

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 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 for treatment of systematic lupus erythematosus or lupus.

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

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

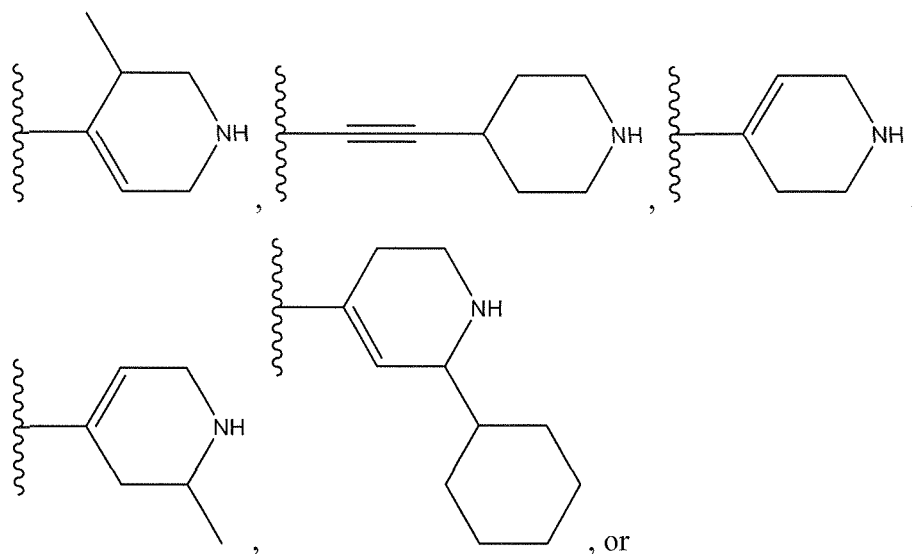
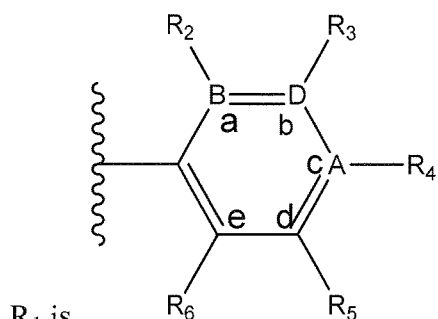
[29] Further examples provide pharmaceutical compositions comprising at least one compound or pharmaceutically acceptable salt of the disclosure and at least one pharmaceutically acceptable carrier.

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

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

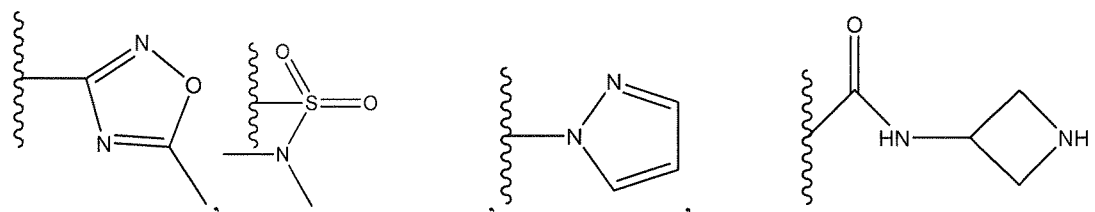
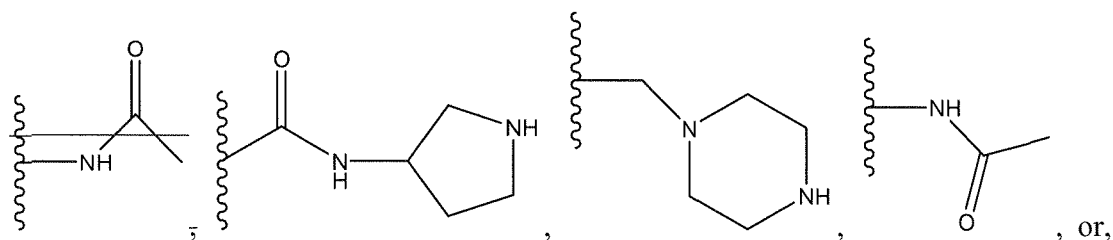
[33] Further examples provide pharmaceutical compositions comprising at least one compound or pharmaceutically acceptable salt of the disclosure and at least one pharmaceutically acceptable carrier.



R₁ 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, or where one of A, B, and D is carbon and the remaining two are nitrogen; and when A is nitrogen R₄ is absent, when B is nitrogen R₂ is absent, and when D is nitrogen R₃ is absent; and wherein

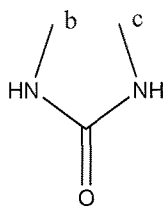
R₂ is H, -CH₃, or F, or, with R₃ and the atoms at positions a and b, forms an optionally substituted pyridine or a pyrazole; and wherein

R₃ is H, F, Cl, -CN, -CH₃, -OCH₃, -OH, -NH₂, methylsulfonyl,



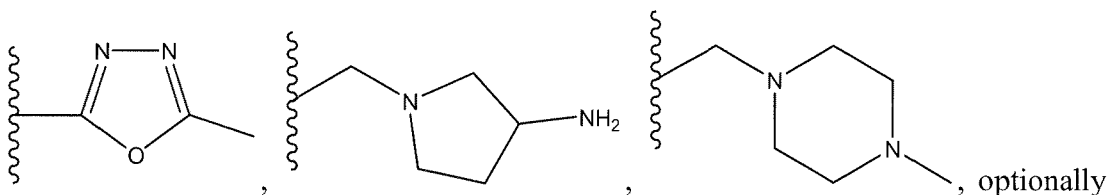
with R₄ and the atoms at b and c, forms an optionally substituted benzene, optionally substituted imidazole, optionally substituted pyrazole, optionally substituted

pyrazolidine, optionally substituted imidazolidine, optionally substituted isothiazole,

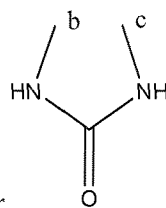


or, with R_2 and the atoms at a and b, forms an optionally substituted pyridine or optionally substituted pyrazole; and wherein

R_4 is F, -CN, -OCH₃, -OEt, H, Cl, Br, -NH-C(O)-CH-(CH₃)₂, -N(CH₃)₂, -CH₃, -CH₂OH,



optionally substituted piperazinyl, 4-hydroxypiperizin-1-yl, optionally substituted piperidinyl not attached to a phenyl group through a nitrogen, or, with R_3 and the atoms at b and c,

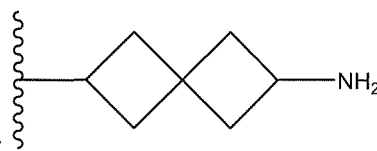


forms an optionally substituted pyrazole ring or , or, with R_5 and the atoms at c and d, forms an optionally substituted pyrazole ring or an optionally substituted pyrrole ring, or,

R_4 is -(q)-C(O)X, where q is a bond, is -NH-, or is -CH₂-, and

where X is -NR₁₁R₁₂,

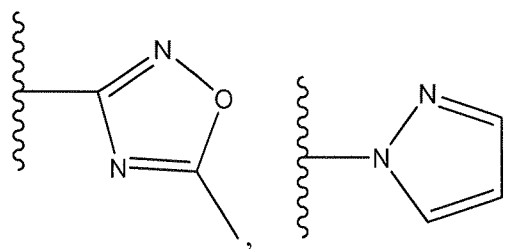
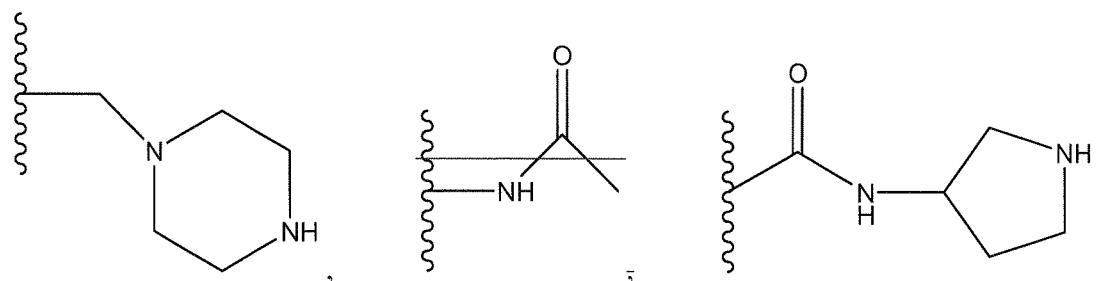
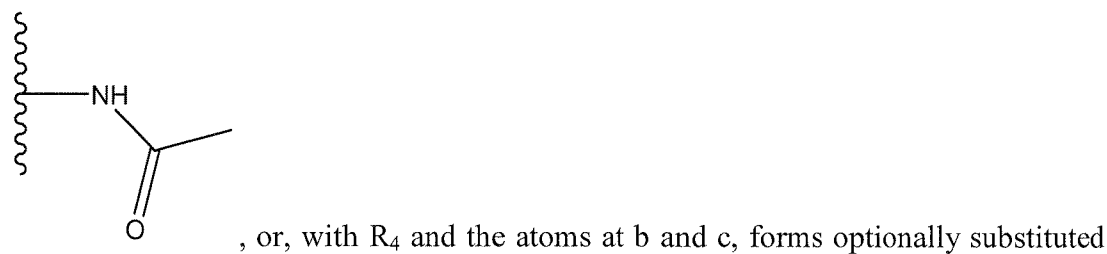
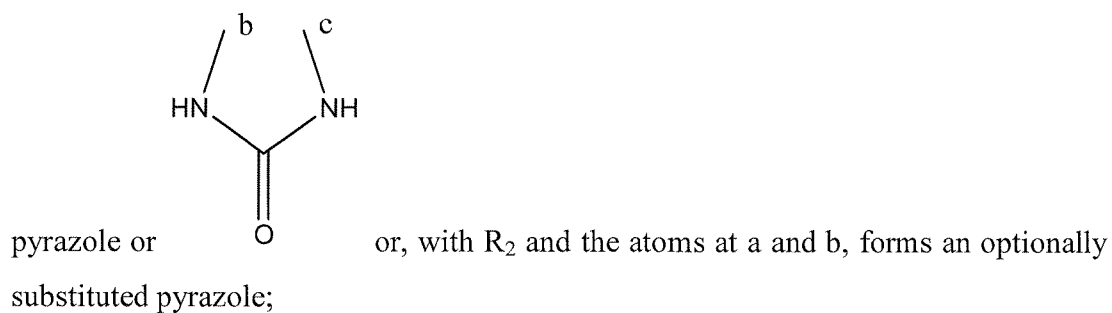
where R_{11} and R_{12} are both H, both -CH₂CH₃, or both -CH₃, or where one of R_{11} and R_{12} is H and the other is 1,1-dimethylethyl, cyclobutyl, cyclopropyl, lower alkyl, methyl alcohol, ethyl alcohol, propyl alcohol, cyclobutylmethyl; 2,3-dihydroxypropyl, benzyl, optionally substituted azetidiny, pyrrolidinyl, piperidinyl, methylazetidiny, optionally substituted pyrrolyl, -CH₂-NH-CH₃,



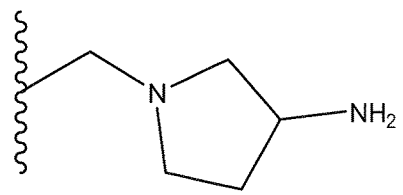
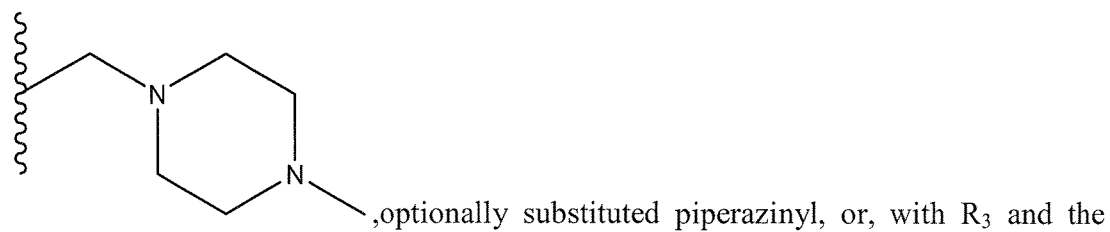
pyrazolyl, piperazinyl, alcohol, -OCH₃, or , or

where X is optionally substituted pyrrolidinyl attached through a nitrogen to the carbonyl group of R_4 , optionally substituted piperidinyl not attached through a nitrogen to the carbonyl group of R_4 , optionally substituted pyrrolidinyl attached through a nitrogen to the carbonyl group of R_4 , optionally substituted piperazinyl

R_3 is H, F, Cl, -CN, -CH₃,



R_4 is -CN, -CH₂OH, H,



(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 for treatment of a systematic lupus erythematosus or lupus.

21. The 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 for antagonizing TLR7.~~

~~23. Use of a compound or pharmaceutically acceptable salt of claim 1 in the manufacture of a medicament for antagonizing TLR8.~~

~~2422.~~ A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt of claim 1 and at least one pharmaceutically acceptable carrier.

~~2523.~~ 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~~24. 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~~25. 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 for antagonizing TLR7.

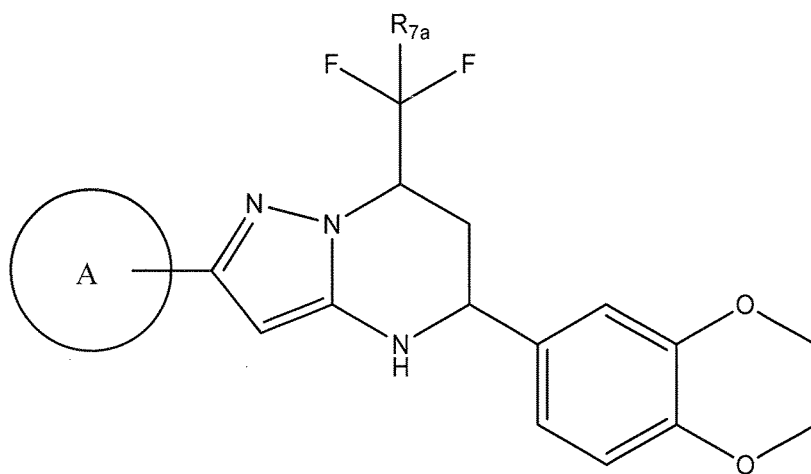
~~29~~26. Use of a compound or pharmaceutically acceptable salt of one of claims ~~25~~23-27~~25~~ in the manufacture of a medicament for treatment of a systematic lupus erythematosus or lupus.

~~30~~27. The use of claim ~~29~~26, 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 for antagonizing TLR8.

~~32~~28. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt of one of claims ~~25~~23-27~~25~~ and at least one pharmaceutically acceptable carrier.

~~33~~29. 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:

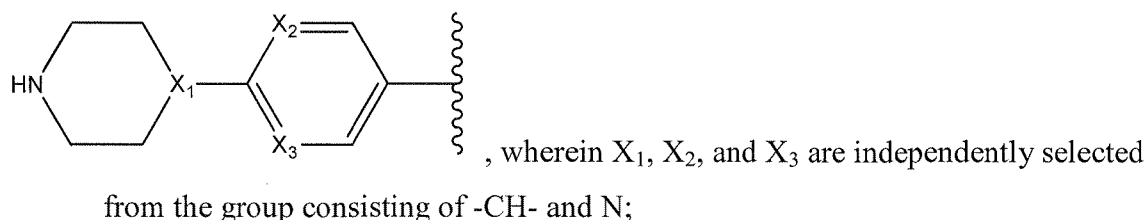
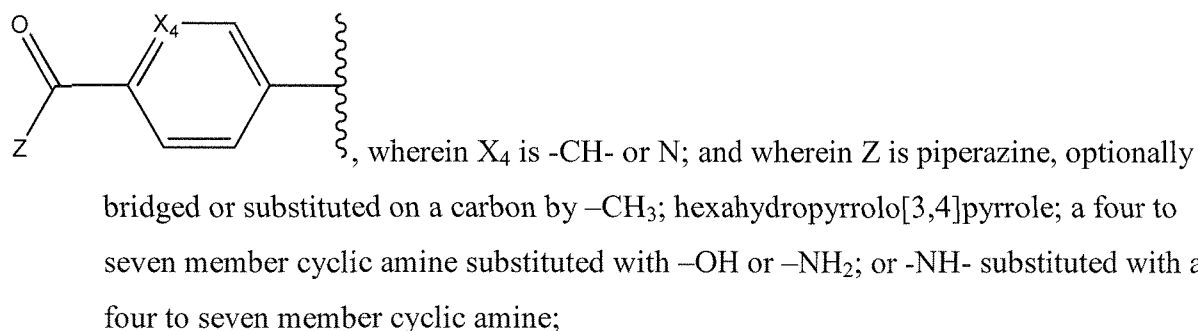
diamine; -C(O)NHCH₂- wherein the -CH₂- is substituted by azetidine; or -C(O)- substituted with a five to seven member cyclic amine wherein the amine includes an -NH₂ substituent; or

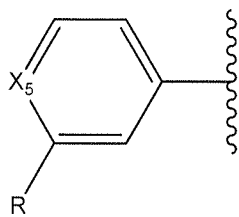
cyanophenyl; isoquinoline; cyclohexene substituted with -NH₂ at the 4' position; 1,4-dimethylindazole-5-yl; 1,6-dimethylindazole-5-yl; cyclohexene substituted with spiropiperidine at the 4' position; 1-piperidinopyrazole; or o-methoxypyridine.

3430. The compound or pharmaceutically effective salt of claim 3329, wherein said compound or pharmaceutically effective salt thereof has an IC₅₀ less than or equal to 100 nM against human TLR7 receptors expressed in a HEK-293 cell line.

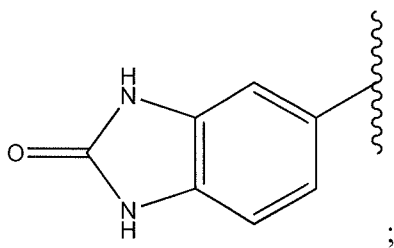
3531. The compound or pharmaceutically effective salt of claim 3430, wherein the IC₅₀ against human TLR7 receptors expressed in a HEK-293 cell line is measured by (1) plating cells of the HEK-293 cell line stably expressing TLR7 in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum 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.

3632. The compound or pharmaceutically effective salt of claim 3329, wherein Ring A is:





, wherein X_5 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.

3733. The compound or pharmaceutically effective salt of claim 3632, wherein said compound or pharmaceutically effective salt thereof has an IC₅₀ less than or equal to 100 nM against human TLR7 receptors.

3834. The compound or pharmaceutically effective salt of claim 3632, wherein said compound or pharmaceutically effective salt thereof has an IC₅₀ less than or equal to 20 nM against human TLR7 receptors expressed in a HEK-293 cell line.

3935. The compound or pharmaceutically effective salt of claim 3733 or claim 3834, wherein 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.

4036. The compound of claim 3329 having the absolute stereochemistry set forth in formula (V):

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

4137. The compound or pharmaceutically effective salt of claim 4036, 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.

4238. The compound or pharmaceutically effective salt of claim 4036, 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.

4339. The compound or pharmaceutically effective salt of claim 4137 or claim 4238, 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°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 $\mu\text{g/ml}$ and incubating the cells for approximately 20 hours; and (4) quantifying NF-kappaB dependent reporter activation by measuring luminescence.

4440. Use of a compound or pharmaceutically acceptable salt of any one of claims 3329-4339 in the manufacture of a medicament for treatment of a systematic lupus erythematosus or lupus.

4541. The use of claim 4440, 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 for antagonizing TLR7.~~

~~47. Use of a compound or pharmaceutically acceptable salt of any one of claims 33-43 in the manufacture of a medicament for antagonizing TLR8.~~

4842. A pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt of any one of claims 3329-4339 and at least one pharmaceutically acceptable carrier.