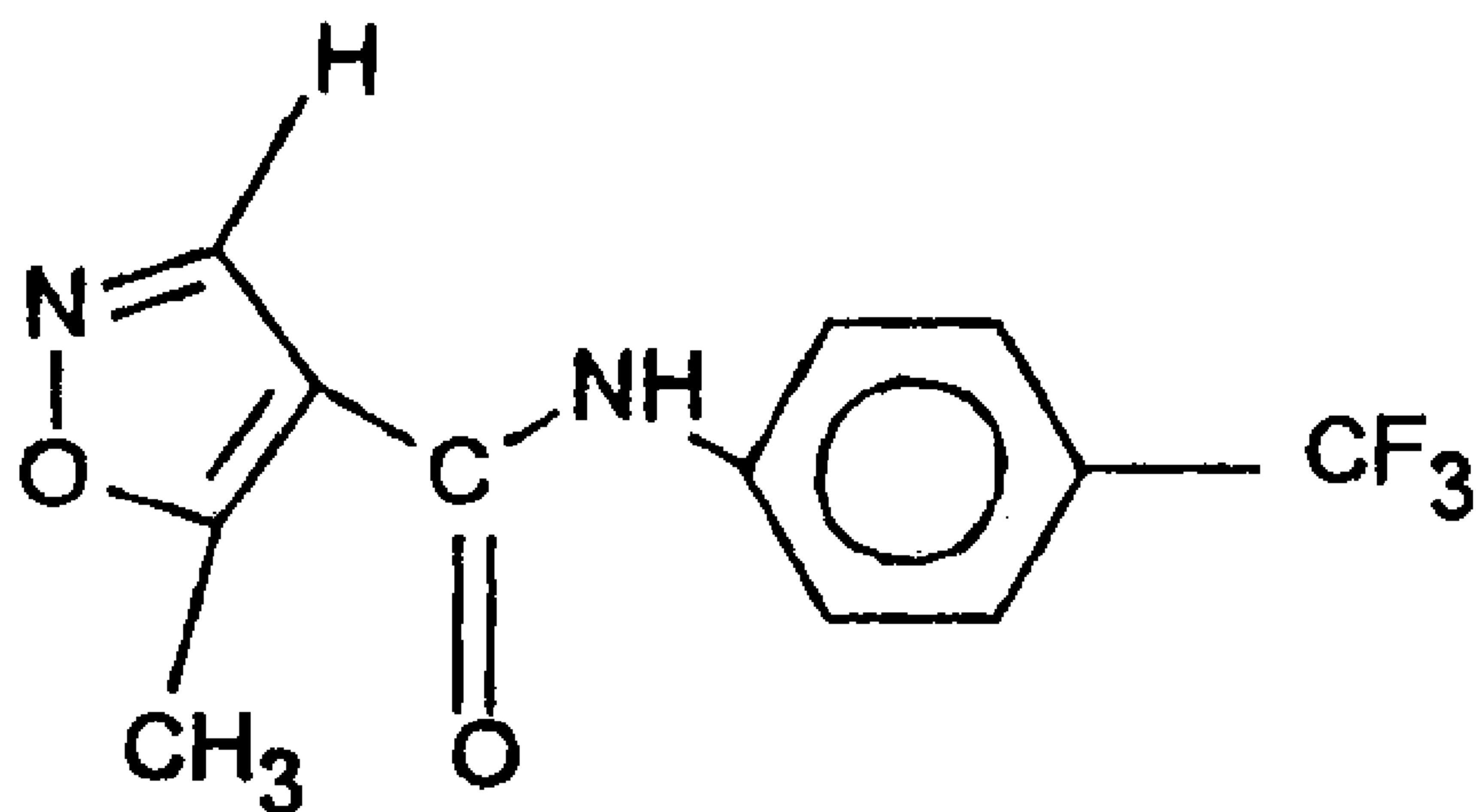




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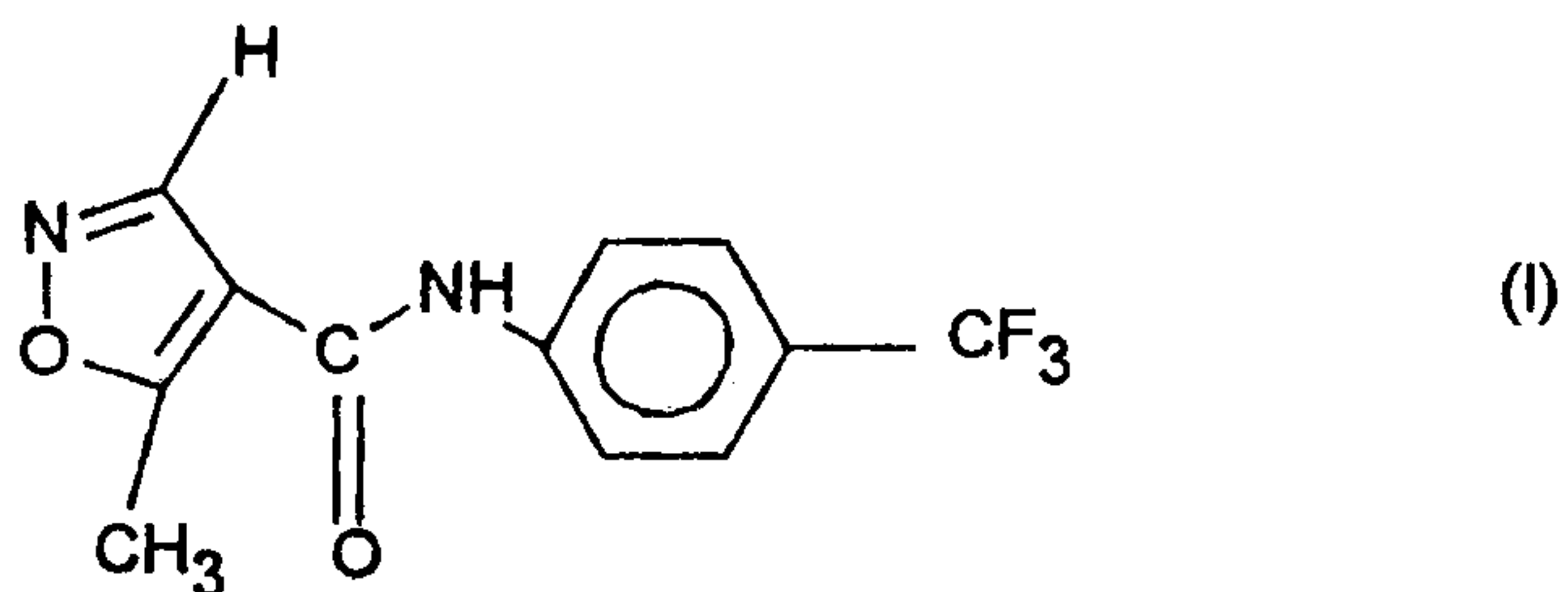
(57) Abrégé/Abstract:

The invention relates to crystal Modification 2 of the compound of the formula I (see formula I) processes for the preparation of crystal Modifications 1 and 2 and the use thereof.

Abstract:

Crystal form of N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide

The invention relates to crystal Modification 2 of the compound of the formula I



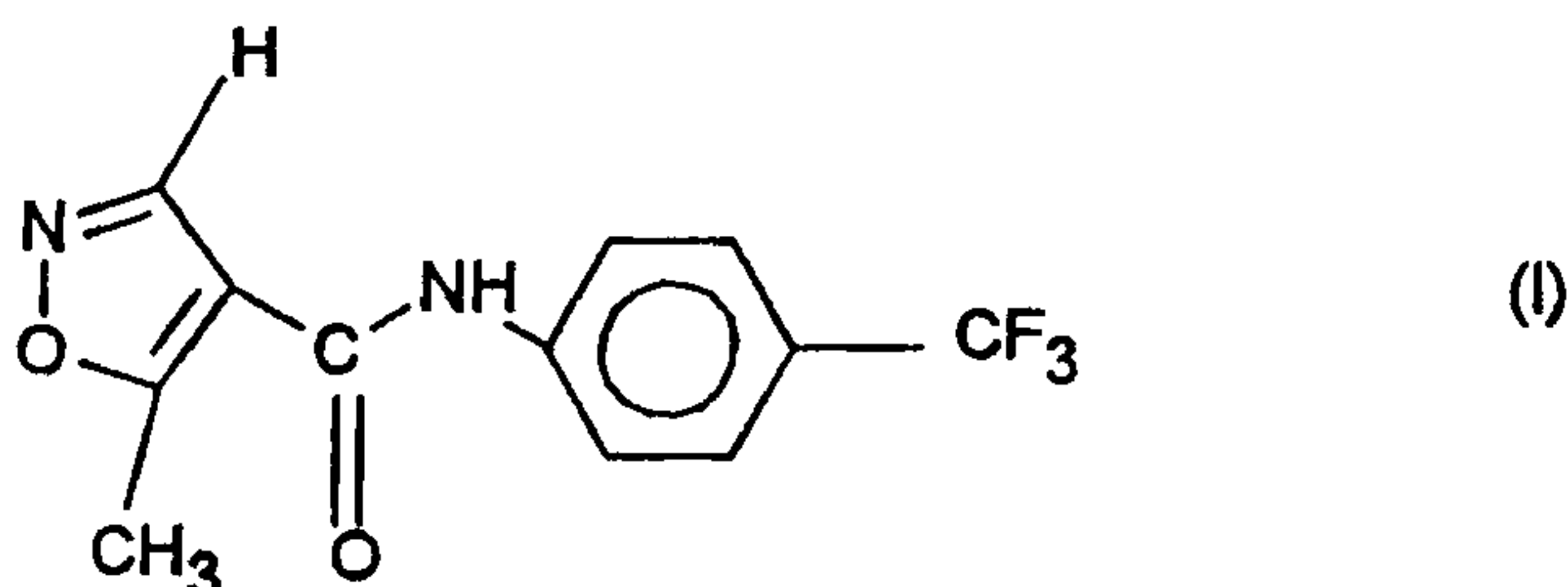
processes for the preparation of crystal Modifications 1 and 2 and the use thereof.

Hoechst Marion Roussel Deutschland GmbH HMR 1997/L 208 Dr. TH/Ba

Description

- 5 Crystal form of N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide

10 The invention relates to a novel read-ily soluble crystal modification (Modification 2) of the compound of the formula I



15 which, in the transmission X-ray diffraction pattern obtained with a focusing Debye-Scherrer beam and Cu-K α 1-radiation, has lines at the following diffraction angles 2 theta ($^{\circ}$):

Lines of strong intensity: 10.65; 14.20; 14.80; 16.10; 21.70; 23.15; 24.40;
24.85; 25.50; 25.85; 26.90; 29.85

20

Lines of medium intensity: 7.40; 9.80; 13.10; 15.45; 16.80; 20.70; 21.45;
22.80; 23.85; 27.25; 28.95

25 The X-ray diffraction pattern of Modification 2 recorded using Cu-K α 1 radiation is shown in Figure 1. The pattern was recorded using the STADI P two-circle diffractometer from Stoe (Darmstadt, Germany) or the computer-assisted single crystal diffractometer R3 m/V from Siemens (radiation used: MoK α).

30 The infrared spectrum of Modification 2 of the compound of the formula I (1 mg in 300 mg of KBr) recorded using an infrared spectrophotometer shows the following main bands (units cm $^{-1}$):

1321	1481	672	3201
1607	3355	763	701
1109	1264	908	948
1065	1384	754	511

2

1536	1361	592	733
1663	852	427	960
1241	1014	3111	1779
1410	3297	3065	1811
1160	877	3221	484
1691	940	974	3442
831	3274	3129	3434
1188	894	628	

The stated wavenumbers are arranged in ascending intensity.

The infrared spectrum of Modification 2 of the compound of the formula I according to Example 1 is furthermore shown in Figure 3, the transmittance in % being stated along the ordinate and the wavenumber in cm^{-1} along the abscissa.

The compound of the formula I crystallizes in Modification 2 in the space group $P2_1/c$ with 8 molecules in the unit cell. Molecules of the compound of the formula I are present as dimers which originate from the individual molecules by formation of a $-\text{C}=\text{O}\dots\text{HN}$ hydrogen bridge bond (2.938 Å), the two molecular levels being virtually perpendicular to one another (91.2°). The two molecules have very different conformations. The angles made by the five- and six-membered rings with the central carbonyl group are 5.4° and 2.1° and 23.4° and 23.1° , respectively. The latter twist creates the steric preconditions permitting the hydrogen bridge bond between the two molecules.

The compound of the formula I is known per se and is also referred to as Leflunomide (HWA 486). It can be obtained in the manner described in US 4,284,786. However, the crystals prepared by recrystallization from, for example, toluene are obtained in crystal Modification 1. The X-ray diffraction pattern ($\text{Cu-K}\alpha_1$ radiation) of Modification 1 is shown in Figure 2 and has characteristic lines at the following diffraction angles 2θ ($^\circ$):

25

Lines of strong intensity: 16.70; 18.90; 23.00; 23.65; 29.05

Lines of medium intensity: 8.35; 12.65; 15.00; 15.30; 18.35; 21.25; 22.15; 24.10; 24.65; 25.45; 26.65; 27.40; 28.00; 28.30

30

The compound of the formula I crystallizes in Modification 1 in the space group $P2_1/c$ with 4 molecules in the unit cell. The molecule is essentially planar. The angle between the planar groups of atoms is less than 2.4° . The molecules are arranged in stacks in the crystal. The molecules lie in stacks adjacent to one another and are arranged in an antiparallel manner. Very weak hydrogen bridge bonds link the dimers in the crystal ($NH \dots N$: 3.1444 Å). The C=O group is not involved in any hydrogen bridge bonding.

The X-ray diffraction patterns furthermore permit the determination of the amount of Modification 2 in a mixture containing both modifications. The line at $2\theta = 8.35^\circ$ of Modification 1 and the line at $2\theta = 16.1^\circ$ of Modification 2 are suitable for the quantitative determination. If the ratio of the peak heights is calculated and is correlated with the content of the modification, a calibration line is obtained. The limit of detection of this method is about 0.3 % of Modification 2 in crystals containing Modification 1.

Modification 2 has better water solubility than Modification 1. At 37°C , 38 mg/l of Modification 2 can be dissolved whereas 25 mg/l of Modification 1 go into solution. Furthermore, Modification 2 is stable in the temperature range from -15°C to $+40^\circ\text{C}$, preferably from 20°C to 40°C , and is not converted into Modification 1.

Modification 2, according to the invention, of the compound of the formula I is obtained, for example, by heating a suspension of crystals of Modification 1 or mixtures of Modification 1 and Modification 2 of the compound of the formula I in a solvent to a temperature of from about 10°C to 40°C , preferably from 15°C to 30°C , in particular from 20°C to 25°C . The preparation rate is essentially dependent on the temperature. Solvents in which the compound of the formula I are poorly soluble are advantageous. For example, it is possible to use water or aqueous solutions containing (C_1 - C_4) alcohols, e.g. methanol, ethanol, propanol, isopropanol, butanol or isobutanol and/or ketones, such as acetone or methyl ethyl ketone. As a rule, the heating is carried out in aqueous suspension, expediently while stirring or shaking. The heat treatment is carried out until Modification 1 has been completely converted into Modification 2.

The complete conversion of Modification 1 to Modification 2 is dependent on the temperature and, as a rule, takes from 36 hours to 65 hours, preferably from 48 hours to 60 hours, at a temperature of 20°C. The reaction is monitored by X-ray diffraction or IR spectroscopy by means of samples taken during the treatment.

A further process for the preparation of Modification 2 of the compound of the formula I comprises dissolving Modification 1 or mixtures of Modifications 1 and 2 in a solvent and then cooling the solution abruptly to temperatures of from about -5°C to -25°C. Suitable solvents are, for example, water-miscible solvents such as (C₁-C₄) alcohols, as well as ketones, such as acetone or methyl ethyl ketone, or other solvents, such as ethyl acetate, toluene or dichloromethane. The dissolution process takes place at room temperature of from 20°C to 25°C or at elevated temperatures up to the boiling point of the solvent under atmospheric pressure or under superatmospheric or reduced pressure. The solution obtained is, if required, filtered in order to separate off undissolved components or crystals from Leflunomide. The filtered solution is then cooled so rapidly that only crystals of Modification 2 form. An adequate cooling process comprises, for example, introducing the filtered solution into a vessel which has been cooled to -15°C or spraying filtered solution into a space cooled to -10°C or cooling the solution under vacuum condensation conditions. The preferred process comprises introducing the compound of the formula I into methanol and carrying out the dissolution process at the boiling point of methanol at atmospheric pressure or reduced pressure, then filtering the hot solution and transferring the filtered solution to a vessel which has been cooled to -15°C, the transfer being effected so slowly that the temperature of the crystal suspension obtained does not increase to more than -10°C. The precipitated crystals are then washed several times with methanol and are dried under reduced pressure. The crystallization can be carried out without seeding with crystals of Modification 2 or preferably by seeding with crystals of Modification 2. The seeding is effected in the cooled vessel. The amount of seed material depends on the amount of the solution and can be easily determined by a person skilled in the art. The abovementioned processes are also suitable for converting mixtures containing Modifications 1 and 2 into an essentially pure Modification 2 of the compound of the formula I.

However, the invention also relates to novel processes for the preparation of the compound of the formula I in Modification 1. By means of the novel processes, it is also possible to convert mixtures containing Modifications 1 and 2 specifically into Modification 1. For this purpose, for example, 5 crystals of Modification 2 or mixtures of Modifications 1 and 2 are dissolved in a solvent. Suitable solvents are, for example, water-miscible solvents, such as (C₁-C₄) alcohols, e.g. methanol, ethanol, propanol, isopropanol, butanol or isobutanol, as well as ketones, such as acetone or methyl ethyl ketone. Mixtures of organic solvents with water, for example of 10 about 40 % to 90 % of isopropanol, have also proven useful. The dissolution process is preferably carried out at elevated temperature up to the boiling point of the respective solvent. The hot solution is kept at the boiling point for some time in order to ensure complete dissolution of the compound of the formula I. The filtered solution is then cooled so slowly 15 that only crystals of Modification 1 form. Cooling is preferably effected to final temperatures of 20°C to -10°C, in particular to temperatures of 10°C to -5°C, very particularly preferably to temperatures of from 10°C to 5°C. The crystals are separated off and washed with isopropanol and then with water. The substance is dried at elevated temperature, preferably at 60 °C 20 under reduced pressure or at atmospheric pressure.

A preferred process comprises dissolving the compound I in an 80 % strength isopropanol at the boiling point of isopropanol and at atmospheric pressure or under reduced pressure and then cooling the hot solution so 25 slowly that the crystallization takes place at temperatures of more than 40°C, preferably from 40°C to 85°C, particularly preferably from 45°C to 80°C, in particular from 50°C to 70°C. The precipitated crystals are then washed several times with isopropanol and are dried under reduced pressure. The crystallization can be carried out without seeding with 30 crystals of Modification 1 or preferably in the presence of crystals of Modification 1, which are introduced by seeding into the solution containing the compound of the formula I. Seeding may possibly be carried out several times at different temperatures. The amount of the seed material depends on the amount of the solution and can be readily 35 determined by a person skilled in the art.

A particularly preferred process for the preparation of the compound of the formula I in Modification 1 comprises

- 5 a) transferring the compound of the formula I which is not present in Modification 1 or mixtures of Modification 1 and other crystal forms of the compound of the formula I into an organic solvent or into mixtures of organic solvents and water,
- b) heating the mixture obtained to a temperature of from 41°C to the boiling point of the organic solvent,
- 10 c) diluting the resulting solution with water or distilling off the organic solvent so that the organic solvent and the water are present in a ratio of from 4:1 to 0.3:1 and
- d) carrying out the crystallization at temperatures above 40°C.

The solution obtained is preferably filtered after process step b).

15 By means of the particularly preferred process, it is also possible to convert mixtures containing Modifications 1 and 2 specifically into Modification 1. For this purpose, crystals of Modification 2 or mixtures of Modifications 1 and 2 are dissolved in a mixture containing organic solvents and water. Suitable solvents are, for example, water-miscible
20 solvents, such as (C₁-C₄) alcohols, e.g. methanol, ethanol, propanol, isopropanol, butanol or isobutanol, as well as ketones, such as acetone or methyl ethyl ketone.

Advantageous mixtures contain organic solvent and water in a ratio of from
25 1:1 to 8:1, preferably from 2:1 to 6:1, in particular from 3:1 to 5:1.

The preparation of the solution is preferably carried out at elevated temperature, in particular at temperatures of from 41°C to the boiling point
of the respective solvent, preferably from 40°C to 85°C. The heated solution, is for example, kept for
30 some time at the boiling point in order to ensure complete dissolution of the compound of the formula I. The dissolution process can also be carried out at superatmospheric pressure. The solution is then filtered. The filter used has a pore diameter of from about 0.1 μm to 200 μm. Water which advantageously has the same temperature as the filtered solution is then
35 added to the filtered solution, or the organic solvent is distilled off. The solutions obtained advantageously contain the organic solvent and water in a ratio of from 4:1 to 0.3:1, preferably from 2:1 to 0.6:1, particularly preferably from 1.6:1 to 0.8:1. Cooling is then carried out slowly to a

minimum temperature of 40°C. The crystals are separated off and are washed with isopropanol and then with water. The substance is advantageously dried at elevated temperature, preferably at 60°C, under reduced pressure or at atmospheric pressure.

5

A particularly preferred process comprises dissolving the compound of the formula I in a mixture of isopropanol and water in a ratio of from 4:1 to 5:1 and at the boiling point of isopropanol at atmospheric pressure or reduced pressure and filtering the solution. Thereafter, water at the same
10 temperature is added to the hot solution in an amount such that a ratio of isopropanol to water of from 2:1 to 0.8:1 is present. The crystallization is then carried out at temperatures of more than 40°C, preferably from 40°C to 85°C, particularly preferably from 45°C to 80°C, in particular from 50°C to 70°C, more preferably from 41°C to 80°C. The precipitated crystals are then washed several times with
15 isopropanol and are dried under reduced pressure.

A further process for the preparation of Modification 1 from Modification 2 or from a mixture containing Modifications 1 and 2 comprises heating the crystals to a temperature of from above 40°C to 130°C, preferably from
20 50°C to 110°C, in particular from 70°C to 105°C, very particularly preferably 100°C. The conversion of Modification 2 into 1 is dependent on the temperature and, for example at 100°C, takes from 2 to 5 hours, preferably from 2 to 3 hours.

25 A further process for the preparation of Modification 1 comprises preparing a suspension containing crystals of Modification 2 or a mixture of crystals containing Modifications 1 and 2 and a solvent.

Modification 1 of the compound of the formula I is obtained by heating the suspension of the crystals in a solvent to a temperature of more than 40°C,
30 preferably from 41°C to 100°C, in particular from 50°C to 70°C. The preparation is essentially dependent on the temperature. Advantageous solvents are those in which the compound of the formula I has poor solubility. For example, it is possible to use water or aqueous solutions containing (C₁-C₄)alcohols and/or containing ketones, such as methyl ethyl
35 ketone or acetone. As a rule, the heating is effected in an aqueous suspension, expediently while stirring or shaking. The heat treatment is carried out until Modification 2 has been completely converted into Modification 1.

7a

A further process for the preparation of crystal modification 1 of the compound of the formula 1 comprises heating the compound of the formula 1, which is not present as crystal modification 1 or is not present as mixtures of crystal modifications 1 and 2, in solid form to a temperature of from 50°C to 130°C.

5

A further process for the preparation of crystal modification 1 of the compound of the formula 1 comprises heating in suspension, suitably aqueous suspension, the compound of the formula 1, which is not present as crystal modification 1 or is not present as mixtures of crystal modifications 1 and 2, to
10 a temperature of more than 40°C, preferably from 41°C to 100°C, more preferably from 50°C to 70°C.

The complete conversion of Modification 2 into Modification 1 is dependent on the temperature and, as a rule, takes from 20 hours to 28 hours, preferably 24 hours, at a temperature of 50°C. The reaction is monitored
5 by X-ray diffraction or IR spectroscopy by means of samples taken during the treatment.

Modification 2, according to the invention, of the compound of the formula I is suitable, for example, for the treatment of

10

- acute immunological episodes, such as sepsis, allergies, graft-versus-host- and host-versus-graft-reactions
- autoimmune diseases, in particular rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis
- 15 - psoriasis, atopic dermatitis, asthma, urticaria, rhinitis, uveitis
- type II diabetes
- liver fibrosis, cystic fibrosis, colitis
- cancers, such as lung cancer, leukemia, ovarian cancer, sarcomas, Kaposi's sarcoma, meningioma, intestinal cancer, lymphatic cancer,
20 brain tumors, breast cancer, pancreatic cancer, prostate cancer or skin cancer.

The invention also relates to drugs comprising an effective content of Modification 2 of the compound of the formula I together with a
25 pharmaceutically suitable and physiologically tolerated excipient, additive and/or active ingredients and adjuvants.

The drugs according to the invention, comprising an effective content of Modification 2 of the compound of the formula I, have the same efficacy in
30 humans who suffer from rheumatic arthritis in comparison with the treatment with a drug comprising an effective content of Modification 1 of the compound of the formula I.

The invention furthermore relates to a process for the preparation of the
35 drug, which comprises processing Modification 2 of the compound of the formula I and a pharmaceutical excipient to give a pharmaceutical dosage form.

The drug according to the invention may be present as a dosage unit in dosage forms such as capsules (including microcapsules), tablets (including sugar-coated tablets, pills) or suppositories, the capsule material performing the function of the excipient where capsules are used and it being possible for the content to be present, for example, as powder, gel, emulsion, dispersion or suspension. However, it is particularly advantageous and simple to prepare oral (peroral) formulations containing Modification 2 of the compound of the formula I, which contain the calculated amount of the active ingredient together with a pharmaceutical excipient. An appropriate formulation (suppository) for rectal therapy may also be used. Transdermal application in the form of ointments or creams or oral administration of tablets or suspensions which contain the formulation according to the invention is also possible.

In addition to the active ingredients, ointments, pastes, creams and powders may contain the conventional excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, talc, zinc oxide, lactose, silica, aluminum hydroxide, calcium silicate and polyamide powder or mixtures of these substances.

The tablets, pills or granules can be prepared by conventional processes, such as compression, immersion or fluidized-bed processes or by coating in a pan and contain excipients and other conventional adjuvants, such as gelatine, agarose, starch (for example potato, corn or wheat starch) cellulose, such as ethyl cellulose, silica, various sugars, such as lactose, magnesium carbonate and/or calcium phosphates. The sugar-coating solution usually comprises sugar and/or starch syrup and generally also contains gelatine, gum arabic, polyvinylpyrrolidone, synthetic cellulose esters, surfactants, plasticizers, pigments and similar additives according to the prior art. Any conventional flow regulators, lubricants, such as magnesium stearate, and external lubricants may be used for the preparation of the formulations.

The dosage to be used is of course dependent on various factors, such as the organism to be treated (i.e. human or animal), age, weight, general state of health, the severity of the symptoms, the disease to be treated, the type of accompanying treatment with other drugs or the frequency of the

treatment. The doses are administered in general several times per day and preferably once to three times per day.

A suitable therapy therefore comprises, for example, administering one, two or 3 single doses of a formulation containing N-(4-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide in Modification 2 in an amount of from 2 to 150 mg, preferably from 10 to 100 mg, in particular from 10 to 50 mg.

The amount of the active ingredients does of course depend on the number of single doses and also on the disease to be treated. The single dose may also comprise a plurality of simultaneously administered dosage units.

Example 1

Preparation of Modification 2

About 40 mg of the compound of the formula I, prepared according to US 4,284,786, were shaken with 40 ml of water in bottles (volume 45 ml). The shaking of the closed bottles was carried out at 15 - 25°C in a water bath. After 48 hours, a sample was taken, filtered and dried and a powder X-ray diffraction pattern was prepared. The measurement was carried out using the STADI P two-circle diffractometer from Stoe (Darmstadt, Germany) with Cu-K_{α1} radiation by the Debye-Scherrer method under transmission conditions.

Fig. 1 shows the resulting X-ray diffraction pattern and is typical of Modification 2 of the compound of the formula I.

Example 2

Solubility in water

Apparatus	flask, magnetic stirrer, water bath 37°C ± 0.5 °C
Medium	water (+37°C)
35 Sampling	5 hours
Preparation	Modifications 1 and 2 according to Examples 1 and 2 were transferred to water and stirred vigorously at 37°C

Detection UV spectroscopy at a wavelength of 258 μm

Result:

Modification 1 25 mg dissolve in 1 liter of water at 37°C

5 Modification 2 38 mg dissolve in 1 liter of water at 37°C

Example 3

Stability of the modification

10 Samples of Modification 2 were prepared as in Example 1 and were stored at various temperatures at atmospheric humidity. After the stated times, samples were taken and an X-ray diffraction pattern was prepared as in Example 1. Table 1 shows the results.

15 Table 1:

Time (Months)	Storage conditions	Crystal modification
1	-15°C	2
3	-15°C	2
6	-15°C	2
1	+25°C	2
3	+25°C	2
6	+25°C	2
1	+40°C	2
3	+40°C	2
6	+40°C	2
1	+40°C/75 % relative humidity	2
3	+40°C/75% relative humidity	2
6	+40°C/75% relative humidity	2
1	+60°C	about 76 % 1 ¹⁾
3	+60°C	1

1) A calibration curve was used for the determination of Modification 1. For preparing the calibration curve for the quantitative determination, the reflection at $2\theta = 8.35^\circ$ was used for phase 1 and the reflection at $2\theta = 16.1^\circ$ was used for phase 2. The ratios of the corresponding peak heights were calculated and were correlated

with the contents of phase 2. The limit of the method is 0.3 %. The sample after storage for 1 month at 60°C contains about 76 % of Modification 1 according to this method.

5 Example 4

Preparation of Modification 1

Water-moist crude Leflunomide is first dissolved in isopropanol/water (corresponding to 16 kg of crude, dry Leflunomide in 28 l of isopropanol plus the amount of water which, together with the water content of the moist product, gives a total amount of water of 9 l).

The mixture is then heated to 78°C to 82°C, stirred at this temperature for 25 minutes (min) and then filtered through a pressure funnel into a vessel also already heated to the same temperature. The pressure filter is rinsed with an amount of isopropanol which, together with isopropanol used (iPrOH), gives an iPrOH/water ratio of 4:1 (in this case 4 l). Thereafter, water also preheated to 78°C to 82°C is added (32 l, gives iPrOH/water = 0.8:1). The solution already becomes cloudy and is then cooled to about 65°C in 20 min, kept at this temperature for about 40 min, then cooled to about 40°C in 70 min and stirred for a further 20 min. The product is isolated by centrifuging.

Table 1 shows the results of 4 batches.

25 Table 1:

Batch	Initial concentration	iPrOH/H ₂ O ratio	Final concentration	Proportion* of crystals of Modification 2	Yield
	[g/l]		[g/l]	[%]	[%]
1	600	4:1	600	n.d.	73.2
2	600	3:1	563	<0.4	71.4
3	400	2:1	333	<0.4	70.5
4	400	0.8:1	222	<0.4	85.6

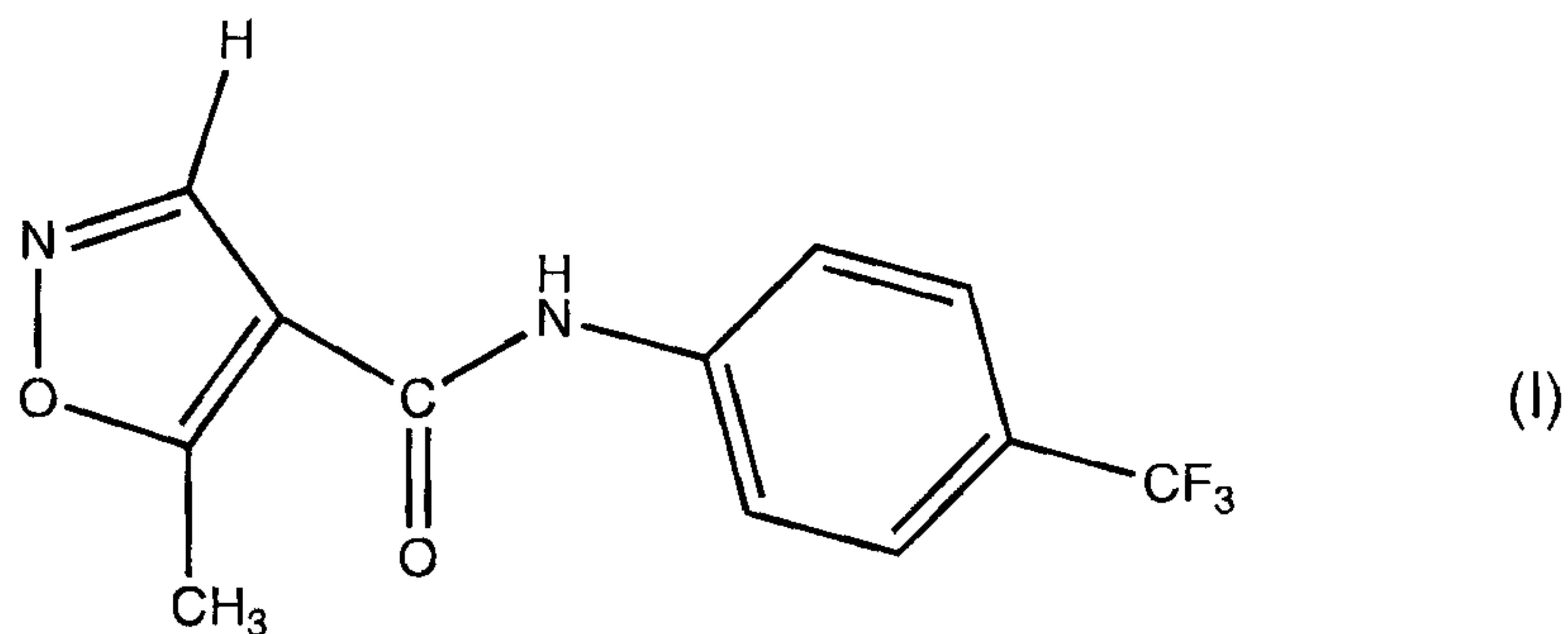
* The determination was carried out by X-ray powder diffractometry; the proportion of Modification 2 was always below the limit of detection, which was about 0.4 %.

30 n.d. means not determined

Patent claims:

1. A process for the preparation of crystal modification 1 of the compound of the formula 1

5



10 which, in the transmission X-ray diffraction pattern obtained with a focusing Debye-Scherrer beam and Cu- $K_{\alpha 1}$ -radiation, has lines at the following diffraction angles 2 theta ($^{\circ}$):

Lines of strong intensity: 16.70; 18.90; 23.00;
23.65; 29.05

15

Lines of medium intensity: 8.35; 12.65; 15.00;
15.30; 18.35; 21.25;
22.15; 24.10; 24.65;
25.45; 26.65; 27.40;
20 28.00; 28.30

comprising

25

- a) dissolving the amorphous compound of the formula 1 in an organic solvent or mixtures of organic solvents and water,
- b) heating the mixture obtained to a temperature of from 41 $^{\circ}$ C to the boiling point of the organic solvent,

c) diluting the resulting solution with water or distilling off the organic solvent so that the organic solvent and the water are present in a ratio of 4:1 to 0.3:1, and

5 d) carrying out the crystallization at temperatures of more than 40°C.

2. The process as claimed in claim 1, wherein the crystallization temperature is from 41°C to 80°C.

10

3. The process as claimed in claim 2, wherein the crystallization temperature is from 50°C to 70°C.

15

4. The process as claimed in any one of claims 1 to 3, wherein the solution obtained is filtered after processing step b).

20

5. The process as claimed in any one of claims 1 to 4, wherein the organic solvent is methanol, ethanol, propanol, isopropanol, butanol, isobutanol, acetone, methyl ethyl ketone or a mixture thereof.

25

6. The process as claimed in any one of claims 1 to 5, wherein the mixture of organic solvent and water according to process step b) is heated to a temperature of from 40°C to 85°C.

30

7. The process as claimed in any one of claims 1 to 5, wherein the ratio of organic solvent to water in process step a) is from 1:1 to 8:1.

8. The process as claimed in claim 7, wherein the ratio is from 2:1 to 6:1.

9. The process as claimed in claim 8, wherein the ratio is from 3:1 to 5:1.
10. The process as claimed in any one of claims 4 to 9,
5 wherein the heated mixture is filtered through a filter of from 0.1 μm to 200 μm pore diameter.
11. The process as claimed in any one of claims 1 to 10,
10 wherein the ratio of organic solvent to water in process step c) is from 2:1 to 0.6:1.
12. The process as claimed in claim 11, wherein the ratio is from 1.6:1 to 0.8:1.
- 15 13. The process as claimed in any one of claims 1 to 12, wherein the temperature is reduced from 83°C to 85°C to slightly above 40°C in the crystallization.
- 20 14. The process as claimed in any one of claims 1 to 13, wherein amorphous compound of formula 1 is crude compound of formula 1.

Fig. 1

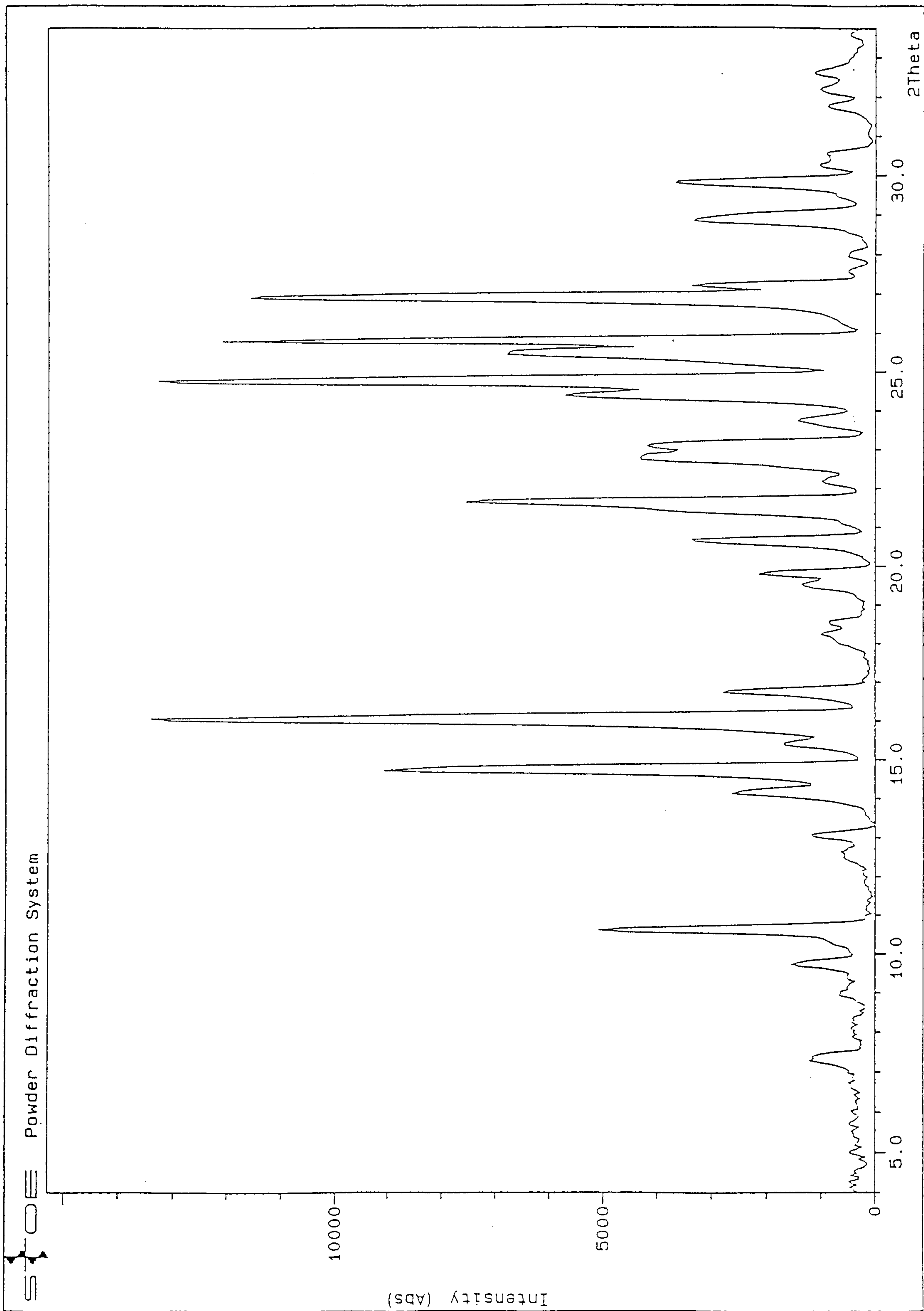


Fig. 2

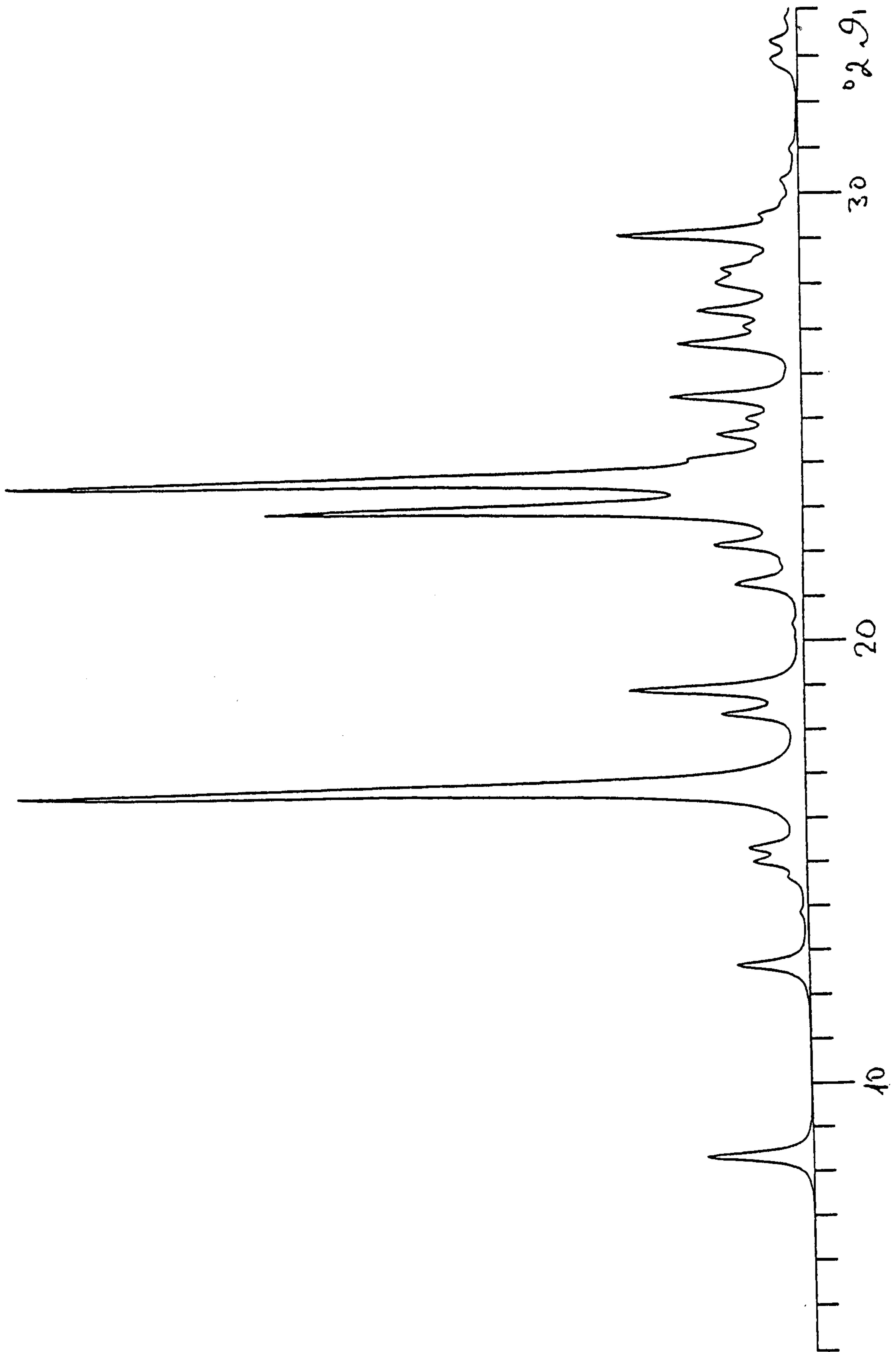
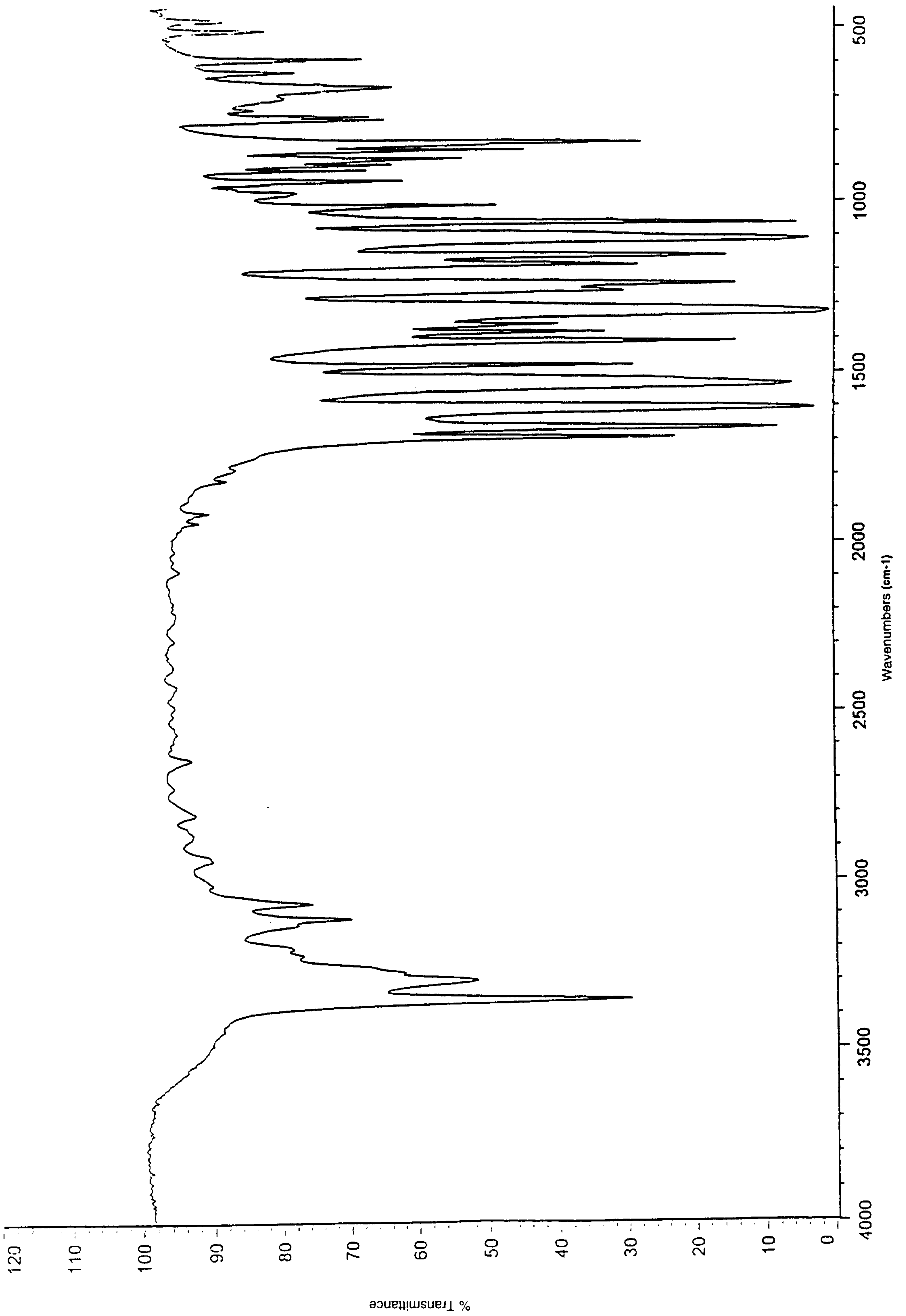
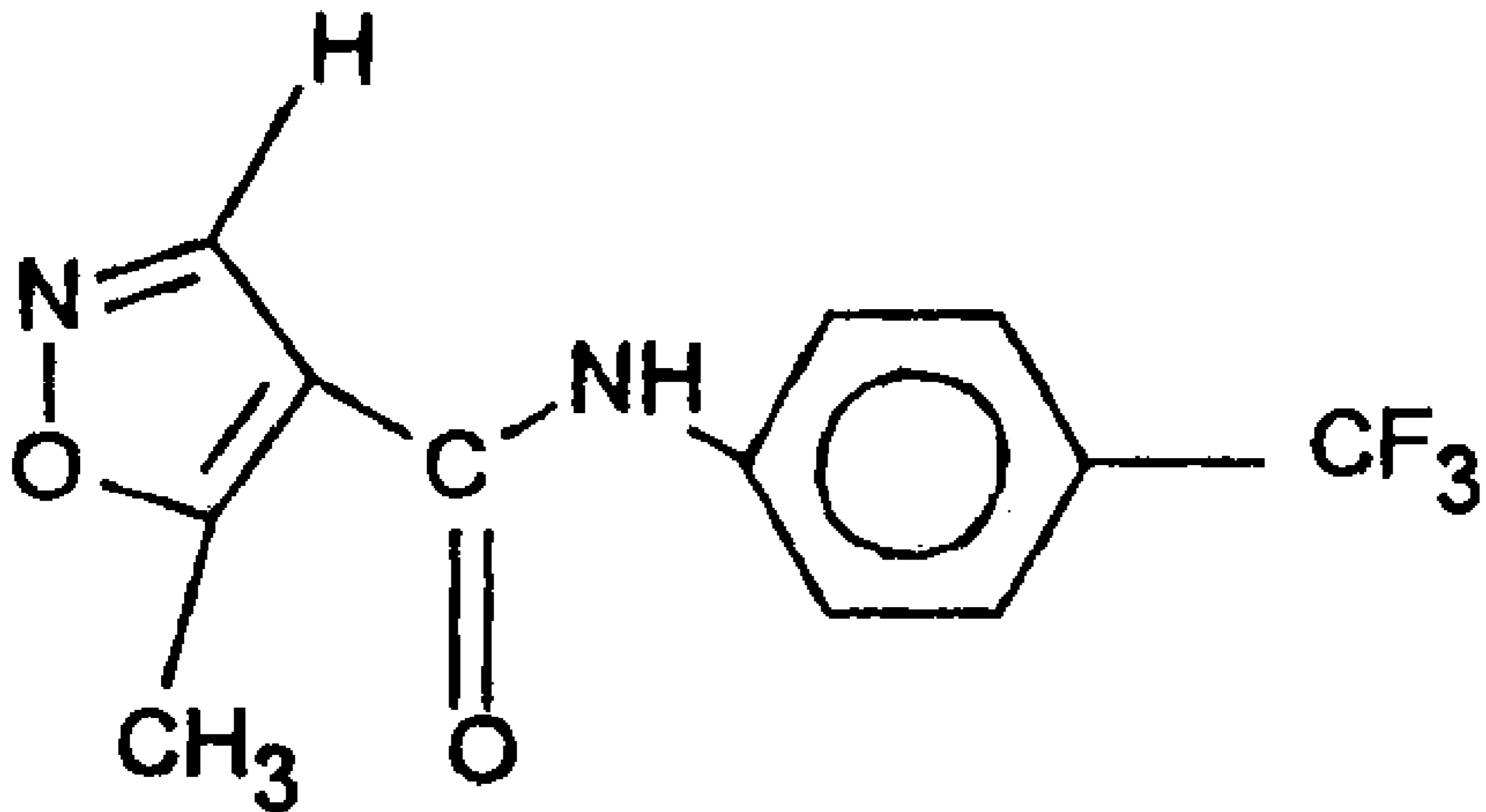


Fig. 3





(1)