(-)-(3R)-3-METHYL-4-(4-(4-(4-PYRIDYL)PIPERAZIN-1-YL)PHENOXY) BUTYRIC ACID AS CELLULAR ADHESION INHIBITOR

The present invention relates to the novel optically active compound (-)-(3R)-3-methyl-4-{4-[4-(4-pyridyl)piperazin-1-yl]phenoxy}butyric acid, [hereinafter (-)-(3R)] and pharmaceutically-acceptable salts, esters, amides or solvates thereof. The invention also relates to processes for the preparation of the optically active compound, pharmaceutical compositions containing it and its use to inhibit cellular adhesion, for example platelet aggregation.

Organic compounds can exist in optically active forms. Such compounds possess the property of being able to rotate the plane of plane-polarised light in either a dextrorotary [prefix (+)] or laevorotary [prefix (-)] manner. Typically an optically active compound possesses an asymmetric or chiral atom such as a tetrahedral carbon atom which is bonded to four different atoms or groups. The four different atoms or groups can be arranged around the asymmetric carbon atom in two ways to give two chiral compounds which are structurally related as mirror images of one another. Such compounds are termed stereoisomers or enantiomers. Enantiomers have identical physical and chemical properties except that they rotate the plane of plane-polarised light by an equal amount but in opposite directions. A racemic mixture is a mixture of equal amounts of a pair of enantiomers. Such a mixture does not cause rotation of the plane of plane-polarised light.

The stereochemical purity of an organic compound can be of importance in the fields of pharmaceutical chemistry and pharmacology. Many macromolecules such as the enzymes and receptors within warm-blooded animals which are involved in the maintenance of life are built up from chiral building blocks such as the chiral amino acids. The individual enantiomers which together make up a racemic mixture of a pharmacologically- active compound may interact to differing extents with a chiral macromolecule such as an enzyme or receptor. The individual enantiomers may therefore possess different potencies as enzyme inhibitors or receptor antagonists. In addition the rate and extent of the absorption, distribution, metabolism and excretion observed when one enantiomer is dosed to a warm-blooded animal may differ from that observed when the mirror image form is so dosed, i.e. the enantiomers may possess different pharmacokinetic properties.

Furthermore the stereochemical purity of an organic compound may also be of importance to the nature and extent of the side effects which may be obtained when a pharmacologically-active compound is dosed. Thus one enantiomer may be a useful compound whereas the other enantiomer may give rise to deleterious side effects or toxicity. It has, for example, been suggested that one of the enantiomers of thalidomide was a safe and effective sedative whereas the other enantiomer controlled the racemic mixture's teratogenic side effect.

The optically active compound of the present invention is an optical isomer of the racemic mixture (3RS)-3-methyl-4-{4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy}butyric acid [hereinafter the (3RS)-racemic mixture] which is disclosed, as the trifluoroacetic acid salt, in Example 132 of International Patent Application No. WO 94/22834 and Example 203 of International Patent Application No. WO 94/22835. It is disclosed therein that such compounds are useful in the treatment of a variety of diseases involving cell adhesion such as the formation of blood thrombi following platelet aggregation. Blood thrombi can lead to diseases such as thrombosis, stroke, thrombotic events accompanying unstable angina, myocardial infarction, atherosclerosis, thromboembolism and reocclusion during or after thrombolytic therapy.

The anti-platelet aggregatory effect of the compounds is stated to be based on the compounds' ability to inhibit the binding of adhesion molecules such as fibrinogen and von Willebrand Factor to glycoprotein IIb/IIIa (hereinafter GPIIb/IIIa) which is held within the membrane of each platelet. Thereby the necessary activation and dimerisation of, for example, the platelet-carrying fibrinogen does not occur and processes such as thrombus formation and platelet aggregation are inhibited.

As a possible aid in the search for compounds with an improved therapeutic ratio, it would be desirable to find a compound with increased potency over the compounds disclosed in International Patent Applications Nos. WO 94/22834 and WO 94/22835.

It is also known that there are several classes of adhesion molecules such as the integrins, selectins and cadherins. Integrins are found on leucocytes and platelets and selectins are found on leucocytes and endothelial cells. Within each class of adhesion molecules there are many members. The integrin family includes, for example, GPIIb/IIIa which binds fibrinogen, the integrin $\alpha_v\beta_3$ which binds vitronectin and the integrin $\alpha_5\beta_1$

which binds fibronectin. It is believed that the more useful therapeutic platelet aggregation inhibitors will possess selectivity of inhibitory effect between classes of adhesion molecules and between family members of each class of adhesion molecules. Thus it would also be desirable to find a compound which possesses this selectivity or which possesses greater selectivity than known platelet aggregation inhibitors.

Furthermore it is known that there are several classes of GPIIb/IIIa antagonists. For example, monoclonal antibody antagonists to GPIIb/IIIa have been raised. In addition, small molecules which inhibit the binding of adhesion molecules to GPIIb/IIIa are also known, for example from US Patent Nos. 5,039,805 and 5,084,446, from Canadian Patent Application Nos. 2,008,161, 2,037,153 and 2,061,661, and from Alig *et al, J. Med. Chem.*, 1992, 35, 4393. Commonly the structures of these compounds are based upon the binding regions of the adhesion molecules, for example the amino acid sequence RGD (arginyl glycyl aspartate) within the structure of fibrinogen. It is believed that such compounds can be used to inhibit platelet aggregation and, for example, thrombus formation for sufficient time to allow healing of damaged tissue without the deleterious sequelae of over-robust platelet aggregation processes. It is a theoretical concern relating to the various classes of GPIIb/IIIa antagonists that the inhibition of platelet aggregation may lead to a decrease in the rate of blood clotting and hence an increase in bleeding events and times. Although a small increase in bleeding times may be acceptable, certain clinically relevant bleeding events such as intracranial haemorrhage could be life-threatening.

Thus it would be desirable to find a compound with the advantage of the potent GPIIb/IIIa antagonist activity disclosed for the compound of Example 132 of International Patent Application No. WO 94/22834 which did not possess, or which possessed to a lesser degree, the disadvantages of increased bleeding times and/or deleterious clinically relevant bleeding events associated with the known GPIIb/IIIa antagonists.

According to the present invention there is provided the optically active compound (-)-(3R)-3-methyl-4-{4-[4-(4-pyridyl)piperazin-1-yl]-phenoxy}butyric acid, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer.

The (-)-(3R) compound possesses substantially better potency as a GPIIb/IIIa antagonist than the corresponding (+)-(3S) isomer (greater than 10-fold more potent). The

(-)-(3R) compound also possesses selectivity of inhibitory effect between classes of adhesion molecules and between family members of those classes. For example, the compound possesses activity against the binding of GPIIb/IIIa to fibrinogen ($pIC_{50} = 7.65$) but not the binding of $\alpha_v\beta_3$ to vitronectin (pIC_{50} less than 4) or the binding of $\alpha_5\beta_1$ to fibronectin (pIC_{50} less than 4).

Accordingly the (-)-(3R) compound is a novel, potent and selective fibrinogen receptor antagonist that substantially reduces the liability or possibility of obtaining adverse effects such as excessive bleeding associated with the administration of other fibrinogen receptor antagonists such as the (3RS)-racemic mixture. Use of the (-)-(3R) compound also eliminates the liability or possibility of obtaining adverse effects associated with the administration of the therapeutically less effective (+)-(3S) compound which is a constituent of the (3RS)-racemic mixture. Use of the (-)-(3R) compound allows a clearer structure-activity-toxicity analysis and provides an improved therapeutic ratio. It is therefore desirable to use the (-)-(3R) compound of the present invention rather that the (3RS)-racemic mixture of Example 132 of International Patent Application No. WO 94/22834.

Particular pharmaceutically-acceptable salts of the (-)-(3R) compound of the invention include, for example, salts with acids affording physiologically-acceptable anions, such as salts with mineral acids, for example a hydrogen halide such as hydrogen chloride or hydrogen bromide, sulphuric acid or phosphoric acid, and salts with organic acids, for example trifluoroacetic acid. Other pharmaceutically-acceptable salts include, for example, salts with inorganic bases such as alkali metal and alkaline earth metal salts e.g. sodium salts, ammonium salts, and salts with organic amines and quaternary bases forming physiologically-acceptable cations such as salts with methylamine, dimethylamine, trimethylamine, ethylenediamine, piperidine, morpholine, pyrrolidine, piperazine, ethanolamine, triethanolamine, N-methylglucamine, tetramethylammonium hydroxide and benzyltrimethylammonium hydroxide.

Particular pharmaceutically-acceptable esters of the (-)-(3R) compound of the invention include, for example, ester derivatives of the carboxylic acid group in the compound of the invention, for example esters formed with alcohols such as (1-6C)alcohols (e.g. methanol, ethanol, propanol and tert-butanol), indanol, adamantol, (1-6C)alkanoyloxy-

(1-4C)alcohols (e.g. pivaloyloxymethanol) and (1-4C)alkoxycarbonyl-(1-4C)alcohols (e.g. methoxycarbonylmethanol).

Particular pharmaceutically-acceptable amides of the (-)-(3R) compound of the invention include, for example, amide derivatives of the carboxylic acid group in the compound of the invention, for example amides formed with amines such as ammonia, (1-4C)alkylamines (e.g. methylamine), di-(1-4C)alkylamines (e.g. dimethylamine, N-ethyl-N-methylamine and diethylamine), (1-4C)alkoxy-(2-4C)alkylamines (e.g. 2-methoxyethylamine), phenyl-(1-4C)alkylamines (e.g. benzylamine) and amino acids (e.g. glycine or an ester thereof). Thus particular amides of the (-)-(3R) compound of the invention include the N-methyl-, N,N-dimethyl-, N-ethyl-N-methyl- and N,N-diethyl-butyramides.

Particular pharmaceutically-acceptable solvates of the (-)-(3R) compound of the invention include, for example, hydrates e.g. a hemi-hydrate, mono-hydrate, di-hydrate or tri-hydrate or an alternative quantity thereof.

The phrase "substantially free of the (+)-(3S) stereoisomer" as used hereinbefore means that there is at least 90% by weight of the (-)-(3R) isomer and 10% by weight or less of the corresponding (+)-(3S) isomer. Preferably there is at least 95% by weight of the (-)-(3R) isomer and 5% by weight or less of the (+)-(3S) isomer. More preferably there is at least 99% by weight of the (-)-(3R) isomer and 1% by weight or less of the (+)-(3S) isomer.

The (-)-(3R) compound of the invention, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof may be prepared by any process known in the art for the preparation of such a compound. Suitable procedures include asymmetric synthesis involving an appropriate chiral intermediate and resolution of the (3RS)-racemic mixture. Such procedures represent a further feature of the invention and include the following:

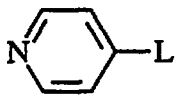
a) Reaction of 4-[4-(4-pyridyl)piperazin-1-yl]phenol, or a reactive derivative thereof, with the chiral intermediate (3R)-4-hydroxy-3-methylbutyric acid or an ester thereof, or a reactive derivative thereof.

The reaction is conveniently performed in the presence of a strong base, such as an alkali metal hydride, for example, sodium hydride. Suitable solvents include amides,

such as dimethylformamide. The reaction is conveniently performed at a temperature in the range of from 0 to 100 °C.

Suitable esters of the chiral intermediate (3R)-4-hydroxy-3-methylbutyric acid include, for example, the methyl, ethyl, propyl and tert-butyl esters. Suitable reactive derivatives thereof include, for example, (3R)-4-halogeno-3-methylbutyric acid or an ester thereof (e.g. a methyl or ethyl ester) such as the 4-chloro and 4-bromo derivatives, (3R)-4-alkanesulphonyloxy-3-methylbutyric acid or an ester thereof (e.g. a methyl or ethyl ester) such as the 4-methanesulphonyloxy derivative or (3R)-4-arylsulphonyloxy-3-methylbutyric acid or an ester thereof (e.g. a methyl or ethyl ester) such as the 4-(p-toluenesulphonyloxy) derivative.

b) Reaction of a compound of formula I



I

in which L is a leaving atom or group, with the chiral intermediate (3R)-3-methyl-4-[4-(piperazin-1-yl)phenoxy]butyric acid, or an acid addition salt thereof.

Examples of values for L include halogen, such as chlorine or bromine, and cyano.

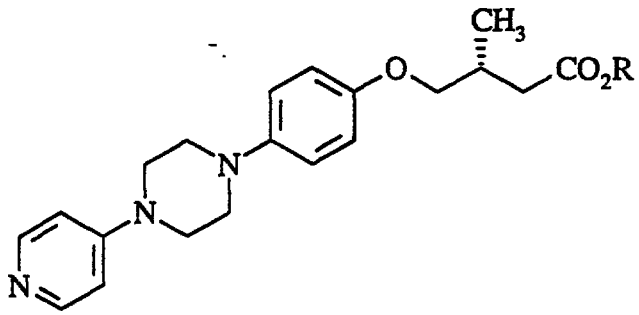
Examples of acid addition salts of (3R)-3-methyl-4-[4-(piperazin-1-yl)-phenoxy]butyric acid include, for example, the hydrochlorides.

The reaction may conveniently be effected at a temperature in the range of from -10 to 120 °C, preferably from 10 to 100 °C. Suitable solvents include, e.g. ethers such as tetrahydrofuran and dioxan, amides such as dimethylformamide, nitriles such as acetonitrile, halogenated hydrocarbons such as dichloromethane, alcohols such as ethanol and water.

In some circumstances, for example when an acid addition salt of (3R)-3-methyl-4-[4-(piperazin-1-yl)phenoxy]butyric acid is used as starting material, the reaction may advantageously be performed in the presence of a base. Examples of suitable bases

include tertiary amines, such as triethylamine, and alkali metal hydroxides, carbonates and bicarbonates, such as sodium or potassium hydroxide, carbonate or bicarbonate.

c) Decomposition of an ester of formula II



II

in which R is a carboxyl protecting group.

R may be any conventional carboxyl protecting group that may be removed without interfering with other parts of the molecule. Examples of carboxyl protecting groups include (1-6C)alkyl groups (such as methyl, ethyl, propyl or t-butyl), phenyl and benzyl, the phenyl moiety in any of which may optionally bear 1 or 2 of halogeno, (1-4C)alkyl, (1-4C)alkoxy or nitro.

The decomposition may be carried out using any one of the conventional reagents and conditions known in the art for converting carboxylic esters into carboxylic acids. Thus, for example, the decomposition may be performed by base catalysed hydrolysis, e.g. using an alkali metal hydroxide such as lithium, potassium or sodium hydroxide, or a tertiary amine such as triethylamine in the presence of water. The base catalysed hydrolysis may be performed in the presence of a solvent such as an alcohol, e.g. methanol or ethanol, or an ether such as tetrahydrofuran or dioxan. Alternatively the decomposition may be carried out by acid catalysed hydrolysis, e.g. using aqueous acetic acid or trifluoroacetic acid. The temperature is conveniently in the range of from -10 to 100°C, for example from 10 to 50°C. When the alcohol residue is t-butyl, this may be removed by heating, e.g. at a temperature in the range of from 80 to 150°C, alone or in the presence of a suitable diluent such as diphenylether or diphenylsulphone. A benzyl group may be removed by catalytic hydrogenation, e.g. by hydrogenation in the presence of

palladium on carbon at a temperature in the range of from -10 to 100°C in the presence of a solvent such as an alcohol, for example methanol or ethanol.

d) Resolution of the (3RS)-racemic mixture, (3RS)-3-methyl-4-{4-[4-(4-pyridyl)-piperazin-1-yl]phenoxy}butyric acid.

The resolution of the butyric acid derivative of the (3RS)-racemic mixture may be carried out by conventional means, for example by salt formation using an optically active base followed by separation, for example by fractional crystallisation of the two salts so produced and regeneration of the separated (-)-(3R) and (+)-(3S) compounds by acidification of the separated salts.

The resolution of the butyric acid derivative of the (3RS)-racemic mixture may also be carried out by the conventional means of forming a diastereoisomeric pair of esters by reaction with an optically active alcohol, separation of the esters, for example by chromatography, and regeneration of the separate (-)-(3R) and (+)-(3S) compounds by hydrolysis of the separated esters. An analogous route involving the preparation of a diastereoisomeric pair of amides may also be employed.

The preparation of the (-)-(3R)-compound and chiral intermediates are described within the accompanying non-limiting Examples which are provided for the purpose of illustration only.

Certain of the chiral intermediates defined hereinbefore are novel, thus according to a further aspect of the invention there is provided the compound tert-butyl (3R)-3-methyl-4-hydroxybutyrate, or a reactive derivative thereof, substantially free of the (3S) stereoisomer. A particular reactive derivative which may be mentioned is tert-butyl (3R)-3-methyl-4-(p-toluenesulphonyloxy)butyrate.

The phrase "substantially free of the (3S) stereoisomer" as used hereinbefore has the same meaning as given in relation to the (-)-(3R) compound of the invention.

When a pharmaceutically-acceptable salt of the (-)-(3R) compound of the invention is required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional procedure. When a pharmaceutically-acceptable ester or amide of the (-)-(3R) compound of the invention is required, it may be obtained, for example, by reaction of said compound with a suitable alcohol or amine as appropriate using a conventional procedure.

The ability of the (-)-(3R) compound of the invention to inhibit platelet aggregation and to inhibit the binding of fibrinogen to GPIIb/IIIa may be demonstrated using the standard test procedures (a) and (b) disclosed in International Patent Application No. WO 94/22834, which test procedures are incorporated herein by way of reference.

The (-)-(3R) compound of the invention possesses activity against the adenosine diphosphate (ADP) induced aggregation of human platelets with a $pA_2 = 7.3$, and against the binding of fibrinogen to GPIIb/IIIa with a $pIC_{50} = 7.65$.

As stated previously, the (-)-(3R) compound of the invention may be used in the therapy or prevention of diseases in which cell adhesion (especially platelet aggregation) is involved, for example venous or arterial thrombosis (e.g. pulmonary embolism, stroke and thrombotic events accompanying unstable angina and transient ischaemic attack), myocardial infarction, atherosclerosis, thromboembolism and reocclusion during and after thrombolytic therapy. The compounds may also be useful for the prevention of reocclusion and restenosis following percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft. It will also be appreciated that the compounds may be useful in the treatment of other diseases mediated by binding of adhesion molecules to GPIIb/IIIa, for example cancer.

According to a further aspect of the invention there is provided the use of the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer as a pharmaceutical.

According to a further aspect of the invention there is provided a method of inhibiting platelet aggregation in a warm-blooded animal requiring such treatment which comprises administering an effective amount of the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer.

According to a further aspect of the invention there is provided a method of inhibiting binding of fibrinogen to GPIIb/IIIa in a warm-blooded animal requiring such treatment which comprises administering an effective amount of the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer.

According to a further aspect of the invention there is provided a method of inhibiting thrombotic events accompanying unstable angina in a warm-blooded animal requiring such treatment which comprises administering an effective amount of the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer.

According to a further aspect of the invention there is provided a method of inhibiting platelet aggregation in a warm-blooded animal requiring such treatment while substantially reducing adverse effects associated with the administration of the (3-RS)-racemic mixture, which comprises administering an effective amount of the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer.

According to a further aspect of the invention there is provided the use of the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer, for the manufacture of a medicament for the prevention or treatment of a disease involving platelet aggregation.

According to a further aspect of the invention there is provided the use of the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer, for the manufacture of a medicament for the prevention or treatment of a disease involving binding of fibrinogen to GPIIb/IIIa.

According to a further aspect of the invention there is provided the use of the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer, for the manufacture of a medicament for the prevention or treatment of thrombotic events accompanying unstable angina.

In general, the (-)-(3R) compound of the invention will be administered for this purpose by an oral, rectal, topical, intravenous, subcutaneous, intramuscular or inhalation route, so that a dose in the range of from 0.01 to 50 mg/kg body weight will be given, depending upon the route of administration, the age and sex of the patient, and the severity of the condition to be treated.

The (-)-(3R) compound of the invention will generally be used in the form of a pharmaceutical composition comprising the (-)-(3R) compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S)

stereoisomer, in admixture with a pharmaceutically-acceptable diluent or carrier. Such a composition is provided as a further feature of the invention and may be in a variety of dosage forms. For example, it may be in the form of tablets, capsules, solutions or suspensions for oral administration; in the form of cream or ointments or a transdermal (skin) patch for topical administration; in the form of a suppository for rectal administration; in the form of a sterile solution or suspension for administration by intravenous or intramuscular injection; in the form of an aerosol or a nebuliser solution or suspension, for administration by inhalation; and in the form of a powder, together with pharmaceutically-acceptable inert solid diluents such as lactose, for administration by insufflation.

Depending upon the route of administration, the composition may comprise, for example, for 0.1 to 99.9% by weight of the (-)-(3R) compound of the invention.

The pharmaceutical compositions may be obtained by conventional procedures using pharmaceutically-acceptable diluents and carriers well known in the art. Tablets and capsules for oral administration may conveniently be formed with an enteric coating, for example comprising cellulose acetate phthalate, to minimise contact of the (-)-(3R) compound of the invention with stomach acids.

The (-)-(3R) compound of the invention may be co-adminstered or co-formulated with one or more agents known to be of value in the diseases or conditions intended to be treated, for example a known platelet aggregation inhibitor (e.g. aspirin, a thromboxane antagonist or a thromboxane synthase inhibitor), hypolipidemic agent, anti-hypertensive agent, thrombolytic agent (such as streptokinase, urokinase, prourokinase, tissue plasminogen activator and derivatives thereof), beta-adrenergic blocker or a vasodilator may usefully also be present in a pharmaceutical composition of the invention for use in treating a heart or vascular disease or condition.

In addition to its use in therapeutic medicine, the (-)-(3R) compound of the invention is also useful as a pharmacological tool in the development and standardisation of test systems for the evaluation of the effects of adhesion molecules in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents. The (-)-(3R) compound of the invention may also be used because of its platelet aggregation inhibitory properties in helping to store blood and to maintain the

viability of blood and blood vessels in warm-blooded animals (or parts thereof) under-going artificial extracorporeal circulation, for example during limb or organ transplants. When used for this purpose the (-)-(3R) compound of the invention will generally be administered so that a steady state concentration in the range, for example, 0.1 to 10 mg per litre is achieved in the blood.

The invention will now be illustrated by the following non-limiting Examples in which unless otherwise stated:

i) concentrations and evaporations were carried out by rotary evaporation *in vacuo*;

ii) operations were carried out at ambient temperature, that is in the range 18-26°C;

iii) column chromatography was carried out on silica gel (Merck 7736) available from E Merck and Co., Darmstadt, Germany;

iv) yields are given for illustration only and are not necessarily the maximum attainable by diligent process development;

v) proton NMR spectra were normally determined at 200 MHz or 250 MHz using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d, doublet; and

vi) the following abbreviations have been used for particular organic solvents: THF for tetrahydrofuran, DMF for N,N-dimethylformamide and DMSO for dimethylsulphoxide.

THIS SHEET HAS BEEN REPLACED

Example 1

(-)-(3R)-3-Methyl-4-{4-[4-(4-pyridyl)piperazin-1-yl]phenoxy}butyric acid hydrochloride

Sodium hydride (60% dispersion in mineral oil, 2.44 g) was added to a stirred suspension of 4-[4-(4-pyridyl)piperazin-1-yl]phenol (15.5 g) in dry DMF (120 ml) and the mixture stirred for 45 min. tert-Butyl (3R)-3-methyl-4-(p-toluenesulphonyloxy)butyrate (20 g) was added and the mixture stirred for 20 hours. The mixture was evaporated and the residue partitioned between dichloromethane and water. The organic layer was washed with water, filtered through phase separating paper (Whatman IPS) and evaporated. The residue was triturated under diethyl ether. The solid so obtained was recrystallised from ethyl acetate to give tert-butyl (-)-(3R)-3-methyl-4-{4-[4-(4-pyridyl)piperazin-1-yl]phenoxy}-butyrate (10.6 g).

m.p. 112-113°C;

$[\alpha]_D$ = -5.5° (conc. = 1g/100ml of methanol; 20°C);

NMR ($CDCl_3$) δ 8.3(2H,d), 6.89(4H,m), 6.7(2H,m), 3.79(2H,d), 3.46(4H,m), 3.28(4H,m), 2.31-2.53(2H,m), 2.08-2.21(1H,m), 1.44(9H,s), 1.07(3H,d).

A mixture of tert-butyl (-)-(3R)-3-methyl-4-{4-[4-(4-pyridyl)piperazin-1-yl]phenoxy}butyrate (10.53 g) and 1N aqueous hydrochloric acid (250 ml) was stirred for 44 hours. 1N aqueous sodium hydroxide solution (250 ml) was added and the mixture cooled to 5°C. The mixture was filtered and the filtrate evaporated. Water (150 ml) was added and the resultant precipitate isolated and washed in turn with water, acetone and diethyl ether. The material so obtained was stirred with 1N aqueous hydrochloric acid (25 ml) for 16 hours. The mixture was cooled to 5°C and filtered. The solid so obtained was washed in turn with water, acetone and diethyl ether and dried to give (-)-(3R)-3-methyl-4-{4-[4-(4-pyridyl)piperazin-1-yl]phenoxy}butyric acid hydrochloride (7.9 g).

m.p. 203-205°C;

$[\alpha]_D$ = -6.2° (conc. = 1g/100ml of methanol; 20°C);

NMR (d_6DMSO) δ 13.8(1H,br), 12.1(1H,br), 8.27(2H,d), 7.28(2H,d), 6.9(4H,m), 3.8(6H,m), 3.18(4H,t), 2.45(1H,m), 2.23(1H,m), 2.12(1H,m), 1.0(3H,d);

m/e 356$(M+H)^+$;

This Sheet Has Been Replaced

Calculated for $C_{20}H_{25}N_3O_3$. HCl. H_2O: C, 58.5; H, 6.8; N, 10.2;
Found: C, 58.3; H, 6.9; N, 10.2%;

The necessary chiral starting material was prepared as follows:

Sodium bis(trimethylsilyl)amide (1M in THF, 170 ml) was added dropwise to a solution of (4S)-4-isopropyl-3-propionyloxazolidin-2-one (*J. Am. Chem. Soc.*, 1981, **103**, 2127; 28.4 g) in dry THF (500 ml) which had been cooled to -70°C and placed under an atmosphere of argon. The rate of addition was adjusted such that the temperature of the reaction mixture did not rise above -67°C. The resultant solution was stirred at -70°C for 30 min. tert-Butyl bromoacetate (42.3 g) was added dropwise and the solution stirred at -70°C for 3 hours. The solution was then allowed to warm to room temperature. The solvent was evaporated and the residue partitioned between diethyl ether and water. The organic phase was separated, filtered through phase separating paper (Whatman IPD) and evaporated. The residue was triturated under hexane at -40°C to give a solid (21.6 g). A second crop of solid (4.4 g) was obtained by evaporation of the hexane solution and purification of the residue by filtration chromatography on silica gel starting with hexane and progressing to 1/10 ethyl acetate/hexane. The two batches of solid were combined and recrystallised from hexane to give (4S)-3-[(2R)-3-tert-butoxycarbonyl-2-methylpropionyl]-4-isopropyloxazolidin-2-one (22.5 g).

m.p. 64-65°C;

NMR($CDCl_3$) δ 4.41(1H,m), 4.21(2H,m), 4.12(1H,m), 2.79(1H,m), 2.28-2.4(2H,m), 1.41(9H,s), 1.16(3H,d), 0.9(6H,m).

Hydrogen peroxide (30%, 44 ml) and lithium hydroxide monohydrate (6.38 g) were added in turn to a stirred mixture of (4S)-3-[(2R)-3-tert-butoxycarbonyl-2-methylpropionyl]-4-isopropyloxazolidin-2-one (22.5 g), water (280 ml) and THF (800 ml) which had been cooled to 5°C. The resultant mixture was stirred at 5°C for 3 hours. A saturated aqueous sodium metabisulphite solution was added to destroy the excess

hydrogen peroxide and the solvent evaporated. The residue was extracted with dichloromethane. The aqueous solution was acidified by the addition of an aqueous citric acid solution and extracted with dichloromethane. The extracts were combined, washed with water and filtered through phase separating paper. The filtrate was evaporated to give 1-tert-butyl (3R)-3-methylsuccinate as an oil (12.9g).

NMR($CDCl_3$) δ 2.9(1H,m), 2.64(1H,m), 2.37(1H,m), 1.4(9H,s), 1.23(3H,d).

Borane-dimethyl sulphide complex (10M, 10.3 ml) was added over 15 min to a stirred mixture of 1-tert-butyl (3R)-3-methylsuccinate (12.9 g) and THF (200 ml) which had been cooled to -10°C and placed under an atmosphere of argon. The mixture was stirred at -10°C for 30 min. The mixture was allowed to warm to room temperature and stirred for 1 hour. The mixture was recooled to 5°C and methanol (50 ml) was added portionwise. The mixture was allowed to warm to room temperature and stirred for 30 min. The mixture was evaporated and the residue partitioned between dichloromethane (100 ml) and water (100 ml). The organic phase was filtered through phase separating paper and evaporated to give tert-butyl (3R)-4-hydroxy-3-methylbutyrate as an oil (11 g).

NMR($CDCl_3$) δ 3.55(2H,m), 2.1-2.4(3H,m), 1.46(9H,s), 0.98(3H,d).

p-Toluenesulphonyl chloride (13.2 g) was added portionwise to a stirred mixture of tert-butyl (3R)-4-hydroxy-3-methylbutyrate (11 g), triethylamine (21 ml) and dichloromethane (120 ml) and the mixture stirred for 20 hours. The mixture was washed in turn with water and dilute aqueous sodium carbonate solution. The organic solution was filtered through phase separating paper and evaporated to give tert-butyl (3R)-3-methyl-4-(p-toluenesulphonyloxy)butyrate as an oil (20 g).

NMR($CDCl_3$) δ 7.6(2H,d), 7.33(2H,d), 3.92(2H,d), 2.45(3H,s), 2.18-2.47(2H,m), 2.0-2.15(1H,m), 1.42(9H,s), 0.95(3H,d).

Example 2

Illustrative pharmaceutical dosage forms suitable for presenting the compound of the invention for therapeutic or prophylactic use include the following, which may be obtained by conventional procedures well known in the art:

a)	Tablet I	mg/tablet
	Active ingredient	1.0
	Lactose Ph. Eur.	93.25
	Croscarmellose sodium	4.0
	Maize starch paste	0.75
	(5% w/v aqueous paste)	
	Magnesium stearate	1.0

b)	Tablet II	mg/tablet
	Active ingredient	50
	Lactose Ph. Eur.	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone	2.25
	(5% w/v aqueous paste)	
	Magnesium stearate	3.0

c)	Tablet III	mg/tablet
	Active ingredient	100
	Lactose Ph. Eur.	182.75
	Croscarmellose sodium	12.0
	Maize starch paste	2.25
	(5% w/v aqueous paste)	
	Magnesium stearate	3.0

(d)	Capsule	mg/capsule

Active ingredient	10
Lactose Ph. Eur.	488.5
Magnesium stearate	1.5

(e)	Injection	mg/ml
	Active ingredient (acid addition salt)	1.0
	Sodium chloride	9.0
	Purified water to 1.0ml	

Example 3

The following is a description of a study of the effects of the (-)-(3R) compound of the invention and the corresponding (3RS)-racemic mixture in the rat. Four groups of ten Alderley Park Wistar rats (each group comprising 5 male and 5 female rats) were dosed orally with the (3RS)-racemic mixture at daily doses of 0, 25, 100 or 500 mg/kg. Dosing was continued for a total of seven days. The animals were killed and examined. Adverse effects were noted in the livers of six of the group of ten rats dosed at 500 mg/kg/day.

Four groups of ten Alderley Park Wistar rats (each group comprising 5 male and 5 female rats) were dosed orally with the (-)-(3R) compound of the invention at daily doses of 0, 50, 250 and 1000 mg/kg. The highest dose was not tolerated. After four or five days, four of the animals from this group were killed. The remaining six animals were dosed at 500 mg/kg/day for the remainder of the study. Dosing was continued for a total of fourteen days. The animals were killed and examined. No adverse effects were noted in the livers of the group of rats dosed at 250 mg/kg/day. The six animals dosed at 1000 mg/kg/day for three or four days and then at 500 mg/kg/day for ten or eleven days also showed no adverse effect on the liver.

Based on such observations, it is seen that the (-)-(3R) compound of the invention causes no significant adverse effect on the rat liver at 500 mg/kg/day.

By implication, the (-)-(3R) compound is less toxic than the (3RS)-racemic mixture.

CLAIMS

1. The optically active compound (-)-(3R)-3-methyl-4-{4-[4-(4-pyridyl)piperazin-1-yl]phenoxy}butyric acid, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, substantially free of the (+)-(3S) stereoisomer.

2. The optically active compound according to claim 1, wherein there is at least 90% by weight of the (-)-(3R) isomer and 10% by weight or less of the corresponding (+)-(3S) isomer.

3. The optically active compound according to claim 1, wherein there is at least 95% by weight of the (-)-(3R) isomer and 5% by weight or less of the corresponding (+)-(3S) isomer.

4. The optically active compound according to claim 1, wherein there is at least 99% by weight of the (-)-(3R) isomer and 1% by weight or less of the corresponding (+)-(3S) isomer.

5. The optically active compound according to any one of claims 1 to 4, wherein the pharmaceutically-acceptable salt is in the form of a hydrochloride salt.

6. The optically active compound according any one of claims 1 to 4, wherein the pharmaceutically-acceptable ester is in the form of methyl, ethyl, propyl or tert-butyl ester.

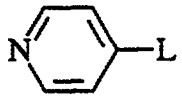
7. The optically active compound according to any one of claims 1 to 4, wherein the pharmaceutically-acceptable amide is in the form of a N-methyl-, N,N-dimethyl-, N-ethyl-N-methyl- or N,N-diethyl-butyramide.

8. The optically active compound according to any one of claims 1 to 4, wherein the pharmaceutically-acceptable solvate is in the form of a hydrate.

9. A process for the preparation of the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of the preceding claims which comprises:

a) reaction of 4-[4-(4-pyridyl)piperazin-1-yl]phenol, or a reactive derivative thereof, with the chiral intermediate (3R)-4-hydroxy-3-methylbutyric acid or an ester thereof, or a reactive derivative thereof;

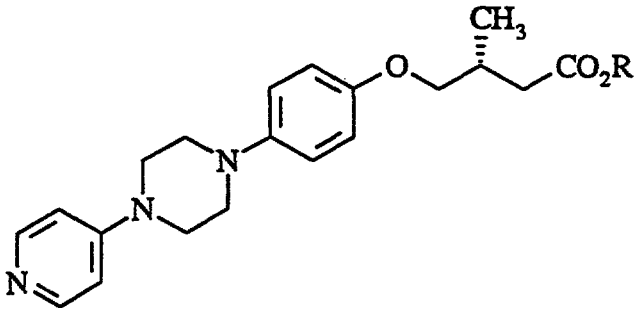
b) reaction of a compound of formula I



I

in which L is a leaving atom or group, with the chiral intermediate (3R)-3-methyl-4-[4-(piperazin-1-yl)-phenoxy]butyric acid, or an acid addition salt thereof;

c) decomposition of an ester of formula II



II

in which R is a carboxyl protecting group;

d) resolution of the (3RS)-racemic mixture, (3RS)-3-methyl-4-{4-[4-(4-pyridyl)-piperazin-1-yl]phenoxy}butyric acid;

and when a pharmaceutically-acceptable salt of the (-)-(3R) compound is required, reaction of the resulting compound with a suitable acid or base; and when a pharmaceutically-acceptable ester or amide of the (-)-(3R) compound is required, reaction of the resulting compound with a suitable alcohol or amide.

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10. The optically active compound tert-butyl (3R)-3-methyl-4-hydroxybutyrate, or a reactive derivative thereof, substantially free of the (3S) stereoisomer.

11. A compound according to claim 10, wherein the reactive derivative is tert-butyl (3R)-3-methyl-4-(p-toluenesulphonyloxy)butyrate.

12. A pharmaceutical composition comprising the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of claims 1 to 8, in admixture with a pharmaceutically-acceptable diluent or carrier.

13. A method of inhibiting platelet aggregation in a warm-blooded animal requiring such treatment which comprises administering an effective amount of the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of claims 1 to 8.

14. A method of inhibiting platelet aggregation in a warm-blooded animal requiring such treatment while substantially reducing adverse effects associated with the administration of the (3-RS)-racemic mixture, which comprises administering an effective amount of the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of claims 1 to 8.

15. A method of inhibiting binding of fibrinogen to GPIIb/IIIa in a warm-blooded animal requiring such treatment which comprises administering an effective amount of the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of claims 1 to 8.

16. A method of inhibiting thrombotic events accompanying unstable angina in a warm-blooded animal requiring such treatment which comprises administering an effective amount of the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of claims 1 to 8.

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17. The use of the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of claims 1 to 8 for the manufacture of a medicament for the prevention or treatment of a disease involving platelet aggregation.

18. The use of the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of claims 1 to 8 for the manufacture of a medicament for the prevention or treatment of a disease involving binding of fibrinogen to GPIIb/IIIa.

19. The use of the optically active compound, or a pharmaceutically-acceptable salt, ester, amide or solvate thereof, according to any one of claims 1 to 8 for the manufacture of a medicament for the prevention or treatment of thrombotic events accompanying unstable angina.

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