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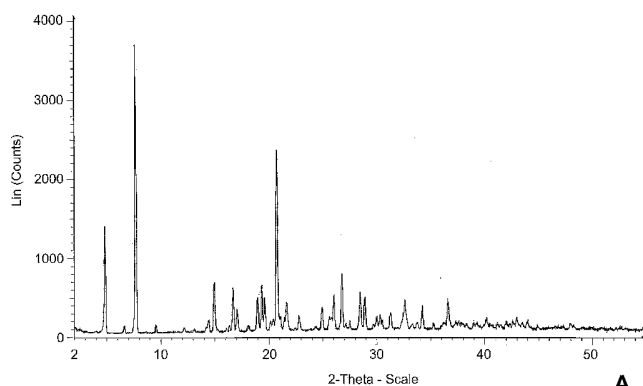
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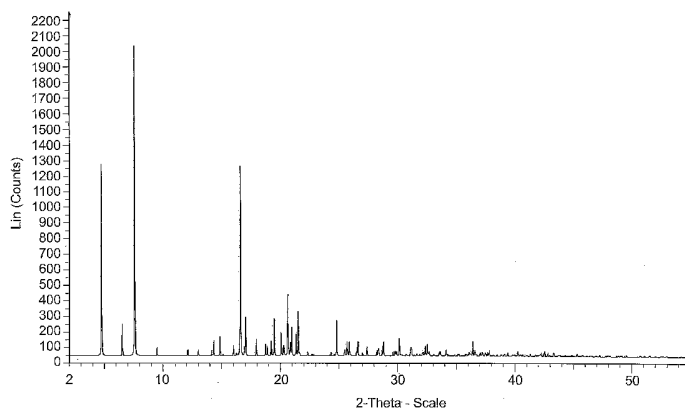
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[Continued on next page]

(54) Title: NEUTRAL ENDOPEPTIDASE INHIBITOR POLYMORPH



A



B

(57) Abstract: Disclosed are
(2S)-2-{1-[(1S)-1-Isobutoxycar-
bonyl-2-(5-phenyl-oxazol-2-yl)-ethylcar-
bamoyl]-cyclopentylmethyl}-4-methoxy-bu-
tyric, Potassium-(2S)-2-{1-[(1S)-1-Isob-
utoxycarbonyl-2-(5-phenyl-oxa-
zol-2-yl)-ethylcarbamoyl]-cyclopentyl-
methyl}-4-methoxy-butyrate, monohydrate
and its Form I polymorph. Also disclosed
are compositions of the described forms,
kits including the described forms, and
methods of using the described forms for
the treatment diseases or disorders where the
use of a neutral endopeptidase inhibitor is
indicated, including cardiovascular diseases
and conditions.



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NEUTRAL ENDOPEPTIDASE INHIBITOR POLYMORPH

FIELD OF THE INVENTION

This invention is in the field of neutral endopeptidase (NEP) inhibitor pharmaceutical agents and specifically relates to Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates, its monohydrate and polymorphic forms.

BACKGROUND OF THE INVENTION

This invention relates to new forms of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates which are potent and selective inhibitors of neutral endopeptidase (NEP) that may be used to treat a number of diseases and conditions including cardiovascular disorders, especially hypertension.

U.S. Patent Application No. 60/448,244, filed February 18, 2003, (PCT/IB03/05981, filed December 12, 2003) hereby incorporated by reference, discloses a class of cyclopentyl substituted glutaramide derivatives and compositions and uses thereof. U.S. Patent Application '244 discloses the preparation of a class of NEP inhibitors and the preparation of pharmaceutical formulations comprising these inhibitors. One such compound is (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates. (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates acid is a NEP inhibitor that can be administered in a therapeutically effective amount where use of an NEP inhibitor is indicated, such as in cardiovascular diseases and conditions, particularly hypertension, pulmonary hypertension, peripheral vascular disease, hypertension, peripheral vascular disease, heart failure, angina, renal insufficiency, acute renal failure, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary) and hypercalcaemia. Example 40 of U.S. Patent Application '244 illustrates the preparation of the amorphous form of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates acid.

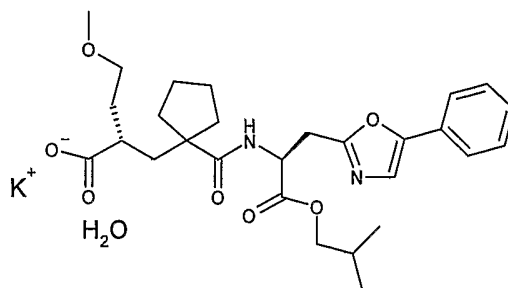
While the product of this synthesis is a potent NEP inhibitor, as with all pharmaceutical compounds and compositions, the chemical and physical properties are important in its commercial development. These properties include, but are not limited to: (1) packing properties such as molar volume, density and hygroscopicity, (2) thermodynamic properties such as melting temperature, vapor pressure and solubility, (3) kinetic properties such as dissolution rate and stability (including stability at ambient conditions, especially to moisture and under storage conditions), (4) surface properties such as surface area, wettability, interfacial tension and shape, (5) mechanical properties such as hardness, tensile strength, compactibility, handling, flow and blend; (6) filtration properties and (7) bioavailability. These properties can affect, for example, the processing and storage of pharmaceutical compositions comprising (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates acid. Solid state forms of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-

ethylcarbamoyl]-cyclopentylmethyl]-4-methoxy-butyric acid that provide an improvement in one or more of these properties relative to the amorphous form of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl]-4-methoxy-butyric acid are desirable.

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SUMMARY OF THE INVENTION

One embodiment of the present invention is Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl]-4-methoxy-butyrate. The formula of the Potassium salt monohydrate is shown below:



10

The present invention also encompasses crystalline forms of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl]-4-methoxy-butyric acid, its salts and/or hydrates thereof.

15

Another embodiment of the present invention is the form I polymorph of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl]-4-methoxy-butyrate, monohydrate (referred to herein as Form 1 polymorph.) Form I polymorph is identified by the characteristic peaks of its PXRD pattern, either a PXRD pattern calculated from analysis of a single crystal or from a PXRD analysis.

Another embodiment of the invention is a pharmaceutical composition comprising any of the above described forms.

20

Another embodiment of the invention is a pharmaceutical composition comprising any of the above described forms with at least one additional therapeutic agent comprising one or more of the following agents: angiotensin receptor blockers, calcium channel blockers, statins, PDE5 inhibitors, beta blockers, ACE inhibitors, alpha-blockers, selective aldosterone receptor antagonists, imidazoline I₁ agonists, endothelin receptor antagonists or endothelin converting

25

enzyme inhibitors.

Another embodiment of the invention is the above pharmaceutical composition of where the angiotensin receptor blocker is losartan, valsartan, telmisartan, candesartan, irbesartan, eprosartan or olmesartan and/or the calcium channel blocker is amlodipine and/or the statin is atorvastatin and/or the PDE5 inhibitor is sildenafil, tadalafil, vardenafil, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, or N-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-propoxyphenyl]sulfonyl]-1-methyl-2-pyrrolidinepropanamide and/or the beta blocker is atenolol or carvedilol and/or the ACE inhibitor is quinapril, enalapril or lisinopril and/or the alpha-

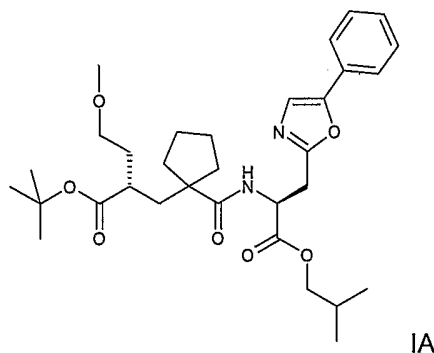
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blocker is doxazosin and/or the selective aldosterone receptor antagonist is eplerenone or spironolactone; and/or the imidazoline I₁ agonist is rilmenidine

Another embodiment of the invention is method of treating a cardiovascular disease or condition in a mammal, including in a human, with a therapeutically effective amount of a compound or pharmaceutical composition of the invention. Such cardiovascular diseases or conditions include but are not limited to hypertension, pulmonary hypertension, peripheral vascular disease, hypertension, peripheral vascular disease, heart failure, angina, renal insufficiency, acute renal failure, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary) and hypercalcinuria.

Another embodiment of the invention is a process for forming the polymorph of the invention comprising:

- (a) reacting (2S)-2-Amino-3-(5-phenyl-oxazol-2-yl) propionic acid isobutyl ester hydrochloride with 1-[(2S)-2-(tert-butoxycarbonyl)-4-methoxybutyl]cyclopentanecarboxylic acid with a coupling agent in the presence of a solvent to form the compound IA;



- (b) deprotecting compound IA
- (c) reacting the product of (b) with a potassium base to yield the potassium salt; and
- (d) recrystallizing the compound of (c) with acetone.

Another embodiment of the invention is a kit comprising: A crystalline form of 2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid, or salt thereof, and instructions advising how to use the kit for the treatment of cardiovascular diseases and conditions.

Another embodiment of the invention is a kit comprising: Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate, monohydrate and/or Form I polymorph and instructions advising how to use the kit for the treatment of cardiovascular diseases and conditions.

Crystalline forms of 2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid, or a salt thereof, can be administered in a therapeutically effective amount where use of an NEP inhibitor is indicated, for example in the treatment of cardiovascular diseases and conditions, including but not limited to hypertension, pulmonary hypertension, peripheral vascular disease, hypertension, peripheral vascular disease,

heart failure, angina, renal insufficiency, acute renal failure, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary) and hypercalciuria. Such crystalline forms include Potassium-(2S)-2-{1-[(1S)-1-isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butylate or a hydrate thereof, including the Form I polymorph.

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BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A shows a representative measured Powder X-ray diffraction pattern (PXRD), on a scale of 2° to 55° of Form I polymorph.

10 Fig. 1B shows the PXRD calculated from a single crystal of Form I polymorph, on a scale of 2° to 55° 2θ.

Fig. 2 shows a differential scanning calorimetry (DSC) thermogram of Form I polymorph directly crystallized from acetone.

15

Fig. 3 shows an evolved gas analysis (EGA) of Form I polymorph. The solid line represents the TGA trace, weight loss at 50-60°C, 2.94 %; Dash-Dot line represents m/e of 18; Dashed Line represents m/e 17.

20 Detailed Description

NEP inhibitors have been demonstrated to lower systolic blood pressure in hypertensive rats and supine blood pressure in humans with essential hypertension. A NEP inhibitor, in combination with an ACE inhibitor, has been shown to cause a marked reduction in both supine and erect blood pressure in humans. Accordingly, the compounds of the invention should treat or prevent cardiovascular diseases and conditions, particularly hypertension, pulmonary hypertension, peripheral vascular disease, heart failure, angina, renal insufficiency, acute renal failure, cyclical oedema, Menière's disease, hyperaldosteronism (primary and secondary) and hypercalciuria. The term hypertension includes all diseases characterized by supranormal blood pressure, such as essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension, and further extends to conditions for which elevated blood pressure is a known risk factor. The term "treatment of hypertension" includes the treatment or prevention of complications arising from hypertension, and other associated co-morbidities, including congestive heart failure, angina, stroke, glaucoma, impaired renal function, including renal failure, obesity, and metabolic diseases (including Metabolic Syndrome). Metabolic diseases include in particular diabetes and impaired glucose tolerance, including complications thereof, such as diabetic retinopathy and diabetic neuropathy.

NEP inhibitors have also been shown to increase vaginal and clitoral blood flow in a rabbit model of female sexual arousal disorder (FSAD). Accordingly the compounds of the invention should treat or prevent female sexual dysfunction, particularly FSAD.

40

NEP inhibitors have also been shown to potentiate nerve-stimulated erections in anaesthetised dog model of penile erections. Accordingly the compounds of the invention should treat or prevent male erectile dysfunction (MED).

As a result of their ability to inhibit NEP, the compounds of the invention should treat or
5 prevent menstrual disorders, pre-term labor, pre-eclampsia, endometriosis, and reproductive disorders (especially male and female infertility, polycystic ovarian syndrome, implantation failure).

In addition, the compounds of the invention should: treat or prevent asthma, inflammation, leukemia, pain, epilepsy, affective disorders, dementia and geriatric confusion, septic shock, obesity and gastrointestinal disorders (especially diarrhea and irritable bowel syndrome); promote
10 wound healing (especially diabetic and venous ulcers and pressure sores); modulate gastric acid secretion; and treat of hyperreninaemia, cystic fibrosis, restenosis, diabetic complications and atherosclerosis.

DEFINITIONS

15 The term "Form 1 polymorph" as used herein refers to the crystalline form of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate, monohydrate.

The term "amorphous" as applied to (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid refers to a solid state
20 wherein the (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid molecules are present in a disordered arrangement and do not form a distinguishable crystal lattice or unit cell. When subjected to X-ray powder diffraction, amorphous (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid does not produce any characteristic
25 crystalline peaks.

The term "crystalline form" as applied to (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid, or a salt thereof, refers to a solid state form wherein the molecules of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid, or a salt thereof, are
30 arranged to form a distinguishable crystal lattice yielding characteristic diffraction peaks when subjected to X-ray radiation.

The term "DSC" means differential scanning calorimetry.

The term "mammal" as used herein includes, but is not limited to, human.

The term "pharmaceutically acceptable" means suitable for use in mammals.

35 The term "salts" is intended to refer to pharmaceutically acceptable salts and to salts suitable for use in industrial processes, such as the preparation of the compound.

The term "pharmaceutically acceptable salts" is intended to refer to either pharmaceutically acceptable acid addition salts or "pharmaceutically acceptable basic addition salts.

40 The term "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I or

any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids, which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example,
5 acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid, and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various
10 hydrophilic organic solvents, and which in comparison to their free base forms, generally demonstrate higher melting points.

The term "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of the compounds represented by Formula I, or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-
15 earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline.

The term "PXRD" means powder X-ray diffraction. PXRD includes calculated and measured PXRD unless otherwise specified.

20 As used herein, the terms "treat", "treating" and "treatment" include palliative, curative and prophylactic treatment.

A) Methods of Characterization

1) Crystal characterization:

25 Transmission Light Microscopy (TLM): Solid was dispersed in 2-3 drops silicone fluid prior to observation. The sample was observed through partially crossed polarisers using a Nikon Labophot microscope, and found to consist of laths and aggregates with a crystallite size range of 10-150µm.

30 2) Powder X-ray Diffraction (PXRD):

Compounds having identical chemical structures may exist in different physical forms. Solid forms may be amorphous or may exist as distinct crystalline forms. Different crystalline forms often have different physical properties (i.e. bioavailability, solubility, melting points, etc). These different crystalline forms are called polymorphs.

35 One method of determining the structure of a crystalline form is referred to as powder X-ray diffraction (PXRD) analysis. PXRD analysis involves collection of crystallographic data from a group of crystals. To perform PXRD analysis, a powdered sample of the crystalline material is placed in a holder and illuminated with X-rays of a fixed wavelength and the intensity of the reflected radiation is recorded. These data can be expressed in graphical form as a PXRD pattern
40 (referred to herein as measured PXRD). One skilled in the art will realize that the relative intensities

of peaks present in a measured PXRD pattern may vary due to the preferred orientation of the particular crystals.

The powder X-ray diffraction patterns depicted in Figure 1A was measured using a Siemens D5000 powder X-ray diffractometer, fitted with a ceramic Copper X-ray tube (run at 40 kV, 40mA) and a graphite secondary monochromator to provide incident $\text{CuK}\alpha$ radiation ($\lambda=1.5406\text{\AA}$). The diffracted X-Ray intensities were recorded using a NaI scintillation detector. Variable slit widths were used during the data collection. The crystalline powdered sample was mounted on a silicon wafer, which was rotated during the data collection. The angular range was 2° to 55° 2θ . Data were processed using Bruker-AXS Ltd EVA evaluation software (version 9.0). This analysis yielded what is referred to herein as measured PXRD.

Another method of determining the structure of a polymorph is single crystal X-ray analysis. In single crystal X-ray analysis, several crystallographic parameters, including unit cell dimensions, space group, and atomic position of all atoms in the compound relative to the origin of its unit cell, are determined based on analysis of a single crystal. Based on these data, one skilled in the art, aided by computer software, can calculate a powder X-ray diffraction pattern (calculated PXRD). This calculated PXRD gives the peaks that are likely to appear in a measured PXRD pattern. However, because this analysis is based on a single crystal, the data obtained are not affected by a preferred orientation of the crystals, as may be the case for a measured PXRD.

Thus, the fact that the measured PXRD and the calculated PXRD pattern are not identical does not mean that a crystal is not the Form 1 polymorph. The presence of selected characteristic peaks, identified from the calculated or measured patterns, may be used to determine whether a crystalline form of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate, monohydrate is the Form 1 polymorph.

The powder X-ray diffraction pattern depicted in Figure 1B was calculated-from the single crystal structure of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate, monohydrate, using the "Reflex Powder Diffraction" module of Accelrys Materials Studio™ [version 2.2]. Pertinent simulation parameters were in each case: wavelength = $1.540562\text{\AA}$ ($\text{Cu K}\alpha$), Polarization Factor = 0.5 and Pseudo-Voigt Profile ($U = 0.01$, $V = -0.001$, $W = 0.002$). The 2θ values for the characteristic peaks are shown in Table 1.

As is readily apparent to one skilled in the art, the results of any particular PXRD analysis may vary. This variance can be due to test sample preparation, the particular model of X-ray diffractometer used, the operator's technique, etc. The term "about", if used in defining a 2θ value in a PXRD pattern, is defined as the stated 2θ value $\pm 0.2^\circ$ 2θ .

Differential Scanning Calorimetry (DSC):

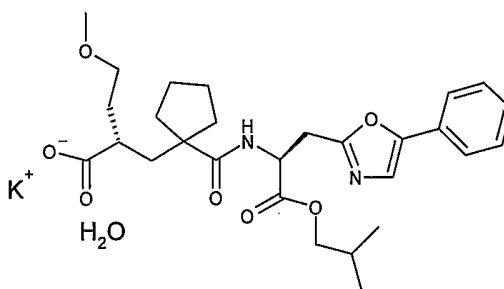
Scanned at $20^\circ\text{C}/\text{minute}$, ambient to 250°C on a Perkin Elmer Diamond DSC. Flow gas was nitrogen. Thermal analysis by DSC revealed two overlapping endothermic events, the first with an onset of 94°C and the second with a peak of 120°C . These events were probed further by EGA.

Evolved Gas Analysis (EGA):

Involves heating of the sample using TGA apparatus, scanned at 20°C/minute from ambient to 300°C using a TA Instruments Q50 with helium purge gas. Analysis of the evolved gases was by mass spectroscopy using a Pfeiffer ThermoStar GSD 300T, using helium carrier gas. The first endothermic event is associated with the loss of approximately one mole equivalent of water (~3 %) i.e. dehydration of a monohydrate, indicated by the associated appearance of the m/e 17 and m/e 18 ions at this time. This loss is complete before the peak temperature of the second DSC endotherm. No further weight loss was associated with the second endotherm suggesting a melt of an anhydrous phase.

B) Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate

As noted above, new forms of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid have been discovered. These forms include the Potassium salt of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate and its monohydrate. The monohydrate is represented by the following formula:



Formula 2

The new form possesses a number of advantages over the amorphous form. These include ease of isolation and purification of the drug substance, long term stability as a solid, formulation and mixing with other drug substances and/or excipients.

C) Form I Polymorph of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate, monohydrate

Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate, monohydrate can exist as a crystalline polymorph. One crystalline polymorph has been identified to date. For simplicity, it will be referred to as the "Form I polymorph" hereinafter.

The Form I polymorph can be identified by its characteristic PXRD pattern. In a substantially pure preparation of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrate, monohydrate, the Form I

polymorph can be identified using either a calculated PXRD pattern from a single crystal analysis or by directly determining the PXRD pattern. One skilled in the art would recognize that the intensities of peaks with a calculated or measured PXRD pattern can vary from lot to lot of compound. Also, one skilled in the art would recognize that the 2θ values may vary depending on the instrument used for the measurement. Table 1 shows 2θ values for the characteristic peaks of Form I polymorph as calculated from the single crystal structure using the "Reflex Powder Diffraction" module of Accelrys Materials Studio™ [version 2.2]. A characteristic peak is one that has a relative intensity of at least 10% of the largest peak in the PXRD pattern. Pertinent simulation parameters were: Wavelength = 1.540562 Å (Cu K α), Polarisation Factor = 0.5 and Pseudo-Voigt Profile (U = 0.01, V = -0.001, W = 0.002).

Table 1

2θ (°)
4.7
6.4
7.5
16.5
17.0
20.6
21.5

In cases where the single crystal is not readily available, determining the PXRD pattern can be done by directly measuring the PXRD pattern of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates, monohydrate.

Table 2 shows 2θ values for the characteristic peaks of Form I polymorph from a measured PXRD

Table 2

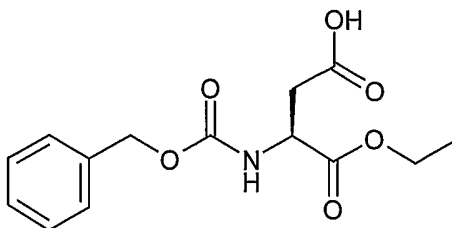
Degrees 2θ
4.7
7.6
14.9
19.2
19.5
20.7
26.0
26.7

D) Method of Preparation

The following non-limiting example illustrates methods for preparing compounds of the invention.

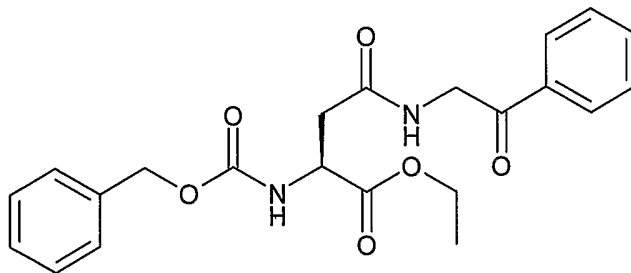
Step 1

(2S)-2-Benzylloxycarbonylamino-succinic acid 1-ethyl ester



A solution of N-carbobenzyloxy-L-aspartic anhydride (100g) in ethanol (600mL) was refluxed for 18 hours. The reaction mixture was concentrated in vacuo, redissolved in ethyl acetate (250mL) and extracted into saturated sodium hydrogencarbonate solution (2x200mL). The aqueous was
 5 acidified with 2M hydrochloric acid and the reaction mixture extracted into ethyl acetate (3x200mL). The organics were combined, dried over magnesium sulphate and concentrated in vacuo. The product was dissolved in ether (500mL) and dicyclohexylamine (92mL) was added to form a precipitate which was collected by filtration. The solid was redissolved in the minimum volume of warm ethanol and stirred until a precipitate formed which was collected by filtration. The solid was
 10 then recrystallized once more from ethanol. The product was suspended in ether and washed with 2M sulphuric acid (2x100mL). The organic solution was dried over magnesium sulphate and concentrated in vacuo to yield the title product, 22g. Re-recrystallization of the mother liquors from ethanol yielded a further 70g; ¹HMMR (DMSOD₆, 400MHz) δ 1.16(s, 3H), 2.57(d, 1H), 2.65(d, 1H), 4.06(d, 2H), 4.39(m, 1H), 5.02(s, 2H), 7.11(m, 5H), 7.71(d, 1H).

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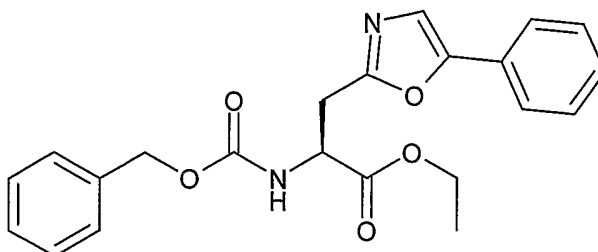
Step 2(2S)-2-Benzylloxycarbonylamino-N-(2-oxo-2-phenyl-ethyl)-succinamic acid ethyl ester

20 Thionyl chloride (4.4mL, 60mmol) and N,N-dimethylformamide (1 drop) were added to a solution of the acid of (2S)-2-Benzylloxycarbonylamino-succinic acid 1-ethyl ester (4.22g, 15mmol) in dichloromethane (50mL) and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated in vacuo and the product (1g, 3mmol) dissolved in dichloromethane (10mL). To this was added a solution of 2-amino-1-phenyl-ethan-1-one (3mmol)
 25 and triethylamine (0.94μL, 6mmol) in dichloromethane (10mL) which had been cooled to 0°C. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with dichloromethane (30mL), washed with 2M hydrochloric acid solution (40mL), washed with saturated sodium hydrogencarbonate solution (100mL) and dried over magnesium sulphate and concentrated in vacuo. The crude product was purified by column chromatography eluting with
 30 pentane:ethyl acetate (66:33 to 33:66) to yield the title product, 918mg; ¹HNMR (CDCl₃, 400MHz) δ

1.23(m, 3H), 2.86(d, 1H), 3.05(d, 1H), 4.21(m, 2H), 4.63(s, 1H), 4.71(s, 2H), 6.00(s, 1H), 6.63(s, 1H), 7.11-7.66(brm, 8H), 7.93(d, 2H); MS ES+ m/z 435 [MNa]⁺.

5 Step 3

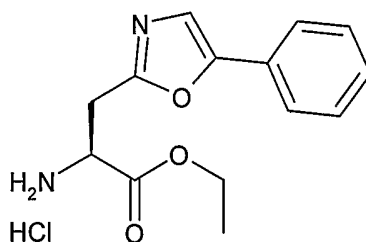
(2S)-2-Benzoyloxycarbonylamino-3-(5-phenyl-oxazol-2-yl)-propionic acid ethyl ester



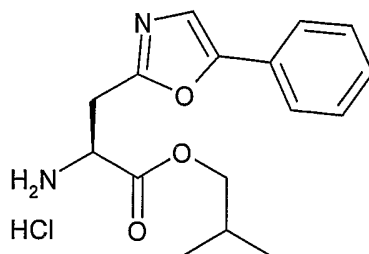
Phosphorous oxychloride (671μL, 7mmol) was added to a solution of (2S)-2-Benzoyloxycarbonylamino-N-(2-oxo-2-phenyl-ethyl)-succinamic acid ethyl ester (1.025g, 2mmol) in
 10 toluene (15mL) and the reaction mixture stirred at 100°C for 90 minutes. The reaction mixture was poured onto ice (20mL), extracted into dichloromethane (2x50mL), dried over magnesium sulphate and concentrated in vacuo. The crude product was purified by column chromatography eluting with pentane:ethyl acetate (80:20 to 66:33) to give the title product, 598mg; ¹HNMR (CDCl₃, 400MHz) δ 1.20(m, 3H), 3.40(m, 2H), 4.21(m, 2H), 4.82(s, 1H), 5.13(s, 2H), 5.96(d, 1H), 7.17(s, 1H), 7.21-7.42
 15 (brm, 10H); MS ES+ m/z 811 [M₂Na]⁺.

Step 4

(2S)-2-Amino-3-(5-phenyl-oxazol-2-yl)-propionic acid ethyl ester hydrochloride



20 A solution of hydrogen bromide in acetic acid (1.1mL) was added to a solution of (2S)-2-benzoyloxycarbonylamino-3-(5-phenyl-oxazol-2-yl)-propionic acid ethyl ester (547mg, 1.23mmol) in acetic acid (1.1mL) and the reaction stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate (20mL) and neutralised with sodium
 25 hydrogencarbonate solution. The organic layer was separated and dried over magnesium sulphate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate:dichloromethane:methanol:ammonium hydroxide (100:0:0:0 to 0:90:10:1) to yield the title product, which was isolated after trituration with 2M hydrochloric acid in
 30 ether, 180mg; ¹HNMR (CDCl₃, 400MHz) δ 1.09(t, 3H), 3.22(s, 2H), 4.13(m, 2H), 4.32(m, 3H), 7.21-7.74(brm, 6H); MS ES+ m/z 261 [MH]⁺.

Step 5(2S)-2-Amino-3-(5-phenyl-oxazol-2-yl)propionic acid isobutyl ester hydrochloride

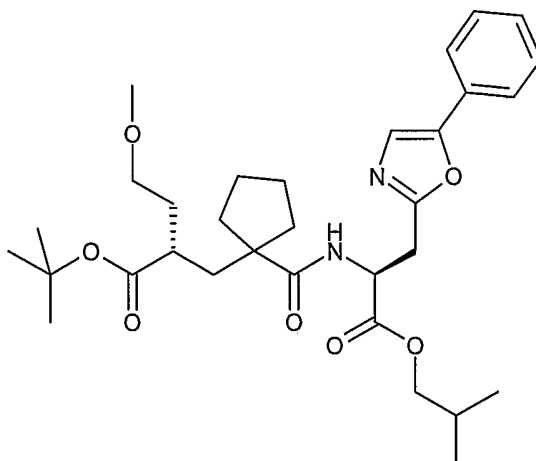
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The title compound was prepared from (2S)-2-Amino-3-(5-phenyl-oxazol-2-yl)-propionic acid ethyl ester hydrochloride and isobutanol. After heating at 70°C for 18 hours the crude product was azeotroped with toluene and concentrated in vacuo; ¹HNMR (DMSO-d₆, 400MHz) δ 0.91(m, 6H), 1.82(m, 1H), 3.46(m, 2H), 3.91(m, 2H), 4.58(m, 1H), 7.33(m, 1H), 7.42(m, 2H), 7.62(m, 1H), 7.66(m, 2H), 8.77(m, 2H); MS ES+ m/z 289 [MH]⁺.

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Step 6(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyric acid tert-butyl ester

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(2S)-2-Amino-3-(5-phenyl-oxazol-2-yl)propionic acid isobutyl ester hydrochloride (22.7g, 69mmol) was added to a solution of 1-[(2S)-2-(tert-butoxycarbonyl)-4-methoxybutyl]cyclopentanecarboxylic acid (WO 0279143 page 71 preparation 69) (20g, 68mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (14g, 74mmol), 1-hydroxybenzotriazole hydrate (10.2g, 74mmol) and 4-methylmorpholine (22mL, 200mmol) in dichloromethane (100mL) and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (700mL), washed with 2M hydrochloric acid (300mL), dried over magnesium sulphate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with pentane:ethyl acetate (80:20 to 66:33 to 50:50) to yield the title product as an oil, 35.7g

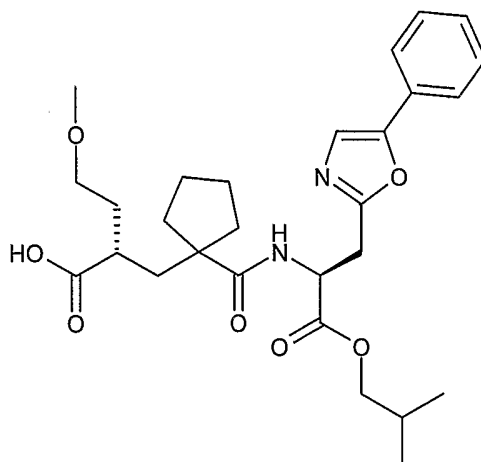
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(94%); ^1H NMR (CDCl_3 , 400MHz) δ 0.88(m, 6H), 1.40(s, 9H), 1.47-2.10(brm, (14H), 3.23(s, 3H), 3.27(m, 2H), 3.48(m, 1H), 3.91(m, 3H), 5.06(m, 1H), 7.11(d, 1H) 7.22-7.72(brm, 6H)
MS APCI m/z 571 $[\text{MH}]^+$

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Step 7

(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butrylic acid

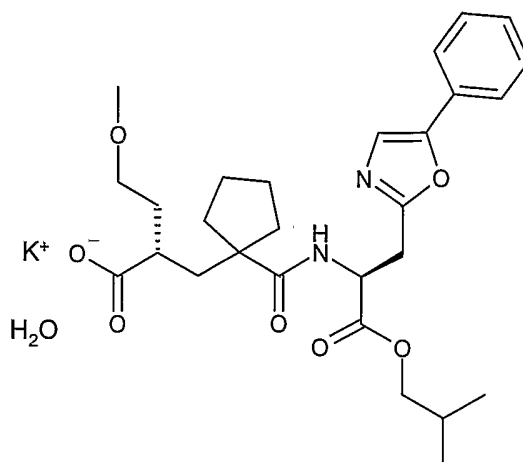


- 10 Trifluoroacetic acid (65mL) was added to a solution of (2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butrylic acid tert-butyl ester (35.7g, 62mmol) in toluene (100mL) and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated in vacuo and azeotroped with toluene (2x200mL). The crude product was purified by column chromatography on silica gel, eluting with ethyl
- 15 acetate:pentane (3:7 to 4:1) to yield the title product, as an oil containing ~50 mol% ethyl acetate (31g, 89%); ^1H NMR (CDCl_3 , 400MHz) δ 0.88(d, 6H), 1.64(m, 6H), 2.01(m, 7H), 3.28(s, 3H), 3.37(m, 2H), 3.46(m, 2H), 3.95(m, 2H), 5.07(m, 1H), 7.03(m, 1H), 7.30(m, 1H), 7.36(m, 1H), 7.41(m, 2H), 7.59(m, 2H), 10.06(brs, 1H);
MS ES- m/z 513 $[\text{MH}]^-$

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Step 8

Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butryate, monohydrate



(2S)-2-{1-[(1S)-1-isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethyl]carbamoyl]-cyclopentylmethyl}-4-methoxybutyric acid (viscous oil, containing approx. 50 mol% ethyl acetate, 2.73g, 4.9mmol) was dissolved in isobutanol (20ml) with gentle warming. Potassium t-butoxide (0.549g, 4.9mmol) was also dissolved in isobutanol (5ml) with gentle warming. The two solutions were allowed to cool to room temperature, and then mixed together. The isobutanol was removed under reduced pressure at 50°C, and the residual oil dried under vacuum (7mm Hg) at room temperature.

The resulting gum was triturated with a mixture of diethyl ether and pentane, the supernatant decanted and replaced with pentane, with further trituration. The decantation/trituration cycle was repeated several times with fresh pentane, until a fine white amorphous powder was obtained. The solvent was decanted, and the powder dried at room temperature under vacuum (7mm Hg) overnight, 2.33g. This material was crystallized from acetone to give colorless rods, 620mg, which were readily recrystallized twice from acetone to give colorless rods, 428mg, m.p. 96-100°C. Some crystals persisted in the melt up to 124°C. Once crystalline, the monopotassium salt readily recrystallized from a variety of solvents, always retaining a similar melting profile. Some of these are listed in order of apparent crystallinity of the product: methyl ethyl ketone, ethyl acetate, methyl isobutyl ketone, toluene. Microanalysis confirmed the product to be a stable monohydrate.

Found: C, 58.79; H, 6.88; N, 4.89. $C_{28}H_{37}N_2O_7K \cdot H_2O$ requires C, 58.93; H, 6.89; N, 4.91% M.W.

570.73

MS ES- m/z 513 [MH]⁺.

¹HNMR(400MHz, CD₃OD) δ: 0.88 (d, 6H), 1.4-1.65 (m, 7H), 1.75 (m, 2H), 1.86 (sept., 1H), 1.95-2.1 (m, 3H), 2.25 (m, 1H), 3.24 (s, 3H), 3.32 (m, 2H), 3.45 (dq, 2H), 3.89 (dd, 2H), 4.98 (t, 1H), 7.3-7.46 (m, 4H), 7.68 (d, 2H).

E) Pharmacology and Dose

The compounds of the invention can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

For example, the compounds of the invention can be administered orally, buccally or sublingually in the form of tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavoring or coloring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The compounds of the invention may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the compounds of the invention may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

General Example

A formulation of the tablet could typically contain between about 0.01mg and 500mg of active compound whilst tablet fill weights may range from 50mg to 1000mg. An example of a formulation for a 10mg tablet is illustrated below:

Ingredient	%w/w
Polymorph form 1	10.000*
Lactose	64.125
Starch	21.375
Croscarmellose Sodium	3.000
Magnesium Stearate	1.500

* Quantity adjusted in accordance with drug activity.

The tablets are manufactured by a standard process, for example, direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention may be combined with various sweetening or flavoring agents, coloring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Modified release and pulsatile release dosage forms may contain excipients such as those detailed for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not exclusively limited to, hydroxypropylmethyl cellulose, methyl cellulose,

sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, Xanthan gum, Carbomer, ammonio methacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients. Release rate modifying excipients may be present both within the dosage form i.e. within the matrix, and/or on the dosage form, i.e. upon the surface or coating.

Fast dispersing or dissolving dosage formulations (FDDFs) may contain the following ingredients: aspartame, acesulfame potassium, citric acid, croscarmellose sodium, crospovidone, diascorbic acid, ethyl acrylate, ethyl cellulose, gelatin, hydroxypropylmethyl cellulose, magnesium stearate, mannitol, methyl methacrylate, mint flavouring, polyethylene glycol, fumed silica, silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, sorbitol, xylitol. The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used i.e. where the drug substance is insoluble a fast dispersing dosage form can be prepared and where the drug substance is soluble a fast dissolving dosage form can be prepared.

The compounds of the invention can also be administered parenterally, for example, intracavernously, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion or needleless injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution that may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

The following dosage levels and other dosage levels herein are for the average human subject having a weight range of about 65 to 70 kg. The skilled person will readily be able to determine the dosage levels required for a subject whose weight falls outside this range, such as children and the elderly.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the invention will usually be from 0.01 mg/kg to 10 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the invention may contain from 1 mg to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The compounds of the invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable

propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide 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. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 to 50 mg of a compound of the invention for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 1 to 50 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

Alternatively, the compounds of the invention can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the invention may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary, vaginal or rectal routes.

They may also be administered by the ocular route, particularly for treating disorders of the eye. For ophthalmic use, the compounds can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubilizer. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

For treating cardiovascular disorders, such as hypertension, the compounds of the invention may be combined with one or more active ingredient selected from the list:

- a) angiotensin receptor blockers (ARB), such as losartan, valsartan, telmisartan, candesartan, irbesartan, eprosartan and olmesartan;
- 5 b) calcium channel blockers (CCB) such as amlodipine;
- c) statins, such as atorvastatin;
- d) PDE5 inhibitors, such as sildenafil, tadalafil, vardenafil, 5-[2-ethoxy-5-(4-ethyl)piperazin-1-ylsulphonyl]pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and; the pyrazolo[4,3-d]pyrimidin-4-ones disclosed in WO00/27848 particularly N-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]-pyrimidin-5-yl)-4-propoxyphenyl]sulfonyl]-1-methyl-2-pyrrolidinepropanamide [DA-8159 (Example 68 of WO00/27848)];
- 10 e) beta blockers, such as atenolol or carvedilol;
- 15 f) ACE inhibitors, such as quinapril, enalapril and lisinopril;
- g) alpha-blockers such as doxazosin;
- h) selective aldosterone receptor antagonists (SARA), such as eplerenone or spironolactone;
- i) imidazoline I₁ agonists, such as rilmenidine and moxonidine; and
- j) endothelin receptor antagonists and endothelin converting enzyme inhibitors.

20 For treating FSAD, the compounds of the invention may be combined with one or more active ingredient selected from the list:

- a) PDE5 inhibitors, such as sildenafil, tadalafil, vardenafil, 5-[2-ethoxy-5-(4-ethyl)piperazin-1-ylsulphonyl]pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and; the pyrazolo[4,3-d]pyrimidin-4-ones disclosed in WO00/27848 particularly N-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]-pyrimidin-5-yl)-4-propoxyphenyl]sulfonyl]-1-methyl-2-pyrrolidinepropanamide [DA-8159 (Example 68 of WO-00/27848)];
- 25 b) dopaminergic agents, preferably apomorphine or a selective D₂, D₃ or D₂/D₃ agonist such as, pramipexole and ropirinol (as claimed in WO-0023056), PNU95666 (as claimed in WO-00/40226);
- c) melanocortin receptor agonists, such as melanotan II; PT-14; PT-141; compounds claimed in WO-99/64002, WO-00/74679, WO-99/55679, WO-01/05401, WO-00/58361, WO-01/14879, WO-01/13112 and WO-99/54358; selective MC4 receptor agonists such as those disclosed by Martin *et al* [European Journal of Pharmacology, 454 71-79 (2002)] particularly (N-[(3*R*)-1,2,3,4-tetrahydroisoquinolinium-3-ylcarbonyl]-(1*R*)-1-(4-chlorobenzyl)-2-[4-cyclohexyl-4-(1H-1,2,4-triazol-1-ylmethyl)piperidin-1-yl]-2-oxoethylamine (THIQ); and selective MC3 receptor agonists
- 35 d) selective estrogen receptor modulators (SERMs) such as lasofoxifene and raloxifene;
- 40 e) tibolone;

- f) an androgen such as androsterone, dehydro-androsterone, testosterone, androstenedione and a synthetic androgen; and
- g) an oestrogen, such as oestradiol, oestrone, oestriol and a synthetic estrogen, such as oestrogen benzoate.

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For treating MED, the compounds of the invention may be combined with one or more active ingredient selected from the list:

- a) PDE5 inhibitors, such as sildenafil, tadalafil, vardenafil, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one and; the pyrazolo[4,3-d]pyrimidin-4-ones disclosed in WO00/27848 particularly N-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-propoxyphenyl]sulfonyl]-1-methyl-2-pyrrolidinepropanamide [DA-8159 (Example 68 of WO00/27848)];
- 15 b) dopaminergic agents, preferably apomorphine or a selective D₂, D₃ or D₂/D₃ agonist such as, pramipexole and ropirinol (as claimed in WO-00/23056), PNU95666 (as claimed in WO-00/40226); and
- c) melanocortin receptor agonists, such as melanotan II; PT-14; PT-141; compounds claimed in WO-99/64002, WO-00/74679, WO-99/55679, WO-01/05401, WO-00/58361, WO-01/14879, WO-01/13112 and WO-99/54358; selective MC4 receptor agonists such as those disclosed by Martin *et al* [European Journal of Pharmacology, 454 71-79 (2002)] particularly (N-[(3R)-1,2,3,4-tetrahydroisoquinolinium-3-ylcarbonyl]-(1R)-1-(4-chlorobenzyl)-2-[4-cyclohexyl-4-(1H-1,2,4-triazol-1-ylmethyl)piperidin-1-yl]-2-oxoethylamine (THIQ); and selective MC3 receptor agonists.

25

If a combination of active agents are administered, then they may be administered simultaneously, separately or sequentially.

The invention also includes the following aspects.

- (i) A pharmaceutical composition including a compound of the invention, together with a pharmaceutically acceptable excipient, diluent or carrier.
- (ii) A compound of the invention for use as a medicament.
- (iii) The use of a compound of the invention as a medicament for treating or preventing a condition for which a beneficial therapeutic response can be obtained by the inhibition of neutral endopeptidase.
- 35 (iv) The use of a compound of the invention as a medicament for treating cardiovascular diseases and conditions, for example: essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, renovascular hypertension, congestive heart failure, angina, stroke, glaucoma, impaired renal function, renal failure, obesity, metabolic diseases (including Metabolic Syndrome), diabetes and

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impaired glucose tolerance, including complications thereof, such as diabetic retinopathy and diabetic neuropathy.

- 5 (v) A method of treating cardiovascular diseases and conditions, including but not limited to, essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, renovascular hypertension, congestive heart failure, angina, stroke, glaucoma, impaired renal function, renal failure, obesity, metabolic diseases (including Metabolic Syndrome), diabetes and impaired glucose tolerance, including complications thereof, such as diabetic retinopathy and diabetic neuropathy in a mammal including treating said mammal with an effective amount of a compound of the invention.
- 10 (vi) A cardiovascular disease treating pharmaceutical composition comprising a compound of the invention together with a pharmaceutically acceptable excipient, diluent or carrier.
- 15 (vii) A compound of the invention for use in treating or preventing cardiovascular diseases and conditions.
- (viii) The use of a compound of the invention in the manufacture of a medicament for treating or preventing cardiovascular diseases and conditions.

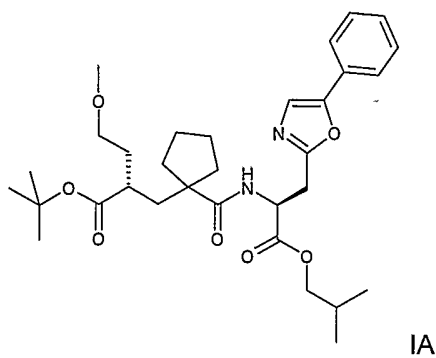
20 The compounds and compositions of the invention may be administered in a unit dosage form contained in a package or kit. The kit includes the unit dosage form and a container. Typically, the kit includes directions for administration of the unit dosage form according to a therapeutic schedule. The container can be in any conventional shape or form as known in the art, for example, a paper box, a glass or plastic bottle, or a blister pack with individual dosage forms

25 pressing out of the back.

CLAIMS

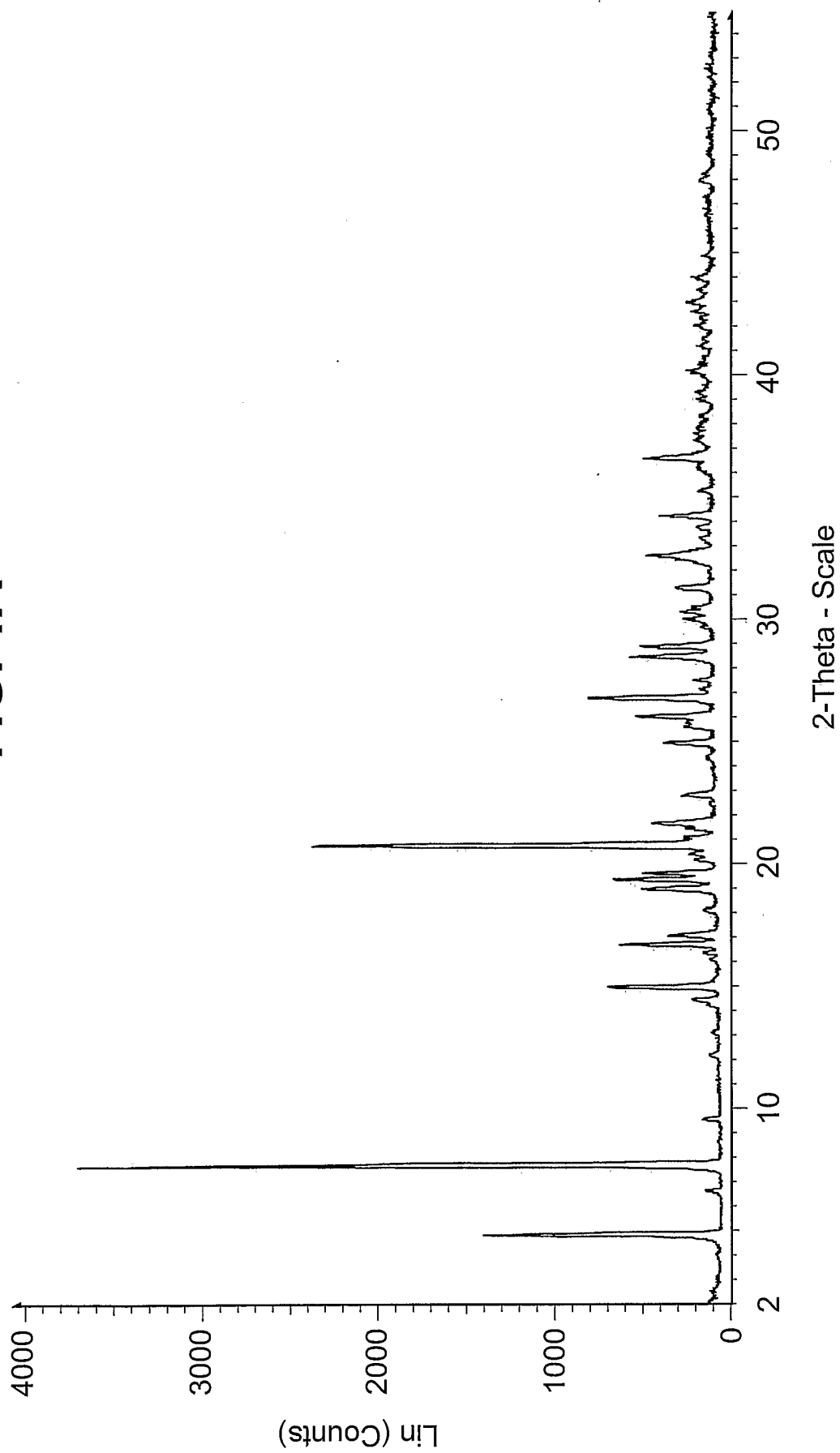
What is claimed is:

1. Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates or hydrates thereof.
2. A crystalline form of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates or hydrates thereof.
3. Form 1 polymorph of Potassium-(2S)-2-{1-[(1S)-1-Isobutoxycarbonyl-2-(5-phenyl-oxazol-2-yl)-ethylcarbamoyl]-cyclopentylmethyl}-4-methoxy-butyrates, monohydrate.
4. A polymorph of claim 2 having a Powder X-ray diffraction pattern substantially as shown in Figure 1A or 1B .
5. A polymorph of claim 2 having a Powder X-ray diffraction pattern with at least one peak at about 4.7, about 7.6, about 14.9, about 19.2, about 19.5, about 20.7, about 26.0 or about 26.7 degrees 2 θ .
6. A crystalline polymorph of claim 5 having a Powder X-ray diffraction pattern with a peak at about 7.6 $\pm$ 0.2 degrees 2 θ .
7. A crystalline polymorph of claim 6 having a Powder X-ray diffraction pattern with at least one additional peak at about 20.7 degrees 2 θ .
8. A crystalline polymorph of claim 7 having a Powder X-ray diffraction pattern with at least one additional peak at about 4.7 degrees 2 θ .
9. A pharmaceutical composition comprising a compound according to any one of claims 1-8 together with a pharmaceutically acceptable excipient, diluent or carrier.
10. A process for forming the polymorph of any one of Claims 1-9, comprising:
 - a) reacting (2S)-2-Amino-3-(5-phenyl-oxazol-2-yl) propionic acid isobutyl ester hydrochloride with 1-[(2S)-2-(tert-butoxycarbonyl)-4-methoxybutyl]cyclopentanecarboxylic acid) with a coupling agent in the presence of a solvent to form the compound 1A;

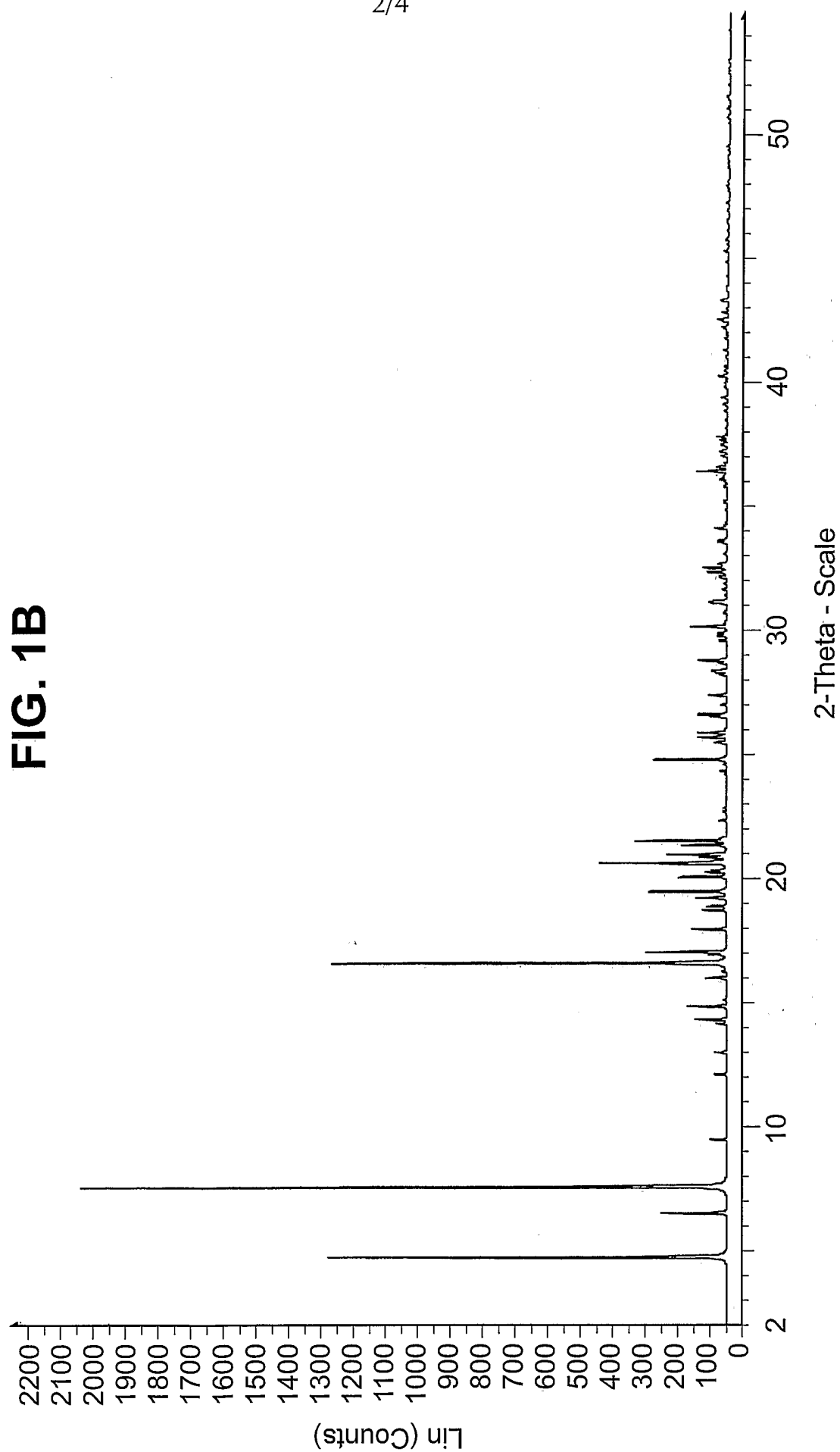


- b) deprotecting compound IA
c) reacting the product of (b) with a potassium base to yield the potassium salt; and
d) crystallizing the compound of (c) with acetone.

1/4

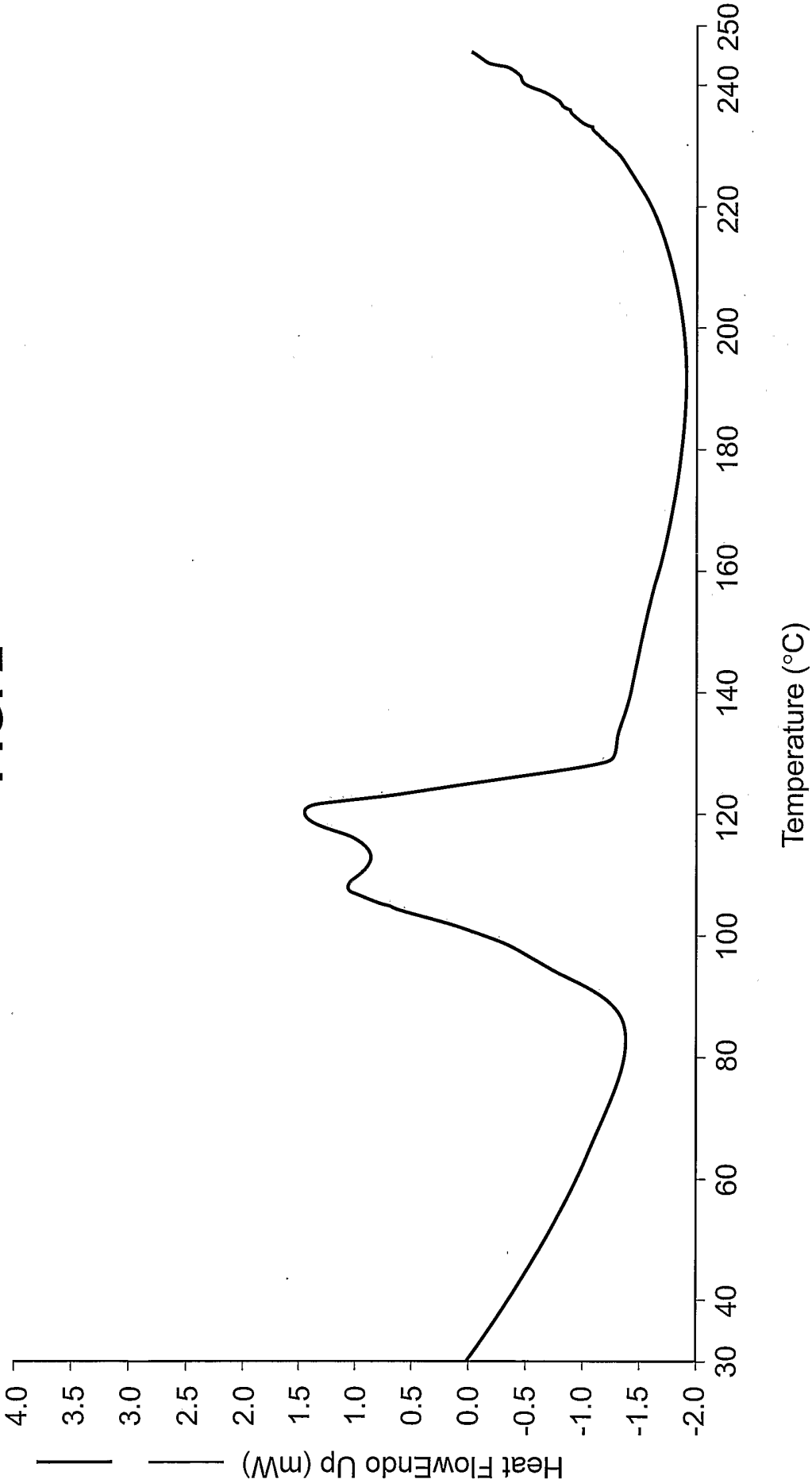
FIG. 1A

2/4



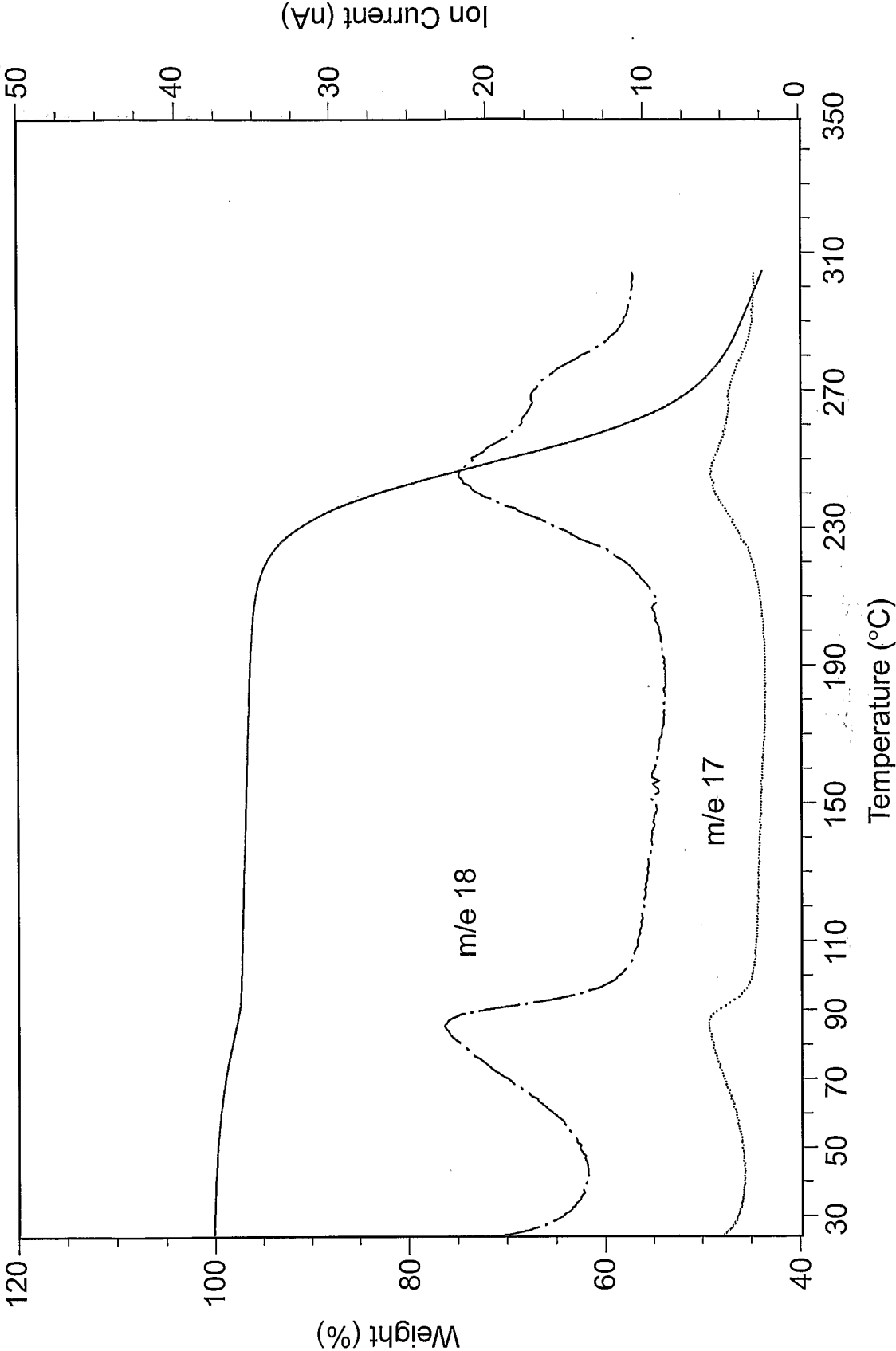
3/4

FIG. 2



4/4

FIG. 3



INTERNATIONAL SEARCH REPORT

Intern: Application No
PCT/IB2005/001911

A. CLASSIFICATION OF SUBJECT MATTER
C07D263/32 A61K31/421 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 180 665 B1 (DUNN PETER JAMES ET AL) 30 January 2001 (2001-01-30) Column 1, Formula (I) column 1, lines 36-42 column 1, line 66 - column 2, line 2 -----	1-10
P,A	WO 2004/056787 A (PFIZER LIMITED; DACK, KEVIN, NEIL; OWEN, DAFYDD, RHYS; WATSON, CHRISTI) 8 July 2004 (2004-07-08) cited in the application Example 28 in combination with Preparation 84 -----	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

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- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *&* document member of the same patent family

Date of the actual completion of the international search

22 November 2005

Date of mailing of the international search report

30/11/2005

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INTERNATIONAL SEARCH REPORT

Internat Application No
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