(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2019 (19.12.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/238629 A1

(51) International Patent Classification:
C07D 413/14 (2006.01) *A61P 37/00* (2006.01)
A61K 31/5355 (2006.01)

(21) International Application Number:
PCT/EP2019/065121

(22) International Filing Date:
11 June 2019 (11.06.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/CN2018/091078
13 June 2018 (13.06.2018) CN

(71) Applicant *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(71) Applicant *(for US only)*: **HOFFMANN-LA ROCHE INC.** [US/US]; Overlook at Great Notch, 150 Clove Road 8th Floor, Suite 8 - Legal Department, Little Falls, New Jersey 07424 (US).

(72) Inventors: **LIU, Haixia**; c/o Roche R&D Center (China) Ltd. Building No. 5, Lane 720, Cailun Road, Shanghai, 201203 (CN). **SHEN, Hong**; c/o Roche R&D Center (China) Ltd. Building No. 5, Lane 720, Cailun Road, Shanghai, 201203 (CN). **ZHU, Wei**; c/o Roche R&D Center (China) Ltd. Building No. 5, Lane 720, Cailun Road, Shanghai, 201203 (CN). **HU, Taishan**; c/o Roche R&D Center (China) Ltd. Building No. 5, Lane 720, Cailun Road, Shanghai, 201203 (CN). **ZHANG, Zhisen**; c/o Roche R&D Center (China) Ltd Building No. 5, Lane 720, Cailun Road, Shanghai, 201203 (CN). **ZHANG, Zhiwei**; c/o Roche R&D Center (China) Ltd Building No. 5, Lane 720, Cailun Road, Shanghai, 201203 (CN). **DEY, Fabian**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **WANG, Xiaoqing**; c/o Roche R&D Center (China) Ltd Building No. 5, Lane 720, Cailun Road, Shanghai, 201203 (CN).

(74) Agent: **BERNARD, Guillaume**; F. HOFFMANN-LA ROCHE AG, Grenzacherstrasse 124, 4070 Basel (CH).

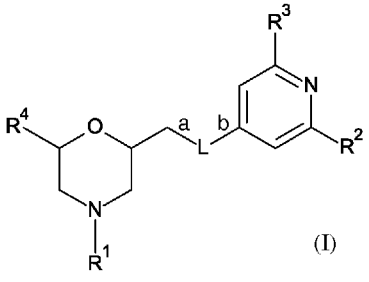
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** PYRIDINYL HETEROCYCLYL COMPOUNDS FOR THE TREATMENT OF AUTOIMMUNE DISEASE



(I)

(57) **Abstract:** The present invention relates to compounds of formula (I), a b (I), wherein R^1 to R^4 and L are as described herein, and their pharmaceutically acceptable salt, enantiomer or diastereomer thereof, and compositions including the compounds and methods of using the compounds.

WO 2019/238629 A1

PYRIDINYL HETEROCYCLYL COMPOUNDS FOR THE TREATMENT OF AUTOIMMUNE DISEASE

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, and in particular to antagonist of TLR7 and/or TLR8 and/or TLR9 useful for treating systemic lupus erythematosus or lupus nephritis.

FIELD OF THE INVENTION

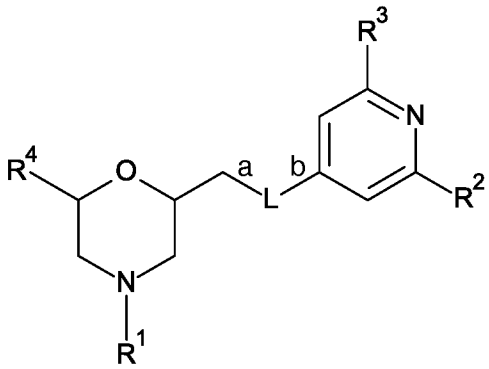
Autoimmune connective tissue disease (CTD) include prototypical autoimmune syndromes such as Systemic Lupus Erythematosus (SLE), primary Sjögren's syndrome (pSjS), mixed connective tissue disease (MCTD), Dermatomyositis/Polymyositis (DM/PM), Rheumatoid Arthritis (RA), and systemic sclerosis (SSc). With the exception of RA, no really effective and safe therapies are available to patients. SLE represents the prototypical CTD with a prevalence of 20-150 per 100,000 and causes broad inflammation and tissue damage in distinct organs, from commonly observed symptoms in the skin and joints to renal, lung, or heart failure. Traditionally, SLE has been treated with nonspecific anti-inflammatory or immunosuppressive drugs. However, long term usage of immunosuppressive drug, e.g. corticosteroids is only partially effective, and is associated with undesirable toxicity and side effects. Belimumab is the only FDA-approved drug for lupus in the last 50 years, despite its modest and delayed efficacy in only a fraction of SLE patients (Navarra, S. V. *et al Lancet* **2011**, *377*, 721.). Other biologics, such as anti-CD20 mAbs, mAbs against or soluble receptors of specific cytokines, have failed in most clinical studies. Thus, novel therapies are required that provide sustained improvement in a greater proportion of patient groups and are safer for chronic use in many autoimmune as well as auto-inflammation diseases.

Toll Like Receptors (TLR) are an important family of pattern recognition receptors (PRR) which can initiate broad immune responses in a wide variety of immune cells. As natural host defense sensors, endosomal TLRs 7, 8 and 9 recognize nucleic acids derived from viruses, bacteria; specifically, TLR7/8 and TLR9 recognize single-stranded RNA (ssRNA) and single-stranded CpG-DNA, respectively. However, aberrant nucleic acid sensing of TRL7,8,9 is considered as a key node in a broad of autoimmune and auto-inflammatory diseases (Krieg, A. M. *et al. Immunol. Rev.* **2007**, *220*, 251. Jiménez-Dalmaroni, M. J. *et al Autoimmun Rev.* **2016**, *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

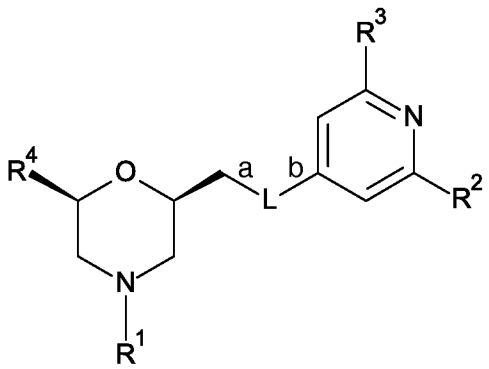
deliver both self-RNA and self-DNA to endosomes. While self-RNA complexes can be recognized by TLR7 and TLR8, self-DNA complexes can trigger TLR9 activation. Indeed, defective clearance of self-RNA and self-DNA from blood and/or tissues is evident in SLE (Systemic Lupus Erythematosus) patients. TLR7 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 OF THE INVENTION

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

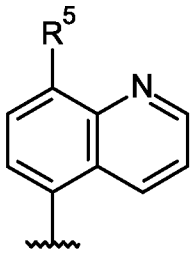
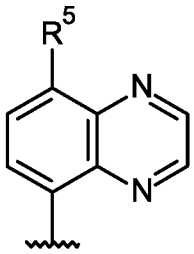
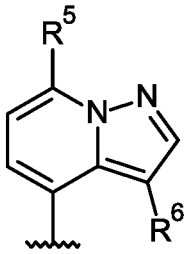
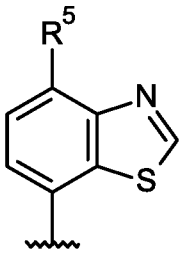


(I) or



(Ia),

wherein

R^1 is  ,  ,  or  ; wherein R^5 is cyano or halogen; R^6 is H or halogen;

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

R^3 is amino, C_{1-6}alkylamino, C_{1-6}alkyl, haloC_{1-6}alkyl, heterocyclyl, hydroxyC_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 is C_{1-6}alkyl;

L is 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl; 1,6-diazaspiro[3.3]heptanyl; 2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl;2,6-diazaspiro[3.3]heptanyl; 2,7-diazaspiro[3.4]octanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; (C_{1-6}alkyl)aminoazetidinyl; aminoazetidinyl; azetidinyl(C_{1-6}alkyl)amino; azetidinylamino; (phenylC_{1-6}alkyl)piperazinyl; (hydroxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)piperazinyl; piperazinyl; piperidinyl; (C_{1-6}alkyl)aminopiperidinyl; aminohalopiperidinyl; amino(hydroxy)piperidinyl; aminopiperidinyl; piperidinylamino; amino(hydroxy)pyrrolidinyl; aminopyrrolidinyl; or pyrrolidinylamino;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another object of the present invention 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, solubility, hPBMC, human microsome stability and SDPK profiles, as well as low CYP inhibition.

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.

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

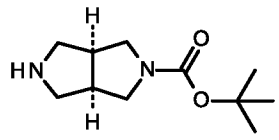
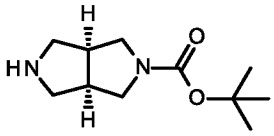
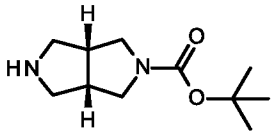
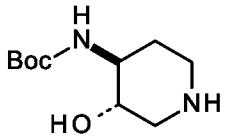
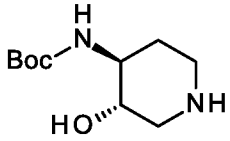
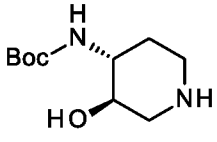
The term "haloC_{1-6}alkyl" denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloC_{1-6}alkyl include monofluoro-, difluoro-or trifluoro-methyl, -ethyl or -propyl, for example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

The term "C_{3-7}cycloalkyl" denotes a saturated monocyclic or bicyclic carbon ring containing from 3 to 7 carbon atoms, particularly from 3 to 6 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[1.1.1]pentanyl and the like. Particular "C_{3-7}cycloalkyl" group is cyclopropyl.

The term "heterocyclyl" denotes a monovalent saturated or partly unsaturated mono-, bicyclic or tricyclic ring system of 3 to 12 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. In particular embodiments, heterocyclyl is a monovalent saturated or partly unsaturated monocyclic or bicyclic ring system of 4 to 10 ring atoms, comprising 1, 2, or 3 ring heteroatoms selected from N, O and S, the remaining ring atoms being carbon. Examples for monocyclic saturated heterocyclyl are aziridinyl, oxiranyl, azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-thienyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholin-4-yl, azepanyl, diazepanyl, homopiperazinyl, or oxazepanyl. Bicyclic heterocyclyl can be spiro ring, fused ring or bridged ring. Examples for partly unsaturated heterocyclyl are dihydrofuryl, imidazolinyl, dihydro-oxazolyl, tetrahydro-pyridinyl, or dihydropyranyl. Monocyclic or bicyclic or tricyclic heterocyclyl can be further substituted once, twice or three times by hydroxyC_{1-6}alkyl, amino, aminoC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkyl, (C_{1-6}alkyl)$_2$amino, C_{3-7}cycloalkyl, C_{3-7}cycloalkylamino, haloC_{1-6}alkyl, halogen, hydroxy, hydroxyC_{1-6}alkyl or pyrrolidinyl.

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 properties, e.g. melting points, boiling points, spectral properties, and reactivities.

The term "*cis*-isomers" and "*trans*-isomers" denote the relative stereochemistry of the molecule or moiety. For example: compound 10b () as the "*cis*-isomers" refers to a mixture of  and  ; similarly, compound 26a () as the "*trans*-isomers" refers to a mixture of  and  . The way of showing relative stereochemistry also applies to the final compounds.

The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts.

The term "pharmaceutically acceptable acid addition salt" denotes those pharmaceutically acceptable salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid, and organic acids selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, and salicyclic acid.

The term "pharmaceutically acceptable base addition salt" denotes those pharmaceutically acceptable salts formed with an organic or inorganic base. Examples of acceptable inorganic bases include sodium, potassium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines

including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, *N*-ethylpiperidine, and polyamine resins.

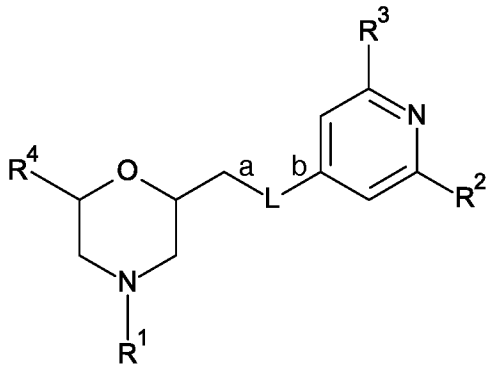
The term "A pharmaceutically active metabolite" denotes a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. After entry into the body, most drugs are substrates for chemical reactions that may change their physical properties and biologic effects. These metabolic conversions, which usually affect the polarity of the compounds of the invention, alter the way in which drugs are distributed in and excreted from the body. However, in some cases, metabolism of a drug is required for therapeutic effect.

The term "therapeutically effective amount" denotes an amount of a compound or molecule of the present invention that, when administered to a subject, (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. The therapeutically effective amount will vary depending on the compound, the disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgement of the attending medical or veterinary practitioner, and other factors.

The term "pharmaceutical composition" denotes a mixture or solution comprising a therapeutically effective amount of an active pharmaceutical ingredient together with pharmaceutically acceptable excipients to be administered to a mammal, e.g., a human in need thereof.

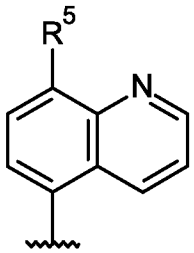
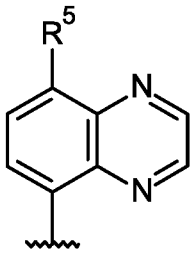
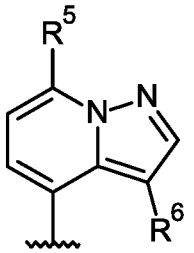
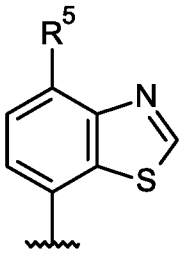
ANTAGONIST OF TLR7 AND/OR TLR8 AND/OR TLR9

The present invention relates to a compound of formula (I),



(I),

wherein

R^1 is  ,  ,  or  ; wherein R^5 is cyano or halogen; R^6 is H or halogen;

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

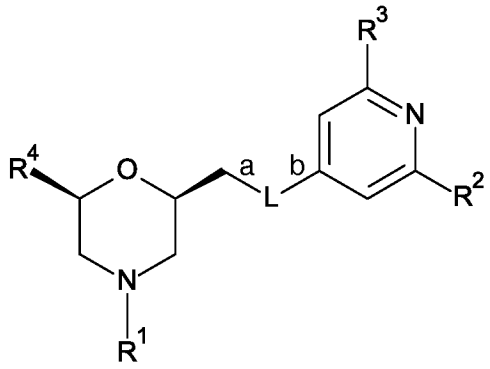
R^3 is amino, C_{1-6}alkylamino, C_{1-6}alkyl, haloC_{1-6}alkyl, heterocyclyl, hydroxyC_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 is C_{1-6}alkyl;

L is 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl; 1,6-diazaspiro[3.3]heptanyl; 2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl;2,6-diazaspiro[3.3]heptanyl; 2,7-diazaspiro[3.4]octanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; (C_{1-6}alkyl)aminoazetidinyl; aminoazetidinyl; azetidinyl(C_{1-6}alkyl)amino; azetidinylamino; (phenylC_{1-6}alkyl)piperazinyl; (hydroxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)piperazinyl; piperazinyl; piperidinyl; (C_{1-6}alkyl)aminopiperidinyl; aminohalopiperidinyl; amino(hydroxy)piperidinyl; aminopiperidinyl; piperidinylamino; amino(hydroxy)pyrrolidinyl; aminopyrrolidinyl; or pyrrolidinylamino;

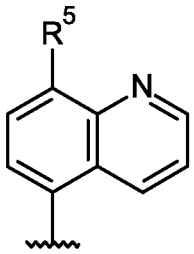
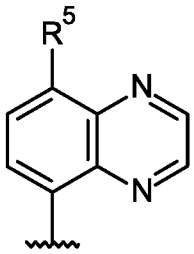
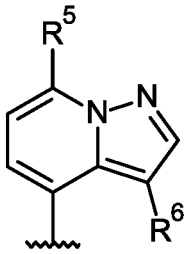
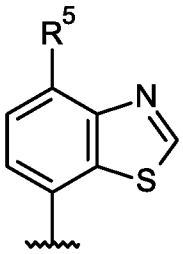
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

A another embodiment of present invention is (ii) a compound of formula (Ia),



(Ia),

wherein

R^1 is  ,  ,  or  ; wherein R^5 is cyano or halogen; R^6 is H or halogen;

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

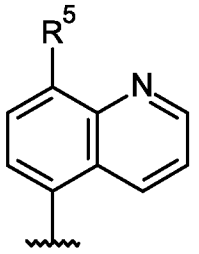
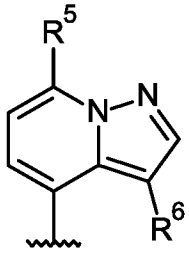
R^3 is amino, C_{1-6}alkylamino, C_{1-6}alkyl, haloC_{1-6}alkyl, heterocyclyl, hydroxyC_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 is C_{1-6}alkyl;

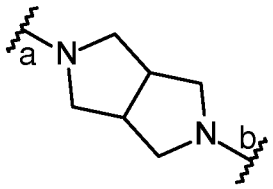
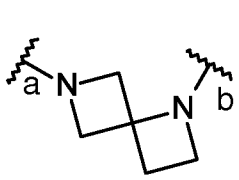
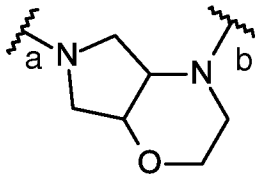
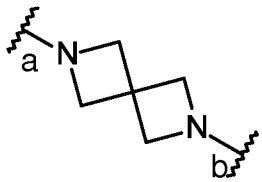
L is 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl; 1,6-diazaspiro[3.3]heptanyl; 2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl;2,6-diazaspiro[3.3]heptanyl; 2,7-diazaspiro[3.4]octanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; (C_{1-6}alkyl)aminoazetidinyl; aminoazetidinyl; azetidinyl(C_{1-6}alkyl)amino; azetidinylamino; (phenylC_{1-6}alkyl)piperazinyl; (hydroxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)piperazinyl; piperazinyl; piperidinyl; (C_{1-6}alkyl)aminopiperidinyl; aminohalopiperidinyl; amino(hydroxy)piperidinyl; aminopiperidinyl; piperidinylamino; amino(hydroxy)pyrrolidinyl; aminopyrrolidinyl; or pyrrolidinylamino;

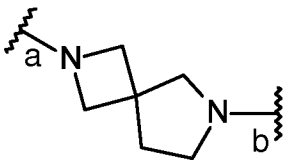
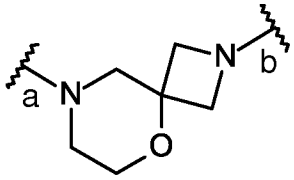
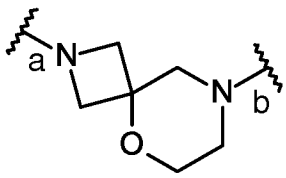
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

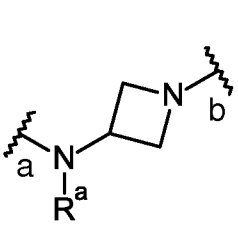
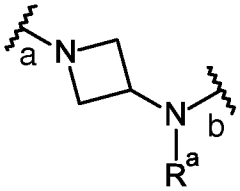
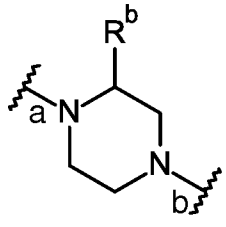
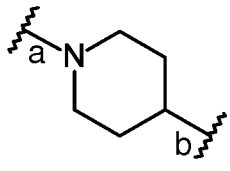
A further embodiment of present invention is (iii) a compound of formula (I) or (Ia) according to (i) or (ii), wherein

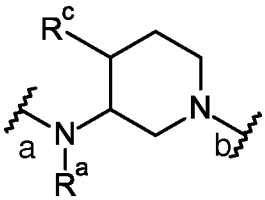
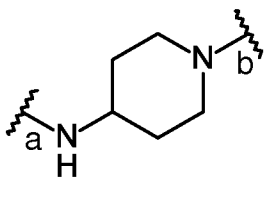
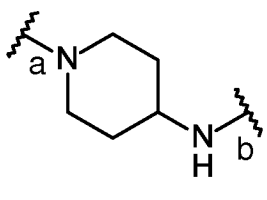
R^1 is  or  ; wherein R^5 is cyano, R^6 is H.

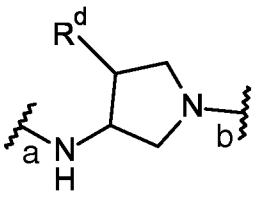
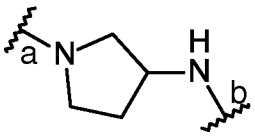
A further embodiment of present invention is (iv) a compound of formula (I) or (Ia) according to (iii), wherein L is

 ,  ,  ,  ,

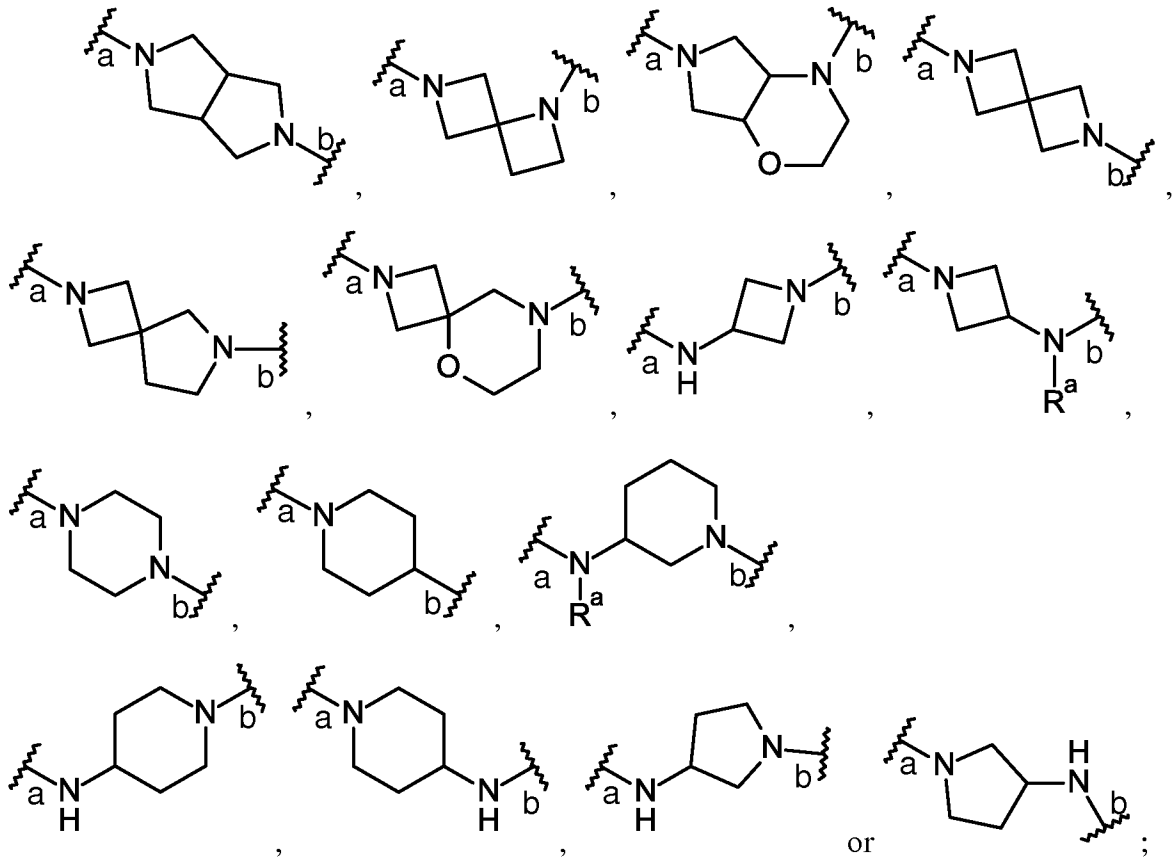
 ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

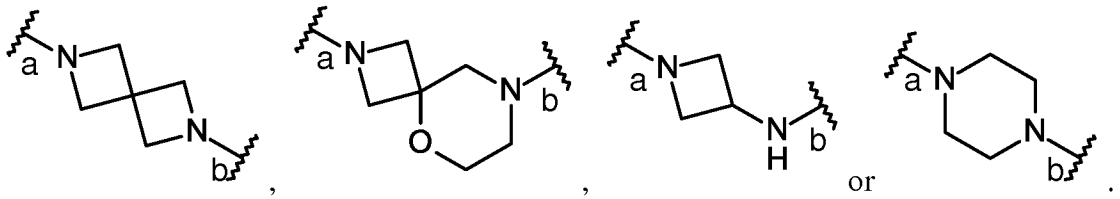
 , or  ; wherein R^a is H or $C_{1\text{-}6}$alkyl; R^b is H, phenyl$C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkyl or $C_{1\text{-}6}$alkyl; R^c is H, halogen or hydroxy; R^d is H or hydroxy.

A further embodiment of present invention is (v) a compound of formula (I) or (Ia) according to (iv), wherein L is



wherein R^a is H or C_{1-6}alkyl.

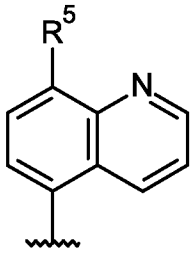
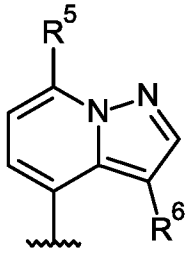
A further embodiment of present invention is (vi) a compound of formula (I) or (Ia) according to (iv), wherein L is



A further embodiment of present invention is (vii) a compound of formula (I) or (Ia) according to (vi), wherein R^3 is amino, C_{1-6}alkylamino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{3-7}cycloalkyl.

A further embodiment of present invention is (viii) a compound of formula (I) or (Ia) according to (vii), wherein R^3 is amino, cyclopropyl, hydroxyethyl, hydroxymethyl, methyl or methylamino.

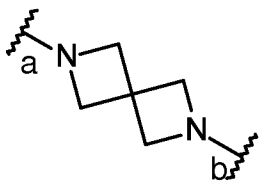
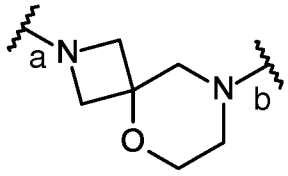
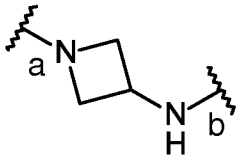
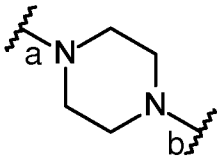
A further embodiment of present invention is (ix) a compound of formula (I) or (Ia) according to (i) or (ii), wherein

R^1 is  or  ; wherein R^5 is cyano; R^6 is H;

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

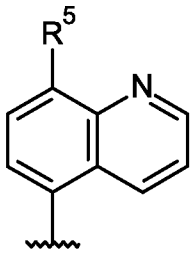
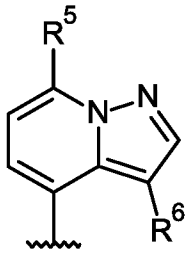
R^3 is $C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkyl or $C_{3\text{-}7}$cycloalkyl;

R^4 is $C_{1\text{-}6}$alkyl;

L is  ,  ,  or  ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

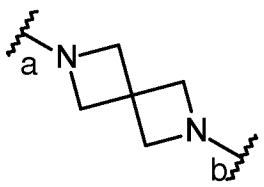
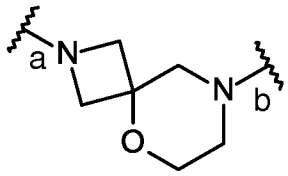
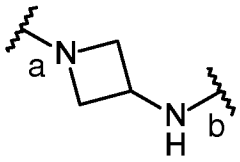
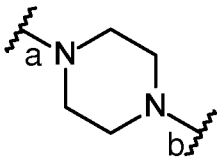
A further embodiment of present invention is (x) a compound of formula (I) or (Ia) according to (ix), wherein

R^1 is  or  ; wherein R^5 is cyano; R^6 is H;

R^2 is H or methyl;

R^3 is methyl, hydroxymethyl or cyclopropyl;

R^4 is methyl;

L is  ,  ,  or  ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of present invention is that (xi) a compound of formula (I) or (Ia) selected from the following:

5-[(2*S*,6*R*)-2-[[2-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[8-(2-cyclopropyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile ;

5-[(2*S*,6*R*)-2-[[4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[(2*S*)-4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[(2*R*)-4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]-1-piperidyl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[3-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]pyrrolidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[3-[(2,6-dimethyl-4-pyridyl)amino]azetidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[1-(2,6-dimethyl-4-pyridyl)-1,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[7-(2,6-dimethyl-4-pyridyl)-2,7-diazaspiro[3.4]octan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

cis-5-[(2*S*,6*R*)-2-[[5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[3-[(2,6-dimethyl-4-pyridyl)-methyl-amino]azetidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-1,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-(2,6-dimethyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-8-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[8-(2,6-dimethyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*R*,6*S*)-2-methyl-6-[[1-(2-methyl-4-pyridyl)-1,6-diazaspiro[3.3]heptan-6-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*R*,6*S*)-2-methyl-6-[[8-(2-methyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

cis-5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-(2-amino-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[1-(2-amino-4-pyridyl)-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3R)-1-(2-amino-4-pyridyl)-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-(2-amino-4-pyridyl)-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[3-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[4-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]azetidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[4-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[1-(2,6-dimethyl-4-pyridyl)-4-hydroxy-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

cis-5-[(2*S*,6*R*)-2-[[[4-fluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[4-fluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[5,5-difluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]azetidin-3-yl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

4-[(2*S*,6*R*)-2-[[2-benzyl-4-(2,6-dimethyl-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]pyrazolo[1,5-a]pyridine-7-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-(2-amino-6-methyl-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[(2*R*)-4-(2-amino-6-methyl-4-pyridyl)-2-(hydroxymethyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*R*,6*S*)-2-methyl-6-[[4-[2-methyl-6-(methylamino)-4-pyridyl]piperazin-1-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-(2-amino-6-methyl-4-pyridyl)-1-piperidyl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-[2-(1-hydroxyethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-[2-amino-6-(hydroxymethyl)-4-pyridyl]piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-[2-(1-hydroxyethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-[2-(difluoromethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-[2-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-(2-cyclopropyl-4-pyridyl)-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile; and

5-[(2*S*,6*R*)-2-[[8-[2-(hydroxymethyl)-4-pyridyl]-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

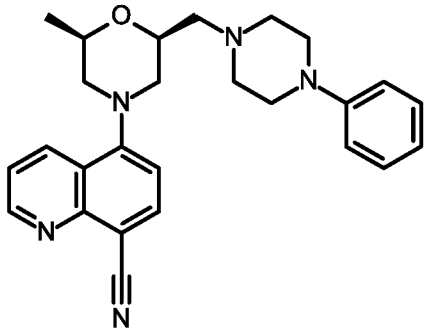
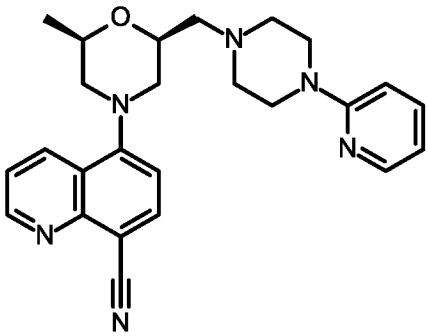
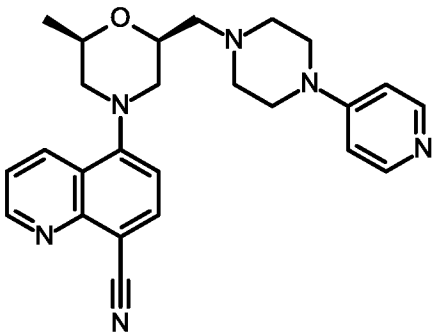
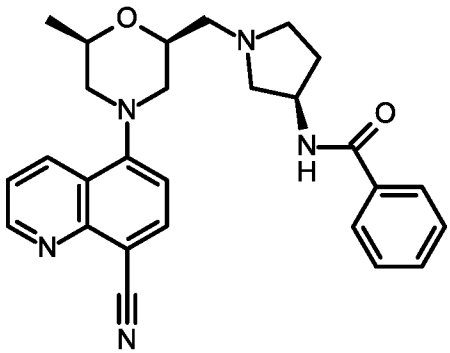
A number of compounds used as reference herein were disclosed in patent US20150105370 showing TLR7 and TLR9 potency data summarized in table 1. Compounds in Table 1 are all characterized with an aromatic ring at the terminal position (phenyl or pyridinyl), however, according to the potency data disclosed, only some of the compounds in Table 1 showed good TLR7 potency, and all of which were lack of TLR9 potency. More examples disclosed in US20150105370 with same structural characteristics confirmed such trend, which suggests the terminal aryl/heteroaryl ring is not favorable for TLR9 activity.

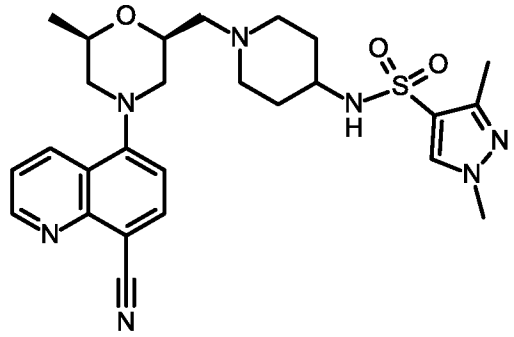
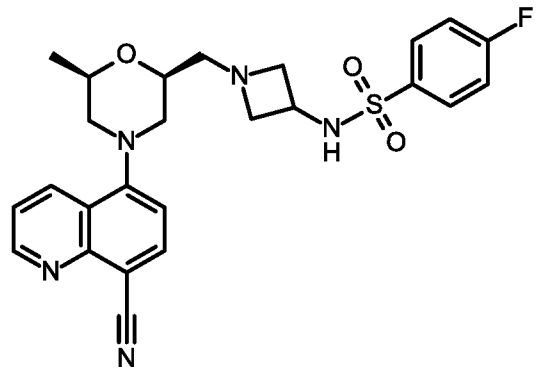
Meanwhile, more analogues of the compounds disclosed in US20150105370, such as compound R1, compound R2 which bear some substituents on the terminal aryl ring, were synthesized to confirm the SAR (structure-activity-relationship). But according to the potency data shown in Table 2, the substituents on the terminal aryl ring may not necessarily improve the potency of TLR9. Therefore, the skill of the art shall not obtain any incitation from the information disclosed in US20150105370 to further optimize such chemical structures.

Surprisingly, the compounds of this invention significantly improved TLR9 potency (>10 folds compared to ER-888286) while keeping excellent TLR7 and TLR8 potency. In another embodiment, the human microsome stability of the compounds of this invention was improved as compared to the reference compounds R1, R2, ER-887258 and ER-888285 (see Table 6). The compounds of formula (I) or (Ia) also showed good hPBMC, cytotoxicity, solubility and SDPK profiles, as well as low CYP inhibition.

Table 1. TLR7 and TLR9 potency of compounds disclosed in US20150105370

Compound	Structure	HEK/hTLR7 IC50 (μM)	HEK/hTLR9 IC50 (μM)

ER-887258		0.0852	>2.0
ER-888285		0.120	>2.0
ER-888286		1.370	>2.0
ER-894544		0.043	>6.2

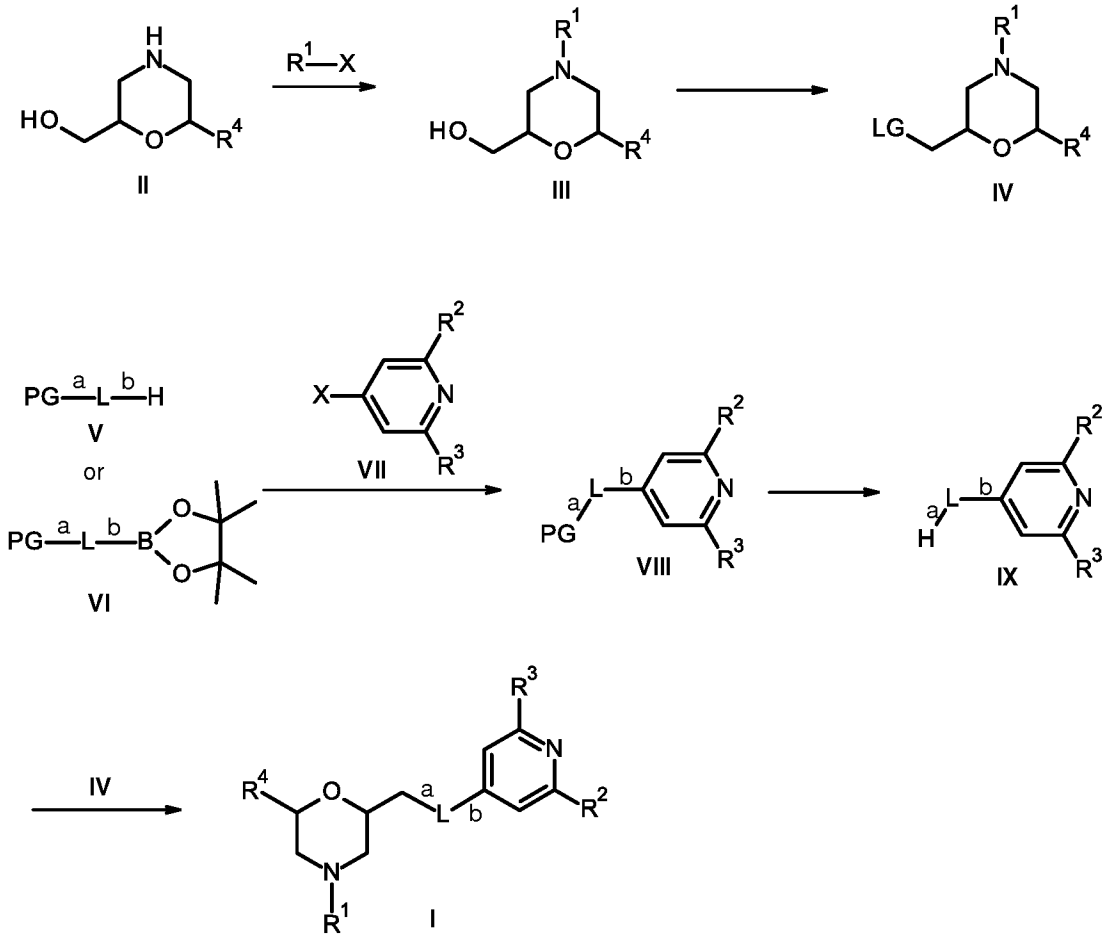
ER-894160		0.1990	>10.0
ER-894155		0.2820	>10.0

SYNTHESIS

The compounds of the present invention can be prepared by any conventional means. Suitable processes for synthesizing these compounds as well as their starting materials are provided in the schemes below and in the examples. All substituents, in particular, R^1 to R^4 are as defined above unless otherwise indicated. Furthermore, and unless explicitly otherwise stated, all reactions, reaction conditions, abbreviations and symbols have the meanings well known to a person of ordinary skill in organic chemistry.

General synthetic routes for preparing the compound of formula (I) are shown below.

Scheme 1



Wherein X is halogen; LG is a leaving group, such as OTf, OTs and OMs; PG is a protecting group, such as Boc and Cbz.

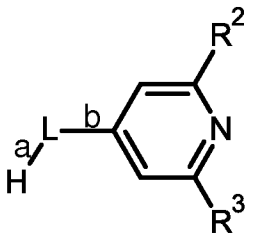
The coupling of compound of formula (II) with R^1-X can be achieved by direct coupling in the presence of a base, such as DIPEA or K_2CO_3, or under Buchwald-Hartwig amination conditions (ref: *Acc. Chem. Res.* 1998, *31*, 805-818; *Chem. Rev.* 2016, *116*, 12564-12649; *Topics in Current Chemistry*, 2002, *219*, 131-209; and references cited therein) with a catalyst, such as RuPhos Pd G2, and a base, such as Cs_2CO_3, to provide compound of formula (III). Subsequently the hydroxy group of compound of formula (III) is converted to a leaving group, such as OTf, OTs, or OMs, under basic condition, such as DIPEA, TEA, K_2CO_3 or 2,6-dimethylpyridine, with Tf_2O, TsCl or MsCl. The coupling of compound of formula (V) with compound of formula (VII) can be achieved by direct coupling under high temperature, or under Buchwald-Hartwig amination conditions with a catalyst, such as RuPhos Pd G2, BrettPhos Pd G3, $Pd_2(dba)_3$/BINAP or $Pd_2(dba)_3$/XantPhos and a base, such as Cs_2CO_3 or *t*-BuONa, to provide compound of formula (VIII). The coupling of compound of formula (VI) with compound of formula (VII) can be achieved by Suzuki coupling reaction with a catalyst, such as $PdCl_2$(dppf) or $PdCl_2$(dtbpf) and a base, such as K_2CO_3 or Na_2CO_3, followed by hydrogenation reaction with a catalyst, such as Pd-

C to provide compound of formula (VIII). The protecting group of compound of formula (VIII) can be removed under high temperature or acidic condition, such as TFA, or hydrogenation condition with a catalyst, such as Pd-C. Compound of formula (IX) was further coupled with compound of formula (IV) in the presence of base, such as K_2CO_3, DIPEA, or Cs_2CO_3, to afford compound of formula (I). In some embodiment, the coupling of compound of formula (IX) and (IV) may give a product containing a protecting group, e.g. Boc, originated from compound of formula (IX), which will be removed before affording the final compound of formula (I). Compounds of formula (Ia) can be synthesized using the chiral compound of formula (II) correspondingly.

Compounds of this invention can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art, e.g. (chiral) HPLC or SFC.

This invention also relates to a process for the preparation of a compound of formula (I) or (Ia) comprising any of the following step:

a) the coupling of compound of formula (IX),



(IX),

with compound of formula (IV) in the presence of a base;

wherein the base can be for example K_2CO_3, DIPEA, or Cs_2CO_3.

A compound of formula (I) or (Ia) when manufactured according to the above process is also an object of the invention.

INDICATIONS AND METHODS OF TREATMENT

The present invention provides compounds that can be used as TLR7 and/or TLR8 and/or TLR9 antagonist, which inhibits pathway activation through TLR7 and/or TLR8 and/or TLR9 as well as respective downstream biological events including, but not limited to, innate and adaptive immune responses mediated through the production of all types of cytokines and all forms of auto-antibodies. Accordingly, the compounds of the invention are useful for blocking TLR7 and/or TLR8 and/or TLR9 in all types of cells that express such receptor(s) including, but not limited to, plasmacytoid dendritic cell, B cell, T cell, macrophage, monocyte, neutrophil, keratinocyte, epithelial cell. As such, the compounds can be used as a therapeutic or prophylactic agent for systemic lupus erythematosus and lupus nephritis.

The present invention provides methods for treatment or prophylaxis of systemic lupus erythematosus and lupus nephritis in a patient in need thereof.

Another embodiment includes a method of treating or preventing systemic lupus erythematosus and lupus nephritis in a mammal in need of such treatment, wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

ABBREVIATIONS

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

Abbreviations used herein are as follows:

ACN: acetonitrile

BINAP: (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)

Boc_2O: di-*tert* butyl dicarbonate

BrettPhos Pd G3: [(2-di-cyclohexylphosphino-3,6-dimethoxy-2′,4′,6′- triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate

t-Bu XPhosPd G3: [(2-di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate

CbzCl: benzylchloroformate

cataCXium A Pd G2: chloro[(di(1-adamantyl)-*N*-butylphosphine)-2-(2-aminobiphenyl)]palladium(II)

DAST: diethylaminosulfur trifluoride

DCM: dichloromethane

DIAD: diisopropyl azodicarboxylate

DIPEA: *N,N*-diisopropylethylamine

DMA: dimethylacetamide

DMEDA: 1,2-dimethylethylenediamine

EtOAc or EA: ethyl acetate

FA: formic acid

HLM human liver microsome

IC_{50}: half inhibition concentration

IPA:	isopropanol
LCMS	liquid chromatography-mass spectrometry
MS:	mass spectrometry
NMP:	*N*-methylpyrrolidin-2-one
$PdCl_2$(dtbpf)	1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride
$Pd_2(dba)_3$:	tris(dibenzylideneacetone)dipalladium(0)
$PdCl_2$(dppf):	1,1′-bis(diphenylphosphino)ferrocene palladium dichloride
PE:	petroleum ether
prep-HPLC:	preparative high performance liquid chromatography
prep-TLC:	preparative thin layer chromatography
PPh_3:	triphenylphosphine
Rf:	retention factor
rt:	room temperature
RuPhos Pd G2:	chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) 2nd generation
SelectFluor:	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SFC:	supercritical fluid chromatography
TEA:	triethylamine
TFA:	trifluoroacetic acid
Tf_2O:	trifluoromethanesulfonic anhydride
THF:	tetrahydrofuran
v/v:	volume ratio
XantPhos:	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos:	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
XPhos Pd G2:	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

GENERAL EXPERIMENTAL CONDITIONS

Intermediates and final compounds were purified by flash chromatography using one of the following instruments: i) Biotage SP1 system and the Quad 12/25 Cartridge module. ii) ISCO combi-flash chromatography instrument. Silica gel brand and pore size: i) KP-SIL 60 Å, particle

size: 40-60 μm; ii) CAS registry NO: Silica Gel: 63231-67-4, particle size: 47-60 micron silica gel; iii) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore: 200-300 or 300-400.

Intermediates and final compounds were purified by preparative HPLC on reversed phase column using XBridge™ Prep-C18 (5 μm, OBDTM 30 × 100 mm) column, SunFire™ Prep-C18 (5 μm, OBD™ 30 × 100 mm) column, Phenomenex Synergi-C18 (10 μm, 25 × 150 mm) or Phenomenex Gemini-C18 (10 μm, 25 × 150 mm). Waters AutoP purification System (Sample Manager 2767, Pump 2525, Detector: Micromass ZQ and UV 2487, solvent system: acetonitrile and 0.1% ammonium hydroxide in water; acetonitrile and 0.1% FA in water or acetonitrile and 0.1% TFA in water). Or Gilson-281 purification System (Pump 322, Detector: UV 156, solvent system: acetonitrile and 0.05% ammonium hydroxide in water; acetonitrile and 0.225% FA in water; acetonitrile and 0.05% HCl in water; acetonitrile and 0.075% TFA in water; or acetonitrile and water).

For SFC chiral separation, intermediates were separated by chiral column (Daicel chiralpak IC, 5 μm, 30 × 250 mm), AS (10 μm, 30 × 250 mm) or AD (10 μm, 30 × 250 mm) using Mettler Toledo Multigram III system SFC, Waters 80Q preparative SFC or Thar 80 preparative SFC, solvent system: CO_2 and IPA (0.5% TEA in IPA) or CO_2 and MeOH (0.1% $NH_3 \cdot H_2O$ in MeOH), back pressure 100bar, detection UV@ 254 or 220 nm.

LC/MS spectra of compounds were obtained using a LC/MS (Waters™ Alliance 2795-Micromass ZQ, Shimadzu Alliance 2020-Micromass ZQ or Agilent Alliance 6110-Micromass ZQ), LC/MS conditions were as follows (running time 3 or 1.5 mins):

Acidic condition I: A: 0.1% TFA in H_2O; B: 0.1% TFA in acetonitrile;

Acidic condition II: A: 0.0375% TFA in H_2O; B: 0.01875% TFA in acetonitrile;

Basic condition I: A: 0.1% $NH_3 \cdot H_2O$ in H_2O; B: acetonitrile;

Basic condition II: A: 0.025% $NH_3 \cdot H_2O$ in H_2O; B: acetonitrile;

Neutral condition: A: H_2O; B: acetonitrile.

Mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion $(MH)^+$.

NMR Spectra were obtained using Bruker Avance 400 MHz.

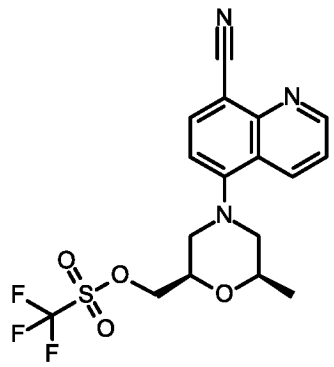
The microwave assisted reactions were carried out in a Biotage Initiator Sixty microwave synthesizer. All reactions involving air-sensitive reagents were performed under an argon or nitrogen atmosphere. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

PREPARATIVE EXAMPLES

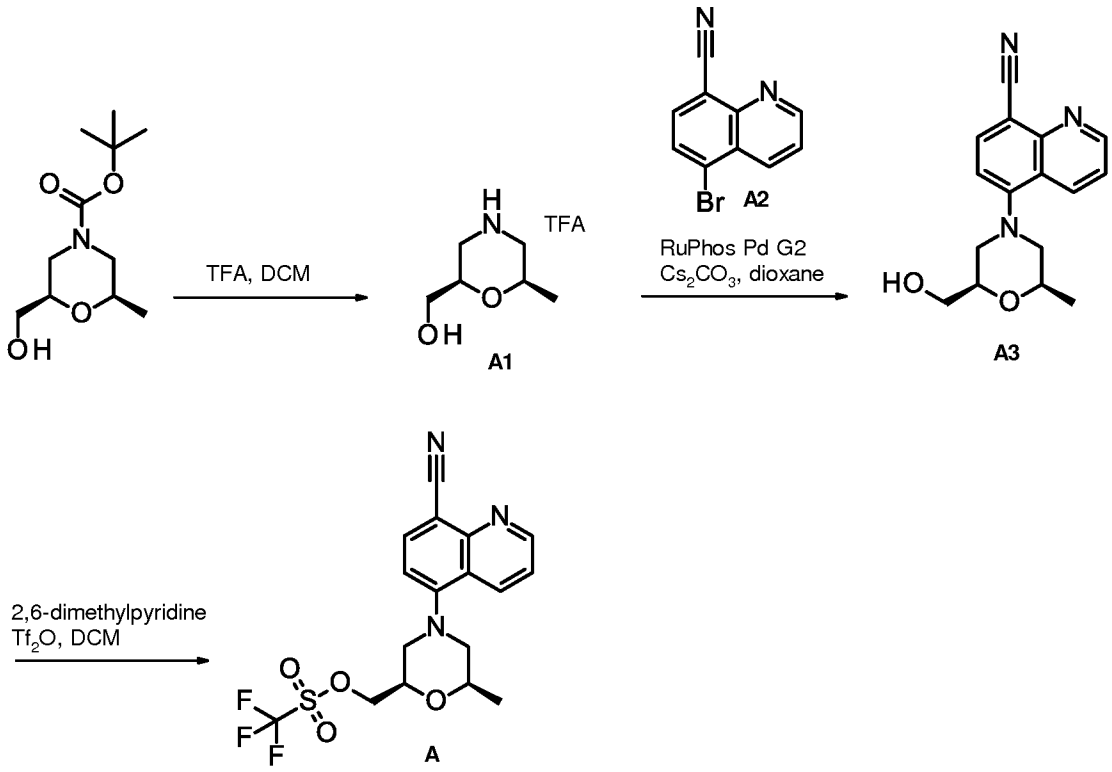
The following examples are intended to illustrate the meaning of the present invention but should by no means represent a limitation within the meaning of the present invention:

Intermediate A

[(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate



The title compound was prepared according to the following scheme:



Step 1: preparation of [(2*R*,6*R*)-6-methylmorpholin-2-yl]methanol;2,2,2-trifluoroacetic acid (compound A1)

To a solution of *tert*-butyl (2*R*,6*R*)-2-(hydroxymethyl)-6-methylmorpholine-4-carboxylate (CAS: 1700609-48-8, Vendor: WuXi Apptec, 1.35 g, 5.84 mmol) in DCM (10 mL) was added 2,2,2-trifluoroacetic acid (2.66 g, 23.30 mmol). The reaction mixture was stirred at rt for 3 hrs.

Then the reaction mixture was concentrated *in vacuo* to give the crude product compound **A1** (1.43 g) which was used in next step directly. MS: calc'd 132 (MH^+), measured 132 (MH^+).

Step 2: preparation of 5-[(2*R*,6*R*)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (compound A3)

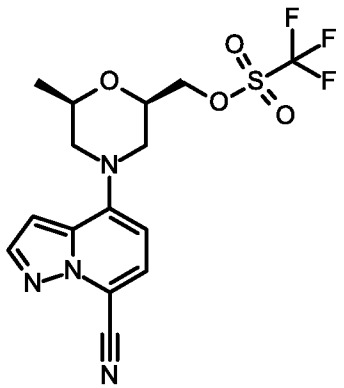
A mixture of 5-bromoquinoline-8-carbonitrile (compound **A2**, CAS: 507476-70-2, Vendor: BePharm, 1.50 g, 6.42 mmol), [(2*R*,6*R*)-6-methylmorpholin-2-yl]methanol;2,2,2-trifluoroacetic acid (compound **A1**, 1.43 g, 5.83 mmol), RuPhos Pd G2 (136 mg, 175 μmol) and Cs_2CO_3 (5.70 g, 17.50 mmol) in 1,4-dioxane (10 mL) was heated to 90 °C overnight under N_2. After being cooled down, the solid was filtered off and washed with EA (10 mL) twice. The combined organics was concentrated, the residue was purified by flash column eluting with a gradient of EA/PE (0 to 100%) to afford compound **A3** (0.71 g) as a light yellow solid. MS: calc'd 284 (MH^+), measured 284 (MH^+).

Step 3: preparation of [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate A)

To a flask was added 5-[(2*R*,6*R*)-2-(hydroxymethyl)-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (compound **A3**, 0.71 g, 2.50 mmol), DCM (10 mL) and 2,6-dimethylpyridine (0.54 g, 577 μL, 5.00 mmol). Then the reaction mixture was cooled with ice bath and trifluoromethanesulfonic anhydride (1.06 g, 634 μL, 3.75 mmol) was added dropwise. After being stirred for 2 hrs, the mixture was concentrated and purified by flash column (EA/PE=0 to 40%) to give product **Intermediate A** (0.72 g) as a yellow solid. MS: calc'd 416 (MH^+), measured 416 (MH^+).

Intermediate B

[(2*R*,6*R*)-4-(7-cyanopyrazolo[1,5-a]pyridin-4-yl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate

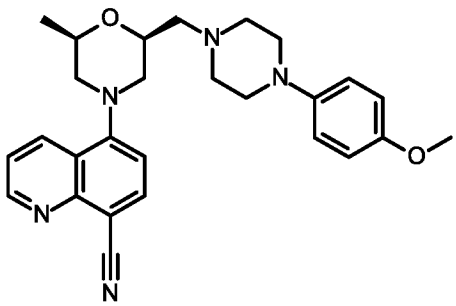


The title compound was prepared in analogy to the preparation of **Intermediate A** by using 4-chloropyrazolo[1,5-a]pyridine-7-carbonitrile (CAS: 1268520-74-6, Vendor:

PharmaBlock) instead of 5-bromoquinoline-8-carbonitrile (compound **A2**). **Intermediate B** (116 mg) was obtained as a white solid. MS: calc'd 405 (MH^+), measured 405 (MH^+).

Reference Compound R1

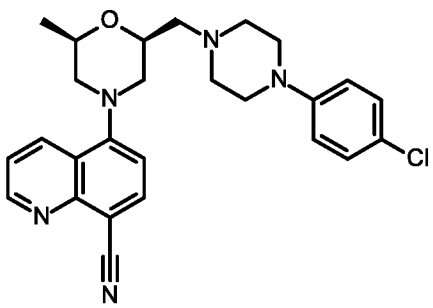
5-[(2*S*,6*R*)-2-[[4-(4-methoxyphenyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the **step 3** in preparation of **Example 1** by using 1-(4-cholophenyl)piperazine (CAS: 38212-33-8, Vendor: BePharm) instead of [4-(2,6-diazaspiro[3.3]heptan-2-yl)-6-methyl-2-pyridyl]methanol;2,2,2-trifluoroacetic acid (compound **1d**). Compound **R1** (22 mg) was obtained as a yellow solid. MS: calc'd 458 (MH^+), measured 458 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.7, 4.2 Hz, 1H), 8.67 (dd, *J*=1.7, 8.6 Hz, 1H), 8.18 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.30 (d, *J*=7.9 Hz, 1H), 7.05 - 6.98 (m, 2H), 6.93 - 6.85 (m, 2H), 4.55 - 4.46 (m, 1H), 4.26 - 4.16 (m, 1H), 3.89 - 3.56 (m, 7H), 3.50 - 3.37 (m, 6H), 3.25 - 3.00 (m, 2H), 2.84 - 2.71 (m, 2H), 1.33 (d, *J*=6.2 Hz, 3H).

Reference Compound R2

5-[(2*S*,6*R*)-2-[[4-(4-chlorophenyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

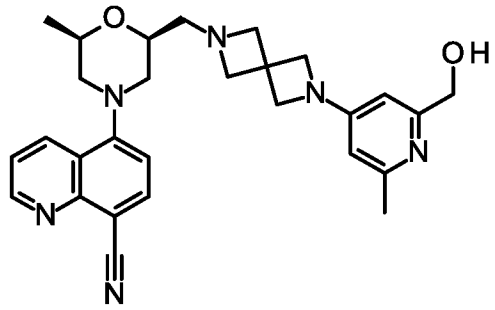


The title compound was prepared in analogy to the preparation of compound **R1** by using 1-(4-cholophenyl)piperazine (CAS: 38212-33-8, Vendor: BePharm) instead of 1-(4-methoxyphenyl)piperazine. Compound **R2** (24 mg) was obtained as a yellow solid. MS: calc'd 462 (MH^+), measured 462 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.6, 4.3 Hz, 1H), 8.67 (dd, *J*=1.7, 8.6 Hz, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.34

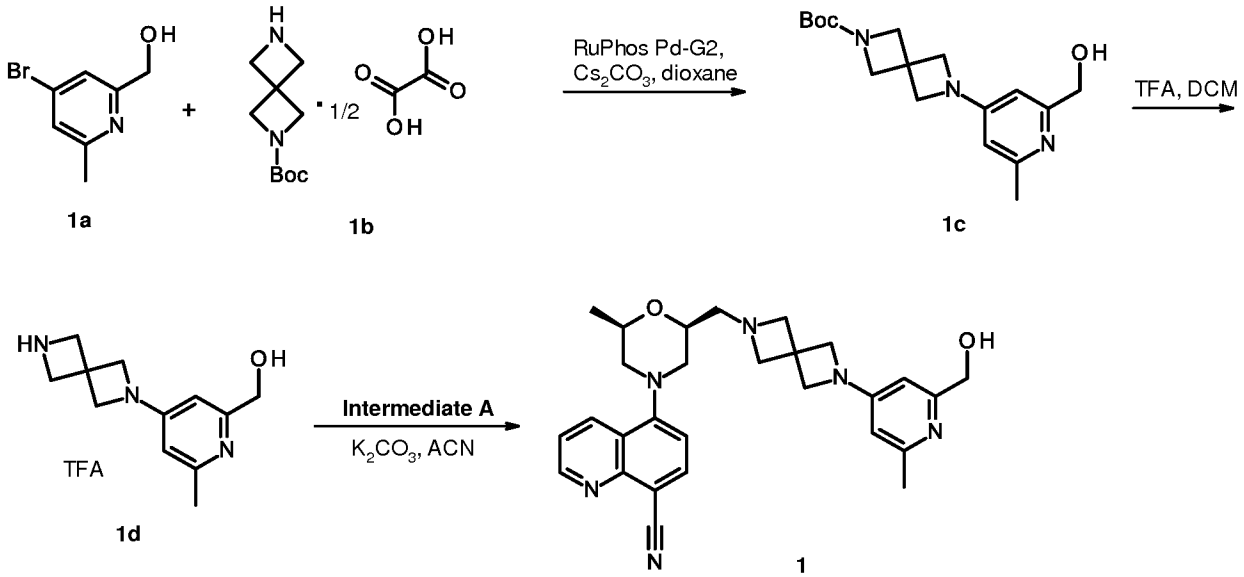
- 7.26 (m, 3H), 7.07 - 6.98 (m, 2H), 4.55 - 4.47 (m, 1H), 4.25 - 4.15 (m, 1H), 3.99 - 3.55 (m, 3H), 3.55 - 3.32 (m, 7H), 3.28 - 3.04 (m, 2H), 2.85 - 2.71 (m, 2H), 1.33 (d, *J*=6.2 Hz, 3H).

Example 1

5-[(2*S*,6*R*)-2-[[2-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 6-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (compound 1c)

To a flask was added (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**, CAS: 448906-60-3, Vendor: BePharm, 150 mg, 742 μmol), *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**, CAS: 1041026-70-3, Vendor: BePharm, 235 mg, 968 μmol), Cs_2CO_3 (726 mg, 2.23 mmol) and 1,4-dioxane (5 mL), the suspension was bubbled with N_2 for 5 mins and Ruphos Pd G2 (29 mg, 37 μmol) was added. The mixture was heated to 120 °C under microwave for 3 hrs. After being cooled down, the mixture was diluted with 10 mL EA and filtered through celite, the filtrate was concentrated and purified by flash column

(MeOH/DCM=0 to 10%) to give compound **1c** (72 mg) as a yellow oil. MS: calc'd 320 (MH^+), measured 320 (MH^+).

Step 2: preparation of [4-(2,6-diazaspiro[3.3]heptan-2-yl)-6-methyl-2-pyridyl]methanol;2,2,2-trifluoroacetic acid (compound 1d)

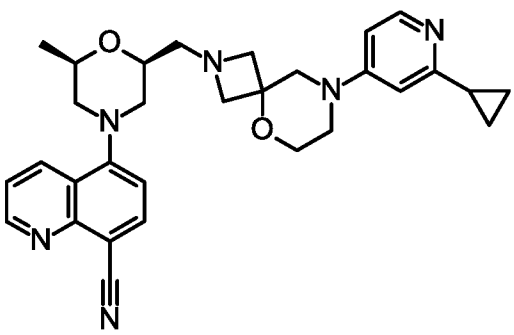
To a solution of *tert*-butyl 6-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (compound **1c**, 72 mg, 225 μmol) in DCM (5 mL) was added TFA (1 mL). After being stirred at rt for 3 hrs, the reaction mixture was concentrated *in vacuo* to give the crude product compound **1d** (75 mg) as a yellow oil which was used in next step directly. MS: calc'd 220 (MH^+), measured 220 (MH^+).

Step 3: preparation of 5-[(2*S*,6*R*)-2-[[2-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (Example 1)

To a tube was added [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **A**, 50 mg, 120 μmol), [4-(2,6-diazaspiro[3.3]heptan-2-yl)-6-methyl-2-pyridyl]methanol;2,2,2-trifluoroacetic acid (compound **1d**, 75 mg, 225 μmol), potassium carbonate (83 mg, 602 μmol) and ACN (6 mL). The reaction mixture was heated to 55 °C for 2 hrs. After being cooled down, the mixture was diluted with some ACN and filtered through celite, the filtrate was concentrated to give a yellow oil which was purified by prep-HPLC to give **Example 1** (40 mg) as a light yellow solid. MS: calc'd 485 (MH^+), measured 485 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.88 (dd, *J*=1.6, 4.3 Hz, 1H), 8.54 (dd, *J*=1.6, 8.6 Hz, 1H), 8.05 (d, *J*=7.9 Hz, 1H), 7.54 (dd, *J*=4.2, 8.6 Hz, 1H), 7.16 (d, *J*=8.1 Hz, 1H), 6.40 (s, 1H), 6.31 (br s, 1H), 4.54 (s, 2H), 4.52 - 4.23 (m, 8H), 4.17 (br t, *J*=9.8 Hz, 1H), 4.08 - 3.96 (m, 1H), 3.43 - 3.35 (m, 1H), 3.35 - 3.24 (m, 3H), 2.72 - 2.54 (m, 2H), 2.40 (s, 3H), 1.19 (d, *J*=6.2 Hz, 3H).

Example 3

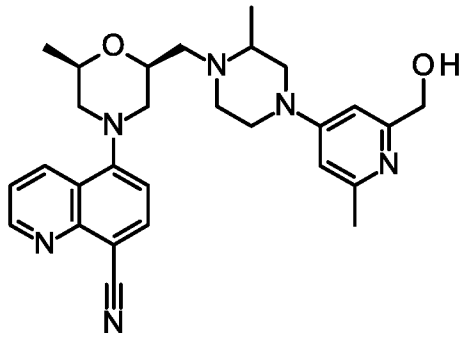
5-[(2*S*,6*R*)-2-[[8-(2-cyclopropyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2-cyclopropyl-pyridine (CAS: 1086381-28-3, Vendor: BePharm) and *tert*-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (CAS: 1251011-05-8, Vendor: PharmaBlock) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 3** (23 mg) was obtained as a light yellow solid. MS: calc'd 511 (MH^+), measured 511 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.86 (dd, *J*=1.6, 4.3 Hz, 1H), 8.53 (dd, *J*=1.7, 8.6 Hz, 1H), 8.04 (d, *J*=8.1 Hz, 1H), 7.94 - 7.82 (m, 1H), 7.52 (dd, *J*=4.2, 8.6 Hz, 1H), 7.14 (d, *J*=8.1 Hz, 1H), 6.65 - 6.56 (m, 2H), 4.01 - 3.85 (m, 2H), 3.68 - 3.59 (m, 2H), 3.50 - 3.37 (m, 4H), 3.27 (br d, *J*=12.3 Hz, 2H), 3.19 (br s, 2H), 3.04 (dd, *J*=6.4, 8.1 Hz, 2H), 2.69 - 2.48 (m, 4H), 1.92 - 1.83 (m, 1H), 1.14 (d, *J*=6.2 Hz, 3H), 0.91 - 0.76 (m, 4H).

Example 4

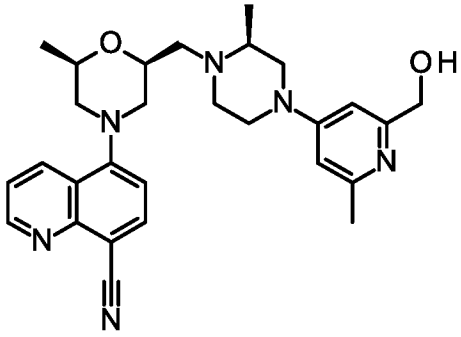
5-[(2*S*,6*R*)-2-[[4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

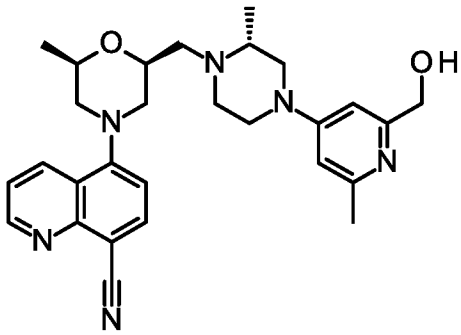


The title compound was prepared in analogy to the preparation of **Example 1** by using *tert*-butyl 2-methylpiperazine-1-carboxylate (CAS: 120737-78-2, Vendor: Accela ChemBio Inc) instead of *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**).

Example 4A and 4B

5-[(2*S*,6*R*)-2-[[(2*S*)-4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile and **5-[(2*S*,6*R*)-2-[[(2*R*)-4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**





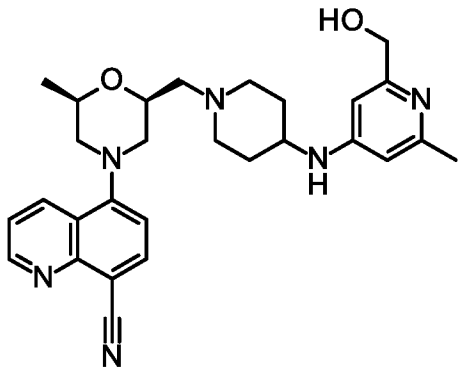
Example 4A (2 mg) and **Example 4B** (4 mg) were obtained through prep-HPLC separation of **Example 4**.

Example 4A: MS: calc'd 487 (MH^+), measured 487 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.6, 4.2 Hz, 1H), 8.69 (dd, *J*=1.6, 8.6 Hz, 1H), 8.20 (d, *J*=8.1 Hz, 1H), 7.68 (dd, *J*=4.3, 8.6 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 1H), 7.16 (s, 1H), 7.11 (s, 1H), 4.74 (s, 2H), 4.49 (br t, *J*=9.8 Hz, 1H), 4.37 - 4.16 (m, 3H), 3.93 - 3.75 (m, 2H), 3.75 - 3.64 (m, 2H), 3.63 - 3.52 (m, 2H), 3.46 (br d, *J*=11.9 Hz, 2H), 3.41 - 3.37 (m, 1H), 2.89 - 2.71 (m, 2H), 2.60 (s, 3H), 1.52 (br d, *J*=5.7 Hz, 3H), 1.34 (d, *J*=6.4 Hz, 3H).

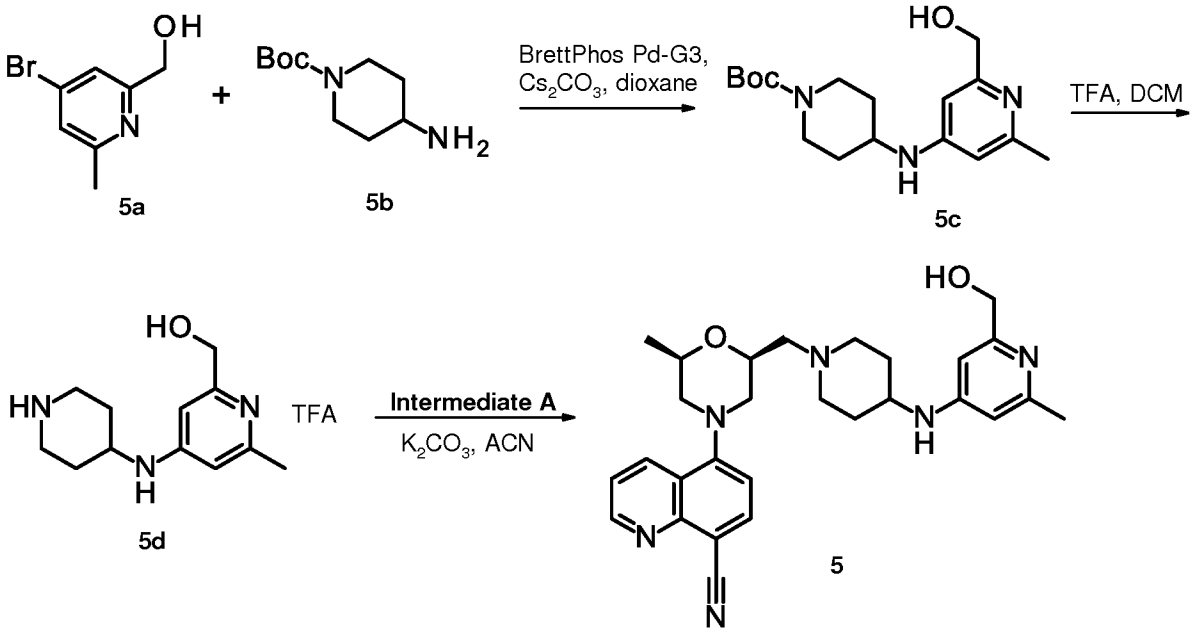
Example 4B: MS: calc'd 487 (MH^+), measured 487 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.7, 4.2 Hz, 1H), 8.69 (dd, *J*=1.6, 8.6 Hz, 1H), 8.19 (d, *J*=7.9 Hz, 1H), 7.68 (dd, *J*=4.3, 8.6 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 1H), 7.13 (s, 1H), 7.09 (s, 1H), 4.73 (s, 2H), 4.47 (br t, *J*=9.9 Hz, 1H), 4.30 - 4.14 (m, 3H), 3.93 - 3.76 (m, 2H), 3.75 - 3.58 (m, 2H), 3.57 - 3.41 (m, 5H), 2.86 - 2.71 (m, 2H), 2.59 (s, 3H), 1.49 (br d, *J*=5.7 Hz, 3H), 1.32 (d, *J*=6.2 Hz, 3H).

Example 5

5-[(2*S*,6*R*)-2-[[4-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]-1-piperidyl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 4-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]piperidine-1-carboxylate (compound 5c)

To a flask was added (4-bromo-6-methyl-2-pyridyl)methanol (compound **5a**, CAS: 448906-60-3, Vendor: BePharm, 150 mg, 742 μmol), *tert*-butyl 4-aminopiperidine-1-carboxylate (compound **5b**, CAS: 87120-72-7, Vendor: BePharm, 223 mg, 1.11 mmol), Cs_2CO_3 (726 mg, 2.23 mmol) and 1,4-dioxane (5 mL), the suspension was bubbled with N_2 for 5 mins and BrettPhos Pd-G3 (20 mg, 22 μmol) was added. The mixture was heated to 100 °C under microwave for 2 hrs. After being cooled down, the mixture was diluted with 10 mL EA and filtered through celite, the filtrate was concentrated to give a brown oil, which was purified by flash column (MeOH/DCM = 0 to 15%) to give compound **5c** (72 mg) as a yellow oil. MS: calc'd 322 (MH^+), measured 322 (MH^+).

Step 2: preparation of [6-methyl-4-(4-piperidylamino)-2-pyridyl]methanol;2,2,2-trifluoroacetic acid (compound 5d)

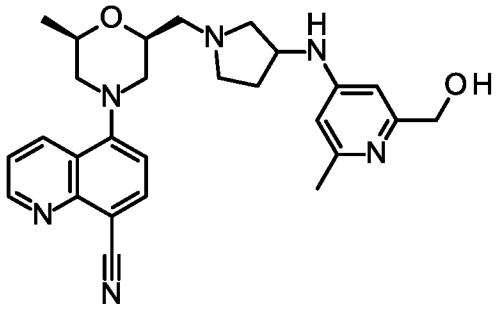
To a solution of *tert*-butyl 4-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]piperidine-1-carboxylate (compound **5c**, 72 mg, 224 μmol) in DCM (5 mL) was added TFA (1 mL) . The reaction mixture was stirred at rt for 3 hrs. Then it was concentrated *in vacuo* to give the crude product compound **5d** (75 mg) which was used in next step directly. MS: calc'd 222 (MH^+), measured 222 (MH^+).

Step 3: preparation of 5-[(2*S*,6*R*)-2-[[4-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]-1-piperidyl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (Example 5)

To a tube was added [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **A**, 40 mg, 96 μmol), [6-methyl-4-(4-piperidylamino)-2-pyridyl]methanol; 2,2,2-trifluoroacetic acid (compound **5d**, 75 mg, 224 μmol), potassium carbonate (67 mg, 481 μmol) and ACN (5 mL). The mixture was heated to 50 °C for 2 hrs. After being cooled down, the mixture was diluted with some ACN and filtered through celite, the filtrate was concentrated and purified by prep-HPLC to give the desired product **Example 5** (19 mg) as a light yellow solid. MS: calc'd 487 (MH^+), measured 487 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.6, 4.3 Hz, 1H), 8.67 (dd, *J*=1.6, 8.6 Hz, 1H), 8.17 (d, *J*=7.9 Hz, 1H), 7.65 (dd, *J*=4.3, 8.6 Hz, 1H), 7.27 (d, *J*=8.1 Hz, 1H), 6.58 (d, *J*=1.7 Hz, 1H), 6.33 (d, *J*=1.8 Hz, 1H), 4.52 (s, 2H), 4.26 - 4.14 (m, 1H), 4.09 (ddd, *J*=2.3, 6.3, 10.1 Hz, 1H), 3.49 - 3.37 (m, 3H), 3.13 (br d, *J*=12.2 Hz, 1H), 2.99 (br d, *J*=11.4 Hz, 1H), 2.76 - 2.63 (m, 2H), 2.63 - 2.45 (m, 2H), 2.41 - 2.24 (m, 5H), 2.10 - 1.95 (m, 2H), 1.68 - 1.51 (m, 2H), 1.27 (d, *J*=6.2 Hz, 3H).

Example 6

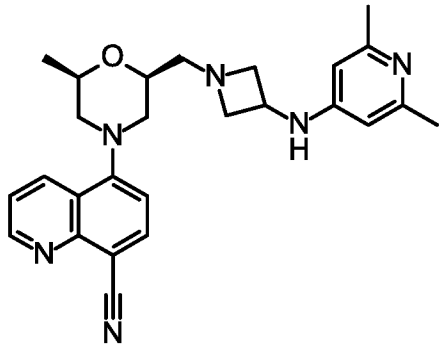
5-[(2*S*,6*R*)-2-[[3-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]pyrrolidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 5** by using *tert*-butyl 3-aminopyrrolidine-1-carboxylate (CAS: 186550-13-0, Vendor: Fudechem) instead of *tert*-butyl 4-aminopiperidine-1-carboxylate (compound **5b**). **Example 6** (4 mg) was obtained as a light yellow solid. MS: calc'd 473 (MH^+), measured 473 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.04 - 8.96 (m, 1H), 8.67 (d, *J*=8.6 Hz, 1H), 8.16 (d, *J*=7.9 Hz, 1H), 7.65 (dd, *J*=4.2, 8.5 Hz, 1H), 7.26 (d, *J*=8.1 Hz, 1H), 6.58 (s, 1H), 6.34 (s, 1H), 4.53 (s, 2H), 4.17 - 4.08 (m, 2H), 3.48 - 3.38 (m, 3H), 3.07 (dd, *J*=7.0, 9.8 Hz, 1H), 2.95 - 2.85 (m, 1H), 2.78 - 2.58 (m, 6H), 2.45 - 2.25 (m, 4H), 1.80 - 1.69 (m, 1H), 1.27 (d, *J*=6.2 Hz, 3H).

Example 7

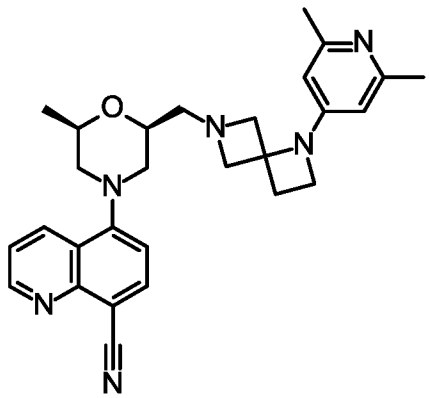
5-[(2*S*,6*R*)-2-[[3-[(2,6-dimethyl-4-pyridyl)amino]azetidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 5** by using 4-bromo-2,6-dimethyl-pyridine (CAS: 5093-70-9, Vendor: Accela ChemBio Inc) and *tert*-butyl 3-aminoazetidine-1-carboxylate (CAS: 193269-78-2, Vendor: PharmaBlock) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **5a**) and *tert*-butyl 4-aminopiperidine-1-carboxylate (compound **5b**). **Example 7** (27 mg) was obtained as a yellow solid. MS: calc'd 443 (MH^+), measured 443 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.99 (dd, *J*=1.3, 4.2 Hz, 1H), 8.65 (dd, *J*=1.3, 8.6 Hz, 1H), 8.16 (d, *J*=7.9 Hz, 1H), 7.65 (dd, *J*=4.2, 8.6 Hz, 1H), 7.28 (d, *J*=8.1 Hz, 1H), 6.67 (br s, 2H), 4.85 - 4.68 (m, 3H), 4.43 - 4.23 (m, 3H), 4.20 - 4.08 (m, 1H), 3.64 - 3.46 (m, 2H), 3.42 (br d, *J*=11.7 Hz, 2H), 2.84 - 2.66 (m, 2H), 2.52 (br s, 6H), 1.30 (d, *J*=6.2 Hz, 3H).

Example 8

5-[(2*S*,6*R*)-2-[[1-(2,6-dimethyl-4-pyridyl)-1,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

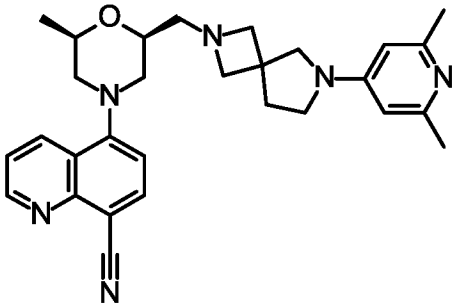


The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2,6-dimethyl-pyridine and *tert*-butyl 1,6-diazaspiro[3.3]heptane-6-carboxylate;oxalic acid (CAS: 1272412-72-2, Vendor: PharmaBlock) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 8** (23 mg) was obtained as a light yellow solid. MS: calc'd 469 (MH^+), measured

469 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.6, 4.3 Hz, 1H), 8.68 (dd, *J*=1.7, 8.6 Hz, 1H), 8.19 (d, *J*=7.9 Hz, 1H), 7.67 (dd, *J*=4.3, 8.6 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 1H), 7.06 (br s, 1H), 6.47 (br s, 1H), 5.15 (br s, 2H), 4.48 (br d, *J*=11.6 Hz, 2H), 4.38 - 4.28 (m, 1H), 4.21 - 4.03 (m, 3H), 3.65 - 3.51 (m, 2H), 3.45 (br t, *J*=10.0 Hz, 2H), 2.94 (t, *J*=7.4 Hz, 2H), 2.87 - 2.70 (m, 2H), 2.55 (br s, 6H), 1.32 (d, *J*=6.2 Hz, 3H).

Example 9

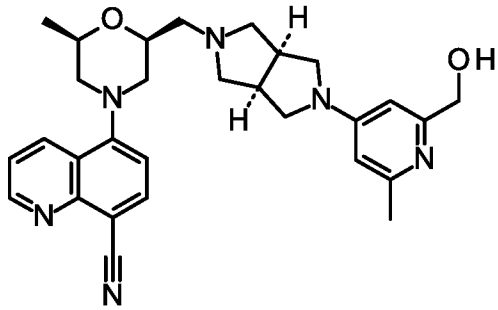
5-[(2*S*,6*R*)-2-[[7-(2,6-dimethyl-4-pyridyl)-2,7-diazaspiro[3.4]octan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2,6-dimethyl-pyridine and *tert*-butyl 2,7-diazaspiro[3.4]octane-2-carboxylate (CAS: 885270-84-8, Vendor: PharmaBlock) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 9** (32 mg) was obtained as a light yellow solid. MS: calc'd 483 (MH^+), measured 483 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.6, 4.2 Hz, 1H), 8.66 (dd, *J*=1.6, 8.6 Hz, 1H), 8.18 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=4.2, 8.6 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 6.65 - 6.52 (m, 2H), 4.52 - 4.28 (m, 5H), 4.20 - 4.09 (m, 1H), 3.98 - 3.74 (m, 2H), 3.69 - 3.60 (m, 2H), 3.60 - 3.47 (m, 2H), 3.42 (br d, *J*=12.5 Hz, 2H), 2.85 - 2.64 (m, 2H), 2.52 (br d, *J*=4.8 Hz, 8H), 1.31 (d, *J*=6.2 Hz, 3H).

Example 10

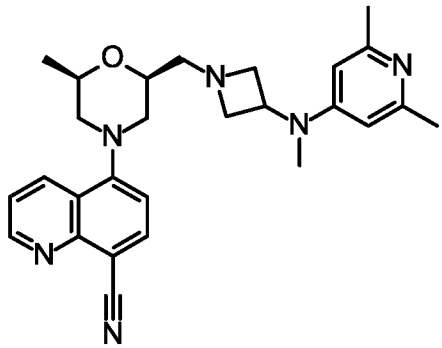
***cis*-5-[(2*S*,6*R*)-2-[[5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**



The title compound was prepared in analogy to the preparation of **Example 1** by using *cis*-*tert*-butyl 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrole-5-carboxylate (compound **10b**, CAS: 141449-85-6, Vendor: PharmaBlock) instead of *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 10** (42 mg) was obtained as a light yellow solid. MS: calc'd 499 (MH^+), measured 499 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.98 (dd, *J*=1.6, 4.3 Hz, 1H), 8.63 (dd, *J*=1.3, 8.5 Hz, 1H), 8.14 (d, *J*=8.1 Hz, 1H), 7.63 (dd, *J*=4.3, 8.6 Hz, 1H), 7.26 (d, *J*=8.1 Hz, 1H), 6.78 (br s, 1H), 6.68 (br s, 1H), 4.70 (s, 2H), 4.42 (br t, *J*=9.9 Hz, 1H), 4.20 - 4.09 (m, 2H), 3.98 - 3.62 (m, 6H), 3.59 - 3.36 (m, 7H), 2.74 (dt, *J*=11.1, 12.7 Hz, 2H), 2.55 (s, 3H), 1.32 (d, *J*=6.2 Hz, 3H).

Example 11

5-[(2*S*,6*R*)-2-[[3-[(2,6-dimethyl-4-pyridyl)-methyl-amino]azetidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

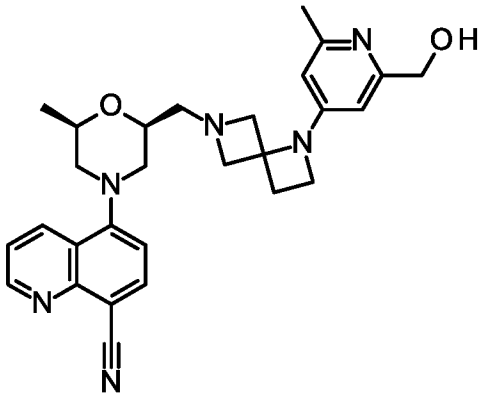


The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2,6-dimethyl-pyridine and *tert*-butyl 3-(methylamino)azetidine-1-carboxylate (CAS: 454703-20-9, Vendor: PharmaBlock) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 11** (34 mg) was obtained as a light yellow solid. MS: calc'd 457 (MH^+), measured 457 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.5, 4.2 Hz, 1H), 8.66 (dd, *J*=1.6, 8.6 Hz, 1H), 8.16 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.28 (d, *J*=8.1 Hz, 1H), 6.87 (s, 2H), 5.30 (br s, 1H), 4.79 - 4.48 (m, 4H), 4.36 (br t, *J*=9.9 Hz, 1H), 4.21 - 4.10

(m, 1H), 3.68 - 3.49 (m, 2H), 3.43 (br d, *J*=12.5 Hz, 2H), 3.30 (s, 3H), 2.86 - 2.68 (m, 2H), 2.57 (s, 6H), 1.31 (d, *J*=6.2 Hz, 3H).

Example 12

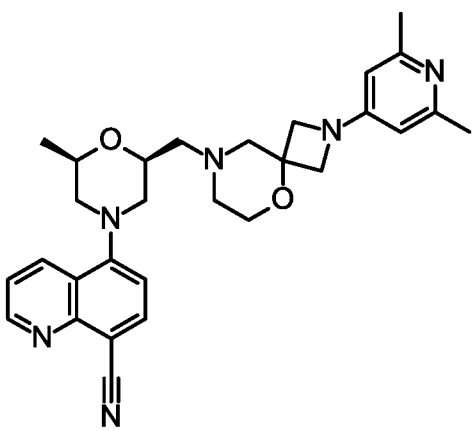
5-[(2*S*,6*R*)-2-[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-1,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using *tert*-butyl 1,6-diazaspiro[3.3]heptane-6-carboxylate;oxalic acid instead of *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 12** (22 mg) was obtained as a light yellow solid. MS: calc'd 485 (MH^+), measured 485 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.6, 4.3 Hz, 1H), 8.67 (dd, *J*=1.6, 8.7 Hz, 1H), 8.19 (d, *J*=8.1 Hz, 1H), 7.67 (dd, *J*=4.3, 8.6 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 1H), 7.09 (br s, 1H), 6.59 (br s, 1H), 5.20 (br s, 2H), 4.75 (br d, *J*=4.5 Hz, 2H), 4.53 (br d, *J*=13.3 Hz, 2H), 4.36 (br t, *J*=9.8 Hz, 1H), 4.22 - 4.05 (m, 3H), 3.69 - 3.53 (m, 2H), 3.49 - 3.39 (m, 2H), 2.96 (t, *J*=7.5 Hz, 2H), 2.88 - 2.68 (m, 2H), 2.60 (br s, 3H), 1.32 (d, *J*=6.2 Hz, 3H).

Example 13

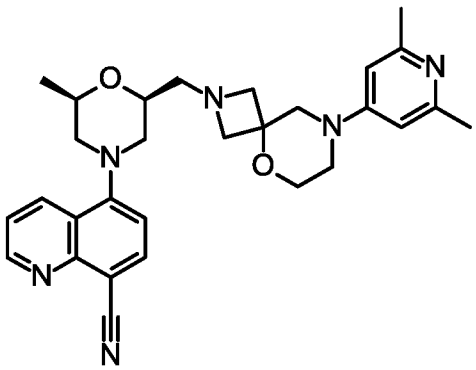
5-[(2*S*,6*R*)-2-[[2-(2,6-dimethyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-8-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2,6-dimethyl-pyridine and *tert*-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-8-carboxylate (CAS: 1251005-61-4, Vendor: PharmaBlock) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 13** (23 mg) was obtained as a light yellow solid. MS: calc'd 499 (MH^+), measured 499 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.98 (br d, *J*=3.1 Hz, 1H), 8.64 (br d, *J*=8.6 Hz, 1H), 8.15 (br d, *J*=7.9 Hz, 1H), 7.63 (dd, *J*=4.3, 8.4 Hz, 1H), 7.27 (br d, *J*=7.9 Hz, 1H), 6.42 (s, 2H), 4.53 - 4.39 (m, 1H), 4.31 (br d, *J*=10.3 Hz, 2H), 4.25 - 4.09 (m, 3H), 4.02 (br s, 2H), 3.74 - 3.37 (m, 5H), 3.26 - 3.11 (m, 3H), 2.75 (td, *J*=11.1, 17.1 Hz, 2H), 2.49 (s, 6H), 1.30 (br d, *J*=6.1 Hz, 3H).

Example 14

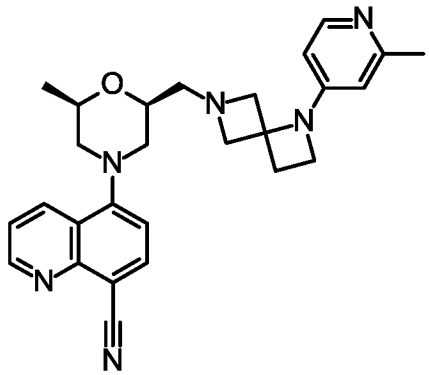
5-[(2*S*,6*R*)-2-[[8-(2,6-dimethyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2,6-dimethyl-pyridine and *tert*-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (CAS: 1251011-05-8, Vendor: PharmaBlock) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 14** (28 mg) was obtained as a white solid. MS: calc'd 499 (MH^+), measured 499 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.98 (br d, *J*=3.1 Hz, 1H), 8.65 (br d, *J*=8.4 Hz, 1H), 8.16 (d, *J*=8.1 Hz, 1H), 7.63 (dd, *J*=4.3, 8.6 Hz, 1H), 7.26 (d, *J*=8.1 Hz, 1H), 6.65 (s, 2H), 4.12 - 3.99 (m, 2H), 3.75 (br t, *J*=4.7 Hz, 2H), 3.60 - 3.48 (m, 4H), 3.39 (br d, *J*=12.0 Hz, 2H), 3.31 - 3.25 (m, 2H), 3.22 - 3.10 (m, 2H), 2.82 - 2.60 (m, 4H), 2.40 (s, 6H), 1.26 (d, *J*=6.1 Hz, 3H).

Example 15

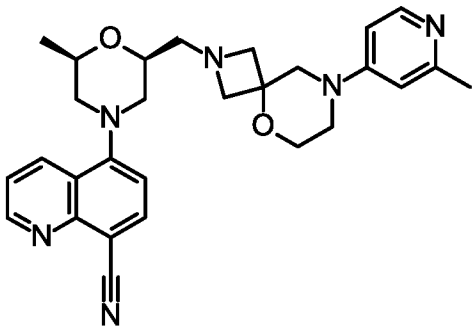
5-[(2*R*,6*S*)-2-methyl-6-[[1-(2-methyl-4-pyridyl)-1,6-diazaspiro[3.3]heptan-6-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2-methyl-pyridine (CAS: 22282-99-1, Vendor: TCI) and *tert*-butyl 1,6-diazaspiro[3.3]heptane-6-carboxylate;oxalic acid instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 15** (34 mg) was obtained as a yellow solid. MS: calc'd 455 (MH^+), measured 455 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.6, 4.2 Hz, 1H), 8.66 (dd, *J*=1.7, 8.6 Hz, 1H), 8.15 (dd, *J*=7.6, 17.1 Hz, 2H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 7.19 (br s, 1H), 6.62 (br s, 1H), 5.23 (br s, 2H), 4.55 (br d, *J*=12.7 Hz, 2H), 4.37 (br t, *J*=9.8 Hz, 1H), 4.22 - 4.04 (m, 3H), 3.73 - 3.54 (m, 2H), 3.44 (br t, *J*=11.4 Hz, 2H), 2.98 (t, *J*=7.5 Hz, 2H), 2.87 - 2.68 (m, 2H), 2.60 (br s, 3H), 1.31 (d, *J*=6.2 Hz, 3H).

Example 16

5-[(2*R*,6*S*)-2-methyl-6-[[8-(2-methyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile

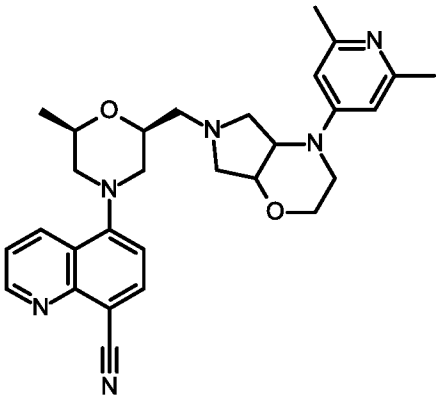


The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2-methyl-pyridine and *tert*-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 16** (35 mg) was obtained as a light yellow solid. MS: calc'd 485 (MH^+), measured 485 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.98 (br d, *J*=3.1 Hz, 1H), 8.63 (br d, *J*=8.3 Hz, 1H), 8.13 (br t,

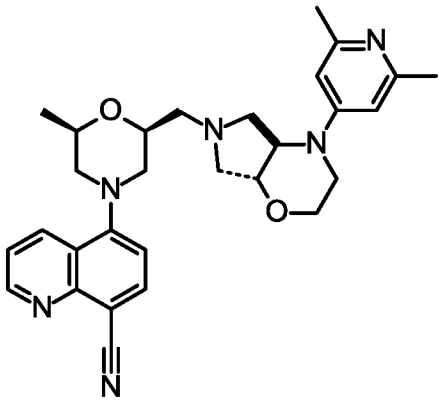
J=6.8 Hz, 2H), 7.64 (br dd, *J*=4.2, 8.4 Hz, 1H), 7.25 (br d, *J*=7.9 Hz, 1H), 7.22 - 7.09 (m, 2H), 4.46 (br s, 2H), 4.35 (br s, 3H), 4.19 - 4.01 (m, 3H), 3.96 (br s, 2H), 3.71 (br s, 2H), 3.65 - 3.57 (m, 1H), 3.57 - 3.46 (m, 1H), 3.40 (br d, *J*=12.0 Hz, 2H), 2.87 - 2.64 (m, 2H), 2.58 (s, 3H), 1.28 (br d, *J*=6.1 Hz, 3H).

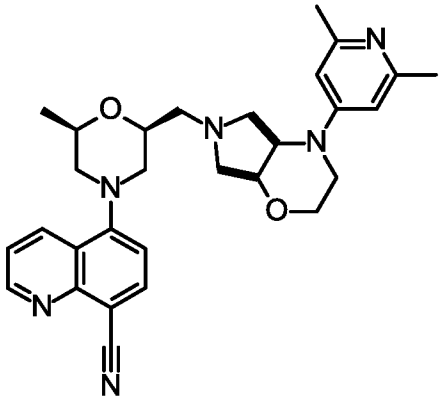
Example 17, 17A and 17B

5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile, ***trans*****-5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile** and ***cis*****-5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**



(Example 17)





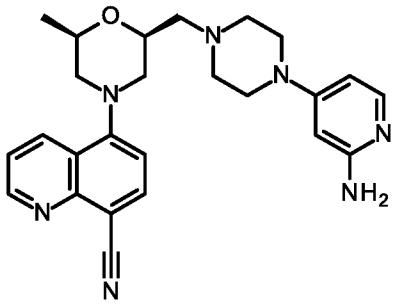
Example 17 was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2,6-dimethyl-pyridine and *tert*-butyl 3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazine-6-carboxylate (CAS: 1360364-21-1, Vendor: PharmaBlock) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). The *trans* and *cis* isomers were obtained by flash column separation (EA/PE=0 to 100%).

Example 17A (38 mg) was obtained as a light yellow solid. MS: calc'd 499 (MH^+), measured 499 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.99 (br s, 1H), 8.66 (br t, *J*=6.8 Hz, 1H), 8.16 (d, *J*=8.1 Hz, 1H), 7.64 (td, *J*=4.1, 8.3 Hz, 1H), 7.26 (br d, *J*=7.9 Hz, 1H), 6.66 (s, 2H), 4.09 (br d, *J*=11.6 Hz, 3H), 3.98 - 3.88 (m, 1H), 3.88 - 3.78 (m, 1H), 3.70 - 3.52 (m, 2H), 3.49 - 3.37 (m, 2H), 3.22 - 3.10 (m, 2H), 3.04 - 2.79 (m, 5H), 2.79 - 2.60 (m, 2H), 2.42 (s, 6H), 1.27 (br d, *J*=4.8 Hz, 3H).

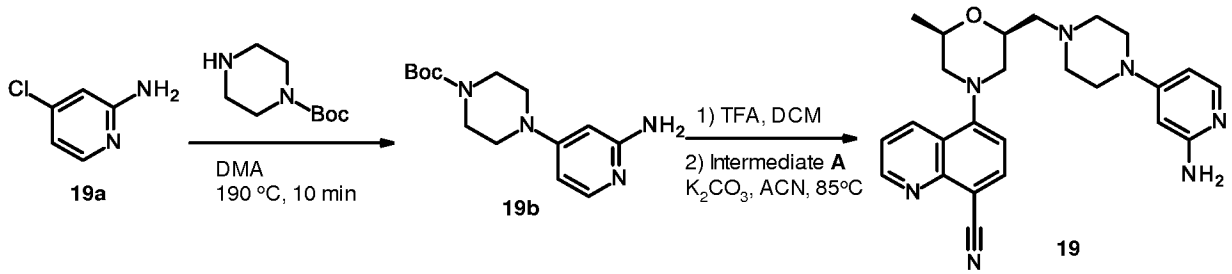
Example 17B (27 mg) was obtained as a light yellow solid. MS: calc'd 499 (MH^+), measured 499 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.98 (br d, *J*=1.7 Hz, 1H), 8.64 (br t, *J*=6.7 Hz, 1H), 8.14 (d, *J*=7.9 Hz, 1H), 7.62 (td, *J*=4.2, 8.5 Hz, 1H), 7.25 (d, *J*=7.9 Hz, 1H), 6.58 (s, 2H), 4.35 - 4.23 (m, 1H), 4.19 - 3.97 (m, 4H), 3.65 (br t, *J*=11.2 Hz, 1H), 3.56 - 3.28 (m, 4H), 3.19 - 3.03 (m, 2H), 2.89 - 2.59 (m, 6H), 2.39 (d, *J*=1.7 Hz, 6H), 1.26 (dd, *J*=1.9, 6.2 Hz, 3H).

Example 19

5-[(2*S*,6*R*)-2-[[4-(2-amino-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 4-(2-amino-4-pyridyl)piperazine-1-carboxylate (compound 19b)

A mixture of 4-chloropyridin-2-amine (compound **19a**, CAS: 19798-80-2, Vendor: Aldrich, 129 mg, 1.00 mmol) and *tert*-butyl piperazine-1-carboxylate (CAS: 57260-71-6, Vendor: Accela ChemBio Inc, 186 mg, 1.00 mmol) in N,N-dimethylacetamide (3 mL) was heated at 190 °C for

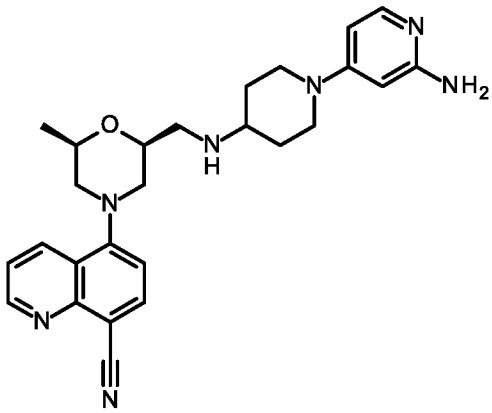
10 minutes. After the reaction mixture was cooled down, the solid was collected by filtration to give compound **19b** (223 mg) as a grey solid. MS: calc'd 279 (MH^+), measured 279 (MH^+).

Step 2: preparation of 5-[(2*S*,6*R*)-2-[[4-(2-amino-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (Example 19)

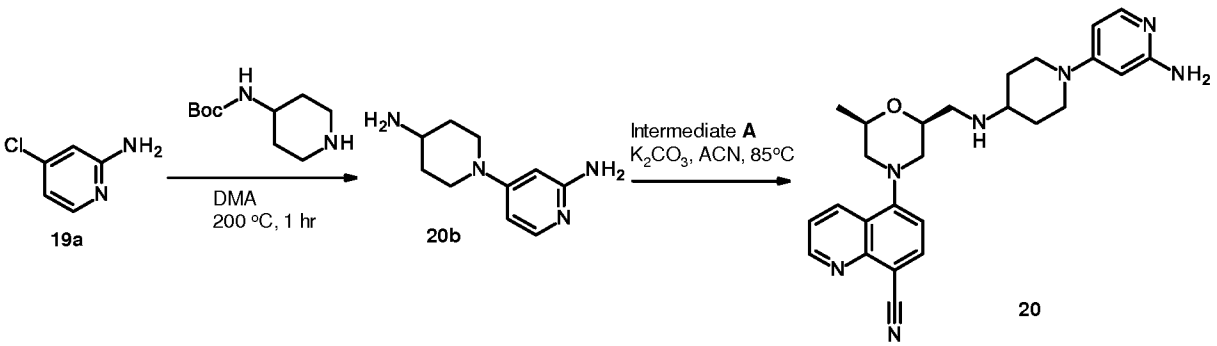
The mixture of *tert*-butyl 4-(2-amino-4-pyridyl)piperazine-1-carboxylate (compound **19b**, 67 mg, 240 μmol) and DCM/TFA=1/2 (3 mL) was stirred at room temperature for 1 h, then it was concentrated and the residue was dissolved in ACN (6 mL), to which K_2CO_3 (83 mg, 600 μmol) and [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **A**, 83 mg, 200 μmol) were added. After being stirred at 85 °C for 2 hrs, the reaction mixture was filtered and then directly purified by prep-HPLC to give **Example 19** (16 mg). MS: calc'd 444 (MH^+), measured 444 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.6, 4.3 Hz, 1H), 8.68 (dd, *J*=1.7, 8.6 Hz, 1H), 8.18 (d, *J*=7.9 Hz, 1H), 7.67 (dd, *J*=4.3, 8.6 Hz, 1H), 7.64 (d, *J*=7.5 Hz, 1H), 7.30 (d, *J*=7.9 Hz, 1H), 6.66 (dd, *J*=2.6, 7.6 Hz, 1H), 6.17 (d, *J*=2.4 Hz, 1H), 4.58 - 4.48 (m, 1H), 4.27 - 4.15 (m, 1H), 4.09 - 3.75 (m, 4H), 3.68 - 3.49 (m, 4H), 3.48 - 3.39 (m, 4H), 2.84 - 2.71 (m, 2H), 1.33 (d, *J*=6.2 Hz, 3H).

Example 20

5-[(2*S*,6*R*)-2-[[[1-(2-amino-4-pyridyl)-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of 4-(4-amino-1-piperidyl)pyridin-2-amine (compound 20b)

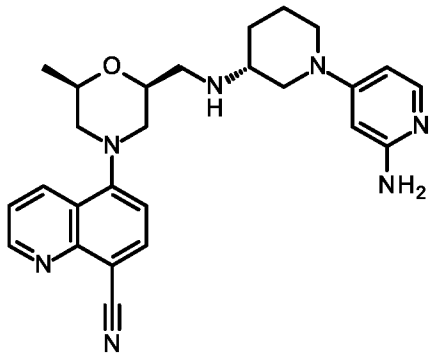
A mixture of 4-chloropyridin-2-amine (129 mg, 1.00 mmol) and *tert*-butyl piperidin-4-ylcarbamate (CAS: 73874-95-0, Vendor: Accela ChemBio Inc, 200 mg, 1.00 mmol) in N,N-dimethylacetamide (3 mL) was stirred at 200 °C for 1 h. After the reaction mixture was cooled down, the solution was added dropwise to methyl *tert*-butyl ether (60 mL). The solid was collected by centrifugation, then dissolved in MeOH (5 mL). To this solution was added 5 drops of 5 M NaOMe solution in methanol. After being stirred for 5 minutes, the reaction mixture was added with solid $NaHCO_3$ (500 mg) and stirred for another 15 minutes, then EA (15 mL) was added. The mixture was filtered and the organic phase was concentrated to give crude compound **20b** (75 mg) which was used directly for next step. MS: calc'd 193 (MH^+), measured 193 (MH^+).

Step 2: preparation of 5-[(2*S*,6*R*)-2-[[[1-(2-amino-4-pyridyl)-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (Example 20)

To a mixture of [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **A**, 50 mg, 120 μmol) and 4-(4-aminopiperidin-1-yl)pyridin-2-amine (compound **20b**, 33 mg, 170 μmol) in ACN (6 mL) was added K_2CO_3 (50 mg, 361 μmol). After being stirred at 85 °C overnight, the reaction mixture was filtered and the organic phase was directly purified by prep-HPLC to give **Example 20** (25 mg). MS: calc'd 458 (MH^+), measured 458 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.5, 4.2 Hz, 1H), 8.65 (dd, *J*=1.6, 8.6 Hz, 1H), 8.16 (d, *J*=7.9 Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.56 (d, *J*=7.6 Hz, 1H), 7.28 (d, *J*=8.1 Hz, 1H), 6.62 (dd, *J*=2.6, 7.6 Hz, 1H), 6.11 (d, *J*=2.6 Hz, 1H), 4.40 - 4.28 (m, 1H), 4.28 - 4.12 (m, 3H), 3.58 (ddd, *J*=4.5, 7.3, 11.6 Hz, 1H), 3.50 - 3.35 (m, 3H), 3.28 - 3.12 (m, 3H), 2.86 - 2.68 (m, 2H), 2.36 - 2.25 (m, 2H), 1.73 (dq, *J*=4.1, 12.2 Hz, 2H), 1.32 (d, *J*=6.4 Hz, 3H).

Example 21

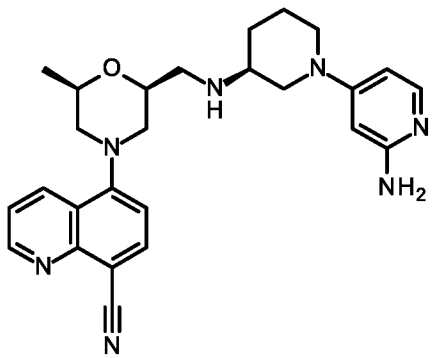
5-[(2*S*,6*R*)-2-[[[(3R)-1-(2-amino-4-pyridyl)-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 20** by using *tert*-butyl N-[(3*R*)-3-piperidyl]carbamate (CAS: 309956-78-3, Vendor: TCI) instead of *tert*-butyl piperidin-4-ylcarbamate. **Example 21** (8 mg) was obtained. MS: calc'd 458 (MH^+), measured 458 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.6, 4.3 Hz, 1H), 8.66 (dd, *J*=1.7, 8.6 Hz, 1H), 8.18 (d, *J*=8.1 Hz, 1H), 7.67 (dd, *J*=4.2, 8.6 Hz, 1H), 7.58 (d, *J*=7.6 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 1H), 6.63 (dd, *J*=2.7, 7.7 Hz, 1H), 6.17 (d, *J*=2.6 Hz, 1H), 4.40 - 4.31 (m, 2H), 4.22 - 4.13 (m, 1H), 3.98 (br d, *J*=13.6 Hz, 1H), 3.51 - 3.37 (m, 4H), 3.35 (s, 1H), 3.31 - 3.27 (m, 1H), 3.25 - 3.14 (m, 1H), 2.87 - 2.70 (m, 2H), 2.40 - 2.32 (m, 1H), 2.06 - 1.94 (m, 1H), 1.88 - 1.66 (m, 2H), 1.33 (d, *J*=6.4 Hz, 3H).

Example 22

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-(2-amino-4-pyridyl)-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

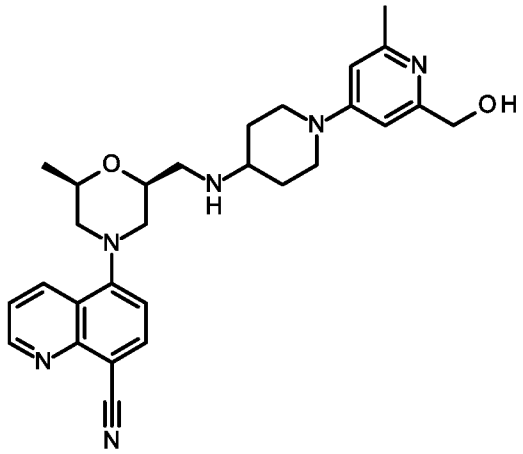


The title compound was prepared in analogy to the preparation of **Example 20** by using *tert*-butyl N-[(3*S*)-3-piperidyl]carbamate (CAS: 216854-23-8, Vendor: TCI) instead of *tert*-butyl piperidin-4-ylcarbamate. **Example 22** (15 mg) was obtained. MS: calc'd 458 (MH^+), measured 458 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.6, 4.3 Hz, 1H), 8.66 (dd, *J*=1.7, 8.6 Hz, 1H), 8.18 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.58 (d, *J*=7.6 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 6.64 (dd, *J*=2.6, 7.6 Hz, 1H), 6.17 (d, *J*=2.6 Hz, 1H), 4.40 - 4.28 (m, 2H), 4.25 - 4.12 (m, 1H), 3.95 (br d, *J*=13.3 Hz, 1H), 3.52 - 3.40 (m, 4H), 3.39 - 3.35 (m, 1H), 3.30 -

3.14 (m, 2H), 2.88 - 2.68 (m, 2H), 2.42 - 2.29 (m, 1H), 2.07 - 1.95 (m, 1H), 1.90 - 1.67 (m, 2H), 1.33 (d, *J*=6.2 Hz, 3H).

Example 23

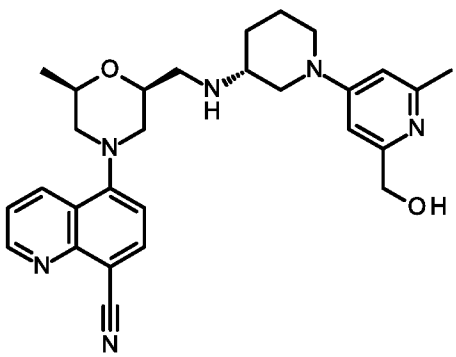
5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using *tert*-butyl piperidin-4-ylcarbamate instead of *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 23** (3 mg) was obtained. MS: calc'd 487 (MH^+), measured 487 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (d, *J*=3.1 Hz, 1H), 8.67 (br d, *J*=8.2 Hz, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=4.2, 8.4 Hz, 1H), 7.28 (d, *J*=7.9 Hz, 1H), 7.03 (s, 1H), 6.97 (s, 1H), 4.68 (s, 2H), 4.35 (br d, *J*=13.4 Hz, 2H), 4.30 - 4.22 (m, 1H), 4.22 - 4.11 (m, 1H), 3.51 - 3.35 (m, 3H), 3.31 - 3.06 (m, 4H), 2.83 - 2.68 (m, 2H), 2.54 (s, 3H), 2.27 (br s, 2H), 1.66 (br s, 2H), 1.31 (d, *J*=6.2 Hz, 3H).

Example 24

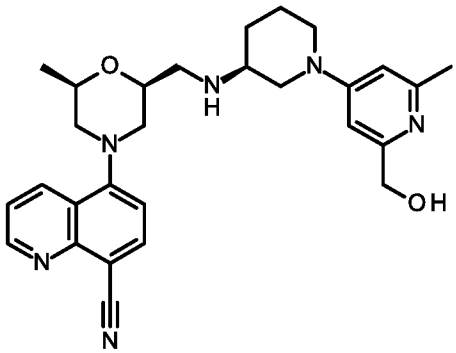
5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using *tert*-butyl N-[(3*R*)-3-piperidyl]carbamate instead of *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 24** (8 mg) was obtained. MS: calc'd 487 (MH^+), measured 487 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.98 (d, *J*=2.9 Hz, 1H), 8.64 (d, *J*=7.6 Hz, 1H), 8.14 (d, *J*=7.9 Hz, 1H), 7.64 (dd, *J*=4.3, 8.6 Hz, 1H), 7.24 (d, *J*=8.1 Hz, 1H), 7.03 (s, 1H), 6.96 (s, 1H), 4.67 (s, 2H), 4.34 (br d, *J*=12.5 Hz, 1H), 4.24 (br s, 1H), 4.18 - 4.05 (m, 2H), 3.44 (br dd, *J*=11.9, 18.6 Hz, 2H), 3.37 - 3.33 (m, 1H), 3.31 - 3.26 (m, 1H), 3.19 - 3.06 (m, 3H), 2.83 - 2.66 (m, 2H), 2.53 (s, 3H), 2.38 - 2.21 (m, 1H), 1.99 (br d, *J*=13.2 Hz, 1H), 1.81 - 1.61 (m, 2H), 1.30 (d, *J*=6.2 Hz, 3H).

Example 25

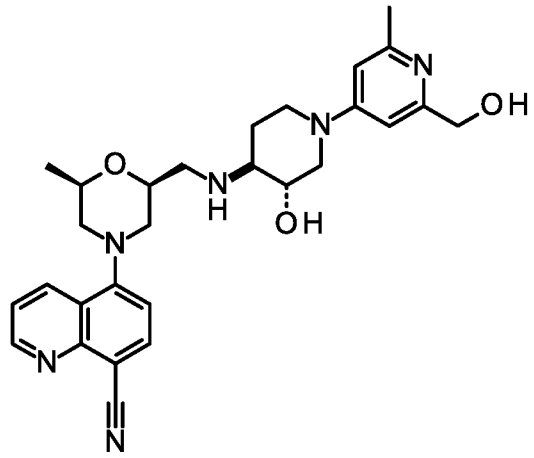
5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



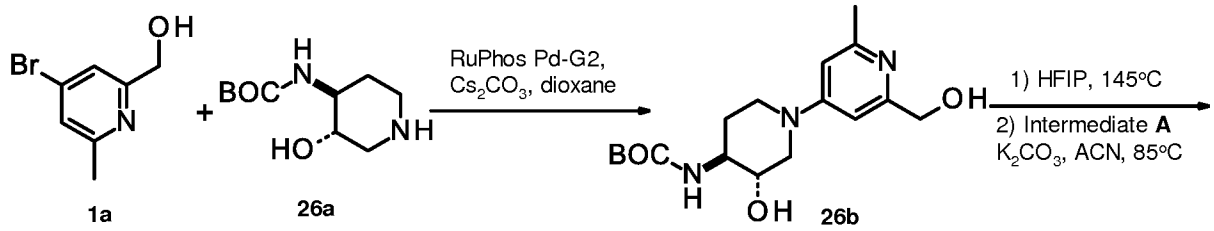
The title compound was prepared in analogy to the preparation of **Example 1** by using *tert*-butyl N-[(3*S*)-3-piperidyl]carbamate instead of *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 25** (1 mg) was obtained. MS: calc'd 487 (MH^+), measured 487 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.5, 4.2 Hz, 1H), 8.66 (dd, *J*=1.6, 8.6 Hz, 1H), 8.17 (d, *J*=7.9 Hz, 1H), 7.65 (dd, *J*=4.3, 8.6 Hz, 1H), 7.26 (d, *J*=8.1 Hz, 1H), 7.03 (d, *J*=2.3 Hz, 1H), 6.95 (d, *J*=2.2 Hz, 1H), 4.70 - 4.65 (m, 2H), 4.26 (br d, *J*=12.6 Hz, 1H), 4.19 - 4.02 (m, 3H), 3.43 (br t, *J*=10.0 Hz, 2H), 3.37 - 3.34 (m, 1H), 3.31 - 3.23 (m, 1H), 3.06 - 2.90 (m, 3H), 2.83 - 2.74 (m, 1H), 2.74 - 2.65 (m, 1H), 2.57 - 2.47 (m, 3H), 2.27 - 2.15 (m, 1H), 2.01 - 1.90 (m, 1H), 1.73 - 1.59 (m, 2H), 1.28 (d, *J*=6.2 Hz, 3H).

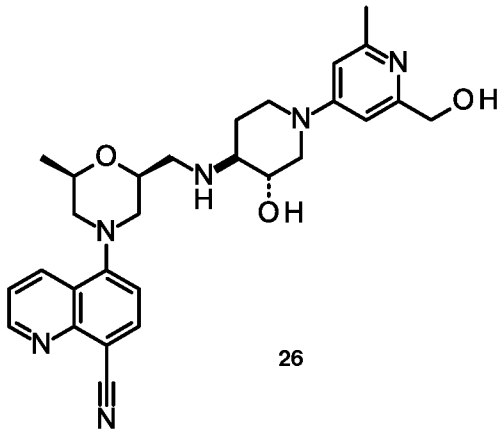
Example 26

***trans*-5-[(2*S*,6*R*)-2-[[[3-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**



The title compound was prepared according to the following scheme:





Step 1: preparation of *trans-tert*-butyl N-[3-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]carbamate (compound 26b)

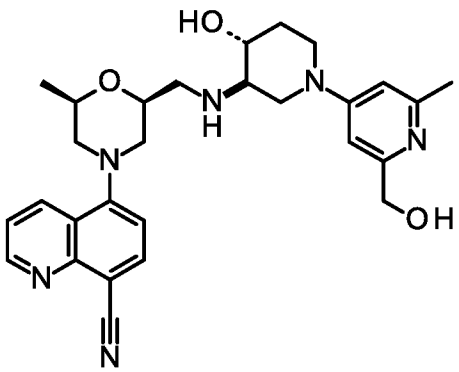
The mixture of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**, 152 mg, 750 μmol), *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (CAS: 859854-66-3, Vendor: PharmaBlock, 108 mg, 500 μmol) and Cs_2CO_3 (326 mg, 1.00 mmol) in 1,4-dioxane (5 mL) was bubbled with N_2 for 5 mins and Ruphos Pd G2 (12 mg, 15 μmol) was added. Then the mixture was sealed and stirred at 85 °C for 4 hrs. After being cooled down, the mixture was diluted with EA (20 mL), filtered and concentrated, the residue was purified by flash column (MeOH/DCM=10 to 20%) to give compound **26b** (110 mg). MS: calc'd 338 (MH^+), measured 338 (MH^+).

Step 2: preparation of *trans*-5-[(2*S*,6*R*)-2-[[[3-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (Example 26)

The mixture of *trans-tert*-butyl N-[3-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]carbamate (compound **26b**, 57 mg, 169 μmol) and 1,1,1,3,3,3-hexafluoro-2-propanol (10 mL) was stirred at 145 °C for 40 minutes under microwave. The reaction mixture was concentrated and the residue was dissolved in dry ACN (5 mL) followed by adding [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **A**, 50 mg, 120 μmol) and K_2CO_3 (50 mg, 361 μmol). After being stirred at 85 °C for 4 hrs, the reaction mixture was filtered and the organic phase was directly purified by prep-HPLC to give **Example 26** (22 mg). MS: calc'd 503 (MH^+), measured 503 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.5, 4.2 Hz, 1H), 8.69 - 8.63 (m, 1H), 8.17 (d, *J*=7.9 Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.29 (d, *J*=7.9 Hz, 1H), 7.08 (s, 1H), 7.02 (s, 1H), 4.71 (s, 2H), 4.46 - 4.32 (m, 3H), 4.23 - 4.13 (m, 1H), 3.83 (dq, *J*=4.8, 9.7 Hz, 1H), 3.54 - 3.40 (m, 4H), 3.40 - 3.34 (m, 1H), 3.30 - 3.23 (m, 1H), 3.18 - 3.09 (m, 1H), 2.86 - 2.69 (m, 2H), 2.56 (s, 3H), 2.46 - 2.33 (m, 1H), 1.80 (dq, *J*=4.0, 12.6 Hz, 1H), 1.32 (dd, *J*=2.2, 6.2 Hz, 3H).

Example 27

***trans*-5-[(2*S*,6*R*)-2-[[[4-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**

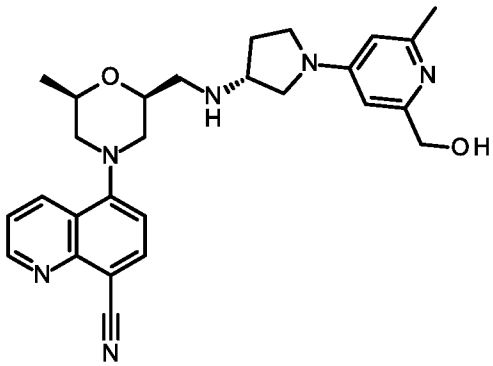


The title compound was prepared in analogy to the preparation of **Example 26** by using *trans-tert*-butyl N-(4-hydroxy-3-piperidyl)carbamate (CAS: 859854-68-5, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 27** (19 mg) was obtained. MS: calc'd 503 (MH^+), measured 503 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.02 - 8.99 (m, 1H), 8.66 (td, *J*=2.0, 8.6 Hz, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=4.2, 8.6 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 7.15 - 7.12 (m, 1H), 7.07 (d, *J*=7.9 Hz, 1H), 4.72 (s, 2H), 4.68 - 4.60 (m, 1H), 4.46 - 4.34 (m, 1H), 4.34 - 4.26 (m, 1H), 4.24 - 4.13 (m, 1H),

4.13 - 4.03 (m, 1H), 3.61 - 3.34 (m, 6H), 3.30 - 3.25 (m, 1H), 2.88 - 2.70 (m, 2H), 2.57 (d, *J*=1.5 Hz, 3H), 2.30 - 2.18 (m, 1H), 1.76 - 1.63 (m, 1H), 1.32 (dd, *J*=6.4, 10.0 Hz, 3H).

Example 28

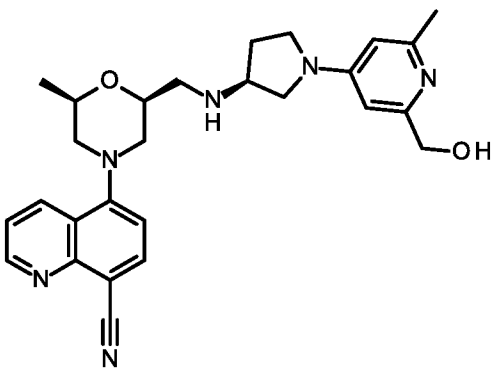
5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 26** by using *tert*-butyl N-[(3*R*)-pyrrolidin-3-yl]carbamate (CAS: 122536-77-0, Vendor: Accela ChemBio Inc) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 28** (15 mg) was obtained. MS: calc'd 473 (MH^+), measured 473 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.7, 4.2 Hz, 1H), 8.66 (dd, *J*=1.6, 8.6 Hz, 1H), 8.18 (d, *J*=7.9 Hz, 1H), 7.66 (dd, *J*=4.2, 8.6 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 6.79 (br d, *J*=5.4 Hz, 1H), 6.76 - 6.66 (m, 1H), 4.71 (s, 2H), 4.37 (br t, *J*=10.0 Hz, 1H), 4.26 - 4.13 (m, 2H), 4.08 - 3.98 (m, 1H), 3.92 - 3.80 (m, 2H), 3.80 - 3.61 (m, 1H), 3.52 - 3.40 (m, 3H), 3.31 - 3.26 (m, 1H), 2.86 - 2.73 (m, 2H), 2.72 - 2.61 (m, 1H), 2.57 (s, 3H), 2.51 - 2.39 (m, 1H), 1.33 (d, *J*=6.2 Hz, 3H).

Example 29

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

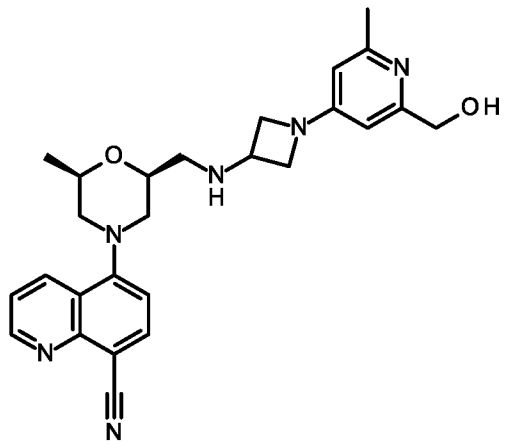


The title compound was prepared in analogy to the preparation of **Example 26** by using *tert*-butyl N-[(3*S*)-pyrrolidin-3-yl]carbamate (CAS: 122536-76-9, Vendor: Accela ChemBio Inc)

instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 29** (17 mg) was obtained. MS: calc'd 473 (MH^+), measured 473 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.6, 4.3 Hz, 1H), 8.67 (dd, *J*=1.7, 8.6 Hz, 1H), 8.19 (d, *J*=8.1 Hz, 1H), 7.67 (dd, *J*=4.2, 8.6 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 1H), 6.80 (br d, *J*=6.1 Hz, 1H), 6.71 (br d, *J*=14.4 Hz, 1H), 4.72 (s, 2H), 4.36 (br t, *J*=10.2 Hz, 1H), 4.26 - 4.14 (m, 2H), 4.07 (br d, *J*=10.4 Hz, 1H), 3.91 - 3.78 (m, 2H), 3.78 - 3.66 (m, 1H), 3.54 - 3.42 (m, 3H), 3.31 - 3.26 (m, 1H), 2.87 - 2.72 (m, 2H), 2.66 (dt, *J*=6.6, 13.8 Hz, 1H), 2.58 (s, 3H), 2.49 - 2.38 (m, 1H), 1.33 (d, *J*=6.2 Hz, 3H).

Example 30

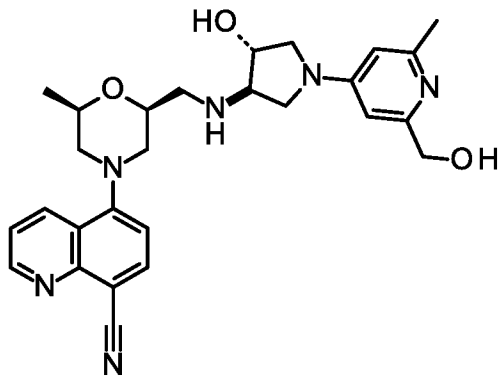
5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]azetidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 26** by using *tert*-butyl N-(azetidin-3-yl)carbamate (CAS: 91188-13-5, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 30** (7 mg) was obtained. MS: calc'd 459 (MH^+), measured 459 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.6, 4.3 Hz, 1H), 8.68 (dd, *J*=1.7, 8.6 Hz, 1H), 8.19 (d, *J*=8.1 Hz, 1H), 7.67 (dd, *J*=4.3, 8.6 Hz, 1H), 7.30 (d, *J*=7.9 Hz, 1H), 6.62 (d, *J*=2.2 Hz, 1H), 6.53 (d, *J*=2.0 Hz, 1H), 4.69 (s, 2H), 4.67 - 4.58 (m, 2H), 4.50 - 4.39 (m, 3H), 4.34 (br t, *J*=9.8 Hz, 1H), 4.25 - 4.14 (m, 1H), 3.51 - 3.42 (m, 2H), 3.40 - 3.35 (m, 1H), 3.23 (dd, *J*=9.6, 12.9 Hz, 1H), 2.86 - 2.71 (m, 2H), 2.55 (s, 3H), 1.34 (d, *J*=6.2 Hz, 3H).

Example 31

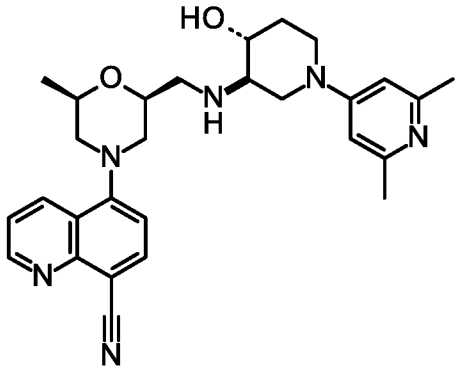
***trans*-5-[(2*S*,6*R*)-2-[[[4-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**



The title compound was prepared in analogy to the preparation of **Example 26** by using *trans-tert*-butyl N-(4-hydroxypyrrolidin-3-yl)carbamate (CAS: 870632-89-6, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 31** (6 mg) was obtained. MS: calc'd 489 (MH^+), measured 489 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 9.02 (td, *J*=1.6, 4.2 Hz, 1H), 8.67 (ddd, *J*=1.7, 6.8, 8.5 Hz, 1H), 8.19 (dd, *J*=1.3, 8.0 Hz, 1H), 7.67 (td, *J*=4.1, 8.4 Hz, 1H), 7.30 (dd, *J*=1.5, 8.0 Hz, 1H), 6.80 (s, 1H), 6.72 (br s, 1H), 4.77 - 4.71 (m, 3H), 4.40 - 4.32 (m, 1H), 4.20 - 3.92 (m, 4H), 3.88 - 3.75 (m, 1H), 3.59 - 3.42 (m, 4H), 3.40 - 3.35 (m, 1H), 2.85 - 2.72 (m, 2H), 2.58 (s, 3H), 1.33 (dd, *J*=2.2, 6.2 Hz, 3H).

Example 32

***trans*-5-[(2*S*,6*R*)-2-[[[1-(2,6-dimethyl-4-pyridyl)-4-hydroxy-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**

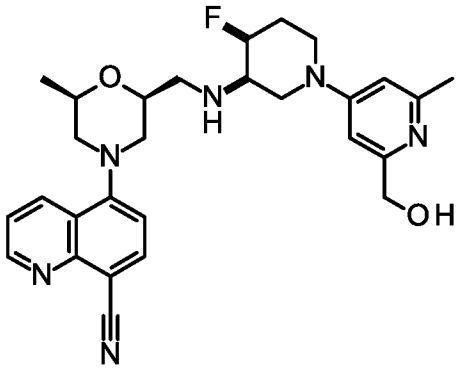


The title compound was prepared in analogy to the preparation of **Example 26** by using *trans-tert*-butyl N-(4-hydroxy-3-piperidyl)carbamate (CAS: 859854-68-5, Vendor: PharmaBlock) and 4-bromo-2,6-dimethyl-pyridine instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**) and (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**). **Example 32** (8 mg) was obtained. MS: calc'd 487 (MH^+), measured 487 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.6, 4.3 Hz, 1H), 8.67 (ddd, *J*=1.7, 3.1, 8.6 Hz, 1H),

8.19 (d, *J*=7.9 Hz, 1H), 7.67 (dd, *J*=4.3, 8.6 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 1H), 7.02 (d, *J*=8.6 Hz, 2H), 4.60 (br d, *J*=11.7 Hz, 1H), 4.44 - 4.26 (m, 2H), 4.26 - 4.14 (m, 1H), 4.14 - 4.00 (m, 1H), 3.57 - 3.40 (m, 4H), 3.38 - 3.35 (m, 1H), 3.31 - 3.20 (m, 2H), 2.89 - 2.70 (m, 2H), 2.54 (d, *J*=2.0 Hz, 6H), 2.30 - 2.19 (m, 1H), 1.75 - 1.62 (m, 1H), 1.32 (dd, *J*=6.2, 12.6 Hz, 3H).

Example 33

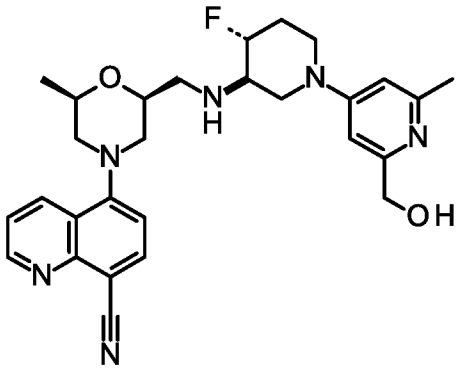
***cis*-5-[(2*S*,6*R*)-2-[[[4-fluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**



The title compound was prepared in analogy to the preparation of **Example 26** by using *cis-tert*-butyl N-(4-fluoro-3-piperidyl)carbamate (CAS: 1363382-99-3, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 33** (9 mg) was obtained. MS: calc'd 505 (MH^+), measured 505 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.6, 4.3 Hz, 1H), 8.68 (d, *J*=8.6 Hz, 1H), 8.19 (d, *J*=8.1 Hz, 1H), 7.67 (ddd, *J*=1.3, 4.3, 8.6 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 1H), 7.15 (s, 1H), 7.09 (d, *J*=2.6 Hz, 1H), 5.54 - 5.33 (m, 1H), 4.72 (s, 2H), 4.60 - 4.51 (m, 1H), 4.43 - 4.33 (m, 1H), 4.28 - 4.15 (m, 2H), 3.80 - 3.61 (m, 2H), 3.58 - 3.42 (m, 4H), 3.41 - 3.35 (m, 1H), 2.90 - 2.71 (m, 2H), 2.58 (s, 3H), 2.44 - 2.30 (m, 1H), 2.16 - 1.95 (m, 1H), 1.36 - 1.29 (m, 3H).

Example 34

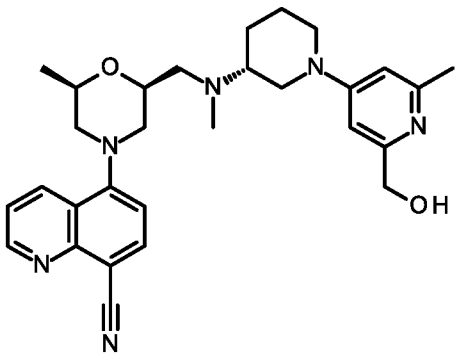
***trans*-5-[(2*S*,6*R*)-2-[[[4-fluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile**



The title compound was prepared in analogy to the preparation of **Example 26** by using *trans-tert*-butyl N-(4-fluoro-3-piperidyl)carbamate (CAS: 1052713-46-8, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 34** (5 mg) was obtained. MS: calc'd 505 (MH^+), measured 505 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.03 - 8.99 (m, 1H), 8.67 (ddd, *J*=1.7, 3.3, 8.6 Hz, 1H), 8.21 - 8.16 (m, 1H), 7.69 - 7.63 (m, 1H), 7.32 - 7.27 (m, 1H), 7.15 (dd, *J*=2.5, 6.3 Hz, 1H), 7.09 (dd, *J*=2.6, 10.1 Hz, 1H), 5.26 - 5.02 (m, 1H), 4.73 (s, 2H), 4.70 - 4.59 (m, 1H), 4.43 - 4.27 (m, 2H), 4.19 (ddd, *J*=2.0, 6.2, 10.0 Hz, 1H), 3.68 (dt, *J*=3.7, 9.8 Hz, 1H), 3.56 - 3.34 (m, 6H), 2.91 - 2.70 (m, 2H), 2.58 (s, 3H), 2.51 - 2.41 (m, 1H), 2.02 - 1.90 (m, 1H), 1.36 - 1.26 (m, 3H).

Example 35

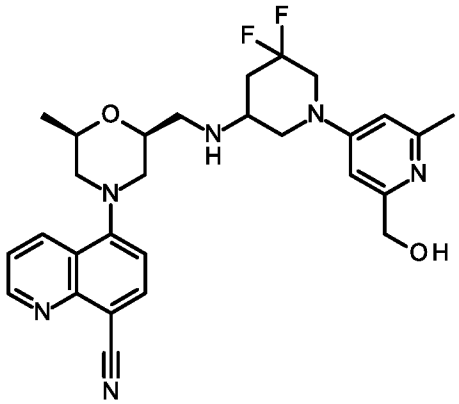
5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 26** by using *tert*-butyl N-methyl-N-[(3*R*)-3-piperidyl]carbamate (CAS: 309962-67-2, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 35** (5 mg) was obtained. MS: calc'd 501 (MH^+), measured 501 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.5, 4.2 Hz, 1H), 8.67 (dd, *J*=1.3, 8.6 Hz, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 7.65 (dd, *J*=4.3, 8.6 Hz, 1H), 7.28 (d, *J*=8.1 Hz, 1H), 7.14 - 7.08 (m, 1H), 7.07 - 7.02 (m, 1H), 4.72 (s, 2H), 4.63 (br d, *J*=12.6 Hz, 1H), 4.56 - 4.46 (m, 1H), 4.30 (br d, *J*=13.6 Hz, 1H), 4.24 - 4.15 (m, 1H), 3.69 - 3.39 (m, 6H), 3.30 - 3.15 (m, 1H), 3.11 (s, 3H), 2.85 - 2.70 (m, 2H), 2.62 - 2.52 (m, 3H), 2.42 - 2.31 (m, 1H), 2.11 (br d, *J*=14.1 Hz, 1H), 2.06 - 1.93 (m, 1H), 1.85 - 1.69 (m, 1H), 1.30 (d, *J*=6.2 Hz, 3H).

Example 36

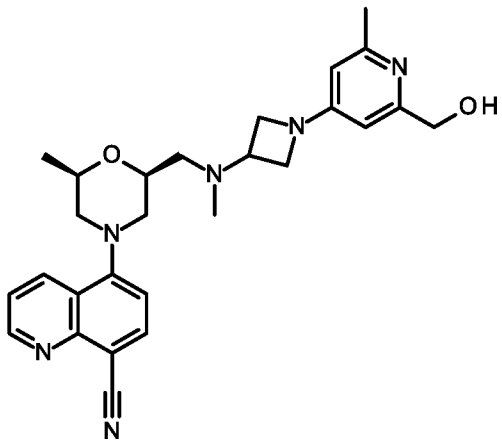
5-[(2*S*,6*R*)-2-[[[5,5-difluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 26** by using *tert*-butyl N-(5,5-difluoro-3-piperidyl)carbamate (CAS: 1303973-94-5, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 36** (9 mg) was obtained. MS: calc'd 523 (MH^+), measured 523 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.7, 4.2 Hz, 1H), 8.67 (dd, *J*=1.6, 8.6 Hz, 1H), 8.19 (d, *J*=8.1 Hz, 1H), 7.67 (dd, *J*=4.2, 8.6 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 1H), 7.25 (t, *J*=3.0 Hz, 1H), 7.20 (d, *J*=2.8 Hz, 1H), 4.75 (s, 2H), 4.66 - 4.55 (m, 2H), 4.42 - 4.31 (m, 1H), 4.22 - 4.13 (m, 1H), 3.85 - 3.66 (m, 2H), 3.66 - 3.55 (m, 1H), 3.51 - 3.39 (m, 3H), 3.38 - 3.34 (m, 1H), 2.94 - 2.72 (m, 3H), 2.61 (s, 3H), 2.52 - 2.32 (m, 1H), 1.33 (d, *J*=6.2 Hz, 3H).

Example 37

5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]azetidin-3-yl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

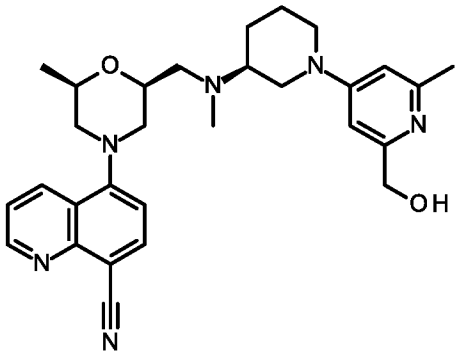


The title compound was prepared in analogy to the preparation of **Example 26** by using *tert*-butyl N-(azetidin-3-yl)-N-methyl-carbamate (CAS: 577777-20-9, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 37** (31 mg) was obtained. MS: calc'd 473 (MH^+), measured 473 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.6, 4.3 Hz, 1H), 8.69 (dd, *J*=1.7, 8.6 Hz, 1H), 8.17 (d, *J*=7.9

Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.28 (d, *J*=7.9 Hz, 1H), 6.63 (d, *J*=2.2 Hz, 1H), 6.53 (d, *J*=2.1 Hz, 1H), 4.69 (s, 2H), 4.66 - 4.46 (m, 6H), 4.25 - 4.16 (m, 1H), 3.51 - 3.40 (m, 2H), 3.39 - 3.35 (m, 2H), 3.07 (s, 3H), 2.84 - 2.70 (m, 2H), 2.55 (s, 3H), 1.32 (d, *J*=6.2 Hz, 3H).

Example 38

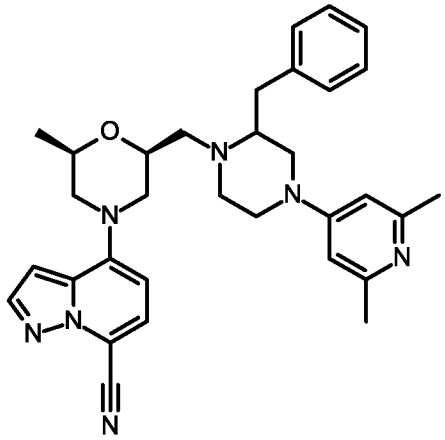
5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



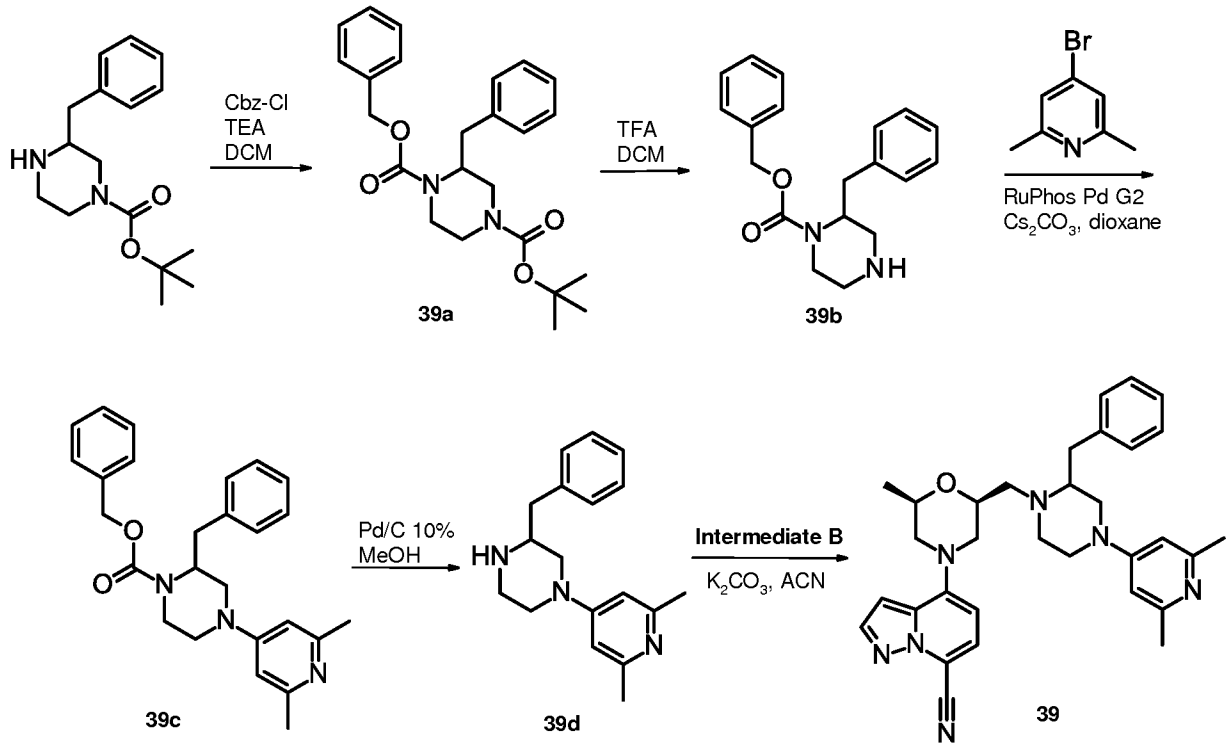
The title compound was prepared in analogy to the preparation of **Example 26** by using *tert*-butyl N-methyl-N-[(3*S*)-3-piperidyl]carbamate (CAS: 309962-63-8, Vendor: PharmaBlock) instead of *trans-tert*-butyl (3-hydroxypiperidin-4-yl)carbamate (compound **26a**). **Example 38** (13 mg) was obtained. MS: calc'd 501 (MH^+), measured 501 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.99 (dd, *J*=1.6, 4.2 Hz, 1H), 8.67 (dd, *J*=1.6, 8.6 Hz, 1H), 8.16 (d, *J*=7.9 Hz, 1H), 7.65 (dd, *J*=4.3, 8.6 Hz, 1H), 7.28 (d, *J*=8.1 Hz, 1H), 7.10 (d, *J*=2.6 Hz, 1H), 7.04 (d, *J*=2.6 Hz, 1H), 4.74 - 4.70 (m, 1H), 4.71 (s, 1H), 4.70 - 4.62 (m, 1H), 4.51 (br t, *J*=10.0 Hz, 1H), 4.33 - 4.14 (m, 2H), 3.69 - 3.38 (m, 6H), 3.29 - 3.15 (m, 1H), 3.10 (s, 3H), 2.84 - 2.70 (m, 2H), 2.63 - 2.50 (m, 3H), 2.40 - 2.27 (m, 1H), 2.16 - 1.95 (m, 2H), 1.82 - 1.68 (m, 1H), 1.31 (d, *J*=6.4 Hz, 3H).

Example 39

4-[(2*S*,6*R*)-2-[[2-benzyl-4-(2,6-dimethyl-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]pyrazolo[1,5-a]pyridine-7-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of benzyl 2-benzylpiperazine-1-carboxylate (compound 39b)

To a flask was added *tert*-butyl 3-benzylpiperazine-1-carboxylate (CAS: 502649-29-8, Vendor: BePharm, 300 mg, 1.09 mmol), TEA (330 mg, 454 μL, 3.26 mmol) and DCM (2 mL). Then it was cooled with ice bath and Cbz-Cl (278 mg, 232 μL, 1.63 mmol) was added drop-wise. After being warmed to rt slowly and stirred for 2 hrs, the reaction mixture was diluted with 20 mL water and extracted with EA (15 mL) twice, the organic layer was dried over Na_2SO_4 and concentrated to give a brown oil. After purification by flash column (EA/PE= 0 to 20%), the compound **39a** (268 mg) was obtained as an oil. MS: calc'd 411 (MH^+), measured 411 (MH^+).

The compound **39a** was dissolved in DCM (2 mL) and TFA (124 mg, 84 μL, 1.09 mmol). The mixture was stirred at rt for 2 hrs, and then concentrated directly to give compound **39b** (200 mg) as an oil. MS: calc'd 311 (MH^+), measured 311 (MH^+).

Step 2: preparation of 3-benzyl-1-(2,6-dimethyl-4-pyridyl)piperazine (compound 39d)

To a flask was added benzyl 2-benzylpiperazine-1-carboxylate (compound **39b**, 65 mg, 209 μmol), 4-bromo-2,6-dimethylpyridine (39 mg, 209 μmol), Cs_2CO_3 (205 mg, 628 μmol) and 1,4-dioxane (5 mL), the suspension was bubbled with N_2 for 5 mins and Ruphos Pd G2 (16 mg, 21 μmol) was added. The mixture was heated to 90 °C and stirred for 12 hrs. After being cooled down, the mixture was diluted with 10 mL EA and filtered through celite, and the filtrate was concentrated to give a yellow oil, which was purified by flash column (EA/PE=0 to 100% & MeOH/EA=10%), the elution was concentrated to give compound **39c** (52 mg) as an oil. MS: calc'd 416 (MH^+), measured 416 (MH^+).

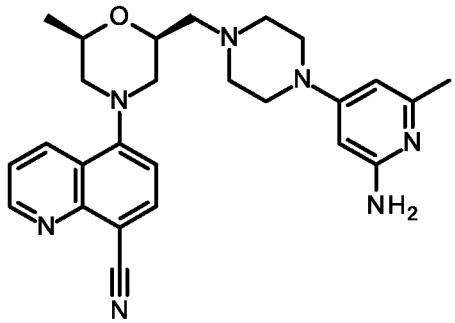
To a flask containing benzyl 2-benzyl-4-(2,6-dimethyl-4-pyridyl)piperazine-1-carboxylate (compound **39c**, 26 mg, 63 μmol) was added Pd/C (10 wt.%, 10 mg, 71 μmol) and MeOH (5 mL). The reaction mixture was stirred at r.t. under hydrogen balloon for 2 hrs, then filtered through celite, and the filtrate was concentrated to give compound **39d** (17 mg) as a semi-solid. MS: calc'd 282 (MH^+), measured 282 (MH^+).

Step 3: preparation of 4-[(2*S*,6*R*)-2-[[2-benzyl-4-(2,6-dimethyl-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]pyrazolo[1,5-a]pyridine-7-carbonitrile (Example 39)

To a tube was added [(2*R*,6*R*)-4-(7-cyanopyrazolo[1,5-a]pyridin-4-yl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **B**, 20 mg, 50 μmol), potassium carbonate (27 mg, 198 μmol), 3-benzyl-1-(2,6-dimethyl-4-pyridyl)piperazine (compound **39d**, 21 mg, 74 μmol) and ACN (4 mL). The suspension was heated to reflux for 2 hrs. After being cooled down, the mixture was diluted with some ACN and filtered through celite, the filtrate was concentrated to give a yellow solid which was purified by prep-HPLC to give **Example 39** (2 mg) as a light yellow powder. MS: calc'd 536 (MH^+), measured 536 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.61 - 8.47 (m, 1H), 8.03 (s, 1H), 7.51 - 7.45 (m, 1H), 7.33 - 7.15 (m, 5H), 6.84 (t, *J*=2.8 Hz, 1H), 6.56 (dd, *J*=2.3, 7.9 Hz, 2H), 3.98 - 3.88 (m, 1H), 3.81 - 3.69 (m, 2H), 3.53 - 3.39 (m, 1H), 3.26 - 3.20 (m, 2H), 3.19 - 3.07 (m, 3H), 3.06 - 2.86 (m, 3H), 2.86 - 2.72 (m, 2H), 2.72 - 2.58 (m, 3H), 2.45 - 2.36 (m, 6H), 1.28 (dd, *J*=3.6, 6.2 Hz, 3H).

Example 40

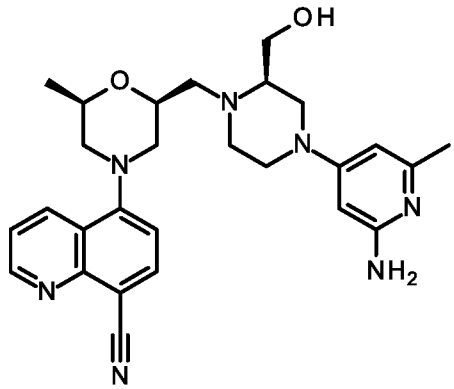
5-[(2*S*,6*R*)-2-[[4-(2-amino-6-methyl-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 19** by using 4-chloro-6-methylpyridin-2-amine (CAS: 5600-21-5, Vendor: Accela ChemBio Inc) instead of 4-chloropyridin-2-amine (compound **19a**). **Example 40** (39 mg) was obtained as a light yellow powder. MS: calc'd 458 (MH^+), measured 458 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.7, 4.2 Hz, 1H), 8.67 (dd, *J*=1.6, 8.6 Hz, 1H), 8.18 (d, *J*=7.9 Hz, 1H), 7.67 (dd, *J*=4.3, 8.6 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 1H), 6.51 (d, *J*=1.7 Hz, 1H), 6.02 (d, *J*=2.2 Hz, 1H), 4.55 - 4.45 (m, 1H), 4.25 - 4.16 (m, 1H), 3.87 (br s, 4H), 3.74 - 3.48 (m, 4H), 3.47 - 3.38 (m, 4H), 2.84 - 2.70 (m, 2H), 2.40 (s, 3H), 1.33 (d, *J*=6.2 Hz, 3H).

Example 41

5-[(2*S*,6*R*)-2-[[(2*R*)-4-(2-amino-6-methyl-4-pyridyl)-2-(hydroxymethyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

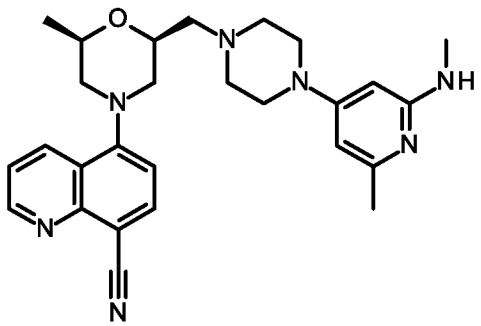


The title compound was prepared in analogy to the preparation of **Example 19** by using 4-chloro-6-methylpyridin-2-amine and *tert*-butyl (2*R*)-2-(hydroxymethyl)piperazine-1-carboxylate (CAS: 169448-87-7, Vendor: BePharm) instead of 4-chloropyridin-2-amine (compound **19a**) and *tert*-butyl piperazine-1-carboxylate. **Example 41** (12 mg) was obtained as a light yellow powder. MS: calc'd 488 (MH^+), measured 488 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.99 (dd, *J*=1.5, 4.2 Hz, 1H), 8.68 (dd, *J*=1.6, 8.6 Hz, 1H), 8.17 (d, *J*=7.9 Hz, 1H), 7.65 (dd, *J*=4.2, 8.6 Hz, 1H), 7.27 (d, *J*=8.2 Hz, 1H), 6.18 (s, 1H), 5.85 (d, *J*=2.2 Hz, 1H), 4.23 - 4.14 (m, 1H), 4.14 - 4.07 (m, 1H), 3.75 - 3.67 (m, 2H), 3.64 - 3.58 (m, 1H), 3.54 - 3.44 (m, 3H), 3.44 - 3.37 (m,

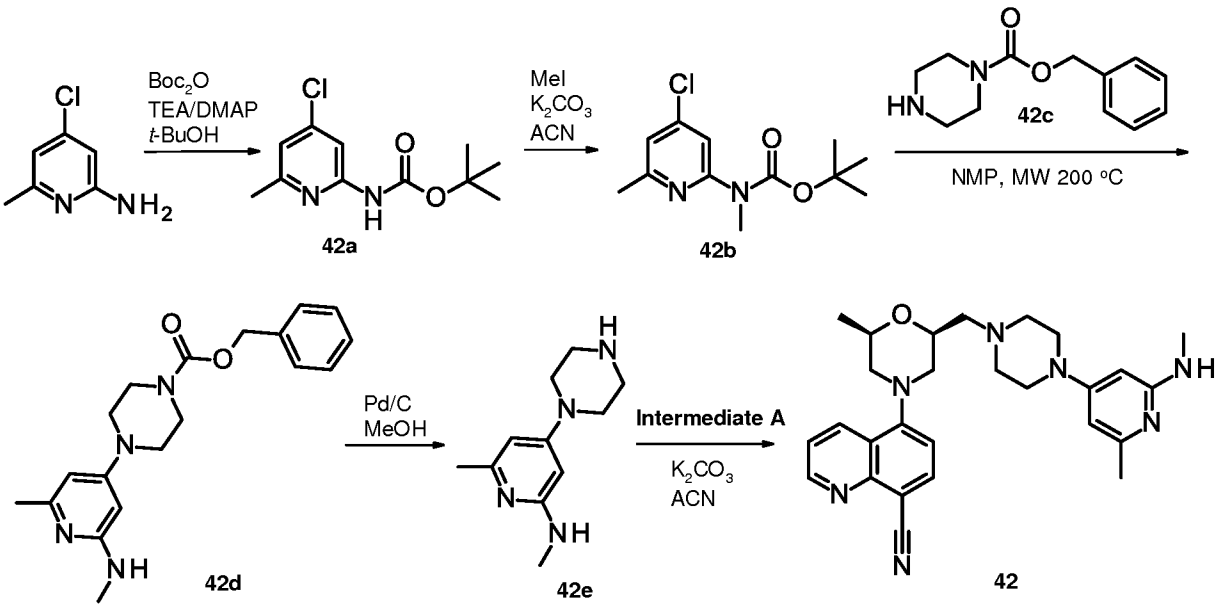
2H), 3.19 - 3.10 (m, 2H), 3.00 (dd, *J*=7.0, 14.0 Hz, 1H), 2.77 - 2.67 (m, 3H), 2.65 - 2.57 (m, 1H), 2.25 (s, 3H), 1.28 (d, *J*=6.2 Hz, 3H).

Example 42

5-[(2*R*,6*S*)-2-methyl-6-[[4-[2-methyl-6-(methylamino)-4-pyridyl]piperazin-1-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl N-(4-chloro-6-methyl-2-pyridyl)carbamate (compound 42a)

To a flask was added 4-chloro-6-methylpyridin-2-amine (200 mg, 1.40 mmol), *t*-BuOH (5 mL), DMAP (17 mg, 140 μmol), TEA (284 mg, 391 μL, 2.81 mmol) and Boc_2O (459 mg, 2.10 mmol). After being stirred at rt for 12 hrs, the mixture was concentrated to give an oil and purified by flash column (EA/PE=0 to 20%) to give compound **42a** (307 mg) as a colorless oil. MS: calc'd 243 (MH^+), measured 243 (MH^+).

Step 2: preparation of *tert*-butyl N-(4-chloro-6-methyl-2-pyridyl)-N-methyl-carbamate (compound 42b)

To a flask was added *tert*-butyl N-(4-chloro-6-methyl-2-pyridyl)carbamate (compound **42a**, 100 mg, 412 μmol) and THF (4 mL), the solution was cooled with ice bath and NaH on oil (60%, 82.4 mg, 2.06 mmol) was added. After being stirred for 10 mins, the reaction mixture was added with iodomethane (234 mg, 1.65 mmol), then warmed to rt slowly and stirred for another 12 hrs. The reaction mixture was quenched with water and extracted with EA (15 mL) three times, the organic layer was dried over Na_2SO_4 and concentrated to give a yellow oil, which was purified by flash column (EA/PE=0 to 5%) to give compound **42b** (87 mg) as an oil. MS: calc'd 257 (MH^+), measured 257 (MH^+).

Step 3: preparation of benzyl 4-[2-methyl-6-(methylamino)-4-pyridyl]piperazine-1-carboxylate (compound 42d)

To a microwave tube was added *tert*-butyl N-(4-chloro-6-methyl-2-pyridyl)-N-methyl-carbamate (compound **42b**, 87 mg, 339 μmol), benzyl piperazine-1-carboxylate (compound **42c**, 97 mg, 441 μmol) and NMP (5 mL), the tube was sealed and stirred under microwave at 200 °C for 30 mins. After being cooled down, the mixture was poured into 20 mL water and adjusted to pH > 7, then it was extracted with DCM (15 mL) twice, the organic layer was dried and concentrated to give a brown crude product which was purified by flash column (EA/PE= 0 to 100% & MeOH/DCM=20%) to give compound **42d** as a brown oil (80 mg). MS: calc'd 341 (MH^+), measured 341 (MH^+).

Step 4: preparation of N,6-dimethyl-4-piperazin-1-yl-pyridin-2-amine (compound 42e)

To a flask was added benzyl 4-[2-methyl-6-(methylamino)-4-pyridyl]piperazine-1-carboxylate (compound **42d**, 80 mg, 235 μmol), Pd/C (10 wt.%, 10 mg, 71 μmol) and MeOH (2 mL), the solution was purged with H_2 for 3 times and stirred at rt for 2 hrs. Then the mixture was filtered and concentrated to give compound **42e** (50 mg) as an oil. MS: calc'd 207 (MH^+), measured 207 (MH^+).

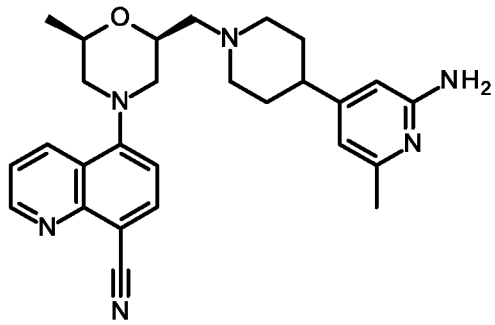
Step 5: preparation of 5-[(2*R*,6*S*)-2-methyl-6-[[4-[2-methyl-6-(methylamino)-4-pyridyl]piperazin-1-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile (Example 42)

To a flask was added [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **A**, 50 mg, 120 μmol), N,6-dimethyl-4-piperazin-1-yl-pyridin-2-amine (compound **42e**, 25 mg, 120 μmol), potassium carbonate (50 mg, 361 μmol) and ACN (4 mL), the mixture was stirred at 85 °C for 2 hrs. Then the mixture was cooled down and filtered through celite, the filtrate was concentrated to give a yellow oil which was purified by

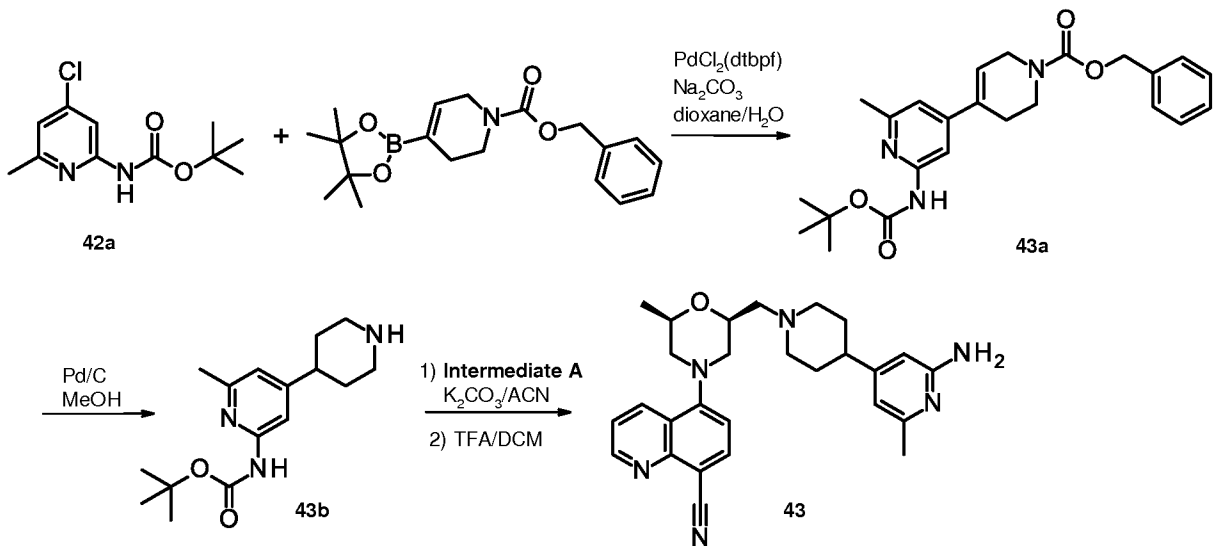
prep-HPLC to give **Example 42** (31 mg) as a light yellow powder. MS: calc'd 472 (MH^+), measured 472 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.99 (dd, *J*=1.7, 4.2 Hz, 1H), 8.66 (dd, *J*=1.7, 8.6 Hz, 1H), 8.16 (d, *J*=7.9 Hz, 1H), 7.65 (dd, *J*=4.3, 8.6 Hz, 1H), 7.28 (d, *J*=7.9 Hz, 1H), 6.48 (d, *J*=1.5 Hz, 1H), 5.93 (d, *J*=2.2 Hz, 1H), 4.50 (dt, *J*=5.3, 7.7 Hz, 1H), 4.24 - 4.14 (m, 1H), 4.06 - 3.71 (m, 4H), 3.65 - 3.46 (m, 4H), 3.45 - 3.36 (m, 4H), 2.96 (s, 3H), 2.83 - 2.69 (m, 2H), 2.40 (s, 3H), 1.32 (d, *J*=6.2 Hz, 3H).

Example 43

5-[(*2S,6R*)-2-[[4-(2-amino-6-methyl-4-pyridyl)-1-piperidyl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of benzyl 4-[2-(*tert*-butoxycarbonylamino)-6-methyl-4-pyridyl]-3,6-dihydro-2H-pyridine-1-carboxylate (compound 43a)

To a tube was added *tert*-butyl N-(4-chloro-6-methyl-2-pyridyl)-N-methyl-carbamate (compound **42a**, 85 mg, 350 µmol), benzyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (CAS: 286961-15-7, Vendor: Bidepharm, 180 mg, 525 µmol), sodium carbonate (111 mg, 1.05 mmol), 1,4-dioxane (4 mL) and water (0.40 mL), the

suspension was bubbled with N_2 for 5 mins and 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (23 mg, 35 μmol) was added. After being stirred at 90 °C for 16 hrs, the mixture was cooled down and filtered, the filtrate was concentrated to give an oil which was purified by flash column (EA/PE=0 to 35%) to give compound **43a** (112 mg) as an oil. MS: calc'd 424 (MH^+), measured 424 (MH^+).

Step 2: preparation of *tert*-butyl N-[6-methyl-4-(4-piperidyl)-2-pyridyl]carbamate (compound 43b)

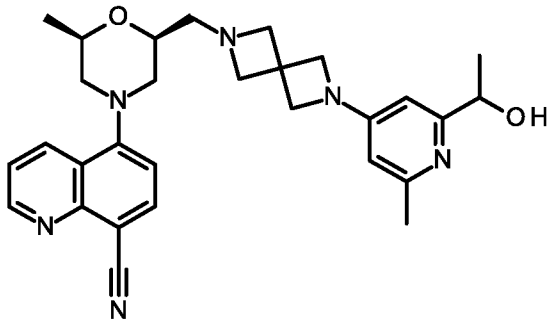
The compound **43a** was dissolved in MeOH (4 mL) and Pd/C (10 wt.%, 15 mg, 107 μmol) was added. The mixture was sucking in vacuum and purged with H_2 for 3 times, then it was stirred at rt for 2 hrs. The mixture was filtered and the filtrate was concentrated to give compound **43b** (76 mg) as an oil. MS: calc'd 292 (MH^+), measured 292 (MH^+).

Step 3: preparation of 5-[(2*S*,6*R*)-2-[[4-(2-amino-6-methyl-4-pyridyl)-1-piperidyl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (Example 43)

To a flask was added [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **A**, 50 mg, 120 μmol), *tert*-butyl N-[6-methyl-4-(4-piperidyl)-2-pyridyl]carbamate (compound **43b**, 42 mg, 144 μmol), potassium carbonate (50 mg, 361 μmol) and ACN (4 mL), the mixture was stirred at 85 °C for 2 hrs. Then the mixture was cooled down and filtered through celite, the filtrate was concentrated to give a yellow oil. The oil was dissolved in DCM (2 mL) and TFA (738 mg, 500 μL, 6.47 mmol), then it was stirred at rt for 2 hrs. The mixture was concentrated directly to give an oil which was purified via prep-HPLC to give **Example 43** (19 mg) as a light yellow powder. MS: calc'd 457 (MH^+), measured 457 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.02 (dd, *J*=1.7, 4.2 Hz, 1H), 8.69 (dd, *J*=1.6, 8.6 Hz, 1H), 8.19 (d, *J*=7.9 Hz, 1H), 7.67 (dd, *J*=4.2, 8.6 Hz, 1H), 7.31 (d, *J*=8.1 Hz, 1H), 6.80 - 6.69 (m, 2H), 4.58 - 4.47 (m, 1H), 4.26 - 4.15 (m, 1H), 3.95 - 3.81 (m, 2H), 3.45 (br d, *J*=11.4 Hz, 2H), 3.38 (br d, *J*=6.2 Hz, 2H), 3.31 - 3.18 (m, 2H), 3.05 - 2.94 (m, 1H), 2.85 - 2.70 (m, 2H), 2.50 (s, 3H), 2.27 - 1.97 (m, 4H), 1.34 (d, *J*=6.2 Hz, 3H).

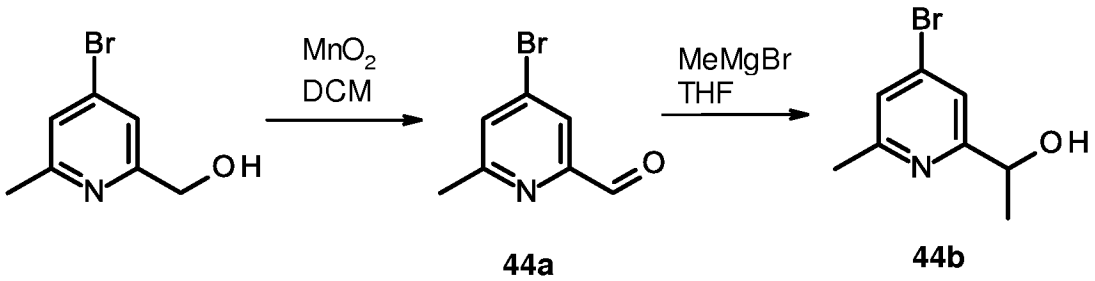
Example 44

5-[(2*S*,6*R*)-2-[[2-[2-(1-hydroxyethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 1-(4-bromo-6-methyl-2-pyridyl)ethanol (compound **44b**) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**). **Example 44** (17 mg) was obtained as a light yellow powder. MS: calc'd 499 (MH^+), measured 499 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.5, 4.2 Hz, 1H), 8.65 (dd, *J*=1.5, 8.6 Hz, 1H), 8.16 (d, *J*=7.9 Hz, 1H), 7.66 (dd, *J*=4.2, 8.6 Hz, 1H), 7.27 (d, *J*=7.9 Hz, 1H), 6.49 (d, *J*=2.1 Hz, 1H), 6.40 (d, *J*=1.7 Hz, 1H), 4.45 - 4.37 (m, 4H), 4.23 - 4.02 (m, 6H), 3.43 - 3.39 (m, 1H), 3.37 (s, 4H), 2.76 (br t, *J*=11.0 Hz, 1H), 2.68 (br t, *J*=11.1 Hz, 1H), 2.51 (s, 3H), 1.51 (d, *J*=6.6 Hz, 3H), 1.29 (d, *J*=6.1 Hz, 3H).

The compound **44b** was prepared according to the following scheme:



44a **44b**

Step 1: preparation of 4-bromo-6-methyl-pyridine-2-carbaldehyde (compound 44a)

To a flask was added (4-bromo-6-methyl-2-pyridyl)methanol (500 mg, 2.47 mmol), manganese dioxide (1.08 g, 12.40 mmol) and DCM (10 mL), a dark suspension was formed. The mixture was heated to reflux and stirred for 10 hrs. Then it was cooled and filtered, the filtrate was concentrated to give compound **44a** (372 mg) as a white solid. MS: calc'd 200 (MH^+), measured 200 (MH^+).

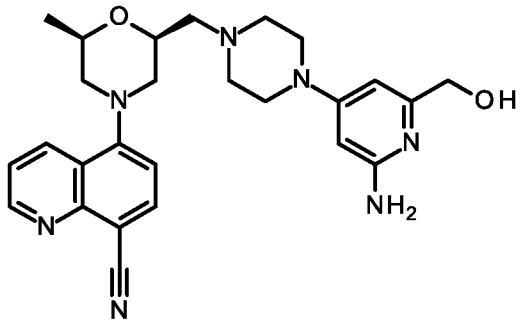
Step 2: preparation of 1-(4-bromo-6-methyl-2-pyridyl)ethanol (compound 44b)

To a flask was added 4-bromo-6-methyl-pyridine-2-carbaldehyde (compound **44a**, 100 mg, 500 µmol) and THF (3 mL), a pale yellow solution was formed, then it was cooled with dry ice/ethanol bath and methylmagnesium bromide (1 M in THF, 1 mL, 1.00 mmol) was added portion wise. The mixture was warmed to rt slowly and stirred for 2 hrs. Then it was quenched with sat. NH_4Cl and diluted with 20 mL water. The mixture was extracted with EA (20 mL)

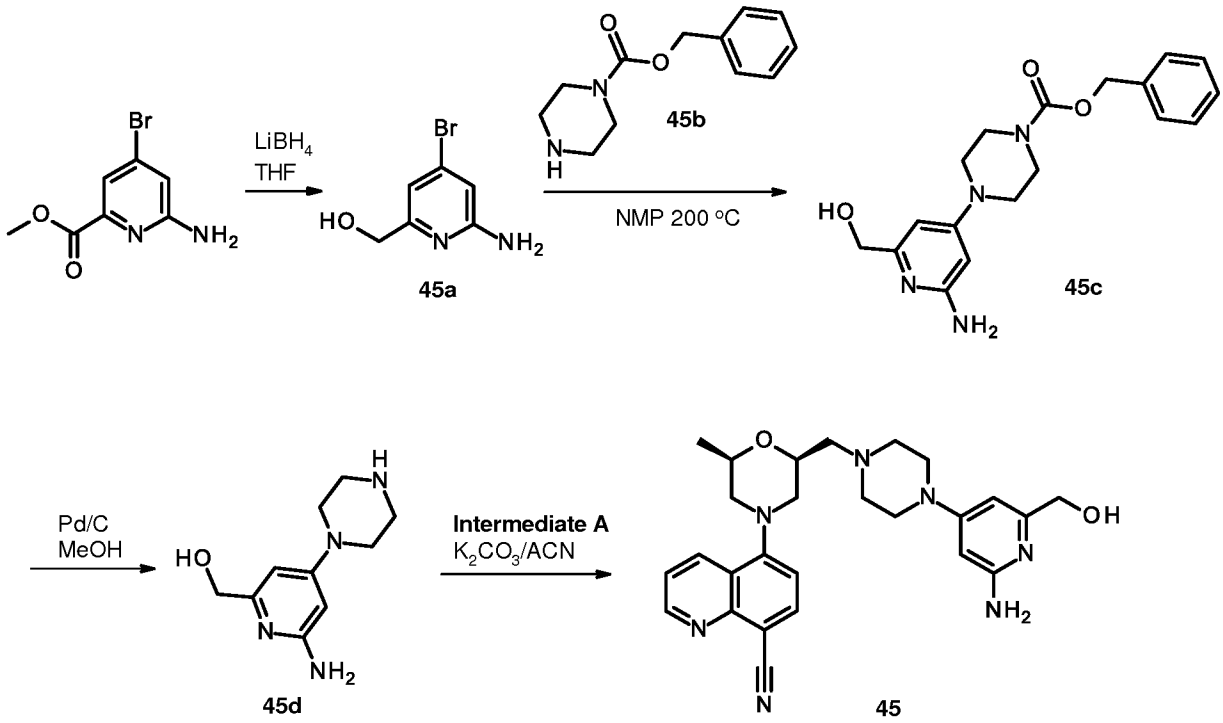
twice, the organic layer was dried over Na_2SO_4 and concentrated to give compound **44b** (105 mg) as a crude oil. MS: calc'd 216 (MH^+), measured 216 (MH^+).

Example 45

5-[(2*S*,6*R*)-2-[[4-[2-amino-6-(hydroxymethyl)-4-pyridyl]piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared according to the following scheme:



Step 1: preparation of (6-amino-4-bromo-2-pyridyl)methanol (compound 45a)

To a microwave tube was added methyl 6-amino-4-bromopicolinate (CAS: 885326-88-5, Vendor: PharmBlock, 231 mg, 1.00 mmol), THF (3 mL) and $LiBH_4$ (2 M in THF, 1 mL, 2.00 mmol). After being stirred at 65 °C for 2 hrs under microwave, the reaction was quenched by adding $Na_2SO_4 \cdot 10H_2O$ and the mixture was stirred at rt for another hour. Then it was filtered through celite and the filtrate was concentrated to give compound **45a** (230 mg) as a crude oil. MS: calc'd 203 (MH^+), measured 203 (MH^+).

Step 2: preparation of benzyl 4-[2-amino-6-(hydroxymethyl)-4-pyridyl]piperazine-1-carboxylate (compound 45c)

To a microwave tube was added (6-amino-4-bromo-2-pyridyl)methanol (compound **45a**, 80 mg, 394 μmol), benzyl piperazine-1-carboxylate (compound **45b**, 87 mg, 394 μmol) and NMP (4 mL), the tube was sealed and stirred under microwave at 200 °C for 1 h. After being cooled down, the mixture was purified via prep-HPLC to give compound **45c** (25 mg) as a pale yellow powder. MS: calc'd 343 (MH^+), measured 343 (MH^+).

Step 3: preparation of (6-amino-4-piperazin-1-yl-2-pyridyl)methanol (compound 45d)

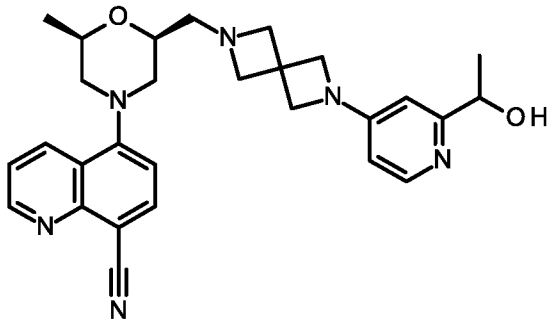
The compound **45c** was dissolved in MeOH (4 mL) and Pd/C (10 wt.%, 10 mg, 71 μmol) was added. The mixture was purged with H_2 for 3 times, and then stirred at rt for 2 hrs. The mixture was filtered and the filtrate was concentrated to give compound **45d** (15 mg) as an oil. MS: calc'd 209 (MH^+), measured 209 (MH^+).

Step 4: preparation of 5-[(2*S*,6*R*)-2-[[4-[2-amino-6-(hydroxymethyl)-4-pyridyl]piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile (Example 45)

To a flask was added [(2*R*,6*R*)-4-(8-cyano-5-quinolyl)-6-methyl-morpholin-2-yl]methyl trifluoromethanesulfonate (Intermediate **A**, 28 mg, 67 μmol), (6-amino-4-piperazin-1-yl-2-pyridyl)methanol (compound **45d**, 14 mg, 67 μmol), potassium carbonate (19 mg, 135 μmol) and ACN (4 mL), the mixture was stirred at 85 °C for 2 hrs. After being cooled down, the mixture was filtered, and the filtrate was concentrated to give a yellow oil which was purified by prep-HPLC to give **Example 45** (20 mg) as a light yellow powder. MS: calc'd 474 (MH^+), measured 474 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.6, 4.3 Hz, 1H), 8.66 (dd, *J*=1.7, 8.6 Hz, 1H), 8.17 (d, *J*=7.9 Hz, 1H), 7.65 (dd, *J*=4.3, 8.6 Hz, 1H), 7.28 (d, *J*=8.1 Hz, 1H), 6.58 (d, *J*=2.3 Hz, 1H), 6.07 (d, *J*=2.4 Hz, 1H), 4.60 (s, 2H), 4.55 - 4.47 (m, 1H), 4.24 - 4.14 (m, 1H), 3.89 (br s, 4H), 3.59 (br s, 4H), 3.46 - 3.39 (m, 4H), 2.83 - 2.76 (m, 1H), 2.76 - 2.68 (m, 1H), 1.32 (d, *J*=6.2 Hz, 3H).

Example 46

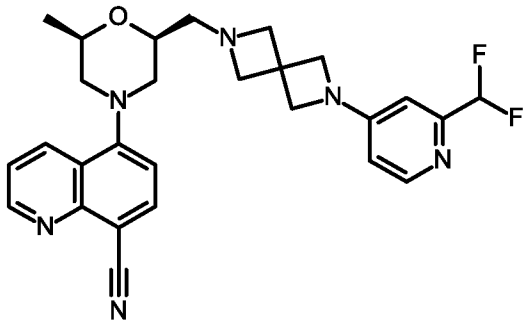
5-[(2*S*,6*R*)-2-[[2-[2-(1-hydroxyethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 1-(4-bromo-2-pyridyl)ethanol (CAS: 1471260-48-6, Vendor: Accela ChemBio Inc) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**). **Example 46** (31 mg) was obtained as a light yellow powder. MS: calc'd 485 (MH^+), measured 485 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.6, 4.3 Hz, 1H), 8.66 (dd, *J*=1.6, 8.6 Hz, 1H), 8.18 (d, *J*=7.9 Hz, 1H), 8.02 (d, *J*=7.2 Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 6.65 - 6.56 (m, 2H), 4.97 - 4.91 (m, 1H), 4.68 - 4.39 (m, 8H), 4.29 (br t, *J*=9.7 Hz, 1H), 4.19 - 4.09 (m, 1H), 3.53 - 3.47 (m, 1H), 3.46 - 3.37 (m, 3H), 2.78 (dd, *J*=10.5, 11.7 Hz, 1H), 2.71 (dd, *J*=10.3, 12.2 Hz, 1H), 1.52 (d, *J*=6.6 Hz, 3H), 1.31 (d, *J*=6.2 Hz, 3H).

Example 47

5-[(2*S*,6*R*)-2-[[2-[2-(difluoromethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile

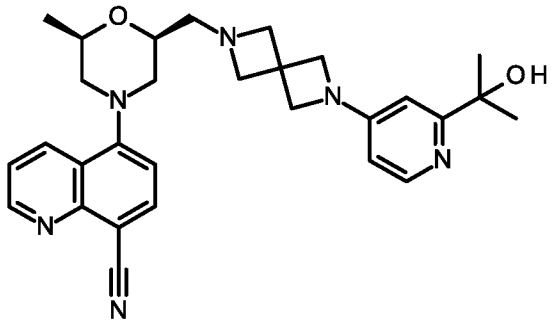


The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2-(difluoromethyl)pyridine (CAS: 1211580-54-9, Vendor: BePharm) instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**). **Example 47** (5 mg) was obtained as a yellow powder. MS: calc'd 491 (MH^+), measured 491 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.00 (dd, *J*=1.7, 4.2 Hz, 1H), 8.65 (dd, *J*=1.7, 8.6 Hz, 1H), 8.17 (dd, *J*=5.2, 7.4 Hz, 2H), 7.65 (dd, *J*=4.3, 8.6 Hz, 1H), 7.28 (d, *J*=8.1 Hz, 1H), 7.07 - 6.78 (m, 2H), 6.71 (dd, *J*=2.4, 6.8 Hz, 1H), 4.71 - 4.41 (m, 8H), 4.27 (br t, *J*=9.8 Hz, 1H), 4.18 - 4.09 (m, 1H), 3.53 -

3.46 (m, 1H), 3.45 - 3.36 (m, 3H), 2.81 - 2.73 (m, 1H), 2.69 (dd, *J*=10.3, 12.0 Hz, 1H), 1.30 (d, *J*=6.2 Hz, 3H).

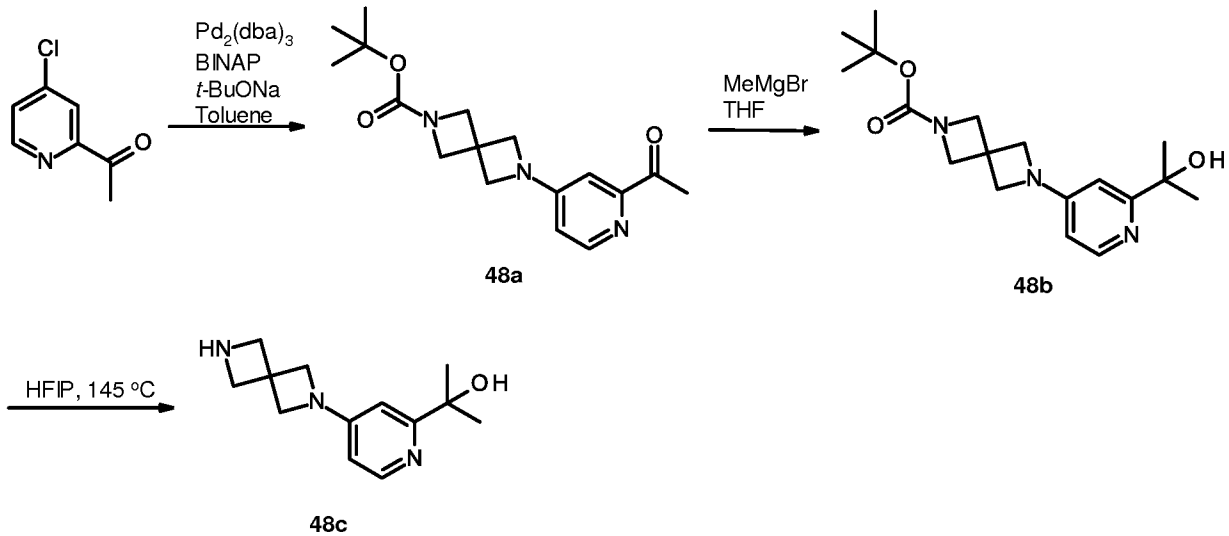
Example 48

5-[(2*S*,6*R*)-2-[[2-[2-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 2-[4-(2,6-diazaspiro[3.3]heptan-2-yl)-2-pyridyl]propan-2-ol (compound **48c**) instead of [4-(2,6-diazaspiro[3.3]heptan-2-yl)-6-methyl-2-pyridyl]methanol;2,2,2-trifluoroacetic acid (compound **1d**). **Example 48** (2 mg) was obtained as a yellow solid. MS: calc'd 499 (MH^+), measured 499 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.7, 4.2 Hz, 1H), 8.66 (dd, *J*=1.7, 8.6 Hz, 1H), 8.18 (d, *J*=7.9 Hz, 1H), 8.00 (d, *J*=7.2 Hz, 1H), 7.66 (dd, *J*=4.3, 8.6 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 6.67 - 6.56 (m, 2H), 4.55 (br s, 8H), 4.31 - 4.22 (m, 1H), 4.18 - 4.09 (m, 1H), 3.49 - 3.36 (m, 4H), 2.78 (t, *J*=11.1 Hz, 1H), 2.70 (dd, *J*=10.3, 12.0 Hz, 1H), 1.60 (s, 6H), 1.31 (d, *J*=6.2 Hz, 3H).

The compound **48c** was prepared according to the following scheme:



Step 1: preparation of *tert*-butyl 6-(2-acetyl-4-pyridyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (compound 48a)

To a microwave tube was added 1-(4-chloro-2-pyridyl)ethanone (CAS: 60159-37-7, Vendor: BePharm, 150 mg, 964 μmol), *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate hemioxalate (328 mg, 675 μmol), sodium *tert*-butoxide (278 mg, 2.89 mmol) and toluene (4 mL), the suspension was bubbled with N_2 for 5 mins and $Pd_2(dba)_3$ (88 mg, 96 μmol) and 2,2'-bis(diphenylphosphaneyl)-1,1'-binaphthalene (120 mg, 193 μmol) were added. The tube was sealed and stirred at 100 °C for 12 hrs. After being cooled down, the mixture was diluted with 10 mL EA and filtered through celite. The filtrate was concentrated to give a brown oil which was purified by flash column (EA/PE=0 to 100%) to give compound **48a** (85 mg) as a yellow oil. MS: calc'd 318 (MH^+), measured 318 (MH^+).

Step 2: preparation of *tert*-butyl 6-[2-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (compound 48b)

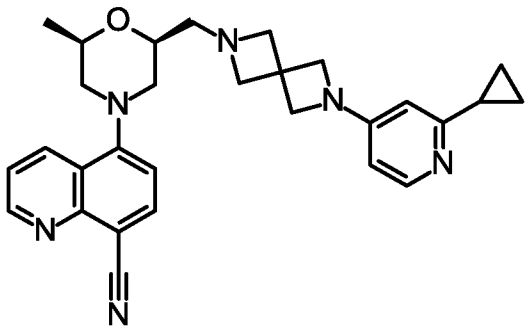
To a flask was added *tert*-butyl 6-(2-acetyl-4-pyridyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (compound **48a**, 85 mg, 268 μmol) and THF (2 mL). After being cooled with dry ice/ethanol bath, the mixture was added with methylmagnesium bromide (3M in Et_2O, 402 μL, 1.21 mmol) portion wise, then warmed to rt slowly and stirred for 2 hrs. Then it was quenched with sat. NH_4Cl and diluted with 20 mL water. The mixture was extracted with EA (20 mL) twice and DCM (15 mL) twice, and the combined organic layer was dried over Na_2SO_4 and concentrated to give compound **48b** (70 mg) as an oil. MS: calc'd 334 (MH^+), measured 334 (MH^+).

Step 3: preparation of 2-[4-(2,6-diazaspiro[3.3]heptan-2-yl)-2-pyridyl]propan-2-ol (compound 48c)

The compound **48b** was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (6.48 g, 4 mL, 38.50 mmol) and heated under microwave at 140 °C for 40 mins. Then the mixture was concentrated directly to give compound **48c** (50 mg) as a brown oil. MS: calc'd 234 (MH^+), measured 234 (MH^+).

Example 49

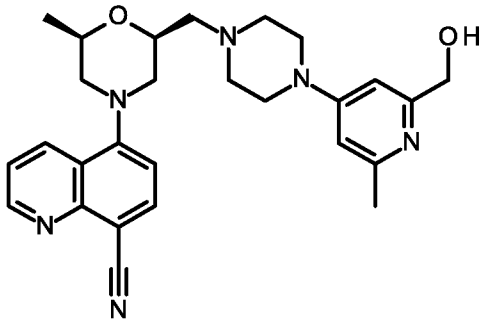
5-[(2*S*,6*R*)-2-[[2-(2-cyclopropyl-4-pyridyl)-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using 4-bromo-2-cyclopropylpyridine instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**). **Example 49** (25 mg) was obtained as a yellow solid. MS: calc'd 481 (MH^+), measured 481 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 8.99 (dd, *J*=1.6, 4.3 Hz, 1H), 8.65 (dd, *J*=1.6, 8.6 Hz, 1H), 8.16 (d, *J*=8.1 Hz, 1H), 7.92 (d, *J*=7.1 Hz, 1H), 7.65 (dd, *J*=4.3, 8.6 Hz, 1H), 7.27 (d, *J*=8.1 Hz, 1H), 6.50 (br d, *J*=4.9 Hz, 1H), 6.26 (s, 1H), 4.64 - 4.38 (m, 8H), 4.26 (br t, *J*=9.5 Hz, 1H), 4.17 - 4.08 (m, 1H), 3.50 - 3.45 (m, 1H), 3.45 - 3.42 (m, 1H), 3.41 - 3.36 (m, 2H), 2.80 - 2.73 (m, 1H), 2.69 (dd, *J*=10.4, 12.1 Hz, 1H), 2.13 - 2.03 (m, 1H), 1.29 (d, *J*=6.2 Hz, 3H), 1.28 - 1.23 (m, 2H), 1.08 - 1.02 (m, 2H).

Example 50

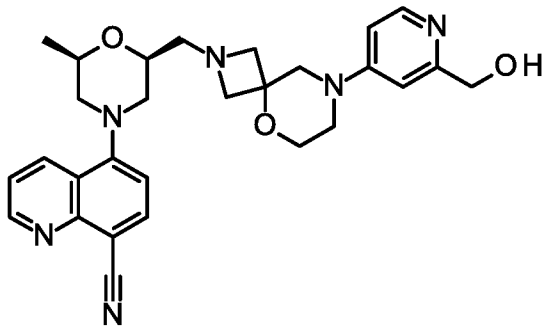
5-[(2*S*,6*R*)-2-[[4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using *tert*-butyl piperazine-1-carboxylate instead of *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 50** (4 mg) was obtained as a yellow solid. MS: calc'd 473 (MH^+), measured 473 (MH^+). ^1H NMR (400MHz, METHANOL-d_4) δ = 9.01 (dd, *J*=1.6, 4.3 Hz, 1H), 8.67 (dd, *J*=1.7, 8.6 Hz, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 7.66 (dd, *J*=4.2, 8.6 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 7.14 (d, *J*=2.6 Hz, 1H), 7.08 (d, *J*=2.4 Hz, 1H), 4.74 (s, 2H), 4.56 - 4.47 (m, 1H), 4.25 - 4.16 (m, 1H), 4.07 (br s, 4H), 3.59 (br s, 4H), 3.45 (br d, *J*=12.8 Hz, 2H), 3.41 - 3.35 (m, 2H), 2.84 - 2.70 (m, 2H), 2.60 (s, 3H), 1.33 (d, *J*=6.2 Hz, 3H).

Example 51

5-[(2*S*,6*R*)-2-[[8-[2-(hydroxymethyl)-4-pyridyl]-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile



The title compound was prepared in analogy to the preparation of **Example 1** by using (4-bromo-2-pyridyl)methanol and *tert*-butyl 5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate instead of (4-bromo-6-methyl-2-pyridyl)methanol (compound **1a**) and *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate;oxalic acid (compound **1b**). **Example 51** (9 mg) was obtained as a light yellow solid. MS: calc'd 501 (MH^+), measured 501 (MH^+). ^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.87 (dd, *J*=1.6, 4.3 Hz, 1H), 8.53 (dd, *J*=1.6, 8.6 Hz, 1H), 8.05 (d, *J*=8.1 Hz, 1H), 8.00 (d, *J*=6.2 Hz, 1H), 7.52 (dd, *J*=4.3, 8.6 Hz, 1H), 7.14 (d, *J*=8.1 Hz, 1H), 6.97 (d, *J*=2.4 Hz, 1H), 6.73 (dd, *J*=2.6, 6.2 Hz, 1H), 4.50 (s, 2H), 4.01 - 3.88 (m, 2H), 3.71 - 3.61 (m, 2H), 3.50 (s, 2H), 3.44 (br dd, *J*=8.5, 16.7 Hz, 2H), 3.31 - 3.24 (m, 4H), 3.06 (dd, *J*=5.7, 8.3 Hz, 2H), 2.70 - 2.48 (m, 4H), 1.14 (d, *J*=6.2 Hz, 3H).

Example 52

The following tests were carried out in order to determine the activity of the compounds of formula (I) and (Ia) in HEK293-Blue-hTLR-7/8/9 cells assay.

HEK293-Blue-hTLR-7 cells assay:

A stable HEK293-Blue-hTLR-7 cell line was purchased from InvivoGen (Cat.#: hkb-htlr7, San Diego, California, USA). These cells were originally designed for studying the stimulation of human TLR7 by monitoring the activation of NF-κB. A SEAP (secreted embryonic alkaline phosphatase) reporter gene was placed under the control of the IFN-β minimal promoter fused to five NF-κB and AP-1-binding sites. The SEAP was induced by activating NF-κB and AP-1 *via* stimulating HEK-Blue hTLR7 cells with TLR7 ligands. Therefore the reporter expression was declined by TLR7 antagonist under the stimulation of a ligand, such as R848 (Resiquimod), for incubation of 20 hrs. The cell culture supernatant SEAP reporter activity was determined using QUANTI-Blue™ kit (Cat.#: rep-qb1, Invivogen, San Diego, Ca, USA) at a wavelength of 640 nm, a detection medium that turns purple or blue in the presence of alkaline phosphatase.

HEK293-Blue-hTLR7 cells were incubated at a density of 250,000~450,000 cells/mL in a volume of 170 μL in a 96-well plate in Dulbecco's Modified Eagle's medium (DMEM) containing 4.5 g/L glucose, 50 U/mL penicillin, 50 mg/mL streptomycin, 100 mg/mL Normocin, 2 mM L-glutamine, 10% (v/v) heat-inactivated fetal bovine serum with addition of 20 μL test compound in a serial dilution in the presence of final DMSO at 1% and 10 μL of 20uM R848 in above DMEM, perform incubation under 37 °C in a CO_2 incubator for 20 hrs. Then 20 μL of the supernatant from each well was incubated with 180 μL Quanti-blue substrate solution at 37 °C for 2 hrs and the absorbance was read at 620~655 nm using a spectrophotometer. The signalling pathway that TLR7 activation leads to downstream NF-κB activation has been widely accepted, and therefore similar reporter assay was modified for evaluating TLR7 antagonist.

HEK293-Blue-hTLR-8 cells assay:

A stable HEK293-Blue-hTLR-8 cell line was purchased from InvivoGen (Cat.#: hkb-htlr8, San Diego, California, USA). These cells were originally designed for studying the stimulation of human TLR8 by monitoring the activation of NF-κB. A SEAP (secreted embryonic alkaline phosphatase) reporter gene was placed under the control of the IFN-β minimal promoter fused to five NF-κB and AP-1-binding sites. The SEAP was induced by activating NF-κB and AP-1 *via* stimulating HEK-Blue hTLR8 cells with TLR8 ligands. Therefore the reporter expression was declined by TLR8 antagonist under the stimulation of a ligand, such as R848, for incubation of 20 hrs. The cell culture supernatant SEAP reporter activity was determined using QUANTI-Blue™ kit (Cat.#: rep-qb1, Invivogen, San Diego, Ca, USA) at a wavelength of 640 nm, a detection medium that turns purple or blue in the presence of alkaline phosphatase.

HEK293-Blue-hTLR8 cells were incubated at a density of 250,000~450,000 cells/mL in a volume of 170 μL in a 96-well plate in Dulbecco's Modified Eagle's medium (DMEM) containing 4.5 g/L glucose, 50 U/mL penicillin, 50 mg/mL streptomycin, 100 mg/mL Normocin, 2 mM L-glutamine, 10% (v/v) heat-inactivated fetal bovine serum with addition of 20 μL test compound in a serial dilution in the presence of final DMSO at 1% and 10 μL of 60uM R848 in above DMEM, perform incubation under 37 °C in a CO_2 incubator for 20 hrs. Then 20 μL of the supernatant from each well was incubated with 180 μL Quanti-blue substrate solution at 37°C for 2 hrs and the absorbance was read at 620~655 nm using a spectrophotometer. The signalling pathway that TLR8 activation leads to downstream NF-κB activation has been widely accepted, and therefore similar reporter assay was modified for evaluating TLR8 antagonist.

HEK293-Blue-hTLR-9 cells assay:

A stable HEK293-Blue-hTLR-9 cell line was purchased from InvivoGen (Cat.#: hkb-htlr9, San Diego, California, USA). These cells were originally designed for studying the stimulation of human TLR9 by monitoring the activation of NF-κB. A SEAP (secreted embryonic alkaline phosphatase) reporter gene was placed under the control of the IFN-β minimal promoter fused to five NF-κB and AP-1-binding sites. The SEAP was induced by activating NF-κB and AP-1 *via* stimulating HEK-Blue hTLR9 cells with TLR9 ligands. Therefore the reporter expression was declined by TLR9 antagonist under the stimulation of a ligand, such as ODN2006 (Cat.#: tlrl-2006-1, Invivogen, San Diego, California, USA), for incubation of 20 hrs. The cell culture supernatant SEAP reporter activity was determined using QUANTI-Blue™ kit (Cat.#: rep-qb1, Invivogen, San Diego, California, USA) at a wavelength of 640 nm, a detection medium that turns purple or blue in the presence of alkaline phosphatase.

HEK293-Blue-hTLR9 cells were incubated at a density of 250,000~450,000 cells/mL in a volume of 170 μL in a 96-well plate in Dulbecco's Modified Eagle's medium (DMEM) containing 4.5 g/L glucose, 50 U/mL penicillin, 50 mg/mL streptomycin, 100 mg/mL Normocin, 2 mM L-glutamine, 10% (v/v) heat-inactivated fetal bovine serum with addition of 20 μL test compound in a serial dilution in the presence of final DMSO at 1% and 10 μL of 20uM ODN2006 in above DMEM, perform incubation under 37 ℃ in a CO_2 incubator for 20 hrs. Then 20 μL of the supernatant from each well was incubated with 180 μL Quanti-blue substrate solution at 37 ℃ for 2 h and the absorbance was read at 620~655 nm using a spectrophotometer. The signaling pathway that TLR9 activation leads to downstream NF-κB activation has been widely accepted, and therefore similar reporter assay was modified for evaluating TLR9 antagonist.

The compounds of formula (I) have human TLR7 and/or TLR8 inhibitory activities (IC_{50} value) <0.5 μM. Moreover, some compounds also have human TLR9 inhibitory activity <0.5 μM. Activity data of the compounds of the present invention were shown in Table 2.

Table 2. The activity of the compounds of present invention in HEK293-Blue-hTLR-7/8/9 cells assays

Example No	HEK/hTLR7 IC_{50} (μM)	HEK/hTLR8 IC_{50} (μM)	HEK/hTLR9 IC_{50} (μM)
R1 (reference compound)	0.095	0.142	6.623
R2 (reference compound)	0.210	0.342	7.034
1	0.028	0.081	0.034

3	<0.003	<0.003	0.048
4A	0.009	0.007	0.148
4B	0.01	0.005	0.145
5	0.059	0.033	0.032
6	0.044	0.053	0.041
7	0.026	0.031	0.039
8	0.007	0.007	<0.032
9	0.016	0.051	0.032
10	0.057	0.022	<0.032
11	0.008	0.011	0.04
12	0.013	0.012	0.049
14	<0.003	<0.003	<0.032
15	0.007	0.006	0.071
16	<0.003	<0.003	0.038
17A	<0.003	<0.003	0.154
17B	0.011	0.003	<0.032
19	0.006	0.003	0.062
20	0.2	0.07	0.036
21	0.062	0.015	<0.032
22	0.037	0.038	0.034
23	0.229	0.041	<0.032
24	0.026	0.01	<0.032
25	0.034	0.014	<0.032
28	0.122	0.032	0.057
29	0.156	0.025	0.059
30	0.065	0.014	0.088
33	0.012	0.007	0.122
34	0.012	0.004	0.155
35	0.017	0.009	0.034
36	0.017	0.012	0.215
37	0.034	<0.003	0.16
38	0.035	0.004	0.039
40	0.008	<0.003	0.041
42	0.013	<0.003	<0.032
43	0.007	0.018	0.054
44	0.02	0.03	<0.032
45	0.039	0.014	0.091
46	0.032	0.09	<0.032
48	0.055	0.198	0.148
49	0.013	0.02	0.034
50	0.01	0.004	0.134
51	<0.003	0.003	0.035

Example 53

hERG channel inhibition assay:

The hERG channel inhibition assay is a highly sensitive measurement that identifies compounds exhibiting hERG inhibition related to cardiotoxicity in vivo. The hERG K^+ channels were cloned in humans and stably expressed in a CHO (Chinese hamster ovary) cell line. CHO_{hERG} cells were used for patch-clamp (voltage-clamp, whole-cell) experiments. Cells were stimulated by a voltage pattern to activate hERG channels and conduct I_{KhERG} currents (rapid delayed outward rectifier potassium current of the hERG channel). After the cells were stabilized for a few minutes, the amplitude and kinetics of I_{KhERG} were recorded at a stimulation frequency of 0.1 Hz (6 bpm). Thereafter, the test compound was added to the preparation at increasing concentrations. For each concentration, an attempt was made to reach a steady-state effect, usually, this was achieved within 3-10 min at which time the next highest concentration was applied. The amplitude and kinetics of I_{KhERG} are recorded in each concentration of the drug which were compared to the control values (taken as 100%). (references: Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, Siegl PK, Strang I, Sullivan AT, Wallis R, Camm AJ, Hammond TG. 2003; Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovasc. Res. 58:32-45, Sanguinetti MC, Tristani-Firouzi M. 2006; hERG potassium channels and cardiac arrhythmia. Nature 440:463-469, Webster R, Leishman D, Walker D. 2002; Towards a drug concentration effect relationship for QT prolongation and torsades de pointes. Curr. Opin. Drug Discov. Devel. 5:116-26).

Results of hERG are given in Table 3. A safety ratio (hERG IC_{20} /EC_{50}) > 30 suggests a sufficient window to differentiate the pharmacology by inhibiting TLR7/8/9 pathways from the potential hERG related cardiotoxicity. According to the calculation of hERG IC_{20} / TLR7/8/9 IC_{50} below which serves as early selectivity index to assess hERG liability, obviously reference compounds ER-887258, ER-888285, ER-888286, R1 and R2 have much narrower safety window compared to the compounds of this invention.

Table 3. hERG and safety ratio results

Example No	hERG IC_{20} (μM)	hERG IC_{50} (μM)	hERG IC_{20} / TLR7 IC_{50}	hERG IC_{20} / TLR8 IC_{50}	hERG IC_{20} / TLR9 IC_{50}
ER-887258	0.687	2.784	8.1	N.A.	0.3
ER-888285	1.006	3.105	8.4	N.A.	0.5
ER-888286	0.348	1.297	0.3	N.A.	0.2

R1	0.879	2.745	9.3	6.2	0.1
R2	0.280	0.770	1.3	0.8	0.0
1	>10.000	>20.000	>357.1	>123.5	>294.1
5	7.184	>20.000	121.8	217.7	224.5
6	5.825	>20.000	132.4	109.9	142.1
7	>10.000	>20.000	>384.6	>322.6	>256.4
30	4.508	>10.000	69.4	322.0	51.2
45	>10.000	>20.000	>256.4	>714.3	>109.9
46	4.690	>10.000	146.6	52.1	146.6

Example 54

The compounds would be desirable to have minimal DDI liabilities. Therefore, the effects of compounds of formula (I) or (Ia) on CYP2D6 are determined.

CYP inhibition assay

This is a high throughput screening assay used for assessment of reversible inhibition of CYP2D6 activity of test compounds in human liver microsome (HLM) in early discovery stage.

Table 4. Chemicals and materials used in the CYP inhibition assay

Substances	**Description**	**Source**	**Cat. No.**	**Final Concentration in incubation**
Human Liver Microsomes		BD-Gentest	452117	0.2 mg/mL
Dextromethorphan	CYP2D6 substrate	Sigma	D-2531	5 µM
Dextrorphan	CYP2D6 product			
Dextrorphan-D3	CYP2D6 internal standard	Promochem	CERD-041	
Quinidine	CYP2D6 inhibitor			0.5 µM

Procedure

10 mM DMSO stock solutions of test compounds were diluted in DMSO to generate 2 mM intermediate stock solution. 250 nL of intermediate stock solution were transferred in duplicate into 3 separate 384 well microtitre plates (assay-ready plates). A mixture of HLM and each substrate was made up. 45 µL of HLM substrate mix was then transferred to each well of an assay ready plate and mixed. The negative (solvent) and positive control (standard inhibitor for CYP 2D6) were included in each assay ready plate. The assay ready plate was warmed to 37°C in an incubator over 10 minutes. 5 µL pre-warmed NADPH regenerating system was added to each incubation well to start the reaction. Final incubation volume was 50 µL. The assay plate

then was placed back in the 37 °C incubator. After 10 minutes incubation, incubates were quenched by addition of 50 µL 100% acetonitrile containing internal standards (20 ng/mL D3-Dextrorphan). The supernatants were collected for RapidFire/MS/MS analysis.

RapidFire online solid phase extraction/sample injection system (Agilent) coupled with API4000 triple quadrupole mass spectrometer (AB Sciex) were used for sample analysis. The mobile phase composed of acetonitrile and water supplemented with 0.1% formic acid. A C4 solid phase extraction cartridge is used for sample separation. MS detection is achieved in positive ion MRM mode.

Data analysis

Peak areas for substrate, metabolite and internal standard are determined using the RapidFire integrator software (version 3.6.12009.12296). Peak area ratios (PAR) of metabolite and internal standard (stable-labelled metabolite) are then calculated. The measurement window for each experiment is then defined:

PAR (0% activity)= average PAR for all incubations containing concentrated inhibitor;

Par (100% activity)= average PAR for all incubations containing no inhibitor (DMSO controls);

% Activity (test inhibitor)

=[PAR(test inhibitor)-PAR(0% activity)]/[PAR(100% activity)-PAR(0% activity)];

% Inhibition (test inhibitor)=100-% Activity (test inhibitor).

The compounds of present invention were found to have low CYP inhibition for CYP2D6 determined in the assays described above.

Table 5. CYP inhibition for CYP2D6

Example No	CYP 2D6 inhibition %@10µM
ER-888286	52.5
1	6
3	6
5	7.5
6	8
7	-21.5
9	-5
10	3.5
11	-7.5
12	-3
14	19
15	4
16	5

17B	5
21	2
22	2
24	-9.5
25	8.5
30	8.5
35	-4
38	0
39	7.5
40	14.5
42	-0.5
43	-13
44	5
45	-2.5
46	17
50	10.5
51	-15.5

ND : not detected; percentage inhibition <0: not or weak inhibitor

Example 55

Human microsome stability assay

The human microsomal stability assay is used for early assessment of metabolic stability of a test compound in human liver microsomes.

Human liver microsomes (Cat.NO.: 452117, Corning, USA;Cat.NO.:H2610, Xenotech, USA) were preincubated with test compound for 10 minutes at 37°C in 100 mM potassium phosphate buffer, pH 7.4. The reactions were initiated by adding NADPH regenerating system. The final incubation mixtures contained 1 μM test compound, 0.5 mg/mL liver microsomal protein, 1 mM $MgCl_2$, 1 mM NADP, 1 unit/mL isocitric dehydrogenase and 6 mM isocitric acid in 100 mM potassium phosphate buffer, pH 7.4. After incubation times of 0, 3, 6, 9, 15 and 30 minutes at 37°C, 300 μL of cold acetonitrile (including internal standard) was added to 100 μL incubation mixture to terminate the reaction. Following precipitation and centrifugation, the amount of compound remaining in the samples were determined by LC-MS/MS. Controls of no NADPH regenerating system at zero and 30 minutes were also prepared and analyzed. The compounds of present invention showed good human liver microsome stability determined in the above assay, results are shown in Table 6 below.

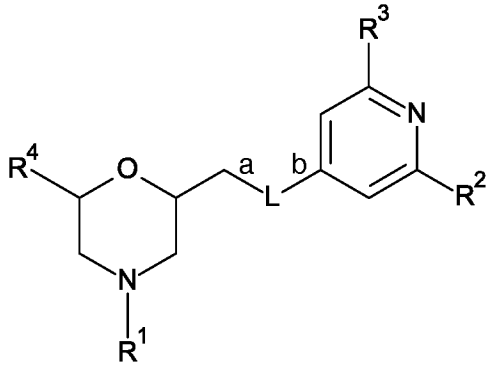
Table 6. Human liver microsome stability of the compounds of present invention

Example No	Clearance of Human microsome (mL/min/kg)

ER-887258	17.86
ER-888285	17.15
R1	10.84
R2	15.43
1	6.35
4A	6.15
5	7.47
6	6.15
7	6.15
9	6.15
20	6.15
26	7.72
27	7.67
28	6.25
30	7.14
31	7.61
37	6.15
40	6.15
44	7.21
46	7.66
48	6.87
49	6.39
50	7.72

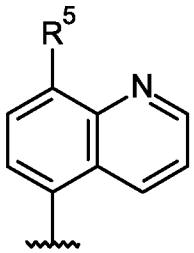
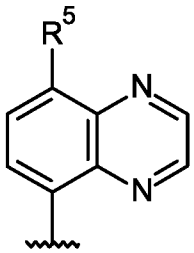
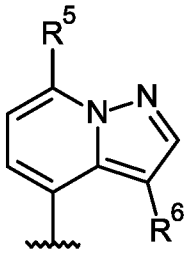
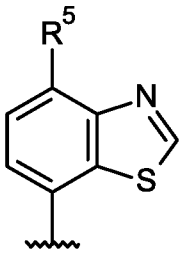
CLAIMS

1. A compound of formula (I),



(I),

wherein

R^1 is  ,  ,  or  ; wherein R^5 is cyano or halogen; R^6 is H or halogen;

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

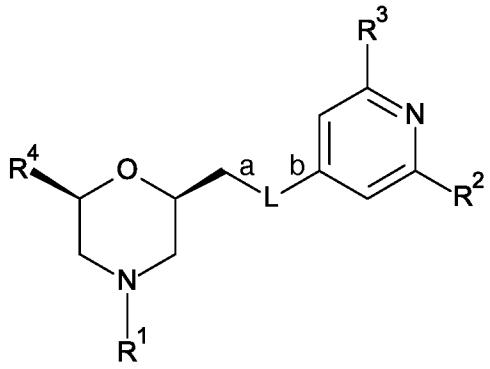
R^3 is amino, C_{1-6}alkylamino, C_{1-6}alkyl, haloC_{1-6}alkyl, heterocyclyl, hydroxyC_{1-6}alkyl or C_{3-7}cycloalkyl;

R^4 is C_{1-6}alkyl;

L is 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl; 1,6-diazaspiro[3.3]heptanyl; 2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl;2,6-diazaspiro[3.3]heptanyl; 2,7-diazaspiro[3.4]octanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; (C_{1-6}alkyl)aminoazetidinyl; aminoazetidinyl; azetidinyl(C_{1-6}alkyl)amino; azetidinylamino; (phenylC_{1-6}alkyl)piperazinyl; (hydroxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)piperazinyl; piperazinyl; piperidinyl; (C_{1-6}alkyl)aminopiperidinyl; aminohalopiperidinyl; amino(hydroxy)piperidinyl; aminopiperidinyl; piperidinylamino; amino(hydroxy)pyrrolidinyl; aminopyrrolidinyl; or pyrrolidinylamino;

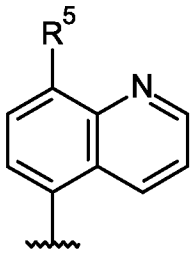
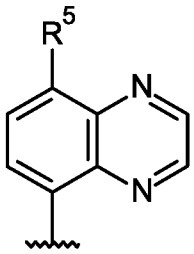
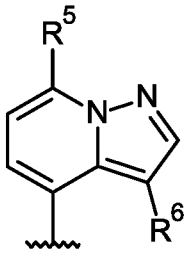
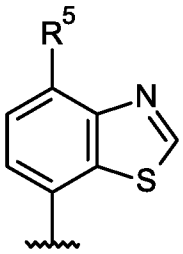
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

2. A compound of formula (Ia),



(Ia),

wherein

R^1 is  ,  ,  or  ; wherein R^5 is cyano or halogen; R^6 is H or halogen;

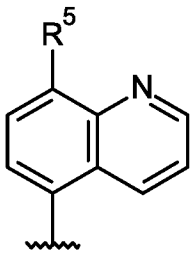
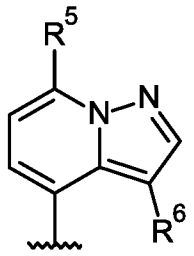
R^2 is H, amino or C_{1-6}alkyl;

R^3 is amino, C_{1-6}alkylamino, C_{1-6}alkyl, haloC_{1-6}alkyl, heterocyclyl, hydroxyC_{1-6}alkyl or C_{3-7}cycloalkyl;

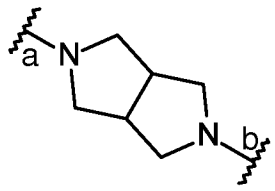
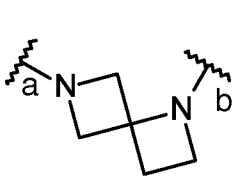
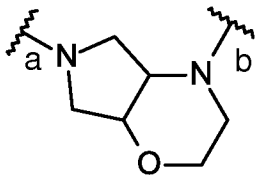
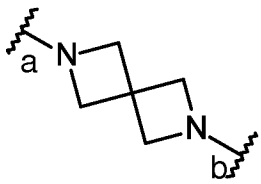
R^4 is C_{1-6}alkyl;

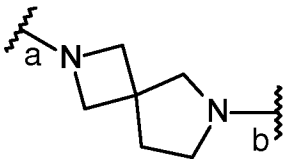
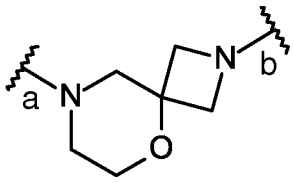
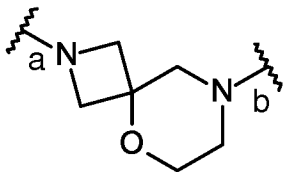
L is 1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl; 1,6-diazaspiro[3.3]heptanyl; 2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazinyl;2,6-diazaspiro[3.3]heptanyl; 2,7-diazaspiro[3.4]octanyl; 5-oxa-2,8-diazaspiro[3.5]nonanyl; (C_{1-6}alkyl)aminoazetidinyl; aminoazetidinyl; azetidinyl(C_{1-6}alkyl)amino; azetidinylamino; (phenylC_{1-6}alkyl)piperazinyl; (hydroxyC_{1-6}alkyl)piperazinyl; (C_{1-6}alkyl)piperazinyl; piperazinyl; piperidinyl; (C_{1-6}alkyl)aminopiperidinyl; aminohalopiperidinyl; amino(hydroxy)piperidinyl; aminopiperidinyl; piperidinylamino; amino(hydroxy)pyrrolidinyl; aminopyrrolidinyl; or pyrrolidinylamino;

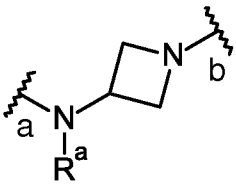
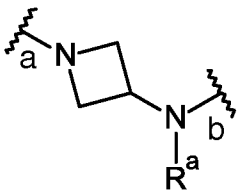
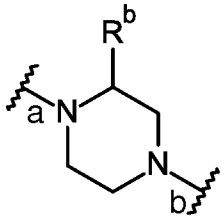
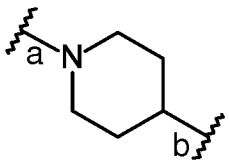
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

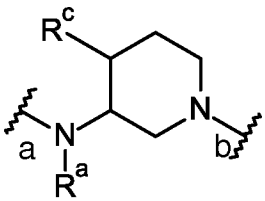
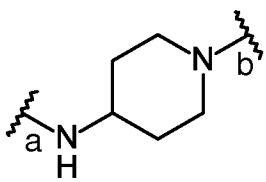
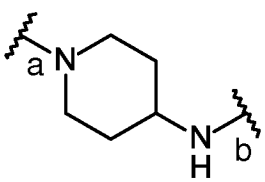
3. A compound according to claim 1 or 2, wherein R^1 is  or  ; wherein R^5 is cyano, R^6 is H.

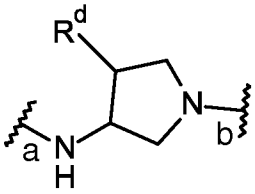
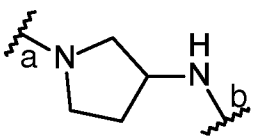
4. A compound according to claim 3, wherein L is

 ,  ,  ,  ,

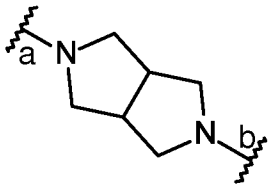
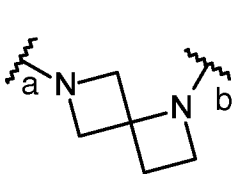
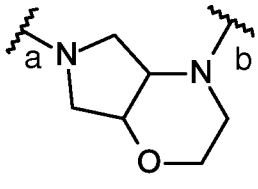
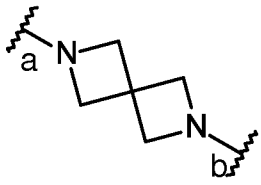
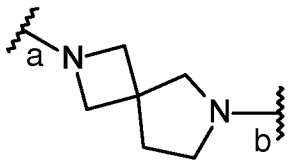
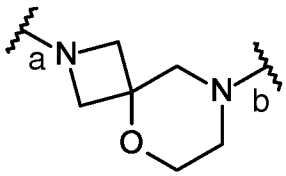
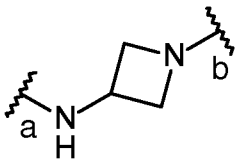
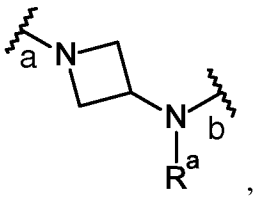
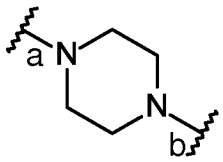
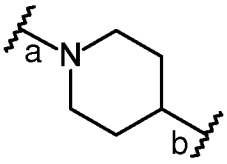
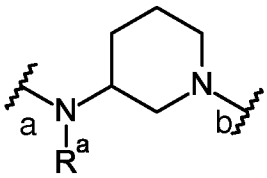
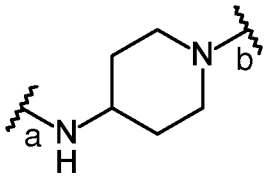
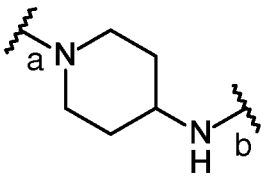
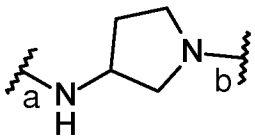
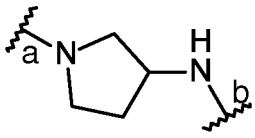
 ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,

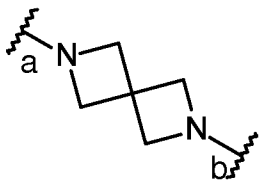
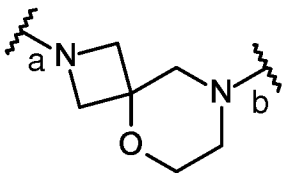
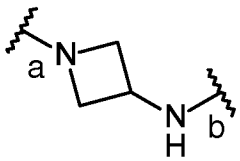
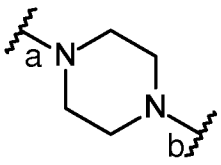
 or  ; wherein R^a is H or C_{1-6}alkyl; R^b is H, phenylC_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{1-6}alkyl; R^c is H, halogen or hydroxy; R^d is H or hydroxy.

5. A compound according to claim 4, wherein L is

wherein R^a is H or C_{1-6}alkyl.

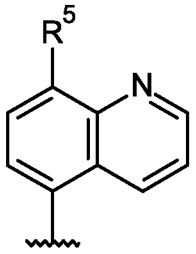
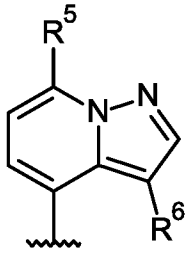
6. A compound according to claim 5, wherein L is

7. A compound according to claim 6, wherein R^3 is amino, C_{1-6}alkylamino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{3-7}cycloalkyl.

8. A compound according to claim 7, wherein R^3 is amino, cyclopropyl, hydroxyethyl, hydroxymethyl, methyl or methylamino.

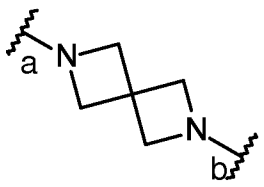
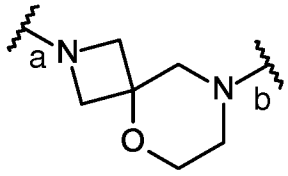
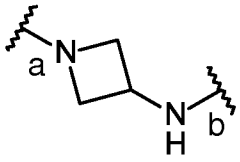
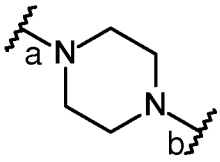
9. A compound according to claim 1 or 2, wherein

R^1 is  or  ; wherein R^5 is cyano; R^6 is H;

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

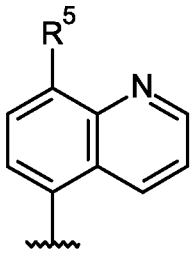
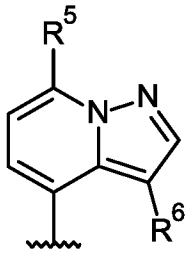
R^3 is $C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkyl or $C_{3\text{-}7}$cycloalkyl;

R^4 is $C_{1\text{-}6}$alkyl;

L is  ,  ,  or  ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

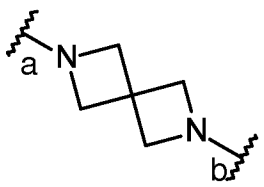
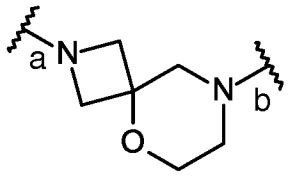
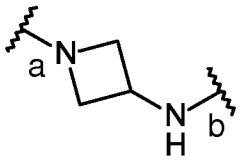
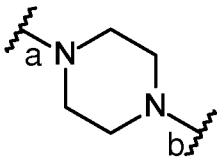
10. A compound according to claim 9, wherein

R^1 is  or  ; wherein R^5 is cyano; R^6 is H;

R^2 is H or methyl;

R^3 is methyl, hydroxymethyl or cyclopropyl;

R^4 is methyl;

L is  ,  ,  or  ;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

11. A compound selected from:

5-[(2*S*,6*R*)-2-[[2-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[8-(2-cyclopropyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile ;

5-[(2*S*,6*R*)-2-[[4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[(2*S*)-4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[(2*R*)-4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-2-methyl-piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]-1-piperidyl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[3-[[2-(hydroxymethyl)-6-methyl-4-pyridyl]amino]pyrrolidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[3-[(2,6-dimethyl-4-pyridyl)amino]azetidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[1-(2,6-dimethyl-4-pyridyl)-1,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[7-(2,6-dimethyl-4-pyridyl)-2,7-diazaspiro[3.4]octan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

cis-5-[(2*S*,6*R*)-2-[[5-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[3-[(2,6-dimethyl-4-pyridyl)-methyl-amino]azetidin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-1,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-(2,6-dimethyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-8-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[8-(2,6-dimethyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*R*,6*S*)-2-methyl-6-[[1-(2-methyl-4-pyridyl)-1,6-diazaspiro[3.3]heptan-6-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*R*,6*S*)-2-methyl-6-[[8-(2-methyl-4-pyridyl)-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

cis-5-[(2*S*,6*R*)-2-[[4-(2,6-dimethyl-4-pyridyl)-2,3,4a,5,7,7a-hexahydropyrrolo[3,4-b][1,4]oxazin-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-(2-amino-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[1-(2-amino-4-pyridyl)-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3R)-1-(2-amino-4-pyridyl)-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-(2-amino-4-pyridyl)-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[3-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-4-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[4-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]azetidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[4-hydroxy-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]pyrrolidin-3-yl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[1-(2,6-dimethyl-4-pyridyl)-4-hydroxy-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

cis-5-[(2*S*,6*R*)-2-[[[4-fluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

trans-5-[(2*S*,6*R*)-2-[[[4-fluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*R*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[5,5-difluoro-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]azetidin-3-yl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[[(3*S*)-1-[2-(hydroxymethyl)-6-methyl-4-pyridyl]-3-piperidyl]-methyl-amino]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

4-[(2*S*,6*R*)-2-[[2-benzyl-4-(2,6-dimethyl-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]pyrazolo[1,5-a]pyridine-7-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-(2-amino-6-methyl-4-pyridyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[(2*R*)-4-(2-amino-6-methyl-4-pyridyl)-2-(hydroxymethyl)piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*R*,6*S*)-2-methyl-6-[[4-[2-methyl-6-(methylamino)-4-pyridyl]piperazin-1-yl]methyl]morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S,6R*)-2-[[4-(2-amino-6-methyl-4-pyridyl)-1-piperidyl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S,6R*)-2-[[2-[2-(1-hydroxyethyl)-6-methyl-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[4-[2-amino-6-(hydroxymethyl)-4-pyridyl]piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-[2-(1-hydroxyethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-[2-(difluoromethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-[2-(1-hydroxy-1-methyl-ethyl)-4-pyridyl]-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

5-[(2*S*,6*R*)-2-[[2-(2-cyclopropyl-4-pyridyl)-2,6-diazaspiro[3.3]heptan-6-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

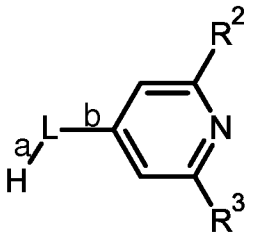
5-[(2*S*,6*R*)-2-[[4-[2-(hydroxymethyl)-6-methyl-4-pyridyl]piperazin-1-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile; and

5-[(2*S*,6*R*)-2-[[8-[2-(hydroxymethyl)-4-pyridyl]-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl]methyl]-6-methyl-morpholin-4-yl]quinoline-8-carbonitrile;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

12. A process for the preparation of a compound according to any one of claims 1 to 11 comprising any of the following step:

a) the coupling of compound of formula (IX),



(IX),

with compound of formula (IV) in the presence of a base;

wherein the base in step a) and b) is K_2CO_3, DIPEA, or Cs_2CO_3; R^2, R^3 and L are defined as in any one of claims 1 to 10.

13. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 11 for use as therapeutically active substance.

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

15. The use of a compound according to any one of claims 1 to 11 for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

16. The use of a compound according to any one of claims 1 to 11 for the preparation of a medicament for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

17. The use of a compound according to any one of claims 1 to 11 as the TLR7 or TLR8 or TLR9 antagonist.

18. The use of a compound according to any one of claims 1 to 11 as the TLR7 and TLR8 antagonist.

19. The use of a compound according to any one of claims 1 to 11 for the preparation of a medicament for TLR7 and TLR8 and TLR9 antagonist.

20. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 11 for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis.

21. A compound or pharmaceutically acceptable salt, enantiomer or diastereomer according to any one of claims 1 to 11, when manufactured according to a process of claim 12.

22. A method for the treatment or prophylaxis of systemic lupus erythematosus or lupus nephritis, which method comprises administering a therapeutically effective amount of a compound as defined in any one of claims 1 to 11.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/065121

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 A61K31/5355 A61P37/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/105370 A1 (CARLSON ERIC [US] ET AL) 16 April 2015 (2015-04-16) cited in the application abstract; claims 1-21; figure 6FF; compounds ER-888286	1-22
A	WO 2017/106607 A1 (MERCK PATENT GMBH [DE]; SHERER BRIAN A [US]; BRUGGER NADIA [US]) 22 June 2017 (2017-06-22) examples 50,57,59; table 1	1-22

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2019	21/08/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rufet, Jacques

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/065121

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015105370 A1	16-04-2015	AR 098014 A1	27-04-2016
		AU 2014334554 A1	02-06-2016
		AU 2018264036 A1	06-12-2018
		CA 2927510 A1	23-04-2015
		CL 2016000662 A1	16-12-2016
		CN 106414432 A	15-02-2017
		CN 110105346 A	09-08-2019
		EP 3057964 A1	24-08-2016
		HK 1223092 A1	21-07-2017
		IL 245131 A	29-11-2018
		JP 6223563 B2	01-11-2017
		JP 6420878 B2	07-11-2018
		JP 2016535003 A	10-11-2016
		JP 2017226700 A	28-12-2017
		JP 2019023220 A	14-02-2019
		KR 20160068949 A	15-06-2016
		KR 20180011874 A	02-02-2018
		MA 39034 A1	31-01-2018
		MD 20160052 A2	30-09-2016
		PE 06082016 A1	08-07-2016
		PH 12016500642 A1	30-05-2016
		SG 10201704327R A	29-06-2017
		SG 11201602818T A	30-05-2016
		TW 201602100 A	16-01-2016
		TW 201838988 A	01-11-2018
		US RE47193 E	08-01-2019
		US 2015105370 A1	16-04-2015
		US 2016326161 A1	10-11-2016
		US 2018030045 A1	01-02-2018
		US 2018354939 A1	13-12-2018
		WO 2015057659 A1	23-04-2015
		ZA 201608132 B	30-01-2019
WO 2017106607 A1	22-06-2017	AU 2016371014 A1	31-05-2018
		BR 112018011556 A2	27-11-2018
		CA 3005766 A1	22-06-2017
		CL 2018001624 A1	21-09-2018
		CN 108699032 A	23-10-2018
		EP 3390389 A1	24-10-2018
		JP 2018537501 A	20-12-2018
		KR 20180094939 A	24-08-2018
		PH 12018501068 A1	21-01-2019
		SG 11201804170R A	28-06-2018
		TW 201730175 A	01-09-2017
		US 2017174653 A1	22-06-2017
		WO 2017106607 A1	22-06-2017