(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 March 2002 (21.03.2002)

PCT

(10) International Publication Number
WO 02/22581 A1

(51) International Patent Classification[7]: C07D 211/72, 211/84, 213/72, 213/75, 215/38, 231/44, 231/50, 257/06, 335/16, A01N 37/12, 37/18, 37/44, 43/40, 43/56, 43/64, 47/28, A61K 31/17, 31/41, 31/44, 31/195, 31/235, 31/415, 31/445

(21) International Application Number: PCT/US01/28431

(22) International Filing Date:
13 September 2001 (13.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/232,540 14 September 2000 (14.09.2000) US

(71) Applicant *(for all designated States except US)*: **GLIATECH, INC.** [US/US]; 23420 Commerce Park Drive, Cleveland, OH 44122 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ALI, Syed, M.** [IN/US]; 34463 Claythorne Drive, Solon, OH 44139 (US). **BRUNDEN, Kurt, R.** [US/US]; 664 Glen Eden Court, Aurora, OH 44202 (US). **JIANG, Jack, B.** [US/US]; 455 Nob Hill Oval, Orange Village, OH 44022 (US).

(74) Agents: **KATZ, Martin, L.** et al.; Rockey, Milnamow & Katz, Ltd., Two Prudential Plaza, Suite 4700, 180 N. Stetson Ave., Chicago, IL 60601 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/22581 A1

(54) Title: NITROGEN-CONTAINING COMPOUNDS AND THEIR USE AS GLYCINE TRANSPORT INHIBITORS

(57) Abstract: A method for the inhibition of high affinity glycine transporters, compounds that inhibit these transporters; pharmaceutically active compositions comprising such compounds; and the use of such compounds either as above, or in formulations for the control or prevention of disease states in which glycine is involved are disclosed.

Nitrogen-Containing Compounds and Their Use as Glycine Transport Inhibitors

Field of the Invention

This invention is directed generally to nitrogen-containing compounds and pharmaceutically acceptable salts thereof. The compounds are inhibitors of high affinity glycine transporters and are thus useful in treating neurological disorders including schizophrenia, dementia, epilepsy, muscle spasticity, mood disorders, learning disorders, neurodegenerative diseases and pain.

Background of the Invention

Glycine acts as a neurotransmitter at two distinct receptor systems. In the spinal cord and certain non-cerebral brain regions, glycine acts much like GABA (γ-amino-n-butyric acid) in causing the opening of an inhibitory Cl^- channel. This activity is mediated by the "strychnine-sensitive" glycine receptor. Glycine also acts as a co-agonist at the NMDA (N-methyl-D-aspartate) glutamate receptor that is localized in the cognitive centers of the brain, including the cortex, hippocampus, and basal ganglia. This receptor has received considerable attention from the pharmaceutical industry since there is compelling evidence that it plays a critical role in learning and cognition. Furthermore, excessive stimulation of the NMDA receptor appears to be responsible for much of the neuronal damage that occurs after stroke-injury and brain trauma. Hence, there are ongoing research efforts to develop both agonists (for increased cognition) and antagonists (for treatment of stroke) to the NMDA receptor.

Recent data suggest that agonists and antagonists to the glutamate site of the NMDA receptor can cause relatively severe side-effects. For example, NMDA antagonists have been shown to cause agitation, hallucinations, and paranoia in stroke patients. Agonists to the glutamate binding site on NMDA receptors have the potential of causing excessive calcium influx and excitotoxic cell damage. In contrast, the glycine site on the NMDA receptor appears to play a modulatory role, and therefore compounds interacting with this site do not appear to evoke such severe side-effects.

Demonstration that Glycine Modulation Improves Cognition

Evidence that molecules acting at the glycine site of the NMDA receptor can effectively enhance receptor activity is provided by several studies showing that glycine agonists or partial agonists are cognitive enhancers *in vivo*. D-cycloserine, a molecule that crosses the blood-brain barrier and which is a partial agonist at the NMDA glycine site, increased the performance of rats in a learning task model. In fact, D-cycloserine was reported to improve the implicit memory performance in a word recall test in Alzheimer's disease patients. However, because D-cycloserine is only a partial agonist at the glycine site, it may be more useful as an antagonist to the NMDA receptor.

A larger number of studies have been performed with the glycine prodrug, milacemide. This molecule (2-N-pentylaminoacetamide HCl) readily crosses the blood-brain barrier and is metabolized by monoamine oxidase B (MAO-B) to glycinamide. The latter is converted to glycine, which then acts at the NMDA receptor. Milacemide improved the performance of rats in a passive-avoidance task and reversed drug-induced amnesia. This compound has also been shown to improve performance in the Morris water maze task and to increase word retrieval skills in young and elderly healthy human adults. Unfortunately, the effectiveness of the drug wanes after continuous administration because the compound leads to irreversible inactivation of MAO-B, thus blocking the drug's own metabolism. Nonetheless, the data obtained with this compound and D-cycloserine demonstrate that increasing the occupancy of the glycine site of the NMDA receptor results in enhanced cognitive performance in animals and humans without side-effects.

The NMDA Receptor in Schizophrenia

The general view has been that schizophrenia primarily results from hyperfunctioning of the dopaminergic system. The typical anti-psychotics, such as thorazine and haloperidol, are relatively potent dopamine D2 receptor antagonists. In fact, there is a general correlation between clinical efficacy of the classical anti-psychotics (or neuroleptics) and their affinity for the D2 receptor. Further evidence of the importance of the dopaminergic system in schizophrenia is provided by studies showing that dopamine agonists, or agents that increase dopamine levels (like amphetamines), induce psychotic behavior.

While the role of dopamine in schizophrenia is well established, there are compelling reasons to believe that the disorder does not result solely from hyperfunctioning of this neurotransmitter system. For example, although amphetamine-induced psychosis includes certain "positive" symptoms such as delusions, hallucination and agitation, common "negative" aspects of schizophrenia, including emotional withdrawal and mental retardation, are not observed. Perhaps the best indication that the dopamine hypothesis is an over-simplified explanation of schizophrenia is the observation that individuals who have taken excessive phencyclidine (PCP) are clinically indistinguishable from schizophrenics. PCP acts as a selective noncompetitive blocker of the glutamate NMDA receptor at concentrations that induce psychosis, with no apparent effect on dopamine binding. Interestingly, PCP and ketamine (another NMDA channel-blocker) also exacerbate the psychosis of schizophrenic patients, whereas the psychomimetic effects of amphetamine are reduced in schizophrenics. These data imply that schizophrenia results from glutamate hypoactivity in addition to dopamine hyperfunction. Since most of schizophrenic patients have some form of information processing deficit also implies that NMDA receptor function may be compromised in this disorder.

Although the available anti-psychotics primarily affect dopaminergic neurotransmission, there is some evidence that they may also have a modest effect on the glutaminergic system. Both haloperidol and clozapine cause an ~40% increase in NMDA receptor activity *in vitro* at concentrations at which clinical efficacy is seen. Thus, some of their anti-psychotic activity may result from action on the NMDA receptor. The most compelling demonstration of glutamate hypofunction in schizophrenia would be clinical evidence that NMDA agonists improve patient outcome. Small clinical studies have been performed with D-cycloserine, and initial indications are that the compound may improve the negative symptoms and cognitive deficits of schizophrenia. That effects are seen with this partial agonist suggests that full glycine agonists may be particularly efficacious. Of particular interest are clinical studies in which schizophrenics were treated with large oral doses of glycine or placebo. Even though glycine does not penetrate the blood-brain barrier effectively, the patients receiving the glycine

treatment showed a statistically significant decrease in negative schizophrenic symptoms.

Modulation of NMDA Receptor Activity Through Inhibition of Glycine Transporters

An approach to enhancing NMDA receptor action is to increase glycine concentrations at the synaptic cleft by inhibiting its removal. While regulation of the transporters for the biogenic amines has been extensively studied, relatively little is known about the types of molecules that inhibit the glycine transporters.

Both astrocytes and neurons are involved in glycine removal. Astrocytic glycine uptake systems have been partially characterized *in vitro* and *in vivo*. The high-affinity glycine transporters that are involved in synaptic regulation have been cloned, and two separate genes appear to encode for these transporters. These proteins belong to the same transporter family as those for the biogenic amines, with transport function being both sodium- and chloride-dependent. The GlyT1 glycine transporter is expressed by astrocytes in the spinal cord, brainstem, and brain hemispheres. Isoforms resulting from mRNA splice variants have been described for both GlyT1 and GlyT2, although the physiological significance of these isoforms is not know. The GlyT2 uptake system is restricted to the spinal cord, brainstem and cerebellum, and is not found in the cortex and other regions of the brain hemispheres. Based on their distributions, it is believed that GlyT2 is involved in regulating glycine that acts at the strychnine-sensitive glycine receptors, whereas GlyT1 is likely involved in removing glycine from synapses containing NMDA receptors.

The selective inhibition of GlyT1 action would appear to be a rational approach to increasing the function of the NMDA receptor without the inherent side-effects associated with modulation of the glutamate binding site. Such an approach could provide useful therapeutic agents to treat, for example, schizophrenia, dementias, learning impairment and various neurodegenerative disorders. The inhibition of GlyT2 would lead to elevated levels of glycine near the strychnine-sensitive glycine receptors. The enhancement of activity at this receptor could prove beneficial in treating muscle spasticity resulting, for example, from

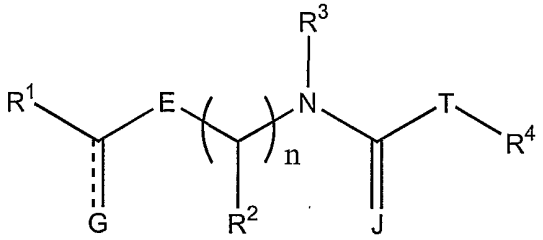
spinal cord injury or multiple sclerosis. Furthermore, GlyT2 inhibitors might provide benefit in the management of chronic pain.

Known glycine transporter inhibitors include substituted amines (WO99/34790, 97/45115 and 45423) and piperazinyl derivatives (WO99/44596 and 45011). The nitrogen-containing compounds of Formula I are novel agents which inhibit glycine transporters.

It is therefore an object of the invention to provide novel compounds which are inhibitors of glycine transporters, a method for treating diseases influenced by glycine and pharmaceutical compositions including such novel compounds.

Brief Summary of the Invention

The invention is directed to novel compounds of Formula I as follows:



Formula I

wherein n is an integer of from zero to three;

J is selected from the group consisting of O, S and NR^5;

T is selected from the group consisting of O, S and NR^6;

G is selected from the group consisting of =O, =S, $=NR^7$, $-OR^8$, $-SR^9$ and $-NR^{10}$;

E is selected from the group consisting of O, S and NR^{11};

R^3, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, aliphatic acyl, -C_1-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino,-C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -CH=NOH, -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxycarbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aroyl,

aryloxy, arylamino, biaryl, thioaryl, heterocyclyl, heterocycloyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, -SO_2-(C_1-C_3 alkyl), -SO_3-(C_1-C_3 alkyl), sulfonamido, carbamate, aryloxyalkyl, carboxyl, and -C(O)NH(benzyl); and

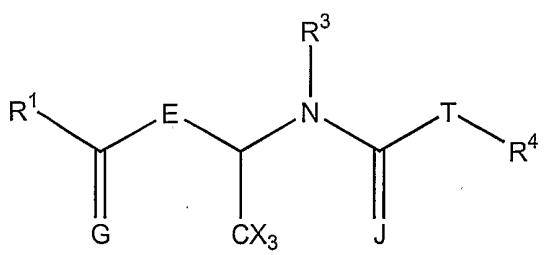
R^1, R^2, and R^4 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, thioalkoxy, hydroxyalkyl, aliphatic acyl, -CF_3, nitro, amino, cyano, carboxy, -N(C_1-C_3 alkyl)-C(O)(C_1-C_3 alkyl), -NHC(O)NH(C_1-C_3 alkyl), -NHC(O)N(C_1-C_3 alkyl)C(O)NH(C_1-C_3 alkyl), -C_1-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino, -C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -CH=NOH, -PO_3H_2, -OPO_3H_2, -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, diarylamino, heterocyclyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, sulfonyl, -SO_2-(C_1-C_3 alkyl), -SO_3-(C_1-C_3 alkyl), sulfonamido, aryloxyalkyl, carboxyl, carbamate and -C(O)NH(benzyl);

wherein R^1, R^2, R^3, R^4, R^5, R^6 , R^7, R^8, R^9, R^{10} and R^{11} are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

or a pharmaceutically acceptable salt thereof.

In preferred compounds of Formula I above, n may be one; G may be =O; J may be =S; E may be -NR^{11}; and T may be -NR^6.

More specifically, the compounds of this invention may be described by Formula II below



Formula II

wherein X, at each occurrence, is independently selected from the group consisting of -Cl, -F, -Br and -I;

J is selected from the group consisting of O, S and NR^5;

T is selected from the group consisting of O, S and NR^6;

G is selected from the group consisting of O, S, NR^7;

E is selected from the group consisting of O, S and NR^{11};

R^3, R^5, R^6, R^7 and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, aliphatic acyl, -C_1-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino, -C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -CH=NOH, -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxycarbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, heterocyclyl, heterocycloyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, -SO_2-(C_1-C_3 alkyl), -SO_3-(C_1-C_3 alkyl), sulfonamido, carbamate, aryloxyalkyl, carboxyl, and -C(O)NH(benzyl); and

R^1 and R^4 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, thioalkoxy, hydroxyalkyl, aliphatic acyl, -CF_3, nitro, amino, cyano, carboxy, -N(C_1-C_3 alkyl)-C(O)(C_1-C_3 alkyl), -NHC(O)NH(C_1-C_3 alkyl), -NHC(O)N(C_1-C_3 alkyl)C(O)NH(C_1-C_3 alkyl), -C_1-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino, -C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -CH=NOH, -PO_3H_2, -OPO_3H_2, -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, diarylamino, heterocyclyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, sulfonyl, -SO_2-(C_1-C_3 alkyl), -SO_3-(C_1-C_3 alkyl), sulfonamido, aryloxyalkyl, carboxyl, carbamate and

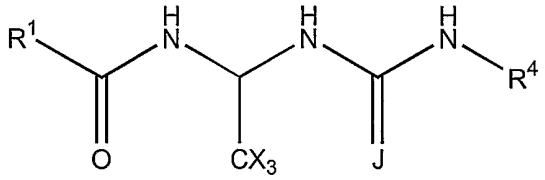
-C(O)NH(benzyl);

wherein R^1, R^3, R^4, R^5, R^6, R^7 and R^{11} are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

or a pharmaceutically acceptable salt thereof.

In preferred compounds of Formula II above, G may be O, J may be =S, E may be NR^{11} and T may be NR^6.

More specifically, the compounds of this invention may be described by Formula III below



Formula III

wherein X, at each occurrence, is selected from the group consisting of -Cl, -F, -Br and -I;

J is selected from the group consisting of O, S and NR^5; and

R^1 and R^4 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, thioalkoxy, hydroxyalkyl, aliphatic acyl, $-CF_3$, carboxy, $-C_1$-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino, -C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, diarylamino, heterocyclyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, aryloxyalkyl, carboxyl, carbamate and -C(O)NH(benzyl);

wherein R^1, R^4 and R^5 are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

or a pharmaceutically acceptable salt thereof.

In preferred compounds of Formula III above, X, at each occurrence, may be -Cl, and J may be =S.

Presently preferred compounds include (2E)-*N*-(1-(((2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))amino)thioxomethyl)amino)-2,2,2-trichloroethyl)-3-(2-naphthyl)prop-2-enamide, (2E)-*N*-(1-(((benzothiazol-6-ylamino)thioxomethyl)amino)-2,2,2-trichloroethyl)-3-phenylprop-2-enamide, (2E)-3-phenyl-*N*-(2,2,2-trichloro-1-((((2-sulfanylphenyl)amino)thioxomethyl) amino)ethyl)prop-2-enamide, (2E)-3-phenyl-*N*-(2,2,2-trichloro-1-(((8-quinolylamino)thioxomethyl)amino)ethyl)prop-2-enamide, methyl 2-((((1-((2E)-3-phenylprop-2-enoylamino)-2,2,2-trichloroethyl)amino)thioxomethyl) amino)acetate, 2-((thioxo((2,2,2-trichloro-1-(2-naphthylcarbonylamino)ethyl) amino)methyl)amino)benzoic acid, 2-naphthyl-*N*-(2,2,2-trichloro-1-((8-quinolylamino)thioxomethyl)amino)ethyl)carboxamide, (2E)-*N*-(1-(((carbamoylmethyl)amino)thioxomethyl)amino)-2,2,2-trichloroethyl)-3-phenylprop-2-enamide, (2E)-3-phenyl-*N*-(2,2,2-trichloro-1-(((2-cyclopropyl(1,2,3,4-tetraazolin-5-yl))amino)thioxomethyl)amino)ethyl)prop-2-enamide, methyl 2-((((1-((2E)-3-phenylprop-2-enoylamino)-2,2,2-trichloroethyl)amino)thioxomethyl) amino)benzoate, (2E)-3-phenyl-*N*-(2,2,2-trichloro-1-((((2-nitro-4-(trifluoromethyl)phenyl)amino) thioxomethyl)amino) ethyl)prop-2-enamide, 2-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino) ethyl)amino)methyl)amino)benzoic acid, *N*-(1-((((2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl)amino)thioxomethyl)amino)-2,2,2-trichloroethyl) cyclohexylcarboxamide, 2-((((1-(2,2-dimethylpropanoylamino)-2,2,2-trichloroethyl)amino)thioxomethyl)amino)benzamide, 2,2-dimethyl-*N*-(2,2,2-trichloro-1-((((2-nitrophenyl)amino)thioxomethyl)amino)ethyl)propanamide, 2-((thioxo((2,2,2-trichloro-1-(2-methylpropanoylamino)ethyl)amino)methyl)amino) benzoic acid, *N*-(1-((((2-acetylphenyl)amino)thioxomethyl)amino)-2,2,2-trichloroethyl)-2,2-dimethylpropanamide, 2-((2,2,2-trichloro-1-(cyclohexylcarbonylamino)ethyl)amino)benzoic acid, methyl 2-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino)ethyl)amino)methyl)amino)acetate, 5-fluoro-2-((thioxo((2,2,2-trichloro-1-(cyclopropylcarbonylamino)ethyl)amino) methyl) amino)benzoic acid, 2-((thioxo((2,2,2-trichloro-1-

(cyclopropylcarbonylamino)ethyl)amino)methyl) amino)benzoic acid and 3-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino)ethyl)amino) methyl)amino)naphthalene-2-carboxylic acid.

Useful derivatives of the compounds of Formulae I, II and III include esters, carbamates, aminals, amides, optical isomers and pro-drugs thereof.

The present invention also relates to a pharmaceutical composition comprising a compound of Formula I, in a pharmaceutically acceptable carrier.

The present invention also relates to a method for selectively inhibiting glycine transporters in a mammal comprising administering to said mammal a therapeutic amount of a compound of Formula I.

Detailed Description of the Invention

Definitions of Terms

The term "alkyl" as used herein alone or in combination refers to C_1-C_{12} straight or branched, substituted or unsubstituted saturated chain radicals derived from saturated hydrocarbons by the removal of one hydrogen atom, unless the term alkyl is preceded by a C_x-C_y designation. Representative examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, and tert-butyl, among others.

The term "alkenyl", alone or in combination, refers to a substituted or unsubstituted straight-chain or substituted or unsubstituted branched-chain alkenyl radical containing from 2 to 10 carbon atoms. Examples of such radicals include, but are not limited to, ethenyl, E- and Z-pentenyl, decenyl and the like.

The term "alkynyl", alone or in combination, refers to a substituted or unsubstituted straight or substituted or unsubstituted branched chain alkynyl radical containing from 2 to 10 carbon atoms. Examples of such radicals include, but are not limited to ethynyl, propynyl, propargyl, butynyl, hexynyl, decynyl and the like.

The term "lower" modifying "alkyl", "alkenyl", "alkynyl" or "alkoxy" refers to a C_1-C_6 unit for a particular functionality. For example lower alkyl means C_1-C_6 alkyl.

The term "aliphatic acyl" alone or in combination, refers to radicals of formula alkyl-C(O)-, alkenyl-C(O)- and alkynyl-C(O)- derived from an alkane-, alkene- or alkyncarboxylic acid, wherein the terms "alkyl", "alkenyl" and "alkynyl" are as defined above. Examples of such aliphatic acyl radicals include, but are not limited to, acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, acryloyl, crotyl, propiolyl and methylpropiolyl, among others.

The term "cycloalkyl" as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings, including, but not limited to cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, and adamantyl among others. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide."Cycloalkyl" includes cis or trans forms. Furthermore, the substituents may either be in endo or exo positions in the bridged bicyclic systems.

The term "cycloalkenyl" as used herein alone or in combination refers to a cyclic carbocycle containing from 4 to 8 carbon atoms and one or more double bonds. Examples of such cycloalkenyl radicals include, but are not limited to, cyclopentenyl, cyclohexenyl, cyclopentadienyl and the like.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a lower alkyl radical, including, but not limited to cyclohexylmethyl.

The term "halo" or "halogen" as used herein refers to I, Br, Cl or F.

The term "haloalkyl" as used herein refers to a lower alkyl radical, to which is appended at least one halogen substituent, for example chloromethyl, fluoroethyl, trifluoromethyl and pentafluoroethyl among others.

The term "alkoxy", alone or in combination, refers to an alkyl ether radical, wherein the term "alkyl" is as defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "alkoxycarbonyl", alone or in combination, refers to an alkoxy group as previously defined appended to the parent molecular moiety through a

carbonyl group. Examples of alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl and isopropoxycarbonyl among others.

The term "alkenoxy", alone or in combination, refers to a radical of formula alkenyl-O-, provided that the radical is not an enol ether, wherein the term "alkenyl" is as defined above. Examples of suitable alkenoxy radicals include, but are not limited to, allyloxy, E- and Z- 3-methyl-2-propenoxy and the like.

The term "alkynoxy", alone or in combination, refers to a radical of formula alkynyl-O-, provided that the radical is not an -ynol ether. Examples of suitable alkynoxy radicals include, but are not limited to, propargyloxy, 2-butynyloxy and the like.

The term "carboxyl" as used herein refers to a carboxylic acid radical, -C(O)OH.

The term "thioalkoxy", refers to a thioether radical of formula alkyl-S-, wherein "alkyl" is as defined above.

The term "sulfonamido" as used herein refers to $-SO_2NH_2$.

The term "carboxaldehyde" as used herein refers to -C(O)R wherein R is hydrogen.

The term "carboxamide" as used herein refers to $-C(O)NR_aR_b$ wherein R_a and R_b are each independently hydrogen, alkyl or any other suitable substituent.

The term "alkoxyalkoxy" as used herein refers to R_cO-R_dO- wherein R_c is lower alkyl as defined above and R_d is alkylene wherein alkylene is $-(CH_2)_{n'}-$ wherein n' is an integer from 1 to 6. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy among others.

The term "alkylamino" as used herein refers to R_eNH- wherein R_e is a lower alkyl group, for example, ethylamino, butylamino, among others.

The term "alkenylamino" alone or in combination, refers to a radical of formula alkenyl-NH-or $(alkenyl)_2N$-, wherein the term "alkenyl" is as defined above, provided that the radical is not an enamine. An example of such alkenylamino radical is the allylamino radical.

The term "alkynylamino", alone or in combination, refers to a radical of formula alkynyl-NH- or $(alkynyl)_2N$- wherein the term "alkynyl" is as defined

above, provided that the radical is not an amine. An example of such alkynylamino radicals is the propargyl amino radical.

The term "dialkylamino" as used herein refers to R_fR_gN- wherein R_f and R_g are independently selected from lower alkyl, for example diethylamino, and methyl propylamino, among others.

The term "amino" as used herein refers to H_2N- .

The term "alkoxycarbonyl" as used herein refers to an alkoxyl group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, and isopropoxycarbonyl among others.

The term "aryl" or "aromatic" as used herein alone or in combination refers to a substituted or unsubstituted carbocyclic aromatic group having about 6 to 12 carbon atoms such as phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl and anthracenyl; or a heterocyclic aromatic group selected from the group consisting of furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, 2,3-dihydrobenzofuranyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxyazinyl, pyrazolo[1,5-c]triazinyl and the like. "Arylalkyl" and "alkylaryl" employ the term "alkyl" as defined above. Rings may be multiply substituted.

The term "aralkyl", alone or in combination, refers to an aryl substituted alkyl radical, wherein the terms "alkyl" and "aryl" are as defined above. Examples of suitable aralkyl radicals include, but are not limited to, phenylmethyl, phenethyl, phenylhexyl, diphenylmethyl, pyridylmethyl, tetrazolyl methyl, furylmethyl, imidazolyl methyl, indolylmethyl, thienylpropyl and the like.

The term "aralkenyl", alone or in combination, refers to an aryl substituted alkenyl radical, wherein the terms "aryl" and "alkenyl" are as defined above.

The term "arylamino", alone or in combination, refers to a radical of formula aryl-NH-, wherein "aryl" is as defined above. Examples of arylamino radicals include, but are not limited to, phenylamino(anilido), naphthlamino, 2-, 3-, and 4- pyridylamino and the like.

The term "biaryl", alone or in combination, refers to a radical of formula aryl-aryl, wherein the term "aryl" is as defined above.

The term "thioaryl", alone or in combination, refers to a radical of formula aryl-S-, wherein the term "aryl" is as defined above. An example of a thioaryl radical is the thiophenyl radical.

The term "aroyl", alone or in combination, refers to a radical of formula aryl-CO-, wherein the term "aryl" is as defined above. Examples of suitable aromatic acyl radicals include, but are not limited to, benzoyl, 4-halobenzoyl, 4-carboxybenzoyl, naphthoyl, pyridylcarbonyl and the like.

The term "heterocyclyl", alone or in combination, refers to a non-aromatic 3- to 10- membered ring containing at least one endocyclic N, O, or S atom. The heterocycle may be optionally aryl-fused. The heterocycle may also optionally be substituted with at least one substituent which is independently selected from the group consisting of hydrogen, halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, aralkyl, alkenyl, alkynyl, aryl, cyano, carboxy, carboalkoxy, carboxyalkyl, oxo, arylsulfonyl and aralkylaminocarbonyl among others.

The term "alkylheterocyclyl" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a heterocyclyl group.

The term "heterocyclylalkyl" as used herein refers to a heterocyclyl group as previously defined appended to the parent molecular moiety through an alkyl group.

The term "heterocycloyl", as used herein refers to radicals of formula heterocyclyl-C(O)-, wherein the term "heterocyclyl" is as defined above. Examples of suitable heterocycloyl radicals include tetrahydrofuranylcarbonyl, piperidinecarbonyl and tetrahydrothiophenecarbonyl among others.

The term "aminal" as used herein refers to a hemi-acetal of the structure $RCH(NH_2)(OH)$.

The term "amide" as used herein refers to a moiety ending with a $-C(O)NH_2$ functional group.

The term "ester" as used herein refers to $-C(O)R_m$, wherein R_m is hydrogen, alkyl or any other suitable substituent.

The term "carbamate" as used herein refers to compounds based on carbamic acid, $NH_2C(O)OH$.

Use of the above terms is meant to encompass substituted and unsubstituted moieties. Substitution may be by one or more groups such as alcohols, ethers, esters, amides, sulfones, sulfides, hydroxyl, nitro, cyano, carboxy, amines, heteroatoms, lower alkyl, lower alkoxy, lower alkoxycarbonyl, alkoxyalkoxy, acyloxy, halogens, trifluoromethoxy, trifluoromethyl, alkyl, aralkyl, alkenyl, alkynyl, aryl, cyano, carboxy, carboalkoxy, carboxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, alkylheterocyclyl, heterocyclylalkyl, oxo, arylsulfonyl and aralkylaminocarbonyl or any of the substituents of the preceding paragraphs or any of those substituents either attached directly or by suitable linkers. The linkers are typically short chains of 1-3 atoms containing any combination of -C-, -C(O)-, -NH-, -S-, -S(O)-, -O-, -C(O)O- or -S(O)O-. Rings may be substituted multiple times.

The terms "electron-withdrawing" or "electron-donating" refer to the ability of a substituent to withdraw or donate electrons relative to that of hydrogen if hydrogen occupied the same position in the molecule. These terms are well-understood by one skilled in the art and are discussed in Advanced Organic Chemistry by J. March, 1985, pp. 16-18, incorporated herein by reference. Electron withdrawing groups include halo, nitro, carboxyl, lower alkenyl, lower alkynyl, carboxaldehyde, carboxyamido, aryl, quaternary ammonium, trifluoromethyl, and aryl lower alkanoyl among others. Electron donating groups include such groups as hydroxy, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, aryloxy, mercapto, lower alkylthio, lower alkylmercapto, and disulfide among others. One skilled in the art will appreciate that the aforesaid substituents may have electron donating or electron withdrawing properties under

different chemical conditions. Moreover, the present invention contemplates any combination of substituents selected from the above-identified groups.

The most preferred electron donating or electron withdrawing substituents are halo, nitro, alkanoyl, carboxaldehyde, arylalkanoyl, aryloxy, carboxyl, carboxamide, cyano, sulfonyl, sulfoxide, heterocyclyl, guanidine, quaternary ammonium, lower alkenyl, lower alkynyl, sulfonium salts, hydroxy, lower alkoxy, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, amine lower alkyl mercapto, mercaptoalkyl, alkylthio and alkyldithio.

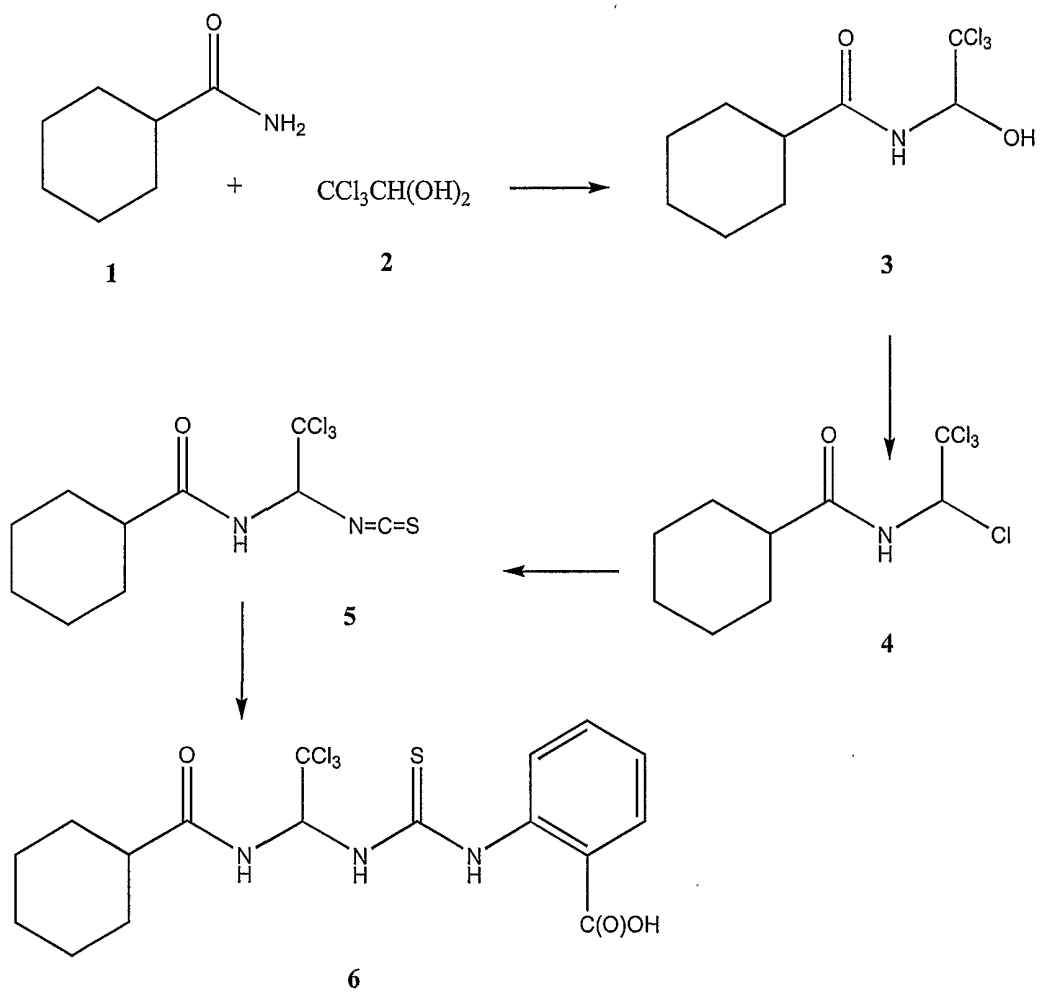
As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from a combination of the specified ingredients in the specified amounts.

The term "optical isomers" as used herein refers to enantiomers which are optically active.

Examples of procedures that may be used to synthesize compounds of the formulae shown above is presented in the following Scheme.

The synthesis of the compounds of the invention is illustrated in Scheme I. A compound of the invention, such as compound **6** was obtained in good yield by treating chloride **4** with potassium thiocyanate followed by reacting the resultant isothiocyanate **5** with anthranilic acid. The chloride was prepared according to a procedure disclosed in Zh. Org. Khim., 24 (2), 453-4, 1988. An alkyl or aryl carboxamide **1** on heating with chloral hydrate **2** in benzene gave the corresponding chloroamide **3**, which was subsequently converted to the corresponding chloride **4** on treatment with thionyl chloride.

Scheme I


O
NH2
+
CCl3CH(OH)2
1
2
O
CCl3
N
H
OH
3
O
CCl3
N
H
Cl
4
O
CCl3
N
H
N=C=S
5
O
CCl3
S
N
H
N
H
N
H
C(O)OH
6

5

10

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 et seq. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphor sulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methane sulfonate, nicotinate, 2-naphthalene sulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or

bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethyl ammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, and ethylammonium among others. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

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

Actual dosage levels of active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active compound(s) which is effective to achieve the desired therapeutic response for a particular patient, compositions and mode of administration. The selected dosage level will depend upon the activity of the particular compound, the route of administration, the severity of the condition being treated and the condition and prior medical history of the patient being treated. However, it is within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. Alternatively, the compound can be administered as a pharmaceutical composition containing the compound of interest in combination with one or more pharmaceutically acceptable excipients. The phrase

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

The total daily dose of the compounds of this invention administered to a human or lower animal may range from about 0.0001 to about 1000 mg/kg/day. For purposes of oral administration, more preferable doses can be in the range from about 0.001 to about 5 mg/kg/day. If desired, the effective daily dose can be divided into multiple doses for purposes of administration; consequently, single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

The present invention also provides pharmaceutical compositions that comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions can be specially formulated for oral administration in solid or liquid form, for parenteral injection or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, parenterally , intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments or drops), bucally or as an oral or nasal spray. The term "parenterally," as used herein, refers

to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

In another aspect, the present invention provides a pharmaceutical composition comprising a component of the present invention and a physiologically tolerable diluent. The present invention includes one or more compounds as described above formulated into compositions together with one or more non-toxic physiologically tolerable or acceptable diluents, carriers, adjuvants or vehicles that are collectively referred to herein as diluents, for parenteral injection, for intranasal delivery, for oral administration in solid or liquid form, for rectal or topical administration, or the like.

The compositions can also be delivered through a catheter for local delivery at a target site, via an intracoronary stent (a tubular device composed of a fine wire mesh), or via a biodegradable polymer. The compounds may also be complexed to ligands, such as antibodies, for targeted delivery.

Compositions suitable for parenteral injection may comprise physiologically acceptable, sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), vegetable oils (such as olive oil), injectable organic esters such as ethyl oleate, and suitable mixtures thereof. These compositions can also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol

and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

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

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

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

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and

sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

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

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

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

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

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

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention

with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

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

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

The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. Prodrugs of the present invention may be rapidly transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press (1987), hereby incorporated by reference.

The present invention contemplates both synthetic compounds of Formulae I, II and III of the present invention, as well as compounds formed by *in vivo* conversion to compounds of the present invention.

Compounds of the present invention may exist as stereoisomers wherein asymmetric or chiral centers are present. These stereoisomers are "R" or "S" depending on the configuration of substituents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present invention may be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

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

The ability of compounds of the present invention to inhibit GlyT1 activity is described in detail hereinafter in the Examples. These Examples are presented to describe preferred embodiments and utilities of the invention and are not meant to limit the invention unless otherwise stated in the claims appended hereto.

Example 1

3-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino)ethyl)amino) methyl)amino)anphthalene-2-carboxylic acid (Compound **6** in Scheme 1) was synthesized according to the following procedure, illustrated by general Scheme I.

Step 1: First, cyclohexyl-*N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamide **3** was synthesized as follows. A mixture of chloral hydrate (9.0 g, 54,5 mmol) and cyclohexane carboxamide (5.0 g, 49.5 mmol) in dry benzene (30 ml) was heated at 80°C in an oil bath. The initial suspension eventually became a clear solution (reaction time depends on the amount of starting materials, in this example it took

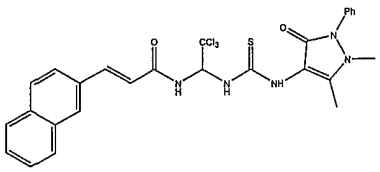
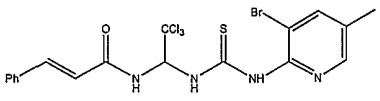
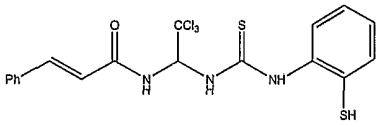
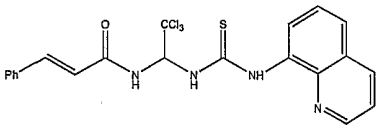
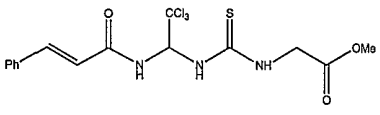
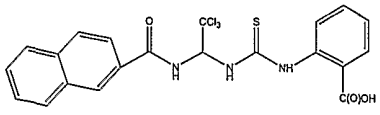
about 6 hours). The mixture was stirred for an additional 30 minutes, then removed from the oil bath, and left at room temperature. Upon cooling, the crystalline solid formed was filtered and washed with hexanes to give the product cyclohexyl-*N*-(2,2,2-trichloro-1-hydroxyethyl)carboxamide **3** (11.0 g). NMR (^{1}H, $CDCl_3$): δ 6.23 (d, J=8.4 Hz, 1H), 5.9 (dd, 1H), 4.35 (broad s, 1H), 2.16 (t, 1H), 1.90-1.22 (m, 10H).

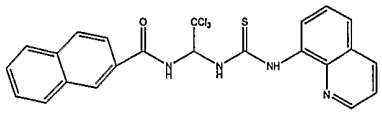
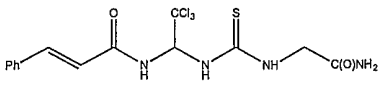
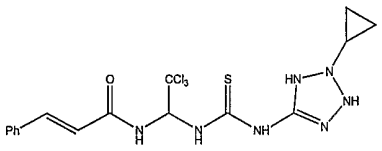
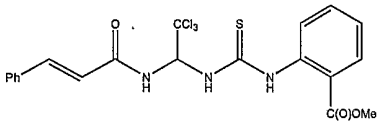
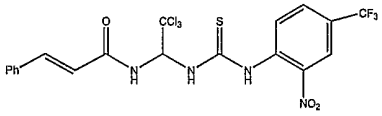
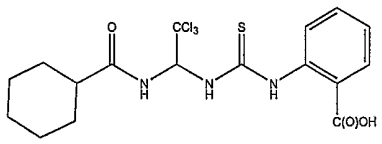
Step 2: Next, cyclohexyl-N-(1,2,2,2-tetrachloro-1-hydroxyethyl) carboxamide **4** was synthesized as follows. A mixture of compound 3 (8.0 g, 20 mmol) and thionyl chloride (4.7 mL, 63.8 mmol, 2.2 equivalents) in dry benzene (30 mL) was heated at 80°C in an oil bath. The initial suspension eventually became a clear solution (reaction time depends on the amount of starting materials, in this example it took about 5 hours). The mixture was stirred for an additional 30 minutes. The solvents were removed by evaporation under reduced pressure (rotovapor), and the resulting white solid was washed with hexanes and filtered, to produce the desired product **4** (7.0 g). NMR (^{1}H, $CDCl_3$): δ 6.59 (d, 1H), 6.30 (d, 1H), 2.19 (m, 1H), 1.89-1.19 (m, 10H).

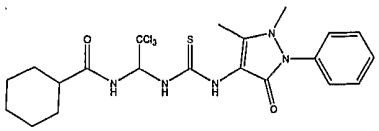
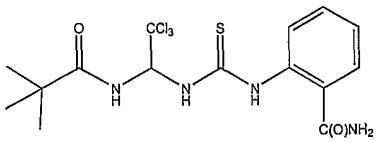
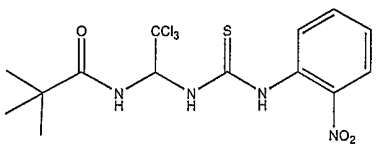
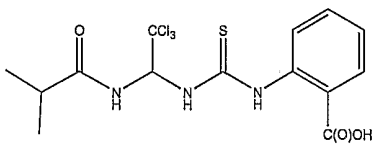
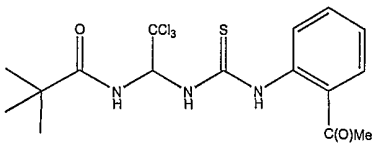
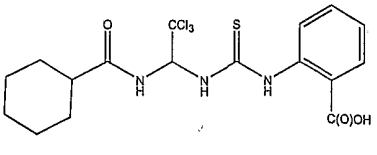
Step 3: Finally, compound **6** was prepared as follows. To a solution of compound **4** (100 mg, 0.34 mmol) in acetonitrile (5.0 mL) was added potassium thiocyanate (0.036 gm 1.1 equivalents). The mixture was stirred for one hour at room temperature when the reaction mixture turned pink. The resulting solid was filtered. The filtrate was treated with a solution of 3-amino-2-naphtholic acid (0.052 gm 1.1 equivalents) and the mixture was stirred for 15 hours to give a solid. The solid was filtered, washed with 5% methanol in ethyl acetate and dried to afford the final product **6** (110 mg).

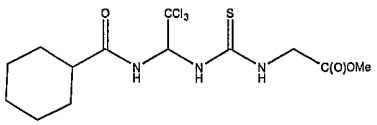
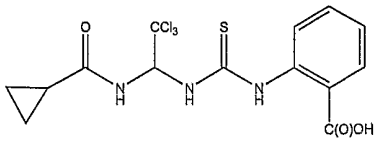
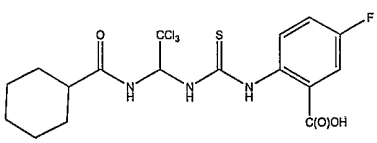
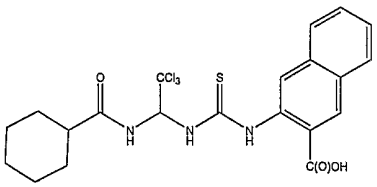
Compounds of Formula I that were synthesized according to the general synthetic procedures are summarized in Table I.

Table I

Structure	Name	Proton NMR δ^1
	(2E)-*N*-(1-(((2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))amino)thioxomethyl) amino)-2,2,2-trichloroethyl)-3-(2-naphthyl)prop-2-enamide	8.40 (s, 1H), 7.98-7.88 (m, 4H), 7.64-7.39 (m, 8H), 3.32 (s, 3H), 3.25 (s, 3H)
	(2E)-*N*-(1-(((benzothiazol-6-ylamino)thioxomethyl) amino)-2,2,2-trichloroethyl)-3-phenylprop-2-enamide	($CDCl_3$) 8.70 (s, 1H), 7.97 (s, 1H), 7.75 (s, 1H), 7.48-7.24 (m, 5H), 6.43 (d, 1H), 6.29 (d, 1H)
	(2E)-3-phenyl-*N*-(2,2,2-trichloro-1-((((2-sulfanylphenyl)amino)thioxo methyl) amino)ethyl)prop-2-enamide	7.65-7.28 (m, 9H), 6.90 (m, 1H), 7.74 (t, 4H), 6.61 (d, 1H)
	(2E)-3-phenyl-*N*-(2,2,2-trichloro-1-(((8-quinolylamino)thioxo methyl)amino)ethyl)prop-2-enamide	9.16, (d, 1H), 8.88 (s, 1H), 8.31 (d, 1H), 7.69-7.57 (m, 9H), 7.38 (s, 1H), 6.76 (d, 1H)
	methyl 2-((((1-((2E)-3-phenylprop-2-enoylamino)-2,2,2-trichloroethyl)amino)thioxo methyl) amino)acetate	7.65-7.38 (m, 7H), 6.73 (d, 1H), 4.26 (ABq, 2H)
	2-((thioxo((2,2,2-trichloro-1-(2-naphthylcarbonylamino) ethyl)amino)methyl)amino) benzoic acid	8.40 (s, 1H), 8.18 (d, 1H), 8.46 (d, 1H), 8.00-7.88 (m, 4H), 7.76 (s, 1H), 7.63-7.53 (m, 3H), 7.24 (t, 1H)

	2-naphthyl-*N*-(2,2,2-trichloro-1-((8-quinolylamino)thioxo methyl)amino)ethyl) carboxamide	9.02, (d, 1H), 8.88 (m, 1H), 8.42 (s, 1H), 8.32 (d, 1H), 8.01-7.90 (m, 4H), 7.82 (s, 1H), 7.7-7.53 (m, 5H)
	(2E)-*N*-(1-(((carbamoylmethyl)amino) thioxomethyl)amino)-2,2,2-trichloroethyl)-3-phenylprop-2-enamide	7.66 (m, 7H), 6.73 (d, 1H), 4.26 (ABq, 2H)
	(2E)-3-phenyl-*N*-(2,2,2-trichloro-1-(((2-cyclopropyl(1,2,3,4-tetraazolin-5-yl))amino)thioxo methyl)amino)ethyl) prop-2-enamide	7.68-7.38 (m, 4H), 7.43 (m, 4H), 6.70 (d, 1H), 2.26 (br m, 1H), 1.17 (br m, 2H), 1.03 (br m, 1H)
	methyl 2-((((1-((2E)-3-phenylprop-2-enoylamino)-2,2,2-trichloroethyl)amino) thioxomethyl) amino)benzoate	8.04 (d, 1H), 7.98 (d, 1H), 7.67-7.53(m, 4H), 7.39 (m, 4H), 7.26 (t, 1H), 6.75 (d, 1H), 3.90 (s, 3H)
	(2E)-3-phenyl-N-(2,2,2-trichloro-1-((((2-nitro-4-(trifluoromethyl)phenyl) amino) thioxomethyl)amino) ethyl)prop-2-enamide	8.43 ((d, 1H), 8.38 (s, 1H), 7.68-7.35 (m, 7H), 6.75 (d, 1H)
	2-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino) ethyl)amino)methyl)amino) benzoic acid	8.19 (d, 1H), 8.03 (d, 1H), 7.53 (t, 1H), 7.44 (s, 1H), 7.22 (t, 1H), 2.30 (m, 1H), 1.81-1.26 (m, 10H)

	*N*-(1-((((2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl)amino)thioxomethyl) amino)-2,2,2-trichloroethyl) cyclohexylcarboxamide	7.55-7.37 (m, 5H), 7.27 (s, 1H), 3.28 (s, 3H), 3.22 (s, 3H), 2.32 (m, 1H), 1.77-1.24 (m, 10H)
	2-((((1-(2,2-dimethyl propanoylamino)-2,2,2-trichloroethyl)amino)thioxo methyl)amino)benzamide	7.89 (d, 1H), 7.68 (d, 1H), 7.51 (t, 1H), 7.46 (s, 1H), 7.29 (t, 1H), 1.21 (s, 9H)
	2,2-dimethyl-*N*-(2,2,2-trichloro-1-((((2-nitrophenyl)amino)thioxo methyl)amino)ethyl) propanamide	8.06 (d, 1H), 7.88 (d, 1H), 7.68 (t, 1H), 7.42 (t, 1H), 7.39 (s, 1H), 1.22 (s, 9H)
	2-((thioxo((2,2,2-trichloro-1-(2-methylpropanoyl amino)ethyl)amino)methyl) amino) benzoic acid	8.19 (d, 1H), 8.03 (d, 1H), 7.54 (t, 1H), 7.44 (s, 1H), 7.22 (t, 1H), 2.55 (m, 3H), 1.40 (2d, 6H)
	*N*-(1-((((2-acetylphenyl)amino)thioxo methyl)amino)-2,2,2-trichloroethyl)-2,2-dimethylpropanamide	8.05 (d, 1H), 7.95 (d, 1H), 7.56 (t,1H), 7.46 (s, 1H), 7.30 (t, 1H), 2.62 (s, 3H), 1.21 (s, 9H)
	2-((2,2,2-trichloro-1-(cyclohexylcarbonylamino) ethyl)amino)benzoic acid	7.96 (d, 1H), 7.37 (t, 1H), 6.77 (m, 2H), 6.21 (s, 1H), 2.27 (m, 1H), 1.79-1.28 (m, 10H)

	methyl 2-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino) ethyl)amino)methyl)amino) acetate	7.26 (s, 1H), 4.34 (ABq, 2H), 3.73 (s, 3H), 2.29 (t, 1H), 1.81-1.28 (m, 10H)
	2-((thioxo((2,2,2-trichloro-1-(cyclopropylcarbonylamino) ethyl)amino)methyl) amino)benzoic acid	8.21 (d, J=7.5 Hz, 1H), 8.03 (d, J=8.1 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.49 (s, 1H), 7.21 (t, J=7.5 Hz, 1H), 1.71 (m, 1H), 0.95-0.81 (m, 4H)
	5-fluoro-2-((thioxo((2,2,2-trichloro-1-(cyclopropylcarbonylamino) ethyl)amino) methyl) amino)benzoic acid	8.51 (d, J= 11.4 Hz, 1H), 8.1 (br, 1H), 7.44 (s, 1H), 6.81 (br, 1H), 2.28 (t, 1H), 1.81-1.26 (m, 10H)
	3-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino) ethyl)amino) methyl)amino)naphthalene-2-carboxylic acid	8.65 (s, 1H), 8.51 (s, 1H), 7.95 (d, J=8.1 Hz, 1H), 7.84 (d, J=8.1 Hz, 1H), 7.60 (t, J= 6.9 Hz, 1H), 7.52 (t, J= 6.9 Hz, 1H), 2.92 (t, 1H), 1.9-1.3 (m, 10H)

1= measured in CD_3OD unless otherwise indicated

Example 2

The ability of compounds to inhibit GlyT1 activity was determined in an assay that utilizes human U373MG astrocytoma cells. The cells were seeded into 96-well plates at 1 x 10^4 cells per well in 0.1 ml of culture medium, and were allowed to grow for an additional two days to come to confluence. Prior to the start of transport studies, the cells were washed thoroughly with Kreb's-Ringer phosphate buffer containing 140 mM NaCl, 5 mM KCl and 0.75 mM $CaCl_2$. One set of triplicate wells was washed with chloride-free buffer to serve as a measure of

low affinity glycine transport, since high-affinity uptake requires Cl^-. Test compounds (10 μM) dissolved in fresh buffer, as well as buffer-only controls, were added to the assay plate (50 μl/well). Uptake analyses were initiated by the addition of buffer containing [^{3}H]glycine (0.5 μCi/well), with a final glycine concentration of 100 nM. Glycine uptake was terminated after an 8 minute period by removing the medium and washing the cells with buffer. The cells in each well were subsequently solubilized in detergent to allow scintillation counting of the internalized [^{3}H]glycine. Untreated cells were lysed prior to initiation of the assay for protein determinations, using the BCA assay (Pierce Chemical Company, Rockford, IL). Glycine uptake is expressed as nmoles glycine/mg protein/min.

When the compounds of Table 1 are tested according to the above procedure, they are shown to inhibit high-affinity glycine uptake by the astrocytoma cells.

All references cited are hereby incorporated by reference.

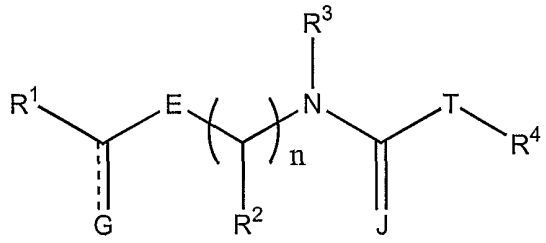
The present invention is illustrated by way of the foregoing description and examples. The foregoing description is intended as a non-limiting illustration, since many variations will become apparent to those skilled in the art in view thereof. It is intended that all such variations within the scope and spirit of the appended claims be embraced thereby.

Changes can be made in the composition, operation and arrangement of the method of the present invention described herein without departing from the concept and scope of the invention as defined in the following claims:

Claims

We claim:

1. A compound of Formula I:



Formula I

wherein n is an integer of from zero to three;

J is selected from the group consisting of O, S and NR^5;

T is selected from the group consisting of O, S and NR^6;

G is selected from the group consisting of =O, =S, $=NR^7$, $-OR^8$, $-SR^9$ and $-NR^{10}$;

E is selected from the group consisting of O, S and NR^{11};

R^3, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, aliphatic acyl, -C_1-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino,-C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -CH=NOH, -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxycarbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, heterocyclyl, heterocycloyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, -SO_2-(C_1-C_3 alkyl), -SO_3-(C_1-C_3 alkyl), sulfonamido, carbamate, aryloxyalkyl, carboxyl, and -C(O)NH(benzyl); and

R^1, R^2, and R^4 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy,

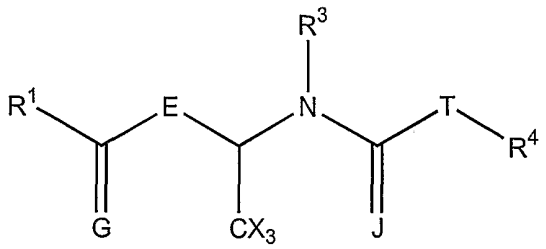
alkenoxy, alkynoxy, thioalkoxy, hydroxyalkyl, aliphatic acyl, $-CF_3$, nitro, amino, cyano, carboxy, $-N(C_1-C_3\ alkyl)-C(O)(C_1-C_3\ alkyl)$, $-NHC(O)NH(C_1-C_3\ alkyl)$, $-NHC(O)N(C_1-C_3\ alkyl)C(O)NH(C_1-C_3\ alkyl)$, $-C_1-C_3$ alkylamino, alkenylamino, alkynylamino, $di(C_1-C_3\ alkyl)$amino, $-C(O)O-(C_1-C_3\ alkyl)$, $-C(O)NH-(C_1-C_3\ alkyl)$, $-CH=NOH$, $-PO_3H_2$, $-OPO_3H_2$, $-C(O)N(C_1-C_3\ alkyl)_2$, haloalkyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, diarylamino, heterocyclyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, sulfonyl, $-SO_2-(C_1-C_3\ alkyl)$, $-SO_3-(C_1-C_3\ alkyl)$, sulfonamido, aryloxyalkyl, carboxyl, carbamate and -C(O)NH(benzyl);

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

or a pharmaceutically acceptable salt thereof.

2. A compound as in claim 1 wherein n may be one; G may be =O; J may be =S; E may be $-NR^{11}$; and T may be $-NR^6$.

3. A compound of Formula II:



Formula II

wherein X, at each occurrence, is independently selected from the group consisting of -Cl, -F, -Br and -I;

J is selected from the group consisting of O, S and NR^5;

T is selected from the group consisting of O, S and NR^6;

G is selected from the group consisting of O, S, NR^7;

E is selected from the group consisting of O, S and NR^{11};

R^3, R^5, R^6, R^7 and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, aliphatic acyl, -C_1-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino, -C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -CH=NOH, -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxycarbonyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, heterocyclyl, heterocycloyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, -SO_2-(C_1-C_3 alkyl), -SO_3-(C_1-C_3 alkyl), sulfonamido, carbamate, aryloxyalkyl, carboxyl, and -C(O)NH(benzyl); and

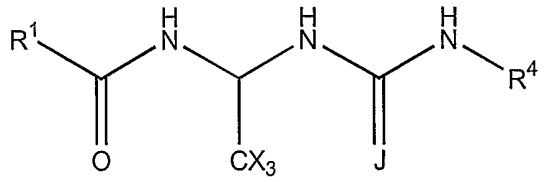
R^1 and R^4 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, thioalkoxy, hydroxyalkyl, aliphatic acyl, -CF_3, nitro, amino, cyano, carboxy, -N(C_1-C_3 alkyl)-C(O)(C_1-C_3 alkyl), -NHC(O)NH(C_1-C_3 alkyl), -NHC(O)N(C_1-C_3 alkyl)C(O)NH(C_1-C_3 alkyl), -C_1-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino, -C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -CH=NOH, -PO_3H_2, -OPO_3H_2, -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, diarylamino, heterocyclyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, sulfonyl, -SO_2-(C_1-C_3 alkyl), -SO_3-(C_1-C_3 alkyl), sulfonamido, aryloxyalkyl, carboxyl, carbamate and -C(O)NH(benzyl);

wherein R^1, R^3, R^4, R^5, R^6, R^7 and R^{11} are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

or a pharmaceutically acceptable salt thereof.

4. A compound as in claim 3 wherein G may be O, J may be =S, E may be NR^{11} and T may be NR^6.

5. A compound of Formula III:



Formula III

wherein X, at each occurrence, is selected from the group consisting of -Cl, -F, -Br and -I;

J is selected from the group consisting of O, S and NR^5; and

R^1 and R^4 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, thioalkoxy, hydroxyalkyl, aliphatic acyl, $-CF_3$, carboxy, $-C_1$-C_3 alkylamino, alkenylamino, alkynylamino, di(C_1-C_3 alkyl)amino, -C(O)O-(C_1-C_3 alkyl), -C(O)NH-(C_1-C_3 alkyl), -C(O)N(C_1-C_3 alkyl)$_2$, haloalkyl, alkoxyalkoxy, carboxaldehyde, carboxamide, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, aryl, aroyl, aryloxy, arylamino, biaryl, thioaryl, diarylamino, heterocyclyl, alkylaryl, aralkenyl, aralkyl, alkylheterocyclyl, heterocyclylalkyl, aryloxyalkyl, carboxyl, carbamate and -C(O)NH(benzyl);

wherein R^1, R^4 and R^5 are unsubstituted or substituted with at least one electron donating or electron withdrawing group;

or a pharmaceutically acceptable salt thereof.

6. A compound of claim 5 wherein X, at each occurrence, is -Cl, and J is =S.

7. A compound as in claim 1 selected from the group consisting of:

(2E)-*N*-(1-(((2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl))amino)thioxomethyl)amino)-2,2,2-trichloroethyl)-3-(2-naphthyl)prop-2-enamide, (2E)-*N*-(1-(((benzothiazol-6-ylamino)thioxomethyl)amino)-2,2,2-trichloroethyl)-3-phenylprop-2-enamide, (2E)-3-phenyl-*N*-(2,2,2-trichloro-1-((((2-sulfanylphenyl)amino)thioxomethyl) amino)ethyl)prop-2-enamide, (2E)-3-phenyl-*N*-(2,2,2-trichloro-1-(((8-quinolylamino)thioxomethyl)amino)ethyl)prop-2-enamide, methyl 2-((((1-((2E)-3-phenylprop-2-enoylamino)-2,2,2-trichloroethyl)amino)thioxomethyl) amino)acetate, 2-((thioxo((2,2,2-trichloro-1-(2-naphthylcarbonylamino)ethyl) amino)methyl)amino)benzoic acid, 2-naphthyl-*N*-(2,2,2-trichloro-1-((8-quinolylamino)thioxomethyl)amino)ethyl)carboxamide, (2E)-*N*-(1-(((carbamoylmethyl)amino)thioxomethyl)amino)-2,2,2-trichloroethyl)-3-phenylprop-2-enamide, (2E)-3-phenyl-*N*-(2,2,2-trichloro-1-(((2-cyclopropyl(1,2,3,4-tetraazolin-5-yl))amino)thioxomethyl)amino)ethyl)prop-2-enamide, methyl 2-((((1-((2E)-3-phenylprop-2-enoylamino)-2,2,2-trichloroethyl)amino)thioxomethyl) amino)benzoate, (2E)-3-phenyl-*N*-(2,2,2-trichloro-1-((((2-nitro-4-(trifluoromethyl)phenyl)amino) thioxomethyl)amino) ethyl)prop-2-enamide, 2-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino) ethyl)amino)methyl)amino)benzoic acid, *N*-(1-((((2,3-dimethyl-5-oxo-1-phenyl(3-pyrazolin-4-yl)amino)thioxomethyl)amino)-2,2,2-trichloroethyl) cyclohexylcarboxamide, 2-((((1-(2,2-dimethylpropanoylamino)-2,2,2-trichloroethyl)amino)thioxomethyl)amino)benzamide, 2,2-dimethyl-*N*-(2,2,2-trichloro-1-((((2-nitrophenyl)amino)thioxomethyl)amino)ethyl)propanamide, 2-((thioxo((2,2,2-trichloro-1-(2-methylpropanoylamino)ethyl)amino)methyl)amino) benzoic acid, *N*-(1-((((2-acetylphenyl)amino)thioxomethyl)amino)-2,2,2-trichloroethyl)-2,2-dimethylpropanamide, 2-((2,2,2-trichloro-1-(cyclohexylcarbonylamino)ethyl)amino)benzoic acid, methyl 2-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino)ethyl)amino)methyl)amino)acetate, 5-

fluoro-2-((thioxo((2,2,2-trichloro-1-(cyclopropylcarbonylamino)ethyl)amino) methyl) amino)benzoic acid, 2-((thioxo((2,2,2-trichloro-1-(cyclopropylcarbonylamino)ethyl)amino)methyl) amino)benzoic acid and 3-((thioxo((2,2,2-trichloro-1-(cyclohexylcarbonylamino)ethyl)amino) methyl)amino)naphthalene-2-carboxylic acid.

8. A pharmaceutical composition comprising a compound of claim1 in a pharmaceutically acceptable carrier.

9. A method for selectively inhibiting glycine transporters in a mammal comprising administering to said mammal a therapeutic amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

Inte_____onal application No.
PCT/US01/28481

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/313, 353, 381, 404, 542, 562, 586; 546/171, 305; 548/251, 368.4; 564/27; 560/16; 562/426, 427

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS ON STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/34790 A1 (OGNYANOV ET AL.) 15 July 1999 (15.07.99), entire document.	1-9
Y	WO 97/45115 A1 (OGNYANOV ET AL.) 04 December 1997 (04.12.97), entire document.	1-9
Y	WO 97/45423 A1 (OGNAYANOV ET AL.) 04 December 1997 (04.12.97), entire document.	1-9
Y	WO 99/44596 A2 (LUYTEN ET AL.) 10 September 1999 (10.09.99), entire document.	1-9
Y	WO 99/45011 A1 (LUYTEN ET AL.) 10 September 1999 (10.09.99), entire document.	1-9

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

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
22 JANUARY 2002	15 FEB 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Felicia D. Bleets for BRIAN J. DAVIS
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/28431

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C07D 211/72, 211/84, 213/72, 213/75, 215/38, 231/44, 231/50, 257/06, 335/16; A01N 37/12, 37/18, 37/44, 43/40, 43/56, 43/64, 47/28; A61K 31/17, 31/41, 31/44, 31/195, 31/235, 31/415, 31/445

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/313, 353, 381, 404, 542, 562, 586; 546/171, 305; 548/251, 368.4; 564/27; 560/16; 562/426, 427