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Published
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(54) Title: CRYSTALLINE TIAGABINE HYDROCHLORIDE MONOHYDRATE, ITS PREPARATION AND USE

(57) Abstract

The invention provides crystalline R-isomer of N-(4,4-di(3-methylthien-2-yl)but-3-enyl-nipecotic acid hydrochloride with the generic name Tiagabine hydrochloride, process for its preparation, compositions containing the same and its therapeutic use as anti-epileptic agent.

LEDIGLICH ZUR INFORMATION

Code, die zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

AT	Österreich	**FI**	Finnland	**MN**	Mongolei
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Crystalline Tiagabine hydrochloride monohydrate, its preparation and use

This invention relates to crystalline Tiagabine and in particular to its monohydrate, its preparation and its use as a therapeutic agent.

Danish Patent no. 156398 discloses a class of novel compounds that exhibit gamma-aminobutyric acid-uptake (GABA-uptake) inhibitory properties and therefore said compounds are valuable for therapeutic use in the treatment of epilepsy and other CNS related diseases.

In Example 2 of Danish Patent 156398 the preparation of N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid hydrochloride is described.

In C. Braestrup et. al., Int. Congr. Ser.-Exerpta Med., 1987, 750 (Pharmacology), 125-8(Ref. 1)), various stereo-isomers of said compound are mentioned.

In Ref. (1) it is described that N- (4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid hydrochloride is available in its R,S-, S- and R-form and that the R-isomer is the preferred form due to better inhibitory effect of ^{3}H-GABA-uptake into rat forebrain synaptosomes.

In the present invention the R-isomer of N-(4,4-di(3-methylthien-2-yl)but-3-enyl-nipecotic acid is referred to by its generic name of Tiagabine (proposed INN).

In Danish Patent 156398 the preferred salts of N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid are described.

In example 2 of the same patent the most preferred salt of N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid is indicated to be the hydrochloride.

Further, it is described that the final crystallization of the hydrochloride salt takes place with ethyl acetate as the crystallizing solvent.

The method of preparation as described in the Danish Patent 156398 is applicable also for the crystallization of the preferred stereochemical form of the compound, the R-isomer. This method of preparation is rather labourous because purification by column chromatography has been be applied before a crystalline compound could be obtained. This kind of purification is rather expensive and unwanted in a commercial production process.

Furthermore analysis has shown that products manufactured by this process contain unwanted amounts of the crystallizing solvent, ethyl acetate.

Use of alternative organic solvents such as acetonitrile, butyl acetate, toluene, acetone, dichloromethane etc. also gives products containing various amounts of the used crystallizing solvent.

These solvents are unwanted because they are either toxic to humans or may give rise to interaction-reactions with other ingredients in the pharmaceuical preparation, resulting in low stability of the dosage form.

Further it has been found that the compound is heavily

soluble in the applied organic solvents, which is very inconvenient when working on larger scale.

It has now been discovered that these disadvantages can be avoided by a new process giving crystals in a manner which is reproducible in a production scale.

The present invention provides R(-)N-4,4-di(3-methyl-thien-2-yl)-but-3-enyl nipecotic acid hydrochloride monohydrate crystals as a novel material, in particular in pharmaceutically acceptable form.

It has now been found that water can be used as a crystallizing solvent for this compound giving very reproducible results of a monohydrate crystal form. These products are stable under normal storage conditions and is very applicable for the pharmaceutical formulations as the only residural solvent in the product is water.

Tiagabine hydrochloride as monohydrate crystals is stable and non- hygroscopic. It is characterized by an X-ray powder diffractogram as shown in fig. 1. A typical ^{1}H-NMR spectrum is shown in fig. 2 and a typical IR-spectrum of the crystals in KBr is shown in fig. 3. The DSC profile of the monohydrate is shown in fig. 4.

Under dissication conditions the bound water may partly be removed, but on exposure to normal humidity the crystals very rapidly will take up water to reform the monohydrate.

The present invention also provides a process for producing crystalline Tiagabine hydrochloride monohydrate, which comprises crystallizing Tiagabine hydrochloride monohydrate from an aqueous solution containing from one to several equivalents of hydrogenchloride. The so-

lution may be obtained either by dissolving the compound as the amphoteric salt or by dissolving the hydrochloride of the compound. Hydrochloric acid can be added either as a diluted or as a concentrated solution in the range of 1-10 equivalents to the aqueous solution of Tiagabine.

The aqueous solution of Tiagabine is usually made at temperatures ranging from 40^{o}-75^{o}C. Higher temperatures may be used, but is not necessary as yields are very high using the above mentioned range. The solution may be seeded in order to start the crystallization, but this can also be omitted.

The aqueous solution of Tiagabine can further be obtained by acid catalyzed hydrolysis of R(-)-ethyl-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotate in aqueous solution. The acid catalyzed hydrolysis can be carried out by using e.g. phosphoric acid, sulfuric acid, hydrobromic acid, hydrochloric acid or hydroiodic acid, preferably hydrochloric acid.

The crystals can be isolated from the solution by normally used procedures, such as filtration, centrifugation etc. The crystals can be rinsed by pure water or a diluted hydrochloric acid solution before drying. Drying can be performed either under vacuum or at normal pressure.

The present invention also provides a pharmaceutical composition comprising crystalline Tiagabine monohydrate which comprises crystalline tiagabine monohydrate and a pharmaceutically acceptable carrier.

The compositions of this invention are usually adapted for oral administration, but formulations for dissolution for parenteral administration are also within the

scope of this invention.

The composition is usually presented as a unit dose composition containing from 1 to 200 mg, more usually from 2 to 100 mg, for example 2 to 50 mg such as 2, 4, 8, 10, 20, 25 or 30 mg. Such composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 4 to 400 mg.

Preferred unit dosage forms include tablets or capsules.

The composition of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or a preservative. These agents may be utilized in conventional manner, for example in a manner similar to that already used for clinically used epileptic agents.

The invention also provides a method of treatment of epilepsy in mammals including humans which method comprises administering an effective amount of pharmaceutically acceptable crystalline Tiagabine monohydrate.

The invention further provides pharmaceutically acceptable crystalline Tiagabine hydrochloride monohydrate for use in the treatment of epilepsy.

The following examples illustrate the invention:

EXAMPLE 1

A. Crude R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride

1.200 g of R(-)-Ethyl-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotate was dissolved in 12 l of 90% ethanol. 360 ml of 36% aqueous solution of sodium hydroxide was added at room temperature. 10 l of water was added slowly under good stirring. When all starting materials had been hydrolized, pH was adjusted to 4.5 with dilute hydrochloric acid. The ethanol was stripped off. The product precipitated as an oil in the water. The oil was taken up in dichloromethane and the water phase was discarded. The organic phase was dried and 0.9 equivalent of dry HCl was added to the solution at 15°C. After stirring overnight the product was recovered by filtration and dried in vacuo at 40°C. Yield: 1170 g of crude crystalline material.

B. Crystallization of R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride monohydrate

1.050 g of crude product was dissolved in 6000 ml of water at 60°C. The solution was filtered to remove any undissolved matter. 1400 g of 1N aqueous hydrochloric acid was added at 60°C. At 45°C the solution was seeded. After 2 h the temperature was lowered to 10°C. The crystalline product was recovered by filtration and dried in vacuo at 40°C. Yield: 960 g.

DSC onsett: 82.6°C.
^{1}H-NMR: comply

HPLC purity: 99.4
X-Ray: comply
H_2O: 4.6%

EXAMPLE 2

R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride monohydrate

220 g of crude R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride was dissolved at 50°C in 1100 ml of water. At 40°C the solution was seeded and crystallisation started giving a suspension of fine crystals. The suspension was cooled to 0°C before filtration. The filtercake was washed with cold water before drying in vacuo at 60°C.
Yield: 193 g.

HPLC purity: 99.3%

EXAMPLE 3

R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride monohydrate

Dissolve 174 g of crude product in 5200 ml of water at 40-50°C. Add 145 ml of conc. hydrochloride acid (37%) to the solution under good stirring. At 40°C 0.5 g of seed crystals are added. The mixture is stirred for 4 h at 40°C before cooling to 20°C. The solid is filtered and vacuum dried at 40°C overnight.
Yield: 140 g.

HPLC purity: 99.7%

The reproducibility is further illustrated by the following results (Table 1) where batches (A-G) are crystallized using different concentrations of the compound and of HCl:

TABLE 1

REPRODUCIBILITY OF CRYSTALLISATION FROM WATER OF

[R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride, monohydrate]

Batch	RECRYSTALLIZATION CONDITIONS				DRYING CONDITIONS		YIELD				
	eqv.HCL added	Dissolv. °C	Conc. g/l	Filter °C	Temp. °C	Time h	%	H_2O %	DSC Onset/max	Purity HPLC %	X-Ray
A	0	60	200	5	45	16	70	4.9	81.6/84.6	99.6	comply
B	0.5	60	130	5	45	16	86	4.9	81.6/83.6	99.5	comply
C	4.4	40	32	10	45	16	86	4-0	81.8/84.0	99.6	comply
D	0.5	60	100	8	50	16	96		82.2/83.6	99.2	comply
E	0.5	60	100	5	40	64	95	4.9	80.8/85.4	99.5	comply
F	0	60	200	5	40	16	91	4.7	81.1/85.9	98.0	comply
G	0.5	60	100	5	40	16	95	4.8	83.0/84.6	99.3	comply

EXAMPLE 4

R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride monohydrate

26 g of R(-)-ethyl-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotate, hydrochloride is dissolved in 385 ml of water. Under good stirring is added 5 ml of conc. hydrochloric acid and the solution is heated to reflux for 5-10 hours until the reaction is completed. The solution is concentrated by destilling off 30-50% of the solvent. Extract with 40 ml of toluene. To the aqueous layer is added hydrocloric acid and the solution is cooled to 5°C before the product is filtered off and dried in vacuo at 40°C. Yield: 20 g of R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride monohydrate.

HPLC purity: 99.5%
X-Ray: comply
H_2O: 4,6%

CLAIMS

1. Crystalline (R(-)-N-(4,4-di(3-methylthien-2-yl)-but-3-enyl)nipecotic acid, hydrochloride monohydrate (Tiagabine hydrochloride monohydrate).

2. Crystalline Tiagabine hydrochloride monohydrate in substantially pure form.

3. Crystalline Tiagabine hydrochloride monohydrate, having substantially the same X-ray diffractogram as set out in Fig. 1, substantially the same IR spectrum, in a KBr, as set out in Fig. 3, and substantially the same DSC profile as set out in Fig. 4.

4. A process for the preparation of crystalline Tiagabine hydrochloride monohydrate, which process comprises forming an aqueous solution of Tiagabine hydrochloride and crystallizing Tiagabine hydrochloride monohydrate from the solution.

5. A process for the preparation of crystalline Tiagabine hydrochloride monohydrate comprising acid catalyzed hydrolysis of the ethyl ester of Tiagabine hydrochloride in an aqueous solution followed by crystallization of Tiagabine hydrochloride monohydrate from the aqueous solution.

6. A pharmaceutical composition comprising Tiagabine hydrochloride monohydrate together with a pharmaceutically acceptable carrier or diluent.

7. A pharmaceutical composition comprising an effective anti-epileptic amount of crystalline Tiagabine hydrochloride monohydrate together with a pharmaceutically acceptable carrier or diluent.

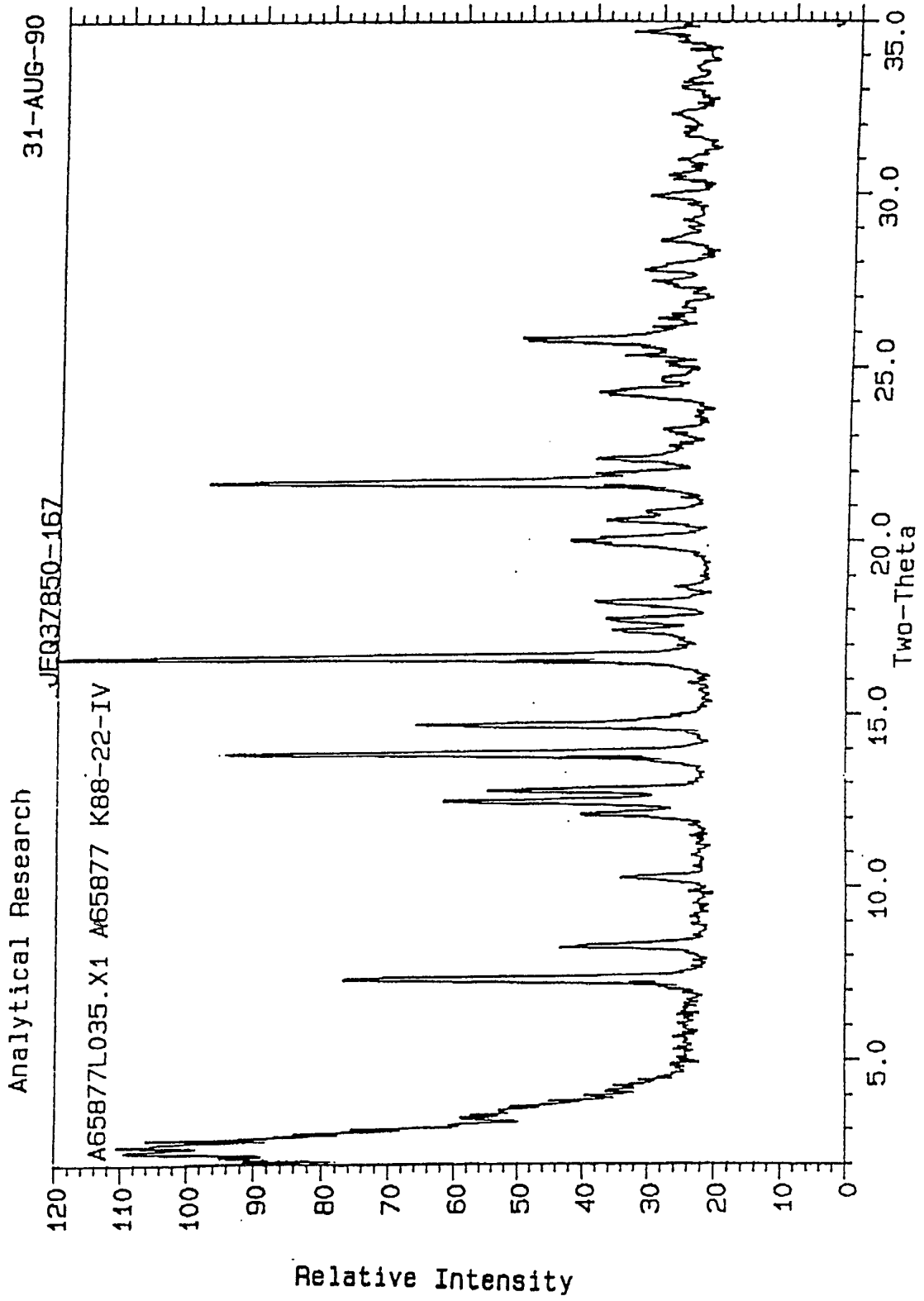
8. The pharmaceutical composition according to claim 6 or 7 in the form of an oral dosage unit containing from 1 to 200 mg of Tiagabine hydrochloride monohydrate.

9. A method of treating epilepsy in mammals comprising administering an effective amount of crystalline Tiagabine hydrochloride monohydrate.

10. A method of treating epilepsy in mammals comprising administering a pharmaceutical composition according to claim 7.

11. The use of Tiagabine hydrochloride monohydrate for the preparation of a medicament useful in treating epilepsy.

1/4 FIGURE 1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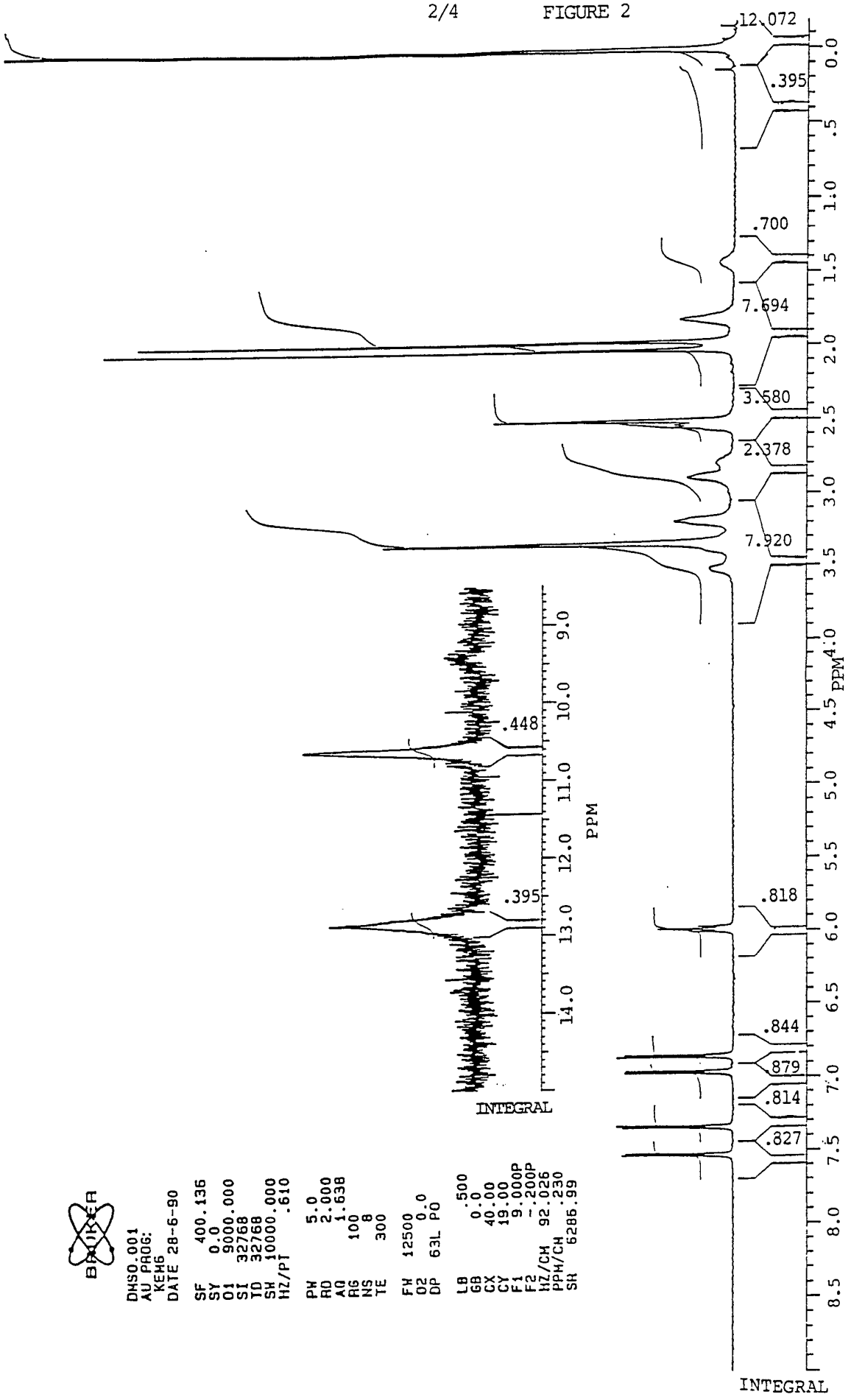
2/4 FIGURE 2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TE 300
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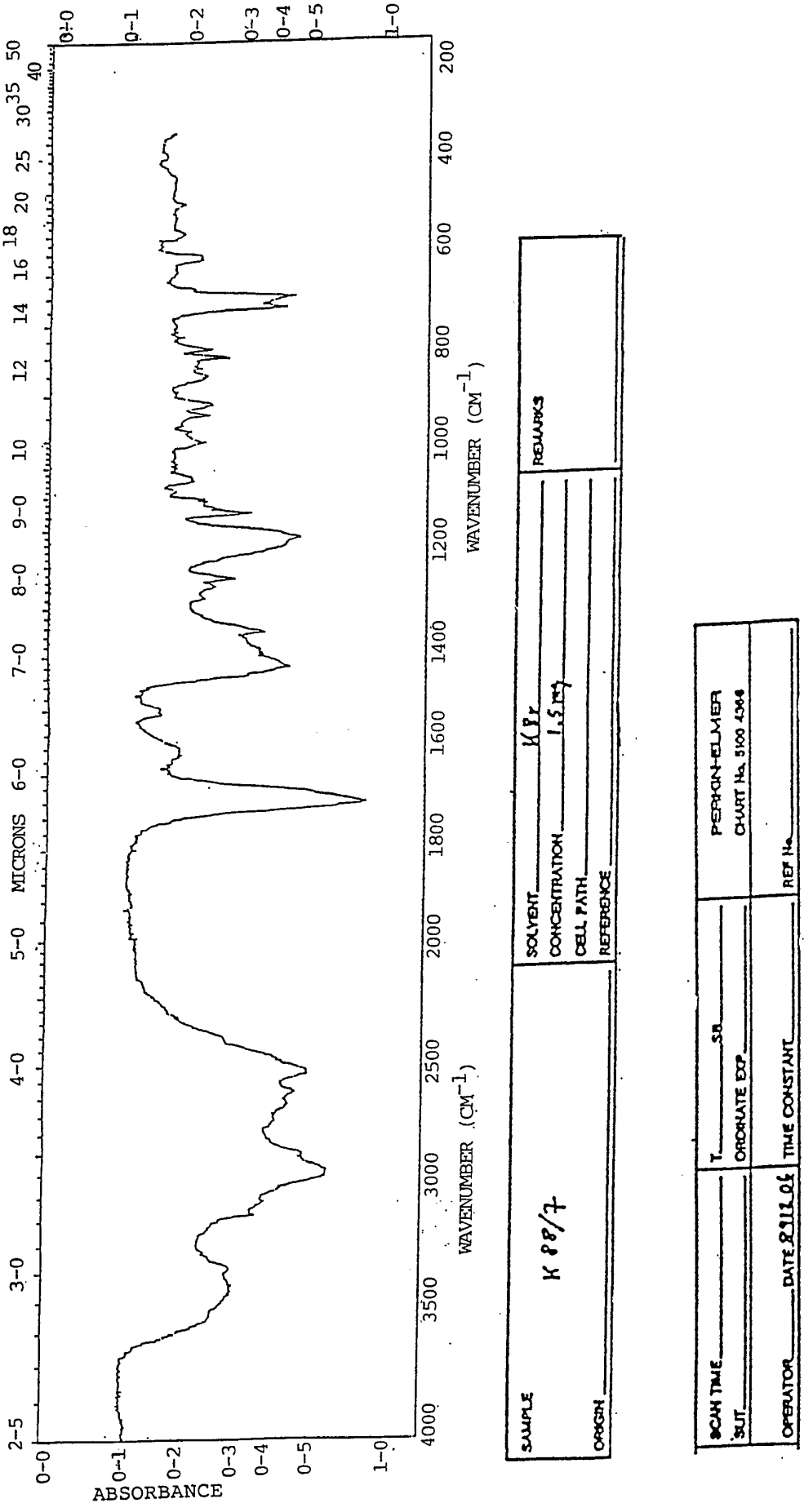
SR 6286.99

FIGURE 3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CONCENTRATION
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CELL PATH
REFERENCE
REMARKS
SCAN TIME
SLIT
OPERATOR
DATE 8.11.91
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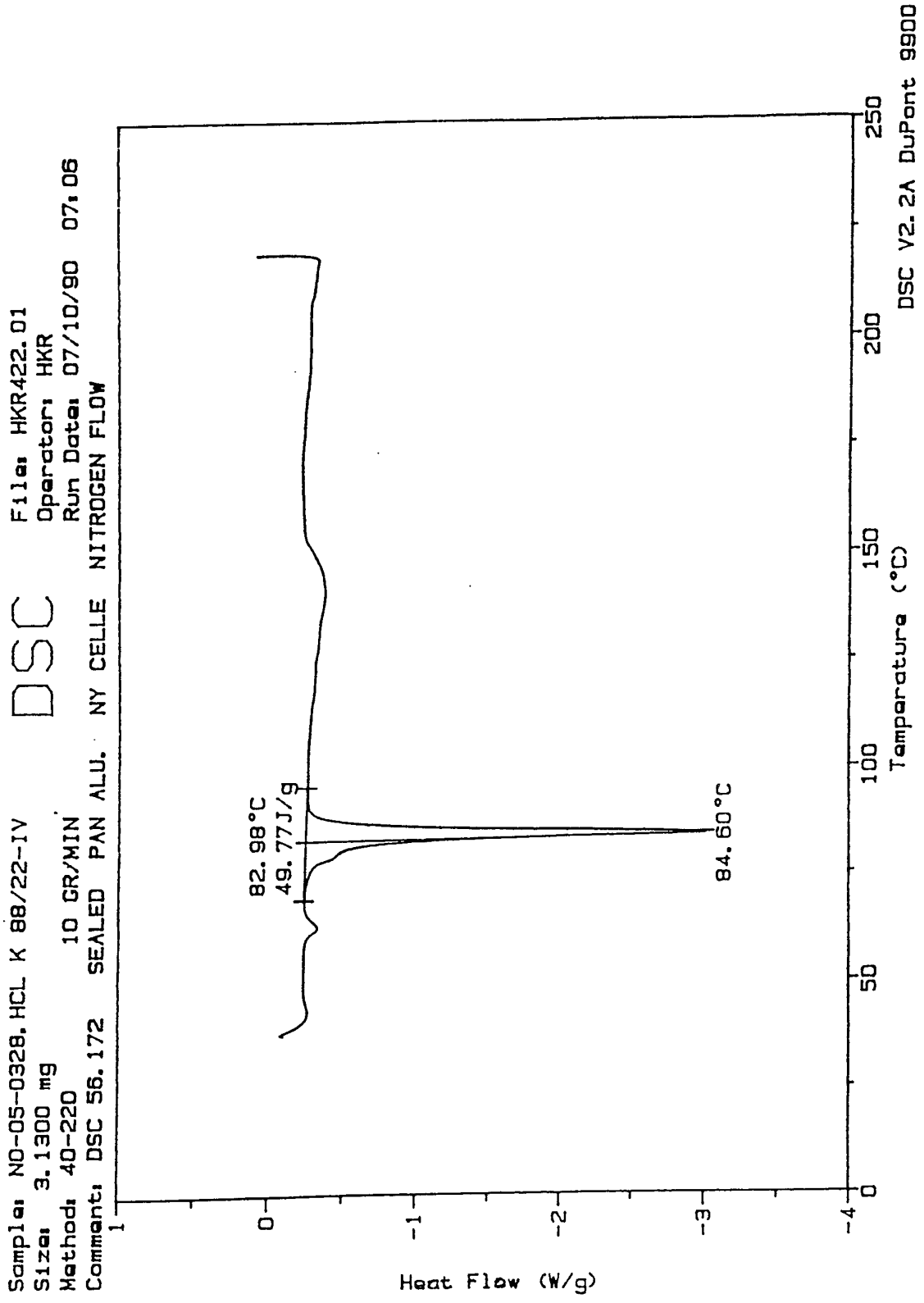
REF No.

4/4 FIGURE 4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49.77J/g
84.60°C
Heat Flow (W/g)
Temperature (°C)
DSC V2.2A DuPont 9900

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 92/00093

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 409/14, A 61 K 31/445

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Neuropharmacology, vol. 27, No. 12, pages 1265-1270, 1988, R.G. Pertwee et al: "Drugs which stimulate or facilitate central GABAergic transmission interact synergistically with delta-9-tetrahydrocannabinol to produce marked catalepsy in mice", see page 1266 --	1-3,6-8
X	Int. Congr. Ser.-Exerpta Med., 1987, 750 (Pharmacology), pages 125-128, see the whole document --	1-3,6-7, 11
A	DK, B, 156398 (NOVO INDUSTRI A/S) 14 August 1989, see especially example 2 --	1-3,6-8, 11
A	Journal of Chromatography, 503 (1990) pages 115-125, Abu M. Rustum et al:"Reversed-phase high-performance liquid chromatographic separation of the enantiomers of N-(4,4-di(3-methylthien-2-yl)-but-3-enyl) nipecotic acid on a Pirkle-type phenylglycine stationary phase", see the whole document --	1-3

* **Special categories of cited documents:**[10]

"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)

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"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

"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.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
14th July 1992	1992 -07- 17
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Göran Karlsson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 9-10 because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claim numbers....., 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. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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 of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] 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 the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 92/00093

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on 29/05/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DK-B- 156398	89-08-14	NONE	