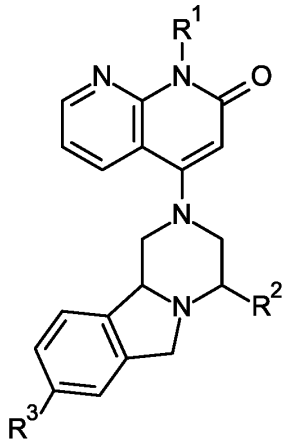
CLAIMS

1. A compound of formula (I),



(I),

wherein

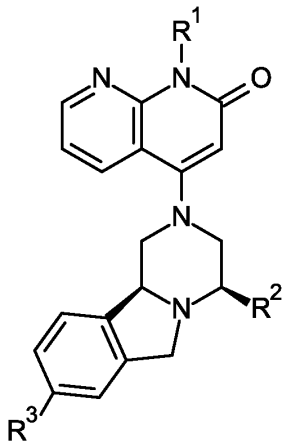
R^1 is C_{1-6}alkyl;

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;

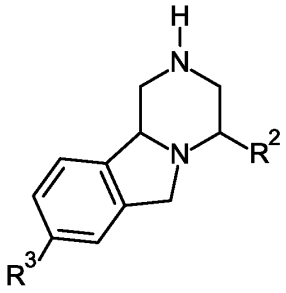
4-[(4*R*,10b*S*)-4-methyl-8-(*exo*-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3,4,6,10b-tetrahydro-1*H*-pyrazino[2,1-a]isoindol-2-yl]-1-methyl-1,8-naphthyridin-2-one; and

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;

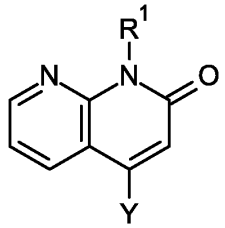
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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

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

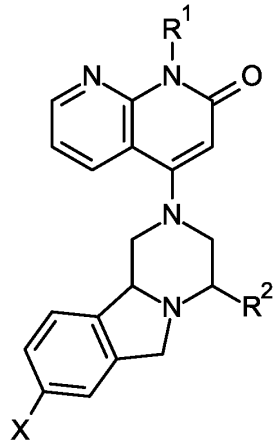


(XII), (XII),



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

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

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

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

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

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

18. 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.