

DESCRIPTION

5 THERMODYNAMICALLY STABLE FORM OF (R)-3-[[[4-
FLUOROPHENYL) SULPHONYL] AMINO]-1, 2, 3, 4-TETRA-
HYDRO-9H-CARBAZOLE-9-PROPANOIC ACID (RAMATRO-
BAN)

The invention relates to a new form of
ramatroban which is thermodynamically stable at room
temperature, a process for its preparation, pharma-
10 ceuticals comprising this form, and their use in the
control of diseases.

The preparation and use of ramatroban as a
thromboxane A₂ antagonist has already been disclosed in
EP 242 518.

15 In the manner described there, ramatroban is
obtained in the form of a crystal modification which is
designated in the following text as modification II.
Mod. II has a melting point of 137°C and a melt enthalpy
of 80 J/g (DSC, heating rate 2 K min⁻¹) and a character-
20 istic X-ray diffractogram, IR spectrum, ¹³C-solid state
NMR spectrum, FIR spectrum, Raman spectrum (Figs. 1-6).
It has now been found that Mod. II is metastable and
therefore is not suitable for use in pharmaceutical
formulations, such as, for example, solid and semi-solid
25 preparations.

Surprisingly, a second modification of rama-
troban has now been found which is thermodynamically
stable and is also stable on storage after processing by
means of suspensions and is therefore particularly
30 suitable for use in pharmaceutical formulations, such
as, for example, suspensions or creams, but also in
other preparations which are prepared by means of sus-
pended active compound, such as, for example, in aqueous
granulation or wet-grinding. This new modification is
35 designated in the following text as modification I. The
present invention also relates to pharmaceutical formu-

lations which contain ramatroban in the modification I as active substance. The formulation can contain one or more pharmaceutically acceptable auxiliaries, such as, for example, binders, solvents, fillers, etc.

5 J. Halbelian, W. McCrowne, J. Pharm. Sci. 58 (1969) 911, and J.-O. Henck et al., Pharm. Ind. 59 (1997) 165-169 disclose that when using a thermodynamically metastable polymorphic form in solid and semi-solid formulations, such as, for example, tablets,
10 suspensions and ointments, the stable form can result. As an attendant phenomenon here, undesired crystal growth, changes in the bioavailability, caking, etc. are observed. The two crystal modifications of ramatroban differ in their solubility at room temperature by 60%.
15 By means of the use according to the invention of the stable modification I, it is ensured that no change in solubility can occur as a result of conversion. This increases the safety of preparations of ramatroban and the risk for the patients is thus reduced.

20 In comparison with Mod. II, Mod. I has a clearly distinguishable DSC thermogram, X-ray diffractogram, ^{13}C -solid state NMR spectrum, FIR spectrum and Raman spectrum (Figs. 1-6). The melting point of Mod. I is 151°C and the melt enthalpy is 87 J/g.

25 The DSC and TGA thermograms were obtained using a DSC 7 and TGA 7 from Perkin-Elmer. The X-ray diffractograms were recorded in a Stoe transmission diffractometer. The IR, FIR and Raman spectra were recorded using Fourier IR spectrometers IFS 66 (IR), IFS
30 66v (FIR) and IFS 88 (Raman) from Bruker. The ^{13}C -solid state NMR spectra were recorded using a Bruker MSL 300.

The crystal modification of ramatroban is employed in high purity in pharmaceutical formulations. For reasons of stability, Mod. I should not contain
35 relatively large proportions of Mod. II. A grade of active compound with less than 10% of Mod. II, very

particularly preferably with less than 5%, is preferred.

Mod. I is prepared by suspending ramatroban of modification II in water or inert substances, e.g. in lower alcohols, ketones or alkanes, seeding with crystals of Modification I and stirring until the desired degree of conversion is achieved, particularly preferably until quantitative conversion to Mod. I. As a rule, this conversion takes place at 20 - 50°C, preferably at 40°C. The crystals of Mod. I obtained are separated off and, to remove solvent present, dried to constant weight at room temperature in vacuo or at elevated temperature.

To prepare the seed crystals needed, the active compound is thoroughly melted and then rapidly cooled to room temperature. The amorphous form of the active compound thus obtained is suspended in an inert solvent at room temperature and stirred until it is completely converted into the thermodynamically stable crystal modification. The residue is filtered and dried to constant mass in vacuo.

20 Examples

Example 1

Preparation of seed crystals from the melt

About 300 mg of ramatroban of Mod. II are thoroughly melted and rapidly cooled to room temperature. The amorphous substance is suspended in 5 ml of ethanol/water (1:1) and the suspension is stirred at room temperature for 24 h. After the end of the stirring time, the suspension is filtered and the residue is dried in vacuo at room temperature.

30 Example 2

Seeding process

130 g of ramatroban (Modification II) are dissolved in 650 g of n-butyl acetate and 15 g of water at about 40°C. 175 g of solvent are distilled off in vacuo at 40 - 45°C. The solution is then seeded with 1 g of ramatroban (Modification I) and a further 300 g of

solvent are distilled off in vacuo at 40 to 45°C. The crystal suspension obtained is cooled to room temperature and stirred for a few hours. It is filtered off with suction, washed with *n*-butyl acetate and methyl
5 tert-butyl ether and dried in vacuo at 50°C. About 100 g of ramatroban are obtained (Modification I).

Example 3

Precipitation method

75 g of ramatroban (Modification II) are dissolved in 135 g of ethyl acetate with warming. 85 g of
10 petroleum ether (35/60) are added dropwise at about 40°C and the batch is seeded with 1 g of ramatroban (Modification I). The mixture is stirred at 40°C for about 2 - 3 hours and then cooled to room temperature. A further
15 130 g of petroleum ether (35/60) are added to the suspension and it is additionally stirred at room temperature for about 5 hours. It is filtered off with suction, washed with 100 g of petroleum ether (35/60) and dried at 50°C in vacuo. About 65 g of ramatroban (Modi-
20 cation I) are obtained.

Example 4

Conversion in suspension 1

50 g of ramatroban (Modification II) are suspended in 75 g of *n*-butyl acetate and mixed with 0.5 g
25 of ramatroban (Modification I). The mixture is stirred at room temperature for about 100 hours. It is then filtered off with suction, washed with methyl tert-butyl ether and dried at 50°C in vacuo. About 40 g of ramatroban (Modification I) are obtained.

30 Example 5

Conversion in suspension 2

About 0.5 g of Mod. I and II (mixing ratio about 1:1) are suspended in 8 ml of *n*-heptane and refluxed at about 80°C. After one week, the suspension
35 is filtered and the residue is dried in vacuo at room temperature for one day.

Example 6Production of tablets

4590 g of microfine ramatroban of Mod. I are dispersed in a homogenizer with 9180 g of an aqueous HPC-L (367 g) and then filtered through a sieve having a 355 μ m mesh width. The granulation liquid is reacted in a granulator with 13,500 g of a premixed and preheated aqueous solution, consisting of 3162 g of lactose, 4860 g of HPC-L and 540 g of HPC-M, to form granules. The resulting granules are dried at 65°C. Pressing is then carried out in a rotary press to give tablets having a diameter of 9.0 mm.

Table 1Differential Scanning Calorimetry

	Mod. I	Mod. II
Melting point	151	137
Melt enthalpy	87	80

Table 2X-ray diffractometry

Peak maxima [2 theta]	
Mod. I	Mod. II
7.5	7.8
9.4	8.7
10.1	10.9
10.6	12.5
12.0	13.8
12.4	14.1
13.7	15.3
14.6	15.6
15.0	16.0
16.0	16.6

Table 2 (continuation)

Peak maxima [2 theta]	
Mod. I	Mod. II
17.3	17.2
17.7	17.3
18.0	17.8
19.2	18.7
19.8	19.4
20.3	20.5
20.7	20.7
21.0	21.3
21.2	21.8
21.7	22.1
21.9	22.6
22.2	23.0
22.7	23.6
22.9	23.8
23.1	24.3
23.6	24.7
23.7	25.7
24.1	25.9
24.9	26.1

Table 2 (continuation)

Peak maxima [2 theta]	
Mod. I	Mod. II
25.6	26.5
26.2	26.8
26.6	27.1
27.5	28.0
28.0	28.4
29.5	29.0
30.0	29.6
30.1	29.9
30.5	30.4
31.0	30.7
31.7	31.2
32.2	32.2
32.6	33.0
32.8	33.4
34.4	33.6
34.6	34.3
35.1	34.7
35.5	35.5
35.8	35.7

Table 2 (continuation)

Peak maxima [2 theta]	
Mod. I	Mod. II
36.2	35.9
36.7	36.9
36.9	37.2
37.0	37.5
37.4	
37.7	

Table 3IR spectroscopy

Peak maxima [cm ⁻¹]	
Mod. I	Mod. II
3338	3298
3316	3244
3053	2943
2944	1697
1708	1615
1614	1591
1592	1495
1496	1466

Table 3 (continuation)

Peak maxima [cm ⁻¹]	
Mod. I	Mod. II
1470	1447
1431	1416
1378	1379
1335	1357
1318	1327
1294	1305
1227	1292
1179	1274
1167	1240
1156	1228
1097	1213
1079	1186
1067	1164
1055	1151
1032	1103
1013	1088
972	1068
922	1055
868	1013

Table 3 (continuation)

Peak maxima [cm ⁻¹]	
Mod. I	Mod. II
836	980
817	931
782	841
746	817
708	782
671	751
615	710
577	674
550	665
542	626
520	590
	575
	556
	538
	520

Table 4 ^{13}C -Solid state NMR spectroscopy

Peak maxima [ppm]	
Mod. I	Mod. II
181.1	179.2
164.0	163.0
139.4	141.5
138.8	137.6
136.2	136.4
135.0	132.5
127.7	129.0
120.0	128.4
118.2	127.5
117.0	122.6
109.3	121.7
107.9	117.2
106.2	115.7
54.0	109.2
53.2	106.6
52.1	51.6
50.6	40.1

Table 4 (continuation)

Peak maxima [ppm]	
Mod. I	Mod. II
38.8	37.5
38.1	35.9
37.1	34.8
36.1	29.8
35.3	27.8
33.9	26.4
32.3	25.5
31.4	22.2
29.6	21.7
29.0	21.3
27.7	
24.9	
24.1	
23.1	
20.8	
19.8	

Table 5FIR spectroscopy

Peak maxima [cm ⁻¹]	
Mod. I	Mod. II
452	498
429	477
413	449
388	432
368	411
350	395
334	373
324	326
297	291
282	281
264	235
231	201
207	177
176	152
148	116
115	101
101	94
88	88

Table 6Raman spectroscopy

Peak maxima [cm^{-1}]	
Mod. I	Mod. II
3080	3070
3069	3046
3056	2960
2955	2925
2925	2850
2898	1615
2851	1589
1613	1570
1580	1467
1566	1443
1471	1354
1438	1315
1412	1290
1369	1273
1293	1228
1277	1186
1236	1150

Table 6 (continuation)

Peak maxima [cm ⁻¹]	
Mod. I	Mod. II
1180	1100
1165	1014
1155	981
1123	921
1091	847
1059	817
1012	794
973	693
928	628
833	567
817	520
785	435
743	330
682	287
629	227
574	91
521	
334	
283	

Table 6 (continuation)

Peak maxima [cm ⁻¹]	
Mod. I	Mod. II
199	
122	
90	
82	

CLAIMS



1. Thermodynamically stable Modification I of ramatroban.
2. Thermodynamically stable Modification I of ramatroban according to Claim 1, characterized in that the substance has a melting point of 151°C (DSC, 2 K min⁻¹).
3. Thermodynamically stable Modification I of ramatroban according to Claim 1, characterized in that its X-ray diffractogram has reflections at 10.1, 12.0 and 19.8 (2 theta).
4. Thermodynamically stable Modification I of ramatroban according to Claim 1, characterized in that its IR spectrum has peak maxima at 3338 cm⁻¹, 1708 cm⁻¹ and 1431 cm⁻¹.
5. Thermodynamically stable Modification I of ramatroban according to Claim 1, characterized in that its ¹³C-solid state NMR spectrum has peak maxima at 107.9; 118.2 and 135.0 ppm.
6. Thermodynamically stable Modification I of ramatroban according to Claim 1, characterized in that its FIR spectrum has a peak maximum at 264 cm⁻¹ and at 207 cm⁻¹.
7. Thermodynamically stable Modification I of ramatroban according to Claim 1, characterized in that its Raman spectrum has peak maxima at 3080 cm⁻¹, 1580 cm⁻¹ and 122 cm⁻¹.
8. Process for the preparation of seed crystals of the thermodynamically stable Modification I of ramatroban according to Claims 1 to 7, characterized in that the active compound is converted into the amorphous form by melting and rapid cooling and this is then converted into the stable Modification I by stirring in inert solvents.
9. Process for the preparation of a thermodynami-



cally stable form of ramatroban according to Claims 1 to 7, characterized in that a thermodynamically metastable modification of ramatroban is suspended in water or inert organic solvents, seeded with the stable Modification I and the conversion is carried out until the desired degree of conversion is achieved.

10. Medicament comprising a thermodynamically stable form of ramatroban according to Claims 1 to 7.

11. Use of a thermodynamically stable modification of ramatroban according to Claims 1 to 7 in the control of diseases.

Fig. 1

DSC thermogram of ramatroban

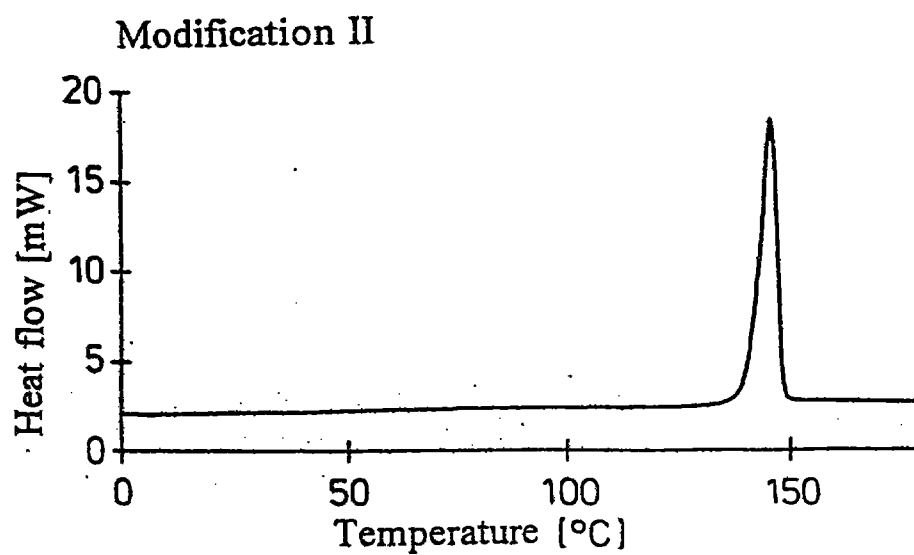
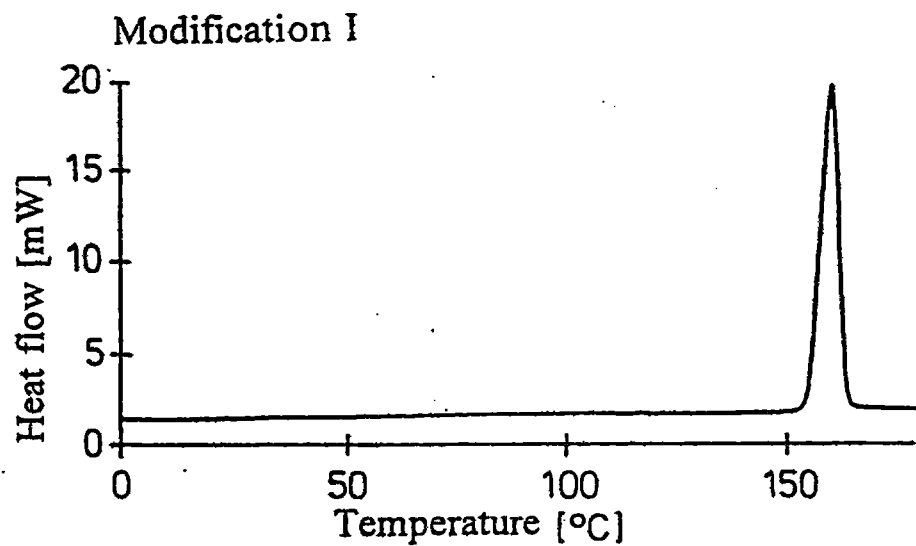


Fig. 2

IR spectra of ramatroban

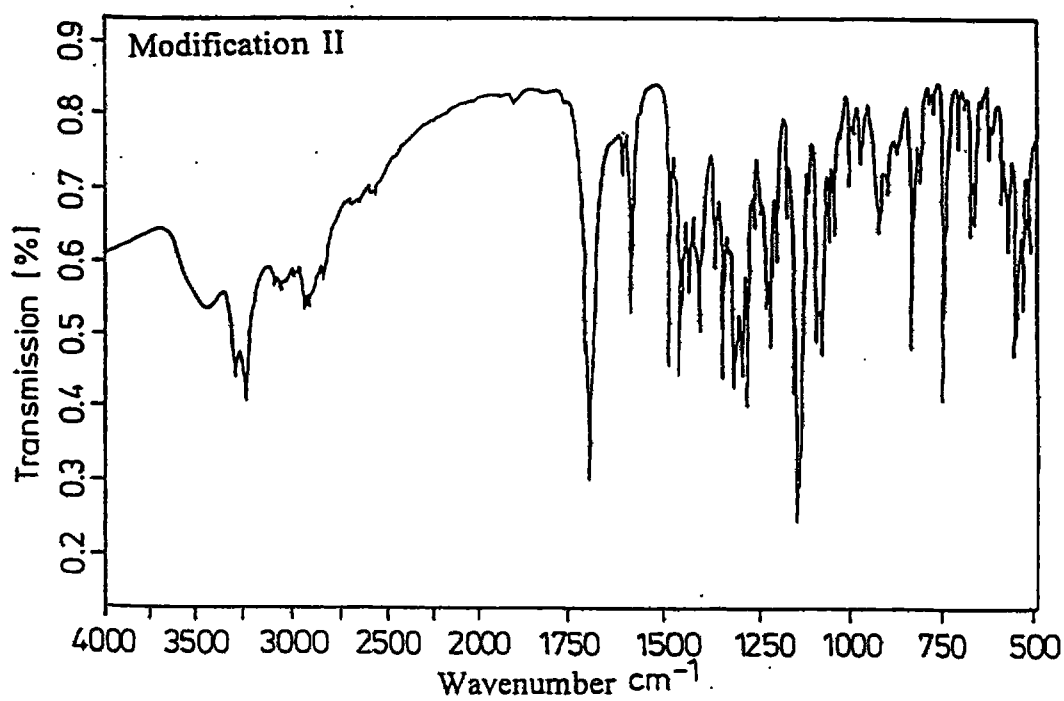
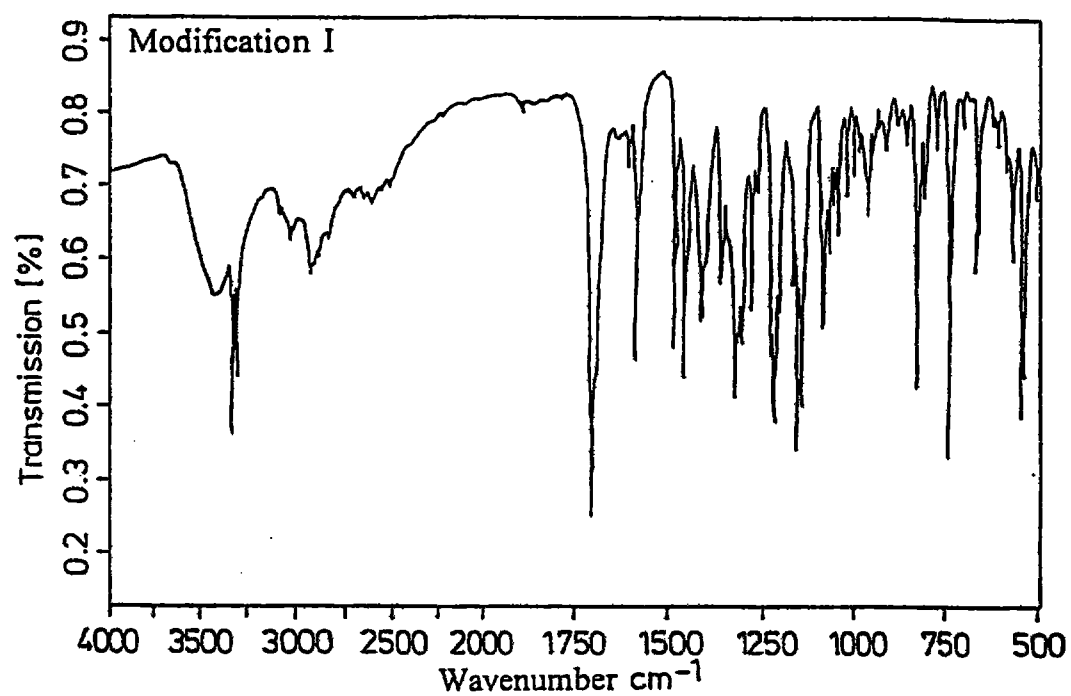
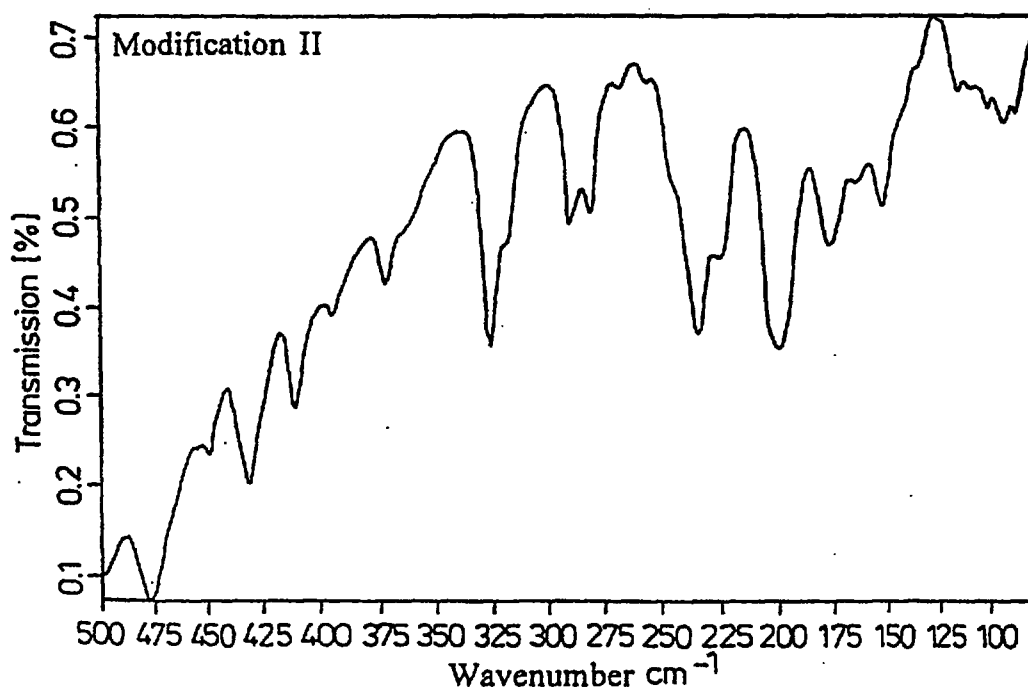
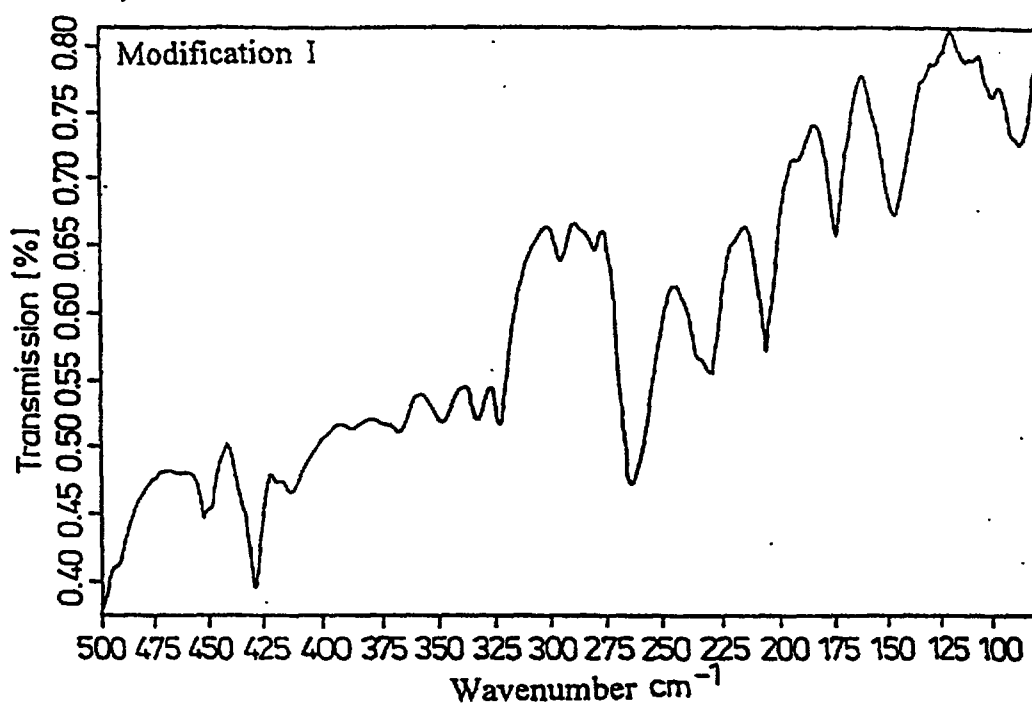


Fig. 3

FIR spectra of ramatroban



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Fig. 4

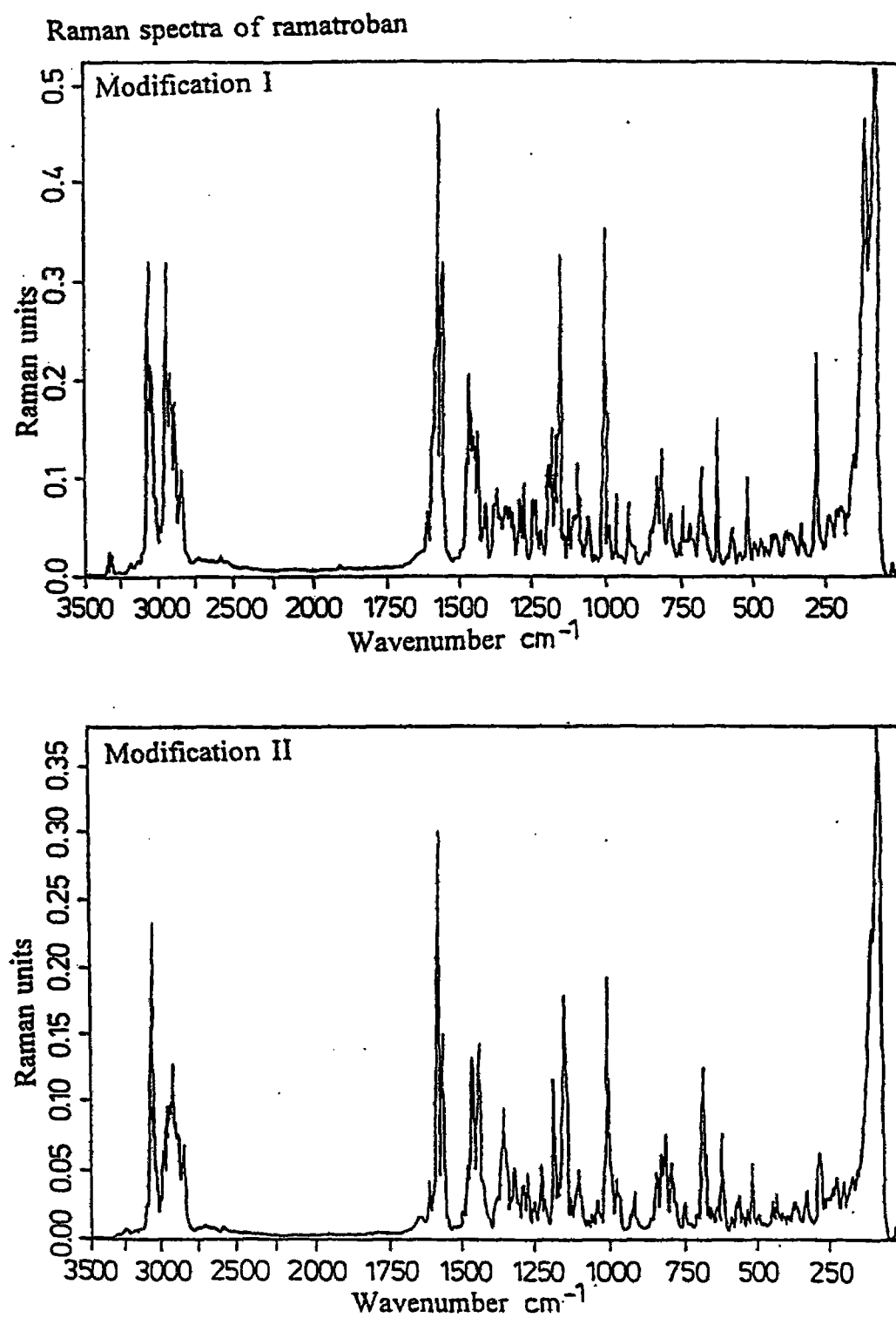


Fig. 5

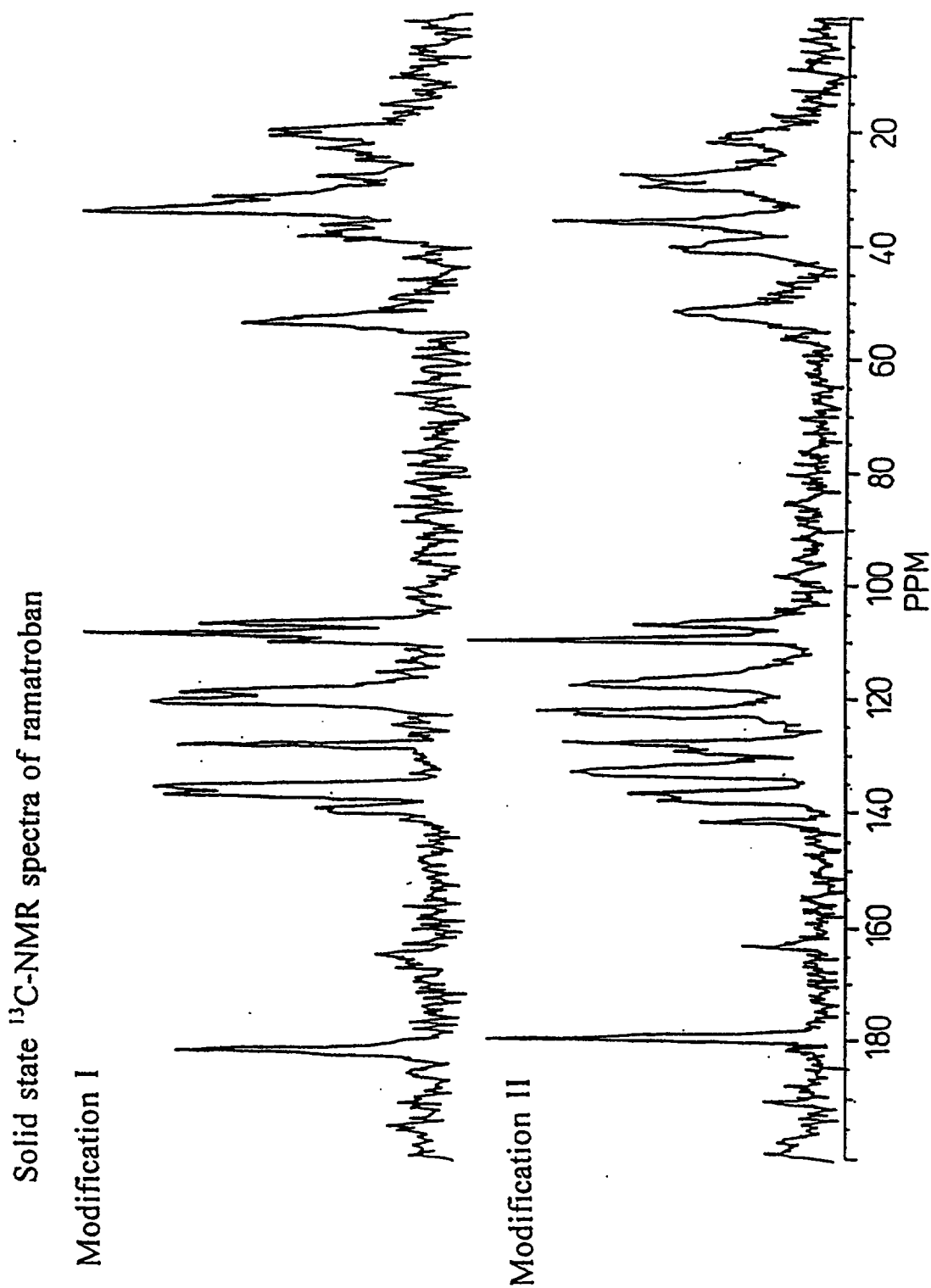
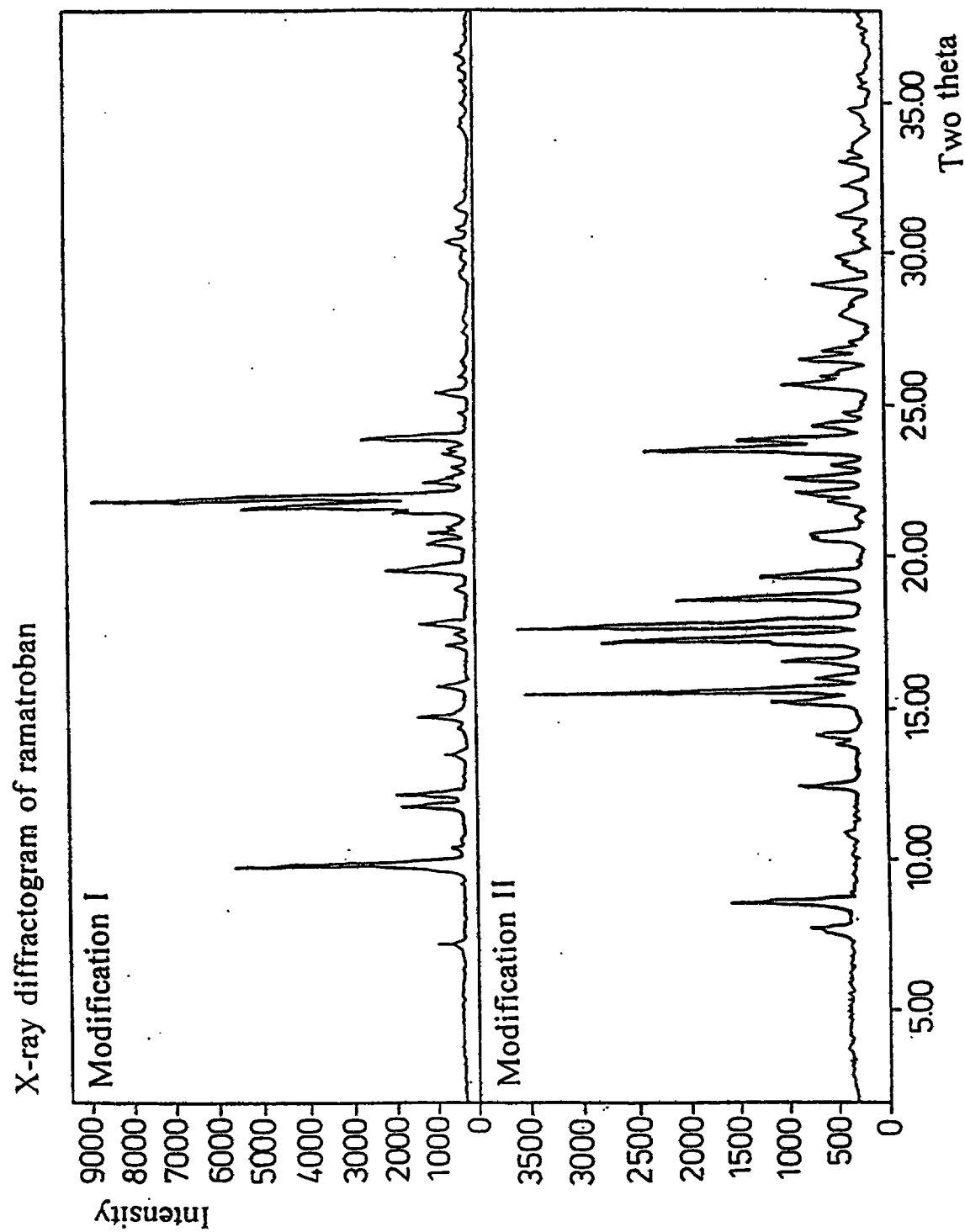


Fig. 6



PCT

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(21) International Application Number: PCT/JP98/05844 (22) International Filing Date: 24 December 1998 (24.12.98) (30) Priority Data: ① 197 57 983.3 24 December 1997 (24.12.97) DE (71) Applicant (for all designated States except US): BAYER YAKUHIN, LTD. (JP/JP); 5-36, Miyahara 3-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8577 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): ① GRUNENBERG, Alfons (DE/DE); Gneisenastrasse 15, D-41539 Dormagen (DE); WAHL, Karl-Heinz (DE/DE); Johann-Häck-Strasse 8, D-51519 Odenthal (DE); VOGES, Klaus-Peter (DE/DE); Schmitteborn 161, D-42389 Wuppertal (DE). (74) Agents: ODAJIMA, Heikichi et al.; Odajima Patent Office, Nippon Jitensha Building, 9-15, Akasaka 1-chome, Minato-ku, Tokyo 107-0052 (JP).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. ✓ 1 PD 1 app'n 3 Invs. IPC: C07D 209/88 IPER 20/5/99	
(54) Title: THERMODYNAMICALLY STABLE FORM OF (R)-3-[[(4-FLUOROPHENYL) SULPHONYL]AMINO] -1,2,3,4-TETRAHYDRO -9H-CARBAZOLE -9-PROPANOIC ACID (RAMATROBAN) ✓		
(I)		
(57) Abstract The present invention relates to a thermodynamically stable modification of the active compound ramatroban of formula (I). The thermodynamically stable form is prepared either by melting of the metastable form and subsequent recrystallization or by seeding a solution of the metastable active compound with a seed crystal of the thermodynamically stable form. The thermodynamically stable active compound can be employed as an asthma agent.		