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(19) **United States**(12) **Patent Application Publication**
Diaz-Fernandez et al.(10) **Pub. No.: US 2008/0280942 A1**(43) **Pub. Date: Nov. 13, 2008**(54) **TETRAHYDRO-BETA-CARBOLIN-SULFONAMIDE
DERIVATIVES AS 5-HT₆ LIGANDS***A61P 3/00* (2006.01)*A61P 25/22* (2006.01)*A61P 25/28* (2006.01)*A61P 25/18* (2006.01)(75) Inventors: **Jose Luis Diaz-Fernandez**,
Barcelona (ES); **Ramon**
Merce-Vidal, Barcelona (ES);
Joerg Holenz, Barcelona (ES)(52) **U.S. Cl. 514/292; 546/87**(57) **ABSTRACT**

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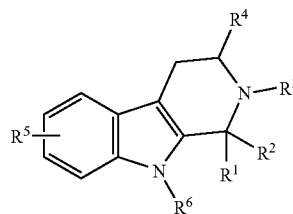
The present invention relates to new tetrahydro-β-carbolin-sulfonamide derivatives of general formula (I), optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of their stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or corresponding physiologically acceptable salts or corresponding solvates. These compounds are suitable as pharmacologically active agents in a medicament for the prophylaxis and/or treatment of disorders or diseases related to 5-HT₆ receptors. The invention also relates to two different methods for obtaining the mentioned compounds and to pharmaceutical compositions containing them.

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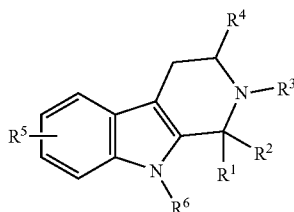
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TETRAHYDRO-BETA-CARBOLIN-SULFONAMIDE DERIVATIVES AS 5-HT₆ LIGANDS

FIELD OF THE INVENTION

[0001] The present invention relates to the use of tetrahydro-β-carbolin-sulfonamide derivatives of general formula (I),



(I)

optionally in form of one of their stereoisomers, preferably enantiomers or diastereomers, their racemates or in form of a mixture of at least two of their stereoisomers, preferably enantiomers or diastereomers, in any mixing ratio, or corresponding physiologically acceptable salts or corresponding solvates. These compounds are suitable as pharmacologically active agents in a medicament for the prophylaxis and/or treatment of disorders or diseases related to 5-HT₆ receptors.

BACKGROUND OF THE INVENTION

[0002] The superfamily of serotonin receptors (5-HT) includes 7 classes (5-HT₁-5-HT₇) encompassing 14 human subclasses [D. Hoyer, et al., *Neuropharmacology*, 1997, 36, 419]. The 5-HT₆ receptor is the latest serotonin receptor identified by molecular cloning both in rats [F. J. Monsma, et al., *Mol. Pharmacol.*, 1993, 43, 320; M. Ruat, et al., *Biochem. Biophys. Res. Commun.*, 1993, 193, 268] and in humans [R. Kohen, et al., *J. Neurochem.*, 1996, 66, 47]. Compounds with 5-HT₆ receptor affinity are useful for the treatment of various disorders of the Central Nervous System and of the gastrointestinal tract, such as irritable intestine syndrome. Compounds with 5-HT₆ receptor affinity are also useful in the treatment of anxiety, depression and cognitive memory disorders [M. Yoshioka, et al., *Ann. NY Acad. Sci.*, 1998, 861, 244; A. Bourson, et al., *Br. J. Pharmacol.*, 1998, 125, 1562; D. C. Rogers, et al., *Br. J. Pharmacol. Suppl.*, 1999, 127, 22P; A. Bourson, et al., *J. Pharmacol. Exp. Ther.*, 1995, 274, 173; A. J. Sleight, et al., *Behav. Brain Res.*, 1996, 73, 245; T. A. Branchek, et al., *Annu. Rev. Pharmacol. Toxicol.*, 2000, 40, 319; C. Routledge, et al., *Br. J. Pharmacol.*, 2000, 130, 1606]. It has been shown that typical and atypical antipsychotic drugs for treating schizophrenia have a high affinity for 5-HT₆ receptors [B. L. Roth, et al., *J. Pharmacol. Exp. Ther.*, 1994, 268, 1403; C. E. Glatt, et al., *Mol. Med.*, 1995, 1, 398; F. J. Mosma, et al., *Mol. Pharmacol.*, 1993, 43, 320; T. Shinkai, et al., *Am. J. Med. Genet.*, 1999, 88, 120]. Compounds with 5-HT₆ receptor affinity are useful for treating infant hyperkinesia (ADHD, attention deficit/hyperactivity disorder) [W. D. Hirst, et al., *Br. J. Pharmacol.*, 2000, 130, 1597; C. Gérard, et al., *Brain Research*, 1997, 746, 207; M. R. Pranzatelli, *Drugs of Today*, 1997, 33, 379]. Moreover, it has been shown that the 5-HT₆ receptor also plays a role in food ingestion [*Neuropharmacology*, 2001, 41, 210-219]. Food ingestion disorders, particularly obesity, are a serious, fast growing threat to the

health of humans of all age groups, since they increase the risk of developing other serious, even life-threatening diseases such as diabetes or coronary diseases.

[0003] Tetrahydro-β-carbolines has shown affinity for other serotonin receptors such as 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} [patent WO 97/00871; J. E. Audia, et al., *J. Med. Chem.*, 1996, 39, 2773-2780].

[0004] Patents WO 02/064590, WO 02/064591, WO 02/088123 and WO 02/098875 disclose tetrahydro-β-carbolines as inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE), in particular PDE5 and their utility in the treatment of cardiovascular disorders and erectile dysfunction.

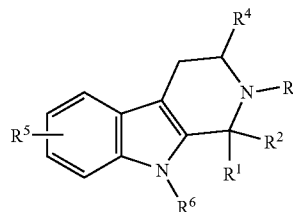
[0005] Patent WO 99/33800 discloses tetrahydro-β-carbolines as inhibitors of factor Xa and their utility in thromboembolic diseases.

[0006] Surprisingly, it has been found that the substituted tetrahydro-β-carbolines compounds of general formula (I) given below show good to excellent affinity for 5-HT₆ receptors. These compounds are therefore particularly suitable as pharmacologically active agents in a medicament for the prophylaxis and/or treatment of disorders or diseases related to 5-HT₆ receptors.

DETAILED DESCRIPTION OF THE INVENTION

[0007] The present invention relates to new compounds with affinity for 5-HT₆ receptor useful in the elaboration of medicaments that are suitable for the prophylaxis and/or treatment of a disorder or a disease that is related to food intake, preferably for the regulation of appetite, for the maintenance, increase or reduction of body weight, for the prophylaxis and/or treatment of obesity, bulimia, anorexia, cachexia or type II diabetes (non insulin dependent diabetes mellitus), preferably type II diabetes that is caused by obesity, or for the prophylaxis and/or treatment of irritable colon syndrome; disorders of the central nervous system; anxiety; panic attacks; depression; bipolar disorders; cognitive disorders; memory disorders; senile dementia; psychosis; neurodegenerative disorders, preferably selected from the group consisting of Morbus Alzheimer, Morbus Parkinson, Morbus Huntington and Multiple Sclerosis; schizophrenia; psychosis; or hyperactivity disorders, preferably attention deficit/hyperactivity disorder (ADHD), or for the improvement of cognition (cognitive enhancement).

[0008] The compounds object of the present invention are related to the general formula (I):



(I)

wherein

R¹ and R², identical or different, represent hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, heteroaryl, C₃-C₆ cycloalkyl or C₃-C₆ heterocycloalkyl, optionally substituted with one or more substituents independently selected from —NO₂; —NH₂; —SH; —OH; —CN; —C(=O)—OH;

—S(=O)2-OH; —C(=O)—NH2; —S(=O)2-NH2; —S(=O)2-R^f; —OR^f; —SR^f; —C(=O)—OR^f; —N(R^f)—S(=O)2-R^g; —NH—R^f; —NR^fR^g; —C(=O)—NHR^f; —C(=O)—NR^fR^g; —S(=O)2-NHR^f; —S(=O)2-NR^fR^g; —O—C(=O)—R^f; —NH—C(=O)—R^f; —NR^f—C(=O)—R^g; —NH—C(=O)—O—R^f; —NR^f—C(=O)—O—R^g; —S(=O)2-O—R^f; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0009] wherein R^f and R^g, independent from one another, each represent a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene, alkenylene or alkynylene group,

or R¹ and R² together form a spiro substituent of 3-6 carbons; R³ represents hydrogen, C₁-C₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ heterocycloalkyl, aryl or heteroaryl; optionally substituted with one or more substituents independently selected from —NO₂; —NH₂; —SH; —OH; —CN; —C(=O)—OH; —S(=O)2-OH; —C(=O)—NH₂; —S(=O)2-NH₂; —S(=O)2-R^f; —OR^f; —SR^f; —C(=O)—OR^f; —N(R^f)—S(=O)2-R^g; —NH—R^f; —NR^fR^g; —C(=O)—NHR^f; —C(=O)—NR^fR^g; —S(=O)2-NHR^f; —S(=O)2-NR^fR^g; —O—C(=O)—R^f; —NH—C(=O)—R^f; —NR^f—C(=O)—R^g; —NH—C(=O)—O—R^f; —NR^f—C(=O)—O—R^g; —S(=O)2-O—R^f; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0010] wherein R^f and R^g, have the meaning defined above R⁴ represents hydrogen, CO—NR^aR^b, CO—OR^a, wherein

[0011] R^a and R^b, identical or different, represent hydrogen, C₁-C₆ alkyl, aryl, heteroaryl, C₃₋₆ cycloalkyl, or C₃₋₆ heterocycloalkyl, optionally substituted with one or more substituents independently selected from —NO₂; —NH₂; —SH; —OH; —CN; —C(=O)—OH; —S(=O)2-OH; —C(=O)—NH₂; —S(=O)2-NH₂; —S(=O)2-R^f; —OR^f; —SR^f; —C(=O)—OR^f; —N(R^f)—S(=O)2-R^g; —NH—R^f; —NR^fR^g; —C(=O)—NHR^f; —C(=O)—NR^fR^g; —S(=O)2-NHR^f; —S(=O)2-NR^fR^g; —O—C(=O)—R^f; —NH—C(=O)—R^f; —NR^f—C(=O)—R^g; —NH—C(=O)—O—R^f; —NR^f—C(=O)—O—R^g; —S(=O)2-O—R^f; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing

cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0012] wherein R^f and R^g, have the meaning defined above R⁵ represents NR^cSO₂R^d, wherein

[0013] R^c represents hydrogen or C₁₋₄ alkyl optionally substituted with one or more substituents independently selected from C₁-C₆ alkyl, aryl, cyano, C₁-C₆ alkoxy and trifluoromethyl;

[0014] R^d represents aryl or heteroaryl optionally substituted with one or more substituents independently selected from —NO₂; —NH₂; —SH; —OH; —CN; —C(=O)—OH; —S(=O)2-OH; —C(=O)—NH₂; —S(=O)2-NH₂; —S(=O)2-R^f; —OR^f; —SR^f; —C(=O)—OR^f; —N(R^f)—S(=O)2-R^g; —NH—R^f; —NR^fR^g; —C(=O)—NHR^f; —C(=O)—NR^fR^g; —S(=O)2-NHR^f; —S(=O)2-NR^fR^g; —O—C(=O)—R^f; —NH—C(=O)—R^f; —NR^f—C(=O)—R^g; —NH—C(=O)—O—R^f; —NR^f—C(=O)—O—R^g; —S(=O)2-O—R^f; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0015] wherein R^f and R^g, have the meaning defined above R⁶ represents hydrogen, C₁₋₄ alkyl, aryl, heteroaryl or SO₂R^e, wherein

[0016] R^e represents aryl, heteroaryl, C₃₋₆ cycloalkyl, C₃₋₆ heterocycloalkyl; optionally substituted with one or more substituents independently selected from —NO₂; —NH₂; —SH; —OH; —CN; —C(=O)—OH; —S(=O)2-OH; —C(=O)—NH₂; —S(=O)2-NH₂; —S(=O)2-R^f; —OR^f; —SR^f; —C(=O)—OR^f; —N(R^f)—S(=O)2-R^g; —NH—R^f; —NR^fR^g; —C(=O)—NHR^f; —C(=O)—NR^fR^g; —S(=O)2-NHR^f; —S(=O)2-NR^fR^g; —O—C(=O)—R^f; —NH—C(=O)—R^f; —NR^f—C(=O)—R^g; —NH—C(=O)—O—R^f; —NR^f—C(=O)—O—R^g; —S(=O)2-O—R^f; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0017] wherein R^f and R^g, have the meaning defined above with the proviso that when R^d is phenyl, R^e is other than phenyl;

optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of its stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a physiologically acceptable salt thereof, or a corresponding solvate thereof.

[0018] In a particular embodiment of the compounds of the invention, R¹, R², R³ and R⁶ are selected from hydrogen, C₁-C₄ alkyl or phenyl, R⁴ is H and R⁵ is NHSO₂R^d, wherein

R^d is an aryl or heteroaryl group selected from phenyl, naphthyl, furanyl (furyl), thiophenyl (thienyl), pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzofurazanyl, indolyl, benzothienophenyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoimidazolyl, indazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl and imidazothiazolyl, optionally substituted.

[0019] In another embodiment, the compounds are selected from the following group:

- [0020] [1] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0021] [2] Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0022] [3] Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0023] [4] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0024] [5] 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0025] [6] Benzo[1,2,5]thiadiazole-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0026] [7] N-[4-(2-Methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)sulfamoyl]-phenyl]-acetamide;
- [0027] [8] 4-Amino-N-(2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-benzenesulfonamide;
- [0028] [9] N-[4-Methyl-5-(2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)sulfamoyl]-thiazol-2-yl]-acetamide;
- [0029] [10] 5-Dimethylamino-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0030] [11] Benzofuran-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0031] [12] Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0032] [13] 5-Methyl-benzo[b]thiophene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0033] [14] 4-Fluoro-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0034] [15] 7-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0035] [16] 6-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0036] [17] 6-Trifluoromethyl-imidazo[2,1-b]thiazole-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0037] [18] 6-Trifluoromethyl-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0038] [19] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0039] [20] Naphthalene-2-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0040] [21] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0041] [22] Benzo[b]thiophene-3-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [0042] [23] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl]-amide;

[0043] [24] 5-Chloro-naphthalene-2-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl]-amide;

[0044] [25] Benzo[b]thiophene-3-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl]-amide;

[0045] [26] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-propyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[0046] [27] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-isopropyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[0047] [28] Naphthalene-2-sulfonic acid (2-methyl-1-phenyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[0048] [29] Benzo[b]thiophene-3-sulfonic acid (2-methyl-1-phenyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[0049] [30] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-amide;

[0050] [31] Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-amide;

[0051] [32] Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-amide;

[0052] [33] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-amide;

[0053] [34] Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide;

[0054] [35] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide;

[0055] [36] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide;

[0056] [37] 5-Chloro-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0057] [38] Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0058] [39] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0059] [40] 5-Dimethylamino-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0060] [41] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0061] [42] Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0062] [43] 2,1,3-Benzothiadiazole-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0063] [44] Benzofuran-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

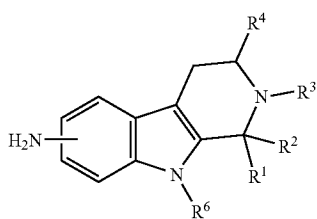
[0064] [45] Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0065] [46] Benzofurazan-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[0066] [47] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide; and

[0067] [48] Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide hydrochloride.

[0068] The present invention also relates to a procedure for preparing a tetrahydro- β -carbolin-sulfonamide derivative of general formula (I), characterised by reacting a compound of general formula (II)



(II)

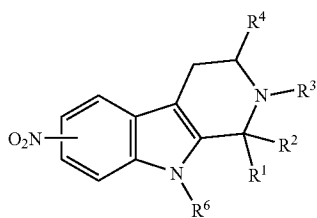
[0069] wherein R^1 , R^2 , R^3 , R^4 and R^6 have the meanings previously given for general formula (I); with a sulfonyl halide of general formula R^dSO_2X , wherein R^d has the meaning previously given for general formula (I) and X is halogen.

[0070] The reaction is preferably carried out in the presence of a suitable organic base as triethylamine or preferably pyridine or an inorganic base such as hydroxides and/or carbonates of alkali metals. Optionally, the reaction is carried out in the presence of an organic reaction medium, such as an dialkyl ether, particularly diethyl ether, or a cyclic ether, particularly tetrahydrofuran or dioxane, a halogenated organic hydrocarbon, particularly methylene chloride or chloroform, an aprotic dipolar solvent, particularly acetonitrile, or dimethylformamide, or any other suitable reaction medium. Mixtures of at least two of the above mentioned classes of compounds or of at least two compounds of one class may, of course, also be used.

[0071] The most suitable reaction temperatures range from 0°C . to ambient temperature, i.e. approximately 25°C ., and the reaction time is preferably from 5 minutes to 24 hours.

[0072] The resulting derivative of general formula (I) may be purified and/or isolated according to conventional methods known to those skilled in the art. Preferably, can be isolated by evaporating the reaction medium, adding water and eventually adjusting the pH so that it is obtained as a solid that can be isolated by filtration; or it can be extracted by a solvent immiscible with water, such as chloroform or ethyl acetate, and purified by chromatography or recrystallisation from a suitable solvent.

[0073] The compounds of general formula R^dSO_2X are commercially available or can be prepared according to standard methods known to those skilled in the art, e.g. by methods analogous to those described in the literature [E. E. Gilbert, *Synthesis*, 1969, 1, 3] and compounds of general formula (II) may be prepared by hydrogenation of compounds of general formula (III).



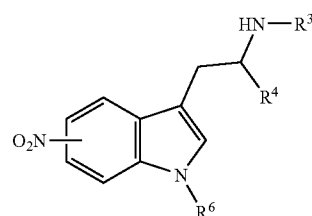
(III)

[0074] Hydrogenation preferably takes place with the aid of a metallic catalyst such as palladium, platinum or rhodium on a suitable support such as carbon, aluminum oxide or barium sulphate, preferably palladium on carbon, with an

initial hydrogen pressure of between 5 and 50 psi, in a solvent such as methanol or ethanol. The reaction time ranges from 1 hour to 24 hours.

[0075] The resulting amine can be isolated by filtering the catalyst and concentrating the filtrate at reduced pressure. The product recovered can be used as is or it can be purified by chromatography or by recrystallization from a suitable solvent.

[0076] Compounds of general formula (III) may be prepared by conventional methods known to those skilled in the art, or according to the methods described in the present invention, for example by a Pictet-Spengler cyclization by reaction between a compound of general formula (IV) and an aldehyde of formula R^1CHO or a ketone of formula R^1R^2CO .



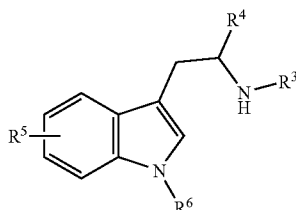
(IV)

[0077] The reaction may be carried out in the presence of an acid as for example acetic acid, sulfuric acid or trifluoroacetic acid, optionally in the presence of an organic solvent such as a halogenated hydrocarbon or an aromatic hydrocarbon. The most suitable reaction temperatures range from ambient temperature to the refluxing temperature of the solvent. Compounds R^1CHO and R^1R^2CO are commercially available or can be prepared according to standard methods. Compounds of general formula (IV) are commercially available or can be prepared according to standard methods known to those skilled in the art, or by analogous methods described in the bibliography [J. Holenz, et al., *J. Med. Chem.*, 2005, 48, 1781-1795; J. E. Macor, et al., *Synt. Comm.*, 1993, 23, 65-72]

[0078] Compounds of general formula (I), (II), (III) and (IV) prepared by this methodology can be prepared as stereoisomers, particularly enantiomers or diastereomers, their racemates or in form of a mixture of at least two of their stereoisomers, particularly enantiomers or diastereomers, in any mixing ratio. Enantiomers can be separated from racemic mixtures by resolution by standard procedures known to those skilled in the art, for example using HPLC on a chiral column, or using separation of salts of stereoisomers. Alternatively, chirality can be induced by analogous methods described in the bibliography [T. Soe, et al., *Tetrahedron Lett.*, 1995, 36, 1857-1860; R. Tsuji, et al., *Tetrahedron: Asymmetry*, 2003, 14, 177-180].

[0079] During one of the synthesis sequences described above, or in the preparation of suitable reactants used it may be necessary and/or desirable to protect sensitive or reactive groups in some of the molecules employed. This can be performed by means of conventional protective groups such as those described in the literature [T. W. Greene & P. G. M. Wuts, *Protective Groups in Organic Chemistry*, John Wiley & Sons, 3rd edition, 1999]. The protective groups can be eliminated in a suitable latter stage by methods known to those skilled in the art. The respective literature descriptions are hereby incorporated by reference and form part of the disclosure.

[0080] The present invention also relates to another procedure for preparing a tetrahydro- β -carbolin-sulfonamide derivative of general formula (I), characterised by a Pictet-Spengler cyclization of a compound of general formula (V)



[0081] wherein R^3 , R^4 , R^5 and R^6 have the meanings previously given for general formula (I); with an aldehyde of formula $R^1\text{CHO}$ or a ketone of formula $R^1R^2\text{CO}$ or with $\text{CH}_2(\text{OMe})_2$ wherein R^1 and R^2 have the meaning previously indicated for general formula (I).

[0082] The reaction may be carried out in the presence of an acid as for example acetic acid, sulfuric acid or trifluoroacetic acid, optionally in the presence of an organic solvent such as a halogenated hydrocarbon or an aromatic hydrocarbon. The most suitable reaction temperatures range from ambient temperature to the refluxing temperature of the solvent. Compounds $R^1\text{CHO}$ and $R^1R^2\text{CO}$ are commercially available or can be prepared according to standard methods. Compounds of general formula (V) are commercially available or can be prepared according to standard methods known to those skilled in the art, or by analogous methods described in the bibliography [J. Holenz, et al., *J. Med. Chem.*, 2005, 48, 1781-1795; J. E. Macor, et al., *Synt. Comm.*, 1993, 23, 65-72].

[0083] Compounds of general formula (V) prepared by this methodology can be prepared as stereoisomers, particularly enantiomers or diastereomers, their racemates or in form of a mixture of at least two of their stereoisomers, particularly enantiomers or diastereomers, in any mixing ratio. Enantiomers can be separated from racemic mixtures by resolution by standard procedures known to those skilled in the art, for example using HPLC on a chiral column, or using separation of salts of stereoisomers. Alternatively, chirality can be induced by analogous methods described in the bibliography [T. Soe, et al., *Tetrahedron Lett.*, 1995, 36, 1857-1860; R. Tsuji, et al., *Tetrahedron: Asymmetry*, 2003, 14, 177-180].

[0084] During one of the synthesis sequences described above, or in the preparation of suitable reactants used it may be necessary and/or desirable to protect sensitive or reactive groups in some of the molecules employed. This can be performed by means of conventional protective groups such as those described in the literature [T. W. Greene & P. G. M. Wuts, *Protective Groups in Organic Chemistry*, John Wiley & Sons, 3rd edition, 1999]. The protective groups can be eliminated in a suitable latter stage by methods known to those skilled in the art. The respective literature descriptions are hereby incorporated by reference and form part of the disclosure.

[0085] The pharmacologically acceptable salts of compounds with the general formula (I) can be prepared by conventional methods known to those skilled in the art, preferably by reaction with a mineral acid, such as hydrochloric, hydrobromic, phosphoric, sulphuric, nitric acids or with organic acids such as citric, maleic, fumaric, tartaric acids or

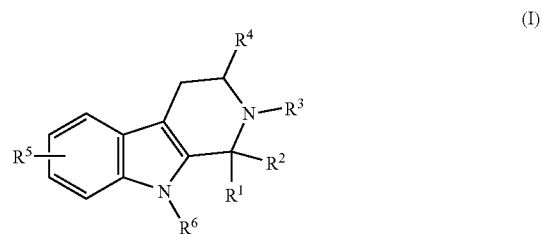
their derivatives, p-toluenesulphonic acid, methanesulphonic acid, etc., in a suitable solvent such as methanol, ethanol, diethyl ether, ethyl acetate, acetonitrile or acetone and obtained with the usual techniques of precipitation or crystallisation of the corresponding salts.

[0086] Preferred physiologically acceptable salts of the derivatives of general formula (I) are the additions salts of mineral acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, and of organic acids, such as citric acid, maleic acid, tartaric acid or derivatives thereof, p-toluenesulphonic acid, methanesulphonic acid, camphorsulphonic acid, etc.

[0087] The physiologically acceptable solvates, particularly hydrates, of the derivatives of general formula (I) or of the corresponding physiologically acceptable salts may be prepared by conventional methods known to those skilled in the art.

[0088] The invention also relates to a tetrahydro- β -carbolin-sulfonamide derivative of general formula (I) as previously disclosed for the prophylaxis and/or treatment of a disorder or a disease related to 5-HT₆ receptors in mammals, including humans. More in particular, for the prophylaxis and/or treatment of a disorder or a disease related to food intake, preferably for the regulation of appetite, for the maintenance, increase or reduction of body weight, for the prophylaxis and/or treatment of obesity, bulimia, anorexia, cachexia or type II diabetes, preferably type II diabetes that is caused by obesity, or for the prophylaxis and/or treatment of irritable colon syndrome; disorders of the central nervous system; anxiety; panic attacks; depression; bipolar disorders; cognitive disorders; memory disorders; senile dementia; psychosis; neurodegenerative disorders, preferably selected from the group consisting of Morbus Alzheimer, Morbus Parkinson, Morbus Huntington and Multiple Sclerosis; schizophrenia; psychosis; or hyperactivity disorders, preferably attention deficit/hyperactivity disorder, or for the improvement of cognition.

[0089] The invention also relates to the use of a tetrahydro- β -carbolin-sulfonamide derivative of general (I):



wherein

R^1 and R^2 , identical or different, represent hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, aryl, heteroaryl, C_3 - C_6 cycloalkyl or C_3 - C_6 heterocycloalkyl, optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or

branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0090] wherein R^f and R^g , have the meaning defined above or R^1 and R^2 together form a spiro substituent of 3-6 carbons; R^3 represents hydrogen, C_1 - C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkinyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, aryl or heteroaryl; optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0091] wherein R^f and R^g , have the meaning defined above R^4 represents hydrogen, $\text{CO}-\text{NR}^a\text{R}^b$, $\text{CO}-\text{OR}^a$, wherein

[0092] R^a and R^b , identical or different, represent hydrogen, C_1 - C_6 alkyl, aryl, heteroaryl, C_3 - C_6 cycloalkyl, or C_3 - C_6 heterocycloalkyl, optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0093] wherein R^f and R^g , have the meaning defined above R^5 represents $\text{NR}^c\text{SO}_2\text{R}^d$, wherein

[0094] R^c represents hydrogen or C_{1-4} alkyl optionally substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, cyano, C_1 - C_6 alkoxy and trifluoromethyl;

[0095] R^d represents aryl or heteroaryl optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$;

$-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

[0096] wherein R^f and R^g , have the meaning defined above R^6 represents hydrogen, C_{1-4} alkyl, aryl, heteroaryl or SO_2R^e , wherein

[0097] R^e represents aryl, heteroaryl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl; optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

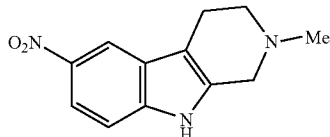
[0098] wherein R^f and R^g , have the meaning defined above optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of its stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a physiologically acceptable salt thereof, or a corresponding solvate thereof;

in the manufacture of a medicament for the prophylaxis and/or treatment of a disorder or a disease related to 5-HT₆ receptors in mammals, including humans. Particularly, for the prophylaxis and/or treatment of a disorder or a disease related to food intake, preferably for the regulation of appetite, for the maintenance, increase or reduction of body weight, for the prophylaxis and/or treatment of obesity, bulimia, anorexia, cachexia or type II diabetes, preferably type II diabetes that is caused by obesity, or for the prophylaxis and/or treatment of irritable colon syndrome; disorders of the central nervous system; anxiety; panic attacks; depression; bipolar disorders; cognitive disorders; memory disorders; senile dementia; psychosis; neurodegenerative disorders, preferably selected from the group consisting of Morbus Alzheimer, Morbus Parkinson, Morbus Huntington and Multiple Sclerosis; schizophrenia; psychosis; or hyperactivity disorders, preferably attention deficit/hyperactivity disorder, or for the improvement of cognition.

[0099] The examples that are indicated below, given by way of illustration, should not in any way limit the scope of the invention.

Description 1: Preparation of 2-methyl-6-nitro-2,3,4,9-tetrahydro-1H- β -carboline

[0100]

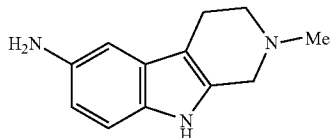


[0101] Under N_2 , formaldehyde (0.56 ml of a 36.5% aqueous solution, 7.3 mmol) was added to a solution of 5-nitro-3-(2-methylaminoethyl)-1H-indole (1.6 g, 7.3 mmol) in glacial acetic acid (10 mL). After 20 h of stirring at room temperature, the mixture was refluxed for 2 h and taken to dryness in vacuo. The residue was treated with H_2O (150 mL) and EtOAc (150 mL) and then basified by the addition of 2M NaOH. The organic phase was separated and the aqueous layer was reextracted with three portions of EtOAc. The combined organic solution was extracted with 10% aqueous H_2SO_4 (3 \times 160 mL). The acidic aqueous phase was cooled in an ice bath, basified with concentrated aqueous NaOH and extracted with tert-butyl methyl ether (4 \times 175 mL). The dried (Na_2SO_4) extract was evaporated to dryness to afford 1.40 g of 2-methyl-6-nitro-2,3,4,9-tetrahydro-1H- β -carboline that were used directly in the next step.

[0102] Using essentially the same general procedure described for description 1 with minor changes, compounds 2-methyl-5-nitro-2,3,4,9-tetrahydro-1H- β -carboline, 2-ethyl-6-nitro-2,3,4,9-tetrahydro-1H- β -carboline, 2-(2,2,2-trifluoroethyl)-6-nitro-2,3,4,9-tetrahydro-1H- β -carboline, 2-propyl-6-nitro-2,3,4,9-tetrahydro-1H- β -carboline, 2-isopropyl-6-nitro-2,3,4,9-tetrahydro-1H- β -carboline, 2-methyl-7-nitro-2,3,4,9-tetrahydro-1H- β -carboline, and 2-methyl-8-nitro-2,3,4,9-tetrahydro-1H- β -carboline, were also prepared. Also, compound 2-methyl-6-nitro-1-phenyl-2,3,4,9-tetrahydro-1H- β -carboline was prepared using the same general procedure but with benzaldehyde instead of formaldehyde.

Description 2: Preparation of 6-amino-2-methyl-2,3,4,9-tetrahydro-1H- β -carboline

[0103]



[0104] To a solution of 2-methyl-6-nitro-2,3,4,9-tetrahydro-1H- β -carboline (description 1) (1.42 g, 6.13 mmol) in EtOH (300 mL), 570 mg of (5%) Pd/C were added. The mixture was hydrogenated under 20 psi at room temperature for 20 h and filtered through a pad of Celite. The EtOH was evaporated to dryness to yield 1.32 g of 6-amino-2-methyl-2,3,4,9-tetrahydro-1H- β -carboline that were used directly to synthesize compounds of formula I.

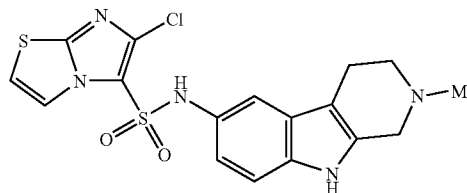
[0105] Using essentially the same general procedure described for description 1 with minor changes, compounds 5-amino-2-methyl-2,3,4,9-tetrahydro-1H- β -carboline, 6-amino-2-ethyl-2,3,4,9-tetrahydro-1H- β -carboline, 6-amino-2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H- β -carboline, 6-amino-2-propyl-2,3,4,9-tetrahydro-1H- β -carboline, 6-amino-2-isopropyl-2,3,4,9-tetrahydro-1H- β -carboline, 7-amino-2-methyl-2,3,4,9-tetrahydro-1H- β -

carboline, 8-amino-2-methyl-2,3,4,9-tetrahydro-1H- β -carboline, and 6-amino-2-methyl-1-phenyl-2,3,4,9-tetrahydro-1H- β -carboline, were also prepared.

EXAMPLE [1]

Preparation of 6-chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0106]



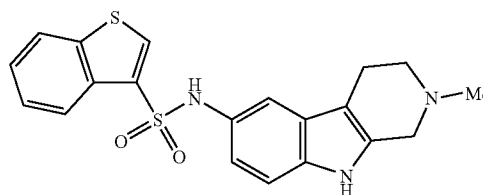
[0107] To a solution of 6-amino-2-methyl-2,3,4,9-tetrahydro-1H- β -carboline (description 2) (150 mg, 0.68 mmol) in pyridine (5 mL) cooled in an ice bath, were added 200 mg of 6-chloro-imidazo[2,1-b]thiazole-5-sulfonyl chloride (0.68 mmol). Under N_2 , the reaction mixture was left to reach room temperature and stirred for 1 h at this temperature. The reaction mixture was basified with aqueous saturated solution of $NaHCO_3$ and the pyridine evaporated. The mixture was treated with EtOAc and H_2O , the organic phase washed with aqueous saturated solution of $NaHCO_3$, separated and dried with Na_2SO_4 . The crude was further purified using SiO_2 column chromatography with EtOAc/MeOH/ NH_3 mixtures to yield 130 mg of 6-chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide. Cream colored amorphous solid, mp 232-233 $^\circ$ C. 1H -NMR (300 MHz, DMSO- d_6): δ (ppm) 2.36 (s, 3H); 2.54 (bb, 2H); 2.61 (bb, 2H); 3.45 (bb, 2H); 6.65 (dd, 1H, J=8.7, 2.1 Hz); 6.99 (d, 1H, J=1.8 Hz); 7.09 (d, 1H, J=8.7 Hz); 7.53 (d, 1H, J=4.5 Hz); 7.81 (d, 1H, J=4.5 Hz); 10.37 (bb, 1H); 10.74 (s, 1H).

[0108] Using essentially the same general procedure described for example 1 with minor changes, compounds 2-7 and 9-46, were also prepared, starting from the corresponding amine derivative of formula (II) (obtained as disclosed in description 2) and the corresponding sulfonyl halide.

EXAMPLE [2]

Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0109]



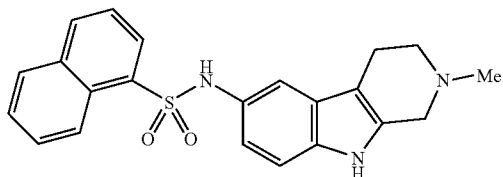
[0110] Cream colored amorphous solid, mp 224-226 $^\circ$ C. 1H -NMR (400 MHz, DMSO- d_6): δ (ppm) 2.34 (s, 3H); 2.50 (bb, 2H); 2.59 (bb, 2H); 3.42 (bb, 2H); 6.59 (dd, 1H, J=8.4, 2.0 Hz); 6.97 (d, 1H, J=2.0 Hz); 7.01 (d, 1H, J=8.8 Hz);

7.43-7.53 (m, 2H); 8.04 (d, 1H, J=7.6 Hz); 8.24 (d, 1H, J=7.6 Hz); 8.30 (s, 1H); 10.03 (bb, 1H); 10.66 (s, 1H).

EXAMPLE [3]

Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0111]

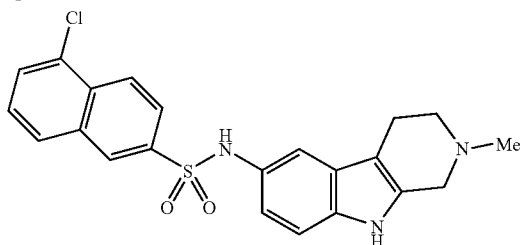


[0112] Cream colored amorphous solid, mp 245-246° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.33 (s, 3H); 2.48 (bb, 2H); 2.57 (bb, 2H); 3.40 (bb, 2H); 6.55 (dd, 1H, J=8.7, 2.1 Hz); 6.92 (d, 1H, J=1.5 Hz); 6.97 (d, 1H, J=8.7 Hz); 7.49 (t, 1H, J=8.1 Hz); 7.64 (t, 1H, J=6.9 Hz); 7.71 (m, 1H); 8.02 (m, 2H); 8.12 (d, 1H, J=8.1 Hz); 8.78 (d, 1H, J=8.4 Hz); 10.10 (bb, 1H); 10.62 (s, 1H).

EXAMPLE [4]

5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0113]

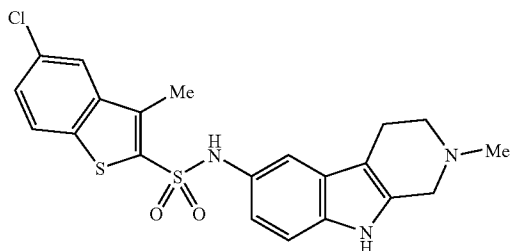


[0114] Cream colored amorphous solid, mp 262-263° C. ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) 2.34 (s, 3H); 2.51 (bb, 2H); 2.59 (bb, 2H); 3.42 (bb, 2H); 6.66 (dd, 1H, J=8.4, 2.0 Hz); 7.03 (d, 1H, J=8.8 Hz); 7.05 (d, 1H, J=2.0 Hz); 7.58 (t, 1H, J=8.0 Hz); 7.83 (d, 1H, J=7.6 Hz); 7.89 (dd, 1H, J=8.8, 1.6 Hz); 8.08 (d, 1H, J=8.4 Hz); 8.28 (d, 1H, J=8.8 Hz); 8.36 (d, 1H, J=2.0 Hz); 9.95 (bb, 1H); 10.67 (s, 1H).

EXAMPLE [5]

5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0115]

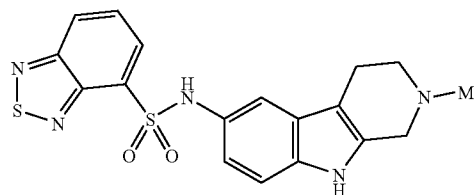


[0116] Orange amorphous solid, mp 259-260° C. ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) 2.33 (s, 3H); 2.35 (s, 3H); 2.52 (bb, 2H); 2.60 (bb, 2H); 3.44 (bb, 2H); 6.69 (dd, 1H, J=8.4, 2.0 Hz); 7.06 (d, 1H, J=2.0 Hz); 7.08 (d, 1H, J=8.4 Hz); 7.50 (dd, 1H, J=8.8, 2.0 Hz); 7.93 (d, 1H, J=2.0 Hz); 7.99 (d, 1H, J=8.4 Hz); 10.16 (bb, 1H); 10.73 (s, 1H).

EXAMPLE [6]

Benzo[1,2,5]thiadiazole-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0117]

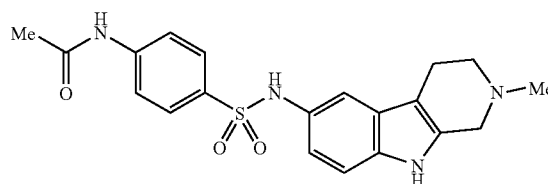


[0118] Yellow amorphous solid, mp 244-245° C. ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) 2.33 (s, 3H); 2.48 (bb, 2H); 2.57 (bb, 2H); 3.40 (bb, 2H); 6.55 (dd, 1H, J=8.4, 2.0 Hz); 6.94 (m, 2H); 7.72 (dd, 1H, J=8.8, 7.2 Hz); 8.06 (dd, 1H, J=6.8, 0.8 Hz); 8.30 (dd, 1H, J=9.2, 1.2 Hz); 10.11 (bb, 1H); 10.63 (s, 1H).

EXAMPLE [7]

N-[4-(2-Methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-ylsulfamoyl)-phenyl]-acetamide

[0119]

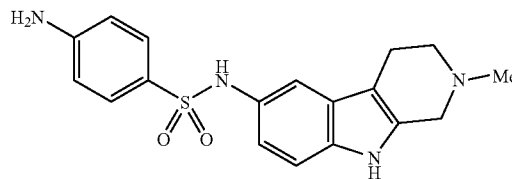


[0120] Cream colored amorphous solid, mp 232-234° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.02 (s, 3H); 2.36 (s, 3H); 2.55 (bb, 2H); 2.60 (bb, 2H); 3.45 (bb, 2H); 6.56 (dd, 1H, J=8.4, 1.5 Hz); 7.00 (s, 1H); 7.06 (d, 1H, J=8.4 Hz); 7.54 (sys AB, 2H, J=8.7 Hz); 7.61 (sys AB, 2H, J=8.7 Hz); 9.60 (bb, 1H); 10.22 (s, 1H); 10.67 (s, 1H).

EXAMPLE [8]

4-Amino-N-(2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-benzenesulfonamide

[0121]

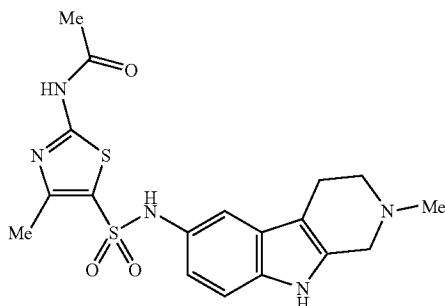


[0122] A solution of N-[4-(2-Methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)sulfamoyl]-phenyl]-acetamide (example 7) (80 mg, 0.2 mmol) in 1 mL of an aqueous 10% de NaOH solution was refluxed for 2 h. The resulting mixture was treated with H₂O (25 mL) and EtOAc (25 mL) and neutralized by addition of AcOH glacial. The aqueous phase was washed again with EtOAc and the combined organic extracts dried to afford 50 mg of 4-amino-N-(2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-benzenesulfonamide as a cream colored amorphous solid, mp 236-237° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.36 (s, 3H); 2.55 (bb, 2H); 2.61 (bb, 2H); 3.45 (bb, 2H); 5.83 (bb, 2H); 6.44 (sys AB, 2H, J=8.7 Hz); 6.68 (dd, 1H, J=8.4, 1.8 Hz); 6.99 (bb, 1H); 7.05 (d, 1H, J=8.4 Hz); 7.25 (sys AB, 2H, J=8.7 Hz); 9.27 (s, 1H); 10.63 (s, 1H).

EXAMPLE [9]

N-[4-Methyl-5-(2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)sulfamoyl]-thiazol-2-yl]-acetamide

[0123]

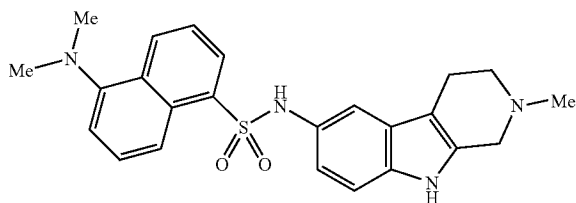


[0124] Yellow amorphous solid, mp 199-200° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.09 (s, 3H); 2.12 (s, 3H); 2.37 (s, 3H); 2.58 (bb, 2H); 2.62 (bb, 2H); 3.47 (bb, 2H); 6.72 (dd, 1H, J=8.4, 1.8 Hz); 7.06 (d, 1H, J=1.8 Hz); 7.13 (d, 1H, J=8.4 Hz); 9.86 (bb, 1H); 10.74 (s, 1H); 12.40 (bb, 1H).

EXAMPLE [10]

5-Dimethylamino-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0125]

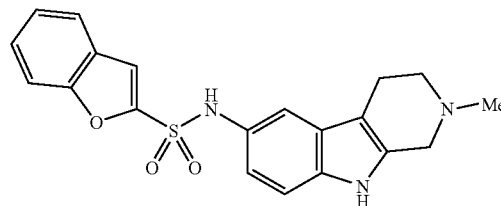


[0126] Yellow amorphous solid, mp 241-242° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.33 (s, 3H); 2.55 (bb, 4H); 2.78 (s, 6H); 3.40 (bb, 2H); 6.59 (dd, 1H, J=8.7, 1.5 Hz); 6.91 (s, 1H); 6.95 (d, 1H, J=8.7 Hz); 7.23 (d, 1H, J=7.5 Hz); 7.47 (dd, 1H, J=8.1, 7.8 Hz); 7.59 (dd, 1H, J=8.4, 7.8 Hz); 8.00 (d, 1H, J=6.9 Hz); 8.36 (d, 1H, J=8.4 Hz); 8.42 (d, 1H, J=8.7 Hz); 10.05 (s, 1H); 10.61 (s, 1H).

EXAMPLE [11]

Benzofuran-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0127]

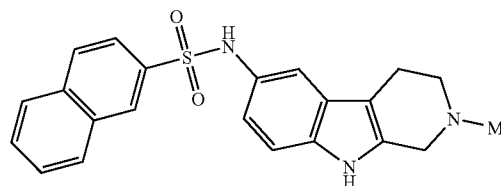


[0128] Orange amorphous solid, mp 165-166° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.33 (s, 3H); 2.59 (bb, 2H); 2.79 (bb, 2H); 3.65 (bb, 2H); 6.75 (dd, 1H, J=8.4, 1.8 Hz); 7.10-7.13 (m, 2H); 7.33 (dd, 1H, J=7.8, 7.2 Hz); 7.40 (s, 1H); 7.48 (dd, 1H, J=7.8, 7.5 Hz); 7.68 (d, 1H, J=7.5 Hz); 7.69 (d, 1H, J=8.4 Hz); 10.33 (bb, 1H); 10.82 (s, 1H).

EXAMPLE [12]

Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0129]

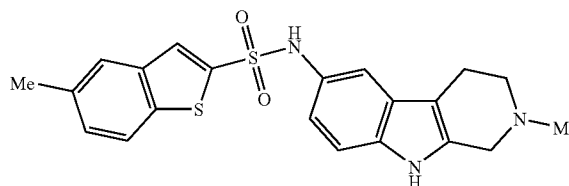


[0130] White amorphous solid, mp 244-245° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.37 (s, 3H); 2.53 (bb, 2H); 2.62 (bb, 2H); 3.47 (bb, 2H); 6.68 (dd, 1H, J=8.4, 1.8 Hz); 7.02-7.06 (m, 2H); 7.56-7.66 (m, 2H); 7.72 (dd, 1H, J=8.7, 1.5 Hz); 7.95 (d, 1H, J=7.8 Hz); 8.01-8.04 (m, 2H); 8.26 (d, 1H, J=1.2 Hz); 9.85 (bb, 1H); 10.67 (s, 1H).

EXAMPLE [13]

5-Methyl-benzo[b]thiophene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0131]

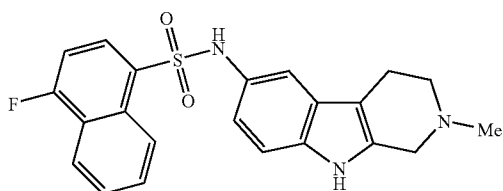


[0132] Brown amorphous solid, mp 241-242° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.36 (s, 3H); 2.48 (s, 3H); 2.63 (bb, 2H); 2.79 (bb, 2H); 3.64 (bb, 2H); 6.77 (dd, 1H, J=8.4, 1.8 Hz); 7.12 (d, 1H, J=8.7 Hz); 7.13 (s, 1H); 7.29 (dd, 1H, J=8.4, 1.2 Hz); 7.67 (bb, 1H); 7.70 (bb, 1H); 7.87 (d, 1H, J=8.4 Hz); 10.10 (bb, 1H); 10.80 (s, 1H).

EXAMPLE [14]

4-Fluoro-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0133]

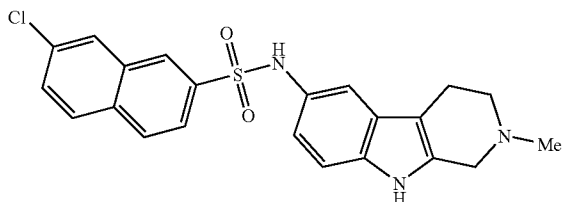


[0134] White amorphous solid, mp 236-238° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.33 (s, 3H); 2.57 (bb, 4H); 3.40 (bb, 2H); 6.51 (d, 1H, J=9.0 Hz); 6.91 (s, 1H); 6.97 (d, 1H, J=9.0 Hz); 7.34 (dd, 1H, J=9.0, 9.0 Hz); 7.73-7.86 (m, 2H); 7.99-8.03 (m, 1H); 8.15 (d, 1H, J=9.0 Hz); 8.81 (d, 1H, J=9.0 Hz); 10.14 (s, 1H); 10.65 (s, 1H).

EXAMPLE [15]

7-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0135]

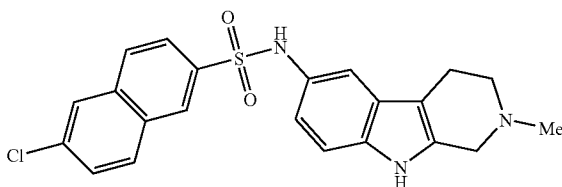


[0136] White amorphous solid, mp 230-231° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.34 (s, 3H); 2.52 (bb, 2H); 2.58 (bb, 2H); 3.42 (bb, 2H); 6.66 (dd, 1H, J=9.0, 3.0 Hz); 7.02 (d, 1H, J=6.0 Hz); 7.04 (bb, 1H); 7.65 (dd, 1H, J=9.0, 3.0 Hz); 7.74 (dd, 1H, J=9.0, 3.0 Hz); 8.01 (d, 1H, J=9.0 Hz); 8.07 (d, 1H, J=9.0 Hz); 8.21 (d, 1H, J=3.0 Hz); 8.27 (bb, 1H); 9.91 (s, 1H); 10.68 (s, 1H).

EXAMPLE [16]

6-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0137]



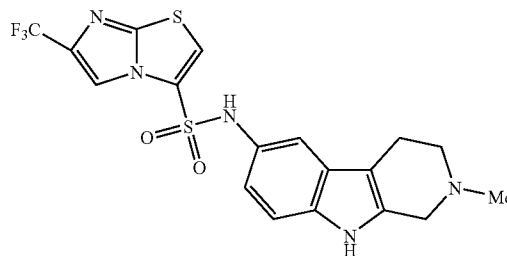
[0138] Yellow amorphous solid, mp 174-175° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.35 (s, 3H); 2.51 (bb, 2H); 2.60 (bb, 2H); 3.43 (bb, 2H); 6.66 (dd, 1H, J=9.0, 3.0 Hz); 7.02 (d, 1H, J=6.0 Hz); 7.04 (s, 1H); 7.60 (dd, 1H, J=9.0, 3.0

Hz); 7.77 (dd, 1H, J=9.0, 3.0 Hz); 8.03 (d, 1H, J=9.0 Hz); 8.10 (d, 1H, J=6.0 Hz); 8.12 (s, 1H); 8.30 (bb, 1H); 9.89 (s, 1H); 10.68 (s, 1H).

EXAMPLE [17]

6-Trifluoromethyl-imidazo[2,1-b]thiazole-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0139]

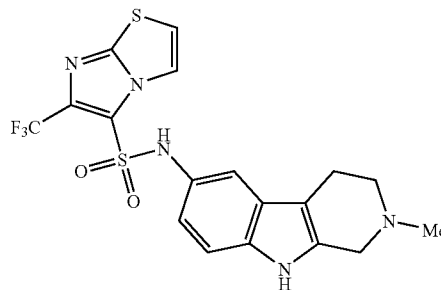


[0140] Orange amorphous solid. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.41 (s, 3H); 2.57 (bb, 2H); 2.69 (bb, 2H); 3.54 (bb, 2H); 6.57 (dd, 1H, J=8.4, 2.1 Hz); 7.01 (d, 1H, J=1.8 Hz); 7.14 (d, 1H, J=8.7 Hz); 7.98 (s, 1H); 8.38 (s, 1H); 10.48 (bb, 1H); 10.84 (bs, 1H).

EXAMPLE [18]

6-Trifluoromethyl-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0141]

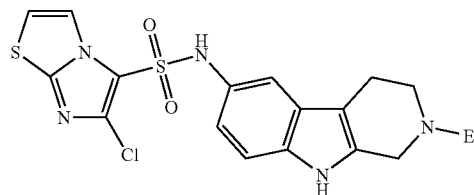


[0142] Orange amorphous solid. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.41 (s, 3H); 2.57 (bb, 2H); 2.69 (bb, 2H); 3.54 (bb, 2H); 6.62 (dd, 1H, J=8.4, 1.8 Hz); 7.00 (d, 1H, J=1.8 Hz); 7.10 (d, 1H, J=8.4 Hz); 7.65 (d, 1H, J=4.5 Hz); 7.94 (d, 1H, J=4.5 Hz); 10.48 (bb, 1H); 10.78 (bs, 1H).

EXAMPLE [19]

6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0143]

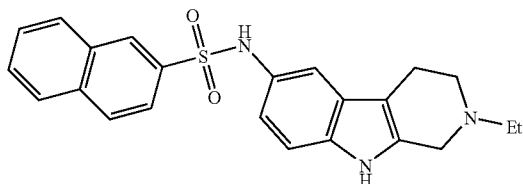


[0144] White amorphous solid, mp 219-222° C. ¹H-NMR (300 MHz, DMSO-d₆): δ(ppm) 1.07 (t, 3H, J=6.9 Hz); 2.53 (bb, 4H); 2.69 (bb, 2H); 3.51 (bb, 2H); 6.66 (d, 1H, J=8.7 Hz); 6.99 (s, 1H); 7.10 (d, 1H, J=8.4 Hz); 7.53 (d, 1H, J=4.5 Hz); 7.81 (d, 1H, J=4.5 Hz); 10.33 (bb, 1H); 10.71 (s, 1H).

EXAMPLE [20]

Naphthalene-2-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H-β-carbolin-6-yl)-amide

[0145]

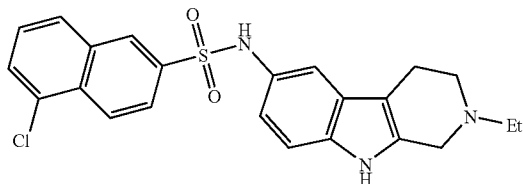


[0146] Cream colored amorphous solid, mp 174-176° C. ¹H-NMR (300 MHz, DMSO-d₆): δ(ppm) 1.04 (t, 3H, J=6.9 Hz); 2.44 (bb, 2H); 2.52 (bb, 2H); 2.63 (bb, 2H); 3.45 (bb, 2H); 6.54 (dd, 1H, J=8.7, 2.1 Hz); 6.90 (d, 1H, J=1.5 Hz); 6.96 (d, 1H, J=8.4 Hz); 7.49 (dd, 1H, J=7.8 Hz); 7.61-7.74 (m, 2H); 7.99-8.05 (m, 2H); 8.12 (d, 1H, J=8.1 Hz); 8.77 (d, 1H, J=8.4 Hz); 10.08 (bb, 1H); 10.59 (s, 1H).

EXAMPLE [21]

5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H-β-carbolin-6-yl)-amide

[0147]

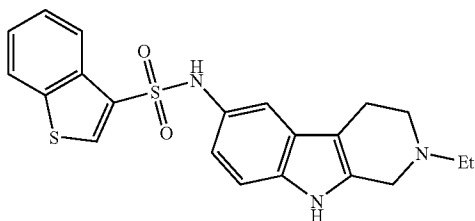


[0148] Yellow amorphous solid, mp 151-153° C. ¹H-NMR (300 MHz, DMSO-d₆): δ(ppm) 1.05 (t, 3H, J=7.2 Hz); 2.51 (bb, 4H); 2.66 (bb, 2H); 3.48 (bb, 2H); 6.66 (dd, 1H, J=8.4, 1.8 Hz); 7.02-7.05 (m, 2H); 7.57 (dd, 1H, J=7.8, 7.8 Hz); 7.83 (d, 1H, J=7.5 Hz); 7.89 (dd, 1H, J=8.7, 1.5 Hz); 8.07 (d, 1H, J=8.1 Hz); 8.28 (d, 1H, J=9.0 Hz); 8.36 (d, 1H, J=1.5 Hz); 9.94 (bb, 1H); 10.65 (s, 1H).

EXAMPLE [22]

Benzo[b]thiophene-3-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H-β-carbolin-6-yl)-amide

[0149]

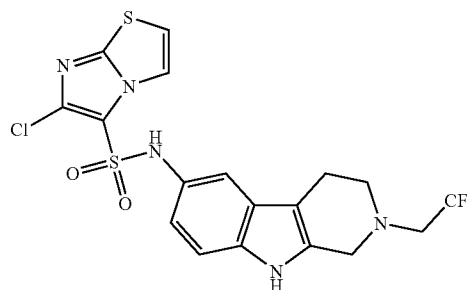


[0150] White amorphous solid, mp 215-216° C. ¹H-NMR (300 MHz, DMSO-d₆): δ(ppm) 1.06 (t, 3H, J=6.9 Hz); 2.54 (bb, 4H); 2.66 (bb, 2H); 3.48 (bb, 2H); 6.59 (dd, 1H, J=8.7, 2.1 Hz); 6.97 (bb, 1H); 7.02 (d, 1H, J=8.7 Hz); 7.43-7.52 (m, 2H); 8.04 (d, 1H, J=7.5 Hz); 8.24 (d, 1H, J=7.2 Hz); 8.30 (s, 1H); 10.03 (s, 1H); 10.65 (s, 1H).

EXAMPLE [23]

6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-β-carbolin-6-yl]-amide

[0151]

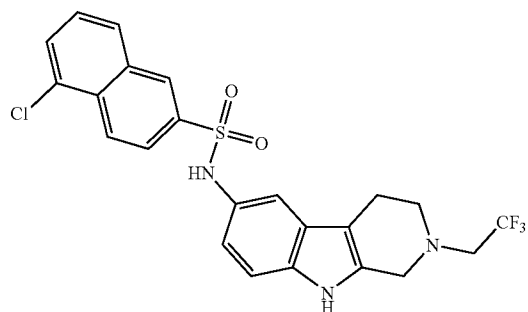


[0152] White amorphous solid, mp 232-233° C. ¹H-NMR (300 MHz, DMSO-d₆): δ(ppm) 2.55 (bb, 2H); 2.93 (bb, 2H); 3.36 (q, 2H, J=10.2 Hz); 3.79 (bb, 2H); 6.64 (dd, 1H, J=8.4, 2.1 Hz); 6.99 (d, 1H, J=2.1 Hz); 7.06 (d, 1H, J=8.5 Hz); 7.49 (d, 1H, J=4.5 Hz); 7.83 (d, 1H, J=4.5 Hz); 9.31 (bb, 1H); 10.66 (bb, 1H).

EXAMPLE [24]

5-Chloro-naphthalene-2-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-β-carbolin-6-yl]-amide

[0153]

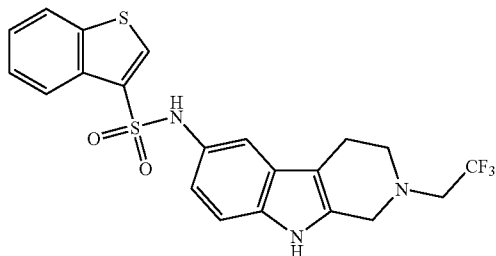


[0154] Yellow amorphous solid, mp 164-166° C. ¹H-NMR (300 MHz, DMSO-d₆): δ(ppm) 2.53 (bb, 2H); 2.92 (bb, 2H); 3.39 (q, 2H, J=10.5 Hz); 3.77 (bb, 2H); 6.68 (dd, 1H, J=8.4, 2.1 Hz); 7.05 (d, 1H, J=8.4 Hz); 7.08 (d, 1H, J=2.1 Hz); 7.58 (dd, 1H, J=8.1, 7.8); 7.83 (dd, 1H, J=7.8, 1.2 Hz); 7.89 (dd, 1H, J=8.7, 1.8 Hz); 8.08 (d, 1H, J=7.5 Hz); 8.28 (d, 1H, J=9.0 Hz); 8.36 (d, 1H, J=1.8 Hz); 9.96 (bb, 1H); 10.70 (s, 1H).

EXAMPLE [25]

Benzo[b]thiophene-3-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl]-amide

[0155]

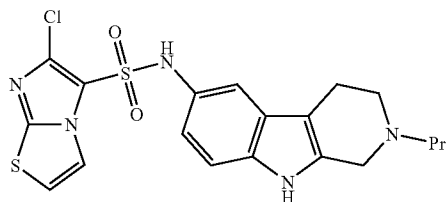


[0156] Yellow amorphous solid, mp 173-175° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.52 (bb, 2H); 2.92 (bb, 2H); 3.35 (q, 2H, J=9.9 Hz); 3.78 (bb, 2H); 6.62 (dd, 1H, J=8.4, 2.1 Hz); 7.00 (d, 1H, J=2.1 Hz); 7.03 (d, 1H, J=8.4 Hz); 7.43-7.54 (m, 2H); 8.04-8.06 (m, 1H); 8.24-8.26 (m, 1H); 8.30 (s, 1H); 10.04 (bb, 1H); 10.69 (s, 1H).

EXAMPLE [26]

6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-propyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0157]

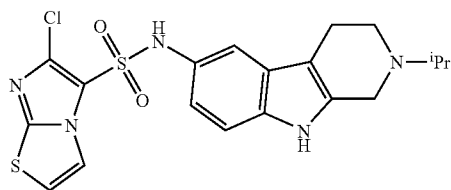


[0158] Yellow amorphous solid, mp 206-207° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 0.95 (t, 3H, J=7.5 Hz); 1.52-1.64 (m, 2H); 2.50-2.61 (m, 4H); 2.77 (bb, 2H); 3.59 (bb, 2H); 6.74 (dd, 1H, J=8.7, 2.1 Hz); 7.08 (d, 1H, J=1.8 Hz); 7.18 (d, 1H, J=8.4 Hz); 7.62 (d, 1H, J=4.5 Hz); 7.90 (d, 1H, J=4.5 Hz); 10.45 (bb, 1H); 10.80 (s, 1H).

EXAMPLE [27]

6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-isopropyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0159]

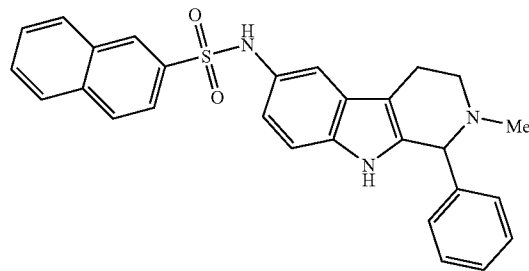


[0160] Orange amorphous solid, mp 234-235° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 1.04 (d, 6H, J=6.0 Hz); 2.52 (bb, 2H); 2.71 (bb, 2H); 2.83-2.96 (m, 1H, J=6.0 Hz); 3.57 (bb, 2H); 6.64 (dd, 1H, J=8.4, 2.1 Hz); 6.98 (bb, 1H); 7.09 (d, 1H, J=8.1 Hz); 7.53 (d, 1H, J=4.2 Hz); 7.81 (d, 1H, J=4.5 Hz); 10.35 (bb, 1H); 10.59 (bb, 1H).

EXAMPLE [28]

Naphthalene-2-sulfonic acid (2-methyl-1-phenyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0161]

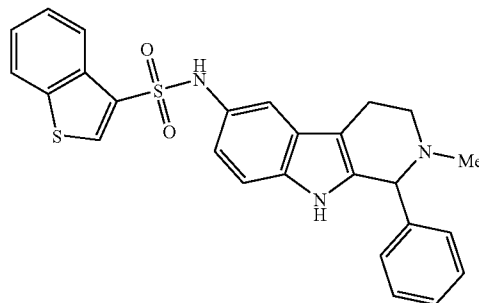


[0162] Yellow amorphous solid, mp 255-260° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.15 (s, 3H); 2.72 (bb, 2H); 3.00 (bb, 2H); 4.28 (bb, 1H); 6.67 (dd, 1H, J=9.0, 3.0 Hz); 6.95 (d, 1H, J=6.0 Hz); 7.12 (bb, 1H); 7.22-7.31 (m, 5H); 7.57-7.68 (m, 2H); 7.76 (dd, 1H, J=9.0, 3.0 Hz); 7.97 (d, 1H, J=9.0 Hz); 8.05 (d, 2H, J=9.0 Hz); 8.29 (bb, 1H); 9.88 (s, 1H); 10.11 (bb, 1H).

EXAMPLE [29]

Benzo[b]thiophene-3-sulfonic acid (2-methyl-1-phenyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0163]

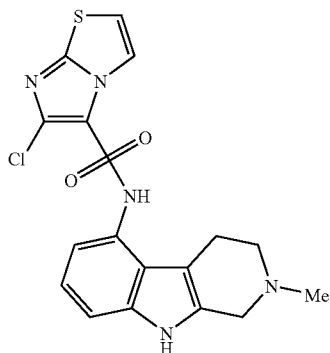


[0164] White amorphous solid, mp 232-234° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.15 (s, 3H); 2.73 (bb, 2H); 3.01 (bb, 2H); 4.27 (bb, 1H); 6.57-6.60 (m, 1H); 6.95 (d, 1H, J=6.0 Hz); 7.07 (bs, 1H); 7.24-7.36 (m, 4H); 7.48-7.56 (m, 3H); 8.08 (d, 1H, J=6.0 Hz); 8.27 (d, 1H, J=9.0 Hz); 8.35 (s, 1H); 10.10 (s, 1H); 10.15 (s, 1H).

EXAMPLE [30]

6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid
(2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-
amide

[0165]

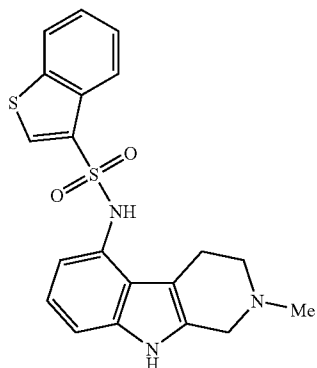


[0166] Yellow amorphous solid, mp 252-253° C. $^1\text{H-NMR}$
(300 MHz, DMSO- d_6): δ (ppm) 2.40 (s, 3H); 2.62 (bb, 2H);
2.83 (bb, 2H); 3.54 (bb, 2H); 6.25 (d, 1H, $J=7.8$ Hz); 6.79 (dd,
1H, $J=8.1, 7.8$ Hz); 7.14 (bb, 1H); 7.44 (bb, 2H); 10.13 (bb,
1H); 10.87 (s, 1H).

EXAMPLE [31]

Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,
9-tetrahydro-1H- β -carbolin-5-yl)-amide

[0167]

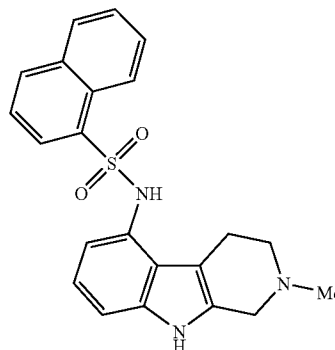


[0168] Orange amorphous solid, mp 236-237° C. $^1\text{H-NMR}$
(300 MHz, DMSO- d_6): δ (ppm) 2.35 (s, 3H); 2.54 (bb, 2H);
2.82 (bb, 2H); 3.47 (bb, 2H); 6.11 (d, 1H, $J=7.8$ Hz); 6.70 (dd,
1H, $J=7.8, 7.8$ Hz); 7.12 (d, 1H, $J=8.1$ Hz); 7.43-7.48 (m, 2H);
8.05-8.12 (m, 2H); 8.23 (s, 1H); 9.77 (bb, 1H); 10.82 (s, 1H).

EXAMPLE [32]

Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tet-
rahydro-1H- β -carbolin-5-yl)-amide

[0169]

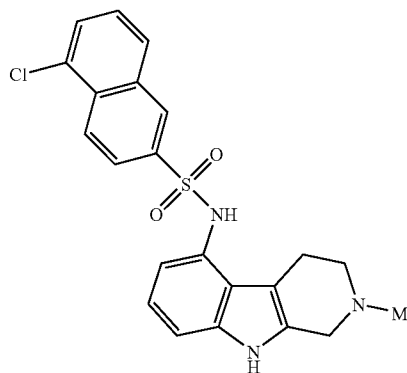


[0170] Orange amorphous solid, mp 217-218° C. $^1\text{H-NMR}$
(300 MHz, DMSO- d_6): δ (ppm) 2.35 (s, 3H); 2.55 (bb, 2H);
2.83 (bb, 2H); 3.47 (bb, 2H); 5.97 (d, 1H, $J=7.2$ Hz); 6.62 (dd,
1H, $J=7.8, 7.8$ Hz); 7.07 (d, 1H, $J=7.8$ Hz); 7.55 (dd, 1H,
 $J=7.8, 7.8$ Hz); 7.63-7.66 (m, 2H); 7.95 (d, 1H, $J=6.6$ Hz);
8.07-8.10 (m, 1H); 8.20 (d, 1H, $J=8.4$ Hz); 8.66-8.69 (m, 1H);
9.80 (bb, 1H); 10.81 (s, 1H).

EXAMPLE [33]

5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,
4,9-tetrahydro-1H- β -carbolin-5-yl)-amide

[0171]

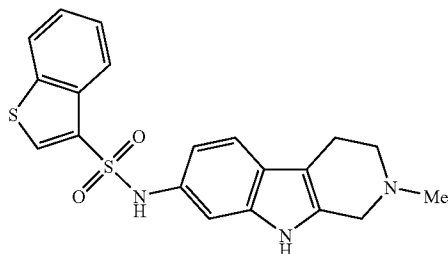


[0172] Orange amorphous solid, mp 245-247° C. $^1\text{H-NMR}$
(300 MHz, DMSO- d_6): δ (ppm) 2.34 (s, 3H); 2.55 (bb, 2H);
2.87 (bb, 2H); 3.47 (bb, 2H); 6.15 (d, 1H, $J=7.5$ Hz); 6.69 (dd,
1H, $J=7.8, 7.8$ Hz); 7.10 (d, 1H, $J=8.1$ Hz); 7.61 (dd, 1H,
 $J=8.1, 7.8$ Hz); 7.87 (d, 1H, $J=7.5$ Hz); 7.92 (dd, 1H, $J=9.0,$
1.5 Hz); 8.10 (d, 1H, $J=8.1$ Hz); 8.32-8.35 (m, 2H); 9.70 (bb,
1H); 10.84 (s, 1H).

EXAMPLE [34]

Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide

[0173]

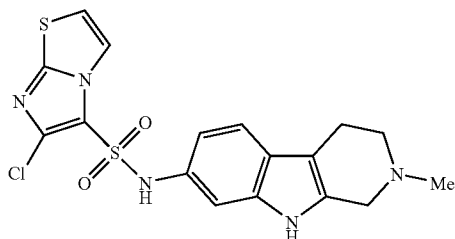


[0174] Cream colored amorphous solid, mp 255-257° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.34 (s, 3H); 2.57 (bb, 4H); 3.41 (bb, 2H); 6.61 (dd, 1H, J=8.4, 1.5 Hz); 6.96 (bb, 1H); 7.10 (d, 1H, J=8.4 Hz); 7.43-7.54 (m, 2H); 8.04 (d, 1H, J=7.8 Hz); 8.27 (d, 1H, J=8.1 Hz); 8.30 (s, 1H); 10.16 (bb, 1H); 10.60 (s, 1H).

EXAMPLE [35]

6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide

[0175]

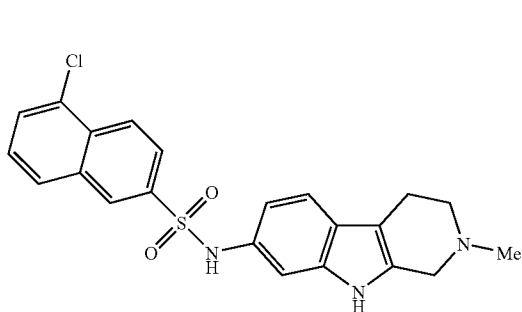


[0176] Orange amorphous solid, mp 225-227° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.38 (s, 3H); 2.60 (bb, 4H); 3.49 (bb, 2H); 6.65 (dd, 1H, J=8.1, 1.5 Hz); 7.01 (d, 1H, J=1.8 Hz); 7.18 (d, 1H, J=8.4 Hz); 7.56 (d, 1H, J=4.5 Hz); 7.89 (d, 1H, J=4.5 Hz); 10.47 (bb, 1H); 10.72 (s, 1H).

EXAMPLE [36]

5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide

[0177]

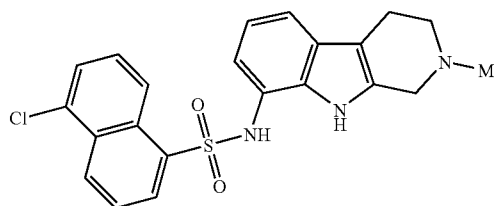


[0178] White amorphous solid, mp 257-259° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.33 (s, 3H); 2.56 (bb, 4H); 3.41 (bb, 2H); 6.67 (dd, 1H, J=8.1, 1.5 Hz); 7.00 (bb, 1H); 7.12 (d, 1H, J=8.4 Hz); 7.58 (dd, 1H, J=8.1, 7.8 Hz); 7.83 (d, 1H, J=7.2 Hz); 7.89 (dd, 1H, J=8.7, 1.5 Hz); 8.08 (d, 1H, J=8.1 Hz); 8.28 (d, 1H, J=9.0 Hz); 8.37 (bb, 1H); 10.05 (bb, 1H); 10.60 (s, 1H).

EXAMPLE [37]

5-Chloro-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0179]

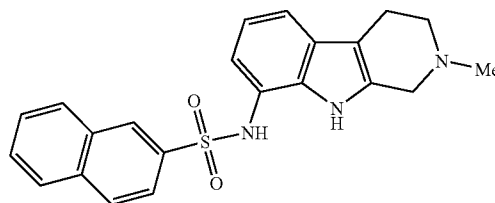


[0180] White amorphous solid, mp 251-252° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.41 (s, 3H); 2.61 (bb, 2H); 2.66 (bb, 2H); 3.54 (bb, 2H); 6.24 (d, 1H, J=7.5 Hz); 6.58 (dd, 1H, J=7.8, 7.5 Hz); 7.04 (d, 1H, J=7.8 Hz); 7.67 (d, 1H, J=7.5 Hz); 7.72 (d, 1H, J=7.2 Hz); 7.85 (d, 1H, J=7.5 Hz); 8.15 (d, 1H, J=6.6 Hz); 8.46 (d, 1H, J=8.7 Hz); 8.80 (d, 1H, J=8.7 Hz); 10.16 (bb, 1H); 10.49 (s, 1H).

EXAMPLE [38]

Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0181]

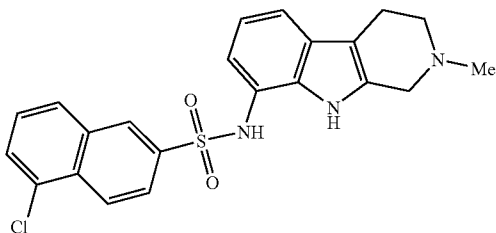


[0182] Orange amorphous solid, mp 240-242° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.39 (s, 3H); 2.62 (bb, 4H); 3.51 (bb, 2H); 6.52 (d, 1H, J=7.5 Hz); 6.67 (dd, 1H, J=8.7, 7.5); 7.08 (d, 1H, J=7.5 Hz); 7.60-7.66 (m, 2H); 7.80 (dd, 1H, J=8.7, 1.8 Hz); 7.98 (d, 1H, J=7.8 Hz); 8.04-8.07 (m, 2H); 8.32 (bb, 1H); 9.85 (bb, 1H); 10.52 (s, 1H).

EXAMPLE [39]

5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0183]

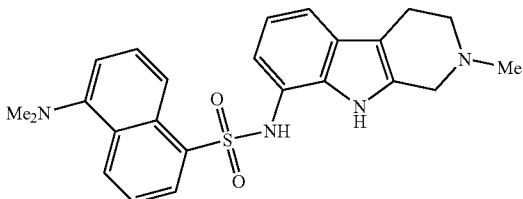


[0184] Yellow amorphous solid, mp 256-257° C. $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ (ppm) 2.40 (s, 3H); 2.62 (bb, 4H); 3.52 (bb, 2H); 6.48 (d, 1H, $J=7.5$ Hz); 6.67 (dd, 1H, $J=7.8, 7.8$ Hz); 7.10 (d, 1H, 7.8 Hz); 7.60 (dd, 1H, $J=7.8, 7.8$ Hz); 7.85 (d, 1H, $J=6.9$ Hz); 7.97 (dd, 1H, $J=9.0, 1.8$ Hz); 8.09 (d, 1H, $J=8.4$ Hz); 8.31 (d, 1H, $J=9.0$ Hz); 8.40 (d, 1H, $J=1.8$ Hz); 9.94 (bb, 1H); 10.54 (s, 1H).

EXAMPLE [40]

5-Dimethylamino-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0185]

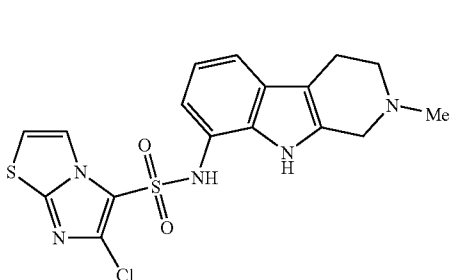


[0186] Yellow amorphous solid, mp 225-226° C. $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ (ppm) 2.39 (s, 3H); 2.61 (bb, 4H); 2.79 (s, 6H); 3.51 (bb, 2H); 6.38 (d, 1H, $J=7.8$ Hz); 6.60 (dd, 1H, $J=7.8, 7.8$ Hz); 7.01 (d, 1H, $J=7.8$ Hz); 7.23 (d, 1H, $J=7.5$ Hz); 7.49-7.62 (m, 2H); 8.06 (d, 1H, $J=6.9$ Hz); 8.39-8.46 (m, 2H); 10.04 (bb, 1H); 10.41 (s, 1H).

EXAMPLE [41]

6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0187]

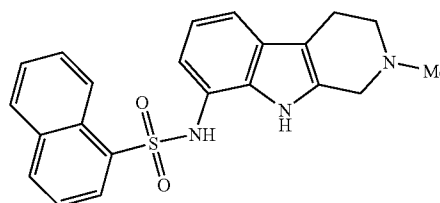


[0188] Yellow amorphous solid, mp 230-232° C. $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ (ppm) 2.45 (s, 3H); 2.64 (bb, 2H); 2.73 (bb, 2H); 3.60 (bb, 2H); 6.47 (d, 1H, $J=8.1$ Hz); 6.69 (dd, 1H, $J=7.8, 7.8$ Hz); 7.46 (d, 1H, $J=4.8$ Hz); 7.60 (d, 1H, $J=4.2$ Hz); 7.95 (d, 1H, $J=4.2$ Hz); 10.40 (s, 1H); 11.05 (s, 1H).

EXAMPLE [42]

Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0189]

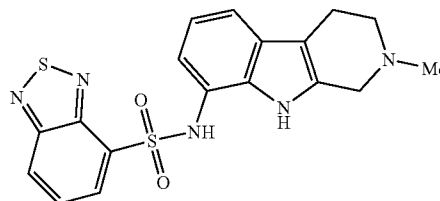


[0190] White amorphous solid, mp 259-260° C. $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ (ppm) 2.40 (s, 3H); 2.61 (bb, 4H); 3.53 (bb, 2H); 6.29 (d, 1H, $J=7.5$ Hz); 6.58 (dd, 1H, $J=7.8, 7.8$ Hz); 7.03 (d, 1H, $J=7.8$ Hz); 7.54 (dd, 1H, $J=7.8, 7.8$ Hz); 7.63-7.74 (m, 2H); 8.04-8.07 (m, 2H); 8.18 (d, 1H, $J=8.1$ Hz); 8.79 (d, 1H, $J=8.4$ Hz); 10.08 (bb, 1H); 10.48 (s, 1H).

EXAMPLE [43]

2,1,3-Benzothiadiazole-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0191]

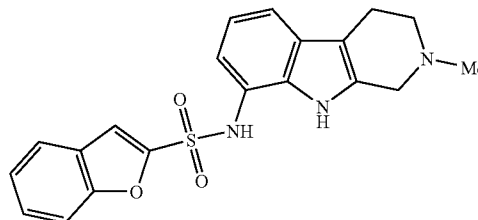


[0192] Yellow amorphous solid, mp 238-240° C. $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ (ppm) 2.39 (s, 3H); 2.60 (bb, 4H); 3.51 (bb, 2H); 6.36 (d, 1H, $J=7.8$ Hz); 6.60 (dd, 1H, $J=7.5, 7.5$ Hz); 7.03 (d, 1H, $J=7.8$ Hz); 7.76 (dd, 1H, $J=8.7, 6.9$ Hz); 8.13 (d, 1H, $J=6.9$ Hz); 8.34 (d, 1H, 8.7 Hz); 10.10 (bb, 1H); 10.47 (s, 1H).

EXAMPLE [44]

Benzofuran-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0193]

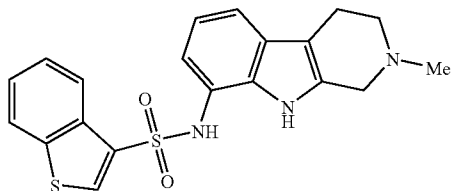


[0194] Brown amorphous solid, mp 229-231° C. $^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ (ppm) 2.39 (s, 3H); 2.68 (bb, 2H); 2.77 (bb, 2H); 3.64 (bb, 2H); 6.60 (d, 1H, $J=7.2$ Hz); 6.73 (dd, 1H, $J=7.8, 7.5$ Hz); 7.12 (d, 1H, $J=7.5$ Hz); 7.35 (dd, 1H, $J=7.8, 7.2$ Hz); 7.39 (bb, 1H); 7.47-7.53 (m, 1H); 7.69-7.73 (m, 2H); 10.34 (bb, 1H); 10.63 (s, 1H).

EXAMPLE [45]

Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0195]

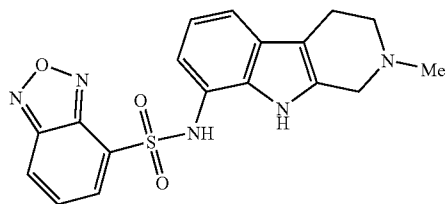


[0196] White amorphous solid, mp 225-226° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.39 (s, 3H); 2.62 (bb, 4H); 3.52 (bb, 2H); 6.39 (d, 1H, J=7.5 Hz); 6.65 (dd, 1H, J=7.8, 7.5 Hz); 7.08 (d, 1H, J=7.8 Hz); 7.43-7.53 (m, 2H); 8.06-8.08 (m, 1H); 8.21-8.24 (m, 1H); 8.38 (s, 1H); 10.01 (bb, 1H); 10.49 (s, 1H).

EXAMPLE [46]

Benzofurazan-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide

[0197]

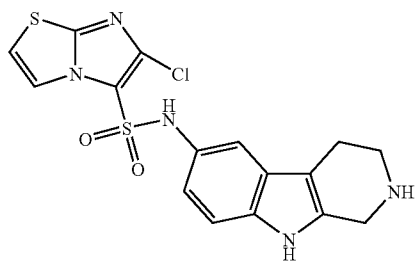


[0198] Yellow amorphous solid, mp 246-247° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.45 (s, 3H); 2.64 (bb, 2H); 2.72 (bb, 2H); 3.60 (bb, 2H); 6.41 (d, 1H, J=7.5 Hz); 6.65 (dd, 1H, J=7.8, 7.5 Hz); 7.06 (d, 1H, J=7.8 Hz); 7.63 (dd, 1H, J=9.0, 6.6 Hz); 7.92 (d, 1H, J=6.6 Hz); 8.28 (d, 1H, J=9.0 Hz); 10.28 (bb, 1H); 10.53 (s, 1H).

EXAMPLE [47]

6-chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide

[0199]

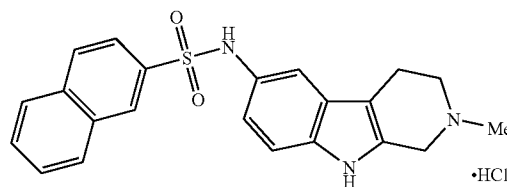


[0200] A solution of N-(3-(2-aminoethyl)-1H-indol-5-yl) 6-chloro-imidazo[2,1-b]thiazole-sulfonamide (according to formula (V), 200 mg, 0.5 mmol) and CH₂(OMe)₂ (175 μ L, 2 mmol) in AcOH (2 mL) was stirred at 100° C. for 48 h (Pictet-Spengler cyclization). The mixture was after that time basified and extracted with ethyl acetate. The organic extracts were dried and concentrated to give the corresponding 6-chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide as a cream colored amorphous solid, mp 242-244° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.76 (bb, 2H); 3.35 (bb, 2H); 4.24 (bb, 2H); 6.45 (dd, 1H, J=8.7, 2.4 Hz); 6.79-6.82 (m, 2H); 7.27 (d, 1H, J=4.5 Hz); 7.88 (d, 1H, J=435 Hz); 9.96 (bb, 2H).

EXAMPLE [48]

Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide hydrochloride

[0201]



[0202] To a solution of 50 mg (0.13 mmol) of naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide (example 12) in 2 mL of ethanol were added 1 mL of a 2.5 N solution of hydrochloric acid in ethanol. The hydrochloride crystallizes at room temperature as white solid, mp 239-241° C. ¹H-NMR (300 MHz, DMSO-d₆): δ (ppm) 2.84 (bb, 2H); 2.92 (s, 3H); 3.31 (bb, 1H); 3.62 (bb, 1H); 4.30 (bb, 1H); 4.43 (bb, 1H); 6.76 (dd, 1H, J=8.7, 1.8 Hz); 7.15 (d, 1H, J=8.7 Hz); 7.18 (d, 1H, J=1.8 Hz); 7.56-7.67 (m, 2H); 7.72 (dd, 1H, J=8.7, 1.8 Hz); 7.96 (bd, 1H, J=8.1 Hz); 8.02-8.06 (m, 2H); 8.29 (bb, 1H); 10.00 (s, 1H); 10.43 (bb, 1H); 11.05 (s, 1H).

Pharmacological Methods:

Binding to Serotonin Receptor 5HT₆

[0203] Cell membranes of HEK-293 cells expressing the 5HT₆-human recombinant receptor were supplied by Receptor Biology. In said membranes the receptor concentration is 2.18 pmol/mg protein and the protein concentration is 9.17 mg/ml. The experimental protocol follows the method of B. L. Roth et al. [B. L. Roth et al., *The Journal of Pharmacology and Experimental Therapeutics*, 1994, 268, 1403] with the following slight changes. The respective part of the literature description is hereby incorporated by reference and forms part of the disclosure.

[0204] The commercial membrane is diluted (1:40 dilution) with the binding buffer: 50 mM Tris-HCl, 10 mM MgCl₂, 0.5 mM EDTA (pH 7.4). The radioligand used is [³H]-LSD at a concentration of 2.7 nM with a final volume of

200 μ l. incubation is initiated by adding 100 μ l of membrane suspension, (\approx 22.9 μ g membrane protein), and is prolonged for 60 minutes at a temperature of 37° C. The incubation is ended by fast filtration in a Brandel Cell Harvester through fiber glass filters made by Schleicher & Schuell GF 3362 pretreated with a solution of polyethylenimine at 0.5%. The filters are washed three times with three milliliters of buffer Tris-HCl 50 mM pH 7.4. The filters are transferred to flasks and 5 ml of Ecoscint H liquid scintillation cocktail are added to each flask. The flasks are allowed to reach equilibrium for several hours before counting with a Wallac Winspectral 1414 scintillation counter. Non-specific binding is determined in the presence of 100 μ M of serotonin. Tests were made in triplicate. The inhibition constants (K_i , nM) were calculated by non-linear regression analysis using the program EBDA/LIGAND described in Munson and Rodbard, *Analytical Biochemistry*, 1980, 107, 220, which is hereby incorporated by reference and forms part of the disclosure.

[0205] The binding results for some of these compounds are given in the following table.

TABLE

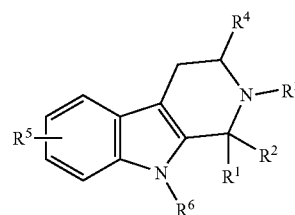
Example	% Inhibition 10 ⁻⁷ M	K _i (nM)
1	80.7	0.9
2	79.5	2.8
4	70.6	
12	89.7	15.9
13	71.1	
16	85.0	
19	97.0	1.1
21	72.8	
22	84.6	36.7
26	87.9	2.0
27	81.8	
35	90.0	8.0
38	73.5	
45	87.1	29.7

[0206] The invention also relates to a pharmaceutical composition containing a compound of general formula (I) and one or more pharmaceutically acceptable excipients. Typically the pharmaceutical compositions and medicaments comprise 1 to 60% by weight of one or more derivatives of general formula (I) and 40 to 99% by weight of one or more excipients.

[0207] The amount of active ingredient to be administered to the patient varies in dependence on the weight of the patient, the route of administration, the indication and the degree of severity of the disorder. Usually 1 to 500 mg of at least one derivative of general formula (I) are administered to the patient in need of treatment per day. The total daily dose may be administered to the patient in one or more portions.

Formula per tablet:	
Compound according to example 1	5 mg
Lactose	60 mg
Crystalline cellulose	25 mg
K 90 Povidone	5 mg
Pregelatinised starch	3 mg
Colloidal silicon dioxide	1 mg
Magnesium stearate	1 mg
Total weight per tablet	100 mg

1. A tetrahydro- β -carbolin-sulfonamide derivative of general formula (I):



wherein

R¹ and R², identical or different, represent hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, aryl, heteroaryl, C₃-C₆ cycloalkyl or C₃-C₆ heterocycloalkyl, optionally substituted with one or more substituents independently selected from —NO₂; —NH₂; —SH; —OH; —CN; —C(=O)—OH; —S(=O)₂-OH; —C(=O)—NH₂; —S(=O)₂-NH₂; —S(=O)₂-R^f; —OR^f; —SR^f; —C(=O)—OR^f; —N(R^f)—S(=O)₂-R^g; —NH—R^f; —NR^f-R^g; —C(=O)—NHR^f; —C(=O)—NR^f-R^g; —S(=O)₂-NHR^f; —S(=O)₂-NR^f-R^g; —O—C(=O)—R^f; —NH—C(=O)—R^f; —NR^f-C(=O)—R^g; —NH—C(=O)—O—R^f; —NR^f-C(=O)—O—R^g; —S(=O)₂-O—R^f; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g, independent from one another, each represent a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene, alkenylene or alkynylene group, or R¹ and R² together form a spiro substituent of 3-6 carbons;

R³ represents hydrogen, C₁-C₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, aryl or heteroaryl; optionally substituted with one or more substituents independently selected from —NO₂; —NH₂; —SH; —OH; —CN; —C(=O)—OH; —S(=O)₂-OH; —C(=O)—NH₂; —S(=O)₂-NH₂; —S(=O)₂-R^f; —OR^f; —SR^f; —C(=O)—OR^f; —N(R^f)—S(=O)₂-R^g; —NH—R^f; —NR^f-R^g; —C(=O)—NHR^f; —C(=O)—NR^f-R^g; —S(=O)₂-NHR^f; —S(=O)₂-NR^f-R^g; —O—C(=O)—R^f; —NH—C(=O)—R^f; —NR^f-C(=O)—R^g; —NH—C(=O)—O—R^f; —NR^f-C(=O)—O—R^g; —S(=O)₂-O—R^f; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear

or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , have the meaning defined above
 R^4 represents hydrogen, $\text{CO}-\text{NR}^a\text{R}^b$, $\text{CO}-\text{OR}^a$, wherein R^a and R^b , identical or different, represent hydrogen, C_1 - C_6 alkyl, aryl, heteroaryl, C_3 - C_6 cycloalkyl, or C_3 - C_6 heterocycloalkyl, optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , have the meaning defined above

R^5 represents $\text{NR}^c\text{SO}_2\text{R}^d$, wherein

R^c represents hydrogen or C_{1-4} alkyl optionally substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, cyano, C_1 - C_6 alkoxy and trifluoromethyl;

R^d represents aryl or heteroaryl optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , have the meaning defined above

R^6 represents hydrogen, C_{1-4} alkyl, aryl, heteroaryl or SO_2R^e , wherein

R^e represents aryl, heteroaryl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl; optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-$

$\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , have the meaning defined above

with the proviso that when R^d is phenyl, R^e is other than phenyl;

optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of its stereoisomers, preferably enantiomers and/or diastereomers, in any mixing ratio, or a physiologically acceptable salt thereof, or a corresponding solvate thereof.

2. A compound according to claim 1, wherein R^1 , R^2 , R^3 and R^6 are selected from hydrogen, C_1 - C_4 alkyl or phenyl, R^4 is H, and R^5 is NHSO_2R^d , wherein R^d is an aryl or heteroaryl group selected from phenyl, naphthyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzofurazanyl, indolyl, benzothiophenyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoimidazolyl, indazolyl, benzoxadiazolyl, benzothiadiazolyl, benzotriazolyl and imidazothiazolyl, optionally substituted.

3. A compound according to claim 1, selected from the following group:

- [1] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [2] Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [3] Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [4] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [5] 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [6] Benzo[1,2,5]thiadiazole-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [7] N-[4-(2-Methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)sulfamoyl]-phenyl]-acetamide;
- [8] 4-Amino-N-(2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-benzenesulfonamide;
- [9] N-[4-Methyl-5-(2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)sulfamoyl]-thiazol-2-yl]-acetamide;
- [10] 5-Dimethylamino-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [11] Benzofuran-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [12] Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [13] 5-Methyl-benzo[b]thiophene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [14] 4-Fluoro-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;
- [15] 7-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[16] 6-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[17] 6-Trifluoromethyl-imidazo[2,1-b]thiazole-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[18] 6-Trifluoromethyl-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[19] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[20] Naphthalene-2-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[21] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[22] Benzo[b]thiophene-3-sulfonic acid (2-ethyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[23] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl]-amide;

[24] 5-Chloro-naphthalene-2-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl]-amide;

[25] Benzo[b]thiophene-3-sulfonic acid [2-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl]-amide;

[26] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-propyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[27] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-isopropyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[28] Naphthalene-2-sulfonic acid (2-methyl-1-phenyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[29] Benzo[b]thiophene-3-sulfonic acid (2-methyl-1-phenyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide;

[30] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-amide;

[31] Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-amide;

[32] Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-amide;

[33] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-5-yl)-amide;

[34] Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide;

[35] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide;

[36] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-7-yl)-amide;

[37] 5-Chloro-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[38] Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[39] 5-Chloro-naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[40] 5-Dimethylamino-naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[41] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[42] Naphthalene-1-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[43] 2,1,3-Benzothiadiazole-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[44] Benzofuran-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

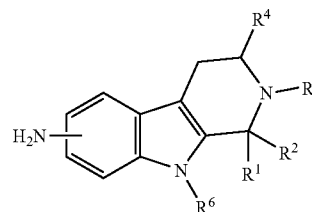
[45] Benzo[b]thiophene-3-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[46] Benzofurazan-4-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-8-yl)-amide;

[47] 6-Chloro-imidazo[2,1-b]thiazole-5-sulfonic acid (2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide; and

[48] Naphthalene-2-sulfonic acid (2-methyl-2,3,4,9-tetrahydro-1H- β -carbolin-6-yl)-amide hydrochloride.

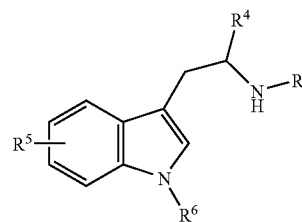
4. A procedure for preparing a tetrahydro- β -carbolin-sulfonamide derivative of general formula (I), characterised by reacting a compound of general formula (II)



(II)

wherein R^1 , R^2 , R^3 , R^4 and R^6 have the meanings given in claim 1; with a sulfonyl halide of general formula $R^d\text{SO}_2\text{X}$, wherein R^d has the meaning given in claim 1 and X is halogen.

5. A procedure for preparing a tetrahydro- β -carbolin-sulfonamide derivative of general formula (I), characterised by a Pictet-Spengler cyclization of a compound of general formula (V)



(V)

wherein R^3 , R^4 , R^5 and R^6 have the meanings given in claim 1; with an aldehyde of formula $R^1\text{CHO}$ or a ketone of formula $R^1R^2\text{CO}$ or with $\text{CH}_2(\text{OMe})_2$ wherein R^1 and R^2 have the meaning given in claim 1.

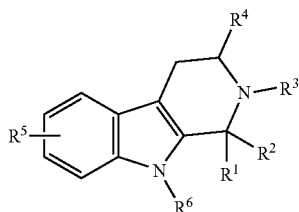
6. A pharmaceutical composition containing a compound according to claim 1 and one or more pharmaceutically acceptable excipients.

7. A tetrahydro- β -carbolin-sulfonamide derivative of general formula (I) according to claim 1 for the prophylaxis and/or treatment of a disorder or a disease related to 5-HT₆ receptors in mammals, including humans.

8. A tetrahydro- β -carbolin-sulfonamide derivative of general formula (I) according to claim 7 for the prophylaxis and/or treatment of a disorder or a disease related to food intake, preferably for the regulation of appetite, for the maintenance, increase or reduction of body weight, for the prophylaxis and/or treatment of obesity, bulimia, anorexia, cachexia or type II diabetes, preferably type II diabetes that is caused by obesity, or for the prophylaxis and/or treatment of irritable colon syndrome; disorders of the central nervous system; anxiety; panic attacks; depression; bipolar disorders; cognitive disorders; memory disorders; senile dementia; psychosis; neurodegenerative disorders, preferably selected

from the group consisting of Morbus Alzheimer, Morbus Parkinson, Morbus Huntington and Multiple Sclerosis; schizophrenia; psychosis; or hyperactivity disorders, preferably attention deficit/hyperactivity disorder, or for the improvement of cognition.

9. Use of a tetrahydro- β -carbolin-sulfonamide derivative of general (I):



(I)

wherein

R^1 and R^2 , identical or different, represent hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, aryl, heteroaryl, C_3 - C_6 cycloalkyl or C_3 - C_6 heterocycloalkyl, optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , independent from one another, each represent a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene, alkenylene or alkynylene group,

or R^1 and R^2 together form a spiro substituent of 3-6 carbons;

R^3 represents hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, aryl or heteroaryl; optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-$

$\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , have the meaning defined above

R^4 represents hydrogen, $\text{CO}-\text{NR}^a/\text{R}^b$, $\text{CO}-\text{OR}^a$, wherein R^a and R^b , identical or different, represent hydrogen, C_1 - C_6 alkyl, aryl, heteroaryl, C_3 - C_6 cycloalkyl, or C_3 - C_6 heterocycloalkyl, optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , have the meaning defined above

R^5 represents $\text{NR}^c\text{SO}_2\text{R}^d$, wherein

R^c represents hydrogen or C_{1-4} alkyl optionally substituted with one or more substituents independently selected from C_1 - C_6 alkyl, aryl, cyano, C_1 - C_6 , alkoxy and trifluoromethyl;

R^d represents aryl or heteroaryl optionally substituted with one or more substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; an halogen atom; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , have the meaning defined above

R^6 represents hydrogen, C_{1-4} alkyl, aryl, heteroaryl or SO_2R^e , wherein

R^e represents aryl, heteroaryl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl; optionally substituted with one or more

substituents independently selected from $-\text{NO}_2$; $-\text{NH}_2$; $-\text{SH}$; $-\text{OH}$; $-\text{CN}$; $-\text{C}(=\text{O})-\text{OH}$; $-\text{S}(=\text{O})_2-\text{OH}$; $-\text{C}(=\text{O})-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{NH}_2$; $-\text{S}(=\text{O})_2-\text{R}^f$; $-\text{OR}^f$; $-\text{SR}^f$; $-\text{C}(=\text{O})-\text{OR}^f$; $-\text{N}(\text{R}^f)-\text{S}(=\text{O})_2-\text{R}^g$; $-\text{NH}-\text{R}^f$; $-\text{NR}^f/\text{R}^g$; $-\text{C}(=\text{O})-\text{NHR}^f$; $-\text{C}(=\text{O})-\text{NR}^f/\text{R}^g$; $-\text{S}(=\text{O})_2-\text{NHR}^f$; $-\text{S}(=\text{O})_2-\text{NR}^f/\text{R}^g$; $-\text{O}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{R}^g$; $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{R}^f$; $-\text{NR}^f-\text{C}(=\text{O})-\text{O}-\text{R}^g$; $-\text{S}(=\text{O})_2-\text{O}-\text{R}^f$; a linear or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical; a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as a ring member containing cycloaliphatic radical, which may be bonded via a linear or branched alkylene group; or an optionally at least mono-substituted aryl or heteroaryl radical, which may be bonded via a linear or branched alkylene group;

wherein R^f and R^g , have the meaning defined above optionally in form of one of its stereoisomers, preferably enantiomers or diastereomers, a racemate or in form of a mixture of at least two of its stereoisomers, preferably

enantiomers and/or diastereomers, in any mixing ratio, or a physiologically acceptable salt thereof, or a corresponding solvate thereof;

in the manufacture of a medicament for the prophylaxis and/or treatment of a disorder or a disease related to 5-HT₆ receptors in mammals, including humans.

10. Use according to claim **9** for the prophylaxis and/or treatment of a disorder or a disease related to food intake, preferably for the regulation of appetite, for the maintenance, increase or reduction of body weight, for the prophylaxis and/or treatment of obesity, bulimia, anorexia, cachexia or type II diabetes, preferably type II diabetes that is caused by obesity, or for the prophylaxis and/or treatment of irritable colon syndrome; disorders of the central nervous system; anxiety; panic attacks; depression; bipolar disorders; cognitive disorders; memory disorders; senile dementia; psychosis; neurodegenerative disorders, preferably selected from the group consisting of Morbus Alzheimer, Morbus Parkinson, Morbus Huntington and Multiple Sclerosis; schizophrenia; psychosis; or hyperactivity disorders, preferably attention deficit/hyperactivity disorder, or for the improvement of cognition.

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