



(22) Date de dépôt/Filing Date: 1998/01/09

(41) Mise à la disp. pub./Open to Public Insp.: 1998/07/23

(45) Date de délivrance/Issue Date: 2012/11/20

(62) Demande originale/Original Application: 2 278 201

(30) Priorité/Priority: 1997/01/20 (DE197 01 694.4)

(51) Cl.Int./Int.Cl. *C07C 271/28* (2006.01),
A61K 31/27 (2006.01), *C07C 269/08* (2006.01)

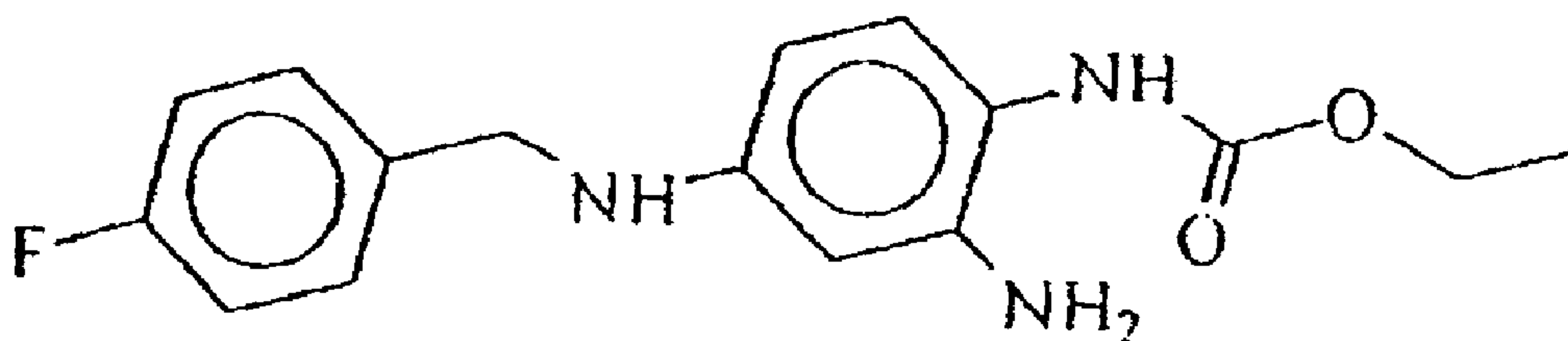
(72) Inventeurs/Inventors:
MEISEL, PETER, DE;
LANDGRAF, KARL-FRIEDRICH, DE;
SCHAFFER, JURGEN, DE;
THIEL, WILFRIED, DE;
RISCHER, MATTHIAS, DE;
OLBRICH, ALFRED, DE;
KUTSCHER, BERNHARD, DE

(73) Propriétaire/Owner:
VIATRIS GMBH & CO. KG, DE

(74) Agent: MARKS & CLERK

(54) Titre : NOUVELLES MODIFICATIONS DU 2-AMINO-4-(4-FLUOROBENZYLAMINO)-1-ETHOXYCARBONYL-AMINOBENZENE ET PROCEDES PERMETTANT DE PREPARER LEDIT COMPOSE

(54) Title: NOVEL MODIFICATIONS TO 2-AMINO-4-(4-FLUOROBENZYLAMINO) -1- ETHOXYCARBONYL-AMINOBENZENE AND PROCESSES FOR PREPARING SAID COMPOUND



(I)

(57) Abrégé/Abstract:

The invention concerns novel modifications to the compound 2-amino-4-(1-ethoxycarbonylamino)aminobenzene of formula. The invention also concerns processes for preparing this compound and its use in pharmaceutical compositions.

ABSTRACT OF THE DISCLOSURE

The invention concerns novel modifications to the compound 2-amino-4-(1-ethoxycarbonyl-aminobenzene) of formula. The invention also concerns processes for preparing this compound and its use in pharmaceutical compositions.

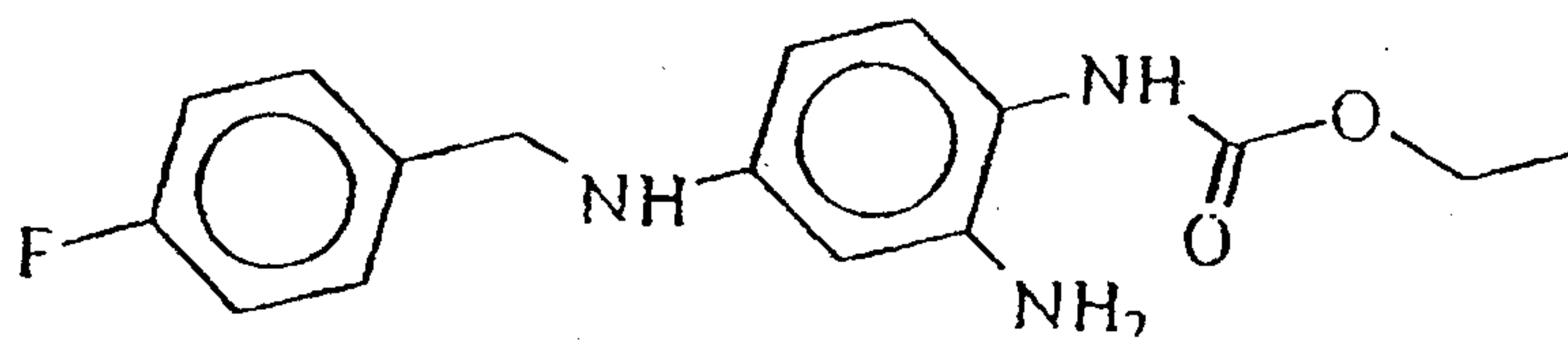
- 1 -

Novel Modifications To 2-Amino-4-(4-Fluorobenzylamino)-
1-Ethoxycarbonyl-aminobenzene And Processes For Preparing
Said Compound

5 This a divisional application of Canadian Patent Application
Serial No. 2,278,201 filed on January 9, 1998.

The invention relates to novel modifications of the compound
2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonyl-
10 aminobenzene of the

formula I



20

processes for their preparation and their use in pharmaceutical
compositions. It should be understood that the expression "the
invention" and the like encompasses the subject matter of both
25 the parent and the divisional applications.

The compound of the formula I and its preparation is
described in the patent DE 42 00 259.

30 This compound has, for example, anticonvulsive, antipyretic
and analgesic activity and can thus be employed in
pharmaceutical preparations.

In the crystallization of the compound of the formula I,
35 however, in some cases very different mixed products are
obtained with respect to the crystal size and form.

- la -

Mixtures of crystal modifications are a great problem for pharmaceutical preparations. In particular, in the case of pharmaceutical forms having a high active compound content, physical inhomogeneties have a disadvantageous effect on adherence to constant pharmaceutical production conditions.

- 2 -

On the other hand, considerable variations in the stability, purity and uniformity of the finished product occur, so that the demands on the pharmaceutical quality of an active compound cannot be
5 satisfied.

It is therefore of great interest to prepare the compound of the formula I in homogeneous crystalline form.

10

The invention is thus based on the object of preparing the compound of the formula I in homogeneous crystalline form which meets the pharmaceutical requirements.

15

It has now surprisingly been found that the compound of the formula I can be prepared in 3 different pure crystal modifications. Thus physically homogeneous compounds of the formula I can be prepared for the
20 production of pharmaceutical finished products.

The 3 modifications, called A, B and C, have different physicochemical properties.

25 Characteristic X-ray diffractograms are used for the identification of these three modifications of the compound of the formula I.

The modifications furthermore differ in their DSC
30 curves (differential scanning calorimetry) and in some cases also in their IR spectra as well as by the crystal forms typical in each case.

The X-ray diffractograms according to Figure 1 were
35 recorded with a powder diffractometer using CuK_α radiation.

The data for the DSC curve according to Figure 2 relate to a heating rate of 10 k/min. The temperatures given

- 3 -

in each case indicate the position of the intensity maximum.

The IR spectra illustrated (Figure 3a, b, c) were recorded on KBr pressed discs.

The modification A is characterized by:

- 10 - the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at $6.97^\circ 2\theta$ (12.67 Å), $18.02^\circ 2\theta$ (4.92 Å) and $19.94^\circ 2\theta$ (4.45 Å),
- 15 - the endothermic A, B conversion effect at approx. 97°C (maximum) below the melting effect of the modification b at approx. 142°C in the DSC curve,
- 20 - the IR spectrum differing from the other two modifications by intensive vibration bands at 3421 cm^{-1} (ν N-H), 3376 cm^{-1} (ν N-H), 1703 cm^{-1} (ν C=O) and 886 cm^{-1} (γ C-H), and
- 25 - mainly nearly isometric to short-columnar crystals.

The modification B is characterized by:

- 30 - the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at $15.00^\circ 2\theta$ (5.90 Å), $19.29^\circ 2\theta$ (4.60 Å) and $19.58^\circ 2\theta$ (4.53 Å),
- 35 - the absence of thermal effects below the melting effect at approx. 142°C in the DSC curve and
- mainly longish-tabular to columnar crystals.

- 4 -

The modification C is characterized by:

- the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, inter alia, at 9.70°2 θ (9.11 Å) and 21.74°9 [sic] (4.09 Å),
- two endothermic effects connected with the phase transmission to the modification B between approx. 130°C and the melting effect of the modification B at approx. 142°C in the DSC curve and
- mainly tabular crystals.

15 The preparation of the 3 modifications of the compound I can be carried out by the following processes, adherence to the conditions being of particular importance.

20 The modifications can be prepared either from the crude product of the compound of the formula I or alternatively by modification conversion.

Preparation of the modification A:

25

The modification A can be prepared from the modifications B and C by stirring in solvents.

30 The crystallization of the modification A is preferably carried out with stirring of a supersaturated solution of the compound I in protic, dipolar-aprotic or non-polar solvents.

35 Protic solvents which can be employed are lower alcohols such as ethanol, 2-propanol, n-butanol, dipolar-aprotic solvents are acetonitrile or acetone and non-polar solvents are [sic] toluene.

- 5 -

The crystallization is preferably carried out in the presence of lower alcohols.

5 The crystallization from the solution is carried in the temperature range from -20°C to 110°C. In particular, in certain solvents, such as n-butanol, the crystallization of the pure modification A can be carried out at temperatures up to 110°C. The pure
10 modification A is preferably obtained by crystallization in the temperature range from 20°C to 50°C.

Preparation of the modification B:

15 The crystallization of the modification B is carried out from a saturated solution of the compound I with slow cooling.

20 The solvents employed can be protic solvents such as water or aprotic solvents such as toluene.

The crystallization is preferably carried out in the presence of toluene.

25 The crystallization from the solution can be carried out in the temperature range between 50°C to [sic] 110°C, but preferably between 80°C - [sic] 100°C.

30 The modification B can also be obtained by thermal phase conversion, preferably from the modification A at temperatures of greater than 80°C.

Preparation of the modification C:

35 The modification C crystallizes out at a temperature of 30°C - 80°C with slow cooling from a saturated solution of the compound I in protic solvents such as ethanol and 2-propanol or aprotic solvents such as toluene.

- 6 -

The crystallization from the solution is preferably carried out at a temperature of 50°C - 70°C.

Each of these modifications of the compound I can be
5 processed for administration in pharmaceutical forms which satisfy the pharmaceutical demands.

The present invention further relates to the use of the modifications A, B and C of the compound I for the
10 production of pharmaceutical preparations. In particular, they are efficacious anti-epileptic agents and neuroprotective agents.

The pharmaceutical preparations can in general contain
15 between 10 mg to [sic] 200 mg of at least one of the modifications of the compound I as an individual dose. Preferred administration forms are tablets.

The modifications of the compound of the formula I can
20 be processed to give the pharmaceutical preparation in a customary manner using suitable excipients and/or auxiliaries.

The modification A of the compound I in particular
25 shows advantageous properties for further pharmaceutical processing.

- The crystal structure is stable up to approx.
80°C. Even after relatively long storage at
30 temperatures up to 60°C and relative atmospheric humidities up to 70%, no lattice changes are observed.

- The modification A undergoes no lattice change on
35 contact with solvents such as, for example, water, ethanol, acetone or toluene.

- 7 -

- The nearly isometric to short-columnar crystal form leads to a grainy substance structure convenient for pharmaceutical processing.

5 The modifications B and C can be employed for specific pharmaceutical forms such as capsules and dry ampoules. Thus, for example, the preferred formation of finely granular and therefore particularly rapidly soluble crystals observed with the modification C can have
10 advantages for the production of dry ampoules.

The preparation processes for the individual modifications will be illustrated in greater detail with the aid of examples:

15

Example 1

Modification A

20 2.34 kg of the compound I and 0.16 kg of active carbon are dissolved by warming with stirring in 7.0 l of ethanol in a 16-l [sic] dissolving vessel. The solution is filtered hot through a pressure filter with stirring into a cooled 32-l [sic] crystallizing vessel with
25 0.5 l of ethanol such that the internal temperature in the crystallizing vessel is kept at $< 45^{\circ}\text{C}$. The remaining solution is then rinsed from the dissolving vessel through the pressure filter into the crystallizing vessel using 0.75 l of hot ethanol and
30 the suspension is swiftly cooled. It is subsequently stirred at $5^{\circ}\text{C} - 12^{\circ}\text{C}$ for 0.5 hours and the solid is filtered off with suction under inert conditions. The product is washed three times with 1.2 l of cooled ethanol each time. The crystallizate is then dried to
35 weight constancy at $50^{\circ}\text{C} - 55^{\circ}\text{C}$ in a vacuum drying oven. 2.04 kg (87% of theory) of the pure modification A is obtained.

- 8 -

Example 2**Modification A**

5 2 g of the modification C are stirred for 2 days at room temperature in 6 ml of ethanol. The modification A is obtained quantitatively.

Example 3

10

Modification A

5 g of the modification B or C are stirred for 2 days at room temperature in 50 ml of toluene. The
15 modification A is obtained quantitatively.

Example 4**Modification A**

20

3 g of the modification B are stirred for 2 days at room temperature in 1.5 ml of acetone. The modification A is obtained quantitatively.

25 Example 5**Modification A**

10 g of the compound I are dissolved in 5 ml of
30 n-butanol with warming. The solution is allowed to crystallize at 105°C - 110°C, the mixture is cooled to 20°C and the crystals are washed with n-butanol after filtering off with suction. The modification A is obtained quantitatively.

- 9 -

Example 6**Modification B**

5 10 g of the compound I are briefly heated to reflux
with 20 ml of toluene and dissolved. The solution is
allowed to crystallize at 90°C - 100°C and the crystals
are filtered off with suction and washed with 5 ml of
10 toluene. After drying, 9.8 g (98% of theory) of needle-
shaped crystals are obtained.

Example 7**Modification B**

15

10 g of substance of the modification A are kept for 8
hours at 100°C in a drying oven. The modification B is
obtained quantitatively.

20 Example 8**Modification C**

3.0 kg of the compound I are dissolved in a 32-l
25 dissolving vessel by stirring with warming after
addition of 0.2 kg of active carbon in 19.6 l of
isopropanol. The solution is filtered hot through a
pressure filter into a 32-l [sic] crystallizing
vessel such that the internal temperature in the
30 crystallizing vessel is kept at 60 - 65°C. The
remaining solution is then rinsed from the dissolving
vessel through the pressure filter into the
crystallizing vessel using 2.5 l of hot isopropanol
(about 70°C). After the start of crystallization at
35 60°C - 65°C, the mixture is subsequently stirred. The
suspension formed is swiftly cooled, subsequently
stirred at 5°C - 12°C and filtered off with suction
under inert conditions. The crystallizate is washed

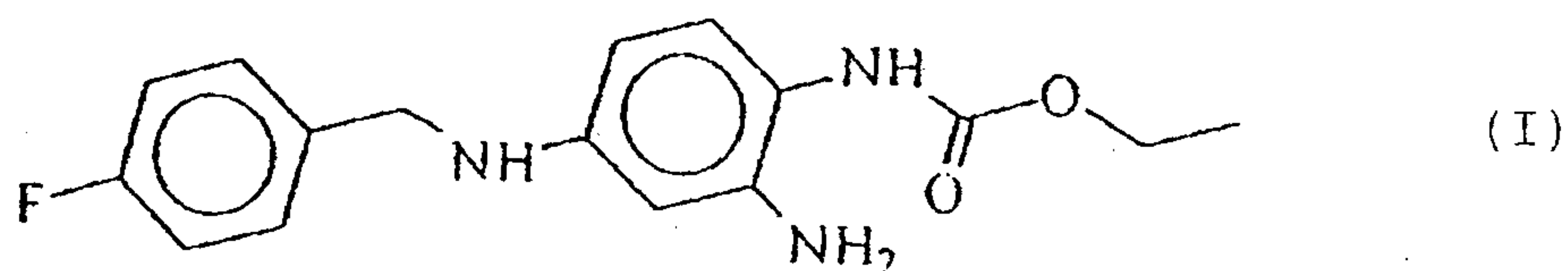
- 10 -

three times with 2.5 l of cooled isopropanol each time.

5 The crystallizate is then dried to weight constancy in vacuo at 50°C - 55°C. 2.64 kg (88% of theory) of the active compound are obtained in modification C.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A crystalline form B of the compound I:



characterized by an X-ray diffractogram with reflections at $15.00^{\circ}2\theta$ (5.90 Å), $19.29^{\circ}2\theta$ (4.60 Å) and $19.58^{\circ}2\theta$ (4.53 Å), not coinciding with reflections at $6.97^{\circ}2\theta$ (12.67 Å), $18.02^{\circ}2\theta$ (4.92 Å), $19.94^{\circ}2\theta$ (4.45 Å), $9.70^{\circ}2\theta$ (9.11 Å) and $21.74^{\circ}2\theta$ (4.09 Å).

2. A process for the preparation of the crystalline form B of the compound I as defined in claim 1, wherein a pure crystal form is allowed to crystallize out at a temperature of greater than 80°C from a saturated solution of the compound I in a protic or non-polar solvent.

3. A process for the preparation of the crystalline form B according to claim 2, wherein the protic solvent employed is water.

4. A process for the preparation of the crystalline form B according to claim 2, wherein the non-polar solvent is toluene.

5. A process for the preparation of crystalline form B as defined in claim 1, wherein the crystalline form B is

prepared from a crystalline form A of the compound I characterized by an X-ray diffractogram with reflections at $15.00^{\circ}2\theta$ (5.90 Å), $19.29^{\circ}2\theta$ (4.60 Å) and $19.58^{\circ}2\theta$ (4.53 Å), not coinciding with reflections at $6.97^{\circ}2\theta$ (12.67 Å), $18.02^{\circ}2\theta$ (4.92 Å), $19.94^{\circ}2\theta$ (4.45 Å), $9.70^{\circ}2\theta$ (9.11 Å) and $21.74^{\circ}2\theta$ (4.09 Å);

at a temperature of greater than 80°C by thermal phase conversion.

6. Use of a crystalline form B of the compound I as defined in claim 1 for the production of a pharmaceutical preparation.

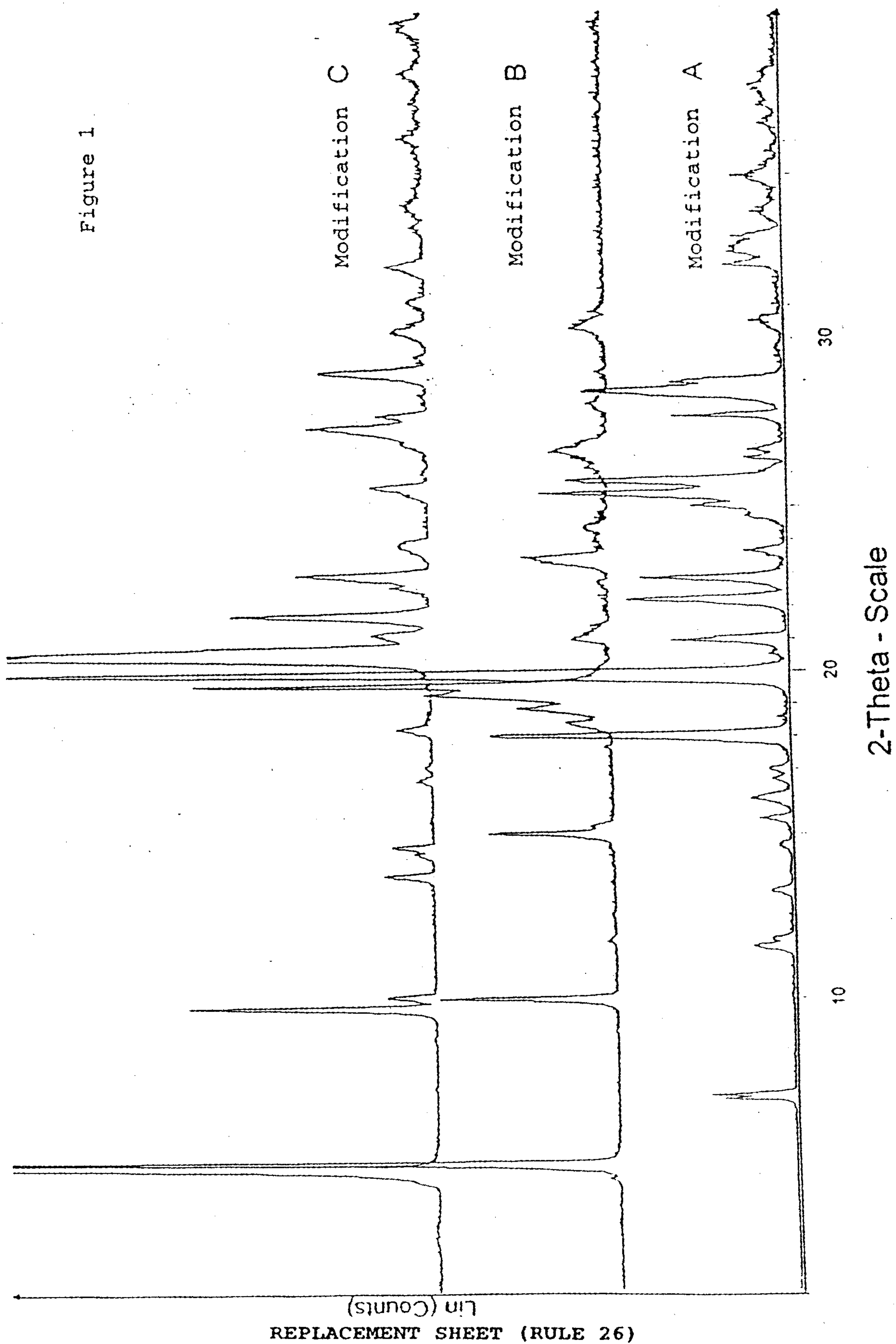
7. A pharmaceutical composition comprising a crystalline form B of the compound I as defined in claim 1 together with a pharmaceutically acceptable carrier.

WO 98/31663

PCT/EP98/00086

1/5

Figure 1

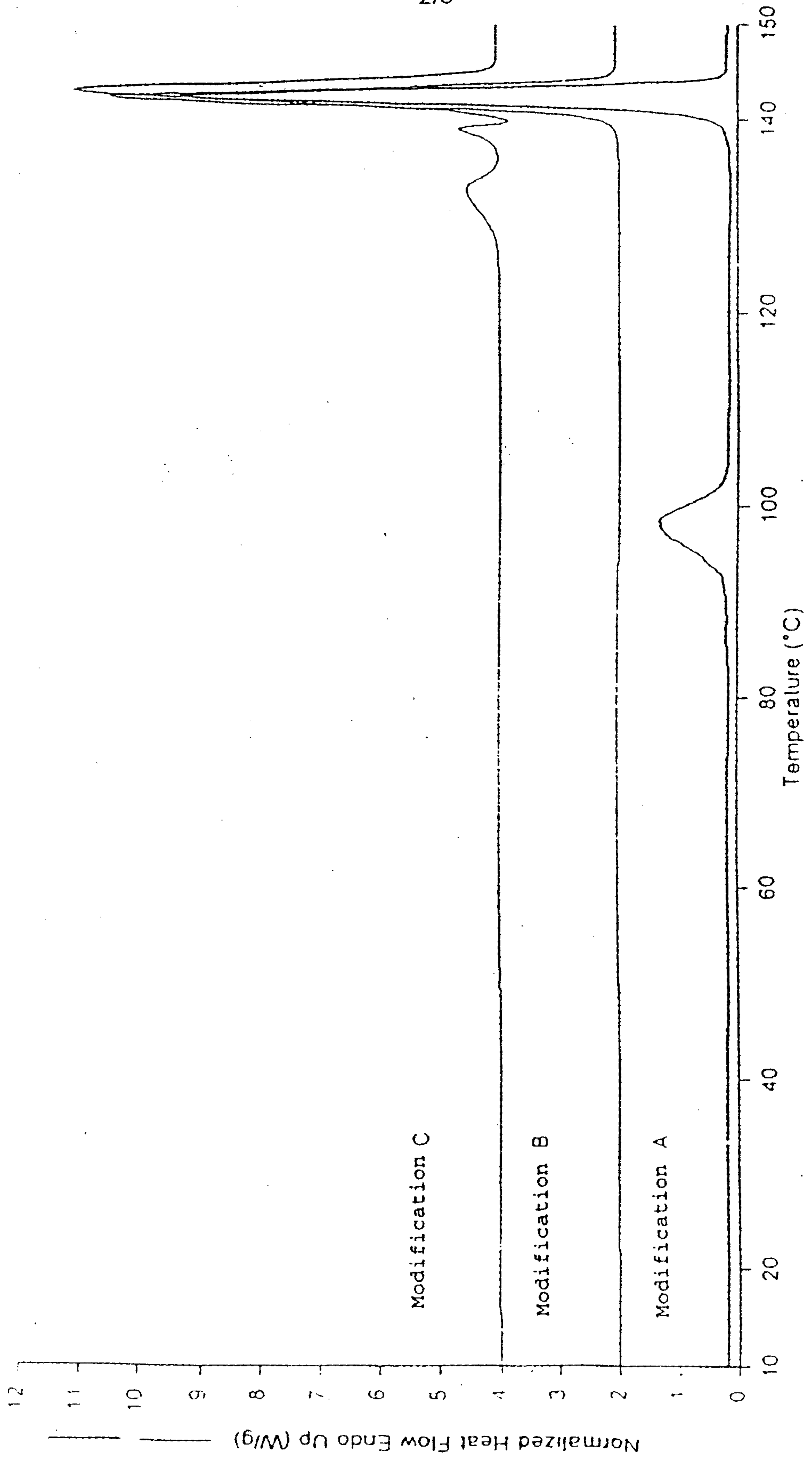


WO 98/31663

PCT/EP98/00086

Figure 2

2/5



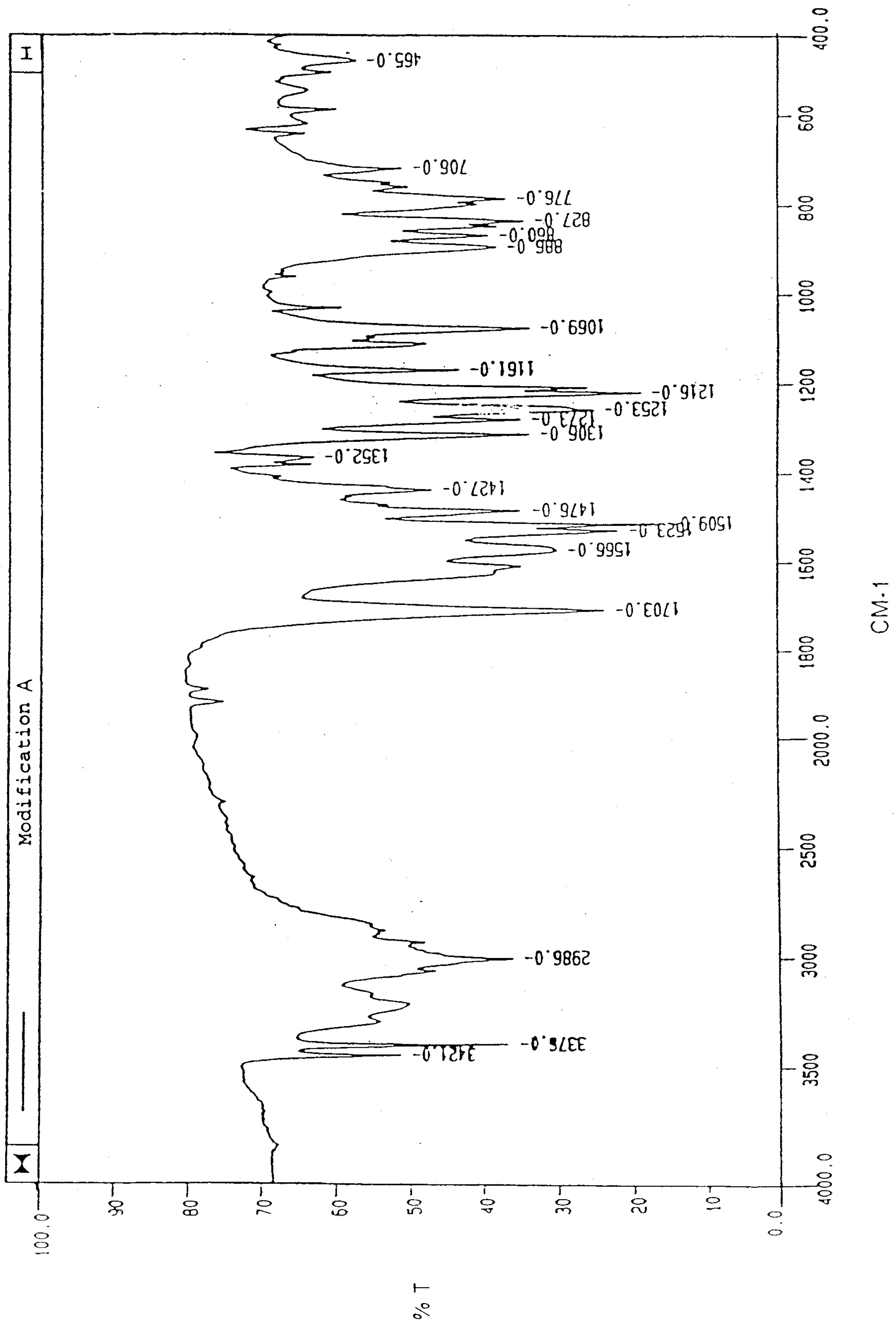
REPLACEMENT SHEET (RULE 26)

WO 98/31663

PCT/EP98/00086

Figure 3a

3/5

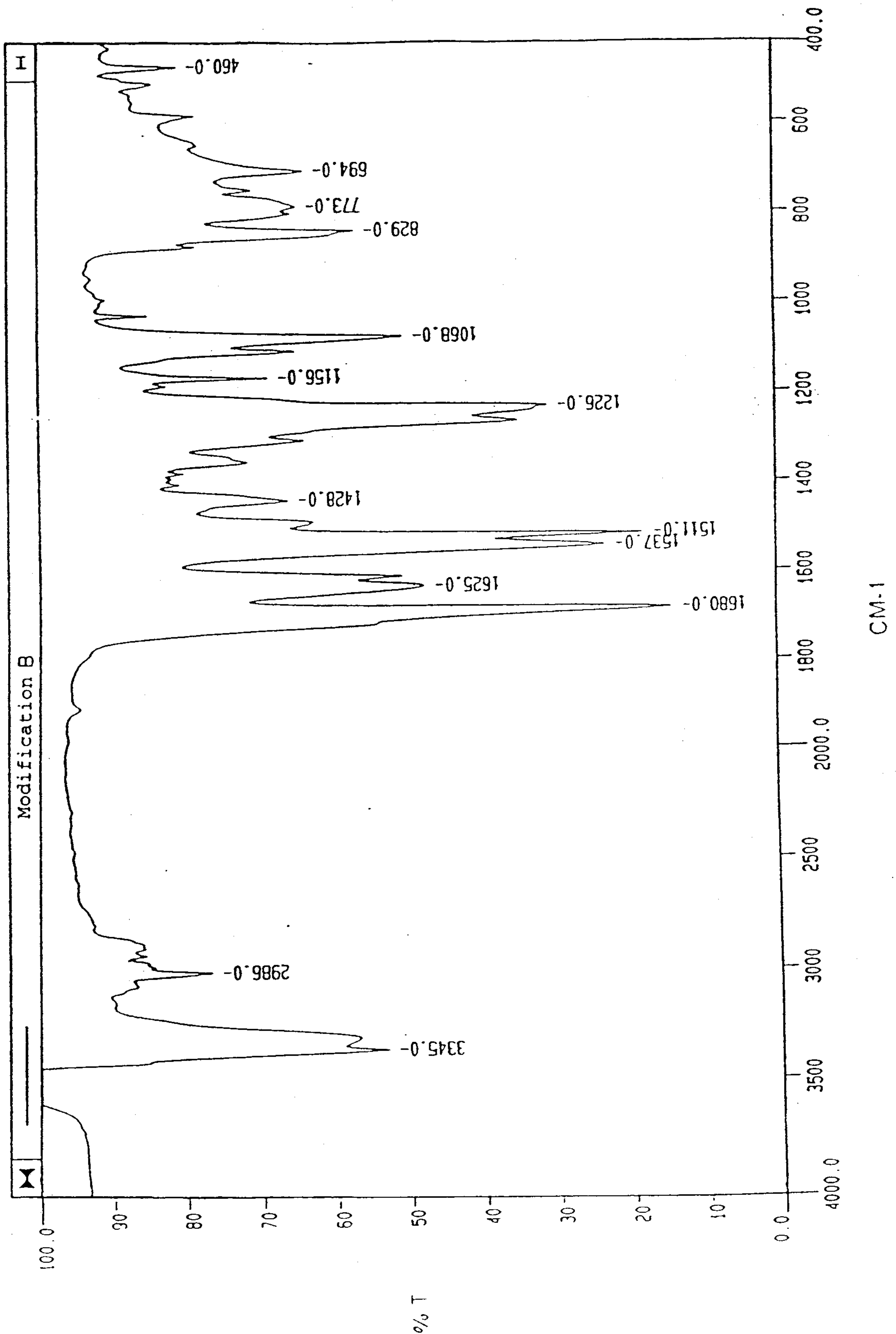


WO 98/31663

PCT/EP98/00086

Figure 3b

4/5



WO 98/31663

PCT/EP98/00086

Figure 3c

5'5

