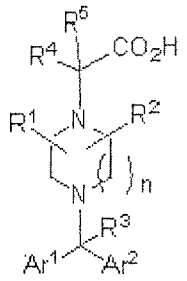
Claims:

1. A method of making a compound Formula (I):



(I)

wherein:

n is an integer from 1 to 3;

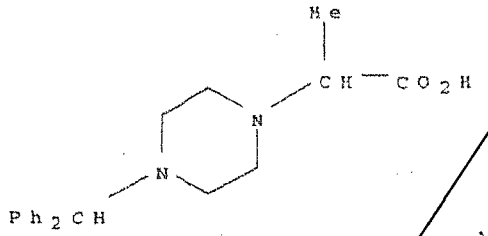
R^1 and R^2 are independently selected from hydrogen, alkyl, haloalkyl, alkoxy, haloalkoxy, aryl, heteroaryl, cycloalkyl, or heterocyclyl wherein the aforementioned rings are optionally substituted with R^a, R^b, or R^c independently selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, monosubstituted amino, or disubstituted amino; or

R^1 and R^2, when attached to the same carbon atom, can combine to form cycloalkyl or monocyclic saturated heterocyclyl to give a spiro ring wherein the cycloalkyl or monocyclic saturated heterocyclyl can be optionally substituted with R^d, R^e, or R^f independently selected from alkyl, alkoxy, fluoro, fluoroalkyl, fluoroalkoxy, hydroxy, monosubstituted amino, or disubstituted amino; or

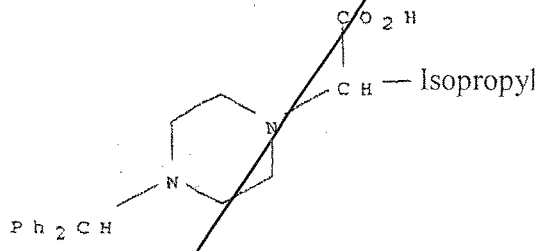
R^1 and R^2, when attached to carbon atoms 2 and 5 or 3 and 6 positions of the piperazine ring, can combine to form $-C_1$-C_3- alkylene chain wherein one of the carbon atoms in the alkylene chain is optionally replaced by a –NR-, -O-, -S(O)n1- (where R is hydrogen or alkyl and n1 is 0-2) and further wherein one or two hydrogen atoms in the alkylene chain can be optionally substituted with one or two alkyl;

R^3, R^4 and R^5 are independently hydrogen, alkyl, fluoro, or fluoroalkyl; and

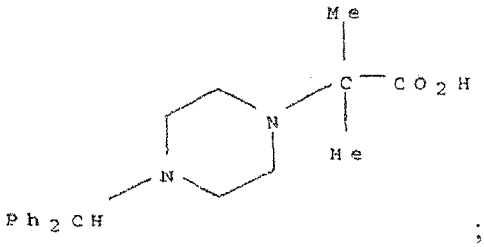
Ar^1 and Ar^2 are independently aryl, heteroaryl, cycloalkyl, or heterocyclyl where each of the aforementioned ring is optionally substituted with R^g, R^h or R^i where R^g is alkyl, -C≡C-R^6 (where R^6 is aryl or heteroaryl), halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, or acylamino and R^h and R^i are independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, acylamino, aryl, heteroaryl, cycloalkyl, or heterocyclyl where the aromatic or alicyclic ring in R^g, R^h and R^i is optionally substituted with R^j, R^k or R^l which are independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, or acylamino; provided that the compound of Formula (I) is not any one of:



,



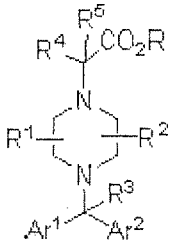
, or



;

comprising:

(a) hydrolyzing the ester group in a compound of formula:



where R is alkyl and R^1, R^2, R^3, R^4, R^5, Ar^1 and Ar^2 groups are as defined above; under acidic or basic hydrolysis reaction conditions;

(b) optionally modifying any of the R^1, R^2, R^3, R^4, R^5, Ar^1 and Ar^2 groups to provide a compound of Formula (I);

(c) optionally forming an acid addition salt of the compound of Formula (I) obtained from Step (a) and/or (b) above;

(d) optionally separating stereoisomers of the compound of Formula (I) obtained from Step (a), (b), and/or (c) above;

provided that when R^1, R^2, R^3, R^4 and R^5 are hydrogen and Ar^1 is phenyl then Ar^2 is not phenyl or 4-chlorophenyl or a salt thereof.

2. The process of Claim 1 where the compound of Formula (I) is where:

R^1 and R^2 are independently hydrogen or alkyl;

R^3, R^4, and R^5 are hydrogen; and

Ar^1 and Ar^2 are independently phenyl, each ring optionally substituted with R^g or R^h where R^g and R^h are independently alkyl, halo, haloalkyl, haloalkoxy, alkylthio, alkoxy, alkylcarbonyl, or alkoxycarbonyl and the stereochemistry at the carbon carrying the R^3, Ar^1 and Ar^2 group is (R).

3. The process of Claim 2 wherein:

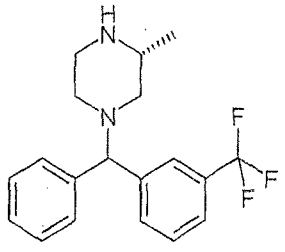
R^1 is hydrogen;

R^2 is hydrogen or methyl where methyl is at the 2- position of piperazine ring the nitrogen atom of the piperazine ring carrying $-CH_2CO_2H$ group is the 1 position;

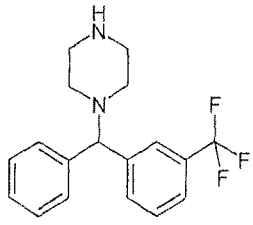
Ar^1 is phenyl; and

Ar^2 is phenyl substituted with R^g where R^g is trifluoromethyl and is attached to the 3-position of the phenyl ring the ring atom attached to the $-CR^3Ar^2$ being position 1 and the stereochemistry at the carbon carrying the R^3, Ar^1 and Ar^2 group is (R).

4. A compound selected from the group consisting of:

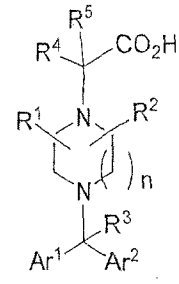


;



or a salt thereof.

5. Use of a compound of Formula (I):



(I)

wherein:

n is an integer from 1 to 3;

R^1 and R^2 are independently selected from hydrogen, alkyl, haloalkyl, alkoxy, haloalkoxy, aryl, heteroaryl, cycloalkyl, or heterocyclyl wherein the aforementioned rings are optionally substituted with R^a, R^b, or R^c independently selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, monosubstituted amino, or disubstituted amino; or

R^1 and R^2, when attached to the same carbon atom, can combine to form cycloalkyl or monocyclic saturated heterocyclyl to give a spiro ring wherein the cycloalkyl or monocyclic saturated heterocyclyl can be optionally substituted with R^d, R^e, or R^f independently selected from alkyl, alkoxy, fluoro, fluoroalkyl, fluoroalkoxy, hydroxy, monosubstituted amino, or disubstituted amino; or

R^1 and R^2, when attached to carbon atoms 2 and 5 or 3 and 6 positions of the piperazine ring, can combine to form $-C_1$-C_3- alkylene chain wherein one of the carbon atoms in the alkylene chain is optionally replaced by a –NR-, -O-, -S(O)n1- (where R is hydrogen or alkyl and n1 is 0-2) and further wherein one or two hydrogen atoms in the alkylene chain can be optionally substituted with one or two alkyl;

R^3, R^4 and R^5 are independently hydrogen, alkyl, fluoro, or fluoroalkyl; and

Ar^1 and Ar^2 are independently aryl, heteroaryl, cycloalkyl, or heterocyclyl where each of the aforementioned ring is optionally substituted with R^g, R^h or R^i where R^g is alkyl, $-C\equiv C-R^6$ (where R^6 is aryl or heteroaryl), halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, or acylamino and R^h and R^i are independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, acylamino, aryl, heteroaryl, cycloalkyl, or heterocyclyl where the aromatic or alicyclic ring in R^g, R^h and R^i is optionally substituted with R^j, R^k or R^l which are independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl,

aminocarbonyl, or acylamino; or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient in the manufacture of a pharmaceutical composition for treating a disease treatable by inhibition of GlyT1 receptor in a patient wherein the pharmaceutical composition is administered in combination with an antipsychotic agent.

6. The use of Claim 5 wherein:

n is 1;

R^1 and R^2 are independently selected from hydrogen, alkyl, haloalkyl, alkoxy, haloalkoxy, aryl, heteroaryl, cycloalkyl, or heterocyclyl wherein the aforementioned rings are optionally substituted with R^a, R^b, or R^c independently selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, monosubstituted amino, or disubstituted amino; or

R^1 and R^2, when attached to the same carbon atom, can combine to form cycloalkyl or monocyclic saturated heterocyclyl to give a spiro ring wherein the cycloalkyl or monocyclic saturated heterocyclyl can be optionally substituted with R^d, R^e, or R^f independently selected from alkyl, alkoxy, fluoro, fluoroalkyl, fluoroalkoxy, hydroxy, monosubstituted amino, or disubstituted amino; or

R^1 and R^2, when attached to carbon atoms 2 and 5 or 3 and 6 positions of the piperazine ring, can combine to form $-C_1$-C_3- alkylene chain wherein one of the carbon atoms in the alkylene chain is optionally replaced by a –NR-, -O-, -S(O)n1- (where R is hydrogen or alkyl and n1 is 0-2) and further wherein one or two hydrogen atoms in the alkylene chain can be optionally substituted with one or two alkyl; and

Ar^1 and Ar^2 are independently aryl, heteroaryl, cycloalkyl, or heterocyclyl where each of the aforementioned ring is optionally substituted with R^g, R^h or R^i where R^g is alkyl, halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, or acylamino and R^h and R^i are independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, acylamino, aryl, heteroaryl, cycloalkyl, or heterocyclyl where the aromatic or alicyclic ring in R^g, R^h and R^i is optionally substituted with R^j, R^k or R^l which are independently selected from alkyl, halo, haloalkyl, haloalkoxy,

alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, or acylamino.

7. The use of Claim 6 wherein R^1 and R^2 are hydrogen.

8. The use of Claim 6 wherein R^1 and R^2 are independently selected from hydrogen, alkyl, haloalkyl, alkoxy, or haloalkoxy provided that at least one of R^1 and R^2 is other than hydrogen.

9. The use of Claim 6 wherein R^1 is hydrogen and R^2 is alkyl.

10. The use of Claim 6 wherein R^1 and R^2 are attached to the same carbon atom and are combined to form cycloalkyl optionally substituted with R^d, R^e or R^f independently selected from alkyl, alkoxy, fluoro, fluoroalkyl, fluoroalkoxy, hydroxy, monosubstituted amino, or disubstituted amino.

11. The use of Claim 6 wherein R^1 and R^2 are attached to the same carbon atom and are combined to form monocyclic saturated heterocyclyl which are optionally substituted with R^d, R^e or R^f independently selected from alkyl, alkoxy, fluoro, fluoroalkyl, fluoroalkoxy, hydroxy, monosubstituted amino, or disubstituted amino.

12. The use of Claim 6 wherein R^1 and R^2 are attached to carbon atoms 2 and 5 or 3 and 6 positions of the piperazine ring, and are combined to form $-C_1$-C_2- alkylene chain wherein one or two hydrogen atoms in the alkylene chain can be optionally substituted with one or two alkyl.

13. The use of Claim 6 wherein R^1, R^2, R^3, R^4 and R^5 are hydrogen and Ar^1 and Ar^2 are phenyl optionally substituted with R^g, R^h or R^i.

14. The use of Claim 6 wherein R^1, R^3, R^4, and R^5 are hydrogen, R^2 is alkyl, and Ar^1 and Ar^2 are phenyl optionally substituted with R^g, R^h or R^i.

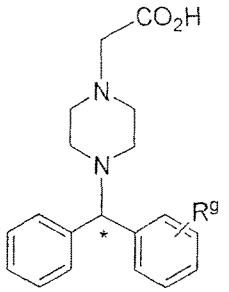
15. The use of Claim 6 wherein R^1, R^2, R^3, R^4 and R^5 are hydrogen, Ar^1 is phenyl optionally substituted with R^g, R^h or R^i and Ar^2 is cycloalkyl.

16. The use of Claim 6 wherein R^1, R^3, R^4, and R^5 are hydrogen, R^2 is alkyl, Ar^1 is phenyl optionally substituted with R^g, R^h or R^i and Ar^2 is cycloalkyl.

17. The use of Claim 6 wherein R^1, R^2, R^3, R^4 and R^5 are hydrogen, Ar^1 is phenyl and Ar^2 is heteroaryl, each ring optionally substituted with R^g, R^h or R^i.

18. The use of Claim 6 wherein R^1, R^3, R^4, and R^5 are hydrogen, R^2 is alkyl, Ar^1 is phenyl and Ar^2 is heteroaryl, each ring optionally substituted with R^g, R^h or R^i.

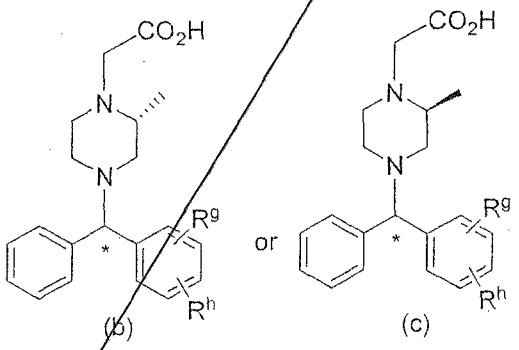
19. The use of Claim 6 wherein the compound has the structure:



(a)

R^g is alkyl, halo, haloalkyl, or haloalkoxy and is attached to the 3-position of the phenyl ring and the stereochemistry at *C is (*R*).

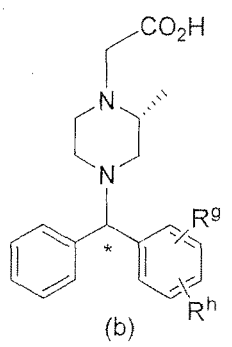
20. The use of Claim 6 wherein the compound has the structure:

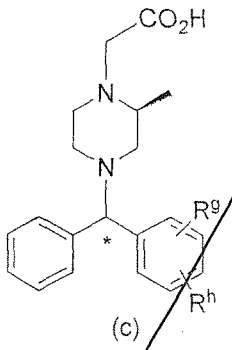


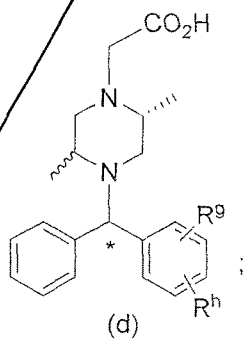
(b) (c)

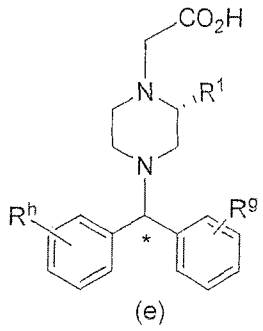
where R^g and R^h are independently hydrogen, alkyl, halo, haloalkyl, or haloalkoxy.

21. The use of Claim 6 wherein the compound of Formula (I) has one of the following structures:


(b)


(c)


(d)


(e)

where R^1 is hydrogen or methyl and R^h is cyano, heteroaryl or phenyl, each ring is optionally substituted with alkyl and R^g is alkyl, halo, haloalkyl, or haloalkoxy.

22. The use of Claim 21 wherein R^g is located at the 3-position of the phenyl ring and the stereochemistry at *C is (*R*).

23. The use of Claim 6 wherein the compound is selected from a group consisting of:

(*R*)-2-(4-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-(4-((3-bromophenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

2-(4-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-(4-((3,5-dichlorophenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

(*S*)-2-(4-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-(4-((4-bromophenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

2-(4-(phenyl(4-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-(4-((2-bromophenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

2-(4-((3-biphenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

(*S*)-2-(4-((4-bromophenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

(*R*)-2-(4-((4-bromophenyl)(phenyl)methyl)piperazin-1-yl)acetic acid ;

(*S*)-2-(4-((3-bromophenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

(*R*)-2-(4-((3-bromophenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-4-((3-bromophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

(*R*)-2-(4-benzhydryl-2-methylpiperazin-1-yl)acetic acid ;

2-((*R*)-4-((*R*)-(3-iodophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*R*)-(3-bromophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*S*)-(3-bromophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-(biphenyl-3-yl-(phenyl)-methyl)-piperazin-1-yl)-acetic acid;

2-((*R*)-2-methyl-4-((*S*)-phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*R*)-phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-4-((4-chlorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-(biphenyl-4-yl-(phenyl)-methyl)-piperazin-1-yl)-acetic acid;

2-((*R*)-4-((4-bromophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((4-cyanophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((3-chlorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

[(*R*)-4-((*R*)-biphenyl-3-yl-(phenyl)-methyl)-2-methyl-piperazin-1-yl]-acetic acid;

2-((*R*)-2-methyl-4-((3-(methylthio)phenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-4-((*S*)-(2-bromophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*R*)-(2-bromophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*R*)-phenyl(m-tolyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-4-((*R*)-(3-isopropylphenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((4-fluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((3-fluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*R*)-phenyl(3-(thiophen-2-yl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*R*)-(3-(methylthio)phenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*S*)-(3-(methylthio)phenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*R*)-(4-(methylthio)phenyl)(phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-4-((*S*)-(2-fluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*R*)-(2-fluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*S*)-phenyl(3-(trifluoromethoxy)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*R*)-phenyl(3-(trifluoromethoxy)phenyl)methyl)piperazin-1-yl)acetic acid;

[(*R*)-4-((*R*)-(biphenyl-4-yl)-(phenyl)-methyl)-2-methyl-piperazin-1-yl]-acetic acid;

{(*R*)-2-methyl-4-[(*R*)-(2'-methyl-biphenyl-4-yl)-(phenyl)-methyl]-piperazin-1-yl]-acetic acid;

{(*R*)-2-methyl-4-[(*R*)-(3'-methyl-biphenyl-4-yl)-(phenyl)-methyl]-piperazin-1-yl]-acetic acid;

{(*R*)-2-methyl-4-[(*R*)-(4'-methyl-biphenyl-4-yl)-(phenyl)-methyl]-piperazin-1-yl]-acetic acid;

2-((*R*)-4-((*S*)-(2,4-difluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*R*)-(2,4-difluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*S*)-(4-fluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*R*)-(4-fluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*S*)-(3-fluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((*R*)-(3-fluorophenyl)(phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*R*)-phenyl(4-(2-phenylethynyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((R)-phenyl(3-(2-pyridin-3-ylethynyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((R)-phenyl(3-(2-pyridin-4-ylethynyl)phenyl)methyl)piperazin-1-yl)acetic acid;

(*S*)-2-(4-benzhydryl-2-methylpiperazin-1-yl)acetic acid;

2-((*S*)-2-methyl-4-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

(*S*)-2-(4-benzhydryl-3-methylpiperazin-1-yl)acetic acid;

(*R*)-2-(4-benzhydryl-3-methylpiperazin-1-yl)acetic acid;

2-((2,5-*trans*)-4-benzhydryl-2,5-dimethylpiperazin-1-yl)acetic acid;

2-((2,5-*cis*)-4-benzhydryl-2,5-dimethylpiperazin-1-yl)acetic acid;

2-((*R*)-3-methyl-4-(phenyl(4-diphenyl)methyl)piperazin-1-yl)acetic acid;

(*R*)-2-(4-(bis(3-chlorophenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

(*R*)-2-(4-(bis(3-fluorophenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-(4-((3-(trifluoromethyl)phenyl)(4-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-(4-((4-fluorophenyl)(3-(diphenyl)methyl))-(*R*)-2-methylpiperazin-1-yl)acetic acid

(*R*)-2-(4-(bis(4-chlorophenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-((*R*)-4-((3-bromophenyl)(4-fluorophenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

(*R*)-2-(4-(bis(4-fluorophenyl)methyl)-3-methylpiperazin-1-yl)acetic acid ;

(*R*)-2-(4-(bis(4-fluorophenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

(*R*)-2-(4-(bis(3-(trifluoromethyl)phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

2-(4-(bis(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-(thiophen-2-yl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*R*)-thiophen-2-yl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-2-methyl-4-((*S*)-thiophen-2-yl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid;

2-((*R*)-4-(cyclopropyl(3-(trifluoromethyl)phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

(*R*)-2-(4-(bis(4-chlorophenyl)methyl)-2-methylpiperazin-1-yl)acetic acid;

(*S*)-2-((*R*)-4-(bis(4-chlorophenyl)methyl)-3-methylpiperazin-1-yl)propanoic acid;

(*S*)-2-((*R*)-4-(bis(4-chlorophenyl)methyl)-2-methylpiperazin-1-yl)propanoic acid;

(*R*)-2-((*R*)-4-(bis(4-chlorophenyl)methyl)-2-methylpiperazin-1-yl)propanoic acid;

2-((2*R*,6*S*)-4-(bis(4-chlorophenyl)methyl)-2,6-dimethylpiperazin-1-yl)acetic acid;

2-(4-(bis(4-chlorophenyl)methyl)-2,2-dimethylpiperazin-1-yl)acetic acid;

2-(4-(bis(4-chlorophenyl)methyl)piperazin-1-yl)propanoic acid;

(*R*)-2-(4-(bis(4-chlorophenyl)methyl)-2-isopropylpiperazin-1-yl)acetic acid;

2-(4-(bis(4-chlorophenyl)methyl)piperazin-1-yl)acetic acid ; and

2-(4-(phenyl(3-(trifluoromethyl)phenyl)methyl)-1,4-diazepan-1-yl)-acetic acid;

or a pharmaceutically acceptable salt thereof

24. The use of Claim 6 wherein the compound selected from:

(*R*)-2-(4-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid; or a pharmaceutically acceptable salt thereof.

25. The use of Claim 6 wherein the compound selected from:

2-((*R*)-4-(cyclopropyl(3-(trifluoromethyl)phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid or a pharmaceutically acceptable salt thereof.

26. The use of Claim 6 wherein the compound selected from:

2-((*R*)-2-methyl-4-((*R*)-phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid; or a pharmaceutically acceptable salt thereof.

27. The use of any of the Claims 5-26 wherein the disease is Schizophrenia.

28. The use of any of the Claims 5-26 wherein the disease is cognitive disorder associated with Schizophrenia.

29. The use of any of the Claims 5-28 wherein the antipsychotic agent is acetophenazine, alentemol, aripiprazole, amisulpride, chlorpromazine, chlorprothixene, clozapine, diazepam, fluphenazine, haloperidol, loxapine, mesoridazine, molindolone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, sulpiride, tetrabenazine, thioridazine, thiothixene, trifluoperazine, or ziprasidone.

GLYCINE TRANSPORTER-1 INHIBITORS

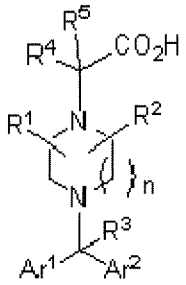
Abstract

The present invention provides compounds of formula (**I**) that are glycine transporter 1 (hereinafter referred to as GlyT-1) inhibitors and are therefore useful for the treatment of diseases treatable by inhibition of GlyT-1 such as cognitive disorders associated with Schizophrenia, **ADHD** (attention deficit hyperactivity disorder), **MCI** (mild cognitive impairment), and the like. Also provided are pharmaceutical compositions containing such compounds and processes for preparing such compounds.

[No suitable figure]

Claims:

1. A method of making a compound Formula (I):



(I)

wherein:

n is an integer from 1 to 3;

R^1 is hydrogen;

R^2 is hydrogen or methyl where methyl is at the 2- position of piperazine ring the nitrogen atom of the piperazine ring carrying $-CH_2CO_2H$ group is the 1 position;

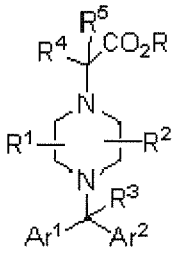
R^3, R^4, and R^5 are hydrogen;

Ar^1 is phenyl; and

Ar^2 is phenyl substituted with R^g where R^g is trifluoromethyl and is attached to the 3-position of the phenyl ring the ring atom attached to the $-CR^3Ar^2$ being position 1 and the stereochemistry at the carbon carrying the R^3, Ar^1 and Ar^2 group is (R);

comprising:

(a) hydrolyzing the ester group in a compound of formula:



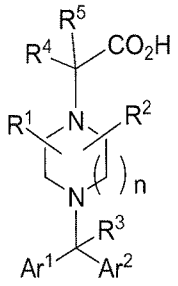
where R is alkyl and R^1, R^2, R^3, R^4, R^5, Ar^1 and Ar^2 groups are as defined above; under acidic or basic hydrolysis reaction conditions;

(b) optionally modifying any of the R^1, R^2, R^3, R^4, R^5, Ar^1 and Ar^2 groups to provide a compound of Formula (I);

(c) optionally forming an acid addition salt of the compound of Formula (I) obtained from Step (a) and/or (b) above;

(d) optionally separating stereoisomers of the compound of Formula (I) obtained from Step (a), (b), and/or (c) above.

2. Use of a compound of Formula (I):



(I)

wherein:

n is an integer from 1 to 3;

R^1 and R^2 are independently selected from hydrogen, alkyl, haloalkyl, alkoxy, haloalkoxy, aryl, heteroaryl, cycloalkyl, or heterocyclyl wherein the aforementioned rings are optionally substituted with R^a, R^b, or R^c independently selected from alkyl, halo, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, monosubstituted amino, or disubstituted amino; or

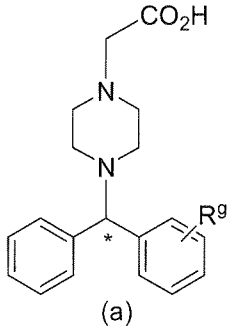
R^1 and R^2, when attached to the same carbon atom, can combine to form cycloalkyl or monocyclic saturated heterocyclyl to give a spiro ring wherein the cycloalkyl or monocyclic saturated heterocyclyl can be optionally substituted with R^d, R^e, or R^f independently selected from alkyl, alkoxy, fluoro, fluoroalkyl, fluoroalkoxy, hydroxy, monosubstituted amino, or disubstituted amino; or

R^1 and R^2, when attached to carbon atoms 2 and 5 or 3 and 6 positions of the piperazine ring, can combine to form $-C_1$-C_3- alkylene chain wherein one of the carbon atoms in the alkylene chain is optionally replaced by a –NR-, -O-, -S(O)n1- (where R is hydrogen or alkyl and n1 is 0-2) and further wherein one or two hydrogen atoms in the alkylene chain can be optionally substituted with one or two alkyl;

R^3, R^4 and R^5 are independently hydrogen, alkyl, fluoro, or fluoroalkyl; and

Ar^1 and Ar^2 are independently aryl, heteroaryl, cycloalkyl, or heterocyclyl where each of the aforementioned ring is optionally substituted with R^g, R^h or R^i where R^g is alkyl, -C=C-R^6 (where R^6 is aryl or heteroaryl), halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, or acylamino and R^h and R^i are independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, acylamino, aryl, heteroaryl, cycloalkyl, or heterocyclyl where the aromatic or alicyclic ring in R^g, R^h and R^i is optionally substituted with R^j, R^k or R^l which are independently selected from alkyl, halo, haloalkyl, haloalkoxy, alkylthio, cyano, alkoxy, amino, monosubstituted amino, disubstituted amino, sulfonyl, acyl, carboxy, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, aminosulfonyl, aminocarbonyl, or acylamino; or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient in the manufacture of a pharmaceutical composition for treating a disease treatable by inhibition of GlyT1 receptor in a patient wherein the pharmaceutical composition is to be administered in combination with an antipsychotic agent; wherein the disease is Schizophrenia or cognitive disorder associated with Schizophrenia.

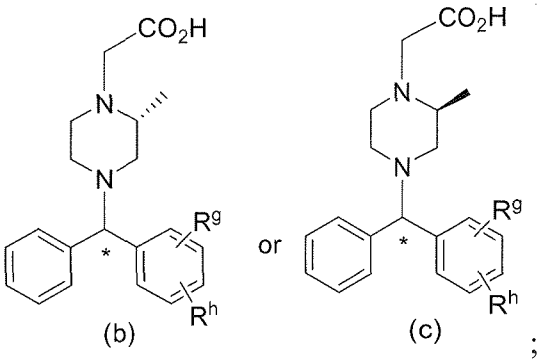
3. The use of Claim 2 wherein the compound has the structure:



(a) ;

wherein R^g is alkyl, halo, haloalkyl, or haloalkoxy and is attached to the 3-position of the phenyl ring and the stereochemistry at *C is (*R*).

4. The use of Claim 2 wherein the compound has the structure:



;

wherein R^g and R^h are independently hydrogen, alkyl, halo, haloalkyl, or haloalkoxy.

5. The use of Claim 2 wherein the compound is selected from:

(*R*)-2-(4-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid; or a pharmaceutically acceptable salt thereof.

6. The use of Claim 2 wherein the compound is selected from:

2-((*R*)-4-(cyclopropyl(3-(trifluoromethyl)phenyl)methyl)-2-methylpiperazin-1-yl)acetic acid or a pharmaceutically acceptable salt thereof.

7. The use of Claim 2 wherein the compound is selected from:

2-((*R*)-2-methyl-4-((*R*)-phenyl(3-(trifluoromethyl)phenyl)methyl)piperazin-1-yl)acetic acid; or a pharmaceutically acceptable salt thereof.

8. The use of any of the Claims 2-7 wherein the antipsychotic agent is acetophenazine, alentemol, aripiprazole, amisulpride, chlorpromazine, chlorprothixene, clozapine, diazepam, fluphenazine, haloperidol, loxapine, mesoridazine, molindolone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, sulpiride, tetrabenazine, thioridazine, thiothixene, trifluoperazine, or ziprasidone.

METHODS FOR THE PREPARATION AND USES OF GLYCINE TRANSPORTER-1 INHIBITORS

Abstract

A process for preparing compounds of formula (I) that are glycine transporter 1 (hereinafter referred to as GlyT-1) inhibitors useful for the treatment of diseases treatable by inhibition of GlyT1 such as cognitive disorders associated with Schizophrenia, ADHA (attention deficit hyperactivity disorder) and MCI (mild congnitive impairment). Also provided are uses of compositions containing such compounds together with an antipsychotic agent. Further, (3R)-3-methyl-1-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazine and 1-(phenyl(3-(trifluoromethyl)phenyl)methyl)piperazine is disclosed.

[No suitable Figure]