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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : PORTER, Roderick, Alan [GB/GB]; PRAIN, Hunter, Douglas [GB/GB]; MURRAY, Kenneth, John [GB/GB]; WARRINGTON, Brian, Herbert [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agent: SMITHKLINE BEECHAM; Corporate Patents, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

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(54) Title: PHENOL DERIVATIVES AS AGONISTS OF A CYCLIC AMP DEPENDENT PROTEIN KINASE

(57) Abstract

Phenol derivatives are described as agonists of a cyclic AMP dependent protein kinase useful as medicaments.

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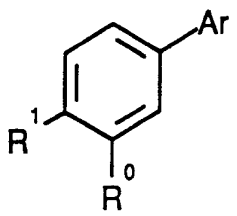
PHENOL DERIVATIVES AS AGONISTS OF A CYCLIC AMP DEPENDENT PROTEIN KINASE

The present invention relates to phenol derivatives, processes for their preparation, intermediates in their preparation, their use as medicaments and to pharmaceutical compositions comprising them.

The compounds of this invention are agonists of a cyclic AMP-dependent protein kinase (cA-PrK) (see J. Biol. Chem., 1989, **264**, 8443 - 8446) and are of use in combatting such conditions where such agonism is thought to be beneficial. They are likely to have anti-proliferative, anti-aggregatory, cholesterol-lowering, smooth muscle relaxant, positive lusitropic, anti-allergic or anti-inflammatory activities. They are likely to be useful in the treatment of cardiovascular diseases where there is a component of diastolic failure, cancer, psoriasis, atheroschlerosis, thrombosis, re-stenosis, chronic reversible lung disease such as asthma and bronchitis, allergic disease such as allergic asthma, allergic rhinitis and urticaria or gut motility disorders such as irritable bowel syndrome.

Accordingly the present invention provides compounds of the formula (1) :



(1)

or pharmaceutically acceptable salts thereof, wherein :

R^0 is OH or a bioprecursor thereof,

R^1 is A^0CO_2H, $P(Z)(OH)(OR^2)$, SO_2H, SO_3H or 5-tetrazolyl or a bioprecursor thereof,

A^0 is CH_2, CHF, CF_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$,

R^2 is phenyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-4}alkyl, or C_{1-8}alkyl optionally substituted by C_{1-4}alkoxy,

R^3 is H, methyl or ethyl,

R^4 is H or C_{1-3}alkyl,

R^5 and R^6 are each C_{1-3}alkyl or together form a 1,2-ethanediyl group or 1,3-propanediyl group,

Z is O or S, and

Ar is phenyl optionally substituted by one to three groups independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}cycloalkyl, C_{3-6}cycloalkoxy, C_{1-6}alkylthio, phenyl, phenylthio, benzyloxy, C_{1-6}polyfluoroalkyl, C_{1-6}polyfluoroalkoxy, halo, $N(R^7)_2$ or $NHCOR^7$ wherein R^7 is H or C_{1-6}alkyl, or $-X(CH_2)_nY-$ attached to adjacent carbon atoms of the phenyl ring wherein X and Y are independently CH_2 or O and n is 1 to 3, wherein said C_{1-6}alkyl, C_{2-6}alkenyl or C_{1-6}alkoxy groups can be independently substituted by OH, C_{1-6}alkoxy, C_{3-6}cycloalkyl, $N(R^7)_2$, CO_2R^7 or $CON(R^7)_2$.

Bioprecursors of the groups R^0 and R^1 are derivatives thereof which are convertible *in vivo* into the groups R^0 and R^1.

A suitable bioprecursor of the group R^0 is OR^8 wherein R^8 is C_{1-4}alkanoyl (for example acetyl), arylC_{1-4}alkanoyl (for example phenyl C_{1-4}alkanoyl such as benzoyl), arylsulphonyl (for example optionally substituted phenylsulphonyl or toluenesulphonyl) or C_{1-4}alkylsulphonyl (for example methylsulphonyl).

When R^1 is A^0CO_2H a suitable bioprecursor is $A^0CO_2R^9$ wherein R^9 is an ester-forming group.

When R^1 is $P(Z)(OH)(OR^2)$ a suitable bioprecursor is $P(Z)(OR^2)_2$ wherein Z and R^2 are as hereinbefore defined or $P(Z)(OR^2)(OR^{10})$ wherein R^{10} is an O-protecting group. Suitable O-protecting groups include pivaloyloxymethyl, propionyloxymethyl and pivalolyloxycarbonyloxymethyl.

When R^1 is 5-tetrazolyl, a suitable biopricursor is a N-protected derivative thereof. Suitable N-protecting groups include pivalolyloxymethyl, propionyloxymethyl and pivalolyloxycarbonyloxymethyl.

Alternatively bioprecursors of the groups R^0 and R^1 are those formed when R^1 and R^0 are linked together to form a cyclic structure such that R^1-R^0 is A^1CO_2 or A^2OCH_2O, in which :

A^1 is CH_2, CHF, CF_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$,

A^2 is $P(Z)OR^2$ or $CR^3(CO_2R^9)$, and

R^2 to R^6, R^9 and Z are as hereinbefore defined.

Suitably R^0 is hydroxy or OR^8, preferably hydroxy.

Suitably R^1 is A^0CO_2H or $A^0CO_2R^9$.

Suitably R^1 is $P(Z)(OH)(OR^2)$ or $P(Z)(OR^2)_2$.

Suitably R^1 is SO_2H, SO_3H or 5-tetrazolyl.

Suitably R^1 and R^0 are linked together such that R^1-R^0 is A^1CO_2.

Suitably R^1 and R^0 are linked together such that R^1-R^0 is A^2OCH_2O.

By the term alkyl is meant both straight- and branched- chain alkyl.

By the term C_{1-6}polyfluoroalkyl is meant a C_{1-6}alkyl group having at least one hydrogen replaced with fluoro, e.g. CF_3 or CF_2CF_2H.

Suitably R^2 is methyl, ethyl, propyl, butyl, pentyl, hexyl, 2-methoxyethyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclopropylmethyl.

Suitably R^3 is H, methyl or ethyl, preferably H or methyl.

Suitably R^4 is H, methyl, ethyl or propyl, preferably H or methyl.

Suitably R^5 and R^6 are independently methyl, ethyl or propyl, preferably together they form a 1,2-ethanediyl group.

Preferably Z is O.

Suitably R^9 is C_{1-4}alkyl optionally substituted by hydroxy, e.g. 2-hydroxyethyl or arylC_{1-4}alkyl (for example phenylC_{1-4}alkyl such as benzyl).

Suitably Ar is phenyl optionally mono-substituted by a group as hereinbefore defined, for example in the 2,3, or 4 positions by C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{1-6}alkylthio, phenyl, phenylthio, benzyloxy, CF_3, halo or $NHCOR^7$.

Suitably Ar is phenyl di-substituted by any groups as hereinbefore defined, for example in the 3,4-,3,5-,2,3-,2,4- or 2,5-, positions by groups independently selected from C_{2-6}alkenyl, C_{1-6}alkoxy, C_{3-6}cycloalkoxy, halo, $-X(CH_2)_nY-$ or C_{1-6}alkoxyC_{1-6} alkoxy.

Suitably Ar is phenyl trisubstituted by any groups as hereinbefore defined, for example in the 2,3,4-, 2,3,5-, or 3,4,5-positions by groups independently selected from C_{2-6}alkenyl, C_{1-6}alkoxy or halo.

Examples of C_{1-6}alkoxy include methoxy, ethoxy, propoxy, butoxy, or pentyloxy.

Examples of C_{1-6}alkyl include methyl, ethyl, propyl, butyl, isobutyl or pentyl.

Examples of halo include fluoro, chloro, bromo or iodo.

Particular compounds of this invention include :

2-(5-tetrazolyl)-5-(2,3-dipropoxyphenyl)phenol, or

ethyl 2-hydroxy-4-(2,3-dipropoxyphenyl)phenyl phosphonate,

and pharmaceutically acceptable salts thereof.

This invention covers all tautomeric, geometric and optical isomeric forms of compounds of formula (1).

Compounds of the formula (1) can form pharmaceutically acceptable base addition salts with metal ions, such as alkali metals for example sodium or potassium, or with an ammonium ion.

In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, sublingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated appropriately in

dosage forms such as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include starch, celluloses, lactose, sucrose and magnesium stearate. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, 2-pyrrolidone, cyclodextrin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such

as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid.

The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free acid. The active ingredient may be administered as required for example from 1 - 8 times a day or by infusion. The compositions of the invention are agonists of a cA-PrK and are of use in combatting such conditions where such agonism is thought to be beneficial. Such conditions can be treated by administration orally, sublingually topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1 - 5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a single pharmaceutical

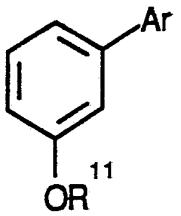
composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, sulbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H_1-antagonists, drugs used in the treatment of cancer such as those which inhibit the synthesis of or inactivate DNA, for example methotrexate, fluoracil, cisplatin, actinomycin D, anti-atherschlerotic agents for example cholesterol lowering drugs such as HMGCoA reductase inhibitors, bile acid sequestrants, drugs for the treatment of psoriasis, for example retinoids, anthralin, anti-inflammatories for example cortiscosteroids, non-steroid anti-inflammatories such as aspirin, antithrombotics for example dipyridamole, or fibrinolytic agents.

In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which process comprises :

a) for compounds wherein R^1 is A^0CO_2H or $A^0CO_2R^9$ and :

i) A^0 is $CR^3(OR^4)$,

reacting in the presence of a strong base a compound of the formula (2) :



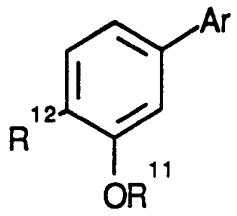
(2)

wherein R^{11} is methyl and Ar is as hereinbefore defined,

with a compound of the formula (3) :

$$R^3COCO_2R^9 \qquad (3)$$

wherein R^3 and R^9 are as hereinbefore defined to form a compound of the formula (4) :



(4)

wherein R^{12} is $CR^3(OH)CO_2R^9$ and R^3, R^9, R^{11}, and Ar are as hereinbefore defined and thereafter optionally reacting with a C_{1-3}alkylating agent to form the corresponding compound wherein R^{12} is $CR^3(OC_{1-3}alkyl)CO_2R^9$,

ii) A^0 is CO,
reacting in the presence of a strong base a compound of the formula (2) as hereinbefore defined with a compound of the formula (5) :

$$R^9O_2CCO_2R^9 \qquad (5)$$

wherein R^9 is as hereinbefore defined to form a compound of the formula (4) wherein R^{12} is $COCO_2R^9$ and R^9, R^{11} and Ar are as hereinbefore defined,

iii) A^0 is CH(OH),
reacting a compound of the formula (4) wherein R^{12} is $COCO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a reducing agent to form the corresponding compound wherein R^{12} is $CH(OH)CO_2R^9$,

iv) A^0 is CH_2,

reacting a compound of the formula (4) wherein R^{12} is $COCO_2H$ or $COCO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a suitable reducing agent to form the corresponding compound wherein R^{12} is CH_2CO_2H,

v) A^0 is $C(OR^5)(OR^6)$,
reacting a compound of the formula (4) wherein R^{12} is $COCO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a C_{1-3}alcohol, 1,2-ethanediol or 1,3-propanediol to form the corresponding compound wherein R^{12} is $C(OR^5)(OR^6)CO_2R^9$,

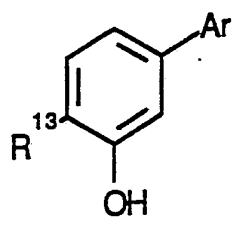
vi) A^0 is CF_2,
reacting a compound of the formula (4) wherein R^{12} is $COCO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a fluorinating agent to form the corresponding compound wherein R^{11} is $CF_2CO_2R^9$, or

vii) A^0 is CHF,
reacting a compound of the formula (4) wherein R^{12} is $CH(OH)CO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a fluorinating agent to form the corresponding compound wherein R^{12} is $CHFCO_2R^9$,

and thereafter optionally :

- converting the group OR^{11} into OH
- converting the group $A^0CO_2R^9$ into A^0CO_2H; or

b) for compounds wherein R^1 is CH_2CO_2H,
converting a compound of the formula (6) :



(6)

wherein R^{13} is acetyl and Ar is as hereinbefore defined into the corresponding compound wherein R^{13} is CH_2CO_2H; or

c) for compounds wherein R^1 is $CH(OR^4)CO_2H$ reacting a compound of the formula (4) wherein R^{12} is -CH(OH)CN with a C_{1-3}alkylating agent and/or converting the group CN into CO_2H, and optionally converting the group OR^{11} into OH; or

d) for compounds wherein R^1 is $P(O)(OH)(OR^2)$, hydrolysing a compound of the formula (6) wherein R^{13} is $P(O)(OR^2)_2$ and R^2, and Ar are as hereinbefore defined; or

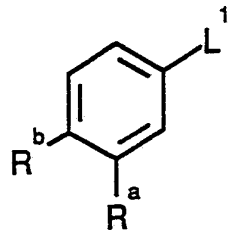
e) for compounds wherein R^1 is $P(S)(OH)(OR^2)$, converting a compound of the formula (6) wherein R^{13} is $P(O)(NHR^{14})(OR^2)$ and R^{14} is phenyl or C_{1-4}alkyl and Ar is as hereinbefore defined into the corresponding compound wherein R^{13} is $P(S)(OH)(OR^2)$; or

f) for compounds where R^1 is SO_3H, reacting in the presence of a strong base a compound of the formula (2) as hereinbefore defined with sulphuryl chloride or a chemical equivalent thereof and optionally converting the group OR^{11} into OH; or

g) for compounds wherein R^1 is SO_2H, reacting in the presence of a strong base a compound of the formula (2) as hereinbefore defined with sulphur dioxide and optionally converting the group OR^{11} into OH; or

h) for compounds wherein R^1 is 5-tetrazolyl, reacting a compound of the formula (4) wherein R^{12} is cyano and R^{11} is as hereinbefore defined or benzenesulphonyl, or a compound of the formula (6) wherein R^{12} is cyano with an azide salt and thereafter if necessary converting the group OR^{11} into OH; or

i) for compounds wherein R^1 is as defined for compounds of the formula (1) reacting in the presence of a palladium catalyst a compound of the formula (7):



(7)

wherein R^b is a group R^1 as hereinbefore defined or a precursor thereof and R^a is R^0 or OR^{11} as hereinbefore defined and L^1 is a leaving group with a compound of the formula (8):

$$ArB(OH)_2 \qquad (8)$$

or a chemical equivalent thereof wherein Ar is as hereinbefore defined and then, if necessary, converting a precursor of R^1 into R^1 and/or converting the group OR^{11} into OH,

and optionally thereafter :

- forming a bioprecursor of R^0 and/or R^1
- forming a pharmaceutically acceptable salt.

Suitably a compound of the formula (2) is reacted with a strong base such as lithium diisopropylamide, or a C_{1-4}alkyl lithium or aryl lithium such as mesityl lithium in an organic solvent such as tetrahydrofuran, diethylether or dimethoxyethane with cooling (-100° - 0°C) to form the anion thereof. The strong base may be formed *in situ*, for example by the addition of a C_{1-4}alkyl lithium e.g. methyllithium followed by a catalytic quantity of diisopropylamine.

The anion of a compound of the formula (2) is suitably reacted with, a compound of the formula (3) or a compound of the formula (5) in an organic solvent such as

tetrahydrofuran, diethylether or dimethoxyethane with cooling (-100° to 0°C) to form a compound of the formula (4) wherein R^{12} is $CR^3(OH)CO_2R^9$ or $COCO_2R^9$ respectively. A suitable compound of the formula (3) is ethylpyruvate, or ethyl glyoxylate or a chemical equivalent thereof and a suitable compound of the formula (5) is diethyloxalate.

A compound of the formula (4) wherein R^{12} is $CR^3(OH)CO_2R^9$ is suitably reacted with a C_{1-3}alkylating agent such as iodomethane, iodopropane or dimethylsulphate in the presence of a base such as sodium hydride or potassium hydroxide in an organic solvent such as dimethylformamide or dimethylsulphoxide at elevated (e.g. 30 - 80°C) or preferably ambient temperature to form the corresponding compound wherein R^{12} is $CR^3(OC_{1-3}alkyl)CO_2R^9$. When potassium hydroxide is used as base the CO_2R^9 group may be directly converted to carboxy.

A compound of the formula (4) wherein R^{12} is $COCO_2R^9$ is suitably reacted with a reducing agent such as sodium borohydride, or diisobutylaluminium hydride in an organic solvent such as dichloromethane, a C_{1-4}alcohol e.g. ethanol, or acetic acid or mixtures thereof at ambient or elevated temperature (e.g. 30 - 80°C), or with cooling (e.g. 0 - 5°C) to form the corresponding compound wherein R^{12} is $CH(OH)CO_2R^9$.

A compound of the formula (4) wherein R^{12} is $COCO_2H$ or $COCO_2R^9$ is suitably reacted with a reducing agent such as a zinc amalgam in hydrochloric acid in the absence of a solvent or in a solvent such as ethanol, acetic acid or dioxan and hydrogen chloride gas at ambient or elevated temperature (e.g. 40-100°C) to form the corresponding compound wherein R^{12} is CH_2CO_2H. Under these reaction conditions the CO_2R^9 group is converted to carboxy.

A compound of the formula (4) wherein R^{12} is $COCO_2R^9$ is suitably reacted with a C_{1-3}alcohol, 1,2-ethanediol or 1,3-propanediol in the presence of an acid catalyst such as

paratoluenesulphonic acid, concentrated sulphuric acid or anhydrous hydrogen chloride, at ambient or elevated temperature to form the corresponding compound wherein R^{12} is $C(OR^5)(OR^6)CO_2R^9$.

A compound of the formula (4) wherein R^{12} is $COCO_2R^9$ or $CHOHCO_2R^9$ is suitably reacted with a fluorinating agent such as diethylaminosulphur trifluoride in an organic solvent such as a halohydrocarbon or an ether such as glyme, or THF at ambient or elevated temperature (e.g. 30-60°C) to form the corresponding compound where R^{12} is $CF_2CO_2R^9$ or $CHFCO_2R^9$ respectively.

A compound of the formula (4) wherein OR^{11} is methoxy can suitably be converted to the corresponding compound wherein OR^{11} is hydroxy by reaction with sodium iodide and chlorotrimethylsilane in an organic solvent such as acetonitrile, or a halohydrocarbon e.g. dichloromethane or chloroform at elevated (e.g. 30 - 80°C) or preferably ambient temperature. This method is particularly suitable for preparing compounds of the formula (1) wherein R^1 is $A^0CO_2R^9$ since the ester-forming group R^9 is not hydrolysed under the reaction conditions. Another method utilises sodium thiomethoxide in an organic solvent such as dimethylformamide at an elevated temperature for example 40 - 120°C. The more forcing conditions of this method are suitable for preparing compounds of formula (1) wherein R^1 is A^0CO_2H.

A compound of the formula (4) wherein R^{12} is $A^0CO_2R^9$ can suitably be converted to the corresponding compound wherein R^{12} is A^0CO_2H by reaction with an aqueous base such as sodium or potassium hydroxide at ambient or elevated temperature (e.g. 40 - 120°). This method is particularly suitable for preparing compounds of the formula (1) wherein R^0 is methoxy since the OR^{11} group is not hydrolysed. Another hydrolysis method utilises aqueous acid such as concentrated hydrochloric acid at an elevated temperature (e.g. 40 - 120°C) which provides directly compounds of the formula (1) wherein R^0 is hydroxy and R^1 is A^0CO_2H.

Suitably a compound of the formula (6) wherein R^{13} is acetyl is converted to the corresponding compound where R^{13} is CH_2CO_2H by reaction with sulphur and morpholine at elevated temperature (e.g. 50 - 200°C), followed by hydrolysis with an aqueous base such as sodium hydroxide at elevated temperature, preferably at the reflux temperature of the reaction mixture.

Suitably a compound of formula (4) where R^{12} is -CH(OH)CN is reacted with a C_{1-3}alkylating agent as hereinbefore described followed by reaction with aqueous mineral acid such as hydrochloric acid at ambient or elevated temperature preferably at reflux in order to prepare the corresponding compound where R^{12} is $CH(OC_{1-3}alkyl)\ CO_2H$. The alkylation can be omitted if the corresponding compound where R^{12} is $CH(OH)CO_2H$ is desired. During the hydrolysis of the CN group the OR^{11} group may be converted to hydroxy. If not and if desired this group can be converted to hydroxy as hereinbefore described.

A compound of the formula (4) wherein R^{12} is -CH(OH)CN can be prepared by reacting the corresponding compound wherein R^{12} is -CHO with a source of cyanide such as potassium cyanide in the presence of an acid such as hydrochloric acid preferably at ambient temperature.

A compound of the formula (4) or (6) where R^{12} or R^{13} is CHO is suitably prepared by reacting the corresponding compound wherein R^{12} or R^{13} is cyano with a suitable reducing agent such as diisobutylaluminium hydride followed by aqueous acidic work-up.

Suitably a compound of the formula (6) wherein R^{13} is $P(O)(OR^2)_2$ is hydrolysed by reaction with an aqueous base such as sodium hydroxide optionally in a cosolvent such as a C_{1-4}alcohol at an elevated temperature (e.g. 40-100°C), preferably at the reflux temperature of the reaction mixture.

Suitably a compound of the formula (6) wherein R^{13} is $P(O)(NHR^{14})(OR^2)$ is converted to the corresponding compound wherein R^9 is $P(S)(OH)(OR^2)$ by reaction with a strong base such as sodium hydride in an organic solvent such as dimethoxyethane at ambient or elevated temperature, (e.g. 40 - 100°C) followed by reaction with carbon disulphide.

Suitably the anion of a compound of the formula (2) prepared as hereinbefore described is reacted with sulphuryl chloride or a chemical equivalent thereof or with sulphur dioxide in an organic solvent such as tetrahydrofuran with cooling (-100° - 0°C) to form after aqueous work-up a compound of the formula (4) wherein R^{12} is SO_3H or SO_2H respectively and OR^{11} is methoxy which if desired can be converted to the corresponding compound wherein OR^{11} is hydroxy as hereinbefore described.

A compound of the formula (4) wherein R^{12} is cyano or a compound of the formula (6) wherein R^{13} is cyano is suitably reacted with an azide salt such as ammonium, sodium or aluminium azide in an organic solvent such as diethylformamide, dimethylsulphoxide, N-methylpyrrolidone or tetrahydrofuran at an elevated temperature e.g. 40-200°C, preferably at 100-150°C to form the corresponding 5-tetrazolyl compound. Preferably in a compound of the formula (4) OR^{11} is benzenesulphonyl which can be introduced in standard manner, for example by reacting the corresponding hydroxy compound with benzenesulphonyl chloride in the presence of a base such as triethylamine. This group can be removed in standard manner, for example by reaction with a base such as sodium hydroxide.

Suitably a compound of the formula (7) is reacted with a compound of the formula (8) in the presence of 1-50 mole %, preferably 2-10 mole %, of a palladium catalyst and a base such as triethylamine, sodium bicarbonate, or aqueous sodium carbonate and optionally lithium chloride in an organic solvent such as dimethylformamide, dimethoxyethane acetonitrile, toluene, tetrahydrofuran, ethanol, or mixtures

thereof, at elevated temperature, (e.g. 30-150°C), preferably at the reflux temperature of the mixture. Suitably L^1 is halo for example iodo, bromo or chloro or a trifluoromethanesulphonate. Subsequently the OR^{11} group can be converted to hydroxy as hereinbefore described for compounds of formula (4). Examples of palladium catalysts that can be used include:

tetrakis(triphenylphosphine)palladium ($Pd[PPh_3]_4$),
bis(triphenylphosphine)palladium dichloride ($Pd[PPh_3]_2Cl_2$),
[1,4-bis-(diphenylphosphine)butane]palladium dichloride ($Pd(dppb)Cl_2$),
[1,3-bis-(diphenylphosphine)propane]palladium dichloride ($Pd(dppp)Cl_2$),
[1,2-bis-(diphenylphosphine)ethane]palladium dichloride ($Pd(dppe)Cl_2$),
bis(tri-o-tolylphosphine)palladium diacetate or dichloride ($Pd(totp)(OAc)_2$ or $Pd(totp)Cl_2$), or
1,1'-bis(diphenylphosphine)ferrocinopalladium diacetate or dichloride ($Pd[dppf](OAc)_2$ or $Pd[dppf]Cl_2$).

By a chemical equivalent of a compound of the formula (8) is meant a reagent that can couple the Ar group onto the pyridyl ring of a compound of the formula (7). For example aryl stannanes can be used, such as $ArSnMe_3$ which can suitably be prepared by reacting a suitable aryl halide (such as ArBr or ArI) with a base such as t-butyl lithium followed by reaction with a trimethyl tin halide (e.g. Me_3SnCl). Alternatively the aryl halide can be reacted with $Me_3SnSnMe_3$ in the presence of a palladium catalyst as hereinbefore described to prepare a suitable aryl stannane.

When R^b is a group R^1 as hereinbefore defined reaction of a compound of the formula (7) with a compound of the formula (8) results directly in compounds of the formula (1).

An example of a precursor for R^1 is when R^b is hydrogen. In this situation reaction of a compound of the formula (7) with a compound of the formula (8) or a chemical equivalent

thereof results in a compound of the formula (2) or a compound of the formula (6) wherein R^{13} is hydrogen. Such compounds can then be converted into a compound of the formula (1) as herein described.

Other precursors for R^1 include CN, CHO or COMe. Reaction of a compound of the formula (7) wherein R^b represents such a precursor with a compound of the formula (8) or a chemical equivalent thereof results in a compound of the formula (4) or a compound of the formula (6) wherein R^{12} or R^{13} is CN, CHO or COMe. Such compounds can be converted to compounds of the formula (1) as herein described.

If desired a compound of the formula (1) wherein R^1 is A^0CO_2H can be converted to the corresponding compound wherein R^1 is $A^0CO_2R^9$ by reaction with a compound R^9OH wherein R^9 is as hereinbefore defined.

A compound of the formula (1) wherein R^0 is OH can be converted to the corresponding compound where R^0 is OR^8 by reaction with R^8L^2 wherein R^8 is as hereinbefore defined and L^2 is a leaving group such as halo e.g. bromo, chloro, iodo.

If desired a compound of the formula (1) wherein R^1 is $P(Z)(OR^2)(OH)$ can be converted to the corresponding compound wherein R^1 is $P(Z)(OR^2)(OR^{10})$ by reaction with a suitable O-protecting agent in standard manner. For example the compound can be reacted with a pivalolyloxymethyl halide.

A compound of the formula (1) wherein R^1 is 5-tetrazole can be reacted with a suitable N-protecting agent in standard manner, for example with a pivalolyloxymethyl halide.

A compound of the formula (1) wherein R^1-R^0 is A^1CO_2 is suitably prepared by heating a compound of the formula (1) wherein R^1 is A^1CO_2H and R^0 is OH with a dehydrating agent such as acetic anhydride, at an elevated temperature (e.g. 40 - 200°C), preferably at the reflux temperature of the reaction mixture.

A compound of the formula (1) wherein R^1-R^0 is A^2OCH_2O is suitably prepared by reacting a compound of the formula (1) wherein R^1 is A^2OH and R^0 is OH with a dihalomethane such as diiodo- or dibromomethane in the presence of silver carbonate in an organic solvent such as dimethylformamide at an elevated temperature (e.g. 40 - 120°C).

A compound of the formula (2) is suitably prepared by reacting a compound of the formula (6) wherein R^{13} is hydrogen with an O-methylating agent such as dimethylformamide dimethylacetal in dimethylformamide or trimethylphosphite at an elevated temperature (e.g. 40 - 120°C) or with iodomethane and silver carbonate in toluene or chloroform. This method can also be used for converting compounds of the formula (6) into corresponding compounds of the formula (4) and compounds of formula (7) wherein R^a is hydroxy into corresponding compounds wherein R^a is OR^{11}.

A compound of the formula (6) wherein R^{13} is acetyl can also be prepared by reacting a compound of the formula (6) wherein R^{13} is cyano with methyl lithium followed by aqueous acidic work up with for example hydrochloric acid.

A compound of the formula (6) wherein R^{13} is hydrogen can be prepared by reacting a compound of the formula (6) wherein R^{13} is cyano with orthophosphoric acid at an elevated temperature, e.g. 50 - 200°C.

A compound of formula (4) wherein R^{12} is cyano is suitably prepared by reacting the anion of a compound of formula (2) wherein Ar and R^{11} are as hereinbefore defined with dimethylformamide with cooling (e.g. -80 to 10°C), followed by ambient temperature and aqueous work-up. The resulting compound of formula (4) wherein R^{12} is carboxaldehyde is treated with hydroxylamine hydrochloride and sodium acetate in a suitable solvent such as ethanol or methanol at elevated temperature, e.g. 40-100°C, preferably at the reflux temperature of the reaction mixture followed by dehydrating

the product obtained for example by heating with acetic anhydride.

A compound of the formula (6) wherein R^{13} is cyano or acetyl and Ar is as hereinbefore defined can be suitably prepared by reaction of a compound of formula (4) wherein R^{12} is cyano or acetyl and R^{11} and Ar are as hereinbefore defined with a demethylating agent such as sodium iodide/chlorotrimethylsilane in the absence of solvent or in an organic solvent such as acetonitrile or chloroform at an elevated temperature (e.g. 40 to 100°C) or at ambient temperature.

A compound of the formula (6) wherein R^{13} is $P(O)(OR^2)_2$ can be prepared by treating a compound of the formula (2) wherein R^{11} is $P(O)(OR^2)_2$ with a strong base such as lithium diisopropylamide in an organic solvent such as tetrahydrofuran with cooling (e.g. -100-0°C).

A compound of the formula (2) wherein R^{11} is $P(O)(OR^2)_2$ is suitably prepared by treating a compound of the formula (6) wherein R^{13} is hydrogen with a compound of the formula (9):

$$L^3P(O)(OR^2)_2 \qquad (9)$$

wherein L^3 is a leaving group and R^2 is as hereinbefore defined with a base such as diisopropylethylamine.

Suitably L^3 is halo, for example chloro or bromo.

A compound of formula (2) wherein R^{11} is $P(O)(OR^2)_2$ can also be prepared by treating a compound of the formula (6) wherein R^{13} is hydrogen with a compound of the formula (10):

$$HP(O)(OR^2)_2 \qquad (10)$$

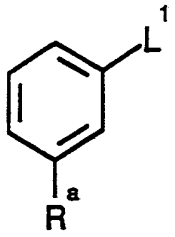
wherein R^2 is as hereinbefore defined in the presence of an amine base such as triethylamine, and carbon tetrachloride.

Alternatively, a compound of the formula (6) wherein R^{13} is $P(O)(OR^2)_2$ is suitably prepared by treating a compound of the formula (6) wherein R^{13} is hydrogen with a compound of the formula (9) in the presence of a strong base such as lithium diisopropylamide in an organic solvent such as tetrahydrofuran with cooling (e.g. -100-0°C) without isolation of the intermediate compound of the formula (2) wherein R^{11} is $P(O)(OR^2)_2$.

A compound of formula (6) wherein R^{13} is hydrogen is suitably prepared by demethylating a compound of formula (2) as hereinbefore defined. Suitably a compound of formula (2) is treated with boron tribromide in an organic solvent such as dichloromethane or toluene with cooling (e.g. -80 to 10°C) followed by ambient temperature and aqueous work-up. Or a compound of formula (2) is treated with sodium iodide and chlorotrimethylsilane at ambient or elevated temperature (e.g. 40-80°C) conveniently ambient temperature in a solvent such as acetonitrile or dichloromethane.

A compound of the formula (6) wherein R^{13} is $P(O)(NHR^{14})(OR^2)$ can be prepared by reaction of a compound of the formula (6) wherein R^{13} is $P(O)(OH)(OR^2)$ with carbon tetrachloride, triphenylphosphine and aniline or a C_{1-4}alkylamine in an organic solvent such as pyridine at ambient temperature or with cooling (e.g. -10 to 5°C). Alternatively a compound of the formula (6) where R^{13} is $P(O)(OH)(OR^2)$ can be reacted with dimethylformamide and oxalyl chloride in an organic solvent such as a halo hydrocarbon e.g. dichloromethane at ambient temperature, followed by reaction with aniline or a C_{1-4}alkylamine preferably with cooling (-10 to 5°C).

Compounds of the formula (7) are known or can be prepared from a compound of the formula (11):



(11)

wherein R^a and L^1 are as hereinbefore defined using similar methods to those described for preparing compounds of the formula (1).

Thus, a compound of the formula (7) wherein R^b is $P(O)(OR^2)_2$ can be prepared by reacting a compound of the formula (11) wherein R^a is OH with a compound of the formula (9) or (10) in similar manner to the reaction of a compound of the formula (6) wherein R^{13} is hydrogen with a compound of the formula (9) or (10). If desired the group R^a can then be converted to OMe.

Similarly, a compound of the formula (11) where R^a is OMe can be treated in the presence of a strong base with a compound of the formula (3), a compound of the formula (5), sulphuryl chloride, sulphur dioxide or dimethylformamide to prepare a compound of the formula (7) wherein R^b is $CR^3(OR^4)CO_2R^9$, $COCO_2R^9$, SO_3H, SO_2H, or CHO respectively in similar manner to the corresponding reaction with a compound of the formula (2) as hereinbefore described. Particularly suitable as a strong base is lithium tetramethyl piperidide.

A compound of the formula (8) is suitably prepared by reacting the organolithium or Grignard reagent, formed from a compound of the formula (12):

$$Ar-L^4 \qquad (12)$$

wherein L^4 is bromo or iodo and Ar is as hereinbefore defined with a tri-C_{1-4}alkylborate such as trimethyl, tri-isopropyl

or tri-n-butyl borate in an organic solvent such as diethyl ether or tetrahydrofuran with cooling (e.g. - 80-10°C).

The Ar group in compounds of the formula (2), (4), (6) or (12) preferably (2) or (4) may be appropriately functionalised by methods of aromatic substitution known in the art. For example, a bromo group may be introduced into a suitably substituted phenyl ring (eg. disubstituted in the 2- and 4-positions by electron-donating groups such as C_{1-6}alkoxy) by reaction with a brominating agent such as N-bromosuccinimide or bromine in a solvent such as dimethylformamide. Alternatively a nitro group can be introduced into a phenyl ring by reaction with a suitable nitrating agent, such as nitronium tetrafluoroborate. Such a group can be readily hydrogenated to an amino group which if desired can be converted to a $NHCOR^7$ group by reaction with $LCOR^7$ wherein L is a leaving group and R^7 is as hereinbefore defined. Suitable examples of the reagent LCOR include acid halides (L is halo eg. chloro or bromo) or acid anhydrides (L is $OCOR^7$).

Other suitable functionalisations include the introduction of an allyl group ortho to a hydroxy substituent on a phenyl ring by reaction with an allyl halide, eg. bromide, to form an allyloxy derivative which on heating undergoes a Claisen rearrangement to form an ortho allyl hydroxy derivative. The hydroxy group can in turn be functionalised, eg. by reaction with a C_{1-6}alkyl halide to form a C_{1-6}alkoxy group. If desired, an allyl group can be converted to an E-1-propenyl group by reaction with a strong base, such as sodium methoxide. An E-1-propenyl group can be cleaved to a formyl group by reaction with an oxidising agent such as N-methylmorpholine-N-oxide in the presence of a catalyst such as osmium tetroxide to form a 1,2,dihydroxypropyl group which on reaction with an oxidising agent such as sodium periodate forms the formyl group. Alternatively the E-1-propenyl group can be converted directly to a formyl group by reaction with a mixture of osmium tetroxide and sodium periodate or by reaction with ozone. A formyl group can in turn be further

functionalised, for example it can be converted to a hydroxymethyl group by reaction with a suitable reducing agent such as sodium borohydride, the hydroxymethyl group then being reacted further, eg. with a C_{1-6}alkyl halide to form a C_{1-6}alkoxymethyl group. Alternatively a formyl group can be reacted with a suitable Horner Wittig or Wittig reagent such as $(R^{15}O)_2P(O)CH_2CO_2R^{15}$ or $Ph_3P{=}CHCO_2R^{15}$ wherein R^{15} is C_{1-4}alkyl to form a $CH{=}CHCO_2R^{15}$ group which can be optionally hydrolysed to a $-CH{=}CHCO_2H$ group. A $-CH{=}CHCO_2R^{15}$ group can be converted to a $-CH{=}CHCON(R^7)_2$ group by reaction with an amine $HN(R^7)_2$ or a chemical equivalent thereof wherein R^7 is as hereinbefore defined. Alternatively a $-CH{=}CHCO_2H$ group can be converted to an acid halide, eg. the acid chloride by reaction with oxalyl chloride, which can then be reacted with an amine $HN(R^7)_2$ or a chemical equivalent thereof. An example of a chemical equivalent is ammonium hydroxide which will form a $CH{=}CHCONH_2$ group.

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

Cyclic-AMP Protein Kinase (cA-PrK) Agonist Activity

Type II cA-PrK was prepared from the cardiac muscle of a cow. The supernatant from a muscle homogenate (3 mls of 10 mM potassium phosphate, 1 mM EDTA per g tissue) was applied to a column of DEAE-cellulose equilibrated with the homogenisation buffer and the type II cA-PrK was eluted with homogenisation buffer containing 350 mM sodium chloride (Rannels et al., 1983, Methods Enzymol., **99**, 55-62).

Type II cA-PrK was assayed for phosphotransferase activity by incubating the enzyme at 30°C for 5 minutes with [γ-^{32}P]-adenosine triphosphate and a suitable peptide

substrate such as malantide (Malencik et al., 1983, Anal. Biochem., **132**, 34-40). The reaction was terminated by the addition of hydrochloric acid and the [^{32}P]-phosphopeptide quantified by spotting the reaction mixture onto phosphocellulose papers. The concentration of compound required to give 10% phosphotransferase activation is given as the EC_{10} (μM). The compounds of Examples 1 and 2 had EC_{10} values of 2.6 and 1.0 μM respectively.

Inhibition of Platelet Aggregation

Human platelet-rich-plasma was separated from freshly drawn blood (in acid/citrate/dextrose) and treated with 100 μM acetylsalicylic acid for 15 minutes at 37°C. A washed platelet suspension was then prepared in a Hepes-isotonic saline buffer after a single centrifugation step and adjusted to a concentration of $1.5x10^8$ cells/ml. Aliquots of this suspension were pre-incubated with compounds for 5 minutes at 37°C, then challenged with 1.0 μM U46619. The extent of aggregation after 2 minutes were expressed as a percentage of control and results obtained are expressed as an IC_{50} (concentration to cause 50% inhibition of platelet aggregation, μM). The compounds of Examples 1 and 2 had IC_{50} values of 20 and 38 μM respectively.

Inhibition of Spontaneous Contraction in Guinea-Pig Colon

Segments of isolated guinea-pig colon (2 cm) were suspended under 2 g tension in standard organ baths containing Krebs solution. The tissues were connected at the free end to isometric transducers which allow recording and display of developed tension on chart recorders. On-line computer capture and analysis was used to quantify the effects of test compounds on spontaneous contractions. Inhibitory responses were calculated as % maximum inhibition of spontaneous contraction distance over 3 consecutive pre and post dose 2 minute readings. The concentration of compound which caused 50% inhibition of the spontaneous contraction is given as the EC_{50} (μM).

Bronchodilatation - In vitro

Spiral strips of guinea-pig trachea were suspended in standard organ baths containing Krebs solution. The tissues were connected at the free end to isometric transducers which allow recording and display of developed tension on chart recorders. Tension was allowed to develop spontaneously and concentrations of test compounds added in a cumulative fashion. The concentration of compound which caused 50% inhibition of the spontaneously developed tension is given as the IC_{50} (μM).

Measurement of cardiac muscle relaxation time in rabbit ventricle

Papillary muscles from the right ventricle of female Albino New Zealand rabbits are mounted in standard organ baths containing oxygenated Krebs solution. One end of the muscle is connected to an isometric transducer which allowed recording of contractile force and its first derivative on chart recorders. Test compounds are added to the bath in a cumulative manner. Relaxation time is calculated as the time taken from peak tension to the end of the contraction. Compounds which cause a decrease in the relaxation time indicate a positive lusitropic effect of use in the treatment of cardiovascular diseases where there is a component of diastolic failure such as congestive heart failure, angina, hypertension and cardiomyopathy.

Example 1

2-(5-Tetrazolyl)-5-(2,3-di-n-propoxyphenyl)phenol

(a) From 1,2-di-n-propoxybenzene (13.8g), 2,3-di-n-propoxyphenylboronic acid (13g) was prepared according to the method of W. J. Thompson and J. Gaudino J. Org. Chem. 1984, 49, 5237.

(b) To methyl 2,4-dihydroxybenzoate (5.95g) and 4-N,N-dimethylaminopyridine (8.65g) in dichloromethane at -50°C, trifluoromethanesulphonic anhydride (10.0g) was added over 5mins. The mixture was warmed to room temperature stirred for 1 hour, treated with 2N hydrochloric acid and the organic phase separated, dried (MgSO4) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, diethyl ether/petroleum ether eluant) to give methyl 2-hydroxy-4-trifluoromethanesulphonyloxy benzoate (5.0g) 1H NMR (CDCl3) 3.99(s,3H), 7.25(d<1H), 7.44(dd,1H) and 8.23(d,1H).

(c) From methyl 2-hydroxy-4-trifluoromethanesulphonyloxy benzoate (8.7g) and 2,3-di-n-propoxyphenylboronic acid (7.4g) and using the method of A. Huth, I. Beetz and I. Schumann, Tetrahedron, 1989, 45, 6679, methyl 2-hydroxy-4-(2,3-di-n-propoxyphenyl)benzoate (4.6g) was prepared. 1H NMR (CDCl3) 0.82(t,3H), 1.08(t,3H), 1.48-1.59(m,2H), 1.81-1.95(m,2H), 3.70(t,2H), 3.96(s,3H), 3.98(t,2H), 6.93(d,2H), 7.07-7.17(m,3H), 7.83(d,1H) and 10.76(s,1H).

(d) Methyl 2-hydroxy-4-(2,3-di-n-propoxyphenyl)benzoate (2.2g) in ethanol (15ml) and dioxane (30ml) was treated with sodium borohydride (1g) and stirred at room temperature for 48 hours. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, dichloromethane eluant) to give 2-hydroxy-4-(2,3-di-n-propoxyphenyl)benzyl alcohol (1.7g). The benzyl alcohol was oxidised according to the method of S. V. Ley et al J. C. S. Chem. Comm., 1987, 1625 to give 2-hydroxy-4-(2,3-di-n-propoxyphenyl)-

benzaldehyde (0.78g). 1H NMR (CDCl3) 0.82(t,3H), 1.08(t,3H), 1.41-1.62(m,2H), 1.84-1.95(m,2H), 3.72(t,2H), 3.99(t,2H), 6.91-6.96(m,2H), 7.09(t,1H), 7.18(s,1H), 7.26(dd,1H), 9.92(s,1H) and 11.06(s,1H).

(e) A solution of 2-hydroxy-4-(2,3-di-n-propoxyphenyl)-benzaldehyde (0.78g) in ethanol (15ml) and saturated aqueous sodium acetate (8ml) containing hydroxylamine hydrochloride (0.23g) was stirred for 16 hours. Solvent was removed at reduced pressure acetic anhydride added and the mixture boiled for 4 hours. Solvent was removed at reduced pressure, the residue dissolved in diethyl ether (50ml) and washed with water (2 x 50ml). The organic layer was dried (MgSO4) and solvent removed at reduced pressure to give 2-hydroxy-4-(2,3-di-n-propoxyphenyl)benzonitrile (0.8g). IR (nujol mull) 2,230cm-1.

(f) A mixture of 2-hydroxy-4-(2,3-di-n-propoxyphenyl)-benzonitrile (0.8g), sodium azide (0.38g) and ammonium chloride (0.35g) in N-methylpyrrolidinone (20ml) was heated at 130°C for 3 hours. The reaction mixture was absorbed onto silica gel and column chromatographed (silica gel, diethyl ether then diethyl ether/methanol 85/15 eluant). Appropriate fractions were combined, solvent removed at reduced pressure and the residue triturated with water to give the title compound (0.26g) m.p. 187-189°C.

Example 2

Ethyl 2-hydroxy-4-(2,3-di-n-propoxyphenyl)phenyl phosphonate

(a) From 3-bromophenol (1.73g) and 2,3-di-n-propoxyphenyl-boronic acid (2.38g), 3-(2,3-di-n-propoxyphenyl)phenol m.p. 78-80°C after column chromatography (silica gel, diethyl ether/petroleum ether 1:9 eluant) was prepared according to the method of Example 1(c).

(b) From 3-(2,3-di-n-propoxyphenyl)phenol (1.0g), diethyl 3-(2,3-di-n-propoxyphenyl) phenyl phosphate (1.2g) was

prepared according to the method of G. W. Kenner and N. R. Williams J. Chem. Soc. 1955, 522.

(c) Diethyl 3-(2,3-di-n-propoxyphenyl)phenyl phosphate (1.2g) was rearranged to diethyl 2-hydroxy-4-(2,3-di-n-propoxyphenyl)phenyl phosphonate according to the method of L. S. Melvin Tet. Letters, 1981, 22, 3375 and subsequently hydrolysed to the title compound, isolated as an oil, by boiling with 5N aqueous sodium hydroxide (10ml). 1H NMR (DMSO-d6) 0.75(t,3H), 1.05(t,3H), 1.20(6H), 1.43-1.53(m,2H), 1.54-1.83(m,2H), 3.72(t,2H, 3.86-3.92(m,4H), 4.03(t,2H), 6.88-7.66(m,5H) and 7.46(dd,1H).

Example 3

Pharmaceutical compositions for oral administration are prepared by combining the following :

		% w/w	
2-(5-tetrazolyl)-5-(2,3-dipropoxyphenyl)phenol	0.5	3.0	7.14
2% w/w Soya lecithin in soya bean oil	90.45	88.2	84.41
Hydrogenated vegetable shortening and beeswax	9.05	8.8	8.45

The formulations are then filled into individual soft gelatin capsules.

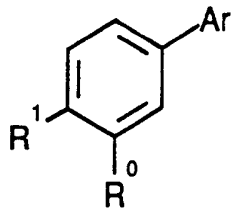
Example 4

A pharmaceutical composition for parenteral administration is prepared by dissolving ethyl 2-hydroxy-4-(2,3-dipropoxyphenyl)phenyl phosphonate (0.02 g) in polyethylene glycol 300 (25 ml) with heating. This solution is then diluted with water for injections Ph. Eur. (to 100 ml). The

solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

Claims

1. A compound of the formula (1) :



or a pharmaceutically acceptable salt thereof, wherein :

R^0 is OH or a bioprecursor thereof,

R^1 is A^0CO_2H, $P(Z)(OH)(OR^2)$, SO_2H, SO_3H or 5-tetrazolyl or a bioprecursor thereof,

A^0 is CH_2, CHF, CF_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$,

R^2 is phenyl, C_{3-5}cycloalkyl, C_{3-5}cycloalkylC_{1-4}alkyl, or C_{1-8}alkyl optionally substituted by C_{1-4}alkoxy,

R^3 is H, methyl or ethyl,

R^4 is H or C_{1-3}alkyl,

R^5 and R^6 are each C_{1-3}alkyl or together form a 1,2-ethanediyl group or 1,3-propanediyl group,

Z is O or S, and

Ar is phenyl optionally substituted by one to three groups independently selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}cycloalkyl, C_{3-6}cycloalkoxy, C_{1-6}alkylthio, phenyl, phenylthio, benzyloxy, C_{1-6}polyfluoroalkyl, C_{1-6}polyfluoroalkoxy, halo, $N(R^7)_2$ or $NHCOR^7$ wherein R^7 is H or C_{1-6}alkyl, or

$-X(CH_2)_nY-$ attached to adjacent carbon atoms of the phenyl ring wherein X and Y are independently CH_2 or O and n is 1 to 3, wherein said C_{1-6}alkyl, C_{2-6}alkenyl or C_{1-6}alkoxy groups can be independently substituted by OH, C_{1-6}alkoxy, C_{3-6}cycloalkyl, $N(R^7)_2$, CO_2R^7 or $CON(R^7)_2$.

2. A compound according to claim 1 wherein R^1 is A^0CO_2H or $A^0CO_2R^9$ in which R^9 is an ester-forming group.

3. A compound according to claim 1 wherein R^1 is $P(Z)(OH)(OR^2)$ or $P(Z)(OR^2)_2$.

4. A compound according to claim 1 wherein R^1 is SO_2H, SO_3H or 5-tetrazolyl.

5. A compound according to claim 1 wherein R^1 and R^0 are linked together such that R^1-R^0 is A^1CO_2 in which A^1 is CH_2, CHF, CF_2, $CR^3(OR^4)$, CO or $C(OR^5)(OR^6)$.

6. A compound according to claim 1 wherein R^1 and R^0 are linked together such that R^1-R^0 is A^2OCH_2O in which A^2 is $P(Z)(OR^2)$ or $CR^3(CO_2R^9)$ and R^9 is an ester-forming group.

7. A compound according to claim 1 which is :

2-(5-tetrazolyl)-5-(2,3-dipropoxyphenyl)phenol, or

ethyl 2-hydroxy-4-(2,3-dipropoxyphenyl)phenyl phosphonate,

or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 7 for use as a medicament.

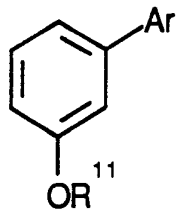
9. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier.

10. A process for preparing a compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof which process comprises :

a) for compounds wherein R^1 is A^0CO_2H or $A^0CO_2R^9$ and :

i) A^0 is $CR^3(OR^4)$,

reacting in the presence of a strong base a compound of the formula (2) :



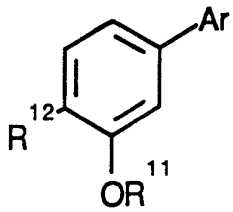
(2)

wherein R^{11} is methyl and Ar is as defined in claim 1,

with a compound of the formula (3) :

$$R^3COCO_2R^9 \qquad (3)$$

wherein R^3 is as defined in claim 1 and R^9 is an ester-forming group to form a compound of the formula (4) :



(4)

wherein R^{12} is $CR^3(OH)CO_2R^9$ and R^3, R^9, R^{11}, and Ar are as hereinbefore defined and thereafter optionally reacting with

a C_{1-3}alkylating agent to form the corresponding compound wherein R^{12} is $CR^3(OC_{1-3}alkyl)CO_2R^9$,

ii) A^0 is CO,
reacting in the presence of a strong base a compound of the formula (2) as hereinbefore defined with a compound of the formula (5) :

$$R^9O_2CCO_2R^9 \qquad (5)$$

wherein R^9 is as hereinbefore defined to form a compound of the formula (4) wherein R^{12} is $COCO_2R^9$ and R^9, R^{11} and Ar are as hereinbefore defined,

iii) A^0 is CH(OH),
reacting a compound of the formula (4) wherein R^{12} is $COCO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a reducing agent to form the corresponding compound wherein R^{12} is $CH(OH)CO_2R^9$,

iv) A^0 is CH_2,
reacting a compound of the formula (4) wherein R^{12} is $COCO_2H$ or $COCO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a suitable reducing agent to form the corresponding compound wherein R^{12} is CH_2CO_2H,

v) A^0 is $C(OR^5)(OR^6)$,
reacting a compound of the formula (4) wherein R^{12} is $COCO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a C1-3alcohol, 1,2-ethanediol or 1,3-propanediol to form the corresponding compound wherein R^{12} is $C(OR^5)(OR^6)CO_2R^9$,

vi) A^0 is CF_2,
reacting a compound of the formula (4) wherein R^{12} is $COCO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a fluorinating agent to form the corresponding compound wherein R^{11} is $CF_2CO_2R^9$, or

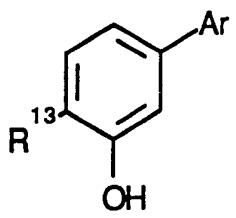
vii) A^0 is CHF,

reacting a compound of the formula (4) wherein R^{12} is $CH(OH)CO_2R^9$ and R^9, R^{11}, and Ar are as hereinbefore defined with a fluorinating agent to form the corresponding compound wherein R^{12} is $CHFCO_2R^9$,

and thereafter optionally :

- converting the group OR^{11} into OH
- converting the group $A^0CO_2R^9$ into A^0CO_2H; or

b) for compounds wherein R^1 is CH_2CO_2H, converting a compound of the formula (6) :



(6)

wherein R^{13} is acetyl and Ar is as hereinbefore defined into the corresponding compound wherein R^{13} is CH_2CO_2H; or

c) for compounds wherein R^1 is $CH(OR^4)CO_2H$ reacting a compound of the formula (4) wherein R12 is -CH(OH)CN with a C_{1-3}alkylating agent and/or converting the group CN into CO_2H, and optionally converting the group OR^{11} into OH; or

d) for compounds wherein R^1 is $P(O)(OH)(OR^2)$, hydrolysing a compound of the formula (6) wherein R^{13} is $P(O)(OR^2)_2$, R^2 is as defined in claim 1 and Ar is as hereinbefore defined; or

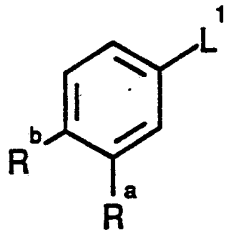
e) for compounds wherein R^1 is $P(S)(OH)(OR^2)$, converting a compound of the formula (6) wherein R^{13} is $P(O)(NHR^{14})(OR^2)$ and R^{14} is phenyl or C_{1-4}alkyl and Ar is as hereinbefore defined into the corresponding compound wherein R^{13} is $P(S)(OH)(OR^2)$; or

f) for compounds where R^1 is SO_3H,
reacting in the presence of a strong base a compound of the formula (2) as hereinbefore defined with sulphuryl chloride or a chemical equivalent thereof and optionally converting the group OR^{11} into OH; or

g) for compounds wherein R^1 is SO_2H,
reacting in the presence of a strong base a compound of the formula (2) as hereinbefore defined with sulphur dioxide and optionally converting the group OR^{11} into OH; or

h) for compounds wherein R^1 is 5-tetrazolyl, reacting a compound of the formula (4) wherein R^{12} is cyano and R^{11} is as hereinbefore defined or benzenesulphonyl, or a compound of the formula (6) wherein R^{12} is cyano with an azide salt and thereafter if necessary converting the group OR^{11} into OH; or

i) for compounds wherein R^1 is as defined for compounds of the formula (1) reacting in the presence of a palladium catalyst a compound of the formula (7):



(7)

wherein R^b is a group R^1 as defined in claim 1 or a precursor thereof and R^a is R^0 or OR^{11} as hereinbefore defined and L^1 is a leaving group with a compound of the formula (8):

$$ArB(OH)_2 \qquad (8)$$

or a chemical equivalent thereof wherein Ar is as hereinbefore defined and then, if necessary, converting a precursor of R^1 into R^1 and/or converting the group OR^{11} into OH,

and optionally thereafter :

- forming a bioprecursor of R^0 and/or R^1
- forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/02119

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D257/04; C07F9/40; A61K31/41; A61K31/66

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; C07F

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	GB,A,1 230 958 (MERCK) 5 May 1971 *Complete specification*	1-10
P,A	WO,A,9 117 987 (SMITH KLINE & FRENCH) 28 November 1991 *Complete specification*	1-10

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"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

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"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.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 JANUARY 1993	- 8. 02. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	LUYTEN H.W.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9202119
SA 66541

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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