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(54) Title: TREATMENT OF CENTRAL NERVOUS SYSTEM AND MENTAL DISORDERS WITH AGONISTS OF BETA-3
ADRENOCEPTOR

(57) Abstract: Methods of using β_3 -adrenoceptor agonists for treatment of central nervous system and mental disorders are dis-
closed. In particular, the invention relates to methods of treating central nervous system and mental disorders with selective agonists
of β_3 -adrenoceptor such as Mirabegron or Amibegron for enhancement of cognitive function, modulation of systemic and central in-
flammation, and prevention of pathological detrition.



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TREATMENT OF CENTRAL NERVOUS SYSTEM AND MENTAL DISORDERS
WITH AGONISTS OF BETA-3 ADRENOCEPTOR

5 **STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT**

 This invention was made with Government support under contract TR001085 awarded by the National Institutes of Health. The Government has certain rights in the invention.

10 **TECHNICAL FIELD**

 The present invention pertains generally to treatment of central nervous system (CNS) and mental disorders. In particular, the invention relates to methods of treating CNS disorders and mental disorder with selective agonists of β_3 -adrenoceptor (ADRB3), such as Mirabegron and Amibegron.

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BACKGROUND

 Neurodegenerative diseases are characterized by the dysfunction and death of neurons, leading to the loss of functions mediated by the brain, spinal cord and the peripheral nervous system. These disorders have a major impact on society. For
20 example, approximately 4 to 5 million Americans are afflicted with the chronic neurodegenerative disease known as Alzheimer's disease. Other examples of chronic neurodegenerative diseases include diabetic peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord injury, Huntington's disease and Parkinson's disease. Normal brain aging is also associated with loss of
25 normal neuronal function and may entail the depletion of certain neurons.

 Stroke is the third ranking cause of death in the United States, and accounts for half of neurology inpatients. Depending on the area of the brain that is damaged, a stroke can cause coma, paralysis, speech problems and dementia. The major causes of cerebral infarction are vascular thrombosis, cerebral embolism, hypotension,
30 hypertensive hemorrhage, and anoxia/hypoxia. However, the adult brain retains capacity for plasticity and functional reorganization throughout the life span, even after stroke or brain ischemia. Neuronal connections are continuously remodeled. The potential capability of the brain to compensate for the damaged part of the brain has

relevance for stroke rehabilitation. Neuroimaging in stroke patients suggests some functional reorganization. Thus, one aspect of brain plasticity is that in stroke patients, the neuronal connections can be modified by sensory input, experience and learning, and the brain can respond by functional and structural reorganization, upregulation or downregulation of a neural response to an event, and the establishment of new functional and structural connections by collateral sprouting and compensatory synaptogenesis, as well as neurogenesis.

There remains a need for better methods of treating CNS disorders and mental disorders.

SUMMARY

The invention is based on the discovery that ADRB3 agonists are effective in treating CNS disorders and mental disorders.

In one aspect, the invention includes a method of treating a subject for a CNS disorder or mental disorder, the method comprising administering to the subject a therapeutically effective amount of an ADRB3 agonist. In certain embodiments, the ADRB3 agonist is selected from the group consisting of Mirabegron and Amibegron. In certain embodiments, the CNS disorder is Alzheimer's disease or stroke (e.g., ischemic or hemorrhagic). In other embodiments, the mental disorder is an anxiety disorder or schizophrenia.

By "therapeutically effective dose or amount" of an ADRB3 agonist (e.g., Mirabegron or Amibegron) is intended an amount that, when administered as described herein, brings about a positive therapeutic response with respect to treatment of an individual for a CNS disorder or mental disorder such as an amount that enhances cognitive function or immune function in the nervous system. For example, a therapeutically effective dose or amount of an ADRB3 agonist may improve learning or memory, modulate peripheral or central inflammation in the nervous system, or reduce pathological neurological deterioration. Additionally, an ADRB3 agonist may have antidepressant or anxiolytic effects.

An ADRB3 agonist may be administered by any suitable mode of administration, but is typically administered orally. Multiple cycles of treatment may be administered to a subject. In certain embodiments, the ADRB3 agonist is administered according to a daily dosing regimen or intermittently.

In certain embodiments, the method further comprises administering an antagonist of ADRB3. Exemplary ADRB3 antagonists include L-748,328, L-748,337, and SR59230A. In one embodiment, the ADRB3 agonist is active in the central nervous system and the ADRB3 antagonist is active in the peripheral nervous system, wherein the ADRB3 antagonist does not cross the blood-brain barrier.

In certain embodiments, the method further comprises administering one or more other drugs for treating a CNS disorder or mental disorder. For example, the method may further comprise administering an acetylcholinesterase inhibitor (e.g., Donepezil (Aricept), Rivastigmine (Exelon), and Galantamine (Razadyne)) or an N-methyl D-aspartate (NMDA) receptor antagonist (e.g., Memantine (Namenda)).

In another aspect, the invention includes a method of improving learning or memory in a subject who has Alzheimer's disease, the method comprising administering to the subject a therapeutically effective amount of an ADRB3 agonist. In certain embodiments, the ADRB3 agonist is selected from the group consisting of Mirabegron and Amibegron.

In another aspect, the invention includes a method of increasing the monocyte or white blood cell count in a subject who has Alzheimer's disease, the method comprising administering to the subject a therapeutically effective amount of an ADRB3 agonist. In certain embodiments, the ADRB3 agonist is selected from the group consisting of Mirabegron and Amibegron.

In another aspect, the invention includes a composition comprising a β_3 -adrenoceptor (ADRB3) agonist for use in the treatment of a central nervous system (CNS) disorder. In certain embodiments, the composition comprises Mirabegron or Amibegron. In another embodiment, the composition further comprises one or more other drugs for treating a CNS disorder or mental disorder. For example, the composition may further comprise an acetylcholinesterase inhibitor (e.g., Donepezil (Aricept), Rivastigmine (Exelon), and Galantamine (Razadyne)) or an N-methyl D-aspartate (NMDA) receptor antagonist (e.g., Memantine (Namenda)).

These and other embodiments of the subject invention will readily occur to those of skill in the art in view of the disclosure herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows expression of beta3-adrenergic receptors, adipsin, and uncoupling protein (UCP) in rat brain regions. RT/PCR utilized the unlabeled primers: $\beta 3e1$ (beta3-adrenergic receptor exon 1), $\beta 3sp$ (beta3-adrenergic receptor intron-spanning), Adp (adipsin) and UCP (uncoupling protein). Following electrophoresis and transfer to nylon membranes, the PCR products were identified by hybridization to independent probes. Product sizes were determined by comparison with a 100 bp DNA ladder.

FIGS. 2A-2D show the selective beta3-adrenergic receptor antagonist L-748,337 impairs cognitive function. FIG. 2A shows the structure of L-748,337. FIGS. 2B-2D show that L-748,337 treated mice have impaired spontaneous alternation behavior in a Y-maze, reflected in the % alternation (FIG. 2A), number of entries (FIG. 2B), and the number of pellets (FIG. 2C) in the Y-maze, indicating that acute inhibition of beta3-adrenergic receptor with the selective antagonist L-748,337 impairs spatial memory. (One-sample t-test versus 50% theoretical mean, $**p < 0.01$)

FIGS. 3A and 3B show structures of beta3-adrenergic receptor agonists. FIG. 3A shows Amibegron (SR-58,611A), the first orally active beta3-adrenergic receptor agonist. It is CNS permeable, and has antidepressant and anxiolytic effects. Fourteen human clinical trials have been completed for its indication in depressive disorder. FIG. 3B shows Mirabegron, a first-in-class agonist of beta3-adrenergic receptors. It has a chiral center, but it was developed as an R-enantiomer. An Oral Controlled Absorption System (OCAS) tablet was approved in the United States since 2014. However, it was not developed for the CNS indication.

FIGS. 4A-4C show that Mirabegron (an example of beta3-adrenoceptor agonist) enhances learning and memory in the Morris water maze (MWM). FIG. 4A shows the MWM, a large water tank (178 cm in diameter) filled with water, which was used for experiments. A circular platform was placed about 1 cm below the water surface approximately 17 cm away from the wall in one quadrant of the tank. Nontoxic tempera paints were used to make the water opaque. During the three consecutive days of hidden platform training, mice were released from drop locations and given 60 seconds to find the platform. Upon completion of the hidden platform training, the platform was removed, and a 60-second probe trial was conducted. Successful learning of MWM was determined by the gradual decrease in escape

latency during the hidden platform training and discriminative quadrant exploration during the probe trial. FIG. 4B shows results with an APP transgenic mouse, a transgenic model of Alzheimer's disease, which expresses human APP751 cDNA containing the London (V717I) and Swedish (K670M/N671L) mutations under the regulatory control of the murine Thy1 gene. APP transgenic mice dosed with Mirabegron (5 mg/kg) exhibited improved learning compare to the vehicle treated APP mice, as indicated by a decrease in escape latency during the hidden platform training. FIG. 4C shows that during the probe trial, APP transgenic mice performed poorly and did not distinguish target quadrant from non-target quadrants, indicating that they had cognitive deficits. APP transgenic mice dosed with Mirabegron spent more time in the target quadrant relative to non-target quadrants, indicating that Mirabegron restored the cognitive deficits associated with Alzheimer's disease.

FIGS. 5A-5D show that Mirabegron (an example of β 3-adrenoceptor agonist) enhances learning and memory in a fear conditioning test. FIG. 5A shows for the assessment of conditional learning and memory, a trace fear conditioning protocol was used for the training day followed by tone-cued and contextual memory retrieval tests. On the first day (training day), mice were placed in the chamber for a 3-minute baseline recording followed by three tone-shock pairings with ITIs (intertone intervals) of 100 second. The shocks (0.5 mA, 2 seconds) were delivered 18 seconds following the tone (80 dB, 2 kHz, 20 seconds). On the second day, a novel context (new olfactory environment, different shape of chamber, new texture of the floor, and blue lighting) was used for tone-cued testing. After 3 minutes of baseline recording, three tones without shocks with ITIs of 100 seconds were presented to the mice. On the third day, mice were placed in the same context as the first day for 5 minutes with no shocks or tones to test contextual memory retrieval. FIGS. 5B-5D show in the fear conditioning test, APP transgenic mice showed deficits in trace memory (FIGS. 5B and 5C) and contextual memory retrieval (FIG. 5D) compared to the wild-type (WT) mice. Mirabegron administration restored the deficits seen in the APP mice to the WT mice level.

FIGS. 6A and 6B show the β 3-adrenergic receptor modulates an inflammatory response. FIGS. 6A and 6B show that activation of the β 3-adrenergic receptor modulates the immune response. APP transgenic mice showed lower white-blood cells (WBCs) and monocytes compared to the wild-type (WT) mice. β 3-

adrenergic receptor activation with the selective agonist Mirabegron increased the WBC (FIG. 6A) and monocytes (FIG. 6B) of APP transgenic mice to the WT levels.

FIG. 7 shows that Mirabegron (an example of a β 3-adrenoceptor agonist) produces anxiolytic effects. Effect of mirabegron on anxiety-related behavior was determined in activity chamber test where mice were placed in the corner of the square arena ($43.2 \times 43.2 \text{ cm}^2$) located inside of a sound-attenuated chamber ($66 \times 55.9 \times 55.9 \text{ cm}^3$) and allowed to freely explore the area for 10 minutes. Distance moved in the center of arena for the first 5 minutes was used as a measure of anxiety-related behavior. The activity chamber test was performed after 2 weeks of once a day administration of mirabegron. APP transgenic mice treated with mirabegron showed higher ambulatory behavior as measured by increased distance moved in the center of the area compared to the vehicle-treated AP mice, indicating that mirabegron produces anxiolytic effects.

DETAILED DESCRIPTION

The practice of the present invention will employ, unless otherwise indicated, conventional methods of medicine, pharmacology, chemistry, and biochemistry, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., *Central Nervous System Diseases and Inflammation* (T.E. Lane, M. Carson, C. Bergmann, and Tony Wyss-Coray eds., Springer, 2008); M. Donaghy *Brain's Diseases of the Nervous System* (Oxford University Press, 12th edition, 2009); *Alzheimer's Disease: Advances in Genetics, Molecular and Cellular Biology* (S.S. Sisodia and R.E. Tanzi eds., Springer; 1st edition, 2007); *Alzheimer's Disease: Targets for New Clinical Diagnostic and Therapeutic Strategies* (Frontiers in Neuroscience, R.D. Wegrzyn and A.S. Rudolph eds., CRC Press; 1st edition, 2012); A.L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition); Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001); *Methods In Enzymology* (S. Colowick and N. Kaplan eds., Academic Press, Inc.).

All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entireties.

I. DEFINITIONS

In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "an agonist" includes a mixture of two or more agonists, and the like.

The term "about," particularly in reference to a given quantity, is meant to encompass deviations of plus or minus five percent.

The term "agonist" means a molecule such as a compound, a drug, an enzyme activator or a hormone that enhances the activity of another molecule or the activity of ADRB3.

"Pharmaceutically acceptable excipient or carrier" refers to an excipient that may optionally be included in the compositions of the invention and that causes no significant adverse toxicological effects to the patient.

"Pharmaceutically acceptable salt" includes, but is not limited to, amino acid salts, salts prepared with inorganic acids, such as chloride, sulfate, phosphate, diphosphate, bromide, and nitrate salts, or salts prepared from the corresponding inorganic acid form of any of the preceding, e.g., hydrochloride, etc., or salts prepared with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, ethylsuccinate, citrate, acetate, lactate, methanesulfonate, benzoate, ascorbate, para-toluenesulfonate, palmoate, salicylate and stearate, as well as estolate, gluceptate and lactobionate salts. Similarly salts containing pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, aluminum, lithium, and ammonium (including substituted ammonium).

"CNS disorders" include, but are not limited to, stroke, ischemic stroke, neurodegenerative diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, diabetic peripheral neuropathy, and multiple sclerosis, inherited ataxias, motor neuron diseases, epilepsy, traumatic brain injury, and spinal cord injury.

The term "stroke" broadly refers to the development of neurological deficits associated with impaired blood flow to the brain regardless of cause. Potential causes include, but are not limited to, thrombosis, hemorrhage and embolism. Thrombus,

embolus, and systemic hypotension are among the most common causes of cerebral ischemic episodes. Other injuries may be caused by hypertension, hypertensive cerebral vascular disease, rupture of an aneurysm, an angioma, blood dyscrasias, cardiac failure, cardiac arrest, cardiogenic shock, septic shock, head trauma, spinal
5 cord trauma, seizure, bleeding from a tumor, or other blood loss.

An "effective amount" of an ADRB3 agonist is an amount sufficient to effect beneficial or desired results, such as an amount that activates ADRB3 or modulates the inflammatory response in the nervous system. An effective amount can be administered in one or more administrations, applications, or dosages.

10 By "therapeutically effective dose or amount" of a ADRB3 agonist is intended an amount that, when administered as described herein, brings about a positive therapeutic response with respect to treatment of an individual for a CNS disorder or mental disorder, such as an amount that enhances cognitive function or immune function in the nervous system. For example, a therapeutically effective dose or
15 amount of an ADRB3 agonist may improve learning or memory, modulate peripheral and central inflammation in the nervous system, and reduce pathological neurological deterioration. Additionally, an ADRB3 agonist may have antidepressant or anxiolytic effects. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition
20 being treated, the particular drug or drugs employed, mode of administration, and the like. An appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation, based upon the information provided herein.

"Substantially purified" generally refers to isolation of a substance (e.g.,
25 compound, molecule, agent) such that the substance comprises the majority percent of the sample in which it resides. Typically in a sample, a substantially purified component comprises 50%, preferably 80%-85%, more preferably 90-95% of the sample.

The terms "subject," "individual," and "patient," are used interchangeably
30 herein and refer to any vertebrate subject, including, without limitation, humans and other primates, including non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such

as mice, rats and guinea pigs; birds, including domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like. The term does not denote a particular age. Thus, both adult and newborn individuals are intended to be covered.

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II. Modes of Carrying Out the Invention

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular formulations or process parameters as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

Although a number of methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

The present invention is based on the discovery that ADRB3 agonists are useful in treating CNS disorders and mental disorders. In particular, the ADRB3 agonist Mirabegron was shown to improve learning and memory, restore immune function, and prevent neurological deterioration (see Examples 1-5).

In order to further an understanding of the invention, a more detailed discussion is provided below regarding ADRB3 agonists and their use in treating CNS disorders and mental disorders.

A. ADRB3 Agonists

As explained above, the methods of the present invention include administering an ADRB3 agonist for treatment of a CNS disorder or mental disorder. Exemplary ADRB3 agonists that can be used in the practice of the invention include, but are not limited to, Mirabegron, Amibegron (SR-58611A), CL-316,243, L-742,791, L-796,568, LY-368,842, Ro40-2148, and Solabegron (GW-427,353). Such agonists may improve learning and memory, restore immune function by modulating peripheral and central inflammation in the nervous system, and prevent pathological neurological deterioration. For a description of various ADRB3 agonists, see, e.g., van Wieringen et al. (2013) Eur. J. Pharmacol. 720(1-3):124-130, Arch et al. (2002) Eur. J. Pharmacol. 440(2-3):99-107, Fu et al. (2008) Eur. J. Pharmacol. 584(1): 202-

206, Candelore et al. (1999) J. Pharmacol. Exp. Ther. 290(2): 649-655, Larsen et al. (2002) Am. J. Clin. Nutr. 76(4):780-788, 76(4):780-788, Gras (2012) Drugs Today (Barc) 48(1):25-32, Hicks et al. (2007) J. Pharmacol. Exp. Ther. 323(1):202-209, Sato et al. (2008) Mol. Pharmacol. 74(5):1417-1428, Thiagamoorthy et al. (2015) Expert Opin. Investig. Drugs 24(10):1299-306, Tamburella et al. (2010) Eur. Neuropsychopharmacol. 20(10):704-13; herein incorporated by reference.

ADRB3 is a G protein-coupled receptor that regulates adenylate cyclase. The receptor is activated physiologically by epinephrine and norepinephrine. One or more agonists, acting alone or in concert may be used to activate ADRB3 for treatment of a CNS disorder or mental disorder.

B. Pharmaceutical Compositions

ADRB3 agonists (e.g., Mirabegron and Amibegron) can be formulated into pharmaceutical compositions optionally comprising one or more pharmaceutically acceptable excipients. Exemplary excipients include, without limitation, carbohydrates, inorganic salts, antimicrobial agents, antioxidants, surfactants, buffers, acids, bases, and combinations thereof. Excipients suitable for injectable compositions include water, alcohols, polyols, glycerine, vegetable oils, phospholipids, and surfactants. A carbohydrate such as a sugar, a derivatized sugar such as an alditol, aldonic acid, an esterified sugar, and/or a sugar polymer may be present as an excipient. Specific carbohydrate excipients include, for example: monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol, sorbitol (glucitol), pyranosyl sorbitol, myoinositol, and the like. The excipient can also include an inorganic salt or buffer such as citric acid, sodium chloride, potassium chloride, sodium sulfate, potassium nitrate, sodium phosphate monobasic, sodium phosphate dibasic, and combinations thereof.

A composition of the invention can also include an antimicrobial agent for preventing or deterring microbial growth. Nonlimiting examples of antimicrobial agents suitable for the present invention include benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol,

phenol, phenylethyl alcohol, phenylmercuric nitrate, thimersol, and combinations thereof.

An antioxidant can be present in the composition as well. Antioxidants are used to prevent oxidation, thereby preventing the deterioration of the ADRB3 agonist, or other components of the preparation. Suitable antioxidants for use in the present invention include, for example, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, and combinations thereof.

A surfactant can be present as an excipient. Exemplary surfactants include: polysorbates, such as "Tween 20" and "Tween 80," and pluronics such as F68 and F88 (BASF, Mount Olive, New Jersey); sorbitan esters; lipids, such as phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines (although preferably not in liposomal form), fatty acids and fatty esters; steroids, such as cholesterol; chelating agents, such as EDTA; and zinc and other such suitable cations.

Acids or bases can be present as an excipient in the composition. Nonlimiting examples of acids that can be used include those acids selected from the group consisting of hydrochloric acid, acetic acid, phosphoric acid, citric acid, malic acid, lactic acid, formic acid, trichloroacetic acid, nitric acid, perchloric acid, phosphoric acid, sulfuric acid, fumaric acid, and combinations thereof. Examples of suitable bases include, without limitation, bases selected from the group consisting of sodium hydroxide, sodium acetate, ammonium hydroxide, potassium hydroxide, ammonium acetate, potassium acetate, sodium phosphate, potassium phosphate, sodium citrate, sodium formate, sodium sulfate, potassium sulfate, potassium fumarate, and combinations thereof.

The amount of the ADRB3 agonist (e.g., when contained in a drug delivery system) in the composition will vary depending on a number of factors, but will optimally be a therapeutically effective dose when the composition is in a unit dosage form or container (e.g., a vial). A therapeutically effective dose can be determined experimentally by repeated administration of increasing amounts of the composition in order to determine which amount produces a clinically desired endpoint.

The amount of any individual excipient in the composition will vary depending on the nature and function of the excipient and particular needs of the

composition. Typically, the optimal amount of any individual excipient is determined through routine experimentation, i.e., by preparing compositions containing varying amounts of the excipient (ranging from low to high), examining the stability and other parameters, and then determining the range at which optimal performance is attained with no significant adverse effects. Generally, however, the excipient(s) will be present in the composition in an amount of about 1% to about 99% by weight, preferably from about 5% to about 98% by weight, more preferably from about 15 to about 95% by weight of the excipient, with concentrations less than 30% by weight most preferred. These foregoing pharmaceutical excipients along with other excipients are described in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), and Kibbe, A.H., Handbook of Pharmaceutical Excipients, 3rd Edition, American Pharmaceutical Association, Washington, D.C., 2000.

The compositions encompass all types of formulations and in particular those that are suited for injection, e.g., powders or lyophilates that can be reconstituted with a solvent prior to use, as well as ready for injection solutions or suspensions, dry insoluble compositions for combination with a vehicle prior to use, and emulsions and liquid concentrates for dilution prior to administration. Examples of suitable diluents for reconstituting solid compositions prior to injection include bacteriostatic water for injection, dextrose 5% in water, phosphate buffered saline, Ringer's solution, saline, sterile water, deionized water, and combinations thereof. With respect to liquid pharmaceutical compositions, solutions and suspensions are envisioned. Additional preferred compositions include those for oral, ocular, or localized delivery.

The pharmaceutical preparations herein can also be housed in a syringe, an implantation device, or the like, depending upon the intended mode of delivery and use. Preferably, the compositions comprising one or more ADRB3 agonists (e.g., Mirabegron and Amibegron) described herein are in unit dosage form, meaning an amount of a conjugate or composition of the invention appropriate for a single dose, in a premeasured or pre-packaged form.

The compositions herein may optionally include one or more additional agents, such as other drugs for treating a CNS disorder or mental disorder, or other medications used to treat a subject for a condition or disease. Particularly preferred

are compounded preparations including at least one ADRB3 agonist (e.g., Mirabegron and Amibegron) and one or more other drugs for treating a CNS disorder or mental disorder, such as analgesics, including nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen and naproxen), acetaminophen, and narcotics; sedatives (e.g., lorazepam, alprazolam, clorazepate, diazepam, and buspirone); anticonvulsants (e.g., carbamazepine, phenytoin, and gabapentin); antidepressants (e.g., tricyclic antidepressants (e.g., amitriptyline), selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, and sertraline), tetracyclic antidepressants (e.g., maprotiline), and monoamine oxidase (MAO) inhibitors (e.g., phenelzine); anti-inflammatory drugs (e.g., nonsteroidal anti-inflammatory drugs, such as aspirin, fenoprofen, ibuprofen, indomethacin, naproxen, and tolmetin); medications for Alzheimer's disease such as cholinesterase inhibitors, (e.g., galantamine, rivastigmine, donepezil) and N-methyl D-aspartate (NMDA) antagonists (e.g., memantine); medications for stroke such as anticoagulants (e.g., warfarin), antiplatelet medicines (e.g., aspirin, dipyridamole, clopidogrel), and cholesterol-lowering and blood-pressure-lowering medicines (e.g., statins, angiotensin II receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, and diuretics). Alternatively, such agents can be contained in a separate composition from the composition comprising an ADRB3 agonist (e.g., Mirabegron or Amibegron) and co-administered concurrently, before, or after the composition comprising an ADRB3 agonist.

C. Administration

At least one therapeutically effective cycle of treatment with an ADRB3 agonist (e.g., Mirabegron and Amibegron) will be administered to a subject for treatment of a CNS disorder or mental disorder. CNS disorders include, but are not limited to stroke, ischemic stroke, neurodegenerative diseases, such as Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, diabetic peripheral neuropathy, and multiple sclerosis, inherited ataxias, motor neuron diseases, epilepsy, traumatic brain injury, and spinal cord injury. Mental disorders include, but are not limited to anxiety disorders and schizophrenia.

By "therapeutically effective cycle of treatment" is intended a cycle of treatment that when administered, brings about a positive therapeutic response with respect to treatment of an individual for a CNS disorder or mental disorder. Of

particular interest is a cycle of treatment with an ADRB3 agonist (e.g., Mirabegron or Amibegron) that enhances cognitive function or immune function in the nervous system. For example, a therapeutically effective dose or amount of an ADRB3 agonist may improve learning or memory, modulate peripheral or central
5 inflammation in the nervous system, or reduce pathological neurological deterioration. Additionally, an ADRB3 agonist may have antidepressant or anxiolytic effects.

In certain embodiments, multiple therapeutically effective doses of compositions comprising one or more ADRB3 agonists (e.g., Mirabegron and
10 Amibegron), and/or one or more other therapeutic agents, such as other drugs for treating a CNS disorder or mental disorder, or other medications will be administered. The compositions of the present invention are typically, although not necessarily, administered orally, via injection (subcutaneously, intravenously, or intramuscularly), by infusion, or locally. Additional modes of administration are also contemplated,
15 such as topical, intralesion, intracerebral, intracerebroventricular, intraparenchymatous, pulmonary, rectal, transdermal, transmucosal, intrathecal, pericardial, intra-arterial, intraocular, intraperitoneal, and so forth.

The preparations according to the invention are also suitable for local treatment. In a particular embodiment, a composition of the invention is used for
20 localized delivery of an ADRB3 agonist for the treatment of a CNS disorder or mental disorder. For example, compositions may be administered locally into cerebrospinal fluid or the brain of a subject. The particular preparation and appropriate method of administration are chosen to target the ADRB3 agonist to the site where activation of ADRB3 is desired.

25 The pharmaceutical preparation can be in the form of a liquid solution or suspension immediately prior to administration, but may also take another form such as a syrup, cream, ointment, tablet, capsule, powder, gel, matrix, suppository, or the like. The pharmaceutical compositions comprising one or more ADRB3 agonists and other agents may be administered using the same or different routes of administration
30 in accordance with any medically acceptable method known in the art.

In another embodiment, the pharmaceutical compositions comprising one or more ADRB3 agonists and/or other agents are administered prophylactically, e.g., to prevent neurological deterioration and cognitive decline associated with progression

of a CNS disorder or mental disorder. Such prophylactic uses will be of particular value for subjects with a genetic predisposition for developing a CNS disorder or mental disorder.

In another embodiment of the invention, the pharmaceutical compositions comprising one or more ADRB3 agonists and/or other agents are in a sustained-release formulation, or a formulation that is administered using a sustained-release device. Such devices are well known in the art, and include, for example, transdermal patches, and miniature implantable pumps that can provide for drug delivery over time in a continuous, steady-state fashion at a variety of doses to achieve a sustained-release effect with a non-sustained-release pharmaceutical composition.

The invention also provides a method for administering a conjugate comprising an ADRB3 agonist as provided herein to a patient suffering from a condition that is responsive to treatment with an ADRB3 agonist contained in the conjugate or composition. The method comprises administering, via any of the herein described modes, a therapeutically effective amount of the conjugate or drug delivery system, preferably provided as part of a pharmaceutical composition. The method of administering may be used to treat any condition that is responsive to treatment with an ADRB3 agonist. More specifically, the compositions herein are effective in treating a CNS disorder (e.g., Alzheimer's disease or stroke) or mental disorder (e.g., anxiety disorder or schizophrenia).

Those of ordinary skill in the art will appreciate which conditions a specific ADRB3 agonist can effectively treat. The actual dose to be administered will vary depending upon the age, weight, and general condition of the subject as well as the severity of the condition being treated, the judgment of the health care professional, and conjugate being administered. Therapeutically effective amounts can be determined by those skilled in the art, and will be adjusted to the particular requirements of each particular case.

Generally, a therapeutically effective amount will range from about 0.50 mg to 5 grams of an ADRB3 agonist daily, more preferably from about 5 mg to 2 grams daily, even more preferably from about 7 mg to 1.5 grams daily. Preferably, such doses are in the range of 10-600 mg four times a day (QID), 200-500 mg QID, 25-600 mg three times a day (TID), 25-50 mg TID, 50-100 mg TID, 50-200 mg TID, 300-600 mg TID, 200-400 mg TID, 200-600 mg TID, 100 to 700 mg twice daily

(BID), 100-600 mg BID, 200-500 mg BID, or 200-300 mg BID. The amount of compound administered will depend on the potency of the specific ADRB3 agonist and the magnitude or effect desired and the route of administration.

A purified ADRB3 agonist (again, preferably provided as part of a pharmaceutical preparation) can be administered alone or in combination with one or more other therapeutic agents, such as other agents for treating a CNS disorder or mental disorder, including, but not limited to, analgesics, including nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen and naproxen), acetaminophen, and narcotics; sedatives (e.g., lorazepam, alprazolam, clorazepate, diazepam, and buspirone); anticonvulsants (e.g., carbamazepine, phenytoin, and gabapentin); antidepressants (e.g., tricyclic antidepressants (e.g., amitriptyline), selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, and sertraline), tetracyclic antidepressants (e.g., maprotiline), and monoamine oxidase (MAO) inhibitors (e.g., phenelzine); anti-inflammatory drugs (e.g., nonsteroidal anti-inflammatory drugs, such as aspirin, fenopufen, ibuprofen, indomethacin, naproxen, and tolmetin); medications for Alzheimer's disease such as cholinesterase inhibitors, (e.g., galantamine, rivastigmine, donepezil) and N-methyl D-aspartate (NMDA) antagonists (e.g., memantine); medications for stroke such as anticoagulants (e.g., warfarin), antiplatelet medicines (e.g., aspirin, dipyridamole, clopidogrel), and cholesterol-lowering and blood-pressure-lowering medicines (e.g., statins, angiotensin II receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, and diuretics); or other medications used to treat a particular condition or disease according to a variety of dosing schedules depending on the judgment of the clinician, needs of the patient, and so forth. The specific dosing schedule will be known by those of ordinary skill in the art or can be determined experimentally using routine methods. Exemplary dosing schedules include, without limitation, administration five times a day, four times a day, three times a day, twice daily, once daily, three times weekly, twice weekly, once weekly, twice monthly, once monthly, and any combination thereof. Preferred compositions are those requiring dosing no more than once a day.

Additionally, an antagonist of ADRB3 may be administered in combination with an ADRB3 agonist, wherein the ADRB3 agonist is active in the central nervous

system and the ADRB3 antagonist is active in the peripheral nervous system and does not cross the blood-brain barrier. Exemplary ADRB3 antagonists include L-748,328, L-748,337, and SR59230A. For a description of ADRB3 antagonists, see, e.g., Candelore et al. (1999) *J. Pharmacol. Exp. Ther.* 290(2):649-655, Nisoli et al. (1996) *Mol. Pharmacol.* 49(1):7-14; herein incorporated by reference.

An ADRB3 agonist can be administered prior to, concurrent with, or subsequent to other agents. If provided at the same time as other agents, one or more ADRB3 agonists can be provided in the same or in a different composition. Thus, one or more ADRB3 agonists and other agents can be presented to the individual by way of concurrent therapy. By “concurrent therapy” is intended administration to a subject such that the therapeutic effect of the combination of the substances is caused in the subject undergoing therapy. For example, concurrent therapy may be achieved by administering a dose of a pharmaceutical composition comprising an ADRB3 agonist and a dose of a pharmaceutical composition comprising at least one other agent, such as another ADRB3 agonist or drug for treating a CNS disorder or mental disorder, or ADRB3 antagonist, which in combination comprise a therapeutically effective dose, according to a particular dosing regimen. Similarly, one or more ADRB3 agonists and one or more other therapeutic agents can be administered in at least one therapeutic dose. Administration of the separate pharmaceutical compositions can be performed simultaneously or at different times (i.e., sequentially, in either order, on the same day, or on different days), as long as the therapeutic effect of the combination of these substances is caused in the subject undergoing therapy.

C. Kits

The invention also provides kits comprising one or more containers holding compositions comprising at least one ADRB3 agonist and optionally one or more other agents for treating a CNS disorder or mental disorder, or an ADRB3 antagonist. Compositions can be in liquid form or can be lyophilized. Suitable containers for the compositions include, for example, bottles, vials, syringes, and test tubes. Containers can be formed from a variety of materials, including glass or plastic. A container may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle).

The kit can further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution, or dextrose solution. It can also contain other materials useful to the end-user, including other pharmaceutically acceptable formulating solutions such as buffers, diluents, filters, needles, and syringes or other delivery devices. The delivery device may be pre-filled with the compositions.

The kit can also comprise a package insert containing written instructions for methods of using the compositions comprising ADRB3 agonists for treating a subject for a CNS disorder or mental disorder. The package insert can be an unapproved draft package insert or can be a package insert approved by the Food and Drug Administration (FDA) or other regulatory body.

III. Experimental

Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

Example 1

Modulation of ADRB3 with Selective Agonists for Treatment of CNS Disorders and Stroke

We have shown that selective agonists of ADRB3 can be used for enhancement of cognitive function, modulation of systemic and central inflammation and prevention of pathological detrition for treatment of CNS disorders and stroke. Mirabegron, an example of a β_3 -adrenoceptor agonist, enhanced learning and memory and modulated the inflammatory response in a Thy1-APPLond/Swe+ mouse model of Alzheimer disease. Mirabegron as well as other ADRB3 agonists can also be used for

enhancement of cognitive function and modulation of the inflammatory response for treatment of neurocognitive disorders.

5

Example 2

The Selective ADRB3 Antagonist L- 748,337 Impairs Cognitive Function

As shown in FIG. 2B, mice treated with L-748,337 showed impaired spontaneous alternation behavior in a Y-maze, indicating that acute inhibition of the beta3-adrenergic receptor with the selective antagonist L-748,337 impaired spatial memory. The pharmacological properties of L-748,337 are shown in Table 1. As shown in Table 1, the L-748,337 antagonist inhibits ADRB3 with a K_i of 4 nM and shows selectivity for ADRB3 over other adrenergic receptors.

15

Table 1. Pharmacological properties of L-748,337		
K_i	beta3-adrenergic receptor	4 nM
	beta2-adrenergic receptor	204 nM
	beta1-adrenergic receptor	390 nM
IC_{50} for beta3-adrenergic receptor		6 nM

Example 3

The Selective ADRB3 Agonist Mirabegron Enhances Learning and Memory in a Morris Water Maze

The ADRB3 agonist, Mirabegron, enhanced learning and memory in an APP transgenic mouse model of Alzheimer's disease. The amyloid precursor protein (APP)

transgenic mouse expresses human APP751 cDNA containing the London (V717I) and Swedish (K670M/N671L) mutations under the regulatory control of the murine Thy1 gene (Faizi et al. (2012) Brain Behav. 2(2):142-154, herein incorporated by reference in its entirety). APP transgenic mice display hyperactivity, deficits in
5 spontaneous alternation behavior, memory retrieval impairment, and apparent decreased social memory and discrimination (Faizi et al., *supra*). The cognitive and psychiatric deficits of these APP transgenic mice mimic those exhibited by human patients who have Alzheimer's disease.

APP transgenic mice were placed in a Morris water maze (MWM) containing
10 a large water tank (178 cm in diameter) filled with water. A circular platform was placed about 1 cm below the water surface approximately 17 cm away from the wall in one quadrant of the tank. Nontoxic tempera paints were used to make the water opaque. During three consecutive days of hidden platform training, mice were released from drop locations and given 60 seconds to find the platform. Upon
15 completion of the hidden platform training, the platform was removed and a 60-second probe trial was conducted. Successful learning of the MWM by the mice was determined by observing a gradual decrease in escape latency during the hidden platform training and discriminative quadrant exploration during the probe trial (FIG. 4A).

20 The APP transgenic mice were dosed with Mirabegron (5 mg/kg) to determine what effects an ADRB3 agonist would have on learning. The APP transgenic mice treated with Mirabegron exhibited improved learning compared to those treated with vehicle as indicated by decreased escape latency during the hidden platform training (FIG. 4B). During the probe trial, APP transgenic mice performed poorly and did not
25 distinguish target quadrant from non-target quadrants, indicating that they had cognitive deficits. APP transgenic mice dosed with Mirabegron spent more time in the target quadrant relative to non-target quadrants, indicating that Mirabegron restored the cognitive deficits associated with Alzheimer's disease (FIG. 4C).

Example 4

The Selective ADRB3 Agonist Mirabegron Enhances Learning and Memory in a Fear Conditioning Test

5

For the assessment of conditional learning and memory, a trace fear conditioning protocol was used for the training day followed by tone-cued and contextual memory retrieval tests. On the first day (training day), APP transgenic mice were placed in the chamber for a 3-minute baseline recording followed by three
10 tone-shock pairings with ITIs (intertone intervals) of 100 seconds. The shocks (0.5 mA, 2 seconds) were delivered for 18 seconds following the tone (80 dB, 2 kHz, 20 seconds). On the second day, a novel context (new olfactory environment, different shape of chamber, new texture of the floor, and blue lighting) was used for tone-cued testing. After 3 minutes of baseline recording, three tones without shocks with ITIs of
15 100 seconds were presented to the mice. On the third day, mice were placed in the same context as the first day for 5 minutes with no shocks or tones to test contextual memory retrieval (FIG. 5A).

In the fear conditioning test, APP transgenic mice showed deficits in trace memory and contextual memory retrieval compared to the wild-type (WT) mice.
20 Mirabegron administration restored the APP mice to the level of functioning of WT mice (FIG. 5B).

Example 5

25

The Selective ADRB3 Agonist Mirabegron Modulates the Inflammatory Response

APP transgenic mice showed lower white-blood cells (WBCs) and monocytes
30 compared to wild-type (WT) mice. Beta3-adrenergic receptor activation with the selective agonist Mirabegron increased the white-blood cells and monocytes of APP transgenic mice to wild-type levels (FIGS. 6A and 6B). Thus, Mirabegron restores the inflammatory response in a mouse model of Alzheimer disease. By modulation of

peripheral and central inflammation, Mirabegron may have pro-cognitive effects and prevent the pathology associated with neurocognitive disorders.

- 5 While the preferred embodiments of the invention have been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

Claims

What is claimed is:

1. A method for treating a subject for a central nervous system (CNS) disorder,
5 the method comprising administering to the subject a therapeutically effective amount of a β_3 -adrenoceptor (ADRB3) agonist.
2. The method of claim 1, wherein the ADRB3 agonist is Mirabegron or Amibegron.
10
3. The method of claim 1, wherein the CNS disorder is Alzheimer's disease or stroke.
4. The method of claim 1, wherein treatment improves learning or memory of the
15 subject.
5. The method of claim 1, wherein treatment modulates inflammation in the peripheral or central nervous system.
- 20 6. The method of claim 1, wherein treatment reduces rate of pathological neurological deterioration in the subject.
7. The method of claim 1, wherein multiple cycles of treatment are administered to the subject.
25
8. The method of claim 7, wherein the ADRB3 agonist is administered intermittently or according to a daily dosing regimen.
9. The method of claim 1, wherein the ADRB3 agonist is administered orally.
30
10. The method of claim 1, wherein the subject is human.

11. The method of claim 1, wherein the ADRB3 agonist is active in the central nervous system.
12. The method of claim 1, further comprising administering an antagonist of ADRB3.
13. The method of claim 12, wherein the antagonist is selected from the group consisting of L-748,328, L-748,337, and SR 59230A.
14. The method of claim 12, wherein the ADRB3 agonist is active in the central nervous system, and the ADRB3 antagonist is active in the peripheral nervous system and does not cross the blood-brain barrier.
15. The method of claim 1, further comprising administering an acetylcholinesterase inhibitor.
16. The method of claim 15, wherein the acetylcholinesterase inhibitor is selected from the group consisting of Donepezil (Aricept), Rivastigmine (Exelon), and Galantamine (Razadyne).
17. The method of claim 1, further comprising administering an N-methyl D-aspartate (NMDA) receptor antagonist.
18. The method of claim 17, wherein the NMDA receptor antagonist is Memantine (Namenda).
19. The method of claim 3, wherein treatment improves recovery after the stroke.
20. The method of claim 3, wherein the stroke is an ischemic or hemorrhagic stroke.

21. A method of increasing monocyte count or white blood cell count in a subject who has Alzheimer's disease, the method comprising administering to the subject a therapeutically effective amount of a β_3 -adrenoceptor (ADRB3) agonist.
- 5 22. The method of claim 21, wherein the ADRB3 agonist is Mirabegron or Amibegron.
23. A method of improving learning or memory in a subject who has Alzheimer's disease, the method comprising administering to the subject a therapeutically effective
10 amount of a β_3 -adrenoceptor (ADRB3) agonist.
24. The method of claim 23, wherein the ADRB3 agonist is Mirabegron or Amibegron.
- 15 25. A method for treating a subject for an anxiety disorder or schizophrenia, the method comprising administering to the subject a therapeutically effective amount of a β_3 -adrenoceptor (ADRB3) agonist.
26. The method of claim 25, wherein the ADRB3 agonist is Mirabegron or
20 Amibegron.
27. The method of claim 25, wherein the ADRB3 agonist is active in the central nervous system.
- 25 28. The method of claim 25, further comprising administering an antagonist of ADRB3.
29. The method of claim 28, wherein the antagonist is selected from the group consisting of L-748,328, L-748,337, and SR 59230A.
30
30. The method of claim 28, wherein the antagonist is active in the peripheral nervous system and does not cross the blood-brain barrier.

31. A composition comprising a β_3 -adrenoceptor (ADRB3) agonist for use in the treatment of a central nervous system (CNS) disorder.

32. The composition of claim 31, wherein the ADRB3 agonist is Mirabegron or
5 Amibegron.

33. The composition of claim 31, wherein the CNS disorder is Alzheimer's disease or stroke.

10

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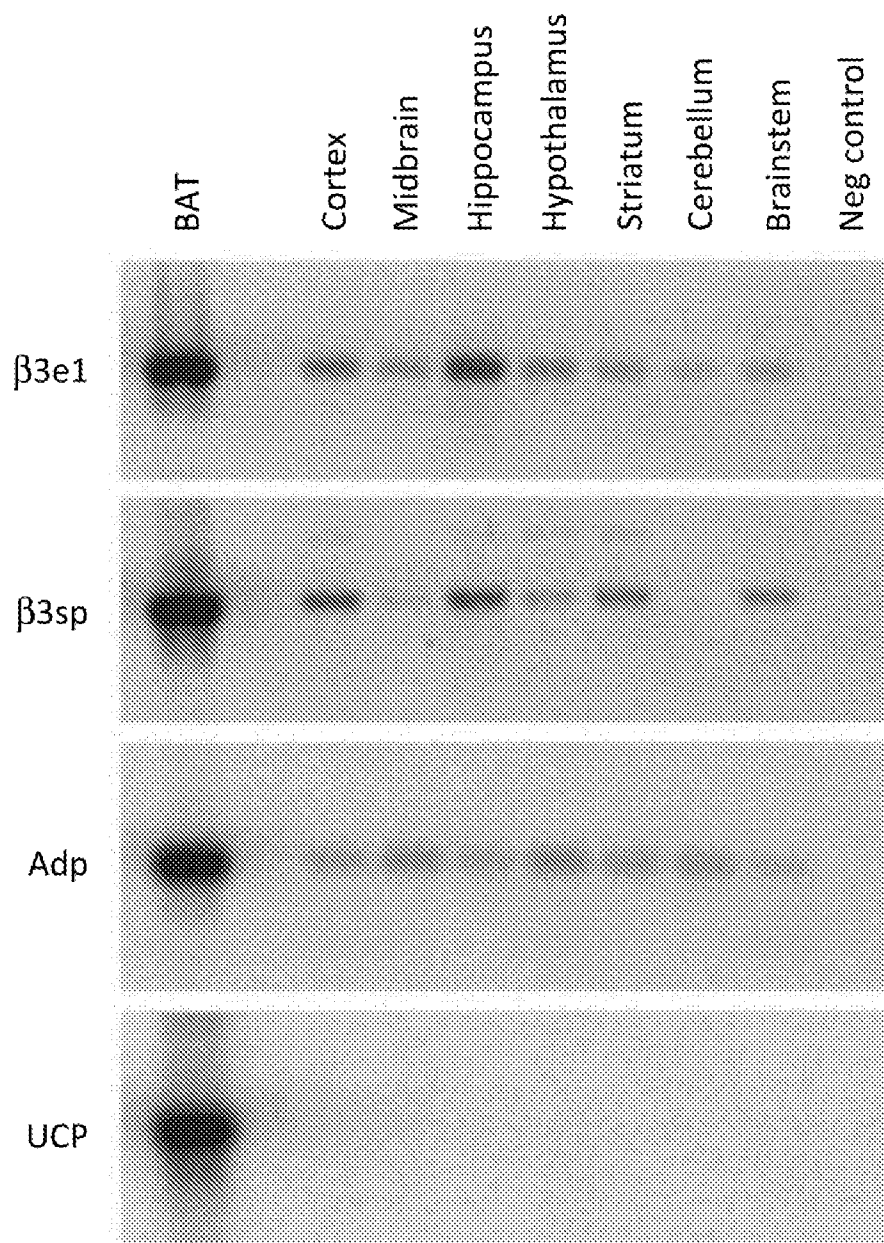


FIG. 1

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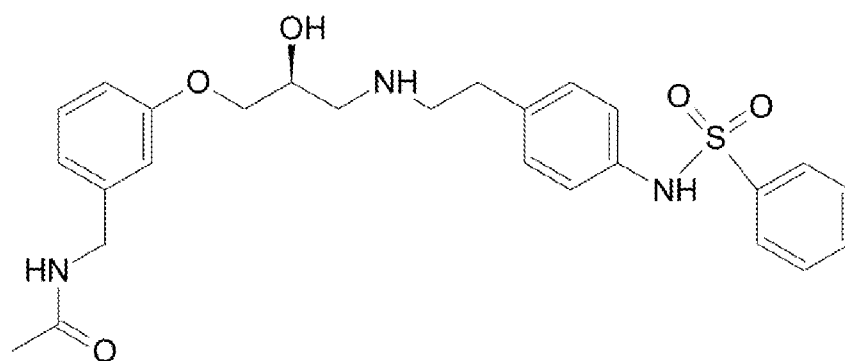


FIG. 2A

3/17

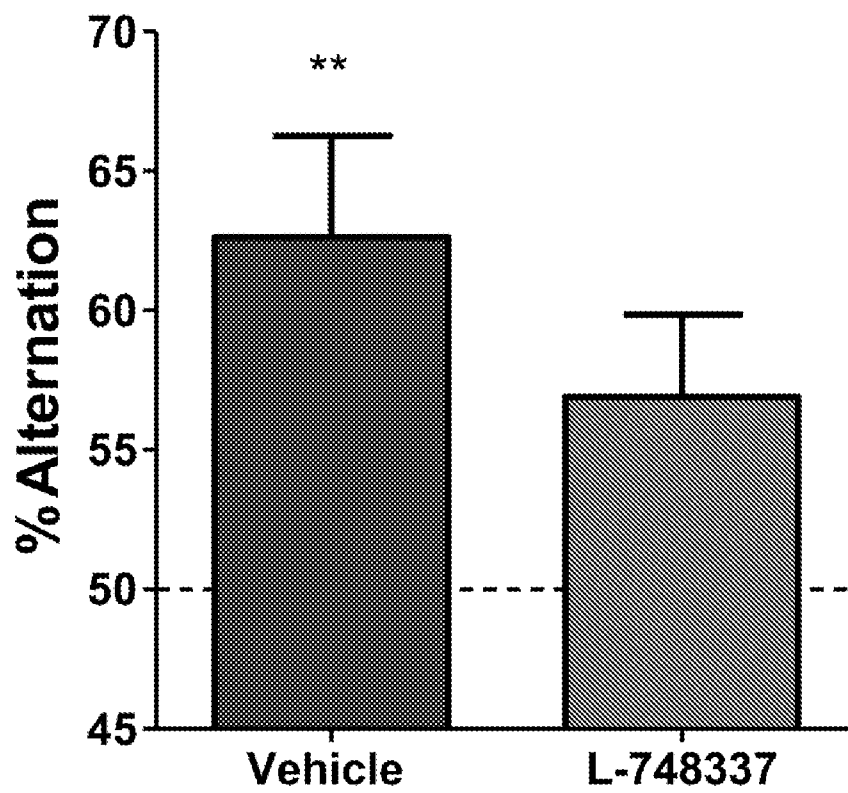


FIG. 2B

4/17

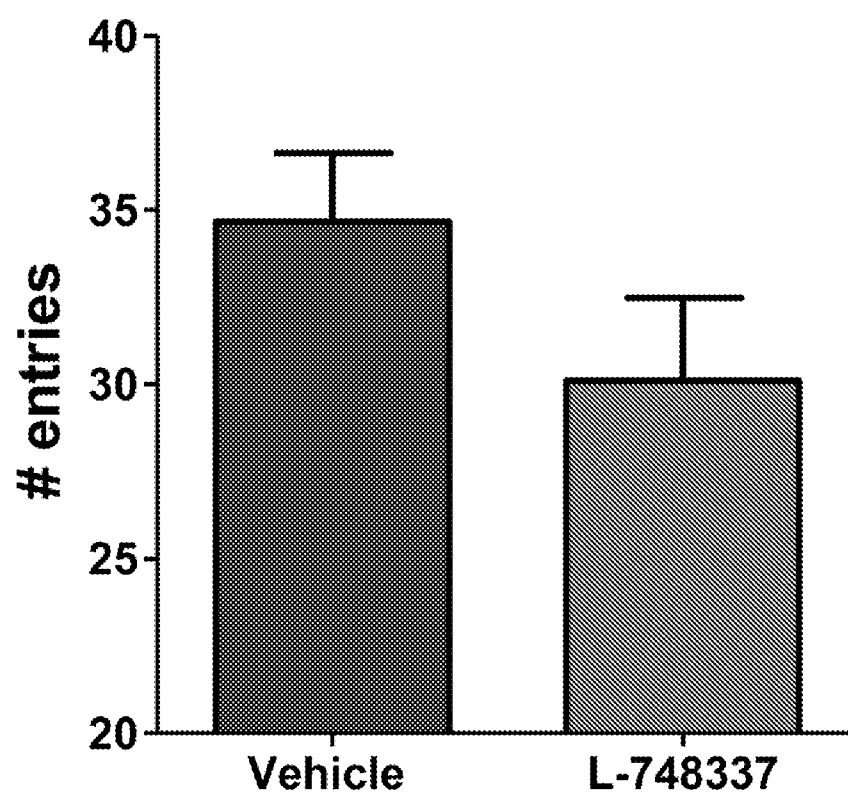


FIG. 2C

5/17

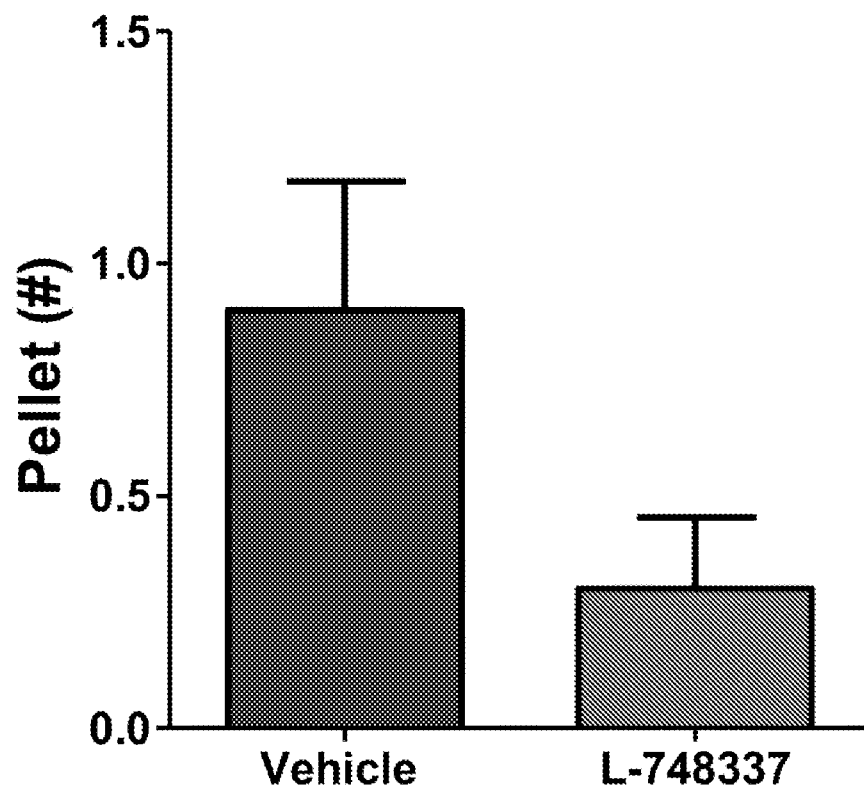


FIG. 2D

6/17

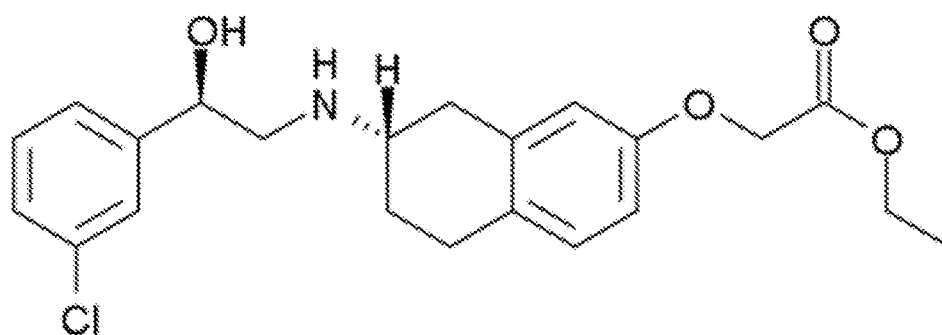
**Amibegron**

FIG. 3A

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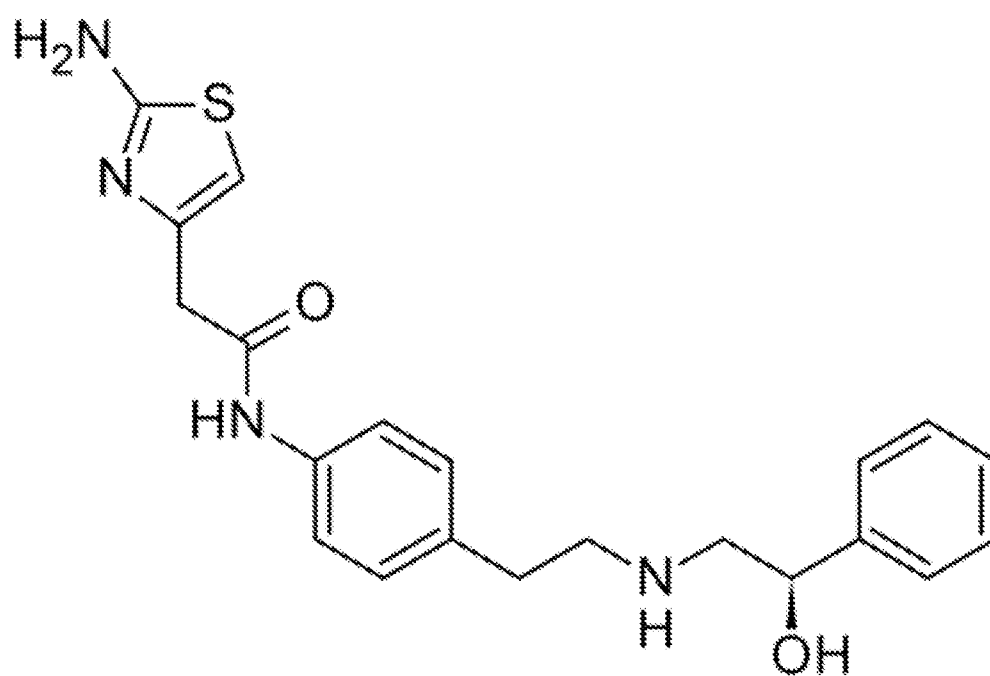
**Mirabegron**

FIG. 3B

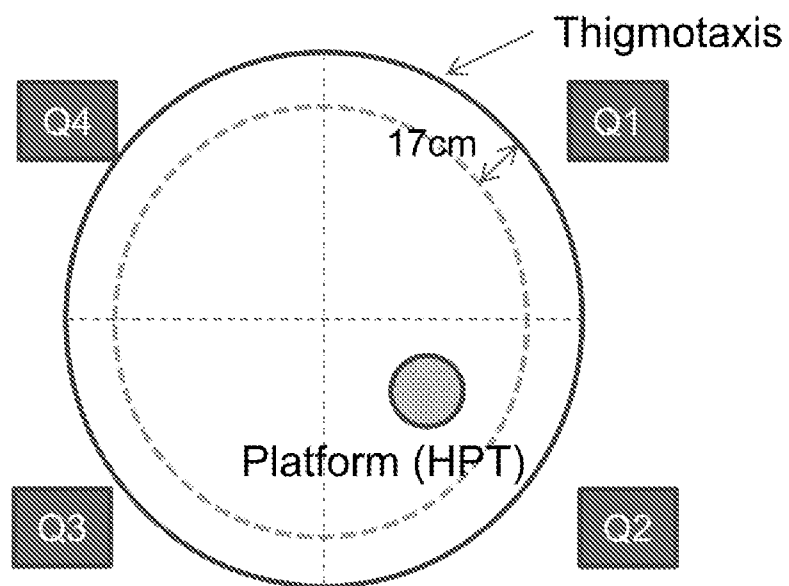


FIG. 4A

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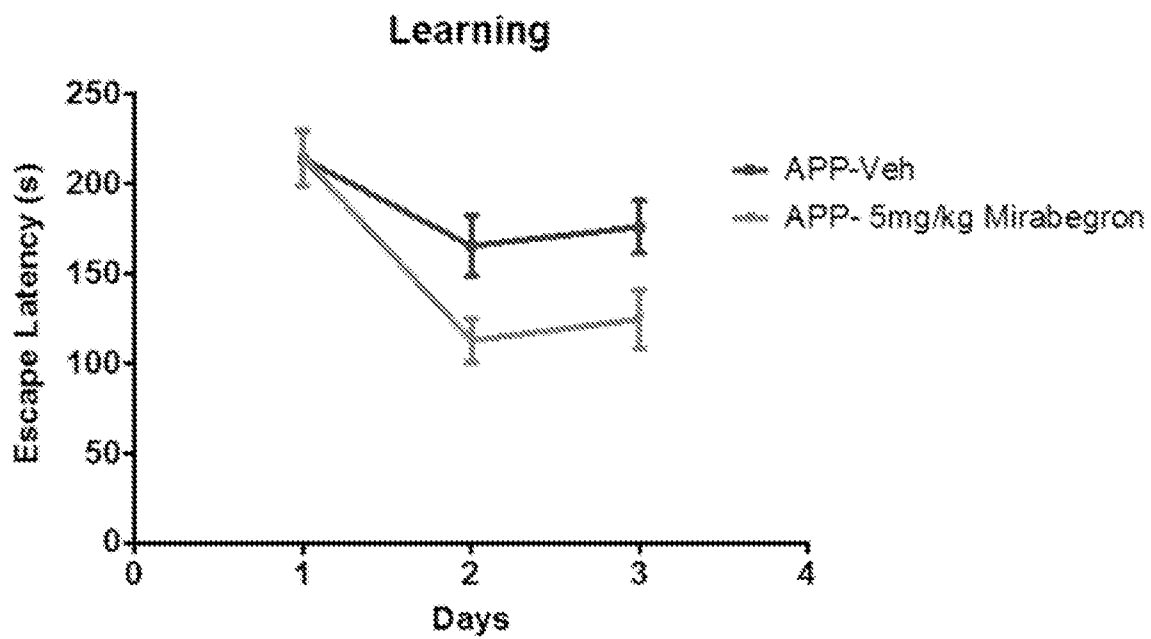


FIG. 4B

10/17

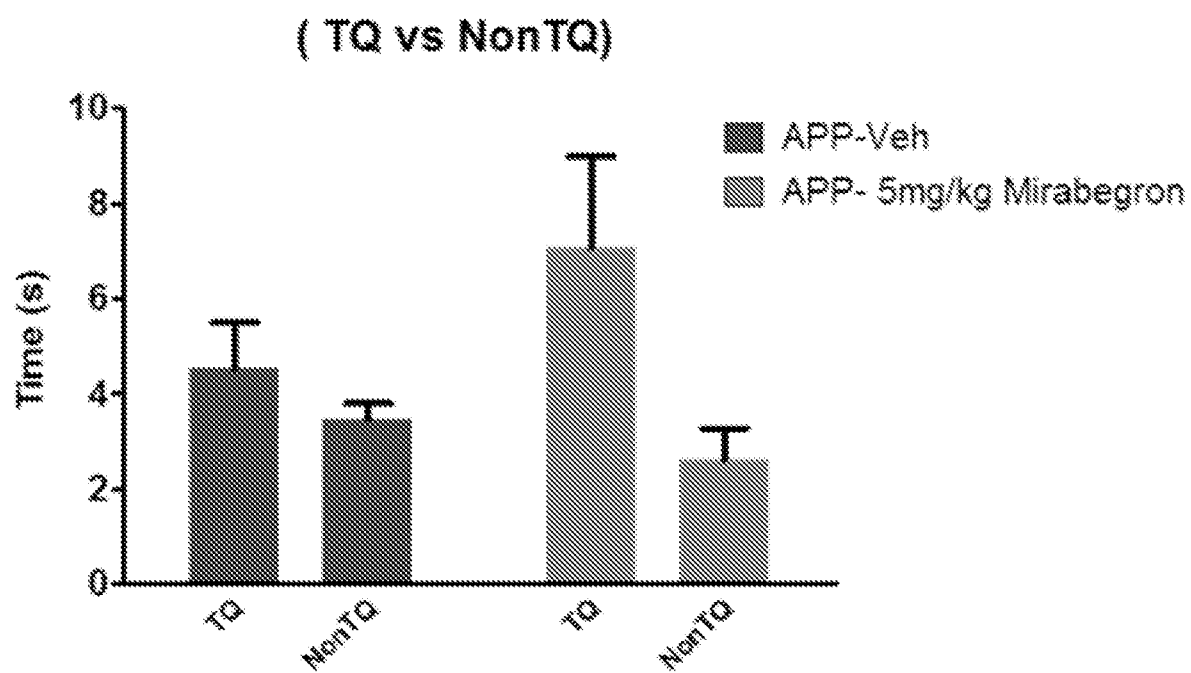


FIG. 4C

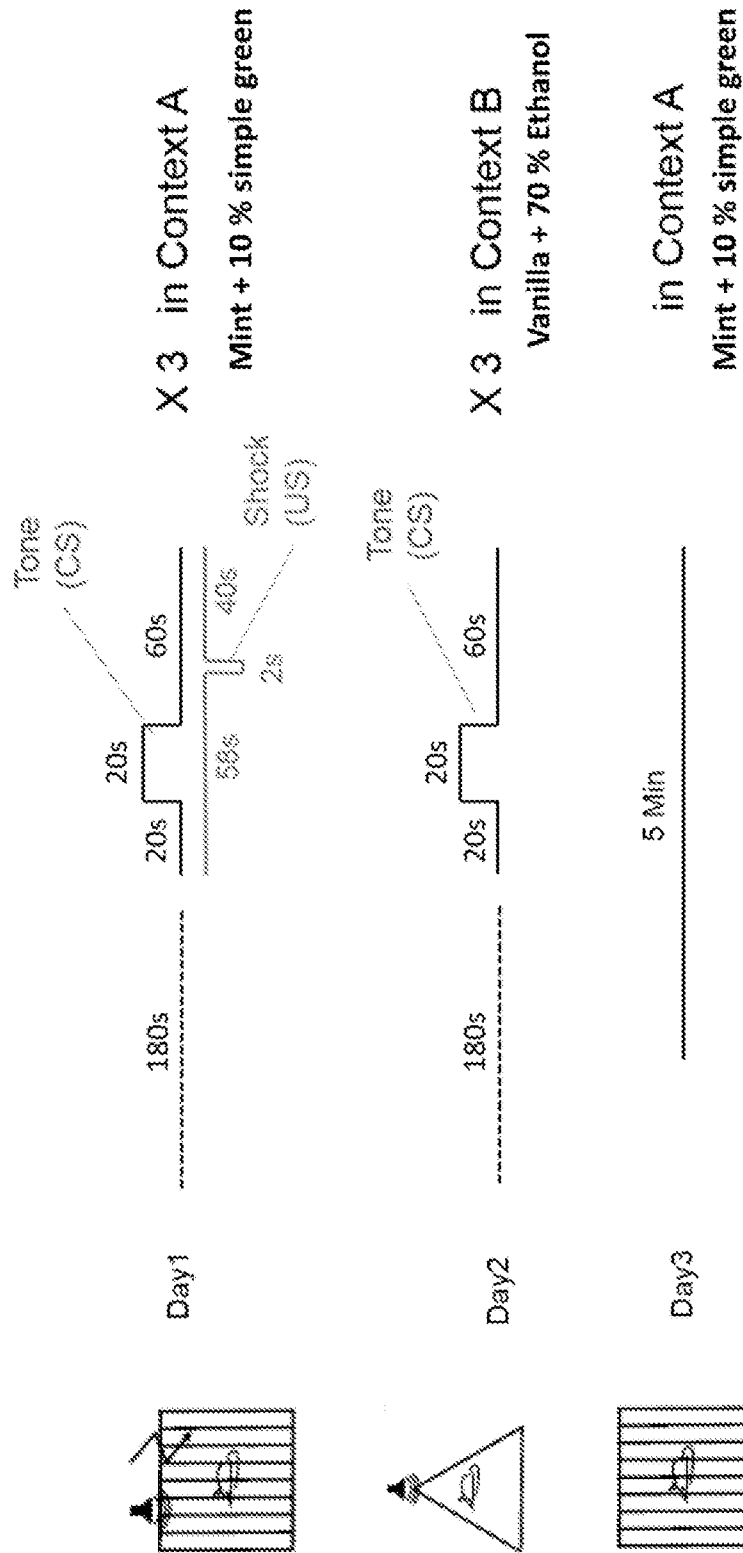


FIG. 5A

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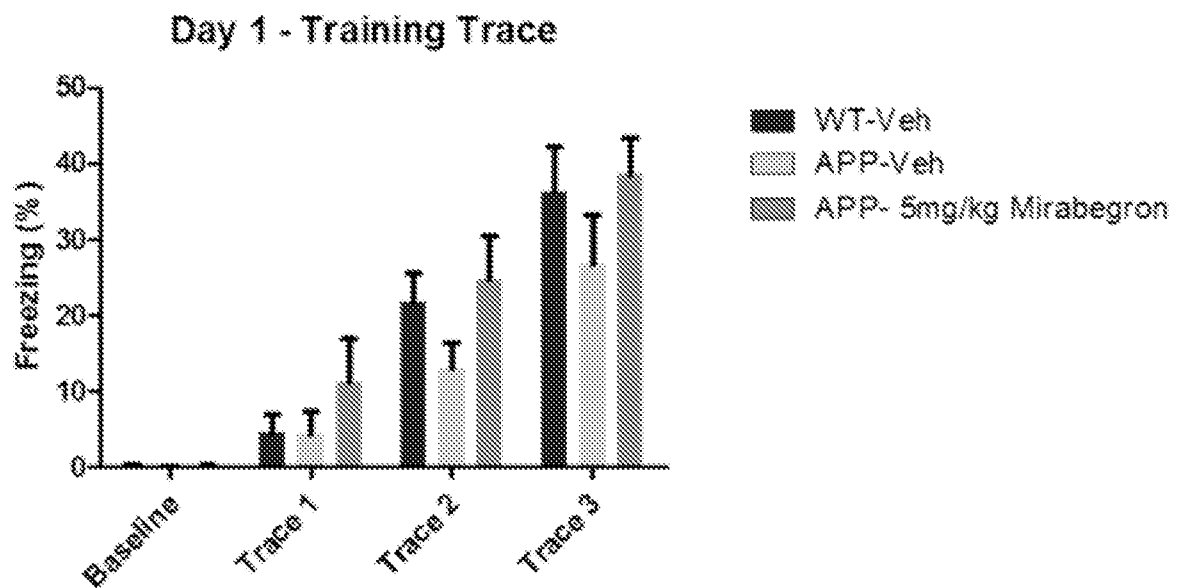


FIG. 5B

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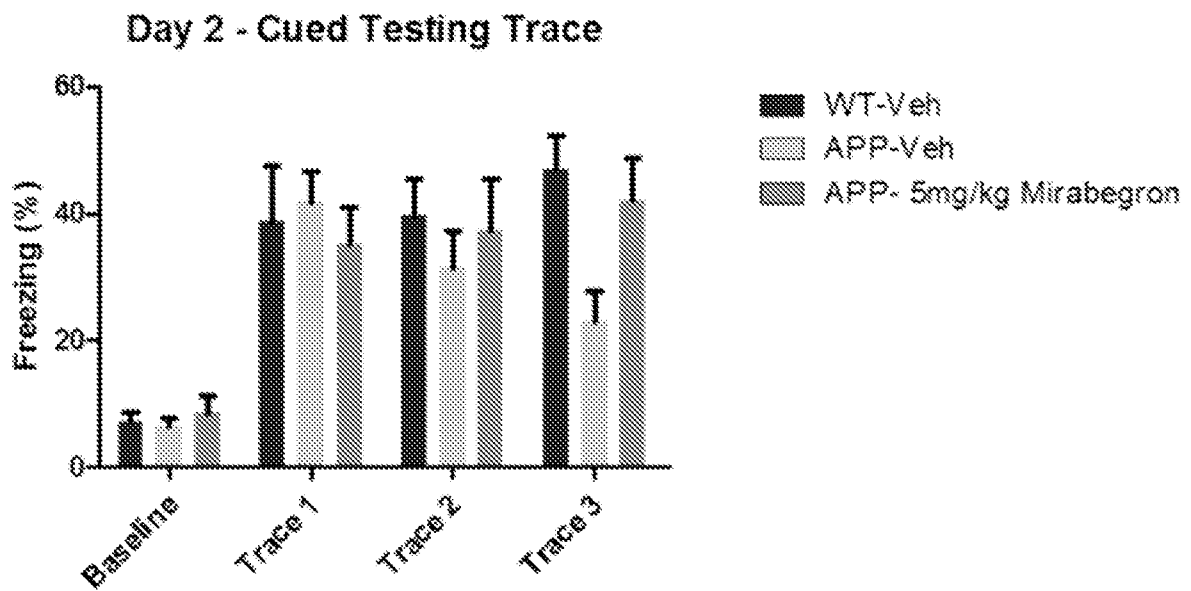


FIG. 5C

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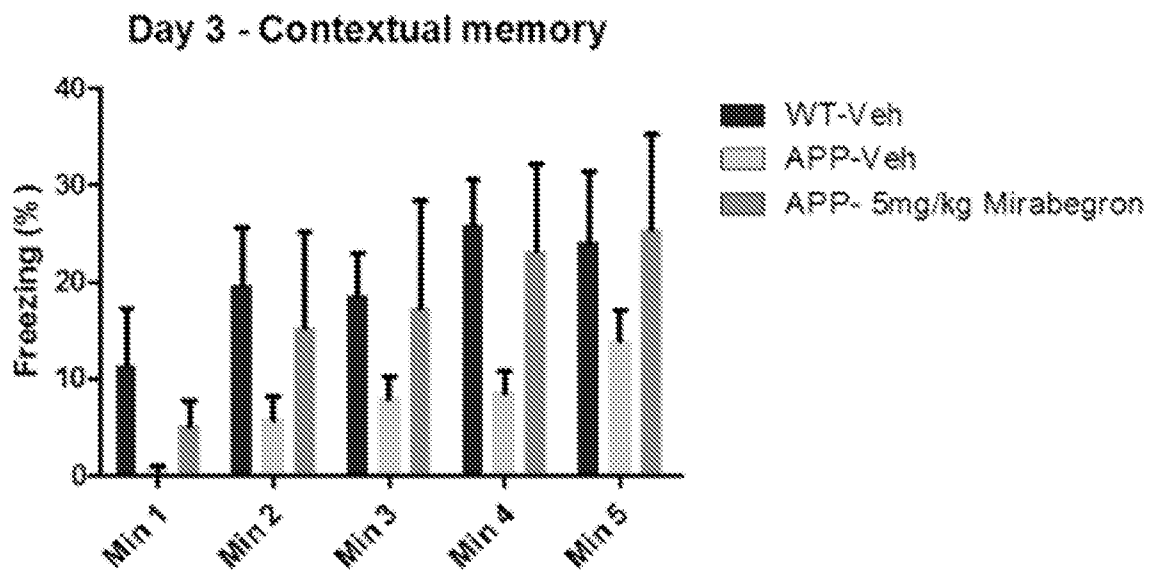


FIG. 5D

15/17

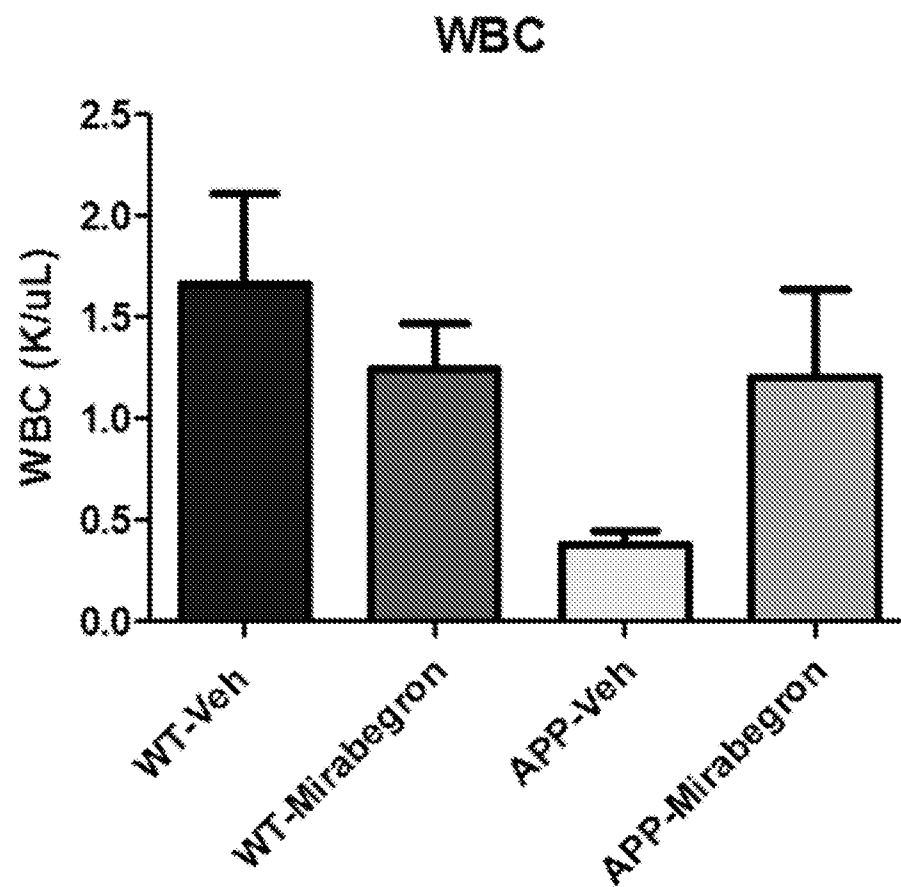


FIG. 6A

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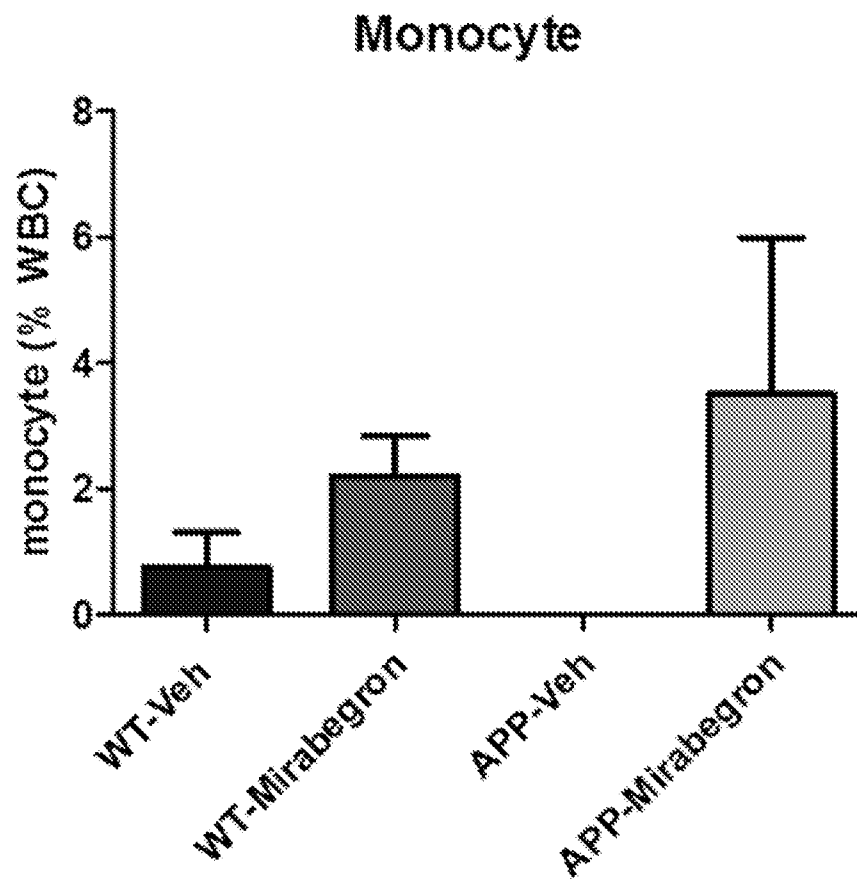


FIG. 6B

17/17

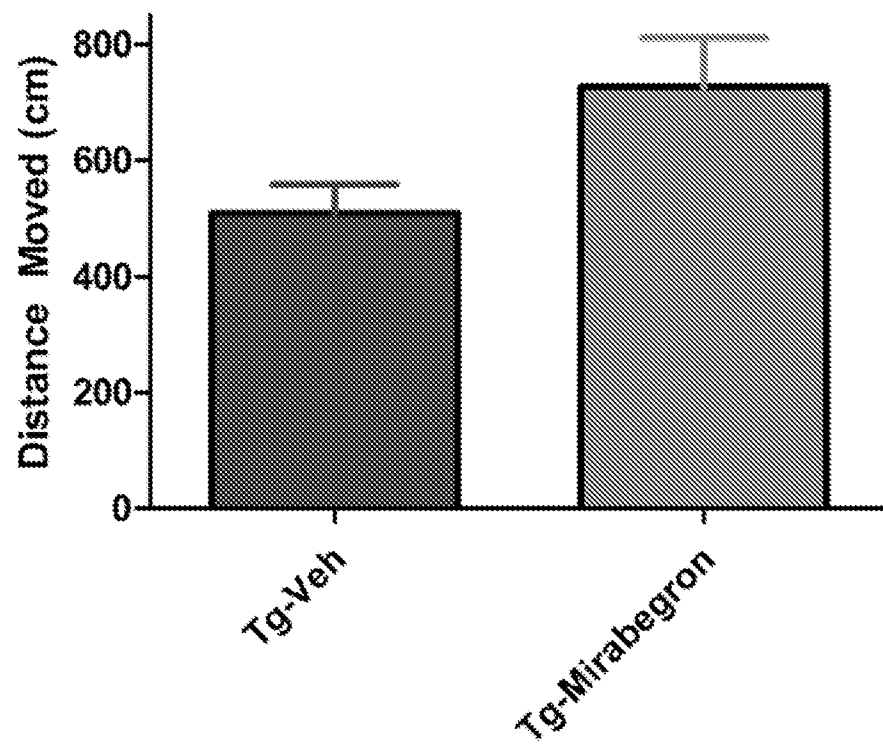


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/67066

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 25/28, A61P 3/00, G01N 27/447 (2017.01)

CPC - C12Q 2600/154, C12Q 2600/158, C12Q 1/6886

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)

IPC(8) - A61P 25/28, A61P 3/00, G01N 27/447 (2017.01)

CPC - C12Q 2600/154, C12Q 2600/158, C12Q 1/6886

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

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

Patbase, Google Patent, Google Web

Search terms used - adrb3 agonist antagonist alzheimer's administered Mirabegron Amibegron SR 58611 L-748,328 L-748,337

Pubchem substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 8,790,889 B2 (Jhaveri et al.) 29 July 2014 (29.07.2014); col 1, ln 44-45, 50-51, col 3, ln 20-22, col 4, ln 24-31, ln 35-38, col 8, ln 21, col 11, 14-15, col 13, ln 3-5	1-4, 6, 9-11, 19-20, 23-24, 31-33 ----- 5, 15-18, 21-22
X -- Y	US 8,906,955 B2 (Lin et al.) 09 December 2014 (09.12.2014); col 2, ln 24-25, col 4, ln 23-25	1, 12-14 ----- 28-30
X -- Y	Stemmelin et al. "Stimulation of the beta3-Adrenoceptor as a Novel Treatment Strategy for Anxiety and Depressive Disorders" Neuropsychopharmacology. 25 April 2007 (25.04.2007) vol 33, pg. 574-587; pg. 574, right col, para 1, pg. 576, left col, para 5, right col, para 2, abstract	1, 7-8, 25-27 ----- 28-30
Y	Mandrekar et al. "Microglia and Inflammation in Alzheimer's Disease" NIH Public Access. 14 May 2013 (14.05.2013) pg. 1-24; pg. 2, para 3, pg. 4, para 3	5
Y	US 2004/0229913 A1 (Emir et al.) 18 November 2004 (18.11.2004); para [0002]	15-16
Y	US 2006/0062851 A1 (Vergez et al.) 23 March 2006 (23.03.2006); para [0008]	17-18
Y	Theriault et al. "The dynamics of monocytes and microglia in Alzheimer's disease" Alzheimer's Research & Therapy. 15 April 2015 (15.04.2015) vol 7, pg. 1-10; pg. 8, right col, para 1	21-22
A	US 2003/0212063 A1 (Lafontaine et al.) 13 November 2003 (13.11.2003); entire document	1-33

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"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

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

08 February 2017

Date of mailing of the international search report

22 MAR 2017

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