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CA 2092510 C 2004/02/03

(11)(21) 2 092 510

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1993/03/25

(41) Mise à la disp. pub./Open to Public Insp.: 1993/09/27

(45) Date de délivrance/Issue Date: 2004/02/03

(30) Priorités/Priorities: 1992/03/26 (MI92 A 000720) IT;
1992/03/26 (MI92 A 000723) IT

(51) Cl.Int.^{5}/Int.Cl.^{5} C07D 451/04, A61K 31/46

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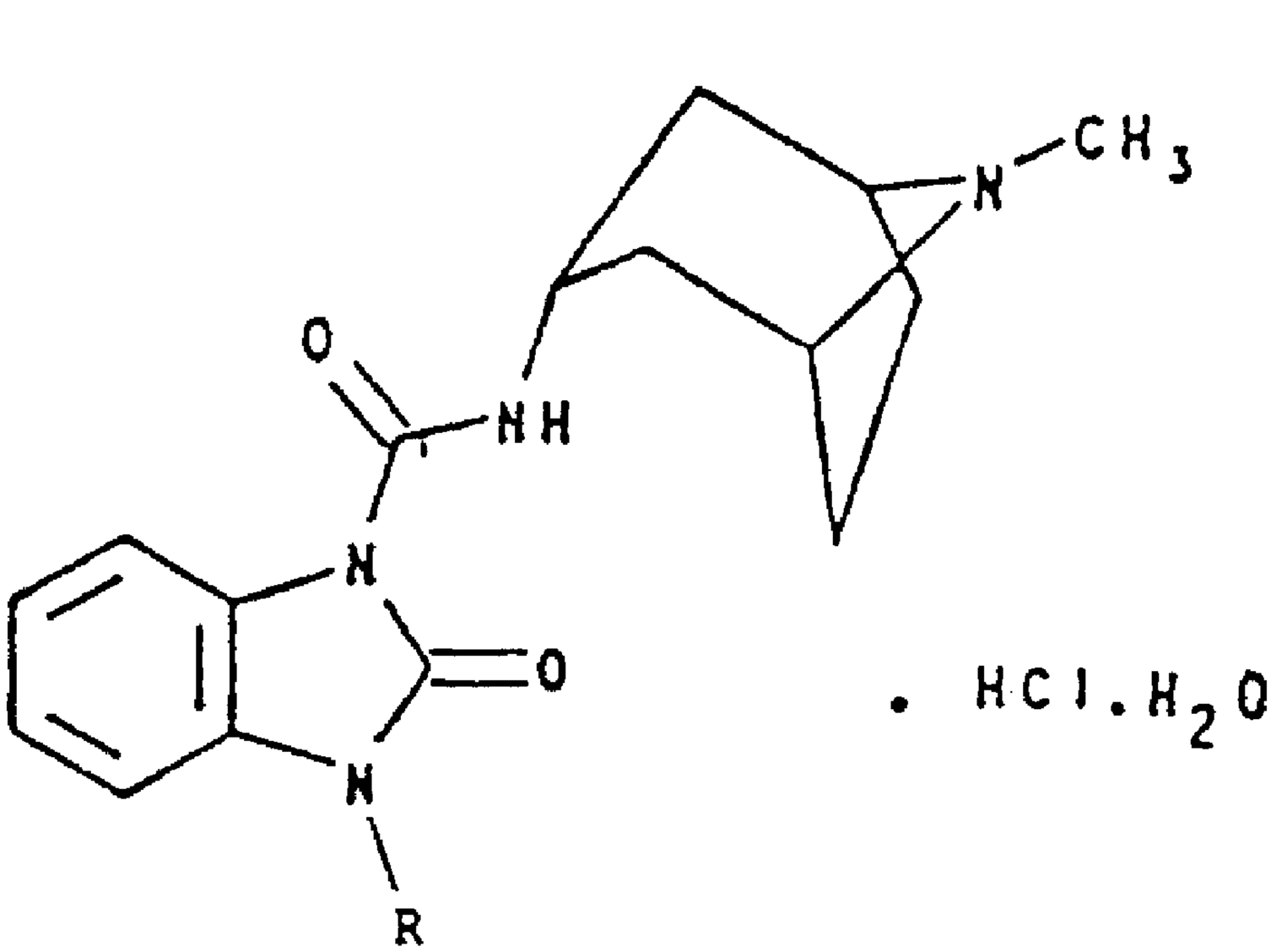
(54) Titre : FORMES CRISTALLINES DE CHLORHYDRATE MONOHYDRATE D'ENDO-2,3-DIHYDRO-N-(8-METHYL-8-AZABICYCLO-[3.2.1.]OCT-3-YL)-2-OXO-1H-BENZIMIDAZOLE-1-CARBOXAMIDE ET DE CHLORHYDRATE MONOHYDRATE D'ENDO-3-ETHYL-2,3-DIHYDRO-N-(8-METHYL-8-AZABICYCLO[3.2.1.]OCT-3-YL)-2-OXO-1H-BENZIMIDAZOLE-1-CARBOXAMIDE

(54) Title: CRYSTALLINE FORMS OF ENDO-2,3-DIHYDRO-N-(8-METHYL-8-AZABICYCLO-[3.2.1.]OCT-3-YL)-2-OXO-1H-BENZIMIDAZOLE-1-CARBOXAMIDE HYDROCHLORIDE MONOHYDRATE AND OF ENDO-3 ETHYL-2,3-DIHYDRO-N-(8-METHYL-8-AZABICYCLO[3.2.1.]OCT-3-YL)-2-OXO-1H-BENZIMIDAZOLE-1-CARBOXAMIDE HYDROCHLORIDE MONOHYDRATE



(57) Abrégé/Abstract:
Crystalline monohydrates of endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride and of endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride of formula (see above formula) (Compound 2a: R = H) (Compound 2b: R - C_2H_5) the processes for their preparation and pharmaceutical compositions containing them.

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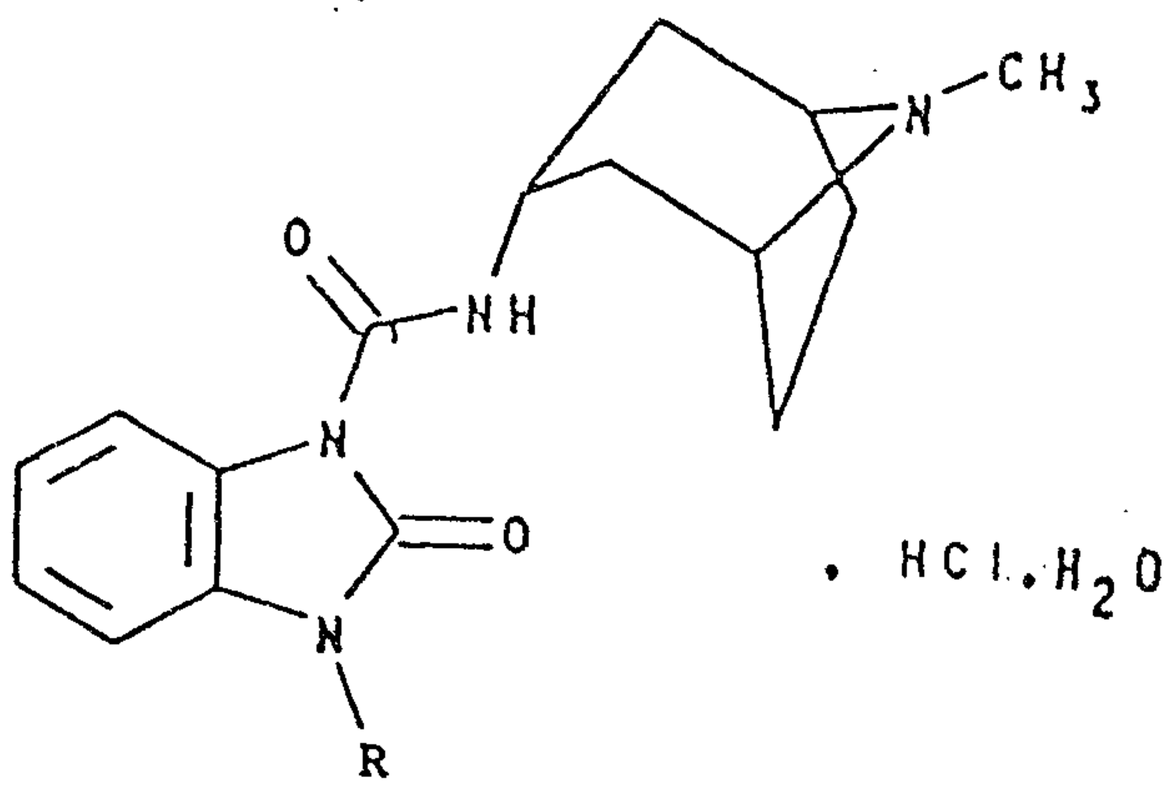
A B S T R A C T

Crystalline monohydrates of azabicyclo-1H-benzimidazole-1-carboxamides, the preparation and use thereof

Crystalline monohydrates of endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride and of endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride of formula



(Compound 2a: R = H)

(Compound 2b: R - C_2H_5)

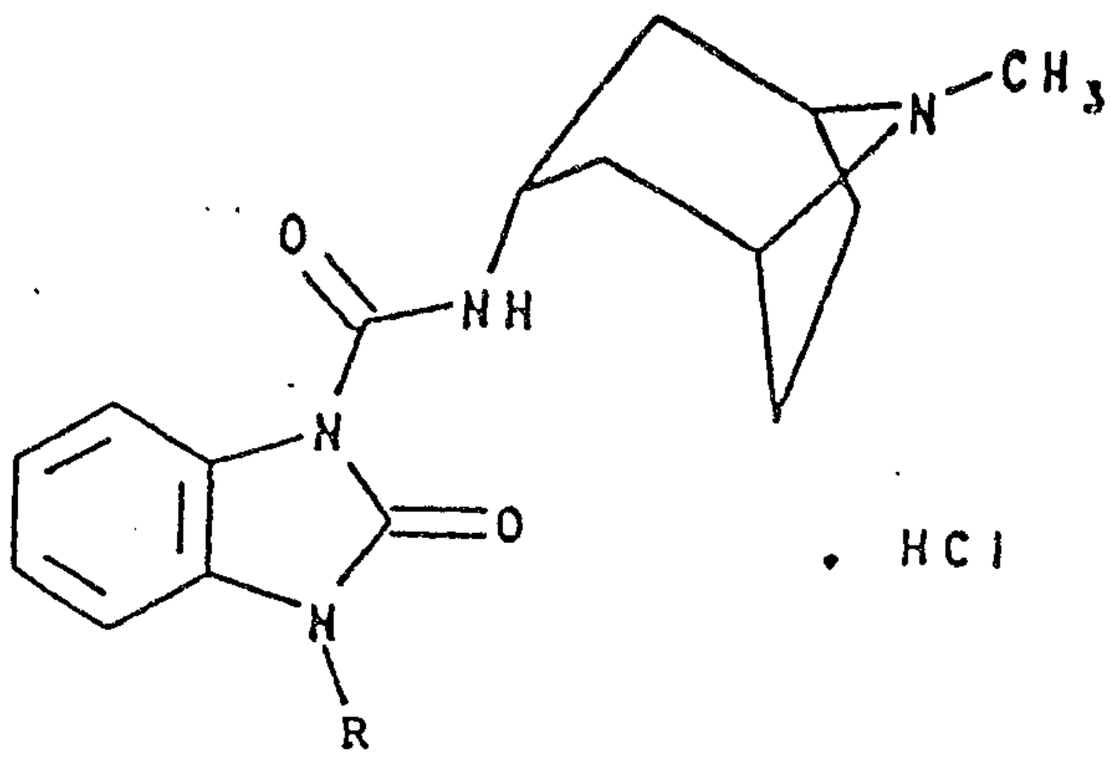
the processes for their preparation and pharmaceutical compositions containing them.

Crystalline monohydrates of azabicyclo-1H-benzimidazole-1-carboxamides, the preparation and use thereof

The present invention relates to the crystalline and pharmacologically active monohydrates of endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride and endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride, to processes for their preparation and to pharmaceutical compositions containing them.

EP 309423 described a group of esters and amides of benzimidazoline-2-oxo-1-carboxylic acid, their physiologically acceptable salts and solvates possessing 5-HT antagonistic properties. These compounds were claimed to be useful in the treatment of chemotherapy and radiation induced nausea and emesis, delayed gastric emptying, gastrointestinal motility disorders, particularly dyspepsia, flatulence, oesophageal reflux, irritable bowel syndrome and hypokinesia. The same compounds were also claimed to be useful in the treatment of certain CNS disorders such as for example motion sickness, migraine, cluster headache, anxiety and psychosis. The anhydrous hydrochloride salts of endo-2,3-dihydro-N-(8-methyl-8-azabicyclo [3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide (compound 1a) and endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo-

[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride (compound 1b) are currently being developed for clinical use as antiemetic and antianxiety agents.



(Compound 1a: R - H)

(Compound 1b: R - C_2H_5)

The same compounds show potential as antipsychotic agents free of extra-pyramidal side effects. The use of compounds 1a and 1b in the treatment of patients suffering from organic mental diseases such as dementia and amnestic syndromes was claimed in the Italian Patent Application no. MI 91 A 001845. Pharmaceutical compositions containing compounds 1a and 1b, as active ingredient, were also claimed in the above mentioned patent applications.

As an example, the administration of compounds 1a and 1b to patients may be conveniently carried out either by the oral route, employing suitable pharmaceutical preparations such as for example tablets, coated tablets and capsules, or by the rectal route, employing for example suppositories.

These administration routes show advantages in comparison with, for example, the parenteral route, because the presence of a doctor, or of a person skilled to give an injection, is not required.

Efficacious manufacturing of the above said preparations useful for the oral administration of an active substance is dependent upon different parameters which are related to the nature of the substance itself. Non limiting examples of such parameters are the substance's stability as a starting material in different ambient conditions, the stability during the manufacturing process and the stability in the final pharmaceutical compositions. The substance used for the preparation of the above said pharmaceutical compositions should be as pure as possible and its stability upon prolonged storage at different ambient conditions must be checked in order to avoid using a degraded substance or a substance with an unpredictably lower titre than that required for the manufacturing process. In such a case, the active drug concentration present in individual tablets or capsules would be unpredictably lower than that expected. Moisture absorption lowers the titre of an active substance because of the weight gain due to the water intake. Substances which tend to absorb moisture must be protected from moisture during prolonged storage for example by adding suitable desiccants or by storing the drug in a room protected from moisture. Furthermore the absorption of moisture may also lower the titre during the manufacturing process when the drug is exposed at normal conditions without any moisture protection.

A correct weight distribution of a drug in individual capsules or tablets is a critical factor, particularly when a low dosage of drug is required. In order to afford the correct weight distribution, one may reduce the particle size of the drug to a suitable value, for example by milling. In fact, particles of small size are more homogeneously distributed in single tablets or capsules.

Since milling may be accompanied by a certain degree of degradation of compounds la and lb (due to the rather harsh conditions required in the process), a high stability to milling represents a considerable advantage since it allows the preparation of capsules and tablets containing the correct amount of drug, avoiding the presence of degradation products. Furthermore, during the milling of a product the supply of energy and the stress can produce polymorphic modifications, amorphisation, and variations in the crystal lattice and the form of the solid surface. These alterations have an important effect on the various subsequent processing stages and on the biopharmaceutical characteristics of the drug.

The stability of a drug in pharmaceutical compositions is important in determining the shelf life period of the pharmaceutical compositions; this period is that in which the drug can be administered without any risks either those due to the presence of an excessive amount of potentially dangerous degradation products or those due to an unacceptably low content of the active ingredient with respect to the stated amount. The high stability of a

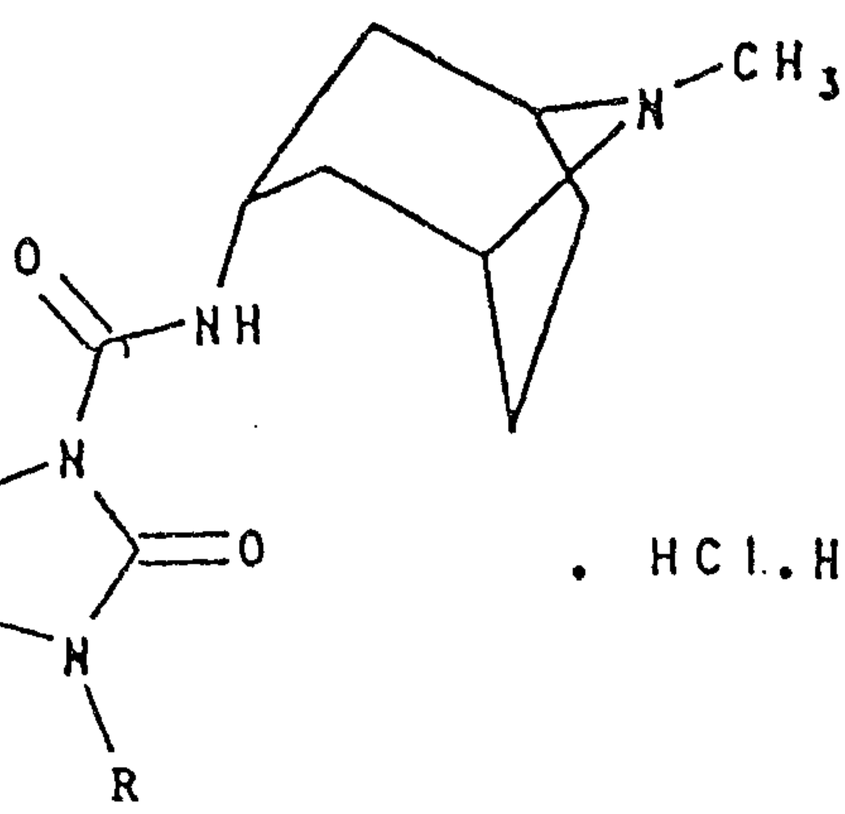
drug in the above pharmaceutical preparations at different conditions of storage represents therefore an additional advantage both to the patients and to the manufacturer since storage in controlled conditions is avoided as well as the frequent replacement of expired compositions.

For the above said reasons, any modification of the solid state of a drug for oral administration (in the form of capsules, tablets or coated tablets) which can improve its physical and chemical stability is expected to afford a consistent advantage over less stable forms of the same drug. Non limiting examples of such modifications include different crystalline forms of the parent drug, also in terms of different or new solvates, and salts with different physiologically acceptable acids or bases, if the drug is amenable to salt formation.

The object of the present invention is therefore the preparation of new crystalline forms of compounds 1a and 1b, which do not show the above mentioned disadvantages.

We have now found novel crystalline monohydrate forms of compounds 1a and 1b (compounds 2a and 2b herein) which are not specifically claimed in EP 309423 and which possess definite advantages in comparison with the anhydrous forms. In fact, compounds 2a and 2b of the invention do not absorb moisture either during storage prior to the manufacturing process of capsules, tablets and coated tablets at different conditions of temperature and relative humidity, or during the process itself; furthermore they are more stable than the respective

compounds 1a and 1b during all phases of the above mentioned manufacturing process, particularly during milling, and they are also more stable to storage in the form of capsules, tablets or coated tablets, at different conditions of temperature and of relative humidity. Moreover, the novel crystalline forms are endowed with antagonist activity at 5-HT receptors. Accordingly, the present invention provides compounds of formula



. HCl.H_2O

(Compound 2a: R - H)

(Compound 2b: R - C_2H_5)

together with a process for their preparation and pharmaceutical preparations containing them.

Compounds 2a and 2b may be prepared by dissolving the compounds 1a and 1b, as free base, in a hot aqueous solvent, preferably a hot aqueous alkanol, by adding the required amount of gaseous hydrogen chloride, filtering the resulting solution and letting it cool to room temperature. In a preferred embodiment of the process acccording to the invention, compound 2a is prepared by using, as an hot aqueous alkanol, hot 85% aqueous ethanol. The crystals of compound 2a may be

collected by vacuum filtration and are washed with a small amount of aqueous ethanol. In a preferred embodiment of the process according to the invention, compound 2b is prepared by using, as an hot aqueous alkanol, hot 95% aqueous isopropanol. The crystals of compound 2b may be collected by vacuum filtration and are washed with a small amount of aqueous isopropanol. The thus obtained crystals of 2a and 2b can be desiccated at a temperature between room temperature and 60°C under vacuum, most preferably at 40°C under 0.1 mm Hg vacuum for 24 hours without any appreciable loss of water content. Water content may be measured by usual techniques such as the Karl Fischer test. Alternatively, compounds 2a and 2b may be conveniently prepared by dissolving the anhydrous form of compounds 1a and 1b, as hydrochloride, in hot aqueous ethanol, preferably 85% ethanol (for 1a) or in hot aqueous isopropanol, preferably 95% isopropanol (for 1b) and allowing the solution to cool to room temperature; crystals of compound 2a (or 2b), separated from the cooled solution, are collected by vacuum filtration and manipulated as previously described. In a further option, compounds 2a and 2b may also be prepared by dissolving the corresponding compounds 1a and 1b, as a free base in an anhydrous hot alcoholic solvent, preferably anhydrous ethanol (for 1a) or anhydrous isopropanol, (for 1b) and adding to the filtered solution 37% aqueous hydrochloric acid. The crystals of compound 2a (or 2b) separated from the cooled solution are collected by vacuum filtration and manipulated as described above.

In another option the same compounds may be prepared by exposing compounds 1a or 1b to a humidified atmosphere of, for example, air or nitrogen at a temperature between room temperature and 40°C, preferably at room temperature. Water absorption may require variable times according mainly to the size of the crystals of the starting compounds and to the relative humidity. The process is over when no further increase in weight is recorded. The water content may be conveniently measured by Karl Fischer assay and for 2a is usually between 5.07% ± 0.5; for 2b between 4.70 ± 0.5; these contents are indicative of a monohydrate. Compounds 1a and 1b, used in the form of free base as starting material for the preparation of compounds 2a and 2b, may be conveniently prepared as described in the example 16 (for 1a) and 14 for (1b), of EP 309423.

Compounds 2a and 2b are novel crystalline monohydrate forms of compounds 1a and 1b. They show different physico-chemical properties and exist in well defined chemical and crystalline structures. In compounds 2a and 2b, the molecules of water are tightly bound into the crystal lattice and the ratio between the drug molecules and the water molecules is 1.

The analytical characterization of compounds 2a and 2b can be performed by different methods, such as Elemental Analysis, Differential Scanning Calorimetry (DSC), Thermal Gravimetric Analysis (TGA), Infrared Spectroscopy (IR), X-Rays Powder Diffraction, Single Crystal X-Ray Diffraction.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was

performed by using a Mettler TA 3000 System equipped with TC 10A Processor and DSC 20 cell. The compound (3.5 mg) was weighed in a standard Alumina crucible. It was sealed with a crimped-on lid in which three small holes were made.

Compound 2a.

The sample was heated in a nitrogen flow of 40 ml/min, starting from 30°C to a final temperature of 320°C at a rate of 10°C/min. Compound 2a showed an endothermic peak due to crystallization water desorption at 110°-160°C, followed by an exothermic peak due to crystal rearrangement.

Finally the compound meltedat 295°C.

Compound 2b.

Heating crystals of compound 2b in a nitrogen flow of 40 ml/min, starting from 30°C to a final temperature of 270°C at a rate of 10°C/min, lead to the desorption of the water of crystallization in the range between 70°C and 160°C (absent in the thermogram corresponding to the anhydrous form) with the highest peak at 150°C, desorption which is shown from the presence of an endothermic peak (see figure 1). Finally the compound melted at 245°C.

Thermal Gravimetric Analysis (TGA)

Thermal Gravimetric Analysis (TGA) was performed by using a Mettler TA 3000 System equipped with TC 10-A Processor, TG 50 oven and M3 balance. 10 mg of the compound under investigation were weighed in a standard Alumina Crucible.

Compound 2a

Heating was done in a nitrogen flow, 200 ml/min.,

starting from 25°C to a final temperature of 295°C, at a rate of 10°C/min. Compound 2a showed a weight loss corresponding to the peak due to crystallization water desorption equal to 5.2%, a value very close to the theoretical value of 5.07% expected for the monohydrate.

Compound 2b

Heating was done in a nitrogen flow, 200 ml/min., starting from 25°C to a final temperature of 255°C, at a rate of 10°C/min. Compound 2b showed a weight loss corresponding to the peak due to crystallization water desorption equal to 4.62%, a value very close to the theoretical value of 4.70% expected for the monohydrate.

Infrared Spectroscopy

Infrared spectra of compounds 1a, 1b, 2a and 2b were recorded on a Perkin-Elmer Mod 298 infrared spectrophotometer. The compounds were analysed as solids in nujol mull.

In the infrared spectrum, compound 2a shows a strong band at 3,400 cm^{-1} which is due to the stretching of the hydroxyl groups of water. This band is absent in the corresponding spectrum of compound 1a. Other differences in the peak shape and their relative intensity are evident at 2,600, 1,430-1,390, 1,350, 1,240, 1,170, 1,110, 1,050, 1,000-900 and 850-750 cm^{-1}. These show that compounds 1a and 2a are different crystalline forms of the same substance (see figure 2).

In the infrared spectrum, compound 2b shows a strong band at 3500 cm^{-1} which is due to the stretching of the hydroxyl groups of water. This band is almost

negligible in the corresponding spectrum of compound 1b. Other differences in the peak shape and their relative intensity are evident at 2600-2500, 1680, 1630, 1480, 1400-1350, 1300-1200, 1160-1100, 1060, 1030, 950-900 and about 750 cm^{-1}. These show that compounds 1b and 2b are different crystalline forms of the same substance (see figure 3).

X-ray Powder Diffraction Pattern

The analysis was carried out in a Philips PW 1800/10 diffractometer equipped with a Digital Microvax 2000 computer on which a Philips APD 1700 program was installed. Setting up parameters, along with the main characteristics of the diffractometer are reported below:

- goniometer -
. scan range: 2° 5 ϑ_2 ϑ
. precision: 0.001° 2 ϑ
. scan speed: 0.02°/second
. scan type: continuous
. analysis time: 40 min.
- slits -
. soller slits
. automatic divergence slits (ADS)
. receiving slit: 0.3 mm
. detector slit: 0.8 mm
- X ray -
. tube type : Cu (long fine focus)
. wavelengths (λ): $K_{\alpha 1}$=1.54060A $K_{\alpha 2}$=1.54439A
- generator -
. voltage height: 40 kV
. tube current: 20 mA

. kV and mA stabilisation: 0.0005% per % mains variation

- *general* -

. irradiated sample length: 10 mm

. monochromator: graphite crystal

. proportional detector

. time constant: 2

The most significant parameters of the main peaks, namely the angles of diffraction (degrees), the values of the interplanar spacings (D), the absolute (Peak/Counts) and relative (I/I_{max}) intensities are shown in Table I and II for compounds 1a and 2a respectively. Significant differences between compound 1a and 2a are particularly evident if we compare the peaks connected with diffraction angles of 6, 13 and 17.6-20 degrees for compound 1a and of 8, 15, 16.8, 21, 26.1 and 26.3 degrees for compound 2a, as shown in figure 4.

T A B L E I
COMPOUND 1a

Peak no.	Angle (deg)	D spac (Ang)	Peak (cts)	I/I max (%)
1	6.6425	13.2961	2440.	51.26
2	7.0300	12.5641	23.	0.48
3	11.3150	7.8138	98.	2.06
4	13.2800	6.6617	4761.	100.00
5	15.0550	5.8801	31.	0.66
6	16.5550	5.3505	388.	8.15
7	16.9550	5.2252	76.	1.59
8	17.6150	5.0309	1037.	21.78
9	18.3100	4.8414	376.	7.91
10	18.7525	4.7282	1576.	33.10
11	19.3500	4.5835	1892.	39.74
12	19.6425	4.5159	234.	4.92
13	19.9525	4.4464	102.	2.14
14	20.4825	4.3326	467.	9.80
15	21.5450	4.1212	380.	7.99
16	21.9850	4.0397	471.	9.89
17	22.7725	3.9018	751.	15.77
18	23.1850	3.8333	207.	4.36
19	23.6150	3.7645	480.	10.07
20	24.8125	3.5854	292.	6.14
21	25.3800	3.5065	222.	4.66
22	25.7275	3.4599	219.	4.60
23	26.2050	3.3980	713.	14.97
24	26.7125	3.3346	790.	16.58
25	26.9050	3.3111	369.	7.74
26	27.4925	3.2417	188.	3.94
27	27.8325	3.2029	250.	5.24
28	28.1550	3.1669	353.	7.42
29	28.7925	3.0982	144.	3.02
30	29.2775	3.0480	299.	6.29
31	29.4950	3.0260	306.	6.43
32	30.1225	2.9644	121.	2.54
33	31.1900	2.8653	102.	2.14
34	31.6225	2.8271	266.	5.58
35	31.9350	2.8002	346.	7.27
36	32.3500	2.7652	219.	4.60
37	33.1125	2.7032	317.	6.65
38	33.5750	2.6670	590.	12.40
39	34.4900	2.5983	353.	7.42
40	35.0025	2.5615	506.	10.63
41	35.7225	2.5115	303.	6.36
42	36.8525	2.4370	204.	4.30
43	37.1650	2.4172	310.	6.51
44	38.0900	2.3606	228.	4.79
45	39.2350	2.2943	144.	3.02
46	39.7675	2.2648	159.	3.33
47	40.5000	2.2255	172.	3.60
48	41.2575	2.1864	166.	3.50
49	42.4050	2.1299	121.	2.54

TABLE I (continued)
COMPOUND 1a

Peak no.	Angle (deg)	D spac (Ang)	Peak (cts)	I/I max (%)
50	43.1425	2.0952	151.	3.18
51	44.6975	2.0258	237.	4.98
52	45.1750	2.0055	121.	2.54
53	46.5625	1.9489	117.	2.45
54	47.6750	1.9060	202.	4.24
55	48.3575	1.8807	259.	5.44
56	49.4600	1.8413	177.	3.73

T A B L E II
COMPOUND 2a

Peak no.	Angle (deg)	D spac (Ang)	Peak (cts)	I/I max (%)
1	7.6775	11.5058	40.	1.88
2	8.2700	10.6828	1505.	71.46
3	10.2450	8.6274	36.	1.71
4	11.1675	7.9167	76.	3.59
5	13.0450	6.7812	751.	35.63
6	13.9225	6.3557	106.	5.04
7	14.1635	6.2485	164.	7.78
8	14.9850	5.9074	1018.	48.30
9	15.9525	5.5512	190.	9.04
10	16.0700	5.5109	231.	10.97
11	16.8750	5.2498	2107.	100.00
12	19.1650	4.6273	392.	18.61
13	19.2575	4.6053	388.	18.42
14	19.9475	4.4475	310.	14.70
15	20.8125	4.2646	1998.	94.84
16	22.0550	4.0271	306.	14.54
17	22.2300	3.9958	335.	15.90
18	22.5475	3.9402	454.	21.53
19	23.0250	3.8596	35.	1.65
20	23.7750	3.7395	67.	3.19
21	24.3300	3.6554	400.	18.99
22	25.7500	3.4570	207.	9.84
23	26.1500	3.4050	1505.	71.46
24	26.3450	3.3802	2098.	99.56
25	27.2225	3.2732	655.	31.11
26	27.4725	3.2440	1089.	51.69
27	29.5325	3.0223	74.	3.51
28	29.9775	2.9784	234.	11.11
29	30.1725	2.9596	324.	15.38
30	30.5650	2.9225	190.	9.04
31	31.4925	2.8385	650.	30.86
32	32.3725	2.7633	380.	18.05
33	32.5925	2.7452	462.	21.94
34	32.9925	2.7128	128.	6.06
35	33.5200	2.6713	146.	6.95
36	33.9450	2.6388	412.	19.56
37	34.8125	2.5750	784.	37.21
38	36.3250	2.4712	182.	8.65
39	36.7950	2.4407	210.	9.98
40	37.1375	2.4190	306.	14.54
41	38.5925	2.3310	900.	42.72
42	39.0700	2.3036	161.	7.66
43	40.1000	2.2468	193.	9.17
44	40.6450	2.2179	458.	21.74
45	42.5125	2.1247	121.	5.74
46	43.2675	2.0894	90.	4.28
47	45.2500	2.0023	177.	8.40
48	46.3950	1.9556	114.	5.43

T A B L E II (continued)
COMPOUND 2a

Peak no.	Angle (deg)	D spac (Ang)	Peak (cts)	I/I max (%)
49	47.1150	1.9273	324.	15.38
50	47.9125	1.8971	146.	6.95
51	48.9800	1.8582	299.	14.21
52	49.9000	1.8261	210.	9.98

Also the difference of the crystalline form of compounds 1b and 2b is further supported by X-ray powder diffraction pattern.

Single Crystal X-Ray Diffraction

The analysis was carried out on a prismatic crystal of compound 2a of dimension equal to 0.41 x 0.23 x 0.08 mm. A Philips PW 1100 four-circle diffractometer equipped with a graphite monochromator was used. 48 Reflections ($2 < \vartheta < 25°$) were used to measure lattice parameters with a Philips LAT routine. Other important experimental parameters were the following:

- $\omega - 2\vartheta$ scan mode, scan speed 0.05 s^{-1}, scan width 2.0°, range 2 - 22°. Three standard reflections every 180 min, mean intensity variation 1.5% max intensity variations 2.6% . 4201 independent data [-11 ≤ 11; 12 ≤ k ≤ 12; 1 ≤ 14), max (sin $\vartheta / \lambda = 0.53A^{-1}$]; 2085 unique reflections, 1186 with I > 3(I). The structure was solved by direct method (MULTAN 80, XANADU). Figures were drawn with ORTEP II.

The analysed compound (formula $C_{16}H_{20}N_4O_2.HCl.H_2O$, Mw = 354.84) possesses a monoclinic $P2_1/c$ cell, a = 11.668 A, b = 11.714 A, c = 13.672 A, α = 90°, β = 114.83°, γ = 90°. The water molecule in the crystalline

structure of compound 2a occupies a well defined space in the crystal lattice being bonded through a hydrogen bond to the unsubstituted nitrogen atom of the benzimidazolone ring. Moreover the same molecule of water is linked to two chloride ions belonging to two other drug molecules.

Compound 2b is characterized by the following data:

Formula $C_{18}H_{24}N_4O_2.HCl.H_2O$, Mw = 382.9; needle like crystal from isopropanol with dimensions of 0.1 x0.1 x 0.55 mm; monoclinic, space group $P2_1/C$, a = 13.869(2), b = 16.449(2), c - 8.550(1) A, ß = 97.64(1)°, V - 1933.1(5)A^3, Z - 4, $d_{calc.}$ = 1.316 g/cm^3.

The figures in the ( ) are the standard deviations of the previous figures. The density of the crystal was determined with the solvent mixture of carbontetrachloride and benzene, and it was 1.313 g/cm^3.

Moisture absorption/desorption studies

The determination of the absorption isotherms was carried out in a hygrostat.

At suitable intervals, the sample was weighed by means of a sample balance. The atmosphere in the hygrostat and therefore around the sample of compound 1a (1b) and 2a (2b) was conditioned and maintained by a saturated solution of a suitable salt:

Li Cl saturated solution	11.3% RH/25°C	11.2% RH/37°C
$Mg(NO_3)$ saturated solution	52.8% RH/25°C	49.2% RH/37°C
Na Cl saturated solution	75.3% RH/25°C	74.8% RH/37°C
KNO_3 saturated solution	93.7% RH/25°C	90.0% RH/37°C

At the end of the experiment, after completing the hysteresis, that is the absorption - desorption cycle of humidity, the compound was assayed for titre and degradation products by TLC and HPLC, the physical state by DSC and water content by TGA.

Compound 2a is stable in condition of storage at different temperatures and relative humidity (RH) as reported in Table III in comparison with compound 1a, which on the contrary, shows a marked tendency to moisture absorption.

T A B L E III

	Compound 1a		Compound 2a	
Duration	Relative humidity 75%	94%	75%	94%
Room Temperature				
2 h	0.68	1.28	5.46	5.49
4 h	0.74	1.92	5.43	5.53
6 h	0.78	2.41	5.37	5.51
1 d	1.25	5.33	5.41	5.49
4 d	2.54	5.39	5.42	5.44
8 d	3.50	5.39	5.36	5.48
20 d	4.59	5.40	5.41	5.49
40 d	4.95	5.42	---	---
37°C				
2 h	0.34	1.93	5.80	5.49
4 h	0.39	3.41	5.75	5.47
6 h	0.59	4.68	5.79	5.53
1 d	1.95	5.04	5.75	5.50
5 d	5.09	5.06	5.80	5.49
9 d	5.13	5.06	5.76	5.48
15 d	5.13	5.04	5.80	5.48

As a consequence, storage of compound 2a may be effected in normal conditions and no particular precautions are needed to avoid exposure to moisture.

The titre of compound 2a, when it is stored in normal conditions, is therefore maintained in contrast to compound 1a which, under the same conditions, may show different titres according to the water content. The hygroscopicity may also influence the drug's titre immediately after the manufacturing of tablets. In fact during the manufacturing process the drug is exposed to normal ambient conditions where it can take up moisture. As emphasized in Table IV, compound 1a increases its water content in comparison with compound 2a which shows a stable water content during the mixing (a) and tableting (b) phases.

TABLE IV

Moisture content (*)

	compound 1a	compound 2a
Start	0.62%	4.90%
Intermediate (a)	0.66%	4.90%
Final (b)	1.02%	4.90%

(*) expressed as % of the weight of compound 1a.

The drug content in individual tablets is therefore more predictable and reproducible when using compound 2a instead of compound 1a.

As reported in Table V, the water content of compound 2a is not affected in the employed conditions, or even inconditions of extreme dryness (11.2% RH, 37°C). The physical stability is therefore a substantial advantage of compound 2a; its titre is stable over a wide range of conditions and its storage and handling appear completely trouble free unlike compound 1a.

TABLE V

At 37° C	Compound 2a 11.2% RH
0	5.26[a)]
2 h	5.32
4 h	5.31
6 h	5.31
21 days	5.29

a) water content expressed as % of the weight of compound 1a.

Compound 2b is stable in conditions of storage at different temperatures and relative humidity (RH) as reported in Table VI in comparison with compound 1b, which on the contrary, shows a marked tendency to moisture absorption.

T A B L E VI

	Compound 1b		Compound 2b	
Duration	Relative humidity 49.2%	74.8%	Relative humidity 49.2%	74.8%
37° C				
0	1.13	1.13	5.00	5.00
2 h	2.18	4.99	5.03	5.05
4 h	2.58	4.93	5.04	5.05
6 h	3.01	4.97	5.00	5.07
1 d	4.07	4.90	5.00	5.07
4 d	4.81	4.92	5.04	5.07
10 d	4.82	4.85	4.95	4.97
30 d	4.81	4.81	5.02	5.00

As a consequence, storage of compound 2b may be

effected in normal conditions and no particular precautions are needed to avoid exposure to moisture. The titre of compound 2b, when it is stored in normal conditions, is therefore maintained in contrast to compound 1b which, under the same conditions, may show different titres according to the water content.

As reported in Table VII the water content of compound 2b is not affected in the employed conditions, even in conditions of extreme dryness (11.2% RH, 37°C). The physical stability is therefore a substantial advantage of compound 2b; its titre is stable over a wide range of conditions and its storage and handling appear completely trouble free, unlike compound 1b.

T A B L E VII

At 37° C	Compound 2b 11.2% RH
0	5.02[a)]
1 h	5.00
2 h	4.85
4 h	4.80
6 h	4.70
6 days	4.70

a) water content expressed as % of the weight of compound 1b.

Milling studies and uniformity content

The milling process was performed by the FRITSCH Pulverisette 14 Rotor Speed Mill supplied with circular stainless steel sieve with trapezoidal 0.080 mm diameter openings. The samples were passed through the mill twice at 20.000 rpm motor speed. The sample is assayed for titre and degradation products by TLC and HPLC, physical state by DSC, water content by TGA,

particle size distribution by Mercury Instrusion Porosimetry. The milled compounds are formulated in capsules and tablets at very low dose level (0.5 mg) by direct mixing and direct compression manufacturing methods, respectively.

On the finished solid dosage forms, the uniformity content test was carried out by determining the compound content for at least 10 individual capsules or tablets. The coefficient of variation has to be less than 15% in order to accept the formulation.

Compound 2a shows an unexpectedly better stability to milling in comparison with compound 1a. The percentage of degradation products after milling compounds 1a and 2a at a rotor speed of 20,000 rpm is 0.65% and 0.0% respectively. In the meantime, the particle size reduction which is another relevant parameter indicative of the milling efficiency, reaches the same rank order for the two compounds as shown by Mercury Porosimetry Analysis.

The higher stability of compound 2a to milling constitutes a significant advantage over compound 1a since higher titres of the active drug can be achieved in the final compositions and the presence of a significant amount of degradation products is avoided.

Compound 2b shows an identical stability to milling in comparison with compound 1b with similar efficacy; in fact the particle size reduction which is another relevant parameter indicative of the milling efficiency, reaches the same rank order for the two compounds as shown by Mercury Porosimetry Analysis.

The higher physical stability of compound 2b to milling (compound 1b passes from a humidity content of 0.87% to 2.32%, whereas compound 2b remains unchanged at 4.8%) constitutes a significant advantage over compound 1b since higher titres of the active drug can be achieved in the final compositions and the presence of a significant amount of humidity can be avoided.

Compounds 2a and 2b show a better stability in tablets and capsules in comparison with compounds 1a and 1b after prolonged storage at different conditions (as reported for 2a in Tables VIII, IX and X). Drug stability in these final compositions may be measured in accelerated stability tests or in long term real time stability tests. In accelerated stability tests, the above pharmaceutical compositions are exposed at high temperatures at different degrees of relative humidity for a period of time. Such tests are considered to be indicative of the stability of the composition at normal conditions. In long term real time stability studies the final compositions are exposed to normal conditions of storage at ambient temperatures at different degrees of relative humidity.

In both the accelerated stability tests and in the long term real time stability tests, compounds 2a and 2b show better titres than those of compounds 1a and 1b.

TABLE VIII

ACCELERATED STABILITY TESTS

	Compound 1a % degradation	Compound 2a % degradation
1 month /55° C (*)	2.0%	0.5%
3 months /55° C	3.2%	1.6%

(*) according to H. Leven Berger Pharm. Act. Helv. 50 (1975) 88-91 it is equivalent to 2 years storage at room temperature.
Tablets and capsules are packaged in PVC/PVDC blister with aluminium foil.

TABLE IX

ACCELERATED STABILITY TESTS

	Compound 1a % degradation	Compound 2a % degradation
3 months/40° C-75% RH(*)	0.8%	0.5%
6 months/40° C-75% RH	1.7%	1.0%

(*) according to "Guidelines for stability studies for Human Drugs and Biologics" (1987) (USA/FDA) it is equivalent to 2 years at room temperature.

Tablets and capsules are packaged in PVC/PVDC blister with aluminium foil.

TABLE X

LONG-TERM REAL TIME STABILITY TESTS

	Compound 1a % degradation	Compound 2a % degradation
3 months/40° C	0.6%	0.4%
6 months/30° C-70% RH	0.5%	0.1%
6 months/40° C	1.1%	0.6%

Tablets and capsules are packaged in PVC/PVDC blister with aluminium foil.

Consequently the packaging of compounds 2a and 2b may be conveniently carried out by using conventional materials without any need to employ films or special

materials in order to protect the integrity of a hygroscopic, or however less stable, product.

According to a further feature of the present invention, there are provided pharmaceutical compositions comprising as active ingredient an effective amount of compounds 2a or 2b, as hereinbefore defined, in association with pharmaceutical carriers or excipients. Compositions for systemic administration are preferred, in particular for oral administration.

The pharmaceutical compositions according to the present invention are obtained by known methods, for example by conventional methods of mixing, granulation, tableting and film-coating. Thus, for example, it is possible to obtain pharmaceutical compositions for oral administration by mixing compound 2a or 2b with one or more solid carriers, and the obtained mixture is optionally granulated and worked by adding other excipients so that tablets or cores to film-coating can be obtained.

Suitable carriers are in particular diluents such as lactose, mannitol, sorbitol and/or dicalcium phosphate, furthermore humid binders such as corn starch, maize starch, methylcellulose, hydroxypropyl-methylcellulose, polyvinylpyrrolidone and/or, if desired, disintegrants such as alginic acid or sodium alginate, starches, cellulose derivatives, polyvinyl-pyrrolidone.

Further excipients are glidants and lubricants, such as colloidal silicon dioxide acid, talc, stearic acid; magnesium or calcium stearate and/or polyethylen-

glycol or its derivatives.

The cores to be film-coated may be covered with suitable coatings, possibly gastro-resistent ones, using concentrated sugary solutions, which optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethyleneglycol and/or titanium dioxide, solutions of lacquer in suitable organic or aqueous solvents for the production of gastro-resistent coatings, solutions of suitable cellulose compounds, such as acethylcellulose phthalate or copolymers of acrylic and metacrylic acid. Additional excipients, for example flavoring and colouring agents may also be present.

The pharmaceutical compositions for oral administration may also be presented as hard gelatine capsules. These capsules may contain compound 2a, (or 2b), mixed with diluents such as lactose, cellulose, calcium phosphate, glidants and lubricants such as talc or magnesium stearate, and/or disintegrants such as starches, cellulose derivatives, and polymers. In the soft capsules compound 2a (or 2b) is mixed with suitable liquid excipients such as arachis oil, paraffin oil, polyethyleneglycol or propylenic glycol, or solutions of hydrogenated starch derivatives.

The pharmaceutical compositions for rectal administration are in the form of suppositories containing compound 2a (or 2b) with conventional suppository bases, such as cocoa butter or other glycerides.

The compositions are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of the active ingredient. Each dosage

unit may conveniently contain from 0.1 to 20 mg and preferably from 0.2 to 15 mg of the above ingredient.

The following examples illustrate the present invention without limiting its scope.

Example 1

Endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride monohydrate (compound 2a)

Endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide (48 g, 0.178 mol) was dissolved into 85% aqueous ethanol (400 ml) with heating and stirring. Gaseous hydrochloric acid was then bubbled into the filtered clear solution until an acid pH was obtained. After two days standing at room temperature the separated white crystals were collected by filtration, washed with 85% aqueous ethanol (50 ml) and dried under vacuum at 40°C for 24 hours. 43.5 g of the title compound were obtained.

H_2O (K.F.) Found % 5.04

Calc. % 5.08

Analysis

Found % C 54.10 H 6.50 N 15.74 Cl 9.95

$C_{16}H_{20}N_4O_2.H_2O.HCl$

Calc. % C 54.16 H 6.53 N 15.79 Cl 9.99

Example 2

(compound 2a)

Endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride (100 g, 0.3 mol) was dissolved into a solution of 95% ethanol (740 ml) and water (87 ml) by gentle heating. After filtering, the clear solution was left at room

temperature for two days. The separated crystals were collected by filtration, washed with 85% ethanol (50 ml) and dried under vacuum at the temperature of 40°C for two days. 65.5 g of the title compound were obtained

H_2O (K.F.) Found % 4.99

Calc. % 5.08

Analysis Found % C 54.21 H 6.48 N 15.83 Cl 9.95

$C_{16}H_{20}N_4O_2.H_2O.HCl$

Calc. % C 54.16 H 6.53 N 15.79 Cl 9.99

Example 3

(compound 2a)

Endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide (5 g, 0.0166 mol) was dissolved in anhydrous ethanol (40 ml) by gentle heating. Then a solution of 37% hydrochloric acid (3 ml) and water (4 ml) was slowly added to the filtered hot solution. The crystals, which separated from the solution left for two days at room temperature, were filtered, washed with aqueous 85% ethanol (5 ml) and dried under vacuum for 24 hours at the temperature of 40°C. 3.6 g of the title compound were obtained.

H_2O (K.F.) Found % 5.00

Calc. % 5.08

Analysis

Found % C 54.20 H 6.50 N 15.70 Cl 10.02

$C_{16}H_{20}N_4O_2.H_2O.HCl$

Calc. % C 54.16 H 6.53 N 15.79 Cl 9.99

Example 4

Endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo-

[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride monohydrate (compound 2b)

Endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo-[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide as base (10 g, 30.4 mmol) was dissolved into an aqueous solution of 95% isopropanol (80 ml) with heating and stirring. Gaseous hydrochloric acid was bubbled into the filtered solution until an acid pH was obtained. After standing, the desired compound as hydrochloride monohydrate was separated from the solution by crystallizing. This was filtered, washed with humidified isopropanol and dried under vacuum at 40°C for 24 hours. 10.5 g, M.p. 244-245°C, KF 4.68%

Analysis

Found %	C 56.10	H 7.04	N 14.51
$C_{18}H_{24}N_4O_2.HCl.H_2O$			
Calc. %	C 56.46	H 7.11	N 14.63

Example 5

(compound 2b)

Endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo-[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride (1.5g) was dissolved into a solution of isopropanol (15 ml) and water (0.5 ml) with heating. The hot solution was filtered and allowed to cool spontaneously. The desired compound was separated, filtered, washed with humidified isopropanol and dried under vacuum for 24 hours at 40°C. 2.85 g, M.p. 241-

243°C, KF 4.75%

Analysis

Found % C 56.20 H 7.13 N 14.56

$C_{18}H_{24}N_4O_2.HCl.H_2O$

Calc. % C 54.46 H 7.11 N 14.63

Example 6

(compound 2b)

Endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo-[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide (240 g, 0.73 mol) was dissolved into isopropanol (2360 ml) with stirring and heating. The solution was filtered and an aqueous solution of 37% hydrochloric acid (125 ml) added. Upon standing, the desired product spontaneously separated, and was then filtered, washed with 95% aqueous isopropanol and dried under vacuum at 40°C for 24 hours. 260 g were obtained, M.p. 243-245°C, KF 4.7%

Analysis

Found % C 55.97 H 7.00 N 14.54

$C_{18}H_{24}N_4O_2.HCl.H_2O$

Calc. % C 56.41 H 7.11 N 14.63

Example 7

Tablets

- compound 2a (or 2b)	0.5 mg
- lactose	140.8 mg
- corn starch	36.0 mg
- colloidal silica	1.8 mg
- magnesium stearate	0.9 mg

Method of preparation: compound 2a (or 2b),

lactose and corn starch were mixed and homogeneously wetted with water. After screening of the moist mass and drying in a tray drier, the mixture was again passed throught a screen and colloidal silica and magnesium stearate were added. Then the mixture was pressed into tablets weighing 180 mg each. Each tablet contains 0.5 mg of compound 2a (or 2b).

Example 8

Capsules

- compound 2a	0.5 mg
- lactose	227.1 mg
- corn starch	58.0 mg
- colloidal silica	2.9 mg
- magnesium stearate	1.5 mg

Method of preparation: compound 2a was mixed with auxiliary products, and the mixture was passed through a screen and mixed homogeneously in a suitable device. The resulting mixture was filled into hard gelatine capsules (290 mg per capsule); each capsule contains 0.5 mg of compound 2a.

Example 9

Capsules

- compound 2b	5.0 mg
- lactose	210.5 mg
- corn starch	60.0 mg
- colloidal silica	3.0 mg
- magnesium stearate	1.5 mg

Method of preparation: compound 2b was mixed with auxiliary products, and the mixture was passed through a screen and mixed homogeneously in a suitable device.

The resulting mixture was filled into hard gelatine capsules (280 mg per capsule); each capsule contains 5 mg of compound 2b.

Example 10

Suppositories

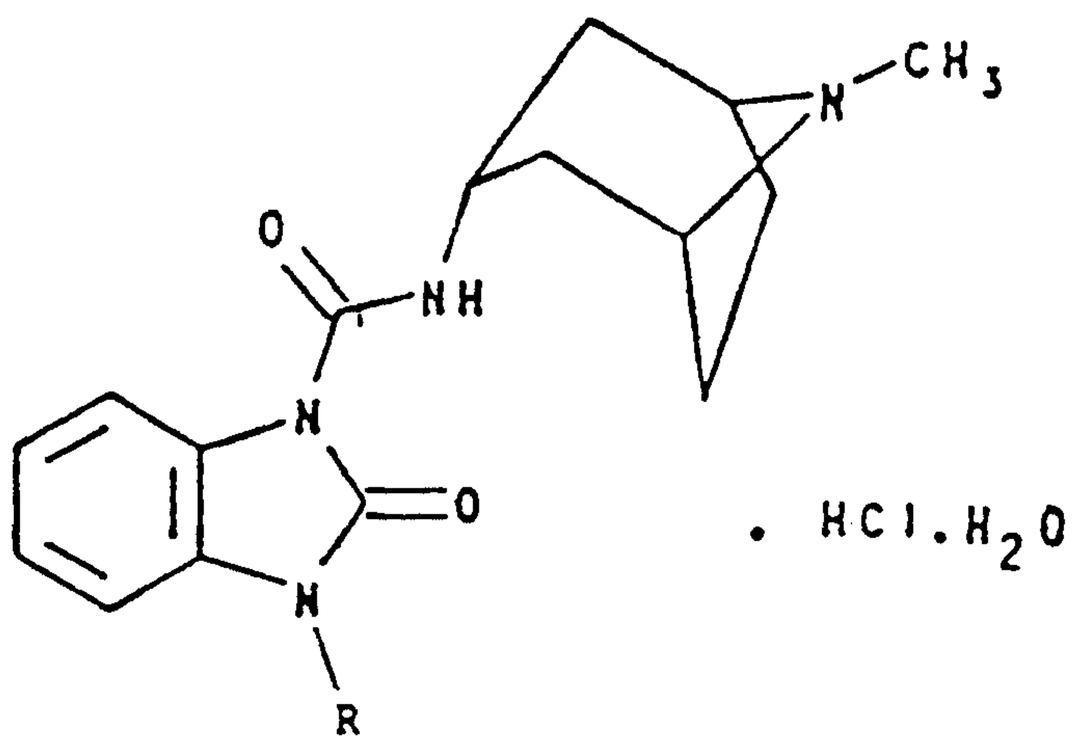
- compound 2a (2b) 15 mg
- semisynthetic glycerides of fatty acids 1185 mg

Method of preparation: The semisynthetic glycerides of fatty acids were melted and the compound 2a (2b) was added while stirring homogeneously. After cooling at a proper temperature the mass was poured into preformed moulds for suppositories weighing 1200 mg each. Each suppository contains 15 mg of compound 2a (2b).

25771-630

C L A I M S

1. Crystalline monohydrates of endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1.]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride and endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride, of formula



(Compound 2a: R = H)

(Compound 2b: R = C_2H_5)

2. A process for the preparation of compounds 2a and 2b as defined in claim 1, in which endo-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide, or endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide, is dissolved in hot aqueous solvent and after adding gaseous hydrogen chloride, the solution is filtered and cooled at room temperature giving the crystals of compound 2a or 2b respectively, which are desiccated at a temperature between room temperature and 60°C under vacuum.

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3. A process as claimed in claim 2, for the preparation of compound 2a, in which the aqueous solvent is 85% aqueous ethanol.

4. A process as claimed in claim 2, for the preparation of compound 2b, in which the aqueous solvent is 95% aqueous isopropanol.

5. A pharmaceutical composition comprising, as active ingredient, a therapeutically effective amount of crystalline monohydrate of endo-2, 3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride, or of endo-3-ethyl-2,3-dihydro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-oxo-1H-benzimidazole-1-carboxamide hydrochloride, according to claim 1 in association with a pharmaceutical acceptable carrier, excipient or diluent.

6. Compounds 2a and 2b as defined in claim 1 for use as 5-HT agents.

7. A use of compound 2a or 2b as defined in claim 1 in the manufacture of a medicament for treating a human or animal subject with a condition in which 5-HT is implicated.

8. A use of compound 2a or 2b as defined in claim 1 for treating a human or animal subject with a condition in which 5-HT is implicated.

FETHERSTONHAUGH & CO.

OTTAWA, CANADA

PATENT AGENTS

FIGURE 1

A = compound 1b

B = compound 2b

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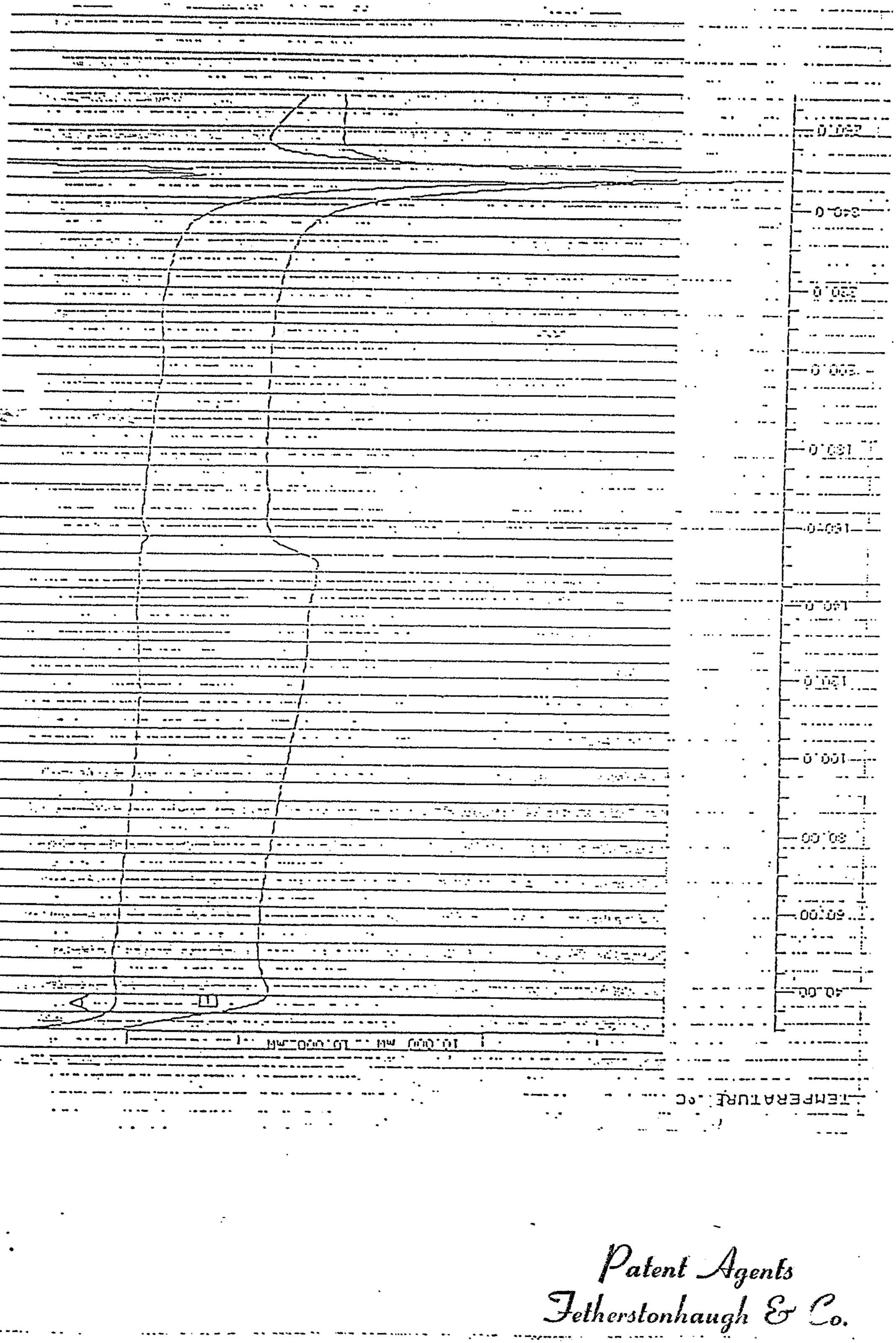

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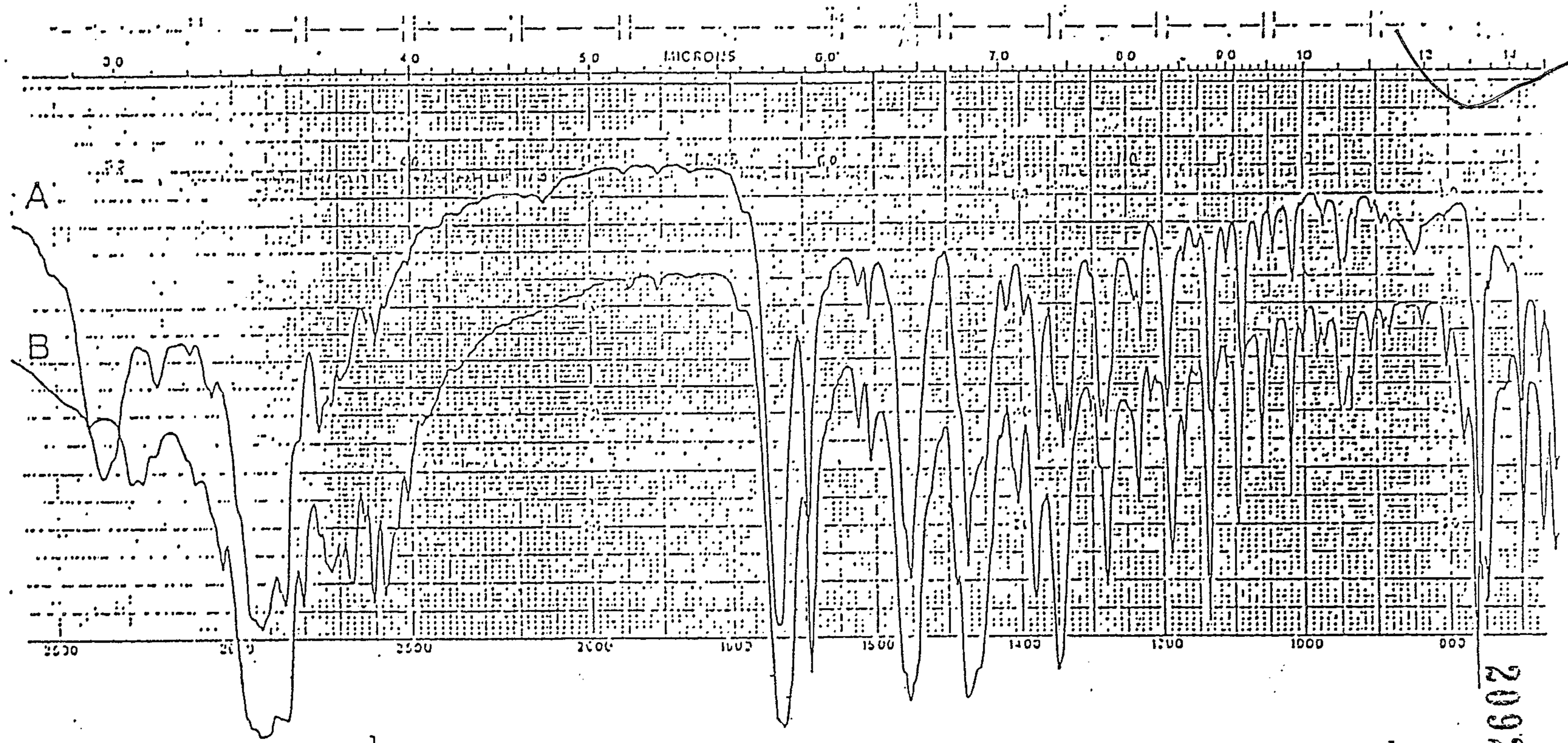
FIGURE 2



A = COMPOUND 2a

B = COMPOUND 1a

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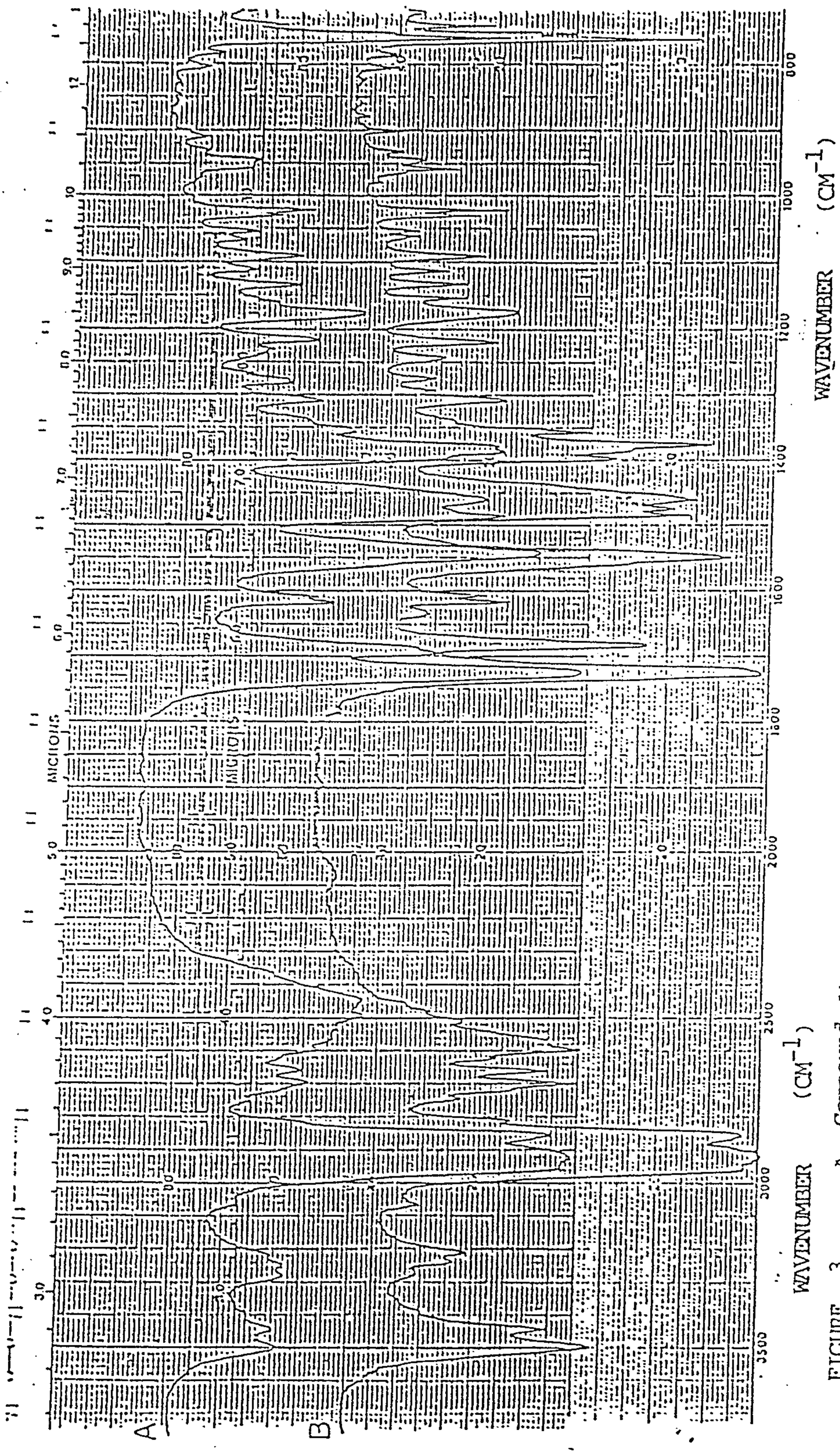

FIGURE 3 A = Compound 1b
B = Compound 2b

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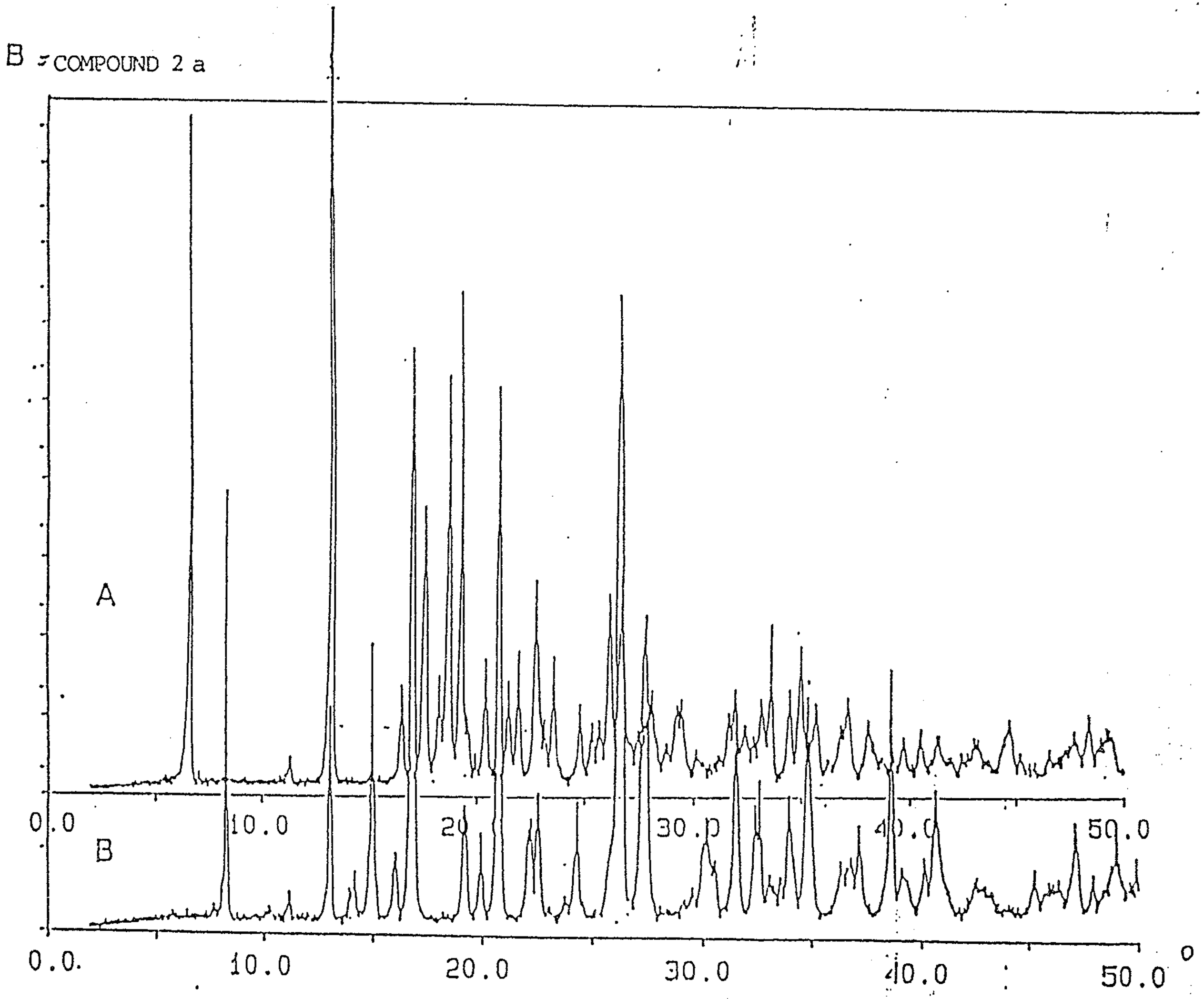
FIGURE 4



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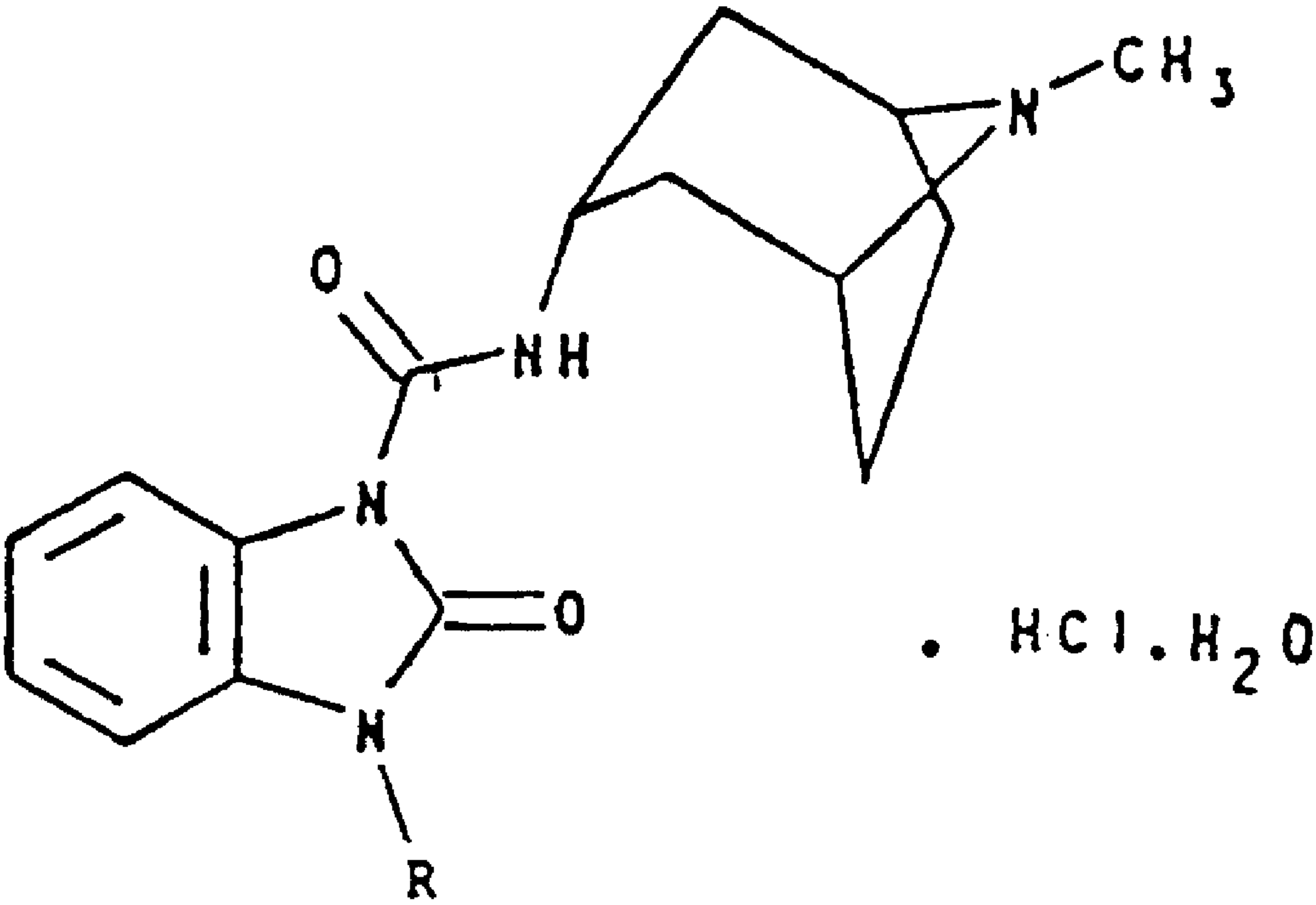

. HCl . H_2O