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(12) **BREVET D'INVENTION**

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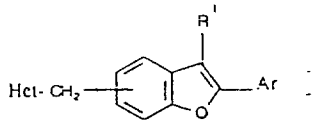
(54) Titre : BENZOFURAN DERIVATIVES.

(57) Abrégé :

The invention provides compounds of the general formula (I)



(I)

or a physiologically acceptable salt, solvate or non-toxic metabolically labile ester thereof

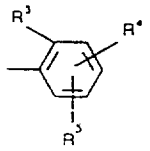
wherein

R^1 represents a hydrogen atom or a halogen atom or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, -CHO, -CO_2H or -COR^2;

Ar represents the group

(suite au verso)

(57) **Abrégé (suite) :**



R^2 represents a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy or the group $-NR^{10}R^{11}$;

R^3 represents a group selected from $-CO_2H$, $-NHSO_2CF_3$ or a C-linked tetrazolyl group;

R^4 and R^5, which may be the same or different, each independently represent a hydrogen atom or a halogen atom or a C_{1-6}alkyl group;

Het represents an N-linked imidazolyl group optionally substituted at the 2-position by a C_{1-6}alkyl, C_{2-6}alkenyl or a C_{1-6}alkylthio group, the imidazolyl group optionally being substituted at the 4- and 5- positions by one or two further substituents selected from a halogen atom or group selected from cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, fluoroC_{1-6}alkyl, $-(CH_2)_mR^6$, $-(CH_2)_nCOR^7$ or $-(CH_2)_pNR^8COR^9$;

R^6 represents a hydroxy or C_{1-6}alkoxy group;

R^7 represents a hydrogen atom or a group selected from hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, phenoxy or the group $-NR^{10}R^{11}$;

R^8 represents a hydrogen atom or a C_{1-6}alkyl group;

R^9 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, phenoxy or the group $-NR^{10}R^{11}$;

R^{10} and R^{11}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-4}alkyl group or $-NR^{10}R^{11}$ forms a saturated heterocyclic ring which has 5 or 6 ring members and may optionally contain in the ring one oxygen atom;

m represents an integer from 1 to 4;

n represents an integer from 0 to 4; and

p represents an integer from 1 to 4.

The compounds may be used in the treatment or prophylaxis of hypertension and diseases associated with cognitive disorders.

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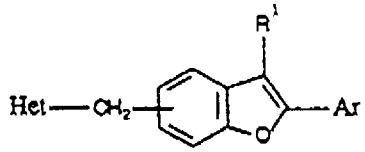
BENZOFURAN DERIVATIVES

This invention relates to benzofuran derivatives, processes for their preparation and pharmaceutical compositions containing them. According to a first aspect of the invention we provide a compound of the general formula (I):

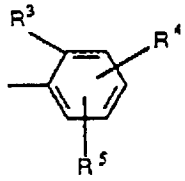


(I)

or a physiologically acceptable salt, solvate (e.g. hydrate) or metabolically labile ester thereof in which

R^1 represents a hydrogen atom or a halogen atom or a group selected from C_{1-6} alkyl, C_{2-6} alkenyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, -CHO, $-CO_2H$ or $-COR^2$;

Ar represents the group



R^2 represents a group selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy or the group $-NR^{10}R^{11}$;

R^3 represents a group selected from $-CO_2H$, $-NHSO_2CF_3$ or a C-linked tetrazolyl group;

R^4 and R^5 which may be the same or different each independently represent a hydrogen atom or a halogen atom or a C_{1-6} alkyl group;

Het represents an N-linked imidazolyl group optionally substituted at the 2-position by a C_{1-6}alkyl, C_{2-6}alkenyl or a C_{1-6}alkylthio group, the imidazolyl group optionally being substituted at the 4- and 5-positions by one or two further substituents selected from a halogen atom or a group selected from cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, fluoroC_{1-6}alkyl, $-(CH_2)_mR^6$, $-(CH_2)_nCOR^7$, or $-(CH_2)_pNR^8COR^9$;

R^6 represents a hydroxy or C_{1-6}alkoxy group;

R^7 represents a hydrogen atom or a group selected from hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, phenoxy or the group $-NR^{10}R^{11}$;

R^8 represents a hydrogen atom or a C_{1-6}alkyl group;

R^9 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, phenoxy or the group $-NR^{10}R^{11}$;

R^{10} and R^{11}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-4} alkyl group or $-NR^{10}R^{11}$ forms a saturated heterocyclic ring which has 5 or 6 ring members and may optionally contain in the ring one oxygen atom;

m represents an integer from 1 to 4, preferably 1 or 2, especially 1;

n represents an integer from 0 to 4, preferably 0, 1 or 2, especially 0 or 1; and

p represents an integer from 1 to 4, preferably 1 or 2..

Where optical isomers may exist formula (I) is intended to cover all enantiomers, diastereoisomers and mixtures thereof including racemates. Compounds containing one or two double bonds may exist in the cis or trans configuration.

The invention also includes within its scope the solvates, especially the hydrates of compounds of general formula (I).

Within the above definition the term 'alkyl' or 'alkoxy' as a group or part of a group means that the group is straight or branched. The term 'alkenyl' as a group or part of a group means that the group is straight or branched and contains at least one carbon-carbon double bond.

The term 'halogen' means a fluorine, chlorine, bromine or iodine atom.

The term 'fluoroC_{1-6}alkyl' means a C_{1-6}alkyl group in which one or more hydrogen atoms have been replaced by a fluorine atom, for example, $-CH_2CF_3$. Particularly preferred are 'perfluoroC_{1-3}alkyl' groups meaning a fully fluorinated C_{1-3}alkyl group, i.e. trifluoromethyl, pentafluoroethyl, heptafluoropropyl or heptafluoroisopropyl.

Within the above definition when $-NR^{10}R^{11}$ represents a saturated heterocyclic ring, this contains 5 or 6 ring members, one of which may be an oxygen atom. Suitable heterocyclic groups are a pyrrolidino, piperidino or morpholino group.

A preferred class of compounds of general formula (I) is that wherein the group Het is substituted at the 2-position by a hydrogen atom or a C_{1-5}alkyl, especially a C_{3-5} alkyl group or a C_{3-5}alkenyl

group. Particularly preferred are those compounds wherein the 2-position substituent is an ethyl, n-propyl or n-butyl group, especially an n-butyl group. Conveniently, the C_{3-5}alkenyl group may be a but-1-enyl group.

Another preferred class of compounds of general formula (I) is that wherein the group Het is optionally substituted by one or two further substituents selected from a halogen atom or a group selected from C_{1-6}alkyl, $-(CH_2)_mR^6$ or $-(CH_2)_nCOR^7$. In particular, R^6 represents a hydroxy or C_{1-6}alkoxy group, and preferably a hydroxy, methoxy, ethoxy, propoxy or butoxy group, and especially a hydroxy or methoxy group. R^7, in particular, represents a hydrogen atom or a hydroxy, C_{1-6} alkoxy or $-NR^{10}R^{11}$ group (especially wherein R^{10} and R^{11} each independently represent a hydrogen atom or a C_{1-4}alkyl group), and preferably a hydrogen atom or a hydroxy, methoxy, ethoxy, propoxy or butoxy group, and especially a hydrogen atom or a hydroxy or methoxy group, and m is 1 or 2 and n is 0, 1 or 2.

In particularly preferred embodiments of the present invention, the substituents are chosen from a chlorine atom and a group selected from $-CH_2OH$, $-CHO$, $-CH_2OCH_3$, $-CO_2H$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CONH_2$ and $-CONHCH_3$.

A yet further preferred class of compounds of general formula (I) is that wherein R^1 represents a hydrogen atom or a halogen atom or a group selected from C_{1-6}alkyl, C_{1-6}alkoxy or fluoroC_{1-6}alkyl, and in particular a hydrogen atom or halogen atom or a C_{1-3}alkyl group. Especially preferred are compounds wherein R^1 is a bromine atom.

Conveniently, in the compounds of general formula (I), the group Het-CH_2- is attached at the 5- or 6-position on the benzofuran ring, and especially the 5-position.

Also conveniently, in the compounds of general formula (I), R^3 may be the group $-CO_2H$, or a C-linked tetrazolyl group. Still conveniently, in the compounds of general formula (I), R^4 and R^5 may each independently represent a hydrogen atom or a halogen atom. In particular R^4 and R^5 each represent hydrogen atoms.

A particularly preferred compound of the invention is:

1-[[3-bromo-2-[2-(1H-tetrazol-5-yl)phenyl]-5-benzofuranyl]methyl]-2-butyl-4-chloro-1H-imidazole-5-carboxylic acid;

and physiologically acceptable salts, solvates and metabolically labile esters thereof.

The physiologically acceptable acid addition salts of the compounds of formula (I) may be derived from inorganic or organic acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, methanesulphonates or trifluoroacetates.

The compounds may also form salts with suitable bases. Examples of such salts are alkali metal (e.g. sodium or potassium), alkaline earth metal (e.g. calcium or magnesium), ammonium and substituted ammonium (e.g. dimethylammonium, triethylammonium, 2-hydroxyethyldimethylammonium, piperazinium, N,N-dimethylpiperazinium, tetralkylammonium, piperidinium, ethylenediammonium and choline).

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable, but other salts may find use, for example, in the preparation of the compounds of formula (I) and the physiologically acceptable salts thereof.

It will be further appreciated that the compounds of general formula (I) may be chemically modified in the form of compounds which <u>in vivo</u> (for example, by enzymic attack) will provide the parent compounds of general formula (I). Such prodrugs may be, for example, physiologically acceptable metabolically labile ester derivatives. These may be formed by esterification, for example of any of the carboxylic acid groups in the parent compound of general formula (I), with prior protection of any other reactive groups present in the molecule. Examples of such esters include lower alkyl esters (e.g. methyl or ethyl esters), alkenyl esters (e.g. vinyl or allyl esters), alkynyl esters(e.g. ethynyl or propynyl esters), alkoxyalkyl esters, (e.g. methoxymethyl or 2-methoxyethyl esters), alkylthioalkyl esters (e.g. methylthiomethyl esters) haloalkyl esters (e.g. 2-iodoethyl or 2,2,2,-trichloromethyl esters), alkanoyloxyalkyl esters (e.g. acetoxymethyl, 1-acetoxyethyl or pivaloyloxymethyl esters), alkoxycarbonyloxyalkyl esters (e.g. 1-ethoxycarbonyloxyethyl or 1-methoxycarbonyloxyethyl esters), aroyloxyalkyl esters (e.g. benzoyloxymethyl or 1-benzoyloxyethyl esters), substituted or unsubstituted aralkyl esters (e.g. benzyl or 4-amidobenzyl esters), substituted or unsubstituted aminoalkyl

esters (e.g aminoethyl or 2-N,N-dimethylaminoethyl esters) or hydroxyalkyl esters (e.g. 2-hydroxyethyl or 2,3-dihydroxypropyl esters).

In addition to the above ester derivatives the present invention includes within its scope compounds of general formula (I) in the form of other physiologically acceptable equivalents, i.e. physiologically acceptable compounds which, like the metabolically labile esters, are converted in vivo into the parent compounds of general formula (I).

According to a second aspect of the present invention we provide a compound of formula (I) or a physiologically acceptable salt, solvate or metabolically labile ester thereof for use in therapy.

In particular, the compounds of the invention may be used in the treatment or prophylaxis of hypertension. They are also potentially useful for the treatment of cognitive disorders such as dementia (e.g. Alzheimer's disease) and other diseases such as renal failure, hyperaldosteronism, thrombosis, cardiac insufficiency, congestive heart failure, post-myocardial infarction, cerebrovascular disorders, glaucoma and disorders of intracellular homeostasis.

According to a further aspect of the present invention we provide a compound of formula (I) or a physiologically acceptable salt, solvate or metabolically labile ester thereof for use in the treatment of the aforementioned diseases, especially hypertension.

According to another aspect of the present invention we provide a compound of formula (I) or a physiologically acceptable salt, solvate or metabolically labile ester solvate thereof for the manufacture of a therapeutic agent for the treatment of the aforementioned diseases, especially hypertension.

According to a further aspect of the present invention we provide a method of treating the aforementioned diseases, especially hypertension, which method comprises administering an effective amount to a patient in need of such treatment of a compound of formula (I) or a physiologically acceptable salt, solvate or metabolically labile ester thereof.

It will be appreciated that the compounds of formula (I) or a physiologically acceptable salt, solvate, or metabolically labile

ester thereof may advantageously be used in conjunction with one or more other therapeutic agents, such as for example diuretics and/or different antihypertensive agents such as β-blockers, calcium channel blockers or ACE inhibitors. It is to be understood that such combination therapy constitutes a further aspect of the present invention.

It will be further appreciated that reference herein to treatment extends to prophylaxis as well as to the treatment and relief of established symptoms.

While it is possible that a compound of general formula (I) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The compounds of formula (I) and their physiologically acceptable salts, solvates and metabolically labile esters may be formulated for administration in any convenient way, and the invention also includes within its scope pharmaceutical compositions comprising at least one compound of formula (I) or a physiologically acceptable salt, solvate or metabolically labile ester thereof adapted for use in human or veterinary medicine. Such compositions may be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Thus, the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, microcrystalline cellulose or maize-starch; lubricants, for example, magnesium stearate or stearic acid; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be

presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup or carboxymethyl cellulose; emulsifying agents, for example, sorbitan mono-oleate; non-aqueous vehicles (which may include edible oils), for example, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The compounds or their salts or esters may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides. For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

It will be appreciated that both tablets and capsules may be manufactured in the form of sustained release formulations, such that they provide a controlled continuous release of the compounds according to the invention over a period of hours.

The compounds of formula (I) and their physiologically acceptable salts, solvates and metabolically labile esters may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoro methane, dichlorotetrafluoroethane or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the

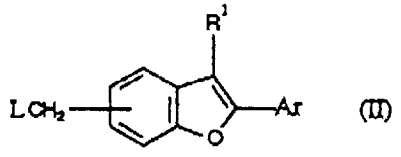
compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The pharmaceutical formulations according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

It will be appreciated that the amount of a compound of general formula (I) required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or veterinarian. In general, however, when the compositions comprise dosage units, each unit will preferably contain 5mg to 500mg, advantageously where the compounds are to be administered orally 25mg to 400mg of the active compound. The daily dosage as employed for adult human treatment will preferably range from 5mg to 3g, most preferably from 25mg to 1g which may be administered in 1 to 4 daily doses.

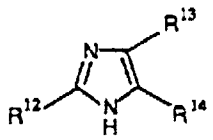
The compounds of the invention may be prepared by a number of processes as described below wherein the various groups are as defined for general formula (I) unless otherwise specified.

Thus, according to a further aspect of the present invention we provide a process (A) for preparing the compounds of general formula (I) which comprises treating a compound of general formula (II)



(II)

(wherein L is a leaving group, for example a halogen atom such as chlorine, bromine or iodine, or a hydrocarbylsulphonyloxy group such as methanesulphonyloxy, or p-toluenesulphonyloxy and R^1 and Ar are as defined in general formula (I)) with an imidazole of formula (III)



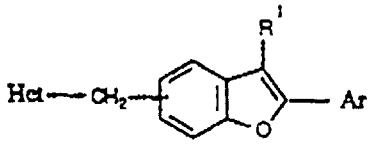
(III)

(wherein R^{12} represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl or C_{1-6}alkylthio; R^{13} and R^{14} which may be the same or different each independently represent a hydrogen or halogen atom, or a group selected from cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, fluoroC_{1-6}alkyl, $-(CH_2)_mR^6$, $-(CH_2)_nCOR^7$, $-(CH_2)_pNR^8COR^9$; and R^6, R^7, R^8, R^9, m, n and p are as defined in general formula (I)) followed by the removal of any protecting groups where present, as described hereinafter.

The reaction is preferably effected under basic conditions, for example, in the presence of sodium hydride, potassium carbonate or sodium methoxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran or dioxan, a ketone e.g. butanone or methyl isobutyl ketone, or a substituted amide e.g. dimethylformamide, at a temperature between 0^0C and the reflux temperature of the solvent.

The intermediate compounds of general formula (II) and their acid addition salts are novel compounds and form a further aspect of the present invention.

In another general process (B) a compound of general formula (I) may be obtained by deprotection of a protected intermediate of general formula (IV)



(IV)

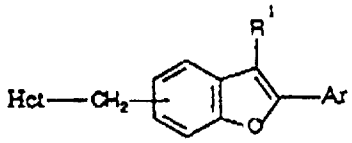
(wherein R^1, Ar and Het are as defined in general formula (I) except that at least one reactive group is blocked by a protecting group).

The protecting groups may be any conventional protecting groups, for example as described in "Protective Groups in Organic Synthesis" by Theodora Greene (John Wiley and Sons Inc., 1981). Examples of carboxyl protecting groups include C_{1-6} alkyl such as methyl or t-butyl, or C_{7-10} aralkyl such as benzyl.

When R^3 is a tetrazole group, this may be protected with, for example, the trityl group -C(phenyl)$_3$, or a p-nitrobenzyl or 1-ethoxyethyl group.

Deprotection to yield the compound of general formula (I) may be effected using conventional techniques. Thus, for example, aralkyl groups may be cleaved by hydrogenolysis in a suitable organic solvent such as an alcohol, e.g. ethanol, in the presence of a noble metal catalyst such as palladium or platinum or an oxide thereof on a support such as charcoal, and conveniently at room temperature and pressure. Carboxyl protecting groups such as alkyl groups may be cleaved by hydrolysis using a base such as an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide) in a suitable solvent (e.g. an aqueous alcohol such as methanol or ethanol) at any suitable temperature up to reflux. Deprotection of the tetrazole group when protected with a trityl group may be effected by acid hydrolysis using trifluoroacetic acid or a mineral acid such as hydrochloric acid in a suitable solvent such as ethanol conveniently at room temperature. Alternatively, when possible, deprotection of the tetrazolyl group can be effected by catalytic hydrogenation as previously described.

In another general process (C) a compound of general formula (I) in which the substituent R^3 in the group Ar represents a C-linked tetrazolyl group (and the imidazolyl group represented by Het is not substituted by a cyano group), may also be prepared from a compound of general formula (Ia)



(Ia)

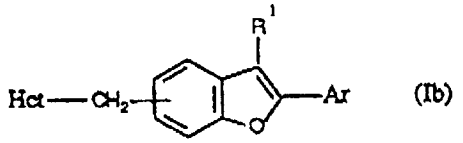
(wherein R^1, Ar and Het are as defined in general formula (I) except that in the group Ar, R^3 represents a nitrile group) by reaction with a suitable azide such as sodium azide, ammonium azide (preferably prepared in situ from sodium azide and ammonium chloride), trialkyl-(e.g triethyl) ammonium azide (preferably prepared in situ from sodium azide and a trialkylamine (e.g. triethylamine)) or tributyl tin azide. The reaction is conveniently effected in a solvent such as xylene at an elevated

temperature, such as the reflux temperature of the solvent, for between 1 and 10 days. Where the azide is tributyl tin azide the reaction may conveniently be effected in the absence of a solvent at a temperature between room temperature and 180°C. Such a reaction leaves the tetrazolyl group protected with a tributyl tin group, which can readily be removed using aqueous base or acid. Where aqueous base is used to effect this deprotection, the compound may be treated with an aqueous acid to liberate the free acid.

Compounds of general formula (Ia) may be prepared by processes analogous to those described herein commencing from a compound of formula (VIII) and a corresponding benzofuran intermediate.

The intermediate compounds of general formula (Ia) and their acid addition salts are novel compounds and form a further aspect of the present invention.

In another general process (D) a compound of general formula (I) in which the substituent R^3 in the group Ar represents $-NHSO_2CF_3$, may also be prepared from a compound of general formula (Ib)



(Ib)

(wherein R^1, Ar and Het are as defined in general formula (I) except that in the group Ar, R^3 represents an amino group) by reaction with trifluoromethanesulphonic anhydride or trifluoromethylsulphonyl chloride, in a suitable solvent such as a halogenated hydrocarbon e.g. chloroform or dichloromethane In the presence of a base e.g. triethylamine.

Compounds of general formula (Ib) may be prepared by processes analogous to those described herein commencing from a compound of formula (IX) and a corresponding benzofuran intermediate.

Alternatively, compounds of general formula (Ib) may be prepared by a Curtius rearrangement of a compound of formula (I) wherein R^3 in the group Ar is $-CO_2H$ (provided that this is the only carboxyl group in the molecule) using, for example, diphenylphosphorylazide in the presence of a base such as triethylamine and in a solvent such as an alcohol (e.g. tert-

butanol) to form a carbamate followed by deprotection of the amine in a conventional manner, for example by acid hydrolysis using hydrochloric acid in a solvent such as ethanol.

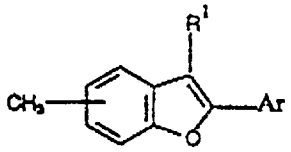
The intermediate compounds of general formula (Ib) and their acid addition salts are novel compounds and form a further aspect of the present invention.

In the processes (A),(B), (C) and (D) described above, the compounds of general formula (I) may be obtained in the form of a salt, conveniently in the form of a physiologically acceptable salt. Where desired, such salts may be converted into the corresponding free acids or free bases using conventional methods.

Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting a compound of general formula (I) with an appropriate acid or base in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol, e.g. methanol, ethanol or isopropanol.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of general formula (I), using conventional methods.

The intermediate compounds of general formula (II) may be prepared from a compound of formula (V):



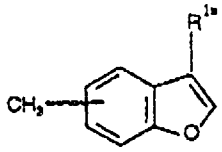
(V)

using any suitable reagent well known in the art for converting the methyl on the 6-membered ring into the group $-CH_2L$ (wherein L is as defined above). Thus, for example, when L is a halogen atom, a compound of formula (V) can be converted into a compound of general formula (II) using N-chloro amides, tert-butyl hypochlorite or N-bromosuccinimide. Halogenation of the side chain may be catalysed by light, thus the reaction can be illuminated with a suitable artificial light source, and preferably in the presence of a free radical initiator such as azobisisobutyronitrile (AIBN) or benzoyl peroxide.

Compounds of formula (V) wherein R^1 is a halogen atom, for example, a bromine atom, may be prepared by halogenation of a

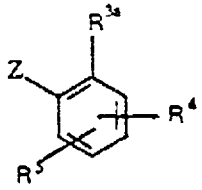
compound of formula (V) wherein R^1 represents a hydrogen atom, using for example, bromine, in a suitable solvent such as a halogenated hydrocarbon, e.g. carbon tetrachloride.

Compounds of formula (V) may be prepared by reaction of a compound of formula (VI)



(VI)

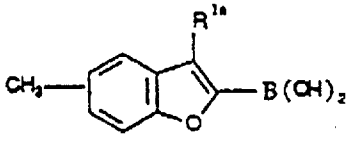
(wherein R^{1a} represents a hydrogen atom or a group selected from C_{1-6}alkyl or C_{2-6}alkenyl) with a compound of formula (VII)



(VII)

(wherein Z represents a bromine or iodine atom or the group $-OSO_2CF_3$, R^4 and R^5 are as defined in general formula (I) and R^{3a} is as defined for R^3 in general formula (I) or is a protected derivative thereof).

The compound of formula (VI) is first treated with an alkyl lithium compound such as n-butyl lithium at a reduced temperature, for example, between -100^0C and 0^0C in a solvent such as an ether (e.g. tetrahydrofuran). The mixture is then treated with a trialkylborate compound such as triisopropylborate and the temperature conveniently brought up to room temperature. Subsequently, water may be added and the mixture treated with a mineral acid such as sulphuric acid thus producing a compound of formula (VIa)



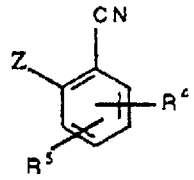
(VIa)

The intermediate compound of formula (VIa) is then reacted with a compound of formula (VII) in the presence of a palladium (0) compound such as tetrakis(triphenylphosphine) palladium (0) in a solvent such as an ether (e.g. dimethoxyethane), and in the presence of a base such as sodium carbonate or thallium hydroxide. The

reaction is conveniently effected at an elevated temperature, such as the reflux temperature of the solvent.

Compounds of formula (V) in which the substituent R^3 in the group Ar represents a C-linked tetrazolyl group may be prepared from a precursor of a compound of formula (V) wherein the substituent R^3 represents a nitrile group using the reagents and conditions described in process (C).

Similarly, intermediates of formula (VII) wherein R^{3a} represents a C-linked tetrazolyl group may be prepared from a compound of formula (VIII)

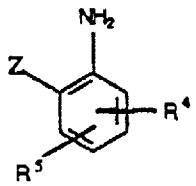


(VIII)

(followed where necessary by protection of any reactive groups), using methods well-known in the art such as those described in process (C).

Compounds of formula (V) in which the substituent R^3 in the group Ar is $-NHSO_2CF_3$ may be prepared from a precursor of a compound of formula (V) wherein the substituent R^3 is an amine group using the reagents and conditions described in process (D).

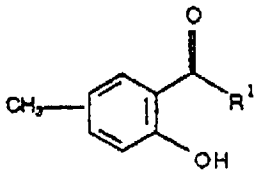
Similarly, intermediates of formula (VII) wherein R^{3a} represents $-NHSO_2CF_3$ may be prepared from a compound of formula (IX),



(IX)

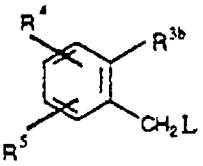
(followed where necessary by the protection of any reactive group) using methods well known in the art such as those described in process (D).

Compounds of formula (V) may also be prepared by an intramolecular cyclisation reaction of a compound of formula (X)



(X)

(wherein R^1 is as previously defined) with a suitably substituted benzene of formula (XI)



(XI)

(wherein L is as previously defined and R^{3b} is as defined for R^{3a} in formula (VII) or is a nitrile group suitable for subsequent conversion into a tetrazolyl group or is an amino group suitable for conversion into $-NHSO_2CF_3$), in the presence of a base such as sodium hydride or potassium carbonate. The cyclisation is a two step reaction which requires one equivalent of base per step. It will be appreciated however that the reaction can be effected in the presence of two equivalents of base to avoid the need to isolate the intermediate. The reaction is conveniently effected in a solvent such as an ether e.g tetrahydrofuran, an alcohol e.g ethanol or a substituted amide e.g dimethylformamide, at a temperature between room temperature and the reflux temperature of the solvent.

It will be appreciated that compounds of formula (V) in which R^1 represents a hydrogen or halogen atom may also be converted into compounds of formula (V) in which R^1 represents the group methyl (via hydrogenolysis of the Mannich base), -CHO or $-COR^2$ (wherein R^2 is as defined in general formula (I)) using techniques well known in the art, such as those described in "Heterocyclic Chemistry" by J.A. Joule and G.F. Smith, Van Nostrand Reinhold Company, London (1972), "Heterocyclic Chemistry" by A. Albert, 2nd Edition, The Athlone Press, London (1968), "Heterocyclic Compounds", Vol. 29 by A. Mustafa, John Wiley and Sons Inc., New York (1974), "Heterocyclic Compounds", Vol. 2 by R.C. Elderfield, John Wiley and Sons Inc., New York (1951) and "Advances in Heterocyclic Chemistry", Vol. 29 by A.R. Katritsky and A.J. Boulton, Academic Press, New York (1981).

The imidazoles of formula (III) may be prepared as described in European Specification No. 0253310A and in US Patent No. 4355040 or by methods analogous to those described therein. The content of these references is hereby incorporated by reference.

Intermediates of formulae (VI), (VII), (VIII), (IX), (X) and (XI), are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

The following examples illustrate the invention. Temperatures are in ^{0}C. "Dried" refers to drying using magnesium sulphate. Thin layer chromatography (t.l.c.) was carried out over silica and column chromatography was carried out on silica (Merck 9385 unless otherwise stated), using one of the following solvent systems : A - ether:hexane, B - ether: dichloromethane, C - dichloromethane:ethanol:conc. aqueous ammonia, D- dichloromethane:ethyl acetate, or E-dichloromethane:ether:acetic acid. The following abbreviations are used : THF - tetrahydrofuran; DME - dimethoxyethane; AIBN - azobisisobutyronitrile; DMF - dimethylformamide; TMEDA - tetramethylethylenediamine; NBS - N-bromosuccinimide; DMAP- 4-dimethylaminopyridine; DEAD - diethyl azodicarboxylate.

Intermediate 1

5-Methylbenzofuran-2-boronic acid

n-Butyl lithium (35.16ml) was added dropwise to a stirred solution of TMEDA (9.58ml) and 5-methylbenzofuran (8.22g) in ether (250ml) maintaining the temperature below - 60^{0}C throughout. The solution was warmed to about -10^{0}C over 45 minutes and stirred at this temperature for 30 minutes. A precipitate formed on warming. The suspension was cooled and triisopropylborate (43ml) was added, maintaining the temperature below -60^{0}C. The solution was warmed gradually to room temperature before quenching with 2N HCl (70ml). The mixture was extracted with ether (3x50ml) and the combined organic extracts washed with 2N HCl (4x30ml), water (2x30ml) and dried before evaporation to give the title compound as an orange solid (12.75g).

t.l.c. System A (1:1), Rf 0.3.

Intermediate 2

2-(5-Methyl-2-benzofuranyl)benzonitrile

Intermediate 1 (20g) was added to a stirred solution of 2-bromobenzonitrile (10.34g) and tetrakistriphenylphosphine palladium (0) (1.5g) in DME (200ml) and 8% $NaHCO_3$ (50ml) at reflux under nitrogen. Further catalyst (1.5g) was added and the reaction continued overnight. The reaction was cooled to room temperature and diluted with ether (200ml). The organic layer was separated, washed with water (3x100ml) and dried. Filtration and evaporation gave a white solid which was purified by chromatography eluting with system A (1:9) to give the title compound (10.58g) as a white solid. T.l.c. System A (1:9), Rf 0.45.

Intermediate 2 was also prepared by the alternative two-step reaction:

a) 2-Hydroxy-5-methylbenzaldehyde

p-Cresol (100g) in dry THF(100ml) was added dropwise to a mechanically stirred, freshly prepared solution of ethyl magnesium bromide [magnesium (25.0g) and bromoethane (75ml)] in THF (500ml) under nitrogen at a rate which maintained a slow reflux (about 30mins). After a further 30mins toluene (1.2l) was added, followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (125ml), and paraformaldehyde (70g). The mixture was then heated at reflux for 16h. The mixture was concentrated by distillation and aqueous hydrochloric acid (2M, 600ml) then added. Water (600ml) was added and the mixture filtered through "hyflo". The organic phase was separated, dried, filtered and concentrated in vacuo to give a brown oil. The oil was steam distilled and the product extracted from the distillate with ether (1 litre). The organic extract was dried, filtered and concentrated in vacuo to give a pale yellow slurry which was cooled to -10^0C, triturated with ether (precooled to -78^0C, 100ml), filtered off rapidly and washed with ether (precooled to -78^0C) to give the title compound as colourless needles, (131.4g).

T.l.c. System A (1:5) Rf 0.5.

b) 2-(5-Methyl-2-benzofuranyl)benzonitrile

A solution of the product of step (a) (130g) in dry DMF (400ml) was added dropwise to a solution of sodium methoxide (56.2g) in ethanol

(400ml) mechanically stirred under nitrogen. After a further 20mins, a solution of 2-(bromomethyl)benzonitrile (182.2g) in dry DMF (400ml) was added dropwise. The mixture was then heated to 75°C for 30min. The solution was allowed to cool for 1h. A slurry of sodium methoxide (56.2g) in dry DMF (100ml) was added and the mixture heated at reflux for 1.5h. The mixture was concentrated in vacuo and then poured into iced water. The solid was collected, and then triturated with methanol to give the title compound (Intermediate 2) as a beige solid (149.4g).

T.l.c. System A (1:9) Rf 0.4.

Intermediate 3

2-(3-Bromo-5-methyl-2-benzofuranyl)benzonitrile

A solution of Intermediate 2 (5.0g) in dichloromethane (80ml) was cooled to -20°C and treated dropwise with 1M bromine in carbon tetrachloride (32ml). The mixture was stirred at -20°C for 1h before being warmed to room temperature. After 1h at room temperature the reaction mixture was filtered and evaporated. The residue was triturated with ether and the resultant solid collected to give the title compound as an orange solid (3.54g).

T.l.c. System A (1:9), Rf 0.40.

Intermediate 4

2-[3-Bromo-5-(bromomethyl)-2-benzofuranyl]benzonitrile

A solution of Intermediate 3 (1.70g) and NBS (0.76g) in carbon tetrachloride (30ml) was heated to reflux under nitrogen with benzoyl peroxide (0.08g). After 18h the reaction was cooled to room temperature, filtered and the concentrated in vacuo. The residue was triturated with ether to give the title compound as a colourless solid (0.58g).

T.l.c. System A (1:6), Rf 0.25.

Intermediate 5

2-[3-Bromo-5-[[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-yl] methyl]-2-benzofuranyl] benzonitrile

A solution of 2-butyl-4-chloro-1H-imidazole-5-methanol (1.23g) and sodium methoxide (0.24g) in DMF (10ml) was treated with Intermediate 4 (1.7g) and stirred at room temperture overnight. The solvent

volume was reduced and the residue diluted with dichloromethane, washed with water (2 x 30ml) and dried. Filtration and evaporation gave a yellow oil which was purified by chromatography eluting with system D (4:1) to give the title compound (0.57g).
T.l.c. System D (4:1), Rf 0.45.

Intermediate 6

5-[2-(5-Methyl-2-benzofuranyl)phenyl]-1H-tetrazole

A suspension of Intermediate 2 (94g) in tri-n-butyl tin azide (268g) was heated at 100-125^{0}C for 1.25h under nitrogen. The resulting solution was then heated at 155-160^{0}C for 2h under nitrogen, then poured into a solution of aqueous sodium hydroxide (0.8N, 3070ml). This solution was extracted with ether. The aqueous phase was acidified to pH1 with 5N hydrochloric acid and the resulting precipitate filtered, washed with water and dried under vacuum. The solid was dissolved in ethyl acetate, washed with brine and dried. The solvent was evaporated to give the title compound as a buff-coloured solid (100.3g).
T.lc. System A (1:1), Rf 0.2.

Intermediate 7

5-[2-(3-Bromo-5-methyl-2-benzofuranyl)phenyl]-1H-tetrazole

A solution of bromine (58g), in carbon tetrachloride (140ml) was added dropwise over 35min to a mechanically stirred solution of Intermediate 6 (50g) in dry dioxan (2090ml) at room temperature under nitrogen. The resulting solution was stirred at room temperature for 3h, then cyclohexene (63ml) was added. Another preparation of the product was carried out simultaneously on the same scale as described above, and at this stage they were combined. The solvent was evaporated and the residual brown oil (260g) partitioned between ether and aqueous sodium hydroxide. The alkaline solution was acidified to pH1 with hydrochloric acid, then extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried and evaporated to give a buff solid (125g) which was triturated under hot toluene, cooled and filtered off to give the title compound as a cream coloured solid (101.8g).
T.l.c. Ether/petroleum ether/acetic acid (50:50:1), Rf 0.27.

Intermediate 8

5-[2-(3-Bromo-5-methyl-2-benzofuranyl)phenyl]-2-(triphenylmethyl)-2H-tetrazole

Triethylamine (57.4g) was added to a mechanically stirred suspension of Intermediate 7 (101g) in dry dichloromethane (2.9 litres) at room temperature under nitrogen. Triphenylmethyl chloride (79.3g) followed by DMAP (1.0g) were added at room temperature and the mixture stirred for 3h under nitrogen. The reaction mixture was washed with water, then brine and dried. The solvent was filtered and concentrated to a volume of about 1.2 litres then filtered through silica (Merck 9385, 14cm diam. column). Elution with dichloromethane gave a colourless solid (158.4g) which was triturated with ether and filtered to give the title compound as a colourless solid (147.9g).

T.l.c. (Dichloromethane/hexane 1:1), Rf 0.28

Intermediate 9

5-[2-[3-Bromo-5-(bromomethyl)-2-benzofuranyl]phenyl]-2-(triphenylmethyl)-2H-tetrazole

Intermediate 8 (74g) was dissolved in carbon tetrachloride (2050ml) by heating the suspension to reflux. The resulting colourless solution was allowed to cool to 50^0C then NBS (22.1g) was added, followed by benzoyl peroxide (1.1g). The reaction mixture was heated at reflux for 3.25h, under nitrogen, then allowed to cool to room temperature. The reaction mixture was washed with water then brine. Another preparation of the product was carried out simultaneously on the same scale as described above, and at this stage they were combined and dried. The solvent was evaporated to give a colourless solid (168g) which was triturated with ether/methanol (1:1) and filtered to give the title compound as a colourless solid (160.8g).

T.l.c. (Dichloromethane/hexane 1:1), Rf 0.15.

Intermediate 10

2-Butyl-4-chloro-1H-imidazole-5-carboxaldehyde

A suspension of 2-butyl-4-chloro-1H-imidazole-5-methanol (22.0g) in dichloromethane:1,4-dioxan (2:1) (690ml) was treated with manganese dioxide (63.15g) and the reaction mixture heated at reflux under

nitrogen for 3.5h. The reaction mixture was cooled, filtered and the filtrate evaporated to leave an off-white solid. The residue was triturated with petroleum ether, filtered and dried to give the title compound as a white solid (17.9g) m.p. 98-99^{0}C.

Intermediate 11

1-[[3-Bromo-2-[2-[2-(triphenylmethyl)-2H-tetrazol-5-yl]phenyl]-5-benzofuranyl]methyl]-2-butyl-4-chloro-1H-imidazole-5-carboxaldehyde

A mixture of Intermediate 10 (500mg), Intermediate 9 (2.73g) and potassium carbonate (407mg) in dry DMF (20ml) was heated at 80^{0}C for 24h. A further quantity of Intermediate 9 (500mg) was added and heating continued for 18h. The reaction mixture was cooled, poured into water (200ml) and extracted with ethyl acetate. The organic extracts were combined, dried and concentrated in vacuo to a yellow foam (3.6g). This was purified by chromatography, eluting with petroleum ether/ether 3:1, 1:1 and then ether to give the title compound (1.78g) as a pale yellow foam.

T.l.c. System A (1:3) Rf 0.28.

Intermediate 12

1-[[3-Bromo-2-[2-[2-(triphenylmethyl)-2H-tetrazol-5-yl]phenyl]-5-benzofuranyl]methyl]-2-butyl-4-chloro-1H-imidazole-5-carboxylic acid

A solution of sodium chlorite (3.39g) and sodium dihydrogen phosphate (3.39g) in water (40ml), was added to a mixture of Intermediate 11 (2.93g) in tert-butanol (50ml) and 2-methyl-2-butene (2M in THF, 22.5ml) and THF (50ml). The mixture was stirred overnight at room temperature after which time most of the solvent was removed in vacuo and the residue partitioned between water (containing 2N sodium hydroxide solution to about pH 12) and ether. The aqueous layer was neutralised with saturated ammonium chloride solution and extracted with ethyl acetate. The organic extracts were combined, backwashed with water and brine, dried and concentrated in vacuo to give the title compound as a white solid (2.95g).

T.l.c. dichloromethane/methanol (10:1), Rf 0.58.

Intermediate 13

1-(Acetoxy)methyl 1-[[3-bromo-2-[2-(triphenylmethyl)-2H-tetrazol-5-yl]phenyl]-5-benzofuranyl]methyl]-2- butyl-4-chloro-1H-imidazole-5-carboxylate

A mixture of Intermediate 12 (2.14g) and potassium carbonate (370mg) in DMF (30ml) was stirred for 20minutes. Bromomethyl acetate (410mg) was added and the reaction mixture stirred for 24h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried and concentrated to give the title compound as a white foam (2.3g).

T.l.c. (Ether). Rf = 0.5.

Example 1

5-[2-[3-Bromo-5-[[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-yl] methyl]-2-benzofuranyl]phenyl]tetrazole

Intermediate 5 (0.5g) was added to tri-n-butyl-tin azide (3g) at 160^{0}C with stirring under nitrogen. The mixture was stirred at 160^{0}C for 1h. The resulting solution was cooled to room temperature before being basified with 5N NaOH. The resultant solid was dissolved in methanol and acidified to pH2 using concentrated HCl. The aqueous layer was extracted with ethyl acetate (3x20ml). The combined organic phases were dried and evaporated to give an orange solid (0.35g) which was purified by reverse phase h.p.l.c. (acetonitrile/water/TFA) to give the title compound (0.125g) as a white powder m.p. 193-197^{0}C.

Assay found: C,52.2; H,3.9; N.15.0

$C_{24}H_{22}BrClN_6O_2.0.1C_2HF_3O_2$ requires: C,52.5; H,4.0; N,15.2%.

Example 2

1-[[3-Bromo-2-[2-(1H-tetrazol-5-yl)phenyl]-5-benzofuranyl]methyl]-2-butyl-4-chloro-1H-imidazole-5-carboxylic acid

A mixture of Intermediate 12 (2.9g), methanol (50ml) and concentrated hydrochloric acid (0.5ml) was stirred at room temperature for 1.5h, after which time sodium hydroxide solution (2N) was added to take the solution to about pH 12. Most of the solvent was removed in vacuo and the residue was diluted with water and extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid (2N) to about pH 3 and extracted with ethyl

acetate. The organic extracts were combined, backwashed with water and brine, dried and concentrated in vacuo to a white foam, which was triturated with ether to give the ethanol solvate of the title compound as a white solid (1.22g), m.p. 183-185^{0}C.

I.r. (Nujol mull, cm^{-1}) 1709, 1529, 1464, 1420, 1377, 1364, 1265, 1142, 1069, 1059, 1043, 780.

Column chromatography of the title compound eluting with System E (75:25:1) provided the title compound as a white solid.

I.r. (Nujol mull, cm^{-1}) 1709, 1520, 1466, 1452, 1370, 1359, 1281, 1261, 1248, 1222, 1145, 1090, 1072, 999, 985, 775, 767, 748.

Example 3

1-[[3-Bromo-2-[2-(1H-tetrazol-5-yl)phenyl]-5-benzofuranyl]methyl]-2-butyl-4-chloro-1H-imidazole-5-carboxylic acid, 1-(acetyloxy)methyl ester

To a suspension of Intermediate 13 (400mg) in ethanol (30ml) was added concentrated HCl (0.1ml) and the mixture stirred at room temperature for 3h. The reaction mixture was basefied with dilute sodium bicarbonate solution and then extracted with ether. These ethereal extracts were discarded. The aqueous phase was neutralised with saturated ammonium chloride solution and then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated to give a colourless oil. This oil was triturated with ether and filtered to give the title compound as a white powder (72mg). m.p. 136-140^{0}C.

T.l.c. (Ether) Rf = 0.4.

Example 4

1-[[3-Bromo-2-[2-(1H-tetrazol-5-yl)phenyl]-5-benzofuranyl]methyl]-2-butyl-4-chloro-1H-imidazole-5-carboxylic acid, dipotassium salt

Ethanolic potassium hydroxide (1.0M), was added to a stirred solution of the product of Example 1 (1.23g), in ethanol (34ml). The solution was concentrated to 5ml then dry ether (40ml) was slowly added and precipitation occurred. The precipitate was allowed to settle, and the supernatant solution decanted. The precipitate was stirred with dry ether and decanted (2x10ml). The solid was dissolved in ethanol (8ml), then precipitated with ether

(2x20ml) and dried to give a white solid (1.445g). mp. 58-62°C (Softens).

Analysis Found C,40.8;H,2.3;N,11.9;K,10.9

$C_{24}H_{18}Br_2ClK_2N_6O_3$ requires C, 40.5;H, 2.55; N,11.8; K, 11.0%

The compounds of the invention are tested in vitro for angiotensin II receptor antagonism. Aortic strips are obtained from male New Zealand white rabbits and prepared for recording isometric contractions in response to cumulative addition of angiotensin II. The potencies of test antagonists are assessed by measuring their abilities to displace the angiotensin II cumulative concentration response curve. The method used is that of Ackerly et al., Proc. Natl. Acad. Sci., 74(12), pp5725-28 (1977) with the exception that the final composition of the physiological salt solution is as given below in Table 1:

TABLE 1

Ingredient	Amount (mM)
Na^+	143.4
K^+	5.9
Mg^{2+}	0.6
Ca^{2+}	1.3
Cl^-	124.5
HPO^{4-}	1.2
SO_4^{2-}	0.6
HCO_3^-	25.0
glucose	11.1
indomethacin	0.005
ascorbic acid	0.1

The tissues are initially challenged with K^+ (80mM) and then washed at 0, 5, 10 and 15 minutes after the response to K^+ has plateaued. After a further 45 minutes an angiotensin II cumulative response curve is constructed (0.1nM to 0.1μM in 10-fold increments) and the tissues are washed as before. A second, third and fourth angiotensin II cumulative response curve (0.1nM to 0.1μM in 3-fold

increments) is then constructed at hourly intervals (15 minutes washing after each curve followed by 45 minutes equilibration). The compounds of the invention (30μM) are tested for angiotensin II receptor antagonism by application 45 minutes before construction of the fourth angiotensin II curve. The third and fourth angiotensin II curves are expressed graphically and a concentration ratio (CR) is calculated by dividing the angiotensin II EC_{50} value obtained in the presence of the test antagonist (i.e. fourth curve) by the angiotensin II EC_{50} value obtained in the absence of the test antagonist (i.e. third curve).

The potency of the test antagonist is expressed as a pKb which is calculated from the equation :

$$pKb = -\log\left[\frac{CR-1}{[antagonist]}\right]$$

which is a rearrangement of equation 4 described by Furchgott, in Handbook of Exp. Pharmacol., 33, p290 (1972) (eds. Blaschkott and Muscholl).

Compounds of the invention will desirably exhibit a pKb in the range between 5 and 12. Thus we have found that the compounds of the invention inhibit the action of the hormone angiotensin II and are therefore useful in the treatment of conditions in which it is desirable to inhibit angiotensin II activity. In particular, the compounds of the Examples are active in the above test.

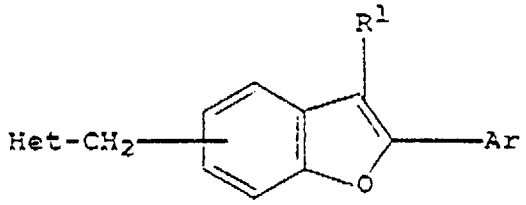
There is thus provided as a further aspect of the invention a compound of general formula (I) or a physiologically acceptable salt, solvate or metabolically labile ester thereof for use in the treatment of conditions associated with excessive or unregulated angiotensin II activity.

In a further or alternative aspect of the invention there is provided a compound of general formula (I) or a physiologically acceptable salt, solvate or metabolically labile ester thereof for the manufacture of a therapeutic agent for the treatment of conditions associated with excessive or unregulated angiotensin II activity.

There is also provided in a further or alternative aspect of the invention a method for the treatment of conditions associated with excessive or unregulated angiotensin II activity in a mammal including man comprising administration of an effective amount to a mammal in need of such treatment a compound of general formula (I) or a physiologically acceptable salt, solvate or metabolically labile ester thereof.

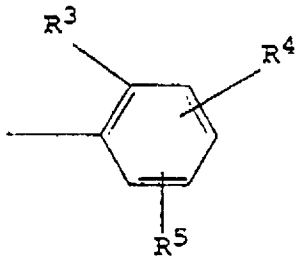
CLAIMS:

1. A compound of the general formula (I)



(I)

or a physiologically acceptable salt, solvate or metabolically labile ester thereof
wherein
R^1 represents a hydrogen atom or a halogen atom or a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, -CHO, $-CO_2H$ or $-COR^2$;
Ar represents the group



;

R^2 represents a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy or the group $-NR^{10}R^{11}$;
R^3 represents a group selected from $-CO_2H$, $-NHSO_2CF_3$ or a C-linked tetrazolyl group;
R^4 and R^5, which may be the same or different, each independently represent a hydrogen atom or a halogen atom

or a C_{1-6}alkyl group;
Het represents an N-linked imidazolyl group optionally substituted at the 2-position by a C_{1-6}alkyl, C_{2-6}alkenyl or a C_{1-6}alkylthio group, the imidazolyl group optionally being substituted at the 4- and 5-positions by one or two further substituents selected from a halogen atom or a group selected from cyano, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, fluoroC_{1-6}alkyl, $-(CH_2)_mR^6$, $-(CH_2)_nCOR^7$ or $-(CH_2)_pNR^8COR^9$;
R^6 represents a hydroxy or C_{1-6}alkoxy group;
R^7 represents a hydrogen atom or a group selected from hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, phenoxy or the group $-NR^{10}R^{11}$;
R^8 represents a hydrogen atom or a C_{1-6}alkyl group;
R^9 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, phenoxy or the group $-NR^{10}R^{11}$;
R^{10} and R^{11}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-4}alkyl group or $-NR^{10}R^{11}$ forms a saturated heterocyclic ring which has 5 or 6 ring members and may optionally contain in the ring one oxygen atom;
m represents an integer from 1 to 4;
n represents an integer from 0 to 4; and
p represents an integer from 1 to 4.

2. The compound:
1-[[3-bromo-2-[2-(1H-tetrazol-5-yl)phenyl]-5-benzofuranyl]-methyl]-2-butyl-4-chloro-1H-imidazloe-5-carboxylic acid, and physiologically acceptable salts, solvates and metabolically labile esters thereof.