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United States Patent [19]

Crow et al.

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[45] Date of Patent: Aug. 10, 1993

[54] TREATMENT OF CONGESTIVE HEART FAILURE

[75] Inventors: **James W. Crow**, Raleigh; **Walker A. Long**, Chapel Hill, both of N.C.

[73] Assignee: **Burroughs Wellcome Co.**, Research Triangle Park, N.C.

[21] Appl. No.: **705,049**

[22] Filed: **May 23, 1991**

[30] **Foreign Application Priority Data**

May 24, 1990 [GB] United Kingdom 9011588

[51] **Int. Cl.**[5] **A61K 31/19**; A61K 31/557

[52] **U.S. Cl.** **514/573**; 514/530

[58] **Field of Search** 514/573, 519

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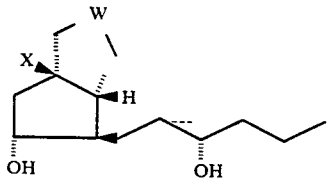
[57] ABSTRACT

The present invention is concerned with the use of a compound of formula (I)



(I)

wherein

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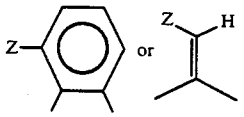

wherein Z is $—V(CH_2)_bCO_2H$ where b is 1 or 2 and V is oxygen when b is 1 or methylene when b is 2;

X is hydrogen, cyano, or —C≡CH; and

the dotted line represents an optional double bond;

and physiologically functional derivatives thereof, in the treatment of congestive heart failure.

8 Claims, No Drawings

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TREATMENT OF CONGESTIVE HEART FAILURE

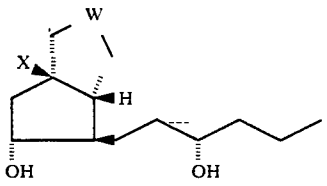
The present invention is concerned with the treatment of congestive heart failure (CHF).

CHF is a clinical syndrome characterized by a limitation of exercise tolerance due to dyspnea and/or fatigue which can be attributed to an abnormality of cardiac function. Such cardiac dysfunction may be secondary to alterations in cardiac filling or cardiovascular transport (or both) and can be associated with identifiable changes in systolic and diastolic function which may lead to pulmonary hypertension.

U.S. Pat. No. 4,306,075 describes novel benzindene prostaglandins which produce various pharmacological responses, such as inhibition of platelet aggregation, reduction of gastric secretion and bronchodilation. It is indicated that these compounds have useful application as anti-thrombotic agents, anti-ulcer agents and anti-asthma agents. There is no suggestion or disclosure that they may be used in the treatment of any type of CHF. Structure activity relationships of benzindene prostaglandins have also been described (P. A. Aristoff, A. W. Harrison, P. D. Johnson, and A. Robert, Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Vol. 15, edited by O. Hayaishi and S. Yamamoto. Raven Press, New York, 1985., Pg. 275-277).

European Patent Specification 0347243 describes a class of benzindene and non-benzindene prostaglandins suitable for use in the prophylaxis, treatment and diagnosis of pulmonary hypertension and Raynaud's disease. We have identified a sub-class of the compounds described in European Patent Specification 0347243(as well as U.S. Ser. No. 07/367,090) which have potent systemic and pulmonary vascular effects which render them suitable for use in the treatment of CHF.

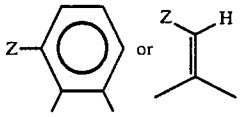
The present invention, therefore, lies in the use of a compound of formula (I)



(I)

wherein

—W— is



where Z is $—V(CH_2)_bCO_2H$ where b is 1 or 2 and V is oxygen when b is 1 or methylene when b is 2;

X is hydrogen, cyano, or —C≡CH; and

the dotted line represents an optional double bond;

and physiologically acceptable base salts, esters and other physiological functional derivatives thereof, for the treatment of congestive heart failure.

The term "physiological functional derivative" is used herein to denote a bioprecursor or "prodrug" which may be converted to a compound of formula (I) in-vivo, for example, an amide wherein the amide nitrogen is optionally substituted by one or two C_{1-4} alkyl groups.

All references hereinafter to "a compound of formula (I)" include references to its physiologically acceptable base salts, esters, and other physiological functional derivatives.

The present invention further lies in the use of the compounds of the present invention in the treatment of CHF which is accompanied by pulmonary hypertension.

In animal tests, compounds of formula (I) are potent pulmonary vasodilators and markedly attenuate the pulmonary vasoconstriction induced by hypoxia. The overall acute beneficial hemodynamic effects observed are substantial reductions in pulmonary vascular resistance, pulmonary arterial pressure, systemic vascular resistance and mean arterial blood pressure and increases in cardiac output and stroke volume. All of these effects are desirable in the treatment of CHF.

In normotensive (i.e., absence of any indication of pulmonary or systemic hypertension) dogs, administration of an ACE-inhibitor, a cardiotonic, or a diuretic, either simultaneously with or immediately prior to, the administration of a compound of formula (I) respectively blocks, attenuates, and potentiates the increase in Angiotensin II plasma concentration induced by the compounds of formula (I) without significantly affecting its hemodynamic profile. Pre-treatment with an ACE-inhibitor also enhanced the cardiovascular effects of the compounds of formula (I). However, it is not considered advisable to administer the compounds of formula (I) with a diuretic in the absence of an ACE-inhibitor and/or a cardiotonic. Preferred compounds for co-administration with a compound of formula (I) include the ACE-inhibitors enalapril, captopril, and linsinopril; the cardiotonic digoxin; and the diuretics forosemide and butemenide.

The compounds of the present invention can be administered as either an acute treatment or a chronic treatment for CHF. The preferred methods of administration of the compounds of the invention are via transdermal delivery or intravenous injection.

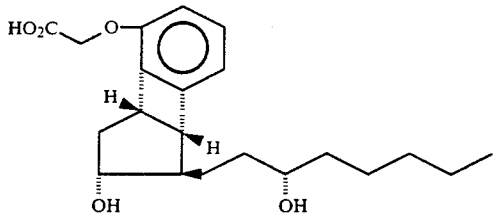
According to a further aspect of the invention, therefore, there is also provided a method for the treatment of CHF in a mammal, such as a human, which comprises the administration of a therapeutically effective amount of a compound of formula (I).

Preferred compounds of formula (I) having particularly advantageous properties in respect of the treatment of CHF are

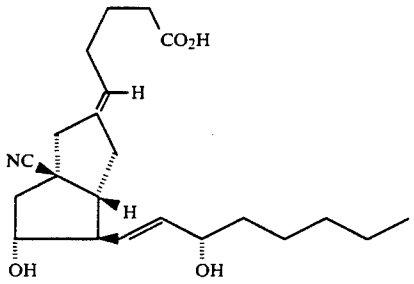
(1R,2R,3aS,9aS)-([2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-((S)-3-hydroxyoctyl)-1H-benz[f]inden-5-yl]oxy)acetic acid (which is also known as [1R-(1α(S*),2α,3aα,9aα)]-([2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-(3-hydroxyoctyl)-1H-benz-[f]inden-5-yl]oxy)acetic acid or 9-deoxy-2′,9-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-interphenylene)-13,14-dihydro-prostaglandin F_1) having formula (A),

(5Z,9R)-9-cyano-6a-carbaprostaglandin I_2 (B), and (5Z,9R)-9-ethynyl-6a-carbaprostaglandin I_2 (C) which have the following structures:

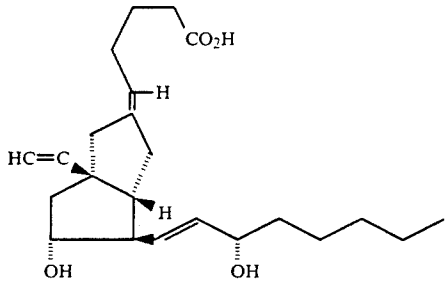
(A)



(B)

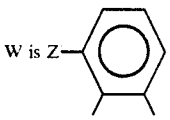


(C)



and physiologically acceptable base salts, esters and other physiologically functional derivatives of any thereof.

Of these preferred compounds of formula (I), compound (A) and its physiologically acceptable base salts, esters and other physiologically functional derivatives are particularly preferred, especially compound (A) itself of formula (I) wherein



Z is $-CH_2CO_2H$

X is H.

Base salts in accordance with the invention include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, salts with organic bases such as dicyclohexylamine and N-methyl-D-glutamine, and salts with amino acids such as arginine and lysine.

The amount of a compound of formula (I), which is required for the treatment of CHF will depend on a number of factors, in particular the nature and severity of the condition being treated and the preferred mode of administration, and the condition of the patient. In general, a daily dose for the treatment of CHF is in the range 25 ug to 250 mg, typically from 1.0 ug to 0.05 mg, per day per kilogram bodyweight. For example, an intravenous dose may be in the range 0.5 ug to 1.5 mg/kg/day, which may conveniently be administered as an infusion of from 0.5 ng to 1.0 ug per kilogram per minute. Infusion fluids suitable for this purpose may contain, for example, from 10 ng to 10 ug per milliliter of the active compound. Ampoules for injection may contain, for example, from 0.1 ug to 1.0 mg and orally administrable unit dose compositions, such as tablets or capsules, may contain, for example, from 0.1 to 100 mg, typically from 1 to 50 mg. In the case of physiologically acceptable salts, the weights indicated above refer to the weight of the active compound ion, that is, the ion derived from the compound of formula (I).

The ACE-inhibitors, cardiotonics and diuretics to be used in accordance with the present invention are administered via the accepted routes and in the accepted dosages.

The manufacture of a pharmaceutical composition in accordance with the invention typically involves admixing a compound of formula (I) or one of its physiologically acceptable salts with one or more carriers and/or excipients. The latter must, of course, be acceptable in the sense of being compatible with any other ingredients in the composition and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the active compound as a unit-dose composition, for example, a tablet, which may contain from 0.05% to 95% by weight of the active compound. The compounds of formula (I) may be incorporated in the compositions of the invention by any of the well known techniques of pharmacy consisting essentially of admixing the components.

The compositions of the invention include those suitable for oral, buccal (e.g. sub-lingual), parenteral (e.g. subcutaneous, intramuscular, intradermal, and intravenous), rectal, topical, transdermal, nasal and pulmonary administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated.

Compositions suitable for oral administration may be presented in discrete units adapted for instant or controlled release such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of formula (I); as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such compositions may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients). In general, the compositions of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or moulding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of formula (I) in a flavored base, usually sucrose and aca-

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