Description

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).

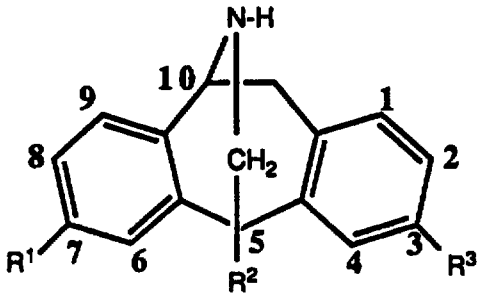
A very potent noncompetitive NMDA-antagonist reported recently is MK-801. Like PCP, MK-801 antagonizes NMDA-induced lethality and protects against cell death in cerebral ischemia models. However, MK-801 competes for the high-affinity PCP binding site in the NMDA-associated ion channel. Furthermore, like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

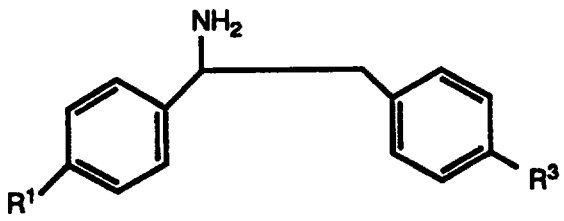
in which R^1 and R^3 are, independently, hydrogen, cyano, nitro, halo or perhaloalkyl of 1 to 6 carbon atoms, with the proviso that one of R^1 and R^3 is other than hydrogen;
R^2 is alkyl of 1 to 6 carbon atoms;
or a pharmaceutically acceptable salt thereof.

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:

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, 1.72×10^{-2} mol), propargyl bromide (80% in toluene, 3.47 g, 2.33×10^{2} mol), and diisopropylethylamine (3.41 g, 2.64×10^{-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, 9.0×10^{-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 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, 1.22×10^{-2} mol) in trifluoromethanesulfonic acid (36 g, 2.5×10^{-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, 2.6×10^{-2} mol), propargyl bromide (80% in toluene, 4.82 gm, 3.2×10^{-2} mol), and diisopropylethylamine (5.04 gm, 3.9×10^{-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, 3.9×10^{-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)ethylaminehydrochloride, 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, 1.4×10^{-2} mol) in trifluoromethanesulfonic acid (22 gm, 1.4×10^{-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, 2.6×10^{-2} mol), propargyl bromide (80% in toluene, 4.82 gm, 3.2×10^{-2} mol), and diisopropylethylamine (5.04 gm, 3.9×10^{-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, 3.9×10^{-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)-ethylaminehydrochloride, 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, 1.07×10^{-2} mol) in trifluoromethanesulfonic acid (16 gm, 1.07×10^{-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, 1.98×10^{-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, 1.98×10^{-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 he 99.9% enantiomerically pure by chiral HPLC.

A stirred solution of S(+)-1-phenyl-2-(4-bromophenyl)ethylamine (0.62 gm, 2.2×10^{-3} mol), propargyl bromide (80% in toluene, 0.58 gm, 4.9×10^{-3} mol), and diisopropylethylamine (0.61 gm, 4.7×10^{-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, $[\alpha]_D^{25}$ = +68.7 (EtOH).

A solution of S(+)-N-propargyl-1-phenyl-2-(4-bromophenyl)ethylaminehydrochloride (0.63 gm, 1.8×10^{-3} mol) in trifluoromethanesulfonic acid (2.7 gm, 1.8×10^{-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, $[\alpha]_D^{25}$ = -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(-)-α-methoxy-α-(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 (-)-α-methoxy-α-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%), $[\alpha]_D^{25}$ = -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, $[\alpha]_D^{25}$ = -69.7 (EtOH).

A solution of R(-)-N-propargyl-1-phenyl-2-(4-bromophenyl)ethylaminehydrochloride (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 exacted 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, $[\alpha]_D^{25}$ = +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

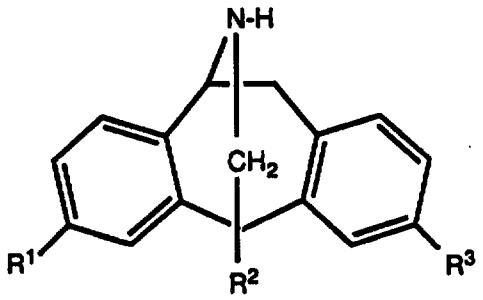
* Functional binding assay without added spermidine.

Thus, the compounds of this invention demonstrate the ability to antagonize NMDA-induced lethality in vivo 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 noncom-

petitive 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-integrating 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.

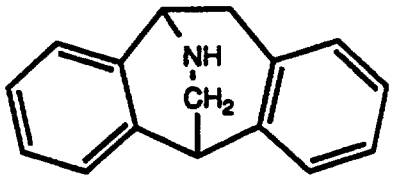
Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable 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.

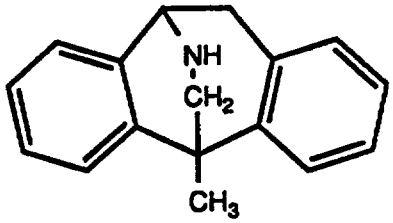
Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, 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

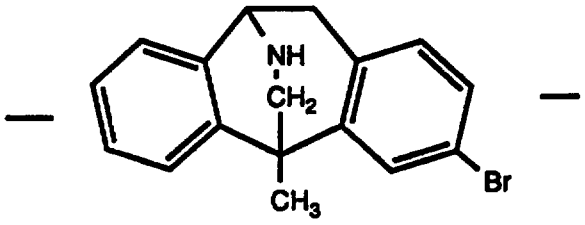


and



Formula XVIII **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 CAI 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 CAI region of hippocampus was microscopically examined and rated on a scale from 0 to 4 (0 - no visible damage; 1 = minor damage to the CAI region; 2 = up to 50% damage to the CAI region; 3 = serious damage (50 - 100%) to the majority of the CAI region; 4 = massive damage extending beyond the CAI 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.

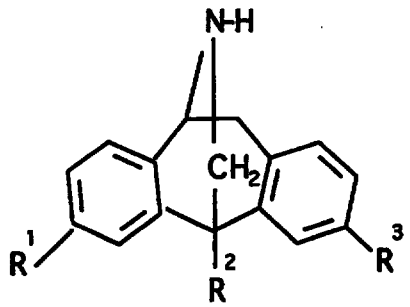
Accordingly, it can be seen that the almost complete neuroprotection obtained with the compound of Example 1 in combination with the greatly expanded dosage range without increased lethality characterizes this compound as possessing very significant and unexpected advantages in efficacy as a neuroprotectant 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

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

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; and

R^2 is alkyl of 1 to 6 carbon atoms;

or a pharmaceutically acceptable salt thereof.

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
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	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

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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.

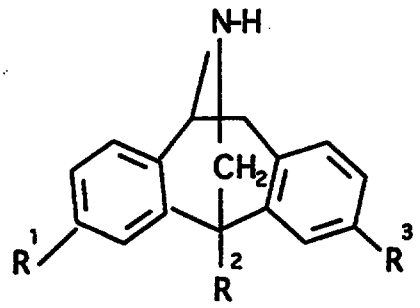
Accordingly, it can be seen that the almost complete neuroprotection obtained with the compound of Example 1 in combination with the greatly expanded dosage range without increased lethality characterizes this compound as possessing very significant and unexpected advantages in efficacy as a neuroprotectant 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

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

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; and

R^2 is alkyl of 1 to 6 carbon atoms;

or a pharmaceutically acceptable salt thereof.

* C L M S *

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.

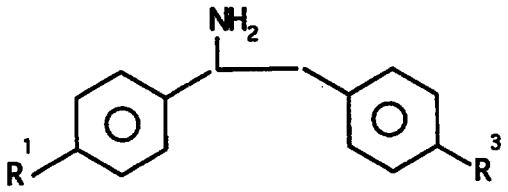
6. A compound, use or composition as claimed in any one of Claims 1 to 5 in which one of R^1 and R^3 is hydrogen and the other is -CN, $-NO_2$, -Cl, -Br, -F, -I or $-CF_3$; and R^2 is alkyl of 1 to 3 carbon atoms.

7. A compound, use or composition as claimed in any one of claims 1 to 6 in which the compound of formula I has the R configuration at position 10.

8. A compound, use or composition according to Claim 6 in which the compound is one of the following:
10,11-dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
10,11-dihydro-7-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
10,11-dihydro-3-chloro-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
10,11-dihydro-3-fluoro-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
(-)-5(R),10(S)- 10,11-dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene, and
(+)-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.

9. A compound, use or composition according to anyone of Claims 1 to 8 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.

10. A process for 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:

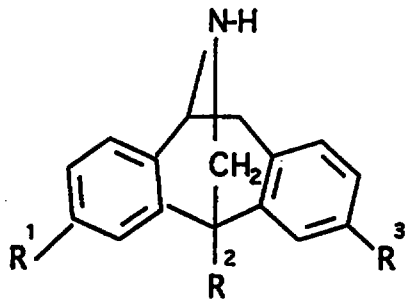
hal $CH_2C{\equiv}CR^4$

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.

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Claims for the following Contracting States : ES, GR

1. A process for preparing a compound of the formula (I):



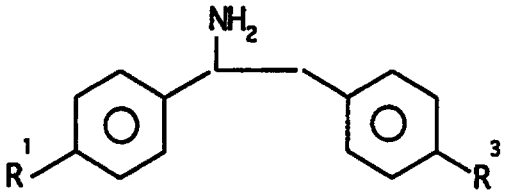
(I)

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 which comprises reacting a compound of formula:



(II)

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

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.

2. A process as claimed in Claim 1 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.

3. A process as claimed in Claim 1 or Claim 2 in which the compound of formula I has the R configuration at position 10.

4. A process according to Claim 1 in which the compound prepared is one of the following:
10,11-dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
10,11-dihydro-7-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
10,11-dihydro-3-chloro-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
10,11-dihydro-3-fluoro-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
(-)-5(R),10(S)- 10,11-dihydro-3-bromo-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptene,
(+)-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.

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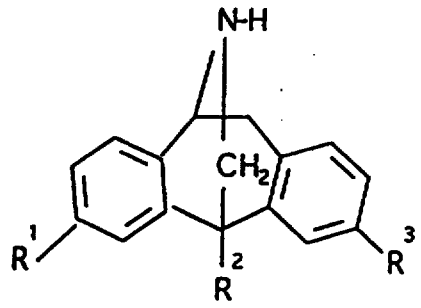
5. A process according to anyone of Claims 1 to 4 in which the compound of formula I is prepared in the form of a salt of an acid selected from: acetic, lactic, citric, tartaric, succinic, maleic, malonic, gluconic, hydrochloric, hydrobromic, phosphoric, nitric, sulphuric and methanesulfonic acid.

6. A process for preparing a pharmaceutical composition which comprises bringing a compound of formula I as shown and defined in Claim 1 or a pharmaceutically acceptable salt thereof into association with a pharmaceutically acceptable carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel (I):



(I)

worin R^1 und R^3 unabhängig Wasserstoff, Cyano, Nitro, Halogen oder Perhalogenalkyl mit 1 bis 6 Kohlenstoffatomen bedeuten, mit der Maßgabe, daß eines von R^1 und R^3 von Wasserstoff verschieden ist; und R^2 Alkyl mit 1 bis 6 Kohlenstoffatomen darstellt; oder ein pharmazeutisch annehmbares Salz hievon.

2. Verbindung der Formel (I) nach Anspruch 1 zur Verwendung als Pharmazeutikum.

3. Pharmazeutische Zusammensetzung, welche eine Verbindung der Formel (I), wie in Anspruch 1 gezeigt und definiert, oder ein pharmazeutisch annehmbares Salz hievon und einen pharmazeutisch annehmbaren Träger umfaßt.

4. Verwendung einer Verbindung der Formel (I), wie in Anspruch 1 gezeigt und definiert, oder eines pharmazeutisch annehmbaren Salzes hievon bei der Herstellung eines Medikamentes zur Prävention von Konvulsionen und/oder neurodegenerativen Störungen, die durch eine Überstimulation exzitativer Aminosäure-Rezeptoren induziert werden.

5. Verwendung einer Verbindung der Formel (I), wie in Anspruch 1 gezeigt und definiert, oder eines pharmazeutisch annehmbaren Salzes hievon bei der Herstellung eines Medikamentes zur Prävention einer Gehirnzellenschädigung, die aus einer Überstimulation durch überschüssige Mengen an exzitativen Aminosäuren resultiert.

6. Verbindung, Verwendung oder Zusammensetzung nach einem der Ansprüche 1 bis 5, wobei eines von R^1 und R^3 Wasserstoff bedeutet, und das andere -CN, $-NO_2$, -Cl, -Br, -F, -I oder $-CF_3$ darstellt; und R^2 Alkyl mit 1 bis 3 Kohlenstoffatomen ist.

7. Verbindung, Verwendung oder Zusammensetzung nach einem der Ansprüche 1 bis 6, wobei die Verbindung der Formel (I) R-Konfiguration in Stellung 10 aufweist.

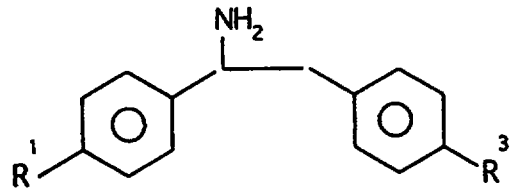
8. Verbindung, Verwendung oder Zusammensetzung nach Anspruch 6, wobei die Verbindung eine der folgenden:
10,11-Dihydro-3-brom-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten,
10,11-Dihydro-7-brom-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten,
10,11-Dihydro-3-chlor-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten,

* C L M S *

10,11-Dihydro-3-fluor-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptен,
(-)-5(R),10(S)-10,11-Dihydro-3-brom-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptен und
(+)-5(S),10(R)-10,11-Dihydro-3-brom-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cycloheptен
oder ein pharmazeutisch annehmbares Salz hievon ist.

9. Verbindung, Verwendung oder Zusammensetzung nach einem der Ansprüche 1 bis 8, wobei die Verbindung der Formel (I) in Form eines Salzes einer Säure vorliegt, ausgewählt aus Essig-, Milch-, Zitronen-, Wein-, Bernstein-, Malein-, Malon-, Glucon-, Salz-, Bromwasserstoff-, Phosphor-, Salpeter-, Schwefel- und Methansulfonsäure.

10. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Salz hievon nach Anspruch 1, welches umfaßt: Umsetzen einer Verbindung der Formel:



(II),

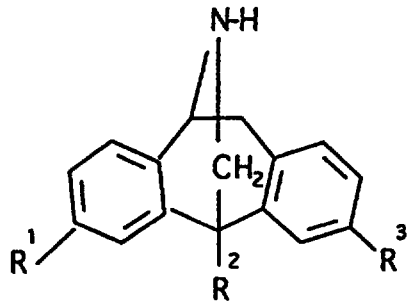
worin R^1 und R^3 wie oben in Anspruch 1 definiert sind, mit einem Propargylhalogenid der Formel:

$halCH_2C{\equiv}CR^4$

worin R^4 Wasserstoff oder Alkyl mit 1 bis 5 Kohlenstoffatomen bedeutet, und hal ein Halogen ist, wenn gewünscht, in Anwesenheit einer Base, gefolgt von einer Behandlung mit einer nichtwässerigen Säure.

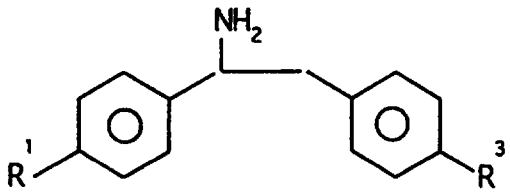
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel (I):



(I) ,

worin R^1 und R^3 unabhängig Wasserstoff, Cyano, Nitro, Halogen oder Perhalogenalkyl mit 1 bis 6 Kohlenstoffatomen bedeuten, mit der Maßgabe, daß eines von R^1 und R^3 von Wasserstoff verschieden ist; und R^2 Alkyl mit 1 bis 6 Kohlenstoffatomen darstellt; oder eines pharmazeutisch annehmbaren Salzes hievon, welches umfaßt: Umsetzen einer Verbindung der Formel:



(II),

worin R^1 und R^3 wie oben definiert sind, mit einem Propargylhalogenid der Formel:

$halCH_2C{\equiv}CR^4$

worin R^4 Wasserstoff oder Alkyl mit 1 bis 5 Kohlenstoffatomen bedeutet, und hal ein Halogen ist, wenn gewünscht, in Anwesenheit einer Base, gefolgt von einer Behandlung mit einer nichtwässerigen Säure.

2. Verfahren nach Anspruch 1, wobei eines von R^1 und R^3 Wasserstoff bedeutet, und das andere -CN, $-NO_2$, -Cl, -Br, -F, -I oder $-CF_3$ darstellt; und R^2 Alkyl mit 1 bis 3 Kohlenstoffatomen ist.

3. Verfahren nach Anspruch 1 oder 2, wobei die Verbindung der Formel (I) R-Konfiguration in Stellung 10 aufweist.

4. Verfahren nach Anspruch 1, bei welchem die hergestellte Verbindung eine der folgenden:
10,11-Dihydro-3-brom-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten,
10,11-Dihydro-7-brom-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten,
10,11-Dihydro-3-chlor-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten,
10,11-Dihydro-3-fluor-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten,
(-)-5(R),10(S)-10,11-Dihydro-3-brom-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten und
(+)-5(S),10(R)-10,11-Dihydro-3-brom-5-methyl-10,5-(iminomethano)-5H-dibenzo[a,d]cyclohepten
oder ein pharmazeutisch annehmbares Salz hievon ist.

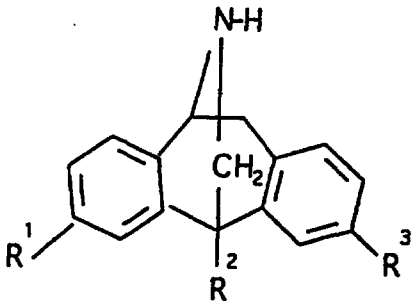
5. Verfahren nach einem der Ansprüche 1 bis 4, bei welchem die Verbindung der Formel (I) in Form eines Salzes einer Säure hergestellt wird, ausgewählt aus Essig-, Milch-, Zitronen-, Wein-, Bernstein-, Malein-, Malon-, Glucon-, Salz-, Bromwasserstoff-, Phosphor-, Salpeter-, Schwefel- und Methansulfonsäure.

6. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, welches das Vereinigen einer Verbindung der Formel (I) wie in Anspruch 1 gezeigt und definiert, oder eines pharmazeutisch annehmbaren Salzes hievon mit einem pharmazeutisch annehmbaren Träger umfaßt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule (I) :



(I)

où :

R^1 et R^3 sont, indépendamment, hydrogène, cyano, nitro, halo ou perhaloalcoyle en 1 à 6 atomes de carbone, avec la condition que l'un des R^1 et R^3 est autre qu'hydrogène;

R^2 est alcoyle en 1 à 6 atomes de carbone, ou

un sel pharmaceutiquement acceptable de celui-ci.

2. Composé de formule (I) suivant la revendication 1, à utiliser comme produit pharmaceutique.

3. Composition pharmaceutique comprenant un composé de formule (I) tel que présenté et défini à la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci et d'un support pharmaceutiquement acceptable.

4. Utilisation d'un composé de formule (I) tel que montré et défini à la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans la préparation d'un médicament pour prévenir les convulsions et/ou les désordres neurodégénératifs induits par une surstimulation des récepteurs des acides aminés excitants.

5. Utilisation d'un composé de formule (I) tel que montré et défini à la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, dans la préparation d'un médicament pour prévenir le dommage des cellules du cerveau résultant de la surstimulation par des quantités excessives d'acides aminés excitants.

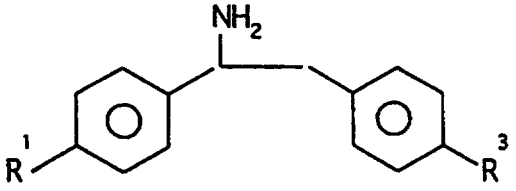
6. Composé, utilisation ou composition suivant l'une quelconque des revendications 1 à 5, dans lequel l'un des R^1 et R^3 est hydrogène et l'autre est -CN, $-NO_2$, -Cl, -Br, -F, -I ou $-CF_3$, et R^2 est alcoyle en 1 à 3 atomes de carbone.

7. Composé, utilisation ou composition suivant l'une quelconque des revendications 1 à 6, où le composé de formule (I) a la configuration R en position 10.

8. Composé, utilisation ou composition suivant la revendication 6, où le composé est l'un des suivants :
le 10,11-dihydro-3-bromo-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]cycloheptène;
le 10,11-dihydro-7-bromo-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]cycloheptène;
le 10,11-dihydro-3-chloro-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]cycloheptène;
le 10,11-dihydro-3-fluoro-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]cycloheptène;
le (-)-5(R),10(S)-10,11-dihydro-3-bromo-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]-cycloheptène, et
le (+)-5(S),10(R)-10,11-dihydro-3-bromo-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]-cycloheptène, ou
un sel pharmaceutiquement acceptable de ceux-ci.

9. Composé, utilisation ou composition suivant l'une quelconque des revendications 1 à 8, où le composé de formule (I) est préparé sous la forme d'un sel d'un acide choisi parmi : les acides acétique, lactique, citrique, tartrique, succinique, maléique, malonique, gluconique, chlorhydrique, bromhydrique, phosphorique, nitrique, sulfurique et méthanesulfonique.

10. Procédé de préparation d'un composé de formule (I) ou d'un sel pharmaceutiquement acceptable de celui-ci, suivant la revendication 1, qui comprend la réaction d'un composé de formule :



(II)

où :
R^1 et R^3 sont tels que définis ci-dessus dans la revendication 1, avec un halogénure de propargyle de formule :

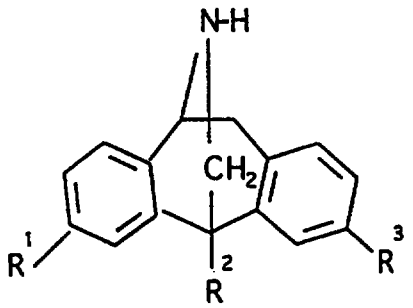
hal-$CH_2C{\equiv}CR^4$

où R^4 est hydrogène ou alcoyle en 1 à 5 atomes de carbone et hal est un halogène, si désiré en présence d'une base, puis le traitement avec un acide non aqueux.

* C L M S *

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'un composé de formule (I) :



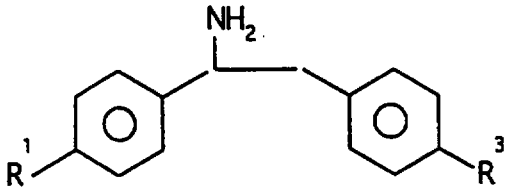
(I)

où :

R^1 et R^3 sont, indépendamment, hydrogène, cyano, nitro, halo ou perhaloalcoyle en 1 à 6 atomes de carbone, à la condition que l'un des R^1 et R^3 est autre qu'hydrogène;

R^2 est alcoyle en 1 à 6 atomes de carbone, ou

un sel pharmaceutiquement acceptable de celui-ci, qui comprend la réaction d'un composé de formule :



(II)

où :

R^1 et R^3 sont tels que définis ci-dessus, avec un halogénure de propargyle de formule :

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

où R^4 est hydrogène ou alcoyle en 1 à 5 atomes de carbone et hal est un halogène, si désiré en présence d'une base, puis le traitement avec un acide non aqueux.

2. Procédé suivant la revendication 1, dans lequel l'un des R^1 et R^3 est hydrogène et l'autre est -CN, $-NO_2$, -Cl, -Br, -F, -I ou $-CF_3$, et R^2 est alcoyle en 1 à 3 atomes de carbone.

3. Procédé suivant la revendication 1 ou 2, dans lequel le composé de formule (I) a la configuration R en position 10.

4. Procédé suivant la revendication 1, dans lequel le composé préparé est l'un des suivants :
le 10,11-dihydro-3-bromo-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]cycloheptène;
le 10,11-dihydro-7-bromo-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]cycloheptène;
le 10,11-dihydro-3-chloro-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]cycloheptène;
le 10,11-dihydro-3-fluoro-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]cycloheptène;
le (-)-5(R),10(S)-10,11-dihydro-3-bromo-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]-cycloheptène, et
le (+)-5(S),10(R)-10,11-dihydro-3-bromo-5-méthyl-10,5-(imminométhano)-5H-dibenzo[a,d]-cycloheptène, ou
un sel pharmaceutiquement acceptable de ceux-ci.

* C L M S *

5. Procédé suivant l'une quelconque des revendications 1 à 4, dans lequel le composé de formule(I) est préparé sous la forme d'un sel d'un acide choisi parmi : les acides acétique, lactique, citrique, tartrique, succinique, maléique, malonique, gluconique, chlorhydrique, bromhydrique, phosphorique, nitrique, sulfurique et méthanesulfonique.

6. Procédé de préparation d'une composition pharmaceutique qui comprend la mise en commun d'un composé de formule (I) tel que montré et défini à la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci avec un support pharmaceutiquement acceptable.