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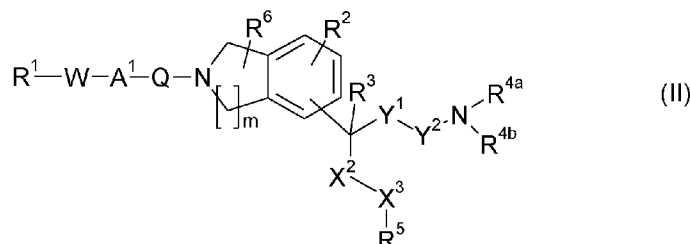
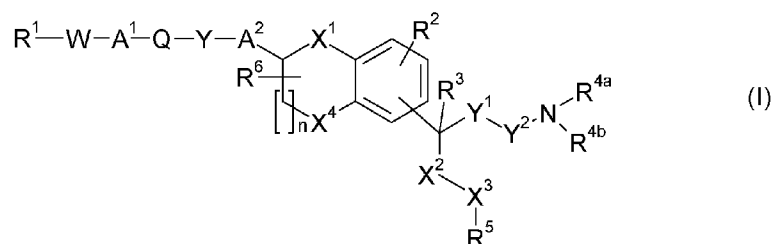
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[Continued on next page]

(54) Title: PHENALKYLAMINE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM, AND THEIR USE IN THERAPY



(57) Abstract: The present invention relates to phenalkylamine derivatives of the formula (I) or (II); or a physiologically tolerated salt thereof. The invention relates to pharmaceutical compositions comprising such phenalkylamine derivatives, and the use of such phenalkylamine derivatives for therapeutic purposes. The phenalkylamine derivatives are GlyT1 inhibitors.



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Phenalkylamine derivatives, pharmaceutical compositions containing them, and their use in therapy

#### Background Of The Invention

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The present invention relates to phenalkylamine derivatives, pharmaceutical compositions comprising such phenalkylamine derivatives, and the use of such phenalkylamine derivatives for therapeutic purposes. The phenalkylamine derivatives are GlyT1 inhibitors.

10 Dysfunction of glutamatergic pathways has been implicated in a number of disease states in the human central nervous system (CNS) including but not limited to schizophrenia, cognitive deficits, dementia, Parkinson disease, Alzheimer disease and bipolar disorder. A large number of studies in animal models lend support to the NMDA hypofunction hypothesis of schizophrenia.

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NMDA receptor function can be modulated by altering the availability of the co-agonist glycine. This approach has the critical advantage of maintaining activity-dependent activation of the NMDA receptor because an increase in the synaptic concentration of glycine will not produce an activation of NMDA receptors in the absence of glutamate. Since synaptic glutamate levels are tightly maintained by high affinity transport mechanisms, an increased activation of the glycine site will only enhance the NMDA component of activated synapses.

20

Two specific glycine transporters, GlyT1 and GlyT2 have been identified and shown to belong to the Na/Cl-dependent family of neurotransmitter transporters which includes taurine, gamma-aminobutyric acid (GABA), proline, monoamines and orphan transporters. GlyT1 and GlyT2 have been isolated from different species and shown to have only 50% identity at the amino acid level. They also have a different pattern of expression in mammalian central nervous system, with GlyT2 being expressed in spinal cord, brainstem and cerebellum and GlyT1 present in these regions as well as forebrain areas such as cortex, hippocampus, septum and thalamus. At the cellular level, GlyT2 has been reported to be expressed by glycinergic nerve endings in rat spinal cord whereas GlyT1 appears to be preferentially expressed by glial cells. These expression studies have led to the suggestion that GlyT2 is predominantly responsible for glycine uptake at glycinergic synapses whereas GlyT1 is involved in monitoring glycine concentration in the vicinity of NMDA receptor expressing synapses. Recent functional studies in rat have shown that blockade of GlyT1 with the potent inhibitor (N-[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl]-sarcosine (NFPS) potentiates NMDA receptor activity and NMDA receptor-dependent long-term potentiation in rat.

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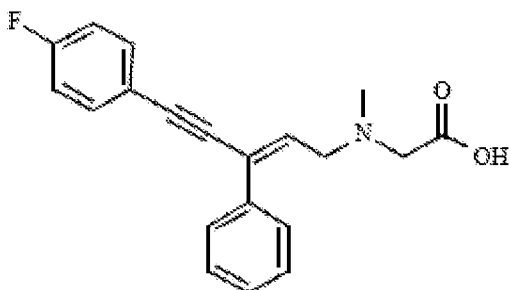
Molecular cloning has further revealed the existence of three variants of GlyT1, termed GlyT-1a, GlyT-1b and GlyT-1c, each of which displays a unique distribution in the brain and peripheral tissues. The variants arise by differential splicing and exon usage, and differ in their N-terminal regions.

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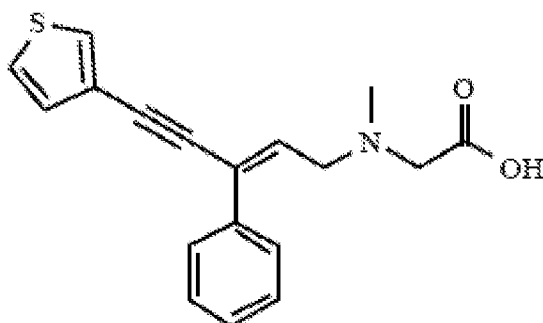
The physiological effects of GlyT1 in forebrain regions together with clinical reports showing the beneficial effects of GlyT1 inhibitor sarcosine in improving symptoms in schizophrenia patients suggest that selective GlyT1 inhibitors represent a new class of antipsychotic drugs.

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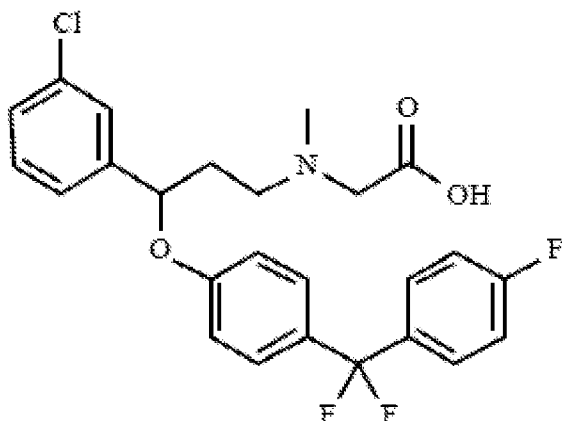
Glycine transporter inhibitors are already known in the art, for example:



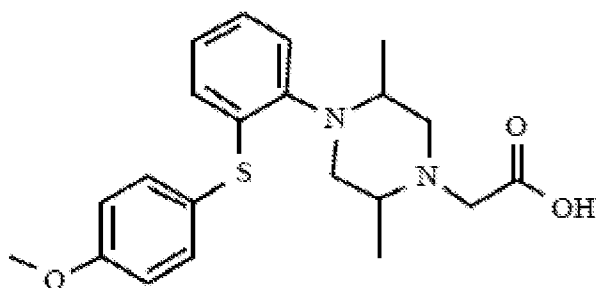
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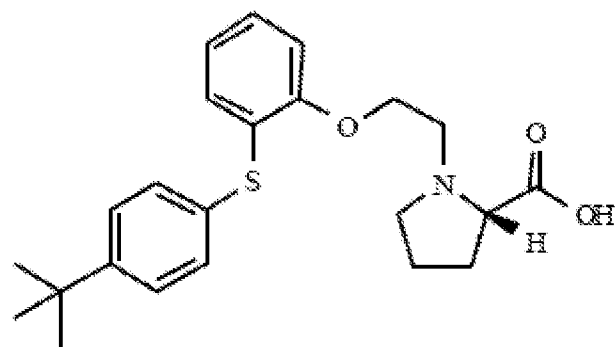
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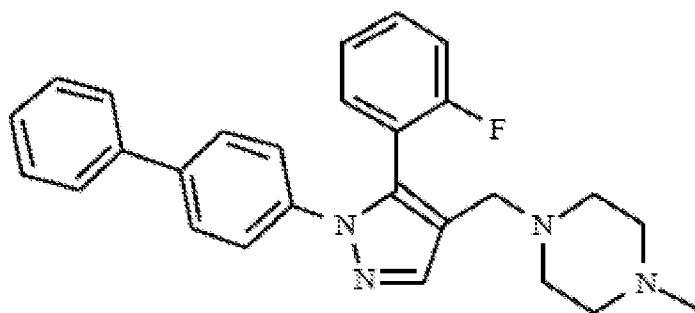
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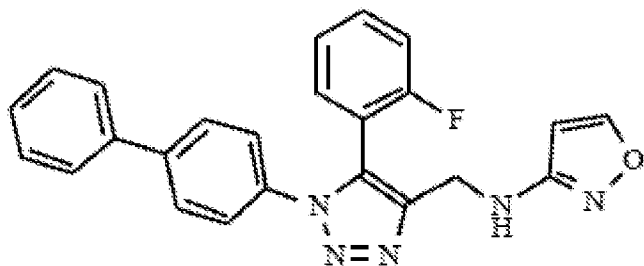
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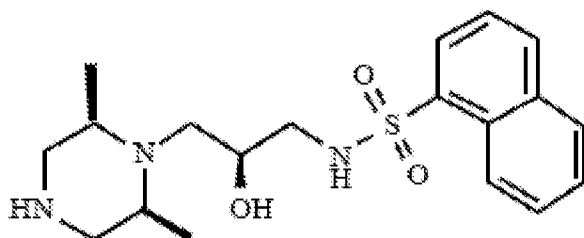
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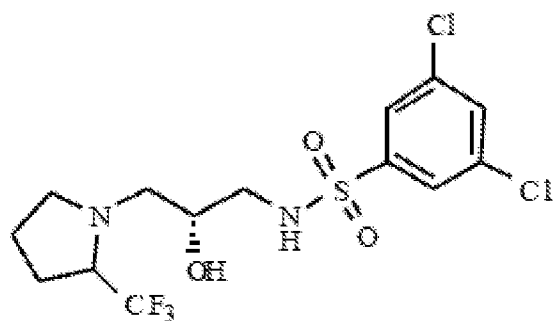
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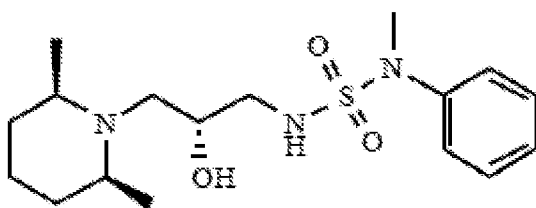
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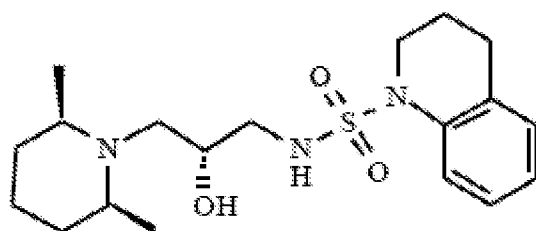
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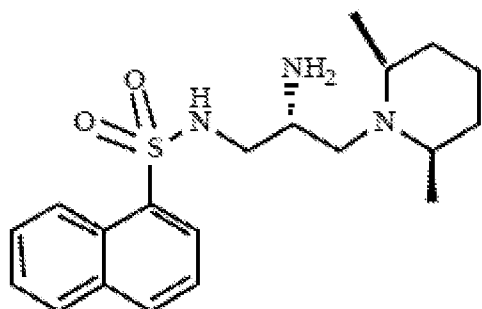
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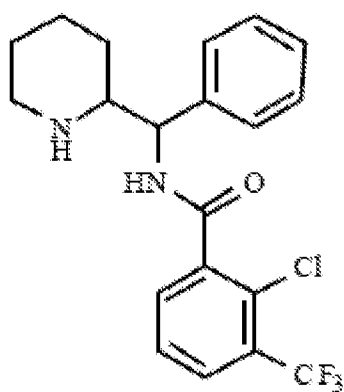
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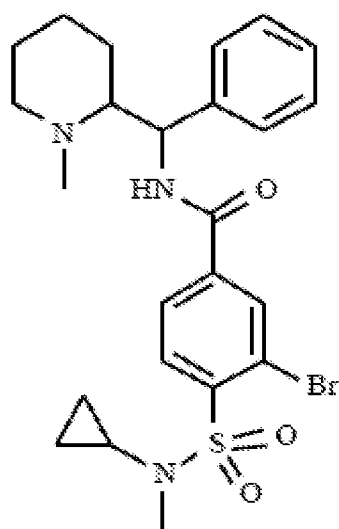
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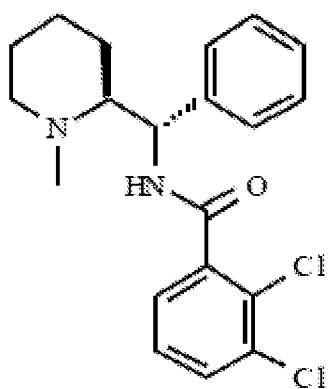
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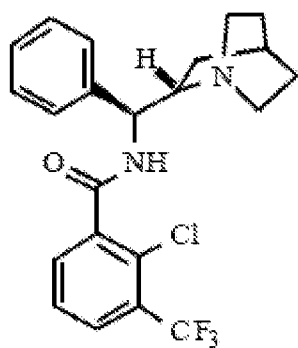
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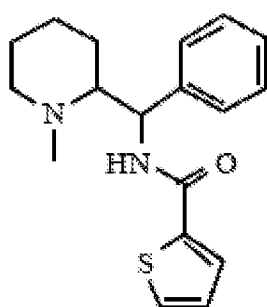
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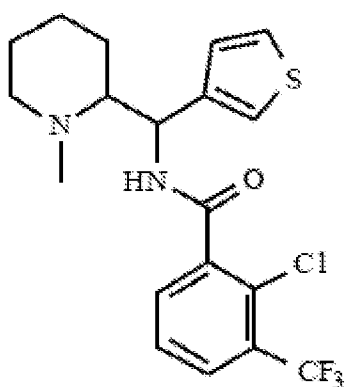
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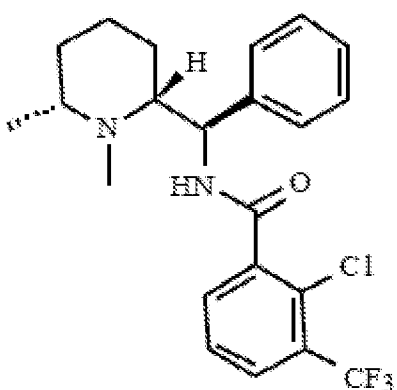
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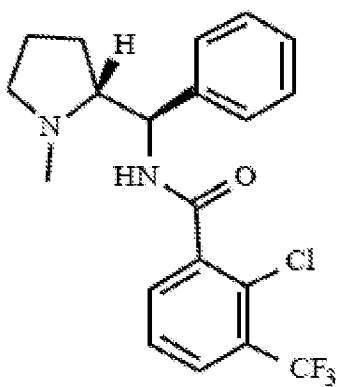
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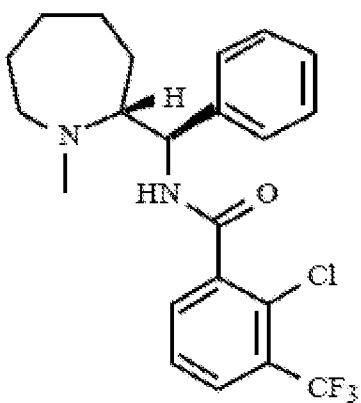
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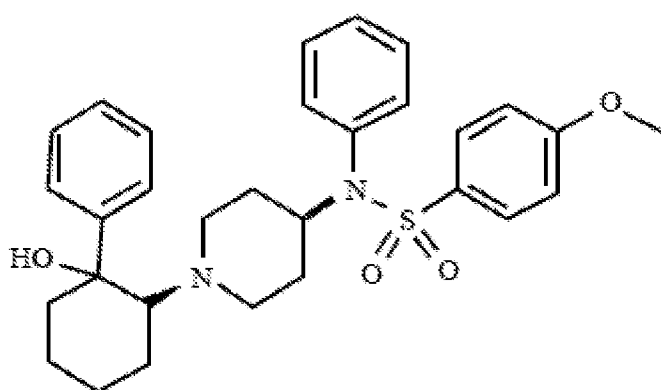


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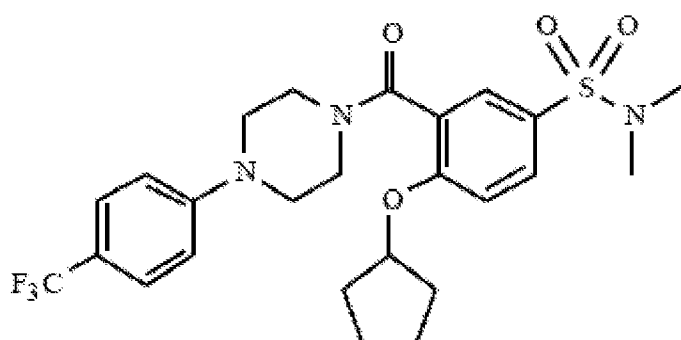


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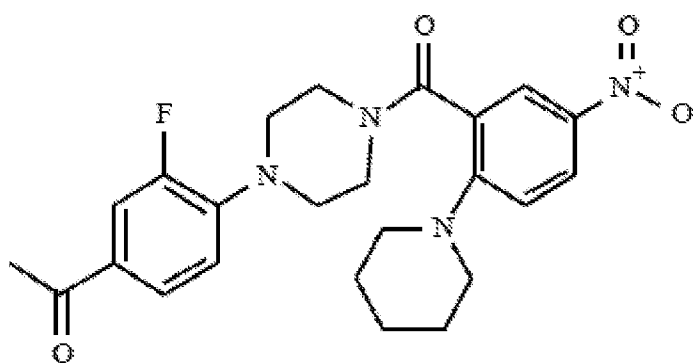




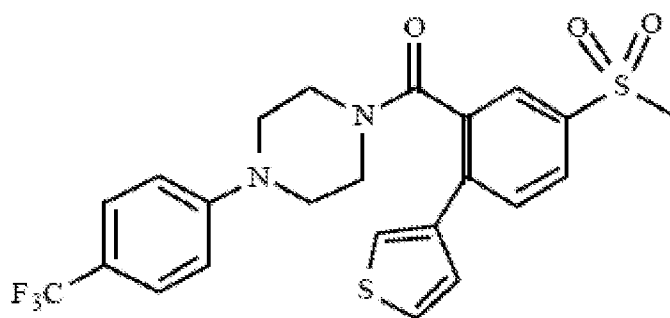
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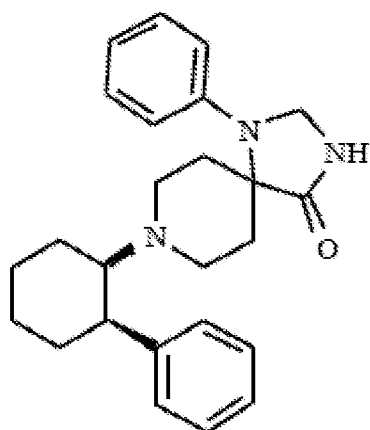
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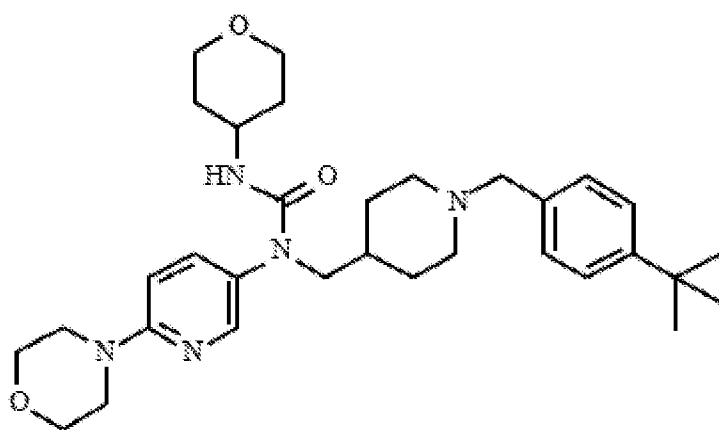
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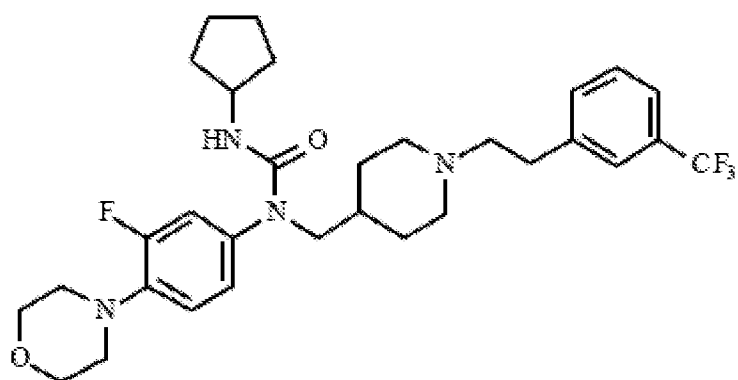
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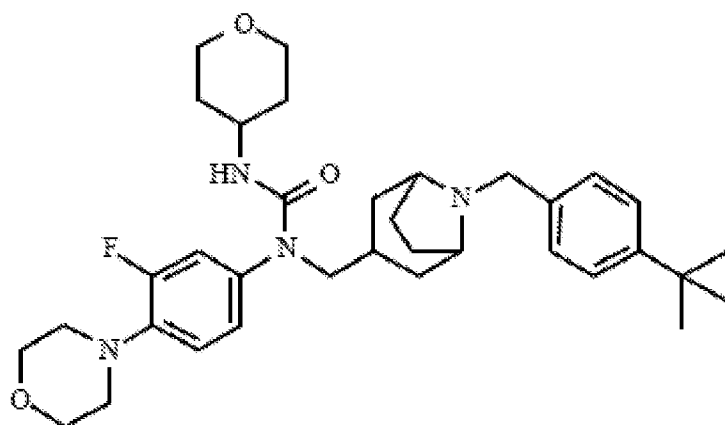
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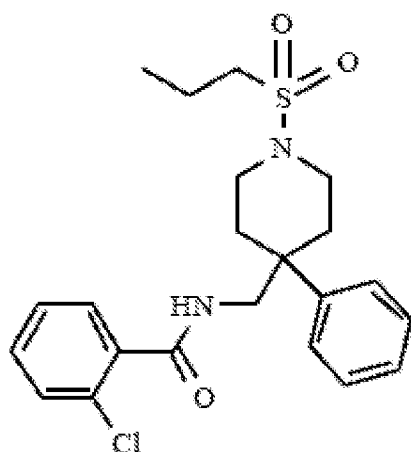
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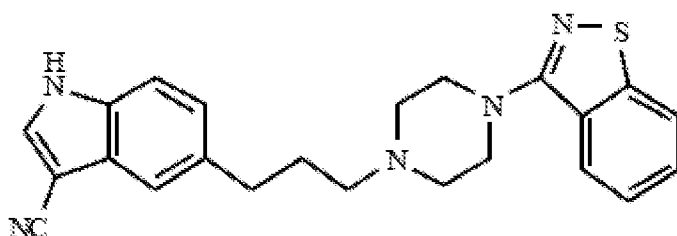
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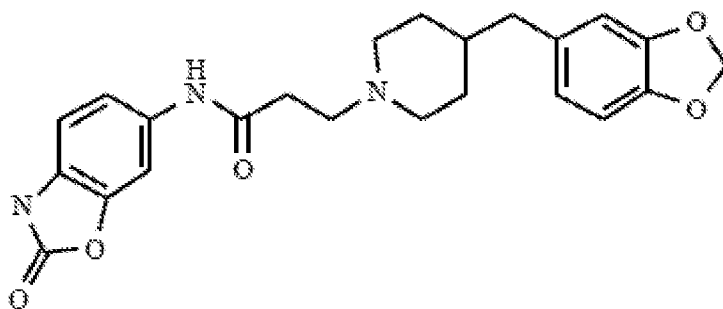
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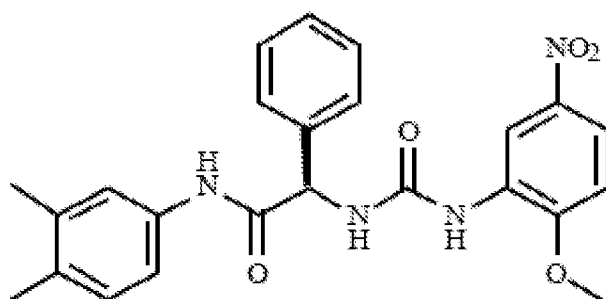
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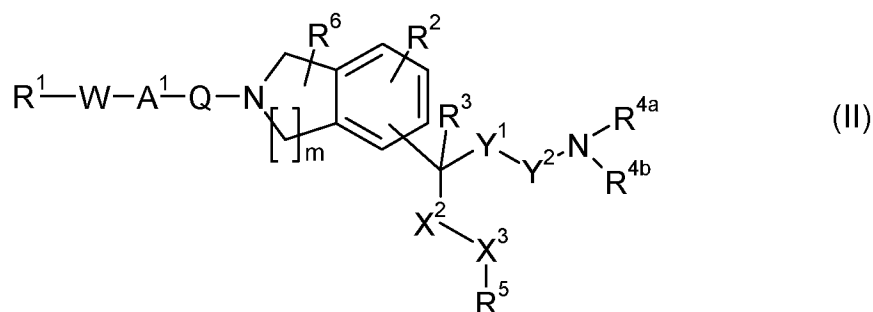
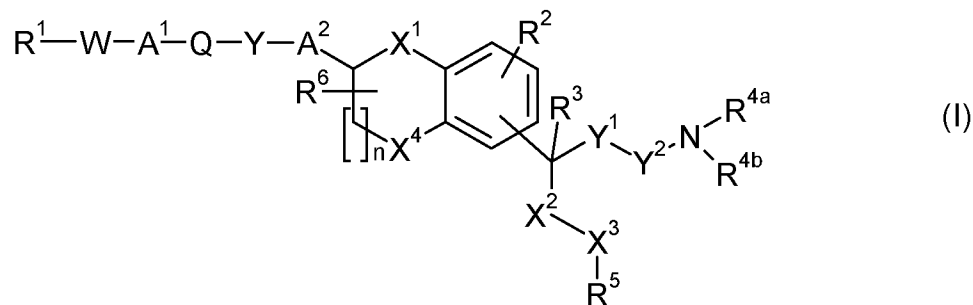
WO 2004022528

- (see also Hashimoto K., Recent Patents on CNS Drug Discovery, 2006, 1, 43–53; Harsing L.G. et al., Current Medicinal Chemistry, 2006, 13, 1017–1044; Javitt D.C., Molecular Psychiatry (2004) 9, 984–997; Lindsley, C.W. et al., Current Topics in Medicinal Chemistry, 2006, 6, 771–785; Lindsley C.W. et al., Current Topics in Medicinal Chemistry, 2006, 6, 1883–1896).

It was one object of the present invention to provide further glycine transporter inhibitors.

## Summary Of The Invention

The present invention relates to phenalkylamine derivatives of the formula (I) or (II)



5

wherein

R<sup>1</sup> is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, trialkylsilylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, alkyloxycarbonylaminoalkyl, alkylaminocarbonylaminoalkyl, dialkylaminocarbonylaminoalkyl, alkylsulfonylaminoalkyl, (optionally substituted arylalkyl) aminoalkyl, optionally substituted arylalkyl, optionally substituted heterocyclalkyl, cycloalkyl, alkylcarbonyl, alkoxy carbonyl, halogenated alkoxy carbonyl, aryloxycarbonyl, amino carbonyl, alkylaminocarbonyl, (halogenated alkyl)aminocarbonyl, arylaminocarbonyl, alkenyl, alkynyl, optionally substituted aryl, hydroxy, alkoxy, halogenated alkoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, alkylcarbonylaminoalkoxy, arylcarbonylaminoalkoxy, alkoxy carbonylaminoalkoxy, arylalkoxy, alkylsulfonylaminoalkoxy, (halogenated alkyl)sulfonylaminoalkoxy, arylsulfonylaminoalkoxy, (arylalkyl)sulfonylaminoalkoxy, heterocyclsulfonylaminoalkoxy, heterocyclalkoxy, aryloxy, heterocyclloxy, alkylthio, halogenated alkylthio, alkylamino, (halogenated alkyl)amino, dialkylamino, di-(halogenated alkyl)amino, alkylcarbonylamino, (halogenated alkyl)carbonylamino, arylcarbonylamino, alkylsulfonylamino, (halogenated alkyl)sulfonylamino, arylsulfonylamino or optionally substituted heterocycl;

25

W is -NR<sup>8</sup>- or a bond;

A<sup>1</sup> is optionally substituted alkylene or a bond;

- Q is  $-S(O)_2-$  or  $-C(O)-$ ;
- Y is  $-NR^9-$  or a bond;
- 5 A<sup>2</sup> is optionally substituted alkylene, alkylene-CO-, -CO-alkylene, alkylene-O-alkylene, alkylene-NR<sup>10</sup>-alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted heteroarylene or a bond;
- 10 X<sup>1</sup> is -O-,  $-NR^{11}-$ , -S-, or  $>CH_2$ ;
- X<sup>4</sup> is -O-,  $-NR^{19}-$ , -S-, or  $>CH_2$ ;
- 15 n is 0, 1, or 2;
- m is 0, 1, or 2;
- 20 R<sup>6</sup> is hydrogen, halogen, alkyl or alkoxy, or two radicals R<sup>6</sup> together with the carbon atom to which they are attached form a carbonyl group;
- R<sup>2</sup> is hydrogen, halogen, alkyl, halogenated alkyl, hydroxyalkyl, -CN, alkenyl, alkynyl, optionally substituted aryl, hydroxy, alkoxy, halogenated alkoxy, alkoxycarbonyl, alkenyloxy, arylalkoxy, alkylcarbonyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, amino-sulfonyl, amino, alkylamino, alkenylamino, nitro or optionally substituted heterocyclyl, or two radicals R<sup>2</sup> together with the ring atoms to which they are bound form a 5- or 6-membered ring;
- 25 R<sup>3</sup> is hydrogen or alkyl;
- 30 X<sup>2</sup> is -O-,  $-NR^7-$ , -S-,  $>CR^{12a}R^{12b}$  or a bond;
- X<sup>3</sup> is -O-,  $-NR^7-$ , -S-,  $>CR^{13a}R^{13b}$  or a bond;
- 35 R<sup>5</sup> is optionally substituted aryl, optionally substituted cycloalkyl or optionally substituted heterocyclyl;
- Y<sup>1</sup> is  $>CR^{14a}R^{14b}$  or a bond;
- 40 Y<sup>2</sup> is  $>CR^{15a}R^{15b}$ ;

5  $R^{4a}$  is hydrogen, alkyl, cycloalkylalkyl, halogenated alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl,  $CH_2CN$ , arylalkyl, cycloalkyl,  $-CHO$ , alkylcarbonyl, (halogenated alkyl)carbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, alkenyl,  $-C(=NH)NH_2$ ,  $-C(=NH)NHCN$ , alkylsulfonyl, arylsulfonyl, amino,  $-NO$  or heterocyclyl;

$R^{4a}$ ,  $R^3$   
together are optionally substituted alkylene; or

10  $R^{4a}$ ,  $R^{14a}$   
together are optionally substituted alkylene; or

15  $R^{4b}$  is hydrogen, alkyl, halogenated alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl,  $CH_2CN$ ,  $-CHO$ , alkylcarbonyl, (halogenated alkyl)carbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, alkenyl,  $-C(=NH)NH_2$ ,  $-C(=NH)NHCN$ , alkylsulfonyl, arylsulfonyl, amino,  $-NO$  or heterocyclyl; or

20  $R^{4a}$ ,  $R^{4b}$   
together are optionally substituted alkylene, wherein one  $-CH_2-$  of alkylene may be replaced by an oxygen atom or  $-NR^{16}$ ;

$R^7$  is hydrogen or alkyl;

25  $R^8$  is hydrogen or alkyl;

$R^9$  is hydrogen, alkyl, cycloalkyl, aminoalkyl, optionally substituted arylalkyl or heterocyclyl; or

30  $R^9$ ,  $R^1$   
together are alkylene; or

$R^9$  is alkylene that is bound to a carbon atom in  $A^2$  and  $A^2$  is alkylene;

35  $R^{10}$  is hydrogen, alkyl or alkylsulfonyl;

$R^{11}$  is hydrogen or alkyl, or

40  $R^9$ ,  $R^{11}$   
together are alkylene,

$R^{12a}$  is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclylalkyl, optionally substituted aryl or hydroxy;

- $R^{12b}$  is hydrogen or alkyl, or
- $R^{12a}$ ,  $R^{12b}$
- 5        together are carbonyl or optionally substituted alkylene, wherein one  $-CH_2-$  of alkylene may be replaced by an oxygen atom or  $-NR^{17}-$ ;
- $R^{13a}$  is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclalkyl, optionally substituted aryl or hydroxy;
- 10         $R^{13b}$  is hydrogen or alkyl, or
- $R^{13a}$ ,  $R^{13b}$
- 15        together are carbonyl or optionally substituted alkylene, wherein one  $-CH_2-$  of alkylene may be replaced by an oxygen atom or  $-NR^{18}-$ ;
- $R^{14a}$  is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl,  $C_3-C_{12}$ -heterocyclalkyl, optionally substituted aryl or hydroxy;
- 20         $R^{14b}$  is hydrogen or alkyl, or
- $R^{14a}$ ,  $R^{14b}$
- 25        together are carbonyl or optionally substituted alkylene, wherein one or two  $-CH_2-$  of alkylene may be replaced by an oxygen atom or  $-NR^{20}-$ ;
- $R^{15a}$  is hydrogen, optionally substituted alkyl, alkylaminoalkyl, dialkylaminoalkyl, heterocyclalkyl, optionally substituted aryl or hydroxy;
- $R^{15b}$  is hydrogen or  $C_1-C_6$ -alkyl, or
- 30         $R^{15a}$ ,  $R^{15b}$
- 35        together are carbonyl or optionally substituted alkylene, wherein one or two  $-CH_2-$  of alkylene may be replaced by an oxygen atom or  $-NR^{20}-$ ;
- $R^{16}$  is hydrogen or  $C_1-C_6$ -alkyl;
- $R^{17}$  is hydrogen or  $C_1-C_6$ -alkyl;
- $R^{18}$  is hydrogen or  $C_1-C_6$ -alkyl;
- 40         $R^{19}$  is hydrogen or  $C_1-C_6$ -alkyl, and

R<sup>20</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl,

or a physiologically tolerated salt thereof.

- 5 Thus, the term phenalkylamine derivative is used herein to denote in particular phenethylamines (Y<sup>1</sup> is a bond) and phenpropylamines (Y<sup>1</sup> is >CR<sup>14a</sup>R<sup>14b</sup>).

Said compounds of formula (I) or (II), i.e., the phenalkylamine derivatives of formula (I) or (II) and their physiologically tolerated salts, are glycine transporter inhibitors and thus useful as pharmaceuticals.

The present invention thus further relates to the compounds of formula (I) or (II) for use in therapy.

- 15 The present invention also relates to pharmaceutical compositions which comprise a carrier and a compound of formula (I) or (II).

In particular, said compounds, i.e., the phenalkylamine derivatives and their physiologically tolerated salts, are inhibitors of the glycine transporter GlyT1.

20 The present invention thus further relates to the compounds of formula (I) or (II) for use in inhibiting the glycine transporter.

The present invention also relates to the use of the compounds of formula (I) or (II) in the manufacture of a medicament for inhibiting the glycine transporter GlyT1 and corresponding methods of inhibiting the glycine transporter GlyT1.

Glycine transport inhibitors and in particular inhibitors of the glycine transporter GlyT1 are known to be useful in treating a variety of neurologic and psychiatric disorders.

30 The present invention thus further relates to the compounds of formula (I) or (II) for use in treating a neurologic or psychiatric disorder.

The present invention further relates to the compounds of formula (I) or (II) for use in treating pain.

40 The present invention also relates to the use of the compounds of formula (I) or (II) in the manufacture of a medicament for treating a neurologic or psychiatric disorder and corresponding methods of treating said disorders. The present invention also relates to the use of the compounds of formula (I) or (II) in the manufacture of a medicament for treating pain and corresponding methods of treating pain.

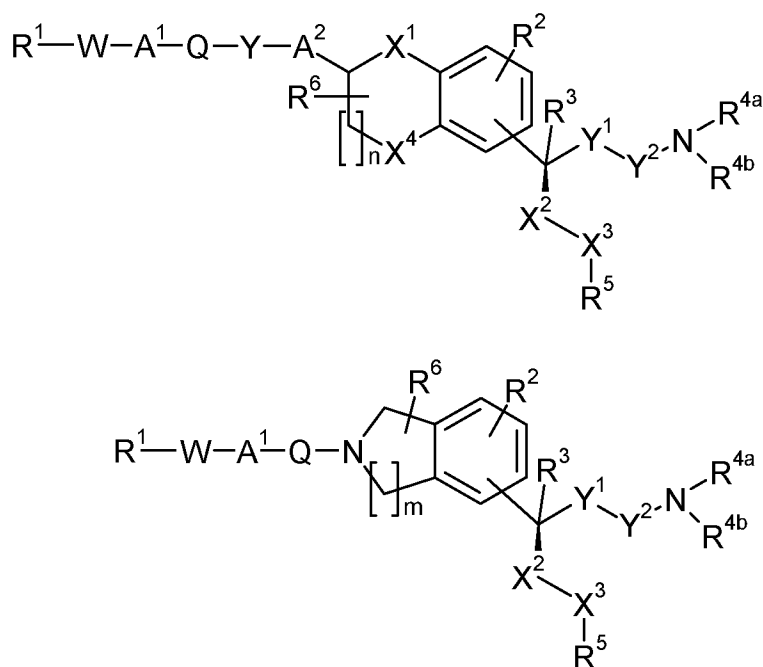


## Detailed Description Of The Invention

5 Provided that the phenalkylamine derivatives of the formula (I) or (II) of a given constitution may exist in different spatial arrangements, for example if they possess one or more centers of asymmetry, polysubstituted rings or double bonds, or as different tautomers, it is also possible to use enantiomeric mixtures, in particular racemates, diastereomeric mixtures and tautomeric mixtures, preferably, however, the respective essentially pure enantiomers, diastereomers and tautomers of the compounds of formula (I) or (II) and/or of their salts.

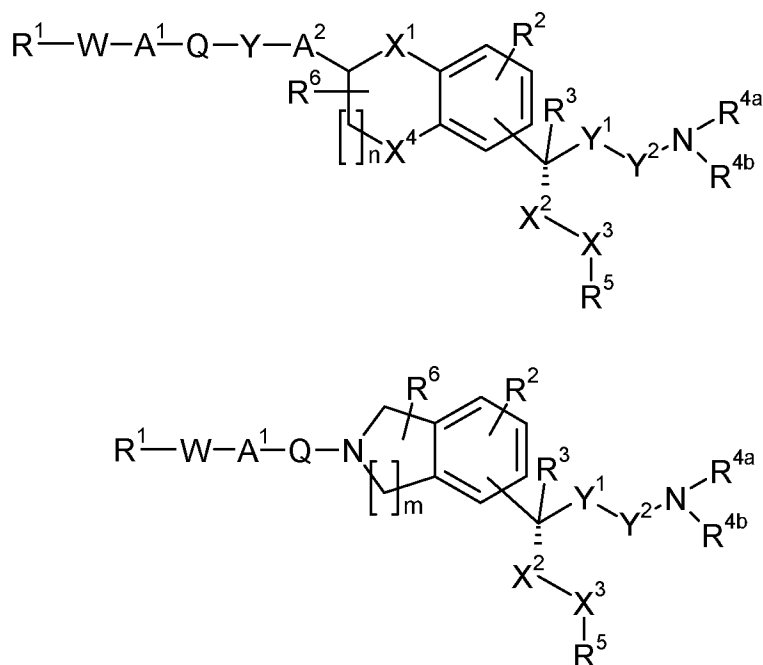
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According to one embodiment, an enantiomer of the phenalkylamine derivatives of the present invention has the following formula:



15 wherein  $R$ ,  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $X^1$ ,  $X^4$ ,  $n$ ,  $m$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein.

According to another embodiment, an enantiomer of the phenalkylamine derivatives of the present invention has the following formula:



wherein  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $X^1$ ,  $X^4$ ,  $n$ ,  $m$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein.

5

The physiologically tolerated salts of the phenalkylamine derivatives of the formula (I) or (II) are especially acid addition salts with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid,  $C_1$ - $C_4$ -alkylsulfonic acids, such as methanesulfonic acid, cycloaliphatic sulfonic acids, such as S-(+)-10-camphor sulfonic acid, aromatic sulfonic acids, such as benzenesulfonic acid and toluenesulfonic acid, di- and tricarboxylic acids and hydroxycarboxylic acids having 2 to 10 carbon atoms, such as oxalic acid, malonic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, citric acid, glycolic acid, adipic acid and benzoic acid. Other utilizable acids are described, e.g., in Fortschritte der

Arzneimittelforschung [Advances in drug research], Volume 10, pages 224 ff., Birkhäuser Verlag, Basel and Stuttgart, 1966. The physiologically tolerated salts of the phenalkylamine derivatives also include salts of a physiologically tolerated anion with a phenalkylamine derivative wherein one or more than one nitrogen atom is quaternized, e.g. with an alkyl residue (e.g. methyl or ethyl).

20

The present invention moreover relates to compounds of formula (I) as defined herein, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope (e.g., hydrogen by deuterium,  $^{12}C$  by  $^{13}C$ ,  $^{14}N$  by  $^{15}N$ ,  $^{16}O$  by  $^{18}O$ ) and preferably wherein at least one hydrogen atom has been replaced by a deuterium atom.

25

Of course, such compounds contain more of the respective isotope than this naturally occurs and thus is anyway present in the compounds (I).

Stable isotopes (e.g., deuterium,  $^{13}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ) are nonradioactive isotopes which contain one or more additional neutron than the normally abundant isotope of the respective atom. Deuterated compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic pathway of the non-deuterated parent compound (Blake et al. *J. Pharm. Sci.* 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., *Advances in Drug Research* Vol. 14, pp. 2-36, Academic Press, London, 1985; Kato et al., *J. Labelled Comp. Radiopharmaceut.*, 36(10):927-932 (1995); Kushner et al., *Can. J. Physiol. Pharmacol.*, 77, 79-88 (1999).

Incorporation of a heavy atom particularly substitution of deuterium for hydrogen, can give rise to an isotope effect that could alter the pharmacokinetics of the drug. This effect is usually insignificant if the label is placed at a metabolically inert position of the molecule.

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

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

metabolite produced by attack at a carbon atom not substituted by deuterium becomes the major pathway a process called "metabolic switching".

Deuterium tracers, such as deuterium-labeled drugs and doses, in some cases repeatedly, of thousands of milligrams of deuterated water, are also used in healthy humans of all ages, including neonates and pregnant women, without reported incident (e.g. Pons G and Rey E, *Pediatrics* 1999 104: 633; Coward W A et al., *Lancet* 1979 7: 13; Schwarcz H P, *Control. Clin. Trials* 1984 5(4 Suppl): 573; Rodewald L E et al., *J. Pediatr.* 1989 114: 885; Butte N F et al. *Br. J. Nutr.* 1991 65: 3; MacLennan A H et al. *Am. J. Obstet Gynecol.* 1981 139: 948). Thus, it is clear that any deuterium released, for instance, during the metabolism of compounds of this invention poses no health risk.

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

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

The hydrogens present on a particular organic compound have different capacities for exchange with deuterium. Certain hydrogen atoms are easily exchangeable under physiological conditions and, if replaced by deuterium atoms, it is expected that they will readily exchange for protons after administration to a patient. Certain hydrogen atoms may be exchanged for deuterium atoms by the action of a deuteriic acid such as D<sub>2</sub>SO<sub>4</sub>/D<sub>2</sub>O. Alternatively, deuterium atoms may be incorporated in various combinations during the synthesis of compounds of the invention. Certain hydrogen atoms are not easily exchangeable for deuterium atoms. However, deuterium atoms at the remaining positions may be incorporated by the use of deuterated starting materials or intermediates during the construction of compounds of the invention.

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

The organic moieties mentioned in the above definitions of the variables are - like the term halogen - collective terms for individual listings of the individual group members. The prefix C<sub>n</sub>-C<sub>m</sub> indicates in each case the possible number of carbon atoms in the group.

Unless indicated otherwise, the term "substituted" means that a radical is substituted with 1, 2 or 3, especially 1, substituent which are in particular selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-heterocyclyl-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkenyl, OH, SH, CN, CF<sub>3</sub>, O-CF<sub>3</sub>, COOH, O-CH<sub>2</sub>-COOH, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, COO-C<sub>1</sub>-C<sub>6</sub>-alkyl, CONH<sub>2</sub>, CONH-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>NH-C<sub>1</sub>-C<sub>6</sub>-alkyl, CON-(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub>, SO<sub>2</sub>N-(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub>, NH<sub>2</sub>, NH-C<sub>1</sub>-C<sub>6</sub>-alkyl, N-(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub>, NH-(C<sub>1</sub>-C<sub>4</sub>-alkyl-C<sub>6</sub>-C<sub>12</sub>-aryl), NH-CO-C<sub>1</sub>-C<sub>6</sub>-alkyl, NH-SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl, SO<sub>2</sub>-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>6</sub>-C<sub>12</sub>-aryl, O-C<sub>6</sub>-C<sub>12</sub>-aryl, O-CH<sub>2</sub>-C<sub>6</sub>-C<sub>12</sub>-aryl, CONH-C<sub>6</sub>-C<sub>12</sub>-aryl, SO<sub>2</sub>NH-C<sub>6</sub>-C<sub>12</sub>-aryl, CONH-C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, oxo (=O) being a further substituent, SO<sub>2</sub>NH-C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, SO<sub>2</sub>-C<sub>6</sub>-C<sub>12</sub>-aryl, NH-SO<sub>2</sub>-C<sub>6</sub>-C<sub>12</sub>-aryl, NH-CO-C<sub>6</sub>-C<sub>12</sub>-aryl, NH-SO<sub>2</sub>-C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, NH-CO-C<sub>3</sub>-C<sub>12</sub>-heterocyclyl and C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, wherein aryl and heterocyclyl in turn may be unsubstituted or substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy and C<sub>1</sub>-C<sub>4</sub>-haloalkoxy.

The term halogen denotes in each case fluorine, bromine, chlorine or iodine, in particular fluorine or chlorine.

C<sub>1</sub>-C<sub>4</sub>-Alkyl is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms. Examples of an alkyl group are methyl, C<sub>2</sub>-C<sub>4</sub>-alkyl such as ethyl, n-propyl, iso-propyl, n-butyl, 2-butyl, iso-butyl or tert-butyl. C<sub>1</sub>-C<sub>2</sub>-Alkyl is methyl or ethyl, C<sub>1</sub>-C<sub>3</sub>-alkyl is additionally n-propyl or isopropyl.

C<sub>1</sub>-C<sub>6</sub>-Alkyl is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms. Examples include methyl, C<sub>2</sub>-C<sub>4</sub>-alkyl as mentioned herein and also pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

Halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms, such as in halogenomethyl, dihalogenomethyl, trihalogenomethyl, (R)-1-halogenoethyl, (S)-1-halogenoethyl, 2-halogenoethyl, 1,1-dihalogenoethyl, 2,2-dihalogenoethyl, 2,2,2-trihalogenoethyl, (R)-1-halogenopropyl, (S)-1-halogenopropyl, 2-halogenopropyl, 3-halogenopropyl, 1,1-dihalogenopropyl, 2,2-dihalogenopropyl, 3,3-dihalogenopropyl, 3,3,3-trihalogenopropyl, (R)-2-halogeno-1-methylethyl, (S)-2-halogeno-1-methylethyl, (R)-2,2-dihalogeno-1-methylethyl, (S)-2,2-dihalogeno-1-methylethyl, (R)-1,2-dihalogeno-1-methylethyl, (S)-1,2-dihalogeno-1-methylethyl, (R)-2,2,2-trihalogeno-1-methylethyl, (S)-2,2,2-trihalogeno-1-methylethyl, 2-halogeno-1-(halogenomethyl)ethyl, 1-(dihalogenomethyl)-2,2-dihalogenoethyl, (R)-1-halogenobutyl, (S)-1-halogenobutyl, 2-halogenobutyl, 3-halogenobutyl, 4-halogenobutyl, 1,1-dihalogenobutyl, 2,2-dihalogenobutyl, 3,3-dihalogenobutyl, 4,4-dihalogenobutyl, 4,4,4-trihalogenobutyl, etc. Particular examples include the fluorinated C<sub>1</sub>-C<sub>4</sub> alkyl groups as defined, such as trifluoromethyl.

C<sub>6</sub>-C<sub>12</sub>-Aryl-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by C<sub>6</sub>-C<sub>12</sub>-aryl, such as in benzyl.

Hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein one or two hydrogen atoms are replaced by one or two hydroxyl groups, such as in hydroxymethyl, (R)-1-hydroxyethyl, (S)-1-hydroxyethyl, 2-hydroxyethyl, (R)-1-hydroxypropyl, (S)-1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, (R)-2-hydroxy-1-methylethyl, (S)-2-hydroxy-1-methylethyl, 2-hydroxy-1-(hydroxymethyl)ethyl, (R)-1-hydroxybutyl, (S)-1-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl.

C<sub>1</sub>-C<sub>6</sub>-Alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, wherein one or two hydrogen atoms are replaced by one or two alkoxy groups having 1 to 6, preferably 1 to 4, in particular 1 or 2 carbon atoms, such as in methoxymethyl, (R)-1-methoxyethyl,

- (S)-1-methoxyethyl, 2-methoxyethyl, (R)-1-methoxypropyl, (S)-1-methoxypropyl, 2-methoxypropyl, 3-methoxypropyl, (R)-2-methoxy-1-methylethyl, (S)-2-methoxy-1-methylethyl, 2-methoxy-1-(methoxymethyl)ethyl, (R)-1-methoxybutyl, (S)-1-methoxybutyl, 2-methoxybutyl, 3-methoxybutyl, 4-methoxybutyl, ethoxymethyl, (R)-1-ethoxyethyl, (S)-1-ethoxyethyl, 2-ethoxyethyl, (R)-1-ethoxypropyl, (S)-1-ethoxypropyl, 2-ethoxypropyl, 3-ethoxypropyl, (R)-2-ethoxy-1-methylethyl, (S)-2-ethoxy-1-methylethyl, 2-ethoxy-1-(ethoxymethyl)ethyl, (R)-1-ethoxybutyl, (S)-1-ethoxybutyl, 2-ethoxybutyl, 3-ethoxybutyl, 4-ethoxybutyl.
- 10 Amino-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by an amino group, such as in aminomethyl, 2-aminoethyl.
- 15 C<sub>1</sub>-C<sub>6</sub>-Alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a C<sub>1</sub>-C<sub>6</sub>-alkylamino group, in particular by a C<sub>1</sub>-C<sub>4</sub>-alkylamino group, such as in methylaminomethyl, ethylaminomethyl, n-propylaminomethyl, iso-propylaminomethyl, n-
- 20 butylaminomethyl, 2-butylaminomethyl, iso-butylaminomethyl or tert-butylaminomethyl.
- Di-C<sub>1</sub>-C<sub>6</sub>-Alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a di-C<sub>1</sub>-C<sub>6</sub>-
- 25 Alkylamino group, in particular by a di-C<sub>1</sub>-C<sub>4</sub>-alkylamino group, such as in dimethylaminomethyl.
- C<sub>1</sub>-C<sub>6</sub>-Alkylcarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a C<sub>1</sub>-C<sub>6</sub>-alkylcarbonylamino group, in particular by a C<sub>1</sub>-C<sub>4</sub>-alkylcarbonylamino group, such as in methylcarbonylaminoethyl, ethylcarbonylaminoethyl, n-propylcarbonylaminoethyl, iso-propylcarbonylaminoethyl, n-butylcarbonylaminoethyl, 2-
- 30 butylcarbonylaminoethyl, iso-butylcarbonylaminoethyl or tert-butylcarbonylaminoethyl.
- 35 C<sub>1</sub>-C<sub>6</sub>-Alkylaminocarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a C<sub>1</sub>-C<sub>6</sub>-alkylaminocarbonylamino group, in particular by a C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonylamino group, such as in methylaminocarbonylaminoethyl, ethylaminocarbonylaminoethyl, n-propylaminocarbonylaminoethyl, iso-propylaminocarbonylaminoethyl, n-butylamino-

carbonylaminomethyl, 2-butylaminocarbonylaminomethyl, iso-butylaminocarbonylaminomethyl or tert-butylaminocarbonylaminomethyl.

Di-C<sub>1</sub>-C<sub>6</sub>-alkylaminocarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a di-C<sub>1</sub>-C<sub>6</sub>-alkylaminocarbonylamino group, in particular by a di-C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonylamino group, such as in dimethylaminocarbonylaminomethyl, dimethylaminocarbonylaminoethyl, dimethylaminocarbonylaminon-propyl.

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C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a C<sub>1</sub>-C<sub>6</sub>-alkylsulfonylamino group, in particular by a C<sub>1</sub>-C<sub>4</sub>-alkylsulfonylamino group, such as in methylsulfonylaminomethyl, ethylsulfonylaminomethyl, n-propylsulfonylaminomethyl, isopropylsulfonylaminomethyl, n-butylsulfonylaminomethyl, 2-butylsulfonylaminomethyl, isobutylsulfonylaminomethyl or tert-butylsulfonylaminomethyl.

(C<sub>6</sub>-C<sub>12</sub>-Aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl)amino-C<sub>1</sub>-C<sub>4</sub> alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by a (C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl)amino group, in particular a (C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>2</sub>-alkyl)amino group, such as in benzylaminomethyl.

C<sub>3</sub>-C<sub>12</sub>-Heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms, preferably 1 to 3 carbon atoms, more preferably 1 or 2 carbon atoms, in particular 1 or two carbon atoms, wherein one hydrogen atom is replaced by C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, such as in N-pyrrolidinylmethyl, N-piperidinylmethyl, N-morpholinylmethyl.

C<sub>3</sub>-C<sub>12</sub>-Cycloalkyl is a cycloaliphatic radical having from 3 to 12 carbon atoms. In particular, 3 to 6 carbon atoms form the cyclic structure, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cyclic structure may be unsubstituted or may carry 1, 2, 3 or 4 C<sub>1</sub>-C<sub>4</sub> alkyl radicals, preferably one or more methyl radicals.

35 Carbonyl is >C=O.

C<sub>1</sub>-C<sub>6</sub>-Alkylcarbonyl is a radical of the formula R-C(O)-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms as defined herein. Examples include acetyl, propionyl, n-butyryl, 2-methylpropionyl, pivaloyl.

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Halogenated C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl is C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a correspond-



ing number of identical or different halogen atoms. Examples include fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl. Further examples are 1,1,1-trifluoroeth-2-ylcarbonyl, 1,1,1-trifluoroprop-3-ylcarbonyl.

- 5 C<sub>6</sub>-C<sub>12</sub>-Arylcarbonyl is a radical of the formula R-C(O)-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include benzoyl.

- C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl is a radical of the formula R-O-C(O)-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms as defined  
10 herein. Examples include methoxycarbonyl and tert-butyloxycarbonyl.

- Halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxy carbonyl is a C<sub>1</sub>-C<sub>6</sub>-alkoxy carbonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

- 15 C<sub>6</sub>-C<sub>12</sub>-Aryloxycarbonyl is a radical of the formula R-O-C(O)-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenoxy carbonyl.

- Cyano is -C≡N.

- 20 Aminocarbonyl is NH<sub>2</sub>C(O)-.

- C<sub>1</sub>-C<sub>6</sub>-Alkylaminocarbonyl is a radical of the formula R-NH-C(O)-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms as defined  
25 herein. Examples include methylaminocarbonyl.

- (Halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl)aminocarbonyl is a C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different hydrogen atoms.

- 30 C<sub>6</sub>-C<sub>12</sub>-Arylaminocarbonyl is a radical of the formula R-NH-C(O)-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylaminocarbonyl.

- 35 C<sub>2</sub>-C<sub>6</sub>-Alkenyl is a singly unsaturated hydrocarbon radical having 2, 3, 4, 5 or 6 carbon atoms, e.g. vinyl, allyl (2-propen-1-yl), 1-propen-1-yl, 2-propen-2-yl, methallyl (2-methylprop-2-en-1-yl) and the like. C<sub>3</sub>-C<sub>5</sub>-Alkenyl is, in particular, allyl, 1-methylprop-2-en-1-yl, 2-buten-1-yl, 3-buten-1-yl, methallyl, 2-penten-1-yl, 3-penten-1-yl, 4-penten-1-yl, 1-methylbut-2-en-1-yl or 2-ethylprop-2-en-1-yl.

- 40 C<sub>2</sub>-C<sub>6</sub>-Alkynyl is a singly unsaturated hydrocarbon radical having 2, 3, 4, 5 or 6 carbon atoms, e.g. ethynyl, 2-propyn-1-yl, 1-propyn-1-yl, 2-propyn-2-yl and the like. C<sub>3</sub>-C<sub>5</sub>-Alkynyl

is, in particular, 2-propyn-1-yl, 2-butyne-1-yl, 3-butyne-1-yl, 2-pentyne-1-yl, 3-pentyne-1-yl, 4-pentyne-1-yl.

5 C<sub>1</sub>-C<sub>4</sub>-Alkylene is straight-chain or branched alkylene group having from 1 to 4 carbon atoms. Examples include methylene and ethylene. A further example is propylene.

C<sub>2</sub>-C<sub>4</sub>-Alkenylene is straight-chain or branched alkenylene group having from 2 to 4 carbon atoms.

10 C<sub>2</sub>-C<sub>4</sub>-Alkynylene is straight-chain or branched alkynylene group having from 2 to 4 carbon atoms. Examples include propynylene.

C<sub>6</sub>-C<sub>12</sub>-Aryl is a 6- to 12-membered, in particular 6- to 10-membered, aromatic cyclic radical. Examples include phenyl and naphthyl.

15 C<sub>3</sub>-C<sub>12</sub>-Arylene is an aryl diradical. Examples include phen-1,4-ylene and phen-1,3-ylene.

Hydroxy is -OH.

20 C<sub>1</sub>-C<sub>6</sub>-Alkoxy is a radical of the formula R-O-, wherein R is a straight-chain or branched alkyl group having from 1 to 6, in particular 1 to 4 carbon atoms. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, 2-butoxy, iso-butoxy (2-methylpropoxy), tert.-butoxy, pentyloxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, 2,2-dimethylpropoxy, 1-ethylpropoxy, hexyloxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 1-methylpentyloxy, 2-methylpentyloxy, 3-methylpentyloxy, 4-methylpentyloxy, 1,1-dimethylbutyloxy, 1,2-dimethylbutyloxy, 1,3-dimethylbutyloxy, 2,2-dimethylbutyloxy, 2,3-dimethylbutyloxy, 3,3-dimethylbutyloxy, 1-ethylbutyloxy, 2-ethylbutyloxy, 1,1,2-trimethylpropoxy, 1,2,2-trimethylpropoxy, 1-ethyl-1-methylpropoxy and 1-ethyl-2-methylpropoxy.

30 Halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxy is a straight-chain or branched alkoxy group having from 1 to 6, preferably from 1 to 4, in particular 1 or 2 carbon atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms, such as in halogenomethoxy, dihalogenomethoxy, trihalogenomethoxy, (R)-1-halogenoethoxy, (S)-1-halogenoethoxy, 2-halogenoethoxy, 1,1-dihalogenoethoxy, 2,2-dihalogenoethoxy, 2,2,2-trihalogenoethoxy, (R)-1-halogenopropoxy, (S)-1-halogenopropoxy, 2-halogenopropoxy, 3-halogenopropoxy, 1,1-dihalogenopropoxy, 2,2-dihalogenopropoxy, 3,3-dihalogenopropoxy, 3,3,3-trihalogenopropoxy, (R)-2-halogeno-1-methylethoxy, (S)-2-halogeno-1-methylethoxy, (R)-2,2-dihalogeno-1-methylethoxy, (S)-2,2-dihalogeno-1-methylethoxy, (R)-1,2-dihalogeno-1-methylethoxy, (S)-1,2-dihalogeno-1-methylethoxy, (R)-2,2,2-trihalogeno-1-methylethoxy, (S)-2,2,2-trihalogeno-1-methylethoxy, 2-halogeno-1-(halogenomethyl)ethoxy, 1-(dihalogenomethyl)-2,2-dihalogenoethoxy, (R)-1-halogenobutoxy, (S)-1-halogenobutoxy, 2-

halogenobutoxy, 3-halogenobutoxy, 4-halogenobutoxy, 1,1-dihalogenobutoxy, 2,2-dihalogenobutoxy, 3,3-dihalogenobutoxy, 4,4-dihalogenobutoxy, 4,4,4-trihalogenobutoxy, etc. Particular examples include the fluorinated C<sub>1</sub>-C<sub>4</sub> alkoxy groups as defined, such as trifluoromethoxy.

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C<sub>1</sub>-C<sub>6</sub>-Hydroxyalkoxy is an alkoxy radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein, wherein one or two hydrogen atoms are replaced by hydroxy. Examples include 2-hydroxyethoxy, 3-hydroxypropoxy, 2-hydroxypropoxy, 1-methyl-2-hydroxyethoxy and the like.

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C<sub>1</sub>-C<sub>6</sub>-Alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4 carbon atoms, preferably 1 or 2 carbon atoms as defined herein, wherein one or two hydrogen atoms are replaced by one or two alkoxy radicals having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methoxymethoxy, 2-methoxyethoxy, 1-methoxyethoxy, 3-methoxypropoxy, 2-methoxypropoxy, 1-methyl-1-methoxyethoxy, ethoxymethoxy, 2-ethoxyethoxy, 1-ethoxyethoxy, 3-ethoxypropoxy, 2-ethoxypropoxy, 1-methyl-1-ethoxyethoxy and the like.

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Amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an amino group. Examples include 2-aminoethoxy.

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C<sub>1</sub>-C<sub>6</sub>-Alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylaminomethoxy, ethylaminomethoxy, n-propylaminomethoxy, isopropylaminomethoxy, n-butylaminomethoxy, 2-butylaminomethoxy, iso-butylaminomethoxy, tert-butylaminomethoxy, 2-(methylamino)ethoxy, 2-(ethylamino)ethoxy, 2-(n-propylamino)ethoxy, 2-(iso-propylamino)ethoxy, 2-(n-butylamino)ethoxy, 2-(2-butylamino)ethoxy, 2-(iso-butylamino)ethoxy, 2-(tert-butylamino)ethoxy.

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Di-C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a di-alkylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include dimethylaminomethoxy, diethylaminomethoxy, N-methyl-N-ethylamino)ethoxy, 2-(dimethylamino)ethoxy, 2-(diethylamino)ethoxy, 2-(N-methyl-N-ethylamino)ethoxy.

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C<sub>1</sub>-C<sub>6</sub>-Alkylcarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylcarbonylamino group wherein the alkyl group has from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylcarbonylaminomethoxy, ethyl-

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carbonylaminomethoxy, n-propylcarbonylaminomethoxy, iso-propylcarbonylaminomethoxy, n-butylcarbonylaminomethoxy, 2-butylcarbonylaminomethoxy, iso-butylcarbonylaminomethoxy, tert-butylcarbonylaminomethoxy, 2-(methylcarbonylamino)ethoxy, 2-(ethylcarbonylamino)ethoxy, 2-(n-propylcarbonylamino)ethoxy, 2-(iso-propylcarbonylamino)ethoxy, 2-(n-butylcarbonylamino)ethoxy, 2-(2-butylcarbonylamino)ethoxy, 2-(iso-butylcarbonylamino)ethoxy, 2-(tert-butylcarbonylamino)ethoxy.

C<sub>6</sub>-C<sub>12</sub>-Arylcarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C<sub>6</sub>-C<sub>12</sub>-arylcarbonylamino group as defined herein. Examples include 2-(benzoylamino)ethoxy.

C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkoxy carbonylamino group wherein the alkoxy group has from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methoxycarbonylaminomethoxy, ethoxycarbonylaminomethoxy, n-propoxycarbonylaminomethoxy, iso-propoxycarbonylaminomethoxy, n-butoxycarbonylaminomethoxy, 2-butoxycarbonylaminomethoxy, iso-butoxycarbonylaminomethoxy, tert-butoxycarbonylaminomethoxy, 2-(methoxycarbonylamino)ethoxy, 2-(ethoxycarbonylamino)ethoxy, 2-(n-propoxycarbonylamino)ethoxy, 2-(iso-propoxycarbonylamino)ethoxy, 2-(n-butoxycarbonylamino)ethoxy, 2-(2-butoxycarbonylamino)ethoxy, 2-(iso-butoxycarbonylamino)ethoxy, 2-(tert-butoxycarbonylamino)ethoxy.

C<sub>2</sub>-C<sub>6</sub>-Alkenyloxy is a radical of the formula R-O-, wherein R is a straight-chain or branched alkenyl group having from 2 to 6, in particular 2 to 4 carbon atoms. Examples include vinyloxy, allyloxy (2-propen-1-yloxy), 1-propen-1-yloxy, 2-propen-2-yloxy, methallyloxy (2-methylprop-2-en-1-yloxy) and the like. C<sub>3</sub>-C<sub>5</sub>-Alkenyloxy is, in particular, allyloxy, 1-methylprop-2-en-1-yloxy, 2-buten-1-yloxy, 3-buten-1-yloxy, methallyloxy, 2-penten-1-yloxy, 3-penten-1-yloxy, 4-penten-1-yloxy, 1-methylbut-2-en-1-yloxy or 2-ethylprop-2-en-1-yloxy.

C<sub>6</sub>-C<sub>12</sub>-Aryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C<sub>6</sub>-C<sub>12</sub>-aryl group as defined herein. Examples include benzyloxy.

C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylsulfonylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include 2-(methylsulfonylamino)ethoxy, 2-(ethylsulfonylamino)ethoxy, 2-[(2-methylpropyl)sulfonylamino]ethoxy.

(Halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)sulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by an alkylsulfonylamino group having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein, wherein the alkyl group is halogenated. Examples include 2-(trifluoromethylsulfonylamino)ethoxy.

C<sub>6</sub>-C<sub>12</sub>-Arylsulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C<sub>6</sub>-C<sub>12</sub>-arylsulfonylamino group as defined herein. Examples include 2-(phenylsulfonylamino)-ethoxy, 2-(naphthylsulfonylamino)ethoxy.

(C<sub>6</sub>-C<sub>12</sub>-Aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl)sulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a (C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl)sulfonylamino group, preferably by a (C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>2</sub>-alkyl)sulfonylamino group. Examples include 2-(benzylsulfonylamino)ethoxy.

C<sub>3</sub>-C<sub>12</sub>-Heterocyclylsulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C<sub>3</sub>-C<sub>12</sub>-heterocyclylsulfonylamino group as defined herein. Examples include 2-(pyridin-3-yl-sulfonylamino)ethoxy.

C<sub>3</sub>-C<sub>12</sub>-Heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy is an alkoxy radical having from 1 to 4, preferably 1 or 2 carbon atoms as defined herein, wherein one hydrogen atom is replaced by a C<sub>3</sub>-C<sub>12</sub>-heterocyclyl group as defined herein. Examples include 2-(N-pyrrolidinyl)ethoxy, 2-(N-morpholinyl)ethoxy and 2-(N-imidazolyl)ethoxy.

C<sub>1</sub>-C<sub>2</sub>-Alkylenedioxy is a radical of the formula -O-R-O-, wherein R is a straight-chain or branched alkylene group having from 1 or 2 carbon atoms as defined herein. Examples include methylenedioxy.

C<sub>6</sub>-C<sub>12</sub>-Aryloxy is a radical of the formula R-O-, wherein R is an aryl group having from 6 to 12, in particular 6 carbon atoms as defined herein. Examples include phenoxy.

C<sub>3</sub>-C<sub>12</sub>-Heterocyclyloxy is a radical of the formula R-O-, wherein R is a C<sub>3</sub>-C<sub>12</sub>-heterocyclyl group having from 3 to 12, in particular from 3 to 7 carbon atoms as defined herein. Examples include pyridin-2-yloxy.

C<sub>1</sub>-C<sub>6</sub>-Alkylthio is a radical of the formula R-S-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylthio, ethylthio, propylthio, butylthio, pentylthio, 1-methylbutylthio, 2-methylbutylthio, 3-methylbutylthio, 2,2-dimethylpropylthio, 1-ethylpropylthio, hexylthio, 1,1-dimethylpropylthio, 1,2-dimethylpropylthio, 1-methylpentylthio, 2-methylpentylthio, 3-methylpentylthio, 4-methyl-

pentylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,2-dimethylbutylthio, 2,3-dimethylbutylthio, 3,3-dimethylbutylthio, 1-ethylbutylthio, 2-ethylbutylthio, 1,1,2-trimethylpropylthio, 1,2,2-trimethylpropylthio, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

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Halogenated C<sub>1</sub>-C<sub>6</sub>-alkylthio is a radical of the formula R-S-, wherein R is a halogenated alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include halogenomethylthio, dihalogenomethylthio, trihalogenomethylthio, (R)-1-halogenoethylthio, (S)-1-halogenoethylthio, 2-halogenoethylthio, 1,1-dihalogenoethylthio, 2,2-dihalogenoethylthio, 2,2,2-trihalogenoethylthio, (R)-1-halogenopropylthio, (S)-1-halogenopropylthio, 2-halogenopropylthio, 3-halogenopropylthio, 1,1-dihalogenopropylthio, 2,2-dihalogenopropylthio, 3,3-dihalogenopropylthio, 3,3,3-trihalogenopropylthio, (R)-2-halogeno-1-methylethylthio, (S)-2-halogeno-1-methylethylthio, (R)-2,2-dihalogeno-1-methylethylthio, (S)-2,2-dihalogeno-1-methylethylthio, (R)-1,2-dihalogeno-1-methylethylthio, (S)-1,2-dihalogeno-1-methylethylthio, (R)-2,2,2-trihalogeno-1-methylethylthio, (S)-2,2,2-trihalogeno-1-methylethylthio, 2-halogeno-1-(halogenomethyl)ethylthio, 1-(dihalogenomethyl)-2,2-dihalogenoethylthio, (R)-1-halogenobutylthio, (S)-1-halogenobutylthio, 2-halogenobutylthio, 3-halogenobutylthio, 4-halogenobutylthio, 1,1-dihalogenobutylthio, 2,2-dihalogenobutylthio, 3,3-dihalogenobutylthio, 4,4-dihalogenobutylthio, 4,4,4-trihalogenobutylthio, etc. Particular examples include the fluorinated C<sub>1</sub>-C<sub>4</sub> alkylthio groups as defined, such as trifluoromethylthio.

C<sub>1</sub>-C<sub>6</sub>-Alkylsulfinyl is a radical of the formula R-S(O)-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, pentylsulfinyl, 1-methylbutylsulfinyl, 2-methylbutylsulfinyl, 3-methylbutylsulfinyl, 2,2-dimethylpropylsulfinyl, 1-ethylpropylsulfinyl, hexylsulfinyl, 1,1-dimethylpropylsulfinyl, 1,2-dimethylpropylsulfinyl, 1-methylpentylsulfinyl, 2-methylpentylsulfinyl, 3-methylpentylsulfinyl, 4-methylpentylsulfinyl, 1,1-dimethylbutylsulfinyl, 1,2-dimethylbutylsulfinyl, 1,3-dimethylbutylsulfinyl, 2,2-dimethylbutylsulfinyl, 2,3-dimethylbutylsulfinyl, 3,3-dimethylbutylsulfinyl, 1-ethylbutylsulfinyl, 2-ethylbutylsulfinyl, 1,1,2-trimethylpropylsulfinyl, 1,2,2-trimethylpropylsulfinyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonyl is a radical of the formula R-S(O)<sub>2</sub>-, wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, 1-methylbutylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, 2,2-dimethylpropylsulfonyl, 1-ethylpropylsulfonyl, hexylsulfonyl, 1,1-dimethylpropylsulfonyl, 1,2-dimethylpropylsulfonyl, 1-methylpentylsulfonyl, 2-methylpentylsulfonyl, 3-methylpentylsulfonyl, 4-methylpentylsulfonyl, 1,1-dimethylbutylsulfonyl, 1,2-dimethylbutylsulfonyl, 1,3-dimethylbutylsulfonyl, 2,2-dimethylbutylsulfonyl, 2,3-dimethylbutylsulfonyl, 3,3-dimethylbutylsulfonyl, 1-ethyl-

butylsulfonyl, 2-ethylbutylsulfonyl, 1,1,2-trimethylpropylsulfonyl, 1,2,2-trimethylpropylsulfonyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

- 5 (Halogenated  $C_1$ - $C_6$ -alkyl)sulfonyl is a  $C_1$ - $C_6$ -alkylsulfonyl as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

$C_6$ - $C_{12}$ -Arylsulfonyl is a radical of the formula  $R-S(O)_2\cdot$ , wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylsulfonyl.

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( $C_6$ - $C_{12}$ -Aryl- $C_1$ - $C_4$ -alkyl)sulfonyl is a radical of the formula  $R-S(O)_2\cdot$ , wherein R is a  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -alkyl radical, in particular a  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_2$ -alkyl radical as defined herein. Examples include benzylsulfonyl.

- 15  $C_3$ - $C_{12}$ -Heterocyclylsulfonyl is a radical of the formula  $R-S(O)_2\cdot$ , wherein R is  $C_3$ - $C_{12}$ -heterocyclyl as defined herein.

Aminosulfonyl is  $NH_2-S(O)_2\cdot$ .

- 20  $C_1$ - $C_6$ -Alkylaminosulfonyl is a radical of the formula  $R-NH-S(O)_2\cdot$  wherein R is an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, iso-propylaminosulfonyl, n-butylaminosulfonyl, 2-butylaminosulfonyl, iso-butylaminosulfonyl, tert-butylaminosulfonyl.

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Di- $C_1$ - $C_6$ -alkylaminosulfonyl is a radical of the formula  $RR'N-S(O)_2\cdot$  wherein R and R' are independently of each other an alkyl radical having from 1 to 6, preferably from 1 to 4 carbon atoms as defined herein. Examples include dimethylaminosulfonyl, diethylaminosulfonyl, N-methyl-N-ethylaminosulfonyl.

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$C_6$ - $C_{12}$ -Arylamino sulfonyl is a radical of the formula  $R-NH-S(O)_2\cdot$  wherein R is an aryl radical having from 6 to 12, preferably 6 carbon atoms as defined herein.

Amino is  $NH_2$ .

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$C_1$ - $C_6$ -Alkylamino is a radical of the formula  $R-NH\cdot$  wherein R is an alkyl radical having from 1 to 6, in particular from 1 to 4 carbon atoms as defined herein. Examples include methylamino, ethylamino, n-propylamino, iso-propylamino, n-butylamino, 2-butylamino, iso-butylamino, tert-butylamino.

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(Halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)amino is a C<sub>1</sub>-C<sub>6</sub>-alkylamino as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

- 5 Di-C<sub>1</sub>-C<sub>6</sub>-alkylamino is a radical of the formula RR'N- wherein R and R' are independently of each other an alkyl radical having from 1 to 6, in particular from 1 to 4 carbon atoms as defined herein. Examples include dimethylamino, diethylamino, N-methyl-N-ethylamino.

- 10 Di-(halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)amino is a di-C<sub>1</sub>-C<sub>6</sub>-alkylamino as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

C<sub>1</sub>-C<sub>6</sub>-Alkylcarbonylamino is a radical of the formula R-C(O)-NH-, wherein R is an alkyl radical having from 1 to 6, in particular from 1 to 4 carbon atoms as defined herein.

- 15 Examples include acetamido (methylcarbonylamino), propionamido, n-butyramido, 2-methylpropionamido (isopropylcarbonylamino), 2,2-dimethylpropionamido and the like.

- 20 (Halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)carbonylamino is a C<sub>1</sub>-C<sub>6</sub>-alkylcarbonylamino as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.

C<sub>6</sub>-C<sub>12</sub>-Arylcarbonylamino is a radical of the formula R-C(O)-NH-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylcarbonylamino.

- 25 C<sub>2</sub>-C<sub>6</sub>-Alkenylamino is a radical of the formula R-NH-, wherein R is a straight-chain or branched alkenyl group having from 2 to 6, in particular 2 to 4 carbon atoms. Examples include vinylamino, allylamino (2-propen-1-ylamino), 1-propen-1-ylamino, 2-propen-2-ylamino, methallylamino (2-methylprop-2-en-1-ylamino) and the like. C<sub>3</sub>-C<sub>5</sub>-Alkenylamino is, in particular, allylamino, 1-methylprop-2-en-1-ylamino, 2-buten-1-ylamino, 3-buten-1-ylamino, methallylamino, 2-penten-1-ylamino, 3-penten-1-ylamino, 4-penten-1-ylamino, 1-methylbut-2-en-1-ylamino or 2-ethylprop-2-en-1-ylamino.
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- 35 C<sub>1</sub>-C<sub>6</sub>-Alkylsulfonylamino is a radical of the formula R-S(O)<sub>2</sub>-NH-, wherein R is an alkyl radical having from 1 to 6, in particular from 1 to 4 carbon atoms as defined herein. Examples include methylsulfonylamino, ethylsulfonylamino, n-propylsulfonylamino, isopropylsulfonylamino, n-butylsulfonylamino, 2-butylsulfonylamino, iso-butylsulfonylamino, tert-butylsulfonylamino.

- 40 (Halogenated C<sub>1</sub>-C<sub>6</sub> alkyl)sulfonylamino is a C<sub>1</sub>-C<sub>6</sub>-alkylsulfonylamino as defined herein, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by 1, 2, 3, 4 or a corresponding number of identical or different halogen atoms.



C<sub>6</sub>-C<sub>12</sub>-Arylsulfonylamino is a radical of the formula R-S(O)<sub>2</sub>-NH-, wherein R is an aryl radical having from 6 to 12 carbon atoms as defined herein. Examples include phenylsulfonylamino.

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Nitro is -NO<sub>2</sub>.

C<sub>3</sub>-C<sub>12</sub>-Heterocyclyl is a 3- to 12-membered heterocyclic radical including a saturated heterocyclic radical, which generally has 3, 4, 5, 6, or 7 ring forming atoms (ring members), an  
10 unsaturated non-aromatic heterocyclic radical, which generally has 5, 6 or 7 ring forming atoms, and a heteroaromatic radical (hetaryl), which generally has 5, 6 or 7 ring forming atoms. The heterocyclic radicals may be bound via a carbon atom (C-bound) or a nitrogen atom (N-bound). Preferred heterocyclic radicals comprise 1 nitrogen atom as ring member atom and optionally 1, 2 or 3 further heteroatoms as ring members, which are selected,  
15 independently of each other from O, S and N. Likewise preferred heterocyclic radicals comprise 1 heteroatom as ring member, which is selected from O, S and N, and optionally 1, 2 or 3 further nitrogen atoms as ring members.

Examples of C<sub>3</sub>-C<sub>12</sub>-heterocyclyl include:

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C- or N-bound 3-4-membered, saturated rings, such as  
2-oxiranyl, 2-oxetanyl, 3-oxetanyl, 2-aziridinyl, 3-thiethanyl, 1-azetidiny, 2-azetidiny, 3-azetidiny;

25 C-bound, 5-membered, saturated rings, such as

tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydropyrrol-2-yl, tetrahydropyrrol-3-yl, tetrahydropyrazol-3-yl, tetrahydro-pyrazol-4-yl, tetrahydroisoxazol-3-yl, tetrahydroisoxazol-4-yl, tetrahydroisoxazol-5-yl, 1,2-oxathiolan-3-yl, 1,2-oxathiolan-4-yl, 1,2-oxathiolan-5-yl, tetrahydroisothiazol-3-yl, tetrahydroisothiazol-4-yl,  
30 tetrahydroisothiazol-5-yl, 1,2-dithiolan-3-yl, 1,2-dithiolan-4-yl, tetrahydroimidazol-2-yl, tetrahydroimidazol-4-yl, tetrahydrooxazol-2-yl, tetrahydrooxazol-4-yl, tetrahydrooxazol-5-yl, tetrahydrothiazol-2-yl, tetrahydrothiazol-4-yl, tetrahydrothiazol-5-yl, 1,3-dioxolan-2-yl, 1,3-dioxolan-4-yl, 1,3-oxathiolan-2-yl, 1,3-oxathiolan-4-yl, 1,3-oxathiolan-5-yl, 1,3-dithiolan-2-yl, 1,3-dithiolan-4-yl, 1,3,2-dioxathiolan-4-yl;

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C-bound, 6-membered, saturated rings, such as

tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, 1,3-dioxan-2-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl, 1,4-dioxan-2-yl, 1,3-dithian-2-yl, 1,3-dithian-4-yl, 1,3-dithian-5-yl, 1,4-dithian-2-yl, 1,3-oxathian-2-yl, 1,3-oxathian-4-yl, 1,3-oxathian-5-yl, 1,3-oxathian-6-yl, 1,4-oxathian-2-yl, 1,4-oxathian-3-yl, 1,2-dithian-3-yl, 1,2-dithian-4-yl, hexahydropyrimidin-2-yl, hexahydropyrimidin-4-yl, hexahydropyrimidin-5-yl,

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hexahydropyrazin-2-yl, hexahydropyridazin-3-yl, hexahydropyridazin-4-yl, tetrahydro-1,3-oxazin-2-yl, tetrahydro-1,3-oxazin-4-yl, tetrahydro-1,3-oxazin-5-yl, tetrahydro-1,3-oxazin-6-yl, tetrahydro-1,3-thiazin-2-yl, tetrahydro-1,3-thiazin-4-yl, tetrahydro-1,3-thiazin-5-yl, tetrahydro-1,3-thiazin-6-yl, tetrahydro-1,4-thiazin-2-yl, tetrahydro-1,4-thiazin-3-yl, tetrahydro-1,4-oxazin-2-yl, tetrahydro-1,4-oxazin-3-yl, tetrahydro-1,2-oxazin-3-yl, tetrahydro-1,2-oxazin-4-yl, tetrahydro-1,2-oxazin-5-yl, tetrahydro-1,2-oxazin-6-yl;

N-bound, 5-membered, saturated rings, such as  
tetrahydropyrrol-1-yl (pyrrolidin-1-yl), tetrahydropyrazol-1-yl, tetrahydroisoxazol-2-yl, tetrahydroisothiazol-2-yl, tetrahydroimidazol-1-yl, tetrahydrooxazol-3-yl, tetrahydrothiazol-3-yl;

N-bound, 6-membered, saturated rings, such as  
piperidin-1-yl, hexahydropyrimidin-1-yl, hexahydropyrazin-1-yl (piperazin-1-yl), hexahydropyridazin-1-yl, tetrahydro-1,3-oxazin-3-yl, tetrahydro-1,3-thiazin-3-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-oxazin-4-yl (morpholin-1-yl), tetrahydro-1,2-oxazin-2-yl;

C-bound, 5-membered, partially unsaturated rings, such as  
2,3-dihydrofuran-2-yl, 2,3-dihydrofuran-3-yl, 2,5-dihydrofuran-2-yl, 2,5-dihydrofuran-3-yl, 4,5-dihydrofuran-2-yl, 4,5-dihydrofuran-3-yl, 2,3-dihydrothien-2-yl, 2,3-dihydrothien-3-yl, 2,5-dihydrothien-2-yl, 2,5-dihydrothien-3-yl, 4,5-dihydrothien-2-yl, 4,5-dihydrothien-3-yl, 2,3-dihydro-1H-pyrrol-2-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,5-dihydro-1H-pyrrol-2-yl, 2,5-dihydro-1H-pyrrol-3-yl, 4,5-dihydro-1H-pyrrol-2-yl, 4,5-dihydro-1H-pyrrol-3-yl, 3,4-dihydro-2H-pyrrol-2-yl, 3,4-dihydro-2H-pyrrol-3-yl, 3,4-dihydro-5H-pyrrol-2-yl, 3,4-dihydro-5H-pyrrol-3-yl, 4,5-dihydro-1H-pyrazol-3-yl, 4,5-dihydro-1H-pyrazol-4-yl, 4,5-dihydro-1H-pyrazol-5-yl, 2,5-dihydro-1H-pyrazol-3-yl, 2,5-dihydro-1H-pyrazol-4-yl, 2,5-dihydro-1H-pyrazol-5-yl, 4,5-dihydroisoxazol-3-yl, 4,5-dihydroisoxazol-4-yl, 4,5-dihydroisoxazol-5-yl, 2,5-dihydroisoxazol-3-yl, 2,5-dihydroisoxazol-4-yl, 2,5-dihydroisoxazol-5-yl, 2,3-dihydroisoxazol-3-yl, 2,3-dihydroisoxazol-4-yl, 2,3-dihydroisoxazol-5-yl, 4,5-dihydroisothiazol-3-yl, 4,5-dihydroisothiazol-4-yl, 4,5-dihydroisothiazol-5-yl, 2,5-dihydroisothiazol-3-yl, 2,5-dihydroisothiazol-4-yl, 2,5-dihydroisothiazol-5-yl, 2,3-dihydroisothiazol-3-yl, 2,3-dihydroisothiazol-4-yl, 2,3-dihydroisothiazol-5-yl, 4,5-dihydro-1H-imidazol-2-yl, 4,5-dihydro-1H-imidazol-4-yl, 4,5-dihydro-1H-imidazol-5-yl, 2,5-dihydro-1H-imidazol-2-yl, 2,5-dihydro-1H-imidazol-4-yl, 2,5-dihydro-1H-imidazol-5-yl, 2,3-dihydro-1H-imidazol-2-yl, 2,3-dihydro-1H-imidazol-4-yl, 4,5-dihydro-oxazol-2-yl, 4,5-dihydrooxazol-4-yl, 4,5-dihydrooxazol-5-yl, 2,5-dihydrooxazol-2-yl, 2,5-dihydrooxazol-4-yl, 2,5-dihydrooxazol-5-yl, 2,3-dihydrooxazol-2-yl, 2,3-dihydrooxazol-4-yl, 2,3-dihydrooxazol-5-yl, 4,5-dihydrothiazol-2-yl, 4,5-dihydrothiazol-4-yl, 4,5-dihydrothiazol-5-yl, 2,5-dihydrothiazol-2-yl, 2,5-dihydrothiazol-4-yl, 2,5-dihydrothiazol-5-yl, 2,3-dihydrothiazol-2-yl, 2,3-dihydrothiazol-4-yl, 2,3-dihydrothiazol-5-yl, 1,3-dioxol-2-yl, 1,3-dioxol-4-yl, 1,3-dithiol-2-yl, 1,3-dithiol-4-yl, 1,3-oxathiol-2-yl, 1,3-oxathiol-4-yl, 1,3-oxathiol-5-yl;

C-bound, 6-membered, partially unsaturated rings, such as

2H-3,4-dihydropyran-6-yl, 2H-3,4-dihydropyran-5-yl, 2H-3,4-dihydropyran-4-yl, 2H-3,4-dihydropyran-3-yl, 2H-3,4-dihydropyran-2-yl, 2H-3,4-dihydrothiopyran-6-yl, 2H-3,4-dihydrothiopyran-5-yl, 2H-3,4-dihydrothiopyran-4-yl, 2H-3,4-dihydrothiopyran-3-yl, 2H-3,4-dihydrothiopyran-2-yl, 1,2,3,4-tetrahydropyridin-6-yl, 1,2,3,4-tetrahydropyridin-5-yl, 1,2,3,4-tetrahydropyridin-4-yl, 1,2,3,4-tetrahydropyridin-3-yl, 1,2,3,4-tetrahydropyridin-2-yl, 2H-5,6-dihydropyran-2-yl, 2H-5,6-dihydropyran-3-yl, 2H-5,6-dihydropyran-4-yl, 2H-5,6-dihydropyran-5-yl, 2H-5,6-dihydropyran-6-yl, 2H-5,6-dihydrothiopyran-2-yl, 2H-5,6-dihydrothiopyran-3-yl, 2H-5,6-dihydrothiopyran-4-yl, 2H-5,6-dihydrothiopyran-5-yl, 2H-5,6-dihydrothiopyran-6-yl, 1,2,5,6-tetrahydropyridin-2-yl, 1,2,5,6-tetrahydropyridin-3-yl, 1,2,5,6-tetrahydropyridin-4-yl, 1,2,5,6-tetrahydropyridin-5-yl, 1,2,5,6-tetrahydropyridin-6-yl, 2,3,4,5-tetrahydropyridin-2-yl, 2,3,4,5-tetrahydropyridin-3-yl, 2,3,4,5-tetrahydropyridin-4-yl, 2,3,4,5-tetrahydropyridin-5-yl, 2,3,4,5-tetrahydropyridin-6-yl, 4H-pyran-2-yl, 4H-pyran-3-yl, 4H-pyran-4-yl, 4H-thiopyran-2-yl, 4H-thiopyran-3-yl, 4H-thiopyran-4-yl, 1,4-dihydropyridin-2-yl, 1,4-dihydropyridin-3-yl, 1,4-dihydropyridin-4-yl, 2H-pyran-2-yl, 2H-pyran-3-yl, 2H-pyran-4-yl, 2H-pyran-5-yl, 2H-pyran-6-yl, 2H-thiopyran-2-yl, 2H-thiopyran-3-yl, 2H-thiopyran-4-yl, 2H-thiopyran-5-yl, 2H-thiopyran-6-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 3,4-dihydropyridin-2-yl, 3,4-dihydropyridin-3-yl, 3,4-dihydropyridin-4-yl, 3,4-dihydropyridin-5-yl, 3,4-dihydropyridin-6-yl, 2,5-dihydropyridin-2-yl, 2,5-dihydropyridin-3-yl, 2,5-dihydropyridin-4-yl, 2,5-dihydropyridin-5-yl, 2,5-dihydropyridin-6-yl, 2,3-dihydropyridin-2-yl, 2,3-dihydropyridin-3-yl, 2,3-dihydropyridin-4-yl, 2,3-dihydropyridin-5-yl, 2,3-dihydropyridin-6-yl, 2H-5,6-dihydro-1,2-oxazin-3-yl, 2H-5,6-dihydro-1,2-oxazin-4-yl, 2H-5,6-dihydro-1,2-oxazin-5-yl, 2H-5,6-dihydro-1,2-oxazin-6-yl, 2H-5,6-dihydro-1,2-thiazin-3-yl, 2H-5,6-dihydro-1,2-thiazin-4-yl, 2H-5,6-dihydro-1,2-thiazin-5-yl, 2H-5,6-dihydro-1,2-thiazin-6-yl, 4H-5,6-dihydro-1,2-oxazin-3-yl, 4H-5,6-dihydro-1,2-oxazin-4-yl, 4H-5,6-dihydro-1,2-oxazin-5-yl, 4H-5,6-dihydro-1,2-oxazin-6-yl, 4H-5,6-dihydro-1,2-thiazin-3-yl, 4H-5,6-dihydro-1,2-thiazin-4-yl, 4H-5,6-dihydro-1,2-thiazin-5-yl, 4H-5,6-dihydro-1,2-thiazin-6-yl, 2H-3,6-dihydro-1,2-oxazin-3-yl, 2H-3,6-dihydro-1,2-oxazin-4-yl, 2H-3,6-dihydro-1,2-oxazin-5-yl, 2H-3,6-dihydro-1,2-oxazin-6-yl, 2H-3,6-dihydro-1,2-thiazin-3-yl, 2H-3,6-dihydro-1,2-thiazin-4-yl, 2H-3,6-dihydro-1,2-thiazin-5-yl, 2H-3,6-dihydro-1,2-thiazin-6-yl, 2H-3,4-dihydro-1,2-oxazin-3-yl, 2H-3,4-dihydro-1,2-oxazin-4-yl, 2H-3,4-dihydro-1,2-oxazin-5-yl, 2H-3,4-dihydro-1,2-oxazin-6-yl, 2H-3,4-dihydro-1,2-thiazin-3-yl, 2H-3,4-dihydro-1,2-thiazin-4-yl, 2H-3,4-dihydro-1,2-thiazin-5-yl, 2H-3,4-dihydro-1,2-thiazin-6-yl, 2,3,4,5-tetrahydropyridazin-3-yl, 2,3,4,5-tetrahydropyridazin-4-yl, 2,3,4,5-tetrahydropyridazin-5-yl, 2,3,4,5-tetrahydropyridazin-6-yl, 3,4,5,6-tetrahydropyridazin-3-yl, 3,4,5,6-tetrahydropyridazin-4-yl, 1,2,5,6-tetrahydropyridazin-3-yl, 1,2,5,6-tetrahydropyridazin-4-yl, 1,2,5,6-tetrahydropyridazin-5-yl, 1,2,5,6-tetrahydropyridazin-6-yl, 1,2,3,6-tetrahydropyridazin-3-yl, 1,2,3,6-tetrahydropyridazin-4-yl, 4H-5,6-dihydro-1,3-oxazin-2-yl, 4H-5,6-dihydro-1,3-oxazin-4-yl, 4H-5,6-dihydro-1,3-oxazin-5-yl, 4H-5,6-dihydro-1,3-oxazin-6-yl, 4H-5,6-dihydro-1,3-thiazin-2-yl, 4H-5,6-dihydro-1,3-thiazin-4-yl, 4H-5,6-dihydro-1,3-thiazin-5-yl, 4H-5,6-dihydro-1,3-thiazin-6-yl, 3,4,5,6-tetrahydropyrimidin-2-yl, 3,4,5,6-tetrahydropyrimidin-4-yl, 3,4,5,6-tetrahydropyrimidin-5-yl, 3,4,5,6-tetrahydropyrimidin-6-yl, 1,2,3,4-tetrahydropyrazin-2-yl,

1,2,3,4-tetrahydropyrazin-5-yl, 1,2,3,4-tetrahydro-pyrimidin-2-yl, 1,2,3,4-tetrahydro-pyrimidin-4-yl, 1,2,3,4-tetrahydropyrimidin-5-yl, 1,2,3,4-tetrahydropyrimidin-6-yl, 2,3-dihydro-1,4-thiazin-2-yl, 2,3-dihydro-1,4-thiazin-3-yl, 2,3-dihydro-1,4-thiazin-5-yl, 2,3-dihydro-1,4-thiazin-6-yl, 2H-1,3-oxazin-2-yl, 2H-1,3-oxazin-4-yl, 2H-1,3-oxazin-5-yl, 2H-1,3-oxazin-6-yl, 2H-1,3-thiazin-2-yl, 2H-1,3-thiazin-4-yl, 2H-1,3-thiazin-5-yl, 2H-1,3-thiazin-6-yl, 4H-1,3-oxazin-2-yl, 4H-1,3-oxazin-4-yl, 4H-1,3-oxazin-5-yl, 4H-1,3-oxazin-6-yl, 4H-1,3-thiazin-2-yl, 4H-1,3-thiazin-4-yl, 4H-1,3-thiazin-5-yl, 4H-1,3-thiazin-6-yl, 6H-1,3-oxazin-2-yl, 6H-1,3-oxazin-4-yl, 6H-1,3-oxazin-5-yl, 6H-1,3-oxazin-6-yl, 6H-1,3-thiazin-2-yl, 6H-1,3-oxazin-4-yl, 6H-1,3-oxazin-5-yl, 6H-1,3-thiazin-6-yl, 2H-1,4-oxazin-2-yl, 2H-1,4-oxazin-3-yl, 2H-1,4-oxazin-5-yl, 2H-1,4-oxazin-6-yl, 2H-1,4-thiazin-2-yl, 2H-1,4-thiazin-3-yl, 2H-1,4-thiazin-5-yl, 2H-1,4-thiazin-6-yl, 4H-1,4-oxazin-2-yl, 4H-1,4-oxazin-3-yl, 4H-1,4-thiazin-2-yl, 4H-1,4-thiazin-3-yl, 1,4-dihydropyridazin-3-yl, 1,4-dihydropyridazin-4-yl, 1,4-dihydropyridazin-5-yl, 1,4-dihydropyridazin-6-yl, 1,4-dihydropyrazin-2-yl, 1,2-dihydropyrazin-2-yl, 1,2-dihydropyrazin-3-yl, 1,2-dihydropyrazin-5-yl, 1,2-dihydropyrazin-6-yl, 1,4-dihydropyrimidin-2-yl, 1,4-dihydropyrimidin-4-yl, 1,4-dihydropyrimidin-5-yl, 1,4-dihydropyrimidin-6-yl, 3,4-dihydropyrimidin-2-yl, 3,4-dihydropyrimidin-4-yl, 3,4-dihydropyrimidin-5-yl or 3,4-dihydropyrimidin-6-yl;

N-bound, 5-membered, partially unsaturated rings, such as  
 2,3-dihydro-1H-pyrrol-1-yl, 2,5-dihydro-1H-pyrrol-1-yl, 4,5-dihydro-1H-pyrazol-1-yl, 2,5-dihydro-1H-pyrazol-1-yl, 2,3-dihydro-1H-pyrazol-1-yl, 2,5-dihydroisoxazol-2-yl, 2,3-dihydroisoxazol-2-yl, 2,5-dihydroisothiazol-2-yl, 2,3-dihydroisoxazol-2-yl, 4,5-dihydro-1H-imidazol-1-yl, 2,5-dihydro-1H-imidazol-1-yl, 2,3-dihydro-1H-imidazol-1-yl, 2,3-dihydro-oxazol-3-yl, 2,3-dihydrothiazol-3-yl;

N-bound, 6-membered, partially unsaturated rings, such as  
 1,2,3,4-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-1-yl, 1,4-dihydro-pyridin-1-yl, 1,2-dihydropyridin-1-yl, 2H-5,6-dihydro-1,2-oxazin-2-yl, 2H-5,6-dihydro-1,2-thiazin-2-yl, 2H-3,6-dihydro-1,2-oxazin-2-yl, 2H-3,6-dihydro-1,2-thiazin-2-yl, 2H-3,4-dihydro-1,2-oxazin-2-yl, 2H-3,4-dihydro-1,2-thiazin-2-yl, 2,3,4,5-tetrahydropyridazin-2-yl, 1,2,5,6-tetrahydropyridazin-1-yl, 1,2,5,6-tetrahydropyridazin-2-yl, 1,2,3,6-tetrahydropyridazin-1-yl, 3,4,5,6-tetrahydropyrimidin-3-yl, 1,2,3,4-tetrahydropyrazin-1-yl, 1,2,3,4-tetrahydropyrimidin-1-yl, 1,2,3,4-tetrahydropyrimidin-3-yl, 2,3-dihydro-1,4-thiazin-4-yl, 2H-1,2-oxazin-2-yl, 2H-1,2-thiazin-2-yl, 4H-1,4-oxazin-4-yl, 4H-1,4-thiazin-4-yl, 1,4-dihydropyridazin-1-yl, 1,4-dihydropyrazin-1-yl, 1,2-dihydropyrazin-1-yl, 1,4-dihydropyrimidin-1-yl or 3,4-dihydropyrimidin-3-yl;

C-bound, 5-membered, heteroaromatic rings, such as  
 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, pyrrol-2-yl, pyrrol-3-yl, pyrazol-3-yl, pyrazol-4-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, imidazol-2-yl, imidazol-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-

yl, 1,3,4-oxadiazol-2-yl, 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazolyl-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl, tetrazol-5-yl;

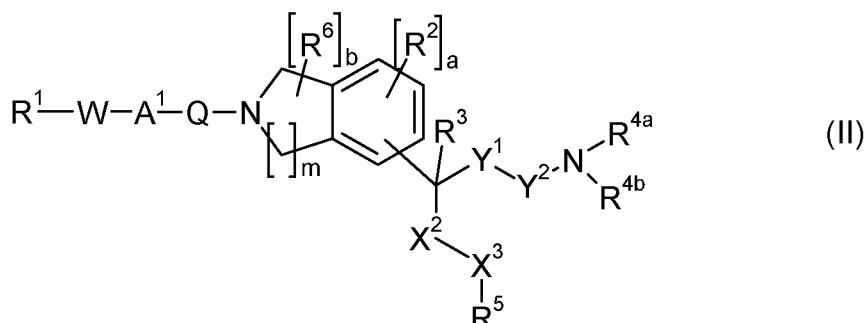
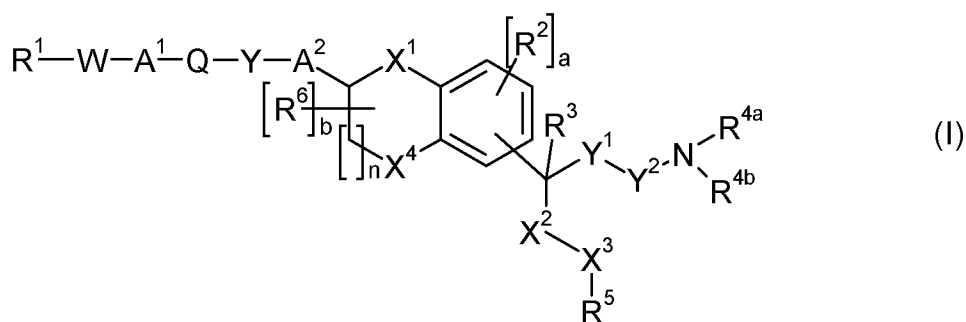
- 5 C-bound, 6-membered, heteroaromatic rings, such as pyridin-2-yl, pyridin-3-yl, pyridin-4-yl (4-pyridyl), pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl, 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,2,4,5-tetrazin-3-yl;
- 10 N-bound, 5-membered, heteroaromatic rings, such as pyrrol-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, tetrazol-1-yl.

- Heterocyclyl also includes bicyclic heterocycles, which comprise one of the described 5- or 6-membered heterocyclic rings and a further anellated, saturated or unsaturated or aromatic carbocycle, such as a benzene, cyclohexane, cyclohexene or cyclohexadiene ring, or a further anellated 5- or 6-membered heterocyclic ring, this heterocyclic ring being saturated or unsaturated or aromatic. These include quinolinyl, isoquinolinyl, indolyl, indoliziny, isoindolyl, indazolyl, benzofuryl, benzthienyl, benzo[b]thiazolyl, benzoxazolyl, benzthiazolyl and benzimidazolyl. Examples of 5- or 6-membered heteroaromatic compounds comprising an anellated cycloalkenyl ring include dihydroindolyl, dihydroindoliziny, dihydroisoindolyl, dihydroquinolinyl, dihydroisoquinolinyl, chromenyl and chromanyl.

- C<sub>3</sub>-C<sub>12</sub>-Heteroarylene is a heteroaryl diradical. Examples include pyrid-2,5-ylene and pyrid-2,4-ylene.

- 25 With respect to the compounds' capability of inhibiting glycine transporter 1, the variables R<sup>1</sup>, W, A<sup>1</sup>, Q, Y, A<sup>2</sup>, X<sup>1</sup>, X<sup>4</sup>, n, m, R<sup>6</sup>, R<sup>2</sup>, R<sup>3</sup>, X<sup>2</sup>, X<sup>3</sup>, R<sup>5</sup>, Y<sup>1</sup>, Y<sup>2</sup>, R<sup>4a</sup>, R<sup>4b</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>21</sup> preferably have the following meanings which, when taken alone or in combination, represent particular embodiments of the phenalkylamine derivatives of the formula (I), (II) or any other formula disclosed herein.

- 35 In said formula (I) or (II), there may be one or more than one substituent R<sup>2</sup> and/or R<sup>6</sup>. More particularly, there may be up to 3 substituents R<sup>2</sup> in formula (I) or (II), and up to 7 substituents R<sup>6</sup> (including R<sup>6</sup> as a substituent of X<sup>1</sup> if X<sup>1</sup> is >CH<sub>2</sub> and including R<sup>6</sup> as a substituent of X<sup>4</sup> if X<sup>4</sup> is >CH<sub>2</sub>) and up to 6 substituents R<sup>6</sup> in formula (II). Preferably there are 1 or 2 substituents R<sup>2</sup> and/or 1 or 2 substituents R<sup>6</sup>. Formulae (I) and (II) may thus be depicted as follows:



wherein a is 1, 2, or 3 and b is 1, 2, 3, 4, 5, 6 or 7 (in formula (I)) or 1, 2, 3, 4, 5 or 6 (in formula (II)). If there is more than one radical  $R^2$ , these may be the same or different radicals. If there is more than one radical  $R^6$ , these may be the same or different radicals.

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- $R^1$  is hydrogen,  $C_1$ - $C_6$ -alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or n-pentyl),  $C_3$ - $C_{12}$ -cycloalkyl- $C_1$ - $C_4$ -alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl), halogenated  $C_1$ - $C_6$ -alkyl (e.g. 3-fluoroprop-1-yl, 3-chloroprop-1-yl or 3,3,3-trifluoroprop-1-yl), tri- $(C_1$ - $C_4$ -alkyl)-silyl- $C_1$ - $C_4$ -alkyl (e.g. trimethylsilylethyl), hydroxy- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkoxy- $C_1$ - $C_4$ -alkyl (e.g. ethoxyethyl), amino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkylcarbonylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkyloxycarbonylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkylaminocarbonylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylaminocarbonylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkylsulfonylamino- $C_1$ - $C_4$ -alkyl, (optionally substituted  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_6$ -alkyl)amino- $C_1$ - $C_4$ -alkyl, optionally substituted  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -alkyl, optionally substituted  $C_3$ - $C_{12}$ -heterocyclyl- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -cycloalkyl (e.g. cyclopropyl or cyclobutyl),  $C_1$ - $C_6$ -alkylcarbonyl,  $C_1$ - $C_6$ -alkoxycarbonyl, halogenated  $C_1$ - $C_6$ -alkoxycarbonyl,  $C_6$ - $C_{12}$ -aryloxycarbonyl, aminocarbonyl,  $C_1$ - $C_6$ -alkylaminocarbonyl, (halogenated  $C_1$ - $C_4$ -alkyl)aminocarbonyl,  $C_6$ - $C_{12}$ -arylaminocarbonyl,  $C_2$ - $C_6$ -alkenyl (e.g. prop-1,2-en-1-yl),  $C_2$ - $C_6$ -alkynyl, optionally substituted  $C_6$ - $C_{12}$ -aryl (e.g. phenyl, 2-methylphenyl), hydroxy,  $C_1$ - $C_6$ -alkoxy (e.g. tert-butyloxy), halogenated  $C_1$ - $C_6$ -alkoxy,  $C_1$ - $C_6$ -hydroxyalkoxy,  $C_1$ - $C_6$ -alkoxy- $C_1$ - $C_4$ -alkoxy, amino- $C_1$ - $C_4$ -alkoxy,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkoxy, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkoxy,  $C_1$ - $C_6$ -alkylcarbonylamino- $C_1$ - $C_4$ -alkoxy,  $C_6$ - $C_{12}$ -arylcarbonylamino- $C_1$ - $C_4$ -alkoxy,  $C_1$ - $C_6$ -alkoxycarbonylamino- $C_1$ - $C_4$ -alkoxy,  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -alkoxy,  $C_1$ - $C_6$ -alkylsulfonylamino- $C_1$ - $C_4$ -alkoxy, (halogenated  $C_1$ - $C_6$ -alkyl)sulfonylamino- $C_1$ - $C_4$ -alkoxy,  $C_6$ - $C_{12}$ -arylsulfonylamino- $C_1$ - $C_4$ -alkoxy, ( $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_6$ -alkyl)sulfonylamino- $C_1$ - $C_4$ -alkoxy,  $C_3$ - $C_{12}$ -heterocyclylsulfonylamino- $C_1$ - $C_4$ -alkoxy,  $C_3$ - $C_{12}$ -heterocyclyl- $C_1$ - $C_4$ -alkoxy,  $C_6$ - $C_{12}$ -aryloxy,  $C_3$ - $C_{12}$ -heterocyclyloxy,  $C_1$ - $C_6$ -alkylthio, halo-

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generated C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylamino, (halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)amino, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino (e.g. dimethylamino), di-(halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)amino, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonylamino, (halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)carbonylamino, C<sub>6</sub>-C<sub>12</sub>-arylcarbonylamino, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonylamino, (halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)sulfonylamino, C<sub>6</sub>-C<sub>12</sub>-arylsulfonylamino or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl (e.g. 3-pyridyl, 2-thienyl, 4-methyl-2-thienyl, 5-methyl-2-thienyl, 5-chloro-2-thienyl, 2,5-dimethyl-3-thienyl, 1,2-diazol-4-yl, 1-methyl-1,2-diazol-4-yl, 1-ethyl-1,2-diazol-4-yl, 1-difluormethyl-1,2-diazol-4-yl, 2-methyl-1,3-diazol-4-yl, 1-methyl-1,3-diazol-4-yl, 2-methyl-1,3-thiazol-5-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 3-pyrrolidinyl, 1-methyl-pyrrol-3-yl, 2-pyridyl, 1-methyl-1,2-diazol-3-yl, 1-methyl-3-trifluoromethyl-1,2-diazol-4-yl, 1, 2-dimethyl-1,3-diazol-4-yl, 5-methylisoxazol-3-yl or 1-methyl-1,2,4-triazol-3-yl).

Preferably, R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, sec-butyl, n-butyl or n-pentyl), C<sub>3</sub>-C<sub>12</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl), halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. 3-fluoroprop-1-yl, 3-chloroprop-1-yl or 3,3,3-trifluoroprop-1-yl), tri-(C<sub>1</sub>-C<sub>4</sub>-alkyl)-silyl-C<sub>1</sub>-C<sub>4</sub>-alkyl (e.g. trimethylsilyl-ethyl), C<sub>1</sub>-C<sub>6</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl (e.g. ethoxyethyl), amino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkyloxycarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkylamino-carbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-cycloalkyl (e.g. cyclopropyl or cyclobutyl), C<sub>2</sub>-C<sub>6</sub>-alkenyl (e.g. prop-1,2-en-1-yl), optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl (e.g. phenyl), hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkylamino, (halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)amino, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl (e.g. 3-pyridyl, 2-thienyl, 4-methyl-2-thienyl, 5-methyl-2-thienyl, 5-chloro-2-thienyl, 2,5-dimethyl-3-thienyl, 1,2-diazol-4-yl, 1-methyl-1,2-diazol-4-yl, 1-ethyl-1,2-diazol-4-yl, 1-difluormethyl-1,2-diazol-4-yl, 2-methyl-1,3-diazol-4-yl, 1-methyl-1,3-diazol-4-yl, 2-methyl-1,3-thiazol-5-yl, 2,4-dimethyl-1,3-thiazol-5-yl or 3-pyrrolidinyl).

In particular, R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. n-propyl), C<sub>3</sub>-C<sub>12</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl (e.g. cyclopropylmethyl), or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl (e.g. 1-methyl-1,2-diazol-4-yl or 1-methyl-1,3-diazol-4-yl).

In connection with R<sup>1</sup>, substituted C<sub>6</sub>-C<sub>12</sub>-aryl in particular includes C<sub>6</sub>-C<sub>12</sub>-aryl, such as phenyl or naphthyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, cyano, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, amino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino, morpholino and piperidinyl. The same applies to substituted C<sub>6</sub>-C<sub>12</sub>-aryl in substituted C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>4</sub>-alkyl.

In connection with R<sup>1</sup>, substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl in particular includes C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, such as pyridyl, thienyl, diazolyl, quinolinyl, piperidinyl, piperazinyl or morpholinyl, pyrrolyl, isoxazolyl and triazolyl being further examples of such C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkyloxycarbonyl, cyano, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, C<sub>1</sub>-

C<sub>4</sub>-alkylsulfonyl, amino, C<sub>1</sub>-C<sub>4</sub>-alkylamino, C<sub>1</sub>-C<sub>4</sub>-dialkylamino, C<sub>6</sub>-C<sub>12</sub>-aryl amino and C<sub>3</sub>-C<sub>12</sub>-heterocyclyl (e.g., morpholino or piperidinyl). The same applies to substituted C<sub>3</sub>-C<sub>12</sub>-heteroaryl in substituted C<sub>3</sub>-C<sub>12</sub>-heteroaryl-C<sub>1</sub>-C<sub>4</sub>-alkyl.

- 5 According to one embodiment, W is -NR<sup>8</sup>- and Y is a bond. According to an alternative embodiment, W is a bond and Y is -NR<sup>9</sup>-. According to a further alternative embodiment, W is a bond and Y is a bond, especially if R<sup>1</sup> is a nitrogen-bound radical, e.g. nitrogen-bound heterocyclyl such as piperazinyl or morpholinyl.

- 10 According to one embodiment, Q is -S(O)<sub>2</sub>-. According to an alternative embodiment, Q is -C(O)-.

- According to a particular embodiment, -W-A<sup>1</sup>-Q-Y- is -W-A<sup>1</sup>-S(O)<sub>2</sub>-NR<sup>9</sup>-, -NR<sup>8</sup>-S(O)<sub>2</sub>-, -A<sup>1</sup>-S(O)<sub>2</sub>- or -S(O)<sub>2</sub>-. According to a further particular embodiment, -W-A<sup>1</sup>-Q-Y- is -W-A<sup>1</sup>-CO-NR<sup>9</sup>- or -NR<sup>8</sup>-CO-.
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- According to a particular embodiment, -W-A<sup>1</sup>-Q- is -W-A<sup>1</sup>-S(O)<sub>2</sub>-, -NR<sup>8</sup>-S(O)<sub>2</sub>-, -A<sup>1</sup>-S(O)<sub>2</sub>- or -S(O)<sub>2</sub>-. According to a further particular embodiment, -W-A<sup>1</sup>-Q- is -W-A<sup>1</sup>-CO- or -NR<sup>8</sup>-CO-.
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- A<sup>1</sup> is optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene or a bond. In connection with A<sup>1</sup>, substituted C<sub>1</sub>-C<sub>4</sub>-alkylene in particular includes C<sub>1</sub>-C<sub>4</sub>-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl and cyano. Preferably, A<sup>1</sup> is a bond. If A<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub>-alkylene, W is preferably -NR<sup>8</sup>-.
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- A<sup>2</sup> is optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene (e.g. methylene, 1,2-ethylene or 1,3-propylene), C<sub>1</sub>-C<sub>4</sub>-alkylene-CO-, -CO-C<sub>1</sub>-C<sub>4</sub>-alkylene, C<sub>1</sub>-C<sub>4</sub>-alkylene-O-C<sub>1</sub>-C<sub>4</sub>-alkylene, C<sub>1</sub>-C<sub>4</sub>-alkylene-NR<sup>10</sup>-C<sub>1</sub>-C<sub>4</sub>-alkylene, optionally substituted C<sub>6</sub>-C<sub>12</sub>-arylene, optionally substituted C<sub>6</sub>-C<sub>12</sub>-heteroarylene or a bond. Additionally, A<sup>2</sup> may be optionally substituted C<sub>2</sub>-C<sub>4</sub>-alkenylene or optionally substituted C<sub>2</sub>-C<sub>4</sub>-alkynylene. Preferably, A<sup>2</sup> is optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene (e.g. methylene, 1,2-ethylene or 1,3-propylene). More preferably, A<sup>2</sup> is C<sub>1</sub>-C<sub>4</sub>-alkylene (e.g. methylene). Alternatively, it is preferred that A<sup>2</sup> is optionally substituted C<sub>6</sub>-C<sub>12</sub>-arylene, in particular C<sub>6</sub>-C<sub>12</sub>-arylene selected from the group consisting of phen-1,4-ylene and phen-1,3-ylene, or optionally substituted C<sub>6</sub>-C<sub>12</sub>-heteroarylene, in particular C<sub>6</sub>-C<sub>12</sub>-heteroarylene selected from the group consisting of pyrid-2,5-ylene and pyrid-2,4-ylene. If A<sup>2</sup> is a bond, X<sup>1</sup> is preferably >CH<sub>2</sub>.
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- 35

- In connection with A<sup>2</sup>, substituted C<sub>1</sub>-C<sub>4</sub>-alkylene in particular includes C<sub>1</sub>-C<sub>4</sub>-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl and cyano.
- 40



In connection with  $A^2$ , substituted  $C_2-C_4$ -alkenylene or substituted  $C_2-C_4$ -alkynylene in particular includes  $C_2-C_4$ -alkenylene or  $C_2-C_4$ -alkynylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen,  $C_1-C_4$ -alkyl,  $C_1-C_4$ -haloalkyl and cyano.

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In connection with  $A^2$ , substituted  $C_6-C_{12}$ -arylene in particular includes  $C_6-C_{12}$ -arylene substituted with 1, 2 or 3 substituents selected from the group consisting of  $C_1-C_4$ -alkyl,  $C_1-C_4$ -haloalkyl,  $C_1-C_4$ -alkoxycarbonyl, cyano,  $C_1-C_4$ -alkoxy,  $C_1-C_4$ -haloalkoxy,  $C_1-C_4$ -alkylsulfonyl, amino,  $C_1-C_4$ -alkylamino,  $C_1-C_4$ -dialkylamino,  $C_6-C_{12}$ -arylamino and  $C_3-C_{12}$ -heterocyclyl (e.g., morpholino or piperidiny).

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In connection with  $A^2$ , substituted  $C_6-C_{12}$ -heteroarylene in particular includes  $C_6-C_{12}$ -heteroarylene substituted with 1, 2 or 3 substituents selected from the group consisting of  $C_1-C_4$ -alkyl,  $C_1-C_4$ -haloalkyl,  $C_1-C_4$ -alkoxycarbonyl, cyano,  $C_1-C_4$ -alkoxy,  $C_1-C_4$ -haloalkoxy,  $C_1-C_4$ -alkylsulfonyl, amino,  $C_1-C_4$ -alkylamino,  $C_1-C_4$ -dialkylamino,  $C_6-C_{12}$ -arylamino and  $C_3-C_{12}$ -heterocyclyl (e.g., morpholino or piperidiny).

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$X^1$  is -O-, -NR<sup>11</sup>-, -S- or >CH<sub>2</sub>. Preferably,  $X^1$  is -O-, -NR<sup>11</sup>, or -S-. More preferably,  $X^1$  is -O-. Alternatively,  $X^1$  is >CH<sub>2</sub>.

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According to a particular embodiment,  $A^2$  is a bond and  $X^1$  is >CH<sub>2</sub>.

According to a particular embodiment,  $R^1-W-A^1-Q-Y-A^2-X^1$  is  $R^1-S(O)_2-NH-A^2-X^1$ ,  $R^1-NH-S(O)_2-A^2-X^1$ ,  $R^1-C(O)-NH-A^2-X^1$  or  $R^1-NH-C(O)-A^2-X^1$ .

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According to a particular embodiment, the structural element -Y-A<sup>2</sup>- comprises at least 1 or 2 atoms in the main chain. According to further particular embodiments the structural element -Y-A<sup>2</sup>- has up to 2, 3 or 4 atoms in the main chain, such as 1 to 4, 1 to 3, or 1 to 2 atoms in the main chain, or especially 1 or 2 atoms in the main chain.

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According to a further particular embodiment, -Y-A<sup>2</sup>- is -NR<sup>9</sup>-C<sub>1</sub>-C<sub>4</sub>-alkylene- (e.g. -NH-CH<sub>2</sub>-, -NH-(CH<sub>2</sub>)<sub>2</sub>- or -NH-(CH<sub>2</sub>)<sub>3</sub>-), with -Y-A<sup>2</sup>- preferably having 1 to 4, or 1 to 3, or especially 1 or 2 atoms in the main chain. In this particular embodiment, R<sup>9</sup> is as defined herein and preferably R<sup>9</sup> is hydrogen,  $C_1-C_6$ -alkyl (e.g. methyl or ethyl) or  $C_3-C_{12}$ -cycloalkyl (e.g. cyclopropyl).

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According to a further particular embodiment, -Y-A<sup>2</sup>- is -C<sub>1</sub>-C<sub>4</sub>-alkylene- (e.g. -CH<sub>2</sub>-), with -Y-A<sup>2</sup> preferably having 1 to 4, or 1 to 3, or especially 1 or 2 atoms in the main chain.

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According to a further particular embodiment, the structural motif -Y-A<sup>2</sup>- as disclosed herein is bound to Q being -S(O)<sub>2</sub>- or -C(O)-. Particular examples for this embodiment are

clude phenalkylamine derivatives of the invention wherein R is  $R^1-S(O)_2-Y-A^2-$  or  $R^1-C(O)-Y-A^2-$ .

$X^4$  is  $-O-$ ,  $-NR^{19}-$ ,  $-S-$ , or  $>CH_2$ . According to a particular embodiment,  $X^4$  is  $-O-$  or  $-NR^{19}-$ .

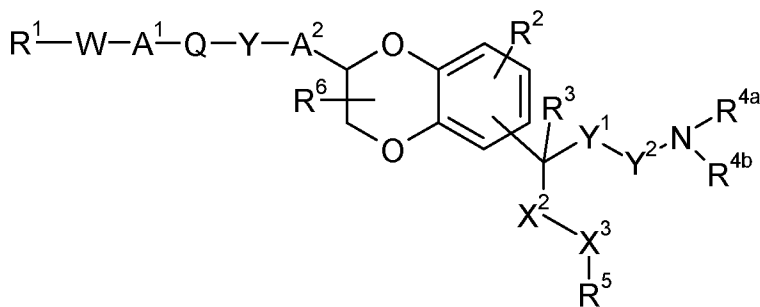
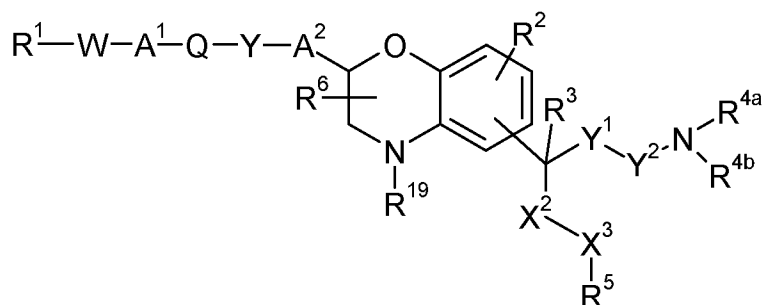
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In the phenalkylamine derivatives of formula (I), n is zero, 1 or 2. According to a particular embodiment, n is 1.

In the phenalkylamine derivatives of formula (II), m is zero, 1 or 2. According to a particular embodiment, m is 1 or 2.

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According to a particular embodiment, the phenalkylamine derivatives of formula (I) have one of the following formulae:

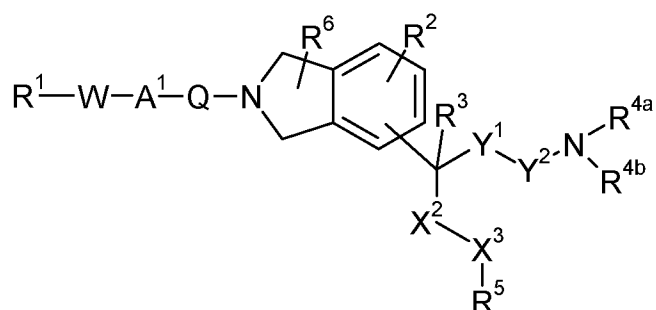
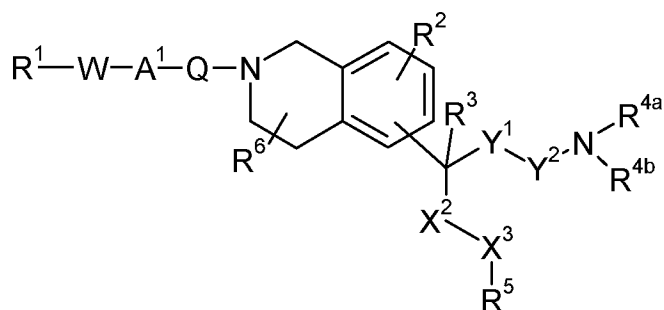


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In said formulae,  $R^1$ , W,  $A^1$ , Q, Y,  $A^2$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein.

According to a further particular embodiment, the phenalkylamine derivatives of formula (II) have one of the following formulae:

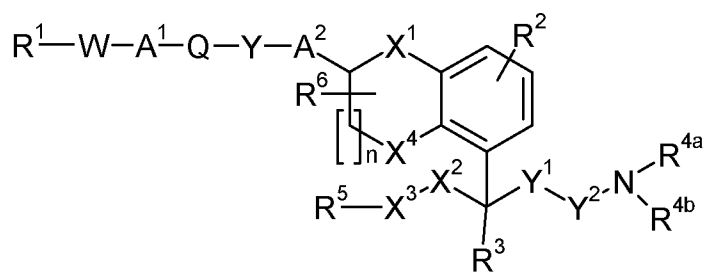
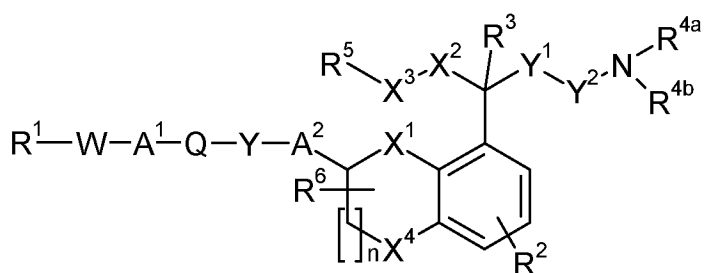
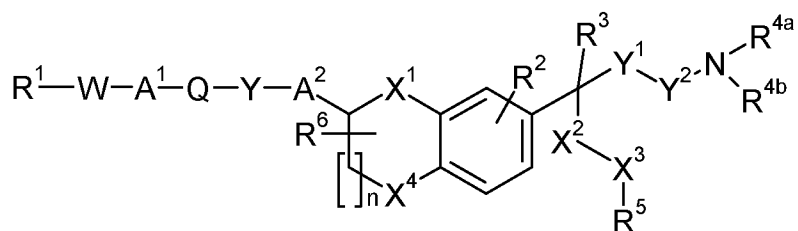
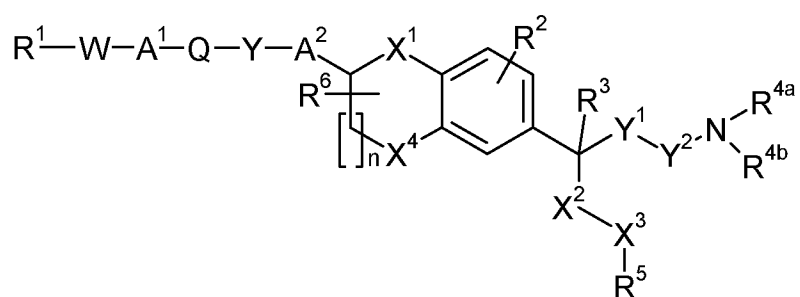
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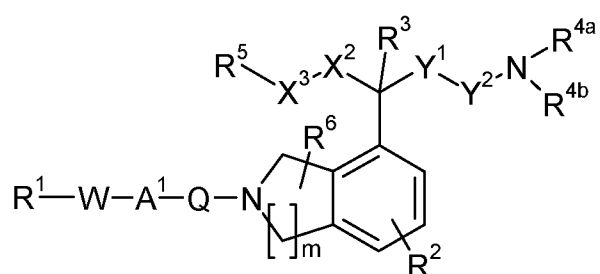
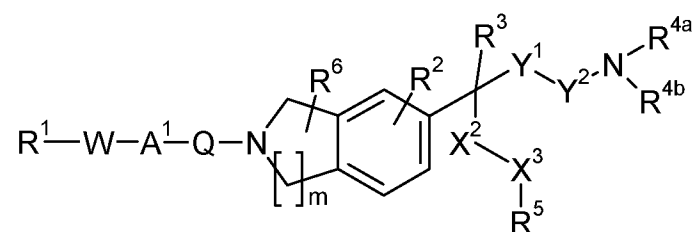
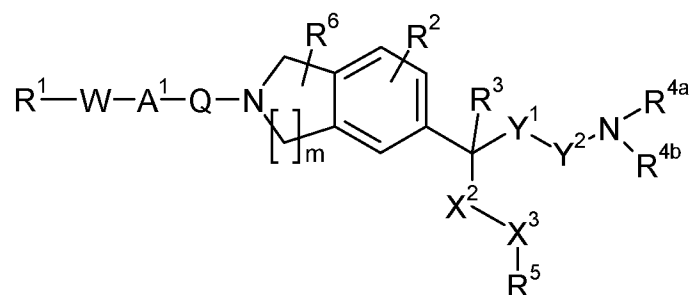
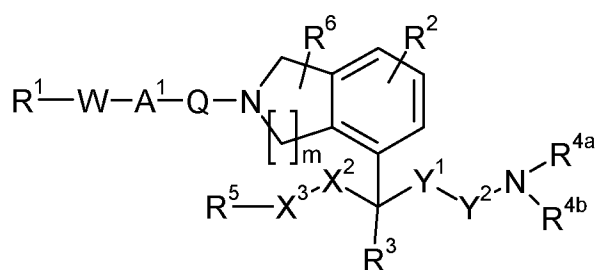
In said formulae,  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$ , are as defined herein.

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In the phenalkylamine derivatives of formula (I) or (II), the alkylamine moiety may, in principle, be bound to the benzene moiety in any available position:



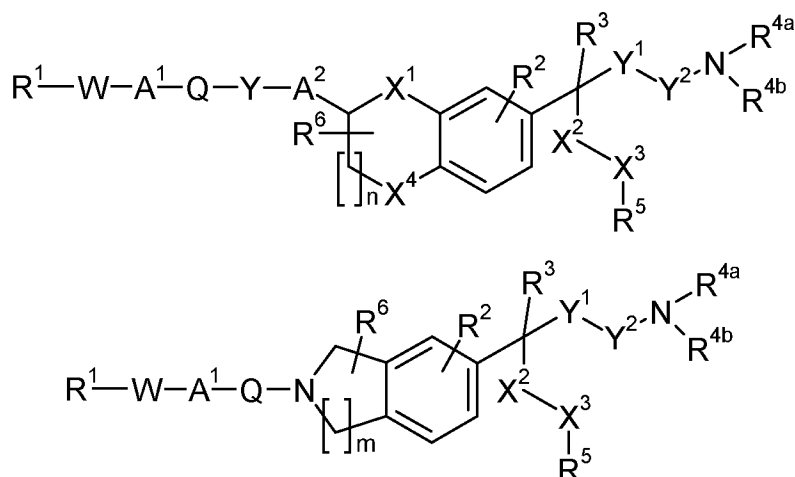
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In said formulae,  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $X^1$ ,  $X^4$ ,  $n$ ,  $m$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein.

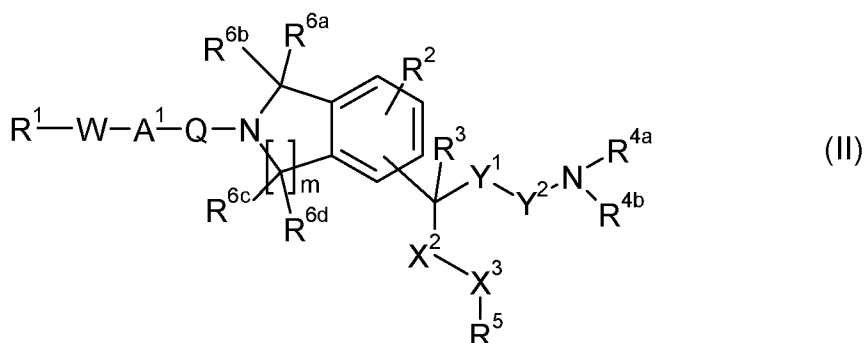
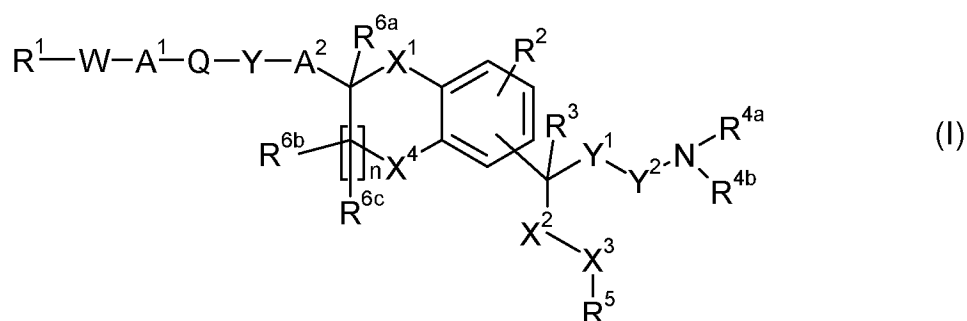
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Particularly preferred are phenalkylamine derivatives having one of the following formulae:



wherein  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $X^1$ ,  $X^4$ ,  $n$ ,  $m$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as  
 5 defined herein.

On the saturated ring, the phenalkylamine derivatives of the invention may be substituted  
 with one or more than one radical  $R^6$ . If there is more than one radical  $R^6$ , these may be  
 the same or different radicals. The phenalkylamine derivatives of the invention may there-  
 10 fore be represented by the following formula:



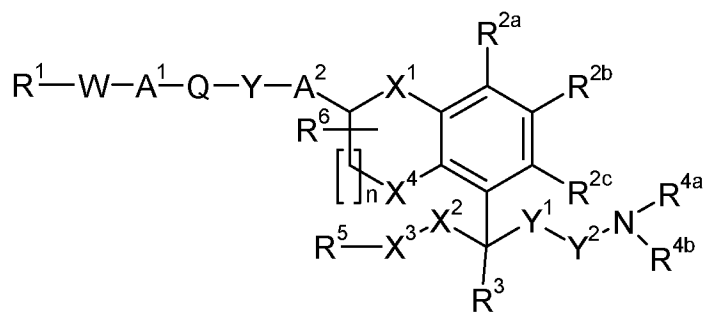
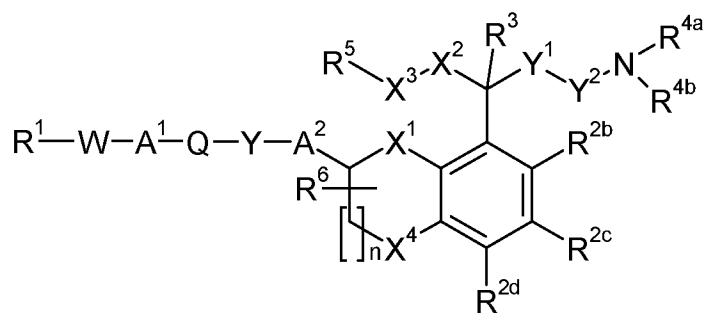
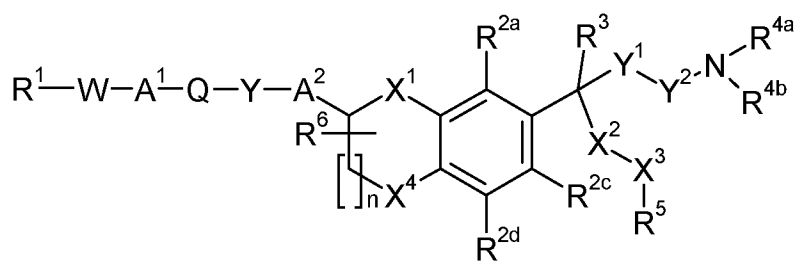
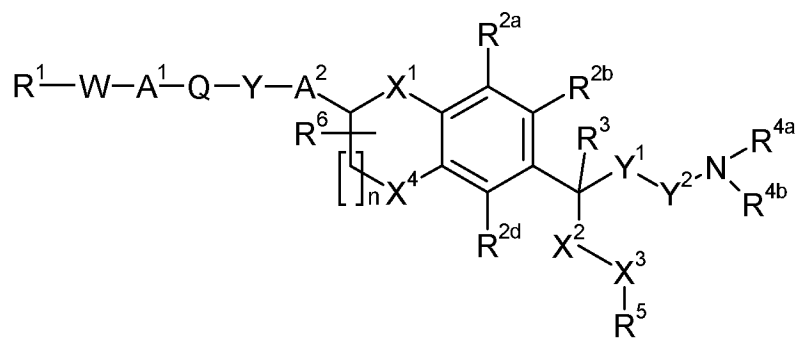
wherein  $R^{6a}$ ,  $R^{6b}$ ,  $R^{6c}$ ,  $R^{6d}$  independently have one of the meanings given for  $R^6$ , and  $R^1$ ,  
 $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $X^1$ ,  $X^4$ ,  $n$ ,  $m$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein.

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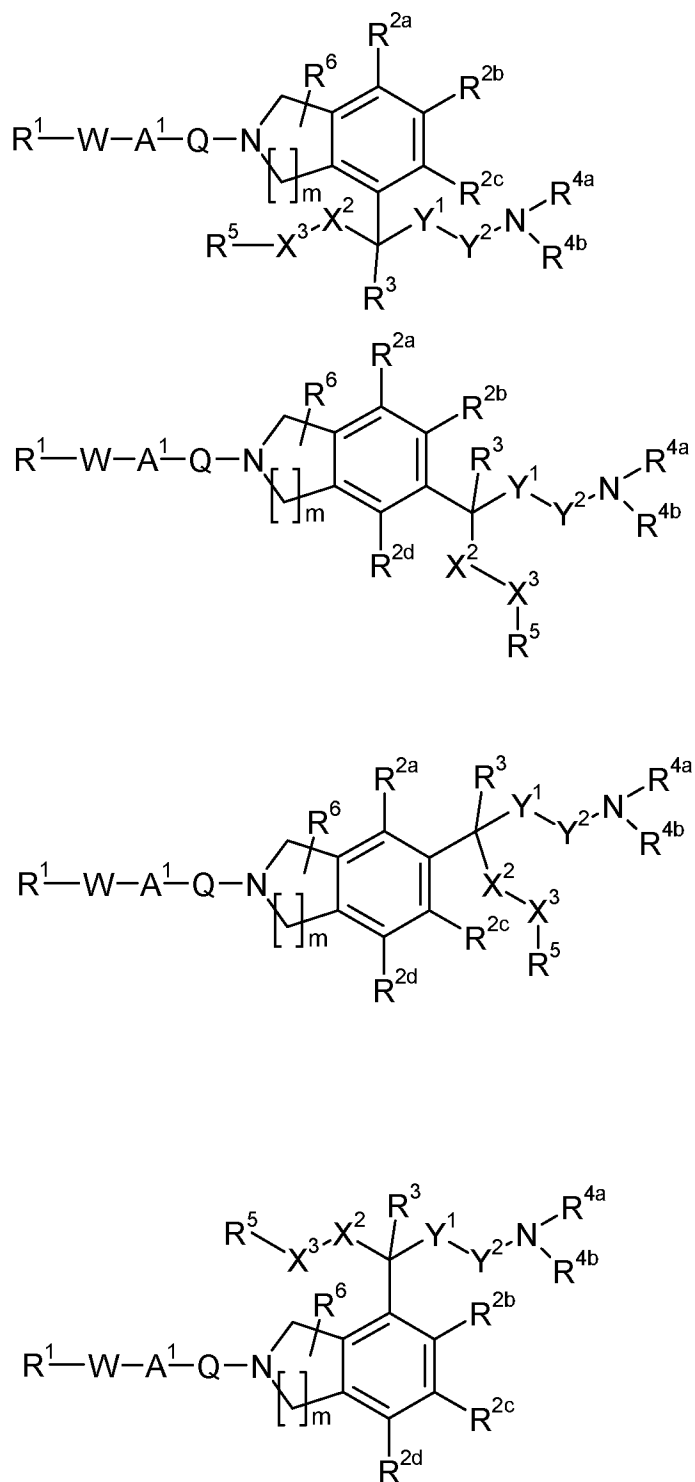
$R^6$  is hydrogen, halogen,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkoxy, or two radicals  $R^6$  together with the  
 carbon atom to which they are attached form a carbonyl group.

Preferably,  $R^6$  is hydrogen or  $C_1$ - $C_6$ -alkyl. In particular,  $R^6$  is hydrogen.

- 5 In addition to the alkylamine moiety, the phenalkylamine derivatives of the invention may have one or more than one further substituent bound to the benzene ring. In these positions, the skeleton of the phenalkylamine derivatives may thus be substituted with one or more than one radical  $R^2$ . If there is more than one radical  $R^2$ , these may be the same or different radicals. The phenalkylamine derivatives of the invention may therefore be represented by one of the following formulae:







wherein  $R^{2a}$ ,  $R^{2b}$ ,  $R^{2c}$ ,  $R^{2d}$  independently have one of the meanings given for  $R^2$ , and  $R^1$ ,  
 5 W,  $A^1$ , Q, Y,  $A^2$ ,  $X^1$ ,  $X^4$ , n, m,  $R^6$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein.

$R^2$  is hydrogen, halogen,  $C_1$ - $C_6$ -alkyl, halogenated  $C_1$ - $C_4$ -alkyl, hydroxy- $C_1$ - $C_4$ -alkyl, -CN,  $C_2$ - $C_6$ -alkenyl,  $C_2$ - $C_6$ -alkynyl, optionally substituted  $C_6$ - $C_{12}$ -aryl, hydroxy,  $C_1$ - $C_6$ -alkoxy, halogenated  $C_1$ - $C_6$ -alkoxy,  $C_1$ - $C_6$ -alkoxycarbonyl,  $C_2$ - $C_6$ -alkenyloxy,  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -

alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyloxy, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, aminosulfonyl, amino, C<sub>1</sub>-C<sub>6</sub>-alkylamino, C<sub>2</sub>-C<sub>6</sub>-alkenylamino, nitro or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, or two radicals R<sup>2</sup> together with the ring atoms to which they are bound form a 5- or 6 membered ring.

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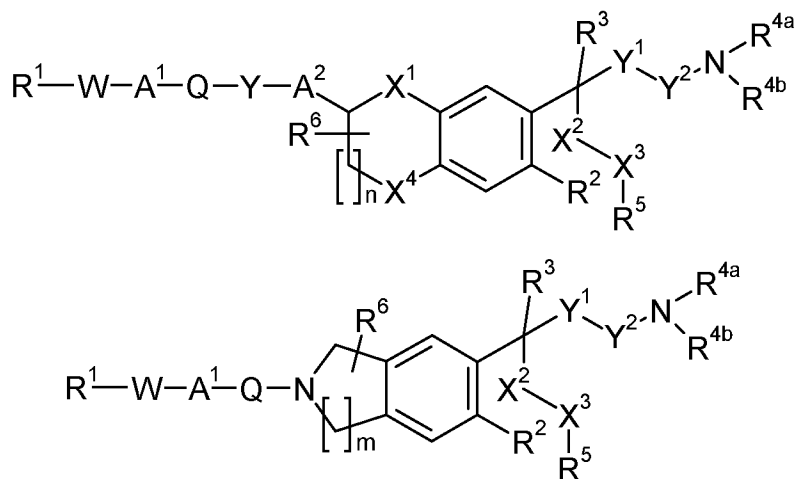
An optionally substituted 5- or 6-membered ring that is formed by two radicals R<sup>2</sup> together with the ring atoms of the benzene ring to which they are bound is, for instance, a benzene ring.

- 10 In connection with R<sup>2</sup>, substituted C<sub>6</sub>-C<sub>12</sub>-aryl in particular includes C<sub>6</sub>-C<sub>12</sub>-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen and C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, cyano, C<sub>1</sub>-C<sub>4</sub>-alkoxy and C<sub>1</sub>-C<sub>4</sub>-haloalkoxy.

- 15 In connection with R<sup>2</sup>, substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl in particular includes C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, such as morpholinyl, pyrrolidinyl and piperidinyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, cyano, C<sub>1</sub>-C<sub>4</sub>-alkoxy and C<sub>1</sub>-C<sub>4</sub>-haloalkoxy.

- 20 Preferably, R<sup>2</sup> is hydrogen, halogen or C<sub>1</sub>-C<sub>6</sub>-alkoxy. In particular, R<sup>2</sup> is hydrogen or halogen.

According to a particular embodiment, the phenalkylamine derivatives of the invention have one of the following formulae:



25

wherein R<sup>1</sup>, W, A<sup>1</sup>, Q, Y, A<sup>2</sup>, X<sup>1</sup>, X<sup>4</sup>, n, m, R<sup>6</sup>, R<sup>2</sup>, R<sup>3</sup>, X<sup>2</sup>, X<sup>3</sup>, R<sup>5</sup>, Y<sup>1</sup>, Y<sup>2</sup>, R<sup>4a</sup>, R<sup>4b</sup> are as defined herein.

- 30 R<sup>3</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl. In particular, R<sup>3</sup> is hydrogen.

X<sup>2</sup> is -O-, -NR<sup>7</sup>-, -S-, >CR<sup>12a</sup>R<sup>12b</sup> or a bond. Preferably, X<sup>2</sup> is >CR<sup>12a</sup>R<sup>12b</sup>.

$X^3$  is -O-, -NR<sup>7</sup>-, -S-, >CR<sup>13a</sup>R<sup>13b</sup> or a bond. Preferably,  $X^3$  is a bond.

Thus, it is preferred if  $X^2$  is >CR<sup>12a</sup>R<sup>12b</sup> and  $X^3$  is a bond.

- 5 R<sup>12a</sup> is hydrogen, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-heterocyclyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl or hydroxy. Preferably, R<sup>12a</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl.

- 10 R<sup>13a</sup> is hydrogen, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-heterocyclyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl or hydroxy. Preferably, R<sup>13a</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl.

- 15 In connection with R<sup>12a</sup> and R<sup>13a</sup>, substituted C<sub>1</sub>-C<sub>6</sub>-alkyl in particular includes C<sub>1</sub>-C<sub>6</sub>-alkyl substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkoxy and amino.

- 20 In connection with R<sup>12a</sup> and R<sup>13a</sup>, substituted C<sub>6</sub>-C<sub>12</sub>-aryl in particular includes C<sub>6</sub>-C<sub>12</sub>-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, cyano, C<sub>1</sub>-C<sub>4</sub>-alkoxy and C<sub>1</sub>-C<sub>4</sub>-haloalkoxy.

R<sup>12b</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl. According to a particular embodiment, R<sup>12b</sup> is hydrogen.

R<sup>13b</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl. According to a particular embodiment, R<sup>13b</sup> is hydrogen.

- 25 Alternatively, R<sup>12a</sup> and R<sup>12b</sup>, or R<sup>13a</sup> and R<sup>13b</sup>, together are together are carbonyl or, preferably, optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene (e.g. 1,3-propylene), wherein one -CH<sub>2</sub>- of C<sub>1</sub>-C<sub>4</sub>-alkylene may be replaced by an oxygen atom or -NR<sup>17</sup>- or NR<sup>18</sup>.

- 30 In connection with R<sup>12a</sup> and R<sup>12b</sup>, or R<sup>13a</sup> and R<sup>13b</sup>, substituted C<sub>1</sub>-C<sub>4</sub>-alkylene in particular includes C<sub>1</sub>-C<sub>4</sub>-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, cyano, C<sub>1</sub>-C<sub>4</sub>-alkoxy and C<sub>1</sub>-C<sub>4</sub>-haloalkoxy.

- 35 According to a particular embodiment, R<sup>12a</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl and R<sup>12b</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl, or R<sup>13a</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl and R<sup>13b</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl.

According to a further particular embodiment, R<sup>12a</sup> is hydrogen and R<sup>12b</sup> is hydrogen, or R<sup>13a</sup> is hydrogen and R<sup>13b</sup> is hydrogen.

- 40 According to a further particular embodiment, R<sup>12a</sup> and R<sup>12b</sup> together are optionally substituted 1,3-propylene, or R<sup>13a</sup> and R<sup>13b</sup> together are optionally substituted 1,3-propylene.

R<sup>5</sup> is optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl (e.g. phenyl, 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 3-chlorophenyl; 3-cyanophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-fluoro-5-chlorophenyl, 3-chloro-4-fluorophenyl, 2,4-dichlorophenyl or 3,4-dichlorophenyl,), optionally substituted C<sub>3</sub>-C<sub>12</sub>-cycloalkyl (e.g. cyclohexyl) or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl.

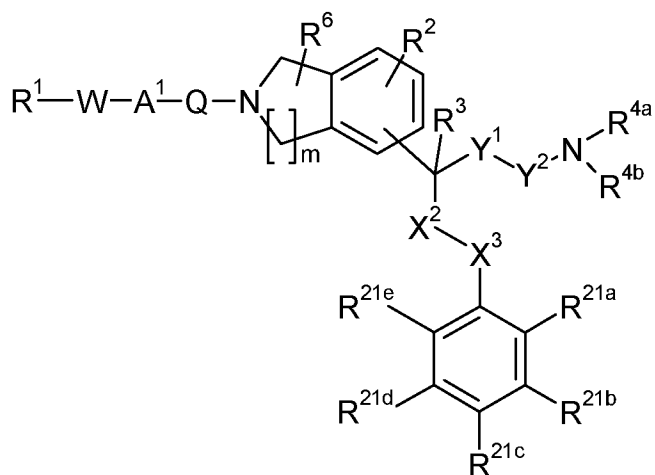
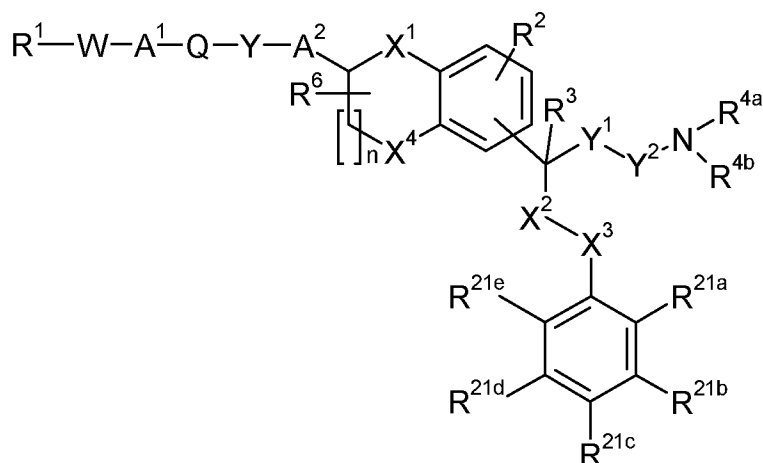
In connection with R<sup>5</sup>, substituted C<sub>3</sub>-C<sub>12</sub>-cycloalkyl in particular includes C<sub>3</sub>-C<sub>12</sub>-cycloalkyl, such as cyclopropyl or cyclohexyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl, CN, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy, halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxy, amino, C<sub>1</sub>-C<sub>6</sub>-alkylamino, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino and C<sub>3</sub>-C<sub>12</sub>-heterocyclyl.

In connection with R<sup>5</sup>, substituted C<sub>6</sub>-C<sub>12</sub>-aryl in particular includes C<sub>6</sub>-C<sub>12</sub>-aryl, such as phenyl, substituted with 1, 2 or 3 substituents selected from the group consisting of halogen (e.g. F, Cl, Br), optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl), halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. trifluoromethyl), CN, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy (e.g. methoxy), halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxy, amino, C<sub>1</sub>-C<sub>6</sub>-alkylamino, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino and C<sub>3</sub>-C<sub>12</sub>-heterocyclyl.

In connection with R<sup>5</sup>, substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl in particular includes C<sub>3</sub>-C<sub>12</sub>-heterocyclyl substituted with 1, 2 or 3 substituents selected from the group consisting of halogen, optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl, halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl, CN, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy, halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxy, amino, C<sub>1</sub>-C<sub>6</sub>-alkylamino, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino and C<sub>3</sub>-C<sub>12</sub>-heterocyclyl.

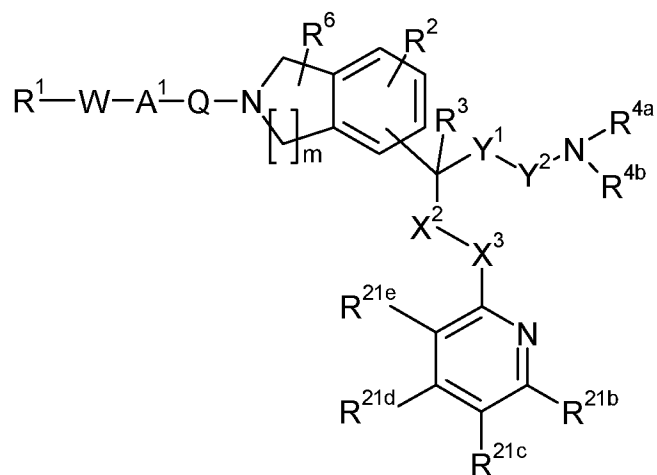
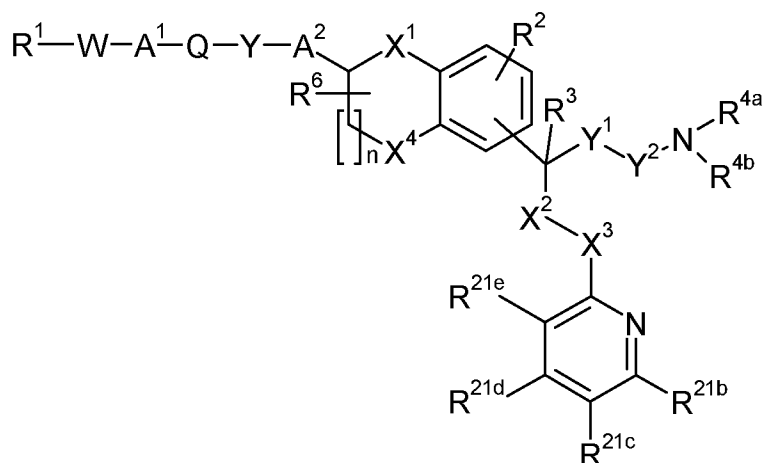
In connection with R<sup>5</sup>, C<sub>3</sub>-C<sub>12</sub>-heterocyclyl in particular is C<sub>3</sub>-C<sub>12</sub>-heteroaryl.

Preferably, R<sup>5</sup> is optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl, in particular as in the phenalkylamine derivatives of the formula:



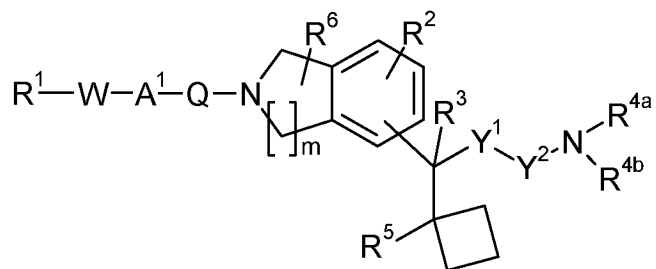
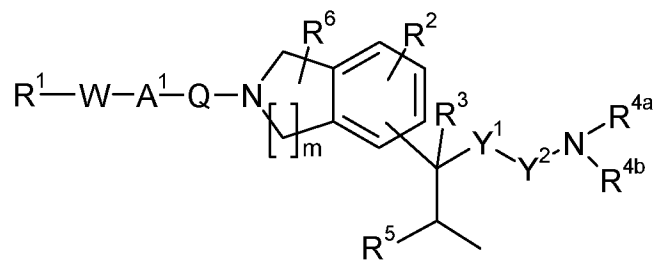
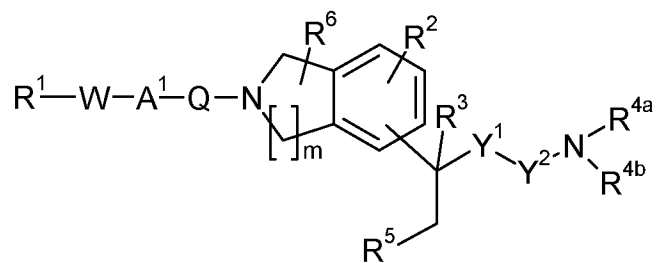
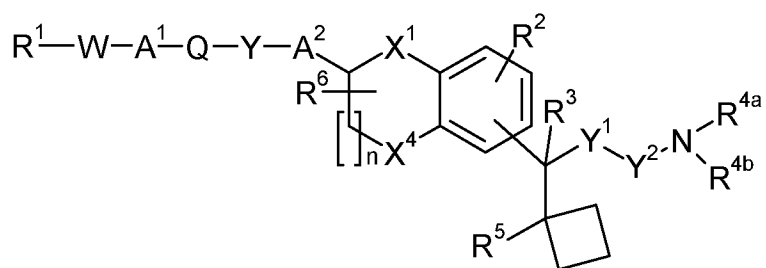
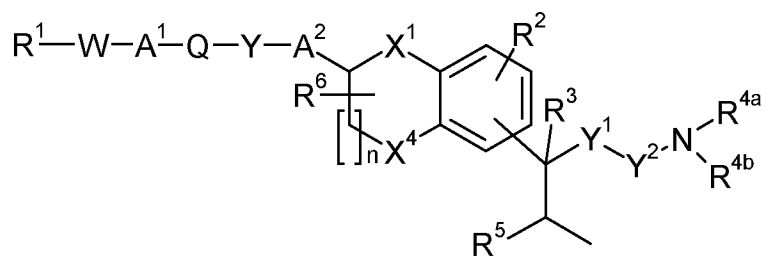
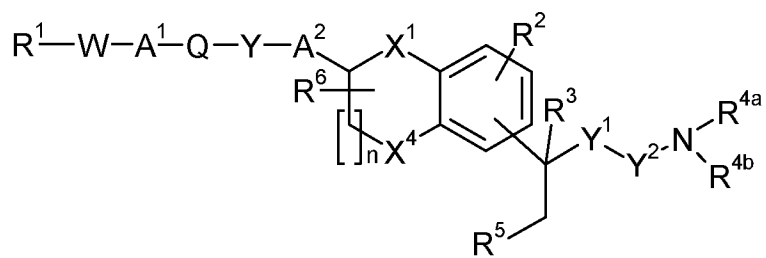
wherein  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $X^1$ ,  $X^4$ ,  $n$ ,  $m$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein, and

- 5  $R^{21a}$ ,  $R^{21b}$ ,  $R^{21c}$ ,  $R^{21d}$ ,  $R^{21e}$  independently are hydrogen, halogen (e.g. F, Cl or Br), optionally substituted  $C_1$ - $C_6$ -alkyl (e.g. methyl), halogenated  $C_1$ - $C_6$ -alkyl (e.g. trifluoromethyl), CN, hydroxy,  $C_1$ - $C_6$ -alkoxy (e.g. methoxy), amino,  $C_1$ - $C_6$ -alkylamino, di- $C_1$ - $C_6$ -alkylamino or  $C_3$ - $C_{12}$ -heterocyclyl.
- 10 It is also preferred if  $R^5$  is optionally substituted  $C_6$ - $C_{12}$ -heteroaryl, in particular as in the phenalkylamine derivatives of the formula:



wherein  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $X^1$ ,  $X^4$ ,  $n$ ,  $m$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein, and

- 5 R<sup>21b</sup>, R<sup>21c</sup>, R<sup>21d</sup>, R<sup>21e</sup> independently are hydrogen, halogen (e.g. F, Cl or Br), optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl), halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. trifluoromethyl), CN, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy (e.g. methoxy), amino, C<sub>1</sub>-C<sub>6</sub>-alkylamino, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino or C<sub>3</sub>-C<sub>12</sub>-heterocyclyl.
- 10 According to a particular embodiment, the invention relates to phenalkylamine derivatives of the formula:



wherein  $R^1$ , W,  $A^1$ , Q, Y,  $A^2$ ,  $X^1$ ,  $X^4$ , n, m,  $R^2$ ,  $R^3$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined herein,  $R^5$  preferably being optionally substituted aryl and in particular optionally substituted phenyl as disclosed herein.

5 In connection with  $R^5$  or  $R^{21a}$ ,  $R^{21b}$ ,  $R^{21c}$ ,  $R^{21d}$ ,  $R^{21e}$ , substituted  $C_1$ - $C_6$ -alkyl in particular includes  $C_1$ - $C_6$ -alkyl, especially  $C_1$ - $C_4$ -alkyl, substituted with 1, 2 or 3 substituents selected from the group consisting of hydroxy,  $C_1$ - $C_6$ -alkoxy, amino,  $C_1$ - $C_6$ -alkylamino, di- $C_1$ - $C_6$ -alkylamino and  $C_3$ - $C_{12}$ -heterocyclyl (e.g. morpholinyl or piperidinyl).

10 According to a particular embodiment,  $R^{21a}$ ,  $R^{21b}$ ,  $R^{21d}$ ,  $R^{21e}$  are hydrogen and  $R^{21c}$  is different from hydrogen (para-mono-substitution).

According to a further particular embodiment,  $R^{21a}$ ,  $R^{21c}$ ,  $R^{21d}$ ,  $R^{21e}$  are hydrogen and  $R^{21b}$  is different from hydrogen (meta-mono-substitution).

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In connection with  $R^{21a}$ ,  $R^{21b}$ ,  $R^{21c}$ ,  $R^{21d}$ ,  $R^{21e}$ ,  $C_3$ - $C_{12}$ -heterocyclyl in particular includes morpholinyl, imidazolyl and pyrazolyl.

$Y^1$  is a bond or  $>CR^{14a}R^{14b}$ . According to one embodiment,  $Y^1$  is a bond.

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$Y^2$  is  $>CR^{15a}R^{15b}$ .

Thus, according to one embodiment  $-Y^1-Y^2-$  is  $>CR^{15a}R^{15b}$ .

25  $R^{14a}$  is hydrogen, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -heterocyclyl- $C_1$ - $C_6$ -alkyl, optionally substituted  $C_6$ - $C_{12}$ -aryl or hydroxyl.

$R^{14b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl.

30

Alternatively,  $R^{14a}$ ,  $R^{14b}$  together are carbonyl or optionally substituted  $C_1$ - $C_4$ -alkylene, wherein one or two  $-CH_2-$  of  $C_1$ - $C_4$ -alkylene may be replaced by an oxygen atom or  $-NR^{20}-$ .

35  $R^{15a}$  is hydrogen, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -heterocyclyl- $C_1$ - $C_6$ -alkyl, optionally substituted  $C_6$ - $C_{12}$ -aryl or hydroxyl.

$R^{15b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl.

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According to a particular embodiment,  $R^{15a}$  is hydrogen and  $R^{15b}$  is hydrogen.



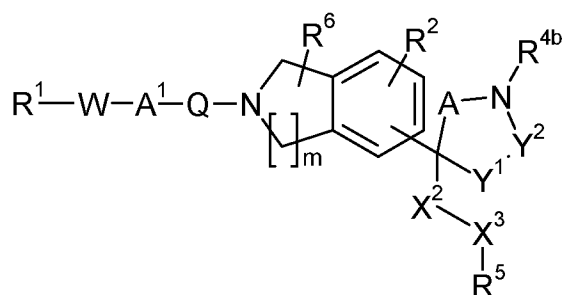
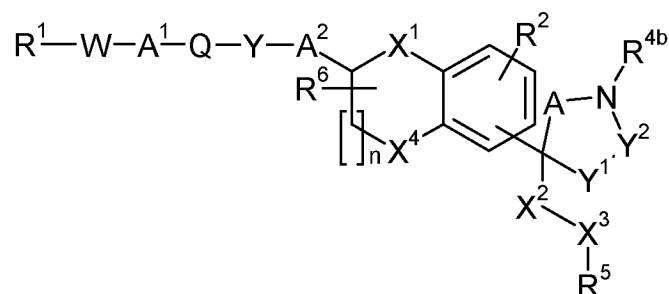
Alternatively,  $R^{15a}$ ,  $R^{15b}$  together are carbonyl or optionally substituted  $C_1$ - $C_4$ -alkylene, wherein one or two  $-CH_2-$  of  $C_1$ - $C_4$ -alkylene may be replaced by an oxygen atom or  $-NR^{20}-$ .

- 5 In connection with  $R^{14a}$  and  $R^{14b}$ , or  $R^{15a}$  and  $R^{15b}$ , substituted  $C_1$ - $C_4$ -alkylene in particular includes  $C_1$ - $C_4$ -alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen,  $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -haloalkyl, cyano,  $C_1$ - $C_4$ -alkoxy and  $C_1$ - $C_4$ -haloalkoxy.
- 10  $R^{4a}$  is hydrogen,  $C_1$ - $C_6$ -alkyl (e.g. methyl, ethyl, n-propyl or isopropyl),  $C_3$ - $C_{12}$ -cycloalkyl- $C_1$ - $C_4$ -alkyl (e.g. cyclopropylmethyl), halogenated  $C_1$ - $C_4$ -alkyl (e.g. 2-fluoroethyl or 2,2,2-trifluoroethyl), hydroxy- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkoxy- $C_1$ - $C_4$ -alkyl, amino- $C_1$ - $C_4$ -alkyl,  $CH_2CN$ ,  $C_3$ - $C_{12}$ -cycloalkyl (e.g. cyclopropyl),  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -alkyl (e.g. benzyl),  $-CHO$ ,  $C_1$ - $C_4$ -alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl or isopropylcarbonyl), (halogenated  $C_1$ -  
15  $C_4$ -alkyl)carbonyl (e.g. fluoromethylcarbonyl, difluoromethylcarbonyl, trifluoromethylcarbonyl, 1,1,1-trifluoroeth-2-ylcarbonyl or 1,1,1-trifluoroprop-3-ylcarbonyl),  $C_6$ - $C_{12}$ -arylcarbonyl (e.g. phenylcarbonyl),  $C_1$ - $C_4$ -alkoxycarbonyl (e.g. ethoxycarbonyl or tert-butyloxy-  
20 carbonyl),  $C_6$ - $C_{12}$ -aryloxy carbonyl (e.g. phenoxycarbonyl),  $C_1$ - $C_6$ -alkylaminocarbonyl,  $C_2$ - $C_6$ -alkenyl,  $-C(=NH)NH_2$ ,  $-C(=NH)NHCN$ ,  $C_1$ - $C_6$ -alkylsulfonyl,  $C_6$ - $C_{12}$ -arylsulfonyl, amino,  
-NO or  $C_3$ - $C_{12}$ -heterocyclyl (e.g. 3-oxetanyl).

- Preferably,  $R^{4a}$  is hydrogen,  $C_1$ - $C_6$ -alkyl (e.g. methyl, ethyl, n-propyl or isopropyl),  $C_3$ - $C_{12}$ -cycloalkyl- $C_1$ - $C_4$ -alkyl (e.g. cyclopropylmethyl), halogenated  $C_1$ - $C_4$ -alkyl (e.g. 2-fluoroethyl or 2,2,2-trifluoroethyl), amino- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -cycloalkyl (e.g. cyclopropyl),  $CH_2CN$ ,  $C_3$ -  
25  $C_{12}$ -cycloalkyl (e.g. cyclopropyl),  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -alkyl (e.g. benzyl),  $C_1$ - $C_4$ -alkylcarbonyl (e.g. methylcarbonyl or isopropylcarbonyl), (halogenated  $C_1$ - $C_4$ -alkyl)carbonyl (e.g. fluoro-  
methylcarbonyl, difluoromethylcarbonyl or trifluoromethylcarbonyl),  $C_6$ - $C_{12}$ -arylcarbonyl (e.g. phenylcarbonyl),  $C_1$ - $C_4$ -alkoxycarbonyl (e.g. ethoxycarbonyl or tert-butyloxy carbonyl),  $C_6$ - $C_{12}$ -aryloxy carbonyl (e.g. phenoxycarbonyl),  $-C(=NH)NH_2$ ,  $-C(=NH)NHCN$ ,  $C_1$ - $C_6$ -alkyl-  
30 sulfonyl, amino, -NO or  $C_3$ - $C_{12}$ -heterocyclyl (e.g. 3-oxetanyl).

In particular,  $R^{4a}$  is hydrogen.

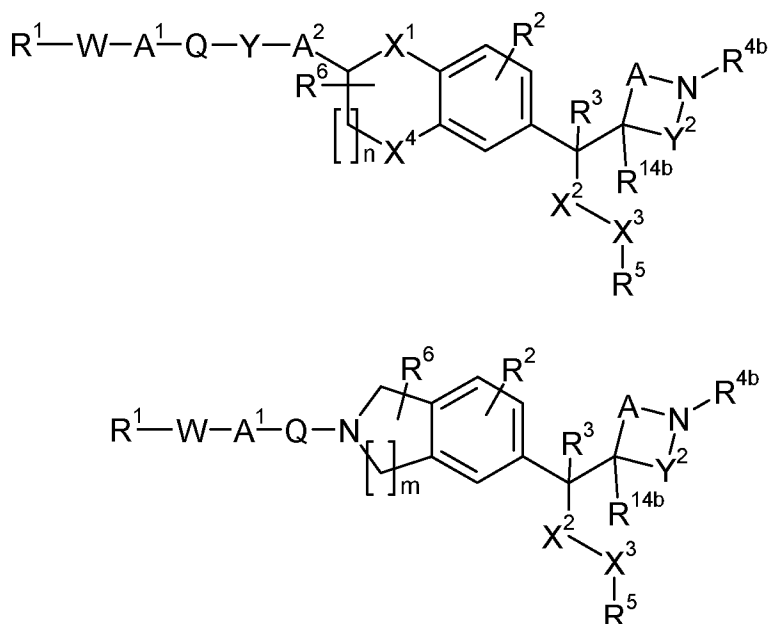
- Alternatively,  $R^{4a}$  and  $R^3$  together are optionally substituted  $C_1$ - $C_4$ -alkylene (e.g. methylene or 1,2 ethylene, a further example being 1,3-propylene, 1-oxo-1,2-ethylene, 1-oxo-1,3-propylene) so that  $R^{4a}$  and  $R^3$  together with the  $-Y^1-Y^2-N-$  moiety and the C atom to which  $R^3$  is bound form an heterocyclic ring having, in particular, 4, 5, or 6 ring member atoms (including the nitrogen atom). With  $R^{4a}$  and  $R^3$  together being optionally substituted  $C_1$ - $C_4$ -alkylene, such phenalkylamine derivatives may be represented by the following  
40 partial structure:



wherein A is optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene and R<sup>1</sup>, W, A<sup>1</sup>, Q, Y, A<sup>2</sup>, X<sup>1</sup>, X<sup>4</sup>, n, m, R<sup>2</sup>, R<sup>3</sup>, X<sup>2</sup>, X<sup>3</sup>, R<sup>5</sup>, Y<sup>1</sup>, Y<sup>2</sup>, R<sup>4b</sup> are as defined herein.

- 5 In connection with R<sup>4a</sup> and R<sup>3</sup>, substituted C<sub>1</sub>-C<sub>4</sub>-alkylene in particular includes C<sub>1</sub>-C<sub>4</sub>-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen (e.g. fluoro), C<sub>1</sub>-C<sub>4</sub>-alkyl or oxo.

- 10 Alternatively, Y<sup>1</sup> is >CR<sup>14a</sup>R<sup>14b</sup> and R<sup>4a</sup> and R<sup>14a</sup> together are optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene (e.g. methylene) so that R<sup>4a</sup> and R<sup>14a</sup> together with the -C(R<sup>14b</sup>)-Y<sup>2</sup>-N- moiety is bound form an heterocyclic ring having, in particular, 4, 5, or 6 ring member atoms (including the nitrogen atom). With R<sup>4a</sup> and R<sup>14a</sup> together being C<sub>1</sub>-C<sub>4</sub>-alkylene, such a ring may be represented by the following partial structure:



wherein A is optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene and R<sup>1</sup>, W, A<sup>1</sup>, Q, Y, A<sup>2</sup>, X<sup>1</sup>, X<sup>4</sup>, n, m, R<sup>2</sup>, R<sup>3</sup>, X<sup>2</sup>, X<sup>3</sup>, R<sup>5</sup>, Y<sup>1</sup>, Y<sup>2</sup>, R<sup>4b</sup> are as defined herein.

5

In connection with R<sup>4a</sup> and R<sup>14a</sup>, substituted C<sub>1</sub>-C<sub>4</sub>-alkylene in particular includes C<sub>1</sub>-C<sub>4</sub>-alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen (e.g. fluoro), C<sub>1</sub>-C<sub>4</sub>-alkyl and oxo.

- 10 R<sup>4b</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl, a further example being ethyl), halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl, hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkyl, CH<sub>2</sub>CN, -CHO, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, (halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl)carbonyl, C<sub>6</sub>-C<sub>12</sub>-arylcabonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, C<sub>6</sub>-C<sub>12</sub>-aryloxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkylaminocarbonyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, -C(=NH)NH<sub>2</sub>, -C(=NH)NHCN, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, C<sub>6</sub>-C<sub>12</sub>-arylsulfonyl, amino, -NO or C<sub>3</sub>-C<sub>12</sub>-heterocyclyl.
- 15

- Preferably, R<sup>4b</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl) or, especially if R<sup>4a</sup> and R<sup>3</sup> together are optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene, R<sup>4b</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl, ethyl, 2-propyl, 2,2,2-trimethylethyl), halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl (e.g. 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl), C<sub>1</sub>-C<sub>6</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl (e.g. 2-methoxyethyl), (halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl)carbonyl (e.g. 2-fluoroacetyl, 2,2-difluoroacetyl, 2,2,2-trifluoroacetyl) or C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl (e.g. ethoxycarbonyl). In particular, R<sup>4b</sup> is hydrogen
- 20

- Alternatively, R<sup>4a</sup>, R<sup>4b</sup> together are optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkylene (e.g. 1,4-butylen, 1,3-propylene, 2-fluoro-but-1,4-ylene or 1-oxo-but-1,4-ylene), wherein one -CH<sub>2</sub>- of C<sub>1</sub>-C<sub>6</sub>-alkylene may be replaced by an oxygen atom (e.g. -CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-) or -NR<sup>16</sup>.
- 25

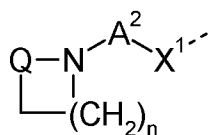
In connection with  $R^{4a}$  and  $R^{4b}$ , substituted  $C_1$ - $C_6$ -alkylene in particular includes  $C_1$ - $C_6$ -alkylene substituted with 1, 2 or 3 substituents selected from the group consisting of halogen (e.g. fluoro or chloro),  $C_1$ - $C_4$ -alkyl, cyano, hydroxy and  $C_1$ - $C_4$ -alkoxy.

5  $R^7$  is hydrogen or  $C_1$ - $C_6$ -alkyl. Preferably,  $R^7$  is hydrogen.

$R^8$  is hydrogen or  $C_1$ - $C_6$ -alkyl. Preferably,  $R^8$  is hydrogen.

10  $R^9$  is hydrogen,  $C_1$ - $C_6$ -alkyl (e.g. methyl or ethyl),  $C_3$ - $C_{12}$ -cycloalkyl (e.g. cyclopropyl), amino- $C_1$ - $C_6$ -alkyl, optionally substituted  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -alkyl or  $C_3$ - $C_{12}$ -heterocyclyl (e.g. 3-azetidiny). Preferably,  $R^9$  is hydrogen or  $C_1$ - $C_6$ -alkyl (e.g. methyl or ethyl).

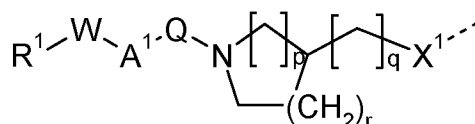
15 According to a particular embodiment,  $R^9$  and  $R^1$  together are  $C_1$ - $C_4$ -alkylene (e.g. 1,3-1,2-ethylene or propylene) so as that  $R^9$  and  $R^1$  together with the atom in Q to which  $R^1$  is bound and the nitrogen atom to which  $R^9$  is bound form an heterocyclic ring having, in particular, 4, 5 or 6 ring member atoms (including the nitrogen atom and Q). With W and  $A^1$  both being a bond, such a ring may be represented by the following partial structure:



20

wherein Q,  $A^2$ ,  $X^1$ , are as defined herein (e.g.  $S(O)_2$ ) and n is 0, 1, 2, 3 or 4.

25 According to a further particular embodiment,  $R^9$  is  $C_1$ - $C_4$ -alkylene (e.g. methylene or 1,3-propylene) that is bound to a carbon atom in  $A^2$  and  $A^2$  is  $C_1$ - $C_4$ -alkylene so that  $R^9$  and at least part of  $A^2$  together with the nitrogen atom to which  $R^9$  is bound form an N-containing heterocyclic ring having, in particular, 4, 5, 6 or 7 ring member atoms (including the nitrogen atom). Such a ring may be represented by the following partial structure:



30 wherein  $R^1$ , W,  $A^1$  and Q are as defined herein, p is 1 or 2, r is 0, 1 or 2 and q is 0, 1 or 2. In this particular embodiment,  $X^1$  preferably is -O-. Particular combinations of p, r and q include p=1, r=0, q=1; and p=1, r=0, q=0. Alternatively, p is 0, r is 3 and q is 1, with  $X^1$  preferably being -O-.

35  $R^{10}$  is hydrogen,  $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_6$ -alkylsulfonyl. Preferably,  $R^{10}$  is hydrogen.

$R^{11}$  is hydrogen or  $C_1$ - $C_6$ -alkyl. Preferably,  $R^{11}$  is hydrogen.

Alternatively, R<sup>9</sup>, R<sup>11</sup> together are C<sub>1</sub>-C<sub>4</sub>-alkylene (e.g. ethylene).

R<sup>16</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl. Preferably, R<sup>16</sup> is hydrogen.

5

R<sup>17</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl. Preferably, R<sup>14</sup> is hydrogen.

R<sup>18</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl. Preferably, R<sup>15</sup> is hydrogen.

10 R<sup>19</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl).

Particular embodiments of phenalkylamine derivatives of the invention result if in formula (I)

R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl;

15 W is a bond;

A<sup>1</sup> is a bond;

Q is -S(O)<sub>2</sub>-;

Y is NR<sup>9</sup>;

A<sup>2</sup> is C<sub>1</sub>-C<sub>4</sub>-alkylene (e.g. methylene);

20 X<sup>1</sup> -O-;

X<sup>4</sup> -O- or NR<sup>19</sup>;

n is 1;

R<sup>6</sup> is hydrogen;

R<sup>2</sup> is hydrogen;

25 R<sup>3</sup> is hydrogen;

X<sup>2</sup> is CR<sup>12a</sup>R<sup>12b</sup>;

X<sup>3</sup> is a bond;

R<sup>5</sup> is phenyl;

Y<sup>1</sup> is a bond;

30 Y<sup>2</sup> is >CR<sup>15a</sup>R<sup>15b</sup>;

R<sup>4a</sup> is hydrogen;

R<sup>4b</sup> is hydrogen;

R<sup>12a</sup> is hydrogen;

R<sup>12b</sup> is hydrogen;

35 R<sup>15a</sup> is hydrogen;

R<sup>15b</sup> is hydrogen; and

R<sup>19</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl).

Particular embodiments of phenalkylamine derivatives of the invention result if in formula (II)

40

R<sup>1</sup> is C<sub>3</sub>-C<sub>12</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl (e.g. cyclopropylmethyl), or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl (e.g. 1-methyl-1,2-diazol-4-yl or 1-methyl-1,3-diazol-4-yl);

- W is a bond;  
 A<sup>1</sup> is a bond;  
 Q is -S(O)<sub>2</sub>- or -C(O)-;  
 m is 2;  
 5 R<sup>6</sup> is hydrogen;  
 R<sup>2</sup> is hydrogen;  
 R<sup>3</sup> is hydrogen;  
 X<sup>2</sup> is >CR<sup>12a</sup>R<sup>12b</sup>;  
 X<sup>3</sup> is a bond;  
 10 R<sup>5</sup> is phenyl;  
 Y<sup>1</sup> is a bond;  
 Y<sup>2</sup> is >CR<sup>15a</sup>R<sup>15b</sup>;  
 R<sup>4a</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl);  
 R<sup>4b</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl (e.g. methyl); or  
 15 R<sup>12a</sup> is hydrogen;  
 R<sup>12b</sup> is hydrogen; or  
 R<sup>15a</sup> is hydrogen; and  
 R<sup>15b</sup> is hydrogen.
- 20 Particular compounds of the present invention are the phenalkylamine derivatives disclosed in preparation examples and physiologically tolerated salts thereof. These include for each preparation example the exemplified compound as well as the corresponding free base and any other physiologically tolerated salts of the free base (if the exemplified compound is a salt), or any physiologically tolerated salt of the free base (if the exemplified
- 25 compound is a free base). These further include enantiomers, diastereomers, tautomers and any other isomeric forms of said compounds, be they explicitly or implicitly disclosed.

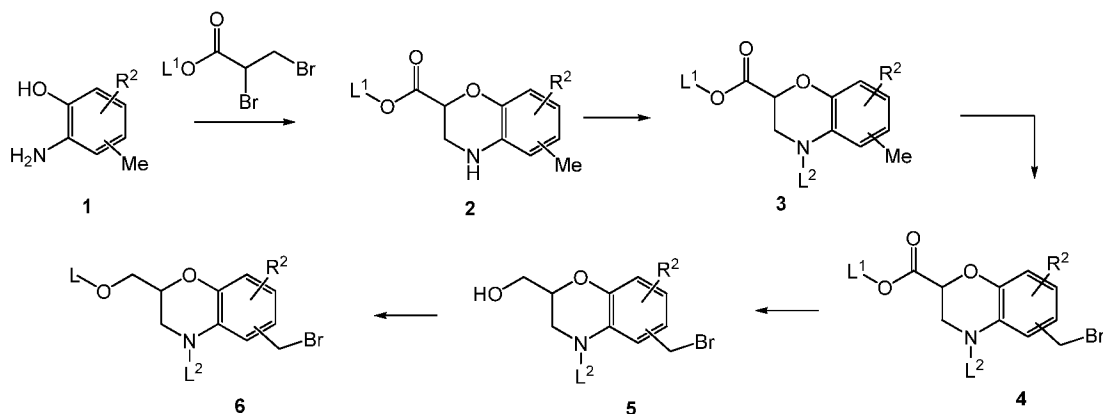
Particular compounds of the present invention are the rigid phenalkylamines derivatives disclosed in preparation examples and physiologically tolerated acid addition salts thereof.

30 The compounds of the formula (I) or (II) can be prepared by analogy to methods which are well known in the art. Suitable methods for the preparation of compounds of formula (I) or (II) are outlined in the following schemes.

35 The compounds of the formula (I) can be prepared by analogy to methods which are well known in the art. A suitable method for the preparation of compounds of formula (I) is outlined in the following schemes. The variables X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, R<sup>2</sup>, R<sup>6</sup> are as defined herein, L<sup>1</sup> represents a alkyl substituent (e.g. Me, Et), L<sup>2</sup> and L are suitable protecting groups (e.g. L<sup>2</sup>= COOtBu and L= tBuMe<sub>2</sub>Si or Bn). The process depicted in scheme 1 is useful for obtaining phenalkylamines of the general formula 5, wherein X<sup>1</sup> is O and X<sup>4</sup> is N.

40

Scheme 1



Compounds of the formula 2 can be obtained by substitution reaction with 2,3-

- 5 dibromopropionic acid derivatives to afford dihydrobenzoxazine type structures of formula 2 (J. Med. Chem. 2006, 49, 7095, Bioorg. & Med. Chem. Letters 2006, 16, 1338). Bromination of the (e.g. methyl) side chain and protection of the aniline leads to structure 4. Subsequent reduction of the ester leads to alcohols of formula 5, which can be protected by suitable protecting group L (e.g. L = tBuMe<sub>2</sub>Si or Bn).

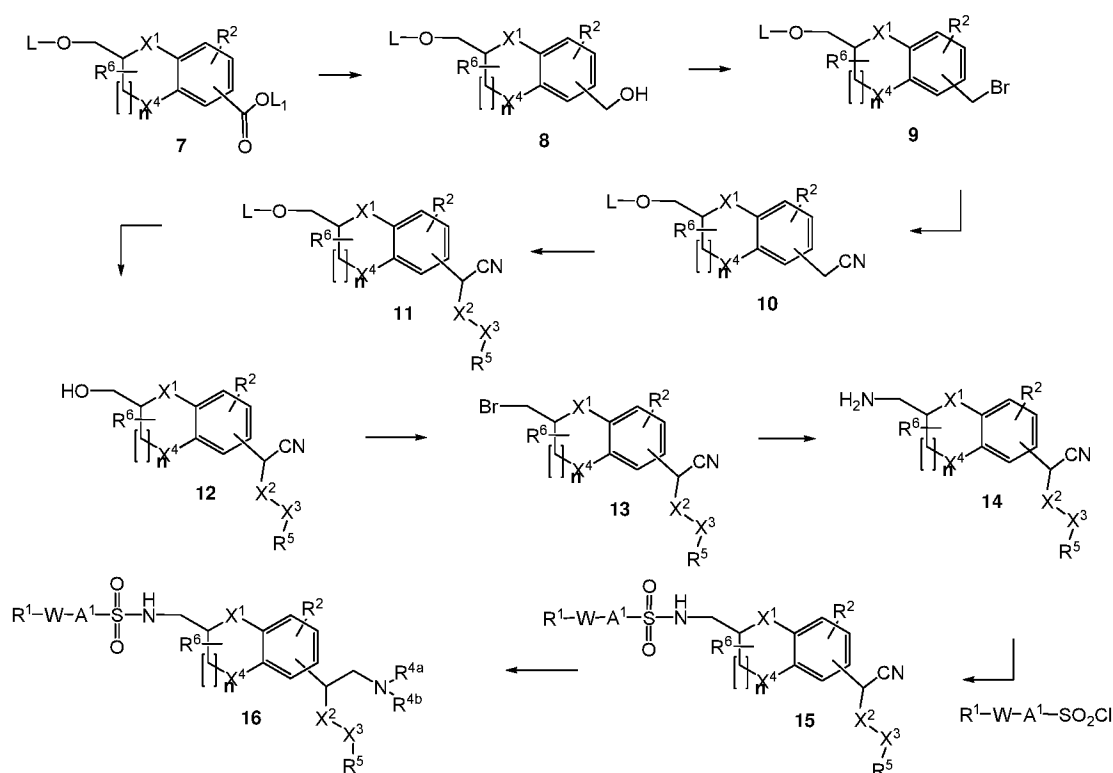
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The process depicted in scheme 2 is useful for obtaining rigid phenalkylamines, wherein the variables X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, R<sup>5</sup> are as defined herein, L is a suitable protecting group (e.g. COOtBu), and L<sup>1</sup> represents a free carboxylic acid or a corresponding ester (e.g. H, Me, Et, alkyl). Compounds of the general formula 7 wherein X<sup>1</sup> and X<sup>4</sup> is O e.g. are well de-

15

Scheme 2

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- As shown in scheme 2, the compound of general formula 7 can easily be reduced to give the compound of general formula 8 by common reducing agents (e.g. borane complexes).
- 5 Conversion to the corresponding bromide via a standard substitution protocol (e.g. PBr<sub>3</sub> in presence of a base like Et<sub>3</sub>N) leads to formula 9. The nitrile 10 can be obtained by a subsequent substitution with a cyanide salt (e.g. NaCN). A subsequent aldol-type condensation reaction in presence of a base (e.g. NaOEt) and a suitable aldehyde (e.g. benzaldehyde) followed by reduction of the initially formed double bond affords rigid phenalkylamines of formula 11. Compound 11 can be further converted to compounds of formula 12 by a deprotection step. As described above, a standard substitution protocol with a bromine source (e.g. PBr<sub>3</sub> in the presence of a base like Et<sub>3</sub>N) can yield bromides of formula 13, which can easily be transformed into the amines of formula 14 via an azide substitution followed by PPh<sub>3</sub> reduction (Staudinger-protocol, Bioorg. & Med. Chem. Letters 2006, 16, 1338). Reaction with sulfonyl chlorides leads to the corresponding sulfonamides of formula 15. Compounds of the general formula 16 can be obtained by reduction of the nitrile (e.g. borane complexes, Raney-Ni).
- 10
- 15

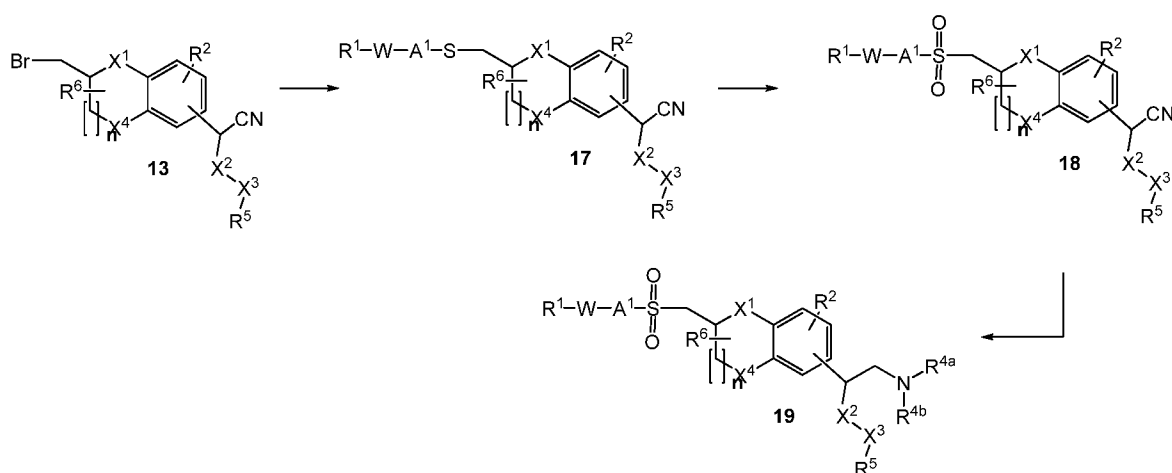
The process depicted in scheme 3 is useful for obtaining rigid phenalkylamines, wherein Y is a bond, A<sup>2</sup> is CH<sub>2</sub> and Q is SO<sub>2</sub> (Journal of Organic Chemistry 1985, 50, 5184).

20

Scheme 3:



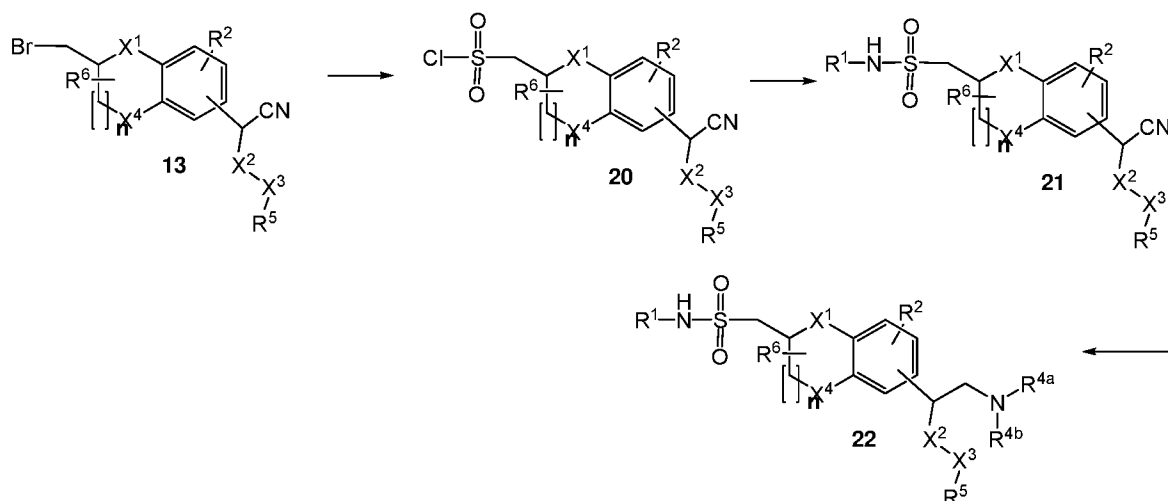
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- Starting from compound of formula 13 the corresponding thio ethers 17 can be obtained by substitution of the bromide by a suitable sulfur nucleophile (e.g. sodium thiolates). Oxidation to the sulfones of formula 18 can be achieved by state of the art procedures (e.g. NaIO<sub>4</sub>, oxone, KMnO<sub>4</sub>, meta-chlorobenzoic acid). Compounds of the general formula 19 can then be obtained via reduction procedures as describes above (scheme 2).

- The process depicted in scheme 4 is useful for obtaining rigid phenalkylamines, wherein Y and A<sup>1</sup> are bonds, A<sup>2</sup> is CH<sub>2</sub>, Q is SO<sub>2</sub> and W is N.

Scheme 4:



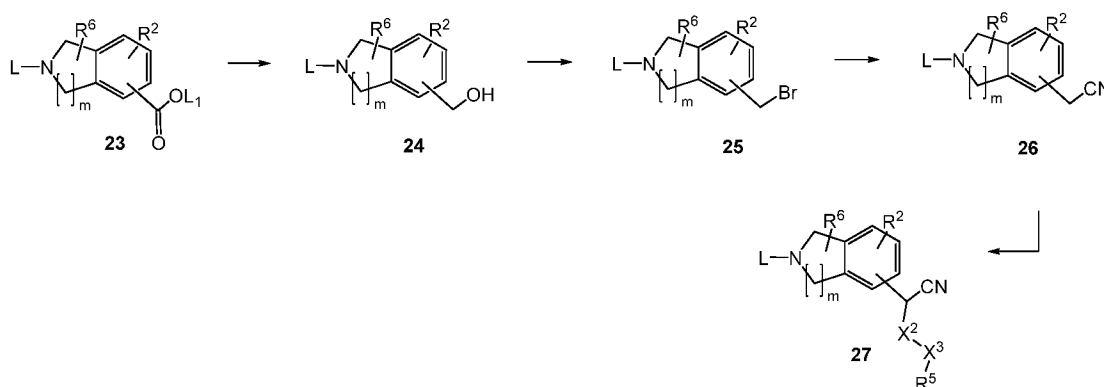
- Starting from compounds of formula 13 the corresponding sulfonylchlorides 20 can be obtained as described in the literature (Org. & Bioorg. Chem. 2007, 51, 1093). Sulfonamides can be obtained by state of the art reaction with a suitable amine to give compound 21, which can be further transformed into compounds of the formula 22 via reduction procedures as describes above (scheme 2).

Formula (II)

The compounds of the formula (II) can be prepared by analogy to methods which are well known in the art. A suitable method for the preparation of compounds of formula (II) is outlined in the following schemes. The variables  $X^2$ ,  $X^3$ ,  $R^5$  are as defined herein and L is a suitable protecting group (e.g. L= COOtBu).

The process depicted in scheme 5 is useful for obtaining rigid phenalkylamines, wherein the variables  $X^2$ ,  $X^3$ ,  $R^5$  are as defined herein, L is a suitable protecting group (e.g. COOtBu), and  $L_1$  represents a free carboxylic acid or a suitable ester (e.g. H, Me, Et, alkyl).

Scheme 5

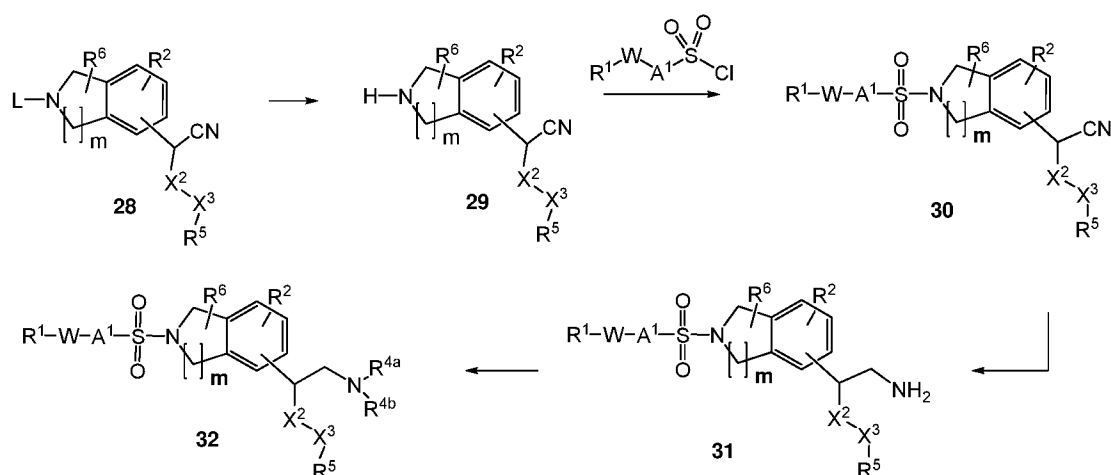


As shown in scheme 5, the compound of general formula 23 can easily be reduced to give the compound of general formula 24 by common reducing agents (e.g. borane complexes). Conversion to the corresponding bromide via standard substitution protocol (e.g.  $PBr_3$  in presence of a base like  $Et_3N$ ) leads to formula 25. The nitrile 26 can be obtained from 25 by a subsequent substitution with a cyanide salt (e.g.  $NaCN$ ). A subsequent aldol-type condensation reaction in presence of a base (e.g.  $NaOEt$ ) and a suitable aldehyde (e.g. benzaldehyde) followed by reduction of the initially formed double bond affords rigid phenalkylamines of formula 27. Compound 27 can be further converted to compounds of general formula 32 as displayed in scheme 6.

25

The process depicted in scheme 6 is useful for obtaining phenalkylamines of the formula II, wherein Q is  $-S(O)_2$ .

30 Scheme 6



In scheme 6, the variables R<sup>1</sup>, W, A<sup>1</sup>, R<sup>2</sup>, R<sup>4a</sup>, R<sup>4b</sup>, X<sup>2</sup>, X<sup>3</sup> are as defined herein and L is a suitable protecting group (e.g. L = COOtBu).

5

As shown in the above scheme 6, the compound of general formula 28 readily undergoes cleavage of the suitable protecting group (e.g. COOtBu). Sulfonylation under basic conditions (e.g. DMAP, pyridine) affords compounds of the general formula 30. Subsequent reduction of the nitrile to the corresponding amines 31 can be achieved using standard protocols (e.g. borane complexes, Raney-Nickel, H<sub>2</sub>). Alkylation leads to rigid phenalkylamines of general formula 32.

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Suitable amino-protecting groups are well known in the art such as those described in Protective Groups in Organic Chemistry, ed. J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

15

The compounds of the formula (I) or (II) are capable of inhibiting the activity of glycine transporter, in particular glycine transporter 1 (GlyT1).

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The utility of the compounds in accordance with the present invention as inhibiting the glycine transporter activity, in particular GlyT1 activity, may be demonstrated by methodology known in the art. For instance, human GlyT1c expressing recombinant hGlyT1c\_5\_CHO cells can be used for measuring glycine uptake and its inhibition (IC<sub>50</sub>) by a compound of formula (I) or (II).

25

Amongst the compounds of the formula (I) or (II) those are preferred which achieve effective inhibition at low concentrations. In particular, compounds of the formula (I) or (II) are preferred which inhibit glycine transporter 1 (GlyT1) at a level of IC<sub>50</sub> < 1 μMol, more preferably at a level of IC<sub>50</sub> < 0.5 μMol, particularly preferably at a level of IC<sub>50</sub> < 0.2 μMol and most preferably at a level of IC<sub>50</sub> < 0.1 μMol.

30

The compounds of the formula (I) or (II) according to the present invention are thus useful as pharmaceuticals.

5 The present invention therefore also relates to pharmaceutical compositions which comprise an inert carrier and a compound of the formula (I) or (II).

The present invention also relates to the use of the compounds of the formula (I) or (II) in the manufacture of a medicament for inhibiting the glycine transporter GlyT1, and to corresponding methods of inhibiting the glycine transporter GlyT1.

10

The NMDA receptor is central to a wide range of CNS processes, and its role in a variety of diseases in humans or other species has been described. GlyT1 inhibitors slow the removal of glycine from the synapse, causing the level of synaptic glycine to rise. This in turn increases the occupancy of the glycine binding site on the NMDA receptor, which

15 increases activation of the NMDA receptor following glutamate release from the presynaptic terminal. Glycine transport inhibitors and in particular inhibitors of the glycine transporter GlyT1 are thus known to be useful in treating a variety of neurologic and psychiatric disorders. Further, glycine A receptors play a role in a variety of diseases in humans or other species. Increasing extracellular glycine concentrations by inhibiting glycine trans-

20 port may enhance the activity of glycine A receptors. Glycine transport inhibitors and in particular inhibitors of the glycine transporter GlyT1 are thus useful in treating a variety of neurologic and psychiatric disorders.

The present invention thus further relates to the use of the compounds of the formula (I) or

25 (II) for the manufacture of a medicament for treating a neurologic or psychiatric disorder, and to corresponding methods of treating said disorders.

According to a particular embodiment, the disorder is associated with glycinergic or glutamatergic neurotransmission dysfunction.

30

According to a further particular embodiment, the disorder is one or more of the following conditions or diseases: schizophrenia or a psychotic disorder including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition and substance-induced psychotic disorder, including both the positive and the negative symptoms of schizophrenia and other psychoses; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, multi-infarct dementia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob

35 disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnesic disorders or cognitive impairment including age related cognitive decline;

40 anxiety disorders including acute stress disorder, agoraphobia, generalized anxiety disorder

der, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; substance-related disorders and addictive behaviors (including substance-induced delirium, persisting dementia, 5 persisting amnesic disorder, psychotic disorder or anxiety disorder; tolerance, dependence or withdrawal from substances including alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); obesity, bulimia nervosa and compulsive eating disorders; bipolar disorders, mood disorders including depressive disorders; depression including unipolar depression, seasonal depression and post-partum depression, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PDD), mood disorders due to a general medical condition, 10 and substance-induced mood disorders; learning disorders, pervasive developmental disorder including autistic disorder, attention deficit disorders including attention-deficit hyperactivity disorder (ADHD) and conduct disorder; movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease, drug-induced parkinsonism, postencephalitic parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification), medication-induced parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced 20 postural tremor), Gilles de la Tourette's syndrome, epilepsy, muscular spasms and disorders associated with muscular spasticity or weakness including tremors; dyskinesias [including tremor (such as rest tremor, postural tremor and intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including 25 generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), and dystonia (including generalised dystonia such as idiopathic dystonia, drug-induced dystonia, symptomatic dystonia and paroxysmal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, spasmodic dysphonia, spasmodic torticollis, axial dystonia, dystonic writer's cramp and hemiplegic dystonia)]; urinary incontinence; neuronal damage including ocular damage, retinopathy or macular degeneration of the eye, tinnitus, hearing impairment and loss, and brain edema; emesis; and sleep disorders including insomnia and narcolepsy.

35 According to a further particular embodiment, the disorder is pain, in particular chronic pain and especially neuropathic pain.

Pain can be classified as acute and chronic pain. Acute pain and chronic pain differ in their etiology, pathophysiology, diagnosis and treatment.

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Acute pain, which occurs following tissue injury, is self-limiting, serves as an alert to ongoing tissue damage and following tissue repair it will usually subside. There are minimal

psychological symptoms associated with acute pain apart from mild anxiety. Acute pain is nociceptive in nature and occurs following chemical, mechanical and thermal stimulation of A-delta and C-polymodal pain receptors.

- 5 Chronic pain, on the other hand, serves no protective biological function. Rather than being the symptom of tissue damage it is a disease in its own right. Chronic pain is unrelenting and not self-limiting and can persist for years, perhaps decades after the initial injury. Chronic pain can be refractory to multiple treatment regimes. Psychological symptoms associated with chronic pain include chronic anxiety, fear, depression, sleeplessness and  
10 impairment of social interaction. Chronic non-malignant pain is predominantly neuropathic in nature and involves damage to either the peripheral or central nervous systems.

- Acute pain and chronic pain are caused by different neuro-physiological processes and therefore tend to respond to different types of treatments. Acute pain can be somatic or  
15 visceral in nature. Somatic pain tends to be a well localised, constant pain and is described as sharp, aching, throbbing or gnawing. Visceral pain, on the other hand, tends to be vague in distribution, paroxysmal in nature and is usually described as deep, aching, squeezing or colicky in nature. Examples of acute pain include post-operative pain, pain associated with trauma and the pain of arthritis. Acute pain usually responds to treatment  
20 with opioids or non-steroidal anti-inflammatory drugs.

- Chronic pain, in contrast to acute pain, is described as burning, electric, tingling and shooting in nature. It can be continuous or paroxysmal in presentation. The hallmarks of chronic pain are chronic allodynia and hyperalgesia. Allodynia is pain resulting from a  
25 stimulus that normally does not elicit a painful response, such as a light touch. Hyperalgesia is an increased sensitivity to normally painful stimuli. Primary hyperalgesia occurs immediately within the area of the injury. Secondary hyperalgesia occurs in the undamaged area surrounding the injury. Examples of chronic pain include complex regional pain syndrome, pain arising from peripheral neuropathies, post-operative pain, chronic fatigue  
30 syndrome pain, tension-type headache, pain arising from mechanical nerve injury and severe pain associated with diseases such as cancer, metabolic disease, neurotropic viral disease, neurotoxicity, inflammation, multiple sclerosis or any pain arising as a consequence of or associated with stress or depressive illness.

- 35 Although opioids are cheap and effective, serious and potentially life-threatening side effects occur with their use, most notably respiratory depression and muscle rigidity. In addition the doses of opioids which can be administered are limited by nausea, emesis, constipation, pruritis and urinary retention, often resulting in patients electing to receive sub-optimal pain control rather than suffer these distressing side-effects. Furthermore, these  
40 side-effects often result in patients requiring extended hospitalisation. Opioids are highly addictive and are scheduled drugs in many territories.

The compounds of formula (I) or (II) are particularly useful in the treatment of schizophrenia, bipolar disorder, depression including unipolar depression, seasonal depression and post-partum depression, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PDD), learning disorders, pervasive developmental disorder including autistic disorder, attention deficit disorders including Attention-Deficit/Hyperactivity Disorder, tic disorders including Tourette's disorder, anxiety disorders including phobia and post traumatic stress disorder, cognitive disorders associated with dementia, AIDS dementia, Alzheimer's, Parkinson's, Huntington's disease, spasticity, myoclonus, muscle spasm, tinnitus and hearing impairment and loss are of particular importance.

Particular cognitive disorders are dementia, delirium, amnesic disorders and cognitive impairment including age-related cognitive decline.

Particular anxiety disorders are generalized anxiety disorder, obsessive-compulsive disorder and panic attack.

Particular schizophrenia or psychosis pathologies are paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder.

Particular neurologic disorders that can be treated with the compounds of the formula (I) or (II) include in particular a cognitive disorder such as dementia, cognitive impairment, attention deficit hyperactivity disorder.

Particular psychiatric disorders that can be treated with the compounds of the formula (I) or (II) include in particular an anxiety disorder, a mood disorder such as depression or a bipolar disorder, schizophrenia, a psychotic disorder.

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

As a rule, the treatment is effected by means of single or repeated daily administration, where appropriate together, or alternating, with other drugs or drug-containing preparations.

The invention also relates to the manufacture of pharmaceutical compositions for treating an individual, preferably a mammal, in particular a human being. Thus, the compounds of the formula (I) or (II) are customarily administered in the form of pharmaceutical compositions which comprise an inert carrier (e.g. a pharmaceutically acceptable excipient) together with at least one compound according to the invention and, where appropriate, other drugs. These compositions can, for example, be administered orally, rectally, transdermally, subcutaneously, intravenously, intramuscularly or intranasally.

Examples of suitable pharmaceutical formulations are solid medicinal forms, such as powders, granules, tablets, in particular film tablets, lozenges, sachets, cachets, sugar-coated tablets, capsules, such as hard gelatin capsules and soft gelatin capsules, suppositories or vaginal medicinal forms, semisolid medicinal forms, such as ointments, creams, hydrogels, pastes or plasters, and also liquid medicinal forms, such as solutions, emulsions, in particular oil-in-water emulsions, suspensions, for example lotions, injection preparations and infusion preparations, and eyedrops and eardrops. Implanted release devices can also be used for administering inhibitors according to the invention. In addition, it is also possible to use liposomes or microspheres.

When producing the compositions, the compounds according to the invention are optionally mixed or diluted with one or more carriers (excipients). Carriers (excipients) can be solid, semisolid or liquid materials which serve as vehicles, carriers or medium for the active compound.

Suitable carriers (excipients) are listed in the specialist medicinal monographs. In addition, the formulations can comprise pharmaceutically acceptable auxiliary substances, such as wetting agents; emulsifying and suspending agents; preservatives; antioxidants; antiirritants; chelating agents; coating auxiliaries; emulsion stabilizers; film formers; gel formers; odor masking agents; taste corrigents; resin; hydrocolloids; solvents; solubilizers; neutralizing agents; diffusion accelerators; pigments; quaternary ammonium compounds; refatting and overfatting agents; raw materials for ointments, creams or oils; silicone derivatives; spreading auxiliaries; stabilizers; sterilants; suppository bases; tablet auxiliaries, such as binders, fillers, glidants, disintegrants or coatings; propellants; drying agents; opacifiers; thickeners; waxes; plasticizers and white mineral oils. A formulation in this regard is based on specialist knowledge as described, for example, in Fiedler, H.P., Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete [Encyclopedia of auxiliary substances for pharmacy, cosmetics and related fields], 4<sup>th</sup> edition, Aulendorf: ECV-Editio-Cantor-Verlag, 1996.

The compounds of formula (I) or (II) may also be suitable for combination with other therapeutic agents.

Thus, the present invention also provides:



- i) a combination comprising a compound of formula (I) or (II) with one or more further therapeutic agents;
- ii) a pharmaceutical composition comprising a combination product as defined in i) above and at least one carrier, diluent or excipient;
- 5 iii) the use of a combination as defined in i) above in the manufacture of a medicament for treating or preventing a disorder, disease or condition as defined herein;
- iv) a combination as defined in i) above for use in treating or preventing a disorder, disease or condition as defined herein;
- v) a kit-of-parts for use in the treatment of a disorder, disease or condition as defined
- 10 herein, comprising a first dosage form comprising a compound of formula (I) or (II) and one or more further dosage forms each comprising one or more further therapeutic agents for simultaneous therapeutic administration,
- vi) a combination as defined in i) above for use in therapy;
- vii) a method of treatment or prevention of a disorder, disease or condition as defined
- 15 herein comprising administering an effective amount of a combination as defined in i) above;
- viii) a combination as defined in i) above for treating or preventing a disorder, disease or condition as defined herein.

20 The combination therapies of the invention may be administered adjunctively. By adjunctive administration is meant the coterminous or overlapping administration of each of the components in the form of separate pharmaceutical compositions or devices. This regime of therapeutic administration of two or more therapeutic agents is referred to generally by those skilled in the art and herein as adjunctive therapeutic administration; it is also known

25 as add-on therapeutic administration. Any and all treatment regimes in which a patient receives separate but coterminous or overlapping therapeutic administration of the compounds of formula (I) or (II) and at least one further therapeutic agent are within the scope of the current invention. In one embodiment of adjunctive therapeutic administration as described herein, a patient is typically stabilised on a therapeutic administration of one or

30 more of the components for a period of time and then receives administration of another component.

The combination therapies of the invention may also be administered simultaneously. By simultaneous administration is meant a treatment regime wherein the individual components

35 are administered together, either in the form of a single pharmaceutical composition or device comprising or containing both components, or as separate compositions or devices, each comprising one of the components, administered simultaneously. Such combinations of the separate individual components for simultaneous combination may be provided in the form of a kit-of-parts.

40

In a further aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of compounds of formula (I) or (II) to a patient

receiving therapeutic administration of at least one antipsychotic agent. In a further aspect, the invention provides the use of compounds of formula (I) or (II) in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one antipsychotic agent. The invention further provides compounds of formula (I) or (II) for use for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of at least one antipsychotic agent.

In a further aspect, the invention provides a method of treatment of a psychotic disorder by adjunctive therapeutic administration of at least one antipsychotic agent to a patient receiving therapeutic administration of compounds of formula (I) or (II). In a further aspect, the invention provides the use of at least one antipsychotic agent in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I) or (II). The invention further provides at least one antipsychotic agent for adjunctive therapeutic administration for the treatment of a psychotic disorder in a patient receiving therapeutic administration of compounds of formula (I) or (II).

In a further aspect, the invention provides a method of treatment of a psychotic disorder by simultaneous therapeutic administration of compounds of formula (I) or (II) in combination with at least one antipsychotic agent. The invention further provides the use of a combination of compounds of formula (I) or (II) and at least one antipsychotic agent in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a psychotic disorder. The invention further provides a combination of compounds of formula (I) or (II) and at least one antipsychotic agent for simultaneous therapeutic administration in the treatment of a psychotic disorder. The invention further provides the use of compounds of formula (I) or (II) in the manufacture of a medicament for simultaneous therapeutic administration with at least one antipsychotic agent in the treatment of a psychotic disorder. The invention further provides compounds of formula (I) or (II) for use for simultaneous therapeutic administration with at least one antipsychotic agent in the treatment of a psychotic disorder. The invention further provides the use of at least one antipsychotic agent in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) or (II) in the treatment of a psychotic disorder. The invention further provides at least one antipsychotic agent for simultaneous therapeutic administration with compounds of formula (I) or (II) in the treatment of a psychotic disorder.

In further aspects, the invention provides a method of treatment of a psychotic disorder by simultaneous therapeutic administration of a pharmaceutical composition comprising compounds of formula (I) or (II) and at least one mood stabilising or antimanic agent, a pharmaceutical composition comprising compounds of formula (I) or (II) and at least one mood stabilising or antimanic agent, the use of a pharmaceutical composition comprising

compounds of formula (I) or (II) and at least one mood stabilising or antimanic agent in the manufacture of a medicament for the treatment of a psychotic disorder, and a pharmaceutical composition comprising compounds of formula (I) or (II) and at least one mood stabilising or antimanic agent for use in the treatment of a psychotic disorder.

5

Antipsychotic agents include both typical and atypical antipsychotic drugs. Examples of antipsychotic drugs that are useful in the present invention include, but are not limited to: butyrophenones, such as haloperidol, pimozide, and droperidol; phenothiazines, such as chlorpromazine, thioridazine, mesoridazine, trifluoperazine, perphenazine, fluphenazine, 10 thiflupromazine, prochlorperazine, and acetophenazine; thioxanthenes, such as thiothixene and chlorprothixene; thienobenzodiazepines; dibenzodiazepines; benzisoxazoles; dibenzothiazepines; imidazolidinones; benziso- thiazolyl-piperazines; triazine such as lamotrigine; dibenzoxazepines, such as loxapine; dihydroindolones, such as molindone; aripiprazole; and derivatives thereof that have antipsychotic activity.

15

Examples of tradenames and suppliers of selected antipsychotic drugs are as follows: clozapine (available under the tradename CLOZARIL®, from Mylan, Zenith Goldline, UDL, Novartis); olanzapine (available under the tradename ZYPREX®, from Lilly); ziprasidone (available under the tradename GEODON®, from Pfizer); risperidone (available under the 20 tradename RISPERDAL®, from Janssen); quetiapine fumarate (available under the tradename SEROQUEL®, from AstraZeneca); haloperidol (available under the tradename HALDOL®, from Ortho-McNeil); chlorpromazine (available under the tradename THORAZINE®, from SmithKline Beecham (GSK)); fluphenazine (available under the tradename PROLIXIN®, from Apothecon, Copley, Schering, Teva, and American Pharmaceutical Partners, Pasadena); thiothixene (available under the tradename NAVANE®, 25 from Pfizer); trifluoperazine (10-[3-(4-methyl-1-piperaziny)propyl]-2- (trifluoromethyl)phenothiazine dihydrochloride, available under the tradename STELAZINE®, from Smith Klein Beckman); perphenazine (available under the tradename TRILAFON®, from Schering); thioridazine (available under the tradename MELLARIL®, from Novartis, Roxane, HiTech, Teva, and Alpharma) ; molindone (available under the tradename MOBAN®, 30 from Endo); and loxapine (available under the tradename LOXITANE(D; from Watson). Furthermore, benperidol (Glianimon®), perazine (Taxilan®) or melperone (Eunerpan®) may be used. Other antipsychotic drugs include promazine (available under the tradename SPARINE®), triflupromazine (available under the tradename VESPRI N®), chlorprothixene (available under the tradename TARACTAN®), droperidol (available under the 35 tradename INAPSINE®), acetophenazine (available under the tradename TINDAL®), prochlorperazine (available under the tradename COMPAZINE®), methotrimeprazine (available under the tradename NOZINAN®), pipotiazine (available under the tradename PI-POTRIL®), ziprasidone, and hoperidone.

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In a further aspect, the invention provides a method of treatment of a neurodegenerative disorder such as Alzheimer Disease by adjunctive therapeutic administration of com-

pounds of formula (I) or (II) to a patient receiving therapeutic administration of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease. In a further aspect, the invention provides the use of compounds of formula (I) or (II) in the manufacture of a medicament for adjunctive therapeutic administration for the

5 treatment of a neurodegenerative disorder such as Alzheimer Disease in a patient receiving therapeutic administration of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides compounds of formula (I) or (II) for use for adjunctive therapeutic administration for the treatment of a neurodegenerative disorder such as Alzheimer Disease in a patient receiving

10 therapeutic administration of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease.

In a further aspect, the invention provides a method of treatment of a neurodegenerative disorder such as Alzheimer Disease by adjunctive therapeutic administration of at least

15 one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease to a patient receiving therapeutic administration of compounds of formula (I) or (II). In a further aspect, the invention provides the use of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of a neurode-

20 generative disorder such as Alzheimer Disease in a patient receiving therapeutic administration of compounds of formula (I) or (II). The invention further provides at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease for adjunctive therapeutic administration for the treatment of a neurodegenerative disorder such as Alzheimer Disease in a patient receiving therapeutic administration of

25 compounds of formula (I) or (II).

In a further aspect, the invention provides a method of treatment of a neurodegenerative disorder such as Alzheimer Disease by simultaneous therapeutic administration of compounds of formula (I) or (II) in combination with at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further

30 provides the use of a combination of compounds of formula (I) or (II) and at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention

35 further provides a combination of compounds of formula (I) or (II) and at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease for simultaneous therapeutic administration in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides the use of compounds of formula (I) or (II) in the manufacture of a medicament for simultaneous therapeutic admini-

40 stration with at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides compounds of formula (I) or (II) for use for

simultaneous therapeutic administration with at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides the use of at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) or (II) in the treatment of a neurodegenerative disorder such as Alzheimer Disease. The invention further provides at least one agent suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease for simultaneous therapeutic administration with compounds of formula (I) or (II) in the treatment of a neurodegenerative disorder such as Alzheimer Disease.

Examples of agents suitable for the treatment of a neurodegenerative disorder such as Alzheimer Disease that are useful in the present invention include, but are not limited to: cholinesterase inhibitors, agents targeting nicotinic or muscarinic acetylcholine receptors, NMDA receptors, amyloid formation, mitochondrial dysfunctions, disease associated calpain activity, neuroinflammation, tumor necrosis factor receptors, NF-kappaB, peroxisome proliferator activator receptor gamma, Apolipoprotein E variant 4 (ApoE4), disease-associated increase of the HPA axis, epileptic discharges, vascular dysfunction, vascular risk factors, and oxidative stress.

Suitable cholinesterase inhibitors which may be used in combination with the compounds of the inventions include for example tacrine, donepezil, galantamine and rivastigmine.

Suitable NMDA receptors targeting agents which may be used in combination with the compounds of the inventions include for example memantine.

Suitable agents affecting increased HPA axis activity which may be used in combination with the compounds of the inventions include for example CRF1 antagonists or V1b antagonists.

In a further aspect therefore, the invention provides a method of treatment of pain by adjunctive therapeutic administration of compounds of formula (I) or (II) to a patient receiving therapeutic administration of at least one agent suitable for the treatment of pain. In a further aspect, the invention provides the use of compounds of formula (I) or (II) in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of pain in a patient receiving therapeutic administration of at least one agent suitable for the treatment of pain. The invention further provides compounds of formula (I) or (II) for use for adjunctive therapeutic administration for the treatment of pain in a patient receiving therapeutic administration of at least one agent suitable for the treatment of pain.

In a further aspect, the invention provides a method of treatment of pain by adjunctive therapeutic administration of at least one agent suitable for the treatment of pain to a pa-

tient receiving therapeutic administration of compounds of formula (I) or (II). In a further aspect, the invention provides the use of at least one agent suitable for the treatment of pain in the manufacture of a medicament for adjunctive therapeutic administration for the treatment of pain in a patient receiving therapeutic administration of compounds of formula (I) or (II). The invention further provides at least one agent suitable for the treatment of pain for adjunctive therapeutic administration for the treatment of pain in a patient receiving therapeutic administration of compounds of formula (I) or (II).

In a further aspect, the invention provides a method of treatment of pain by simultaneous therapeutic administration of compounds of formula (I) or (II) in combination with at least one agent suitable for the treatment of pain. The invention further provides the use of a combination of compounds of formula (I) or (II) and at least one agent suitable for the treatment of pain in the manufacture of a medicament for simultaneous therapeutic administration in the treatment of pain. The invention further provides a combination of compounds of formula (I) or (II) and at least one agent suitable for the treatment of pain for simultaneous therapeutic administration in the treatment of pain. The invention further provides the use of compounds of formula (I) or (II) in the manufacture of a medicament for simultaneous therapeutic administration with at least one agent suitable for the treatment of pain in the treatment of pain. The invention further provides compounds of formula (I) or (II) for use for simultaneous therapeutic administration with at least one agent suitable for the treatment of pain in the treatment of pain. The invention further provides the use of at least one agent suitable for the treatment of pain in the manufacture of a medicament for simultaneous therapeutic administration with compounds of formula (I) or (II) in the treatment of pain. The invention further provides at least one agent suitable for the treatment of pain for simultaneous therapeutic administration with compounds of formula (I) or (II) in the treatment of pain.

Examples of agents suitable for the treatment of pain that are useful in the present invention include, but are not limited to: NSAIDs (Nonsteroidal Antiinflammatory Drugs), anti-convulsant drugs such as carbamazepine and gabapentin, sodium channel blockers, antidepressant drugs, cannabinoids and local anaesthetics.

Suitable agents used in combination with the compounds of the inventions include for example celecoxib, etoricoxib, lumiracoxib, paracetamol, tramadol, methadone, venlafaxine, imipramine, duloxetine, bupropion, gabapentin, pregabalin, lamotrigine, fentanyl, parecoxib, nefopam, remifentanyl, pethidine, diclofenac, rofecoxib, nalbuphine, sufentanil, pethidine, diamorphine and butorphanol.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, antidepressant agents such as 5HT<sub>3</sub> antagonists, serotonin agonists, NK-1 antagonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake

inhibitors (SNRI), tricyclic antidepressants, dopaminergic antidepressants, H3 antagonists, 5HT1A antagonists, 5HT1 B antagonists, 5HT1 D antagonists, D1 agonists, M1 agonists and/or anticonvulsant agents, as well as cognitive enhancers.

- 5     Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

10

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

- 15     Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, chlormipramine and nortriptyline.

20

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

- 25     Suitable anticonvulsant agents which may be used in combination of the compounds of the invention include for example divalproex, carbamazepine and diazepam.

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

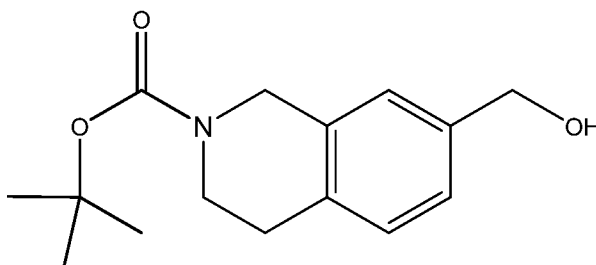
- 30     The compounds were characterized by mass spectrometry, generally recorded via HPLC-MS in a fast gradient on C18-material (electrospray-ionisation (ESI) mode).

#### Preparation Examples

Example 1:

- 35     {2-(2-(1-Methyl-1H-imidazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine}

1.1     tert-Butyl-7-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

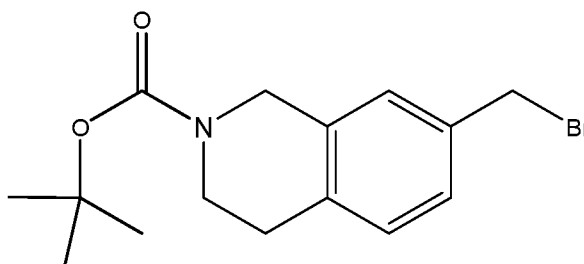


To a solution of 0.245 mmol of 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid in 2 ml dry THF were added at room temperature 0.736 mmol borane dimethyl sulphide complex and the mixture was stirred over night. The mixture was diluted with EtOAc and washed with saturated  $\text{Na}_2\text{CO}_3$  solution and brine. The aqueous layer was extracted with EtOAc. The combined organic layers were washed, dried over  $\text{MgSO}_4$  and filtered. Evaporation of the solvent gave 60 mg of a pale yellow oil (93 %).

ESI-MS  $[\text{M}+\text{Na}^+] = 286$

Calculated for  $\text{C}_{15}\text{H}_{21}\text{NO}_3 = 263$

#### 1.2 tert-Butyl-7-(bromomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate



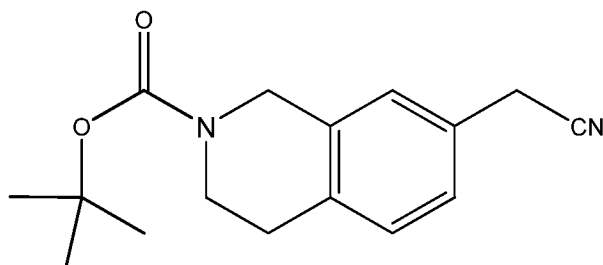
To a solution of 0.380 mmol of tert-butyl-7-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate in 2.5 ml  $\text{CH}_2\text{Cl}_2$  were added at  $0^\circ\text{C}$  1.139 mmol  $\text{Et}_3\text{N}$  and 0.456 mmol tribromophosphine. The mixture was allowed to warm to room temperature and stirred for 1 h. To the reaction mixture were added saturated  $\text{NaHCO}_3$  solution and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed, dried over  $\text{MgSO}_4$  and filtered. Evaporation of the solvent gave 105 mg of crude material that was purified by flash chromatography to yield 76 mg of colorless oil (61.3 %).

ESI-MS  $[\text{M}+\text{Na}^+] = 348/350$

Calculated for  $\text{C}_{15}\text{H}_{20}\text{BrNO}_2 = 326$

#### 1.3 tert-Butyl-7-(cyanomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate



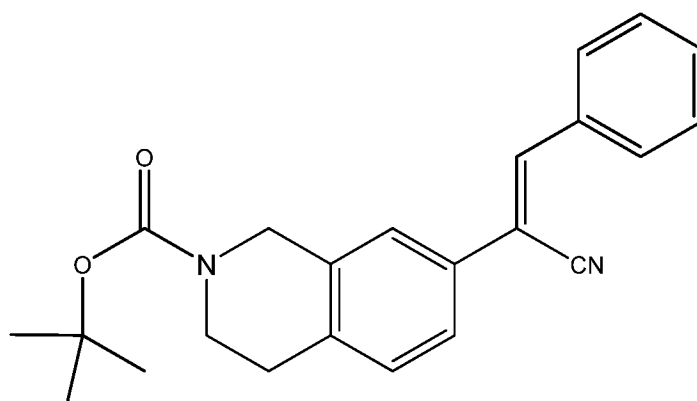


To a solution of 21.76 mmol of tert-butyl-7-(bromomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate in 80 ml DMF were added at 0°C 65.3 mmol sodium cyanide in small portions. The mixture was stirred at room temperature for 2 h. Brine solution was added to the mixture and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and filtered. Evaporation of the solvent gave 5.6 g of a brown oil. The material was purified by flash chromatography to yield 1.63 g of a pale yellow solid (27.5 %).

ESI-MS [M+Na<sup>+</sup>] = 295

Calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub> = 272

1.4 (Z)-tert-Butyl-7-(1-cyano-2-phenylvinyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

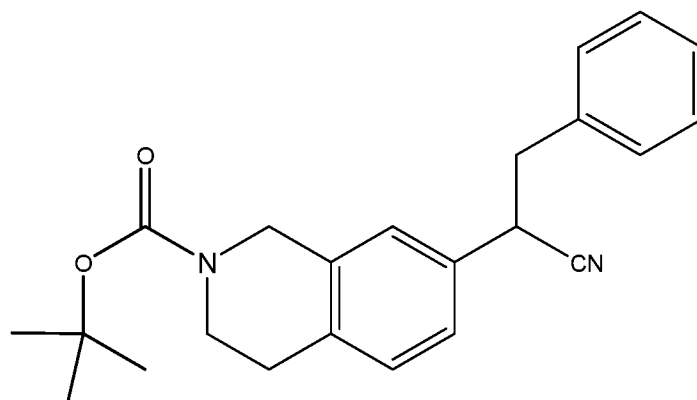


To a solution of 0.231 mmol tert-butyl-7-(cyanomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate in 2 ml ethanol were added 0.278 mmol of NaOEt solution (21%) and 0.254 mmol benzaldehyde. The mixture was stirred at room temperature over night. The mixture was diluted with ethanol and H<sub>2</sub>O, and a white precipitation observed. The solid was filtered off and washed with ethanol and H<sub>2</sub>O. The white solid was dissolved in methanol. Evaporation of the solvent gave 64 mg (77%) of solid material.

ESI-MS [M+Na<sup>+</sup>] = 383

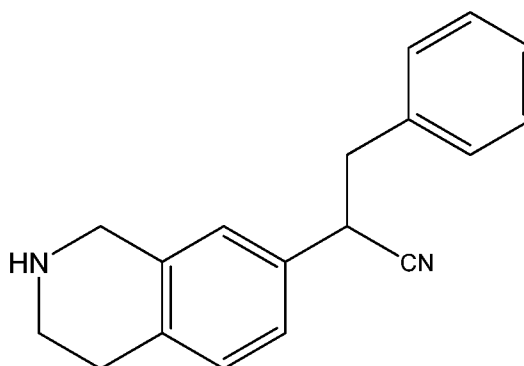
Calculated for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> = 360

1.5 tert-Butyl-7-(1-cyano-2-phenylethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate



To a suspension of 0.178 mmol of (Z)-tert-butyl-7-(1-cyano-2-phenylvinyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate in 2 ml ethanol were added at 0°C 0.178 mmol of sodium borohydride. The mixture was allowed to warm to room temperature and stirred for 3 d. The mixture was poured on ice water and citric acid (5%) was added until acidic. The aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine, dried over MgSO<sub>4</sub>, and filtered. Evaporation of the solvent gave 61.2 mg (95 %) of a crude slightly yellow oil, that was directly submitted to Boc deprotection.

#### 1.6 3-Phenyl-2-(1,2,3,4-tetrahydroisoquinolin-7-yl)propanenitrile

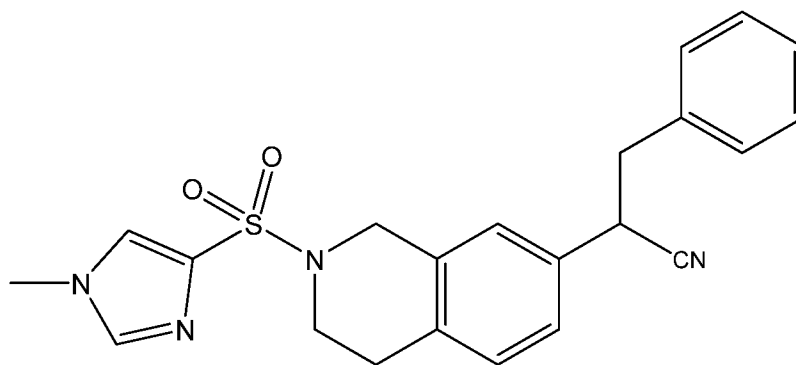


0.171 mmol tert-butyl-7-(1-cyano-2-phenylethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate were dissolved in 1.3 ml formic acid and stirred at room temperature for 1 h. After addition of saturated NaHCO<sub>3</sub> solution the mixture was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub> and filtered. Evaporation of the solvent gave 38.5 mg of solid material (86%).

ESI-MS [M+H<sup>+</sup>] = 262

Calculated for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub> = 263

#### 1.7 2-(2-(1-Methyl-1H-imidazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropanenitrile

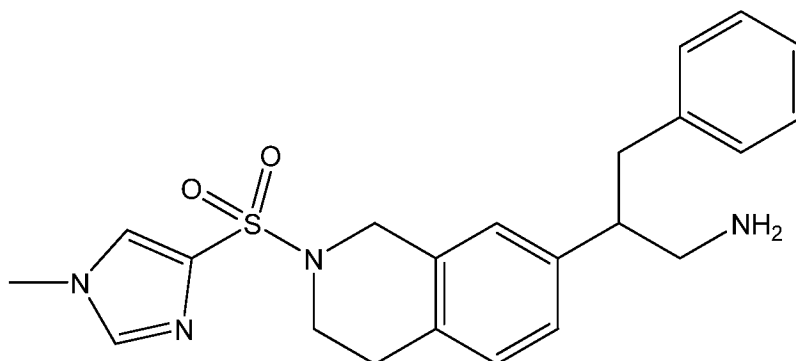


To a solution of 0.135 mmol 3-phenyl-2-(1,2,3,4-tetrahydroisoquinolin-7-yl)propanenitrile in 2 ml  $\text{CH}_2\text{Cl}_2$  were added 0.203 mmol DMAP and 0.162 mmol 1-methyl-1H-imidazole-4-sulfonyl chloride. The mixture was stirred at room temperature for 3 h. Additional 0.162 mmol 1-methyl-1H-imidazole-4-sulfonyl chloride were added and the mixture was stirred for 3 d. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with 1N HCl, saturated  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$ . The combined aqueous layers were extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phase was dried over  $\text{MgSO}_4$  and filtered. Evaporation of the solvent gave 90 mg of the crude material. The material was purified by flash chromatography to yield 53 mg of a white solid (97%).

ESI-MS  $[\text{M}+\text{H}^+] = 406$

Calculated for  $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_2\text{S} = 407$

1.8 2-(2-(1-Methyl-1H-imidazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine

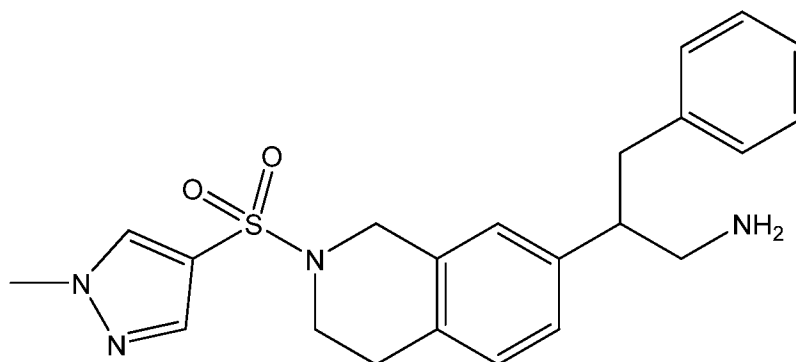


The synthesis was performed starting from 0.123 mmol of 2-(2-(1-methyl-1H-imidazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropanenitrile, which was dissolved in THF (1 ml), after which 0.37 mmol of  $\text{BH}_3$  THF complex (1 M in THF) was added at  $0^\circ\text{C}$ . The mixture was warmed to room temperature and stirred for 2 h. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with 1 N HCl, saturated  $\text{NaHCO}_3$  and  $\text{H}_2\text{O}$ . The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ . Combined organic phase was dried over  $\text{MgSO}_4$  and filtered. Evaporation of the solvent gave 50 mg of the crude material. The material was purified by flash chromatography to yield 11 mg of a white solid (22%).

ESI-MS  $[M+H]^+ = 411$ Calculated for  $C_{22}H_{26}N_4O_2S = 410$ 

Example 2:

- 5 {2-(2-(1-Methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine}



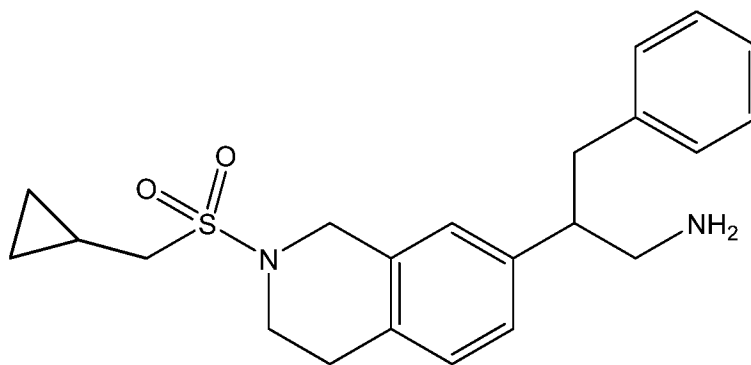
- 10 2-(2-(1-methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine was prepared in analogy to example 1 using 1-methyl-1H-pyrazole-4-sulfonyl chloride in place of 1-methyl-1H-imidazole-4-sulfonyl chloride.

ESI-MS  $[M+H]^+ = 411$ Calculated for  $C_{22}H_{26}N_4O_2S = 410$ 

15

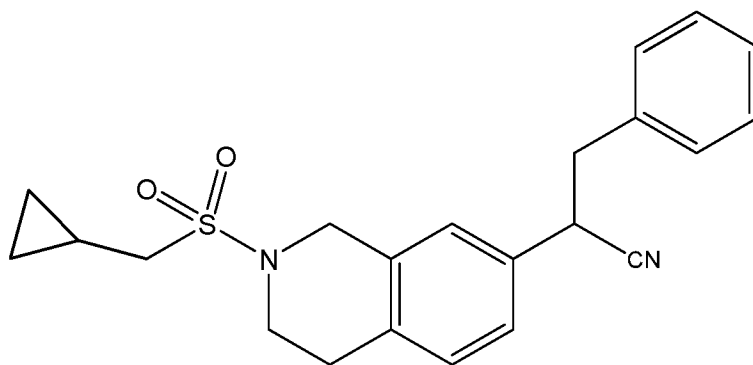
Example 3:

- 2-(2-(1-Methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine



20

- 3.1 2-(2-(cyclopropylmethylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropanenitrile



2-(2-(Cyclopropylmethylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropanenitrile  
was prepared in analogy to example 1 using cyclopropylmethanesulfonyl chloride in place  
5 of 1-methyl-1H-imidazole-4-sulfonyl chloride.

ESI-MS  $[M+Na^+] = 403$       Calculated for  $C_{22}H_{24}N_2O_2S = 380$

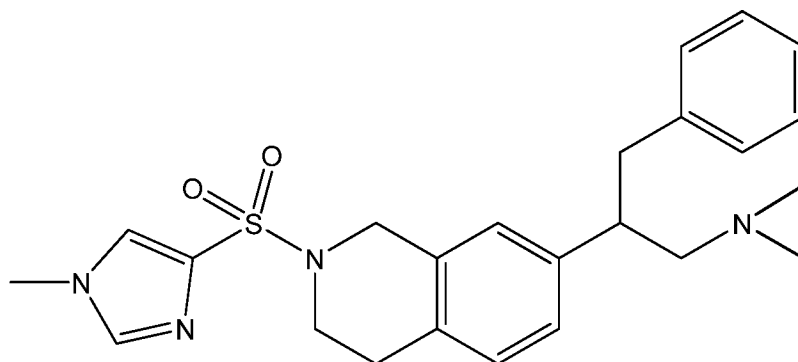
3.2 2-(2-(1-Methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-  
10 phenylpropan-1-amine

2-(2-(Cyclopropylmethylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropanenitrile  
was dissolved in methanol and hydrogenated using H-Cube technology (Raney-Ni  
cartridge, 1 bar, full  $H_2$  mode). The reaction mixture was concentrated and 1 N HCl was  
15 added. Then  $H_2O$  and  $CH_2Cl_2$  were added and the aqueous phase was extracted by  
 $CH_2Cl_2$ . The aqueous phase was freeze dried and gave 2.8 mg (8.7 %) of a hygroscopic  
solid.

ESI-MS  $[M+H^+] = 385$       Calculated for  $C_{22}H_{28}N_2O_2S = 384$   
20

Example 4:

N,N-Dimethyl-2-(2-(1-methyl-1H-imidazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-  
3-phenylpropan-1-amine

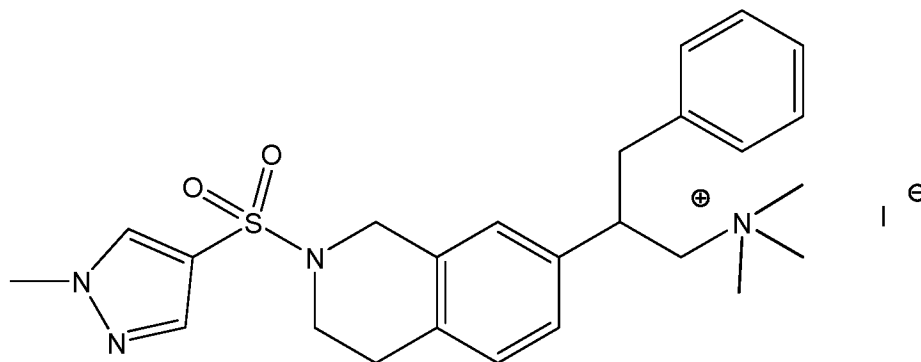


0.058 mmol of 2-(2-(1-methyl-1H-imidazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine (example 1) were dissolved in 2 ml of methanol. A solution of formaldehyde (0.351 mmol, 37 %) and 0.351 mmol of sodium cyanotrihydroborate were added and the mixture was stirred at room temperature over night. H<sub>2</sub>O was added to the reaction mixture and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over MgSO<sub>4</sub> and filtered. The filtrate was concentrated to 6 mg of crude solid material. The solid was washed with diisopropyl ether and dissolved in methanol. An equimolar amount of 1 N HCl was added and the volatiles removed in vacuo. The residue was washed with diethyl ether, dissolved in H<sub>2</sub>O, acidified with 1 N HCl and washed with additional diethyl ether. The aqueous phase was freeze dried to give 4.6 mg of the desired product (16.5 %).

ESI-MS [M+H<sup>+</sup>] = 439Calculated for C<sub>24</sub>H<sub>30</sub>N<sub>4</sub>O<sub>2</sub>S = 438

## 15 Example 5:

N,N,N-Trimethyl-2-(2-(1-methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-aminium iodide



0.022 mmol of 2-(2-(1-methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine (example 2) were dissolved in 1 ml acetonitrile. To this solution 0.022 mmol of iodomethane and 0.044 mmol of cesium carbonate were added at room temperature and the mixture was stirred over night. H<sub>2</sub>O and CH<sub>2</sub>Cl<sub>2</sub> were added to the reaction mixture and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over MgSO<sub>4</sub> and filtered. The filtrate was concentrated to yield 4 mg of crude solid material. The solid was washed with diethyl ether and dried in vacuo. 0.5 mg of the desired product were obtained (4.6 %).

ESI-MS [M+H<sup>+</sup>] = 453Calculated for C<sub>25</sub>H<sub>33</sub>N<sub>4</sub>O<sub>2</sub>S = 453

## Biological testing

1. [<sup>3</sup>H]-Glycine uptake into recombinant CHO cells expressing human GlyT1:  
Human GlyT1c expressing recombinant hGlyT1c\_5\_CHO cells were plated at 20,000 cells  
5 per well in 96 well Cytostar-T scintillation microplates (Amersham Biosciences) and cul-  
tured to sub-confluency for 24h. For glycine uptake assays the culture medium was aspi-  
rated and the cells were washed once with 100 µl HBSS (Gibco BRL, #14025-050) with 5  
mM L-Alanine (Merck #1007). 80 µl HBSS buffer were added, followed by 10 µl inhibitor  
or vehicle (10% DMSO) and 10 µl [<sup>3</sup>H]-glycine (TRK71, Amersham Biosciences) to a final  
10 concentration of 200 nM for initiation of glycine uptake. The plates were placed in a Wal-  
lac Microbeta (PerkinElmer) and continuously counted by solid phase scintillation spec-  
trometry during up to 3 hours. Nonspecific uptake was determined in the presence of 10  
µM Org24598. IC<sub>50</sub> calculations were made by four-parametric logistic nonlinear regres-  
sion analysis (GraphPad Prism) using determinations within the range of linear increase of  
15 [<sup>3</sup>H]-glycine incorporation between 60 and 120 min.
2. Radioligand binding assays using recombinant CHO cell membranes expressing  
human GlyT1:
- 20 Radioligand binding to human GlyT1c transporter-expressing membranes was determined  
as described in Mezler et al., Molecular Pharmacology 74:1705-1715, 2008.

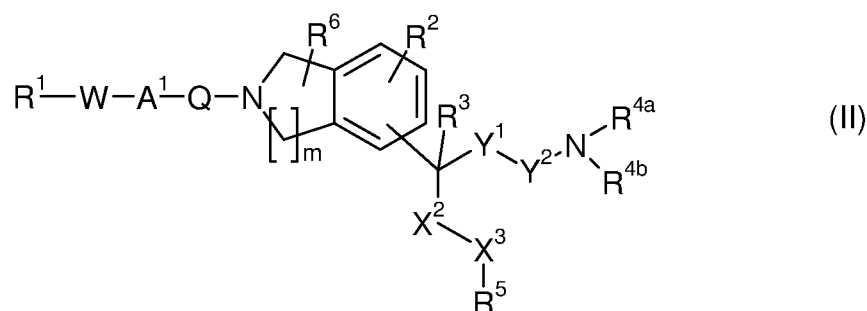
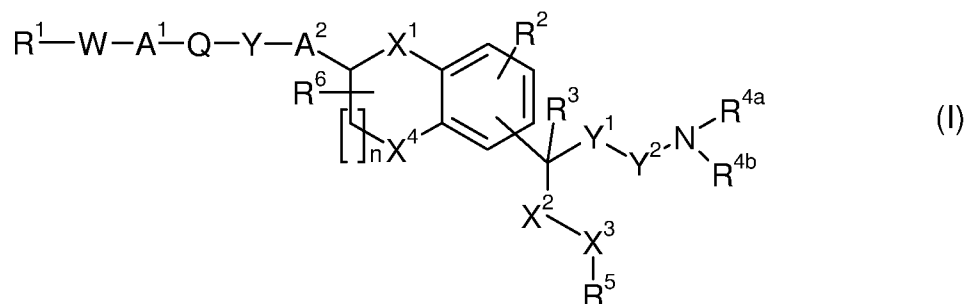
The following results were obtained with the compounds disclosed in the examples:

25 Table 1:

	radioligand binding
Example	K <sub>iapp</sub> [nM]
1	≤ 10000
2	≤ 10000
3	≤ 10000

We claim:

1. Phenalkylamine derivatives of the formula (I) or (II)



5

wherein

R<sup>1</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl, tri-  
(C<sub>1</sub>-C<sub>4</sub>-alkyl)-silyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-  
C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-  
alkylcarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkyloxycarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-  
alkylaminocarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, di-C<sub>1</sub>-C<sub>6</sub>-alkylaminocarbonylamino-C<sub>1</sub>-C<sub>4</sub>-  
alkyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkyl, (optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>6</sub>-  
alkyl)amino-C<sub>1</sub>-C<sub>4</sub>-alkyl, optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>4</sub>-alkyl, optionally  
substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-cycloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl,  
C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>6</sub>-C<sub>12</sub>-aryloxycarbonyl,  
aminocarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkylaminocarbonyl, (halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl)aminocarbonyl,  
C<sub>6</sub>-C<sub>12</sub>-arylaminocarbonyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, optionally substituted C<sub>6</sub>-  
C<sub>12</sub>-aryl, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy, halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-hydroxyalkoxy,  
C<sub>1</sub>-C<sub>6</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy, amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, di-  
C<sub>1</sub>-C<sub>6</sub>-alkylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>6</sub>-C<sub>12</sub>-  
arylcarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>6</sub>-C<sub>12</sub>-  
aryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, (halogenated C<sub>1</sub>-C<sub>6</sub>-  
alkyl)sulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>6</sub>-C<sub>12</sub>-arylsulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, (C<sub>6</sub>-C<sub>12</sub>-  
aryl-C<sub>1</sub>-C<sub>6</sub>-alkyl)sulfonylamino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>12</sub>-heterocyclylsulfonylamino-C<sub>1</sub>-  
C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>12</sub>-heterocyclyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>6</sub>-C<sub>12</sub>-aryloxy, C<sub>3</sub>-C<sub>12</sub>-heterocycloxy,



- 5 C<sub>1</sub>-C<sub>6</sub>-alkylthio, halogenated C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylamino, (halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)amino, di-C<sub>1</sub>-C<sub>6</sub>-alkylamino, di-(halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)amino, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonylamino, (halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)carbonylamino, C<sub>6</sub>-C<sub>12</sub>-arylcabonylamino, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonylamino, (halogenated C<sub>1</sub>-C<sub>6</sub>-alkyl)sulfonylamino, C<sub>6</sub>-C<sub>12</sub>-arylsulfonylamino or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl;
- W is -NR<sup>8</sup>- or a bond;
- 10 A<sup>1</sup> is optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene or a bond;
- Q is -S(O)<sub>2</sub>- or -C(O)-;
- Y is -NR<sup>9</sup>- or a bond;
- 15 A<sup>2</sup> is optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkylene, C<sub>1</sub>-C<sub>4</sub>-alkylene-CO-, -CO-C<sub>1</sub>-C<sub>4</sub>-alkylene, C<sub>1</sub>-C<sub>4</sub>-alkylene-O-C<sub>1</sub>-C<sub>4</sub>-alkylene, C<sub>1</sub>-C<sub>4</sub>-alkylene-NR<sup>10</sup>-C<sub>1</sub>-C<sub>4</sub>-alkylene, optionally substituted C<sub>2</sub>-C<sub>4</sub>-alkenylene, optionally substituted C<sub>2</sub>-C<sub>4</sub>-alkynylene, optionally substituted C<sub>6</sub>-C<sub>12</sub>-arylene, optionally substituted C<sub>6</sub>-C<sub>12</sub>-heteroarylene or a bond;
- 20 X<sup>1</sup> is -O-, -NR<sup>11</sup>-, -S-, or >CH<sub>2</sub>;
- X<sup>4</sup> is -O-, -NR<sup>19</sup>-, -S-, or >CH<sub>2</sub>;
- 25 n is 0, 1, or 2;
- m is 0, 1, or 2;
- 30 R<sup>6</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>6</sub>-alkoxy, or two radicals R<sup>6</sup> together with the carbon atom to which they are attached form a carbonyl group;
- 35 R<sup>2</sup> is hydrogen, halogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl, hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, -CN, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl, hydroxy, C<sub>1</sub>-C<sub>6</sub>-alkoxy, halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>2</sub>-C<sub>6</sub>-alkenyloxy, C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyloxy, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, aminosulfonyl, amino, C<sub>1</sub>-C<sub>6</sub>-alkylamino, C<sub>2</sub>-C<sub>6</sub>-alkenylamino, nitro or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl, or two radicals R<sup>2</sup> together with the ring atoms to which they are bound form a 5- or 6 membered ring;
- 40 R<sup>3</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl;

$X^2$  is -O-, -NR<sup>7</sup>-, -S-, >CR<sup>12a</sup>R<sup>12b</sup> or a bond;

$X^3$  is -O-, -NR<sup>7</sup>-, -S-, >CR<sup>13a</sup>R<sup>13b</sup> or a bond;

5  $R^5$  is optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl, optionally substituted C<sub>3</sub>-C<sub>12</sub>-cycloalkyl or optionally substituted C<sub>3</sub>-C<sub>12</sub>-heterocyclyl;

$Y^1$  is >CR<sup>14a</sup>R<sup>14b</sup> or a bond;

10  $Y^2$  is >CR<sup>15a</sup>R<sup>15b</sup>;

15  $R^{4a}$  is hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl, hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkyl, CH<sub>2</sub>CN, C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-cycloalkyl, -CHO, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, (halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl)carbonyl, C<sub>6</sub>-C<sub>12</sub>-arylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, C<sub>6</sub>-C<sub>12</sub>-aryloxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkylaminocarbonyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, -C(=NH)NH<sub>2</sub>, -C(=NH)NHCN, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, C<sub>6</sub>-C<sub>12</sub>-arylsulfonyl, amino, -NO or C<sub>3</sub>-C<sub>12</sub>-heterocyclyl; or

20  $R^{4a}$ ,  $R^3$  together are optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkylene; or

$R^{4a}$ ,  $R^{14a}$  together are optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkylene;

25  $R^{4b}$  is hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl, hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, amino-C<sub>1</sub>-C<sub>4</sub>-alkyl, CH<sub>2</sub>CN, -CHO, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, (halogenated C<sub>1</sub>-C<sub>4</sub>-alkyl)carbonyl, C<sub>6</sub>-C<sub>12</sub>-arylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, C<sub>6</sub>-C<sub>12</sub>-aryloxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkylaminocarbonyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, -C(=NH)NH<sub>2</sub>, -C(=NH)NHCN, C<sub>1</sub>-C<sub>6</sub>-alkylsulfonyl, C<sub>6</sub>-C<sub>12</sub>-arylsulfonyl, amino, -NO or C<sub>3</sub>-C<sub>12</sub>-heterocyclyl; or

30

$R^{4a}$ ,  $R^{4b}$  together are optionally substituted C<sub>1</sub>-C<sub>6</sub>-alkylene, wherein one -CH<sub>2</sub>- of C<sub>1</sub>-C<sub>6</sub>-alkylene may be replaced by an oxygen atom or -NR<sup>16</sup>; or

35  $R^7$  is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl;

$R^8$  is hydrogen or C<sub>1</sub>-C<sub>6</sub>-alkyl;

40  $R^9$  is hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>12</sub>-cycloalkyl, amino-C<sub>1</sub>-C<sub>6</sub>-alkyl, optionally substituted C<sub>6</sub>-C<sub>12</sub>-aryl-C<sub>1</sub>-C<sub>4</sub>-alkyl or C<sub>3</sub>-C<sub>12</sub>-heterocyclyl; or

$R^9, R^1$

together are  $C_1$ - $C_4$ -alkylene; or

5  $R^9$  is  $C_1$ - $C_4$ -alkylene that is bound to a carbon atom in  $A^2$  and  $A^2$  is  $C_1$ - $C_4$ -alkylene;

$R^{10}$  is hydrogen,  $C_1$ - $C_6$ -alkyl or  $C_1$ - $C_6$ -alkylsulfonyl;

$R^{11}$  is hydrogen or  $C_1$ - $C_6$ -alkyl, or

10

$R^9, R^{11}$

together are  $C_1$ - $C_4$ -alkylene,

$R^{12a}$  is hydrogen, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -heterocyclyl- $C_1$ - $C_6$ -alkyl, optionally substituted  $C_6$ - $C_{12}$ -aryl or hydroxy;

15

$R^{12b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl, or

20

$R^{12a}, R^{12b}$

together are carbonyl or optionally substituted  $C_1$ - $C_4$ -alkylene, wherein one  $-CH_2-$  of  $C_1$ - $C_4$ -alkylene may be replaced by an oxygen atom or  $-NR^{17}-$ ;

$R^{13a}$  is hydrogen, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -heterocyclyl- $C_1$ - $C_6$ -alkyl, optionally substituted  $C_6$ - $C_{12}$ -aryl or hydroxy;

25

$R^{13b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl, or

30

$R^{13a}, R^{13b}$

together are carbonyl or optionally substituted  $C_1$ - $C_4$ -alkylene, wherein one  $-CH_2-$  of  $C_1$ - $C_4$ -alkylene may be replaced by an oxygen atom or  $-NR^{18}-$ ;

$R^{14a}$  is hydrogen, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -heterocyclyl- $C_1$ - $C_6$ -alkyl, optionally substituted  $C_6$ - $C_{12}$ -aryl or hydroxy;

35

$R^{14b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl, or

$R^{14a}$ ,  $R^{14b}$

together are carbonyl or optionally substituted  $C_1$ - $C_4$ -alkylene, wherein one or two - $CH_2$ - of  $C_1$ - $C_4$ -alkylene may be replaced by an oxygen atom or  $-NR^{20}$ ;

- 5  $R^{15a}$  is hydrogen, optionally substituted  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -heterocyclyl- $C_1$ - $C_6$ -alkyl, optionally substituted  $C_6$ - $C_{12}$ -aryl or hydroxy;

$R^{15b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl, or

10

$R^{15a}$ ,  $R^{15b}$

together are carbonyl or optionally substituted  $C_1$ - $C_4$ -alkylene, wherein one or two - $CH_2$ - of  $C_1$ - $C_4$ -alkylene may be replaced by an oxygen atom or  $-NR^{20}$ ;

- 15  $R^{16}$  is hydrogen or  $C_1$ - $C_6$ -alkyl;

$R^{17}$  is hydrogen or  $C_1$ - $C_6$ -alkyl;

$R^{18}$  is hydrogen or  $C_1$ - $C_6$ -alkyl,

20

$R^{19}$  is hydrogen or  $C_1$ - $C_6$ -alkyl, and

$R^{20}$  is hydrogen or  $C_1$ - $C_6$ -alkyl,

- 25 or a physiologically tolerated salt thereof.

2. Compound as claimed in claim 1, wherein  $-Y-A^2$  comprises at least 1 or 2 atoms in the main chain.

- 30 3. Compound as claimed in claim 1 or 2, wherein  $R^1$  is  $C_1$ - $C_6$ -alkyl,  $C_3$ - $C_{12}$ -cycloalkyl- $C_1$ - $C_4$ -alkyl, halogenated  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -alkoxy- $C_1$ - $C_4$ -alkyl, amino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl, di- $C_1$ - $C_6$ -alkylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkyloxycarbonylamino- $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_6$ -alkylaminocarbonylamino- $C_1$ - $C_4$ -alkyl,  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -alkyl,  $C_3$ - $C_{12}$ -cycloalkyl,  $C_2$ - $C_6$ -alkenyl, optionally substituted  $C_6$ - $C_{12}$ -aryl, hydroxy,  $C_1$ - $C_6$ -alkylamino, (halogenated  $C_1$ - $C_6$ -alkyl)amino, di- $C_1$ - $C_6$ -alkylamino or optionally substituted  $C_3$ - $C_{12}$ -heterocyclyl.

35

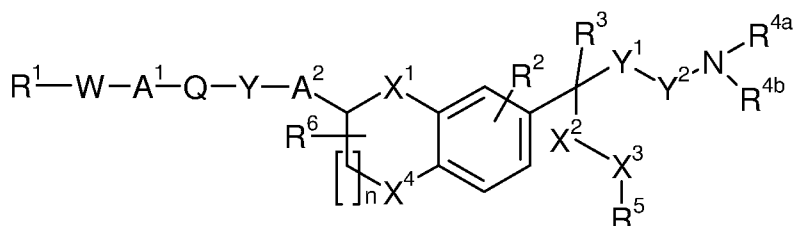
4. Compound as claimed in any one of claims 1 to 3, wherein W is  $-NR^8$ - and Y is a bond, or W is a bond and Y is  $-NR^9$ -.

40

5. Compound as claimed in any one of claims 1 to 4, wherein  $A^1$  is a bond.

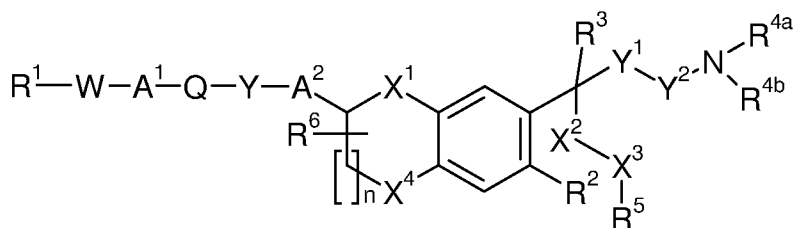
6. Compound as claimed in any one of claims 1 to 4, wherein  $A^1$  is  $C_1$ - $C_4$ -alkylene and W is  $-NR^8-$ .

7. Compound as claimed in any one of claims 1 to 6, having the formula



wherein  $R^1$ , W,  $A^1$ , Q, Y,  $A^2$ ,  $X^1$ ,  $X^4$ , n,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined in any one of claims 1 to 6.

8. Compound as claimed in claim 7, having the formula



wherein  $R^1$ , W,  $A^1$ , Q, Y,  $A^2$ ,  $X^1$ ,  $X^4$ , n,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined in any of claims 1 to 6.

9. Compound as claimed in any one of claims 1 to 8, wherein  $A^2$  is  $C_1$ - $C_4$ -alkylene.

10. Compound as claimed in any one of claims 1 to 8, wherein  $A^2$  is  $C_6$ - $C_{12}$ -arylene selected from the group consisting of phen-1,4-ylene and phen-1,3-ylene, or  $C_6$ - $C_{12}$ -heteroarylene selected from the group consisting of pyrid-2,5-ylene and pyrid-2,4-ylene.

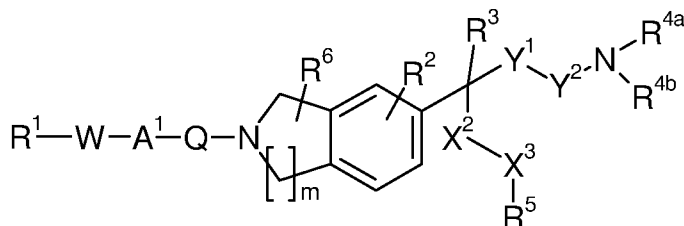
11. Compound as claimed in any one of claims 1 to 8, wherein  $X^1$  is  $-O-$  or  $-NR^{11}$ , or  $X^1$  is  $>CH_2$  and  $A^2$  is a bond.

12. Compound as claimed in any one of claims 1 to 11, wherein  $R^1$ -W- $A^1$ -Q-Y- $A^2$  is  $R^1$ -S(O)<sub>2</sub>-NH- $A^2$ ,  $R^1$ -NH-S(O)<sub>2</sub>- $A^2$ ,  $R^1$ -C(O)-NH- $A^2$ - or  $R^1$ -NH-C(O)- $A^2$ -.

13. Compound as claimed in any one of claims 1 to 12, wherein n is 1.

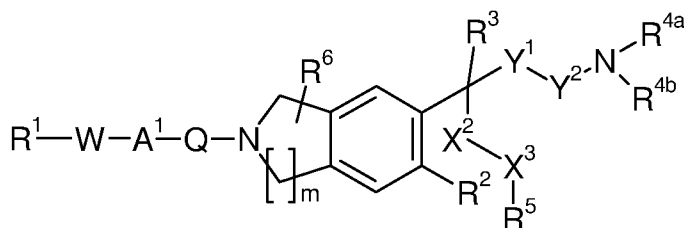
14. Compound as claimed in any one of claims 1 to 13, wherein  $X^4$  is  $-O-$  or  $-NR^{19}$ .

15. Compound as claimed in any one of claims 1 to 6, having the formula



- 5 wherein  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $m$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined in any one of claims 1 to 6.

16. Compound as claimed in claim 15, having the formula



- 10 wherein  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $m$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $R^5$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined in any of claims 1 to 6.

- 15 17. Compound as claimed in any one of claims 1 to 6, 15 or 16, wherein  $R^1$ - $W$ - $A^1$ - $Q$ - is  $R^1$ - $S(O)_2$ -NH-,  $R^1$ -NH- $S(O)_2$ -,  $R^1$ -C(O)-NH- or  $R^1$ -NH-C(O)-.

18. Compound as claimed in any one of claims 1 to 6, or 15 to 17, wherein  $m$  is 1 or 2.

19. Compound as claimed in any one of claims 1 to 18, wherein  $R^6$  is hydrogen.

20. Compound as claimed in any one of claims 1 to 19, wherein  $R^2$  is hydrogen or halogen.

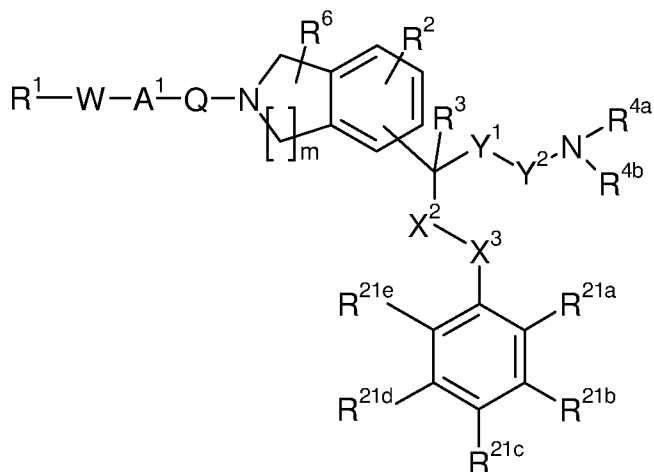
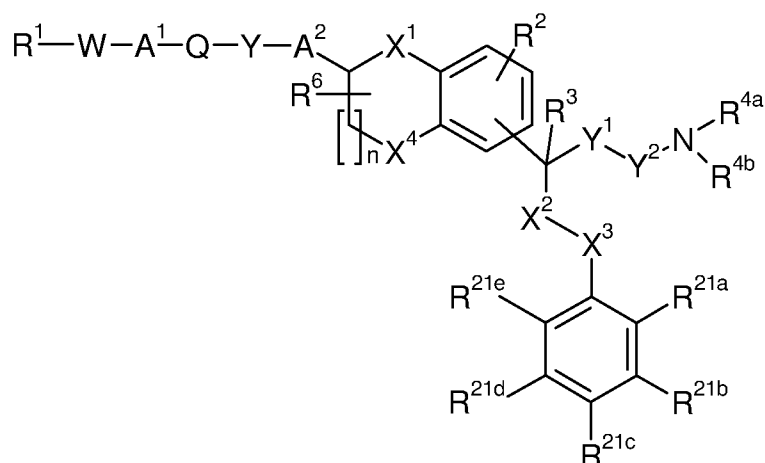
21. Compound as claimed in any one of claims 1 to 20, wherein  $R^3$  is hydrogen.

- 25 22. Compound as claimed in any one of claims 1 to 21, wherein  $X^2$  is  $CR^{12a}R^{12b}$ .

23. Compound as claimed in any one of claims 1 to 22, wherein  $X^3$  is a bond.

- 30 24. Compound as claimed in any one of claims 1 to 23, wherein  $R^{12a}$  is hydrogen or  $C_1$ - $C_6$ -alkyl and  $R^{12b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl.

25. Compound as claimed in any one of claims 1 to 23, wherein  $R^{12a}$ ,  $R^{12b}$  together are optionally substituted  $C_1$ - $C_4$ -alkylene.
26. Compound as claimed in any one of claims 1 to 25, wherein  $R^5$  is optionally substituted aryl or optionally substituted  $C_3$ - $C_{12}$ -cycloalkyl.
27. Compound as claimed in claim 26, having the formula



- wherein  $R^1$ ,  $W$ ,  $A^1$ ,  $Q$ ,  $Y$ ,  $A^2$ ,  $X^1$ ,  $X^4$ ,  $n$ ,  $m$ ,  $R^6$ ,  $R^2$ ,  $R^3$ ,  $X^2$ ,  $X^3$ ,  $Y^1$ ,  $Y^2$ ,  $R^{4a}$ ,  $R^{4b}$  are as defined in any one of claims 1 to 26; and  $R^{21a}$ ,  $R^{21b}$ ,  $R^{21c}$ ,  $R^{21d}$ ,  $R^{21e}$  independently are hydrogen, halogen, optionally substituted  $C_1$ - $C_6$ -alkyl, halogenated  $C_1$ - $C_6$ -alkyl, CN, hydroxy,  $C_1$ - $C_6$ -alkoxy, amino,  $C_1$ - $C_6$ -alkylamino, di- $C_1$ - $C_6$ -alkylamino or  $C_3$ - $C_{12}$ -heterocyclyl.
28. Compound as claimed in any one of claims 1 to 27, wherein  $Y^1$  is a bond.

29. Compound as claimed in any one of claims 1 to 28, wherein  $Y^2$  is  $>CR^{15a}R^{15b}$ .
30. Compound as claimed in claim 1 to 29, wherein  $R^{4a}$  is hydrogen,  $C_1$ - $C_6$ -alkyl,  $C_3$ - $C_{12}$ -cycloalkyl- $C_1$ - $C_4$ -alkyl, halogenated  $C_1$ - $C_4$ -alkyl, amino- $C_1$ - $C_4$ -alkyl,  $CH_2CN$ ,  $C_6$ - $C_{12}$ -aryl- $C_1$ - $C_4$ -alkyl, -CHO,  $C_1$ - $C_4$ -alkylcarbonyl, (halogenated  $C_1$ - $C_4$ -alkyl)carbonyl,  $C_6$ - $C_{12}$ -arylcarbonyl,  $C_3$ - $C_{12}$ -cycloalkyl,  $C_1$ - $C_4$ -alkoxycarbonyl,  $C_6$ - $C_{12}$ -aryloxycarbonyl, -C(=NH)NH<sub>2</sub>, -C(=NH)NHCN,  $C_1$ - $C_6$ -alkylsulfonyl, amino, -NO or  $C_3$ - $C_{12}$ -heterocyclyl.
31. Compound as claimed in any one of claims 1 to 29, wherein  $R^{4a}$ ,  $R^3$  together are optionally substituted  $C_1$ - $C_4$ -alkylene.
32. Compound as claimed in any one of claims 1 to 29, wherein  $R^{4a}$ ,  $R^{14a}$  together are optionally substituted  $C_1$ - $C_4$ -alkylene.
33. Compound as claimed in claim 32, wherein  $R^{14b}$  is hydrogen.
34. Compound as claimed in any one of claims 1 to 33, wherein  $R^{4b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl.
35. Compound as claimed in any one of claims 1 to 29, wherein  $R^{4a}$ ,  $R^{4b}$  together are optionally substituted  $C_1$ - $C_6$ -alkylene, wherein one -CH<sub>2</sub>- of  $C_1$ - $C_4$ -alkylene may be replaced by an oxygen atom.
36. Compound as claimed in any one of claims 1 to 35, wherein  $R^{15a}$  is hydrogen and  $R^{15b}$  is hydrogen.
37. Compound as claimed in any one of claims 1 to 35, wherein  $R^{15a}$  and  $R^{15b}$  together are carbonyl.
38. Compound as claimed in any one of claims 1 to 37, wherein  $R^9$  is hydrogen or  $C_1$ - $C_6$ -alkyl.
39. Compound as claimed in any one of claims 1 to 38, wherein  $R^{19}$  is hydrogen or  $C_1$ - $C_6$ -alkyl.
40. Compound as claimed in claim 1, which is a compound of formula (I) wherein
- $R^1$  is  $C_1$ - $C_6$ -alkyl or optionally substituted  $C_3$ - $C_{12}$ -heterocyclyl;
- W is a bond;



A<sup>1</sup> is a bond;

Q is -S(O)<sub>2</sub>-;

5 Y is NR<sup>9</sup>;

A<sup>2</sup> is C<sub>1</sub>-C<sub>4</sub>-alkylene

10 X<sup>1</sup> -O-

X<sup>4</sup> -O- or NR<sup>19</sup>;

n is 1;

15 R<sup>6</sup> is hydrogen;

R<sup>2</sup> is hydrogen;

20 R<sup>3</sup> is hydrogen;

X<sup>2</sup> is CR<sup>12a</sup>R<sup>12b</sup>;

X<sup>3</sup> is a bond;

25 R<sup>5</sup> is phenyl;

Y<sup>1</sup> is a bond;

30 Y<sup>2</sup> is >CR<sup>15a</sup>R<sup>15b</sup>;

R<sup>4a</sup> is hydrogen;

R<sup>4b</sup> is hydrogen;

35 R<sup>12a</sup> is hydrogen;

R<sup>12b</sup> is hydrogen;

40 R<sup>15a</sup> is hydrogen;

R<sup>15b</sup> is hydrogen; and

$R^{19}$  is  $C_1$ - $C_6$ -alkyl.

41. Compound as claimed in claim 1, which is a compound of formula (II) wherein

$R^1$  is  $C_3$ - $C_{12}$ -cycloalkyl- $C_1$ - $C_4$ -alkyl, or optionally substituted  $C_3$ - $C_{12}$ -heterocyclyl;

W is a bond;

$A^1$  is a bond;

Q is  $-S(O)_2-$  or  $-C(O)-$ ;

m is 1 or 2;

$R^6$  is hydrogen;

$R^2$  is hydrogen;

$R^3$  is hydrogen;

$Y^1$  is a bond;

$Y^2$  is  $>CR^{15a}R^{15b}$ ;

$R^{4a}$  is hydrogen, or  $C_1$ - $C_6$ -alkyl;

$R^{4b}$  is hydrogen or  $C_1$ - $C_6$ -alkyl;

$X^2$  is  $CR^{12a}R^{12b}$ ;

$X^3$  is a bond;

$R^5$  is phenyl;

$R^{12a}$  is hydrogen;

$R^{12b}$  is hydrogen;

$R^{15a}$  is hydrogen; and

R<sup>15b</sup> is hydrogen.

42. The compound as claimed in claim 1, which is:

2-(2-(1-Methyl-1H-imidazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine;

2-(2-(1-Methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine;

2-(2-(1-Methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine;

N,N-Dimethyl-2-(2-(1-methyl-1H-imidazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine;

N,N,N-Trimethyl-2-(2-(1-methyl-1H-pyrazol-4-ylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-phenylpropan-1-amine;

or a physiologically tolerated salt thereof.

43. The compound as claimed in any one of claims 1 to 42 for use in therapy.

44. Pharmaceutical composition which comprises a carrier and a compound of any one of claims 1 to 42.

45. A method for inhibiting the glycine transporter GlyT1 in a mammal in need thereof which comprises the administration of an effective amount of a compound of any one of claims 1 to 42.

46. The use of a compound of any one of claims 1 to 42 in the manufacture of a medicament for inhibiting the glycine transporter GlyT1.

47. A method for treating a neurologic or psychiatric disorder or pain in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 42.

48. The use of a compound of any one of claims 1 to 42 in the manufacture of a medicament for treating a neurologic or psychiatric disorder or pain.

49. The compound of any one of claims 1 to 42 for use in a method of treating a neurologic or psychiatric disorder or pain.

50. The method, use or compound as claimed in any one of claims 43 to 49, wherein the disorder is associated with glycinergic or glutamatergic neurotransmission dysfunction.

51. The method, use or compound as claimed in any one of claims 43 to 50, wherein the neurologic disorder is a cognitive disorder such as dementia, cognitive impairment, or attention deficit disorder.
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52. The method, use or compound as claimed in claim 51, wherein the attention deficit disorder is an attention deficit disorder with hyperactivity.
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53. The method, use or compound as claimed in any one of any one of claims 43 to 50, wherein the psychiatric disorder is an anxiety disorder, a mood disorder such as depression, a bipolar disorder, schizophrenia, or a psychotic disorder.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2011/063978

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> INV. C07D217/02    C07D401/12    A61K31/472    A61K31/4725    A61P25/18 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/121872 A2 (ABBOTT GMBH & CO KG [DE]; AMBERG WILHELM [DE]; OCHSE MICHAEL [DE]; LAN) 8 October 2009 (2009-10-08) page 1, line 6 - line 8; claim 1; examples 1-203 <div style="text-align: center; margin-top: 20px;">-----</div>	1-53
<div style="display: flex; justify-content: space-between; align-items: center;"> <div> <input type="checkbox"/> Further documents are listed in the continuation of Box C.         </div> <div> <input checked="" type="checkbox"/> See patent family annex.         </div> </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search	Date of mailing of the international search report	
28 September 2011	10/10/2011	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Seelmann, Ingo	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/063978

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009121872 A2	08-10-2009	CA 2720004 A1	08-10-2009
		CN 102083797 A	01-06-2011
		EP 2271625 A2	12-01-2011
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