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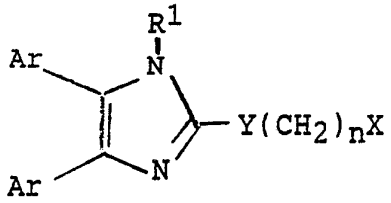
(54) Title: IMIDAZOLE DERIVATIVES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS



(I)

(57) Abstract

Substituted 4,5-diaryl-2-alkoxyimidazoles of structure (I), in which each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl; R^1 is hydrogen, alkyl, optionally substituted phenyl or optionally substituted heteroaryl; Y is oxygen or sulphur; n is 4 to 12; and X is 5-tetrazolyl, SO_3H, $P(O)(OR)_2$, $P(O)(OH)_2$, or P(O)(R)(OR) in which R is hydrogen or alkyl, or a pharmaceutically acceptable salt thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy, inter alia, in the treatment of cardiovascular disorders.

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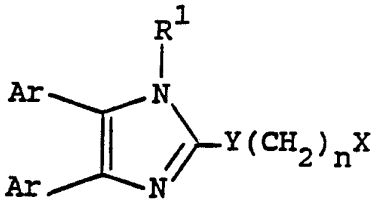
IMIDAZOLE DERIVATIVES, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS

The present invention relates to novel substituted imidazole compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

The present invention therefore provides in a first aspect compounds of structure (I):



(I)

in which

each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;

R^1 is hydrogen, C_{1-4}alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

Y is oxygen or sulphur;

n is 4 to 12; and

X is 5-tetrazolyl, SO_3H, $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_{1-4}alkyl,

or a pharmaceutically acceptable salt thereof.

Suitably, each group Ar is the same and is optionally substituted phenyl or optionally substituted heteroaryl. More suitably, each group Ar is the same and is optionally substituted phenyl. Preferably each group Ar is the same and is unsubstituted phenyl.

Suitably, R^1 is hydrogen, C_{1-4}alkyl, optionally substituted phenyl or optionally substituted heteroaryl.

Preferably R^1 is optionally substituted phenyl; most preferably unsubstituted phenyl.

Suitably, Y is oxygen or sulphur; preferably Y is oxygen.

Suitably, n is 4 to 12; preferably n is 4 to 8, most preferably n is 6 or 7.

Suitably, X is 5-tetrazolyl, SO_3H, $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_{1-4}alkyl. Preferably X is SO_3H.

Suitable substituents for phenyl groups Ar and R^1 include, for example, 1-3 groups which may be the same or different and are selected from C_{1-4}alkyl, haloC_{1-4}alkyl such as CF_3, halogen, hydroxy and C_{1-4}alkoxy.

Suitable heteroaryl groups include, for example, saturated or unsaturated 5- or 6-membered rings comprising 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur.

Preferred such rings include, for example, thienyl and furyl rings.

Particularly preferred compounds of structure (I) include:

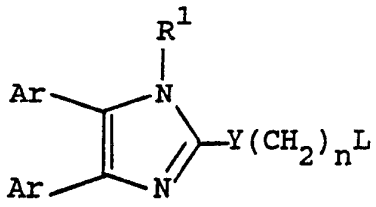
sodium 6-(1,4,5-triphenylimidazol-2-yloxy)hexane-sulphonate;

sodium 7-(1,4,5-triphenylimidazol-2-yloxy)heptane-sulphonate;

7-(1,4,5-triphenylimidazol-2-yloxy)heptanemethyl-phosphinate; and

7-(1,4,5-triphenylimidazol-2-yloxy)heptanephosphonate.

The compounds of structure (I) can be prepared using procedures analogous to those known in the art. The present invention therefore provides in a further aspect a process for the preparation of compounds of structure (I) in which X is other than 5-tetrazolyl which comprises reaction of a compound of structure (II):



(II)

in which
Ar, R^1, Y and n are as described for structure (I) and L is a leaving group, with a suitable source of the group X; and optionally thereafter forming a pharmaceutically acceptable salt thereof.

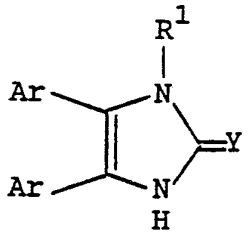
Compounds of structure (I) in which X is 5-tetrazolyl, can be prepared from compounds of structure (II) by standard techniques, for example, when L is bromine, by reaction with sodium cyanide in a suitable solvent such as dimethylsulphoxide, to form the intermediate compound in which L is cyano; followed by reaction with tri-n-butyl tin azide in, for example, tetrahydrofuran to form the desired compound of structure (I).

Suitable leaving groups L will be apparent to those skilled in the art and include, for example, halogen, such as bromine.

Suitable sources of the group X will again be apparent to those skilled in the art and include, for example, where X is SO_3Na, sodium sulphite.

The reaction between the compounds of structure (II) and the source of X is carried out in a solvent at elevated temperature. Preferably, for example where X is SO_3Na the reaction is carried out in aqueous ethanol at reflux temperature for a suitable period to allow the reaction to go to completion; and where X is a phosphorus containing group the reaction is carried out in an organic solvent such as toluene or xylene.

The compounds of structure (II) can be prepared from compounds of structure (III):



(III)

in which
Ar, Y and R^1 are as described for structure (I) by reaction with, for example, a compound of formula $L^1(CH_2)_nL$, in which L and L^1 are suitable leaving groups, in the presence of a base such as potassium carbonate and a suitable solvent such as butanone. Suitable groups L are as described for structure (II). Suitable groups L^1 will be apparent to those skilled in the art, and include halogen, in particular bromine.

Compounds of structure (III) are known or can be prepared by standard techniques.

The compounds of structure (I) and their pharmaceutically acceptable salts have been found to be PGI_2 agonists and as such are useful in therapy for the treatment of disease conditions in which such an effect is beneficial.

More specifically, the compounds are expected to have utility as antithrombotic, vasodilatory, anti-atherosclerotic, antiinflammatory and cytoprotective agents. In particular, as antithrombotic and vasodilatory agents, the compounds are expected to be useful in the treatment of cardiovascular occlusive disorders including spasmodic and thrombotic disorders; coronary heart disease (primary and secondary prevention); stroke; post-operative thrombosis utilisation including post-angioplasty; deep vein thrombosis; peripheral vascular disease and Reynaud's disease. As antiatherosclerotic agents the compounds would be expected to reduce atherosclerotic plaque formation; and as cytoprotective agents the compounds would be expected to protect liver and gastric mucosa, protect against mucosal and ulcerative damage and reduce infarct size in myocardial infarct.

In addition to the foregoing utilities the compounds have antihyperlipidaemic properties and as such are expected to be of use as lipid lowering agents, and in the treatment of atherosclerosis and its sequelae.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example

syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of structure (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the structure (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The present invention also provides a method of mimicking the effects of PGI_2 which comprises administering to a mammal in need thereof an effective amount of a compound of the structure (I) or a pharmaceutically acceptable salt thereof; and a method of treatment of cardiovascular disorders which comprises administering to a mammal in need thereof an effective amount of a compound of the structure (I) or a pharmaceutically acceptable salt thereof.

The pharmaceutically acceptable compounds of the invention will normally be administered to a subject in a daily dosage regimen. For an adult patient this may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the structure (I) or a pharmaceutically

acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

The following Examples serve to illustrate the invention. Temperatures are recorded in degrees centigrade.

EXAMPLE 1

Sodium 6-(1,4,5-triphenylimidazol-2-yloxy)hexanesulphonate

A mixture of 1,4,5-triphenylimidazol-2-one (6.25g), dibromohexane (24.4g) and potassium carbonate (5.53g) in dry butanone (300ml) was heated at reflux temperature for 24 hours. The mixture was cooled and the filtrate evaporated to an oil which was chromatographed on silica gel (hexane/ethyl acetate) to give 1,4,5-triphenyl-2-(6-bromohexyloxy)imidazole (2.8g, 29%) as a white solid, m.p. 87-9°C.
NMR δ ($CDCl_3$) 1.3-1.9 (8H, m, 5 x CH_2), 3.4 (2H, t, $-CH_2Br$), 4.5 (2H, t, $-CH_2O$), 7.0-7.6 (15H, m, 3 x pH) ppm.

1,4,5-Triphenyl-2-(6-bromohexyloxy)imidazole (0.95g) was dissolved in hot ethanol (5ml) and a solution of sodium sulphite (0.25g) in hot water (3ml) was added. The white suspension was heated at reflux for 24 hours then evaporated to dryness. The residue was recrystallised from ethanol then methanol/ethanol to give sodium 6-(1,4,5-triphenylimidazol-2-yloxy)hexane-sulphonate (0.15g, 15%) as a colourless solid, m.p. 265°C.
Found: C, 64.22; H, 5.51; N, 5.32; S, 6.24%
$C_{27}H_{27}N_2NaO_4S$ + 1.2% H_2O + 0.5% EtOH
Requires: C, 64.20; H, 5.57; N, 5.52; S, 6.32%.

EXAMPLE 2

Sodium 7-(1,4,5-triphenylimidazol-2-yloxy)heptane-sulphonate

A mixture of 1,4,5-triphenylimidazol-2-one (15.3g), dibromoheptane (50.6g) and potassium carbonate (13.8g) was heated at reflux temperature in dry butanone (750ml)

for 20 hours. The mixture was cooled, filtered and the filtrate evaporated to an oil which was chromatographed on silica gel (hexane/ethyl acetate) to give 1,4,5-triphenyl-2-(7-bromoheptyloxy)imidazole (5.0g, 21%) as a white solid, m.p. 97-9°C.
NMR δ ($CDCl_3$) 1.3-1.9 (10H, m, 5 x CH_2), 3.4 (2H, t, $-CH_2Br$), 4.5 (2H, t, $-CH_2O$), 7.0-7.6 (15H, m, 3 x Ph) ppm.

A solution of 1,4,5-triphenyl-2-(7-bromoheptyloxy)-imidazole (2.0g) in ethanol (10ml) was refluxed with a solution of sodium sulphite (0.55g) in water (5ml) for 20 hours. More sodium sulphite (0.2g) in water (1ml) was added and refluxed a further 20 hours. The mixture was evaporated to dryness, boiling ethanol added and filtered hot. Chromatography of the filtrate on silica gel (dichloromethane/methanol 5:1) followed by crystallisation from ethanol/isopropanol gave sodium 7-(1,4,5-triphenylimidazol-2-yloxy)heptanesulphonate (0.3g, 15%) as a colourless solid, m.p. 246-8°C.
Found: C, 64.47; H, 5.85; N, 5.09; S, 5.50%
$C_{28}H_{29}N_2NaO_4S$ + 2% isopropanol + 2% water
Requires: C, 64.19; H, 5.96; N, 5.25; S, 6.01%.

EXAMPLE 3

Ethyl 7-(1,4,5-triphenylimidazol-2-yloxy)heptanemethyl-phosphinate

A solution of 1,4,5-triphenyl-2-(7-bromoheptyloxy)-imidazole (1.75g) and diethyl methylphosphonite (2.45g) in toluene (10 ml) was heated at reflux temperature for 48 hours. Methanol and water were added and the mixture evaporated to an oil. This was chromatographed on silica gel (ethyl acetate/ethanol). The resulting oil slowly crystallised and was triturated with ether/petroleum

ether, filtered then recrystallised from ethanol/ether to give ethyl 7-(1,4,5-triphenylimidazol-2-yloxy)heptane-methylphosphinate (1.06g, 57%) as a white solid, m.p. 101-2°C.

Found: C, 72.05; H, 7.26; N, 5.52%

$C_{31}H_{37}N_2O_3P$

Requires: C, 72.07; H, 7.22; N, 5.42%.

EXAMPLE 4

Diethyl 7-(1,4,5-triphenylimidazol-2-yloxy)heptane-phosphonate

A mixture of 1,4,5-triphenyl-3-(7-bromoheptyl)-imidazol-2-one (1.0g) and triethyl phosphite (1.66g) was heated at reflux temperature in xylene (5 ml) for 40 hours. The solution was evaporated to an oil and re-evaporated from ethanol. The oil was partitioned between ether and water, the ether solution was separated, dried over magnesium sulphate and evaporated to an oil which was chromatographed on silica gel (ethyl acetate) to give diethyl 7-(1,4,5-triphenylimidazol-2-yl-oxy)heptanephosphonate as an oil which solidified on standing to a white solid (0.83g; 75%), m.p. 76-7°C.

Found: C, 70.49; H, 7.40; N, 4.94%

$C_{32}H_{39}N_2O_4P$

Requires: C, 70.31; H, 7.19; N, 5.12%.

BIOLOGICAL DATA

METHOD FOR MEASUREMENT OF AGGREGATION OF WASHED HUMAN PLATELETS

Platelets were prepared from freshly drawn human blood. Blood was collected into acid citrate anticoagulant, centrifuged (5 min at 500g), and the upper layer of platelet-rich plasma was removed. This platelet-rich plasma was incubated with aspirin (100μM) for 10 min at 37°C and then centrifuged (15 min at 200g). The platelet pellet was resuspended (at approx. 1.5×10^8 cells/ml) in medium containing NaCl (145mM), KCl (5mM), $MgCl_2$ (1mM), $CaCl_2$ (0.2mM), Hepes (10mM, pH 7.4 at 37°C), glucose (10mM), apyrase (10μg/ml). Aggregation was monitored (as a change in optical density) at 37°C in a 4 channel aggregometer (PAP-4 from Biodata Corp.). Fibrinogen (1mg/ml) and $CaCl_2$ (1mM) were added to aliquots of platelets that were continuously stirred. The test compound (or 0.1% DMSO vehicle) was added 2 min before the aggregatory stimulus (1μM U46619). The extent of aggregation was assessed 4 min after addition of the stimulus, and was calculated as % of the control response in the absence of test compound. Dose-response curves were constructed for measurement of IC_{50} values for each compound.

METHOD FOR MEASUREMENT OF K_I FOR INHIBITION OF [^{3}H]ILOPROST BINDING TO HUMAN PLATELET MEMBRANES

Membranes were prepared from outdated platelet-rich plasma concentrates obtained from the Blood Transfusion Service. The platelets were homogenised in buffer containing Tris-Cl (5mM, pH 7.4 at 20°C) and EDTA

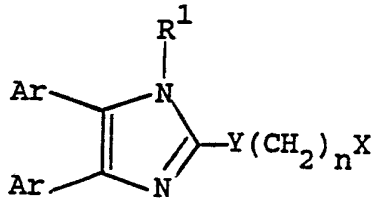
(0.25mM), and then centrifuged (10 min at 26,000g). The membrane pellet was washed twice by homogenisation in buffer containing Tris-Cl (50mM, pH 7.4 at 20°C) and EDTA (0.25 mM), followed by centrifugation. For measurement of [^{3}H]iloprost binding, membranes (0.4-0.8mg) were incubated in the presence of Tris-Cl (50mM, pH 7.4 at 20°C), $MgCl_2$ (4mM), EDTA (40μM), [^{3}H]iloprost (10nM), DMSO (1.85%), and varying concentrations of the test compounds. For determination of non-specific binding, 20μM iloprost was included. The tubes (triplicates for each condition) were set up on ice, and then incubated for 30 min at 37°C. The incubations were terminated by rapid filtration on Whatman GF/B filters using a Brandel Harvester. The filters were washed and then counted for radioactivity. The K_i of the test compounds for inhibition of binding of [^{3}H]iloprost to human platelet membranes was calculated from the IC_{50} for displacement of [^{3}H]iloprost binding.

RESULTS

EXAMPLE NO.	AGGREGATION IC_{50} (μM)	Ki (μM)
EXAMPLE 1	0.072	2.1
EXAMPLE 2	0.042	0.8
EXAMPLE 3	25% @ 30μM	17.8
EXAMPLE 4	63	60.0

Claims:

1. A compound of structure (I):



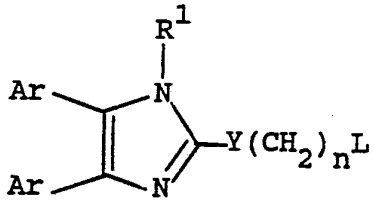
(I)

in which
each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;
R^1 is hydrogen, C_{1-4}alkyl, optionally substituted phenyl or optionally substituted heteroaryl;
Y is oxygen or sulphur;
n is 4 to 12; and
X is 5-tetrazolyl, SO_3H, $P(O)(OR)_2$, $P(O)(OH)_2$, or $P(O)(R)(OR)$ in which R is hydrogen or C_{1-4}alkyl,
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which each group Ar is phenyl, R^1 is phenyl, Y is oxygen and X is SO_3H.

3. A compound according to claim 2 in which n is 6 or 7.

4. A process for preparing a compound according to claim 1 in which X is other than 5-tetrazolyl which comprises reaction of a compound of structure (II):



(II)

in which
Ar, R^1, Y and n are as described for structure (I) and L is a leaving group, with a suitable source of the group X; and optionally thereafter forming a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutical carrier.

6. A compound according to claim 1 for use in therapy.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01544

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 C07D233/70; A61K31/415; C07D233/84; C07D403/12
C07F9/6506

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K ; 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	US,A,3 714 179 (G.D.SEARLE & CO.) 30 January 1973 ---	
A	EP,A,0 019 688 (CIBA-GEIGY AG) 10 December 1980 ---	
A	EP,A,0 104 342 (A.NATTERMANN & CIE.GMBH) 4 April 1984 ---	
A	EP,A,0 130 526 (A.NATTERMANN & CIE.GMBH) 9 January 1985 ---	
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P,A	WO,A,9 110 662 (RHONE-POULENC RORER S.A.) 25 July 1991 ---	

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° Special categories of cited documents : [10]

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"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.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27 NOVEMBER 1991	03. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	DE BUYSER I.A.F.

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101544 SA 51170

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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EP-A-0359197	21-03-90	US-A-	4900744	13-02-90
		AU-A-	4136189	22-03-90
		JP-A-	2174762	06-07-90
WO-A-9110662	25-07-91	None		
WO-A-9109021	27-06-91	AU-A-	7049291	18-07-91