



Novel compounds and their use as glycine transport inhibitors

The present invention provides novel compounds of the general formula I, and their use as glycine transport inhibitors.

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Background of the invention

Glutamic acid is the major excitatory amino acid in the mammalian central nervous system (CNS), and acts through two classes of receptors, the ionotropic and metabotropic receptors, respectively. The ionotropic glutamate receptors are divided into three subtypes based on the affinities of agonists for these receptors, namely *N*-methyl-D-aspartate (NMDA), (*R,S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) and kainic acid (or kainate) receptors.

The NMDA receptor contains binding sites for modulatory compounds such as glycine and polyamines. Binding of glycine to its receptor enhances the NMDA receptor activation. Such NMDA receptor activation may be a potential target for the treatment of schizophrenia and other diseases linked to NMDA receptor dysfunction. An activation can be achieved by an inhibitor of the glycine transporter.

Molecular cloning has revealed the existence of two types of glycine receptors, GlyT-1 and GlyT-2, wherein GlyT-1 can be further subdivided into GlyT-1a, GlyT-1b and GlyT-1c.

The NMDA receptor is blocked by compounds such as phencyclidine which induce a psychotic state which resembles schizophrenia. Likewise, the NMDA antagonists, such as ketamine, induce negative and cognitive symptoms similar to schizophrenia. This indicates that NMDA receptor dysfunction is involved in the pathophysiology of schizophrenia.

The NMDA receptor has been associated with a number of diseases, such as pain (Yaksh *Pain* 1989, 37, 111-123), spasticity, myoclonus and epilepsy (Truong et. al. *Movement Disorders* 1988, 3, 77-87), learning and memory (Rison et. al. *Neurosci. Biobehav. Rev.* 1995, 19, 533-552,).

Thus, glycine transporter antagonistists or inhibitors are believed to be highly beneficial in the treatment of schizophrenia, including both the positive and the negative symptoms of schizophrenia, other psychoses, dementia, and improving cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS



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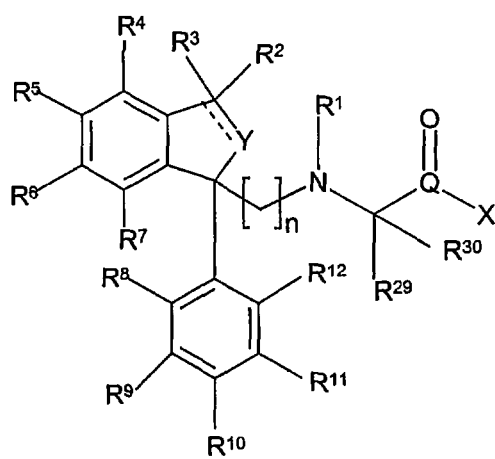
dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke.

Clinical trials with glycine have been reported (Javitt et. al. *Am. J. Psychiatry* **1994**, 151, 1234-1236), (Leiderman et. al. *Biol. Psychiatry* **1996**, 39, 213-215). The treatment with high-dose glycine is reported to improve the symptoms of schizophrenia. There is a need for more efficient compounds as ligands for the glycine transporter for the treatment of NMDA associated diseases.

The compounds of the present invention are potent ligands for the glycine transporter.

Summary of the invention

The invention provides novel compounds of the formula I below:



I

wherein

R^1 represents hydrogen, C_{1-6} -alkyl, cycloalkyl or cycloalkylalkyl;

R^2 and R^3 independently represent hydrogen, halogen, C_{1-6} -alkyl, C_{3-8} cycloalkyl or C_{3-8} cycloalkyl- C_{1-6} -alkyl or R^2 and R^3 together form a C_{3-8} -cycloalkyl;

R^4 , R^5 , R^6 and R^7 independently represent hydrogen, halogen, CF_3 , NO_2 , CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, OH, SH, $NR^{14}R^{15}$, wherein R^{14} and R^{15} independently represent hydrogen or C_{1-6} -alkyl; $-COR^{16}$ wherein R^{16} represents OH, C_{1-6} -alkyl, C_{1-6} -alkoxy, $NR^{17}R^{18}$, wherein R^{17} and R^{18} independently represent hydrogen or C_{1-6} -alkyl; aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more

times with halogen, CF_3 , OCF_3 , CN , NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{1-6} thioalkyl, OH , SH or $\text{NR}^{24}\text{R}^{25}$, wherein R^{24} and R^{25} independently represent hydrogen or C_{1-6} -alkyl;

or R^4 and R^5 , or R^5 and R^6 , or R^6 , and R^7 together form a fused, aromatic, saturated or partly saturated ring which optionally contains one or more heteroatoms such as O, N or S;

R^8 , R^9 , R^{10} , R^{11} and R^{12} independently represent hydrogen, halogen, CF_3 , OCF_3 , CN , NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{1-6} -alkylthio, OH , SH , $\text{NR}^{19}\text{R}^{20}$, wherein R^{19} and R^{20} independently represent hydrogen or C_{1-6} -alkyl; or R^8 , R^9 , R^{10} , R^{11} and R^{12}

independently represent $-\text{COR}^{21}$, wherein R^{21} represents OH , C_{1-6} -alkoxy, $\text{NR}^{22}\text{R}^{23}$, wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} -alkyl; or R^8 , R^9 , R^{10} , R^{11} , and R^{12}

independently represent aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with halogen, CF_3 , OCF_3 , CN , NO_2 , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, OH , SH , COR^{26} , wherein R^{26} represents

OH , C_{1-6} alkoxy or C_{1-6} alkyl; or $\text{NR}^{30}\text{R}^{31}$, wherein R^{30} and R^{31} independently represent hydrogen or C_{1-6} -alkyl;

R^8 and R^9 , or R^9 and R^{10} , or R^{10} and R^{11} , or R^{11} and R^{12} together form a fused, aromatic, saturated or partly saturated ring which optionally contains one or more heteroatoms such as O, N, or S;

Y is O, S, CH_2 or CH, and when Y is CH then the dotted line is a bond;
n is 2, 3, 4, 5 or 6;

Q represents C, P-OR^{29} , or S=O , wherein R^{29} represents hydrogen or C_{1-6} -alkyl;

X is OR^{13} or $\text{NR}^{27}\text{R}^{28}$, wherein R^{13} , R^{27} , and R^{28} independently represent hydrogen, C_{1-6} -alkyl, aryl or aryl- C_{1-6} -alkyl, wherein aryl may be substituted with halogen, CF_3 , OCF_3 , CN , NO_2 , or C_{1-6} alkyl; optionally R^{27} and R^{28} together form a ring which may contain further nitrogen, oxygen or sulfur atoms and the ring may optionally be partly saturated;

R^{29} and R^{30} represent hydrogen, C_{1-6} -alkyl, cycloalkyl or cycloalkylalkyl

or a pharmaceutically acceptable addition salt thereof;

The compounds are useful as inhibitors of the glycine transporter and useful in treatment of diseases responsive to the inhibition of the glycine transporter.

Detailed description of the invention

In a preferred embodiment of the invention, Q is C;

Other preferred embodiments are wherein n is 2 or 3;

Another preferred embodiment is wherein R¹ is CH₃;

Yet another preferred embodiment is wherein X is OH or C₁₋₆-alkoxy; more preferred is

wherein X is OH, OCH₃ or OC₂H₅

Other preferred embodiments are wherein R⁷ represent hydrogen, and R⁴, R⁵ or R⁶ represent hydrogen, CN, halogen, C₁₋₆-alkyl, CF₃ or phenyl optionally substituted one or more times with halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, CF₃, or R⁴, R⁵ or R⁶ represent heteroaryl optionally substituted one or more times with halogen, or wherein R⁴ and R⁵ or R⁵ and R⁶ together form a fused aryl;

Another preferred embodiment of the invention is wherein R⁸, R⁹, R¹⁰, R¹¹ or R¹²

independently represent hydrogen, halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, or R⁸ and R⁹ or R⁹ and R¹⁰ together form a fused aryl;

In an more preferred embodiment, one or two of R⁸, R⁹, R¹⁰, R¹¹ or R¹² represent halogen, C₁₋₆-alkyl, CF₃ or C₁₋₆-alkoxy;

In a more preferred embodiment of the invention R⁴, R⁶, R⁷, R⁸, R⁹ and R¹² are all hydrogen and R⁵ represents halogen, CF₃, CN, C₁₋₆ alkyl, C₁₋₆ alkoxy or -COR¹⁶, wherein R¹⁶ represents C₁₋₆-alkyl; and R¹⁰ and R¹¹ represent hydrogen, halogen, CF₃, or CN, provided that at least one of R¹⁰ and R¹¹ is not hydrogen;

R²⁹ and R³⁰ independently represent hydrogen or C₁₋₆-alkyl or R² and R³ together form a C₃₋₈-cycloalkyl;

Another preferred embodiment of the invention is wherein the compounds are the following

N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}glycine ethyl ester,

N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine ethyl ester,

5 N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}glycine,
N-{3-[5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[1-(3-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-

10 methylglycine,

N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-ethyl)glycine,

N-{3-[1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

15 N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,
N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-ethyl)glycine,

N-{3-[4-chloro-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

20 N-{3-[4-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,

N-{3-[6-chloro-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-

25 methylglycine,

N-{3-[6-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[6-chloro-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

30 N-{3-[6-chloro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-fluoro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-fluoro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

5 N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,

10 N-{3-[5-cyano-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{3-[5-cyano-1-(4-cyanophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine,

N-{3-[5-cyano-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

15 N-{3-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine, N-{2-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]ethyl}-N-methylglycine,

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylglycine,

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylalanine,

20 N-{3-[3-cyclo-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylglycine,

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylalanine,

25 N-{3-[1-(4-Fluoro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methylglycine,

N-{3-[5-Bromo-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine,

N-{2-[1-(4-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methylglycine,

30 N-[3-(3-methyl-1-phenyl-1*H*-inden-1-yl)-propyl]-N-methylglycine,

N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylglycine,

N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methyl (1-ethyl)-glycine,

N-[3-(3-methyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,

N-[3-(3-methyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methyl (1-ethyl)-glycine,

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methylalanine,

N-[3-(3,3-Dimethyl-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methylalanine,

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methyl-(1-ethyl)glycine,

N-[3-(3,3-Dimethyl-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-ethyl]-N-methyl-(1-ethyl)glycine,

N-[3-(3,3-Diethyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,

N-[3-(3,3-Diethyl-1-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine,

N-[3-(3,3-Diethyl-1-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylglycine,

N-[3-(1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylalanine,

N-{3-[1-(4-Chloro-phenyl)-3,3-dimethyl-indan-1-yl]-propyl}-N-methylglycine,

N-{3-[1-(4-Chloro-phenyl)-3,3-diethyl-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methylalanine,

N-[2-(3-methyl-1-phenyl-indan-1-yl)-ethyl]-amino}-N-methyl alanine,

N-[3-(1-phenyl-(1*H*)-inden-1-yl)-propyl]-N-methyl-alanine,

N-{3-[1-(4-Fluoro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methyl-glycine,

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methyl-alanine,

N-{3-[1-(4-chloro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(2-thiophenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

5 N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

10 N-{3-[1-(4-chloro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{2-[1-(4-Chloro-phenyl)-5-(5-chloro-thiophen-2-yl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

15 N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

20 N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine ,

25 N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

30 N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

5 N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine,

N-{3-[1-(4-chloro-phenyl)-5-(2-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine ,

or a pharmaceutically acceptable addition salt thereof.

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The invention provides a pharmaceutical composition comprising at least one compound of Formula I as defined above or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.

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The invention also provides the use of compounds as above for the manufacture of medicaments for treatment of diseases responsive to ligands of the glycine transporter.

The invention provides a method for treatment of diseases responsive to ligands of the glycine transporter.

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In preferred embodiments of the invention, the ligands are antagonists of the glycine transporter.

25 Pharmaceutically acceptable addition salts are those which form pharmacological acceptable anions such as maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-
30 halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The compound of the invention may be administered in any suitable way such as orally or parenterally, and it may be presented in any suitable form for such administration, for example in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the compound of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art.

Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tableting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

Furthermore, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (e.g. enantiomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods, for example by separation of diastereomeric salts thereof with an optically active acid and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g. by fractional crystallisation of d- or l- (tartrates, mandelates or

camphorsulphonate) salts for example. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

Definition of substituents

Halogen means fluoro, chloro, bromo or iodo. Preferred halogens are F and Cl.

The term C₁₋₆-alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl. Preferred alkyls are methyl and ethyl.

Similarly, C₂₋₆-alkenyl and C₂₋₆-alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl, and butynyl.

The term C₃₋₈-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term C₃₋₈-cycloalkylalkyl designates a cycloalkyl as defined above and an alkyl as above.

The terms C₁₋₆-alkoxy and C₁₋₆-alkylthio designate such groups in which the alkyl group is C₁₋₆-alkyl as defined above.

The term aryl designates an aromatic hydrocarbon such as phenyl or naphthyl.

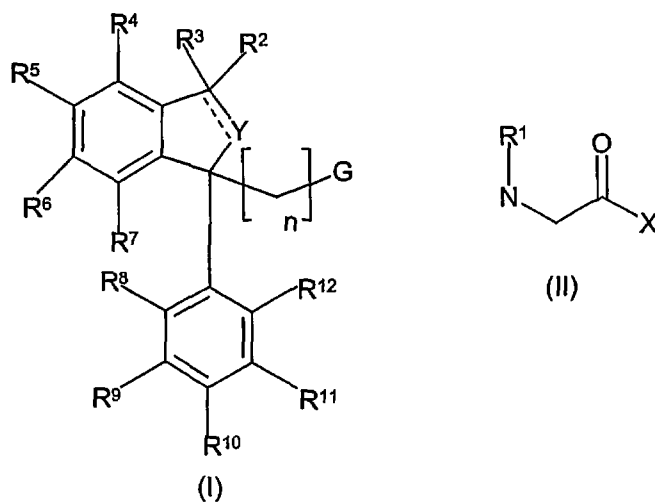
The term heteroaryl refers to a mono- or bicyclic heterocyclic aromatic group containing at least one N, S or O atom, such as furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyridyl, pyrimidyl, tetrazolyl, benzofuranyl, benzothienyl, benzimidazolyl, indolyl. Preferred heteroaryls are monocyclic heteroaryls. Especially preferred is thienyl.

Preparatory examples

The compounds of the invention may be prepared as follows:

- 1) alkylating an amine of formula II with an alkylating agent of formula I

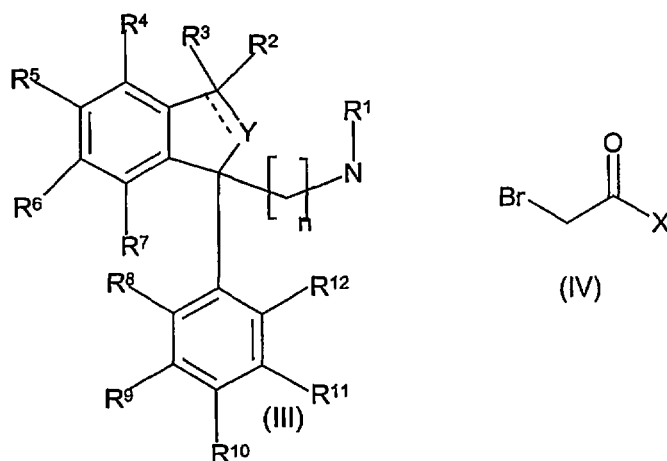
G is a suitable leaving group such as e.g. halogen or mesylate.



the substituents R¹-R¹², n, Y and X are as defined above;

- 2) alkylating an amine of formula III with an alkylating agent of formula IV

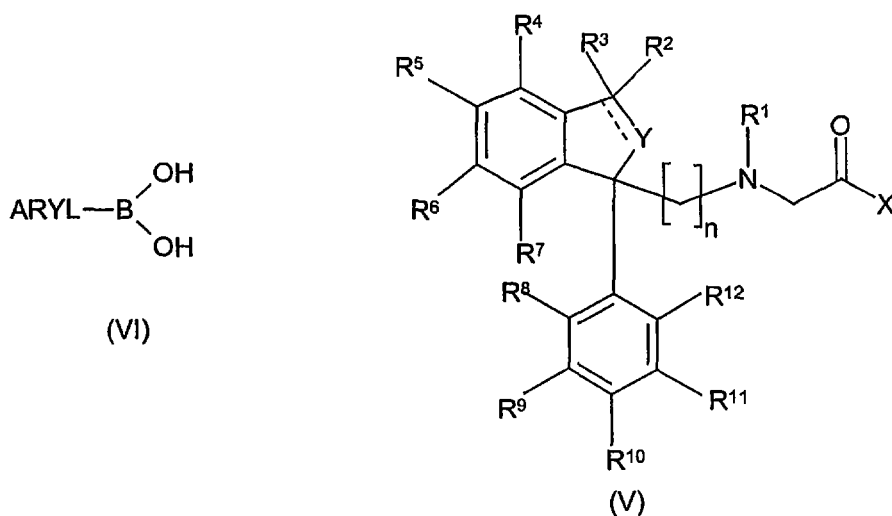
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wherein the substituents R^1 - R^{12} , n , Y and X are as defined above;

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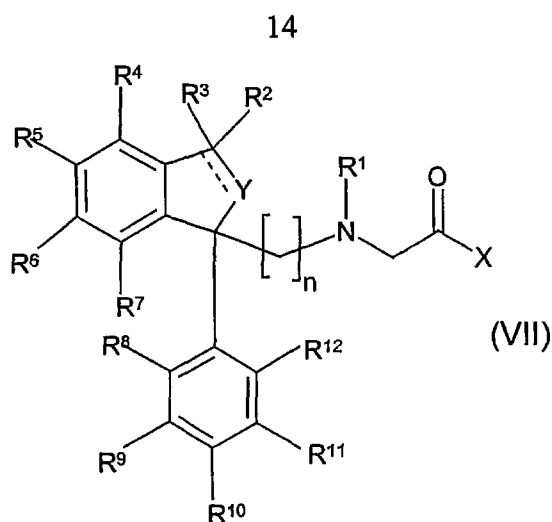
3) Coupling of an aryl substituent of formula VI to the aryl bromide derivative of formula V wherein the substituents R^4 - R^7 are halogens, R^1 - R^3 and R^8 - R^{12} , n , Y and X are as defined above



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4) hydrolysing the ester group of a compound of formula VII to obtain the corresponding carboxylic acid derivative

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the substituents R^1 - R^{12} , n , and Y are as defined above and X is OH in the final product.

The alkylations according to methods 1 and 2 are conveniently carried out in an inert solvent
 5 such as a suitably boiling alcohol or ketone or in tetrahydrofuran, preferably in the presence of
 an organic or inorganic base (potassium carbonate, diisopropylethylamine or triethylamine) at
 reflux temperature. Alternatively, the alkylation can be performed at a fixed temperature
 which is different from the boiling point in one of the above-mentioned solvents or in
 dimethylformamide, dimethylsulfoxide or N-methylpyrrolidin-2-one, preferably in the
 10 presence of a base.

Reagents of formula I are prepared by methods described in the literature, see. e.g. US
 3,549,656, GB 1166711 and Dykstra et al. *J. Med. Chem.* **1967**, 10(3), 418-28.

Glycine derivatives of formula II are well described in the literature.

15 Amines of formula III are prepared as described by Bigler et. al. *Eur. J. Med. Chem.* **1977**, 12,
 289.

Biaryl derivatives of formula IV are prepared by suzuki type coupling of an aryl boronic acid
 with the desired halide in dimethoxyethane, tetrahydrofuran or toluene containing an
 inorganic base such as sodium carbonate and a palladium catalyst at a temperature between
 20 room temperature and the boiling point of the solvent.

The hydrolysis according to method 4 is conveniently performed in a suitably boiling alcohol
 in the presence of an aqueous base such as e.g. sodium hydroxide at ambient temperature. The
 starting materials of formula V are prepared by methods 1 or 2.

Experimental

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray
5 source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (50 X 4.6 mm YMC ODS-A with 5 μ m particle size) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times, R_t , are expressed in minutes.

10 Mass spectra were obtained by an alternating scan method to give molecular weight information. The molecular ion, MH^+ , was obtained at low orifice voltage (5-20V) and fragmentation at high orifice voltage (100V).

Preparative LC-MS-separation was performed on the same instrument. The LC conditions (50 X 20 mm YMC ODS-A with 5 μ m particle size) were linear gradient elution with
15 water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

1H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl
20 sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard.

Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet, b=broad singlet. NMR signals corresponding to acidic protons are generally omitted. Content
25 of water in crystalline compounds was determined by Karl Fischer titration. Standard workup procedures refer to extraction with the indicated organic solvent from proper aqueous solutions, drying of combined organic extracts (anhydrous $MgSO_4$ or Na_2SO_4), filtering and evaporation of the solvent *in vacuo*. For column chromatography, silica gel of type Kieselgel 60, 230-400 mesh ASTM was used. For ion-exchange chromatography, SCX, 1 g, Varian
30 Mega Bond Elut®, Chrompack cat. No. 220776 was used. Prior use of the SCX-columns was pre-conditioned with 10 % solution of acetic acid in methanol (3 mL).

The following examples will illustrate the invention further. They are, however, not to be construed as limiting. **Example 1**

1a, N-(3-(5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)glycine.ethyl ester.

A stirred mixture of 3-(5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl amine (1.5 g), potassium carbonate (1.3 g) and ethanol (15 mL) was treated dropwise with a solution of ethyl bromoacetate (0.75 g) in ethanol (15 mL) at room temperature. After reflux for 1.5 h, the mixture was cooled and concentrated *in vacuo*. Standard work-up with ethyl acetate gave an oil which was purified by flash chromatography (eluent heptane/ethyl acetate/triethylamine 26:70:4). The title compound was obtained as a clear oil (0.77 g). LC/MS (m/z) 383 (MH⁺), purity (UV): >99%.

Example 2

2a, N-(3-(5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)-N-methylglycine.ethyl ester.

A stirred mixture of 3-(5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl iodide (3.1 g), ethyl N-methylglycinate (4.4 g) and diethylisopropylamine (4.4 g) in tetrahydrofuran (50 mL) was refluxed for 16 h. Standard work-up with ethyl acetate gave an oil which was purified by flash chromatography (eluent heptane/ethyl acetate/triethylamine 64:32:4) giving the title compound as a clear oil (1.4 g). LC/MS (m/z) 397 (MH⁺), purity (UV): >99%

Example 3

3a, N-(3-(5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)glycine hydrochloride

A mixture of N-(3-(5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)glycineethyl ester (0.7 g), methanol (6 mL) and 6 M sodium hydroxide (2 mL) was

stirred at room temperature for 2 h. Adjustment of pH to < 6.5 with dilute hydrochloric acid followed by standard work-up with ethyl acetate gave the title compound as an oil (0.2 g).

LC/MS (m/z) 355 (MH⁺), purity (UV): >90%

5 In a similar manner, the following compound were prepared:

3b, N-(3-(5-Cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-1-propyl)-N-methylglycine hydrochloride.

LC/MS (m/z) 369 (MH⁺), purity (UV): >90%

10 **3c**, Example 4:

N-{3-[1-(3-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 360 (MH⁺), purity (UV 90%)

3d, Example 5:

15 N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 394 (MH⁺), purity (UV 79%)

3e, Example 6:

20 N-{3-[1-(3-trifluoromethylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-ethyl)glycine hydrochloride

LC/MS (m/z) 422 (MH⁺), purity (UV 79%)

3f, Example 7:

N-{3-[1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

25 LC/MS (m/z) 378 (MH⁺), purity (UV 91%)

3g, Example 8:

N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 344 (MH⁺), purity (UV 81%)

30 **3h**, Example 9

N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine hydrochloride

LC/MS (m/z) 358 (MH⁺), purity (UV 81%)

3i, Example 10

5 N-{3-[1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methyl (1-ethyl)glycine hydrochloride

LC/MS (m/z) 372 (MH⁺), purity (UV 86%)

3j, Example 11

10 N-{3-[4-chloro-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 392 (MH⁺), purity (UV 86%)

3k, Example 12

N-{3-[4-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

15 LC/MS (m/z) 394 (MH⁺), purity (UV 98%)

3l, Example 13

N-{3-[5-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine hydrochloride

LC/MS (m/z) 408 (MH⁺), purity (UV 85%)

20 **3m, Example 14**

N-{3-[6-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 394 (MH⁺), purity (UV 99%)

3n, Example 15

25 N-{3-[6-chloro-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 374 (MH⁺), purity (UV 76%)

3o, Example 16

30 N-{3-[6-chloro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 390 (MH⁺), purity (UV 98%).

3p, Example 17

N-{3-[5-fluoro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 378 (MH⁺), purity (UV 85%).

5 **3q, Example 18**

N-{3-[5-fluoro-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 378 (MH⁺), purity (UV 99%).

3r, Example 19

10 N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 412 (MH⁺), purity (UV 81%)

3s, Example 20.

15 N-{3-[5-trifluoromethyl-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine hydrochloride

LC/MS (m/z) 426 (MH⁺), purity (UV 98%).

3t, Example 21

N-{3-[5-cyano-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

20 LC/MS (m/z) 383 (MH⁺), purity (UV 83%).

3u, Example 22

N-{3-[5-cyano-1-(4-cyanophenyl)-indan-1-yl]-1-propyl}-N-methylalanine hydrochloride.

LC/MS (m/z) 388 (MH⁺), purity (UV 80%).

3v, Example 23

25 N-{3-[5-cyano-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 381 (MH⁺), purity (UV 81%)..

3x, Example 24

30 N-{3-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 369 (MH⁺), purity (UV 98%)

3y, Example 25

N-{2-[5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]ethyl}-N-methylglycine hydrochloride.

LC/MS (m/z) 355 (MH⁺), purity (UV 94%)

5 **3z, Example 26**

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylglycine hydrochloride

LC/MS (m/z) 392 (MH⁺), purity (UV 98%)

3aa, Example 27

N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylalanine hydrochloride

10

LC/MS (m/z) 406 (MH⁺), purity (UV 95%)

3ab, Example 28

N-{3-[3-spirocyclopentyl-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine hydrochloride

3ac, Example 2915

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylglycine hydrochloride

3ad, Example 30

N-[3-(3,3-Dimethyl-1-phenyl-1,3-dihydro-benzo[c]thiophen-1-yl)-propyl]-N-methylalanine
LC/MS (m/z) 370 purity (UV 96%)

20 **3ae, Example 32**

N-{3-[5-Bromo-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine

LC/MS (m/z) 440 (MH⁺), purity (ELSD 93%)

3af, Example 3325

N-{2-[1-(4-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methylglycine

LC/MS (m/z) 374 (MH⁺), purity (UV 72%)

3ag, Example 34

N-[3-(3-methyl-1-phenyl-1*H*-inden-1-yl)-propyl]-N-methylglycine

30

LC/MS (m/z) 336 (MH⁺), purity (UV 85%)

3ah, Example 35

N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine
LC/MS (m/z) 380 (MH⁺), purity (UV 85%)

3ai, Example 36

N-[3-(5-Chloro-1-thiophen-2-yl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methyl (1-ethyl)-
glycine

LC/MS (m/z) 394 (MH⁺), purity (UV 80%)

3aj, Example 37

N-[3-(3-methyl-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-propyl]-N-methylalanine
LC/MS (m/z) 354 (MH⁺), purity (UV 78%)

3ak, Example 38

N-[2-(3-methyl-1-phenyl-indan-1-yl)-ethyl]-amino}-N-methyl alanine
LC/MS (m/z) 451, purity (UV 92%)

3al, Example 39

N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-
methyl-glycine

Example 4

4a, N-{3-[5-Bromo-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-ethyl}-N-methylglycine ethyl ester (226mg, 0.5mmol) was dissolved in a 1:1 mixture of tetrahydrofuran and dimethoxyethane (3 mL) containing tetrakis (triphenylphosphine)palladium under nitrogen. To the reaction was added 4-chlorophenyl boronic acid (102mg, 0.75 mmol) and 0.5M aqueous sodium carbonate solution (2 mL, 1mmol) and the reaction was heated to 65 °C for 18 hours. The solution was diluted with water (5 mL) and ethyl acetate (7 mL). The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (5 mL). The organic extractions were combined and washed with saturated brine solution (7 mL) before being evaporated in the presence of 1g of silica gel. The crude product absorbed on silica gel was poured on top of a 20g silica gel cartridge and eluted with a gradient solvent system eluting from heptane to heptane/ethyl

acetat (1:1) over 37 minutes. The product was isolated as a light oil (135 mg, 64%). LC/MS 479.

The compound was hydrolysed as described for Experimental 3a to give the N-methylglycine hydrochloride derivative.

5 LC/MS (m/z) 436, purity (UV 92%)

In an analogous fashion, the following compounds were prepared:

4b, Example 40

N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

10 LC/MS (m/z) 452, purity (UV 94%)

4c, Example 41

N-{3-[1-(4-Chloro-phenyl)-5-(2-thiophenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 428, purity (UV 96%)

15 **4d, Example 42**

N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 450, purity 91%

4e, Example 43

20 N-{3-[1-(4-Chloro-phenyl)-5-(4-methoxy-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 466, purity (UV 95%)

4f, Example 44

25 N-{3-[1-(4-chloro-phenyl)-5-(4-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 504, purity (UV 89%)

4g, Example 45

N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

30 LC/MS (m/z) 456, purity 96%

4h, Example 46

N-{2-[1-(4-Chloro-phenyl)-5-(5-chloro-thiophen-2-yl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 462, purity 74%

4i, Example 47

5 N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 436, purity UV 94 %

4j, Example 48

10 N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 436, purity (UV 91%)

4k, Example 49

N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

15 LC/MS (m/z) 490, purity 94%

4l, Example 50

N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 490, purity 89%

20 **4m**, Example 51

N-{3-[1-(4-chloro-phenyl)-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 506, purity 91%

4n, Example 52

25 N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine

LC/MS (m/z) 490, purity 89%

4o, Example 53

30 N-{3-[1-(4-Chloro-phenyl)-5-(4-chloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 470, purity (UV 94%)

4p, Example 54

N-{3-[1-(4-Chloro-phenyl)-5-(3-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 450, purity 96%

5 **4q, Example 55**

N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 450, purity 93%

4r, Example 56

10 N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 506, purity 91%

4s, Example 57

15 N-{3-[1-(4-Chloro-phenyl)-5-(3,4-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

LC/MS (m/z) 504, purity 95%

4t, Example 58

N-{3-[1-(4-chloro-phenyl)-5-(2-trifluoromethyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine

20 LC/MS (m/z) 504, purity 78%

Pharmacological Testing

25 The compounds of the invention were tested in a well-recognised and reliable test measuring glycine uptake:

[³H]-Glycine uptake

30 Cells transfected with the human GlyT-1b were seeded in 96 well plates. Prior to the experiment the cells were washed twice in HBS (10 mM Hepes-tris (pH 7,4), 2,5 mM KCl, 1

mM CaCl₂, 2,5 mM MgSO₄,) and pre-incubated with test compound for 6 minutes. Afterwards, 10 nM ³H-glycine was added to each well and the incubation was continued for 15 minutes. The cells were washed twice in HBS. Scintillation fluid was added and the Plates were counted on a Trilux (Wallac) scintillation counter.

5

The test results were as follows:

Inhibition of Glycine Transport by hGlyT-

Compound	Compound Name	IC ₅₀ GlyT-1b
3f	N-{3-[1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	5400
3k	N-{3-[4-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	4100
3l	N-{3-[5-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylalanine	5500
3m	N-{3-[6-chloro-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	7200
3n	N-{3-[6-chloro-1-(4-methylphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	9600
3t	N-{3-[5-cyano-1-(3-methyl-4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine.	5700
3v	N-{3-[5-cyano-1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine	8600
3z	N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylglycine	1100
3aa	N-{3-[5-Chloro-1-(4-chloro-phenyl)-indan-1-yl]-propyl}-N-methylalanine	470
3ae	N-{3-[5-Bromo-1-(4-chlorophenyl)-1,3-dihydroisobenzofuran-1-yl]-1-propyl}-N-methylglycine	4000

3af	N-{2-[1-(4-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methylglycine	3500
3ak	N-[2-(3-methyl-1-phenyl-indan-1-yl)-ethyl]-amino}-N-methyl alanine	2200
3al	N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine	2200
4c	N-{3-[1-(4-Chloro-phenyl)-5-(2-thiophenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine	1200
4d	N-{3-[1-(4-Chloro-phenyl)-5-(4-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-N-methyl-glycine	1500
4j	N-{3-[1-(4-Chloro-phenyl)-5-(2-methyl-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine	710
4k	N-{3-[1-(4-Chloro-phenyl)-5-(2,5-dichloro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-ethyl}-N-methyl-glycine	950

The above results demonstrate that the compounds of the invention are able to inhibit glycine uptake into synaptosomes in micromolar concentrations

and R²³ independently represent hydrogen or C₁₋₆-alkyl; or R⁸, R⁹, R¹⁰, R¹¹ and R¹² independently represent aryl or heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with halogen, CF₃, OCF₃, CN, NO₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, OH, SH, COR²⁶, wherein R²⁶ represents
 5 OH, C₁₋₆ alkoxy or C₁₋₆ alkyl; or NR³⁰R³¹, wherein R³⁰ and R³¹ independently represent hydrogen or C₁₋₆-alkyl;
 R⁸ and R⁹, or R⁹ and R¹⁰, or R¹⁰ and R¹¹, or R¹¹ and R¹² together form a fused, aromatic, saturated or partly saturated ring which optionally contains one or more heteroatoms such as O, N or S;

10 Y is O, S, CH₂ or CH, and when Y is CH then the dotted line is a bond;
 n is 2, 3, 4, 5 or 6;

Q represents C, P-OR²⁹ or S=O, wherein R²⁹ represents hydrogen or C₁₋₆-alkyl;

X is OR¹³ or NR²⁷R²⁸, wherein R¹³, R²⁷, and R²⁸ independently represent hydrogen, C₁₋₆-alkyl, aryl or aryl-C₁₋₆-alkyl, wherein aryl may be substituted with halogen, CF₃, OCF₃, CN, NO₂, or

15 C₁₋₆ alkyl; Optionally R²⁷ and R²⁸ together form a ring which may contain further nitrogen, oxygen or sulfur atoms and the ring may optionally be partly saturated,
 R²⁹ and R³⁰ represent hydrogen, C₁₋₆-alkyl, cycloalkyl or cycloalkylalkyl;

or a pharmaceutically acceptable addition salt thereof.

20

2. The compound according to any of the preceding claims, wherein n is 2 or 3.
3. The compound according to any of the preceding claims, wherein R¹ is CH₃.
4. The compound according to any of the preceding claims, wherein Q is C.
5. The compound according to any of the preceding claims, wherein X is OH or C₁₋₆-alkoxy.
- 25 6. The compound according to any of the preceding claims, wherein R⁷ represents hydrogen, and R⁴, R⁵ or R⁶ represent hydrogen, C₁₋₆-alkyl, CN, halogen, CF₃ or phenyl optionally substituted one or more times with halogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, CF₃, or R⁴, R⁵ or R⁶ represent heteroaryl optionally substituted one or more times with halogen or wherein R⁴ and R⁵, or R⁵ and R⁶ together form a fused aryl.

7. The compound according to any of the preceding claims wherein R^8 , R^9 , R^{10} , R^{11} or R^{12} independently represent hydrogen, halogen, alkyl, alkoxy, or R^8 and R^9 , or R^9 and R^{10} together form a fused aryl.
8. The compound according to any of the preceding claims wherein R^8 , R^9 , R^{10} , R^{11} or R^{12}
5 independently represent halogen, C_{1-6} -alkyl, C_{1-6} -alkoxy.
9. A pharmaceutical composition comprising at least one compound according to any of the preceding claims, or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.
10. The use of a compound according to claims 1-8, for the manufacture of a medicament for
10 the treatment of diseases responsive to modulation of the glycine transporter.
11. The use according to claim 10 wherein the disease is responsive to antagonism of the glycine transporter;
12. The use according to claims 10 and 11, wherein the disease is selected from the group
15 consisting of the positive and the negative symptoms of schizophrenia, psychoses, dementia, pain, improving cognition, Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke.
- 20 13. A method for the treatment of a disease responsive to modulation of the glycine transporter by administering to a patient in need thereof, an effective amount of a compound according to claims 1-8.
14. The method according to claim 13 wherein the diseases are responsive to antagonism of the glycine transporter.
- 25 15. The method according to claims 13 and 14, wherein the diseases to be treated are selected from the group consisting of the positive and the negative symptoms of schizophrenia, psychoses, dementia, pain, improving cognition, Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as
30 trauma to the head or stroke.