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(71) Applicant *(for all designated States except US)*: BOEHRINGER MANNHEIM PHARMACEUTICALS CORPORATION-SMITHKLINE BEECHAM CORPORATION LIMITED PARTNERSHIP NO. 1 [US/US]; 101 Orchard Ridge Drive, Gaithersburg, MD 20878 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: FEUERSTEIN, Giora, Zeev [US/US]; 405 Ballytore Road, Wynnewood, PA 19096 (US). YUE, Tian-Li [CN/US]; 308 Earlington Road, Havertown, PA 19083 (US).

(74) Agents: McCARTHY, Mary, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(54) Title: METHOD FOR INHIBITING THE EXPRESSION OF FAS

(57) Abstract

The present invention provides a method for inhibiting the expression of Fas which comprises administering to a mammal in need thereof an effective amount of a compound which is a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist.

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METHOD FOR INHIBITING THE EXPRESSION OF FAS

Field of the Invention

The present invention relates to a new method of treatment using compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for inhibiting the expression of Fas, a cell surface protein.

Background of the Invention

Cell proliferation, differentiation, and survival are often regulated by growth, differentiation, and survival factors, respectively, which are collectively called cytokines. Cytokines bind to their complementary receptors, which transduce the extracellular signal into an intracellular signaling cascade. Fas ligand (FasL) is a cytokine. It is one of the few known cytokines that is a death factor. This ligand binds to its receptor, Fas, a cell-surface protein, and induces apoptosis (cell death). Many tissues and cell lines weakly express Fas, but abundant expression has been found in mouse heart, liver, lung, kidney, ovary and thymus (R. Watanabe-Fukunaga, et al., *J. Immunol.*, **148**, 1274-1279 (1992)). In the immune system, Fas and FasL are involved in down-regulation of immune reactions as well as in T cell-mediated cytotoxicity. Malfunction of the Fas system causes lymphoproliferative disorders and accelerates autoimmune diseases, whereas its exacerbation may cause tissue destruction (S. Nagata, et al., *Science*, **267**, 1449-1456 (1995)).

Surprisingly, it has been found that carvedilol, a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist, inhibits the expression of Fas. This inhibition may mean that carvedilol and related Formula I compounds are useful for diseases wherein inhibition of Fas-mediated apoptosis is indicated. Particularly, this inhibition may mean that carvedilol and related Formula I compounds are useful for blocking ischemia-induced apoptosis in cardiac cells, for preventing or inhibiting tissue remodeling, in particular in cardiac tissue and blood vessels, for treating autoimmune diseases, and for inhibiting tumor growth and metastasis.

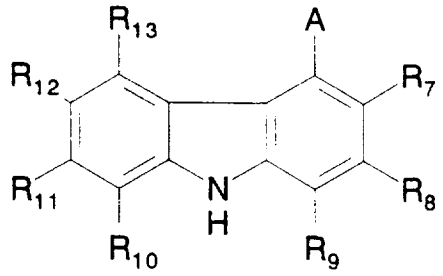
Summary of the Invention

The present invention relates to a new method of treatment using compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for inhibiting the expression of Fas. The invention also relates to a method of treatment using compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for inhibiting apoptosis. Furthermore, this invention relates to a method of treatment using compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for diseases wherein inhibition of Fas-mediated apoptosis is indicated. In particular, this invention is directed to the use of Formula I compounds, preferably carvedilol, to specifically induce Fas-mediated apoptosis of undesirable cells, such as cancer or autoreactive immune cells. Additionally, when control of aberrant forms of Fas activation is desired, the Formula I compounds, preferably carvedilol, are used to prevent cell depletion in AIDS or neurodegenerative diseases.

This invention also relates to a method of treatment using compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for preventing or inhibiting tissue remodeling, in particular in cardiac tissue and blood vessels. The present method includes the use of compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, to block ischemia-induced apoptosis in cardiac cells.

Detailed Description of the Invention

The present invention provides a new method for inhibiting the expression of Fas using compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists. Preferably, this invention provides a new method for inhibiting the expression of Fas using compounds of Formula I:

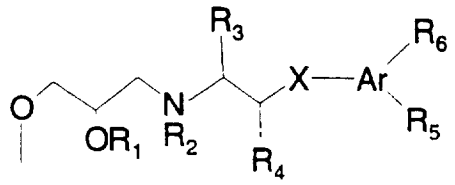


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

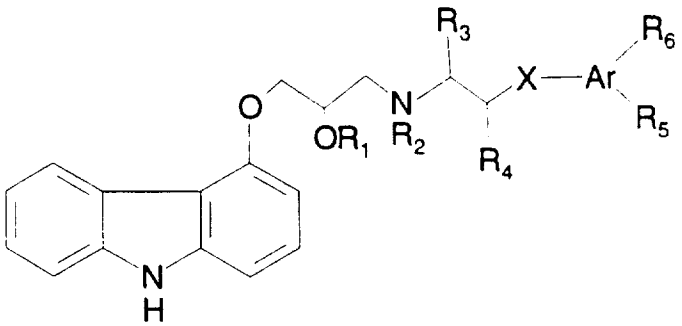
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

More preferably, the present invention provides a new method for inhibiting the expression of Fas using compounds of Formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a single bond, $-CH_2$, oxygen or sulfur;

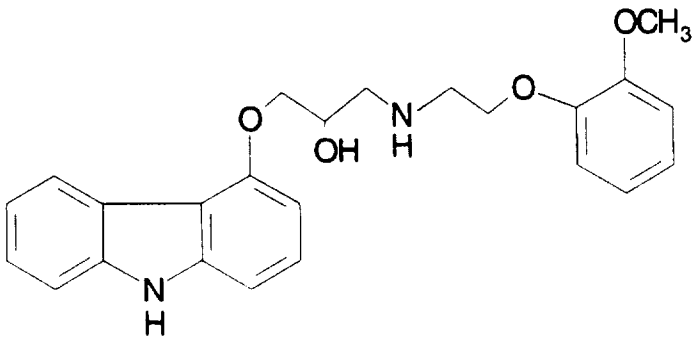
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

Most preferably, the present invention provides a new method for inhibiting the expression of Fas using a compound of Formula IV, better known as carvedilol or (1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol):



(IV).

The compounds of the present invention are novel multiple action drugs useful in the treatment of mild to moderate hypertension. Carvedilol is known to be both a competitive non-selective 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. *See* Willette, R.N., Sauermelch, C.F. & Ruffolo, R.R., Jr. (1990) *Eur. J. Pharmacol.*, **176,** 237-240; Nichols, A.J., Gellai, M. & Ruffolo, R.R., Jr. (1991) *Fundam. Clin. Pharmacol.*, **5,** 25-38; Ruffolo, R.R., Jr., Gellai, M., Hieble, J.P., Willette, R.N. & Nichols, A.J. (1990) *Eur. J. Clin. Pharmacol.*, **38,** S82-S88; Ruffolo, R.R., Jr., Boyle, D.A., Venuti, R.P. & Lukas, M.A. (1991) *Drugs of Today,* **27,** 465-492; and Yue, T.-L., Cheng, H., Lysko, P.G., Mckenna, P.J., Feuerstein, R., Gu, J., Lysko, K.A., Davis, L.L. & Feuerstein, G. (1992) *J. Pharmacol. Exp. Ther.*, **263,** 92-98.

The antihypertensive action of carvedilol is mediated primarily by decreasing total peripheral vascular resistance without causing the concomitant reflex changes in heart rate commonly associated with other antihypertensive agents. Willette, R.N., et al. *supra*; Nichols, A.J., et al. *supra*; Ruffolo, R.R., Jr., Gellai, M., Hieble, J.P., Willette, R.N. & Nichols, A.J. (1990) *Eur. J. Clin. Pharmacol.*, **38,** S82-S88.. Carvedilol also markedly reduces infarct size in rat, canine and porcine models of acute myocardial infarction, Ruffolo, R.R., Jr., et al., *Drugs of Today, supra*, possibly as a consequence of its antioxidant action in attenuating oxygen free radical-initiated lipid peroxidation. Yue, T.-L., et al. *supra*.

Recently, it has been discovered that compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the compounds of Formula I, preferably carvedilol, inhibit the expression of Fas and inhibit Fas-mediated apoptosis. Based on this mechanism of action, the instant compounds can be used to treat diseases wherein inhibition or control of Fas-mediated apoptosis is indicated. In particular, the compounds of the current invention, preferably carvedilol, can be used for blocking ischemia-induced apoptosis in cardiac cells, for preventing or inhibiting tissue remodeling, in particular in cardiac tissue and blood vessels, for treating autoimmune diseases, and for inhibiting tumor growth and metastasis. Additionally, when control of aberrant

forms of Fas activation is desired, the Formula I compounds, preferably carvedilol, are used to prevent cell depletion in AIDS or neurodegenerative diseases.

Some of the compounds of Formula I are known to be metabolites of carvedilol. Certain 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 R_7, R_9, or R_{10} is -OH, are metabolites of carvedilol.

Compounds of Formula I may be conveniently prepared as described in U.S. Pat. No. 4,503,067. Reference should be made to said patent for its full disclosure, the entire disclosure of which is incorporated herein by reference.

Pharmaceutical compositions of the compounds of Formula I, including carvedilol, may be administered to patients according to the present invention in any medically acceptable manner, preferably orally. For parenteral administration, the pharmaceutical composition will be in the form of a sterile injectable liquid stored in a suitable container such as an ampoule, or in the form of an aqueous or nonaqueous liquid suspension. The nature and composition of the pharmaceutical carrier, diluent or excipient will, of course, depend on the intended route of administration, for example whether by intravenous or intramuscular injection

Pharmaceutical compositions of the compounds of Formula I for 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, polyvinyl-pyrrolidone, 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.

Dosing in humans for the treatment of disease according to the present invention should not exceed a dosage range of from about 3.125 to about 50 mg of the compounds of Formula I, particularly carvedilol, preferably given twice daily. As one of ordinary skill in the art will readily comprehend, the patient should be started on a low dosage regimen of the desired compound of Formula I, particularly carvedilol, and monitered for well-known symptoms of intolerance, e.g., fainting, to such compound. Once the patient is found to tolerate such compound, the patient should be brought slowly and incrementally up to the maintenance dose. The choice of initial dosage most appropriate for the particular patient is determined by the practitioner using well-known medical principles, including, but not limited to, body weight. In the event that the patient exhibits medically acceptable tolerance of the compound for two weeks, the dosage is doubled at the end of the two weeks and the patient is maintained at the new, higher dosage for two more weeks, and observed for signs of intolerance. This course is continued until the patient is brought to a maintenance dose

It will be appreciated that the actual preferred dosages of the compounds being used in the compositions of this invention will vary according to the particular composition formulated, the mode of administration, the particular site of administration and the host being treated.

No unacceptable toxicological effects are expected when the compounds of Formula I are used according to the present invention.

The example which follows is intended in no way to limit the scope of this invention, but is provided to illustrate how to use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

Experimental

The effect of carvedilol on myocardial apoptosis was investigated in a rabbit model of cardiac ischemia and reperfusion (R. Gottlieb, et al., *J. Clin. Invest.*, **94**, 1621-1628 (1994)). In this model, ischemia and reperfusion elicits widespread

apoptosis in cardiac myocytes. Carvedilol treatment prior to the ischemic insult significantly reduced the apoptotic myocytes from 14.7 cells per field to 4.5 cells per field ($p<0.01$).

Immunochemical Detection of Fas Expression of Rabbit Cardiomyocytes

Heart tissue was fixed in NBF for 24-48 hr at 4°C and cut longitudinally into 2-3 mm-thick piece. Following standard histological processing and embedding in paraffin, 5 μm-thick sections were prepared for immunoperoxidase staining using the Vectastain ABC kit (Vector Laboratories) according to the manufacturer's instructions. Briefly, endogenous peroxidase was quenched with 0.3% H_2O_2 in methanol for 30 minutes. Nonspecific immunoglobulin binding sites were blocked with normal goat serum for 1 hour and then the sections were incubated with the primary antibody (mouse anti-FAS, 2 μg/ml, Upstate Biotechnology) for 1 hour at room temperature. The sections were then incubated for 30 minutes with a biotinylated goat anti-mouse IgM secondary antibody (1:200, Vector Laboratories) followed by 30 minutes of incubation with the Vectastain ABC reagent solution. Immunoglobulin complexes were visualized upon incubation with 3,3'-diaminobenzidine (DAB, Vector Laboratories) at 0.5 mg/ml in 50 mM Tris-HCl, pH 7.4 and 3% H_2O_2. DAB staining was enhanced by treating the sections for 10 seconds with DAB Enhancing Solution (Vector Laboratories). Sections were washed, counterstained with Gill's Hematoxylin, cleared, mounted with Aquamount (Polysciences), and then examined by light microscopy.

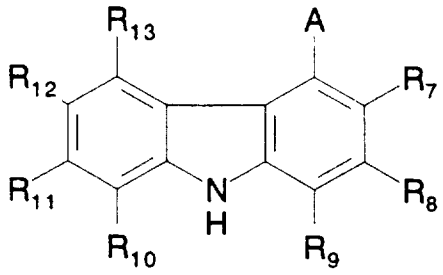
In summary, comparative studies were conducted wherein basil levels of Fas was expressed in normal heart cardiomyocytes. In ischemic reperfusion injury, the expression of Fas in cardiomyocytes was stimulated. With carvedilol treatment, this reperfusion-induced expression of Fas in cardiomyocytes was inhibited.

The foregoing is illustrative of the use of the compounds of this invention. This invention, however, is not limited to the precise embodiment described herein, but encompasses all modifications within the scope of the claims which follow.

What is claimed is:

1. A method for inhibiting the expression of Fas which comprises administering to a mammal in need thereof an effective amount of a compound which is a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist.

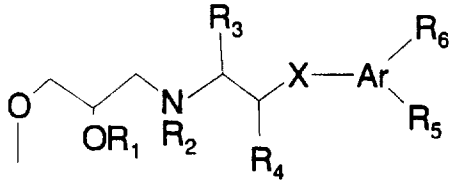
2. The method of claim 1 wherein the compound is a compound of Formula I:



(I)

wherein:

R_7-R_{13} are independently -H or-OH; and
A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

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

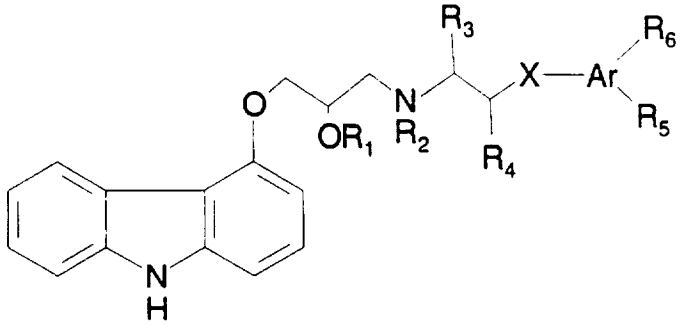
R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower

alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

3. The method of claim 1 wherein the compound is a compound of Formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a valency bond, $-CH_2$, oxygen or sulfur;

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

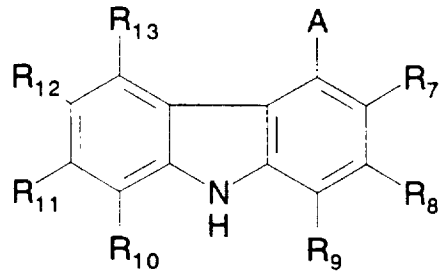
R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

or a pharmaceutically acceptable salt thereof.

4. The method according to Claim 1 wherein said compound is carvedilol.

5. A method for inhibiting Fas-mediated apoptosis which comprises administering to a mammal in need thereof an effective amount of a compound which is a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist.

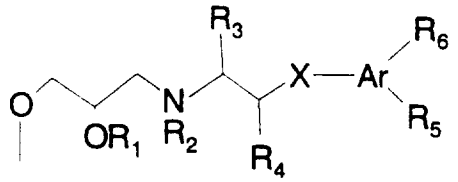
6. The method of claim 5 wherein the compound is a compound of Formula I:



(I)

wherein:

R_7-R_{13} are independently -H or-OH; and
A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

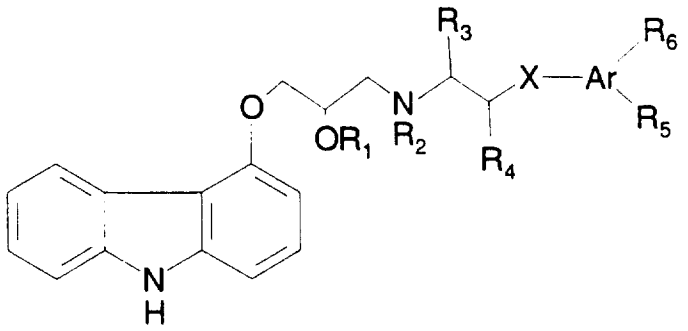
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

7. The method of claim 5 wherein the compound is a compound of Formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a valency bond, $-CH_2$, oxygen or sulfur;

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

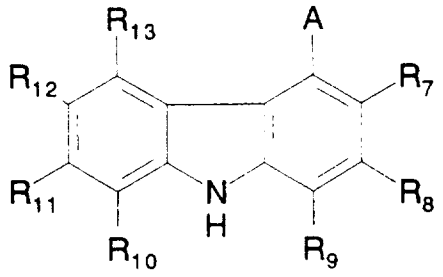
R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

or a pharmaceutically acceptable salt thereof.

8. The method according to Claim 5 wherein said compound is carvedilol.

9. A method for treating diseases wherein inhibition of Fas-mediated apoptosis is indicated which comprises administering to a mammal in need thereof an effective amount of a compound which is a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist.

10. The method of claim 9 wherein the compound is a compound of Formula I:

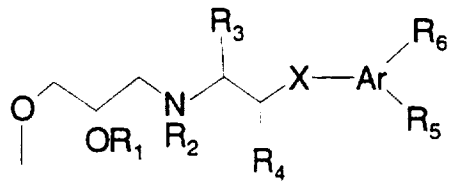


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

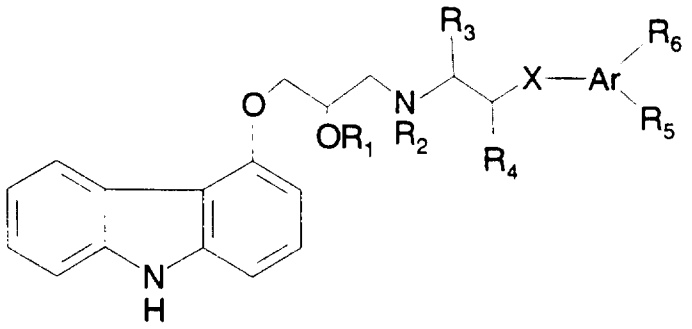
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

11. The method of claim 9 wherein the compound is a compound of Formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a valency bond, $-CH_2$, oxygen or sulfur;

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

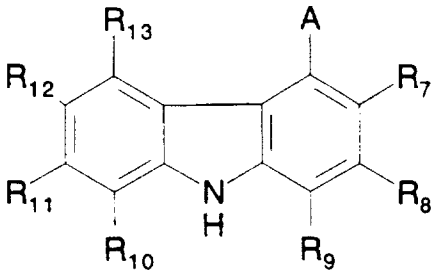
R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

or a pharmaceutically acceptable salt thereof.

12. The method according to Claim 9 wherein said compound is carvedilol.

13. A method for blocking ischemia-induced apoptosis in cardiac cells which comprises administering to a mammal in need thereof an effective amount of a compound which is a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist.

14. The method of claim 13 wherein the compound is a compound of Formula I:

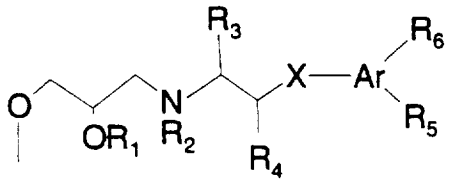


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

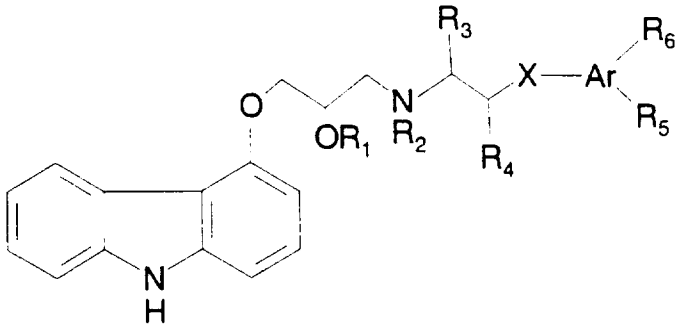
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

15. The method of claim 13 wherein the compound is a compound of Formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a valency bond, $-CH_2$, oxygen or sulfur;

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

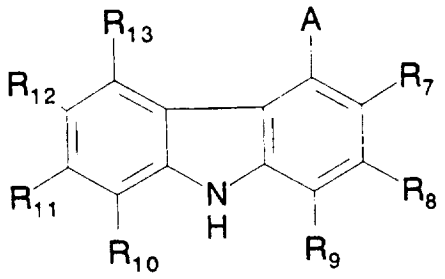
R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

or a pharmaceutically acceptable salt thereof.

16. The method according to Claim 13 wherein said compound is carvedilol.

17. A method for preventing or inhibiting tissue remodeling, for treating autoimmune diseases, or for inhibiting tumor growth and metastasis which comprises administering to a mammal in need thereof an effective amount of a compound which is a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist.

18. The method of claim 17 wherein the compound is a compound of Formula I:

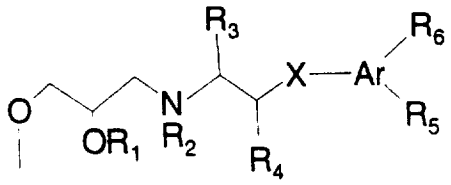


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

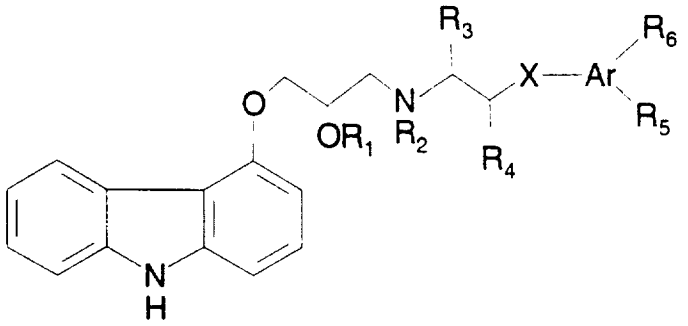
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

19. The method of claim 17 wherein the compound is a compound of Formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a valency bond, $-CH_2$, oxygen or sulfur;

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

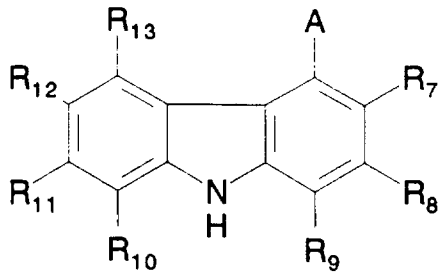
R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

or a pharmaceutically acceptable salt thereof.

20. The method according to Claim 17 wherein said compound is carvedilol.

21. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist in the manufacture of a medicament for inhibiting the expression of Fas.

22. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 21 of the formula I:

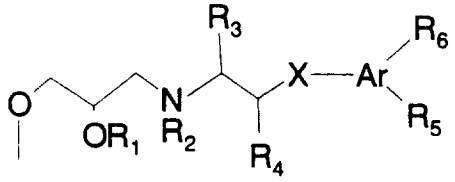


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

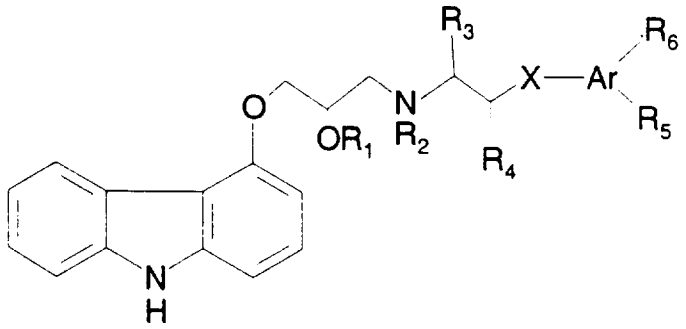
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

23. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 21 of the formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a single bond, $-CH_2$, oxygen or sulfur;

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

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

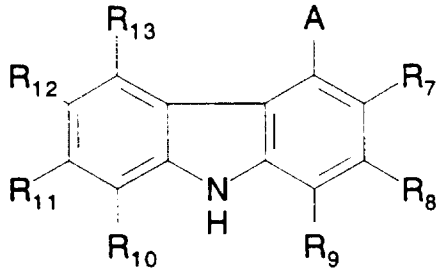
R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

24. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 21 wherein said antagonist is carvedilol.

25. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist in the manufacture of a medicament for inhibiting Fas-mediated apoptosis.

26. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 25 of the formula I:

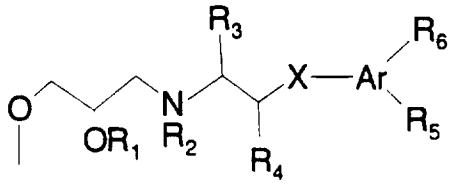


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-O-;

X is a single bond, -CH_2, oxygen or sulfur;

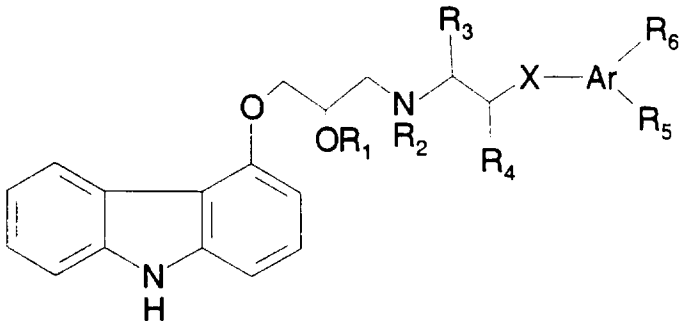
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

27. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 25 of the formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a single bond, $-CH_2$, oxygen or sulfur;

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

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

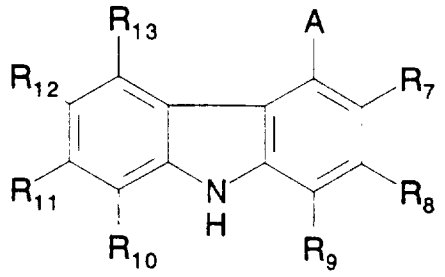
R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

28. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 25 wherein said antagonist is carvedilol.

29. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist in the manufacture of a medicament for treating diseases wherein inhibition of Fas-mediated apoptosis is indicated.

30. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 29 of the formula I:

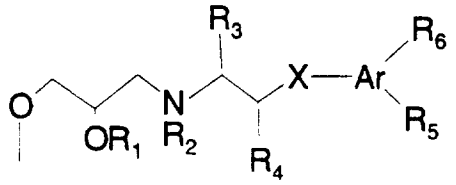


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

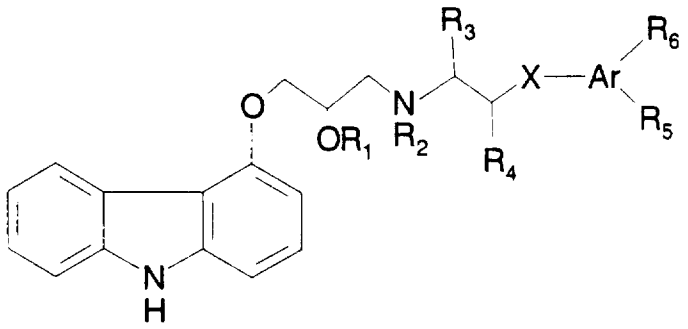
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

31. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 29 of the formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a single bond, $-CH_2$, oxygen or sulfur;

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

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

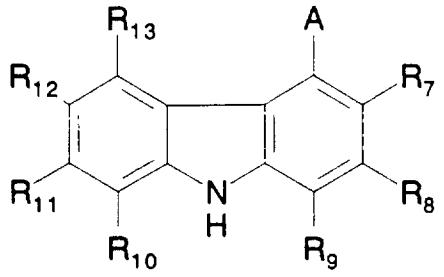
R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

32. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 29 wherein said antagonist is carvedilol.

33. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist in the manufacture of a medicament for blocking ischemia-induced apoptosis in cardiac cells.

34. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 33 of the formula I:

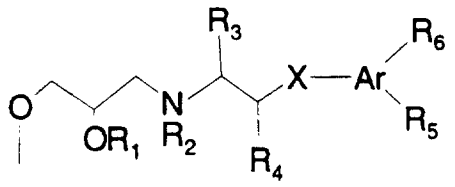


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-0-;

X is a single bond, -CH_2, oxygen or sulfur;

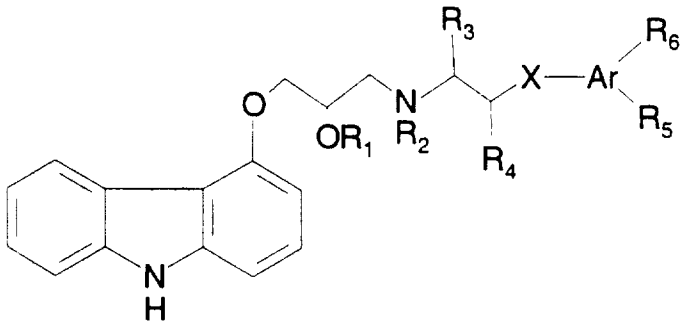
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

35. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 33 of the formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a single bond, $-CH_2$, oxygen or sulfur;

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

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

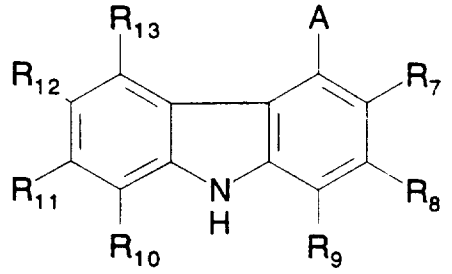
R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

36. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 33 wherein said antagonist is carvedilol.

37. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist in the manufacture of a medicament for preventing or inhibiting tissue remodeling, for treating autoimmune diseases, or for inhibiting tumor growth and metastasis.

38. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 37 of the formula I:

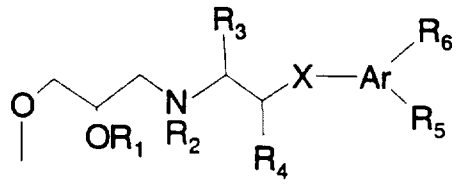


(I)

wherein:

R_7-R_{13} are independently -H or-OH; and

A is a moiety of Formula II:



(II)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent -CH_2-O-;

X is a single bond, -CH_2, oxygen or sulfur;

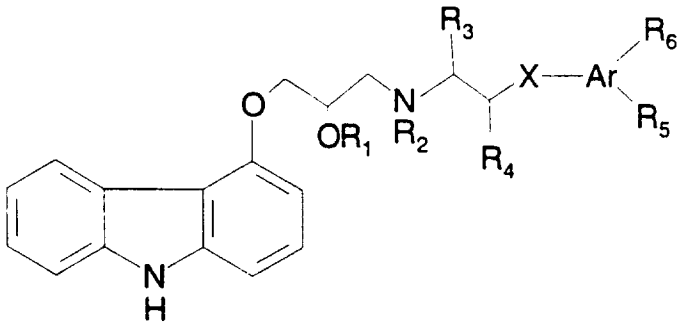
Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -$CONH_2$- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

39. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 37 of the formula III:



(III)

wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $-CH_2-O-$;

X is a single bond, $-CH_2$, oxygen or sulfur;

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

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $-CONH_2-$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

and pharmaceutically acceptable salts thereof.

40. The use of a dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonist according to claim 37 wherein said antagonist is carvedilol.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14792

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A01N 43/38; 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

NONE

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

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database HCAPLUS on STN, LF, Masarykovy Univ., (Brno, Czech Rep.), Document No. 124:250307, VACEK et al., "Protective effect of carvedilol on reperfusion blood flow and tissue injury in the rat ischemic kidney", abstract, Vnitr. Lek., 40(4), 215-218, 1994.	1-40
X	Database HCAPLUS on STN, SmithKline Beecham Pharmaceuticals, (King of Prussia, PA), Document No. 124:75193, FEUERSTEIN et al., "Carvedilol update III: rationale for use in congestive heart failure", abstract, Drugs Today, Volume Date 1995 31(Suppl. F), 1-23, 1995.	1-40

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

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be 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
"B"	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)	"&"	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 13 OCTOBER 1997	Date of mailing of the international search report 02 DEC 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer IW for DWAYNE C. JONES Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/14792

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

HCAPLUS, REGISTRY search terms: structure search, folic(w)acid#, (cd95 or cd(w)95)(s)antigen, apoptosis, cell(4a)death, (?cancer? or ?neoplas? or ?immune? or ?immuno?, ?tumor?, ischem?, tissue(4a)remodel?, metastas?, cytokin?, dual(4a)?adrenoreceptor?