



(51) International Patent Classification:

C07D 401/12 (2006.01) *A61P 25/22* (2006.01)
C07D 405/12 (2006.01) *A61P 25/28* (2006.01)
C07D 207/16 (2006.01) *A61P 25/18* (2006.01)
A61P 25/24 (2006.01) *A61P 25/30* (2006.01)
A61P 25/14 (2006.01) *A61P 3/10* (2006.01)
A61P 9/00 (2006.01) *A61K 31/40* (2006.01)

(21) International Application Number:

PCT/US2018/023376

(22) International Filing Date:

20 March 2018 (20.03.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/474,407 21 March 2017 (21.03.2017) US

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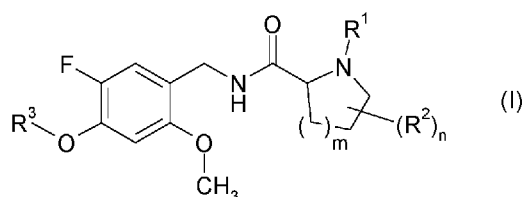
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

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

Published:

- with international search report (Art. 21(3))
- with amended claims (Art. 19(1))

(54) Title: PROLINE AMIDE COMPOUNDS AND THEIR AZETIDINE ANALOGUES CARRYING A SPECIFICALLY SUBSTITUTED BENZYL RADICAL



(57) Abstract: The present invention relates to proline amide compounds and their azetidine derivatives of formula I wherein the variables are as defined in the claims and the description. The invention further relates to a pharmaceutical composition containing such compounds, to their use as modulators, especially agonists or partial agonists, of the 5-HT_{2C} receptor, their use for preparing a medicament for the prevention or treatment of conditions and disorders which respond to the modulation of 5-HT_{2C} receptor, to a method for preventing or treating conditions and disorders which respond to the modulation of the 5-HT_{2C} receptor, and processes for preparing such compounds and compositions.



**PROLINE AMIDE COMPOUNDS AND THEIR AZETIDINE ANALOGUES
CARRYING A SPECIFICALLY SUBSTITUTED BENZYL RADICAL**

FIELD OF THE INVENTION

5 The present invention relates to proline amide compounds and their azetidine deriva-
tives carrying on the amide nitrogen atom a benzyl radical the phenyl ring of which car-
ries a fluorine atom, a methoxy radical and an O-bound radical containing fluoro substi-
tution, to a pharmaceutical composition containing such compounds, to their use as
modulators, especially agonists or partial agonists, of the 5-HT_{2C} receptor, their use for
10 preparing a medicament for the prevention or treatment of conditions and disorders
which respond to the modulation of 5-HT_{2C} receptor, to a method for preventing or
treating conditions and disorders which respond to the modulation of the 5-HT_{2C} recep-
tor, and processes for preparing such compounds and compositions.

BACKGROUND OF THE INVENTION

15 Diseases, disorders and conditions where 5-HT_{2C} modulation is desired are for
example depression, anxiety, schizophrenia, bipolar disorder, obsessive compulsive
disorder, migraine, pain, epilepsy, substance abuse, eating disorders, obesity, diabetes,
erectile dysfunction and others.

20 Serotonin (5-hydroxytryptamine, 5-HT), a monoamine neurotransmitter and local
hormone, is formed by the hydroxylation and decarboxylation of tryptophan. The great-
est concentration is found in the enterochromaffin cells of the gastrointestinal tract, the
remainder being predominantly present in platelets and in the Central Nervous System
(CNS). 5-HT is implicated in a vast array of physiological and pathophysiological
25 pathways. In the periphery, it contracts a number of smooth muscles and induces endo-
thelium-dependent vasodilation. In the CNS, it is believed to be involved in a wide
range of functions, including the control of appetite, mood, anxiety, hallucinations,
sleep, vomiting and pain perception.

 Neurons that secrete 5-HT are termed serotonergic. The function of 5-HT is ex-
30 erted upon its interaction with specific (serotonergic) neurons. Seven types of 5-HT
receptors have been identified: 5-HT₁ (with subtypes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}
and 5-HT_{1F}), 5-HT₂ (with subtypes 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}), 5-HT₃, 5-HT₄, 5-HT₅

(with subtypes 5-HT_{5A} and 5-HT_{5B}), 5-HT₆ and 5-HT₇. Most of these receptors are coupled to G-proteins that affect the activities of adenylate cyclase or phospholipase C γ .

Alterations in the activity of multiple neurotransmitter receptor systems (dopamine, serotonin, glutamate, GABA, acetylcholine) have been implicated in the manifestation of the symptoms of schizophrenia. The most widely accepted "Dopamine Hypothesis of Schizophrenia" in its simplest form states that the positive symptoms of this pathology relate to a functional hyperactivity of the mesolimbic dopaminergic system, while the negative and cognitive aspects can be traced to a functional hypoactivity of the mesocortical dopaminergic projections. Atypical antipsychotics block the mesolimbic dopaminergic neurotransmission, thereby controlling positive symptoms, with little or no effect on the nigrostriatal system, leading to less induction of extrapyramidal side effects (EPS).

Primary negative and cognitive symptoms of schizophrenia reflect a dysfunction of the frontal cortex ("hypofrontality"), which is thought to be induced by a decreased tone in the mesocortical dopaminergic projection field [Davis KL, Kahn RS, Ko G and Davidson M (1991). Dopamine in schizophrenia: a review and re-conceptualization. *Am J Psychiatry* 148: 1474 – 86. Weinberger DR and Berman KF (1996). Prefrontal function in schizophrenia: confounds and controversies. *Philos Trans R Soc Lond B Biol Sci* 351: 1495 - 503]. Agents that selectively enhance dopamine levels in the cortex have the potential to address the negative symptoms of this disorder. Atypical antipsychotics lack robust efficacy against negative and cognitive components of the schizophrenic syndrome.

The schizophrenic symptomatology is further complicated by the occurrence of drug-induced so-called secondary negative symptoms and cognitive impairment, which are difficult to distinguish from primary negative and cognitive symptoms [Remington G and Kapur S (2000). Atypical antipsychotics: are some more atypical than others? *Psychopharmacol* 148: 3 – 15]. The occurrence of secondary negative symptoms not only limits therapeutic efficacy but also, together with these side effects, negatively affects patient compliance.

It may thus be hypothesized that a novel mechanistic approach that blocks dopaminergic neurotransmission in the limbic system but does not affect the striatal and pituitary projection fields, and stimulates frontocortical projection fields, would provide an

efficacious treatment for all parts of the schizophrenic pathology, including its positive, negative and cognitive symptoms. Moreover, a selective compound that is substantially free of the ancillary pharmacology that characterizes current agents would be expected to avoid a variety of off-target side effects that plague current treatments such as extrapyramidal side effects (EPS) and weight gain.

The 5-HT_{2C} receptor, previously named 5-HT_{1C}, is a G-protein-coupled receptor, which couples to multiple cellular effector systems including the phospholipase C, A and D pathways. It is found primarily in the brain and its distribution is particularly high in the plexus choroideus, where it is assumed to control cerebrospinal fluid production [Kaufman MJ, Hirata F (1996) Cyclic GMP inhibits phosphoinositide turnover in choroid plexus: evidence for interactions between second messengers concurrently triggered by 5-HT_{2C} receptors. *Neurosci Lett* 206:153-156]. Very high levels were also found in the retrosplenial, piriform and entorhinal cortex, anterior olfactory nucleus, lateral septal nucleus, subthalamic nucleus, amygdala, subiculum and ventral part of CA3, lateral habenula, substantia nigra pars compacta, several brainstem nuclei and the whole grey matter of the spinal cord [Pompeiano M, Palacios JM, Mengod G (1994). Distribution of the serotonin 5-HT₂ receptor family mRNAs: comparison between 5-HT_{2A} and 5-HT_{2C} receptors. *Brain Res Mol Brain Res* 23:163-178]. A comparison of the distribution of 5-HT_{2C} mRNA with that of 5-HT_{2C} protein in monkey and human brains has revealed both pre- and postsynaptic localization [Lopez-Gimenez JF, Mengod G, Palacios JM, Vilaro MT (2001) Regional distribution and cellular localization of 5-HT_{2C} receptor mRNA in monkey brain: comparison with [³H]mesulergine binding sites and choline acetyltransferase mRNA. *Synapse* 42:12-26].

It is anticipated that modulation of the 5-HT_{2C} receptor will improve disorders such as depression, anxiety, schizophrenia, cognitive deficits of schizophrenia, obsessive compulsive disorder, bipolar disorder, neuropsychiatric symptoms in Parkinson's disease, in Alzheimer's disease or Lewy Body dementia, migraine, epilepsy, substance abuse, eating disorders, obesity, diabetes, sexual dysfunction/erectile dysfunction, sleep disorders, psoriasis, Parkinson's disease, pain conditions and disorders, and spinal cord injury, smoking cessation, ocular hypertension and Alzheimer's disease. Modulators of the 5-HT_{2C} receptor are also shown to be useful in the modulation of bladder function, including the prevention or treatment of urinary incontinence.

Compounds with a structure similar to the compounds of the present invention have been described in WO 2012/053186 and WO 2006/055184.

K. K.-C. Liu et al. describe in *Bioorganic & Medicinal Chemistry Letters* 2010, 20, 2365-2369 substituted N-benzyl proline amides to be highly selective 5-HT_{2c} agonists and useful for the treatment of obesity. However, it has been found that the metabolic stability of these N-benzyl proline amides is not satisfactory.

It was thus an object of the present invention to provide compounds with a comparable activity on the 5-HT_{2c} receptor, but with a better metabolic stability than the compounds described by K. K.-C. Liu et al.

It is further desirable that the compounds have low affinity to adrenergic receptors, such as the α_1 -adrenergic receptor, histamine receptors, such as the H₁-receptor, and dopaminergic receptors, such as the D₂-receptor, in order to avoid or reduce side effects associated with modulation of these receptors, such as postural hypotension, reflex tachycardia, potentiation of the antihypertensive effect of prazosin, terazosin, doxazosin and labetalol or dizziness associated with the blockade of the α_1 -adrenergic receptor, weight gain, sedation, drowsiness or potentiation of central depressant drugs associated with the blockade of the H₁-receptor, or extrapyramidal movement disorder, such as dystonia, parkinsonism, akathisia, tardive dyskinesia or rabbit syndrome, or endocrine effects, such as prolactin elevation (galactorrhea, gynecomastia, menstrual changes, sexual dysfunction in males), associated with the blockade of the D₂-receptor, and even more important no induction of weight gain in combination with severe metabolic dysfunction found for marketed antipsychotic drugs.

It is moreover desirable that the compounds have low affinity or alternatively an antagonistic effect to/on other serotonergic receptors, especially the 5-HT_{2A} and/or 5-HT_{2B} receptors, in order to avoid or reduce side effects associated with modulation of these receptors, such as changes (thickening) of the heart tissue associated with agonism at the 5-HT_{2B} receptor, and psychotomimetic effect induced by agonism at the 5-HT_{2A} receptor. Ideally they should show an agonistic action on the 5-HT_{2C} receptor, an antagonistic action on the 5-HT_{2A} receptor or alternatively no affinity to the 5-HT_{2A} receptor and no affinity to the 5-HT_{2B} receptor or alternatively an antagonistic action on the 5-HT_{2B} receptor. Even more ideally the compounds should display an agonistic action on

the 5-HT_{2C} receptor in combination with an antagonistic action on the 5-HT_{2A} receptor and no affinity to the 5-HT_{2B} receptor.

Besides the affinity and selectivity for the 5-HT_{2C} receptor and a sufficiently high metabolic stability (for example determined from the half-lives, measured in vitro, in
5 liver microsomes from various species such as rat or human), further properties may be advantageous for the treatment and/or prophylaxis of 5-HT_{2C}-related disorders, such as, for example:

1.) no or only low inhibition of cytochrome P450 (CYP) enzymes: cytochrome P450 (CYP) is the name for a superfamily of heme proteins having enzymatic activity
10 (oxidase). They are also particularly important for the degradation (metabolism) of foreign substances such as drugs or xenobiotics in mammalian organisms. The principal representatives of the types and subtypes of CYP in the human body are: CYP 1A2, CYP 2C9, CYP 2D6 and CYP 3A4. If CYP 3A4 inhibitors (e.g. grapefruit juice, cimetidine, erythromycin) are used at the same time as medicinal substances which are de-
15 graded by this enzyme system and thus compete for the same binding site on the enzyme, the degradation thereof may be slowed down and thus effects and side effects of the administered medicinal substance may be undesirably enhanced;

2.) a suitable solubility in water (in mg/mL);

3.) suitable pharmacokinetics (time course of the concentration of the compound
20 of the invention in plasma or in tissue, for example brain). The pharmacokinetics can be described by the following parameters: half-life (in h), volume of distribution (in l•kg⁻¹), plasma clearance (in l•h⁻¹•kg⁻¹), AUC (area under the curve, area under the concentration-time curve, in ng•h•l⁻¹), oral bioavailability (the dose-normalized ratio of AUC after oral administration and AUC after intravenous administration), the so-called brain-
25 plasma ratio (the ratio of AUC in brain tissue and AUC in plasma);

4.) no or only low blockade of the hERG channel: compounds which block the hERG channel may cause a prolongation of the QT interval and thus lead to serious disturbances of cardiac rhythm (for example so-called "torsade de pointes"). The potential of compounds to block the hERG channel can be determined by means of the displacement assay with radiolabelled dofetilide which is described in the literature (G. J. Diaz et al., Journal of Pharmacological and Toxicological Methods, 50 (2004), 187
30 199). A smaller IC₅₀ in this dofetilide assay means a greater probability of potent

hERG blockade. In addition, the blockade of the hERG channel can be measured by electrophysiological experiments on cells which have been transfected with the hERG channel, by so-called whole-cell patch clamping (G. J. Diaz et al., Journal of Pharmacological and Toxicological Methods, 50 (2004), 187-199).

5 It was an object of the present invention to provide compounds for the treatment or prophylaxis of various 5-HT_{2C}-related diseases. The compounds were intended to have a high affinity to the 5-HT_{2C} receptor and be potent and efficacious 5-HT_{2C} agonists. In addition, the compounds of the invention were intended to have sufficiently high metabolic stability. Further they should show low affinity on other serotonergic
10 receptors, and especially the lack of potent agonistic effect (antagonism preferred) on the 5-HT_{2A} and/or 5-HT_{2B} receptors. Additionally they should have one or more of those advantages mentioned under 1.) to 4.), and especially under 3.) (oral bioavailability in vivo).

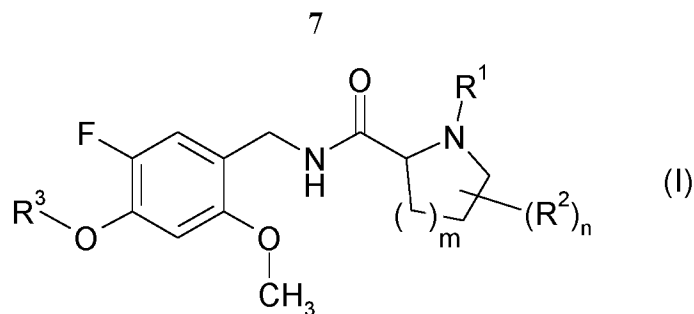
15 The present invention provides compounds which have an affinity for the 5-HT_{2C} receptor, thus allowing the treatment of disorders related to or affected by the 5-HT_{2C} receptor.

SUMMARY OF THE INVENTION

20 The present invention relates to proline amide compounds and their azetidine derivatives carrying on the amide nitrogen atom a benzyl radical the phenyl ring of which carries a fluorine atom, a methoxy radical and an O-bound radical containing fluoro substitution, to a pharmaceutical composition containing such compounds, to their use as modulators, especially agonists or partial agonists, of the 5-HT_{2C} receptor, their use
25 for preparing a medicament for the prevention or treatment of conditions and disorders which respond to the modulation of 5-HT_{2C} receptor, to a method for preventing or treating conditions and disorders which respond to the modulation of 5-HT_{2C} receptor, and processes for preparing such compounds and compositions.

In one aspect, the present invention relates to compounds of the formula (I):

30



wherein

R^1 is hydrogen or methyl;

5

R^2 is fluoro or methyl;

R^3 is selected from the group consisting of C_3 - C_7 -cycloalkyl which carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated C_1 - C_4 -alkyl; fluorinated C_1 - C_8 -alkyl; C_3 - C_7 -cycloalkyl- C_1 - C_4 -alkyl, where the cycloalkyl moiety carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated C_1 - C_4 -alkyl; phenyl- C_1 - C_4 -alkyl, where the phenyl ring carries 1, 2, 3, 4 or 5 substituents selected from the group consisting of fluoro and fluorinated C_1 - C_4 -alkyl, and may additionally carry one or more substituents selected from the group consisting of Cl, methyl and methoxy; and hetaryl- C_1 - C_4 -alkyl, where hetaryl is a 5- or 6-membered monocyclic heteroaromatic ring containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S as ring members, where the heteroaryl ring carries 1, 2, 3, 4 or 5 substituents selected from the group consisting of fluoro and fluorinated C_1 - C_4 -alkyl, and may additionally carry one or more substituents selected from the group consisting of Cl, methyl and methoxy;

10

15

20

m is 0 or 1; and

25 n is 0 or 1;

or a stereoisomer or a pharmaceutically acceptable salt thereof; or the compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium.

5 In another aspect, the invention relates to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of formula I or a stereoisomer or a pharmaceutically acceptable salt thereof or of at least one compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium, in combination with at least one pharmaceutically acceptable carrier
10 and/or auxiliary substance.

 In yet another aspect, the invention relates to a compound of formula I or a stereoisomer or a pharmaceutically acceptable salt thereof or to a compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium, for use as a medicament.

15 In yet another aspect, the invention relates to a compound of formula I or a stereoisomer or a pharmaceutically acceptable salt thereof or to a compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium, for use in the treatment of disorders which responds to the modulation of the 5-HT_{2C} receptor.

20 In yet another aspect, the invention relates to a compound of formula I or a stereoisomer or a pharmaceutically acceptable salt thereof or to a compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium, for use in the treatment of disorders selected from the group consisting of damage of the central nervous system, disorders of the central nervous system, eating disorders, ocular
25 hypertension, cardiovascular disorders, gastrointestinal disorders and diabetes, and especially from the group consisting of bipolar disorder, depression, atypical depression, mood episodes, adjustment disorders, anxiety, panic disorders, post-traumatic syndrome, psychoses, schizophrenia, cognitive deficits of schizophrenia, memory loss, dementia of aging, Alzheimer's disease, neuropsychiatric symptoms in Alzheimer's disease (e.g. aggression), behavioral disorders associated with dementia, social phobia,
30 mental disorders in childhood, attention deficit hyperactivity disorder, organic mental disorders, autism, mutism, disruptive behavior disorder, impulse control disorder, bor-

derline personality disorder, obsessive compulsive disorder, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, seizure disorders, epilepsy, substance use disorders, alcohol abuse, cocaine abuse, tobacco abuse, smoking cessation, sexual dysfunction/erectile dysfunction in males, sexual dysfunction in females, premenstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, sleep disorders, sleep apnoea, chronic fatigue syndrome, psoriasis, Parkinson's disease, neuropsychiatric symptoms in Parkinson's disease (e.g. aggression), Lewy Body dementia, neuropsychiatric symptoms in Lewy Body dementia (e.g. aggression), spinal cord injury, trauma, stroke, pain, bladder dysfunction/urinary incontinence, encephalitis, meningitis, eating disorders, obesity, bulimia, weight loss, anorexia nervosa, ocular hypertension, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, diabetes mellitus, type I diabetes, type II diabetes, type III diabetes, diabetes secondary to pancreatic diseases, diabetes related to steroid use, diabetes complications, hyperglycemia and insulin resistance.

15 In yet another aspect, the invention relates to the use of a compound of formula I or of a stereoisomer or a pharmaceutically acceptable salt thereof or of a compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium, for the manufacture of a medicament for the treatment of disorders which respond to the modulation of the 5-HT_{2C} receptor.

20 In yet another aspect, the invention relates to the use of a compound of formula I or of a stereoisomer or a pharmaceutically acceptable salt thereof or of a compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium for the manufacture of a medicament for the treatment of disorders selected from the group consisting of damage of the central nervous system, disorders of the central nervous system, eating disorders, ocular hypertension, cardiovascular disorders, gastrointestinal disorders and diabetes, and especially from the group consisting of bipolar disorder, depression, atypical depression, mood episodes, adjustment disorders, anxiety, panic disorders, post-traumatic syndrome, psychoses, schizophrenia, cognitive deficits of schizophrenia, memory loss, dementia of aging, Alzheimer's disease, neuropsychiatric symptoms in Alzheimer's disease (e.g. aggression), behavioral disorders associated with dementia, social phobia, mental disorders in childhood, attention deficit hyperactivity disorder, organic mental disorders, autism, mutism, disruptive behavior

disorder, impulse control disorder, borderline personality disorder, obsessive compulsive disorder, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, seizure disorders, epilepsy, substance use disorders, alcohol abuse, cocaine abuse, tobacco abuse, smoking cessation, sexual dysfunction/erectile
5 dysfunction in males, sexual dysfunction in females, premenstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, sleep disorders, sleep apnoea, chronic fatigue syndrome, psoriasis, Parkinson's disease, neuropsychiatric symptoms in Parkinson's disease (e.g. aggression), Lewy Body dementia, neuropsychiatric symptoms in Lewy Body dementia (e.g. aggression), spinal cord injury, trauma, stroke, pain, bladder
10 dysfunction/urinary incontinence, encephalitis, meningitis, eating disorders, obesity, bulimia, weight loss, anorexia nervosa, ocular hypertension, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, diabetes mellitus, type I diabetes, type II diabetes, type III diabetes, diabetes secondary to pancreatic diseases, diabetes related to steroid use, diabetes complications, hyperglycemia and insulin resistance.

15 In yet another aspect, the invention relates to a method for treating disorders which respond to the modulation of the 5-HT_{2C} receptor, which method comprises administering to a subject in need thereof at least one compound of formula I or a stereoisomer or a pharmaceutically acceptable salt thereof or at least one compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium.
20

In yet another aspect, the invention relates to a method for treating disorders selected from the group consisting of damage of the central nervous system, disorders of the central nervous system, eating disorders, ocular hypertension, cardiovascular disorders, gastrointestinal disorders and diabetes, and especially from the group consisting
25 of bipolar disorder, depression, atypical depression, mood episodes, adjustment disorders, anxiety, panic disorders, post-traumatic syndrome, psychoses, schizophrenia, cognitive deficits of schizophrenia, memory loss, dementia of aging, Alzheimer's disease, neuropsychiatric symptoms in Alzheimer's disease (e.g. aggression), behavioral disorders associated with dementia, social phobia, mental disorders in childhood, attention
30 deficit hyperactivity disorder, organic mental disorders, autism, mutism, disruptive behavior disorder, impulse control disorder, borderline personality disorder, obsessive compulsive disorder, migraine and other conditions associated with cephalic pain or

other pain, raised intracranial pressure, seizure disorders, epilepsy, substance use disorders, alcohol abuse, cocaine abuse, tobacco abuse, smoking cessation, sexual dysfunction/erectile dysfunction in males, sexual dysfunction in females, premenstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, sleep disorders, sleep apnoea, chronic fatigue syndrome, psoriasis, Parkinson's disease, neuropsychiatric symptoms in Parkinson's disease (e.g. aggression), Lewy Body dementia, neuropsychiatric symptoms in Lewy Body dementia (e.g. aggression), spinal cord injury, trauma, stroke, pain, bladder dysfunction/urinary incontinence, encephalitis, meningitis, eating disorders, obesity, bulimia, weight loss, anorexia nervosa, ocular hypertension, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, diabetes mellitus, type I diabetes, type II diabetes, type III diabetes, diabetes secondary to pancreatic diseases, diabetes related to steroid use, diabetes complications, hyperglycemia and insulin resistance, which method comprises administering to a subject in need thereof at least one compound of formula I or a stereoisomer or a pharmaceutically acceptable salt thereof or at least one compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium.

In yet another aspect, the invention relates to a method for modulating 5HT_{2C} receptor activity in a subject, in particular in a subject suffering of one of the above-listed disorders.

20

DETAILED DESCRIPTION

The compounds of the formula I may exist in different spatial arrangements. For example, if the compounds possess one or more centers of asymmetry or polysubstituted rings, or may exist as different tautomers, the present invention contemplates the possible use of enantiomeric mixtures, in particular racemates, diastereomeric mixtures and tautomeric mixtures, as well as the respective essentially pure enantiomers, diastereomers and/or tautomers of the compounds of formula I and/or their salts.

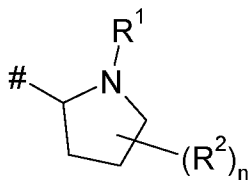
One center of chirality is for example the carbon atom via which the pyrrolidine or azetidine ring is bound to C(O). Other centers of chirality are for example asymmetry centers in the radical R³. Moreover, if R² is present (n = 0), the carbon atom of the pyrrolidine or azetidine ring carrying the substituent R² is a center of chirality.

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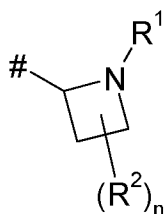
It is likewise possible to use physiologically tolerated salts of the compounds of the formula I, especially acid addition salts with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, acetic acid, trifluoroacetic acid, C₁-C₄-alkylsulfonic acids, such as methanesulfonic acid, aromatic sulfonic acids, such as benzenesulfonic acid and toluenesulfonic acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, adipic acid and benzoic acid. Other utilizable acids are described in Fortschritte der Arzneimittelforschung [Advances in drug research], Volume

10 Amide/imidic acid tautomerism in the C(O)-NH group may be present.

Compounds wherein m is 1 are pyrrolidine rings:



Compounds wherein m is 0 are azetidine rings:



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The organic moieties mentioned in the above definitions of the variables are, like the term halogen, collective terms for individual listings of the individual group members. The prefix C_n-C_m indicates in each case the possible number of carbon atoms in the group.

20

The term "alkyl" as used herein and in the alkyl moieties of alkoxy and the like refers to saturated straight-chain or branched hydrocarbon radicals having 1 to 2 ("C₁-C₂-alkyl"), 1 to 3 ("C₁-C₃-alkyl"), 1 to 4 ("C₁-C₄-alkyl"), 1 to 6 ("C₁-C₆-alkyl") or 1 to 8 ("C₁-C₈-alkyl") carbon atoms. C₁-C₂-Alkyl is methyl or ethyl. C₁-C₃-Alkyl is additionally propyl and isopropyl. C₁-C₄-Alkyl is additionally butyl, 1-methylpropyl (sec-butyl), 2-methylpropyl (isobutyl) or 1,1-dimethylethyl (tert-butyl). C₁-C₆-Alkyl is additionally

25

also, for example, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, or 1-ethyl-2-methylpropyl. C₁-C₈-Alkyl is additionally also, for example, heptyl, octyl and the position isomers thereof.

The term "fluorinated alkyl" as used herein refers to straight-chain or branched alkyl groups having 1 or 2 ("fluorinated C₁-C₂-alkyl"), 1 to 3 ("fluorinated C₁-C₃-alkyl"), 1 to 4 ("fluorinated C₁-C₄-alkyl"), 1 to 6 ("fluorinated C₁-C₆-alkyl") or 1 to 8 ("fluorinated C₁-C₈-alkyl") carbon atoms (as mentioned above), where some or all of the hydrogen atoms in these groups are replaced by fluorine atoms. Fluorinated methyl is fluoromethyl, difluoromethyl or trifluoromethyl. Fluorinated C₁-C₂-alkyl is an alkyl group having 1 or 2 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by fluorine atoms, such as fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, (R)-1-fluoroethyl, (S)-1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl. Fluorinated C₁-C₄-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by fluorine atoms. Examples are, apart those listed above for fluorinated C₁-C₂-alkyl, 1-fluoropropyl, (R)-1-fluoropropyl, (S)-1-fluoropropyl, 2-fluoropropyl, (R)-2-fluoropropyl, (S)-2-fluoropropyl, 3-fluoropropyl, 1,1-difluoropropyl, 2,2-difluoropropyl, 1,2-difluoropropyl, 2,3-difluoropropyl, 1,3-difluoropropyl, 3,3-difluoropropyl, 1,1,2-trifluoropropyl, 1,2,2-trifluoropropyl, 1,2,3-trifluoropropyl, 2,2,3-trifluoropropyl, 3,3,3-trifluoropropyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl, 1,1,1-trifluoroprop-2-yl, 2-fluoro-1-methylethyl, (R)-2-fluoro-1-methylethyl, (S)-2-fluoro-1-methylethyl, 2,2-difluoro-1-methylethyl, (R)-2,2-difluoro-1-methylethyl, (S)-2,2-difluoro-1-methylethyl, 1,2-difluoro-1-methylethyl, (R)-1,2-difluoro-1-methylethyl, (S)-1,2-difluoro-1-methylethyl, 2,2,2-trifluoro-1-methylethyl, (R)-2,2,2-trifluoro-1-methylethyl, (S)-2,2,2-trifluoro-1-methylethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, 1-(trifluoromethyl)-2,2,2-trifluoroethyl,

1-(trifluoromethyl)-1,2,2,2-tetrafluoroethyl, 1-fluorobutyl, (R)-1-fluorobutyl, (S)-1-fluorobutyl, 2-fluorobutyl, (R)-2-fluorobutyl, (S)-2-fluorobutyl, 3-fluorobutyl, (R)-3-fluorobutyl, (S)-3-fluorobutyl, 4-fluorobutyl, 1,1-difluorobutyl, 2,2-difluorobutyl, 3,3-difluorobutyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, 3,3,4,4-tetrafluorobutyl, 3,4,4,4-tetrafluorobutyl, 2,2,4,4,4-pentafluorobutyl, 3,3,4,4,4-pentafluorobutyl, 2,2,3,4,4,4-hexafluorobutyl, 1-methyl-2,2,3,3-tetrafluoropropyl and the like. Fluorinated C₁-C₆-alkyl is a straight-chain or branched alkyl group having 1 to 6 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by fluorine atoms. Examples are, apart those listed above for fluorinated C₁-C₄-alkyl, 1-fluoropentyl, (R)-1-fluoropentyl, (S)-1-fluoropentyl, 2-fluoropentyl, (R)-2-fluoropentyl, (S)-2-fluoropentyl, 3-fluoropentyl, (R)-3-fluoropentyl, (S)-3-fluoropentyl, 4-fluoropentyl, (R)-4-fluoropentyl, (S)-4-fluoropentyl, 5-fluoropentyl, (R)-5-fluoropentyl, (S)-5-fluoropentyl, 2-methyl-4,4,4-trifluorobutyl, 1-fluorohexyl, (R)-1-fluorohexyl, (S)-1-fluorohexyl, 2-fluorohexyl, (R)-2-fluorohexyl, (S)-2-fluorohexyl, 3-fluorohexyl, (R)-3-fluorohexyl, (S)-3-fluorohexyl, 4-fluorohexyl, (R)-4-fluorohexyl, (S)-4-fluorohexyl, 5-fluorohexyl, (R)-5-fluorohexyl, (S)-5-fluorohexyl, 6-fluorohexyl, (R)-6-fluorohexyl, (S)-6-fluorohexyl, and the like. Fluorinated C₁-C₈-alkyl is a straight-chain or branched alkyl group having 1 to 8 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by fluorine atoms. "Fluorinated C₂-C₆-alkyl, where the carbon atom of the alkyl group which bound to O does not carry any fluorine atom" is for example 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-fluoropropyl, (R)-2-fluoropropyl, (S)-2-fluoropropyl, 3-fluoropropyl, 2,2-difluoropropyl, 2,3-difluoropropyl, 3,3-difluoropropyl, 2,2,3-trifluoropropyl, 3,3,3-trifluoropropyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl, 2-fluoro-1-methylethyl, (R)-2-fluoro-1-methylethyl, (S)-2-fluoro-1-methylethyl, 2,2-difluoro-1-methylethyl, (R)-2,2-difluoro-1-methylethyl, (S)-2,2-difluoro-1-methylethyl, 2,2,2-trifluoro-1-methylethyl, (R)-2,2,2-trifluoro-1-methylethyl, (S)-2,2,2-trifluoro-1-methylethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 1-(trifluoromethyl)-1,2,2,2-tetrafluoroethyl, 2-fluorobutyl, (R)-2-fluorobutyl, (S)-2-fluorobutyl, 3-fluorobutyl, (R)-3-fluorobutyl, (S)-3-fluorobutyl, 4-fluorobutyl, 2,2-difluorobutyl, 3,3-difluorobutyl, 4,4-difluorobutyl,

4,4,4-trifluorobutyl, 3,3,4,4-tetrafluorobutyl, 3,4,4,4-tetrafluorobutyl, 2,2,4,4,4-pentafluorobutyl, 3,3,4,4,4-pentafluorobutyl, 2,2,3,4,4,4-hexafluorobutyl, 1-methyl-2,2-3,3-tetrafluoropropyl, 2-fluoropentyl, (R)-2-fluoropentyl, (S)-2-fluoropentyl, 3-fluoropentyl, (R)-3-fluoropentyl, (S)-3-fluoropentyl, 4-fluoropentyl, (R)-4-fluoropentyl, (S)-4-fluoropentyl, 5-fluoropentyl, (R)-5-fluoropentyl, (S)-5-fluoropentyl, 2-methyl-4,4,4-trifluorobutyl, 2-fluorohexyl, (R)-2-fluorohexyl, (S)-2-fluorohexyl, 3-fluorohexyl, (R)-3-fluorohexyl, (S)-3-fluorohexyl, 4-fluorohexyl, (R)-4-fluorohexyl, (S)-4-fluorohexyl, 5-fluorohexyl, (R)-5-fluorohexyl, (S)-5-fluorohexyl, 6-fluorohexyl, (R)-6-fluorohexyl, (S)-6-fluorohexyl, and the like.

10 "C₄-C₆-Cycloalkyl" refers to monocyclic saturated hydrocarbon radicals having 4 to 6 carbon atoms. Examples are cyclobutyl, cyclopentyl and cyclohexyl. "C₃-C₇-Cycloalkyl" refers to monocyclic saturated hydrocarbon radicals having 3 to 7 carbon atoms. Examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

15 "C₃-C₇-Cycloalkyl-methyl" refers to monocyclic saturated hydrocarbon radicals having 3 to 7 carbon atoms as defined above which are bound to the remainder of the molecule via a methyl group. Examples are cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl.

20 "C₃-C₇-Cycloalkyl-C₁-C₄-alkyl" refers to monocyclic saturated hydrocarbon radicals having 3 to 7 carbon atoms as defined above which are bound to the remainder of the molecule via a C₁-C₄-alkyl group. Examples are cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, 1-cyclopropylethyl, 1-cyclobutylethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 1-cycloheptylethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 2-cycloheptylethyl, 1-cyclopropylpropyl, 1-cyclobutylpropyl, 1-cyclopentylpropyl, 1-cyclohexylpropyl, 1-cycloheptylpropyl, 2-cyclopropylpropyl, 2-cyclobutylpropyl, 2-cyclopentylpropyl, 2-cyclohexylpropyl, 2-cycloheptylpropyl, 3-cyclopropylpropyl, 3-cyclobutylpropyl, 3-cyclopentylpropyl, 3-cyclohexylpropyl, 3-cycloheptylpropyl, 2-cyclopropyl-1-methylethyl, 2-cyclobutyl-1-methylethyl, 2-cyclopentyl-1-methylethyl, 2-cyclohexyl-1-methylethyl, 2-cycloheptyl-1-methylethyl, 1-cyclopropylbutyl, 1-cyclobutylbutyl, 1-cyclopentylbutyl, 1-cyclohexylbutyl, 1-cycloheptylbutyl, 2-cyclopropylbutyl, 2-cyclobutylbutyl, 2-cyclopentylbutyl, 2-cyclohexylbutyl, 2-cycloheptylbutyl, 3-cyclopropylbutyl, 3-cyclobutylbutyl, 3-cyclopentylbutyl, 3-

cyclohexylbutyl, 3-cycloheptylbutyl, 4-cyclopropylbutyl, 4-cyclobutylbutyl, 4-cyclopentylbutyl, 4-cyclohexylbutyl, 4-cycloheptylbutyl and the like.

Phenyl-C₁-C₄-alkyl" refers to phenyl bound to the remainder of the molecule via a C₁-C₄-alkyl group. Examples are benzyl, 1-phenylethyl, 2-phenylethyl (phenethyl), 1-phenylpropyl, 2-phenylpropyl, 3-phenylpropyl,

Examples for hetaryl (or heteroaryl) being a 5- or 6-membered monocyclic heteroaromatic ring containing 1 heteroatom selected from the group consisting of N and O as ring member are 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridinyl, 3-pyridinyl and 4-pyridinyl.

Examples for hetaryl (or heteroaryl) being a 5- or 6-membered monocyclic heteroaromatic ring containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S as ring member are 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,3,4-triazol-1-yl, 1,3,4-triazol-2-yl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl and 1,3,5-triazin-2-yl.

Hetaryl-C₁-C₄-alkyl is a 5- or 6-membered monocyclic heteroaromatic ring containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S as ring members (examples therefor see above) which is bound via a C₁-C₄-alkyl group to the remainder of the molecule.

The remarks made above and in the following with respect to preferred aspects of the invention, e.g. to preferred meanings of the variables R¹, R², R³, m and n of compounds I, to preferred compounds I and to preferred embodiments of the method or the use according to the invention, apply in each case on their own or in particular to combinations thereof.

In one embodiment, R¹ is hydrogen. In another embodiment, R¹ is methyl. Preferably, however, R¹ is hydrogen.

In one preferred embodiment, R³ is C₄-C₆-cycloalkyl which carries 1, 2, 3 or 4 substituents selected from the group consisting of fluoro and fluorinated methyl. In par-

ticular, R^3 is C₄-C₆-cycloalkyl which carries 1 or 2 substituents selected from the group consisting of fluoro and fluorinated methyl. Specifically, R^3 is C₄-C₆-cycloalkyl which carries 1 or 2 fluoro substituents or one substituent which is selected from fluorinated methyl (i.e. from CH₂F, CHF₂ or CF₃).

5 In another preferred embodiment, R^3 is fluorinated C₂-C₆-alkyl, where the carbon atom of the alkyl group which is bound to O does not carry any fluorine atom. In particular, R^3 is fluorinated C₃-C₅-alkyl, where the carbon atom of the alkyl group which is bound to O does not carry any fluorine atom. Specifically, the fluorinated alkyl group contains 3 to 6 fluorine atoms.

10 In another preferred embodiment, R^3 is C₃-C₇-cycloalkyl-methyl, where the cycloalkyl moiety carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated methyl. In particular, R^3 is C₃-C₆-cycloalkyl-methyl, where the cycloalkyl moiety carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated methyl. More particularly, R^3 is C₃-C₆-cycloalkyl-methyl,
15 where the cycloalkyl moiety carries 1, 2, 3, 4, 5 or 6 fluoro substituents or carries one substituent which is selected from fluorinated methyl (i.e. from CH₂F, CHF₂ or CF₃).

In another preferred embodiment, R^3 is phenyl-C₁-C₂-alkyl, where the phenyl ring carries 1, 2, 3 or 4 substituents selected from the group consisting of fluoro and fluorinated methyl, and may additionally carry one Cl substituent. In particular, R^3 is benzyl
20 or phenethyl, where the phenyl ring in the two last-mentioned radicals carries 1, 2, 3 or fluorine atoms and optionally also a chlorine atom or carries one substituent which is selected from fluorinated methyl (i.e. from CH₂F, CHF₂ or CF₃).

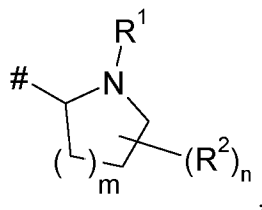
In another preferred embodiment, R^3 is hetaryl-C₁-C₂-alkyl, where hetaryl is a 5-
25 or 6-membered monocyclic heteroaromatic ring containing 1 heteroatom selected from the group consisting of N and O as ring member, where the heteroaryl ring carries 1 or 2 substituents selected from the group consisting of fluoro and fluorinated methyl. In particular, R^3 is hetaryl-methyl, where hetaryl is a 5- or 6-membered monocyclic heteroaromatic ring containing 1 heteroatom selected from the group consisting of N and O as ring member, where the heteroaryl ring carries 1 or 2 fluoro substituents or carries one
30 substituent which is selected from fluorinated methyl (i.e. from CH₂F, CHF₂ or CF₃).

In one embodiment, m is 1. In another embodiment, m is 0. Preferably, however, m is 1.

In a preferred embodiment, n is 0.

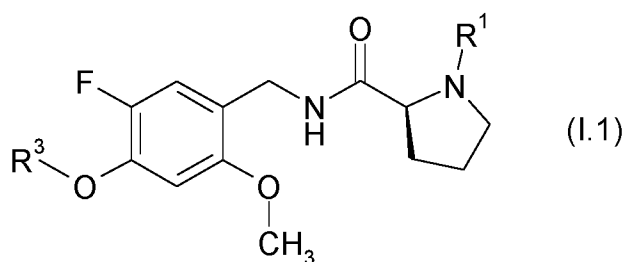
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In one embodiment, in compounds I at least one of the hydrogen atoms of the moiety



where # is the attachment point to C(O), has been replaced by a deuterium atom. In particular, at least one of the hydrogen atoms bound to a carbon ring atom of the pyrrolidine (m = 1) or azetidine (m = 0) ring of the above moiety has been replaced by a deuterium atom. Specifically, in the above moiety, all hydrogen atoms bound to carbon ring atoms have been replaced by deuterium atoms.

15 In a particular embodiment, the compounds of formula I are compounds of formula I.1

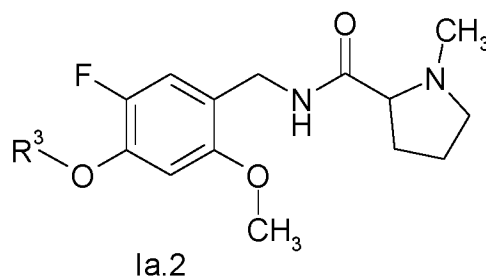
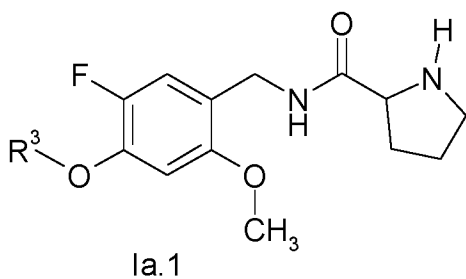


where R¹ and R³ have one of the above general or, in particular, one of the above preferred meanings.

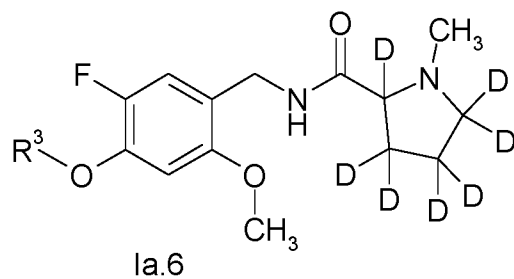
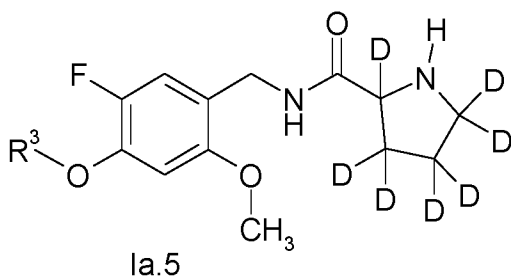
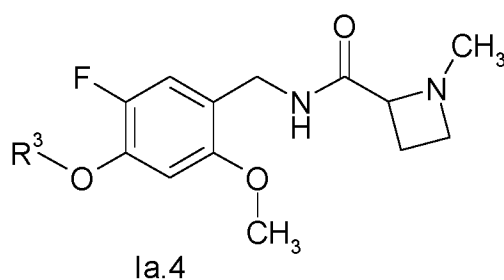
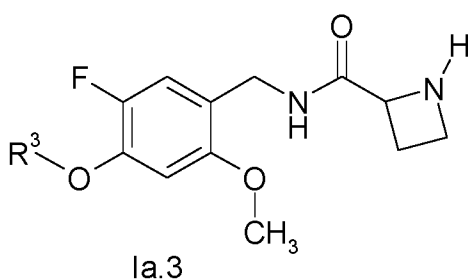
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Examples of preferred compounds are compounds of the following formulae Ia.1 to Ia.6 and the stereoisomers thereof and the pharmaceutically acceptable salts thereof, where R³ is as defined in table A. For an individual compound R³ corresponds in each case to one row of table A. Moreover, the meanings mentioned below for R³ are per se,

independently of the combination in which they are mentioned, a particularly preferred embodiment of this substituent.



5



10 Table A

| No. | R ³ |
|-----|-----------------------------------|
| 1. | CH ₂ F |
| 2. | CHF ₂ |
| 3. | CF ₃ |
| 4. | CH ₂ CH ₂ F |
| 5. | CH ₂ CHF ₂ |
| 6. | CH ₂ CF ₃ |
| 7. | CHFCH ₃ |
| 8. | CF ₂ CH ₃ |

| No. | R ³ |
|-----|---|
| 9. | CHFCH ₂ F |
| 10. | CHFCHF ₂ |
| 11. | CHFCH ₂ F |
| 12. | CF ₂ CH ₂ F |
| 13. | CF ₂ CHF ₂ |
| 14. | CF ₂ CF ₃ |
| 15. | CH ₂ CH ₂ CH ₂ F |
| 16. | CH ₂ CH ₂ CHF ₂ |

| No. | R ³ |
|-----|---|
| 17. | CH ₂ CH ₂ CF ₃ |
| 18. | CH ₂ CHFCH ₃ |
| 19. | CH ₂ CF ₂ CH ₃ |
| 20. | CH ₂ CHFCH ₂ F |
| 21. | CH ₂ CHFCHF ₂ |
| 22. | CH ₂ CHFCF ₃ |
| 23. | CH ₂ CF ₂ CH ₂ F |
| 24. | CH ₂ CF ₂ CHF ₂ |
| 25. | CH ₂ CF ₂ CF ₃ |
| 26. | CHFCH ₂ CH ₃ |
| 27. | CHFCH ₂ CH ₂ F |
| 28. | CHFCH ₂ CHF ₂ |
| 29. | CHFCH ₂ CF ₃ |
| 30. | CHFCHFCH ₃ |
| 31. | CHFCH ₂ CH ₃ |
| 32. | CHFCHFCH ₂ F |
| 33. | CHFCHFCHF ₂ |
| 34. | CHFCHFCF ₃ |
| 35. | CHFCH ₂ CH ₂ F |
| 36. | CHFCH ₂ CHF ₂ |
| 37. | CHFCH ₂ CF ₃ |
| 38. | CF ₂ CH ₂ CH ₃ |
| 39. | CF ₂ CH ₂ CH ₂ F |
| 40. | CF ₂ CH ₂ CHF ₂ |
| 41. | CF ₂ CH ₂ CF ₃ |
| 42. | CF ₂ CHFCH ₃ |
| 43. | CF ₂ CF ₂ CH ₃ |
| 44. | CF ₂ CHFCH ₂ F |
| 45. | CF ₂ CHFCHF ₂ |
| 46. | CF ₂ CHFCF ₃ |

| No. | R ³ |
|-----|---|
| 47. | CF ₂ CF ₂ CH ₂ F |
| 48. | CF ₂ CF ₂ CHF ₂ |
| 49. | CF ₂ CF ₂ CF ₃ |
| 50. | CF(CH ₃) ₂ |
| 51. | CH(CH ₃)CH ₂ F |
| 52. | CH(CH ₃)CHF ₂ |
| 53. | CH(CH ₃)CF ₃ |
| 54. | CF(CH ₃)CH ₂ F |
| 55. | CF(CH ₃)CHF ₂ |
| 56. | CF(CH ₃)CF ₃ |
| 57. | CH(CF ₃) ₂ |
| 58. | CF(CF ₃) ₂ |
| 59. | CH ₂ CH ₂ CH ₂ CH ₂ F |
| 60. | CH ₂ CH ₂ CH ₂ CHF ₂ |
| 61. | CH ₂ CH ₂ CH ₂ CF ₃ |
| 62. | CH ₂ CH ₂ CHFCH ₃ |
| 63. | CH ₂ CH ₂ CF ₂ CH ₃ |
| 64. | CH ₂ CH ₂ CHFCH ₂ F |
| 65. | CH ₂ CH ₂ CHFCHF ₂ |
| 66. | CH ₂ CH ₂ CHFCH ₂ F |
| 67. | CH ₂ CH ₂ CF ₂ CH ₂ F |
| 68. | CH ₂ CH ₂ CF ₂ CHF ₂ |
| 69. | CH ₂ CH ₂ CF ₂ CF ₃ |
| 70. | CH ₂ CHFCH ₂ CH ₃ |
| 71. | CH ₂ CHFCH ₂ CH ₂ F |
| 72. | CH ₂ CHFCH ₂ CHF ₂ |
| 73. | CH ₂ CHFCH ₂ CF ₃ |
| 74. | CH ₂ CHFCHFCH ₃ |
| 75. | CH ₂ CHFCH ₂ CF ₃ |
| 76. | CH ₂ CHFCHFCH ₂ F |

| No. | R ³ |
|------|---|
| 77. | CH ₂ CHFCHFCHF ₂ |
| 78. | CH ₂ CHFCHFCHCF ₃ |
| 79. | CH ₂ CHFCHF ₂ CH ₂ F |
| 80. | CH ₂ CHFCHF ₂ CHF ₂ |
| 81. | CH ₂ CHFCHF ₂ CF ₃ |
| 82. | CH ₂ CF ₂ CH ₂ CH ₃ |
| 83. | CH ₂ CF ₂ CH ₂ CH ₂ F |
| 84. | CH ₂ CF ₂ CH ₂ CHF ₂ |
| 85. | CH ₂ CF ₂ CH ₂ CF ₃ |
| 86. | CH ₂ CF ₂ CHFCH ₃ |
| 87. | CH ₂ CF ₂ CF ₂ CH ₃ |
| 88. | CH ₂ CF ₂ CHFCH ₂ F |
| 89. | CH ₂ CF ₂ CHFCHF ₂ |
| 90. | CH ₂ CF ₂ CHFCHCF ₃ |
| 91. | CH ₂ CF ₂ CF ₂ CH ₂ F |
| 92. | CH ₂ CF ₂ CF ₂ CHF ₂ |
| 93. | CH ₂ CF ₂ CF ₂ CF ₃ |
| 94. | CHFCH ₂ CH ₂ CH ₃ |
| 95. | CHFCH ₂ CH ₂ CH ₂ F |
| 96. | CHFCH ₂ CH ₂ CHF ₂ |
| 97. | CHFCH ₂ CH ₂ CF ₃ |
| 98. | CHFCH ₂ CHFCH ₃ |
| 99. | CHFCH ₂ CF ₂ CH ₃ |
| 100. | CHFCH ₂ CHFCH ₂ F |
| 101. | CHFCH ₂ CHFCHF ₂ |
| 102. | CHFCH ₂ CHFCHCF ₃ |
| 103. | CHFCH ₂ CF ₂ CH ₂ F |
| 104. | CHFCH ₂ CF ₂ CHF ₂ |
| 105. | CHFCH ₂ CF ₂ CF ₃ |
| 106. | CHFCHFCH ₂ CH ₃ |

| No. | R ³ |
|------|---|
| 107. | CHFCHFCH ₂ CH ₂ F |
| 108. | CHFCHFCH ₂ CHF ₂ |
| 109. | CHFCHFCH ₂ CF ₃ |
| 110. | CHFCHFCHFCH ₃ |
| 111. | CHFCHFCHF ₂ CH ₃ |
| 112. | CHFCHFCHFCH ₂ F |
| 113. | CHFCHFCHFCHF ₂ |
| 114. | CHFCHFCHFCHCF ₃ |
| 115. | CHFCHFCHF ₂ CH ₂ F |
| 116. | CHFCHFCHF ₂ CHF ₂ |
| 117. | CHFCHFCHF ₂ CF ₃ |
| 118. | CHFCH ₂ CH ₂ CH ₃ |
| 119. | CHFCH ₂ CH ₂ CH ₂ F |
| 120. | CHFCH ₂ CH ₂ CHF ₂ |
| 121. | CHFCH ₂ CH ₂ CF ₃ |
| 122. | CHFCH ₂ CHFCH ₃ |
| 123. | CHFCH ₂ CF ₂ CH ₃ |
| 124. | CHFCH ₂ CHFCH ₂ F |
| 125. | CHFCH ₂ CHFCHF ₂ |
| 126. | CHFCH ₂ CHFCHCF ₃ |
| 127. | CHFCH ₂ CF ₂ CH ₂ F |
| 128. | CHFCH ₂ CF ₂ CHF ₂ |
| 129. | CHFCH ₂ CF ₂ CF ₃ |
| 130. | CF ₂ CH ₂ CH ₂ CH ₂ F |
| 131. | CF ₂ CH ₂ CH ₂ CHF ₂ |
| 132. | CF ₂ CH ₂ CH ₂ CF ₃ |
| 133. | CF ₂ CH ₂ CHFCH ₃ |
| 134. | CF ₂ CH ₂ CF ₂ CH ₃ |
| 135. | CF ₂ CH ₂ CHFCH ₂ F |
| 136. | CF ₂ CH ₂ CHFCHF ₂ |

| No. | R ³ |
|------|---|
| 137. | CF ₂ CH ₂ CHFCF ₃ |
| 138. | CF ₂ CH ₂ CF ₂ CH ₂ F |
| 139. | CF ₂ CH ₂ CF ₂ CHF ₂ |
| 140. | CF ₂ CH ₂ CF ₂ CF ₃ |
| 141. | CF ₂ CHFCH ₂ CH ₃ |
| 142. | CF ₂ CHFCH ₂ CH ₂ F |
| 143. | CF ₂ CHFCH ₂ CHF ₂ |
| 144. | CF ₂ CHFCH ₂ CF ₃ |
| 145. | CF ₂ CHFCHFCH ₃ |
| 146. | CF ₂ CHFCF ₂ CH ₃ |
| 147. | CF ₂ CHFCHFCH ₂ F |
| 148. | CF ₂ CHFCHFCHF ₂ |
| 149. | CF ₂ CHFCHFCF ₃ |
| 150. | CF ₂ CHFCF ₂ CH ₂ F |
| 151. | CF ₂ CHFCF ₂ CHF ₂ |
| 152. | CF ₂ CHFCF ₂ CF ₃ |
| 153. | CF ₂ CF ₂ CH ₂ CH ₃ |
| 154. | CF ₂ CF ₂ CH ₂ CH ₂ F |
| 155. | CF ₂ CF ₂ CH ₂ CHF ₂ |
| 156. | CF ₂ CF ₂ CH ₂ CF ₃ |
| 157. | CF ₂ CF ₂ CHFCH ₃ |
| 158. | CF ₂ CF ₂ CF ₂ CH ₃ |
| 159. | CF ₂ CF ₂ CHFCH ₂ F |
| 160. | CF ₂ CF ₂ CHFCHF ₂ |
| 161. | CF ₂ CF ₂ CHFCF ₃ |
| 162. | CF ₂ CF ₂ CF ₂ CH ₂ F |
| 163. | CF ₂ CF ₂ CF ₂ CHF ₂ |
| 164. | CF ₂ CF ₂ CF ₂ CF ₃ |
| 165. | CH(CH ₃)CH ₂ CH ₂ F |
| 166. | CH(CH ₃)CH ₂ CHF ₂ |

| No. | R ³ |
|------|---|
| 167. | CH(CH ₃)CH ₂ CF ₃ |
| 168. | CH(CH ₃)CHFCH ₃ |
| 169. | CH(CH ₃)CHFCH ₂ F |
| 170. | CH(CH ₃)CHFCHF ₂ |
| 171. | CH(CH ₃)CHFCF ₃ |
| 172. | CH(CH ₃)CF ₂ CH ₂ F |
| 173. | CH(CH ₃)CF ₂ CHF ₂ |
| 174. | CH(CH ₃)CF ₂ CF ₃ |
| 175. | CH ₂ CH(CH ₃)CH ₂ F |
| 176. | CH ₂ CH(CH ₃)CHF ₂ |
| 177. | CH ₂ CH(CH ₃)CF ₃ |
| 178. | CH ₂ CH(CF ₃) ₂ |
| 179. | C(CH ₃) ₂ (CF ₃) |
| 180. | C(CF ₃) ₂ (CH ₃) |
| 181. | C(CF ₃) ₃ |
| 182. | CH ₂ CH ₂ CH ₂ CH ₂ F |
| 183. | CH ₂ CH ₂ CH ₂ CH ₂ CHF ₂ |
| 184. | CH ₂ CH ₂ CH ₂ CH ₂ CF ₃ |
| 185. | CH ₂ CH ₂ CH ₂ CHFCH ₃ |
| 186. | CH ₂ CH ₂ CH ₂ CF ₂ CH ₃ |
| 187. | CH ₂ CH ₂ CH ₂ CHFCH ₂ F |
| 188. | CH ₂ CH ₂ CH ₂ CHFCHF ₂ |
| 189. | CH ₂ CH ₂ CH ₂ CHFCF ₃ |
| 190. | CH ₂ CH ₂ CH ₂ CF ₂ CH ₂ F |
| 191. | CH ₂ CH ₂ CH ₂ CF ₂ CHF ₂ |
| 192. | CH ₂ CH ₂ CH ₂ CF ₂ CF ₃ |
| 193. | CH ₂ CH ₂ CHFCH ₂ CH ₃ |
| 194. | CH ₂ CH ₂ CHFCH ₂ CH ₂ F |
| 195. | CH ₂ CH ₂ CHFCH ₂ CHF ₂ |
| 196. | CH ₂ CH ₂ CHFCH ₂ CF ₃ |

| No. | R ³ |
|------|--|
| 197. | CH ₂ CH ₂ CHFCHFCH ₃ |
| 198. | CH ₂ CH ₂ CHFCH ₂ CF ₂ CH ₃ |
| 199. | CH ₂ CH ₂ CHFCHFCH ₂ F |
| 200. | CH ₂ CH ₂ CHFCHFCHF ₂ |
| 201. | CH ₂ CH ₂ CHFCHFCF ₃ |
| 202. | CH ₂ CH ₂ CHFCH ₂ CF ₂ CH ₂ F |
| 203. | CH ₂ CH ₂ CHFCH ₂ CHF ₂ |
| 204. | CH ₂ CH ₂ CHFCH ₂ CF ₂ CF ₃ |
| 205. | CH ₂ CH ₂ CF ₂ CH ₂ CH ₃ |
| 206. | CH ₂ CH ₂ CF ₂ CH ₂ CH ₂ F |
| 207. | CH ₂ CH ₂ CF ₂ CH ₂ CHF ₂ |
| 208. | CH ₂ CH ₂ CF ₂ CH ₂ CF ₃ |
| 209. | CH ₂ CH ₂ CF ₂ CHFCH ₃ |
| 210. | CH ₂ CH ₂ CF ₂ CF ₂ CH ₃ |
| 211. | CH ₂ CH ₂ CF ₂ CHFCH ₂ F |
| 212. | CH ₂ CH ₂ CF ₂ CHFCHF ₂ |
| 213. | CH ₂ CH ₂ CF ₂ CHFCH ₂ F |
| 214. | CH ₂ CH ₂ CF ₂ CF ₂ CH ₂ F |
| 215. | CH ₂ CH ₂ CF ₂ CF ₂ CHF ₂ |
| 216. | CH ₂ CH ₂ CF ₂ CF ₂ CF ₃ |
| 217. | CH ₂ CHFCH ₂ CH ₂ CH ₃ |
| 218. | CH ₂ CHFCH ₂ CH ₂ CH ₂ F |
| 219. | CH ₂ CHFCH ₂ CH ₂ CHF ₂ |
| 220. | CH ₂ CHFCH ₂ CH ₂ CF ₃ |
| 221. | CH ₂ CHFCH ₂ CHFCH ₃ |
| 222. | CH ₂ CHFCH ₂ CF ₂ CH ₃ |
| 223. | CH ₂ CHFCH ₂ CHFCH ₂ F |
| 224. | CH ₂ CHFCH ₂ CHFCHF ₂ |
| 225. | CH ₂ CHFCH ₂ CHFCH ₂ F |
| 226. | CH ₂ CHFCH ₂ CF ₂ CH ₂ F |

| No. | R ³ |
|------|---|
| 227. | CH ₂ CHFCH ₂ CF ₂ CHF ₂ |
| 228. | CH ₂ CHFCH ₂ CF ₂ CF ₃ |
| 229. | CH ₂ CHFCHFCH ₂ CH ₃ |
| 230. | CH ₂ CHFCHFCH ₂ CH ₂ F |
| 231. | CH ₂ CHFCHFCH ₂ CHF ₂ |
| 232. | CH ₂ CHFCHFCH ₂ CF ₃ |
| 233. | CH ₂ CHFCHFCHFCH ₃ |
| 234. | CH ₂ CHFCHFCH ₂ CF ₂ CH ₃ |
| 235. | CH ₂ CHFCHFCHFCH ₂ F |
| 236. | CH ₂ CHFCHFCHFCHF ₂ |
| 237. | CH ₂ CHFCHFCHFCH ₂ F |
| 238. | CH ₂ CHFCHFCH ₂ CF ₃ |
| 239. | CH ₂ CHFCHFCH ₂ CHF ₂ |
| 240. | CH ₂ CHFCHFCH ₂ CF ₂ CF ₃ |
| 241. | CH ₂ CHFCH ₂ CH ₂ CH ₃ |
| 242. | CH ₂ CHFCH ₂ CH ₂ CH ₂ F |
| 243. | CH ₂ CHFCH ₂ CH ₂ CHF ₂ |
| 244. | CH ₂ CHFCH ₂ CH ₂ CF ₃ |
| 245. | CH ₂ CHFCH ₂ CHFCH ₃ |
| 246. | CH ₂ CHFCH ₂ CF ₂ CH ₃ |
| 247. | CH ₂ CHFCH ₂ CHFCH ₂ F |
| 248. | CH ₂ CHFCH ₂ CHFCHF ₂ |
| 249. | CH ₂ CHFCH ₂ CHFCH ₂ F |
| 250. | CH ₂ CHFCH ₂ CF ₂ CH ₂ F |
| 251. | CH ₂ CHFCH ₂ CF ₂ CHF ₂ |
| 252. | CH ₂ CHFCH ₂ CF ₂ CF ₃ |
| 253. | CH ₂ CF ₂ CH ₂ CH ₂ CH ₂ F |
| 254. | CH ₂ CF ₂ CH ₂ CH ₂ CHF ₂ |
| 255. | CH ₂ CF ₂ CH ₂ CH ₂ CF ₃ |
| 256. | CH ₂ CF ₂ CH ₂ CHFCH ₃ |

| No. | R ³ |
|------|---|
| 257. | CH ₂ CF ₂ CH ₂ CF ₂ CH ₃ |
| 258. | CH ₂ CF ₂ CH ₂ CHFCH ₂ F |
| 259. | CH ₂ CF ₂ CH ₂ CHFCHF ₂ |
| 260. | CH ₂ CF ₂ CH ₂ CHFCH ₂ F |
| 261. | CH ₂ CF ₂ CH ₂ CF ₂ CH ₂ F |
| 262. | CH ₂ CF ₂ CH ₂ CF ₂ CHF ₂ |
| 263. | CH ₂ CF ₂ CH ₂ CF ₂ CF ₃ |
| 264. | CH ₂ CF ₂ CHFCH ₂ CH ₃ |
| 265. | CH ₂ CF ₂ CHFCH ₂ CH ₂ F |
| 266. | CH ₂ CF ₂ CHFCH ₂ CHF ₂ |
| 267. | CH ₂ CF ₂ CHFCH ₂ CF ₃ |
| 268. | CH ₂ CF ₂ CHFCHFCH ₃ |
| 269. | CH ₂ CF ₂ CHFCH ₂ CH ₃ |
| 270. | CH ₂ CF ₂ CHFCHFCH ₂ F |
| 271. | CH ₂ CF ₂ CHFCHFCHF ₂ |
| 272. | CH ₂ CF ₂ CHFCHFCH ₂ F |
| 273. | CH ₂ CF ₂ CHFCH ₂ CH ₂ F |
| 274. | CH ₂ CF ₂ CHFCH ₂ CHF ₂ |
| 275. | CH ₂ CF ₂ CHFCH ₂ CF ₃ |
| 276. | CH ₂ CF ₂ CF ₂ CH ₂ CH ₃ |
| 277. | CH ₂ CF ₂ CF ₂ CH ₂ CH ₂ F |
| 278. | CH ₂ CF ₂ CF ₂ CH ₂ CHF ₂ |
| 279. | CH ₂ CF ₂ CF ₂ CH ₂ CF ₃ |
| 280. | CH ₂ CF ₂ CF ₂ CHFCH ₃ |
| 281. | CH ₂ CF ₂ CF ₂ CF ₂ CH ₃ |
| 282. | CH ₂ CF ₂ CF ₂ CHFCH ₂ F |
| 283. | CH ₂ CF ₂ CF ₂ CHFCHF ₂ |
| 284. | CH ₂ CF ₂ CF ₂ CHFCH ₂ F |
| 285. | CH ₂ CF ₂ CF ₂ CF ₂ CH ₂ F |
| 286. | CH ₂ CF ₂ CF ₂ CF ₂ CHF ₂ |

| No. | R ³ |
|------|---|
| 287. | CH ₂ CF ₂ CF ₂ CF ₂ CF ₃ |
| 288. | CH(CH ₃)CH ₂ CH ₂ CH ₂ F |
| 289. | CH(CH ₃)CH ₂ CH ₂ CHF ₂ |
| 290. | CH(CH ₃)CH ₂ CH ₂ CF ₃ |
| 291. | CH(CH ₃)CH ₂ CHFCH ₃ |
| 292. | CH(CH ₃)CH ₂ CF ₂ CH ₃ |
| 293. | CH(CH ₃)CH ₂ CHFCH ₂ F |
| 294. | CH(CH ₃)CH ₂ CHFCHF ₂ |
| 295. | CH(CH ₃)CH ₂ CHFCH ₂ F |
| 296. | CH(CH ₃)CH ₂ CF ₂ CH ₂ F |
| 297. | CH(CH ₃)CH ₂ CF ₂ CHF ₂ |
| 298. | CH(CH ₃)CH ₂ CF ₂ CF ₃ |
| 299. | CH ₂ CH(CH ₃)CH ₂ CH ₂ F |
| 300. | CH ₂ CH(CH ₃)CH ₂ CHF ₂ |
| 301. | CH ₂ CH(CH ₃)CH ₂ CF ₃ |
| 302. | CH ₂ CH(CH ₃)CHFCH ₃ |
| 303. | CH ₂ CH(CH ₃)CHFCHF ₂ |
| 304. | CH ₂ CH(CH ₃)CHFCH ₂ F |
| 305. | CH ₂ CH(CH ₃)CF ₂ CH ₂ F |
| 306. | CH ₂ CH(CH ₃)CF ₂ CHF ₂ |
| 307. | CH ₂ CH(CH ₃)CF ₂ CF ₃ |
| 308. | CH ₂ CH(CF ₃)CH ₂ CH ₃ |
| 309. | CH ₂ CH ₂ CH(CH ₃)CH ₂ F |
| 310. | CH ₂ CH ₂ CH(CH ₃)CHF ₂ |
| 311. | CH ₂ CH ₂ CH(CH ₃)CF ₃ |
| 312. | CH ₂ CH ₂ CH(CF ₃) ₂ |
| 313. | A.1 |
| 314. | A.2 |
| 315. | A.3 |
| 316. | A.4 |

| No. | R ³ |
|------|----------------|
| 317. | A.5 |
| 318. | A.6 |
| 319. | A.7 |
| 320. | A.8 |
| 321. | A.9 |
| 322. | A.10 |
| 323. | A.11 |
| 324. | A.12 |
| 325. | A.13 |
| 326. | A.14 |
| 327. | A.15 |
| 328. | A.16 |
| 329. | A.17 |
| 330. | A.18 |
| 331. | A.19 |
| 332. | A.20 |
| 333. | A.21 |
| 334. | A.22 |
| 335. | A.23 |
| 336. | A.24 |
| 337. | A.25 |
| 338. | A.26 |
| 339. | A.27 |
| 340. | A.28 |
| 341. | A.29 |
| 342. | A.30 |
| 343. | A.31 |
| 344. | A.32 |
| 345. | A.33 |
| 346. | A.34 |

| No. | R ³ |
|------|-----------------------|
| 347. | A.35 |
| 348. | A.36 |
| 349. | A.37 |
| 350. | A.38 |
| 351. | A.39 |
| 352. | A.40 |
| 353. | A.41 |
| 354. | A.42 |
| 355. | A.43 |
| 356. | A.44 |
| 357. | A.45 |
| 358. | A.46 |
| 359. | A.47 |
| 360. | A.48 |
| 361. | A.49 |
| 362. | A.50 |
| 363. | A.51 |
| 364. | A.52 |
| 365. | A.53 |
| 366. | A.54 |
| 367. | A.55 |
| 368. | A.56 |
| 369. | A.57 |
| 370. | A.58 |
| 371. | -CH ₂ -A.1 |
| 372. | -CH ₂ -A.2 |
| 373. | -CH ₂ -A.3 |
| 374. | -CH ₂ -A.4 |
| 375. | -CH ₂ -A.5 |
| 376. | -CH ₂ -A.6 |

| No. | R ³ |
|--------|------------------------|
| 377. | -CH ₂ -A.7 |
| 378. y | -CH ₂ -A.8 |
| 379. | -CH ₂ -A.9 |
| 380. | -CH ₂ -A.10 |
| 381. | -CH ₂ -A.11 |
| 382. | -CH ₂ -A.12 |
| 383. | -CH ₂ -A.13 |
| 384. | -CH ₂ -A.14 |
| 385. | -CH ₂ -A.15 |
| 386. | -CH ₂ -A.16 |
| 387. | -CH ₂ -A.17 |
| 388. | -CH ₂ -A.18 |
| 389. | -CH ₂ -A.19 |
| 390. | -CH ₂ -A.20 |
| 391. | -CH ₂ -A.21 |
| 392. | -CH ₂ -A.22 |
| 393. | -CH ₂ -A.23 |
| 394. | -CH ₂ -A.24 |
| 395. | -CH ₂ -A.25 |
| 396. | -CH ₂ -A.26 |
| 397. | -CH ₂ -A.27 |
| 398. | -CH ₂ -A.28 |
| 399. | -CH ₂ -A.29 |
| 400. | -CH ₂ -A.30 |
| 401. | -CH ₂ -A.31 |
| 402. | -CH ₂ -A.32 |
| 403. | -CH ₂ -A.33 |
| 404. | -CH ₂ -A.34 |
| 405. | -CH ₂ -A.35 |
| 406. | -CH ₂ -A.36 |

| No. | R ³ |
|------|------------------------|
| 407. | -CH ₂ -A.37 |
| 408. | -CH ₂ -A.38 |
| 409. | -CH ₂ -A.39 |
| 410. | -CH ₂ -A.40 |
| 411. | -CH ₂ -A.41 |
| 412. | -CH ₂ -A.42 |
| 413. | -CH ₂ -A.43 |
| 414. | -CH ₂ -A.44 |
| 415. | -CH ₂ -A.45 |
| 416. | -CH ₂ -A.46 |
| 417. | -CH ₂ -A.47 |
| 418. | -CH ₂ -A.48 |
| 419. | -CH ₂ -A.49 |
| 420. | -CH ₂ -A.50 |
| 421. | -CH ₂ -A.51 |
| 422. | -CH ₂ -A.52 |
| 423. | -CH ₂ -A.53 |
| 424. | -CH ₂ -A.54 |
| 425. | -CH ₂ -A.55 |
| 426. | -CH ₂ -A.56 |
| 427. | -CH ₂ -A.57 |
| 428. | -CH ₂ -A.58 |
| 429. | -CH ₂ -A.59 |
| 430. | -CH ₂ -A.60 |
| 431. | -CH ₂ -A.61 |
| 432. | -CH ₂ -A.62 |
| 433. | -CH ₂ -A.63 |
| 434. | -CH ₂ -A.64 |
| 435. | -CH ₂ -A.65 |
| 436. | -CH ₂ -A.66 |

| No. | R ³ |
|------|------------------------|
| 437. | -CH ₂ -A.67 |
| 438. | -CH ₂ -A.68 |
| 439. | -CH ₂ -A.69 |
| 440. | -CH ₂ -A.70 |
| 441. | -CH ₂ -A.71 |
| 442. | -CH ₂ -A.72 |
| 443. | -CH ₂ -A.73 |
| 444. | -CH ₂ -A.74 |
| 445. | -CH ₂ -A.75 |
| 446. | -CH ₂ -A.76 |
| 447. | -CH ₂ -A.77 |
| 448. | -CH ₂ -A.78 |
| 449. | -CH ₂ -A.79 |
| 450. | -CH ₂ -A.80 |
| 451. | -CH ₂ -A.81 |
| 452. | -CH ₂ -A.82 |
| 453. | -CH ₂ -A.83 |
| 454. | -CH ₂ -A.84 |
| 455. | -CH ₂ -A.85 |
| 456. | -CH ₂ -A.86 |
| 457. | -CH ₂ -A.87 |
| 458. | -CH ₂ -A.88 |
| 459. | -CH ₂ -A.89 |
| 460. | -CH ₂ -A.90 |
| 461. | -CH ₂ -A.91 |
| 462. | -CH ₂ -A.92 |
| 463. | -CH ₂ -A.93 |
| 464. | -CH ₂ -A.94 |
| 465. | -CH ₂ -A.95 |
| 466. | -CH ₂ -A.96 |

| No. | R ³ |
|------|-------------------------|
| 467. | -CH ₂ -A.97 |
| 468. | -CH ₂ -A.98 |
| 469. | -CH ₂ -A.99 |
| 470. | -CH ₂ -A.100 |
| 471. | -CH ₂ -A.101 |
| 472. | -CH ₂ -A.102 |
| 473. | -CH ₂ -A.103 |
| 474. | -CH ₂ -A.104 |
| 475. | -CH ₂ -A.105 |
| 476. | -CH ₂ -A.106 |
| 477. | -CH ₂ -A.107 |
| 478. | -CH ₂ -A.108 |
| 479. | -CH ₂ -A.109 |
| 480. | -CH ₂ -A.110 |
| 481. | -CH ₂ -A.111 |
| 482. | -CH ₂ -A.112 |
| 483. | -CH ₂ -A.113 |
| 484. | -CH ₂ -A.114 |
| 485. | -CH ₂ -A.115 |
| 486. | -CH ₂ -A.116 |
| 487. | -CH ₂ -A.117 |
| 488. | -CH ₂ -A.118 |
| 489. | -CH ₂ -A.119 |
| 490. | -CH ₂ -A.120 |
| 491. | -CH ₂ -A.121 |
| 492. | -CH ₂ -A.122 |
| 493. | -CH ₂ -A.123 |
| 494. | -CH ₂ -A.124 |
| 495. | -CH ₂ -A.125 |
| 496. | -CH ₂ -A.126 |

| No. | R ³ |
|------|---------------------------------------|
| 497. | -CH ₂ -A.127 |
| 498. | -CH ₂ -A.128 |
| 499. | -CH ₂ -A.129 |
| 500. | -CH ₂ -A.130 |
| 501. | -CH ₂ -A.131 |
| 502. | -CH ₂ -A.132 |
| 503. | -CH ₂ -A.133 |
| 504. | -CH ₂ -A.134 |
| 505. | -CH ₂ -A.135 |
| 506. | -CH ₂ -A.136 |
| 507. | -CH ₂ -A.137 |
| 508. | -CH ₂ -A.138 |
| 509. | -CH ₂ -A.139 |
| 510. | -CH ₂ -A.140 |
| 511. | -CH ₂ -A.141 |
| 512. | -CH ₂ -A.142 |
| 513. | -CH ₂ -A.143 |
| 514. | -CH ₂ -A.144 |
| 515. | -CH ₂ -A.145 |
| 516. | -CH ₂ -A.146 |
| 517. | -CH ₂ -A.147 |
| 518. | -CH ₂ -A.148 |
| 519. | -CH ₂ -A.149 |
| 520. | -CH ₂ -A.150 |
| 521. | -CH ₂ CH ₂ -A.1 |
| 522. | -CH ₂ CH ₂ -A.2 |
| 523. | -CH ₂ CH ₂ -A.3 |
| 524. | -CH ₂ CH ₂ -A.4 |
| 525. | -CH ₂ CH ₂ -A.5 |
| 526. | -CH ₂ CH ₂ -A.6 |

| No. | R ³ |
|--------|--|
| 527. | -CH ₂ CH ₂ -A.7 |
| 528. | -CH ₂ CH ₂ -A.8 |
| 529. | -CH ₂ CH ₂ -A.9 |
| 530. y | -CH ₂ CH ₂ -A.10 |
| 531. | -CH ₂ CH ₂ -A.11 |
| 532. | -CH ₂ CH ₂ -A.12 |
| 533. | -CH ₂ CH ₂ -A.13 |
| 534. | -CH ₂ CH ₂ -A.14 |
| 535. | -CH ₂ CH ₂ -A.15 |
| 536. | -CH ₂ CH ₂ -A.16 |
| 537. | -CH ₂ CH ₂ -A.17 |
| 538. | -CH ₂ CH ₂ -A.18 |
| 539. | -CH ₂ CH ₂ -A.19 |
| 540. | -CH ₂ CH ₂ -A.20 |
| 541. | -CH ₂ CH ₂ -A.21 |
| 542. | -CH ₂ CH ₂ -A.22 |
| 543. | -CH ₂ CH ₂ -A.23 |
| 544. | -CH ₂ CH ₂ -A.24 |
| 545. | -CH ₂ CH ₂ -A.25 |
| 546. | -CH ₂ CH ₂ -A.26 |
| 547. | -CH ₂ CH ₂ -A.27 |
| 548. | -CH ₂ CH ₂ -A.28 |
| 549. | -CH ₂ CH ₂ -A.29 |
| 550. | -CH ₂ CH ₂ -A.30 |
| 551. | -CH ₂ CH ₂ -A.31 |
| 552. | -CH ₂ CH ₂ -A.32 |
| 553. | -CH ₂ CH ₂ -A.33 |
| 554. | -CH ₂ CH ₂ -A.34 |
| 555. | -CH ₂ CH ₂ -A.35 |
| 556. | -CH ₂ CH ₂ -A.36 |

| No. | R ³ |
|------|--|
| 557. | -CH ₂ CH ₂ -A.37 |
| 558. | -CH ₂ CH ₂ -A.38 |
| 559. | -CH ₂ CH ₂ -A.39 |
| 560. | -CH ₂ CH ₂ -A.40 |
| 561. | -CH ₂ CH ₂ -A.41 |
| 562. | -CH ₂ CH ₂ -A.42 |
| 563. | -CH ₂ CH ₂ -A.43 |
| 564. | -CH ₂ CH ₂ -A.44 |
| 565. | -CH ₂ CH ₂ -A.45 |
| 566. | -CH ₂ CH ₂ -A.46 |
| 567. | -CH ₂ CH ₂ -A.47 |
| 568. | -CH ₂ CH ₂ -A.48 |
| 569. | -CH ₂ CH ₂ -A.49 |
| 570. | -CH ₂ CH ₂ -A.50 |
| 571. | -CH ₂ CH ₂ -A.51 |
| 572. | -CH ₂ CH ₂ -A.52 |
| 573. | -CH ₂ CH ₂ -A.53 |
| 574. | -CH ₂ CH ₂ -A.54 |
| 575. | -CH ₂ CH ₂ -A.55 |
| 576. | -CH ₂ CH ₂ -A.56 |
| 577. | -CH ₂ CH ₂ -A.57 |
| 578. | -CH ₂ CH ₂ -A.58 |
| 579. | -CH ₂ CH ₂ -A.59 |
| 580. | -CH ₂ CH ₂ -A.60 |
| 581. | -CH ₂ CH ₂ -A.61 |
| 582. | -CH ₂ CH ₂ -A.62 |
| 583. | -CH ₂ CH ₂ -A.63 |
| 584. | -CH ₂ CH ₂ -A.64 |
| 585. | -CH ₂ CH ₂ -A.65 |
| 586. | -CH ₂ CH ₂ -A.66 |

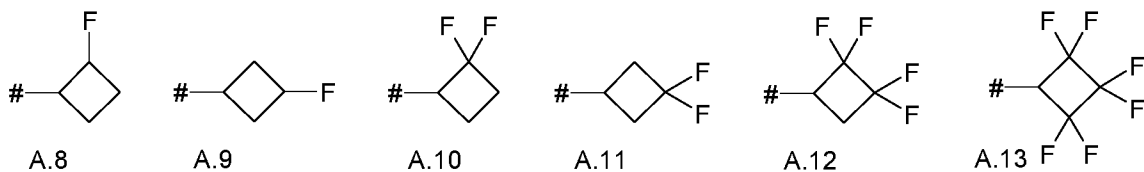
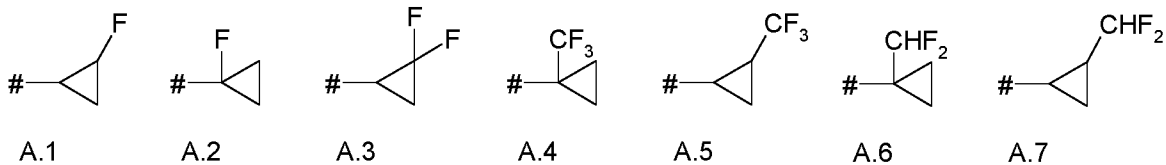
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|------|--|
| 587. | -CH ₂ CH ₂ -A.67 |
| 588. | -CH ₂ CH ₂ -A.68 |
| 589. | -CH ₂ CH ₂ -A.69 |
| 590. | -CH ₂ CH ₂ -A.70 |
| 591. | -CH ₂ CH ₂ -A.71 |
| 592. | -CH ₂ CH ₂ -A.72 |
| 593. | -CH ₂ CH ₂ -A.73 |
| 594. | -CH ₂ CH ₂ -A.74 |
| 595. | -CH ₂ CH ₂ -A.75 |
| 596. | -CH ₂ CH ₂ -A.76 |
| 597. | -CH ₂ CH ₂ -A.77 |
| 598. | -CH ₂ CH ₂ -A.78 |
| 599. | -CH ₂ CH ₂ -A.79 |
| 600. | -CH ₂ CH ₂ -A.80 |
| 601. | -CH ₂ CH ₂ -A.81 |
| 602. | -CH ₂ CH ₂ -A.82 |
| 603. | -CH ₂ CH ₂ -A.83 |
| 604. | -CH ₂ CH ₂ -A.84 |
| 605. | -CH ₂ CH ₂ -A.85 |
| 606. | -CH ₂ CH ₂ -A.86 |
| 607. | -CH ₂ CH ₂ -A.87 |
| 608. | -CH ₂ CH ₂ -A.88 |
| 609. | -CH ₂ CH ₂ -A.89 |
| 610. | -CH ₂ CH ₂ -A.90 |
| 611. | -CH ₂ CH ₂ -A.91 |
| 612. | -CH ₂ CH ₂ -A.92 |
| 613. | -CH ₂ CH ₂ -A.93 |
| 614. | -CH ₂ CH ₂ -A.94 |
| 615. | -CH ₂ CH ₂ -A.95 |
| 616. | -CH ₂ CH ₂ -A.96 |

| No. | R ³ |
|------|---|
| 617. | -CH ₂ CH ₂ -A.97 |
| 618. | -CH ₂ CH ₂ -A.98 |
| 619. | -CH ₂ CH ₂ -A.99 |
| 620. | -CH ₂ CH ₂ -A.100 |
| 621. | -CH ₂ CH ₂ -A.101 |
| 622. | -CH ₂ CH ₂ -A.102 |
| 623. | -CH ₂ CH ₂ -A.103 |
| 624. | -CH ₂ CH ₂ -A.104 |
| 625. | -CH ₂ CH ₂ -A.105 |
| 626. | -CH ₂ CH ₂ -A.106 |
| 627. | -CH ₂ CH ₂ -A.107 |
| 628. | -CH ₂ CH ₂ -A.108 |
| 629. | -CH ₂ CH ₂ -A.109 |
| 630. | -CH ₂ CH ₂ -A.110 |
| 631. | -CH ₂ CH ₂ -A.111 |
| 632. | -CH ₂ CH ₂ -A.112 |
| 633. | -CH ₂ CH ₂ -A.113 |
| 634. | -CH ₂ CH ₂ -A.114 |
| 635. | -CH ₂ CH ₂ -A.115 |
| 636. | -CH ₂ CH ₂ -A.116 |
| 637. | -CH ₂ CH ₂ -A.117 |
| 638. | -CH ₂ CH ₂ -A.118 |
| 639. | -CH ₂ CH ₂ -A.119 |
| 640. | -CH ₂ CH ₂ -A.120 |
| 641. | -CH ₂ CH ₂ -A.121 |
| 642. | -CH ₂ CH ₂ -A.122 |
| 643. | -CH ₂ CH ₂ -A.123 |

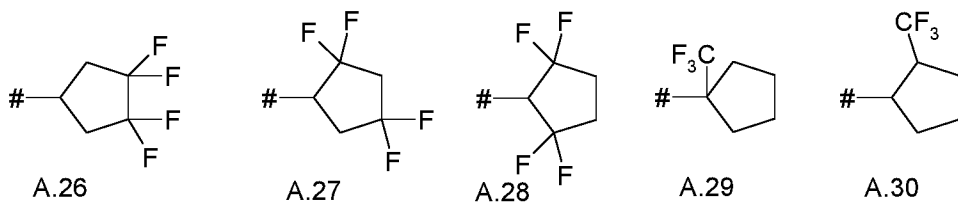
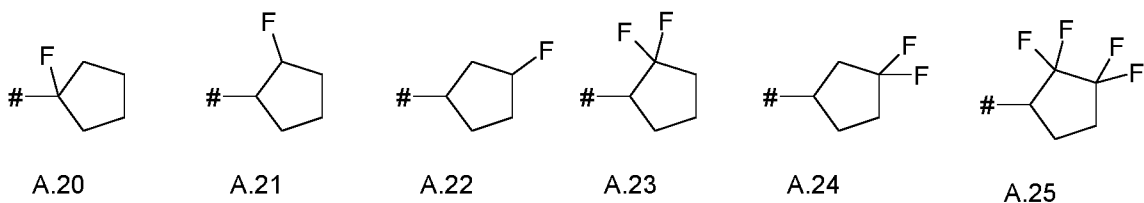
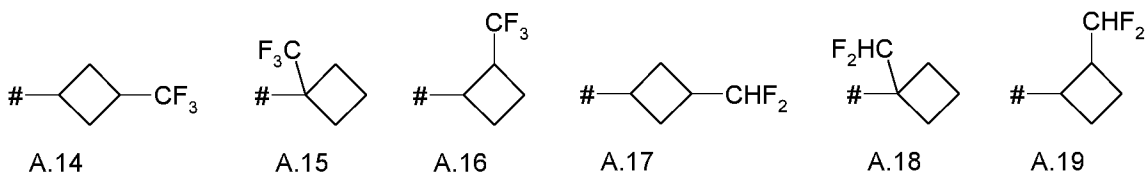
| No. | R ³ |
|------|---|
| 644. | -CH ₂ CH ₂ -A.124 |
| 645. | -CH ₂ CH ₂ -A.125 |
| 646. | -CH ₂ CH ₂ -A.126 |
| 647. | -CH ₂ CH ₂ -A.127 |
| 648. | -CH ₂ CH ₂ -A.128 |
| 649. | -CH ₂ CH ₂ -A.129 |
| 650. | -CH ₂ CH ₂ -A.130 |
| 651. | -CH ₂ CH ₂ -A.131 |
| 652. | -CH ₂ CH ₂ -A.132 |
| 653. | -CH ₂ CH ₂ -A.133 |
| 654. | -CH ₂ CH ₂ -A.134 |
| 655. | -CH ₂ CH ₂ -A.135 |
| 656. | -CH ₂ CH ₂ -A.136 |
| 657. | -CH ₂ CH ₂ -A.137 |
| 658. | -CH ₂ CH ₂ -A.138 |
| 659. | -CH ₂ CH ₂ -A.139 |
| 660. | -CH ₂ CH ₂ -A.140 |
| 661. | -CH ₂ CH ₂ -A.141 |
| 662. | -CH ₂ CH ₂ -A.142 |
| 663. | -CH ₂ CH ₂ -A.143 |
| 664. | -CH ₂ CH ₂ -A.144 |
| 665. | -CH ₂ CH ₂ -A.145 |
| 666. | -CH ₂ CH ₂ -A.146 |
| 667. | -CH ₂ CH ₂ -A.147 |
| 668. | -CH ₂ CH ₂ -A.148 |
| 669. | -CH ₂ CH ₂ -A.149 |
| 670. | -CH ₂ CH ₂ -A.150 |

A.1 to A.150 are the rings depicted below, where # is the attachment point to O:

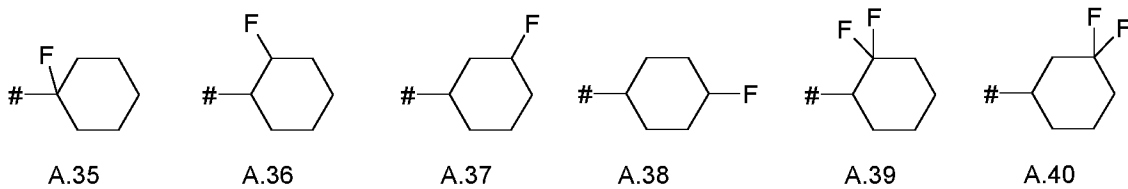
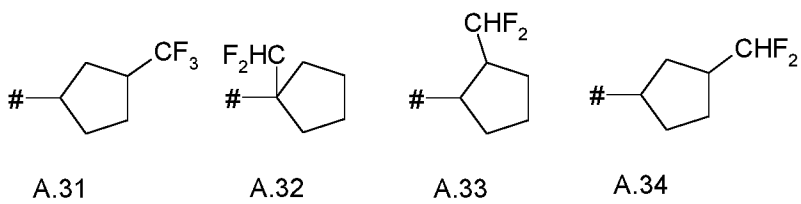
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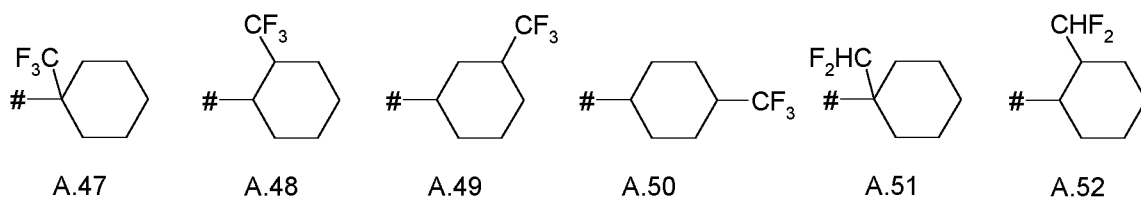
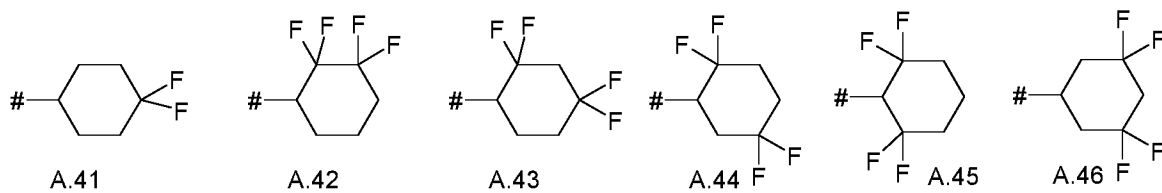
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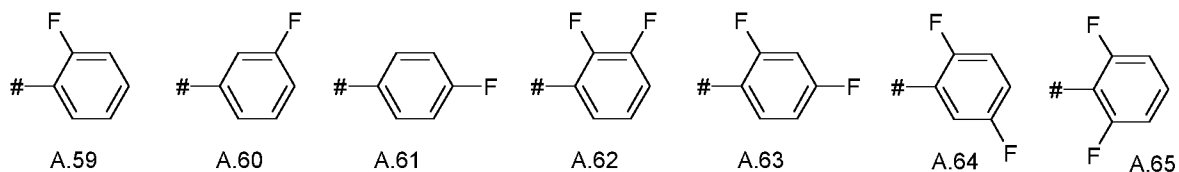
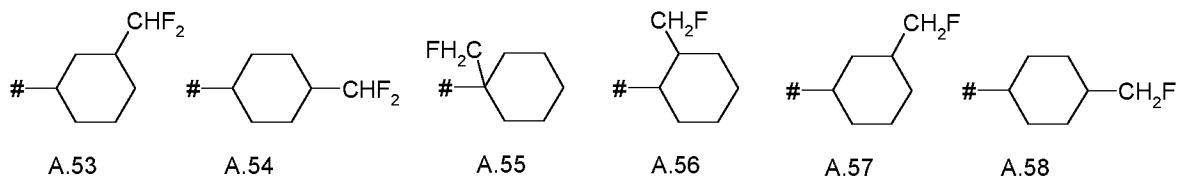
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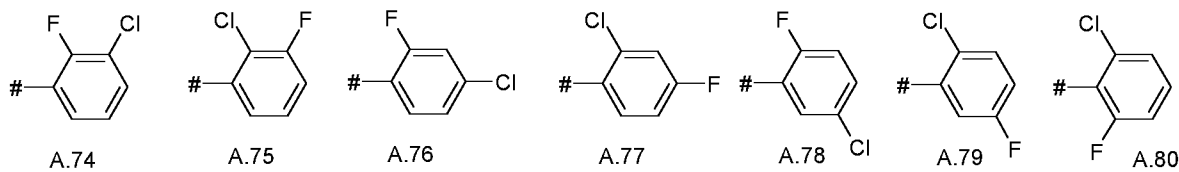
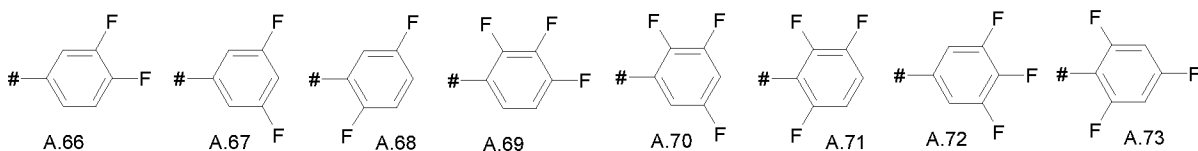
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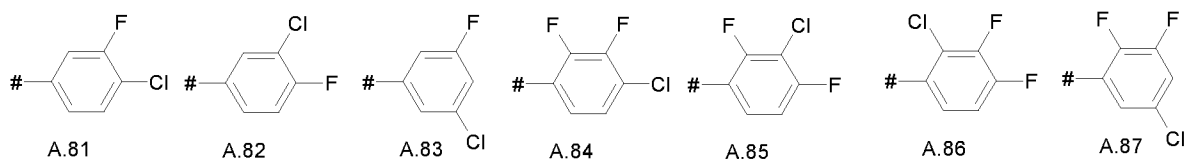
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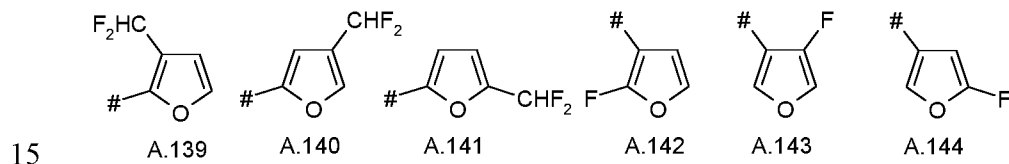
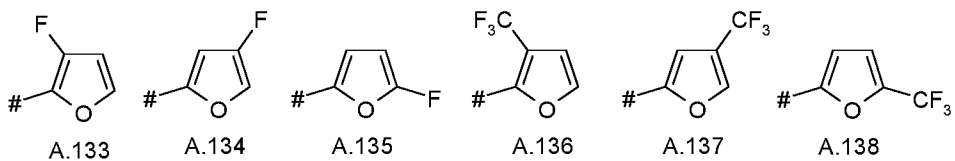
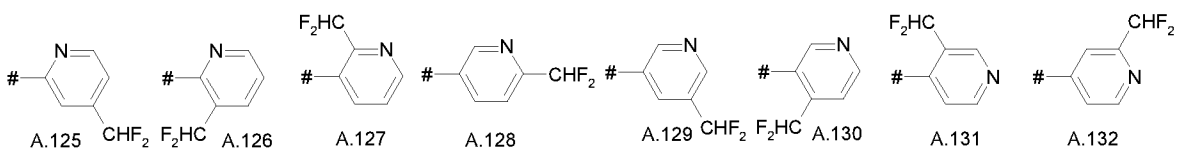
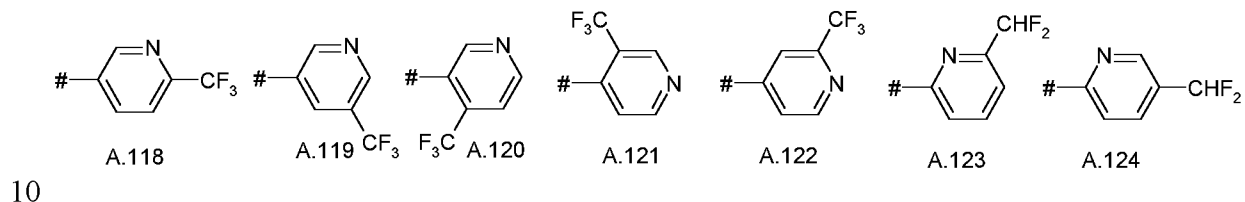
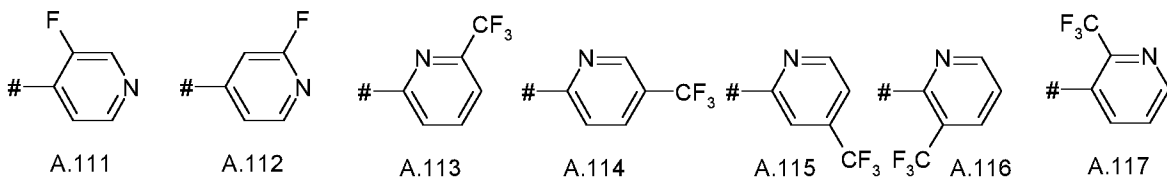
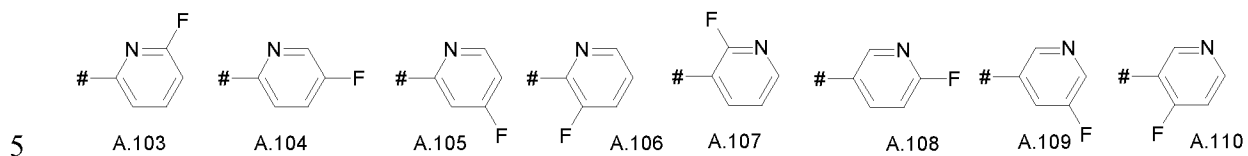
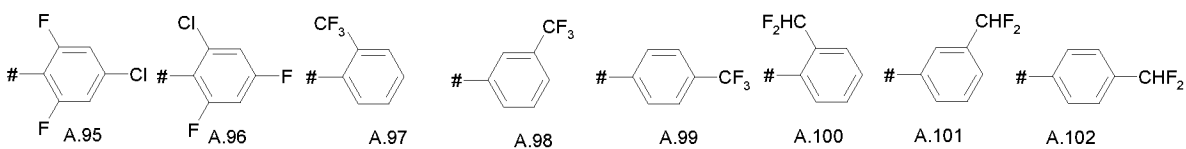
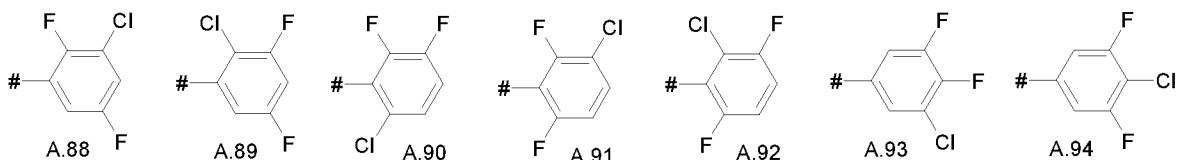
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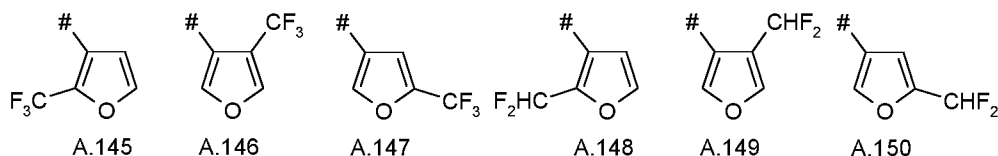
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Among the above structures Ia.1 to Ia.6, preference is given to compounds Ia.1.

5 In a specific embodiment, the invention relates to compounds I selected from the compounds of the examples, either in form of free bases or of any pharmaceutically acceptable salt thereof or a stereoisomer, the racemate or any mixture of stereoisomers thereof or a tautomer or a tautomeric mixture or an N-oxide thereof.

10 The compounds of the present invention can be prepared by using routine techniques familiar to a skilled person. In particular, the compounds of the formula I can be prepared according to the following schemes, wherein the variables, if not stated otherwise, are as defined above.

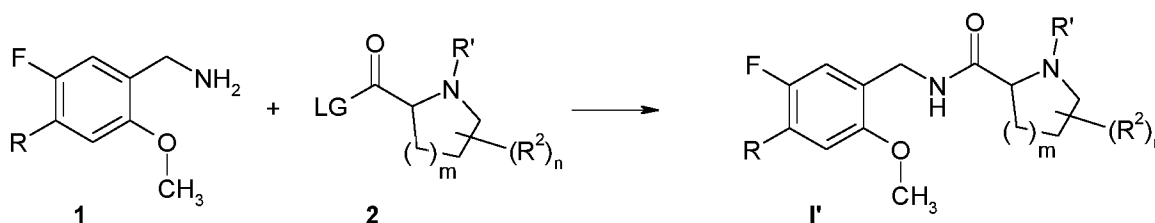
15 Compounds of formula I or precursors thereof wherein the group R^3 or the group OR^3 is not yet present (called hereinafter compounds I') can be prepared as outlined in scheme 1 below. Amine **1** is coupled with the pyrrolidine or azetidine acid derivative **2** under standard amidation conditions, wherein LG represents a suitable leaving group, such as Cl, Br, I or a sulfonate, such as tosylate, mesylate, triflate or nonaflate. The reaction is generally carried out under basic conditions. Alternatively, LG is OH and amidation is carried out in the presence of a coupling reagent. Suitable coupling reagents (activators) are well known and are for instance selected from carbodiimides, such as DCC (dicyclohexylcarbodiimide), DCI (diisopropylcarbodiimide) and EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), benzotriazol derivatives, such as HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate), HBTU ((O-
20 benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) and HCTU (1H-benzotriazolium-1-[bis(dimethylamino)methylene]-5-chloro tetrafluoroborate) and phosphonium-derived activators, such as BOP ((benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate), Py-BOP ((benzotriazol-1-yloxy)-
25 tripyrrolidinophosphonium hexafluorophosphate) and Py-BrOP (bromotripyrroli-

dinphosphonium hexafluorophosphate). Generally, the activator is used in excess. The benzotriazol and phosphonium coupling reagents are generally used in a basic medium.

R stands for OR^3 , OR^{3a} or OH, where R^{3a} is a precursor of R^3 . R' stands for a protective group or for CH_3 .

- 5 Suitable protective groups are for example C_1 - C_4 -alkylcarbonyl (e.g. acetyl), C_1 - C_4 -haloalkylcarbonyl (e.g. trifluoroacetyl), C_3 - C_4 -alkenylcarbonyl (e.g. allylcarbonyl), C_1 - C_4 -alkoxycarbonyl (e.g. Boc), C_1 - C_4 -haloalkoxycarbonyl, C_3 - C_4 -alkenyloxy-carbonyl, C_1 - C_4 -alkylaminocarbonyl, di- $(C_1$ - C_4 -alkyl)-aminocarbonyl, C_1 - C_4 -alkyl-sulfonyl, C_1 - C_4 -haloalkylsulfonyl or benzyl. The choice of the protective group depends
- 10 on the reaction conditions in the amidation reaction. The protective group is chosen so that it is not hydrolyzed during the amidation reaction.

Scheme 1



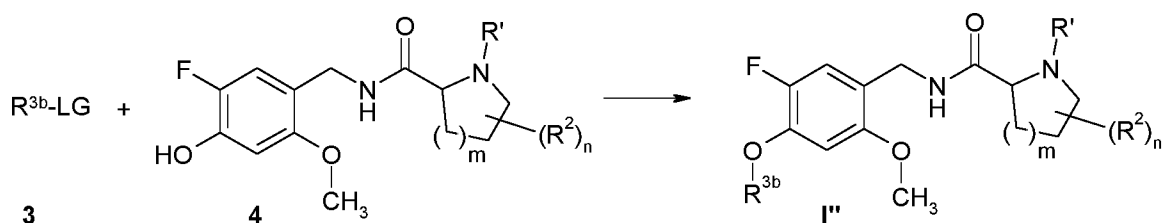
15

If R is OR^3 and R' is a protective group, compound I' is deprotected to give compounds I. Deprotection conditions depend on the protective group used.

- If R is OR^{3a} and R' is a protective group, the group R^{3a} is generally first converted into the group R^3 before the protective group is removed. Analogously, if R is OH,
- 20 generally R is first converted into the group OR^3 before the protective group is removed.

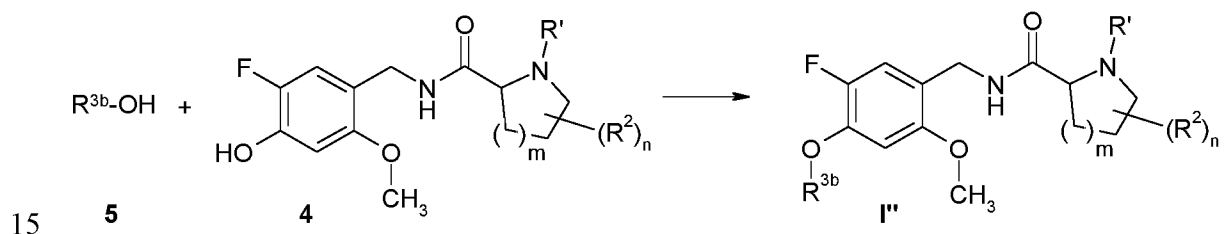
- The conversion of compounds I' wherein R is OH (called hereinafter compounds 4) into compounds I' wherein R is OR^3 or OR^{3a} (called hereinafter compounds I'') can be carried out as outlined in scheme 2 below. The compound 3 and the hydroxyphenyl compound 4 are reacted under ether formation to I''. R^{3b} is R^3 or a precursor R^{3a} of R^3 .
- 25 LG is a leaving group, such as Cl, Br, I or a sulfonate, e.g. tosylate, mesylate, triflate or nonaflate. The reaction is generally carried out under basic conditions.

Scheme 2



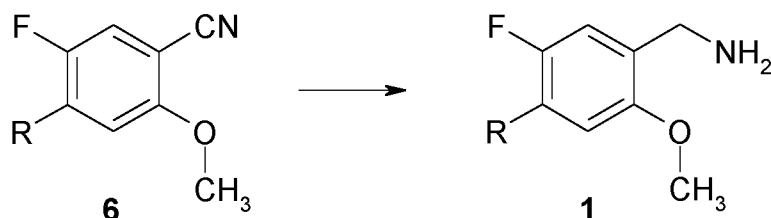
Alternatively, the conversion of compounds I' wherein R is OH (called hereinafter compounds 4) into compounds I' wherein R is OR³ or OR^{3a} (called hereinafter compounds I'') can be carried out as outlined in scheme 3 below. The two hydroxy compounds 4 and 5 are reacted under Mitsunobu conditions to I'' using triphenylphosphine and an azodicarboxylate such as diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), di-tert-butylazodicarboxylate or di-(4-chlorobenzyl)azodicarboxylate (DCAD). Instead of triphenylphosphine, resin-bound triphenylphosphine, such as PS-PPh₃ (resin = crosslinked poly(styrene-codivinylbenzene), can be used. R^{3b} is R³ or a precursor R^{3a} of R³.

Scheme 3



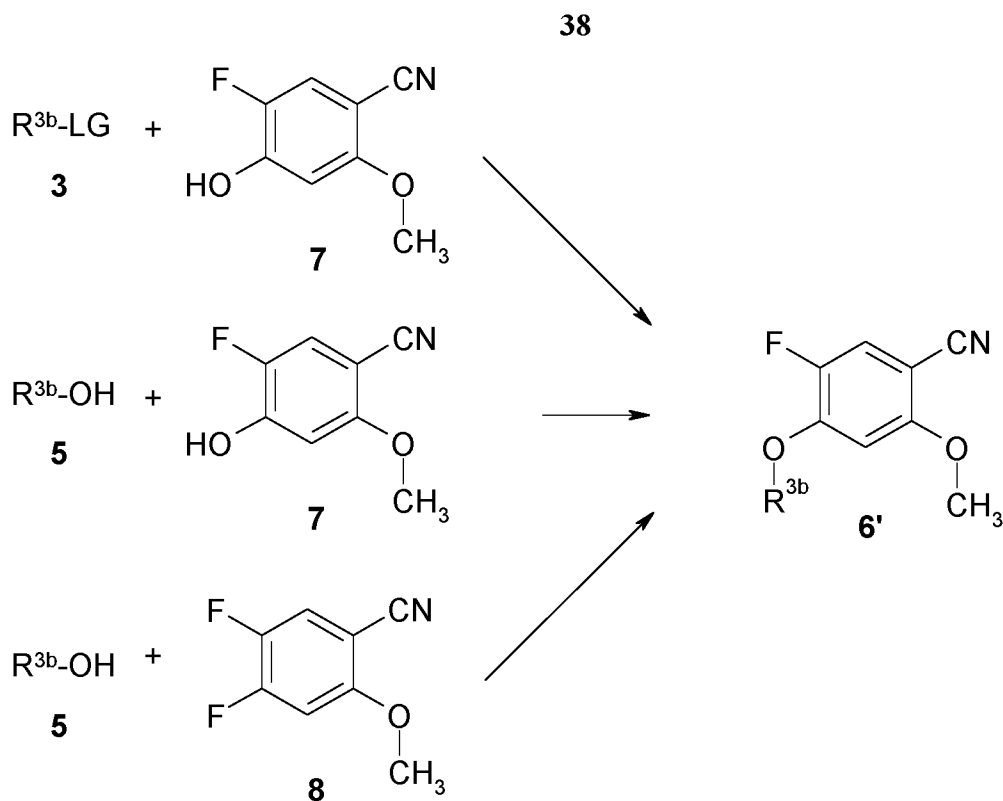
Compounds 1 can be prepared by reduction of the corresponding benzonitrile 6, as depicted in scheme 4 below. Suitable reduction agents are hydrogen (generally in form of a catalytic hydrogenation using, e.g. Pd/C or Ni, e.g. in form of Raney Ni), complex hydrides, such as sodium boron hydride (NaBH₄), sodium boron hydride (NaBH₄)/cobalt-II-chloride, lithium triethylborohydride (superhydride); LiBH(CH₂CH₃)₂, lithium tri-*sec*-butyl(hydrido)borate (L-selectride); LiBH(CH(CH₃)CH₂CH₃)₂, lithium aluminum hydride (LAH; LiAlH₄) or diisobutylaluminum hydride (DIBAL-H; ((CH₃)₂CHCH₂)₂AlH), or boranes, e.g. diborane or borane complexes, such as borane-dimethylsulfide complex, borane-diethylether complex or borane-THF complex.

Scheme 4



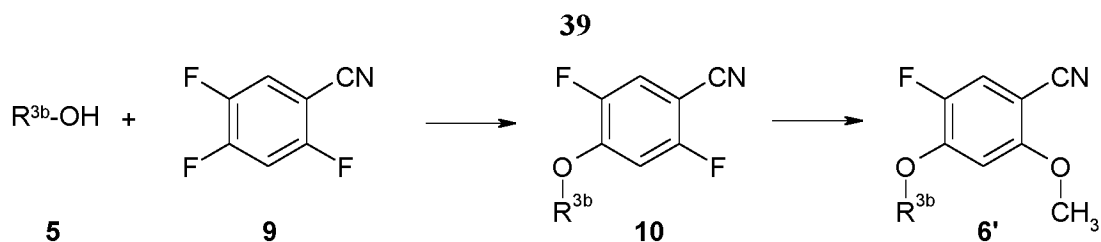
- 5 Compounds **6**, wherein R is OR³ or OR^{3a} (called hereinafter compounds **6'**), can be prepared in analogy to the reactions depicted in schemes 2 and 3 by reacting compounds **6**, wherein R is OH (called hereinafter compounds **7**), with **3** or the alcohol **5**. Suitable conditions for the respective reactions correspond to those detailed above in context with schemes 2 and 3. Alternatively, compounds **6'** can be prepared starting
- 10 from compounds **6** wherein R is F (called hereinafter compounds **8**). The conversion of compounds **8** into compounds **6'** is carried out under basic conditions. Generally, the alcohol **5** is first deprotonated using strong, non-nucleophilic bases, such as NaH or potassium tert-butanolate, before **8** is added. The above reactions are outlined in scheme 5 below. R^{3b} is R³ or a precursor R^{3a} of R³. LG is a leaving group, such as Cl, Br, I or a
- 15 sulfonate, e.g. tosylate, mesylate, triflate or nonaflate.

Scheme 5



Alternatively, compounds **6'** can be prepared starting from the trifluoro compound **9**, as shown in scheme 6 below. Due to the para-directing effect of CN the regioselectivity (as compared to the substitution of the fluorine substituent in ortho-position to CN and to the substitution of both fluorine atoms by $-\text{OR}^{3b}$) is high if **9** and **5** are used in approximately stoichiometric amounts. Use of **5** in excess yields mixtures of the two regioisomers as well as compounds in which both fluorine atoms are replaced by $-\text{OR}^{3b}$. In this case **10** has to be separated from the undesired side products by usual means, such as chromatography etc..). The reaction of compounds **9** with **5** is generally carried out under basic conditions. Generally, the alcohol **5** is first deprotonated using strong, non-nucleophilic bases, such as NaH or potassium tert-butanolate, before **9** is added. Subsequent reaction of **10** with methanol, also generally under basic conditions, with methanol being generally first deprotonated using strong, non-nucleophilic bases, such as NaH or potassium tert-butanolate, before **10** is added, yields **6'**.

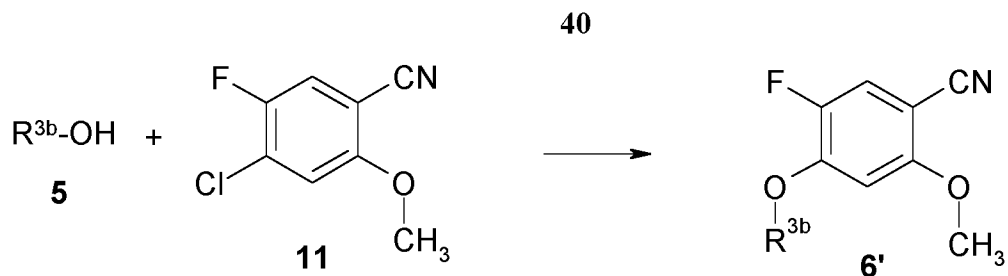
Scheme 6



Alternatively, compounds **6'** can be prepared by a Buchwald-Hartwig-analogous Pd coupling of **11** with the alcohol **5**. The Pd catalyst is usually used with a phosphorus ligand, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), [1,1'-biphenyl]-2-diisopropyl phosphine, 1,1'-bis(diphenylphosphino)ferrocene (dppf), X-phos, di-tert-butyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (t-BuXPhos), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos), 4,5-bis-(di-1-(3-methylindolyl)-phosphoramidit)-2,7,9,9-tetramethylxanthene (MeSkatOX), triphenylphosphine, triphenylphosphite, tri-(2-(1,1-dimethylethyl)-4-methoxy-phenyl)-phosphite, tricyclohexylphosphine, butyldi-1-adamantylphosphine (cataCXium), 1,6-bis(diphenylphosphino)hexane (DPPH), 2,6-bis(2,5-dimethylphenyl)-1-octyl-4-phenylphosphacyclohexan (PCH), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (RuPhos) and the like. The reaction is generally carried out in the presence of a base, advantageously a non-nucleophilic base, e.g. a carbonate, such as lithium, sodium, potassium or caesium carbonate, DBU, DBN and the like, or a sterically hindered nucleophilic alcoholate, like sodium or potassium tert-butanolate. Sterically non-demanding nucleophilic bases can be used if they are first reacted with the alcohol **5** before compound **11** is added. Suitable bases for this purpose are e.g. methanolates, e.g. sodium or potassium methanolate, ethanolates, e.g. sodium or potassium ethanolate, hydroxides, such as sodium or potassium hydroxide, hydrides, such as sodium or potassium hydride, and LDA. Non-nucleophilic bases or sterically hindered nucleophilic alcoholates can of course also be used for first deprotonating the alcohol **5** before compound **11** is added, as long as they are strong enough for the deprotonation.

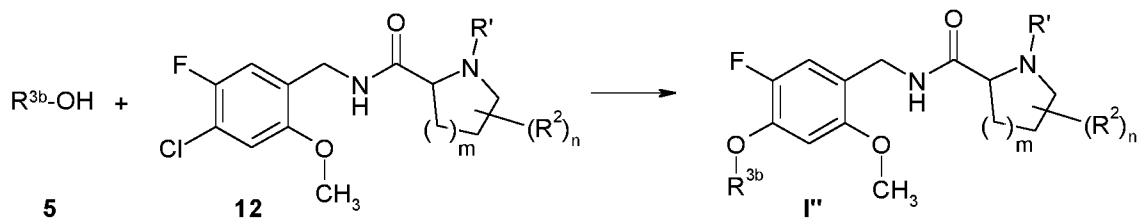
25

Scheme 7



The above-described Buchwald-Hartwig coupling can also be applied in a downstream reaction step, as depicted in scheme 8, to obtain compounds **I'**. The reaction conditions correspond to those described above in context with scheme 7. R^{3b} is R^3 or a precursor R^{3a} of R^3 .

Scheme 8



Compounds **12** can be prepared in analogy to scheme 1.

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In the above reactions, precursor groups R^{3a} are expediently used instead of the final groups R^3 if the desired group R^3 is susceptible to the reaction conditions or can compete in one of the required reaction steps. An example for such a group is a radical CH_2F . In this case, it is expedient, for example, to use the respective alcohol precursor group $\text{CH}_2\text{-OH}$, suitably in protected form, and convert the alcohol into the CH_2F group only at end of the reaction (deprotection, if R' is a protective group, can however ensue). Suitable protective groups are known and are generally selected from silyl protective groups, such as TMS (trimethylsilyl), TES (triethylsilyl), TBDMS (tert-butyldimethylsilyl), TIPS (triisopropylsilyl) or TBDPS (tert-butyldiphenylsilyl). As the OH group is not very reactive towards fluorination agents, this is suitably first converted into a better leaving group, e.g. by reaction to a sulfonate, such as methylsulfonate, tolylsulfonate and the like. This is then reacted with a fluorination agent, such as an alkali metal fluoride, e.g. NaF, KF or CsF; HF, optionally in combination with SbCl_5 or with Cl_2 and SbF_3 ; SF_4 , optionally in combination with HF or $\text{BF}_3[\text{O}(\text{C}_2\text{H}_5)_2]$; phenylsulfur trifluoride (Ph-SF_3), optionally in combination with HF and pyridine; 4-tert-butyl-2,6-

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dimethylphenylsulfur trifluoride ("Fluoled"); and bis(2-methoxyethyl)aminosulfur trifluoride $[(\text{CH}_3\text{OCH}_2\text{CH}_2)_2\text{NSF}_3]$.

If not otherwise indicated, the above-described reactions are generally carried out in a solvent at temperatures between room temperature and the boiling temperature of the solvent employed. Alternatively, the activation energy which is required for the reaction can be introduced into the reaction mixture using microwaves, something which has proved to be of value, in particular, in the case of the reactions catalyzed by transition metals (with regard to reactions using microwaves, see *Tetrahedron* 2001, 57, p. 9199 ff. p. 9225 ff. and also, in a general manner, "Microwaves in Organic Synthesis", André Loupy (Ed.), Wiley-VCH 2002).

The acid addition salts of compounds I are prepared in a customary manner by mixing the free base with a corresponding acid, where appropriate in solution in an organic solvent, for example a lower alcohol, such as methanol, ethanol or propanol, an ether, such as methyl tert-butyl ether or diisopropyl ether, a ketone, such as acetone or methyl ethyl ketone, or an ester, such as ethyl acetate.

Routine experimentations, including appropriate manipulation of the reaction conditions, reagents and sequence of the synthetic route, protection of any chemical functionality that may not be compatible with the reaction conditions, and deprotection at a suitable point in the reaction sequence of the preparation methods are within routine techniques.

Suitable protecting groups and the methods for protecting and deprotecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protective Groups in Organic Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is herein incorporated by reference in its entirety. Synthesis of the compounds of the invention may be accomplished by methods analogous to those described in the synthetic schemes described hereinabove and in specific examples.

Starting materials, if not commercially available, may be prepared by procedures selected from standard organic chemical techniques, techniques that are analogous to the synthesis of known, structurally similar compounds, or techniques that are analo-

gous to the above described schemes or the procedures described in the synthetic examples section.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the procedures described herein using an optically active starting material (prepared, for example, by asymmetric induction of a suitable reaction step), or by resolution of a mixture of the stereoisomers of the compound or intermediates using a standard procedure (such as chromatographic separation, recrystallization or enzymatic resolution).

Similarly, when a pure geometric isomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure geometric isomer as a starting material, or by resolution of a mixture of the geometric isomers of the compound or intermediates using a standard procedure such as chromatographic separation.

The present invention moreover relates to compounds of formula I as defined above, wherein at least one hydrogen atom has been replaced by a deuterium atom.

Of course, the unlabeled compounds according to the invention might naturally include certain amounts of this isotope. Therefore, when referring to compounds I, wherein at least one of the hydrogen atoms has been replaced by deuterium, it will be understood that the D isotope is present in a higher amount than would naturally occur.

Deuterated compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the non deuterated parent compound (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., *Advances in Drug Research* Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al., *J. Labelled Comp. Radiopharmaceut.*, 36(10):927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999).

Substitution of deuterium for hydrogen can give rise to an isotope effect that could alter the pharmacokinetics of the drug.

Stable isotope labeling of a drug can alter its physico-chemical properties such as pKa and lipid solubility. These changes may influence the fate of the drug at different steps along its passage through the body. Absorption, distribution, metabolism or excretion can be changed. Absorption and distribution are processes that depend primarily on the molecular size and the lipophilicity of the substance. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction.

Drug metabolism can give rise to large isotopic effect if the breaking of a chemical bond to a deuterium atom is the rate limiting step in the process. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. In any reaction in which the breaking of this bond is the rate limiting step, the reaction will proceed slower for the molecule with the heavy isotope due to "kinetic isotope effect". A reaction involving breaking a C-D bond can be up to 700 percent slower than a similar reaction involving breaking a C-H bond. If the C-D bond is not involved in any of the steps leading to the metabolite, there may not be any effect to alter the behavior of the drug. If a deuterium is placed at a site involved in the metabolism of a drug, an isotope effect will be observed only if breaking of the C-D bond is the rate limiting step. There is evidence to suggest that whenever cleavage of an aliphatic C-H bond occurs, usually by oxidation catalyzed by a mixed-function oxidase, replacement of the hydrogen by deuterium will lead to observable isotope effect. It is also important to understand that the incorporation of deuterium at the site of metabolism slows its rate to the point where another metabolite produced by attack at a carbon atom not substituted by deuterium becomes the major pathway a process called "metabolic switching".

Deuterium tracers, such as deuterium-labeled drugs and doses, in some cases repeatedly, of thousands of milligrams of deuterated water, are also used in healthy humans of all ages, including neonates and pregnant women, without reported incident (e.g. Pons G and Rey E, *Pediatrics* 1999 104: 633; Coward W A et al., *Lancet* 1979 7: 13; Schwarcz H P, *Control. Clin. Trials* 1984 5(4 Suppl): 573; Rodewald L E et al., J.

Pediatr. 1989 114: 885; Butte N F et al. Br. J. Nutr. 1991 65: 3; MacLennan A H et al. Am. J. Obstet Gynecol. 1981 139: 948). Thus, it is clear that any deuterium released, for instance, during the metabolism of compounds of this invention poses no health risk.

The weight percentage of hydrogen in a mammal (approximately 9%) and natural
5 abundance of deuterium (approximately 0.015%) indicates that a 70 kg human normally contains nearly a gram of deuterium. Furthermore, replacement of up to about 15% of normal hydrogen with deuterium has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, Ann. N.Y. Acad. Sci. 1960 84: 770; Thomson J F,
10 Ann. New York Acad. Sci 1960 84: 736; Czakja D M et al., Am. J. Physiol. 1961 201: 357). Higher deuterium concentrations, usually in excess of 20%, can be toxic in animals. However, acute replacement of as high as 15%-23% of the hydrogen in humans' fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Har-
15 ling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp.125-134; Diabetes Metab. 23: 251 (1997)).

Increasing the amount of deuterium present in a compound above its natural abundance is called enrichment or deuterium-enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37,
20 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %.

The hydrogens present on a particular organic compound have different capacities for exchange with deuterium. Certain hydrogen atoms are easily exchangeable under physiological conditions and, if replaced by deuterium atoms, it is expected that they will readily exchange for protons after administration to a patient. Certain hydrogen
25 atoms may be exchanged for deuterium atoms by the action of a deuteriacid such as D₂SO₄/D₂O. Alternatively, deuterium atoms may be incorporated in various combinations during the synthesis of compounds of the invention. Certain hydrogen atoms are not easily exchangeable for deuterium atoms. However, deuterium atoms at the remaining positions may be incorporated by the use of deuterated starting materials or inter-
30 mediates during the construction of compounds of the invention.

Deuterated and deuterium-enriched compounds of the invention can be prepared by using known methods described in the literature. Such methods can be carried out utiliz-

ing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. Relevant procedures and intermediates are disclosed, for instance in Lizondo, J et al.,
5 Drugs Fut, 21(11), 1116 (1996); Brickner, S J et al., J Med Chem, 39(3), 673 (1996);
Malleham, B et al., Org Lett, 5(7), 963 (2003); PCT publications WO1997010223,
WO2005099353, WO1995007271, WO2006008754; US Patent Nos. 7538189;
7534814; 7531685; 7528131; 7521421; 7514068; 7511013; and US Patent Application
10 Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238;
20090111840; 20090105338; 20090105307; 20090105147; 20090093422;
20090088416; 20090082471, the methods are hereby incorporated by reference.

The present invention further relates to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound I as defined above or an N-
15 oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof, in combination with at least one pharmaceutically acceptable carrier and/or auxiliary substance; or comprising at least one compound I wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, preferably wherein at least one hydrogen atom has been replaced by a deuterium atom, in combination with at least one
20 pharmaceutically acceptable carrier and/or auxiliary substance.

The present invention further relates to a compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof for use as a medicament.

The present invention also relates to a compound I as defined above or an N-
25 oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof for use in the treatment of disorders which respond to the modulation of the 5-HT_{2C} receptor.

The present invention also relates to the use of a compound I as defined above or of an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt
30 thereof for the manufacture of a medicament for the treatment of disorders which respond to the modulation of the 5-HT_{2C} receptor, and to a method for treating disorders which respond to the modulation of the 5-HT_{2C} receptor, which method comprises ad-

ministering to a subject in need thereof at least one compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof.

The compounds of the present invention are modulators of the 5-HT_{2C} receptor. Specifically, the compounds of formula I are agonists or partial agonists of the 5-HT_{2C} receptor. Thus, in a specific embodiment, the invention relates to a compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof for the treatment of disorders which respond to 5-HT_{2C} receptor agonists, further to the use of a compound I as defined above or of an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of disorders which respond to 5-HT_{2C} receptor agonists, and to a method for treating disorders which respond to 5-HT_{2C} receptor agonists, which method comprises administering to a subject in need thereof at least one compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof.

Within the meaning of the invention, the term "disorder" denotes disturbances and/or anomalies which are as a rule regarded as being pathological conditions or functions and which can manifest themselves in the form of particular signs, symptoms and/or malfunctions. While the treatment according to the invention can be directed toward individual disorders, i.e. anomalies or pathological conditions, it is also possible for several anomalies, which may be causatively linked to each other, to be combined into patterns, i.e. syndromes, which can be treated in accordance with the invention.

In one aspect of the invention, the diseases to be treated are disorders are damage of the central nervous system, disorders of the central nervous system, eating disorders, ocular hypertension, cardiovascular disorders, gastrointestinal disorders and diabetes.

Disorders or diseases of the central nervous system are understood as meaning disorders which affect the spinal cord and, in particular, the brain. These are, for example, cognitive dysfunction, attention deficit disorder/hyperactivity syndrome and cognitive deficits related with schizophrenia, attention deficit/hyperactivity syndrome, personality disorders, affective disorders, motion or motor disorders, pain, migraine, sleep disorders (including disturbances of the Circadian rhythm), feeding disorders, diseases associated with neurodegeneration, addiction diseases, obesity or psoriasis.

Examples of cognitive dysfunction are deficits in memory, cognition, and learning, Alzheimer's disease, age-related cognitive decline, and mild cognitive impairment, or any combinations thereof. Examples of personality disorders are schizophrenia and cognitive deficits related to schizophrenia. Examples of affective disorders are depression, anxiety, bipolar disorder and obsessive compulsive disorders, or any combination thereof. Examples of motion or motor disorders are Parkinson's disease and epilepsy. Examples of feeding disorders are obesity, bulimia, weight loss and anorexia, especially anorexia nervosa. Examples of diseases associated with neurodegeneration are stroke, spinal or head trauma, and head injuries, such as hydrocephalus.

10 Pain condition includes nociceptive pain, neuropathic pain or a combination thereof. Such pain conditions or disorders can include, but are not limited to, post-operative pain, osteoarthritis pain, pain due to inflammation, rheumatoid arthritis pain, musculoskeletal pain, burn pain (including sunburn), ocular pain, the pain associated with dental conditions (such as dental caries and gingivitis), post-partum pain, bone
15 fracture, herpes, HIV, traumatic nerve injury, stroke, post-ischemia, fibromyalgia, reflex sympathetic dystrophy, complex regional pain syndrome, spinal cord injury, sciatica, phantom limb pain, diabetic neuropathy, hyperalgesia and cancer.

In certain other embodiments, the disease condition is bladder dysfunction, including urinary incontinence.

20 Diabetes includes diabetes insipidus, diabetes mellitus, type I diabetes, type II diabetes, type III diabetes, diabetes secondary to pancreatic diseases, diabetes related to steroid use, diabetes complications, hyperglycemia and insulin resistance.

The addiction diseases include psychiatric disorders and behavioral disturbances which are caused by the abuse of psychotropic substances, such as pharmaceuticals or narcotics, and also other addiction diseases, such as addiction to gaming (impulse control disorders not elsewhere classified). Examples of addictive substances are: opioids (e.g. morphine, heroin and codeine), cocaine; nicotine; alcohol; substances which interact with the GABA chloride channel complex, sedatives, hypnotics and tranquilizers, for example benzodiazepines; LSD; cannabinoids; psychomotor stimulants, such as 3,4-
25 methylenedioxy-*N*-methylamphetamine (ecstasy); amphetamine and amphetamine-like
30 substances such as methylphenidate, other stimulants including caffeine and nicotine. Addictive substances which come particularly into consideration are opioids, cocaine,

amphetamine or amphetamine-like substances, nicotine and alcohol. Especially, addiction disorders include alcohol abuse, cocaine abuse, tobacco abuse and smoking cessation.

5 With regard to the treatment of addiction diseases, particular preference is given to those compounds according to the invention of the formula (I) which themselves do not possess any psychotropic effect. This can also be observed in a test using rats, which, after having been administered compounds which can be used in accordance with the invention, reduce their self administration of psychotropic substances, for example cocaine.

10 Examples of gastrointestinal disorders are irritable bowel syndrome.

Preferably, the disorders are selected from the group consisting of bipolar disorder, depression, atypical depression, mood episodes, adjustment disorders, anxiety, panic disorders, post-traumatic syndrome, psychoses, schizophrenia, cognitive deficits of schizophrenia, memory loss, dementia of aging, Alzheimer's disease, neuropsychiatric symptoms in Alzheimer's disease (e.g. aggression), behavioral disorders associated with dementia, social phobia, mental disorders in childhood, attention deficit hyperactivity disorder, organic mental disorders, autism, mutism, disruptive behavior disorder, impulse control disorder, borderline personality disorder, obsessive compulsive disorder, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, seizure disorders, epilepsy, substance use disorders, alcohol abuse, cocaine abuse, tobacco abuse, smoking cessation, sexual dysfunction/erectile dysfunction in males, sexual dysfunction in females, premenstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, sleep disorders, sleep apnoea, chronic fatigue syndrome, psoriasis, Parkinson's disease, psychosis in Parkinson's disease, neuropsychiatric symptoms in Parkinson's disease (e.g. aggression), Lewy Body dementia, neuropsychiatric symptoms in Lewy Body dementia (e.g. aggression), spinal cord injury, trauma, stroke, pain, bladder dysfunction/urinary incontinence, encephalitis, meningitis, eating disorders, obesity, bulimia, weight loss, anorexia nervosa, ocular hypertension, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, diabetes mellitus, type I diabetes, type II diabetes, type III diabetes, diabetes secondary to pancreatic diseases, diabetes related to steroid use, diabetes complications, hyperglycemia and insulin resistance, and are specifically schizophrenia, depression, bipolar disorders, obesity,

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substance use disorders, neuropsychiatric symptoms in Alzheimer's disease (e.g. aggression) or neuropsychiatric symptoms in Parkinson's disease (e.g. aggression).

The compounds of the invention may be used for a preventive treatment (prophylaxis), in particular as relapse prophylaxis or phase prophylaxis, but are preferably used for a treatment in its proper sense (i.e. non-prophylactic), i.e. for the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example as the suppression of symptoms. It can be effected over a short period, be orientated over the medium term or can be a long-term treatment, for example within the context of a maintenance therapy.

10 In another embodiment, the present invention relates to the use of a compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof for preparing a medicament for preventing (the development of) a disease condition as described above and to a method for preventing (the development of) a disease condition as described above comprises administering to the subject in
15 need of treatment thereof (e.g., a mammal, such as a human) a therapeutically effective amount of a compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof. As used herein, the term "prevent" a disease condition by administration of any of the compounds described herein means that the detectable physical characteristics or symptoms of the disease or condition do
20 not develop following the administration of the compound described herein. Alternatively, the method comprises administering to the subject a therapeutically effective amount of a compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of at least one cognitive enhancing drug.

25 In yet another embodiment, the present invention relates to the use a compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof for preparing a medicament for preventing the progression (e.g., worsening) of a disease condition and to a method for preventing the progression (e.g., worsening) of a disease condition, which method comprises administering to the subject
30 in need of treatment thereof (e.g., a mammal, such as a human) a therapeutically effective amount of a compound I as defined above or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutically acceptable salt thereof.

There are several lines of evidence suggesting that 5-HT_{2C} agonists or partial agonists would have therapeutic use in a variety of diseases, disorders and conditions.

Knockout mice models lacking the 5-HT_{2C} receptor exhibit hyperphagia, obesity and are more prone to seizures and sudden death [Tecott LH, Sun LM, Akana SF, Strack AM, Lowenstein DH, Dallman MF, Julius D (1995) Eating disorder and epilepsy in mice lacking 5-HT_{2C} serotonin receptors. *Nature* 374:542-546]. They also exhibit compulsive-like behavior [Chou-Green JM, Holscher TD, Dallman MF, Akana SF (2003). Compulsive behavior in the 5-HT_{2C} receptor knockout mouse. *Phys. Behav.* 78:641-649], hyperresponsiveness to repeated stress [Chou-Green JM, Holscher TD, Dallman MF, Akana SF (2003). Repeated stress in young and old 5-HT_{2C} receptor knockout mouse. *Phys. Behav.* 79:217-226], wakefulness [Frank MG, Stryker MP, Tecott LH (2002). Sleep and sleep homeostasis in mice lacking the 5-HT_{2C} receptor. *Neuropsychopharmacology* 27:869-873], hyperactivity and drug dependence [Rocha BA, Goulding EH, O'Dell LE, Mead AN, Coufal NG, Parsons LH, Tecott LH (2002). Enhanced locomotor, reinforcing and neurochemical effects of cocaine in serotonin 5-hydroxytryptamine 2C receptor mutant mice. *J. Neurosci.* 22:10039-10045].

5-HT_{2C} is unique among other G-protein-coupled receptors (GPCRs) in that its pre-mRNA is a substrate for base modification via hydrolytic deamination of adenosines to yield inosines. Five adenosines, located within a sequence encoding the putative second intracellular domain can be converted to inosines. This editing can alter the coding potential of the triplet codons and allows for the generation of multiple different receptor isoforms. The edited receptor isoforms were shown to have reduced ability to interact with G-proteins in the absence of agonist stimulation [Werry, TD, Loiacono R, Sexton PA, Christopoulos A (2008). RNA editing of the serotonin 5-HT_{2C} receptor and its effects on cell signaling, pharmacology and brain function. *Pharmac. Therap.* 119:7-23].

Edited 5-HT_{2C} isoforms with reduced function are significantly expressed in the brains of depressed suicide victims [Schmauss C (2003) Serotonin 2C receptors: suicide, serotonin, and runaway RNA editing. *Neuroscientist* 9:237-242. Iwamoto K, Kato T (2003). RNA editing of serotonin 2C receptor in human postmortem brains of major mental disorders. *Neurosci. Lett.* 346:169-172] and in the learned helplessness rats (a well established animal model of depression) [Iwamoto K, Nakatanib N, Bundoa M,

Yoshikawab T, Katoa T (2005). Altered RNA editing of serotonin 2C receptor in a rat model of depression. *Neurosci. Res.* 53: 69-76] suggesting a link between 5-HT_{2C} function and depression. There are also implications of edited 5-HT_{2C} isoforms and spatial memory [Du Y, Stasko M, Costa AC, Davisson MT, Gardiner KJ (2007). Editing of the serotonin 2C receptor pre-mRNA Effects of the Morris Water Maze. *Gene* 391:186-197]. In addition, fully edited isoforms of the human 5-HT_{2C} receptor display a striking reduction in sensitivity to lysergic acid diethylamide (LSD) and to atypical antipsychotic drugs clozapine and loxapine, suggesting a possible role of the receptor in the etiology and pharmacology of schizophrenia [Niswender CM, Herrick-Davis K, Dilley GE, Meltzer HY, Overholser JC, Stockmeier CA, Emeson RB, Sanders-Bush E (2001). RNA Editing of the Human Serotonin 5-HT_{2C} Receptor: Alterations in Suicide and Implications for Serotonergic *Pharmacotherapy. Neuropsychopharm.* 24:478–491].

Recently, the availability of potent and selective 5-HT_{2C} receptor agonists made it possible to directly investigate the effects of 5-HT_{2C} agonists and their therapeutic potential. Thus recent studies demonstrated that selective 5-HT_{2C} agonists resulted in decreased food intake and body weight gain in normal and obese rats [Smith BM, et al. (2008). Discovery and structure-activity relationship of (1*R*)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (Lorcaserin), a selective serotonin 5-HT_{2C} receptor agonist for the treatment of obesity. *J Med Chem* 51:305-313. Thomsen WJ, Grottick AJ, Menzaghi F, Reyes-Saldana H, Espitia S, Yuskin D, Whelan K, Martin M, Morgan M, Chen W, Al-Shama H, Smith B, Chalmers D, Behan D (2008) Lorcaserin, A Novel Selective Human 5-HT_{2C} Agonist: In Vitro and In Vivo Pharmacological Characterization. *J Pharmacol Exp Ther.* 325:577-587. Rosenzweig-Lipson S, Zhang J, Mazandarani H, Harrison BL, Sabb A, Sabalski J, Stack G, Welmaker G, Barrett JE, Dunlop J (2006) Antiobesity-like effects of the 5-HT_{2C} receptor agonist WAY-161503. *Brain Res.* 1073-1074:240-251. Dunlop J, Sabb AL, Mazandarani H, Zhang J, Kalganker S, Shukhina E, Sukoff S, Vogel RL, Stack G, Schechter L, Harrison BL, Rosenzweig-Lipson S (2005). WAY-163909 [9*bR*, 10*aR*]-1,2,3,4,8,9,10,10*a*-octahydro-7*bH*-cyclopenta-[*b*][1,4]diazepino[6,7,1*hi*]indole], a novel 5-hydroxytryptamine 2C receptor –selective agonist with anorectic activity. *J Pharmacol Exp Ther.* 313:862-869.]

Furthermore, selective 5-HT_{2C} receptor agonists produce antidepressant effects in animal models of depression comparable to those of SSRIs but with a much faster onset of action and a therapeutic window that avoids antidepressant-induced sexual dysfunction. These agonists were also effective in animal models of compulsive behavior such as scheduled induced polydipsia and they also exhibited decreased hyperactivity and aggression in rodents [Rosenzweig-Lipson S, Sabb A, Stack G, Mitchell P, Lucki I, Malberg JE, Grauer S, Brennan J, Cryan JF, Sukoff Rizzo SJ, Dunlop J, Barrett JE, Marquis KL (2007) Antidepressant-like effects of the novel, selective, 5-HT_{2C} receptor agonist WAY-163909 in rodents. *Psychopharmacology* (Berlin) 192:159-170.

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10 Rosenzweig-Lipson S, Dunlop J, Marquis KL (2007) 5-HT_{2C} receptor agonists as an innovative approach for psychiatric disorders. *Drug news Perspect*, 20: 565-571.

Cryan, JF, Lucki I (2000). Antidepressant-like behavioral effects mediated by 5-Hydroxytryptamine 2C receptors. *J. Pharm. Exp. Ther.* 295:1120-1126.].

Acute or chronic administration of 5-HT_{2C} agonists decreases the firing rate of ventral tegmental area dopamine neurons but not that of substantia nigra. In addition 5-HT_{2C} agonists reduce dopamine levels in the nucleus accumbens but not in the striatum (the region of the brain mostly associated with extrapyramidal side effects) [Di Matteo, V., Di Giovanni, G., Di Mascio, M., & Esposito, E. (1999). SB 242084, a selective serotonin 2C receptor antagonist, increases dopaminergic transmission in the mesolimbic system. *Neuropharmacology* 38, 1195 – 1205. Di Giovanni, G., Di Matteo, V., Di Mascio, M., & Esposito, E. (2000). Preferential modulation of mesolimbic vs. nigrostriatal dopaminergic function by serotonin2C/2B receptor agonists: a combined in vivo electrophysiological and microdialysis study. *Synapse* 35, 53 – 61. Marquis KL, Sabb AL, Logue SF, Brennan JA, Piesla MJ, Comery TA, Grauer SM, Ashby CR, Jr., Nguyen HQ, Dawson LA, Barrett JE, Stack G, Meltzer HY, Harrison BL, Rosenzweig-Lipson S (2007) WAY-163909 [(7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1hi]indole]: A novel 5-hydroxytryptamine 2C receptor-selective agonist with preclinical antipsychotic-like activity. *J Pharmacol Exp Ther* 320:486-496.]. Therefore it is expected that 5-HT_{2C} receptor agonists will selectively decrease mesolimbic dopamine levels without affecting the nigrostriatal pathway thus avoiding the EPS side effects of typical antipsychotics. Several 5-HT_{2C} receptor agonists have shown antipsychotic activity in animal models of schizophrenia without EPS

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based on the lack of effect in catalepsy [Marquis KL, Sabb AL, Logue SF, Brennan JA, Piesla MJ, Comery TA, Grauer SM, Ashby CR, Jr., Nguyen HQ, Dawson LA, Barrett JE, Stack G, Meltzer HY, Harrison BL, Rosenzweig-Lipson S (2007) WAY-163909 [(7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1hi]indole]: A novel 5-hydroxytryptamine 2C receptor-selective agonist with pre-clinical antipsychotic-like activity. *J Pharmacol Exp Ther* 320:486-496. Siuciak JA, Chapin DS, McCarthy SA, Guanowsky V, Brown J, Chiang P, Marala R, Patterson T, Seymour PA, Swick A, Iredale PA (2007) CP-809,101, a selective 5-HT_{2C} agonist, shows activity in animal models of antipsychotic activity. *Neuropharmacology* 52:279-290]. The antipsychotic activity of 5-HT_{2C} receptor agonists without EPS coupled with their beneficial effects in mood disorders and cognition and their antiobesity like effects render 5-HT_{2C} receptor agonists as unique agents to treat schizophrenia [Rosenzweig-Lipson S, Dunlop J, Marquis KL (2007) 5-HT_{2C} receptor agonists as an innovative approach for psychiatric disorders. *Drug news Perspect*, 20: 565-571. Dunlop J, Marquis KL, Lim HK, Leung L, Kao J, Cheesman C, Rosenzweig-Lipson S (2006). Pharmacological profile of the 5-HT_{2C} receptor agonist WAY-163909; therapeutic potential in multiple indications. *CNS Dug Rev*. 12:167-177.].

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- 15 Modulation of 5HT₂ receptors may be beneficial in the treatment of conditions related to bladder function, in particular, urinary incontinence. [Discovery of a novel azepine series of potent and selective 5-HT_{2C} agonists as potential treatments for urinary incontinence. Brennan, Paul E.; Whitlock, Gavin A.; Ho, Danny K. H.; Conlon, Kelly; McMurray, Gordon. *Bioorganic & Medicinal Chemistry Letters* (2009), 19(17), 4999-5003. Investigation of the role of 5-HT₂ receptor subtypes in the control of the bladder and the urethra in the anesthetized female rat. Mbaki, Y.; Ramage, A. G. Department of Pharmacology, University College London, London, UK. *British Journal of Pharmacology* (2008), 155(3), 343-356.] In particular, compounds with agonist activity at 5-HT_{2C} have been shown to be useful in treating urinary incontinence, see for example U.S. Patent application publications US2008/0146583 and US 2007/0225274.

Further pre-clinical data suggest that 5-HT_{2C} agonists could be useful for the treatment of a number of psychiatric diseases, including schizophrenia, bipolar disorders, depression/anxiety, substance use disorders and especially disorders like neuropsychiatric symptoms in Alzheimer's disease: Aggression, psychosis/ agitation represent key unmet medical needs. Clinical (Shen JHQ et al., A 6-week randomized, double-blind, placebo-controlled, comparator referenced trial of vabicaserin in acute schizophrenia.

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Journal of Psychiatric Research 53 (2014) 14-22; Liu J et al., Prediction of Efficacy of Vabicaserin, a 5-HT_{2C} Agonist, for the Treatment of Schizophrenia Using a Quantitative Systems Pharmacology Model. CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e111; and preclinical data (Dunlop J et al., Characterization of Vabicaserin (SCA-136), a Selective 5-Hydroxytryptamine 2C Receptor Agonist. J Pharmacol Exp Ther (2011) 337, 673-80; Siuciak J et al., CP-809,101, a selective 5-HT_{2C} agonist, shows activity in animal models of antipsychotic activity. Neuropharmacology 52 (2007) 279-290; Mosienko V et al., Exaggerated aggression and decreased anxiety in mice deficient in brain serotonin. Transl Psychiatry (2012) 2, e122; Del Guidice T et al., Stimulation of 5-HT_{2C} Receptors Improves Cognitive Deficits Induced by Human Tryptophan Hydroxylase2 Loss of Function Mutation. Neuropsychopharmacology (2014) 39, 1125-1134; Rosenzweig-Lipson et al., Antidepressant-like effects of the novel, selective, 5-HT_{2C} receptor agonist WAY-163909 in rodents. Psychopharmacology (2007) 192:159-170) suggest 5-HT_{2C} receptor stimulation to result in therapeutic efficacy in aggression, psychosis agitation and moderate pro-cognitive effects (Del Guidice T et al., Stimulation of 5-HT_{2C} Receptors Improves Cognitive Deficits Induced by Human Tryptophan Hydroxylase2 Loss of Function Mutation. Neuropsychopharmacology (2014) 39, 1125-1134; Siuciak J et al., CP-809,101, a selective 5-HT_{2C} agonist, shows activity in animal models of antipsychotic activity. Neuropharmacology 52 (2007) 279-290).

In the use and the method of the invention, an effective quantity of one or more compounds, as a rule formulated in accordance with pharmaceutical and veterinary practice, is administered to the individual to be treated, preferably a mammal, in particular a human being, productive animal or domestic animal. Whether such a treatment is indicated, and in which form it is to take place, depends on the individual case and is subject to medical assessment (diagnosis) which takes into consideration signs, symptoms and/or malfunctions which are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

Actual dosage levels of active ingredients in the pharmaceutical compositions of the present invention can be varied so as to obtain an amount of the active compound(s) that is effective to achieve the desired therapeutic response for a particular subject (e.g., a mammal, preferably, a human (patient)), compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the

route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is
5 achieved.

Compounds of the present invention can also be administered to a subject as a pharmaceutical composition comprising the compounds of interest in combination with at least one pharmaceutically acceptable carriers. The phrase "therapeutically effective amount" of the compound of the present invention means a sufficient amount of the
10 compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex
15 and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well-known in the medical arts. For example, it is well within the skill of the art to start
20 doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The total daily dose of the compounds of this invention administered to a subject (namely, a mammal, such as a human) ranges from about 0.01 mg/kg body weight to
25 about 100 mg/kg body weight. More preferable doses can be in the range of from about 0.01 mg/kg body weight to about 30 mg/kg body weight. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

30 In one aspect, the present invention provides pharmaceutical compositions. The pharmaceutical compositions of the present invention comprise the compounds of the present invention or an N-oxide, a tautomeric form, a stereoisomer or a pharmaceutical-

ly acceptable salt or solvate thereof. The pharmaceutical compositions of the present invention comprise compounds of the present invention that can be formulated together with at least one non-toxic pharmaceutically acceptable carrier.

In yet another embodiment, the present invention provides a pharmaceutical
5 composition comprising compounds of the present invention or an N-oxide, a tautomer-
ic form, a stereoisomer or a pharmaceutically acceptable salt thereof, and one or more
pharmaceutically acceptable carriers, alone or in combination with one or more com-
pounds that are not the compounds of the present invention. Examples of one or more
compounds that can be combined with the compounds of the present invention in phar-
10 maceutical compositions, include, but are not limited to, one or more cognitive enhanc-
ing drugs.

The pharmaceutical compositions of this present invention can be administered
to a subject (e.g., a mammal, such as a human) orally, rectally, parenterally, intracister-
nally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops),
15 buccally or as an oral or nasal spray. The term "parenterally" as used herein, refers to
modes of administration which include intravenous, intramuscular, intraperitoneal, in-
trasternal, subcutaneous and intraarticular injection and infusion.

The term "pharmaceutically acceptable carrier" as used herein, means a non-
toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formula-
20 tion auxiliary of any type. Some examples of materials which can serve as pharmaceu-
tically acceptable carriers are sugars such as, but not limited to, lactose, glucose and
sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and
its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellu-
lose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as,
25 but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to,
peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil;
glycols; such a propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl
laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and
aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solu-
30 tion; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compati-
ble lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate,
as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and

perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Pharmaceutical compositions of the present invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, disper-
5 sions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), vegetable oils (such as olive oil), injectable organic esters (such as ethyl oleate) and suitable mixtures thereof.
10 Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microor-
15 ganisms can be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

20 In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alter-
25 natively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug
30 release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared

by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such carriers as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned carriers.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

10 Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating carriers or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals which are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are natural and synthetic phospholipids and phosphatidyl cholines (lecithins) used separately or together.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

Dosage forms for topical administration of a compound of the present invention include powders, sprays, ointments and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which may be required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio.

Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in (*J. Pharmaceutical Sciences*, 1977, 66: 1 et seq.). The salts can be prepared in situ during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, malate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as, but not limited to, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as, but not limited to, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others.

Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid and such organic acids as acetic acid, fumaric acid, maleic acid, 4-methylbenzenesulfonic acid, succinic acid and citric acid.

Basic addition salts can be prepared in situ during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as, but not limited to, the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as, but not limited to, lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, ethylammonium and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

The compounds of the present invention can exist in unsolvated as well as solvated forms, including hydrated forms, such as hemi-hydrates. In general, the solvated forms, with pharmaceutically acceptable solvents such as water and ethanol among others are equivalent to the unsolvated forms for the purposes of the invention.

The following examples serve to explain the invention without limiting it.

25 Examples

Abbreviations:

| | |
|------------|-------------------------|
| h, hr, hrs | hour(s) |
| min | minutes |
| 30 RT | room temperature (25°C) |
| ACN | acetonitrile |
| DCE | dichloroethane |

| | | |
|----|---------------------|--|
| | DCM | dichloromethane |
| | DMF | dimethylformamide |
| | DMSO | dimethylsulfoxide |
| | EtOAc | ethyl acetate |
| 5 | EtOH | ethanol |
| | PE | petrol ether |
| | THF | tetrahydrofuran |
| | Boc, Boc, BOC | tert-butoxycarbonyl |
| | DIAD | diisopropyl azodicarboxylate |
| 10 | DIPEA | diisopropylethyl amine |
| | HATU | O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate |
| | HBTU | (O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate |
| 15 | PS-PPh ₃ | resin-bound triphenylphosphine [resin = crosslinked poly(styrene-co-divinylbenzene)] |
| | TFA | trifluoroacetic acid |

The compounds were either characterized via proton-NMR in d₆-dimethylsulfoxide, d-chloroform or d₄-methanol on a 400 MHz, 500 MHz or 600 MHz NMR instrument (Bruker AVANCE), or by ¹³C-NMR at 125 MHz, or by ¹⁹F-NMR at 470 MHz, or by mass spectrometry, generally recorded via HPLC-MS in a fast gradient on C18-material (electrospray-ionisation (ESI) mode).

25 The magnetic nuclear resonance spectral properties (NMR) refer to the chemical shifts (δ) expressed in parts per million (ppm). The relative area of the shifts in the ¹H-NMR spectrum corresponds to the number of hydrogen atoms for a particular functional type in the molecule. The nature of the shift, as regards multiplicity, is indicated as singlet (s), broad singlet (br s), doublet (d), broad doublet (br d), triplet (t), broad triplet (br
30 t), quartet (q), quintet (quint.), multiplet (m), doublet of doublets (dd), doublet of doublets of doublets (ddd), triplet of doublets (td), triplet of triplets (tt), doublet of triplets

of doublets (dtd), doublet of triplets of triplets (dtt), doublet of triplets of quartets (dtq), quartet of doublets (qd), quartet of doublets of doublets (qdd) etc..

I. Synthetic examples

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Example 1

(2S)-N-[[5-Fluoro-4-[(3-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its fumaric acid addition salt

Potassium 2-methylpropan-2-olate (7.86 g, 70.0 mmol) was suspended in THF
10 (80 mL) and the mixture was cooled to 0°C. Phenylmethanol (13.77 g, 127 mmol) was added and the solution was stirred at 0°C for 30min followed by dropwise addition to 2,4,5-trifluorobenzonitrile (10 g, 63.7 mmol) in THF(80 mL) at -78 °C under nitrogen. The solution was stirred at -78 °C for 3h, warmed to room temperature over 1.5h and stirred at RT for 20h. The solution was diluted with EtOAc (500 mL) and washed with
15 water (2*70 mL). The water phases were re-extracted with DCM (100 mL*2) and the combined organic phases were concentrated to give crude product, which was recrystallized from EtOH and resulted in 4-(benzyloxy)-2,5-difluorobenzonitrile (10.5 g, 42.8 mmol, 67.3 % yield).

Potassium 2-methylpropan-2-olate (5.86 g, 52.2 mmol) was suspended in THF
20 (50mL) and the mixture was cooled to 0°C. Methanol (1.672 g, 52.2 mmol) was added and the solution was stirred at 0°C for 30 min followed by dropwise addition to 4-(benzyloxy)-2,5-difluorobenzonitrile (8 g, 32.6 mmol) in THF(50 mL) at -50°C under nitrogen. The solution was stirred at -50°C for 1 h, warmed to room temperature over 0.5 h and stirred at RT for 20 h. The solution was diluted with EtOAc (500 mL) and
25 washed with water (2*70 mL). The water phases were re-extracted with DCM (200 mL*2) and the combined organic phases were concentrated to give crude product, which was recrystallized from EtOH resulting in 4-(benzyloxy)-5-fluoro-2-methoxybenzonitrile (6.7 g, 26.0 mmol, 80 % yield) as white solid.

To a mixture of 4-(benzyloxy)-5-fluoro-2-methoxybenzonitrile (3 g, 11.66 mmol)
30 in methanol (15 mL), 1.5 mL conc. HCl and Pd/C(150 mg) were added, the resulting mixture was evacuated and filled with hydrogen (0.118 g, 58.3 mmol), and the resulting mixture was stirred at 40°C under hydrogen (0.118 g, 58.3 mmol) for 16 h . Data LCMS

showed the consumption of the starting material. Then the mixture was filtered, the filtrate was concentrated under reduced pressure to give a residue. The residue was dissolved in 25mL EtOAc, filtered, the solid was collected, 4-(aminomethyl)-2-fluoro-5-methoxyphenol hydrochloride (1.9 g, 9.24 mmol, 79 % yield) was obtained as light yellow solid.

To a mixture of (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (3 g, 13.94 mmol) in DMF (16 mL), DIPEA (6.29 g, 48.8 mmol) and HATU (6.36 g, 16.73 mmol) were added, and the mixture was stirred at room temperature for 20 min. After that, 4-(aminomethyl)-2-fluoro-5-methoxyphenol hydrochloride (3.15 g, 15.33 mmol) was added, and the resulting mixture was stirred at room temperature overnight. Data LCMS showed ms of the desired product. The reaction mixture was diluted in 160 mL DCM, then the mixture was washed with water (60 mL*4) for four times, the organic layer was dried over Na₂SO₄, filtered, concentrated and the residue was purified through column (silica gel; UV 254) eluting with 0-50%EtOAc/PE to give a residue, which was washed with mixed solvents (EtOAc/PE=1:2), white solid was precipitated, filtered, the solid was collected. (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)-carbamoyl)pyrrolidine-1-carboxylate (3.3 g, 8.96 mmol, 64.3 % yield) was obtained as white solid.

(S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (50 mg, 0.136 mmol) was dissolved in DMF (3 mL), cesium carbonate (88 mg, 0.271 mmol) was added and the reaction mixture stirred for 15 min at room temperature. Subsequently 1-(bromomethyl)-3-fluorobenzene (0.017 mL, 0.136 mmol) was added and the reaction mixture stirred overnight at room temperature. Water was added, the reaction mixture extracted three times with ethyl acetate, and the organic phases were combined and dried over sodium sulfate. Evaporation of the solvent and purification of the raw material by column chromatography resulted in (S)-tert-butyl 2-((5-fluoro-4-((3-fluorobenzyl)oxy)-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate as white foam (58 mg; 90% yield).

(S)-tert-butyl 2-((5-fluoro-4-((3-fluorobenzyl)oxy)-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (58 mg, 0.122 mmol) was dissolved in DCM (4 mL) 2,2,2-trifluoroacetic acid (0.234 mL, 3.04 mmol) was added and the reaction mixture stirred overnight at room temperature. After further dilution with DCM the reaction mixture

was extracted three times with 1M NaOH to remove 2,2,2-trifluoroacetic acid, the organic phase was dried over sodium sulfate and the solvent evaporated in vacuum.

(S)-N-(5-fluoro-4-((3-fluorobenzyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide (23 mg; 49% yield) was obtained as film in the vessel.

5 (S)-N-(5-fluoro-4-((3-fluorobenzyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide (16.6 mg, 0.044 mmol) was dissolved in ethanol (0.7 mL), fumaric acid (5.1 mg, 0.0441 mmol) was added, and the mixture stirred at room temperature for 1 h. The solvent was evaporated, water was added to the residue and the solution lyophilized to obtain (S)-N-(5-fluoro-4-((3-fluorobenzyl)oxy)-2-methoxybenzyl)pyrrolidine-2-
10 carboxamide fumarate as white powder (19.6 mg; 89% yield).

LC-MS (M/Z [M+H]⁺): 377.1

¹H NMR (600 MHz, methanol-*d*₄) δ 7.39 (td, *J* = 7.9, 5.8 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.19 (dt, *J* = 9.9, 2.0 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.77 (d, *J* = 7.0 Hz, 1H), 6.69 (s, 2H), 5.19 (s, 2H), 4.34, 4.30 (ABq, *J* = 14.7 Hz, 2H), 4.19 (dd, *J* = 8.4, 7.0 Hz, 1H),
15 3.80 (s, 3H), 3.38 (dt, *J* = 11.4, 7.1 Hz, 1H), 3.31 – 3.25 (m, 1H), 2.41 – 2.35 (m, 1H), 2.07 – 2.00 (m, 2H), 2.00 – 1.92 (m, 1H).

Example 2:

**(2S)-N-[[5-Fluoro-2-methoxy-4-[(2,3,5-trifluorophenyl)methoxy]phenyl]methyl]-
20 pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt**

A 4 mL vial was charged with a stir bar, to which was added (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (30 mg, 1 eq., 0.08 mmol; see example 1) in 0.5 ml of dimethyl acetamide followed by 1-(bromomethyl)-2,3,5-trifluorobenzene (22 mg, 1.2 eq, 0.10 mmol) in 0.5 ml of dimethyl
25 acetamide and cesium carbonate (80 mg, 0.24 mmol, 3 eq.). This mixture was allowed to stir at 60 °C overnight until completion of reaction. Upon completion, the mixture was then filtered and concentrated to dryness. The residue was dissolved in 0.5 ml of 1:1 TFA:Dichloromethane and allowed to stir for 6 hours. Upon completion of the deprotection, the reaction was dried and purified by reverse phase HPLC (TFA method).

30 Samples were purified by preparative HPLC on a Phenomenex Luna C8(2) 5 μm 100Å AXIA column (30mm × 150mm). A gradient of ACN (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50mL/min (0-0.5 min 5% A, 0.5-8.5 min linear

gradient 5-100% A, 8.7-10.7 min 100% A, 10.7 -11.0 min linear gradient 100-5% A). to afford the desired compound (2S)-N-[[5-fluoro-2-methoxy-4-[(2,3,5-trifluorophenyl)methoxy]phenyl]methyl]pyrrolidine-2-carboxamide as 2,2,2-trifluoroacetic acid salt.

5 MS(APCI+) (M/Z [M+H]⁺): 413

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (t, *J* = 5.7 Hz, 1H), 7.53 (dddd, *J* = 10.8, 9.1, 6.2, 3.1 Hz, 1H), 7.28 (ddt, *J* = 7.7, 4.9, 2.7 Hz, 1H), 7.06 (d, *J* = 11.7 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.34 – 5.25 (m, 2H), 4.24 (t, *J* = 3.0 Hz, 2H), 4.17 (t, *J* = 7.8 Hz, 1H), 3.31 – 3.16 (m, 2H), 2.35 – 2.25 (m, 1H), 1.96 – 1.78 (m, 3H).

10

Example 3:

(2S)-N-[[5-Fluoro-4-[(4-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 2 starting from 1-
15 (bromomethyl)-4-fluorobenzene and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and purification by reverse phase HPLC the desired product (2S)-N-[[5-fluoro-4-[(4-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide 2,2,2-trifluoroacetic acid salt was obtained.

20 MS(APCI+) (M/Z [M+H]⁺): 377

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.52 (dd, *J* = 8.6, 5.6 Hz, 2H), 7.28 – 7.19 (m, 2H), 7.03 (d, *J* = 11.8 Hz, 1H), 6.91 (d, *J* = 7.3 Hz, 1H), 5.19 (s, 2H), 4.22 (s, 2H), 4.16 (t, *J* = 7.9 Hz, 1H), 3.23 (ddt, *J* = 31.4, 11.3, 7.2 Hz, 2H), 2.31 (dt, *J* = 13.6, 6.3 Hz, 1H), 1.95 – 1.76 (m, 3H).

25

Example 4:

(2S)-N-[[4-[(2,3-Difluorophenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 2 starting from 1-
30 (bromomethyl)-2,3-difluorobenzene and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and purification by reverse phase HPLC the desired product (2S)-N-[[4-[(2,3-

difluorophenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide 2,2,2-trifluoroacetic acid salt was obtained.

MS(APCI+) (M/Z [M+H]⁺): 395

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (t, *J* = 5.7 Hz, 1H), 7.52 – 7.34 (m, 2H), 7.27
5 (tdd, *J* = 8.1, 5.0, 1.5 Hz, 1H), 7.04 (d, *J* = 11.7 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.29
(s, 2H), 4.24 (t, *J* = 3.0 Hz, 2H), 4.17 (t, *J* = 7.9 Hz, 1H), 3.33 – 3.14 (m, 2H), 2.32
(ddd, *J* = 14.9, 12.4, 6.7 Hz, 1H), 1.98 – 1.90 (m, 2H), 1.90 – 1.77 (m, 1H).

Example 5:

10 **(2S)-N-[[4-[(3,5-Difluorophenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt**

The compound was prepared according to example 2 starting from 1-(bromomethyl)-3,5-difluorobenzene and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and puri-
15 fication by reverse phase HPLC the desired product (2S)-N-[[4-[(3,5-difluorophenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide 2,2,2-trifluoroacetic acid salt was obtained.

MS(APCI+) (M/Z [M+H]⁺): 395

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.24 – 7.12 (m, 3H), 7.06 (d, *J* = 11.7 Hz, 1H), 6.90
20 (d, *J* = 7.3 Hz, 1H), 5.25 (s, 2H), 4.23 (d, *J* = 4.1 Hz, 2H), 4.17 (t, *J* = 7.9 Hz, 1H), 3.79
(s, 3H), 3.33 – 3.14 (m, 2H), 2.39 – 2.26 (m, 1H), 1.98 – 1.90 (m, 2H), 1.90 – 1.76 (m, 1H).

Example 6:

25 **(2S)-N-[[5-Fluoro-4-[(2-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt**

The compound was prepared according to example 2 starting from 1-(bromomethyl)-2-fluorobenzene and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and puri-
30 fication by reverse phase HPLC the desired product (2S)-N-[[5-fluoro-4-[(2-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide 2,2,2-trifluoroacetic acid salt was obtained.

MS(APCI+) (M/Z [M+H]⁺): 377

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.56 (td, *J* = 7.6, 1.8 Hz, 1H), 7.51 – 7.40 (m, 1H), 7.31 – 7.21 (m, 2H), 7.04 (d, *J* = 11.7 Hz, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 5.24 (s, 2H), 4.23 (s, 2H), 4.17 (t, *J* = 7.9 Hz, 1H), 3.82 (s, 3H), 3.23 (ddt, *J* = 31.2, 11.4, 7.1 Hz, 2H), 2.31 (ddd, *J* = 12.7, 8.3, 6.3 Hz, 1H), 1.98 – 1.87 (m, 2H), 1.87 – 1.76 (m, 1H).

Example 7:

(2S)-N-[[4-[(2-Chloro-3,6-difluoro-phenyl)methoxy]-5-fluoro-2-methoxy-phenyl]-methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

10 The compound was prepared according to example 2 starting from 2-(bromomethyl)-3-chloro-1,4-difluorobenzene and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and purification by reverse phase HPLC the desired product (2S)-N-[[4-[(2-chloro-3,6-difluoro-phenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-

15 carboxamide 2,2,2-trifluoroacetic acid salt was obtained.

MS(APCI+) (M/Z [M+H]⁺): 429

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 (t, *J* = 5.7 Hz, 1H), 7.62 – 7.53 (m, 1H), 7.39 (td, *J* = 9.1, 4.2 Hz, 1H), 7.06 – 6.98 (m, 2H), 5.31 (d, *J* = 1.8 Hz, 2H), 4.24 (t, *J* = 3.0 Hz, 2H), 4.17 (t, *J* = 7.8 Hz, 1H), 3.31 – 3.15 (m, 2H), 2.37 – 2.25 (m, 1H), 1.97 – 1.76

20 (m, 3H).

Example 8:

(2S)-N-[[5-fluoro-4-[(2-fluoro-4-pyridyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

25 The compound was prepared according to example 2 starting from 4-(bromomethyl)-2-fluoropyridine and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and purification by reverse phase HPLC the desired product (2S)-N-[[5-fluoro-4-[(2-fluoro-4-pyridyl)methoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide 2,2,2-

30 trifluoroacetic acid salt was obtained.

MS(APCI+) (M/Z [M+H]⁺): 378

Example 9:

(2S)-N-[[5-Fluoro-4-[(5-fluoro-3-pyridyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 2 starting from 3-(bromomethyl)-5-fluoropyridine and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and purification by reverse phase HPLC the desired product (2S)-N-[[5-fluoro-4-[(5-fluoro-3-pyridyl)methoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide 2,2,2-trifluoroacetic acid salt was obtained.

10 MS(APCI+) (M/Z [M+H]⁺): 378

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 (d, *J* = 2.8 Hz, 1H), 8.55 (d, *J* = 1.8 Hz, 1H), 7.87 – 7.75 (m, 1H), 7.06 (d, *J* = 11.8 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 5.31 (s, 2H), 4.24 (d, *J* = 4.0 Hz, 2H), 4.17 (t, *J* = 7.8 Hz, 1H), 3.81 (s, 3H), 3.23 (ddt, *J* = 30.6, 11.5, 7.1 Hz, 2H), 2.32 (ddd, *J* = 15.0, 12.4, 6.5 Hz, 1H), 1.88 (ddt, *J* = 31.4, 13.3, 7.2 Hz, 3H).

Example 10:

(2S)-N-[[5-fluoro-2-methoxy-4-[[6-(trifluoromethyl)-3-pyridyl]methoxy]phenyl]methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

20 The compound was prepared according to example 2 starting from 5-(bromomethyl)-2-(trifluoromethyl)pyridine and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and purification by reverse phase HPLC the desired product (2S)-N-[[5-fluoro-2-methoxy-4-[[6-(trifluoromethyl)-3-pyridyl]methoxy]phenyl]methyl]pyrrolidine-2-carboxamide 2,2,2-trifluoroacetic acid salt was obtained.

25 MS(APCI+) (M/Z [M+H]⁺): 428

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 (s, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 8.01 – 7.91 (m, 1H), 7.06 (d, *J* = 11.7 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.39 (s, 2H), 4.23 (s, 2H), 4.17 (t, *J* = 7.9 Hz, 1H), 3.29 – 3.15 (m, 2H), 2.37 – 2.25 (m, 1H), 1.97 – 1.77 (m, 3H).

30

Example 11:

(2S)-N-[[5-Fluoro-4-[2-(4-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

In a 4 ml vial was added 200mg of PS-PPh₃ followed by (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (35mg, 0.1mmol) dissolved in 2ml of THF, and 2-(4-fluorophenyl)ethanol (28mg, 0.2mmol) dissolved in 0.3mL THF. The mixture was allowed to react for 10 minutes. 50μL of DIAD was then added and vial was sealed and shaken for 72 h. The reaction was filtered, and concentrated to dryness. Then 1.0 mL of HCl/dioxane was added and reaction was shaken for 1 hour. After that the reaction was concentrated to dryness again and was re-dissolved in 1800 μL of a 1:1 v/v solution of DMSO/MeOH, checked by LC/MS and purified by reverse phase HPLC (TFA method) to provide the desired product (2S)-N-[[5-fluoro-4-[2-(4-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide which was obtained as 2,2,2-trifluoroacetic acid salt (66% yield).

MS(APCI+) (M/Z [M+H]⁺): 391

¹H NMR (400 MHz, DMSO-d₆ /D₂O, Temp = 27°C) δ 8.76 (t, J = 5.8 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.19 – 7.07 (m, 2H), 6.99 (d, J = 11.8 Hz, 1H), 6.76 (d, J = 7.2 Hz, 1H), 4.27 (t, J = 6.6 Hz, 2H), 4.24 – 4.18 (m, 2H), 4.15 (t, J = 7.8 Hz, 1H), 3.77 (s, 3H), 3.30 – 3.13 (m, 2H), 3.03 (t, J = 6.6 Hz, 2H), 2.37 – 2.24 (m, 1H), 1.97 – 1.84 (m, 2H), 1.84 – 1.72 (m, 1H)

Example 12:

(2S)-N-[[5-Fluoro-4-[2-(3-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 11 by Mitsunobu reaction starting from 2-(3-fluorophenyl)ethanol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-4-[2-(3-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt (58% yield).

MS(APCI+) (M/Z [M+H]⁺): 391

¹H NMR (400 MHz, DMSO-d₆/D₂O, Temp = 27°C) δ 8.76 (t, J = 5.7 Hz, 1H), 7.46 – 7.28 (m, 1H), 7.24 – 7.12 (m, 2H), 7.07 – 7.02 (m, 1H), 7.00 (d, J = 11.8 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 4.30 (t, J = 6.6 Hz, 2H), 4.25 – 4.18 (m, 2H), 4.15 (t, J = 7.9 Hz, 1H), 3.78 (s, 3H), 3.35 – 3.11 (m, 2H), 3.06 (t, J = 6.5 Hz, 2H), 2.38 – 2.19 (m, 1H),
5 1.97 – 1.84 (m, 2H), 1.86 – 1.73 (m, 1H).

Example 13:

(2S)-N-[[5-Fluoro-4-[2-(2-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

10 The compound was prepared according to example 11 by Mitsunobu reaction starting from 2-(2-fluorophenyl)ethanol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-4-[2-(2-fluorophenyl)ethoxy]-2-methoxy-phenyl]-
15 methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt (42% yield).

MS(APCI+) (M/Z [M+H]⁺): 391

¹H NMR (400 MHz, DMSO-d₆/D₂O, Temp = 27°C) δ 8.77 (t, J = 5.8 Hz, 1H), 7.50 – 7.38 (m, 1H), 7.38 – 7.25 (m, 1H), 7.24 – 7.11 (m, 2H), 7.01 (d, J = 11.7 Hz, 1H), 6.79
20 (d, J = 7.3 Hz, 1H), 4.31 (t, J = 6.7 Hz, 2H), 4.25 – 4.20 (m, 2H), 4.16 (t, J = 7.8 Hz, 1H), 3.79 (s, 3H), 3.33 – 3.14 (m, 2H), 3.09 (t, J = 6.6 Hz, 2H), 2.43 – 2.23 (m, 1H), 2.00 – 1.87 (m, 2H), 1.87 – 1.73 (m, 1H)

Example 14:

25 **(2S)-N-[[5-Fluoro-2-methoxy-4-[2-[4-(trifluoromethyl)phenyl]ethoxy]phenyl]-methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt**

The compound was prepared according to example 11 by Mitsunobu reaction starting from 2-(4-(trifluoromethyl)phenyl)ethanol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection
30 tion with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-2-methoxy-4-[2-[4-(trifluoromethyl)phenyl]-

ethoxy]phenyl]methyl]pyrrolidine-2-carboxamide which was obtained as 2,2,2-trifluoroacetic acid salt (40% yield).

MS(APCI+) (M/Z [M+H]⁺): 441

¹H NMR (400 MHz, DMSO-d₆/D₂O, Temp = 27°C) δ 8.77 (t, J = 5.7 Hz, 1H), 7.73 – 7.58 (m, 2H), 7.58 – 7.49 (m, 2H), 7.01 (d, J = 11.8 Hz, 1H), 6.78 (d, J = 7.3 Hz, 1H), 4.35 (t, J = 6.5 Hz, 2H), 4.28 – 4.20 (m, 2H), 4.16 (t, J = 7.8 Hz, 1H), 3.79 (s, 3H), 3.31 – 3.18 (m, 2H), 3.18 – 3.10 (m, 2H), 2.37 – 2.22 (m, 1H), 2.00 – 1.85 (m, 2H), 1.85 – 1.75 (m, 1H)

10 Example 15:

(2S)-N-[[5-fluoro-2-methoxy-4-[[5-(trifluoromethyl)-2-furyl]methoxy]phenyl]-methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 2 starting from 2-(bromo-methyl)-5-(trifluoromethyl)furane and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxy-15 benzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and purification by reverse phase HPLC the desired product (2S)-N-[[5-fluoro-2-methoxy-4-[[5-(trifluoromethyl)-2-furyl]methoxy]phenyl]methyl]pyrrolidine-2-carboxamide 2,2,2-trifluoroacetic acid salt was obtained.

MS(APCI+) (M/Z [M+H]⁺): 417

20 ¹H NMR (400 MHz, DMSO-d₆) δ 8.79 (t, J = 5.8 Hz, 1H), 7.22 (dt, J = 3.6, 1.3 Hz, 1H), 7.04 (d, J = 11.7 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.83 (d, J = 3.5 Hz, 1H), 5.27 (s, 2H), 4.24 (t, J = 2.9 Hz, 2H), 4.17 (t, J = 7.9 Hz, 1H), 3.82 (s, 3H), 3.23 (ddt, J = 30.9, 11.4, 7.1 Hz, 2H), 2.32 (ddd, J = 14.8, 12.4, 6.4 Hz, 1H), 1.98 – 1.87 (m, 2H), 1.87 – 1.76 (m, 1H).

25

Example 16:

(S)-N-(5-Fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide and its fumaric acid addition salt

Ketone reduction:

30 5.0 g 4-fluorocyclohexanone (43.1 mmol) was dissolved in methanol (290 mL) and cooled to 0°C with an ice-water bath. Then, 2.44 g sodium borohydride (64.6 mmol, 1.5 eq.) was added in portions while keeping the temperature. The reaction mixture was

allowed to reach room temperature and stirred overnight. TLC (ethyl acetate/heptane 1:9) indicated full conversion of the starting ketone. The methanolic solution was concentrated in vacuum, diluted with ethyl acetate and carefully quenched with water, and further neutralized with aqueous HCl. The organic phase was separated and the aqueous phase extracted with ethyl acetate (2x) again. Combined extracts were dried over Na₂SO₄ and the solvent was removed in vacuum. The alcohol remained as a brownish oil which slowly started crystallizing upon standing. Yield: 5.03 g (42.65 mmol, 99%) as a 2:1 mixture of cis/trans-isomers (A:B, A = cis, B = trans) as indicated by proton NMR.

¹H NMR (500 MHz, Chloroform-d): δ 1.38 – 1.80 (m, CH₂), 1.90 – 2.10 (m, CH₂), 3.67 – 3.76 (m, 1H, CHOH, isomer A), 3.83 (tt, J = 7.8, 3.5 Hz, 1H, CHOH, isomer B), 4.63 (dtt, J = 48.5, 8.2, 3.5 Hz, 1H, CHF, isomer B), 4.69 (dtt, J = 48.8, 5.5, 2.7 Hz, 1H, CHF, isomer A).

¹⁹F NMR (471 MHz, Chloroform-d): δ -181.77 – -179.97 (m, isomer B), -179.86 – -178.49 (m, isomer A).

LC-MS: No ionization observed.

Benzoylation:

To a solution of 5.0 g 4-fluorocyclohexanone (42.3 mmol, cis/trans-mixture) in dichloromethane (250 mL) was added 30 mL triethylamine (215 mmol, 5.1 eq.) and slowly 10 mL benzoyl chloride (86 mmol, 2.0 eq.) at room temperature. Stirring was continued overnight in order to reach full conversion. Then, the reaction mixture was washed with aqueous ammonium chloride (2x) and with water. The organic layer was dried over MgSO₄ and the solvent evaporated. The crude benzoates were absorbed on Celite and purified by flash chromatography on silica (ethyl acetate/heptane). Yield: 2.32 g (10.44 mmol, 25%) of trans isomer (1r,4r)-4-fluorocyclohexyl benzoate as colorless oil and 5.50 g (24.75 mmol, 59%) of cis isomer (1s,4s)-4-fluorocyclohexyl benzoate as white solid.

Cis-isomer:

¹H NMR (600 MHz, Chloroform-d): δ 1.73 – 1.88 (m, 4H), 1.94 – 2.12 (m, 4H), 4.74 (dtt, J = 48.5, 6.4, 3.0 Hz, 1H, CHF), 5.08 (ddt, J = 11.7, 8.1, 3.4 Hz, 1H, CHOBz), 7.43 – 7.49 (m, 2H), 7.54 – 7.60 (m, 1H), 8.03 – 8.08 (m, 2H).

LC-MS: No ionization observed.

Trans isomer:

^1H NMR (600 MHz, Chloroform-d): δ 1.70 – 1.90 (m, 4H), 1.96 – 2.13 (m, 4H), 4.80 (dtt, $J = 51.3, 6.6, 2.9$ Hz, 1H, CHF), 5.18 (tt, $J = 6.8, 3.1$ Hz, 1H, CHOBz), 7.40 – 7.49 (m, 2H), 7.54 – 7.60 (m, 1H), 8.02 – 8.05 (m, 2H).

5 LC-MS: No ionization observed.

Hydrolysis:

Trans Isomer:

2.32 g trans-4-fluorocyclohexyl benzoate (10.44 mmol) was dissolved in a mixture of THF (21 mL), methanol (31 mL) as well as water (52 mL) and 350 mg lithium hydroxide (14.6 mmol, 1.4 eq.) was added. The reaction mixture was stirred at room temperature overnight. Volatiles were removed in vacuum and the aqueous concentrate was extracted with ethyl acetate (2x). Combined extracts were washed with water (2x), brine (1x), dried over MgSO_4 and carefully evaporated to dryness. The trans-4-fluorocyclohexanol remained as colorless oil. Yield: 1.09 g (9.23 mmol, 88%).

15 ^1H NMR (600 MHz, Chloroform-d): $\delta = 1.43$ (dtd, $J = 13.7, 9.5, 9.0, 3.9$ Hz, 2H), 1.59 – 1.69 (m, 2H), 1.92 – 2.10 (m, 5H), 3.84 (tt, $J = 7.9, 3.6$ Hz, 1H, CHOH), 4.64 (dtt, $J = 48.7, 8.2, 3.7$ Hz, 1H, CHF).

Cis Isomer:

Cis-4-fluorocyclohexanol was prepared in a similar fashion (scale: 24.75 mmol).

20 Yield: 2.54 g (21.5 mmol, 87%).

^1H NMR (600 MHz, Chloroform-d): $\delta = 1.53 - 1.80$ (m, 6H), 1.99 – 2.10 (m, 2H), 3.72 (dddd, $J = 12.9, 7.0, 5.1, 3.3$ Hz, 1H, CHOH), 4.70 (dtt, $J = 48.5, 5.4, 2.7$ Hz, 1H, CHF).

Nucleophilic reaction:

170 mg Sodium hydride (60%, 4.26 mmol, 2.4 eq.) were dispersed in DMF (5 mL) under a nitrogen atmosphere. 251 mg cis-4-fluorocyclohexanol (2.13 mmol, 1.2 eq.) dissolved in DMF (3 mL) were added at room temperature and the mixture was stirred for 10 min. Finally, 300 mg 4,5-difluoro-2-methoxybenzotrile (1.77 mmol) were dissolved in DMF (3 mL) and added. The reaction mixture was heated up to 60°C and was stirred for 1 hour. It was allowed to cool down to room temperature and stirring was continued overnight. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2x). The combined organic phases were dried

with MgSO₄ and evaporated to dryness. The residue was purified flash chromatography on silica (ethyl acetate/heptane). 5-Fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxybenzotrile was obtained as a colorless resin. Yield: 339 mg (1.27 mmol, 72%).

5 LC-MS (M/Z [M+H]⁺): 268.20

Nitrile reduction:

339 mg 5-Fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxybenzotrile (1.27 mmol) were dissolved in THF (10 mL) and heated to reflux. Then, 0.3 mL of borane dimethyl sulfide complex (3.17 mmol, 2.5 q.) was added via syringe and the mixture
10 was refluxed for 2 hours. After the reaction mixture had reached room temperature, excess hydride was carefully decomposed by addition of 2.5 M HCl in ethanol until hydrogen evolution was completed. Stirring was continued for 15 min. All volatiles were evaporated and the crude resin co-distilled with toluene (2x). The solid residue was precipitated with diethylether and dried in vacuum. The (5-fluoro-4-((cis-4-
15 fluorocyclohexyl)oxy)-2-methoxyphenyl)methanamin hydrochloride was obtained as white crystals. Yield: 393 mg (1.27 mmol, 100%).

LC-MS (M/Z [M-NH₃]⁺) : 255.25

Peptide coupling:

275 mg L-Boc proline (1.27 mmol, 1.0 eq.) were dissolved in DMF (7.5 mL) and
20 228 mg carbonyldiimidazol (1.40 mmol, 1.1 eq.) were added at room temperature. The mixture was heated to 50°C and stirred for 30 min. 393 mg (5-fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxyphenyl)methanamin hydrochloride (1.27 mmol) were dissolved in pyridine (7.5 mL) and stirred for 30 min at room temperature. This pyridine
25 solution of the amine was added to the imidazolide via syringe, the mixture was heated to 80°C for 2 hours and stirring was continued at room temperature overnight. The reaction mixture was concentrated in vacuum and co-distilled with toluene (2x). The residue was purified by flash chromatography on silica (dichloromethane/ methanol). (S)-tert-Butyl 2-((5-fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)carbamoyl)-pyrrolidine-1-carboxylate was obtained as yellowish resin. Yield: 596 mg (1.27 mmol,
30 100%)

LC-MS (M/Z [M+H]⁺): 469.35

Deprotection:

596 mg (S)-tert-Butyl 2-((5-fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (1.27 mmol) were dissolved in dichloromethane (20 mL) and cooled down with an ice-water bath. Then, 2.5 mL TFA (31.8 mmol, 25 eq.) were added and the mixture was stirred at 0°C for 1 h before it was allowed to reach room temperature and stirred overnight. The reaction mixture was partitioned between saturated sodium bicarbonate and dichloromethane. The organic phase was separated and the aqueous phase extracted with dichloromethane (2x). The combined organic phases were dried with MgSO₄ and evaporated to dryness. The product was obtained as colorless resin. The product was further purified by flash chromatography on silica (dichloromethane/methanol). (S)-N-(5-fluoro-4-(((1s,4R)-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide Yield: 327 mg (0.89 mmol, 70%).

LC-MS (M/Z [M+H]⁺): 369.35

Salt formation:

103 mg Fumaric acid (0.89 mmol, 1.0 eq.) were dissolved in warm ethanol (2 mL) and added to a warm solution of 327 mg (S)-N-(5-fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide (0.89 mmol) in ethanol (10 mL). Cooling of the solution did not result in crystallization, therefore the solution was evaporated to dryness. The residue was taken up with a little methanol and diluted with dichloromethane. The solution was concentrated in vacuum, resulting in white, stable foam. The foam was crystallized via trituration with diethylether. The crystals of the fumaric acid salt of (S)-N-(5-fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide were filtered off, washed with diethylether and dried in vacuum. Yield: 433 mg (0.88 mmol, 100%).

¹H NMR (600 MHz, methanol-d₄): δ = 1.68 – 1.82 (m, 4H), 1.85 – 1.93 (m, 2H), 1.94 – 2.08 (m, 5H), 2.36 – 2.44 (m, 1H), 3.39 (dt, J = 11.3, 7.0 Hz, 1H), 3.82 (s, 3H), 4.22 (dd, J = 8.5, 7.0 Hz, 1H), 4.29 – 4.38 (m, 2H), 4.41 (tt, J = 7.3, 3.4 Hz, 1H), 4.66 (ddt, J = 48.7, 6.9, 3.6 Hz, 1H), 6.69 (s, 2H), 6.74 (d, J = 6.9 Hz, 1H), 7.02 (d, J = 11.4 Hz, 1H).

¹⁹F NMR (471 MHz, methanol-d₄): δ = -144.98 (dd, J = 11.7, 7.4 Hz).

LC-MS (M/Z [M+H]⁺): 369.30

Example 17:

(S)-N-(5-Fluoro-4-((trans-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide and its fumaric acid addition salt

The trans-product was prepared according to example 16 starting from trans-4-
5 fluorocyclohexanol (see example 16) and 4,5-difluoro-2-methoxybenzotrile. After
nitrile reduction, coupling with BOC-L-proline, deprotection and salt formation the de-
sired product (S)-N-(5-fluoro-4-((trans-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)-
pyrrolidine-2-carboxamide fumaric acid salt was obtained.

¹H NMR (500 MHz, methanol-d₄): δ = 1.65 – 1.77 (m, 4H), 1.92 – 2.11 (m, 7H), 2.39
10 (ddt, J = 12.8, 8.2, 6.1 Hz, 1H), 3.39 (dt, J = 11.4, 7.1 Hz, 1H), 3.82 (s, 3H), 4.21 (dd, J
= 8.4, 6.9 Hz, 1H), 4.28 – 4.39 (m, 2H), 4.51 (dd, J = 6.6, 3.4 Hz, 1H), 4.67 – 4.80 (m,
1H), 6.69 (s, 2H), 6.74 (d, J = 7.0 Hz, 1H), 7.01 (d, J = 11.5 Hz, 1H).

¹⁹F NMR (471 MHz, methanol-d₄): δ -145.36 (dd, J = 11.3, 6.9 Hz).

LC-MS (M/Z [M+H]⁺): 369.30

15

Example 18:

**(2S)-N-[[4-(4,4-Difluorocyclohexoxy)-5-fluoro-2-methoxy-phenyl]methyl]-
pyrrolidine-2-carboxamide and its fumaric acid addition salt**

Potassium 2-methylpropan-2-olate (1.704 g, 15.19 mmol) was suspended in THF
20 (40mL) and the mixture was cooled to 0°C. 4,4-Difluorocyclohexanol (2.23 g, 16.38
mmol) was added and the solution was stirred at 0°C for 30min. The temperature was
lowered to -78°C followed by dropwise addition of 2,4,5-trifluorobenzonitrile (2.339 g,
14.89 mmol) in THF(25 mL) at -78 °C under nitrogen. The solution was stirred at -78
°C for 2h and warmed to room temperature over 1.5h. Water (200 mL) was added to the
25 reaction mixture, extracted with EtOAc (100 mL*3), the combined organic phases were
washed with water and brine, dried over sodium sulfate and the solvent was removed in
vacuum. The residue was purified by flash chromatography on silica (hep-
tane/EtOAc:95/5% to 52/48%). 4-((4,4-Difluorocyclohexyl)oxy)-2,5-
difluorobenzonitrile was obtained as viscous oil (3.08 g; yield 76%).

30 Potassium 2-methylpropan-2-olate (2.070 g, 18.45 mmol) was suspended in THF
(22 mL) and the mixture was cooled to 0°C. Methanol (0.591 g, 18.45 mmol, 18.45
mmol, 0.75 mL) was added and the solution was stirred at 0°C for 30min. The tempera-

ture was lowered to -50°C followed by dropwise addition of 4-((4,4-difluorocyclohexyl)oxy)-2,5-difluorobenzonitrile (3.6 g, 13.18 mmol) in THF(40 mL) at -50 °C under nitrogen. The solution was stirred at -50 °C for 1h and warmed to room temperature overnight. Water (300 mL) was added to the reaction mixture, extracted with EtOAc (100 mL*3), the combined organic phases were washed with water and brine, dried over sodium sulfate and the solvent was removed in vacuum. The residue was purified by flash chromatography on silica (heptane/EtOAc). 4-((4,4-Difluorocyclohexyl)oxy)-5-fluoro-2-methoxybenzonitrile was obtained as white foam (2.54 g; yield 68%).

Nitrile reduction, peptide coupling, deprotection and subsequent salt formation were performed as described in example 16. (2S)-N-[[4-(4,4-difluorocyclohexoxy)-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide fumarate was obtained as white hard foam.

LC-MS (M/Z [M+H]⁺): 387.2

¹H NMR (600 MHz, methanol-*d*₄) δ 7.03 (d, *J* = 11.5 Hz, 1H), 6.78 (d, *J* = 6.9 Hz, 1H), 6.69 (s, 2H), 4.58 (dt, *J* = 6.0, 3.0 Hz, 1H), 4.36, 4.31 (ABq, *J* = 14.8 Hz, 2H), 4.23 (dd, *J* = 8.4, 6.9 Hz, 1H), 3.83 (s, 3H), 3.43 – 3.35 (m, 1H), 3.35 – 3.28 (m, 1H), 2.45 – 2.36 (m, 1H), 2.19 – 2.07 (m, 2H), 2.09 – 2.01 (m, 2H), 2.03 – 1.86 (m, 7H).

Example 19:

(2S)-N-[[5-Fluoro-2-methoxy-4-(3,3,3-trifluoropropoxy)phenyl]methyl]pyrrolidine-2-carboxamide and its fumaric acid addition salt

(S)-tert-Butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (400 mg, 1.086 mmol, see example 1), triphenylphosphine (575 mg, 2.172 mmol) and 3,3,3-trifluoropropan-1-ol (0.144 mL, 1.629 mmol) were dissolved in THF (12 mL) under inert atmosphere. The reaction mixture was cooled to -10°C and DIAD (0.444 mL, 2.172 mmol) was added dropwise via syringe and stirring at -10°C continued for 2h. Subsequently the cooling bath was removed and the reaction mixture stirred at room temperature over the weekend. Since the reaction was not complete, additional triphenylphosphine (575 mg, 2.172 mmol), 3,3,3-trifluoropropan-1-ol (0.144 mL, 1.629 mmol) and DIAD (0.444 mL, 2.172 mmol) were added to the reaction mixture at -5°C and the reaction stirred at room temperature overnight. Since the reaction was still incomplete, once again DIAD (0.444 mL, 2.172 mmol) was added at -5°C and the reac-

tion stirred at room temperature overnight. Water was added, the reaction mixture extracted three times with ethyl acetate, the organic phases were combined and dried over sodium sulfate. Evaporation of the solvent and purification of the raw material by column chromatography resulted in (S)-tert-butyl 2-((5-fluoro-2-methoxy-4-(3,3,3-trifluoropropoxy)benzyl)carbamoyl)pyrrolidine-1-carboxylate (180 mg; yield 37%)
5 BOC deprotection and subsequent salt formation was performed as described in example 1 resulting in (2S)-N-[[5-fluoro-2-methoxy-4-(3,3,3-trifluoropropoxy)phenyl]-methyl]pyrrolidine-2-carboxamide fumarate as white powder after lyophilization.

LC-MS (M/Z [M+H]⁺): 365.2

10 ¹H NMR (500 MHz, methanol-*d*₄) δ 7.03 (d, *J* = 11.5 Hz, 1H), 6.74 (d, *J* = 7.0 Hz, 1H), 6.68 (s, 2H), 4.36, 4.31 (ABq, *J* = 14.8 Hz, 2H), 4.30 (t, *J* = 6.1 Hz, 2H), 4.23 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.85 (s, 3H), 3.39 (dt, *J* = 11.4, 7.0 Hz, 1H), 3.35 – 3.27 (m, 1H), 2.76 – 2.63 (m, 2H), 2.45 – 2.34 (m, 1H), 2.08 – 1.92 (m, 3H).

15 Example 20:

(2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]-pyrrolidine-2-carboxamide and its hydrochloride

The compound was prepared according to example 19 by Mitsunobu reaction starting from 2,2,3,3-tetrafluoropropan-1-ol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and salt
20 formation the desired product (2S)-N-[[5-fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride salt was obtained as white powder after lyophilization.

LC-MS (M/Z [M+H]⁺): 383.2

25 ¹H NMR (500 MHz, methanol-*d*₄) δ 7.04 (d, *J* = 11.5 Hz, 1H), 6.82 (d, *J* = 7.0 Hz, 1H), 6.31 (tt, *J* = 52.6, 5.3 Hz, 1H), 4.54 (tt, *J* = 12.5, 1.6 Hz, 2H), 4.34, 4.30 (ABq, *J* = 14.9 Hz, 2H), 3.96 – 3.89 (m, 1H), 3.85 (s, 3H), 3.22 – 3.13 (m, 1H), 3.13 – 3.06 (m, 1H), 2.31 – 2.21 (m, 1H), 1.93 – 1.81 (m, 3H).

30 Example 21:

(2S)-N-[[5-Fluoro-4-(2,2,3,4,4,4-hexafluorobutoxy)-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 11 by Mitsunobu reaction starting from 2,2,3,4,4,4-hexafluorobutan-1-ol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-4-(2,2,3,4,4,4-hexafluorobutoxy)-2-methoxyphenyl]methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

MS(APCI+) (M/Z [M+H]⁺): 433

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.06 (d, *J* = 11.8 Hz, 1H), 6.95 (d, *J* = 7.1 Hz, 1H), 4.76 (m, 2H), 4.68 (m, 1H), 4.23 (s, 2H), 4.04 (m, 1H), 3.82 (m, 3H), 3.14 (m, 2H), 2.24 (m, 1H), 1.80 (m, 3H).

Example 22:

(2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoro-1-methyl-propoxy)phenyl]methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 11 by Mitsunobu reaction starting from 3,3,4,4-tetrafluorobutan-2-ol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-2-methoxy-4-(2,2,3,3-tetrafluoro-1-methyl-propoxy)phenyl]methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

MS(APCI+) (M/Z [M+H]⁺): 397

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.08 (d, *J* = 11.5 Hz, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 6.77 – 6.42 (m, 1H), 5.06 (dd, *J* = 14.1, 7.1 Hz, 1H), 4.24 (s, 2H), 4.17 (t, *J* = 7.8 Hz, 1H), 3.81 (s, 3H), 3.33 – 3.10 (m, 2H), 2.39 – 2.23 (m, 1H), 2.05 – 1.79 (m, 3H), 1.41 (d, *J* = 6.4 Hz, 3H).

Example 23:

(2S)-N-[[5-Fluoro-2-methoxy-4-(4,4,4-trifluorobutoxy)phenyl]methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 11 by Mitsunobu reaction starting from 4,4,4-trifluorobutan-1-ol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-2-methoxy-4-(4,4,4-trifluorobutoxy)phenyl]-methyl]-pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

MS(APCI+) (M/Z [M+H]⁺): 379

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.04 (d, *J* = 11.8 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 4.78 (p, *J* = 6.2 Hz, 2H), 4.23 (s, 2H), 4.19 – 4.11 (m, 3H), 3.34 – 3.14 (m, 2H), 2.49 – 2.23 (m, 3H), 2.04 – 1.73 (m, 5H).

Example 24:

(2S)-N-[[5-Fluoro-2-methoxy-4-(3,3,4,4,4-pentafluorobutoxy)phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 11 by Mitsunobu reaction starting from 3,3,4,4,4-pentafluorobutan-1-ol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-2-methoxy-4-(3,3,4,4,4-pentafluorobutoxy)phenyl]-methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

MS(APCI+) (M/Z [M+H]⁺): 415

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.05 (d, *J* = 11.8 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 1H), 4.38 (t, *J* = 5.7 Hz, 2H), 4.24 (s, 2H), 4.17 (t, *J* = 7.9 Hz, 1H), 3.23 (ddt, *J* = 30.9, 11.3, 7.1 Hz, 2H), 2.74 (tt, *J* = 18.8, 5.6 Hz, 2H), 2.38 – 2.27 (m, 1H), 1.97 – 1.80 (m, 3H).

Example 25:

(2S)-N-[[5-Fluoro-2-methoxy-4-(4,4,4-trifluoro-2-methyl-butoxy)phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 11 by Mitsunobu reaction starting from 4,4,4-trifluoro-2-methylbutan-1-ol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA meth-

od) the desired product (2S)-N-[[5-fluoro-2-methoxy-4-(4,4,4-trifluoro-2-methylbutoxy)phenyl]methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

MS(APCI+) (M/Z [M+H]⁺): 393

5 ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.04 (d, *J* = 11.7 Hz, 1H), 6.81 (d, *J* = 7.3 Hz, 1H), 4.86 – 4.72 (m, 1H), 4.24 (d, *J* = 4.0 Hz, 2H), 4.17 (t, *J* = 7.8 Hz, 1H), 3.99 (qd, *J* = 9.6, 5.2 Hz, 2H), 3.80 (s, 3H), 3.33 – 3.11 (m, 2H), 2.39 – 2.19 (m, 3H), 2.00 – 1.75 (m, 3H), 1.11 (d, *J* = 5.9 Hz, 3H).

10 Example 26:

(2S)-N-[[4-[(2,2-Difluorocyclopropyl)methoxy]-5-fluoro-2-methoxy-phenyl]-methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 11 by Mitsunobu reaction starting from (2,2-difluorocyclopropyl)methanol and (S)-tert-butyl 2-((5-fluoro-4-
15 hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[4-[(2,2-difluorocyclopropyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

20 MS(APCI+) (M/Z [M+H]⁺): 359

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.04 (d, *J* = 11.8 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 4.30 (ddd, *J* = 10.1, 6.2, 3.3 Hz, 1H), 4.23 (s, 2H), 4.21 – 4.13 (m, 1H), 4.04 (dd, *J* = 10.8, 9.0 Hz, 1H), 3.81 (s, 3H), 3.23 (ddt, *J* = 30.6, 11.4, 7.2 Hz, 2H), 2.32 (ddd, *J* = 12.5, 8.1, 6.2 Hz, 1H), 2.27 – 2.14 (m, 1H), 2.04 – 1.86 (m, 2H), 1.86 – 1.78 (m, 1H),
25 1.80 – 1.68 (m, 1H), 1.45 (dtd, *J* = 13.7, 7.8, 4.1 Hz, 1H).

Example 27:

(2S)-N-[[5-Fluoro-2-methoxy-4-[[1-(trifluoromethyl)cyclopropyl]methoxy]phenyl]-methyl]pyrrolidine-2-carboxamide and its hydrochloride

30 The compound was prepared according to example 19 by Mitsunobu reaction starting from (1-(trifluoromethyl)cyclopropyl)methanol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC depro-

tection and salt formation the desired product (2S)-N-[[5-fluoro-2-methoxy-4-[[1-(trifluoromethyl)cyclopropyl]methoxy]phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride salt was obtained as white powder.

LC-MS (M/Z [M+H]⁺): 391.2

- 5 ¹H NMR (500 MHz, Methanol-*d*₄) δ 6.97 (d, *J* = 11.6 Hz, 1H), 6.71 (d, *J* = 7.0 Hz, 1H), 4.30 (d, *J* = 1.9 Hz, 2H), 4.18 (s, 2H), 3.83 (s, 3H), 3.83 – 3.78 (m, 1H), 3.14 – 3.06 (m, 1H), 3.03 (dt, *J* = 10.9, 6.7 Hz, 1H), 2.27 – 2.12 (m, 1H), 1.88 – 1.76 (m, 3H), 1.15 – 1.05 (m, 2H), 1.05 – 0.95 (m, 2H).

- 10 Example 28:

(2S)-N-[[4-(3,3-Difluorocyclobutoxy)-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its hydrochloride

- The compound was prepared according to example 19 by Mitsunobu reaction starting from 3,3-difluorocyclobutanol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-
15 methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and salt formation the desired product (2S)-N-[[4-(3,3-difluorocyclobutoxy)-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride salt was obtained as white powder after lyophilization.

LC-MS (M/Z [M+H]⁺): 359.2

- 20 ¹H NMR (500 MHz, methanol-*d*₄) δ 7.01 (d, *J* = 11.5 Hz, 1H), 6.59 (d, *J* = 7.0 Hz, 1H), 4.84 – 4.76 (m, 1H), 4.33, 4.29 (ABq, *J* = 14.9 Hz, 2H), 4.03 – 3.96 (m, 1H), 3.84 (s, 3H), 3.27 – 3.19 (m, 1H), 3.19 – 3.04 (m, 3H), 2.81 – 2.66 (m, 2H), 2.36 – 2.24 (m, 1H), 1.97 – 1.83 (m, 3H).

- 25 Example 29:

(2S)-N-[[4-[(3,3-Difluorocyclobutyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its fumaric acid addition salt

- The compound was prepared as described in example 1. (S)-tert-Butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (300 mg,
30 0.814 mmol) was dissolved in DMF (10 mL), cesium carbonate (318 mg, 0.977 mmol) was added and the reaction mixture stirred for 15 min at 50°C. (3,3-difluorocyclobutyl)-methyl 4-methylbenzenesulfonate (247 mg, 0.896 mmol) was added and the reaction

mixture stirred for 30min at 50°C and subsequently overnight at room temperature. Water was added, the reaction mixture extracted three times with ethyl acetate, the organic phases were combined and dried over sodium sulfate. Evaporation of the solvent and purification of the raw material by column chromatography resulted in (S)-tert-butyl 2-
5 ((4-((3,3-difluorocyclobutyl)methoxy)-5-fluoro-2-methoxybenzyl)carbamoyl)-pyrrolidine-1-carboxylate as white foam (363 mg; 94% yield).

After BOC deprotection and salt formation the desired product (2S)-N-[[4-[(3,3-difluorocyclobutyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide fumaric acid salt was obtained as white powder after lyophilization.

10 LC-MS (M/Z [M+H]⁺): 373.1

¹H NMR (600 MHz, methanol-*d*₄) δ 7.01 (d, *J* = 11.5 Hz, 1H), 6.74 (d, *J* = 7.0 Hz, 1H), 6.68 (s, 2H), 4.35, 4.31 (ABq, *J* = 14.8 Hz, 2H), 4.20 (dd, *J* = 8.5, 6.9 Hz, 1H), 4.11 (d, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 3.39 (dt, *J* = 11.3, 7.1 Hz, 1H), 3.33 – 3.26 (m, 1H), 2.76 – 2.65 (m, 2H), 2.65 – 2.56 (m, 1H), 2.56 – 2.43 (m, 2H), 2.43 – 2.34 (m, 1H), 2.07 –
15 1.93 (m, 3H).

Example 30:

(2S)-N-[[5-Fluoro-2-methoxy-4-[(2,2,3,3-tetrafluorocyclobutyl)methoxy]phenyl]-methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

20 The compound was prepared according to example 11 by Mitsunobu reaction starting from (2,2,3,3-tetrafluorocyclobutyl)methanol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-2-methoxy-4-[(2,2,3,3-tetrafluorocyclobutyl)-
25 methoxy]phenyl]methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

MS(APCI⁺) (M/Z [M+H]⁺): 409

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.05 (d, *J* = 11.7 Hz, 1H), 6.85 (d, *J* = 7.1 Hz, 1H), 4.38 – 4.25 (m, 2H), 4.23 (s, 2H), 4.15 (t, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.36 (s, 1H),
30 3.22 (ddt, *J* = 29.1, 11.3, 7.1 Hz, 2H), 2.85 (td, *J* = 15.4, 7.2 Hz, 1H), 2.31 (ddd, *J* = 14.8, 12.5, 6.9 Hz, 1H), 1.98 – 1.72 (m, 3H).

Example 31:

(2S)-N-[[4-[(3,3-Difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its fumaric acid addition salt

The compound was prepared according to example 19 by Mitsunobu reaction starting from (3,3-difluorocyclopentyl)methanol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and salt formation the desired product (2S)-N-[[4-[(3,3-difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide fumaric acid salt was obtained as white powder after lyophilization.

LC-MS (M/Z [M+H]⁺): 387.2

¹H NMR (500 MHz, methanol-*d*₄) δ 7.01 (d, *J* = 11.5 Hz, 1H), 6.72 (d, *J* = 7.1 Hz, 1H), 6.69 (s, 2H), 4.35, 4.30 (ABq, *J* = 14.8 Hz, 2H), 4.22 (dd, *J* = 8.4, 6.8 Hz, 1H), 4.07 – 3.97 (m, 2H), 3.84 (s, 3H), 3.39 (dt, *J* = 11.4, 7.1 Hz, 1H), 3.35 – 3.26 (m, 1H), 2.69 – 2.56 (m, 1H), 2.45 – 2.34 (m, 1H), 2.34 – 2.25 (m, 1H), 2.25 – 2.13 (m, 1H), 2.13 – 1.91 (m, 6H), 1.77 – 1.64 (m, 1H).

Example 32:

(2S)-N-[[4-[(4,4-Difluorocyclohexyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its fumaric acid addition salt

The compound was prepared according to example 19 by Mitsunobu reaction starting from (4,4-difluorocyclohexyl)methanol and (S)-tert-butyl 2-((5-fluoro-4-hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and salt formation the desired product (2S)-N-[[4-[(4,4-difluorocyclohexyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide fumaric acid salt was obtained as white powder after lyophilization.

LC-MS (M/Z [M+H]⁺): 401.2

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.66 (t, *J* = 5.8 Hz, 1H), 7.00 (d, *J* = 11.9 Hz, 1H), 6.80 (d, *J* = 7.3 Hz, 1H), 6.52 (s, 2H), 4.19 (d, *J* = 5.8 Hz, 2H), 4.07 – 4.00 (m, 1H), 3.96 (d, *J* = 6.2 Hz, 2H), 3.81 (s, 3H), 3.12 – 3.05 (m, 2H), 2.23 – 2.13 (m, 1H), 2.09 – 1.99 (m, 2H), 1.94 – 1.84 (m, 4H), 1.83 – 1.71 (m, 4H), 1.39 – 1.27 (m, 2H).

Example 33:

(S)-N-(5-Fluoro-4-((trans-4-trifluoromethyl-cyclohexyl)oxy)-2-methoxybenzyl)-pyrrolidine-2-carboxamide and its fumaric acid addition salt

The compound was prepared according to example 19 by Mitsunobu reaction starting from cis 4-(trifluoromethyl)cyclohexanol and (S)-tert-butyl 2-((5-fluoro-4-
5 hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection and salt formation the desired product (S)-N-(5-fluoro-4-((trans-4-trifluoromethyl-cyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide fumaric acid salt was obtained as white powder.

LC-MS (M/Z [M+H]⁺): 419.2

10 ¹H NMR (500 MHz, methanol-*d*₄) δ 7.00 (d, *J* = 11.6 Hz, 1H), 6.74 (d, *J* = 6.9 Hz, 1H), 6.70 (s, 2H), 4.36, 4.31 (d, *J* = 14.7 Hz, 2H), 4.28 – 4.19 (m, 2H), 3.83 (s, 3H), 3.40 (dt, *J* = 11.3, 7.1 Hz, 1H), 3.34 – 3.29 (m, 1H), 2.45 – 2.34 (m, 1H), 2.25 – 2.14 (m, 3H), 2.09 – 1.93 (m, 5H), 1.56 – 1.41 (m, 4H).

15 Example 34:

(S)-N-(5-Fluoro-4-((cis-4-trifluoromethyl-cyclohexyl)oxy)-2-methoxybenzyl)-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 19 by Mitsunobu reaction starting from trans 4-(trifluoromethyl)cyclohexanol and (S)-tert-butyl 2-((5-fluoro-4-
20 hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with TFA the desired product (S)-N-(5-fluoro-4-((cis-4-trifluoromethyl-cyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide 2,2,2-trifluoroacetic acid salt was obtained as off white foam after lyophilization.

LC-MS (M/Z [M+H]⁺): 419.2

25 ¹H NMR (600 MHz, methanol-*d*₄) δ 7.02 (d, *J* = 11.4 Hz, 1H), 6.74 (d, *J* = 7.0 Hz, 1H), 4.66 – 4.62 (m, 1H), 4.36, 4.32 (ABq, *J* = 14.7 Hz, 2H), 4.20 (dd, *J* = 8.5, 6.9 Hz, 1H), 3.82 (s, 3H), 3.42 – 3.36 (m, 1H), 3.31 – 3.26 (m, 1H), 2.44 – 2.35 (m, 1H), 2.28 – 2.18 (m, 1H), 2.09 (dd, *J* = 13.8, 3.4 Hz, 2H), 2.07 – 1.94 (m, 3H), 1.82 – 1.69 (m, 4H), 1.68 – 1.59 (m, 2H).

30

Example 35:

(2S)-N-[[5-Fluoro-2-methoxy-4-[3-(trifluoromethyl)cyclohexoxy]phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 11 by Mitsunobu reaction starting from 3-(trifluoromethyl)cyclohexanol and (S)-tert-butyl 2-((5-fluoro-4-
5 hydroxy-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate. After BOC deprotection with HCl and purification of the raw material by reverse phase HPLC (TFA method) the desired product (2S)-N-[[5-fluoro-2-methoxy-4-[3-(trifluoromethyl)cyclohexoxy]phenyl]methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

10 MS(APCI+) (M/Z [M+H]⁺): 419

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.04 (d, *J* = 11.8 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 4.47 – 4.35 (m, 1H), 4.23 (s, 2H), 4.17 (t, *J* = 7.9 Hz, 1H), 3.79 (s, 3H), 3.23 (ddt, *J* = 30.9, 11.5, 7.1 Hz, 2H), 2.33 (ddd, *J* = 15.0, 12.3, 6.4 Hz, 1H), 2.19 (d, *J* = 11.8 Hz, 1H), 2.08 (d, *J* = 11.3 Hz, 1H), 1.99 – 1.75 (m, 5H), 1.69 – 1.24 (m, 5H).

15

Example 36:

(2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide and its hydrochloride

(S)-N-(5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)benzyl)pyrrolidine-2-
20 carboxamide (22 mg, 0.058 mmol; example 20) was dissolved in DCE (2 mL) under nitrogen and formaldehyde (0.434 mL, 5.75 mmol) and sodium triacetoxyborohydride (31.4 mg, 0.144 mmol) were added. The reaction mixture was stirred at room temperature overnight. Subsequently EtOAc and saturated NaHCO₃-solution were added, the organic layer was separated, the NaHCO₃-layer was washed twice with EtOAc and the
25 combined organic layers were dried with sodium sulfate, filtered and concentrated. The compound was purified by flash chromatography to obtain (2S)-N-[[5-fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide as white foam (17 mg, yield 67%). One equivalent hydrochloric acid and water were added and the resulting solution lyophilized to obtain (2S)-N-[[5-fluoro-2-
30 methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide hydrochloride as white powder.

LC-MS (M/Z [M+H]⁺): 397.2

¹H NMR (500 MHz, methanol-*d*₄) δ 7.02 (d, *J* = 11.5 Hz, 1H), 6.82 (d, *J* = 6.9 Hz, 1H), 6.31 (tt, *J* = 52.6, 5.2 Hz, 1H), 4.54 (tt, *J* = 12.5, 1.7 Hz, 2H), 4.34, 4.30 (ABq, *J* = 15.0 Hz, 2H), 3.85 (s, 3H), 3.27 – 3.21 (m, 1H), 3.13 (br s, 1H), 2.60 – 2.51 (m, 1H), 2.47 (s, 3H), 2.33 – 2.22 (m, 1H), 1.95 – 1.79 (m, 3H).

5

Example 37:

(2S)-N-[[4-(3,3-Difluorocyclobutoxy)-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide and its hydrochloride

The compound was prepared according to example 36 by reductive amination starting from (S)-N-(4-(3,3-difluorocyclobutoxy)-5-fluoro-2-methoxybenzyl)-1-methyl-pyrrolidine-2-carboxamide (example 28) and formaldehyde. The desired product (2S)-N-[[4-(3,3-difluorocyclobutoxy)-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide hydrochloride salt was obtained as white powder after lyophilization.

15 LC-MS (M/Z [M+H]⁺): 373.2

¹H NMR (500 MHz, methanol-*d*₄) δ 6.98 (d, *J* = 11.5 Hz, 1H), 6.59 (d, *J* = 7.0 Hz, 1H), 4.84 – 4.76 (m, 1H), 4.32, 4.28 (ABq, *J* = 14.9 Hz, 2H), 3.84 (s, 3H), 3.28 – 3.20 (m, 1H), 3.17 – 3.04 (m, 3H), 2.82 – 2.66 (m, 2H), 2.54 (q, *J* = 8.5 Hz, 1H), 2.46 (s, 3H), 2.33 – 2.20 (m, 1H), 1.94 – 1.78 (m, 3H).

20

Example 38:

(2S)-N-[[4-[(3,3-Difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide and its fumaric acid addition salt

The compound was prepared according to example 36 by reductive amination starting from (2S)-N-[[4-[(3,3-difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide (example 31) and formaldehyde. The desired product (2S)-N-[[4-[(3,3-difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide fumaric acid salt was obtained as white powder after lyophilization.

30 LC-MS (M/Z [M+H]⁺): 401.2

¹H NMR (500 MHz, methanol-*d*₄) δ 7.00 (d, *J* = 11.5 Hz, 1H), 6.73 (d, *J* = 7.0 Hz, 1H), 6.70 (s, 2H), 4.36, 4.31 (ABq, *J* = 14.7 Hz, 2H), 4.07 – 3.97 (m, 2H), 3.84 (s, 3H), 3.79

(dd, $J = 9.1, 6.9$ Hz, 1H), 3.62 – 3.54 (m, 1H), 3.02 (dt, $J = 11.0, 8.3$ Hz, 1H), 2.79 (s, 3H), 2.68 – 2.57 (m, 1H), 2.53 – 2.41 (m, 1H), 2.37 – 2.25 (m, 1H), 2.25 – 1.91 (m, 7H), 1.77 – 1.64 (m, 1H).

5 Example 39:

(2S)-N-(5-Fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)oxy)benzyl)-1-methyl-pyrrolidine-2-carboxamide and its fumaric acid addition salt

The compound was prepared according to example 36 by reductive amination starting from (S)-N-(5-fluoro-4-((trans-4-trifluoromethyl-cyclohexyl)oxy)-2-
10 methoxybenzyl)pyrrolidine-2-carboxamide (example 33) and formaldehyde. The desired product (2S)-N-(5-fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)-oxy)benzyl)-1-methyl-pyrrolidine-2-carboxamide fumaric acid salt was obtained as white powder after lyophilization.

LC-MS (M/Z [M+H]⁺): 433.2

15 ¹H NMR (500 MHz, methanol-*d*₄) δ 6.99 (d, $J = 11.4$ Hz, 1H), 6.74 (d, $J = 7.0$ Hz, 1H), 6.70 (s, 2H), 4.36, 4.31 (ABq, $J = 14.7$ Hz, 2H), 4.28 – 4.20 (m, 1H), 3.83 (s, 3H), 3.78 (dd, $J = 9.0, 6.8$ Hz, 1H), 3.62 – 3.53 (m, 1H), 3.06 – 2.97 (m, 1H), 2.78 (s, 3H), 2.53 – 2.39 (m, 1H), 2.25 – 2.15 (m, 3H), 2.15 – 2.05 (m, 1H), 2.05 – 1.92 (m, 4H), 1.56 – 1.41

20 Example 40:

(2S)-N-[[4-(4,4-Difluorocyclohexoxy)-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide and its fumaric acid addition salt

To a mixture (4-((4,4-difluorocyclohexyl)oxy)-5-fluoro-2-
methoxyphenyl)methanamine (0.225 g, 0.778 mmol; see example 18) in DMF (7.8 mL),
25 (S)-1-methylpyrrolidine-2-carboxylic acid (0.121 g, 0.933 mmol), DIPEA (0.272 mL, 1.556 mmol) and HBTU (0.354 g, 0.933 mmol) were added at 0°C. The reaction mixture was stirred at 0°C for 1h and overnight at room temperature. Data LCMS showed MS of the desired product. Water was added to the reaction mixture and extracted three times with tert.-butylmethylether. The combined organic phases were washed once with
30 water and brine, dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (EtOAc/heptane 20:80 -> 80:20, 12g-column, flow 12ml/min) to obtain the desired product (2S)-N-[[4-(4,4-difluorocyclohexoxy)-5-

fluoro-2-methoxy-phenyl)methyl]-1-methyl-pyrrolidine-2-carboxamide (244 mg, 78% yield) as colorless oil. (2S)-N-[[4-(4,4-difluorocyclohexoxy)-5-fluoro-2-methoxy-phenyl)methyl]-1-methyl-pyrrolidine-2-carboxamide fumaric acid salt was obtained as white foam (305 mg, yield 97%).

5 LC-MS (M/Z [M+H]⁺): 401.2

¹H NMR (500 MHz, DMSO-*d*₆) δ 8.13 (t, *J* = 6.2 Hz, 1H), 6.91 (d, *J* = 11.8 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.61 (s, 2H), 4.66 – 4.58 (m, 1H), 4.23 – 4.10 (m, 2H), 3.79 (s, 3H), 3.07 (tt, *J* = 6.6, 2.7 Hz, 1H), 2.87 (dd, *J* = 9.4, 5.5 Hz, 1H), 2.38 – 2.28 (m, 4H), 2.16 – 1.89 (m, 5H), 1.89 – 1.80 (m, 4H), 1.80 – 1.64 (m, 3H)

10

Example 41:

(2S)-N-[[5-Fluoro-2-methoxy-4-[trans 4-(trifluoromethyl)cyclohexoxy]phenyl]-methyl]azetidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

To a solution of potassium 2-methylpropan-2-olate (0.280 g, 2.498 mmol) in THF
15 (4 mL) was added dropwise a solution of trans-4-(trifluoromethyl)cyclohexanol (0.4 g, 2.379 mmol) in THF (2 mL) at 0°C, then it was stirred for 1 hour, the resulting above solution was added dropwise to a solution of 2,4,5-trifluorobenzonitrile (0.448 g, 2.85 mmol) in THF (4 mL) at -70°C over 40 minutes. Then the reaction mixture was stirred at -70°C for 3 h and allowed to warm to 20°C over 1.5 h and stirred at 20°C for 16 h. It
20 was quenched with water, extracted with EtOAc three times, the extracts were washed with brine, dried over Na₂SO₄, filtered, concentrated to give the crude product, which was recrystallized from PE/EtOAc (5:1) to give 2,5-difluoro-4-((trans-4-(trifluoromethyl)cyclohexyl)oxy)benzonitrile (0.480 g, 1.573 mmol, 66.1 % yield) as light yellow solid.

25 To a solution of potassium 2-methylpropan-2-olate (0.239 g, 2.129 mmol) in THF (4 mL) was added dropwise a solution of methanol (0.0789 g, 2.457 mmol) in THF (1 mL) at 0°C, then it was stirred for 1 hour, the resulting above solution was added dropwise to a solution of 2,5-difluoro-4-(trans-4-(trifluoromethyl)cyclohexyl)oxy)-benzonitrile (0.5 g, 1.638 mmol) in THF (5 mL) at -50°C over 30 minutes. Then the
30 reaction mixture was stirred at -50°C for 3 h and allowed to warm to 20°C over 1.5 h and stirred at 20°C for 16 h. It was quenched with water, extracted with EtOAc three times, the extracts were washed with brine, dried over Na₂SO₄, filtered, concentrated to

give the crude product, which was recrystallized from PE/EtOAc (5:1) to give 5-fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)oxy)benzotrile (0.4 g, 1.261 mmol, 77 % yield) as white solid.

To a solution of 5-fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)-oxy)benzotrile (0.1 g, 0.315 mmol) in MeOH (4 mL) was added Pd/C (0.1 g, 10%, wet) and hydrogen chloride (0.263 mL, 3.15 mmol), the resulting mixture was stirred at 25°C under H₂ atmosphere (40 psi) for 16 h. Then it was filtered, concentrated under reduced pressure to give (5-fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)-oxy)phenyl)methanamine hydrochloride (0.1 g, 98% yield) as light yellow solid.

In 4 ml vial a solution of (S)-1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid (29mg, 0.14mmol) was added dissolved in N,N-dimethylacetamide (0.5mL), followed by a solution of HATU (76mg, 0.2 mmol) dissolved in N,N-dimethylacetamide (0.5ml), followed by 34μL of N,N-diisopropylethylamine neat. Then a solution of (5-fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)methanamine (31mg, 0.1mmol) dissolved in N,N-dimethylacetamide (1.0μL) was added, and the reaction was shaken at room temperature for 4 hours. Then the reaction was concentrated to dryness and 1.0mL of HCl/dioxane was added and shaken for 2 hours. After that the reaction was concentrated to dryness and was re-dissolved in 1800 μL of a 1:1 v/v solution of DMSO/MeOH, checked by LC/MS and purified by reverse phase HPLC (TFA method) to provide the desired compound (2S)-N-[[5-fluoro-2-methoxy-4-[trans 4-(trifluoromethyl)cyclohexoxy]phenyl]methyl]azetidine-2-carboxamide as 2,2,2-trifluoroacetic acid salt (29% yield).

MS(APCI+) (M/Z [M+H]⁺): 405

¹H NMR (400 MHz, DMSO-d₆/D₂O, Temp = 27°C) δ 7.03 (d, J = 11.6 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 4.98 – 4.80 (m, 1H), 4.45 – 4.29 (m, 1H), 4.22 (s, 2H), 4.07 – 3.92 (m, 1H), 3.81 – 3.72 (m, 4H), 2.74 – 2.60 (m, 1H), 2.46 – 2.23 (m, 2H), 2.23 – 2.06 (m, 2H), 2.03 – 1.82 (m, 2H), 1.52 – 1.34 (m, 4H).

Example 42:

2,3,3,4,4,5,5-Heptadeuterio-N-[[5-fluoro-2-methoxy-4-[4-(trifluoromethyl)cyclohexoxy]phenyl]methyl]pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

The compound was prepared according to example 41 by peptide coupling of (5-fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)oxy)phenyl)methanamine with deuterated (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid-D₇. After BOC deprotection with TFA and purification of the raw material by reverse phase HPLC the desired product 2,3,3,4,4,5,5-heptadeuterio-N-[[5-fluoro-2-methoxy-4-[4-(trifluoromethyl)cyclohexoxy]phenyl]methyl]pyrrolidine-2-carboxamide was obtained as 2,2,2-trifluoroacetic acid salt.

MS (ESI+) m/z [M+H]⁺: 426,30

10 Example 43:

(2S)-N-[[5-Fluoro-4-[4-(fluoromethyl)cyclohexoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide and its 2,2,2-trifluoroacetic acid addition salt

43.1 4-((4-(((tert-Butyldimethylsilyl)oxy)methyl)cyclohexyl)oxy)-5-fluoro-2-methoxybenzonitrile:

15 To 185 mg sodium hydride (50% weight percent, 3.85 mmol, 2.10 eq.) in DMF (30 ml) was added 493 mg 4-((tert-butyldimethylsilyl)oxy)methyl)cyclohexanol (2.02 mmol, 1.1 eq.) under an argon atmosphere at room temperature. The reaction mixture was stirred for 10 h at room temperature. 310 mg 4,5-Difluoro-2-methoxybenzonitrile (1.833 mmol, 1.0 eq.) was added and the reaction mixture was heated to 60°C for 2 h.

20 The reaction mixture was allowed to cool to room temperature and water was slowly added. The reaction mixture was extracted with ethyl acetate. The combined organic phases were washed twice with water and once with brine, dried with MgSO₄. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (eluent: 0-10% methanol in dichloromethane) to yield the title

25 compound (574 mg, 80% yield).

ESI-MS: m/z (%): 394.30 (100, [M+H]⁺).

43.2 4-((4-(((tert-Butyldimethylsilyl)oxy)methyl)cyclohexyl)oxy)-5-fluoro-2-methoxyphenyl)methanamine:

To a solution of 290 mg 4-((4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)-oxy)-5-fluoro-2-methoxybenzonitrile (0.737 mmol, 1.00 eq) in THF (10 ml) was slowly added 1.1 ml of a 2 molar borane-methyl sulfide complex in THF solution (2.21 mmol, 3.00 eq.). The reaction mixture was heated in a microwave unit to 60°C for 1 h. The

30

reaction mixture was cooled to 0°C and slowly aqueous ammonium chloride solution was added. The reaction mixture was extracted with dichloromethane. The organic phase was dried with MgSO₄, filtrated and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (eluent: 5 0-10% methanol in dichloromethane) to yield the title compound (116 mg, 40% yield). ESI-MS: m/z (%): 381.30 (100, [M-CH₃]⁺).

43.3 (S)-tert-Butyl 2-((4-((4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)oxy)-5-fluoro-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate:

57.4 mg Boc-L-Proline (0.267 mmol, 1.00 eq) was dissolved in DMF (10 ml) and 10 43.2 mg 1,1'-carbonyldiimidazole (CDI) was added. The mixture was heated to 50°C for 30 min. 106 mg (4-((4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexyl)oxy)-5-fluoro-2-methoxyphenyl)methanamine (0.267 mmol, 1.00 eq) was dissolved in pyridine (10 ml) and then added to the reaction mixture which was then further heated for 5 h at 80°C and overnight at room temperature. The reaction mixture was evaporated under 15 reduced pressure and codistilled twice with toluene. The obtained residue was partitioned between bicarbonate solution and ethyl acetate. The organic phase was separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic phases were washed with bicarbonate solution, dried with MgSO₄, filtrated and the solvent was evaporated under reduced pressure. The crude product was purified by column 20 chromatography on silica (eluent: 0-10% methanol in dichloromethane) to yield the title compound (86 mg, 54% yield).

ESI-MS: m/z (%): 617.40 (100, [M+Na]⁺).

43.4 (S)-tert-Butyl 2-(((5-fluoro-4-((4-(hydroxymethyl)cyclohexyl)oxy)-2-methoxybenzyl)methyl)carbamoyl)pyrrolidine-1-carboxylate:

25 To a solution of 83 mg (S)-tert-butyl 2-((5-fluoro-4-((4-hydroxymethyl)cyclohexyl)oxy)-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (0.140 mmol, 1.00 eq) in THF (6 mL) was added 0.28 mL tetrabutylammonium fluoride (1M in THF, 0.28 mmol, 2.00 eq). The mixture was stirred at room temperature for 18 h. Then a saturated aqueous NH₄Cl solution was added and the mixture was extracted with ethyl acetate. 30 The organic phase was dried over MgSO₄, filtrated and the solvent was evaporated. The crude product was purified by column chromatography on silica (eluent: 0-10% methanol in dichloromethane) to yield the title compound (81%, 0.112 mmol).

ESI-MS: m/z (%): 381.30 (100, [M-Boc+H]⁺), 481.30 (20, [M+H]⁺), 503.30 (80, [M+Na]⁺).

43.5 (S)-tert-Butyl 2-(((5-fluoro-2-methoxy-4-((4-(((methylsulfonyl)oxy)methyl)cyclohexyl)oxy)benzyl)methyl)carbamoyl)pyrrolidine-1-carboxylate:

5 A solution of 54 mg (S)-tert-butyl 2-(((5-fluoro-4-((4-(hydroxymethyl)cyclohexyl)oxy)-2-methoxybenzyl)methyl)carbamoyl)pyrrolidine-1-carboxylate (0.112 mmol, 1.00 eq) and 0.031 mL triethylamine (0.225 mmol, 2.00 eq) in dichloromethane (2 ml) was cooled to 0°C and 14.2 mg methanesulfonyl chloride (0.124 mmol, 1.10 eq) was slowly added. Then the mixture was warmed to room temperature and stirred for 2
10 h. Then water was added and the solution was extracted with dichloromethane. The organic phase was dried over MgSO₄, filtrated, the solvent was evaporated. The crude product was purified by column chromatography on silica (eluent: 0-10% methanol in dichloromethane) to yield the title compound (30 mg, 48% yield).

ESI-MS: m/z (%): 459.30 (100, [M-Boc+H]⁺), 581.30 (90, [M+Na]⁺).

15 43.6 (S)-tert-Butyl 2-(((5-fluoro-4-((4-(fluoromethyl)cyclohexyl)oxy)-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate:

A solution of 33 mg (S)-tert-butyl 2-(((5-fluoro-2-methoxy-4-((4-(((methylsulfonyl)oxy)methyl)cyclohexyl)oxy)benzyl)carbamoyl)pyrrolidine-1-carboxylate (0.054 mmol, 1.00 eq) and 32.6 mg cesium fluoride (0.215 mmol, 4.00 eq) in t-butanol
20 (2 ml) was heated in the microwave at 80 °C for 18h and at 90°C for 32h. Then a saturated aqueous NaHCO₃ solution was added and the mixture was extracted with dichloromethane. The combined organic phases were dried over MgSO₄ and the solvent was evaporated. The crude product was purified by column chromatography on silica (eluent: 0-10% methanol in dichloromethane) to yield the title compound (19.7 mg,
25 76% yield).

ESI-MS: m/z (%): 383.20 (90, [M-Boc+H]⁺), 505.20 (100, [M+Na]⁺).

43.7 (S)-N-((5-Fluoro-4-((4-(fluoromethyl)cyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide, trifluoroacetate:

A solution of 19.7 mg (S)-tert-butyl 2-(((5-fluoro-4-((4-(fluoromethyl)cyclohexyl)oxy)-2-methoxybenzyl)carbamoyl)pyrrolidine-1-carboxylate (0.041 mmol,
30 1.00eq) and 0.016 mL trifluoroacetic acid (0.204 mmol, 5.00 eq) in dichloromethane (2 mL) was stirred at room temperature for 24 h. Then the solvent was evaporated and the

crude product was purified via preparative HPLC to yield the title compound as TFA salt (1.4 mg, 7% yield).

ESI-MS: m/z (%): 383.20 (100, [M+H]⁺).

¹H NMR (600 MHz, CDCl₃): δ 7.40 (bs, 1H), 6.95 (d, 1H), 6.55 (d, 1H), 4.60 (m, 1H),
5 4.35 (m, 2H), 4.30 (m, 1H), 4.20 (m, 1H), 4.10 (m, 1H), 3.80 (s, 3H), 3.40 (m, 1H), 3.35
(m, 1H), 2.40 (m, 1H), 2.15 (m, 2H), 2.10 – 1.95 (m, 3H), 1.90 (m, 2H), 1.75 – 1.60 (m,
2H), 1.55 – 1.45 (m, 2H), 1.20 – 1.10 (m, 2H).

II. Biological tests

10

Functional activity

1. Human 5-HT_{2C} Functional Assay

The functional activity of compounds of formula I was assayed by incubation with
15 U2OS_HTR_{2C}_β-Arrestin cells (DiscoverX, 93-0289C3) to induce beta-arrestin2 re-
cruitment to the 5-HT_{2C} receptor. The agonist-induced recruitment and proximity of the
receptor and beta-arrestin2 leads to complementation and formation of active β-
galactosidase. The enzyme complementation results in enzyme activity, which is meas-
ured following the termination of the agonist incubation using DiscoverX's detection
20 reagent, which contains a chemiluminescent substrate which produces a high intensity
signal. Cells were plated and a medium-change to a 1% serum containing medium was
performed 24h later. The next day, test compounds were added and incubated for 1.5 h
before addition of detection reagent.

The response produced was measured and compared with the response produced by 10
25 [μ]M 5-HT or the maximal effect induced by 5-HT (defined as 100%) to which it was
expressed as a percentage response (relative efficacy). Dose response curves were con-
structed using Graphpad Prism (Graph Software Inc.) or using in house adapted soft-
ware using a 4 parameter dose response model with variable slope (fit = (Bottom +
(Top-Bottom)/(1+10^{^(-(LogEC50-x)*HillSlope))}res = (y-fit)). Results are compiled in
30 the table below.

2. Human 5-HT_{2A} Functional Assay

Functional activity on the 5-HT_{2A} receptor was determined by testing the effect of the compounds I on calcium mobilisation in CHO-K1 cells, stably transfected with human 5-HT_{2A} receptor. Cells were seeded into sterile black 384-well plates with clear bottom at 25,000 cells/well in a volume of 25 µl and grown for 5-6 hours at 37°C, in 5% CO₂ in tissue culture medium (“Ultra CHO” by LONZA), containing 1% dialysed FCS and 50 µg/ml gentamicin (Invitrogen). After this incubation, medium was replaced by a serum free version of the same tissue culture medium followed by incubation overnight at 37°C and in 5% CO₂. Cells were then loaded with a fluorescent calcium-sensitive dye in the presence of 0.07% probenecid for an hour at 37°C, according to the manufacturer’s protocol (Ca5-Assay Kit, Molecular Devices), followed by an additional 60 min incubation at room temperature. Serial compound dilutions (final concentrations of 10⁻¹⁰ to 10⁻⁵M, prepared in HBSS + 50 mM HEPES) were first added to the cells alone (“first addition” to assess agonism on the 5-HT_{2A} receptor), then after 8 min, serotonin was added to the same wells at a final concentration of 3×10⁻⁸ M (“second addition” to see potential antagonistic effect) and the maximal calcium response was determined using a FLIPR® Tetra instrument (Molecular Devices) in each of the two steps. The relative efficacy of the compounds was calculated as a percentage of the maximal effect induced by serotonin alone (defined as 100%). To determine EC₅₀/IC₅₀ values, concentration-response curves were fitted using a four-parameter logistic equation (IDBS Bio-book™). K_b values were calculated from IC₅₀ values, according to Cheng & Prusoff.

3. Human 5-HT_{2B} Functional Assay

Functional activity on the 5-HT_{2B} receptor was determined by testing the effect of the compounds I on calcium mobilisation in CHO-FlpIn cells, stably transfected with human 5-HT_{2B} receptor. Cells were seeded into sterile black 384-well plates with clear bottom at 30,000 cells/well in a volume of 25 µl and grown overnight at 37°C, in 5% CO₂ in tissue culture medium (“CHO-S-SFM II” by Invitrogen), containing 1% dialysed FCS and 50 µg/ml gentamicin (Invitrogen). On the next morning, medium was replaced by a serum free version of the same tissue culture medium for a further incubation for 4 hours at 37°C and in 5% CO₂. Cells were then loaded with a fluorescent calcium-sensitive dye in the presence of 0.07% probenecid for an hour at 37°C, according to the manufacturer’s protocol (Ca5-Assay Kit, Molecular Devices), followed by an

additional 60 min incubation at room temperature. Serial compound dilutions (final concentrations of 10^{-10} to 10^{-5} M, prepared in HBSS + 50 mM HEPES) were first added to the cells alone (“first addition” to assess agonism on the 5-HT_{2B} receptor), then after 8 min, serotonin was added to the same wells at a final concentration of 10^{-8} M (“second addition” to see potential antagonistic effect) and the maximal calcium response was determined using a FLIPR® Tetra instrument (Molecular Devices) in each of the two steps. The relative efficacy of the compounds was calculated as a percentage of the maximal effect induced by serotonin alone (defined as 100%). To determine EC₅₀/IC₅₀ values, concentration-response curves were fitted using a four-parameter logistic equation (IDBS Biobook™). K_b values were calculated from IC₅₀ values, according to Cheng & Prusoff.

4. Metabolic Stability

Samples of the tested compounds (0.5 μM) were preincubated together with rat liver microsomes (0.25 mg of microsomal protein/mL) in 0.05 M potassium phosphate buffer of pH 7.4 in microtiter plates at 37 °C for 5 minutes. The reaction was started by adding NADPH (1.0 mM). After 0, 5, 10, 15, 20 and 30 minutes, an aliquot was removed, the reaction was cooled and stopped by adding twice the amount of quench solution consisting of acetonitrile/methanol 1:1, and containing 0.2 μM carbutamide as internal standard. The samples were frozen until analyzed. The remaining concentration of undegraded test substance was determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The half-life (t_{1/2}) was determined from the gradient of the ratio of the signal of (test substance/internal standard)/unit time plot, allowing the calculation of the half-life of the test substance, assuming first order kinetics, from the decrease in the concentration of the compound with time. The microsomal clearance (mClint) was calculated as follows: $mClint = ((\ln(2)/t_{1/2}) / \text{Microsomal Protein Concentration (mg/ml)}) * 1000$, leading to the unit of uL/min/mg. The scaled clearance (mClin_scaled) was calculated as $mClin_scaled = mClint * (\text{Microsomal Yield (mg/kg BW)}) / 1000000 * 60$, leading to the units L/h/kg. The Microsomal Yield is defined by the specifics of the used microsomes. Calculations were modified from references: Di, The Society for Biomolecular Screening, 2003, 453-462; Obach, DMD, 1999 vol 27. N 11, 1350-1359.

Unbound Fraction in Microsomes (fu mic)

A suspension of 0.25 mg/ml microsomal protein spiked with 0.5 μ M of test compound was pipetted on one side of a HTDialysis device (HTDialysis LLC,37 Ledgewood Drive, Gales Fery CT 06335) separated by a membrane with a MWcut off 12-14 K. 50 mM K-Phosphate buffer (pH 7.4) was added on the other side of the well. After incubation at 37°C for 4 h while shaking at 150 rpm, aliquots of both sides were taken, quenched with MeOH/ACN 1:1 and 0.2 μ M of internal standard and frozen until analysis by LCMSMS.

10 Calculation of unbound intrinsic clearance

$$Cl \text{ int unbound} = Cl \text{ int} / fu \text{ mic}$$

The compounds were used in form of their respective acid addition salts.

| Ex. No. | EC50 5-HT _{2C} ¹ | % efficacy | Cl int,mic unb. ² (r) [l/h/kg] |
|---------|--------------------------------------|------------|---|
| 1 | +++ | +++ | + |
| 2 | ++ | +++ | + |
| 3 | +++ | +++ | + |
| 4 | ++ | +++ | + |
| 5 | +++ | +++ | + |
| 6 | + | +++ | + |
| 7 | + | +++ | + |
| 8 | + | +++ | +++ |
| 9 | + | +++ | ++ |
| 10 | + | +++ | ++ |
| 11 | ++ | +++ | + |
| 12 | ++ | +++ | + |
| 13 | +++ | +++ | + |
| 14 | ++ | +++ | + |
| 15 | ++ | +++ | + |

| Ex. No. | EC50 5-HT _{2C} ¹ | % efficacy | Cl int,mic unb. ² (r) [l/h/kg] |
|---------|--------------------------------------|------------|---|
| 16 | + | +++ | +++ |
| 17 | ++ | +++ | +++ |
| 18 | ++ | +++ | +++ |
| 19 | + | +++ | +++ |
| 20 | +++ | +++ | +++ |
| 21 | +++ | +++ | +++ |
| 22 | ++ | +++ | +++ |
| 23 | +++ | +++ | +++ |
| 24 | ++ | +++ | +++ |
| 25 | +++ | +++ | ++ |
| 26 | + | +++ | +++ |
| 27 | ++ | +++ | ++ |
| 28 | ++ | +++ | +++ |
| 29 | ++ | +++ | +++ |
| 30 | +++ | +++ | +++ |

| Ex. No. | EC50 5-HT _{2C} ¹ | % efficacy | Cl int,mic unb. ² (r) [l/h/kg] |
|---------|--------------------------------------|------------|---|
| 31 | ++ | +++ | +++ |
| 32 | ++ | +++ | +++ |
| 33 | +++ | +++ | +++ |
| 34 | ++ | +++ | + |
| 35 | +++ | +++ | ++ |
| 36 | + | +++ | ++ |
| 37 | ++ | +++ | ++ |

| Ex. No. | EC50 5-HT _{2C} ¹ | % efficacy | Cl int,mic unb. ² (r) [l/h/kg] |
|---------|--------------------------------------|------------|---|
| 38 | + | +++ | + |
| 39 | + | +++ | ++ |
| 40 | + | +++ | ++ |
| 41 | +++ | ++ | +++ |
| 42 | +++ | +++ | +++ |
| 43 | + | +++ | +++ |

¹ Potency (EC50 5-HT_{2C}) in functional assay

² unbound intrinsic clearance (human)

Potency (EC50):

- 5 + from 15 nM to < 30 nM
- ++ from 5 nM to < 15 nM
- +++ < 5 nM

% Efficacy:

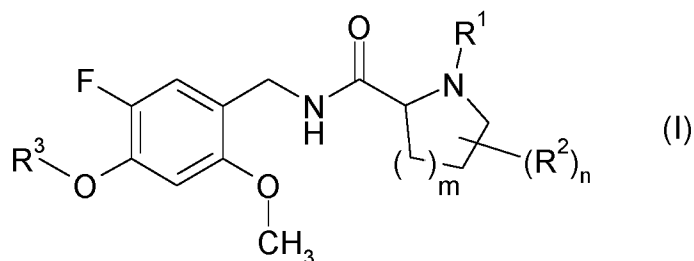
- 10 + from 30 to 50%
- ++ from > 50 to 70%
- +++ > 70%

Unbound intrinsic clearance:

- 15 + from 80 to 250 l/h/kg
- ++ from 30 to < 80 l/h/kg
- +++ < 30 l/h/kg

We claim:

1. A compound of formula I



5 wherein

R^1 is hydrogen or methyl;

R^2 is fluoro or methyl;

10

R^3 is selected from the group consisting of C₃-C₇-cycloalkyl which carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated C₁-C₄-alkyl; fluorinated C₁-C₈-alkyl; C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated C₁-C₄-alkyl; phenyl-C₁-C₄-alkyl, where the phenyl ring carries 1, 2, 3, 4 or 5 substituents selected from the group consisting of fluoro and fluorinated C₁-C₄-alkyl, and may additionally carry one or more substituents selected from the group consisting of Cl, methyl and methoxy; and hetaryl-C₁-C₄-alkyl, where hetaryl is a 5- or 6-membered monocyclic heteroaromatic ring containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S as ring members, where the heteroaryl ring carries 1, 2, 3, 4 or 5 substituents selected from the group consisting of fluoro and fluorinated C₁-C₄-alkyl, and may additionally carry one or more substituents selected from the group consisting of Cl, methyl and methoxy;

15

20

25

m is 0 or 1; and

n is 0 or 1;

or a stereoisomer or a pharmaceutically acceptable salt thereof; or the compound of the general formula I, wherein at least one of the hydrogen atoms has been replaced by deuterium.

5

2. The compound as claimed in claim 1, where R^1 is hydrogen.

10

3. The compound as claimed in any of the preceding claims, where R^3 is C_4 - C_6 -cycloalkyl which carries 1 or 2 substituents selected from the group consisting of fluoro and fluorinated methyl.

4. The compound as claimed in any of claims 1 or 2, where R^3 is fluorinated C_2 - C_6 -alkyl, where the carbon atom of the alkyl group which is bound to O does not carry any fluorine atom.

15

5. The compound as claimed in any of claims 1 or 2, where R^3 is C_3 - C_7 -cycloalkyl-methyl, where the cycloalkyl moiety carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated methyl.

20

6. The compound as claimed in any of claims 1 or 2, where R^3 is phenyl- C_1 - C_2 -alkyl, where the phenyl ring carries 1, 2, 3 or 4 substituents selected from the group consisting of fluoro and fluorinated methyl, and may additionally carry one Cl substituent.

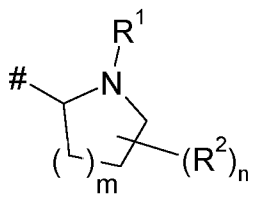
25

7. The compound as claimed in any of claims 1 or 2, where R^3 is hetaryl- C_1 - C_2 -alkyl, where hetaryl is a 5- or 6-membered monocyclic heteroaromatic ring containing 1 heteroatom selected from the group consisting of N and O as ring member, where the heteroaryl ring carries 1 or 2 substituents selected from the group consisting of fluoro and fluorinated methyl.

30

8. The compound as claimed in any of the preceding claims, where m is 1.

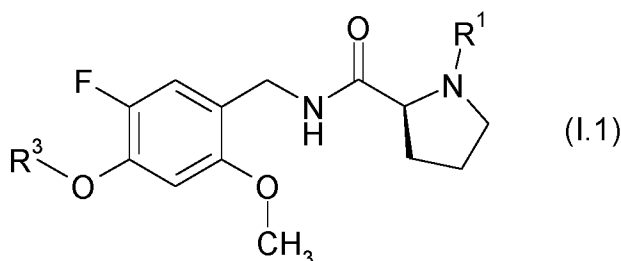
9. The compound as claimed in any of the preceding claims, where n is 0.
10. The compound as claimed in any of the preceding claims, where at least one of the hydrogen atoms of the moiety



5

where # is the attachment point to C(O), has been replaced by a deuterium atom.

11. The compound as claimed in any of claims 1 to 9, of formula I.1



10 where R¹ and R³ are as defined in any of claims 1 to 7.

12. A compound selected from the group consisting of
- (2S)-N-[[5-Fluoro-4-[(3-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
 - 15 - (2S)-N-[[5-Fluoro-2-methoxy-4-[(2,3,5-trifluorophenyl)methoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
 - (2S)-N-[[5-Fluoro-4-[(4-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
 - (2S)-N-[[4-[(2,3-Difluorophenyl)methoxy]-5-fluoro-2-methoxy-phenyl]-methyl]-pyrrolidine-2-carboxamide;
 - 20 - (2S)-N-[[4-[(3,5-Difluorophenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
 - (2S)-N-[[5-Fluoro-4-[(2-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;

- (2S)-N-[[4-[(2-Chloro-3,6-difluoro-phenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-fluoro-4-[(2-fluoro-4-pyridyl)methoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- 5 - (2S)-N-[[5-Fluoro-4-[(5-fluoro-3-pyridyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[5-fluoro-2-methoxy-4-[[6-(trifluoromethyl)-3-pyridyl]methoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-4-[2-(4-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-
10 pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-4-[2-(3-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-
pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-4-[2-(2-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-
pyrrolidine-2-carboxamide;
- 15 - (2S)-N-[[5-Fluoro-2-methoxy-4-[2-[4-(trifluoromethyl)phenyl]ethoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-fluoro-2-methoxy-4-[[5-(trifluoromethyl)-2-furyl]methoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (S)-N-(5-Fluoro-4-((cis-4-fluorocyclohexyl)oxy))-2-
20 methoxybenzyl]pyrrolidine-2-carboxamide; fumaric
- (S)-N-(5-Fluoro-4-((trans-4-fluorocyclohexyl)oxy))-2-
methoxybenzyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[4-(4,4-Difluorocyclohexoxy)-5-fluoro-2-methoxy-phenyl]methyl]-
pyrrolidine-2-carboxamide;
- 25 - (2S)-N-[[5-Fluoro-2-methoxy-4-(3,3,3-trifluoropropoxy)phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]-
pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-4-(2,2,3,4,4,4-hexafluorobutoxy)-2-methoxy-
30 phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoro-1-methyl-propoxy)phenyl]methyl]pyrrolidine-2-carboxamide;

- (2S)-N-[[5-Fluoro-2-methoxy-4-(4,4,4-trifluorobutoxy)phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(3,3,4,4,4-pentafluorobutoxy)phenyl]methyl]-pyrrolidine-2-carboxamide;
- 5 - (2S)-N-[[5-Fluoro-2-methoxy-4-(4,4,4-trifluoro-2-methylbutoxy)phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(2,2-Difluorocyclopropyl)methoxy]-5-fluoro-2-methoxy-phenyl]-methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-[[1-(trifluoromethyl)cyclopropyl]methoxy]-phenyl]methyl]pyrrolidine-2-carboxamide;
- 10 - (2S)-N-[[4-(3,3-Difluorocyclobutoxy)-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(3,3-Difluorocyclobutyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- 15 - (2S)-N-[[5-Fluoro-2-methoxy-4-[(2,2,3,3-tetrafluorocyclobutyl)methoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(3,3-Difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(4,4-Difluorocyclohexyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- 20 - (S)-N-(5-Fluoro-4-((trans-4-trifluoromethyl-cyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide;
- (S)-N-(5-Fluoro-4-((cis-4-trifluoromethyl-cyclohexyl)oxy)-2-methoxybenzyl)-pyrrolidine-2-carboxamide;
- 25 - (2S)-N-[[5-Fluoro-2-methoxy-4-[3-(trifluoromethyl)cyclohexoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide;
- (2S)-N-[[4-(3,3-Difluorocyclobutoxy)-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide;
- 30 - (2S)-N-[[4-[(3,3-Difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide;

- (2S)-N-(5-Fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)oxy)-benzyl)-1-methyl-pyrrolidine-2-carboxamide;
- (2S)-N-[[4-(4,4-Difluorocyclohexoxy)-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide;
- 5 - (2S)-N-[[5-Fluoro-2-methoxy-4-[trans 4-(trifluoromethyl)cyclohexoxy]phenyl]methyl]azetidine-2-carboxamide;
- 2,3,3,4,4,5,5-Heptadeuterio-N-[[5-fluoro-2-methoxy-4-[4-(trifluoromethyl)-cyclohexoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-4-[4-(fluoromethyl)cyclohexoxy]-2-methoxy-phenyl]-
10 methyl]pyrrolidine-2-carboxamide;

or a stereoisomer, a stereoisomeric mixture or a pharmaceutically acceptable salt thereof.

- 15 13. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound as claimed in any of the preceding claims or a stereoisomer or a pharmaceutically acceptable salt thereof, in combination with at least one pharmaceutically acceptable carrier and/or auxiliary substance.
- 20 14. The compound as claimed in any of claims 1 to 12 or a stereoisomer or a pharmaceutically acceptable salt thereof for use as a medicament.
15. The compound as claimed in any of claims 1 to 12 or a stereoisomer or a pharmaceutically acceptable salt thereof for use in the treatment of disorders which respond to the modulation of the 5-HT_{2c} receptor.
25
16. The use of a compound as claimed in any of claims 1 to 12 or of a stereoisomer or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of disorders which respond to the modulation of the 5-HT_{2c} receptor.
30

17. A method for treating disorders which respond to the modulation of the 5-HT_{2c} receptor, which method comprises administering to a subject in need thereof at least one compound as defined in any of claims 1 to 12 or a stereoisomer or a pharmaceutically acceptable salt thereof.
- 5
18. The compound as claimed in claim 15 or the use as claimed in claim 16 or the method as claimed in claim 17, where the disorders are selected from the group consisting of damage of the central nervous system, disorders of the central nervous system, eating disorders, ocular hypertension, cardiovascular disorders, gastrointestinal disorders and diabetes.
- 10
19. The compound or the use or the method as claimed in claim 18, where the disorders are selected from the group consisting of bipolar disorder, depression, atypical depression, mood episodes, adjustment disorders, anxiety, panic disorders, post-traumatic syndrome, psychoses, schizophrenia, cognitive deficits of schizophrenia, memory loss, dementia of aging, Alzheimer's disease, neuropsychiatric symptoms in Alzheimer's disease, behavioral disorders associated with dementia, social phobia, mental disorders in childhood, attention deficit hyperactivity disorder, organic mental disorders, autism, mutism, disruptive behavior disorder, impulse control disorder, borderline personality disorder, obsessive compulsive disorder, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, seizure disorders, epilepsy, substance use disorders, alcohol abuse, cocaine abuse, tobacco abuse, smoking cessation, sexual dysfunction/erectile dysfunction in males, sexual dysfunction in females, premenstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, sleep disorders, sleep apnoea, chronic fatigue syndrome, psoriasis, Parkinson's disease, psychosis in Parkinson's disease, neuropsychiatric symptoms in Parkinson's disease, Lewy Body dementia, neuropsychiatric symptoms in Lewy Body dementia, spinal cord injury, trauma, stroke, pain, bladder dysfunction/urinary incontinence, encephalitis, meningitis, eating disorders, obesity, bulimia, weight loss, anorexia nervosa, ocular hypertension, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, diabetes mellitus, type I diabetes, type II diabetes, type III diabetes, di-
- 15
- 20
- 25
- 30

abetes secondary to pancreatic diseases, diabetes related to steroid use, diabetes complications, hyperglycemia and insulin resistance.

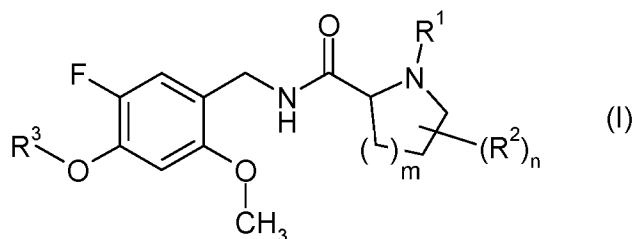
20. The compound or the use or the method as claimed in claim 19, where the disorders are selected from schizophrenia, depression, bipolar disorders, obesity, substance use disorders, neuropsychiatric symptoms in Alzheimer's disease and neuropsychiatric symptoms in Parkinson's disease.

AMENDED CLAIMS

received by the International Bureau on 20 July 2018 (20.07.2018)

We claim:

- 5 1. A compound of formula I



wherein

10 R¹ is hydrogen or methyl;

R² is fluoro or methyl;

15 R³ is selected from the group consisting of C₃-C₇-cycloalkyl which carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated C₁-C₄-alkyl; fluorinated C₁-C₈-alkyl; C₃-C₇-cycloalkyl-C₁-C₄-alkyl, where the cycloalkyl moiety carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated C₁-C₄-alkyl; phenyl-C₁-C₄-alkyl, where the phenyl ring carries 1, 2, 3, 4 or 5 substituents selected from the group consisting of fluoro and fluorinated C₁-C₄-alkyl, and may additionally carry one or more substituents selected from the group consisting of Cl, methyl and methoxy; and hetaryl-C₁-C₄-alkyl, where hetaryl is a 5- or 6-membered monocyclic heteroaromatic ring containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S as ring members, where the heteroaryl ring carries 1, 2, 3, 4 or 5 substituents selected from the group consisting of fluoro and fluorinated C₁-C₄-alkyl, and may additionally carry one or more substituents selected from the group consisting of Cl, methyl and methoxy;

20

25

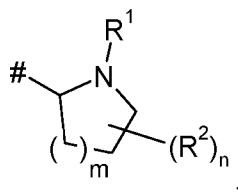
m is 0 or 1; and

n is 0 or 1;

5 or a pharmaceutically acceptable salt thereof.

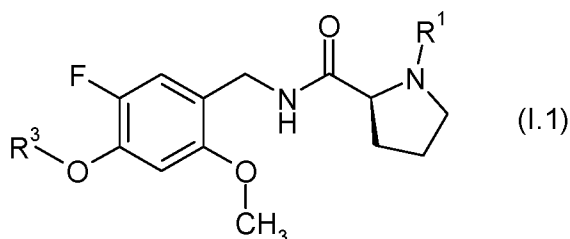
2. The compound as claimed in claim 1, where R¹ is hydrogen.
3. The compound as claimed in any of the preceding claims, where R³ is C₄-C₆-cycloalkyl which carries 1 or 2 substituents selected from the group consisting of
10 fluoro and fluorinated methyl.
4. The compound as claimed in any of claims 1 or 2, where R³ is fluorinated C₂-C₆-alkyl, where the carbon atom of the alkyl group which is bound to O does not
15 carry any fluorine atom.
5. The compound as claimed in any of claims 1 or 2, where R³ is C₃-C₇-cycloalkyl-methyl, where the cycloalkyl moiety carries 1, 2, 3, 4, 5 or 6 substituents selected from the group consisting of fluoro and fluorinated methyl.
20
6. The compound as claimed in any of claims 1 or 2, where R³ is phenyl-C₁-C₂-alkyl, where the phenyl ring carries 1, 2, 3 or 4 substituents selected from the group consisting of fluoro and fluorinated methyl, and may additionally carry one Cl substituent.
25
7. The compound as claimed in any of claims 1 or 2, where R³ is hetaryl-C₁-C₂-alkyl, where hetaryl is a 5- or 6-membered monocyclic heteroaromatic ring containing 1 heteroatom selected from the group consisting of N and O as ring member, where the heteroaryl ring carries 1 or 2 substituents selected from the group consisting of fluoro and fluorinated methyl.
30

8. The compound as claimed in any of the preceding claims, where m is 1.
9. The compound as claimed in any of the preceding claims, where n is 0.
- 5 10. The compound as claimed in any of the preceding claims, where at least one of the hydrogen atoms of the moiety



where # is the attachment point to C(O), has been replaced by a deuterium atom.

- 10 11. The compound as claimed in any of claims 1 to 9, of formula I.1



where R¹ and R³ are as defined in any of claims 1 to 7.

12. A compound selected from the group consisting of
- 15 - (2S)-N-[[5-Fluoro-4-[(3-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-[(2,3,5-trifluorophenyl)methoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-4-[(4-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-
- 20 pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(2,3-Difluorophenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(3,5-Difluorophenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;

- (2S)-N-[[5-Fluoro-4-[(2-fluorophenyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(2-Chloro-3,6-difluoro-phenyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- 5 - (2S)-N-[[5-fluoro-4-[(2-fluoro-4-pyridyl)methoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-4-[(5-fluoro-3-pyridyl)methoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[5-fluoro-2-methoxy-4-[[6-(trifluoromethyl)-3-pyridyl]methoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- 10 - (2S)-N-[[5-Fluoro-4-[2-(4-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-4-[2-(3-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- 15 - (2S)-N-[[5-Fluoro-4-[2-(2-fluorophenyl)ethoxy]-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-[2-[4-(trifluoromethyl)phenyl]ethoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-fluoro-2-methoxy-4-[[5-(trifluoromethyl)-2-furyl]methoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- 20 - (S)-N-(5-Fluoro-4-((cis-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide; fumaric
- (S)-N-(5-Fluoro-4-((trans-4-fluorocyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide;
- 25 - (2S)-N-[[4-(4,4-Difluorocyclohexoxy)-5-fluoro-2-methoxy-phenyl]methyl]-pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(3,3,3-trifluoropropoxy)phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]-pyrrolidine-2-carboxamide;
- 30 - (2S)-N-[[5-Fluoro-4-(2,2,3,4,4,4-hexafluorobutoxy)-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;

- (2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoro-1-methyl-propoxy)phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(4,4,4-trifluorobutoxy)phenyl]methyl]pyrrolidine-2-carboxamide;
- 5 - (2S)-N-[[5-Fluoro-2-methoxy-4-(3,3,4,4,4-pentafluorobutoxy)phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(4,4,4-trifluoro-2-methyl-butoxy)phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(2,2-Difluorocyclopropyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- 10 - (2S)-N-[[5-Fluoro-2-methoxy-4-[[1-(trifluoromethyl)cyclopropyl]methoxy]-phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[4-(3,3-Difluorocyclobutoxy)-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- 15 - (2S)-N-[[4-[(3,3-Difluorocyclobutyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-[(2,2,3,3-tetrafluorocyclobutyl)methoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[4-[(3,3-Difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- 20 - (2S)-N-[[4-[(4,4-Difluorocyclohexyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;
- (S)-N-(5-Fluoro-4-((trans-4-trifluoromethyl-cyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide;
- 25 - (S)-N-(5-Fluoro-4-((cis-4-trifluoromethyl-cyclohexyl)oxy)-2-methoxybenzyl)pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-[3-(trifluoromethyl)cyclohexoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-(2,2,3,3-tetrafluoropropoxy)phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide;
- 30 - (2S)-N-[[4-(3,3-Difluorocyclobutoxy)-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide;

- (2S)-N-[[4-[(3,3-Difluorocyclopentyl)methoxy]-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide;
- (2S)-N-(5-Fluoro-2-methoxy-4-((trans-4-(trifluoromethyl)cyclohexyl)oxy)-benzyl)-1-methyl-pyrrolidine-2-carboxamide;
- 5 - (2S)-N-[[4-(4,4-Difluorocyclohexoxy)-5-fluoro-2-methoxy-phenyl]methyl]-1-methyl-pyrrolidine-2-carboxamide;
- (2S)-N-[[5-Fluoro-2-methoxy-4-[trans 4-(trifluoromethyl)cyclohexoxy]phenyl]methyl]azetidine-2-carboxamide;
- 2,3,3,4,4,5,5-Heptadeuterio-N-[[5-fluoro-2-methoxy-4-[4-(trifluoromethyl)cyclohexoxy]phenyl]methyl]pyrrolidine-2-carboxamide;
- 10 - (2S)-N-[[5-Fluoro-4-[4-(fluoromethyl)cyclohexoxy]-2-methoxy-phenyl]methyl]pyrrolidine-2-carboxamide;

or a pharmaceutically acceptable salt thereof.

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13. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound as claimed in any of the preceding claims or a pharmaceutically acceptable salt thereof, in combination with at least one pharmaceutically acceptable carrier and/or auxiliary substance.
- 20 14. The use of a compound as claimed in any of claims 1 to 12 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of disorders which respond to the modulation of the 5-HT_{2c} receptor.
- 25 15. A method for treating disorders which respond to the modulation of the 5-HT_{2c} receptor, which method comprises administering to a subject in need thereof at least one compound as defined in any of claims 1 to 12 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/023376

| | | | | | |
|--|------------|------------|------------|-----------|-----------|
| A. CLASSIFICATION OF SUBJECT MATTER | | | | | |
| INV. | C07D401/12 | C07D405/12 | C07D207/16 | A61P25/24 | A61P25/14 |
| | A61P9/00 | A61P25/22 | A61P25/28 | A61P25/18 | A61P25/30 |
| | A61P3/10 | A61K31/40 | | | |

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D 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. |
|-----------|--|-----------------------|
| X | LIU K K C ET AL: "Orally active and brain permeable proline amides as highly selective 5HT2c agonists for the treatment of obesity", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 20, no. 7, 1 April 2010 (2010-04-01), pages 2365-2369, XP026971079, ISSN: 0960-894X [retrieved on 2010-01-25] | 1-11, 13-20 |
| A | compounds 8, 11 ----- | 12 |

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

| | |
|---|---|
| <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> | <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> |
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| Date of the actual completion of the international search <p align="center">9 May 2018</p> | Date of mailing of the international search report <p align="center">23/05/2018</p> |
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| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016 | Authorized officer <p align="center">Gutke, Hans-Jürgen</p> |
|--|--|