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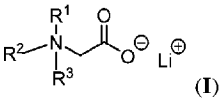
(54) Titre : SELS DE LITHIUM DE COMPOSES DE GLYCINE N-SUBSTITUES ET UTILISATIONS ASSOCIEES
(54) Title: LITHIUM SALTS OF N-SUBSTITUTED GLYCINE COMPOUNDS AND USES THEREOF



(I)

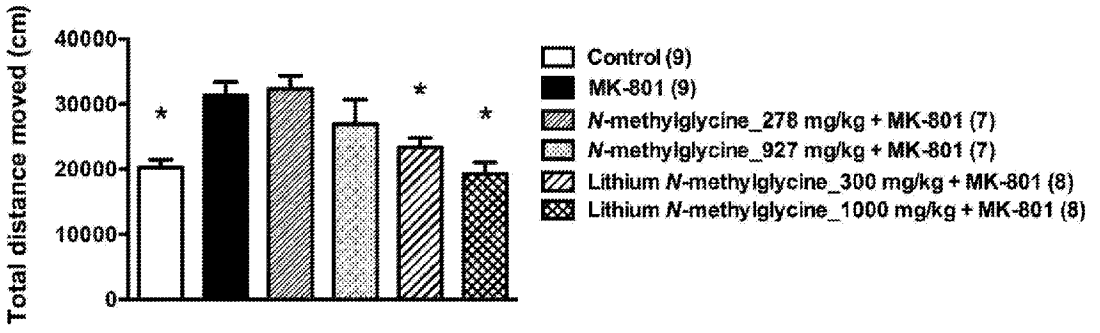


Figure 1

(57) Abrégé/Abstract:
The present invention relates to a composition comprising a lithium salt of an N-substituted glycine compound and a carrier, wherein the lithium salt of the N-substituted glycine compound is of Formula (I) in which R^1, R^2, and R^3 each are independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, carbocyclyl, aryl, or heteroaryl, or one of R^1, R^2, and R^3 is absent. Also provided in the present invention is a method of mitigating at least one symptom of a neuropsychiatric disorder, comprising administering to a subject in need thereof the lithium salt of an N-substituted glycine compound of Formula (I).

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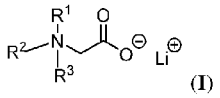
(54) **Title:** LITHIUM SALTS OF N-SUBSTITUTED GLYCINE COMPOUNDS AND USES THEREOF



(I)

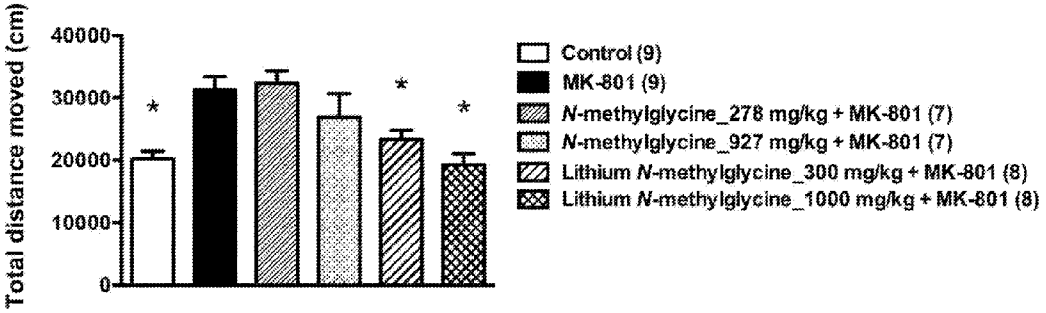


Figure 1

(57) **Abstract:** The present invention relates to a composition comprising a lithium salt of an *N*-substituted glycine compound and a carrier, wherein the lithium salt of the *N*-substituted glycine compound is of Formula (I) in which R^1, R^2, and R^3 each are independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, carbocyclyl, aryl, or heteroaryl, or one of R^1, R^2, and R^3 is absent. Also provided in the present invention is a method of mitigating at least one symptom of a neuropsychiatric disorder, comprising administering to a subject in need thereof the lithium salt of an *N*-substituted glycine compound of Formula (I).

WO 2019/014207 A1

[Continued on next page]

WO 2019/014207 A1

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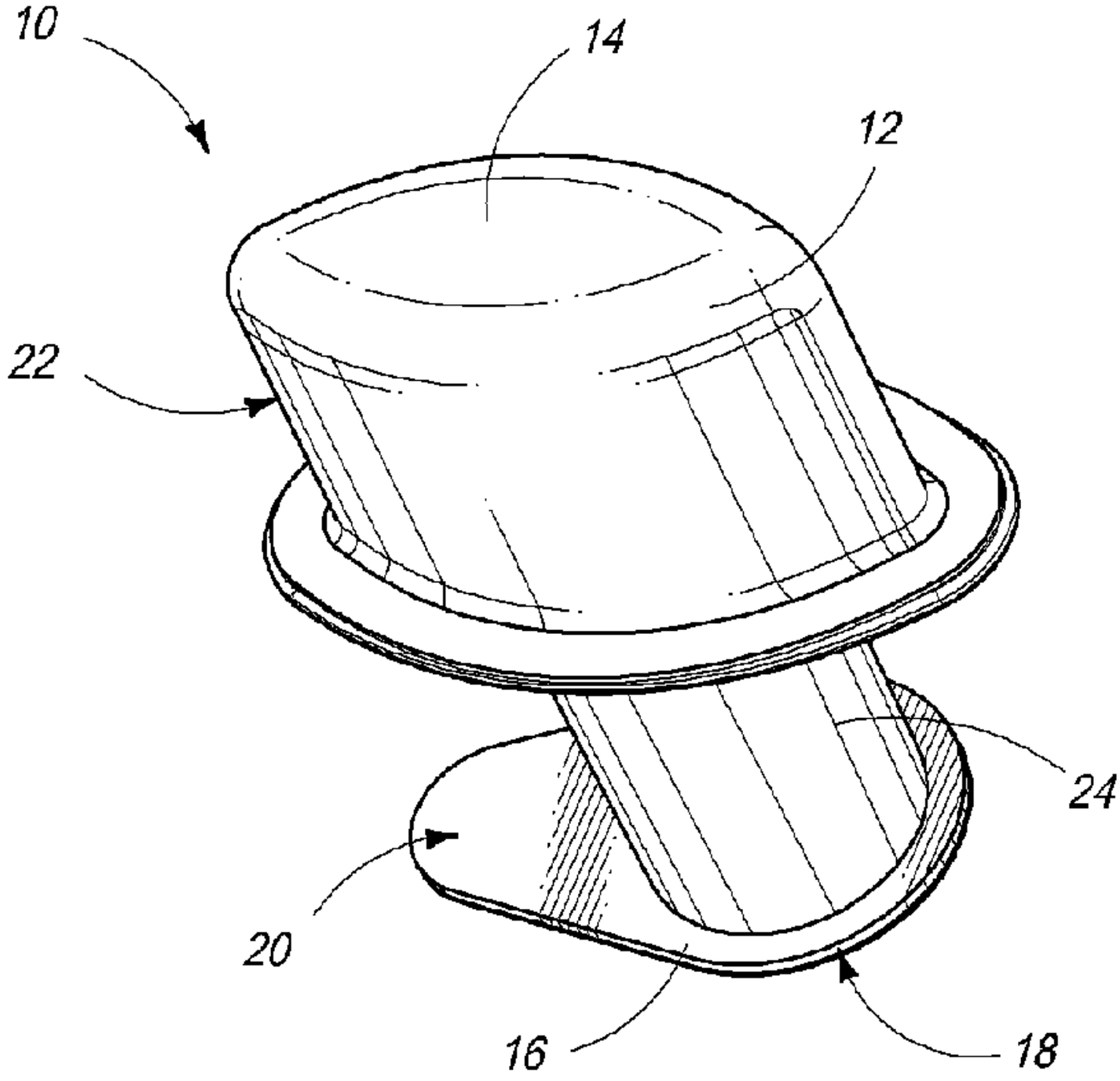
10
14
12
22
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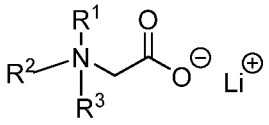
16
18

What Is Claimed Is:

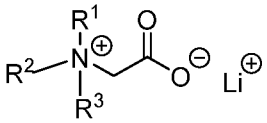
1. A composition comprising a lithium salt of an *N*-substituted glycine compound and a carrier, wherein the lithium salt of the *N*-substituted glycine compound is of Formula (**I**):



(**I**), in which R^1, R^2, and R^3 each are independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, carbocyclyl, aryl, or heteroaryl, or one of R^1, R^2, and R^3 is absent.

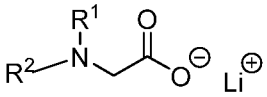
2. The composition of claim 1, wherein the lithium salt of the *N*-substituted glycine compound is of:

Formula (**I-A**):



(**I-A**), in which R^1, R^2, and R^3 each are independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, carbocyclyl, aryl, or heteroaryl; or

Formula (**I-B**):



(**I-B**), in which R^1 and R^2 each are independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, carbocyclyl, aryl, or heteroaryl.

3. The composition of claim 1, wherein at least two of R^1, R^2, and R^3 each are independently hydrogen or alkyl.

4. The composition of claim 3, wherein the alkyl is C_{1-3} alkyl.

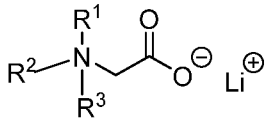
5. The composition of claim 4, wherein the C_{1-3} alkyl is methyl.

6. The composition of claim 5, wherein R^1 and R^2 are each methyl and R^3 is absent.

7. The composition of claim 4, wherein R^1 is methyl, R^2 is hydrogen, and R^3 is absent.

8. The composition of claim 1, which is a pharmaceutical composition, a nutraceutical composition, a health food, or a medical food.

9. A method for mitigating a symptom of a neuropsychiatric disorder, comprising administering to a subject in need thereof an effective amount of a lithium salt of an *N*-substituted glycine compound or a composition comprising the lithium salt, wherein the lithium salt of the *N*-substituted glycine compound is of Formula (**I**):



(**I**), in which R^1, R^2, and R^3 each are independently hydrogen, alkyl, alkenyl, alkynyl, aralkyl, carbocyclyl, aryl, or heteroaryl, or one of R^1, R^2, and R^3 is absent.

10. The method of claim 9, wherein the neuropsychiatric disorder is a neuropsychiatric disorder with hyperactivity symptoms.

11. The method of claim 10, wherein the neuropsychiatric disorder is selected from the group consisting of schizophrenia, bipolar disorder, attention-deficit hyperactivity disorder, obsessive compulsive disorder, Tourette's syndrome, autism spectrum disorders, Fragile X syndrome, Parkinson's disease, dementia with Lewy bodies, and senile dementia.

12. The method of claim 9, wherein the neuropsychiatric disorder is a neuropsychiatric disorder having sensorimotor deficit.

13. The method of claim 12, wherein the neuropsychiatric disorder is selected from the group consisting of schizophrenia, major depressive disorder, bipolar disorder, attention deficit disorder, attention-deficit hyperactivity disorder, tic disorder, obsessive compulsive disorder, Tourette's syndrome, blepharospasm, post-traumatic stress disorder, panic disorder, Asperger's disorder, mild dementia of Alzheimer, dementia with Lewy bodies,

Huntington's disease, personality disorders, nocturnal enuresis, and non-epileptic seizures.

14. The method of claim 9, wherein the neuropsychiatric disorder is a neuropsychiatric disorder with a deficit in learning and memory.

15. The method of claim 14, wherein the neuropsychiatric disorder is selected from the group consisting of schizophrenia, depression, obsessive compulsive disorder, post-traumatic stress disorder, addiction disorders, Alzheimer's disease, frontotemporal dementia, Parkinson's disease, Duchenne muscular dystrophy, stroke, Fragile X syndrome, and amyotrophic lateral sclerosis.

16. The method of claim 9, wherein the subject is treated by an additional pharmaceutical agent for the neuropsychiatric disorder.

17. The method of claim 16, wherein the additional pharmaceutical agent is selected from the group consisting of an antipsychotic, an antidepressant, a mood stabilizer, an anxiolytic, or a psychostimulant.

18. The method of claim 17, wherein the additional pharmaceutical agent is an antipsychotic selected from the group consisting of butyrophenone, phenothiazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, mesoridazine, promazine, triflupromazine, levomepromazine, promethazine, thioxanthene, chlorprothixene, flupentixol, thiothixene, zuclopenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, asenapine, paliperidone, aripiprazole, cannabidiol, LY2140023, droperidol, pimozide, butaperazine, carphenazine, remoxipride, piperacetazine, sulpiride, acamprosate, tannic acid, and tetrabenazine.

19. The method of claim 17, wherein the additional pharmaceutical agent is an antidepressant selected from the group consisting of monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs), noradrenergic and specific serotonergic antidepressants (NASSAs), norepinephrine (noradrenaline) reuptake inhibitors, norepinephrine- dopamine reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors (SNRIs).

20. The method of claim 17, wherein the additional pharmaceutical agent is an antidepressant selected from the group consisting of fluoxetine, paroxetine, escitalopram, citalopram, sertraline, fluvoxamine, venlafaxine, milnacipran, duloxetine, mirtazapine, mianserin, reboxetine, bupropion, amitriptyline, nortriptyline, protriptyline, desipramine, trimipramine, amoxapine, bupropion, clomipramine, desipramine, doxepin, isocarboxazid, tranylcypromine, trazodone, nefazodone, phenelzine, lamatrogine, lithium, topiramate, gabapentin, carbamazepine, oxcarbazepine, valproate, maprotiline, brofaromine, gepirone, moclobemide, isoniazid, and iproniazid.

21. The method of claim 17, wherein the additional pharmaceutical agent is a psychostimulant selected from the group consisting of methylphenidate, dextro-threo-methylphenidate, isopropylphenidate, cocaine, amphetamine, methamphetamine, dextroamphetamine, 3,4-methylenedioxymethamphetamine, pemoline, phenmetrazine, diethylpropion, chlorphentermine, pipradol, p-hydroxymorphedrine, fenfluramine, 1-(2,5-dimethoxy-4-methylphenyl)-2- aminopropane, bupropion, statins, modafinil, arecoline, dexmethylphenidate, lisdexamfetamine dimesylate, mixed salts amphetamine, atomoxetine, clonidine hydrochloride, guanfacine hydrochloride, and arecoline.

22. The method of claim 17, wherein the additional pharmaceutical agent is a mood stabilizer selected from the group consisting of lithium, lamotrigine, carbamazepine, topiramate, zolpidem, carbamazepine, and valproate.

23. The method of claim 17, wherein the additional pharmaceutical agent is an anxiolytic selected from the group consisting of diazepam, alprazolam, triazolam, indiplon, zaleplon, bromazepam, oxazepam, buspirone, hydroxyzine, mecloqualone, medetomidine, metomidate, adinazolam, chlordiazepoxide, clobenzepam, flurazepam, lorazepam, clonazepam, loprazolam, midazolam, alpidem, alseroxlon, amphenidone, azacyclonol, bromisovalum, chlorazepate, calcium *N*-carboamoylaspartate, captodiamine, capuride, carbcloral, carbromal, chloral betaine, enciprazine, flesinoxan, ipsapiraone, ipsapirone, lesopitron, loxapine, methaqualone, methprylon, propanolol, tandospirone, trazadone, zopiclone, and zolpidem.

24. The method of claim 16, wherein the disorder is Alzheimer's disease (AD) and the additional pharmaceutical agent is selected from the group consisting of donepezil, rivastigmine, galantamine, memantine, selfotel, midafotel, tacrine, selegiline, and vitamin E.

25. The method of claim 16, wherein the additional pharmaceutical agent is administered prior to, concurrently with, or subsequent to the administration of the lithium salt of the *N*-substituted glycine compound.

26. The method of any one of claims 9-25, wherein the lithium salt of the *N*-substituted glycine compound is administered to the subject at about 50 mg/kg to about 300 mg/kg.

27. The method of claim 26, wherein the lithium salt of the *N*-substituted glycine compound is administered to the subject at about 120 mg/kg to about 300 mg/kg.

28. The method of claim 26, wherein the lithium salt of the *N*-substituted glycine compound is administered to the subject at about 50 mg/kg to about 120 mg/kg.

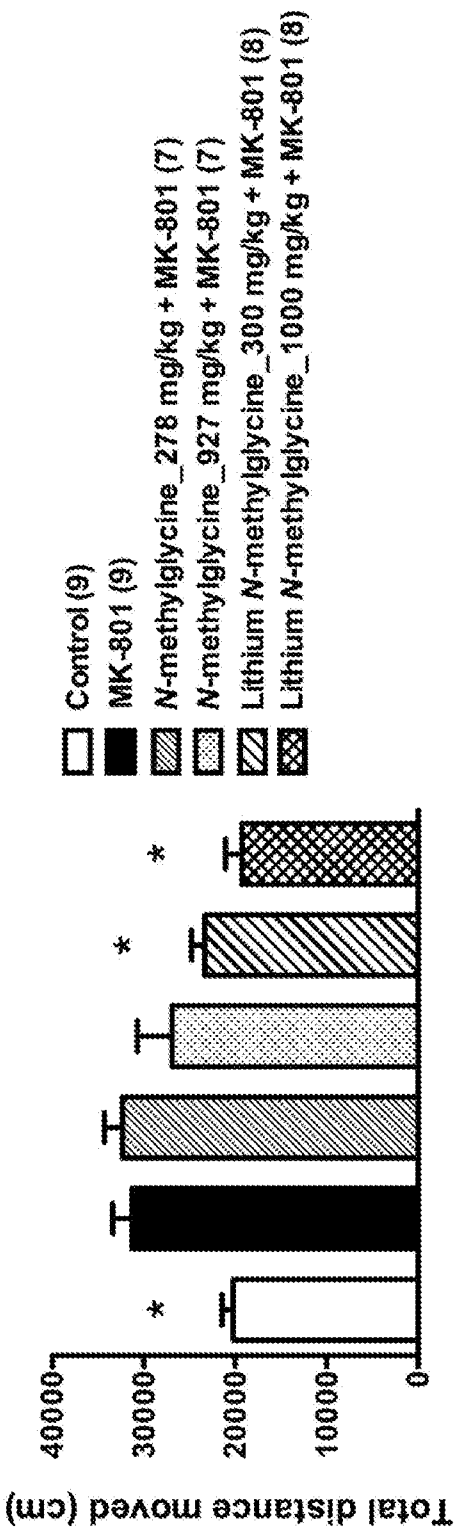

Control (9)
MK-801 (9)
N-methylglycine_278 mg/kg + MK-801 (7)
N-methylglycine_927 mg/kg + MK-801 (7)
Lithium N-methylglycine_300 mg/kg + MK-801 (8)
Lithium N-methylglycine_1000 mg/kg + MK-801 (8)
Total distance moved (cm)
40000
30000
20000
10000
0
*
*
*

Figure 1

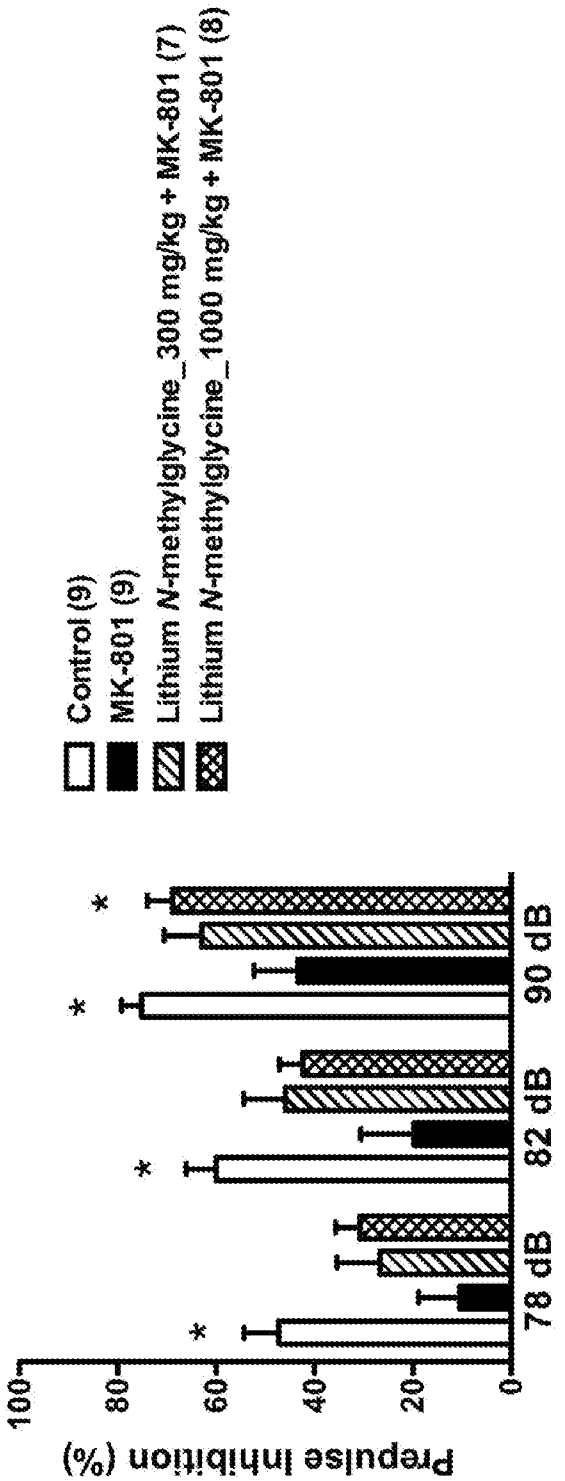

Control (9)
MK-801 (9)
Lithium N-methylglycine_300 mg/kg + MK-801 (7)
Lithium N-methylglycine_1000 mg/kg + MK-801 (8)
Prepulse Inhibition (%)
100
80
60
40
20
0
78 dB
82 dB
90 dB
*
*
*
*

Figure 2

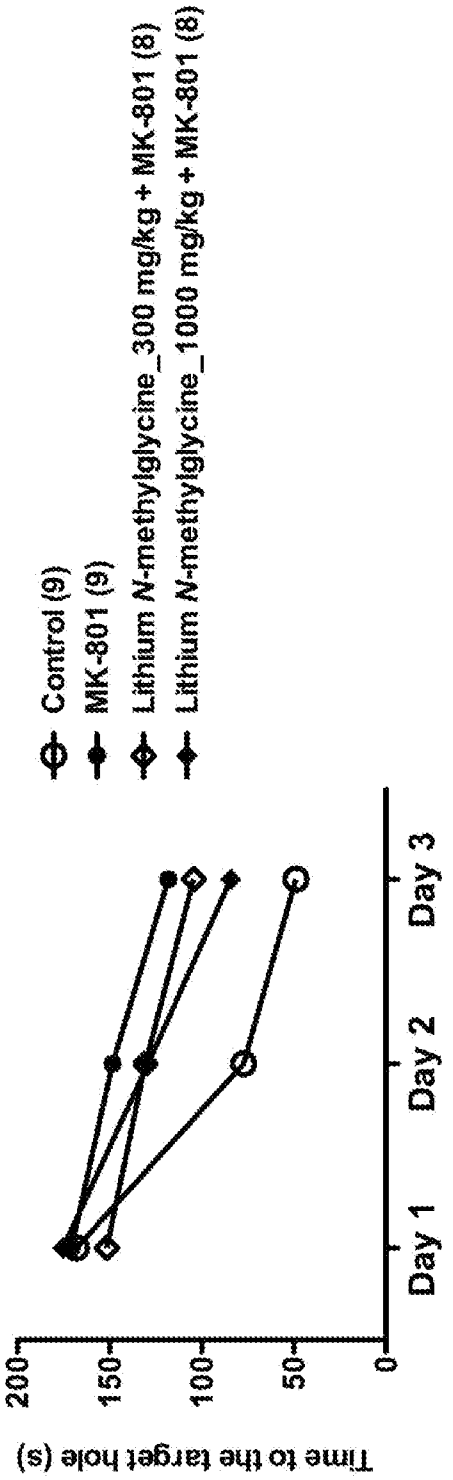

Control (9)
MK-801 (9)
Lithium N-methylglycine_300 mg/kg + MK-801 (8)
Lithium N-methylglycine_1000 mg/kg + MK-801 (8)
Time to the target hole (s)
200
150
100
50
0
Day 1
Day 2
Day 3

Figure 3

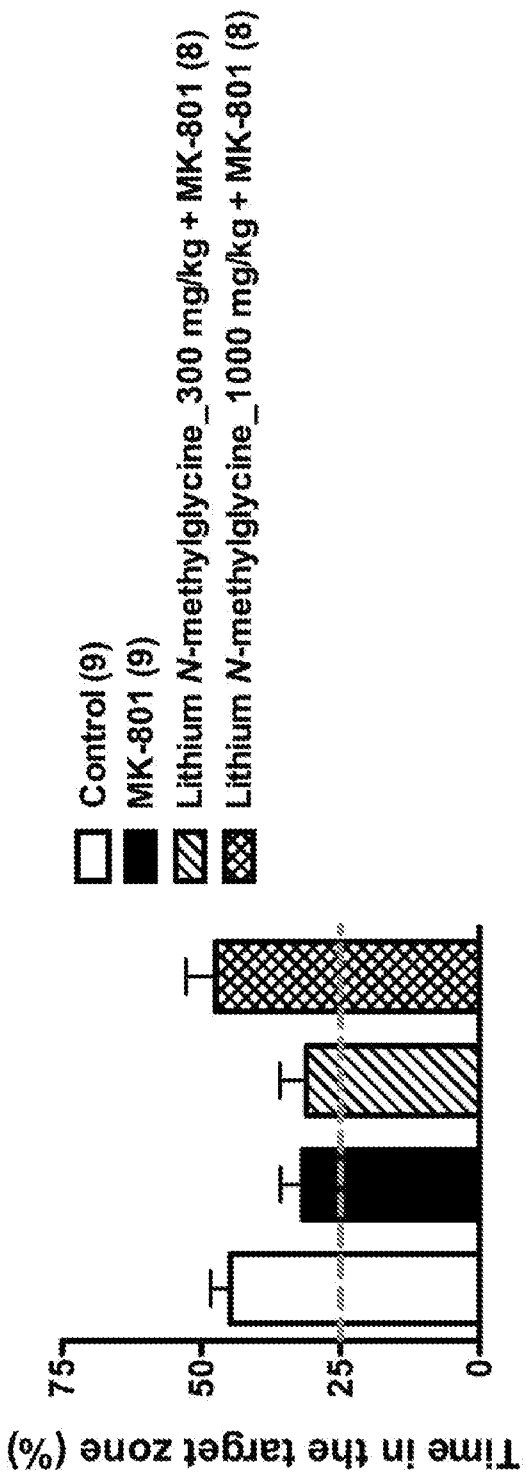

Control (9)
MK-801 (9)
Lithium N-methylglycine_300 mg/kg + MK-801 (8)
Lithium N-methylglycine_1000 mg/kg + MK-801 (8)
Time in the target zone (%)
75
50
25
0

Figure 4

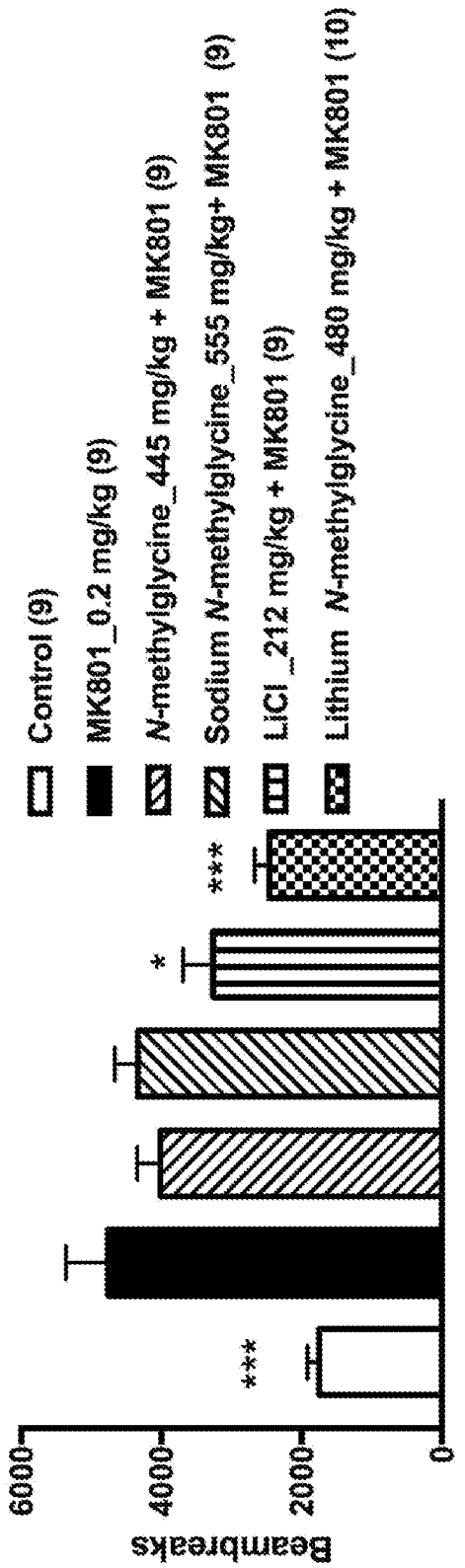

Control (9)
MK801_0.2 mg/kg (9)
N-methylglycine_445 mg/kg + MK801 (9)
Sodium N-methylglycine_555 mg/kg+ MK801 (9)
LiCl _212 mg/kg + MK801 (9)
Lithium N-methylglycine_480 mg/kg + MK801 (10)
***
*
***
Beambreaks
6000
4000
2000
0

Figure 5

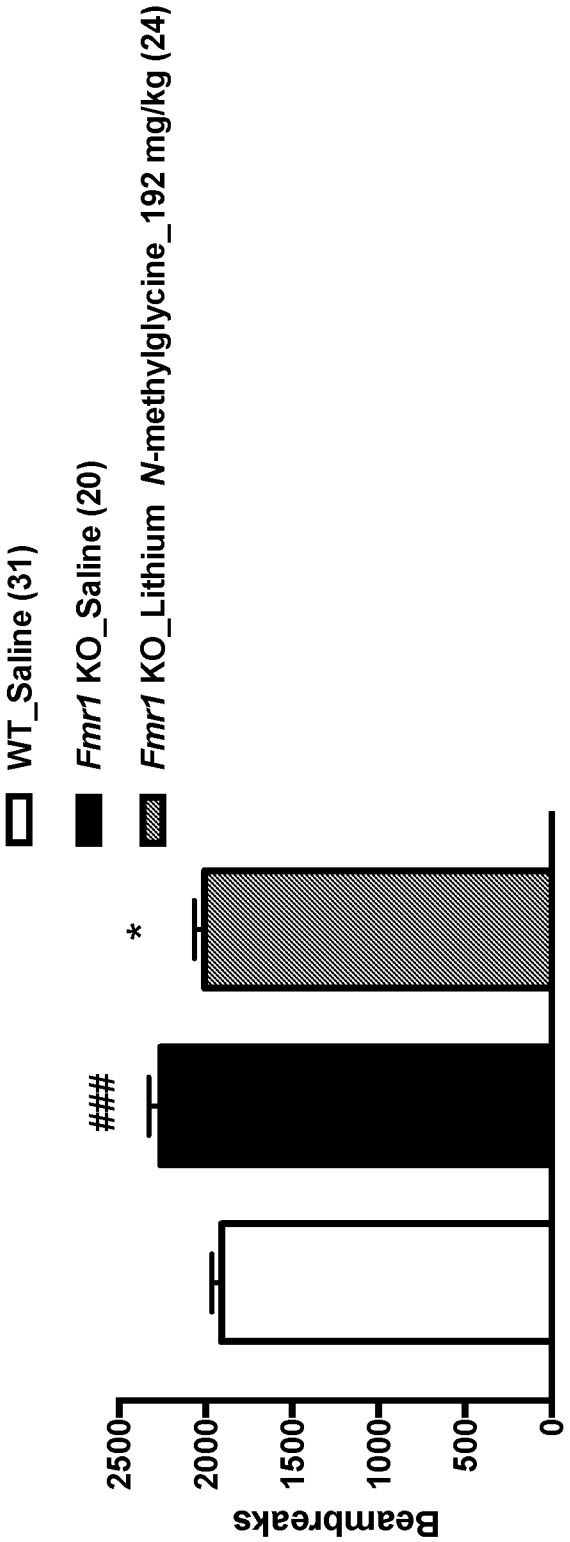

WT_Saline (31)
Fmr1 KO_Saline (20)
Fmr1 KO_Lithium N-methylglycine_192 mg/kg (24)
###
*
Beambreaks
2500
2000
1500
1000
500
0

Figure 6

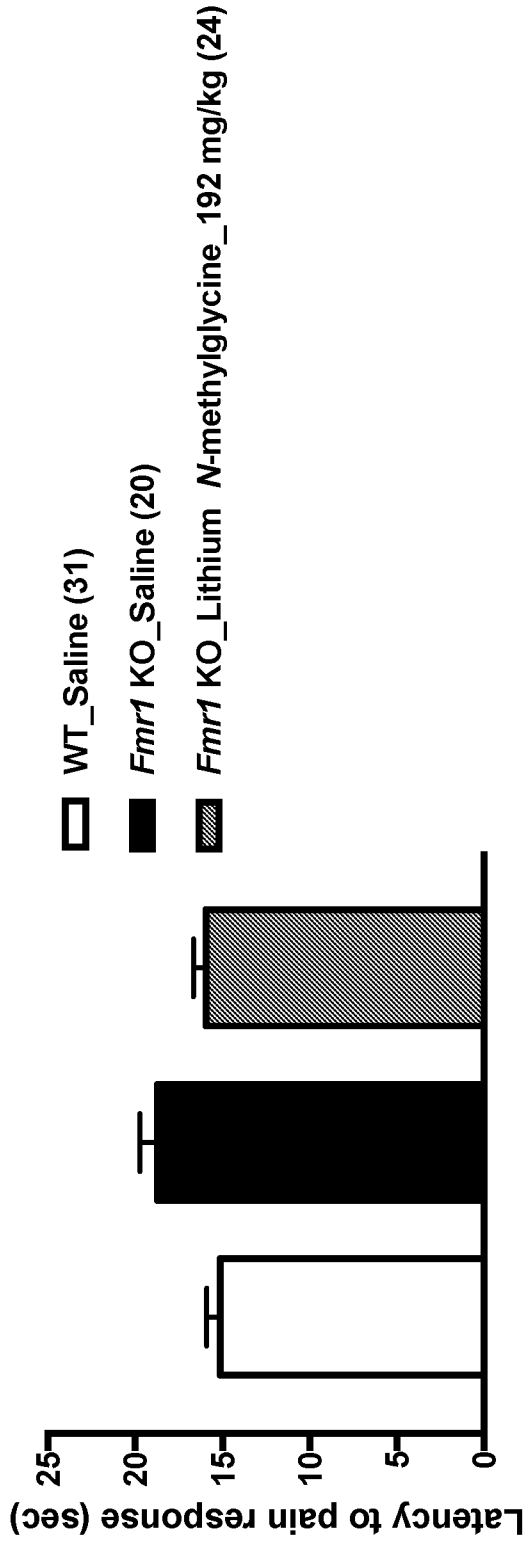

WT_Saline (31)
Fmr1 KO_Saline (20)
Fmr1 KO_Lithium N-methylglycine_192 mg/kg (24)
Latency to pain response (sec)
0
5
10
15
20
25

Figure 7

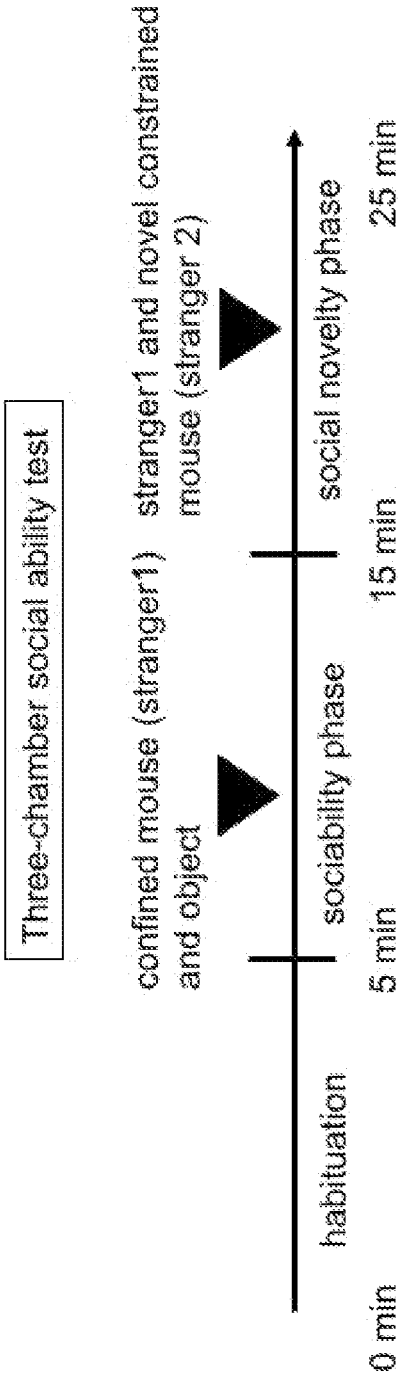

Three-chamber social ability test
confined mouse (stranger1) and object
stranger1 and novel constrained mouse (stranger 2)
habituation
sociability phase
social novelty phase
0 min
5 min
15 min
25 min

Figure 8

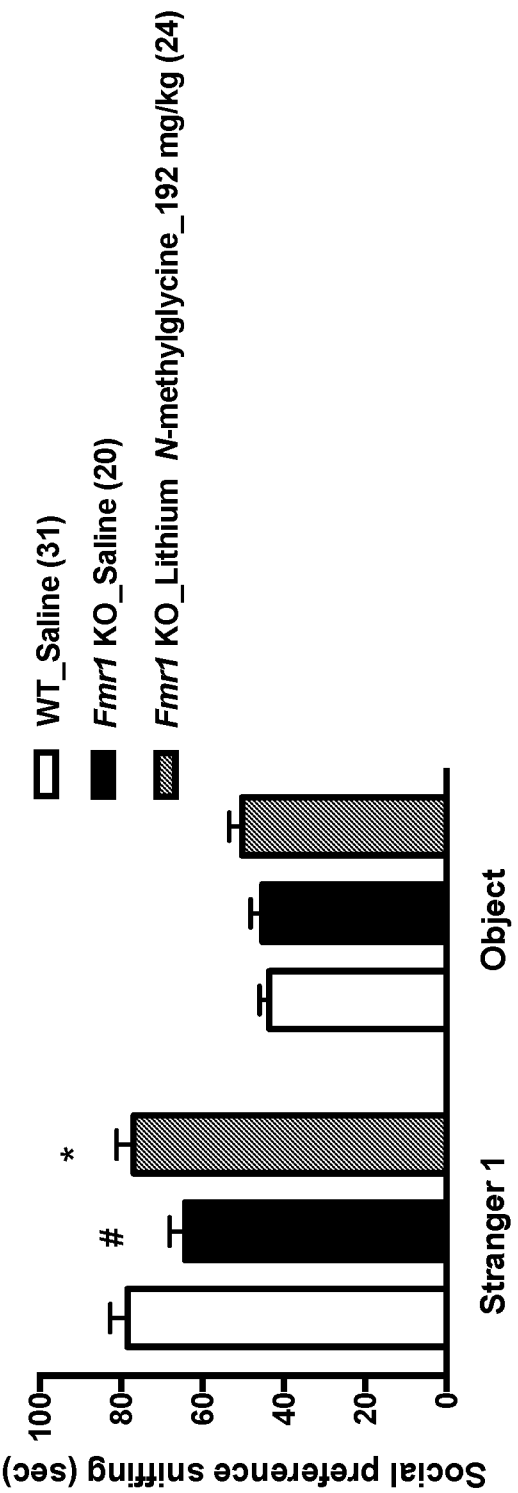

WT_Saline (31)
Fmr1 KO_Saline (20)
Fmr1 KO_Lithium N-methylglycine_192 mg/kg (24)
Social preference sniffing (sec)
100
80
60
40
20
0
*
#
Stranger 1
Object

Figure 9

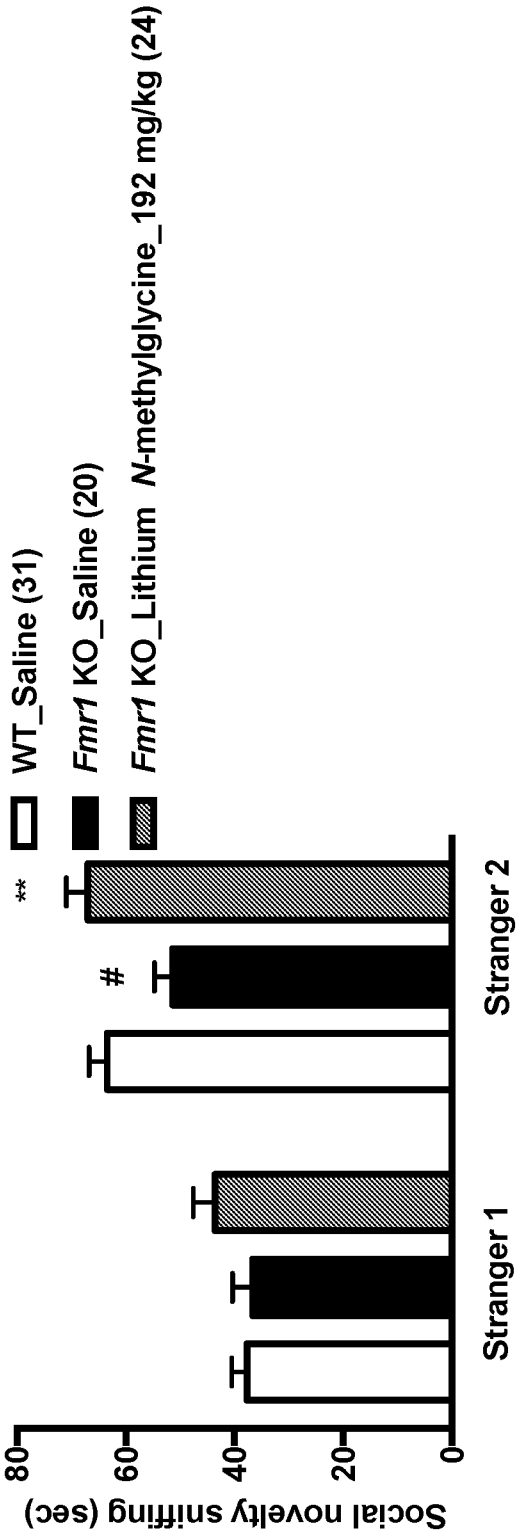

WT_Saline (31)
Fmr1 KO_Saline (20)
Fmr1 KO_Lithium N-methylglycine_192 mg/kg (24)
**
#
Stranger 1
Stranger 2
Social novelty sniffing (sec)
0
20
40
60
80

Figure 10

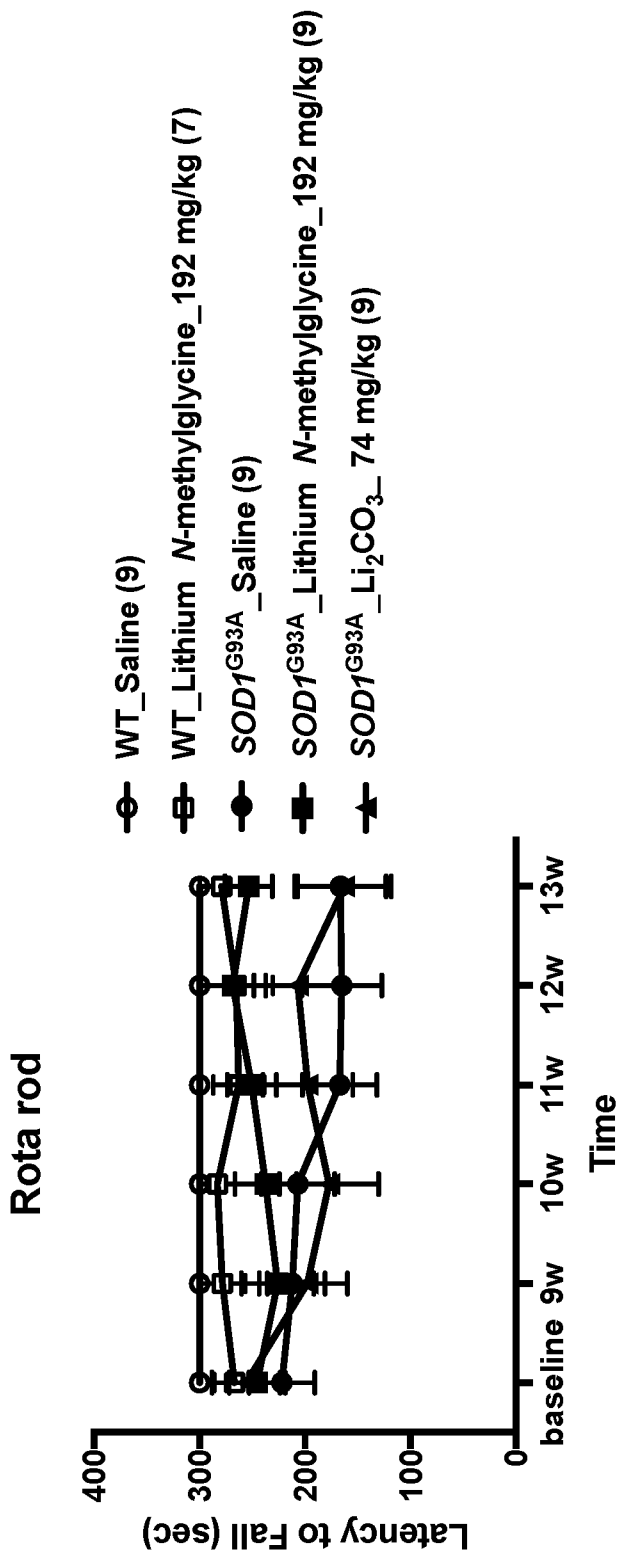

Rota rod
WT_Saline (9)
WT_Lithium N-methylglycine_192 mg/kg (7)
SOD1G93A_Saline (9)
SOD1G93A_Lithium N-methylglycine_192 mg/kg (9)
SOD1G93A_Li2CO3_ 74 mg/kg (9)
Latency to Fall (sec)
400
300
200
100
0
baseline
9w
10w
11w
12w
13w
Time

Figure 11

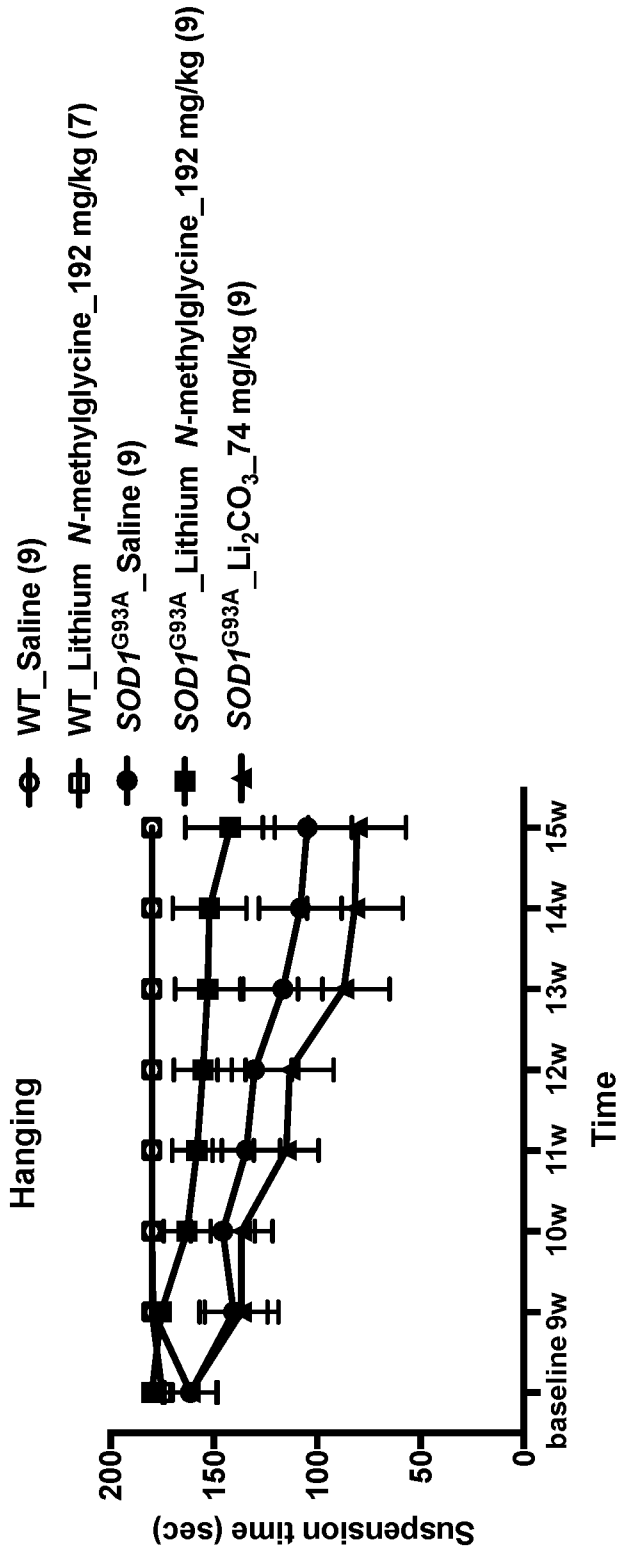
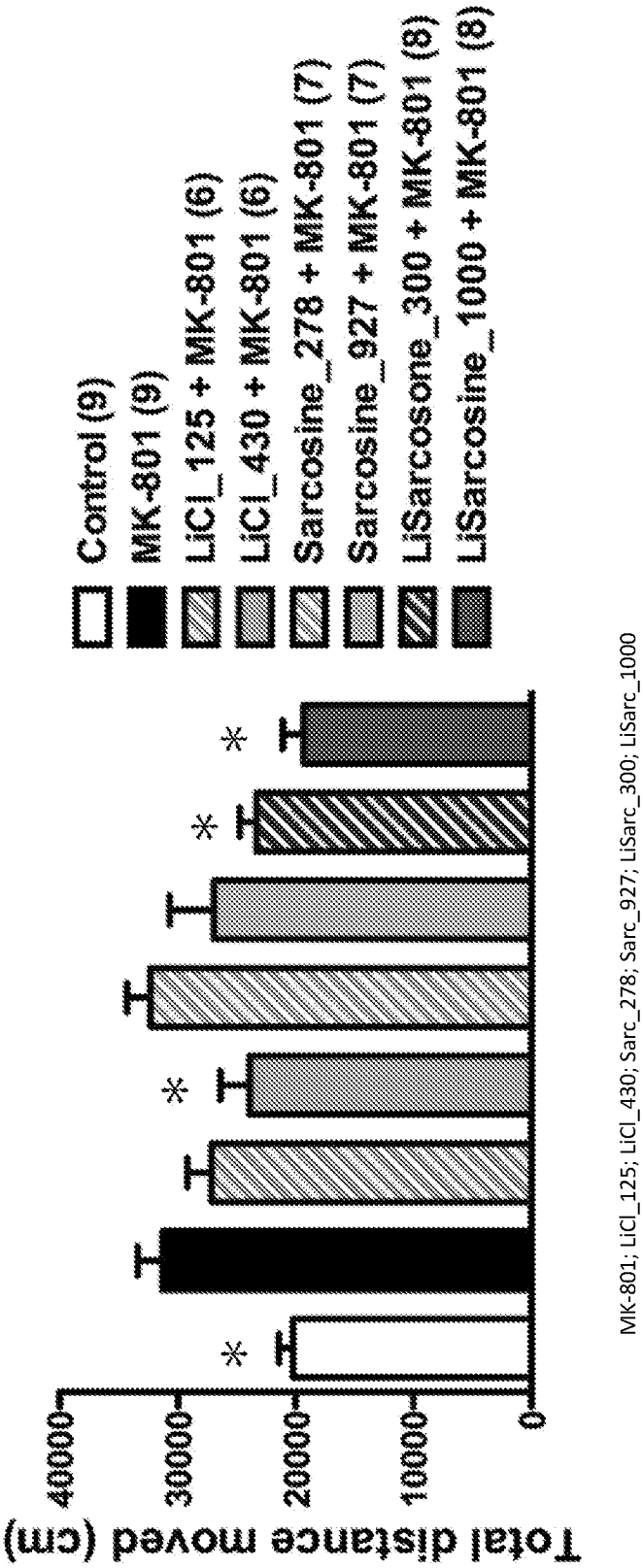
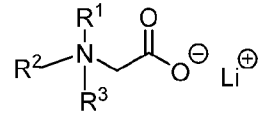

Hanging
WT_Saline (9)
WT_Lithium N-methylglycine_192 mg/kg (7)
SOD1G93A_Saline (9)
SOD1G93A_Lithium N-methylglycine_192 mg/kg (9)
SOD1G93A_Li2CO3_74 mg/kg (9)
Suspension time (sec)
200
150
100
50
0
baseline
9w
10w
11w
12w
13w
14w
15w
Time

Figure 12



MK-801; LiCl_125; LiCl_430; Sarc_278; Sarc_927; LiSarc_300; LiSarc_1000

Figure 13


R1
O
R2
N
O
Li
R3

(I)

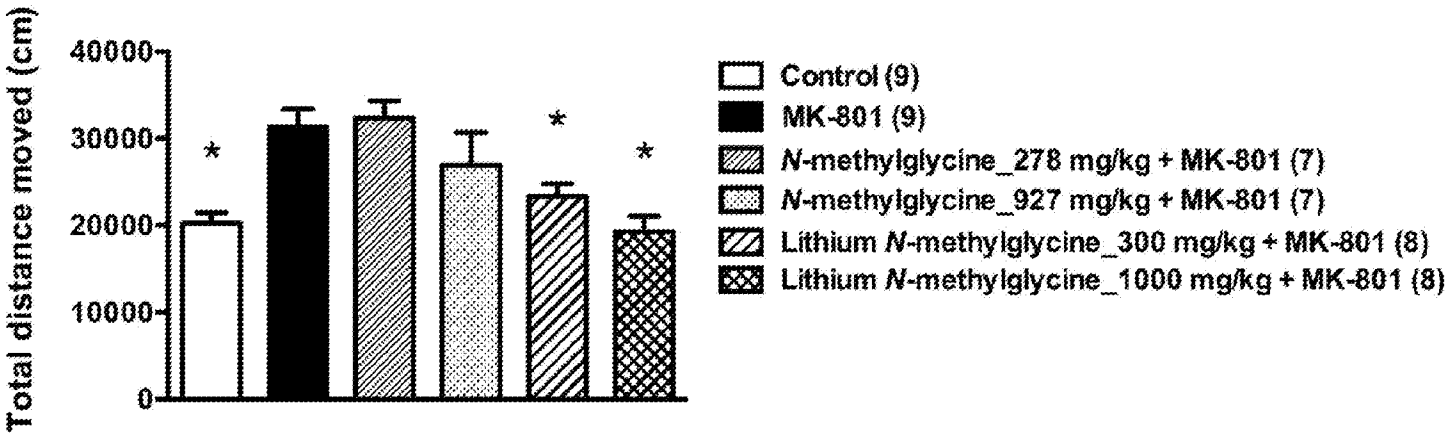

Total distance moved (cm)
40000
30000
20000
10000
0
*
*
*
Control (9)
MK-801 (9)
N-methylglycine_278 mg/kg + MK-801 (7)
N-methylglycine_927 mg/kg + MK-801 (7)
Lithium N-methylglycine_300 mg/kg + MK-801 (8)
Lithium N-methylglycine_1000 mg/kg + MK-801 (8)

Figure 1