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PIPERIDINYLCYCLOPENTANOL HEPTENOIC ACID SALT

The endoperoxides prostaglandins G_2 and H_2 and thromboxane A_2 are naturally occurring reactive metabolites of arachidonic acid in human platelets. They are not only potent aggregatory agents but are also constrictors of vascular and bronchial smooth muscle, and therefore substances which antagonise their effects are of considerable interest in human medicine.

We have now found a new compound which has shown endoperoxide and thromboxane antagonist activity, and is therefore of interest in the treatment of asthma and cardiovascular diseases.

This compound is [1R-[1α(Z),2β,3β,5α]]-(+)-7-[5-[[(1,1'-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid, hydrochloride (referred to below as compound A). The invention is particularly concerned with pharmaceutical compositions containing compound A and one or more pharmaceutical carriers.

The parent amino acid of Compound A is described in our copending British Patent Specification 2097397A, together with other aminocyclopentanol acids and esters. Compound A is advantageous in a number of respects as compared to these compounds generally and in particular to its parent amino acid and other salts or solvates thereof, both as regards its preparation and its use in medicine. Thus for example compound A is readily isolatable from reaction mixtures in which it is prepared, and it is obtainable in a crystalline form of high purity which has desirable characteristics for pharmaceutical formulation.

Compound A inhibits blood platelet aggregation and bronchoconstriction. To determine inhibition of blood platelet aggregation, starved guinea pigs

are dosed orally with the compound in a suitable vehicle. Platelet rich plasma is prepared from each animal and aggregation to a range of collagen concentrations is measured after the method of Born (Nature 194, 927-929, (1962)). Collagen concentration effect curves for each sample of plasma are calculated and results are expressed as the shift of the curves following treatment with the compound.

The ability of compound A to inhibit bronchoconstriction is determined in the anaesthetized guinea pig by measuring the effect of the compound on the dose response curve of the bronchoconstrictor [1R-[1α,4α,5β(Z),6α(1E, 3S*)]]-7-[6-(3-hydroxy-1-octenyl)-2-oxabicyclo [2,2,1]hept-5-yl]-5-heptenoic acid (U-46619)

Compound A is thus of interest in the treatment of asthma, and as an inhibitor of platelet aggregation and thrombosis for use in renal dialysis and the treatment and prevention of occlusive vascular diseases such as arteriosclerosis, atherosclerosis, peripheral vascular disease, cerebral vascular disease including transient ischaemic attacks, stroke, pulmonary embolism, diabetic retinopathy, post operative thrombosis, angina and myocardial infarction. It may be formulated in conventional manner for use, with one or more pharmaceutical carriers.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, or syrups prepared by conventional means with acceptable excipients.

The compound may be formulated for parenteral administration by bolus injections or continuous infusion. Formulations for injections may be presented in unit dosage form in ampoules, or in multi-dose containers, with an added preservative.

For administration by inhalation the compound is conveniently delivered in the form of an aerosol

spray presentation from pressurised packs or a nebuliser, or as a cartridge from which the powdered composition may be inhaled with the aid of a suitable device. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

For use as an antithrombotic agent, compound A is preferably administered orally, for example in amounts of 0.05 to 5 mg/kg body weight, 1 to 4 times daily.

For use in the treatment of asthma, the compound may also be administered orally in amounts of 0.05 to 5 mg/kg body weight, 1 to 4 times daily; preferably however it is administered by inhalation at doses varying from 0.3 to 30 mg, 1 to 4 times daily. The compound may be used in combination with other anti-asthmatic agents.

The unit dose formulations thus usually contain 3.5 to 350 mg of compound A. The precise dose administered will of course depend on the age and condition of the patient.

Suitable methods for preparing compound A are described below.

Compound A may be prepared by treating the parent amino acid or an appropriate ester (e.g. the trityl ester) with hydrogen chloride or hydrochloric acid. The salt is for example prepared by adding hydrogen chloride to a solution of the parent amino acid in an organic solvent such as ether, ethyl acetate, CH_2Cl_2 or dimethoxyethane, at temperatures of for example 0°C to room temperature.

The following examples illustrate the invention. Temperatures are in °C,

The following abbreviations are used:

T.L.C. - Thin layer chromatography, using SiO_2 unless otherwise stated.

ER - ether;

EA - ethyl acetate;

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THF - tetrahydrofuran;
DIBAL - diisobutylaluminium hydride;

Chromatography was carried out using silica gel.
'Dried' refers to drying with $MgSO_4$.
'Hyflo' (trade mark) is a filtration aid.
The preparations of Intermediates 1 and 2 are described in British Patent Specification 2097397A.

Intermediate 1
[1R-[1α(Z),2β,3β,5α]-(+)-Methyl 7-[5-[[(1,1'-Biphenyl-4-yl]methoxy]-3-hydroxy-2-(1-piperdinyl)cyclopentyl]-4-heptenoate

Intermediate 2
[1R-(1α,2β,3α,5α)]-5-[[(1,1'-Biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentane acetaldehyde

Intermediate 3
[1R-(1α,2β,3α,5α)]-(+)-5-[[(1,1'-Biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentane propanal.

A solution of Intermediate 2 (13.0g) in toluene (39ml) was added dropwise to a suspension of potassium tert-butoxide (5.96g) in toluene (52ml). Methoxymethyltriphenylphosphonium chloride (15.93g) was added and the mixture stirred overnight (18h).
2N Hydrochloric acid (52ml) was added and the mixture was heated with stirring at 40° for 30 min. Solid K_2CO_3 (13g) was added, the organic phase separated, washed with water (52 ml) and dried azeotropically to give a solution of Intermediate 3 in toluene (115ml). A portion of the solution (8.8ml) was purified by chromatography eluting with 9:1 EA-methanol to give the title compound as a foam (0.53g).
T.L.C. 4:1 EA-methanol Rf 0.15

Intermediate 4

[1R-[1α(Z),2β,3α,5α]]-(+)-7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid, hydrochloride

To a solution of potassium tert-butoxide (21.49g) in toluene (198ml) and THF (52ml) under N_2 was added 3-(carboxypropyl)triphenylphosphonium bromide (41.14g). After 1 1/2h a solution of Intermediate 3 (24.5g) in toluene (220ml) was added and the mixture stirred for 3h. Water (125ml) was added, the mixture vigorously shaken and the phases separated. The aqueous phase was washed with toluene (2 x 225ml) (discarded), then acidified (to pH 7.5) with 2N hydrochloric acid and extracted with CH_2Cl_2 (2 x 225ml). The combined CH_2Cl_2 extracts were dried and evaporated to give the title compound, base (24.47g) as a gum.

A solution of the base (93mg) in CH_2Cl_2(1.5ml) was treated with an excess of ethereal hydrogen chloride. The solvents were removed and the residual oil triturated with ER (5ml). The resulting solid was filtered, washed with ER and dried to give the title compound (82mg) m.p 132.5 - 136° (softens at 128°)

Intermediate 5

[1R-[1α(Z),2β,3α,5α]]-(+)-Triphenylmethyl 7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoate

Triethylamine (2.49ml) was added to a cold (5°) solution of Intermediate 4, base (5.88g) and trityl chloride (4.4g) in CH_2Cl_2(24ml). The mixture was stirred for 30min then water (60ml) and further CH_2Cl_2(30ml) added. The organic phase was separated then evaporated in vacuo. The residue was azeotroped with CH_2Cl_2 (60ml) to give an oil (10.13g) which

was chromatographed on alumina (500g), eluting with EA to give the title compound as an oil (5.14g). T.L.C. (Al_2O_3) 49:1 EA- methanol Rf 0.52

Intermediate 6

[1R-[1α(Z),2β,5α]]-(-)-Triphenylmethyl 7-[5[[(1,1'-Biphenyl)-4-yl]methoxy]-3-oxo-2-(1-piperidinyl) cyclopentyl]-4-heptenoate

Triethylamine (9.17ml) was added at 2° to a stirred solution of Intermediate 5 (6.47g) in CH_2Cl_2(65ml), followed by a solution of pyridine/SO_3 complex (5.75g) in dimethylsulphoxide (65ml). The resulting solution was stirred at 3-5° for 2h and quenched by the dropwise addition of ice-water (65ml). The reaction mixture was extracted with diethyl ether (2 x 65ml) and the extract washed with water (65ml), 1M citric acid (4 x 10ml) and water (10 ml). Evaporation of the dried (Na_2SO_4) solvents gave the title compound as a foam (5.9g). IR ($CHBr_3$) 1740 cm^{-1}

Example 1

[1R-[1α(Z),2β,3β,5α]]-(+)-7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid, hydrochloride

Intermediate 1 (10.38g) was stirred with ethanol (60 ml) and 5N NaOH (30 ml) at 20° for 16h. The solution was diluted with water (400 ml) and then extracted with ER (2 x 150ml). The aqueous phase was adjusted to pH 6 with 2N HCl and extracted with CH_2Cl_2 (3 x 200ml). Evaporation of the combined extracts gave a foam (9.45g), the majority (9.3g) of which was taken up into CH_2Cl_2 (50ml) and treated with excess of an ethereal solution of hydrogen chloride. Evaporation in vacuo and trituration

of the residue with ER (4 x 75ml) gave the title compound as a powder (9.28g). Crystallisation of a sample from EA-methanol gave material of m.p. 124-126°.

$[\alpha]_D^{25}$ = + 63.1° ($CHCl_3$)

Example 2

[1R-[1α(Z),2β,3β,5α]]-(+)-7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid, hydrochloride

DIBAL (1M in hexane, 5.5 ml) was added dropwise at 0-2° to a stirred solution of 2,6-di-t-butyl-4-methylphenol (2.9g) in CH_2Cl_2 (13ml). The solution was stirred at -5 to 0° for 1h and then cooled to -20°. A solution of Intermediate 6 (1.3g) in CH_2Cl_2 (13ml) was added at -18 to -20°. The mixture was stirred at this temperature for 2 1/2h, 1N hydrochloric acid (20ml) was then added dropwise, and the mixture was stirred at room temperature for 1/2h. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (10ml). The organic extracts were combined, washed with brine, dried (Na_2SO_4) and evaporated to give a yellow gum. The product was triturated with diethyl ether to give a pale yellow powder (0.68g). Recrystallisation from EA-methanol gave m.p. 128-130°; $[\alpha]_D^{23}$ =+66.5°($CHCl_3$)

Pharmaceutical Examples

Tablets

These may be prepared by direct compression or wet granulation. The direct compression method is preferred but may not be suitable in all cases as it is dependent upon the dose level and physical characteristics of the active ingredient.

A. Direct Compression	mg/tablet
Compound A	100.00
Microcrystalline Cellulose B.P.C.	298.00

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Magnesium Stearate	2.00
Compression Weight	400.00 mg

Compound A is sieved through a 250 m^{-6} sieve, blended with the excipients and compressed using 10.0mm punches. Tablets of other strengths may be prepared by altering the compression weight and using punches to suit.

B. Wet Granulation	mg/tablet
Compound A	100.00
Lactose B.P.	238.00
Starch B.P.	40.00
Pregelatinised Maize Starch B.P.	20.00
Magnesium Stearate B.P.	2.00
Compressed Weight	400.00 mg

Compound A is sieved through a 250 m^{-6} sieve and blended with the lactose, starch and pre-gelatinised starch. The mixed powders are moistened with purified water, granules are made, dried, screened and blended with the magnesium stearate. The lubricated granules are compresssed into tablets as described for the direct compression formula.

The tablets may be film coated with suitable film forming materials, e.g. methyl cellulose or hydroxylpropyl methyl cellulose using standard techniques. Alternatively the tablets may be sugar coated.

Capsules	mg/capsule
Compound A	100.00
*STA-RX 1500	99.00
Magnesium Stearate B.P.	1.00
Fill Weight	200.00 mg

* A form of directly compressible starch supplied by Colorcorn Ltd., Orpington, Kent.

Compound A is sieved through a 250 m^{-6} sieve and blended with the other materials. The mix is filled into No.2 hard gelatin capsules using a suitable filling machine. Other doses may be

prepared by altering the fill weight and if necessary changing the capsule size to suit.

Inhalation cartridges	mg/cartridge
Compound A (micronised)	3.00
Lactose B.P. to	25.00

Compound A is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No.3 hard gelatin capsules on a suitable encapsulating machine.

The contents of the cartridges are administered using a powder inhaler.

Metered Dose Pressurised Aerosol

	mg/metered dose	Per can
Compound A (micronised)	0.500	120 mg
Oleic Acid B.P.	0.050	12 mg
Trichlorofluoromethane B.P.	22.25	5.34 g
Dichlorodifluoromethane B.P.	60.90	14.62 g

Compound A is micronised in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichlorofluoromethane at a temperature of 10-15°C and the micronised drug is mixed into this solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering a metered dose of 85 mg of suspension, are crimped onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

Syrup	mg/5ml dose
Compound A	100.00
Sucrose B.P	2750.00
Glycerine B.P.	500.00
Buffer)	
Flavour)	
Colour)	as required
Preservative)	

(25)

Distilled Water to 5.00 ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water, and the glycerine is added. The remainder of the water is heated to 80°C and the sucrose is dissolved in this and cooled. The two solutions are combined, adjusted to volume and mixed. The syrup produced is clarified by filtration.

Injection for Intravenous Administration

Compound A 50 mg

Water for injections BP to 5 ml

Sodium chloride or any other suitable material may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability of the active ingredient using dilute acid or alkali or by the addition of suitable buffer salts.

The solution is prepared, clarified and filled into appropriate sized ampoules sealed by fusion of the glass. The injection is sterilised by heating in a autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen.

CLAIMS

1. [1R-[1α(Z),2β,3β,5α]]-(+)-7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid, hydrochloride.

2. The compound of claim 1 in a form having a melting point of 128-130°.

3. A pharmaceutical composition containing the compound of claim 1 or claim 2 and one or more pharmaceutical carriers.

4. A composition as claimed in claim 3 in the form of a tablet.

5. A composition as claimed in claim 3 in the form of a capsule.

6. A composition as claimed in claim 3 in the form of a powder.

7. A composition as claimed in claim 3 in the form of a solution.

8. A composition as claimed in claim 3 in the form of a syrup.

9. A composition as claimed in claim 3 in the form of an ampoule.

10. A composition as claimed in claim 3 in the form of an aerosol spray formulation.

11. A composition as claimed in claim 3 in a unit dose form containing 3.5 to 350 mg of the compound of claim 1.

12. A composition as claimed in claim 11 in the form of a solution for injection containing about 50 mg of the compound of claim 1.

13. A composition as claimed in claim 3 which includes a further anti-asthmatic agent.

14. A composition as claimed in claim 3, substantially as described herein in any of the pharmaceutical examples.

15. A method of producing a composition as claimed in claim 3 which comprises formulating the compound of claim 1 or claim 2 with one or more pharmaceutical carriers.

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16. A composition as claimed in claim 3 when produced by a method as claimed in claim 15.

17. A process for the preparation of the compound as claimed in claim 1 which comprises treating the parent amino acid with hydrogen chloride or hydrochloric acid.

18. A process as claimed in claim 17 substantially as described herein in Example 1.

19. The compound of claim 1 when prepared by a process as claimed in claim 17 or claim 18.

ERRATUM

SPECIFICATION NO 2127406B

Page No 11 Line Nos 3 and 4 delete whole lines insert
2. The compound of claim 1 in crystalline form.

THE PATENT OFFICE
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