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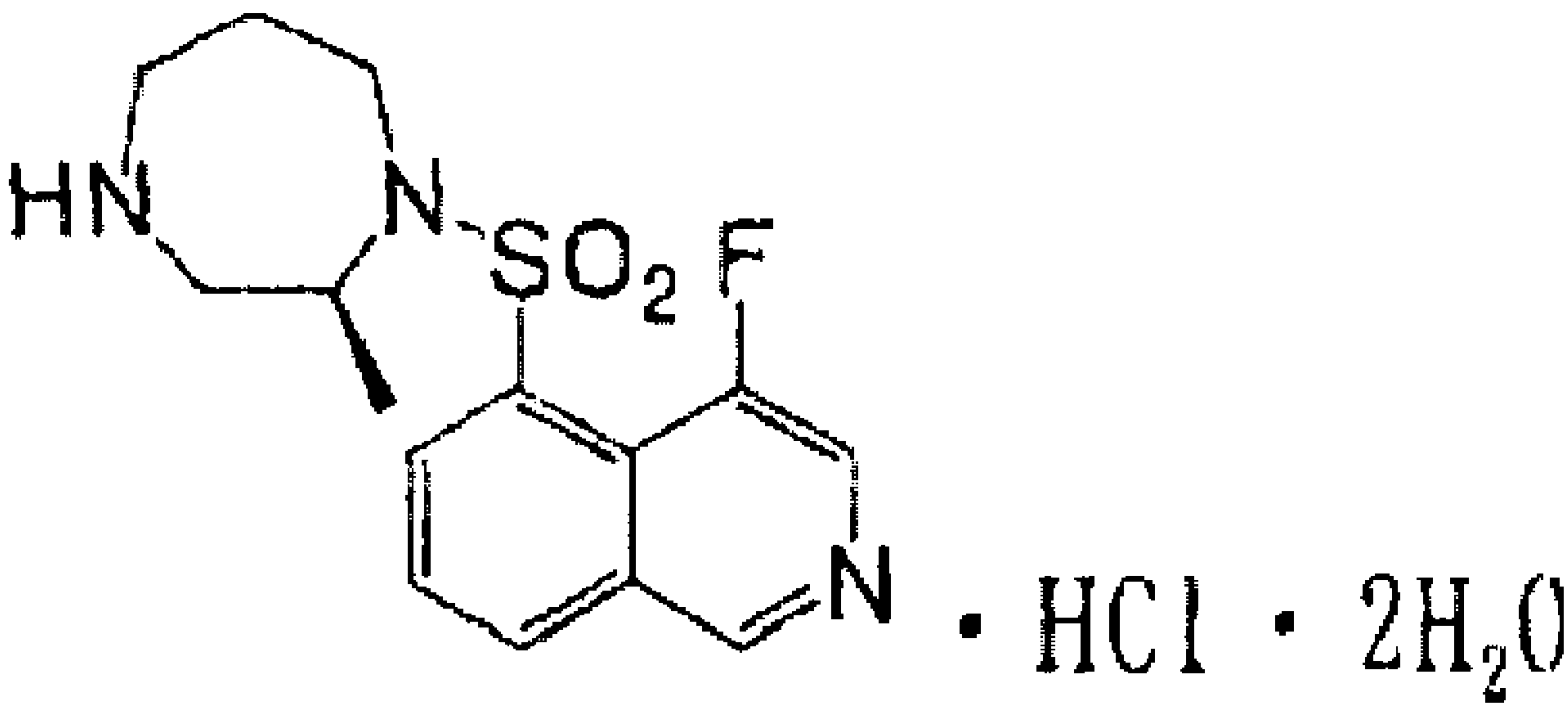
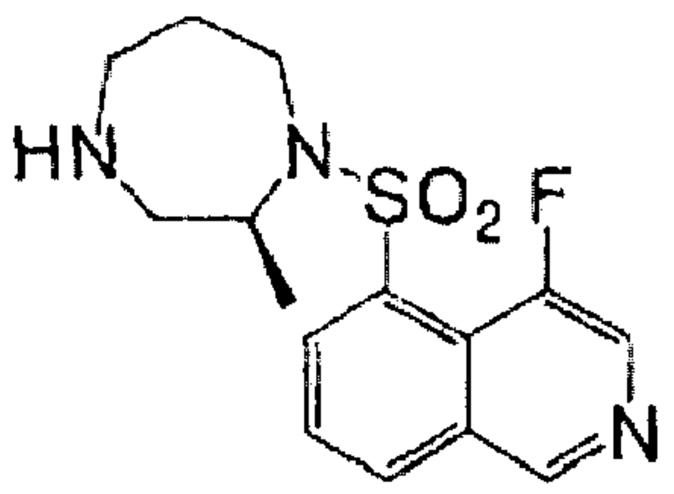
(54) **Titre :** DIHYDRATE D'HYDROCHLORURE (S) - (-) 1 (4-FLUOROISOQUINOLINE-5-YL)SULFONYLE-2-METHYL-1,4-HOMOPIPERAZINE
(54) **Title:** (S)-(-)-1-(4-FLUOROISOQUINOLIN-5-YL)SULFONYL-2-METHYL-1,4-HOMOPIPERAZINE HYDROCHLORIDE DIHYDRATE



(57) **Abrégé/Abstract:**
The present invention is directed to (S)-(-)-1-(4-5-yl)sulfonyl-2-methyl-1,4-homopiperazine fluoroisoquinolin hydrochloride dihydrate represented by the formula: (see formula 2) to a method producing the dihydrate, and to a drug composition containing the dihydrate. The compound of the present invention has less hygroscopicity as compared with (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride anhydrous crystals and thus, exhibits excellent chemical stability.

Abstract

The present invention is directed to (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate represented by the formula:



$\cdot HCl \cdot 2H_2O$ (2)

to a method producing the dihydrate, and to a drug composition containing the dihydrate. The compound of the present invention has less hygroscopicity as compared with (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride anhydrous crystals and thus, exhibits excellent chemical stability.

Description

(S)-(-)-1-(4-Fluoroisoquinolin-5-yl)sulfonyl-2-Methyl-1,4-Homopiperazine Hydrochloride Dihydrate

[Technical Field]

[0001]

The present invention relates to (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate, which has excellent hygroscopic stability

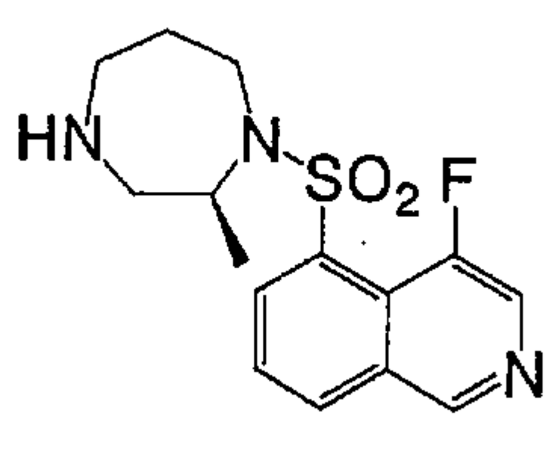
[Background Art]

[0002]

(S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride is a compound represented by formula (1):

[0003]

[F1]



·HCl (1)

[0004]

(see Patent Document 1) and assumes the form of anhydrous crystals which are water-soluble. The compound (1) is known to be a useful drug for preventing and treating cerebrovascular disorders such as cerebral infarction, cerebral hemorrhage, subarachnoidal hemorrhage, and cerebral edema, particularly for suppressing cerebrovasospasm-related diseases such as cerebral stroke (see Patent Document 1).

[0005]

Conventionally, only (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride anhydrous crystals (hereinafter may be referred to simply as "anhydrous crystals") are known to be the crystal form of compound (1) (see Patent Document 1). The anhydrous crystals have a water content, as determined through Karl Fischer's method, of 1 wt.% (hereinafter referred to simply as "%") or less.

[0006]

However, water content of the anhydrous crystals increases with elapsed time at 25°C and a relative humidity (RH) of 92%, and eventually reaches about 40% (Fig. 5). When the anhydrous crystals are stored under humid conditions (relative humidity higher than 50%), the anhydrous crystal structure thereof changes due to a hygroscopic phenomenon, concomitant with change in volume of the crystals. In other words, the anhydrous crystals undergo change in crystal structure via a hygroscopic phenomenon.

[0007]

As has been generally known, when a main drug component or an excipient has problematic hygroscopicity or other problems, change in weight and in crystal form of the compound occurs, resulting in change in volume, possibly causing changes in hardness and cracks in tablets. Such a phenomenon is disadvantageous in the production of tablets. Thus, from the viewpoint of drug preparation and storage of drugs, compounds free from problems in hygroscopicity and other properties are used. In addition, change in crystal form caused by water absorption may impair stability and bioavailability of the compound. As a compound which is required to have very high purity to be suitably used as a base material for a medicine, the above problems need to be solved.

[0008]

Since the anhydrous crystals of compound (1) have a drawback of problematic hygroscopicity, the anhydrate must be stored under rigorous moisture control. However, such rigorous control is difficult to carry out in an actual situation. Thus, there is a demand for a compound to be used as base material for a medicine as described above which has low hygroscopicity and high storage stability.

Patent Document 1: International Publication WO 99/20620 pamphlet

[Disclosure of the Invention]

[Problems to be solved by the Invention]

[0009]

Thus, an object of the present invention is to improve chemical instability of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride anhydrous crystals, the chemical instability including change in weight and in crystal form of a compound as a base material for a medicine caused by hygroscopicity of the anhydrous crystals as well as change in volume of the crystals concomitant therewith.

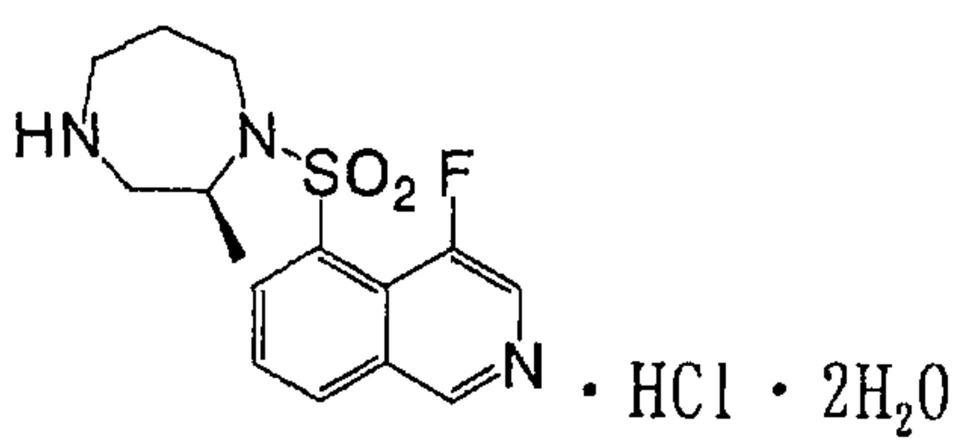
[Means for Solving the Problems]

[0010]

Under such circumstances, the present inventors have carried out extensive studies, and have found that (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate (hereinafter may be referred to simply as "dihydrate" or "dihydrate crystals"), which is a novel compound represented by formula (2):

[0011]

[F2]



(2)

[0012]

exhibits excellent hygroscopic stability; assumes the form of virtually non-hygroscopic crystals, whereby change in weight and in crystal form induced by absorption of moisture as well as change in volume concomitant therewith are prevented; and exhibits high thermal stability. The present invention has been accomplished on the basis of this finding.

Accordingly, the present invention provides (S)-(-)-1-

(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate, which is a novel compound.

[0013]

The present invention also provides a method for producing (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate, comprising dissolving (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride in water at 50 to 100°C, subsequently, adding a hydrophilic organic solvent to the solution, and cooling the mixture to 0 to 30°C.

[0014]

The present invention also provides a drug composition comprising (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate and a pharmaceutically acceptable carrier.

[0015]

The present invention also provides a medicine comprising (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate.

[0016]

The present invention also provides use of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate for manufacture of a medicine.

[0017]

The present invention also provides a method for preventing or treating cerebrovascular disorders comprising administering to a subject in need thereof an effective amount of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate.

[Effects of the Invention]

[0018]

(S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate, which is a novel compound of the present invention, is non-hygroscopic. Therefore, problems originating from moisture absorption can be avoided. In addition, the dihydrate has excellent thermal stability. Thus, the dihydrate of the present invention is a remarkably useful compound as a base material for a medicine from the viewpoint of storage and drug preparation.

[Brief Description of the Drawings]

[0019]

Fig. 1 is a chart showing an infrared absorption spectrum of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (anhydrous crystals) (top) and that of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate (bottom).

Fig. 2 is a chart showing a X-ray powder diffraction pattern of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate.

Fig. 3 is a chart showing a X-ray powder diffraction pattern of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (anhydrous crystals).

Fig. 4 is a graph showing thermal analyses of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate.

Fig. 5 is a graph showing thermal analyses of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (anhydrous crystals).

Fig. 6 is a graph showing a hygroscopic behavior (time-dependent change) of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (anhydrous crystals) at 25°C and a relative humidity of 92%.

Fig. 7 is a graph showing a hygroscopic behavior (time-dependent change) of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate.

Fig. 8 shows time-dependent change in X-ray powder diffraction pattern of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate upon temperature elevation for changing water content, and a thermal analysis curve of the hydrate.

[Best Modes for Carrying Out the Invention]

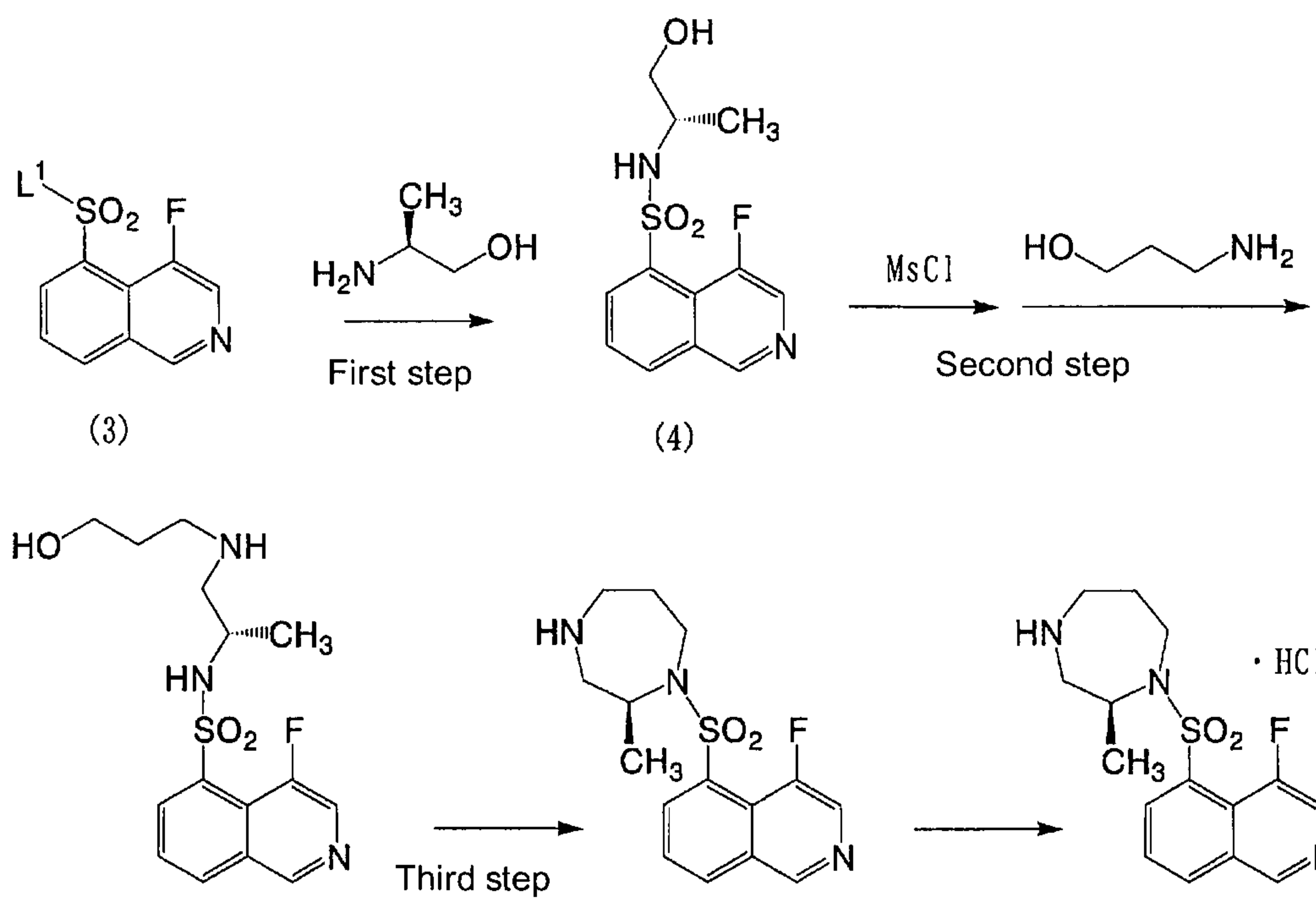
[0020]

The (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate (2) of the present invention, which is a novel compound, can be produced through the following method.

Firstly, (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (1) can be produced through a method as disclosed in Patent Document 1, a reaction scheme of which is shown below.

[0021]

[F3]



(3) (4) (5) (6) (1)

L^1 represents a leaving group

[0022]

Specifically, (S)-(+)-2-aminopropanol is reacted with a sulfonic acid derivative represented by compound (3) in methylene chloride in the presence of triethylamine, to thereby synthesize compound (4) (first step). Then, the compound (4) is reacted with methanesulfonyl chloride in methylene chloride in the presence of triethylamine, to thereby convert the hydroxyl group to a mesyl group, followed by reacting with 3-aminopropanol, to thereby synthesize compound (5) (second step). The compound (5) is subjected to ring-closure in tetrahydrofuran through the Mitsunobu Reaction employing triphenylphosphine and diisopropyl azodicarboxylate, to thereby synthesize compound (6) (third step). The thus-obtained compound (6) is converted to the corresponding hydrochloride in ethanol by use of a 1N-hydrogen chloride ether solution, to thereby produce (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (1).

[0023]

The (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (1) produced through the above procedure is dissolved in water at 50 to 100°C, preferably at 80°C. While the solution is maintained at the temperature, a hydrophilic organic solvent is added to the solution. The resultant mixture is cooled to 0 to 30°C, whereby crystals are precipitated. The crystals are dried at 0 to 30°C for 20 to 30 hours, to thereby yield (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate (2) of the present invention in the form of crystals.

[0024]

Preferably, water is used in an amount 1.0 to 2.0 times by weight, more preferably 1.3 to 1.7 times the amount of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-

homopiperazine hydrochloride (1). The amount of the hydrophilic organic solvent is 2 to 6 times the amount of water added, preferably 4 times.

[0025]

Examples of the hydrophilic organic solvent include alcohols such as methanol, ethanol, n-propanol, isopropanol, and n-butanol; acetone; N,N-dimethylformamide; dimethylsulfoxide; and diethylene glycol dimethyl ether. Of these, ethanol, isopropanol, and acetone are particularly preferred. The cooling temperature and drying temperature are 0 to 30°C, preferably about room temperature. The drying time is 20 to 30 hours, preferably about 24 hours.

[0026]

The thus-produced dihydrate of the present invention has a water content of 8.80 to 9.40% as determined through Karl Fischer's method, preferably 8.87 to 9.13% as determined through Karl Fischer's method (Tables 6 and 7). As shown in Fig. 7, water content of the dihydrate of the present invention has been found to be constant at 25°C and a relative humidity of 92%RH for 14 days. Furthermore, the dihydrate of the present invention does not decompose or undergoes undesired reaction even when the dihydrate is stored under severe conditions (i.e., at 80°C for two weeks). Thus the dihydrate has been found to have high thermal stability (Table 5).

In contrast, water content of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride anhydrate increases with elapsed time under the same conditions. Seven days after, the water content has been increased to 40% (Fig. 6).

[0027]

The dihydrate of the present invention is a useful active ingredient contained in a drug for preventing or treating diseases originating from a cerebrovascular disorder such as cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and cerebral edema. No particular limitation is imposed on the type of administration of the dihydrate of the present invention, and either oral administration or parenteral administration (e.g., intramuscular, subcutaneous, intravenous, suppository, eye drops) may be employed.

[0028]

In the case where a peroral formulation is prepared, excipient and, in accordance with needs, a pharmaceutically acceptable carrier such as a binder, a disintegrant, a lubricant, a coloring agent, or a sweetening/flavoring agent is added to the dihydrate. The mixture may be formed into tablets, coated tablet, granules, capsules, solution, syrup, elixir, or oil- or water-soluble suspension through a routine method.

Examples of the excipient include lactose, corn starch, white sugar, glucose, sorbitol, and crystalline cellulose. Examples of the binder include polyvinyl alcohol, polyvinyl ether, ethyl cellulose, methyl cellulose, gum arabic, tragacanth gum, gelatin, shellac, hydroxypropyl cellulose, hydroxypropyl starch, and polyvinyl pyrrolidone.

[0029]

Examples of the disintegrant include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextran, and pectin. Examples of the lubricant include sodium stearate, talc, polyethylene glycol, silica, and hardened vegetable oil. As a coloring agent, those which are acceptable to use in drugs may be employed. Examples of the sweetening/flavoring agent which may be used include cocoa powder, menthol, aromatic acid, peppermint oil, borneol, and cinnamon powder. In accordance with needs, these tablets and granules may be appropriately coated with sugar, gelatin, or other materials.

[0030]

When injections and eye drops are prepared, an additive such as a pH regulator, a buffer, a stabilizer, or a preservative is added to the dihydrate in accordance with needs. Through a routine method, the mixture is formed into subcutaneous injections, intramuscular injections, or intravenous injections. In an alternative embodiment, a drug solution such as an injection or eye drops preparation is charged into a container, and through lyophilization or a similar technique, is formed into a solid preparation, which is reconstituted upon use. One dose may be placed in a single container. Alternatively, a plurality of doses may be placed in a single container.

[0031]

The dihydrate of the present invention is generally administered to an adult human at a daily dose of 0.01 to 1000 mg, preferably 0.1 to 100 mg. The daily dose may be administered once a day or 2 to 4 divided times a day.

[Examples]

[0032]

The present invention will next be described in more detail by way of examples and test examples, which should not be construed as limiting the invention thereto.

[0033]

Example 1

(S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (1) (2.0 g) prepared through the method described in the pamphlet of International Publication WO 99/20620 was dissolved in water (3 mL) under heating at 80°C. Subsequently, isopropanol (12 mL) was added to the solution under heating. After the mixture had been confirmed to be homogeneous, the mixture was allowed to stand overnight at room temperature for crystallization. The thus-precipitated crystals were collected through filtration, followed by drying at room temperature for 24 hours, to thereby yield 1.76 g of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate (80.0%).

[0034]

Elemental analysis: as $C_{15}H_{18}N_3O_2FS \cdot HCl \cdot 2H_2O$

Calculated: C 45.51%; H 5.86%; N 10.61%; Cl 8.96%

Found: C 45.50%; H 5.84%; N 10.57%; Cl 8.93%

[0035]

The infrared absorption spectrum of the dihydrate measured by means of an infrared spectrophotometer (AVATAR™ 370, product of Thermo Nicolet; ATR method) exhibits absorption peaks attributable to dihydrate virtually at 854, 974, 1146, 1323, and 3418 cm^{-1} (Fig. 1, bottom). Specific data of wave number and intensity of the peaks are shown in Table 1. The absorption spectrum of the corresponding anhydrous crystals is shown in Fig. 1 (top) and the absorption peaks are shown in Table 2.

[0036]

[Table 1]

Infrared absorption of dihydrate
(Wave number: cm^{-1}, Intensity: %R)

Wave number:	764.51	Intensity:	80.630
Wave number:	779.76	Intensity:	91.146
Wave number:	794.63	Intensity:	91.621
Wave number:	854.41	Intensity:	90.857
Wave number:	882.98	Intensity:	91.724
Wave number:	894.42	Intensity:	89.039
Wave number:	974.74	Intensity:	86.245
Wave number:	1020.91	Intensity:	93.720
Wave number:	1043.96	Intensity:	90.273
Wave number:	1074.70	Intensity:	90.454
Wave number:	1092.36	Intensity:	94.291
Wave number:	1130.49	Intensity:	86.130
Wave number:	1146.17	Intensity:	81.445
Wave number:	1178.81	Intensity:	91.941
Wave number:	1272.85	Intensity:	89.759
Wave number:	1323.30	Intensity:	75.088
Wave number:	1350.82	Intensity:	91.048
Wave number:	1377.13	Intensity:	93.358
Wave number:	1418.51	Intensity:	94.514

Wave number:	1448.58	Intensity:	94.730
Wave number:	1479.05	Intensity:	94.217
Wave number:	1494.35	Intensity:	93.546
Wave number:	1588.71	Intensity:	93.721
Wave number:	2774.45	Intensity:	94.646
Wave number:	2984.37	Intensity:	95.357
Wave number:	3418.71	Intensity:	93.908

[0037]

[Table 2]

Infrared absorption of anhydrate

(Wave number: cm^{-1}, Intensity: %R)

Wave number:	679.34	Intensity:	99.252
Wave number:	762.59	Intensity:	92.637
Wave number:	773.67	Intensity:	97.136
Wave number:	790.25	Intensity:	97.978
Wave number:	807.65	Intensity:	99.013
Wave number:	840.68	Intensity:	98.725
Wave number:	871.31	Intensity:	97.249
Wave number:	898.03	Intensity:	96.797
Wave number:	939.89	Intensity:	98.506
Wave number:	954.86	Intensity:	97.913
Wave number:	992.25	Intensity:	93.757
Wave number:	1044.93	Intensity:	99.087
Wave number:	1061.07	Intensity:	98.394
Wave number:	1073.37	Intensity:	99.155
Wave number:	1098.17	Intensity:	99.056
Wave number:	1112.48	Intensity:	97.383
Wave number:	1129.22	Intensity:	96.590
Wave number:	1151.65	Intensity:	93.492
Wave number:	1205.14	Intensity:	96.423
Wave number:	1221.03	Intensity:	97.745
Wave number:	1273.55	Intensity:	95.943
Wave number:	1301.49	Intensity:	97.917
Wave number:	1314.42	Intensity:	97.117
Wave number:	1329.07	Intensity:	92.494
Wave number:	1354.18	Intensity:	97.487
Wave number:	1381.27	Intensity:	98.752
Wave number:	1414.12	Intensity:	99.324
Wave number:	1455.71	Intensity:	97.838
Wave number:	1497.05	Intensity:	99.039
Wave number:	1586.02	Intensity:	97.437
Wave number:	1623.73	Intensity:	99.643
Wave number:	2534.92	Intensity:	98.913
Wave number:	2648.09	Intensity:	98.692

Wave number:	2797.78	Intensity:	99.062
Wave number:	2945.10	Intensity:	99.554

[0038]

Fig. 2 shows a X-ray powder diffraction pattern of the dihydrate obtained by means of a diffractometer (Miniflex™, product of Rigaku Denki Kogyo). The apparatus was used in the following procedure. As shown in Table 3, X-ray diffraction peaks attributable to dihydrate were observed at diffraction angles (2θ) of 8.660, 15.240, 17.180, 25.100, 25.780, 26.780, 28.100, 30.060, and 33.200°. Width at half-height (at 1/2 intensity), crystaline plane spacing (d value), diffraction X-ray intensity (intensity), and diffraction X-ray relative intensity (relative intensity) of the peaks are also shown in Table 3.

The X-ray powder diffraction pattern of the corresponding anhydrate is shown in Fig. 3, and diffraction angle, Width at half-height, d value, intensity, and relative intensity of the diffraction peaks are shown in Table 4.

[0039]

[Table 3-1/2]

Diffraction angles of dihydrate

Peak number	2θ	Width at half-height	d	Intensity	Relative intensity
1	3.420	0.141	25.8122	571	26
2	3.700	0.118	23.8595	1002	45
3	3.900	0.165	22.6364	991	44
4	4.140	0.212	21.3246	878	39
5	8.060	0.118	10.9600	360	16
6	8.660	0.165	10.2019	2151	96
7	12.780	0.118	6.9208	469	21
8	13.240	0.165	6.6814	487	22
9	13.540	0.165	6.5340	543	25
10	15.020	0.188	5.8933	1269	57
11	15.240	0.165	5.8088	1955	87
12	15.460	0.141	5.7266	1759	78
13	17.180	0.188	5.1569	1184	53
14	19.560	0.212	4.5345	520	24
15	20.040	0.235	4.4270	596	27
16	21.180	0.188	4.1912	916	41
17	21.540	0.165	4.1219	674	30
18	21.980	0.188	4.0404	1757	78
19	22.380	0.188	3.9691	1100	49
20	23.000	0.212	3.8635	653	29
21	24.860	0.118	3.5785	714	32
22	25.100	0.212	3.5448	1471	66
23	25.460	0.165	3.4955	1031	46
24	25.780	0.165	3.4528	2258	100
25	26.780	0.165	3.3261	1425	64
26	27.060	0.188	3.2923	875	39
27	27.600	0.165	3.2291	1112	50
28	28.100	0.212	3.1728	1219	54
29	29.000	0.141	3.0763	610	27
30	29.100	0.118	3.0660	570	26

[Table 3-2/2]

Diffraction angles of dihydrate

Peak number	2θ	Width at half-height	d	Intensity	Relative intensity
31	29.840	0.141	2.9916	1079	48
32	30.060	0.188	2.9702	1157	52
33	30.700	0.188	2.9098	745	33
34	30.980	0.141	2.8841	628	28
35	32.160	0.165	2.7809	732	15
36	32.800	0.118	2.7281	575	26
37	33.200	0.282	2.6961	1339	60
38	34.260	0.118	2.6151	577	26
39	35.840	0.188	2.5034	738	33
40	36.100	0.165	2.4859	669	30
41	36.620	0.118	2.4518	739	33
42	37.700	0.235	2.4275	806	36
43	38.320	0.212	2.3469	823	37
44	38.900	0.165	2.3122	750	34
45	39.340	0.118	2.2883	605	27
46	39.480	0.212	2.2805	628	28
47	39.580	0.118	2.2750	595	27
48	40.900	0.306	2.2046	674	30
49	42.260	0.118	2.1367	637	29
50	44.160	0.235	2.0491	610	27
51	46.240	0.212	1.9646	614	28
52	46.460	0.118	1.9529	563	25
53	46.940	0.235	1.9340	627	28

[0040]

[Table 4-1/2]

Diffraction angles of anhydrate

Peak number	2θ	Width at half-height	d	Intensity	Relative intensity
1	3.520	0.165	25.0791	488	11
2	3.800	0.118	23.2318	719	16
3	4.120	0.259	21.4281	698	15
4	8.700	0.212	10.1551	729	16
5	9.720	0.235	9.0916	389	9
6	11.240	0.118	7.8653	386	9
7	11.560	0.118	7.6483	452	10
8	11.880	0.212	7.4430	973	21
9	12.040	0.141	7.3445	972	21
10	12.780	0.212	6.9208	1140	25
11	13.140	0.141	6.7320	414	9
12	13.340	0.118	6.6315	424	9
13	14.480	0.188	6.1119	1696	36
14	15.320	0.165	5.7786	812	18
15	15.560	0.165	5.6900	712	16
16	17.260	0.188	5.1332	569	13
17	17.920	0.212	4.9456	1310	28
18	18.680	0.212	4.7461	1003	22
19	19.120	0.212	4.6378	712	16
20	20.400	0.188	4.3496	582	13
21	21.020	0.259	4.2227	650	14
22	21.340	0.118	4.1601	561	12
23	21.840	0.259	4.0660	1668	36
24	21.860	0.118	4.0623	1643	35
25	22.500	0.212	3.9482	607	13
26	25.480	0.212	3.4928	4713	100
27	25.840	0.165	3.4449	957	21
28	26.220	0.141	3.3959	768	17
29	26.620	0.188	3.3457	1125	24
30	27.160	0.235	3.2804	1044	23

[Table 4-2/2]

Diffraction angles of anhydrate

Peak number	2θ	Width at half-height	d	Intensity	Relative intensity
31	27.700	0.118	3.2177	704	15
32	28.180	0.165	3.1640	569	13
33	28.700	0.141	3.1078	892	19
34	29.000	0.118	3.0763	879	19
35	29.320	0.165	3.0435	695	15
36	29.880	0.188	2.9877	643	14
37	30.940	0.188	2.8877	654	14
38	31.560	0.259	2.8324	677	15
39	32.480	0.235	2.7542	837	18
40	32.980	0.118	2.7136	595	13
41	34.800	0.141	2.5758	590	13
42	36.560	0.118	2.4557	620	14
43	36.980	0.165	2.4288	710	16
44	38.520	0.259	2.3351	623	14
45	41.300	0.353	2.1841	653	14
46	45.820	0.235	1.9786	559	12

[0041]

Figs. 4 and 5 show the results of thermal analysis carried out by means of an analyzer (XRD-DSC, product of Rigaku Denki Kogyo).

[0042]

Example 2

The procedure of Example 1 was repeated, except that ethanol was used instead of isopropanol, to thereby yield (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate (2).

[0043]

Example 3

(S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride (1) (50.0 g) was dissolved in water (75 mL) under heating at 80°C. Subsequently, acetone (300 mL) was added to the solution under heating. After the mixture had been confirmed to be homogeneous, the mixture was allowed to stand overnight at room temperature for crystallization. The thus-precipitated crystals were collected through filtration, followed by drying at room temperature for 24 hours, to thereby yield 45.4 g of (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate (2) (82.5%).

[0044]

mp 258°C

Elemental analysis: as $C_{15}H_{18}N_3O_2FS \cdot HCl \cdot 2H_2O$

Calculated: C 45.51%; H 5.86%; N 10.61%; Cl 8.96%

Found: C 45.49%; H 5.82%; N 10.56%; Cl 8.95%

[0045]

Test Example 1 (thermal stability)

The dihydrate of the present invention produced in Example 1 was placed in sealable containers such that each container included 1 g of the dihydrate. After sealing, these containers were maintained in thermostats at 40, 60, and 80°C for 7 and 14 days, so as to evaluate thermal stability. Table 5 shows the results.

[0046]

[Table 5]

Storage temp.	Storage period	Percent remain (%)
40°C	7 days	100.0
	14 days	99.6
60°C	7 days	99.6
	14 days	99.8
80°C	7 days	99.8
	14 days	99.8

[0047]

As is clear from Table 5, the dihydrate of the present invention exhibits high thermal stability even after storage at 40°C, 60°C, or 80°C for two weeks.

[0048]

Test Example 2 (hygroscopicity)

Each of the dihydrate of the present invention produced in Example 1 and (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride anhydrate (each 100 mg) was placed in a weighing bottle. The bottle was allowed to stand in a container maintained at 25°C and an RH of 33% or 92%, with the container being opened. The weighing bottle was time-dependently weighed, to thereby determine increase in weight for evaluation of hygroscopicity. Figs. 6 and 7 show the results.

[0049]

As is clear from Figs. 6 and 7, water content of the anhydrate increased from 0 to 40% with elapse of time, indicating poor hygroscopic stability. In contrast, the dihydrate of the present invention exhibited no change in its water content, indicating excellent hygroscopic stability. The dihydrate of the present invention was still stable even after storage for two weeks under the same conditions.

[0050]

The results of elemental analysis, water content, X-ray powder diffraction, and infrared absorption spectrum of the dihydrate of the present invention produced in Examples 1 to 3 are collectively shown in Table 6.

[0051]

[Table 6]

Organic solvent	Isopropanol	Ethanol	Acetone
Elemental analysis (C,H,N,Cl)	Ex. 1*	Ex. 1**	Ex. 3*
Water content (%)	9.05	9.13	8.94
X-ray powder diffraction	Ex. 1*	Ex. 1**	Ex. 1**
IR absorption spectrum	Ex. 1*	Ex. 1**	Ex. 1**

*: described in

**: coinciding with

[0052]

As is clear from Table 6, when ethanol or acetone was employed as an organic solvent instead of isopropanol, the same elemental analysis results, water content, X-ray powder diffraction results, and infrared absorption spectrum as those of the dihydrate were obtained.

[0053]

Example 4 (reproducibility on a large scale)

In a manner similar to that of Example 3, two more lots of the dihydrate of the present invention were produced. Reproducibility in physical properties was confirmed. Table 7 shows the results.

[0054]

[Table 7]

Lot	1 (Ex. 3)	2	3
Elemental analysis (C,H,N,Cl)	Ex. 3*	Ex. 3**	Ex. 3**
Water content (%)	8.87	8.89	8.90
X-ray powder diffraction	Ex. 1**	Ex. 1**	Ex. 1**
IR absorption spectrum	Ex. 1**	Ex. 1**	Ex. 1**

*: described in

**: coinciding with

Note: Lot No. 1 refers to the dihydrate obtained in Example 3

[0055]

As is clear from Table 7, all the lots exhibited the physical properties including elemental analysis, water content, X-ray powder diffraction, and infrared absorption spectrum, characteristic to the dihydrate. The results indicate that the dihydrate of the present invention can be produced with high reproducibility in large-scale production.

Claims

1. (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate.

2. (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate as described in claim 1, which has a water content of 8.80 to 9.40%, as determined through Karl Fischer's method.

3. (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate as described in claim 1 or 2, which exhibits characteristic peaks, in a X-ray powder diffraction pattern, at diffraction angle (2θ) of 8.660, 15.240, 17.180, 25.100, 25.780, 26.780, 28.100, 30.060, and 33.200°.

4. (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate as described in any one of claims 1 to 3, which exhibits characteristic absorption peaks, in an infrared absorption spectrum, at near 854, 974, 1146, 1323, and 3418 cm^{-1}.

5. A method for producing (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate as recited in any one of claims 1 to 4, comprising dissolving (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride in water at 50 to 100°C, subsequently, adding a hydrophilic organic solvent to the solution, and cooling the mixture to 0 to 30°C.

6. A method for producing (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate as described in claim 5, wherein water is used in an amount 1.0 to 2.0 times by weight with respect to (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride.

7. A method for producing (S)-(-)-1-(4-fluoroisoquinolin-5-yl)sulfonyl-2-methyl-1,4-homopiperazine hydrochloride dihydrate as described in claim 5 or 6, wherein the ratio by weight of water to the hydrophilic organic solvent is 1:2 to 1:6.

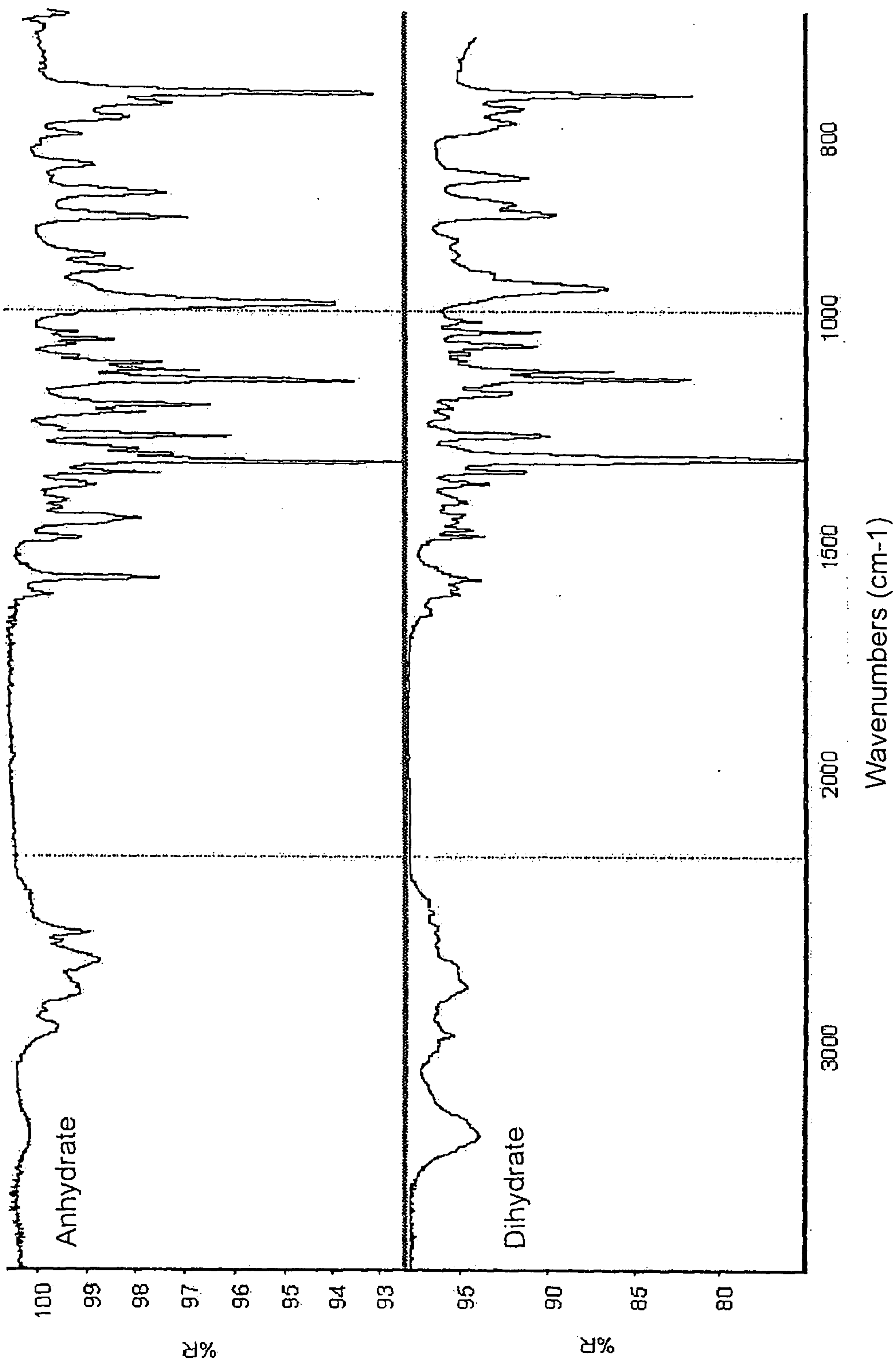

Anhydrate
Dihydrate
%R
100
99
98
97
96
95
94
93
%R
95
90
85
80
3000
2000
1500
1000
800
Wavenumbers (cm-1)

Fig. 1

Fig. 2

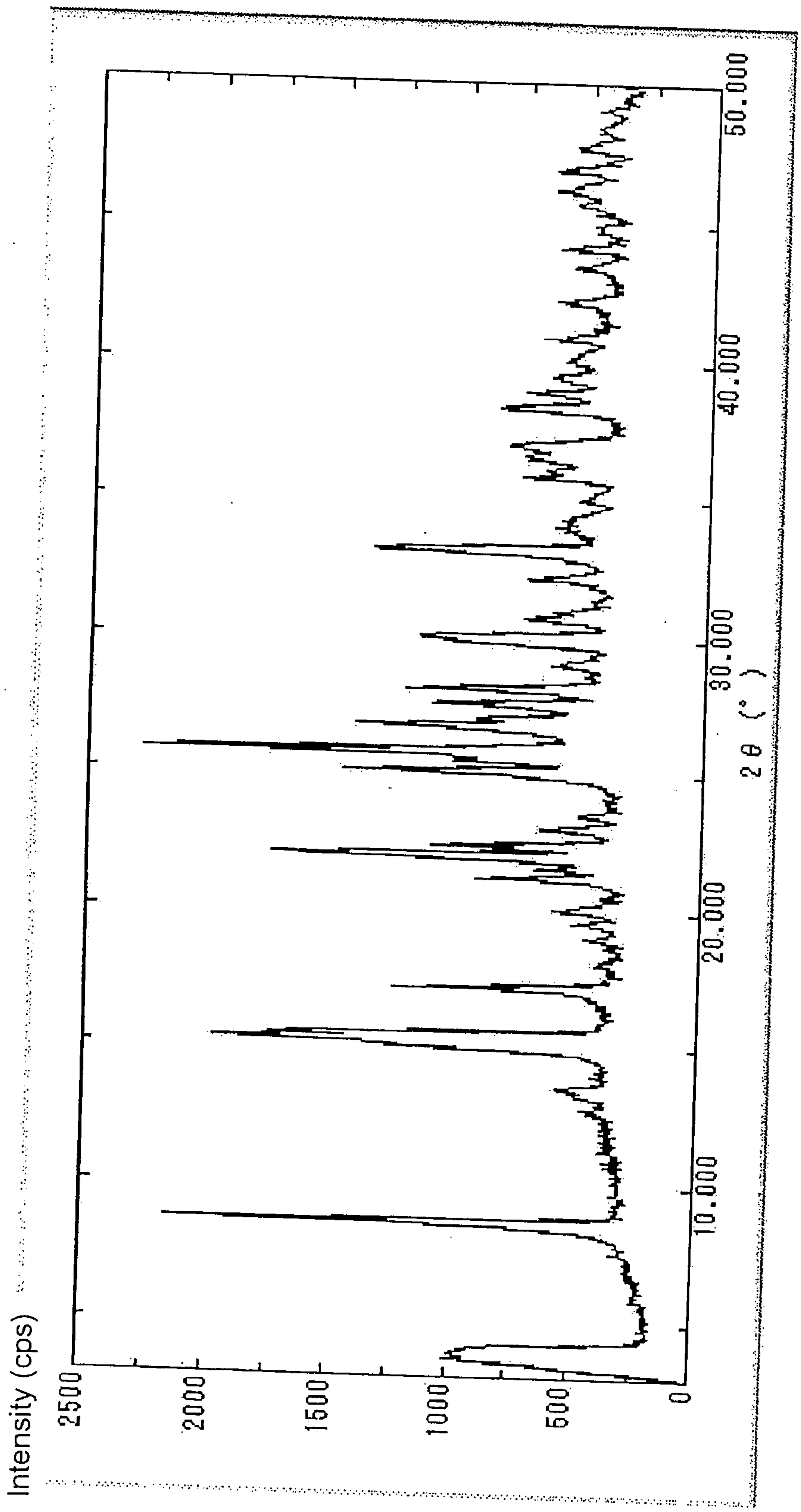
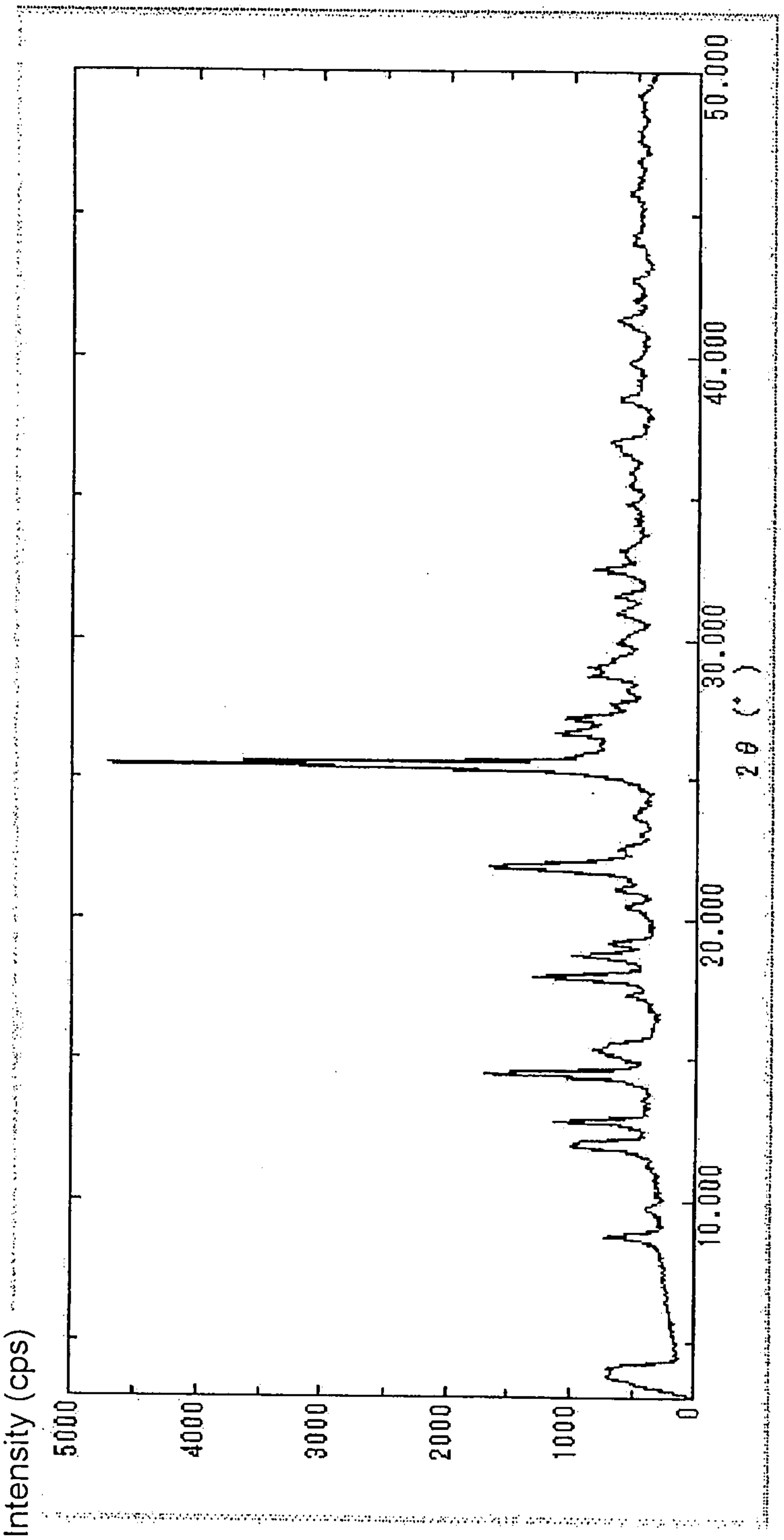

Intensity (cps)
2500
2000
1500
1000
500
0
10.000
20.000
30.000
40.000
50.000
2θ (°)

Fig. 3


Intensity (cps)
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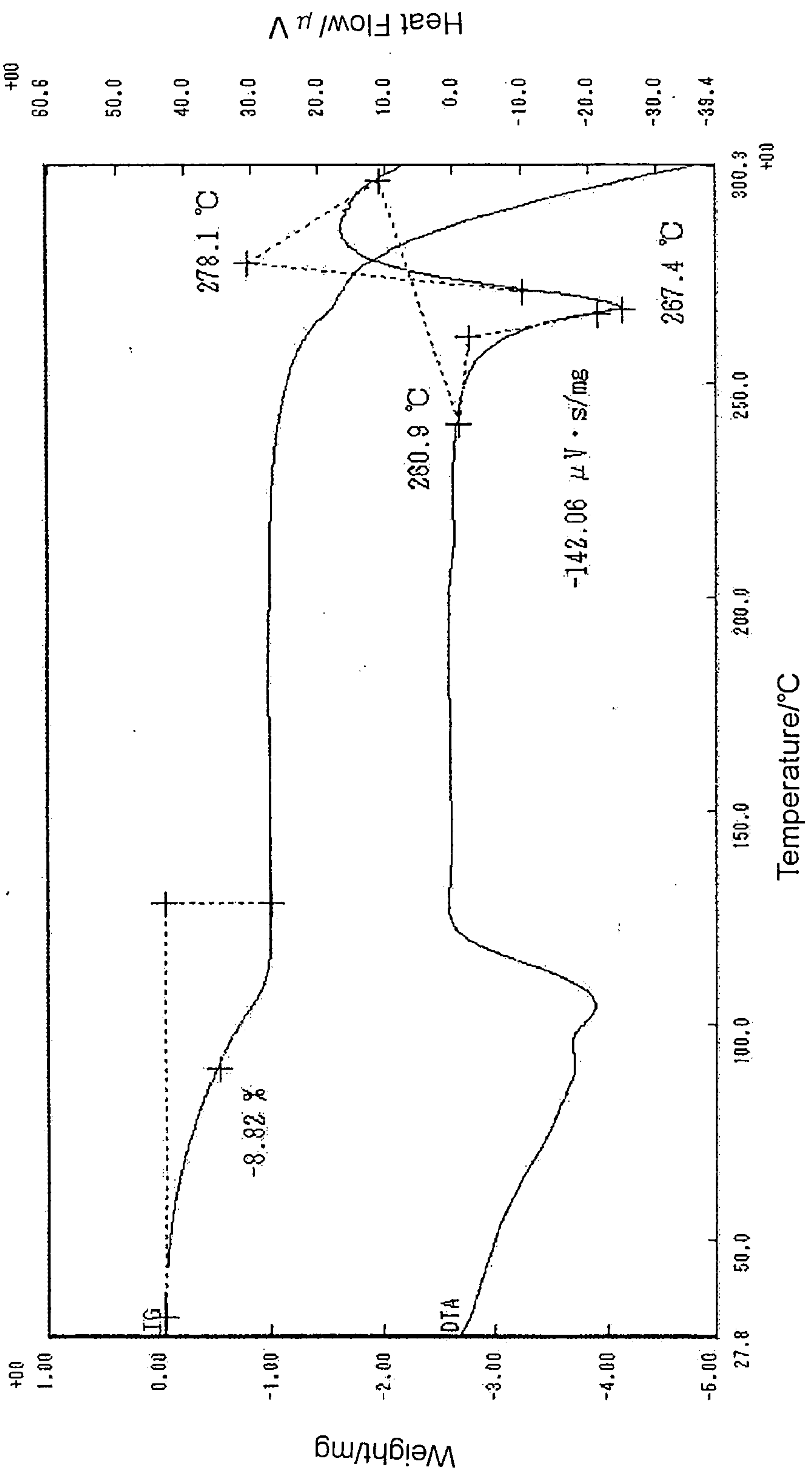
4000
3000
2000
1000
0
10.000
20.000
30.000
40.000
50.000
2θ (°)


Heat Flow/μV
Temperature/°C
Weight/mg
TG
DTA
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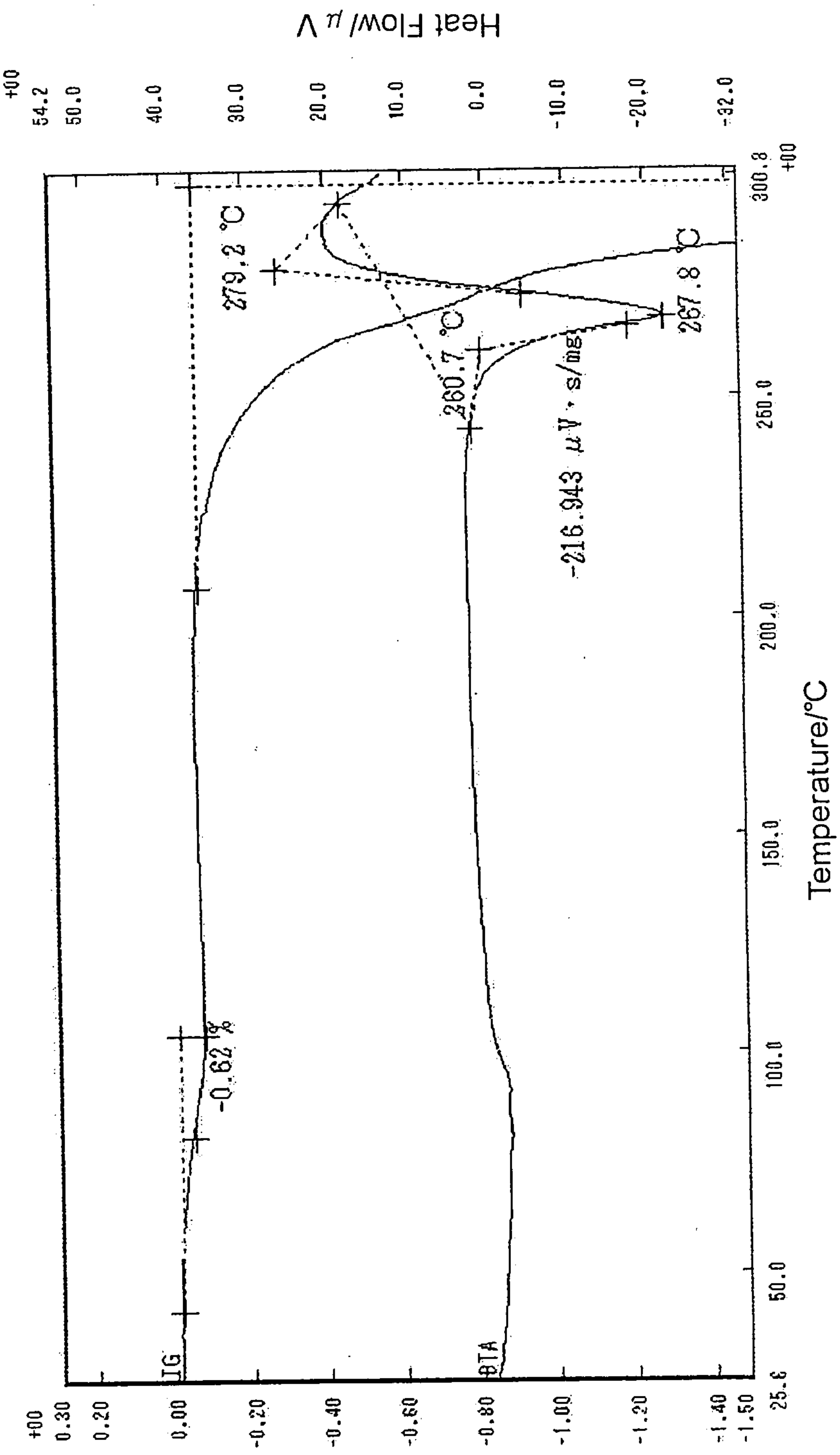
267.4 °C
260.9 °C
-142.06 μV・s/mg
-8.82 %

Fig. 4


Heat Flow/μV
Temperature/°C
Weight/mg
TG
DTA
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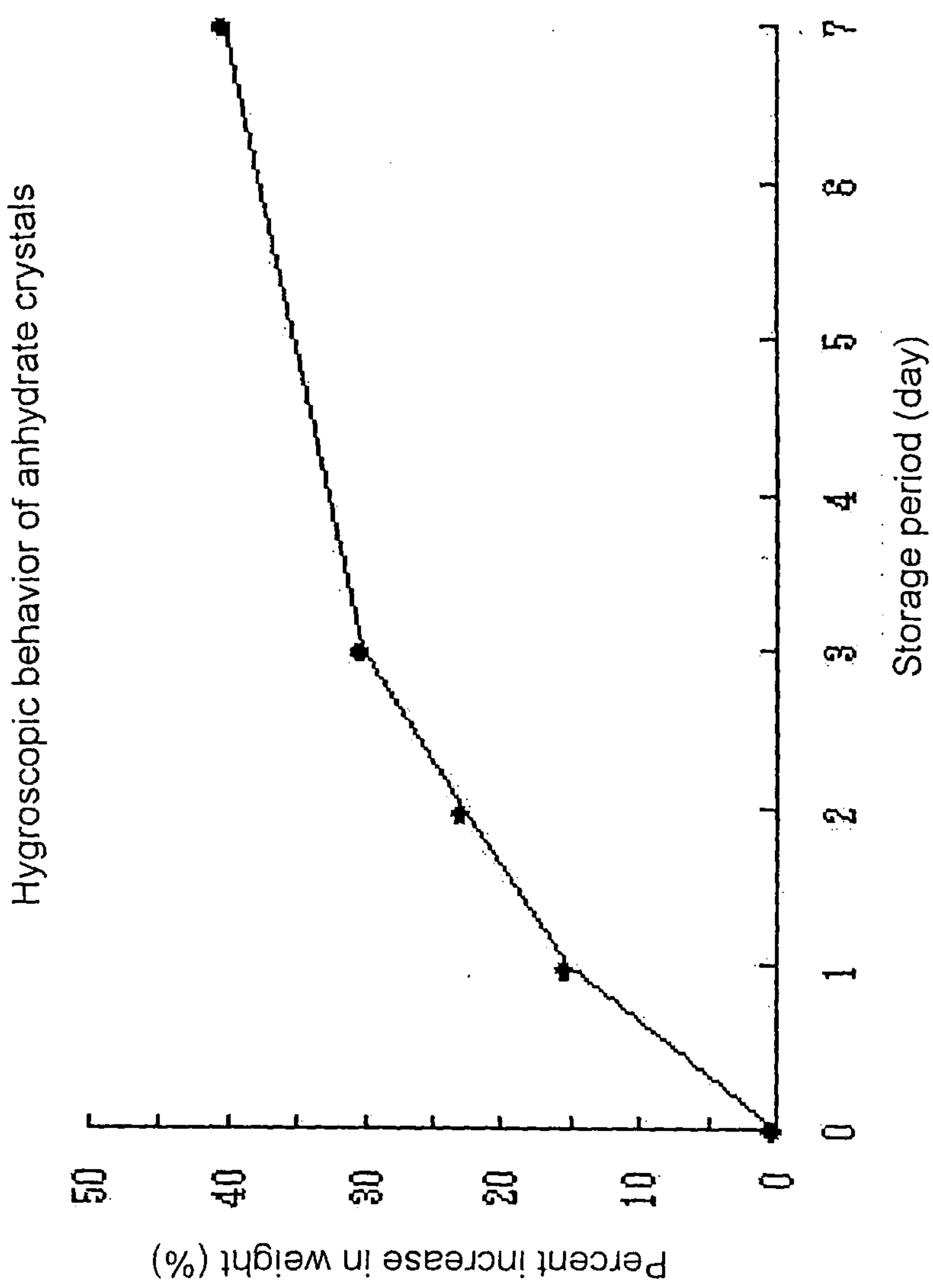
260.7 °C
267.8 °C
-216.943 μV・s/mg
-0.62%

Fig. 5

Fig. 6


Hygroscopic behavior of anhydrate crystals
Percent increase in weight (%)
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10
20
30
40
50
Storage period (day)
0
1
2
3
4
5
6
7

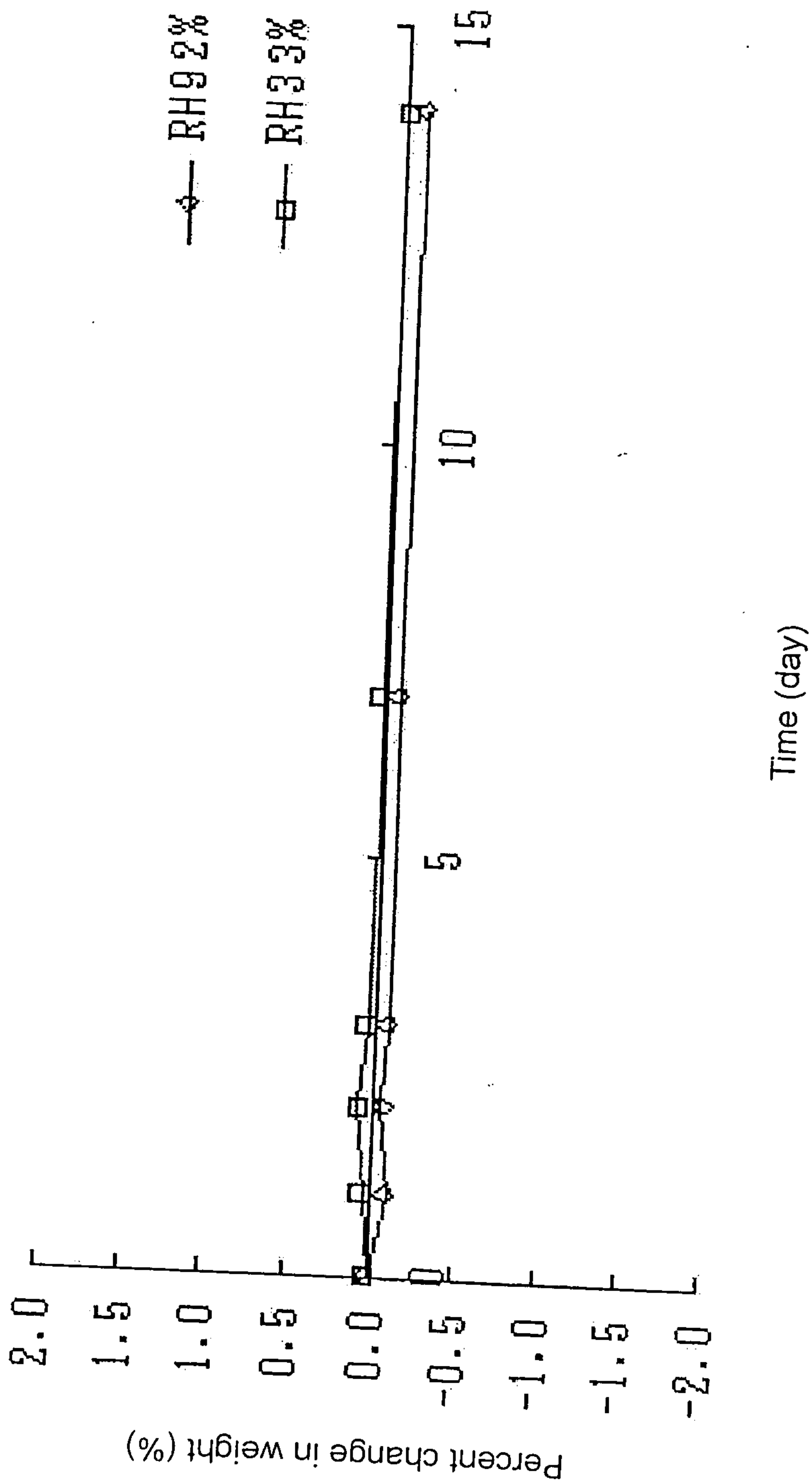

RH92%
RH33%
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Percent change in weight (%)
5
10
15
Time (day)

Fig. 7

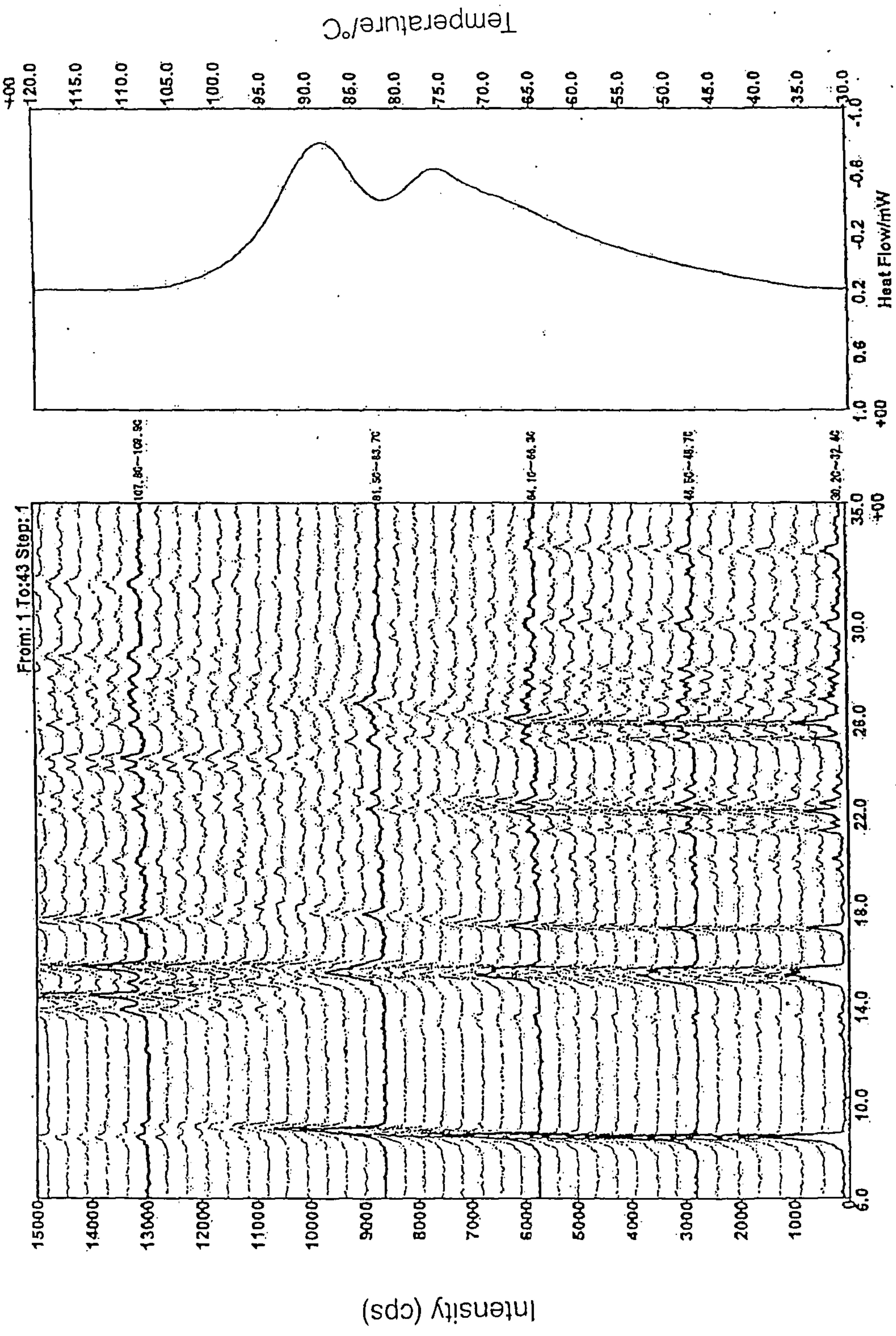
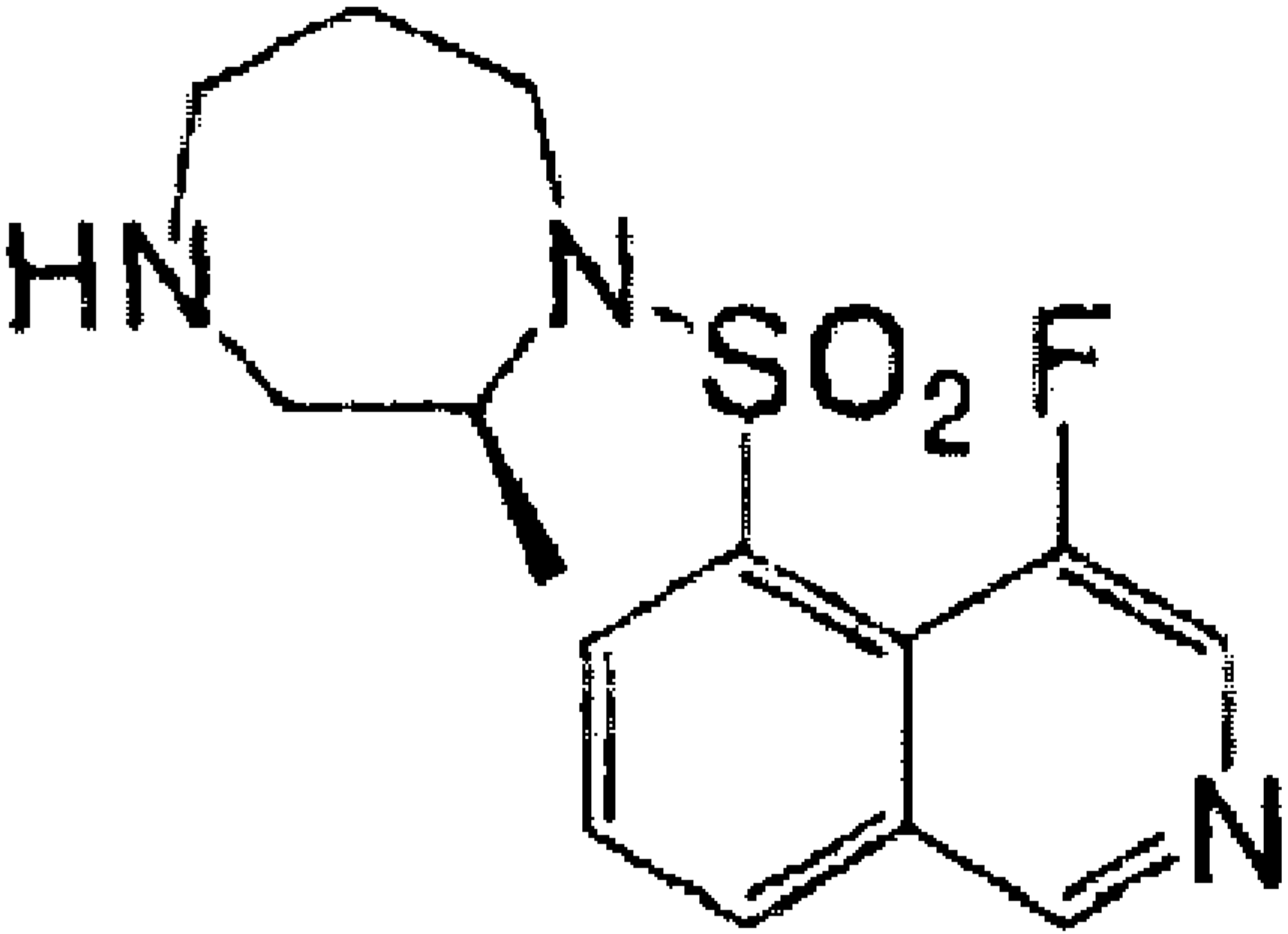

Temperature/°C
Heat Flow/mW
From: 1 To:43 Step: 1
2Theta (deg)
Intensity (cps)

Fig. 8



$\cdot HCl \cdot 2H_2O$ (2)