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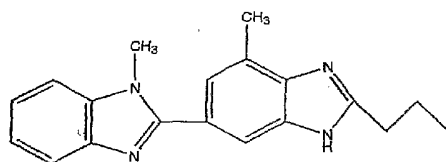
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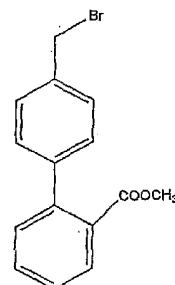
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF TELMISARTAN



(II)



(III)

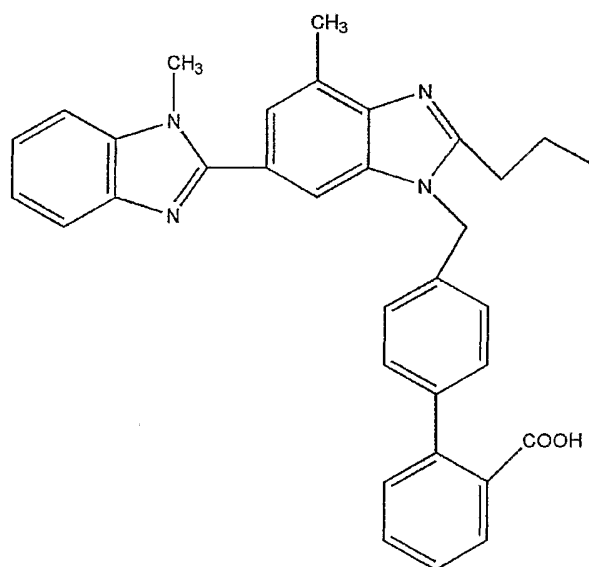
(57) Abstract: An improved process for the preparation of telmisartan, or a pharmaceutically acceptable salt thereof, comprises subjecting 1H-Benzimidazole-2-n-propyl-4-methyl-6-(1'-methyl benimidazole-2'yl) of formula (II) and methyl-4-(bromomethyl) biphenyl-2-carboxylate of formula (III) to condensation and hydrolysis in a single step.

WO 2005/108375 A1

PROCESS FOR THE PREPARATION OF TELMISARTAN

The present invention relates to a process for the preparation of telmisartan [4' - [2-n-propyl-4-methyl-6-(1-methyl-benzimidazol-2-yl) benzimidazol-1-yl methyl] biphenyl-2-carboxylic acid] in a "one pot" synthesis, which is thus simple and cost effective, and produces telmisartan with high product yield and quality.

Telmisartan is known from EP 0502314B and has the following chemical structure of formula (I)



(I)

Telmisartan is an angiotensin II receptor antagonist, which by virtue of its pharmacological properties is particularly useful in the treatment of hypertension and cardiac insufficiency.

Chinese Patent CN 1344172 discloses the preparation of telmisartan in two steps: namely condensation and hydrolysis.

US 5591762 discloses the preparation of telmisartan from its tertiary butyl ester. Hydrolysis is carried out using trifluoro acetic acid in dimethyl formamide at room temperature and maintained for about 12 hours. The crude product obtained is purified over a silica gel column and finally crystallized from acetone.

US 2002/0094997 is a divisional application of US 6358986. US 2002/0094997 discloses polymorphs of telmisartan, particularly polymorphic form B, polymorphous mixtures and their preparation. Accordingly, telmisartan Form A is dissolved in a mixture of solvents consisting of water, formic acid and an organic solvent that is miscible therewith; the solution is heated followed by distillation and telmisartan containing Form A and Form B is precipitated from the mixture by addition of a base. The disclosure further refers to advantages of the polymorphic Form B mixture, for example it is easily filterable and has a low tendency to electrostatic charging. The disclosure still further refers to the fact that Form A, which is obtained according to the basic patent, is difficult to filter, is characterized by a very long drying time and exhibits a strong tendency to electrostatic charging. The two telmisartan polymorphs of Form A and B as characterised by US 2002/0094997 differ considerably in their melting point: Form B melts at 183°C (determined by DSC), Form A at 269°C (determined by DSC). The polymorphs A and B also differ in their IR spectrum. Pure polymorph A has a characteristic band at 815 cm⁻¹ in the IR spectrum. In polymorph B, this oscillation is shifted to 830 cm⁻¹.

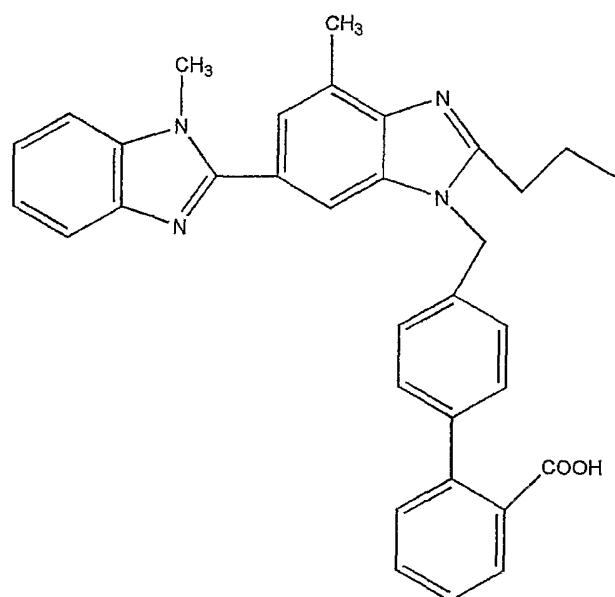
In all the prior art processes, telmisartan is prepared in two or three steps, which is time consuming, product is lost during intermediate isolation, and as such there is a resulting low yield of the final product. It is also suggested in the prior art that the use of dimethyl formamide and alkali metal carbonates as solvent resulted in dimer formation, which also contributed to low yield.

The aim of the present invention is, therefore, to provide an improved process for the preparation of telmisartan. In particular, it is an aim of the present invention to prepare telmisartan in a one step process, thereby increasing the yield, decreasing the cost and avoiding filtration and drying problems.

Surprisingly, it has been found according to the present invention that telmisartan can be synthesised in one step from intermediates [1H – Benzimidazole – 2- n-propyl-4-methyl-6-(1'-methyl benzimidazole-2'-yl)] and methyl-4-(bromomethyl) biphenyl-2-carboxylate.

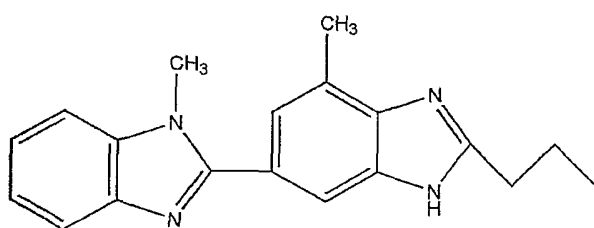
According to the present invention, therefore, there is provided a process for the preparation of telmisartan of formula (I), or a pharmaceutically acceptable salt thereof

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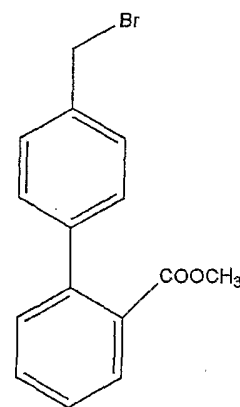


(I)

characterised in that 1H-Benzimidazole-2-n-propyl-4-methyl-6-(1'-methyl benzimidazole-2'yl) of formula (II), and methyl-4-(bromomethyl) biphenyl-2-carboxylate of formula (III), are subjected to condensation and hydrolysis in a single step (in other words, a "one pot" synthesis)



(II)



(III)

Intermediate compounds of formulae (II) and (III) are preferably reacted according to a process of the present invention in a polar aprotic solvent in the presence of a base. Polar aprotic solvents are well known in the art and can include, for example, dimethyl acetamide, dimethyl formamide, dimethyl sulphoxide, and the like, with the use of dimethyl formamide

or dimethyl sulphoxide being preferred, especially dimethyl sulphoxide. Preferred bases for use in a method according to the present invention are alkali metal hydroxides.

A process according to the present invention is preferably carried out at a temperature in the range of about 10 to 80°C, with a preferred temperature being in the range of about 25 to 50°C. The reaction time for a process according to the present invention is typically in the range of from about a few minutes to a few hours, depending on the exothermicity of the reaction. Telmisartan is then typically isolated from the reaction mass by adjusting the pH using aqueous acids, suitably for example the pH is adjusted to be in the range of about 3 to 4.5 using acetic acid, optionally followed by extraction in a water-immiscible solvent.

Telmisartan can be isolated directly after pH adjustment by filtration without proceeding to extraction in a water-immiscible solvent. However, the use of the extraction phase is preferred because telmisartan as obtained directly after pH adjustment can be slimy in nature, thereby resulting in slow filtration properties. It is therefore preferable to extract telmisartan into a suitable solvent and isolate it from a non-solvent. A preferred water-immiscible solvent for extraction can be any of dichloromethane, ethyl acetate, chloroform or any other suitable water-immiscible solvent, with the use of dichloromethane being preferred. The organic layer is then suitably concentrated and isolated by addition of a suitable solvent, such as methanol, acetone, diisopropyl ether, acetonitrile or isopropyl acetate, with the use of acetone being preferred.

The present invention further provides telmisartan, or a pharmaceutically acceptable salt thereof, prepared by a process substantially as hereinbefore described. Telmisartan as prepared and isolated (typically employing acetone) by a process according to the present invention advantageously comprises free flowing polymorphic Form A, which can be similarly characterised by the melting point and IR properties as described above for Form A as defined in US 2002/0094997. Telmisartan Form A as provided by the present invention, however, is preferable over telmisartan Form A as prepared by prior art methods, in view of the free flowing properties of telmisartan as provided by the present invention compared to the poor flow characteristics of telmisartan Form A as provided by the prior art, for which the filtration rate can be very slow.

Telmisartan Form A as prepared by a process according to the present invention advantageously has a purity of at least about 97% and is typically obtained in a yield of about 80-88%.

The invention may also comprise further purification of telmisartan so as to achieve a highly pure compound. Preferably, telmisartan is subjected to purification by dissolving it in methanol and a methanolic ammonia mixture and isolating. Preferably, isolation is done by adjusting the pH using acetic acid, suitably to a pH of 3.5 – 4.0.

According to a preferred embodiment of the present invention, it may be desirable to isolate telmisartan as a pharmaceutically acceptable salt, such as the sodium or potassium salt of telmisartan. Telmisartan in salt form is suitably isolated from the reaction mass prior to pH adjustment.

Telmisartan, or a pharmaceutically acceptable salt thereof, has pharmaceutical utility as an angiotensin II receptor antagonist, and in view of the pharmacological properties thereof, telmisartan, or a pharmaceutically acceptable salt thereof, is suitable for the treatment of hypertension and cardiac insufficiency and also for treating ischaemic peripheral circulatory disorders, myocardial ischaemia (angina), for the prevention of the progression of cardiac insufficiency after myocardial infarction and for treating diabetic nephropathy, glaucoma, gastrointestinal diseases and bladder diseases. In particular, telmisartan, or a pharmaceutically acceptable salt thereof, as provided by the present invention is useful for the treatment of hypertension.

Telmisartan, or a pharmaceutically acceptable salt thereof, as provided by the present invention is also suitable for treating pulmonary diseases, e.g. lung oedema and chronic bronchitis, for preventing arterial restenosis after angioplasty, for preventing thickening of blood vessel walls after vascular operations, and for preventing arteriosclerosis and diabetic angiopathy. In view of the effects of angiotensin on the release of acetyl-choline and dopamine in the brain, telmisartan, or a pharmaceutically acceptable salt thereof, as provided by the present invention is also suitable for alleviating central nervous system disorders, e.g. depression, Alzheimer's disease, Parkinson syndrome, bulimia and disorders of cognitive function.

The present invention further provides, therefore, a pharmaceutically acceptable

composition for administering to a patient, suffering from, or susceptible to, a disease state prevented, ameliorated or eliminated by the administration of an angiotensin II receptor antagonist, which composition comprises a therapeutically effective amount of telmisartan, or a pharmaceutically acceptable salt thereof, prepared according to the present invention, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

As used herein, the term "therapeutically effective amount" means an amount of telmisartan, or a pharmaceutically acceptable salt thereof, which is capable of preventing, ameliorating or eliminating a disease state for which administration of an angiotensin II receptor antagonist is indicated.

By "pharmaceutically acceptable composition" it is meant that the carrier, diluent or excipient is compatible with telmisartan, or a pharmaceutically acceptable salt thereof, and not deleterious to a recipient thereof. For this purpose, telmisartan, or a pharmaceutically acceptable salt thereof, optionally in conjunction with other active substances, such as hypotensives, diuretics and/or calcium antagonists, may be incorporated together with one or more inert conventional carriers and/or diluents, for example with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene-glycol, propylene-glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, in conventional pharmaceutical preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The pharmaceutical compositions of the present invention may be prepared by conventional methods known in the art. For example, tablets may be prepared by mixing telmisartan, or a pharmaceutically acceptable salt thereof, according to the present invention, with known adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. The particular dosage form of telmisartan, or a pharmaceutically acceptable salt thereof, required to treat a disease state prevented, ameliorated or eliminated by the administration of an angiotensin II receptor antagonist as described herein in a patient, will depend on the particular disease state or condition, and the symptoms and severity thereof. Dosage, routes of administration, and frequency of dosing are best decided by an attending physician.

The present invention further provides telmisartan, or a pharmaceutically acceptable salt thereof, prepared according to the present invention, for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of an angiotensin II receptor antagonist as described herein.

The present invention also provides a method of treating a disease state prevented, ameliorated or eliminated by the administration of an angiotensin II receptor antagonist in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of telmisartan, or a pharmaceutically acceptable salt thereof, prepared according to the present invention, substantially as hereinbefore described.

The present invention will now be further illustrated by the following Examples, which do not limit the scope of the invention in any way.

Example 1

Preparation of [4'-(2-n-propyl-4-methyl-6-(1-methyl benzimidazol-2-yl) benzimidazol-1-yl methyl] biphenyl-2-carboxylic acid]

50 gm of [1H — Benzimidazole-2-n-propyl-4-methyl-6-(1-methyl benzimidazole-2'-yl)] was added to 200 ml dimethyl sulfoxide and 50 gm of potassium hydroxide. To this was added 60 gm of methyl-4-(bromomethyl) biphenyl-2-carboxylate at ambient temperature. The contents were stirred for 2 hours at 25-30°C, then heated to 40-50°C and maintained for 2 hours. About 500 ml water was added to the reaction mixture at room temperature and acidified to pH 4 with acetic acid. The reaction mixture was filtered and washed with purified water, dried under reduced pressure at 50-60°C to give 80 gm (88 %) of the title product.

Example 2

Preparation of [4'-(2-n-propyl-4-methyl-6-(1-methyl benzimidazol-2-yl)benzimidazol —1-yl methyl]biphenyl-2-carboxylic acid]

50 gm of [1H — Benzimidazole-2-n-propyl-4-methyl-6-(1'- methyl benzimidazole-2'-yl)] was added to 200 ml dimethyl sulphoxide and 50 gm of potassium hydroxide. To this

was added 60 gm of methyl-4- (bromomethyl) biphenyl-2-carboxylate at ambient temperature. The contents were stirred for 2 hours at 25-30°C. The contents were heated to 40-50°C and maintained for 2 hours. About 500 ml water was added to the reaction mixture at room temperature and acidified with acetic acid to pH 3.8, extracted twice with 250 ml of dichloromethane and the combined extracts were concentrated and isolated by filtration after addition of 300 ml acetone, dried under reduced pressure at 50-60°C to give 75 gm (80 %) of the title product

Example 3

Preparation of [4' - [2-n-propyl-4-methyl-6-(1-methyl benzimidazol-2-yl) benzimidazol -1-yl methyl] biphenyl-2-carboxylic acid]

50 gm of [1H — Benzimidazole-2-n - propyl-4-methyl-6-(1'-methyl benzimidazole-2'-yl)] was added to 200 ml dimethyl sulfoxide and 50 gm of sodium hydroxide. To this was added 60 gm of methyl-4- (bromomethyl) biphenyl-2-carboxylate at ambient temperature. The contents were stirred for 2 hours at 25-30°C and then heated to 40-50 and maintained for 2 hours. About 500 ml water was added to the reaction mixture and acidified with acetic acid to pH 4.2, extracted twice with 250 ml of dichloromethane and the combined extracts were concentrated and isolated by filtration after addition of 300 ml acetone, dried under reduced pressure at 50-60°C to give 75.0 gm (80%) of the title compound.

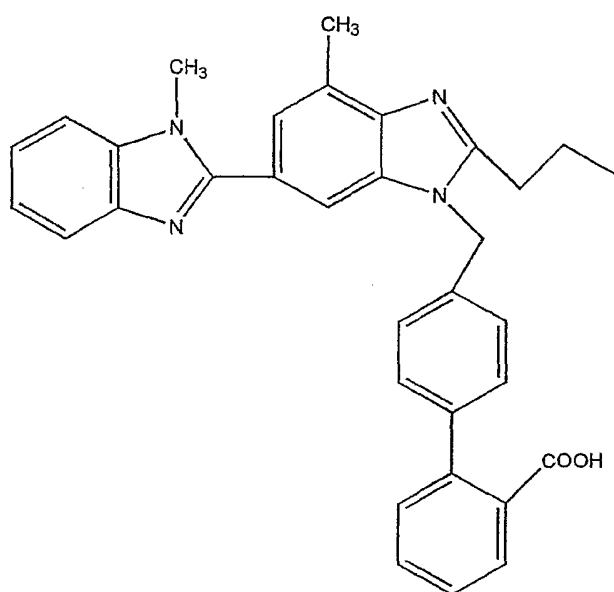
Example 4

Purification of [4' - [2-n-propyl-4-methyl-6-(1-methyl benzimidazol-2-yl) benzimidazol-1-yl methyl] biphenyl-2-carboxylic acid]

50gm of [4' - [2-n-propyl-4-methyl-6-(1-methyl benzimidazol-2-yl) benzimidazol-1-yl methyl] biphenyl-2-carboxylic acid] (obtained according to any of Examples 1, 2 or 3) was added to 500ml of methanol. To this was slowly added 50ml of methanolic ammonia (10-15%) at 25-30°C. The contents were stirred for 30 minutes at 25-30°C. About 3gm charcoal was added and stirred at 25-30°C for 30 minutes. The reaction mixture was filtered over hyflo, bed washed with methanol. The clear filtrate pH was adjusted to 3.5-4.0 using acetic acid. The contents were stirred at 20-30°C for 1 hour. Pure telmisartan was isolated by filtration, dried under reduced pressure at 50-60°C to yield 45gm (90%) of the title product with HPLC purity of about 99.3%.

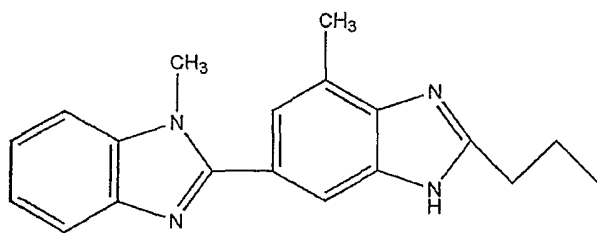
CLAIMS

1. A process for the preparation of telmisartan of formula (I), or a pharmaceutically acceptable salt thereof

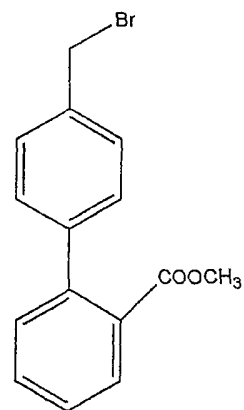


(I)

characterised in that 1H-Benzimidazole-2-n-propyl-4-methyl-6-(1'-methyl benzimidazole-2'yl) of formula (II) and methyl-4-(bromomethyl) biphenyl-2-carboxylate of formula (III) are subjected to condensation and hydrolysis in a single step



(II)



(III)

2. A process according to claim 1, wherein intermediate compounds of formulae (II) and (III) are reacted in a polar aprotic solvent in the presence of a base.
3. A process according to claim 2, wherein said polar aprotic solvent is selected from the group consisting of dimethyl acetamide, dimethyl formamide and dimethyl sulphoxide.
4. A process according to claim 3, wherein said polar aprotic solvent is either dimethyl formamide or dimethyl sulphoxide.
5. A process according to claim 4, wherein said polar aprotic solvent is dimethyl sulphoxide.
6. A process according to any of claims 2 to 5, wherein said base is an alkali metal hydroxide.
7. A process according to any of claims 1 to 6, which is carried out at a temperature in the range of about 10 to 80°C.
8. A process according to claim 7, which is carried out at a temperature in the range of about 25 to 50°C.
9. A process according to any of claims 1 to 8, wherein telmisartan, or a pharmaceutically acceptable salt thereof, is isolated from the reaction mass by adjusting the pH using an aqueous acid.
10. A process according to claim 9, wherein said pH is adjusted to be in the range of about 3 to 4.5.
11. A process according to claim 9 or 10, wherein said aqueous acid is acetic acid.

12. A process according to any of claims 9 to 11, wherein telmisartan, or a pharmaceutically acceptable salt thereof, is isolated by filtration directly after pH adjustment by said acid.
13. A process according to any of claims 9 to 11, wherein further to pH adjustment telmisartan is extracted into a suitable water-immiscible solvent and then isolated from a non-solvent.
14. A process according to claim 13, wherein said water-immiscible solvent is selected from the group consisting of dichloromethane, ethyl acetate and chloroform.
15. A process according to claim 14, wherein said water immiscible solvent is dichloromethane.
16. A process according to any of claims 13 to 15, wherein said non-solvent is selected from the group consisting of methanol, acetone, diisopropyl ether, acetonitrile and isopropyl acetate.
17. A process according to claim 16, wherein said non-solvent is acetone.
18. A process according to any of claims 1 to 17, wherein telmisartan is isolated as a pharmaceutically acceptable salt thereof.
19. A process according to claim 18, wherein telmisartan is isolated as the sodium or potassium salt thereof.
20. A process according to any of claims 1 to 19, which prepares telmisartan, or a pharmaceutically acceptable salt thereof, with a purity of at least about 97%.
21. A process according to any of claims 1 to 20, which prepares telmisartan, or a pharmaceutically acceptable salt thereof, in a yield of about 80-88%.

22. A process according to any of claims 1 to 21, which prepares telmisartan, or a pharmaceutically acceptable salt thereof, as telmisartan Form A.
23. Telmisartan, or a pharmaceutically acceptable salt thereof, prepared by a process according to any of claims 1 to 22.
24. Telmisartan according to claim 23, which is telmisartan Form A.
25. Telmisartan according to claim 23 or 24, which has a purity of at least about 97%.
26. A pharmaceutically acceptable composition for administering to a patient, suffering from, or susceptible to, a disease state prevented, ameliorated or eliminated by the administration of an angiotensin II receptor antagonist, which composition comprises a therapeutically effective amount of telmisartan, or a pharmaceutically acceptable salt thereof, according to any of claims 23 to 25, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.
27. Telmisartan, or a pharmaceutically acceptable salt thereof, according to any of claims 23 to 25, for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of an angiotensin II receptor antagonist.
28. A method of treating a disease state prevented, ameliorated or eliminated by the administration of an angiotensin II receptor antagonist in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of telmisartan, or a pharmaceutically acceptable salt thereof, according to any of claims 23 to 25.

INTERNATIONAL SEARCH REPORT

 Internat. Application No
 PCT/GB2005/001799

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D235/18 A61K31/4184 A61P9/02 A61P9/04

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)
 IPC 7 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, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 502 314 A (THOMAE, DR. KARL, G.M.B.H., GERMANY) 9 September 1992 (1992-09-09) cited in the application methods b) and c) pp.12-13; example 9	1-28
X	US 6 358 986 B1 (SCHNEIDER, HEINRICH) 19 March 2002 (2002-03-19) cited in the application column 1, lines 19-51 column 5, line 55 - column 6, line 11; claims 1,2	23-28
X	US 2002/094997 A1 (SCHNEIDER HEINRICH ET AL) 18 July 2002 (2002-07-18) cited in the application column 1, paragraph 2-6; claim 1	23-28
	-/--	

 Further documents are listed in the continuation of box C.

 Patent family members are listed in annex.

° Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *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
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

3 August 2005

Date of mailing of the international search report

10/08/2005

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2
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 Fax: (+31-70) 340-3016

Authorized officer

Schuemacher, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/001799

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/27397 A (GLAXO GROUP LIMITED; BOEHRINGER INGELHEIM INTERNATIONAL GMBH) 18 May 2000 (2000-05-18) page 1, lines 16-29; claims 1-3 -----	26-28
P,X	WO 2004/087676 A1 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH, GERMANY; BOEHRINGER INGELHEIM) 14 October 2004 (2004-10-14) claim 1 ----- -----	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/001799

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 28 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/GB2005/001799

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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