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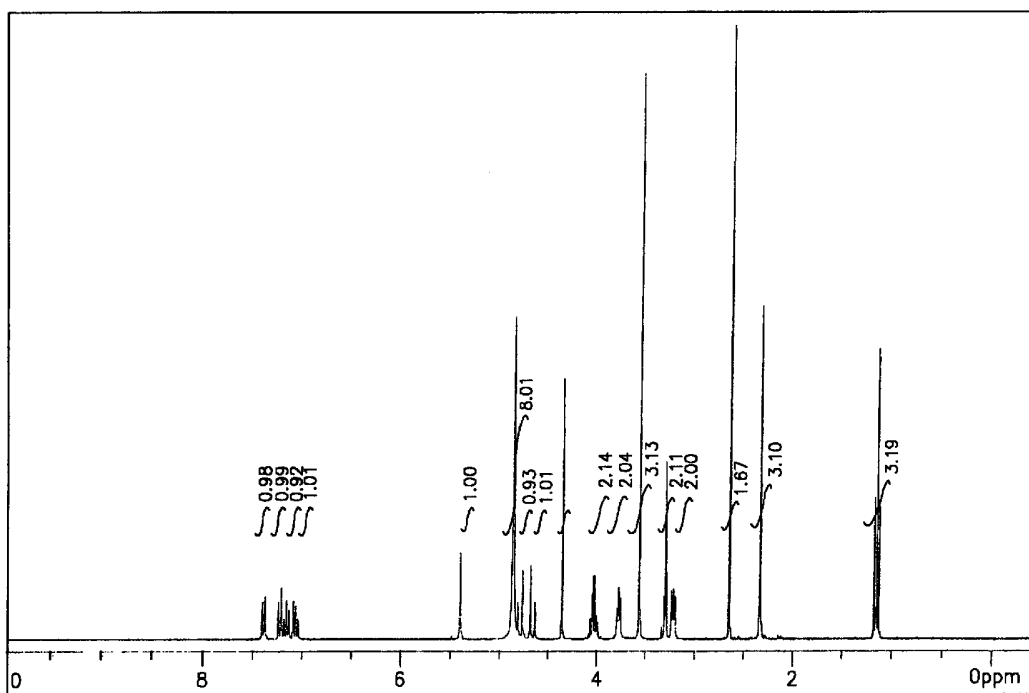
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- (71) Applicant (for all designated States except US): **HANLIM PHARMACEUTICAL CO., LTD.** [KR/KR]; 1656-10 Seocho-dong, Seocho-gu, Seoul 137-071 (KR).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **CHUNG, You-Sup** [KR/KR]; 101-802 Neulpureun Byuksan Apt., 488, Manpo-dong, Paldal-gu, Suwon-city, Kyungki-do 442-400 (KR). **HA, Mun-Choun** [KR/KR]; 105-1707 Injeong Melody Apt., Dunjeon-ri, Pogok-myun, Yongin-city, Kyungki-do 449-812 (KR).
- (74) Agent: **KIM, Eui-Bak**; The Cheonghwa Bldg., 1571-18 Seocho-dong, Seocho-gu, Seoul 137-874 (KR).
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(54) Title: PROCESSES FOR THE PREPARATION OF S-(-)-AMLODIPINE



(57) Abstract: The present invention provides a process for the preparation of S-(-)-amlodipine from (R,S)-amlodipine in industrial-scale using L-(+)-tartaric acid, which is much cheaper than D-(-)-tartaric acid.

WO 2004/024689 A1

PROCESSES FOR THE PREPARATION OF S-(-)-AMLODIPINE

Technical Field

5 The present invention relates to a process for the preparation of S-(-)-amlodipine, more specifically, to a process for the preparation of S-(-)-amlodipine from (R,S)-amlodipine in industrial-scale using L-(+)-tartaric acid, which is much cheaper than D-(-)-tartaric acid.

10 Background Art

 Amlodipine, with a chemical name of 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate, is a potent and long-acting calcium channel blocker useful as an anti-ischaemic and anti-hypertensive agent. It is known that two types of enantiomers of amlodipine have different pharmacological profiles. S-(-)-isomer is a more potent calcium channel blocker than R-(+)-isomer, while the R-(+)-isomer also exhibits an activity in the treatment or prevention of atherosclerosis.

20 *J. Med. Chem.* (1986) 29 1696 discloses a process for the preparation of the two enantiomers of amlodipine via separation of the diastereomeric azide esters, and EP 331,315 A1 discloses the use of cinchonidine salts for the resolution of intermediates to eventually give enantiomerically pure amlodipine isomers. *J. Med. Chem.* (1992) 35 3341 discloses a chromatographic separation of diastereomeric amide isomers.

25 Further, WO 95/25722 discloses a method for the separation of the (R)-(+)- and (S)-(-)-isomers of amlodipine from mixtures thereof, which comprises reacting the mixture of isomers with either L-(+)- or D-(-)-tartaric acid in dimethyl sulfoxide (DMSO) for the preparation of, respectively, a DMSO solvate of an L-tartrate salt of (R)-(+)-amlodipine, or a DMSO solvate of a D-tartrate salt of (S)-(-)-amlodipine.

In order to manufacture (S)-(-)-amlodipine, having a more potent calcium channel blocking activity, the process according to WO 95/25722 employs D-tartaric acid. However, the fact that D-(-)-tartaric acid is very expensive compared to L-(+)-tartaric acid is unfavorable for industrial-scale mass
5 production of (S)-(-)-amlodipine.

Therefore, a method of industrial-scale mass production of (S)-(-)-amlodipine has been in demand.

Disclosure of the Invention

10

The present invention provides a process for the preparation of S-(-)-amlodipine from (R,S)-amlodipine in industrial-scale using L-(+)-tartaric acid, which is much cheaper than D-(-)-tartaric acid.

Further, the present invention provides synthetic intermediates for the
15 preparation of S-(-)-amlodipine.

In one aspect of the present invention, there is provided a process for the preparation of S-(-)-amlodipine, which comprises (i) reacting (R,S)-amlodipine with L-(+)-tartaric acid in dimethyl sulfoxide (DMSO); (ii) filtering off the resulting precipitate of step (i); (iii) precipitating
20 (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate by adding methylene chloride to the filtrate of step (ii); (iv) optionally forming (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate by adding an alcohol to (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate obtained in step (iii); and (v) treating with a base (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate obtained
25 in step (iii) or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate obtained in step (iv).

In another aspect of the present invention, there is provided (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate, each being useful for the
30 preparation of S-(-)-amlodipine.

Brief Description of the Drawings

The above and other features and advantages of the present invention will become more apparent by describing in detail illustrative, non-limiting embodiments thereof with reference to the attached drawings, in which:

5 FIG. 1 shows a $^1\text{H-NMR}$ chart of (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate; and

 FIG. 2 shows shows a $^1\text{H-NMR}$ chart of (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate.

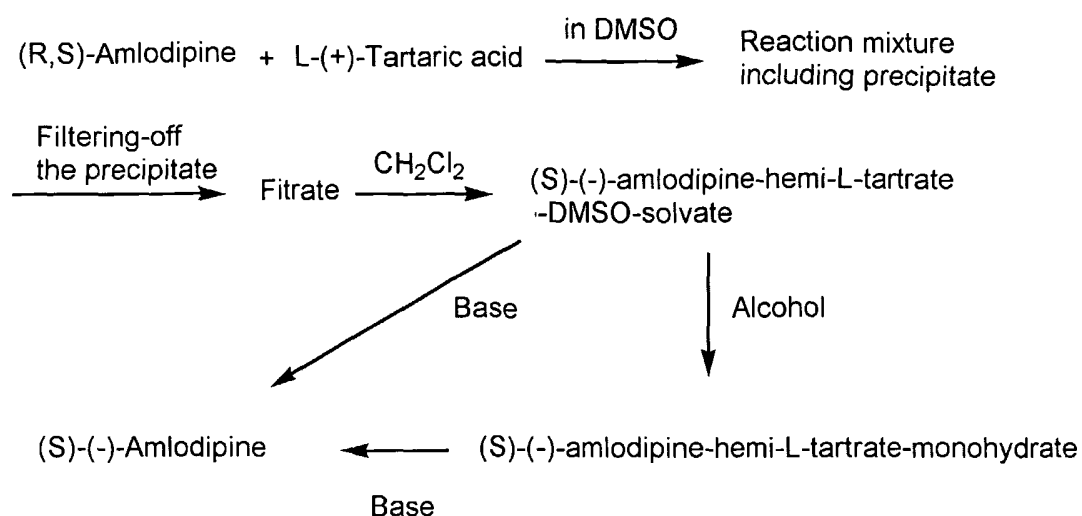
10 Best mode for carrying out the Invention

The present invention provides an economic process for preparing S-(-)-amlodipine in high yield and enantiomeric purity. According to the process of the present invention, (R,S)-amlodipine is reacted with L-(+)-tartaric acid in dimethyl sulfoxide (DMSO) and the resulting precipitate is filtered off. The resultant filtrate is added with methylene chloride to precipitate (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate. Optionally, (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate is added with an alcohol to form (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate. or (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate is treated with a base.

The following reaction scheme illustrates the process of the present invention.

25

Reaction Scheme :



L-(+)-tartaric acid is much cheaper than D-(-)-tartaric acid, and greatly
downs the production cost, which is very favorable for industrial-scale mass
5 production of S-(-)-amlodipine. Preferably, the amount of L-(+)-tartaric acid is
about 0.5~0.55 eq. to 1 eq. of (R,S)-amlodipine.

In one embodiment, (R,S)-Amlodipine is reacted with L-(+)-tartaric acid
in dimethyl sulfoxide (DMSO) to give a precipitate,
(R)-(+)-amlodipine-hemi-L-tartrate-DMSO-solvate, which is then filtered off.
10 The amount of DMSO is about 4 – 6 times, preferably about 5 times, in volume
(ml) to 1 gram of the racemic mixture, i.e., (R,S)-amlodipine. In case an
excess of DMSO is used (e.g., about 10 ml of DMSO to 1 gram of
(R,S)-amlodipine), about 10 % of
(R)-(+)-amlodipine-hemi-L-tartrate-DMSO-solvate may exist in DMSO, which
15 unfavorably causes lowering the optical purity of the final product, i.e.,
(S)-amlodipine.

In filtering-off (R)-(+)-amlodipine-hemi-L-tartrate-DMSO-solvate, any
conventional filtration methods can be used, preferably under a reduced
pressure. For example, conventional centrifugation methods can be used. In
20 this case, a supernatant obtained by the centrifugation is used as the filtrate in
the subsequent step. Therefore, the filtering-off process according to the
present invention should be construed to include any applicable conventional
methods for removing a precipitate.

Addition of methylene chloride to the filtrate gives a precipitate, i.e., (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate. The amount of methylene chloride may be about 100 – 200 % by volume based on the volume of DMSO used in the step (i).

5 The process of the present invention may further comprise a recrystallization step for forming (S)-(-)-amlodipine L-(+)-tartrate free from DMSO, i.e., (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate. The optical purity of (S)-amlodipine may be increased by further performing the recrystallization step. The recrystallization may be performed using an alcohol, including
10 methanol.

The process of the present invention comprises treating with a base (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate to give optically pure (S)-(-)-amlodipine. The base includes, but not limited to, a metal hydroxide, an
15 oxide, a carbonate, a bicarbonate, and an amide. Preferably, the base is sodium bicarbonate. Further, the treatment with a base may be performed in an organic solvent, preferably methylene chloride.

The present invention also includes, within its scope, synthetic intermediates for the preparation of S(-)-amlodipine. That is, the present
20 invention provides (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate, each being useful for the preparation of S(-)-amlodipine. (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate may be in a form of 1/4-, 1/2-(i.e., hemi-), or mono- DMSO solvate; or in a form of the mixture thereof,
25 e.g., the mixture of 1/4- and 1/2- DMSO solvate. Preferably, (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate is the form of 1/4-DMSO solvate, i.e., (S)-(-)-amlodipine-hemi-L-tartrate-1/4-DMSO-solvate.

Although the present invention may be more detailed explained by reference to the following Examples, the following Examples are not intended to
30 limit the scope of the present invention.

Example 1. Preparation of S-(-)-amlodipine from (R,S)-amlodipine

(1) (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate

5 The solution of L-(+)-tartaric acid (1.872 g, 0.51 mole equivalents) in dimethyl sulfoxide (25 ml) was added to the solution of (R,S)-amlodipine (10 g, 24.46 mmole) in dimethyl sulfoxide (25 ml) under stirring. Precipitation was observed within 5 minutes after the addition, and the resulting slurry was stirred overnight at room temperature. The resulting solid was filtered off. CH₂Cl₂
10 (50 ml) was added to the obtained filtrate, which was then stirred at room temperature for 40 hours. The resulting slurry was cooled to 5 °C, stirred for 2 hours, and then filtered. The resulting solid was dried overnight at 50 °C *in vacuo* to give a solid (5.48 g) having the following ¹H-NMR data. Fig. 1 shows the ¹H-NMR chart of the solid, which means that the solid is
15 (S)-(-)-amlodipine-hemi-L-tartrate-1/4-DMSO-solvate.

¹H-NMR (CD₃OD): 7.04-7.41(m, 4H), 5.40(s, 1H), 4.72(gq, 2H), 4.36(s, 1H), 4.02(m, 2H), 3.77(m, 2H), 3.57(s, 3H), 3.28(m, 2H), 2.65(s, DMSO), 2.31(s, 3H), 1.15(t, 3H)

20

(2) (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate

The (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate (5.48 g) obtained in Step (1) was refluxed in methanol (25 ml) to obtain a solution. The solution
25 was cooled to room temperature. The resulting slurry was stirred overnight at room temperature and filtered to obtain a solid. The solid was dried overnight at 50 °C *in vacuo* to give a solid (4.92 g) having the following ¹H-NMR data. Fig. 2 shows the ¹H-NMR chart of the solid, which means that the solid is
30 (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate.

¹H-NMR (CD₃OD): 7.04-7.41(m, 4H), 5.40(s, 1H), 4.72(gq, 2H), 4.34(s, 1H), 4.04(m, 2H), 3.77(m, 2H), 3.57(s, 3H), 3.29(m, 2H), 2.33(s, 3H), 1.15(t, 3H)

5 (3) S-(-)-amlodipine

2N NaHCO₃ (44 ml) was added to the slurry of (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate (4.92 g) obtained in Step (2) in CH₂Cl₂ (44 ml) at 5 °C. The reaction mixture was stirred for 20 minutes. The
10 resulting organic layer was washed with water twice and concentrated. The solution of the resulting mixture in the mixed solvent of 30 ml of n-hexane and ethyl acetate (2:1, v/v) was cooled to 5 °C and filtered. The resulting solid was dried overnight at 50 °C *in vacuo* to give S-(-)-amlodipine (3.45 g).

15 Yield : 69 %

Melting Point : 108-110 °C

¹H-NMR (CD₃OD) 7.03-7.41(m, 4H), 5.39(s, 1H), 4.67(gq, 2H), 3.98-4.06(m, 2H), 3.55-3.58(t, 2H), 3.57(s, 3H), 2.86(m, 2H), 2.33(s, 3H), 1.15(t, 3H)

20 $[\alpha]_D^{25} = -31.2$ (c=1, MeOH)

Chiral HPLC : 97.9 %e.e.

Example 2.

25 The procedure of Step (3) in Example 1 was repeated, except that (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate (3 g) prepared in accordance with Step (1) of Example 1 was used instead of (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate, to obtain 2.1 g of S-(-)-amlodipine.

30

$[\alpha]_D^{25} = -26.4$ (c=1, MeOH)

What is claimed is:

1. A process for the preparation of S-(-)-amlodipine, which comprises:

5 (i) reacting (R,S)-amlodipine with L-(+)-tartaric acid in dimethyl sulfoxide (DMSO);

(ii) filtering off the resulting precipitate of the step (i);

(iii) precipitating (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate by adding methylene chloride to the filtrate of the step (ii);

10 (iv) optionally forming (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate by adding an alcohol to (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate obtained in the step (iii); and

(v) treating with a base (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate obtained in the step (iii) or (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate
15 obtained in the step (iv).

2. The process of claim 1, wherein the amount of L-(+)-tartaric acid is about 0.5~0.55 eq. to 1 eq. of (R,S)-amlodipine.

20 3. The process of claim 1, wherein the amount of DMSO is about 4 – 6 times in volume (ml) to 1 gram of (R,S)-amlodipine.

4. The process of claim 1, wherein the amount of methylene chloride in the step (iii) is about 100 – 200 % by volume based on the volume of DMSO
25 used in the step (i).

5. The process of claim 1, wherein the alcohol is methanol.

6. The process of claim 1, wherein the base is a metal hydroxide, an
30 oxide, a carbonate, a bicarbonate, or an amide.

7. The process of claim 6, wherein the base is sodium bicarbonate.

8. The process of claim 1, wherein the step (v) is performed in an organic solvent.
- 5 9. The process of claim 8, wherein the organic solvent is methylene chloride.
10. (S)-(-)-amlodipine-hemi-L-tartrate-DMSO-solvate.
- 10 11. (S)-(-)-amlodipine-hemi-L-tartrate-monohydrate.

FIG. 1

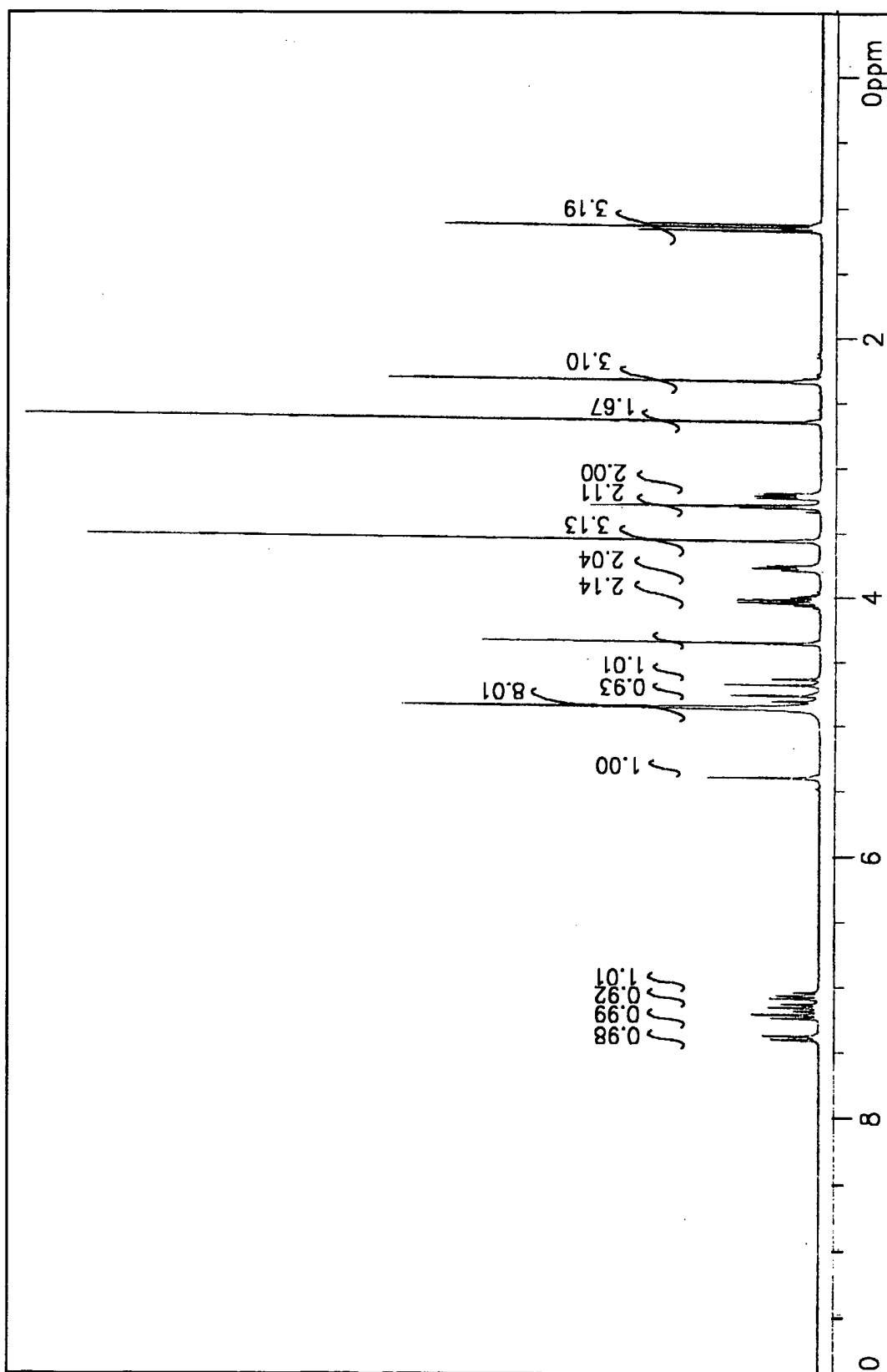
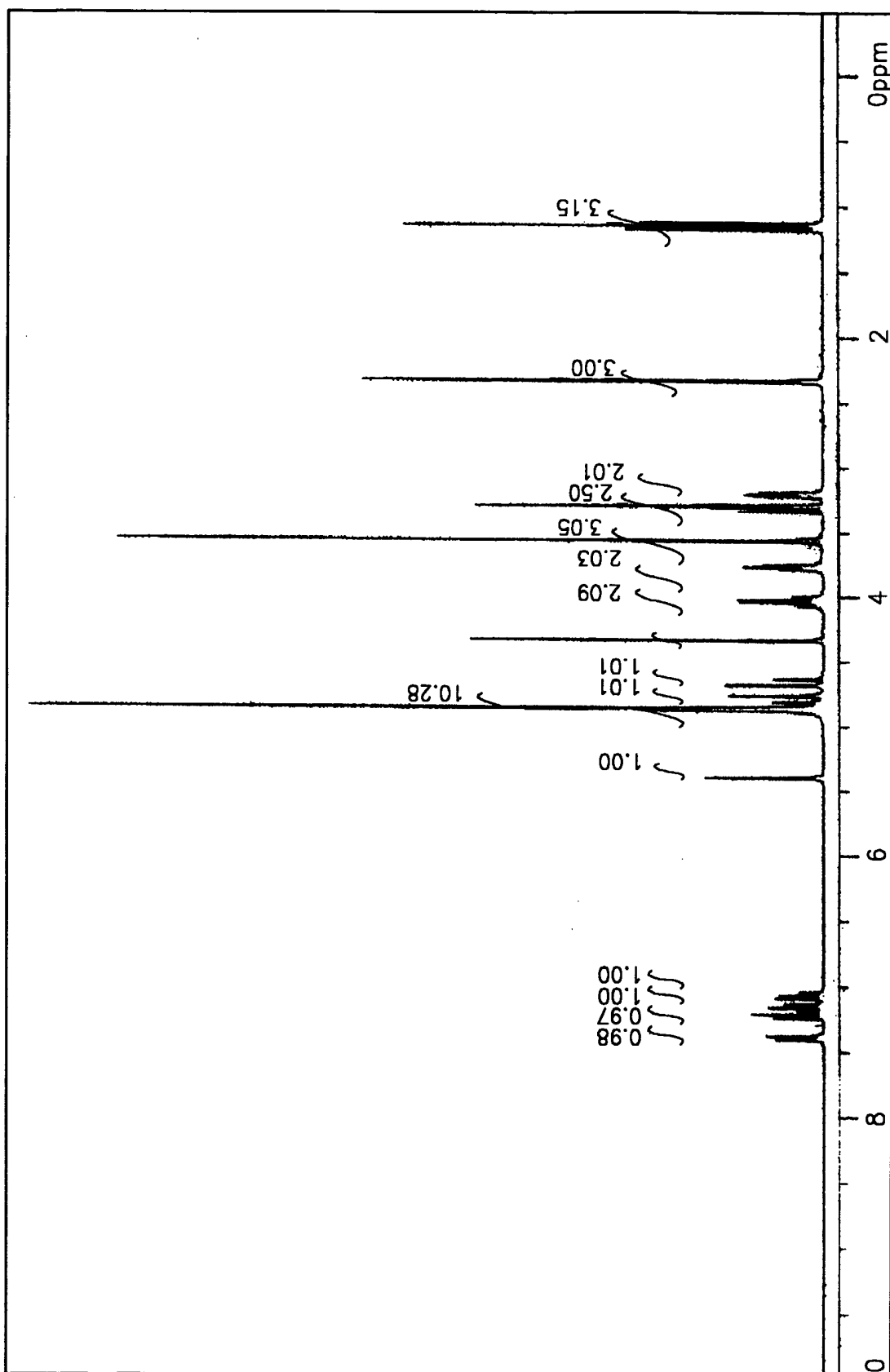


FIG. 2



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/01849

A. CLASSIFICATION OF SUBJECT MATTER				
IPC7 C07D 211/90				
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) ICP 07 C07D, A61K				
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 practicable, search terms used) CAS online (STN), Medline				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
E, X	US2003/0176706A1 (None) 18. Sept. 2003 See whole document	1-11		
A	WO95/25722 (Pfizer Ltd.) 28. Sept. 1995 See page 10 (examples 5, 6)	1-11		
A	WO01/60799 A1 (None) 23. Aug. 2001 See whole document	1-11		
A	EP0331315 (Pfizer Ltd.) 06. Sept. 1989 See whole document	1-11		
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<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="width: 50%; border: none; vertical-align: top;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>			
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Name and mailing address of the ISA/KR	Authorized officer			
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR03/01849

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US030176706A1	18.09.2003	None	
W09525722A1	28.09.1995	AT166050T CA2186263A1 CN1144523A CZ9602784A3 ES2116737T3 F1963775A HU76290A2 JP2843681B2 NZ282404A W09525722A1 ZA9502362A	15.05.1998 28.09.1995 05.03.1997 12.03.1997 16.07.1998 23.09.1996 28.07.1997 06.01.1999 24.11.1997 28.09.1995 23.09.1996
W00160799A1	23.08.2001	US030028031A1 EP1258477A4 AU0118494A5	06.02.2003 02.04.2003 27.08.2001
EP0331315A2	06.09.1989	DK86889A EP0331315A2 F1890888A JP1254661A PT89836A	28.08.1989 06.09.1989 28.08.1989 11.10.1989 04.10.1989