FORM 25 (12) PATENT granted by (19) AP

AFRICAN REGIONAL INDUSTRIAL PROPERTY ORGANISATION (ARIPO)

830

(11) (A)

(21) Application Number: AP/P/97/00982

(22) Filing Date: 19970508

(24) Date of Grant & (45) Publication: 20000503

(30) Priority Data

(33) Country: GB

(31) Number: 9609641.7

(32) Date: 19960509

(84) Designated States:

BW GM KE MW UG ZM ZW

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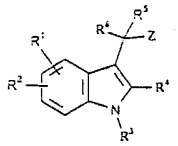
(51) International Patent Classification (Int.Cl.7): C07D209/18; A61K 31/40

(54) Title: Indole Derivatives Useful In Therapy

(57) Abstract: Compounds of formula I, and their pharmaceutically acceptable derivatives.



I

wherein

$R^1$ and $R^2$ are optional substituents and independently represent $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl [optionally substituted by $CO_2H$ or $CO_2(C_{1-6}$ alkyl)], $C_{2-6}$ alkynyl, halogen, $C_{1-3}$ perfluoroalkyl, $(CH_2)_mAr^1$, $(CH_2)_mHet^1$, $(CH_2)_mCONR^7R^8$, $(CH_2)_mCO_2R^8$, $O(CH_2)_qCO_2R^8$, $(CH_2)_mCOR^8$, $(CH_2)_mOR^8$, $O(CH_2)_pOR^8$, $(CH_2)_mNR^7R^8$, $CO_2(CH_2)_qNR^7R^8$, $(CH_2)_mCN$, $S(O)_nR^8$, $SO_2NR^7R^8$, $CONH(CH_2)_mAr^1$ or $CONH(CH_2)_mHet^1$;

$R^3$ represents H, $C_{1-6}$ alkyl, $(CH_2)_pNR^9R^{10}$, $SO_2R^{10}$, $SO_2NR^9R^{10}$, $(CH_2)_mCOR^{10}$, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $(CH_2)_mCONR^9R^{10}$, $(CH_2)_mCO_2R^{10}$, $(CH_2)_pCN$, $(CH_2)_pR^{10}$ or $(CH_2)_pOR^{10}$;

$R^4$ represents H or $C_{1-6}$ alkyl;

$R^5$ represents H or OH;

$R^6$ represents phenyl optionally fused to a heterocyclic ring, the group as a whole being optionally substituted;

$R^{7-10}$ are fully defined herein and may independently represent $Ar^2$ or $Het^2$;

Z represents $CO_2H$, CONH(tetrazol-5-yl), $CONHSO_2O(C_{1-4}$ alkyl), $CO_2Ar^3$, $CO_2(C_{1-6}$ alkyl), tetrazol-5-yl, $CONHSO_2Ar^3$, $CONHSO_2(CH_2)_qAr^3$ or $CONHSO_2(C_{1-6}$ alkyl);

$Ar^{1-3}$ independently represent phenyl, naphthyl, or an aromatic heterocycle, which groups are optionally fused and optionally substituted; and

$Het^1$ and $Het^2$ independently represent a non-aromatic heterocycle which is optionally substituted;

are useful in the treatment of restenosis, renal failure and pulmonary hypertension.

(56) Documents Cited: EP 0617001 A; WO 94/14434 A

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Indole derivatives useful in therapy

This invention relates to indole derivatives useful in the treatment of a variety of diseases including restenosis, renal failure and pulmonary hypertension, and to pharmaceutical formulations containing such compounds.

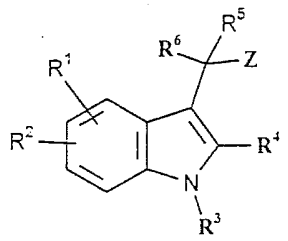
International Patent Application WO 94/14434 discloses indole derivatives which are indicated as endothelin receptor antagonists. European Patent Application 617001 discloses a large number of phenoxyphenylacetic acid derivatives which are also indicated as endothelin receptor antagonists.

Bergman *et al*, Tetrahedron, Vol 31, N° 17, 1975, pages 2063-2073, disclose a number of indole-3-acetic acids. Similar compounds are disclosed by Rusinova *et al*, Khim Geterotsikl Soedin, 1974, (2), 211-213 (see also Chemical Abstracts, Vol 81, N° 7, 19 August 1974, abstract N° 37455a), and Yarovenko *et al*, J Gen Chem USSR (English translation), Vol 39, 1969, page 2039 (see also Beilstein, Registry Number 431619). These compounds are not indicated in any kind of therapy, and proviso (i) below relates to them.

Julian *et al*, J Chem Soc, Chemical Communications, N° 1, 1973, disclose an N-p-chlorobenzoylindole derivative as a by-product of a photo-addition reaction. The compound is not indicated in any kind of therapy, and proviso (ii) below relates to it.

Yamamoto *et al*, Japanese Patent N° 70 041 381 (see also Chemical Abstracts, Vol 75, N° 3, 1971, abstract N° 20189v), disclose an N-p-chlorobenzoylindole derivative which is indicated as an anti-inflammatory. Proviso (iii) below relates to it.

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




I

wherein

$R^1$ and $R^2$ are optional substituents and independently represent $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl [optionally substituted by $CO_2H$ or $CO_2(C_{1-6}$ alkyl)], $C_{2-6}$ alkynyl, halogen, $C_{1-3}$ perfluoroalkyl, $(CH_2)_mAr^1$, $(CH_2)_mHet^1$, $(CH_2)_mCONR^7R^8$, $(CH_2)_mCO_2R^8$, $O(CH_2)_qCO_2R^8$, $(CH_2)_mCOR^8$, $(CH_2)_mOR^8$, $O(CH_2)_pOR^8$, $(CH_2)_mNR^7R^8$, $CO_2(CH_2)_qNR^7R^8$, $(CH_2)_mCN$, $S(O)_nR^8$, $SO_2NR^7R^8$, $CONH(CH_2)_mAr^1$ or $CONH(CH_2)_mHet^1$;

$R^3$ represents H, $C_{1-6}$ alkyl, $(CH_2)_pNR^9R^{10}$, $SO_2R^{10}$, $SO_2NR^9R^{10}$, $(CH_2)_mCOR^{10}$, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $(CH_2)_mCONR^9R^{10}$, $(CH_2)_mCO_2R^{10}$, $(CH_2)_pCN$, $(CH_2)_pR^{10}$ or $(CH_2)_pOR^{10}$;

$R^4$ and $R^9$ independently represent H or $C_{1-6}$ alkyl;

$R^7$ represents H, $C_{1-6}$ alkyl or $C_{1-6}$ alkoxy;

$R^5$ represents H or OH;

$R^6$ represents phenyl optionally fused to a saturated or unsaturated 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, S and O, the group as a whole being optionally substituted by one or more groups selected from $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and halogen, and wherein any members of the heterocyclic ring which are S may be substituted by one or two oxygen atoms;

$R^8$ and $R^{10}$ independently represent H, $C_{1-6}$ alkyl, $Ar^2$, $Het^2$ or $C_{1-6}$ alkyl substituted by $Ar^2$ or $Het^2$;

Z represents $CO_2H$, CONH(tetrazol-5-yl), $CONHSO_2O(C_{1-4}$ alkyl), $CO_2Ar^3$, $CO_2(C_{1-6}$ alkyl), tetrazol-5-yl, $CONHSO_2Ar^3$, $CONHSO_2(CH_2)_qAr^3$ or $CONHSO_2(C_{1-6}$ alkyl);

m represents 0, 1, 2 or 3;

n represents 0, 1 or 2;

p represents 2, 3 or 4;

q represents 1, 2 or 3;

$Ar^{1-3}$ independently represent phenyl, naphthyl, or an aromatic heterocycle having 5 or 6 ring members up to 4 of which are selected from N, S and O, which aromatic heterocycle is optionally fused to a benzene ring, and which phenyl group is optionally fused to an aromatic heterocycle as defined immediately above, the group as a whole being optionally substituted by one or more groups falling within the definition of $R^1$ above; and

$Het^1$ and $Het^2$ independently represent a non-aromatic heterocycle having 5 or 6 ring members up to 4 of which are selected from N, S and O, which group is optionally

substituted by one or more groups falling within the definition of $R^1$ above, and is further optionally substituted by =O or =S;

provided that:

(i) when $R^1$ represents methoxy or is absent, $R^2$ is absent, $R^3$ represents H, $R^4$ represents H, methyl or ethyl, and $R^6$ represents unsubstituted phenyl, then Z does not represent $CO_2H$ or $CO_2(C_{1-6}$ alkyl);

(ii) when $R^1$ and $R^2$ are absent, $R^3$ represents $CO(p\text{-}ClC_6H_4)$, $R^4$ represents H, and $R^6$ represents unsubstituted phenyl, then Z does not represent $CO_2(C_{1-6}$ alkyl); and

(iii) when $R^1$ represents methoxy, $R^2$ is absent, $R^3$ represents $CO(p\text{-}ClC_6H_4)$, $R^4$ represents methyl, and $R^6$ represents unsubstituted phenyl, then Z does not represent $CO_2H$;

or a pharmaceutically acceptable derivative thereof.

Pharmaceutically acceptable derivatives include those compounds in which the functional groups explicitly recited above have been derivatised to provide prodrugs which can be converted to the parent compound *in vivo*. Such prodrugs are discussed in Drugs of Today, Vol 19, 499-538 (1983) and Annual Reports in Medicinal Chemistry, Vol 10, Ch 31 p306-326. In addition, pharmaceutically acceptable derivatives include pharmaceutically acceptable salts, such as alkali metal salts (for example sodium salts) of any acidic groups that may be present.

"Halogen" includes fluorine, chlorine, bromine and iodine.

Alkyl groups which $R^{1-4}$, $R^{6-10}$ and Z represent or comprise may be straight chain, branched or cyclic.

Besides phenyl and naphthyl, specific groups that $Ar^{1-3}$ may represent or comprise include indolyl, pyridinyl, thienyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, thiazolinidyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl and pyrimidinyl.

Specific groups that $Het^1$ and $Het^2$ may represent or comprise include oxazolidinyl, triazolethione, triazolone, oxadiazolone, oxadiazolethione, imidazolidinyl, morpholinyl, piperidinyl and piperazinyl.

Preferred groups of compounds which may be mentioned include those in which:

(a) $R^1$ represents halogen, $(CH_2)_mCONR^7R^8$, $(CH_2)_mCO_2R^8$, $(CH_2)_mCOR^8$, $(CH_2)_mOR^8$ or $(CH_2)_mCN$. In these groups it is preferred that $R^7$ and $R^8$ represent H or $C_{1-6}$ alkyl. Preferably, m is 0 or 1. Thus, specific groups which may be mentioned are $CONH_2$, $CO_2H$, $CH_2OH$, F or $CH_3CO$. $R^1$ is preferably attached to the 6-position of the indole ring.

(b) $R^2$ is absent (i.e. its place on the indole ring is occupied by H).

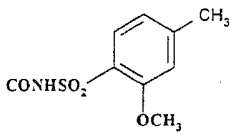
(c) $R^3$ represents H, $C_{1-6}$ alkyl or $(CH_2)_pOR^{10}$. Preferably, $R^{10}$ is $C_{1-6}$ alkyl and p is 2. Thus, specific groups which may be mentioned are methyl and $(CH_2)_2OCH_3$.

(d) $R^4$ represents H.

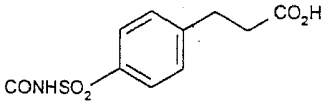
(e) $R^5$ represents H.

(f) $R^6$ represents phenyl fused to a saturated 5-membered heterocyclic ring, for example 3,4-methylenedioxyphenyl.

(g) Z represents $CO_2H$ or $CONHSO_2Ar^3$. Preferably, $Ar^3$ is phenyl substituted by one or more groups selected from $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and $C_{1-6}$ alkyl substituted by carboxy. Thus, specific groups which may be mentioned are:

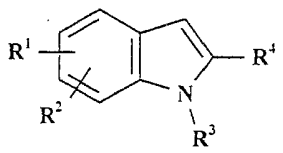



and



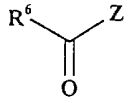

There is further provided a process for the production of the compounds of the invention, comprising:

(a) when $R^5$ represents H, reaction of a compound of formula IIA,




IIA

wherein $R^{1-4}$ are as defined above, with a compound of formula III,

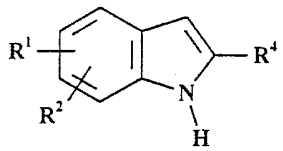


III

wherein $R^6$ and Z are as defined above, in the presence of a Lewis acid or trifluoroacetic acid, and a tri($C_{1-6}$ alkyl)silane;

(b) when $R^5$ represents OH, reaction of a compound of formula IIA, as defined above, with a compound of formula III, as defined above, in the presence of a Lewis acid;

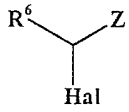
(c) when $R^3$ represents H and $R^5$ represents H, treatment of a compound of formula IIB,



IIB

wherein $R^1$, $R^2$ and $R^4$ are as defined above, with a Grignard reagent, followed by reaction with a compound of formula III, as defined above, followed by treatment with a Lewis acid or trifluoroacetic acid, and a tri($C_{1-6}$ alkyl)silane;

(d) when $R^3$ represents H and $R^5$ represents H, treatment of a compound of formula IIB, as defined above, with a Grignard reagent, followed by reaction with a compound of formula IV,



IV

wherein $R^6$ and Z are as defined above, and Hal represents halogen;

(e) when $R^5$ represents H, reaction of a compound of formula IIA, as defined above, with a compound of formula IV, as defined above, in the presence of a hindered, non-nucleophilic base;

(f) reacting a compound of formula I, in which $R^1$ represents Br, with CO gas in the presence of a palladium catalyst and a reducing agent, to provide the corresponding compound of formula I in which $R^1$ represents CHO;

(g) reacting a compound of formula I, in which $R^1$ represents Br, with CO gas in the presence of a palladium catalyst and a $C_{1-6}$ alkanol, to provide the corresponding compound of formula I in which $R^1$ represents $CO_2$($C_{1-6}$ alkyl);

(h) coupling a compound of formula I in which Z represents $CO_2H$ with a compound of formula VI,

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$H_2NSO_2Ar^3$ VI

wherein $Ar^3$ is as defined above, to provide the corresponding compound of formula I in which Z represents $CONHSO_2Ar^3$; or

(i) reacting a compound of formula I, in which $R^1$ represents Br, with an alkyl lithium reagent and quenching with dimethylformamide or carbon dioxide, to give a corresponding compound in which $R^1$ represents CHO or $CO_2H$ respectively;

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable derivative thereof or vice versa.

In process (a), suitable Lewis acids include boron trifluoride diethyletherate. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dichloromethane, at a temperature below room temperature, for example -40 to -78°C. A preferred tri($C_{1-6}$ alkyl)silane is triethylsilane. Intermediate compounds in which $R^5$ represents OH may be isolated from this process.

In process (b), suitable Lewis acids include boron trifluoride diethyletherate. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dichloromethane, at a temperature below room temperature, for example -40 to -78°C. The reaction is followed by basic work up.

In process (c), suitable Grignard reagents include methylmagnesium iodide. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example toluene, below room temperature, for example -70°C. Suitable Lewis acids include boron trifluoride diethyletherate. The acid treatment may be carried out in a solvent which does not adversely affect the reaction, for example dichloromethane, at a temperature of 0°C to room temperature. A preferred tri($C_{1-6}$ alkyl)silane is triethylsilane.

In process (d), suitable Grignard reagents include methylmagnesium iodide. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example toluene, at or around room temperature. The reaction mixture may be worked up with a weak acid such as aqueous ammonium chloride. Hal is preferably Br.

In process (e), suitable hindered non-nucleophilic bases include 2,6-dimethylpyridine. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dimethylformamide, at an elevated temperature, for example 80°C.

In process (f), suitable palladium catalysts include dichlorobis(triphenylphosphine)-palladium(II). Suitable reducing agents include sodium formate. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dimethylformamide, at an elevated temperature, for example 110°C.

In process (g), suitable palladium catalysts include dichlorobis(triphenylphosphine)-palladium(II). The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dimethylformamide, at an elevated temperature, for example the reflux temperature of the reaction mixture.

In process (h), the reaction may be facilitated by the use of conventional coupling agents, for example N,N-carbonyl diimidazole. When using this agent, the acid is first reacted with the agent (for example in dichloromethane at the reflux temperature of the solvent), and then the product of this reaction is reacted with the amine (preferably in the presence of a strong hindered amine base such as 1,8-diazabicyclo[5.4.0]undec-7-ene, in a solvent such as dichloromethane at the reflux temperature of the solvent). An alternative agent is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide which reacts at room temperature.

In process (i), suitable alkyl lithium reagents include n-butyl lithium. The reaction is carried out by adding the alkyl lithium reagent to the compound of formula I in a solvent such as tetrahydrofuran, at a temperature below room temperature (for example -40 to -78°C), and stirring for about 2 hours. Dimethylformamide or solid carbon dioxide is then added and the reaction mixture allowed to warm to room temperature.

Compounds of formulae IIA, IIB, III, IV and VI are either known or may be prepared by conventional methods well known to those skilled in the art. For example, compounds of formulae IIA and IIB may be prepared by the Fischer, Reissert and Madelung syntheses. In addition, International Patent Application WO 94/14434 discloses a number of routes to

2-carboxy indole derivatives (see page 8 onwards) which may be decarboxylated readily (using copper and quinoline) to give compounds of formulae IIA or IIB in which $R^4$ is H, or reduced to give compounds of formulae IIA or IIB in which $R^4$ is alkyl. Other methods for the preparation of indoles are described by Moyer et al, J Org Chem, 1986, 51, 5106-5110; Wender et al, Tetrahedron, 1983, 39 N° 22, 3767-3776; Uhle, J Am Chem Soc, 1949, 71, 761; Uhle et al, J Am Chem Soc, 1960, 82, 1200; Nagasaka et al, Heterocycles, 1977, 8, 371; Bowman et al, J Chem Soc, Perkin Trans 1, 1972, 1121; Bowman et al, J Chem Soc, Perkin Trans 1, 1972, 1926; and Clark et al, Heterocycles, 1984, 22, 195.

Compounds of formula III in which $R^6$ is an electron-rich group (for example 1,3-benzodioxole) and Z is $CO_2CH_2CH_3$ may be prepared by a Friedel-Crafts acylation between a compound of formula $R^6H$ and the compound of formula $ClCOCO_2CH_2CH_3$. The reaction is preferably carried out in the presence of a Lewis acid (for example $AlCl_3$), in a solvent which does not adversely affect the reaction, for example dichloromethane, below room temperature (for example 0°C).

Compounds of formula III in which $R^6$ is not an electron-rich group (for example groups substituted by halogen or OH) and Z is $CO_2CH_3$ may be prepared by reaction of a compound of formula $R^6Li$ with a compound of formula $CH_3OCOCO_2CH_3$. The reaction may be carried out in a solvent which does not adversely affect the reaction, for example tetrahydrofuran, below room temperature (for example -40°C to -78°C).

Compounds of formula $R^6Li$ may be prepared by reacting a compound of formula $R^6Br$ and butyl lithium. The reaction may be carried out in a solvent which does not adversely affect the reaction, for example tetrahydrofuran, below room temperature (for example -78°C).

Compounds of formula IV may be prepared by halogenating the corresponding alcohol with an agent such as hydrobromic acid. When Z represents $CO_2(C_{1-6}$ alkyl), compounds of formula $R^6CH(OH)Z$ may be prepared by reacting an aldehyde of formula $R^6CHO$ with bromoform under basic conditions, and treating the crude carboxylic acid intermediate with a $C_{1-6}$ alkanol.