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(54) Title: ANTIOXIDANT NEUROPROTECTIVE USE OF, AND METHOD OF TREATMENT USING, HYDROXYCARBAZOLE COMPOUNDS (57) Abstract A new antioxidant neuroprotective use of and method of treatment using, selected hydroxycarbazole compounds or pharmaceutically acceptable salts thereof. The new use of, and method of treatment using, the antioxidant compounds prevents oxidative tissue damage to organs, particularly the central nervous system including the brain in mammals afflicted with disease-induced ischemic trauma, particularly stroke.		

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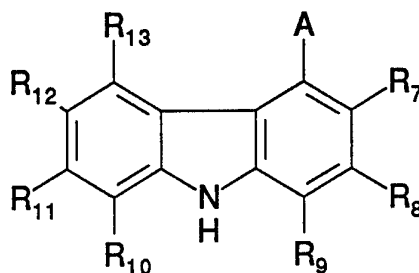
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ANTIOXIDANT NEUROPROTECTIVE USE OF, AND METHOD OF TREATMENT USING, HYDROXYCARBAZOLE COMPOUNDS

Field of the Invention

The present invention relates to a new medical use of, and method of treatment using, the hydroxycarbazole compounds of Formula I, as oxygen radical scavengers, or antioxidants, for protection of vital organs, particularly the central nervous system including the brain, from oxidative damage. In particular, the present invention provides a new use for such hydroxycarbazole compounds for making pharmaceutical compositions useful in prevention of organ reperfusion injury including related acute inflammation, particularly neuroprotection, that is, protection of the central nervous system from traumatic and post-traumatic injury associated with stroke, e. g., prevention of stroke and neurotrauma, and reduction of morbidity resulting from the sequelae of stroke.

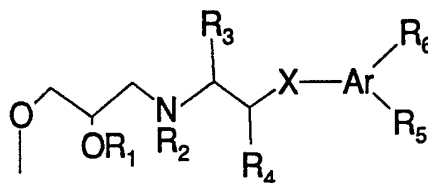


(I)

wherein:

R₇-R₁₃ are independently -H or -OH; and

A = is independently H, -OH, or a moiety of Formula II:



(II)

wherein:

R₁ is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R₂ is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R₃ is hydrogen or lower alkyl of up to 6 carbon atoms;

R₄ is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R₄ together with R₅ can represent -CH₂-O-;

X is a valency bond, -CH₂, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R₅ and R₆ are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R₅ and R₆ together represent methylenedioxy; and pharmaceutically acceptable salts thereof.

Background of the Invention

Morbidity and mortality associated with disease-induced ischemic trauma of the vital organs, for instance as seen in stroke, represent major health problems in the developed world.

Considerable biochemical, physiological and pharmacological evidence supports the occurrence and importance of oxygen free radical-induced lipid peroxidation (LPO) in cardiac ischemia/reperfusion injury (Meerson, F. Z. et al., *Basic Res. Cardiol.* (1982) **77**, 465-485; Downey, J. M., *Ann. Rev. Physiol.* (1990) **52**, 487-504). It has been proposed that reoxygenation of ischaemic myocardium leads to generation of O₂ and H₂O₂ within the tissue which can, in the presence of transition metal ions, become converted into highly-reactive hydroxyl radicals (OH) which initiate LPO, a radical chain reaction, leading to changes in cell membrane integrity and tissue injury (McCord, J. M., *N. Engl. J. Med.* (1985), **312**, 159-163; McCord, J. M., *Fed. Proc.*, (1987) **46**, 2402; Kagan, V. E., *Lipid Peroxidation in Biomembranes*, (1988) CRC Press, Boca Raton Florida). Marked activation of LPO in experimental myocardial infarction, as well as reoxygenation following transitory ischemia, have been demonstrated (Meerson et al., 1982; Rao et al., *Adv. Exp. Med. Biol.*, (1983) **161**, 347-363). Exposure of myocytes or whole heart to oxidant-generating systems produced severe injury, including inactivation of the ATP-dependent Ca⁺⁺ sequestering system of cardiac sarcoplasmic reticulum (Halliwell, B. and Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*, 2d ed., (1989) Clarendon Press, Oxford, England, 442-444). A significant increase in plasma LPO

levels has also been reported recently in patients with myocardial infarction, especially during the initial 48 hrs after an attack (Loeper et al., *Clinica Chimica Acta*, (1991) **196**, 119-126). The importance of LPO and oxygen radicals in tissue damage associated with ischemia is further supported by the protective effect of natural and synthetic antioxidants such as vitamin E and the lazaroid U-74500A (Levitt, M.A., *Clin. Res.* (1991) **39**, 265A) or antioxidant enzymes such as superoxide dismutase (SOD) and catalase in diverse ischemic models (for review see Halliwell and Gutteridge, 1989).

Given the high incidence of disease-induced ischemic trauma of the vital organs, in particular, of the central nervous system including the brain, e.g., stroke and its sequelae, together with the high survival rate of patients suffering these traumas in the developed world, there is a great need for pharmaceutical agents which prevent the occurrence of such traumas as well as which protect the vital organs of patients in post-traumatic recovery from organ ischemic reperfusion injury.

Summary of the Invention

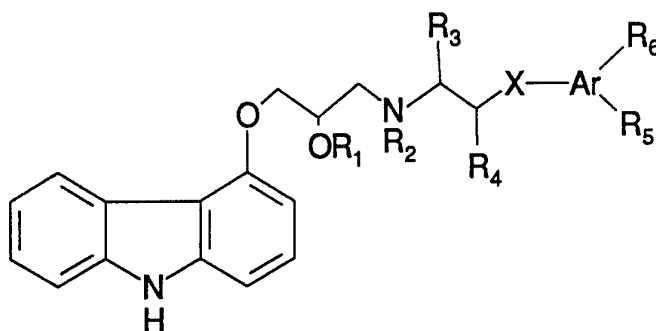
In a first aspect, the present invention provides a new medical use for the hydroxycarbazole compounds of Formula I as oxygen radical scavengers or antioxidants for protection of vital organs from oxidative damage. In particular, the present invention provides a new use for compounds preferably selected from the group consisting essentially of the compounds of Formula I wherein A is the moiety of Formula II wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H, and one of R₇, R₉, or R₁₀ is -OH, most preferably the compound of Formula I wherein A is the moiety of Formula II wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H, and R₇ is -OH, or a pharmaceutically acceptable salt thereof, said compounds being used to make pharmaceutical compositions useful in the prevention of organ reperfusion injury, including related acute inflammation generally, and particularly useful in neuroprotection, that is, prevention of stroke and reduction of morbidity resulting from the sequelae of stroke.

In a second aspect, the present invention also provides a method of treatment for prevention of oxidative tissue damage to organs afflicted with disease-induced ischemic trauma, particularly neuroprotection, that is, prevention of stroke and reduction of morbidity resulting from the sequelae of stroke, in mammals comprising internally administering to a mammal, preferably a human, in need thereof an effective amount of a compound selected from the group consisting

essentially of the compounds of Formula I, preferably selected from the group consisting essentially of the compounds of Formula I wherein A is the moiety of Formula II wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H, and one of R₇, R₉, or R₁₀ is -OH, most preferably the compound of Formula I wherein A is the moiety of Formula II wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H, and R₇ is -OH, or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

U.S. Pat. No. 4,503,067 discloses carbazolyl-(4)-oxypropanolamine compounds of Formula III:



(III)

wherein:

R₁ is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R₂ is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R₃ is hydrogen or lower alkyl of up to 6 carbon atoms;

R₄ is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R₄ together with R₅ can represent -CH₂-O-;

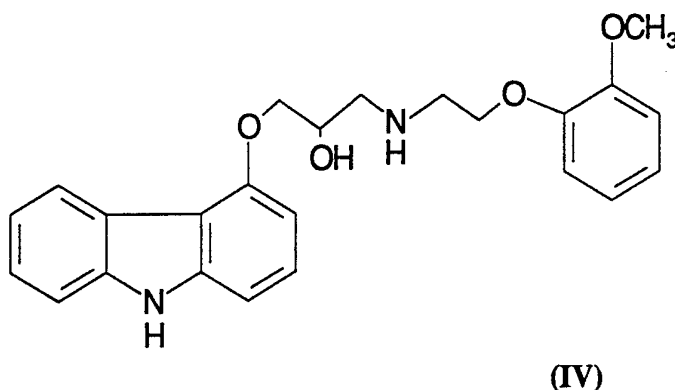
X is a valency bond, -CH₂, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R₅ and R₆ are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R₅ and R₆ together represent methylenedioxy;
and pharmaceutically acceptable salts thereof.

This patent further discloses a compound of Formula III, better known as carvedilol (1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol), having the structure shown in Formula IV:



These compounds, of which carvedilol is exemplary, are novel multiple action drugs useful in the treatment of mild to moderate hypertension and having utility in angina and congestive heart failure (CHF). Carvedilol is known to be both a competitive β -adrenoceptor antagonist and a vasodilator, and is also a calcium channel antagonist at higher concentrations. The vasodilatory actions of carvedilol result primarily from α_1 -adrenoceptor blockade, whereas the β -adrenoceptor blocking activity of the drug prevents reflex tachycardia when used in the treatment of hypertension. These multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals, particularly in humans, as well as for utility in the treatment of angina and CHF.

During ischemic organ trauma, as in stroke, a high proportion of ischemic organ cells become irreversibly damaged and necrotic, the extent of injury being dependent upon the length of time that the trauma, e.g. the arterial occlusion, persists. The protection of central nervous system neurons from such damage and necrosis during occlusion occurring in stroke and post-traumatic reperfusion is essential to achieving the therapeutic goal of restoration of neurological function; here and throughout this application this property is referred to by the term "neuroprotection" and its synonyms.

While traditional β -adrenoceptor antagonists, for instance propranolol, have a significant cardioprotective effect, they also often have undesirable side effects such as bradycardia, elevated diastolic blood pressure and total peripheral resistance cardiodepression. However, carbazolyl-(4)-oxypropanolamine compounds of

Formula I, particularly carvedilol, are effective cardioprotective agents at antihypertensive doses which unexpectedly minimize these consequences. At antihypertensive doses the combination of β -adrenoceptor blocking and vasodilatory properties of carvedilol provides cardioprotection during and after acute myocardial infarction. It is believed that the cardioprotective effects of β -adrenoceptor antagonists at such dosages result from an improvement in the balance between myocardial oxygen supply and demand by reducing myocardial work, which occurs secondary to reductions in both heart rate and contractility.

Some of the compounds of Formula I are known to be metabolites of carvedilol in human and other mammalian (e.g. gerbil) systems. The preferred compounds of the present invention, that is, the compounds of Formula I wherein A is the moiety of Formula II wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H, and one of R7, R9, or R10 is -OH are known to be metabolites of carvedilol.

We have recently discovered, by use of electron paramagnetic resonance (EPR) studies, that the hydroxycarbazole compounds of Formula I are oxygen radical scavengers. We have also discovered that, as oxygen scavengers, the above-described compounds act to inhibit LPO, and further that the hydroxycarbazole compounds of Formula I are surprisingly effective protective agents in generally preventing a wide variety of disease states associated with oxidative tissue damage to the organs due to LPO following ischemic traumas. In particular, the compounds of the present invention are especially useful in neuroprotection, that is, prevention of stroke, and reduction of morbidity resulting from the sequelae of stroke.

As is further illustrated below, the compounds of Formula I, preferably selected from the group consisting essentially of the compounds of Formula I wherein A is the moiety of Formula II wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H, and one of R7, R9, or R10 is -OH, most preferably the compound of Formula I wherein A is the moiety of Formula II wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H, and R7 is -OH, exhibit neuroprotection, and are especially useful for protecting cerebral tissue from stroke and neurotrauma as well as for preventing oxidative tissue damage of ischemic human cerebral tissue following occurrence of an ischemic event such as stroke or cerebral trauma. Thus, chronic administration of these compounds can both reduce the risk of cerebral ischemia or stroke in individuals at risk thereof as well as provide adjunctive therapy by reducing the magnitude of oxidative tissue damage following an ischemic cerebral event. Because hypertensive individuals are at increased risk of stroke, the neuroprotective use of the present compounds at appropriate dosing

regimens in combination with antihypertensive therapy significantly reduces the risk of stroke, and the sequelae of stroke in such patients.

The compounds of Formula I, preferably those selected from the group consisting essentially of the compounds of Formula I wherein A is the moiety of Formula II wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H, and one of R7, R9, or R10 is -OH, most preferably the compound of Formula I wherein A is the moiety of Formula II wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H, and R7 is -OH, are useful for neuroprotection in humans according to the present invention at dosages ranging from about 1-3 mg/kg i.v. b.i.d. and 3-30 .mg/kg p.o. b.i.d.

The present invention also provides a method of treatment for prevention of oxidative tissue damage to organs afflicted with disease-induced ischemic trauma in mammals comprising internally administering to a mammal, preferably a human, in need thereof an effective amount of a compound selected from the group consisting essentially of the compounds of Formula I, preferably those selected from the group consisting essentially of the compounds of Formula I wherein A is the moiety of Formula II wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H, and one of R7, R9, or R10 is -OH, most preferably the compound of Formula I wherein A is the moiety of Formula II wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H, and R7 is -OH, or a pharmaceutically acceptable salt thereof.

Compounds of Formula I may be conveniently prepared as described by way of example in Example 1.

Pharmaceutical compositions of the compounds of Formula I for neuroprotective use according to the present invention, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternatively, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or

liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, ethanol, and water. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

The following Example is purely illustrative and is provided to teach how to make the compounds of the present invention, but is not intended to limit the scope of the present invention in any manner.

In the Example, all temperatures are in degrees Centigrade (°C).

EXAMPLES

Example 1

The compound of Formula I wherein R7 is -OH, and R8 - R13 are all -H, and A is the moiety of Formula II wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H was synthesized as follows and is exemplary of the synthetic route to the compounds of Formula I.

3-Benzoyloxy-4-hydroxycarbazole

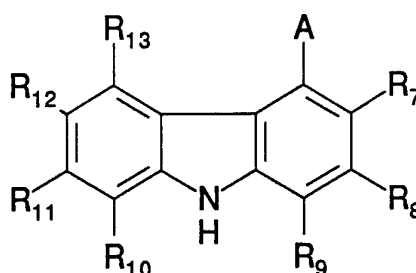
Benzoyl peroxide (881mg, 2.73 mmol) was added in one portion to a suspension of 4-hydroxycarbazole (500 mg, 2.73 mmol) in 20 mL CHCl_3 at 25 °C. The mixture was stirred for 2 h, then washed with water. The organic layer was dried over sodium sulfate and concentrated. Flash chromatography of the residue (silica, methylene chloride) provided 15 mg of 3-benzoyloxy-4-hydroxycarbazole. MS (DCI/ NH_3): 304.2 (M+H)⁺.

Subsequent steps to yield the product are well-known: reaction with epichlorohydrin, then 2-methoxyphenethylamine, and finally saponification of the benzoyl ester.

The above description fully discloses how to make and use the present invention. However, the present invention is not limited to the particular embodiment described hereinabove, but includes all modifications thereof within the scope of the following claims.

We claim:

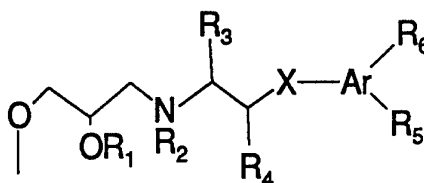
1. A method of treatment for prevention of oxidative tissue damage to organs afflicted with disease-induced ischemic trauma in mammals comprising internally administering to a mammal in need thereof an effective amount of a compound selected from the group consisting essentially of the compounds of Formula I:



(I)

wherein:

R₇-R₁₃ are independently -H or -OH; and
A = is independently H, -OH, or a moiety of Formula II:



(II)

wherein:

R₁ is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R₂ is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R₃ is hydrogen or lower alkyl of up to 6 carbon atoms;

R₄ is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R₄ together with R₅ can represent -CH₂-O-;

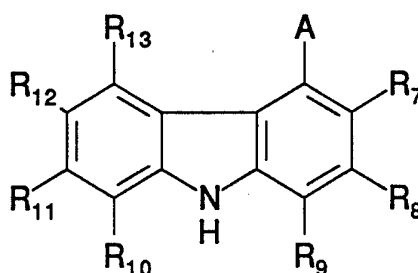
X is a valency bond, -CH₂, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R₅ and R₆ are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R₅ and R₆ together represent methylenedioxy;
and pharmaceutically acceptable salts thereof.

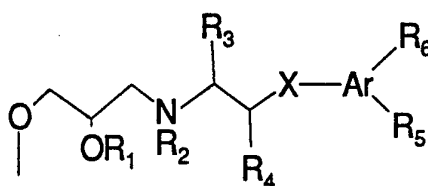
2. A method of treatment according to Claim 1 wherein said mammal is human.
3. A method of treatment according to Claim 1 wherein said compound is a compound of Formula I wherein:
A is the moiety of Formula II wherein wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H; and one of R₇, R₉, or R₁₀ is -OH.
4. A method of treatment for neuroprotection in mammals comprising internally administering to a mammal in need thereof an effective amount of a compound selected from the group consisting essentially of compounds of Formula I:



(I)

wherein:

R₇-R₁₃ are independently -H or -OH; and
A = is independently H, -OH, or a moiety of Formula II:



(II)

wherein:

R₁ is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R₂ is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R₃ is hydrogen or lower alkyl of up to 6 carbon atoms;

R₄ is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R₄ together with R₅ can represent -CH₂-O-;

X is a valency bond, -CH₂, oxygen or sulfur;

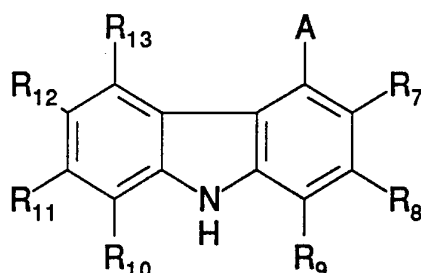
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R₅ and R₆ are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R₅ and R₆ together represent methylenedioxy;
and pharmaceutically acceptable salts thereof.

5. A method of treatment according to Claim 4 wherein said mammal is human.
6. A method of treatment according to Claim 4 wherein said compound is a compound of Formula I wherein:
A is the moiety of Formula II wherein wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H ; and one of R₇, R₉, or R₁₀ is -OH.
7. A method of treatment according to Claim 6 wherein said compound is a compound of Formula I wherein:
A is the moiety of Formula II wherein wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H ; and R₇ is -OH.
8. A method of treatment for neuroprotection of human patients surviving a stroke, comprising internally administering to a patient in need thereof an effective dose of a pharmaceutical composition comprising a compound according to Claim 1, said treatment reducing the risk of oxidative damage to cerebral tissue.
9. A method of treatment according to Claim 1 wherein said compound is used to make a pharmaceutical composition suitable for parenteral administration.

10. A use of a compound selected from the group consisting essentially of compounds of Formula I:

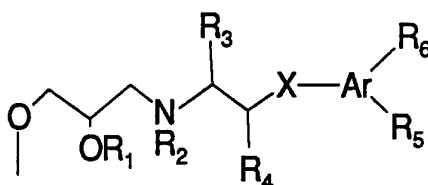


(I)

wherein:

R₇-R₁₃ are independently -H or -OH; and

A = is independently H, -OH, or a moiety of Formula II:



(II)

wherein:

R₁ is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R₂ is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R₃ is hydrogen or lower alkyl of up to 6 carbon atoms;

R₄ is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R₄ together with R₅ can represent -CH₂-O-;

X is a valency bond, -CH₂, oxygen or sulfur;

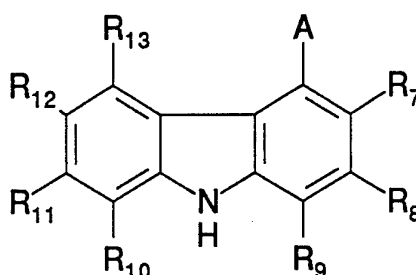
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R₅ and R₆ are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R₅ and R₆ together represent methylenedioxy;

or a pharmaceutically acceptable salt thereof, for prevention of oxidative tissue damage to organs in mammals afflicted with disease-induced ischemic trauma.

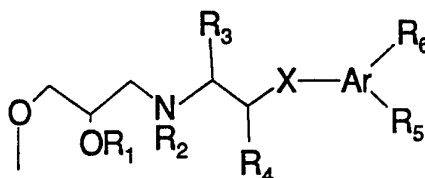
11. A use according to Claim 10 wherein said mammal is human.
12. A use according to Claim 10 wherein said compound is a compound of Formula I wherein:
- A is the moiety of Formula II wherein wherein R1 is -H, R2 is -H, R3 is -H, R4 is -H, X is O, Ar is phenyl, R5 is *ortho* -OH, and R6 is -H; and one of R7, R9, or R10 is -OH.
13. A use of a compound selected from the group consisting essentially of compounds of Formula I:



(I)

wherein:

R7-R13 are independently -H or -OH; and
A = is independently H, -OH, or a moiety of Formula II:



(II)

wherein:

R1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R4 together with R5 can represent -CH2-O-;

X is a valency bond, -CH2, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R₅ and R₆ are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R₅ and R₆ together represent methylenedioxy;
or a pharmaceutically acceptable salt thereof, for neuroprotection in mammals.

14. A use according to Claim 13 wherein said mammal is human.

15. A use according to Claim 13 wherein said compound is a compound of Formula I wherein:

A is the moiety of Formula II wherein wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H ; and one of R₇, R₉, or R₁₀ is -OH.

16. A use according to Claim 15 wherein said compound is a compound of Formula I wherein:

A is the moiety of Formula II wherein wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is O, Ar is phenyl, R₅ is *ortho* -OH, and R₆ is -H ; and R₇ is -OH.

17. A use of a compound according to Claim 13 for neuroprotection of human patients surviving a stroke, said use reducing the risk of oxidative damage to cerebral tissue.

18. A use according to Claim 13 wherein said pharmaceutical composition is suitable for parenteral administration.

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/US93/11598

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/40

US CL :514/411

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/411

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

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

CAS, BIOSIS, MEDLINE, APS- CARVEDILOL FOR NEUROPROTECTION OR OXIDATIVE TISSUE DAMAGE OR STROKE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<u>X</u> Y	The Journal of Pharmacology and Experimental Therapeutics, Vol. 263 No. 1, issued 1992 (U.S.A.), Yue et al., "Carvedilol, a New Vasodilator and Beta Adrenoreceptor Antagonist, Is an Antioxidant and Free Radical Scavenger", pages 92-98, see the abstract particularly.	<u>4,6,7</u> 1-3,5,8-18
<u>X</u> Y	Chemical Abstracts Vol. 118 No. 7, issued 1992, Lysko et al., "Neuroprotective Effects of Carvedilol a New Antihypertensive Agent, In Cultured Rat Cerebellar Neurons And In Gerbil Global Brain Ischemia", Stroke 23(11), 1630-6.	<u>4,6,7</u> 1-3,5,8-18

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" Inter 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
"A" document defining the general state of the art which is not considered to be part of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"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
"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)	"G" document member of the same patent family
"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	

Date of the actual completion of the international search 02 MARCH 1994	Date of mailing of the international search report MAR 15 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. 703-305-3220	Authorized officer M. MOEZZE <i>Jella Collins Inc</i> Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11598

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<u>X</u> Y	Chemical Abstracts Vol. 118 No. 11, issued 1992, Lysko et al., "Neuroprotective Effects of Carvedilol a New Antihypertensive, at the N-methyl-D- aspartate Receptor", see abstract no. 94036w, Neurosci. Lett. 148(1-2), 34-8.	<u>4,6,7</u> 1-3,5,8-18
Y	US,A, 4,503,067 (WIEDEMANN ET AL) 05 MARCH 1985, see abstract particularly.	1-18