Express Mail Label No.: EEV392125245US
Date of Deposit: December 10, 2004

Attorney Docket No. 22531-801A PRO

13146 U.S.PTO 121004

11800 U.S.PTO 60/635365 121004

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR § 1.53(c)

INVENTORS / APPLICANTS

Given Name (last name, first name, and middle initial [if any])			Residence (City and State or Foreign Country)
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TITLE OF THE INVENTION

USE OF UN-COMPETITIVE NMDA ANTAGONISTS IN THE TREATMENT OF TSC

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ENCLOSED APPLICATION PARTS

☒ **Specification** Number of Pages: 16
☐ **Sequence Listing** Number of Pages:
☐ **Drawings** (☐ Formal; ☐ Informal) Number of Sheets:
☐ **Other documents** (specify):

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government:
☒ No.
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Respectfully submitted,

Date: December 10, 2004

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TRA 1986331v1

Use of Un-Competitive NMDA Antagonists in the Treatment of TSC

Background

Tuberous sclerosis Complex (TSC) is an autosomal dominant disorder characterized by widespread development of growths in many tissues and organs. TSC afflicts 1/10,000 people. Typically, persons suffering from TSC display a wide range of neural effects including seizures and a variety of tumors. There are two genes that have been associated with TSC -- TSC1 and TSC2. Although the mechanism are unknown, recent work with TSC knock-out models and basic molecular biology are leading to a better understanding of the role of these genes in neural development and function.

In particular, Ultman et al. (Ann Neurol. 2002 Sep;52(3):285-96.) have shown that a conditional TSC1 knockout mouse exhibits seizures at an age of 1 month and dies within 4 months. Moreover, analysis of gene and protein expression in this model indicates that proteins involved in glutamate transport are down regulated. If this is indeed the case in TSC, then the region around affected cells should exhibit elevated concentrations of glutamate, making those cells susceptible to cell death via a number of mechanisms, including excess NMDAr activity.

Certain adamantane derivatives have been used to treat illnesses. Rimantadine 5 (1-(1-aminoethyl)adamantane) is used for the prophylaxis and treatment of influenza in humans. Amantadine has been used for the treatment of both influenza and Parkinson's disease (Schwab et al., *J. Am. Med. Assoc.* (1969) 208:1168). Another derivative, memantine, is currently under clinical investigation for the treatment of various neurodegenerative diseases and has been licensed for the treatment of Parkinson's associated spasticity in Germany (Schneider et al., *Dtsch. Med. Wschr.* (1984) 109:987).

Memantine protects cortical and retinal neuron cultures from the toxicity of glutamate, NMDA and the HIV-1 coat protein gp120 (Dreyer et al., *Science* (1990) 248:364). Recent studies demonstrate that it prevents quinolinic acid-induced hippocampal damage in rats (Keihoff and Wolf., Eur. *J. Pharmacol.* (1992) 219:45 1). Memantine demonstrates antiphypoxic properties in vitro and in vivo. It is thought that

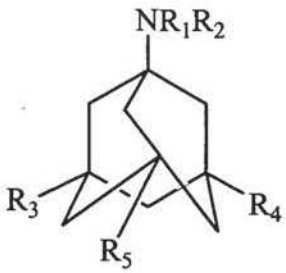
memantine exerts a neuroprotective effect because it is a micromolar antagonist of the NMDA receptor (Bormann J., *Eur. J. Pharmacol.* (1989) 166:59 1).

SUMMARY OF THE INVENTION

There are no safe, effective treatments for TSC. Moreover, many of the antiepileptic compounds are not effective against TSC seizures. Treatment of TSC with NMDAr channel antagonists will both address the seizure severity and frequency, as well as reduce the rate of neural degeneration.

This invention deals with the treatment of TSC with NMDAr channel antagonists, including memantine and its derivatives, that are capable of reducing the effects of elevated glutamate on neurons, preserving them from death. Most preferred are un-competitive NMDAr antagonists that possess the property of blocking excessively active NMDAr channels while leaving normal NMDAr channels unaffected.

The present invention also provides methods of treating TSC. The methods include administering to a patient a pharmaceutically acceptable carrier and one or more compounds of the following formula, or pharmaceutically acceptable salts thereof:



The substituents of the compounds are independently defined. R_1 is H, alkyl, 5 heteroalkyl, aryl, heteroaryl, $C(O)OR_6$ or $C(O)R_6$. R2 is H, alkyl, heteroalkyl, aryl, heteroaryl, $C(O)OR_6$ or $C(O)R_6$. R_3 is H, alkyl, heteroalkyl, aryl or heteroaryl. R_4 is H, alkyl, heteroalkyl, aryl or heteroaryl. R_5 is OR_7, alkyl-OR_7 or heteroalkyl-OR_7. R_6 is alkyl, heteroalkyl, aryl or heteroaryl. R_7 is NO_2, C(O)alkyl-ONO_2 or C(O)heteroalkyl-ONO_2. The following substituents are preferred: R_1 and R2 are H; R_3 and R_4 are H or alkyl; and, R_7 is NO_2 or C(O)alkyl-ONO_2.

Preferably the compound is memantine, rimantadine, 1-adamantanamine, 1-acetamido-3,5-dimethyl-7-hydroxyadamantane, 1-amino-3,5-dimethyl-7-hydroxyadamantane hydrochloride, 1-tert-butylcarbamate-3,5-dimethyl-7-hydroxy-adamantane, 1-tert-butylcarbamate-3,5-dimethyl-7-nitrate-adamantane, 1-acetamido-3,5-dimethyl-7-nitrateadamantane, 1,1-dibenzylamino-3,5-dimethyl-7-hydroxy-adamantane, 1-amino-3,5-dimethyl-7-acetoxyadamantane hydrochloride, 1-(benzyloxycarbonyl)amino-3,5-dimethyl-7-hydroxyadamantane, 1-(benzyloxycarbonyl)amino-3,5-dimethyl-7-(3-bromopropylcarbonyloxy)adamantane, 1-(benzyloxycarbonyl)amino-3,5-dimethyl-7-(3-nitratepropylcarbonyloxy)adamantane, 1-(benzyloxycarbonyl)amino-3,5-dimethyl-7-hydroxymethyl adamantane, 1-(benzyloxycarbonyl)amino-3,5-dimethyl-7-nitratemethyl-adamantane, 1-amino-3,5-dimethyl-7-nitratemethyladamantane hydrobromide, 1-acetamido-3,5-dimethyl-7-nitratemethyl-adamantane, or 1,1-dibenzylamino-3,5-dimethyl-7-acetoxyadamantane

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "Alkyl" refers to unsubstituted or substituted linear, branched or cyclic alkyl carbon chains of up to 15 carbon atoms. Linear alkyl groups include, for example, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl and n-octyl. Branched alkyl groups include, for example, iso-propyl, sec-butyl, iso-butyl, tert-butyl and neopentyl. Cyclic alkyl groups include, for example, cyclopropyll, cyclobutyl, cyclopentyl and cyclohexyl. Alkyl groups can be substituted with one or more substituents. Nonlimiting examples of such substituents include NO_2, ONO_2, F, Cl, Br, I, OH, OCH_3, CO_2H, CO_2CH_3, CN, aryl and heteroaryl. Where "alkyl" is used in a context such as "alkyl-ONO_2," it refers to an alkyl group that is substituted with a ONO_2 moiety. Where "alkyl" is used in a context such as "C(O)alkyl-ONO_2," it refers to an alkyl group that is connected to a carbonyl group at one position and that is substituted with a ONO_2 moiety.

The term "Heteroalkyl" refers to unsubstituted or substituted linear, branched or cyclic chains of up to 15 carbon atoms that contain at least one heteroatom (e.g., nitrogen, oxygen or sulfur) in the chain. Linear heteroalkyl groups include, for example, CH_2CH_2, $CH_2CH_2N(CH_3)_2$ and $CH_2CH_2SCH_3$. Branched groups include, for example,

$CH_2CH(OCH_3)CH_3$, $CH_2CH(N(CH_3)_2)CH_3$ and $CH_2CH(OCH_3)CH_3$. Cyclic heteroalkyl groups include, for example, $CH(CH_2CH_2)_2O$, $CH(CH_2CH_2)_2NCH_3$ and $CH(CH_2CH_2)_2S$. Heteroalkyl groups can be substituted with one or more substituents. Nonlimiting examples of such substituents include NO_2, ONO_2, F, Cl, Br, I, OH, OCH_3, CO_2H, CO_2CH_3, CN, aryl and heteroaryl. Where "heteroalkyl" is used in a context such as "heteroalkyl-ONO_2," it refers to a heteroalkyl group that is substituted with an ONO_2 moiety. Where "heteroalkyl" is used in a context such as "C(O)heteroalkyl-NO_2," it refers to an alkyl group that is connected to a carbonyl group at one position and that is substituted with a ONO_2 moiety.

The term "Halo" refers to F, Cl, Br or I.

The term "Aryl" refers to an unsubstituted or substituted aromatic, carbocyclic group. Aryl groups are either single ring or multiple condensed ring compounds. A phenyl group, for example, is a single ring, aryl group. An aryl group with multiple condensed rings is exemplified by a naphthyl group. Aryl groups can be substituted with one or more substituents. Nonlimiting examples of such substituents include NO_2, ONO_2, F, Cl, Br, I, OH, OCH_3, CO_2H, CO_2CH_3, CN, aryl and heteroaryl.

The term "Heteroaryl" refers an unsubstituted or substituted aromatic group having at least one heteroatom (e.g., nitrogen, oxygen or sulfur) in the aromatic ring. Heteroaryl groups are either single ring or multiple condensed ring compounds. Single ring heteroaryl groups having at least one nitrogen include, for example, tetrazoyl, pyrrolyl, pyridyl, pyridazinyl, indolyl, quinolyl, imidazolyl, isoquinolyl, pyrazolyl, pyrazinyl, pyrimidinyl and pyridazinonyl. A furyl group, for example is a single ring heteroaryl group containing one oxygen atom. A condensed ring heteroaryl group containing one oxygen atom is exemplified by a benzofuranyl group. Thienyl, for example, is a single ring heteroaryl group containing one sulfur atom. A condensed ring heteroaryl group containing one sulfur atom is exemplified by benzothienyl. In certain cases, heteroaryl groups contain more than one kind of heteroatom in the same ring. Examples of such groups include furazanyl, oxazolyl, isoxazolyl, thiazolyl arid phenothiazinyl. Heteroaryl groups can be substituted with one or more substituents. Nonlimiting examples of such substituents include NO_2, ONO_2, F, Cl, Br, I, OH, OCH_3, CO_2H, CO_2CH_3, CN, aryl and heteroaryl.

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