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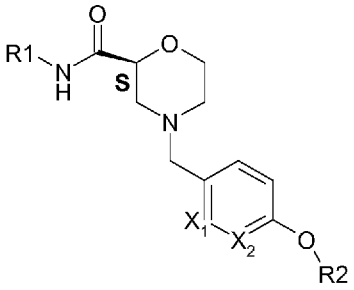
(54) Title: 4-PYRIDINYLMETHYL-MORPHOLINE DERIVATIVES AND THE USE THEREOF AS MEDICAMENT



A

(57) Abstract: The present invention relates to novel 4-Pyridinylmethyl-morpholine derivatives of general formula 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.

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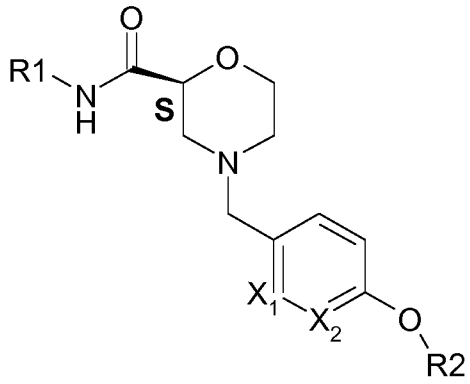
4-Pyridinylmethyl-morpholine derivatives and the use thereof as medicament

The present invention relates to novel 4-Pyridinylmethyl-morpholine derivatives 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.

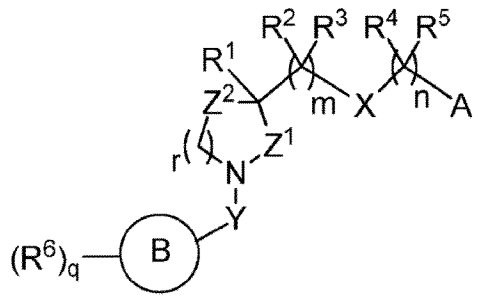
The compounds of the invention according to general formula **A** show NR2B negative allosteric modulating properties.

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.

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. Neuropharmacol.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

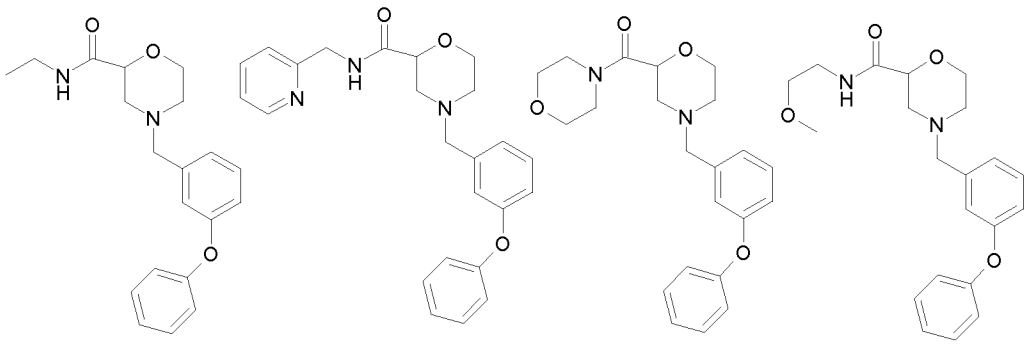
1990s, it was found that multiple NMDA receptor subtypes exist, which contain different NR2(A-D) subunits (Paoletti et al., 2013 Nat Rev. Neurosci 14:383). More recently, NR2B subtype selective NMDA receptor negative allosteric modulators (NR2B NAM) have raised interest and have shown potential in a 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)).

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**

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).

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 pyridyl substructure in place of the meta-disubstituted phenyl ring.

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).

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.

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 favorable characteristic for compounds that are to be used for drugs acting primarily in the CNS.

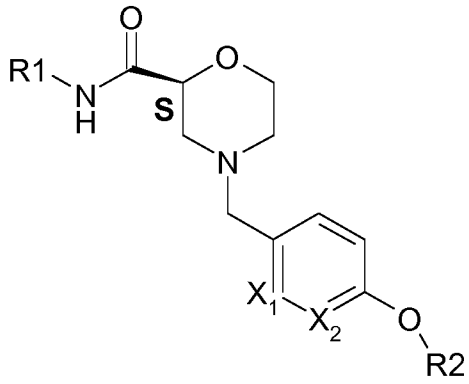
Further, the compounds of the present invention are metabolically stable in human liver microsomes (see Table 6, metabolic stability). Therefore, compounds of the present invention are expected to have a favorable in vivo clearance and thus the desired duration of action in humans.

Stability in human liver microsomes refers to the susceptibility of compounds to biotransformation 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.

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

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

The present invention provides novel 4-Pyridinylmethyl-morpholine derivatives of formula **A**



A

in which

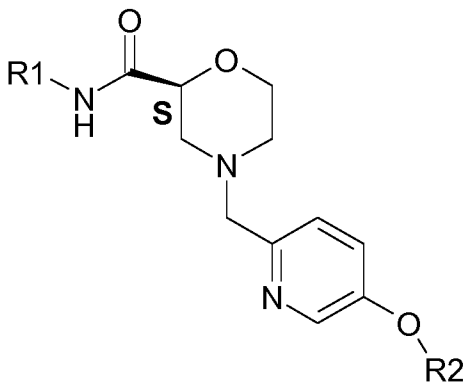
$\mathbf{X_1}$ is N and $\mathbf{X_2}$ is CH, or
$\mathbf{X_1}$ is CH and $\mathbf{X_2}$ is N,

R^1 represents methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, $H_3C\text{-}CH_2\text{-}CH_2\text{-}CH_2$-, cyclobutyl;

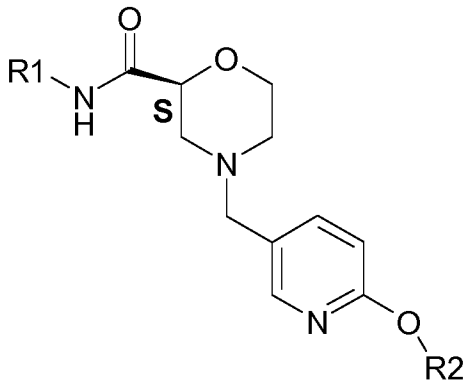
R^2 represents phenyl which is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of fluoro, chloro, methyl, ethyl, cyclopropyl;

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

According to another embodiment, the present invention comprises compounds of the general formula **A1** or formula **A2**



A1



A2,

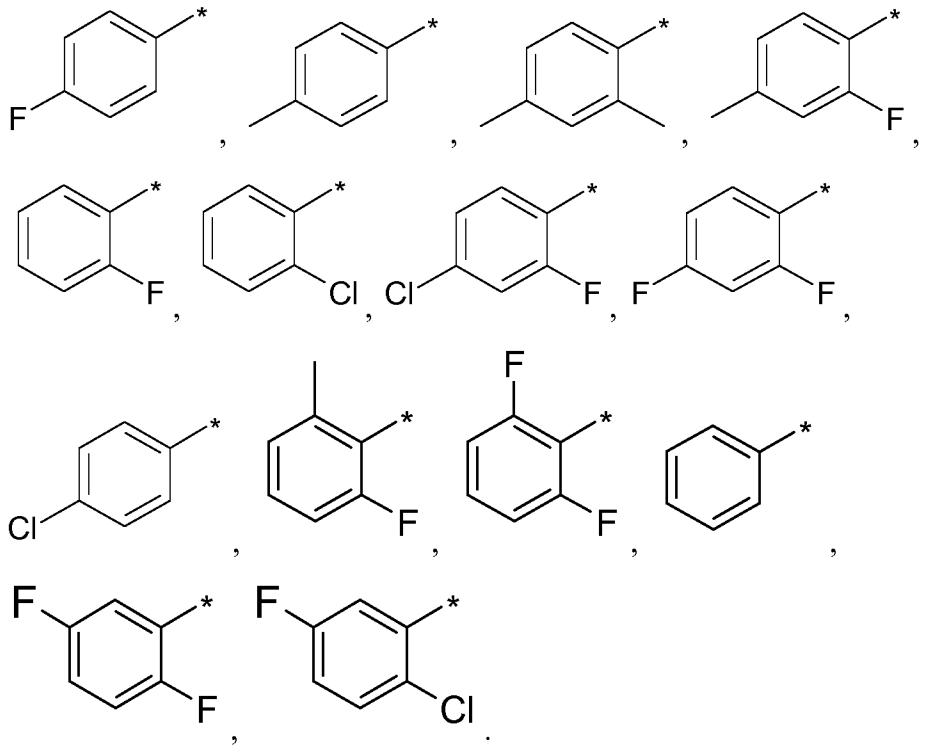
in which $\mathbf{R^1}$ and $\mathbf{R^2}$ have the same meaning as defined in any of the preceding embodiments.

In another embodiment, in the general formula **A**, **A1**, **A2**, X_1, X_2, R^2 have the same meaning as defined in any of the preceding embodiments, and

R^1 represents methyl.

In another embodiment, in the general formula **A**, **A1**, **A2**, X_1, X_2, R^1 have the same meaning as defined in any of the preceding embodiments, and

R^2 represents



The present invention provides novel 4-Pyridinylmethyl-morpholine derivatives of general formula **A** that unexpectedly are potent and selective negative allosteric modulators of NR2B.

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.

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.

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.

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.

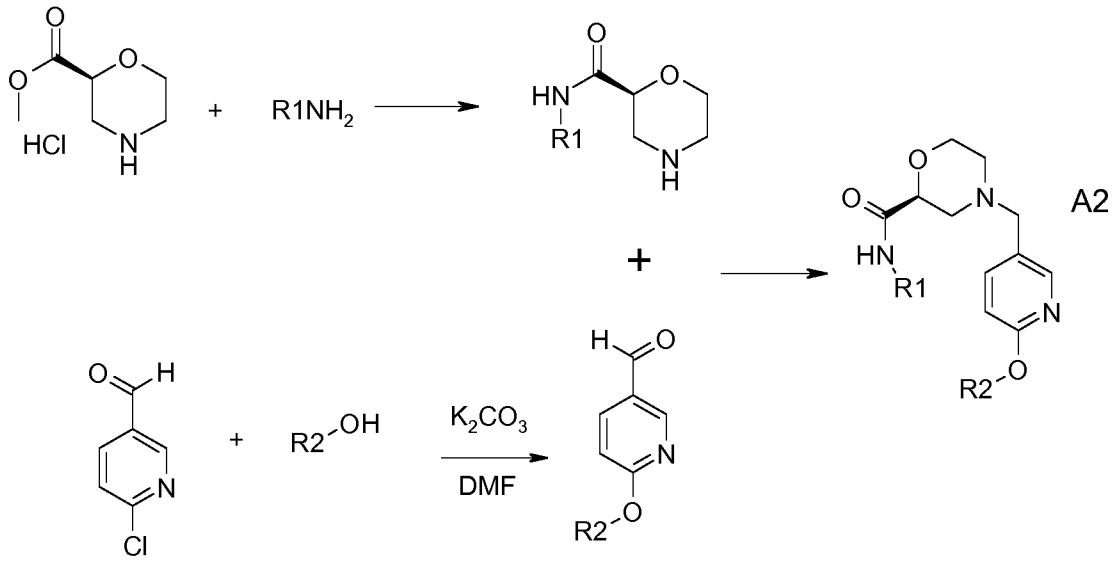
A further aspect of the present invention refers to compounds according to formula **A**, for the use in the prevention and/or treatment of disorders associated with NR2B negative allosteric modulators.

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

Preparation

The following schemes 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 schemes.

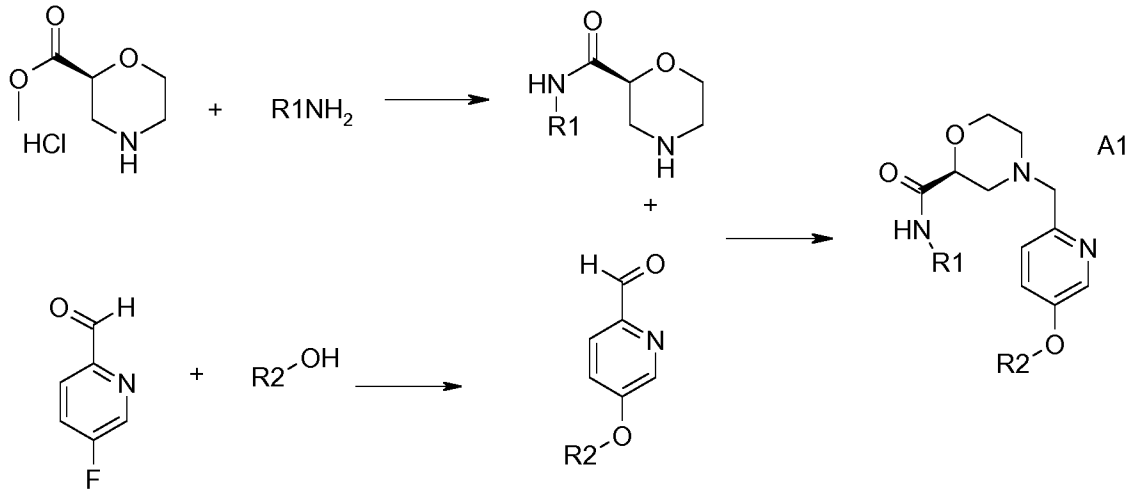
Scheme 1



Scheme 1 illustrates the synthesis of pyridine derivatives of general formula **A2**.The first step is a nucleophilic substitution of a substituted phenol derivative R2-OH and 6-chloro-pyridine-3-carbaldehyde; the last step is represented by a reductive amination involving the aldehyde 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.

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

Scheme 2



Scheme 2 illustrates the synthesis of pyridine derivatives of general formula **A1**.The first step is a nucleophilic substitution of a substituted phenol derivative R2-OH and 5-Fluoro-pyridine-2-carbaldehyde; the last step is represented by a reductive amination involving the aldehyde 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.

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

GENERAL DEFINITIONS

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.

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

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.

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.

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:

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:

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.

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.

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.

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.

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. trifluoro-acetate salts) also comprise a part of the invention.

BIOLOGICAL ASSAYS AND DATA

List of abbreviations

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

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

Method:

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:

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

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:

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: HHBS (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:

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.

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	IC_{50} [nM]
11	103
12	117
13	442
14	198

Example number	IC_{50} [nM]
15	69
16	205
17	188
19	199
29	194
30	454
31	275
32	255
33	366
34	133
35	457
36	353
37	203
38	419
39	282
40	452
41	286

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

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

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.

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

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

External Recording Solution

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

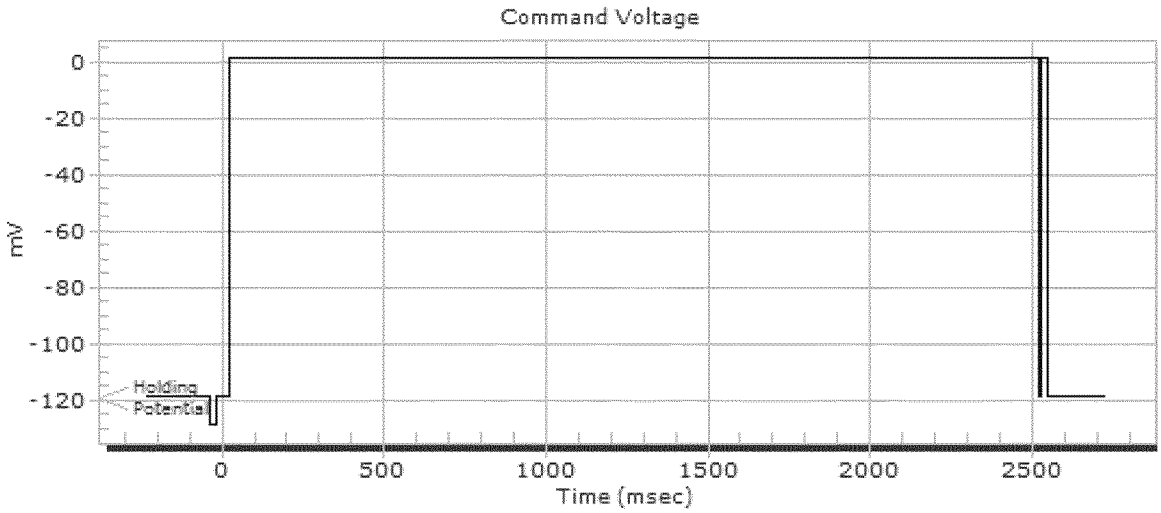
CsF 90mM
CsCl 45mM
HEPES 10mM
EGTA 10mM
pH 7.3 (titrated with 1M CsOH)

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

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

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).

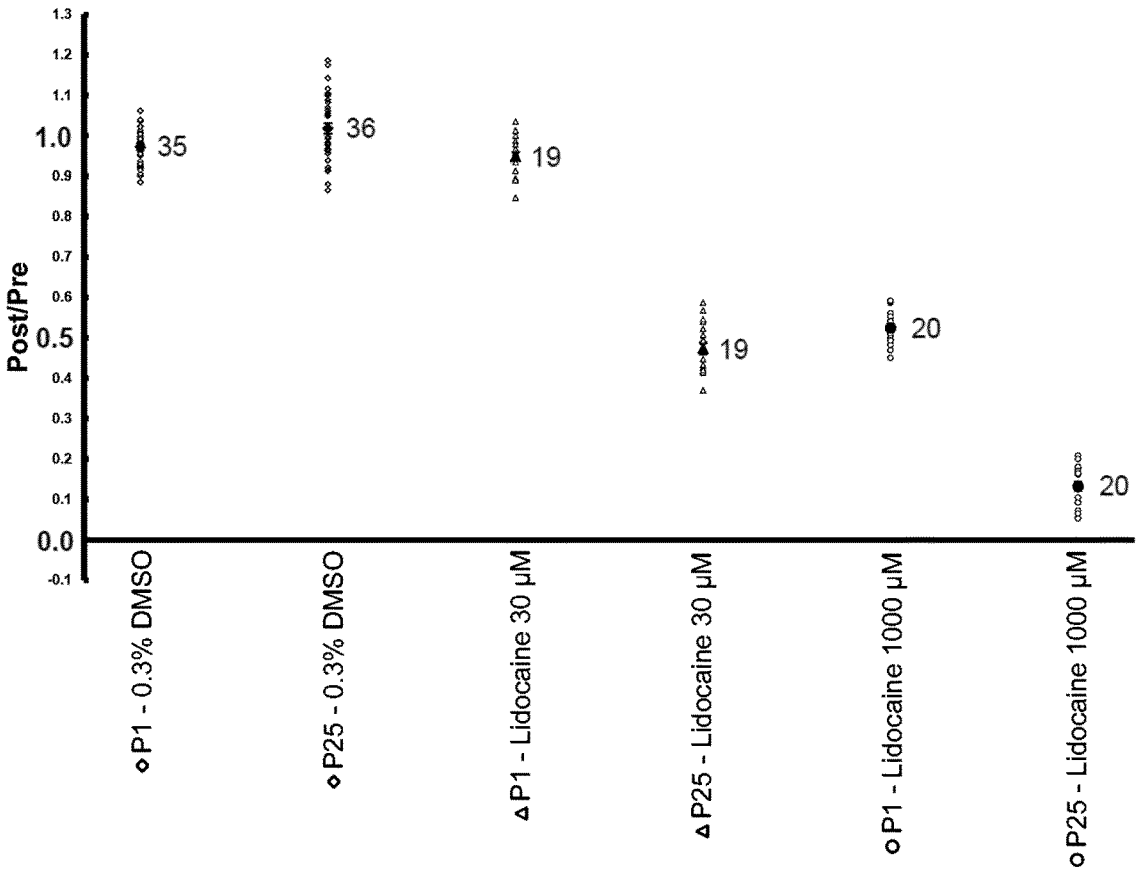
IonChannel Profiler Data Filters

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

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 **19** of the present invention show-

ing -6.3% 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.

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
11	4.2	-3.6	2.7	3.9
12	5.1	10.2	3.9	0.7
13	-3.1	-1.8	1.0	6.6
14	0.7	0.4	-	2.5

Example number	Normalized %inhibition at 1 µM	Normalized %inhibition at 5 µM	Percentage SEM at 1 µM	Percentage SEM at 5 µM
15	-17.4	-1.4	5.5	3.4
16	-0.5	7.1	2.1	4.4
17	22	-4.3	4.3	4.2
19	5.2	-6.3	1.4	-
29	1.8	3.0	3.4	2.5
30	7.6	6.8	0.7	3.6

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

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 (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

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
11	72	0.6
12	80	0.7
13	45	1.0
14	92	0.4
15	42	0.7
16	51	0.7
17	67	0.6
19	75	0.7
29	58	0.8
30	86	0.5
31	63	0.7
32	80	0.5
33	71	0.5
34	58	0.8

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

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
11	>130
12	>130
13	>130
14	>130
15	>130
16	>130
17	>130
19	>130
29	>130
30	>130
31	>130
32	>130
33	>130
34	>130

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

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

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.

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/method of use

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).

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.

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 anx-

ious 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.

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.

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.

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

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.

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.

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.

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.

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.

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.

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EXPERIMENTAL SECTION

Abbreviations:

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	ethylacetate
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 CO_2
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:

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.

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

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

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

Method Name:	***Z017_S04***
Device description:	Agilent 1200 with DA- and MS-Detector
Column:	Sunfire C18_3.0 x 30 mm_1.8 µm
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: G_IG_IPA_NH_3_001

Method Name:	G_IG_IPA_NH_3_001
Device description:	Agilent 1260 SFC with DAD and MS
Column:	CHIRALPAK® IG_4.6 x 250 mm_5 µm
Column producer:	Daicel

Gradient/Solvent Time [min]	% Sol [scCO2]	% Sol [IPA 20mM NH_3]	Flow [ml/min]	Temp [°C]	Back pressure [PSI]
0.0	95.0	5.0	4.0	40.0	2175.0
9.0	40.0	60.0	4.0	40.0	2175.0
10.0	40.0	60.0	4.0	40.0	2175.0

Method 5: G_IG_MeOH_NH_3_001

Method Name:	G_IG_MeOH_NH_3_001
Device description:	Agilent 1260 SFC with DAD and MS
Column:	CHIRALPAK® IG_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	95.0	5.0	4.0	40.0	2175.0
9.0	40.0	60.0	4.0	40.0	2175.0
10.0	40.0	60.0	4.0	40.0	2175.0

Method 6: G_C4_MeOH_NH_3_001

Method Name:	G_C4_MeOH_NH_3_001
Device description:	Agilent 1260 SFC with DAD and MS
Column:	LUX® Cellulose-4 6 x 250 mm_5 µm
Column producer:	Phenomenex

Gradient/Solvent Time [min]	% Sol [scCO2]	% Sol [MeOH 20mM NH_3]	Flow [ml/min]	Temp [°C]	Back pressure [PSI]
0.0	95.0	5.0	4.0	40.0	2175.0
9.0	40.0	60.0	4.0	40.0	2175.0
10.0	40.0	60.0	4.0	40.0	2175.0

Method 7: I_SA_20_MEOH_NH_3_001

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	80.0	20.0	4.0	40.0	2175.0
10.0	80.0	20.0	4.0	40.0	2175.0

Method 8: I_IC_30_IPA_NH_3_001

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

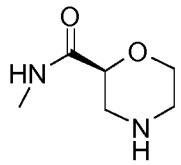
Microwave equipment: Biotage Initiator $^+$

Preparative HPLC method for purification:

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:

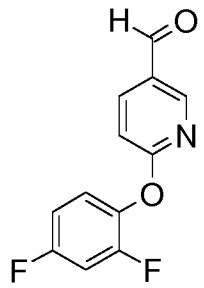
Example 1a



(S)-Morpholine-2-carboxylic acid methyl ester hydrochloride (35.0 g; 193 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:	
Chiral SFC Method: I__IC_30_IPA_NH_3_001.M	Rt [min]: 3.72; e.e. 100%
	MS: 145 $(M+H)^+$

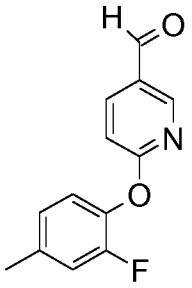
Example 5a



6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2,4-difluoro-phenol (1.22 ml; 12.7 mmol) are dissolved in DMF (10 ml) in a microwave vial; K_2CO_3 (2.20 g; 15.9 mmol) is added and the reaction mixture is stirred at 110 °C during 30 minutes. The reaction mixture is then partitioned between Ethyl Acetate (150 ml) and Water (80 ml); the organic phase is separated and washed with a solution of K_2CO_3 (10 % in water) and the dried over Na_2SO_4. The crude product obtained after evaporation of the solvent is purified by flash-chromatography (Eluent: Petrol Ether / Ethyl Acetate 4/1). Obtained 2.3g of the desired compound (content 70%) used as such in the next step.

Example 5a:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.98	MS: 236 [$M+H]^+$

Example 5b

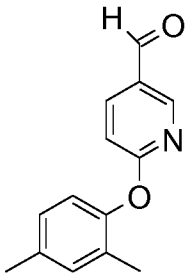


Example 5b was synthesised in analogy to Example 5a. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2-fluoro-4-methylphenol (1.38 ml; 12.7 mmol).

The crude obtained after work up was passed through a silica pad (Eluent: Petrol Ether / Ethyl Acetate 4/1). Obtained 1.60 g of the desired compound (content 50%) used as such in the next step.

Example 5b:	
HPLC-MS (Method): Z017_S04 R_t [min] : 1.02	MS: 232 $[M+H]^+$

Example 5c

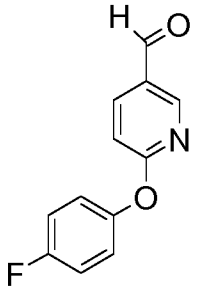


Example 5c was synthesised in analogy to Example 5a. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2,-4-dimethylphenol (1.51 ml; 12.7 mmol).

The crude obtained after work up was passed through a silica pad (Eluent: Petrol Ether / Ethyl Acetate 4/1). Obtained 2.30 g of the desired compound (content 50%) used as such in the next step.

Example 5c:	
HPLC-MS (Method): Z017_S04 R_t [min] : 1.06	MS: 228 $[M+H]^+$

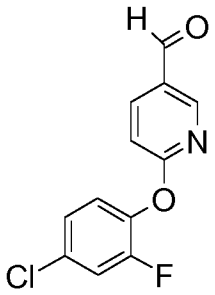
Example 5d



Example 5d was synthesised in analogy to Example 5a. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 4-fluoro-phenol (1.43 g; 12.7 mmol). Obtained 1.40 g of the desired compound used as such in the next step.

Example 5d:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.94	MS: 218 $[M+H]^+$; 250 $(M+H+MeOH)^+$

Example 5e

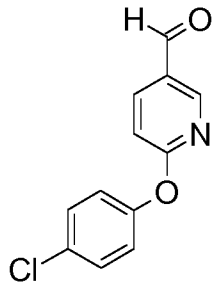


Example 5e was synthesised in analogy to Example 5a. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2-fluoro-4-chloro-phenol (1.35 ml; 12.7 mmol).

Obtained 2.20 g of the desired compound (content 80-90%) used as such in the next step.

Example 5e:	
HPLC-MS (Method): Z017_S04 R_t [min] : 1.05	MS: 252 and 254 $[M+H]^+$; Isotopic pattern for 1 Cl observed

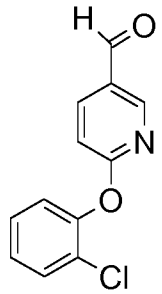
Example 5f



Example 5f was synthesised in analogy to Example 5a. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 4-chloro-phenol (1.63 g; 12.7 mmol). Obtained 2.40 g of the desired compound used as such in the next step.

Example 5f:	
HPLC-MS (Method): Z017_S04 R_t [min] : 1.02	MS: 234 and 236 $[M+H]^+$; Isotopic pattern for 1 Cl observed

Example 5g

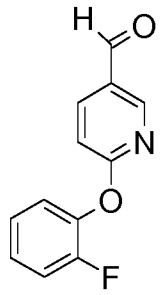


Example 5g was synthesised in analogy to Example 5a. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2-chloro-phenol (1.29 ml; 12.7 mmol).

Obtained 2.40 g of the desired compound used as such in the next step.

Example 5g:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.99	MS: 234 and 236 $[M+H]^+$; Isotopic pattern for 1 Cl observed

Example 5h

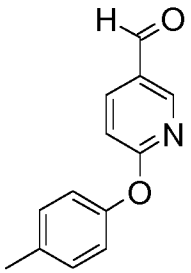


Example 5h was synthesised in analogy to Example 5a. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2-fluoro-phenol (1.13 ml; 12.7 mmol).

Obtained 2.00 g of the desired compound used as such in the next step.

Example 5h:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.95	MS: 218 $[M+H]^+$

Example 5i

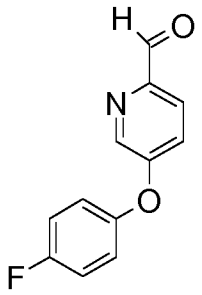


Example 5i was synthesised in analogy to Example 5a. Starting materials: 6-bromo-pyridine-3-carbaldehyde (1.89 g; 10.2 mmol) and 4-methyl-phenol (1.10 g; 10.2 mmol).

Obtained 2.40 g of the desired compound (content 70 %) used as such in the next step.

Example 5i:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.95	MS: 214 $[M+H]^+$

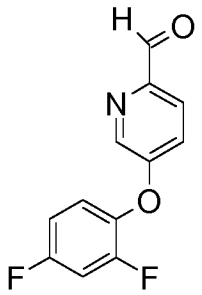
Example 5j



4-Fluoro-phenol (1.34 g; 12.0 mmol) was dissolved in DMSO (30 ml); potassium tert-butoxide (1.48 g; 13.2 mmol) was added at room temperature and the mixture was stirred for 1 h at room temperature. 5-Fluoro-2-formyl pyridine (1.50 g; 12.0 mmol) was then added and the reaction mixture was stirred at room temperature during 16 hours. 200 ml of a 1/1 mixture Dietyl ether/Ethyl Acetate was added followed by 70 ml of water. The phases were separated and the organic phase washed once more with water (20 ml). The organic phase was then dried over Na_2SO_4; the residue obtained after evaporation of solvents was purified by flash-chromatography employing as eluent Petrol Ether/Ethyl Acetate (ratio: 7/3). Obtained 1.80 g.

Example 5j:	
HPLC-MS (Method): Z017_S04 R_t [min]: 0.90	MS: 218 $[M+H]^+$

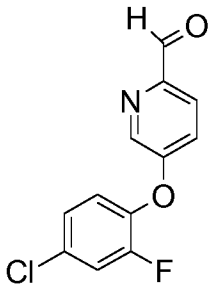
Example 5k



5-Fluoro-2-formyl pyridine (0.25 g; 2.00 mmol) and Cs_2CO_3 (0.98g; 3.00 mmol) were suspended in DMF (10 ml); 2,4-difluoro-phenol (0.31 g; 2.40 mmol) was added and the reaction mixture was stirred at 80°C during 3 hours. Acetonitrile (20 ml) was added and the mixture was filtered before being purified via preparative HPLC. Obtained 0.25 g of the desired compound.

Example 5k:	
HPLC-MS (Method):): Z011_S03;R_t [min]: 0.96	MS: 236 $[M+H]^+$

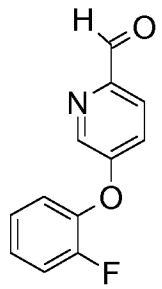
Example 5l



Example 5l was synthesised in analogy to example 5k. Starting materials: 5-Fluoro-2-formyl pyridine (0.25 g; 2.00 mmol) and 4-chloro-2-fluoro-phenol (0.26 ml; 2.40 mmol). Obtained: 0.35 g of the desired product.

Example 5l:	
HPLC-MS (Method):): Z011_S03; Rt [min]: 1.03	MS: 252 and 254 $[M+H]^+$; Isotopic pattern for 1 Cl observed

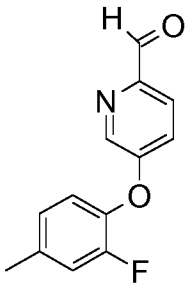
Example 5m



Example 5m was synthesised in analogy to example 5k. Starting materials: 5-Fluoro-2-formyl pyridine (0.25 g; 2.00 mmol) and 2-fluoro-phenol (0.21 ml; 2.40 mmol). Obtained: 0.23 g of the desired product.

Example 5m:	
HPLC-MS (Method):): Z011_S03: Rt [min]: 0.94	MS: 218 $[M+H]^+$

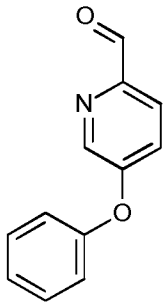
Example 5n



Example 5n was synthesised in analogy to example 5k. Starting materials: 5-Fluoro-2-formyl pyridine (0.25 g; 2.00 mmol) and 2-fluoro-4-methyl-phenol (0.30 g; 2.40 mmol). Obtained: 0.34 g of the desired product.

Example 5n:	
HPLC-MS (Method): Z011_S03: R_t [min]: 1.02	MS: 232 $[M+H]^+$

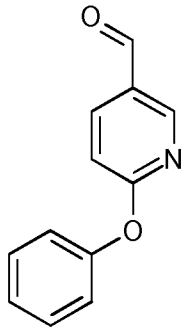
Example 5o



5-Fluoro-2-formylpyridine (0.50 g; 4.00 mmol) and Phenol (0.45 g; 4.80 mmol) were dissolved in DMF (8 ml); Cs_2CO_3 (1.43 g; 4.40 mmol) was added and the reaction mixture was stirred at 80°C during 16 hours. The reaction mixture was then partitioned between ethyl acetate (80 ml) and water (40 ml); the organic phase was separated and dried over Na_2SO_4. The crude product obtained after evaporation of the solvent was diluted with MeOH/H2O (10 mL), filtered and purified by preparative HPLC. Obtained 216 mg of the desired compound.

Example 5o:	
HPLC-MS (Method): Z017_S04: R_t [min]: 0.94	MS: 200 $[M+H]^+$

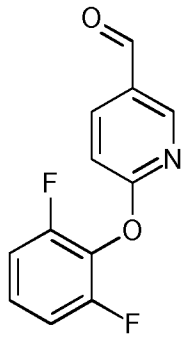
Example 5p



6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and Phenol (1.20 g; 12.7 mmol) were dissolved in DMF (10 ml) in a microwave vial; K_2CO_3 (2.20 g; 15.9 mmol) was added and the reaction mixture was stirred at 110 °C during 30 minutes. The reaction mixture was diluted with water (50 ml) and the obtained precipitate was filtered off, washed with water and dried in the air. Obtained 1.38 g of the desired compound.

Example 5p:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.93	MS: 200 [M+H]$^+$

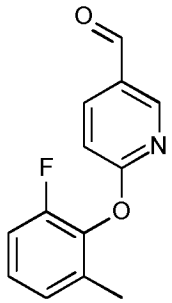
Example 5q



6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2,6-difluoro-phenol (1.65 g; 12.7 mmol) were dissolved in DMF (10 ml) in a microwave vial; K_2CO_3 (2.20 g; 15.9 mmol) was added and the reaction mixture was stirred at 110 °C during 30 minutes. The reaction mixture was then diluted with water (50 ml) and extracted with diethylether (70 ml). The organic phase was separated and dried over Na_2SO_4. The crude product obtained after evaporation was used as such in the next step. Obtained 2.30 g of the desired compound.

Example 5q:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.98	MS: 236 [M+H]$^+$

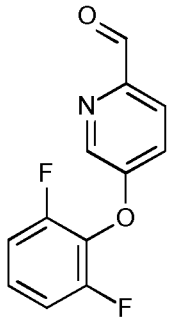
Example 5r



Example 5r was synthesised in analogy to example 5q. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (0.40 g; 2.83 mmol) and 2-fluoro-6-methyl-phenol (0.39 g; 3.11 mmol). Obtained: 0.43 g of the desired product (content 85%).

Example 5r:	
HPLC-MS (Method): Z017_S04: R_t [min]: 1.01	MS: 232 $[M+H]^+$

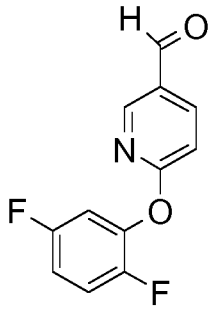
Example 5s



5-Fluoro-2-formylpyridine (0.50 g; 4.00 mmol) and 2,6-Difluorophenol (0.62 g; 4.80 mmol) were dissolved in DMF (8 ml) in a microwave vial; Cs_2CO_3 (1.56 g; 4.80 mmol) was added and the reaction mixture was stirred at 80°C during 16 hours. The reaction mixture was diluted with water (40 ml) and the obtained precipitate was filtered off, washed with water and dried in the air. Obtained 0.73 g of the desired compound (content 85%).

Example 5s:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.97	MS: 236 [$M+H]^+$

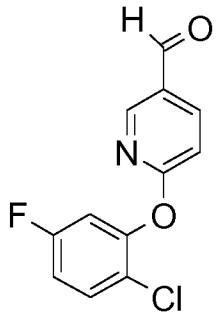
Example 5t



6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2,5-difluoro-phenol (1.65 g; 12.7 mmol) were dissolved in DMF (10 ml) in a microwave vial; K_2CO_3 (2.20 g; 15.9 mmol) is added and the reaction mixture is stirred at 110 °C during 30 minutes. Water (50 ml) was added and the reaction mixture stirred over 30 min. The precipitate obtained after filtration was washed a second time with water (20 ml), dried and used as such in the next step.Obtained 2.32 g of the desired compound.

Example 5t:	
HPLC-MS (Method): Z017_S04 R_t [min] : 0.98	MS: 236 [M+H]$^+$

Example 5u

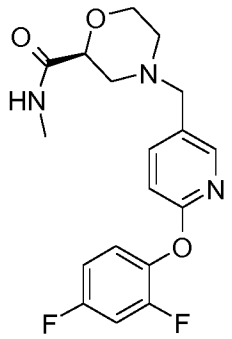


Example 5u was synthesised in analogy to Example 5t. Starting materials: 6-Chloro-pyridine-3-carbaldehyde (1.50 g; 10.6 mmol) and 2-chloro-5-difluoro-phenol (1.32 ml; 12.7 mmol). Obtained 2.4 g of the desired cpd.

Example 5u:	
HPLC-MS (Method): Z017_S04 R_t [min] : 1.02	MS: 252 and 254 [M+H]$^+$; isotopic pattern of 1 Cl observed

EXEMPLARY EMBODIMENTS

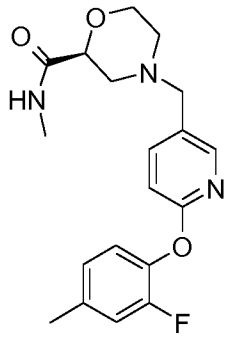
Example 11



Example 1a (150 mg; content 70%; 0.45 mmol) and Example 5a (77.2 mg, 0.54 mmol) were dissolved in DMF; Acetic acid (0.08 ml; 1.34 mmol) and DIPEA (0.11 ml; 0.63 mmol) were added and the reaction mixture was stirred 30 min. at 50°C; $NaBH(OAc)_3$ (0.14 g; 0.67 mmol) was then added and the mixture was the stirred 22 hours at room temperature. The reaction mixture was then diluted with MeOH, filtered via a syringe filter and the obtained solution purified via preparative HPLC. Obtained 120 mg of the desired compound.

Example 11	
HPLC-MS (Method): Z011_S03; R_t [min]: 0.93	MS: 364 $[M+H]^+$
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: 1.89 (t, *J*=10.81 Hz, 1 H); 2.06 - 2.14 (m, 1 H); 2.57 (d, *J*=4.71 Hz, 3 H); 2.63 (br d, *J*=11.17 Hz, 1 H); 2.88 (br d, *J*=11.17 Hz, 1 H); 3.40 - 3.59 (m, 3 H); 3.82 - 3.89 (m, 2 H); 7.09 - 7.16 (m, 1 H); 7.11 (d, *J*=8.44 Hz, 1 H); 7.36 - 7.45 (m, 2 H); 7.67 (q, *J*=4.42 Hz, 1 H); 7.81 (dd, *J*=8.42, 2.37 Hz, 1 H); 7.99 (d, *J*=2.33 Hz, 1 H).	

Example 12



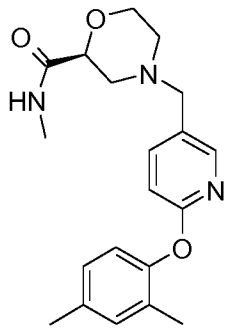
Example 12 was synthesised in analogy to example 11.

Starting materials: Example 5b (150 mg; content 50%; 0.32 mmol) + Example 1a (56.1 mg; 0.39 mmol).

The crude was purified by preparative HPLC. Obtained 105 mg of the desired compound.

Example 12	
HPLC-MS Method : Z003_S05; R_t [min] : 1.11	MS: 360 $[M+H]^+$
Chiral SFC Method: I_SA_20_IPA_NH_3_001	R_t [min]: 2.39; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.89 (t, *J*=10.81 Hz, 1 H); 2.09 (br dd, *J*=11.47, 8.19 Hz, 1 H); 2.33 (s, 3 H); 2.54 - 2.59 (m, 3 H); 2.60 - 2.65 (m, 1 H); 2.88 (br d, *J*=11.28 Hz, 1 H); 3.40 - 3.59 (m, 3 H); 3.82 - 3.89 (m, 2 H); 7.05 (t, *J*=10.04 Hz, 2 H); 7.13 - 7.21 (m, 2 H); 7.67 (br d, *J*=5.09 Hz, 1 H); 7.78 (dd, *J*=8.42, 2.38 Hz, 1 H); 7.97 (d, *J*=2.35 Hz, 1 H).	

Example 13



Example 13 was synthesised in analogy to example 11.

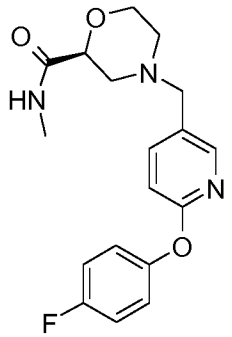
Starting materials: Example 5c (200 mg; content 50%; 0.44 mmol) + Example 1a (76.1 mg; 0.53 mmol).

The crude was purified by preparative HPLC. Obtained 119 mg of the desired compound.

Example 13	
HPLC-MS Method : Z011_S03; R_t [min] : 0.98	MS: 356 $[M+H]^+$
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: 1.88 (t, *J*=10.81 Hz, 1 H); 2.00 - 2.12 (m, 1 H);	

2.03 (s, 3 H); 2.28 (s, 3 H); 2.53 - 2.59 (m, 3 H); 2.60 - 2.65 (m, 1 H); 2.89 (br d, *J*=11.28 Hz, 1 H); 3.39 - 3.59 (m, 4 H); 3.80 - 3.90 (m, 2 H); 6.92 (dd, *J*=8.27, 1.87 Hz, 2 H); 7.02 (dd, *J*=8.16, 2.22 Hz, 1 H); 7.10 (s, 1 H); 7.64 - 7.77 (m, 2 H); 7.98 (d, *J*=2.38 Hz, 1 H).

Example 14



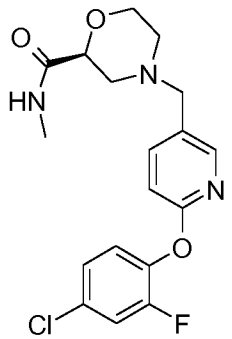
Example 14 was synthesised in analogy to example 11.

Starting materials: Example 5d (150 mg; 0.69 mmol) + Example 1a (119 mg; 0.83 mmol). The crude was purified by preparative HPLC.

Obtained 149 mg of the desired compound.

Example 14	
HPLC-MS Method : Z003_S05; R_t [min]: 1.05	MS: 346 $[M+H]^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 2.23; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.89 (t, *J*=10.82 Hz, 1 H); 2.11 (td, *J*=11.37, 3.33 Hz, 1 H); 2.54 - 2.59 (m, 3 H); 2.60 – 2.68 (m, 1 H); 2.89 (dt, *J*=11.19, 2.12 Hz, 1 H); 3.41 - 3.60 (m, 3 H); 3.83 - 3.89 (m, 2 H); 7.01 (d, *J*=8.40 Hz, 1 H); 7.15 - 7.26 (m, 4 H); 7.62 - 7.71 (m, 1 H); 7.78 (dd, *J*=8.40, 2.39 Hz, 1 H); 8.03 (s, 1 H).	

Example 15

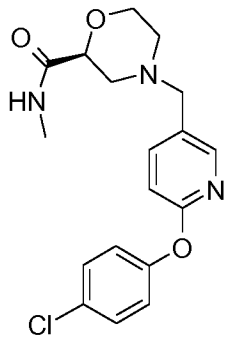


Example 15 was synthesised in analogy to example 11.

Starting materials: Example 5e (150 mg; content 85%; 0.51 mmol) + Example 1a (87.7 mg; 0.61 mmol). The crude was purified via preparative HPLC. Obtained 132 mg of the desired compound.

Example 15	
HPLC-MS Method : Z003_S05; R_t [min]: 1.14	MS: 380 and 382 $[M+H]^+$; isotopic pattern for 1 Cl observed
Chiral SFC Method: I_SA_20_IPA_NH_3_001	R_t [min]: 2.48; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm 1.89 (t, *J*=10.80 Hz, 1 H); 2.06 - 2.14 (m, 1 H); 2.52 - 2.59 (m, 3 H); 2.60 - 2.65 (m, 1H); 2.88 (dt, *J*=11.22, 2.13 Hz, 1 H); 3.41 - 3.60 (m, 3 H); 3.81 - 3.90 (m, 2 H); 7.13 (d, *J*=8.40 Hz, 1 H); 7.31 - 7.41 (m, 2 H); 7.60 (dd, *J*=10.46, 2.40 Hz, 1 H); 7.64 - 7.70 (m, 1 H); 7.82 (dd, *J*=8.42, 2.37 Hz, 1 H); 7.99 (d, *J*=2.28 Hz, 1 H).	

Example 16



Example 16 was synthesised in analogy to example 11.

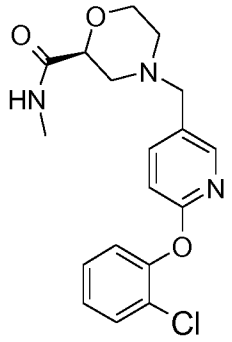
Starting materials: Example 5f (150 mg; 0.64 mmol) + Example 1a (111 mg; 0.77 mmol).

The crude was purified by preparative HPLC. Obtained 85 mg of the desired compound.

Example 16	
HPLC-MS Method: Z003_S05; R_t [min] : 1.12	MS: 362 and 364 $[M+H]^+$; isotopic pattern for 1 Cl observed
Chiral SFC Method: I_SA_20_IPA_NH_3_001	R_t [min]: 3.21; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm 1.90 (t, *J*=10.81 Hz, 1 H); 2.11 (td, *J*=11.38,	

3.33 Hz, 1 H); 2.56 – 2.67 (m, 4 H); 2.90 (br d, *J*=11.29 Hz, 1 H); 3.41 - 3.60 (m, 3 H); 3.83 - 3.89 (m, 2 H); 7.04 (d, *J*=8.37 Hz, 1 H); 7.15 - 7.20 (m, 2 H); 7.43 - 7.48 (m, 2 H); 7.67 (q, *J*=4.63 Hz, 1 H); 7.80 (dd, *J*=8.39, 2.40 Hz, 1 H); 8.04 (d, *J*=2.38 Hz, 1 H).

Example 17



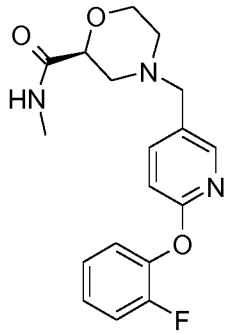
Example 17 was synthesised in analogy to example 11.

Starting materials: Example 5g (150 mg; content 90%; 0.58 mmol) + Example 1a (100 mg; 0.69 mmol).

The crude was purified by preparative HPLC. Obtained 191 mg of the desired compound.

Example 17	
HPLC-MS Method: Z003_S05; R_t [min] : 1.08	MS: 362 and 364 $[M+H]^+$; isotopic pattern for 1 Cl observed
Chiral SFC Method: I_SA_20_IPA_NH_3_001	R_t [min]: 2.75; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.89 (t, *J*=10.81 Hz, 1 H); 2.05 - 2.16 (m, 1 H); 2.52 - 2.67 (m, 4 H); 2.89 (br d, *J*=11.43 Hz, 1 H); 3.41 - 3.60 (m, 3 H); 3.79 - 3.92 (m, 2 H); 7.08 (d, *J*=8.39 Hz, 1 H); 7.25 - 7.32 (m, 2 H); 7.37 - 7.42 (m, 1 H); 7.57 (dd, *J*=7.94, 1.58 Hz, 1 H); 7.63 - 7.72 (m, 1 H); 7.80 (dd, *J*=8.42, 2.38 Hz, 1 H); 7.99 (d, *J*=2.36 Hz, 1 H).	

Example 19

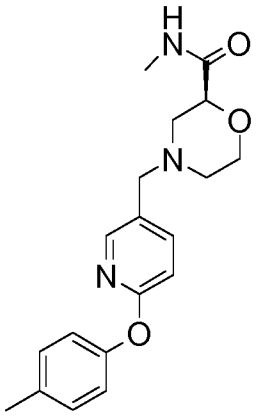


Example 19 was synthesised in analogy to example 11.

Starting materials: Example 5h (150 mg; 0.69 mmol) + Example 1a (119 mg; 0.83 mmol). The crude was purified by preparative HPLC. Obtained 147 mg of the desired compound.

Example 19	
HPLC-MS Method: Z003_S05; R_t [min] : 1.04	MS: 346 $[M+H]^+$
Chiral SFC Method: I_SA_20_IPA_NH_3_001	R_t [min]: 2.11; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.89 (t, *J*=10.81 Hz, 1 H); 2.10 (td, *J*=11.35, 3.25 Hz, 1 H); 2.56 – 2.66 (m, *J*=4.71 Hz, 4 H); 2.89 (br d, *J*=11.23 Hz, 1 H); 3.41 - 3.60 (m, 3 H); 3.83 - 3.89 (m, 2 H); 7.10 (d, *J*=8.40 Hz, 1 H); 7.21 - 7.37 (m, 4 H); 7.62 - 7.72 (m, 1 H); 7.80 (dd, *J*=8.42, 2.38 Hz, 1 H); 7.99 (d, *J*=2.34 Hz, 1 H).	

Example 29



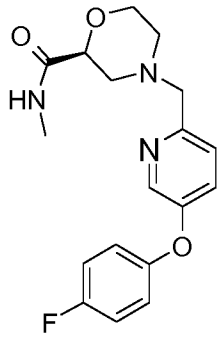
Example 29 was synthesised in analogy to example 11.

Starting materials: Example 5i (250 mg; 60% content; 0.70 mmol) and Example 1a (127 mg; content 80%; 0.70 mmol). The crude was purified via preparative HPLC.

Obtained 174 mg of the desired product.

Example 29	
HPLC-MS ; Method: Z011_S03; R_t [min]: 0.94	MS: 342 $(M+H)^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 3.23; e.e. 99%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.89 (t, *J*=10.83 Hz, 1 H); 2.06 - 2.14 (m, 1 H); 2.30 - 2.33 (m, 3 H); 2.54 - 2.67 (m, 4 H); 2.86 - 2.92 (m, 1 H); 3.40 - 3.59 (m, 3 H); 3.83 - 3.89 (m, 2 H); 6.93 - 7.02 (m, 3 H); 7.20 (d, *J*=7.77 Hz, 2 H); 7.64 - 7.70 (m, 1 H); 7.75 (dd, *J*=8.46, 2.41 Hz, 1 H); 8.02 (d, *J*=2.21 Hz, 1 H).	

Example 30



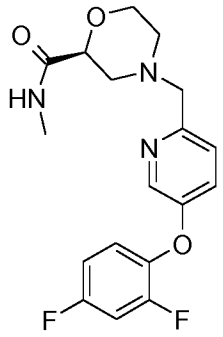
Example 30 was synthesised in analogy to Example 11.

Starting materials: Example 5j (150 mg; 0.69 mmol) and Example 1a (124.5 mg; content 80%; 0.69 mmol). The crude was purified by preparative HPLC.

Obtained 157 mg of the desired compound.

Example 30	
HPLC-MS ; Method: Z011_S03; R_t [min]: 0.89	MS: 346$[M+H]^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 2.22; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.98 (m, 1 H); 2.18 (m, 1 H); 2.55 - 2.59 (m, 3 H); 2.64 - 2.71 (m, 1 H); 2.95 (m, 1 H); 3.55 - 3.65 (m, 3 H); 3.84 - 3.91 (m, 2 H); 7.11 - 7.16 (m, 2 H); 7.22 – 7.28 (m, 2 H); 7.37 - 7.47 (m, 2 H); 7.68 (m, 1 H) 8.28 (m, 1 H).	

Example 31

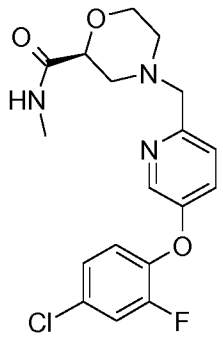


Example 1a (67.4 mg; 0.47 mmol) and example 5k (100 mg; 0.43 mmol) were dissolved in THF (3 ml); DIPEA (0.11 ml; 0.64 mmol) was added and the reaction mixture stirred 30 min before the addition of NaBH(OAc)3 (126 mg; 0.60 mmol). The mixture was stirred over 3 hours at room temperature, diluted with MeOH, filtered through a syringe filter and purified by preparative HPLC.

Obtained 53 mg of the desired compound.

Example 31	
HPLC-MS ; Method: Z003_S05; R_t [min] : 1.074	MS: 364 $(M+H)^+$
Chiral SFC Method: : G_IG_IPA_NH_3_001	R_t [min]: 5.75; e.e. 94.8%
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.98 (m, 1 H); 2.18 (m, 1 H); 2.57 (m, 3 H); 2.62 - 2.71 (m, 1 H); 2.93 (m, 1 H); 3.54 - 3.66 (m, 3 H); 3.83 - 3.92 (m, 2 H); 7.12 - 7.18 (m, 1 H); 7.33 - 7.53 (m, 4 H); 7.60 - 7.72 (m, 1 H); 8.29 (m, 1 H).	

Example 32



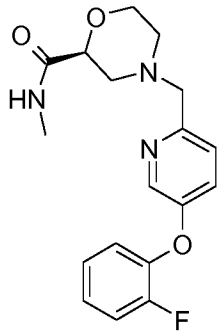
Example 32 was synthesised in analogy to example 31.

Starting materials: Example 5l (100 mg; 0.40 mmol) and Example 1a (63.0 mg; 0.44 mmol).

The crude was purified by preparative HPLC. Obtained 21 mg of the desired compound.

Example 32	
HPLC-MS ; Method: Z003_S05; R_t [min] : 1.139	MS: 380 and 382 $[M+H]^+$; isotopic pattern for 1 Cl observed
Chiral SFC Method: : G_C4_MeOH_NH_3_001	R_t [min]: 4.26; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.99 (m, 1 H); 2.18 (m, 1 H); 2.57 (m, 3 H); 2.62 - 2.75 (m, 1 H); 2.94 (m, 1 H); 3.55 - 3.66 (m, 3 H); 3.83 - 3.92 (m, 2 H); 7.26 - 7.35 (m, 2 H); 7.41 - 7.48 (m, 2 H); 7.62 - 7.72 (m, 2 H); 8.33 (m, 1 H).	

Example 33

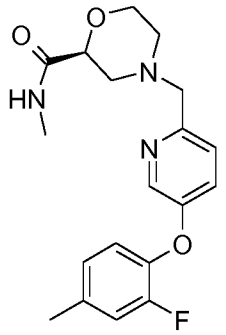


Example 33 was synthesised in analogy to example 31.

Starting materials: Example 5m (100 mg; 0.46 mmol) and Example 1a (73.0 mg; 0.51 mmol). The crude was purified by preparative HPLC. Obtained 42 mg of the desired compound.

Example 33	
HPLC-MS ; Method: Z003_S05; R_t [min] : 1.056	MS: 346 $[M+H]^+$
Chiral SFC Method: : G_IG_IPA_NH_3_001	R_t [min]: 6.41; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.99 (m, 1 H); 2.18 (m, 1 H); 2.58 (m, 3 H); 2.63 - 2.70 (m, 1 H); 2.94 (m, 1 H); 3.55 - 3.65 (m, 3 H); 3.84 - 3.91 (m, 2 H); 7.23 - 7.33 (m, 3 H); 7.34 - 7.50 (m, 4 H); 7.67 (m, 1 H); 8.30 (m, 1 H).	

Example 34



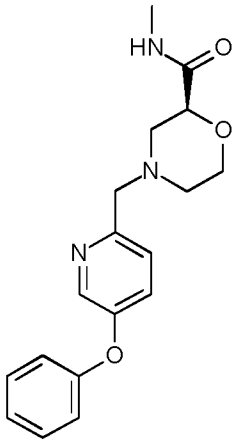
Example 34 was synthesised in analogy to example 31.

Starting materials: Example 5n (100 mg; 0.43 mmol) and Example 1a (74.8 mg; 0.52 mmol). The crude was purified by preparative HPLC.

Obtained 62 mg of the desired compound.

Example 34	
HPLC-MS ; Method: Z003_S05; R_t [min] : 1.12	MS: 360 $[M+H]^+$
Chiral SFC Method: : G_IG_MeOH_NH_3_001	R_t [min]: 5.96; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.98 (m, 1 H); 2.12 - 2.23 (m, 1 H); 2.33 (s, 3 H); 2.57 (m, 3 H); 2.62 - 2.69 (m, 1 H); 2.93 (m, 1 H); 3.54 - 3.64 (m, 3 H); 3.83 - 3.91 (m, 2 H); 7.03 - 7.09 (m, 1 H); 7.16 (m, 1H); 7.24 (m, 1H); 7.32 (m, 1 H); 7.42 (m, 1 H); 7.66 (m, 1 H); 8.26 (m, 1 H).	

Example 35

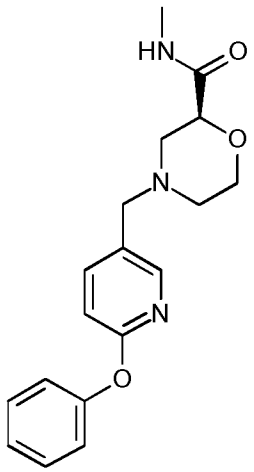


Example 35 was synthesised in analogy to example 31.

Starting materials: Example 5o (100 mg; 0.50 mmol) and Example 1a (79.6 mg; 0.55 mmol). The mixture was stirred at room temperature overnight. The crude was purified by preparative HPLC. Obtained 95.0 mg of the desired compound.

Example 35	
HPLC-MS ; Method: Z011_S03; R_t [min]: 0.88	MS: 328 $(M+H)^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 2.5; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (m, 1 H) 2.19 (m, 1 H) 2.58 (m, 3 H) 2.68 (m, 1 H) 2.96 (m, 1 H) 3.56 - 3.65 (m, 3 H) 3.84 - 3.92 (m, 2 H) 7.07 (m, 2 H) 7.18 (m, 1 H) 7.39 - 7.48 (m, 4 H) 7.62 - 7.72 (m, 1 H) 8.29 (m, 1 H)	

Example 36

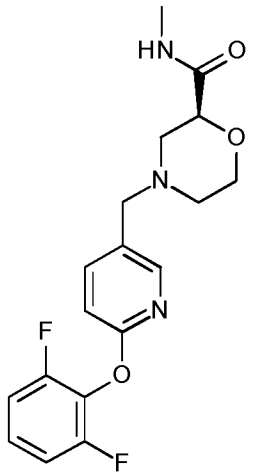


Example 36 was synthesised in analogy to example 31.

Starting materials: Example 5p (120 mg; 0.60 mmol) and Example 1a (95.5 mg; 0.66 mmol). The mixture was stirred at room temperature during 18 hours. The crude was purified by preparative HPLC. Obtained 140 mg of the desired compound.

Example 36	
HPLC-MS ; Method: Z011_S03; R_t [min]: 0.88	MS: 328 $[M+H]^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 2.73; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.90 (m, 1 H); 2.11 (m, 1 H); 2.57 (m, 3 H); 2.61 - 2.67 (m, 1 H); 2.90 (m, 1 H); 3.43 - 3.60 (m, 3 H); 3.83 - 3.89 (m, 2 H); 6.99 (d, *J*=8.37 Hz, 1 H); 7.10 - 7.23 (m, 3 H); 7.41 (t, *J*=7.53 Hz, 2 H); 7.62 - 7.71 (m, 1 H); 7.78 (dd, *J*=8.40, 2.41 Hz, 1 H); 8.04 (d, *J*=2.36 Hz, 1 H).	

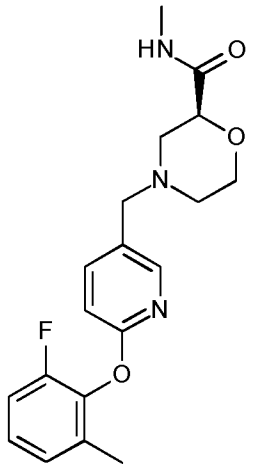
Example 37



Example 1a (76.9 mg; 0.53 mmol) and example 5q (120 mg; content 95%; 0.49 mmol) were dissolved in THF (3 ml); DIPEA (0.12 ml; 0.68 mmol) was added and the reaction mixture stirred 30 min before the addition of $NaBH(OAc)_3$ (126 mg; 0.60 mmol). The mixture was stirred over 18 hours at room temperature, diluted with MeOH, filtered through a syringe filter and purified by preparative HPLC. The product was diluted with water (5 ml) and the obtained precipitate is filtered off, washed with water and dried in the air. Obtained 106 mg of the desired compound.

Example 37	
HPLC-MS ; Method: Z011_S03; R_t [min]: 0.93	MS: 364 $(M+H)^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 1.8; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.91 (m, 1 H); 2.05 - 2.16 (m, 1 H); 2.54 - 2.65 (m, 4 H); 2.89 (m, 1 H); 3.46 - 3.59 (m, 3 H); 3.82 - 3.89 (m, 2 H); 7.19 - 7.36 (m, 4 H); 7.62 - 7.69 (m, 1 H); 7.85 (m, 1 H); 7.99 (m, 1 H).	

Example 38

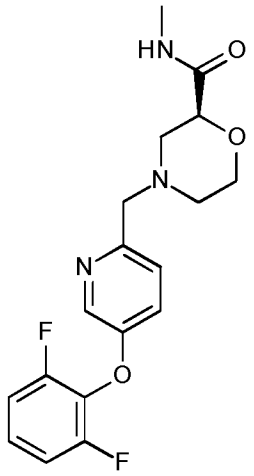


Example 1a (75.8 mg; 0.53 mmol) and example 5r (130 mg; content 85%; 0.48 mmol) were dissolved in THF (3 ml); DIPEA (0.12 ml; 0.67 mmol) was added and the reaction mixture stirred 30 min before the addition of $NaBH(OAc)_3$ (152 mg; 0.72 mmol). The mixture was stirred over 18 hours at room temperature, diluted with MeOH (3 ml), filtered through a syringe filter and purified by preparative HPLC.

Obtained 129 mg of the desired compound.

Example 38	
HPLC-MS ; Method: Z003_S05; R_t [min]: 1.10	MS: 360 $(M+H)^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 1.9; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.89 (m, 1 H); 2.05 - 2.14 (m, 4 H); 2.57 (m, 3 H); 2.60 - 2.65 (m, 1 H); 2.89 (m, 1 H); 3.41 - 3.59 (m, 3 H); 3.82 - 3.90 (m, 2 H); 7.09 - 7.19 (m, 4 H); 7.64 - 7.70 (m, 1 H); 7.80 (m, 1 H); 7.96 (m, 1 H).	

Example 39

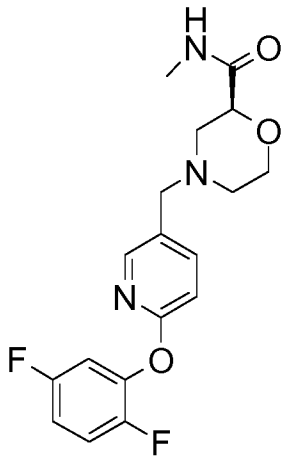


Example 39 was synthesised in analogy to example 38.

Starting materials: Example 5s (130 mg; content 85%; 0.47 mmol) and Example 1a (74.5 mg; 0.52 mmol). The mixture was stirred at room temperature during 18 hours. The crude was purified by preparative HPLC. Obtained 75.0 mg of the desired compound.

Example 39	
HPLC-MS ; Method: Z003_S05; R_t [min]: 1.06	MS: 364 $[M+H]^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 1.98; e.e. 100%
^{1}H NMR (400 MHz, DMSO-d_6); δ ppm: 1.98 (m, 1 H); 2.17 (m, 1 H); 2.57 (m, 3 H); 2.61 - 2.69 (m, 1 H); 2.93 (m, 1 H); 3.54 - 3.65 (m, 3 H); 3.83 - 3.91 (m, 2 H); 7.31 - 7.45 (m, 5 H); 7.67 (m, 1 H); 8.32 (m, 1 H).	

Example 40



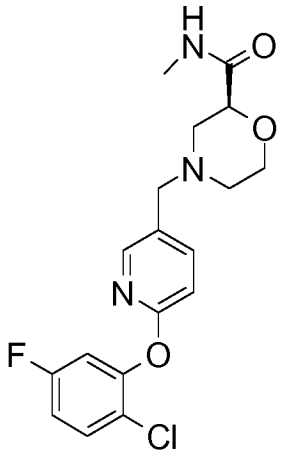
Example 40 was synthesised in analogy to example 38.

Starting materials: Example 5t (100 mg; 0.43 mmol) and Example 1a (67.43 mg; 0.47 mmol).

The crude was purified by preparative HPLC. Obtained 130 mg of the desired compound.

Example 40	
HPLC-MS ; Method: Z003_S05; R_t [min]: 1.08	MS: 364 $[M+H]^+$
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 1.78; e.e. 100%

Example 41



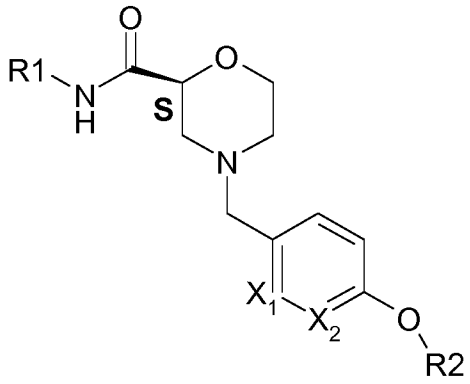
Example 41 was synthesised in analogy to example 38.

Starting materials: Example 5u (100 mg; 0.4 mmol) and Example 1a (63 mg; 0.44 mmol). Obtained 135 mg of the desired compound.

Example 41	
HPLC-MS ; Method: Z003_S05; R_t [min]: 1.11	MS: 380 and 382 $[M+H]^+$; isotopic pattern for 1 Cl observed
Chiral SFC Method: : I_SA_20_IPA_NH_3_001	R_t [min]: 2.22; e.e. 100%

CLAIMS

1. A compound of formula **A**



A

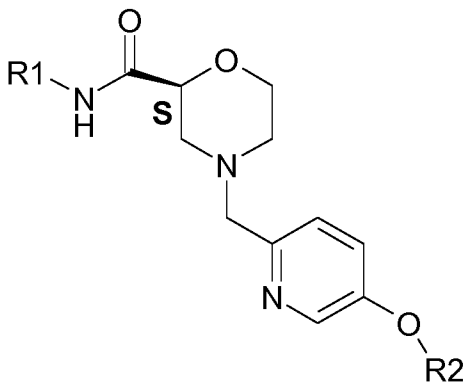
in which

$\mathbf{X_1}$ is N and $\mathbf{X_2}$ is CH, or
$\mathbf{X_1}$ is CH and $\mathbf{X_2}$ is N,

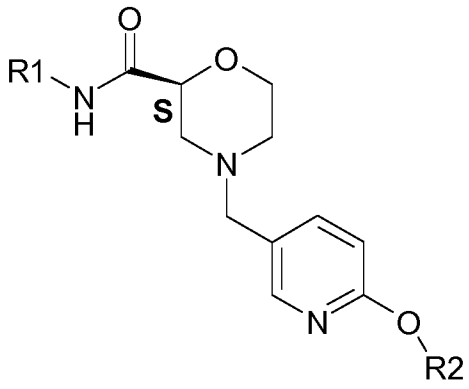
$\mathbf{R^1}$ methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, $H_3C\text{-}CH_2\text{-}CH_2\text{-}CH_2$-, cyclobutyl;

$\mathbf{R^2}$ 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, namely a compound of formula **A1** or of formula **A2**



A1



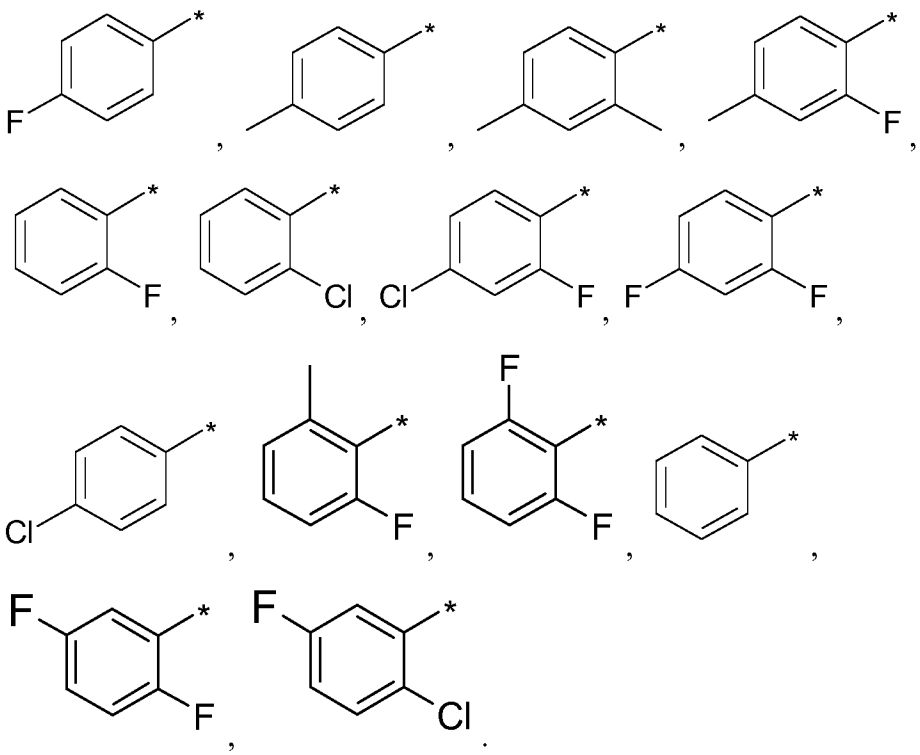
A2,

in which $\mathbf{R^1}$ and $\mathbf{R^2}$ have the same meaning as defined in claim 1.

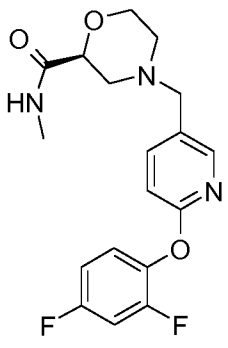
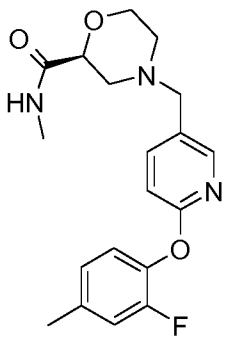
3. The compound according to any one of claims 1 to 2, wherein

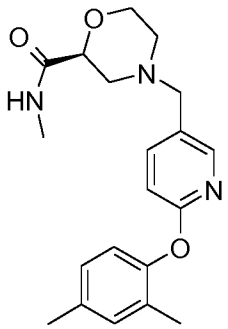
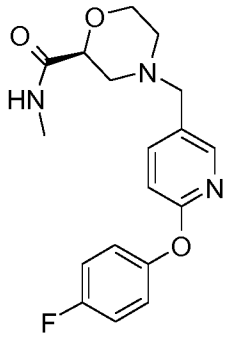
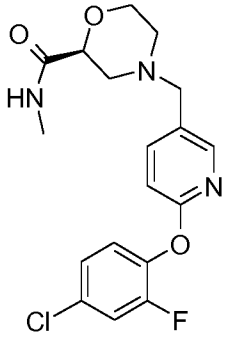
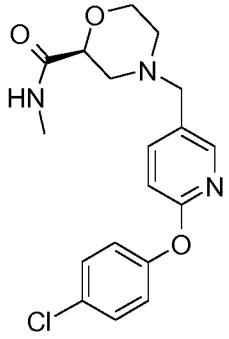
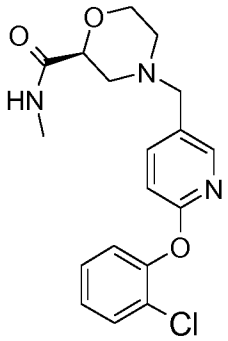
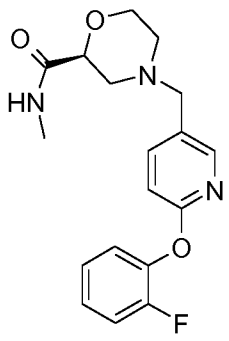
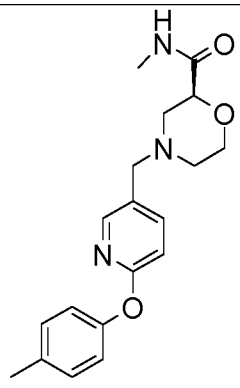
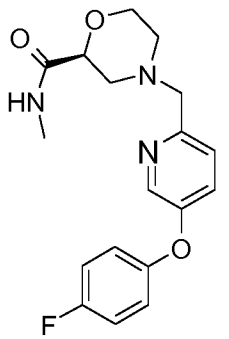
R^1 represents methyl;

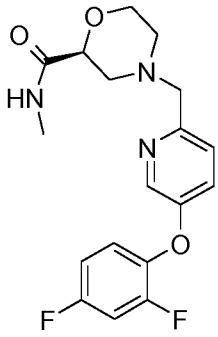
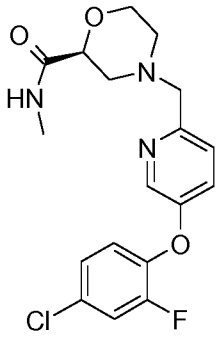
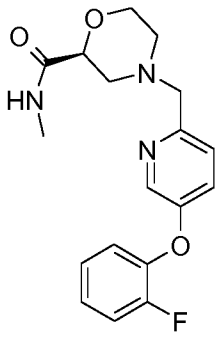
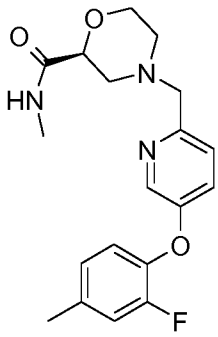
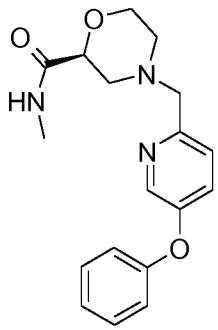
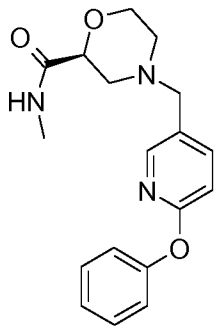
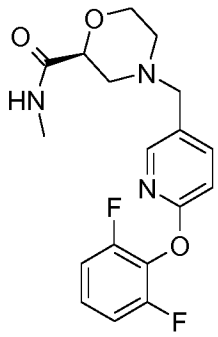
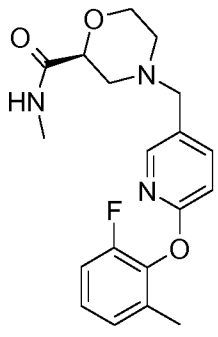
R^2 represents

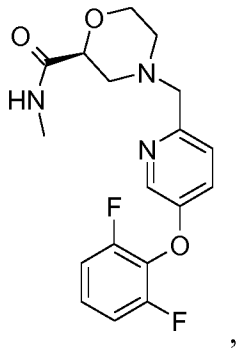
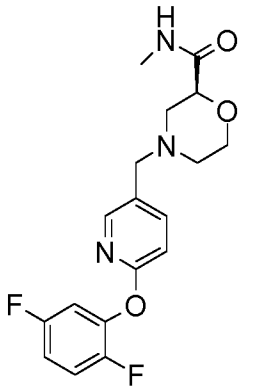
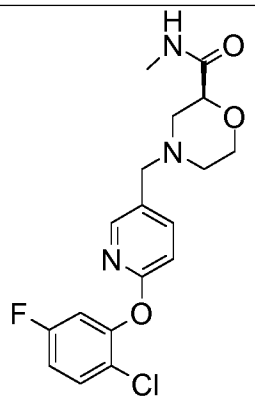


4. The *(S)*-enantiomer according to any one of claims 1 to 3, namely a compound selected from the group consisting of

Ex.		Ex	
11		**12**	

Ex.		Ex	
13	 ,	**14**	 ,
15	 ,	**16**	 ,
17	 ,	**19**	 ,
29	 ,	**30**	 ,

Ex.		Ex	
31	 ,	**32**	 ,
33	 ,	**34**	 ,
35	 ,	**36**	 ,
37	 ,	**38**	 ,

Ex.		Ex	
39	 ,	**40**	 ,
41	 .		

5. A pharmaceutically acceptable salt of a compound according to any one of claims 1 to 4.

6. The compound according to any one of claims 1 to 5 for use as a medicament.

7. The compound according to any one of claims 1 to 5 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.

8. The compound according to any one of claims 1 to 5 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.

9. The compound for use according to any one of claims 6 to 8 characterized in that the compound is administered in addition to treatment with another antidepressant drug.

10. The compound for use according to any one of claims 6 to 8 characterized in that the compound is administered in addition to behavioural therapy.

11. A pharmaceutical composition comprising the compound according to any one of claims 1 to 5 in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/078031

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/5377 C07D413/06 A61P25/24 A61P25/22
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/128582 A2 (HYUNDAI PHARM CO LTD [KR]; LEE IN HEE [KR] ET AL.) 27 September 2012 (2012-09-27) claim 1	1-11
A	WO 2007/067511 A2 (MERCK & CO INC [US]; THOMPSON WAYNE J [US]; MELAMED JEFFREY Y [US]) 14 June 2007 (2007-06-14) claim 1	1-11
A	WO 02/080928 A1 (MERCK & CO INC [US]; LIVERTON NIGEL J [US] ET AL.) 17 October 2002 (2002-10-17) claim 1	1-11
A	WO 2017/066368 A1 (BRISTOL-MYERS SQUIBB COMPANY [US]) 20 April 2017 (2017-04-20) claim 1	1-11

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

☒ See patent family annex.

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 2020	27/01/2020

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/078031

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		WO 2017066368 A1	20-04-2017