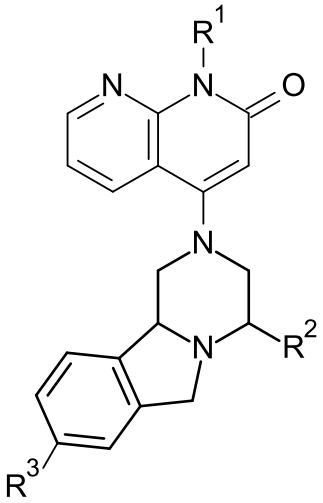
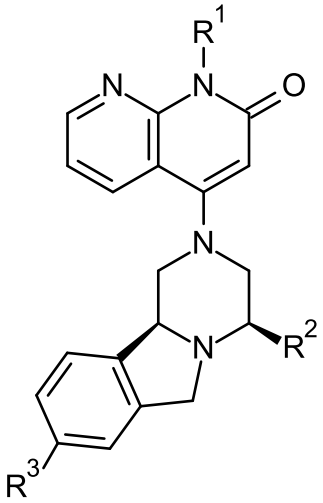
anti-DNA antibodies are well established diagnostic markers of SLE, and these antibodies can deliver both self-RNA and self-DNA to endosomes. While self-RNA complexes can be recognized by TLR7 and TLR8, self-DNA complexes can trigger TLR9 activation. Indeed, defective clearance of self-RNA and self-DNA from blood and/or tissues is evident in SLE (Systemic Lupus Erythematosus) patients. TLR7 and TLR9 have been reported to be upregulated in SLE tissues, and correlate with chronicity and activity of lupus nephritis, respectively. In B cells of SLE patients, TLR7 expression correlates with anti-RNP antibody production, while TLR9 expression with IL-6 and anti-dsDNA antibody levels. Consistently, in lupus mouse models, TLR7 is required for anti-RNA antibodies, and TLR9 is required for anti-nucleosome antibody. On the other hand, overexpression of TLR7 or human TLR8 in mice promotes autoimmunity and autoinflammation. Moreover, activation of TLR8 specifically contributes to inflammatory cytokine secretion of mDC/macrophages, neutrophil NETosis, induction of Th17 cells, and suppression of Treg cells. In addition to the described role of TLR9 in promoting autoantibody production of B cells, activation of TLR9 by self-DNA in pDC also leads to induction of type I IFNs and other inflammatory cytokines. Given these roles of TLR9 in both pDC and B cells, both as key contributors to the pathogenesis of autoimmune diseases, and the extensive presence of self-DNA complexes that could readily activate TLR9 in many patients with autoimmune diseases, it may have extra benefit to further block self-DNA mediated TLR9 pathways on top of inhibition of TLR7 and TLR8 pathways. Taken together, TLR7, 8, and 9 pathways represent new therapeutic targets for the treatment of autoimmune and auto-inflammatory diseases, for which no effective steroid-free and non-cytotoxic oral drugs exist, and inhibition of all these pathways from the very upstream may deliver satisfying therapeutic effects. As such, we invented oral compounds that target and suppress TLR7, TLR8 and TLR9 for the treatment of autoimmune and auto-inflammatory diseases.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~disclosure relates to novel compounds of formula (I) and (Ia),



(I) and



(Ia),

wherein

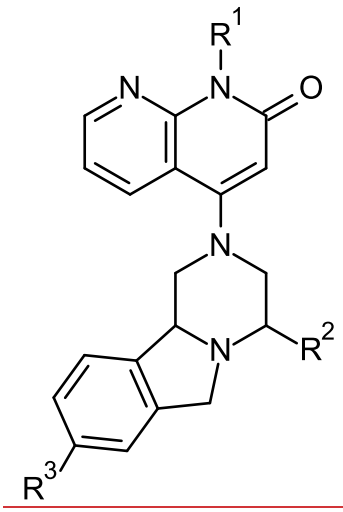
R^1 is $C_{1\text{-}6}$alkyl;

R^2 is $C_{1\text{-}6}$alkyl;

R^3 is ($C_{1\text{-}6}$alkoxy$C_{1\text{-}6}$alkyl)piperazinyl; ($C_{1\text{-}6}$alkyl)$_2$amino$C_{1\text{-}6}$alkoxy; 2,5-diazabicyclo[2.2.1]heptanyl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,8-diazabicyclo[3.2.1]octanyl; 3-oxa-9-azabicyclo[3.3.1]nonanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; amino($C_{1\text{-}6}$alkoxy)piperidinyl; amino($C_{1\text{-}6}$alkoxy)pyrrolidinyl; amino($C_{1\text{-}6}$alkyl)azetidinyl; amino($C_{1\text{-}6}$alkyl)piperidinyl; amino($C_{1\text{-}6}$alkyl)pyrrolidinyl; amino-1,4-oxazepanyl; aminohalopyrrolidinyl; aminopiperidinyl; $C_{1\text{-}6}$alkyl-2,6-diazaspiro[3.3]heptanyl; $C_{1\text{-}6}$alkylpiperazinyl; morpholinyl$C_{3\text{-}7}$cycloalkyl; piperazinyl; piperidinyl or pyrrolidinyl;

or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure relates to a compound of formula (I),



(I),

wherein

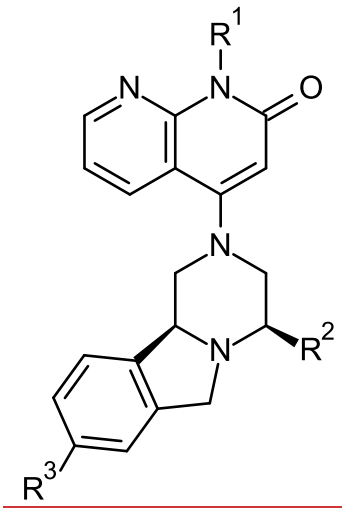
R^1 is C_{1-6}alkyl;

R^2 is C_{1-6}alkyl;

R^3 is (C_{1-6}alkoxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)$_2$aminoC_{1-6}alkoxy; 2,5-diazabicyclo[2.2.1]heptanyl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,8-diazabicyclo[3.2.1]octanyl; 3-oxa-9-azabicyclo[3.3.1]nonanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; amino(C_{1-6}alkoxy)piperidinyl; amino(C_{1-6}alkoxy)pyrrolidinyl; amino(C_{1-6}alkyl)azetidinyl; amino(C_{1-6}alkyl)piperidinyl; amino(C_{1-6}alkyl)pyrrolidinyl; amino-1,4-oxazepanyl; aminohalopyrrolidinyl; aminopiperidinyl; C_{1-6}alkyl-2,6-diazaspiro[3.3]heptanyl; C_{1-6}alkylpiperazinyl; morpholinylC_{3-7}cycloalkyl; piperazinyl; piperidinyl or pyrrolidinyl;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a compound of formula (Ia),



(Ia),

wherein

R^1 is C_{1-6}alkyl;

R^2 is C_{1-6}alkyl;

R^3 is (C_{1-6}alkoxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)$_2$aminoC_{1-6}alkoxy; 2,5-diazabicyclo[2.2.1]heptanyl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,8-diazabicyclo[3.2.1]octanyl; 3-oxa-9-azabicyclo[3.3.1]nonanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; amino(C_{1-6}alkoxy)piperidinyl; amino(C_{1-6}alkoxy)pyrrolidinyl; amino(C_{1-6}alkyl)azetidinyl; amino(C_{1-6}alkyl)piperidinyl; amino(C_{1-6}alkyl)pyrrolidinyl; amino-1,4-oxazepanyl; aminohalopyrrolidinyl; aminopiperidinyl; C_{1-6}alkyl-2,6-diazaspiro[3.3]heptanyl; C_{1-6}alkylpiperazinyl; morpholinylC_{3-7}cycloalkyl; piperazinyl; piperidinyl or pyrrolidinyl;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a compound selected from:

4-[(4*R*,10b*S*)-8-(3-amino-3-methyl-azetidin-1-yl)-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4R,10bS)-4-methyl-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(4a*R*,7a*R*)-3,4,4a,5,7,7a-hexahydro-2*H*-pyrrolo[3,4-b][1,4]oxazin-6-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*S*,4*S*)-4-amino-3-methoxy-1-piperidyl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*S*,4*S*)-3-amino-4-methoxy-1-piperidyl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(2*S*)-2-(methoxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(5-oxa-2,8-diazaspiro[3.5]nonan-8-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-piperazin-1-yl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-[(3*S*)-3-methylpiperazin-1-yl]-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-[(3*R*)-3-methylpiperazin-1-yl]-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*S*)-3-amino-3-methyl-1-piperidyl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*R*)-3-amino-1-piperidyl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-[(2*R*)-2-methylpiperazin-1-yl]-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-(4-amino-4-methyl-1-piperidyl)-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4R,10bS)-8-(3,8-diazabicyclo[3.2.1]octan-3-yl)-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[2-(dimethylamino)ethoxy]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(4-piperidyl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(3-piperidyl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-pyrrolidin-3-yl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(*trans*-4-morpholinocyclohexyl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(*cis*-4-morpholinocyclohexyl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(*endo*-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(*exo*-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one; and

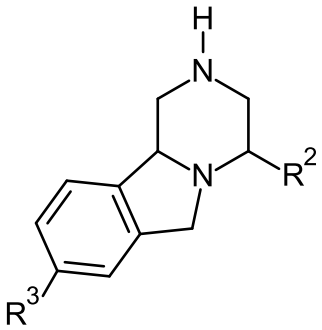
4-[(4*R*,10b*S*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-ethyl-1,8-naphthyridin-2-one;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

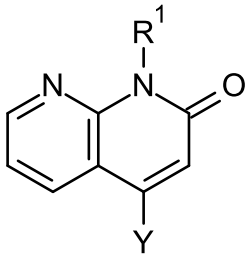
Another object of the present ~~invention~~disclosure is related to novel compounds of formula (I) or (Ia), their manufacture, medicaments based on a compound in accordance with the ~~invention~~disclosure and their production as well as the use of compounds of formula (I) or (Ia) as TLR7 and/or TLR8 and/or TLR9 antagonist, and for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis. The compounds of formula (I) or (Ia) show superior TLR7 and/or TLR8 and/or TLR9 antagonism activity. In addition, the compounds of formula (I) or (Ia) also show good hPBMC, cytotoxicity, solubility, human microsome stability and SDPK profiles, as well as low CYP inhibition.

In another aspect, the present disclosure relates to a process for the preparation of a compound as described herein comprising any of the following steps:

a) the substitution reaction or Buchwald-Hartwig amination of compound of formula

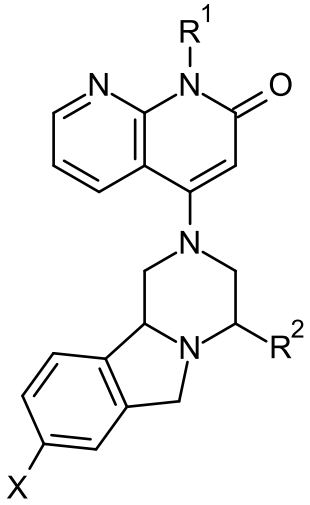


(XII), (XII),



and compound of formula (XIII), (XIII);

b) the Buchwald-Hartwig amination reaction of compound of formula (XV),



(XV),

and amine HR^3; or Suzuki coupling reaction between compound of formula (IX) and R^3-boronic acid or R^3-boronic ester;

wherein X is halogen; R^1 to R^3 are as described herein.

In another aspect, the present disclosure relates to a compound or pharmaceutically acceptable salt, enantiomer or diastereomer as described herein for use as therapeutically active substance.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as described herein and a therapeutically inert carrier.

In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

In another aspect, the present disclosure relates to the use of a compound as described herein as the TLR7 or TLR8 or TLR9 antagonist.

In another aspect, the present disclosure relates to the use of a compound as described herein as the TLR7 and TLR8 and TLR9 antagonist.

In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for TLR7 and TLR8 and TLR9 antagonist.

In another aspect, the present disclosure relates to a compound or pharmaceutically acceptable salt, enantiomer or diastereomer as described herein for use in the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

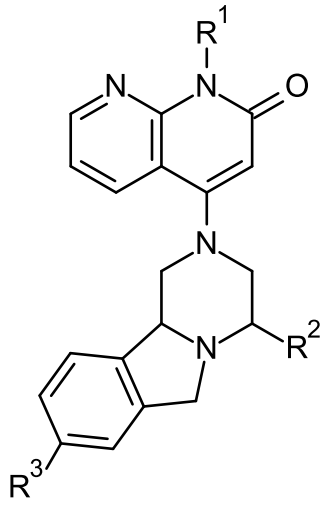
In another aspect, the present disclosure relates to a compound or pharmaceutically acceptable salt, enantiomer or diastereomer as described herein when manufactured according to a process as described herein.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

CLAIMS

1. A compound of formula (I),



(I),

wherein

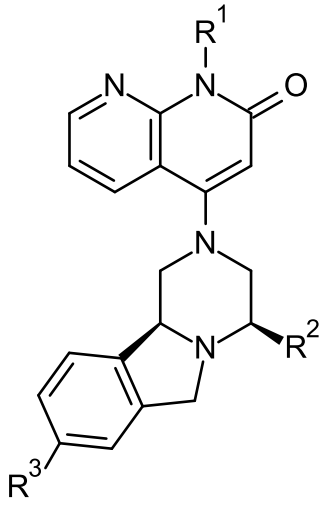
R^1 is C_{1-6}alkyl;

R^2 is C_{1-6}alkyl;

R^3 is (C_{1-6}alkoxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)$_2$aminoC_{1-6}alkoxy; 2,5-diazabicyclo[2.2.1]heptanyl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,8-diazabicyclo[3.2.1]octanyl; 3-oxa-9-azabicyclo[3.3.1]nonanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; amino(C_{1-6}alkoxy)piperidinyl; amino(C_{1-6}alkoxy)pyrrolidinyl; amino(C_{1-6}alkyl)azetidinyl; amino(C_{1-6}alkyl)piperidinyl; amino(C_{1-6}alkyl)pyrrolidinyl; amino-1,4-oxazepanyl; aminohalopyrrolidinyl; aminopiperidinyl; C_{1-6}alkyl-2,6-diazaspiro[3.3]heptanyl; C_{1-6}alkylpiperazinyl; morpholinylC_{3-7}cycloalkyl; piperazinyl; piperidinyl or pyrrolidinyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (Ia),



(Ia),

wherein

R^1 is C_{1-6}alkyl;

R^2 is C_{1-6}alkyl;

R^3 is (C_{1-6}alkoxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)$_2$aminoC_{1-6}alkoxy; 2,5-diazabicyclo[2.2.1]heptanyl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,8-diazabicyclo[3.2.1]octanyl; 3-oxa-9-azabicyclo[3.3.1]nonanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; amino(C_{1-6}alkoxy)piperidinyl; amino(C_{1-6}alkoxy)pyrrolidinyl; amino(C_{1-6}alkyl)azetidinyl; amino(C_{1-6}alkyl)piperidinyl; amino(C_{1-6}alkyl)pyrrolidinyl; amino-1,4-oxazepanyl; aminohalopyrrolidinyl; aminopiperidinyl; C_{1-6}alkyl-2,6-diazaspiro[3.3]heptanyl; C_{1-6}alkylpiperazinyl; morpholinylC_{3-7}cycloalkyl; piperazinyl; piperidinyl or pyrrolidinyl;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2, wherein

R^1 is methyl or ethyl;

R^2 is methyl;

R^3 is 2-(dimethylamino)ethoxy; 2-(methoxymethyl)piperazin-1-yl; 2,5-diazabicyclo[2.2.1]heptan-2-yl; 2-methylpiperazin-1-yl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl; 3,8-diazabicyclo[3.2.1]octan-3-yl; 3-amino-1-piperidinyl; 3-amino-3-methyl-1-piperidinyl; 3-amino-3-methyl-azetidin-1-yl; 3-amino-3-methyl-pyrrolidin-1-yl; 3-amino-4-fluoro-pyrrolidin-1-yl; 3-amino-4-methoxy-1-piperidinyl; 3-amino-4-methoxy-pyrrolidin-1-yl; 3-methylpiperazin-1-yl; 3-oxa-9-azabicyclo[3.3.1]nonan-7-yl; 3-piperidinyl; 4-amino-3-methoxy-1-piperidinyl; 4-amino-4-methyl-1-piperidinyl; 4-morpholinocyclohexyl; 4-piperidinyl; 5-oxa-2,8-

diazaspiro[3.5]nonan-2-yl; 5-oxa-2,8-diazaspiro[3.5]nonan-8-yl; 6-amino-1,4-oxazepan-4-yl; 6-methyl-2,6-diazaspiro[3.3]heptan-2-yl; piperazin-1-yl or pyrrolidin-3-yl;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 or 2, wherein R^3 is amino(C_{1-6}alkoxy)pyrrolidinyl; amino(C_{1-6}alkyl)piperidinyl; amino-1,4-oxazepanyl; aminopiperidinyl; C_{1-6}alkyl-2,6-diazaspiro[3.3]heptanyl; C_{1-6}alkylpiperazinyl; C_{1-6}alkylpiperazinyl; morpholinylC_{3-7}cycloalkyl; piperazinyl; piperidinyl or 3-oxa-9-azabicyclo[3.3.1]nonanyl.

5. A compound according to claim 4, wherein R^3 is 3-amino-1-piperidinyl; 3-amino-3-methyl-1-piperidinyl; 3-amino-4-methoxy-pyrrolidin-1-yl; 3-methylpiperazin-1-yl; 4-amino-4-methyl-1-piperidinyl; 4-morpholinocyclohexyl; 4-piperidinyl; 6-amino-1,4-oxazepan-4-yl; 6-methyl-2,6-diazaspiro[3.3]heptan-2-yl; piperazin-1-yl or 3-oxa-9-azabicyclo[3.3.1]nonan-7-yl.

6. A compound according to claim 1 or 2, wherein

R^1 is C_{1-6}alkyl;

R^2 is C_{1-6}alkyl;

R^3 is amino(C_{1-6}alkoxy)pyrrolidinyl; amino(C_{1-6}alkyl)piperidinyl; amino-1,4-oxazepanyl; aminopiperidinyl; C_{1-6}alkyl-2,6-diazaspiro[3.3]heptanyl; C_{1-6}alkylpiperazinyl; C_{1-6}alkylpiperazinyl; morpholinylC_{3-7}cycloalkyl; piperazinyl; piperidinyl or 3-oxa-9-azabicyclo[3.3.1]nonanyl;

or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6, wherein

R^1 is methyl;

R^2 is methyl;

R^3 is 3-amino-1-piperidinyl; 3-amino-3-methyl-1-piperidinyl 3-amino-4-methoxy-pyrrolidin-1-yl; 3-methylpiperazin-1-yl; 4-amino-4-methyl-1-piperidinyl; 4-morpholinocyclohexyl; 4-piperidinyl; 6-amino-1,4-oxazepan-4-yl; 6-methyl-2,6-diazaspiro[3.3]heptan-2-yl; piperazin-1-yl or 3-oxa-9-azabicyclo[3.3.1]nonan-7-yl;

or a pharmaceutically acceptable salt thereof.

8. A compound selected from:

4-[(4*R*,10b*S*)-8-(3-amino-3-methyl-azetidin-1-yl)-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4R,10bS)-4-methyl-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(4a*R*,7a*R*)-3,4,4a,5,7,7a-hexahydro-2*H*-pyrrolo[3,4-b][1,4]oxazin-6-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*S*,4*S*)-4-amino-3-methoxy-1-piperidyl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*S*,4*S*)-3-amino-4-methoxy-1-piperidyl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(2*S*)-2-(methoxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(5-oxa-2,8-diazaspiro[3.5]nonan-8-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-piperazin-1-yl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-[(3*S*)-3-methylpiperazin-1-yl]-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-[(3*R*)-3-methylpiperazin-1-yl]-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*S*)-3-amino-3-methyl-1-piperidyl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(3*R*)-3-amino-1-piperidyl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-[(2*R*)-2-methylpiperazin-1-yl]-3,4,6,10b-tetrahydro-1*H*-

pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-(4-amino-4-methyl-1-piperidyl)-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4R,10bS)-8-(3,8-diazabicyclo[3.2.1]octan-3-yl)-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-8-[2-(dimethylamino)ethoxy]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(4-piperidyl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(3-piperidyl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-pyrrolidin-3-yl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(*trans*-4-morpholinocyclohexyl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(*cis*-4-morpholinocyclohexyl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

4-[(4*R*,10b*S*)-4-methyl-8-(*endo*-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one;

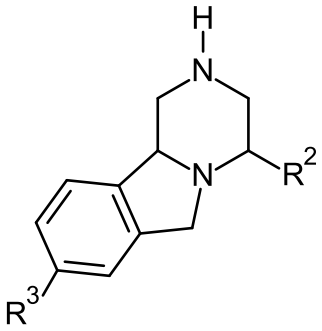
4-[(4*R*,10b*S*)-4-methyl-8-(*exo*-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one; and

4-[(4*R*,10b*S*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-ethyl-1,8-naphthyridin-2-one;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

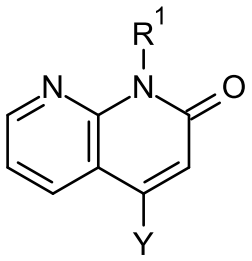
9. A process for the preparation of a compound according to any one of claims 1 to 8 comprising any of the following steps:

a) the substitution reaction or Buchwald-Hartwig amination of compound of formula



(XII),

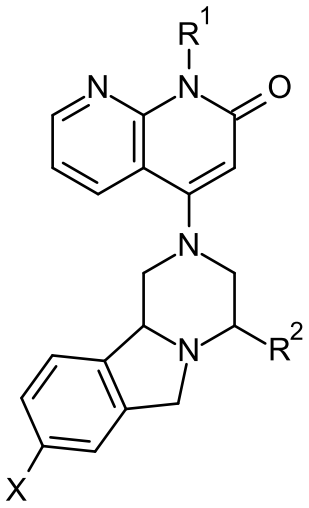
(XII),



and compound of formula (XIII),

(XIII);

b) the Buchwald-Hartwig amination reaction of compound of formula (XV),



(XV),

and amine HR^3; or Suzuki coupling reaction between compound of formula (IX) and R^3-boronic acid or R^3-boronic ester;

wherein X is halogen; R^1 to R^3 are defined as in any one of claims 1 to 7.

10. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 8 for use as therapeutically active substance.

11. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 8 and a therapeutically inert carrier.

~~12. The use of a compound according to any one of claims 1 to 8 for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.~~

~~13~~12. The use of a compound according to any one of claims 1 to 8 ~~for~~in the preparation of a medicament for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

~~14~~13. The use of a compound according to any one of claims 1 to 8 as the TLR7 or TLR8 or TLR9 antagonist.

~~15~~14. The use of a compound according to any one of claims 1 to 8 as the TLR7 and TLR8 and TLR9 antagonist.

~~16~~15. The use of a compound according to any one of claims 1 to 8 ~~for~~ in the preparation of a medicament for TLR7 and TLR8 and TLR9 antagonist.

~~17~~16. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 8 for use in the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

~~18~~17. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 8 when manufactured according to a process of claim 9.

~~19. A method for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis, which method comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 8.~~