

pressed in glia and neurons, and it is found to be located at glutamatergic synapses (Cubelos et al., 2005, Cereb. Cortex 15:448-459).

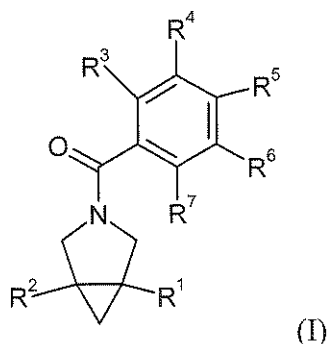
Glycine transporter inhibitors are suitable for the treatment of neurological and psychiatric disorders. The majority of diseases states implicated are psychoses, schizophrenia (Armer RE and Miller DJ, 2001, Exp. Opin. Ther. Patents 11: 563-572), psychotic mood disorders such as severe major depressive disorder, mood disorders associated with psychotic disorders such as acute mania or depression, associated with bipolar disorders and mood disorders, associated with schizophrenia, (Pralong ET et al., 2002, Prog. Neurobiol., 67:173-202), autistic disorders (Carlsson ML, 1998, J. Neural Trans. 105:525-535), cognitive disorders such as dementias, including age related dementia and senile dementia of the Alzheimer type, memory disorders in a mammal, including a human, attention deficit disorders and pain (Armer RE and Miller DJ, 2001, Exp. Opin. Ther. Patents, 11:563-572).

Thus, increasing activation of NMDA receptors via GlyT1 inhibition may lead to agents that treat psychosis, schizophrenia (positive, negative and cognitive symptoms), dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders, Alzheimer's disease, or other neurological and psychiatric disorders.

All these concepts to medicinally benefit from the inhibition of GlyT1 are of high interest, in particular with respect to cognitive impairment associated with Alzheimer's disease or Schizophrenia.

BRIEF SUMMARY OF THE INVENTION

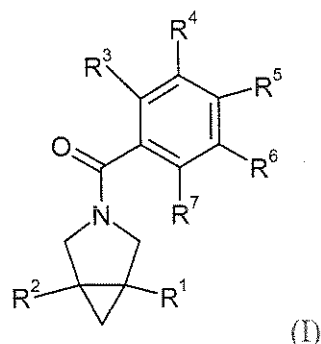
The present invention disclosure relates to substituted phenyl-3-aza-bicyclo[3.1.0]hex-3-yl-methanones of general formula (I)



wherein

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as herein described or salts thereof, preferably a
 5 pharmaceutically acceptable salt thereof.

In an aspect, there is provided a compound of general formula (I) or a salt thereof



wherein

R^1 is selected from the group of

- 10 a) 5 or 6 membered monocyclic heteroaryl, having 1, 2, 3 or 4 heteroatoms independently
selected from the group of O, N and S(O)_r,
 b) 5 or 6 membered monocyclic partially saturated heterocycloalkyl, having 1, 2 or 3
heteroatoms independently selected from the group of O, N and S(O)_r, and
 c) 9 or 10 membered bicyclic heteroaryl, having 1, 2 or 3 heteroatoms independently
 15 selected from the group of O, N and S(O)_r,

wherein r is 0, 1 or 2;

wherein each of said groups a), b) and c) is optionally substituted with 1 or more substituents independently selected from the group of C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, C₃₋₆-cycloalkyl- and C₃₋₆-cycloalkyl-O- and in case a substituent is attached to a nitrogen ring atom said substituent is selected from the group of C₁₋₄-alkyl-, C₁₋₄-alkyl-CO-, C₃₋₆-cycloalkyl- and C₃₋₆-cycloalkyl-CO-, and wherein each of said C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-CO-, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-CO- or C₃₋₆-cycloalkyl-O- substituents may be substituted by 1 or more substituents independently selected from the group of fluoro, -CF₃, -CHF₂, -CH₂F and -CN;

R^2 is selected from the group of hydrogen, C₁₋₄-alkyl-, C₁₋₄-alkyl-O-, -CN and C₃₋₆-cycloalkyl-,

wherein each of said C₁₋₄-alkyl-, C₁₋₄-alkyl-O- and C₃₋₆-cycloalkyl-group may be optionally substituted with 1, 2, 3 or more substituents independently selected from the group of fluoro, -CF₃, -CHF₂, -CH₂F and -CN;

R^3 is selected from the group of C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl-O-, morpholino, pyrazolyl and a 4 to 7 membered, monocyclic heterocycloalkyl-O- with 1 oxygen atom as ring member and optionally 1 or 2 heteroatoms independently selected from the group of O, N and S(O)_s with s = 0, 1 or 2, ,

wherein said C₁₋₆-alkyl-O- and said C₃₋₆-cycloalkyl-O- may be optionally substituted with 1, 2, 3 or more substituents independently selected from the group of fluoro, -CF₃, -CHF₂, -CH₂F, -CN, C₁₋₄-alkyl-, C₃₋₆-cycloalkyl-, C₁₋₆-alkyl-O- and C₃₋₆-cycloalkyl-O-;

R^4 is hydrogen;

or R^3 and R^4 together with the ring atoms of the phenyl group to which they are bound may form a 4, 5 or 6 membered, monocyclic, partially saturated heterocycloalkyl or a heteroaryl each of which having 1, 2 or 3 heteroatoms independently selected from the group of O, N and $S(O)_s$ with $s = 0, 1$ or 2 , wherein there must be 1 ring oxygen atom that is directly attached to the ring carbon atom of said phenyl group to which R^3 is attached to in general formula (I):

wherein said heterocycloalkyl group may be optionally substituted with 1, 2, 3 or more substituents independently selected from the group of fluoro, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CN$, C_{1-4} -alkyl-, C_{3-6} -cycloalkyl-, C_{1-6} -alkyl-O-, C_{3-6} -cycloalkyl-O-, oxetanyl-O-, tetrahydrofuranyl-O- and tetrahydropyranyl-O-;

R^5 is hydrogen:

R^6 is selected from the group of hydrogen, C_{1-4} -alkyl- SO_2 -, C_{3-6} -cycloalkyl- SO_2 - and $-CN$;

R^7 is hydrogen:

or one of the pairs a) R^6 and R^7 or b) R^6 and R^5 form together with the ring atoms of the phenyl group to which they are bound, a 5 or 6 membered, partially saturated monocyclic heterocycloalkyl group having 1, 2 or 3 heteroatoms independently selected from the group of O, N and $S(O)_u$ with $u = 0, 1$ or 2 , wherein there must be 1 $-SO_2$ - member that is directly attached to the ring carbon atom of said phenyl group to which R^6 is attached to in general formula (I),

wherein said heterocycloalkyl group may be optionally substituted with 1, 2, 3 or more substituents independently selected from the group of fluoro, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CN$, C_{1-4} -alkyl-, C_{1-6} -alkyl-O- and C_{3-6} -cycloalkyl-O-;

or one of the pairs a) R^6 and R^7 or b) R^6 and R^5 form together with the ring atoms of the phenyl group to which they are bound a partially saturated monocyclic heterocycloalkyl group having 1, 2 or 3 heteroatoms independently selected from the group of O, N and $S(O)_u$ with $u = 0, 1$ or 2 , wherein there must be 1 $-SO_2-$ member that is directly attached to the ring carbon atom of said phenyl group to which R^6 is attached to in general formula (I), wherein said heterocycloalkyl group may be optionally substituted with 1, 2, 3 or more substituents independently selected from the group of fluoro, $-CF_3$, $-CHF_2$, $-CH_2F$ and $-C_{1-4}$ -alkyl-.

The invention disclosure further relates to the manufacture of said active compounds, pharmaceutical compositions comprising a compound according to general formula (I), and the use of said active compounds for the treatment of various conditions such as conditions concerning positive and negative symptoms of schizophrenia as well as cognitive impairments associated with schizophrenia, Alzheimer's Disease and other neurological and psychiatric disorders.

The use comprises the manufacture of medicaments for the treatment of the corresponding diseases.

In another aspect, there is provided a compound as defined herein for use in or for use as a medicament, wherein the use of the medicament or the medicament is for a therapeutic or prophylactic method

- (a) for the treatment, amelioration or prevention of a condition selected from the group consisting of positive and negative symptoms of schizophrenia, psychoses and cognitive impairments associated with schizophrenia, Alzheimer's Disease, prodromal Alzheimer's disease, amnestic mild cognitive impairment and psychiatric disorders;
- (b) for the treatment of Alzheimer's disease, prodromal Alzheimer's disease, amnestic mild cognitive impairment or cognitive impairment associated with Alzheimer's disease,
- (c) for the treatment of schizophrenia or cognitive impairment associated with schizophrenia.

(d) for the treatment of psychoses.

In another aspect, there is provided a pharmaceutical composition or medicament comprising a compound as defined herein.

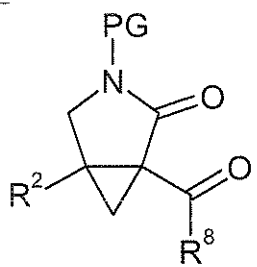
In another aspect, there is provided a combination of a compound as defined herein with another active agent, that

(a) is useful for the therapeutic treatment of a disease or condition as defined herein under (a) or (b) or (c) or (d) or

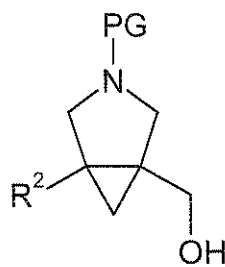
(b) is useful for the prophylactic treatment of a condition or disease as defined herein under (a) or (b) or (c) or (d) or

(c) is useful for the manufacture of a medicament for the treatment of a condition or disease as defined herein under (a) or (b) or (c) or (d).

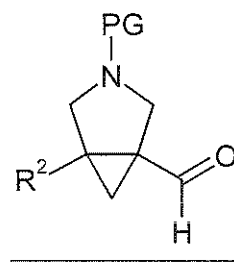
In another aspect, there is provided a compound of general formula (II), (III), (IV), (V) or (VI):



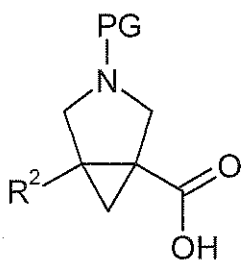
general formula (II)



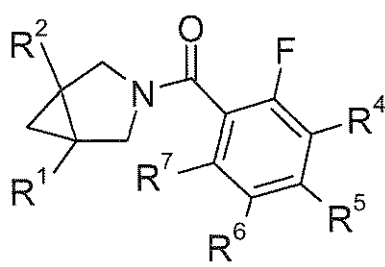
general formula (III)



general formula (IV)



general formula (V)



general formula (VI)

wherein in each of those independent formulas

R^1 , R^4 , R^5 , R^6 , and R^7 have the meaning as defined herein.

R^2 in general formula (II) to (V) is selected from the group consisting of C_{1-4} -alkyl-, C_{1-4} -alkyl-O-, -CN and C_{3-6} -cycloalkyl-,

R^2 in general formula (VI) is selected from the group consisting of hydrogen, C_{1-4} -alkyl-, C_{1-4} -alkyl-O-, -CN and C_{3-6} -cycloalkyl-,

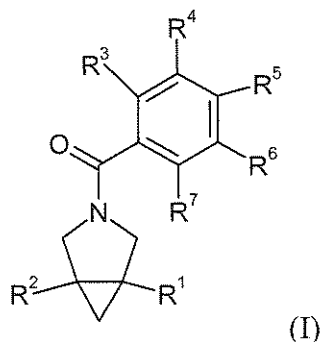
wherein each of said C_{1-4} -alkyl-, C_{1-4} -alkyl-O- and C_{3-6} -cycloalkyl-group may be optionally substituted with 1, 2, 3 or more substituents independently selected from the group of fluoro, -CF₃, -CHF₂, -CH₂F and -CN;

R^8 is C_{1-4} alkyl-O-, optionally substituted by 1 or more substituents independently selected from each other from the group of fluoro, chloro, bromo, -CN, C_{1-4} alkyl-O-, C_{1-4} alkyl-, phenyl and benzyl, wherein phenyl and benzyl optionally may be substituted with one or more substituents independently selected from each other from the group of fluoro, chloro, bromo, -CN, C_{1-4} alkyl-O-, C_{1-4} alkyl-; and

PG is a protecting group for an amino function selected from the group consisting of tert-butoxycarbonyl-, 9-fluorenylmethoxycarbonyl-, benzyl-, and 2,4-dimethoxybenzyl-.

DETAILED DESCRIPTION OF THE INVENTION

The present inventions relate to substituted phenyl-3-aza-bicyclo[3.1.0]hex-3-yl-methanones of general formula (I)



(I)