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<p>(21) International Application Number: PCT/IE98/00051</p> <p>(22) International Filing Date: 26 June 1998 (26.06.98)</p> <p>(30) Priority Data: 970519 15 July 1997 (15.07.97) IE</p> <p>(71) Applicant (for all designated States except US): RUSSINSKY LIMITED [IE/IE]; 90 South Mall, Cork (IE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): NIKOLOPOULOS, Angelo [DE/IE]; 9 Avondale, Model Farm Road, Cork (IE). SCHICKANEDER, Helmut [DE/IE]; 10 South Channel Court, South Terrace, Cork (IE).</p> <p>(74) Agents: O'BRIEN, John, A. et al.; John A. O'Brien & Associates, Duncairn House, 3rd floor, 14 Carysfort Avenue, Blackrock, County Dublin (IE).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DE (Utility model), DK, DK (Utility model), EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, 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, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: TRAMADOL, SALTS THEREOF AND PROCESS FOR THEIR PREPARATION</p>		
<p>(57) Abstract</p>		
<p>Cis-Tramadol hydrochloride is prepared by forming a Mannich hydrochloride, liberating the Mannich base, reacting the Mannich base with a Grignard reagent to form a base hydrate of cis-Tramadol which is used to form pure cis-Tramadol hydrochloride. Also claimed is the base hydrate of cis-Tramadol per se and its use as a medicament.</p>		

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TRAMADOL, SALTS THEREOF AND PROCESS FOR THEIR PREPARATION

Introduction

5 The invention relates to a new, stable and pure Tramadol derivative, a specific process for preparing it and its use. The invention also relates to a process for producing Tramadol and salts thereof, especially Tramadol hydrochloride using the derivative.

10 Tramadol is the compound $\text{cis}(+/-)\text{-}2\text{-}[(\text{dimethylamino})\text{-methyl}]\text{-}1\text{-}(3\text{-methoxyphenyl})$ cyclohexanol which, in the form of the hydrochloride salt is widely used as an analgesic.

15 Tramadol hydrochloride assumes a special position among centrally acting analgesics since this active ingredient acts as a strong inhibitor of pain without the side effects which are known for opioids (T. Pharmacol. Exptl. Ther. 267,331 (1993)).

20 The compound per se is described in US 3,652,589 and UK 997,399. Tramadol is obtained in the *cis*-racemate form as the major synthetic product. In known processes, the *trans*-racemate is present as a minor component of the reaction mixture. US 3,652,589 describes an isolation process for the pure *cis*-racemate-isomer in which a complex Grignard reaction mixture is distilled and the crude mixture of the isomers is precipitated and filtered. However, there is still a
25 relatively high level of the *trans*-racemate-isomer present in the final product.

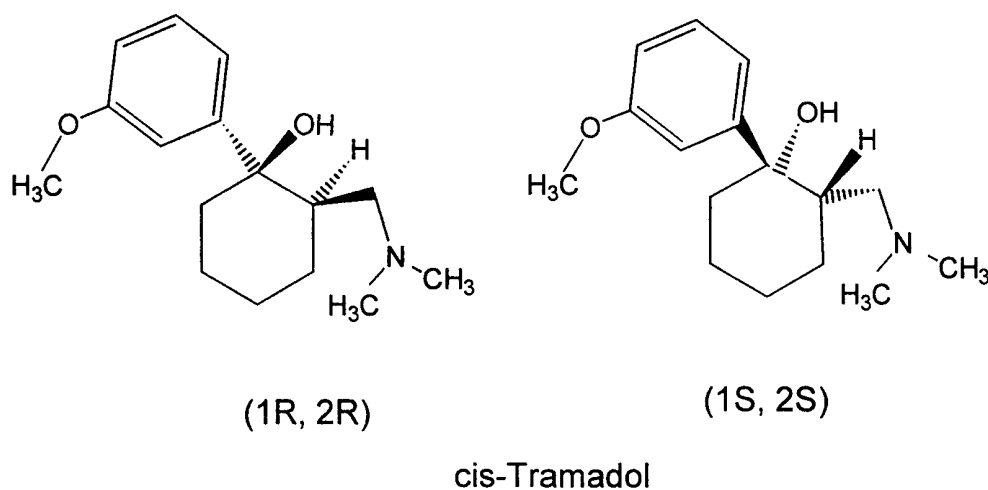
30 US 5,414,129 describes a process for the purification and separation of $\text{cis}(+/-)\text{-}2\text{-}[(\text{dimethylamino})\text{ methyl}]\text{-}1\text{-}(3\text{-methoxyphenyl})$ cyclohexanol-hydrochloride from a reaction mixture containing the *cis*-racemate-isomer, the *trans*-racemate-isomer and Grignard reaction side products. In that process, the reaction mixture is combined with a solution of hydrochloric acid in a $\text{C}_2\text{-C}_3$ alcohol or with gaseous

hydrogen chloride in the presence of specific solvents. The process is said to effect the selective precipitation of cis(+/-)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol-hydrochloride. A specific example using isopropanol is given and the process is also said to have been successful using one of the following solvents as an alternative: butyl acetate, MIBK, 1-butanol, 1-pentanol, 5 PAA (primary amyl alcohol mixture), 1-hexanol, cyclohexanol, 1-octanol, 2-ethylhexanol, anisole.

However, the yield of the cis(+/-)-isomer is still relatively low and the content of the trans(+/-)-isomer is relatively high in most cases. 10

There is therefore a need for an improved process for preparing the pure cis form of Tramadol without several further purification steps.

15 Tramadol can exist in either its cis or trans isomer forms. In this specification cis-Tramadol means the racemic mixture of cis-Tramadol as shown by the following chemical structures:



Statements of Invention

According to the invention, there is provided the base hydrate of cis-Tramadol as herein defined.

5

The invention also provides the use of the base hydrate of cis-Tramadol as an intermediate in a process for preparing Tramadol Hydrochloride.

The invention further provides the use of the base hydrate of cis-Tramadol as a
10 medicament.

In addition, the invention provides a pharmaceutical composition including the base hydrate of cis-Tramadol. The composition may be in a form for oral, buccal, topical and parenteral or of rectal administration, especially parenteral
15 administration.

In another aspect, the invention provides a process for preparing pure cis-Tramadol hydrochloride comprising the steps of:-

20 reacting a Mannich base with a Grignard reagent to form a base hydrate of cis-Tramadol; and

forming cis-Tramadol hydrochloride from the base hydrate of cis-Tramadol.

25

In a preferred embodiment of the invention the Mannich base is formed by forming a Mannich hydrochloride and liberating the Mannich base.

30 Preferably, the Mannich hydrochloride is formed by reaction of cyclohexanone with paraformaldehyde and diethylamine hydrochloride to form

dimethylaminomethyl-cyclohexanone hydrochloride. In one embodiment of the invention, the Mannich base is liberated by treating the Mannich hydrochloride with a base such as sodium hydroxide in a solvent system which may comprise a mixture of toluene, methyl t-butylether and water.

5

In a preferred embodiment of the invention, the cis-Tramadol hydrochloride is formed from the cis-Tramadol base hydrate by acidification with hydrochloric acid.

10 The invention also provides Tramadol and salts thereof whenever prepared by the process of the invention.

We have found that pure cis-2[(dimethylamino)methyl]-1-(3-dimethoxyphenyl) cyclohexanol forms very selectively with equimolar amount of water a
15 monohydrate which solidifies in a crystalline form.

In comparison cis-Tramadol base in anhydrous form at room temperature is an oil. Surprisingly it was found that cis-Tramadol base monohydrate is a stable derivative, which can be crystallised very easily, purified and can be used to
20 produce pure cis-Tramadol hydrochloride.

The base monohydrate of cis-Tramadol can also be formulated in different forms. The invention therefore includes therapeutical drugs, which can be used in human or veterinerian medicines. Such drugs can be formulated with the usual
25 pharmaceuticals ingredients.

The base hydrate of cis-Tramadol can be formulated for oral, buccal, topical, parenteral or rectal use. For example, for the oral application the base monohydrate of cis-Tramadol can be formulated as tablets, in capsules, powder,
30 in solution, as a syrup or in suspension, which can be stabilised and produced with emulsion of oily ingredients.

Detailed Description of the Invention

The invention will be more clearly understood from the following description thereof given by way of example only.

5

In the improved process of the invention, the first step is the reaction of cyclohexanone with paraformaldehyde and dimethylamine hydrochloride to form the Mannich hydrochloride, dimethylaminomethylcyclohexanone hydrochloride, which is recovered from acetone.

10

The Mannich hydrochloride formed in Step 1 is treated with sodium hydroxide in a mixture of toluene, methyl t-butyl ether and water to liberate the Mannich base.

The Mannich base is then reacted with a Grignard reagent to form a crude
15 cis-Tramadol base hydrate.

The cis-Tramadol base hydrate is then purified by recrystallisation from ethyl acetate.

20 Finally, cis-Tramadol hydrochloride is formed from the cis-Tramadol base hydrate by acidification with hydrochloric acid.

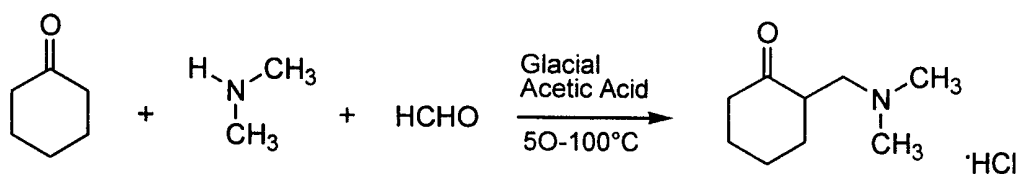
In general, the reaction scheme may be illustrated as follows.

25 In this scheme only the (RR)-enantiomer of the Tramadol Base Hydrate is illustrated. It will be appreciated that both the (RR) and (SS) enantiomers are present in the same way as cis-Tramadol as defined above.

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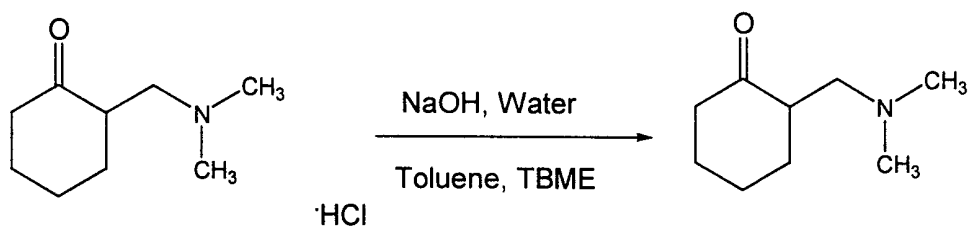
Step 1 Formation of Dimethylaminomethyl Cyclohexanone Hydrochloride



5

Dimethylaminomethyl
Cyclohexanone Hydrochloride

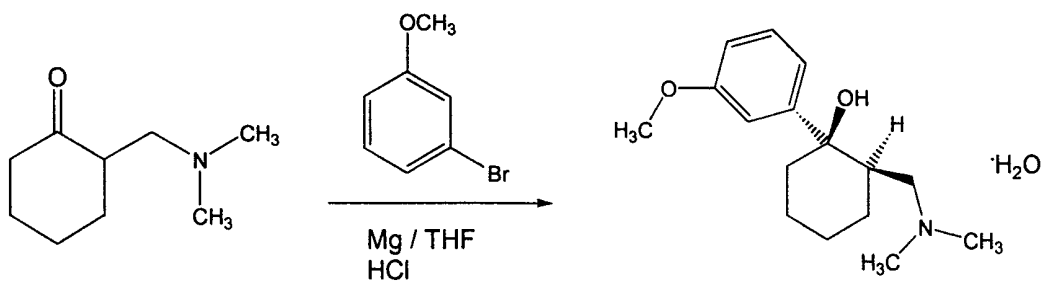
Step 2 Formation of Tramadol Mannich Base



Tramadol Mannich Base

10

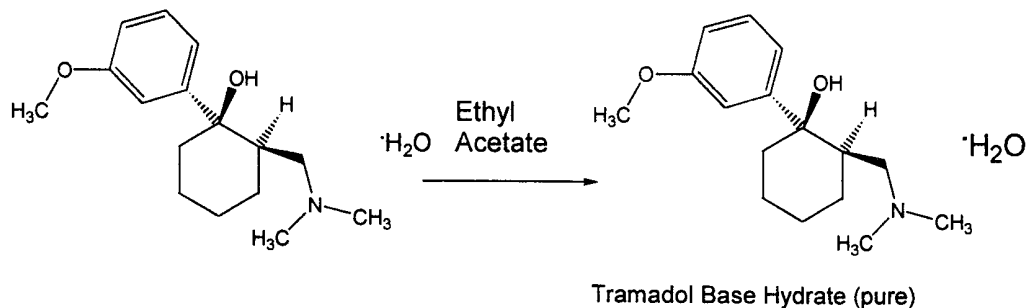
Step 3 Formation of Tramadol Base Hydrate



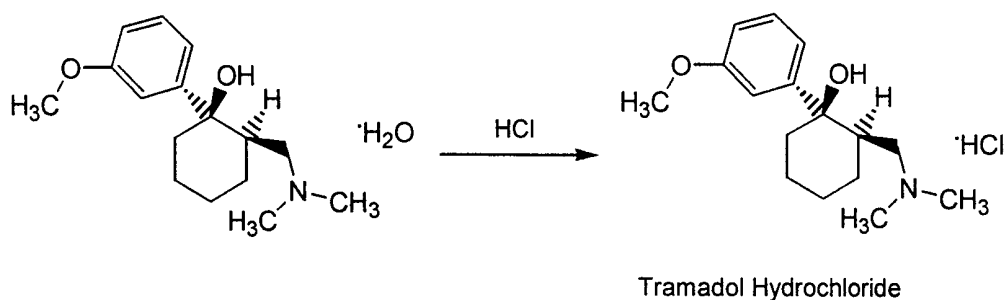
Tramadol Base Hydrate (crude)

15

Step 4 Purification of Tramadol Base Hydrate



Step 5 Formation of Tramadol Hydrochloride

5 Example 1

To produce the Tramadol base hydrate, a reaction vessel is charged successively with 69 Kg of Magnesium, 400 l of dry Tetrahydrofuran (THF) and 15 l of 3-bromoanisole.

10

With careful heating, the reactor temperature is brought up to ca. 30°C. The Grignard initiates at this point and exotherms to approximately 50°C. A further 5 l of bromoanisole are added which maintains reflux. 400 l of THF are then added before the remainder of the bromoanisole. This addition of the remainder of the bromoanisole is carried out slowly so as to sustain a gentle reflux. The reaction is refluxed after complete addition of 3-bromoanisole. The vessel is cooled and Mannich base is added. When addition is complete, the vessel is reheated to reflux for 30 minutes to ensure complete reaction. After cooling to ca. 15 10°C, 2,300 l of water are added to quench the reaction. When complete, part of

the solvents are distilled under vacuum. Approximately 260 l of concentrated HCl is added at a low temperature until a pH of 0 – 1 is reached. This aqueous phase is extracted with toluene. The toluene phases are discarded and ethyl acetate is added to the aqueous phase. 30% Ammonia solution is then charged to reach pH 9 – 10 and the phases are separated. The aqueous phases are extracted again with ethyl acetate and finally all ethyl acetate layers are combined and washed twice with water. Ethyl acetate is then distilled from the reaction solution at atmospheric pressure. Process water is added and the solution cooled to 20°C and seeded. After crystallisation, the vessel is cooled to –5 to 0°C and stirred for one hour.

The product is centrifuged at this temperature and washed with cold ethyl acetate 5 x 50 l. Approximately 310 – 360 Kg of moist cis-Tramadol base hydrate are obtained.

Purification

A reactor vessel is charged successively with cis-Tramadol base hydrate (crude) 200 Kg and ethyl acetate 300 l and the contents of the vessel heated to 50°C until all solids are in solution. The vessel is then cooled to –5 to 0°C and the product crystallises. Stirring is continued for two hours and the product is then centrifuged and washed with cold ethyl acetate, 2 x 25 l. Approximately 165 - 175 Kg (moist) of cis(+/-) Tramadol base hydrate are obtained from this procedure.

The overall process produced high yields of cis-Tramadol with a trans isomer content of less than 0.03%.

Analytical data of the base hydrate of cis-Tramadol

Melting point: 79 - 80°C (in comparison cis-Tramadol base anhydrous is an oil).

Water content (KF) : 6.52% (=monohydrate)

5 IR-spectrum of the base hydrate of cis-Tramadol (see Fig. 1).

IR-spectrum (=cis-Tramadol base anhydrous, see Fig. 2).

The invention provides a unique process in which a base hydrate of cis-Tramadol is selectively crystallised without impurities. The base hydrate is processed to readily form cis-Tramadol hydrochloride. The process is substantially simpler than known processes and does not require the use of potentially toxic solvents. Thus the process is environmentally friendly.

10 The base hydrate of cis-Tramadol prepared may also be used in various formulations.

The base hydrate of cis-Tramadol may be formulated in the form of a solid with a slow release profile. For example, slow release pellets may be prepared by coating a suitable core material with a coating, for example, of ethylcellulose/schellack solution (4:1) and suitable pharmaceutical excipients. The pellets have typical average diameter of 0.6 to 1.6 mm. The pellets may be readily converted into gelatine capsules or pressed into tablet form using well-known techniques.

25 Alternatively the base hydrate of cis-Tramadol may be formulated into effervescent tablets by forming granules of the base hydrate with acidity/taste modifiers and a suitable effervescent base such as sodium hydrogen carbonate/anhydrous sodium carbonate (12:1). The ingredients are typically blended in a mixer/granulator and heated until granulation occurs. The resulting granules may be pressed into tablet form, on cooling.

Of particular interest is the use of the base hydrate of cis-Tramadol in a form for parenteral use/injectables. The base hydrate is typically dissolved in water together with suitable excipients (as necessary). The solution is filtered through a membrane to remove solid fibres or particles. The filtered solution may then be
5 filled into ampoules, typically containing 10.0 mg of the active compound. Usually the formulation is prepared for intramuscular injection.

The invention is not limited to the embodiments hereinbefore described which
10 may be varied in detail.

CLAIMS

1. The base hydrate of cis-Tramadol as herein defined.
- 5 2. Use of the base hydrate of cis-Tramadol as an intermediate in a process for preparing Tramadol hydrochloride.
3. Use of the base hydrate of cis-Tramadol as a medicament.
- 10 4. A pharmaceutical composition including the base hydrate of cis-Tramadol.
5. A composition as claimed in claim 4 in a form for oral, buccal, topical, parenteral or rectal administration.
- 15 6. A composition as claimed in claim 4 or 5 in a form for parenteral administration.
7. A process for preparing pure cis-Tramadol hydrochloride comprising the steps of :-
20
 reacting a Mannich base with a Grignard reagent to form the base hydrate of cis-Tramadol as herein defined;
 and
25
 forming cis-Tramadol hydrochloride from the base hydrate of cis-Tramadol.

8. A process as claimed in claim 7 wherein the Mannich base is formed by:-

forming a Mannich hydrochloride; and

5 liberating the Mannich base.

9. A process as claimed in claim 8 wherein the Mannich hydrochloride is formed by reaction of cyclohexanone with paraformaldehyde and diethylamine hydrochloride to form dimethylaminomethylcyclohexanone hydrochloride.

10

10. A process as claimed in claim 8 or 9 wherein the Mannich base is liberated by treating the Mannich hydrochloride with a base such as sodium hydroxide in a solvent system which may comprise a mixture of toluene, methyl t-butylether and water.

15

11. A process as claimed in any of claims 7 to 10, wherein the Tramadol hydrochloride is formed from the base hydrate of cis-Tramadol by acidification with hydrochloric acid.

20

12. A process substantially as hereinbefore described with reference to the Examples.

13. Tramadol and salts thereof, especially Tramadol hydrochloride whenever prepared by a process a claimed in any of claims 7 to 12.

25

Fig 1

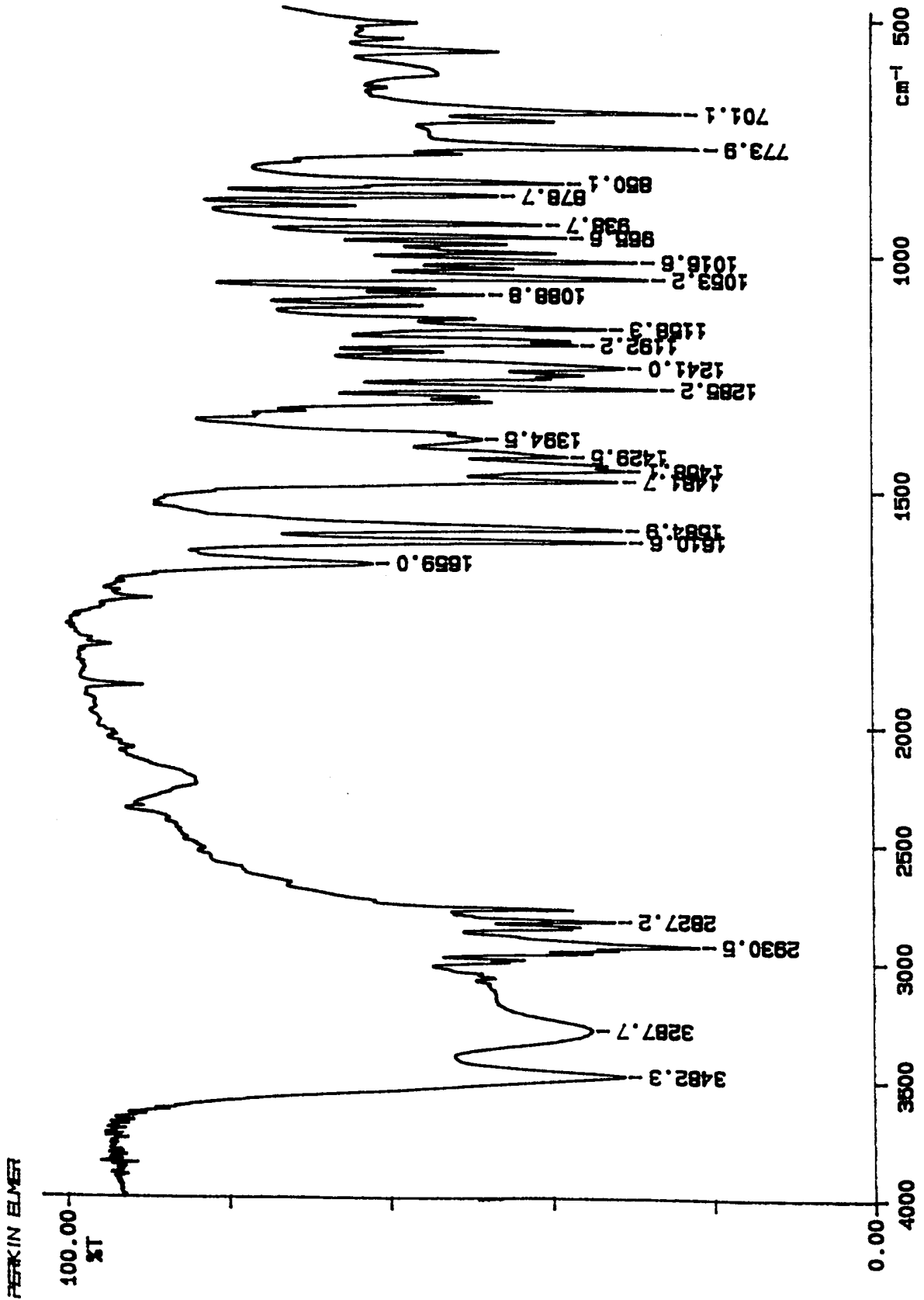
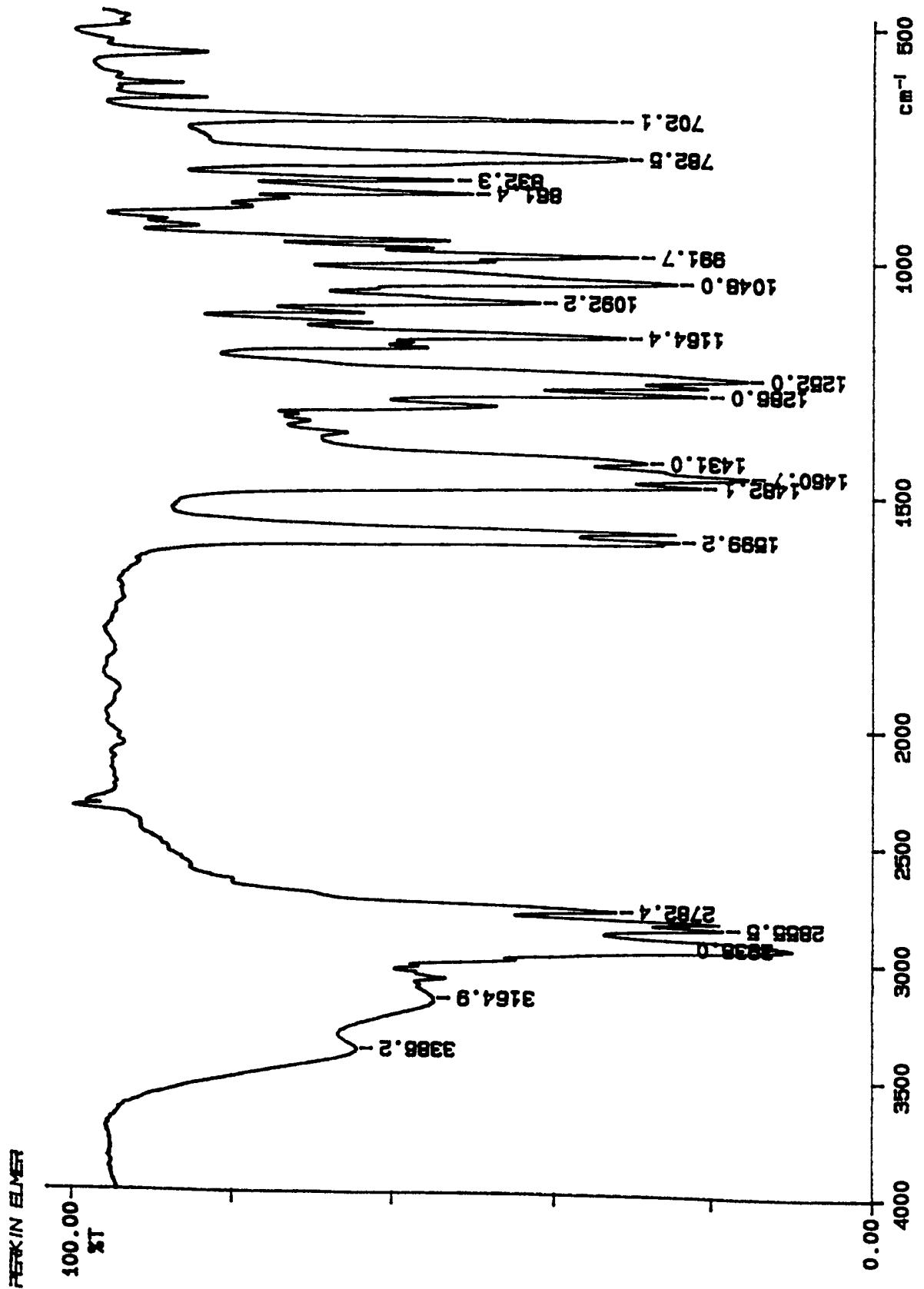


Fig 2



INTERNATIONAL SEARCH REPORT

International Application No

PCT/IE 98/00051

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C213/10 C07C213/00 A61K31/135 C07C217/74

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)

IPC 6 C07C 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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 778 262 A (CHEMAGIS LTD) 11 June 1997 see the whole document ---	1-13
X,P	EP 0 787 715 A (GRUENENTHAL GMBH) 6 August 1997 see page 2, column 2, line 21 - line 27; claims 1-5; examples 1,2 ---	1-6, 11-13
X	US 5 414 129 A (CHERKEZ STEPHEN ET AL) 9 May 1995 cited in the application see the whole document ---	1-6, 13
P,X	EP 0 831 082 A (CHEMAGIS LTD) 25 March 1998 see claim 10 ---	13
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

9 October 1998

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Rufet, J

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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