independently selected from lower alkyl, methoxy-, -OH, -NH₂, -CH₂-NH-CH₂, -OCH₂CH₂CH₃, or -OCH(CH₃)₂. If the optionally substituted moiety is cyclic, then the optional substitution may be a methyl bridge between two atoms in the ring.

[35] The symbol “C(O)” as used herein refers to a carbonyl group having the formula C=O.

[36] Unless otherwise specified, “a” and “an” as used in this disclosure, including the claims, mean “one or more.”

[37] As used herein, “lower alkyl” refers to straight, or, in the case of three- and four-carbon groups, straight, branched, or cyclic saturated hydrocarbons having between one and four carbon atoms.

[38] As used herein, the term “attached through a nitrogen” when referring to a heterocyclic moiety including nitrogen, means that a point of attachment of the moiety to another structure is through a nitrogen that is part of the heterocycle.

[39] As used herein, the term “TLR7/8” means “TLR7 and TLR8” or “TLR7 or TLR8” or “TLR7 and/or TLR8.” The particular meaning can be understood by a person skilled in the art based upon the context in which “TLR7/8” appears.

[40] Heterocyclic moieties recited herein include azetidiny, pyrrolidinyl, piperidinyl, methylazetidiny, pyrazolyl, piperazinyl, morpholinyl, thiazolyl, pyrrolopyrrolyl, imidazolidinyl, and isothiazolyl. Where a heterocyclic group is mentioned, unless otherwise indicated it will be understood that the heterocyclic atom(s) in the group may be at any position in the group. It will further be understood that imidazolyl, pyrazolyl, thiazolyl, and pyrrolyl may be unsaturated or partially unsaturated. An embodiment example of the disclosure may include a pharmaceutical composition that includes one or more compounds of the disclosure with a pharmaceutically acceptable excipient. These pharmaceutical compositions may be used to treat or prevent a disease or condition characterized by TLR7/8 activation in a patient, typically a human patient, who has or is predisposed to have such a condition or disease. Examples of diseases or conditions characterized by TLR7/8 activation include systemic lupus erythematosus (SLE) and lupus nephritis.

[41] As used herein, “effective amount” of a compound of an embodiment example of the disclosure is effective amount of the above-identified compounds in an amount sufficient to treat or prevent SLE and lupus nephritis.

[42] ~~Embodiments~~Examples presented herein may include asymmetric or chiral centers. Embodiments include the various stereoisomers and mixtures thereof. Individual stereoisomers of compounds of ~~embodiments~~examples of the disclosure may be prepared synthetically from commercially available starting materials that contain asymmetric or chiral centers, or by preparation of mixtures of enantiomeric compounds followed by resolution of those compounds. Suitable methods of resolution include attachment of a racemic mixture of enantiomers, designated (+/-), to a chiral auxiliary, separation of the resulting diastereomer by chromatography or recrystallization and separation of the optically pure product from the auxiliary; or direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

[43] ~~Embodiments~~Examples of the disclosure also include a pharmaceutical composition including any compound of the disclosure as well as a pharmaceutically acceptable excipient. The pharmaceutical compositions can be used to treat or prevent SLE and lupus nephritis. Therefore, ~~embodiments~~examples of the disclosure may also feature a method for treating or preventing SLE or lupus nephritis in a human patient having or predisposed to having lupus nephritis or SLE.

[44] ~~Embodiments~~Examples of the disclosure include pharmaceutically acceptable salts of the compounds presented herein. The term "pharmaceutically acceptable salt" refers to those salts that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, or allergic response. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al., describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* 66:1-19, 1977. Salts can be prepared in situ during final isolation and purification of a compound or separately by reacting a free base group with a suitable organic acid. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, monomaleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, trifluoroacetate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium,

(4-(7-(difluoromethyl)-5-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)-3-fluorophenyl)((2R,5S)-2,5-dimethylpiperazin-1-yl)methanone hydrochloride;
 (4-((5S,7R)-7-(difluoromethyl)-5-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)phenyl)(piperazin-1-yl)methanone;
 2-(4-(7-(difluoromethyl)-5-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)phenyl)-1-(piperazin-1-yl)ethanone hydrochloride;
 4-(7-(difluoromethyl)-5-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)-N-((S)-piperidin-3-yl)benzamide hydrochloride;
 (4-(7-(difluoromethyl)-5-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)-3-methylphenyl)(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone hydrochloride;
 3-(7-(difluoromethyl)-5-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)-N-(piperidin-4-yl)benzamide hydrochloride;
 3-(7-(difluoromethyl)-5-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)-N-((R)-pyrrolidin-3-yl)benzamide hydrochloride; and
 1-(4-(5-(1,3-dimethyl-1H-pyrazol-4-yl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)phenyl)urea.

19. The compound or pharmaceutically acceptable salt of claim 1, wherein said compound is (5S,7R)-5-(3,4-dimethoxyphenyl)-2-(pyridin-4-yl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine.

20. Use of a compound or pharmaceutically acceptable salt of claim 1 in the manufacture of a medicament A method for treatment of a systematic lupus erythematosus or lupus, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of claim 1.

21. The ~~method~~ use of claim 20, wherein said compound is to be administered as a pharmaceutically acceptable salt.

22. Use of a compound or pharmaceutically acceptable salt of claim 1 in the manufacture of a medicament A method for antagonizing TLR7, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of claim 1.

23. Use of a compound or pharmaceutically acceptable salt of claim 1 in the manufacture of a medicament A method for antagonizing TLR8, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of claim 1.

24. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt of claim 1 and at least one pharmaceutically acceptable carrier.

25. The compound (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 or a pharmaceutically acceptable salt thereof.

26. The compound (4-((5R,7S)-5-(3,4-dimethoxyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)phenyl)(piperazin-1-yl)methanone or a pharmaceutically acceptable salt thereof.

27. A racemic mixture of the compound (4-(5-(3,4-dimethoxyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-2-yl)phenyl)(piperazin-1-yl)methanone or a pharmaceutically acceptable salt thereof.

28. Use of a compound or pharmaceutically acceptable salt of one of claims 25-27 in the manufacture of a medicament A method for antagonizing TLR7, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of one of claims 25-27.

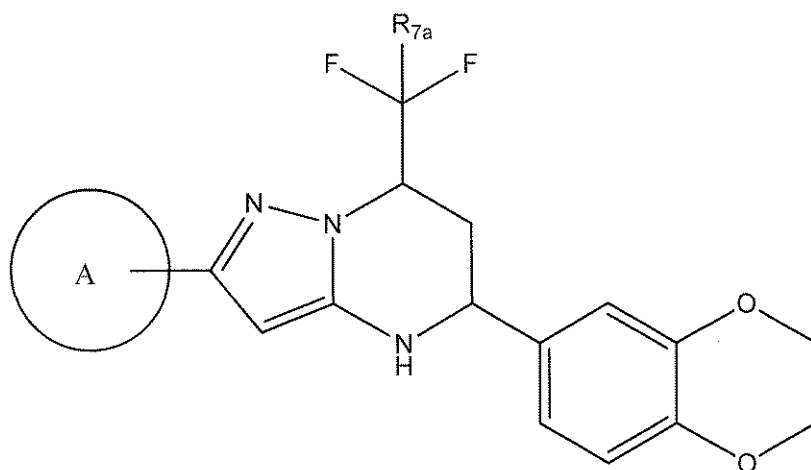
29. Use of a compound or pharmaceutically acceptable salt of one of claims 25-27 in the manufacture of a medicament A method for treatment of a systematic lupus erythematosus or lupus, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of one of claims 25-27.

30. The method use of claim 29, wherein said compound is to be administered as a pharmaceutically acceptable salt.

31. Use of a compound or pharmaceutically acceptable salt of one of claims 25-27 in the manufacture of a medicament A method for antagonizing TLR8, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of one of claims 25-27.

32. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt of one of claims 25-27 and at least one pharmaceutically acceptable carrier.

33. A compound of formula (IV)



Formula

(IV)

or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof or mixture of stereoisomers thereof, wherein: R_{7a} is H or F; and wherein

Ring A is:

1-piperidinopyrazole; cyclohexene substituted with $-NH_2$ at the 4' position; cyclohexene substituted with spiropiperidine at the 4' position; or 2-methoxypyridine-4-yl.

41. The compound or pharmaceutically effective salt of claim 40, wherein said compound or pharmaceutically effective salt thereof has an IC_{50} less than or equal to 100 nM against human TLR7 receptors in a HEK-293 cell line.

42. The compound or pharmaceutically effective salt of claim 40, wherein said compound or pharmaceutically effective salt thereof has an IC_{50} less than or equal to 20 nM against human TLR7 receptors expressed in a HEK-293 cell line.

43. The compound or pharmaceutically effective salt of claim 41 or claim 42, wherein the IC_{50} against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line stably expressing TLR7 in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum at a density of 2.22×10^5 cells/ml into a 384-well plate and incubating for 2 days at $37^\circ C$, 5% CO_2 ; (2) adding the compound or pharmaceutically acceptable salt thereof and incubating the cells for 30 minutes; (3) adding CL097 (InvivoGen) at 3 $\mu g/ml$ and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence.

44. Use of a compound or pharmaceutically acceptable salt of any one of claims 33-43 in the manufacture of a medicament A method for treatment of a systematic lupus erythematosus or lupus, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of any one of claims 33-43.

45. The ~~method~~ use of claim 44, wherein said compound is to be administered as a pharmaceutically acceptable salt.

46. Use of a compound or pharmaceutically acceptable salt of any one of claims 33-43 in the manufacture of a medicament A method for antagonizing TLR7, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of any one of claims 33-43.

47. Use of a compound or pharmaceutically acceptable salt of any one of claims 33-43 in the manufacture of a medicament A method for antagonizing TLR8, comprising administering a pharmaceutically effective amount of a compound or pharmaceutically acceptable salt of any one of claims 33-43.

48. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt of any one of claims 33-43 and at least one pharmaceutically acceptable carrier.