

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

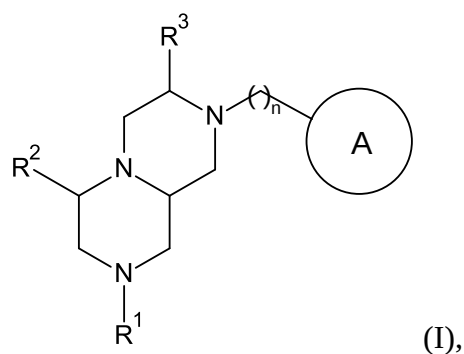
The present disclosure relates to novel compounds of formula (I) or (Ia) or (Ib),

R³ is H;

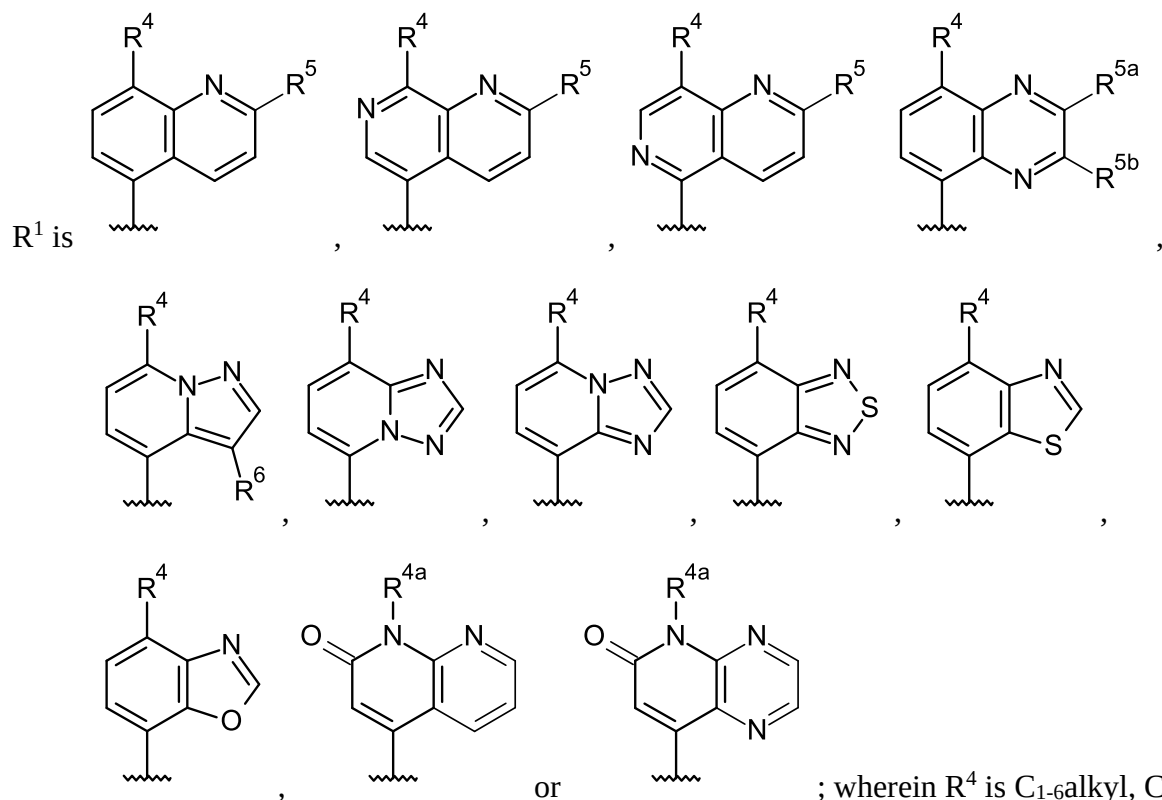
Ring A is a 5-7 membered monocyclic aryl or heteroaryl; or a 7-12 membered bicyclic heterocyclyl;

or a pharmaceutically acceptable salt thereof.

5 In one aspect, the present disclosure provides a compound of formula (I),



wherein



; wherein R⁴ is C₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkyl, halogen, nitro or cyano; R^{4a} is C₁₋₆alkyl or C₃₋₇cycloalkyl; R⁵, R^{5a} and R^{5b} are independently selected from H and deuterium; R⁶ is H or halogen;

R² is H or C₁₋₆alkyl;

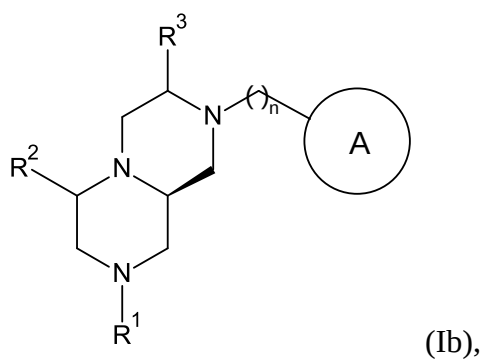
R³ is H;

Ring A is an unsubstituted or substituted 5-7 membered monocyclic aryl or heteroaryl; or an unsubstituted or substituted 7-12 membered bicyclic heterocyclyl;

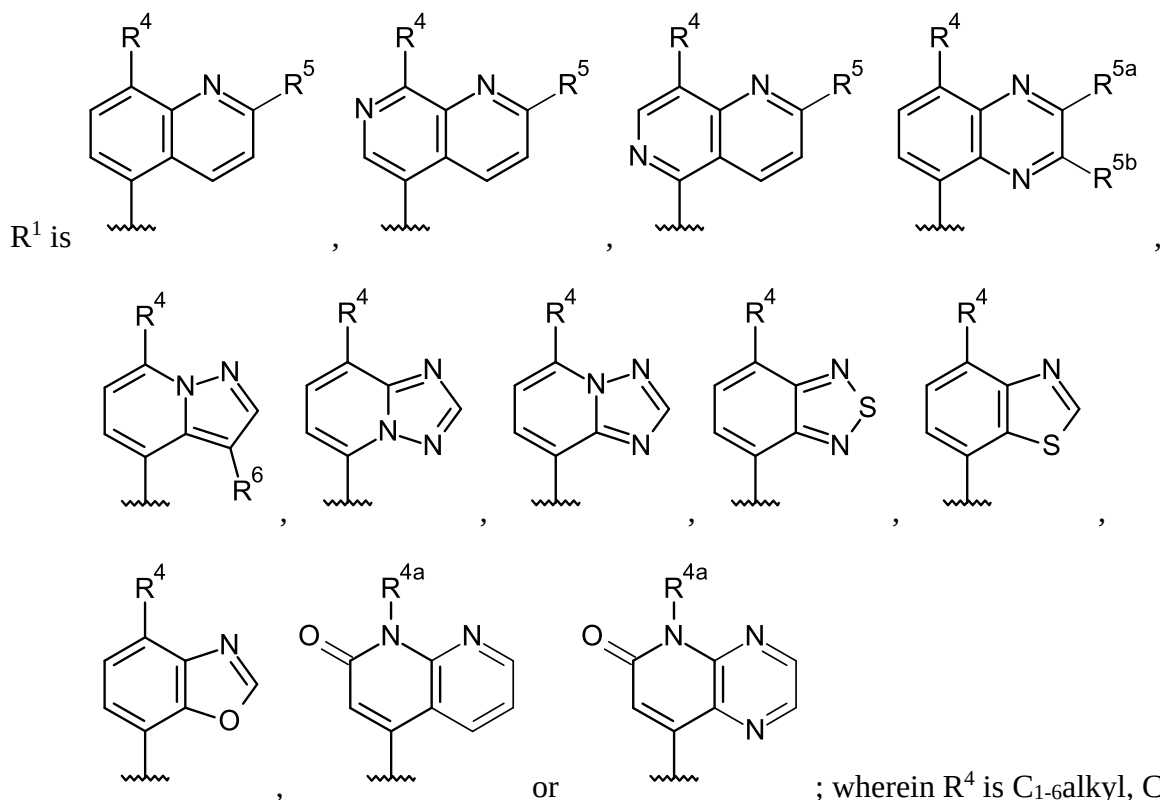
n is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

5 In another aspect, the present disclosure provides a compound of formula (Ib),



wherein



R² is H or C₁₋₆alkyl;

R³ is H;

Ring A is 1,2,3,4-tetrahydroisoquinoliny;

5,6,7,8-tetrahydro-1,6-naphthyridinyl;

5,6,7,8-tetrahydro-2,6-naphthyridinyl;

5,6,7,8-tetrahydro-2,7-naphthyridinyl;

isoindoliny;

phenyl substituted by amino(C₁₋₆alkoxy)pyrrolidinyl, 5-oxa-2,8-

diazaspiro[3.5]nonanyl, morpholiny or piperazinyl;

pyridinyl substituted once or twice by substituents independently selected from

(halopyrrolidinyl)amino; 1,4-diazepanyl; 2,5-diazabicyclo[2.2.1]heptanyl;

3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,6-

diazabicyclo[3.1.1]heptanyl; 3,8-diazabicyclo[3.2.1]octanyl; 5-oxa-2,8-

diazaspiro[3.5]nonanyl; 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl; amino(C₁₋

6alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidiny; amino(C₁₋₆alkyl)pyrrolidinyl;

amino-1,4-oxazepanyl; amino-2-azaspiro[3.3]heptanyl; aminoazetidiny;

aminohalopyrrolidinyl; C₁₋₆alkyl; C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanecarbonyl;

C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanyl; C₁₋₆alkylpiperazinyl and piperazinyl; or

pyrimidinyl substituted once or twice by substituents independently selected from

amino(C₁₋₆alkoxy)pyrrolidinyl, amino(C₁₋₆alkyl)azetidiny, aminoazetidiny,

C₁₋₆alkyl and piperazinyl;

n is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

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

5-[*cis*-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-7-ylmethyl)-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[*cis*-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-5-yl)-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[*cis*-4-methyl-8-[(2-piperazin-1-yl-4-pyridyl)methyl]-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-*[cis-8-isoindolin-4-yl-4-methyl-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-*[(4R,9aS)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-7-ylmethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5 5-*[(4R,9aS)-4-methyl-8-(5,6,7,8-tetrahydro-1,6-naphthyridin-3-ylmethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-*[(4R,9aS)-4-methyl-8-[2-(4-piperazin-1-ylphenyl)ethyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

10 5-*[(4R,9aS)-4-methyl-8-[(6-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-*[(4R,9aS)-8-isoindolin-4-yl-4-methyl-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-*[(4R,9aS)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-6-ylmethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

15 5-*[(4R,9aS)-4-methyl-8-[2-(6-piperazin-1-yl-3-pyridyl)ethyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-*[(4R,9aS)-8-[2-[6-[(3R,4R)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

20 5-*[(4R,9aS)-8-[2-[5-[(3R,4R)-3-amino-4-methoxy-pyrrolidin-1-yl]-2-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-*[(4R,9aS)-8-[6-(1,4-diazepan-1-yl)-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-*[(4R,9aR)-4-methyl-8-(5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

25 5-*[(4R,9aS)-8-[2-[6-[(3R,4S)-3-amino-4-fluoro-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-*[(4R,9aS)-8-[2-[6-[(3R,4R)-3-amino-4-fluoro-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]*quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[5-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-2-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-[5-[(3*S*)-3-methylpiperazin-1-yl]-2-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-[(3*S*)-3-methylpiperazin-1-yl]-2-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[4-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]phenyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,9*aS*)-4-methyl-8-[(6-piperazin-1-yl-2-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-[4-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)phenyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,9*aR*)-4-methyl-8-(4-piperazin-1-ylpyrimidin-2-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-(6-methyl-2-piperazin-1-yl-pyrimidin-4-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(2-piperazin-1-yl-4-pyridyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,9*aR*)-4-methyl-8-(2-piperazin-1-ylpyrimidin-4-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-(4-piperazin-1-yl-2-pyridyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-(8-isoindolin-4-yl-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl)quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[2-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]pyrimidin-4-yl]-4-methyl-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,9*aR*)-8-[4-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]pyrimidin-2-yl]-4-methyl-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[2-(4-methyl-6-piperazin-1-yl-3-pyridyl)-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-8-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,9*aR*)-8-[4-(3-aminoazetidin-1-yl)pyrimidin-2-yl]-4-methyl-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[(3*S*,4*R*)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-pyridyl]-4-methyl-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-(3-aminoazetidin-1-yl)-4-pyridyl]-4-methyl-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,9*aS*)-4-methyl-8-(5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-(5-methyl-4-piperazin-1-yl-pyrimidin-2-yl)-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,9*aR*)-4-methyl-8-(5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[2-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-6-methyl-pyrimidin-4-yl]-4-methyl-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[2-[6-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3-pyridyl]-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-8-yl]quinoline-8-carbonitrile;

25 5-[*trans*-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-5-yl)-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[(6*S*)-6-amino-1,4-oxazepan-4-yl]-4-pyridyl]-4-methyl-3,4,6,7,9,9a-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[2-(3-amino-3-methyl-azetidin-1-yl)-6-methyl-pyrimidin-4-yl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,9*aS*)-8-[2-(3-amino-3-methyl-azetidin-1-yl)-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(5-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-[(3*R*)-3-methylpiperazin-1-yl]-2-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)-3-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(2-methyl-6-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-7-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

20 5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

25 5-[(4*R*,9*aS*)-8-[2-[6-(3-amino-3-methyl-azetidin-1-yl)-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

4-[(4*R*,9*aS*)-8-[2-[4-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]phenyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,9*aS*)-8-[2-[4-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]phenyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl] pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-7-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-8-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-(isoindolin-4-ylmethyl)-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-(3-amino-3-methyl-azetidin-1-yl)-6-methyl-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

4-[(4*R*,9*aS*)-8-[2-[6-(3-amino-3-methyl-azetidin-1-yl)-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-(3-amino-3-methyl-azetidin-1-yl)-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(6-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-(3-amino-3-methyl-azetidin-1-yl)-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[[2-methyl-6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-

5 8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

10 5-[(4*R*,9*aS*)-8-[[6-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[[2-methyl-6-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-pyridyl]methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

15 5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[[2-methyl-6-[(2*S*)-2-methylpiperazin-1-yl]-3-pyridyl]methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,9*aS*)-4-methyl-8-[[2-methyl-6-[(3*R*)-3-methylpiperazin-1-yl]-3-pyridyl]methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(4-methyl-6-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(3-methyl-6-piperazin-1-yl-2-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

25 5-[(4*R*,9*aS*)-8-[2-[2-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

4-[(4*R*,9*aR*)-4-methyl-8-(3-methyl-5-piperazin-1-yl-2-pyridyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-1-methyl-1,8-naphthyridin-2-one;

10 5-[(4*R*,9*aS*)-8-[[6-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-4-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

15 5-[(4*R*,9*aR*)-8-[5-[(3*R*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[5-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

20 5-[(4*R*,9*aS*)-8-[[6-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

25 5-[(4*R*,9*aR*)-8-[5-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[5-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

30 5-[(4*R*,9*aR*)-8-[5-(6-amino-2-azaspiro[3.3]heptan-2-yl)-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-[3-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptane-2-carbonyl)-2-pyridyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-4-methyl-8-[3-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptane-2-carbonyl)-2-pyridyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*S*,9*aS*)-4-methyl-8-[4-[(2*R*)-morpholin-2-yl]phenyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aS*)-4-methyl-8-[4-[(2*S*)-morpholin-2-yl]phenyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[5-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[5-[2-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]ethyl]-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[5-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

4-[(4*S*,9*aR*)-4-methyl-8-[3-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-2-pyridyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-1-methyl-1,8-naphthyridin-2-one;

5-[(4*S*,9*aR*)-8-[5-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[6-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[6-[2-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]ethyl]-3-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5 5-[(4*S*,9*aR*)-8-[5-(3-amino-3-methyl-azetidin-1-yl)-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-4-methyl-8-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

10 5-[(4*S*,9*aR*)-8-[5-[2-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]ethyl]-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[5-[[3-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]methyl]-6-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

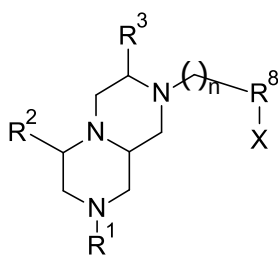
15 5-[(4*R*,9*aS*)-8-[2-[6-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile; and

5-[(4*S*,9*aS*)-4-methyl-8-[4-[(2*R*)-morpholin-2-yl]phenyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

20 or a pharmaceutically acceptable salt thereof.

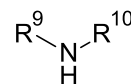
In another aspect, the present disclosure provides a process for the preparation of a compound according to the disclosure comprising any one of the following steps:

a) Buchwald-Hartwig amination reaction or nucleophilic substitution between compound



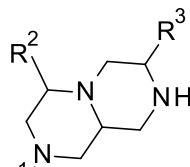
of formula (IX),

(IX), and amine (X),



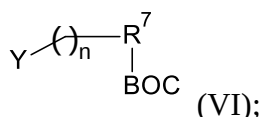
(X);

b) Buchwald-Hartwig amination reaction or nucleophilic substitution between compound



of formula (V),

(V), and compound of formula (VI),



(VI);

5 wherein n is 0, 1 or 2; X is halogen; Y is halogen or methanesulfonate; R⁷ and R⁸ is aryl or heteroaryl; R⁹ and R¹⁰ together with the nitrogen atom they are attached to form a heterocyclyl.

In another aspect, the present disclosure provides a compound or pharmaceutically acceptable salt according to the disclosure for use as therapeutically active substance.

10 In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound in accordance with the disclosure and a therapeutically inert carrier.

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

15 In another aspect, the present disclosure provides the use of a compound according to the disclosure as the TLR7 or TLR8 or TLR9 antagonist.

In another aspect, the present disclosure provides the use of a compound according to the disclosure as the TLR7 and TLR8 antagonist.

In another aspect, the present disclosure provides the use of a compound according to the disclosure as the TLR7 and TLR8 and TLR9 antagonist.

20 In another aspect, the present disclosure provides the use of a compound according to the disclosure in the preparation of a medicament for TLR7 and TLR8 and TLR9 antagonist.

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

In another aspect, the present disclosure provides a compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to the disclosure, when manufactured according to a process of the disclosure.

Another object of the present disclosure is related to novel compounds of formula (I) or (Ia), their manufacture, medicaments based on a compound in accordance with the invention 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 cytotoxicity, phototoxicity, solubility, hPBMC, human microsome stability and SDPK profiles, as well as low CYP inhibition.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

The term “C₁₋₆alkyl” denotes a saturated, linear or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms, for example methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl and the like. Particular “C₁₋₆alkyl” groups are methyl, ethyl and *n*-propyl.

The term “halogen” and “halo” are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

The term “haloC₁₋₆alkyl” denotes a C₁₋₆alkyl group wherein at least one of the hydrogen atoms of the C₁₋₆alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloC₁₋₆alkyl include monofluoro-, difluoro- or trifluoro-methyl, -ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, trifluoroethyl, fluoromethyl, difluoromethyl, difluoroethyl or trifluoromethyl.

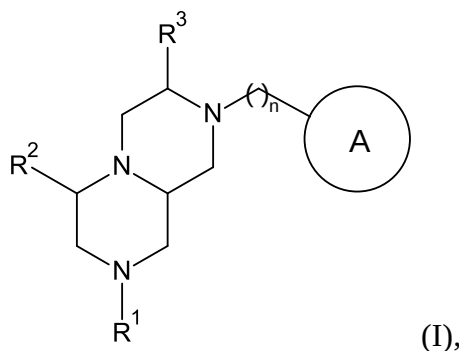
The term “halopyrrolidinyl” denotes a pyrrolidinyl substituted once, twice or three times by halogen. Examples of halopyrrolidinyl include, but not limited to, difluoropyrrolidinyl and fluoropyrrolidinyl.

The term “C₃₋₇cycloalkyl” denotes a saturated carbon ring containing from 3 to 7 carbon atoms, particularly from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Particular “C₃₋₇cycloalkyl” groups are cyclopropyl, cyclopentyl and cyclohexyl.

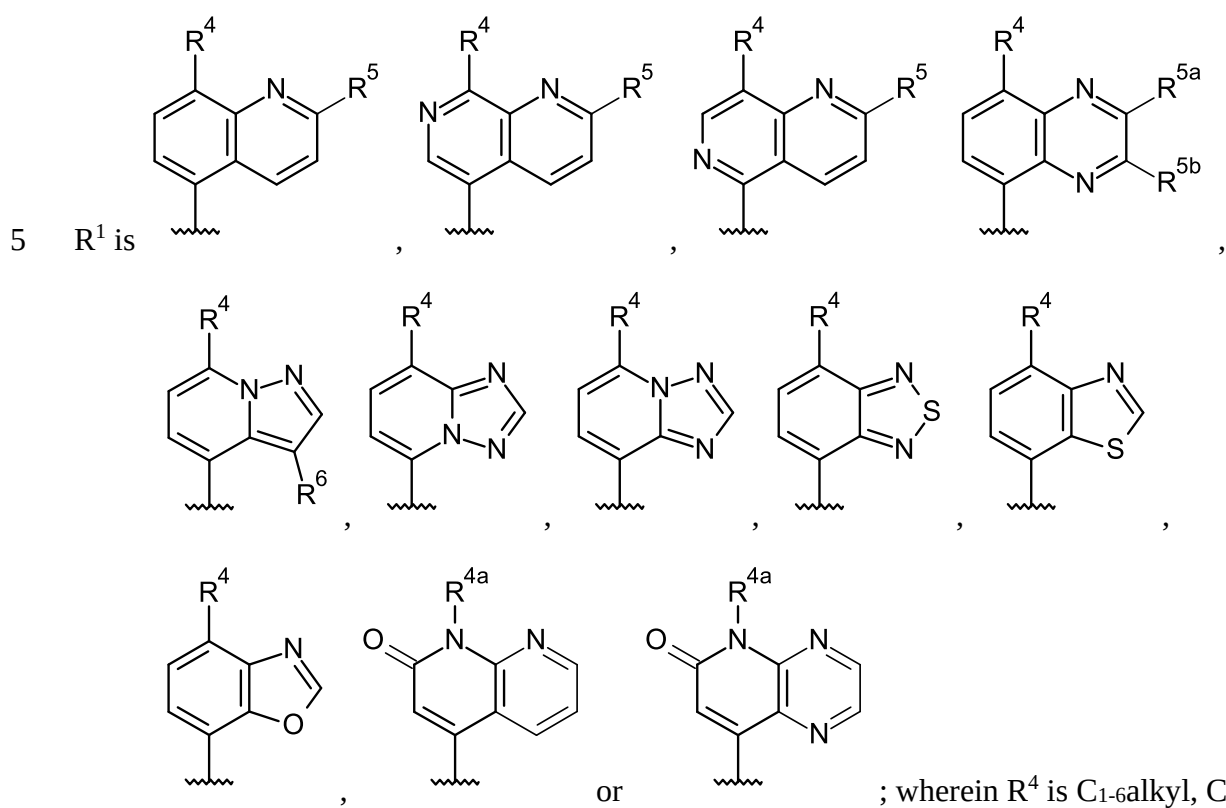
- 5 The term “aryl” denotes an aromatic hydrocarbon mono- or bicyclic ring system of 5 to 12 ring atoms. Examples of aryl include, but not limited to, phenyl and naphthyl. Aryl can be

CLAIMS

1. A compound of formula (I),



wherein



10 R² is H or C₁₋₆alkyl;

R³ is H;

Ring A is an unsubstituted or substituted 5-7 membered monocyclic aryl or heteroaryl; or an unsubstituted or substituted 7-12 membered bicyclic heterocycl;

n is 0, 1 or 2;

15 or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

Ring A is 1,2,3,4-tetrahydroisoquinolinyl;

5,6,7,8-tetrahydro-1,6-naphthyridinyl;

5,6,7,8-tetrahydro-2,6-naphthyridinyl;

5,6,7,8-tetrahydro-2,7-naphthyridinyl;

isoindolinyl;

phenyl substituted by amino(C₁₋₆alkoxy)pyrrolidinyl, 5-oxa-2,8-diazaspiro[3.5]nonanyl, morpholinyl or piperazinyl;

pyridinyl substituted once or twice by substituents independently selected from

(halopyrrolidinyl)amino; 1,4-diazepanyl; 2,5-diazabicyclo[2.2.1]heptanyl;

3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,6-

diazabicyclo[3.1.1]heptanyl; 3,8-diazabicyclo[3.2.1]octanyl; 5-oxa-2,8-

diazaspiro[3.5]nonanyl; 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl; amino(C₁₋

6alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidiny; amino(C₁₋

6alkyl)pyrrolidinyl; amino-1,4-oxazepanyl; amino-2-azaspiro[3.3]heptanyl;

aminoazetidiny; aminohalopyrrolidinyl; C₁₋₆alkyl; C₁₋₆alkyl-2,6-

diazaspiro[3.3]heptanecarbonyl; C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanyl; C₁₋

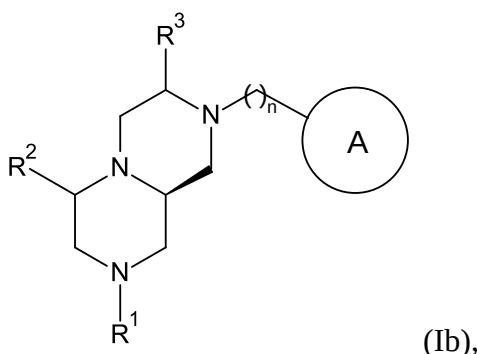
6alkylpiperazinyl and piperazinyl; or

pyrimidinyl substituted once or twice by substituents independently selected from

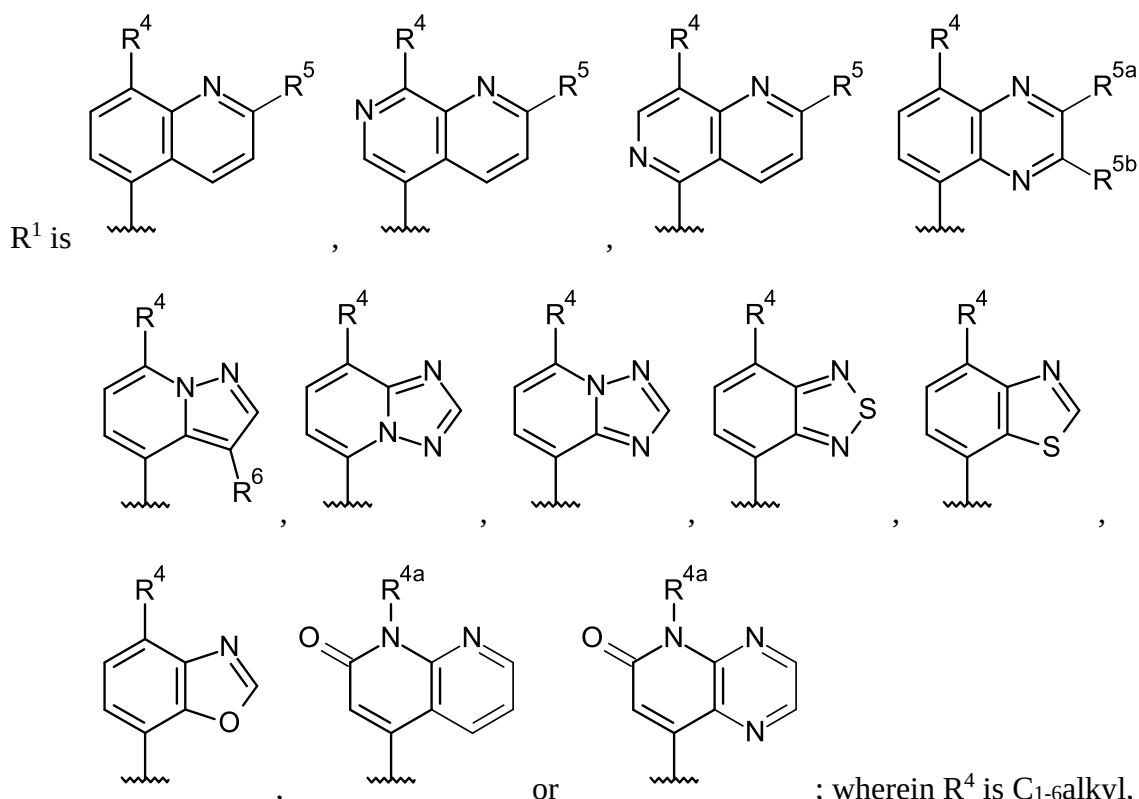
amino(C₁₋₆alkoxy)pyrrolidinyl, amino(C₁₋₆alkyl)azetidiny,

aminoazetidiny, C₁₋₆alkyl and piperazinyl.

3. A compound of formula (Ib),



wherein



; wherein R⁴ is C₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkyl, halogen, nitro or cyano; R^{4a} is C₁₋₆alkyl or C₃₋₇cycloalkyl; R⁵, R^{5a} and R^{5b} are independently selected from H and deuterium; R⁶ is H or halogen;

R² is H or C₁₋₆alkyl;

R³ is H;

Ring A is 1,2,3,4-tetrahydroisoquinolinyl;

5,6,7,8-tetrahydro-1,6-naphthyridinyl;

5,6,7,8-tetrahydro-2,6-naphthyridinyl;

5,6,7,8-tetrahydro-2,7-naphthyridinyl;

isoindolinyl;

phenyl substituted by amino(C₁₋₆alkoxy)pyrrolidinyl, 5-oxa-2,8-diazaspiro[3.5]nonanyl, morpholinyl or piperazinyl;

pyridinyl substituted once or twice by substituents independently selected from (halopyrrolidinyl)amino; 1,4-diazepanyl; 2,5-diazabicyclo[2.2.1]heptanyl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,6-diazabicyclo[3.1.1]heptanyl; 3,8-diazabicyclo[3.2.1]octanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl; amino(C₁₋₆alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidiny; amino(C₁₋₆alkyl)pyrrolidinyl; amino-1,4-oxazepanyl; amino-2-azaspiro[3.3]heptanyl; aminoazetidiny; aminohalopyrrolidinyl; C₁₋₆alkyl; C₁₋₆alkyl-2,6-

diazaspiro[3.3]heptanecarbonyl; C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanyl; C₁₋₆alkylpiperazinyl and piperazinyl; or

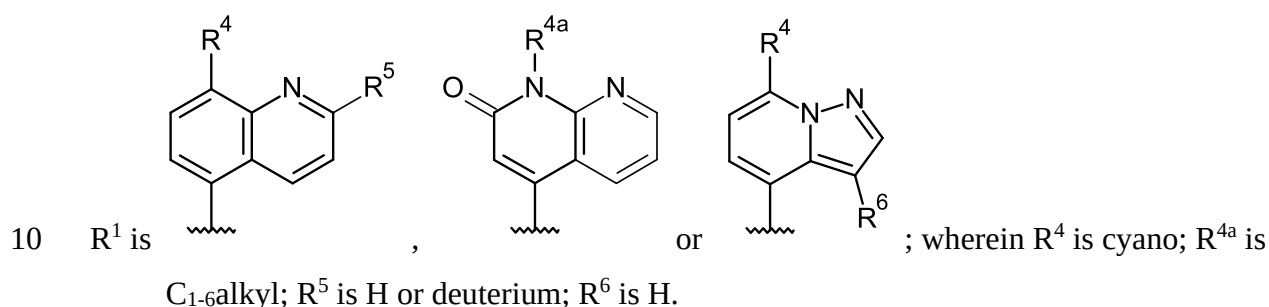
pyrimidinyl substituted once or twice by substituents independently selected from amino(C₁₋₆alkoxy)pyrrolidinyl, amino(C₁₋₆alkyl)azetidiny,

5 aminoazetidiny, C₁₋₆alkyl and piperazinyl;

n is 0, 1 or 2;

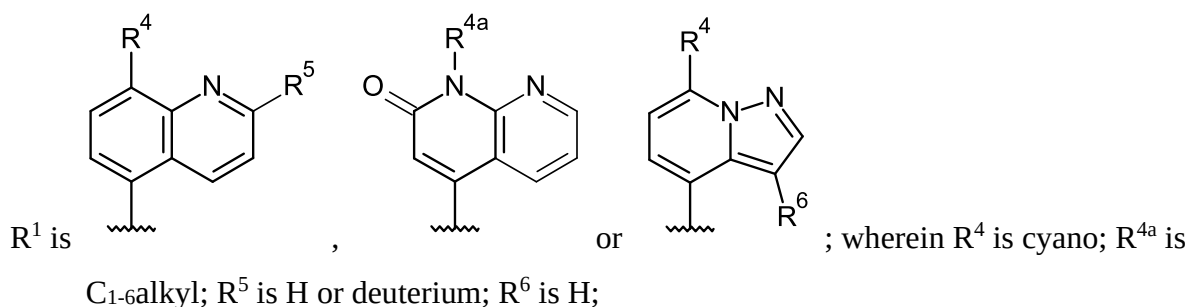
or a pharmaceutically acceptable salt thereof.

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



5. A compound according to claim 4, wherein R² is C₁₋₆alkyl.

15 6. A compound according to claim 5, wherein



R² is methyl;

R³ is H;

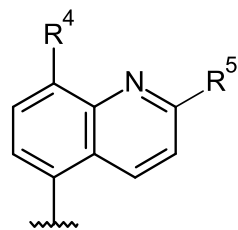
20 Ring A is 1,2,3,4-tetrahydroisoquinolin-7-yl; 1,2,3,4-tetrahydroisoquinolin-5-yl; 1,2,3,4-tetrahydroisoquinolin-6-yl; 1,2,3,4-tetrahydroisoquinolin-7-yl; 1,2,3,4-tetrahydroisoquinolin-8-yl; 5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl; 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl; 5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl; 5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl; isoindolin-4-yl; 3-amino-4-methoxy-pyrrolidin-1-ylphenyl; 5-oxa-2,8-diazaspiro[3.5]nonan-2-ylphenyl; morpholin-2-ylphenyl;

25 piperazin-1-ylphenyl; (4-fluoropyrrolidin-3-yl)amino(methyl)pyridinyl; 1,4-diazepan-1-

5 ylpuridinyl; 2,5-diazabicyclo[2.2.1]heptan-2-yl(methyl)puridinyl; 2,5-
 diazabicyclo[2.2.1]heptan-2-ylpuridinyl; 2-methylpiperazin-1-yl(methyl)puridinyl;
 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl(methyl)puridinyl;
 (3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl)puridinyl; 3,6-
 10 diazabicyclo[3.1.1]heptan-3-yl(methyl)puridinyl; 3,8-diazabicyclo[3.2.1]octan-3-
 yl(methyl)puridinyl; 3,8-diazabicyclo[3.2.1]octan-3-ylpuridinyl; 3-amino-3-methyl-
 azetidin-1-yl(methyl)puridinyl; 3-amino-3-methyl-azetidin-1-ylpuridinyl; 3-amino-3-
 methyl-pyrrolidin-1-yl(methyl)puridinyl; 3-amino-3-methyl-pyrrolidin-1-ylpuridinyl;
 3-amino-4-fluoro-pyrrolidin-1-ylpuridinyl; 3-amino-4-methoxy-pyrrolidin-1-
 10 yl(methyl)puridinyl; 3-amino-4-methoxy-pyrrolidin-1-ylpuridinyl; 3-aminoazetidin-1-
 ylpuridinyl; 3-methylpiperazin-1-yl(methyl)puridinyl; 3-methylpiperazin-1-ylpuridinyl;
 5-oxa-2,8-diazaspiro[3.5]nonan-2-ylpuridinyl; 6-amino-1,4-oxazepan-4-
 yl(methyl)puridinyl; 6-amino-1,4-oxazepan-4-ylpuridinyl; 6-amino-2-
 azaspiro[3.3]heptan-2-yl(methyl)puridinyl; 6-methyl-2,6-diazaspiro[3.3]heptan-2-
 15 yl(methyl)puridinyl; 6-methyl-2,6-diazaspiro[3.3]heptan-2-ylpuridinyl; 6-methyl-2,6-
 diazaspiro[3.3]heptane-2-carbonyl(methyl)puridinyl; 9-oxa-3,7-
 diazabicyclo[3.3.1]nonan-3-yl(methyl)puridinyl; piperazin-1-yl(methyl)puridinyl;
 piperazin-1-ylpuridinyl; 3-amino-3-methyl-azetidin-1-yl(methyl)pyrimidinyl; 3-amino-
 4-methoxy-pyrrolidin-1-yl(methyl)pyrimidinyl; 3-amino-4-methoxy-pyrrolidin-1-
 20 ylpuridinyl; 3-aminoazetidin-1-ylpyrimidinyl; piperazin-1-yl(methyl)pyrimidinyl or
 piperazin-1-ylpyrimidinyl;

n is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.



25 7. A compound according to claim 5, wherein R¹ is  ; wherein R⁴ is cyano;
 R⁵ is H or deuterium.

8. A compound according to claim 7, wherein

Ring A is 1,2,3,4-tetrahydroisoquinolinyl;

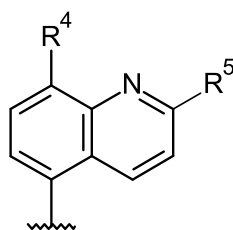
30 phenyl substituted by morpholinyl;

pyridinyl substituted once or twice by substituents independently selected from
 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; amino(C₁₋₆alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidiny; aminohalopyrrolidinyl;
 C₁₋₆alkyl; C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanyl and piperazinyl;
 5 pyrimidinyl substituted twice by substituents independently selected from
 amino(C₁₋₆alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidiny and C₁₋₆alkyl.

9. A compound according to claim 8, wherein ring A is 1,2,3,4-tetrahydroisoquinolinyl;
 morpholinylphenyl; piperazinylpyridinyl; (amino(C₁₋₆alkoxy)pyrrolidinyl)pyridinyl;
 10 (aminohalopyrrolidinyl)pyridinyl; piperazinyl(C₁₋₆alkyl)pyridinyl; (amino(C₁₋₆alkoxy)pyrrolidinyl)pyridinyl; (aminohalopyrrolidinyl)pyridinyl; (C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanyl)pyridinyl; (amino(C₁₋₆alkyl)azetidiny)pyridinyl; C₁₋₆alkyl(amino(C₁₋₆alkyl)azetidiny)pyridinyl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl(C₁₋₆alkyl)pyridinyl; (3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl)pyridinyl; C₁₋₆alkyl(amino(C₁₋₆alkyl)azetidiny)pyrimidinyl or C₁₋₆alkyl(amino(C₁₋₆alkoxy)pyrrolidinyl)pyrimidinyl.
 15

10. A compound according to claim 9, wherein ring A is 1,2,3,4-tetrahydroisoquinolin-7-yl;
 morpholin-2-ylphenyl; (3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl)-2-methyl-3-pyridinyl;
 20 (3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl)-3-pyridinyl; (3-amino-4-fluoro-pyrrolidin-1-yl)-3-pyridinyl; (3-amino-4-fluoro-pyrrolidin-1-yl)-3-pyridinyl; (3-amino-4-methoxy-pyrrolidin-1-yl)-3-pyridinyl; (3-amino-4-methoxy-pyrrolidin-1-yl)-3-pyridinyl; 2-methyl-6-piperazin-1-yl-3-pyridinyl; 6-(3-amino-3-methyl-azetid-1-yl)-2-methyl-3-pyridinyl; 6-(3-amino-3-methyl-azetid-1-yl)-3-pyridinyl; 6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridinyl; 6-piperazin-1-yl-3-pyridinyl; (3-amino-4-methoxy-pyrrolidin-1-yl)-6-methyl-pyrimidin-4-yl or (3-amino-3-methyl-azetid-1-yl)-6-methyl-pyrimidin-4-yl.
 25

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



30 R¹ is ; wherein R⁴ is cyano; R⁵ is H or deuterium;

R² is C₁₋₆alkyl;

R³ is H;

Ring A is 1,2,3,4-tetrahydroisoquinolinyl;

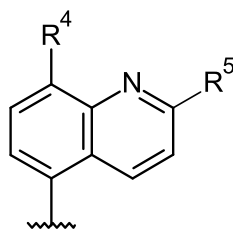
phenyl substituted by morpholinyl;

- 5 pyridinyl substituted once or twice by substituents independently selected from
3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; amino(C₁₋₆alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidiny; aminohalopyrrolidinyl;
C₁₋₆alkyl; C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanyl and piperazinyl;
pyrimidinyl substituted twice by substituents independently selected from
10 amino(C₁₋₆alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidiny and C₁₋₆alkyl;

n is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 11, wherein



- 15 R¹ is ; wherein R⁴ is cyano; R⁵ is H or deuterium;

R² is C₁₋₆alkyl;

R³ is H;

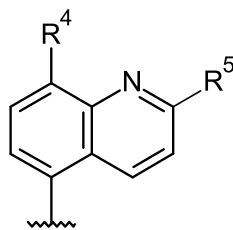
Ring A is 1,2,3,4-tetrahydroisoquinolinyl; morpholinylphenyl; piperazinylpyridinyl;

- (amino(C₁₋₆alkoxy)pyrrolidinyl)pyridinyl; (aminohalopyrrolidinyl)pyridinyl;
20 piperazinyl(C₁₋₆alkyl)pyridinyl; amino(C₁₋₆alkoxy)pyrrolidinyl)pyridinyl;
(aminohalopyrrolidinyl)pyridinyl; (C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanyl)pyridinyl;
(amino(C₁₋₆alkyl)azetidiny)pyridinyl; C₁₋₆alkyl(amino(C₁₋₆alkyl)azetidiny)pyridinyl;
3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl(C₁₋₆alkyl)pyridinyl;
(3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl)pyridinyl; C₁₋₆alkyl
25 6alkyl(amino(C₁₋₆alkyl)azetidiny)pyrimidinyl or C₁₋₆alkyl(amino(C₁₋₆alkoxy)pyrrolidinyl)pyrimidinyl;

n is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

- 30 13. A compound according to claim 11, wherein



R¹ is ; wherein R⁴ is cyano; R⁵ is H or deuterium;

R² is methyl;

R³ is H;

Ring A is 1,2,3,4-tetrahydroisoquinolin-7-yl; 4-(morpholin-2-yl)phenyl; (3,4,4a,5,7,7a-

5 hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl)-2-methyl-3-pyridinyl; (3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl)-3-pyridinyl; (3-amino-4-fluoro-pyrrolidin-1-yl)-3-pyridinyl; (3-amino-4-fluoro-pyrrolidin-1-yl)-3-pyridinyl; (3-amino-4-methoxy-pyrrolidin-1-yl)-3-pyridinyl; (3-amino-4-methoxy-pyrrolidin-1-yl)-3-pyridinyl; 2-methyl-6-piperazin-1-yl-3-pyridinyl; 6-(3-amino-3-methyl-azetidin-1-yl)-2-methyl-3-pyridinyl; 6-(3-amino-3-methyl-azetidin-1-yl)-3-pyridinyl; 6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridinyl; 6-piperazin-1-yl-3-pyridinyl; (3-amino-4-methoxy-pyrrolidin-1-yl)-6-methyl-pyrimidin-4-yl or (3-amino-3-methyl-azetidin-1-yl)-6-methyl-pyrimidin-4-yl;

n is 0, 1 or 2;

15 or a pharmaceutically acceptable salt thereof.

14. A compound selected from:

5-[*cis*-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-7-ylmethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]quinoline-8-carbonitrile;

20 5-[*cis*-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-5-yl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[*cis*-4-methyl-8-[(2-piperazin-1-yl-4-pyridyl)methyl]-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]quinoline-8-carbonitrile;

25 5-[*cis*-8-isindolin-4-yl-4-methyl-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-7-ylmethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(5,6,7,8-tetrahydro-1,6-naphthyridin-3-ylmethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[1,2-a]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-(4-piperazin-1-ylphenyl)ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(6-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,9*aS*)-8-isoindolin-4-yl-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-6-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,9*aS*)-4-methyl-8-[2-(6-piperazin-1-yl-3-pyridyl)ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[5-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-2-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,9*aS*)-8-[[6-(1,4-diazepan-1-yl)-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-(5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*R*)-3-amino-4-fluoro-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[5-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-2-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,9*aS*)-4-methyl-8-[2-[5-[(3*S*)-3-methylpiperazin-1-yl]-2-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-[(3*S*)-3-methylpiperazin-1-yl]-2-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[4-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]phenyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,9*aS*)-4-methyl-8-[(6-piperazin-1-yl-2-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-[4-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)phenyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,9*aR*)-4-methyl-8-(4-piperazin-1-ylpyrimidin-2-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-(6-methyl-2-piperazin-1-yl-pyrimidin-4-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(2-piperazin-1-yl-4-pyridyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,9*aR*)-4-methyl-8-(2-piperazin-1-ylpyrimidin-4-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-(4-piperazin-1-yl-2-pyridyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

20 5-(8-isoindolin-4-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[2-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]pyrimidin-4-yl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[4-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]pyrimidin-2-yl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

25 5-[2-(4-methyl-6-piperazin-1-yl-3-pyridyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-8-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[4-(3-aminoazetidin-1-yl)pyrimidin-2-yl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,9*aS*)-8-[2-[(3*S*,4*R*)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-(3-aminoazetidin-1-yl)-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-(5-methyl-4-piperazin-1-yl-pyrimidin-2-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-(5,6,7,8-tetrahydro-2,7-naphthyridin-4-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,9*aR*)-8-[2-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-6-methyl-pyrimidin-4-yl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[2-[6-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3-pyridyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-8-yl]quinoline-8-carbonitrile;

10 5-[*trans*-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-5-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[(6*S*)-6-amino-1,4-oxazepan-4-yl]-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,9*aS*)-8-[2-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[2-(3-amino-3-methyl-azetidin-1-yl)-6-methyl-pyrimidin-4-yl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-(3-amino-3-methyl-azetidin-1-yl)-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,9*aS*)-4-methyl-8-[(5-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-[(3*R*)-3-methylpiperazin-1-yl]-2-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)-3-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(2-methyl-6-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-7-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

30 5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5 5-[(4*R*,9*aS*)-4-methyl-8-[2-[6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]ethyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-(3-amino-3-methyl-azetidin-1-yl)-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

10 4-[(4*R*,9*aS*)-8-[2-[4-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]phenyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

15 4-[(4*R*,9*aS*)-8-[2-[4-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]phenyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl] pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-7-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

20 5-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-5-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-(1,2,3,4-tetrahydroisoquinolin-8-ylmethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,9*aS*)-8-(isoindolin-4-ylmethyl)-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-(3-amino-3-methyl-azetidin-1-yl)-6-methyl-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

30 4-[(4*R*,9*aS*)-8-[2-[6-(3-amino-3-methyl-azetidin-1-yl)-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,9*aS*)-8-[2-[6-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-(3-amino-3-methyl-azetidin-1-yl)-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(6-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-(3-amino-3-methyl-azetidin-1-yl)-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[[2-methyl-6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[[2-methyl-6-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3-pyridyl]methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[6-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[[2-methyl-6-[(2*S*)-2-methylpiperazin-1-yl]-3-pyridyl]methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[[2-methyl-6-[(3*R*)-3-methylpiperazin-1-yl]-3-pyridyl]methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(4-methyl-6-piperazin-1-yl-3-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-4-methyl-8-[(3-methyl-6-piperazin-1-yl-2-pyridyl)methyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[2-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5 5-[(4*R*,9*aS*)-8-[[6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

10 5-[(4*R*,9*aS*)-8-[[6-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

4-[(4*R*,9*aR*)-4-methyl-8-(3-methyl-5-piperazin-1-yl-2-pyridyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-1-methyl-1,8-naphthyridin-2-one;

15 5-[(4*R*,9*aS*)-8-[[6-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-4-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

20 5-[(4*R*,9*aR*)-8-[5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[5-[(3*R*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

25 5-[(4*R*,9*aR*)-8-[5-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[[6-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-2-methyl-3-pyridyl]methyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

30 5-[(4*R*,9*aR*)-8-[5-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-8-[5-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5 5-[(4*R*,9*aR*)-8-[5-(6-amino-2-azaspiro[3.3]heptan-2-yl)-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aR*)-4-methyl-8-[3-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptane-2-carbonyl)-2-pyridyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

10 5-[(4*S*,9*aR*)-4-methyl-8-[3-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptane-2-carbonyl)-2-pyridyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,9*aS*)-8-[2-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-4-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

15 5-[(4*S*,9*aS*)-4-methyl-8-[4-[(2*R*)-morpholin-2-yl]phenyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aS*)-4-methyl-8-[4-[(2*S*)-morpholin-2-yl]phenyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[5-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

20 5-[(4*R*,9*aR*)-8-[5-[2-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]ethyl]-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[5-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

25 5-[(4*S*,9*aR*)-8-[5-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[6-(3,8-diazabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

30 4-[(4*S*,9*aR*)-4-methyl-8-[3-methyl-5-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-2-pyridyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-1-methyl-1,8-naphthyridin-2-one;

5-[(4*S*,9*aR*)-8-[5-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5 5-[(4*S*,9*aR*)-8-[6-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-3-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[6-[2-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]ethyl]-3-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

10 5-[(4*S*,9*aR*)-8-[5-(3-amino-3-methyl-azetidin-1-yl)-3-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-4-methyl-8-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

15 5-[(4*S*,9*aR*)-8-[5-[2-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]ethyl]-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*S*,9*aR*)-8-[5-[[3-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]methyl]-6-methyl-2-pyridyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]-2-deuterio-quinoline-8-carbonitrile;

20 5-[(4*R*,9*aS*)-8-[2-[6-[(4*aR*,7*aR*)-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3-pyridyl]ethyl]-4-methyl-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile; and

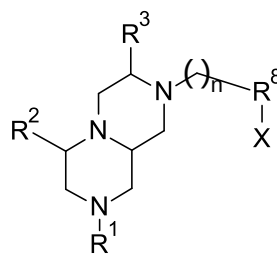
5-[(4*S*,9*aS*)-4-methyl-8-[4-[(2*R*)-morpholin-2-yl]phenyl]-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[1,2-*a*]pyrazin-2-yl]quinoline-8-carbonitrile;

or a pharmaceutically acceptable salt thereof.

25

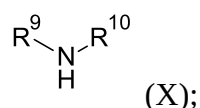
15. A process for the preparation of a compound according to any one of claims 1 to 14 comprising any one of the following steps:

a) Buchwald-Hartwig amination reaction or nucleophilic substitution between



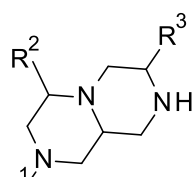
compound of formula (IX),

(IX), and amine (X),



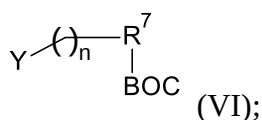
(X);

b) Buchwald-Hartwig amination reaction or nucleophilic substitution between



compound of formula (V),

(V), and compound of formula (VI),



(VI);

wherein n is 0, 1 or 2; X is halogen; Y is halogen or methanesulfonate; R⁷ and R⁸ is aryl or heteroaryl; R⁹ and R¹⁰ together with the nitrogen atom they are attached to form a heterocyclyl.

10

16. A compound or pharmaceutically acceptable salt according to any one of claims 1 to 14 for use as therapeutically active substance.

15

17. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 14 and a therapeutically inert carrier.

20

18. The use of a compound according to any one of claims 1 to 14 in the preparation of a medicament for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

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

20. The use of a compound according to any one of claims 1 to 14 as the TLR7 and TLR8 antagonist.

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

22. The use of a compound according to any one of claims 1 to 14 in the preparation of a medicament for TLR7 and TLR8 and TLR9 antagonist.

10

23. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 14 for use in the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

15 24. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 14, when manufactured according to a process of claim 15.