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(54) **4-PYRAZIN-2-YLMETHYL-MORPHOLINE DERIVATIVES AND THE USE THEREOF AS MEDICAMENT**

4-PYRAZIN-2-YLMETHYL-MORPHOLIN-DERIVATE UND VERWENDUNG DAVON ALS MEDIKAMENT

DÉRIVÉS DE 4-PYRAZIN-2-YLMÉTHYL-MORPHOLINE ET LEUR UTILISATION COMME MÉDICAMENT

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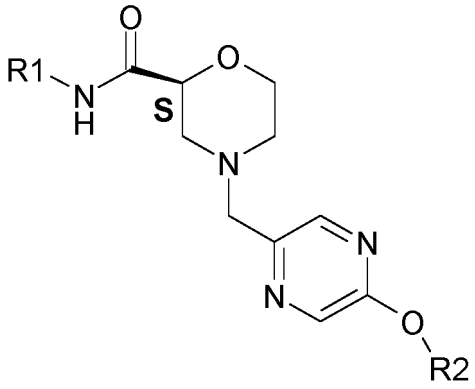
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Description

[0001] The present invention relates to novel 4-pyrazin-2-ylmethyl-morpholines of general formula **A**



A,

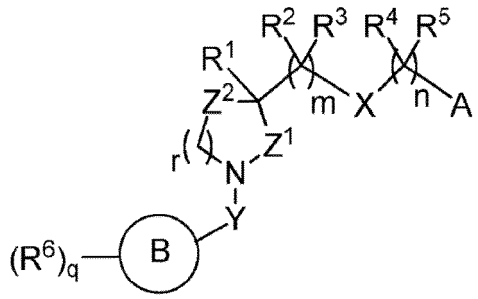
processes for their preparation, pharmaceutical compositions containing them and their use in therapy, particularly in the treatment or prevention of conditions having an association with NR2B negative allosteric modulating properties.

[0002] The compounds of the invention according to general formula **A** show NR2B negative allosteric modulating properties.

[0003] Extensive studies over the past twenty years have indicated that N-methyl-D-aspartate receptors (NMDA) play a relevant role in Alzheimer's disease, Parkinson's disease, dyskinesia, stroke, motor neuron disease, psychosis, epilepsy, anxiety, schizophrenia and pain.

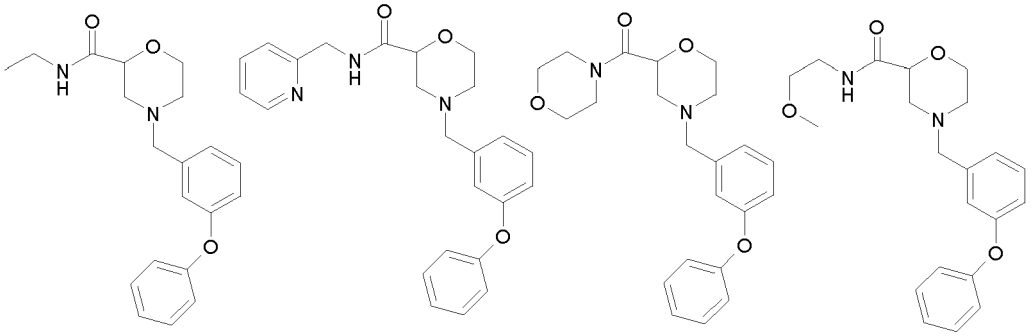
[0004] The non-selective NMDA receptor antagonist ketamine, (racemic as well as the S enantiomer), a medication mainly used for starting and maintaining anaesthesia, has demonstrated over the last years clinical efficacy in treating major depressive disorder (MDD) at subanaesthetic doses (Murrough et al. 2013, Am J Psychiatry. 170: 1134; Singh et al. 2016, Biol Psychiatry. 80: 424). More precisely, ketamine elicits a rapid onset of efficacy which lasts several days in MDD patients insufficiently responding to standard drug therapy (Berman et al. 2000. Biol Psychiatry 47:351, Serafini et al. 2014. Curr. Neuro-pharmacol. 12:444). However, non-selective NMDA receptor antagonists have a range of undesirable effects which limit their application. In particular dissociative and psychogenic side effects are prominent for the non-selective NMDA receptor antagonists such as ketamine (Krystal et al. 1994. Arch. Gen. Psychiatry 51:199). In the early 1990s, it was found that multiple NMDA receptor subtypes exist, which contain different NR2(A-D) subunits (Paoletti et al., 2013 Nat Rev. Neurosci 14:383). More recently, NR2B subtype selective NMDA receptor negative allosteric modulators (NR2B NAM) have raised interest and have shown potential in a wide range of clinical indications, such as attention, emotion, mood, and pain, as well as being involved in a number of different human disorders (Mony et. al. 2009. Br. J. Pharmacol. 157:1301; Chaffey et al., Current Anaesthesia & Critical Care 19, 183). In particular, NR2B NAM have also demonstrated antidepressant efficacy in the early stage of clinical trials (Preskorn et al. 2008. J Clin Psychopharmacol 70:58). Preclinical studies using NR2B NAM as well as applying various transgenic mice strains have shown that NR2B containing NMDA-receptors are mediating the positive effect of ketamine in e.g. the Forced Swim Test (Miller et al. 2014 eLife 3:e03581; Kiselycznyk et al. 2015, Behav Brain Res, 287:89). Furthermore, selective NR2B NAM have advantages over unselective NMDA receptor antagonists, such as ketamine, due to greatly diminished dissociative and psychotomimetic side effects (Jimenez-Sanchez et al. 2014. Neuropsychopharmacology 39:2673). NR2B NAM described to date have exhibited drawbacks with regard to their receptor pharmacology and/or to other drug properties which have limited potential use in human drug therapy (Taylor, et al., 2006, Clin Pharmacokinet.45: 989;Addy et al. 2009 J of Clinical Pharmacology 49:856)).

[0005] WO2010/088408, WO03/010159 and Chaffey, 19(4), (2008), pp 183-201 describe NMDA inhibitors which however do not show the present combination of a morpholine and pyrazine connected by a methylene spacer. WO2015/130905 discloses compounds of formula (I)



(I)

that are inhibitors of Nav1.6 useful in the treatment of multiple sclerosis, polyneuritis, multiple neuritis, amyotrophic lateral sclerosis, Alzheimer's disease or Parkinson's disease. WO2015/130905 discloses the specific examples **100**, **105**, **106** and **107** in which ring B corresponds to a meta-disubstituted phenyl ring.



Example **100** Example **105** Example **106** Example **107**

[0006] WO2015/130905 reports specific examples **100**, **105**, **106** and **107** to be weak Nav1.6 inhibitors (Nav 1.6 blockage of examples **100**, **105** and **107** at 1-5 μM, and Nav 1.6 blockage of example **106** at >5 μM).

[0007] Compounds of the present invention are generically encompassed by formula (I) of WO2015/130905. The compounds of the present invention differ structurally from the examples **100**, **105**, **106** and **107** explicitly disclosed in WO2015/130905 in that they contain a para-disubstituted pyrazinyl substructure in place of the meta-disubstituted phenyl ring.

[0008] The structural differences unexpectedly result in potent NR2B negative allosteric modulators (see Table 1), whereas the specific examples **100**, **105**, **106** and **107** of WO2015/130905 do not show any activity on the NR1-NR2B ion channel (see Table 2). Furthermore, compounds of the present invention do not inhibit Nav 1.6 at concentrations at which specific examples **100** and **105** of WO2015/130905 inhibit Nav 1.6 (5 μM; see Tables 3 and 4).

[0009] Further, the compounds of the present invention show good membrane permeability and no in vitro efflux (see Table 5 for MDCK assay MDR1 (P-gp)). Therefore, compounds of the present invention are expected to show a favorable brain penetration which is required for efficacious CNS medicaments.

[0010] The MDCK assays provide information on the potential of a compound to pass the blood brain barrier. Permeability measurements across polarized, confluent MDCK-MDR1 cell monolayers grown on permeable filter supports are used as an in vitro absorption model: apparent permeability coefficients (PE) of the compounds across the MDCK-MDR1 cell monolayers are measured (pH 7.4, 37°C) in apical-to-basal (AB) and basal-to-apical (BA) transport direction. The AB permeability (PEAB) represents drug absorption from the blood into the brain and the BA permeability (PEBA) drug efflux from the brain back into the blood via both, passive permeability as well as active transport mechanisms mediated by efflux and uptake transporters that are expressed on the MDCK-MDR1 cells, predominantly by the overexpressed human MDR1. Identical or similar permeabilities in both transport directions indicate passive permeation (PEBA/PEAB ≤1), vectorial permeability points to additional active transport mechanisms. Higher PEBA than PEAB (PEBA/PEAB >5) indicates the involvement of active efflux mediated by MDR1, which might compromise the goal to achieve sufficient brain exposure. Therefore, this assay provides valuable support for selection of compounds applicable for further in vivo testing. High permeability not limited by efflux at the blood brain barrier is a favourable characteristic for compounds that are to be used for drugs acting primarily in the CNS.

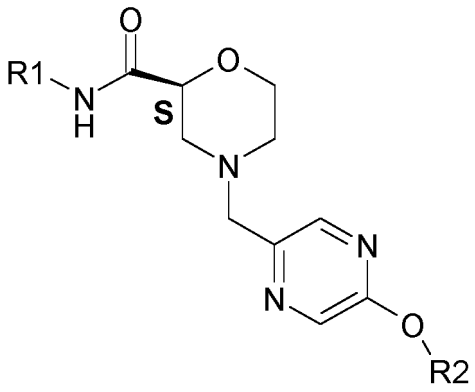
[0011] Further, the compounds of the present invention are metabolically stable in human liver microsomes (see Table 6, metabolic stability). Therefore, compounds of the present invention are expected to have a favorable in vivo clearance and thus the desired duration of action in humans.

[0012] Stability in human liver microsomes refers to the susceptibility of compounds to bio-transformation in the context of selecting and/or designing drugs with favorable pharmacokinetic properties. The primary site of metabolism for many drugs is the liver. Human liver microsomes contain the cytochrome P450s (CYPs), and thus represent a model system for studying drug metabolism in vitro. Enhanced stability in human liver microsomes is associated with several advantages, including increased bioavailability and adequate half-life, which can enable lower and less frequent dosing of patients. Thus, enhanced stability in human liver microsomes is a favorable characteristic for compounds that are to be used for drugs.

[0013] Consequently, compounds of the present invention must be more viable for human use.

[0014] The objective technical problem is thus to provide potent and selective NR2B negative allosteric modulators.

[0015] The present invention provides novel 4-pyrazin-2-ylmethyl-morpholines of formula **A**



A

in which

R^1 represents methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, H_3C-CH_2-CH_2-CH_2-, cyclobutyl;

R^2 represents phenyl which is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of fluoro, chloro, methyl, ethyl, cyclopropyl;

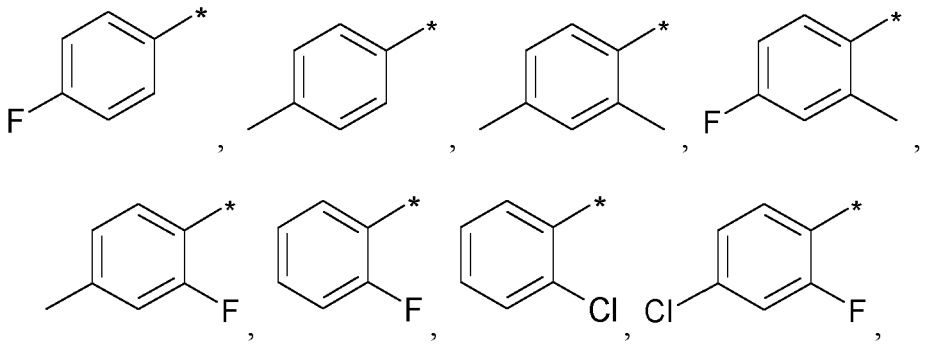
or a salt thereof, particularly a pharmaceutically acceptable salt thereof.

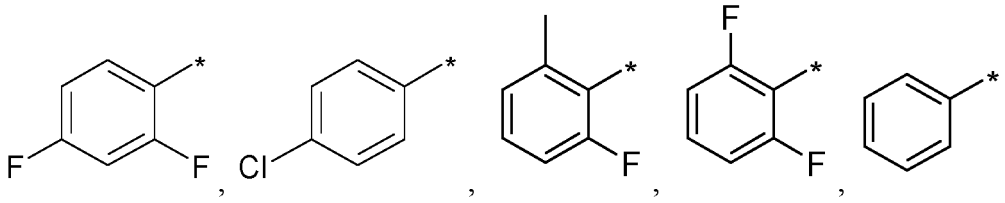
[0016] In another embodiment, in the general formula **A**, **R^2** has the same meaning as defined in any of the preceding embodiments, and

R^1 represents methyl, ethyl.

[0017] In another embodiment, in the general formula **A**, **R^1** has the same meaning as defined in any of the preceding embodiments, and

R^2 represents





[0018] The present invention provides novel 4-pyrazin-2-ylmethyl-morpholines of general formula **A** that unexpectedly are potent and selective negative allosteric modulators of NR2B .

[0019] Another aspect of the invention refers to compounds according to formula **A** as potent and selective NR2B negative allosteric modulators having high membrane permeability and no in vitro efflux.

[0020] Another aspect of the invention refers to compounds according to formula **A** as potent and selective NR2B negative allosteric modulators having high metabolic stability in human liver microsomes.

[0021] Another aspect of the invention refers to compounds according to formula **A** as potent and selective NR2B negative allosteric modulators having high membrane permeability, no in vitro efflux, and high metabolic stability in human liver microsomes.

[0022] Another aspect of the invention refers to pharmaceutical compositions, containing at least one compound according to formula **A** optionally together with one or more inert carriers and/or diluents.

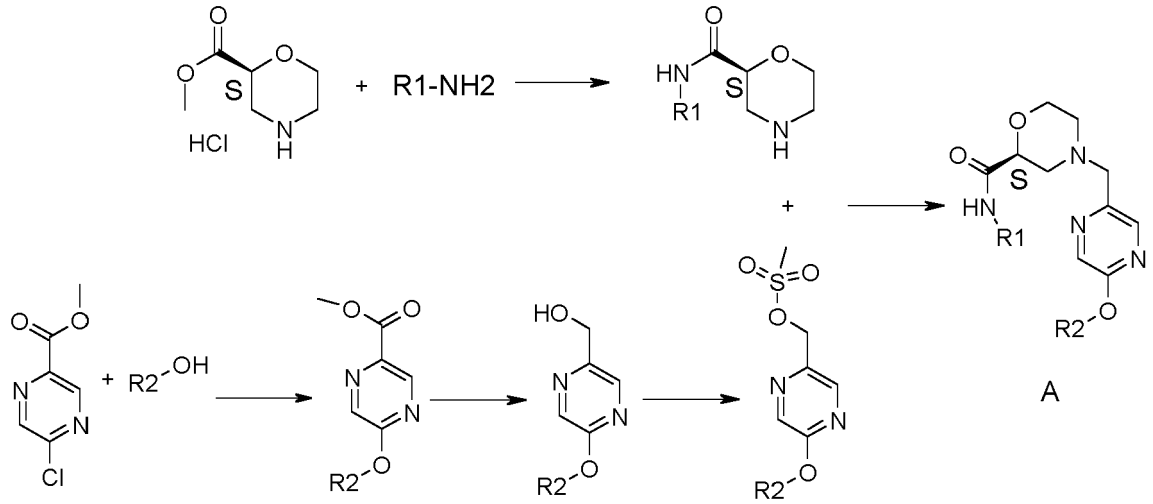
[0023] A further aspect of the present invention refers to compounds according to formula **A**, for the use in the prevention and/or treatment of disorders associated with NR2B negative allosteric modulators.

[0024] Another aspect of the invention refers to processes of manufacture of the compounds of the present invention.

Preparation

[0025] The following scheme shall illustrate generally how to manufacture the compounds according to general formula **A** and the corresponding intermediate compounds by way of example. The abbreviated substituents may be as defined above if not defined otherwise within the context of the scheme.

Scheme 1



[0026] Scheme 1 illustrates the synthesis of pyrazine derivatives of general formula **A**.The first step is a nucleophilic substitution of a substituted phenol derivate R2-OH and 5-chloropyrazine-2-carboxylic acid methyl ester; the ester group is reduced to the corresponding alcohol with $NaBH_4$; the hydroxy group is then converted into a leaving group (e.g. mesylate).

[0027] The last step is represented by a nucleophilic displacement employing the mesylate and a slight excess of an amide derivative of the (S)-Morpholine-2-carboxylic acid obtained by reacting (S)-Morpholine-2-carboxylic acid methyl ester with the corresponding amine R1-NH_2.

[0028] The described synthetic approach can be used also for gram scale synthesis applying different purification techniques such as crystallization or column chromatography.

GENERAL DEFINITIONS

[0029] Terms not specifically defined herein should be given the meanings that would be given to them by one skilled in the art in light of the disclosure and the context.

[0030] NR2B ion channel should be understood as NMDA receptor containing the NR2B protein.

[0031] In case a compound of the present invention is depicted in form of a chemical name as well as a formula, the formula shall prevail in case of any discrepancy.

[0032] An asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule or to the substituent to which it is bound as defined.

[0033] The term "substituted" as used herein means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's viable valence number is not exceeded, and that the substitution results in a stable compound.

Stereochemistry:

[0034] Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass rotamers, tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereoisomers, *E*/*Z* isomers etc.) and racemates thereof, as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereoisomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist.

Salts:

[0035] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

[0036] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound forms a salt or a complex with an acid or a base.

[0037] Examples for acids forming a pharmaceutically acceptable salt with a parent compound containing a basic moiety include mineral or organic acids such as benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gentisic acid, hydrobromic acid, hydrochloric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, 4-methyl-benzenesulfonic acid, phosphoric acid, salicylic acid, succinic acid, sulfuric acid or tartaric acid.

[0038] Examples for cations and bases forming a pharmaceutically acceptable salt with a parent compound containing an acidic moiety include Na^+, K^+, Ca^{2+}, Mg^{2+}, NH_4^+, L-arginine, 2,2'-iminobisethanol, L-lysine, N-methyl-D-glucamine or tris(hydroxymethyl)-aminomethane.

[0039] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof. Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoroacetate salts) also comprise a part of the invention.

BIOLOGICAL ASSAYS AND DATA

List of abbreviations

[0040]

DMEM	Dulbecco's Modified Eagle's Medium
FBS	fetal Bovine Serum
FLIPR	fluorometric imaging plate reader
HEK293	cell line derived from human embryonic kidney cells
HEPES	hydroxyethyl-piperazineethane-sulfonic acid buffer
IC50	half maximal inhibitory concentration
MDCK	Madin-Darby canine kidney
MDR1	Multi drug resistance protein 1

P-gp	p-Glycoprotein
SEM	standard error mean
EGTA	(ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid), also known as egtazic acid

***In-vitro* effect:**

Determination of in vitro Pharmacological Activity

[0041] The activity of the compounds of the invention may be demonstrated using the following in vitro NMDA NR1/NR2B cell assays:

Method:

[0042] A human HEK293 cell line with tetracyclin-inducible expression of NMDA NR1/NR2B receptor was used as a test system for compound efficacy and potency. The cell line was purchased from ChanTest, Catalog #CT6121. Compound activity was determined by measuring the effect of compounds on intracellular calcium concentration induced by glycine/glutamate agonism in a FLIPRtetra system (Molecular Devices).

Cell culture:

[0043] The cells were obtained as frozen cells in cryo-vials and stored until use at -150°C.

[0044] Cells were grown in culture medium (DMEM/F12, 10% FBS, 5μg/mL Blasticidin, 150 μg/mL Zeozin, 500μg/mL Geneticin). It is important that density does not exceed 80% confluence. For sub-culturing the cells were detached from flasks by Versene. For the assay, cells were detached, washed twice with induction medium (DMEM/F12 without glutamine, 10% FBS, 2μg/mL Tetracycline, 2mM Ketamine) and seeded to 384 well pure coat amine plates (Becton Dickinson, 50000 cells per well in 50 μl) 48 h prior to assay in induction medium.

Compound preparation

[0045] The test compounds were dissolved in 100% DMSO at a concentration of 10 mM and in a first step diluted in DMSO to a concentration of 5 mM, followed by serial dilution steps in 100% DMSO. Dilution factor and number of dilution steps may vary according to needs. Typically 8 different concentrations by 1:5 dilutions were prepared in duplicate, further intermediate dilutions (1:37.5) of the substances were carried out with aqueous assay buffer (137mM NaCl, 4mM KCl, 1.8mM $CaCl_2$, 10mM HEPES, 10mM Glucose, pH 7.4) resulting in a compound concentration 3 times above the final test concentration and DMSO at 2.7% resulting in 0.9% final DMSO concentration in the assay.

FLIPR assay:

[0046] At the assay day cells were washed 3x with assay buffer (as described above), 10 μL buffer remained in the wells after washing. 10 μL Ca kit loading buffer (AAT Bioquest; prepared from the kit containing the following components: Component A: Fluo-8 NW dissolved in 200μL DMSO and 20 μl of this solution are mixed with 10 ml buffer prepared out of component B and C , Component B: 10X Pluronic® F127 Plus diluted 1:10 in component C, Component C: HUBS (Hanks with 20 mM Hepes) was added to the cells and the plates were incubated with lid for 60 minutes at room temperature. 20 μl assay buffer containing 60 μM glycine (20μM final) and 3 μM glutamate (1 μM final) was added to column 1-23, column 24 got assay buffer without glycine/glutamate to serve as negative unstimulated control. Fluorescence (indicating the calcium influx as a result of the NR1/NR2B ion channel activation) was read on the FLIPRtetra device for 60 seconds to monitor the glutamate induced effects. After 2 minutes 20 μL of compound dilution prepared as described above or controls (row 1-22) in assay buffer were carefully added to the wells. Fluorescence was read on the FLIPR tetra device for additional 6 minutes to monitor the compound induced effects after activation by agonists. The average of 2 measurements at 5 minutes and 5 min 10 seconds after compound addition is calculated and further used for IC50 calculations. Each assay microtiter compound dilution plate contained wells (in column 23 or 24) with DMSO controls instead of compound as controls for glycine/glutamate induced fluorescence (high controls) and wells with 1 μM of a reference NR2B NAM as low controls (Compound 22; reference: Layton, Mark E et al, ACS Chemical Neuroscience 2011, 2(7), 352-362).

Data evaluation and calculation:

[0047] The output file of the reader contains the well number and measured average fluorescence units. For data

evaluation and calculation, the measurement of the low control was set as 0% control and the measurement of the high control was set as 100% control. The IC50 values were calculated using the standard 4 parameter logistic regression formula. Calculation: [y=(a-d)/(1+(x/c)^b)+d], a = low value, d = high value; x = conc M; c=IC50 M; b = slope.

[0048] NR2B negative allosteric modulators covered by general structure **A** and exhibiting a low IC_{50} value are preferred.

Table 1 In vitro NR2B affinity of the compounds of the present invention as obtained in the FLIPR assay

Example number	IC50 [nM]
1	968
2	123
3	690
4	1200
5	110
6	87
7	1002
8	856
9	210
18	222
30	595
31	524
33	807
34	644
35	197
36	542

Table 2 In vitro NR2B affinity of the closest prior art compounds (examples **100**, **105**, **106** and **107** in WO2015/130905) as obtained in the same FLIPR assay as compounds in Table 1

Example number in WO2015/130905	**IC50 [nM]**
100	>8887
105	>9261
106	>9255
107	>9257

Determination of Nav 1.6.Inhibition

Equipment:

IonWorks Quattro electrophysiological platform

Compound Plate Preparation

[0049] The compounds were prepared in DMSO at 300x the final assay concentrations of 1 and 5μM.

[0050] The 300x DMSO stock solutions were transferred into assay plates where 2μl per well of each 300x stock solution were placed. All assay plates were stored at -80°C until the day of assay.

[0051] On the day of the assay, the appropriate assay plate was thawed at room temperature, centrifuged, and 198μl of external recording solution was added and mixed thoroughly. This provided a 1:100 dilution. A further 1:3 dilution

occurred upon addition to the cells in the IonWorks Quattro electrophysiological platform, giving a 1:300 dilution in total. On each assay plate, at least 8 wells were reserved for vehicle control (0.3% DMSO) and at least 8 wells for each positive control specific to the cell line tested. The positive controls were tested at a maximal blocking and an approximate IC50 concentration. As positive control Lidocaine at concentrations of 30 and 1000 μM was used.

Electrophysiological Recording Solutions

[0052] The solutions for recording **Nav1.6** currents were as follows:

External Recording Solution

[0053]

NaCl 137mM
KCl 4mM
$MgCl_2$ 1mM
$CaCl_2$ 1.8mM
HEPES 10mM
Glucose 10mM
pH 7.3 (titrated with 10M NaOH)

Internal Recording Solution

[0054]

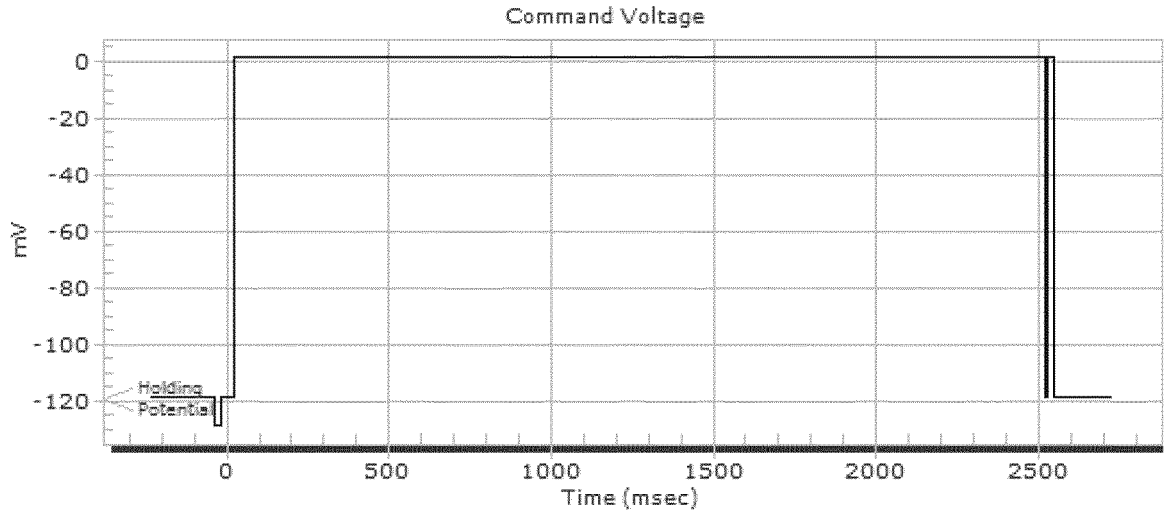
CsF 90mM
CsCl 45mM
HEPES 10mM
EGTA 10mM
pH 7.3 (titrated with 1M CsOH)

[0055] Amphotericin B was used to obtain electrical access to the cell interior at a final concentration of 200μg/ml in internal recording solution.

Experimental Protocols & Data Analysis

Nav1.6 Experimental Protocol

[0056] State-dependent inhibition: Sodium channels when held at depolarized potential or long test pulse, the channels open and inactivate and then stay inactivated until the membrane potential is stepped back to hyperpolarized potentials, when the inactivated channels recover from inactivation into closed state. An example is Tetracaine inhibition, which is much stronger at depolarized potentials than at hyperpolarized potential.



Nav1.6 Data Analysis

[0057] Cells were held at -120mV. In order to completely inactivate the sodium channels (pulse 1), the cells were pulsed to +0mV for 2500ms and stepped back to -120mV for 10ms (to completely recover from inactivation, however channels that had drugs bound to them will not recover from inactivation) before stepping to +0mV for 20ms (pulse 2).

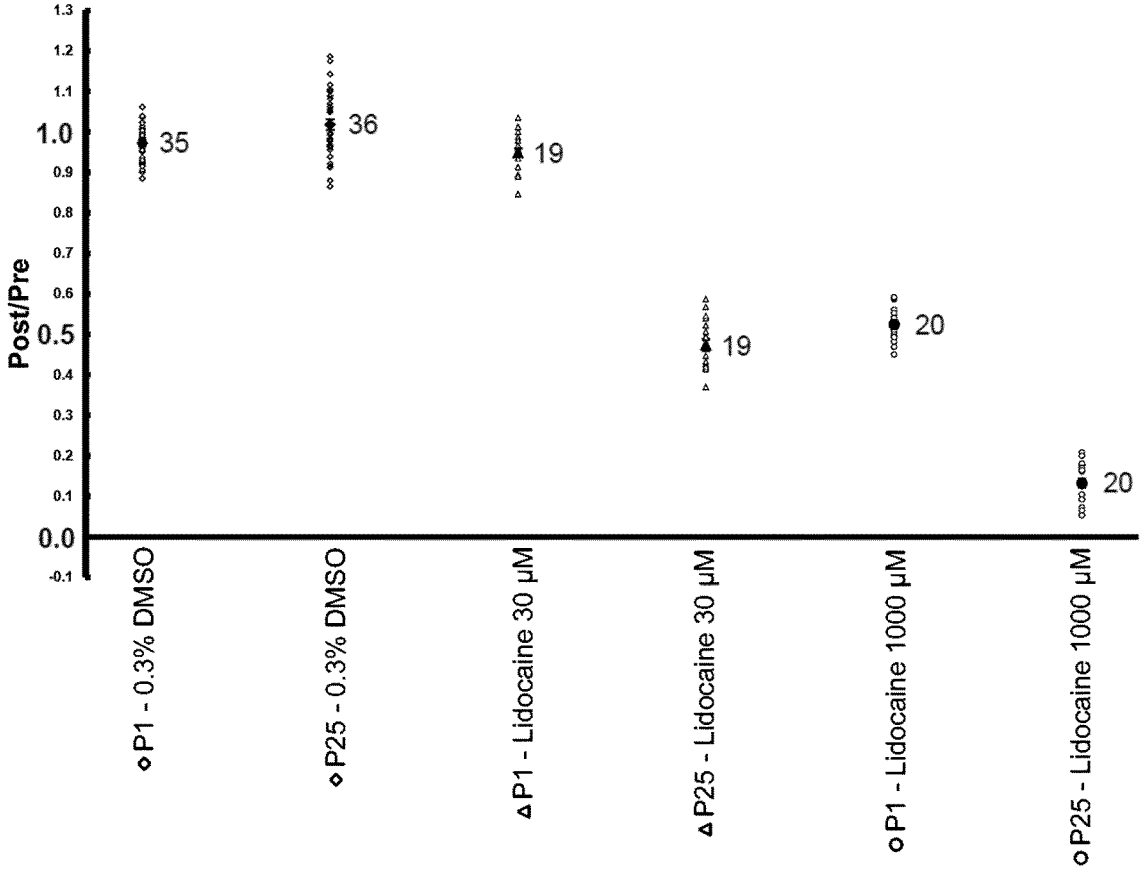
IonChannel Profiler Data Filters

[0058]

Data Filter	Platform	Criteria
Seal Quality	IonWorks Quattro	>30MΩ
Seal Drop	IonWorks Quattro	<50% Seal Drop (Seal Pre-Compound/Seal Post Compound)
Current Amplitude	IonWorks Quattro	>200pA

Assay Control Results

[0059] Both the positive and vehicle control data associated with each cell line assayed are shown below as an example. The mean is shown for each positive and negative control as solid symbol with the total number of individual well replicates given next to the solid symbol. In addition, the individual data of each well are shown on the graph as open symbols so that the variation about the mean value can be readily assessed. These data are provided to aid in determining whether a compound has activities on the ion channel relative to the control data and provides an indication of assay variability and accordingly is used to judge the effect size of a compound-specific effect that can be detected. Shown below are the assay controls for the Nav1.6 IonWorks Quattro assay. Lidocaine, a Nav1.6 reference compound, inhibited evoked currents in a concentration and use dependent manner as predicted.



P1 - pulse 1; P25 - pulse 25.

A Post/Pre value of 1.0 corresponds to 0% inhibition, a Post/Pre value of 0.0 corresponds to 100% inhibition. To illustrate the variation of the assay, both example **106** of WO2015/130905 showing 14% inhibition of Nav 1.6 at 5 μM (normalized, see Table 3) and example 7 of the present invention showing -15% inhibition of Nav 1.6 at 5 μM (normalized, see Table 4), respectively, are within the variation of the assay when compared to assay control data, and are therefore not showing any significant inhibition of the Nav 1.6 channel at 5 μM.

[0060] Tables 3 and 4 show the normalized percentage inhibition of Nav1.6 channel. The normalized data show the compound data normalized to vehicle control (0% inhibition) and maximal inhibition control (100% inhibition); maximum inhibition at P1 by 1000 μM lidocaine (not normalized) was ranging from 46.4% to 47.2% across the experiments. (see also the figure Assay Control Results above).

Table 3 Normalized in vitro Nav 1.6 inhibition of the closest prior art compounds (examples **100**, **105**, **106** and **107** in WO2015/130905) as obtained in the same electrophysiology assay as compounds in Table 4 (concentrations: 1 μM and 5 μM).

Example number in WO2015/130905	**Normalized %inhibition at 1 μM**	**Normalized %inhibition at 5 μM**	**Percentage SEM at 1 μM**	**Percentage SEM at 5 μM**
100	2.2	37.8	6.2	8.4
105	18.2	68	2.6	4.1
106	-0.7	14	1.6	0.4
107	-8.5	13.1	3.9	2.8

Table 4 Normalized in vitro Nav 1.6 inhibition of the compounds of the present invention as obtained in the same electrophysiology assay as prior art compounds in Table 3 (concentrations: 1 μM and 5 μM).

Example number	Normalized %inhibition at 1 μM	Normalized %inhibition at 5 μM	Percentage SEM at 1 μM	Percentage SEM at 5 μM
1	-9	0.5	5.5	3.8
2	-4.4	-4.0	3.8	4.2
3	4.6	6.8	2.5	0.9
4	3.4	5	5.0	5.1
5	-3.9	3.7	1.9	2.2
6	5.6	0.2	2.1	2.7
7	-9	-15	5.4	1.6
8	3	1.1	5.1	4.2
9	0	4.6	0	3.8
18	-5	-10	4.3	3.7
30	-13.4	-9.4	5.3	4.6
31	-5.8	-7	3.6	1.2
33	-10.5	-6.6	4.6	1.0

[0061] NR2B negative allosteric modulators covered by general structure **A** which are not showing any significant Nav1.6 inhibition are preferred.

[0062] The compounds of the present invention do not show any significant inhibition of the Nav 1.6 channel at 1 and 5 μM, respectively (see Table 4 and Assay Control Results), whereas examples **100** and **105** of WO2015/130905 show 37.8% and 68% inhibition of Nav 1.6 at 5μM, respectively (see Table 3). Examples **106** and **107** of WO2015/130905 do not show any significant inhibition of the Nav 1.6 channel at 1 and 5 μM, respectively (i.e. inhibition is within assay variability, see Table 3 and Assay Control Results).

MDCK assay P-gp

[0063] Apparent permeability coefficients (Papp) of the compounds across the MDCK-MDR1 monolayers (MDCKII cells transfected with human MDR1 cDNA expression plasmid) are measured in apical-to-basal (AB) and basal-to-apical (BA) direction. MDCK-MDR1 cells (6 x 10^5 cells/cm^2) are seeded on filter inserts (Corning, Transwell, polycarbonate, 0.4 μm pore size) and cultured for 9 to 10 days. Compounds dissolved in DMSO stock solution (1 - 20 mM) are diluted with HTP-4 aqueous buffer (128.13 mM NaCl, 5.36 mM KCl, 1 mM $MgSO_4$, 1.8 mM $CaCl_2$, 4.17 mM $NaHCO_3$, 1.19 mM Na_2HPO_4, 0.41 mM NaH_2PO_4, 15 mM HEPES, 20 mM glucose, pH 7.4) supplemented with 0.25% BSA to prepare the transport solutions (final concentration: 1 or 10 μM, final DMSO <= 0.5 %). The transport solution is applied to the apical or basolateral donor side for measuring A-B or B-A permeability, respectively. The receiver side contains HTP-4 buffer supplemented with 0.25% BSA. Samples are collected at the start and end of experiment from the donor and at various time intervals for up to 2 hours also from the receiver side for concentration measurement by HPLC-MS/MS (Rapid-Fire High-throughput MS System (Agilent) coupled to QTrap 6500 (AB Sciex) or TSQ Vantage (Thermo Scientific)). Sampled receiver volumes are replaced with fresh receiver solution. Efflux ratio is calculated dividing the Papp (b-a) values by the Papp (a-b) values. Results are shown in Table 5.

Table 5

Ex.	Papp (a-b) mean [10-6 cm/s]	efflux ratio PEBA/PEAB
1	59	0.7
2	76	0.6
3	75	0.7
4	61	0.7

(continued)

Ex.	Papp (a-b) mean [10-6 cm/s]	efflux ratio PEBA/PEAB
5	59	0.8
6	71	0.8
7	66	0.7
8	70	0.6
9	62	0.9
18	61	0.8
30	81	0.4
31	66	0.6
33	59	0.7

[0064] The experimental results above show that compounds of the present invention are potent NR2B NAMs having high membrane permeability and no in vitro efflux anticipating excellent capability to cross the blood brain barrier.

Metabolic stability

[0065] The metabolic degradation of the test compound was assayed at 37 °C with pooled human liver microsomes. The final incubation volume of 60 μl per time point contains TRIS buffer pH 7.6 at room temperature (0.1 M), magnesium chloride (5 mM aqueous solution), microsomal protein (1 mg/mL for human) and the test compound at a final concentration of 1 μM. Following a short preincubation period at 37°C, the reactions were initiated by addition of betanicotinamide adenine dinucleotide phosphate, reduced form (NADPH, 1 mM), and terminated by transferring an aliquot into acetonitril after different time points. After centrifugation (10000 g, 5 min), an aliquot of the supernatant was assayed by HPLC-MS/MS as described above for the MDCK assay P-gp for the amount of parent compound. The half-life was determined by the slope of the semi-logarithmic plot of the concentration-time profile. Results are shown in Table 6.

Table 6

Ex.	Half-life - t1/2 [min] human liver microsomes
1	>130
2	>130
3	>130
4	>130
5	>130
6	>130
7	>130
8	>130
9	>130
18	>130
30	>130
31	>130
33	>130

[0066] The experimental results above show that compounds of the present invention are potent NR2B NAMs having high stability in human liver microsomes.

[0067] The present invention provides compounds according to formula **A** that unexpectedly result in a favorable combination of the following key parameters:

1) potent and selective negative allosteric modulation of NR2B,
2) high stability in human liver microsomes, and
3) high permeability and no in vitro efflux at MDCK-MDR1 cell transporters.

Pharmaceutical Composition

[0068] Suitable preparations for administering the compounds of the present invention will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives, powders, etc.. The content of the pharmaceutically active compound(s) may vary in the range from 0.1 to 95 wt.-%, preferably 5.0 to 90 wt.-% of the composition as a whole.

[0069] Suitable tablets may be obtained, for example, by mixing a compound of the present invention with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants and pressing the resulting mixture to form tablets.

Use in treatment

[0070] Human therapeutic applications of NR2B NAM have been summarized in reviews by Traynelis et al. (Traynelis et al., Pharmacology Reviews, 2010, 62:405), Beinat et al. (Beinat et al., Current Medicinal Chemistry, 2010, 17:4166) and Mony et al. (Mony et al., British J. Pharmacology, 2009, 157:1301).

[0071] The present invention relates to compounds which are useful in the treatment of psychiatric disorders, diseases and conditions wherein negative allosteric modulation of NR2B is of therapeutic benefit, including: (1) mood disorders and mood affective disorders; (2) schizophrenia spectrum disorders; (3) neurotic, stress-related and somatoform disorders including anxiety disorders; (4) disorders of psychological development; (5) behavioral syndromes associated with physiological disturbances and physical factors; (6) substance-related and addictive disorders; (7) disease associated with symptoms of negative and positive valence; (8) pain; (9) cerebrovascular diseases; (10) episodic and paroxysmal disorders; (11) neurodegenerative diseases.

[0072] In view of their pharmacological effect, compounds of the present invention are suitable for use in the treatment of a disorder, disease or condition selected from the list consisting of

(1) treatment of mood disorders and mood affective disorders including bipolar disorder I depressed, hypomanic, manic and mixed form; bipolar disorder II; depressive disorders, such as single depressive episode or recurrent major depressive disorder, minor depressive disorder, depressive disorder with postpartum onset, depressive disorders with psychotic symptoms; major depressive disorder with or without concomitant anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia.

(2) treatment of mood disorders belonging to the schizophrenia spectrum and other psychotic disorders including schizophrenia and schizoaffective disorder with associated negative and cognitive symptoms.

(3) treatment of disorders belonging to the neurotic, stress-related and somatoform disorders including anxiety disorders, general anxiety disorder, panic disorder with or without agoraphobia, specific phobia, social phobia, chronic anxiety disorders; obsessive compulsive disorder; reaction to sever stress and adjustment disorders, such as post-traumatic stress disorder; other neurotic disorders such as depersonalisation-derealisation syndrome.

(4) treatment of disorders of psychological development including pervasive developmental disorders, including Asperger's syndrome and Rett's syndrome, autistic disorders, childhood autism and overactive disorder associated with mental retardation and stereotyped movements, specific developmental disorder of motor function, specific developmental disorders of scholastic skills, attention deficit/hyperactivity disorder.

(5) treatment of behavioral syndromes associated with physiological disturbances and physical factors including mental and behavioural disorders associated with the puerperium, including postnatal and postpartum depression; eating disorders, including anorexia nervosa and bulimia nervosa and other impulse control disorders.

(6) treatment of disorders of substance-related and addicitive disorders, which are substance use disorders induced by alcohol, cannabis, hallucinogen, stimulant, hypnotic, tobacco.

(7) treatment of disease associated with symptoms of negative and positive valence including anhedonia, sustained threat and loss, suicidal ideation.

(8) treatment of acute and chronic pain which is related to neuropathy, e.g. diabetic neuropathy or polyneuropathy, physiological processes and physical disorders including e.g. low back pain, pain in the joints, disease of the musculoskeletal system and connective tissue, e.g. rheumatism, myalgia, nerve, nerve root and plexus disorders, e.g. phantom limb syndrome with pain, carpal tunnel syndrome.

(9) treatment of cerebrovascular diseases, e.g. intracerebral or subararchnoid haemorrhage, cerbral infarction, stroke, occlusion and stenosis, cerebral atherosclerosis, cerebral amyloid angiopathy.

(10) treatment of episodic and paroxymal disorders, e.g. epilepsy.
(11) treatment of diseases which include forms of neurodegeneration, e.g. stroke, Alzheimer's disease and Huntingon's disease.

[0073] As used herein, unless otherwise noted, the terms "treating", "treatment" shall include the management and care of a human subject or human patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present invention to prevent the onset of the symptoms or complications, alleviate the symptoms or complications, or eliminate the disease, condition, or disorder.

[0074] As used herein, unless otherwise noted, the term "prevention" shall include (a) reduction in the frequency of one or more symptoms; (b) reduction in the severity of one or more symptoms; (c) the delay or avoidance of the development of additional symptoms; and/or (d) delay or avoidance of the development of the disorder or condition. According to another aspect, the present invention provides a compound of formula **A** or a pharmaceutically acceptable salt thereof for use in the treatment and/or prevention of the above mentioned conditions.

[0075] According to another aspect, the present invention provides a compound of formula **A** according to any one of the preceding aspects characterized in that the compound of formula **A** is used in addition to behavioural therapy, TMS (transcranial magnetic stimulation), ECT (electroconvulsive therapy) and other therapies.

Combination Therapy

[0076] Compounds according to the present invention can be combined with other treatment options known to be used in the art in connection with a treatment of any of the indications the treatment of which is in the focus of the present invention.

[0077] According to another aspect, the present invention provides a compound of formula **A** according to any one of the preceding aspects characterized in that the compound of formula **A** is administered in addition to treatment with one or more antidepressant selected from the list consisting of duloxetine, escitalopram, bupropion, venlafaxine, desvenlafaxine, sertraline, paroxetine, fluoxetine, vortioxetine, mirtazapine, citalopram, vilazodone, trazodone, amitriptyline, clomipramine, agomelatine, levomilnacipran, lithium, doxepin, nortriptyline. The term "antidepressant" shall mean any pharmaceutical agent or drug which can be used to treat depression or diseases assocaited with depressive symptoms.

[0078] According to another aspect, the present invention provides a compound of formula **A** according to any one of the preceding aspects characterized in that the compound of formula **A** is administered in addition to treatment with one or more antipsychotic selected from the list consisting of aripiprazole, paliperidone palmitate, lurasidone, quetiapine, risperidone, olanzapine, paliperidone, brexpiprazole, clozapine, asenapine, chlorpromazine, haloperidol, cariprazine, ziprasidone, amisulpride, iloperidone, fluphenazine, blonanserin, aripiprazole lauroxil. The term "antipsychotic" shall mean any pharmaceutical agent or drug which can be used to treat diseases associated with psychotic or depressive symptoms.

[0079] According to another aspect, the present invention provides a compound of formula **A** according to any one of the preceding aspects characterized in that the compound of formula **A** is administered in addition to treatment with one or more psychostimulant selected from the list consisting of lisdexamfetamine, methylphenidate, amfetamine, dexamfetamine, dexmethylphenidate, armodafinil, modafinil. The term "psychostimulant" shall mean any pharmaceutical agent or drug which can be used to treat diseases like mood disorders, or impulse control disorders.

[0080] According to another aspect, the present invention provides a compound of formula **A** according to any one of the preceding aspects characterized in that the compound of formula **A** is administered in addition to treatment with nootropics selected from the list consisting of oxiracetam, piracetam, or the natural product St John's-wort.

[0081] According to another aspect, the present invention provides a compound of formula **A** which is administered in addition to treatment with one or more antidepressant, antipsychotic, psychostimulant, nootropics or natural product according to any one of the preceding aspects characterized in that the combination of compound of formula **A** and one or more antidepressant, antipsychotic, psychostimulant, nootropics or natural product is used in addition to behavioural therapy, TMS (transcranial magnetic stimulation), ECT (electroconvulsive therapy) and other therapies.

EXPERIMENTAL SECTION

Abbreviations:

[0082]

ACN	acetonitrile
APCI	Atmospheric pressure chemical ionization
Boc	tert-butyloxycarbonyl

CDI	1,1'-carbonyldiimidazole
CO_2	Carbon Dioxide
D	day
DA	Diode Array
DCM	dichloromethane
DIPE	diisopropylether
DIPEA	diisopropylethylamine
DMF	dimethylformamide
e.e.	enantiomeric excess
ESI	electrospray ionization (in MS)
EtOAc	ethyl acetate
EtOH	ethanol
Ex.	example
h	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate
HPLC	high performance liquid chromatography
HPLC-MS	coupled high performance liquid chromatography-mass spectrometry
M	molar (mol/L)
MeOH	methanol
min	minute(s)
MS	mass spectrometry
MW	molecular weight
NH3	ammonia
PSI	Pound per square inch
rt	room temperature
R_t	retention time
scCO2	supercritical CO2
solv	solvent
TBTU	*O*-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
SFC	Supercritical fluid chromatography

Abbreviations within spectral data:

[0083]

1H- NMR	Proton nuclear magnetic resonance
br	broad
δ	chemical shift
d	doublet
dd	doublet of doublets
dt	doublet of triplets
DMSO-d_6	hexa-deutero-dimethylsulfoxide
H	proton
Hz	Hertz (=1/second)
J	coupling constant
m	multiplet
ppm	parts per million
q	quartet
s	singlet
t	triplet
td	triplet of doublets

General Analytics.

[0084] All reactions were carried out using commercial grade reagents and solvents. NMR spectra were recorded on a Bruker AVANCE III HD 400 MHz instrument using Top-Spin 3.2 pl6 software. Chemical shifts are given in parts per million (ppm) downfield from internal reference trimethylsilane in δ units. Selected data are reported in the following manner: chemical shift, multiplicity, coupling constants (*J*), integration. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 F254 plates. All compounds were visualized as single spots using short wave UV light. Low resolution mass spectra were obtained using a liquid chromatography mass spectrometer (LCMS) that consisted of an Agilent 1100 series LC coupled to a Agilent 6130 quadrupole mass spectrometer (electrospray positive ionization).

Methods:

HPLC-MS methods:

Method 1

[0085]

Method Name:	***Z003_S05***				
Device description:	Agilent 1200 with DA- and MS-Detector				
Column:	XBridge C18_3.0 x 30 mm_2.5 μm				
Column producer:	Waters				
Description:					
Gradient/Solvent Time [min]	% Sol [Water 0.1% NH_3]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]	Back pressure [PSI]
0.0	95.0	5.0	2.2	60.0	
0.2	95.0	5.0	2.2	60.0	
1.2	0.0	100.0	2.2	60.0	
1.25	0.0	100.0	3.0	60.0	
1.4	0.0	100.0	3.0	60.0	

Method 2

[0086]

Method Name:	***Z011_S03***
Device description:	Agilent 1200 with DA- and MS-Detector
Column:	XBridge C18_3.0 x 30 mm_2.5 μm
Column producer:	Waters
Description:	

Gradient/Solvent Time [min]	% Sol [Water 0.1% NH_3]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]	Back pressure [PSI]
0.0	97.0	3.0	2.2	60.0	
0.2	97.0	3.0	2.2	60.0	
1.2	0.0	100.0	2.2	60.0	
1.25	0.0	100.0	3.0	60.0	
1.4	0.0	100.0	3.0	60.0	

Method 3

[0087]

Method Name:	***Z017_S04***
Device description:	Agilent 1200 with DA- and MS-Detector
Column:	Sunfire C18_3.0 x 30 mm_1.8μm
Column producer:	Waters
Description:	

Gradient/Solvent Time [min]	% Sol [Water 0.1% TFA]	% Sol [Acetonitrile]	Flow [ml/min]	Temp [°C]	Back pressure [PSI]
0.0	97.0	3.0	2.2	60.0	
0.2	97.0	3.0	2.2	60.0	
1.2	0.0	100.0	2.2	60.0	
1.25	0.0	100.0	3.0	60.0	
1.4	0.0	100.0	3.0	60.0	

Chiral SFC analytical methods:

Method 4: I_SA_20_IPA_NH_3_001

[0088]

Method Name:	***I_SA_20_IPA_NH_3_001***
Device description:	Agilent 1260 SFC with DAD and MS
Column:	CHIRAL ART® Amylose SA_4.6 x 250 mm_5 μm
Column producer:	YMC

Gradient/Solvent Time [min]	% Sol [scCO2]	% Sol [ETOH 20mM NH_3]	Flow [ml/min]	Temp [°C]	Back pressure [PSI]
0.0	85.0	15.0	4.0	40.0	2175.0
10.0	85.0	15.0	4.0	40.0	2175.0

Method 5: I_IC_30_IPA_NH_3_001

[0089]

Method Name:	***I_IC_30_IPA_NH_3_001***
Device description:	Agilent 1260 SFC with DAD and MS
Column:	Chiralpak® IC_4.6 x 250 mm_5 μm
Column producer:	Daicel

Gradient/Solvent Time [min]	% Sol [scCO2]	% Sol [MEOH 20mM NH_3]	Flow [ml/min]	Temp [°C]	Back pressure [PSI]
0.0	70.0	30.0	4.0	40.0	2175.0
10.0	7.0	30.0	4.0	40.0	2175.0

Preparative HPLC conditions for purification:

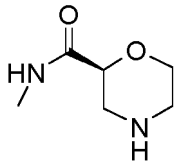
[0090]

Instrument: (Agilent 1100). Eluents: Water - NH_4OH 5% solution in Water - CH_3CN;
Flow: 50 ml/min; Temperature 60°C; Column: XBridge C18.

Preparation of Intermediates:

Example 1a

[0091]

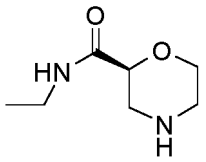


[0092] (S)-Morpholine-2-carboxylic acid methyl ester hydrochloride (35 g; 192.7 mmol) was mixed together with 400 ml of a 8M solution of Methylamine in EtOH. The reaction mixture was stirred at room temperature over 60 hours. The solvent was removed under reduced pressure, THF (500 ml) and TEA (50 ml) were added and the reaction mixture stirred at room temperature during 12 hours. A precipitate was formed; the suspension was filtered via a glass filter and the filtrate solution was evaporated under reduced pressure. Obtained 23.5 g of the desired product as solid.

Example 1a: Analytical data	
Chiral SFC Method: I_IC_30_IPA_NH_3_001.M	Rt [min]: 3.72; e.e. 100%
MS: 145 $(M+H)^+$	

Example 1b

[0093]

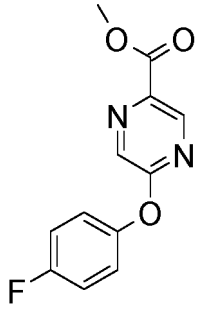


[0094] (S)-Morpholine-2-carboxylic acid methyl ester hydrochloride (5 g; 27.5 mmol) was mixed together with 138 ml of a 2M solution of Ethylamine in THF. The reaction mixture was stirred at room temperature over 60 hours. The solvent was removed under reduced pressure, THF (500 ml) and TEA (50 ml) were added and the reaction mixture stirred at room temperature during 12 hours. A precipitate was formed; the suspension was filtered via a glass filter and the filtrate solution was evaporated under reduced pressure. Obtained 4.3 g of the desired product as solid.

Example 1b:	
Chiral SFC Method: I_IC_30_IPA_NH_3_001.M	Rt [min]: 3.23; e.e. > 99%
MS: 159 $(M+H)^+$	

Example 2a

[0095]

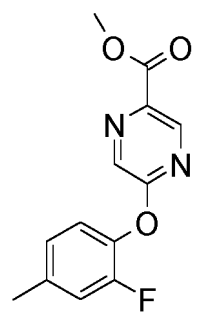


[0096] 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol) and 4-Fluoro-phenol (0.78g; 6.95 mmol) were dissolved in DMSO (10 ml); K_2CO_3 (1.2g; 8.69 mmol) was added and the reaction mixture was stirred 45 min at 60°C. The reaction mixture was poured into water (50 ml) and stirred 15 minutes. The obtained precipitate was washed with water, a 10% aqueous solution of K_2CO_3 and dried. Obtained 1.4 g of solid.

Example 2a:	
HPLC-MS; Method : Z011_S03; R_t [min] : 0.92	MS: 249 $(M+H)^+$

Example 2b

[0097]



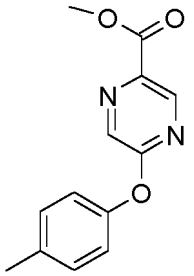
[0098] Example 2b was synthesised in analogy to Example 2a.

[0099] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 2-Fluoro-4-methyl phenol (0.75 ml; 6.95 mmol). Obtained 1.5g of the desired compound as a solid.

Example 2b:	
HPLC-MS; Method : Z011_S03; R_t [min] : 0.99	MS: 263 $(M+H)^+$

Example 2c

[0100]



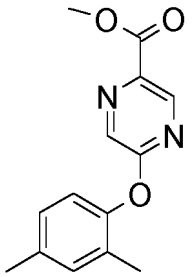
[0101] Example 2c was synthesised in analogy to Example 2a.

[0102] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 4-methyl phenol (0.73 ml; 6.95 mmol). Obtained 1.35g of the desired compound as a solid.

Example 2c:	
HPLC-MS; Method : Z011_S03; R_t [min] : 0.97	MS: 245 $(M+H)^+$

Example 2d

[0103]



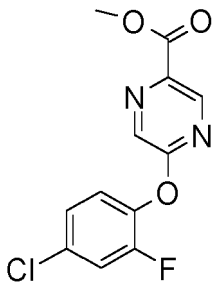
[0104] Example 2d was synthesised in analogy to Example 2a.

[0105] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 2,4-dimethyl phenol (0.83 ml; 6.95 mmol). Obtained 1.45g of the desired compound as a solid.

Example 2d:	
HPLC-MS; Method : Z018_S04; R_t [min] : 1.02	MS: 259 $(M+H)^+$

Example 2e

[0106]



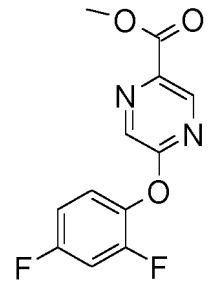
[0107] Example 2e was synthesised in analogy to Example 2a.

[0108] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 4-chloro-2-Fluoro-phenol (0.74 ml; 6.95 mmol). Obtained 1.55 g of the desired compound as a solid.

Example 2e:	
HPLC-MS (Z011_S03): R_t [min]: 1.01	MS: 283 and 285 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 2f

[0109]



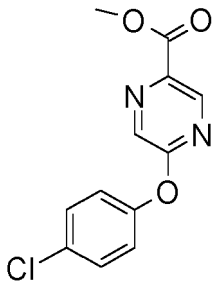
[0110] Example 2f was synthesised in analogy to Example 2a.

[0111] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 2,4-difluoro phenol (0.67 ml; 6.95 mmol). Obtained 1.50 g of the desired compound as a solid.

Example 2f:	
HPLC-MS (Z011_S03): R_t [min]: 0.95	MS: 267 $(M+H)^+$

Example 2g

[0112]



[0113] Example 2g was synthesised in analogy to Example 2a.

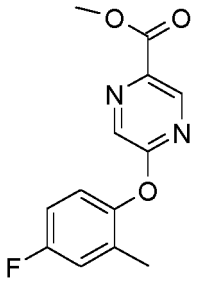
[0114] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 4-chloro-phenol (0.89 g;

6.95 mmol). Obtained 1.5 g of the desired compound as a solid.

Example 2g	
HPLC-MS (Z011_S03): Rt [min]: 0.99	MS: 265 and 267 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 2h

[0115]



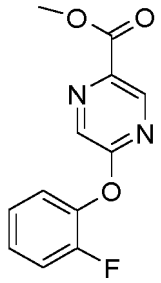
[0116] Example 2h was synthesised in analogy to Example 2a.

[0117] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 4-fluoro-2-methyl phenol (0.88 g; 6.95 mmol). Obtained 1.5 g of the desired compound as a solid.

Example 2h	
HPLC-MS (Z011_S03): R_t [min]: 0.97	MS: 263 $(M+H)^+$

Example 2i

[0118]



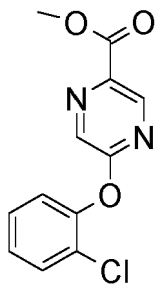
[0119] Example 2i was synthesised in analogy to Example 2a.

[0120] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 2-fluoro phenol (0.62 ml; 6.95 mmol). Obtained 1.22 g of the desired compound as a solid.

Example 2i	
HPLC-MS (Z011_S03): R_t [min]: 0,92	MS: 249 $(M+H)^+$

Example 2k

[0121]

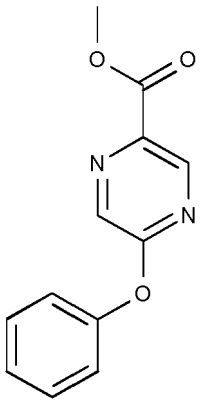


[0122] Example 2k was synthesised in analogy to Example 2a.
[0123] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1g; 5.79 mmol), 2-chloro phenol (0.71 ml; 6.95 mmol). Obtained 1.51 g of the desired compound as a solid.

Example 2k	
HPLC-MS (Z011_S03): R_t [min]: 0.97	MS: 265 and 267 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 2j

[0124]

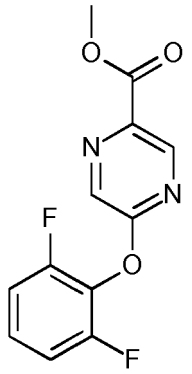


[0125] Example 2j was synthesised in analogy to Example 2a.
[0126] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1.00 g; 5.80 mmol), Phenol (0.65 g; 6.95 mmol). Obtained 1.30 g of the desired compound as a solid.

Example 2j	
HPLC-MS (Z017_S04): R_t [min]: 0.92	MS: 231 $(M+H)^+$

Example 21

[0127]



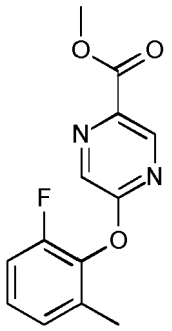
[0128] Example 21 was synthesised in analogy to Example 2a.

[0129] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (1.00 g; 5.80 mmol), 2.6-Difluorophenol (0.90 g; 6.95 mmol). Obtained 1.52 g of the desired compound as a solid.

Example 21	
HPLC-MS (Z017_S04): R_t [min]: 0.97	MS: 267 $(M+H)^+$

Example 2m

[0130]



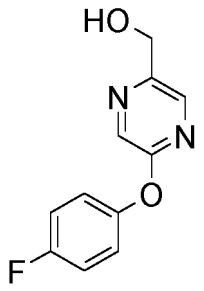
[0131] Example 2m was synthesised in analogy to Example 2a.

[0132] Starting materials: 5-Chloro-pyrazine-2-carboxylic acid methyl ester (320 mg; 1.85 mmol), 2-fluoro-6-methyl-phenol (257 mg; 2.04 mmol). Obtained 480 mg of the desired compound as a solid.

Example 2m	
HPLC-MS (Z017_S04): R_t [min]: 1.00	MS: 263 $(M+H)^+$

Example 3a

[0133]

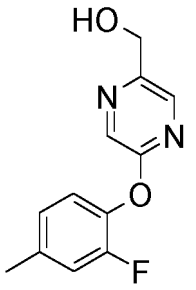


[0134] Example 2a (1.4g; 5.64 mmol) was dissolved in MeOH (15 ml); $NaBH_4$ (0.64g; 16.9 mmol) was added and the reaction mixture stirred 3 hours at room temperature. Water was added to quench the reaction; the reaction mixture was then evaporated under reduced pressure and the residue partitioned between EtOAc (100 ml) and a 10% aqueous solution of K_2CO_3 (30 ml). The organic phase was dried over Na_2SO_4 and the residue obtained after evaporation of the solvents purified by flash chromatography (Eluent: gradient starting with Petrol Ether/EtOAc 3/1 to Petrol Ether/EtOAc 2/1) . Obtained 0.8 g of the desired compound (oil).

Example 3a	
HPLC-MS; Method : Z011_S03; R_t [min] : 0.80	MS: 221 $(M+H)^+$

Example 3b

[0135]

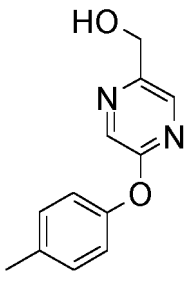


[0136] Example 3b was prepared in analogy to Example 3a. Starting materials: Example 2b (1.5g; 5.72 mmol). Obtained 1g of the desired compound.

Example 3b	
HPLC-MS; Method : Z011_S03; R_t [min] : 0.88	MS: 235 $(M+H)^+$

Example 3c

[0137]

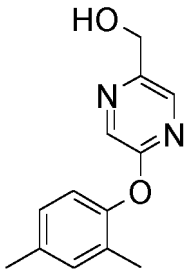


[0138] Example 3c was prepared in analogy to Example 3a. Starting materials: Example 2c (1.35 g; 5.53 mmol). Obtained 0.95 g of the desired compound.

Example 3c	
HPLC-MS (Z011_S03): R_t [min]: 0.86	MS: 217 $(M+H)^+$

Example 3d

[0139]

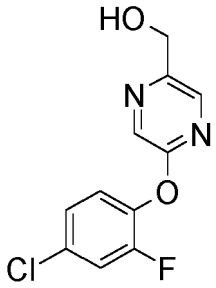


[0140] Example 3d was prepared in analogy to Example 3a. Starting materials: Example 2d (1.45 g; 5.61 mmol). Obtained 0.83 g of the desired compound.

Example 3d	
HPLC-MS (Method): Z011_S03 R_t [min] : 0.91	MS: 231 $(M+H)^+$

Example 3e

[0141]

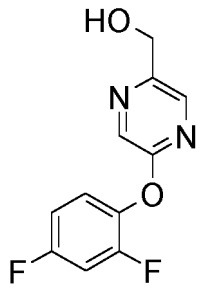


[0142] Example 3e was prepared in analogy to Example 3a. Starting materials: Example 2e (1.55 g; 5.48 mmol). Obtained 1.02 g of the desired compound.

Example 3e	
HPLC-MS (Method): Z011_S03 R_t [min] : 0.91	MS: 255 and 257 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 3f

[0143]

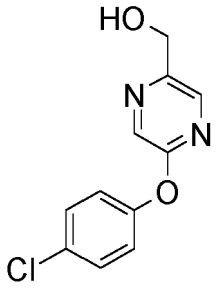


[0144] Example 3f was prepared in analogy to Example 3a. Starting materials: Example 2f (1.50 g; 5.64 mmol). Obtained 1.04 g of the desired compound.

Example 3f	
HPLC-MS (Method): Z011_S03 R_t [min] : 0.83	MS: 239 $(M+H)^+$

Example 3g

[0145]

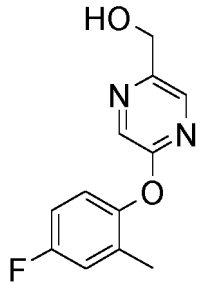


[0146] Example 3g was prepared in analogy to Example 3a. Starting materials: Example 2g (1.5 g; 5.67 mmol). Obtained 0.83 g of the desired compound.

Example 3g	
HPLC-MS (Method): Z011_S03 R_t [min] : 0.88	MS: 237 and 239 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 3h

[0147]

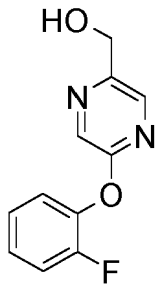


[0148] Example 3h was prepared in analogy to Example 3a. Starting materials: Example 2h (1.5 g; 5.72 mmol). Obtained 0.86 g of the desired compound.

Example 3h	
HPLC-MS (Method): Z011_S03 R_t [min] : 0.86	MS: 235 $(M+H)^+$

Example 3i

[0149]

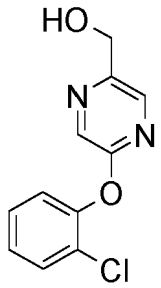


[0150] Example 3i was prepared in analogy to Example 3a. Starting materials: Example 2i (1.22 g; 4.92 mmol). Obtained 0.75 g of the desired compound.

Example 3i	
HPLC-MS (Method): Z011_S03 R_t [min] : 0.8	MS: 221 $(M+H)^+$

Example 3k

[0151]

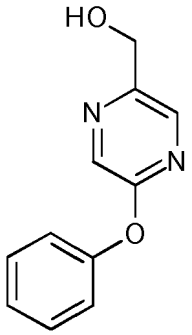


[0152] Example 3k was prepared in analogy to Example 3a. Starting materials: Example 2k (1.51 g; 5.71 mmol). Obtained 0.85 g of the desired compound.

Example 3k	
HPLC-MS (Method): Z011_S03 R_t [min] : 0.85	MS: 237 and 239 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 3j

[0153]

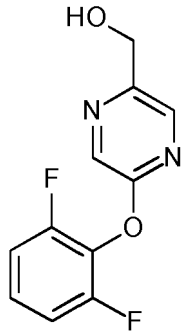


[0154] Example 3j was prepared in analogy to Example 3a. Starting materials: Example 2k (1.30 g; 5.65 mmol). The crude obtained after evaporation of the organic solvents was used as such in the next steps. Obtained 0.98 g of the desired compound (content 70%).

Example 3j	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.79	MS: 203 $(M+H)^+$

Example 31

[0155]

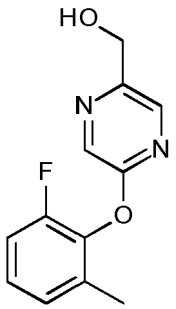


[0156] Example 31 was prepared in analogy to Example 3a. Starting materials: Example 21 (1.52 g; 5.71 mmol). The crude obtained after evaporation of the organic solvents was used as such in the next steps. Obtained 1.30 g of the desired compound (content 85%).

Example 31	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.84	MS: 238 $(M^*)^+$

Example 3m

[0157]

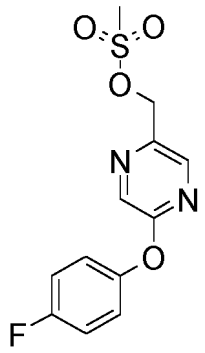


[0158] Example 3m was prepared in analogy to Example 3a. Starting materials: Example 2m (480 mg; 1.83 mmol). The crude product after evaporation of the organic solvents was used as such in the next steps. Obtained 420 mg of the desired compound (content 85%).

Example 3m	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.87	MS: 235 $(M+H)^+$

Example 4a

[0159]

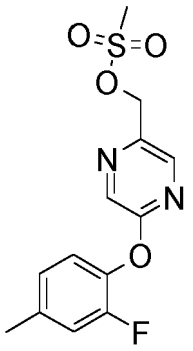


[0160] Example 3a (0.8 g; 3.63 mmol) was dissolved in 2-methyl-THF (Aldrich) (40 ml); TEA (0.76 ml; 5.45 mmol) was added dropwise, followed by Methansulphonyl Chloride (0.3 ml; 4 mmol). The mixture was stirred 1.5 hours at rt before being worked up. A 5% $NaHCO_3$ solution in water was added to reaction mixture, the phases were separated and dried over Na_2SO_4. The crude obtained after evaporation of the organic solvents was used as such in the next steps. Obtained 1.05 g of the desired product.

Example 4a	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.93	MS: 299 $(M+H)^+$

Example 4b

[0161]

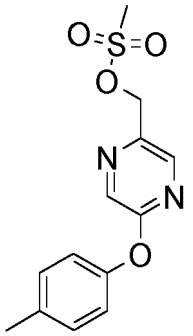


[0162] Example 4b was prepared in analogy to example 4a. Starting material: Example 3b (1g; 4.27 mmol). Obtained 1.3g. The product was used as such in the next step.

Example 4b	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.99	MS: 313 $(M+H)^+$

Example 4c

[0163]

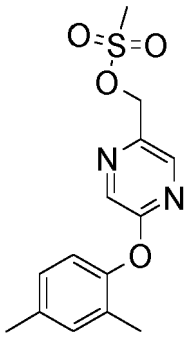


[0164] Example 4c was prepared in analogy to example 4a. Starting material: Example 3c (0.95 g; 4.39 mmol). Obtained 1.25 g. The product obtained after work up was used as such in the next step.

Example 4c	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.98	MS: 295 $(M+H)^+$

Example 4d

[0165]

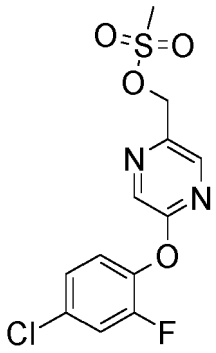


[0166] Example 4d was prepared in analogy to example 4a. Starting material: Example 3d (0.83 g; 3.61 mmol). Obtained 1.1g. The product obtained after work was used as such in the next step.

Example 4d	
HPLC-MS (Method): Z017_S04 R_t [min] : 1.02	MS: 309 $(M+H)^+$

Example 4e

[0167]

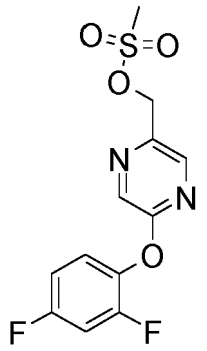


[0168] Example 4e was prepared in analogy to example 4a. Starting material: Example 3e (1.02 g; 4.0 mmol). Obtained 1.32 g. The product obtained after work was used as such in the next step.

Example 4e	
HPLC-MS (Method): Z017_S04 R_t [min] : 1.01	MS: 333 and 335 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 4f

[0169]

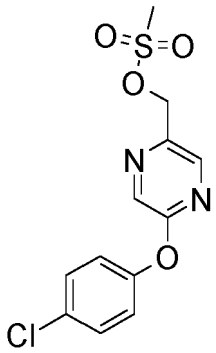


[0170] Example 4f was prepared in analogy to example 4a. Starting material: Example 3f (1.04 g; 4.37 mmol). Obtained 1.35 g. The product obtained after work was used as such in the next step.

Example 4f	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.95	MS: 317 $(M+H)^+$

Example 4g

[0171]

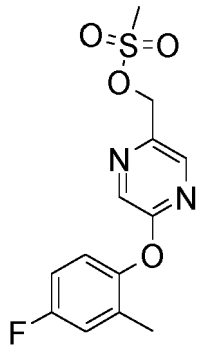


[0172] Example 4g was prepared in analogy to example 4a. Starting material: Example 3g (0.83 g; 3.51 mmol). Obtained 1.1 g. The product obtained after work was used as such in the next step.

Example 4g	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.99	MS: 315 and 317 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 4h

[0173]

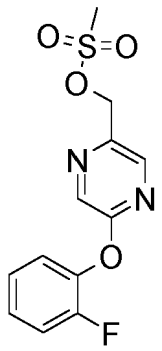


[0174] Example 4h was prepared in analogy to example 4a. Starting material: Example 3h (0.86 g; 3.67 mmol). Obtained 1.12 g. The product obtained after work was used as such in the next step.

Example 4h	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.97	MS: 313 $(M+H)^+$

Example 4i

[0175]

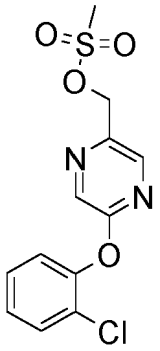


[0176] Example 4i was prepared in analogy to example 4a. Starting material: Example 3i (0.75 g; 3.41 mmol). Obtained 1.0 g. The product obtained after work was used as such in the next step.

Example 4i	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.93	MS: 299 $(M+H)^+$

Example 4k

[0177]

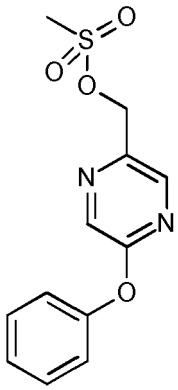


[0178] Example 4k was prepared in analogy to example 4a. Starting material: Example 3k (0.85 g; 3.59 mmol). Obtained 1.1 g. The product obtained after work was used as such in the next step.

Example 4k	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.97	MS: 315 and 317 $(M+H)^+$; Isotopic pattern for 1 Cl observed

Example 4j

[0179]

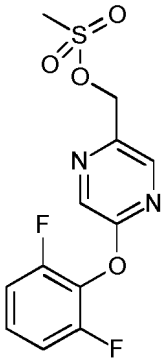


[0180] Example 4j was prepared in analogy to example 4a. Starting material: Example 3k (0.98 g; content 70%; 3.39 mmol). The product obtained after work up was used as such in the next step. Obtained 1.35 g of the desired product (content 70%).

Example 4j	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.91	MS: 281 $(M+H)^+$

Example 41

[0181]

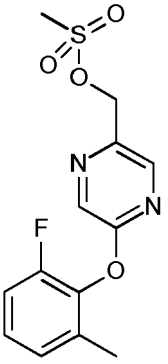


[0182] Example 41 was prepared in analogy to example 4a. Starting material: Example 31 (1.30 g; content 85%; 4.64 mmol). The product obtained after work up was used as such in the next step. Obtained 1.70 g (content 85%).

Example 41	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.95	MS: 317 $(M+H)^+$

Example 4m

[0183]



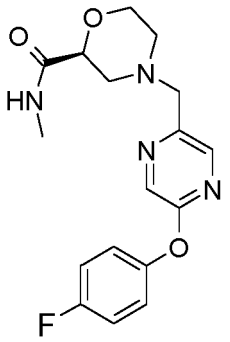
[0184] Example 4m was prepared in analogy to example 4a. Starting material: Example 3m (0.42 g; content 85%; 1.52 mmol). Obtained 0.55 g. The product obtained after work up was used as such in the next step.

Example 4m	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.98	MS: 313 $(M+H)^+$

EXEMPLARY EMBODIMENTS

Example 1

[0185]

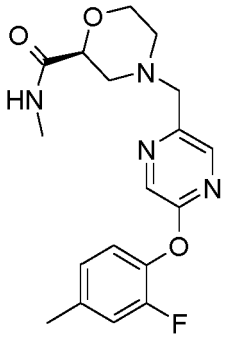


[0186] Example 4a (100 mg; 0.34 mmol) and Example 1a (53.17 mg; 0.37 mmol) were dissolved in THF (5 ml); pyridine (0.08 ml; 1 mmol) was added and the reaction mixture heated at 50°C during 5 hours. The reaction mixture was cooled to rt, diluted with MeOH (3 ml) and filtered via a syringe filter. The obtained solution was purified by preparative HPLC. Obtained 53 mg of the desired compound.

Example 1	
HPLC-MS; Method :Z011_S03; R_t [min] : 0.87	MS: 347 $(M+H)^+$
Chiral SFC; Method: I_SA_20_IPA_NH_3_001	Rt [min]: 2.00; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.02 (m, 1 H); 2.17 - 2.24 (m, 1 H); 2.58 (m, 3 H); 2.66 - 2.71 (m, 1 H); 2.95 (m, 1 H); 3.54 - 3.69 (m, 3 H); 3.83 - 3.90 (m, 2 H); 7.27 (m, 4 H); 7.67 (m, 1 H); 8.19 (m, 1 H); 8.47 (m, 1 H).	

Example 2

[0187]



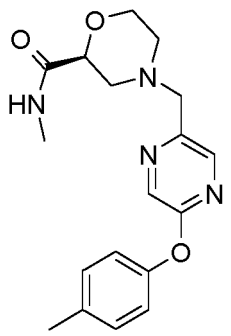
[0188] Example 2 was synthesised in analogy to example 1.

[0189] Starting materials: Example 4b (100 mg; 0.32 mmol) + Example 1a (50.78 mg; 0.35 mmol). The crude was purified by preparative HPLC. Obtained 105 mg of the desired compound.

Example 2	
HPLC-MS:Method : Z011_S03;; R_t [min]: 0.93	MS: 361 $(M+H)^+$
Chiral SFC Method: I_SA_20_IPA_NH_3_001	Rt [min]; 1.96; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.02 (m, 1 H); 2.16 - 2.24 (m, 1 H); 2.32 - 2.36 (m, 3 H); 2.57 (m, 3 H); 2.65 - 2.70 (m, 1 H); 2.94 (m, 1 H); 3.54 - 3.69 (m, 3 H); 3.83 - 3.90 (m, 2 H); 7.07 (m, 1 H); 7.21 (m, 1 H); 7.26 (m, 1 H); 7.67 (m, 1 H); 8.17 (m, 1 H); 8.55 (m, 1 H).	

Example 3

[0190]



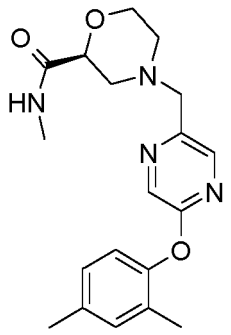
Example 3 was synthesised in analogy to example 1.

[0191] Starting materials: Example 4c (100 mg; 0.34 mmol) + Example 1a (53.9 mg; 0.37 mmol). The crude was purified by preparative HPLC. Obtained 80 mg of the desired compound.

Example 3	
HPLC-MS: Method : Z011_S03; R_t [min]: 0.91	MS; 343 $(M+H)^+$
Chiral SFC; Method: I_SA_20_IPA_NH_3_001	Rt [min]: 2.34; e.e. 99.59%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.02 (m, 1 H); 2.16 - 2.24 (m, 1 H); 2.30 - 2.34 (m, 3 H); 2.57 (m, 3 H); 2.68 (m, 1 H); 2.95 (m, 1 H); 3.54 - 3.68 (m, 3 H); 3.83 - 3.90 (m, 2 H); 7.06 - 7.10 (m, 2 H); 7.23 (m, 2 H); 7.63 - 7.70 (m, 1 H); 8.18 (m, 1 H); 8.43 (m, 1 H).	

Example 4

[0192]



[0193] Example 4 was synthesised in analogy to example 1.

[0194] Starting materials: Example 4d (100 mg; 0.32 mmol) + Example 1a (51.4 mg; 0.36 mmol). The crude was purified by preparative HPLC. Obtained 55 mg of the desired compound.

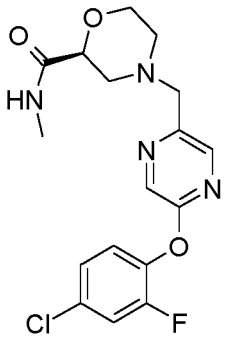
Example 4	
HPLC-MS Z003_S05: R_t [min]: 1.14	MS: 357 (M+H)+
Chiral SFC; Method: I_SA_20_IPA_NH_3_001	Rt [min]: 2.07; e.e. 94%

(continued)

Example 4
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.99 - 2.07 (m, 4 H); 2.15 - 2.24 (m, 1 H); 2.26 - 2.32 (m, 3 H); 2.57 (m, 3 H); 2.68 (m, 1 H); 2.94 (m, 1 H); 3.54 - 3.67 (m, 3 H); 3.83 - 3.89 (m, 2 H); 6.97 - 7.06 (m, 2 H); 7.11 - 7.14 (m, 1 H); 7.67 (m, 1 H); 8.13 - 8.16 (m, 1 H); 8.44 (m, 1 H).

Example 5

[0195]



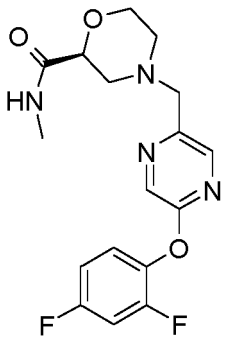
[0196] Example 5 was synthesised in analogy to example 1.

[0197] Starting materials: Example 4e (100 mg; 0.30 mmol) + Example 1a (47.66 mg; 0.33 mmol). The crude was purified by preparative HPLC. Obtained 70 mg of the desired compound.

Example 5	
HPLC-MS Z011_S03: R_t [min]: 10.96	MS: 381 and 383 $(M+H)^+$; Isotopic pattern for 1 Cl observed
Chiral SFC; Method: I_SA_20_IPA_NH_3_001	Rt [min]: 2.27; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.03 (m, 1 H); 2.21 (m, 1 H); 2.57 (m, 3 H); 2.65 - 2.70 (m, 1 H); 2.94 (m, 1 H); 3.54 - 3.70 (m, 3 H); 3.83 - 3.90 (m, 2 H); 7.37 (m, 1 H); 7.47 (m, 1 H); 7.63 - 7.69 (m, 2 H); 8.20 (d, *J*=1.31 Hz, 1 H); 8.61 (d, *J*=1.33 Hz, 1 H).	

Example 6

[0198]



Example 6 was synthesised in analogy to example 1.

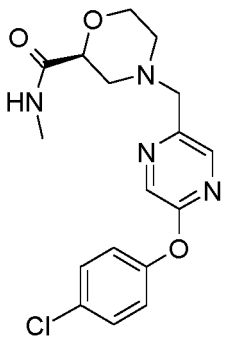
[0199] Starting materials: Example 4f (100 mg; 0.32 mmol) + Example 1a (50.14 mg; 0.35 mmol). The crude was

purified by preparative HPLC. Obtained 81 mg of the desired compound.

Example 6	
HPLC-MS: Method: Z003_S05; R_t [min]:1.05	MS: 365 $(M+H)^+$
Chiral SFC; Method: I_SA_20_IPA_NH_3_001	Rt [min]: 1.67; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.99 - 2.07 (m, 1 H); 2.20 (m, 1 H); 2.57 (m, 3 H); 2.64 - 2.72 (m, 1 H); 2.94 (m, 1 H); 3.54 - 3.71 (m, 3 H); 3.83 - 3.90 (m, 2 H); 7.14 - 7.20 (m, 1 H); 7.44 - 7.52 (m, 2 H); 7.63 - 7.72 (m, 1 H); 8.19 (d, *J*=1.37 Hz, 1 H); 8.60 (d, *J*=1.35 Hz, 1 H).	

Example 7

[0200]



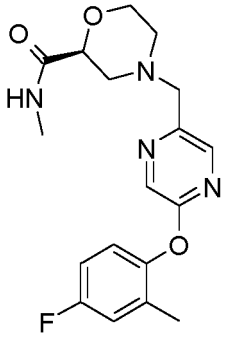
[0201] Example 7 was synthesised in analogy to example 1.

[0202] Starting materials: Example 4g (100 mg; 0.32 mmol) + Example 1a (50.39 mg; 0.35 mmol). The crude was purified by preparative HPLC. Obtained 97 mg of the desired compound.

Example 7	
HPLC-MS (Method): Z011_S03; R_t [min]: 0.93;	MS: 363 and 365 $(M+H)^+$; Isotopic pattern for 1 Cl observed
Chiral SFC; Method: I_SA_20_IPA_NH_3_001	R_t [min]:2.95; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.02 (m, 1 H) 2.21 (m, 1 H) 2.57 (m, 3 H) 2.65 - 2.74 (m, 1 H) 2.96 (m, 1 H) 3.54 - 3.70 (m, 3 H) 3.83 - 3.91 (m, 2 H) 7.24 - 7.29 (m, 2 H) 7.47 - 7.51 (m, 2 H) 7.68 (m, 1 H) 8.21 (d, *J*=1.35 Hz, 1 H) 8.50 (d, *J*=1.35 Hz, 1 H)	

Example 8

[0203]



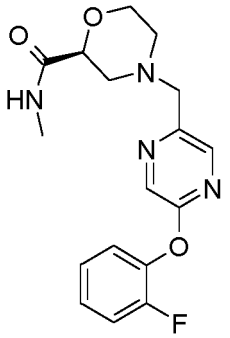
[0204] Example 8 was synthesised in analogy to example 1.

[0205] Starting materials: Example 4h (100 mg; 0.32 mmol) + Example 1a (50.78 mg; 0.35 mmol). The crude was purified by preparative HPLC. Obtained 60 mg of the desired compound.

Example 8	
HPLC-MS (Method): Z003_S05; R_t [min] : 1.09	MS: 361 $(M+H)^+$
Chiral SFC Method: I_SA_20_IPA_NH_3_001	R_t [min]: 1.79 e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.99 - 2.06 (m, 1 H); 2.08 - 2.10 (m, 3 H); 2.16 - 2.25 (m, 1 H); 2.57 (d, *J*=4.74 Hz, 3 H); 2.65 - 2.71 (m, 1 H); 2.95 (m, 1 H); 3.54 - 3.68 (m, 3 H); 3.83 - 3.90 (m, 2 H); 7.05 - 7.10 (m, 1 H); 7.16 - 7.22 (m, 2 H); 7.64 - 7.70 (m, 1 H); 8.16 (d, *J*=1.33 Hz, 1 H); 8.49 (d, *J*=1.32 Hz, 1 H).	

Example 9

[0206]



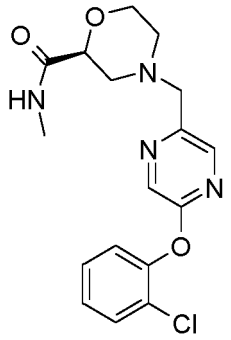
[0207] Example 9 was synthesised in analogy to example 1.

[0208] Starting materials: Example 4i (100 mg; 0.34 mmol) + Example 1a (53.17 mg; 0.37 mmol). The crude was purified by preparative HPLC. Obtained 49 mg of the desired compound.

Example 9	
HPLC-MS (Method): Z003_S05; R_t [min] : 1.03	MS: 347 $(M+H)^+$
Chiral SFC Method: I_SA_20_IPA_NH_3_001	R_t [min]: 1.84; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.02 (m, 1 H); 2.20 (m, 1 H); 2.56 - 2.59 (m, 3 H); 2.65 - 2.70 (m, 1 H); 2.94 (m, 1 H); 3.54 - 3.70 (m, 3 H); 3.83 - 3.90 (m, 2 H); 7.25 - 7.43 (m, 4 H); 7.64 - 7.69 (m, 1 H); 8.19 (m, 1 H); 8.59 (m, 1 H).	

Example 18

[0209]



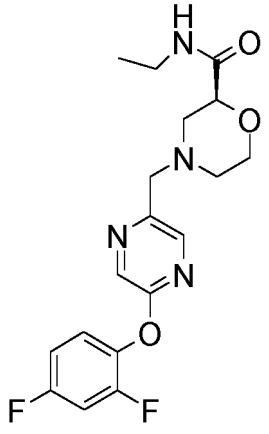
[0210] Example 18 was synthesised in analogy to example 1.

[0211] Starting materials: Example 4k (100 mg; 0.32 mmol) + Example 1a (50.78 mg; 0.35 mmol). The crude was purified by preparative HPLC. Obtained 64 mg of the desired compound.

Example 18	
HPLC-MS Method: Z003_S05; R_t [min] : 1.07	MS: 363 and 365 $(M+H)^+$; Isotopic pattern for 1 Cl observed
Chiral SFC Method: I_SA_20_IPA_NH_3_001	R_t [min]: 2.38; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.02 (m, 1 H); 2.21 (m, 1 H); 2.57-2.58 (m, 3 H); 2.64 - 2.71 (m, 1 H); 2.95 (m, 1 H); 3.54 - 3.70 (m, 3 H); 3.83 - 3.90 (m, 2 H); 7.30 - 7.36 (m, 1 H); 7.38 - 7.46 (m, 2 H); 7.59 - 7.63 (m, 1 H); 7.63 - 7.70 (m, 1 H); 8.18 (d, *J*=1.33 Hz, 1 H); 8.57 (d, *J*=1.34 Hz, 1 H).	

Example 30

[0212]



[0213] Example 30 was synthesised in analogy to example 1.

[0214] Starting materials: Example 4f (100 mg; 0.32 mmol) and Example 1b (60 mg; 0.38 mmol). The crude was purified via preparative HPLC. Obtained 58 mg.

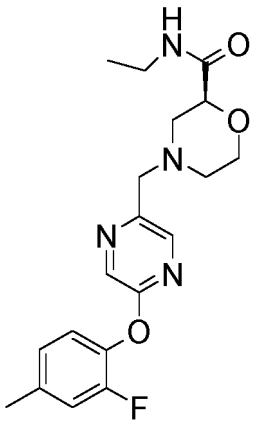
Example 30	
HPLC-MS ; Method: Z003_S05; Rt [min]: 1.10	MS: 379 $(M+H)^+$

(continued)

Example 30	
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 1.55; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 0.98 (t, *J*=7.18 Hz, 3 H); 2.02 (m, 1 H); 2.21 (m, 1 H); 2.65 - 2.70 (m, 1 H); 2.93 (m, 1 H); 3.04 - 3.11 (m, 2 H); 3.54 - 3.62 (m, 1 H); 3.64 - 3.68 (m, 2 H); 3.84 - 3.88 (m, 2 H); 7.14 - 7.20 (m, 1 H); 7.44 - 7.52 (m, 2 H); 7.69 (m, 1 H); 8.19 (br s, 1 H); 8.60 (m, 1 H).	

Example 31

[0215]



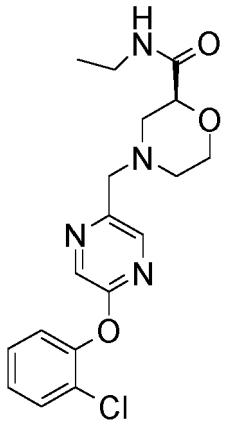
[0216] Example 31 was synthesised in analogy to example 1.

[0217] Starting materials: Example 4b (100 mg; 0.32 mmol) and Example 1b (60 mg; 0.38 mmol). The crude was purified via preparative HPLC. Obtained 57 mg.

Example 31	
HPLC-MS ; Method: Z011_S03; R_t [min]: 0.98	MS: 375 $(M+H)^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 1.83; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 0.99 (t, *J*=7.16 Hz, 3 H); 2.02 (t, *J*=10.77 Hz, 1 H); 2.21 (m, 1 H); 2.32 - 2.36 (m, 3 H); 2.67 (m, 1 H); 2.93 (m, 1 H); 3.08 (m, 2 H); 3.54 - 3.69 (m, 3 H); 3.83 - 3.89 (m, 2 H); 7.07 (m, 1 H); 7.21 (m, 1 H); 7.26 (t, *J*=8.17 Hz, 1 H); 7.69 (m, 1 H); 8.17 (m, 1 H); 8.55 (m, 1 H).	

Example 33

[0218]

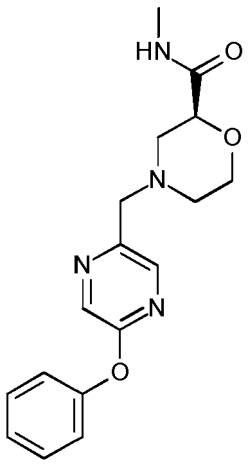


[0219] Example 33 was synthesised in analogy to example 1.
[0220] Starting materials: Example 4k (100 mg; 0.32 mmol) and Example 1b (60 mg; 0.38 mmol). The crude was purified via preparative HPLC. Obtained 37 mg.

Example 33	
HPLC-MS ; Method: Z003_S05; Rt [min]: 0.96	MS: 377 and 379 $(M+H)^{+;}$ isotopic pattern for 1 Cl observed
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 2.16; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 0.99 (t, *J*=7.18 Hz, 3 H); 2.02 (t, *J*=10.76 Hz, 1 H); 2.21 (td, *J*=11.31, 3.19 Hz, 1 H); 2.65 - 2.71 (m, 1 H); 2.94 (m, 1 H); 3.04 - 3.11 (m, 2 H); 3.54 - 3.70 (m, 3 H); 3.83 - 3.89 (m, 2 H); 7.30 - 7.46 (m, 3 H); 7.61 (dd, *J*=7.96, 1.44 Hz, 1 H); 7.69 (m, 1 H); 8.18 (d, *J*=1.33 Hz, 1 H); 8.57 (d, *J*=1.32 Hz, 1 H).	

Example 34

[0221]



[0222] Example 34 was synthesised in analogy to example 1.
[0223] Starting materials: Example 4j (100 mg; content 70%; 0.25 mmol) and Example 1a (39.6 mg; 0.28 mmol). The crude was purified via preparative HPLC. Obtained 71.0 mg of the desired product.

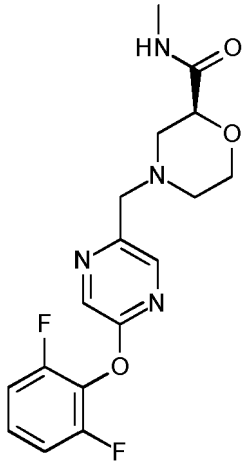
Example 34	
HPLC-MS ; Method: Z011_S03; R_t [min]: 0.85	MS: 329 $(M+H)^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 2.29; e.e. 100%

(continued)

Example 34
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.03 (m, 1 H); 2.21 (m, 1 H); 2.58 (m, 3 H); 2.69 (m, 1 H); 2.96 (m, 1 H); 3.54 - 3.69 (m, 3 H); 3.83 - 3.91 (m, 2 H); 7.18 - 7.28 (m, 3 H); 7.44 (m, 2 H); 7.63 - 7.71 (m, 1 H); 8.20 (d, *J*=1.37 Hz, 1 H); 8.46 (d, *J*=1.35 Hz, 1 H).

Example 35

[0224]



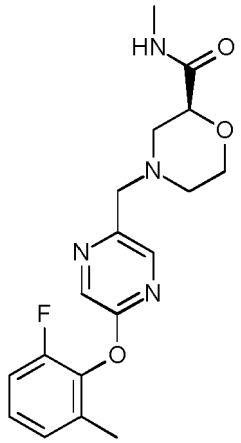
Example 35 was synthesised in analogy to example 1.

[0225] Starting materials: Example 41 (130 mg; 0.35 mmol) and Example 1a (55.4 mg; 0.38 mmol). The crude was purified via preparative HPLC. Obtained 71.0 mg of the desired product.

Example 35	
HPLC-MS ; Method: Z003_S05; Rt [min]: 1.06	MS: 365 $(M+H)^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 1.63; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.04 (m, 1 H); 2.21 (m, 1 H); 2.57 (m, 3 H); 2.63 - 2.71 (m, 1 H); 2.94 (m, 1 H); 3.57 (m, 1 H); 3.68 (s, 2 H); 3.82 - 3.91 (m, 2 H); 7.28 - 7.44 (m, 3 H); 7.60 - 7.74 (m, 1 H); 8.21 (d, *J*=1.37 Hz, 1 H); 8.71 (d, *J*=1.35 Hz, 1 H).	

Example 36

[0226]



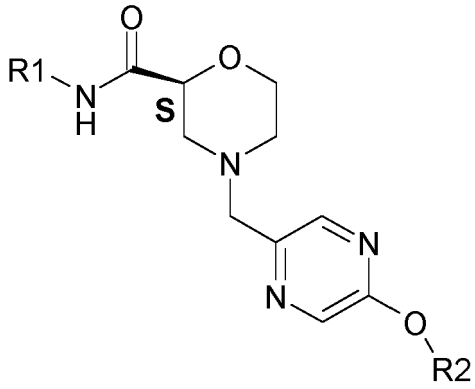
[0227] Example 36 was synthesised in analogy to example 1.

[0228] Starting materials: Example 4m (130 mg; 0.42 mmol) and Example 1a (66.0 mg; 0.46 mmol). The crude was purified via preparative HPLC. Obtained 87.0 mg of the desired product.

Example 36	
HPLC-MS ; Method: Z011_S03; R_t [min]: 0.92	MS: 361 $(M+H)^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 1.71; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 2.03 (m, 1 H); 2.15 - 2.22 (m, 4 H); 2.57 (m, 3 H); 2.62 - 2.75 (m, 1 H); 2.95 (m, 1 H); 3.52 - 3.61 (m, 1 H); 3.66 (s, 2 H); 3.80 - 3.93 (m, 2 H); 7.12 - 7.27 (m, 3 H); 7.62 - 7.74 (m, 1 H); 8.16 (d, *J*=1.38 Hz, 1 H); 8.62 (d, *J*=1.35 Hz, 1 H).	

Claims

1. A compound of formula A



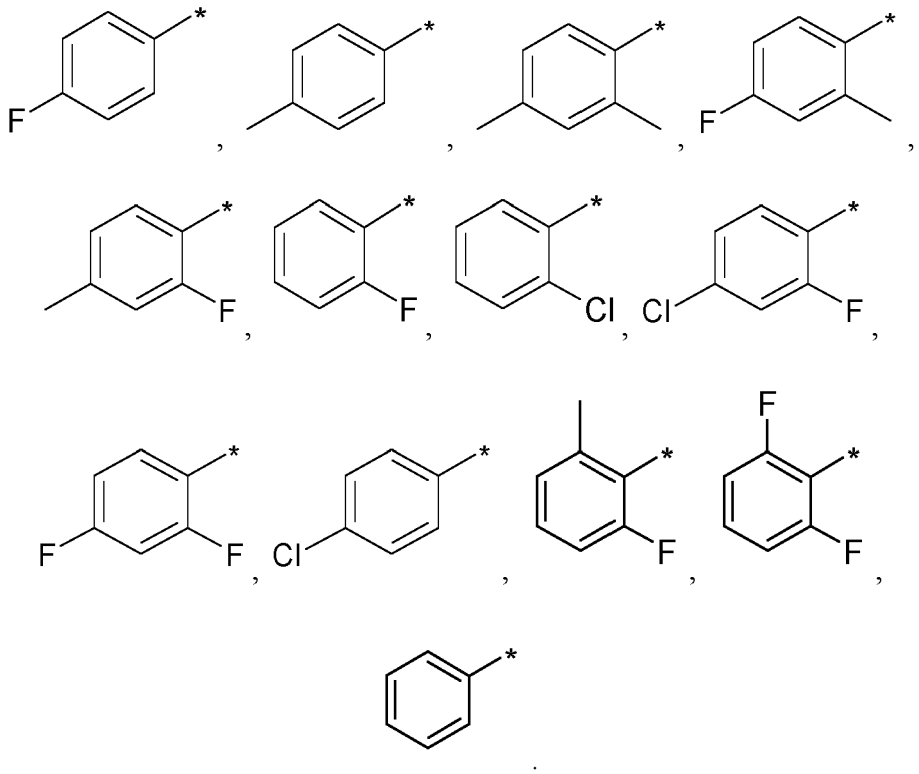
A

in which

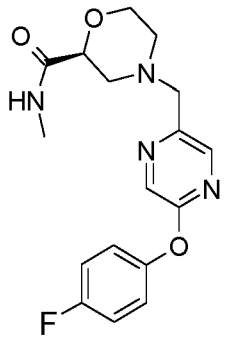
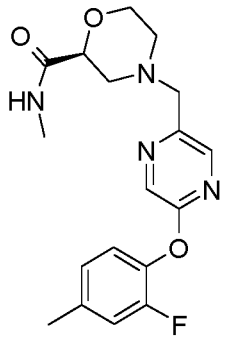
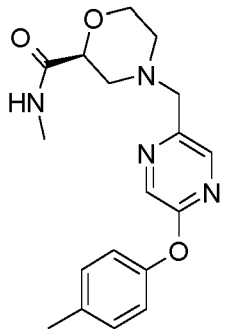
R^1 represents methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, H_3C-CH_2-CH_2-CH_2-, cyclobutyl;
R^2 represents phenyl which is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of fluoro, chloro, methyl, ethyl, cyclopropyl.

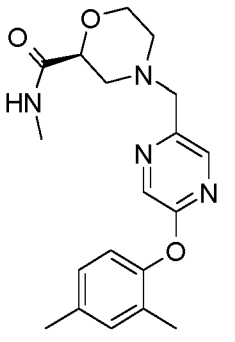
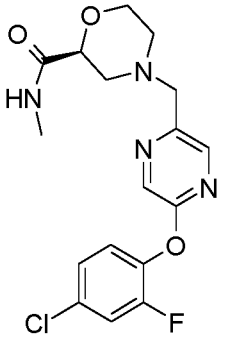
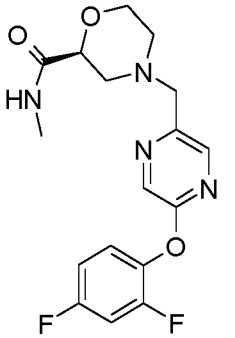
2. The compound according to claim 1, wherein

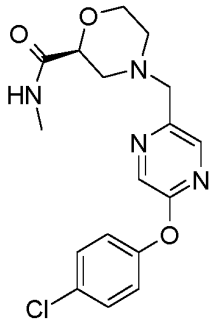
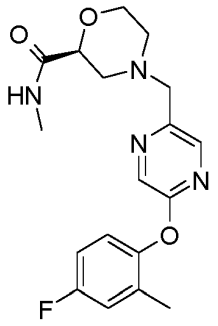
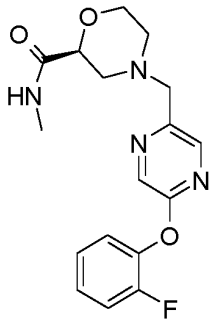
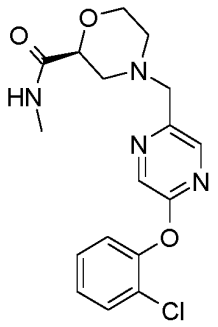
R^1 represents methyl, ethyl;
R^2 represents

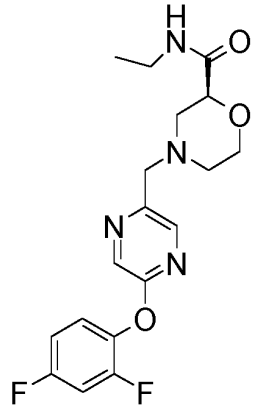
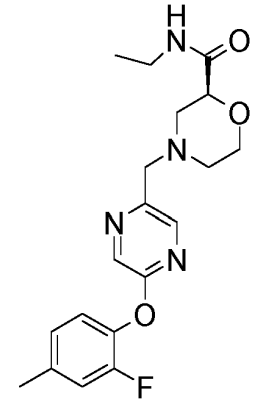
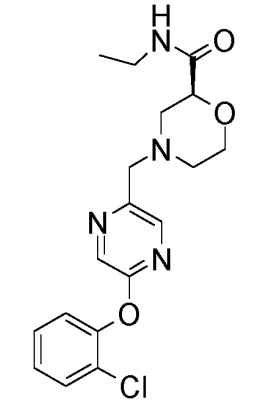
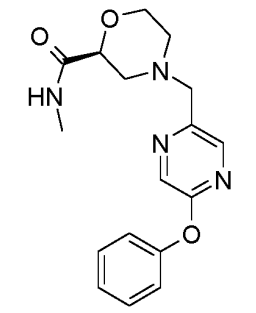


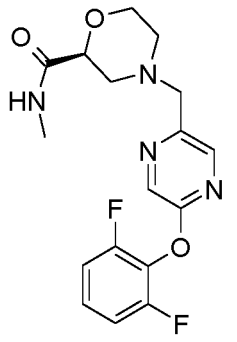
3. The *(S)*-enantiomer according to any one of claims 1 to 2, namely a compound selected from the group consisting of

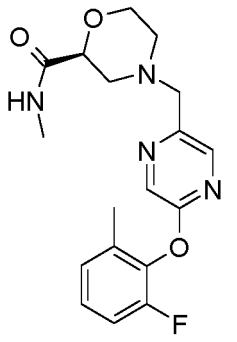
Ex.	
1	 ,
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Ex.	
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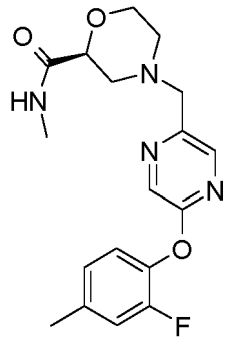
Ex.	
7	 ,
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Ex.	
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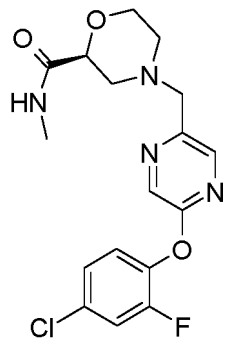
Ex.	
35	

Ex.	
36	

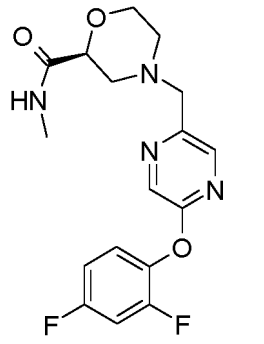
4. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

2	

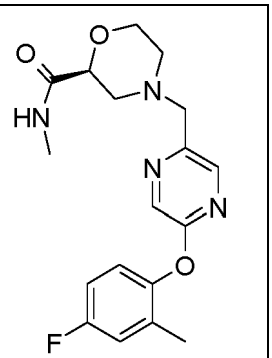
5. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

5	

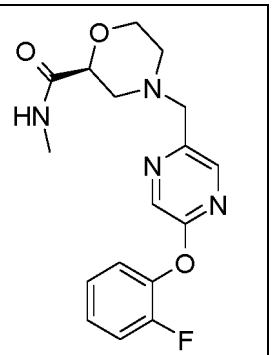
6. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

6	

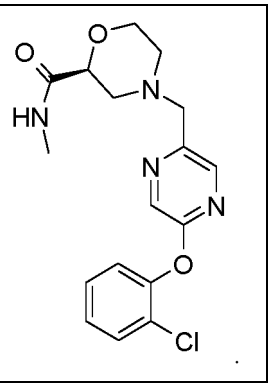
7. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

8	

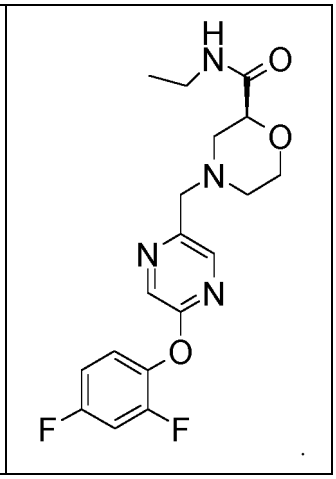
8. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

9	

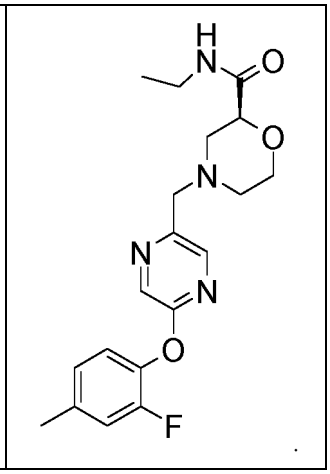
9. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

18	

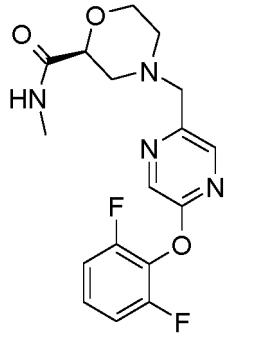
10. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

30	

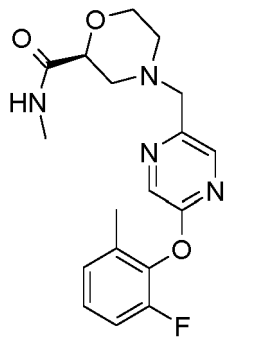
11. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

31	

12. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

35	

13. The *(S)*-enantiomer according to any one of claims 1 to 3 having the structure:

36	

14. A pharmaceutically acceptable salt of a compound according to any one of claims 1 to 13.

15. The compound according to any one of claims 1 to 14 for use as a medicament.

16. The compound according to any one of claims 1 to 14 for use in the treatment and/or prevention of bipolar disorder I depressed, hypomanic, manic and mixed form; bipolar disorder II; depressive disorders; major depressive disorder with or without concomitant anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia.

17. The compound according to any one of claims 1 to 14 for use in the treatment and/or prevention of single depressive episode or recurrent major depressive disorder, minor depressive disorder, depressive disorder with postpartum onset, depressive disorders with psychotic symptoms.

18. The compound for use according to any one of claims 15 to 17 **characterized in that** the compound is administered in addition to treatment with another antidepressant drug.

19. The compound for use according to any one of claims 15 to 17 **characterized in that** the compound is administered in addition to behavioural therapy.

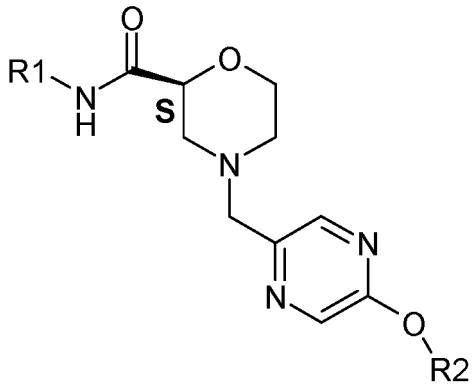
20. The compound according to any one of claims 1 to 14 for use in the treatment of acute and chronic pain which is related to neuropathy, physiological processes and physical disorders, disease of the musculoskeletal system and connective tissue, nerve, nerve root and plexus disorders.

21. The compound according to any one of claims 1 to 14 for use in the treatment of diabetic neuropathy, polyneuropathy, low back pain, pain in the joints, rheumatism, myalgia, phantom limb syndrome with pain, carpal tunnel syndrome.

22. A pharmaceutical composition comprising the compound according to any one of claims 1 to 14 in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

Patentansprüche

1. Verbindung der Formel A



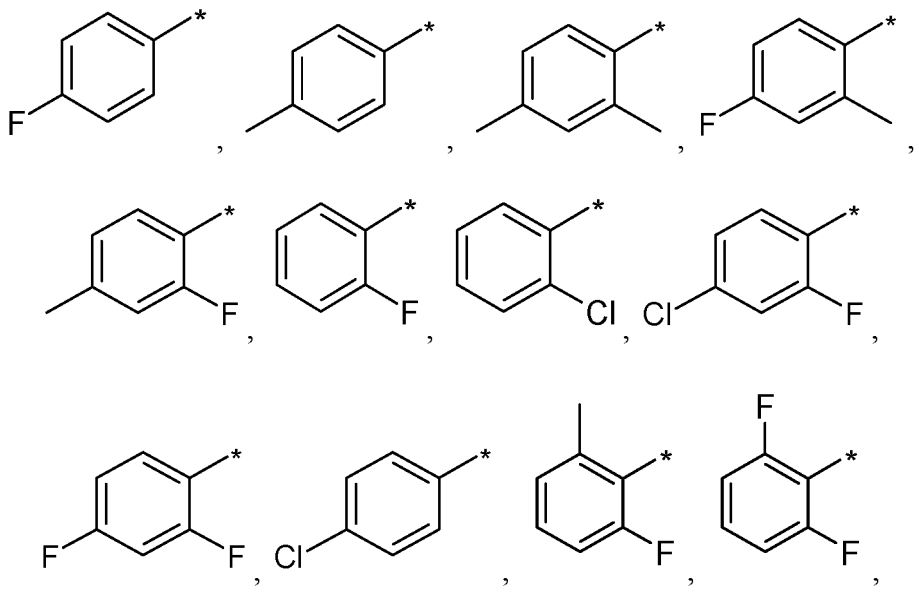
A

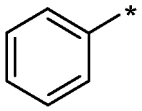
worin

R^1 Methyl, Ethyl, Propyl, *iso*-Propyl, Cyclopropyl, H_3C-CH_2-CH_2-CH_2-, Cyclobutyl darstellt;
R^2 Phenyl darstellt, das gegebenenfalls mit 1, 2 oder 3 Substituenten substituiert ist, ausgewählt aus der Gruppe, bestehend aus Fluor, Chlor, Methyl, Ethyl, Cyclopropyl.

2. Verbindung nach Anspruch 1, wobei

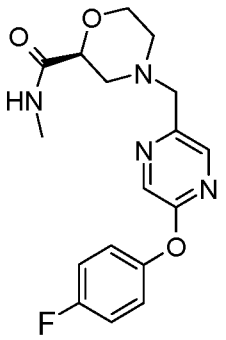
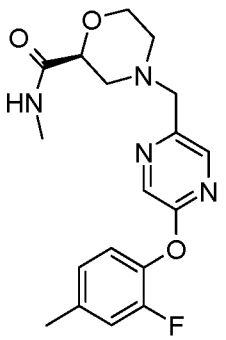
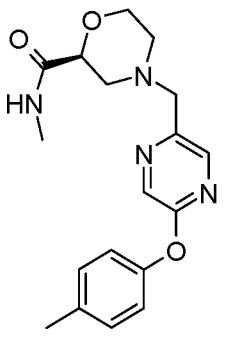
R^1 Methyl, Ethyl darstellt;
R^2 stellt

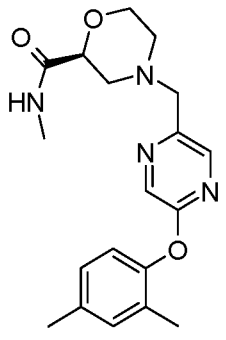
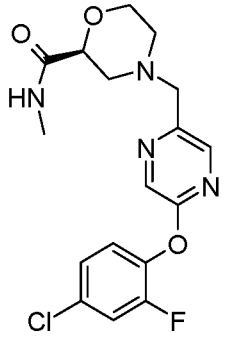
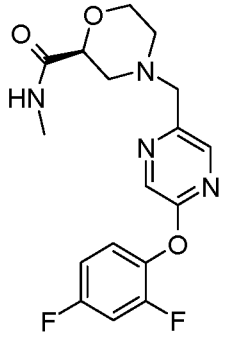


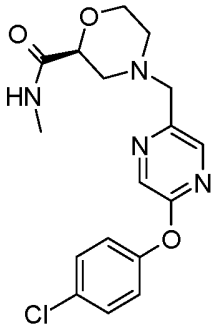
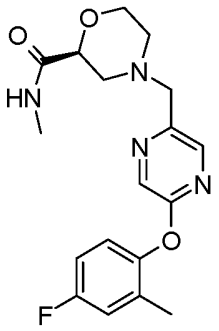
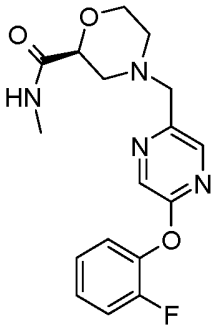
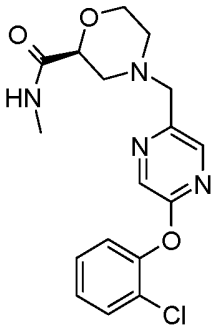


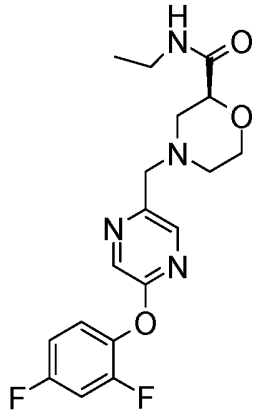
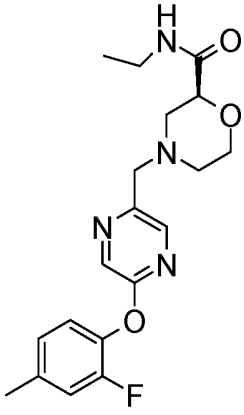
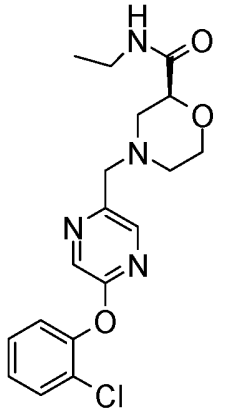
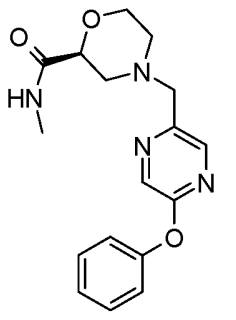
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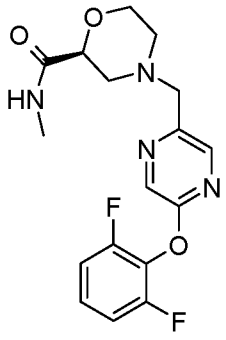
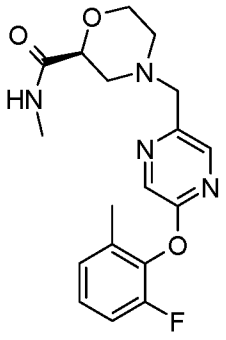
3. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 2, nämlich eine Verbindung, ausgewählt aus der Gruppe, bestehend aus

Bsp.	
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3	 ,

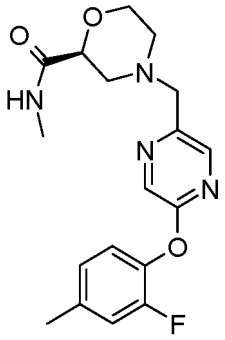
Bsp.	
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Bsp.	
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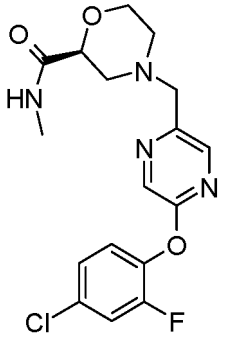
Bsp.	
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31	 ,
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Bsp.		Bsp.	
35		**36**	

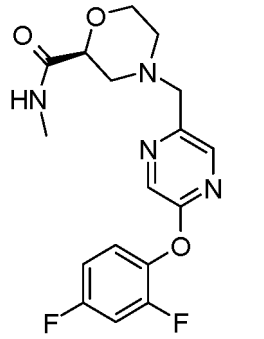
4. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

2	

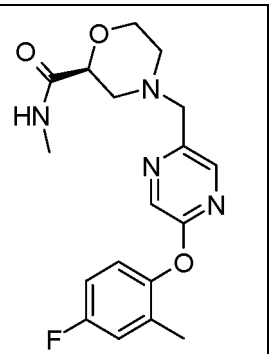
5. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

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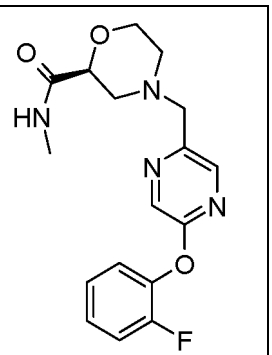
6. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

6	

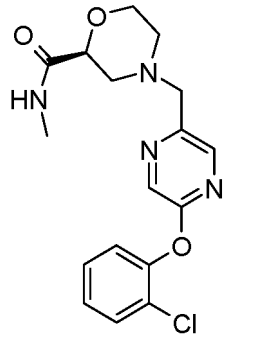
7. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

8	

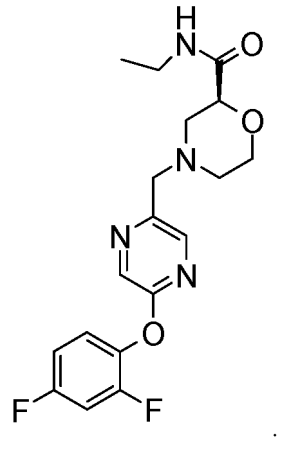
8. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

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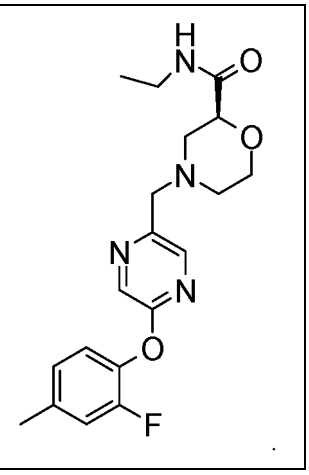
9. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

18	

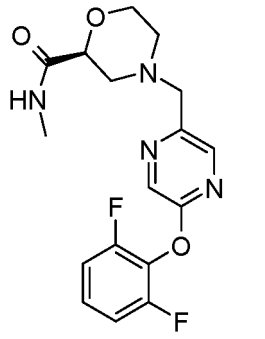
10. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

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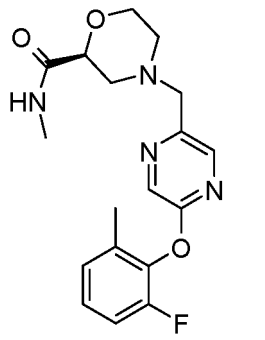
11. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

31	

12. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

35	

13. Das *(S)*-Enantiomer nach irgendeinem der Ansprüche 1 bis 3 mit der Struktur:

36	

14. Pharmazeutisch akzeptables bzw. annehmbares Salz einer Verbindung nach irgendeinem der Ansprüche 1 bis 13.

15. Verbindung nach irgendeinem der Ansprüche 1 bis 14 zur Verwendung als Medikament.

16. Verbindung nach irgendeinem der Ansprüche 1 bis 14 zur Verwendung in der Behandlung und/oder Vorbeugung einer bipolaren Störung I, depressive, hypomanische, manische und gemischte Form; einer bipolaren Störung II; depressiven Störungen; einer schweren depressiven Störung mit oder ohne begleitende Angstzustände, gemischte Merkmale, melancholische Merkmale, atypische Merkmale, stimmungskongruente psychotische Merkmale, stimmungs-inkongruente psychotische Merkmale, Katatonie.

17. Verbindung nach irgendeinem der Ansprüche 1 bis 14 zur Verwendung in der Behandlung und/oder Vorbeugung einer einzelnen depressiven Episode oder einer rezidivierenden schweren depressiven Störung, einer leichten depressiven Störung, einer depressiven Störung nach der Geburt, einer depressiven Störung mit psychotischen Symptomen.

18. Verbindung zur Verwendung nach irgendeinem der Ansprüche 15 bis 17, **dadurch gekennzeichnet, dass** die Verbindung zusätzlich zur Behandlung mit einem anderen antidepressiven Wirkstoff verabreicht wird.

19. Verbindung zur Verwendung nach irgendeinem der Ansprüche 15 bis 17, **dadurch gekennzeichnet, dass** die Verbindung zusätzlich zu Verhaltenstherapie verabreicht wird.

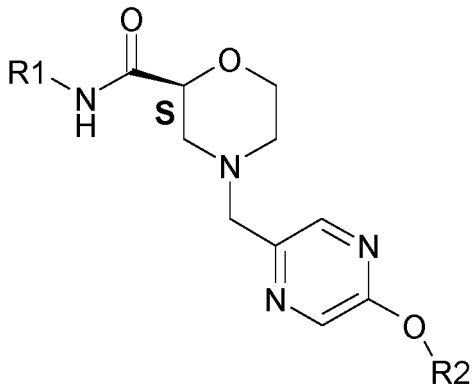
20. Verbindung nach irgendeinem der Ansprüche 1 bis 14 zur Verwendung in der Behandlung von akuten und chronischen Schmerzen, die mit Neuropathie, physiologischen Prozessen und körperlichen Störungen, Erkrankungen des Bewegungsapparats und des Bindegewebes, Nerven-, Nervenwurzel- und Plexuserkrankungen in Zusammenhang stehen.

21. Verbindung nach irgendeinem der Ansprüche 1 bis 14 zur Verwendung in der Behandlung von diabetischer Neuropathie, Polyneuropathie, Kreuzschmerzen, Gelenkschmerzen, Rheumatismus, Myalgie, Phantomgliederschmerzsyndrom, Karpaltunnelsyndrom.

22. Pharmazeutische Zusammensetzung, umfassend die Verbindung nach irgendeinem der Ansprüche 1 bis 14 in Mischung mit einem pharmazeutisch akzeptablen bzw. annehmbaren Hilfsstoff, Verdünnungsmittel und/oder Träger.

Revendications

1. Composé de formule A



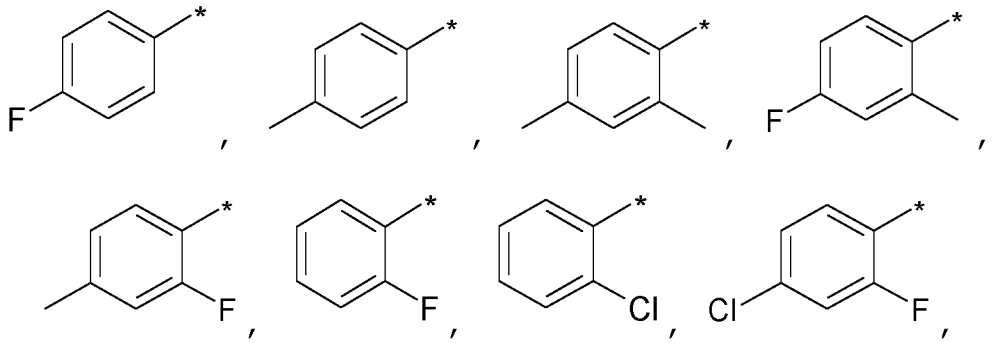
A

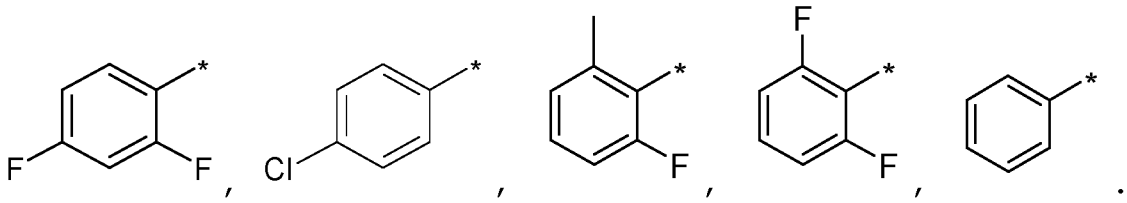
dans laquelle

R1 représente un méthyle, un éthyle, un propyle, un iso-propyle, un cyclopropyle, H_3C-CH_2-CH_2-CH_2-, un cyclobutyle ;
R2 représente un phényle qui est facultativement substitué avec 1, 2 ou 3 substituants sélectionnés dans le groupe consistant en un fluoro, un chloro, un méthyle, un éthyle, un cyclopropyle.

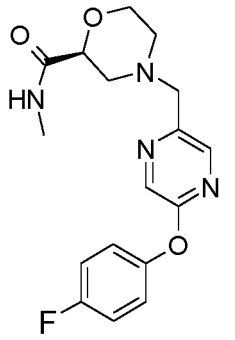
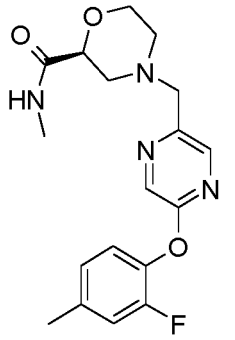
2. Composé selon la revendication 1, dans lequel

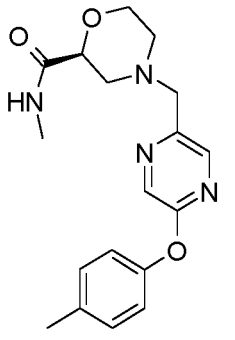
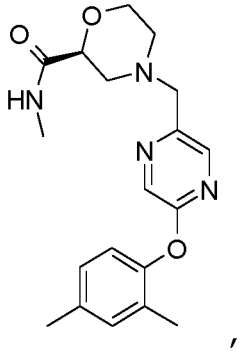
R1 représente un méthyle, un éthyle ;
R2 représente

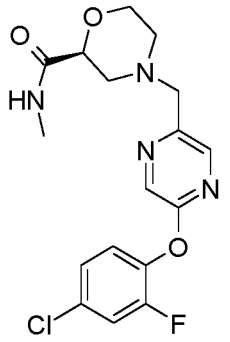
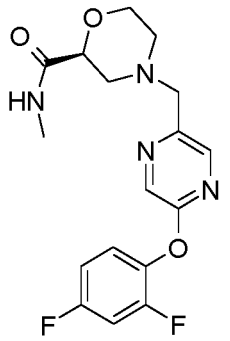
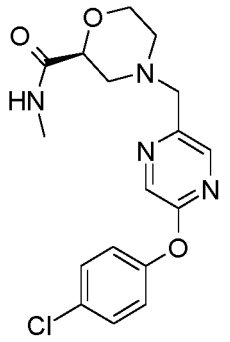
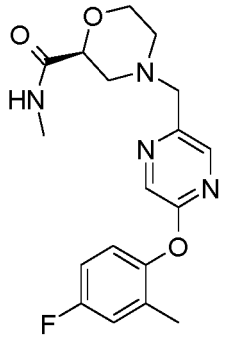


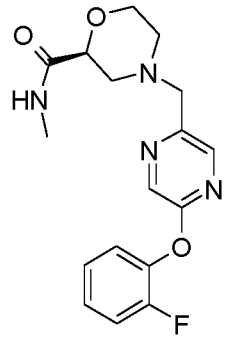
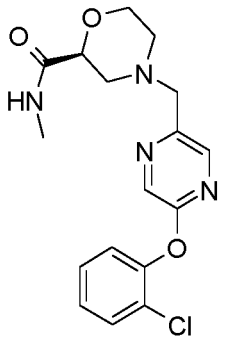
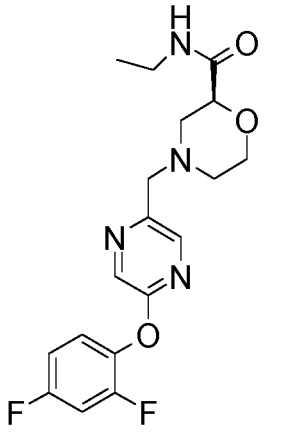
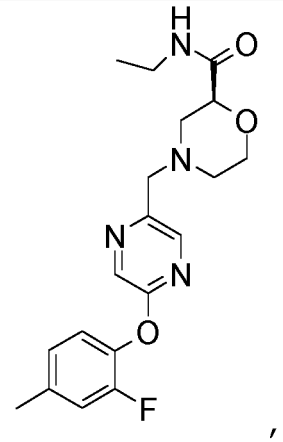


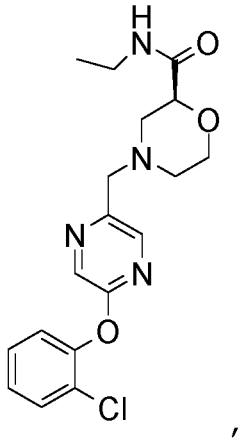
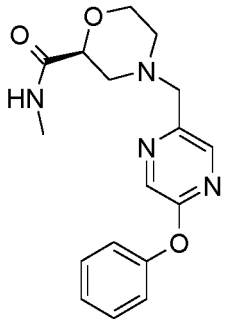
3. Énantiomère (S) selon l'une quelconque des revendications 1 à 2, à savoir un composé sélectionné dans le groupe consistant en

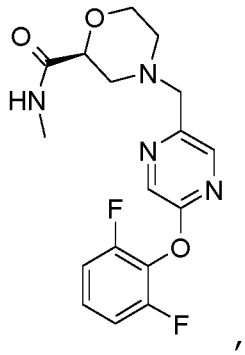
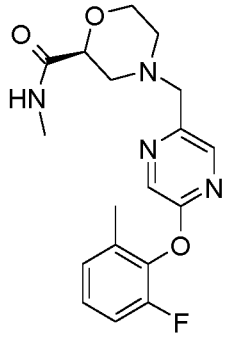
Ex.	
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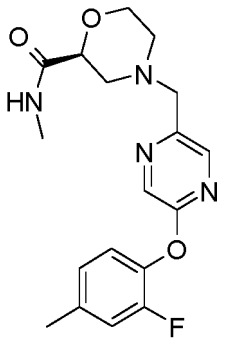
Ex.	
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Ex.	
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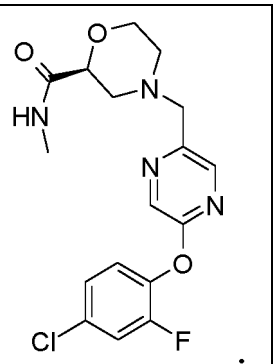
Ex.	
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Ex.	
35	 ,
36	 .

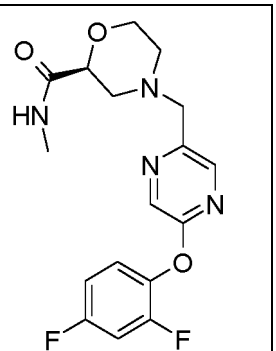
4. Énantiomère (S) selon l'une quelconque des revendications 1 à 3 ayant la structure :

2	 .

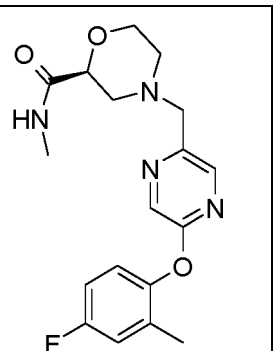
5. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

5	

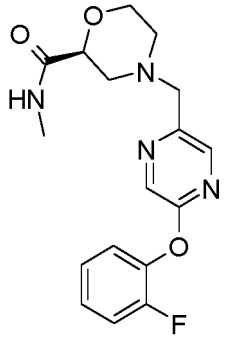
6. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

6	

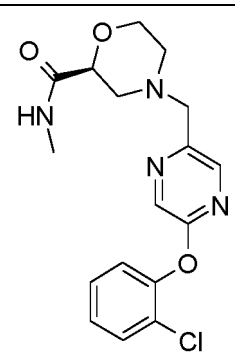
7. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

8	

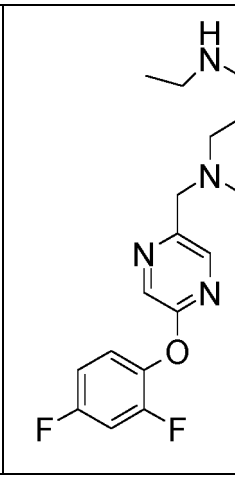
8. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

9	

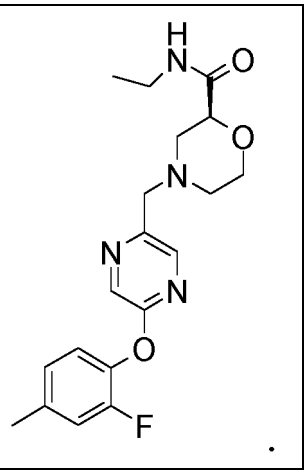
9. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

18	

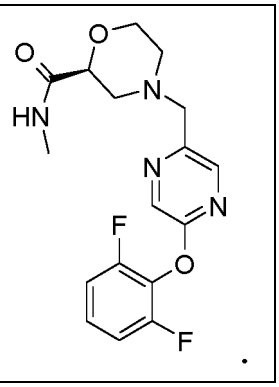
10. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

30	

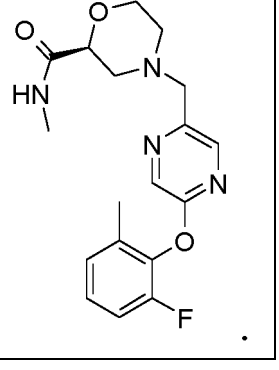
11. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

31	

12. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

35	

13. Énantiomère (*S*) selon l'une quelconque des revendications 1 à 3 ayant la structure :

36	

14. Sel pharmaceutiquement acceptable d'un composé selon l'une quelconque des revendications 1 à 13.

15. Composé selon l'une quelconque des revendications 1 à 14 pour son utilisation comme médicament.

16. Composé selon l'une quelconque des revendications 1 à 14 pour son utilisation dans le traitement et/ou la prévention d'un trouble bipolaire I sous forme dépressive, hypomaniaque, maniaque et mixte ; d'un trouble bipolaire II ; des troubles dépressifs ; d'un trouble dépressif majeur avec ou sans détresse anxieuse, caractéristiques mixtes, carac-

téristiques mélancoliques, caractéristiques atypiques, caractéristiques psychotiques en accord avec l'humeur, caractéristiques psychotiques non en accord avec l'humeur, catatonie concomitantes.

17. Composé selon l'une quelconque des revendications 1 à 14 pour son utilisation dans le traitement et/ou la prévention d'un épisode dépressif unique ou d'un trouble dépressif majeur récurrent, d'un trouble dépressif mineur, d'un trouble dépressif avec apparition postpartum, des troubles dépressifs avec symptômes psychotiques.

18. Composé pour son utilisation selon l'une quelconque des revendications 15 à 17, **caractérisé en ce que** le composé est administré en plus d'un traitement avec un autre médicament antidépresseur.

19. Composé pour son utilisation selon l'une quelconque des revendications 15 à 17, **caractérisé en ce que** le composé est administré en plus d'une thérapie comportementale.

20. Composé selon l'une quelconque des revendications 1 à 14 pour son utilisation dans le traitement d'une douleur aiguë et chronique qui est associée à une neuropathie, à des processus physiologiques et à des troubles physiques, à une maladie du système musculosquelettique et à des troubles du tissu conjonctif, d'un nerf, d'une racine nerveuse et du plexus.

21. Composé selon l'une quelconque des revendications 1 à 14 pour son utilisation dans le traitement d'une neuropathie diabétique, d'une polyneuropathie, d'une lombalgie, d'une douleur articulaire, d'un rhumatisme, d'une myalgie, du syndrome du membre fantôme avec douleur, du syndrome du canal carpien.

22. Composition pharmaceutique comprenant le composé selon l'une quelconque des revendications 1 à 14 en mélange avec un adjuvant, un diluant et/ou un support pharmaceutiquement acceptables.

REFERENCES CITED IN THE DESCRIPTION

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