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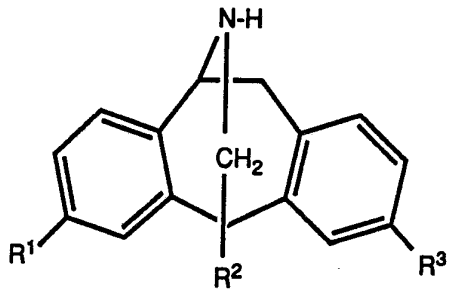

(I)

(57) Abstract

This invention involves novel neuroprotectant agents of formula (I), in which R^1 and R^3 are, independently, hydrogen, cyano, nitro, halo or perhaloalkyl, with the proviso that one of R^1 and R^3 is other than hydrogen; R^2 is alkyl; or a pharmaceutically acceptable salt thereof, processes for preparing them, compositions containing them and their use as NMDA antagonists.

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NEUROPROTECTANT AGENTS

Background of the Invention

This invention relates to neuroprotectant agents, more particularly to substituted dibenzo[a,d]cycloheptene derivatives, processes for preparing them, compositions containing them and their use as NMDA antagonists.

Antagonism of the centrally-acting excitatory amino acids (EAA), especially at the N-methyl-D-aspartate (NMDA) - specific receptor complex, is believed to represent a useful approach to the treatment of several CNS disorders, including senile dementia, Alzheimer's disease, Huntingdon's chorea, stroke, hypoglycemia, cerebral palsy, cerebral ischemia, epilepsy, and olivo-ponto-cerebellar atrophy. Two approaches to NMDA-antagonism have been pursued in recent years, namely competitive antagonism of the NMDA receptor and noncompetitive blockade of the NMDA-associated ion channel. To date, noncompetitive antagonists have proved more potent and more orally active than their competitive counterparts in blocking NMDA-induced responses in vivo and in protecting against cell death associated with induced cerebral ischemia.

Data suggest that phencyclidine (PCP) and other related "dissociative anesthetics" noncompetitively antagonize NMDA-induced responses by binding to the NMDA-associated ion channel and blocking ion permeability. Unfortunately, PCP possesses undesirable psychotomimetic side effects and causes ataxia in several animal models. In fact, the separation between a compound's NMDA-antagonist activity and ataxic activity (often expressed as an "efficacy ratio" of the ED_{50}'s of these two activities) has been extensively used to evaluate its therapeutic usefulness versus its liabilities. In our studies, PCP is approximately equipotent in its abilities to antagonize NMDA-induced lethality in mice and cause ataxia as measured by the traction reflex deficit model, giving an efficacy ratio (ED_{50}/TD_{50}) of approximately 1.4 (Table 1, infra).

A very potent noncompetitive NMDA-antagonist reported recently is MK-801. Like PCP, MK-801 antagonizes NMDA-induced lethality and protects against cell death in cerebral ischemia models. However, MK-801 competes for the high-affinity PCP

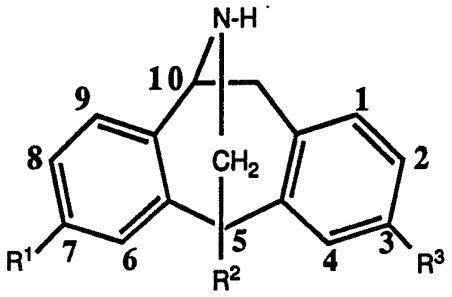
binding site in the NMDA-associated ion channel. Furthermore, like PCP, there is no separation between MK-801's ability to antagonize NMDA-induced lethality and cause ataxia (efficacy ratio = 0.9, Table 1 infra). In fact, in drug discrimination experiments, MK-801 generalizes for PCP, suggesting that MK-801 may possess PCP-like psychotomimetic side effects.

Dextromethorphan, an over-the-counter antitussive, also noncompetitively antagonizes NMDA-induced responses (Table 1, infra). Its proposed binding site in the ion channel may be different from that shared by PCP and MK-801. While not as potent as PCP and MK-801 in antagonizing NMDA-induced lethality, dextromethorphan shows a better antagonism/ataxia efficacy ratio (2.1). However, dextromethorphan is metabolized to dextrorphan in man. Dextrorphan's efficacy ratio is essentially the same as that for dextromethorphan, but data suggests that dextrorphan may exert its effects by interacting with the high-affinity PCP binding site in the NMDA-associated ion channel. This fact again raises the question PCP-like psychotomimetic side effects.

In accordance with this invention, there is provided a group of novel compounds which because of the CNS activity profile are considered to be useful in the treatment of neurodegenerative diseases such as Alzheimer's disease, Huntingdon's chorea, senile dementia, Parkinson's syndrome, and olivo-ponto-cerebellar atrophy, as well as epilepsy, stroke, hypoglycemia, cerebral palsy, cerebral ischemia and anxiety. Surprisingly, these compounds are intermediates useful in the product of the neuroprotectant agents disclosed in our earlier patent, U.S. 4,940,789.

U.S. Patent No. 5,011,834, published 30 April 1991 discloses inter alia racemic 5-methyl 10,5-(iminomethano)-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene having NMDA antagonist activity. However, there is no specific teaching of an aromatic ring substituted derivative nor any test result therefore and indeed a preference for the ring unsubstituted derivative is stated. No preference for optical forms is given. As shown hereinafter the compounds disclosed herein are markedly superior to the preferred compounds disclosed in U.S. 5,011,834.

Compounds of the present invention are described by the generic formula (I):



(I)

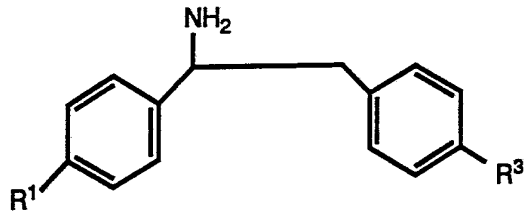
in which R^1 and R^3 are, independently, hydrogen, cyano, nitro, halo or perhaloalkyl of 1 to 6 carbon atoms, with the proviso that one of R^1 and R^3 is other than hydrogen;
R^2 is alkyl of 1 to 6 carbon atoms;
or a pharmaceutically acceptable salt thereof.

Preferred neuroprotectants from the standpoint of production economics and activity profile are those of the formula I in which one of R^1 and R^3 is hydrogen and the other is -CN, -NO_2, -Cl, -Br, -F, -I or -CF_3;
R^2 is alkyl of 1 to 3 carbon atoms;
or a pharmaceutically acceptable salt thereof.

Preferably, R^1 and/or R^3 is halogen, most preferably R^3 is halogen e.g. bromine. Most preferably R^2 is methyl.

The pharmaceutically acceptable salts of the compounds of this invention are prepared conventionally from organic or inorganic acids such as acetic, lactic, citric, tartaric, succinic, maleic, malonic, gluconic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids.

The compounds of this invention may be prepared via a variety of routes using conventional methods and commercially available starting materials. Thus, the desried substituted 10,11-dihydro-5-alkyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptenes can be prepared from appropriately substituted 1,2-diphenylethylamines of formula:



(II)

wherein R^1 and R^3 are as defined above using the methods of R D Waigh et al., J. Chem. Soc. Perkin I (1973) 2588 and H Takayama et al., Chem. Lett (1978) 856, employing a suitably substituted propargyl halide of formula:

$$\text{hal}\ \ CH_2C{\equiv}CR^4$$

where R^4 is hydrogen or alkyl of 1 to 5 carbon atoms and a suitable base such as diisopropylethylamine followed by treatment with a suitable non-aqueous acid such as trifluoromethanesulfonic acid.

The compounds of this invention are chiral having an asymmetric centre at the 5- and 10-positions. As such, they appear as racemic mixtures which may be resolved into their optical isomers by routine methods within the skill of the medicinal chemist. Also, the desired isomer may be obtained by stereospecific synthesis employing the desired isomeric reactant form. Enantiomers having the R configuration at position 10 are markedly more potent than the corresponding 10(S) enamtiomers; such compounds are preferably prepared from a compound of formula II having the R configuration.

The following examples illustrate, without limitation, the preparation of representative compounds of this invention.

Example 1

10,11-Dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene

A stirred solution of 1-phenyl-2-(4-bromophenyl)ethylamine (4.37 g, 1.6×10^{-2} mol), propargyl bromide (80% in toluene, 3.10 g, 2.1×10^{-2} mol), and diisopropylethylamine (3.07 g, 2.4×10^{-2} mol) in 120 ml of anhydrous tetrahydrofuran

was refluxed at 90°C under a dry nitrogen atmosphere for three hours. Then, an additional portion of propargyl bromide (0.59 g, 4.0×10^{-3} mol) was added, and reflux was continued for another two hours. The reaction mixture was cooled to room temperature, and the resulting white precipitate was removed by filtration. The mother liquor was concentrated on a rotary evaporator, the residue was diluted with 200 ml of diethyl ether, and the resulting white precipitate was again removed by filtration. The etheral mother liquor was quickly extracted with two 75 ml portions of 2N aqueous HCl. Upon standing, the combined aqueous layers yielded the desired intermediate, N-propargyl-1-phenyl-2-(4-bromophenyl)ethylamine hydrochloride, as a yellow precipitate which was recrystallized from ethanol/diethyl ether (4.54 g, 81%), mp=197-199°C.

A solution of N-propargyl-1-phenyl-2-(4-bromophenyl)ethylamine hydrochloride (4.47 g, 1.3×10^{-2} mol) in trifluoromethanesulfonic acid (20 g, 1.3×10^{-1} mol) was allowed to stand at room temperature under a dry nitrogen atmosphere for 18 hours. The reaction mixture was then poured onto ice, and the pH of the aqueous mixture was adjusted to 10 with 50% aqueous NaOH. The resulting basic mixture was diluted to 200 ml with water and extracted three times with 100 ml portions of chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The title compound (TLC on silica gel using a 5% methanol in methylene chloride solvent system, Rf=0.26) was isolated by preparative HPLC on silica gel using a gradient of 50% methylene chloride in ethyl acetate to 20% methanol in ethyl acetate. It was then converted to the HCl salt with isopropanolic HCl (2.67 g, 59%), mp=321-322°C.

Elemental analysis for $C_{17}H_{16}NBr \cdot HCl \cdot 1/16\ H_2O$

Calc'd: C, 58.04; H, 4.90; N, 3.98

Found: C, 57.75; H, 4.58; N, 3.92

Example 2

10,11-Dihydro-7-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene

A stirred solution of 1-(4-bromophenyl)-2-phenylethylamine (4.76 g, 1.72x 10^{-2} mol), propargyl bromide (80% in toluene, 3.47 g, 2.33x10^{-2} mol), and diisopropylethylamine (3.41 g, 2.64x10^{-2} mol) in 125 ml of anhydrous tetrahydrofuran was refluxed at 90°C under a dry nitrogen atmosphere for three hours. Then, an additional portion of propargyl bromide (1.34 g, 9.0x10^{-3} mol) was added, and reflux was continued for another two hours. The reaction mixture was cooled to room temperature, and the resulting white precipitate was removed by filtration. The mother liquor was concentrated on a rotary evaporator, the residue was diluted with 250 ml of diethyl ether, and the resulting white precipitate was again removed by filtration. The etheral mother liquor was quickly extracted with two 100 ml portions of 2N aqueous HCl. Upon standing, the combined aqueous layers yielded the desired intermediate, N-propargyl-1-(4-bromophenyl)-2-phenylethylamine hydrochloride, as an orange precipitate which was recrystallized from ethanol/diethyl ether (4.47 g, 74%), mp=164-165°C.

A solution of N-propargyl-1-(4-bromophenyl)-2-phenylethylamine hydrochloride (4.30 g, 1.22x10^{-2} mol) in trifluoromethanesulfonic acid (36 g, 2.5x10^{-1} mol) was allowed to stand at 50°C under a dry nitrogen atmosphere for 24 hours. The reaction mixture was then poured onto ice, and the pH of the aqueous mixture was adjusted to 10 with 50% aqueous NaOH. The resulting basic mixture was diluted to 400 ml with water and extracted three times with 200 ml portions of chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The title compound (TLC on silica gel using a 5% methanol in methylene chloride solvent system, Rf = 0.26) was isolated by preparative HPLC on silica gel using a gradient of 50% methylene chloride in ethyl acetate to 20% methanol in ethyl acetate. A 1.0 g sample of the free base was then converted to the HCl salt with isopropanolic HCl (0.93 g, 59%), mp=309-311°C.

Elemental analysis for $C_{17}H_{16}NBr \cdot HCl$

Calc'd: C, 58.23; H, 4.89; N, 3.99

Found: C, 57.30; H, 5.06; N, 3.78

Example 3

10,11-Dihydro-3-chloro-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene

A stirred solution of 1-phenyl-2-(4-chlorophenyl)ethylamine (6.00 gm, 2.6 x 10^{-2} mol), propargyl bromide (80% in toluene, 4.82 gm, 3.2 x 10^{-2} mol), and diisopropylethylamine (5.04 gm, 3.9 x 10^{-2} mol) in 50 ml of anhydrous tetrahydrofuran was refluxed at 90°C under a dry nitrogen atmosphere for four hours. Then, an additional portion of propargyl bromide (0.48 gm, 3.9 x 10^{-3} mol) was added, and reflux was continued to another two hours. The reaction mixture was cooled to room temperature, and the resulting white precipitate was removed by filtration. The mother liquor was concentrated on a rotary evaporator, the residue was diluted with 100 ml of diethyl ether, and the resulting white precipitate was again removed by filtration. The etheral mother liquor was quickly extracted with two 50 ml portions of 2N aqueous HCl. Upon standing, the combined aqueous layers yielded the desired intermediate, N-propargyl-1-phenyl-2-(4-chlorophenyl)ethylamine hydrochloride, as an off-white precipitate, which was washed with diethyl ether (4.53 gm, 57%), mp=191-193°.

A solution of N-propargyl-1-phenyl-2-(4-chlorophenyl)ethylamine hydrochloride (4.40 gm, 1.4 x 10^{-2} mol) in trifluoromethanesulfonic acid (22 gm, 1.4 x 10^{-1} mol) was allowed to stand under a dry nitrogen atmosphere for 24 hours. The reaction mixture was then poured onto ice and the pH of the aqueous mixture was adjusted to 10 with 50% aqueous sodium hydroxide. The resulting basic mixture was diluted to 200 ml with water and extracted 3 times with 100 ml portions of dichloromethane. The combined organic layers were dried over anydrous sodium sulfate and concentrated on a rotary evaporator. The title compound (TLC on silica gel using a 5% methanol in methylene chloride solvent system, Rf = 0.21) was isolated using column chromatography on silica gel by first eluting with 1%

methanol/dichloromethane and then with 10% methanol/dichloromethane. The amine was then converted to its hydrochloride salt with isopropanolic HCl (1.80 gm, 41%), mp=308-310°C.

Elemental analysis for $C_{17}H_{16}NCl \cdot HCl$

Calc'd: C, 66.68; H, 5.60; N, 4.57

Found: C, 66.68; H, 5.62; N, 4.38

Example 4

10,11-Dihydro-3-fluoro-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene

A stirred solution of 1-phenyl-2-(4-fluorophenyl)ethylamine (5.60 gm, 2.6 x 10^{-2} mol), propargyl bromide (80% in toluene, 4.82 gm, 3.2 x 10^{-2} mol), and diisopropylethylamine (5.04 gm, 3.9 x 10^{-2} mol) in 50 ml of anhydrous tetrahydrofuran was refluxed at 90°C under a dry nitrogen atmosphere for four hours. Then, an additional portion of propargyl bromide (0.48 gm, 3.9 x 10^{-3} mol) was added, and reflux was continued for another two hours. The reaction mixture was cooled to room temperature, and the resulting white precipitate was removed by filtration. The mother liquor was concentrated on a rotary evaporator, the residue was diluted with 100 ml of diethyl ether, and the resulting white precipitate was again removed by filtration. The etheral mother liquor was quickly extracted with two 50 ml portions of 2N aqueous HCl. Upon standing, the combined aqueous layers yielded the desired intermediate. N-propargyl-1-phenyl-2-(4-fluorophenyl)ethylamine hydrochloride, as an off-white precipitate, which was washed with diethyl ether (3.70 gm, 49%), mp=190-191°C.

A solution of N-propargyl-1-phenyl-2-(4-fluorophenyl)ethylamine hydrochloride (3.09 gm, 1.07 x 10^{-2} mol) in trifluoromethanesulfonic acid (16 gm, 1.07 x 10^{-1} mol) was allowed to stand under a dry nitrogen atmosphere for 24 hours. The reaction mixture was then poured onto ice and the pH of the aqueous mixture was adjusted to 10 with 50% aqueous sodium hydroxide. The resulting basic mixture was diluted to 200 ml with water and extracted 3 times with 100 ml portions of

dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The title compound (TLC on silica gel using a 5% methanol in methylene chloride solvent system, Rf = 0.20) was isolated using column chromatography on silica gel by first eluting with 1% methanol/dichloromethane and then with 10% methanol/dichloromethane. The amine was then converted to its hydrochloride salt with isopropanolic HCl (1.34 gm, 43%), mp=321-323°C.

Elemental analysis for $C_{17}H_{16}NF \cdot HCl$

Calcd: C, 70.46; H, 5.25; N, 4.88

Found: C, 70.07; H, 5.39; N, 4.89

Example 5

5(R)10(S)(-)-10,11-Dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene

1-phenyl-2-(4-bromophenyl)ethylamine (5.48 g, 1.98 x 10^{-2} mol) was dissolved in 20 ml of 10% ethyl acetate/ethanol. To this was added a solution of R(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (4.65 gm, 1.98 x 10^{-2} mol) in 20 ml of 10% ethyl acetate/ethanol. The resulting solution was warmed to 75°C, and then allowed to stand at room temperature for 72 hours. The mixture was then left in the freezer for 24 hours. The resulting white precipitate was collected by vacuum filtration, washed with diethyl ether, and dried in vacuo to yield the desired (+)-α-methoxy-α-(trifluoromethyl)phenyl acetate of (+)-1-phenyl-2-(4-bromophenyl)ethylamine (1.49 gm, 29%), mp=144-146°C. The salt was treated with 30 ml of 2.5N aqueous NaOH, extracted with three 30 ml portions of dichloromethane, and the combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to yield the desired (+)-1-phenyl-2-(4-bromophenyl)ethylamine as a yellow oil (0.62 gm, 23% yield), $[\alpha]_D^{25}$ = +58.3 (EtOH), shown to be 99.9% enantiomerically pure by chiral HPLC.

A stirred solution of S(+)-1-phenyl-2-(4-bromophenyl)ethylamine (0.62 gm, 2.2 x 10^{-3} mol), propargyl bromide (80% in toluene, 0.58 gm, 4.9 x 10^{-3} mol), and

diisopropylethylamine (0.61 gm, 4.7 x10^{-3} mol) in 10 ml of anhydrous tetrahydrofuran was refluxed at 90°C under a dry nitrogen atmosphere for four hours. The reaction mixture was cooled to room temperature, and the mother liquor was concentrated on a rotary evaporator. The residue was diluted with 30 ml of diethyl ether, and the resulting white precipitate was removed by filtration. The etheral mother liquor was quickly extracted with 30 ml of 2N aqueous HCl. Upon standing, the combined aqueous layers yielded the desired intermediate, (+)-N-propargyl-t-phenyl-2-(4-bromophenyl)ethylamine hydrochloride, as a yellow precipitate, which was washed with ethyl ether (0.69 gm, 89%), mp=205-207°C, $[a]_D^{25}$ = +68.7 (EtOH).

A solution of S(+)-N-propargyl-1-phenyl-2-(4-bromophenyl)ethylamine hydrochloride (0.63 gm, 1.8 x 10^{-3} mol) in trifluoromethanesulfonic acid (2.7 gm, 1.8 x 10^{-2} mol) was allowed to stand under a dry nitrogen atmosphere for 24 hours. The reaction mixture was then poured onto ice and the pH of the aqueous mixture was adjusted to 10 with 50% aqueous sodium hydroxide. The resulting basic mixture was diluted to 50 ml with water and extracted 3 times with 20 ml portions of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The title compound (TLC on silica gel using a 5% methanol in methylene chloride solvent system, Rf = 0.21) was isolated using column chromatography on silica gel by first eluting with 1% methanol/dichloromethane and then with 10% methanol/dichloromethane. The amine was then converted to its hydrochloride salt with isopropanolic HCl (0.30 gm, 49%), mp=312-314°C, $[a]_D^{25}$ = -239.2 (EtOH).

Elemental analysis for $C_{17}H_{16}NBr \cdot HCl$

Calc'd: C, 58.22; H, 4.89; N, 3.99

Found: C, 58.16; H, 4.96; N, 3.85

Example 6

5(S)10(R)(+)-10,11-Dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene

1-Phenyl-2-(4-bromophenyl)ethylamine (6.71 gm, 2.43 x 10^{-2} mol) was dissolved in 40 ml of 25% ethyl acetate/ethanol. This solution was then added to a solution of S(-)-a-methoxy-a-(trifluoromethyl)phenylacetic acid (5.69 gm, 2.43 x 10^{-2} mol) in 40 ml of 25% ethyl acetate/ethanol. The resulting solution was warmed to 60°C, and then allowed to stand at room temperature for 116 hours. The mixture was then left in a freezer for 24 hours. The resulting white precipitate was collected by vacuum filtration, washed with ethyl ether, and dried in vacuo to yield the desired (-)-a-methoxy-a-trifluoromethyl)phenyl acetate of R(-)-1-phenyl-2-(4-bromophenyl)ethylamine (2.93 gm). The mother liquor was concentrated to dryness under reduced pressure, and the residue was crystallized as described above using 60 ml of 25% ethyl acetate/ethanol to yield an additional 0.63 gm of the phenylacetate of (-)-1-phenyl-2-(4-bromophenyl)ethylamine. The combined precipitates (3.56 gm, 57%, mp=143-145°C) were treated with 30 ml of 2.5N aqueous NaOH, extracted with three 30 ml portions of dichloromethane, and the combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to yield the desired R(-)-1-phenyl-2-(4-bromophenyl)ethylamine as a yellow oil (1.74 gm, 52%), $[a]_D^{25}$ = -62.7 (EtOH), shown to be 99.8% enantiomerically pure by chiral HPLC.

A stirred solution of (-)-1-phenyl-2-(4-bromophenyl)ethylamine (2.06 gm, 7.5 x 10^{-3} mol), propargyl bromide (80% in toluene, 1.66 gm, 11.2 x 10^{-3} mol), and diisopropylethylamine (1.45 gm, 16.2 x 10^{-3} mol) in 20 ml of anhydrous tetrahydrofuran was refluxed at 90°C under a dry nitrogen atmosphere for five hours. The reaction mixture was cooled to room temperature, and the mother liquor was concentrated on a rotary evaporator. The residue was diluted with 75 ml of diethyl ether, and the resulting white precipitate was removed by filtration. The etheral mother liquor was quickly extracted with 50 ml of 2N aqueous HCl. Upon standing, the combined aqueous layers yielded the desired intermediate, R(-)-N-propargyl-1-phenyl-2-(4-bromophenyl)ethylamine hydrochloride, as a yellow precipitate, which was washed with ethyl ether (1.25 gm, 48%), mp=212-213°C, $[a]_D^{25}$ = -69.7 (EtOH).

A solution of R(-)-N-propargyl-1-phenyl-2-(4-bromophenyl)ethylamine hydrochloride (1.16 gm, 3.3 x 10^{-3} mol) in trifluoromethanesulfonic acid (5.0 gm, 3.3 x 10^{-2} mol) was allowed to stand under a dry nitrogen atmosphere for 24 hours. The reaction mixture was then poured onto ice and the pH of the aqueous mixture was adjusted to 10 with 50% aqueous sodium hydroxide. The resulting basic mixture was diluted to 75 ml with water and extracted 4 times with 50 ml portions of chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The title compound (TLC on silica gel using a 5% methanol in methylene chloride solvent system, Rf = 0.21) was isolated using column chromatography on silica gel by first eluting with 1% methanol/dichloromethane and then with 10% methanol/dichloromethane. The amine was then converted to its hydrochloride salt with isopropanolic HCl (0.67 gm, 58%), mp=314-316°C, $[a]_D^{25}$ = +237.9 (EtOH).

Elemental analysis for $C_{17}H_{16}NBr \cdot HCl$

Calc'd: C, 58.22; H, 4.89; N, 3.99

Found: C, 57.99; H, 4.97; N, 3.84

The properties of these compounds were directly established by demonstrating the NMDA antagonist properties of representative compounds in male Swiss-albino mice (CD-1 strain, Charles River) 18-22 grams in weight after 18 hours of food deprivation which had been habituated to an observation chamber for 30 minutes. The mice were pretreated with the representative test compounds followed thirty minutes later with NMDA (195 mg/kg, i.p., the ED_{90} dose for generalized myoclonus). The mice were then observed for 30 minutes, noting the latency of onset of generalized myoclonus (uncontrollable hind leg scratching or limbs and/or torso muscle jerking with loss of righting reflex) and death. From the latter, the ED_{50} for survival is determined. In this standard experimental test procedure, the specific compounds tested and their activity, which representatively establish the activity for all the compounds herein, are presented in Table I as follows:

TABLE 1

NMDA-Induced Lethality and Traction Reflex Deficit (Ataxia)

Compound of Example	*ED_{50} Inhibition of NMDA-Induced Lethality (mg/kg, ip)	@TD_{50}-Traction Reflex Deficit (mg/kg, ip)	Efficacy Ratio (ED_{50}/TD_{50})
1	4.6	14.7	3.2
2	#60% (20)		
3	4.6	7.5	1.6
4	#90% (5)		
5	#40% (5)		
6	2.2	6.2	2.8
PCP	1.9	2.7	1.4
MK-801	0.19	0.17	0.9
Dextromethorphan	21	45	2.1
Dextrorphan	13	29	2.2

* As measured in mice. Defined as the dose required to produce 50% survival rate.

@ As measured in mice. Defined as the dose which produced the deficit in 50% of animals tested.

Percent of animals which survived at the dose indicated.

In addition, the compounds involved herein were shown to displace 1-(2-thienyl)-1-(1-piperidinyl)cyclohexane (TCP) from its binding site in the NMDA-associate ion channel in rat frontal cortex homogenates, by loading rat brain homogenate with radiolabeled TCP and subsequently measuring the amount of TCP

displaced by the test compounds of this invention. The inhibitory concentration in nM which displaced 50% of the radiolabeled TCP was found to be as presented in Table 2.

TABLE 2

Ability to Displace [^{3}H]-TCP from the NMDA Ion Channel

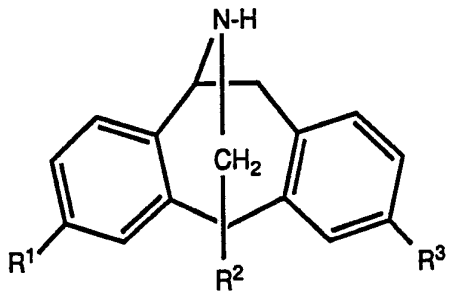
Compound of Example	*IC_{50} (nM)
1	192
2	110
5	1,010
6	89
MK-801	2.6
PCP	28.2
Dextromethorphan	745

* Functional binding assay without added spermidine.

Thus, the compounds of this invention demonstrate the ability to antagonize NMDA-induced lethality in vivo in mice (Table 1). They did not compete with 3-(2-carboxypiperazinyl-4-yl)-propyl-1-phosphonic acid (CPP), a known competitive NMDA-antagonist, for its binding site in rat frontal cortex homogenates. Compounds of the present invention displaced 1-(2-thienyl)-1-(1-piperidinyl)cyclohexane (TCP) from its binding site in the NMDA-associated ion channel in rat frontal cortex homogenates (Table 2) which characterizes them as noncompetitive NMDA antagonists. Compounds of the present invention also provide robust neuroprotection in a gerbil global ischemia model when given at a dose of 30 mg/kg i.p., 2 x 4 hours apart. The compounds of this invention showed efficacy ratios for antagonizing NMDA-induced lethality over ataxia superior to those seen with PCP, MK-801, dextrorphan, and dextromethorphan (Table 1). In addition, they demonstrated more potent neuroprotection (with less lethality) than dextrorphan, dextromethorphan, or the N-substituted derivatives disclosed in U.S. 4,940,789 which are not aryl-substituted.

The combination of oral activity, greater potency with respect to dextromethorphan and dextrorphan, and better efficacy ratios relative to standard NMDA antagonists, including PCP, MK-801, dextromethorphan, and dextrorphan, makes the compounds of this invention superior to presently available noncompetitive NMDA antagonists. Compounds with such a profile are useful in the treatment of CNS disorders such as senile dementia, Alzheimer's disease, Huntingdon's chorea, stroke, hypoglycemia, cerebral palsy, cerebral ischemia, epilepsy, and olivo-ponto cerebellar atrophy.

Hence, there is herewith provided in addition to the novel compounds, supra, a method for preventing neurodegenerative disorders induced by overstimulation of excitatory amino acid receptors in brain and spinal cord, which comprises administering to a mammal suffering from such degenerative disease states, an NMDA antagonist of the formula:



in which

R^1 and R^3 are, independently, hydrogen, cyano, nitro, halo or perhaloalkyl of 1 to 6 carbon atoms, with the proviso that one of R^1 and R^3 is other than hydrogen;

R_2 is alkyl of 1 to 6 carbon atoms;

or a pharmaceutically acceptable salt thereof.

As such, the compounds of this invention may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

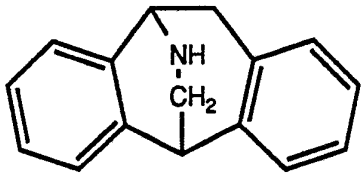
Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellent.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds can also be administered orally either in liquid or solid composition form.

Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

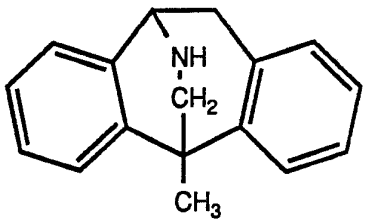
To determine the effective amount of compound to be administered in alleviation of CNS degenerative dysfunctions, the physician need only evaluate the effects of a given NMDA antagonist in the patient by incrementally increasing the oral dosage from about 1 mg/kg to about 20 mg/kg until the desired symptomatic relief level is achieved. The continuing dose regimen may then be modified to achieve the desired result, with the range of about 1 to 100 mg/day. Similar techniques are followed by determining the effective dose range upon i.v. or i.m. administration. When using the compounds prophylactically to arrest declining cognitive function as in Alzheimer's dementia, a more subjective approach is taken such as by relating the drug dosage to improved memory reponses or analogous desired responses which can be related to relief of overstimulation of the excitatory amino acid receptors.

Compounds of formula



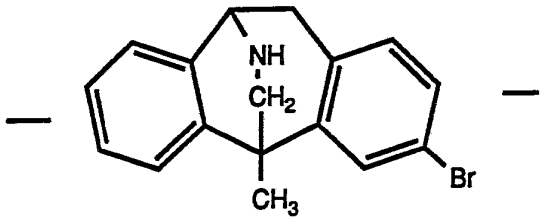
Formula XVIII

and



Formula XIX

disclosed in U.S. Patent 5,011,834 (vide supra) and the product of Example 1 disclosed hereinabove having the formula



were tested in the following standard experimental model of neuroprotection which assesses a compound's ability to protect the CA1 region of the hippocampus against ischemia induced by transient interruption of global (fore brain) blood flow from the carotid arteries:

Gerbil Global Ischemia

Female Mongolian gerbils were anesthetised with 2% halothane, secured, and prepared for surgery. The carotid arteries were then surgically exposed and clamped with microaneurysm clips for ten minutes. At the completion of the occlusion period, the clips were removed and the neck was closed with braided silk sutures. Rectal body temperature was monitored at various intervals both pre- and post-occlusion. Test compounds were administered in an appropriate vehicle according to a dosing regimen which provides for approximately 8 hours of drug availability (taking into account the duration of action with the drug demonstrates in the NMDA-Induced Lethality Assay).

At the termination of the experiment (4 days), the test animals were decapitated and the brains were harvested and frozen. Tissue was sliced in 20 micron sections, mounted on slides, and stained with cresyl violet. The CA1 region of hippocampus was microscopically examined and rated on a scale from 0 to 4 (0 - no visible damage; 1 = minor damage to the CA1 region; 2 = up to 50% damage to the CA1 region; 3 = serious damage (50 - 100%) to the majority of the CA1 region; 4 = massive damage extending beyond the CA1 region).

Data for the test compounds are reported as the change in the rating scale at a certain dose.

The results obtained in this test were as follows:

Compound	Dose (mg/kg ip) Dosing Regimen	Control Brain Rating Score	Drug Treated Brain Rating Score	Number of Test Animal Deaths
XVIII	3 mg/kg (given once)	3.0	3.0	0/13
	30 mg/kg (given once)	3.0	2.5	1/13
	54 mg/kg (given once)	3.0	2.0	9/13
XIX	30 mg/kg (given 4 times 2 hours apart)	3.0	2.0	1/13
Example 1	30 mg/kg (given 2 times 4 hours apart)	3.0	1.0	1/12
	54 mg/kg (given 2 times 4 hours apart)	3.0	1.0	1/12
	100 mg/kg (given 2 times 4 hours apart)	3.0	1.0	1/12

From this data, it can be seen that for compound XVIII, a 30 mg/kg ip dose provides only weak neuroprotection. The dose of XVIII at which moderate neuroprotective activity became apparent (54 mg/kg ip) was lethal to 9 out of 13 gerbils tested.

The 5-methyl analogue XIX provided only moderate neuroprotection despite the dosing regimen (four doses, given two hours apart) which more than compensated for its three hour duration of action.

In sharp contrast with XVII and XIX, the compound of Example 1 provided robust neuroprotection (brain rating score - 1.0) and it was more readily tolerated than XVIII, with test animal lethality not becoming apparent at up to 100 mg/kg.

In these studies, the lethality rate with control animals was about 1/12 or 1/13.

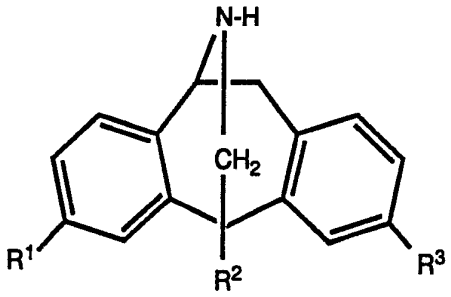
Accordingly, it can be seen that the almost complete neuroprotection obtained with the compound of Example 1 in combination with the greatly expanded dosage range without increased lethality characterizes this compound as possessing very significant and unexpected advantages in efficacy as a neuroprotectant in comparison with the preferred compounds of U.S. 5,011,834 patent.

The compound of Example 1 is shown by the results above to be safe and about nine-times more effective as a neuroprotectant when compared with XVIII, the most preferred compound of US Patent 5,011,834.

CLAIMS:

- 1 -

A compound of the formula (I):



(I)

in which

R^1 and R^3 are, independently, hydrogen, cyano, nitro, halo or perhaloalkyl of 1 to 6 carbon atoms, with the proviso that one of R^1 and R^3 is other than hydrogen;

R_2 is alkyl of 1 to 6 carbon atoms;

or a pharmaceutically acceptable salt thereof.

- 2 -

A compound of formula I as claimed in Claim 1 for use as a pharmaceutical.

- 3 -

A pharmaceutical composition comprising a compound of formula I as shown and defined in Claim 1, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

- 4 -

Use of a compound of formula I as shown and defined in Claim 1 or pharmaceutically acceptable salt thereof in the preparation of a medicament for preventing convulsions and/or neurodegenerative disorders induced by overstimulation of excitatory amino acid receptors.

- 5 -

Use of a compound of formula I as shown and defined in Claim 1 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for preventing brain cell damage resulting from overstimulation by excessive amounts of excitatory amino acids.

- 6 -

A method for preventing convulsions and/or neurodegenerative disorders induced by overstimulation of excitatory amino acids which comprises administering to a mammal in need thereof an effective amount of a compound of fomrula I as shown and defined in Claim 1, or a pharmaceutically acceptable salt thereof.

- 7 -

A method for preventing brain cell damage resulting from overstimulation by excessive amounts of excitatory amino acids which comprises administering to a mammal in need thereof an effective amount of a compound of formula I as claimed in Claim 1, or a pharmaceutically acceptable salt thereof.

- 8 -

A compound use composition or method as claimed in any one of Claims 1 to 7 in which one of R^1 and R^3 is hydrogen and the other is -CN, -NO_2, -C1, -Br, -F, -I or -CF_3; and R^2 is alkyl of 1 to 3 carbon atoms.

- 23 -

- 9 -

A compound, use, composition or method as claimed in any one of Claims 1 to 8 in which the compound of formula I has the R configuration at position 10.

- 10 -

A compound, use, composition or method according to Claim 8 in which the compound is 10,11-dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene, or a pharmaceutically acceptable salt thereof.

- 11 -

A compound, use, composition or method according to Claim 8 in which the compound is 10,11-dihydro-7-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene, or a pharmaceutically acceptable salt thereof.

- 12 -

A compound, use, composition or method according to Claim 8 in which the compound is 10,11-dihydro-3-chloro-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene, or a pharmaceutically acceptable salt thereof.

- 13 -

A compound, use, composition or method according to Claim 8 in which the compound is 10,11-dihydro-3-fluoro-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene, or a pharmaceutically accceptable salt thereof.

- 14 -

A compound, use, composition or method according to Claim 8 in which the compound is (-)5(R),10(S)-10,11-dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene, or a pharmaceutically acceptable salt thereof.

- 15 -

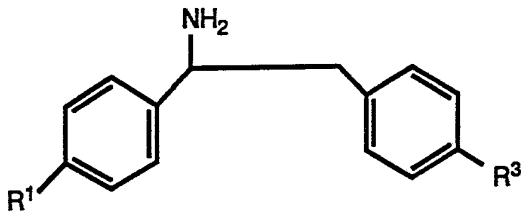
A compound, use, composition or method according to Claim 9 in which the compound is (+)-5(S),10(R)-10,11-dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene, or a pharmaceutically acceptable salt thereof.

- 16 -

A compound, use, composition or method according to anyone of Claims 1 to 15 in which the compound of formula I is in the form of a salt of an acid selected from: acetic, lactic, citric, tartaric, succinic, maleic, malonic, gluconic, hydrochloric, hydrobromic, phosphoric, nitric, sulphuric and methanesulfonic acid.

- 17 -

A process of preparing a compound of formula I or a pharmaceutically acceptable salt thereof as claimed in Claim 1 which comprises reacting a compound of formula:



(II)

wherein R^1 and R^3 are as defined above in Claim 1 with a propargyl halide of formula

$$\text{hal}\ \ CH_2C{\equiv}CR^4$$

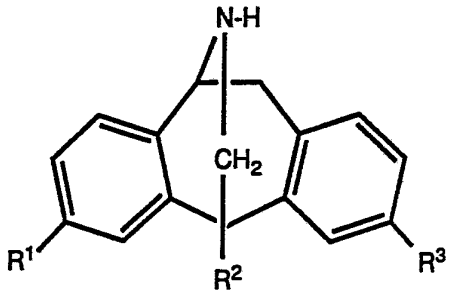
wherein R^4 is hydrogen or alkyl of 1 to 5 carbon atoms and hal is a halogen, if desired in the presence of a base, followed by treatment with a non-aqueous acid.

- 18 -

A process as claimed in Claim 17 wherein the compound of formula II has the R-configuration.

Abstract of the Disclosure

This invention involves novel neuroprotectant agents of the formula:



in which R^1 and R^3 are, independently, hydrogen, cyano, nitro, halo or perhaloalkyl, with the proviso that one of R^1 and R^3 is other than hydrogen; R^2 is alkyl; or a pharmaaceutically acceptable salt thereof, processes for preparing them, compositions containing them and their use as NMDA antagonists.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01204

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classrfication and IPC

Int.Cl.5 C 07 D 471/08 A 61 K 31/55 //(C 07 D 471/08
C 07 D 223:00 C 07 D 221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
2 X	WO,A,9012575 (STATE OF OREGON) 1 November 1990, see claim 1 & US,A,5011834 (cited in the application)	1,3

° Special categories of cited documents : [10]

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

"E" earlier document 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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22-06-1992	04. 08. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	I. Alfaro

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201204 SA 57730

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 16/07/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9012575	01-11-90	US-A- 5011834	30-04-91
		AU-A- 5448890	16-11-90
		EP-A- 0470127	12-02-92