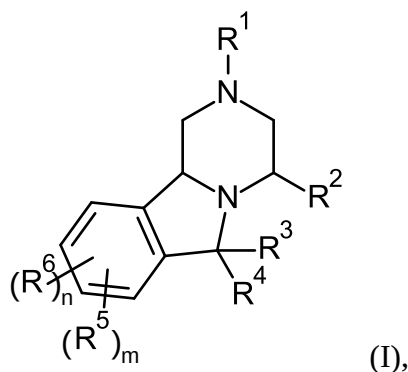


15, 1. Chen, J. Q., *et al. Clinical Reviews in Allergy & Immunology* **2016**, 50, 1.). Anti-RNA and anti-DNA antibodies are well established diagnostic markers of SLE, and these antibodies can deliver both self-RNA and self-DNA to endosomes. While self-RNA complexes can be recognized by TLR7 and TLR8, 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, in one aspect, relates to a compound of formula (I),



The present disclosure is also related to novel compounds of formula (I) or (Ia) or (Ib), 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) or (Ib) 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) or (Ib) show superior TLR7 and/or TLR8 and/or TLR9 antagonism activity. In addition, the compounds of formula (I) or (Ia) or (Ib) also show good hPBMC, cytotoxicity, solubility, human microsome stability and SDPK profiles, as well as low CYP inhibition.

In another aspect, there is provided a compound selected from:

5-[(4*R*,10*bS*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*S*,10*bR*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-(8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl)quinoline-8-carbonitrile;

7-(8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl)-1,3-benzothiazole-4-carbonitrile;

4-[(4*R*,10*bS*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

7-[(4*R*,10*bS*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-1,3-benzothiazole-4-carbonitrile;

8-[(4*R*,10*bS*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoxaline-5-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-7-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(4-piperidyl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(2*R*)-2-(hydroxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(2*S*)-2-(hydroxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*)-3-(hydroxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-(6-hydroxy-1,4-diazepan-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(*trans*-3-amino-4-methoxy-pyrrolidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(*cis*-3-amino-4-methoxy-pyrrolidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,10*bS*)-8-(5-amino-2-oxa-7-azaspiro[3.4]octan-7-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[3-amino-3-(hydroxymethyl)pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,10*bS*)-8-[(3*R*)-3-aminopyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(*trans*-3-amino-4-hydroxy-pyrrolidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(3-aminoazetidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-methoxy-4-(methylamino)pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

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

30 5-[(4*R*,10*bS*)-8-[2-(dimethylamino)ethoxy]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[2-(dimethylamino)ethylamino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(azetidin-3-yloxy)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(azetidin-3-ylamino)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(azetidin-3-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-methoxypyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,10*bS*)-4-methyl-8-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(2,6-diazaspiro[3.3]heptan-2-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,10*bS*)-8-(1,6-diazaspiro[3.3]heptan-6-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(3-amino-3-methyl-azetidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-amino-4-hydroxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-hydroxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,10*bS*)-8-(3*a*-methoxy-1,2,3,4,6,6*a*-hexahydropyrrolo[3,4-*c*]pyrrol-5-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-hydroxy-4-(methylamino)pyrrolidin-1-yl]-4-methyl-3,4,6, 10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-[(3*R*,4*R*)-3-hydroxy-4-(methylamino)pyrrolidin-1-yl]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-4-methyl-8-[(4aR,7aR)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl]-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-4-methyl-8-[*trans*-(3R,4R)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3R,4R)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3S,4S)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3S,4R)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3R,4S)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3R,4R)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3S,4S)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3R)-3-(methoxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-(4-amino-4-methyl-1-piperidyl)-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

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

5-[(4R,10bS)-8-[(6S)-6-hydroxy-1,4-diazepan-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(6R)-6-hydroxy-1,4-diazepan-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-(6-amino-1,4-oxazepan-4-yl)-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(6R)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(6S)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(6-hydroxy-6-methyl-1,4-diazepan-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(6*S*)-6-hydroxy-6-methyl-1,4-diazepan-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-[(6*R*)-6-hydroxy-6-methyl-1,4-diazepan-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(1,4-oxazepan-6-ylamino)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-4-methyl-8-[(6*R*)-1,4-oxazepan-6-yl]amino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-[(6*S*)-1,4-oxazepan-6-yl]amino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(morpholin-3-ylmethylamino)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,10*bS*)-4-methyl-8-[(2*S*)-morpholin-2-yl]methylamino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-[(2*R*)-morpholin-2-yl]methylamino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-methoxypyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-4-methoxypyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-methoxypyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-methoxypyrrolidin-3-yl]amino]-4,9-dimethyl-3,4,6, 10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-methoxypyrrolidin-3-yl]-methyl-amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,10*bS*)-4-methyl-8-[(3*R*)-3-piperidyl]amino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-3-methoxy-4-piperidyl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(2-morpholinoethylamino)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[2-[(3*S*)-3-hydroxypyrrolidin-1-yl]ethylamino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3-fluoroazetidin-3-yl)methylamino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-[(2*S*,4*S*)-4-fluoropyrrolidin-2-yl]methylamino]-4-methyl-3,4,6, 10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(8*aS*)-3-oxo-1,5,6,7,8,8*a*-hexahydroimidazo[1,5-*a*]pyrazin-2-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-8-[(8*aR*)-3-oxo-1,5,6,7,8,8*a*-hexahydroimidazo[1,5-*a*]pyrazin-2-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-fluoropyrrolidin-3-yl]oxy-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(2*S*,4*S*)-4-fluoropyrrolidin-2-yl]methoxy]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

15 (4*R*,10*bS*)-*N*-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]-4-methyl-2-(8-methyl-5-quinolyl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-8-amine;

(4*R*,10*bS*)-*N*-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]-4-methyl-2-(8-methylquinoxalin-5-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-8-amine;

(4*R*,10*bS*)-*N*-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]-4-methyl-2-[8-(trifluoromethyl)quinoxalin-5-yl]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-8-amine;

7-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-1,3-benzothiazole-4-carbonitrile;

(4*R*,10*bS*)-2-(8-chloro-5-quinolyl)-*N*-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-8-amine;

25 5-[(4*R*,10*bS*)-7-[2-[(3*S*)-3-hydroxypyrrolidin-1-yl]ethylamino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-7-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-9-fluoro-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-9-fluoro-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(2,6-diazaspiro[3.3]heptan-2-yl)-9-fluoro-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-9-fluoro-4-methyl-8-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(piperazine-1-carbonyl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carbonyl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(4-amino-4-methyl-piperidine-1-carbonyl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-8-(3,8-diazabicyclo[3.2.1]octane-3-carbonyl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

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

5-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-2-deuterio-quinoline-8-carbonitrile;

15 5-[(4*R*,10*bS*)-8-(3-amino-3-methyl-azetidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-2-deuterio-quinoline-8-carbonitrile;

20 4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*)-3-aminopyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

25 4-[(4*R*,10*bS*)-4-methyl-8-[(3*R*)-3-methylpiperazin-1-yl]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

30 4-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-(4-amino-4-methyl-1-piperidyl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-4-methyl-8-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

5 4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-amino-3-methoxy-1-piperidyl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-4-amino-3-methoxy-1-piperidyl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

10 4-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-3-amino-4-methoxy-1-piperidyl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-4-methyl-8-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

15 4-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-hydroxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

20 4-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-amino-4-hydroxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

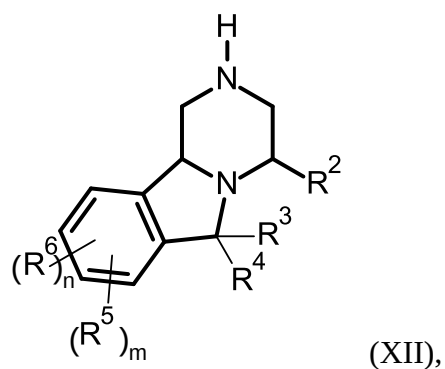
4-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile; and

25 4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

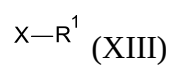
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In another aspect, there is provided a process for the preparation of a compound as defined herein comprising any of the following steps:

- a) the substitution reaction of compound of formula (XII),

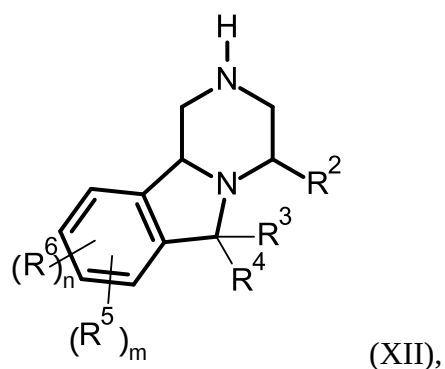


and halide of formula (XIII)

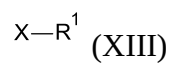


- 5 in the presence of a base;

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

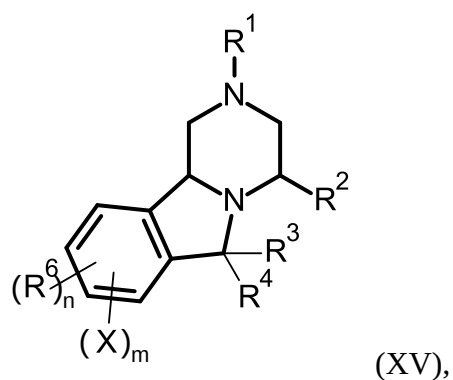


and halide of formula (XIII)

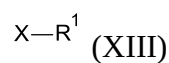


- 10 in the presence of a catalyst and a base;

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

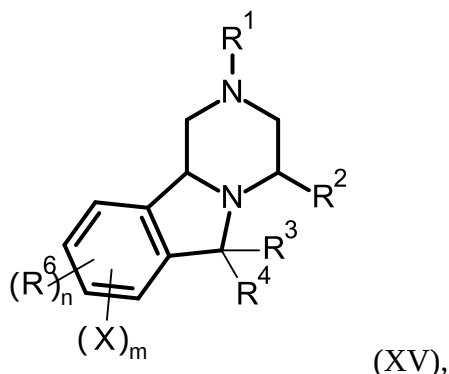


and halide of formula (XIII)



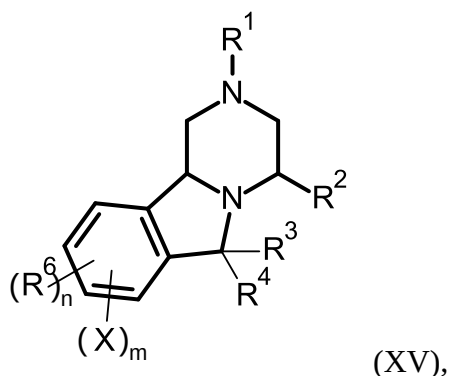
in the presence of a catalyst and a base;

d) the Suzuki coupling reaction of compound of formula (XV),



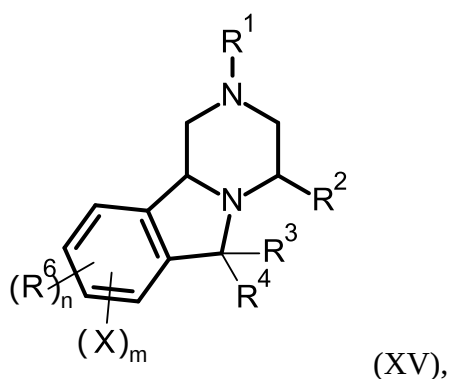
and boronic reagent in the presence of a catalyst and a base;

5 e) the Stille coupling reaction of compound of formula (XV),



and organotin reagent in the presence of a catalyst;

f) the Negishi coupling reaction of compound of formula (XV),



10 and organozinc reagent in the presence of a catalyst;

wherein the base in step a) is DIPEA; the catalyst in step b) and c) is Ruphos Pd-G2; the base in step b) and c) is Cs₂CO₃; the catalyst in step d) is

tetrakis(triphenylphosphine)palladium(0) or [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium (II); the base in step d) is K₂CO₃; the

15 catalyst in step e) is tetrakis(triphenylphosphine)palladium(0); the catalyst in step f) is

tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II); X is halogen; m is 0, 1, 2, or 3; n is 1, 2, 3 or 4; $m+n \leq 4$; R^7 is Boc; R^8 is benzyl; R^9 is alkylsilyl; and R^1 to R^6 are as defined herein.

In another aspect, there is provided a compound or pharmaceutically acceptable salt, 5 enantiomer or diastereomer as defined herein for use as therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically inert carrier.

In another aspect, there is provided use of a compound as defined herein in the preparation of a medicament for the treatment or prophylaxis of systemic lupus erythematosus or lupus 10 nephritis.

In another aspect, there is provided a compound or pharmaceutically acceptable salt, enantiomer or diastereomer as defined herein for use in the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

15 **DETAILED DESCRIPTION OF THE INVENTION**

DEFINITIONS

The term “ C_{1-6} alkyl” 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 “ C_{1-6} alkyl” groups are methyl, ethyl and *n*-propyl.

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

The term “halo C_{1-6} alkyl” denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of halo C_{1-6} alkyl include monofluoro-, difluoro- or trifluoro-methyl, - 25 ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoroethyl.

The term “oxy” denotes -O-.

The term “ C_{1-6} alkoxy” denotes C_{1-6} alkyl-O-.

The term “halopyrrolidinyl” denotes a pyrrolidinyl substituted once, twice or three times 30 by halogen. Examples of halopyrrolidinyl include, but not limited to, difluoropyrrolidinyl and fluoropyrrolidinyl.

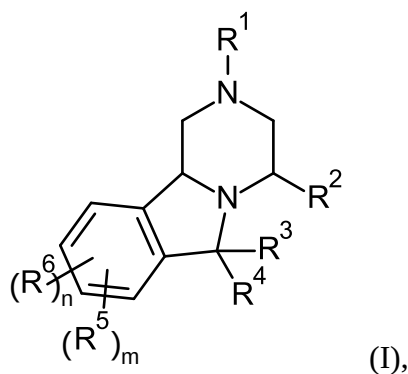
The term “haloazetidiny” denotes a azetidiny substituted once, twice or three times by halogen. Examples of halopyrrolidinyl include, but not limited to, difluoroazetidiny and fluoroazetidiny.

The term “enantiomer” denotes two stereoisomers of a compound which are non-superimposable mirror images of one another.

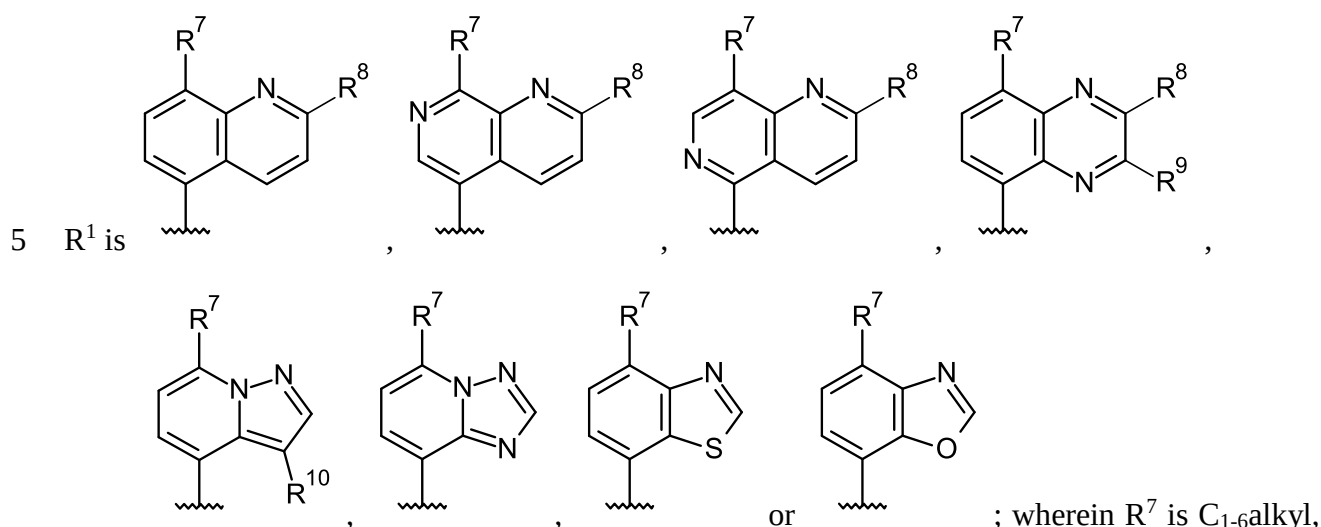
The term “diastereomer” denotes a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical
5 properties, e.g. melting points, boiling points, spectral properties, and reactivities.

CLAIMS

1. A compound of formula (I),



wherein



C_{1-6} alkoxy, halo C_{1-6} alkyl, halogen, nitro or cyano; R^8 is H or deuterium; R^9 is H, deuterium or C_{1-6} alkyl; R^{10} is H or halogen;

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

10 R^3 is H;

R^4 is H;

R^5 is H, piperazinyl, halogen, C_{1-6} alkyl, halopyrrolidinylamino or hydroxypyrrolidinyl C_{1-6} alkylamino;

R^6 is H;

15 $(C_{1-6}alkyl)_2aminoC_{1-6}alkoxy$;

$(C_{1-6}alkyl)_2aminoC_{1-6}alkylamino$;

1,2,3,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl substituted by C_{1-6} alkoxy;

1,4-diazepanyl substituted by one or two substituents independently selected from hydroxy and C_{1-6} alkyl;

20 1,4-oxazepanyl substituted by amino;

1,4-oxazepanylamino;

- 1,6-diazaspiro[3.3]heptanyl;
 2,5-diazabicyclo[2.2.1]heptanylcarbonyl;
 2,6-diazaspiro[3.3]heptanyl unsubstituted or substituted by C₁₋₆alkyl;
 2-oxa-7-azaspiro[3.4]octanyl substituted by amino;
 5 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl;
 3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl;
 3,8-diazabicyclo[3.2.1]octanylcarbonyl;
 3-oxa-7,9-diazabicyclo[3.3.1]nonanyl;
 3-oxo-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazinyl;
 10 5-oxa-2,8-diazaspiro[3.5]nonanyl;
 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl;
 amino(C₁₋₆alkyl)piperidinylcarbonyl;
 azetidiny unsubstituted or substituted by one or two substituents independently selected
 from amino and C₁₋₆alkyl;
 15 azetidinylamino;
 azetidinyloxy;
 C₁₋₆alkoxypiperidinylamino;
 C₁₋₆alkoxypyrrolidinyl(C₁₋₆alkyl)amino;
 C₁₋₆alkoxypyrrolidinylamino;
 20 haloazetidiny(C₁₋₆alkyl)amino;
 halopyrrolidinylamino;
 halopyrrolidinylC₁₋₆alkoxy;
 halopyrrolidinylC₁₋₆alkylamino;
 halopyrrolidininyloxy;
 25 hydroxypyrrolidinylC₁₋₆alkylamino;
 morpholinylC₁₋₆alkylamino;
 piperazinyl unsubstituted or substituted by C₁₋₆alkoxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl or C₁₋₆alkyl;
 piperazinylcarbonyl;
 30 piperidinyl unsubstituted or substituted by one or two substituents independently selected
 from amino, C₁₋₆alkoxy and C₁₋₆alkyl;
 piperidinylamino; or
 pyrrolidinyl substituted by one, two or three substituents independently selected from
 amino, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆alkylamino, halogen, hydroxy and hydroxyC₁₋₆alkyl;
 35 m is 0, 1, 2, or 3;

n is 1, 2, 3 or 4;

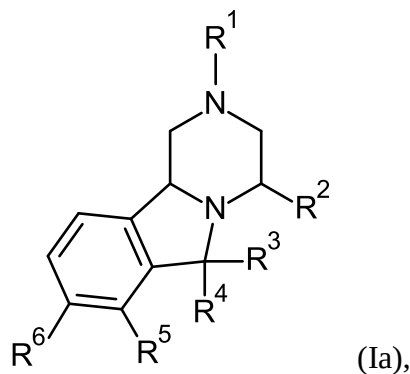
m+n≤4;

with the proviso that R⁵ and R⁶ are not H simultaneously;

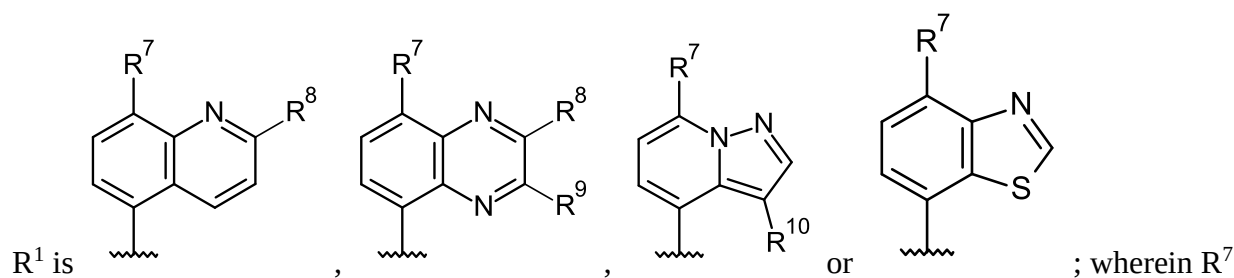
or a pharmaceutically acceptable salt thereof.

5

2. The compound of claim 1, wherein the compound has a formula (Ia),



wherein



10 is C₁₋₆alkyl, haloC₁₋₆alkyl, halogen or cyano; R⁸ is H or deuterium; R⁹ is H or deuterium; R¹⁰ is H or halogen;

R² is H or C₁₋₆alkyl;

R³ is H;

R⁴ is H;

15 R⁵ is H, piperazinyl, halopyrrolidinylamino or hydroxypyrrolidinylC₁₋₆alkylamino;

R⁶ is H;

(C₁₋₆alkyl)₂aminoC₁₋₆alkoxy;

(C₁₋₆alkyl)₂aminoC₁₋₆alkylamino;

1,2,3,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl substituted by C₁₋₆alkoxy;

20 1,4-diazepanyl substituted by one or two substituents independently selected from hydroxy and C₁₋₆alkyl;

1,4-oxazepanyl substituted by amino;

1,4-oxazepanyl amino;

1,6-diazaspiro[3.3]heptanyl;

2,5-diazabicyclo[2.2.1]heptanylcarbonyl;

2,6-diazaspiro[3.3]heptanyl unsubstituted or substituted by C₁₋₆alkyl;

2-oxa-7-azaspiro[3.4]octanyl substituted by amino;

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

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

3,8-diazabicyclo[3.2.1]octanylcarbonyl;

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl;

3-oxo-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazinyl;

5-oxa-2,8-diazaspiro[3.5]nonanyl;

10 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl;

amino(C₁₋₆alkyl)piperidinylcarbonyl;

azetidiny unsubstituted or substituted by one or two substituents independently selected
from amino and C₁₋₆alkyl;

azetidinylamino;

15 azetidinyloxy;

C₁₋₆alkoxypiperidinylamino;

C₁₋₆alkoxypyrrolidinyl(C₁₋₆alkyl)amino;

C₁₋₆alkoxypyrrolidinylamino;

haloazetidiny(C₁₋₆alkyl)amino;

20 halopyrrolidinylamino;

halopyrrolidinylC₁₋₆alkoxy;

halopyrrolidinylC₁₋₆alkylamino;

halopyrrolidininyloxy;

hydroxypyrrolidinylC₁₋₆alkylamino;

25 morpholinylC₁₋₆alkylamino;

piperazinyl unsubstituted or substituted by C₁₋₆alkoxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl or C₁₋₆alkyl;

piperazinylcarbonyl;

piperidinyl unsubstituted or substituted by one or two substituents independently selected
30 from amino, C₁₋₆alkoxy and C₁₋₆alkyl;

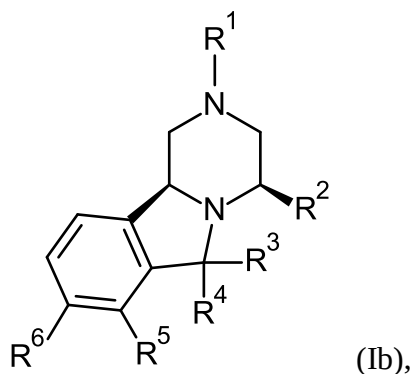
piperidinylamino; or

pyrrolidinyl substituted by one, two or three substituents independently selected from

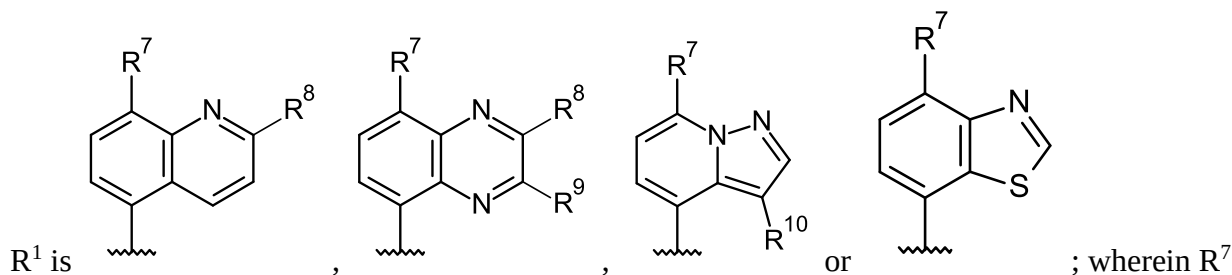
amino, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆alkylamino, halogen, hydroxy and hydroxyC₁₋₆alkyl;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound has a formula (Ib),



wherein



5 is C_{1-6} alkyl, halo C_{1-6} alkyl, halogen or cyano; R^8 is H or deuterium; R^9 is H or deuterium; R^{10} is H or halogen;

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

R^3 is H;

R^4 is H;

10 R^5 is H, piperazinyl, halopyrrolidinylamino or hydroxypyrrolidinyl C_{1-6} alkylamino;

R^6 is H;

(C_{1-6} alkyl)₂amino C_{1-6} alkoxy;

(C_{1-6} alkyl)₂amino C_{1-6} alkylamino;

1,2,3,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl substituted by C_{1-6} alkoxy;

15 1,4-diazepanyl substituted by one or two substituents independently selected from hydroxy and C_{1-6} alkyl;

1,4-oxazepanyl substituted by amino;

1,4-oxazepanylamino;

1,6-diazaspiro[3.3]heptanyl;

20 2,5-diazabicyclo[2.2.1]heptanylcarbonyl;

2,6-diazaspiro[3.3]heptanyl unsubstituted or substituted by C_{1-6} alkyl;

2-oxa-7-azaspiro[3.4]octanyl substituted by amino;

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

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

3,8-diazabicyclo[3.2.1]octanylcarbonyl;

3-oxa-7,9-diazabicyclo[3.3.1]nonanyl;

3-oxo-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazinyl;

5-oxa-2,8-diazaspiro[3.5]nonanyl;

5 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl;

amino(C₁₋₆alkyl)piperidinylcarbonyl;

azetidinyl unsubstituted or substituted by one or two substituents independently selected
from amino and C₁₋₆alkyl;

azetidinylamino;

10 azetidinyloxy;

C₁₋₆alkoxypiperidinylamino;

C₁₋₆alkoxypyrrolidinyl(C₁₋₆alkyl)amino;

C₁₋₆alkoxypyrrolidinylamino;

haloazetidinyl(C₁₋₆alkyl)amino;

15 halopyrrolidinylamino;

halopyrrolidinylC₁₋₆alkoxy;

halopyrrolidinylC₁₋₆alkylamino;

halopyrrolidininyloxy;

hydroxypyrrolidinylC₁₋₆alkylamino;

20 morpholinylC₁₋₆alkylamino;

piperazinyl unsubstituted or substituted by C₁₋₆alkoxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl or C₁₋₆alkyl;

piperazinylcarbonyl;

piperidinyl unsubstituted or substituted by one or two substituents independently selected

25 from amino, C₁₋₆alkoxy and C₁₋₆alkyl;

piperidinylamino; or

pyrrolidinyl substituted by one, two or three substituents independently selected from

amino, C₁₋₆alkoxy, C₁₋₆alkyl, C₁₋₆alkylamino, halogen, hydroxy and hydroxyC₁₋₆alkyl;

or a pharmaceutically acceptable salt thereof.

30

4. A compound according to any one of claims 1, 2 or 3, wherein

R⁶ is H; (C₁₋₆alkoxyC₁₋₆alkyl)piperazinyl; (C₁₋₆alkyl)₂aminoC₁₋₆alkoxy; (C₁₋₆alkyl)₂aminoC₁₋₆alkylamino; (hydroxyC₁₋₆alkyl)piperazinyl; 1,4-oxazepanylamino; 1,6-diazaspiro[3.3]heptanyl; 2,5-diazabicyclo[2.2.1]heptanylcarbonyl; 2,6-diazaspiro[3.3]heptanyl; 3,4,4a,5,7,7a-hexahydro-
35 2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 3,8-

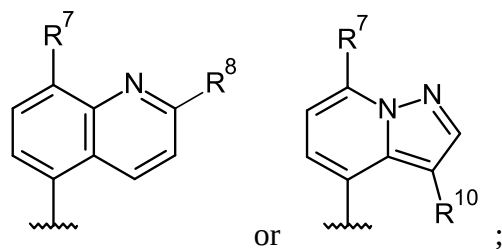
diazabicyclo[3.2.1]octanylcarbonyl; 3-oxa-7,9-diazabicyclo[3.3.1]nonanyl; 3-oxo-1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazinyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl; amino(C₁₋₆alkoxy)piperidinyl; amino(C₁₋₆alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidiny; amino(C₁₋₆alkyl)piperidinyl; amino(C₁₋₆alkyl)piperidinylcarbonyl; 5 amino(C₁₋₆alkyl)pyrrolidinyl; amino(hydroxy)(C₁₋₆alkyl)pyrrolidinyl; amino(hydroxy)pyrrolidinyl; amino(hydroxyC₁₋₆alkyl)pyrrolidinyl; amino-1,4-oxazepanyl; amino-2-oxa-7-azaspiro[3.4]octanyl; aminoazetidiny; aminohalopyrrolidinyl; aminopyrrolidinyl; azetidiny; azetidinylamino; azetidinyloxy; C₁₋₆alkoxy(C₁₋₆alkylamino)pyrrolidinyl; C₁₋₆alkoxy-1,2,3,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl; C₁₋₆alkoxypiperidinylamino; C₁₋ 10 6alkoxypyrrolidinyl(C₁₋₆alkyl)amino; C₁₋₆alkoxypyrrolidinylamino; C₁₋₆alkyl-2,6-diazaspiro[3.3]heptanyl; C₁₋₆alkylpiperazinyl; haloazetidiny(C₁₋₆alkyl)amino; halopyrrolidinylamino; halopyrrolidinylC₁₋₆alkoxy; halopyrrolidinylC₁₋₆alkylamino; halopyrrolidinylloxy; hydroxy(C₁₋₆alkyl)-1,4-diazepanyl; hydroxy(C₁₋₆alkylamino)pyrrolidinyl; hydroxy-1,4-diazepanyl; hydroxypyrrolidinylC₁₋₆alkylamino; morpholinylC₁₋₆alkylamino; 15 piperazinyl; piperazinylcarbonyl; piperidinyl or piperidinylamino.

5. A compound according to claim 4, wherein

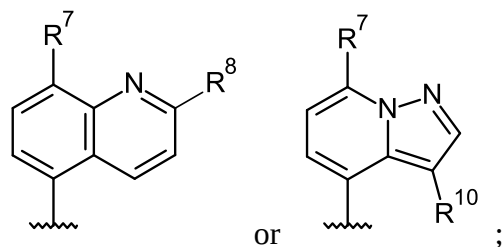
R⁶ is H; (hydroxymethyl)piperazin-1-yl; 1,4-oxazepan-6-ylamino; 1,6-diazaspiro[3.3]heptan-6-yl; 2-(dimethylamino)ethoxy; 2-(dimethylamino)ethylamino; 2,5-diazabicyclo[2.2.1]heptanyl-2- 20 carbonyl; 2,6-diazaspiro[3.3]heptan-2-yl; 2-morpholinylethylamino; 3-(methoxymethyl)piperazin-1-yl; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl; 3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl; 3,8-diazabicyclo[3.2.1]octanyl-3-carbonyl; 3a-methoxy-1,2,3,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl; 3-amino-3-(hydroxymethyl)pyrrolidin-1-yl; 3-amino-3-methyl-azetidin-1-yl; 3-amino-3-methyl-pyrrolidin- 25 1-yl; 3-amino-4-fluoro-pyrrolidin-1-yl; 3-amino-4-hydroxy-pyrrolidin-1-yl; 3-amino-4-methoxy-1-piperidinyl; 3-amino-4-methoxy-pyrrolidin-1-yl; 3-aminoazetidin-1-yl; 3-aminopyrrolidin-1-yl; 3-fluoroazetidin-3-ylmethylamino; 3-hydroxy-4-(methylamino)pyrrolidin-1-yl; 3-hydroxypyrrolidin-1-ylethylamino; 3-methoxy-4-(methylamino)pyrrolidin-1-yl; 3-methoxy-4-piperidinylamino; 3-methylpiperazin-1-yl; 3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl; 3-oxo- 30 1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyrazin-2-yl; 3-piperidinylamino; 4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl; 4-amino-3-methoxy-1-piperidinyl; 4-amino-4-methyl-1-piperidinyl; 4-amino-4-methyl-piperidinyl-1-carbonyl; 4-fluoropyrrolidin-2-ylmethoxy; 4-fluoropyrrolidin-2-ylmethylamino; 4-fluoropyrrolidin-3-ylamino; 4-fluoropyrrolidin-3-yloxy; 4-methoxypyrrolidin-3-yl(methyl)amino; 4-methoxypyrrolidin-3-ylamino; 5-amino-2-oxa-7-azaspiro[3.4]octan-7-yl; 35 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-hydroxy-1,4-diazepan-1-yl; 6-hydroxy-6-methyl-1,4-diazepan-1-yl; 6-methyl-2,6-diazaspiro[3.3]heptan-2-yl; 9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl; azetidin-3-yl; azetidin-3-ylamino; azetidin-3-yloxy; hydroxy-1,4-diazepan-1-yl; morpholin-2-ylmethylamino; morpholin-3-ylmethylamino; piperazin-1-yl; piperazinyl-1-carbonyl or piperidin-4-yl.

5



6. A compound according to claim 4, wherein R¹ is
wherein R⁷ is cyano; R⁸ is H or deuterium; R¹⁰ is H or halogen.



7. A compound according to claim 6, wherein R¹ is
wherein R⁷ is cyano; R⁸ is H or deuterium; R¹⁰ is H or fluoro.

10

8. A compound according to claim 6, wherein R² is C₁₋₆alkyl and R⁵ is H.

9. A compound according to claim 8, wherein

15

R⁶ is (C₁₋₆alkyl)₂aminoC₁₋₆alkylamino;

1,4-diazepanyl substituted by hydroxy;

1,4-oxazepanyl substituted by amino;

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

5-oxa-2,8-diazaspiro[3.5]nonanyl;

20

9-oxa-3,7-diazabicyclo[3.3.1]nonanyl;

azetidinyl substituted twice by amino and C₁₋₆alkyl;

C₁₋₆alkoxypyrrolidinylamino;

halopyrrolidinylamino; or

pyrrolidinyl substituted by two or three substituents independently selected from amino,

25

C₁₋₆alkoxy, C₁₋₆alkyl and hydroxy.

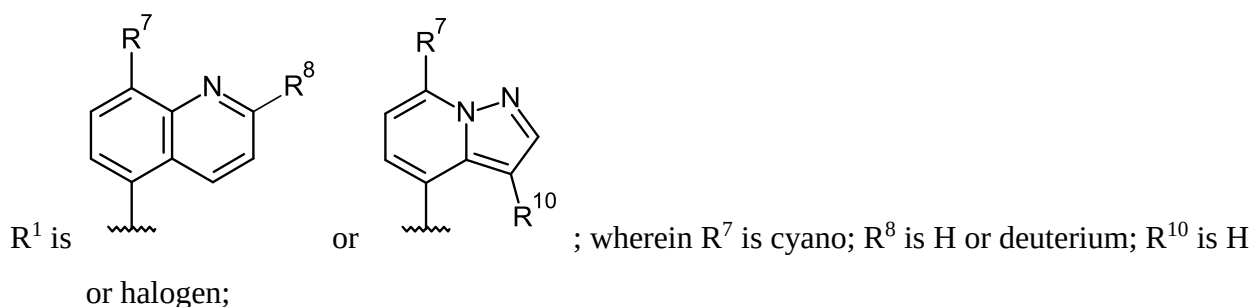
10. A compound according to claim 9, wherein

R⁶ is (C₁₋₆alkyl)₂aminoC₁₋₆alkylamino; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl; amino(C₁₋₆alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidyl; amino(C₁₋₆alkyl)pyrrolidinyl; amino(hydroxy)(C₁₋₆alkyl)pyrrolidinyl; amino(hydroxy)pyrrolidinyl; amino-1,4-oxazepanyl; C₁₋₆alkoxypyrrolidinylamino; halopyrrolidinylamino or hydroxy-1,4-diazepanyl.

11. A compound according to claim 10, wherein

R⁶ is 2-(dimethylamino)ethylamino; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl; 3-amino-3-methyl-azetidin-1-yl; 3-amino-3-methyl-pyrrolidin-1-yl; 3-amino-4-hydroxy-pyrrolidin-1-yl; 3-amino-4-methoxy-pyrrolidin-1-yl; 4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl; 4-fluoropyrrolidin-3-ylamino; 4-methoxypyrrolidin-3-ylamino; 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; 9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl or hydroxy-1,4-diazepan-1-yl.

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



R² is C₁₋₆alkyl;

R³ is H;

R⁴ is H;

R⁵ is H;

R⁶ is (C₁₋₆alkyl)₂aminoC₁₋₆alkylamino;

1,4-diazepanyl substituted by hydroxy;

1,4-oxazepanyl substituted by amino;

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

5-oxa-2,8-diazaspiro[3.5]nonanyl;

9-oxa-3,7-diazabicyclo[3.3.1]nonanyl;

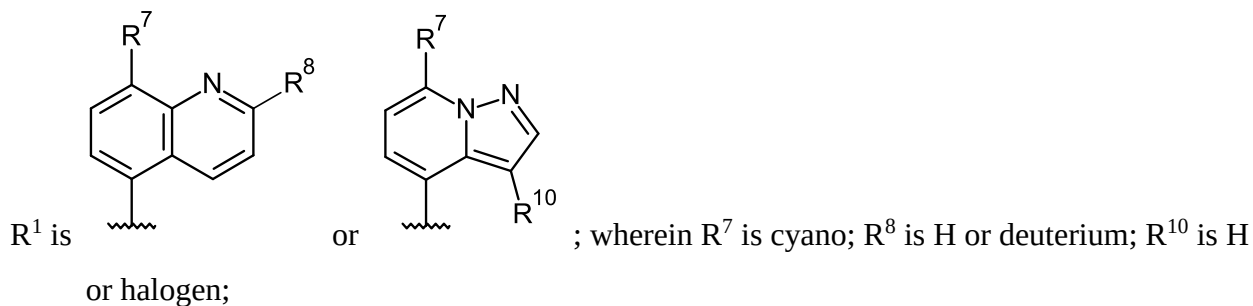
azetidyl substituted twice by amino and C₁₋₆alkyl;

C₁₋₆alkoxypyrrolidinylamino;

halopyrrolidinylamino; or

pyrrolidinyl substituted by two or three substituents independently selected from amino, C₁₋₆alkoxy, C₁₋₆alkyl and hydroxy; or a pharmaceutically acceptable salt thereof.

5 13. A compound according to claim 12, wherein



R² is C₁₋₆alkyl;

R³ is H;

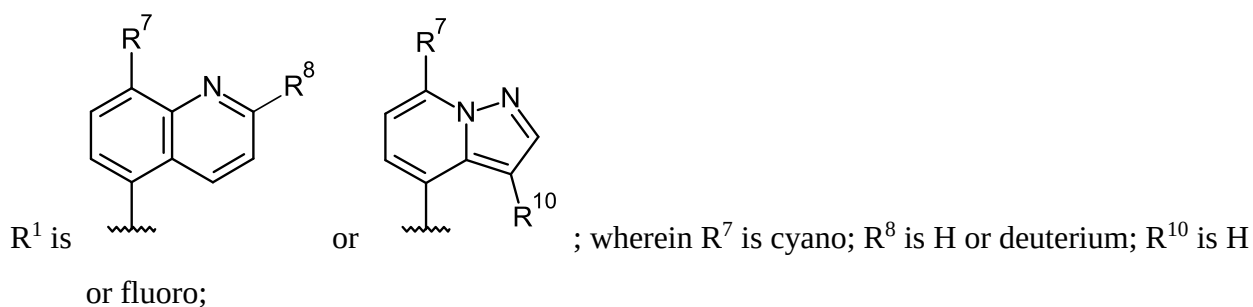
10 R⁴ is H;

R⁵ is H;

R⁶ is (C₁₋₆alkyl)₂aminoC₁₋₆alkylamino; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazinyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; 9-oxa-3,7-diazabicyclo[3.3.1]nonanyl; amino(C₁₋₆alkoxy)pyrrolidinyl; amino(C₁₋₆alkyl)azetidyl; amino(C₁₋₆alkyl)pyrrolidinyl; amino(hydroxy)(C₁₋₆alkyl)pyrrolidinyl; amino(hydroxy)pyrrolidinyl; amino-1,4-oxazepanyl; C₁₋₆alkoxypyrrolidinylamino; halopyrrolidinylamino or hydroxy-1,4-diazepanyl;

or a pharmaceutically acceptable salt thereof.

20 14. A compound according to claim 12 or 13, wherein



R² is methyl;

R³ is H;

25 R⁴ is H;

R⁵ is H;

R⁶ is 2-(dimethylamino)ethylamino; 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-6-yl; 3-amino-3-methyl-azetidin-1-yl; 3-amino-3-methyl-pyrrolidin-1-yl; 3-amino-4-hydroxy-pyrrolidin-1-yl; 3-amino-4-methoxy-pyrrolidin-1-yl; 4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl; 4-fluoropyrrolidin-3-ylamino; 4-methoxypyrrolidin-3-ylamino; 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; 9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl or hydroxy-1,4-diazepan-1-yl; or a pharmaceutically acceptable salt thereof.

15. A compound selected from:

- 10 5-[(4*R*,10*bS*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;
5-[(4*S*,10*bR*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;
5-(8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl)quinoline-8-
15 carbonitrile;
7-(8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl)-1,3-benzothiazole-4-carbonitrile;
4-[(4*R*,10*bS*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;
20 7-[(4*R*,10*bS*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-1,3-benzothiazole-4-carbonitrile;
8-[(4*R*,10*bS*)-4-methyl-8-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoxaline-5-carbonitrile;
5-[(4*R*,10*bS*)-4-methyl-7-piperazin-1-yl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-
25 2-yl]quinoline-8-carbonitrile;
5-[(4*R*,10*bS*)-4-methyl-8-(4-piperidyl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;
5-[(4*R*,10*bS*)-8-[(2*R*)-2-(hydroxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;
30 5-[(4*R*,10*bS*)-8-[(2*S*)-2-(hydroxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;
5-[(4*R*,10*bS*)-8-[(3*S*)-3-(hydroxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;
5-[(4*R*,10*bS*)-4-methyl-8-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-3,4,6,10*b*-tetrahydro-
35 1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(6-hydroxy-1,4-diazepan-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-[(*trans*-3-amino-4-methoxy-pyrrolidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(*cis*-3-amino-4-methoxy-pyrrolidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(5-amino-2-oxa-7-azaspiro[3.4]octan-7-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,10*bS*)-8-[3-amino-3-(hydroxymethyl)pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*R*)-3-aminopyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,10*bS*)-8-[(*trans*-3-amino-4-hydroxy-pyrrolidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(3-aminoazetidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-methoxy-4-(methylamino)pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,10*bS*)-4-methyl-8-(5-oxa-2,8-diazaspiro[3.5]nonan-8-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[2-(dimethylamino)ethoxy]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,10*bS*)-8-[2-(dimethylamino)ethylamino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(azetidin-3-yloxy)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(azetidin-3-ylamino)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(azetidin-3-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[[*(3S,4R)*]-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-[[*(3S,4S)*]-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[[*(3R,4S)*]-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-8-[[*(3R,4R)*]-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[[*(3R,4R)*]-4-methoxypyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

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

15 5-[(4*R*,10*bS*)-8-(2,6-diazaspiro[3.3]heptan-2-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(1,6-diazaspiro[3.3]heptan-6-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,10*bS*)-4-methyl-8-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(3-amino-3-methyl-azetidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[[*(3S,4S)*]-3-amino-4-hydroxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,10*bS*)-8-[[*(3R,4R)*]-3-amino-4-hydroxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(3*a*-methoxy-1,2,3,4,6,6*a*-hexahydropyrrolo[3,4-*c*]pyrrol-5-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,10*bS*)-8-[[*(3S,4S)*]-3-hydroxy-4-(methylamino)pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-[[*(3R,4R)*]-3-hydroxy-4-(methylamino)pyrrolidin-1-yl]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

35 5-[(4*R*,10*bS*)-4-methyl-8-[[*(4*aR*,7*aR*)*]-3,4,4*a*,5,7,7*a*-hexahydro-2*H*-pyrrolo[3,4-*b*][1,4]oxazin-6-yl]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-4-methyl-8-[*trans*-(3R,4R)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3R,4R)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4R,10bS)-8-[(3S,4S)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3S,4R)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4R,10bS)-8-[(3R,4S)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3R,4R)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(3S,4S)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

15 5-[(4R,10bS)-8-[(3R)-3-(methoxymethyl)piperazin-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-(4-amino-4-methyl-1-piperidyl)-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

20 5-[(4R,10bS)-8-(3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl)-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(6S)-6-hydroxy-1,4-diazepan-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(6R)-6-hydroxy-1,4-diazepan-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

25 5-[(4R,10bS)-8-(6-amino-1,4-oxazepan-4-yl)-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(6R)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

30 5-[(4R,10bS)-8-[(6S)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-(6-hydroxy-6-methyl-1,4-diazepan-1-yl)-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4R,10bS)-8-[(6S)-6-hydroxy-6-methyl-1,4-diazepan-1-yl]-4-methyl-3,4,6,10b-tetrahydro-1H-pyrazino[2,1-a]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(6*R*)-6-hydroxy-6-methyl-1,4-diazepan-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(1,4-oxazepan-6-ylamino)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-4-methyl-8-[(6*R*)-1,4-oxazepan-6-yl]amino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-[(6*S*)-1,4-oxazepan-6-yl]amino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-4-methyl-8-(morpholin-3-ylmethylamino)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-[(2*S*)-morpholin-2-yl]methylamino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-[(2*R*)-morpholin-2-yl]methylamino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

15 5-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-methoxypyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-4-methoxypyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

20 5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-methoxypyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-methoxypyrrolidin-3-yl]amino]-4,9-dimethyl-3,4,6, 10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-methoxypyrrolidin-3-yl]-methyl-amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,10*bS*)-4-methyl-8-[(3*R*)-3-piperidyl]amino]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-3-methoxy-4-piperidyl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,10*bS*)-4-methyl-8-(2-morpholinoethylamino)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[2-[(3*S*)-3-hydroxypyrrolidin-1-yl]ethylamino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3-fluoroazetidin-3-yl)methylamino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(2*S*,4*S*)-4-fluoropyrrolidin-2-yl]methylamino]-4-methyl-3,4,6, 10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(8*aS*)-3-oxo-1,5,6,7,8,8*a*-hexahydroimidazo[1,5-*a*]pyrazin-2-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-[(8*aR*)-3-oxo-1,5,6,7,8,8*a*-hexahydroimidazo[1,5-*a*]pyrazin-2-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-fluoropyrrolidin-3-yl]oxy-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

10 5-[(4*R*,10*bS*)-8-[(2*S*,4*S*)-4-fluoropyrrolidin-2-yl]methoxy]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

(4*R*,10*bS*)-*N*-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]-4-methyl-2-(8-methyl-5-quinolyl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-8-amine;

(4*R*,10*bS*)-*N*-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]-4-methyl-2-(8-methylquinoxalin-5-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-8-amine;

15 (4*R*,10*bS*)-*N*-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]-4-methyl-2-[8-(trifluoromethyl)quinoxalin-5-yl]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-8-amine;

7-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-1,3-benzothiazole-4-carbonitrile;

20 (4*R*,10*bS*)-2-(8-chloro-5-quinolyl)-*N*-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-8-amine;

5-[(4*R*,10*bS*)-7-[2-[(3*S*)-3-hydroxypyrrolidin-1-yl]ethylamino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-7-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

25 5-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-9-fluoro-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-9-fluoro-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

30 5-[(4*R*,10*bS*)-8-(2,6-diazaspiro[3.3]heptan-2-yl)-9-fluoro-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-9-fluoro-4-methyl-8-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(piperazine-1-carbonyl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carbonyl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(4-amino-4-methyl-piperidine-1-carbonyl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

5 5-[(4*R*,10*bS*)-8-(3,8-diazabicyclo[3.2.1]octane-3-carbonyl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]quinoline-8-carbonitrile;

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

10 5-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-8-(3-amino-3-methyl-azetidin-1-yl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-2-deuterio-quinoline-8-carbonitrile;

5-[(4*R*,10*bS*)-4-methyl-8-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-2-deuterio-quinoline-8-carbonitrile;

15 4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

20 4-[(4*R*,10*bS*)-8-[(3*R*)-3-aminopyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-4-methyl-8-[(3*R*)-3-methylpiperazin-1-yl]-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*S*,4*R*)-4-fluoropyrrolidin-3-yl]amino]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

25 4-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-3-amino-4-fluoro-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-(4-amino-4-methyl-1-piperidyl)-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

30 4-[(4*R*,10*bS*)-8-[(6*R*)-6-amino-1,4-oxazepan-4-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-4-methyl-8-(5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*)-3-amino-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

35 4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-amino-3-methoxy-1-piperidyl]-4-methyl-3,4,6,10*b*-tetrahydro-

1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-4-amino-3-methoxy-1-piperidyl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*,4*S*)-3-amino-4-methoxy-1-piperidyl]-4-methyl-3,4,6,10*b*-tetrahydro-

5 1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-4-methyl-8-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

10 4-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-hydroxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

15 4-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-3-amino-4-hydroxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

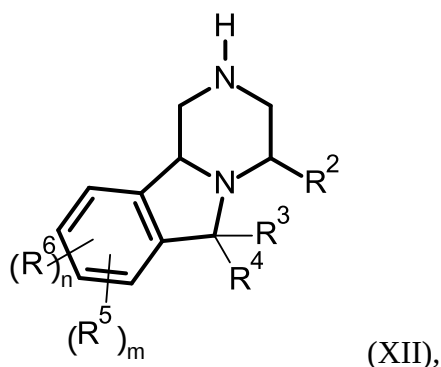
4-[(4*R*,10*bS*)-8-[(3*S*,4*S*)-4-amino-3-hydroxy-3-methyl-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile; and

20 4-[(4*R*,10*bS*)-8-[(3*R*,4*R*)-3-amino-4-methoxy-pyrrolidin-1-yl]-4-methyl-3,4,6,10*b*-tetrahydro-1*H*-pyrazino[2,1-*a*]isoindol-2-yl]-3-fluoro-pyrazolo[1,5-*a*]pyridine-7-carbonitrile;

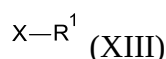
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

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

25 a) the substitution reaction of compound of formula (XII),

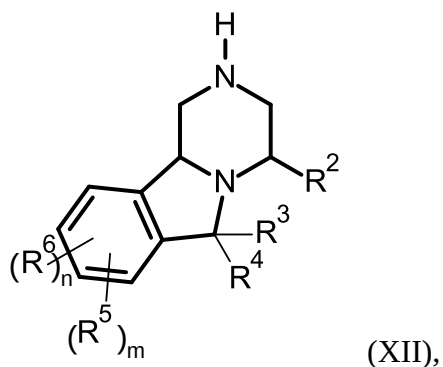


and halide of formula (XIII)

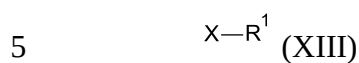


in the presence of a base;

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

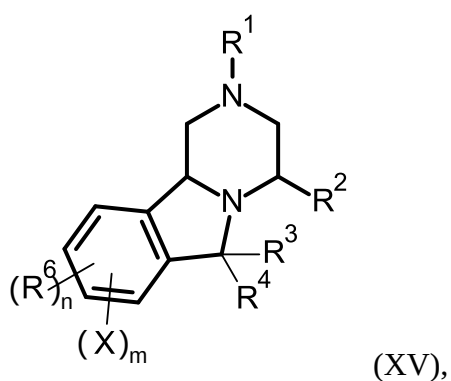


and halide of formula (XIII)



in the presence of a catalyst and a base;

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

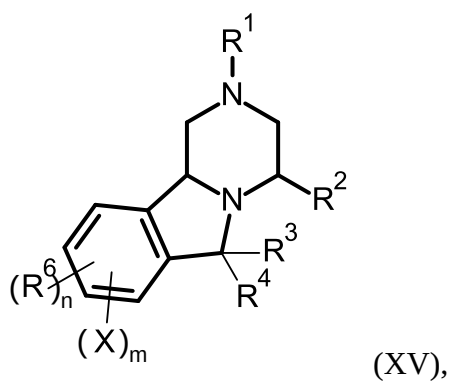


and halide of formula (XIII)



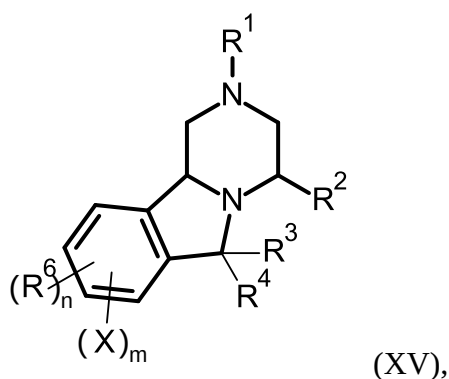
in the presence of a catalyst and a base;

- d) the Suzuki coupling reaction of compound of formula (XV),



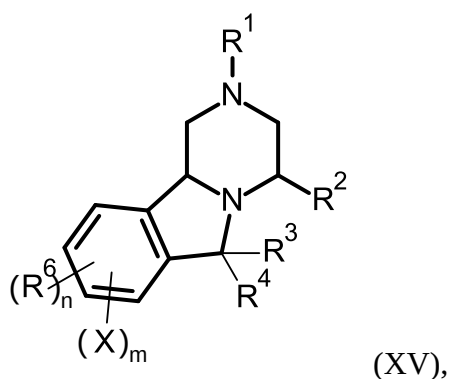
and boronic reagent in the presence of a catalyst and a base;

- 15 e) the Stille coupling reaction of compound of formula (XV),



and organotin reagent in the presence of a catalyst;

f) the Negishi coupling reaction of compound of formula (XV),



5 and organozinc reagent in the presence of a catalyst;

wherein the base in step a) is DIPEA; the catalyst in step b) and c) is Ruphos Pd-G2; the base in step b) and c) is Cs₂CO₃; the catalyst in step d) is tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II); the base in step d) is K₂CO₃; the catalyst in step e) is tetrakis(triphenylphosphine)palladium(0); the catalyst in step f) is tetrakis(triphenylphosphine)palladium(0) or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II); X is halogen; m is 0, 1, 2, or 3; n is 1, 2, 3 or 4; m+n≤4; R⁷ is Boc; R⁸ is benzyl; R⁹ is alkylsilyl; and R¹ to R⁶ are defined as in any one of claims 1 to 14.

15 17. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 15 for use as therapeutically active substance.

18. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 15 and a therapeutically inert carrier.

20

19. The use of a compound according to any one of claims 1 to 15 in the preparation of a medicament for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

20. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 15 for use in the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.
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