

EXHIBIT A



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United States Patent [19]

Tadepalli et al.

[11] **Patent Number:** 5,153,222[45] **Date of Patent:** Oct. 6, 1992[54] **METHOD OF TREATING PULMONARY HYPERTENSION WITH BENZIDINE PROSTAGLANDINS**[75] **Inventors:** Anjaneyulu S. Tadepalli, Durham; Walker A. Long, Chapel Hill; James W. Crow, Raleigh; Kenneth B. Klein, Chapel Hill, all of N.C.[73] **Assignee:** Burroughs Wellcome Co., Research Triangle Park, N.C.[21] **Appl. No.:** 715,439[22] **Filed:** Jun. 14, 1991**Related U.S. Application Data**

[62] Division of Ser. No. 367,090, Jun. 16, 1989, abandoned.

[30] **Foreign Application Priority Data**

Jun. 17, 1988 [GB] United Kingdom 8814438

[51] **Int. Cl.⁵** A61K 31/19[52] **U.S. Cl.** 514/571[58] **Field of Search** 524/454, 569; 514/571[56] **References Cited****U.S. PATENT DOCUMENTS**

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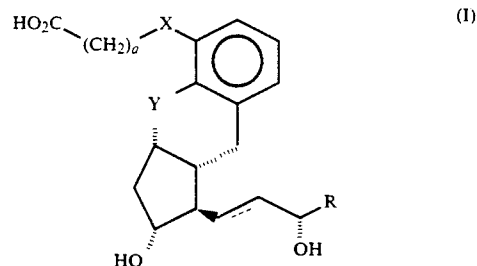
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[57] **ABSTRACT**

The present invention is concerned with methods for the prophylaxis, treatment and diagnosis of pulmonary hypertension which comprise the administration of an effective amount of a compound of formula (I)



wherein a is an integer of from 1 to 3;

X and Y, which may be the same or different, are selected from —O— and —CH₂—;

R is —(CH₂)₅R¹ wherein R¹ is hydrogen or methyl, or R is cyclohexyl, or

R is —CH(CH₃)CH₂C≡CCH₃; and

the dotted line represents an optional double bond;

or of a physiologically acceptable salt or acid derivative thereof.

Medicaments and diagnostic aids for use in the methods of the invention are also within the scope of the invention.

2 Claims, No Drawings

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METHOD OF TREATING PULMONARY HYPERTENSION WITH BENZIDINE PROSTAGLANDINS

This is a divisional of copending application(s) Ser. No. 07/367,090 filed on Jun. 16, 1989, now abandoned.

The present invention is concerned with prostaglandins, specifically benzindene prostaglandins, for use in the treatment, or diagnosis of pulmonary hypertension. Their use in the manufacture of medicaments for the treatment of pulmonary hypertension and in the manufacture of diagnostic aids for identifying PPH patients having active pulmonary vasoconstriction and the medicaments and diagnostic aids obtained thereby are within the scope of the invention.

All blood is driven through the lungs via the pulmonary circulation in order, among other things, to replenish the oxygen which it dispenses in its passage around the rest of the body via the systemic circulation. The flow through both circulations is in normal circumstances equal, but the resistance offered to it in the pulmonary circulation is generally much less than that of the systemic circulation. When the resistance to pulmonary blood flow increases, the pressure in the circulation is greater for any particular flow. This is referred to as pulmonary hypertension. Generally, pulmonary hypertension is defined through observations of pressures above the normal range pertaining in the majority of people residing at the same altitude and engaged in similar activities.

Most often pulmonary hypertension is a manifestation of an obvious or explicable increase in resistance, such as obstruction to blood flow by pulmonary emboli, malfunction of the heart's valves or muscle in handling blood after its passage through the lungs, diminution in pulmonary vessel calibre as a reflex response to hypoventilation and low oxygenation, or a mismatch of vascular capacity and essential blood flow, such as shunting of blood in congenital abnormalities or surgical removal of lung tissue. Such pulmonary hypertension is referred to as secondary hypertension.

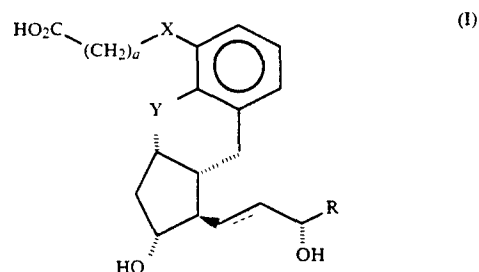
There remain some cases of pulmonary hypertension where the cause of the increased resistance is as yet inexplicable. They are described as primary pulmonary hypertension (PPH) and are diagnosed by and after exclusion of the causes of secondary pulmonary hypertension. Despite the possibility of a varied aetiology, cases of primary pulmonary hypertension tend to comprise a recognisable entity. Approximately 65% are female and young adults are most commonly afflicted, though it has occurred in children and patients over 50. Life expectancy from the time of diagnosis is short, about 3 to 5 years, though occasional reports of spontaneous remission and longer survival are to be expected given the nature of the diagnostic process. Generally, however, progress is inexorable via syncope and right heart failure and death is quite often sudden. Until now, no successful treatment was known.

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 the compounds have useful application as anti-thrombotic agents, anti-ulcer agents, and anti-asthma agents. There is no indication that these compounds may be used in the treatment of any form of hypertension.

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We have now discovered that within the class of benzindene prostaglandins described in the U.S. Patent, there is a sub-class of compounds of formula (I) as defined hereinbefore which are suitable for use in the treatment of pulmonary hypertension. The term "pulmonary hypertension" is used herein to include both primary and secondary pulmonary hypertension as ordinarily understood by clinicians (*vide supra*). The compounds of the invention may also be used in the treatment of Raynaud's disease. PPH patients having active pulmonary vasoconstriction are considered suitable candidates for long-term oral vasodilator therapy (R J Lambert et al, Chest 89, 459S (1986)). The ability of the compounds of the invention to reduce pulmonary vascular resistance in such patients provides a useful diagnostic aid for identifying suitable candidates for long-term vasodilator therapy.

According to the present invention, therefore, there is provided a compound of formula (I)



for use in the treatment, or diagnosis of pulmonary hypertension

wherein a is an integer of from 1 to 3;

X and Y, which may be the same or different, are selected from —O— and —CH₂—;

R is —(CH₂)₅R¹ wherein R¹ is hydrogen or methyl, or R is cyclohexyl, or

R is —CH(CH₃)CH₂C≡CCH₃; and

the dotted line represents an optional double bond; and pharmaceutically acceptable salts and acid derivatives thereof.

The term "acid derivative" is used herein to describe C₁₋₄ alkyl esters and amides, including amides wherein the nitrogen is optionally substituted by one or two C₁₋₄ alkyl groups.

The invention also includes bioprecursors or "pro-drugs" of the above-defined compounds, that is, compounds which are converted in vivo to compounds of formula (I) or pharmaceutically active derivatives thereof.

Further aspects of the present invention are concerned with the use of a compound of formula (I), or a pharmaceutically acceptable salt or acid derivative thereof, in the manufacture of a medicament for the treatment of pulmonary hypertension or in the manufacture of a diagnostic aid for identifying PPH patients having active pulmonary vasoconstriction and with medicaments and diagnostic aids obtained thereby which may be administered when primary or secondary pulmonary hypertension is indicated.

Preferred compounds of formula (I) having particularly desirable pulmonary anti-hypertensive properties include those wherein

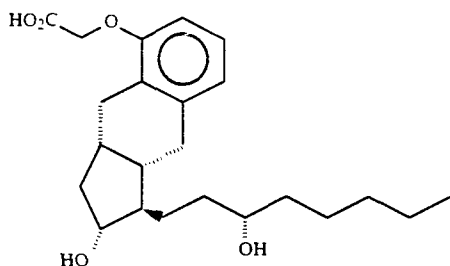
X is —O—;

Y is —CH₂—; and

R is —(CH₂)₄CH₃.

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A particularly preferred compound of formula (I) having exceptional pulmonary anti-hypertensive properties is 9-deoxy-2',9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁, which has the following structure:



and pharmaceutically acceptable salts and acid derivatives thereof.

Other compounds of the invention which show pulmonary anti-hypertensive activity include:

9-Deoxy-2',9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-prostaglandin F₁

9-Deoxy-2',9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-15-cyclohexylprostaglandin F₁

9-Deoxy-2',9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-20-methylprostaglandin F₁

(15S,16RS)-9-Deoxy-2',9 α -methano-16-methyl-3-oxa-18,18,19,19-tetradehydro-4,5,6-trinor-3,7-(1',3'-interphenylene)prostaglandin F₁

The present invention extends to non-physiologically acceptable salts of the compounds of formula (I) which may be used in the preparation of the pharmacologically active compounds of the invention. The physiologically acceptable salts of compounds of formula (I) include salts derived from bases. Base salts 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-glucamine, and salts with amino acids such as arginine and lysine.

Quaternary ammonium salts can be formed, for example, by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides, with dialkyl sulphates, with long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides, and with aralkyl halides, such as benzyl and phenethyl bromides.

The amount of a compound of formula (I), or a physiologically acceptable salt or acid derivative thereof, which is required in a medication or diagnostic aid according to the invention to achieve the desired effect will depend on a number of factors, in particular the specific application, the nature of the particular compound used, the mode of administration, and the condition of the patient. In general, a daily dose per patient for the treatment of pulmonary hypertension is in the range 25 μ g to 250 mg; typically from 0.5 μ g to 2.5 mg, preferably from 7 μ g to 285 μ g, per day per kilogram bodyweight. For example, an intravenous dose in the range 0.5 μ g to 1.5 mg per kilogram bodyweight per day may conveniently be administered as an infusion of from 0.5 ng to 1.0 μ g per kilogram bodyweight per minute. Infusion fluids suitable for this purpose contain, for example, from 10 ng to 10 μ g per milliliter. Ampoules for injection contain, for example, from 0.1 μ g to 1.0 mg and orally administrable unit dose formulations,

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such as tablets or capsules, contain, for example, from 0.1 to 100 mg, typically from 1 to 50 mg. For diagnostic purposes, a single unit dose formulation may be administered. 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).

In the manufacture of a medicament or diagnostic aid according to the invention, hereinafter referred to as a "formulation", the compounds of formula (I) and their physiologically acceptable salts and acid derivatives are typically admixed with, inter alia, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation 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 compound as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the active compound. One or more compounds of formula (I) and/or their physiologically acceptable salts or acid derivatives may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

In addition to compounds of formula (I), other pharmacologically active substances may be present in the formulations of the present invention. For example, the compounds of the invention may be present in combination with tissue plasminogen activator, a substance known to dissolve the fibrin network of blood clots which has found utility in the treatment of thrombotic disorders (see, for example, The New England Journal of Medicine, 312(14), 932, (1985)).

The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual), parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular compound of formula (I), or the physiologically acceptable salt or acid derivative thereof, which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of a compound of formula (I) or a physiologically acceptable salt or acid derivative thereof; 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 formulations 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 formulations 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

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made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a compound of formula (I), or a physiologically acceptable salt or acid derivative thereof, in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of formula (I), or a physiologically acceptable salt or acid derivative thereof, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Injectable formulations according to the invention generally contain from 0.1 to 5% w/v of active compound and are administered at a rate of 0.1 ml/min/kg.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing a compound of formula (I), or a physiologically acceptable salt or acid derivative thereof, with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from 0.1 to 15% w/w, for example, from 0.5 to 2% w/w. Formulations for transdermal administration may be delivered by iontophoresis (see, for example, Pharmaceutical Research 3(6), 318, (1986)) and typically take the form of an optionally buffered aqueous solution of a compound of formula (I) or of a salt or acid derivative thereof. Suitable formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

The compounds of the present invention are conveniently prepared by methods the same as or analogous to those described in U.S. Pat. No. 4,306,075.

For a better understanding of the invention, the following Examples are given by way of illustration.

EXAMPLES

The effects of 9-deoxy-2', 9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁ monitored in experimental pulmonary hypertension models. In Example 1, the model used was an open chest preparation of an anaesthetised cat (anaesthetic: chloralose and urethane). In Example 2, the model was a conscious spontaneously hypertensive rat.

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EXAMPLE 1

A series of glycine buffer solutions of the test compound were successively administered to each animal by i.v. infusion at doses equivalent to 100 ng, 300 ng, 1 μ g, and 3 μ g/kg/min. Each solution was infused over a period of 20 minutes, hypoxia being induced in the animal during the last 5 minutes of infusion by ventilating with 10% oxygen in nitrogen. A 15-minute 'recovery' period was observed between successive infusions. Following surgery, the animal was allowed to stabilize for 30 minutes, after which two 5-minute hypoxic challenges were given 15 minutes apart which were averaged to obtain the control hypoxic responses. 15 minutes after the second control hypoxic challenge, the animal started to receive the test compound. The averaged control hypoxic responses were compared with those obtained during infusion of the test compound.

The following parameters were monitored during the course of each experiment: systemic arterial pressure (MAP), pulmonary arterial (PAP) and venous (PVP) pressure, and cardiac output (CO, aortic blood flow). From the values obtained, the systemic vascular resistance (MAP/CI where CI=CO/body weight in kg) and the pulmonary vascular resistance (PAP/CI) were calculated.

The test compound was found to reduce hypoxia-induced increase in pulmonary arterial pressure and pulmonary vascular resistance in a dose-related manner without appreciably affecting cardiac output or heart rate. At higher doses, the test compound reduced systemic arterial pressure and systemic vascular resistance. Thus hypoxia-induced pulmonary vasoconstriction could be reduced without disturbing the systemic haemodynamics by suitably adjusting the dose. The hypoxia-induced vasoconstriction did not return to its control value within 15 minutes of terminating the final infusion indicating a relatively long duration of action for the compound.

EXAMPLE 2

The test compound was administered to a series of animal at doses of 0.1, 0.3, 1.0 and 3.0 mg/kg P.O. and the systolic and diastolic pressures and heart rate of each animal were monitored for 24 hours after administration of the compound. At doses of 0.3 mg/kg P.O. and above, a dose-dependent fall in systolic and diastolic pressures were observed for a period of up to 8 hours after administration indicating that the compound had good oral bioavailability.

What is claimed:

1. A method of treating pulmonary hypertension in a patient, which comprises administering to said patient an effective pulmonary hypertension treatment amount of the compound 9-deoxy-2',9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydro-prostaglandin F₁.

2. A method of treating pulmonary hypertension in a patient, which comprises administering to said patient an effective pulmonary hypertension treatment amount of a pharmaceutically acceptable salt of the compound 9-deoxy-2',9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydroprostaglandin F₁.

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